## DO STATINS IMPROVE OUTCOMES IN PATIENTS WITH ASTHMA ON INHALED CORTICOSTEROID THERAPY? A RETROSPECTIVE COHORT ANALYSIS

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DO STATINS IMPROVE OUTCOMES IN PATIENTS WITH ASTHMA ON INHALED CORTICOSTEROID THERAPY? A RETROSPECTIVE COHORT ANALYSIS

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Key words: Statins, Asthma, Inhaled Corticosteroids, Propensity Scores, Medicaid

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ABSTRACT

Objectives: Animal studies and clinical trials have examined the potential benefits of the anti-inflammatory statins in asthma management with contradictory results. The objective of this study was to determine if asthma patients on concurrent statins are less likely to have asthma-related hospitalizations.


Participants: Asthma patients ≥18 years were identified using the ICD9 code 493.xx, from Jul 1, 2002 through Dec 31, 2003. The index date for an exposed subject was any date within the identification period, 180 days prior to which the subject had at least one inhaled corticosteroid (ICS) prescription and at least an 80% adherence rate to statins. Asthma patients on ICSs, but not on statins were selected as the unexposed population. The two groups were matched and followed for one year beginning the index date.

Main outcomes measures: Patient outcomes in terms of hospitalizations and ER visits were compared using conditional logistic regression.

Results: After matching, there were 479 exposed subjects and 958 corresponding unexposed subjects. The odds of asthma-related hospitalization and/or ER visits for asthma patients on concurrent statins were almost half the odds for patients not on statins (OR = 0.55; 95% CI [0.37, 0.84]; p = 0.0059). Similarly, the odds of asthma-related ER visits were significantly lower for patients on statins (OR = 0.48; 95% CI [0.28, 0.82]; p = 0.0069).

Conclusion: The findings suggest beneficial effects of statins in asthma management. Further prospective investigations are required to provide more conclusive evidence.
ARTICLE SUMMARY

Article focus

- Statins have been shown to have promising therapeutic potential in mediating anti-inflammatory processes in animal model studies as well as clinical trials of rheumatoid arthritis, autoimmune encephalomyelitis, inflammatory colitis and psoriasis.

- Along the same line of reasoning recently there has been some discussion regarding the use of statins in asthma management in addition to inhaled corticosteroid therapy.

- The purpose of this study was to investigate the beneficial effects of statins on asthma outcomes using the Mississippi Medicaid claims database.

Key messages

- The findings suggest that statins may be beneficial in asthma management.

- The study accounts for several additional potential confounders not previously explored in the other observational studies.

Strengths and limitations of this study

- The study uses a propensity score-matched cohort study design, which in itself should take into account potential confounding effects.

- The study was conducted using Medicaid claims data and therefore there is a possibility of misclassification due to coding errors during claims processing.
**INTRODUCTION**

Inhibitors of 3-hydroxy-3-methylglutaryl coenzymes A (HMG CoA) reductase i.e., statins are conventionally prescribed as anti-hyperlipidemics. In the past decade, they have been shown to have promising therapeutic potential in mediating inflammatory processes.[1-5] Statins have been shown to be effective in animal model studies as well as clinical trials of rheumatoid arthritis,[6-8] autoimmune encephalomyelitis,[9, 10] inflammatory colitis,[11, 12] and even psoriasis [13] due to their anti-inflammatory properties. A recent observational study reported a striking 41% reduction in mortality [odds ratio, 0.59; 95% confidence interval, 0.38-0.92] in persons on statins either prior to or during hospitalization with influenza infection.[14] Given this, there has been some discussion pertaining to the use of statins in the management of asthma.[15-19]

Animal model studies using rats suggest that systemic lovastatin inhibits antigen-induced bronchial smooth muscle hyper-responsiveness.[20] It also reduces the increased cell number in bronchoalveolar lavage (BAL) fluids and histological changes induced by antigen exposure. Levels of Immunoglobulin E in sera and interleukins -4, -6, and -13 in the BAL fluids did not change significantly. Similar experiments have been conducted with mice,[21, 22] with findings that support the beneficial role of statins in asthma management. The proposed mechanism of action for this observation is that statins inhibit the geranylgeranylation of a monomeric GTP binding protein RhoA and its downstream metabolites, which are involved in the agonist induced Ca2+ sensitization of airway smooth muscle contraction. The RhoA/ Rho kinase pathway is now being investigated as the new target for the treatment of airway hyper-responsiveness. A study conducted by McKay and colleagues showed the inhibitory effects of simvastatin on inflammatory cell infiltration in a murine model of allergic asthma.[23] Similar experiments have been conducted with pravastatin and simvastatin, the results of which suggest asthma management to be an emerging indication for statins.[24-26]
Apart from the animal model studies described above, four small-scale clinical trials have been conducted with mixed results. A randomized double-blind crossover placebo-controlled trial investigated the effect of oral atorvastatin on measures of asthma control and airway inflammation.[27] The trial included 54 adults with allergic asthma receiving inhaled corticosteroids alone. The authors found no clinically important improvements in a range of clinical indices of asthma control measures despite expected changes in serum lipids. They concluded that statins were ineffective for the short-term therapy of asthmatic inflammation. However, a change in the airway inflammation as well as a reduction in the sputum macrophage count was observed indicating that statins could have beneficial effects in other chronic lung diseases. A similar clinical trial with oral simvastatin was conducted using 16 patients with asthma whereby the authors found no improvement in asthma symptoms, pulmonary function or measures of asthmatic inflammation.[28] Two other clinical trials showed improvements in asthma symptoms, lung function and sputum eosinophil counts in subjects on statins.[29, 30] A recent study of short-term treatment with atorvastatin in seventy one smokers with asthma failed to show improvements in lung function but may have improved their asthma quality of life score.[31] Given the small samples and contradicting conclusions of the above studies, these results should be interpreted cautiously.

