PEDIATRIC ASTHMA INCIDENCE IN TEXAS AND ASSOCIATIONS WITH AMBIENT OZONE LEVELS IN AN URBAN AREA

AN ANALYSIS USING MEDICAID CLAIMS DATA

by

JUDITH K. WENDT, MPH

APPROVED:

ELAINE SYMANSKI, PHD

WENYAW CHAN, PHD

XIANGLIN L DU, MD, PHD

THOMAS H STOCK, PHD

DEAN, THE UNIVERSITY OF TEXAS
SCHOOL OF PUBLIC HEALTH

DEDICATION

To Joanne Kristynik

PEDIATRIC ASTHMA INCIDENCE IN TEXAS AND ASSOCIATIONS WITH AMBIENT OZONE LEVELS IN AN URBAN AREA

AN ANALYSIS USING MEDICAID CLAIMS DATA

by

JUDITH K WENDT, MPH

Presented to the Faculty of The University of Texas

School of Public Health

in Partial Fulfillment

of the Requirements

for the Degree of

DOCTOR OF PHILOSOPHY

THE UNIVERSITY OF TEXAS
SCHOOL OF PUBLIC HEALTH
Houston, Texas
May, 2012

ProQuest LLC.
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106 - 1346

PREFACE

This doctoral dissertation is presented as two separate manuscripts for publication. Chapters I and II provide an introduction to the project, and study methods, respectively. Chapters III and IV were written in manuscript form suitable for publication. Chapter III has been accepted for publication in *The American Journal of Epidemiology*. Chapter V provides a summary of results and conclusions from the two manuscripts.

This dissertation uses data from the Centers for Medicare and Medicaid Services (CMS) under Data Use Agreement 21177, and from the U.S. Environmental Protection Agency (EPA). While completing this work, I was funded as an Occupational Epidemiology trainee as part of the NIOSH Southwest Center for Occupational and Environmental Health Training Grant #T42OH008421.

ACKNOWLEDGEMENTS

I would like to express sincere thanks to my advisor Elaine Symanski, and committee members Xianglin Du, Thomas Stock and Wenyaw Chan for their guidance and support. You were truly teachers in the best sense of the word.

I am grateful for family, friends and co-workers who have cheered me on along the way. Special thanks to my mom, Joanne, for supporting me in countless ways, and to Keith for encouraging me and keeping me focused.

And most of all, to my daughters Rebekah and Melissa, and son Joey, thank you for your incredible patience with my marathon.

PEDIATRIC ASTHMA INCIDENCE IN TEXAS AND ASSOCIATIONS WITH AMBIENT OZONE LEVELS IN AN URBAN AREA

AN ANALYSIS USING MEDICAID CLAIMS DATA

Judith K. Wendt, MPH, PhD
The University of Texas
School of Public Health, 2012

Dissertation Chair: Elaine Symanski, PhD

Few recent estimates of childhood asthma incidence exist in the literature, although the importance of incidence surveillance for understanding asthma risk factors has been recognized. Asthma prevalence, morbidity and mortality reports have repeatedly shown that low-income children are disproportionately impacted by the disease. The aim of this study was to demonstrate the utility of Medicaid claims data for providing statewide estimates of asthma incidence. Medicaid Analytic Extract (MAX) data for Texas children ages 0-17 enrolled in Medicaid between 2004 and 2007 were used to estimate incidence overall and by age group, gender, race and county of residence. A 13+ month period of continuous enrollment was required in order to distinguish incident from prevalent cases identified in the claims data. Age-adjusted incidence of asthma was 4.26/100 person-years during 2005-2007, higher than reported in other populations. Incidence rates decreased with age, were higher for males than females, differed by race, and tended to be higher in rural than urban areas. With this study, we were able to demonstrate the utility of MAX data for estimating asthma incidence, and create a dataset of incident cases to use in further analysis.

In subsequent analyses, we investigated a possible association between ambient air pollutants and incident asthma among Medicaid-enrolled children in Harris County Texas between 2005 and 2007. This population is at high risk for asthma, and living in an area with historically poor air quality. We used a time-stratified case-crossover design and conditional logistic regression to calculate odds ratios, adjusted for weather variables and aeroallergens, to assess the effect of increases in ozone, NO_2 and $PM_{2.5}$ concentrations on risk of developing asthma. Our results show that a 10 ppb increase in ozone was significantly associated with asthma during the warm season (May-October), with the strongest effect seen when a 6-day cumulative lag period was used to compute the exposure metric (OR=1.05, 95% CI, 1.02–1.08). Similar results were seen for NO_2 and $PM_{2.5}$ (OR=1.07, 95% CI, 1.03–1.11 and OR=1.12, 95% CI, 1.03–1.22, respectively). $PM_{2.5}$ also had significant effects in the cold season (November-April), 5-day cumulative lag: OR=1.11, 95% CI, 1.00–1.22. When compared with children in the lowest quartile of O_3 exposure, the risk for children in the highest quartile was 20% higher. This study indicates that these pollutants are associated with newly-diagnosed childhood asthma in this low-income urban population, particularly during the summer months.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

CHAPTER I: BACKGROUND AND INTRODUCTION

The Burden of Asthma

The Centers for Disease Control and Prevention (CDC) estimates that nearly 10% of U.S. children had asthma in 2009 (1). Asthma is a leading cause of illness and hospitalizations among children, with significant impacts on both health and quality of life. The direct and indirect costs of asthma are substantial, ranging from those associated with medical care, to missed work and school days (2). Recent analysis of the Medical Expenditure Panel Survey (MEPS) underscored the significant cost of asthma in the US: in 1996, among children ages 5 to 17, 2.52 million were treated for asthma at a cost of $1009.8 million, 6.3 million missed days of school were attributed to asthma, $719.1 million in costs were associated with productivity loss of parents with asthmatic children, and an estimated 211 children died (3).

Children enrolled in Medicaid have been shown repeatedly to have a higher risk of morbidity, complications and hospitalization related to asthma than privately insured children (4, 5). Studies have shown that they are more likely to present to the hospital with severe asthma symptoms compared to privately insured children (4), and more likely to be re-admitted to the hospital after an initial stay for asthma treatment (6). Over 123,000 Medicaid enrollees in Texas were treated for asthma in 1999, with costs totaling $41.6 million (7).

Many studies have investigated factors leading to the exacerbation of symptoms among asthmatic children, but less is known about factors leading to its development. Genetic factors are known to play a role, and there is evidence that indoor and possibly outdoor pollutants may be related to asthma incidence as well (8-10). Asthma is more

common in male children than in females, and in black children compared to whites or Hispanics, although it is not clear if this is due to socioeconomic factors rather than race/ethnicity (8, 11). A better understanding of asthma incidence is critical to the determination of risk factors for the disease, leading the CDC to call for a greater emphasis on tracking asthma incidence in U.S. asthma surveillance programs (12).

Estimates of Asthma Incidence and the Use of Health Claims Data

Estimates of childhood asthma incidence are rare in the literature. Rudd and Moorman published one of the few comprehensive studies estimating asthma incidence in the U.S. (13). Using data from the National Health Interview Survey (NHIS), they calculated incidence rates of self-reported physician-diagnosed asthma between 1980 and 1996. Incidence rates among children in this study ranged from 5.7/1,000 in 1980 to 10.1/1,000 in 1996. The question regarding asthma onset was removed from the NHIS in 1997, so estimation of asthma incidence for the years since 1996 is not possible using this data source. A recent Canadian study reported incidence in 2004-2005 ranging from 31.3/1,000 person-years for children under 5 to 5.6/1,000 person-years in 10-14 year-olds (14). Others have reported incidence rates in children ranging from 4.8/1,000 person-years to 24.6/1,000 person-years (15, 16).

The feasibility of using longitudinal claims data to estimate the incidence of chronic diseases has been demonstrated. This methodology generally involves defining an algorithm to identify cases (i.e., based on diagnosis, procedure or drug codes) during a particular calendar year, examining claims data to identify those meeting the case definition and selecting the earliest claim date as the diagnosis date, then for each case identified, examining claims for a period of time (e.g., 12 months) prior to the diagnosis date in order to

eliminate prevalent cases. This requires defining a population without gaps in medical plan enrollment. Researchers have used Medicare and Medicaid claims data to study the incidence of breast cancer (17-22), colorectal cancer (23), prostate cancer (24), lung cancer (25) and chronic eye disease (26). Other studies have estimated incidence of asthma (27) and osteoporosis-related fractures (28) using commercial health insurance claims data.

Only two studies were found which used claims data to estimate asthma incidence (14, 27). Siwik et al. reported an annual incidence rate of 2.5% among 6-8 year old privately-insured children during five years of follow-up (27). Asthma cases were defined based on medical claim diagnosis codes and prescription claim records. The Canadian study described previously used claims records from their universal health system administrative data to identify incident cases of childhood asthma (14). No studies were found which attempted to estimate state or national level incidence rates using claims data.

Numerous studies have used Medicaid claims data to describe asthma prevalence and patterns of care (29-32). These data have been used to look at ethnic (33-35) or geographic (36) disparities in care, and trends in adherence to treatment guidelines (37, 38). Others have evaluated the impact of gaps in enrollment on quality of care (39). However, no studies were found which used these data for incidence estimates. Medicaid claims data is a readily-available source of medical and pharmacy encounters for children at perhaps the greatest risk of developing asthma, and were used in this study to estimate asthma incidence among this population of Texas children.

Ozone and Asthma

Elevated levels of ambient ozone (O_3) have been associated in several studies with worsening lung function and asthma symptoms (40-43) and similar results have been seen in

studies of $PM_{2.5}$ and NO_2 (41, 44, 45). The design and results of a number of these recent studies are summarized in Appendix A. A recent cross-sectional study found that children from communities in the highest quartile of ambient O_3 levels (maximum 8-hour O_3 level=30.8-40.2 ppb) were 38% more likely to have had an asthma attack in the previous year than children in the lowest quartile (2.3-11.7 ppb), and each 5 ppb increase in O_3 concentration was associated with an 8% greater likelihood of having a current asthma diagnosis (41). Ko et al reported a slight increase in risk of asthma hospitalization with each 10 $\mu g/m^3$ increase in average 8-hour O_3 (relative risk [RR]=1.034, 95% confidence interval [CI]=1.029-1.039) (42). Another recent study of a New York state birth cohort found that each 1 ppb increase in maximum 1-hour O_3 was associated with a 16% higher risk of asthma hospitalization. The association was stronger in younger children (<2 yrs), blacks and Hispanics, and those with low family income (43). Two studies have reported greater risk of asthma hospitalization for Medicaid vs. non-Medicaid beneficiaries (43, 46). However, other recent investigations of an O_3/asthma association have shown no effect (47-50).

There are some indications that high ambient O_3 levels may increase the risk of asthma development in children as well, particularly among those with higher baseline risk due to activity patterns or genetic susceptibility (9, 10, 51). Asthma incidence studies that have appeared in the literature have been based on a small number of cohorts, including the Children's Health Study (CHS) in Southern California, the Prevention and Incidence of Asthma and Mite Allergy Study (PIAMA) in the Netherlands (52), and other datasets in Europe (53), Canada (54) and France (55). These studies have shown positive effects of traffic-related pollutants (47, 52), NO_2 (47, 56), $PM_{2.5}$ (54) and O_3 (51). The O_3 findings are primarily from the CHS. McConnell et al. reported a greater risk of asthma development

among children living in Southern California communities with higher O_3 levels, although the effect was seen only in those with a high level of sports participation. For children living in communities with higher ambient O_3 concentrations (mean daytime O_3=56.9 ppb), those involved in 3 or more sports had more than a three-fold risk of developing asthma over a 5-year period compared to those with no sports participation. There was no increased risk of incident asthma, however, when O_3 levels were examined across all levels of sports participation, or when low O_3 communities were compared to high O_3 communities (51).

Air Quality in the Greater Houston Area

Houston is the nation's fourth largest city and sixth largest metropolitan area (57). In 2004, the Houston-Galveston-Brazoria area was designated a non-attainment area for the eight-hour O_3 standard which went into effect in 1997 (58). Since October 2008, the greater Houston area has been designated a severe non-attainment area, with an attainment date of June 2019 (58). More than 140,000,000 person-miles are driven on Houston roads on an average day and the city is characterized by an extensive industrial area, and automotive and industrial emissions (e.g., nitrogen oxides and volatile organic compounds), combined with a warm, sunny climate, produce O_3 and present unique challenges in terms of air quality (59, 60)

In addition to estimating asthma incidence in Texas, this study also investigated the effects of temporal and spatial variation in ambient O_3 levels on the development of asthma among Medicaid children residing in Harris County between 2004 and 2007. We characterized exposure levels for each zip code in Harris County, and evaluated the effects of both temporal and spatial changes in O_3 exposure on asthma development. We also evaluated co-pollutant effects of NO_2 and $PM_{2.5}$.

The Case-Crossover Design in Air Pollution Epidemiology

This study used a case-crossover design (61), which is well-suited to investigate short-term acute effects of air pollution since it allows the researcher to control for person-level (i.e., genetic and lifestyle) and time-dependent (i.e., air monitoring levels by day of the week, season of the year, etc.) factors. This design has been used in many air pollution epidemiology studies (62), including some among Medicare beneficiaries. Wellenius et al. published a series of case-crossover studies looking at cardiovascular disease hospitalizations, reporting increases in congestive heart failure (63, 64), and stroke (65) admissions following short-term increases of particulate air pollution. Another study found that increases in traffic-related pollutants were related to higher rates of hospital admissions for myocardial infarction and pneumonia among Medicare beneficiaries in Boston (66).

Several case-crossover studies have evaluated associations between air pollutants and asthma (summarized in Appendix B). Some have focused on emergency room (ER) visits for asthma among children in France (67), Australia (68), Korea (69) and Canada (70), and found positive associations with O_3. Risk estimates for asthma ER visits are generally within the range of a 4-16% higher with each interquartile range (IQR, range: 17 to 25 ppb) increase in O_3 level, or 6-10% higher for each 10 μg/m3 increase. Effects were typically seen only in warm weather months, and differed by age group, lag period chosen and socioeconomic status. Other researchers have studied the association of asthma morbidity (particularly hospital admissions) and short-term changes in air pollutant levels (71-75). Several studies reported increased risk of hospitalization following episodes of higher pollutant levels, although the risk magnitude for specific pollutants varied across studies.

Public Health Significance

Medicaid-enrolled children are at greater risk for asthma, and the treatment of pediatric asthma accounts for a significant portion of Medicaid resources. Nearly 2.5 million Texas children are enrolled in Medicaid, the second highest enrollment count of any state in the U.S. Current studies focusing on asthma morbidity have shed light on effective treatment strategies and health care disparities, but a better understanding of who develops asthma could elucidate risk factors for the disease. Despite this, few national or statewide estimates of asthma incidence exist.

There were two major contributions of this study. First, we demonstrated the utility of Medicaid claims data for estimating pediatric asthma incidence among Texas Medicaid beneficiaries. Secondly, we used a time-stratified case-crossover design to study the impact of ambient O_3, NO_2 and $PM_{2.5}$ levels in Harris County, TX on the development of asthma, using exposure estimates which incorporated both temporal and spatial variability during the study period. While air pollutants have been associated with asthma morbidity, less data is available on whether they also contribute to the initial development of the disease.

Specific Aims

This study contributed to the literature in the areas of asthma incidence, and its association with ambient O_3, NO_2 and $PM_{2.5}$ concentrations, using a large population at high risk and living in an area with historically poor air quality. The results of this study help bridge a gap in our knowledge of asthma incidence rates in the U.S. among this group of children, and offer opportunities to explore factors associated with their increased risk of asthma.

The specific aims of this study were:

1. To estimate the annual incidence and prevalence of asthma from 2005- 2007 among Texas children enrolled in the Medicaid Program. Asthma cases were identified using Medicaid medical and pharmacy claims data from 2004 through 2007. For each asthma case identified, the date of the earliest claim meeting our asthma case definition was the diagnosis date, and claims history immediately prior to the diagnosis date (minimum 12 continuous months) was used to determine whether the case was incident or prevalent. Cases were excluded if they did not have at least 12 months of continuous enrollment immediately before the diagnosis date (due to gaps in enrollment or if the case first appeared in 2004), or if they were determined to be prevalent cases.

2. To determine whether temporal variations in ambient O_3, NO_2 and $PM_{2.5}$ levels are related to the risk of developing asthma among Medicaid-enrolled children in Harris County, Texas between 2005-2007. Using U.S. Environmental Protection Agency (EPA) monitoring data from 2005-2007, daily maximum 8-hour average O_3 levels, 1-hour maximum NO_2 and 24-hour average $PM_{2.5}$ were averaged across all monitoring sites in Harris County, and cases of childhood asthma were determined based on Medicaid medical and pharmacy claims data.

3. To evaluate the air pollutant/incident asthma association using ambient O_3 and NO_2 measures which also incorporate spatial variability across Harris County. Air pollutant levels were estimated for each zip code using the average of measurements from the three closest monitors to the centroid of the zip code. Sensitivity analysis was also performed for enrollees residing within close proximity (e.g., 6 miles) of an O_3 or NO_2 monitoring site to validate the risk estimates based on these averaged values. $PM_{2.5}$ was not included in this analysis due to the small number of monitors in Harris County.

CHAPTER II: METHODS

Data Sources

Centers for Medicare and Medicaid Services – Enrollment and Claims Data

Medicaid enrollment and claims data were obtained from the Centers for Medicare and Medicaid Services (CMS), specifically, Medicaid Analytic Extract (MAX) personal summary (PS), inpatient (IP), other services (OT) and pharmacy (RX) files for the state of Texas for 2004, 2005, 2006 and 2007. MAX files contain beneficiary-level enrollment and health care utilization data for each calendar year, including final adjudicated claims, and have undergone extensive edit checks. The files are considered 'research identifiable' as they contain variables such as zip code of residence, date of birth and dates of service; however, other identifiers including SSN, name and residence address are not provided in the files. CMS data files are made available for epidemiology research under the Privacy Act Disclosure Exceptions (Research Routine Use exception), and only after an extensive application, review and approval process.

The PS file included a record for each person enrolled in Medicaid at least one day during the calendar year and was the initial file used to identify the study populations and confirm at least 12 months of continuous enrollment. The IP and OT files contained medical claims records for the calendar year including dates of service and ICD-9 diagnosis codes. The RX file contained a record for each final action paid pharmacy claim, including a National Drug Code (NDC) for each prescription. Specific variables from each file used in the analysis are listed below.

From the 'Personal Summary' files, 2004-2007:

- ELIGIBLE BIRTH DATE (to calculate age)

- ELIGIBLE SEX CODE
- ELIGIBLE RACE/ETHNICITY CODE
- ELIGIBLE RESIDENCE COUNTY CODE
- ELIGIBLE RESIDENCE ZIP CODE
- MAX UNIFORM ELIGIBILITY CODE (Months 01-12) – to determine duration of continuous coverage
- RESTRICTED BENEFITS FLAG (Months 01-12) – indicates whether enrollee was entitled to a full range of benefits
- RECIPIENT INDICATOR – indicates whether the enrollee had only capitated payment claims
- PRIVATE INSURANCE MONTHS COUNT

From the 'Inpatient Record' files, 2004-2007:

- MAX TYPE OF SERVICE CODE (i.e., physician, inpatient hospital, etc.)
- SERVICE BEGINNING DATE
- ENDING DATE OF SERVICE
- PRINCIPAL DIAGNOSIS CODE (select records with value of 493.xx)

From the 'Other Services Record' files, 2004-2007:

- MAX TYPE OF SERVICE CODE (i.e., physician, inpatient hospital, etc.)
- SERVICE BEGINNING DATE
- ENDING DATE OF SERVICE
- DIAGNOSIS CODE-1 (select records with value of 493.xx)

From the 'Drug Record' files, 2004-2007:

- PRESCRIBED DATE
- PRESCRIPTION FILLED DATE
- NEW OR REFILL INDICATOR (if refill, will indicate how many times it was refilled)
- NATIONAL DRUG CODE
- QUANTITY OF SERVICE (i.e., # of pills, # of inhalers, etc.)
- DAYS SUPPLY

Study Subjects

Two study populations were constructed based on Medicaid enrollment and claims files:

1. 'State of Texas' population defined as all children enrolled in the Texas Medicaid program between January 1, 2004 and December 31, 2007, who had at least 12 months of continuous enrollment during the 4-year period, and resided in Texas during this entire 12+ month period. This population was used to address specific aim #1.
2. 'Harris County' population defined as all children enrolled in the Texas Medicaid program between January 1, 2004 and December 31, 2007, who had at least 12 months of continuous enrollment during the 4-year period, and resided in Harris County during this entire 12+ month period. This population was used to address specific aims #2 and #3.

An asthma case was defined as a beneficiary with one or more outpatient or inpatient records having a primary diagnosis of asthma (ICD-CM, 9th revision = 493.xx), or 4 or more asthma medication dispensing events during a 365-day period. Asthma medications were compiled based on the National Drug Code list used by the National Committee for Quality Assurance in their Healthcare Effectiveness Data and Information Set asthma compliance

measures, and included all medications used for treatment or prevention of asthma during the study period. A dispensing event was defined as an asthma prescription for up to a 30-day supply. If a pharmacy record indicated a supply greater than 30 days, this value was divided by 30 and rounded up to calculate the number of 30-day dispensing events. This is the standard definition used to identify asthma cases by the CDC and CMS (personal communication, Dr. Beth Benedict, CMS), and was the proposed case definition to use in a standardized national framework for asthma surveillance (76). The diagnosis or 'event' date was defined as either the date of service associated with the first asthma claim seen for the child, or the date the first of 4+ asthma medication prescriptions was written.

U.S. Environmental Protection Agency – Ambient Air Monitoring Data (Specific Aims #2 and #3)

O_3, NO_2 and $PM_{2.5}$ measurements for 2005, 2006 and 2007 were obtained from the publically-available U.S. EPA Air Quality System (AQS) (77). Data were available from 22 O_3 monitoring stations located in the Houston-Galveston-Brazoria (HGB) metropolitan area. The monitors were concentrated in Harris County (n=17), with two monitors in Galveston County, two in Brazoria County, and one in Montgomery County. The sampling duration was one hour, and samples were taken 24-hours a day, 365 days per year. One-hour NO_2 samples were collected 24-hours a day, 365 days per year at 17 monitoring sites across the HGB metropolitan area: 12 in Harris County, two in Brazoria County, two in Galveston County and one in Montgomery County.

There were seven monitoring sites in Harris County and two sites in neighboring counties which performed 24-hour $PM_{2.5}$ (local conditions) measurements between 2005 and 2007. Beginning in September 2005, measurements were discontinued at the two sites in

adjacent counties, and the number of monitoring sites in Harris County measuring this parameter decreased from seven to four. Also, two of the four monitors were co-located at a single site, one which took daily samples, and a second which took samples every six days, and we used only the sample measurements taken daily from this location. $PM_{2.5}$ measurements were collected from the other area monitors every six days. $PM_{10-2.5}$ and PM_{10} were also pertinent pollutants to explore in relation to asthma but due to the small number of PM_{10} samples taken each week (monitoring was performed at seven sites across Harris county, with samples taken every sixth day), we were not able to include them in the study.

Meteorological and Aeroallergen Data

These data were used to assess potential confounding effects, as has been done in many prior studies of asthma and air pollution (70, 78-82). Daily maximum outdoor temperature and daily average percent relative humidity were measured at 24 and 6 monitoring sites across Harris County, respectively, and these data were also obtained from the AQS (77). Mold spore and tree, grass and weed pollen counts were available for the Houston area from the City of Houston archives (83), and measured as counts per cubic meter of air. These measurements were generally available for each weekday during the study period, except holidays or days that measurements could not be taken because of rain.

Data Analysis

Estimation of asthma prevalence and incidence (Specific Aim 1)

Annual asthma prevalence was estimated for each of the three years (2005-2007) in order to assess consistency with rates from other published reports (e.g., NHIS). Prevalence proportions were calculated using a count of all asthma cases identified during the calendar year in the numerator, and the number of children with 11 or more months of enrollment

during the year in the denominator. Incidence rates for the three-year period were calculated using newly identified cases in the numerator, and the sum of person-months of follow-up for each child during the same period. Both prevalence proportions and incidence rates were directly age- and sex-adjusted using the 2000 U.S. population as the standard population, and incidence rates were expressed per 1,000 person-years. The PS file was used to derive the denominator for state and county rates, and by gender, age group (prevalence: 0-4, 5-9, 10-14, 15-17; incidence: 1-4, 5-9, 10-14, 15-17) and race (i.e., white, black, Hispanic, other).

For each case identified during one of these years, data from the child's prior claims history were used to confirm that he or she was an incident rather than prevalent case. Specifically, for each asthma case identified in the 2005-2007 claims data, the case's prior claims history (for a minimum of 12 continuous months prior to earliest diagnosis date, but including all available claims for the child between 2004 and 2007) were examined for a previous asthma diagnosis. If one was found, the child was considered a prevalent case, and excluded from the incidence rate calculation. If no asthma claim was found prior to the 2005-2007 diagnosis, the child was considered an incident case. Cases were excluded if they did not have at least 12 months of continuous enrollment immediately before the diagnosis date (due to gaps in enrollment, or if the case first appeared in 2004), or if they were determined to be prevalent cases based on examination of their previous claims. Claims files from 2004 were used only to determine whether cases identified in 2005 were incident or prevalent. (Chapter 3 describes our results for estimating asthma incidence among Texas Medicaid-enrolled children ages 0-17, 2005-2007; refer to Appendix C for our age-adjusted estimates of asthma prevalence).

Association of asthma with temporal variation in ambient ozone levels (Specific Aim 2)

The analysis of temporal trends in O_3 levels and asthma incidence used a time-stratified case-crossover design(61), with cases (and controls) identified using Medicaid medical and pharmacy claims files for children enrolled between 2004 and 2007, limited to beneficiaries residing in Harris County. In a case-crossover study, rather than assembling a population of cases and controls who are different individuals, the case/control set represents a single individual, but the two are distinguished by the date of exposure. The case-crossover design allowed for the control of individual-level confounders such as smoking in the home, genetic factors associated with asthma risk and socioeconomic status, as well as co-pollutants (e.g., $PM_{2.5}$, NO_2,) and seasonal aeroallergens. This design allowed us to study different lag periods (i.e., same-day ambient levels vs. several days prior to the asthma event) and averaging periods (i.e., single day vs. multi-day averaged levels) to help identify the pertinent window of susceptibility and exposure metric(s) related to asthma outcomes. We specified 28-day strata beginning with January 1, 2005, and matched each asthma case-day with the three referent dates in the pre-defined strata which were the same day of the week as the case-day (84, 85). For example, a case occurring on Wednesday, January 12, 2005 was matched to control dates on the remaining Wednesdays in the stratum (i.e., January 5, 19 and 26), as shown in Figure 1 below.

January 2005						
Sun	***Mon***	***Tue***	***Wed***	***Thu***	***Fri***	***Sat***
						1
2	**3** Case 2 – Control date	**4**	**5** Case 1 – Control date	**6**	**7** Case 3 – Control date	**8**
9	**10** Case 2 – Control date	**11**	**12** Case 1 – Asthma diagnosis date	**13**	**14** Case 3 – Control date	**15**
16	**17** Case 2 – Asthma diagnosis date	**18**	**19** Case 1 – Control date	**20**	**21** Case 3 – Control date	**22**
23	**24** Case 2 – Control date	**25**	**26** Case 1 – Control date	**27**	**28** Case 3 – Asthma diagnosis date	**29**
30	**31**					

Figure 1. Illustration of the method for selecting case and control dates for a case-crossover study using pre-defined 28-day strata.

Daily pollutant and meteorological variable values were calculated by averaging measurements (i.e., maximum 8-hour O_3, 24-hour mean $PM_{2.5}$, daily 1-hour maximum NO_2) from all monitors in Harris County on that date. A total of 12 exposure variables were constructed for each pollutant on each case and control date, including lagged values and cumulative mean exposure levels. Lag periods were chosen with consideration of both the irritant nature of the pollutants, and the potential number of symptomatic days that might pass before a physician's visit was scheduled. For each case/control date, we constructed single-day measures for maximum 8-hour average O_3, 1-hour maximum NO_2 and 24-hour mean $PM_{2.5}$ using lagged values of 0 days (i.e., L0 = same-day pollutant measurement, taken on the case or control date), one day (L1 = pollutant measurement the day before the case or control date), two days (L2 = two days before the case/control date), three days (L3 = three days before the case/control date), four days (L4 = four days before the case/control date) and five days (L5 = five days before the case/control date). In addition to the single-day measures, variables were constructed for each of the three pollutants using multi-day averaging periods: two-day (L01 = average of case/control date and the prior day), three-day (L02 = same day and prior two days), four-day (L03 = same day and prior three days), five-day (L04 = same day and prior four days) and six-day (L05 = same day and prior 5 days). For specific aim #2, we considered only temporal changes in pollutant concentrations, meaning that exposure was estimated for each calendar day, but for that calendar day, was the same regardless of where in Harris County the child resided.

Each case date was matched to 3 control dates (i.e., 1:3 matching) (86). We used conditional logistic regression to calculate odds ratios which estimated the change in risk of incident asthma associated with changes in ambient pollutant concentration, while

controlling for same-day maximum temperature, mean percent relative humidity, and tree pollen, grass pollen, weed pollen and mold spore counts. We evaluated each pollutant on a linear scale as well as through the use of categories (i.e., quartiles of exposure). We also evaluated possible effect modification by age group, gender and race using stratified analysis.

Association of asthma with temporal and spatial variation in ambient ozone levels (Specific Aim 3)

This analysis considered spatial variability in O_3 and NO_2 exposure, in addition to temporal variability. That is, pollutant estimates for each case/control day were based on the average of measurements from the three closest monitors to the centroid of the zip code of residence. GIS software was used to identify the appropriate O_3 and NO_2 monitoring sites for each case. As in specific aim #2, occurrence of asthma on that date was the dependent variable, and pollutant exposure level was the independent variable. Conditional logistic regression was used to calculate odds ratios for the development of asthma, but daily O_3 and NO_2 estimates potentially differed on a given calendar day depending on the place of residence within Harris County. Same-day maximum temperature, average percent relative humidity and aeroallergen counts were included in all models. $PM_{2.5}$ values were averaged across Harris County for this analysis due to the small number of monitors measuring this pollutant. Other spatial modeling methods such as inverse distance weighting were not used due to the unavailability of street address in the MAX PS files.

A weakness of the spatial averaging method described above is that zip codes without nearby monitors have less accurate exposure values, which may result in inaccurate exposure estimates for cases who reside a greater distance away from a monitoring station. For this reason, we performed a sensitivity analysis restricted to asthma cases living in zip codes in

which the centroid was within six miles of at least one O_3 or NO_2 monitoring station. We calculated average pollutant values across all monitors within a six mile radius on this sub-set of cases to evaluate whether odds ratios resulting from these exposure estimation methods were robust, irrespective of whether the case lived near a monitoring site.

Sample Size Calculation and Study Power

There were approximately 2.5 million Texas children enrolled in Medicaid in 2006. Based on data presented in the MAX data validation tables, approximately 50% of beneficiaries were enrolled for a continuous 12-month period (personal communication, Gerri Barosso, Research Data Assistance Center [ResDAC]). If we assumed that 50% of beneficiaries were enrolled for at least 12 continuous months between 2004 and 2007, the 'State of Texas' study population would comprise approximately 1,250,000 children, before excluding prevalent asthma cases. Similarly, there were approximately 350,000 children enrolled in Medicaid in Harris County. If we assumed 50% were enrolled for at least 12 continuous months, the 'Harris County' population would include approximately 175,000 children.

