IMPACT OF ANTI-ALLERGIC MEDICATIONS ON ASTHMA INCIDENCE, COST AND AN EXPLORATORY ANALYSIS FOR RISK FACTORS FOR ASTHMA

by

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(Under the Direction of Bradley C. Martin)

ABSTRACT

Asthma is a chronic pediatric disease characterized by inflammation of the airways. The objectives of this study were to explore risk factors for asthma incidence, estimate the effects of exposure to anti-allergic medication on asthma incidence in a patients suffering from atopic dermatitis or allergic rhinitis and to explore the impact of these medications on asthma cost.

Continuously eligible newborn children in GA Medicaid and MarketScan were included in the exploratory analysis. Asthma risk factors of interest such as diagnosis of atopic conditions and such were assessed. For the treatment exposure, continuously eligible newborn children with a diagnosis of atopic dermatitis (ICD-9-CM=691.8, 692.9 and 373.3) OR allergic rhinitis (ICD-9-CM=477.**) were studied. Exposure to anti-inflammatory agents such as first generation, second generation antihistamines (FGAH, SGAH), intra-nasal steroids (INS) was recorded. Cox Proportional Hazards models along with sample selection methods were used to explore the impact of these agents on asthma incidence. Impact of these agents on annual treatment costs was also explored.

The exploratory analysis suggested that patterns of asthma development follow certain patterns. While maternal asthma, lower respiratory tract infections were significant risk factors for asthma, the impact of atopic disease could not be refuted or established. Asthma incidence was 8.46% and 3.44% in GA(N=79,957) and the commercial AD/AR cohort(N=16,051). In GA

AD/AR, exposure to all anti-inflammatory agents (vs. no exposure) reduced the likelihood of a diagnosis of asthma by 92% and was significantly protective in the commercial cohort was well.. However, exposure to only FGAH increased the risk for an asthma diagnosis in commercial AD/AR. In GA Medicaid, exposure to any agent was associated with a non-significant lower net per member per year(PMPY) mean total cost of $ -87 and in the commercial exposure was associated with a non-significant reduction in mean PMPY net costs by $ 546.

Asthma is associated with a set of risk factors that is fairly stable across different populations. Exposure to anti-inflammatory agents seemed to reduce the risk of an asthma diagnosis in groups of children suffering from AD or AR. This set of information can be used to formulate intervention programs against asthma development.

Keywords: Asthma, risk factors, atopic dermatitis, allergic rhinitis, first generation and second generation anti-histamines, intra-nasal steroids, costs, Medicaid, MarketScan

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CHAPTER 1

INTRODUCTION

Asthma is a result of complex interaction between genetics and the environment and is a multi-factorial disease with numerous risk factors. Investigations of asthma risk factors have implicated atopy as one of the most important predictors for the development of asthma (Weiss 1998; Wood 2002). Atopy is a genetic tendency to mount IgE antibodies in response to inhaled allergens. Atopic dermatitis (AD), allergic rhinitis (AR) and asthma are the clinical definitions of atopic illness and the progression of atopic diseases from AD to AR to asthma is often referred to as the atopic march (Asher2000; MacLean2001).

The rapid increase in asthma prevalence has prompted a need to reassess control and prevention strategies for asthma. AD and AR may be considered as early precursors of the underlying inflammatory process in asthma and may therefore present opportunities for tertiary prevention of asthma. Evidence for this comes from 4 randomized clinical trials which have demonstrated that early intervention in the atopic march from atopic dermatitis (AD) and or allergic rhinitis (AR) to asthma using agents that have a biological capacity to interfere with the allergic cascade can prevent or delay asthma onset by targeting high-risk infants (Iikura1992; Warner 2001; Moller2002; Grembiale2000). Agents used in these clinical trials were limited to immunotherapies (for AR only) and second generation antihistamines (evaluated in infants suffering from AD in two trials). Effect of other allergic anti-inflammatory medications such as first-generation antihistamines, corticosteroids, cromolyns or combination therapies (for example: second generation antihistamines and steroids commonly used in clinical practices) have not been evaluated in high-risk groups in a real world setting. Another potential benefit of these classes of medicines that has not been evaluated is whether these medicines impact asthma severity. Atopy modulates asthma severity such that atopic children are more likely to suffer from severe asthma that persists into adulthood (Sears2001). Interfering with the atopic march before asthma onset

may reduce the severity of asthma by reducing airway inflammation and the related hyperresponsiveness associated with asthma, even after asthma onset. Allergic anti-inflammatory medications for the purpose of this study will be defined as medications capable of interfering with the allergic inflammatory process. Medications that fall into this class are first generation antihistamines (FGAH), second generation antihistamines (SGAH), corticosteroids, cromolyns, leukotriene inhibitors and immunotherapy. This study will focus mainly on the effects of first generation antihistamines (FGAH), second generation antihistamines (SGAH), intranasal steroids (INS) and cromolyns (CM) and any combination therapies of these agents.

There is also an emerging hypothesis that not all asthma is associated with atopy or allergy. Asthma not associated with atopy is not as well investigated and risk factors for non-atopic asthma range from upper and lower respiratory tract infections (bacterial or viral) to low birth weight (Hide 1996; Douwes2002). Most studies that assess risk factors for atopic or non-atopic asthma have been subject to recall bias (Bodner1998), incomplete medical information or lack of information about simultaneous exposures (von Mutius1999; Grupp-Phelan2001), intermediate outcomes such as wheezing or bronchial hyperresponsiveness or have been subject to temporal bias (Paunio2000). A longitudinal study that utilizes comprehensive diagnostic information to assess and clarify risk factors for incident asthma establishes a clear temporal relationship between risk factors and incident asthma and elucidates the combined effect of these risk factors in a manner not subject to recall bias is clearly lacking. A retrospective database analysis will facilitate understanding of the nature of incident asthma and its risk factors, which are not subject to recall bias. More importantly, protective effects of anti-allergic medications on atopy related asthma and asthma severity can be assessed in a real world setting.

An exploratory study for risk factors for pediatric incident asthma was conducted using a birth cohort analysis in which children who were eligible for at least one year after birth were followed up until an asthma diagnosis or loss of eligibility. Risk factors for asthma incidence were recorded and relative risk for asthma with respect to these exposures was analyzed using

survival analytic techniques. The study was conducted using claims data for an indigent population (Georgia Medicaid) and claims data for persons with employer-sponsored health insurance (Marketscan data, Medstat) in parallel. This was followed by the primary objective of this study which was to assess if and to what extent allergic anti-inflammatory medications delay and or prevent asthma incidence in children with a diagnosis of atopic diseases namely, Atopic dermatitis (AD) and/or Allergic rhinitis (AR). Children continuously eligible from birth until a diagnosis of AD and/or AR were retained in the primary cohort. The primary cohort will be followed up from AD/AR diagnosis until an asthma diagnosis or until loss of eligibility. Exposure to first-generation antihistamines (FGAH), second-generation antihistamines (SGAH), intranasal steroids (INS), cromolyns (CM) or combination therapies with either of these agents in the follow up periods was recorded and subsequent impact on asthma incidence was examined stratified by exposure to these agents and no exposure to these agents. A tertiary objective was to examine the effect of FGAH, SGAH, INS, CM or combination therapy of these agents on the total direct health care costs for children in the primary cohort who develop asthma. The comparison cohort for the asthma cost outcome were children in the primary cohort with no exposure to FGAH, SGAH, INS, CM or combination therapies who develop asthma. This study will combine survival analysis techniques with Heckman's two-stage model to control for differential selection into treatment groups and to assess the impact of allergic anti-inflammatory medication as defined on subsequent asthma incidence and health care costs for asthma (Heckman 1976; Terza 1999).

The specific objectives of this study are to:

1. To explore factors that may confer protection or increase risk for incident asthma in a birth cohort of children.

Specific factors of particular interest that will be explored include allergic diseases and lower respiratory tract infection and the impact of factors such as exposure to antibiotics and demographics.

2. Estimate the effect of exposure to FGAH, SGAH, INS, CM or combination of these for children diagnosed with AD or AR on two outcomes:

-incident asthma

-the total direct health care costs for children (one year costs post-asthma diagnosis). The impact of the medications studied on the outcomes will be examined by levels of exposure for these medication classes compared to no exposure (comparison group) and between exposure groups themselves.

This study will test the following hypothesis:

1) Ha1 (Alternate hypothesis): The incidence of asthma differs significantly between groups with no exposure to FGAH, SGAH, INS, CM or combination of these and groups with exposure to FGAH, SGAH, INS, CM or combinations of these, in children who are diagnosed with AD and/or AR.

2) Ha2 (Alternate hypothesis): Cost of treating asthma in the year after an incident asthma diagnosis differs significantly between those exposed to FGAH, SGAH, INS, CM or combination of these and those unexposed, in children who are diagnosed with AD and or AR and who develop asthma.

Additional hypotheses will be tested by contrasting levels of exposure to these medications compared to no exposure and between exposure levels themselves and between the drug classes, for example: between SGAH (high dose) vs. no exposure and FGAH+INS vs. INS.

CHAPTER 2

BACKGROUND AND SIGNIFICNACE

ATOPY, ATOPIC DISEASES AND ASTHMA

Atopy (recognized clinically by skin prick tests) is one of the most important risk factors for the development and persistence of asthma in children (Table 2.1) (NHLBI 1997(2)). Atopy is defined as a genetically determined capacity to mount IgE responses to common allergens, especially inhaled allergens and food allergens (http://www.aaaai.org). It is the genetic tendency to develop the "classical" allergic diseases, atopic dermatitis (AD), allergic rhinitis (AR) and asthma. There is a meaningful genetic familial component of Atopy, as up to 60%-80% of children who develop AD and approximately 69% who develop AR and asthma have a first-degree relative with a history of AD, AR, or asthma (Matsuoka 1999).

Allergic diseases with an atopic diathesis such as AD and AR may be considered to be early indicators of an allergic inflammatory profile in children at risk for developing asthma. These atopic diseases have in common one or more mechanisms of the allergic inflammatory process and often present as a sequence of one another. Other links between AD, AR and asthma are 1) Mediators from the nose and or sinuses via blood or postnasal drip spread to the lower respiratory tract and cause inflammation of the airways (Simons 1999). Chronic airway inflammation aggravated by repeated exposure to allergens is an early and persistent part of asthma. Airway markers of inflammation also correlate with bronchial hyperresponsivness and airway inflammation; hyperresponsiveness are important in the pathogenesis of the asthma syndrome and the clinical severity of the disease (Chiappara 2001; NHLBI 1997(2)). Evidence suggests that early intervention with anti-inflammatory therapies may modify the asthma disease process by controlling inflammation, hyperresponsivness associated with asthma at an early stage (NHLBI 1997(2)). 2) Neural or nasobronchial reflexes such that nasal allergen challenge results

in bronchial hyperreponsiveness (Larsen 2001). Since the inflammatory process in AD, AR and asthma share some common elements and especially because AD and asthma may be considered to represent extreme ends of a spectrum of inflammation, control of inflammation at an early stage may control injury to the airways and therefore prevent serious consequences such as asthma.

AD and AR have also been established as risk factors for asthma in numerous observational studies (Table 2.1) and in a few retrospective studies (Dik 2004). The link between allergic rhinitis and asthma is also supported by evidence, which indicates that 75% of patients with both disease experience onset of the other disease within two years of the first (Pederson 1983). Onset of asthma was strongly associated with allergic rhinitis (OR =5.7, CI=2.2-14.6) among atopics (defined using skin prick test) and also among non-atopics (OR=3.5, CI=0.9-13.5) (Plaschke 2000). AR therefore seems to increase risk of asthma regardless of atopic status.

These atopic manifestations are not only risk factors for asthma onset but also seem to modify/aggravate asthma severity. It is possible that treatment with allergic anti-inflammatory medication in children with a diagnosis of AR or AD may reduce asthma symptom severity after asthma onset. This may be because while up to 50% of children with asthma eventually outgrow it, asthmatic children with atopy are more likely to have asthma that is more severe and that persists into adulthood (Weiss 2001). If the degree of inflammation during asthma symptoms is reduced by prior exposure to allergic anti-inflammatory medication then exposure to such agents may reduce costs of treating asthma after other factors such as asthma treatment adequacy are taken into consideration. Measuring health care cost of children diagnosed with asthma with respect to exposure to allergic anti-inflammatory medications may provide an insight as to whether these medications reduce asthma severity after adjusting for asthma control.

Typically an atopic individual develops a spectrum of atopic diseases with age (Wahn 2001). Atopic diseases generally manifest in the first years of life with eczematous skin

symptoms often caused by food allergies. Rhinitis to inhalant allergens and asthma proceeds later. The progression from food allergies to asthma is often referred to as the atopic march (Asher 2000).

ALLERGIC INFLAMMATION IN ASTHMA AND ROLE OF FIRST GENERATION, SECOND GENERATION ANTI-HISTAMINES, INTRANASAL STEROIDS AND CROMOLYNS

Asthma is primarily an inflammatory disorder of the airways and inflammatory cells such as mast cells, eosinophils, epithelial cells, macrophages and activated T-cells (NHLBI 1997(2)). The inflammation mainly orchestrated by the cytokines of the t-helper(TH) 2 cells (interleukin [IL]-4, IL-4 and IL-3) thickens all layers and the entire length of the airways and the inflammatory mediators causes contraction of the smooth muscle, leading to all the symptoms of asthma (Woolcock 1997).

Atopic asthma can be considered a two-step process. The first step involves the development of allergen-specific immunological memory (IgE) against inhaled allergens during childhood. IgE antibodies therefore serve as an important trigger for disorders mediated by T-cells such as asthma and eczema. Hypersensitivity responses and chronic allergic disease mediated by IgE differ in the wide range of cellular responses that underlie the latter including the production of inflammatory mediators. Repeated cycles of allergen-driven activation of Th cells (present in the airway mucosa of atopic asthmatics and producing Th2 cytokines) results in chronic ‘wound-healing/repair’ response in the airway tissues and this is central to the structural and functional changes in the airway wall that are characteristic of the asthmatic state (Holt 1999). Although the underlying process is similar in AD, AR, and asthma it is not clear why there is target organ selectivity i.e.: skin, nose or lungs or all of these organs in subgroups of children. Antihistamines, steroids, cromolyns, leukotriene inhibitors are all capable of blocking all or some of the mediators of this allergic cascade. Anti-inflammatory action of second

generation antihistamines (SGAH) is by 1) inhibiting the synthesis and release of arachinoid acid metabolites including leukotriene C4, histamines from mast cells, basophils and neutrophils (superoxide anions) 2) suppressing influx of eosinophils into airways after allergen challenge, reducing degradation of eosinophils and generation of superoxide 3) down-regulation of intracellular adhesion molecules such as ICAM-1 on epithelial membranes thereby prevention accumulation and activation of inflammatory cells in the airways 4) Azelastin, Kotitifen inhibit interlukin (IL-2, IL-3, IL-4 IL-5) production by mitogen-stimulated peripheral blood lymphocytes indicating that these drugs attenuate the production of allergic inflammation by inhibiting the production of TH2-type T-lymphocyte derived cytokines (Hayashi 1999). FGAH such as Azatadine, Chlorpheniramine, Promethazine also demonstrate some allergic anti-inflammatory activity similar to SGAH but first generations have not been studied as extensively (Assanasen 2002).

Corticosteroids (INS) are the most effective treatment for the treatment of atopic diseases. Principle action of corticosteroids is to suppress multiple inflammatory genes by binding to a glucocorticoid receptor, which ultimately binds to DNA to activate these genes (Barnes 1999). These agents mainly act by inhibition of transcription factors that regulate inflammatory gene expression. This leads to a down-regulation of the production of cytokines, inflammatory enzymes, adhesion molecules and also anti-inflammatory mediator receptors.

Cromolyns (CM) are the most specific anti-allergic drug available, yet their exact mechanism of action remains unclear. It is believed that they may mediate their effect by blocking chloride channels present on mast cells and other inflammatory cells and thereby prevent mast cell degranulation and activation of eosinophils (Barnes 1999).

TERTIARY PREVENTION OF ASTHMA

Tertiary prevention of asthma involves interfering with the atopic march after AD or AR development but before the development of the first signs of asthma and is based on the hypothesis that asthma might be preventable in these high-risk groups if repeated expression of allergic symptoms in atopics against allergens can be forestalled or circumvented.

In one of the earliest studies Ketotifen, (0.8 mg-1.2 mg/day b.i.d) (Iikura 1992) significantly reduced the proportion of children developing asthma in the exposure group (13.1%) as compared to placebo (41.6%) ($p<0.001$). In a two year RCT, Cetirizine (total daily dose of 0.5/kg) significantly reduced the incidence of asthma for patients sensitized to grass pollen (RR for placebo = 1.7 (1.4 to 2.1)) or house dust mite (RR for placebo= 1.6 (1.3 to 1.9)). However, in the population that included all infants with normal and elevated total or specific IgE, there was no difference between the numbers of infants developing asthma while receiving cetirizine or placebo (Warner 2001). The clinical trials for SGAH were limited by a short observation window, limited number of patients (Iikura 1992) and were limited to children suffering from AD only (Iikura1992; Warner 2001). The trials evaluated only a limited number of allergic anti-inflammatory medicines that are capable of modifying the allergic march. Nasal corticosteroids, other second generation antihistamines and cromolyns have not been evaluated to assess potential benefits of asthma prevention or reduction in asthma severity in children suffering from AD or AR.

Treatment of allergic rhinitis symptoms has been documented to reduce asthma exacerbations in adults. The incidence density ratio for the treated allergic rhinitis group was 0.53 (0.36 to 0.76) for asthma related hospitalizations and emergency visits as compared to asthma patients not being treated for AR (Crystal-Peters 2002). Intranasal steroids and prescription antihistamines were also studied for their effect on emergency department visits for asthma in another retrospective study after controlling for asthma severity (rate of beta-agonist and inhaled steroids dispensing) and other demographics. The overall relative risk for ED visits

was 0.7 (CI=0.5 to 0.94) for intranasal steroids and was 0.9 (CI=0.78 to 1.11) for anti-histamines (Adams 2002). Selection bias, over the counter drug exposure, asthma severity and seasonality were not accounted for in either of the two studies.

NON-ATOPIC ASTHMA AND OTHER RISK FACTORS FOR ASTHMA

AD and AR are important risk factors for asthma but are modified by the influence of other risk factors. A summary of asthma risk factors along with the associated risks is presented in Table 2.1. Given the genetic component in asthma, maternal asthma and to lesser extent paternal asthma are predominant risk factors for asthma development. Asthmatic mothers are also more likely to have premature delivery than non-asthmatic mothers (OR=1.49, CI=1.10 to 1.65) (Kelly 1995) and premature birth, respiratory distress at birth which may retard normal development are significant risk factors for asthma development as well (Dik2004). Demographic and socio-economic factors such race, sex, age and residence setting (urban vs. rural) also plays a vital role in asthma development. Race, an important risk factor for asthma related morbidity and mortality is often a proxy for other factors such as urbanicity, smoking exposure or socio-economic conditions(Table 2.1) (Eisner 2001; Aligne 2000). This study will attempt to isolate the effect of race on asthma incidence after controlling for urbanicity, socio-economic index. Sex is an important risk factor too, such that asthma incidence may be more in young males than females with a reversal in incidence pattern with age (de Marco 2000). The age of onset of atopic sensitization appears to play a major role in the development of asthma i.e.: children with persistent asthma have an earlier onset of atopic sensitization (blood IgE measured) (Illi 2001). Another important risk factor for asthma development independent of atopic status is lower respiratory tract infections. Viral infections such as respiratory Synctial virus (RSV) (Douwes 2002) may act to increase the risk of asthma independent of atopy by damaging lung tissue or by impairing development or by serving as triggers for asthma episodes in atopic children. But, infections that lead to increased protection or susceptibility are ill defined since repeated infections in early infancy may also cause a shift from Th2 (allergic) to Th1 (non-

allergic) immunity and thereby confer protection against allergic diseases (Broide 2001). Effects of other infections such as measles, mumps, and rubella in early childhood are also more controversial. Measles alone had a weak protective effect after age 3 on asthma incidence (OR =0.5, (0.3 to 0.9) (Bodner 1998) but when considering sum of rubella, mumps and varicella together, risk of asthma was at least twice the group with no infections (OR=2.2 (0.9 to 5), p-value =0.054 for trend). Effect of anti-biotic exposure on asthma incidence has shown mixed results with an increased risk of asthma (von Mutius 1999; Farooqi 1998) with an OR=3.19, CI=2.43 to 4.18 and consistent effects across at least three other studies. But at least two other longitudinal studies (Celedon 2002; Illi et al. 2001) have rejected the hypothesis that antibiotics use in early childhood (age $\leq$ 1 yr) is associated with an increased risk of asthma (OR=0.5, CI=0.2-1.5).

Diseases that present as co-morbidities with AR or asthma such as Otitis Media and sinusitis have not been evaluated for their effect on asthma incidence, although children with multiple visits for Otitis media, sinusitis were 1.8 to 12 times more likely to have diagnosis of asthma in the same year (Grupp-Phelan 2001). Similarly the effect of GERD on asthma incidence has not been evaluated given the indirect evidence that there is a reemission of asthma symptoms after anti-reflux surgery (Field 1999). There are some other risk factors for asthma such as maternal age and breastfeeding that are also debated as risk factors. A number of longitudinal studies did not find them to be significant risk factors (Strachan 1996; Lewis 1995).

Most of the studies to assess risk factors for asthma are based on survey data with periodic evaluations and have been limited by 1) Reliance on intermediate outcomes such as wheezing, airway hyperresponsiveness (Stein 1999) 2) Ascertaining effects of risk factors in isolation i.e.: without assessing the effects of other protective factors or risk factors simultaneously (McKeever 2002). 3) Most of these studies have used surveys and are therefore subject to recall bias (Jenkins 1994) 4) Unknown validity of asthma diagnosis, for example:

using only nocturnal coughs as an asthma diagnosis (Roorda 1993). 5) Cross sectional studies and therefore difficult to establish temporal effects (von Mutius1999; de Marco2000).

SIGNIFICANCE OF THE STUDY

Asthma prevalence has increased by an average of 4.3% per year from 1980 to 1995 in children from ages 0 to 17 years (Akinbami 2002) making it the most common chronic pediatric disease. The nearly two fold increase in asthma prevalence over the last 15 years has occurred in both sexes and in all ethnic groups, with the sharpest increases occurring in children younger than 5 years and in urban, predominantly minority populations (Wood 2002). Asthma onset occurs mainly in childhood with more than 80-90% of the cases being diagnosed by age six (Weiss 2001). Asthma is the number one reason for missed school days (accounts for 9% of indirect costs) and one of the main reasons for hospitalizations in children (Weiss 2001). The burden of asthma preponderance in preschool children is also reflected in the fact that children less than 4 years of age represent less than 30% of pediatric population (ages 0-17) but account for nearly 50% of all pediatric direct costs for asthma (Smith 1997). The overall monetary burden of asthma is significant, being estimated at 12.7 billion dollars in 1998 (Weiss 2001). Indirect costs of asthma account for about 42% of the total cost.

Coinciding with the temporal increase in asthma prevalence, there has also been rapid increases in prevalence among other atopic disease mainly food allergy, allergic rhinitis (AR) and atopic dermatitis (AD) (Weiss 2001; TePas 2000). Like asthma, AD is predominantly a pediatric condition with 80% of the cases starting in the first year of life (Oranje 2002). Allergic rhinitis affects 10% to 30% of adults and up to 40% of children and estimated direct costs for AR are approximately $5.3 billion in 1996 (direct and indirect costs excluding asthma and sinusitis) (Dykewicz 1998). The prevalence of AD was reported to range from 12% to 25% in developed countries and studies done in UK from 1946 to 1970 indicate that AD has risen from 5.1% to 12.2% (Jarvis 1998).

This increasing prevalence in allergic conditions world-wide has prompted considerable interest in the understanding the common etiology of these disease and in assessing any potential prevention of asthma. These efforts have ranged from primary prevention (in-utero studies manipulating maternal diet, smoking, allergen exposure-before sensitization) to secondary prevention (after sensitizations but before development of disease) in high-risk groups with mixed results (Schonberger 1998). Tertiary prevention has shown promising results with a limited number of agents capable of modifying the atopic march in certain high-risk groups. Given that 80% of asthma in children is triggered or exacerbated by exposure to allergens (Shapiro 2000) tertiary prevention may present an opportunity in delaying or preventing asthma incidence. Tertiary measures may also be enhanced with reduction to exposure to allergens i.e. by combining secondary and tertiary prevention given the pathophysiology of asthma. Medications such as antihistamines, steroids, cromolyns and potentially even immunotherapy and leukotriene inhibitors that target allergic inflammation therefore may have a major role to play in controlling or preventing asthma evolution or exacerbations related to AR or AD. Potential preventative effects of these medications on asthma incidence therefore needs to be urgently assessed in real world settings given the economic and societal burden of asthma and the rapid increase in prevalence in children.

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Table 2.1: Documented risk factors for asthma incidence developed after an extensive literature survey

Risk factors for developing asthma	Strength of association, Odds ratio (95% CI)	Study
Atopy (Elevated IgE levels)	2.7 (1.3 to 5.8)	Plaschke 2000 (Sweden)
Sensitization to		
Any allergen	4.56 (3.16 to 6.57)	Arshad 2001(UK)
Cat dander	4.53 (2.60 to 7.88)	
Mites	7.6 (5.00 to 11.3)	
Food Sensitization	2.2 (0.7 to 6.2)	Illi 2001 (Germany)
Food sensitization +AR	11.1 (4.7 to 26.0)	Illi 2001
Allergic Rhinitis	4.9 (2.3 to 10.4)	Plaschke 2000
Atopic Dermatitis	2.4 (1.3 to 4.6)	Martinez 1995
Family history of asthma (maternal)	4.1 (2.1 to 7.9)	Martinez 1995 (Tucson , Arizona)
Paternal asthma	1.6 (1.0 to 2.4)	Jenkins 1994
Maternal asthma	1.9 (1.2 to 2.8)	Jenkins 1994
Pre-term delivery (< 36 weeks gestation)		
Females	2.6 (1.4 to 4.7)	Mutius1993
Females+ ventilatory support (to premature males ,no support)	3.3 (1.0 to 10.2)	
Smoking Mother	2.3 (1.2 to 4.4)	Martinez 1995 (Tucson , Arizona)
Sex		
Male Sex	1.9 (1.2 to 3.0)	Marinez1995
Urbanicity (compared to non-urban and non-poor)	1.44 (1.05 to 1.95)	Aligne2000
Respiratory synctial virus(RSV)	4.3 (2.2 to 8.7)	Stein 1999
Para-influenza	2.4 (0.8 to 7.4)	
Other agents (Not RSV or PI)	2.9 (1.1 to 7.8), $p < 0.01$	
Pneumonia	3.3 (1.4 to 7.8), $p < 0.01$	
Lower respiratory tract infection/ No pneumonia	2.4 (1.3 to 4.2) $p < 0.02$	Castro-Rodriguez 1999

CHAPTER 3

METHODS

OVERVIEW

An exploratory study to assess risk factors for asthma incidence was conducted using a birth cohort study in the GA Medicaid and MarketScan databases in which continuously eligible newborn children were retained. Subjects were censored upon either a diagnosis for asthma or on loss of eligibility. All risk factors for asthma incidence that could be measured using the given data were examined for their impact on the likelihood of an asthma diagnosis in these pediatric populations. The treatment effects of allergic anti-inflammatory medications on asthma incidence, was further examined in a retrospective cohort study composed of patients with a diagnosis of AD/AR in GA Medicaid and MarketScan databases.