Stanek and colleagues conducted the first observational study using the Medco National Integrated Database to explore the relationship between statin treatment and asthma.[32] A total of 6,574 inhaled corticosteroid-treated adult asthmatics were studied. Statin exposure was independently associated with a significant 33% reduction in recurrent asthma-related hospitalization/ER visits over 12 months [odds ratio, 0.67; 95% confidence interval, 0.58-0.76; p < 0.0001]. A recent study using the Taiwan National Health Insurance Database found statin use in patients with asthma to be independently associated with the decreased risk of hospitalization due to asthma [hazard ratio, 1.02; 95% confidence interval, 1.02-1.03; p < 0.001].[33]
The contradicting results between small clinical trials and larger observational studies clearly suggest that more studies investigating the potential role of statins in the management of asthma are required to make any clinical or policy-guiding decisions. The purpose of this study was to investigate the beneficial effects of statins on asthma outcomes using the Mississippi Medicaid claims database. The various animal model studies and clinical trials described above show varying results and have their own limitations. Another observational study using a different dataset is economically more feasible and provides us with an overview of the situation in the real-world setting. This study uses a propensity score-matched cohort study design, which in itself should take into account confounding effects due to the variables used to compute the propensity scores.[34] Prior hospitalizations, ER and office visits due to asthma, adherence to ICS medications and average number of short-acting β agonists during the study period were used to compute the propensity scores. These had not been taken into account in the earlier observational studies. Prior hospitalizations due to asthma and average number of short-acting β agonists can be an indicator of the severity of the disease, whereas non-compliance to the medications is a potential confounder as it could lead to hospitalization/ER visits.

METHODS

Data Source

For the purpose of the study, the 2002-2004 Mississippi Medicaid claims data were analyzed. Medicaid is a federal program that provides health care coverage to many of the most vulnerable populations in the United States, including low-income children and their parents, low-income elderly, pregnant women with low family income and the disabled poor. The claims data for each year is comprised of a Person Summary File and four Claims Files - inpatient (IP), institutional long-term care (LT), prescription drug (RX) and other services (OT). The Person Summary File includes person-level data on eligibility, demographics, managed care enrollment, a summary of utilization and Medicaid payment by type of service. Each observation in the claims files represents a transaction or record of the charges and
payments made to the health care provider for the services rendered to the Medicaid enrollee, including
details such as the date of service, expenditures for utilized services, associated diagnostic information,
and provider and procedure type. The Person Summary File has a record for every individual enrolled in
the program at anytime during the year; however, the claims files may have more than one or no records
for each Medicaid beneficiary depending on his/her utilization of services. The study was approved by
the Institutional Review Board (IRB) of the University of Mississippi and use of the data was approved
by a data use agreement finalized by the Centers for Medicare and Medicaid Services (CMS).

Study Design and Sample

A retrospective cohort design was utilized. The study involved analysis of the Medicaid beneficiary
claims from January 1, 2002 to December 31, 2004. It is important to note that because the study period
under consideration is prior to the implementation of Medicare Part D, the database does include
prescription claims for Medicaid-eligible patients aged 65 and older. Asthmatic adults above 18 years of
age were identified using the ICD9 code 493.xx, within the 18 month identification period starting July 1,
2002 and concluding December 31, 2003 as graphically represented in Figure 1. The index date for a
particular subject in the exposed group was any date within the identification period, six months prior to
which the subject had at least one prescription for an inhaled corticosteroid (ICS), at least an 80%
adherence rate to statins (i.e. proportion of days covered (PDC) ≥ 0.8), in addition to already having been
diagnosed with asthma. The subjects on statin and ICS therapy were identified using the National Drug
Codes (NDC) for these drugs respectively. A total of 589 beneficiaries were initially identified to be in
the exposed group. Similarly, Medicaid beneficiaries identified as asthmatics and on ICS therapy were
selected as the unexposed population with the only difference being that these patients were not on
concurrent statin therapy.
The study design included a washout period from January 1, 2002 to June 31, 2002 in order to track the prescription records of patients identified and included in the study. The 589 subjects in the exposed group were initially matched to a pool of 7,390 subjects in the unexposed group using propensity scores (within a range of ±0.005) computed using the covariates described later. Each exposed subject was matched to 10 corresponding subjects from the unexposed group; following which the unexposed subjects were assigned the index date of the exposed subjects they were matched to. This was done in order to maximize the number of exposed subjects that had at least 2 corresponding subjects from the unexposed group with an ICS prescription six months prior to the index date and were eligible throughout the same period. Following these procedures, 479 exposed subjects were obtained, along with corresponding 958 unexposed subjects. A detailed flow diagram representing subject selection can be found in Figure 2. The two cohorts were then followed for a period of one year beginning the index date, and their outcomes in terms of asthma-related hospitalizations and ER visits were compared.

Study Variables

Covariates

The exposed and unexposed groups were matched on age, gender, race, regions of Mississippi and Charlson Comorbidity Index using propensity scoring. The age of the subjects as of December 31, 2002 was computed. Gender was classified into male and female. Race was grouped into three categories:
whites, blacks and others. Additionally, subjects were categorized into rural and urban regions of Mississippi based on the county of residence. This variable was used to serve as a surrogate indicator of the access to care and control for differences in provider type. The Charlson Comorbidity Index (CCI) was computed and used as an indicator of additional comorbidities.

Adherence to ICS, average number of short-acting β agonists per subject, prior hospitalizations, ER visits, office, and laboratory visits due to asthma were additionally controlled for in the analysis performed on the matched cohorts. These could only be computed after the unexposed subjects were assigned their index dates and hence could not be used for the propensity score calculations. The PDC was used as an indication of adherence to ICS therapy and was computed for the six months prior to the index date for each subject. Short-acting β agonists are the most effective therapy for rapid reversal of airflow obstruction and prompt relief of asthmatic symptoms. The average number of short-acting β agonists per subject was computed for the six months prior to the index date and was used as an indicator of the severity of the disease. The number of hospitalizations, ER visits, office, and laboratory visits attributed to a primary diagnosis of asthma in the six month washout period prior to the index date were also used as indicators of the severity of the disease.

Outcome variables

Hospitalization due to asthma was coded dichotomously (as occurrence and non-occurrence of event), using the principal diagnosis code for hospitalization, through one year post the index date for both the exposed and unexposed. Additionally, ER visit due to asthma was computed in a similar manner.

Statistical Analysis

Descriptive statistics were calculated for the exposed and unexposed subjects pre- and post-matching. Means and standard deviations were calculated for continuous data, whereas percentages were used for
categorical data. Differences between exposed and unexposed groups were assessed using t tests or chi-square tests depending on whether the variable was continuous or categorical.

After the identification of the exposed and unexposed based on the inclusion criteria described previously, propensity scores were calculated for the subjects in both groups. The propensity score for an individual is defined as the conditional probability of being treated given the individual’s covariates and thus reduces bias by balancing the covariates in the two groups.[34] Logistic regression was used to compute and save the probability of being in the exposed group for all subjects based on their age, gender, race, region and CCI as discussed previously.

After the matched exposed and unexposed cohorts were obtained, conditional logistic regression was used to assess the relationship between statin use and the two outcome variables, asthma-related hospitalizations and ER visits.

