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Do Statins Improve Outcomes in Patients With Asthma on Inhaled Corticosteroid Therapy? A Retrospective Analysis of the Mississippi Medicaid Database 2002-2004.

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DO STATINS IMPROVE OUTCOMES IN PATIENTS WITH ASTHMA ON INHALED CORTICOSTEROID THERAPY? A RETROSPECTIVE ANALYSIS OF THE MISSISSIPPI MEDICAID DATABASE 2002-2004.

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ABSTRACT

Animal model studies and clinical trials have looked at the potential benefits of the anti-inflammatory properties of statins in asthma management with contradictory results. Therefore, the objective of this study is to determine if asthma patients on concurrent statin therapy are less likely to have asthma-related hospitalizations and emergency room (ER) visits.

We conducted a retrospective cohort study using Medicaid data for 2002-2004. Asthma patients ≥18 years old 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 1 inhaled corticosteroid (ICS) prescription and at least an 80% adherence rate to statins. Medicaid beneficiaries identified as asthmatics and on ICS therapy, but not on statins were selected as the unexposed population. Each subject in the exposed group was matched to 2 subjects from the unexposed population using propensity scores computed using age, gender, race, urban/rural region and Charlson Comorbidity Index. The two groups were followed for 1 year beginning on the index date, and their outcomes in terms of hospitalizations and ER visits were compared using conditional logistic regression, further adjusted for adherence to ICS therapy, average number of short-acting β agonists per subject, prior hospitalizations, ER, lab and office visits due to asthma.

After matching, there were 479 exposed subjects with 958 corresponding controls. After adjusting for the above mentioned covariates, asthma patients not on concurrent statin therapy are almost two times as likely to have hospitalization and/or ER visits or both due to asthma (adjusted OR = 0.55; 95% CI [0.37, 0.84]; $p = 0.0059$), in comparison to patients on statin

therapy. Similarly, they are also twice as likely to visit the ER due to asthma exacerbations as patients on statins (adjusted OR = 0.48; 95% CI [0.28, 0.82]; p = 0.0069).

The findings of this study suggest that there may be beneficial effects of statins in preventing asthma exacerbations. Further prospective investigations are required to provide conclusive evidence.

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I. INTRODUCTION

Asthma is a chronic inflammation of the airways, leading to poor air exchange that causes shortness of breath and wheezing. Around 300 million across the globe[1] and 22 million in the United States[2] are afflicted with the disease leading to an annual burden of approximately $20.7 billion dollars (2010)[3] to the U.S. health care system. Medications used in the management of the disease are categorized into acute relief and long-term maintenance, with Inhaled Corticosteroids (ICSs) being the most widely prescribed for long-term control of the condition. Recently, there has been considerable discussion about the anti-inflammatory properties of statins and hence their potential therapeutic benefit in the treatment of asthma.

Statins are inhibitors of 3-hydroxy-3-methylglutaryl coenzymes A (HMG CoA) reductase, conventionally prescribed as anti-hyperlipidemics. However, their beneficial anti-inflammatory properties have led to several studies evaluating their role in the management of asthma. Animal model studies[4-10] suggest various mechanisms of action by which statins may have potential benefits in the treatment of asthma with promising results. There have been two published clinical trials[11,12] that have reached conclusions that conflict the findings of the animal model studies. Here, the authors failed to find statins effective for the short-term therapy of asthmatic inflammation, but one of them documented a reduction in the sputum macrophage counts in mild to moderate atopic asthma. It should be noted that the clinical trials have sample size limitations.

There has been one retrospective analysis[13] so far that investigates the relationship between statins and asthma outcomes using the Medco National Integrated Database. This study concludes that statin exposure is independently associated with a significant 33% relative risk reduction for recurrent asthma- related hospitalizations and emergency room (ER) visits.

Some researchers are of the opinion that we already have effective medications for the treatment of allergic asthma in the form of ICS and that adding a statin to an appropriate dose of ICS would not provide any additional benefit for patients with asthma.[14] But, in spite of ICS being an effective therapy, the burden of asthma, in terms of healthcare dollars and loss of productivity, continues to increase.[3,15]

Thus, we are left with exciting data but a nagging dilemma and results so far 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. In light of the evidence so far, the purpose of this study is to investigate the potential role of statins on asthma outcomes in particular, using a retrospective cohort study design, with the specific objectives being:

1. To describe the baseline characteristics such as age, gender, race of Medicaid beneficiaries with asthma who are on statin therapy and those not on statin therapy.

2. To compare the outcomes, using ER visits and hospitalizations as a measure, amongst asthmatic Medicaid beneficiaries on statin therapy to those not on statin therapy.

3. To compare the costs incurred by asthmatic Medicaid beneficiaries on statin therapy to those not on statin therapy including the prescription costs, ER visits and hospitalization costs.

II. LITERATURE REVIEW

Asthma Prevalence and Costs

Approximately 300 million people across the globe suffer from asthma according to the executive summary of the Global Initiative for Asthma (GINA) Dissemination Committee Report.[1] The GINA program was initiated in 1989 in an effort to raise awareness about the increasing prevalence of asthma worldwide, with the Dissemination Committee being responsible for providing data on the burden of asthma. Estimates from the report also suggest that asthma prevalence increases globally by 50% every decade with some of the highest numbers seen amongst data from developed countries such as United Kingdom (>15%), New Zealand (15.1%), Australia (14.7%), the Republic of Ireland (14.6%), and the United States (10.9%). Numbers from the World Health Organization (WHO) fact sheet on bronchial asthma attribute 180,000 deaths globally to asthma each year and estimate that the economic costs associated with asthma exceed those of tuberculosis and HIV/AIDS combined.[16] The financial burden on patients with asthma in different western countries ranges from $300 to $1,300 per patient per year[17] with those suffering from severe asthma being responsible for 50% of all direct and indirect costs even though this patient population represents just 10-20% of all those suffering from the condition.[15,18] Thus, the economic burden disproportionately affects those with the most severe disease.

In accordance with the 2007 National Asthma Education and Prevention Program Expert Panel Report 3[2] more than 22 million have asthma in the U.S. The burden of asthma affects

patients and their families in terms of lost work and school days, lessened quality of life, and avoidable emergency department visits, hospitalizations and deaths. Estimates of the annual costs of asthma in the U.S. range between $12.7 and $20.7 billion.[3,19] Researchers at the University of Georgia developed an estimate of the lifetime costs of asthma for children born in the year 2000, documenting the total lifetime impact of asthma for this birth cohort to be $7.2 billion.[20] They also concluded that losses in productivity are significant and thus interventions that help better manage the disease, reduce the number of missed work days, and decrease the number of asthma exacerbations could have significant indirect cost savings.

The National Surveillance for Asthma 2001- 2003 summary[21] reported 55.6% of current asthmatics as having one or more attacks during the preceding 12 months. Amongst other statistics, the summary mentions an average annual 61.2 office visits, 6.7 hospital outpatient visits and 8.8 emergency department visits for asthma per 100 persons with current asthma. Analysis of cross-sectional survey data from an on-going community-based panel study of adults with asthma based in northern California reported $4,912 as the total per person annual costs of asthma with hospital admissions and indirect costs due to loss in productivity accounting for 9.75% and 35% of the total costs respectively.[22] A review of various cost of illness studies estimated the mean direct cost of asthma per year per patient to be $1,100 approximately, stating it accounted for 50% of total costs.[23] Thus, it is evident that significant healthcare savings can be accrued if costs due to hospitalizations and loss of productivity are prevented via better management of the condition, preventing asthma exacerbations.

