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**VALIDATING SHORT-TERM BETA-AGONIST
PRESCRIPTION REFILLS AS A MARKER FOR ASTHMA**

Xiaoming Bao, Vanja Dukic, Edward Naureckas, Paul Rathouz

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Although the research described in this article has been funded wholly or in part by the United States Environmental Protection Agency through STAR Cooperative Agreement #R-82940201 to The University of Chicago, it has not been subjected to the Agency's required peer and policy review and therefore does not necessarily reflect the views of the Agency, and no official endorsement should be inferred.

Validating short-term beta-agonist prescription refills as a marker for asthma

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Abstract

Asthma is a chronic disease that affects the smooth muscle in the airways. Prevalence of asthma is thought to have increased over last 2 decades; however, the associated mortality and morbidity have increased at a rate greater than what would be expected based on the observed prevalence increase, especially in poorer populations. Asthma is a major public health problem, and an increasing concern in the United States.

Most researchers have focused on the relationship between asthma hospital visits (HV) or emergency department visits (ED), and air quality. But prescription refills for medication such as short-term acting beta-Agonists may be a more sensitive indicator of asthma than ED or hospital admissions. The goal of this study is to validate the use of short-term beta-Agonists as a marker for asthma. The target population in this study is the Medicaid population in the city of Chicago.

Mantel-Haenszel method will be used to characterize the association between short-term beta-Agonist prescriptions and the traditionally studied asthma outcomes (ED and HV) as a function of time lag. The analysis will be adjusted for the subject and within-person correlation. Bootstrap, a re-sampling method, will be performed to quantify uncertainty. As an alternative approach, the receiver operating characteristic (ROC) analysis will be used to assess the accuracy of the use of short-term beta-Agonist prescriptions in diagnosing asthma, treating ED and HV as a gold standard.

Our research results demonstrate the validity of the short-term beta-Agonist use as a marker for asthma, but future work is needed to develop more effective methods for adjusting for time-varying confounding factors and between-subject heterogeneity.

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1. Introduction

1.1 Physiology and prevalence of asthma

Asthma is a chronic disease that affects the smooth muscle of the airways, thus inhibiting the normal flow of air in and out of lungs. Asthma is a major public health problem of increasing concern in the United States. Every year, fifteen million people are diagnosed with asthma; there are two million emergency department (ED) visits attributed to asthma; there are half a million hospitalizations due to asthma; and, there are five thousand asthma-related deaths in the US. Prevalence of asthma has thought to have increased over the last 2 decades, but this could be due to better diagnoses and greater public awareness. However, the associated mortality and morbidity has increased at a rate greater than would have been expected based on the observed prevalence increase alone. This is especially true in poorer populations (MMWR Weekly; May 2, 2003).

1.2 Asthma management and treatment

Currently, there is no cure for asthma. However, asthma can be managed by taking regular medications that can prevent occurrences of serious symptoms, or acute asthma attacks. The most common medications prescribed today for immediate relief of mild to moderate asthma symptoms are the short-term beta-agonist inhalers (such as Albuterol). Severe asthma is treated by inhaled steroids, which tend to be administered over a longer period of time. People who have asthma can still lead quality, productive lives if they control their asthma. If asthma is not well managed, people may have acute asthma attacks that can be severe enough to interfere with their life activities. In addition, asthma is one of the leading causes of children missing school.

1.3 Relationship between asthma and air pollution

Asthma may be controlled in several ways. One is to control levels of exposure to environmental "triggers", such as smoke, dust, pets, molds and airborne particulate matter thought to agitate airway muscles. It has been of foremost importance to many asthma researchers to characterize the impact of air quality on respiratory health, and to provide recommendation on policy guidelines as well as to point out needed future research directions. The other way is to take proper medication. People who have asthma should be warned by accurate alarms and forecasts of increased levels of triggers that may worsen their asthma symptoms, so that they can adapt by minimizing exposure or taking proper medication.

1.4 Traditional asthma outcomes versus short-term beta-agonist prescriptions

Historically, in air pollution epidemiology, most research has focused on characterizing the relationship between most severe asthma outcomes, such as hospital and emergency department (ED) visits, and air quality (Skoner, et al., 2002) (Roux, et al., 1999) (Abbey, et al., 1999) (Naeher, et al., 1999) (Triche, et al., 2002). But medication such as short-term beta-agonists may be a more sensitive marker for asthma than ED visits or hospital admission. This is argued to be so because these prescriptions are more rapidly refilled in response to an acute asthma episode, therefore detecting a lower threshold of the respiratory disease. Furthermore, a database for short-term beta-agonist prescriptions will generally be much larger than any corresponding database containing ED visits and hospitalizations alone. Given the fact that the effects of air quality are generally small in magnitude, the statistical analysis aimed at identifying these effects will benefit from these larger numbers.

It is thus of interest to determine the degree to which these prescriptions are useful as a marker for asthma, and whether and how they are related to the more traditional asthma outcomes examined in the literature, namely emergency department and hospital visits. More specifically, we will investigate the relationship between short-term beta-agonist prescriptions and hospitalizations or emergency department visits attributed to asthma.

1.5 Goals of the study

The target population in our study is those people who joined Medicaid in the City of Chicago. Medicaid is a program funded by the federal and state governments, which pays for medical care for those who are not able to afford it on their own. Typically, most of the patients on Medicaid are poor and female (mostly mothers with small children).

The main goals of our analysis are as follows:

- 1 Confirm the existence of association between short-term beta-agonist prescription and hospitalization or ED visits, i.e., validate short-term beta-agonists as a marker for asthma with respect to the traditional asthma outcomes
- 2 Characterize the association as a function of time lag, adjusting for within-person correlation
- 3 Identify the effect of steroid use on this relationship
- 4 Further check the reliability of our analysis on additional asthma datasets

To address these study goals, we had to preprocess our database in such a way that it would be easily used for our statistical analysis. Thus, we dedicated Part 2 to the discussion of the structure of our data, construction of key variables, and preprocessing algorithms.

One of the statistical tools we will use to characterize association between short-term beta-agonist prescription and more traditional asthma outcomes (ED and hospital visits) is the Mantel-Haenszel (MH) odds ratio. Part 3 will discuss this approach along

with the stratified MH method, and present the results of both. Finally, bootstrap, a re-sampling method, will be performed to quantify uncertainty in the correlation estimates. Results based on other factors such as steroid use will be also discussed.

Part 4 will present an evaluation of the performance of prescriptions as a diagnostic test for asthma. Receiver operating characteristic (ROC) analysis relating short-term beta-agonist prescription to the traditional asthma outcomes (ED and hospital visits) treated as gold standard will be presented here. We conclude this paper with discussion of the limitations of this study and plans for future research in this area.

2 Sample, Data and Study Design

2.1 Medicaid population in Chicago

The asthma data were obtained from the Illinois Department of Public Aid (IDPA) Bureau of Budget. They are generated from medical claims for all persons enrolled in the Medicaid program at any time from July 1, 1995 through June 30, 1998 (fiscal years 1995 through 1998). In general, a person is eligible for Medicaid if one or more of these things are true:

- 1) His/her family makes a low amount of money and has children.
- 2) S/he receives or is eligible to receive Supplemental Security Income
- 3) She is a pregnant woman whose family income is at or below 133% of the federal poverty level. This would include, for example, a family of four who makes \$23,225 a year or less.
- 4) His/her family's assets are below a certain threshold, depending on family size
- 5) She/he is a recipient of adoption assistance or foster care

Thus, all conclusions from this study are limited to the asthma-suffering Medicaid population. However, this is an important population to study because it is socio-economically disadvantaged, and poor populations seem to be disproportionately affected by asthma. In addition, such populations have been underrepresented in much of the asthma research to date.

2.2 Raw data and key variables

The database we received from IDPA consists of all Medicaid claim records for persons treated for asthma at least once during the three-year period 7/1/1995-6/30/1998. Medicaid claims data contain one record for each medical care event that occurred, be it a doctor visit, a prescription fill, a visit to the emergency department, etc. For purposes of reimbursement, each claim record has an associated medical diagnosis. At our request, the IDPA defined asthma-sufferers as all Medicaid participants who have at least one claim with an asthma diagnosis during our study period. The cohort definition was all Medicaid recipients during the specified time

frame who had at least one claim with ICD-9 code 493.XX or DRG 096, 097 or 098 for a hospitalization. If the patient had no office, hospital, or ED visits for asthma, they would not be in the cohort.

For purposes of this study, we have restricted the database to contain records for only three types of claims: short-term beta-agonist prescription fills or refills (A), emergency department visits (ED) and hospital admissions (H), all associated with asthma diagnosis. In addition, there is information about other asthma-related medication such as inhaled steroid use. These criteria yielded a starting database that comprises 723,577 records on 59,766 subjects. Each record (observation) represents an asthma medical event occurring on a certain date for a certain subject. If a subject has two events on the same day, there will be two records. Note importantly that E and H are fairly specific markers of severe acute asthma occurrence on or to the date of record, while A is a more general marker of increased asthma severity on or around the date of record.

The raw data format is based on records of events happening. For any given subject, there are no records on dates on which nothing happened. However, as we see below, the dates with no events are just as important as the dates with events. This will pose some data management challenges, which will be described in more detail in Section 3.1.

The **key variables** in this data set that are relevant to our study are listed below:

Recipient ID:	ID of patients (59,766 subjects, 732,578 records in total)
zip code:	ZIP of recipient residence as of July 1, 1998 (1,500 in total)
Sex:	1=Male (23,559 subjects, 275,513 records in total); 2=Female (36,207 subjects, 457,065 records in total)
Age98:	Age on Jan 1 of fiscal year 1998
Age:	age98 - (1998-fiscal year of date). Note that this is not the age when the event occurs.
Date:	the date when event occurs
Event:	A (short-term beta-agonist prescription), E (ED visits) and H (hospital admits)
Q_{year}:	binary variable for steroid use in a certain year (1-- ICH>3, steroid use; 0-- ICH≤3, non-steroid use)
Steroid:	binary variable for steroid use for all three fiscal years (1-- ICH>8, steroid use; 0-- ICH≤8, non-steroid use)

There are two additional points about the data worth mentioning here:

First, there can be more than one event on any given day for any given subject. That is, a subject could have filled a short-term beta-agonist prescription on the same day as going to the hospital or visiting the emergency department. Thus, for this subject, there could be more than one record at this date.

Secondly, redundancy exists in this dataset in the sense that an event may occur more than once on a given day for a given subject. For example, some subjects have more than one short-term beta-agonist prescription filled on the same day. In this analysis, we will only be interested in the occurrence of the event rather than its frequency a specific day for a particular subject. We will remove this redundant information. Table 2.1 shows the detailed information about redundancies in our data. We see that there are 71,877 redundant records in total. Furthermore, in our analysis we will not distinguish between an ED visit and a hospitalization and will therefore denote each H and ED as E. In this case, the number of redundant records grows to 86,479, i.e., there are 14,602 (86,479-71,877) additional reductions where events ($H \geq 1$ and $ED \geq 1$) happen on the same day for one subject.

Redundant Records In the Raw Data	
Event	Number
$A \geq 2$	70,778
$ED \geq 2$	1,072
$H \geq 2$	27
Total	71,877

Table 2.1 Redundant records

After eliminating these redundancies, our dataset contains:

- 9,182 records where A and E occur on the same day;
- 584,931 records where only A occurs;
- 51,986 records where only E occurs.

2.3 “Children” versus “adults”

The differences in health care coverage under Medicaid for children and adults might result in differences in their seeking and accessing health care. Therefore we analyze the data for children and adults separately. To do this, we regard the subject as a child if his/her age is less than 18. However, caution should be taken as we do not have the exact age of the subject. Because of privacy concerns, what we are given for each subject is his/her age in years (with no month) on Jan 1, 1998 (this is the variable `Age98`). This means that for some subjects in some years we do not know if they are younger than 18 or 18-or-older during that given year.

Each fiscal year is the current calendar year of the event date when the month is less than or equal to June; while it is the next calendar year of a date when the month is greater than June. i.e.,

$$\begin{aligned} \text{Fiscal year} &= \text{year of event date} && \text{if month} \leq 6 \\ \text{Fiscal year} &= \text{year of event date} + 1 && \text{if month} \geq 7 \end{aligned}$$

Thus, our dataset runs from fiscal year 1996 through 1998, i.e.,

Fiscal year 96: from July 1, 1995 to Jun 30, 1996
 Fiscal year 97: from July 1, 1996 to Jun 30, 1997
 Fiscal year 98: from July 1, 1997 to Jun 30, 1998

Correspondingly, Age98 is the age of subject on Jan 1 of fiscal year 1998 in which the event occurred.

We need therefore to use Age98 to approximate the real age of the subject at the time when the event occurs. However, it is possible that the actual age differs by up to one year from the age indicated by Age98. Thus, the subjects may not be correctly classified as children or adults. To be conservative, we only classify a subject as “child” (“adult”) for a given fiscal year if we are certain that she/he is either a child (“adult”) for the entirety of that year. For instance, if a person's age on Jan 1 for a given fiscal year is less than 17, then any events for that person for that fiscal year are included, and that person is classified as a child for that fiscal year. If a person's age for a given fiscal year is greater or equal to 19, then any events for that person for that fiscal year are included, and that person is counted as an adult for that fiscal year.

Based on the conservative principle mentioned above, those subjects with unclear children/adults classification will be removed from our final database. Table 2.2 shows the corresponding final inclusion criteria:

Fiscal years of participation		
Age98	In “child” study	In “adult” study
<17	1996 -- 1998	none
17	1996 -- 1997	none
18	1996	none
19	none	1998
20	none	1997 -- 1998
>20	none	1996 - 1998
Total number of subject	28,376	30,523
Total number of records	212,071	420,749

Table 2.2 Child Study vs. Adult Study (Note that the number of records is based on the new data after we delete redundant information as mentioned in Section 2.1)

Looking closely, we see that when Age98 is 18, subjects can be classified as “child” only in 1996. If Age98 is 17, subjects could be classified as “child” for both 1996 and 1997, while the subject is always qualified as “child” if Age98 is less than 17.

Clearly, while some subjects may be considered “child” for all three fiscal years, others may only for one year. Thus, different subjects may have different time periods of enrollment.