To determine the effect of FAGH, SGAH, INS, CM on asthma incidence in a group of asthma susceptible children, pediatric patients with an AD/AR diagnosis and who were continuously eligible from birth until such a diagnosis were retained in the primary AD/AR cohort. Patients in the AD/AR cohort were followed up until the development of asthma or until loss of eligibility. Exposure to FAGH, SGAH, INS, CM and combination therapies with these agents was recorded and patients were stratified according to the observed exposure. Comparison of AD/AR patients with no exposure to FGAH, SGAH, INS or CM to patients with some exposure to these agents then provided a measure of the effect of these agents on asthma outcomes. As a sensitivity analysis to explore the effect of different asthma case definitions, the asthma outcome was expanded to include all patients who received a beta-agonist prescription (a potential proxy for asthma case definition). An additional outcome of this study was to assess the impact of exposure to FGAH, SGAH, INS or CM on direct medical health care costs for patients who develop asthma in the AD/AR cohort and are eligible for one year after asthma diagnosis.

Total cost of care for these patients was then examined between patients who received these anti-allergic medications to patients who did not have such exposure.

DATA SOURCE

This study utilized data from two sources:

Georgia Medicaid Claims data

The claims data for GA Medicaid from 1995 to 1997 was obtained from Electronic Data Systems Inc (EDS), which is the fiscal agent for Georgia Department of Medical Assistance (GDMA), the state agency responsible for operating the Medicaid program in Georgia. The GA Medicaid data from 1998 to 2001 was obtained from The Medstat Group, Inc. All of the above data is housed at the University of Georgia. These data sets have been converted to SAS data sets. The data has been found to be consistent with supplied documentation. The GA Medicaid data has been utilized in epidemiological studies and has been found to be valid (Martin 2001). There were however some data discrepancies that were noted for the GA Medicaid data. They were 1) In GA Medicaid, the percentage of patients born between 1995 to 1997 and continuously eligible for 1997 was below the percentages for other years. Eligibility for 1997 was therefore constructed using a proxy measure where eligibility was confirmed by the presence of claim (medical or prescription) every month. 2) For the last quarter of 1997, the claims volume for the medical and the prescription files were below averages of the other quarters. 3) In the 1998 medical files, claims in first two months were bunched in the month of March leading to lower volume of claims in March.

The GA Medicaid database contains the entire medical and prescription utilization of eligible recipients including inpatient, outpatient, physician visits and emergency services used. Children may qualify for Medicaid services under the following categories 1) Right From The Start Medicaid (RSM adults) for pregnant mothers: Pregnant women with a family income at or below 235% of the federal poverty limit are eligible for Medicaid services and stay eligible for 60 days post-partum. Children born to such a mother stay eligible until one year of age if the mother

was eligible for one-month during pregnancy and lives in the same household as the mother. 2) Right from the start Medicaid (RSM Children): Children are covered up to age 18 depending on age and income level. 3) Medically Needy pregnant women, infants, and children: If the pregnant women / children do not qualify for Medicaid because of family resources but meet this limit due to medical spend down. In addition to a unique scrambled id for each patient that was used to link all the files, the GA Medicaid data from 1998 to 2001 also contained a variable that provided a potential link between subjects selected in the study and maternal ids. This potential link was further confirmed by pregnancy diagnosis and procedural codes for these 'maternal ids'.

MarketScan Research Database (www.medstat.com)

The MarketScan data is a commercial claims and encounter database, which contains the healthcare experience of approximately seven million individuals (annually) who are covered under a variety of health plans. Data from January 1998 to December 2001 were acquired, and these data from MarketScan form the commercial population. The data provides access to all medical claims, drug data (approximately 2.6 million covered lives) and enrollment details for the working population and their dependents. The data are organized into these major files: 1) patient and demographic information 2) health plan features 3) financial information 4) inpatient and outpatient medical information 5) drug information 6) enrollment information. The data was obtained in the form of SAS transport files which were converted to SAS data files and examined for data consistency. The MarketScan data base also has an in-built variable that flags family units which was used to establish child-mother linkages. All of the data were examined for consistency and outliers. The GA Medicaid data and the MarketScan data have been used previously in studying asthma and other epidemiological studies and has been found to valid and consistent (Crystal-Peters 2002). The analysis will be done in parallel for the two datasets.

OPERATIONAL DEFINTIONS

Research subjects for the birth cohort study

The inclusion criterion for the birth cohorts in GA Medicaid and the commercial data for the exploratory studies for asthma development were as follows:

-Born between January1995 to January2001 for GA Medicaid and between January1998 to January 2001 for commercial

-Continuously eligible for at least one year after birth.

Exclusion Criteria for the exploratory study were:

-Any diagnosis of AIDS/HIV or cystic fibrosis.

- Death in the first year of follow-up

Establishing risk factors for asthma to be investigated

A comprehensive literature review was undertaken to identify all risk factors for asthma development. Atopic diseases such as AD and AR were of primary interest in this exploratory study. Due to the overlap in diagnosis between allergic and non-allergic rhinitis and the difficulty in differentiating atopic and non-atopic dermatitis, these conditions were explored in two ways (Adams 2002; Oranje 2002). A broad definition was explored by the inclusion of two composite dichotomized variables for dermatitis and rhinitis pooling together both allergic and non-allergic manifestations. In a separate model, the exposure of interest was restricted to only allergic rhinitis and allergic dermatitis as dichotomous variables (Table 3.1). In a separate analysis atopic dermatitis and allergic rhinitis was also modeled as the number of infections prior to asthma development.

Other key risk factors of interest were lower respiratory tract infections such as Respiratory Synctial virus (RSV), pneumonia, bronchitis, and bronchiolitis. These infections may act to increase the risk of asthma independent of atopy by damaging lung tissue or by impairing development or by serving as triggers for asthma episodes in atopic children (Stein 1999; Castro-Rodriguez 2000). Any diagnosis of lower respiratory tract infection was

dichotomized separately for these four infections. Upper respiratory tract infections such as the common cold and p-influenza infections were also investigated for their effect on asthma incidence. The role of upper respiratory tract conditions (i.e.: common cold and p-influenza on asthma development) is not as clear because repeated infections in early infancy may cause a shift from Th2 (allergic) to Th1 (non-allergic) immunity leading to increased protection or susceptibility (Broide 2001). The number of such 'common cold episodes' was therefore modeled as a continuous variable. An other factor that may affect a switch in asthma development is the impact of anti-biotics in the first year of life. Effect of anti-biotic exposure on asthma incidence has shown mixed results, with an increased risk of asthma in at least three studies while two other longitudinal studies have rejected this hypothesis (Farooqi 1998; von Mutius 1999; Celedon 2002; Illi 2001). The number of anti-biotic prescriptions in the first year of life were classified into seven categories as described in Table 3.1, and modeled as a continuous variable. In addition, overall exposure to any anti-biotic in the first year of life was also investigated as any exposure vs. none. Common co-morbidities for AR such as Otitis Media and sinusitis have been linked to an increased likelihood of an asthma diagnosis (Grupp-Phelan 2001). These risk factors were therefore also investigated for their impact on asthma incidence. Similarly, effect of gastro-esophageal reflux disease (GERD) on asthma incidence has not been evaluated given the indirect evidence that there is a re-emission of asthma symptoms after anti-reflux surgery (Field 1999). GERD was also therefore investigated as a risk factor for asthma development. Table 3.1 presents a list of risk factors and their operational definitions as were used in this study. Certain risk factors for asthma development such as allergen exposure or maternal asthma are not recorded in the data and could not be controlled for in the analyses.

All of the medical risk factors for asthma were recorded from birth until an asthma diagnosis was established or until patients were censored on loss of eligibility or death. In the event that the patients were classified as asthmatic based on multiple criteria, the data of the first such criteria was recorded as the end for the observation period for risk factors. Since there were

many patients who received a asthma prescription that was not a part of an asthma diagnosis, since it was not followed by an asthma diagnosis in the required time interval, the date of receipt of such a prescription was the recorded end date for observation for such patients.

Measurement of the outcome for the exploratory study

The main outcome for this exploratory analysis was all incident cases of asthma for the birth cohort between January1995 to December2001 GA Medicaid and January1998 to December 2001 for MarketScan/commercial data. The analysis was limited to definite asthma cases that were defined as follows:

-One inpatient claim with a primary (first listed) or secondary ICD-9-CM code for asthma (ICD-9-CM=493.**) (Lozano 1997) OR

-Two outpatient claims with a primary or secondary ICD-9-CM code for asthma (ICD-9-CM=493.**) not separated by more than 365 days, since one outpatient diagnosis might represent a rule out diagnosis (Nash 1999) OR

-An outpatient diagnosis for asthma and two or more prescriptions belonging to separate asthma medication class or two or more medications for the same class separated by at least 30 days in any 365 day period (Leone 1999).

The asthma medications for this study was broadly divided into: 1) Adrenergic bronchodilators, 2) Leukotriene inhibitors, 3) Other Respiratory inhalants, 3) Anti-asthmatic combinations, 5) Methyxanthines, 6) Oral corticosteroids, 7) Inhaled corticosteroids.

Drug markers have been used in isolation to identify asthma cases (Nash et al. 1999). Drugs used to control asthma symptoms such as beta-agonist show high specificity, but specificity of some other asthma medication classes is low (Himmel 2001). For example, cromolyns and now leukotriene inhibitors are used to treat asthma and AR. Therefore, using diagnostic information concurrently with drug markers was used to increase specificity, recognizing the trade-off that some asthma cases may be missed.

Data Analysis

Unadjusted risk ratios evaluated the univariate relationship between individual risk factors and asthma incidence and the significance was tested using the chi-square analysis. For continuous variables, means were also tested between the groups (asthma vs. non-asthma) using the two-sample t-test. Cox proportional hazards regression (PROC PHREG) was used to analyze the impact of risk factor exposure on asthma incidence and to estimate hazard ratios and 95% CI after stratifying for sex (Allison 1995). The response variable was the time from birth until asthma incidence or until being censored on loss of eligibility or death. In addition to the censoring (1 if developed asthma, 0 otherwise) status variable, all other risk factors for asthma incidence as described above were added as additional covariates. The effects of rhinitis, dermatitis (allergic and non-allergic separately), otitis media, sinusitis and URTI and all lower respiratory tract infections were also explored as time-dependent covariates (depending on year of onset of these conditions). Appropriateness of the constant hazard assumption was confirmed by inspection of log (-log [survival]) curves. The data was managed using SAS software Version 8.02 and the statistical analysis was conducted using SAS and STATA Version 8.0. The study was approved by the University of Georgia Institutional Review board.

Study Population for the treatment effects study

Research subjects for the treatment effects study

Inclusion of children with a diagnosis of allergic disease with an atopic diathesis into the AD/AR primary cohorts was based on the following scheme:

-Born between January1995 to October2001 for GA Medicaid and January1998 to October 2001 for commercial data.

-Between January1995 to December2001 in GA Medicaid and January1998 to December 2001 in commercial data have one or more of the following diagnoses:

-Any ICD-9-CM diagnosis code for atopic dermatitis (ICD-9-CM=691.8, 692.9 and 373.3) (Ellis 2002) OR

-Any ICD-9-CM diagnosis code for allergic rhinitis (ICD-9-CM=477.**) (Crystal-Peters et al. 2002)

-Continuously eligible from birth until a diagnosis of AD or AR.

Patients were excluded from the AD/AR primary cohort based on the following criteria

-Diagnosis of HIV/AIDS and or cystic fibrosis

-A prescription for an asthma medication or a diagnosis for asthma prior to their first AD / AR diagnosis in the primary cohort

For the cost outcome in this phase of study, this analysis was restricted to patients in the AD/AR cohort who developed asthma and were continuously eligible for at least 12 months after the first asthma diagnosis flag.

Measuring exposure to anti-inflammatory agents

The main agents of interest in this study were first generation anti-histamines (FGAH), second generation anti-histamines (SGAH) and intra-nasal steroids (INS) and cromolyns (CM) which were recorded from the outpatient prescription files as shown in Table 3.2. All cough and cold medication were screened to include those which contained FGAH. These combination products were included if they contained at least one of the active ingredients listed in Table 3.2. Since the sample sizes for CM were very small in both populations (<100), this exposure category was dropped from all further analysis. The cumulative exposure to FGAH, SGAH and INS was recorded as the sum of the 'days supply' variable from birth until an asthma diagnosis was established or until subjects were censored. In some cases, subjects in the AD/AR cohorts received a prescription for a short acting beta-agonist (SABA) prior to and that was not a part of the asthma diagnosis. In these instances, the date of receipt of this prescription was the end date of the observation period for these subjects. In patients who received a SABA prescription but did not develop asthma, the date of receipt of the SABA prescription was the recorded end date for these patients.

As-treated approach

Impact of exposure to FGAH, SGAH and INS was analyzed on asthma outcome in an 'as treated' analysis. In the first comparison, exposure levels or dose levels were ignored and subjects included in the primary cohort were classified into one unique exposure category ranging from no-exposure to exposure to all drug classes. The seven mutually exclusive exposure categories were as follows: I) Single agent exposure only: Exposure category 1) FGAH 2) SGAH 3) INS, II) Dual agent exposure only: Exposure category 4) FGAH+ SGAH 5) FGAH+INS 6) SGAH+INS; III) Exposure to all: Exposure category 7) FGAH+SGAH+INS. Groups with exposure to the study drugs or any combination of the study drugs were compared individually in separate analyses to the group with no exposure to any of these agents. For example: Single agent exposure (FGAH only) vs. no exposure or Dual agent exposure only (FGAH+SGAH only) vs. no exposure. Groups with exposure to one study drug or study drug combinations were also compared to groups with different exposure to study drugs, for example: Single agent exposure only to dual exposure or SGAH only vs. SGAH+INS (Table 3.3). The second level of comparison was based on the cumulative exposure to these agents in the study period. Based on the distribution of use of these agents in the AD/AR cohorts an exposure level below or equal to 10 days in the entire study period was ignored. Exposure days greater than 10 but less than 60 days was classified as low exposure and exposure days greater than 60 were classified as high exposure. Subjects in the cohorts were again reclassified into one unique exposure category based on this interaction of dose level and exposure category. For instance: Low exposure FGAH only, High Exposure FGAH and such. The categories were as follows: I) Six Single exposure categories (Low FGAH only, High FGAH only, Low SGAH only and so on) II) Twelve Dual Agent exposure (Low FGAH and Low SGAH only, High FGAH and High SGAH only and so on) III) Eight Exposure to all category (Low FGAH and Low FHA and Low INS and so on). Comparisons were then made between these exposure categories and no exposure to any agent. The comparisons were made contingent upon sufficient sample size for each exposure category.

Intent to treat analysis

In the intent to treat analysis, exposure to FGAH, SGAH was explored as any exposure to these agents. The comparator groups in these analyses were groups with no exposure to the agent of interest. For instance: exposure to FGAH as the cumulative days supply vs. no exposure to FGAH and so on.

Cumulative exposure to all agents

Exposure to FGAH, SGAH and INS was also explored as the cumulative exposure (in days supply) to all agents in a separate analysis on asthma outcome.

Measurement of Outcomes

Asthma in the AD/AR primary cohort was defined as described in the outcomes section of the exploratory study.

A secondary outcome for the AD/AR cohort was the total asthma cost for subjects in the AD/AR cohort who were eligible for at least 12 months after the first asthma inclusion criteria was recorded. Since this study focused on a third-party payer perspective, net paid amount in GA Medicaid and the commercial population were used to calculate the total cost. Total cost was calculated as the sum of the amount in the paid amount field for both datasets. Total costs were also examined by category of service namely inpatient, physician, outpatient, other miscellaneous medical utilization, asthma related prescription and non-asthma related prescriptions.

DEALING WITH SELECTION BIAS (HECKMAN TWO-STAGE ESTIMATION)

Treatment exposure in this study may be thought to be a function of observed (captured in the database) or unobservable factors. Observed factors could be confounders such as age at the first diagnosis, or the number of times the children may present with a symptom or even aggressive treatment depending on physician specialty. Unobservable confounders may be factors such as severity of the disease, parent's propensity to seek care that may affect the observed outcomes. In an attempt to estimate and control for such baseline difference in characteristics, Heckman's two-stage model was used (Heckman 1976; Terza 1999; Sosin 2002).

In the first stage of the Heckman procedure, the expected value of the error term (M1) was calculated using a probit regression modeling the probability of receiving any treatment which was then used as an additional regressor in the second stage. The study sample was segmented into mutually exclusive categories for the dependent variable (for example: those that were treated with FGAH, or SGAH or dual exposure or exposure to all or those with no exposure at all) and treatment models were estimated. For this study, exposure to treatment was modeled as function of patients characteristics (i.e.: sex, age of onset of AD and AR, income category), diagnosis of diseases such as Otitis media, Sinusitis (disease burden) over the study period and if subjects had a specialist visit in the first year of follow up and any specialist claim thereafter (Table 3.1). A probit model was used in the first step (the selection equation) to estimate the expected value of the error as follows:

Step I: In step one the probit model was defined as:

$$Pr(y=1|x) = cdf(Xb) \text{ or } P = Z*alpha + U$$

Where cdf is the standard cumulative normal probability distribution,

Z – Matrix of observable covariates that may predict treatment (Table 3.1 (column 2)),

b or alpha – Matrix of coefficients for the X variables,

P=1 if treatment is observed, 0 otherwise,

U = error term, which is normally distributed with constant variance.

The expected value of the error is then calculated as:

$$M1 = \frac{pdf(Z*alpha1)}{cdf(Z*alpha1)}$$

where M1 = estimate of expected value of error

alpha1 = estimate of alpha

pdf = probability density function

cdf = cumulative density function

Table 3.1 lists all the additional variables that were used to model this likelihood to exposure. The vector of coefficients of the covariates estimated through this model was used to calculate the expected value of error (M1). Heckmans' sample selection models were planned between exposure vs. non-exposure and between exposure groups themselves (Table 3.3), between dose level comparisons vs. no exposure comparisons and the intent to treat analysis.

Analysis for the treatment effects model

Univariate risk ratios for asthma incidence was compared between exposure of interest using the chi-square tests. Two sample t-tests were used to compare the differences between groups for continuous variables such as day's supply of FGAH, SGAH or INS. In the first step of the analysis, M1 the estimate of the expected value of error, was obtained using probit regression as explained in the methods used to deal with sample selection bias. In the second stage, impact of the exposure to anti-inflammatory agents on risk of an asthma diagnosis was modeled using the Cox proportional hazards model (PROC PHREG) and stratified for sex (Allison 1995). Asthma incidence was modeled as a function of covariates listed in Table 3.1, a dummy variable for treatment exposure and the M1 the expected value of the error term calculated from the first model. The dependent variable was the time in days from birth until an asthma diagnosis or until the patient was censored. In addition, a variable to indicate censoring status was also built (1 = asthma diagnosis, 0 = censored). Differences in survival curves were tested using the log-rank test or Gehans-Wilcoxon test. The proportional hazards assumption was confirmed by inspection of log (-log [survival]) curves. Hazard ratios for asthma incidence and 95% confidence intervals for the relative risk of asthma given the exposure are reported.

Multivariate ordinary least squares regression using Huber-white heteroscedasticity consistent variance–covariance matrix was used to compare direct medical costs post asthma incidence between groups with exposure to FGAH, SGAH, INS and all combination therapies to groups with no exposure to these agents. The dependent variable was the total direct cost and the explanatory variable of interest was a binary variable indicating treatment exposure or no

exposure to FGAH, SGAH or INS. Other covariates that can affect costs and that can be measured in the data set as described in Table 3.1 were included. In addition, the estimate of the error term (M1) from the probit regression was also included as an additional covariate. Exposure to FGAH and SGAH and INS was also stratified into dose levels based on the cumulative exposure and impact on cost outcomes was examined. In addition to total cost, costs by categories of service were also investigated. SAS software Version 8.02 was used to manage the data and perform statistical analysis. The study was approved by the University of Georgia Institutional Review board.

SENSITIVITY ANALYSIS

Sensitivity analysis was conducted to analyze the impact of change in the operational definition of risk factors on asthma diagnosis and also to assess the impact of change in asthma case definition itself.

Expanding asthma case definitions

An additional post-hoc outcome that was investigated was the receipt of a prescription for a short acting beta-agonist (SABA) used as additional criteria for defining Asthma. The Asthma case definition was expanded to include all patients who received a SABA prescription and also those patients termed asthmatics by the original asthma case definitions. In the event that patients had a SABA prescription prior to establishing their asthma diagnosis, the date of first recorded SABA prescription was the end date for observation for such patients. This was undertaken since many pediatric patients have multiple wheezing episodes that are treated with SABA yet do not receive an asthma diagnosis (Osborne 1995; Silvestri 2004). This outcome therefore served as sensitivity analysis for the conservative asthma case definition used, which may have missed some potential asthma cases. This sensitivity analysis was conducted for both the exploratory study for risk factors for asthma and for the treatment effects study of FGAH, SAGH and INS as well.

Definition of upper respiratory infections (URI)

Risk factors in the exploratory study were defined separately for upper respiratory conditions such as AR, Sinusitis, URTI (defined as common cold), and p-influenza infections. However, all of these conditions present with very similar symptoms and may be difficult to differentiate from one another (Lack 2001). Sinus disease is inherently associated with viral upper respiratory tract infections and occurs in 90% of individuals with the common cold (Desrosiers 2002). Similarly, there is a considerable overlap in Rhinitis and sinusitis so much so that these conditions are sometimes referred to as Rhinosinusitis (Meltzer 2004). Upper respiratory infections (URI) were therefore defined as any episode of rhinitis, sinusitis, para-influenza or common cold (defined in the exploratory study as URTI). An alternative definition for URI was such that only sinusitis episodes were excluded from the above definition.

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Table 3.1: List of covariates, other than treatment exposure that may influence treatment assignment and also outcomes

	Covariates for the exploratory study	Covariates in the 1st stage Heckman two stage estimator	Covariates for treatment effects models and 2nd stage of Heckman model for asthma incidence	Covariates in the cost of asthma model and 2nd stage of Heckman model for cost
Demographics (Sex and Race)	Yes	Yes	Yes	Yes
Year of Birth	Yes	Yes	Yes	Yes
Age at first diagnosis of allergic disease	No	Yes	Yes	Yes
Maternal Asthma	Yes	No	Yes	Yes
Type of health plan for MarketScan data	Yes	Yes	Yes	Yes
Premature birth (ICD-9-CM=765.1*)	Yes	No	Yes	Yes
Respiratory difficulties at birth (ICD-9-CM=769)	Yes	No	Yes	Yes
Rhinitis (seasonal and perennial) (ICD-9-CM=477.*, 472.*)	Yes	Yes	NA	NA
Dermatitis (ICD-9-CM=691.* to 693.*, 708.*, 995.3)	Yes	Yes	NA	NA
Allergic Rhinitis (ICD-9-CM=477.*)	Yes	Yes	NA	NA
Atopic Dermatitis (ICD-9-CM=691.8, 692.9 and 373.3)	Yes	Yes	NA	NA
Diagnosis of measles (ICD-9-CM=055.*), mumps(ICD-9-CM=072.*), rubella(ICD-9-CM=056.*)	Yes	No	Yes	No
Diagnosis of Sinusitis (ICD-9-CM=461.*, 473.*) (McCaig2002)	Yes	Yes	Yes	Yes
Diagnosis of Otitis Media (ICD-9-CM=381.0, 381.4, 382.0, 382.4, 382.9) (McCaig2002)	Yes	Yes	Yes	Yes
Diagnosis of URTI (ICD-9-CM=460, 465.*), P.Influenza (ICD-9-M=487.**) (McCaig 2002)	Yes	Yes	Yes	Yes
Diagnosis of Pneumonia (ICD-9-CM=480.** to 486.**), Bronchitis (ICD-9-CM=466.0, 490), RSV infection (ICD_9-CM=079.6*), Bornchilitis (ICD-9-CM=466.1* excluding 466.19) (Boyce 2000)	Yes	Yes	Yes	Yes
Number of anti-biotic prescriptions belonging to the following classes 1) Azithromycin/ clarithromycin 2) Cephalosporin's 3) Erythromycins 4)	Yes	Yes	Yes	Yes

Penicillin's 5) Quinolones 6) tetracycline's 7) Others in the first year of life (McKeever 2002)				
Any diagnosis of GERD (ICD-9-CM= 530.1, 530.10, 530.11, 530.19, 530.3, 530.8, 530.81) (Holzman 2001)	Yes	No	Yes	Yes
Co morbidity based risk adjustment method (modeled as presence of a condition vs. none) (Ricci June2002))	No	No	No	Yes
Season of birth (Fall, winter, summer, spring)	Yes	No	Yes	Yes
Physician Specialty (Resnick 1996)	No	Yes	Yes	Yes
^Number of oral steroids prescriptions	No	No	Yes	Yes
^Number of topical steroids prescriptions	No	No	Yes	Yes
^Number of leukotreiene inhibitors prescriptions	No	No	Yes	Yes
Asthma treatment *	No	No	No	Yes
Socio-economic index (using zip-code)	Yes	Yes	Yes	Yes

** Asthma treatment adequacy implying good clinical asthma control is an important factor that can impact asthma costs by preventing adverse outcomes such as emergency visits and hospitalizations. The number of beta-agonist, inhaled steroids and oral steroids dispensing will therefore be used as a surrogate measure for clinical asthma control (Adams2002).*
^Number of topical steroids, oral steroids (prescribed for exacerbations), leukotriene inhibitors (after 1998 if used for AR) will be controlled for in all analysis.

Table 3.2: List of drug classes and generic names.

Drug classes	Generic names
First generation antihistamines (FGAH)	Brompheniramine, Chlorpheniramine, Hydroxyzine, Diphenhydramine, Clemastine, Cyproheptadine, Triprolidine Diphenhydramine, Clemastine, Carbinoxamine, Azatadine, Dexchlorphinaramine, Diphenhydramine, Doxylamine, Hyroxyzine, Meclizine, Cyclizine, Tripelennamine, Pyrilamine.
Second generation antihistamines (SGAH)	Ceterizine HCL, Azelastin HCL, Astemizole (withdrawn in 1999), Fexofenadine, Loratadine, Levocabastine
Intranasal Steroids (INS)	Beclomethasone Dipropioante, Budesonide, Flunisolide, Fluticasone Dipropioante, Mometasone furoate, Triamcinalone Acetonide
Cromolyns (CM)	Sodium cromoglicate or Cromolyn sodium (nasal and ophthalmic forms)

Table 3.3: Schematic representation of all possible treatment comparisons under Heckman two stage models.