Asthma Treatment

Asthma has been defined as "*a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role; in particular mast cells, eosinophils, neutrophils (especially in sudden onset, fatal exacerbations, occupational asthma, and patients who smoke), T lymphocytes, macrophages and epithelial cells. In susceptible individuals this inflammation causes recurrent episodes of coughing (particularly at night or early in the morning), wheezing, breathlessness, and chest tightness. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment.*"[2] Airway inflammation is said to bring about a majority of the changes in the airway and thus future studies are targeted at determining if different treatment approaches will benefit the different patterns of inflammation. Definitive causes that bring about the inflammatory process have not yet been established although genetics, environmental factors as well as the balance between Th1- and Th2-type cytokine responses are amongst a few that have been suggested.[24]

Medications that attenuate the inflammation are the most effective in the management of asthma symptoms and are currently classified as quick relief or long-term control medications.[25] Controller medications are generally prescribed when quick-acting bronchodilators are needed to relieve symptoms more than two days a week or more than twice a month for night time awakenings caused by exacerbations.[2,24] Figure I is a schematic diagram illustrating the stepwise control of the disease.

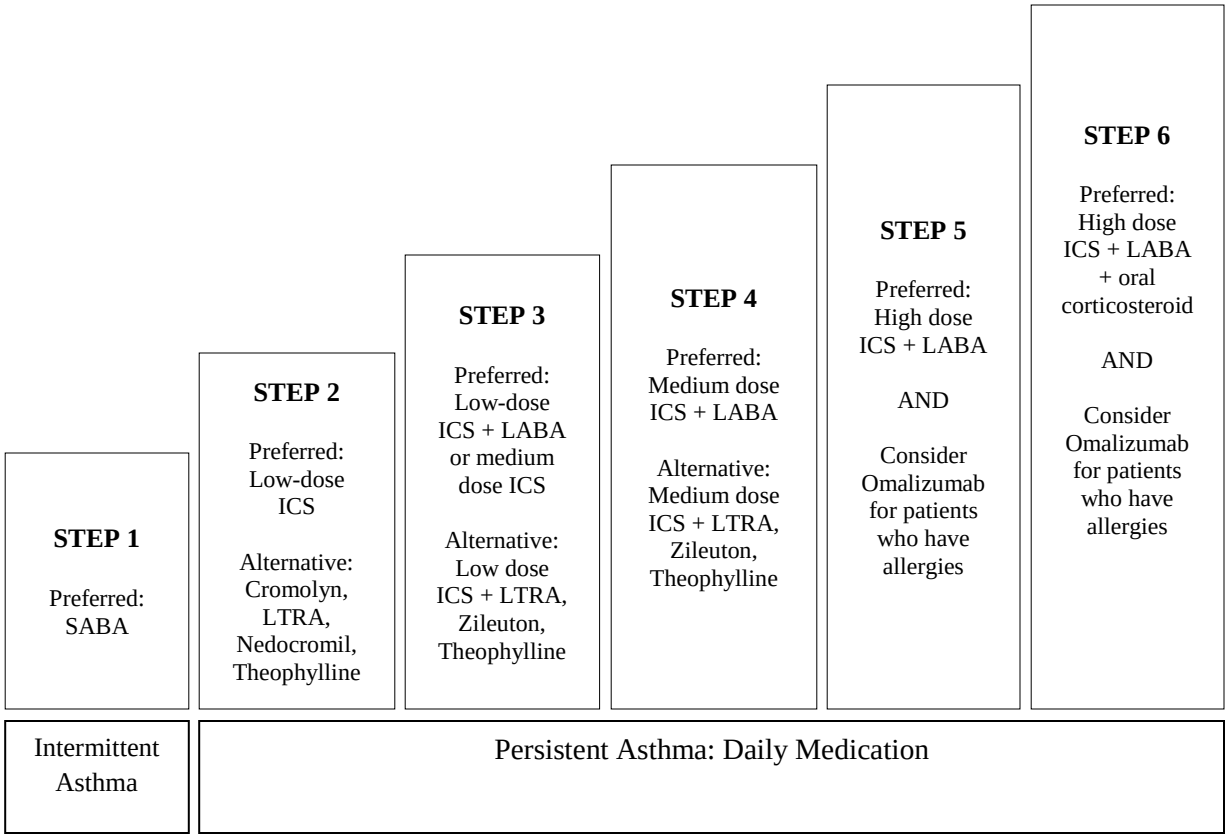

Figure I. Stepwise approach for Asthma Management in Adults (National Asthma Education and Prevention Program Expert Panel Report 3)[2]

- SABA – Short Acting β Agonists
- LABA – Long Acting β Agonists
- LTRA – Leukotriene Receptor Antagonists

Inhaled Corticosteroids (ICSs) are the most consistently effective long-term control medications at all steps of care for persistent asthma. They reduce airway hyper responsiveness, inhibit inflammatory cell migration and activation and block late phase reaction to allergens.[2] ICSs reduce impairment and risk of exacerbations but evidence to suggest they prevent the progressive decline in lung function is lacking.[26,27] Strategies that achieve asthma control without using high doses of ICS are desirable as the dose therapeutic response curve for these medications is relatively flat whereas the dose-systemic absorption curve appears to be linear.[28]

This indicates an increasing availability of the drug in the systemic circulation with increasing doses; however, the therapeutic benefits achieved do not necessarily differ with higher doses. Cromolyn sodium and nedocromil, immunomodulators that prevent binding of IgE to the receptors on basophils and mast cells, leukotriene modifiers, long-acting β agonists (LABAs) and methylxanthines are some of the other long-term control medications. Leukotriene modifiers and LABAs are generally used in combination with ICSs. Anticholinergics, short-acting β agonists (SABAs) and systemic corticosteroids are the quick-relief medications used to treat acute symptoms and exacerbations.[2,24]

Statins in the Treatment of Asthma

Recently statins, inhibitors of 3-hydroxy-3-methylglutaryl coenzymes A (HMG-CoA), have been shown to have promising therapeutic potential in mediating inflammatory processes.[29-32] They are amongst the most widely prescribed medicines and are primarily used to treat hyperlipidemia and prevent cardiovascular diseases. However, in the past decade studies have shown statins to be effective in animal model studies as well as clinical trials of rheumatoid arthritis[33-35], autoimmune encephalomyelitis[36,37], inflammatory colitis[38,39] and even psoriasis[40] due to their anti-inflammatory properties. Given this, there has been some discussion pertaining to the use of statins in the treatment of asthma and various studies have suggested asthma management as an emerging indication for statins.[41-45]

Certain researchers believe that the addition of a statin to ICS therapy in clinical practice will not prove beneficial in the management of asthma referring to this setting as a 'snake oil panacea'[14], while others believe it might actually be harmful.[46] These have just been voiced as

opinions in the literature and there is lack of evidence in support of these concerns. Alternatively, the majority of the arguments are in favor of adding a statin to ICS therapy, and not without evidence. A number of studies have shown the beneficial effects of statins in the management of asthma and these will be discussed shortly. It has been suggested that statin treatment could improve asthma control in smokers with asthma who are insensitive to treatment with ICS.[47,48] Additionally, some patients with severe asthma require additional oral corticosteroids, a long-term treatment which is associated with such side effects as adrenal suppression, growth suppression, and osteoporosis.[42,49] Statins on the other hand are one of the most widely prescribed medications and have a better safety profile. In certain cases severe asthma is steroid-resistant, and hence alternative therapy is needed for such patients.[49]

It has been suggested that the pleiotropic effects of statins are independent of their lipid-lowering abilities[45, 50] and are in part related to their lipophilicity, and thus each compound in the class exhibits different effects on the inflammatory cells. Simvastatin and atorvastatin are said to have the greatest anti-inflammatory potential.[51] The rationale behind this observation is the preferential ability of lipophilic statins to enter a variety of somatic cells, in contrast with hydrophilic compounds such as pravastatin that are reliant on active uptake by hepatocytes to mediate their metabolic activity.[52] Hence, important within class differences exist between the drugs.