Recent estimates of childhood asthma incidence in the literature have ranged from 5.6/1,000 person-years to 31.3/1,000 person-years, with higher rates expected in lower income, minority populations. Assuming an incidence rate of 2.25/100 person-years, and an 11.5% prevalence of asthma among Texas Medicaid children (87, 88), we expected to exclude approximately 144,000 children from the Texas population, leaving approximately 1,106,000 for follow-up in 2005-2007, and an estimated 25,000 new cases each year statewide. Similarly, in the Harris County population, we expected to find approximately 20,000 prevalent cases of asthma, leaving a study sample of ~ 155,000 and approximately

3,400 new cases each year. Texas has the second highest number of Medicaid-enrolled children in the U.S. (89) and this large sample size allowed stable statewide estimates, as well as estimates by county, age group, gender and race/ethnicity.

The following calculations used an interactive program by DuPont and Plummer to estimate study power for a matched case-control analysis (90, 91). We estimated the power of the study to detect odds ratios between 1.05 and 1.25, comparing risk of asthma development among children in the highest tertile of ozone exposure compared to the lowest tertile (i.e., prevalence of exposure among controls = 0.33), and assuming exposure correlation coefficients of cases vs. controls (Φ) of 0.2, 0.4, 0.6 and 0.8 (i.e., estimation of the percent of cases and controls with the same level of exposure) (92). The calculations also assumed a Type I error level of 0.05, and four controls per case. Figures 2, 3 and 4 below show power curves assuming the identification of 2,000, 3,000 and 4,000 new cases of asthma each year in Harris County, respectively, during the three years of follow-up.

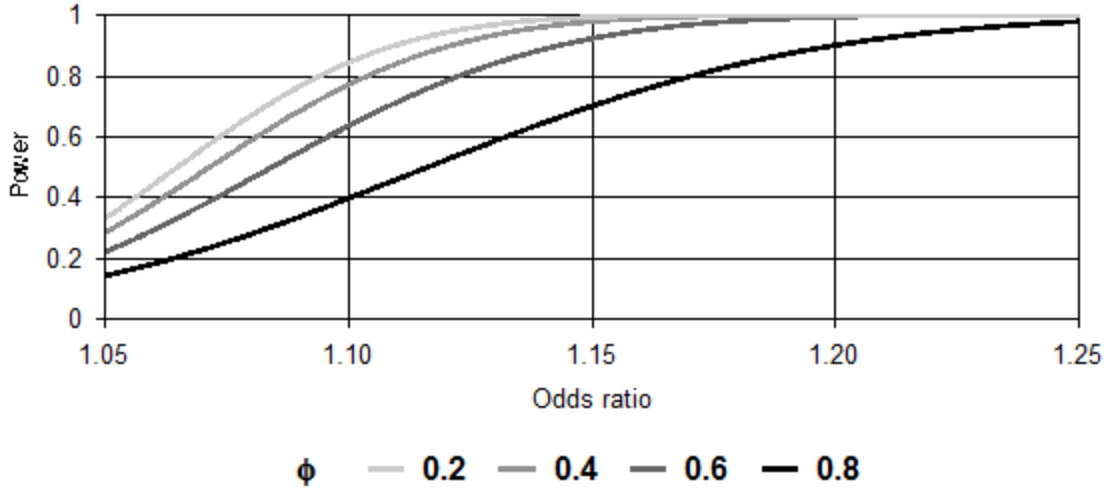


Figure 2. Power curves for the study of ozone exposure and development of asthma among Medicaid-enrolled children in Harris County TX, assuming the identification of 6,000 new cases of asthma between 2005 and 2007 (2,000 cases per year).

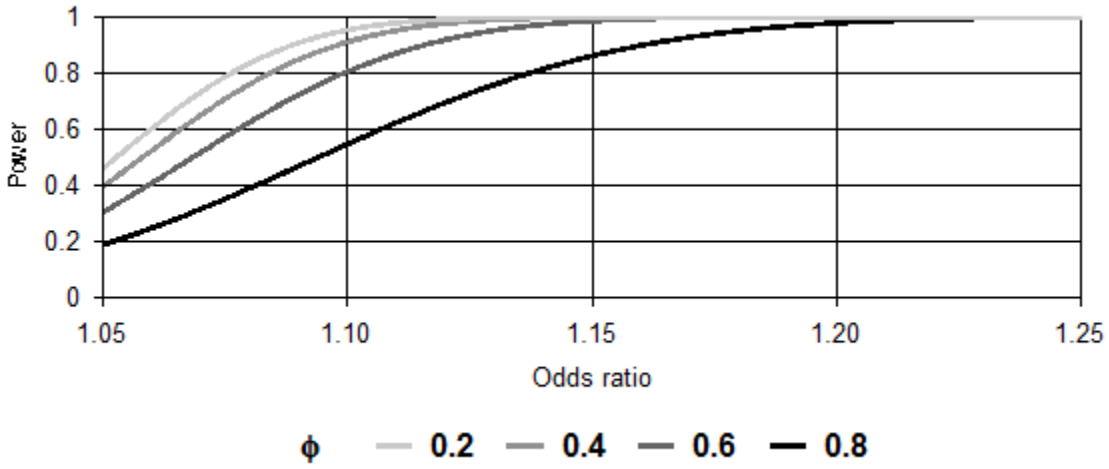


Figure 3. Power curves for the study of ozone exposure and development of asthma among Medicaid-enrolled children in Harris County TX, assuming the identification of 9,000 new cases of asthma between 2005 and 2007 (3,000 cases per year).

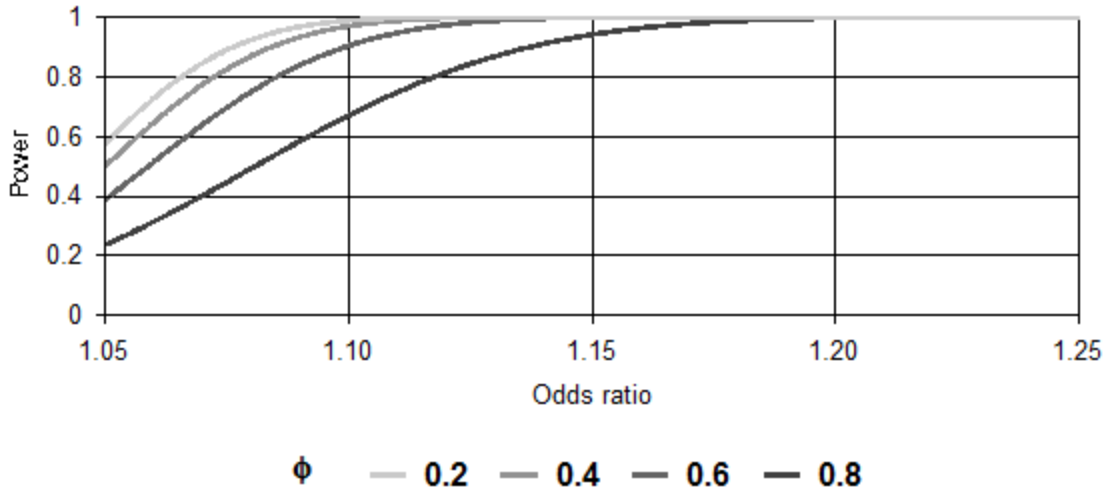


Figure 4. Power curves for the study of ozone exposure and development of asthma among Medicaid-enrolled children in Harris County TX, assuming the identification of 12,000 new cases of asthma between 2005 and 2007 (4,000 cases per year).

Data Analysis Software

All analysis was performed using SAS (Version 9.2, SAS Institute, Inc, Cary, NC). ArcGIS (Version 10, Environmental Systems Research Institute, Inc, Redlands, CA) was used to generate a map of county-specific IRs in Texas, and to identify the O_3 and NO_2 monitoring sites nearest each zip code.

Human Subjects

We obtained approval from the Committee for the Protection of Human Subjects at the University of Texas Health Science Center at Houston (Reference Number: 064546). To ensure the privacy of beneficiaries whose information was contained in the CMS files, the data files were stored and processed within the following data security framework. CMS data files were uploaded to a secure UTSPH server protected by three distinct firewall products and with no access to the general internet in any direction. The server was backed

up every evening, and permissions were assigned only for those who need access. Data were accessed for analysis from either the University of Texas School of Public Health (UTSPH) data center or remotely via the school's VPN system (virtual private network) using a file repository and sharing system known as XFiles. Data were fully encrypted when in transit over the network, including all sessions using the VPN. Physical storage media containing the original files from CMS were placed in locked storage within the UTSPH data center. All investigators participating in the study had undergone training in the protection of human subjects and the study was reviewed by the Committee for Protection of Human Subjects.

The UTSPH computing system is a member of the University domain and is enrolled in a number of security policies and systems, including:

- Automated application and operating system patch management using Microsoft WSUS server. All operating system patches are tested and pushed within 48 hours of release.
- Automated virus/malware patch management using McAfee Electronic Policy Orchestrator (EPO): Virus definitions and engine updates are pushed from McAfee daily, even before there is public knowledge of a given patch release.
- Domain Group Policy Objects: All desktop computers must comply with University GPO's including screen saver timeouts and strong password enforcement.
- Desktop Firewall: While the University maintains a complex and robust enterprise firewall for the network, all desktops additionally have a software firewall implemented to further restrict incoming requests for service or data.

The UTSPH maintains a high speed Local Area Network based on gigabit technology with 100 megabit per second access to each workstation within the building. Advanced

network monitoring technologies supply the school with diagnostic and corrective tools to maintain the ever expanding network. IT Services maintains advanced server technology for database development and access. Additional servers are used to provide high end data storage, backup services and auditing and control systems. All servers containing non-public confidential information are placed behind a sophisticated firewall system with only privileged access allowed.

All data storage environments are housed at the UTSPH Data Center which is protected with high end surveillance equipment and access protocols, a FM200 fire suppression system and uninterruptible power and emergency power if needed. The room meets HIPAA certifications for data protection. The data center has also been weather-proofed against possible hurricanes as it is located on the 8th floor, has no external walls, no windows, and dual layer walls of gypsum with wood and steel reinforcement. All storage systems are clustered and using RAID 5 storage for the highest level of data protection possible. Only authorized systems administrators have access to the data center. In addition, the UTSPH building utilizes an electronic card key door access system to gain entrance through the main doors of the building and to gain entrance into the work areas for each floor from the elevator lobbies. The electronic card key door access system is activated to lock the doors after work hours and on weekends to provide restricted building access. Also, a University of Texas security officer is stationed in the main lobby of the building. An event log tracks who gains access to the servers.

UTHealth policy mandates encryption of all data in transit on the network, and the use of built-in encryption technology on all USB and external drive media. The policy is intended to limit the use of encryption to methods that receive substantial public review and

work effectively, and provides direction to ensure compliance with Federal regulations. The policy specifies that:

- Proven, standard encryption methods (e.g. DES, Blowfish, RSA, RC5, IDEA, etc.) must be used as the basis for encryption technologies.
- Symmetric Cryptosystem key lengths must be at least 128 bits.
- Asymmetric Cryptosystem keys must be of a length that yields equivalent strength.
- UTHealth's key length requirements are reviewed annually and upgraded as technology allows.
- Authorized users may not use proprietary encryption algorithms for any purpose.

Local system audits are conducted by the Office of Institutional Compliance, a non-IT entity employing attorneys with technology emphasis to conduct compliance and security audits throughout the year. In addition, the University IT Security department conducts credentialed quarterly scans of all servers for security and compliance matters. The University has employed two full-time network security analysts to watch and oversee real time data movement issues throughout the system, looking and taking action on any anomalies occurring.

No data for this study were stored on a laptop or desktop computer. No CMS data were transmitted via email or other unsecured means, and hard copy output were secured in a locked cabinet within the UTSPH. As requested by CMS, we suppressed printing table cells containing fewer than 11 observations in any of our reported results. Upon the conclusion of the study, the data will be destroyed and a "Certification of Destruction" will be forwarded to CMS.

CHAPTER III: ESTIMATION OF ASTHMA INCIDENCE AMONG LOW-INCOME CHILDREN IN TEXAS: A NOVEL APPROACH USING MEDICAID CLAIMS DATA

Abstract

Few recent estimates of childhood asthma incidence exist in the literature, although the importance of incidence surveillance for understanding asthma risk factors has been recognized. Asthma prevalence, morbidity and mortality reports have repeatedly shown that low-income children are disproportionately impacted by the disease. The aim of this study was to demonstrate the utility of Medicaid claims data for providing statewide estimates of asthma incidence. Medicaid Analytic Extract (MAX) data for Texas children ages 0-17 enrolled in Medicaid between 2004 and 2007 were used to estimate incidence overall and by age group, gender, race and county of residence. A 13+ month period of continuous enrollment was required in order to distinguish incident from prevalent cases identified in the claims data. Age-adjusted incidence of asthma was 4.26/100 person-years during 2005-2007, higher than reported in other populations. Incidence rates decreased with age, were higher for males than females, differed by race, and tended to be higher in rural than urban areas. This study demonstrates the utility of MAX data for estimating asthma incidence and describes the methodology required for a population with unstable enrollment.

Introduction

Nearly 10% of children in the U.S. had asthma in 2009 (1). Asthma is a leading cause of illness and hospitalizations among children, with significant impacts on health and quality of life. Direct and indirect costs of asthma are substantial, from increased medical care to missed school days (1, 2). Low-income children are disproportionately impacted,

accounting for 37% of the U.S. population, but 58% of prevalent asthma cases (3). Medicaid-enrolled children have higher risk of asthma-related morbidity, complications and hospitalization than privately-insured children (4-6).

While asthma prevalence and morbidity are well described, estimates of childhood asthma incidence are rare. Rudd and Moorman estimated annual asthma incidence in U.S. children ranging from 5.7/1,000 in 1980 to 10.1/1,000 in 1995 (7). A recent Canadian study reported incidence in 2004-2005 ranging from 31.3/1,000 person-years for children under 5 to 5.6/1,000 person-years in 10-14 year-olds (8). Others have reported incidence rates in children ranging from 8.4/1,000 person-years to 24.6/1,000 person-years (9, 10).

Medicaid provides health and long-term care coverage to nearly 60 million low-income and disabled Americans, including 30% of U.S. children, and is funded jointly by state and federal governments (11). Broad federal guidelines mandate that states cover certain benefits like hospital and physician services, but other benefits are optional, including prescription drug coverage. States set eligibility criteria and cost sharing requirements, within federal standards (12).

Medicaid claims data have been used to describe asthma prevalence, morbidity and healthcare utilization patterns (13-22). While two studies estimated asthma incidence using claims data (8, 23), we found none which used Medicaid data to estimate national- or state-level incidence. Thus, we conducted this investigation to demonstrate the utility of Medicaid claims data for estimating asthma incidence among Texas children enrolled in Medicaid, a population of over 2.5 million (24).

Materials and Methods

We used Centers for Medicare and Medicaid Services (CMS) Medicaid Analytic Extract (MAX) files, produced by CMS specifically for research. MAX files contain annual, person-level data on Medicaid eligibility and healthcare utilization reported by the states. The files contain final adjudicated claims by date of service and have undergone quality checks and corrections (25, 26). We obtained enrollment ('Personal Summary, (PS)'), inpatient and outpatient medical claims, and pharmacy claims files from CMS for Texas beneficiaries ages 0- 17 enrolled in Medicaid for any length of time between 2004 and 2007. Claims submitted only to reflect capitated payments were not included in the CMS files.

Identification of study population

The PS files contained indicators which were used to determine which months each child was enrolled and eligible for the full scope of Medicaid benefits, until their 18th birthday. Even if enrolled, children were considered ineligible during any year they had private insurance coverage, as this could result in incomplete claims history. Children with only premium (i.e., capitated) payment claims during the year were also considered ineligible to eliminate follow-up time during which no medical or pharmacy claims would be found in the MAX files. Once eligible months were determined for each child, the 4 PS files were combined into a single enrollment file (Figure 1).

The beginning and ending months for each child's period(s) of enrollment were derived from the combined, 4-year enrollment file. Children were included in the study population if they had 1 or more continuous 13+ month span of enrollment between 2004 and 2007, allowing for a single 1-month enrollment gap during the 4-year period. This

continuous enrollment span provided a 'wash-out' period which enabled us to distinguish incident from prevalent cases.

Identification of asthma cases

We combined all medical and pharmacy claims for the 4-year period, and defined cases as children with a primary diagnosis of asthma (International Classification of Diseases, 9th revision code = 493.xx) on one or more outpatient or inpatient records, or 4 or more asthma medication (27) dispensing events (30-day supply) during a 365-day period. For a medication prescription with more than 30 days' supply, we divided days by 30 and rounded up to calculate the number of 30-day dispensing events. For each case, the earliest of either date of service for the first asthma medical claim or prescribed date of the first asthma prescription dispensed was kept as the date of diagnosis.

Analysis

Records from the enrollment and case files were joined, and cases without an enrollment record (i.e., did not have a 13+ month span of continuous enrollment between 2004 and 2007) were excluded. We also excluded cases who were in the enrollment file, but not enrolled continuously in the 12 month period prior to diagnosis, as we could not determine whether these were incident or prevalent cases. For the remaining study population, person-months were calculated beginning with the 13^{th} month of follow-up (the first month in which a subject could become an incident case). Follow-up ended on the earliest of (1) the last month of the enrollment span, (2) the month of asthma diagnosis, or (3) 12/31/2007. Hence, person-months of follow-up ranged from 1 to 36. PS and claims files from 2004 were not used in the analysis other than to provide a wash-out period for children in the 2005 files.

Asthma incidence rates (IRs) were calculated for Texas overall and by age group (1-4, 5-9, 10-14 and 15-17), gender, race (white, black, Hispanic, Asian, American Indian) and county (n=254) between 2005 and 2007. Rates (other than by age group) were age-adjusted based on the proportion in the age group in the 2000 U.S. Census (28), and reported as cases/100 person-years. Age and county of residence reflected values at first enrollment. IRs were calculated by dividing the number of incident cases in 2005-2007 by person-months of follow-up for the study population during the same period. County rates were statistically different from the Texas rate if the 95% confidence interval for the county rate did not include the statewide point estimate. IRs for counties with fewer than 16 asthma cases (n=36) were not calculated, due to unstable rates.

Analyses were performed using SAS version 9.2. A map of county-specific IRs was generated with ArcGIS version 10. The study was approved by the CMS Privacy Board and the University of Texas Health Science Center Committee for the Protection of Human Subjects.

Results

The 2004-2007 MAX enrollment files included 4,152,664 Texas children ages 0-17. After excluding children without a 13+ month continuous enrollment span between 2004 and 2007, the remaining sample included 2,164,463 children free of asthma at baseline, and 2,467,757 person-years of follow-up. The study population was evenly distributed between males and females, and over half were under the age of 5 (Table 1). Sixty-five percent were Hispanic, and approximately 16% each white and black.

We identified 129,588 incident asthma cases between 2005 and 2007 (Table 1). Most cases (75%) were identified from an outpatient record, and 91% of these also had at least one

subsequent asthma medication claim. Fewer than 1% were identified through inpatient records. The remaining 25% received their diagnosis on the date they filled the first of 4 prescriptions, and of these, over 40% had a subsequent outpatient record. Overall age-adjusted asthma incidence in this population was 4.26 cases/100 person-years (95% confidence interval (CI): 4.23, 4.30). Incidence was higher in males than females, and decreased with age. White and black children had the highest incidence, while rates were lowest among Asians. IRs for white and black males approached 5 cases per 100 person-years.

County-specific IRs were generally higher in southern border counties, and lower in larger metropolitan areas (Figure 2). Counties including Houston, Dallas, Fort Worth, Austin and El Paso had IRs significantly below the statewide rate, from 3.08 (95% CI: 2.90, 3.27) to 3.95/100 person-years (95% CI: 3.84, 4.06). Of the state's largest population centers, only Bexar County, which includes San Antonio, surpassed the state average (IR = 5.19/100 person-years, 95% CI: 5.06, 5.32). The thirty-six counties with fewer than 16 cases had total population sizes from 67 to 8,854, with between 2 and 474 children enrolled in Medicaid (24, 28).

Discussion

Forty percent of Texas children are enrolled in Medicaid, and the cost of asthma-related treatment for these children exceeded $242 million in 2004 (29). Based on our analysis, Medicaid-enrolled children in Texas were newly diagnosed with asthma at a rate of 4.26/100 person-years between 2005 and 2007. Our estimates are higher than previously reported in the U.S. (7) and Canada (8), but not unexpected among low-income children. IRs were higher for males and decreased with age, consistent with other reports (8, 9). As in the

Canadian study, we found that IRs were higher for males than females in the youngest age groups, but similar in children ages 15-17 (males = 2.8%, females = 3.0%). The median age at diagnosis was 4.9 years, consistent with clinical experience that most children with asthma will develop symptoms by age 5 (30).

Higher incidence among whites than blacks was unexpected, as most prevalence studies report the reverse. Some (31, 32) but not all (33, 34) have shown a lessened effect of race on childhood asthma prevalence after adjusting for socioeconomic status. Our results may reflect lower healthcare utilization among blacks, who generally have fewer primary care visits, and more emergency room visits and inpatient hospital stays than whites (5, 19, 35, 36). Although we identified few cases through inpatient claims, lower primary care visit rates could result in underestimated incidence among blacks.

The primary strengths of our study are the large sample size and 3-year timeframe which allowed estimation of stable rates by age group, gender, race/ethnicity and county. We applied methodology previously used in cancer research (37-45) to estimate rates of newly-occurring asthma, using a data source with both medical and pharmacy claims. Date of onset was determined directly from claims data, and not subject to recall bias. Requiring a 13+ month continuous enrollment period without evidence of asthma decreased the likelihood of classifying prevalent cases as incident cases, particularly for a disease with seasonal morbidity patterns (46).

Weaknesses of the study include the lack of a gold standard for measuring asthma incidence, making it difficult to validate this method. Our results are not generalizable to the general population in Texas, as they represent low-income children with health insurance benefits. IR estimates across states using this methodology and data source may not be

directly comparable due to differences in Medicaid eligibility, benefits and coverage. The Medicaid population is fluid, resulting in variable lengths of follow-up and potential selection bias. Nearly 11% of children were enrolled for only 13 months, while 15% were enrolled for the entire 3-year period.

The inclusion of beneficiaries from capitated managed care (HMO) plans and fee-for-service (FFS) plans may have introduced bias in our estimates. Although claims reporting for HMO plans improved over time, data completeness and quality likely differed between the two types of plans (47). Most children in Texas' nine major metropolitan areas are required to enroll in a capitated program, whereas a FFS program covers the rest of the state. It is unclear whether underreporting of HMO claims may have contributed to lower IRs in urban areas, or to what extent statewide rates were underestimated. Lower asthma prevalence in urban areas has been reported among other Medicaid populations, and may be partially attributable to higher smoking rates in rural areas (48). We should note that pharmacy claims in Texas are paid on a FFS basis. While using both medical and pharmacy records is CMS' preferred method for identifying asthma cases, relying on pharmacy records alone can also provide reliable estimates (16).

The Centers for Disease Control and Prevention has called for a greater emphasis on tracking incidence in U.S. asthma surveillance programs, while acknowledging the inherent challenges and limited data sources (49, 50). In this unique study, we estimated population-based asthma incidence using statewide Medicaid claims data, a rich source for studying diseases disproportionately impacting low-income children. Our results indicate that Medicaid-enrolled children are at greater risk of being given an asthma diagnosis than those in the general population. Knowledge of asthma incidence patterns is critical to

understanding associated risk factors, and we hope that this novel approach will be applied to other Medicaid populations to increase understanding of this disabling and costly disease.

References

1. Akinbami LJ, Moorman JE, Liu X. Asthma prevalence, health care use, and mortality: United States, 2005-2009. *Natl Health Stat Report*. 2011;12(32):1-14.

2. Selgrade MK, Lemanske RF Jr, Gilmour MI, et al. Induction of asthma and the environment: what we know and need to know. *Environ Health Perspect*. 2006;114(4):615-619.

3. Markus AR, Lyon M, Rosenbaum S. *Changing Policy: The Elements for Improving Childhood Asthma Outcomes*. Washington D.C.: The George Washington University School of Public Health and Health Services, Department of Health Policy, 2010.

4. Bai Y, Hillemeier MM, Lengerich EJ. Racial/ethnic disparities in symptom severity among children hospitalized with asthma. *J Health Care Poor Underserved*. 2007;18(1):54-61.

5. Ortega AN, Belanger KD, Paltiel AD, et al. Use of health services by insurance status among children with asthma. *Med Care*. 2001;39(10):1065-1074.

6. Lozano P, Sullivan SD, Smith DH, et al. The economic burden of asthma in US children: estimates from the National Medical Expenditure Survey. *J Allergy Clin Immunol*. 1999;104(5):957-963.

7. Rudd RA, Moorman JE. Asthma incidence: data from the National Health Interview Survey, 1980-1996. *J Asthma*. 2007;44(1):65-70.

8. Gershon AS, Guan J, Wang C, et al. Trends in asthma prevalence and incidence in Ontario, Canada, 1996-2005: A population study. *Am J Epidemiol*. 2010;172(6):728-736.

9. Simpson CR, Sheikh A. Trends in the epidemiology of asthma in England: a national study of 333,294 patients. *J R Soc Med*. 2010;103(3):98-106.

10. Gilliland FD, Berhane K, Islam T, et al. Obesity and the risk of newly diagnosed asthma in school-age children. *Am J Epidemiol*. 2003;158(5):406-415.

11. The Henry J. Kaiser Family Foundation. Medicaid: A Primer. Washington DC: The Henry J. Kaiser Family Foundation; 2010. (http://www.kff.org/medicaid/upload/7334-04.pdf). (Accessed January 12, 2012).

12. Centers for Medicare and Medicaid Services, US Department of Health and Human Services. Medicaid Information by Topic. Baltimore, MD: Centers for Medicare and Medicaid Services; 2012. (http://www.medicaid.gov/Medicaid-CHIP-Program-Information/By-Topics/By-Topic.html). (Accessed January 12, 2012).

13. Piecoro LT, Potoski M, Talbert JC, et al. Asthma prevalence, cost, and adherence with expert guidelines on the utilization of health care services and costs in a state Medicaid population. *Health Serv Res*. 2001;36(2):357-371.

14. Smith MJ, Rascati KL, Barner JC. A descriptive analysis of asthma-related medical services and prescription utilization among recipients in a Medicaid program. *J Asthma*. 2005;42(6):447-453.

15. Buescher PA, Jones-Vessey K. Using Medicaid data to estimate state- and county-level prevalence of asthma among low-income children. *Matern Child Health J*. 1999;3(4):211-216.

16. Dombkowski KJ, Wasilevich EA, Lyon-Callo SK. Pediatric asthma surveillance using Medicaid claims. *Public Health Rep*. 2005;120(5):515-524.

17. Pawar V, Smith MJ. Asthma-related healthcare services utilization by African-Americans enrolled in West Virginia Medicaid. *Respir Med*. 2006;100(9):1579-1587.

18. Roberts EM. Racial and ethnic disparities in childhood asthma diagnosis: the role of clinical findings. *J Natl Med Assoc*. 2002;94(4):215-223.

19. Shields AE, Comstock C, Weiss KB. Variations in asthma care by race/ethnicity among children enrolled in a state Medicaid program. *Pediatrics*. 2004;113(3 Pt 1):496-504.

20. Dombkowski KJ, Cabana MD, Cohn LM, et al. Geographic variation of asthma quality measures within and between health plans. *Am J Manag Care*. 2005;11(12):765-772.

21. Stevenson MD, Heaton PC, Moomaw CJ, et al. Inhaled corticosteroid use in asthmatic children receiving Ohio Medicaid: trend analysis, 1997-2001. *Ann Allergy Asthma Immunol*. 2008;100(6):538-544.

22. Wilson SE, Leonard A, Moomaw C, et al. Underuse of controller medications among children with persistent asthma in the Ohio Medicaid population: evolving differences with new medications. *Ambul Pediatr*. 2005;5(2):83-89.

23. Siwik JP, Johnson CC, Havstad SL, et al. Airway hyperresponsiveness to methacholine at age 6 to 8 years in nonasthmatic patients is not related to increased health-care utilization for asthma in the ensuing 5 years: a longitudinal study of a birth cohort. *Chest*. 2005;128(4):2420-2426.

24. Texas Health and Human Services Commission. Final Count – Medicaid Enrollment by Month. Austin, TX: Texas Health and Human Services Commission; 2011. (http://www.hhsc.state.tx.us/research/MedicaidEnrollment/ME-Monthly.asp). (Accessed October 6, 2010).

25. Centers for Medicare and Medicaid Services, US Department of Health and Human Services. Medicaid Analytic eXtract (MAX) General Information. Baltimore, MD: Centers for Medicare and Medicaid Services; 2011.

(https://www.cms.gov/MedicaidDataSourcesGenInfo/07_MAXGeneralInformation.asp). (Accessed October 19, 2011).

26. Hennessy S, Leonard CE, Palumbo CM, et al. Quality of Medicaid and Medicare data obtained through Centers for Medicare and Medicaid Services (CMS). *Med Care*. 2007;45(12):1216-1220.

27. National Committee for Quality Assurance HEDIS 2011 NDC Lists: Use of Appropriate Medications for People with Asthma (ASM). Washington, DC: National Committee for Quality Assurance; 2011. (http://www.ncqa.org/tabid/1274/Default.aspx). (Accessed January 27, 2011).

28. Bureau of the Census, US Department of Commerce. Census 2000 Summary File 3. Washington, DC: Bureau of the Census; 2011. (http://factfinder.census.gov/servlet/DatasetMainPageServlet?_ds_name=DEC_2000_SF3_U&_program=DEC&_lang=en). (Accessed June 17, 2011).

29. Agency for Healthcare Research and Quality. Asthma Care Quality Improvement: A Resource Guide for State Action. Rockville, MD: Agency for Healthcare Research and Quality; 2009. (http://www.ahrq.gov/qual/asthmacare/asthmatab1_4.htm). (Accessed October 6, 2010).

30. Kemp JP, Kemp JA. Management of asthma in children. *Am Fam Physician*. 2001;63(7):1341-1348.

31. Akinbami LJ, LaFleur BJ, Schoendorf KC. Racial and income disparities in childhood asthma in the United States. *Ambul Pediatr*. 2002;2(5):382-387.

32. Aligne CA, Auinger P, Byrd RS, et al. Risk factors for pediatric asthma. Contributions of poverty, race, and urban residence. *Am J Respir Crit Care Med*. 2000;162(3 Pt 1):873-877.

33. Forno E, Celedon JC. Asthma and ethnic minorities: socioeconomic status and beyond. *Curr Opin Allergy Clin Immunol*. 2009;9(2):154-160.

34. Moorman JE, Zahran H, Truman BI, et al. Current asthma prevalence - United States, 2006-2008. *MMWR Surveill Summ*. 2011;60(suppl):84-86.

35. Nash DR, Childs GE, Kelleher KJ. A cohort study of resource use by Medicaid children with asthma. *Pediatrics*. 1999;104(2 Pt 1):310-312.

36. Lozano P, Connell FA, Koepsell TD. Use of health services by African-American children with asthma on Medicaid. *JAMA*. 1995;274(6):469-473.

37. Gold HT, Do HT. Evaluation of three algorithms to identify incident breast cancer in Medicare claims data. *Health Serv Res*. 2007;42(5):2056-2069.

38. Nattinger AB, Laud PW, Bajorunaite R, et al. An algorithm for the use of Medicare claims data to identify women with incident breast cancer. *Health Serv Res*. 2004;39(6 Pt 1):1733-1749.

39. Koroukian SM, Cooper GS, Rimm AA. Ability of Medicaid claims data to identify incident cases of breast cancer in the Ohio Medicaid population. *Health Serv Res*. 2003;38(3):947-960.

40. Wang PS, Walker AM, Tsuang MT, et al. Finding incident breast cancer cases through US claims data and a state cancer registry. *Cancer Causes Control*. 2001;12(3):257-265.

41. Cooper GS, Yuan Z, Jethva RN, et al. Use of Medicare claims data to measure county-level variation in breast carcinoma incidence and mammography rates. *Cancer Detect Prev*. 2002;26(3):197-202.

