Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature:

_____ _____

Caitlin A. Marsh Date

Emergency department utilization for infantile acute bronchiolitis and subsequent risk of childhood asthma

By

Caitlin A. Marsh

Master of Public Health

Department of Epidemiology

Matthew Strickland

Faculty Thesis Advisor

An abstract of

A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of
Master of Public Health
in Epidemiology

2014

Abstract

Emergency department utilization for infantile acute bronchiolitis and subsequent risk of childhood asthma

By Caitlin A. Marsh

Background: Asthma etiology is poorly understood; early diagnosis and treatment are recommended for optimum symptom control. Studies using existing datasets, such as emergency department (ED) information, allow investigation of associations between early risk factors and subsequent asthma. Infantile acute bronchiolitis (AB) is considered a possible risk factor.

Methods: Linked datasets of ED utilization and birth records were used to assemble a cohort of children born in the state of Georgia between 2002 and 2004; children included had at least one ED visit before, and survived to, age one. Outcome (asthma ED visit after age five vs. none) and exposure (AB before age one) status were assigned on the basis of ED record ICD-9 codes. The effects of loss to follow-up in this dataset were evaluated through a sensitivity analysis of three additional study designs using variations of the sample population reflecting different patterns of loss to follow-up.

Results: Logistic regression resulted in an adjusted odds ratio (95% CI) of 1.83 (1.70, 1.96). . Sensitivity analysis of cumulative case-control designs produced ORs of 2.01 (1.86, 2.15) for the total population (including those potentially lost to follow-up), and 1.99 (1.85, 2.14) for a population subset excluding those without ED visits after age five (less loss to follow-up). An incidence density sampled case-control study resulted in an OR of 1.92 (1.78-2.07).

Conclusion: A positive association was observed between ED utilization for infantile AB and subsequent asthma ED visits after age five; loss to follow-up appeared to have little effect on the estimate.

Emergency department utilization for infantile acute bronchiolitis and subsequent risk of childhood asthma

By

Caitlin A. Marsh

B.A., B.S.

Alma College

2012

Faculty Thesis Advisor: Matthew Strickland, PhD

A thesis submitted to the Faculty of the

Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of
Master of Public Health
in Epidemiology

2014

Table of Contents

Chapter I: Background

Asthma is a complex disease that is becoming increasingly common in many places throughout the world. It is particularly common in children, where its effects can include not only difficulties with symptom management, but also considerable disruption to daily routines. Unfortunately, the causes of asthma are not well understood, which poses a problem for clinicians. Since early diagnosis and treatment are recommended for optimal symptom management, this current gap in knowledge is a challenge. However, an improved understanding of risk factors associated with asthma development may offer clinicians a new tool in identifying children at risk for asthma at a young age. While some factors are relatively well understood, others, especially the role of infantile acute bronchiolitis (AB), remain somewhat controversial. One means of helping to answer these lingering questions is to utilize existing health data in the form of administrative datasets, such as hospital and birth records. As more and more information is available through digital record keeping, it is becoming possible to link these datasets together to assemble a detailed record of an individual's health history and factors which may affect it. The scale of these digital databases allows these records to be compiled for any number of various populations. With these techniques, it may be possible to detect associations between infantile AB and subsequent asthma in children, which would demonstrate a clear, existing risk factor that would be easily recognizable by both clinicians and laypersons.

A consistent increase in the prevalence of asthma and related conditions has been reported in a number of countries over the past several decades (1, 2). In the United States, for example, the prevalence climbed by roughly 3% each year between 2001 and 2010; a

considerable portion of the cases included in these statistics were children under the age of 17 (2). Between 2008 and 2010 in the United States, 9.5% of children under the age of 17 had a current asthma diagnosis, compared to only 7.7% of adults 18 and older (2). The numbers only continue to rise; the prevalence among children was increasing by a rate of 1.4% per year during this same time period (2). Treatment recommendations advocate early diagnosis and care as the best means of controlling the disease and preventing not only worsening symptoms and potential complications, but also the accompanying disruption of normal routines. For children, this can include such varied repercussions as poor sleep and increased absences from school, which may in turn lead to poor academic performance (2,3). In addition, children with poorly controlled asthma face an increased need for medical services, ranging from prescription medication to emergency department (ED) visits (2, 3).