A few animal model studies suggest that statins might have potential as therapeutic agents in the treatment of asthma.[4-10] *Y. Chiba et al.* have carried out a number of such studies with lovastatin. Their experiments with rats suggest that systemic lovastatin inhibits antigen-induced bronchial smooth muscle hyper-responsiveness in addition to reducing the increased cell number in bronchoalveolar lavage (BAL) fluids and histological changes induced by antigen

exposure.[4] They also demonstrated that levels of Immunoglobulin E in sera and interleukins -4, -6, and -13 in the bronchoalveolar lavage fluids were not significantly changed. The authors have carried out similar experiments in mice, with findings that support the beneficial role of statins in asthma management.[5] 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 Ca^{2+} 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.

Another animal model study conducted by *Y. Chiba et al.* shows that lovastatin ameliorates the antigen induced infiltration of inflammatory cells such as eosinophils into the airways.[6] Inhibition of the geranylgeranylation of Rho family GTPases in leukocytes has been cited as the proposed mechanism again. Similarly, a study conducted by *McKay* and colleagues showed the inhibitory effects of simvastatin on inflammatory cell infiltration in a murine model of allergic asthma.[7] They also showed a reduction in the BAL cytokine levels which is contradictory to the results of the experiments conducted by *Y. Chiba* and colleagues.

Similarly, experiments have been conducted with pravastatin and simvastatin showing beneficial effects whereby the former was shown to suppress systemic sensitization to allergen due to inhibition of interleukin 17[8] and the latter prevents the infiltration of inflammatory cells in the bronchoalveolar lavage fluids[9] and has been shown to reduce the CD4 T cell numbers.[10]

Apart from the animal model studies described above, two clinical trials have been conducted, whereby the relationship between statins and asthma has been further explored. A randomized double-blind crossover placebo controlled trial was designed to investigate the effect

of oral atorvastatin on measures of asthma control and airway inflammation in 54 adults with allergic asthma receiving inhaled corticosteroids alone.[11] The authors found no clinically important improvements in a range of clinical indices of asthma control despite expected changes in serum lipids and thus 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 using 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.[12] All anti-inflammatory asthma medications including inhaled corticosteroids were tapered and stopped completely for the duration of this study, which was the major difference in the protocols of the two clinical trials. However, a small sample size is one of the major limitations of the above cited clinical trials and thus the results should be interpreted cautiously.

In 2007, E. Stanek and colleagues conducted an observational study using the Medco National Integrated Database to explore the relationship between statin treatment and asthma. This is the first observational study to investigate the topic.[13] A total of 6,574 inhaled corticosteroid-treated adult asthmatics were studied and statin exposure was independently associated with a significant 33% relative risk reduction for recurrent asthma-related hospitalization/ER visits over 12 months. They included subjects who had received an ICS prescription anytime from January 2006 to December 2006 and had recorded at least one asthma specific hospitalization/emergency room visit in the 12 months prior to the index ICS

prescription selected. These were then stratified by statin exposure following evidence of an index ICS prescription.

Study Purpose

With the above study being the only retrospective database analysis conducted so far to explore the role of statins in the management of asthma, further such studies are warranted. Additionally, a definitive conclusion regarding the potential benefits of statins in the treatment of asthma has not yet been reached as the various animal model studies and clinical trials described above show varying results and have their own limitations. Thus, another secondary database analysis, using a different dataset, will be economically more feasible and will provide 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 any confounding effects due to the variables used to compute the propensity scores. Prior hospitalizations, ER and office visits due to asthma, compliance 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 study conducted by E. Stanek and colleagues. Prior hospitalizations due to asthma and average number of short-acting β agonists can be an indicator of the severity of the disease, whereas compliance to the medications is a potential confounder as it could lead to hospitalization/ER visits. Thus, conducting a study on a different dataset with a different study design will make a significant addition to the research done so far on this topic. Moreover, the results of this study will aid in the decision as to whether to design further clinical trials on larger scales.

Bearing the significance in mind, the purpose of the study is to make explicit the role of statins in the management of asthma in the real-world setting. There seems to be some ambiguity concerning the potential anti-inflammatory benefits of the HMG-CoA reductase inhibitors for asthmatic patients with the animal model studies and the observational study showing positive results and the clinical trials suggesting otherwise. Thus, this study can provide additional evidence to help make the picture clearer, as it will overcome some of the limitations of the work done so far.

To achieve the above purpose, the main objectives of this study are

1. To describe the baseline characteristics such as age, gender, race of Medicaid beneficiaries with asthma who are on statin therapy and those not on statin therapy.
2. To compare the outcomes, using ER visits and hospitalizations as a measure, amongst asthmatic Medicaid beneficiaries on statin therapy to those not on statin therapy.
3. To compare the costs incurred by asthmatic Medicaid beneficiaries on statin therapy to those not on statin therapy including the prescription costs, ER visits and hospitalization costs.

III. METHODS AND STUDY DESIGN

A retrospective cohort study of the Mississippi Medicaid claims database was conducted. The study involved analysis of the Medicaid beneficiary claims from January 1st 2002 to December 31st 2004. As mentioned earlier, the primary objective of this study was to compare the asthma related outcomes- ER visits, hospitalizations- of Medicaid beneficiaries diagnosed with asthma and on concurrent statin therapy versus those not on statin therapy. Apart from this, the study also looked into the costs incurred by asthmatic Medicaid beneficiaries on statin therapy versus those not on statin therapy in terms of prescription costs, hospitalization and ER visits costs. The study was approved by the Institutional Review Board (IRB) of the University of Mississippi.

Data Source

Medicaid is a federal health care 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 program is jointly run by the federal and state governments whereby the former establishes general guidelines for the program and the latter decides upon the eligibility criteria.

The Mississippi Medicaid claims database was used for this study. It is an administrative claims database, comprising of one 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 is created to include person level data on eligibility, demographics, managed care enrollment, a summary of utilization and Medicaid payment by type of service. Whereas, each observation in the claims files represents a transaction or record of the payment made to the health care provider for the services offered by him/her to the Medicaid enrollee, including details like 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 a Medicaid beneficiary depending on his/her utilization of the services. The following variables from each dataset were used in the study:

1. Medicaid Analytic Extract Personal Summary Record: It contains a record for each unique person, based on his/her MSIS Identification Number, which is a unique number used to identify a Medicaid eligible in the Medicaid Statistical Information System (MSIS). The unique encrypted patient identification number was used as the linking variable to club records of a particular patient from all the other data files into one file. The other variables that were required from the personal summary record are eligible birth date, eligible sex code, eligible race/ethnicity code, eligible residency county and max uniform eligibility code.

2. Medicaid Analytic Extract Inpatient Record: The inpatient record provides information on inpatient hospital stays for each patient. The MSIS type of service code, Medicaid payment amount, the principal diagnosis code as well as all the other diagnoses codes were the fields used from this file.

3. Medicaid Analytic Extract Drug Record: The drug record provides information on drugs and other services provided by a pharmacy for each recipient. The Medicaid payment amount, prescription filled date, new or refill indicators, NDC, quantity of service and days' supply were the required fields.

4. Medicaid Analytic Extract Other Services Record: The other services record provides information on services for each recipient, other than those provided by an inpatient hospital, long term care facility or pharmacy. The diagnoses codes from this record were also used to identify asthmatic patients. Additionally, the procedure codes and place of visit codes were used to identify office and lab visits attributed to a primary diagnosis of asthma.

Study Period and Study Population

The Medicaid records from January 1st 2002 through December 31st 2004 were analyzed. It is important to note here that, since the study period under consideration is prior to the implementation of Medicare Part D, the database does include elderly patients. Asthmatic adults above 18 years of age were identified using the ICD9 code 493.xx, within the 18 month identification period starting July 1st 2002 and concluding December 31st 2003 as graphically represented in Figure II. 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. a medication possession ratio (MPR) of 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. The list of drugs considered has been provided in Appendix

I. 589 beneficiaries were thus 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 inclusion criteria for the exposed as well as unexposed groups have been laid out in Table I.

