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Seasonal and geographic variations in the incidence of asthma exacerbations in the United States

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ABSTRACT

Background: Exacerbations drive the burden of asthma and lead to significant morbidity and consumption of health care resources. Many prior studies of the epidemiology of asthma exacerbations have relied upon data from hospital care. **Objective:** The objective of this study was to determine US patterns of geographic and seasonal variations of asthma exacerbations being defined as asthma episodes requiring hospital care and/or a prescription for oral steroid. **Methods:** The study was a retrospective observational cohort study using administrative claims data for insured individuals from the Health-Core Integrated Research Database, including around 43 million members in the United States. Analyses examined 3 age groups, 6–17, 18–64, and ≥65 years and four US regions, Northeast, Southeast, Central, and Western. **Results:** Monthly rates of asthma exacerbations showed the greatest variation over the year in children, less so in adults and in the elderly. Clinically important differences in rates of asthma exacerbation were observed between regions with the Western Region having the lowest in all three age groups followed by the Northeast, Central, and Southeast regions. Peaks in children occurred in the early fall following troughs in the summer months, and peaks at year-end occurred in adults, particularly in those over 65 years. **Conclusions:** There is a striking seasonal variation in asthma exacerbations in the United States. Substantial differences between regions of the United States in asthma exacerbation rates cannot readily be explained and invite further investigation.

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Introduction

An estimated 25.7 million Americans had a diagnosis of asthma in 2009 [1], and the consequent costs in the United States, including medical and indirect costs, grew from approximately \$53 billion in 2002 to \$56 billion in 2007 [2].

Exacerbations drive the burden of asthma and lead to significant morbidity and consumption of health care resources. In the United States, the asthma-related health care costs are double (\$1740 vs \$847 per year) in patients with persistent asthma who exacerbate compared to those that do not, and the overall direct health care costs are 80% greater (\$9223 vs \$5011 per year) [3]. In a 2007 US national survey of 1003 patients with uncontrolled asthma, 36% of patients had had at least one emergency department visit and 14% at least one hospitalization due to asthma during the previous year [4]. In 2007, approximately one-third of the total \$50 billion annual asthma-related health care expenditures in the United States was for hospitalizations [3].

Asthma exacerbations are an important outcome in clinical investigations of the disease, but how those are defined is poorly standardized [5,6]. One recent report showed that 16% of asthma exacerbations led to hospital care, and 84% triggered an oral steroid order without hospital care being required [7]. Defining asthma exacerbations as events requiring an emergency department visit and/or hospital admission may significantly reduce the generalizability of the study results. Thus, the American Thoracic Society/European Respiratory Society definition of a severe asthma exacerbation includes one or more of treatment with systemic corticosteroids or a hospitalization or emergency department visit because of asthma, which included treatment with systemic corticosteroids [5].

For database studies, however, where the information on systemic corticosteroids in connection with a hospitalization or emergency department visit is unknown, the recommendation is to define an asthma exacerbation as an event including any one of a *filled* prescription for

systemic corticosteroids or a hospitalization or emergency department visit because of asthma [5], which we applied in the current study.

Indicators of asthma morbidity as well as its prevalence show regional variation across the United States [8]. Asthma prevalence is estimated to be at a lowest at 7.6% of the population in the Southern Region, rising to 8.8% in the Northeast with the West lying at 8%. Striking variation has been reported in rates of emergency department visits among people with current asthma. The highest rate is in the Northeast at 100.3 visits/1000 followed by the Midwest at 88, the South at 77, and the West at 59 [8].