	No Exposure	Single agent exposure (Exposure category 1 to 3)	Dual agent exposure (exposure category 4 to 6)	Exposure to all agents i.e.: FGAH+SGAH + INS
Single agent exposure (exposure category 1 to 3)	X	X (for example: FAGH to SGAH)	X	X
Dual agent exposure (exposure category 4 to 6)	X	X	X (For example: FGAH+ INS vs. FGAH+SGAH)	X
Exposure to all agents i.e.: FGAH+SGAH+INS	X	X	X	X

X- represents a separate comparison using the Heckmans two-stage sample selection procedure (comparisons will be done contingent on adequate sample sizes)

CHAPTER 4

AN EXPLORATORY ANALYSIS OF RISK FACTORS FOR INCIDENT ASTHMA IN A PEDIATRIC POPULATION [1]

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ABSTRACT

INTRODUCTION: Asthma, a leading cause for hospitalizations in children and a common chronic pediatric disease is the result of complex interactions between genetics and the environment. Atopy and atopic diseases such as allergic rhinitis (AR), and atopic dermatitis (AD), lower respiratory tract infections and genetics are some of the recognized risk factors for asthma. Some other risk factors for asthma such as sinusitis, gastro-esophageal reflux disease (GERD) and anti-biotic use are the more contentious factors for the development of this disease. The objective of this study was to assess the impact of medical and non-medical risk factors on asthma development and to understand the interaction that atopic and other risk factors have on disease development in children.

METHODS: A retrospective birth cohort study was conducted in GA Medicaid from 1995 to 2001 and in MarketScan database from 1998 to 2001 in which newborn children continuously eligible for at least one year after birth were retained. Any patients with a diagnosis for AIDS or cystic fibrosis were excluded. Asthma risk factors of interest namely 1) Number of upper respiratory tract infections or a para-influenza diagnosis 2) Diagnosis of lower respiratory tract infections as defined by a diagnosis of pneumonia, bronchitis and RSV infection or bronchiolitis 3) sinusitis 4) Otitis media diagnosis 5) Diagnosis of dermatitis of any origin, rhinitis (seasonal and perennial) 6) GERD diagnosis. In addition, all anti-biotic prescriptions in the first year of life were recorded and examined for their effect on asthma development. Cox Proportional Hazards models were used to assess the impact of these conditions on asthma incidence.

RESULTS: There were 369,286 children in the GA Medicaid population of which 40,730 (11%) of patients developed asthma. 61,576 patients were retained in the commercial population birth cohort of which 3, 689 (5.99%) developed asthma. In the adjusted analysis, all lower respiratory tract infections were associated with an increased risk of asthma diagnosis in both datasets (HR ranged from 2.27 to 1.39). Impact of rhinitis, dermatitis and their allergic manifestations were mostly non-significant with regards to their impact on asthma, expect dermatitis seemed to

increase the risk in the commercial population as much as 54% when the timing of such infections was taken into consideration. Effect of anti-biotics, socio-economic index also varied depending on the nature of population under study. GERD was a consistent risk factor for asthma development across both datasets.

CONCLSUION: This exploratory study was neither able to establish nor refute the impact of atopic disease such as AR or AD on asthma incidence. This study was however able to identify some factors that influence asthma development in a pediatric population. This information along with other knowledge about the development of asthma can be utilized to develop interventions that may control or inhibit asthma development.

Keyword: Asthma, risk-factors, incidence, Medicaid, MarketScan

INTRODUCTION

Asthma is a result of complex interactions between genetic factors and the environment and is a multifactorial disease with numerous risk factors. Asthma prevalence in children (age 0 – 17 years) has increased from 3.6% in 1980 to 6.2% in 1995 (Akinbami 2002), making it the most common chronic pediatric disease encountered in the US (Wood 2002). Investigations of asthma risk factors have implicated Atopy as one of the most important predictors for the development of asthma where Atopy is the genetic tendency to mount IgE antibodies in response to inhaled allergens (Wood 2002); (Weiss 1998). Not at all asthma is associated with atopy and the complex patterns of asthma incidence are evidenced by the fact that although the prevalence of atopy (as defined by skin prick tests) is approximately 58% in children the proportion of asthma cases attributable to Atopy ranges from 25% to 63 % with a weighted mean of 38% in children (Pearce 1999).

Asthma not associated with atopy is not as well investigated and risk factors for non-atopic asthma range from upper and lower respiratory tract infections (bacterial or viral) to low birth weight (Hide 1996; Douwes 2002). Most studies that assess risk factors for atopic or non-

atopic asthma have been subject to recall bias (Bodner 1998), incomplete medical information or lack of information about simultaneous exposures (von Mutius 1999; Grupp-Phelan 2001), use of intermediate outcomes such as wheezing or bronchial hyperresponsiveness or have been subject to temporal bias (Paunio 2000). A longitudinal study that utilizes comprehensive diagnostic information to assess and clarify risk factors for incident asthma, establishes a clear temporal relationship between risk factors and incident asthma and elucidates the combined effect of these risk factors in a manner not subject to recall bias is clearly lacking. An exploratory study was therefore undertaken to comprehend how different risk factors in pediatric populations influence asthma incidence. A retrospective database analysis will facilitate an understanding of the nature of incident asthma and its risk factors, which are not subject to recall bias. The objective of this exploratory study was to assess the impact of medical and non-medical risk factors on asthma development and, more importantly, to understand the interaction that atopic and other risk factors have on disease development.

METHODS

Data Sources

Data from GA Medicaid from 1995 to 2001 and the MarketScan database from 1998 to 2001 were utilized. The GA Medicaid data describes all adjudicated claims for GA Medicaid eligible beneficiaries including all institutional, outpatient and prescription claims, which is patient linked to program eligibility information. Children may qualify for Medicaid services under the following categories 1) Right From the Start Medicaid (RSM adults) for pregnant mothers. 2) Right from the start Medicaid (RSM Children): Children are covered up to age 18 depending on age and income level. 3) Pregnant Women, infants and children medically needy: If the pregnant women /children do not qualify for Medicaid because of family resources but meet this limit due to medical spend down. The GA Medicaid data from 1998 to 2001 contained an additional variable that provided a potential link between mother-child pairs. This information was used in GA Medicaid to build mother-child linkages.

The MarketScan data is a commercial claims and encounter database, which contains the healthcare experience of approximately seven million individuals (annually) who are covered under a variety of health plans. Data from MarketScan form the commercial population. Data from January 1998 to December 2001 were acquired and provided access to all medical claims, drug data (approximately 2.6 million covered lives) and enrollment details for the working population and their dependents. The data are organized into these major files: 1) patient and demographic information 2) health plan features 3) financial information 4) inpatient and outpatient medical information 5) drug information 6) enrollment information. A unique scrambled patient identifier is encoded for each record in all of the above files in both datasets that facilitates linkage. In addition, the MarketScan data base also has in-built variables that flag family units which were used to establish the child-mother linkage. All of the data were examined for consistency and outliers. The GA Medicaid data and the MarketScan data has been used previously in studying asthma and other epidemiological studies and has been found to valid and consistent (Martin 2001; Crown 2003). The analysis was done in parallel for the two datasets.

Study Design

The study design was a retrospective birth cohort study wherein risk factors for development of childhood asthma were studied prospectively in children born from 1995 to 2001 in GA Medicaid and in 1998-2001 in MarketScan/ commercial data. Children alive and eligible for at least one year after birth were retained and risk factors for asthma development were recorded from birth until asthma development or until loss of eligibility (or death). Pediatric patients were included in the Medicaid and commercial population based on the following inclusion criteria:

-Born between January1995 to January 2001 for GA Medicaid and January1998 to January2001 for the commercial population.

-Continuously eligible for at least one year after birth.

Patients were excluded from this cohort if they had a diagnosis for AIDS/HIV or cystic fibrosis or death in the first year of follow-up

Establishing medical risk factors for asthma

A comprehensive literature review was undertaken to identify all risk factors for asthma development. Atopic diseases such as AD and AR were of primary interest in this exploratory study. Due to the overlap in diagnosis between allergic and non-allergic rhinitis and the difficulty in differentiating atopic and non-atopic dermatitis, these conditions were explored in two ways (Adams 2002); (Oranje 2002). A broad definition was explored by the inclusion of two composite dichotomized variables for dermatitis and rhinitis, pooling together both allergic and non-allergic manifestations. In a separate model the exposure of interest was restricted to only allergic rhinitis and allergic dermatitis as dichotomous variables (Table 4.2). In a separate analyses atopic dermatitis and allergic rhinitis was also modeled as the number of infections prior to asthma development. Impact of Dermatitis and Rhinitis was also examined on asthma outcome by sub-categories based on diagnosis codes. An attempt was also made to determine the use of diagnostic tests for establishing a diagnosis of Atopic dermatitis and/or allergic rhinitis. Procedural codes (in GA population) and procedural and revenue codes (in commercial) were used to determine the prevalence of use of such tests. Procedure codes that were used were (CPT-4 codes = '86003', '86005', '82785' , '82784', '82784', '82787', '86628', '86849', '95004', '95024', 95027').

Other key risk factors of interest were lower respiratory tract infections, such as Respiratory Synctial virus (RSV), pneumonia, bronchitis, and bronchiolitis. These infections may act to increase the risk of asthma independent of atopy by damaging lung tissue or by impairing development or by serving as triggers for asthma episodes in atopic children (Stein 1999). Any diagnosis of lower respiratory tract infection was dichotomized separately for these four infections. Upper respiratory tract infections such as the common cold and p-influenza infections were also investigated for their effect on asthma incidence. The role of upper

respiratory tract conditions(i.e.: common cold and p-influenza) on asthma development is not as clear because repeated infections in early infancy may cause a shift from Th2 (allergic) to Th1 (non-allergic) immunity, leading to increased protection or susceptibility (Broide 2001). The number of such 'common cold episodes' was therefore modeled as continuous variable. Another factor that may affect such a switch is the impact of anti-biotics in the first year of life on asthma development. Effect of anti-biotic exposure on asthma incidence has shown mixed results, with an increased risk of asthma in at least three studies, while two other longitudinal studies have rejected this hypothesis (Farooqi 1998; von Mutius et al. 1999; Celedon 2002); (Illi 2001). Anti-biotic prescriptions in the first year of life were classified into seven categories as described in Table 4.2 and modeled as a continuous variable. In addition, overall exposure to any anti-biotic in the first year of life was also investigated as any exposure vs. none. Common co-morbidities for AR such as Otitis Media and sinusitis have been linked to an increased likelihood of an asthma diagnosis (Grupp-Phelan et al. 2001). These risk factors were therefore also investigated for their impact on asthma incidence. Similarly effect of gastro-esophageal reflux disease (GERD) on asthma incidence has not been previously evaluated given the indirect evidence that there is a reemission of asthma symptoms after anti-reflux surgery (Field 1999). GERD was also therefore investigated as a risk factor for asthma development. Table 4.2 presents a list of risk factors and their operational definitions as were used in this study. Certain risk factors for asthma development such as allergen exposure or maternal asthma are not recorded in the data and could not be controlled for in the analysis.

All of the available medical risk factors for asthma were recorded from birth until an asthma diagnosis was established or until patients were censored on loss of eligibility or death. In the event that the patients were classified as asthmatic based on multiple criteria, the data of the first such criteria was recorded as the end for the observation period for risk factors. Since there were many patients who received a asthma prescription that was not a part of an asthma

diagnosis, since it was not followed by an asthma diagnosis in the required time interval, the date of receipt of such a prescription was the recorded end date for observation for such patients.

Other covariates

Other covariates that were controlled for in the study included maternal asthma, which is a stronger determinant of asthma in offspring as compared to paternal asthma (Wahn 2001). Maternal asthma was defined as an outpatient or inpatient diagnosis for asthma (ICD-9-CM='493.**') or two or more prescriptions for asthma (excluding oral steroids) not separated by more than 365 days. In GA Medicaid a mother to child link (case number) was available in the claims data from 1998 to 2001. This information was then retrospectively applied to claims data from 1995 to 2001 to establish a tentative mother to child link. Using this link and pregnancy diagnosis codes and procedural codes for delivery, an attempt was made to confirm a mother to child tie for every child in the GA Medicaid population. Since, it is possible that such a tie may not be established for all the subjects included in the GA population, maternal asthma status was defined using two variables. For subjects in the GA Medicaid population where mother-child status could be established, mother diagnosed as 'not asthmatics' were the reference group (Maternal asthma Unknown=1; 0 otherwise and Mother with asthma=1; 0 otherwise). The commercial data has an in-built variable to identify member of a family unit. Using this variable and pregnancy diagnosis code and procedural codes for delivery, a mother-child link was again confirmed in the commercial population.. In addition, other risk factors such as premature delivery, respiratory complications requiring mechanical ventilation, race/ethnicity, and socio-economic index i.e.: urban vs. rural location and median income for the zip code of residence was controlled for. Location of patients and income was determined by linking the patient's zip code to the information at the US census web site (http://www.census.gov). Season of birth for the patients in the cohort was classified into four categories namely fall, spring, summer and winter and controlled for in the multivariate analysis. In addition, other covariates such as plan-type in the commercial population were also controlled for in the analysis.

Measurement of Outcome

The main outcome for the exploratory analysis was all incident cases of asthma for the birth cohort between January1995 to December2001 in GA Medicaid and January1998 to December 2001 for the commercial population data.

A definite asthma diagnosis in birth cohorts was defined as follows:

-One inpatient claim with a primary (first listed) or secondary ICD-9-CM code for asthma (ICD-9-CM=493.**) (Lozano 1997) OR

-Two outpatient claims with a primary or secondary ICD-9-CM code for asthma (ICD-9-CM=493.**) not separated by more than 365 days, since one outpatient diagnosis might represent a rule out diagnosis (Nash 1999) OR

-An outpatient diagnosis for asthma and two or more prescriptions belonging to separate asthma medication classes or two or more medications for the same class separated by at least 30 days in any 365 day period (Leone 1999).

The asthma medications for this study were broadly divided into: 1) Adrenergic bronchodilators, 2) Leukotriene inhibitors, 3) Other Respiratory inhalants, 4) Anti-asthmatic combinations, 5) Methyxanthines, 6) Oral corticosteroids, 7) Inhaled corticosteroids.

Drug markers have been used in isolation to identify asthma cases (Nash et al. 1999). Drugs used to control asthma symptoms such as beta-agonist show high specificity, but specificity of some other asthma medication classes is low (Himmel 2001). For example, cromolyns and now leukotriene inhibitors are used to treat asthma and AR. Therefore using diagnostic information concurrently with drug markers was used to increase specificity, recognizing the trade-off that some asthma cases may be missed.

An additional post-hoc outcome that was investigated was the receipt of a prescription for a short acting beta-agonist (SABA) in both populations. Asthma case definition was expanded to include all patients who received a SABA prescription and also those patients termed asthmatics

by the original asthma case definitions. In the event that patients had a SABA prescription prior to establishing their asthma diagnosis, the date of first recorded SABA prescription was the end date for observation for such patients. This was undertaken since many pediatric patients have multiple wheezing episodes that are treated with SABA yet do not receive an asthma diagnosis (Osborne 1995; Silvestri 2004). This outcome therefore served as sensitivity analysis for the conservative asthma case definition used which may have missed some potential asthma cases.

Analysis

Unadjusted risk ratios evaluated the univariate relationship between individual risk factors and asthma incidence and significance was assessed using chi-square tests. For continuous variables, means were also tested between the groups (asthma vs. non-asthma) using the two-sample t-test. Cox proportional hazards regression (PROC PHREG) was used to analyze the impact of risk factor exposure on asthma incidence and to estimate hazard ratios and 95% CIs after stratifying for sex (Allison 1995). The dependent variable was the time from birth until asthma incidence or until being censored. In addition to the censoring (1 if developed asthma, 0 otherwise) status variable, all other risk factors for asthma incidence as described above and in Table 4.2 was added as additional covariates. The effects of rhinitis, dermatitis (allergic and non-allergic separately), otitis media, sinusitis and URTI and all lower respiratory tract infections were also explored as time-dependent covariates (depending on year of onset of these conditions). The model was specified as follows:

$$\log h_i(t) = \alpha(t) + \beta_{1\text{-}11} X_{i1\text{-}11}(t) + \beta_{12\text{-}21} X_{i12\text{-}21}$$

Where, $h_i(t)$=hazard for individual *i* at time *t*

$\alpha(t) = \log \lambda_0(t)$ where $\lambda_0(t)$ is the baseline hazard function.

X1-X11= are the time-dependent covariates for Dermatitis/Allergic Dermatitis, Rhinitis/Allergic rhinitis, sinusitis, Otitis media, pneumonia, bronchitis, bronchiolitis, any diagnosis of URTI, RSV, p-influenza, defined as any diagnosis vs. none in the year the

censoring event (asthma, loss of eligibility, or death) occurs. Effect of timing of such a diagnosis was also examined by setting the observation year back by one in different iterations

X12-X21= fixed covariates such as maternal asthma, location, season of birth, plan type for the commercial population data and such as listed in Table 4.2

Appropriateness of the constant hazard assumption was confirmed by inspection of log (-log [survival]) curves. The data was managed using SAS software Version 8.02 and the statistical analysis was conducted using SAS and STATA Version 8.0. The study was approved by the University of Georgia Institutional Review board.

RESULTS

There were 369,286 children who were retained in the birth cohort in GA Medicaid. This birth cohort represents 48% of the children of children ages 0-6 years who were eligible for benefits in GA Medicaid and were born between from 1995 to 2001 (Figure4.1). There were 40,730 patients who were identified as asthmatics in GA Medicaid population leading to a incidence of 11% from 1995 to 2001 in GA Medicaid population. A total of 4850 (11.90%) asthmatic children had an inpatient asthma claim, 25,417 (62.40%) had two or more outpatient claims, and 13,625 (33.45%) had an outpatient diagnosis for asthma and two or more prescription claims for asthma medications. 382 children in the GA Medicaid cohort died after inclusion into the study of which 84 children had an asthma outcome.

A total of 61,576 patients were retained in the commercial population of which 3,689 (5.99%) developed asthma (Figure4.2). 549 asthmatics (14.88%) had at least one inpatient asthma claim, 1,949 (52.83%) had two or more outpatient claims and 1,528 (41.42%) had at least one outpatient diagnosis and prescription for asthma not separated by more than 365 days. 11 children in the commercial cohort died after inclusion into the study

There were 14,736 (3.99%) patients in the GA Medicaid population and 917 patients (1.48%) in the commercial population data who received a prescription for short acting beta-

agonist prior to establishing their asthma diagnosis. But there were 111,143(30.09%) patients in GA Medicaid and 13,054(21.19%) patients in the commercial population who received a prescription for short acting beta-agonist but did not develop asthma according to the original study criteria.

In GA Medicaid, a slightly higher proportion of blacks/African Americans were likely to stay eligible for one year after birth than whites. Of the 369,286 patients in GA Medicaid population, a mother child relationship was established for 106,576(28.86%) patients. 97.3% of these mothers also had a diagnosis code for pregnancy and procedural code for birth from 1995 to 2001. Similarly, in the commercial population, child-mother relationship could be established for 59,875 (97.23%) patients and 98% of these 'mothers' had a pregnancy diagnosis or procedural code for pregnancy.

The average follow up for the patients in the GA Medicaid population from birth was 1.97 years (STD:1.29) and was 2.07 years (STD=0.84) for the commercial population. About 70% of GA Medicaid population was below age two, 14% were between the ages of two and three and 17% were above age three when censored. In the commercial population, 51.68% were below age two, 29% were between the ages of two and three and 20% were above age three when censored.

A majority of the children in both birth cohorts; 310,643 (84.11%) in GA Medicaid and 50,703 (82.34%) in the commercial population; had at least one medical risk factor for asthma (Table 4.3, 4.5). Unadjusted risk ratios for asthma incidence in GA Medicaid and commercial population are presented in Tables 4.3 and 4.5 respectively. In the univariate analyses, lower respiratory tract infections (RSV, pneumonia, bronchitis, and brochiolitis) were very significant risk factors for asthma across both datasets. Rhinitis (including allergic and non-allergic) disease was a significant risk factor in GA Medicaid but was not in the commercial population. Dermatitis (allergic and non-allergic) was not a significant risk factor in either populations in the unadjusted analysis. Maternal asthma was a significant predictor for asthma development in the

univariate analysis and was consistent across both populations. In the univariate analysis, exposure to antibiotics before age one in GA Medicaid was protective. In the commercial population however, exposure to erythromycin and Cephalosporin increased the likelihood of an asthma diagnosis. Tables 4.4 and Table 4.6 report the mean and standard deviation for the number of episodes of URTI, anti-biotics by class for GA Medicaid and the commercial population. In the GA Medicaid population, the group that did not develop asthma had slightly level of exposure than groups that did develop asthma.

Adjusted hazard ratios (non-time dependent covariates) for the GA Medicaid and commercial populations after stratifying by gender are presented in Table 4.7 and 4.8. Adjusted hazard ratios for asthma development presented the same trend as the un-adjusted estimates. A diagnosis of dermatitis reduced the risk of an asthma diagnosis in both datasets while rhinitis was not significant in GA Medicaid. Allergic rhinitis and allergic dermatitis presented the same trend when investigated in a separate model for both datasets (Table 4.7 and Table 4.8). When rhinitis was investigated as 'the number of such infections' before asthma incidence there was no significant effect on asthma incidence in the commercial population cohort (HR=0.99, p=0.96) and was marginally risk increasing in GA Medicaid population (HR=1.02, $p < 0.01$). When the effect of allergic rhinitis and allergic dermatitis was investigated as the number of episodes, the HR in the commercial population was not significant (HR=1.01, HR=1.00). In GA Medicaid however the HRs for the number of AD and AR episodes was 0.87 and 0.93 ($p<0.01$).

Lower respiratory tract infections increased the risk of an asthma diagnosis for all four infections and infections such as Bronchiolitis almost doubled the risk of asthma (HR=2.27 in GA population and 2.29 in the commercial) as compared to children with no such infection. GERD was also a significant risk factor for an asthma diagnosis and increased the risk by as much as 50% in the GA Medicaid and 33% in the commercial population. Respiratory distress at birth and premature birth were significant risk factors for asthma as well across both datasets. An increase in the number of Azithromycin or Cephalosporin prescriptions in the first year of life

decreased the hazard of an asthma diagnosis as much as 20% and 10% respectively in GA Medicaid population (Table 4.7). Anti-biotic use however presented a contrasting picture in the commercial population with increasing erythromycin use increasing the hazard of an asthma diagnosis by as much as 13% (HR=1.13, 95% CI:1.08-1.18)

Maternal asthma increased the risk of asthma by 50-70% in both populations. In GA Medicaid both whites and being African-Americans were associated with an increased risk for asthma development compared to non-whites and non-black. Urban location was protective in GA Medicaid but living in a zip code with higher incomes was associated with an increased risk for asthma. In contrast to this, in the commercial population, urban location was associated with increased risk of asthma and increase in income was associated with lower risk of asthma (HR=0.83 to 0.88).

Table 4.9 presents the results of the analysis when rhinitis, dermatitis, sinusitis, Otitis media, para-influenza and all lower respiratory tract infections were modeled as time dependent variables (year of asthma diagnosis or censoring). In addition, the observation year was extended back by one year (12-month periods) with successive iterations. When Dermatitis and Rhinitis were taken into consideration in the year of asthma diagnosis or censoring, these risk factors increased the risk of an asthma diagnosis. However, when observation periods were extended back by 12 month periods, the hazard ratios for these risk factors and other LRTIs presented a decreasing trend.

In addition, the over all models for asthma incidence in GA Medicaid was estimated for patients for whom a mother-child link was established (N=106,576). The HR ratio for dermatitis and rhinitis was not effected by this sub-group analysis (HR=0.90, 0.97, $p<0.01$, $p=0.33$). The results were also robust for the other risk factors of interest in the study.

SENSITIVITY ANALYSIS

Sensitivity analysis was conducted to analyze the impact of change in the operational definition of risk factors on asthma diagnosis and also to assess the impact of change in asthma case definition itself.

Definition of Upper respiratory Tract Infections

Upper respiratory infections were defined as any diagnosis of rhinitis, sinusitis, UTRI (common-cold), para-influenza. In GA Medicaid population, HRs for upper respiratory infection was 1.04 (95% CI: 1.01 to 1.06). When a diagnosis of sinusitis was excluded from the above definition, the HR was 1.06 (95% CI: 1.03 to 1.08). In the commercial population, the HRs were 0.70 (95% CI: 0.72 to 0.81) for upper respiratory infections and when sinusitis was excluded from the upper respiratory infection definition the HR was 0.78 (95% CI: 0.73 to 0.82).

Expanding asthma case definition

There were 151,466(41.02%) asthma cases using the expanded asthma case in GA Medicaid. Of these, 111,143(30.09%) patients in GA Medicaid had a SABA prescription but did not develop asthma as per the asthma case definition. There were also 5,253 patients with an asthma diagnosis as per the original criteria who did not have SABA prior to or as part of their first asthma diagnosis flag. In the commercial population, 16,692 (27.10%) asthma cases were identified using the expanded definitions. 13,054 (21.19%) had a SABA prescription but did develop asthma as per the asthma original case definition. 900 (1.46%) patients with an asthma diagnosis as per original criterion did not have SABA prescription prior to their first asthma diagnosis flag. The HRs for a beta-agonist prescription presented the same trends as the HR for an asthma diagnoses in both populations. In the GA Medicaid population, HR for Dermatitis was (0.83(95% CI: 0.82 to 0.84)), for Rhinitis was (0.86(95%CI:0.84 to 0.87)). In the commercial population, in the same order, the HR were as follows: Dermatitis (0.70(95% CI: 0.66 to 0.73); Rhinitis (0.70 (95%CI: 0.70 to 0.79).

DISCUSSION

This study is among the very limited retrospective claims studies that seeks to understand the relationship between comprehensive childhood risk factors for asthma and asthma disease progression without a recall bias. This study utilized multiple criteria to identify asthma cases and even with a conservative case definition asthma incidence was as high as 11% in GA Medicaid and 6% in the commercial population. Asthma prevalence in pediatric population is estimated at 5-7% (Akinbami et al. 2002). The asthma incidence in GA Medicaid was much higher than this, which is in keeping with the nature of this population. While the impact of lower respiratory tract infections on the likelihood of an asthma diagnosis was consistent, the impact of conditions such as dermatitis, rhinitis, sinusitis and other upper respiratory tract infection was harder to quantify.