Despite the impact of asthma on a growing number of patients, as well as their families, employers, etc, little is known about the etiology of the disease. Like other atopic diseases, this process is likely extremely complex, resulting from a variety of both internal and external factors. Since early detection and control are key to adequate maintenance, however, the ability to identify individuals at increased risk for asthma, particularly at an early age, would be of great benefit. Many risk factors have already been proposed, including age, sex, family history of asthma or other atopic disease, increased exposure to pollution or allergens, and even such factors as diet and exercise habits (2, 3, 4, 5). One factor, however, remains a source of contention in the literature surrounding this topic. Many studies have shown conflicting results regarding the role of acute bronchiolitis (AB) in the subsequent development of asthma.

Though it is common for studies to differ as to the extent of an association, there is seldom the kind of schism that has developed surrounding the relationship of AB and asthma.

There are many studies supporting the "hygiene hypothesis" proposed in 1989 by Strachan, which suggests that disease exposure in childhood may have a protective effect in regards to developing atopic disease later in life (1, 6, 7, 8, 9). Other studies, however, have shown an increased risk for asthma among children who suffer from AB (1, 8, 9, 10). This is a testament to the complexity of the disease and surrounding risk factors, and also to the difficulty of developing studies which can adequately explore such complexity. It is possible that these apparently conflicting results both represent support of the same relationship, differing only in how the study in question has approached the issue.

For example, Strachan's hygiene hypothesis was originally developed on a premise of childhood *exposures* rather than instances of illness. Strachan's original study noted an inverse relationship between family size and hay fever in adults; the presence of older siblings in particular seemed to be associated with decreased instance of atopic disease (6). Other studies have continued in this vein, examining exposures in a number of different ways. Some have used immunologic testing to confirm contact with a particular pathogen, while others relied, like Strachan, on proxy measures of exposure, such as family size and structure, birth order, or time spent attending daycare or school (4, 7, 8). This type of study tends to find decreased risk of asthma for individuals with childhood exposures. In contrast, other studies have relied not on exposure, but instances of childhood illness.

There is rather more variation among the design of studies examining the impact of childhood illness on subsequent asthma. A variety of illnesses have been studied as the exposure of interest, ranging from parent-reported instances of runny nose to hospitalization for pneumonia (9, 10). The results of these studies have been similarly varied. However, as Mallia and Johnston discuss in their extensive review of such studies, even here a trend may exist (1).

Studies examining less severe instances of childhood illness tend to report a protective effect, while those considering more severe illness, particularly AB including wheezing as a symptom, often report an increased risk associated with subsequent asthma (1, 9, 10). It has been suggested that this pattern may be reflecting asthma as an underlying condition rather than an outcome. Clinicians have documented the difficulty in differentiating between infantile AB and early asthma symptoms (8, 11). Even without understanding the underlying etiology, the existence of such an association could still prove beneficial in identifying young children at risk for developing asthma, or who may already be struggling with unrecognized symptoms.

If there is indeed an association between infantile AB and subsequent asthma in children, this could provide a clear and apparent risk factor status that is easily comprehensible for both laypersons and clinicians. Unlike examining exposure to respiratory pathogens, this risk factor does not require additional testing to determine exposure status, nor does it suffer the same potential for inaccuracy as using proxy measures. Additionally, as these instances of illness often warrant clinical intervention, it is increasingly possible to track such illness over time and examine potential associations with future outcomes. As medical records and other patient information is frequently digitized and linked, it is now possible to apply the information stored in this vast cloud of data to examining relationships not even considered when it was originally collected.

Administrative databases may include everything from hospital admittance and release records, to International Classification of Diseases (ICD) codes, as well as birth and death information. These may provide researchers with a wealth of insight into the health of large populations without the struggle of recollecting this data. Linking these datasets together can help create an even fuller picture of a population, allowing for complex matching or control of

confounding variables (12). In such research, care must be taken to ensure that rigorous ethical standards are upheld, particularly as linked datasets continue to provide ever more specific information on individuals. With these considerations in place, these large, detailed datasets could allow for the examination of any number of associations.

These databases, however, are not without faults. As they are not developed with the end goals of a researcher in mind, important variables may be missing, poorly defined or poorly collected. The population may suffer from extensive loss to follow-up, or selection bias inherent in its very construction. For example, the dataset used in this study contains only instances of emergency department utilization, which captures both the population using these services occasionally for true emergency care as well as those using emergency department services in lieu of primary care. The resulting dataset does not allow for a full exploration of what data may be missing and the factors associated with this loss to follow-up.