Asthma exacerbations have been reported to be associated with viral respiratory tract infections (VRTI) since the 1970s [9,10], and an association of common colds with asthma symptom worsening has been observed for centuries [11,12]. In children, infectious agents have been detected in between 60 and 80% of asthma exacerbations [13,14], with estimates of rates of viral detection as high as 95% [15]. Among these, human rhinovirus (HRV) is most commonly detected [16]. Bacteria such as *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* may also play significant roles [15]. In preschool-age children, respiratory syncytial virus (RSV) is detected in 25% of asthma exacerbations [15]. RSV may cause infantile bronchiolitis and has been associated with future risk of asthma in young children [17]. Although RSV infection in older children and adults is less common than in the young, it has been demonstrated that 7.2% of hospitalizations for asthma in those older than 65 years were associated with RSV infection [18]. In adults, respiratory viruses are detected in approximately half of asthma exacerbations [19], with HRV being the most common although both influenza and coronaviruses are also prominent [17]. Asthma exacerbations are most frequently precipitated by common colds in both children and adults, and among these colds, HRV is detected in more than 50% [20]. Patterns of asthma exacerbations requiring medical intervention show strong seasonal variation reflecting in part patterns of seasonal prevalence of the respiratory viruses usually associated with them [14–16].

The majority of previous studies describing seasonal variation in asthma exacerbations have defined exacerbations when hospitalization or emergency department visits occurred and did not include prescribing of oral corticosteroids [5].

The objective of this study was to examine the seasonal incidence of asthma exacerbations by calendar month between January 2007 and December 2010 between regions of the United States and between age groups.

Improved understanding of temporal and geographic patterns of asthma exacerbations and therapy may identify opportunities for improved disease management.

Therapies aimed at reducing morbidity associated with VRTI may be of value to asthma patients, particularly during periods of higher risk [21].

Study design and methodology

The study was a retrospective observational cohort study using administrative claims data for insured individuals from the HealthCore Integrated Research Database (HIRD), a commercial health insurance claims database covering 43 million subjects in 14 US states.

Study population

The study population denominator included all patients registered with at least one International Classification of Diseases Version 9 diagnosis for asthma AND the filling of one or more prescriptions for an asthma medication during the 12 months prior to and including the month of interest in the HealthCore database between January 1st 2007 and December 31st 2010. The numerator included patients with an asthma exacerbation defined as filling of a prescription for systemic corticosteroid and/or inpatient hospitalization and/or an emergency room (ER) visit for asthma during a given study month. The demographic characteristics of the study population have been described previously [22].

For the analysis, subjects were divided into age groups (6–17 years, 18–64 years, and ≥ 65 years); US geographic regions (Northeast [PA, NJ, DE, MD, NY, MA, CT, VT, NH, ME, RI], Southeast [FL, GA, SC, NC, VA, AL, DC], Central [WV, TN, KY, OH, IN, IL, MO], and West [CA, NV]); index year (2007, 2008, 2009, 2010).

Data analysis

This study is descriptive, and no hypothesis testing or statistical analyses were performed. The findings are presented graphically.

Results

Monthly numbers of subjects in the HIRD database who had a claim for medical care with a diagnosis of asthma ranged between 225,000 and 260,000 over the four-year study period.

Table 1 shows monthly average numbers of study patients and asthma exacerbations during the four study years.

Figure 1a–c shows monthly rates (number of patients per month experiencing an exacerbation/total number of patients in respective age cohort $\times 100$) of asthma exacerbation over the 4-year study period by sex for age groups 6–17 years, 18–64 years, and over 65 years, respectively.

Table 1. Average monthly numbers of study subjects and asthma exacerbations 2007–2010.

	Average monthly number of subjects	Average monthly number of asthma exacerbations	Average monthly rate of asthma exacerbation (%)
Northeast	57,619	3637	6.3
Southeast	46,293	3480	7.5
Central	75,753	5559	7.3
Western	47,471	2435	5.1

In children of 6–17 years, the annual cycles of asthma exacerbations were pronounced with monthly exacerbation rates ranging from 3% to 8%. No clear differences were observed between the sexes in exacerbation patterns. Consistently, over the 4 study years, a sharp decline in the rate of asthma exacerbations occurred in the summer months followed by a rapid acceleration in the rate of events to a peak in mid-fall. In 2009, the fall peak was particularly pronounced climbing from a low point of a 3% rate of exacerbations in July to 8% in October/November. These elevated levels were sustained during the early winter with a decline in late winter followed by further growth in exacerbation rates in the spring. The extraordinary peak in fall 2009 coincided with the North American epidemic of H1N1 influenza.