42. Freeman JL, Zhang D, Freeman DH, et al. An approach to identifying incident breast cancer cases using Medicare claims data. *J Clin Epidemiol*. 2000;53(6):605-614.

43. Cooper GS, Yuan Z, Stange KC, et al. Use of Medicare claims data to measure county-level variations in the incidence of colorectal carcinoma. *Cancer*. 1998;83(4):673-678.

44. Cooper GS, Yuan Z, Jethva RN, et al. Determination of county-level prostate carcinoma incidence and detection rates with Medicare claims data. *Cancer*. 2001;92(1):102-109.

45. Ramsey SD, Scoggins JF, Blough DK, et al. Sensitivity of administrative claims to identify incident cases of lung cancer: a comparison of 3 health plans. *J Manag Care Pharm*. 2009;15(8):659-668.

46. Gergen PJ, Mitchell H, Lynn H. Understanding the seasonal pattern of childhood asthma: results from the National Cooperative Inner-City Asthma Study (NCICAS). *J Pediatr*. 2002;141(5):631-636.

47. Texas External Quality Review Organization. *Validating encounter data: Texas Medicaid managed care and Children's Health Insurance Program managed care organization medical record review, fiscal year 2006*. Gainesville, FL: Texas External Quality Review Organization, 2008.

48. Valet RS, Gebretsadik T, Carroll KN, et al. High asthma prevalence and increased morbidity among rural children in a Medicaid cohort. *Ann Allergy Asthma Immunol*. 2011;106(6):467-473.

49. Akinbami LJ, Moorman JE, Garbe PL, et al. Status of childhood asthma in the United States, 1980-2007. *Pediatrics*. 2009;123(suppl 3):S131-S145.

50. Redd SC. Asthma in the United States: burden and current theories. *Environ Health Perspect*. 2002;110(suppl 4):557-560.

Table 1. Age-adjusted incidence rates[a] of childhood asthma among Texas Medicaid-enrolled children ages 1-17, 2005-2007.

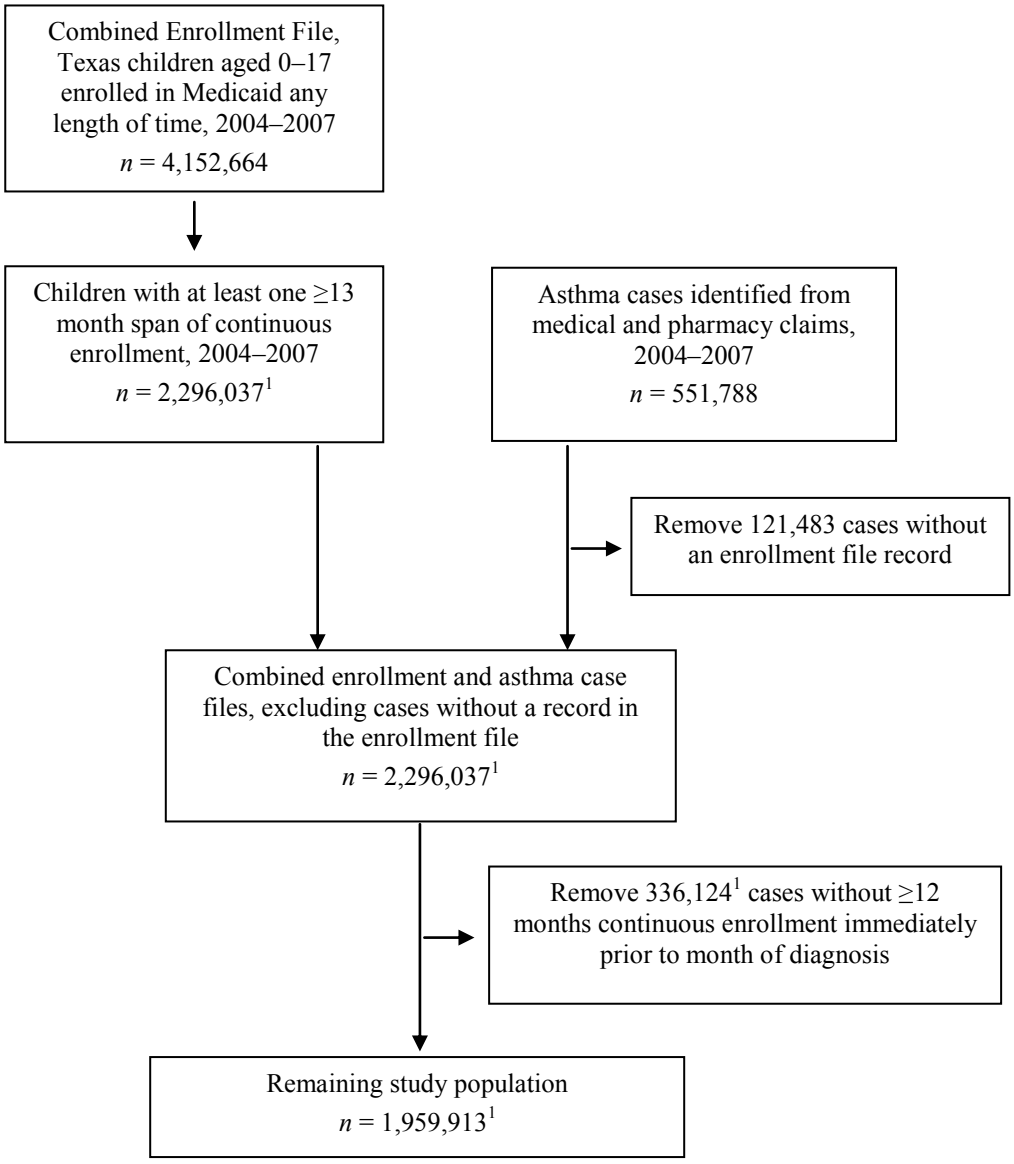
	Person-Years (%)	Asthma Cases (%)	Incidence Rate/100 Person-Years	95% CI
Total	2,467,757	129,588	4.26	4.23, 4.30
Age Group				
1-4 years	1,304,611 (52.9%)	85,390 (65.9%)	6.55	6.50, 6.59
5-9 years	603,279 (24.4%)	26,131 (20.2%)	4.33	4.28, 4.38
10-14 years	487,355 (19.7%)	15,949 (12.3%)	3.27	3.22, 3.32
15-17 years	72,512 (2.9%)	2,118 (1.6%)	2.92	2.80, 3.05
Gender				
Female	1,235,010 (50%)	58,722 (45.3%)	3.95	3.90, 3.99
Male	1,232,706 (50%)	70,864 (54.7%)	4.57	4.52, 4.62
Unknown	40 (<0.1%)	2 (<0.1%)		
Race				
White	406,837 (16.5%)	23,079 (17.8%)	4.78	4.69, 4.86
Black	390,526 (15.8%)	20,617 (15.9%)	4.45	4.37, 4.52
American Indian	7,465 (0.3%)	409 (0.3%)	3.84	3.33, 4.36
Asian	29,990 (1.2%)	1,407 (1.1%)	3.54	3.29, 3.79
Hispanic	1,608,753 (65.2%)	82,612 (63.7%)	4.18	4.14, 4.22
Unknown	24,187 (1.0%)	1,464 (1.1%)		
Race/Gender				
White/Male	203,965 (8.3%)	12,489 (9.7%)	4.92	4.80, 5.03
Black/Male	193,951 (7.9%)	11,479 (9.0%)	4.89	4.78, 5.01
American Indian/Male	3,866 (0.2%)	251 (0.2%)	4.27	3.63, 4.91

Asian/Male	14,741 (0.6%)	794 (0.6%)	3.82	3.47, 4.17
Hispanic/Male	807,900 (32.9%)	44,915 (35.1%)	4.52	4.46, 4.57
White/Female	202,865 (8.3%)	10,590 (8.3%)	4.62	4.50, 4.74
Black/Female	196,573 (8.0%)	9,137 (7.1%)	4.00	3.90, 4.10
American Indian/Female	3,598 (0.1%)	158 (0.1%)	3.42	2.58, 4.26
Asian/Female	14,882 (0.6%)	613 (0.5%)	3.25	2.90, 3.61
Hispanic/Female	814,428 (33.2%)	37,697 (29.4%)	3.84	3.79, 3.89

Abbreviation: CI, confidence interval.

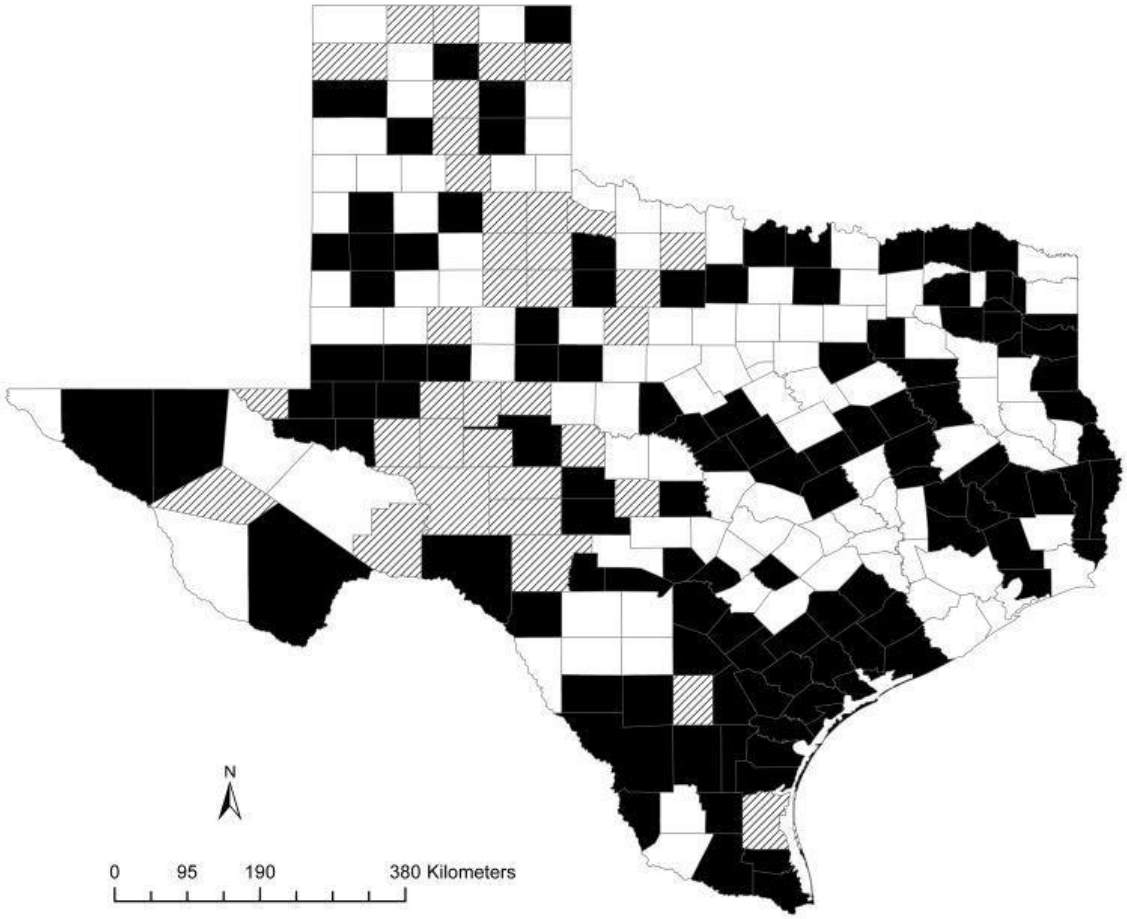
[a]Per 100 person-years. Age-adjusted to the proportion of the 2000 U.S. Census population in each age category, with the exception of rates presented by age group.

Figure 1. Description of process used to identify study population and cases from the original MAX files containing enrollment and claims records for Texas Medicaid-enrolled children aged 0-17, 2004-2007



[1]The numbers of children with at least 1 ≥13 month enrollment span, in the combined enrollment and case file and in the remaining study population represent the number of ≥13 month enrollment spans; a child could have more than 1 enrollment span during the 4–year study period.

Figure 2. County-specific asthma incidence[1] per 100 person-years among Medicaid-enrolled children in Texas, ages 1-17, 2005-2007.



[1]Counties shaded in black are those with incidence above the statewide incidence rate while those shaded in white were below the state rate. Counties with hash marks had fewer than 16 cases and therefore incidence rates were not calculated.

CHAPTER IV: ASSOCIATION OF AMBIENT AIR POLLUTION WITH NEWLY-DIAGNOSED ASTHMA AMONG MEDICAID-ENROLLED CHILDREN IN A METROPOLITAN AREA

Abstract

In this study, we investigated possible associations between ambient ozone, $PM_{2.5}$ and NO_2 concentrations and incident asthma, using a large population at high risk for the disease, and living in an area with historically high ozone levels. The study population included 18,289 incident asthma cases identified among Medicaid-enrolled children in Harris County Texas between 2005-2007, through the use of Medicaid Analytic Extract (MAX) enrollment and claims files. We used a time-stratified case-crossover design and conditional logistic regression to calculate odds ratios, adjusted for weather variables and aeroallergens, assessing the effect of increases in ozone, NO_2 and $PM_{2.5}$ concentrations on the risk of incident asthma. Our results show that 10 ppb increases in ozone were significantly associated with asthma during the warm season (May-October), and that the strongest effect was seen when a 6-day cumulative lag period was used to compute the exposure metric (OR=1.05, 95% CI, 1.02–1.08). Similar results were seen for NO_2 and $PM_{2.5}$ (OR=1.07, 95% CI, 1.03–1.11 and OR=1.12, 95% CI, 1.03–1.22, respectively). $PM_{2.5}$ also had significant effects in the cold season (November-April), 5-day cumulative lag: OR=1.11, 95% CI, 1.00–1.22. When compared with children in the lowest quartile of O_3 exposure, the risk for children in the highest quartile was 20% higher. This is the first study to evaluate the association of incident childhood asthma and ambient air pollution in the Houston metropolitan area, and our results indicate that increased levels of these pollutants are

associated with the onset of asthma in this low-income urban population, particularly during the summer months.

Introduction

Many studies have investigated factors leading to the exacerbation of symptoms among asthmatic children, but less is known about factors leading to its development. Genetic factors are known to play a role (Yeatts et al. 2006), and there is evidence that indoor and possibly outdoor pollutants may also be related to asthma incidence (Gilliland 2009; Gilmour et al. 2006). Asthma prevalence is higher in male children than in females, and in black children compared to whites or Hispanics, although it is not clear if this is due to socioeconomic or other factors rather than race/ethnicity (Akinbami et al. 2005). Poverty is consistently associated with higher childhood asthma prevalence (Akinbami et al. 2002), and even among insured children, low-income children covered by Medicaid are more likely to have asthma-related morbidity, complications and hospitalizations than children with private insurance (Bai et al. 2007; Lozano et al. 1999; Ortega et al. 2001). A recent study among Medicaid-enrolled children in Texas provided evidence that asthma incidence rates are also higher in this low-income population compared to previous population estimates (Wendt et al. 2012).

Elevated levels of ambient ozone (O_3) have been associated in several studies with worsening lung function and asthma symptoms in children (Akinbami et al. 2010; Lewis et al. 2005; Lin et al. 2008; Mortimer et al. 2000), and similar results have been seen in studies of childhood asthma and fine particulate matter ($PM_{2.5}$) or nitrogen dioxide (NO_2) (Akinbami et al. 2010; Parker et al. 2009; Slaughter et al. 2003). Fewer studies have evaluated an

association between ambient pollutants and the risk of developing asthma (Gilmour et al. 2006). Asthma incidence studies that have appeared in the literature have been based on a small number of cohorts, including the Children's Health Study (CHS) in Southern California, the Prevention and Incidence of Asthma and Mite Allergy Study (PIAMA) in the Netherlands (Brauer et al. 2007), and other datasets in Europe (Morgenstern et al. 2007), Canada (Carlsten et al. 2011) and France (Zmirou et al. 2004). These studies have shown positive effects of traffic-related pollutants (TRP) (Brauer et al. 2007; McConnell et al. 2010), NO_2 (Jerrett et al. 2008; McConnell et al. 2010), $PM_{2.5}$ (Carlsten et al. 2011) and O_3 (McConnell et al. 2002). The O_3 findings are primarily from the CHS, and have provided evidence that an O_3 association with new-onset asthma is mediated by the level of personal exposure and genetic susceptibility (Li et al. 2006; McConnell et al. 2002; Romieu et al. 2006).

The Houston metropolitan area is the nation's sixth largest (U.S. Census Bureau 2012), and in 2004, was designated a non-attainment area for the eight-hour O_3 standard which went into effect in 1997 (Texas Commission on Environmental Quality 2010). Since October 2008, the greater Houston area has been designated a severe non-attainment area, with an attainment date of June 2019 (Texas Commission on Environmental Quality 2010). More than 140,000,000 person-miles are driven on Houston roads on an average day (Sexton et al. 2007) and the city is characterized by an extensive industrial area. Automotive and industrial emissions (e.g., nitrogen oxides and volatile organic compounds), combined with a warm, sunny climate, produce ozone and present unique challenges in terms of air quality (Sexton et al. 2007; Texas Commission on Environmental Quality 2009).

In this study, we used a time-stratified case-crossover design (Janes et al. 2005) to investigate possible associations of ambient O_3, NO_2 and $PM_{2.5}$ levels with incident childhood asthma. Our study population comprises Medicaid-enrolled children residing in Harris County, Texas between 2005 and 2007, a large population at high risk for asthma, and living in an area with historically high ozone levels.

Methods

Identification of Incident Asthma Cases

Our description of the methods used to identify incident asthma cases from the Centers for Medicare and Medicaid Services (CMS) Medicaid Analytic Extract (MAX) files among Medicaid-enrolled children in Texas has been described elsewhere (Wendt et al. 2012). We restricted these analyses to children residing at the time of enrollment in Harris County, Texas between 2005 and 2007. Briefly, MAX files are created by CMS specifically for research, and contain annual data on Medicaid eligibility and healthcare utilization as reported by the states. The eligibility files contain person-level data including age, gender, race, zip code of residence, dates of enrollment and scope of Medicaid coverage. Due to privacy concerns, street address is not provided in the MAX files. The claims files contain final adjudicated claims by date of service and have undergone quality checks and corrections (Hennessy et al. 2007). We obtained enrollment, inpatient and outpatient medical claims, and pharmacy claims files from CMS for Texas beneficiaries under the age of 18 who were enrolled in Medicaid between 2004 and 2007.

Monthly enrollment and eligibility indictors in the PS files were used to identify children enrolled for at least 13 continuous months (with allowance for a single 1-month gap) during the 4-year period. Children were considered ineligible during any year in which the

respective PS file indicated that they had private insurance coverage, or only premium (i.e., capitated) payment claims during the year. The requirement of a 13+ continuous enrollment span was necessary in order to provide a 'wash-out' period to distinguish incident from prevalent asthma cases.

All medical and pharmacy claims for the 4-year period were combined, and asthma cases were defined as children with a primary diagnosis of asthma (International Classification of Diseases, 9th revision code = 493.xx) on at least one outpatient or inpatient record, or 4 or more asthma medication (National Committee for Quality Assurance 2011) dispensing events (30-day supply) during a 365-day period. If a prescription was written with more than 30 days' supply, days were divided by 30 and rounded up to calculate the number of 30-day dispensing events. For each case, the diagnosis or 'event' date was either the date of service associated with the child's earliest asthma medical claim, or the date the first of 4+ asthma medication prescriptions was written.

We then joined records from the enrollment and asthma case files, and excluded cases without an enrollment record (i.e., those who did not have a 13+ month span of continuous enrollment between 2004 and 2007). Any cases who were in the enrollment file but not enrolled continuously during the 12 months prior to diagnosis were also excluded, as we could not determine whether these were incident or prevalent cases. Enrollment and claims files from 2004 were only used in the analysis to provide a wash-out period for children in the 2005 files. Using these methods, we identified 18,289 incident asthma cases among Medicaid-enrolled children aged 1-17 residing in Harris County during the period 2005-2007, with an age-adjusted incidence rate of 3.12/100 person-years.

Ambient Air Pollutant Data

Air monitoring data for O_3 (daily maximum 8-hour moving average), NO_2 (daily 1-hour maximum) and $PM_{2.5}$ (daily 24-hour mean) were obtained from the U.S. EPA Air Quality System (AQS) (U.S. Environmental Protection Agency 2010). O_3 data were available from 22 monitoring stations located in the Houston-Galveston-Brazoria (HGB) metropolitan area. The monitors are concentrated in Harris County (n = 17), with two monitors in Galveston County, two in Brazoria County, and one in Montgomery County. O_3 is monitored continuously 24-hours a day, 365 days per year. The O_3 data are available as 1-hour averages. NO_2 is also monitored continuously 24-hours a day, 365 days per year at 17 monitoring sites across the HGB metropolitan area: 12 in Harris County, two in Brazoria County, two in Galveston County and one in Montgomery County. The NO_2 data are available as 1-hour averages. For $PM_{2.5}$, there were seven monitoring sites in Harris County and two sites in neighboring counties which performed 24-hour measurements of $PM_{2.5}$ (local conditions) between 2005 and 2007. Beginning in September 2005, measurements were discontinued at the two sites in adjacent counties, and the number of monitoring sites in Harris County measuring this parameter decreased from seven to four. Also, two of the four monitors were co-located at a single site, of which one took daily samples, and a second took samples every six days, and for this site, we included only the 24-hour mean values in AQS for the monitor with daily sampling in our analysis. Daily 24-hour mean $PM_{2.5}$ measurements were available for the other area monitors every sixth day.

Meteorological and Aeroallergen Data

Daily maximum outdoor temperature and daily average percent relative humidity were measured at 24 and 6 monitoring sites, respectively, across Harris County and these

data were also obtained from the AQS. Mold spore and tree, grass and weed pollen counts were available for the Houston area from the City of Houston archives (City of Houston 2010), and measured as counts per cubic meter of air. These measurements were generally available for each weekday during the study period, except holidays or days that measurements could not be taken because of rain.

Study Design and Statistical Analysis

We used a time-stratified, case-crossover design (Janes et al. 2005) to evaluate the association of ambient pollutant levels and the development of childhood asthma. Forty 28-day strata were specified beginning with January 1, 2005, and each asthma case-day was matched with the three referent dates in the pre-defined strata which were the same day of the week as the case-day. For example, a case occurring on Tuesday, January 11, 2005 was matched to control dates on the remaining Tuesdays in the stratum (i.e., January 4, 18 and 25). Since the last of the 40 strata ended on December 28, 2007, cases occurring on the final three days of the study period were excluded from the analysis ($n = 25$). The case-crossover design has been frequently used to investigate short-term acute effects of air pollution as it allows for control of person-level (i.e., genetic and lifestyle) and time-dependent (i.e., air monitoring levels by day of the week, season of the year) factors (Carracedo-Martinez et al. 2010).

We first considered only temporal changes in O_3 exposure, by averaging all maximum 8-hour samples from monitoring sites across Harris County for each calendar day. In this way, daily means of the maximum 8-hour O_3 concentrations were estimated; therefore for each calendar day, these were the same regardless of where in Harris County the child

resided. A similar method was used to calculate daily $PM_{2.5}$ and NO_2 values for Harris County, that is, 24-hour mean $PM_{2.5}$ and daily 1-hour maximum NO_2 measurements were averaged across all monitoring sites in Harris County for each calendar day.

Secondly, we considered spatial, in addition to temporal variability in O_3 and NO_2 exposure. Daily pollutant levels were estimated using the average of measurements taken at the three closest O_3 and NO_2 monitoring sites, respectively, to the centroid of the zip code of residence for each case. Monitored pollutant values were potentially drawn from all sites in the HGB area, as the nearest three monitors to a particular zip code may have been located outside of Harris County. $PM_{2.5}$ values were averaged across Harris County in all analyses because of the small number of monitoring sites.

Because cases who reside a greater distance away from a monitoring station may have less accurate exposure estimates than those residing in zip codes with nearby monitors, we performed a sensitivity analysis restricted to asthma cases living in zip codes where the centroid was within 6 miles of at least one O_3 or NO_2 monitoring station. In this third analysis we estimated O_3 exposure levels by averaging daily maximum 8-hour values across all O_3 monitoring sites within the 6-mile radius of the child's zip code. Likewise, we estimated NO_2 exposure by averaging daily 1-hour maximum values across all NO_2 monitoring sites within the 6-mile radius of the child's zip code. Analysis on this sub-set of cases allowed us to evaluate whether estimated odds ratios resulting from the temporal and spatial exposure estimation methods were robust, irrespective of whether the case lived near a monitoring station.

For all three analyses, a series of lagged and average cumulative pollutant exposure variables were constructed for each case and control date. Since there is no consensus on the most pertinent exposure metric for these pollutants with respect to asthma, lag and averaging periods were explored with consideration of both their irritant nature, and the potential number of symptomatic days that might pass before a physician's visit is scheduled. For each case/control date, we determined same-day pollutant values, values lagged 1 through 5 days, and cumulative values averaged over 2 day (i.e., same day and lag 1) through 6 day (i.e., same day through lag 5) periods.

Conditional logistic regression was used to estimate odds ratios for each lag period and pollutant, per an increase in the pollutant level equal to the inter-quartile range (IQR), or an increase of 10 ppb for O_3 and NO_2, and 10 $\mu g/m^3$ for $PM_{2.5}$. We also calculated odds ratios comparing the highest quartile of exposure with the lowest quartile for each pollutant, with quartiles defined based on the distribution of the pollutant on control days. Single and co-pollutant models were evaluated, and in co-pollutant models, the same lag or cumulative lag metric was used for both pollutants. All models included same-day maximum temperature and mean percent relative humidity, averaged across all Harris County monitoring sites. Same-day mold spore, tree pollen, grass pollen and weed pollen counts were also included in all models, and although lagged aeroallergen values may have greater biological relevance, the lack of weekend data meant that case and control dates occurring on Mondays (21% of the total) would have been excluded from the analysis due to missing covariate values. In contrast, fewer case/control dates occurred on Saturdays and Sundays, 6% and <2%, respectively. We also performed stratified analysis by age group (1-4, 5-9, 10-14, 15-17), gender, race (white, black, Hispanic), pollutant quartiles and season. Season was

dichotomized into either 'warm' (i.e., May-October) or 'cold' (i.e., November-April), and was intended to distinguish between periods of higher and lower seasonal O_3 levels. Non-parametric Spearman rank-correlation coefficients were used to assess the degree of correlation between all pollutant, meteorological and aeroallergen variables included in the logistic regression models as this test does not require an assumption that the variables are normally distributed. Results presented reflect pollutant exposures averaged across Harris County unless otherwise stated.

We used SAS version 9.2 for all analyses. Conditional logistic regression was performed using PROC LOGISTIC, matching on case number. ArcGIS version 10 was used to identify the monitoring sites nearest each zip code, and the distance between each site and zip code centroid. The study was approved by the CMS Privacy Board and the University of Texas Health Science Center at Houston Committee for the Protection of Human Subjects.

Results

A description of the 18,264 incident asthma cases identified between 1/1/2005 and 12/28/2007 is shown in Table 1. Nearly three-fourths of this population was under the age of 5 and 61% were Hispanic. A greater proportion of cases (56.0%) were male.

Descriptive measures of pollutants and meteorological variables are presented in Table 2 and Table 3. Mean O_3, NO_2 and $PM_{2.5}$ levels for the 3-year period across all monitoring sites in Harris County were 37.87 ppb, 39.26 ppb and 14.97 $\mu g/m^3$, respectively. O_3 and $PM_{2.5}$ levels were 31% and 22% higher in the warm season, respectively, while NO_2 levels were 12% higher in the cold season than in warmer months. Aeroallergen levels

differed by season, with higher tree pollen counts in the cold season (peak in March) and higher weed pollen counts in the warm season (peak in October).

O_3 had a moderately strong correlation with NO_2 (Spearman rank correlation coefficient, r=0.49) and a weaker correlation with $PM_{2.5}$ (r=0.32), while NO_2 and $PM_{2.5}$ were more weakly correlated (r=0.21) (Table 4). Daily maximum temperature was positively correlated with O_3 (r=0.33) and $PM_{2.5}$ (r=0.36) but negatively correlated with NO_2 (r=-0.23). Daily percent relative humidity was negatively correlated with both O_3 (r=-0.49) and NO_2 (r=-0.39). There was a weak correlation between grass pollen and O_3 (r=0.23), and a moderately strong correlation between mold spore and weed pollen counts (r=0.50).

O_3, NO_2 and $PM_{2.5}$ all showed significant associations with risk of asthma, although odds ratios and statistical significance differed by lag and cumulative lag period, and by season (Figure 1). During the warm season, each 10 ppb increase in O_3 raised the odds of an initial asthma diagnosis by between 3.3% and 5.2%, depending on the exposure metric. Likewise, a 10 ppb increase in NO_2 was associated with significant increases ranging from 2.7% to 7.0%. No effect was seen during the cold season for either O_3 or NO_2. In contrast, significant effects of $PM_{2.5}$ were seen in both the warm and cold seasons. For each 10 $\mu g/m^3$ increase, the risk of asthma increased between 5.8% and 12.5% during the warm season, and between 7.6% and 11.3% during the cold season. For all pollutants, the most pertinent metrics were the longer cumulative lag periods (i.e., L04, L05 and L06).

Odds ratios for each pollutant by quartile of exposure are shown in Table 5. For children in the highest quartile of O_3 exposure compared to the lowest, the risk of incident asthma was 20% higher (OR=1.20, 95% CI, 1.06–1.36). Risk of asthma was also higher in the highest quartiles of exposure for $PM_{2.5}$ and NO_2 when compared to the lowest quartiles

(OR=1.10, 95% CI, 1.02–1.18 and OR=1.19, 95% CI=1.10–1.29, respectively). Statistically significant increases were also seen when comparing children in the second quartiles to those in the lowest quartiles of O_3 and NO_2 exposure (OR=1.11, 95% CI, 1.03–1.19 and OR=1.11, 95% CI, 1.03–1.21, respectively).

Single and co-pollutant model results are presented in Table 6, with odds ratios reflecting increases in risk per IQR increase in 6-day cumulative mean pollutant levels by season. In single pollutant models, significant odds ratios were seen for O_3 and NO_2 only during the warm season (OR=1.16, 95% CI, 1.07–1.25 and OR=1.14, 95% CI, 1.06–1.24) whereas significant increases were seen in both seasons for $PM_{2.5}$ (warm: OR=1.10, 95% CI, 1.03–1.17 and cold: OR=1.06, 95% CI, 1.00–1.14). Odds ratios for O_3 were unchanged by season in co-pollutant models with $PM_{2.5}$, but in models with NO_2, ORs for both pollutants decreased and although still above the null, were no longer statistically significant. In co-pollutant models with O_3 and with NO_2, the effect of $PM_{2.5}$ during the warm season was diminished, and no longer statistically significant, but effect estimates during the cold season were unchanged.

Odds ratios of asthma in association with ambient O_3 were further stratified by season and demographics (Table 7). The OR of asthma in association with ambient O_3 was considerably higher in the oldest age group of children (15-17), with increases of 22% overall and 35% in the summer months for each 10 ppb increase in ambient levels of O_3. For the other age groups, risk generally lessened with decreasing age. The association between ambient O_3 and asthma was similar between males and females, but appeared to differ when stratified by race, with the highest ORs seen in blacks (OR=1.08, 95% CI, 1.03-1.13) and the

lowest in whites (OR=1.01, 95% CI, 0.93-1.10). Black children had a significant 9% increase in odds of incident asthma with each 10 ppb increase in O_3 during the summer months, and a significant 4% increase was seen in Hispanic children during the warm season.