The data contained within these administrative datasets may also be problematic. It may be impossible to verify how the information was collected, or that it was done with any kind of consistency. For this reason, it is important to carefully consider the methodology of studies utilizing such data sources. If approached with an awareness of these limitations, however, such sources still represent a substantial opportunity for researchers to further their knowledge on a variety of matters, including the complex question of the potential role of infantile AB in the development of asthma in children.

While the etiology of asthma is not yet well understood, it is known that early diagnosis and intervention can have an impact on the maintenance of asthma symptoms. This is particularly important in children, who suffer from asthma at higher rates than adults. Some risk

factors have been established, but others are less well defined. Despite the complexities and apparent disagreement surrounding the role of AB in asthma development, this particular risk factor has the potential to be a clear clinical indicator of risk, if the existence of such an association could be supported. In this endeavor, new applications for administrative datasets in research could help assemble information on substantial study populations. Coupled with continued research into the biological mechanisms behind asthma etiology, this represents the potential for an important tool in the clinical management of asthma in children.

Chapter II: Manuscript

Title: Emergency department utilization for infantile acute bronchiolitis and subsequent risk of childhood asthma

Author: Caitlin A. Marsh

Abstract:

Background: Asthma etiology is poorly understood; early diagnosis and treatment are recommended for optimum symptom control. Studies using existing datasets, such as emergency department (ED) information, allow investigation of associations between early risk factors and subsequent asthma. Infantile acute bronchiolitis (AB) is considered a possible risk factor.

Methods: Linked datasets of ED utilization and birth records were used to assemble a cohort of children born in the state of Georgia between 2002 and 2004; children included had at least one ED visit before, and survived to, age one. Outcome (asthma ED visit after age five vs. none) and exposure (AB before age one) status were assigned on the basis of ED record ICD-9 codes. The effects of loss to follow-up in this dataset were evaluated through a sensitivity analysis of three additional study designs using variations of the sample population reflecting different patterns of loss to follow-up.

Results: Logistic regression resulted in an adjusted odds ratio (95% CI) of 1.83 (1.70, 1.96). Sensitivity analysis of cumulative case-control designs produced ORs of 2.01 (1.86, 2.15) for the total population (including those potentially lost to follow-up), and 1.99 (1.85, 2.14) for a population subset excluding those without ED visits after age five (less loss to follow-up). An incidence density sampled case-control study resulted in an OR of 1.92 (1.78-2.07).

Conclusion: A positive association was observed between ED utilization for infantile AB and subsequent asthma ED visits after age five; loss to follow-up appeared to have little effect on the estimate.

Asthma is a complex disease common in children; between 2008 and 2010 in the United States, 9.5% of children under the age of 17 had a current asthma diagnosis (1, 2). In this population, the repercussions of asthma include poor sleep and increased absences from school, which may in turn lead to poor academic performance. In addition, children with poorly controlled asthma require increased medical services, ranging from prescription medication to emergency department (ED) visits (2,3). Early diagnosis and treatment are recommended for optimal symptom management, but the causes of asthma are not well understood, making identification of at-risk individuals difficult. Many risk factors have been proposed, including infantile acute bronchiolitis (AB), which has been a source of conflicting results in research of asthma etiology (2-5, 8-10). However, the use of large administrative databases may allow for the identification of factors associated with asthma regardless of any role they may play in underlying etiology.

Digitized administrative databases may include everything from hospital admittance and release records, to International Classification of Diseases (ICD) codes, as well as birth and death information. Generated and compiled by various organizations including hospitals and health departments, these extensive databases make it possible to investigate associations throughout a large population or within a particular subpopulation (12). In this case, such a

database from the state of Georgia is used to investigate associations between ED visits for infantile AB and subsequent ED visits for asthma after age five.

