ADULT ASTHMA: THE USE OF NOVEL PUBLIC HEALTH METHODS TO INVESTIGATE THE PREVALENCE OF ENVIRONMENTAL RISK FACTORS

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Although the incidence of new cases of asthma has decreased in recent years, the prevalence of asthma morbidity continues to be a significant clinical and public health issue. The measures of morbidity include the need for urgent medical care and high-dose asthma medications due to uncontrolled asthma symptoms. However, the risk factors for uncontrolled asthma symptoms are poorly defined, especially for the adult asthmatic. Much interest in the host-environment interaction has evolved in response to the greater morbidity observed in adult asthmatics. Thus, the need to identify risk factors is greater than ever. An underlying problem is that surveillance for asthma does not exist at the local or state level. Here we address the concept of environmental health surveillance by demonstrating the utility of local asthma hospitalization data to estimate the burden of asthma morbidity in hopes of identifying environmental risk factors. We examine this burden within 2 geographic settings: 1. a selected urban-rural setting in Pennsylvania and 2. within the 89 zip codes in Allegheny County, Pennsylvania. We also demonstrate that such hospitalization records are a rich source for data needed to generate hypotheses with respect to the prevalence of environmental risk factors and chronic disease morbidity. Lastly, we demonstrate the use of a non-invasive biomarker (i.e. antibodies specific for atypical respiratory pathogens) to assess the risk of exposure to a biological environmental agent to adult asthma morbidity. Given the poor understanding of risk factors for adult asthma prevalence and morbidity, this research is both relevant and important in addressing environmental public health disparities.

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1. INTRODUCTION

1.1. Overview of asthma

Prevalence of disease. Asthma currently affects 7.4 million people over the age of 15 in the United States (Arif *et al.*, 2003; Mannino *et al.*, 2002). Although asthma-specific mortality rates for this age group have decreased, the increasing number of hospitalizations and attacks continue to be a significant problem (Arif et al., 2003). The prevalence of asthma morbidity in the US, specifically the need for frequent medical care, has increased steadily in the last decade (E. S. Ford et al., 2003). A similar increase in prevalence of asthma has also been reported in Western Europe (ENFUMOSA, 2003). These phenomena are not restricted to the US or "developed westernized" countries. The increasing incidence and prevalence is also reported in developing countries like Chile and China (Chan-Yeung *et al.*, 2002; Corvalan *et al.*, 2005; Rona *et al.*, 2005). Thus, asthma should be considered a multi-factorial disorder with varying etiological and heritable factors (Lemanske & Busse, 2003).

Local surveillance for asthma incidence and prevalence does not currently exist. This is most likely due to the fact that asthma is not an infectious disease and has a low mortality rate. However, the prevalence of asthma morbidity is monitored by the Centers for Disease Control (CDC). The CDC uses health care utilization information to estimate the prevalence of asthma morbidity (C. D. C. National Center for Environmental Health, 2003). The information is collected from two of their programs: the National Hospitalization Discharge Survey (NHDS) and the Behavioral Risk Factor Surveillance Survey (BRFSS). The data and subsequent analysis resulting from these two programs are periodically published in the CDC's *Morbidity and*

Mortality Weekly Report (MMWR). The latest asthma-specific *MMWR* in 2002 stated that 40 million people responding to the BRFSS reported being diagnosed with asthma by a physician (Mannino et al., 2002; C. D. C. National Center for Environmental Health, 2003). In addition, the latest NHDS in 2004 reported that 57,000 asthma hospitalizations occurred during that year (National Center for Health Statsitics, 2004).

Asthma, previously thought to be a childhood disease, has also increased in prevalence within the adult population (Brogger et al., 2003). Adult asthmatics report more frequent use of health care for asthma symptoms and often have more diminished lung function than child asthmatics (Bel, 2004). Asthma severity, including a more frequent need for high dose (ie corticosteroids) and rescue medications (ie short-acting beta-agonists), is also more common in adults than in children (Lemanske & Busse, 2003). Finally, the gender distribution in child asthma vs adult asthma is different. For childhood asthma, the male to female ratio is 2:1 whereas the same ratio is adult asthmatics is 1:2 (Fuhlbrigge *et al.*, 2002).

Patho-physiology of asthma. Asthma is a chronic inflammatory disease that affects both adults and children (Lemanske & Busse, 2003). Although there is not a cure for asthma, many children have been reported to "outgrow" their asthma symptoms. However, studies investigating the rate of remission during adulthood are few. Asthma can be managed quite effectively with the use of corticosteroids, the cornerstone drug for asthma (Peters, 2004). Recently, therapy has been expanded to include the use of additional controller medications such as long acting beta agonists, leukotriene modifiers, and anti IgE medication (Ilowite et al., 2004).

The heterogenous nature of asthma is the presents a major obstacle in the proper diagnosis and management of this disease (NHLBI, 1997). The lack of uniformity in diagnosis and disease severity classification has been a challenge with respect to asthma management (Bacharier *et al.*, 2004; Baker *et al.*, 2003). Within the public health context, the primary interest is the identification of risk factors that influence disease severity and the recognition of these risk factors by clinicians and patients alike (Arruda *et al.*, 2005). Previously thought to be a childhood disease, adult-onset asthma has emerged in the past decade as a major public health issue (W. Busse *et al.*, 1995).

The adult-onset asthmatic tends to have greater measures of morbidity (i.e. rapidly declining lung function) than the asthmatic who was diagnosed as a child (Bel, 2004). Previous studies have also cited that the diminished lung capacity in the adult-onset asthmatic is not reflective of disease duration (Jenkins et al., 2003). Thus, it is a common theme amongst researchers that adult-onset asthma may be a distinct disorder from childhood-onset asthma.

At the cellular level, adult asthma can also be distinguished from childhood asthma. Whereas childhood asthmatics have a greater involvement of cellular components indicative of atopy and allergy (i.e. eosinophils and IgE), the adult asthmatic tends to be non-atopic and has greater measures of severity including the involvement of neutrophils (ENFUMOSA, 2003). Adult asthmatics have also been reported to produce a larger amount of enzymes known as matrix metalloproteinases (i.e. MMP-9) that are involved in the remodeling process within the bronchial epithelium (Cundall et al., 2003). The source of MMP-9 in these studies has been neutrophils. Finally, although corticosteroids are very effective in reducing inflammation caused

by eosinophils (Bloom et al., 2004), they are much less effective at reducing inflammation caused by neutrophils (Cundall et al., 2003).

The economic burden of asthma. It is estimated that approximately 10% of adult asthmatics can be classified as severe (W. W. Busse *et al.*, 2000). However, this sub-group of asthmatics shares a disproportionate burden of direct medical costs related to asthma (Godard *et al.*, 2002). Total direct medical expenditures for asthma care in the US are estimated to be in excess of $11.3 billion, not including indirect costs such as lost work days. This figure, estimated to be 60% of the $14 billion spent annually for medical care, is primarily attributed to pharmacological agents (Apter et al., 2003).

1.2. Health disparities and asthma

Population-based disparities. In 2000, the US Public Health Service's goals for the decade were outlined in the document *Healthy People 2010 (HP 2010)* (U.S. Department of Health and Human Services, 2000). Aimed at eliminating health disparities, *HP2010,* identified disease-based goals and objectives where disparities have been clearly documented and where in many cases were preventable. One of the goals addressed asthma incidence and prevalence. A key question was why asthma mortality continued to decrease but measures asthma morbidity continued to increase. Published studies identify the way health care is delivered in the US as the culprit (Adams *et al.*, 2003). The argument is that adequate preventive health care is often an expense that is not covered by private health insurance thus those with less disposable income are likely to seek medical attention unless the need is dire. But disparities are seen in countries outside the US that are clearly influenced by socioeconomic status (Basagana et al., 2004).

Interestingly, each measure of SES is different so regardless of how you measure social class, the lower stratum often shares a disproportionate burden of asthma morbidity (Cesaroni *et al.*, 2003; Y. Chen *et al.*, 2004b). One tool being used to address this disparity is through patient education which involves increasing the patient's perception of the risk conferred by poor control of their asthma (i.e. need to adhere to medication protocols) and reduction of exposure to environmental risk factors (i.e environmental tobacco smoke) (Castro et al., 2003).

With respect to asthma, the issue of race/ ethnicity and disparities in health outcomes has gained widespread attention (Burchard et al., 2004). A contributing factor to the race/ ethnic-specific health disparities is that racial and ethnic minorities are overrepresented in the population that is currently living below the federal poverty guidelines (Boudreaux *et al.*, 2003). Related to the availability or lack of disposable income are housing choices. Often affordable housing is located in neighborhoods where continuous environmental exacerbations, especially for those with respiratory disease, exist. Thus we realize that a large contribution to higher health disparities in racial and ethnic subpopulations may be income-related.

With the advancements being made in pharmacogenomics, population-specific risk of asthma exacerbations due to certain asthma drugs have been identified (J. G. Ford *et al.*, 2002). New research regarding race-specific polymorphisms may help to explain why certain subgroups within the asthmatics population have a higher frequency of poor response to asthma (R. G. Barr *et al.*, 2001; Federico *et al.*, 2005). However controversial, the use of phamcogenomics and toxicogenomics to investigate race- and ethnic-specific health disparities is regarded as promising.

Geographic-based disparities (urban vs rural) Recent studies regarding the variable distribution of asthma incidence and prevalence have been conducted in Europe (Eder & von Mutius, 2004). A hypothesis for this distribution known as the "hygiene hypothesis" states that early exposures to rural elements in the environment (i.e. livestock and endotoxin) confer a protective risk for developing allergy and asthma as child (Adler *et al.*, 2005). However, these same exposures (i.e. endotoxin) are well-published risk factors for exacerbation of asthma symptoms in adults (Merchant et al., 2005). Thus, an increased emphasis has been placed on the timing of exposures (de Marco *et al.*, 2004). In the US, studies investigating the prevalence of asthma and asthma morbidity within the context of the urban-rural environment have been few. This is likely due to the fact that the definition of rural in the US is varied. However, many studies have been conducted assessing the relationship of urban characteristics and the incidence, prevalence, and morbidity of asthma (Crain et al., 2002; Kim et al., 2004b; Kunzli et al., 2003; U.S. Department of Health and Human Services, 2000). These characteristics of urban life include such as traffic density, population density, and poor housing. However, there have been very few published reports comparing these characteristics within the urban-rural context and assessing their effect on asthma.

1.3 Cellular events that contribute to asthma morbidity

Characteristic features of asthma include reversible airflow obstruction and hyperresponsiveness in the upper and lower airways (W. W. Busse et al., 2003). Asthma research has focused on mechanisms of airway inflammation, regulation of these processes, and how these events result in altered lung function due to tissue remodeling.

Inflammation. Airway hyperresponsiveness to a variety of environmental stimuli is one of the characteristic features of asthma (NHLBI, 1997). These stimuli include may include those that are chemical (i.e. irritants), physical (i.e.cold air), or biological (i.e. respiratory pathogens) in nature. In all cases, the result is an inflammatory response that involves an increased production of granulocytes, particularly eosinophils once considered to be a bystander cell in during the immune response. Studies have shown that eosinophils exacerbate and prolong inflammatory responses in asthma by the production of immune regulatory cytokines, chemokines, and growth factors (Adamko *et al.*, 2002). These factors further aggravate inflammation during an asthma attack by attracting more cells to the site of inflammation and activating these on their arrival. In asthma, eosinophils are thought to self-propagate and prolong their own survival through the production of cytokines such as granulocyte-macrophage colony-stimulating factor (GM-CSF).

The Th1 vs Th2 paradigm in asthma. In 1994, 2 subsets of T helper lymphocytes were identified and come to be known Th1 and Th2 cells (Mosmann *et al.*, 1986). Studies since have shown that that activated Th2 lymphocytes and the production of certain cytokines such as interleukin (IL)-4, IL-13, and IL-5 are responsible for eosinophil activation and IgE production (Chinen & Shearer, 2003). For asthmatics, this set of events results in the underlying inflammation responsible for asthma symptoms (Lemanske, 2000). Although the Th1 and Th2 subsets develop from the same precursor cells known as naïve $CD4^+$ T lymphocytes their differentiation is determined by environmental stimuli present early during immune responses.

Th2 differentiation occurs in response to environmental allergens and helminths via activated antigen-presenting cells under the influence of IL-4 (Ngoc *et al.*, 2005). Activated Th2

lymphocytes produce IL- 4, IL-13, and IL-5, which are responsible for IgE production by B cells, eosinophil activation and recruitment, and mucus production (Liu *et al.*, 2004). In contrast, Th1 cells differentiate from naïve $CD4^+$ cells in response to microbial activation of antigen-presenting cells under the influence of IL-12. Differentiated Th1 cells secrete interferon-gamma (IFN- γ) which is important in the intracellular destruction of phagocytosed microbes. Furthermore, IFN- γ produced by Th1 cells and IL-4 produced by Th2 counter-regulate each other. Early asthma studies focused on a the T-cell repertoire, specifically the Th1/ Th2 "imbalance", in hopes of explaining the pathophysiology of asthma (Umetsu *et al.*, 2003). However, recent studies have identified the other players such as T-regulatory cells and natural killer (NK) T-cells as having a more prominent role in asthma. Thus, the explanation of asthma patho-physiology using the Th1/ Th2 paradigm may have been an oversimplification of a complex disease.

Remodeling. Airway remodeling is a term that is indicative of changes in the composition, quantity and organization of the cellular and molecular components of the airway wall (S. T. Holgate et al., 2004). The epithelial–mesenchymal trophic unit is a concept that describes how the integrity of the airway wall depends upon the maintenance of signals between the epithelium and the underlying mesenchyme. The mesenchyme is a basement membrane surrounded by layers of fibroblasts, ECM (extracellular matrix) and smooth muscle cells that is interspersed by vessels, neural elements and an immune network. It is the disruption of this trophic state leads to airway remodeling. In asthma, the disruption is caused by airway hyper-responsiveness (AHR) and inflammation.

An increase in the thickness of the layer immediately beneath the basement membrane, known as fibrosis, has been an observed in asthma and increases proportionately with disease severity (Matsumoto et al., 2005). Multiple studies have also documented the thickening of the airway wall in asthma. Although some of this thickening may be temporary due to inflammation, most are likely permanent. The permanent changes in basement membrane thickness involve matrix deposition and increased muscle mass and increases with both disease severity and duration of asthma (Bai & Knight, 2005; Cundall et al., 2003).

1.4 Heritability, genetics and asthma

Familial. Parental atopy has been identified as a risk factor for childhood asthma (Jaakkola *et al.*, 2005). Jaakkola, et al reported that the likelihood of children of developing asthma was greater if their parents were atopic (IRR = 1.52, CI =1.08-2.13). Further investigation into the influence of parental asthma history on the risk of childhood asthma revealed that a higher risk is conferred by the father's asthma status than the mother's (Alford et al., 2004). Asthma status in the fathers, whether it was childhood-only, adulthood-only, or persistent, was associated with current asthma in the children. These investigators also reported a significant relationship between allergy in the father and atopy in the study children. An additional study found that children whose parents were atopic were more likely to have positive dust mite skin test (Cole Johnson *et al.*, 2004).

Candidate asthma genes and pharmaco-genomics. ADAM 33, the first gene identified as a candidate for asthma, now has a postulated role in myogenesis, airway modeling, and signaling via protein shedding (Blakey et al., 2005). Recently, a variant in ADAM33 was identified

(Jongepier et al., 2004). The authors concluded that this variant may not only important in the development of asthma but also in disease progression and enhanced airway remodeling. With the progress being made in the field of genomics, we are likely find that environmental factors do influence the expression of genes and the ultimate clinical phenotype of asthma and atopy (Blumenthal, 2005). Additional studies have addressed polymorphisms in cellular receptors and surface markers required for the inflammation seen during asthma. Alterations in the genes encoding for the interleukin (IL)-8 receptor (Stemmler et al., 2005), IL-4 (Basehore et al., 2004), and the major histocompatibility coplex (MHC) (Aron et al., 1999) all have potential implications with respect to the inflammatory process seen in asthmatics. With respect to pharmacotherapy, polymorphisms in the genes encoding for the B-adrenergic receptor and the glucocorticoid receptor (Hawkins et al., 2004) may have implications with respect to the drug therapy and the control of asthma symptoms. Finally, understanding why asthmatics have a lack of tolerance to common environmental stimuli may be realized with the identification of polymorphisms in the genes encoding for toll-like receptors, a key player in the innate immune response (Davies, 2001; Lazarus et al., 2004).

Gene-environment interaction. As previously mentioned, polymorphisms in the genes that regulate our tolerance for common environmental stimuli have been identified (Aron et al., 1999). Deficiency of the antioxidant Glutathione–S–Transferase (GST) in children and *in utero* exposure to passive environmental tobacco smoke has been associated with the development of asthma (Kabesch et al., 2004). The lack of antioxidants obtained through diet and polymorphisms in the gene encoding for a class of GST have been associated with asthma and wheeze in children who live in areas with high levels of ozone (Romieu et al., 2004).

Polymorphisms in the gene that encodes for the enzymes that modulate the production of the cysteinyl-leukotrienes (cys-LTs), another class of proinflammatory mediators in asthma (Kedda et al., 2004). This could explain why certain asthmatics are not able to tolerate aspirin as cys-LTs are produced as a by-product after aspirin ingestion. With the identification of toll-like receptors and their respective polymorphisms, the differential response of the host to pathogens incurred naturally and during infections is better understood (D. N. Cook *et al.*, 2004; Leung *et al.*, 2005).

1.5. Phenotypes of asthma

In the literature, phenotypes of asthma are often described by the clinical manifestations, suspected origin, or age of onset. The following are brief descriptions of the phenotypes of asthma within these contexts.

Clinically-based. The term severe asthma most often describes a pathology where persistent eosinophilic inflammation exists despite the use of high dose corticosteroids (S. Wenzel, 2003). This the term “steroid” resistant has also been used to describe this phenotype (W. W. Busse et al., 2000).

Etiology-based. Aspirin-sensitive asthma has been used to describe the phenotype in which asthmatic individuals exhibit severe asthma symptoms upon ingestion of aspirin/ non-steroid anti-inflammatory drugs (Morwood *et al.*, 2005). This phenotype is observed more often in severe asthmatics. Occupational asthma and wheeze has been used to describe airway hyper-responsiveness due to an “asthmogen” exposure within the occupational setting (Bang *et al.*,

2005; Hoppin *et al.*, 2004). Additional phenotypes such as exercise-induced asthma (Abu-Hasan *et al.*, 2005) and cold weather-induced asthma (Storms, 2003) have been reported but their prevalence in the general population is not known.

Adult vs Childhood. In children, three asthma phenotypes are now well defined: transient infant wheezing, nonatopic wheezing of the toddler, and IgE-mediated wheezing/asthma (Bel, 2004). In adults, asthma persisting from childhood into adulthood should be distinguished from asthma starting in adulthood. The risk factors for childhood asthma include atopy (Arshad *et al.*, 2005), respiratory viruses (Gern *et al.*, 2005), and exposure to cigarette smoke (Arruda et al., 2005; Cantani & Micera, 2005). However, much less is known about the risk factors for adult-onset asthma.

1.6. Risk factors for adult asthma morbidity

Female gender. The prevalence of female within the adult asthma population has been well documented (Arif et al., 2003). However, the contributing factors to this trend are less known. In 2004, Barr et al found that hormone replacement therapy was a risk factor for newly diagnosed asthma for women enrolled in the Nurses Health Study (R. Graham Barr, 2004). With respect to aspirin-sensitive asthma, polymorphisms within the promoter region of the COX2 gene have been identified. Individuals who are homozygous for this variation have an increased production of prostaglandins, are more likely to be female and tend to have the severe form of asthma (Szczeklik *et al.*, 2004).

Current age. Current age in addition to nocturnal asthma symptoms and hospitalization have been identified as risk factors for asthma morbidity in adults (Ellman et al., 1997). A recent study found that medication and health care utilization (surrogates for disease severity) was higher in older adult asthmatic females (Schatz & Camargo, 2003).

BMI. The role that obesity, as measured by body mass index (BMI), plays in the pathology of asthma is unclear. The parallel increase in asthma and obesity raises the question if BMI is a risk factor for developing asthma (E. S. Ford, 2005). In addition, asthmatic adults are more likely to be obese when compared to non-asthmatics (E. S. Ford & Mannino, 2005). Recent studies have also found that BMI increases with asthma severity (Akerman *et al.*, 2004). The gender-specific association of BMI with asthma has been observed equally in both genders during adulthood (Thomsen et al., 2005) but is higher in school-age boys (Gilliland et al., 2003). The relationship between the built environment and obesity and asthma is now a focus of some studies (Brisbon *et al.*, 2005).

Age of onset and length of disease. Although the length of disease is associated with disease severity in child-onset asthmatics, there is no relationship in those who developed asthma as an adult (Jenkins et al., 2003). Length of disease in conjunction with house dust mite allergy and aspirin sensitivity were cited as risk factors by Kupczyk, et al (Kupczyk *et al.*, 2004). Miranda, et al found that subjects with early-onset, severe asthma had significantly more allergen and more allergic symptoms than subjects with adult-onset asthma (Miranda *et al.*, 2004). This was in contrast to adult-onset asthmatics that had lower lung function than early-onset, despite a shorter duration of illness.

Comorbdities Rhinitis has been shown to be associated with both atopic and non-atopic adult asthma (Guerra *et al.,* 2002). Other co-morbidities such as gastroesophageal reflux disease (GERD) and chronic sinusitis have been associated with the increased need for high dose corticosteroids (Liou *et al.*, 2003).

Allergy and atopy history. Within the adult asthma population, the atopic and non-atopic subgroups have distinguishing characteristics (Nieves *et al.*, 2005; Romanet-Manent *et al.*, 2002). Within the non- atopic adult asthmatic group, the majority are female, tend to have adult-onset of asthma, have lower lung function, and are older. Within the atopic group, the majority are male, tend to have seasonal allergies symptoms, and are more likely to have developed asthma as a child.

1.7. Environmental triggers of asthma and asthma morbidity

*Chemica*l. It has been shown that exposure to cigarette smoke is not only a risk factor for childhood asthma, but it also impedes the efficacy of glucocorticoids in adult asthmatics (Chaudhuri et al., 2003). Exposure to high levels of indoor nitrogen dioxide in combination with respiratory viral infections is also a risk factor for asthma exacerbations (Chauhan et al., 2003). Atopic asthmatics are at an increased risk of exacerbations after exposure to low levels of ozone suggesting an increase in allergen sensitivity due to this chemical (L. L. Chen *et al.*, 2004a). Another study found an association with the time spent outdoors and respiratory symptoms in children who lived in areas with high ozone levels (McConnell et al., 2002). Other pollutants that contribute to the ambient air quality have been associated with asthma exacerbations (Farhat

et al., 2005; Kunzli et al., 2003). In addition to ozone, these pollutants include carbon monoxide, particulate matter, nitrogen dioxide, and sulfur dioxide. Source apportionment of these pollutants and the relationship to asthma symptoms has also been investigated (Kim et al., 2004a). Kim, et al found that even at low levels of traffic-source pollution, respiratory effects in children were observed. In addition, the respiratory effects decreased as the distance to the roads increased.

Biological (ie viral, bacterial, fungi). Individuals with asthma are not at an increased risk for rhinovirus (Corne et al., 2002). However, virus-induced (primarily rhinovirus) asthma exacerbations is likely be around 80–85% in school-aged children (Contoli *et al.*, 2005). These studies suggest that the asthmatic is more likely to suffer ill-consequences from this synergistic relationship. Interestingly, the relationship of influenza and asthma symptoms is not known even though less than 50% of asthmatics report being vaccinated against the flu (E. S. Ford *et al.*, 2004). The association between bacterial respiratory pathogens and adult asthma severity has been published recently (Gencay *et al.*, 2001; Lemanske, 2003; Martin *et al.*, 2001). However, it is not clear if the effect is due to infection or to antigenic response to components of the pathogen, such as heat shock proteins (Huittinen *et al.*, 2001; Kinnunen *et al.*, 2001). Co-infection with another respiratory bacteria or virus has also been cited as a risk factor for asthma symptoms in adults (Lieberman et al., 2003).

1.8. Remaining uncertainties with respect to asthma morbidity in adults.

It is obvious that much of research regarding risk factors for asthma incidence and asthma morbidity has focused on children. Although it is unlikely that the risk conferred to children by tobacco smoke and air pollution is less in adults, the risk conferred by co-morbidities and infection is not known. In addition, without a chronic disease surveillance system at the local level, we are not able to address the population distribution of asthma morbidity in either children or adults. Finally, the influence of the protective "rural" environment has not been investigated in Pennsylvania. Of interest if whether this protection is conferred by the presence of rural characteristics such as farming and agriculture or by the lack of urban characteristics such as traffic and industry.

1.9 Literature cited

Abu-Hasan, M., Tannous, B., & Weinberger, M. (2005). Exercise-induced dyspnea in children and adolescents: if not asthma then what? *Ann Allergy Asthma Immunol, 94*(3), 366-371.

Adamko, D., Lacy, P., & Moqbel, R. (2002). Mechanisms of eosinophil recruitment and activation. *Curr Allergy Asthma Rep, 2*(2), 107-116.

Adams, R. J., Weiss, S. T., & Fuhlbrigge, A. (2003). How and by whom care is delivered influences anti-inflammatory use in asthma: Results of a national population survey. *J Allergy Clin Immunol, 112*(2), 445-450.

Akerman, M. J., Calacanis, C. M., & Madsen, M. K. (2004). Relationship between asthma severity and obesity. *J Asthma, 41*(5), 521-526.

Alford, S. H., Zoratti, E., Peterson, E. L., Maliarik, M., Ownby, D. R., & Johnson, C. C. (2004). Parental history of atopic disease: disease pattern and risk of pediatric atopy in offspring. *J Allergy Clin Immunol, 114*(5), 1046-1050.

Apter, A. J. (2003). Clinical advances in adult asthma. *J Allergy Clin Immunol, 111*(3 Suppl), S780-784.

Arif, A. A., Delclos, G. L., Lee, E. S., Tortolero, S. R., & Whitehead, L. W. (2003). Prevalence and risk factors of asthma and wheezing among US adults: an analysis of the NHANES III data. *Eur Respir J, 21*(5), 827-833.

Aron, Y., Busson, M., Polla, B. S., Dusser, D., Lockhart, A., Swierczewski, E., et al. (1999). Analysis of hsp70 gene polymorphism in allergic asthma. *Allergy, 54*(2), 165-170.