We also assessed the additional impact of spatial variability in ambient pollutant levels on risk of asthma, by estimating daily exposure based on O_3 and NO_2 samples taken at the three monitors which were nearest the centroid of each zip code. On average, the 3 closest O_3 monitors were 12.8 miles from the zip code centroid (median=8.9 miles, range: 0.3 to 56 miles) and the 3 closest NO_2 monitors were 13.7 miles from the zip code centroid (median=10.3 miles, range=0.4 to 56.1 miles). Odds ratios for the two pollutants were very similar between the two methods (Figure 2, comparison of methods [a] and [b]). In further sensitivity analysis to assess the reliability of O_3 and NO_2 exposure estimates based on Harris County averages, we restricted our case group to children who lived within 6 miles of a monitor at the time of diagnosis. We observed only slight differences in the ORs for O_3 and NO_2, using this method compared to those using the county averages (Figure 2, comparison of methods [a] and [c]). Mean O_3 concentrations from the three estimation methods (i.e., county average, average of three closest monitors, average of monitors within 6 miles) were very similar (37.87, 36.52, 37.82 ppb, respectively), while mean NO_2 measurements were more variable (39.26, 36.40, 27.65 ppb, respectively, data not shown).

Discussion

Although general research on air pollution and asthma prevalence and morbidity is substantial, studies investigating a possible role of ambient pollutant levels in the development of asthma have only recently begun to build. One of the earliest analyses from

the CHS reported a significant increase (relative risk (RR)=3.3, 95% CI, 1.9-5.8) in new-onset asthma among Southern California-area children living in higher O_3 communities who participated in three or more team sports (McConnell et al. 2002). No association was found among children without this level of sports participation, indicating that the inhaled dose of O_3 is a factor in susceptibility. There was also no overall association between ambient O_3 or NO_2 levels and new-onset asthma between low- and high- O_3 communities (mean daytime O_3 concentration=40.0 and 59.6 ppb, respectively).

Later studies of this CHS cohort were done in the context of TRP exposure, and have included estimates of asthma risk associated with O_3, NO_2, and $PM_{2.5}$ (Jerrett et al. 2008; McConnell et al. 2010). Ambient NO_2 levels were associated with new-onset asthma (hazard ratio (HR)=2.17, 95% CI, 1.18–4.00) across a 23.6 ppb range of exposure, in an area with average NO_2 measurements equal to 20.4 ppb (McConnell et al. 2010). No significant effects of O_3 or $PM_{2.5}$ were seen in univariate models. The effect of NO_2 was lessened in models adjusted for TRP, indicating that NO_2 may have served as a marker for TRP levels. A similar conclusion was reached in an earlier study of this cohort in which risk of new-onset asthma increased with NO_2 concentrations measured through the use of personal monitors (Jerrett et al. 2008). Analyses of the CHS and other cohorts investigating a genetic effect on susceptibility to air pollutants have found differences in onset of asthma and wheeze, and asthma exacerbation with variability in genotype expression (Islam et al. 2008; Li et al. 2006; Romieu et al. 2006).

Another study in Canada reported an increased risk of incident asthma by age 7 among high risk children (defined based on family history of asthma or allergic disease) who

had experienced higher ambient NO_2 and $PM_{2.5}$ levels during year of birth (Carlsten et al. 2011). The risk of developing physician-diagnosed asthma increased three-fold for every 4.1 $\mu g/m^3$ increase in $PM_{2.5}$ (OR=3.1, 95% CI, 1.3–7.4) in a community with a median $PM_{2.5}$ ambient concentration of 5.11 $\mu g/m^3$. A similar, though non-significant odds ratio of 1.5 (95% CI, 0.9–2.5) was seen per every 7.2 $\mu g/m^3$ increase in NO_2, with median community-level exposure of 32.2 $\mu g/m^3$. A Dutch study found positive associations of new-onset asthma with air pollutants including NO_2 and $PM_{2.5}$, although results were sensitive to model selection (Brauer et al. 2007).

To our knowledge, this is the first study evaluating the association of incident childhood asthma and ambient air pollution in the Houston area. The burden of asthma is higher among Medicaid-enrolled children, and while our results may not be generalizable to children with higher family incomes, they may represent risk for a susceptible sub-population in an area with historically poor air quality. We found small but significant increases in incident asthma among Medicaid-enrolled children with increasing ambient pollutant levels. Low-income children consistently fare worse on asthma measures including prevalence, morbidity, hospitalizations and mortality, than children from higher income families (Akinbami et al. 2002; Burra et al. 2009). In addition to a higher disease burden, low-income children also appear to be more vulnerable to the effects of air pollution, although it is not clear to what extent this is attributable to greater susceptibility, higher exposure levels or other factors. Genetic variation, underlying health status and access to healthcare all impact personal susceptibility, and closer residential proximity to stationary and mobile pollution sources could lead to higher personal exposure (Cakmak et al. 2006; Gilliland 2009; Lipfert 2004). The degree of correlation between ambient pollutant levels and actual personal

exposure is clearly a function of many environmental and personal variables such as amount of time and time of day spent outdoors, activity patterns and outdoor air ventilation rates in the home (Lee et al. 2004).

The strength of association between incident asthma and ambient O_3 levels differed by age group and race. Older children (15 to 17 year-olds) seemed more sensitive to the effects of O_3 than children in younger age groups, particularly during the warm season. The higher effect estimates in teens could be due to comparatively higher personal exposure to pollutants from a combination of more time spent outdoors working or playing sports, and higher ventilation rates (Silverman and Ito 2010; Spier et al. 1992). This finding seems to be supported by a recent study in New York City-area children that reported higher asthma hospitalization rates in children aged 6-18 compared to younger children, with relative risks peaking around ages 15-16 (Silverman and Ito 2010). Similarly, effect estimates of O_3 on incident asthma differed by race, with statistically significant ORs in blacks, and to a lesser extent among Hispanics, but not in whites. Some have reported an independent effect of black race on asthma prevalence and morbidity when controlling for income (Miller 2000) while others have not (Gwynn and Thurston 2001). Our finding may be due to chance, or could reflect differential susceptibility to the effects of air pollution by race, even within this population of low-income children (Islam et al. 2008).

In our earlier estimation of asthma incidence rates by county, we found that in almost all cases, rates were lower in the major urban areas than in Texas as a whole (Wendt et al. 2012). This may argue against an effect of air pollutants on the development of asthma, which are typically higher in metropolitan areas and considered to be a factor in higher

asthma prevalence among inner-city children (American Lung Association 2001). Others have demonstrated higher asthma prevalence in Medicaid-enrolled children residing in rural areas, and attributed this to higher smoking rates or levels of aeroallergens (Valet 2011). While the effect of smoking was controlled for in our study design, we were not able to assess the possible interaction of smoking and the effect of air pollutants.

There was the potential for misclassification of asthma cases due to inaccurate diagnostic coding on the medical claims records. For example, a case may have been identified based on a claim from a physician's visit which actually ruled out asthma. And although most cases of asthma are diagnosed by the age of 5 (Kemp and Kemp 2001), distinguishing asthma from other respiratory illness such as bronchitis is particularly difficult in young children (Brauer et al. 2007). Claims records also reflect healthcare utilization patterns, and to the extent that these differ by age, race or income level (Lozano et al. 1995; Shields et al. 2004), this may have introduced selection bias in our study.

There was also potential for bias in our pollutant exposure estimates. Most analyses used O_3 and NO_2 data averaged across Harris County. This use of county-wide ambient pollutant concentrations as an estimate of personal exposure may have introduced ecological bias. O_3 and NO_2 risk estimates were similar when using the county average or an average of the three closest monitors. Exposure estimates which used results only from monitors within six miles led to slightly lower O_3 ORs and slightly higher NO_2 ORs at the longer cumulative lags periods which were the focus of this report. O_3 concentrations are typically more homogenous across a geographic area than NO_2 levels (Darrow et al. 2011), and this pattern was seen in our study as well. We relied on the zip code of residence to identify nearby

monitors, and given the lack of a complete street address, more refined spatial interpolation methods such as inverse distance weighting or a population-weighted average may have had limited benefit. A variety of methods have been used to estimate pollutant concentrations in previous asthma studies including averaging across monitors (Mortimer et al. 2000; Slaughter et al. 2003), population-weighted averaging across monitors (Strickland et al. 2010), maximum concentration across monitors (Babin et al. 2008; Luginaah et al. 2005; Schildcrout et al. 2006), measurements from a single centrally-located monitor (McConnell et al. 2010), and inverse distance weighting (Moore et al. 2008). A recent study from Atlanta demonstrated high correlations between estimated O_3, $PM_{2.5}$ and NO_2 concentrations when comparing unweighted averages across monitors and population-weighted estimates (r=0.988, 0.995 and 0.919, respectively) (Strickland et al. 2011).

Other potential weaknesses should be noted. The City of Houston included counts of additional mold spore and pollen types beginning in the fall of 2006, and while seasonal patterns for the aeroallergens were generally consistent from year to year, the absolute counts were much higher in 2007. It is not clear to what extent this reflected a particularly high allergen period versus changes due to sampling methodology, and although this may have introduced error in our effect estimates, the bias in the estimates was likely non-differential. We also made a large number of comparisons by pollutant, exposure metric, and stratification variables, and therefore would expect some statistically significant associations by chance alone. We did not attempt to correct for errors that may have arisen due to multiple comparisons.

Conclusion

This is the first study evaluating the association of incident childhood asthma and ambient air pollution in the Houston metropolitan area. We found small but significant increases in incident asthma with increasing ambient O_3, NO_2 and $PM_{2.5}$ concentrations among Medicaid-enrolled children. Children with the highest levels of O_3, NO_2 and $PM_{2.5}$ exposure had significantly higher risk of incident asthma than those with the lowest exposure levels. When stratified by season, effects of O_3 and NO_2 were limited to warm months, but associations with $PM_{2.5}$ were seen in both warm and cold seasons. For all pollutants, exposure metrics based on longer cumulative lag periods (i.e., 4-, 5- and 6-day averages) had the strongest effect. This study provides evidence of an association between urban ambient air pollutant levels and incident asthma among low-income children.

References

Akinbami LJ, LaFleur BJ, Schoendorf KC. 2002. Racial and income disparities in childhood asthma in the United States. Ambul Pediatr 2(5):382-387.

Akinbami LJ, Rhodes JC, Lara M. 2005. Racial and ethnic differences in asthma diagnosis among children who wheeze. Pediatrics 115(5):1254-1260.

Akinbami LJ, Lynch CD, Parker JD, Woodruff TJ. 2010. The association between childhood asthma prevalence and monitored air pollutants in metropolitan areas, United States, 2001-2004. Environ Res 110(3):294-301.

American Lung Association. 2001. Urban air pollution and health inequities: A workshop report. Environ Health Perspect 109(Suppl 3):357-374.

Babin S, Burkom H, Holtry R, Tabernero N, Davies-Cole J, Stokes L et al. 2008. Medicaid patient asthma-related acute care visits and their associations with ozone and particulates in Washington, DC, from 1994-2005. Int J Environ Health Res 18(3):209-221.

Bai Y, Hillemeier MM, Lengerich EJ. 2007. Racial/ethnic disparities in symptom severity among children hospitalized with asthma. J Health Care Poor Underserved 18(1):54-61.

Brauer M, Hoek G, Smit HA, de Jongste JC, Gerritsen J, Postma DS et al. 2007. Air pollution and development of asthma, allergy and infections in a birth cohort. Eur Respir J 29(5):879-888.

Burra TA, Moineddin R, Agha MM, Glazier RH. 2009. Social disadvantage, air pollution, and asthma physician visits in Toronto, Canada. Environ Res 109(5):567-574.

Cakmak S, Dales RE, Judek S. 2006. Respiratory health effects of air pollution gases: Modification by education and income. Arch Environ Occup Health 61(1):5-10.

Carlsten C, Dybuncio A, Becker A, Chan-Yeung M, Brauer M. 2011. Traffic-related air pollution and incident asthma in a high-risk birth cohort. Occup Environ Med 68(4):291-295.

Carracedo-Martinez E, Taracido M, Tobias A, Saez M, Figueiras A. 2010. Case-crossover analysis of air pollution health effects: A systematic review of methodology and application. Environ Health Perspect; doi: 10.1289/ehp.0901485.

City of Houston. 2010. Pollen and Mold Spore Count Archives. http://www.houstontx.gov/health/Pollen-Mold/pollenarchive.html Houston, TX.: City of Houston Department of Health and Human Services.

Darrow LA, Klein M, Sarnat JA, Mulholland JA, Strickland MJ, Sarnat SE et al. 2011. The use of alternative pollutant metrics in time-series studies of ambient air pollution and respiratory emergency department visits. J Expo Sci Env Epid 21(1):10-19.

Gilliland FD. 2009. Outdoor air pollution, genetic susceptibility, and asthma management: Opportunities for intervention to reduce the burden of asthma. Pediatrics 123(Suppl 3):S168-73.

Gilmour MI, Jaakkola MS, London SJ, Nel AE, Rogers CA. 2006. How exposure to environmental tobacco smoke, outdoor air pollutants, and increased pollen burdens influences the incidence of asthma. Environ Health Perspect 114(4):627-633.

Gwynn RC, Thurston GD. 2001. The burden of air pollution: Impacts among racial minorities. Environ Health Perspect 109(Suppl 4):501-506.

Hennessy S, Leonard CE, Palumbo CM, Newcomb C, Bilker WB. 2007. Quality of Medicaid and Medicare data obtained through Centers for Medicare and Medicaid Services (CMS). Med Care 45(12):1216-1220.

Islam T, McConnell R, Gauderman WJ, Avol E, Peters JM, Gilliland FD. 2008. Ozone, oxidant defense genes, and risk of asthma during adolescence. Am J Respir Crit Care Med 177(4):388-395.

Janes H, Sheppard L, Lumley T. 2005. Case-crossover analyses of air pollution exposure data: Referent selection strategies and their implications for bias. Epidemiology 16(6):717-726.

Jerrett M, Shankardass K, Berhane K, Gauderman WJ, Kunzli N, Avol E et al. 2008. Traffic-related air pollution and asthma onset in children: A prospective cohort study with individual exposure measurement. Environ Health Perspect 116(10):1433-1438.

Kemp JP, Kemp JA. 2001. Management of asthma in children. Am Fam Physician 63(7):1341-1348.

Lee K, Parkhurst WJ, Xue J, Ozkaynak AH, Neuberg D, Spengler JD. 2004. Outdoor/Indoor/Personal ozone exposures of children in Nashville, Tennessee. J Air Waste Manage Assoc 54(3):352-359.

Lewis TC, Robins TG, Dvonch JT, Keeler GJ, Yip FY, Mentz GB et al. 2005. Air pollution-associated changes in lung function among asthmatic children in Detroit. Environ Health Perspect 113(8):1068-1075.

Li YF, Gauderman WJ, Avol E, Dubeau L, Gilliland FD. 2006. Associations of tumor necrosis factor G-308A with childhood asthma and wheezing. Am J Respir Crit Care Med 173(9):970-976.

Lin S, Liu X, Le LH, Hwang SA. 2008. Chronic exposure to ambient ozone and asthma hospital admissions among children. Environ Health Perspect 116(12):1725-1730.

Lipfert FW. 2004. Air pollution and poverty: Does the sword cut both ways? J Epidemiol Commun Health 58(1):2-3.

Lozano P, Connell FA, Koepsell TD. 1995. Use of health services by African-American children with asthma on Medicaid. JAMA 274(6):469-473.

Lozano P, Sullivan SD, Smith DH, Weiss KB. 1999. The economic burden of asthma in US children: Estimates from the National Medical Expenditure Survey. J Allergy Clin Immunol 104(5):957-963.

Luginaah IN, Fung KY, Gorey KM, Webster G, Wills C. 2005. Association of ambient air pollution with respiratory hospitalization in a government-designated "area of concern": The case of Windsor, Ontario. Environ Health Perspect 113(3):290-296.

McConnell R, Berhane K, Gilliland F, Molitor J, Thomas D, Lurmann F et al. 2010. Childhood incident asthma and traffic-related air pollution at home and school. Environ Health Perspect 118(7);1021-1026.

McConnell R, Berhane K, Gilliland F, London SJ, Islam T, Gauderman WJ et al. 2002. Asthma in exercising children exposed to ozone: A cohort study. Lancet 359(9304):386-391.

Miller JE. 2000. The effects of race/ethnicity and income on early childhood asthma prevalence and health care use. Am J Public Health. Substance Use, Including Tobacco 90(3):428-430.

Moore K, Neugebauer R, Lurmann F, Hall J, Brajer V, Alcorn S et al. 2008. Ambient ozone concentrations cause increased hospitalizations for asthma in children: An 18-year study in Southern California. Environ Health Perspect 116(8):1063-1070.

Morgenstern V, Zutavern A, Cyrys J, Brockow I, Gehring U, Koletzko S et al. 2007. Respiratory health and individual estimated exposure to traffic-related air pollutants in a cohort of young children. Occup Environ Med 64(1):8-16.

Mortimer KM, Tager IB, Dockery DW, Neas LM, Redline S. 2000. The effect of ozone on inner-city children with asthma: Identification of susceptible subgroups. Am J Respir Crit Care Med 162(5):1838-1845.

National Committee for Quality Assurance. HEDIS 2011 NDC Lists: Use of Appropriate Medications for People with Asthma (ASM). Washington, DC: National Committee for Quality Assurance; 2011. (http://www.ncqa.org/tabid/1274/Default.aspx).

Ortega AN, Belanger KD, Paltiel AD, Horwitz SM, Bracken MB, Leaderer BP. 2001. Use of health services by insurance status among children with asthma. Med Care 39(10):1065-1074.

Parker JD, Akinbami LJ, Woodruff TJ. 2009. Air pollution and childhood respiratory allergies in the United States. Environ Health Perspect 117(1):140-147.

Romieu I, Ramirez-Aguilar M, Sienra-Monge JJ, Moreno-Macias H, del Rio-Navarro BE, David G et al. 2006. GSTM1 and GSTP1 and respiratory health in asthmatic children exposed to ozone. Eur Respir J 28(5):953-959.

Schildcrout JS, Sheppard L, Lumley T, Slaughter JC, Koenig JQ, Shapiro GG. 2006. Ambient air pollution and asthma exacerbations in children: An eight-city analysis. Am J Epidemiol 164(6):505-517.

Sexton K, Linder SH, Marko D, Bethel H, Lupo PJ. 2007. Comparative assessment of air pollution-related health risks in Houston. Environ Health Perspect 115(10):1388-1393.

Shields AE, Comstock C, Weiss KB. 2004. Variations in asthma care by race/ethnicity among children enrolled in a state Medicaid program. Pediatrics 113(3 Pt 1):496-504.

Silverman RA, Ito K. 2010. Age-related association of fine particles and ozone with severe acute asthma in New York City. J Allergy Clin Immun 125(2):367-373.e5.

Slaughter JC, Lumley T, Sheppard L, Koenig JQ, Shapiro GG. 2003. Effects of ambient air pollution on symptom severity and medication use in children with asthma. Ann Allerg Asthma Im 91(4):346-353.

Spier CE, Little DE, Trim SC, Johnson TR, Linn WS, Hackney JD. 1992. Activity patterns in elementary and high school students exposed to oxidant pollution. J Expo Anal Environ Epidemiol 2(3):277-293.

Strickland MJ, Darrow LA, Klein M, Flanders WD, Sarnat JA, Waller LA et al. 2010. Short-term associations between ambient air pollutants and pediatric asthma emergency department visits. Am J Respir Crit Care Med 182(3):307-316.

Strickland MJ, Darrow LA, Mulholland JA, Klein M, Flanders WD, Winquist A et al. 2011. Implications of different approaches for characterizing ambient air pollutant concentrations within the urban airshed for time-series studies and health benefits analyses. Environ Health-Glob 10:36.

Texas Commission on Environmental Quality. 2009. HGB Reasonable Further Progress SIP revision for the 1997 eight-hour ozone standard. Chapter 1: General. http://www.tceq.state.tx.us/assets/public/implementation/air/sip/hgb/hgb_sip_2009/09017SIP_Ch1_ado.pdf Austin, TX.: Texas Commission on Environmental Quality.

Texas Commission on Environmental Quality. 2010. SIP Revisions: Houston-Galveston-Brazoria, March 10, 2010.

http://www.tceq.state.tx.us/implementation/air/sip/HGB_eight_hour.html Austin, TX.: Texas Commission on Environmental Quality.

U.S. Census Bureau. Table 20: Large Metropolitan Statistical Areas-Population: 1990-2010. http://www.census.gov/compendia/statab/2012/tables/12s0020.pdf.

U.S. Environmental Protection Agency. 2010. Technology Transfer Network (TTN), Air Quality System (AQS). www.epa.gov/ttnairs1/airsaqs/ Washington, D.C.: U.S. Environmental Protection Agency.

Valet RS, Gebretsadik T, Carroll KN, Wu P; Dupont WD, Mitchel EF et al. 2011. High asthma prevalence and increased morbidity among rural children in a Medicaid cohort. Ann Allergy Asthma Immunol 106(6):467-473.

Wendt JK, Symanski E, Du XL. 2012. Estimation of asthma incidence among low-income children in Texas: A novel approach using Medicaid claims data. Am J Epidemiol (in press).

Yeatts K, Sly P, Shore S, Weiss S, Martinez F, Geller A et al. 2006. A brief targeted review of susceptibility factors, environmental exposures, asthma incidence, and recommendations for future asthma incidence research. Environ Health Perspect 114(4):634-640.

Zmirou D, Gauvin S, Pin I, Momas I, Sahraoui F, Just J et al. 2004. Traffic related air pollution and incidence of childhood asthma: Results of the Vesta case-control study. J Epidemiol Commun H 58(1):18-23.

Table 1. Description of incident asthma cases identified among Harris County, Texas children enrolled in Medicaid between 2005 and 2007.

	Number	Percent
Total	18,264	100%
Age Group		
1-4	13,232	72.5%
5-9	3,192	17.5%
10-14	1,644	9.0%
15-17	196	1.1%
Gender		
Female	8,046	44.1%
Male	10,218	56.0%
Race		
White	1,450	7.9%
Black	4,760	26.1%
Am. Indian	84	0.5%
Asian	522	2.9%
Hispanic	11,191	61.3%
Unknown	257	1.4%

Table 2. Description of pollutants, meteorological conditions and aeroallergens averaged across monitoring sites in Harris County, Texas, 2005-2007.

Pollutant	N	Mean	SD	Min	25%	50%	75%	Max	IQR
O_3 (8-hr max, ppb)	1,094	37.87	15.99	3.75	25.88	34.25	47.53	96.88	21.65
NO_2 (1-hr max, ppb)	1,091	39.26	14.07	12.00	29.00	38.00	48.00	108.00	19.00
$PM_{2.5}$ (24-hr mean, $\mu g/m^3$)	1,035	14.97	6.02	2.70	10.70	14.00	18.30	44.20	7.60
Temperature (daily max, °F)	1,095	78.55	12.18	36.96	71.42	80.68	88.95	99.63	17.53
Relative humidity (daily mean, %)	1,093	69.63	11.63	27.26	62.94	71.28	77.65	93.21	14.71
Mold (spores/m^3)	675	2,680.13	3,153.22	36.00	707.00	1,301.00	3,665.00	22,596.00	2,958.00
Tree pollen (grains/m^3)	657	285.15	776.55	0.00	0.00	12.00	150.00	6,776.00	150.00
Grass pollen (grains/m^3)	657	13.44	37.12	0.00	2.00	4.00	10.00	441.00	8.00
Weed pollen (grains/m^3)	650	51.91	208.38	0.00	0.00	0.00	8.00	1,782.00	8.00

Table 3. Description of pollutants, meteorological conditions and aeroallergens by season, averaged across monitoring sites in Harris County, Texas, 2005-2007.

Pollutant	N	Mean	SD	Min	25%	50%	75%	Max	IQR
				Warm Season (May-Oct)					
O_3 (8-hr max, ppb)	551	42.93	17.83	10.82	27.75	40.75	56.25	96.88	28.50
NO_2 (1-hr max, ppb)	548	36.98	13.93	12.00	26.00	36.00	46.00	108.00	20.00
$PM_{2.5}$ (24-hr mean, $\mu g/m^3$)	525	16.42	6.41	2.70	11.80	15.20	19.90	44.20	8.10
Temperature (daily max, °F)	552	87.47	5.65	65.57	84.13	88.79	91.41	99.63	7.28
Relative humidity (daily mean, %)	550	70.06	8.74	41.28	64.65	70.66	75.74	90.30	11.09
Mold (spores/m^3)	348	3,192.96	3,764.49	36.00	798.50	1,342.50	4,490.00	22,596.00	3,691.50
Tree pollen (grains/m^3)	334	41.00	138.43	0.00	0.00	0.00	19.00	1,310.00	19.00
Grass pollen (grains/m^3)	334	13.10	40.56	0.00	2.00	6.00	10.00	441.00	8.00
Weed pollen (grains/m^3)	334	98.25	282.94	0.00	0.00	3.00	32.00	1,782.00	32.00
				Cold Season (Nov-Apr)					
O_3 (8-hr max, ppb)	543	32.73	11.86	3.75	25.13	30.88	39.59	80.06	14.46
NO_2 (1-hr max, ppb)	543	41.56	13.86	12.00	32.00	41.00	50.00	105.00	18.00
$PM_{2.5}$ (24-hr mean, $\mu g/m^3$)	510	13.48	5.15	2.75	9.80	12.80	16.20	33.85	6.40
Temperature (daily max, °F)	543	69.49	10.19	36.96	63.00	71.88	77.17	88.83	14.17

Relative humidity (daily mean, %)	543	69.21	13.95	27.26	60.03	72.22	79.47	93.21	19.44
Mold (spores/m^3)	327	2,134.36	2,211.96	40.00	629.00	1,215.00	2,888.00	11,507.00	2,259.00
Tree pollen (grains/m^3)	323	537.61	1,040.64	0.00	10.00	82.00	443.00	6,776.00	433.00
Grass pollen (grains/m^3)	323	13.79	33.25	0.00	0.00	4.00	10.00	255.00	10.00
Weed pollen (grains/m^3)	316	2.93	12.35	0.00	0.00	0.00	0.00	137.00	0.00

Table 4. Spearman rank-correlation matrix for pollutants, meteorological variables and aeroallergens, averaged across monitoring sites in Harris County, Texas, 2005-2007.

Pollutant	O_3 (8-hour mean)	NO_2 (1-hr max)	$PM_{2.5}$ (24-hr mean)	Temperature (daily max, °F)	Relative humidity (daily mean, %)	Mold (spores/m^3)	Tree pollen (grains/m^3)	Grass pollen (grains/m^3)	Weed pollen (grains/m^3)
O_3 (8-hour max)	1.00								
NO_2 (1-hr max)	0.49*	1.00							
$PM_{2.5}$ (24-hr mean)	0.32*	0.21*	1.00						
Temperature (daily max, °F)	0.33*	-0.23*	0.36*	1.00					
Relative humidity (daily mean, %)	-0.49*	-0.39*	-0.04	0.02	1.00				
Mold (spores/m^3)	-0.05	-0.01	-0.04	-0.01	0.13*	1.00			
Tree pollen (grains/m^3)	0.04	0.15*	-0.18*	-0.49*	0.04	0.14*	1.00		
Grass pollen (grains/m^3)	0.23*	0.02	-0.02	0.09*	-0.03	0.25*	0.31*	1.00	
Weed pollen (grains/m^3)	0.09*	0.06	0.06	0.24*	-0.02	0.50*	-0.14*	0.17*	1.00

*$p<0.05$

Table 5. Adjusted[1] odds ratios (OR) and 95% confidence intervals (95% CI) of the association between 6-day cumulative means (lag 0 to lag 5) and asthma, by quartile, among Harris County, Texas children enrolled in Medicaid between 2005 and 2007.

Pollutant	Range	No. of Cases (%)	No. of Controls (%)	Odds Ratio	95% CI
Ozone (ppb)					
Q1	< 28.13	4,469 (24.5%)	13,701 (25.0%)	1.00	
Q2	28.13 – < 35.04	4,587 (25.1%)	13,723 (25.1%)	1.11	1.03, 1.19
Q3	35.04 – < 44.76	4,513 (24.7%)	13,637 (24.9%)	1.06	0.95, 1.19
Q4	≥ 44.76	4,695 (25.7%)	13,731 (25.1%)	1.20	1.06, 1.36
$PM_{2.5}$ ($\mu g/m^3$)					
Q1	< 11.91	4,508 (24.8%)	13,794 (25.3%)	1.00	
Q2	11.91 – < 13.52	4,494 (24.7%)	13,378 (24.6%)	0.98	0.91, 1.05
Q3	13.52 – < 16.34	4,472 (24.6%)	13,660 (25.1%)	1.04	0.97, 1.23
Q4	≥ 16.34	4,734 (26.0%)	13,656 (25.1%)	1.10	1.02, 1.18
NO_2 (ppb)					
Q1	< 34.5	4,483 (24.6%)	13,668 (25.0%)	1.00	
Q2	34.5 – < 40.83	4,607 (25.2%)	13,648 (24.9%)	1.11	1.03, 1.21
Q3	40.83 – < 46.17	4,570 (25.0%)	13,847 (25.3%)	1.06	0.97, 1.15
Q4	≥ 46.17	4,604 (25.2%)	13,629 (24.9%)	1.19	1.10, 1.29

[1] Adjusted for same-day maximum temperature, mean relative humidity and mold spore, tree pollen, grass pollen and weed pollen counts.

Table 6. Adjusted[1] odds ratios and 95% confidence intervals for single pollutant and co-pollutant models per IQR change in pollutants. Study population includes Harris County, Texas children enrolled in Medicaid between 2005 and 2007. All pollutant metrics are 6-day cumulative means (i.e., L05: lag 0 to lag 5).

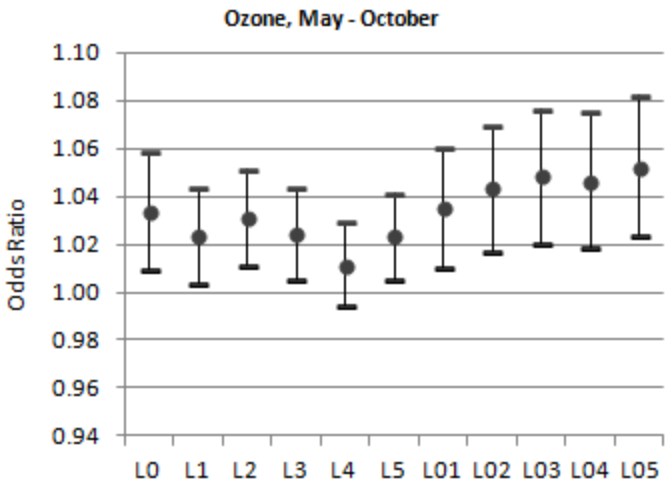
Pollutant	May - Oct			Nov - Apr		
	IQR	Odds Ratio	95% CI	IQR	Odds Ratio	95% CI
Single Pollutant Models						
O_3 (8-hr max, ppb)	28.50	1.16	1.07, 1.25	14.46	1.02	0.96, 1.09
$PM_{2.5}$ (24-hr mean, µg/m^3)	8.10	1.10	1.03, 1.17	6.40	1.06	1.00, 1.14
NO_2 (1-hr max, ppb)	20.00	1.14	1.06, 1.24	18.00	1.02	0.96, 1.08
O_3 and $PM_{2.5}$						
O_3 (8-hr max, ppb)	28.50	1.14	1.03, 1.26	14.46	1.02	0.95, 1.09
$PM_{2.5}$ (24-hr mean, µg/m^3)	8.10	1.03	0.94, 1.12	6.40	1.06	0.99, 1.13
O_3 and NO_2						
O_3 (8-hr max, ppb)	28.50	1.09	0.94, 1.26	14.46	1.02	0.94, 1.11
NO_2 (1-hr max, ppb)	20.00	1.07	0.93, 1.23	18.00	1.00	0.93, 1.09
$PM_{2.5}$ and NO_2						
$PM_{2.5}$ (24-hr mean, µg/m^3)	8.10	1.04	0.97, 1.12	6.40	1.06	0.99, 1.14
NO_2 (1-hr max, ppb)	20.00	1.13	1.04, 1.24	18.00	1.00	0.93, 1.07

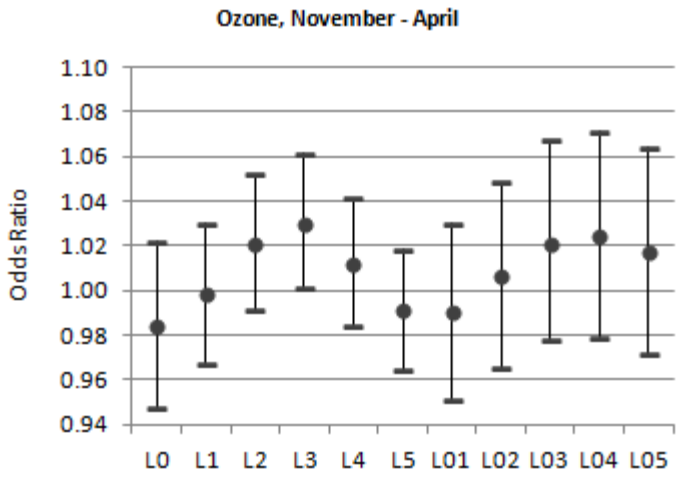
[1] Adjusted for same-day maximum temperature, mean relative humidity and mold spore, tree pollen, grass pollen and weed pollen counts.