The cost of this conservative inclusion principle is that we lose some information because we only include those subjects that are definitely correctly classified. However, because health care coverage could be so different for children and for adults, we believe that this conservative approach is worth sacrificing a bit of information (3%).

2.4 Simple statistical summaries of the data

Some simple statistics can give us a general idea of short-term beta-agonists prescription and ED visit and hospitalizations. As mentioned, the difference in health care coverage under Medicaid for children and adult might cause difference about their seeking and accessing health care; therefore, the analysis of children and adult should be completely separated.

First, we can look at the distribution of average short-term beta-agonists prescription during the entire period of all subjects. Here, we look at the raw data before any processing to remove redundant records. That is, we do not delete records with more than once prescription per day for certain subjects. This way, we may further investigate whether there is a possibility that some people got short-term beta-agonists for sale instead of taking it themselves. More particularly, we will consider a subject with more than twenty-four short-term beta-agonists and less than two ED visit or hospitalizations per year as a suspect who may have to be removed from our dataset.

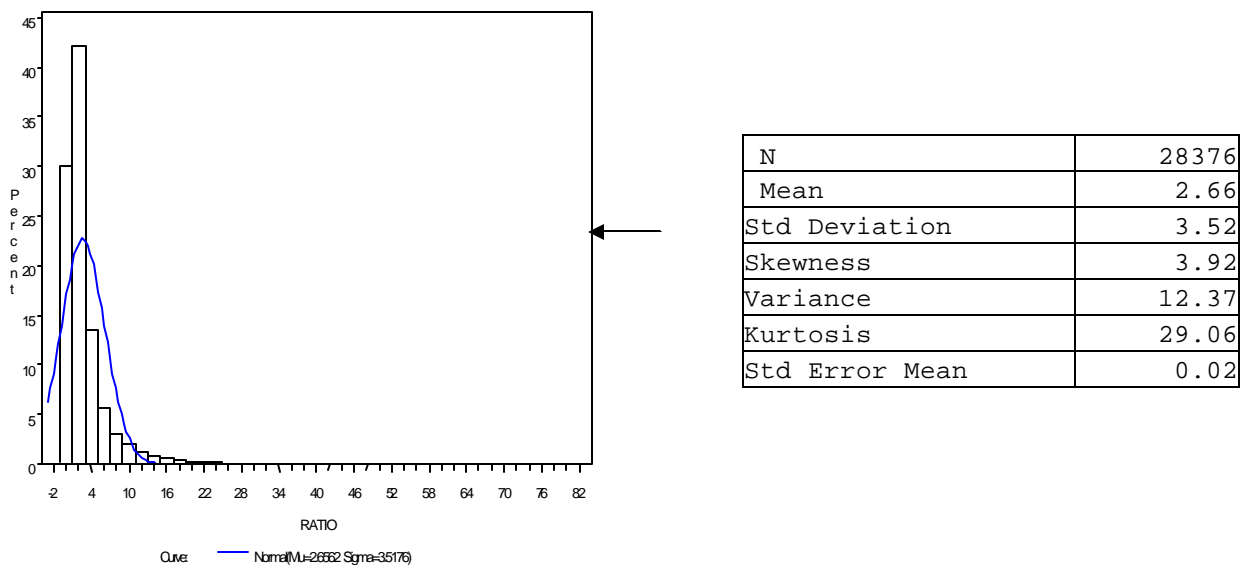
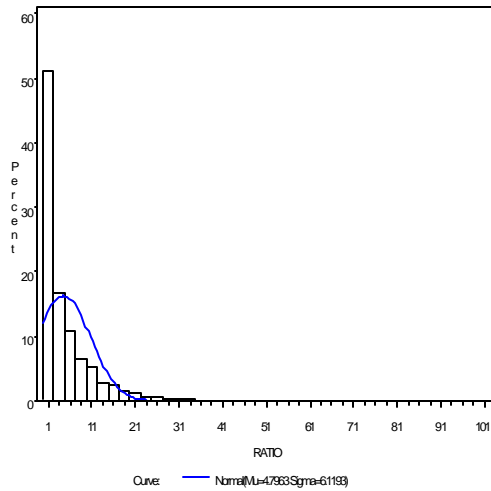


Figure 2.1 Distribution of short-term beta-agonists prescription / year (for children)

Figure 2.1 shows that the distribution is apparently skewed. The average short-term beta-agonists is 2.65. Some extreme observations exist, ranging from 0 to 82 per year.

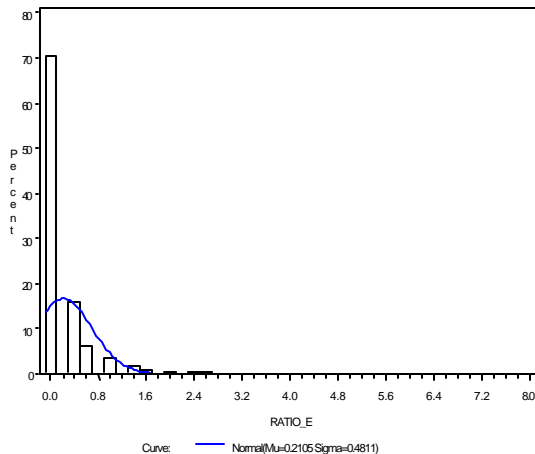


N	30523
Mean	4.80
Std Deviation	6.12
Skewness	2.70
Variance	37.45
Kurtosis	12.41
Std Error Mean	0.04

Figure 2.2 Distribution of short-term beta-agonists prescription / year (for adults)

Figure 2.2 shows that the distribution of adults is also skewed. The average short-term beta-agonists is 4.8. Some extreme observations exist, ranging from 0 to 101 per year.

Correspondingly, we can investigate the distribution of average ED or HV during the entire period of each subject. Note that we do not need to distinguish ED and HV, so we just treat HV as ED, which refers to the number after we delete any redundancy.



N	28376
Mean	0.21
Std Deviation	0.48
Skewness	4.51
Variance	0.23
Kurtosis	32.65
Std Error Mean	0.00

Figure 2.3 Distribution of ED (HV) / year (for children)

Figure 2.3 shows that children are far less likely to have ED/HV, compared with short-term beta-agonists prescription. The distribution of ED (HV) per year is highly skewed.

The average ED/HV is only 0.21 per year. But this value ranges from 0 to 8 for different subjects.

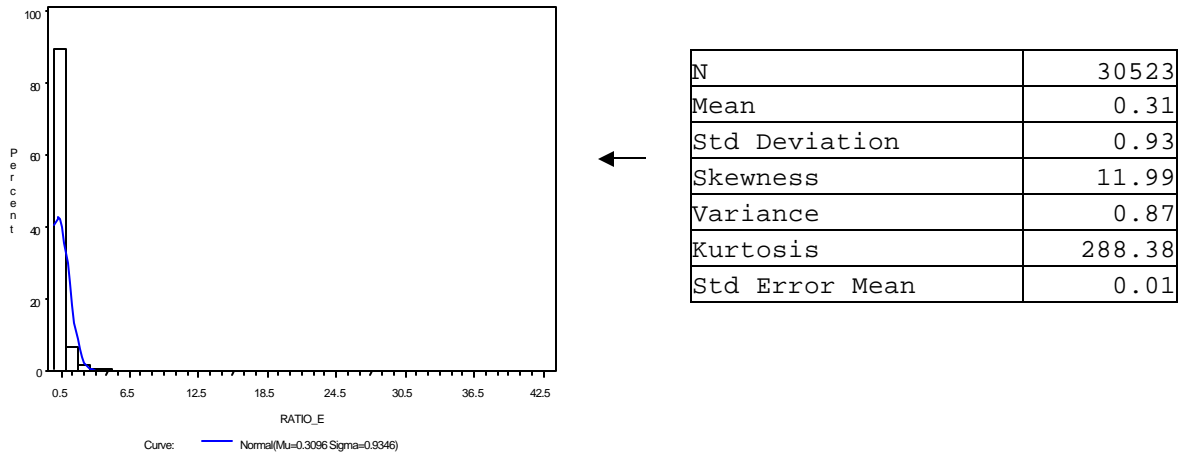


Figure 2.4 Distribution of ED (HV) / year (for adults)

Figure 2.4 shows that the skewness of ED/per year distribution for adults is more severe than that for children. The mean is 0.31. This value is ranging from 0 to 43.

As mentioned, severe asthma is treated by inhaled steroids, which tend to be administered over a longer period of time. Steroid use may introduce additional and unpredictable complication into our analysis. Thus, it is better to separate the data into two groups. i.e., steroid user group and non-steroid user group. Then we can perform statistical analysis for these two groups separately. Table 2.3 shows the adults are more likely to be steroid user than children. The detailed analysis will be shown in Section 3.4.

	Number of Steroid User	Number of Non-Steroid User	Proportion of Steroid User (%)
Children	1179	27197	4.2
Adults	3278	27245	10.74

Table 2.3 Structure of data based on steroid use

3 Statistical Method

3.1 Preliminary Processing and Data manipulation

Contingency Table

In our analysis we encounter response measures that are categorical in nature. The outcomes are indicators of whether or not a subject has an A or E on a given day. Frequently, categorical data are presented in tabular form, known as contingency table (Agresti, 2000). In our case, an important contingency table will be 2x2, with each person-day as one observation. A general table will cross-tabulate the number

of short-term beta-agonists (“A”) or no short-term beta-agonists (“No A”) person-days with the number of ED visits or hospitalizations (“E”) or no ED visits or hospitalizations (“No E”) person-days.

We can compute different tables depending on whether we are interested in A and E being on the same day, separated by a one-day lag, or longer lags, etc. In this section, we describe in more detail how such tables are constructed. Analyses described in the following sections will be based on these tables.

Time lag is a very important concept in our analysis as we are specifically interested in the relative timing of short-term beta-agonist prescription fills and clinical visits during acute asthma episodes. Different events could occur on the same day, or they could occur on different days, separated by a positive or negative value of time lag L. Our research interest will focus on measuring the association between A (short-term beta-agonist prescription fill) and E (ED visit or hospitalization) separated by time lag L. All measures of association are based on contingency tables for A and E separated by L.

A contingency table can be constructed for each subject during a certain time period separately, or for the entire dataset. A contingency table can be used to describe two scenarios:

- a) The short-term beta-agonist prescription (A) occurs at a time point t while ED visit or hospital admission (E) occurs at time point t +L (L>=0). We call this scenario the “positive direction”.
- b) In the opposite situation, ED visit or hospital admission (E) occurs first and short-term beta-agonist prescription (A) follows L days later. We call this scenario the “negative direction”.

We will take “positive direction” as an example to illustrate how we build contingency table.

First, we need to build the contingency table for Person k at time t

		Date t + L	
		E	NO E
Date t	A	a_{kt}	b_{kt}
	NO A	c_{kt}	d_{kt}

Table 3.1 Contingency table for Person k at time t

a_{kt} is a binary variable (1, when A happens and E also happens L days later; 0, otherwise) ;

b_{kt} is a binary variable (1, when A happens but E does not follow L days later; 0, otherwise);

c_{kt} is a binary variable (1, when E happens but without A preceding it by L days; 0, otherwise);

d_{kt} is a binary variable (1, when A does not happen, and L days later E does not happen.; 0, otherwise).

Secondly, we Sum up a_{kt} , b_{kt} , c_{kt} , d_{kt} over all time t and person k to get crude Association Between A at t and E at t + L

		Date t + L	
		E	NO E
Date t	A	$A = \sum_{k=1}^n \sum_{t=1}^T a_{kt}$	$B = \sum_{k=1}^n \sum_{t=1}^T b_{kt}$
	NO A	$C = \sum_{k=1}^n \sum_{t=1}^T c_{kt}$	$D = \sum_{k=1}^n \sum_{t=1}^T d_{kt}$

Table 3.2 Contingency table for positive direction

A is number of person-days when A happens and E follows after L days;

B is number of person-days when A happens but E does not follow L days later;

C is number of person-days when E happens but without A preceding it by L days;

D is number of person-days when A does not happen, and L days later E does not happen.

Similarly, we can get contingency table for the “negative direction”, i.e, when $L < 0$.

As all measures of association are based on contingency tables as the ones above, we need to be able to manipulate data efficiently to produce them. Our algorithms and for doing so are presented in the Appendix.

ROC Analysis

An alternative analysis will use ROC (receiver operating characteristics) curves and these will require a different type of contingency table.

The basic idea of the ROC analysis is that instead of treating short-term beta-agonist prescription and ED visit or hospitalization as two equivalent events, we treat short-term beta-agonists as a diagnostic test for asthma, which can be measured on an ordinal scale, while ED or HV are treated as a gold standard of asthma diagnosis. This way we can assess how “accurate” the beta-agonist prescriptions are in serving as a measure for asthma as compared to the traditional outcomes (ED visits and hospitalizations).

The short-term beta-agonist prescriptions are counts and therefore expressed on an

True Condition Status	Test Results	
	Test Positive ($A \geq t$)	Test Negative ($A < t$)
Present (E=1)	a_{kt}	b_{kt}
Absent (E=0)	c_{kt}	d_{kt}

ordinal scale. However, the diagnostic test for asthma is usually a dichotomous rule (test positive = asthma present; test negative = asthma absent). Thus, we need to define a threshold number for short-term beta-agonist prescription number to use as the definition of the binary test decision. In other words, the test outcome will be based on whether or not the test result exceeds a given threshold value (Pepe, 2003). For instance, if we define Y as the number of short-term beta-agonist prescriptions filled in a given time-period, and use c as a threshold to define whether asthma is present or absent, then

$$\begin{aligned} \text{Test will be positive if } Y &\geq c \\ \text{Test will be negative if } Y &< c \end{aligned}$$

Let the corresponding true and false positive fractions at the threshold c be TPF(c) and FPF(c), respectively, where

$$\begin{aligned} \text{TPF}(c) &= P [Y \geq c | E=1] \\ \text{FPF}(c) &= P [Y \geq c | E=0] \end{aligned}$$

The true positive rate of a test is also known as the sensitivity of the test at the given threshold (Pepe, 2003). It gives the probability of correctly diagnosing acute asthma attack when in fact the disease (acute asthma) is present. The false positive rate is known as 1-specificity, and it measures the probability that the test will wrongly declare a patient as having an asthma attack while in fact the patient is in fact not having one. Sensitivity and specificity are two most commonly used measures that quantify the diagnostic accuracy of a diagnostic test. They however are tied to a particular threshold and cannot be interpreted without knowing what the set test threshold is.