Arruda, L. K., Sole, D., Baena-Cagnani, C. E., & Naspitz, C. K. (2005). Risk factors for asthma and atopy. *Curr Opin Allergy Clin Immunol, 5*(2), 153-159.

Arshad, S. H., Kurukulaaratchy, R. J., Fenn, M., & Matthews, S. (2005). Early life risk factors for current wheeze, asthma, and bronchial hyperresponsiveness at 10 years of age. *Chest, 127*(2), 502-508.

Bacharier, L. B., Strunk, R. C., Mauger, D., White, D., Lemanske Jr, R. F., & Sorkness, C. A. (2004). Classifying Asthma Severity in Children-Mismatch Between Symptoms, Medication Use and Lung Function. *Am J Respir Crit Care Med*.

Bai, T. R., & Knight, D. A. (2005). Structural changes in the airways in asthma: observations and consequences. *Clin Sci (Lond), 108*(6), 463-477.

Baker, K. M., Brand, D. A., & Hen, J., Jr. (2003). Classifying asthma: disagreement among specialists. *Chest, 124*(6), 2156-2163.

Bang, K. M., Hnizdo, E., & Doney, B. (2005). Prevalence of asthma by industry in the US population: a study of 2001 NHIS data. *Am J Ind Med, 47*(6), 500-508.

Barr, R. G. (2004). Propective Study of Postmenopausal Hormone Use and Newly Diagnosed Asthma and Chronic Obstructive Pulmonary Disease. *Archives of Internal Medicine, 164*(February 23,2004), 379-386.

Barr, R. G., Cooper, D. M., Speizer, F. E., Drazen, J. M., & Camargo, C. A., Jr. (2001). Beta(2)-adrenoceptor polymorphism and body mass index are associated with adult-onset asthma in sedentary but not active women. *Chest, 120*(5), 1474-1479.

Basagana, X., Sunyer, J., Kogevinas, M., Zock, J. P., Duran-Tauleria, E., Jarvis, D., et al. (2004). Socioeconomic status and asthma prevalence in young adults: the European community respiratory health survey. *Am J Epidemiol, 160*(2), 178-188.

Basehore, M. J., Howard, T. D., Lange, L. A., Moore, W. C., Hawkins, G. A., Marshik, P. L., et al. (2004). A comprehensive evaluation of IL4 variants in ethnically diverse populations: Association of total serum IgE levels and asthma in white subjects. *J Allergy Clin Immunol, 114*(1), 80-87.

Bel, E. H. (2004). Clinical phenotypes of asthma. *Curr Opin Pulm Med, 10*(1), 44-50.

Blakey, J., Halapi, E., Bjornsdottir, U. S., Wheatley, A., Kristinsson, S., Upmanyu, R., et al. (2005). Contribution of ADAM33 polymorphisms to the population risk of asthma. *Thorax, 60*(4), 274-276.

Bloom, J. W., Chacko, J., Lohman, I. C., Halonen, M., Martinez, F. D., & Miesfeld, R. L. (2004). Differential control of eosinophil survival by glucocorticoids. *Apoptosis, 9*(1), 97-104.

Blumenthal, M. N. (2005). The role of genetics in the development of asthma and atopy. *Curr Opin Allergy Clin Immunol, 5*(2), 141-145.

Boudreaux, E. D., Emond, S. D., Clark, S., & Camargo, C. A., Jr. (2003). Acute asthma among adults presenting to the emergency department: the role of race/ethnicity and socioeconomic status Race/ethnicity and asthma among children presenting to the emergency department: differences in disease severity and management. *Chest, 124*(3), 803-812.

Brisbon, N., Plumb, J., Brawer, R., & Paxman, D. (2005). The asthma and obesity epidemics: The role played by the built environment-a public health perspective. *J Allergy Clin Immunol, 115*(5), 1024-1028.

Brogger, J., Bakke, P., Eide, G. E., Johansen, B., Andersen, A., & Gulsvik, A. (2003). Long-term changes in adult asthma prevalence. *Eur Respir J, 21*(3), 468-472.

Burchard, E. G., Avila, P. C., Nazario, S., Casal, J., Torres, A., Rodriguez-Santana, J. R., et al. (2004). Lower bronchodilator responsiveness in Puerto Rican than in Mexican subjects with asthma. *Am J Respir Crit Care Med, 169*(3), 386-392.

Busse, W., Banks-Schlegel, S. P., & Larsen, G. L. (1995). Childhood- versus adult-onset asthma. *Am J Respir Crit Care Med, 151*(5), 1635-1639.

Busse, W. W., Banks-Schlegel, S., & Wenzel, S. E. (2000). Pathophysiology of severe asthma. *J Allergy Clin Immunol, 106*(6), 1033-1042.

Busse, W. W., Rosenwasser, L. J., Lenfant, C., Lemanske, R. F., Jr., Banks-Schlegel, S., & Wenzel, S. E. (2003). Mechanisms of asthma. *J Allergy Clin Immunol, 111*(3 Suppl), S799-804.

Cantani, A., & Micera, M. (2005). Epidemiology of passive smoke: a prospective study in 589 children. *Eur Rev Med Pharmacol Sci, 9*(1), 23-30.

Castro, M., Zimmermann, N. A., Crocker, S., Bradley, J., Leven, C., & Schechtman, K. B. (2003). Asthma intervention program prevents readmissions in high healthcare users. *Am J Respir Crit Care Med, 168*(9), 1095-1099.

Cesaroni, G., Farchi, S., Davoli, M., Forastiere, F., & Perucci, C. A. (2003). Individual and area-based indicators of socioeconomic status and childhood asthma. *Eur Respir J, 22*(4), 619-624.

Chan-Yeung, M., Zhan, L. X., Tu, D. H., Li, B., He, G. X., Kauppinen, R., et al. (2002). The prevalence of asthma and asthma-like symptoms among adults in rural Beijing, China. *Eur Respir J, 19*(5), 853-858.

Chaudhuri, R., Livingston, E., McMahon, A. D., Thomson, L., Borland, W., & Thomson, N. C. (2003). Cigarette smoking impairs the therapeutic response to oral corticosteroids in chronic asthma. *Am J Respir Crit Care Med, 168*(11), 1308-1311.

Chauhan, A. J., Inskip, H. M., Linaker, C. H., Smith, S., Schreiber, J., Johnston, S. L., et al. (2003). Personal exposure to nitrogen dioxide (NO2) and the severity of virus-induced asthma in children. *Lancet, 361*(9373), 1939-1944.

Chen, L. L., Tager, I. B., Peden, D. B., Christian, D. L., Ferrando, R. E., Welch, B. S., et al. (2004). Effect of ozone exposure on airway responses to inhaled allergen in asthmatic subjects. *Chest, 125*(6), 2328-2335.

Chen, Y., Stewart, P., Dales, R., Johansen, H., Scott, G., & Taylor, G. (2004). Ecological measures of socioeconomic status and hospital readmissions for asthma among Canadian adults. *Respir Med, 98*(5), 446-453.

Chinen, J., & Shearer, W. T. (2003). Basic and clinical immunology. *J Allergy Clin Immunol, 111*(3 Suppl), S813-818.

Cole Johnson, C., Ownby, D. R., Havstad, S. L., & Peterson, E. L. (2004). Family history, dust mite exposure in early childhood, and risk for pediatric atopy and asthma. *J Allergy Clin Immunol, 114*(1), 105-110.

Contoli, M., Caramori, G., Mallia, P., Johnston, S., & Papi, A. (2005). Mechanisms of respiratory virus-induced asthma exacerbations. *Clin Exp Allergy, 35*(2), 137-145.

Cook, D. N., Pisetsky, D. S., & Schwartz, D. A. (2004). Toll-like receptors in the pathogenesis of human disease. *Nat Immunol, 5*(10), 975-979.

Corne, J. M., Marshall, C., Smith, S., Schreiber, J., Sanderson, G., Holgate, S. T., et al. (2002). Frequency, severity, and duration of rhinovirus infections in asthmatic and non-asthmatic individuals: a longitudinal cohort study. *Lancet, 359*(9309), 831-834.

Corvalan, C., Amigo, H., Bustos, P., & Rona, R. J. (2005). Socioeconomic Risk Factors for Asthma in Chilean Young Adults. *Am J Public Health, 95*(8), 1375-1381.

Crain, E. F., Walter, M., O'Connor, G. T., Mitchell, H., Gruchalla, R. S., Kattan, M., et al. (2002). Home and allergic characteristics of children with asthma in seven U.S. urban communities and design of an environmental intervention: the Inner-City Asthma Study. *Environ Health Perspect, 110*(9), 939-945.

Cundall, M., Sun, Y., Miranda, C., Trudeau, J. B., Barnes, S., Wenzel, S. E., et al. (2003). Neutrophil-derived matrix metalloproteinase-9 is increased in severe asthma and poorly inhibited by glucocorticoids Mechanisms of severe asthma Pathology of difficult asthma. *J Allergy Clin Immunol, 112*(6), 1064-1071.

Davies, D. E. (2001). The bronchial epithelium: translating gene and environment interactions in asthma. *Curr Opin Allergy Clin Immunol, 1*(1), 67-71.

de Marco, R., Pattaro, C., Locatelli, F., & Svanes, C. (2004). Influence of early life exposures on incidence and remission of asthma throughout life. *J Allergy Clin Immunol, 113*(5), 845-852.

Eder, W., & von Mutius, E. (2004). Hygiene hypothesis and endotoxin: what is the evidence? *Curr Opin Allergy Clin Immunol, 4*(2), 113-117.

Ellman, M. S., Viscoli, C. M., Sears, M. R., Taylor, D. R., Beckett, W. S., & Horwitz, R. I. (1997). A new index of prognostic severity for chronic asthma. *Chest, 112*(3), 582-590.

ENFUMOSA. (2003). The ENFUMOSA cross-sectional European multicentre study of the clinical phenotype of chronic severe asthma. European Network for Understanding Mechanisms of Severe Asthma. *Eur Respir J, 22*(3), 470-477.

Farhat, S. C., Paulo, R. L., Shimoda, T. M., Conceicao, G. M., Lin, C. A., Braga, A. L., et al. (2005). Effect of air pollution on pediatric respiratory emergency room visits and hospital admissions. *Braz J Med Biol Res, 38*(2), 227-235.

Federico, M. J., Covar, R. A., Brown, E. E., Leung, D. Y., & Spahn, J. D. (2005). Racial differences in T-lymphocyte response to glucocorticoids. *Chest, 127*(2), 571-578.

Ford, E. S. (2005). The epidemiology of obesity and asthma. *J Allergy Clin Immunol, 115*(5), 897-909.

Ford, E. S., & Mannino, D. M. (2005). Time trends in obesity among adults with asthma in the United States: findings from three national surveys. *J Asthma, 42*(2), 91-95.

Ford, E. S., Mannino, D. M., Homa, D. M., Gwynn, C., Redd, S. C., Moriarty, D. G., et al. (2003). Self-reported asthma and health-related quality of life: findings from the behavioral risk factor surveillance system. *Chest, 123*(1), 119-127.

Ford, E. S., Williams, S. G., Mannino, D. M., & Redd, S. C. (2004). Influenza vaccination coverage among adults with asthma: findings from the 2000 Behavioral Risk Factor Surveillance System. *Am J Med, 116*(8), 555-558.

Ford, J. G., Iqbal, J., & Sunmonu, Y. (2002). Beta2-agonists: friend or foe? *Semin Respir Crit Care Med, 23*(4), 369-376.

Fuhlbrigge, A., Jackson, B., & Wright, R. (2002). Gender and Asthma. *Immunology and Allergy Clinics of North America, 22*(4).

Gencay, M., Rudiger, J. J., Tamm, M., Soler, M., Perruchoud, A. P., & Roth, M. (2001). Increased frequency of Chlamydia pneumoniae antibodies in patients with asthma. *Am J Respir Crit Care Med, 163*(5), 1097-1100.

Gern, J. E., Rosenthal, L. A., Sorkness, R. L., & Lemanske, R. F., Jr. (2005). Effects of viral respiratory infections on lung development and childhood asthma. *J Allergy Clin Immunol, 115*(4), 668-674; quiz 675.

Gilliland, F. D., Berhane, K., Islam, T., McConnell, R., Gauderman, W. J., Gilliland, S. S., et al. (2003). Obesity and the risk of newly diagnosed asthma in school-age children. *Am J Epidemiol, 158*(5), 406-415.

Godard, P., Chanez, P., Siraudin, L., Nicoloyannis, N., & Duru, G. (2002). Costs of asthma are correlated with severity: a 1-yr prospective study. *Eur Respir J, 19*(1), 61-67.

Guerra, S., Sherrill, D. L., Martinez, F. D., & Barbee, R. A. (2002). Rhinitis as an independent risk factor for adult-onset asthma. *J Allergy Clin Immunol, 109*(3), 419-425.

Hawkins, G. A., Amelung, P. J., Smith, R. S., Jongepier, H., Howard, T. D., Koppelman, G. H., et al. (2004). Identification of polymorphisms in the human glucocorticoid receptor gene (NR3C1) in a multi-racial asthma case and control screening panel. *DNA Seq, 15*(3), 167-173.

Holgate, S. T., Holloway, J., Wilson, S., Bucchieri, F., Puddicombe, S., & Davies, D. E. (2004). Epithelial-mesenchymal communication in the pathogenesis of chronic asthma. *Proc Am Thorac Soc, 1*(2), 93-98.

Hoppin, J. A., Umbach, D. M., London, S. J., Alavanja, M. C., & Sandler, D. P. (2004). Diesel Exhaust, Solvents, and Other Occupational Exposures as Risk Factors for Wheeze Among Farmers. *Am J Respir Crit Care Med*.

Huittinen, T., Hahn, D., Anttila, T., Wahlstrom, E., Saikku, P., & Leinonen, M. (2001). Host immune response to Chlamydia pneumoniae heat shock protein 60 is associated with asthma. *Eur Respir J, 17*(6), 1078-1082.

Ilowite, J., Webb, R., Friedman, B., Kerwin, E., Bird, S. R., Hustad, C. M., et al. (2004). Addition of montelukast or salmeterol to fluticasone for protection against asthma attacks: a randomized, double-blind, multicenter study. *Ann Allergy Asthma Immunol, 92*(6), 641-648.

Jaakkola, J. J., Hwang, B. F., & Jaakkola, N. (2005). Home dampness and molds, parental atopy, and asthma in childhood: a six-year population-based cohort study. *Environ Health Perspect, 113*(3), 357-361.

Jenkins, H. A., Cherniack, R., Szefler, S. J., Covar, R., Gelfand, E. W., & Spahn, J. D. (2003). A comparison of the clinical characteristics of children and adults with severe asthma. *Chest, 124*(4), 1318-1324.

Jongepier, H., Boezen, H. M., Dijkstra, A., Howard, T. D., Vonk, J. M., Koppelman, G. H., et al. (2004). Polymorphisms of the ADAM33 gene are associated with accelerated lung function decline in asthma. *Clin Exp Allergy, 34*(5), 757-760.

Kabesch, M., Hoefler, C., Carr, D., Leupold, W., Weiland, S. K., & von Mutius, E. (2004). Glutathione S transferase deficiency and passive smoking increase childhood asthma. *Thorax, 59*(7), 569-573.

Kedda, M. A., Shi, J., Duffy, D., Phelps, S., Yang, I., O'Hara, K., et al. (2004). Characterization of two polymorphisms in the leukotriene C4 synthase gene in an Australian population of subjects with mild, moderate, and severe asthma. *J Allergy Clin Immunol, 113*(5), 889-895.

Kim, J. J., Smorodinsky, S., Lipsett, M., Singer, B. C., Hodgson, A. T., & Ostro, B. (2004a). Traffic-related Air Pollution Near Busy Roads: The East Bay Children's Respiratory Health Study. *Am J Respir Crit Care Med*.

Kim, J. J., Smorodinsky, S., Lipsett, M., Singer, B. C., Hodgson, A. T., & Ostro, B. (2004b). Traffic-related air pollution near busy roads: the East Bay Children's Respiratory Health Study. *Am J Respir Crit Care Med, 170*(5), 520-526.

Kinnunen, A., Paavonen, J., & Surcel, H. M. (2001). Heat shock protein 60 specific T-cell response in chlamydial infections. *Scand J Immunol, 54*(1-2), 76-81.

Kunzli, N., McConnell, R., Bates, D., Bastain, T., Hricko, A., Lurmann, F., et al. (2003). Breathless in Los Angeles: the exhausting search for clean air. *Am J Public Health, 93*(9), 1494-1499.

Kupczyk, M., Kuprys, I., Gorski, P., & Kuna, P. (2004). Aspirin intolerance and allergy to house dust mites: important factors associated with development of severe asthma. *Ann Allergy Asthma Immunol, 92*(4), 453-458.

Lazarus, R., Raby, B. A., Lange, C., Silverman, E. K., Kwiatkowski, D. J., Vercelli, D., et al. (2004). Toll-like Receptor 10 (TLR10) Genetic Variation is Associated with Asthma in Two Independent Samples. *Am J Respir Crit Care Med*.

Lemanske, R. F., Jr. (2000). Inflammatory events in asthma: an expanding equation. *J Allergy Clin Immunol, 105*(6 Pt 2), S633-636.

Lemanske, R. F., Jr. (2003). Is asthma an infectious disease? Thomas A. Neff lecture. *Chest, 123*(3 Suppl), 385S-390S.

Lemanske, R. F., Jr., & Busse, W. W. (2003). 6. Asthma. *J Allergy Clin Immunol, 111*(2 Suppl), S502-519.

Leung, T. F., Tang, N. L., Wong, G. W., & Fok, T. F. (2005). CD14 and Toll-Like Receptors: Potential Contribution of Genetic Factors and Mechanisms to Inflammation and Allergy. *Curr Drug Targets Inflamm Allergy, 4*(2), 169-175.

Lieberman, D., Printz, S., Ben-Yaakov, M., Lazarovich, Z., Ohana, B., Friedman, M. G., et al. (2003). Atypical pathogen infection in adults with acute exacerbation of bronchial asthma. *Am J Respir Crit Care Med, 167*(3), 406-410.

Liou, A., Grubb, J. R., Schechtman, K. B., & Hamilos, D. L. (2003). Causative and contributive factors to asthma severity and patterns of medication use in patients seeking specialized asthma care. *Chest, 124*(5), 1781-1788.

Liu, L., Jarjour, N. N., Busse, W. W., & Kelly, E. A. (2004). Enhanced generation of helper T type 1 and 2 chemokines in allergen-induced asthma. *Am J Respir Crit Care Med, 169*(10), 1118-1124.

Mannino, D. M., Homa, D. M., Akinbami, L. J., Moorman, J. E., Gwynn, C., & Redd, S. C. (2002). Surveillance for asthma--United States, 1980-1999. *MMWR Surveill Summ, 51*(1), 1-13.

Martin, R. J., Kraft, M., Chu, H. W., Berns, E. A., & Cassell, G. H. (2001). A link between chronic asthma and chronic infection. *J Allergy Clin Immunol, 107*(4), 595-601.

Matsumoto, H., Niimi, A., Takemura, M., Ueda, T., Minakuchi, M., Tabuena, R., et al. (2005). Relationship of airway wall thickening to an imbalance between matrix metalloproteinase-9 and its inhibitor in asthma. *Thorax, 60*(4), 277-281.

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

Merchant, J. A., Naleway, A. L., Svendsen, E. R., Kelly, K. M., Burmeister, L. F., Stromquist, A. M., et al. (2005). Asthma and farm exposures in a cohort of rural Iowa children. *Environ Health Perspect, 113*(3), 350-356.

Miranda, C., Busacker, A., Balzar, S., Trudeau, J., & Wenzel, S. E. (2004). Distinguishing severe asthma phenotypes: role of age at onset and eosinophilic inflammation. *J Allergy Clin Immunol, 113*(1), 101-108.

Morwood, K., Gillis, D., Smith, W., & Kette, F. (2005). Aspirin-sensitive asthma. *Intern Med J, 35*(4), 240-246.

Mosmann, T. R., Cherwinski, H., Bond, M. W., Giedlin, M. A., & Coffman, R. L. (1986). Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins. *J Immunol, 136*(7), 2348-2357.

National Center for Environmental Health, C. D. C. (2003). *Asthma*. Retrieved 7 Sept 2004, from http://www.cdc.gov/nceh/airpollution/asthmaataglance/asthmaAAG.pdf

National Center for Health Statsitics. (2004). National Hospital Discharge Survey. Retrieved Aug 29, 2004 from http:www.cdc.gov/nchs

Ngoc, P. L., Gold, D. R., Tzianabos, A. O., Weiss, S. T., & Celedon, J. C. (2005). Cytokines, allergy, and asthma. *Curr Opin Allergy Clin Immunol, 5*(2), 161-166.

National Heart, Lung, and Blood Institue (1997). NAEPP Exert Panel Report for Asthma Diagnosis and Management.. Retrieved 10 Sept 2004, from http://ww.nhlbi.nih.gov

Nieves, A., Magnan, A., Boniface, S., Proudhon, H., Lanteaume, A., Romanet, S., et al. (2005). Phenotypes of asthma revisited upon the presence of atopy. *Respir Med, 99*(3), 347-354.

Peters, S. P. (2004). Asthma treatment in the 21st century: what's next? *Clin Rev Allergy Immunol, 27*(3), 197-205.

Romanet-Manent, S., Charpin, D., Magnan, A., Lanteaume, A., & Vervloet, D. (2002). Allergic vs nonallergic asthma: what makes the difference? *Allergy, 57*(7), 607-613.

Romieu, I., Sienra-Monge, J. J., Ramirez-Aguilar, M., Moreno-Macias, H., Reyes-Ruiz, N. I., Estela del Rio-Navarro, B., et al. (2004). Genetic polymorphism of GSTM1 and antioxidant supplementation influence lung function in relation to ozone exposure in asthmatic children in Mexico City. *Thorax, 59*(1), 8-10.

Rona, R. J., Smeeton, N. C., Bustos, P., Amigo, H., Diaz, P. V., Corvalan, C., et al. (2005). The early origins hypothesis with an emphasis on growth rate in the first year of life and asthma: a prospective study in Chile Socioeconomic Risk Factors for Asthma in Chilean Young Adults. *Thorax, 60*(7), 549-554.

Schatz, M., & Camargo, C. A., Jr. (2003). The relationship of sex to asthma prevalence, health care utilization, and medications in a large managed care organization. *Ann Allergy Asthma Immunol, 91*(6), 553-558.

Stemmler, S., Arinir, U., Klein, W., Rohde, G., Hoffjan, S., Wirkus, N., et al. (2005). Association of interleukin-8 receptor alpha polymorphisms with chronic obstructive pulmonary disease and asthma. *Genes Immun, 6*(3), 225-230.

Storms, W. W. (2003). Review of exercise-induced asthma. *Med Sci Sports Exerc, 35*(9), 1464-1470.

Szczeklik, W., Sanak, M., & Szczeklik, A. (2004). Functional effects and gender association of COX-2 gene polymorphism G-765C in bronchial asthma. *J Allergy Clin Immunol, 114*(2), 248-253.

Thomsen, S. F., Ulrik, C. S., Kyvik, K. O., Larsen, K., Skadhauge, L. R., Steffensen, I., et al. (2005). The incidence of asthma in young adults. *Chest, 127*(6), 1928-1934.

U.S. Department of Health and Human Services. (2000). *Healthy People 2010: Respiratory Diseases (Goal 24)*. Retrieved 10 Sept 2004, from http://www.healthypeople.gov/Document/pdf/Volume2/24Respiratory.pdf

Umetsu, D. T., Akbari, O., & Dekruyff, R. H. (2003). Regulatory T cells control the development of allergic disease and asthma. *J Allergy Clin Immunol, 112*(3), 480-487; quiz 488.

Wenzel, S. (2003). Mechanisms of severe asthma Pathology of difficult asthma. *Clin Exp Allergy, 33*(12), 1622-1628.

2. SPECIFIC AIMS

The overall goal of this research was to address study questions that remain regarding the prevalence of, and the risk factors for, adult asthma morbidity. The specific aims were as follows:

1) To assess if the degree of urbanization (as measured by traffic and population density) contributes to adult asthma hospitalizations, within the urban-rural context. We used adult asthma hospitalization data to assess these rates and frequencies for adult asthmatics in 6 Pennsylvania counties.
2) To assess the utility of local asthma hospitalization data as an environmental health indicator. Of interest was the demographic, temporal, and geographic distribution of adult asthma hospitalizations for Allegheny County's 89 zip codes.
3) To assess the risk conferred to adult severe asthmatics by respiratory infection due to atypical respiratory pathogens (i.e. *Mycoplamsa pneumonia, and Chlamydia pneumonia*). For this aim, our study population was a cohort enrolled in the multi-city Severe Asthma Research Project.

3. RESULTS

3.1. Chapter 1

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COMMUNITY URBANIZATION AND HOSPITALIZATION OF ADULTS FOR ASTHMA

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3.1.1 Preface

Published investigations regarding the prevalence of asthma morbidity within the urban-rural context in the United States are rare. Here we test the hypothesis that indices of urbanization (i.e. traffic, population) are risk factors for adult asthma hospitalizations.

3.1.2. Abstract

Asthma research has traditionally focused on children and the elderly, two populations considered the most susceptible to complications. However, the prevalence of asthma in the adult population (19-64 years) is gaining recognition as a formidable clinical and public health problem. In addition, few studies have assessed the incidence of adult asthma hospitalizations in urban vs. non-urban areas. Using population size, population density, and traffic-related factors to define urban vs. non-urban environments, six Pennsylvania counties were selected to test the hypothesis that the degree of urbanization influences the asthma hospitalization rate for adults. The study group was comprised of adults, 19-64 years, who were hospitalized for asthma (as the primary diagnosis) from 1999-2001. To define urbanization related to traffic, daily vehicular traffic count and miles of roads/highways for each of the 6 counties were used. We found, in some of the counties, a decrease in the adult asthma hospitalization rate as urbanization decreased. However, for other counties, the rate increased as urbanization decreased. The counties in which the latter was observed had depressed measures of socio-economic status (SES). Our findings suggest that depressed socioeconomic conditions may supersede exposure to traffic-related pollution with respect to asthma hospitalizations.