Methods:

Sample- We retrospectively assembled a cohort of children using three large administrative datasets. The primary dataset consisted of birth records for infants born in the U.S. state of Georgia between 2002 and 2004 (N=265,590). Staff at the Office of Health Indicators for Planning, Georgia Department of Public Health, routinely link birth records to Georgia death records to identify infant deaths (N=500) and to a database of ED visits assembled by the Georgia Hospital Association. The ED visit database used in this study consisted of all pediatric ED visits in Georgia between January 1, 2002 and June 30, 2010. Birth records were geocoded to Census 2000 block groups. Individuals without ED visits in the first year of life (N=122,332) were excluded, resulting in a cohort of 143,258 children.

Measurements- Exposure was a dichotomous indicator defined as one or more ED visits before age one with a recorded ICD-9 code for acute bronchiolitis (AB) (ICD-9 codes 466.1, 466.11, 466.19, N=11,564). The outcome was defined as one or more ED visits after age five years for which asthma was indicated among the ICD-9 diagnosis codes (ICD-9 codes beginning with 493, N=7,536). Limiting the outcome to visits after age five excludes children who have reactive airway disease at young ages but who do not go on to develop asthma, focusing instead on those who experience symptoms over a longer period of time (13).

Analysis- Logistic regression was used to estimate the odds ratio and 95% confidence interval for the association between any ED visit during the first year of life for AB and any ED visit for

asthma at or after age five. Variables incorporated into the regression model to control for confounding included infant's preterm birth status (born at <37 weeks gestation) and low birth weight status (<2500 grams), as well as year and season of birth, sex, and race (black, white, or other). Maternal variables included in the model were age, alcohol and tobacco use, education level, marital status, Medicaid enrollment, and previous births alive at the time of delivery. Percentage of residents in the census tract living at or below the poverty level ($17,463 for a family of four) was obtained from Census 2000 based on maternal residence at the time of delivery and included in the model.

Because the sample cohort was assembled from only ED data and birth records, there were concerns about loss to follow-up of individuals with no future ED visits. To evaluate the extent to which this impacted the results of the analysis, a sensitivity analysis was performed by comparing the results of similar regression analyses using three additional study designs selected to reflect differing patterns of loss to follow-up. The first additional design used conditional logistic regression to analyze matched cases and controls. Individuals with one or more asthma-related ED visits after age five were considered cases (N=11,882), and all others considered controls (N=253,208). Cases were matched to multiple controls based on month and year of birth, sex, race, and month and year of ED admittance to control for time at risk. This population (N=265,090) included children with any ED visit, assuming they act as controls and were not lost to follow-up. To evaluate the effect of excluding these potentially lost to follow-up individuals, a second additional design included only children with one or more ED visits after age five (N=101,141). Definitions of cases (N=11,882) were otherwise identical to the previous design, while controls included only children with

non-asthma ED visits after age five (N=89,259). Both these designs were cumulative case-control models, wherein individuals serve either as case or control. A third design used conditional logistic regression to examine case-control relationships in an incidence density sampled population of ED visits (N=103,424). Case visits were defined as an individual's first asthma ED visit after age five (N=11,882). Control visits were defined as non-asthma ED visits after age five which were not preceded by an asthma visit; to eliminate overrepresentation of individuals with multiple control visits, one visit was randomly selected for each individual (N=91,542). This population limited the number of potentially lost-to-follow-up individuals included in the analysis while comparing cases and controls at risk over the same time period. All three additional analyses controlled for the same potential confounders as the primary analysis via either matching or inclusion in the model. All analyses were performed using SAS version 9.3.

Results:

Of the 143,258 individuals in the study cohort, 11,564 (0.8%) had one or more ED visits wherein AB was included among the ICD codes (Table 1). Due to the very large sample size, chi-squared tests for significant differences of categorical variables between the exposed and unexposed populations were all significant at the 95% confidence level. The exposed individuals were more frequently male (6.5% fewer females than unexposed), born July-September (3.8% higher than unexposed), and more frequently born preterm and low birthweight (3.3% and 2.3% higher, respectively). Mothers of exposed individuals reflected somewhat conflicting percentages, as a slightly greater proportion (2.0%) reported low educational attainment, but 2.7% more of these mothers also reported living in low poverty

census tracts (0.0-6.75% of residents at or below poverty level). There were 4,863 total individuals with at least one ED visit for asthma after age five (3.39% of study population). Logistic regression resulted in an unadjusted odds ratio (95% CI) of 1.88 (1.75, 2.01). Controlling for potential confounding factors produced an adjusted odds ratio of 1.83 (1.70, 1.96). Individuals missing information on any of these factors were excluded from the analysis; the adjusted odds ratio was therefore obtained using 138,160 individuals, or 96.4% of the total population.