Conditions such as dermatitis, rhinitis, and Otitis media and upper respiratory tract infections, para-influenza presented contrasting pictures in the different datasets used. The results also varied depending on the way these conditions were modeled (non-time dependent vs. time-dependent variables). A diagnosis of dermatitis or allergic dermatitis seemed to protect against a diagnosis of asthma when modeled as a dichotomous non-time dependent variable when the dermatitis diagnosis preceded the asthma diagnosis in less than one year. The risk factors trended towards one the longer the period time between the risk factor diagnoses from the asthma diagnosis. This may suggest that AD and AR may influence asthma in the short term; however, if one dose not develop asthma soon after an AD or AR diagnosis, there does not appear to be an increased risk of asthma. While Rhinitis was marginally risk increasing when modeled as the number of episodes before an asthma diagnosis, it was generally not significant otherwise.

This suggests that the time of detection of these conditions and the number of such episodes is crucial for their effect on asthma. A recent study performed using retrospective claims data was able to establish a link between dermatitis and allergic rhinitis when modeled as time-dependent covariates. However, univariate risk ratios were not reported and asthma

incidence was high as 14% in this population which used one diagnosis code to establish asthma (Dik 2004). A drawback of using such time-dependent covariates may be that effect for AD or AR noted may be a result of patients seeking care for AD or AR leading to more interactions with the health care providers and therefore a better detection of asthma. This study attempts to establish a clear temporal link between atopic disease and asthma. However, this study is able to detect AD or AR before asthma only when patients (or parents) seek care for such conditions. Since parents may be more likely to seek care for asthma than for conditions such as AD or AR, it is possible that AD or AR is detected in this analysis after a diagnosis of asthma, which may not reflect the real life sequence. AD, AR and asthma were co morbid in 16% to 25% of the patients in this study when the temporal sequence was ignored. Conversely, it may also be that the onset of asthma drives atopic conditions such as AD or AR given their common etiology. Retrospective studies that have established an increased likelihood of an asthma diagnosis with conditions such as Otitis media, sinusitis, AD or AR do not seek to establish a clear temporal trend (von Mutius et al. 1999; Grupp-Phelan et al. 2001) or have other limitations such as recall bias (Jenkins 1994; de Marco 2000). This study was also able to establish a definite link between GERD and asthma development. While there have some studies that demonstrate that treatment of GERD alleviate asthma symptoms, this is first study that established a clear link between GERD and asthma incidence (Harding 1996).

The effect of anti-biotics was divergent between the GA Medicaid and the commercial populations. This was also the case for income and urban vs. rural location variables. Asthma prevalence is generally higher in an indigent population and in an urban location (Crain 2002; Levesque 2004). The results observed in this study actually provide evidence that asthma is a result of complex interactions between the environment and risk factors in early life and may present very different outcomes in different populations. Genetics, especially maternal asthma is an important risk factor for asthma development and was validated in this analysis. Since a child-mother link could not be established in more than 50% of the GA Medicaid population birth

cohort, the overall models were re-estimated for subjects where such a link could be established. The results were robust in this sub-group analysis.

There are a number of study limitations that must be addressed. Firstly, as mentioned before, different disease severity associated with AD or AR or asthma may drive patients differentially to seek care and therefore establishing a temporal relationship between these disease using retrospective claims data is a daunting task. However, this study is free from other problems such as recall bias. This study was also able to assess significant risk factors for asthma incidence in a comprehensive manner. This study utilized diagnosis codes for AR, AD and other conditions to define asthma risk factors. However, for conditions such as AR, sensitivity of such definitions is suspect. For instance, a retrospective claims study looking at prevalence of AR and other conditions noted that only 47% of patients with a prescription for agents used to treat AR had a diagnosis code for this condition (Crown2003). Also, very few patients (<50) in both populations had any tests for determining their allergic status and this may have led to an inclusion of false positives for Atopic Dermatitis and allergic rhinitis definitions. Smoking, allergen exposure and exposure to environmental contaminants such as animal dander significantly impacts the development of asthma and could not be controlled for in this analysis. In GA Medicaid, the claims volume (medical and prescription) for 1997 from October to December were below the average volume of claims observed for other periods, along with a minor discrepancy in 1998 medical claims file. This may have lead to missing some asthma cases or some risk factors in the GA Medicaid data. However, given the length of the study and the integrity of the remaining data, impact of this on the study findings is not of significant concern.

CONCLUSION

This study, which was an exploratory study, was able to demonstrate an increased risk of an asthma diagnosis associated with lower respiratory tract infections, GERD, and maternal asthma. While the impact of AD or AR on asthma incidence could not be clearly demonstrated, impact of these disease on asthma could not be refuted.

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FIGURE 4.1: Schematic outline for the GA birth AD/AR cohort (N=369,288)

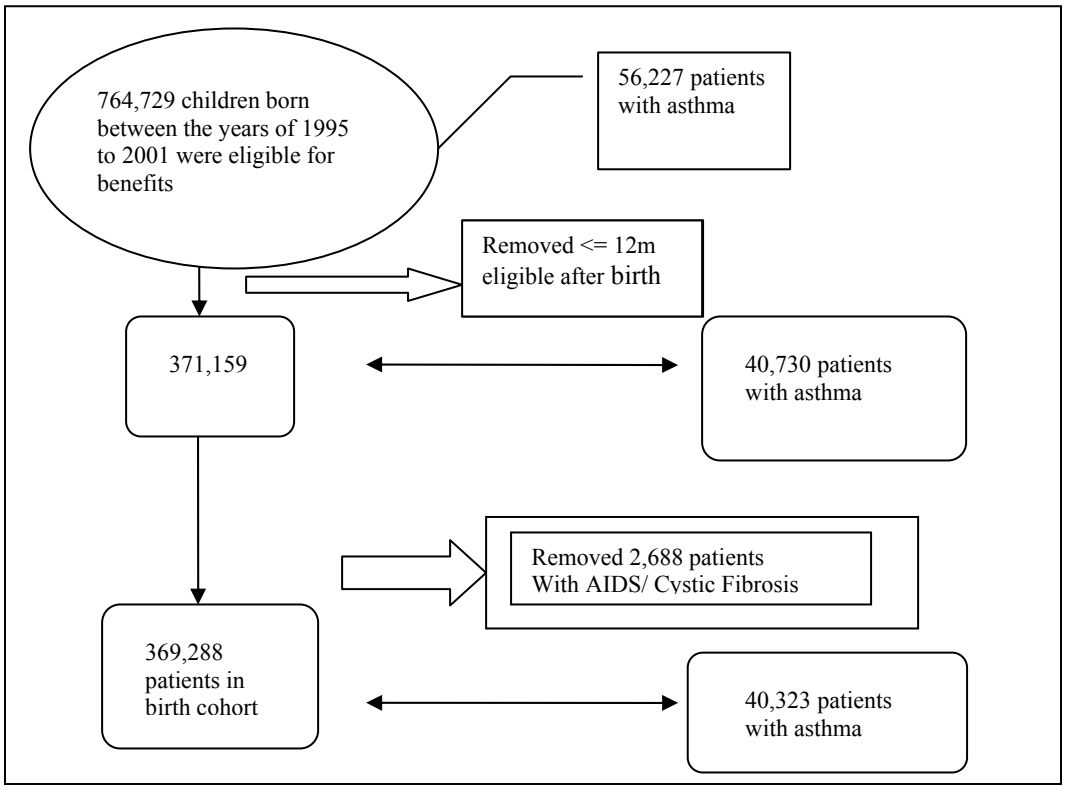

Figure 4.2: Schematic outline for the commercial population birth cohort (N=61,576)

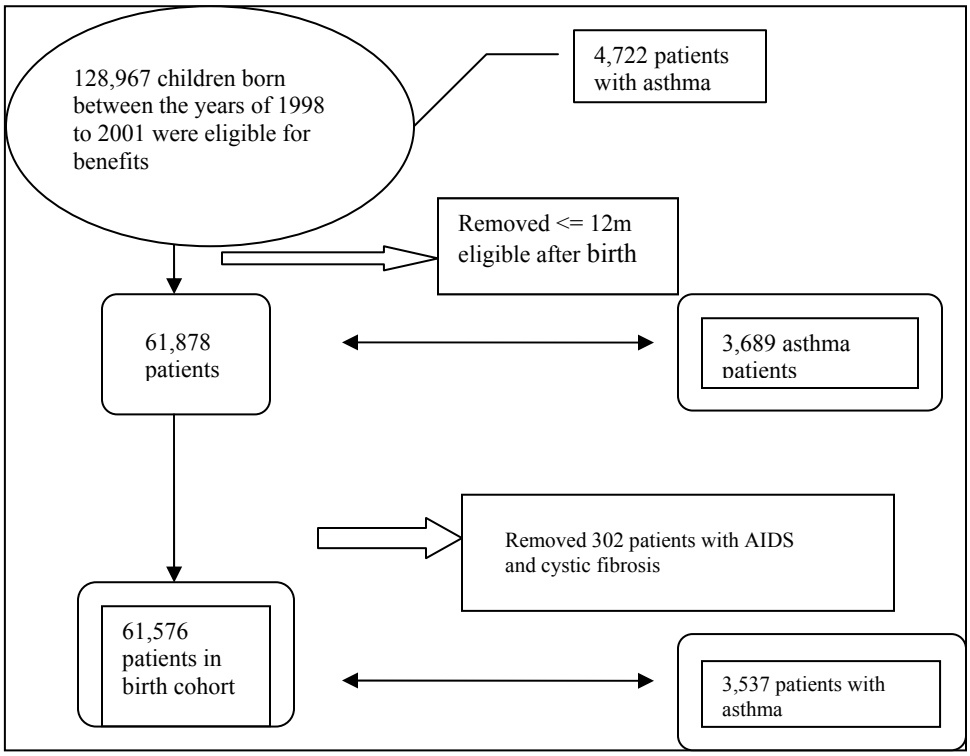

Table 4.1. Documented risk factors for asthma incidence

Risk factors for developing asthma	Strength of association, Odds ratio (95% CI)	Study
Atopy (Elevated IgE levels)	2.7 (1.3 to 5.8)	Plaschke 2000 (Sweden)
Sensitization to		
Any allergen	4.56 (3.16 to 6.57)	Arshad 2001(UK)
Cat dander	4.53 (2.60 to 7.88)	
Mites	7.6 (5.00 to 11.3)	
Food Sensitization	2.2 (0.7 to 6.2)	Illi 2001 (Germany)
Food sensitization +AR	11.1 (4.7 to 26.0)	Illi 2001
Allergic Rhinitis	4.9 (2.3 to 10.4)	Plaschke 2000
Atopic Dermatitis	2.4 (1.3 to 4.6)	Martinez 1995
Family history of asthma (maternal)	4.1 (2.1 to 7.9)	Martinez 1995 (Tucson , Arizona)
Paternal asthma	1.6 (1.0 to 2.4)	Jenkins 1994
Maternal asthma	1.9 (1.2 to 2.8)	Jenkins 1994
Pre-term delivery (< 36 weeks gestation)		
Females	2.6 (1.4 to 4.7)	Mutius1993
Females+ ventilatory support (to premature males ,no support)	3.3 (1.0 to 10.2)	
Smoking Mother	2.3 (1.2 to 4.4)	Martinez 1995 (Tucson , Arizona)
Sex		
Male Sex	1.9 (1.2 to 3.0)	Marinez1995
Urbanicity (compared to non-urban and non-poor)	1.44 (1.05 to 1.95)	Aligne2000
Respiratory synctial virus(RSV)	4.3 (2.2 to 8.7)	Stein 1999
Para-influenza	2.4 (0.8 to 7.4)	
Other agents (Not RSV or PI)	2.9 (1.1 to 7.8), $p < 0.01$	
Pneumonia	3.3 (1.4 to 7.8), $p < 0.01$	
Lower respiratory tract infection/ No pneumonia	2.4 (1.3 to 4.2) $p<0.02$	Castro-Rodriguez 1999

Table 4.2: Operation definitions for risk factors in GA Medicaid and the commercial population

Demographics (Sex and Race)
Year of birth
Maternal Asthma
Type of health plan for MarketScan data
Premature birth (ICD-9-Cm=765.1*)
Number of episodes/consultations for AD or AR
Respiratory difficulties at birth (ICD-9-CM=769)
Rhinitis (seasonal and perennial) (ICD-9-CM=477.*, 472.*)
Dermatitis (ICD-9-CM=691.* to 693.*, 708.*, 995.3)
Allergic Rhinitis (ICD-9-CM=477.*)
Atopic Dermatitis (ICD-9-CM=691.8, 692.9 and 373.3)
Diagnosis of measles (ICD-9-CM=055.*), mumps(ICD-9-CM=072.*), rubella(ICD-9-CM=056.*)
Diagnosis of Sinusitis (ICD-9-CM=461.*, 473.*) (McCaig2002)
Diagnosis of Otitis Media (ICD-9-CM=381.0, 381.4, 382.0, 382.4, 382.9) (McCaig2002)
Diagnosis of URTI (ICD-9-CM=460, 465.*), P.Influenza (ICD-9-M=487.**)
Diagnosis of Pneumonia (ICD-9-CM=480.** to 486.**), Bronchitis (ICD-9-CM=466.0, 490), RSV infection (ICD_9-CM=079.6*), Bornchilitis (ICD-9-CM=466.1* excluding 466.19)
Number of anti-biotic prescriptions belonging to the following classes 1) Azithromycin/ clarithromycin 2) Cephalosporin's 3) Erythromycins 4) Penicillin's 5) Quinolones 6) tetracycline's 7) Others in the first year of life (Mckeever2002)
Any diagnosis of GERD (ICD-9-CM= 530.1, 530.10, 530.11, 530.19, 530.3, 530.8, 530.81)
Season of birth (Fall, Spring, Summer, Winter)
Socio-economic index (using zip-code)

Table 4.3: Unadjusted risk ratios for an asthma diagnosis in the GA Medicaid population (N=369,288)

	Number with asthma	% Develop asthma	Unadjusted Relative Risks	95% Confidence Interval	*p-value*	Mean (STD) of months of follow-up for patients with risk factor who developed asthma
Sex						
Male (N=187,400)	24,368	13.00				9.84 (9.02)
Female (N=181,886)	15,955	8.77	0.78	(0.77, 0.79)	<0.01	10.72 (9.70)
Race						
White (N= 133,612)	14,775	11.06	1.00	(0.99, 1.02)	0.04	10.69 (9.82)
Black (N= 139,600)	19,555	14.01	1.32	(1.31, 1.34)	<0.01	9.32 (8.26)
Specific Medical Risk Factors						
Dermatitis (N=98,478)	10,145	10.30	0.93	(0.92, 0.95)	<0.01	12.50 (10.88)
Atopic Dermatitis (N= 93,530)	9,715	10.38				
Rhinitis (N=38,207)	4,375	11.45	1.05	(1.02, 1.08)	<0.01	13.36 (11.5)
Allergic Rhinitis (N=19,838)	2,131	10.74	0.98	(0.94, 1.02)	0.41	14.48 (12.27)
P-Influenza (N=5,286)	511	9.67	0.87	(0.79, 0.95)	<0.01	14.06 (12.70)
Pneumonia (N= 28,996)	5,719	19.72	2.00	(1.95, 2.06)	<0.01	11.59 (10.32)
Sinusitis (N= 31,198)	2,504	8.03	0.71	(0.68, 0.74)	<0.01	15.95 (12.51)
Bronchitis(N=61,368)	10,032	16.35	1.59	(1.56, 1.62)	<0.01	11.56 (10.39)
Otitis Media (N= 167,368)	15,686	9.37	0.84	(0.83, 0.85)	<0.01	12.94 (10.37)
RSV (N=2,510)	613	24.42	2.63	(2.41, 2.88)	<0.01	7.50 (6.13)
Premature Birth (N=27,779)	4,700	16.92	1.66	(1.61, 1.71)	<0.01	10.09 (8.59)
Bronchiolitis (N= 10,277)	2,701	26.28	2.90	(2.78, 3.03)	<0.01	7.95 (6.71)
Respiratory Distress (N=12,592)	2,592	20.98	2.11	(2.02, 2.20)	<0.01	10.19 (8.856)
GERD (N=27,286)	4,489	16.45	1.60	(1.56, 1.65)	<0.01	
MMR(N=158)	7	4.43	0.37	(0.17, 0.80)	0.08	18.14 (7.69)
Any URTI episode (N= 208,209)	23,788	11.42	1.05	(1.04, 1.06)	<0.01	11.20 (9.88)
Other Risk Factors						
Maternal asthma Unknown (N=262,712)	25,970	9.88	0.89	(0.88, 0.91)	<0.01	9.76 (7.96)
Maternal Asthma (N=22,775)	4,445	19.52	1.97	(1.92, 2.04)	<0.01	12.18 (10.99)
**Rural (N=106,627)	12,808	12.01				9.91 (9.02)
**Urban (N=261,229)	27,409	10.49	0.95	(0.94, 0.96)	<0.01	10.33 (9.44)
Any antibiotic exposure (N=110,415)	9,916	8.98	0.80	(0.79, 0.82)	<0.01	13.69 (10.53)
Any Azithromycin rx (N=33,926)	2,544	7.50	0.66	(0.63, 0.68)	<0.01	14.37 (9.61)
Any Cephalosporin rx (N= 68,658)	6,178	9.00	0.80	(0.79, 0.82)	<0.01	14.22 (10.82)

Any Other Rx (N=22,095)	1,739	7.87	0.69	(0.66, 0.73)	<0.01	15.46 (11.73)
Any Quinolones Rx (N=131)	2	1.53	0.12	(0.03, 0.51)	<0.01	16.5 (4.94)
Any Erythromycin Rx (N=24,570)	2,573	10.47	0.95	(0.91, 0.99)	0.02	13.70 (10.96)
Any Penicillin Rx (N= 1,410)	137	9.72	0.83	(0.73, 1.04)	0.15	14.10 (10.33)
Any Tetracycline Rx (N=61)	4	6.56	0.57	(0.21, 1.57)	0.27	18.75 (14.10)

^ Any risk factors includes a diagnosis of medical risk factor before an asthma diagnosis (or a beta-agonist prescription) or a prescription for any antibiotics before age one

** Could not be determined for 1,430 patients

Table 4.4: Comparisons of means and std between groups that develop asthma and that are asthma free at the end of study period for GA Medicaid population

	Did not develop asthma (N=328,965)	Developed asthma (N=40,323)	*p-value*
	Mean (STD)	Mean (STD)	
Number of URTI episodes	1.54 (2.22)	1.49 (1.98)	<0.01
Number of Azithromycin rxs	0.12 (0.45)	0.08 (0.37)	<0.01
Number of Cephalosporin rxs	0.30 (0.753)	0.23 (0.67)	<0.01
Number of Other rxs	0.08(0.387)	0.05 (0.29)	<0.01
Number of Erythromycin rxs	0.08 (0.34)	0.07 (0.33)	0.01
Number of Penicillin rxs	0.007 (0.23)	0.007 (0.20)	0.62
Number of Tetracycline rxs	0.0002 (0.05)	0.0002 (0.00)	0.23

Table 4.5: Unadjusted risk ratios for an asthma diagnosis in the commercial population (N=61,576)

	Number with asthma	% Develop asthma	Unadjusted Relative Risks	95% CI	*p-value*	Mean (STD) of months of follow-up for patients with risk factor who developed asthma
Sex						
Male (N=31,685)	2,398	7.57				10.47 (8.12)
Female (N=29,891)	1,240	4.15	0.68	(0.66, 0.72)	<0.01	11.91 (9.05)
Specific Medical Risk Factors						
Dermatitis (N= 10,364)	543	5.24	0.88	(0.81, 0.95)	0.18	15.23 (9.70)
Rhinitis (N= 4,801)	241	5.02	0.84	(0.74, 0.95)	<0.01	15.31 (10.38)
Allergic Dermatitis (N=9,277)	510	5.49	0.91	(0.84, 0.99)	0.04	15.43 (9.87)
Allergic Rhinitis (N=3,063)	152	4.96	0.83	(0.70, 0.97)	0.02	15.47 (8.85)
P-Influenza (N= 1,033)	49	4.74	0.79	(0.59, 1.05)	0.10	16.04 (9.94)
Pneumonia (N= 3,084)	381	12.35	2.24	(2.03, 2.48)	<0.01	13.71 (9.68)
Sinusitis (N= 6,681)	246	3.68	0.60	(0.54, 0.68)	<0.01	16.39 (9.54)
Bronchitis(N= 7,106)	595	8.37	1.45	(.35, 1.57)	<0.01	13.32 (9.50)
Otitis Media (N= 31,799)	1,537	4.83	0.80	(0.77, 0.84)	<0.01	13.84 (8.96)
RSV(N=245)	30	12.24	2.22	(152, 3.25)	0.01	10.53 (6.74)
Premature Birth(N=3,200)	358	11.19	2.00	(1.81, 2.22)	<0.01	10.61 (7.57)
Bronchiolitis (N=1,088)	155	14.25	2.64	(2.24, 3.13)	<0.01	10.01 (7.46)
Respiratory Distress (N=1,452)	184	12.67	2.31	(1.98, 2.68)	<0.01	10.34 (8.05)
GERD (N=2,954)	262	8.87	1.54	(1.37, 1.75)	<0.01	11.45 (8.47)
MMR (N=10)	0	0	na			10.96 (8.48)
Any URTI episode (N=31,481)	1,725	5.47	0.92	(0.89, 0.95)	<0.01	12.89 (8.99)
Other Risk Factors						
Maternal Asthma (N=7,133)	686	9.62	1.69	(1.58, 1.82)	<0.01	11.43 (8.84)
Rural (N= 16,117)	886	5.50			0.05	9.70 (7.57)
Urban (N=34,126)	2,016	5.91	0.99	(0.97,1.03)	0.99	10.11 (8.67)
Any antibiotic exposure (N=34,172)	2,285	6.68	1.14	(1.11, 1.17)	<0.01	11.48 (8.24)
Any Penicillin Rx (N=29,887)	1,893	6.33	1.07	(1.04, 1.11)	0.01	11.94 (8.35)
Any B-Lactam antibiotic Rx (N=687)	29	4.22	0.70	(0.48, 1.01)	0.05	11.48 (8.54)
Any Cyclosporin Rx (N=11,611)	754	6.49	1.10	(1.03, 1.18)	0.20	12.41 (8.511)
Any Erythromycin Rx (N= 10,237)	774	7.56	1.30	(1.22, 1.39)	<0.01	11.66 (8.23)
Any Anti-infective Rx (N=1,374)	97	6.91	1.18	(0.96, 1.45)	0.10	11.53 (8.17)

Any Tetracycline Rx (N=126)	4	3.17	0.52	(0.19, 1.41)	0.17	14.25 (4.85)

Table 4.6: Comparisons of means and std between groups that develop asthma and that are asthma free at the end of study period for the commercial population (N=61,576)

	Did not develop asthma (N=59,938)	Developed asthma (N=3,638)	*p-value*
	Mean (STD)	Mean (STD)	
Number of URTI episodes	2.77 (2.85)	3.03 (3.32)	<0.01
Number of anti-infectives	0.03 (0.22)	0.03 (0.23)	0.26
Number of Cephalosporin rxs	0.32 (0.85)	0.33 (0.79)	0.75
Number of B-Lactam antibiotics Rxs	0.01 (0.15)	0.01 (0.12)	0.06
Number of Quinolone rxs			
Number of Erythromycin rxs	0.23 (0.64)	0.30 (0.68)	<0.01
Number of Penicillin rxs	1.03 (1.55)	1.02 (1.44)	0.84
Number of Tetracycline rxs	0.01 (0.07)	0.01 (0.03)	0.13

Table 4.7: Hazard Ratios (with 95% CI) for an asthma diagnosis in the GA Medicaid population (model with no time –dependent covariates) (N=369,288)

Variables	Hazard Ratios	95% Confidence Intervals	*p-value*
Medical Risk factors			
Dermatitis	0.90	(0.87, 0.91)	p<0.01
Rhinitis	1.02	(098, 1.05)	0.18
Atopic Dermatitis*	0.91	(0.89, 0.92)	p<0.01
Allergic Rhinitis*	0.95	(0.91, 0.98)	0.03
Atopic Dermatitis and related conditions (ICD-9-CM='691')^	0.92	(0.89, 0.94)	p<0.01
Contact Dermatitis and other Eczema (ICD-9-CM='692')^	0.85	(0.82, 0.87)	p<0.01
Dermatitis due to substances taken internally (ICD-9-CM='693')^	1.07	(0.94, 1.21)	0.31
Urticaria including allergic and idiopathic (ICD-9-CM='708')^	0.73	(0.65, 0.81)	p<0.01
Contact and allergic dermatitis of the eyelid (ICD-9-CM='373.3')^	0.63	(0.34, 1.13)	0.19
Allergy, unspecified (ICD-9-CM='995.3')^	0.80	(0.73, 0.87)	p<0.01
Rhinitis (ICD-9-CM='472')^	1.05	(1.01, 1.09)	0.01
Allergic Rhinitis (ICD-9-CM='477')^	0.92	(0.88, 0.96)	p<0.01
P-Influenza	0.72	(0.65,0.78)	0.03
Pneumonia	1.66	(1.61, 1.70)	p<0.01
Sinusitis	0.66	(0.63, 0.68)	p<0.01
Bronchitis	1.53	(1.49, 1.56)	p<0.01
Otitis Media	0.69	(0.67, 0.70)	p<0.01
RSV	1.46	(1.34, 1.58)	p<0.01
Premature Birth	1.32	(1.27,1.36)	p<0.01
Bronchiolitis	2.27	(2.18,2.36)	p<0.01
Respiratory Distress	1.45	(1.38,1.51)	p<0.01
GERD	1.50	(1.45,1.54)	p<0.01
MMR	0.41	(0.19,0.86)	p<0.01
Number of URTI episodes	0.96	(0.95,0.96)	p<0.01
Number of Penicillin Rxs	0.98	(0.93,1.01)	0.32
Number of Cephalosporin Rxs	0.90	(0.88,0.91)	p<0.01
Number of Azithromycin Rxs	0.81	(0.79, 0.83)	p<0.01
Number of Erythromycin Rxs	0.93	(0.90,0.95)	p<0.01
Number of Missc. Rxs	0.84	(0.81,0.86)	p<0.01
Number of Quinolone Rxs	0.20	(0.05,0.74)	0.01
Number of Tetracycline Rxs	0.69	(0.26,1.78)	0.43
Demographic and other factors			

Maternal asthma Unknown	0.99	(0.96, 1.01)	0.53
Maternal Asthma known	1.52	(1.46,1.57)	p<0.01
Year of birth	0.97	(0.95, 0.96)	p<0.01
Race (White)	1.74	(1.70, 1.77)	p<0.01
Race (African American)	1.85	(1.85, 1.92)	p<0.01
Location (Urban)	0.91	(0.88,0.93)	p<0.01
Season of birth (Winter)	0.99	(0.96,1.01)	0.50
Season of birth (Summer)	1.07	(1.04,1.09)	p<0.01
Season of birth (Spring)	1.03	(1.00,1.05)	0.02
Income category one ($20,000- $50,000)	1.17	(1.09, 1.25)	p<0.01
Income category two (> $50,000)	1.12	(1.04, 1.21)	p<0.01