3.1.3. Introduction

It is estimated that 150 million people worldwide are living with asthma including 15 million people in the United States (Mannino et al., 2002). Asthma has been defined as a "chronic inflammatory disease of the airways that involves many cells and cellular elements" (National Institutes of Health Asthma Education and Prevention Program [NAEPP], 2002). The inflammation is accompanied by increased airway hyper-responsiveness to a variety of environmental stimuli that include airborne allergens, viruses, tobacco smoke, and particulate matter (Etzel, 2003; Sotir, Yeatts, & Shy, 2003). In *Healthy People 2010*, asthma is cited as a major clinical and public health problem (U.S. Department of Health and Human Services, 2000). One of the key objectives in the government document is reduction of environmental exposures that contribute to events associated with diminished lung function, such as asthma hospitalization.

Risk factors for asthma include:

- Gender and prior diagnosis of allergies (Arif, Declos, Lee, Tortolero, & Whitehead, 2003; National Center for Environmental Health [NCEH], 2003)
- Communities with large populations and/or high household density (Crain et al., 2002)
- Proximity to heavy traffic patterns, although the extent of their contribution to asthma hospitalizations is not known (English et al., 1999; Garshick, Laden, Hart & Caron, 2003; Kim et al., 2004)
- Chronic exposure to nitrogen oxides and carbon monoxide which have been documented to exacerbate the inflammatory response in the asthmatic (Delfino, Gong, Linn, Pellizzari, & Hu, 2003; Ford et al., 2003; Gehring et al., 2002; Lin, Munsie, Hwang,

Fitzgerald, & Cayo, 2002; Nicolai et al., 2003; United States Environmental Protection Agency [U.S. EPA], 2005).

Traffic-related air pollution accounts for much of the diminished air quality seen especially in urban areas (Kunzli et al., 2003). Although emission standards are regulated by the Environmental Protection Agency, traffic volume and type are not (U.S. EPA, 2005). Heavy traffic patterns are a problem not only in large city centers, but also in areas of rapid suburban growth (Tibbetts, 2002). Thus, traffic "corridors" are becoming more common irrespective of their proximity to pre-exiting communities (Lwebuga-Mukasa, Oyana, Thenappan, & Ayirookuzhi, 2004).

In the past decade, there has been a surge in adult asthma and associated complications. The factors contributing to this increase are poorly understood although environmental factors of urbanization are suspect. However, measurement of "urbanization" is difficult. In the current study we assessed community urbanization by population size/density, the amount of vehicular traffic per day, and the total number of roads and highways. We tested the hypothesis that the degree of urbanization of 6 Pennsylvania counties, as measured by these criteria, is an environmental risk factor for adult asthma hospitalization.

3.1.4. Methods

Selection of counties

The Pennsylvania counties selected for this study were Allegheny, Dauphin, Erie, Fayette, Lancaster, and York. These counties were selected primarily as a sample of their varied distances to major urban centers. We further typify urbanization by incorporating both population and motor vehicle characteristics of an urban community. We used 4 measures: total population, population density (persons/mi^2), miles of roads/highways, and daily vehicle miles traveled. The population data were obtained from the 2000 Census published by the United States Census Bureau (United States Census Bureau [U.S. Census], 2000). Traffic-related information, obtained from the Pennsylvania Department of Transportation, consisted of miles of roads/ highways and daily vehicle miles traveled in each county. The counties were ranked for urbanization on a scale of 1-6 with respect to population size/ density, daily traffic density, and total miles of roads/ highways. The overall urbanization rank of each county was determined by averaging the scores for each of the four measures. The air quality of each county was evaluated using data contained in the Environmental Protection Agency's Toxic Release Inventory (U.S. EPA, 2000).

Case definitions

Hospitalization data for adults aged 19-64 were obtained from the Pennsylvania Health Care Cost Containment Council (Pennsylvania Health Care Cost Containment Council, 2005). During this three-year period, asthma (ICD code 493) was the primary diagnosis upon admission of 3156 cases. To control for patients hospitalized more than once during a calendar year, we utilized the patient identifier code (a randomly generated number unique to each individual in the

dataset). Thus, only one event per patient identifier code was used for rate analysis. The dataset also included demographic descriptors that allowed calculation of age-specific and gender-specific asthma hospitalization rates.

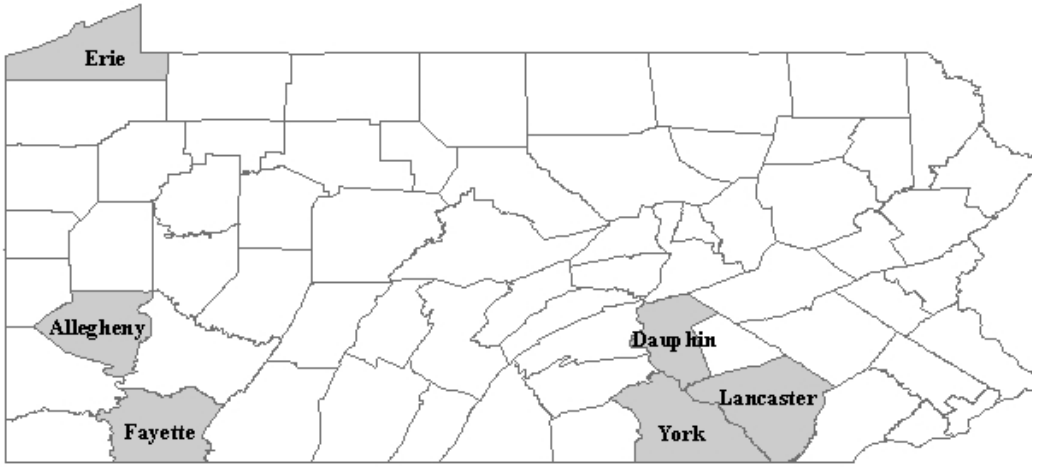
Data analysis

Hospitalization rates/ 10,000 standardized to population data from the 2000 United States Census (U.S. Census, 2000) were determined for asthma causes. Age-specific rates were calculated using the population counts also provided in the 2000 US Census. To be consistent with age-specific data published by the Centers for Disease Control, the population ages were stratified into 3 groups: 19-34, 35-44, and 45-64 yrs (NCEH, 2003). Poisson regression analysis was used to assess statistically significant contributions to the adult asthma hospitalization rates by each of the independent covariates (county rank, gender, and age). Previous studies have cited factors related to income and educational attainment as contributing to poor health outcomes (Boudreaux, Emond, Clark, & Camargo, 2003). Since we did not have such data for the individuals in our study population, we employed graphical methods using EXCEL to describe the distribution of socioeconomic data for each county and the relationship of such data to adult asthma hospitalization rates within the county. Statistical analyses were performed using STATA 8.0 and EXCEL for determination of relative risk. All estimates of significance were at $p = 0.05$.

3.1.5 Results

The degree of urbanization of each county was evaluated using the 4 measures described above. The results (table 1.1) indicate that ranks were consistent irrespective of the measure used. Allegheny County ranked first in each of the four categories. Fayette County ranked sixth in 3 of the 4 categories, and ranked fifth in the category of miles of roads/highways.

Table 1.1. Measures and rank of urbanization in the six Pennsylvania counties.



[a] Average of the four measures of urbanization
[b] Data obtained from the United States Census Bureau

County	Overall rank[a]	Total population[b]	Population density[b] [persons /mi^{2}]	Miles of roads/ highways[c]	Daily vehicle miles traveled[c]
Allegheny	1	1,270,612 (1)	1755 (1)	5688 (1)	25,154,896 (1)
Lancaster	2	474,601 (2)	496 (2)	3821 (2)	10,429,462 (2)
York	3	386,299 (3)	422 (4)	3691 (3)	8,462,878 (3)
Erie	4	279,636 (4)	350 (5)	2564 (4)	6,280,805 (5)
Dauphin	4	251,316 (5)	479 (3)	1866 (6)	8,166,979 (4)
Fayette	6	147,367 (6)	188 (6)	2075 (5)	2,744,746 (6)

[c] Data obtained from the Pennsylvania Dept of Transportation
The rank of the county with respect to each measure of urbanization is shown in parenthesis

Age adjusted adult asthma hospitalization rates (x/ 10,000) for each county are shown in figure 1.1. The counties are ordered from left to right by decreasing rank of urbanization. The hospitalization rate initially decreases with decreased urbanization, then increases as urbanization further decreases. Fayette County, which ranked as the least urbanized county, had an asthma hospitalization rate greater than that of Allegheny County, the most urbanized county.

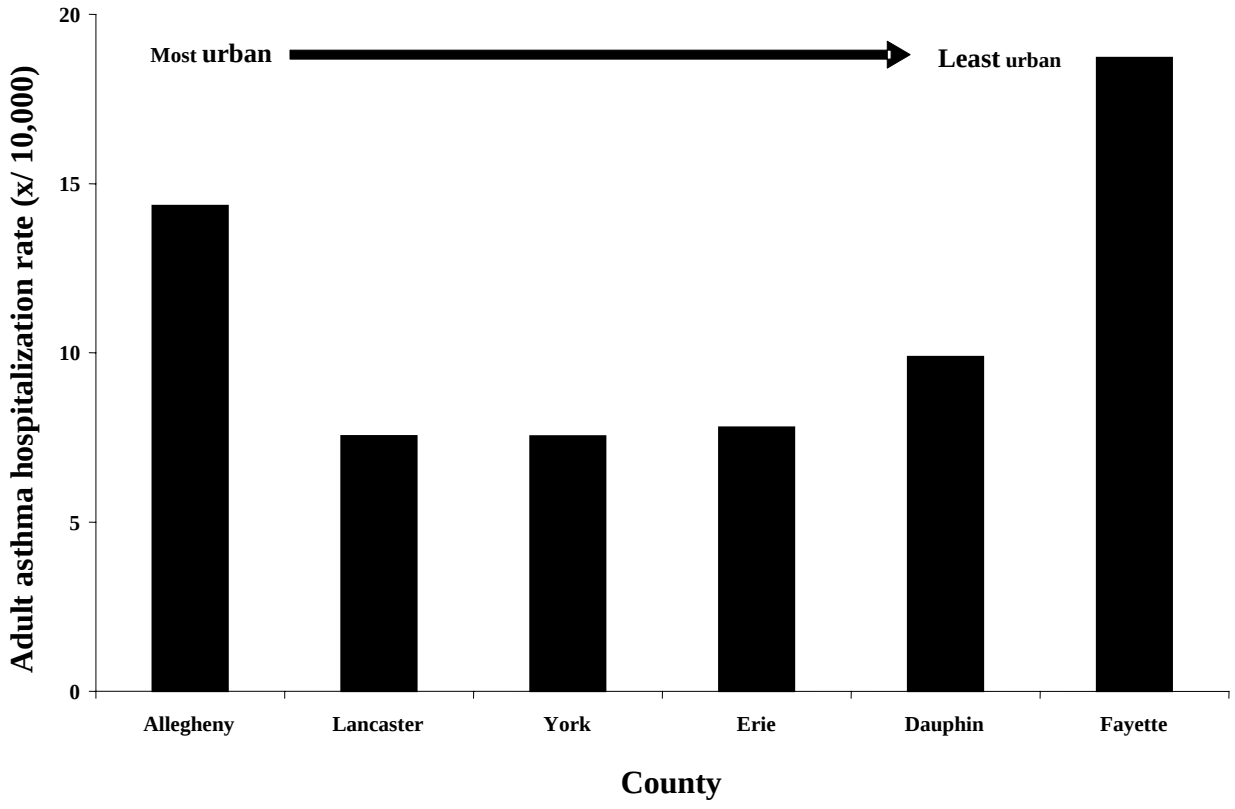


Figure 1.1. Adult asthma hospitalizations in descending order of urbanization.

Gender is recognized as a risk factor for asthma incidence and severity (Arif et al., 2003; Brogger et al., 2003). We examined adult asthma hospitalization rates of males and females in each county (figure 1.2). In all counties, females had higher hospitalization rates when compared with males. In addition, an age-related trend of increasing hospitalizations was observed for females. Using Poisson regression, urbanization, gender, and age were individually assessed for their contribution to adult asthma hospitalization rate within each county (table 1.2). Results indicated that urbanization rank was not a significant contributor to the model (RR=1.04, p = 0.131). However, gender (RR = 3.34, p = 0.0001) and age (RR = 1.17, p= 0.016) were each statistically significant. A statistical model that included all 3 of the covariates was validated using a χ^2 goodness-of-fit test ($\chi^2 = 46.12$, p=0.0518, r^2 = 0.38) indicating the model is appropriate.

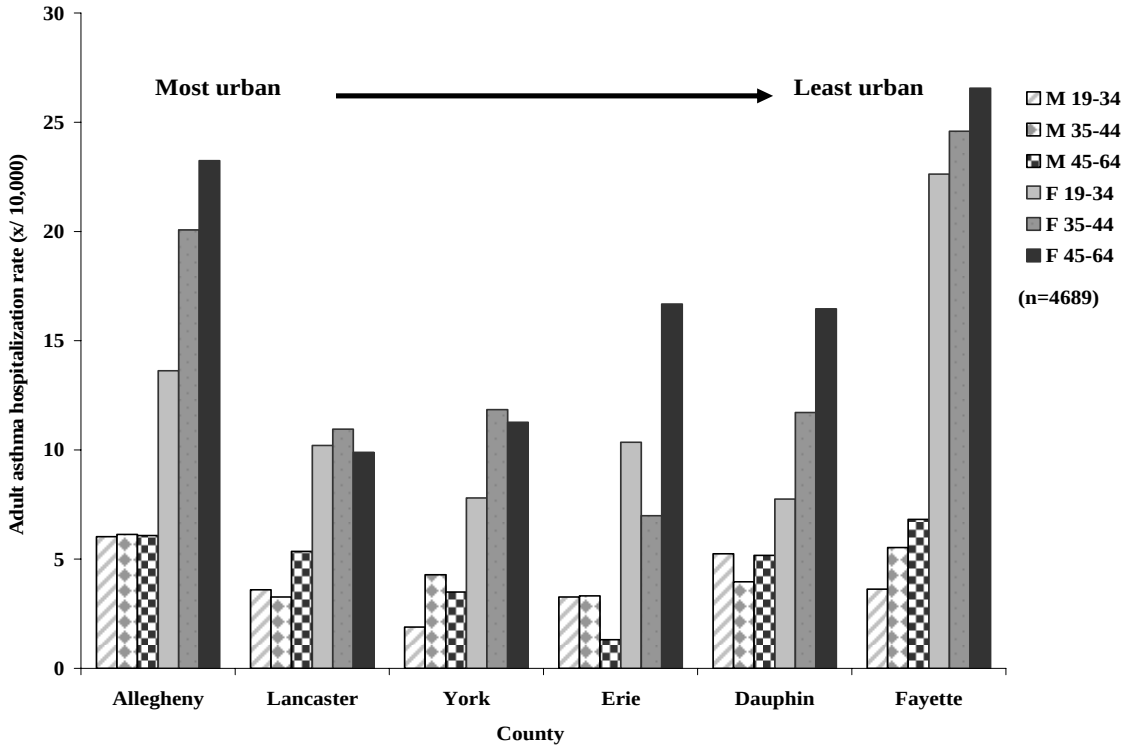


Figure 1.2. Age- X gender-specific rates in descending order of urbanization.

Table 1.2. Results of statistical analysis.

		GOODNESS OF FIT FOR MODEL	**χ^2= 46.02 P= 0.05**
		PSEUDO R^2	**0.3793**
CO-VARIATE	**RELATIVE RISK**	**p-VALUE**	**CONFIDENCE INTERVAL**
Gender	**3.34**	**0.0001**	**2.60-4.31**
Age group	**1.17**	**0.016**	**1.03-1.33**
County rank	**1.05**	**0.131**	**0.99-1.12**

Socioeconomic factors have been associated with the frequency of asthmatic attacks (Boudreaux, et al., 2003). Although individual data for these factors were not available, aggregate data at the county level were obtained from the 2000 U.S Census (U.S. Census, 2000). The county-specific profiles of these factors in relation to the adult asthma hospitalizations are shown in figure 1.3, panels a-c. There was a correlation between the hospitalization rate and the percentage of the population living below the federal poverty level (figure 1.3a). An inverse relationship was observed for hospitalization and both median income and median property value (figure 1.3b, 1.3c). Although low education has been cited as a risk factor for poor disease management, the profiles of educational attainment in the 6 counties were similar.

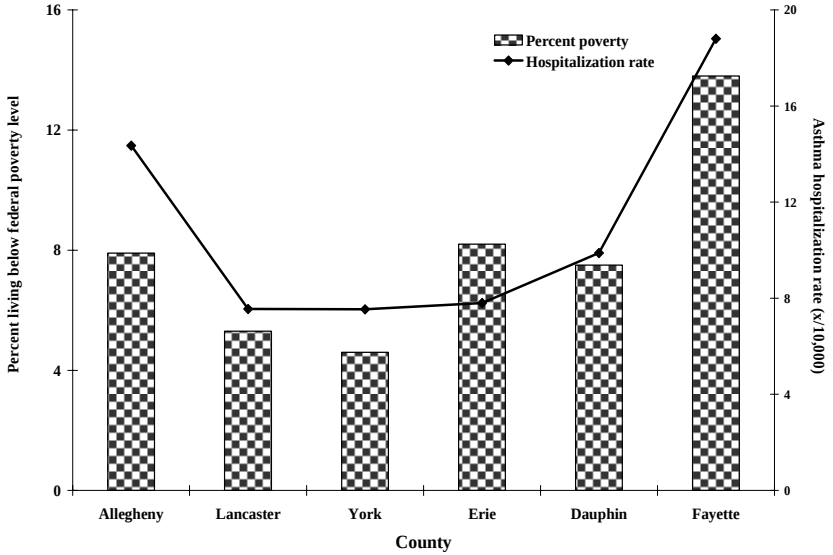


Figure 1.3a. By percent poverty

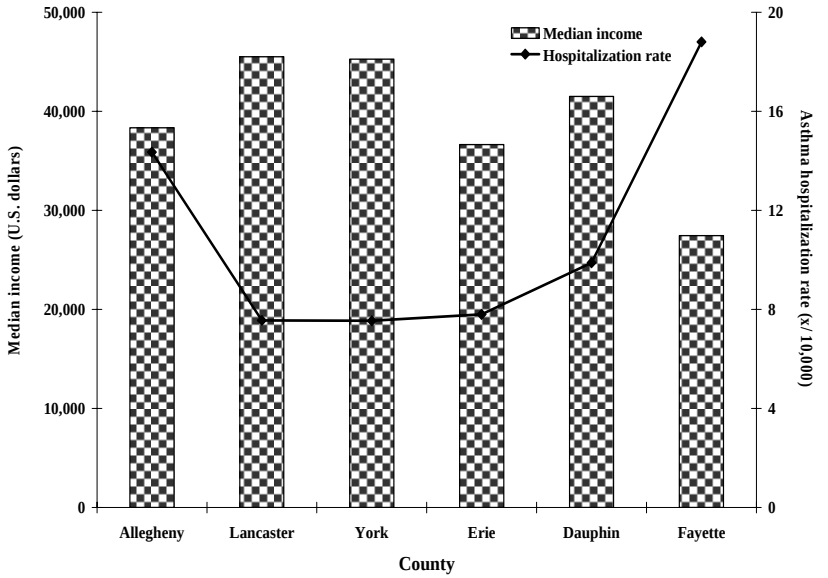


Figure 1.3b. By median income

Figure 1.3. Indices of socioeconomic status and County-specific adult asthma hospitalization rates in descending order of urbanization

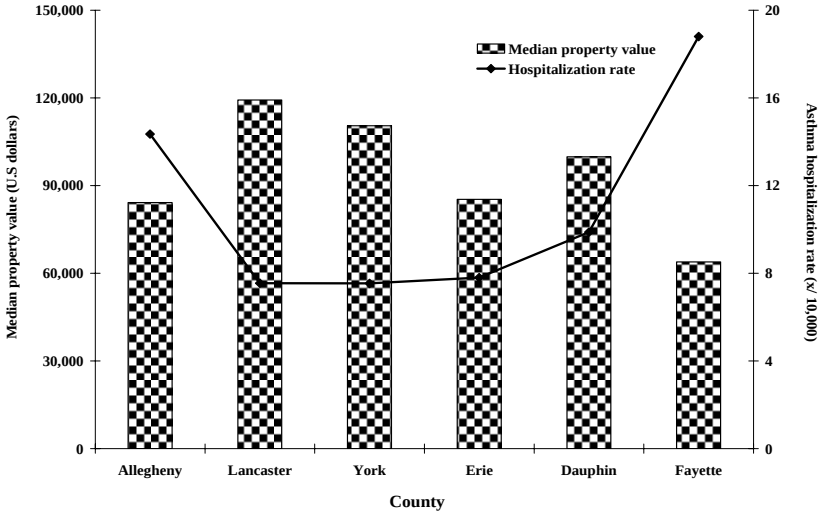


Figure 1.3c. By median property value

3.1.6 Discussion

Traditionally regarded as a childhood disorder, in recent years asthma has emerged as a public health concern of adults age 19-64. Unlike childhood asthma, adult asthma affects more females than males and tends to be more difficult to treat (Dolan et al., 2004).

Abundant roads and highways to accommodate heavy traffic often characterize an urban community. Most studies that address the relationship of this urban characteristic with the frequency and severity of asthma symptoms have focused on children (Nicolai et al., 2003). For example, (Kim et al., 2004) the proximity of roads to schools, and their relationship with asthma symptoms. The authors found spatial variability in traffic related pollutants and an influence of this variability on the frequency of asthma symptoms in children.

Previous studies have shown that emissions from trucks is more detrimental than car emissions with respect to respiratory symptoms (Janssen et al., 2003; van Vliet et al., 1997). We were able to obtain vehicular traffic count, the Pennsylvania Department of Transportation (Pennsylvania Department of Transportation, 2004). Previous studies have noted a disparate prevalence of commercial trucking routes in geographical areas with low SES (Brown et al., 2003; Lwebuga-Mukasa et al., 2004). This may explain why Fayette County, an area characterized as least urban, but with low SES, had the highest adult asthma hospitalization rate.

EPA collects and monitors information regarding the geographic distribution of facilities that release known respiratory irritants and toxins (U.S. EPA, 2000; White, Berger-Frank,

Middleton, & Falk, 2002). In addition, prevailing wind patterns in the area of the emission sources contribute to reduced air quality (Peled et al., 2005). Using geographical information systems (Nuckols, Ward, & Jarup, 2004; Vine, Degnan, & Hanchette, 1997), this information can be visualized for the Commonwealth of Pennsylvania (figure 1.4a and figure 1.4b). However, because we did not have the home addresses of our study population, our ability to assess the relationship between pollutant releases and individual health outcomes was limited.

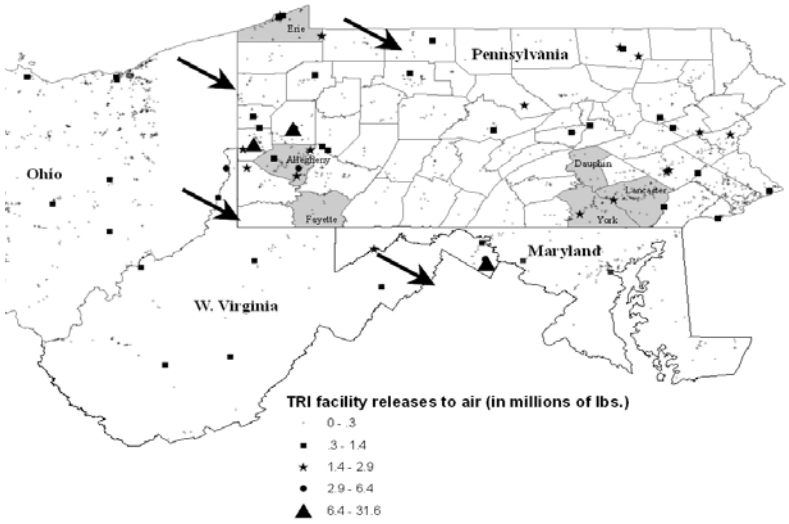


Figure 1.4a. Prevailing wind direction and locations of EPA-TRI facilities in the study area and neighboring states

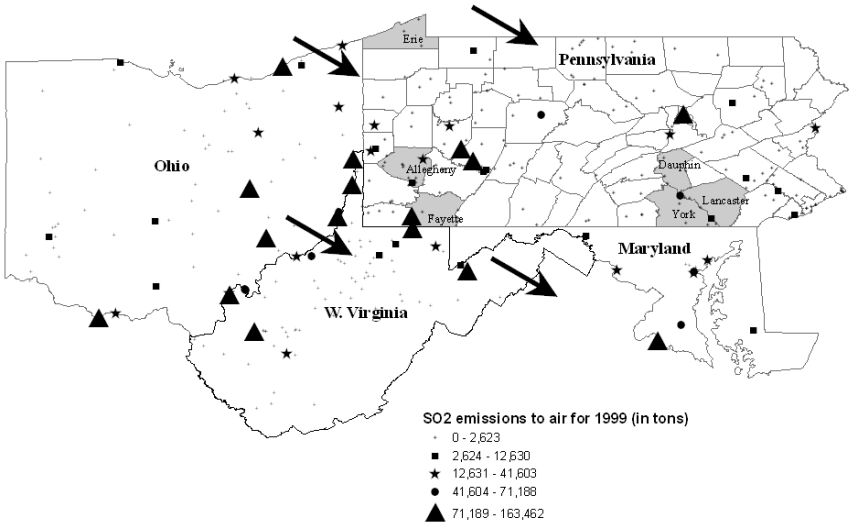


Figure 1.4b. Prevailing wind direction and locations of SO2 releasing facilities in the study area and neighboring states

Figure 1.4. The locations of industrial releases within our study sites.

Epidemiological studies have suggested that a rural environment confers protection against the development of childhood asthma (von Mutius, 2001). More recent reports from China and Europe have indicated a reduction in the prevalence of childhood asthma in rural settings (Chan-Yeung et al., 2002; Waser et al., 2005). This "hygiene hypothesis" suggests that exposures from farming and livestock tend to protect children from the development of asthma. We did not observe a protective effect of a farming environment for adult asthmatics. Lancaster County and Erie County both have substantial agricultural industry, yet their adult asthma hospitalization rates were substantially different.

Increased asthma morbidity in adult females has been reported (NAEPP, 2002). We found asthma hospitalization rates in all 6 counties were higher for females than for males. This is reflective of the National Institutes of Health's report that 61% of adult asthmatics are female. A recent European study found that females, regardless of their geographic location, had higher indices of chronic disease severity than males (ENFUMOSA, 2003). Biological mechanisms, such the endocrine shift during the menstrual cycle, or menopause, have been suggested to be responsible for this gender disparity (Haggerty, Ness, Kelsey, & Waterer, 2003; Vrieze, Postma, & Kerstjens, 2003). It has also been hypothesized that the health seeking behavior of women, when compared with men, may explain gender disparities in chronic disease (McCance-Katz, Carroll, & Rounsaville, 1999; Meyer-Weitz, Reddy, Van den Borne, Kok, & Pietersen, 2000). Further cohort studies are needed to gain a better understanding of the gender disparity in adult asthma hospitalization rates.