ROC curve is a plot of sensitivity versus specificity across the range of all possible thresholds that could be used for a given diagnostic test. As such, the ROC represents a profile of diagnostic accuracy of the test for any given threshold.

For illustration, Table 3.3 a) and Table 3.3 b) describe the situation when we examine the number of short-term beta-agonists in a time period length L, and define c = “t refills” to be the diagnostic threshold used to define the presence of an acute asthma attack.

First, Table 3.3 a) is an individual table to show the relationship between true status (having ED or not) and the test results (test positive or not)

Table 3.3 a) The diagnostic test for Person k at time t

a_{kt} is a binary variable (1, when test is positive and ED occurs; 0, otherwise)
 b_{kt} is a binary variable (1, when test is negative and ED occurs; 0, otherwise)
 c_{kt} is a binary variable (1, when test is positive and no ED occurs; 0, otherwise)
 d_{kt} is a binary variable (1, when test is negative and no ED occurs; 0, otherwise)

Table 3.3 b) is an overall table which sums up $a_{kt}, b_{kt}, c_{kt}, d_{kt}$ over all time t and person k

True Condition Status	Test Results	
	Test Positive	Test Negative
Present (E=1)	$A = \sum_{k=1}^n \sum_{t=1}^T a_{kt}$	$B = \sum_{k=1}^n \sum_{t=1}^T b_{kt}$
Absent (E=0)	$C = \sum_{k=1}^n \sum_{t=1}^T c_{kt}$	$D = \sum_{k=1}^n \sum_{t=1}^T d_{kt}$

Table 3.3 b) The overall diagnostic table for threshold t

A is number of cases when test is positive and ED visit occurs during a certain time period;

B is number of cases when test is positive but ED visit does not occur during a certain time period;

C is number of cases when test is negative and ED visit occurs during a certain time period;

D is number cases when test is negative but ED visit does not occur during a certain time period;

Thus, for this particular threshold, the sensitivity and specificity are:

$$\text{Sens}(c) = \text{TPF}(c) = P [Y \geq c | E=1] = At/(At+Bt)$$

$$\text{Spec}(c) = 1 - \text{FPF}(c) = 1 - P [Y \geq c | E=0] = Dt/(Ct+Dt)$$

And the ROC curve would be a plot of all (Sens(c), Spec(c)) as the threshold c varies from 0 to L. Note that L is the maximum number of prescriptions filled in a given time period of L days because only one prescriptions is allowed to be filled per day.

Once again, we need to process the data in order to apply the ROC methodology. The principle of “matching method” (see Appendix), by which we construct the contingency tables, is still the algorithm of choice. This algorithm is based on the matching of the short-term beta-agonist prescription at time point t with the ED visit at time point t + L. However, there is some difference between the exact matching methods used for constructions of contingency tables and of ROC tables. For contingency tables, we only get the value of two time points, while for ROC tables, we have to calculate the cumulative short-term beta-agonist prescriptions

from time t to time $t + L$. Thus for ROC tables, instead of matching the two time points (t and $t + L$), we need to match a time point $t + L$ (when ED occurs), with a time period from t to $t + L$ (cumulative value of short-term beta-agonist prescriptions). In our data manipulation procedure, this involves the generation of a new variable $LagA$, which describes the short-term beta-agonists use at L days before ED/HV. The SAS program is attached at the end of the paper.

After the necessary data manipulation and construction of the contingency and ROC tables, we present the actual statistical analyses and inference. Detailed description of the statistical methodology is given in the following sections.

3.2 Association between beta-agonist and hospitalization or ED visit

3.2.1 Crude association measured by the odds ratio

After data manipulation as shown in Sec 3.1, the raw data can be summarized by contingency tables, which will be directly used to estimate an odds ratio. A fundamental goal of this analysis is to measure association for A (short-term beta-agonist prescription) and E (ED visit or hospitalization) occurring at days separated by a time lag L . This method can quantify the degree of relationship by a common measurement of association—the odds ratio, which ranges from 0 to infinity.

By investigating the odds ratio between A at time t and E at time $t + L$, we have the following formula:

$$OR\hat{R} = \frac{\hat{p}_1 / (1 - \hat{p}_1)}{\hat{p}_2 / (1 - \hat{p}_2)} = \frac{A * D}{B * C}$$

where $\hat{p}_1 = \frac{A}{A + B}$, $\hat{p}_2 = \frac{C}{C + D}$

Interpretation of OR

- When OR is 1, there is no association between the short-term beta-agonist prescription and ED visit or hospital admits;
- When OR is greater than 1, subjects who have short-term beta-agonist prescription are more likely to have an ED visit or be admitted to hospital at a positive situation- A before E);
- When OR is less than 1, subjects who have short-term beta-agonist prescription are less likely to have an ED visit or be admitted to hospital at a given lag L .

Like other statistical methods, this estimator relies on some assumptions, such as for example independence. Some of these assumptions however will be violated in our Medicaid data. We will discuss the impact of these violations and present potential solutions in the following sections.

3.2.2 Problems of crude odds ratio

As we know, Mantel-Haenszel analysis relies on the following assumptions:

1. independence between subjects;
2. independence between short-term beta-agonist prescriptions on different time lags.

Clearly, there are some problems in the crude analysis. First, people are not equally healthy in different time period. The odds ratio can be inflated due to the fact that for each person, during some period, he or she is more or less prone to asthma attacks.

Another issue should be addressed is the different contribution of subjects: sicker patients contribute many more observations to the analysis than others in the dataset. Note that among the 59,766 subjects in our data, the frequency of the events for different subjects varied a lot. In fact, the detailed data analysis shows that while many patients appear just once in our data set, some patients have over a 100 events from June 1, 1995 to June 30, 1998. This means that some subjects will have much higher contribution to the statistical analysis than others, which may make our results heavily dependent on some subjects while ignoring others. Thus, this unequal contribution from subjects is another issue we have to take into account.

3.2.3 Stratum method using Mantel-Haenszel Estimator

Based the problems mentioned above, it is clear that crude odds ratio cannot give us desirable results. The violation of assumptions confounds our analysis. Hence, we need to adjust for these confounders in order to get a realistic measure of association. To control for these confounding processes, we must stratify our data

- 1) by subjects to adjust for the unequal contributions of subjects
- 2) by a certain time interval to adjust for slowly-varying time-dependent unobserved confounders which are assumed to be approximately constant over such intervals

We present Mantel-Haenszel odds ratio adjusted step by step to show the effect of different stratification methods. The estimates of association based on this three-step analysis will be examined and discussed separately. Therefore the MH analysis will be done in the following three stages:

- 1) the first strategy is to calculate unadjusted odds ratio when we do not consider any confounding factors;
- 2) the second strategy is to calculate odds ratios adjusted for subject so that the subject factor can be removed;
- 3) the third strategy is to give the results after adjusting for both subject and a fixed time interval. In this stage, we also need to examine which time intervals are most suitable for our stratification analysis, and to compare results under several different “resolutions” or lengths of these stratifying time intervals. The log odds ratios based on different time intervals, ranging from one month to two weeks, will be examined.

Finally, we also need to address the impact that some known factors such as steroid use, may have on our analysis.

We undertook a completely separate analysis for children and adults. Based on our preliminary findings, we have observed that the basic conclusions are in fact similar for children and adults, except that the association appears slightly stronger for children. Thus, we will only show and interpret the results based on children data in the following sections.

3.3 Results and interpretation of Mantel-Haenszel analysis

3.3.1 Strategy One: crude odds ratio, without adjustment

In this unstratified analysis we estimate the odds ratio from the data by simply combining all individual person-day 2x2 tables together.

The model is:

$$\text{Log odds (A at t)} = \mathbf{g} + \mathbf{b} \mathbf{I} (\text{E at t + L})$$

where \mathbf{g} is the overall intercept

\mathbf{b} is the log (OR)

The unadjusted log odds ratio for a given lag L is (Rothman et al., 1998):

$$\text{Log } (OR_{MH}) = \frac{(\sum_{k=1}^n \sum_{t=1}^T a_{kt})(\sum_{k=1}^n \sum_{t=1}^T d_{kt})}{(\sum_{k=1}^n \sum_{t=1}^T b_{kt})(\sum_{k=1}^n \sum_{t=1}^T c_{kt})} = \frac{A * D}{B * C}$$

The standard error for log (OR_{MH}) is (Rothman et al., 1998):

$$\mathcal{S}(\log(OR_{MH})) = (1/A + 1/B + 1/C + 1/D)^{0.5}$$

where

k is the k^{th} subject;

n is the total number of subject;
i is time point when events occurs;
 a_{kt} , b_{kt} , c_{kt} , d_{kt} refer to the interpretations in contingency table
(Table3.1);
A, B, C, D refer to the interpretations in contingency table (Table3.2);

The results are summarized in Table 3.4. Note that since our analysis is only based on one dataset, we are not sure how representative our statistical inference is. In order to quantify uncertainty, we will use standard errors based bootstrap results, which is usually larger. The detail is shown in Section 3.3.3.2.

The comparison between the results based on original data and bootstrap is listed in attachment.

MH Log odds ratio without any adjustment

Time Lag	Positive Direction		Negative Direction	
	Value	Standard Error based on bootstrap	Value	Standard Error based on bootstrap
0	3.6014	0.0226	3.6014	0.0226
1	1.8165	0.0385	3.0287	0.0226
2	1.1584	0.0474	2.8320	0.0228
3	0.8794	0.0527	2.5206	0.0247
4	0.8110	0.0516	2.1189	0.0280
5	0.7996	0.0572	1.7378	0.0366
6	0.6498	0.0627	1.3721	0.0441
7	0.6470	0.0567	1.1829	0.0460
8	0.7273	0.0620	1.0677	0.0489
9	0.6721	0.0604	0.9089	0.0531
10	0.6721	0.0578	0.7844	0.0526
11	0.7598	0.0594	0.8120	0.0540
12	0.6385	0.0631	0.6532	0.0606
13	0.7031	0.0667	0.7332	0.0546
14	0.7915	0.0530	0.8102	0.0558
15	0.6536	0.0598	0.8045	0.0532
16	0.7535	0.0580	0.7865	0.0594
17	0.8263	0.0621	0.7658	0.0573
18	0.7287	0.0570	0.8087	0.0525
19	0.7129	0.0599	0.9319	0.0508
20	0.7765	0.0605	0.8946	0.0554
21	0.8247	0.0578	0.8757	0.0529
22	0.8220	0.0633	0.9220	0.0526
23	0.7305	0.0547	0.8444	0.0587
24	0.7209	0.0588	0.7647	0.0538
25	0.7374	0.0550	0.8426	0.0513
26	0.7346	0.0594	0.8741	0.0508
27	0.7319	0.0576	0.8229	0.0573
28	0.8217	0.0586	0.8201	0.0573

Table 3.4 Unadjusted log odds ratios for children

Conclusion

There is substantial evidence to support the claim that there is strong association between short-term beta-agonist prescriptions and ED/HV. For both directions, all log odds ratios, ranging from time lag L=0 to time lag L=28, are positive, indicating that, compared to those without a beta-agonist prescription, subjects who have short-term beta-agonist prescription are more likely to visit (have visited) an ED or hospital after (before) a given time lag. When short-term beta-agonist prescription and ED/HV occur at the same day, the association is the strongest. The odds ratio is $\exp(3.6109) = 36.9993$, meaning that the odds of having an ED or hospital visit for subjects who have short-term beta-agonist prescription filled at the same day are around 37 times as big as for those who do not have prescription filled.

Looking carefully, we can see that log odds ratios are not evenly distributed among the 28 time lags. As expected, the strength of association diminishes with the increase of time lag. When the time lag is 2 days, the log odds ratio are also high and above 1, so the odds of ED/HV for subjects who have short-term beta-agonist prescription are more than 3 times the odds of ED/HV for those who do not have prescription filled within (before or after) 2 days of discharge.

However, if we examine the relationship between short-term beta-agonist prescription and ED/HV beyond 2 day lags, the log odds ratios become consistently lower than 1, with the association becoming weaker with the increase of time lag, as would be expected.

Although the results show strong association, a "cautious interpretation" of these results is necessary. Recall that problems exist in this crude analysis. One is that the different contributions of patients cause heterogeneity across subjects. Also, the association can be inflated since people are more or less prone to asthma in different period. Therefore, further adjustment is necessary to get valid results.

3.3.2 Strategy Two: Mantel-Haenszel method, adjusting for subject effect

As discussed before, stratifying by subject is an effective way to adjust for the subject effect.

$$\text{Log odds (A at t)} = \mathbf{g}_k + \mathbf{b} \text{I (E at t + L)}$$

where \mathbf{g}_k is intercept for the k^{th} subject

\mathbf{b} is $\log(\text{OR})$

Log odds ratio adjusted by subject (Rothman et al., 1998) is:

$$\text{Log} (\hat{OR}_{MH2}) = \text{Log} \left(\frac{\sum_{k=1}^n (A_k * D_k) / N_k}{\sum_{k=1}^n (B_k * C_k) / N_k} \right)$$

The standard error is (Rothman et al., 1998):

$$\begin{aligned}
\hat{S}(\log(O\hat{R}_{MH2})) &= \frac{\sum_{k=1}^n (A_k + D_k) * (A_k * D_k) / N_k^2}{2(\sum_{k=1}^n (A_k * D_k) / N_k)^2} \\
&+ \frac{\sum_{K=1}^n [(A_k + D_k)(A_k * D_k) + (B_k + C_k)(B_k * C_k)] / N_K^2}{2(\sum_{K=1}^n A_k * D_k / N_K)(\sum_{k=1}^n (B_k * C_k) / N_K)} \\
&+ \frac{\sum_{k=1}^n (B_k + C_k) * (B_k * C_k) / N_k^2}{2(\sum_{k=1}^n (B_k * C_k) / N_k)^2}
\end{aligned}$$

where

k is the k^{th} subject;

n is the total number of subjects;

A_k, B_k, C_k, D_k correspond to the number of A_cell, B_cell, C_cell and D_cell respectively for k^{th} subject in the contingency table (Table3.1);

N_k is the total number of A_cell, B_cell, C_cell and D_cell in the contingency table (Table3.1)

Applying this formula to data yields the following results. Like previous analysis, we will use standard errors based bootstrap results.