* In separate models, ^ In separate models

Table 4.8: Hazard Ratios (with 95% CI) for an asthma diagnosis in the commercial population (model with no time –dependent covariates) (N=61,576)

Variables	Hazard Ratios	95% Confidence Intervals	p-value
Specific Medical Risk Factors			
Dermatitis	0.85	(0.77,0.93)	p<0.01
Rhinitis	0.86	(0.75, 0.98)	0.03
Allergic Dermatitis*	0.89	(0.81, 0.97)	0.02
Allergic Rhinitis*	0.85	(0.72, 0.99)	0.05
Atopic Dermatitis and related conditions (ICD-9-CM='691')^	1.01	(0.89, 1.13)	0.89
Contact Dermatitis and other Eczema (ICD-9-CM='692')^	0.87	(0.76, 0.99)	0.04
Dermatitis due to substances taken internally (ICD-9-CM='693')^	0.97	(0.65,1.44)	0.89
Urticaria including allergic and idiopathic (ICD-9-CM='708')^	0.52	(0.36, 0.73)	p<0.01
Contact and allergic dermatitis of the eyelid (ICD-9-CM='373.3')^	2.56	(0.63,10.25)	0.18
Allergy, unspecified (ICD-9-CM='995.3')^	1.08	(0.80, 1.45)	0.58
Rhinitis (ICD-9-CM='472')^	0.88	(0.72, 1.07)	0.20
Allergic Rhinitis (ICD-9-CM='477')^	0.87	(0.73, 1.02)	0.09
P-Influenza	0.73	(0.54, 0.96)	0.03
Pneumonia	1.92	(1.71, 2.14)	p<0.01
Sinusitis	0.55	(0.48, 0.62)	p<0.01
Bronchitis	1.39	(1.26,1.52)	p<0.01
Otitis Media	0.59	(0.55, 0.62)	p<0.01
RSV	1.47	(1.00, 2.14)	0.04
Premature Birth	1.63	(1.43,1.85)	p<0.01
Bronchiolitis	2.29	(1.92, 2.72)	p<0.01
Respiratory Distress	1.38	(1.16,1.64)	p<0.01
GERD	1.33	(1.17, 1.51)	p<0.01
Any URTI episode	0.99	(0.98,1.00)	0.38
Number of Penicillin Rx	1.02	(0.99, 1.04)	0.25
Number of B-Lactam antibiotics Rx	0.71	(0.53, 0.95)	0.02
Number of Cyclosporin Rx	1.02	(0.97, 1.06)	0.36
Number of Erythromycin Rx	1.13	(1.08, 1.18)	p<0.01
Number of Anti-infective Rx	1.02	(0.89, 1.17)	0.74
Number of Tetracycline Rx	0.47	(0.19, 1.11)	0.09
Demographic and other factors			
Maternal Asthma	1.7	(1.56,1.85)	p<0.01
Location (Urban)	1.22	(1.06, 1.40)	p<0.01
Year of birth	0.88	(0.84, 0.91)	p<0.01

Plan type- Comprehensive	0.91	(0.83, 1.00)	0.07
Plan type - POS capitated with PCP	0.9	(0.82, 0.98)	0.03
Plan type - PPO	0.81	(0.72, 0.90)	p<0.01
Season of birth (Winter)	0.95	(0.85, 1.05)	0.39
Season of birth (Summer)	0.97	(0.89, 1.05)	0.49
Season of birth (Spring)	1	(0.92, 1.09)	0.91
Income category one ($20,000-$50,000)	0.83	(0.75, 0.92)	p<0.01
Income category two (> $50,000)	0.88	(0.76, 1.00)	0.07

* In separate models, ^ In separate models

Table 4.9: Hazard Ratios (with 95% CI) for Asthma in GA Medicaid and the commercial population (model with time –dependent covariates)^

	For GA Medicaid		For MarketScan data	
	HR	95% CI	HR	95% CI
1-Year Look Back				
Dermatitis	2.37	(2.30, 2.44)	1.29	(1.13, 1.48)
Rhinitis	1.36	(1.28, 1.43)	1.06	(0.88, 1.26)
P-Influenza	1.29	(1.15, 1.43)	1.72	(1.19, 2.48)
Pneumonia	2.28	(2.20, 2.36)	3.45	(3.01, 3.96)
Sinusitis	0.84	(0.80, 0.88)	0.54	(0.45, 0.65)
Bronchitis	2.87	(2.79, 2.94)	2.70	(2.41, 3.02)
Otitis Media	1.46	(1.42, 1.49)	1.38	(1.27, 1.50)
RSV	1.97	(1.79, 2.15)	2.12	(1.33, 3.38)
Bronchiolitis	3.80	(3.62, 3.98)	4.77	(3.86, 5.88)
Any URTI episode	4.57	(4.46, 4.67)	2.02	(1.86, 2.19)
2-Year Look Back				
Dermatitis	1.18	(1.15, 1.20)	1.16	(1.02, 1.31)
Rhinitis	1.08	(1.03, 1.13)	1.07	(0.89, 1.28)
P-Influenza	0.92	(0.84, 1.00)	0.87	(0.59, 1.27)
Pneumonia	2.07	(2.01, 2.12)	1.65	(1.38, 1.96)
Sinusitis	0.74	(0.71, 0.77)	0.73	(0.61, 0.87)
Bronchitis	1.90	(1.85, 1.94)	1.63	(1.43, 1.85)
Otitis Media	0.87	(0.85, 0.89)	0.84	(0.76, 0.92)
RSV	1.57	(1.44, 1.70)	1.98	(0.92, 4.25)
Bronchiolitis	2.82	(2.70, 2.93)	2.98	(2.10, 4.23)
Any URTI episode	1.32	(1.29, 1.34)	1.05	(0.97, 1.42)
3-Year Look Back				
Dermatitis	0.83	(0.80, 0.86)	0.93	(0.83, 1.04)
Rhinitis	0.92	(0.86, 0.99)	0.95	(0.80, 1.13)
P-Influenza	0.79	(0.68, 0.91)	0.64	(0.44, 0.93)
Pneumonia	1.48	(1.41, 1.56)	1.41	(1.19, 1.66)
Sinusitis	0.72	(0.71, 0.77)	0.59	(0.50, 0.70)
Bronchitis	1.10	(1.06, 1.14)	1.21	(1.06, 1.36)
Otitis Media	0.63	(0.61, 0.65)	0.51	(0.46, 0.56)
RSV	0.44	(0.29, 0.67)	2.48	(1.15, 5.32)
Bronchiolitis	0.61	(0.51, 0.72)	3.13	(2.25, 4.34)
Any URTI episode	0.70	(0.68, 0.71)	0.73	(0.67, 0.79)

^ Adjusted for all other covariates

CHAPTER 5

TREATMENT EFFECTS OF ANTI-HISTAMINES AND INTRANASAL STEROIDS ON ASTHMA INCIDENCE IN A PEDIATRIC ATOPIC POPULATION [1]

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ABSTRACT

INTRODUCTION: Asthma is a chronic pediatric disease, has been increasing in prevalence in the last decade. Atopic diseases such as allergic rhinitis (AR) and atopic dermatitis (AD) are significant risk factors for asthma incidence and present opportunities for the tertiary prevention of asthma. The study objective was to estimate the effect of exposure to first generation antihistamines (FGAH), second generation anti-histamines (SGAH), intra-nasal steroids (INS), cromolyns (CM) or a combination of these on asthma incidence for children diagnosed with AD or AR. Impact on asthma incidence was also examined by levels of exposure for these medication classes as compared to no exposure and between the exposure groups themselves.

METHODS: GA Medicaid data from 1995 to 2001 and MarketScan (commercial) data from 1998 to 2001 were utilized in this study. Continuously eligible newborn children with a diagnosis of allergic disease with an atopic diathesis {atopic dermatitis (ICD-9-CM=691.8, 692.9 and 373.3) OR any ICD-9-CM diagnosis code for allergic rhinitis (ICD-9-CM=477.**)} were studied. Children were excluded if they had any diagnosis of HIV/AIDS and or cystic fibrosis, a prescription for an asthma medication or a diagnosis for asthma prior to their first AD or AR diagnosis. The cumulative exposure to FGAH, SGAH and INS was recorded from birth until an asthma diagnosis was established or until subjects were censored. Cox Proportional Hazards models along with sample selection methods were used to explore the impact of FGAH, SGAH and INS on asthma incidence.

RESULTS: 79,957 patients were included in the GA Medicaid AD/AR cohort, of which 6,771 patients developed asthma (asthma incidence of 8.46%). There were 16,051 in the primary AD/AR commercial cohort of which 642 patients developed asthma leading to an asthma incidence of 3.44 % in the commercial AD/AR cohort. There were 26,352 patients in the GA and 10,787 patients in the commercial AD/AR cohort with no exposure to FGAH, SGAH and INS.

The HRs for the intent to treat analysis in GA Medicaid for any FGAH was 0.68 (95% CI: 0.65 to 0.70), for SGAH was 0.42 (95% CI: 0.37 to 0.47) and for any exposure was 0.67(0.64 to 0.69). In commercial AD/AR cohort the HRs for any exposure to FGAH was 1.57 (95%CI: 1.37 to 1.87) and was 0.94 (0.68 to 1.28) for any SGAH and was 1.52 (1.27 to 1.81) for any exposure. In the GA Medicaid cohort, exposure to all anti-inflammatory agents (as compared to no exposure) reduced the likelihood of a diagnosis of asthma as much as 92% (HR=0.08 , 95%CI: 0.04 to 0.14). For the commercial AD/AR cohort however, exposure to only FGAH was associated with an increase in the diagnosis of an asthma by 64% (HR=1.64 (1.37, 1.95)). Exposure to all (FGAH and SGAH and INS) was, however, significantly protective against an asthma diagnosis in the commercial AD/AR cohort. In GA Medicaid, exposure to FGAH, SGAH or INS was protective regardless of dose while the results were non conclusive in commercial data. Impact of these agents on asthma incidence (with an expanded asthma case definition) was however protective in both cohorts.

CONCLUSIONS: The results of this study suggest that FGAH, SGAH and INS may play a role in the tertiary prevention of asthma at least in an indigent AD/AR population. In a commercial population, impact on asthma incidence was mixed. Randomized trials using a combination of pharmacologic and non-pharmacologic interventions against asthma development are needed before treatment guidelines can be formulated.

Keywords: Asthma, Atopic dermatitis, Allergic Rhinitis, first and second generation anti-histamines, nasal steroids, risk factor, treatment

INTRODUCTION

Atopic diseases such as asthma, atopic dermatitis and allergic rhinitis have seen a world-wide increase in prevalence in the last decade. Asthma prevalence has increased by an average of 4.3% per year from 1980 to 1995 in children from ages 0 to 17 years (Akinbami 2002) making it the most common chronic pediatric disease. Coinciding with the temporal increase in asthma

prevalence, there has also been rapid increases in prevalence among other atopic disease mainly food allergy, allergic rhinitis (AR) and atopic dermatitis (AD) (Weiss 2001; TePas 2000). Investigations of asthma risk factors have implicated atopy as one of the most important predictors for the development of asthma (Weiss 1998; Wood 2002). Atopy is a genetic tendency to mount IgE antibodies in response to inhaled allergens. Atopic dermatitis (AD), allergic rhinitis (AR) and asthma are the clinical definitions of atopic illness and the progression of atopic diseases from AD to AR to asthma is often referred to as the atopic march (Asher 2000; MacLean 2001).

These atopic diseases also have in common one or more mechanisms of the allergic inflammatory process and often present as a sequence of one another. Mediators from the nose and or sinuses via blood or postnasal drip spread to the lower respiratory tract and cause inflammation of the airways (Simons 1999). Chronic airway inflammation aggravated by repeated exposure to allergens is an early and persistent part of asthma. Airway markers of inflammation also correlate with bronchial hyperresponsivness and airway inflammation, hyperresponsiveness are important in the pathogenesis of the asthma syndrome and the clinical severity of the disease (Chiappara 2001; NHLBI 1997(2)). The other link between AR and asthma is the neural or nasobronchial reflex such that nasal allergen challenge results in bronchial hyperreponsiveness (Larsen 2001). AD and AR have also been established as risk factors for asthma in numerous observational studies (Martinez 1995; Plaschke 2000) and in one retrospective claims study (Dik 2004). The link between allergic rhinitis and asthma is also supported by evidence, which indicates that 75% of patients with both disease experience onset of the other disease within two years of the first (Pederson 1983). Onset of asthma was strongly associated with allergic rhinitis (OR =5.7, CI=2.2-14.6) among atopics (defined using skin prick test) and also among non-atopics (OR=3.5, CI=0.9-13.5) (Plaschke2000).

Since the inflammatory process in AD, AR and asthma share some common elements and especially because AD and asthma may be considered to represent extreme ends of a spectrum of inflammation, control of inflammation at an early stage may control injury to the airways and therefore prevent serious consequences such as asthma. Evidence suggests that early intervention with anti-inflammatory therapies may modify the asthma disease process by controlling inflammation, hyperresponsivness associated with asthma at an early stage (NHLBI 1997(2)). Evidence for a possible prevention of asthma also comes from at least 4 randomized clinical trials which have demonstrated that early intervention in the atopic march from atopic dermatitis (AD) and or allergic rhinitis (AR) to asthma using agents that have a biological capacity to interfere with the allergic cascade can prevent or delay asthma onset by targeting high-risk infants (Iikura 1992; Warner 2001; Moller 2002; Grembiale 2000). Agents used in these clinical trials were limited to immunotherapies (for AR only) and second generation antihistamines (evaluated in infants suffering from AD in two trials). Effect of other allergic anti-inflammatory medications such as first-generation antihistamines, corticosteroids, cromolyns or combination therapies example: second generation antihistamines and steroids commonly used in clinical practices have not been evaluated in high-risk groups in a real world setting.

The study objective was to estimate the effect of exposure to first generation antihistamines (FGAH), second generation anti-histamines (SGAH), intra-nasal steroids (INS), cromolyns (CM) or a combination of these on asthma incidence for children diagnosed with AD or AR. Impact on asthma incidence was also examined by contrasting levels of exposure to these medications as compared to no exposure.

METHODS

Data Sources

Data from GA Medicaid from 1995 to 2001 and MarketScan database from 1998 to 2001 were utilized. The GA Medicaid data describes all adjudicated claims for GA Medicaid eligible

beneficiaries including all institutional, outpatient and prescription claims, which is patient linked to program eligibility information. Children may qualify for Medicaid services under the following categories 1) Right From the Start Medicaid (RSM adults) for pregnant mothers. 2) Right from the start Medicaid (RSM Children): Children are covered up to age 18 depending on age and income level. 3) Pregnant Women, infants and children medically needy: If the pregnant women /children do not qualify for Medicaid because of family resources but meets this limit due to medical spend down. The GA Medicaid data from 1998 to 2001 contained an additional variable that provided a potential link between mother child pairs. This information was used in GA Medicaid to build mother-child linkages.

The MarketScan data is a commercial claims and encounter database, which contains the healthcare experience of approximately seven million individuals (annually) who are covered under a variety of health plans. Data from MarketScan form the commercial population. Data from January 1998 to December 2001 were acquired and provided access to all medical claims, drug data (approximately 2.6 million covered lives) and enrollment details for the working population and their dependents. The data are organized into these major files: 1) patient and demographic information 2) health plan features 3) financial information 4) inpatient and outpatient medical information 5) drug information 6) enrollment information. A unique scrambled patient identifier is encoded for each record in all of the above files in both datasets that facilitates linkage. In addition, the MarketScan data base also has in-built variables that flag family units which were used to establish the child-mother linkage. All of the data was examined for consistency and outliers. The GA Medicaid data and the MarketScan data has used before in studying asthma and other epidemiological studies and has been found to valid and consistent (Martin 2001; Crown 2003). The analysis was done in parallel for the two datasets.

Study Population

Inclusion of children with a diagnosis of allergic disease with an atopic diathesis into the AD/AR primary cohorts was based on the following scheme:

-Born between January1995 to October2001 for GA Medicaid and January1998 to October2001 for MarketScan/commercial data.

-Between January1995 to December2001 in GA Medicaid and January1998 to December 2001 in commercial data have a diagnosis of the following:

-Any ICD-9-CM diagnosis code for atopic dermatitis (ICD-9-CM=691.8, 692.9 and 373.3) (Ellis 2002) OR

-Any ICD-9-CM diagnosis code for allergic rhinitis (ICD-9-CM=477.**) (Crystal-Peters 2002)

-Continuously eligible from birth until a diagnosis of AD or AR.

Patients were excluded from the ADAR primary cohort based on the following criteria

-Diagnosis of HIV/AIDS and or cystic fibrosis

-A prescription for an asthma medication or a diagnosis for asthma prior to their inclusion in the primary cohort

- Patients who died before their inclusion in the AD/AR cohort

Measuring exposure to anti-inflammatory agents

The main agents of interest in this study were first generation anti-histamines (FGAH), second generation anti-histamines (SGAH) and intra-nasal steroids (INS) and cromolyns (CM) which were recorded from the outpatient prescription files as in Table 5.1. All cough and cold medication were screened to include those which contained FGAH. These combination products were included if they contained at least one of the active ingredients listed in Table 5.1. Since the sample sizes for CM were very small in both populations (<100), this exposure category was dropped from all further analysis. The cumulative exposure to FGAH, SGAH and INS was

recorded as the sum of the 'days supply' variable from birth until an asthma diagnosis was established or until subjects were censored. In some cases, subjects in the AD/AR cohorts received a prescription for a short acting beta-agonist (SABA) prior to their first asthma diagnosis flag and that was not a part of the asthma diagnosis. In these instances, the date of receipt of this prescription was the end date of the observation period for these subjects. In patients who received a SABA prescription but did not develop asthma, the date of receipt of the SABA prescription was the recorded end date for these patients.

As-treated approach

Impact of exposure to FGAH, SGAH and INS was analyzed on asthma outcome in an as treated analysis. In the first comparison, exposure levels or dose levels were ignored and subjects included in the primary cohort were classified into one unique exposure category ranging from no-exposure to exposure to all drug classes. The seven mutually exclusive exposure categories were as follows: I) Single agent exposure only: Exposure category 1) FGAH 2) SGAH 3) INS II) Dual agent exposure only: Exposure category 4) FGAH+ SGAH 5) FGAH+INS 6) SGAH+INS III) Exposure to all: Exposure category 7) FGAH+SGAH+INS. Groups with exposure to the study drugs or any combination of the study drugs were compared individually in separate analyses to the group with no exposure to any of these agents. For example: Single agent exposure (FGAH only) vs. no exposure or Dual agent exposure (FGAH+SGAH only) vs. no exposure. Groups with exposure to one study drug or study drug combinations were also compared to groups with different exposure to study drugs, for example: Single agent exposure only to dual exposure or SGAH only vs. SGAH+INS (Table 5.2). The second level of comparison was based on the cumulative exposure to these agents in the study period. Based on the distribution of use of these agents in the AD/AR cohorts an exposure level below or equal to 10 days in the entire study period was ignored. Exposure days greater than 10 but less than 60 days was classified as low exposure and exposure days greater than 60 were classified as high exposure. Subjects in the cohorts were again reclassified into one unique exposure category

based on this interaction of dose level and exposure category. For instance: Low exposure FGAH only, High Exposure FGAH and such. The categories were as follows: I) Six Single exposure categories (Low FGAH only, High FGAH only, Low SGAH only and so on) II) Twelve Dual Agent exposure (Low FGAH and Low SGAH only, High FGAH and High SGAH only and so on) III) Eight Exposure to all category (Low FGAH and Low FHA and Low INS and so on). Comparisons were then made between these exposure categories and no exposure to any agent. The comparisons were made contingent upon sufficient sample size for each exposure category.

Intent to treat analysis

In the intent to treat analysis exposure to FGAH, SGAH and INS was explored as any exposure to these agents. The comparator groups in these analyses were groups with no exposure to agent of interest. For instance: exposure to FGAH as the cumulative days supply vs. no exposure to FGAH and so on.

Cumulative exposure to all agents

Exposure to FGAH, SGAH and INS was also explored as the cumulative exposure (in days supply) to all agents in a separate analysis on asthma outcome.

Measurement of Outcomes

Asthma in the AD/AR primary cohort was defined as follows:

-One-inpatient claim with a primary (first listed) or secondary ICD-9-CM code for asthma (ICD-9-CM=493.**) (Lozano 1997) OR

-Two outpatient claims with a primary or secondary ICD-9-CM code for asthma (ICD-9-CM=493.**) not separated by more than 365 days, since one outpatient diagnosis might represent a rule out diagnosis (Nash 1999) OR

-An outpatient diagnosis for asthma and two or more prescriptions belonging to separate asthma medication class or two or more medications for the same class separated by at least 30 days in any 365 day period (Leone 1999).

The asthma medications for this study were broadly divided into: 1) Adrenergic bronchodilators 2) Leukotriene inhibitors 3) Other Respiratory inhalants 3) Anti-asthmatic combinations 5) Methyxanthines 6) Oral corticosteroids 7) Inhaled corticosteroids.

Drug markers have been used in isolation to identify asthma cases (Nash et al. 1999). Drugs used to control asthma symptoms such as beta-agonist show high specificity, but specificity of some other asthma medication classes is low (Himmel 2001). For example, cromolyns and now leukotriene inhibitors are used to treat asthma and AR. Therefore using diagnostic information concurrently with drug markers was used to increase specificity, recognizing the trade-off that some asthma cases may be missed.

Other Covariates

Other covariates that were controlled for in the first stage of the sample selection model and subsequent model are listed in Table 5.3.Maternal asthma was an additional important variable that was included when modeling asthma incidence but was not included in the sample selection models. Maternal asthma was defined an outpatient or inpatient diagnosis for asthma (ICD-9-CM='493.**') or two or more prescriptions for asthma (excluding oral steroids) not separated by more than 365 days. In GA Medicaid a mother to child link (case number) was available in the claims data from 1998 to 2001. This information was then retrospectively applied to claims data from 1995 to 2001 to establish a tentative mother to child link. Using this link and the pregnancy diagnosis and procedural codes for delivery an attempt was made to confirm a mother to child tie for every child in GA Medicaid AD/AR cohort. Since, it is possible that such a tie may not be established for all the subjects included in the GA cohort, maternal asthma status was defined using two variables. For subjects in the GA Medicaid cohort where mother-child status could be established, mother diagnosed as 'not asthmatics' were the reference group (Maternal asthma Unknown=1; 0 otherwise and Mother with asthma=1; 0 otherwise). The commercial data has an in built variable to identify member of a family unit. Using this variable

and pregnancy diagnosis and procedural codes for delivery, a mother-child link was again confirmed in the commercial data.

In addition, other risk factors such as premature delivery, respiratory complications requiring mechanical ventilation, race/ethnicity, and socio-economic index i.e.: urban vs. rural location and median income were controlled for in all of the multivariate analysis. This information was obtained by linking the patient's zip code to the information at the US census web site (www.census.gov). Season of birth for the patients in the cohort were classified into four categories namely fall, spring, summer and winter and controlled for in the multivariate analysis. In addition other covariates such as plan-type in the commercial data were also controlled for in the analysis.

Analysis

Treatment exposure in retrospective claims studies such as these may be thought to be a function of observed (captured in the database) or unobservable factors. Observed factors could be confounders such as age at the first diagnosis, or the number of times the children may present with a symptom or even aggressive treatment depending on physician specialty. Unobservable confounders may be factors such as severity of the disease, parent's propensity to seek care that may affect the observed outcome. In an attempt to estimate and control for such baseline difference in characteristics, Heckmans two-stage model was used (Heckman 1976; Terza 1999; Sosin 2002). In the first stage of the Heckman procedure, the expected value of the error term was calculated using a probit regression modeling the probability of receiving any treatment which was then used as an additional regressor in the second stage. The study sample were segmented into mutually exclusive categories for the dependent variable (for example: those that were treated with FGAH, or SGAH or dual exposure or exposure to all or those with no exposure at all) and treatment models were estimated. For this study, exposure to treatment was modeled as function of patients characteristics (i.e.: sex, age of onset of AD and AR, income category), diagnosis of diseases such as Otitis media, Sinusitis (disease burden) over the study period and if

subjects had a specialist visit in the first year of follow up and any specialist claim thereafter. Table 5.3 lists all the additional variables that were used to model this likelihood to exposure. The vector of coefficients of the covariates estimated through this model was used to calculate the expected value of error (M1). Heckmans' sample selection models were performed between exposure vs. non-exposure, between exposure groups themselves (Table 5.3), between dose level vs. no exposure comparisons and the intent to treat analysis for asthma outcome as well as for the sesntivity analysis (expanded asthma case defitntion).

Univariate risk ratios for asthma incidence were compared between exposures of interest using chi-square tests. Two sample t-tests were used to compare the differences between groups for continuous variables. In the first step of the analysis, M1 the estimate of the expected value of error was obtained using probit regression as explained in the methods used to deal with sample selection bias. In the second stage, impact of the exposure to anti-inflammatory agents on risk of an asthma diagnosis was modeled using the Cox proportional hazards model (PROC PHREG) and stratified for sex (Allison 1995). Asthma incidence was modeled as a function of covariates listed in Table 5.3, a dummy variable for treatment exposure (or variable indicating days supply in certain models) and the M1 the expected value of the error term calculated form the first model. The dependent t variable was the time in days from birth until an asthma diagnosis or until the patient was censored. In addition, a variable to indicate censoring status was also built (1 = asthma diagnosis, 0 = censored). Differences in survival curves were tested using the log-rank test or Gehans Wilcoxon test. The proportional hazards assumption was confirmed by inspection of log (-log [survival]) curves. Hazard ratios for asthma incidence and 95% confidence intervals for the relative risk of asthma given the exposure are reported. SAS software Version 8.02 was used to manage the data and perform statistical analysis. The study was approved by the University of Georgia Institutional Review board.

RESULTS

There were 108,961 patients who developed AD/AR in GA Medicaid and were eligible until that diagnosis. 17,553 (16%) patients of the 108,961 AD/AR group also had an asthma diagnosis. On removing patients who had a prescription for an asthma medication (excluding oral steroids) that was not a part of an asthma diagnosis before an AD/AR diagnosis and removing patients whose asthma diagnosis that preceded an AD/AR diagnosis, there were 80,326 AD/AR patients who remained. 369 patients were excluded based on a diagnosis of HIV/ AIDS/ Cystic fibrosis resulting in 79,957 patients who were retained in the GA Medicaid primary AD/AR cohort. There were 6,771 patients in the primary AD/AR cohort who developed asthma leading to an asthma incidence of 8.46% in the GA AD/AR cohort. 63,038 of the patients in the AD/AR had a diagnosis for AD while 16,997 of these patients had a diagnosis for AR. There were also 22,866 (28.60 %) patients in primary AD/AR cohort who received a prescription for SABA before being censored. About 15% of the cohort was added each year which dipped to about 10% in 2001. 49 children died after inclusion into the GA AD/AR cohort of which 9 had asthma.