Sensitivity analysis-

Conditional logistic regression of the cumulative case-control design including the entire study population produced adjusted odds ratio of 2.01 (1.86, 2.15) (Table 2). This analysis included all individuals in the original data set who were not missing data for predictors (N=255,473, 96.4% of total N). The second cumulative case-control design under consideration, including only individuals with ED visits after age five who were not missing data for predictors, (N=97,802, 96.7% of total N) produced an adjusted odds ratio of 1.99 (1.85, 2.14). The incidence density sampled population of case and control visits produced an adjusted odds ratio of 1.92 (1.78, 2.07) using observations with data for all predictors (N=100,012, 96.7% of total N).

Comments:

These results suggest a significant positive association between ED utilization for infantile AB and subsequent ED utilization for asthma after age five. The similarity of odds ratios obtained by various study design suggests that the loss to follow-up in this population may not greatly impact this overall finding, which aligns well with similar studies. Work by Henderson et al obtained an odds ratio of 2.5 (1.4, 4.3) comparing hospital admission for

infantile respiratory syncytial virus (RSV) bronchiolitis and subsequent doctor diagnosed asthma (5). Clark et al identified a similar relationship between hospital admission for pneumonia and subsequent asthma diagnosis, albeit in a somewhat older population of children (10). Together, these findings suggest a close link between severe infantile respiratory illness and asthma later in childhood, though this association does not help to resolve questions of underlying etiology. As work continues into defining the biological mechanisms of asthma, however, clinicians can use this information to identify and potentially treat children at increased risk for asthma, as well as in monitoring at-risk infants as they grow.

Strengths and limitations-

The size of this study served as both a great advantage and a limitation. It was beneficial in that information on a very large population was collected and utilized without the effort of re-obtaining this data directly from individuals for the sole purposes of this study. However, because this information was collected without the goals of this study in mind, information that would have been helpful, such as family history of asthma or allergy, was not collected. The large study population also requires additional consideration in that statistical significance becomes a poor measure of practical significance when comparing population differences. For the purposes of this study, differences in percent population were used to compare and contrast the exposed and unexposed populations, with differences greater than 2% considered to be of note. The use of confidence intervals for the odds-ratios, however, allows the statistical significance of these to be assessed while still taking full advantage of the study size. Other disadvantages to pre-collected data include difficulties in verifying how the information was collected, or that it was done in a consistent manner from individual to

individual. ICD codes are a subjective measure of outcome and exposure, but more precise measurements (*i.e.* immunological testing, etc.) are unavailable in this pre-collected dataset. Additionally, the structure of the dataset itself poses difficulties in that it includes only individuals with ED visits. Therefore, this relationship may best reflect the population most likely to use emergency treatment rather than primary care to manage conditions such as asthma.

Future directions:

Given the limits of this ED-specific study, further research using information from primary care providers may provide a better understanding of this association throughout the general population. Additional work examining the patterns of loss to follow-up in ED utilizing populations such as this could also prove beneficial as more research is conducted using large datasets.

References

1. Mallia P, Johnston S. Respiratory viruses: do they protect from or induce asthma? *Allergy.* 2002; 57 (12): 1118-1129.

2. National Center for Health Statistics. National Surveillance of Asthma: United States 2001-2010. Hyattsville, MD: National Center for Health Statistics; 2012. (Vital and health statistics, series 3:analytical and epidemiological studies, no. 35) (DHHS publication no. (PHS) 2013-1419).

3. Wasilewski Y, Clark N, Evans D, et al. Factors associated with emergency department visits by children with asthma: implications for health education. *Am J Public Health*. 1996; 86 (10): 1410-1415.

4. Sly P, Boner A, Björksten B, et al. Early identification of atopy in the predication of persistent asthma in children. *The Lancet.* 2008; 372 (9643): 1100-1106.

5. Henderson J, Hilliard T, Sherriff A, et al. Hospitalization for RSV bronchiolitis before 12 months of age and subsequent asthma, atopy, and wheeze: a longitudinal birth cohort study. *Pediatr Allergy Immunol.* 2005; 16 (5): 386-392.