The comparison between the results based on original data and bootstrap is listed in attachment.

Log odds Ratio After adjusting for subject

Time Lag	Positive Direction		Negative Direction	
	Value	Standard Error based on bootstrap	Value	Standard Error based on bootstrap
0	2.9937	0.0312	2.9937	0.0312
1	1.2184	0.0397	2.4156	0.0285
2	0.5528	0.0473	2.2227	0.0279
3	0.2697	0.0540	1.9177	0.0290
4	0.2004	0.0514	1.5186	0.0318
5	0.1888	0.0566	1.1362	0.0394
6	0.0365	0.0633	0.7663	0.0464
7	0.0335	0.0557	0.5765	0.0460
8	0.1154	0.0596	0.4598	0.0492
9	0.0589	0.0583	0.2993	0.0526
10	0.0589	0.0563	0.1736	0.0501
11	0.1478	0.0595	0.2019	0.0551
12	0.0249	0.0636	0.0409	0.0605
13	0.0906	0.0642	0.1216	0.0543
14	0.1812	0.0529	0.2000	0.0555
15	0.0409	0.0577	0.1947	0.0518
16	0.1428	0.0577	0.1766	0.0592
17	0.2168	0.0612	0.1553	0.0552
18	0.1178	0.0585	0.1989	0.0515
19	0.1019	0.0595	0.3243	0.0519
20	0.1666	0.0606	0.2860	0.0529
21	0.2157	0.0556	0.2668	0.0531
22	0.2126	0.0635	0.3138	0.0528
23	0.1197	0.0539	0.2349	0.0578
24	0.1107	0.0585	0.1532	0.0549
25	0.1273	0.0552	0.2329	0.0510
26	0.1254	0.0576	0.2652	0.0506
27	0.1232	0.0567	0.2126	0.0552
28	0.2153	0.0582	0.2109	0.0572

Table 3. 5 Log odds ratio adjusted by subject, for children

Conclusion

According to these estimates after adjusting for subjects, we see that the general pattern is similar to the one observed in the unadjusted Strategy One, i.e., short-term beta-agonist prescription fills appear to be positively associated with ED visit or hospitalization.

However, the odds ratios are lower than their counterparts from the unadjusted analysis, which means that the strength of association between short-term beta-agonist prescription and hospitalization or ED visit has been attenuated after we adjusted for subject effect. For instance, when time lag is 0, the odds ratio is 19.96 ($\exp(2.9937)$) after adjusting for subject, while it was 36.99 before adjustment. Clearly, the crude odds ratio overestimates the association.

The adjusted results are more convincing than the unadjusted ones because different contribution of individuals was taken into account. Though weaker than before, the association still shows strength, especially when the time lag is within one day.

Overall association

Consider again the Mantel-Haenszel odds ratio. After adjusting for subject, we get better estimates of association between short-term beta-agonist prescriptions and ED/HV compared with the simple log odds ratio shown in Strategy One. In fact, when we treat each subject as a stratum, we can use more powerful statistics to describe the relationship if the majority of subjects have the same direction of association. We call this method the Mantel-Haenszel statistic.

Mantel-Haenszel statistic tests the overall association of short-term beta-agonist prescription and ED visit or hospital admits, adjusting for the stratification factor—which in our case is subject. The formula is (57) (Stokes, et al., 2000):

$$Q_{MH} = \frac{(\sum_{i=1}^n A - \sum_{i=1}^n E(A))^2}{\sum_{i=1}^n V(A)}$$

Where i is the i^{th} subject;

A is counts of `A_cell` of a subject in the contingency table (Table 3.1);

$E(A)$ and $V(A)$ are its expectation and variance within one subject

$$E(A) = \frac{n_{1+}n_{+1}}{n^i}; \quad V(A) = \frac{n_{1+}n_{2+}n_{+1}n_{+2}}{(n^i)^2(n^i - 1)}$$

Where

n^i is the total number of contingency table (Table 3.1) for i^{th} subject;

n_{1+}^i is the total number of 1st row of contingency table
(Table 3.1) for i^{th} subject;

n_{+1}^i is the total number of 1st column of contingency table
(Table 3.1) for i^{th} subject;

Q_{MH} has approximately a chi-square distribution with one degree of freedom when the combined row sample sizes are greater than 30. It addresses the hypothesis of no association between short-term beta-agonist prescriptions and ED visit or hospital admission, adjusting for the effect of subject; and it is effective for detecting patterns of association across strata when there is strong tendency to expect the predominate majority to have the same sign. But it fails to detect an association when the association is of opposite directions with roughly the same magnitude (Stokes, 2000). For example, if half of the subjects show positive log odds ratio, the other half show negative log odds ratio, and if the magnitude is close, then it is hard to detect the association based on subject stratum, although the association indeed exists. The result of Mantel-Haenszel estimators for common odds ratio is show in Table 3.6.

Cochran-Mantel-Haenszel Statistics				
Time Lag	Positive		Negative	
	MH value	P value	MH value	P value
0	124770.00	<.0001	124770.00	<.0001
1	3727.80	<.0001	45992.43	<.0001
2	705.87	<.0001	31829.52	<.0001
3	295.23	<.0001	17281.73	<.0001
4	244.40	<.0001	7402.26	<.0001
5	232.06	<.0001	3176.94	<.0001
6	128.32	<.0001	1266.42	<.0001
7	119.51	<.0001	753.42	<.0001
8	172.79	<.0001	557.78	<.0001
9	140.43	<.0001	329.42	<.0001
10	125.37	<.0001	219.56	<.0001
11	188.62	<.0001	237.26	<.0001
12	114.90	<.0001	132.01	<.0001
13	156.78	<.0001	178.96	<.0001
14	217.08	<.0001	237.97	<.0001

Table 3.6 Cochran-Mantel-Haenszel

Clearly, Q_{MH} for all subjects are clearly significant (P values are less than 0.0001). The associations in the individual tables based on each subject reinforce each other so that the overall association is stronger than that observed in any individual table. Based on the above results, we can say that there is strong association between short-term beta-agonist prescriptions and ED visit or hospital admits, adjusting for subjects.

3.3.3 Strategy Three: Mantel-Haenszel Method, adjusting for subject effect and one-month time lag

Up to now, we have removed the subject effect and obtained more convincing results. Nevertheless, another important point we need to address is time dependency. As we know, the presence of correlation in the outcomes may cause problem for statistical interpretation. To account for time-dependent confounders, we need to further partition the analysis into time intervals. The guideline to this approach is that we treat each subject for every one-month period as a unique stratum.

The model is

$$\text{Log odds (A at t)} = \mathbf{g}_{ki} + \mathbf{b} \text{ I (E at t + L)}$$

where \mathbf{g}_{ki} is intercept for the k^{th} subject at time i^{th} window
 \mathbf{b} is log (OR)

The log odds ratios after subject and one-month adjustment are as follows. Note that we will use standard errors based bootstrap results.

The comparison between the results based on original data and bootstrap is listed in attachment.

**Log odds Ratio After adjusting for subject
and time lag (one month)**

Time Lag	Positive Direction		Negative Direction	
	Value	Standard Error based on bootstrap	Value	Standard Error based on bootstrap
0	2.1251	0.0229	2.1251	0.0229
1	0.2548	0.0380	1.5039	0.0229
2	-0.4095	0.0472	1.3121	0.0225
3	-0.6740	0.0537	1.0066	0.0252
4	-0.7029	0.0525	0.6073	0.0284
5	-0.6870	0.0571	0.2390	0.0376
6	-0.8225	0.0625	-0.1264	0.0441
7	-0.8993	0.0570	-0.3863	0.0463
8	-0.6257	0.0607	-0.3063	0.0491
9	-0.6706	0.0599	-0.4740	0.0539
10	-0.6773	0.0575	-0.5614	0.0529
11	-0.5360	0.0592	-0.5142	0.0558
12	-0.6220	0.0633	-0.6555	0.0599
13	-0.5138	0.0650	-0.5351	0.0529
14	-0.3831	0.0536	-0.4293	0.0560
15	-0.4895	0.0588	-0.4086	0.0535
16	-0.3494	0.0586	-0.3809	0.0589
17	-0.2231	0.0618	-0.3658	0.0567
18	-0.2653	0.0581	-0.2843	0.0515
19	-0.2325	0.0597	-0.1227	0.0502
20	-0.1313	0.0609	-0.1146	0.0551
21	-0.0213	0.0554	-0.1134	0.0531
22	0.0112	0.0625	-0.0141	0.0528
23	-0.0047	0.0545	-0.0564	0.0585
24	0.0412	0.0599	-0.0798	0.0545
25	0.1073	0.0576	0.0391	0.0510
26	0.1760	0.0589	0.1147	0.0494
27	0.2283	0.0571	0.1091	0.0564
28	0.3780	0.0586	0.1380	0.0582

Table 3.7 log odds ratio adjusted by subject and one-month time lag, for children

In light of the log odds ratios shown above, we see an import feature not present in Strategy One and Two analyses. The striking point is that the log odds ratio is not always positive after adjusting by subject and one-month time lag. Specifically, when ED occurs first, the chance of having Altuterol use is greater within the next 5 days than that for subjects who did not have ED event; at least two days early, when A occurs first, chance of getting more sever asthma outcome is smaller than that for subjects who did not take and who have a similar level of asthma severity. However,

this “preventive” function of short-term beta-agonists disappears if the subjects do not fill the prescription in time.

To compare the results of three different Mantel-Haenszel analyses, we summarize the results of the three stages in the following graph shown in Figure 3.1.

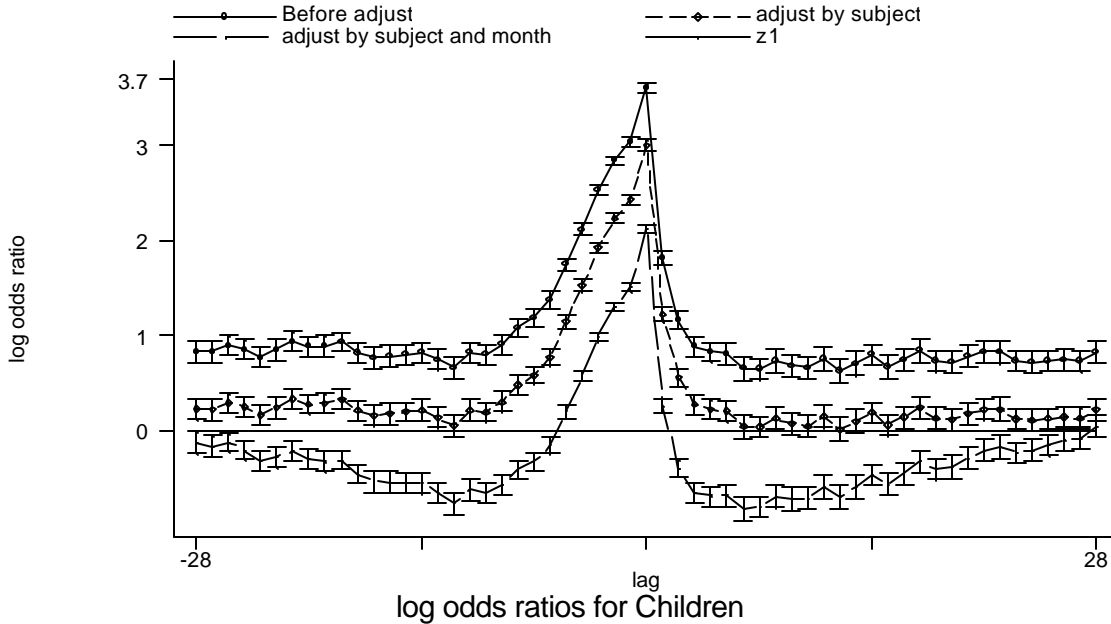


Figure 3.1 Log odds ratios of before adjustment, after adjusting subject and after adjusting both subject and one-month time lag (for children)

Again, Figure 3.1 clearly shows the importance of stratum method. The interpretation of Mantel-Haenszel odds ratio will be distorted without making adjustment. The distortion can be large and it can even change the direction of the association.

3.3.3.1 Sufficient stratification -- finding the most appropriate time lag to control for time-varying confounders

The next issue is to decide upon is which resolution to take to remove the within-subject correlation. We are not sure whether one month is appropriate for removing the trend due to unobserved time-varying confounders. To thoroughly examine this question, we will look at multiple resolutions and compare results and interesting features from all of these analyses.

To illustrate, we will show the log odds ratios based on different resolutions ranging from one week to one month. Since one week can only construct 6-day time lag at most, we will list the results from time lag 0 to 6 for all resolutions (Table 3.8). Note that this analysis based on bootstrap is listed in attachment.

**Log odds ratio after adjusting subject
and time lag**

Time lag	4 weeks	3 weeks	2 weeks	1 weeks
0	2.0863	1.9453	1.7111	1.3508
1	0.2087	0.0501	-0.2256	-0.7233
2	-0.4346	-0.5978	-0.8779	-1.3844
3	-0.6937	-0.8576	-1.1340	-1.6484
4	-0.6936	-0.9112	-1.2031	-1.6790
5	-0.7297	-0.9154	-0.9904	-1.6441
6	-0.8522	-0.9681	-1.2398	-1.7681
7	0	0	0	0

Table 3.8 Comparison of log odds ratio based on different time lag adjustment (one-month, 3-week, 2-week and 1-week)

The difference between results is subtle but we can still detect a pattern. One-month and three-week adjustment shows similar trend, i.e., the direction of association between short-term beta-agonist prescription and ED/HV is positive for lags 0 and 1 and then it turns negative. Nevertheless, if we further narrow this time lag to two-week or one-week, this positive direction occurs only when the two events occur on the same day.