RESULTS

As discussed previously, 589 subjects met the inclusion criteria for the exposed cohort. The pool of unexposed subjects included 7,390 individuals prior to matching on the propensity scores. Table 1 compares the demographic characteristics among the exposed and unexposed cohorts before and after matching. Prior to matching, the average age of asthma patients on concurrent statin therapy was significantly higher than that of patients not on statin therapy (48.87 [±0.22] vs. 63.28 [±0.50]). A significantly higher proportion of asthma patients who were not on concurrent statin therapy were black as compared to those on statin therapy (54.44% vs. 42.95%) before matching. Additionally, those on concurrent statin therapy had a significantly higher average CCI than those not on concurrent statin therapy (4.01[±0.10] vs. 2.65 [± 0.03]).

After matching, the exposed cohort comprised of 479 individuals with 958 individuals in the unexposed cohort. Post-matching, a significantly higher proportion of asthma patients on concurrent statin therapy
were from the rural areas of Mississippi (71.19% vs. 65.45%; \( p = 0.0287 \)) as compared to those not on statin therapy (Table 1). Additionally, the average CCI of patients on concurrent statin therapy was higher than that of patients not on statin therapy (3.75 [±0.10] vs. 3.48 [±0.07]; \( p = 0.03 \)), but the difference was much smaller compared to the difference prior to matching.

### Table 1: Study sample characteristics before and after matching

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Before Matching</th>
<th>After Matching</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exposed (589)</td>
<td>Unexposed (7390)</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>63.28 (± 12.25)</td>
<td>48.87 (± 19.17)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td>0.5750</td>
</tr>
<tr>
<td>Male</td>
<td>125 (21.22)</td>
<td>1,642 (22.22)</td>
</tr>
<tr>
<td>Female</td>
<td>464 (78.78)</td>
<td>5,748 (77.78)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td>&lt;.0001*</td>
</tr>
<tr>
<td>White</td>
<td>334 (56.71)</td>
<td>3,321 (44.94)</td>
</tr>
<tr>
<td>Black</td>
<td>253 (42.95)</td>
<td>4,023 (54.44)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (0.34)</td>
<td>46 (0.62)</td>
</tr>
<tr>
<td>Region, n (%)</td>
<td></td>
<td>0.0544</td>
</tr>
<tr>
<td>Urban</td>
<td>167 (28.35)</td>
<td>2,379 (32.19)</td>
</tr>
<tr>
<td>Rural</td>
<td>422 (71.65)</td>
<td>5,011 (67.81)</td>
</tr>
<tr>
<td>Charlson Comorbidity Index, mean (SD)</td>
<td>4.01 (± 2.48)</td>
<td>2.65 (± 2.17)</td>
</tr>
</tbody>
</table>

\* \( p < 0.05 \)

The proportion of exposed and unexposed subjects using additional medications, besides ICS, for asthma management can be found in Table 2.

### Table 2: Additional medications used for asthma management

<table>
<thead>
<tr>
<th>Medication</th>
<th>Exposed (479)</th>
<th>Unexposed (958)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( n (%) )</td>
<td>( n (%) )</td>
</tr>
</tbody>
</table>
Descriptive information on the covariates adjusted for in the final conditional logistic regression model can be found in Table 3. Subjects with asthma on concurrent statin therapy were significantly less adherent to their ICS therapy (0.47 [± 0.27] vs. 0.51 [± 0.28]), used lesser number of short-acting β agonist prescriptions on an average (2.74 [± 2.10] vs. 3.49 [± 2.85]) and had fewer ER visits due to asthma six months prior to the index date (0.02 [± 0.14] vs. 0.06 [0.29]) when compared to subjects not on concurrent statin therapy.

Table 3 Additional covariates adjusted for in the conditional logistic regression analysis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Exposed (479) Mean (±SD)</th>
<th>Unexposed (958) Mean (±SD)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherence to ICS therapy (PDC)</td>
<td>0.47 (0.27)</td>
<td>0.51 (0.28)</td>
<td>0.0146*</td>
</tr>
<tr>
<td>Average no. of short-acting β agonist prescriptions per subject</td>
<td>2.74 (2.10)</td>
<td>3.49 (2.85)</td>
<td>&lt;.0001*</td>
</tr>
<tr>
<td>No. of asthma office &amp; lab visits 6 months prior the index date</td>
<td>0.21 (0.64)</td>
<td>0.24 (0.65)</td>
<td>0.5031</td>
</tr>
<tr>
<td>No. of asthma hospitalization events 6 months prior the index date</td>
<td>0.03 (0.19)</td>
<td>0.05 (0.24)</td>
<td>0.1002</td>
</tr>
<tr>
<td>No. of asthma ER events 6 months prior the index date</td>
<td>0.02 (0.14)</td>
<td>0.06 (0.29)</td>
<td>0.0063*</td>
</tr>
</tbody>
</table>

* p < 0.05

**ICS: Inhaled Corticosteroids; PDC: Proportion of Days Covered

The results of the conditional logistic regression conducted on the matched data and the odds ratios for hospitalization/ER admission due to asthma amongst patients on concurrent statin therapy as opposed to those not on statin therapy are displayed in Table 4. At least one asthma-related hospitalization was
observed in 3.79% of the subjects on concurrent statin therapy, and 6.47% of the subjects not on concurrent statin therapy, twelve months post index date. At least one ER visit due to asthma was observed in 4.18% of the subjects on concurrent statin therapy and 9.08% of the subjects not on concurrent statin therapy, twelve months post index date. The odds of a hospital visit and/or ER visit due to asthma for asthma patients on concurrent statin therapy were almost half the odds for patients not on statin therapy (unadjusted OR = 0.51; 95% CI [0.34, 0.76]). Similarly, they were also less likely to be hospitalized (unadjusted OR = 0.56; 95% CI [0.32, 0.98]) and visit the ER (unadjusted OR = 0.44; 95% CI [0.27, 0.73]) due to asthma exacerbations as opposed to those not on statin therapy. The above odds ratios have not been adjusted for additional variables such as prior asthma-related hospitalizations, ER visits, office and lab visits, number of short-acting β agonist prescriptions, and adherence to ICS therapy.

The adjusted conditional odds ratios after accounting for these factors are also found in Table 4. A statistically significant relationship between statin use and the combined endpoint as well as asthma-related ER visits remained after adjustment for these other variables.