In adults of 18–65 years, a trough was observed in July, but the overall range of monthly rates of asthma exacerbations was between 5% and 7% in men and 6% and 9% in women. In adults of 65 years and over, monthly exacerbation rates ranged from 7 to 10% over the year with lowest levels in the summer.

No differences in annual asthma exacerbation cycles between the sexes were observed in children or adults over 65 years. However, in adults aged 18–64 years, women had monthly rates 25–30% greater than men over the whole study period.

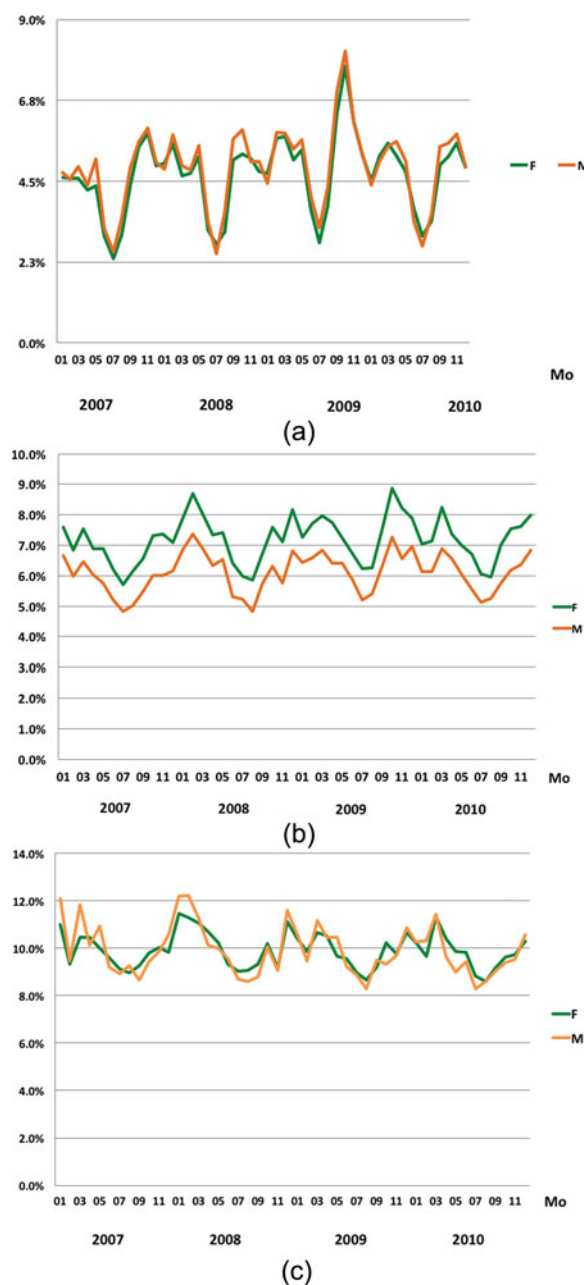
Figure 2a–c shows the monthly rates of asthma exacerbation by study year in the four study regions for children aged 6–17, adults 18–64, and people aged 65 years or over, respectively.

In all regions, the temporal patterns observed were similar to those seen in Figure 1a–c for all age groups. The 2009 fall peak in children was particularly pronounced in the Central Region, less so in the Southeast and not distinguishable from other years in the Northeast and West regions.

In adults, rates of asthma exacerbations were greatest in the Southeast followed by Central Region, Northeast and West regions. There was some crossover between the Central Region and Southeast in exacerbation rates in children and adults aged 65 years and over, but in both these age groups, the Northeast followed by the West had lower rates than the other two regions.

Figure 3a–c shows rates of asthma exacerbation by month for all years combined in the four study regions for children aged 6–17, adults 18–64, and people aged 65 or over, respectively.