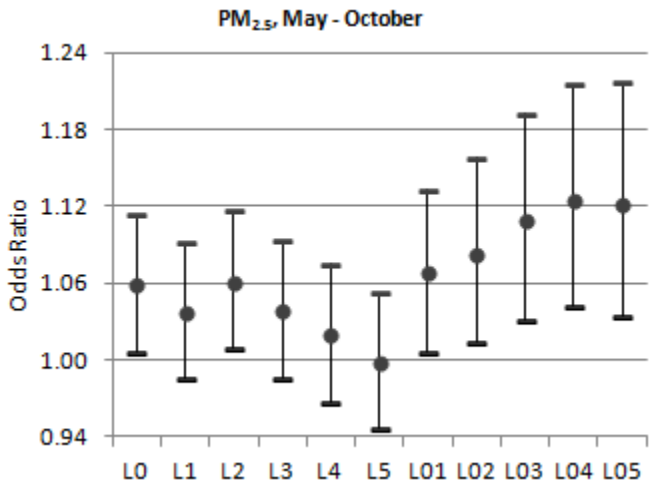
Table 7. Stratified analysis of associations between 10 ppb increases in 6-day cumulative mean O_3, and incident asthma among Harris County, Texas children enrolled in Medicaid between 2005 and 2007, by season.

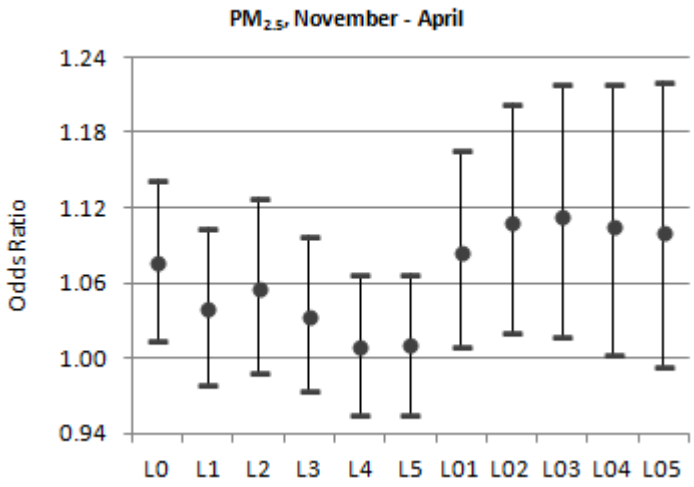
	All Months			May - Oct			Nov - Apr		
Variable	No. of Cases	Odds Ratio[1]	95% Confidence Interval	No. of Cases	Odds Ratio[1]	95% Confidence Interval	No. of Cases	Odds Ratio[1]	95% Confidence Interval
Age Group									
1 – 4	10,165	1.03	1.00, 1.06	4,445	1.03	1.00, 1.07	5,720	0.99	0.93, 1.04
5 - 9	2,420	1.09	1.03, 1.15	993	1.07	1.00, 1.15	1,427	1.14	1.02, 1.27
10 – 14	1,227	1.10	1.02, 1.19	563	1.15	1.05, 1.26	664	1.02	0.88, 1.20
15 - 17	143	1.22	0.99, 1.51	60	1.35	1.04, 1.75	83	1.02	0.65, 1.61
Gender									
Male	7,779	1.05	1.01, 1.08	3,401	1.06	1.02,1.10	4,378	1.00	0.94, 1.06
Female	6,176	1.05	1.01, 1.09	2,660	1.05	1.00, 1.09	3,516	1.04	0.97, 1.11
Race									
White	1,115	1.01	0.93, 1.10	507	0.98	0.88, 1.08	608	1.07	0.91, 1.26
Black	3,688	1.08	1.03, 1.13	1,706	1.09	1.04, 1.15	1,982	1.05	0.96, 1.15
Hispanic	8,502	1.03	1.00, 1.07	3,559	1.04	1.01, 1.08	4,943	0.99	0.93, 1.05

[1] Adjusted for same-day maximum temperature, mean relative humidity and mold spore, tree pollen, grass pollen and weed pollen counts.


Ozone, May - October
Odds Ratio
1.10
1.08
1.06
1.04
1.02
1.00
0.98
0.96
0.94
L0 L1 L2 L3 L4 L5 L01 L02 L03 L04 L05


Ozone, November - April
Odds Ratio
1.10
1.08
1.06
1.04
1.02
1.00
0.98
0.96
0.94
L0 L1 L2 L3 L4 L5 L01 L02 L03 L04 L05


PM2.5, May - October
Odds Ratio
1.24
1.18
1.12
1.06
1.00
0.94
L0 L1 L2 L3 L4 L5 L01 L02 L03 L04 L05


PM2.5, November - April
Odds Ratio
1.24
1.18
1.12
1.06
1.00
0.94
L0 L1 L2 L3 L4 L5 L01 L02 L03 L04 L05

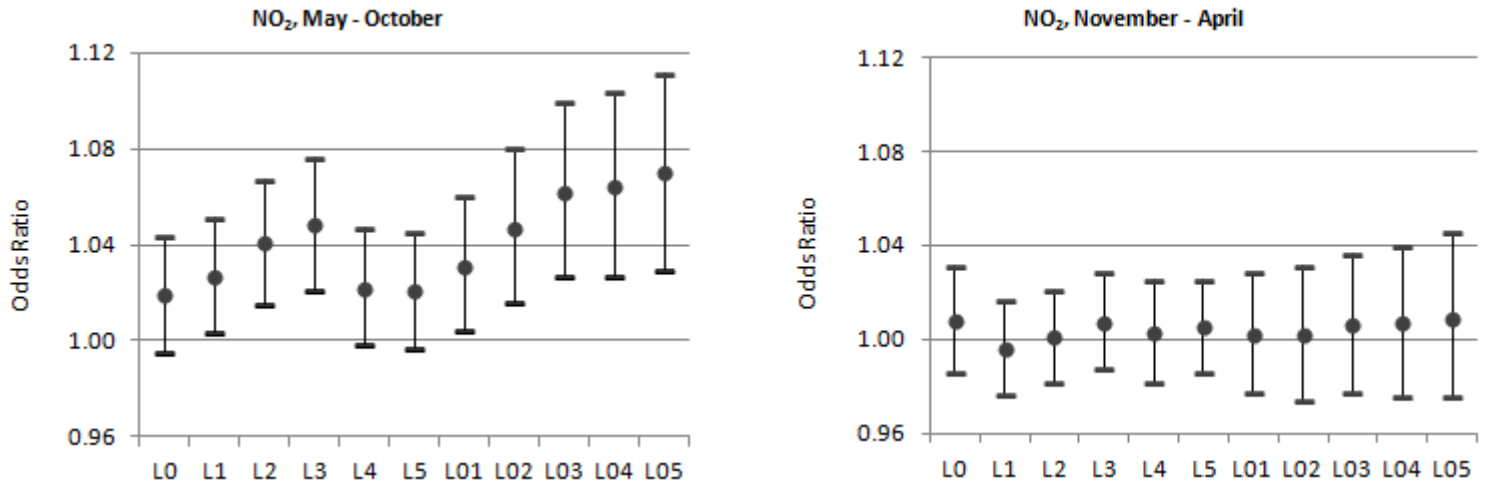
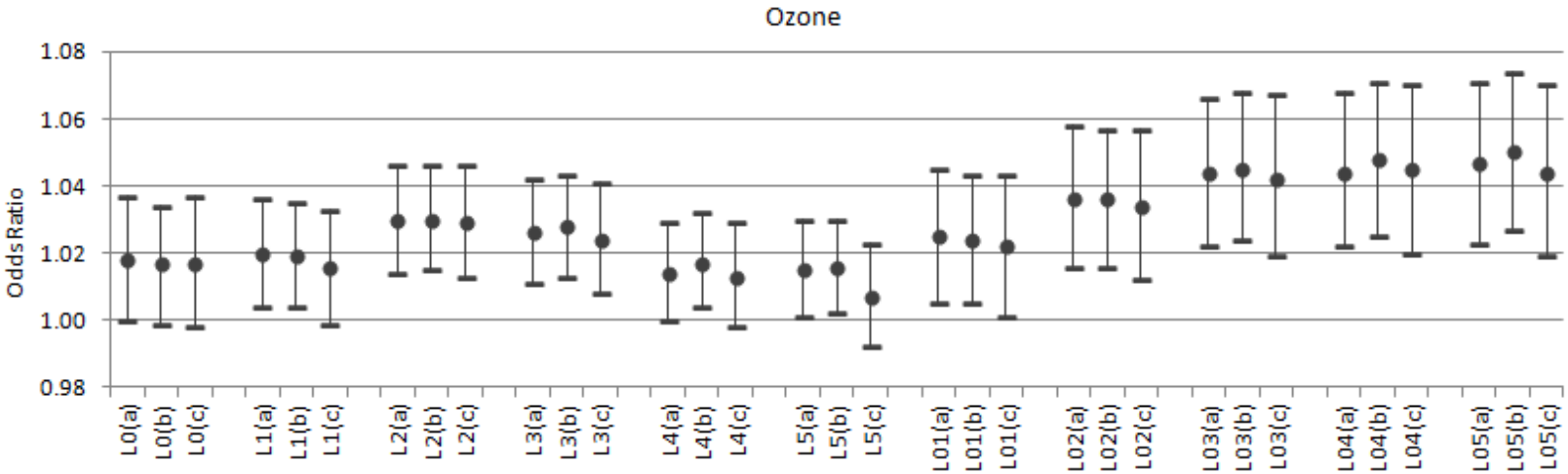


Figure 1. Adjusted odds ratios and 95% confidence intervals for each pollutant at various lags and cumulative lags, by season. Odds ratios indicate risk associated with 10 ppb increases in O_3 and NO_2, and 10 $\mu g/m^3$ increase in $PM_{2.5}$. Study population includes Harris County, Texas children enrolled in Medicaid between 2005 and 2007. All models are adjusted for same-day maximum temperature, mean relative humidity and mold spore, tree pollen, grass pollen and weed pollen counts. L0 through L5 indicate single same-day through lag 5 day pollutant values, and L01 through L05 indicate 2-day through 6-day cumulative mean pollutant values.


Ozone
Odds Ratio
1.08
1.06
1.04
1.02
1.00
0.98
L0(a) L0(b) L0(c) L1(a) L1(b) L1(c) L2(a) L2(b) L2(c) L3(a) L3(b) L3(c) L4(a) L4(b) L4(c) L5(a) L5(b) L5(c) L01(a) L01(b) L01(c) L02(a) L02(b) L02(c) L03(a) L03(b) L03(c) L04(a) L04(b) L04(c) L05(a) L05(b) L05(c)

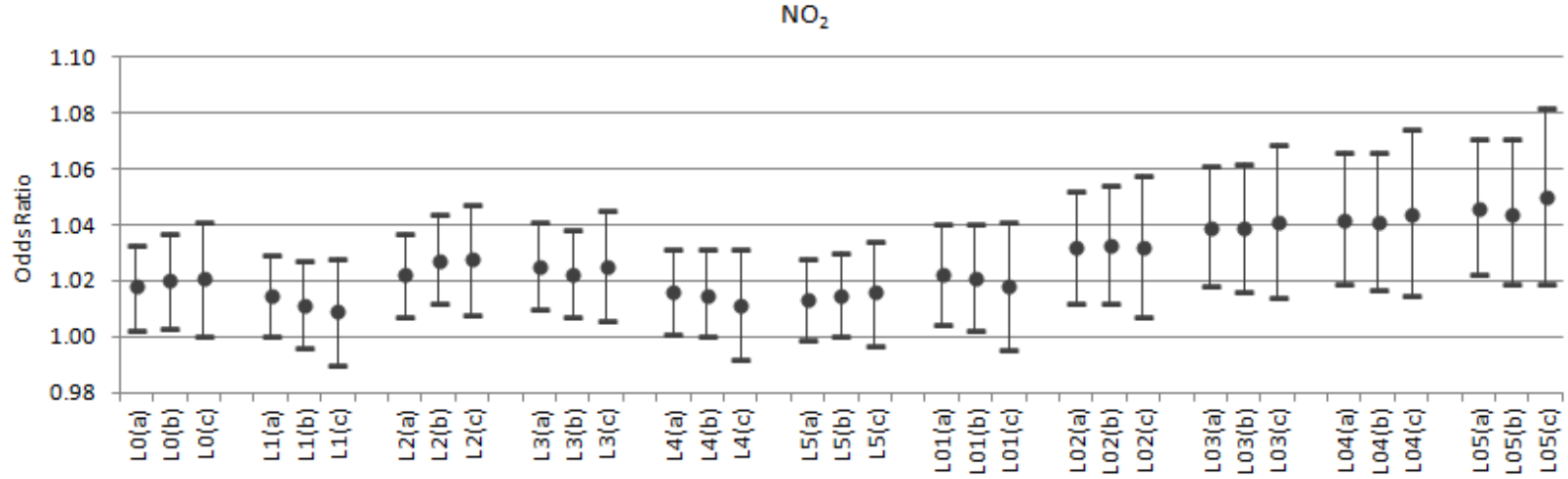

NO2
Odds Ratio
1.10
1.08
1.06
1.04
1.02
1.00
0.98
L0(a) L0(b) L0(c) L1(a) L1(b) L1(c) L2(a) L2(b) L2(c) L3(a) L3(b) L3(c) L4(a) L4(b) L4(c) L5(a) L5(b) L5(c) L01(a) L01(b) L01(c) L02(a) L02(b) L02(c) L03(a) L03(b) L03(c) L04(a) L04(b) L04(c) L05(a) L05(b) L05(c)

Figure 2. Adjusted odds ratios and 95% confidence intervals for O_3 and NO_2 exposure metrics determined by (a) Harris County averages, (b) the three closest monitors to centroid of zip code of residence, and (c) monitors within 6 miles of the zip code of residence. ORs presented are per 10 ppb increase in exposure. Study population includes Harris County, Texas children enrolled in Medicaid between 2005 and 2007. All models are adjusted for same-day maximum temperature, mean relative humidity and mold spore, tree pollen, grass pollen and weed pollen counts. L0 through L5 indicate single same-day through lag 5 day pollutant values, and L01 through L05 indicate 2-day through 6-day cumulative mean pollutant values.

CHAPTER V: CONCLUSION

The Centers for Disease Control and Prevention has called for a greater emphasis on tracking incidence in U.S. asthma surveillance programs, while acknowledging the inherent challenges and limited data sources. In this unique study, we estimated population-based asthma incidence using statewide Medicaid claims data, a rich source for studying diseases disproportionately impacting low-income children. This new methodology allows for estimation of asthma incidence for specific geographic areas, and by age, gender and race using a data source produced specifically for research. Our results indicate that Medicaid-enrolled children are at greater risk of being given an asthma diagnosis than those in the general population.

Low income children consistently fare worse on asthma measures including prevalence, morbidity, hospitalizations and mortality than children from higher income families. In addition to a higher disease burden, these children also appear to be more vulnerable to the effects of air pollution, although it is not clear to what extent this is attributable to greater susceptibility, higher exposure levels or other factors. While many studies have demonstrated an effect of ambient air pollutants on asthma morbidity, it is much less clear whether air pollutants also play a role in the development of the disease in children. Our study addressed this question, evaluating the association of incident childhood asthma and ambient air pollution, primarily ozone, in the Houston metropolitan area.

Ozone has generally not been associated with new-onset asthma, except in cases of presumably higher personal exposure or among children with greater genetic susceptibility.

In our study of Medicaid-enrolled children in Harris County, Texas, we found small but significant increases in incident asthma with increasing ambient O_3, NO_2 and $PM_{2.5}$ concentrations. Children in the highest quartiles of O_3, NO_2 and $PM_{2.5}$ exposure had significantly higher risk of incident asthma than children in the lowest quartiles. While effects of O_3 and NO_2 were limited to warm months (May-October), associations with $PM_{2.5}$ were seen in both warm and cold seasons (November-April). For all pollutants, exposure metrics based on longer cumulative lag periods (i.e., 4-, 5- and 6-day averages) had the strongest effect.

To our knowledge, this was the first study to estimate asthma incidence using Medicaid claims data. While this methodology has been applied to cancer incidence studies (17-25), it was the first to explore the use of claims data to study the development of asthma. Texas has the second highest number of Medicaid-enrolled children in the U.S. (89), and this large sample size of children at increased risk of asthma allowed for stable statewide estimates, as well as the ability to estimate rates by county, age group, gender and race/ethnicity.

The study used a case-crossover design, which enabled us to evaluate associations between these pollutants and incident asthma, while controlling for individual-level risk factors. This is particularly useful for a disease such as asthma for which personal, genetic and household factors are known to contribute to an individual's risk of disease (8-10). This study design is typically used to study diseases with a well-defined date of onset. While it can be argued that using the initial diagnosis date seen in claims data for the child does not accurately capture date of onset for asthma, it would be an indication that the disease became

severe enough that the child required medical attention. In this sense, it is similar to the determination of onset date for other diseases which develop over time.

Medicaid managed care enrollment increased between 2004 and 2007 and is delivered throughout Texas either through the State of Texas Access Reform (STAR) program (a capitated, HMO model) or through a primary care case management (PCCM) program (a non-capitated, fee-for-service model). For the nine major metropolitan areas in Texas, Medicaid beneficiaries are required to enroll in the STAR program (with few exceptions), while the PCCM program covers the rest of the state. The percent of Texas enrollees in the STAR HMO Plan ranged from 26.6% in 2004 to 37.8% in 2007, while the percent in PCCM ranged from 12.6% 2004 to 34.2% in 2006 to 26.0% in 2007. Enrollees in a traditional fee-for-service program ranged from 58.6% in 2004 to 32.2% in 2007.

Approximately 85% of children enrolled in Medicaid in Harris County are in managed care (i.e., STAR). One concern was that medical claims submitted by providers under a capitated payment plan may not contain the level of detail on diagnosis that a fee-for-service claim would contain, and that this might have resulted in an underestimation of asthma cases in this analysis. A recent validation study by the Texas Health and Human Services Commission (93) compared electronic claims records and medical chart data for a sample of 2006 Medicaid HMO encounters (n=1,000), with comparisons going back to 2002. The authors reported that for the three managed care organizations studied, 63.3% to 85.6% of encounters had the same diagnosis in the medical chart and claims record (average of 78% across the three plans for the three years). An average of 16% of encounters studied reported a diagnosis in the medical chart that was not in the claims record, and an average of 6%

reported a diagnosis in the claims record that did not appear in the medical chart. These are general percentages, including all ages, diagnoses, and metropolitan areas, but offer evidence that encounter (i.e., HMO) data available in the MAX files were fairly reliable.

In this study, asthma cases were identified using both medical and pharmacy claims, and pharmacy claims are paid based on fee-for-service, not a capitated (per person) basis. A recent study which used claims data to estimate childhood asthma prevalence among North Carolina Medicaid enrollees reported that among all cases identified, >90% had at least one asthma medication prescribed (31). Others have shown that using both medical and pharmacy claims to identify asthma cases is preferable to using medical claims alone (76, 94). Dombkowski et al. concluded that identifying asthma cases in Medicaid claims files using the criteria of 4+ pharmacy claims in a 12-month period provided the greatest year-to-year consistency and least bias of the algorithms considered, but also resulted in lower prevalence estimates than if cases were identified from a combination of medical and pharmacy claims (32). While the use of both medical and pharmacy records is considered by CMS to be the preferred method for identifying asthma cases, relying on pharmacy records has also been shown to provide reliable estimates. Although we acknowledge the potential issue associated with a capitated payment system, the percent of agreement reported by in the HHSC validation study and our ability to use pharmacy as well as medical claims lessened the potential for bias in our estimates.

We did not have personal pollutant exposure estimates, but rather relied on values either averaged across monitoring results for Harris County, or estimated based on monitoring results near the child's zip code of residence which may have introduced

exposure misclassification. We also did not have data on time activity patterns or indoor exposure levels for the identified cases, although we expect that restricting the study population to a single county (and presumably to a group with less heterogeneity in socioeconomic status) reduced variability in factors such as air conditioning use in the home and time spent outdoors at particular times of the year.

Knowledge of asthma incidence patterns is critical to understanding associated risk factors. To our knowledge, this is the first study evaluating the association of incident childhood asthma and ambient air pollution in the Houston area. While our results may not be generalizable to children with higher family incomes, they may represent risk for a susceptible sub-population in an area with historically poor air quality. This novel approach can be used to identify new-onset asthma cases for incidence rate estimations and analysis of possible risk factors in other Medicaid populations, thus increasing understanding of this disabling and costly disease.

APPENDICES

Appendix A. Summary of studies evaluating an association between ambient ozone on asthma, 2000-2010

Table 1. Summary of study design

Source	Setting	Study Design	Sample Size	Definition of Exposure	Definition of Outcome
Akinbami et al. (2010)(41)	U.S. Metropolitan Statistical Areas (MSAs) sampled in the **National Health Interview Survey** (NHIS)	Cross-sectional	34,073 children ages 3-17 sampled in the 2001-2004 NHIS	From EPA Aerometric Information Retrieval System (AIRS) by county; rolling 12-month average values based on quarterly measures of O_3 (8-h max); PM_{10}, $PM_{2.5}$, SO_2, NO_2 (24-h avg.). Exposure level for each child was avg. for 4-quarters prior to their NHIS interview.	**Current asthma**: yes responses to "Has a doctor…ever told you that you child has asthma?" and "Does your child still have asthma?" **Asthma attack**: yes response to "During the past 12 months, has your child had an episode or asthma or an asthma attack?"
Babin et al. (2008)(78)	Washington D.C. area Medicaid beneficiaries, 1994-2005	Ecologic/Time series analysis	61,218 patient encounters during the 11-year period (n=9,970 for children ages 0-4, and n=7,841 for children ages 5-12)	Daily maximum 8-hour average	**Daily general acute care (GAC) visits for asthma:** based on ICD-9 code of 493.xx in one of the first three diagnosis code fields in the claims records; excluded records due to routine asthma care and follow-up (focused on asthma exacerbations). Included GAC's in spring and summer months only.
Burra et al. (2009)(49)	Toronto Ontario; claims records from Ontario Health Insurance Plan, 1992-2001	Time series	1,051,315 children ages 1-17	Daily maximum 1-hour O_3 Lag periods: L0, L01, L02, L03, L04	**Ambulatory (physician) visits for asthma**: based on ICD-9 code of 493.xx in claims records

Fauroux et al. (2000)(79)	Paris, Jan 1-Dec 31, 1988	Time series	715 children ages 1-15	From existing monitoring network throughout Paris; mean daily 8-h O_3 (10 am – 6 pm)	**Daily incidence of asthma**: number of daily ER visits for acute asthma (defined per intl. consensus statement: recurrent wheezing and/or coughing, especially at night and triggered by allergens, exercise, or viral infections, provided other conditions have been excluded).
Gent et al. (2003)(95)	Connecticut and Springfield, MA area, Apr 1-Sept 30, 2001	Time series	271 asthmatic children, <12 years of age; had respiratory symptoms or used asthma meds in previous 12 months	Monitoring results from 14 sites in the region were averaged; maximum daily 1-h and 8-h averages; categorized as quintiles but also modeled as continuous.	**Respiratory symptoms**: wheeze, persistent cough, chest tightness, shortness of breath **Rescue medication (bronchodilator) use**
Jaffe et al. (2003)(96)	Cincinnati, Cleveland, Columbus OH	Time series (ecologic)	4,416 Medicaid enrollees ages 5-34 with a primary asthma diagnosis in any patient encounter record during summer months (Jun-Aug): 7/1/91-6/30/96	From EPA Aerometric Information Retrieval System (AIRS) by city; measures included O_3 (max 8-h daily avg.), PM_{10} (24-h daily mean), SO_2 (24-h daily mean), NO_2 (1-h daily max); highest daily mean from all monitoring sites in each city was used. Restricted analysis to June-Aug each year.	**Number of daily Emergency Department episodes for asthma**: ICD9 code of 493.xx listed as first diagnosis for any ED visit.
Jalaludin et al. (2000)(80)	Children from 6 elementary schools in Sydney Australia	Prospective cohort	125 children • Group 1 (n=45): Hx of wheeze in past 12 months and positive histamine	From air monitoring stations located within 2 km of each school; measures included max 1-h and mean daytime O_3 values. Used either values averaged across all sites (for population regression model) or values from the site nearest the	**Highest of three evening peak expiratory flow rate (PEFR) measurements**

			challenge and doctor-diagnosed asthma. • Group 2 (n=60): Hx of wheeze in past 12 months and doctor-diagnosed asthma. • Group 3 (n=20): Hx of wheeze in past 12 months	child's school (for generalized estimating equation models). Lag periods: 0, 1, 2, 3, 4	
Jalaludin et al. (2004)(81)	Children from 6 elementary schools in Sydney Australia	Prospective cohort study	125 children • Group 1 (n=45): Hx of wheeze in past 12 months and positive histamine challenge and doctor-diagnosed asthma. • Group 2 (n=60): Hx of wheeze in past 12 months and doctor-diagnosed asthma. • Group 3 (n=20): Hx of	From air monitoring stations located within 2 km of each school; measures included max 1-h and mean daytime O_3 values. Used either values averaged across all sites (for population regression model) or values from the site nearest the child's school (for generalized estimating equation models). Lag periods: 0, 1, 2, 3, 4	**Respiratory symptoms (daily occurrence)**: wheeze, wet cough, dry cough **Asthma medication use (daily)** **Visit to a Dr for asthma (past 24 hours)**

			wheeze in past 12 months		
Ko et al. (2007)(42)	Hong Kong: hospitalization records for 15 major hospitals in Taiwan between Jan 2000 and Dec 2005	Retrospective ecological study (time series)	69,716 hospitalization episodes, including 23,596 children ages 0-14	Daily mean O_3 concentration between 9 am and 5 pm. Lag days: 0-5, cumulative lags (0-1,0-2,0-3,0-4,0-5)	**Hospitalizations**: with ICD=493.xx as primary diagnosis
Lewis et al. (2005)(97)	Two communities within Detroit MI (eastside and southwest) with high proportion of low-income residents from black and Latino ethnic groups	Prospective cohort study	298 children with current persistent asthma, per screening questionnaire (included parent report of respiratory symptom frequency, physician diagnosis of asthma, prescribed asthma medication use). Final study population include n=86 children with observed lung function tests.	Daily mean O_3 concentration, and daily maximum 8-hr average (i.e., 8-hr peak) for each of the two communities Conducted during 11 2-week seasonal measurement campaigns between Oct 1999 and May 2002	**Lung Function tests:** Peak flow (PF) and forced expiratory volume in 1 second (FEV_1) • Lowest daily value (lower of the morning and evening values for the day) • Diurnal variability (difference between morning and evening value divided by the larger of the 2 values for the day)

Lin et al. (2008)(98)	New York State birth cohort, births between Jan 1995 and Dec 1999 (excluding Staten Island)	Retrospective cohort study	1,204,396 eligible births, with 10,429 (0.87%) children hospitalized for asthma through 12/31/2000	Daily maximum hourly O_3 value between 10 am and 6 pm, averaged for each of 11 regions in the state. Constructed 3 exposure indicators per region: • mean concentration during follow-up period • mean concentration during ozone season (Apr-Oct) • exceedance proportion [% of follow-up days with O_3 levels >70 ppb {90^{th} percentile}] Also categorized exposure into tertiles for NYC and all other regions to analyze dose-response.	**Asthma hospital admissions:** between 1/1/1996 and 12/31/2000, with principal ICD9 diagnosis code of 493
McConnell et al. (2002)(51)	**Children's Health Study**: Twelve communities in Southern CA with low residential mobility	Prospective cohort	3,535 children ages 9-16 with no prior asthma diagnosis, recruited in 1993 and 1996, followed through 1998, annual follow-up survey	4-year mean O_3 levels per community: ('94-'97) • Daily mean 24-h • Daily mean 8-h • Daily maximum 1-h Communities were ranked based on 4-yr averages and dichotomized into the 6 with highest 4-yr means, and 6 with lowest 4-yr means.	**Incident asthma:** 'yes' response to 'Has a Doctor ever said you had asthma?' since prior year's survey
McConnell et al. (2003)(99)	**Children's Health Study**: Twelve communities in Southern CA with low residential mobility	Prospective cohort	475 children with asthma at study entry who completed 2+ follow-up questionnaires from 1996-1999	Annual average of 10am-6pm average O_3 levels and four-year mean levels (1996-1999) were calculated for each community.	**Bronchitic symptoms**: during previous year, child's report of daily cough for 3 months in a row, congestion or phlegm for at least 3 months in a row, or bronchitis.

McConnell et al. (2010)(47)	**Children's Health Study**: Twelve communities in Southern CA with low residential mobility	Prospective cohort	2,497 children with no history of wheeze or asthma	Daily average 8-h O_3, 10 am – 6 pm per community Local traffic related pollutant exposure incorporating monitoring data, as well as modeled values based on address of residence and school, distance to freeway/roadways, traffic density, modeled values of vehicle emissions.	**Incident asthma**: physician-diagnosed asthma reported on a yearly questionnaire during the 3 years of follow-up. Date of onset assigned as midpoint between the two questionnaire dates before and after the report of asthma.
Millstein et al. (2004)(100)	**Children's Health Study**: Twelve communities in Southern CA with low residential mobility, 2003-2005	Retrospective cohort/time series analysis	2,081 4th grade children	Monthly average levels of O_3 for each community, based on 8-h avg. between 10am-6pm	**Monthly prevalence of wheeze**: parent answered yes to 'Has your child's chest ever sounded wheezy or whistling, including times when he or she had a cold?' **Monthly asthma medication use** (children with physician-diagnosed asthma)
Moore et al. (2008)(101)	Southern California (Los Angeles and surrounding area)	Ecologic study	13,209,192	Quarterly average concentrations of 1-h daily maximum O_3; spatial interpolation (inverse distance weighting) used to estimate O_3 levels for each of 200 10 km x 10 km grids.	**Quarterly hospital discharges for asthma**: ICD9=493.xx, ICD10=J45/46 as first discharge code or as second if acute sinusitis or pneumonia was listed first; compiled per zip code -> grid
Mortimer et al. (2000)(102)	**National Cooperative Inner-City Asthma Study (NCICAS):** Children recruited from eight urban areas incl. Bronx and E Harlem NY,	Cross-sectional	846 children, ages 4-10	Daily average 8-h O_3, 10 am – 6 pm, per urban area June 1 1993 –August 31 1993 levels	**%PEFR:** daily % change from diary-specific median of peak flow readings **Incidence of symptoms**: occurrence of wheezing, cough or chest tightness among children who were symptom-free the previous day.