Table I: Inclusion criteria for the 'exposed' and 'unexposed' groups

	'EXPOSED'	'UNEXPOSED'
1. Diagnosed with Asthma	✓	✓
2. 180 day prescription history of statins prior to the index date with a MPR ≥ 0.8	✓	✗
3. At least 1 prescription for an ICS 6 months prior to index date	✓	✓
4. Continuous eligibility for a period of 18 months beginning 6 months prior to and ending a year after the index date	✓	✓

The study design included a washout period from January 1st 2002 to June 31st 2002 in order to track the prescription records of patients identified and included in the study after June 31st 2002. The 589 subjects in the exposed group were matched to the 7390 subjects in the unexposed group using propensity scores (within a range of ±0.005) computed using certain covariates, which shall be explained in detail 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. 479 exposed subjects were thus obtained, along with corresponding 958 unexposed subjects and a detailed flow diagram representing this has been provided (Figure III). The two cohorts were then followed for a period of one year beginning the index date, and their outcomes in terms of hospitalizations and ER visits were compared.

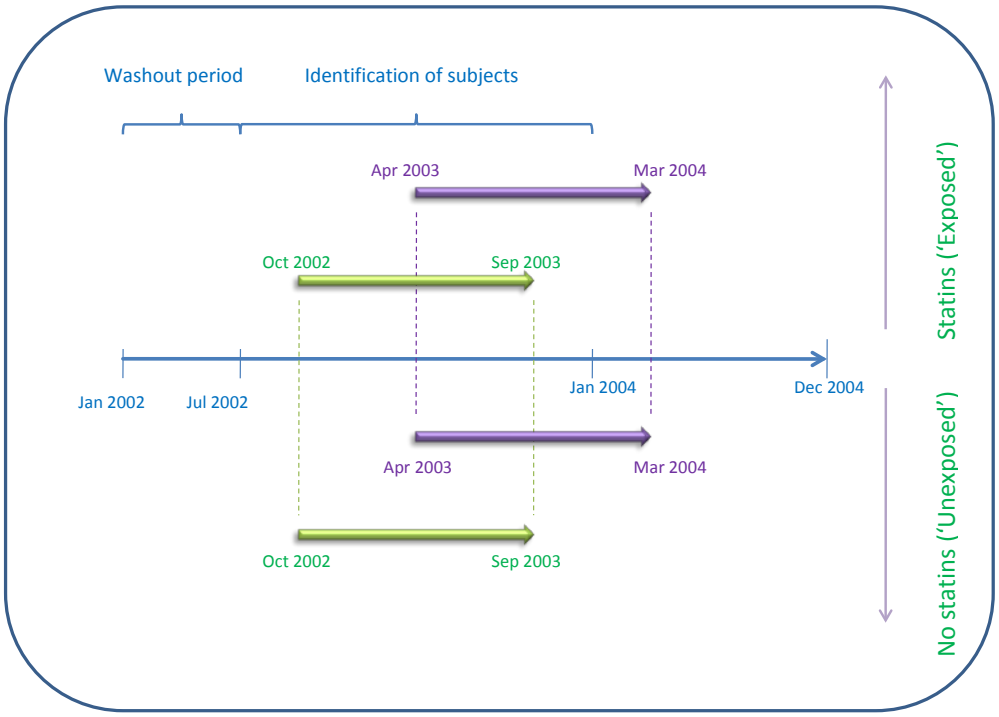

Figure II. Graphical representation of the study design

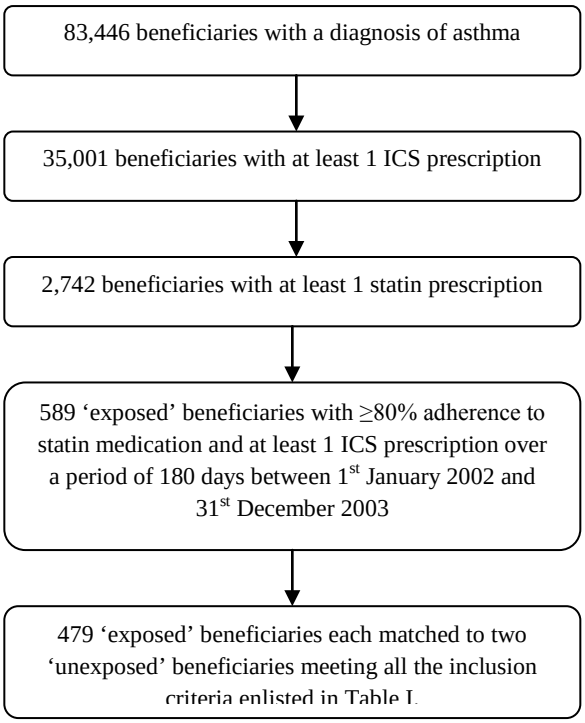

Figure III. Algorithm displaying how the final study subjects were identified.

Rationale for including only Asthmatics on Inhaled Corticosteroid Therapy

Inhaled Corticosteroids (ICSs) are the most consistently effective long-term control medication at all steps of care for persistent asthma and they improve asthma control more effectively than any other single long-term control medication.[2] They are anti-inflammatory medications that reduce airway hyper responsiveness, inhibit inflammatory cell migration and activation and block late phase reaction to allergens.[2] Statins are also hypothesized to be of potential benefit in asthma management due to their anti-inflammatory properties and hence only

those patients on ICS therapy were included in the study design so as to avoid confounding. If being on ICS therapy is not one of the inclusion criteria, the potential beneficial effect of statins amongst the exposed population might be mitigated due to patients not on ICS therapy, in case there are more subjects in the unexposed group on ICS therapy. Similarly, the results will be affected if a larger number of exposed patients are on ICS therapy as compared to the unexposed. ICSs are used for the control of asthma rather than for quick relief of symptoms and thus majority of the asthmatic patients are expected to be on ICS therapy. Thus, it was feasible to incorporate it into the study design as an inclusion criterion rather than control for it.

Study Variables

Covariates:

The exposed and unexposed groups were matched on the following variables using propensity scoring.

i. Age. The age of the subjects as of 31st December 2002 was computed using their date of birth.

ii. Gender. The two categories were:

Male
Female

iii. Race. The three categories considered were:

Whites
Blacks
Others

iv. Regions of Mississippi. The subjects were categorized into Rural and Urban based on the county numbers listed in Appendix II. This variable was used to serve as an indication of the access to care and control for differences in provider type.

v. Comorbidities. The Charlson Comorbidity Index (CCI) was computed and used in the calculation of the propensity scores.

The following variables were additionally controlled for in the analysis performed on the matched cohorts.

i. Adherence to ICS. The MPR 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[53].

ii. Average number of short-acting β agonists per 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 list of drugs considered has been provided in Appendix I.

iii. Prior hospitalizations due to asthma. The number of hospitalizations attributed to a primary diagnosis of asthma in the six month washout period prior to the index date was used as an indicator of the severity of the disease.

iv. Prior ER visits due to asthma. In addition to the inpatient visits, the number of ER visits attributed to a primary diagnosis of asthma in the six month washout period prior to the index date was also used as an indicator of the severity of the disease.

v. Prior office and lab visits due to asthma. The number of office and lab visits attributed to a primary diagnosis of asthma six months prior to the index date was accounted for as an additional measure of severity of the disease.

Outcome variables

i. Hospitalization due to asthma. Hospitalization due to asthma was one of the outcome variables based on which the exposed subjects were compared against the unexposed group. The variable 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 groups.

ii. ER visits due to asthma. ER visit was used as a measure of the outcomes similar to the hospitalization visits. Again the occurrence or non-occurrence of an ER visit one year post the index date for each subject was computed.

iii. Costs due to asthma. The prescription, inpatient visit, ER visit, office and lab visit costs due to asthma, from Medicaid's perspective, was used to calculate the costs incurred. The prescription costs due to statins will be taken into account for the exposed group.

Analysis Plan

The following two hypotheses were tested using the described analyses.