Age has been identified as a risk factor for asthma complications in adults (Bellia et al., 2000). We found that older adults (45-64 years) were 1.2 times more likely to be hospitalized for asthma than younger adults. This finding is consistent with a report that older adults tend to have more difficulty managing their asthma (NAEPP, 2002). It is unclear if the age-related trend is due to the age at disease onset or the duration of disease in an individual (Burrows, Barbee, Cline, Knudson, & Lebowitz, 1991; Busse, Banks-Schlegal, & Wenzel, 2000; Lange, Parner, Vestbo, Schnohr, & Jensen, 1998; Peat, Woolcock, & Cullen, 1987).

There were some limitations to our study. The first was a lack of individual data related to socioeconomic status, educational attainment, environmental exposure and behavioral risk factors (*i.e.*, smoking). Variability between individuals in each county or between counties was not assessed. These limitations are inherent in epidemiological studies that are ecological since such studies consider group characteristics when assessing an association between exposure and disease process (Gordis, 2000). Another limitation was the absence of information related to healthcare coverage and use of preventive health services. Such information would be useful for assessing the utilization of primary health care services for asthma management as opposed to seeking care only in acute situations.

This study is the first to address measures of urbanization and the influence of urbanization on adult asthma hospitalization rates. The Commonwealth contains areas with high population density and others with low population density. It also has a stable population that tends to relocate infrequently. This stability is important when assessing the change over time in hospitalization frequency. The unexpected trend of increased hospitalization with decreasing

size of the populace and decreased urbanization suggests a strong influence of demographic and socioeconomic factors. These factors should be further explored to better understand their influence on human respiratory health.

3.1.7. Literature cited

Arif, A.A., Delclos, G.L., Lee, E.S., Tortolero, S.R., & Whitehead, L.W. (2003). Prevalence and risk factors of asthma and wheezing among U.S. adults: An analysis of the NHANES III data. *European Respiratory Journal, 21*(5), 827-833.

Bellia, V., Pistelli, R., Filippazzo, G., Cibella, F., Scichilone, N., Catalano, F., & Cuttitta, G. (2000). Prevalence of nocturnal asthma in a general population sample: determinants and effect of aging. *Journal of Asthma, 37*(7), 595-602.

Boudreaux, E.D., Emond, S.D., Clark, S., & Camargo, C.A., Jr. (2003). Acute asthma among adults presenting to the emergency department: The role of race/ethnicity and socioeconomic status. *Chest, 124*(3), 803-812.

Brogger, J., Bakke, P., Eide, G.E., Johansen, B., Andersen, A., & Gulsvik, A. (2003). Long-term changes in adult asthma prevalence. *European Respiratory Journal, 21*(3), 468-472.

Brown, P., Mayer, B., Zavestoski, S., Luebke, T., Mandelbaum, J., & McCormick, S. (2003). The health politics of asthma: Environmental justice and collective illness experience in the United States. *Social Science and Medicine, 57*(3), 453-464.

Burrows, B., Barbee, R.A., Cline, M.G., Knudson, R.J., & Lebowitz, M.D. (1991). Characteristics of asthma among elderly adults in a sample of the general population. *Chest, 100*(4), 935-942.

Busse, W.W., Banks-Schlegel, S., & Wenzel, S.E. (2000). Pathophysiology of severe asthma. *Journal of Allergy and Clinical Immunology, 106*(6), 1033-1042.

Chan-Yeung, M., Zhan, L.X., Tu, D.H., Li, B., He, G.X., Kauppinen, R., Neiminen, M., & Enarson, D.A.(2002). The prevalence of asthma and asthma-like symptoms among adults in rural Beijing, China. *European Respiratory Journal, 19*(5), 853-858.

Crain, E.F., Walter, M., O'Connor, G.T., Mitchell, H., Gruchalla, R.S., Kattan, M., Malindsak, G.S., Enright, P., Evans, R III, Morgan, W., & Stout, J.W. (2002). Home and allergic characteristics of children with asthma in seven U.S. urban communities and design of an environmental intervention: The Inner-City Asthma Study. *Environmental Health Perspectives, 110*(9), 939-945.

Delfino, R.J., Gong, H., Jr., Linn, W.S., Pellizzari, E.D., & Hu, Y. (2003). Asthma symptoms in Hispanic children and daily ambient exposures to toxic and criteria air pollutants. *Environmental Health Perspectives, 111*(4), 647-656.

Dolan, C.M., Fraher, K.E., Bleecker, E.R., Borish, L., Chipps, B., Hayden, M.L., Weiss, S., Zheng, B., Johnson, C. & Wenzel, S. (2004). Design and baseline characteristics of the epidemiology and natural history of asthma: Outcomes and Treatment Regimens

(TENOR) study: A large cohort of patients with severe or difficult-to-treat asthma. *Annals of Allergy, Asthma, & Immunology, 92*(1), 32-39.

ENFUMOSA. (2003). The ENFUMOSA cross-sectional European multicentre study of the clinical phenotype of chronic severe asthma. European Network for Understanding Mechanisms of Severe Asthma. *European Respiratory Journal, 22*(3), 470-477.

English, P., Neutra, R., Scalf, R., Sullivan, M., Waller, L., & Zhu, L. (1999). Examining associations between childhood asthma and traffic flow using a geographic information system. *Environmental Health Perspectives, 107*(9), 761-767.

Etzel, R.A. (2003). How environmental exposures influence the development and exacerbation of asthma. *Pediatrics, 112*(1 Pt 2), 233-239.

Ford, E.S., Heath, G.W., Mannino, D.M., & Redd, S.C. (2003). Leisure-time physical activity patterns among US adults with asthma. *Chest, 124*(2), 432-437.

Garshick, E., Laden, F., Hart, J.E., & Caron, A. (2003). Residence near a major road and respiratory symptoms in U.S. Veterans. *Epidemiology, 14*(6), 728-736.

Gehring, U., Cyrys, J., Sedlmeir, G., Brunekreef, B., Bellander, T., Fischer, P., Bauer, C.P., Reinhardt, D., Wichmann, H.E., & Heinrich, J. (2002). Traffic-related air pollution and respiratory health during the first 2 yrs of life. *European Respiratory Journal, 19*(4), 690-698.

Gordis, L. (2000). *Epidemiology* (2nd ed.): WB Sauders Co.

Haggerty, C.L., Ness, R.B., Kelsey, S., & Waterer, G.W. (2003). The impact of estrogen and progesterone on asthma. *Annals of Allergy, Asthma, & Immunology, 90*(3), 284-291; quiz 291-283, 347.

Janssen, N.A., Brunekreef, B., van Vliet, P., Aarts, F., Meliefste, K., Harssema, H., & Fischer, P. (2003). The relationship between air pollution from heavy traffic and allergic sensitization, bronchial hyperresponsiveness, and respiratory symptoms in Dutch schoolchildren. *Environmental Health Perspectives, 111*(12), 1512-1518.

Kim, J.J., Smorodinsky, S., Lipsett, M., Singer, B.C., Hodgson, A.T., & Ostro, B. (2004). Traffic-related air pollution near busy roads: The East Bay Children's Respiratory Health Study. *American Journal of Respiratory & Critical Care Medicine, 170*(5), 520-526.

Kunzli, N., McConnell, R., Bates, D., Bastain, T., Hricko, A., Lurmann, F., Avol, E., Gilliland, F., & Peters, J. (2003). Breathless in Los Angeles: The exhausting search for clean air. *American Journal of Public Health, 93*(9), 1494-1499.

Lange, P., Parner, J., Vestbo, J., Schnohr, P., & Jensen, G. (1998). A 15-year follow-up study of ventilatory function in adults with asthma. *New England Journal of Medicine, 339*(17), 1194-1200.

Lin, S., Munsie, J.P., Hwang, S.A., Fitzgerald, E., & Cayo, M.R. (2002). Childhood asthma hospitalization and residential exposure to state route traffic. *Environmental Research, 88*(2), 73-81.

Lwebuga-Mukasa, J.S., Oyana, T., Thenappan, A., & Ayirookuzhi, S.J. (2004). Association between traffic volume and health care use for asthma among residents at a U.S.-Canadian border crossing point. *Journal of Asthma, 41*(3), 289-304.

Mannino, D.M., Homa, D.M., Akinbami, L.J., Moorman, J.E., Gwynn, C., & Redd, S.C. (2002). Surveillance for asthma--United States, 1980-1999. *Morbidity & Mortality Weekly Report Surveillance Summary, 51*(1), 1-13.

McCance-Katz, E.F., Carroll, K.M., & Rounsaville, B.J. (1999). Gender differences in treatment-seeking cocaine abusers--implications for treatment and prognosis. *American Journal of Addiction, 8*(4), 300-311.

Meyer-Weitz, A., Reddy, P., Van den Borne, H.W., Kok, G., & Pietersen, J. (2000). Health care seeking behaviour of patients with sexually transmitted diseases: Determinants of delay behaviour. *Patient Education & Counseling, 41*(3), 263-274.

National Center for Environmental Health, Centers for Disease Control (2003). *Asthma*. Retrieved 07 Sept 2004, from http://www.cdc.gov/nceh/airpollution/asthmaataglance.

National Institutes of Health Asthma Education and Prevention Program. (2002) *Expert Panel Report 2: Guidelines for the diagnosis and management of asthma.* Retrieved 05 Oct 2004, from http://www.nhlbi.nih.gov/guidelines/asthma.

Nicolai, T., Carr, D., Weiland, S.K., Duhme, H., von Ehrenstein, O., Wagner, C., & von Mutius, E. (2003). Urban traffic and pollutant exposure related to respiratory outcomes and atopy in a large sample of children. *European Respiratory Journal, 21*(6), 956-963.

Nuckols, J.R., Ward, M.H., & Jarup, L. (2004). Using geographic information systems for exposure assessment in environmental epidemiology studies. *Environmental Health Perspectives, 112*(9), 1007-1015.

Peat, J.K., Woolcock, A.J., & Cullen, K. (1987). Rate of decline of lung function in subjects with asthma. *European Journal of Respiratory Disease, 70*(3), 171-179.

Peled, R., Friger, M., Bolotin, A., Bibi, H., Epstein, L., Pilpel, D., & Schraf, S. (2005). Fine particles and meteorological conditions are associated with lung function in children with asthma living near two power plants. *Public Health, 119*(5), 418-425.

Pennsylvania Department of Transportation. (2004) *Internet Traffic Monitoring System.* Retrieved 15 July 2004, from http://www.dot7.state.pa.us/itms.

Pennsylvania Health Care Cost Containment Council. (2005). *PHC4-About Us.* Retrieved 1 July 2005, from http://www.phc4.org/council.

Sotir, M., Yeatts, K., & Shy, C. (2003). Presence of asthma risk factors and environmental exposures related to upper respiratory infection-triggered wheezing in middle school-age children. *Environmental Health Perspectives, 111*(4), 657-662.

Tibbetts, J. (2002). Buildings awareness of the built environment. *Environmental Health Perspectives, 110*(11), A670-673.

U.S. Department of Health and Human Services. (2000). *Healthy People 2010: Respiratory Diseases (Goal 24). Conference edition, Vol II.* Retrieved 10 Sept 2004, from http://www.healthypeople.gov/Document/pdf/Volume2/24Respiratory.pdf.

United States Census Bureau. (2000). *American Fact Finder*. Retrieved 15 Aug 2004, from http://www.census.gov.

United States Environmental Protection Agency. (2000). *TRI Explorer Chemical Report.* Retrieved 5 June 2005, from http://www.epa.gov/triexplorer.

United States Environmental Protection Agency. (2005). *What are the six common air pollutants.* Retrieved 26 June 2005, from http://www.epa.gov/ebtpages/pollairpocriteriaairpollutants.html.

van Vliet, P., Knape, M., de Hartog, J., Janssen, N., Harssema, H., & Brunekreef, B. (1997). Motor vehicle exhaust and chronic respiratory symptoms in children living near freeways. *Environmental Research, 74*(2), 122-132.

Vine, M.F., Degnan, D., & Hanchette, C. (1997). Geographic information systems: Their use in environmental epidemiologic research. *Environmental Health Perspectives, 105*(6), 598-605.

von Mutius, E. (2001). Infection: Friend or foe in the development of atopy and asthma? The epidemiological evidence. *European Respiratory Journal, 18*(5), 872-881.

Vrieze, A., Postma, D.S., & Kerstjens, H.A. (2003). Perimenstrual asthma: A syndrome without known cause or cure. *Journal of Allergy & Clinical Immunology, 112*(2), 271-282.

Waser, M., von Mutius, E., Riedler, J., Nowak, D., Maisch, S., Carr, D., Eder, W., Tebow, G., Schierl, R., Schreuer, M., & Braun-Fahrlander, C. (2005). Exposure to pets, and the association with hay fever, asthma, and atopic sensitization in rural children. *Allergy, 60*(2), 177-184.

White, M.C., Berger-Frank, S.A., Middleton, D.C., & Falk, H. (2002). Addressing community concerns about asthma and air toxics. *Environmental Health Perspectives, 110 Suppl 4*, 561-564.

3.2. Chapter 2

Manuscript in preparation

ENVIRONMENTAL HEALTH SURVEILLANCE IN ALLEGHENY COUNTY, PA: ASSESSMENT OF ADULT ASTHMA HOSPITALIZATION RATES AS AN ENVIRONMENTAL HEALTH INDICATOR

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3.2.1 Preface

The prevalence of local asthma morbidity is not quite known. Although estimates are provided by the CDC, local surveillance does not exist. Here we examine the utility of local adult asthma hospitalization data as a source for surveillance. We demonstrate that these data are useful not only to assess the baseline prevalence of asthma morbidity in Allegheny County but also as an environmental health indicator (as described by the Centers for Disease Control).

3.2.2 Abstract

Objective We sought to evaluate the use of local hospital discharge data as an environmental health indicator. Using these data, the demographic, temporal, and geographic distribution of adult asthma hospitalizations in Allegheny County were assessed.

Methods: Asthma hospitalization data from 1999-2001 were obtained for adults 19-64 years. Hospitalization rates for demographic subgroups were assessed and compared with those published by the CDC. Daily hospitalization frequencies were assessed for a temporal relationship with the EPA's daily Air Quality Index (AQI). Using the patient's zip code of residence, ARC-VIEW GIS software was employed to visualize the geographic distribution of rates.

Results: The adult asthma hospitalization rates were comparable to rates published by the CDC. The relationship between the daily hospitalization frequencies and the daily AQI was not statistically significant. However, the geographic distribution analysis revealed 14 zip codes, primarily in the Southeast quadrant of the county, where elevated adult asthma hospitalization rates were statistically significant.

Conclusion: A geographic-specific risk was identified for adult asthma hospitalizations. Continued evaluation of such of data as an environmental health surveillance tool is suggested.

3.2.3 Introduction

One goal of *Healthy People 2010* is to improve the surveillance of environmentally-related disease through the use of environmental health indicators (U.S. Department of Health and Human Services, 2000). Environmental public health indicators (EPHIs) can be used to assess a population's health or risk of disease as it relates to the environment (C. f. D. C. National Center for Environmental Health, 2005). Indicators can also be used to assess the baseline prevalence of disease and to build core surveillance capacity in state and local agencies. There are 4 categories of EHPIs.; hazard indicators, exposure indicators, health effect indicators, and intervention indicators. EPHIs are further categorized into 3 tiers; core, optional, and developmental. Core indicators are those regularly used by state agencies for environmental health surveillance. Optional and developmental indicators encompass those that may be developed for future use or for intervention purposes. The CDC has categorized asthma hospitalizations as a core health effect EPHI indicating the importance of the indicator and its measure with respect to policy or program considerations.

Asthma currently affects 14 million people in the United States (Mannino et al., 2002). Total direct medical expenditures for asthma care in the US are estimated to be in excess of $14 billion, not including indirect costs such as lost work days (Weiss & Sullivan, 2001). Although the prevalence of asthma has increased worldwide, the etiological factors with respect to pathophysiology remain uncertain (S. Holgate, 2001). In addition, environmental factors that influence the prevalence asthma hospitalizations are poorly understood (S. T. Holgate, 1999). Asthma research has traditionally focused on children and the elderly, two populations

considered the most susceptible to complications, with little focus on adults 19-64 years. However, the prevalence of asthma in the latter group is gaining recognition as a formidable clinical and public health problem.

Studies have shown that outdoor air pollutants can trigger asthma symptoms (Delfino *et al.*, 2003; McConnell et al., 2002). The profiles of outdoor air pollution are seasonal. Particulate matter (PM) and ozone (O_3) are primary air pollutants during the winter and the summer months, respectively (United States Environmental Protection Agency, 2005). Although the technology is improving for daily monitoring of PM, particularly for PM< 2.5μm, studies assessing the health impact of this criteria pollutant are few.

The geographic distribution of environmentally-related disease, including numerous cancers, has garnered increasing attention in public health (Olden & White, 2005; White *et al.*, 2002). Of particular interest is the relationship between the exposure to elements in the environment (ie. poor air quality, prevalence of industrial facilities) and disease prevalence . With the advent of new technologies, such as mapping software, studies investigating the incidence and prevalence of disease as it relates to the environment are possible (Nuckols *et al.*, 2004; Vine *et al.*, 1997).

To be consistent with the CDC's Environmental Public Health Indicator project, we employed local hospital discharge data to assess the rates and frequencies of adult asthma hospitalizations. We used this core indicator to investigate the baseline prevalence of adult asthma morbidity in Allegheny County, Pennsylvania.

3.2.4 Methods

Dataset

Hospital discharge data were obtained from the Pennsylvania Cost Containment Council (Pennsylvania Health Care Cost Containment Council, 2005). The population of interest was adults 18-64 years of age (N=2082) from Allegheny County, Pennsylvania who had been hospitalized for asthma (ICD 493.0-493.9) between 1999-2001. Included in this dataset were the patient's age, gender, race, and zip code of residence.

Demographic-specific rate calculations

For the calculation of hospitalization rates, the year 2000 was selected since it coincided with the 2000 U.S. Census. Age-adjusted and age-specific adult asthma hospitalization rates were calculated, including rates stratified by gender and race. Race-specific rates were calculated only for Caucasians and African Americans since other races and ethnicities in Allegheny County make up less than 3% of the total population. Age-specific rates were stratified by the same age groups used by the CDC (18-44 and 45-64 years). The standard population used for age-adjustment was obtained from the 2000 US Census (U.S. Department of Commerce, 2002). The unique patient identifier code enabled us to control for individuals who had multiple hospital admissions for asthma within one calendar year.

Temporal assessment of hospitalization frequencies

A relationship between daily asthma hospitalization frequencies and daily air quality was assessed for the 3 year period. The Environmental Protection Agency's (EPA) Daily Air Quality

Index (AQI) is an approximate indicator of overall air quality within a geographic area (U.S. Environmental Protection Agency, 2005a). The criteria pollutants used to calculate the AQI include: carbon monoxide, nitrogen dioxide, ozone, sulfur dioxide, particulate matter < 2.5 μm ($PM_{2.5}$), and particulate matter < 10 μm(PM_{10}). A daily index value is calculated for each criteria pollutant that is measured. The AQI represents the highest of these indices and the corresponding pollutant is referred to as the "main pollutant". A relationship between the daily hospitalization frequencies and the daily main pollutant was further investigated. For statistical analysis, AQI and hospitalization data over the 3-year period was pooled.

Geographic specific rate calculations

Using the subject's zip code of residence, the geographic distribution of adult asthma hospitalizations was examined. Subgroups were stratified by age, gender, and race. Of Allegheny County's 89 zip codes, only 56 had "stable" populations which were extracted for analysis of geo-specific adult asthma hospitalization rates. The measure of comparison was to the rates published by the CDC. In addition, standardized incidence ratios (SIR) with corresponding confidence intervals (CI) were calculated. Statistical significance was determined when a zip code's SIR was > 100 (the null value) and the corresponding confidence interval did not include 100.

The contribution of zip code-specific characteristics to asthma hospitalization rates

Since individual patient characteristics related to socioeconomic status (SES) and environmental exposures were not provided in the dataset, we sought to assess the influence of area characteristics on adult asthma hospitalization rates. After zip code-specific rates were calculated

(as described in the preceding methods section), each of Allegheny County's 89 zip codes was stratified as follows:

1= Adult asthma hospitalization rates at or below that reported by CDC

2= Rates higher than those reported the CDC but not statistically significant and

3= Rates higher than those reported the CDC elevated and statistically significant

A relationship of select zip code-specific characteristics to the aforementioned stratification assignment was assessed. These characteristics included socioeconomic status (SES) and the prevalence of industrial facilities listed on the EPAs Toxic Release Inventory (TRI) (U.S. Environmental Protection Agency, 2005b). Using logistic regression analysis, the influence of selected geographic factors on a zip code's stratification assignment was evaluated.

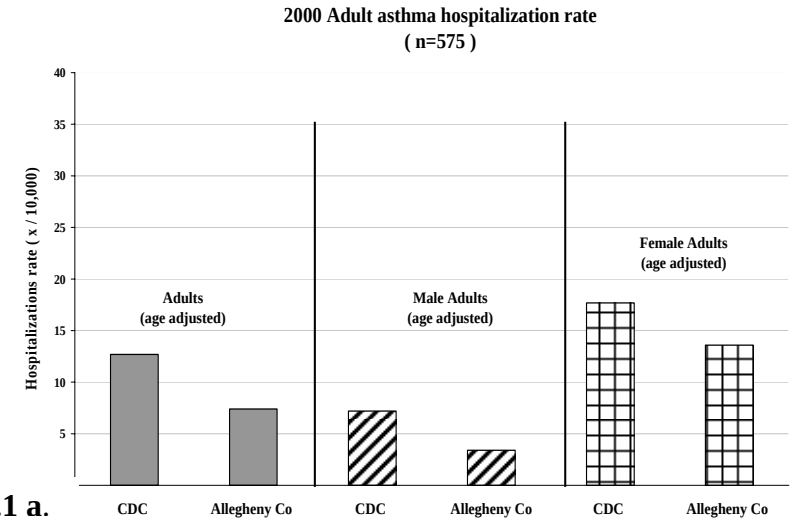
Statistical analysis

Distribution analysis was visualized using MS-EXCEL. Geographic distributions of adult asthma hospitalization trends within Allegheny County were visualized using the mapping software ARC-VIEW GIS 9.0. For modeling of zip codes characteristics where rates were observed to be higher than expected, multivariate logistic regression was used to assess their relationship (*STATA Corp. College Station, TX*). Exponentiated coefficients of these relationships are represented as odds ratios. All estimates of significance were at the level p=0.05.

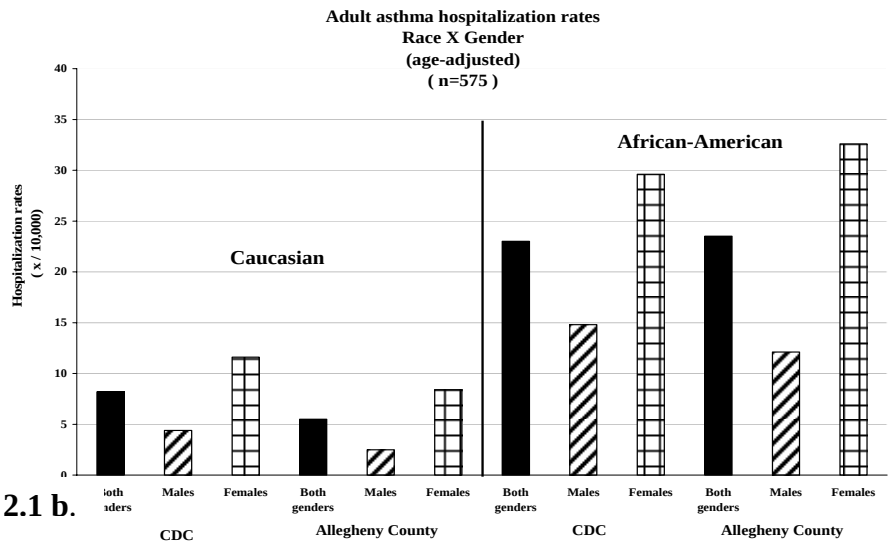
3.2.5 Results

Demographic distribution of rates

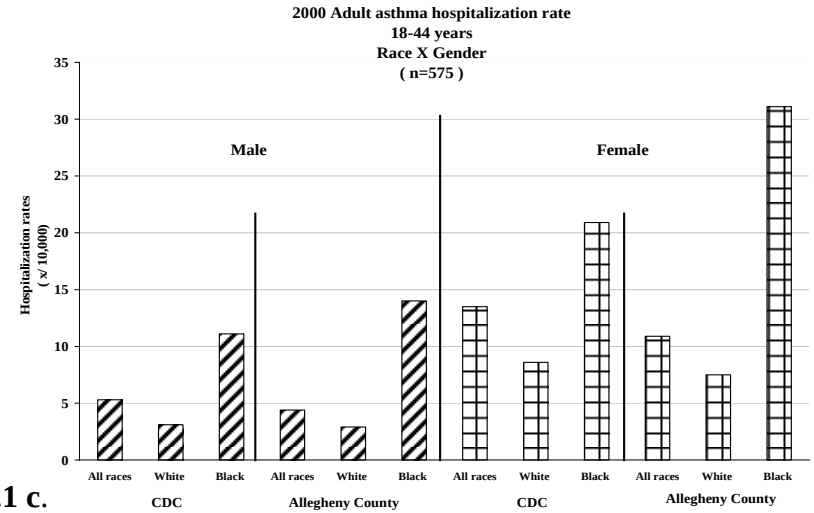
When compared with the nation al trends published by the Center's for Disease Control (CDC) (National Center for Health Statistics, 2005), the rates for all adults, adult males and adult females in Allegheny County were lower (figure 2.1a). Although the local race-specific profiles were comparable to those reported by the CDC, there was a slight increase for Black females and a slight decrease for White females (figure 2.1b). Age-group specific rates stratified by race and gender were similar to the CDC's rates except for those of Black females which were noticeably higher in the age group 18-44 years and lower in Black males 45-64 years (figures 2.1c and 2.1d).