	Baltimore, Washington DC, Detroit, Cleveland, Chicago & St. Louis				
O'Connor et al. (2008)(103)	Inner-City Asthma Study; low income census tracts in Boston, the Bronx, Chicago, Dallas, New York, Seattle and Tucson, 8/1998 – 7/2001	Panel study	861 children, ages 5-12	Mean 1-h O_3 concentration for the 19 days prior to interview, averaged for each community	Symptoms reported by caretaker interview, per 2 week period: **Days with wheeze, tightness in chest, cough** **Nights child woke up because of asthma** **Days child slowed down or stopped play** **Number of school days missed**
Penard-Morand et al. (2005)(104)	Six French communities; children recruited from 108 randomly chosen schools	Cross-sectional	6,672 children, ages 9-11	Three-year averaged O_3 concentration for each school (1/1/1998 – 12/31/2000) address. Exposure classified two ways: • Low vs. high (i.e., above vs. below median at each school) • Continuous variable, per 10 μg/m^3 increase	**Exercise-induced bronchial reactivity (EIB)**:peak expiratory flow (PEF) decrease >10% after exercise (during clinical evaluation) **Flexural dermatitis**: itchy rash on elbow, knee, ankle, neck or eyes (during clinical evaluation) **Past year symptoms of wheeze, asthma, rhinoconjunctivitis, atopic dermatitis**: assessed on International Study of Asthma & Allergies in Childhood (ISAAC) questionnaire; asthma defined as combination of 'yes' to wheeze in past year and 'yes' to 'Has you child ever had asthma?' **Lifetime asthma, allergic rhinitis, atopic dermatitis**: from ISAAC questionnaire…'Has child ever had asthma/hay fever/eczema.'

					Lifetime atopy: 1+ positive skin prick test (SPT) to one of the 7 tested aeroallergens (i.e., pollen, indoor allergens, molds)
Petroeschevsky et al. (2001)(105)	Brisbane City, Australia (population ~ 763,000); daily hospital admissions between 1/1/1987 and 12/31/1994	Time-series study	13,246 admissions for asthma (all ages)	Daily average 8-h O_3, 10 am – 6 pm, and daily maximum 1-h concentration Lag periods used: 0, 1, 2, 3, 0-2, 0-4	**Daily (emergency) hospital admissions for asthma**: ICD9=493; daily counts of admissions to public hospitals by Brisbane residents
Rabinovitch et al. (2004)(106)	Denver CO; study conducted over 3 consecutive winters (Nov-Mar) with asthmatic children recruited from a single school.	Panel study	year 1: n=41, year 2: n=63, year 3: n=43; ages 6-12	Daily 1-h maximum O_3 '3-day moving average': Lag period 0-2 (presumed)	**Asthma symptom exacerbation**: based on daily reported need for inhaled steroids or prednisone; also, based on weekly reports of hospitalization, emergency or urgent care for asthma. Treated as a dichotomous variable.
Ramadour et al. (2000)(107)	L'Etang-de-Berre area of France, 30 km west of Marseille (highest O_3 levels in France due to petrochemical industry, heavy traffic, sun exposure).	Cross-sectional study	2,445 children, ages 13-14	Daily average 8-h O_3 for each town	**Prevalence of asthma and asthmatic symptoms:** based on children's questionnaire responses (history of asthma attack, wheeze ever, wheeze last 12 months, severe wheeze last 12 months)

	'Control' population sampled from Arles and Salon-de-Provence, nearby but further from industrial sites.				
Schildcrout et al. (2006)(48)	Eight North American cities (Albuquerque NM, Baltimore MD, Boston MA, Denver CO, San Diego CA, Seattle WA, St Louis MO, Toronto ON)	Meta-analysis of 8 large within-city panel studies	990 children, ages 5-12 years	Daily 1-h maximum O_3 for each city (May-Sept only) Lag periods used: 0, 1, 2, 0-2	**Daily record of asthma symptoms**: **0** = no asthma symptoms **1** = 1-3 mild asthma episodes, each lasting <=2h **2** = 4+ mild asthma episodes or 1+ that temporarily interfered with activity, play, school or sleep **3** = 1+ asthma episodes lasting >2h or resulting in shortening of normal activity, seeing a Dr for acute care or going to a hospital for acute care • Eventually dichotomized into 0 vs. 1-3 **Daily number of rescue inhaler puffs**
Szyszkowicz (2008)(108)	Edmonton Canada; daily asthma ER visits between 1/1/1992 and 3/31/2002	Time series	62,563 asthma ER visits over 3,652 days; ages 0-19 (n=30,396), ages 0-9 (n=18,891	Daily average 24-h O_3 Lag periods: L0, L1, L2	**Daily ER asthma visits**: discharge diagnosis of asthma (ICD9=493.xx)
Tolbert et al. (2000)(46)	Atlanta, GA; summers of 1993-1995	Ecologic, case-control, time series	128,969 pediatric ER visits and of these 5,934 (5%) were for asthma,	Daily average 8-h O_3, 1-day lag Daily maximum 8-h O_3 Used universal kriging to model O_3 concentration	**Asthma ER admissions:** from 7 of 8 major Atlanta-area ERs (handle 80% of pediatric emergency care in the city).

			among children ages 0-16		Any diagnosis of asthma (ICD9=493.xx), wheezing (ICD9=786.09) or reactive airway disease (ICD9=519.1) in diagnostic codes for the visit.
Wilhelm et al. (2008)(109)	Los Angeles and San Diego Counties, CA Sampled from **California Health Interview Survey** (assessing feasibility of linking CHIS and other data sources)	Cross-sectional	612 children ages 0-17, previously diagnosed with asthma by a physician	Annual average O_3 concentration, based on 1-h measurements; estimated for each subject based on nearest monitor within 5 miles of reported residential cross-street intersection, for the 1-year period prior to interview date.	During past 12 months: **Frequency of asthma symptoms (coughing, wheezing, shortness of breath, chest tightness, phlegm)** : dichotomized to children reporting daily/weekly symptoms in past year vs. those reporting less than weekly symptoms **Asthma hospitalization or ER visit**: dichotomized to children reporting 1 or more ER visit or hospitalization vs. those reporting none

Table 2. Confounders and effect modifiers assessed/included in studies

Source	Confounders	Effect Measure Modifiers
Akinbami et al. (2010)(41)	Age (at time of interview) Sex Parental education (<HS, HS or greater, unknown) Race (white, black, Am Indian, Asian, other, Puerto Rican, Mexican, other Hispanic) Adult smoker in household (yes, unknown) Single parent household Poverty status (based on reported income and US Census poverty thresholds) Region of residence (US Census regions: Northeast, South, Midwest, West)	
Babin et al. (2008)(78)	Tree pollen, grass pollen, weed pollen, mold spores, $PM_{2.5}$, PM_{10}, max/min daily temperature, daily average dew point temperature, day of the week	Age group (all, 5-12, 21-49) and ward (specific outcome estimates not provided)
Burra et al. (2009)(49)	Sex, maximum temperature, relative humidity, barometric pressure, day of the week	Income quintile (based on average census tract family income), age group (1-17, 18-64)
Fauroux et al. (2000)(79)	Daily average temperature and relative humidity Home visits by Paris ER doctor organization for flu-like symptoms Pollen counts (Betulae and Graminae) Month, day of the week Holidays	
Gent et al. (2003)(95)	Maximum daily temperature Co-pollutant models which included $PM_{2.5}$	Any maintenance medication use during the 183-day period (proxy for asthma severity)
Jaffe et al. (2003)(96)	Day of the week Minimum daily temperature Year Dispersion parameter An overall trend (presence of a linear time trend for the entire study period)	City
Jalaludin et al. (2000)(80)	Co-pollutants (PM_{10}, NO_2) Meteorological variables (temperature and humidity) Time trends (number of days since the start of the study)	Among children with history of wheeze, presence/absence of airway hyper-responsiveness to histamine challenge and presence/absence of a

	Season (Feb-Apr, May-Sep, Oct-Dec) Number of hours spent outdoors Total pollen and Alternaria counts	doctor diagnosis of asthma.
Jalaludin et al. (2004)(81)	Co-pollutants (PM_{10}, NO_2) Meteorological variables (temperature and humidity) Time trends (number of days since the start of the study) Season (Feb-Apr, May-Sep, Oct-Dec) Number of hours spent outdoors Total pollen and Alternaria counts	Among children with history of wheeze, presence/absence of airway hyper-responsiveness to histamine challenge and presence/absence of a doctor diagnosis of asthma.
Ko et al. (2007)(42)	Co-pollutants (NO_2, SO_2,PM_{10}, $PM_{2.5}$), mean daily temperature, mean daily relative humidity, day of the week, holiday indicator, season	Age group (0-14, 15-65)
Lewis et al. (2005)(97)	Child's sex, home location (eastside, southwest), annual family income (<$10,000, $10,000-$19,900, $20,000-$39,999, $40,000+) , presence of 1 or more smokers in the home, race (black, other), season, intervention group (vs. control group). Also included multi-pollutant models with $PM_{2.5}$ and PM_{10}	From daily medication & symptom diary completed by parent: Maintenance corticosteroid use (=[a] at least 7 of 14 diary days were completed, and [b] parent reported use of an inhaled or oral steroid for >=50% of the days that were completed. Presence of upper respiratory infection (='yes' to 'Does your child have a cold, the flu, or other respiratory infection today?')
Lin et al. (2008)(98)	Child's sex, birth weight (<=2500 g, >2500 g), gestational age (<260 days, >=260 days), age at admission or end of study (range, 1-6 yrs), maternal age at delivery (<20 or>35 yrs, 20-35 yrs), smoking status during pregnancy (yes, no), maternal race (black, other), ethnicity (Hispanic, non-Hispanic), education level (<12 yrs, >=12 yrs), insurance type during pregnancy (Medicaid, self-paid, other), geographic area (NYC, other). Also, census block-group information including median household income, % population below poverty level (highest quartile vs. others), hospital density (# hospitals per 100 km^2 in each ozone region. Proportion of days during entire follow-up period with extreme temperatures (90^{th} percentile of the daily average temperature [72.3° F] – compared highest quartile with all others); effects of co-pollutants using Air Quality Index (AQI) for PM_{10}, $PM_{2.5}$, NO_2, CO, SO_2 – cumulative AQI for each region was the average level of daily AQI during the follow-up period. Dropped hospital density,	Geographic region (NYC vs. other), child's age (1-2 vs. >2), % below poverty level (highest quartile vs. other), maternal education (<12 yrs v. >=12 yrs), Medicaid/self-paid birth vs. other insurance, ethnicity (Hispanic vs. non-Hispanic)

	median household income and AQI values in the final model.	
McConnell et al. (2002)(51)	Child's sex, age (<9.7 yrs, 9.7-11.49 yrs, 11.49+ yrs), race/ethnicity, history of allergies, reported time spent outdoors, current maternal smoking, history of asthma in either parent, membership of a health insurance plan, SES (low: <$15,000 income or if income not reported, <12th grade education; high: >=$100,000 family income or if not reported, postgraduate training; medium: all other; body mass index at baseline	Sports team participation (i.e., number of sports played)
McConnell et al. (2003)(99)	Child's sex, age, race, history of allergies, whether child smoked, *in utero* tobacco smoke exposure, family history of asthma in either parent, membership in a health insurance plan, low SES (<$15,000 income or <12th grade education), team sport participation, amount of time spent outdoor from 2-6 pm	
McConnell et al. (2010)(47)	Race/ethnicity, sex, age at study entry, exposure to cigarette and wildfire smoke, health insurance, housing characteristics, history of allergy, parental asthma	Source of exposure (home vs. school)
Millstein et al. (2004)(100)	Age, sex, race, allergies, pet cats, carpet in home, environmental tobacco smoke, heating fuel, heating system, water damage in home, education level of parent, physician-diagnosed asthma	Season, time typically spent outdoors
Moore et al. (2008)(101)	Race, income, quarterly average temperature, relative humidity, foreign born	
Mortimer et al. (2000)(102)	Occurrence of rain past 24-hrs (yes/no), wet-bulb temperature past 12-hrs, urban area, time of data collection (baseline, 3-, 6-, 9-mo assessment), day of study (since 6/1/1993); analyses stratified by time of day (morning vs. evening)	Sex, race, birth characteristics (normal vs. low BW, full-term vs. premature), atopy (0, 1-3, 4+), medications at baseline, household crowding, air conditioner, type of stove, allergen exposure (carpeting in bedroom [dust mite levels], cat in home, cockroaches in home, any antigen). Of these, results presented only for normal birth weight/full-term vs. LBW/premature
O'Connor et al. (2008)(103)	Site, month, temperature, call number, household environmental intervention group, monthly pollutant values by city	

Penard-Morand et al. (2005)(104)	Age, sex, family history of allergy (i.e., father or mother ever had asthma, allergic rhinitis or eczema), passive smoking (any current exposure to cigarettes/pipes/cigars in the home), parental education (highest parental school education)	
Petroeschevsky et al. (2001)(105)	Year, influenza admission, holiday indicator, day of the week, maximum and minimum temperature, humidity	Season
Rabinovitch et al. (2004)(106)	Temperature, humidity, barometric pressure, year, time trend, weekend, holiday, upper respiratory infection.	
Ramadour et al. (2000)(107)	Family history of asthma (at least one case among 1st-degree relatives), SES (assessed by occupation and presence of sibling in child's bedroom – low/med/high), smoking status (=smoker if smoked at least 1 cigarette daily for at least 6 months), passive smoking (# cigarettes smoked at home by family members), co-pollutants (SO_2, NO_2)	
Schildcrout et al. (2006)(48)	Day of the week, ethnicity (white, black, Hispanic/Latin, other), annual family income (<$15,000, $15,000-$29,999, $30,000-$49,999, $50,000+, no answer), age- and log-transformed sensitivity to the methacholine challenge, seasonal factors (temperature, humidity), calendar date, monthly pollutant values by city	
Szyszkowicz (2008)(108)	Temperature, relative humidity	Gender, age group (<10 , >=10 yrs), season (all, warm, cold)
Tolbert et al. (2000)(46)	Age (0-1.9, 2-5, 6-10, 11-16), race (black, white, other, unknown), sex, day of summer*year, Medicaid payment status	
Wilhelm et al. (2008)(109)	Race/ethnicity, poverty level, co-pollutants ($PM_{2.5}$, PM_{10}); age, sex, insurance status, delays in receiving asthma care, asthma medication use, county were dropped from final models	

Table 3. Summary of results

Source	Subgroup analysis	Measure of Association	95% Confidence Interval
Akinbami et al. (2010)(41)	**Current asthma**: 5 ppb increase Quartiles (2^{nd}, 3^{rd}, 4^{th} compared to 1^{st}) **Asthma attack**: 5 ppb increase Quartiles (2^{nd}, 3^{rd}, 4^{th} compared to 1^{st}) O_3 levels: median=39.8 ppb, IQR=35.9-43.7 ppb Quartiles: 2.3-11.7, 11.8-21.2, 21.3-30.7, 30.8-40.2 ppb	 OR = 1.08 [adjusted] OR = 0.99, 1.09, 1.56 [adjusted] OR = 1.07 [adjusted] OR = 0.89, 0.98, 1.38 [adjusted]	(1.02, 1.14) (0.78, 1.26), (0.85, 1.41), (1.15, 2.10) (1.00, 1.13) (0.67, 1.17), (0.73, 1.32), (0.99, 1.91)
Babin et al. (2008)(78)	**% Average change in general acute care visits for asthma**: (per 0.01 ppm increase in max 8-h average O_3) Ages 5-12	 Percent change: 2.4%	 (0.2%, 4.6%)
Burra et al. (2009)(49)	**Asthma ambulatory visits**, ages 1-17: (per 20 ppb) Males • Q1 (lowest SES) • Q5 (highest SES) • Q1/Q5 Females • Q1 (lowest SES) • Q5 (highest SES) • Q1/Q5 (Lag 0 listed above but results for other lag periods were similar) O_3 levels: mean 1-h max=33.3 ppb, max 1-h max=121 ppb, IQR=20 ppb	 0.961 0.966 0.995 0.955 0.962 0.993	 (0.956, 0.966) (0.961, 0.972) (0.994, 0.995) (0.949, 0.961) (0.955, 0.969) (0.983,1.003)

Fauroux et al. (2000)(79)	**Asthma ER visits**: (per 100 µg/m^3 increase) Lag 0 Lag 1 Lag 2 O_3 levels: mean=31.0 µg/m^3, min/max=1.5-133 µg/m^3	 RR = 1.15 RR = 1.52 RR = 1.01	 (0.80, 1.66) (1.06, 2.19) (0.70, 1.47)
Gent et al. (2003)(95)	**Respiratory Symptoms**: (per 50 ppb same day increase in 1-h avg.) Wheeze Chest tightness **Respiratory Symptoms**: (8-h avg. >= 63.3 ppb, same day) Chest tightness Shortness of breath Bronchodilator use O_3 levels: mean 1-h avg.=59 ppb, mean 8-h avg.=51 ppb Quintiles (1-h): <43.2, 43.2-51.5, 51.6-58.8, 58.9-72.6, >=72.7 ppb Quintiles (8-h): <39.1, 39.1-45.8, 45.9-52.0, 52.1-63.2, >=63.3 ppb	 OR = 1.35 OR = 1.47 OR = 1.64 OR = 1.45 OR = 1.09 [all results are for maintenance medication users; no significant associations with non-users]	 (1.11, 1.65) (1.18, 1.84) (1.23, 2.17) (1.10, 1.91) (1.02, 1.17)
Jaffe et al. (2003)(96)	**Percent change in ED visits for asthma** (per 0.01 ppm increase in O_3) **Attributable risk for an asthma ED visit** (per 0.01 ppm increase in O_3)	Percent Change: 3% Cincinnati: 0.60; Cleveland: 0.11; Columbus: 0.57	(0, 6%)
Jalaludin et al. (2000)(80)	**Daily mean deviation in PEFR and same-day O_3 concentration** All children Group 1 Group 2 Group 3	 B-coefficient = -0.88 B-coefficient = -2.61 B-coefficient = -0.36 B-coefficient = 1.91	 p = 0.04 p = 0.001 p = 0.46 p = 0.04

Jalaludin et al. (2004)(81)	**All children** Wheeze Dry cough Wet cough Inhaled β_2-agonist use Inhaled corticosteroid use Doctor visit for asthma [no significant associations by group or lag time for O_3] O_3 levels: mean 24-h avg.=1.2 pphm, max=4.3 pphm, IQR=0.83 Quartile (24-h avg) means: 0.58, 1.03, 1.49, 2.34 pphm	 OR = 0.98 OR = 0.97 OR = 1.00 OR = 0.97 OR = 0.98 OR = 0.89	 (0.89, 1.09) (0.88, 1.07) (0.93, 1.07) (0.91, 1.03) (0.95, 1.02) (0.64, 1.24)
Ko et al. (2007)(42)	**Asthma Hospitalizations**: (per 10 $\mu g/m^3$ increase in O_3) Single pollutant model, ages 0-14 ('best' lag: cumulative 0-5)	RR = 1.039	(1.030, 1.048)
Lewis et al. (2005)(97)	Greater association with O_3 daily 8-hr peak levels than daily mean. No significant associations seen for children not on CSs, and little effect seen for children not reporting URIs. Strongest effects seen for lag 1 and lag 2, not for lag 3-5. **Single Pollutant Model:** O_3 daily 8-hr peak Diurnal variability FEV1, per 1 IQR (children on maintenance CSs) • Lag 1 • Lag 2 Lowest daily value FEV1, per 1 IQR (children on maintenance CSs) • Lag 1 • Lag 2 Diurnal variability FEV1, per 1 IQR (children reporting URI on that day) • Lag 1 • Lag 2	 Coefficient = 1.75 Coefficient = 3.19 Coefficient = -1.00 Coefficient = -3.95 Coefficient = 5.79 Coefficient = 4.74 Coefficient = -3.00 Coefficient = -2.64	 (-0.20, 3.70) (0.29, 6.08) (-5.68, 3.68) (-6.78, -1.12) (1.74, 9.85) (0.46, 9.02) (-5.16, -0.84) (-5.45, 0.18)

	Lowest daily value FEV1, per 1 IQR (children reporting URI on that day) • Lag 1 • Lag 2 **O_3 levels:** Daily mean: 27.6 ppb (Eastside), 26.5 ppb (Southwest), IQR=14.5 Daily peak 8-hr mean: 40.4 ppb (Eastside), 41.4 ppb (Southwest), IQR=16.0		
Lin et al. (2008)(98)	**Asthma Hospitalizations** (per 1-ppb increase/day) Mean concentration during follow-up period Mean concentration during ozone season Exceedance proportion (%)>70 ppb with IQR increase Child's age (month) / 1-2 vs. >2 Race (black vs. other) Sex (female vs. male) Ethnicity (Hispanic vs. non-Hispanic) Birth weight (low vs. normal) Poverty level (highest quartile vs. other) Maternal insurance (Medicaid vs. other) / Medicaid & self-paid vs. other **O_3 levels:** Mean during entire follow-up period=41.06 ppb Mean during O_3 season=50.62 ppb Exceedance proportion IQR=2.51% increase, avg=9.72%, range 1.66-26.27% Tertiles (NYC): 31.46-37.29, 37.30-38.11, 38.12-50.13 ppb Tertiles (NY State): 33.50-42.57, 42.58-45.06, 45.07-55.19 ppb	**Overall / Stratified** OR = 1.16 OR = 1.22 OR = 1.68 OR = 0.93 / 1.29 vs. 1.03 OR = 1.97 OR = 0.58 OR = 1.99 / 1.27 vs. 1.13 OR = 1.55 OR = 1.21 / 1.25 vs. 1.14 OR = 1.26 / 1.22 vs. 1.11	**Overall only** (1.15, 1.17) (1.21, 1.23) (1.64, 1.73) (0.93, 0.94) (1.88, 2.07) (0.56, 0.61) (1.89, 2.09) (1.44, 1.67) (1.15, 1.27) (1.19, 1.33)
McConnell et al. (2002)(51)	**Asthma Incidence (IR) and relative risks (RR)** <u>Low ozone communities</u> 0 sports played 1	 IR = 0.027, RR = 1.0 IR = 0.033, RR = 1.3	 (0.9, 1.9) (0.5, 1.4)
		IR = 0.023, RR = 0.8	(0.4, 1.6)

	2 >=3 <u>High ozone communities</u> 0 sports played 1 2 >=3 **O_3 levels – Low ozone communities** (4-yr median / range): Maximum 1-h O_3: 47.6 ppb / 37.7-67.9 ppb Mean 8-h O_3: 40.7 ppb / 30.6-50.9 ppb Mean 24-h O_3: 25.1 ppb / 20.6-28.7 ppb **O_3 levels – High ozone communities** (4-yr median / range): Maximum 1-h O_3: 73.5 ppb / 69.3-87.2 ppb Mean 8-h O_3: 56.9 ppb / 55.8-69.0 ppb Mean 24-h O_3: 33.1 ppb / 30.7-59.8 ppb	IR = 0.019, RR = 0.8 IR = 0.018, RR = 1.0 IR = 0.021, RR = 1.3 IR = 0.020, RR = 1.3 IR = 0.050, RR = 3.3	 (0.8, 2.0) (0.7, 2.3) (1.9, 5.8)
McConnell et al. (2003)(99)	**Bronchitic symptoms**: (per 1 ppb increase in O_3) Between communities Within communities O_3 levels (4-yr avg.): mean=47.2 ppb, min-max=28.3-65.8 ppb	 OR = 0.99 OR = 1.06	 (0.98, 1.01) (1.00, 1.12)
McConnell et al. (2010)(47)	**New onset asthma**: (per 30.3 ppb increase in O_3) Adjusted for age, race, sex, random effects for community/school Adjusted also for traffic-related pollution at home and school O_3 levels (4-yr avg.): mean=44.6 ppb, min-max=29.5-59.8 ppb, IQR=11.1 ppb	 HR = 0.76 HR = 1.01	 (0.38, 1.54) (0.49, 2.11)
Millstein et al. (2004)(100)	**Monthly prevalence of asthma medication use**: (per IQR=27.83 ppb increase in O_3) Annual	 1.80	 (1.19, 2.70)

	Mar-Aug Sep-Feb **Monthly prevalence of wheeze**: (per IQR=27.83 ppb increase in O_3) Annual Mar-Aug Sep-Feb **Monthly prevalence of wheeze**: (per IQR=27.83 ppb increase in O_3) Time spent outdoors above the median Time spent outdoors below the median	2.35 1.31 0.84 2.87 0.55 3.07 1.13	(0.92, 6.05) (0.57, 3.01) (0.62, 1.14) (0.65, 12.63) (0.34, 0.90) (1.61, 5.86) (0.47, 2.71)
Moore et al. (2008)(101)	**Number of asthma discharges**: (for each 10 ppb increase in quarterly average 1-h maximum O_3) **Proportion of asthma discharges at median O_3 concentration (87.7 ppb)**: (for each 10 ppb increase above the median)	1.4 discharges/105 age-eligible population 4.6% increase in discharges	(0.71, 2.09 per 105 popn)
Mortimer et al. (2000)(102)	**%PEFR (morning)**: (for each 15 ppb increase in O_3 concentration) Normal BW and full-term LBW or premature **Incidence of morning symptoms**: (for each 15 ppb increase in O_3) Normal BW and full-term LBW or premature O_3 levels: mean across cities: 48 ppb; <5% of days exceeded 80 ppb (8-h mean) Strongest effect seen in 3-5 day averaged lag	 -0.30% -1.83% OR = 1.09 OR = 1.42	 (-0.79 - 0.19) (-2.65 - 1.01) (0.95, 1.24) (1.10, 1.82)
O'Connor et al. (2008)(103)	Comparison of 90th to 10th percentile change (26.7 ppb):	('pollution impact' measures % change in symptom frequency – based on coefficient of negative	

	Wheeze-cough days/2 wk **Nighttime asthma, nights/2 wk** **Slow play-days/2 wk** **Missed school, >= 1 vs. 0 days/d wk**	binomial model) Pollution Impact = 1.03 Pollution Impact = 0.85 Pollution Impact = 0.87 OR = 1.31	(0.82, 1.28) (0.64, 1.14) (0.67, 1.14) (0.83, 2.06)
Penard-Morand et al. (2005)(104)	**Past year asthma** (per 10 µg/m^3 increase in O_3) **Past year wheeze** (per 10 µg/m^3 increase in O_3) **Lifetime asthma** (per 10 µg/m^3 increase in O_3) O_3 levels (3-yr avg.): 'Low': mean=34.1 µg/m^3, range=30.0-39.3 µg/m^3 'High': mean=50.9 µg/m^3, range=43.7-63.7 µg/m^3 57.6% of children were in schools with high exposure	OR = 1.11 OR = 1.12 OR = 1.09	(0.94, 1.30) (0.98, 1.28) (0.97, 1.22)
Petroeschevsky et al. (2001)(105)	**Asthma Hospital Admissions** (per 1 pphm increase in 8-hr mean O_3) **O_3 levels:** 8-hr: mean=1.90 pphm, min-max=0.17-6.47 pphm 1-hr max: mean=2.53 pphm, min-max=0.25-10.73 pphm	RR = 1.064	(1.015, 1.115)
Rabinovitch et al. (2004)(106)	**Asthma symptom exacerbation** (per 1 SD increase in O_3 = 11.4 ppb) **Mean days with symptoms** (per 1 SD increase in O_3) (no associations with pulmonary function or medication use) **O_3 levels:** 1-hr max: mean=28.2 ppb, min-max=0-70 ppb	OR = 0.910 OR = 1.083	(0.785, 1.056) (1.002, 1.170)
Ramadour et al. (2000)(107)	**Regression analysis:** average O_3 level vs. prevalence 'ever asthma' **Regression analysis:** average O_3 level vs. prevalence 'wheezing past 12 mos' **Logistic Regression** (per 1 µg/m^3 increase in O_3) 'Ever asthma' by family history of asthma 'Ever asthma' by history of respiratory disease in infancy	R = 0.959 R = 0.714 OR = 3.01 OR = 4.3 OR = 2.5 OR = 4.3	p < 0.001 p < 0.05 (2.05, 4.43) (2.7, 6.9) (1.7, 3.6) (2.7, 7.0)

	12-mth history of wheezing by family history of asthma 12-mth history of wheezing by history of respiratory disease in infancy		
Schildcrout et al. (2006)(48)	**GEE analysis** (single pollutant model, per 30 ppb increase in max 1-h O_3) **Asthma symptoms** Lag 0 Lag 1 Lag 2 Lag 0-2 **Inhaler Use** Lag 0 Lag 1 Lag 2 Lag 0-2 **O_3 levels:** medians (ppb) Albuquerque 55.0, Baltimore 65.8, Boston 52.2, Denver 60.5, San Diego 59.3, Seattle 43.0, St. Louis 59.3, Toronto 43.5	 OR = 1.06 OR = 1.00 OR = 1.02 OR = 1.01 OR = 1.01 OR = 0.99 OR = 1.00 OR = 1.00	 (0.92, 1.23) (0.88, 1.14) (0.92, 1.13) (0.94, 1.09) (0.92, 1.10) (0.92, 1.06) (0.95, 1.06) (0.95, 1.04)
Szyszkowicz (2008)(108)	**% Change in relative risk for ED visits** (per IQR increase in 24-h mean O_3) Lag 0 • Full year • Warm season • Cold season Lag 1 • Full year • Warm season • Cold season **O_3 levels:** 24-hr mean=18.6 ppb, IQR=14.0 ppb	 %RR = 8.4% %RR = 10.8% %RR = 10.1% %RR = 5.2% %RR = 7.3% %RR = 6.4%	 (4.0, 12.9) (4.1, 18.0) (4.1, 16.3) (1.0, 9.6) (0.7, 14.3) (0.7, 12.5)

Tolbert et al. (2000)(46)	**GEE analysis** – rate ratio per 20 ppb increase in max 8-h O_3	RR = 1.040	(1.008, 1.074)
	Logistic regression analysis - per 20 ppb (?) increase in max 8-h O_3		
	Overall (kriged, 8-hr avg., 1-day lag)	OR = 1.04	(1.02, 1.07)
	Black vs. white	OR = 2.17	(2.03, 2.31)
	Male vs. female	OR = 1.40	(1.33, 1.48)
	Medicaid vs. non-Medicaid	OR = 1.25	(1.18, 1.33)
	>=100 ppb vs. <50 ppb	OR = 1.23	(1.07, 1.40)
	O_3 levels: Mean 8-h avg.=59.3 ppb, range=18.2-113 Mean 1-h avg.=68.8 ppb, range=22.8-132		
Wilhelm et al. (2008)(109)	**Daily/weekly asthma symptoms** (per 1 pphm increase in O_3)		
	• Single pollutant model, crude	OR = 1.96	(1.23, 3.13)
	• Single pollutant model, adjusted for race/ethnicity, poverty level	OR = 2.09	(1.28, 3.41)
	• Two pollutant model, adjusted for PM_{10}, race/ethnicity, poverty level	OR = 2.29	(1.01, 5.23)
	• Two pollutant model, adjusted for $PM_{2.5}$, race/ethnicity, poverty level	OR = 3.51	(1.45, 8.46)
	ED visit or hospitalization (per 1 pphm increase in O_3)		
	• Single pollutant model, crude	OR = 1.16	(0.74, 1.81)
	• Single pollutant model, adjusted for race/ethnicity, poverty level	OR = 1.35	(0.85, 2.14)
	• Two pollutant model, adjusted for PM_{10}, race/ethnicity, poverty level	OR = 2.89	(1.32, 6.34)
	• Two pollutant model, adjusted for $PM_{2.5}$, race/ethnicity, poverty level	OR = 2.48	(1.14, 5.38)
	O_3 levels: annual mean=2.1 pphm, range: 1.1 - 4.2 pphm		

Table 4. Strengths and limitations of studies reviewed

Source	Strengths	Limitations
Akinbami et al. (2010)(41)	• Large sample, representative of US metropolitan areas • Availability of numerous potential person-level confounders (age/race/sex, smoker in household, poverty status, etc.) • Analysis of multi-pollutant models • Estimation of effects at relatively low ambient O_3 levels	• Possible exposure misclassification from the use of aggregate (county-level) air pollution measures for estimating personal exposure • Potential misclassification bias related to the assumption that subjects resided at the same address for the entire 12-month study period • Possible confounding from unavailability of co-pollutant estimates for a large number of subjects, unmeasured person-level factors (asthma medication use, genetic factors, smoking status, family history of smoking, respiratory allergies), lack of meteorological data, and no ability to account for season-varying exposure levels
Babin et al. (2008)(78)	• Large sample size with 11-year follow-up • Analysis of children at high-risk of asthma (Medicaid beneficiaries) • Investigation of differing effects by SES indicators/area of residence and age group • Inclusion of aeroallergens	• Ecologic design – potential for unmeasured confounders • Possible exposure misclassification due to averaging of ozone measurements over study area
Burra et al. (2009)(49)	• Large claims database covering ~95% of ambulatory physician visits in Toronto • Wide gradient of estimated family incomes in groups compared	• Possible exposure misclassification re: socioeconomic position (SEP) due to census-tract level assignments, the limited network of monitoring sites (n=6) used to estimate exposure across the entire city • Possible selection bias due to unavailability of emergency department claims records – may be related to SEP • Potential for confounding as models unadjusted for person-level factors, multiple pollutants, seasonal allergies , respiratory infections, weather patterns, transportation patterns

Fauroux et al. (2000)(79)	• Adjusted for potential confounders influenza patterns and outdoor allergens • Several lag periods evaluated	• Possible exposure misclassification due to averaging of ozone measurements over study area • Short one-year follow-up period & small sample size (mean 3 ER visits per day) • No adjustment for person-level confounders or co-pollutants
Gent et al. (2003)(95)	• Minimized information bias through frequent phone follow-up to collect outcome data • Co-pollutant models including $PM_{2.5}$ • Included both 1-h peak and 8-h average O_3 measurements • Used maintenance medication use to determine asthma severity	• Possible exposure misclassification due to averaging of ozone measurements over study area • Possible uncontrolled confounding due to lack of person-level information (i.e., race), although handled somewhat through study design
Jaffe et al. (2003)(96)	• Effects analyzed between major cities	• Ecologic design – potential for unmeasured confounders • Potential for exposure misclassification by use of maximum O_3 measure for each city each day
Jalaludin et al. (2000)(80)	• Evaluated several single-day and cumulative lag periods • Multi-pollutant models were considered • Longitudinal design • Adjusted for potential confounders including time spent outdoors and outdoor allergens • Evaluated effect modification in different susceptibility groups • O_3 level based on monitor nearest child's school • Several lag periods evaluated	• Low variability in ambient ozone levels • Relatively small sample size and short follow-up period • Possible selection bias: over ¼ of subjects withdrew early in the study and ~15% were excluded because they had fewer than 30 diary days for the 11-month period • Potential outcome misclassification due to use of evening measures in the analysis rather than morning measures
Jalaludin et al. (2004)(81)	• Evaluated several single-day and cumulative lag periods • Multi-pollutant models were considered • Separate analyses by season • Longitudinal design • Evaluated effect modification in different susceptibility groups • O_3 level based on monitor nearest child's school • Several lag periods evaluated	• Low ambient ozone levels (mean 12 ppb, max 26 ppb) • Relatively small sample size and short follow-up period • Possible selection bias: over ¼ of subjects withdrew early in the study and ~15% were excluded because they had fewer than 30 diary days for the 11-month period • Potential outcome misclassification due to use of evening measures in the analysis rather than morning measures • Uncontrolled confounding…data were available on person-level confounders but the authors don't state that these variables were included in the logistic regression models.