Hypothesis 1: Asthmatic patients on concurrent statin therapy are less likely to have asthma-related hospitalizations and ER visits.

Hypothesis 2: Asthmatic patients on concurrent statin therapy bear lesser costs due to the management of asthma.

Descriptive statistics were reported for the exposed and unexposed subjects pre- and post-matching. PROC MEANS with the t-test option specified was used to compute mean and standard deviations along with differences in the average age and CCI of the two cohorts pre- and post-matching. Similarly, PROC FREQ was used to compute frequencies and percentages for categorical variables such as gender, race and region and to determine differences in percentages across these variables between the two cohorts pre- and post matching.

After the identification of the exposed and unexposed based on the inclusion criteria described previously, propensity scores (PS) 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. PROC LOGISTIC 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, the two groups were analyzed using conditional logistic regression, via PROC LOGISTIC with the STRATA option specified, to compare the hospitalization and ER visits and test hypothesis 1. The difference in the costs accrued by the two groups was analyzed using a general linear model accounting for the dependencies in the data.

IV. RESULTS

As discussed previously, 589 subjects met the inclusion criteria for the exposed cohort and the pool of unexposed subjects comprised of 7,390 individuals prior to matching on the propensity scores. 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 [±0.5]; $p < 0.0001$). 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%; $p < 0.0001$) before matching (Table II). 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]; $p < 0.0001$).

Table II. Sample descriptives before matching

Characteristic	Exposed (589)	Unexposed (7390)	*P*
Age, *mean* (SD)	63.28 (± 0.50)	48.87 (± 0.22)	<.0001*
Gender, *n* (%)			0.5750
Male	125 (21.22%)	1642 (22.22%)	
Female	464 (78.78%)	5748 (77.78%)	
Race, *n* (%)			<.0001*
White	334 (56.71%)	3321 (44.94%)	
Black	253 (42.95%)	4023 (54.44%)	
Other	2 (0.34%)	46 (0.62%)	
Region, *n* (%)			0.0544
Urban	167 (28.35%)	2379 (32.19%)	
Rural	422 (71.65%)	5011 (67.81%)	
Charleson Comorbidity Index, *mean* (SD)	4.01 (± 0.10)	2.65 (± 0.03)	<.0001*

* $p < 0.05$

The spread of the computed propensity of being in the exposed cohort for each subject in the study before matching is displayed in Figure IV.

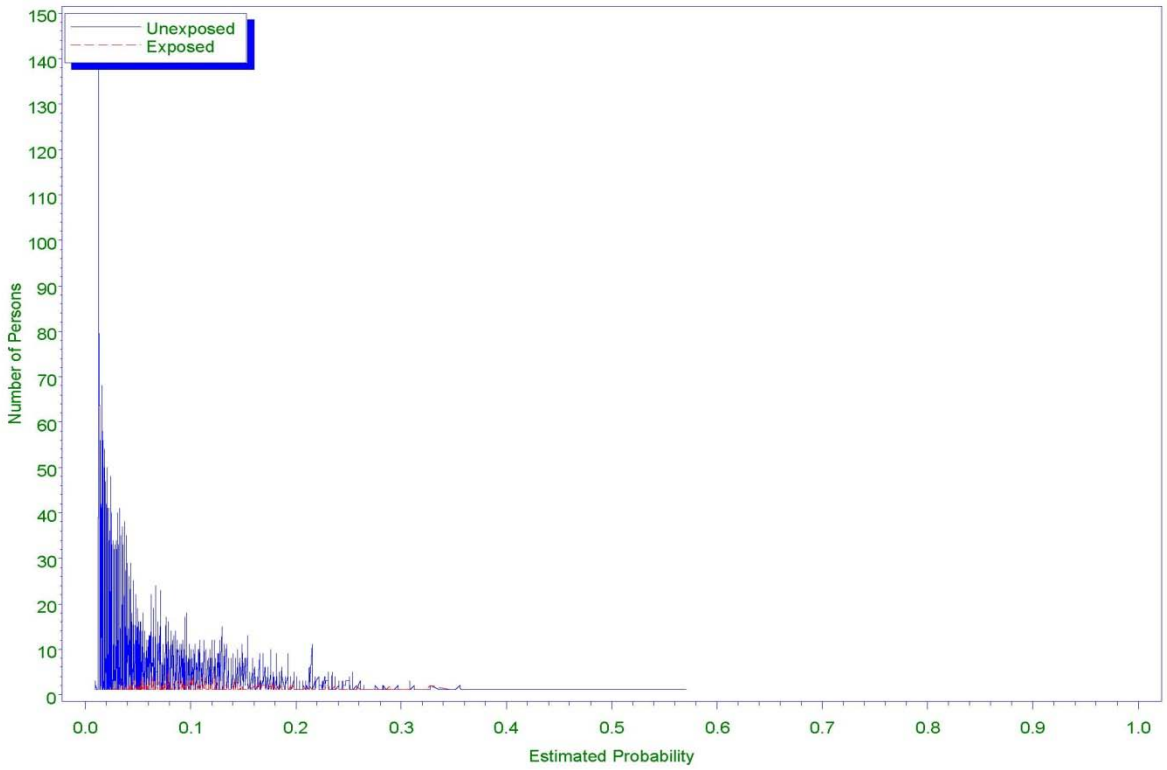

Figure IV. Distribution of propensity scores before matching

After matching, the exposed cohort comprised of 479 individuals with 958 individuals in the unexposed cohort. Post-matching on propensity scores, 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 III). 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]; $p = 0.03$).

Table II. Sample descriptives after matching

Characteristic	Exposed (479)	Unexposed (958)	*P*
Age, *mean* (SD)	62.59 (0.55)	63.48 (0.42)	0.2124
Gender, *n* (%)			0.1994
Male	101 (21.09%)	231 (24.11%)	
Female	378 (78.91%)	727 (75.89%)	
Race, *n* (%)			0.4716
White	269 (56.16%)	540 (56.37%)	
Black	208 (43.42%)	417 (43.53%)	
Other	2 (0.42%)	1 (0.1%)	
Region, *n* (%)			0.0287*
Urban	138 (28.81%)	331 (34.55%)	
Rural	341 (71.19%)	627 (65.45%)	
Charleson Comorbidity Index, *mean* (SD)	3.75 (±0.10)	3.48 (±0.07)	0.0300*

* $p < 0.05$

The range of the propensity scores of each individual in the study post-matching has been shown in Figure V.