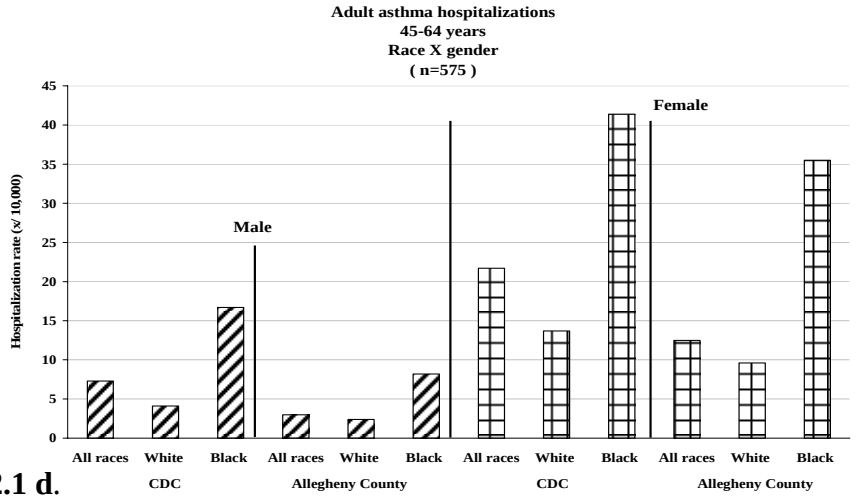
2.1 a.



2.1 b.



2.1 c.

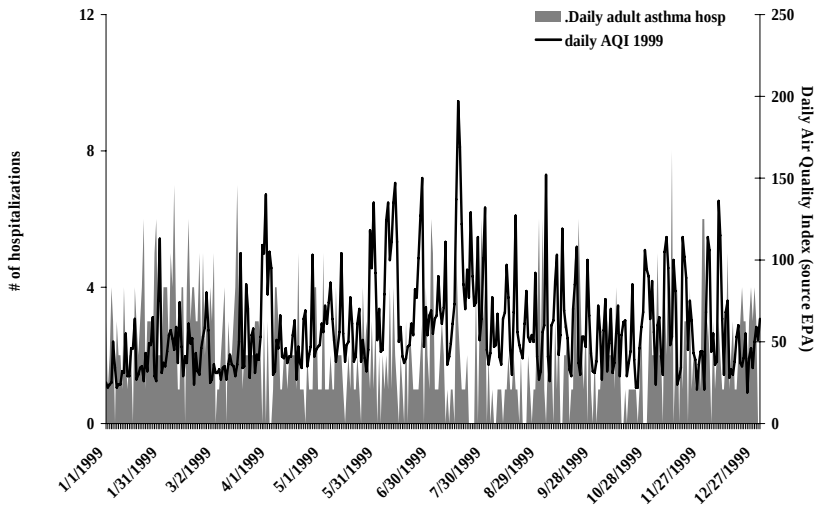


2.1 d.

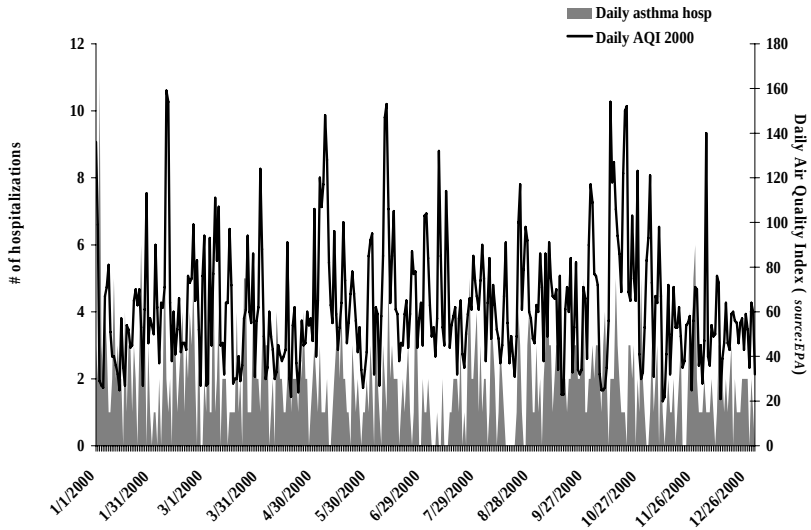
Figure 2.1.Total and gender-specific adult asthma hospitalization rates. The rates shown are comparable to the CDC estimates (1a). Age-adjusted rate comparisons suggest a disparity amongst African-American females (1b), and more specifically in the age group 18-44 years (1c).

Temporal distribution

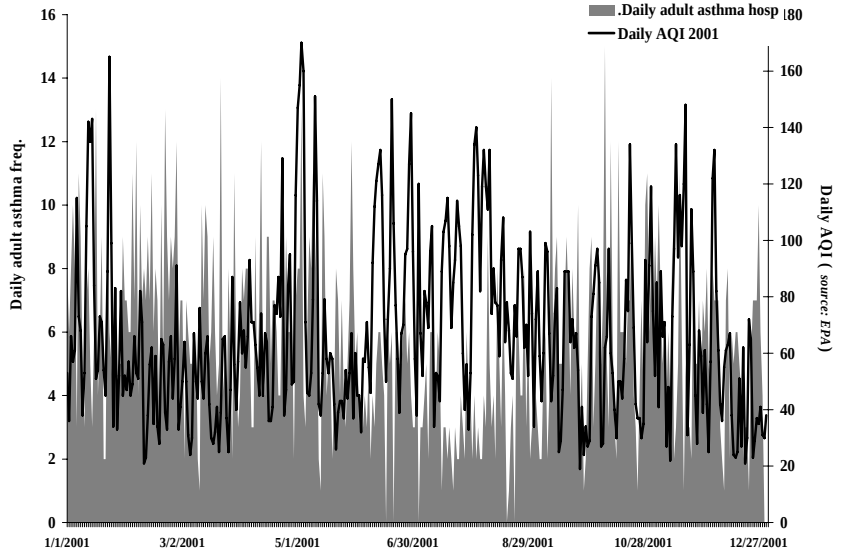
Adult asthma hospitalization frequencies were stable for the years 1999, 2000, and 2001 (748, 703, and 631 respectively). Daily adult asthma hospitalization frequencies for the 3-year period were assessed for a relationship to the daily Air Quality Index that is published by the EPA (figures 2.2 a, 2.2b, and 2.2c). A consistent pattern was apparent of fewer hospitalizations on days when the AQI was higher (a threat to human health) and higher hospitalizations on days when the AQI was lower (not a threat to human health). However, pooled data analysis for the 3-year period revealed that the relationship was not statistically significant (OR= 1.0, CI= .994 - 1.00, p=0.30). Further pooled analysis of the relationship between hospitalization frequencies and the daily main pollutant indicated a positive correlation for days when the main pollutant was PM_{10} (OR= 1.87, CI= 1.47 - 2.39, $p<0.001$), and an inverse correlation for days when the main pollutant was ozone (OR = 0.685, CI = 0.515 - 0.912, p=0.009). For the days when the main pollutant was $PM_{2.5}$ and sulfur dioxide, there was not a relationship of hospitalization frequency with the main pollutant.



2.2a. Profile for 1999



2.2b. Profile for 2000



2.2c. Profile for 2001

Figure 2.2. The relationship between daily Air Quality Index (AQI) and daily adult asthma hospitalizations The daily AQI is represented by the solid black line and daily adult asthma hospitalization frequency, represented by the gray shaded area, is shown for the years 1999-2001. The EPA calculates the AQI for the five major air pollutants regulated by the Clean Air Act: ground-level ozone, particle pollution (also known as particulate matter), carbon monoxide, sulfur dioxide, and nitrogen dioxide. The higher the AQI value, the greater the level of air pollution and health concern.

Geographic distribution

Adult asthma hospitalization rates were calculated for each of the county's zip codes. Of the county's 89 zip codes, 32 had hospitalization rates that were higher than those published by the CDC. Of these, 16 had rates that were statistically significant (p=0.05) (figure 2.3). This included rates for subgroups stratified by gender, age, and race. The majority of the zip codes with elevated rates are located within the southeastern quadrant of the county.

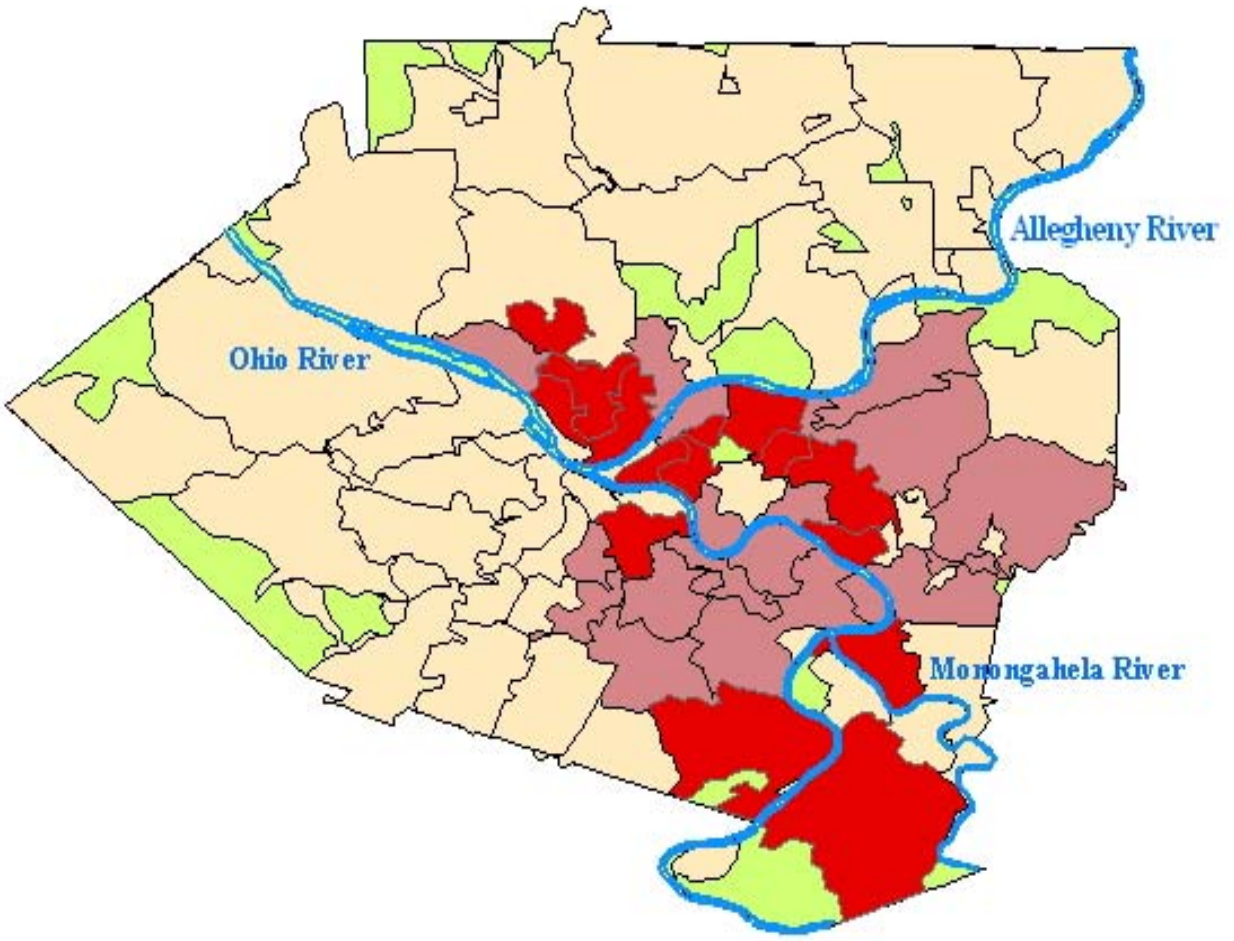


Figure 2.3. The distribution of adult asthma hospitaliziation rates by zip code. The light pink areas represent zip codes where the adult athma hospitalization rates were equal to or less than of Allegheny County as a whole. The mauve shaded areas represent zip codes where rates were elevated but not statistically significant. The red shaded areas represent the zip codes where rates were elevated and were statistically significant.

Assessment of the contribution of zip code-specific characteristics

As described in the method section, each zip code was stratified based on their respective adult asthma hospitalization rates. Zip code-specific characteristics were selected for assessment of their relationship to the hospitalization rates. The characteristics included those related to income, demographics, educational attainment, and the prevalence of industry. The results of multinomial logistic regression analysis are shown in table 2.1. Of the select area characteristics (n=10), 3 were statistically significant risk factors. These were % of African Americans (OR= 1.15, CI= , p=0.002), % living below the poverty level (OR=1.20, CI= , p<0.001) and % of individuals with less than a high school education (OR=1.10 , CI= , p=0.023). Neither the number of industrial facilities within a zip code nor their total amount of emissions (per year) showed a relationship to adult asthma hospitalization rates.

Table 2.1. Zip code-specific characteristics that were assessed for their influence on the respective adult asthma hospitalization rates.

Area Characteristics	Relative risk	p-value
% of African-Americans	**1.15**	**0.002**
Percent living below federal poverty guidelines	**1.20**	**< 0.001**
< High school education	**1.10**	**0.023**
Median income	**1.0**	**0.001**
Median property value	**1.0**	**0.003**
High school education or GED	**1.01**	**0.664**
Some college	**1.03**	**0.684**
Bachelor's degree and beyond	**0.968**	**0.159**
Total # of facilities listed on the EPA's TRI database	**1.05**	**0.791**
Total lbs. of emissions released into the air by facilities listed on the EPA's TRI database	**1.0**	**0.361**

3.2.6 Discussion

For the past decade, evidence supporting the disproportionate distribution of environmentally-related disease amongst the US population has increased (Gold & Wright, 2005; Olden & White, 2005). However, prospective surveillance of such has yet to be developed and utilized on a regular and timely fashion. *Healthy People 2010,* the US Department of Health and Human Service's program for addressing health disparities has prioritized the reduction of exposures that contribute to the etiology of environmentally-related disease (U.S. Department of Health and Human Services, 2000).

Currently, the Centers for Disease Control's (CDC) Behavioral Risk Factor Surveillance Survey (BRFSS) is the most frequently utilized tool to estimate baseline prevalence of chronic disease in the US (Centers for Disease Control, 2005a). This random-number telephone survey samples populations periodically for incidence and prevalence of disease. Changes in such prevalence over time are often published by the CDC in their Morbidity and Mortality Weekly Report (MMWR) (Centers for Disease Control, 2005b). However, since these estimates are at the national level, the CDC encourages local adaptation of the BRFSS. State and local agencies have adopted the BRFSS to address local public health issues but the BRFSS is rarely used by to estimate the local prevalence and morbidity of chronic disease.

Recently, the CDC has established a program tasked with developing local surveillance capacity for environmentally-related disease (C. f. D. C. National Center for Environmental Health, 2005). The Environmental Public Health Indicator (EPHI) project aims to develop this capacity by identifying indicators of environmental health. The long-term goal is to incorporate

the local surveillance of the prevalence and morbidity of non-infectious chronic diseases into a national public health surveillance system.

One index of chronic disease prevalence and morbidity that has been cited in the CDC's MMWR is hospital discharge statistics (C. f. D. C. National Center for Health Statsitics, 2005). The National Center for Health Statistics at the CDC regularly collects these data via a sample survey of hospitals in the US. As a health effects indicator, the CDC has recognizes the utility of hospitalization data as a source to detect unusual patterns of events specific to environmentally-related disease. One such disease is asthma.

Asthma is a chronic respiratory disease whose etiology is suspected of being environmentally-related (Allacci, 2005; S. Holgate, 2001; S. T. Holgate, 1999). In the past decade the incidence of newly diagnosed asthma has decreased, the prevalence of persistent asthma symptoms has increased (Lawson & Senthilselvan, 2005). Although many studies have published that address the risk factors for childhood asthma, the risk factors for adult asthma remain poorly defined (Bel, 2004). In addition, the prevalence of adult asthma morbidity is believed to be greatly underestimated (W. Busse et al., 2004; National Institutes of Health Asthma Education and Prevention Program, 2002). Here we report the utilization of local adult asthma hospitalization data as an environmental health indicator in Allegheny County., Pennsylvania which includes the city of Pittsburgh. These data include all hospitalizations at all health care facilities within the county.

The total adult asthma hospitalization rate for Allegheny County was comparable to the CDC's latest estimates (National Center for Health Statistics, 2005). Although the risk factors for adult asthma morbidity include female gender, current age, and race/ethnicity (Apter, 2003), comparable profiles were observed for both gender-specific and age specific rates. However, the race-specific rates for African –Americans were slightly elevated. This suggests the possibility of a greater burden of adult asthma hospitalizations in Blacks even though their percentage of the total Allegheny County population is about equal to that in the US and in the Commonwealth.

Most studies investigating the temporal distribution of asthma events have focused on the daily ambient air quality (Galan *et al.*, 2003; Neidell, 2004; Wilson *et al.*, 2005). Air quality in the US is based on the concentrations of criteria air pollutants as defined by the Environmental Protection Agency (EPA) (United States Environmental Protection Agency, 2005). The criteria pollutants are defined as such due to their harmful effects to human health. They include sulfur dioxide (SO^2), nitrogen dioxide (NO^2), carbon monoxide (CO), ozone (O^3), and particulate matter <10um (PM_{10}) and <2.5um ($PM_{2.5}$). The EPA's daily Air Quality Index (AQI) is reflective of the concentrations of the main pollutant on the day of interest; the higher the index, the poorer the air quality. With respect to health effects, the most investigated pollutant is ozone. Published studies have shown the adverse effects of ozone even in healthy individuals (McConnell et al., 2002; Mudway & Kelly, 2004).

Our study showed that on days of increased adult asthma hospitalizations, the air quality index was lower (i.e. better air quality). In addition, the main pollutant on these days was not ozone but particulate matter. Further assessment of the relationship of the daily main pollutant

and hospitalization frequencies demonstrated identified a positive correlation of PM_{10} and an inverse correlation of ozone. These results differ from studies investigating the effects of ozone on child asthma hospitalizations (Farhat et al., 2005). However, numerous studies have cited a relationship between respiratory and cardiopulmonary hospitalizations on or about days where PM is the main pollutant (Delfino *et al.*, 2005; Kappos *et al.*, 2004; Ruidavets *et al.*, 2005; Thurston & Bates, 2003). An explanation could be that the severe form of asthma, which is found more often in adults, is characterized by higher degree of lung obstruction due to remodeling rather than airway hyper-responsiveness (Bai & Knight, 2005; S. Wenzel et al., 2005). Another explanation may be that the influence of seasonal bacterial respiratory infections on adult asthma morbidity. Although the sero-prevalence of pathogens responsible for pneumonia is higher in asthmatics, the age-specific effect has yet to be delineated(Johnston & Martin, 2005).

The impact that the environment has on health effects and disease prevalence is frequently cited within the context of environmental justice. One tenet of environmental justice is that individuals must have control over exposures in their environment (Apelberg *et al.*, 2005; Brulle & Pellow, 2005; Gee & Payne-Sturges, 2004). Since our dataset included the patient's zip code of residence, we assessed the influence of zip-code specific characteristics such as poverty and the prevalence of industrial facilities on the respective rates. We found an elevated risk of adult asthma hospitalization associated with factors of SES such as poverty and lower educational attainment. The 14 zip codes with higher rates, located predominantly in the Southeastern quadrant of the county, also had higher percentage of African-Americans residents. In addition, indices of exposure to industrial sites were not statistically significant. However, since the exact

address of patients in this study were not available, further quantification of exposure effects was not possible.

There were limitations to this study primarily related to personal information regarding the cohort. The lack of individual addresses for the patients did not allow further analysis of exposures due to factors such the regional prevalence of power plants and incinerators. These data when accompanied by wind direction and residential addresses have shown compelling results with respect to health effects due to exposure (Peled *et al.*, 2005; Villeneuve *et al.*, 2005). In addition, personal medical history with respect to asthma (i.e. age of onset, health care delivery and access) are often cited as risk factors for asthmatic adults who have poor control of the disease (Adams et al., 2003). Finally, personal habits related to tobacco smoke exposure and daily exposure to traffic-related pollution have been associated with airway hyper-responsiveness in both asthmatics and non-asthmatics (Lwebuga-Mukasa *et al.*, 2005).

We have shown that hospitalization data that includes all health care facilities are a useful tool for estimating disease morbidity within a community. The Commonwealth of Pennsylvania is only one of three states within the US that collects such data. The timeliness and availability of the data adds to its utility of being used in the capacity of an environmental health indicator.

This is the first study to estimate the burden of asthma morbidity within Allegheny County, PA using the criteria set forth by the CDC for environmental health surveillance. Such surveillance is necessary so that temporal or geographic changes over time may be detected. By developing this environmental health capacity, meaningful and appropriate public health interventions can be implemented.

3.2.7. Literature cited

Adams, R. J., Weiss, S. T., & Fuhlbrigge, A. (2003). How and by whom care is delivered influences anti-inflammatory use in asthma: Results of a national population survey. *J Allergy Clin Immunol, 112*(2), 445-450.

Allacci, M. S. (2005). Identifying environmental risk factors for asthma emergency care" a multilevel approach for ecological study. *J Ambul Care Manage, 28*(1), 2-15.

Apelberg, B. J., Buckley, T. J., & White, R. H. (2005). Socioeconomic and racial disparities in cancer risk from air toxics in Maryland. *Environ Health Perspect, 113*(6), 693-699.

Apter, A. J. (2003). Clinical advances in adult asthma. *J Allergy Clin Immunol, 111*(3 Suppl), S780-784.

Bai, T. R., & Knight, D. A. (2005). Structural changes in the airways in asthma: observations and consequences. *Clin Sci (Lond), 108*(6), 463-477.

Bel, E. H. (2004). Clinical phenotypes of asthma. *Curr Opin Pulm Med, 10*(1), 44-50.

Brulle, R. J., & Pellow, D. N. (2005). Environmental Justice: Human Health and Environmental Inequalities. *Annu Rev Public Health*.

Busse, W., Banks-Schlegel, S., Noel, P., Ortega, H., Taggart, V., & Elias, J. (2004). Future Research Directions in Asthma: An NHLBI Working Group Report. *Am J Respir Crit Care Med*.

Centers for Disease Control. (2005a). *Asthma: Behavioral Risk Factor Surveillance Survey*. Retrieved Aug 19, 2005, from http://www.cdc.gov/asthma/brfss/default.htm

Centers for Disease Control. (2005b). *The Morbidity and Mortality Weekly Report: Know What Matters*. Retrieved Sept 4, 2005, from http://www.cdc.gov/mmwr/about.html

Delfino, R. J., Gong, H., Jr., Linn, W. S., Pellizzari, E. D., & Hu, Y. (2003). Asthma symptoms in Hispanic children and daily ambient exposures to toxic and criteria air pollutants. *Environ Health Perspect, 111*(4), 647-656.

Delfino, R. J., Sioutas, C., & Malik, S. (2005). Potential role of ultrafine particles in associations between airborne particle mass and cardiovascular health. *Environ Health Perspect, 113*(8), 934-946.

Farhat, S. C., Paulo, R. L., Shimoda, T. M., Conceicao, G. M., Lin, C. A., Braga, A. L., et al. (2005). Effect of air pollution on pediatric respiratory emergency room visits and hospital admissions. *Braz J Med Biol Res, 38*(2), 227-235.

Galan, I., Tobias, A., Banegas, J. R., & Aranguez, E. (2003). Short-term effects of air pollution on daily asthma emergency room admissions. *Eur Respir J, 22*(5), 802-808.

Gee, G. C., & Payne-Sturges, D. C. (2004). Environmental health disparities: a framework integrating psychosocial and environmental concepts. *Environ Health Perspect, 112*(17), 1645-1653.

Gold, D. R., & Wright, R. (2005). Population disparities in asthma. *Annu Rev Public Health, 26*, 89-113.

Holgate, S. (2001). Mechanisms of allergy and adult asthma. *Curr Opin Allergy Clin Immunol, 1*(1), 47-50.

Holgate, S. T. (1999). Genetic and environmental interaction in allergy and asthma. *J Allergy Clin Immunol, 104*(6), 1139-1146.

Johnston, S. L., & Martin, R. J. (2005). Chlamydophila pneumoniae and Mycoplasma pneumoniae: a Role in Asthma Pathogenesis? *Am J Respir Crit Care Med*.

Kappos, A. D., Bruckmann, P., Eikmann, T., Englert, N., Heinrich, U., Hoppe, P., et al. (2004). Health effects of particles in ambient air. *Int J Hyg Environ Health, 207*(4), 399-407.

Lawson, J. A., & Senthilselvan, A. (2005). Asthma epidemiology: has the crisis passed? *Curr Opin Pulm Med, 11*(1), 79-84.

Lwebuga-Mukasa, J. S., Oyana, T. J., & Johnson, C. (2005). Local ecological factors, ultrafine particulate concentrations, and asthma prevalence rates in Buffalo, New York, neighborhoods. *J Asthma, 42*(5), 337-348.

Mannino, D. M., Homa, D. M., Akinbami, L. J., Moorman, J. E., Gwynn, C., & Redd, S. C. (2002). Surveillance for asthma--United States, 1980-1999. *MMWR Surveill Summ, 51*(1), 1-13.

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

Mudway, I. S., & Kelly, F. J. (2004). An investigation of inhaled ozone dose and the magnitude of airway inflammation in healthy adults. *Am J Respir Crit Care Med, 169*(10), 1089-1095.

National Center for Environmental Health, C. f. D. C. (2005). *Environmental Public Health Indicators Project*. Retrieved July 10, 2005, from http://www.cdc.gov/nceh/indicators/default.htm

National Center for Health Statistics, C. f. D. C. (2005). *Asthma Prevalence, Health Care Use, and Mortality, 2002*. Retrieved June 14, 2005, from http://www.cdc.gov/nchs/products/pubs/pubd/hestats/asthma/asthma.htm

National Center for Health Statsitics, C. f. D. C. (2005). *National Hospital Discharge and Ambulatory Surgery Data*. Retrieved May 10, 2005, from http://www.cdc.gov/nchs/about/major/hdasd/nhdsdes.htm

National Institutes of Health Asthma Education and Prevention Program. (2002, 10 Sept 2004). *Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma.*, from http://www.nhlbi.nih.gov/guidelines/asthma/

Neidell, M. J. (2004). Air pollution, health, and socio-economic status: the effect of outdoor air quality on childhood asthma. *J Health Econ, 23*(6), 1209-1236.