Ko et al. (2007)(42)	• Long (6-yr) follow-up using claims database with large study population (captured >90% of the Hong Kong patient population) • Assessment of several single-day and cumulative lag periods, and multi-pollutant models • Wider variability of O_3 monitoring results than seen in other studies	• Unmeasured person-level confounding resulting from ecologic design • Potential for exposure misclassification by averaging O_3 monitoring results across the entire study area for the daily measures
Lewis et al. (2005)(97)	• Assessment of lung function across seasons (not clear whether O_3 was evaluated across seasons or only in a single winter) • FEV_1 assessment of lung function, observed to ensure validity of measures • Identification of children with greater susceptibility (on maintenance meds and reporting URIs) • Assessment of co-pollutants, particularly PM_{10} and $PM_{2.5}$	• Small sample size (n=86); possible selection bias related to this subset of original cohort of 510 – 36% of those eligible chose not to participate, 16% of remaining children were lost to follow-up, and final 86 were chosen based on other whether children enrolled in the study attended their school • Ozone measurements only available for 1 winter for lung function assessment • Potential for exposure misclassification by excluding outlying FEV_1 measurements, and relying on parent report for use of maintenance medications • Potential for unmeasured confounding due to lack of data on person-level factors
Lin et al. (2008)(98)	• Large study population, from integrated dataset including health outcomes, child and maternal information and air pollution assessment data • Evaluation of numerous person- and community- level confounders, and effect modification by maternal/infant factors • Assessment of several exposure metrics reflecting both chronic and acute exposures • Retrospective cohort design	• Some remaining uncontrolled confounding such as genetic susceptibility, • Potential exposure misclassification due to limited availability on residential address changes, and no personal exposure estimates based on time activity patterns • Possible selection bias as only most severe cases would likely be captured when looking at hospital admissions
McConnell et al. (2002)(51)	• Prospective cohort design • One of the few studies on asthma incidence in children • Availability of data on potential person- and household level confounders including children's outdoor activity patterns • Study conducted in high ozone area of the U.S. (southern CA)	• Potential exposure misclassification due to inclusion of only sports team participation, not individual physical activity including running and cycling; also, communities dichotomized into high and low exposure based on median levels of annual 24-hr mean O_3 values • Possible disease misclassification due to self-reported (not clinically-confirmed) asthma diagnosis; in some cases, asthma questions answered by children (?), not

		the parent
McConnell et al. (2003)(99)	• Prospective cohort design • Availability of data on potential person- and household level confounders including *in-utero* tobacco exposure, family history of asthma, health insurance coverage • Study conducted in high ozone area of the U.S. (southern CA)	• Possible disease misclassification due to self-reported (not clinically-confirmed) asthma diagnosis • Recall bias likely as number of continuous days with asthma symptoms was assessed only annually • Possible unmeasured confounding by indoor/outdoor allergens • Potential for exposure misclassification based on community-level O_3 exposure assessments, and low annual variability within the 12 communities
McConnell et al. (2010)(47)	• Prospective cohort design • Availability of data on potential person- and household level confounders, including parental asthma, housing characteristics, exposure to cigarette and wildfire smoke • Study conducted in high ozone area of the U.S. (southern CA) • Estimate of main effects from traffic related pollution, in addition to ambient pollutant levels, and effects from exposures at school and at home	• Relatively short follow-up period • Possible unmeasured confounding as early life risk factors were assessed retrospectively • Possible selection bias due to loss to follow-up; Hispanic children and those with lower parental education and no insurance were more likely lost to follow-up
Millstein et al. (2004)(100)	• Retrospective cohort design • Availability of data on potential person- and household level confounders, including time spent outdoors • Study conducted in high ozone area of the U.S. (southern CA)	• Possible disease misclassification due to parent-reported monthly asthma medication use and wheezing, and possible lack of precision in estimating month of wheeze occurrence • Recall bias likely as symptoms and medication use assessed up to 12 months prior • Potential for exposure misclassification based on single monitoring site used to estimate community-level O_3 exposure, averaged monthly
Moore et al. (2008)(101)	• Long follow-up period and large population size • More sophisticated statistical analysis and O_3 modeling methods than in other studies • O_3 estimates at residence zip code level • Study conducted in high ozone area of the U.S. (southern CA)	• Potential for confounding as analysis used community level variables from census data rather than person-level data • Possible exposure misclassification as O3 levels were modeled as quarterly averages

	• Multi-pollutant models considered	
Mortimer et al. (2000)(102)	• Availability of data on potential person- and household level confounders, including parental smoking, housing characteristics, children's allergies • Inner-city population at increased risk of asthma • Analysis of susceptible sub-groups	• Potential for exposure misclassification: i.e., LBW was based on maternal self-report, not medical records; also, medication use reported at baseline interview (up to 6 months prior to symptoms recorded in daily diaries) and may have changed in the interim; no daily medication use collected • Potential for unmeasured confounding: single-pollutant models only, no data collected on aeroallergens • Short follow-up period (1 summer)
O'Connor et al. (2008)(103)	• Inner-city population at increased risk of asthma • Analysis of single and multi-pollutant models • Various lag periods analyzed • Estimation of effects at elatively low ambient O_3 levels	• Potential for exposure misclassification based on community-level O_3 exposure assessments • Possible recall bias; symptoms reported by caretakers at end of each 2-wk period, no daily diary mentioned • Possible selection bias as ½ of the sample were enrolled in a household environmental intervention group
Penard-Morand et al. (2005)(104)	• Availability of data on potential person-level confounders, including parental smoking and education, history of allergy	• Potential for exposure misclassification based on 3-yr averaged values at each school, and dichotomized exposure categories • Outcomes defined broadly ('problem with sneezing, or a running or blocked nose ..in past 12 months'), not clinically confirmed (i.e., diagnosis of asthma) and required recall of up to 12 months at a time.
Petroeschevsky et al. (2001)(105)	• Long follow-up period and large population size • Multi-pollutant models considered • Various lag periods analyzed	• Potential for exposure misclassification based on city-wide O_3 exposure assessments
Rabinovitch et al. (2004)(106)	• Daily diaries assessing symptoms/medication use • Supervised pulmonary function testing • Various lag periods analyzed	• Small panel study • Study period did not include summer months • No measurement of individual susceptibility or exposure
Ramadour et al. (2000)(107)	• High participation rate • Availability of data on potential person-level confounders	• Cross-sectional survey • Potential for exposure misclassification based on O_3 exposure assessments by town

		• Possible outcome misclassification since surveys were filled out by 13 and 14 year old children, with no clinical confirmation • Possible recall bias since symptoms were assessed up to 12 months prior
Schildcrout et al. (2006)(48)	• Relatively large study in 8 cities spread across the U.S. • 22-month follow-up, assessment across seasons • Supervised (family) daily recording of symptoms by the children • Various lag periods analyzed • Single and two-pollutant models analyzed • Inclusion of some person-level potential confounders	• Potential for exposure misclassification based on O_3 exposure assessments by city • Sample size may have been too small for season-specific analyses, pertinent for O_3
Szyszkowicz (2008)(108)	• Large sample size with 10 years of follow-up	• Potential for exposure misclassification based on O_3 exposure assessments across the city
Tolbert et al. (2000)(46)	• Large sample of pediatric asthma ER visits, with data collected over 3 summer seasons • Used kriging to model O_3 exposure • Adjustment for some potential confounders (age, race, Medicaid enrollment) • Relatively high ambient O_3 levels, with significant variability across zip codes and during study period • Single and two-pollutant models analyzed • Used 3 types of analysis: GEE, logistic regression, Bayesian and found consistent results	• Potential for exposure misclassification based on O_3 exposure assessments across the city • Limited data available on potential confounders (i.e., time spent indoors, A/C usage, exposure to cigarette smoke) • Possible selection bias – study excluded 1 ER which did not agree to participate (20% of Atlanta-area ER visits); also did not include those presenting to facilities other than ERs – may be differential by SES, etc.
Wilhelm et al. (2008)(109)	• Data collected on a number of potential confounders including tobacco smoke exposure, indoor allergens, parental history of asthma, breast feeding history • Data sampled from large, population based survey • Ozone estimates based on nearest monitoring site (within 5 miles) • Study included estimates of traffic related pollution	• Cross-sectional survey • Potential for exposure misclassification resulting from address assessment (and corresponding O_3 exposure estimate) at one point in time; also, O3 exposure assigned as annual average of nearest monitor, not taking into account time spent outdoors, time activity patterns, etc. • Possible outcome misclassification resulting from self-reported physician-diagnosed asthma • Possible recall bias from reporting symptoms up to a

		year prior • Potential selection bias – survey data the sample was drawn from had a 40% non-response rate

Appendix B. Summary of case-crossover studies which have evaluated air pollution and childhood asthma

Table 1. Summary of study design

Source	Setting	Study Design	Sample Size	Definition of Exposure	Definition of Outcome
Barnett et al. (2005)(71)	Five large cities in Australia (Brisbane, Canberra, Melbourne, Perth, Sydney) and two in New Zealand (Auckland, Christchurch), 1998-2001	Time-stratified	~2.5 million children ages 0-14	24-h $PM_{2.5}$, IQR=3.8 $\mu g/m^3$ 24-h PM_{10}, IQR=7.5 $\mu g/m^3$ 1-h NO_2, IQR=9.0 ppb 24-h NO_2, IQR=5.1 ppb 8-h CO, IQR=? 1-h SO_2, IQR=5.4 ppb 1-h O_3, IQR=9.8 ppb 24-h BSP, IQR=0.18*10^{-4}/m • Pollutant data averaged across all monitors in each city • Measures reflect average of current and previous day • Effect measured per IQR (mean across all cities) of each pollutant	**Daily respiratory hospital admissions**; based on ICD diagnosis codes for Total Respiratory Disease, Asthma, Pneumonia and Acute Bronchitis
Hinwood et al. (2006)(72)	Perth, Australia, 1992-1998	Time-stratified	~500,000 hospitalizations/yr (sample size not reported by age or diagnosis, i.e. asthma; mean asthma hospitalizations per day for children <15 was	1-h max O_3 4-h max O_3 8-h max O_3 1-h max NO_2 24-h avg NO_2 1-h max BSP 24-h avg BSP 8-h max CO	**Daily hospital admissions**, asthma results reported separately, based on primary discharge in the patient's chart (ICD9=493)

			5.6)	24-h avg PM_{10} 24-h avg $PM_{2.5}$ (modeled) Data from three monitoring sites used to estimate daily pollutant levels city-wide Lag periods: L0, L1, L2, L3, L01, L02, L03	
Jalaludin et al. (2008)(68)	Sydney, Australia, 1997-2001	Time-stratified	1,826 emergency department visits for pediatric asthma, ages 1-14	24-h $PM_{2.5}$, IQR=4.8 $\mu g/m^3$ 24-h PM_{10}, IQR=7.6 $\mu g/m^3$ 1-h NO_2, IQR=9.5 ppb 8-h CO, IQR=0.7 ppm 24-h SO_2, IQR=0.8 ppb 1-h O_3, IQR=13.6 ppb Daily pollutant values averaged across all monitors in the city Lag periods: L0, L1, L2, L3, L01	**Emergency Department visits for asthma**; based on ICD9 diagnosis code of 493.xx
Laurent et al. (2008)(82)	Strasbourg, France, 2000-2005	Time-stratified	446,905 residents No. of asthma ER calls: n=4,677 (all ages), n=954 (ages 0-19)	24-h avg PM_{10} (Jan-Dec) 24-h avg NO_2 (Jan-Dec) 24-h avg SO_2 (Jan-Dec) 8-h max O_3 (Apr-Sep) Daily concentrations modeled for each census block Lag periods: L0, L01, L02, L03, L04, L05	**Telephone calls to a pre-hospital emergency center for an 'asthma attack'**; (not defined)
Lin et al.	Toronto, Ontario, 1981-	Bi-directional and uni-	7,319 asthma	24-h avg $PM_{2.5}$, IQR=9.3	**Asthma**

(2002)(110)	1993	directional; also used time-series analysis	hospitalizations for children ages 6-12	µg/m^3 24-h avg $PM_{10-2.5}$, IQR=8.4 µg/m^3 24-h avg PM_{10}, IQR=14.8 µg/m^3 Daily pollutant values averaged across all monitors in the city Lag periods: L0, L01, L02, L03, L04, L05, L06	**hospitalizations**, defined as an admission for which asthma (ICD9=493.xx) was the primary diagnosis responsible for the highest number of hospital days of stay; restricted to children living in and hospitalized in Toronto
Lin et al. (2003)(111)	Toronto, Ontario, 1981-1993	Bi-directional	7,319 asthma hospitalizations for children ages 6-12	24-h avg CO, IQR=0.5 ppm 24-h avg SO_2, IQR=7 ppb 24-h avg NO_2, IQR=11 ppb 1-h max O_3, IQR=20 ppb Daily pollutant values averaged across all monitors in the city Lag periods: L0, L01, L02, L03, L04, L05, L06	**Asthma hospitalizations**, defined as an admission for which asthma (ICD9=493.xx) was the primary diagnosis ; restricted to children living in and hospitalized in Toronto
Paulu and Smith (2008)(112)	State of Maine, 2000-2003	Time-stratified	8,020 asthma ER visits, n=1,430 for children ages 2-14	8-h max O_3 (primary exposure) 24-h avg $PM_{2.5}$ Values interpolated (using kriging) to estimate daily ambient levels at each zip code centroid, mid-May through mid-Sept	**Asthma ER visits**, based on principal diagnosis code for asthma (ICD9=493.xx), restricted to Maine residents

				Lag periods: L0, L1, L2, L3, L4, L03	
Smargiassi et al. (2009)(73)	Montreal, Canada (four zip codes surrounding oil refineries), 1996-2004	Time-stratified	263 asthma hospitalizations and 1,579 ED visits, children 2-4	24-h avg SO_2 1-h peak SO_2 Measured levels at 2 monitors (East and SW of refineries), and also used AERMOD to model daily SO_2 levels in the same two areas Lag period: L0, L1, L04	**Asthma hospital admissions and ER visits**, based on primary ICD9 diagnosis code 493.xx
Tecer et al. (2008)(113)	Zonguldak, Turkey (area of significant coal mining), Dec 2004 – Oct 2005	Bi-directional	2,779 hospitalizations for children ages 0-14 (count includes asthma and other respiratory disease admissions)	24-h max $PM_{2.5}$, IQR=14.0 $\mu g/m^3$ 24-h max $PM_{10-2.5}$, IQR=13.7 $\mu g/m^3$ 24-h max PM_{10}, IQR=26.7 $\mu g/m^3$ Daily pollutant values measured at a single monitor in the city center Lag periods: L0, L1, L2, L3, L4	**Asthma hospital admissions**, based on ICD9 diagnosis code 493.xx
Villeneuve et al. (2007)(70)	Edmonton, Alberta, Apr 1992-Mar 2002	Time-stratified	57,912 asthma ER visits, n=7,247 for ages 2-4 and n=13,145 for ages 5-14	24-h avg SO_2, IQR= 3.0 ppb 24-h avg NO_2, IQR=13.5 ppb 24-h avg CO, IQR=0.5 ppm 8-h max O_3, IQR=18.0 ppb 24-h avg $PM_{2.5}$, IQR=6.3 g/m^3	**Asthma ER visits**, based on principal diagnosis code for asthma (ICD9=493.xx)

				24-h avg PM_{10},IQR=16.0 g/m^3 Daily pollutant values averaged across all monitors in the city Lag periods: L0, L1, L2, L3, L02, L04	

Table 2. Confounders and effect modifiers assessed/included in studies

Source	Confounders	Effect Measure Modifiers
Barnett et al. (2005)(71)	Temperature, current minus previous day's temperature, relative humidity, pressure, extremes of hot and cold (coldest/warmest 1% of days), day of the week, public holiday (y/n), day after a public holiday (y/n)	For each city: average pollutant level, number of monitors, temperature, % of population <15 years of age, hotter/colder than other cities. Also separated cool (May-Oct) and warm (Nov-Apr) seasons Higher average temperature was the only significant EMM
Hinwood et al. (2006)(72)	Average temperature on previous day, change of temperature on the day before (min-max), maximum humidity on current day, public holidays, day of the week	Age group (all, 0-14, 65+), season (Nov-Apr and May-Oct)
Jalaludin et al. (2008)(68)	Same-day average temperature, same-day relative humidity, daily temperature range (max-min temp), school holidays, public holidays	Age group (1-4, 5-9, 10-14, 1-14), warm (Nov–Apr) vs. (May–Oct) months
Laurent et al. (2008)(82)	Daily temperature, atmospheric pressure, relative humidity, daily pollen counts, weekly influenza case counts	Age group, socioeconomic deprivation stratum (based on income, education, job, housing characteristics, family structure, etc.) – analyzed as quintiles and as continuous
Lin et al. (2002)(110)	Daily max and min temperatures, average relative humidity (also modeled squared terms for each), day of the week, levels of CO, SO_2, NO_2, O_3	Gender
Lin et al. (2003)(111)	Daily max and min temperatures, average relative humidity (also modeled squared terms for each), levels of $PM_{2.5}$, $PM_{10-2.5}$	Gender
Paulu and Smith (2008)(112)	Daily max and min temperatures, average relative humidity, max relative humidity, barometric pressure, major holiday, day after major holiday, levels of $PM_{2.5}$ (dropped from final model due to collinearity)	Age group, gender
Smargiassi et al. (2009)(73)	Daily mean concentrations of regional SO_2, O_3, NO_2, $PM_{2.5}$ (using same lags as the local SO_2 measurements), relative humidity and temperature (same lag period as local SO_2)	Source of SO_2 data (monitored vs. modeled) and location relative to refineries
Tecer et al. (2008)(113)	Average and maximum wind speed, temperature, vapor pressure, humidity, cloudiness parameter	
Villeneuve et al. (2007)(70)	Temperature, relative humidity, seasonal epidemics of viral related respiratory disease, aeroallergens (grass, tree, weed pollens; mold spores)	Age group, season (Apr-Sep, Oct-Mar)

Table 3. Summary of results

Source	Subgroup analysis	Measure of Association	95% Confidence Interval
Barnett et al. (2005)(71)	**Asthma admissions, % increase** (per IQR increase) • 24-h NO_2, ages 5-14 • 24-h NO_2, ages 5-14 – Australian cities • 24-h NO_2, ages 5-14 – New Zealand cities • 24-h NO_2, ages 5-14 – Cool season • 24-h NO_2, ages 5-14 – Warm season • 8-h O_3, ages 1-4 • 8-h O_3, ages 5-14 No significant associations for children ages 1-4 Mean pollutant levels (range across cities) 24-h $PM_{2.5}$, 8.1–11.0 μg/m^3 24-h PM_{10}, 16.5-20.6 μg/m^3 1-h NO_2, 15.7-23.2 ppb 24-h NO_2, 7.0-11.7 ppb 8-h CO, 0.5-2.1 ppb 1-h SO_2, 3.7-10.1 ppb 24-h SO_2, 0.9-4.3 ppb 1-h O_3, 23.7-33.6 ppb 4-h O_3, 21.8-31.3 ppb 8-h O_3, 19.0-28.5 ppb 24-h BSP, 0.2-0.3*10^{-4}/m	 6.0% 3.8% 18.4% 7.0% 10.2% -2.1% -4.1%	 (0.2, 12.1) (-1.3, 9.3) (6.7, 31.4) (-2.4, 17.3) (2.6, 18.4) (-9.8, 6.4) (-12.6, 5.2)

Hinwood et al. (2006)(72)	**Asthma hospitalizations**, ages 1-14 (per 1 unit increase) (specific OR's and 95% CI for these not reported, but rather graphed): 24-h bsp - OR's varied near 1.00, no statistically significant results 24-h NO_2 - OR's varied near 1.00, no statistically significant results 1-h and 8-h O_3 - OR's generally <1.00, no statistically significant results 8-h CO - OR's generally <1.00, no statistically significant results Specific OR reported in text; lag period listed was statistically significant 24-h $PM_{2.5}$ (lag 2) Mean concentrations (all year): 1-h max O_3=31.6 ppb, 4-h max O_3=28.8 ppb, 8-h max O_3=25.9 ppb 1-h max NO_2=24.8 ppb, 24-h avg NO_2=10.3 ppb 1-h max BSP=1.2 bscat/10^4, 24-h avg BSP= 0.25 bscat/10^4 8-h max CO=2.3 ppm 24-h avg PM_{10}=19.6 ppb, 24-h avg $PM_{2.5}$=9.2 ppb	OR = 1.005	p< 0.05
Jalaludin et al. (2008)(68)	**Asthma ER admissions, % increase**, ages 1-14 (per IQR increase),: Warm Season • 24-h PM_{10} • 24-h $PM_{2.5}$ • 1-h O_3 • 1-h NO_2 • 8-h CO • 24-h SO_2 Cool Season • 24-h PM_{10}	 1.2 0.9 1.5 2.6 0.2 0.5 -0.3	 (0.5, 1.9) (0.4, 1.5) (0.7, 2.4) (1.3, 3.8) (-1.7, 2.2) (-0.7, 1.8) (-1.3, 0.7)

	• 24-h $PM_{2.5}$ • 1-h O_3 • 1-h NO_2 • 8-h CO • 24-h SO_2	0.8 -0.9 1.0 1.5 1.3	(-0.1, 1.8) (-2.4, 0.5) (-0.4, 2.3) (0.6, 2.3) (0.1, 2.5)
Laurent et al. (2008)(82)	**Odds of emergency asthma call**, ages 0-19 (per 10 µg/m^3 increase) • PM_{10} • NO_2 • SO_2 • O_3 **Influence of social deprivation** (β from fixed-effects model) • NO_2 • SO_2 • PM_{10} Mean concentrations: PM_{10}: 22.6 µg/m^3 SO_2: 8.9 µg/m^3 NO_2: 36 µg/m^3 O_3: 57.7 µg/m^3	 1.047 1.003 1.122 0.966 -0.0027 -0.0103 -0.0024	 (0.961, 1.141) (0.926, 1.086) (0.945, 1.334) (0.891, 1.048) p-value = 0.49 p-value = 0.18 p-value = 0.48
Lin et al. (2002)(110)	**Relative risk of asthma hospitalization** (per IQR increase in pollutant, L05) Boys: • $PM_{2.5}$ • $PM_{10-2.5}$ • PM_{10} Girls: • $PM_{2.5}$ • $PM_{10-2.5}$[1] • PM_{10}	0.92 1.17 1.01 0.93 1.16 0.99	 (0.83, 1.02) (1.03, 1.33) (0.90, 1.12) (0.82, 1.06) (0.98, 1.38) (0.85, 1.15)

	(results presented from bi-directional case-crossover analysis, adjusted for gaseous pollutants) [1]RR (95% CI) estimate unadjusted for gaseous pollutants: 1.18 (1.02, 1.36) Mean concentrations (µg/m^3): $PM_{2.5}$=17.99, $PM_{10-2.5}$=12.17, PM_{10}=30.16 Max concentrations (µg/m^3): $PM_{2.5}$=89.59, $PM_{10-2.5}$=68.00, PM_{10}=116.20		
Lin et al. (2003)(111)	**Relative risk of asthma hospitalization** (per IQR increase in pollutant) Boys (L03): • CO • SO_2 • NO_2 • O_3 Girls (L06): • CO • SO_2 • NO_2 • O_3 (results presented for lag period with strongest effects per gender, adjusted for $PM_{10-2.5}$ and $PM_{2.5}$) Mean levels: CO_5=1.18 ppm, SO_2=5.36 ppb, NO_2=25.24 ppb, O_3=30.39 ppb Max levels: CO_5=6.10 ppm, SO_2=57.00 ppb, NO_2=82.00 ppb, O_3=141.00 ppb	 1.10 0.95 1.15 0.88 1.05 1.28 1.21 0.89	 (1.02, 1.20) (0.85, 1.05) (1.04, 1.27) (0.77, 1.00) (0.93, 1.20) (1.08, 1.51) (1.03, 1.42) (0.72, 1.12)
Paulu and Smith (2008)(112)	**Asthma ER admissions, % increase** (per 10-ppb O_3 increase), ages 2-14: Females Males	 4% 17%	 (-12%, 21%) (3%, 32%)

Smargiassi et al. (2009)(73)	**Odds of asthma hospitalization** (per IQR increase, adjusted, L0) Daily mean Daily peak **Odds of asthma ED visits** (per IQR increase, adjusted, L0) Daily mean Daily peak **SO_2 concentrations (ppb):** East: Monitored / Modeled; Southwest: Monitored / Modeled 24-h mean: 6.9 / 3.7 / 4.4 / 2.4 24-h mean IQR: 6.3 / 5.5 / 4.3 / 3.0 1-h peak: 23.8 / 19.2 / 12.8 / 16.0 1-h peak IQR: 23.1 / 31.6 / 11.9 / 30.4	1.14 1.42 1.04 1.10	(1.00, 1.30) (1.10, 1.82) (0.98, 1.10) (1.00, 1.22)
Tecer et al. (2008)(113)	**Odds of asthma hospitalization** (per 10 μg/m^3 increase in pollutant) • $PM_{2.5}$ – Lag 0 / Lag 4 • $PM_{10-2.5}$ – Lag 0 / Lag 4 • PM_{10} – Lag 0 / Lag 4 **Odds of asthma hospitalization** (per IQR increase in pollutant) • $PM_{2.5}$ – Lag 0 / Lag 4 • $PM_{10-2.5}$ – Lag 0 / Lag 4 • PM_{10} – Lag 0 / Lag 4 Mean concentrations (μg/m^3): $PM_{2.5}$=29.1, $PM_{10-2.5}$=24.3, PM_{10}=53.3 Max concentrations (μg/m^3): $PM_{2.5}$=95.65, $PM_{10-2.5}$=195.8,	1.15 / 1.25 1.18 / 1.17 1.14 / 1.16 1.22 / 1.37 1.26 / 1.24 1.42 / 1.47	(0.99, 1.34) / (1.05, 1.50) (1.01, 1.39) / (1.05, 1.31) (1.03, 1.26) / (1.06, 1.26) (0.99, 1.51) / (1.06, 1.76) (1.01, 1.57) / (1.07, 1.44) (1.09, 1.84) / (1.17, 1.86)

	PM_{10}=237.5		
Villeneuve et al. (2007)(70)	**Odds of asthma ER visit** (per IQR increase in pollutant) Ages 2-4 (5-day average – strongest associations seen) Winter: O_3 Summer: NO_2 CO O_3 $PM_{2.5}$ PM_{10} Ages 5-14 (5-day average – strongest associations seen) Winter: NO_2 CO Summer: NO_2 CO O_3 $PM_{2.5}$ PM_{10} Median concentrations (summer): SO_2=2.0 ppb, NO_2=17.5 ppb, CO=0.6 ppm, O_3=38.0 ppb, $PM_{2.5}$=7.0 g/m^3, PM_{10}=22.0 g/m^3 Median concentrations (winter): SO_2=3.0 ppb, NO_2=28.5 ppb, CO=0.9 ppm, O_3=24.3 ppb, $PM_{2.5}$=7.3 g/m^3, PM_{10}=19.0 g/m^3	 1.16 1.50 1.48 1.06 1.16 1.16 1.07 1.04 1.13 1.09 1.14 1.10 1.14	 (1.01, 1.34) (1.31, 1.71) (1.27, 1.72) (0.94, 1.19) (1.04, 1.28) (1.05, 1.28) (1.00, 1.15) (1.00, 1.09) (1.02, 1.24) (0.98, 1.22) (1.05, 1.24) (1.02, 1.17) (1.06, 1.22)

