

Bias in observational study of the effectiveness of nasal corticosteroids in asthma

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Background: A recent observational study suggests that intranasal corticosteroids used to treat allergic rhinitis are effective at preventing asthma outcomes, such as emergency visits. The approach to data analysis may have led to biased results because of misclassification of immortal time.

Objective: To illustrate the bias in the cohort approach and to present the proper time-dependent analysis by replicating the recent study using data from another source.

Methods: From an existing cohort of 30,569 patients with asthma age 5 to 44 years and identified from the Saskatchewan Health databases (1975-1997), we formed the cohort of all subjects who were in the source population between January 1, 1989, and December 31, 1991. Subjects were followed to the first asthma hospitalization. All prescriptions dispensed during follow-up were identified. We replicated the time-fixed approach to data analysis used in the recent study and compared it with time-dependent approaches.

Results: The cohort included 20,173 subjects, of whom 1849 were hospitalized for asthma between January 1, 1989, and December 31, 1991. The time-fixed approach misclassified more than 5000 person-years of follow-up, corresponding to 44% of the exposed person-time. As a result, the rate ratio of asthma hospitalization after any use of nasal corticosteroids (NCSs) was 0.57 by the biased time-fixed approach compared with 1.13 by the proper time-dependent approach. The time-fixed approach produced a paradoxical protective effect of NCS with 1 or less canisters dispensed per year (odds ratio, 0.47), which was further exaggerated when the cohort was extended to

5 years (odds ratio, 0.33). Adjusted time-dependent analyses found no protective effect, even when NCSs were dispensed regularly (rate ratio, 1.10; 95% CI, 0.54-2.21).

Conclusion: The time-fixed approach to the analysis of the effectiveness of NCSs on asthma outcomes leads, by its inherent misclassification of immortal time, to a considerable exaggeration of the protective effect of these medications in preventing severe asthma exacerbations. (*J Allergy Clin Immunol* 2005;115:714-9.)

Key words: Cohort studies, biases, drug effectiveness, databases, nasal corticosteroids

Allergic rhinitis and asthma are linked in many ways.^{1,2} First, the majority of patients with asthma diagnosed in childhood or early adulthood also have rhinitis.³ Subjects with allergic rhinitis alone have increased bronchial hyperresponsiveness⁴ and are at significant risk of developing overt asthma in the future.⁵⁻⁷ Both disorders have a common allergic etiology^{7,8} as well as similar inflammatory pathophysiology.⁵ Topical corticosteroids have been shown to be the most effective therapeutic agents in both disorders.⁹⁻¹¹ Recently, allergenic nasal challenge has been shown to worsen bronchial inflammation¹² and segmental bronchial challenge appears to provoke a nasal inflammatory response in subjects with allergic rhinitis.¹³ Presumably, this occurs via a systemic component of the inflammatory response.¹⁴ Asthma and allergic rhinitis combine to affect quality of life adversely,¹⁵ and the presence of allergic rhinitis substantially increases health care charges among patients with asthma.³

Several studies have reported reduced asthma symptoms and lower airway responsiveness when nasal corticosteroids (NCSs) are given before allergen exposure,^{16,17} although the effect on lower airway function is small and has not been reproduced in 1 study.¹⁸ In 2002, Adams et al¹⁹ conducted an observational study by using a cohort formed from a health claims database. They reported a significant benefit of NCS on emergency department (ED) visits for asthma. A surprising finding is the 26% reduction in the rate of ED visits for asthma over a 3-year period with just 1 or fewer prescriptions of NCS per year compared with patients with no such prescriptions. The authors claim that these results are plausible given the high efficacy of NCS when used on an as-needed basis during allergy season. We argue instead that the study design and analysis introduce a variation of immortal time bias that leads to significant distortion of the results.

