Short-Acting ß-Agonist Prescription Fills as a Marker for Asthma Morbidity

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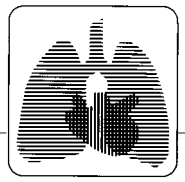

clinical investigations

Short-Acting β-Agonist Prescription Fills as a Marker for Asthma Morbidity*

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Objectives: **Hospital admissions and emergency department (ED) visits have traditionally been used to assess the strength of association between environmental exposures, such as air pollution, and asthma morbidity. In the current study, we evaluate the use of short-acting β-agonist (SABA) prescriptions as a surrogate marker for asthma exacerbation with respect to these more traditional markers.**

Methods: **Claims data for recipients covered by Illinois Medicaid with a diagnosis of asthma were obtained for fiscal-years 1996 through June 1998. Claims for short-acting bronchodilators and asthma-related ED visits and hospital admissions for 31,140 adults were identified. The odds ratio for the association of either an ED visit or hospital admission and an SABA prescription was calculated for time lags ranging from − 28 to + 28 days. Individual-subject heterogeneity and seasonal effects were corrected for using the Mantel-Haenszel method.**

Results: **After adjustment for individual and seasonal effects, there was a significant positive association between SABA prescriptions and ED visits or hospital admissions for asthma on any single day. In addition, a significant positive association was also found between the ED visits or hospital admissions occurring on the few days prior to an SABA prescription. No significant relation was found (after adjusting for subject and seasonal effects) between prescriptions and admissions when an SABA prescription date preceded that of a hospital admission or an ED visit.**

Conclusions: **A very strong and significant association between ED visits or hospital admissions for asthma and SABA prescriptions was observed, which suggests that SABA prescription fills can be used as a marker for asthma morbidity. In addition, a temporal association exists between claims for ED visits or hospital admissions for asthma and SABA prescription claims when an ED visit or hospital admission precedes the SABA prescription.** ***(CHEST 2005; 128:602–608)***

Key words: administrative database; asthma; asthma emergency department visits; asthma hospitalizations; asthma outcomes; β-agonists

Abbreviations: CI = confidence interval; ED = emergency department; ICD9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; *L* = lag in days between events; MDI = metered-dose inhaler; OR = odds ratio; SABA = short-acting β-agonist

Data on the utilization of medical resources assessed through either existing databases or by surveys have been commonly used in population-based studies to examine the effect of environmental factors on asthma morbidity and mortality. Previous asthma studies[1–4] have focused for the most part on mortality, hospitalizations, and emergency department (ED) visits. Population-based epidemiologic studies[1–4] utilizing these outcomes have demonstrated important associations between outdoor pollutants and asthma exacerbations.

The advantages of population studies include access to a large sample size, effectively a census of the

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entire relative population, increased study power, and absence of selection bias as (at least in theory) the entire population is evaluated. There are also a number of disadvantages depending on the outcome used. For example, outcomes such as hospitalizations, and especially mortality, represent serious events that occur in only the most acutely ill individuals and may be insensitive to the variations in disease activity occurring in the majority of the population.[5]

As the approach to epidemiologic studies of the health effects of environmental hazards has moved from investigations of large metropolitan regions to small-area analysis,[6] the relative infrequency of these events seriously limits the analyses that can be performed and effects that can be detected. As a result, no reasonable models for understanding spatial relationship across areas can be fitted. Such outcomes may even negate the sample size advantages inherent in population-based studies. Although asthma admissions and ED visits occur in large numbers when an entire population is observed over an extended period of time, the events occurring on a single day within a small area, such as a particular zip code, are actually quite rare.

In so far as these studies are based on administrative claims data, other, more frequently occurring events are available to assess health-care utilization. Asthma prescriptions may provide an alternative means of assessing asthma morbidity in population studies. The use of short-acting β-agonists (SABAs) is commonly included as an indicator of exacerbation in many clinical trials[7–10] of asthma therapy and exposures; in these studies, β-agonist use is tracked by means of diary cards or auto-recording metered-dose inhaler (MDI) devices. However, the parallel approach using prescription fills for SABAs in an epidemiologic time series analysis has not been previously used for evaluations of asthma morbidity in large-scale population studies.