Table 4. Strengths and limitations of studies reviewed

Source	Strengths	Limitations
Barnett et al. (2005)(71)	• Multi-pollutant models considered • Large, geographically diverse population • Separate analysis for season, between-city variations in temperature	• Potential exposure misclassification since pollutant estimates were averaged over an entire city • Possibility of outcome misclassification resulting from diagnostic errors in claims data
Hinwood et al. (2006)(72)	• 6-year follow-up which included all hospitals in the Perth metropolitan area • Many different pollutant metrics and lag periods analyzed	• Potential exposure misclassification since pollutant levels were generally based on three monitors (O_3 and CO only monitored at two sites) and averaged over an entire city • Data presentation lacking – specific risk estimates generally not presented in favor of graphing all lag periods evaluated • Little detail provided on how outcome data was gathered • Possibility of confounding as estimates unadjusted for community-level factors, including co-pollutant effects
Jalaludin et al. (2008)(68)	• Multi-pollutant models considered • 4-year follow-up capturing 95% of ED visits in Sydney • Separate analysis for season	• Potential exposure misclassification since pollutant estimates were averaged over an entire city • Possibility of outcome misclassification resulting from diagnostic errors in claims data
Laurent et al. (2008)(82)	• Exposure modeled at census block level rather than averaged across city • Separate analysis by socioeconomic strata	• Potential for outcome misclassification as 'asthma attack' not defined clearly or confirmed clinically • Socioeconomic deprivation defined at census block level; potential for exposure misclassification • Potential exposure misclassification since pollutant estimates were averaged over census block, rather than specific to individuals • Poor correlation between modeled and measured ambient SO_2 concentrations (r=0.06) • Relatively small sample size
Lin et al. (2002)(110)	• Large population with 12 years of follow-up • Uni-directional case-crossover and time series analysis also done	• Potential exposure misclassification since pollutant estimates were averaged across the city, rather than

	• Relatively low pollutant levels so could estimate effects at levels below current standards	specific to individuals • Possibility of outcome misclassification resulting from diagnostic errors in claims data • Possibility of confounding as estimates unadjusted for community-level factors
Lin et al. (2003)(111)	• Large population with 12 years of follow-up • Relatively low pollutant levels so could estimate effects at levels below current standards	• Potential exposure misclassification since pollutant estimates were averaged across the city, rather than specific to individuals • Possibility of outcome misclassification resulting from diagnostic errors in claims data • Possibility of confounding as estimates unadjusted for community-level factors
Paulu and Smith (2008)(112)	• Ambient O_3 levels estimated at the zip code level, using spatial interpolation	• Unexplained inconsistency of results between 2000-2002 and 2003 • Possibility of outcome misclassification resulting from diagnostic errors in claims data • Possibility of confounding as estimates unadjusted for community-level factors
Smargiassi et al. (2009)(73)	• Data source captured almost all hospitalizations and ER visits in the study area • Geographically restricted study population (near SO_2 point source) • 10 years of follow-up • Able to compare monitored and modeled SO_2 values, and adjust for regional pollutants	• Variable results depending on which SO_2 estimates used; demonstrates the likelihood of exposure misclassification – effect estimates using modeled data generally higher than those using monitor results • Unable to estimate effects of the other regional effects • Possible selection bias: children living within a few miles of a refinery likely differ from the general Montreal population in terms of personal or housing characteristics related to both exposure and outcome • Possibility of outcome misclassification resulting from diagnostic errors in claims data
Tecer et al. (2008)(113)	• High PM levels, and measures of $PM_{2.5}$, $PM_{10-2.5}$ and PM_{10}	• Potential exposure misclassification since PM levels were measured at a single site; no individual-specific estimates • Number of asthma admissions not specified, but likely small

		• Potential selection bias? Not clear if the hospital in the study was the only one in the area, and no discussion of patient characteristics there vs. other hospitals in the city • Possible outcome misclassification; not clear how asthma diagnosis was determined • Short 10-month follow-up period
Villeneuve et al. (2007)(70)	• Large population with 10 years of follow-up • Adjustment for covariates such as influenza patterns and aeroallergen levels	• Potential exposure misclassification since pollutant levels were averaged for the city; no individual-specific estimates. Estimates are probably better reflections of personal exposure in the summer months. • Residual confounding of aeroallergens since data collected at only a single site for the entire city • Possibility of outcome misclassification resulting from diagnostic errors in claims data (although children<2 excluded to help eliminate bronchiolitis cases coded as asthma) • Possibility of confounding as estimates unadjusted for community-level factors

Appendix C. Age-adjusted[a] prevalence of asthma among Texas Medicaid-enrolled children ages 0-17, 2005-2007

	2005		2006		2007	
	Prevalence Proportion (%)	95% CI	Prevalence Proportion (%)	95% CI	Prevalence Proportion (%)	95% CI
Total	10.56	10.50, 10.61	10.48	10.42, 10.53	11.41	11.36, 11.47
Age Group						
0-4 years	13.03	12.95, 13.11	13.84	13.76, 13.92	15.44	15.36, 15.52
5-9 years	11.57	11.46, 11.69	11.59	11.47, 11.71	12.86	12.74, 12.99
10-14 years	9.10	8.98, 9.21	8.70	8.58, 8.82	9.37	9.24, 9.50
15-17 years	7.38	7.14, 7.62	6.24	5.84, 6.63	6.00	5.53, 6.47
Gender						
Female	9.32	9.29, 9.36	9.21	9.17, 9.25	10.10	10.07, 10.14
Male	11.74	11.70, 11.78	11.67	11.63, 11.71	12.65	12.61, 12.69
Race						
White	11.79	11.72, 11.86	11.71	11.64, 11.78	12.63	12.56, 12.71
Black	11.15	11.08, 11.22	11.19	11.12, 11.26	12.69	12.61, 12.76
Am. Indian	9.86	9.38, 10.34	9.27	8.79, 9.75	13.26	12.70, 13.81
Asian	7.95	7.72, 8.17	8.56	8.32, 8.79	10.24	9.99, 10.50
Hispanic	10.15	10.12, 10.18	10.05	10.01, 10.08	10.82	10.78, 10.85
Race/Gender						
White/Male	12.65	12.55, 12.75	12.47	12.37, 12.57	13.65	13.55, 13.76

Black/Male	12.75	12.65, 12.86	12.81	12.71, 12.92	14.33	14.22, 14.44
American Indian/Male	10.82	10.13, 11.51	9.89	9.19, 10.57	15.49	14.68, 16.31
Asian/Male	9.26	8.93, 9.60	9.93	9.58, 10.28	11.67	11.30, 12.04
Hispanic/Male	11.32	11.27, 11.37	11.27	11.22, 11.32	12.01	11.96, 12.06
White/Female	10.86	10.76, 10.95	10.85	10.75, 10.95	11.54	11.43, 11.64
Black/Female	9.48	9.39, 9.58	9.51	9.41, 9.60	10.93	10.84, 11.03
American Indian/Female	8.74	8.07, 9.40	8.50	7.82, 9.17	10.58	9.86, 11.30
Asian/Female	6.50	6.21, 6.80	7.11	6.80, 7.42	8.72	8.38, 9.06
Hispanic/Female	8.93	8.89, 8.98	8.77	8.72, 8.81	9.57	9.53, 9.62

Abbreviation: CI, confidence interval.

[a]Age-adjusted to the proportion of the 2000 U.S. Census population in each age category, with the exception of prevalence presented by age group.

Appendix D. Notice of approval to begin research, October 6, 2010

THE UNIVERSITY of TEXAS
HEALTH SCIENCE CENTER AT HOUSTON

The Committee for the Protection of Human Subjects
Office of Research Support Committees

6410 Fannin, Suite 1100
Houston, TX 77030

Dr. Judith Wendt
UT Houston

NOTICE OF APPROVAL TO BEGIN RESEARCH October 06, 2010

HSC-SPH-10-0493 - Pediatric asthma incidence in Texas and associations with ambient ozone levels in an urban area: an analysis using Medicaid claims data.

PROVISIONS: This approval relates to the research to be conducted under the above referenced title and/or to any associated materials considered by the Committee for the Protection of Human Subjects, e.g. study documents, informed consent, etc.

APPROVED: By Expedited Review and Approval

REVIEW DATE: October 6, 2010

APPROVAL DATE: 10/6/2010

EXPIRATION DATE: 9/30/2011

CHAIRPERSON: Anne Dougherty, MD

Subject to any provisions noted above, you may now begin this research.

CHANGES: The principal investigator (PI) must receive approval from the CPHS before initiating any changes, including those required by the sponsor, which would affect human subjects, e.g. changes in methods or procedures, numbers or kinds of human subjects, or revisions to the informed consent document or procedures. The addition of co-investigators must also receive approval from the CPHS. **ALL PROTOCOL REVISIONS MUST BE SUBMITTED TO THE SPONSOR OF THE RESEARCH.**

INFORMED CONSENT: When Informed consent is required, it must be obtained by the PI or designee(s), using the format and procedures approved by the CPHS. The PI is responsible to instruct the designee in the methods approved by the CPHS for the consent process. The individual obtaining informed consent must also sign the consent document. Please note that only copies of the stamped approved informed consent form can be used when obtaining consent.

HEALTH INSURANCE PORTABILITY and ACCOUNTABILITY ACT (HIPAA):
The study must meet all HIPAA research requirements. For compliance guidelines see details on the Committee for the Protection of Human Subjects website at:
http://www.uth.tmc.edu/ut_general/research_acad_aff/orsc/cphs/guidelines/hipaa.htm

UNANTICIPATED RISK OR HARM, OR ADVERSE DRUG REACTIONS: The PI will immediately inform the CPHS of any unanticipated problems involving risks to subjects or others, of any serious harm to subjects, and of any adverse drug reactions.

REFERENCES

1. Akinbami LJ, Moorman JE, Liu X. Asthma prevalence, health care use, and mortality: United States, 2005-2009. Natl Health Stat Report. 2011;12(32):1-14.

2. Selgrade MK, Lemanske RF J, Gilmour MI, et al. Induction of asthma and the environment: what we know and need to know. Environ Health Perspect. 2006;114(4):615-619.

3. Wang LY, Zhong Y, Wheeler L. Direct and indirect costs of asthma in school-age children. Prev Chronic Dis. 2005;2(1):A11.

4. Bai Y, Hillemeier MM, Lengerich EJ. Racial/ethnic disparities in symptom severity among children hospitalized with asthma. J Health Care Poor Underserved. 2007;18(1):54-61.

5. Merrick NJ, Houchens R, Tillisch S, et al. Quality of hospital care of children with asthma: Medicaid versus privately insured patients. J Health Care Poor Underserved. 2001;12(2):192-207.

6. Liu SY, Pearlman DN. Hospital readmissions for childhood asthma: the role of individual and neighborhood factors. Public Health Rep. 2009;124(1):65-78.

7. Interim report submitted by the Health and Human Services Commission, as required by SB616, HB 342, and Rider 51, 77th Legislature, to the Governor and members of the legislature. Austin, TX., Texas Health and Human Services Commission, 2002. (http://www.hhsc.state.tx.us/Medicaid/mc/proj/asthma/pdf/pilot_forms/1stPilotInterrimReport.pdf).

8. Yeatts K, Sly P, Shore S, et al. A brief targeted review of susceptibility factors, environmental exposures, asthma incidence, and recommendations for future asthma incidence research. Environ Health Perspect. 2006;114(4):634-640.

9. Gilmour MI, Jaakkola MS, London SJ, et al. How exposure to environmental tobacco smoke, outdoor air pollutants, and increased pollen burdens influences the incidence of asthma. Environ Health Perspect. 2006;114(4):627-633.

10. Gilliland FD. Outdoor air pollution, genetic susceptibility, and asthma management: opportunities for intervention to reduce the burden of asthma. Pediatrics. 2009;123(Suppl 3):S168-173.

11. Akinbami LJ, Rhodes JC, Lara M. Racial and ethnic differences in asthma diagnosis among children who wheeze. Pediatrics. 2005;115(5):1254-1260.

12. Akinbami LJ, Moorman JE, Garbe PL, et al. Status of childhood asthma in the United States, 1980-2007. Pediatrics. 2009;123(Suppl 3):S131-145.

13. Rudd RA, Moorman JE. Asthma incidence: data from the National Health Interview Survey, 1980-1996. J Asthma. 2007;44(1):65-70.

14. Gershon AS, Guan J, Wang C, et al. Trends in asthma prevalence and incidence in Ontario, Canada, 1996-2005: A population study. Am J Epidemiol. 2010;172(6):728-736.

15. Simpson CR, Sheikh A. Trends in the epidemiology of asthma in England: a national study of 333,294 patients. J R Soc Med. 2010;103(3):98-106.

16. Gilliland FD, Berhane K, Islam T, et al. Obesity and the risk of newly diagnosed asthma in school-age children. Am J Epidemiol. 2003;158(5):406-415.

17. Gold HT, Do HT. Evaluation of three algorithms to identify incident breast cancer in Medicare claims data. Health Serv Res. 2007;42(5):2056-2069.

18. Nattinger AB, Laud PW, Bajorunaite R, et al. An algorithm for the use of Medicare claims data to identify women with incident breast cancer. Health Serv Res. 2004;39(6 Pt 1):1733-1749.

19. Koroukian SM, Cooper GS, Rimm AA. Ability of Medicaid claims data to identify incident cases of breast cancer in the Ohio Medicaid population. Health Serv Res. 2003;38(3):947-960.

20. Wang PS, Walker AM, Tsuang MT, et al. Finding incident breast cancer cases through US claims data and a state cancer registry. Cancer Causes Control. 2001;12(3):257-265.

21. Cooper GS, Yuan Z, Jethva RN, et al. Use of Medicare claims data to measure county-level variation in breast carcinoma incidence and mammography rates. Cancer Detect Prev. 2002;26(3):197-202.

22. Freeman JL, Zhang D, Freeman DH, et al. An approach to identifying incident breast cancer cases using Medicare claims data. J Clin Epidemiol. 2000;53(6):605-614.

23. Cooper GS, Yuan Z, Stange KC, et al. Use of Medicare claims data to measure county-level variations in the incidence of colorectal carcinoma. Cancer. 1998;83(4):673-678.

24. Cooper GS, Yuan Z, Jethva RN, et al. Determination of county-level prostate carcinoma incidence and detection rates with Medicare claims data. Cancer. 2001;92(1):102-109.

25. Ramsey SD, Scoggins JF, Blough DK, et al. Sensitivity of administrative claims to identify incident cases of lung cancer: a comparison of 3 health plans. J Manag Care Pharm. 2009;15(8):659-668.

26. Sloan FA, Brown DS, Carlisle ES, et al. Estimates of incidence rates with longitudinal claims data. Arch Ophthalmol. 2003;121(10):1462-1468.

27. Siwik JP, Johnson CC, Havstad SL, et al. Airway hyperresponsiveness to methacholine at age 6 to 8 years in nonasthmatic patients is not related to increased health-care utilization for asthma in the ensuing 5 years: a longitudinal study of a birth cohort. Chest. 2005;128(4):2420-2426.

28. Islam S, Liu Q, Chines A, et al. Trend in incidence of osteoporosis-related fractures among 40- to 69-year-old women: analysis of a large insurance claims database, 2000-2005. Menopause. 2009;16(1):77-83.

29. Piecoro LT, Potoski M, Talbert JC, et al. Asthma prevalence, cost, and adherence with expert guidelines on the utilization of health care services and costs in a state Medicaid population. Health Serv Res. 2001;36(2):357-371.

30. Smith MJ, Rascati KL, Barner JC. A descriptive analysis of asthma-related medical services and prescription utilization among recipients in a Medicaid program. J Asthma. 2005;42(6):447-453.

31. Buescher PA, Jones-Vessey K. Using Medicaid data to estimate state- and county-level prevalence of asthma among low-income children. Matern Child Health J. 1999;3(4):211-216.

32. Dombkowski KJ, Wasilevich EA, Lyon-Callo SK. Pediatric asthma surveillance using Medicaid claims. Public Health Rep. 2005;120(5):515-524.

33. Pawar V, Smith MJ. Asthma-related healthcare services utilization by African-Americans enrolled in West Virginia Medicaid. Respir Med. 2006;100(9):1579-1587.

34. Roberts EM. Racial and ethnic disparities in childhood asthma diagnosis: the role of clinical findings. J Natl Med Assoc. 2002;94(4):215-223.

35. Shields AE, Comstock C, Weiss KB. Variations in asthma care by race/ethnicity among children enrolled in a state Medicaid program. Pediatrics. 2004;113(3 Pt 1):496-504.

36. Dombkowski KJ, Cabana MD, Cohn LM, et al. Geographic variation of asthma quality measures within and between health plans. Am J Manag Care. 2005;11(12):765-772.

37. Stevenson MD, Heaton PC, Moomaw CJ, et al. Inhaled corticosteroid use in asthmatic children receiving Ohio Medicaid: trend analysis, 1997-2001. Ann Allergy Asthma Immunol. 2008;100(6):538-544.

38. Wilson SE, Leonard A, Moomaw C, et al. Underuse of controller medications among children with persistent asthma in the Ohio Medicaid population: evolving differences with new medications. Ambul Pediatr. 2005;5(2):83-89.

39. Cooper WO, Arbogast PG, Hickson GB, et al. Gaps in enrollment from a Medicaid managed care program: effects on emergency department visits and hospitalizations for children with asthma. Med Care. 2005;43(7):718-725.

40. Delfino RJ. Epidemiologic evidence for asthma and exposure to air toxics: linkages between occupational, indoor, and community air pollution research. Environ Health Perspect. 2002;110(Suppl 4):573-589.

41. Akinbami LJ, Lynch CD, Parker JD, et al. The association between childhood asthma prevalence and monitored air pollutants in metropolitan areas, United States, 2001-2004. Environ Res. 2010;110(3):294-301.

42. Ko FW, Tam W, Wong TW, et al. Effects of air pollution on asthma hospitalization rates in different age groups in Hong Kong. Clin Exp Allergy. 2007;37(9):1312-1319.

43. Lin S, Liu X, Le LH, et al. Chronic exposure to ambient ozone and asthma hospital admissions among children. Environ Health Perspect. 2008;116(12):1725-1730.

44. Slaughter JC, Lumley T, Sheppard L, et al. Effects of ambient air pollution on symptom severity and medication use in children with asthma. Ann Allergy Asthma Immunol. 2003;91(4):346-353.

45. Parker JD, Akinbami LJ, Woodruff TJ. Air pollution and childhood respiratory allergies in the United States. Environ Health Perspect. 2009;117(1):140-147.

46. Tolbert PE, Mulholland JA, MacIntosh DL, et al. Air quality and pediatric emergency room visits for asthma in Atlanta, Georgia, USA. Am J Epidemiol. 2000;151(8):798-810.

47. McConnell R, Berhane K, Gilliland F, et al. Childhood incident asthma and traffic-related air pollution at home and school. Environ Health Perspect. 2010;118(7):1021-1026.

48. Schildcrout JS, Sheppard L, Lumley T, et al. Ambient air pollution and asthma exacerbations in children: an eight-city analysis. Am J Epidemiol. 2006;164(6):505-517.

49. Burra TA, Moineddin R, Agha MM, et al. Social disadvantage, air pollution, and asthma physician visits in Toronto, Canada. Environ Res. 2009;109(5):567-574.

50. Luginaah IN, Fung KY, Gorey KM, et al. Association of ambient air pollution with respiratory hospitalization in a government-designated "area of concern": the case of Windsor, Ontario. Environ Health Perspect. 2005;113(3):290-296.

51. McConnell R, Berhane K, Gilliland F, et al. Asthma in exercising children exposed to ozone: a cohort study. Lancet. 2002;359(9304):386-391.

52. Brauer M, Hoek G, Smit HA, et al. Air pollution and development of asthma, allergy and infections in a birth cohort. Eur Respir J. 2007;29(5):879-888.

53. Morgenstern V, Zutavern A, Cyrys J, et al. Respiratory health and individual estimated exposure to traffic-related air pollutants in a cohort of young children. Occup Environ Med. 2007;64(1):8-16.

54. Carlsten C, Dybuncio A, Becker A, et al. Traffic-related air pollution and incident asthma in a high-risk birth cohort. Occup Environ Med. 2011;68(4):291-295.

55. Zmirou D, Gauvin S, Pin I, et al. Traffic related air pollution and incidence of childhood asthma: results of the Vesta case-control study. J Epidemiol Community Health. 2004;58(1):18-23.

56. Jerrett M, Shankardass K, Berhane K, et al. Traffic-related air pollution and asthma onset in children: a prospective cohort study with individual exposure measurement. Environ Health Perspect. 2008;116(10):1433-1438.

57. U.S. Census Bureau. Table 20: Large Metropolitan Statistical Areas-Population: 1990-2010. http://www.census.gov/compendia/statab/2012/tables/12s0020.pdf.

58. SIP Revisions: Houston-Galveston-Brazoria, March 10, 2010. Austin, TX., Texas Commission on Environmental Quality, 2010. (http://www.tceq.state.tx.us/implementation/air/sip/HGB_eight_hour.html).

59. Sexton K, Linder SH, Marko D, et al. Comparative assessment of air pollution-related health risks in Houston. Environ Health Perspect. 2007;115(10):1388-1393.

60. HGB Reasonable Further Progress SIP Revision for the 1997 Eight-Hour Ozone Standard. Chapter 1: General. Austin, TX., Texas Commission on Environmental Quality,

2009.

(http://www.tceq.state.tx.us/assets/public/implementation/air/sip/hgb/hgb_sip_2009/09017SIP_Ch1_ado.pdf).

61. Maclure M, Mittleman MA. Should we use a case-crossover design? Annu Rev Public Health. 2000;21:193-221.

62. Carracedo-Martinez E, Taracido M, Tobias A, et al. Case-crossover analysis of air pollution health effects: a systematic review of methodology and application. Environ Health Perspect. 2010. (doi: 10.1289/ehp.0901485).

63. Wellenius GA, Bateson TF, Mittleman MA, et al. Particulate air pollution and the rate of hospitalization for congestive heart failure among Medicare beneficiaries in Pittsburgh, Pennsylvania. Am J Epidemiol. 2005;161(11):1030-1036.

64. Wellenius GA, Schwartz J, Mittleman MA. Particulate air pollution and hospital admissions for congestive heart failure in seven United States cities. Am J Cardiol. 2006;97(3):404-408.

65. Wellenius GA, Schwartz J, Mittleman MA. Air pollution and hospital admissions for ischemic and hemorrhagic stroke among Medicare beneficiaries. Stroke. 2005;36(12):2549-2553.

66. Zanobetti A, Schwartz J. Air pollution and emergency admissions in Boston, MA. J Epidemiol Community Health. 2006;60(10):890-895.

67. Boutin-Forzano S, Adel N, Gratecos L, et al. Visits to the emergency room for asthma attacks and short-term variations in air pollution. A case-crossover study. Respiration. 2004;71(2):134-137.

68. Jalaludin B, Khalaj B, Sheppeard V, et al. Air pollution and ED visits for asthma in Australian children: a case-crossover analysis. Int Arch Occup Environ Health. 2008;81(8):967-974.

69. Kim SY, O'Neill MS, Lee JT, et al. Air pollution, socioeconomic position, and emergency hospital visits for asthma in Seoul, Korea. Int Arch Occup Environ Health. 2007;80(8):701-710.

70. Villeneuve PJ, Chen L, Rowe BH, et al. Outdoor air pollution and emergency department visits for asthma among children and adults: a case-crossover study in northern Alberta, Canada. Environ Health Global Access Sci Source. 2007;6:40-54.

71. Barnett AG, Williams GM, Schwartz J, et al. Air pollution and child respiratory health: a case-crossover study in Australia and New Zealand. Am J Respir Crit Care Med. 2005;171(11):1272-1278.

72. Hinwood AL, De Klerk N, Rodriguez C, et al. The relationship between changes in daily air pollution and hospitalizations in Perth, Australia 1992-1998: a case-crossover study. Int J Environ Health Res. 2006;16(1):27-46.

73. Smargiassi A, Kosatsky T, Hicks J, et al. Risk of asthmatic episodes in children exposed to sulfur dioxide stack emissions from a refinery point source in Montreal, Canada. Environ Health Perspect. 2009;117(4):653-659.

74. Tsai SS, Cheng MH, Chiu HF, et al. Air pollution and hospital admissions for asthma in a tropical city: Kaohsiung, Taiwan. Inhal Toxicol. 2006;18(8):549-554.

75. Yang CY, Chen CC, Chen CY, et al. Air pollution and hospital admissions for asthma in a subtropical city: Taipei, Taiwan. J Toxicol Environ Health Part A. 2007;70(2):111-117.

76. Dombkowski KJ, Wasilevich EA, Lyon-Callo S, et al. Asthma surveillance using Medicaid administrative data: a call for a national framework. J Public Health Manag Pract. 2009;15(6):485-493.

77. Technology Transfer Network (TTN), Air Quality System (AQS).Washington, D.C., U.S. Environmental Protection Agency, 2010. (www.epa.gov/ttnairs1/airsaqs/).

78. Babin S, Burkom H, Holtry R, et al. Medicaid patient asthma-related acute care visits and their associations with ozone and particulates in Washington, DC, from 1994-2005. Int J Environ Health Res. 2008;18(3):209-221.

79. Fauroux B, Sampil M, Quenel P, et al. Ozone: a trigger for hospital pediatric asthma emergency room visits. Pediatr Pulmonol. 2000;30(1):41-46.

80. Jalaludin BB, Chey T, O'Toole BI, et al. Acute effects of low levels of ambient ozone on peak expiratory flow rate in a cohort of Australian children. Int J Epidemiol. 2000;29(3):549-557.

81. Jalaludin BB, O'Toole BI, Leeder SR. Acute effects of urban ambient air pollution on respiratory symptoms, asthma medication use, and doctor visits for asthma in a cohort of Australian children. Environ Res. 2004;95(1):32-42.

82. Laurent O, Pedrono G, Segala C, et al. Air pollution, asthma attacks, and socioeconomic deprivation: a small-area case-crossover study. Am J Epidemiol. 2008;168(1):58-65.

83. Pollen and Mold Spore Count Archives.Houston, TX., City of Houston Department of Health and Human Services, 2010. (http://www.houstontx.gov/health/Pollen-Mold/pollenarchive.html).

84. Janes H, Sheppard L, Lumley T. Case-crossover analyses of air pollution exposure data: referent selection strategies and their implications for bias. Epidemiology. 2005;16(6):717-726.

85. Levy D, Lumley T, Sheppard L, et al. Referent selection in case-crossover analyses of acute health effects of air pollution. Epidemiology. 2001;12(2):186-192.

86. Hosmer DW, Lemeshow S. Applied Logistic Regression. New York, NY: John Wiley & Sons, Inc., 2000.

87. Asthma Care Quality Improvement: A Resource Guide for State Action. Rockville, MD., Agency for Healthcare Research and Quality, 2009. (http://www.ahrq.gov/qual/asthmacare/asthmatab1_4.htm).

88. Final Count – Medicaid Enrollment by Month. Austin, TX., Texas Health and Human Services Commission, 2012. (http://www.hhsc.state.tx.us/research/MedicaidEnrollment/MedicaidEnrollment.asp;).

89. The Kaiser Family Foundation, stathealthfacts.org – Monthly Medicaid Enrollment for Children. Washington, D.C., The Henry J. Kaiser Family Foundation, 2010. (http://statehealthfacts.org/comparetable.jsp?ind=612&cat=4&sub=52&yr=1&typ=1).

90. Dupont WD, Plummer Jr. WD. Power and Sample Size Calculations: A Review and Computer Program. Controlled Clin Trials. 1990;11:116-128.

91. Dupont WD. Power calculations for matched case-control studies. Biometrics. 1988;44(4):1157-1168.

92. Kunzli N, Schindler C. A call for reporting the relevant exposure term in air pollution case-crossover studies. J Epidemiol Community Health. 2005;59(6):527-530.

93. Texas External Quality Review Organization. Validating encounter data: Texas Medicaid managed care and Children's Health Insurance Program managed care organization medical record review, fiscal year 2006. Gainesville, FL.: Texas External Quality Review Organization, 2008.

94. Twiggs JE, Fifield J, Apter AJ, et al. Stratifying medical and pharmaceutical administrative claims as a method to identify pediatric asthma patients in a Medicaid managed care organization. J Clin Epidemiol. 2002;55(9):938-944.

95. Gent JF, Triche EW, Holford TR, et al. Association of low-level ozone and fine particles with respiratory symptoms in children with asthma. JAMA. 2003;290(14):1859-1867.

96. Jaffe DH, Singer ME, Rimm AA. Air pollution and emergency department visits for asthma among Ohio Medicaid recipients, 1991-1996. Environ Res. 2003;91(1):21-28.

97. Lewis TC, Robins TG, Dvonch JT, et al. Air pollution-associated changes in lung function among asthmatic children in Detroit. Environ Health Perspect. 2005;113(8):1068-1075.

98. Lin S, Liu X, Le LH, et al. Chronic exposure to ambient ozone and asthma hospital admissions among children. Environ Health Perspect. 2008;116(12):1725-1730.

99. McConnell R, Berhane K, Gilliland F, et al. Prospective study of air pollution and bronchitic symptoms in children with asthma. Am J Respir Crit Care Med. 2003;168(7):790-797.

100. Millstein J, Gilliland F, Berhane K, et al. Effects of ambient air pollutants on asthma medication use and wheezing among fourth-grade school children from 12 Southern

California communities enrolled in The Children's Health Study. Arch Environ Health. 2004;59(10):505-514.

101. Moore K, Neugebauer R, Lurmann F, et al. Ambient ozone concentrations cause increased hospitalizations for asthma in children: an 18-year study in Southern California. Environ Health Perspect. 2008;116(8):1063-1070.

102. Mortimer KM, Tager IB, Dockery DW, et al. The effect of ozone on inner-city children with asthma: identification of susceptible subgroups. Am J Respir Crit Care Med. 2000;162(5):1838-1845.

103. O'Connor GT, Neas L, Vaughn B, et al. Acute respiratory health effects of air pollution on children with asthma in US inner cities. J Allergy Clin Immunol. 2008;121(5):1133-1139.e1.

104. Penard-Morand C, Charpin D, Raherison C, et al. Long-term exposure to background air pollution related to respiratory and allergic health in schoolchildren. Clin Exp Allergy. 2005;35(10):1279-1287.

105. Petroeschevsky A, Simpson RW, Thalib L, et al. Associations between outdoor air pollution and hospital admissions in Brisbane, Australia. Arch Environ Health. 2001;56(1):37-52.

106. Rabinovitch N, Zhang L, Murphy JR, et al. Effects of wintertime ambient air pollutants on asthma exacerbations in urban minority children with moderate to severe disease. J Allergy Clin Immunol. 2004;114(5):1131-1137.

107. Ramadour M, Burel C, Lanteaume A, et al. Prevalence of asthma and rhinitis in relation to long-term exposure to gaseous air pollutants. Allergy. 2000;55(12):1163-1169.

108. Szyszkowicz M. Ambient air pollution and daily emergency department visits for asthma in Edmonton, Canada. Int J Occup Med Environ Health. 2008;21(1):25-30.

109. Wilhelm M, Meng YY, Rull RP, et al. Environmental public health tracking of childhood asthma using California Health Interview Survey, traffic, and outdoor air pollution data. Environ Health Perspect. 2008;116(9):1254-1260.

110. Lin M, Chen Y, Burnett RT, et al. The influence of ambient coarse particulate matter on asthma hospitalization in children: case-crossover and time-series analyses. Environ Health Perspect. 2002;110(6):575-581.

111. Lin M, Chen Y, Burnett RT, et al. Effect of short-term exposure to gaseous pollution on asthma hospitalisation in children: a bi-directional case-crossover analysis. J Epidemiol Community Health. 2003;57(1):50-55.

112. Paulu C, Smith AE. Tracking associations between ambient ozone and asthma-related emergency department visits using case-crossover analysis. J Public Health Manag Pract. 2008;14(6):581-591.

113. Tecer LH, Alagha O, Karaca F, et al. Particulate matter (PM(2.5), PM(10-2.5), and PM(10)) and children's hospital admissions for asthma and respiratory diseases: a bidirectional case-crossover study. J Toxicol Environ Health Part A. 2008;71(8):512-520.