Immortal time is a period of follow-up in a cohort study during which, by design, the study outcome cannot

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Abbreviations used

ED: Emergency department
NCS: Nasal corticosteroid
RR: Rate ratio

occur.^{20,21} For the exposed subjects of the study by Adams et al,¹⁹ for example, the time from cohort entry to the first prescription for a NCS is immortal because no ED visit could have occurred during this span; had one occurred, the subject would have been censored at that point and classified in the unexposed group. An incorrect consideration of such immortal time (incorrectly classified as exposed to NCS when in fact unexposed until the first NCS prescription) in the analysis of a cohort study will seriously bias the results. Two forms of this bias have been shown to occur in the context of cohort studies of the effectiveness of inhaled corticosteroids in chronic obstructive pulmonary disease on mortality.²²⁻²⁵ In these studies, drug exposure was measured dichotomously, and subjects were considered as either exposed or unexposed throughout the entire cohort follow-up, irrespective of when they started treatment. The bias in those studies resulted because the data analysis did not properly account for changes in the drug exposure over time, particularly the fact that a subject was unexposed from cohort entry to the start of inhaled corticosteroid therapy and exposed only thereafter. Misclassifying or simply excluding this unexposed period will considerably bias the results toward an apparent protective effect.^{24,25}

Although the nature of the bias in the study by Adams et al¹⁹ is similar, its appearance is quite different from these other studies. In their study, the exposure measurement appears to account for time by using the mean number of NCS prescriptions per year. This approach can give the impression that the time-dependency of drug exposure is properly taken into account and therefore free of immortal time bias. In this article, we show that the approach used in this cohort study, by its exposure definition, is equally subject to immortal time bias. We describe and illustrate the bias by using data from another cohort of patients with asthma.

METHODS

To describe the nature of the bias, we replicated the design used in the study by Adams et al¹⁹ in another cohort formed from the Saskatchewan Health databases. Although this replication is not entirely exact because of the differences in the databases, the similarities are sufficient to clearly demonstrate the bias.

Source of data

The source population of patients was obtained by using the computerized databases of Saskatchewan Health.²⁶ Briefly, these databases developed as a result of the universal health insurance program provided to all residents of this Canadian province since

1975. Two million people have been covered by this program since its inception. We selected from this population all 30,569 beneficiaries age between 5 and 44 years who received at least 3 prescriptions of an antiasthma medication in any 1-year period between September 1975 and December 1991. The medications included all antiasthma medications, except for oral corticosteroids, covered by the health insurance plan during the study period, namely beclomethasone, budesonide, triamcinolone acetate, flunisolide, sodium cromoglycate, ketotifen, nedocromil, salbutamol, fenoterol, terbutaline, isoproterenol, metaproterenol, procaterol, epinephrine bitartrate, ipratropium bromide, and any compound of theophylline. Oral corticosteroids were not included to avoid selecting subjects with conditions other than asthma. However, all oral corticosteroids prescriptions were subsequently obtained for the selected subjects. The subjects were followed from the date of the third prescription for an antiasthma drug until their 55th birthday, the date of death, the date of emigration from the province, or December 31, 1997, whichever occurred first.

Study cohort

For the purposes of the current analyses, we selected all subjects who were in the source population at any time during the 3 years spanned by January 1, 1989, to December 31, 1991. We restricted the analyses in this way to mimic the study of Adams et al¹⁹ and to allow the sensitivity analysis described here. The beginning of follow-up was therefore January 1, 1989, or the start of eligibility in the health insurance program, whereas the end of follow-up was December 31, 1991, the end of coverage as a result of leaving the province or death, or the occurrence of the study outcome, namely the first hospitalization for asthma.

To emphasize the nature of the bias, we performed a sensitivity analysis by creating another cohort from this population of patients with asthma with a wider observation period (5 years, 1989-1993).

Outcome

The outcome was the first admission to hospital with a primary diagnosis of asthma during the 3-year follow-up. Subjects with this outcome were considered cases. All information and person-time after the outcome were censored.

NCS exposure

We identified all prescriptions of NCS dispensed to the cohort members during follow-up. This included nasal formulations of beclomethasone, budesonide, flunisolide, and triamcinolone.

Because the bias we describe in this article depends on the exposure definition, we present various definitions. The first measure of NCS exposure is the measure used by Adams et al,¹⁹ namely the mean number of canisters per year. It is calculated by dividing, for each subject, the number of canisters of NCS dispensed during the follow-up period by the duration of this period in years. This approach classifies subjects who received NCS at anytime during follow-up as exposed to this mean value for the entire follow-up, including the period preceding the first observed prescription of NCS. Subjects were considered unexposed if they received no prescriptions for NCS during their entire follow-up. We call this measure *time-fixed* because it does not change over time; the subject receives the same value of exposure for the entire follow-up.