6. Strachan D. Hay fever, hygiene, and household size. *BMJ* 1989; 299 (6710): 1259-1260.

7. Lebowitz M, Holberg C, Martinez F. A longitudinal study of risk factors in asthma and chronic bronchitis in childhood. *Eur J Epidemiol.* 1990; 6 (4): 341-347.

8. Velissariou I, Papadopoulos N. The role of respiratory viruses in the pathogenesis of pediatric asthma. *Pediatr Ann.* 2006; 35 (9): 637-642.

9. Illi S, von Mutius E, Lau S, et al. Early childhood infectious diseases and the development of asthma up to school age: a birth cohort study. *Br Med J.* 2001; 322 (7283): 390-395.

10. Clark C, Coote J, Silver D, et al. Asthma after childhood pneumonia: a six year follow up study. *Br Med J.* 2000; 320 (7248): 1514-1516.

11. Dunsky, E. Bronchiolitis: different from infantile asthma. *Pediatr Ann.* 1977; 6 (7): 45,47-51,55-56.

12. Moore H, Klerk N, Jacoby P, et al. Can linked emergency department data help assess the out-of-hospital burden of acute lower respiratory infections? A population-based cohort study. *BMC Public Health.* 2012; 12 (703): (doi:10.1186/1471-2458-12-73).

13. National Asthma Education and Prevention Program. *Guidelines for the Diagnosis and Treatment of Asthma*. Bethesda, MD: National Heart, Lung, and Blood Institute; 2007. (Expert Panel Report, no. 3) (NIH publication no. 08-5846).

Tables

Table 1. Demographic characteristics of cohort by exposure status

	Emergency Department visit for acute bronchiolitis n (%) or mean ± SD [a]	
	Yes (n=11,564)	**No (n=131,694)**
Characteristics of Individual		
Female	4,797 (41.5)	63,204 (48.0)
Race		
White	5,245 (45.4)	60,090 (45.6)
Black	4,507 (39.0)	53,121 (40.3)
Other/Unknown	1,812 (15.7)	18,483 (14.0)
Birth Season		
Jan-Mar	2,277 (19.7)	32,128 (24.4)
Apr-Jun	2,731 (23.6)	32,144 (24.4)
Jul-Sep	3,457 (29.9)	34,421 (26.1)
Oct-Dec	3,099 (26.8)	33,001 (25.1)
Low Birthweight	1,364 (11.8)	12,474 (9.5)
Born Preterm	1,909 (16.5)	17,415 (13.2)
Characteristics of Mother		
Used Alcohol While Pregnant	53 (0.5)	742 (0.6)
Missing Data	33 (0.1)	282 (2.1)
Used Tobacco While Pregnant	1,271 (11.0)	14,093 (10.7)
Missing Data	34 (0.1)	288 (2.2)
Education		
No High School	943 (8.2)	8,172 (6.2)
Some High School, No Diploma	3,056 (26.4)	32,186 (24.4)
High School Diploma or GED	3,808 (32.9)	44,756 (34.0)
College Education or Higher	3,527 (30.5)	44,764 (34.0)
Missing Data	230 (2.0)	1,816 (1.4)
Married [b]	5,573 (48.2)	64,484 (49.0)
Percentage of Census Tract at or Below Poverty		
0.0 – 6.57	2,853 (24.7)	29,012 (22.0)
6.58 – 10.91	2,465 (21.3)	25,931 (19.7)
10.92 – 15.97	2,208 (19.1)	25,496 (19.4)
15.98 – 23.59	1,969 (17.0)	24,859 (18.9)
23.60 – 75.65	1,932 (16.7)	23,915 (18.2)
Missing	137 (1.2)	2,481 (1.9)
Enrolled in Medicaid	7,456 (64.5)	82,466 (62.6)
Age in Years	25.1±5.9	25.1±5.9

a. For all comparisons, $p<0.05$ due to large sample size
b. One observation missing data (no AB)

Table 2. Results of sensitivity analysis by study design

Study Design	Total N	Cases	Observations used in analysis	OR (95% CI)
Cohort study [a]	143,258	4,863 [b]	138,160	1.83 (1.70, 2.15)
Cumulative case-control, total population [c]	265,090	11,882	255,473	2.01 (1.86, 2.15)
Cumulative case-control, population subset [d]	101,141	11,882	97,802	1.99 (1.85, 2.14)
Incidence density sampled case-control [e]	103,424	11,882	100,012	1.92 (1.78, 2.07)

a. Primary study design, provided for comparison
b. Reflects the total number of individuals with disease rather than "case" status
c. Design includes all individuals in study population and assigns either case or control status; potentially lost to follow-up individuals are included as controls
d. Design limits loss to follow up by limiting analysis to individuals with ED visits after age five
e. Design limits loss to follow up by limiting analysis to individuals with ED visits after age five; employs incidence density sampling to provide estimate based on time at risk.