Note that care is needed in determining what constitutes sufficient stratification. In this study we prefer not to make the interval less than two weeks. Too many strata will lead to an estimator with higher variance. We can see these points from the results based on different stratification when time lag is 0 as shown in Table 3.9. Note that this analysis based on bootstrap is listed in attachment.

Analysis of lag 0

Trend of Log odds ratio for lag=0

Stratum	Log odds ratio	Se based on bootstrap
6 weeks	2.2652	0.0229
5 weeks	2.1893	0.0220
4 weeks	2.0863	0.0217
3 weeks	1.9453	0.0225
2 weeks	1.7111	0.0219
1 weeks	1.3508	0.0222
6 days	1.2710	0.0226
5 days	1.1915	0.0225
4 days	1.1195	0.0236
3 days	1.0467	0.0266
2 days	0.9577	0.0295
1 day	0	0.0000

Table 3.9 Adjusted log odds ratio for time lag 0 after adjusting subject and different time lag

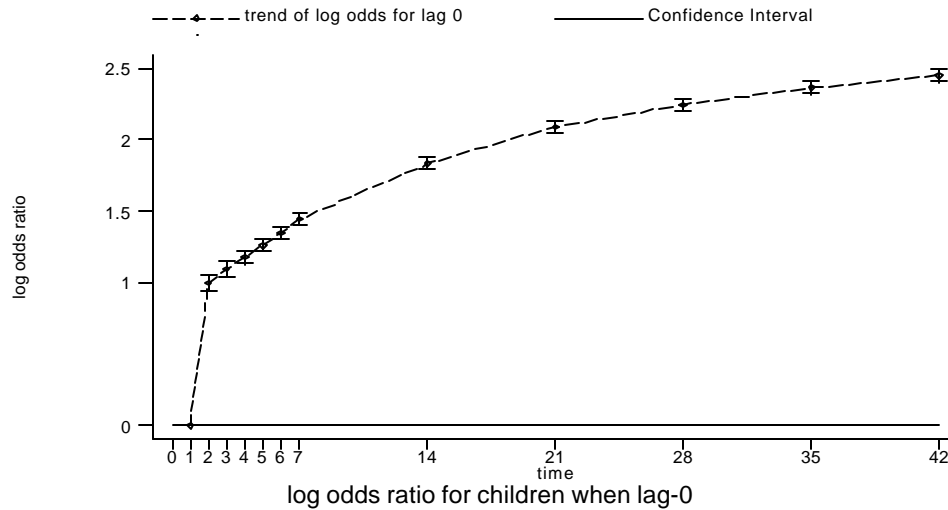


Figure 3.2 Log odds ratio after adjusting by subject and different time lag for time lag 0

Figure 3.2 clearly shows that with the increase of adjustment resolution, the magnitude of the association decreases, and the variance of estimate is increasing. Particularly, when we treat each day for each subject as a stratum, the estimated log odds ratio is simply zero. This is an extreme case, but it tells us that too many strata can make the estimation meaningless. Our final analyses will be based on strata defined by two-week period for each subject. We choose two week as the time period of interest because any association due to trends in asthma on time scales longer than two weeks is not of primary concern.

3.3.3.2 Bootstrap Method

The subject-time adjusted analysis is quite unique, and we are not sure how accurate the statistics such as log odds ratios and their corresponding standard errors are. To assess this variability, we use the bootstrap method (Efron, et al., 1993), which is a computer-intensive resampling method that uses simulation to carry out statistical tests. It has been widely applied by quantitative researchers in medical sciences. The basic idea of the bootstrap is that, in the absence of any other information about the distribution, the observed sample contains all the available information, and hence resampling the sample is the best guide to our statistical inference.

Bootstrap method allows us to quantify uncertainty by calculating standard errors, confidence intervals, and performing significance tests. There are several advantages to bootstrap, namely there are fewer assumptions (distributions need not be known, or sample sizes be large), and bootstrap method may be more accurate in practice than classical methods that rely on asymptotics (Phillip Good, et al., 2001).

Bootstrap algorithm

Step 1: Resample. Create 200 new samples with replacement.

We start with the entire original sample, i.e., 28,293 subjects from children data. The subjects are randomly sampled with replacement 200 times. Thus, any

subject can be drawn once, more than once, or not at all. But the total number of subjects in each of the 200 generated datasets is still 28,293.

Step 2: Calculate the statistic for each bootstrap sample

For each new dataset, calculate log odds ratio and its corresponding standard errors according to the previous program. Note that the whole procedure is based on the stratum method, i.e., calculate statistics for each month per subject. The advantage of stratum method is that it can remove some correlation between time factors for a subject. Thus, for each time lag ranging from 0 to 14, we have 200 log odds ratios and 200 standard errors for positive direction.

Step 3: Perform statistical inference on the bootstrap sample of statistics

Lag	$\log(\widehat{OR})_{original}$	$mean(\log(\widehat{OR}^{*b})_{bootstrap})$	$s\hat{e}(\log(\widehat{OR}))_{original}$	$sd(\log(\widehat{OR}^{*b})_{bootstrap})$
-14	-0.42931	-0.56058	0.05525	0.05600
-13	-0.53508	-0.65812	0.05731	0.05294
-12	-0.65552	-0.77099	0.05952	0.05989
-11	-0.51423	-0.62648	0.05528	0.05576
-10	-0.56137	-0.67001	0.05576	0.05291
-9	-0.47401	-0.57884	0.05277	0.05387
-8	-0.30629	-0.41685	0.04849	0.04912
-7	-0.38634	-0.33599	0.04600	0.04633
-6	-0.12639	-0.16043	0.04234	0.04410
-5	0.23903	0.20180	0.03575	0.03757
-4	0.60730	0.57238	0.03030	0.02842
-3	1.00658	0.98343	0.02562	0.02520
-2	1.31213	1.30043	0.02274	0.02254
-1	1.50386	1.50692	0.02119	0.02288
0	2.12505	2.12533	0.01801	0.02293
1	0.25481	0.25796	0.03476	0.03802
2	-0.40949	-0.40186	0.04694	0.04718
3	-0.67399	-0.66563	0.05359	0.05373
4	-0.70288	-0.69566	0.05503	0.05250
5	-0.68702	-0.68703	0.05553	0.05709
6	-0.82246	-0.82698	0.05972	0.06250
7	-0.89925	-0.80889	0.05953	0.05697
8	-0.62568	-0.69974	0.05753	0.06074
9	-0.67055	-0.72815	0.05936	0.05990
10	-0.67734	-0.72306	0.06018	0.05746
11	-0.53601	-0.59697	0.05718	0.05922
12	-0.62199	-0.70579	0.06089	0.06330
13	-0.51377	-0.59065	0.05860	0.06499
14	-0.38312	-0.46484	0.05625	0.05355

Table 3.10 Comparison of original results and bootstrap results (log odds ratio after adjusting for subject and month) for children data

where

$\log(\widehat{OR})_{original}$ - Log odds ratio for original data, according to Mantel-Haenszel method (adjusting for subject effect).

$mean(\log(\widehat{OR}^{*b})_{bootstrap})$ - Average of log odds ratios for 200 bootstrap samples.

$$= \frac{1}{200} \sum_{b=1}^{200} \log(\widehat{OR}^{*b}_{bootstrap})$$

$s\hat{e}(\log(\widehat{OR}))_{original}$ - Standard error of logs odds ratios for original data, according to Mantel-Haenszel method (adjusting for subject effect).

$sd(\log(\widehat{OR}^{*b})_{bootstrap})$ - Standard error of log odds ratios for 200 bootstrap samples.

$$= \left\{ \sum_{b=1}^{200} [\log(\widehat{OR}^{*b}_{bootstrap}) - mean(\log(\widehat{OR}^{*b}_{bootstrap}))]^2 / (200 - 1) \right\}^{\frac{1}{2}}$$

Conclusion

If we compare statistical inference based on original data and that based on 200 bootstrap samples, we find that the results are different, especially at larger lags. Also, bootstrap estimates generally have higher standard errors. The difference is due to overlapping time lags on some subjects, the residual dependency may also introduce bias. More theoretical work is needed in order to understand the nature of this bias.

3.4 Use of inhaled steroids

As mentioned earlier, this study aims to investigate association between short-term beta-agonist prescriptions and hospitalization or ED visits. Yet another factor in our study may play a confounding role besides the time-dependency and different subject contribution. Some individuals in this asthma data are steroid users while others are not. Steroids used to treat asthma are called corticosteroids and are intended to control more severe asthma for longer periods of time. Thus, steroid use may introduce additional and unpredictable complication into our analysis. We felt that it would be best to look at steroid and non-steroid users separately in order to understand the full impact of steroid use on the association between short-term beta-agonists and ED and hospital visits.

In our asthma data, there are two ways to identify whether the subject is a steroid user.

Method One is based the total amount of steroid use from July 1,1995 to June 30, 1998. The subject is defined as a steroid user when the total number of steroid prescriptions is greater than 8. In our data, it is denoted by a binary variable “steroid”, as shown in Section 2.1.

Method Two is a yearly equivalent of the above method. Instead of only checking the total number of steroid prescriptions for three years, we check for these prescriptions year by year, i.e., the subject “steroid” status is defined annually. When this number is greater than 3 in any particular year, the subject is regarded as a steroid user in that year. This yearly steroid use is denoted by variable “ Q_x ”, which is a binary variable with 1 meaning steroid use, 0 meaning no steroid, and x denoting year. Based on this method, one subject can be in different datasets (steroid data or non-steroid data) in different years. More specifically,

1. If $Q_{1996} = Q_{1997} = Q_{1998} = 1$, the subject is identified as steroid user from July 1, 1995 to June 30, 1998;
2. If only $Q_{1996} = Q_{1997} = 1$ while $Q_{1998} \neq 1$, the subject is identified as steroid user from July 1, 1995 to June 30, 1997; while he/she is a non-steroid user from July 1, 1997 to June 30, 1998;
3. If $Q_{1996} = Q_{1998} = 1$ while $Q_{1997} \neq 1$, then we will treat this as two different steroid users. One is from July 1, 1995 to June 30, 1996; the other is from July 1, 1997 to June 30, 1998.

Compared with the first method, this second method is more precise because it makes full use of information in the data. Hence we prefer that our analysis be based on the second method. As previous analysis shows, 4.2% children use steroid while 10.74% adults use steroid. It is clear that adults are more likely to use steroids than children.

To see the effect of steroids on our analysis, we separate the dataset into two sub-datasets: steroid data vs. non-steroid and run separate analyses. For each dataset, we calculate the Mantel-Haenszel log odds ratio after adjusting by subject and two-week time lag, just as we did before. The results are shown in Table 3.11 and Figure 3.3.

The comparison between the results based on original data and bootstrap is listed in attachment.

Log odds Ratio After adjusting for subject
and time (2 weeks)

Time Lag	Steroid Group		Non-Steroid Group	
	Value	Standard Errors based on bootstrap	Value	Standard Errors based on bootstrap
0	1.0211	0.0627	1.8324	0.0219
1	-0.0118	0.0775	-0.2760	0.0431
2	-0.4145	0.0888	-1.0075	0.0576
3	-0.5735	0.0913	-1.3093	0.0720
4	-0.5809	0.1047	-1.4094	0.0644
5	-0.1996	0.0889	-1.2454	0.0719
6	-0.7185	0.1135	-1.3914	0.0797
7	-0.6949	0.1052	-1.3942	0.0767
8	-0.3625	0.0973	-1.4104	0.0743
9	-0.5963	0.1067	-1.3505	0.0726
10	-0.6835	0.1189	-1.2715	0.0804
11	-0.5640	0.1027	-1.1469	0.0661
12	-0.5092	0.0984	-1.3196	0.0789
13	-0.5830	0.1423	-1.1359	0.0721
-1	0.5212	0.0681	1.1459	0.0239
-2	0.6395	0.0628	0.9068	0.0258
-3	0.5346	0.0683	0.5417	0.0301
-4	0.4036	0.0673	0.0541	0.0338
-5	0.4977	0.0693	-0.2417	0.0441
-6	-0.0781	0.0876	-0.6632	0.0486
-7	-0.2121	0.0812	-0.8688	0.0551
-8	-0.3123	0.0894	-0.9674	0.0575
-9	-0.5477	0.1064	-1.0709	0.0646
-10	-0.4734	0.1103	-1.2550	0.0676
-11	-0.4406	0.0973	-1.1955	0.0717
-12	-0.6485	0.1107	-1.2850	0.0671
-13	-0.6308	0.1126	-1.1376	0.0734

Table 3.11 Log odds Ratio for Steroid Group & Non-Steroid Group (children)

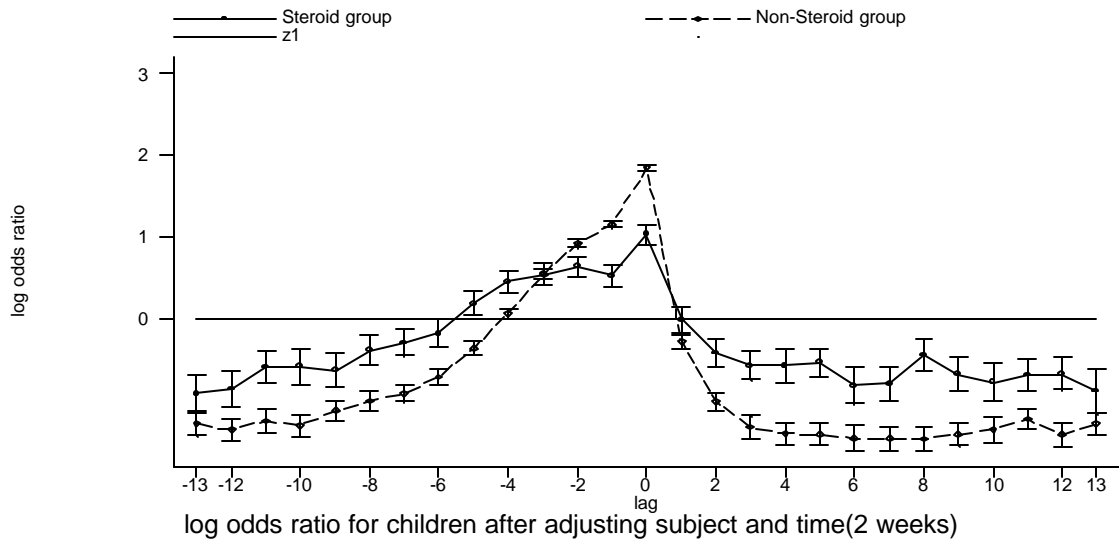


Figure 3.3 Log odds Ratio for Steroid Group & Non-Steroid Group (children)

These results tell us that the steroid use does in fact have impact on our asthma data analysis.