A total of 19,962 patients developed AD/AR in the overall commercial data and were eligible until that diagnosis. 1,674 (8.38%) patients this AD/AR group developed asthma but after removing patients who have a prescription for an asthma medication (excluding oral steroids) before an AD/AR diagnosis and removing patients whose asthma diagnosis preceded AD/AR diagnosis, 16,139 patients remained in the AD/AR group. Upon removing 88 patients because of diagnosis of HIV/ AIDS/ Cystic fibrosis 16,051 were retained in the primary AD/AR commercial cohort. A majority of these patients (12,335) had a diagnosis for AD and 4,911 patients had a diagnosis for AR. There were 642 patients with asthma in this cohort leading to an asthma incidence of 3.44 % in the commercial AD/AR cohort. There were 2,529 (15.76%) patients who had prescription for a beta-agonist before being censored.

The average age, calculated as age from birth until follow-up in the final GA Medicaid AD/AR cohort (N=79,957) was 2.06 years (STD:1.49). 15% of this cohort was below age one and 48% were between the ages of one and two. In the commercial AD/AR cohort (N=16,051) the average age until follow up was 1.87 yrs (STD: 1.04) with 24% cohort below age one and 30% of the cohort between age one and two. Both primary cohorts were composed of an equal proportion of male to females but African Americans composed approximately 48% of GA Medicaid AD/AR cohort. Race information was not available for the commercial cohort. The average age of onset of AD/AR was slightly lower at 0.34 yrs (STD: 0.44) and 0.50 yrs (STD: 0.51) in patients with a asthma diagnosis in GA and commercial and was 0.56 yrs (STD: 0.72) and 0.71 yrs (STD: 0.69) for patients who did not develop asthma. The average time of follow up for patients who developed asthma in the GA Medicaid cohort was 410 days (STD:349) and was 467 days(STD:293) in commercial and was 722 days (STD:528) and 676 days (STD:383) for patients who did not develop asthma in the two cohorts respectively. Mother-child link was established for 23,613 (29.53%) patients in GA Medicaid and for 14,616(92%) patients in the commercial data.

Tables 5.4 and Table 5.6 report the univariate risk ratios for asthma incidence in the GA Medicaid and the commercial AD/AR cohort respectively and the mean follow up for the members of the cohort with a particular exposure and who develop asthma. Exposure to FGAH, SGAH and INS significantly decreased the likelihood of an asthma diagnosis (Table 5.4) in GA Medicaid. In the commercial AD/AR cohort, any INS exposure was associated with a significantly lower risk of an asthma diagnosis (RR=0.93, CI: 0.06 to 0.91) in the univariate analysis (Table 5.6). Tables 5.5 and 5.7 compare the mean exposure to FGAH, SGAH, INS and other risk factors by asthma outcome for both cohorts. Subjects in the AD/AR cohort who developed asthma had lower exposure to FGAH, SGAH and INS in both cohorts. Tables 5.8 and 5.10 report the univariate risk ratios for the expanded asthma case outcome (receipt of a SABA prescription and/or an asthma diagnosis) in the GA AD/AR and commercial cohorts respectively.

In the GA AD/AR cohort exposure to SGAH reduced the likelihood of receiving an SABA prescription as much as 50% and was significantly protective for FGAH and SGAH as well. Conversely, in the commercial cohort exposure to FGAH was associated with a 34% increase in the risk of SABA prescription and/or asthma diagnosis and was non-conclusive for the other exposures (Table 5.10). There were 26,352 patients in GA and 10,787 patients in commercial with no exposure to FGAH, SGAH and INS.

85% of the GA AD/AR cohort saw a specialist in the first year of follow up and 35% saw a specialist in the latter years. In the commercial, this was 63% and 37% in the first and latter years of observation. In the adjusted analysis, maternal asthma was a consistent predictor for increased likelihood of an asthma diagnosis. Similarly, lower respiratory tract infections such as pneumonia, bronchitis, and bronchiolitis were also associated with an increased risk of asthma across both cohorts. Adjusted HR (95% CI) for the as-treated analysis comparing treatment exposure to no exposure to these agents and between treatment exposures themselves (ignoring exposure levels) for GA and commercial data are reported in Table 5.12 and Table 5.14. In GA Medicaid data, exposure to all anti-inflammatory agent (as compared to no exposure) reduced the likelihood of a diagnosis of asthma as much as 92% (HR=0.08 , 95%CI: 0.04 to 0.14). Exposure to all agents FGAH, SGAH and INS was the most protective against an asthma diagnosis when compared to exposures to other agents. For the commercial AD/AR cohort however, exposure to only FGAH (vs. no exposure to any agent) actually increased the diagnosis of an asthma diagnosis by 64% (Table 5.14) (HR=1.64 (1.37, 1.95)). Exposure to all three FGAH and SGAH and INS drugs collectively was however significantly protective against an asthma diagnosis. Table 5.13 and Table 5.15 present the adjusted HR after stratifying by dose levels. In GA Medicaid, exposure to FGAH, SGAH or INS was protective regardless of dose while the results were non conclusive in the commercial cohorts and higher levels of exposure were generally associated with lower risks of developing asthma.

The HRs for the intent to treat analyses are presented in Table 5.16 and Table 5.17. Over all the HRs for the intent to treat analysis presented the same trend as the as treated analysis. However, in the commercial AD/AR cohort when any exposure to FGAH was modeled as the number of cumulative days supply in the commercial AD/AR cohort the HRs was close to 1 (Table 5.17). But when any exposure to FGAH or SGAH or INS was modeled the HR was 1.52 (95% CI: 1.27 to 1.81).

For both the AD/AR cohorts, exposure to any anti-inflammatory agents (in a single model) was also modeled as the cumulative dose from birth until asthma diagnosis or censoring in both datasets. The HR for asthma diagnosis were, for FGAH=1.00 (CI: 0.99 to 1.00), for SGAH=0.99 (CI: 0.98 to 0.99) and 0.96 (CI: 0.93 to 0.99) for INS in MarketScan data. In GA Medicaid, results were as follows FGAH, HR=0.99 (CI:0.98 to 0.99), SGAH, HR=0.99 (CI: 0.98 to0.99) and for INS: HR=0.98 (CI:0.98 to 0.99).

Since a mother-child link in GA Medicaid was established in only30% of the patients, the analyses was repeated only in those in patients in GA Medicaid from whom a mother-child link was established. The results for the GA Medicaid AD/AR cohort were robust to this analysis.

SENSITIVITY ANALYSIS

Expanded asthma case definition

22,866 (28.60 %) patients in GA AD/AR cohort and 2,529 (15.76%) patients in the commercial had a prescription for SABA. 17,249 (21.57%) patients in the GA Medicaid and 2,077 (12.94) in the commercial AD/AR cohort patients received a SABA prescription but did not have an asthma diagnosis. 1,154 (17.04%) of asthmatics as per original criteria (N=6,771) in GA Medicaid and 190 (29.59) of asthmatics as per original criterion (N=642) in commercial had a asthma diagnosis but did not have SABA prior to their asthma or as part of their asthma diagnosis. Using the expanded asthma case definition there were 24,020 (incidence of 30.04%) asthma patients in the GA Medicaid and 2,719 (incidence of 16.94%) asthmatics in the

commercial AD/AR cohort. The average time of follow up for patients who received a prescription for SABA and/or a asthma diagnosis in the GA Medicaid cohort was 393 days (STD:333) and was 483 days(STD:283) in MarketScan and was 670 days (STD:506) and 652 days (STD:382) for patients who did not have either outcome. Adjusted HRs for a SABA and/or asthma diagnosis was modeled using intent to treat analysis as any exposure to FGAH, any exposure to SGAH or any exposure to FGHA or SGAH or INS as compared to patients with no exposure to agent of interest. In GA Medicaid AD/AR cohort the HR for a SABA prescription and/or asthma diagnosis for any FGAH exposure was HR=0.59 (95% CI: 0.57 to 0.60); for any SGAH was HR=0.45(95% CI: 0.42 to 0.48); any FGAH or SGAH or INS was HR=0.58 (95% CI:0.56 to 0.59). HRs in the commercial AD/AR cohort for any exposure to FGAH was 0.81 (0.74 to 0.87); for any SGAH was HR=0.62 (95% CI: 0.55 to 0.69); any FGAH or SGAH or INS was 0.79 (0.72 to 0.86).

DISCUSSION

The incidence of AD in GA Medicaid was 8.24% from 1995 to 2001 and was 9.56% in the MarketScan data from 1998 to 2001. Similarly, AR incidence was 2.2% in GA Medicaid and 3.80% in MarketScan. The over all prevalence of AD is estimated to be between 10-15% in a childhood population and is estimated to be as high as 40% for AR (O'Connell2004). There are almost no studies using administrative claims data that have studied these diseases especially in such young groups. In GA Medicaid, the incidence of asthma in the AD/AR cohort was 1.11% higher than the asthma incidence in the over all population. In MarketScan data however, these percentages were very similar. One of the reasons for this may be that patients (or parents) with private insurance are more are more likely to seek care for asthma (or symptoms suggestive of asthma) than for AD or AR symptoms and this may be driven to a greater extent by the co-payment and other deductibles in the MarketScan system. It may therefore be that patients are diagnosed with AD, and or AR after they are diagnosed with asthma which may not reflect the real life sequence. The overall prevalence of asthma in the AD/AR cohorts ignoring the temporal

sequence is much higher at nearly 16% in GA Medicaid and 8% in MarketScan data.. The difference in asthma incidence between the two populations is expected given that asthma disproportionately affects lower income groups. Moreover, physicians may also be more reluctant to diagnose and label children with asthma in the commercial as compared to physicians in Medicaid. The study used a very conservative definition for an asthma diagnosis to reduce to the number of false positives. Despite this the asthma incidence in GA Medicaid was much higher as compared to other studies which estimate the asthma prevalence at 5-7% in the general childhood population (Akinbami2002). This asthma case definition was important especially given the high number of children who wheeze and may be treated with asthma medications but may never receive a diagnosis of asthma. This analysis was restricted only to those who had at least one diagnosis of asthma and a majority of the patients with an asthma outcome had at least one inpatient code and 2 or more outpatient codes.

Exposure to all agents FGAH, SGAH, and INS were very protective against an asthma diagnosis in GA Medicaid while seemed to have a moderate impact on asthma incidence in MarketScan data. The protective effects were highest for those with exposure to all agents and were significant across both GA and the MarketScan primary cohorts. Exposure to INS was protective in the MarketScan data in the univariate analysis but the distribution of exposure to this agent (or sample sizes) was such that it prevented direct comparison with other exposures. In the intent to treat analysis, any exposure to FGAH (dichotomized) presented the same trend. However, when any exposure to FGAH was modeled as a continuous variable the risk was closer to being non-significant. Asthma incidence was much higher in GA AD/AR cohort and the commercial cohorts using the expanded asthma case definition (30% and 17%). In GA Medicaid, exposure to any FGAH, any SGAH or any FGAH, SGAH or INS presented the same trends as for the original case definition. However, in the commercial population any exposure to FGAH reduced the risk of a SABA prescription and/or asthma diagnosis by 20% and was significant. Exposure to this outcome was significantly protective for any SGAH and any treatment exposure

as well in the commercial AD/AR cohort. There have been at least two prospective randomized double blind study of SGAHs demonstrating significant benefit against asthma development in children suffering from AD (Iikura et al. 1992; Warner 2001). However, this is first study to demonstrate a potential benefit of FGAH, SGAH and INS against asthma development in atopic cohort at least in an indigent population and to some extent in a more general population i.e.: MaketScan. Treatment of AR symptoms has been documented to reduce asthma exacerbations such as asthma related hospitalizations and emergency visits in adults by as much as 50% (Crystal-Peters2002) and a similar effect was noted for intranasal steroids and prescription antihistamines (Adams 2002). These studies however examined co morbid AR and asthma and did not attempt to establish any temporal relationship. None of these studies evaluated if exposure to these agents actually impacts asthma incidence. Given that asthma onset occurs mainly in childhood with more than 80-90% of the cases being diagnosed by age six (Weiss 2001) the results of this study demonstrate that there is a potential to prevent or delay asthma incidence in atopic children.

There are a number of limitations to this study that must be addressed. OTC medications are not covered in the MarketScan database and this may lead to a miss-classification bias where children with exposure to these agents are classified as non exposure. Channeling bias may exist in spite of controlling for sample selection and may explain the results observed for FGAH on asthma outcome in the commercial AD/AR cohort. The impact of missing covariate information especially in such an analysis is of concern. For instance, environmental exposure such as smoking, exposure to allergens may interact with diseases in childhood and modify the genetic profile leading to increase or decreased risk of asthma. Environmental exposures could not be controlled for this study and may be a major drawback especially when looking at asthma development. Given the genetic basis for asthma development and the concern that a child-mother link was established in only 30% of GA AD/AR cohort, treatment effects of these agents may be overstated in GA Medicaid. However, the results were robust in an analysis restricted to

those subjects for whom a mother-child link could be established. Another limitation may be that patients included in the AD/AR cohorts represent patients who seek care and therefore receive a diagnosis. There may be many more patients where a diagnosis for AD/AR was missed. Randomized studies in a pediatric population at highest risk for developing asthma (genetic basis for asthma) are needed before definitive conclusions can be drawn about the effect of these agents on asthma incidence. The lower volume of claims in GA Medicaid in 1997 in the last quarter and the discrepancy in 1998 medical claims files may have lead to certain asthma diagnosis or exposure to FGAH, SGAH and INS being missed. However, given the length of the study in GA Medicaid and the non-dependence of this study of monthly claims volume, the impact of this on the results is not as much a concern.

CONCLUSION

Exposure to FGAH, SGAH and INS were significantly protective against an asthma diagnosis in an indigent population. This protection was highest with exposure to all agents. This was robust when using asthma case definitions also. In the commercial data however while exposure to all agents was protective, exposure to only FGAH was actually increased the risk of an asthma diagnosis. Exposure to any FGAH was however protective in the commercial cohorts using a more liberal asthma case definition. But this may be the effect of a channeling bias not fully accounted for by our sample selection methods. This study suggests that there may be a potential role for FGAH, SGAH or INS in the tertiary prevention of asthma in children suffering from AD and or AR. But randomized trails evaluating these agents are needed before treatment guidelines can be formulated.

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Table 5.1: List of all first generation anti-histamines, second generation histamines and intranasal steroids and cromolyns used in the study.

Drug classes	Generic names
First generation antihistamines (FGAH)	Brompheniramine, Chlorpheniramine, Hydroxyzine, Diphenhydramine, Clemastine, Cyproheptadine, Triprolidine Diphenhydramine, Clemastine, Carbinoxamine, Azatadine, Dexchlorphinaramine, Diphenhydramine, Doxylamine, Hyroxyzine, Meclizine, Cyclizine, Tripelennamine, Pyrilamine.
Second generation antihistamines (SGAH)	Ceterizine HCL, Azelastin HCL, Astemizole (withdrawn in 1999), Fexofenadine, Loratadine, Levocabastine
Intranasal Steroids (INS)	Beclomethasone Diproppioante, Budesonide, Flunisolide, Fluticasone Dipropioante, Mometasone furoate, Triamcinalone Acetonide
Cromolyns (CM)	Sodium cromoglicate or Cromolyn sodium (nasal and ophthalmic forms)

Table 5.2: List of covariates, other than treatment exposure that may influence treatment assignment and outcomes for the AD/AR cohorts

Demographics
Age at first diagnosis of allergic disease ,
Sex and Race
Maternal Asthma (Included in the second stage of analysis (i.e.: in the asthma incidence models only)
Type of health plan for Marketscan data
Premature birth (ICD-9-Cm=765.1*)
Respiratory difficulties at birth (ICD-9-CM=769)
Rhinitis (seasonal and perennial) (ICD-9-CM=477.*, 472.*)
Dermatitis (ICD-9-CM=691.* to 693.*, 708.*, 995.3)
Diagnosis of measles (ICD-9-CM=055.*), mumps(ICD-9-CM=072.*), rubella(ICD-9-CM=056.*)
Diagnosis of Sinusitis (ICD-9-CM=461.*, 473.*)
Diagnosis of Otitis Media (ICD-9-CM=381.0, 381.4, 382.0, 382.4, 382.9) (McCaig2002)
Diagnosis of URTI (ICD-9-CM=460, 465.*), P.Influenza (ICD-9-M=487.**)
Diagnosis of Pneumonia (ICD-9-CM=480.** to 486.**), Bronchitis (ICD-9-CM=466.0, 490), RSV infection (ICD_9-CM=079.6*), Bornchilitis (ICD-9-CM=466.1* excluding 466.19)
Number of anti-biotic prescriptions belonging to the following classes 1) Azithromycin/ clarithromycin 2) Cephalosporin's 3) Erythromycins 4) Penicillin's 5) Quinolones 6) tetracycline's 7) Others in the first year of life
Any diagnosis of GERD (ICD-9-CM= 530.1, 530.10, 530.11, 530.19, 530.3, 530.8, 530.81)
Season of birth (fall, spring, summer, winter)
Diagnosis claim from 'specialist' on the first year of observation and in subsequent years
Number of oral steroids prescriptions
Number of topical steroids prescriptions
Number of Lukotriene receptor antagonists prescriptions
Socio-economic index (using zip-code)

Table 5.3: Schematic representation of all possible treatment comparisons under Heckman two stage models.

	No Exposure	Single agent exposure (Exposure category 1 to 3)	Dual agent exposure (exposure category 4 to 6)	Exposure to all agents i.e.: FGAH+SGAH + INS
Single agent exposure (exposure category 1 to 3)	X	X (for example: FAGH to SGAH)	X	X
Dual agent exposure (exposure category 4 to 6)	X	X	X (For example: FGAH+ INS vs. FGAH+SGAH)	X
Exposure to all agents i.e.: FGAH+SGAH+INS	X	X	X	X

X- represents a separate comparison using the Heckmans two-stage sample selection procedure (comparisons will be done contingent on adequate sample sizes)

Table 5.4: Unadjusted risk ratios for an asthma diagnosis for the GA Medicaid AD/AR cohort (N=79,957)

	Number with asthma	% Develop asthma	Un-adjusted Relative Risks	95% Confidence Interval	*p-value*	Mean (STD) of months of follow-up for patients with risk factor who developed asthma
Any exposure to FGAH (N=53,128)	4,333	8.15	0.95	(0.94, 0.97)	<0.01	15.56 (12.29)
Any exposure to SGAH (N=5,404)	227	4.20	0.47	(0.41, 0.54)	<0.01	27.53 (15.53)
Any exposure to INS (N=1,504)	79	5.25	0.59	(0.45, 0.73)	<0.01	23.97 (15.85)
Any exposure to Cromolyns (N=76)	2	2.66	0.31	(0.07, 1.29)	0.09	18.5 (10.60)
AD (N= 63,038)	5,369	8.52				13.25 (11.44)
AR (N=16,997)	1,412	8.31				14.17 (11.53)
Sex						
Male (N=40,201)	4,065	10.11				12.91 (10.99)
Female (N=39,756)	2,706	6.81	0.78	(0.76, 0.81)	<0.01	14.25 (12.10)
Race						
White (N=25,930)	1,923	7.42	0.86	(0.82, 0.90)	<0.01	12.95 (10.89)
Black (N=38,426)	4,051	10.54	1.27	(1.24 1.30)	<0.01	14.17 (11.93)
Maternal asthma unknown (N=56,344)	4,106	7.28	0.84	(0.83, 0.86)	<0.01	11.68 (10.00)
Maternal Asthma (N=5,389)	784	14.55	1.84	(1.71, 1.97)	<0.01	15.19 (12.16)
Rural (N=22,491)	2,007	8.92				13.43 (11.43)
Urban (N= 57,218)	4,750	8.30	0.97	(0.96, 0.99)	<0.01	13.47 (11.49)
Other co morbidities						
P-Influenza (N=1,489)	99	6.65	0.76	(0.63, 0.94)	<0.01	22.6 (15.72)
Pneumonia (N= 5,737)	949	16.54	2.14	(2.01, 2.28)	<0.01	16.74 (12.81)
Sinusitis (N=8,464)	661	7.81	0.91	(0.85, 0.98)	0.02	21.60 (14.98)
Bronchitis (N=14,260)	1,956	13.72	1.71	(1.65, 1.78)	<0.01	15.48 (12.79)
Otitis Media (N=37,889)	3,263	8.61	1.01	(0.99, 1.04)	0.16	16.92 (12.57)
RSV (N=252)	45	17.86	2.34	(1.70, 3.24)	<0.01	10.91 (10.83)
Premature Birth (N=2,905)	404	13.91	1.74	(1.57, 1.93)	<0.01	14.81 (11.88)
Bronchiolitis (N=1,040)	248	23.85	3.38	(2.94, 3.89)	<0.01	10.90 (7.53)
Respiratory Distress (N= 1,153)	184	15.96	2.05	(1.76, 2.39)	<0.01	16.92 (12.34)
GERD (N=5,758)	677	11.77	1.44	(1.33, 1.55)	<0.01	13.65 (11.25)
MMR(N=50)	4	8.00	0.93	(0.33, 2.61)	0.90	18.5 (9.47)
Number of URTI (N=46,483)	4,403	9.47	1.13	(1.11, 1.15)	<0.01	15.25 (12.32)
Any antibiotic exposure						
Any Azithromycin Rx (N=13,154)	1,436	10.91	1.32	(1.26, 1.39)	<0.01	13.61 (9.67)
Any Cephalosporine	2,381	10.22	1.23	(1.18 1.27)	<0.01	15.16 (11.84)

Rx (N=23,285)						
Any Other antibiotic Rx (N=6,944)	548	7.89	0.92	(0.85, 1.00)	0.07	17.84 (14.06)
Any Quinolone Rx (N=11)	2	20.00	2.40	(0.50, 11.1)	0.24	13.5 (9.19)
Any Erythromycin Rx (N=8,234)	934	11.34	1.38	(1.29, 1.47)	<0.01	14.84 (11.69)
Any Penicillin Rx (N=475)	41	8.63	1.02	(0.74, 1.41)	0.89	17.46 (10.32)
Any Tetracycline Rx (N=20)	2	10.00	1.20	(0.29, 5.17)	0.73	28.5 (12.02)
Any Oral Steroid Rx (N=14,631)	3,119	21.31	2.92	(2.84, 3.01)	<0.01	13.53 (11.14)
Any Topical Steroid Rx (N=14,667)	1,262	7.89	1.01	(0.97, 1.07)	0.51	15.79 (13.00)
Any Lukotriene receptor antagonists Rx (N=117)	33	27.35	4.24	(2.84, 6.34)	<0.01	26.81 (15.14)

Table 5.5: Comparison between mean exposure levels and other continuous variables for the GA Medicaid AD/AR cohort by asthma outcome

	Did not develop asthma (N= 73,186)	Developed asthma (N= 6,771)	*p-value*
	Mean (STD)	Mean (STD)	
Days supply of FGAH	42.77 (73.21)	36.34 (66.34)	<0.01
Days supply of SGAH	3.37 (18.43)	1.37 (10.41)	<0.01
Days supply of INS	0.66 (6.50)	0.29 (3.23)	<0.01
Number of Lukotriene receptor antagonists	0.001 (0.00)	0.004 (0.07)	<0.01
Number of Topical Steroids	0.34 (1.189)	0.33 (1.02)	0.41
Number of URTI	2.53 (3.86)	2.60 (3.38)	0.16
Number of Azithromycin rxs	0.22 (0.60)	0.28 (0.66)	<0.01
Number of Penicillin Rxs	0.01 (0.26)	0.01 (0.27)	0.72
Number of Cephalosporin Rxs	0.47 (0.96)	0.58 (1.01)	<0.01
Number of Erythromycin Rxs	0.12 (0.43)	0.17 (0.49)	<0.01
Number of Other anti-biotic rx	0.11 (0.46)	0.11 (0.43)	0.10

Table 5.6: Unadjusted risk ratios for an asthma diagnosis in the AD/AR commercial cohort (N=16,051)

	Number with asthma	% Develop asthma	Unadjusted Relative Risks	95% CI	*p-value*	Mean (STD) of months of follow-up for patients with risk factor who developed asthma
Any exposure to FGAH (N=4,775)	209	4.37	1.09	(0.98, 1.23)	0.11	18.22 (9.48)
Any exposure to SGAH (N=1,421)	47	3.30	0.82	(0.62, 1.08)	0.16	20.91 (9.15)
Any exposure to INS (N=214)	2	0.93	0.22	(0.06, 0.91)	0.02	24 (2.82)
AD (N=12,335)	478	3.88				15.55 (9.63)
AR (N=4,911)	213	4.34				16.06 (10.15)
Sex						
Male (N=8,457)	418	4.94				14.62 (9.31)
Female (N=7,594)	224	2.95	0.72	(0.66, 0.81)	<0.01	16.61 (10.11)
Mother Asthma (N=1,954)	120	6.14	1.57	(1.33, 1.86)	<0.01	14.93 (9.51)
Urban (N=8,392)	355	4.23	1.06	(0.98, 1.13)	0.11	15.71 (9.93)
Rural (N=4,925)	164	3.33	0.83	(0.72, 0.95)	<0.01	13.41 (8.42)
Other co morbidities						
P-Influenza (N=415)	12	2.89	0.71	(0.40, 1.26)	0.24	20.5 (12.59)
Pneumonia (N=962)	102	10.6	2.85	(2.36, 3.44)	<0.01	16.76 (9.68)
Sinusitis (N=2,578)	110	4.27	1.07	(0.90, 1.27)	0.45	18.79 (9.46)
Bronchitis (N=2,329)	207	8.89	2.34	(2.08, 2.64)	<0.01	16.01 (9.40)
Otitis Media (N=9,138)	430	4.71	1.19	(1.12, 1.25)	<0.01	16.62 (9.48)
RSV (N= 76)	1	1.32	0.32	(0.04, 2.29)	0.23	15 (0)
Premature Birth (N=806)	52	6.45	1.66	(1.26, 2.17)	<0.01	13.13 (8.11)
Bronchiolitis (N=274)	33	12.04	3.28	(2.30, 4.69)	<0.01	14.57 (9.17)
Respiratory Distress (N=340)	21	6.18	1.58	(1.02, 2.44)	0.04	16.23 (10.48)
GERD (N=1,339)	67	5	1.26	(1.00, 1.60)	0.05	13.44 (8.27)
MMR (N=5)	0	0	0	0	0	15.31 (9.63)
Any URTI (N=9,985)	473	4.73	1.19	(1.14, 1.25)	<0.01	16.67 (9.79)
Other medication exposure						
Any Oral Steroid Rx (N=1,856)	191	10.29	2.75	(2.42, 3.12)	<0.01	16.02 (9.84)
Any Lukotriene receptor antagonists Rx (N=47)	7	14.89	4.20	(1.88, 9.33)	<0.01	26.71 (13.27)
Any Topical Steroid Rx (N=1,702)	96	5.64	1.43	(1.19, 1.73)	<0.01	15.27 (8.42)

Table 5.7: Comparison between mean exposure levels and other continuous variables in the AD/AR commercial cohort by asthma outcome