**Table 4** Conditional odds ratios of hospitalizations due to asthma associated with statin use

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Unadjusted OR†</th>
<th>p</th>
<th>Adjusted OR¶</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(95% CI)</td>
<td></td>
<td>(95% CI)</td>
<td></td>
</tr>
<tr>
<td>Asthma hospitalization and/or ER visit</td>
<td>0.51 (0.34 – 0.76)</td>
<td>0.0010*</td>
<td>0.55 (0.36 – 0.84)</td>
<td>0.0059*</td>
</tr>
<tr>
<td>Asthma hospitalization</td>
<td>0.56 (0.32 – 0.98)</td>
<td>0.0436*</td>
<td>0.63 (0.35 – 1.13)</td>
<td>0.1183</td>
</tr>
<tr>
<td>Asthma ER visit</td>
<td>0.44 (0.27 – 0.73)</td>
<td>0.0013*</td>
<td>0.47 (0.28 – 0.82)</td>
<td>0.0069*</td>
</tr>
</tbody>
</table>

* p < 0.05

†Adjusted for variables used to create propensity scores.

¶Adjusted for prior asthma-related hospitalizations, ER visits, office and lab visits, number of short-acting β agonist prescriptions, and adherence to ICS therapy.
DISCUSSION

Over the three years of data analyzed, 589 subjects met the inclusion criteria for the exposed cohort, prior to matching and were classified as subjects on statin therapy, with 7,390 subjects in the unexposed cohort. When comparing the demographic characteristics of patients on concurrent statin therapy to those not on statins, significant differences were observed. The average age of the asthmatic patients on statin therapy was significantly higher than those not on statin therapy. This was not surprising as patients with statin therapy would likely have hyperlipidemia, a condition more prevalent in older adults. Additionally, a significantly higher proportion of patients on statin therapy were white when compared to the unexposed population and also had a higher average CCI score. In order to control for the above differences, propensity scores were computed and the study groups were matched on their propensity to be in the exposed cohort.

The final sample comprised of considerably older subjects with the average age of the exposed and unexposed being 62.59 (±0.55) years and 63.48 (±0.42) years, respectively. Most of the study subjects were females, which is consistent with previous prevalence reports which indicate that asthma is more prevalent in females in general.[35] Additionally, a higher proportion of the sample was white, lived in rural regions and had a considerable number of comorbid conditions.

A higher proportion of the unexposed subjects were on additional asthma controller therapy (Table 2). It is interesting to note however, that the average number of short-acting β agonist prescriptions were significantly higher for patients not on statin therapy and thus one might expect their condition to be better managed, which does not seem to be the case. Thus, the other way to look at it is that their condition is more severe or is not being managed well and hence the higher average number of quick relief prescriptions.
A significant reduction in the odds of hospitalization and ER visits due to asthma was found to be associated with statin use. Even after controlling for the confounders mentioned above, patients not on concurrent statin therapy were almost twice as likely to have hospitalization and/or ER visits attributable to asthma when compared to patients on statin therapy. These findings suggest that statins are beneficial in asthma management. This is in accordance with other observational studies conducted to investigate this relationship.[32, 33]

There are several limitations of this study. The study was conducted using Medicaid claims data and therefore there is a possibility of misclassification due to coding errors during claims processing. Further, even though the subjects in the unexposed group were matched to the exposed population based on their propensity scores, significant differences between the two groups were still observed when compared across their CCI scores and the region (urban versus rural) to which they belonged. This could be attributed to two plausible explanations. Firstly, the cohorts were matched on propensity scores allowing a range of ±0.005. Secondly, each subject was initially matched to 10 corresponding subjects from the unexposed pool, following which two controls were selected based on their continuous eligibility throughout the study period and ICS prescription records within 180 days prior to the index date. However, both of the above measures were incorporated into the study design to maximize the sample size. Even after matching, subjects on statin therapy had a significantly higher average CCI score compared to those not on statin therapy. It is unlikely that this difference could have biased the findings towards a lower risk of hospitalization due to asthma in these subjects. Another limitation is that the population studied had an average age of approximately 63 years and were sicker patients in general due to the higher CCI scores, which limits the generalizability of the study to some extent.

The findings of this study contribute significantly to the growing body of literature that suggests statins have beneficial effects in preventing asthma exacerbations. Some researchers suggest that the addition of a statin to ICS therapy in clinical practice will not prove beneficial in the management of asthma referring
to practice as a ‘snake oil panacea’. [36] However, further investigation employing different datasets, different methodologies and accounting for other confounding variables which may have been overlooked, is required to provide conclusive evidence.
FUNDING STATEMENT

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.
REFERENCES


83,446 beneficiaries with a diagnosis of asthma

35,001 beneficiaries with at least 1 ICS prescription

2,742 beneficiaries with at least 1 statin prescription

589 ‘exposed’ beneficiaries with ≥80% adherence to statin medication and at least 1 ICS prescription over a period of 180 days between January 1, 2002 and December 31, 2004

479 ‘exposed’ beneficiaries each matched to ‘unexposed’ beneficiaries meeting all the inclusion criteria enlisted in Table 1
Dear Dr. Sands:

The research article titled ‘Do Statins Improve Outcomes in Patients with Asthma on Inhaled Corticosteroid Therapy? A Retrospective Cohort Analysis’ was previously submitted to Thorax for review and publication. As I mentioned in my cover letter, we wanted to take the opportunity to address the Thorax reviewers’ comments in our submission to BMJ Open. We have attempted below to summarize our responses to the reviewers; some changes have been made to the manuscript and we briefly outline these as well. We believe that the Thorax reviewers have provided sound feedback that has improved our manuscript and we look forward to receiving feedback from the BMJ Open reviewers. If you have any questions, please do not hesitate to contact me.

REVIEWER: 1

Comments to the Author

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

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

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?

**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.
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.

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’.


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.
Sincerely,

Tasneem Lokhandwala, B.S. (Pharmacy), M.S.
Graduate Student
School of Pharmacy
The University of Mississippi
University, MS 38677
E-mail: ttlokan@olemiss.edu
Office: (662)915-6685
STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of cross-sectional studies