For all three age groups, the Southeast and Central regions had the greatest rates of asthma exacerbation, followed by the Northeast and then by the West. Monthly variation in exacerbation rates was also more extreme in the Southeast and Central regions compared to the other two regions. In the West, children appeared to experience only a modestly increased exacerbation rate

**Figure 1.** (a) Monthly rate of asthma exacerbations in children aged 6–17 years. (b) Monthly rate of asthma exacerbations in adults aged 18–64 years. (c) Monthly rate of asthma exacerbations in adults aged ≥65 years.

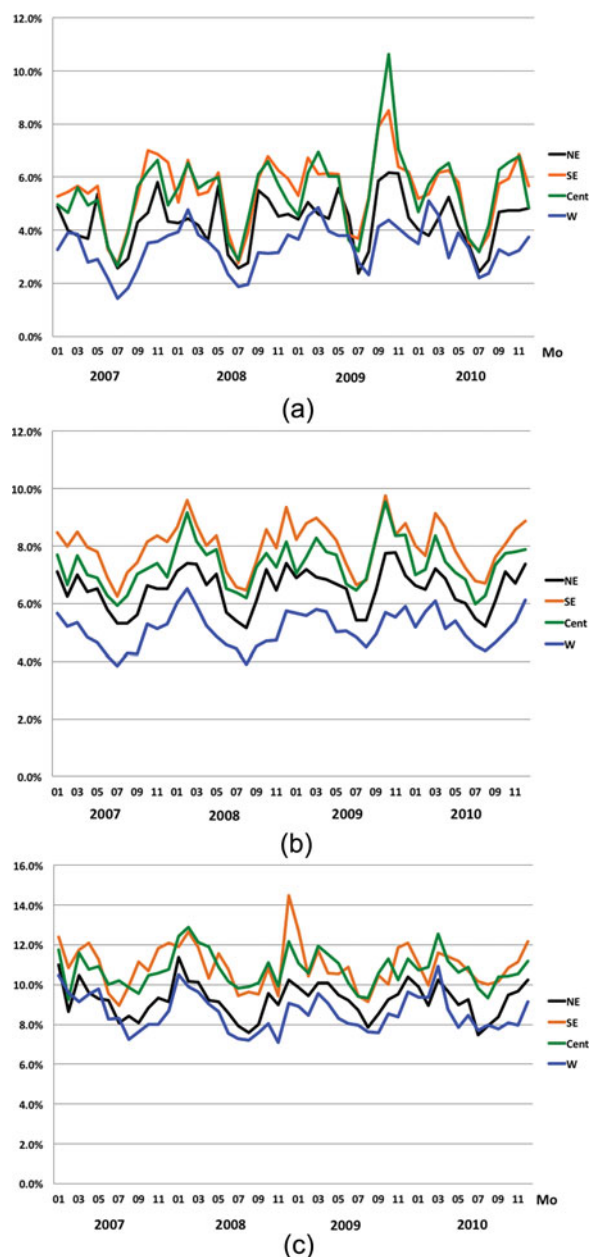


Figure 2. (a) Monthly rate of asthma exacerbations in children aged 6–17 years by US regions. (b) Monthly rate of asthma exacerbations in adults aged 18–64 years by US regions. (c) Monthly rate of asthma exacerbations in adults aged ≥65 years by US regions.

in the early fall period, and in contrast to the Southeast and Central regions, the greatest period of risk for asthmatic children was in the late winter and early spring.

Overall, the annual exacerbation rates were lowest in children but had the greatest variation with a range of 3–8%. Adults of 18–65 years had a greater exacerbation rate than children, ranging from 5% to 7% in women and 6% to 9% in men, and the exacerbation rate was greatest in adults over 65 years with a range of 8–11%.