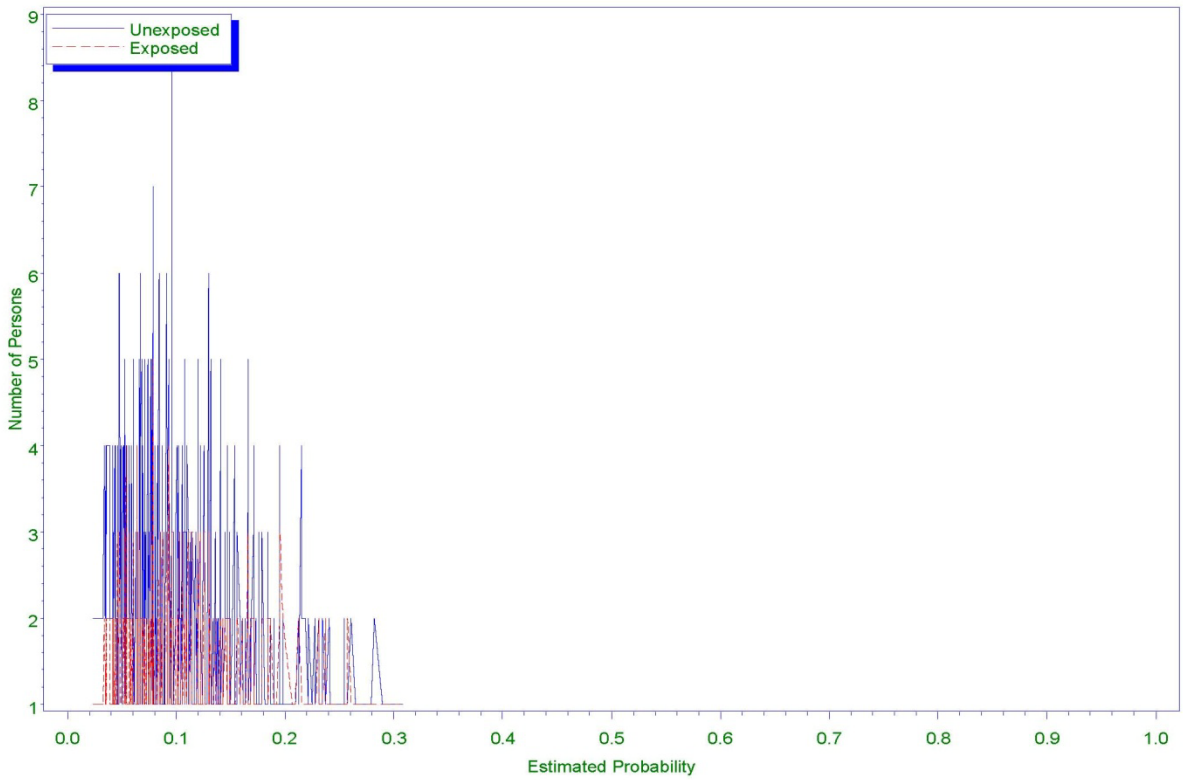

Figure V. Distribution of propensity scores after matching

The proportion of exposed and unexposed subjects using additional medications, besides ICS, for asthma management has been reported in Table IV.

Table IV. Additional medications used for asthma management

Medication	Exposed (479) *n* (%)	Unexposed (958) *n* (%)
Mast cell stabilizers	2 (<1)	5 (<1)
Leukotriene modifiers	134 (28)	318 (33)
Long- acting β agonists	48 (10)	126 (13)
Theophylline	42 (9)	142 (15)
Ipratropium	31 (6)	100 (10)
Short-acting β agonists (SABA)	180 (38)	462 (48)
Oral corticosteroids	81 (17)	294 (31)

* The list of drugs considered for each of the above classes has been provided in Appendix I

Descriptive information on the various covariates adjusted for in the final conditional logistic regression model has been provided in Table V.

Table V. Descriptives of covariates adjusted for

Characteristic	Exposed (479) *mean, (SD)*	Unexposed (958) *mean, (SD)*	*P* value
Adherence to ICS therapy (Proportion of days covered)	0.47 (0.2684)	0.51 (0.2811)	0.0146*
Average no. of SABA prescriptions per subject	2.74 (2.10)	3.49 (2.85)	<.0001*
No. of asthma office & lab visits 6 months prior the index date	0.21 (0.6375)	0.24 (0.6535)	0.5031
No. of asthma hospitalization events 6 months prior the index date	0.03 (0.1860)	0.05 (0.2406)	0.1002
No. of asthma ER events 6 months prior the index date	0.02 (0.1359)	0.06 (0.2908)	0.0063*

* $p < 0.05$

The proportion of the exposed and unexposed subjects where the occurrence of the outcome events were observed, have been reported in Table VI.

Table VI. Occurrence of the outcomes studied

Outcome	Exposed (479) *n (%)*	Unexposed (958) *n (%)*
≥1 asthma hospitalization events 12 months post index date	19 (3.79)	62 (6.47)
≥1 asthma ER events 12 months post index date	20 (4.18)	87 (9.08)

Table VII represents the results of the conditional logistic regression conducted on the matched data to obtain the odds of hospitalization/ER admission due to asthma amongst patients on concurrent statin therapy as opposed to those not on statin therapy. Asthma patients not on concurrent statin therapy were almost two times as likely to have hospital visits and/or ER visits or both due to asthma (unadjusted OR = 0.51; 95% CI [0.34, 0.76]), in comparison to patients on

statin therapy. Similarly, they were also more 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 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 and adherence to ICS therapy. The adjusted conditional odds ratios after accounting for all the above mentioned factors have also been reported in Table VII. Asthma patients not on concurrent statin therapy were almost two times as likely to have hospitalization and/or ER visits or both due to asthma (adjusted OR = 0.55; 95% CI [0.36, 0.84]; $p = 0.0059$), in comparison to patients on statin therapy. Similarly, they were also significantly more likely to visit the ER due to asthma exacerbations when compared to patients on statins (adjusted OR = 0.47; 95% CI [0.28, 0.82]; $p = 0.0069$).

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

Outcome	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Asthma hospitalization and/or ER visit	0.511 (0.342 – 0.762)	0.0010*	0.547 (0.356 – 0.840)	0.0059*
Asthma hospitalization	0.562 (0.321 – 0.983)	0.0436*	0.629 (0.352 – 1.125)	0.1183
Asthma ER visit	0.442 (0.269 – 0.726)	0.0013*	0.474 (0.275 – 0.815)	0.0069*

* $p < 0.05$

When the costs incurred per subject due to asthma were compared across the two groups, the average prescription costs due to asthma ($1,166 [± $1,005] vs. $1,536 [± $1,303]; $p = <.0001$), hospitalization ($125 [±$710] vs. $252[±1,264]; $p = 0.0376$) and ER visit ($3 [± $19] vs. $10 [± $47]; $p <.0013$) costs incurred by patients not on concurrent statin therapy over the study period (18 months) are significantly higher (Table VIII). Similarly, the average total costs

inclusive of prescription, hospitalization, ER, office and lab visit costs due to asthma were significantly higher for patients not on concurrent statin therapy when compared to those on statin therapy ($1,852 [± $1,944] vs. $1,337[$1,264]; p <.0001). However, when the prescription costs due to statins are included for the exposed patients, the average total costs were significantly higher for patients on concurrent statin therapy when compared to those not on statin therapy ($2,578 [$1,373] vs. $1,852 [$1,944]; p < .0001).

Table VIII. Average costs incurred per patient over the study period (18 months)

Costs	Exposed (479), *mean (SE)*	Unexposed (958), *mean (SE)*	*P*
Due to asthma			
Prescription	$1,166 ($1,005)	$1,536 ($1,303)	<.0001*
Hospitalization	$125 ($710)	$252 ($1,264)	0.0376*
ER	$3 ($19)	$10 ($47)	0.0013*
Office & lab	$42 ($116)	$53 ($128)	0.0961
Total	**$1,337 ($1,264)**	**$1,852 ($1,944)**	**<.0001***
Statin therapy costs	$1,241 ($501)	NA	NA
Total	**$2,578 ($1,373)**	**$1,852 ($1,944)**	**<.0001***

* $p < 0.05$

V. DISCUSSION

This study aims at exploring the benefits of statins on asthma outcomes such as ER visits and hospitalizations, using the Mississippi Medicaid claims data (2002-2004). Using a retrospective cohort study design we compared the outcomes of asthma patients on concurrent statin therapy versus those not on statin therapy. Further the costs incurred by Medicaid due to asthma were also compared across the two groups.

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 is not surprising as patients with statin therapy would likely have a co-diagnosis of 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 two groups could have been directly matched on each of the covariates listed in Table II; however, this would lead to a considerable decrease in the sample size and hence was not preferred. Additionally, the outcome events, i.e. hospitalizations and ER visits due to asthma 12 months post the index date, were observed in

5.67% and 7.4% of the study subjects, respectively. This can be considered a rare outcome and therefore, using propensity scores was considered suitable. After matching, there were 479 subjects in the exposed group and 958 corresponding controls.

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. A majority of them were females, which is consistent with previous prevalence reports which indicate that asthma is more prevalent in females[21] in general. Additionally, a higher proportion of the sample was white, belonged to rural regions and had a considerable number of comorbid conditions as is evident from the higher average CCI score.