The second definition of exposure is a simple time-dependent measure that classifies exposure according to person-time of follow-up and not subjects. This approach follows the basic principles of cohort studies.^{20,21} Thus, the person-time of a subject is classified as unexposed to NCS from the start of follow-up until the time of the first NCS prescription and as exposed thereafter. By this simple definition,

TABLE I. Characteristics of cases hospitalized for asthma and noncases identified from the 3-year cohort (1989-1991)

	Cases	Noncases
Number of subjects	1,849	18,324
Duration of follow-up in years (mean $\pm$ SD)	1.5 $\pm$ 0.9	2.9 $\pm$ 0.3
Age at cohort entry in years (mean $\pm$ SD)	17.6 $\pm$ 13.0	21.8 $\pm$ 13.4
Male sex (%)	58.4	57.4
Use of asthma medications during follow-up (%)		
Inhaled β_2 -agonists	85.7	91.9
Xanthines	34.3	22.9
Cromolyn	30.4	28.4
Oral corticosteroids	19.4	14.3
Inhaled corticosteroids	28.1	41.0
NCSs	13.1	21.2

as soon as a subject receives 1 prescription, the subject is considered exposed until the end of follow-up.

The third definition is a more accurate time-dependent measure that considers the timing of each NCS prescription dispensed during follow-up. Assuming that each prescription lasts as long as 45 days, each person-day of follow-up was classified as exposed or unexposed. This allowed us to define *current use*. We also computed a measure of the regularity of use as the proportion of days before any given day of follow-up and including that day that the subject was exposed to NCSs.

Data analysis

To illustrate the bias, we first describe the time to the first hospitalization among subjects with this outcome and compare it with the mean duration of follow-up among the nonhospitalized subjects. These follow-up times are used to compute the mean number of canisters per year that forms the basis for the time-fixed exposure measure used in the approach by Adams et al.¹⁹

For this time-fixed exposure measure, we first estimated the rates of asthma hospitalization among the exposed and unexposed subjects. We also estimated the corresponding rate ratio (RR) and the confidence intervals were obtained from the Poisson distribution.^{20,21} To assess the effect of this measure of exposure, we used the same approach with the exception that now, the person-time before the first prescription of NCS is classified as unexposed and subsequent person-time is classified as exposed. This is the simple time-dependent measure.

We then used the same approach used in the study by Adams et al.,¹⁹ namely logistic regression with the time-fixed definition of exposure, to estimate odds ratios of asthma hospitalization for NCS-exposed subjects relative to the unexposed. This technique was used specifically to illustrate the effect of the length of follow-up of the cohort and quantity of use on the estimates of the odds ratio. For simplicity, we stratified quantity of use as 1 or less canisters and more than 1 canister per year.

Last, we used Cox's proportional hazards model with the more accurate time-dependent measure of exposure, which allows estimating the RR for exposures that vary over time. In particular, this technique was used to estimate the RR of asthma hospitalization associated with the current use of NCSs, as well as the regularity of use, adjusted for age, sex, exposure to concurrent use of orally inhaled corticosteroids (time-dependent), and the rates of prescriptions of β -agonists, theophylline, oral corticosteroids, and cromolyn. All

TABLE II. Rates and crude RRs of asthma hospitalization comparing the time-fixed and simple time-dependent definitions of exposure with NCSs from the Saskatchewan asthma cohort

NCS exposure	Number of subjects	Person-years	Number of cases	Rate*	RR
Time-fixed analysis					
NCSs at any time	4,131	11,937	243	20.4	0.57
No NCSs at any time	16,042	44,518	1,606	36.1	1.00
Time-dependent analysis					
NCSs	4,131	6,660	243	36.5	1.13
No NCSs	20,173	49,795	1,606	32.3	1.00
At any time	16,042	44,518	1,606	36.1	
during follow-up					
Before first NCS†	4,131	5,277	0	0	

*Rate of asthma hospitalization per 1000 patients per year.

†Immortal person-time (and unexposed) before starting NCS exposure.

analyses were performed by using SAS software version 8.2 (1999-2001; SAS Institute Inc, Cary, NC).

RESULTS

The cohort included 20,173 subjects with asthma, of whom 1,849 (9.2%) were hospitalized for asthma (cases) during the 3 years of follow-up. Table I compares these cases with the 18,324 who were not hospitalized during this period. The cases are younger, more likely to have received xanthines and cromolyn, and less likely to have been dispensed orally inhaled and NCSs. At any time during follow-up, 21% of all cohort members received NCS. As expected, because follow-up stops with the occurrence of an asthma hospitalization, duration of follow-up is around 50% shorter among the cases.