<table>
<thead>
<tr>
<th>Section/Topic</th>
<th>Item #</th>
<th>Recommendation</th>
<th>Reported on page #</th>
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<tbody>
<tr>
<td><strong>Title and abstract</strong></td>
<td>1</td>
<td>(a) Indicate the study’s design with a commonly used term in the title or the abstract</td>
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<tr>
<td></td>
<td>(b)</td>
<td>Provide in the abstract an informative and balanced summary of what was done and what was found</td>
<td>2</td>
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<tr>
<td><strong>Introduction</strong></td>
<td>2</td>
<td>Explain the scientific background and rationale for the investigation being reported</td>
<td>4-5</td>
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<tr>
<td><strong>Objectives</strong></td>
<td>3</td>
<td>State specific objectives, including any prespecified hypotheses</td>
<td>6</td>
</tr>
<tr>
<td><strong>Methods</strong></td>
<td>4</td>
<td>Present key elements of study design early in the paper</td>
<td>6, 7-8</td>
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<td>Study design</td>
<td>5</td>
<td>Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection</td>
<td>6</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>6</td>
<td>(a) Give the eligibility criteria, and the sources and methods of selection of participants</td>
<td>7</td>
</tr>
<tr>
<td>Variables</td>
<td>7</td>
<td>Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable</td>
<td>8-9</td>
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<tr>
<td>Data sources/</td>
<td>8*</td>
<td>For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group</td>
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<td>measurement</td>
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<td>Bias</td>
<td>9</td>
<td>Describe any efforts to address potential sources of bias</td>
<td>6</td>
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<tr>
<td>Study size</td>
<td>10</td>
<td>Explain how the study size was arrived at</td>
<td>7-8, Figure 2</td>
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<tr>
<td>Quantitative variables</td>
<td>11</td>
<td>Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why</td>
<td>8-9</td>
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<tr>
<td>Statistical methods</td>
<td>12</td>
<td>(a) Describe all statistical methods, including those used to control for confounding</td>
<td>9-10</td>
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<td>(b) Describe any methods used to examine subgroups and interactions</td>
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<td>(c) Explain how missing data were addressed</td>
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<td>(d) If applicable, describe analytical methods taking account of sampling strategy</td>
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<td>(e) Describe any sensitivity analyses</td>
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For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 7-8, Figure 2 |
| (b) Give reasons for non-participation at each stage | | | |
| (c) Consider use of a flow diagram | | Figure 2 |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 10-11, Table 1 |
| (b) Indicate number of participants with missing data for each variable of interest | NA |
| Outcome data | 15* | Report numbers of outcome events or summary measures | 13, Table 4 |
| Main results | 16 | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 12-13, Table 3, Table 4 |
| (b) Report category boundaries when continuous variables were categorized | 8-9 |
| (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | NA |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | NA |
| Discussion | | Key results | 18 | Summarise key results with reference to study objectives | 15 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 15 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 14-16 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 15-16 |
| Other information | | Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 17 |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

DO STATINS IMPROVE OUTCOMES IN PATIENTS WITH ASTHMA ON INHALED CORTICOSTEROID THERAPY? A RETROSPECTIVE COHORT ANALYSIS

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<td>16-Apr-2012</td>
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<td>Lokhandwala, Tasneem; University of Mississippi, Pharmacy Administration; West-Strum, Donna; University of Mississippi, Pharmacy Administration Banahan, Benjamin; University of Mississippi, Pharmacy Administration Bentley, John; University of Mississippi, Pharmacy Administration Yang, Yi; University of Mississippi, Pharmacy Administration</td>
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<td>Asthma &lt; THORACIC MEDICINE, Inhaled Corticosteroids, Statins, Propensity Scores, Medicaid</td>
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DO STATINS IMPROVE OUTCOMES IN PATIENTS WITH ASTHMA ON INHALED CORTICOSTEROID THERAPY? A RETROSPECTIVE COHORT ANALYSIS

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Key words: Statins, Asthma, Inhaled Corticosteroids, Propensity Scores, Medicaid

Word Count: 3265
ABSTRACT

Objectives: Animal studies and clinical trials have examined the potential benefits of the anti-inflammatory statins in asthma management with contradictory results. The objective of this study was to determine if asthma patients on concurrent statins are less likely to have asthma-related hospitalizations.


Participants: Asthma patients ≥18 years were identified using the ICD9 code 493.xx, from Jul 1, 2002 through Dec 31, 2003. The index date for an exposed subject was any date within the identification period, 180 days prior to which the subject had at least one inhaled corticosteroid (ICS) prescription and at least an 80% adherence rate to statins. Asthma patients on ICSs, but not on statins were selected as the unexposed population. The two groups were matched and followed for one year beginning the index date.

Main outcomes measures: Patient outcomes in terms of hospitalizations and ER visits were compared using conditional logistic regression.

Results: After matching, there were 479 exposed subjects and 958 corresponding unexposed subjects. The odds of asthma-related hospitalization and/or ER visits for asthma patients on concurrent statins were almost half the odds for patients not on statins (OR = 0.55; 95% CI [0.37, 0.84]; p = 0.0059). Similarly, the odds of asthma-related ER visits were significantly lower for patients on statins (OR = 0.48; 95% CI [0.28, 0.82]; p = 0.0069).

Conclusion: The findings suggest beneficial effects of statins in asthma management. Further prospective investigations are required to provide more conclusive evidence.
ARTICLE SUMMARY

Article focus

- Statins have been shown to have promising therapeutic potential in mediating anti-inflammatory processes in animal model studies as well as clinical trials of rheumatoid arthritis, autoimmune encephalomyelitis, inflammatory colitis and psoriasis.

- Along the same line of reasoning recently there has been some discussion regarding the use of statins in asthma management in addition to inhaled corticosteroid therapy.

- The purpose of this study was to investigate the beneficial effects of statins on asthma outcomes using the Mississippi Medicaid claims database.

Key messages

- The findings suggest that statins may be beneficial in asthma management.

- The study accounts for several additional potential confounders not previously explored in the other observational studies.

Strengths and limitations of this study

- The study uses a propensity score-matched cohort study design, which in itself should take into account potential confounding effects.

- The study was conducted using Medicaid claims data and therefore there is a possibility of misclassification due to coding errors during claims processing.
INTRODUCTION

Inhibitors of 3-hydroxy-3-methylglutaryl coenzymes A (HMG CoA) reductase i.e., statins are conventionally prescribed as anti-hyperlipidemics. In the past decade, they have been shown to have promising therapeutic potential in mediating inflammatory processes.[1-5] Statins have been shown to be effective in animal model studies as well as clinical trials of rheumatoid arthritis,[6-8] autoimmune encephalomyelitis,[9, 10] inflammatory colitis,[11, 12] and even psoriasis [13] due to their anti-inflammatory properties. A recent observational study reported a striking 41% reduction in mortality [odds ratio, 0.59; 95% confidence interval, 0.38-0.92] in persons on statins either prior to or during hospitalization with influenza infection.[14] Given this, there has been some discussion pertaining to the use of statins in the management of asthma.[15-19]