A higher proportion of the unexposed subjects were on additional asthma controller therapy, besides ICS, such as mast cell stabilizers, leukotriene modifiers, long-acting β agonists, theophylline, ipratropium, short-acting β agonists and oral corticosteroids. Short-acting β agonists are the most effective therapy for rapid reversal of airflow obstruction and prompt relief of asthmatic symptoms.[25] Thus, the average number of short-acting β agonist prescriptions per patient was controlled for in the final analysis as an indicator of the severity of the condition. 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.

The additional factors controlled for included adherence to ICS therapy, average number of short-acting β agonist prescriptions per subject, prior hospitalizations, ER, lab and office visits

due to asthma. The adherence to ICS therapy among the study subjects was considerably low, with the exposed and unexposed subjects being 47% and 51% adherent, respectively. It is important to note here that the unexposed cohort in this study did have higher adherence rates to ICS therapy. Systematic reviews conducted by the Cochrane collaboration of the adherence to ICS therapy literature, also suggest underuse of prescribed ICSs on 24% to 69% of days.[54] Additional studies assessing prescription refills of ICSs report MPRs within a range of 8% to 50%.[53,55-58] Thus the low adherence among our study subjects is not surprising, and was controlled for as it is associated with adverse asthma outcomes. However, this also brings to light that adherence to ICS therapy is a problem and more effort is required to help patients better manage their asthma.

The average number of asthma hospitalizations, ER, office and lab visits per subject over a period of 6 months is consistent with the rates reported by the National Surveillance for Asthma 2001-2003.[21] The report mentions an average annual 61.2 office visits, 8.8 ER visits and 2.5 hospitalizations for asthma per 100 persons with current asthma.

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 cofounders 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 are in accordance with the only other observational study[13] conducted to investigate the beneficial effects of statins in asthma therapy. The authors reported that statin therapy was associated with a 33% lower risk of hospitalization or ER visit for asthma in adult asthmatic patients on inhaled corticosteroid therapy. The difference in the results reported in our study could be attributable to the differences in the dataset as well as methodology used. We

conducted our analyses on matched cohorts and additional factors such as adherence to ICS medication, prior hospitalizations, ER, lab and office visits due to asthma were accounted for, in order to control for the severity of the condition. Additionally, the proportions of subjects in both groups on additional controller medications for asthma have also been reported. Although, the study conducted by Stanek and colleagues is the only other that analyzes claims data, further support for the beneficial role of statins in asthma is found in numerous animal model studies.[4-10]

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. The 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. Further, the average age of the population studied was around 63 years, which suggests that a considerable number of subjects were dual-eligibles. Thus some might suggest that all the claims for this population might not be present in the dataset as Medicare is their primary payer. However, since Medicaid contributes towards the

copayment one can argue that the claim would still be present in the dataset; however, the total costs associated with that claim will not be available. Thus, although this should not bias the results of the conditional logistic regression, a potential limitation would be that the costs associated with asthma hospitalization are likely to be underestimated. Additionally, 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 total average per person cost of asthma over the study period (18 months) is $1,337 (±$1,264) for those on concurrent statin therapy and $1,852 (±$1,944) for those not on statins. However, when statin prescription costs are included, the average total costs for the exposed group amounts to $2,578 (±1,373). Thus, the results are not in favor of our proposed hypotheses. However, these need to be interpreted with caution as they may be underestimated, as mentioned above, due to dual-eligibility. The average direct annual cost of asthma per-person reported using cross-sectional survey data of 401 adults with asthma is $3,180,[59] which is higher than the costs reported in our study. Further the average ER and hospitalization costs reported in our study are very low. An explanation for this observation may be the fact that these events were observed in few patients thus decreasing the average considerably.

The findings of this study contribute significantly to the growing body of literature that suggests statins have beneficial effects in preventing asthma exacerbations. 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. Although, two clinical trials[11,12] conducted earlier have failed to show clinically important improvements in asthma symptoms and a range of other clinical indices in asthma

control, these suffer from sample size limitations and hence their results should be interpreted with caution. Further, the results of a recent animal model study [10], although supporting the anti-inflammatory effects of simvastatin suggest that the effect of simvastatin on lung inflammation in asthma are controversial and differ between species. Thus, in the light of the evidence so far, and considering the results of this study, the role of statins in the treatment of asthma definitely warrants further investigation.

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APPENDIX I

List of statins and statin combinations considered

- Amlodipine-atorvastatin
- Aspirin-pravastatin
- Atorvastatin
- Cerivastatin
- Ezetimibe-simvastatin
- Fluvastatin
- Lovastatin
- Lovastatin-niacin
- Niacin-simvastatin
- Pravastatin
- Rosuvastatin
- Simvastatin

List of inhaled corticosteroids and combination drugs with inhaled corticosteroids considered

- Beclomethasone
- Budenoside
- Budesonide-formoterol
- Ciclesonide
- Flunisolide
- Fluticasone
- Fluticasone-salmeterol
- Mometasone
- Triamcinolone

List of drugs considered as additional controller therapy for asthma management

- Mast cell stabilizers
  - Cromolyn
  - Nedocromil
- Leukotriene modifiers
  - Montelukast
  - Zafirlukast
  - Zileuton
- Long-acting β agonists
  - Formoterol
  - Salmeterol
- Methylxanthines
  - Theophylline
- Short-acting β agonists
  - Albuterol
  - Levalbuterol
  - Pirbuterol
- Systemic corticosteroids
  - Methylprednisolone
  - Prednisolone
  - Prednisone

APPENDIX II

Rural/Urban county codes for counties in Mississippi

FIPS Code	State	County Name	2003 Rural-urban Continuum Code	2000 Population	Description for 2003 codes	Rural/Urban code used in study
28003	MS	Alcorn County	7	34,558	Nonmetro county with urban population of 2,500-19,999, not adjacent to a metro area	0
28005	MS	Amite County	8	13,599	Nonmetro county completely rural or less than 2,500 urban population, adj. to metro area	0
28007	MS	Attala County	6	19,661	Nonmetro county with urban population of 2,500-19,999, adjacent to a metro area	0
28009	MS	Benton County	8	8,026	Nonmetro county completely rural or less than 2,500 urban population, adj. to metro area	0
28011	MS	Bolivar County	5	40,633	Nonmetro county with urban population of 20,000 or more, not adjacent to a metro area	0
28013	MS	Calhoun County	7	15,069	Nonmetro county with urban population of 2,500-19,999, not adjacent to a metro area	0
28015	MS	Carroll County	9	10,769	Nonmetro county completely rural or less than 2,500 urban population, not adj. to metro area	0
28017	MS	Chickasaw County	7	19,440	Nonmetro county with urban population of 2,500-19,999, not adjacent to a metro area	0
28019	MS	Choctaw County	9	9,758	Nonmetro county completely rural or less than 2,500 urban population, not adj. to metro area	0
28021	MS	Claiborne County	6	11,831	Nonmetro county with urban population of 2,500-19,999, adjacent to a metro area	0
28023	MS	Clarke County	9	17,955	Nonmetro county completely rural or less than 2,500 urban population, not adj. to metro area	0
28025	MS	Clay County	7	21,979	Nonmetro county with urban population of 2,500-19,999, not adjacent to a metro area	0
28027	MS	Coahoma County	5	30,622	Nonmetro county with urban population of 20,000 or more, not adjacent to a metro area	0
28029	MS	Copiah County	2	28,757	County in metro area of 250,000 to 1 million population	1
28031	MS	Covington County	8	19,407	Nonmetro county completely rural or less than 2,500 urban population, adj. to metro area	0
28033	MS	DeSoto County	1	107,199	County in metro area with 1 million population or more	1
28035	MS	Forrest County	3	72,604	County in metro area of fewer than 250,000 population	1