The association between β-agonist use and other markers of asthma morbidity and mortality has been long recognized.[11–14] Whether this association represents adverse effects of β-agonist use or is entirely due to disease severity is a matter of ongoing debate. As a number of factors may influence the timing of a prescription fill by patients with asthma, it is unclear whether the aggregate analysis of association between asthma morbidity and β-agonist use will necessarily agree with the individual-level association between β-agonist prescription fills and asthma exacerbations. We hypothesized that individuals with worsening asthma would utilize SABAs at an increase rate, resulting in an early prescription fill, and at the same time be at increased risk for other asthma-related events. Thus, we would expect an increase in the odds of a hospitalization or ED visit for asthma in the days following a short acting β-agonist prescription fill. In the current study, this question is investigated by examining the temporal association of SABA prescriptions with hospitalizations and ED visits based on the individual patients' Medicaid claims data from Illinois.

Materials and Methods

Data for this study were obtained from an administrative database provided by the Illinois Department of Public Aid Bureau of Budget and Analysis. This database includes all claims for services rendered to, and prescriptions filled by, Illinois Medicaid recipients between July 1995 and June 1998. The cohort was limited to those recipients with at least one claim coded with diagnosis-related group 096–098, or with a primary diagnosis of asthma (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD9-CM] codes 493.00–493.99) during the study period. Records related to each patient were linked using a coded recipient number to allow the data to be analyzed at an individual level while maintaining confidentiality. Approval for the use of this limited data set was obtained from the University of Chicago Institutional Review Board. Demographics for each recipient were restricted to age, gender, and zip code of residence. Information associated with each claim included the date of service, primary ICD9-CM diagnosis and procedure codes. Claims for prescriptions also contained the generic name of the medication filled.

In the current study, the analysis was restricted to individuals ≥ 17 years old at the time of the claim. The date of fill was determined for all claims for SABAs. In the rare event that the patient had more than one SABA fill on a given day (*eg*, both an MDI and nebulized formulation), it was considered as a single event in the analysis. The admission date for all inpatient hospitalizations for asthma (diagnosis-related group 096–098) as well as ED visits for a primary ICD9-CM coding for a respiratory-related diagnosis was also determined. Duplicate claims (*eg*, an ED visit followed by a hospital admission on the same day) and claims by individuals with excessive use of SABAs but with minimal other health-care utilization (>24 β-agonists per year with one or fewer asthma-related ED visits or hospitalizations) were removed. As the degree of asthma control is known to affect β-agonist utilization, individuals were also stratified into subjects receiving inhaled steroids (three or more prescriptions for steroids in a given fiscal-year) and those not receiving inhaled steroids.

The temporal association between a prescription fill event and an ED visit or hospitalization event that happen days apart (lag in days between events [L]) was assessed by calculating the odds ratio (OR) of either a hospital admission or an ED visit by an individual on day (date of SABA fill + L) given a prescription fill event for an SABA using a series of contingency tables. L varied from + 28 days (hospitalization or ED event 28 days after SABA fill) to – 28 days (hospitalization or ED visit 28 days before SABA fill). To account for correlation among repeated observations within individuals, as a sicker patient would be expected to both use more β-agonists and have more hospitalizations or ED visits than a patient with mild disease, a stratified analysis was performed adjusting for subject-level effects, with each subject acting as his or her own stratum, using the Mantel-Haenszel method.[15] As asthma activity is subject to seasonal trends even within individuals, a secondary stratification was done using a

28-day strata to adjust for unobserved time-dependent confounders (such as an increase in asthma activity due to the winter viral infections or seasonal allergies) specific to each subject. This is because we assume that these time-dependent confounders are slowly varying and do not change over the course of 1 month within each individual. We believe that this assumption is reasonable in the field of asthma-related seasonal confounders. Additional subanalysis was performed by grouping individuals by inhaled steroid use and by gender, as described above, to assess whether use of controller medication altered the temporal relationship. SEs were estimated using bootstrap methods.[16]

Results

Table 1 summarizes data for the 31,140 individuals in the cohort. As expected in an adult Medicaid population, the majority of subjects were women (78%). There was an average of 6.7 SABA fills per person per year. However, the use of β-agonists varied widely between individuals with no SABA fills to an individual with as many as 85 fills in 1 year. The yearly hospitalization rate in the cohort was quite high, averaging at 138 hospitalizations per thousand individuals for men and 116 per thousand for women. The rate of ED visits for a respiratory-related diagnosis was also high, with a rate for the entire cohort of 459 visits per year per 1,000 individuals. As with hospitalizations, the majority (78%) of recipients had no ED visits. Only 9% of individuals had more than one ED visit per year.