Table II compares the rates and RRs obtained from the time-fixed definition of exposure used by Adams et al.¹⁹ with the simple time-dependent definition. With the time-fixed definition, by which the subjects who received NCSs at any time during follow-up are classified as exposed for their entire follow-up, the rate of asthma hospitalization is 20.4 per 1000 per year. The reference rate, computed among subjects who did not receive any nasal corticosteroids during follow-up, is 36.1. Thus, the RR for any nasal corticosteroid use is 0.57. With the time-dependent definition, where person-time before the first prescription of NCS is classified as unexposed and subsequent person-time is classified as exposed, the 11,937 person-years generated by subjects who received NCS at anytime during follow-up are divided into 5,277 person-years accumulated before the first prescription of NCS and 6660 subsequent to NCS exposure. As a result of this reclassification of exposure, the rates of asthma hospitalization become 36.5 after NCS exposure compared with 32.3 with no NCS at any time. The resulting RR for NCS exposure relative to no use with the time-dependent definition is 1.13. This analysis indicates that 44% (5,277/11,937) of the person-time considered exposed by the time-fixed

TABLE III. Crude odds ratios of asthma hospitalization by yearly quantity of use of NCSs by the time-fixed approach (logistic regression)

	Cases	Noncases	Odds ratio (95% CI)
Three-year cohort (n = 20,173)	1,849	18,324	
Any use during follow-up	13.1%	21.2%	0.56 (0.49-0.65)
>0 to 1 canister per year	6.6%	12.9%	0.47 (0.39-0.57)
>1 canister per year	6.5%	8.3%	0.71 (0.58-0.86)
Five-year cohort (n = 22,001)	2,521	19,480	
Any use during follow-up	15.3%	26.3%	0.51 (0.45-0.57)
>0 to 1 canister per year	7.3%	19.2%	0.33 (0.29-0.39)
>1 canister per year	8.0%	7.2%	0.97 (0.83-1.13)

approach is misclassified. This person-time is also immortal; no asthma hospitalizations could have occurred during this period, or subjects would have been classified as not exposed to NCS.

Table III shows the results of the logistic regression analysis to estimate the odds ratio of asthma hospitalization with the time-fixed measure of NCS exposure, as used by Adams et al.¹⁹ This analysis produces an apparently greater protective effect of NCS with 1 or less canisters dispensed per year (odds ratio, 0.47) compared with more than 1 canister per year (odds ratio, 0.71). Furthermore, this protective effect of NCS with 1 or less canisters dispensed per year is exaggerated when extending the length of observation of the cohort from 3 years to 5 years (odds ratio, 0.33).

Table IV provides estimates of the RR of asthma hospitalization by using the more accurate time-dependent definition of exposure that accounts for the timing of each prescription and classifies each day of follow-up as either exposed or nonexposed to NCS. The adjusted RR of asthma hospitalization for current use of NCS is 1.31. The analysis of regularity of use shows a trend of lowering rates of asthma hospitalization with greater regularity of NCS use, but even those dispensed this medication for $\frac{2}{3}$ or more of the days of observation appear to have no benefit (RR, 1.10; 95% CI, 0.54-2.21).

DISCUSSION

We identified an important bias in an observational study which proposed that NCSs used by patients with asthma are effective at preventing ED visits for asthma. The bias arises from misclassifying as exposed subjects who are in fact unexposed during the period preceding the first NCS prescription. This results in an artificial increase in the rate of events among the remaining unexposed

TABLE IV. Crude and adjusted RRs of asthma hospitalization for current use and by regularity of use of NCSs by Cox's proportional hazards regression model with time-dependent exposure

NCS use	Cases	Person-days	RR	
			Crude	Adjusted* (95% CI)
Number	1,849	20,618,129		
Current use	3.7%	2.8%	1.31	1.31 (1.02-1.67)
Regularity of use (% time)				
>0% to 33%			1.19	1.20 (1.04-1.39)
34% to 66%			1.01	1.18 (0.79-1.76)
67% to 100%			0.79	1.10 (0.54-2.21)

*Adjusted for similar categories of orally inhaled corticosteroids, as well as age, sex, and the rate of prescriptions of β -agonists, theophylline, oral corticosteroids, and cromolyn.

subjects, leading to a spurious appearance of effectiveness. Our reanalysis of comparable data from another cohort of patients with asthma, from which we were able to reproduce the biased analysis accurately, indicates that the bias is important. The fact that we used hospitalizations instead of ED visits as the outcome is irrelevant because we were able, by using the biased approach, to replicate the protective effect of NCS, thus demonstrating that the bias is not affected by this difference in choice of outcome.