Nuckols, J. R., Ward, M. H., & Jarup, L. (2004). Using geographic information systems for exposure assessment in environmental epidemiology studies. *Environ Health Perspect, 112*(9), 1007-1015.

Olden, K., & White, S. L. (2005). Health-related disparities: influence of environmental factors. *Med Clin North Am, 89*(4), 721-738.

Peled, R., Friger, M., Bolotin, A., Bibi, H., Epstein, L., Pilpel, D., et al. (2005). Fine particles and meteorological conditions are associated with lung function in children with asthma living near two power plants. *Public Health, 119*(5), 418-425.

Pennsylvania Health Care Cost Containment Council. (2005). Retrieved July 15, 2005, from http://www.phc4.org/

Ruidavets, J. B., Cassadou, S., Cournot, M., Bataille, V., Meybeck, M., & Ferrieres, J. (2005). Increased resting heart rate with pollutants in a population based study. *J Epidemiol Community Health, 59*(8), 685-693.

Thurston, G. D., & Bates, D. V. (2003). Air pollution as an underappreciated cause of asthma symptoms. *Jama, 290*(14), 1915-1917.

U.S. Department of Commerce. (2002). *US Census 2000*. Retrieved Nov 10, 2004, from http://www.census.gov/

U.S. Department of Health and Human Services. (2000). *Healthy People 2010: Respiratory Diseases (Goal 24)*. Retrieved 10 Sept 2004, from http://www.healthypeople.gov/Document/pdf/Volume2/24Respiratory.pdf

U.S. Environmental Protection Agency. (2005a). *Air and Radiation: Basic Information*. Retrieved May 5, 2005, from http://www.epa.gov/air/basic.html

U.S. Environmental Protection Agency. (2005b). *Toxic Release Inventory Program*. Retrieved May 10, 2005, from http://www.epa.gov/tri/

United States Environmental Protection Agency. (2005). *What Are the Six Common Air Pollutants*. Retrieved June 26, 2005, from http://www.epa.gov/ebtpages/pollairpocriteriaairpollutants.html

Villeneuve, P. J., Leech, J., & Bourque, D. (2005). Frequency of emergency room visits for childhood asthma in Ottawa, Canada: the role of weather. *Int J Biometeorol*.

Vine, M. F., Degnan, D., & Hanchette, C. (1997). Geographic information systems: their use in environmental epidemiologic research. *Environ Health Perspect, 105*(6), 598-605.

Weiss, K. B., & Sullivan, S. D. (2001). The health economics of asthma and rhinitis. I. Assessing the economic impact. *J Allergy Clin Immunol, 107*(1), 3-8.

Wenzel, S., Balzar, S., Chu, H. W., Silkoff, P., Cundall, M., Trudeau, J. B., et al. (2005). Severe asthma in adults *Am J Respir Crit Care Med, 172*(2), 149-160.

White, M. C., Berger-Frank, S. A., Middleton, D. C., & Falk, H. (2002). Addressing community concerns about asthma and air toxics. *Environ Health Perspect, 110 Suppl 4*, 561-564.

Wilson, A. M., Wake, C. P., Kelly, T., & Salloway, J. C. (2005). Air pollution, weather, and respiratory emergency room visits in two northern New England cities: an ecological time-series study. *Environ Res, 97*(3), 312-321.

3.3. Chapter 3

Manuscript in preparation

RISK FACTORS FOR SEVERE ADULT ASTHMA: THE SEROPREVALENCE OF BIOMARKERS FOR INFECTION BY ATYPICAL RESPIRATORY PATHOGENS

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3.3.1. Preface

Currently, biomarkers that identify risk of asthma symptoms does not exist. With respect to environmental exposures, characteristics within our daily environment have been identified as risk factors for asthma symptoms (ie. environmental tobacco smoke, ozone, respiratory infection). However, estimating the threshold that asthmatics can tolerate these exposures without exacerbations is difficult without non-invasive prognostic biomarkers. Here we assess the utility of serological biomarkers to assess the relationship of exposure to atypical respiratory pathogens and asthma severity classification in a clinical cohort of adult asthmatics.

3.3.2. Abstract

Asthma currently affects 7.4 million adults in the United States. The phenotype of "severe" asthma affects approximately 10% of all adult asthmatics. Lack of uniformity in recognition of risk factors, diagnosis of severe asthma and treatment thereof are challenges for both patients and clinicians. Of particular interest is the risk conferred by atypical pathogens to the severe asthma phenotype. The seroprevalence of biomarkers indicating infection by the atypical pathogens, *Mycoplama pneumonia (Mpn)* and *Chlamydia pneumonia (Cpn)*, was assessed in a cohort of adult asthmatics as part of the Severe Asthma Research Project (SARP). Participants (N = 215) were stratified according to disease severity as follows; mild/ moderate asthma (n= 152) and severe asthma (n = 63). With respect to disease severity, the risk conferred from infection with *Cpn* was not statistically significant (OR = 1.140, CI = 0.674 – 1.928, p =0.629). However, the risk for *Mpn* infection was lower for the severe group and was statistically significant (OR = 0.518, CI = 0.289 - 0.928, p=0.027). Further characterization of the severe asthma group revealed a higher frequency of treatment with antibiotics for sinusitis (OR = 2.741, CI =1.493 – 5.034, p = 0.009) and high-dose corticosteroids with additional anti-inflammatory drugs (OR = 13.171, CI = 5.735 – 30.251, p < 0.0001). The results suggest that the risk of severe asthma conferred by atypical pathogens may be modulated by the patient's current asthma therapy which includes combination anti-inflammatory medication and concurrent treatment with antibiotics. Further investigation should include analysis of bronchial specimens and the delineation of concurrent antibiotic and anti-inflammatory drug therapy in this sub-population of adult asthmatics.

3.3.3. Introduction

Asthma currently affects 7.4 million people over the age of 15 in the United States (Arif et al., 2003; Mannino et al., 2002). Although asthma-specific mortality rates for this age group have decreased, the increasing number of hospitalizations and attacks continue to be a significant problem for adults (E. S. Ford et al., 2003). The adult-onset asthmatic tends to have greater measures of morbidity (i.e. rapidly declining lung function) when compared with child-onset asthmatics (Bel, 2004). Previous studies have also cited that the diminished lung capacity in the adult-onset asthmatic is not reflective of disease duration (Jenkins et al., 2003). Thus, it is believed that adult-onset asthma may be a distinct disorder.

The "severe" asthma phenotype of represents < 10% of all adult asthmatics although this group accounts for a disproportionate share of the $14 billion spent annually for asthma-specific direct medical care (W. W. Busse et al., 2000; Godard et al., 2002). The lack of uniformity regarding the recognition of risk factors and diagnosis of severe asthma has been a clinical and public health challenge (National Institutes of Health Asthma Education and Prevention Program, 2002). Risk factors for adult asthma such as female gender, age, and BMI have been cited in previous studies (Arif et al., 2003; Ellman et al., 1997). However, their contribution to the severe phenotype is less understood. In addition, there are few studies that investigate the extent to which host-environment interaction affects progression to severe asthma are few. Of particular interest is how environmental biological agents, such as bacteria and viruses, contribute to the patho-physiology of adult severe asthma (Douglass & O'Hehir, 2000; Lemanske, 2003; Lemanske & Busse, 2003). For example, recent studies have demonstrated a

relationship between respiratory viruses and frequency of asthma symptoms in asthmatic children (Gern & Lemanske, 2003). However, for adult asthmatics this relationship has involved respiratory bacteria rather than respiratory viruses (Kraft, 2000).

One class of bacteria, atypical respiratory bacteria, is highly suspect as a risk factor in the pathogenesis of severe asthma (Blasi *et al.*, 1998; P. J. Cook *et al.*, 1998; Kraft, 2000; Martin et al., 2001). Atypical respiratory bacteria is a term used to distinguish a group of bacteria (i.e. *Chlamydia*, *Mycoplasma*) from those such as streptococcus that are "typically" recognized as being responsible for respiratory infections (Hammerschlag, 2001, 2003). Here we test the hypothesis that sero-prevalence of biomarkers indicating infection by *Chlamydia pneumonia* and *Mycoplasma pneumonia* is a risk factor for severe asthma in adults.

3.3.4. Methods

Study cohort

Subjects, age 15-68 years, were enrolled in the multi-city Severe Asthma Research Project (SARP) funded by the National Heart, Lung, and Blood Institute of the National Institutes of Health. Each city worked under a standardized definition of severe asthma (as defined by the SARP steering committee) and uniform inclusion criteria for severe asthma. Patients who reported having been diagnosed with asthma were assessed for asthma severity based on the following criteria:

Major criteria (individual must satisfy at least one of the following):

- Treatment with continuous or near-continuous oral corticosteroids
- Treatment with continuous high-dose inhaled corticosteroids

Minor Criteria: (individual must satisfy at least two of the following)

- Require daily treatment with controller medication in addition to inhaled corticosteriods
- Asthma symptoms require short-acting β-agonist use on a daily or near daily basis
- Persistent airway obstruction, as determined by FEV1 < 80% predicted and diurnal PEF variability > 20%
- One or more urgent care visits for asthma per year
- Three or more oral corticosteroid bursts per year
- Prompt deterioration with reduction in oral or inhaled corticosteroid dose
- Near-fatal asthma event in the past

Asthmatic subjects who did not satisfy the above criteria for severe asthma were classified as not severe.

Data

General. Upon enrollment into the SARP, all qualified subjects were asked to sign a consent form that permits the sharing of their data and/or biological samples across the SARP study sites.

Screening. Prospective study subjects were screened for eligibility based on their smoking history, prevalence of respiratory disease other than asthma (i.e. Cystic Fibrosis and Vocal Cord Dysfunction), diagnosis with asthma, length of disease, asthma medication and attack history, and satisfaction of the aforementioned major and minor criteria for severe asthma.

Serological analysis for respiratory pathogens. Serum was obtained from study subjects for serological analysis of antibodies indicative of respiratory infection cause by *Mycoplasma pneumoniae (Mpn)* and *Chlamydia pneumoniae (Cpn).* An Enzyme-Linked Immunosorbent Assay (ELISA) specific for the detection of Mpn- and Cpn-specific antibodies was used (Savyon Diagnostics, Ashdod, Israel). In addition to being assessed for the presence of *Cpn* or *Mpn* antibodies, the study subjects were assessed for the degree of infection as follows: IgM (current infection), IgG (past infection) and IgA (chronic infection).

Clinical assessments Blood drawn from all study subjects was assessed at each site laboratory for white blood cell differentials, IgE, hematocrit, and hemoglobin. Allergy skin testing was performed on all adult SARP study subjects. The protocol for the allergen skin test and panel of allergens used in the skin test was standardized across the 10 sites. Spirometry or lung function measurements were used by the SARP to determine the severity of asthma in the study subjects.

Questionnaire. Upon qualification for study enrollment, the participant was asked to complete the self-administered SARP questionnaire. These sections included:

- Asthma-specific quality of life
- Atopy history
- Demographic information
- Environmental factors specific to pet ownership
- Family allergy and asthma history
- General symptoms of respiratory disease
- Medical history, including co-morbidities and health care utilization
- Medication history
- Provoking factor exposure specific to asthma symptoms
- Smoking and ETS exposure history
- Symptoms and exposures exclusive to women (i.e. reproductive, hormones).

Statistical analysis

Controlling for confounding variables. Based on the recent literature regarding risk factors for adult asthma severity, current age and female gender were selected as variables that were controlled. Since recent evidence suggests that a person's body mass index (BMI) may contribute to poor health outcomes in those with chronic disease, BMI was also selected (E. S. Ford, 2005). At the time of this analyses, the SARP cohort was limited in the racial/ ethnic makeup. Therefore, we were not able to control for race/ ethnicity.

Logistic regression. The goal of logistic regression is to correctly predict the category of outcome for individual cases by finding the best fitting model to describe the relationship between the dependent variable (i.e severe asthma) and a set of independent (predictor or explanatory) variables (Friese and Long, 2003; Rosner, 2005). Logistic regression generates the coefficients (and its standard errors and significance levels) of a formula to predict a *logit transformation* of the probability of presence of the characteristic of interest:

$$\text{logit}(p) = b_0 + b_1 X_1 + b_2 X_2 + b_3 X_3 + \ldots + b_k X_k$$

where p is the probability of presence of the characteristic of interest. The logit transformation is defined as the logged odds or odds ratio:

$$\text{Odds ratio} = \frac{p}{1-p} = \frac{\text{probability of presence of character}}{\text{probability of absence of characteristic}}$$

Univariate analysis. Using logistic regression, all variables were assessed individually for their relationship to severe asthma. Those with a p-value $\leq$ 0.15 were extracted and retained for further stepwise regression analysis.

Stepwise "backward" regression analysis and severe asthma model. Stepwise regression is a form of logistic regression that tests the fit of the model after individual variables are added or deleted and is used to explore the relationship of predictor variables to the outcome of interest. Backward stepwise regression is the analysis that begins with a full or saturated model and variables are deleted from the model in an iterative process. The fit of the model is tested after

the elimination of each variable to ensure that the model still adequately fits the data. When no further variables can be eliminated from the model, the analysis has been completed. In all cases, the p-value criteria for entry into the model must be less than for its removal. Standard practice in epidemiology and biostatistics is p= 0.15 for entry of a predictor variable into the stepwise elimination model and p= 0.20 for removal (Friese and Long, 2003; Hosmer Jr. and Lemeshow, 2000).

The additional information collected from the SARP study subjects via a self- administered questionnaire and various clinical measurements were each assessed for statistical significance as a predictive variable. Those variables whose p-value was 0.15 or less were extracted for multivariate analysis. These variables were group into 6 sets and each set was analyzed using backward stepwise multivariate regression modeling while controlling for age, gender, and BMI. The resulting variables from each of the 6 sets were re-analyzed in a final model for asthma severity.

3.3.5. Results

Descriptive characteristics of study cohort.

Upon enrollment, the SARP study participants were categorized as normal/ no asthma (n = 18), mild/ moderate asthma (n = 152), or severe asthma (n = 53) (table 3.1). The gender distribution across these 3 groups was similar with an approximate ratio of females to males 2:1. The median age distribution and range of ages increased with disease morbidity regardless of gender. BMI also increased with disease morbidity but was more noticeable in females.

Table 3.1. Descriptive characteristics of SARP cohort (n = 233).

	Normal N = 18	**Mild/moderate asthma N = 152**	**Severe asthma N = 63**
Gender			
Male # (%)	7 (39)	43 (28.3)	23 (36.5)
Female # (%)	11 (61)	109 (71.7)	40 (63.5)
Age			
(median -range)	25.9 (18.9 –49.0)	30.8 (13.0 – 63.2)	44.1 (16.7 - 68.1)
By gender			
Male	25.9 (22.5 – 42.4)	28.4 (13.2 – 57.7)	44.9 (22.1 – 66.5)
Female	24.3 (18.9 – 48.0)	32.9 (13.0 – 63.2)	43.8 (16.7 – 68.1)
BMI			
median (range)	26.7 (20.6 – 47.6)	28.0 (17.4 – 63.9)	30.0 (19.8 – 55.7)
By gender			
Male	26.4 (23.9 – 47.6)	26.4 (17.4 – 41.2)	28.7 (20.1 – 45.0)
Female	27.0 (20.6 – 37.6)	28.2 (17.8 – 63.9)	31.3 (19.8 – 55.7)

Seroprevalence of biomarkers and provocation of asthma symptoms

During the SARP enrollment process, subjects had been asked if their asthma symptoms were provoked by respiratory infection (table 3.2). Although a slightly larger percentage of severe asthmatics compared with mild/ moderate asthmatics responded "yes" to this question, the difference was not statistically significant (OR = 2.090, CI = 0.579 - 7.542). Also shown in table 3.2 is the results of the serological analysis that compared the prevalence of *Mpn*- and *Cpn*-specific antibodies between the mild/moderate asthmatics and the severe asthmatics. For the seroprevalence of *Mpn* –specific antibodies, severe asthmatics were at a decreased risk (OR = 0.518, CI = 0.289 - 0.928, p= 0.027). The severe group also exhibited an increased risk of testing positive for *Cpn*-specific antibodies but this observation was not statistically significant (OR = 1.140, CI = 0.674 - 1.928, p= 0.625). With respect to degree of infection, past infection with *Mpn* was the most frequent finding in mild/moderate asthmatics and past/ chronic infection with *Cpn* was the most frequent finding in severe asthmatics.

Table 3.2. The seroprevalence of *Cpn*- and *Mpn- specific* antibodies between the 2 asthmatic groups. In addition, results of univariate analysis with the respective odds ratios and corresponding confidence intervals and p-values are shown.

	Mild/moderate asthma N = 152 # (%)	**Severe asthma N = 63 # (%)**	**Odds ratio (CI)**	**p-value**
Asthma provoked by respiratory infection	134 (91)	60 (95)	2.090 (0.579 - 7.542)	0.230
Mycoplasma pneumonia + subjects	89 (61.8)	31 (45.6)	0.518 (0.289 - 0.928)	0.027
By degree of infection				
Current	3 (2.0)	3 (4.8)	2.162 (0.426 – 10.968)	0.352
Past	49 (32.5)	19 (30.2)	0.728 9 0.397 – 1.334)	0.300
Chronic	9 (5.9)	0	0.408 (0.087 – 1.909)	0.215
Borderline	18 (11.8)	9 (14.3)	1.003 (0.431 – 2.333)	0.994
Current / past	11 (7.2)	0	0.182 (0.023 – 1.434)	0.106
Past / chronic	8 (5.3)	3 (4.8)	0.785 (0.202 – 3.046)	0.727
Current / past / chronic	4 (2.6)	2 (3.2)	1.060 (0.190 – 5.916)	0.947
Chlamydia pneumonia + subjects	72 (50)	36 (52.9)	1.140 (0.674 - 1.928)	0.625
By degree of infection				
Current	1 (0.7)	1 (1.6)	2.000 (0.123 – 32.377)	0.629
Past	26 (17.1)	14 (22.2)	1.391 (0.727 – 2.663)	0.323
Chronic	10 (6.6)	0	0.189 (0.024 – 1.503)	0.115
Borderline	0	1 (1.6)	--------	-----
Current / past	3 (2.0)	0	--------	-----
Past / chronic	33 (21.7)	18 (28.6)	1.325 (0.725 – 2.421)	0.363
Current / past / chronic	4 (2.6)	0	-------	-----

Assessment of additional potential risk factors

Additional information was collected from the SARP study subjects via a self- administered questionnaire and various clinical measurements (table 3.3). As mentioned in the Methods section, variables that were statistically significant after univariate analysis were extracted, grouped into 6 sets (based on their respective relevance), and further analyzed using multivariate logistic regression.

Table 3.3. Additional SARP subject characteristics that were assessed for the risk of asthma severity.

Category of factor	Sample of factors
Allergy (atopy) history	Age of onset, seasonal symptom frequency, age allergy onset
Allergy skin test	Mold, vegetation, cat, dog, dust mite
Asthma history	Yrs with asthma, age of onset
Asthma quality of life measurements	Domains include activity, emotions, environment stimuli, and asthma symptoms
Asthma symptoms	Frequency of cough, sputum, chest tightness, wheeze, shortness of breath, nocturnal breathing difficulty, use of rescue inhaler; duration of asthma attacks
Blood analysis	White blood cell differentials, Hemoglobin, Hematocrit
Co-morbidities including respiratory and non- respiratory	Pneumonia, acute and chronic bronchitis, sinusitis, sinus surgery, nasal polyps, polyp surgery
Family history	Asthma, allergies, eczema (father, mother, sibling, child)
Female –specific factors	Pre-menstrual symptoms, HRT, ovarian or uterine surgery
Lung function test (Spirometry)	FEV, FVC, PEF, FEF
Medical care utilization	Need for urgent care, doctor office visits, ED or hospitalization, ICU
Medication use	ICS and B-agonist use, need for rescue inhaler, additional controller meds
Pet ownership	Cat, dog, rodent, bird
Provoking factors	Animal, activity, exercise, aspirin
Tobacco use and exposure	Smoking status, including length and beginning age; exposure to environmental tobacco smoke

Symptom-frequency set. Study subjects were asked questions regarding both factors that provoke asthma attacks and the length of their asthma attacks. Subjects were also administered an Asthma Quality of Life Questionnaire (used with permission from Dr. Elisabeth Juniper). The results of univariate analyses are shown in table 3.4. Backward stepwise regression resulted in the retention of provocation due to either exercise (OR = 1.96 , CI= 0.82 – 4.70) or normal daily activity (OR = 3.66 , CI =1.17–11.48) as risk factors for this set.

Table 3.4. Symptom-specific risk model for severe asthma. Shown are the significant risk factors after univariate analysis and those that remained after multivariate analysis

	Univariate analysis		**Multivariate analysis**	
	Odds ratio (Confidence interval)	**Global p-value**	**Symptom model OR**	**Symptom model CI**
Asthma provoked by routine physical activity	3.30 (1.70 – 6.41)	0.0002	1.96	0.82 – 4.70
Asthma provoked by exercise	3.08 (1.141 – 8.317)	0.0140	3.66	1.17 – 11.48
Asthma quality of life score	1.60 (1.26 – 2.05)	0.0001	-------	-------
Duration of asthma attacks	1.56 (1.155 – 2.107)	0.0040	-------	-------
Symptom frequency score	1.09 (1.042 – 1.142)1	0.0001	-------	-------

Health care utilization and medication use set. The need for urgent medical care and use of rescue and/or additional asthma medication was assessed. For the severe asthma group, higher frequencies of unscheduled doctor appointments, emergency room visits, and hospital/ ICU admissions for breathing problems were all risk factors (table 3.5). With respect to medication use, using a daily short acting beta-agonist inhaler and use of additional controller medication were identified as risk factors following univariate analysis. After backward stepwise regression, seeing a doctor in the last 12 months (OR = 3.53, CI = 0.89 – 13.92) and ever having been admitted to an ICU due to breathing problems (OR =3.11 , CI = 0.98 – 9.82) in addition to the use additional controller medications (OR 4.63 = , CI =1.45 – 14.80) remained as risk factors within this model.

Table 3.5. Health care- and medication-specific model for severe asthma. Shown are the significant risk factors after univariate analysis and those that remained after multivariate analysis

	Univariate analysis		**Multivariate analysis**	
	Odds ratio (Confidence interval)	**Global p-value**	**Health care/ medication Model OR**	**Health care/ medication Model CI**
One or more urgent care visits in the last 12 months due to breathing problems	2.766 (1.572 – 4.865)	0.0004	-------	-------
Seen a doctor in the last 12 months due to breathing problems	7.44 (3.32 – 16.68)	< 0.0001	3.53	0.89 – 13.92
ER ever for breathing problems	2.17 (1.12 – 4.22)	0.0180	-------	-------
Hospitalization ever for breathing problems	3.79 (2.05 – 7.03)	< 0.0001	-------	-------
Hospitalization last 12 months for breathing problems	5.43 (1.39 – 21.31)	0.0080	-------	-------
ICU ever	5.33 (2.28 – 12.46)	0.0001	3.11	0.98 – 9.82
Daily use of β -agonist inhaler	4.70 (2.66 – 8.20)	< 0.0001		

Female-specific model. Univariate analysis of surgical removal of the ovaries, surgical removal of the uterus, and current use of hormone replacement therapy resulted in inclusion of these factors for stepwise regression (table 3.6). However, only current treatment with hormone replacement therapy (OR = 9.95, CI = 1.91 – 51.8) remained in the female-specific model.

Table 3.6. Female-specific model for severe asthma. Shown are the significant risk factors after univariate analysis and those that remained after multivariate analysis

	Univariate analysis		**Multivariate analysis**	
	Odds ratio (Confidence interval)	**Global p-value**	**Female-specific Model OR**	**Female-specific Model CI**
Surgical removal of the uterus	2.55 (0.927 – 7.039)	0.076	-------	-------
Surgical removal of the ovaries	3.26 (1.13 – 9.40)	0.032	-------	-------
Currently on hormone replacement therapy	13.81 (2.79 – 68.40)	0.002	9.95	1.91 – 51.8

Comorbidity-specific model. In addition to gastroesophageal reflux disease (GERD), all respiratory comorbidities that were assessed for a relationship to severe asthma qualified for inclusion in the stepwise model (table 3.7). In the final comorbidity model, having been treated with antibiotics for sinusitis (OR = 1.72 , CI= 0.81 – 3.64), current GERD (OR = 3.27 , CI =1.43 – 7.31), and ever having nasal polys (OR = 3.57 , CI =1.19 – 10.75) or pneumonia (OR = 2.09 , CI = 0.99 – 4.44) remained as predictive factors for severe asthma.

Table 3.7. Co-morbidity specific model for severe asthma. Shown are the significant risk factors after univariate analysis and those that remained after multivariate analysis

	Univariate analysis		**Multivariate analysis**	
	Odds ratio (Confidence interval)	**Global p-value**	**Co-morbidity Model OR**	**Co-morbidity Model CI**
Bronchitis treated with antibiotics	1.66 (0.916 – 3.01)	0.0940	-------	-------
Gastroesophageal reflux disease (GERD)	3.97 (2.06 – 7.65)	< 0.0001	3.27	1.43 – 7.31
Nasal polyps	4.38 (1.78 – 10.76)	0.0010	3.57	1.19 – 10.75
Nasal polyp surgery	5.88 (2.24 – 15.40)	0.0002	-------	-------
Pneumonia	2.91 (1.58 – 5.36)	0.0005	2.09	0.99 – 4.44
Sinus surgery	3.43 (1.64 – 7.17)	0.0010	-------	-------
Sinusitis treated with antibiotics	2.74 (1.49 – 5.03)	0.0009	1.72	0.81 – 3.64

Atopy- and inflammation-specific model. Although severe asthmatics had lower reactivity to allergens applied during the allergy skin test, they reported higher frequency of seasonal specific symptoms. This observation was reflected in the total seasonal atopy score that was a statistically significant risk factor after univariate analysis (OR =1.151, CI = 1.026 – 1.291) (table 3.8). While the risk of serological indices for allergy (i.e. eosinophils, IgE) were elevated in the mild/ moderate group, the severe group had an elevated risk of higher neutrophil counts, higher neutrophil percentage, and a higher hematocrit. After stepwise regression, only the percentage of neutrophils and the total atopy score remained in the model specific for atopy and inflammation.

Table 3.8. Atopy- and inflammation -specific model for severe asthma. Shown are the significant risk factors after univariate analysis and those that remained after multivariate analysis.