The association of a respiratory-related ED visit/asthma hospitalization event and an SABA prescription fill event occurring the same day is demonstrated in Table 2. The same association with *L* is demonstrated graphically in Figures 1, 2. Most apparent from this analysis is that the greatest association between a prescription fill and another event was with a lag of zero; *ie*, the event occurred on the same day the prescription was filled. The proportion of individuals filling prescriptions the same day was greater for ED visits not resulting in a hospitalization for asthma. For these individuals, 16.7% filled SABA prescriptions the same day. From the information contained in the database, it is impossible to determine whether the fill occurred before or after the ED visit. There was a rapid decrease in the number of fills on subsequent days, with only 5.7% filling prescriptions 1 day following an ED visit. For hospitalized individuals, 2.1% had an SABA fill the day of admission, presumably before being admitted. The pattern following discharge was similar, with the majority of fills for SABAs occurring on the day of discharge, with a rapidly decreasing number of fills occurring on subsequent days.

We examined ORs for steroid and nonsteroid male and female recipients in four separate analyses. For each gender-steroid grouping, we examined three separate ORs: crude (nonadjusted), subject-only adjusted, and subject-and-time adjusted. The primary focus of our analysis is on subject-by-time adjusted ORs only, but the other analyses are shown to illustrate the amount of bias may be present if correlations among multiple observations on the same subjects and also over time are not accounted for.

Table 2—*ORs of Having an SABA Prescription Fill and ED/Hospital Visit on the Same Day, for Four Adult Groups, Grouped by Steroid Use and by Gender*

Gender/Inhaled Steroids/Analysis	OR (CI)
Male	
No	
Crude	11.6 (10.8–12.5)
Subject adjusted	7.2 (6.6–7.8)
Subject and time adjusted	4.6 (4.2–5.0)
Yes	
Crude	5.5 (4.3–4.9)
Subject adjusted	4.1 (3.6–4.6)
Subject and time adjusted	3.4 (3.0–3.8)
Female	
No	
Crude	16.1 (15.4–16.8)
Subject adjusted	9.8 (9.4–10.3)
Subject and time adjusted	5.5 (5.3–5.8)
Yes	
Crude	4.3 (4.0–4.7)
Subject adjusted	3.6 (3.3–3.9)
Subject and time adjusted	2.9 (2.7–3.1)

Table 1—*Subject Characteristics

Gender	Age, yr	Inhaled Steroids, %	SABA Fills/yr	ED Visits/yr	Hospitalizations/yr
Male (n = 6,956)	45.3 ± 16.0 (18–100)	11.0	7.310 ± 6.533 (0–83)	0.562 ± 2.110 (0–67)	0.139 ± 0.630 (0–26)
Female (n = 31,140)	41.7 ± 16.0 (18–104)	10.1	6.217 ± 5.931 (0–85)	0.432 ± 1.230 (0–38)	0.156 ± 0.564 (0–25)
Total (n = 31,140)	42.6 ± 16.0 (18–104)	10.3	6.451 ± 6.081 (0–85)	0.462 ± 1.464 (0–67)	0.153 ± 0.579 (0–26)

*Data are presented as mean ± SD (range).