Animal model studies using rats suggest that systemic lovastatin inhibits antigen-induced bronchial smooth muscle hyper-responsiveness.[20] It also reduces the increased cell number in bronchoalveolar lavage (BAL) fluids and histological changes induced by antigen exposure. Levels of Immunoglobulin E in sera and interleukins -4, -6, and -13 in the BAL fluids did not change significantly. Similar experiments have been conducted with mice,[21, 22] with findings that support the beneficial role of statins in asthma management. The proposed mechanism of action for this observation is that statins inhibit the geranylgeranylation of a monomeric GTP binding protein RhoA and its downstream metabolites, which are involved in the agonist induced Ca2+ sensitization of airway smooth muscle contraction. The RhoA/ RhoA kinase pathway is now being investigated as the new target for the treatment of airway hyper-responsiveness. A study conducted by McKay and colleagues showed the inhibitory effects of simvastatin on inflammatory cell infiltration in a murine model of allergic asthma.[23] Similar experiments have been conducted with pravastatin and simvastatin, the results of which suggest asthma management to be an emerging indication for statins.[24-26]
Apart from the animal model studies described above, four small-scale clinical trials have been conducted with mixed results. A randomized double-blind crossover placebo-controlled trial investigated the effect of oral atorvastatin on measures of asthma control and airway inflammation.[27] The trial included 54 adults with allergic asthma receiving inhaled corticosteroids alone. The authors found no clinically important improvements in a range of clinical indices of asthma control measures despite expected changes in serum lipids. They concluded that statins were ineffective for the short-term therapy of asthmatic inflammation. However, a change in the airway inflammation as well as a reduction in the sputum macrophage count was observed indicating that statins could have beneficial effects in other chronic lung diseases. A similar clinical trial with oral simvastatin was conducted using 16 patients with asthma whereby the authors found no improvement in asthma symptoms, pulmonary function or measures of asthmatic inflammation.[28] Two other clinical trials showed improvements in asthma symptoms, lung function and sputum eosinophil counts in subjects on statins.[29, 30] A recent study of short-term treatment with atorvastatin in seventy one smokers with asthma failed to show improvements in lung function but may have improved their asthma quality of life score.[31] Given the small samples and contradicting conclusions of the above studies, these results should be interpreted cautiously.

Stanek and colleagues conducted the first observational study using the Medco National Integrated Database to explore the relationship between statin treatment and asthma.[32] A total of 6,574 inhaled corticosteroid-treated adult asthmatics were studied. Statin exposure was independently associated with a significant 33% reduction in recurrent asthma-related hospitalization/ER visits over 12 months [odds ratio, 0.67; 95% confidence interval, 0.58-0.76; \( p < 0.0001 \)]. A recent study using the Taiwan National Health Insurance Database found statin use in patients with asthma to be independently associated with the decreased risk of hospitalization due to asthma [hazard ratio, 1.02; 95% confidence interval, 1.02-1.03; \( p < 0.001 \)].[33]
The contradicting results between small clinical trials and larger observational studies clearly suggest that more studies investigating the potential role of statins in the management of asthma are required to make any clinical or policy-guiding decisions. The purpose of this study was to investigate the beneficial effects of statins on asthma outcomes using the Mississippi Medicaid claims database. The various animal model studies and clinical trials described above show varying results and have their own limitations. Another observational study using a different dataset is economically more feasible and provides us with an overview of the situation in the real-world setting. This study uses a propensity score-matched cohort study design, which in itself should take into account confounding effects due to the variables used to compute the propensity scores. Prior hospitalizations, ER and office visits due to asthma, adherence to ICS medications and average number of short-acting β agonists during the study period were used to compute the propensity scores. These had not been taken into account in the earlier observational studies. Prior hospitalizations due to asthma and average number of short-acting β agonists can be an indicator of the severity of the disease, whereas non-compliance to the medications is a potential confounder as it could lead to hospitalization/ER visits.

METHODS

Data Source

For the purpose of the study, the 2002-2004 Mississippi Medicaid claims data were analyzed. Medicaid is a federal program that provides health care coverage to many of the most vulnerable populations in the United States, including low-income children and their parents, low-income elderly, pregnant women with low family income and the disabled poor. The claims data for each year is comprised of a Person Summary File and four Claims Files - inpatient (IP), institutional long-term care (LT), prescription drug (RX) and other services (OT). The Person Summary File includes person-level data on eligibility, demographics, managed care enrollment, a summary of utilization and Medicaid payment by type of service. Each observation in the claims files represents a transaction or record of the charges and...
payments made to the health care provider for the services rendered to the Medicaid enrollee, including
details such as the date of service, expenditures for utilized services, associated diagnostic information,
and provider and procedure type. The Person Summary File has a record for every individual enrolled in
the program at anytime during the year; however, the claims files may have more than one or no records
for each Medicaid beneficiary depending on his/her utilization of services. The study was approved by
the Institutional Review Board (IRB) of the University of Mississippi and use of the data was approved
by a data use agreement finalized by the Centers for Medicare and Medicaid Services (CMS).

Study Design and Sample

A retrospective cohort design was utilized. The study involved analysis of the Medicaid beneficiary
claims from January 1, 2002 to December 31, 2004. It is important to note that because the study period
under consideration is prior to the implementation of Medicare Part D, the database does include
prescription claims for Medicaid-eligible patients aged 65 and older. Asthmatic adults above 18 years of
age were identified using the ICD9 code 493.xx, within the 18 month identification period starting July 1,
2002 and concluding December 31, 2003 as graphically represented in Figure 1. The index date for a
particular subject in the exposed group was any date within the identification period, six months prior to
which the subject had at least one prescription for an inhaled corticosteroid (ICS), at least an 80%
adherence rate to statins (i.e. proportion of days covered (PDC) ≥ 0.8), in addition to already having been
diagnosed with asthma. The subjects on statin and ICS therapy were identified using the National Drug
Codes (NDC) for these drugs respectively. A total of 589 beneficiaries were initially identified to be in
the exposed group. Similarly, Medicaid beneficiaries identified as asthmatics and on ICS therapy were
selected as the unexposed population with the only difference being that these patients were not on
concurrent statin therapy.
The study design included a washout period from January 1, 2002 to June 31, 2002 in order to track the prescription records of patients identified and included in the study. The 589 subjects in the exposed group were initially matched to a pool of 7,390 subjects in the unexposed group using propensity scores (within a range of ±0.005) computed using the covariates described later. Each exposed subject was matched to 10 corresponding subjects from the unexposed group; following which the unexposed subjects were assigned the index date of the exposed subjects they were matched to. This was done in order to maximize the number of exposed subjects that had at least 2 corresponding subjects from the unexposed group with an ICS prescription six months prior to the index date and were eligible throughout the same period. Following these procedures, 479 exposed subjects were obtained, along with corresponding 958 unexposed subjects. A detailed flow diagram representing subject selection can be found in Figure 2. The two cohorts were then followed for a period of one year beginning the index date, and their outcomes in terms of asthma-related hospitalizations and ER visits were compared.