Discussion

Knowledge of the epidemiology of asthma exacerbations is largely based on data from clinical trials, where specific and often restricting and limiting criteria have been applied for inclusion and exclusion of patients, and which frequently rely on data for in-patient or ER hospital care. These may not reflect the true burden of asthma exacerbations in the population served [23] or may not meet the need to monitor advances in asthma management [24]. Furthermore, the lack of a standardized definition of asthma exacerbations in clinical research limits the possibilities to undertake comparisons over multiple studies [5]. In the present study, we have examined the occurrence of objectively defined asthma exacerbations in a

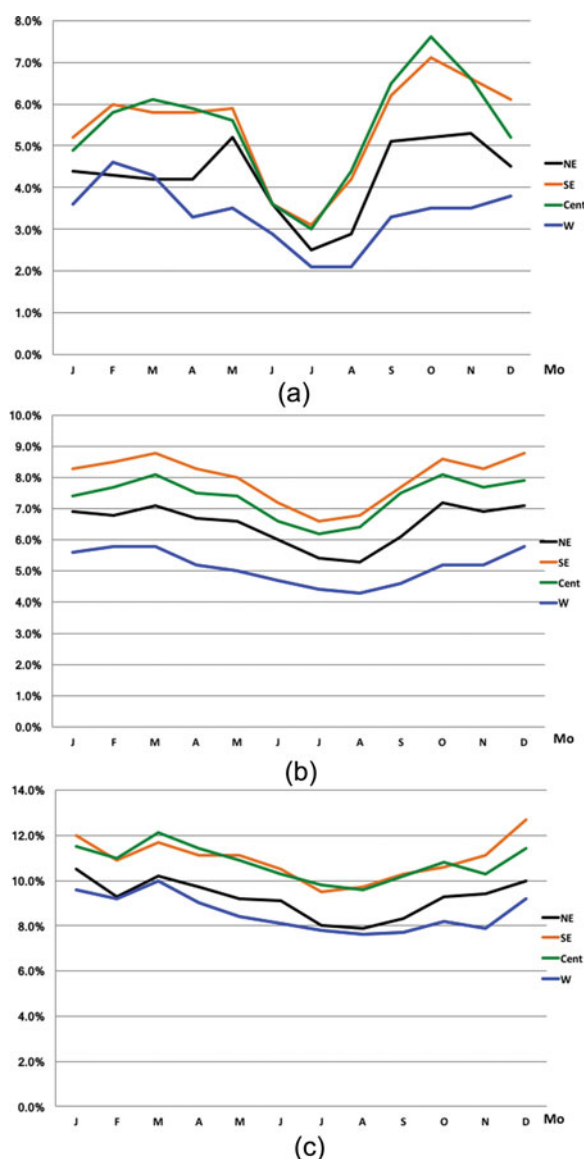


Figure 3. (a) Monthly rate of asthma exacerbations in children aged 6–17 years by US regions. (b) Monthly rate of asthma exacerbations in adults aged 18–64 years by US regions. (c) Monthly rate of asthma exacerbations in adults aged ≥65 years by US regions.

large patient population, irrespective of site of care, across the United States.

Temporal patterns of asthma exacerbations observed in this study are consistent with those reported in other countries in the Northern Hemisphere with children showing summer troughs in rates followed by peaks in the fall and continuing at high levels through winter [14,25,26]. Adults of 18–65 years showed less extreme variation in monthly exacerbation rates than children, with a smaller peak in the fall and highest levels occurring in the winter period. Adults over 65 years show even less monthly variation than younger adults but with a similar annual cycle. We surmise that the extreme peak in asthma exacerbation rates observed most strikingly in the Central Region in children in the fall of 2009 was associated with the H1N1 influenza epidemic [27].

The observed differences in exacerbation rates between regions of the United States in asthma exacerbation rates in this study are striking and consistent across age groups. The higher rates of asthma exacerbations observed in women compared to men between 18 and 64 years of age are consistent with previous findings [26]. We observed no difference between the sexes in rates of asthma exacerbations in children. This may have been because the data we had available were grouped (6–17 years) for both pre- and post-pubescent children. Before puberty, rates of asthma exacerbations are greater in men than in women, and the reverse is true after puberty [26].