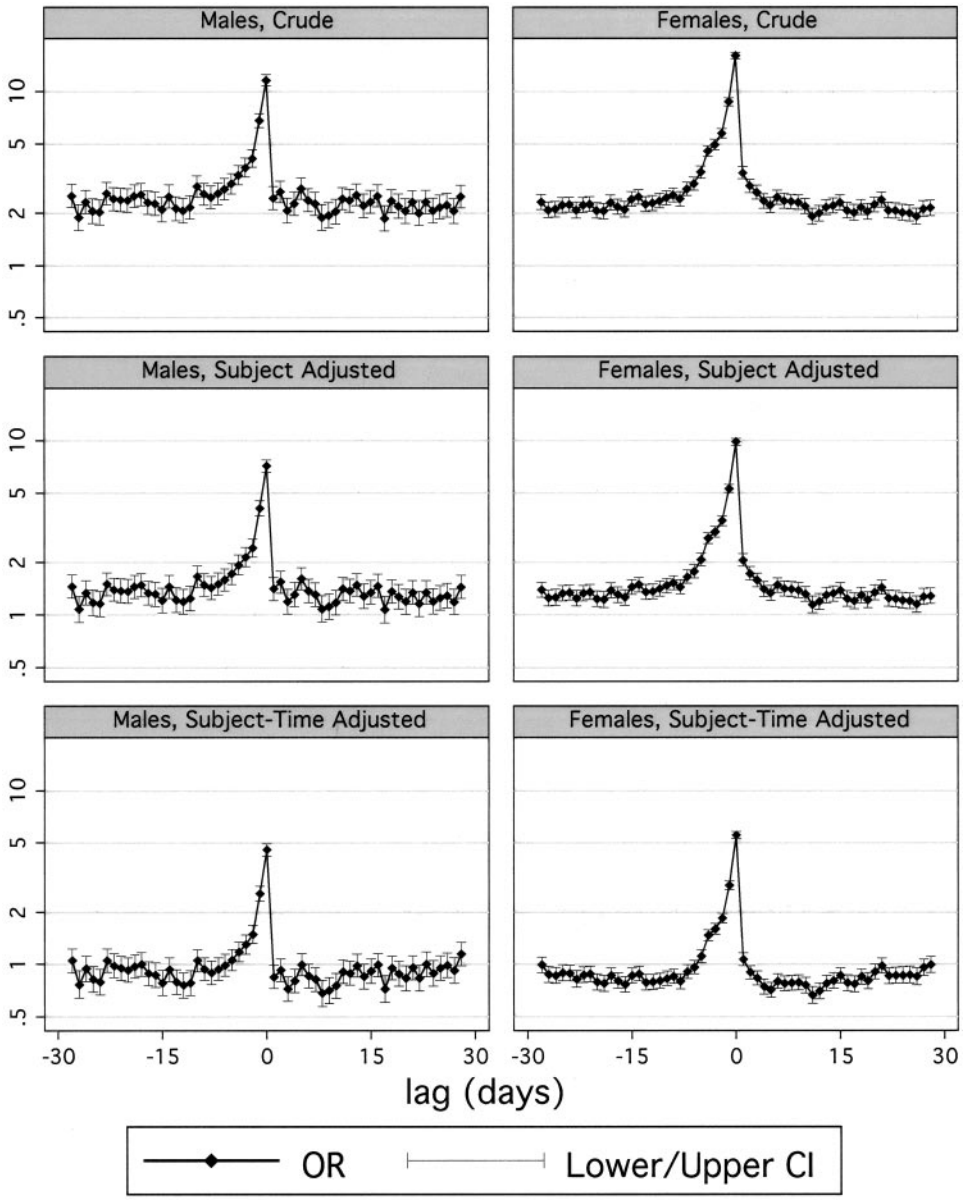

FIGURE 1. ORs for Illinois Medicaid recipients with asthma not receiving regular inhaled steroids. The lag represents the number of days between SABA prescription fill and an asthma hospitalization or an ED visit for a respiratory-related diagnosis. ORs are plotted on a logarithmic scale. Error bars represent 95% CIs.

The association between β-agonists and ED/hospital visit on the same day is larger for nonsteroid users (OR range, 4.6 to 16.1) [depending on gender and adjustment for within-subject and time-dependent effects], than for steroid users (OR range, 2.9 to 5.5). While the differences in corresponding ORs between steroid and nonsteroid users were all statistically significant, there was still a strong association between an SABA fill and an ED or hospitalization event for both steroid and nonsteroid users. Among nonsteroid users, a stronger same-day association was observed among women (range, 16.1 for unadjusted OR, to 9.8 for subject-adjusted OR, to 5.5 for subject- and time-adjusted OR) then men. Male nonsteroid users had lower association on the same day (range, 11.6 for unadjusted OR, to 7.2 for subject-adjusted OR, to 4.6 for subject- and time-adjusted OR. Among steroid users, a slightly stronger association was observed for male than female patients, although the differences between male and female patients do not appear significant. ORs range from 5.5 (unadjusted) to 4.1 (subject adjusted) to 3.4 (subject and time adjusted) for male patients, and from 4.3 to 3.6 to 2.9 for corresponding ORs for female patients.