Study Variables

Covariates

The exposed and unexposed groups were matched on age, gender, race, regions of Mississippi and Charlson Comorbidity Index using propensity scoring. The age of the subjects as of December 31, 2002 was computed. Gender was classified into male and female. Race was grouped into three categories:
whites, blacks and others. Additionally, subjects were categorized into rural and urban regions of Mississippi based on the county of residence. This variable was used to serve as a surrogate indicator of the access to care and control for differences in provider type. The Charlson Comorbidity Index (CCI) was computed and used as an indicator of additional comorbidities.

Adherence to ICS, average number of short-acting $\beta$ agonists per subject, prior hospitalizations, ER visits, office, and laboratory visits due to asthma were additionally controlled for in the analysis performed on the matched cohorts. These could only be computed after the unexposed subjects were assigned their index dates and hence could not be used for the propensity score calculations. The PDC was used as an indication of adherence to ICS therapy and was computed for the six months prior to the index date for each subject. Short-acting $\beta$ agonists are the most effective therapy for rapid reversal of airflow obstruction and prompt relief of asthmatic symptoms. The average number of short-acting $\beta$ agonists per subject was computed for the six months prior to the index date and was used as an indicator of the severity of the disease. The number of hospitalizations, ER visits, office, and laboratory visits attributed to a primary diagnosis of asthma in the six month washout period prior to the index date were also used as indicators of the severity of the disease.

Outcome variables

Hospitalization due to asthma was coded dichotomously (as occurrence and non-occurrence of event), using the principal diagnosis code for hospitalization, through one year post the index date for both the exposed and unexposed. Additionally, ER visit due to asthma was computed in a similar manner.

Statistical Analysis

Descriptive statistics were calculated for the exposed and unexposed subjects pre- and post-matching. Means and standard deviations were calculated for continuous data, whereas percentages were used for
categorical data. Differences between exposed and unexposed groups were assessed using t tests or chi-square tests depending on whether the variable was continuous or categorical.

After the identification of the exposed and unexposed based on the inclusion criteria described previously, propensity scores were calculated for the subjects in both groups. The propensity score for an individual is defined as the conditional probability of being treated given the individual’s covariates and thus reduces bias by balancing the covariates in the two groups.[34] Logistic regression was used to compute and save the probability of being in the exposed group for all subjects based on their age, gender, race, region and CCI as discussed previously.

After the matched exposed and unexposed cohorts were obtained, conditional logistic regression was used to assess the relationship between statin use and the two outcome variables, asthma-related hospitalizations and ER visits.

RESULTS

As discussed previously, 589 subjects met the inclusion criteria for the exposed cohort. The pool of unexposed subjects included 7,390 individuals prior to matching on the propensity scores. Table 1 compares the demographic characteristics among the exposed and unexposed cohorts before and after matching. Prior to matching, the average age of asthma patients on concurrent statin therapy was significantly higher than that of patients not on statin therapy (48.87 [±0.22] vs. 63.28 [±0.50]). A significantly higher proportion of asthma patients who were not on concurrent statin therapy were black as compared to those on statin therapy (54.44% vs. 42.95%) before matching. Additionally, those on concurrent statin therapy had a significantly higher average CCI than those not on concurrent statin therapy (4.01[±0.10] vs. 2.65 [± 0.03]).

After matching, the exposed cohort comprised of 479 individuals with 958 individuals in the unexposed cohort. Post-matching, a significantly higher proportion of asthma patients on concurrent statin therapy
were from the rural areas of Mississippi (71.19% vs. 65.45%; \(p = 0.0287\)) as compared to those not on statin therapy (Table 1). Additionally, the average CCI of patients on concurrent statin therapy was higher than that of patients not on statin therapy (3.75 [±0.10] vs. 3.48 [±0.07]; \(p = 0.03\)), but the difference was much smaller compared to the difference prior to matching.

Table 1 Study sample characteristics before and after matching

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<td>Unexposed (7390)</td>
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<tr>
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<td>48.87 (± 19.17)</td>
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<td>62.59 (± 12.13)</td>
<td>63.48 (± 12.92)</td>
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<td>Gender, n (%)</td>
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<tr>
<td>Male</td>
<td>125 (21.22)</td>
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<td>Female</td>
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<td>Race, n (%)</td>
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<td>Black</td>
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<td>Region, n (%)</td>
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</tr>
<tr>
<td>Charlson Comorbidity Index, mean (SD)</td>
<td>4.01 (± 2.48)</td>
<td>2.65 (± 2.17)</td>
<td>&lt;.0001*</td>
</tr>
<tr>
<td></td>
<td>3.75 (± 2.22)</td>
<td>3.48 (± 2.16)</td>
<td>0.0300*</td>
</tr>
</tbody>
</table>

* \(p < 0.05\)

The proportion of exposed and unexposed subjects using additional medications, besides ICS, for asthma management can be found in Table 2.

Table 2 Additional medications used for asthma management

<table>
<thead>
<tr>
<th>Medication</th>
<th>Exposed (479)</th>
<th>Unexposed (958)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n (%))</td>
<td>(n (%))</td>
</tr>
</tbody>
</table>

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Descriptive information on the covariates adjusted for in the final conditional logistic regression model can be found in Table 3. Subjects with asthma on concurrent statin therapy were significantly less adherent to their ICS therapy (0.47 [± 0.27] vs. 0.51 [± 0.28]), used lesser number of short-acting β agonist prescriptions on an average (2.74 [± 2.10] vs. 3.49 [± 2.85]) and had fewer ER visits due to asthma six months prior to the index date (0.02 [± 0.14] vs. 0.06 [0.29]) when compared to subjects not on concurrent statin therapy.

Table 3 Additional covariates adjusted for in the conditional logistic regression analysis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Exposed (479)</th>
<th>Unexposed (958)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherence to ICS therapy (PDC)</td>
<td>Mean (±SD)</td>
<td>Mean (±SD)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.47 (0.27)</td>
<td>0.51 (0.28)</td>
<td>0.0146*</td>
</tr>
<tr>
<td>Average no. of short-acting β agonist prescriptions per subject</td>
<td>2.74 (2.10)</td>
<td>3.49 (2.85)</td>
<td>&lt;.0001*</td>
</tr>
<tr>
<td>No. of asthma office &amp; lab visits 6 months prior the index date</td>
<td>0.21 (0.64)</td>
<td>0.24 (0.65)</td>
<td>0.5031</td>
</tr>
<tr>
<td>No. of asthma hospitalization events 6 months prior the index date</td>
<td>0.03 (0.19)</td>
<td>0.05 (0.24)</td>
<td>0.1002</td>
</tr>
<tr>
<td>No. of asthma ER events 6 months prior the index date</td>
<td>0.02 (0.14)</td>
<td>0.06 (0.29)</td>
<td>0.0063*</td>
</tr>
</tbody>
</table>