	Did not develop asthma (N=15,409)	Developed asthma (N=642)	*p-value*
	Mean (STD)	Mean (STD)	
Days supply of FGAH	11.87 (31.49)	10.53 (24.01)	0.28
Days supply of SGAH	0.57 (6.80)	0.15 (3.42)	0.12
Days supply of INS	0.14 (0.47)	0.36 (0.61)	<0.01
Number of Leukotriene receptor antagonists	0.002 (0.05)	0.01 (0.10)	<0.01
Topical Steroids	0.16 (0.64)	0.24 (0.73)	<0.01
Number of URTI	1.80 (2.34)	2.26 (2.54)	<0.01

Table 5.8: Unadjusted risk ratios for an SABA prescription and/or a asthma outcome in the AD/AR GA Medicaid cohort (N=79,957)

	Number with beta-agonists	% who receive beta-agonists	Unadjusted Relative Risks	95% CI	*p-value*	Mean (STD) of months of follow-up for patients with risk factor who received beta-agonists
Any exposure to FGAH (N=53,128)	15,835	29.81	0.98	(0.97 0.99)	0.04	15.17 (11.88)
Any exposure to SGAH (N=5,404)	985	18.23	0.51	(0.48, 0.55)	<0.01	28.32 (16.74)
Any exposure to INS (N=1,504)	387	25.73	0.80	(0.71, 0.90)	<0.01	27.82 (17.98)
Any exposure to Cromolyns (N=76)	36	47.37	2.07	(1.33, 3.28)	<0.01	18.72 (12.87)
AD (N= 63,038)	19,227	30.50				12.34 (10.45)
AR (N= 16,997)	4819	28.35				15.06 (12.43)
Sex						
Male (N=40,201)	13,174	32.77				11.42 (9.71)
Female (N=39,756)	10,846	27.88	0.87	(0.87, 0.88)	<0.01	13.65 (11.54)
Race						
White (N=25,930)	7,357	28.37	0.92	(0.90, 0.94)	<0.01	12.94 (10.52)
Black (N=38,426)	13,080	34.03	1.20	(1.18, 1.22)	<0.01	13.47 (11.55)
Maternal Asthma Unknown (N=56,344)	15,067	26.74	0.85	(0.84, 0.86)	<0.01	11.42 (9.15)
Maternal Asthma (N=5,389)	2,358	43.76	1.81	(1.72, 1.90)	<0.01	15.51 (12.79)
Rural (N=22,491)	6,841	30.41				12.26 (10.24)
Urban (N= 57,218)	17,113	29.91	0.99	(0.98 1.00)	0.19	12.76 (10.88)
Other co morbidities						
P-Influenza (N=1,489)	452	30.36	1.01	(0.91, 1.13)	0.78	20.82 (15.95)
Pneumonia (N= 5,737)	2,737	47.71	2.12	(2.02, 2.23)	<0.01	16.40 (12.84)
Sinusitis (N=8,464)	2,665	31.49	1.07	(1.02, 1.11)	<0.01	20.85 (14.66)
Bronchitis (N=14,260)	6,703	47.01	2.06	(2.00, 2.12)	<0.01	15.19 (12.50)
Otitis Media (N=37,889)	12,367	32.64	1.12	(1.11, 1.14)	0.37	16.34 (12.24)
RSV (N=252)	133	52.78	2.60	(2.03, 3.33)	<0.01	12.14 (11.08)
Premature Birth (N=2,905)	1,132	38.97	1.48	(1.38, 1.59)	<0.01	13.86 (11.51)
Bronchiolitis (N=1,040)	712	68.46	5.05	(4.44, 5.75)	<0.01	10.11 (8.63)
Respiratory Distress (N= 1,153)	477	41.33	1.64	(1.46, 1.84)	<0.01	14.30 (11.84)
GERD (N=5,758)	2,202	38.24	1.44	(1.37, 1.51)	<0.01	12.86 (10.23)
MMR (N=50)	19	38.00	1.42	(0.81, 2.52)	0.21	24.52 (13.15)
Number of URTI (N=46,483)	15,887	34.18	1.20	(1.19, 1.22)	<0.01	14.58 (11.91)
Any antibiotic exposure						
Any Azithromycin Rx (N=13,154)	5,181	39.39	1.51	(1.46, 1.56)	<0.01	13.01 (9.50)
Any Cephalosporin	8,319	35.37	1.29	(1.26, 1.32)	<0.01	14.41 (11.21)

Rx (N=23,285)						
Any Other antibitotic Rx (N=6,944)	2,316	33.35	1.16	(1.11, 1.22)	0.13	16.31 (12.22)
Any Quinolone Rx (N=11)	3	27.27	0.87	(0.23, 3.29)	0.84	12.66 (6.02)
Any Erythromycin Rx (N=8,234)	3,379	41.04	1.62	(1.55, 1.68)	21.43	13.51 (11.48)
Any Penicillin Rx (N=475)	137	28.84	0.94	(0.77, 1.15)	0.56	17.60 (13.61)
Any Tetracycline Rx (N=20)	9	45.00	1.90	(0.79, 4.59)	0.14	17.66 (18.22)
Any other medication exposure						
Any Oral Steroid Rx (N=14,631)	8,406	57.45	3.14	(3.05, 3.23)	<0.01	13.72 (11.57)
Any Topical Steroid Rx (N= 14,667)	4,317	29.43	0.99	(0.94, 1.00)	0.07	14.97 (12.33)

Table 5.9: Comparison between mean exposure levels and other continuous variables in GA Medicaid AD/AR cohort by beta-agonist (SABA) outcome

	Did not receive beta-agonists (N=55,937)	Received beta-agonists (N=24,020)	*p-value*
	Mean (STD)	Mean (STD)	
Days supply of FGAH	43.76 (74.394)	38.65 (68.55)	<0.01
Days supply of SGAH	3.86 (20.00)	1.69 (11.48)	<0.01
Days supply of INS	0.70(6.87)	0.47 (4.66)	<0.01
Number of URTI	2.45 (3.90)	2.74 (3.61)	<0.01
Number of Azithromycin	0.20 (0.59)	0.28 (0.64)	<0.01
Number of Cephalosporins	0.44 (0.94)	0.57 (1.01)	<0.01
Number of Other	0.11 (0.45)	0.12 (0.47)	<0.01
Number of Erythromycin	0.11 (0.41)	0.17 (0.49)	<0.01
Number of Penicillin	0.01 (0.29)	0.009 (0.19)	0.27
Number of Oral Steroids	0.15 (0.55)	0.46 (0.79)	<0.01
Number of Topical Steroids	0.35 (1.22)	0.32 (1.06)	<0.01

Table 5.10: Unadjusted risk ratios for receipt of SABA prescription and/or a asthma outcome in the AD/AR cohort for commercial data (N=16,051)

	Number with beta-agonists	% who receive beta-agonists	Unadjusted Relative Risks	95% CI	*p-value*	Mean (STD) of months of follow-up for patients with risk factor who received beta-agonists
Any exposure to FGAH (N=4,775)	1,027	21.51	1.34	(1.27, 1.42)	<0.01	17.40 (9.49)
Any exposure to SGAH (N=1,421)	263	18.51	1.11	(0.98, 1.26)	0.09	22.57 (8.79)
Any exposure to INS (N=214)	36	16.82	0.99	(0.69, 1.41)	0.96	24.55 (8.45)
AD (N=12,335)	2,013	16.32				13.69 (9.16)
AR (N=4,911)	908	18.49				16.50 (9.86)
Sex						
Male (N=8,457)	1,608	19.01				13.93 (9.36)
Female (N=7,594)	1,111	14.63	0.84	(0.80 0.88)	<0.01	14.57 (9.30)
Maternal Asthma (N=1,954)	456 |	23.34	1.49	(1.35, 1.64)	<0.01	15.12 (9.85)
Rural (N=4,925)	845	17.16				12.80 (8.26)
Urban (N=8,392)	1,427	17.00	1.00	(0.96, 1.04)	0.80	14.47 (9.58)
Other co morbidities						
P-Influenza (N=415)	67	16.14	0.94	(0.72, 1.22)	0.66	18.23 (10.63)
Pneumonia (N=962)	295	30.67	2.16	(1.90, 2.47)	<0.01	16.58 (9.35)
Sinusitis (N=2,578)	516	20.02	1.22	(1.12, 1.33)	<0.01	19.72 (10.00)
Bronchitis (N=2,329)	710	30.49	2.15	(1.98, 2.32)	<0.01	15.11 (9.39)
Otitis Media (N=9,138)	1,758	19.24	1.16	(1.13, 1.20)	<0.01	16.43 (9.46)
RSV (N= 76)	13	17.11	1.01	(0.55, 1.83)	0.96	13.46 (7.50)
Premature Birth (N=806)	191	23.70	1.52	(1.30, 1.78)	<0.01	13.82 (8.96)
Bronchiolitis (N=274)	108	39.42	3.19	(2.51, 4.05)	<0.01	12.79 (9.30)
Respiratory Distress (N=340)	70	20.59	1.27	(0.98, 1.64)	0.06	13.65 (8.74)
GERD (N=1,339)	290	21.66	1.35	(1.19, 1.53)	0.05	14.31 (9.12)
MMR(N=5)			0	0	0	14.19 (9.34)
Any URTI (N=9,985)	1,895	18.98	1.14	(1.11, 1.18)	<0.01	15.58 (9.52)
Other medication						
Any Oral Steroid Rx (N=1,856)	723	38.95	3.12	(2.87, 3.40)	<0.01	15.95 (9.67)
Any Topical Steroid Rx (N=1,702)	348	20.45	1.26	(1.12, 1.40)	<0.01	15.61 (9.47)
Any antibiotic exposure						
Any Penicillin Rx (N=8,109)	1,709	21.08	1.30	(1.26, 1.35)	<0.01	14.17 (9.32)
Any B-Lactam Antibiotic Rx (N=292)	76	26.03	1.72	(1.33, 2.23)	<0.01	13.94 (9.11)
Any Cyclosporin Rx	984	24.56	1.59	(1.50, 1.69)	<0.01	14.03 (8.78)

(N=4,006)						
Any Erythromycin Rx (N=3,401)	927	27.26	1.83	(1.72, 1.95)	<0.01	13.66 (8.77)
Any Anti-infective Rx (N=478)	120	25.10	1.64	(1.34, 2.01)	<0.01	13.46 (8.16)
Any Tetracycline Rx (N=50)	19	38.00	3.00	(1.70, 5.31)	<0.01	12. 94 (6.11)

Table 5.11: Comparison between mean exposure levels and other continuous variables in commercial AD/AR cohort by beta-agonist (SABA) outcome

	Did not receive beta-agonists (N= 13,797)	Received beta-agonists (N=2,254)	
	Mean (STD)	Mean (STD)	*p-value*
Days supply of FGAH	11.52 (31.8)	13.31 (26.14)	<0.01
Days supply of SGAH	5.97 (31.68)	5.46 (25.48)	0.42
Days supply of INS	0.57 (6.98)	0.45 (5.07)	0.87
Number of URTI	1.77 (2.37)	2.05 (2.22)	<0.01
Number of Oral Steroids	0.11 (0.42)	0.33 (0.67)	<0.01
Number of Penicillin	1.29 (2.02)	2.03 (2.68)	<0.01
Number of B-Lactam Antibiotics	0.02 (0.20)	0.04 (0.27)	<0.01
Number of Cephalosporins	0.46 (1.14)	0.89 (1.64)	<0.01
Number of Erythromycin	0.32 (0.86)	0.66 (1.28)	<0.01
Number of Anti-infectives	0.03 (0.24)	0.06 (0.34)	<0.01
Number of Tetracycline	0.003 (0.07)	0.01 (0.17)	<0.01
Number of Topical Steroids	0.16 (0.64)	0.20 (0.70)	<0.01

**Area (Urban/Rural) and Income could be determined for 2,734 patients in the AD/AR cohort

Table 5.12: HR (95% CI) for an asthma diagnosis in the GA Medicaid AD/AR cohort classified using exposure status alone^

Baseline groups ►	No exposure, N=26,352	FGAH alone	SGAH alone	FGAH+SGAH	FGAH+INS
Exposure of interest (comparison group in all analysis)	HR(95% CI)	HR(95% CI)	HR(95% CI)	HR(95% CI)	HR(95% CI)
FGAH alone (N=47,423)	0.67 (0.63, 0.70)	X	X	X	X
SGAH alone (N=399)	0.30 (0.16, 0.53)	0.54 (0.30, 0.95)	X	X	X
FGAH+SGAH (N=4279)	0.23 (0.19, 0.27)*	0.52 (0.45, 0.59)	1.02 (0.56, 1.83)*	X	X
FGAH+INS (N=733)	0.30 (0.21, 0.42)	0.71 (0.54, 0.93)	1.52 (0.73, 3.13)*	1.59 (1.16, 2.17)*	X
Exposure to all (N=693)	0.08 (0.04, 0.14)	0.32 (0.20, 0.49)	0.52 (0.21, 1.28)*	0.52 (0.33, 0.81)	0.39 (0.22, 0.67)

* Co-efficient of estimate of the error term was not significant

Table 5.13: HR (95% CI) for an asthma diagnosis in the GA Medicaid AD/AR cohort stratified by interaction of exposure levels and exposure categories^

Low Exposure	N	HR (95% CI)
FGAH	26,550	0.73 (0.68, 0.77)
SGAH	548	0.46 (0.29, 0.70)
FGAH+SGAH	1,373	0.36 (0.27, 0.46)
FGAH+INS	219	0.41 (0.24, 0.69)
FGAH+SGAH+INS	116	0.45 (0.18, 1.08)
High Exposure		
FGAH	14,223	0.47 (0.43, 0.51)
FGAH+SGAH	456	0.06 (0.03, 0.11)

^ HRs adjusted for all variables

Table 5.14: HR (95% CI) for an asthma diagnosis in the commercial AD/AR cohort for exposure classified using exposure status alone^

Baseline groups ►	No exposure, N=10,787	FGAH alone	SGAH alone	FGAH+SGAH
Exposure of interest (comparison group in all analysis)	HR(95% CI)	HR(95% CI)	HR(95% CI)	HR(95% CI)
FGAH alone (N=3,750)	1.64 (1.37, 1.95)	X	X	X
SGAH alone (N=450)	1.18 (0.69, 2.00)*	0.64 (0.36, 1.10)*	X	X
FGAH+SGAH (N=850)	1.24 (0.82, 1.87)*	0.93 (0.62, 1.37)*	1.08 (0.52, 2.23)*	X
Exposure to all (N=100)	0.09 (0.012, 0.69)	0.08 (0.01, 0.63)	.	0.01 (0.0001, 0.53)

Table 5.15: HR (95% CI) for an asthma diagnosis in the commercial AD/AR cohort for exposure based on interaction of exposure levels and exposure categories when compared to groups with no exposure.^

Low Exposure	N	HR (95% CI)
FGAH	2310	1.30 (1.03, 1.63)
SGAH	347	1.29 (0.77, 2.14)*
FGAH+SGAH	322	1.28 (0.72, 2.26)*
High Exposure		
FGAH	539	1.79 (1.16, 2.75)
HFGLSG	174	1.14 (0.41, 3.19)*
LFGHSG	120	1.30 (0.46, 3.61)*

* Co-efficient of estimate of the error term was not significant

^ HRs adjusted for all variables

Table 5.16: HRs (95% confidence intervals) for the GA Medicaid AD/AR cohort for the intent to treat analysis

	N (for exposure of interest)	HR	95% CI
Any FGAH (FGAH=1 vs. FGAH=0) vs. none	53,128	0.68	0.65 to 0.70
Any FGAH vs. none(FGAH=∑ Days supply vs. FGAH=0)	53,128	0.99	0.98 to 0.99
Any SGAH (SGAH=1 vs. SGAH=0) vs. none	5,404	0.42	0.37 to 0.47
Any SGAH vs. none(SGAH=∑ Days supply vs. SGAH=0)	5,404	0.98	(0.98 to 0.99)
Any FGAH or SGAH vs. no exposure to FGAH or SGAH	53,560	0.67	0.64 to 0.69
Any FGAH or SGAH or INS vs. no exposure to FGAH or SGAH or INS	53,605	0.67	0.64 to 0.69

Table 5.17: HRs (95% confidence intervals) for the commercial AD/AR cohort for the intent to treat analysis

	N (for exposure of interest)	HR	95% CI
Any FGAH (FGAH=1 vs. FGAH=0) vs. none	4,775	1.57	1.37 to 1.87
Any FGAH vs. none(FGAH=∑ Days supply vs. FGAH=0)	4,775	1	0.99 to 1.00
Any SGAH (SGAH=1 vs. SGAH=0)* vs. none	1,421	0.94	0.68 to 1.28
Any SGAH vs. none(SGAH=∑ Days supply vs. SGAH=0)	1,421	0.99	0.98 to 0.99
Any FGAH or SGAH vs. no exposure to FGAH or SGAH	5,246	1.55	1.29 to 1.84
Any FGAH or SGAH or INS vs. no exposure to FGAH or SGAH or INS	5,264	1.52	1.27 to 1.81

CHAPTER 6

TREATMENT EFFECT OF ANTI-INFLAMMATORY AGENTS ON INCIDENT ASTHMA TREATMENT COSTS IN AN ATOPIC COHORT

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ABSTRACT

INTRODUCTION: Asthma and other allergic conditions have significant world-wide burden. Allergic conditions such as allergic rhinitis (AR) drive asthma exacerbations and therefore asthma costs. Atopic dermatitis (AD) drives asthma burden but effect on asthma cost has not been systematically evaluated. The objective of this study was to evaluate the impact of anti-inflammatory agents such as first generation anti-histamines (FGAH), second generation anti-histamines (SGAH) and intra-nasal steroids (INS) on asthma treatment costs in a cohort of AD or AR patients who develop asthma.

METHODS: Data from GA Medicaid from 1995 to 2001 and MarketScan database from 1998 to 2001 was utilized. This analysis focused on newborn children who developed asthma in an AD/AR cohort in GA Medicaid and MarketScan population and were eligible for at least 12 months after the first inclusion into the asthma cohort. In addition, patients with a diagnosis of malignancy or metastatic solid tumor in the year of observation for asthma treatment costs were excluded. All FGAH, SGAH and INS prescriptions from birth until an asthma diagnosis were recorded. The main outcome for this study was the total direct health care costs for subjects in the AD/AR cohort who were eligible for at least 12 months after the first recorded asthma inclusion criteria. Multivariate ordinary least squares regression using Huber-white heteroscedasticity consistent variance–covariance matrix was used to compare direct medical costs post asthma incidence between groups with exposure to FGAH, SGAH, INS and all combination therapies to groups with no exposure to these agents. Total costs were also examined by category of service namely inpatient, physician, outpatient, other miscellaneous medical utilization, asthma related prescription, non-asthma related prescriptions.

RESULTS: 4,277 asthma patients in GA Medicaid and 353 in the commercial cohort who were eligible for 12 months after their first asthma diagnosis flag were retained for this analysis. 2,906 (68%) in GA Medicaid and 228 (64%) in the commercial cohorts had at least one prescription for a FGAH, SGAH or INS from birth until they developed asthma. In GA Medicaid any exposure

to FGAH or SGAH or INS were associated with a non-significant lower net per member per year mean total cost of $ -87. In the commercial sub-cohorts, exposure to FGAH, SGAH, and INS seemed to reduce mean PMPY net costs by $ 546 but was not statistically significant. Total medical costs (excluding prescriptions) and physician costs were however significantly lower for the exposure groups as compared to the non-exposure groups in the commercial data.

CONCLSUIONS: Exposure to anti-inflammatory agents reduced asthma direct medical costs in patients with regards to total medical costs (excluding prescriptions). Since asthma treatment costs correlate with asthma severity, treatment with FGAH, SGAH and INS may translate into lower severity for asthma in such patients

INTRODUCTION

Asthma and other allergic conditions have a significant economic burden in the US and world-wide. Asthma, one of the most common chronic pediatric diseases has been increasing in prevalence in the last decade accompanied by a temporal increase in allergic conditions such as AR and AD. The overall monetary burden of asthma is significant, being estimated at 12.7 billion dollars in 1998 (Weiss 2001). Indirect costs of asthma account for about 42% of the total cost. Asthma is the number one reason for missed school days (accounts for 9% of indirect costs) and one of the main reasons for hospitalizations in children (Weiss 2001). The burden of asthma preponderance in preschool children is also reflected in the fact that children less than 4 years of age represent less than 30% of pediatric population (ages 0-17) but account for nearly 50% of all pediatric direct costs for asthma (Smith 1997).

Allergic rhinitis (AR), a risk factor for asthma development and persistence has also been associated with increased asthma treatment costs. In studies, where costs for co morbid AR and asthma were compared to asthmatic patients without AR , presence of AR increased asthma costs by as much as $ 350 (Halpern 2004). Direct health care costs for patients with AR and asthma are as much as 50% higher as compared to patients with either disease alone (Meltzer 2004).

Studies looking at AR treatment in such comorbid AR-asthma patients have also demonstrated a protection against asthma related exacerbations (Crystal-Peters 2002); (Adams 2002). It is recognized that interfering with the allergic cascade in AR which has a considerable overlap with asthma etiology may modify or attenuate asthma severity (Sears 1997). Atopic dermatitis (AD) is another significant risk factor for asthma development and persistence which has significant economic burden. However, there have been no systematic studies that examine that impact of comorbid AD-asthma on asthma treatment costs.

Interference with repeated allergic cascade in diseases such as atopic dermatitis and or AR may prevent the chronic 'wound-healing/repair' response in the airway tissues that is central to the structural and functional changes in the airway wall that are characteristic of the asthmatic state (Holt 1999). Evaluating the effect of treatment for AR or atopic dermatitis in newly diagnosed asthmatics may provide a better picture of asthma progression and it may be possible to assess impact of such treatment on asthma severity in such patients. Since asthma costs are driven by asthma severity and exacerbations, reducing the asthma severity may result in lowered asthma costs for AR patients who are treated with FGAH, SGAH and INS prior to asthma development.

The objective of this study was to evaluate the impact of anti-inflammatory agents such as first generation anti-histamines (FGAH), second generation anti-histamines(SGAH) and intra-nasal steroids(INS) on asthma treatment costs in a cohort of AD or AR patients in the year after asthma incidence. More specifically, costs for patients in an AD/ AR cohort who developed asthma was examined for one year after asthma incidence and compared to patients who developed asthma in the AD, AR cohort but were not treated with FGAH, SGAH and INS.

METHODS

Data Sources

Data from GA Medicaid from 1995 to 2001 and MarketScan database from 1998 to 2001 were utilized. The GA Medicaid data describes all adjudicated claims for GA Medicaid eligible beneficiaries including all institutional, outpatient and prescription claims, which is patient linked to program eligibility information. Children may qualify for Medicaid services under the following categories 1) Right From The Start Medicaid (RSM adults) for pregnant mothers: Pregnant women with a family income at or below 235% of the federal poverty limit are eligible for Medicaid services and stay eligible for 60 days post-partum. The child born to such a mother stays eligible until one year of age if the mother was eligible for one-month during pregnancy and lives in the same household as the mother. 2) Right from the start Medicaid (RSM Children): Children are covered up to age 18 depending on age and income level. 3) Pregnant Women, infants and children medically needy: If the pregnant women /children do not qualify for Medicaid because of family resources but meets this limit due to medical spend down. An additional feature of the GA Medicaid data from 1998 to 2001 was the presence of a variable that was used to build mother to child linkages. The MarketScan data is a commercial Claims and Encounters database, which contains the healthcare experience of approximately seven million individuals (annually) who are covered under a variety of health plans. Data from the MarketScan database from the commercial population. Data from January 1998 to December 2001 was acquired and provided access to all medical claims, drug data (approximately 2.6 million covered lives) and enrollment details for the working population and their dependents. Data from MarketScan database constitute the commercial cohort. The data are organized into these major files: 1) patient and demographic information 2) health plan features 3) financial information 4) inpatient and outpatient medical information 5) drug information 6) enrollment information. A unique scrambled patient identifier is encoded for each record in all of the above

files in both datasets that facilitates linkage. The MarketScan data base also has an in-built variable that flags family units which was used to establish the child-mother linkage. All of the data was examined for consistency and outliers. The GA Medicaid data and the MarketScan data has used before in studying asthma and other epidemiological studies and has been found to valid and consistent (Martin 2001); (Crown 2003). The analysis will be done in parallel for the two datasets.

Study Population

The study design was a retrospective cohort study where annual health care costs for patients with newly developed asthma in an AD/AR cohort were compared between groups treated for AD/AR and not treated for AD/AR (Fig1). This analysis is developed further from a study that examined asthma development in an AD/AR cohort in GA Medicaid and MarketScan population.

Patients were included based on the following criteria:

-Born between 1995-2001 for GA Medicaid and 1998-2001 for commercial data

-Between January1995 to December2001 for GA Medicaid and January1998 to December 2001 for commercial have a diagnosis of the following:

-Any ICD-9-CM diagnosis code for atopic dermatitis (ICD-9-CM=691.8, 692.9 and 373.3) (Ellis 2002) OR any ICD-9-CM diagnosis code for allergic rhinitis (ICD-9-CM=477.**) (Crystal-Peters et al. 2002)

-Continuously eligible from birth until a diagnosis of AD or AR and for twelve months after their first Asthma diagnosis.

-Had to have at least one claim for AD or AR prior to their asthma diagnosis.

Patients were excluded from the ADAR primary cohort based on the following criteria:

-Diagnosis of HIV/AIDS, cystic fibrosis, or a diagnosis of malignancy or metastatic solid tumor

-A prescription for an asthma medication or a diagnosis for asthma prior to their first AD/AR diagnosis claim

In addition, patients with a in the year of observation for asthma treatment costs were excluded.

Asthma was defined for patients in the AD/AR cohort based on the following inclusion criteria:

-One-inpatient claim with a primary (first listed) or secondary ICD-9-CM code for asthma (ICD-9-CM=493.**) (Lozano 1997) OR

-Two outpatient claims with a primary or secondary ICD-9-CM code for asthma (ICD-9-CM=493.**) not separated by more than 365 days, since one outpatient diagnosis might represent a rule out diagnosis (Nash 1999) OR

-An outpatient diagnosis for asthma and two or more prescriptions belonging to separate asthma medication class or two or more medications for the same class separated by at least 30 days in any 365 day period (Leone 1999).

Patients also had to be eligible for at least 12 months after the first inclusion into the asthma cohort.

Measuring Exposure

The main agents of interest in this study were first generation anti-histamines (FGAH), second generation anti-histamines (SGAH) and intra-nasal steroids (INS) and cromolyns (CM) which were recorded from the outpatient prescription files as in Table 6.1. All cough and cold medication were screened to include those which contained FGAH. These combination products were included if they contained at least one of the active ingredients listed in Table 6.1. Since the sample sizes for CM were very small in both populations (<100), this exposure category was dropped from all further analysis. The cumulative exposure to FGAH, SGAH and INS was recorded as the sum of the 'days supply' variable from birth until an asthma diagnosis was established or until subjects were censored. In some cases, subjects in the AD/AR cohorts received a prescription for a short acting beta-agonist (SABA) prior to their first asthma diagnosis

flag and that was not a part of the asthma diagnosis. In these instances, the date of receipt of this prescription was the end date of the observation period for treatment exposure for these subjects.