	Univariate analysis		**Multivariate analysis**	
	Odds ratio (Confidence interval)	**Global p-value**	**Atopy/ inflammation Model OR**	**Atopy/ inflammation Model CI**
Neutrophil ct	1.156 (0.964 – 1.387)	0.117	-------	-------
Neutrophil %	1.029 (1.0 – 1.059)	0.047	1.029	0.996 - 1.062
Hematocrit	1.058 (0.979 – 1.143)	0.151	-------	-------
Allergies make you breath worse	5.8 (0.741 – 45.386)	0.034	-------	-------
Total seasonal atopy score	1.151 (1.026 – 1.291)	0.014	1.269	1.099 - 1.465

Lung function-specific model. Severe asthmatics were more likely to have a higher baseline forced expiratory volume (the amount of air forcibly expired in 1 second) as measured the FEV_1 percent predicted (table 3.9). However, this group was more likely to perform poorly when measured for forced vital capacity (the amount of air forcibly expelled in 6 seconds) before and after bronchodilator administration. In addition, severe asthmatics were less likely to perform well in pre- and post-bronchodilator measurements of FEF and PEF when compared with mild/ moderate asthmatics. For the final lung function model, FEV_1 percent predicted (OR = 1.09, CI =1.008 - 1.178), post-bronchodilator FVC (OR =1.984 , CI= 0.981 - 4.014) and pre- and post-bronchodilator FEF (OR = 0.441 , CI =0.250 - 0.777 ; OR = 1.697, CI =0.975 - 2.817) were retained as risk factors for severe asthma.

Table 3.9. Lung function-specific model for severe asthma. Shown are the significant risk factors after univariate analysis and those that remained after multivariate analysis.

	Univariate analysis		**Multivariate analysis**	
	Odds ratio (Confidence interval)	**Global p-value**	**Lung function Model OR**	**Lung function Model CI**
FEV_1 percent predicted	1.090 (1.008 – 1.178)	0.0310	1.090	1.008 - 1.178
FVC baseline	0.578 (0.423 – 0.789)	0.0002	-------	-------
Pre-bronchodilator FEF	0.393 (0.269 – 0.574)	< 0.0001	-------	-------
Pre-bronchodilator PEF	0.702 (0.589 – 0.837)	< 0.0001	0.441	0.250 - 0.777
Post-bronchodilator FVC	0.654 (0.484 – 0.884)	0.004	1.984	0.981 - 4.014
Post-bronchodilator FEF	0.418 (0.301 – 0.581)	< 0.0001	--------	--------
Post-bronchodilator PEF	0.730 (0.612 – 0.871)	0.0002	1.657	0.975 - 2.817

Final severe asthma model. Risk factors from the 6 aforementioned sets that remained in their respective model after backward stepwise regression modeling (n = 14) were grouped together for a final analysis. The set of final predictor variables (n = 8) is shown in table 3.10 in descending order of statistical significance.

Table 3.10. Final model for severe asthma. Hosmer-Lemeshow goodness of fit $\chi^2 = 12.06$, p = 0.06.

	Severe asthma Model OR	**Severe asthma Model CI**
Seen a doctor in the last 12 months due to breathing problems	5.904	1.829 - 19.056
Use of additional controller medication (i.e. anti IgE, long acting β agonist, etc)	4.593	1.524 - 13.846
Nasal polyps	3.613	0.821 - 15.890
ICU ever	3.507	0.921 - 13.361
Gastroesophageal reflux disease (GERD)	3.245	1.196 - 8.805
Provoking of asthma symptoms due to exercise	2.788	0.808 - 9.618
Pneumonia	2.544	0.974 - 6.644
FEV_1 percent predicted	0.970	0.946 – 0.995

Post estimation tests. Shown in figure 3.1 are the results of the post-test estimations for model's goodness of fit. With respect to the predictive variables in the final severe asthma model, the sensitivity (i.e.the probability of predicting severe asthma) was 72.7% and specificity (i.e. the probability of predicting not severe asthma) was 93.3%. Further validation of the final model is shown in Figure 1 which shows the area under the curve (AUC) of the receiving operating characteristic (ROC) = 0.91. Using the Hosmer-Lemeshow goodness of fit test for the model, the resulting $\chi^2 = 12.06$, p =0.06. Therefore, the model is appropriate for the data.

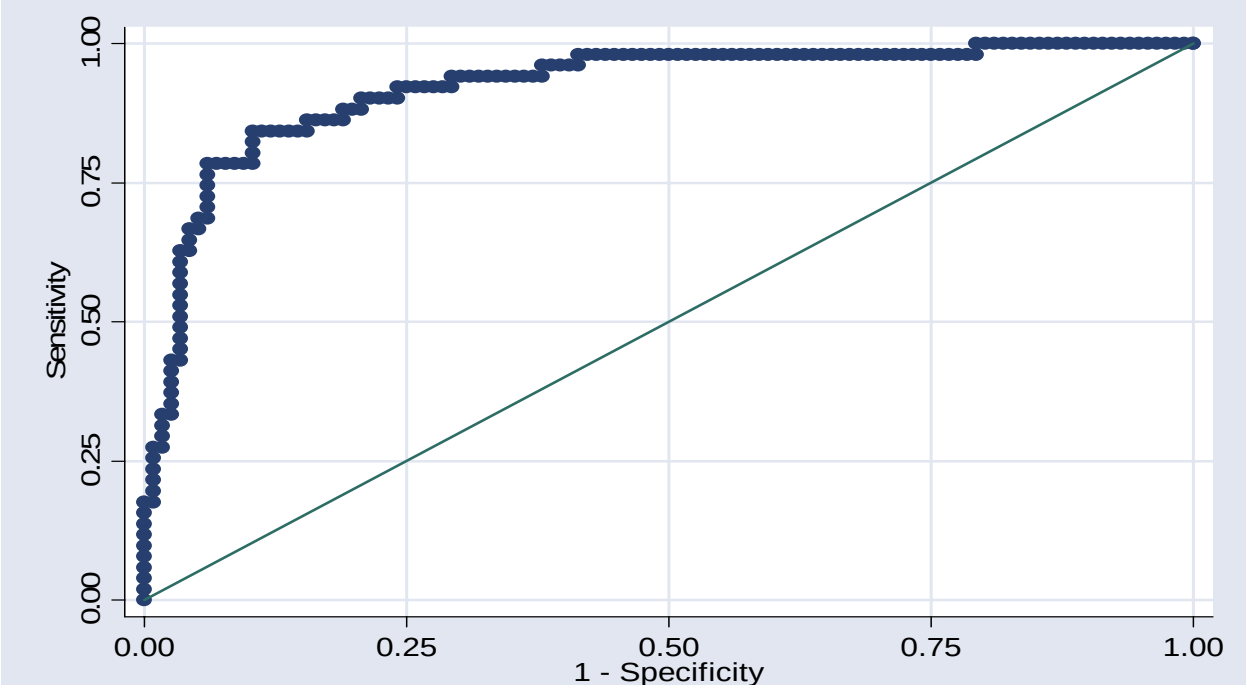

Figure 3.1. Post-test estimates. The predictable power of the final severe asthma model = 92%. The graph reflects this since the closer the curve follows the left-hand border and then the top border of the ROC space, the more accurate the test. The area under the curve (AUC) of the receiver operator characteristic (ROC) is the measure discrimination (i.e. the ability of the test to correctly classify those with and without severe asthma).

3.3.6. Discussion

The etiology of adult asthma is not fully understood. One question that remains is why have measures of asthma morbidity have steadily increased over the past decade even though the asthma-specific mortality rate has steadily decreased (National Institutes of Health Asthma Education and Prevention Program, 2002). These measures of morbidity include the need for continuous high-dose corticosteroids to control asthma symptoms and the frequent need for acute medical care due to these symptoms.

It is estimated that annual total direct health care expenditures for asthma care in the US is in excess of $11.3 billion (Weiss & Sullivan, 2001). This estimate does not include indirect health costs such as lost work days. Of the $11.3 billion, approximately 60% is attributed to the costs of asthma medication. It has been reported that although severe asthmatics comprise a small fraction of the total asthmatic population (i.e. 10%), they share a disproportionate burden of the total direct medical costs related to asthma spent every year in the US (S. Wenzel et al., 2005). A contributing factor to this expenditure is the lack of uniformity in asthma diagnosis, treatment, and severe asthma classification.

Individual characteristics such as female gender, and age have been identified as risk factors for severe asthma in the adult (Arruda et al., 2005; Kelley *et al.*, 2005; King *et al.*, 2004). Other factors such as comorbidities (i.e. sinusitis, bronchitis, GERD) and certain respiratory pathogens have recently garnered attention as additional risk factors for severe asthma (P. J. Cook et al., 1998; Liou et al., 2003). Some studies have shown an association with the frequency and

severity of asthma symptoms in the adult and infection caused by respiratory bacteria (Kraft, 2000). This is the different from what is observed in asthmatic children who tend to be more susceptible to respiratory viruses (Lemanske, 2003). The increased interest in risk factors for severe adult asthma is supported by the observation that adult-onset asthmatics tend to have a greater and more rapid decline in lung function that is not reflective of disease duration (Miranda et al., 2004). Thus, it is believed that adult-onset asthma, specifically adult severe asthma, may be a disorder distinct from childhood-onset asthma.

Atypical respiratory bacteria is a term used to distinguish a group of bacteria (ie. Chlamydia, Mycoplasma, Legionella) from those such as streptococcus that are "typically" recognized as being responsible for respiratory infections (Hammerschlag, 2000, 2001). One research question is how these pathogens are able to influence the prevalence and frequency of asthma symptoms. It is suggested that components of the bacteria, such as chaperone proteins, may evoke a persistent antigenic response in asthmatics (Bertorelli *et al.*, 1998; Betsou *et al.*, 2003; Costa *et al.*, 2002; Huittinen et al., 2001). This could explain the presence of pro-inflammatory cytokines and persistent elevated levels of IgE in the absence of atopy in these patients.

The relationship between asthma symptoms and atypical pathogens has been strictly associative. A published study in 1995 showed that within a pediatric study population, persistent infection with Chlamydia pneumonia (*Cpn)* resulted in chronic immune activation (Emre *et al.*, 1995). In a study by Nagy, et al, it was found that those who had a variation in the gene that encodes for a defense protein that acts against microbes were at higher risk for asthma (Nagy et al., 2003). A group headed by ten Brinke in the Netherlands showed that adults with

non-atopic asthma and positive *Cpn* IgG experienced persistent airflow limitation when compared with their matched controls (ten Brinke et al., 2001)**.** The most recent study to address this relationship in adults was conducted at National Jewish Hospital in Denver, CO. Drs. Richard Martin and Monica Kraft observed elevated amounts of *Cpn*-specific m-RNA and *Cpn*-specific antibodies in the bronchial cells of their study population (Kraft, 2000; Kraft *et al.*, 2001; Martin et al., 2001)**.** They interpreted their findings to indicate that *Cpn* antigens can evoke an IgE mediated response. However, authors concur that the further investigation of the relationship between infections caused by atypical respiratory pathogens and adult asthma severity needs to be tested in a larger samples fo asthmatics stratified by disease severity.

This study tested the hypothesis that infections caused by the atypical pathogens, Mycoplasma pneumonia (*Mpn*) and Chlamydia pneumonia (*Cpn*) are risk factors for severe asthma. The study population (n = 233), which was enrolled in the Severe Asthma Research Project (SARP), ranged in age was age 15-68 years and was stratified into three groups: normal controls, mild/moderate asthmatics, and severe asthmatics. The gender distribution across all 3 groups was a fair representation of the gender distribution in adult asthma (ENFUMOSA, 2003). In addition, the personal characteristics of the group reflected previous studies that have shown severe asthmatics tend to be older and have a higher BMI (Akerman et al., 2004; Varraso *et al.*, 2005).

To determine infection by *Mpn* or *Cpn*, peripheral serum samples were evaluated for the presence of antibodies specific to these pathogens. Distribution analysis revealed a higher prevalence of *Mpn* infection in the mild/moderate asthmatics (data not shown). This translated

into a lower risk conferred by *Mpn* infection for severe asthmatics that was statistically significant (OR =0.518 CI = 0.289 - 0.928). Conversely, although severe asthmatics had a slightly higher prevalence of *Cpn* infection, it was not statistically significant. One explanation could be the fact that most of the severe asthmatics regularly use high-dose anti-inflammatory drugs to control their asthma. In addition, treatment with antibiotics for bronchitis and sinusitis was significantly higher in the severe asthma group when compared to the mild/ moderate group. These 2 factors may account for the finding of an elevated risk of infection in the mild/moderate group.

In addition to testing the aforementioned hypothesis, we were able to assess other factors contributing to the severe asthma phenotype. With respect to disease severity, statistically significant risk factors that were identified in these models included current diagnosis of gastroesophageal reflux disease (GERD) and current use of hormone replacement therapy (HRT). In the Nurses Health Study Higher, a higher prevalence of HRT was reported in women who developed asthma as an adult (R. Graham Barr, 2004; R. G. Barr & Camargo, 2004). It has also been previously reported that GERD and obesity are associated with nocturnal asthma symptoms (Gunnbjornsdottir et al., 2004) We interpret the finding of GERD and HRT as statistically significant risk factors for severe asthma as a biologically plausible mechanism regarding the higher prevalence of severe asthma in females.

The role that allergy and inflammation have in the pathophysiology of severe asthma is not clear. In our cohort, severe asthmatics in our cohort had lower measures of allergic sensitization via the allergy skin test and lower measures of peripheral serum inflammatory biomarkers (i.e

IgE, eosinophils). However, the risk conferred from self-reported seasonal allergy symptoms and the percentage of serum neutrophils was statistically significant. Finally, other studies have noted an increased percentage of neutrophils in severe asthmatics hypothesizing that this is due to the pharmacological nature of high-dose inhaled corticosteroids (Jatakanon et al., 1999; Little et al., 2002; S. E. Wenzel et al., 1997). However, since neutrophils are part of the innate immune response to pathogens, the role of respiratory infection in this phenomenon should be further explored.

This is the largest published study to date that has investigated the relationship of atypical respiratory infection and the patho-physiology of severe adult asthma. Although we were limited to testing this hypothesis in the peripheral serum of study subjects, further investigation of this hypothesis should include bronchial specimens obtained from the SARP study participants.

The opportunity created by this NIH-funded study will allow investigators to address the uncertainties regarding the risk factors for severe adult asthma. Thorough understanding of this complex disease will have long-reaching public health effects through appropriate clinical intervention and management of relevant exposures and risk factors.

3.3.7 Literature cited

Akerman, M. J., Calacanis, C. M., & Madsen, M. K. (2004). Relationship between asthma severity and obesity. *J Asthma, 41*(5), 521-526.

Arif, A. A., Delclos, G. L., Lee, E. S., Tortolero, S. R., & Whitehead, L. W. (2003). Prevalence and risk factors of asthma and wheezing among US adults: an analysis of the NHANES III data. *Eur Respir J, 21*(5), 827-833.

Arruda, L. K., Sole, D., Baena-Cagnani, C. E., & Naspitz, C. K. (2005). Risk factors for asthma and atopy. *Curr Opin Allergy Clin Immunol, 5*(2), 153-159.

Barr, R. G. (2004). Propective Study of Postmenopausal Hormone Use and Newly Diagnosed Asthma and Chronic Obstructive Pulmonary Disease. *Archives of Internal Medicine, 164*(February 23,2004), 379-386.

Barr, R. G., & Camargo, C. A., Jr. (2004). Hormone replacement therapy and obstructive airway diseases. *Treat Respir Med, 3*(1), 1-7.

Bel, E. H. (2004). Clinical phenotypes of asthma. *Curr Opin Pulm Med, 10*(1), 44-50.

Bertorelli, G., Bocchino, V., Zhuo, X., Chetta, A., Del Donno, M., Foresi, A., et al. (1998). Heat shock protein 70 upregulation is related to HLA-DR expression in bronchial asthma. Effects of inhaled glucocorticoids. *Clin Exp Allergy, 28*(5), 551-560.

Betsou, F., Sueur, J. M., & Orfila, J. (2003). Anti-Chlamydia pneumoniae heat shock protein 10 antibodies in asthmatic adults. *FEMS Immunol Med Microbiol, 35*(2), 107-111.

Blasi, F., Allegra, L., & Tarsia, P. (1998). Chlamydia pneumoniae and asthma. *Thorax, 53*(12), 1095.

Busse, W. W., Banks-Schlegel, S., & Wenzel, S. E. (2000). Pathophysiology of severe asthma. *J Allergy Clin Immunol, 106*(6), 1033-1042.

Cook, P. J., Davies, P., Tunnicliffe, W., Ayres, J. G., Honeybourne, D., & Wise, R. (1998). Chlamydia pneumoniae and asthma. *Thorax, 53*(4), 254-259.

Costa, C. P., Kirschning, C. J., Busch, D., Durr, S., Jennen, L., Heinzmann, U., et al. (2002). Role of chlamydial heat shock protein 60 in the stimulation of innate immune cells by Chlamydia pneumoniae. *Eur J Immunol, 32*(9), 2460-2470.

Douglass, J. A., & O'Hehir, R. E. (2000). What determines asthma phenotype? Respiratory infections and asthma. *Am J Respir Crit Care Med, 161*(3 Pt 2), S211-214.

Ellman, M. S., Viscoli, C. M., Sears, M. R., Taylor, D. R., Beckett, W. S., & Horwitz, R. I. (1997). A new index of prognostic severity for chronic asthma. *Chest, 112*(3), 582-590.

Emre, U., Sokolovskaya, N., Roblin, P. M., Schachter, J., & Hammerschlag, M. R. (1995). Detection of anti-Chlamydia pneumoniae IgE in children with reactive airway disease. *J Infect Dis, 172*(1), 265-267.

ENFUMOSA. (2003). The ENFUMOSA cross-sectional European multicentre study of the clinical phenotype of chronic severe asthma. European Network for Understanding Mechanisms of Severe Asthma. *Eur Respir J, 22*(3), 470-477.

Ford, E. S. (2005). The epidemiology of obesity and asthma. *J Allergy Clin Immunol, 115*(5), 897-909.

Ford, E. S., Mannino, D. M., Homa, D. M., Gwynn, C., Redd, S. C., Moriarty, D. G., et al. (2003). Self-reported asthma and health-related quality of life: findings from the behavioral risk factor surveillance system. *Chest, 123*(1), 119-127.

Friese and Long. (2003). *Regression Models for Categorical Dependent Variables Using Stata, Revised Edition*: STATA Press.

Gern, J. E., & Lemanske, R. F., Jr. (2003). Infectious triggers of pediatric asthma. *Pediatr Clin North Am, 50*(3), 555-575, vi.

Godard, P., Chanez, P., Siraudin, L., Nicoloyannis, N., & Duru, G. (2002). Costs of asthma are correlated with severity: a 1-yr prospective study. *Eur Respir J, 19*(1), 61-67.

Gunnbjornsdottir, M. I., Omenaas, E., Gislason, T., Norrman, E., Olin, A. C., Jogi, R., et al. (2004). Obesity and nocturnal gastro-oesophageal reflux are related to onset of asthma and respiratory symptoms. *Eur Respir J, 24*(1), 116-121.

Hammerschlag, M. R. (2000). Chlamydia pneumoniae and the lung. *Eur Respir J, 16*(5), 1001-1007.

Hammerschlag, M. R. (2001). Mycoplasma pneumoniae infections. *Curr Opin Infect Dis, 14*(2), 181-186.

Hammerschlag, M. R. (2003). Pneumonia due to Chlamydia pneumoniae in children: Epidemiology, diagnosis, and treatment. *Pediatr Pulmonol, 36*(5), 384-390.

Hosmer Jr. and Lemeshow. (2000). *Applied Logistic Regression* (2nd ed.): Wiley.

Huittinen, T., Hahn, D., Anttila, T., Wahlstrom, E., Saikku, P., & Leinonen, M. (2001). Host immune response to Chlamydia pneumoniae heat shock protein 60 is associated with asthma. *Eur Respir J, 17*(6), 1078-1082.

Jatakanon, A., Uasuf, C., Maziak, W., Lim, S., Chung, K. F., & Barnes, P. J. (1999). Neutrophilic inflammation in severe persistent asthma. *Am J Respir Crit Care Med, 160*(5 Pt 1), 1532-1539.

Jenkins, H. A., Cherniack, R., Szefler, S. J., Covar, R., Gelfand, E. W., & Spahn, J. D. (2003). A comparison of the clinical characteristics of children and adults with severe asthma. *Chest, 124*(4), 1318-1324.

Kelley, C. F., Mannino, D. M., Homa, D. M., Savage-Brown, A., & Holguin, F. (2005). Asthma phenotypes, risk factors, and measures of severity in a national sample of US children. *Pediatrics, 115*(3), 726-731.

King, M. E., Mannino, D. M., & Holguin, F. (2004). Risk factors for asthma incidence. A review of recent prospective evidence. *Panminerva Med, 46*(2), 97-110.

Kraft, M. (2000). The role of bacterial infections in asthma. *Clin Chest Med, 21*(2), 301-313.

Kraft, M., Hamid, Q., Chrousos, G. P., Martin, R. J., & Leung, D. Y. (2001). Decreased steroid responsiveness at night in nocturnal asthma. Is the macrophage responsible? *Am J Respir Crit Care Med, 163*(5), 1219-1225.

Lemanske, R. F., Jr. (2003). Is asthma an infectious disease? Thomas A. Neff lecture. *Chest, 123*(3 Suppl), 385S-390S.

Lemanske, R. F., Jr., & Busse, W. W. (2003). 6. Asthma. *J Allergy Clin Immunol, 111*(2 Suppl), S502-519.

Liou, A., Grubb, J. R., Schechtman, K. B., & Hamilos, D. L. (2003). Causative and contributive factors to asthma severity and patterns of medication use in patients seeking specialized asthma care. *Chest, 124*(5), 1781-1788.

Little, S. A., MacLeod, K. J., Chalmers, G. W., Love, J. G., McSharry, C., & Thomson, N. C. (2002). Association of forced expiratory volume with disease duration and sputum neutrophils in chronic asthma. *Am J Med, 112*(6), 446-452.

Mannino, D. M., Homa, D. M., Akinbami, L. J., Moorman, J. E., Gwynn, C., & Redd, S. C. (2002). Surveillance for asthma--United States, 1980-1999. *MMWR Surveill Summ, 51*(1), 1-13.

Martin, R. J., Kraft, M., Chu, H. W., Berns, E. A., & Cassell, G. H. (2001). A link between chronic asthma and chronic infection. *J Allergy Clin Immunol, 107*(4), 595-601.

Miranda, C., Busacker, A., Balzar, S., Trudeau, J., & Wenzel, S. E. (2004). Distinguishing severe asthma phenotypes: role of age at onset and eosinophilic inflammation. *J Allergy Clin Immunol, 113*(1), 101-108.

Nagy, A., Kozma, G. T., Keszei, M., Treszl, A., Falus, A., & Szalai, C. (2003). The development of asthma in children infected with Chlamydia pneumoniae is dependent on the modifying effect of mannose-binding lectin. *J Allergy Clin Immunol, 112*(4), 729-734.

National Institutes of Health Asthma Education and Prevention Program. (2002). *Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma.*, Retrieved 10 Sept 2004 from http://www.nhlbi.nih.gov/guidelines/asthma/

Rosner, B. (2005). *Fundamentals of Biostatistics* (6th ed.): Brooks/ Cole.

ten Brinke, A., van Dissel, J. T., Sterk, P. J., Zwinderman, A. H., Rabe, K. F., & Bel, E. H. (2001). Persistent airflow limitation in adult-onset nonatopic asthma is associated with serologic evidence of Chlamydia pneumoniae infection. *J Allergy Clin Immunol, 107*(3), 449-454.

Varraso, R., Siroux, V., Maccario, J., Pin, I., & Kauffmann, F. (2005). Asthma severity is associated with body mass index and early menarche in women. *Am J Respir Crit Care Med, 171*(4), 334-339.

Weiss, K. B., & Sullivan, S. D. (2001). The health economics of asthma and rhinitis. I. Assessing the economic impact. *J Allergy Clin Immunol, 107*(1), 3-8.

Wenzel, S., Balzar, S., Chu, H. W., Silkoff, P., Cundall, M., Trudeau, J. B., et al. (2005). Severe asthma in adults *Am J Respir Crit Care Med, 172*(2), 149-160.

Wenzel, S. E., Szefler, S. J., Leung, D. Y., Sloan, S. I., Rex, M. D., & Martin, R. J. (1997). Bronchoscopic evaluation of severe asthma. Persistent inflammation associated with high dose glucocorticoids. *Am J Respir Crit Care Med, 156*(3 Pt 1), 737-743.

4. DISCUSSION

4.1.Overview

For the past decade, evidence supporting the disproportionate distribution of environmentally-related disease amongst the US population has increased (Gold & Wright, 2005; Olden & White, 2005). *Healthy People 2010,* the US Department of Health and Human Service's program for addressing health disparities has prioritized the reduction of exposures that contribute to the etiology of environmentally-related disease (U.S. Department of Health and Human Services, 2000). However, surveillance for environmentally related disease does not exist. Asthma is one such disease.

Currently, the Centers for Disease Control's (CDC) Behavioral Risk Factor Surveillance System (BRFSS) is the most frequently utilized tool to estimate baseline prevalence of chronic disease in the US (Centers for Disease Control, 2005a). This random-number telephone survey samples populations periodically for incidence and prevalence of disease. Changes in such prevalence over time are often published by the CDC in their Morbidity and Mortality Weekly Report (MMWR) (Centers for Disease Control, 2005b). However, since these estimates are at the national level, the CDC encourages local adaptation of the BRFSS. State and local agencies have adopted the BRFSS to address local public health issues but the BRFSS is rarely used by to estimate the local prevalence and morbidity of chronic disease.

Recently, the CDC has established the Environmental Public Health Indicator (EPHI) project(C. f. D. C. National Center for Environmental Health, 2005). The long-term goal is to incorporate the local surveillance of the prevalence and morbidity of non-infectious chronic diseases into a national public health surveillance system by identifying indicators of environmental health.

One index of chronic disease prevalence and morbidity that has been cited in the CDC's MMWR is hospital discharge statistics (C. f. D. C. National Center for Health Statsitics, 2005). The National Center for Health Statistics at the CDC regularly collects these data via a sample survey of hospitals in the US. As a health effects indicator, the CDC has recognizes the utility of hospitalization data as a source to detect unusual patterns of events specific to environmentally-related disease. One such disease is asthma.