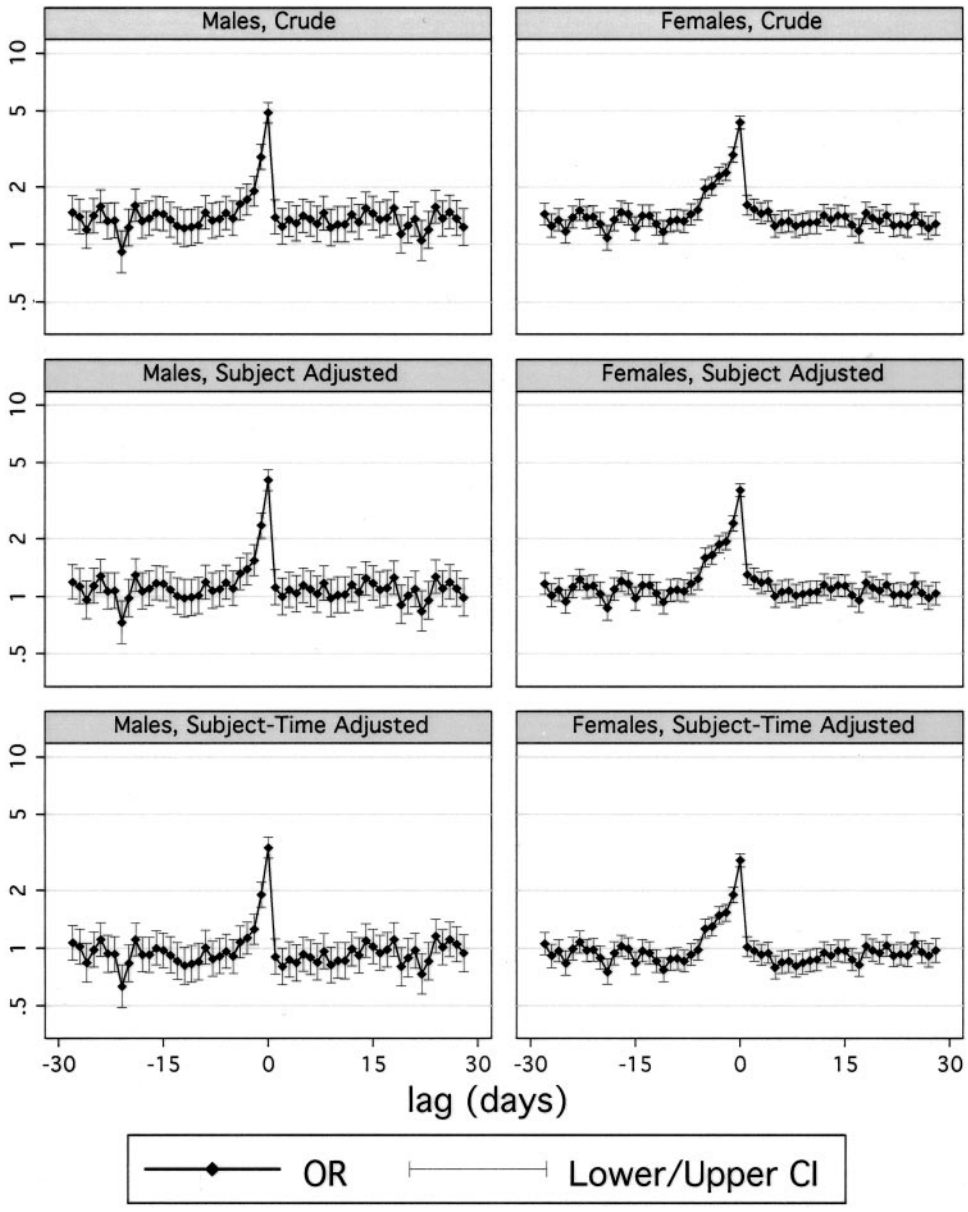

FIGURE 2. ORs for Illinois Medicaid recipients with asthma receiving regular inhaled steroids (three or more prescription fills per year). The lag represents the number of days between SABA prescription fill and an asthma hospitalization or an ED visit for a respiratory-related diagnosis. ORs are plotted on a logarithmic scale. Error bars represent 95% CIs.

When adjusting for subject and time, male steroid users had about a 3.4-times higher odds of filling a prescription on a day they had an ED or hospital visit vs a day they did not have an ED/hospital visit (confidence interval [CI], 3.0 to 3.8). For female steroid users, the equivalent OR was somewhat lower, estimated at 2.9 (CI, 2.7 to 3.1). For male nonsteroid users, the OR of filling a prescription on the day as an ED or hospital visit was 4.6 times (CI, 4.2 to 5.0) the OR if they did not have an ED/hospital visit. For female nonsteroid users, the OR of filling a prescription on the day of an ED or hospital visit was 5.5 times (CI, 5.3 to 5.8) times the OR on the day they did not have an ED/hospital visit.