First, when short-term beta-agonists and ED/HV occur at the same day, short-term beta-agonist prescription is positively associated with ED/HV, and odds ratio for non-steroid group after adjusting by subject and time is 6.25 ($\exp(1.8324)$), much higher than that for steroid group 2.78 ($\exp(1.0211)$). This makes sense from a clinical point of view. Airway inflammation is a key component in the pathogenesis of asthma. Anti-inflammatory therapies like steroids are therapies for patients with more severe asthma. For those sicker patients on steroids the short-term relief obtained by beta-agonists may not matter as much as it does for the less sick non-steroid users. Moreover, proper steroid use can, at least to some extent, decrease the occurrence of severe asthma attacks, leading to the association of between A and E that is not as strong as that observed for non-steroid users.

On the other hand, when short-term beta-agonists and ED/HV occur on different days, short-term beta-agonist prescriptions are negatively associated with ED visit or hospitalization. Once again, this shows that taking short-term beta-agonists earlier can, to some extent, prevent a more severe outcome. Most importantly, the absolute value of log odds ratio for non-steroid group is higher than that for the steroid group. These results show that the efficacy of short-term beta-agonists is more pronounced in patients who do not use steroids.

3.5. Beta-agonist as a diagnostic test – ROC curve

Instead of using Mantel-Haenszel odds ratio to explore the association between two events, we can examine that relationship by another tool—ROC (receiver operating characteristic) curve. In Sec 3.1, we introduced the ROC analysis and

discussed it mainly in the context of the necessary data management process. In this section, we will discuss the ROC analysis further from a statistical standpoint.

The primary aim of the ROC analysis is to describe the intrinsic accuracy of the conclusion that a short-term beta-agonist prescription is a good marker for asthma. Thus, the null hypothesis of ROC is that the prescriptions are unrelated to ED/HV. The performance of short-term beta-agonists is judged by how accurately the pattern of these prescriptions can “diagnose” asthma. In principle, the true asthma status is the ‘gold standard’ against which short-term beta-agonists should be measured. However, we do not know the true asthma status of any patient. Instead, what we have is the ED visit or hospital admission, which we believe can reasonably indicate the best available asthma status. Hence, we will in fact be judging the accuracy of beta-agonist prescriptions in diagnosing ED/HV due to asthma.

The advantages of ROC analysis can be summarized as follows:

- Does not require selection of a particular decision threshold since all possible decision thresholds are considered.
- Because sensitivity and specificity are independent of prevalence, so, too, is the ROC curve.
- ROC curve provides a direct visual comparison of two or more tests on a common set of scales.

3.5.1 Constructing an ROC curve

In practice, we need two steps to get the graph of ROC [Xiao H Zhou et al., 1998].

Step One: Get the counts of diagnostics for each cell for a given threshold

True Status (ED/HV)	Test Results		Total
	Positive (A>threshold)	Negative (A< threshold)	
Present (E=1 or H=1)	s_1	s_0	n_1
Absent (E=0 & H=0)	r_1	r_0	n_0
Total	m_1	m_0	N

Table 3.12 Basic ROC count table

where s_1 is the number of true positive (TPs)
 r_0 is the number of true negatives (TNs)
 s_0 is the number of false negatives (FNs),
 r_1 is the number of false positives (FPs),

Note that “true” and “false” pertain to the test: “true” indicates the correct diagnosis; “false” indicates the incorrect diagnosis. False-negative results cause harm by delaying treatment and provide false reassurance. Similarly, false positive is a false detection of the condition and leads to unnecessary, perhaps risky confirmation tests, and potentially inappropriate.

Step Two: Get the fraction of true and false diagnostics for a given threshold

True Status (ED/HV)	Test Results (short-term beta-agonists use)		Total
	Positive (A> threshold)	Negative (A< threshold)	
Present (E=1 or H=1)	$Se = s_1 / n_1$	$FNR = s_0 / n_1$	1.0
Absent (E=0 & H=0)	$FPR = r_1 / n_0$	$Sp = r_0 / n_0$	1.0

Table 3.13 2x2 probability ROC table

where Se is sensitivity

Sp is specificity

s_0/n_1 is the false-negative fraction (FNF) or rate (FNR);

r_1/n_0 is the false-positive fraction (FRF) or rate (FPR);

It is clear that reporting of the (FPR, TPF) attained at only a single threshold is very limited. Moreover, such reporting makes it difficult to compare the results when different thresholds are employed. Thus, we introduce another descriptive device-ROC curve, where on the x-axis is FPR, i.e., 1- specificity, and on the y-axis is TPF, i.e., sensitivity. ROC depicts the trade-off between the true and false positive fractions attained by dichotomizing short-term beta-agonist prescription based on different thresholds. That is,

$$ROC(.) = \{(FPF(c), TPF(c)), c \in (0,L)\}$$

where L is the length of the time period over which we are assessing the relationship.

3.5.2 Area under ROC curve (AUC)

One of the most important concepts in ROC analysis is “area under ROC” (“AUC”). The area under the ROC curve (AUC) is commonly used as a summary measure of diagnostic accuracy (Xiao-Hua Zhou, et al., 2002). It can take values from 0.0 to 1.0. The AUC can be interpreted as the probability that a randomly selected person who filled short-term beta-agonists prescription will be regarded with greater suspicion to have asthma (ED/HV) than a randomly selected person who did not fill non-short-term beta-agonists prescription.

The ROC curve is a monotone increasing function mapping (0,1) onto (0,1). An uninformative diagnostic test is one such that short-term beta-agonist prescription is unrelated to the asthma outcome marker (ED/HV). That is, the probability distributions for

short-term beta-agonist prescriptions are the same in the ED/HV as non-ED/HV populations, and therefore for any threshold c we have $TPF(c) = FPF(c)$. The ROC curve for such a useless test is therefore $ROC(t) = t$, which is a line with unit slope.

To illustrate, we take an example of the two-week period to see how these ROC curves work. We take one week before the asthma outcome ED/HV, and one week after it. So we have 15 days in total. We want to know that if the true asthma outcome (ED/HV) occurs in the middle of the period (on the 8th day), how well the test (short-term beta-agonist prescriptions) can predict this asthma outcome based on different decision thresholds. Note that if a short-term beta-agonist prescription occurs on the 8th day as well, we take it into account.

There are two different ROC curves: parametric ROC curves and non-parametric ROC curves.

3.5.3. Non-parametric ROC curves

"Nonparametric" refers to the lack of any underlying parametric model behind the ROC curve. The points on the non-parametric ROC curve are generated by using every possible outcome of the diagnostic test as a potential classification cut-point and computing the corresponding sensitivity and 1-specificity. These points are then connected by straight lines, and the area under the resulting ROC curve is computed using the trapezoidal rule.

Table 3.14 shows the detailed results based on the non-parametric approach. The cut-point of 1 (≥ 1) implies that the total count of short-term beta-agonist prescriptions being less or equal to 1 predicts "non-ED/HV" and that with a count of 1 or greater predicts "ED/HV". The resulting sensitivity and specificity are 64.48% and 99.38%, respectively. Using this particular cut-point, we correctly classified 99.35% of all the children subjects. Note that each cut-point corresponds to a point on the nonparametric ROC curve. The first cut-point (≥ 0) corresponds to the point at (1,1) and the last cut-point (≥ 5), to the point at (0,0).

Cut point	Correctly		Classified
	Sensitivity	Specificity	
(≥ 0)	100.00%	0.00%	0.08%
(≥ 1)	64.48%	99.38%	99.35%
(≥ 2)	7.63%	99.94%	99.87%
(≥ 3)	0.48%	100.00%	99.92%
(≥ 4)	0.02%	100.00%	99.92%
(≥ 5)	0.00%	100.00%	99.92%
(≥ 6)	0.00%	100.00%	99.92%
(> 6)	0.00%	100.00%	99.92%

Table 3.14 Detailed report for non-parametric ROC (lag=15 with ED is in the middle of two weeks)

From the information in Table 3.14, we can draw non-parametric ROC curve, which is shown in Figure 3.4.

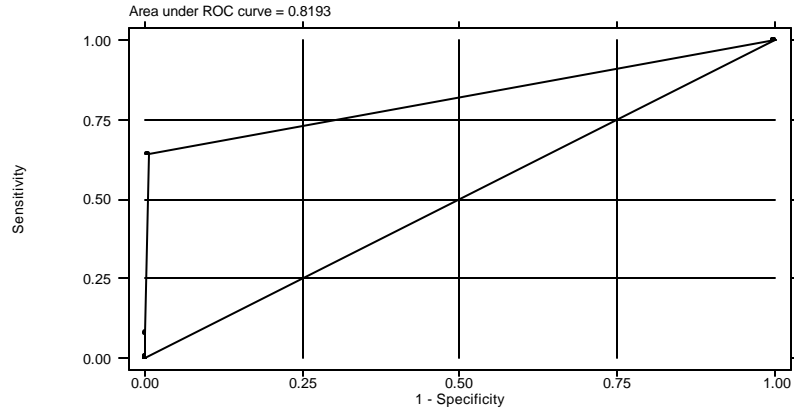


Figure 3.4 ROC curve for non-parametric (lag=15 with ED is in the middle of two weeks)

In this case, the AUC is 0.8193. This means that the probability that test results from randomly selected pair of ED and non-ED subjects are correctly ordered is 0.8193. For example, we select two subjects at random. One has ED, the other has no ED. Y_{ED} is the number of A for ED subject, $Y_{\overline{ED}}$ is the number of A for non-ED subject. Then the probability that $Y_{ED} > Y_{\overline{ED}}$ is 81.93%.

3.5.4. Parametric ROC curves

"Parametric" methodology refers to inference based on the underlying parametric bivariate distribution. Without loss of generality, this distribution may be assumed to be normal distribution for both cases with the ED/HV and for cases without ED/HV. Basically, we want to obtain maximum likelihood estimates of the parameters for a smooth ROC curve. More particularly, suppose now that we adopt a parametric form for the ROC curve:

$$g(\text{ROC}(t)) = \sum_s \mathbf{a}_s h_s(t)$$

where g is a link function and $h = \{h_1, \dots, h_s\}$ are specified functions. As a special case, the binormal model is specified by the above formula when $g = \mathbf{f}^{-1}$, $h_1(t) = 1$ and $h_2(t) = \mathbf{f}^{-1}(t)$. This ROC model defines a generalized linear model with link function g and covariates $\{h_s(t), s = 1, \dots, S\}$. The ROC-GLM approach (Pepe, 2000; Alonzo and Pepe, 2002) is to use procedures for fitting generalized linear models to ordinary data in order to estimate the parameters \mathbf{a} .

Table 3.15 shows the detailed information about results based on the parametric approach.

	Coef.	Std. Err.	z	P> z	[95% Conf. Interval]	
intercept	6.128009	0.045988	133.25	0.000	6.037875	6.218143
slope (*)	2.305419	0.016765	77.86	0.000	2.272560	2.338278

_cut1	2.500080	0.000816	3062.78	0.000	2.498480	2.501680
_cut2	3.263380	0.002184	1494.16	0.000	3.259099	3.267660
_cut3	3.889879	0.006040	644.05	0.000	3.878041	3.901717
_cut4	4.462498	0.019585	227.85	0.000	4.424111	4.500884
_cut5	4.791093	0.042147	113.68	0.000	4.708487	4.873699
_cut6	5.123599	0.094148	54.42	0.000	4.939072	5.308126

		Indices from binormal fit			[95% Conf. Interval]	
Index	Estimate	Std. Err.				
ROC area	0.992627	0.000089			0.992453	0.992802
delta(m)	2.658089	0.003349			2.651526	2.664652
d(e)	3.707856	0.009800			3.688648	3.727064
d(a)	3.448651	0.006174			3.436549	3.460752

Table 3.15 Report for parametric ROC (lag=15 with ED is in the middle of two weeks)

Suppose the normality assumption holds, i.e., both ED visit and non-ED visit population are normally distributed with means m_a and m_n , and variance S_n^2 and S_a^2 , respectively; then the intercept from the fitted line is a measurement of $(m_n - m_a)/S_a$ and slope measures S_n/S_a .

Figure 3.5 shows the graph of ROC based on this method

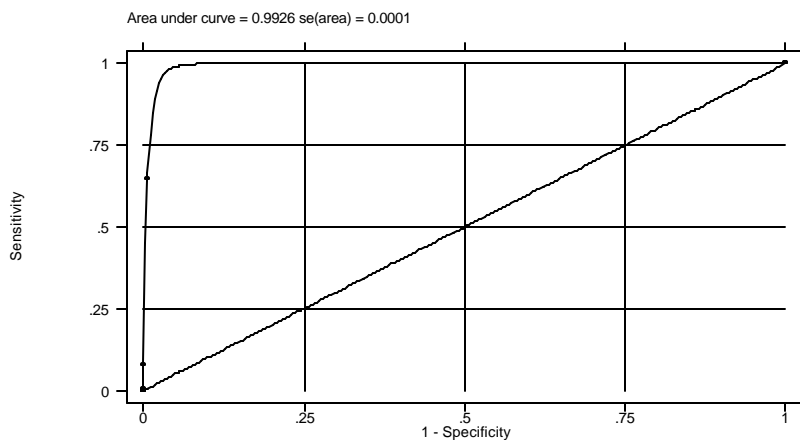


Figure 3.5 ROC curve for parametric (lag=15 with ED is in the middle of two weeks)

In this case, the AUC is 0.992627, it implies that there is 99.26% likelihood that a randomly selected short-term beta-agonist prescription case will be perceived as more-likely to have ED/HV than a randomly selected non- short-term beta-agonist prescription case.

Due to the fact that there are only two informative thresholds, both with very high specificity, information to estimate parametric ROC curve is very weak here. Therefore, the following analyses are based on non-parametric AUC estimates.