Measuring Outcome

The main outcome for this study was the total direct health care costs for subjects in the AD/AR cohort who were eligible for at least 12 months after the first recorded asthma inclusion criteria. Since this study focused on a third-party payer perspective net paid amount in GA Medicaid and the commercial data were used to calculate the total cost. Total cost was calculated as the sum of the amount in the paid amount field in both detests. Total costs was also examined by category of service namely inpatient, physician, outpatient, other miscellaneous medical utilization, asthma related prescription, non-asthma related prescriptions.

Sample Selection Models (Heckman Sample selection models)

The Heckman sample selection model was used to control for unobservable factors that may determine exposure to FGAH, SAGH or INS. These unobserved covariates may not only influence treatment selection but also affect the outcome. Observed factors could be confounders such as age at the first diagnosis, or the number of times the children may present with a symptom or even aggressive treatment depending on physician specialty. Unobservable confounders may be factors such as severity of AD/AR or parent's propensity to seek care that may affect asthma treatment costs. In an attempt to estimate and control for such baseline difference in characteristics, Heckmans two-stage model was used (Heckman 1976; Terza 1999; Sosin 2002). In the first stage of the Heckman procedure, the expected value of the error term (M1) was calculated using a probit regression modeling the probability of receiving any treatment which was then used as an additional regressor in the second stage. Asthma groups of interest were stratified into exposure and non-exposure groups and treatment model was estimated using a probit regression. In addition to patients demographics (sex, race when available, age of onset of AD/AR), any consultation with a specialist in the first year of follow up and any subsequent

claim thereafter, income, location (urban vs. rural.), and co morbidities as in Table 6.2 were included as additional covariates. For the commercial data, plan type was also included.

ANALYSIS

Comparison of direct health care costs for incident asthma was done for groups in the exposure and non-exposure groups who develop asthma. Multivariate ordinary least squares regression using Huber-white heteroscedasticity consistent variance–covariance matrix was used to compare direct medical costs post asthma incidence between groups with exposure to FGAH, SGAH, INS and all combination therapies to groups with no exposure to these agents. The dependent variable was the total direct cost and the independent variable of interest was a binary variable indicating any treatment exposure to FGAH or SGAH or INS or no exposure to FGAH, SGAH or INS. Other covariates that can affect costs and that can be measured in the data set as described in Table 6.1 were included. In addition, the estimate of the error term (M1) from the probit regression was also included as an additional covariate.

Exposure to FGAH and SGAH and INS were also stratified into dose levels based on the cumulative exposure and impact on cost outcomes was examined. The only category with sufficient sample size to perform such an analysis was exposure only to high dose of FGAH in GA Medicaid. High dose was defined as greater than 60days of exposure to agent of interest and exposure below 60days was considered to be low dose. In addition to total cost, cost by categories of service was also investigated.

RESULTS

There were 108,961 patients with a AD/AR diagnosis in GA Medicaid. On removing patients who had a prescription for an asthma medication (excluding oral steroids) that was not a part of an asthma diagnosis before an AD/AR diagnosis and removing patients whose asthma diagnosis that preceded an AD/AR diagnosis, there were 80,326 AD/AR patients who remained. 369 patients were excluded based on a diagnosis of HIV/ AIDS/ Cystic fibrosis resulting in 79,957 patients. There were 6,771 patients (of the 79,957) who developed asthma of which 4,277

(63.16%) asthma patients in GA Medicaid were eligible for 12 patients after their first asthma flag and were retained for this study; 60% were male. 66% of the GA Medicaid asthma cohort was black. Of these patients 2,906 (68%) had at least one prescription for a FGAH, SGAH or INS from birth until they developed asthma. The average days supply for FGAH was 58 days (STD: 81.88), for SGAH was 1.30 days (STD: 9.49) and INS was 0.46 days (STD: 3.89).

A total of 19,962 patients developed AD/AR in the overall commercial data and were eligible until that diagnosis. After removing patients who have a prescription for an asthma medication (excluding oral steroids) before an AD/AR diagnosis and removing patients whose asthma diagnosis preceded AD/AR diagnosis, 16,139 patients remained in the AD/AR group. Upon removing 88 patients because of diagnosis of HIV/ AIDS/ Cystic fibrosis 16,051 were retained of which 642 patients were diagnosed with asthma. 353 (54.98%) asthma patients were eligible for 12 months after their first asthma diagnosis flag of which 65% were male. Race information was not available for the commercial data. Of these patients 228 (64%) had at least one prescription for a FGAH, SGAH or INS from birth until they developed asthma. The average days supply for FGAH was 30days (STD: 36.30), for SGAH was 9 days (STD:26.94) and INS was 0.69 days (STD:7.66).

Mean costs and Standard deviation for the GA Medicaid and the commercial asthma cohorts of interest are reported in Table 6.3 and Table 6.4. In the univariate comparisons, mean per member per year total costs for patients with no exposure to FGAH or SGAH or INS were $ 237 more as compared to patients with exposure to these agents in GA Medicaid (p=0.07). Total medical costs (excluding all prescriptions costs) were actually $ 253 higher for the non-exposure groups as compared to the exposure groups (p=0.02). The total number of inhaled and oral corticosteroids, and beta-agonist prescriptions were similar for the exposure and non-exposure groups in GA Medicaid. Univariate comparison between High FGAH (only) and no exposure to any agent in GA Medicaid are presented in Table 6.5.

In the commercial data, patients with exposure to FGAH or SGAH or INS had lower mean per member per year total cost as compared to patients with no exposure to these agents. However, mean PMPY asthma prescription costs were almost double for the exposure groups as compared to the non-exposure groups ($p<0.01$). The numbers of beta-agonists, oral steroids were also significantly greater for the exposure groups as compared to the non-exposure groups. Adjusted net costs for the GA Medicaid and commercial cohorts are presented in Table 6.6. In GA Medicaid any exposure to FGAH or SGAH or INS was associated with non-significant net per member per year total cost ($ -87). In commercial, exposure to FGAH, SGAH, INS seemed to reduce mean PMPY net costs by $ 546 but was not statistically significant. Total medical costs $702 (excluding prescriptions) and physician costs ($429) were however significantly lower for the exposure groups as compared to the non-exposure groups in the commercial data ($p<0.05$)

There were also 854 patients in the GA Medicaid cohort with greater than 60 days of cumulative exposure to FGAH. The costs for these patients were compared in a similar analysis to patients with no exposure to FGAH, SGAH and INS. While most categories of service presented the same trends as the overall GA results, adjusted net mean PMPY inpatient costs were $ 304 lower for this sub-group (95% CI: -490 to -119) and adjusted net mean PMPY outpatient costs were $70 lower (95% CI: -111.43 to -28.83)

DISCUSSION

The national annual health care cost for pediatric asthma is approximately $3 billion, of which direct treatment costs account for approximately $2 billion and indirect costs $1 billion. Children with asthma had more inpatient hospital days (0.23 versus 0.11 per year), required 65% more non-urgent outpatient clinic visits, filled 2.8 times more prescriptions, and incurred 88% higher medical expenses than those without asthma (Mellon 2004). Because hospitalizations account for a large proportion of direct costs of pediatric asthma (74% and 34% of direct costs in children aged 0 to 4 years and 5 to 17 years, respectively), measures aimed at improving care to reduce hospital use would significantly decrease the overall costs of pediatric asthma. Treatment

of allergic rhinitis symptoms has been documented to reduce asthma exacerbations in adults as compared to asthma patients not being treated for AR (Crystal-Peters et al. 2002). Intranasal steroids and prescription antihistamines also reduced the risk of asthma ED visits as much as 30% after controlling for asthma severity (rate of beta-agonist and inhaled steroids dispensing) and other demographics (Adams et al. 2002). AR and asthma and AD and asthma co-exist in as much as 14-21% of the population (Crown et al. 2003); (Illi 2001)). These co morbidities drive asthma exacerbations and therefore asthma treatment costs. AR increases asthma treatment costs as much as $350 (Halpern et al. 2004). This study which examines the effect of treatment for AD/AR on new diagnosed asthma treatment costs was able to demonstrate some potential benefits of this exposure. Total medical costs were significantly lower in MarketScan asthma cohort treated for AD/AR as compared to patients not treated for this condition after adjusting for asthma control. Results were not conclusive in adjusted analysis in the overall GA Medicaid but were significantly lower for high dose of FGAH exposure especially with regards to inpatient and outpatient costs. Adjusted net PMPY total costs for the exposure cohort were $ 87 dollars lower in GA Medicaid and $ 546 lower in MarketScan data although it did not achieve significance (Table 6.6).

There are several limitations to this study that must be addressed. OTC medication not covered by GA Medicaid and MarketScan could not be controlled for in the analysis. Asthma severity is also modified by the environment may affect as much as 30% of asthma treatment costs (Mellon2004). This impact could not be controlled for in the analysis. This study accounts for only direct medical costs and indirect asthma costs are not included which constitute a significant portion of asthma costs. The lower volume of claims in GA Medicaid in 1997 in the last quarter and the discrepancy in 1998 medical claims files may have lead to certain asthma diagnosis or exposure to FGAH, SGAH and INS being missed. However, given the length of the study in GA Medicaid and the non-dependence of this study of monthly claims volume, the impact of this on the results is not as much a concern.

CONCLUSION

Exposure to anti-inflammatory agents reduced asthma direct medical costs in patients with regards to total medical costs (excluding prescriptions). Since asthma treatment costs correlate with asthma severity, treatment with FGAH, SGAH and INS may translate into lower severity for asthma in such patients. Efficacy of these pharmacologic interventions may be improved by a combination with allergen avoidance and other interventions.

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FIGURE 6.1: Outline of study layout for asthma treatment cost study

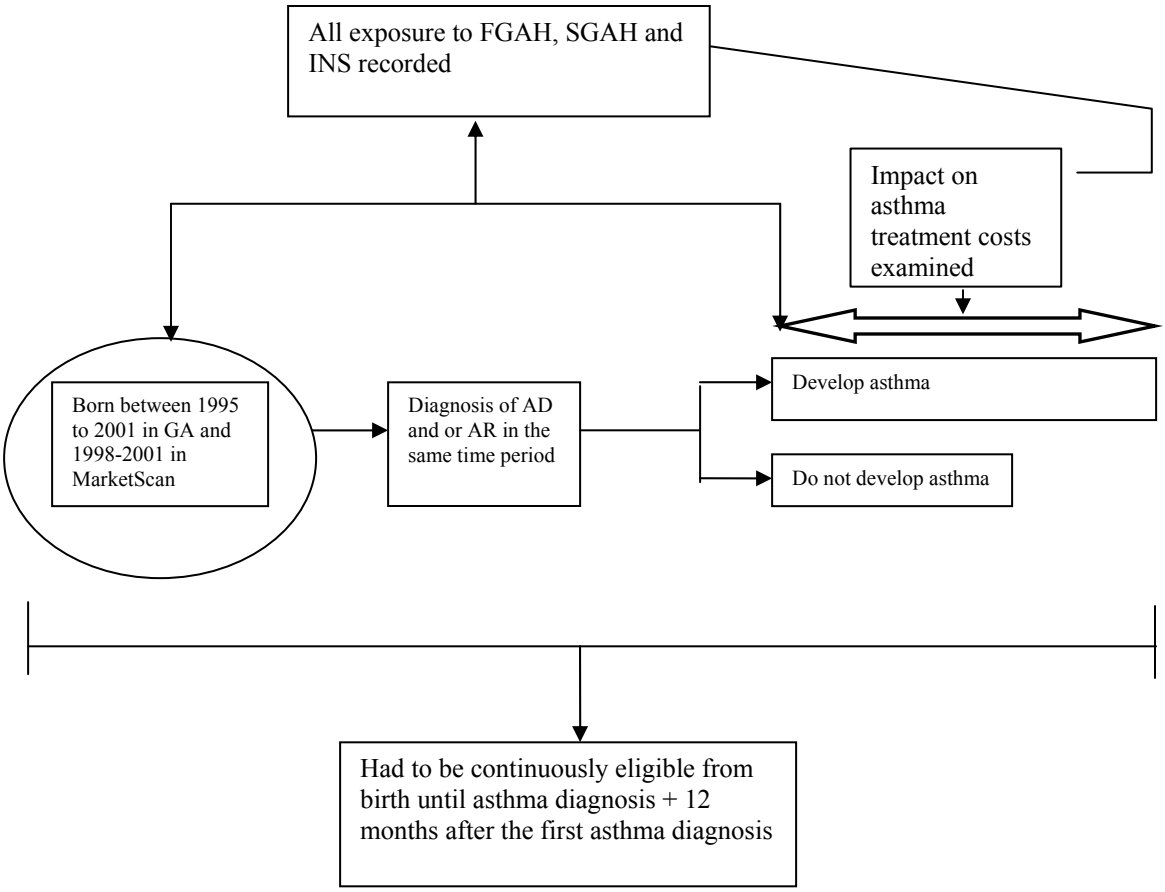

Table 6.2: List of covariates, other than treatment exposure that may influence treatment assignment and also cost outcomes

	Covariates in the cost of asthma model (2b) and 2nd stage of Heckman model for cost
Demographics Age at first diagnosis of allergic disease ,	Yes
Sex and Race	Yes
Type of health plan for Marketscan data	Yes
Premature birth, Respiratory difficulties at birth	Included in the treatment selection models
Any diagnosis of Sinusitis, Otitis Media, URTI, P.Influenza, Pneumonia, Bronchitis, RSV infection, Bornchilitis, GERD^^	Yes
Co morbidity based risk adjustment method (Ricci2002) Any diagnosis of Congestive Heart failure, Valvular disease, Peripheral Vascular Disease, Hypertension, Hemiplegia, Neurological Disorder , Hypothyroidism, Renal failure and chronic disorder, Liver Disease, Peptic Ulcer Disease, Aids, Coagulopathy, Obesity, Weight Loss, Fluid and Electrolyte disorder, Anemia, Cerebrovascular disease	Included in the second stage of modeling
Season of birth (Fall, spring, summer, winter)	Yes
Physician Specialty (Resnick 1996)	Yes
^Number of oral corticosteroids prescriptions	Included in the second stage of modeling
^Number of beta-agonist prescriptions	Included in the second stage of modeling
^Number of inhaled corticosterido prescriptions	Included in the second stage of modeling
Socio-economic index (using zip-code)	Yes

^^ For the treatment selection models, observation period was the time from birth until the first asthma diagnosis. For the cost models, observation period was the one year after the asthma diagnosis.

Table 6.3: Direct medical costs, medical utilization for patients in the AD/AR cohort stratified by exposure to anti-allergic medication for GA Medicaid for 12 months after asthma incidence, N=4,277

	For asthma patients with no exposure to FGAH, SGAH, INS or cromolyns, N= 1,462			For asthma patients with at least one prescription of FGAH, SGAH, INS or cromolyns, N=2,815				
	Number of patients (% with any claim)	Mean (STD) of number of claims	Mean Per Member Per year (STD) for paid amounts $	Number of patients (% with any claim)	Mean(STD) of number of claims	Mean Per Member Per year (STD) for paid amounts $	p-value comparing utilization	p-value for costs
Adrenergic bronchodilators	877 (65.11)	2.17 (3.02)	$ 50 (94.42)	1754	2.11 (2.85)	$ 53 (117.2)	0.55	0.34
Oral Corticosteroids	651 (48.33)	1.04 (1.56)	$ 13 (20.98)	1323	1.02 (1.50)	$ 13 (20.85)	0.69	0.28
Lukotriene Inhibitors	34 (2.52)	0.07 (0.64)	$ 4 (40.081)	112	0.13 (0.93)	$ 9 (60.71)	0.02	0.01
Other respiratory inhalants	194	0.27 (0.96)	$ 14 (59.64)	368	0.30 (1.16)	$ 16 (64.34)	0.36	0.39
Asthma combinations	6	0.01 (0.09)	$ 0.05 (1.37)	22	0.01 (0.20)	$ 0.14 (1.89)	0.05	0.05
Methylxanthines	9	0.01(0.13)	$ 0.08 (1.16)	12	0.01(0.11)	$ 0.06 (1.07)	0.49	0.40
Inhaled Corticosteroids	113	0.15 (0. 67)	$ 7 (31.46)	187	0.14 (0.72)	$ 6 (32.21)	0.86	0.71
Non-asthma Medications	953	6.38 (8.32)	$ 187 (655.91)	1988	7.38 (8.39)	$ 183 (338.64)	< 0.01	0.81
Inpatient	139	0.12 (0.45)	$ 561 (2159.71)	234	0.11 (0.48)	$ 473 (2329.17)	0.5	0.23
Other Medical	278	1.09 (4.61)	$ 86 (947.29)	492	0.89 (4.26)	$ 58 (311.26)	0.16	0.14
Outpatient	501	4.27 (7.21)	$ 204 (564.57)	912	3.62 (6.57)	$ 169 (494.16)	< 0.01	0.03
Physician visit	1314	25.89(24.65)	$ 2,052(2092.51)	2548	24.18 (17.66)	$ 1,950 (1648.66)	< 0.01	0.08
Emergency	3	0.002 (0.04)	$ 0.33 (7.88)	4	0.001 (0.05)	$ 0.10 (3.50)	0.86	0.20
Total asthma prescriptions	1347	3.72 (5.09)	$ 88.17 (173.31)	2587	3.74 (4.92)	$ 98.06 (185.92)	0.88	0.09
Total medical	1347	34.09 (23.80)	$ 2,905 (3290.00)	2587	31.32 (17.03)	$ 2,652 (3114.02)	0.01	< 0.01
Total Cost	1347	41.43 (31.08)	$ 3,189 (3487.34)	2587	39.87 (25.51)	$ 2,952 (3203.40)	0.07	0.02

Table 6.4: Asthma costs, medical utilization for patients in the AD/AR cohort stratified by exposure to anti-allergic medication for MarketScan for 12 months after asthma incidence, N=351

	For asthma patients with no exposure to FGAH, SGAH, INS , N=228			For asthma patients with at least one prescription of FGAH, SGAH, INS, N=123				
	Number of patients (% with any claim)	Mean (STD) of number of claims	Mean Per Member Per year (STD) for paid amounts $	Number of patients (% with any claim)	Mean (STD) of number of claims	Mean Per Member Per year (STD) for paid amounts $	p-value comparing utilization	p-value for costs
Adrenergic bronchodilators	143 (69.75)	1.74 (1.91)	$ 21 (46.16)	105 (88.23)	2.48 (3.40)	$ 47 (96.40)	0.01	0.01
Oral Corticosteroids	91 (44.39)	0.79 (1.12)	$ 7 (13.66)	78 (65.54)	1.25 (1.38)	$ 12 (17.73)	< 0.01	0.01
Lukotriene Inhibitors	5 (2.43)	0.04 (0.45)	$ 2 (18.77)	10 (8.40)	0.30 (1.29)	$ 16 (72.59)	< 0.01	0.01
Other respiratory inhalants	30 (14.63)	0.37 (1.27)	$ 14 (46.43)	22 (18.48)	0.43 (1.21)	$ 17 (51.89)	0.5	0.68
Inhaled Corticosteroids	15 (7.31)	0.16 (0.91)	$ 5 (32.30)	16 (13.44)	0.30 (0.96)	$ 11 (38.40)	0.17	0.16
Non-asthma Medications	169 (82.43)	8.688 (8.45)	$ 242 (377.69)	118 (99.15)	14.78 (10.33)	$ 362 (346.42)	< 0.01	< 0.01
Inpatient	183 (89.26)	13.64 (20.82)	$ 710 (4436.79)	117 (98.31)	16.81 (35.63)	$ 528 (1174.48)	0.37	0.65
Outpatient	176 (85.85)	3.56 (7.73)	$192 (572.29)	94 (78.99)	2.80 (5.57)	$157 (342.49)	0.33	0.52
Physician visit	10 (4.87)	12.91 (17.74)	$ 865 (1451.57)	9 (7.56)	7.36 (11.98)	$ 659 (1521.45)	<0.01	0.21
Emergency	50 (24.39)	0.89 (2.14)	$ 100 (311.36)	24 (20.16)	1.05(3.36)	$ 72 (201.27)	0.59	0.37
AcuteCare Hospitalizations	8 (3.90)	0.83 (0.65)	$ 15.65 (108.19)	6 (5.04)	0.17 (1.0457)	$ 11 (50.68)	0.33	0.60
Other Medical	15 (7.31)	0.57 (2.74)	$ 48 (258.89)	5 (4.20)	0.99 (3.82)	$ 40 (185.50)	0.95	0.77
Total asthma prescriptions		3.15 (3.81)	$ 51 (99.78)		4.78 (5.67)	$ 103 (182.71)	< 0.01	< 0.01
Total medical	324	31.68 (33.49)	$ 1933 (5255.50)	324	28.73 (42.62)	$ 1,469 (2432.55)	0.39	0.35
Total		44.55 (34.50)	2195 (5264.99)		51.43 (48.96)	1966 (2561.24)	0.12	0.65

Table 6.5: Direct medical costs, medical utilization for patients in the GA AD/AR cohort with high exposure to FGAH (> 60 days) for 12 months after asthma incidence, N=854

	For patients with high exposure to FGAH in GA Medicaid (N=854)		
	Number of patients (% with any claim)	Mean (STD) of number of claims	Mean Per Member Per year (STD) for paid amounts $
Adrenergic bronchodilators	529	2.04 (2.81)	52 (137.08)
Oral Corticosteroids	392	0.95 (1.46)	13.66 (21.63)
Lukotriene Inhibitors	49	0.19 (1.08)*	13.03 (75.37)*
Other respiratory inhalants	120	0.35 (1.17)	18.44 (66.50)
Inhaled Corticosteroids	61	0.53(0.19)	2.79 (25.89)
Non-asthma Medications	640	7.85 (8.41)*	203 (352.52)
Inpatient	53	0.08 (0.34)*	287 (1318.85)*
Other Medical	125	0.69 (3.93)**	45 (279.43)
Outpatient	267	2.89 (5.56)*	128 (356.75)*
Physician visit	764	23.66 (16.80)**	1935 (1589.513)
Emergency	2	0.0035 (0.076)	0.10 (2.6226)
Total asthma prescriptions	854	3.71 (4.80)	103 (208.66)
Total medical	854	27 (17.60)*	2396 (2117.33)*
Total Cost	854	39 (24.73)	2728 (2282.04)*

* $p < 0.01$ as compared to No-exposure to FGAH or SGAH or INS (N=1,462)

** $p = 0.01$ as compared to No-exposure to FGAH or SGAH or INS (N=1,462)

Table 6.6 Mean per member per year net adjusted costs for GA Medicaid and MarketScan asthma cohorts

	GA Medicaid	MarketScan
	Adjusted Net Costs (95% CI)	Adjusted Net Costs (95% CI)
Total Cost	$ -87 (-281.56 to 105.65)	$ -546 (-1108.41 to 16.37)
Total Asthma Prescription costs	$ 12 (0.98 to 23.28)	$ 11 (-9.31 to 31.41)
Total Medical Costs	$ -103 (-293.44 to 86.10)	$ -702 (-1252.79 to -151.73)
Inpatient	$ -33 (-184.33 to 117.64)	$ -206 (-643.38 to 229.388)
Outpatient	$ -12 (43.27 to 17.98)	$ -37 (-119.73 to 44.07)
Physician	$ -53 (-153.29 to 46.39)	$ -429 (-712.08 to -146.34)
Other Medical	$ -3.90 (-30.64 to 22.83)	$ -20 (-85.71 to 44.27)

CHAPTER 7

CONCLUSION

Exploratory analysis for risk factors for asthma incidence was able to establish that the natural course of asthma does somehow have a pattern. Maternal asthma, lower respiratory tract infections such as RSV, bronchitis, Bronchiolitis and pneumonia were consistent risk factors for an asthma diagnosis. There were some interactions between the nature of the population under study i.e.: indigent vs. a more commercial population and the patterns of asthma incidence with regards to factors such as income and location. While living in a urban location was protective against an asthma diagnosis in the indigent population, opposite was true for the commercial. GERD, which has not investigated as an independent risk factor for asthma incidence was also a significant risk factor for asthma development. Effect of exposure to anti-biotics on asthma incidence also varied by the nature of the population under study. However, this study was not able to either establish or refute the impact of dermatitis (allergic or non-allergic) and rhinitis (allergic and non-allergic) on asthma incidence, however the impact of dermatitis and rhinitis appears to confer a relatively quick progression to asthma or none at all as diagnoses that precede an asthma diagnosis of more than 1 year do not appear to increase the risk of asthma.

Assessing the impact of anti-inflammatory agents such as first generation anti-histamines (FGAH), second generation anti-histamines (SGAH) and intranasal steroids (INS) on asthma development also provided an interesting insight into the tertiary prevention of asthma. Exposure to these agents was significantly protective against an asthma diagnosis in GA Medicaid in a cohort of children with atopic dermatitis (AD) or allergic rhinitis (AR). Exposure to all i.e.: FGAH, SGAH and INS were the most protective against such a diagnosis in GA Medicaid. In the MarketScan data, while exposure to FGAH seemed to increase the risk of an asthma diagnosis as compared to no exposure, exposure to SGAH and INS were non-conclusive against an asthma diagnosis. Exposure to all agents in MarketScan data was however associated with a significant

protection against an asthma diagnosis. FGAH, SGAH and INS were protective against asthma development in both populations when the expanded asthma case definitions were used. Effect of anti-allergic medications i.e.: FGAH, SGAH and INS on asthma incidence were inconsistent across the populations in the study. Overall, exposure to anti-allergic medication such as FGAH, SGAH, and INS did not seem to affect asthma incidence. In the GA Medicaid population however, exposure to these agents did confer some protection against asthma but given the contrasting results in the commercial data this effect warrants further investigation. When a person was exposed to all three FGAH, SGAH and INS, a protective effect of asthma in both populations was observed when a broad definition for asthma was utilized. However, given that this definition may have included patients with wheezing episodes or non-asthmatics, effects of these agents on asthma incidence may be overstated.

Exposure to these agents also seemed to lower total annual asthma direct medical costs as compared to patients in the AD/AR cohort not treated with these agents. Since asthma costs are driven in part by asthma severity, these agents may act to lower asthma costs by modulating the severity of AD or AR and therefore the severity of asthma.

Asthma is chronic pediatric disease with a high economic burden that is increasing in prevalence. This study was able to demonstrate that there are certain inherent patterns in asthma development. Pharmacologic intervention with FGAH, SGAH and INS are very promising with regards to their ability to prevent asthma and reduce asthma disease severity even after its onset. These measures may be combined with non-pharmacologic interventions and patient education to get a grip on this ‘non-infectious’ epidemic.