Other than the day of admission, the highest association between prescription fills and other events occurred with a L of -1 to -4 days, *ie*, on the days when the hospitalization or an ED visit occurred before an SABA prescription. The mean length of stay for patients hospitalized within this cohort was 3.44 ± 2.59 days. One can observe from Figures 1 and 2 that when the adjustments for seasonality or for individual-level effects are not made, there is a residual association for a hospital-

ization or an ED visit receiving an SABA prescription that never returns to 1, even after a prolonged lag period. With the subject-and-time adjustment is made, the OR falls to 1 at the lag – 6 days and is slightly negative for the next 10 to 15 lags in both directions. This decrease in the association to less than one does not imply a protective effect of the prescription fill but rather is likely due to the high associations the day of the prescription fill leading to a lesser chance that rare events will be reoccurring a few days apart.

Discussion

The results of this study demonstrate a strong temporal association between prescription fills for SABAs and asthma events associated with the need for unscheduled asthma care in the setting of asthma exacerbation. The presence of this association is reasonable assuming that an individual with asthma who is having increasing symptoms would be expected to have increased β-agonist consumption triggering an early refill of his or her inhaler. How closely linked in time the onset of an exacerbation would be to the refill event is influenced by a variety of factors, including remaining refills on file at a pharmacy, access to a prescribing physician either through an urgent care visit (outside of the ED) or over the telephone, and access to alternate sources of medications such as multiple unused prior inhalers or a relative with the same medication.

Our initial hypothesis underlying this study was that ED visits and hospitalizations would represent a failure of the patient to be able to treat their own symptoms with MDI or home nebulizer treatment. In this formulation, a β-agonist fill should precede most hospitalizations or ED visits, thus resulting in a positive *L* association, with the patient seeking care after the use of home therapy has not caused an improvement in symptoms. The results of this study indicated that SABA fills tended to occur at or the day following contact with the medical system, either in the ED or in the following hospitalization. Despite the unexpected lag direction, the association was still marked.

It is important to note that most fills for SABAs occurred without any ED visit or hospitalization. Analysis of outpatient visits, which would be another source of SABA prescriptions in the event of an exacerbation, is thwarted by the fact that there is no way to discern an unscheduled visit for urgent care from a routine visit using claims data alone. The ICD9-CM code for acute asthma exacerbation (493.02), which might have identified at least a portion of these unscheduled visits, was not in use at the time this data were collected. There is unfortunately also no way to clearly assess whether early refills were occurring independently of any office visits (for instance following a phone call to the patient's primary care physician).

Another important finding of this study is the observation that the temporal relationship between SABA fills and other markers of asthma morbidity persists in patients receiving inhaled steroids, although the magnitude of the association is significantly reduced. This finding is helpful when assessing ability to apply the results of this study outside of the Medicaid population, or to more recent data sets, where the percentage of patients utilizing regular inhaled steroids might be expected to be higher.[17] A significant result was seen both in men, who might be expected to be a highly select group in the Medicaid population, and in women, who, while having a low income, might better represent the general populations. Despite the above observations, questions remain whether identical results will be seen in other groups with asthma.

The findings of this study are also of interest in light of the long-standing debate regarding whether inhaled β-agonists directly contribute to asthma morbidity.[18] There has been renewed focus on this issue in light of recent evidence that β-agonist receptor polymorphisms may contribute to asthma exacerbations.[19–20] A direct adverse effect of β-agonist therapy does not appear to be supported by the results of our study. If SABA usage were causal of hospitalizations and ED visits as opposed to simply being associated with these events, one would expect a lag to occur in the positive direction, that is, the hospitalization or ED event occurring after refill of an SABA. It should be noted, however, that this study was not originally designed to investigate this issue.

Conclusions

While the association between SABA prescription fills and other markers of asthma morbidity was strongest when an SABA fill preceded a hospitalization or ED event (opposite from the temporal association initially expected), the results of this study still demonstrate a strong relationship. While asthma deaths, hospitalizations, and ED visits have often been used to assess the effects of outdoor air pollution, these relatively rare events may well not be the best means of assessing asthma morbidity. The vast majority of patients who have an exacerbation are neither admitted to the hospital nor treated in the ED. These events could be considered to represent the "tip of the iceberg," as being the most severe

episodes of the disease, with the majority of patients with asthma destinations not visible through these means. The use of SABA prescription fills may provide a way of assessing asthma morbidity on a wider basis. In addition, many existing databases contain pharmaceutical data without other data on health-care utilization. These databases are becoming increasingly more available through pharmacies, health insurance providers, and pharmacy marketing firms. The validation of prescription asthma medication usage as a marker for asthma as demonstrated in this study shows that the use of these other databases, both for asthma surveillance and to study the effects of other environmental hazards, is warranted.

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