3.5.5 Comparison of nonparametric and parametric approach (Xiao-Hua Zhou, et al., 2002]

Both parametric approach and nonparametric approach have their own appealing points and drawbacks.

The advantage of nonparametric approach is that it does not require any distributional assumptions. However, nonparametric area estimates will tend to underestimate the AUCs for rating data. In particular, this method does not yield a smooth estimate of the ROC curve.

On the contrary, parametric approach can offer a smooth estimate of the ROC curve. But its validity relies on the assumption that data are binormal (or any monotone transformation of that) on the underlying latent scale.

Since our data are highly skewed, directly estimating the parameters can seriously bias the ML estimates of the area. Therefore, the nonparametric approach to estimating the AUC might be more reliable than the parametric approach, and we focus only on that approach in the following analysis.

3.5.6. Maximization of AUC

The example in this part is based on 15 days when ED/HV occurs in the middle of this period. We can call this scenario “symmetric window” since the number of days before and after ED is exactly the same. In fact, we can also change the position of the window to see in which situation we can achieve the maximum area of ROC. For example, window position -1 means ED/HV occurs on the previous day of middle point (the 8th day), -2 means ED/HV occurs two days before the middle point. Similarly, $+1$ means one day after middle point, $+2$ means two days after middle point, and so on. For each position of window, we perform the similar analysis as before, and then compare the areas of ROC and see what position may help short-term beta-agonist prescriptions predict asthma outcome best. Again, we perform this analysis based on 200 samples from bootstrap (See Table 3.16 and Figure 4.3).

Actual Day	Window position	ROC area for empirical based on bootstrap	Standard Error based on bootstrap	Lower bound of C.I	Upper bound of C.I
1	-7	0.8121	0.0016	0.80909	0.81517
2	-6	0.8173	0.0015	0.81424	0.82027
3	-5	0.8200	0.0015	0.81703	0.82304
4	-4	0.8217	0.0015	0.81870	0.82470
5	-3	0.8219	0.0015	0.81894	0.82494
6	-2	0.8222	0.0015	0.81919	0.82518
7	-1	0.8212	0.0015	0.81311	0.81915
8	0	0.8193	0.0015	0.81626	0.82228
9	1	0.8161	0.0015	0.81311	0.81915
10	2	0.8102	0.0016	0.80721	0.81329
11	3	0.8008	0.0016	0.79778	0.80391
12	4	0.7856	0.0016	0.78251	0.78871
13	5	0.7600	0.0016	0.75688	0.76315
14	6	0.7235	0.0016	0.72040	0.72665
15	7	0.6011	0.0013	0.59855	0.60362

Table 3.16 ROC area based on different window for lag=15

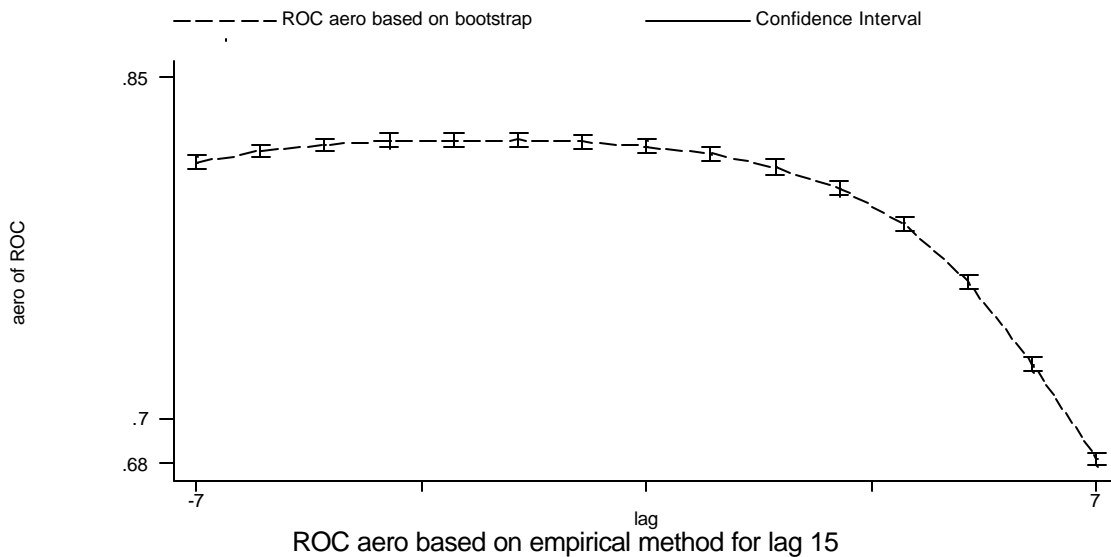


Figure 3.6 ROC area based on different window for lag=15

The above results show that the AUC will be higher when the position of window is before the middle point. This ‘best’ test design is practically telling us the same thing as the MH in that the practical association between beta-agonist prescriptions and ED/HV is the strongest for the negative lags, i.e. when prescriptions happen after the ED/HV.

3.5.7 Comparison between Mantel-Haenszel method and ROC analysis

Toward this end, two different statistical methods have been applied to this study: Mantel-Haenszel Method and ROC curve. They are similar in the sense that they both validate the relationship between short-term beta-agonist prescription and ED/HV from different statistical angles.

However, they measure different things. Mantel-Haenszel method not only confirms the existence of the association between short-term beta-agonist prescription and hospitalization or ED visits, but also characterizes the association as a function of time lag, adjusting for within-person correlation on this relationship. ROC curve measures the accuracy of the use of short-term beta-agonists to predict the ED/HV, also as a function of the time, but rather time-window and not time-lag. Mantel-Haenszel can have double-direction while ROC blurs this directionality by design.

Second, Mantel-Haenszel Method relies on some strong assumptions that do not fit our data. We need to adjust that to validate our results. ROC also has such problems but to a lesser degree (which we did not address).

Third, Mantel-Haenszel Method only focuses on whether an event occurs or not. It does not care about the frequency of the event. ROC analysis cumulatively adds up short-term beta-agonist prescriptions within the time window we are interested in.

4 Conclusions

In the light of the analyses summarized above, the available evidence overwhelmingly proclaims that association between short-term beta-agonist prescriptions and emergency department visits/hospital admissions is valid.

- For both children and adults, a refill of short-term beta-agonists in advance (at least more than 1 days before ED occurs) is associated with a reduction in the chance of a more severe outcome (ED/HV).
- Children are more sensitive to short-term beta-agonists. The absolute value of odds ratio is higher for children than for adults, and just-in-time Medication seems more crucial to children.
- Steroid use decreases serious instances of asthma, lowering the association of between A and E. Non-steroid users seem more sensitive to short-term beta-agonists, and the efficacy of short-term beta-agonists is more pronounced for them than for the steroid dependant subjects.

- There is more than 80% likelihood that a randomly selected short-term beta-agonist prescription case will rank as more-likely to have ED/HV than a randomly selected non- short-term beta-agonist prescription case.
- Although Mantel-Haenszel Method and ROC analysis are not exactly tell the same thing, it is reassuring that the results obtained thereby are in such close agreement. These findings may have important implications for the design of alternative treatment approaches for recalcitrant asthma. The use of short-term beta-agonists is a good way to detect the potential serious outcome such as ED/HV.

5 Limitations and Future Research

Limitations

The rich tradition of asthma research is now being extended to address the prescription medication. As illustrated, both Mantel-Haenszel Method and ROC approach give us apparently significant results about the validity of the use of short-term beta-agonist as a marker for asthma. Obviously, each method has certain drawbacks that need further analysis.

First, we use stratum method to justify our result from Mantel-Haenszel Method. However, some ambiguity can arise in determining proper analysis strata since we have no clear standard on how fine the stratification need be to adequately remove time trends. Stratification that is too coarse may not remove the dependency, while the one that is too fine may increase the variance and may adjust away the signal we are trying to estimate.

Secondly, a problem exists when we perform ROC analysis. Recall that we regard ED/HV as “gold standard”. But unless additional information is available, we are unlikely to identify how precisely the ED/HV and consequently beta-agonist prescriptions alone could be used as a marker of asthma)[Xiao H Zhou, et al., 1998].

A firm understanding of these statistical tests is crucial to any valid medical understanding and interpretation. As illustrated in this paper, we did much adjustment to justify our statistical analysis. Even with those improvements, we should always bear in mind the assumptions on which our interpretation was based on.

Future Research

Based on the limitations mentioned above, we want to know how effective our interpretation is after we remove all confounding factors. This question is not easily answered and still needs further investigation. More work is needed to obtain some theoretical results.

Considered in total, our primary interest lies in the public perception of results but there are other angles as well, including public health concern and regulatory concerns. The available evidence overwhelmingly proclaims the utility of short-term beta-agonists when used timely and properly can predict serious asthma event such as ED/HV. With this idea in mind, the critical question in the later study will be no longer whether short-term beta-agonist prescription is effective way to predict asthma, but how much short-term beta-agonists can be best be promoted and distributed to ensure that they are utilized by those people who are most in need of the protection they provide.

6 Appendix

Data management—Matching Method

As mentioned, Mantel-Haenszel approach, the statistical method we will perform later, is based on above contingency tables. Thus, we need to be able to manipulate data efficiently to produce contingency table. The key point is to count the dates with no events. Although this Medicare data only has records with events, we can account for dates with no events by proper data management. There are three ways to achieve this. We call them Interval method, Subject Specific method, and Matching Method respectively.

The basic idea for interval method is to compare the interval of two sample-based events and the time lag we are interested in. If interval is bigger, then we know there is nothing occurs between them, which belong to D cell in contingency table; if interval is less than the time lag, the case could be one of A, B, C cell, depending which event it is. This method won't take too much time but it is relatively complex, we will not use it. The detailed program is listed in Attachment.

Subject specific method is to combine each of the subjects with his/her corresponding calendar, and then the date with no event can be counted. This method is logically simple but very time-consuming. Again, it is not our preference to use it. We just attach the detailed program for reference.

The method that works best in our study is Matching Method. It is logically easy and very efficient. The goal of the Matching Method is to build a contingency table based on time lag for each subject. Instead of looping over subjects, we make another dataset in which variable “date” has been change to “date + lag”, and the A and E have been renamed to Lag_A and Lag_E, and we merge this new dataset with original dataset by id and date, so we get the information of this time lag for a particular subject. Note that the A, E Lag_A and Lag_E are indicators of whether the event occurs. So they are binary variables. Here, the definition of A, B and C cell are based on Table 3.1. The calculation is shown as followed:

$$\begin{aligned}\text{Counts of A cell} &= \sum (\text{Lag_A} * \text{E}) \\ \text{Counts of B cell} &= \sum (1 - \text{Lag_A} * \text{E}) \\ \text{Counts of C cell} &= \sum \text{Lag_A} * (1 - \text{E})\end{aligned}$$

The count of D is different. Note that our data has only records that event occurs, it does not involve the situation that the subject does not have events even though he is qualified for his/her classification (child or adult) according to Table 2. Since D means A does not occur at time t and E does not occurred at time t + L, we can obtain its counts by using the difference between the qualified period and the sum of A, B and C for a subject. Here the qualified period can be calculated by start date and end date for this subject according to Table2.

Qualified period=end date-start date+1

Note that every subject has his own start date and end date. For instance, if a subject is less than 17 in 1998 (fiscal year), then his start date and end date are July 1, 1995 and Jun 30, 1998 respectively; if he/she is exactly 17 in 1998 (fiscal year), then his start date and end date turn out to be July 1, 1995 and Jun 30, 1997 etc.

Thus, the counts of D cell are:

$$\text{Counts of D cell} = \text{Qualified period} - \sum \text{counts of (A_Cell + B_Cell + C_cell)}$$

ROC PROGRAMMING

```

%MACRO Generate1(p);
*****;
%DO i=1 %TO &p;
DATA New;
    SET New;

                                LA&i=LAG&i(A);
    LE&i=LAG&i(E);
                                Lag_A&i=0;
                                Lag_E&i=0;
    LDate&i=LAG&i(Date);
                                L_ID=LAG&i(ID);
                                IF L_ID ~= ID THEN Ldate&i=.;
                                DROP L_ID;

%END;
*****;
%MEND Generate1;

%MACRO Generate2(p);
*****;
%DO u=1 %TO &p;
DATA haha;
    SET haha;

                                QA&u=LAG&u(A);
                                QE&u=LAG&u(E);
                                Qag_A&u=0;
                                Qag_E&u=0;
    QDate&u=LAG&u(Date);
                                Q_ID=LAG&u(ID);
                                IF Q_ID ~= ID THEN Qdate&u=.;
                                DROP Q_ID;

%END;
*****;
%MEND Generate2;

%MACRO Adj(p,pp);
*****;
DATA New2;
    SET Complete;
    ARRAY LD[&p] Ldate1-Ldate&p;
    ARRAY LA[&p] LA1-LA&p;
    ARRAY LAGA[&p] Lag_A1-Lag_A&p;
    ARRAY QD[&pp] Qdate1-Qdate&pp;
    ARRAY QA[&pp] QA1-QA&pp;
    ARRAY QAGA[&pp] Qag_A1-Qag_A&pp;

DO    k=1    TO    &p    WHILE(LD[k]>=Date-&p    &    LD[k]~=.    );
    *LD[i]<=Date+&p*****;
    LAGA[Date-LD[k]]=LA[k];
    *LAGA[LD[i]-Date]=LA[i]*****;
END;

DO    w=1    TO    &pp    WHILE(QD[w]<=Date+&pp    &    QD[w]~=.    );
    *LD[i]<=Date+&p*****;