Chapter III: Summary, Public Health Implications, Possible Future Directions

By examining linked administrative datasets, this study identified an association between ED utilization for infantile AB and subsequent ED utilization for asthma after age five. Among children with asthma ED visits, the odds of having had an ED visit for AB before age one were nearly twice those of their unexposed counterparts. This association does not clarify the etiology of asthma; as indicated in previous research, infantile AB may be an expression of existing asthma, or possibly cause damage leading to asthma later in life. Whatever the causal pathway, however, knowledge of this association is still valuable to clinicians. Because early identification and treatment of asthma is important in properly managing symptoms, identifying infants with AB ED visits as potentially at higher risk for asthma later in life provides clinicians, and even laypersons, a clear risk factor that requires no additional immunologic testing or complex procedures. These children can therefore be more easily monitored and treated early should asthma develop, and as the prevalence of asthma continues to climb around the world, this could have an important impact in both the short and long term.

The use of administrative datasets in this analysis is also of note. As more information is digitized and condensed into large databases, these are becoming more and more frequently a tool of choice for researchers in various fields, including public health. These datasets can provide a wealth of information on a variety of populations; their uses are only just now beginning to be explored. Along with their benefits, their drawbacks are also relatively new. Large datasets pose difficulties in terms of study design as they can indicate statistically significant differences for populations that are, for practical purposes, not dissimilar. The data itself may lead to false conclusions based not on the information it contains, but rather on information that is systematically (though not intentionally) included. For example, the dataset

used in this study contained only emergency department records, which means that the results of this study may apply only to the population using ED services rather than primary care for asthma and AB treatment. This was taken into consideration in designing the study, and a sensitivity analysis was used to assess the effect of differing patterns of follow-up. Other studies using similar datasets will likely face similar issues, making study design considerations an important part of assessing potential relationships.

In summary, this study represents a practical application of linked administrative datasets in public health research. While it does not further explain the biological etiology of asthma, these findings may nonetheless have useful applications for clinicians seeking to provide timely and appropriate care for children at risk for this disease. Other health outcomes may benefit from similar research into early risk or protective factors, research which will become increasingly possibly as administrative datasets continue to grow. As research continues to explore the applications of these datasets, more nuanced and precise methods may be developed to cope with their idiosyncrasies and unique challenges, resulting in new methodologies and applications for this avenue of public health research.

Appendix: IRB Approval

EMORY UNIVERSITY

Institutional Review Board

TO: Matthew Strickland, PhD
Principal Investigator
Envir & occup Health

DATE: November 7, 2012

RE: **Notification of Amendment Approval**
AM4_IRB00045413
IRB00045413
Novel Estimates of Air Pollutant Mixtures and Pediatric Health in Two Birth Cohorts

Thank you for submitting an amendment request. The Emory IRB reviewed and approved this amendment under the expedited review process on **11/7/2012**. This amendment includes the following:

Personnel Change only: Adding Caitlin Marsh as other Emory study staff.

In future correspondence with the IRB about this study, please include the IRB file ID, the name of the Principal Investigator and the study title. Thank you.

Sincerely,

Donna Thomas
Administrative Assistant
This letter has been digitally signed

CC

Chang	Howard	Biostatistics
Darrow	Lyndsey	Envir & occup Health
Fitzpatrick	Anne	Pulmonolog
Klein	Mitchel	Envir & occup Health
Liu	Yang	Envir & occup Health
Schechter	Michael	Pulmonolog
Tolbert	Paige	Envir & occup Health
Waller	Lance	Biostatistics

Emory University
1599 Clifton Road, 5th Floor - Atlanta, Georgia 30322
Tel: 404.712.0720 - Fax: 404.727.1358 - Email: irb@emory.edu - Web: http://www.irb.emory.edu/