28037	MS	Franklin County	9	8,448	Nonmetro county completely rural or less than 2,500 urban population, not adj. to metro area	0
28039	MS	George County	3	19,144	County in metro area of fewer than 250,000 population	1
28041	MS	Greene County	8	13,299	Nonmetro county completely rural or less than 2,500 urban population, adj. to metro area	0
28043	MS	Grenada County	7	23,263	Nonmetro county with urban population of 2,500-19,999, not adjacent to a metro area	0
28045	MS	Hancock County	3	42,967	County in metro area of fewer than 250,000 population	1
28047	MS	Harrison County	3	189,601	County in metro area of fewer than 250,000 population	1
28049	MS	Hinds County	2	250,800	County in metro area of 250,000 to 1 million population	1
28051	MS	Holmes County	6	21,609	Nonmetro county with urban population of 2,500-19,999, adjacent to a metro area	0
28053	MS	Humphreys County	7	11,206	Nonmetro county with urban population of 2,500-19,999, not adjacent to a metro area	0
28055	MS	Issaquena County	9	2,274	Nonmetro county completely rural or less than 2,500 urban population, not adj. to metro area	0
28057	MS	Itawamba County	7	22,770	Nonmetro county with urban population of 2,500-19,999, not adjacent to a metro area	0
28059	MS	Jackson County	3	131,420	County in metro area of fewer than 250,000 population	1
28061	MS	Jasper County	9	18,149	Nonmetro county completely rural or less than 2,500 urban population, not adj. to metro area	0
28063	MS	Jefferson County	7	9,740	Nonmetro county with urban population of 2,500-19,999, not adjacent to a metro area	0
28065	MS	Jefferson Davis County	8	13,962	Nonmetro county completely rural or less than 2,500 urban population, adj. to metro area	0
28067	MS	Jones County	4	64,958	Nonmetro county with urban population of 20,000 or more, adjacent to a metro area	0
28069	MS	Kemper County	9	10,453	Nonmetro county completely rural or less than 2,500 urban population, not adj. to metro area	0
28071	MS	Lafayette County	6	38,744	Nonmetro county with urban population of 2,500-19,999, adjacent to a metro area	0
28073	MS	Lamar County	3	39,070	County in metro area of fewer than 250,000 population	1
28075	MS	Lauderdale County	5	78,161	Nonmetro county with urban population of 20,000 or more, not adjacent to a metro area	0
28077	MS	Lawrence County	8	13,258	Nonmetro county completely rural or less than 2,500 urban population, adj. to metro area	0
28079	MS	Leake County	6	20,940	Nonmetro county with urban population of 2,500-19,999, adjacent to a metro area	0
28081	MS	Lee County	5	75,755	Nonmetro county with urban population of 20,000 or more, not adjacent to a metro area	0

28083	MS	Leflore County	5	37,947	Nonmetro county with urban population of 20,000 or more, not adjacent to a metro area	0
28085	MS	Lincoln County	6	33,166	Nonmetro county with urban population of 2,500-19,999, adjacent to a metro area	0
28087	MS	Lowndes County	5	61,586	Nonmetro county with urban population of 20,000 or more, not adjacent to a metro area	0
28089	MS	Madison County	2	74,674	County in metro area of 250,000 to 1 million population	1
28091	MS	Marion County	6	25,595	Nonmetro county with urban population of 2,500-19,999, adjacent to a metro area	0
28093	MS	Marshall County	1	34,993	County in metro area with 1 million population or more	1
28095	MS	Monroe County	7	38,014	Nonmetro county with urban population of 2,500-19,999, not adjacent to a metro area	0
28097	MS	Montgomery County	7	12,189	Nonmetro county with urban population of 2,500-19,999, not adjacent to a metro area	0
28099	MS	Neshoba County	7	28,684	Nonmetro county with urban population of 2,500-19,999, not adjacent to a metro area	0
28101	MS	Newton County	7	21,838	Nonmetro county with urban population of 2,500-19,999, not adjacent to a metro area	0
28103	MS	Noxubee County	7	12,548	Nonmetro county with urban population of 2,500-19,999, not adjacent to a metro area	0
28105	MS	Oktibbeha County	5	42,902	Nonmetro county with urban population of 20,000 or more, not adjacent to a metro area	0
28107	MS	Panola County	6	34,274	Nonmetro county with urban population of 2,500-19,999, adjacent to a metro area	0
28109	MS	Pearl River County	6	48,621	Nonmetro county with urban population of 2,500-19,999, adjacent to a metro area	0
28111	MS	Perry County	3	12,138	County in metro area of fewer than 250,000 population	1
28113	MS	Pike County	7	38,940	Nonmetro county with urban population of 2,500-19,999, not adjacent to a metro area	0
28115	MS	Pontotoc County	7	26,726	Nonmetro county with urban population of 2,500-19,999, not adjacent to a metro area	0
28117	MS	Prentiss County	7	25,556	Nonmetro county with urban population of 2,500-19,999, not adjacent to a metro area	0
28119	MS	Quitman County	6	10,117	Nonmetro county with urban population of 2,500-19,999, adjacent to a metro area	0
28121	MS	Rankin County	2	115,327	County in metro area of 250,000 to 1 million population	1
28123	MS	Scott County	6	28,423	Nonmetro county with urban population of 2,500-19,999, adjacent to a metro area	0
28125	MS	Sharkey County	9	6,580	Nonmetro county completely rural or less than 2,500 urban population, not adj. to metro area	0
28127	MS	Simpson County	2	27,639	County in metro area of 250,000 to 1 million population	1

28129	MS	Smith County	8	16,182	Nonmetro county completely rural or less than 2,500 urban population, adj. to metro area	0
28131	MS	Stone County	3	13,622	County in metro area of fewer than 250,000 population	1
28133	MS	Sunflower County	5	34,369	Nonmetro county with urban population of 20,000 or more, not adjacent to a metro area	0
28135	MS	Tallahatchie County	7	14,903	Nonmetro county with urban population of 2,500-19,999, not adjacent to a metro area	0
28137	MS	Tate County	1	25,370	County in metro area with 1 million population or more	1
28139	MS	Tippah County	7	20,826	Nonmetro county with urban population of 2,500-19,999, not adjacent to a metro area	0
28141	MS	Tishomingo County	8	19,163	Nonmetro county completely rural or less than 2,500 urban population, adj. to metro area	0
28143	MS	Tunica County	1	9,227	County in metro area with 1 million population or more	1
28145	MS	Union County	7	25,362	Nonmetro county with urban population of 2,500-19,999, not adjacent to a metro area	0
28147	MS	Walthall County	9	15,156	Nonmetro county completely rural or less than 2,500 urban population, not adj. to metro area	0
28149	MS	Warren County	4	49,644	Nonmetro county with urban population of 20,000 or more, adjacent to a metro area	0
28151	MS	Washington County	5	62,977	Nonmetro county with urban population of 20,000 or more, not adjacent to a metro area	0
28153	MS	Wayne County	7	21,216	Nonmetro county with urban population of 2,500-19,999, not adjacent to a metro area	0
28155	MS	Webster County	9	10,294	Nonmetro county completely rural or less than 2,500 urban population, not adj. to metro area	0
28157	MS	Wilkinson County	8	10,312	Nonmetro county completely rural or less than 2,500 urban population, adj. to metro area	0
28159	MS	Winston County	7	20,160	Nonmetro county with urban population of 2,500-19,999, not adjacent to a metro area	0
28161	MS	Yalobusha County	7	13,051	Nonmetro county with urban population of 2,500-19,999, not adjacent to a metro area	0
28163	MS	Yazoo County	6	28,149	Nonmetro county with urban population of 2,500-19,999, adjacent to a metro area	0

*Information available at http://www.ers.usda.gov/Data/RuralUrbanContinuumCodes/

VITA

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She completed her Bachelor of Pharmaceutical Sciences at the University Department of Chemical Technology, (U.D.C.T.), Mumbai in 2008. After which she enrolled in the PhD program in Pharmacy Administration at The University of Mississippi.

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