```

```

QAGA[QD[w]-Date]=QA[w];
*LAGA[LD[i]-Date]=LA[i]*****;
END;

*DROP LA1-LA&p QA1-QA&p;
*****;
%MEND Adj;

%MACRO Table(p,pp,Cut);
*****;
%LET z1=2;%LET z2=2;
%IF &p~=0 %THEN %LET z1=&p;
%IF &pp~=0 %THEN %LET z2=&pp;

DATA New3;
SET New2;

ARRAY LA[&z1] Lag_A1-Lag_A&z1;
ARRAY QA[&z2] Qag_A1-Qag_A&z2;

A_cut=0;B_cut=0;AA=0;BB=0;CC=0;Sum=0;

DO j1=1 TO &p ;
Sum=Sum+LA[j1];
END;
DO j2=1 TO &pp ;
Sum=Sum+QA[j2];
END;

Sum=Sum+A;
IF Sum=&Cut & E=1 THEN A_cut=1;
IF Sum=&Cut & E=0 THEN B_cut=1;

IF Sum>=&Cut & E=1 THEN AA=1;
IF Sum>=&Cut & E=0 THEN BB=1;
IF Sum<&Cut & E=1 THEN CC=1;

PROC SORT DATA=New3 ;by ID;run;

PROC MEANS DATA=New3 NOPRINT;
BY ID;

ID Length;
OUTPUT OUT=New4 SUM(A_Cut B_Cut AA BB
CC)=A_Cut B_Cut AA BB CC;

DATA New5;
SET New4;

DD=Length-AA-BB-CC;

PROC MEANS DATA=New5 NOPRINT;
OUTPUT OUT=Totals SUM(A_Cut B_Cut AA BB CC DD)=A_Cut B_Cut AA
BB CC DD;

DATA _NULL_;
SET Totals;

```

```

FILE  '~/DATA/Original/Asthma/Output/roc15_area.txt' DSD DLM='09'X
      MOD;
      a=&t; b=&Cut;
      PUT a b A_Cut B_Cut AA BB CC DD;
*****;
%MEND Table;

%MACRO Iteration(Lag1, Lag2);
*****;
      %DO t=1 %TO 15;
          %Table(&Lag1,&Lag2,&t);
      %END;
*****;
%MEND Iteration;

*****Program Start Here*****;
LIBNAME  As_Lib  '~/DATA/Original/Asthma/Output/As_Lib';

DATA New;
      SET As_Lib.CHD;
      Length=End_date-Start_date+1;
      DROP AGE98 _TYPE_ _FREQ_ FY End_date Start_date;

DATA haha;
      SET New;

PROC SORT DATA=haha ;by DESCENDING ID DESCENDING date;run;

****(Lag,Point)*****;
%Generate1(13)
%Generate2(1)

PROC SORT DATA=haha ;by ID date;run;
DATA Complete;
      MERGE HAHA NEW;          * / Merge one person data with
          his calendar. /;
      BY ID DATE;RUN;

%Adj(13,1)
%Iteration(13,1)
run;

```

Bootstrap Results After Considering Steroid Use

Log odds Ratio After adjusting for subject and time (2 weeks)

Lag	Steroid Group			Non-Steroid Group		
	Value based On raw data	mean of bootstrap value	S.e (bootstrap)	Value based On raw data	mean of bootstrap value	S.e (bootstrap)
0	1.0211	1.0263	0.0627	1.8324	1.8341	0.0219
1	-0.0118	-0.0174	0.0775	-0.276	-0.2892	0.0431
2	-0.4145	-0.4217	0.0888	-1.0075	-1.0170	0.0576
3	-0.5735	-0.5697	0.0913	-1.3093	-1.3268	0.0720
4	-0.5809	-0.5770	0.1047	-1.4094	-1.4050	0.0644
5	-0.1996	-0.5404	0.0889	-1.2454	-1.4121	0.0719
6	-0.7185	-0.8208	0.1135	-1.3914	-1.4643	0.0797
7	-0.6949	-0.7942	0.1052	-1.3942	-1.4666	0.0767
8	-0.3625	-0.4418	0.0973	-1.4104	-1.4713	0.0743
9	-0.5963	-0.6791	0.1067	-1.3505	-1.4116	0.0726
10	-0.6835	-0.7774	0.1189	-1.2715	-1.3545	0.0804
11	-0.564	-0.6921	0.1027	-1.1469	-1.2278	0.0661
12	-0.5092	-0.6783	0.0984	-1.3196	-1.4185	0.0789
13	-0.583	-0.8868	0.1423	-1.1359	-1.2839	0.0721
-1	0.5212	0.5214	0.0681	1.1459	1.1507	0.0239
-2	0.6395	0.6353	0.0628	0.9068	0.9103	0.0258
-3	0.5346	0.5405	0.0683	0.5417	0.5415	0.0301
-4	0.4036	0.4428	0.0673	0.0541	0.0565	0.0338
-5	0.4977	0.1838	0.0693	-0.2417	-0.3633	0.0441
-6	-0.0781	-0.1848	0.0876	-0.6632	-0.7108	0.0486
-7	-0.2121	-0.2980	0.0812	-0.8688	-0.9131	0.0551
-8	-0.3123	-0.3911	0.0894	-0.9674	-1.0077	0.0575
-9	-0.5477	-0.6318	0.1064	-1.0709	-1.1245	0.0646
-10	-0.4734	-0.5888	0.1103	-1.255	-1.3041	0.0676
-11	-0.4406	-0.5921	0.0973	-1.1955	-1.2532	0.0717
-12	-0.6485	-0.8640	0.1107	-1.285	-1.3620	0.0671
-13	-0.6308	-0.9167	0.1126	-1.1376	-1.2902	0.0734

Bootstrap Results When Without Any Adjustment

MH Log odds ratio without any adjustment

Lag	Positive Direction			Negative Direction		
	Value based On raw data	mean of bootstrap value	S.e (bootstrap)	Value based On raw data	mean of bootstrap value	S.e (bootstrap)
0	3.6014	3.6101	0.0226	3.6014	3.6101	0.0226
1	1.8165	1.8201	0.0385	3.0287	3.0426	0.0226
2	1.1584	1.1588	0.0474	2.8320	2.8425	0.0228
3	0.8794	0.8792	0.0527	2.5206	2.5305	0.0247
4	0.8110	0.8266	0.0516	2.1189	2.1201	0.0280
5	0.7996	0.8103	0.0572	1.7378	1.7459	0.0366
6	0.6498	0.6508	0.0627	1.3721	1.3746	0.0441
7	0.6470	0.6442	0.0567	1.1829	1.1842	0.0460
8	0.7273	0.7299	0.0620	1.0677	1.0838	0.0489
9	0.6721	0.6788	0.0604	0.9089	0.9052	0.0531
10	0.6721	0.6563	0.0578	0.7844	0.7953	0.0526
11	0.7598	0.7527	0.0594	0.8120	0.8168	0.0540
12	0.6385	0.6216	0.0631	0.6532	0.6572	0.0606
13	0.7031	0.7041	0.0667	0.7332	0.7441	0.0546
14	0.7915	0.7973	0.0530	0.8102	0.8176	0.0558
15	0.6536	0.6666	0.0598	0.8045	0.8023	0.0532
16	0.7535	0.7450	0.0580	0.7865	0.7812	0.0594
17	0.8263	0.8423	0.0621	0.7658	0.7656	0.0573
18	0.7287	0.7297	0.0570	0.8087	0.8158	0.0525
19	0.7129	0.7183	0.0599	0.9319	0.9327	0.0508
20	0.7765	0.7822	0.0605	0.8946	0.8881	0.0554
21	0.8247	0.8258	0.0578	0.8757	0.8822	0.0529
22	0.8220	0.8239	0.0633	0.9220	0.9339	0.0526
23	0.7305	0.7278	0.0547	0.8444	0.8454	0.0587
24	0.7209	0.7144	0.0588	0.7647	0.7716	0.0538
25	0.7374	0.7288	0.0550	0.8426	0.8532	0.0513
26	0.7346	0.7472	0.0594	0.8741	0.8945	0.0508
27	0.7319	0.7288	0.0576	0.8229	0.8237	0.0573
28	0.8217	0.8213	0.0586	0.8201	0.8278	0.0573

Bootstrap Results When Without After Adjusting For Subject

MH Log odds ratio after adjusting for subject

Lag	Positive Direction			Negative Direction		
	Value based On raw data	mean of bootstrap value	S.e (bootstrap)	Value based On raw data	mean of bootstrap value	S.e (bootstrap)
0	2.9937	3.0047	0.0312	2.9937	3.0047	0.0312
1	1.2184	1.2234	0.0397	2.4156	2.4325	0.0285
2	0.5528	0.5553	0.0473	2.2227	2.2351	0.0279
3	0.2697	0.2718	0.0540	1.9177	1.9297	0.0290
4	0.2004	0.2186	0.0514	1.5186	1.5220	0.0318
5	0.1888	0.2018	0.0566	1.1362	1.1467	0.0394
6	0.0365	0.0397	0.0633	0.7663	0.7714	0.0464
7	0.0335	0.0328	0.0557	0.5765	0.5801	0.0460
8	0.1154	0.1202	0.0596	0.4598	0.4783	0.0492
9	0.0589	0.0679	0.0583	0.2993	0.2979	0.0526
10	0.0589	0.0450	0.0563	0.1736	0.1870	0.0501
11	0.1478	0.1427	0.0595	0.2019	0.2089	0.0551
12	0.0249	0.0099	0.0636	0.0409	0.0472	0.0605
13	0.0906	0.0938	0.0642	0.1216	0.1348	0.0543
14	0.1812	0.1893	0.0529	0.2000	0.2096	0.0555
15	0.0409	0.0562	0.0577	0.1947	0.1944	0.0518
16	0.1428	0.1363	0.0577	0.1766	0.1734	0.0592
17	0.2168	0.2354	0.0612	0.1553	0.1573	0.0552
18	0.1178	0.1211	0.0585	0.1989	0.2082	0.0515
19	0.1019	0.1096	0.0595	0.3243	0.3271	0.0519
20	0.1666	0.1745	0.0606	0.2860	0.2816	0.0529
21	0.2157	0.2189	0.0556	0.2668	0.2755	0.0531
22	0.2126	0.2167	0.0635	0.3138	0.3279	0.0528
23	0.1197	0.1191	0.0539	0.2349	0.2379	0.0578
24	0.1107	0.1062	0.0585	0.1532	0.1624	0.0549
25	0.1273	0.1207	0.0552	0.2329	0.2457	0.0510
26	0.1254	0.1404	0.0576	0.2652	0.2882	0.0506
27	0.1232	0.1221	0.0567	0.2126	0.2156	0.0552
28	0.2153	0.2168	0.0582	0.2109	0.2209	0.0572

Bootstrap Results After Adjusting For Subject And Time Lag (one month)

MH Log odds ratio after adjusting for subject and time lag (one month)

Lag	Positive Direction			Negative Direction		
	Value based On raw data	mean of bootstrap value	S.e (bootstrap)	Value based On raw data	mean of bootstrap value	S.e (bootstrap)
0	2.1251	2.1253	0.0229	2.1251	2.1253	0.0229
1	0.2548	0.2580	0.0380	1.5039	1.5069	0.0229
2	-0.4095	-0.4019	0.0472	1.3121	1.3004	0.0225
3	-0.6740	-0.6656	0.0537	1.0066	0.9834	0.0252
4	-0.7029	-0.6957	0.0525	0.6073	0.5724	0.0284
5	-0.6870	-0.6870	0.0571	0.2390	0.2018	0.0376
6	-0.8225	-0.8270	0.0625	-0.1264	-0.1604	0.0441
7	-0.8993	-0.8089	0.0570	-0.3863	-0.3360	0.0463
8	-0.6257	-0.6997	0.0607	-0.3063	-0.4169	0.0491
9	-0.6706	-0.7282	0.0599	-0.4740	-0.5788	0.0539
10	-0.6773	-0.7231	0.0575	-0.5614	-0.6700	0.0529
11	-0.5360	-0.5970	0.0592	-0.5142	-0.6265	0.0558
12	-0.6220	-0.7058	0.0633	-0.6555	-0.7710	0.0599
13	-0.5138	-0.5907	0.0650	-0.5351	-0.6581	0.0529
14	-0.3831	-0.4648	0.0536	-0.4293	-0.5606	0.0560
15	-0.4895	-0.5699	0.0588	-0.4086	-0.5512	0.0535
16	-0.3494	-0.4582	0.0586	-0.3809	-0.5484	0.0589
17	-0.2231	-0.3289	0.0618	-0.3658	-0.5418	0.0567
18	-0.2653	-0.4132	0.0581	-0.2843	-0.4602	0.0515
19	-0.2325	-0.3897	0.0597	-0.1227	-0.3143	0.0502
20	-0.1313	-0.2914	0.0609	-0.1146	-0.3309	0.0551
21	-0.0213	-0.2107	0.0554	-0.1134	-0.3050	0.0531
22	0.0112	-0.1758	0.0625	-0.0141	-0.2190	0.0528
23	-0.0047	-0.2390	0.0545	-0.0564	-0.2829	0.0585
24	0.0412	-0.2128	0.0599	-0.0798	-0.3276	0.0545
25	0.1073	-0.1606	0.0576	0.0391	-0.2099	0.0510
26	0.1760	-0.1030	0.0589	0.1147	-0.1309	0.0494
27	0.2283	-0.0876	0.0571	0.1091	-0.1702	0.0564
28	0.3780	0.0404	0.0586	0.1380	-0.1328	0.0582

Bootstrap Analysis of lag 0

Stratum	log odds based on bootstrap	Se based on bootstrap
6 weeks	2.4503	0.0229
5 weeks	2.3643	0.0220
4 weeks	2.2454	0.0217
3 weeks	2.0900	0.0225
2 weeks	2.0900	0.0225
1 weeks	1.4449	0.0222
6 days	1.3486	0.0226
5 days	1.2602	0.0225
4 days	1.1783	0.0236
3 days	1.0956	0.0266
2 days	0.9964	0.0295
1 day	0.0000	0.0000

Bootstrap log odds ratio based on different time lag adjustment (one-month, 3-week, 2-week and 1-week)

Log odds ratio after adjusting subject and time lag

Time lag	4 weeks	3 weeks	2 weeks	1 weeks
0	2.0883	1.9453	1.7126	1.3513
1	0.2056	0.0501	-0.2291	-0.7288
2	-0.4520	-0.5978	-0.8912	-1.3904
3	-0.7237	-0.8576	-1.1518	-1.6454
4	-0.7589	-0.9112	-1.1964	-1.6926
5	-0.7545	-0.9154	-1.1843	-1.6689
6	-0.8734	-0.9681	-1.3070	-1.8183
7	0	0	0	0

LIST OF REFERENCES

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