In the study by Adams et al,¹⁹ subjects were followed from October 1, 1991, and the follow-up lasted 3 years for the majority of subjects. However, for all 1031 subjects who incurred an ED visit, the duration of follow-up was necessarily shorter than 3 years because follow-up stopped once this outcome event occurred. Therefore, subjects in whom the event occurred had, on average, a shorter follow-up with less opportunity to be prescribed NCS (or any other medication for that matter), and therefore, such unexposed cases will be overrepresented when calculating rates of events such as ED visits or asthma hospitalizations. This overrepresentation of cases without exposure to a medication is exaggerated further as the length of follow-up increases, and this is particularly obvious when one examines the effect of very occasional use of a medication. This leads to biologically implausible results, as we were able to show by using the time-fixed approach to analysis of use of NCS over a 5-year period. Use of 1 canister or less of NCS per year was associated with a highly statistically significant $\frac{2}{3}$ decrease in the risk of being hospitalized for asthma (RR, 0.33; 95% CI, 0.29-0.39), whereas use of more than 1 canister per year was not protective (RR, 0.97; 95% CI, 0.83-1.13). The exposure category defined as 1 canister or less of NCS per year is particularly noteworthy. Subjects in this category must necessarily have more than 1 year of follow-up, which excludes from this category all subjects hospitalized in the first year and explains in part their lower rate of hospitalization.

This bias is accentuated by the fact that under the approach used by Adams et al,¹⁹ the period preceding the

first NCS prescription is a period during which the subject is not only unexposed (and misclassified as exposed), but also immortal. Indeed, no hospitalizations occurred or could have occurred during this period for any of the subjects. If a hospitalization had occurred before this first NCS prescription, the subject would have been classified as unexposed. Therefore, subjects who are considered exposed under this approach have a guaranteed advantage with this immortal period. Not surprisingly, such exposed subjects will thus have an artificially lower rate of hospitalization.

Interestingly, this biased approach has been used in 2 previous studies that suggested a reduction in the risk of severe exacerbations of asthma leading to ED visits or hospitalization with very occasional use of orally inhaled corticosteroids or cromolyn.^{27,28} Both studies used the same time-fixed approach to assessing exposure to these medications. The surprising benefit of only occasional use of orally inhaled corticosteroids (less than 1 canister per year) is in stark contrast with other studies that used a time-dependent approach to show that only regular use decreases the risk of hospitalization whereas irregular use, and especially discontinuation of use, is associated with adverse asthma outcomes.²⁹⁻³²

Our illustration also has the common limitations of observational studies conducted with databases. First, although the diagnosis of asthma was not confirmed, the use of asthma-specific medications and the age restriction between 5 and 44 years (mean, around 20 years old at cohort entry) likely produced a valid population of patients with asthma. Second, our inability to show a protective effect of NCS on the risk of hospitalization for asthma, even when examining stricter adherence to regular therapy with these agents, may result from confounding by indication. Such confounding induced by the absence of random allocation of patients to treatment with NCS would result in an underestimation of the true benefit of NCS if patients who are prescribed these drugs also have more severe asthma. In contrast with our results, Crystal-Peters et al³³ did find fewer asthma-related hospitalizations and ED visits in patients with asthma dispensed NCS. Insufficient details were provided about the analyses performed for us to judge whether immortal time bias might have also explained their results. Finally, as in all studies using claims databases, the absence of an effect with regular use of NCS could have been affected by the fact that dispensing a prescription does not imply that the patient actually took the drug. It is noteworthy, however, that by using a time-dependent approach, a beneficial effect of orally inhaled corticosteroids in preventing asthma hospitalizations was clearly shown.^{29,30}

In conclusion, until larger databases are properly analyzed, taking into account the time-dependent nature of exposures to medications, or randomized trials are performed to assess the benefit of these medications over a prolonged period, one cannot conclude that NCSs diminish the risk of severe asthma exacerbations leading to hospitalization or ED visits.

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