The differences in asthma exacerbation rates between regions that we observed may be related to ecological or climate variation although annual hospital treatment cycles for asthma have also been shown to be similar in countries with warm [28], cooler, and damp [14,26] climates. In Canada, asthma hospitalization rates were found to be similar in all areas of the country [25]. Recognizing that hospitalization data as used in the above studies, especially for in-patient events, may not reflect true population morbidity, and that the data used in this study may do so more closely, it still seems unlikely that ecological factors alone could explain the regional differences we have found. One US study [29] found that concordance with emergency department asthma management guidelines was significantly lower in the US South and West compared to the Midwest and Northeast, and treatment variation between the regions in the current study may have existed.

A study using a uniform national data set examined Canadian cities with significantly different climates adjusting for this, season and ambient air pollution levels and found that a doubling in spore and pollen levels was associated with increases in daily asthma hospitalization rates of 3.3% (95% confidence interval (CI) 2.3–4.1%) for

basidiomycetes and 2.0% (95% CI 1.1–2.8%) for grasses [30].

Thunderstorm activity is associated with significant increases in rates of asthma exacerbation and appears to coincide with high ambient levels of fungal spores and grass pollens. A six-fold increase in calls to a general practitioner home visit call center was recorded during a bout of severe thunderstorms in the United Kingdom [31] and increases in ER use for asthma coinciding with thunderstorms have been reported in well-conducted studies in North America and Australia [32,33]. High concentrations of aeroallergens, especially grass pollens and fungal spores, coincided with thunderstorm activity in all these studies. A case-control study at one hospital in the United Kingdom of a 2002 epidemic of asthma hospitalization following a thunderstorm compared 26 subjects who sought emergency care to 31 control subjects with seasonal asthma [34]. Twenty-three of 26 cases had IgE antibodies to *Alternaria* species as did 10 of 11 controls who reported having asthma exacerbations during thunderstorms [34].

While beyond the scope of this study to quantify, it is possible that regional variation in weather patterns, particularly the occurrence of violent storms, may contribute to the regional differences we have found.

It is possible that there are differences between the populations insured by HealthCore in the West and Southeast compared to the Central and Northeast regions that may influence asthma exacerbation rates, such as socioeconomic status and its determinants. It is possible as well that there has been greater success in asthma management in the West and Northeast compared to the other two regions. Subjects whose claims are managed by HealthCore may receive care from health care providers of different types. There may be regional differences between receipt of care from different types of health care delivery organizations, which could have influenced the rates of asthma exacerbation as defined in this study. We did not have access to data on the type of health service provider or purchaser in this study. We acknowledge that filling of a prescription for systemic steroids may not necessarily coincide with an asthma exacerbation but may occur when prescribed as a contingency for exacerbation occurrence. Our data did not permit differentiation of prescription filling for either of these possibilities. We surmise that there is no reason to expect a systematic difference between regions or age groups in the likelihood of the two, but the possibility of such an effect on our findings must be recognized.

In summary, we have shown that there is a striking seasonal variation in asthma exacerbations in the United States, with peaks in children occurring in the early fall following troughs in the summer months, and at

year-end in adults, particularly in those over 65 years. These patterns are consistent across regions of the United States, but there are regional differences in the intensity of these seasonal differences that cannot readily be explained. These findings confirm the importance of understanding periods of high risk for asthma patients and ensuring that asthma management plans and therapy are up to date when these occur. While it has not been reported in other settings, it is possible that some of the differences we have observed between regions of the United States reflect differences in patterns of respiratory pathogen prevalence and variation in disease management.

Declaration of interest

The authors have reported the following conflicts: Mr Johnston has received research funding and/or honoraria from Merck Canada Inc., GlaxoSmithKline Canada and AstraZeneca PLC. Authors Gerhardsson de Verdier, Gustafson, McCrae, and Edsbacker are employed by AstraZeneca and own shares in the company.

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