* p < 0.05

**ICS: Inhaled Corticosteroids; PDC: Proportion of Days Covered

The results of the conditional logistic regression conducted on the matched data and the odds ratios for hospitalization/ER admission due to asthma amongst patients on concurrent statin therapy as opposed to those not on statin therapy are displayed in Table 4. At least one asthma-related hospitalization was
observed in 3.79% of the subjects on concurrent statin therapy, and 6.47% of the subjects not on concurrent statin therapy, twelve months post index date. At least one ER visit due to asthma was observed in 4.18% of the subjects on concurrent statin therapy and 9.08% of the subjects not on concurrent statin therapy, twelve months post index date. The odds of a hospital visit and/or ER visit due to asthma for asthma patients on concurrent statin therapy were almost half the odds for patients not on statin therapy (unadjusted OR = 0.51; 95% CI [0.34, 0.76]). Similarly, they were also less likely to be hospitalized (unadjusted OR = 0.56; 95% CI [0.32, 0.98]) and visit the ER (unadjusted OR = 0.44; 95% CI [0.27, 0.73]) due to asthma exacerbations as opposed to those not on statin therapy. The above odds ratios have not been adjusted for additional variables such as prior asthma-related hospitalizations, ER visits, office and lab visits, number of short-acting β agonist prescriptions, and adherence to ICS therapy. The adjusted conditional odds ratios after accounting for these factors are also found in Table 4. A statistically significant relationship between statin use and the combined endpoint as well as asthma-related ER visits remained after adjustment for these other variables.

Table 4 Conditional odds ratios of hospitalizations due to asthma associated with statin use

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Unadjusted OR† (95% CI)</th>
<th>p</th>
<th>Adjusted OR¶ (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma hospitalization and/or ER visit</td>
<td>0.51 (0.34 – 0.76)</td>
<td>0.0010*</td>
<td>0.55 (0.36 – 0.84)</td>
<td>0.0059*</td>
</tr>
<tr>
<td>Asthma hospitalization</td>
<td>0.56 (0.32 – 0.98)</td>
<td>0.0436*</td>
<td>0.63 (0.35 – 1.13)</td>
<td>0.1183</td>
</tr>
<tr>
<td>Asthma ER visit</td>
<td>0.44 (0.27 – 0.73)</td>
<td>0.0013*</td>
<td>0.47 (0.28 – 0.82)</td>
<td>0.0069*</td>
</tr>
</tbody>
</table>

* p < 0.05

†Adjusted for variables used to create propensity scores.

¶Adjusted for prior asthma-related hospitalizations, ER visits, office and lab visits, number of short-acting β agonist prescriptions, and adherence to ICS therapy.
DISCUSSION

Over the three years of data analyzed, 589 subjects met the inclusion criteria for the exposed cohort, prior to matching and were classified as subjects on statin therapy, with 7,390 subjects in the unexposed cohort. When comparing the demographic characteristics of patients on concurrent statin therapy to those not on statins, significant differences were observed. The average age of the asthmatic patients on statin therapy was significantly higher than those not on statin therapy. This was not surprising as patients with statin therapy would likely have hyperlipidemia, a condition more prevalent in older adults. Additionally, a significantly higher proportion of patients on statin therapy were white when compared to the unexposed population and also had a higher average CCI score. In order to control for the above differences, propensity scores were computed and the study groups were matched on their propensity to be in the exposed cohort.

The final sample comprised of considerably older subjects with the average age of the exposed and unexposed being 62.59 (±0.55) years and 63.48 (±0.42) years, respectively. Most of the study subjects were females, which is consistent with previous prevalence reports which indicate that asthma is more prevalent in females in general.[35] Additionally, a higher proportion of the sample was white, lived in rural regions and had a considerable number of comorbid conditions.

A higher proportion of the unexposed subjects were on additional asthma controller therapy (Table 2). It is interesting to note however, that the average number of short-acting β agonist prescriptions were significantly higher for patients not on statin therapy and thus one might expect their condition to be better managed, which does not seem to be the case. Thus, the other way to look at it is that their condition is more severe or is not being managed well and hence the higher average number of quick relief prescriptions.
A significant reduction in the odds of hospitalization and ER visits due to asthma was found to be associated with statin use. Even after controlling for the confounders mentioned above, patients not on concurrent statin therapy were almost twice as likely to have hospitalization and/or ER visits attributable to asthma when compared to patients on statin therapy. These findings suggest that statins are beneficial in asthma management. This is in accordance with other observational studies conducted to investigate this relationship.[32, 33]

There are several limitations of this study. The study was conducted using Medicaid claims data and therefore there is a possibility of misclassification due to coding errors during claims processing. Further, even though the subjects in the unexposed group were matched to the exposed population based on their propensity scores, significant differences between the two groups were still observed when compared across their CCI scores and the region (urban versus rural) to which they belonged. This could be attributed to two plausible explanations. Firstly, the cohorts were matched on propensity scores allowing a range of ±0.005. Secondly, each subject was initially matched to 10 corresponding subjects from the unexposed pool, following which two controls were selected based on their continuous eligibility throughout the study period and ICS prescription records within 180 days prior to the index date. However, both of the above measures were incorporated into the study design to maximize the sample size. Even after matching, subjects on statin therapy had a significantly higher average CCI score compared to those not on statin therapy. It is unlikely that this difference could have biased the findings towards a lower risk of hospitalization due to asthma in these subjects. Another limitation is that the population studied had an average age of approximately 63 years and were sicker patients in general due to the higher CCI scores, which limits the generalizability of the study to some extent.

The findings of this study contribute significantly to the growing body of literature that suggests statins have beneficial effects in preventing asthma exacerbations. Some researchers suggest that the addition of a statin to ICS therapy in clinical practice will not prove beneficial in the management of asthma referring
to practice as a ‘snake oil panacea’. However, further investigation employing different datasets, different methodologies and accounting for other confounding variables which may have been overlooked, is required to provide conclusive evidence.
FUNDING STATEMENT

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REFERENCES


83,446 beneficiaries with a diagnosis of asthma

35,001 beneficiaries with at least 1 ICS prescription

2,742 beneficiaries with at least 1 statin prescription

589 ‘exposed’ beneficiaries with ≥80% adherence to statin medication and at least 1 ICS prescription over a period of 180 days between January 1, 2002 and December 31, 2004

479 ‘exposed’ beneficiaries each matched to ‘unexposed’ beneficiaries meeting all the inclusion criteria enlisted in Table 1