Asthma is a chronic respiratory disease whose etiology is suspected of being environmentally-related (Allacci, 2005; S. Holgate, 2001; S. T. Holgate, 1999). In the past decade as the incidence of newly diagnosed asthma has remained stable, the prevalence of persistent asthma symptoms has increased (Lawson & Senthilselvan, 2005). One question that remains is why these measures of asthma morbidity have steadily increased (National Institutes of Health Asthma Education and Prevention Program, 2002). Measures of morbidity also include health care utilization. It is estimated that annual total direct health care expenditures for asthma care in the US is in excess of $11.3 billion (Weiss & Sullivan, 2001). Of the $11.3 billion, approximately 60% is attributed to the costs of asthma medication. Traditionally

regarded as a childhood disorder, in recent years asthma has emerged as a public health concern of adults age 19-64 (Dolan et al., 2004).

Adult- or late-onset asthma has been added to the current phenotypes of asthma (Bel, 2004). Although many studies have published that address the risk factors for child-onset asthma, the risk factors for adult-onset asthma remain poorly defined. Without surveillance or a standardized protocol for diagnosis, the prevalence of adult asthma and adult asthma morbidity morbidity is believed to be greatly underestimated (W. Busse et al., 2004; National Institutes of Health Asthma Education and Prevention Program, 2002).

It has been reported that individuals with one phenotype of asthma, severe asthma, comprise a small fraction of the total asthmatic population (i.e. 10%). As the name implies, severe or difficult-to-treat asthma, has grater difficult managing their disease (S. Wenzel *et al.*, 2005). In addition, this subpopulation of asthmatics shares a disproportionate burden of the total direct medical costs related to asthma spent every year in the US. A contributing factor to this expenditure is the lack of uniformity in asthma diagnosis, treatment, and severe asthma classification.

Risk factors for severe asthma in the adult include female gender, race, and age (Arruda *et al.*, 2005; Kelley *et al.*, 2005; King *et al.*, 2004). It is unclear if age as a risk factor is due to the age at disease onset or the duration of disease in an individual (Burrows, Barbee, Cline, Knudson, & Lebowitz, 1991; Busse, Banks-Schlegal, & Wenzel, 2000; Lange, Parner, Vestbo, Schnohr, & Jensen, 1998; Peat, Woolcock, & Cullen, 1987). Additional risk factors for severe asthma include comorbidities such as sinusitis, bronchitis, and GERD. (P. J. Cook et al., 1998;

Liou et al., 2003). Infection with certain respiratory pathogens have also been identified for risk factors ((P. J. Cook et al., 1998; Liou et al., 2003). The need for understanding risk factors for severe adult asthma is supported by the fact that adult-onset asthmatics tends to have a greater and more rapid decline in lung function that is not reflective of disease duration (Miranda *et al.*, 2004). Thus, it is believed that adult-onset asthma, specifically adult severe asthma, may be a distinct disorder from childhood-onset asthma. Therefore, the public health significance of delineating risk factors for adult asthma morbidity is greater than ever.

Environmental epidemiology uses interdisciplinary approaches to address suspect risk factors of health outcomes related to the environment. These can range from molecular and cellular biology for assessing the prevalence of biomarkers to environmental engineering to assess the spatial distribution of exposures and health outcomes (Boffetta, 2002; Briggs, 2005; Kunzli, 2005). Environmental engineering has also contributed the concept of "source apportionment"; the identification of the source of elements in air pollution (i.e. industry, commercial vehicles, agriculture). The advent of electronic medical records is increasingly a data source for the development of local disease morbidity. The expansion of biostatistical methods with respect to predicting health outcomes, including the assessment of a range of risk factors while controlling for numerous confounding variables, has furthered the development of environmental epidemiology. Here we summarize the use of these novel approaches to assess the prevalence of environmental risk factors for adult asthmatics.

4.2. Summary of results

4.2.1. Using mapping technology and Poisson statistics to assess adult asthma hospitalization rates within the urban-rural context.

Epidemiological studies have suggested that a rural environment confers protection against the development of childhood asthma (von Mutius, 2001). More recent reports from China and Europe have indicated a reduction in the prevalence of childhood asthma in rural settings (Chan-Yeung et al., 2002; Waser et al., 2005). This "hygiene hypothesis" suggests that exposures from farming and livestock tend to protect children from the development of asthma. In our first study, we did not observe a protective effect of a farming environment for adult asthmatics. Lancaster County and Erie County both have substantial agricultural industry, yet their adult asthma hospitalization rates were substantially different.

Abundant roads and highways to accommodate heavy traffic often characterize an urban community. Most studies that address the relationship of this urban characteristic with the frequency and severity of asthma symptoms have focused on children (Nicolai et al., 2003). For example, (Kim et al., 2004) the proximity of roads to schools, and their relationship with asthma symptoms. The authors found spatial variability in traffic related pollutants and an influence of this variability on the frequency of asthma symptoms in children.

Previous studies have shown that emissions from commercial traffic is more detrimental than car emissions with respect to respiratory symptoms (Janssen et al., 2003; van Vliet et al., 1997). Geographical areas with low SES have been reported to have a higher prevalence of

commercial trucking routes (Brown et al., 2003; Lwebuga-Mukasa et al., 2004). This may explain why Fayette County, an area characterized as least urban, but with low SES, had the highest adult asthma hospitalization rate.

Increased asthma morbidity in adult females has been reported (NAEPP, 2002). We found asthma hospitalization rates in all 6 counties were higher for females than for males. This is reflective of the National Institutes of Health's report that 61% of adult asthmatics are female. A recent European study found that females, regardless of their geographic location, had higher indices of chronic disease severity than males (ENFUMOSA, 2003). Biological mechanisms, such the endocrine shift during the menstrual cycle, or menopause, have been suggested to be responsible for this gender disparity (Haggerty, Ness, Kelsey, & Waterer, 2003; Vrieze, Postma, & Kerstjens, 2003). It has also been hypothesized that the health seeking behavior of women, when compared with men, may explain gender disparities in chronic disease (McCance-Katz, Carroll, & Rounsaville, 1999; Meyer-Weitz, Reddy, Van den Borne, Kok, & Pietersen, 2000). Further cohort studies are needed to gain a better understanding of the gender disparity in adult asthma hospitalization rates.

4.2.2. Using local asthma hospitalization data and mapping technology to assess the local burden of asthma morbidity.

Here we report the utilization of local adult asthma hospitalization data as an environmental health indicator in Allegheny County., Pennsylvania which includes the city of Pittsburgh.

The total adult asthma hospitalization rate for Allegheny County was comparable to the CDC's latest estimates (National Center for Health Statistics, 2005). Comparable profiles were

observed for both gender-specific and age specific rates. However, the race-specific rates for African –Americans were slightly elevated. This suggests the possibility of a greater burden of adult asthma hospitalizations in Blacks.

Most studies investigating the temporal distribution of asthma events have focused on the daily ambient air quality (Galan *et al.*, 2003; Neidell, 2004; Wilson *et al.*, 2005). Air quality in the US is based on the concentrations of criteria air pollutants as defined by the Environmental Protection Agency (EPA) (United States Environmental Protection Agency, 2005). They include sulfur dioxide (SO^2), nitrogen dioxide (NO^2), carbon monoxide (CO), ozone (O^3), and particulate matter <10um (PM_{10}) and <2.5um ($PM_{2.5}$). The EPA's daily Air Quality Index (AQI) is reflective of the concentrations of the main pollutant on the day of interest; the higher the index, the poorer the air quality. With respect to health effects, the most investigated pollutant is ozone. Published studies have shown the adverse effects of ozone even in healthy individuals (McConnell *et al.*, 2002; Mudway & Kelly, 2004).

Our study showed that on days of increased adult asthma hospitalizations, the air quality index was lower (i.e. better air quality). In addition, the main pollutant on these days was not ozone but particulate matter. Further assessment of the relationship of the daily main pollutant and hospitalization frequencies demonstrated identified a positive correlation of PM_{10} and an inverse correlation of ozone. Numerous studies have cited a relationship between respiratory and cardiopulmonary hospitalizations on or about days where PM is the main pollutant (Delfino *et al.*, 2005; Kappos *et al.*, 2004; Ruidavets *et al.*, 2005; Thurston & Bates, 2003). An explanation may be that the degree of obstruction due to tissue remodeling is greater in the adult (Bai &

Knight, 2005; S. Wenzel et al., 2005). Another explanation may be that the influence of seasonal bacterial respiratory infections on adult asthma morbidity is greater than previously thought.

The impact that the environment has on health effects and disease prevalence is frequently cited within the context of environmental justice. One tenet of environmental justice is that individuals must have control over exposures in their environment (Apelberg *et al.*, 2005; Brulle & Pellow, 2005; Gee & Payne-Sturges, 2004). Since our dataset included the patient's zip code of residence, we assessed the influence of zip-code specific characteristics such as poverty and the prevalence of industrial facilities on the respective rates. We found an elevated risk of adult asthma hospitalization associated with factors of SES such as poverty and lower educational attainment. The 14 zip codes with higher rates, located predominantly in the Southeastern quadrant of the county, also had higher percentage of African-Americans residents. In addition, indices of exposure to industrial sites were not statistically significant. However, since the exact address of patients in this study were not available, further quantification of exposure effects was not possible

4.2.3 Integrating laboratory methods into environmental epidemiology

Our third study tested the hypothesis that infections caused by the atypical pathogens, Mycoplasma pneumonia (*Mpn*) and Chlamydia pneumonia (*Cpn*) are risk factors for severe asthma. The rationale for this hypothesis was the aforementioned observation that adult asthmatics have a higher frequency of hospitalization during the winter. These bacteria belong to a class known as atypical respiratory pathogens. The term "atypical" bacteria is used to

distinguish a group of bacteria (ie. Chlamydia, Mycoplasma, Legionella) from those such as streptococcus that are "typically" recognized as being responsible for respiratory infections (Hammerschlag, 2000, 2001).

The relationship between asthma symptoms and atypical pathogens has been strictly associative. Emre, et al observed in their pediatric population that persistent infection with Chlamydia pneumonia (*Cpn)* resulted in chronic immune activation (Emre *et al.*, 1995). In a study by Nagy, et al, it was found that those who had a variation in the gene that encodes for a defense protein that acts against microbes were at higher risk for asthma (Nagy *et al.*, 2003). A group headed by ten Brinke in the Netherlands showed that adults with non-atopic asthma and positive *Cpn* IgG experienced persistent airflow limitation when compared to their matched controls (ten Brinke *et al.*, 2001)**.** The most recent study to address this relationship in adults was at National Jewish Hospital in Denver, CO. Drs. Richard Martin and Monica Kraft observed elevated amounts of *Cpn*-specific m-RNA and *Cpn*-specific antibodies in the bronchial cells of their study population (Kraft, 2000; Kraft *et al.*, 2001; Martin *et al.*, 2001)**.** They interpreted their findings that with respect to the *Cpn*-specific IgE, antigens of *Cpn* can evoke an IgE mediated response. However, a common theme across all of the studies is that the contribution of atypical pathogens to asthma severity needs to be tested in a larger sample of asthmatics stratified by disease severity.

Our study population (n = 233), which was enrolled in the Severe Asthma Research Project (SARP), ranged in age was age 15-68 years and was stratified into three groups: normal controls, mild/moderate asthmatics, and severe asthmatics. The gender distribution across all 3 groups was a fair representation of the gender distribution in adult asthma (ENFUMOSA, 2003). In

addition, the personal characteristics of the group reflected previous studies which have shown that severe asthmatics tend to be older and have a higher BMI (Akerman *et al.*, 2004; Varraso *et al.*, 2005).

To determine infection by *Mpn* or *Cpn*, peripheral serum samples were evaluated for the presence of antibodies specific to these pathogens. Distribution analysis revealed a higher prevalence of *Mpn* infection in the mild/moderate asthmatics (data not shown). This translated into a lower risk conferred by *Mpn* infection for severe asthmatics that was statistically significant (OR =0.518 CI = 0.289 - 0.928). In comparison, severe asthmatics had a slightly higher prevalence of *Cpn* infection, it was not statistically significant. One explanation could be the fact that the all of the severe asthmatics are currently using high-dose anti-inflammatory drugs to control their asthma. In addition, the use additional anti-inflammatory asthma medications and treatment with antibiotics for bronchitis and sinusitis was significantly higher in the severe asthma group when compared to the mild/ moderate group. Finally, it has been cited that individuals with severe chronic disease are more likely to take preventive measures that would have a negative impact on their health. Thus, severe asthmatics may take extra measures to care to reduce environmental exposures that would precipitate an exacerbation.

In addition to testing the aforementioned hypothesis, we were able to assess additional information gathered from the study participants. Various predictive models with respect to disease severity were generated using backward stepwise regression analysis. Statistically significant risk factors that were identified in these models included current diagnosis of gastroesophageal reflux disease (GERD) and current use of hormone replacement therapy

(HRT). Higher prevalence of HRT use in women enrolled in the Nurses Health Study who developed asthma as an adult was reported last year (R. Graham Barr, 2004; R. G. Barr & Camargo, 2004). It has also been previously reported that GERD and obesity is associated with nocturnal asthma symptoms (Gunnbjornsdottir *et al.*, 2004) We interpret the finding of GERD and HRT as statistically significant risk factors for severe asthma as a biologically plausible mechanism regarding the higher prevalence of severe asthma in females.

The role that allergy and inflammation plays in the pathology of severe asthma is also not quite understood. Severe asthmatics in our cohort had lower measures of allergic sensitization via the allergy skin test and lower measures of peripheral serum inflammatory biomarkers (i.e IgE, eosinophils). However, the risk conferred from seasonal allergy symptoms and the percentage of serum neutrophils was statistically significant. Self-reported frequency and severity of seasonal allergy symptoms by the severe asthma group was higher during the fall and winter. Thus, one could infer that exacerbations due to seasonal environmental exposures such as particulate matter and cold weather could be interpreted as allergies. Finally, other studies investigating the increased percentage of neutrophils observed in severe asthmatics hypothesize that this observation is due to the pharmacological nature of high-dose inhaled corticosteroids (Jatakanon *et al.*, 1999; Little *et al.*, 2002; S. E. Wenzel *et al.*, 1997). However, since neutrophils are part of the innate immune response to foreign agents, such as pathogens, the role that respiratory infection plays in this phenomenon should be further explored.

Our final model for severe asthma identified GERD and having nasal polyps with higher odds ratios for predicting severe asthma. These were also stronger predictive factors that pneumonia and frequent need for medical care due to asthma.

4.3. The public health significance and future directions

These studies represent 3 projects that had yet to be addressed in local asthma research. The urban-rural study was first such study to address measures of urbanization and the influence of urbanization on adult asthma hospitalization rates. The Commonwealth contains areas with high population density and others with low population density. It also has a stable population that tends to relocate infrequently. This stability is important when assessing the change over time in hospitalization frequency. The unexpected trend of increased hospitalization with decreasing size of the populace and decreased urbanization suggests a strong influence of demographic and socioeconomic factors. These factors should be further explored to better understand their influence on human respiratory health.

In our second study, we showed that hospitalization data that includes all health care facilities are a useful tool for estimating disease morbidity within a community. The Commonwealth of Pennsylvania is only one of three states within the US that collects such data. The timeliness and availability of the data adds to its utility of being used in the capacity of an environmental health indicator. In addition, this is the first study to estimate the burden of asthma morbidity within Allegheny County, PA using the criteria set forth by the CDC for environmental health surveillance. By developing this environmental health capacity, meaningful and appropriate public health interventions can be implemented.

The third study is the largest published study to date that has investigated the relationship of atypical respiratory infection and the patho-physiology of severe asthma in adults. Although we were limited to testing this hypothesis in the serum, future directions include further investigation of this hypothesis using bronchial specimens obtained from the SARP study participants. The opportunity created by this NIH-funded study will allow investigators to address the uncertainties regarding the risk factors. Thorough understanding of this complex disease will have long-reaching public health effects through appropriate clinical intervention and management of relevant environmental exposures and risk factors.

4.4 Literature cited

Adams, R. J., Weiss, S. T., & Fuhlbrigge, A. (2003). How and by whom care is delivered influences anti-inflammatory use in asthma: Results of a national population survey. *J Allergy Clin Immunol, 112*(2), 445-450.

Akerman, M. J., Calacanis, C. M., & Madsen, M. K. (2004). Relationship between asthma severity and obesity. *J Asthma, 41*(5), 521-526.

Allacci, M. S. (2005). Identifying environmental risk factors for asthma emergency care" a multilevel approach for ecological study. *J Ambul Care Manage, 28*(1), 2-15.

Apelberg, B. J., Buckley, T. J., & White, R. H. (2005). Socioeconomic and racial disparities in cancer risk from air toxics in maryland. *Environ Health Perspect, 113*(6), 693-699.

Arruda, L. K., Sole, D., Baena-Cagnani, C. E., & Naspitz, C. K. (2005). Risk factors for asthma and atopy. *Curr Opin Allergy Clin Immunol, 5*(2), 153-159.

Bai, T. R., & Knight, D. A. (2005). Structural changes in the airways in asthma: Observations and consequences. *Clin Sci (Lond), 108*(6), 463-477.

Barr, R. G. (2004). Propective study of postmenopausal hormone use and newly diagnosed asthma and chronic obstructive pulmonary disease. *Archives of Internal Medicine, 164*(February 23,2004), 379-386.

Barr, R. G., & Camargo, C. A., Jr. (2004). Hormone replacement therapy and obstructive airway diseases. *Treat Respir Med, 3*(1), 1-7.

Bel, E. H. (2004). Clinical phenotypes of asthma. *Curr Opin Pulm Med, 10*(1), 44-50.

Boffetta, P. (2002). Molecular epidemiology: A tool for understanding mechanisms of disease. *Eur J Surg Suppl*(587), 62-69.

Briggs, D. (2005). The role of GIS: Coping with space (and time) in air pollution exposure assessment. *J Toxicol Environ Health A, 68*(13-14), 1243-1261.

Brulle, R. J., & Pellow, D. N. (2005). Environmental justice: Human health and environmental inequalities. *Annu Rev Public Health*.

Busse, W., Banks-Schlegel, S., Noel, P., Ortega, H., Taggart, V., & Elias, J. (2004). Future research directions in asthma: An nhlbi working group report. *Am J Respir Crit Care Med*.

Centers for Disease Control. (2005a). *Asthma: Behavioral risk factor surveillance survey*. Retrieved Aug 19, 2005, from http://www.cdc.gov/asthma/brfss/default.htm

Centers for Disease Control. (2005b). *The Morbidity and Mortality Weekly Report: Know what matters.* Retrieved Sept 4, 2005, from http://www.cdc.gov/mmwr/about.html

Cook, P. J., Davies, P., Tunnicliffe, W., Ayres, J. G., Honeybourne, D., & Wise, R. (1998). Chlamydia pneumoniae and asthma. *Thorax, 53*(4), 254-259.

Delfino, R. J., Sioutas, C., & Malik, S. (2005). Potential role of ultrafine particles in associations between airborne particle mass and cardiovascular health. *Environ Health Perspect, 113*(8), 934-946.

Emre, U., Sokolovskaya, N., Roblin, P. M., Schachter, J., & Hammerschlag, M. R. (1995). Detection of anti-chlamydia pneumoniae ige in children with reactive airway disease. *J Infect Dis, 172*(1), 265-267.

ENFUMOSA. (2003). The enfumosa cross-sectional european multicentre study of the clinical phenotype of chronic severe asthma. European network for understanding mechanisms of severe asthma. *Eur Respir J, 22*(3), 470-477.

Galan, I., Tobias, A., Banegas, J. R., & Aranguez, E. (2003). Short-term effects of air pollution on daily asthma emergency room admissions. *Eur Respir J, 22*(5), 802-808.

Gee, G. C., & Payne-Sturges, D. C. (2004). Environmental health disparities: A framework integrating psychosocial and environmental concepts. *Environ Health Perspect, 112*(17), 1645-1653.

Gold, D. R., & Wright, R. (2005). Population disparities in asthma. *Annu Rev Public Health, 26*, 89-113.

Gunnbjornsdottir, M. I., Omenaas, E., Gislason, T., Norrman, E., Olin, A. C., Jogi, R., et al. (2004). Obesity and nocturnal gastro-oesophageal reflux are related to onset of asthma and respiratory symptoms. *Eur Respir J, 24*(1), 116-121.

Hammerschlag, M. R. (2000). Chlamydia pneumoniae and the lung. *Eur Respir J, 16*(5), 1001-1007.

Hammerschlag, M. R. (2001). Mycoplasma pneumoniae infections. *Curr Opin Infect Dis, 14*(2), 181-186.

Holgate, S. (2001). Mechanisms of allergy and adult asthma. *Curr Opin Allergy Clin Immunol, 1*(1), 47-50.

Holgate, S. T. (1999). Genetic and environmental interaction in allergy and asthma. *J Allergy Clin Immunol, 104*(6), 1139-1146.

Jatakanon, A., Uasuf, C., Maziak, W., Lim, S., Chung, K. F., & Barnes, P. J. (1999). Neutrophilic inflammation in severe persistent asthma. *Am J Respir Crit Care Med, 160*(5 Pt 1), 1532-1539.

Kappos, A. D., Bruckmann, P., Eikmann, T., Englert, N., Heinrich, U., Hoppe, P., et al. (2004). Health effects of particles in ambient air. *Int J Hyg Environ Health, 207*(4), 399-407.

Kelley, C. F., Mannino, D. M., Homa, D. M., Savage-Brown, A., & Holguin, F. (2005). Asthma phenotypes, risk factors, and measures of severity in a national sample of us children. *Pediatrics, 115*(3), 726-731.

King, M. E., Mannino, D. M., & Holguin, F. (2004). Risk factors for asthma incidence. A review of recent prospective evidence. *Panminerva Med, 46*(2), 97-110.

Kraft, M. (2000). The role of bacterial infections in asthma. *Clin Chest Med, 21*(2), 301-313.

Kraft, M., Hamid, Q., Chrousos, G. P., Martin, R. J., & Leung, D. Y. (2001). Decreased steroid responsiveness at night in nocturnal asthma. Is the macrophage responsible? *Am J Respir Crit Care Med, 163*(5), 1219-1225.

Kunzli, N. (2005). Unifying susceptibility, exposure, and time: Discussion of unifying analytic approaches and future directions. *J Toxicol Environ Health A, 68*(13-14), 1263-1271.

Lawson, J. A., & Senthilselvan, A. (2005). Asthma epidemiology: Has the crisis passed? *Curr Opin Pulm Med, 11*(1), 79-84.

Liou, A., Grubb, J. R., Schechtman, K. B., & Hamilos, D. L. (2003). Causative and contributive factors to asthma severity and patterns of medication use in patients seeking specialized asthma care. *Chest, 124*(5), 1781-1788.

Little, S. A., MacLeod, K. J., Chalmers, G. W., Love, J. G., McSharry, C., & Thomson, N. C. (2002). Association of forced expiratory volume with disease duration and sputum neutrophils in chronic asthma. *Am J Med, 112*(6), 446-452.

Lwebuga-Mukasa, J. S., Oyana, T. J., & Johnson, C. (2005). Local ecological factors, ultrafine particulate concentrations, and asthma prevalence rates in buffalo, new york, neighborhoods. *J Asthma, 42*(5), 337-348.

Martin, R. J., Kraft, M., Chu, H. W., Berns, E. A., & Cassell, G. H. (2001). A link between chronic asthma and chronic infection. *J Allergy Clin Immunol, 107*(4), 595-601.

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

Miranda, C., Busacker, A., Balzar, S., Trudeau, J., & Wenzel, S. E. (2004). Distinguishing severe asthma phenotypes: Role of age at onset and eosinophilic inflammation. *J Allergy Clin Immunol, 113*(1), 101-108.

Mudway, I. S., & Kelly, F. J. (2004). An investigation of inhaled ozone dose and the magnitude of airway inflammation in healthy adults. *Am J Respir Crit Care Med, 169*(10), 1089-1095.

Nagy, A., Kozma, G. T., Keszei, M., Treszl, A., Falus, A., & Szalai, C. (2003). The development of asthma in children infected with chlamydia pneumoniae is dependent on the modifying effect of mannose-binding lectin. *J Allergy Clin Immunol, 112*(4), 729-734.

National Center for Environmental Health, C. f. D. C. (2005). *Environmental Public Health IndicatorsPproject.* Retrieved July 10, 2005, from http://www.cdc.gov/nceh/indicators/default.htm

National Center for Health Statistics, C. f. D. C. (2005). *Asthma prevalence, health care use, and mortality, 2002.* Retrieved June 14, 2005, from http://www.cdc.gov/nchs/products/pubs/pubd/hestats/asthma/asthma.htm

National Center for Health Statsitics, C. f. D. C. (2005). *National hospital discharge and ambulatory surgery data.* Retrieved May 10, 2005, from http://www.cdc.gov/nchs/about/major/hdasd/nhdsdes.htm

National Institutes of Health Asthma Education and Prevention Program. (2002). *Expert panel report 2: Guidelines for the diagnosis and management of asthma.* Retrieved 10 Sept 2004 from http://www.nhlbi.nih.gov/guidelines/asthma/

Neidell, M. J. (2004). Air pollution, health, and socio-economic status: The effect of outdoor air quality on childhood asthma. *J Health Econ, 23*(6), 1209-1236.

Olden, K., & White, S. L. (2005). Health-related disparities: Influence of environmental factors. *Med Clin North Am, 89*(4), 721-738.

Peled, R., Friger, M., Bolotin, A., Bibi, H., Epstein, L., Pilpel, D., et al. (2005). Fine particles and meteorological conditions are associated with lung function in children with asthma living near two power plants. *Public Health, 119*(5), 418-425.

Ruidavets, J. B., Cassadou, S., Cournot, M., Bataille, V., Meybeck, M., & Ferrieres, J. (2005). Increased resting heart rate with pollutants in a population based study. *J Epidemiol Community Health, 59*(8), 685-693.

ten Brinke, A., van Dissel, J. T., Sterk, P. J., Zwinderman, A. H., Rabe, K. F., & Bel, E. H. (2001). Persistent airflow limitation in adult-onset nonatopic asthma is associated with

serologic evidence of chlamydia pneumoniae infection. *J Allergy Clin Immunol, 107*(3), 449-454.

Thurston, G. D., & Bates, D. V. (2003). Air pollution as an underappreciated cause of asthma symptoms. *JAMA, 290*(14), 1915-1917.

U.S. Department of Health and Human Services. (2000). *Healthy People 2010: Respiratory diseases (goal 24). Conference edition, Vol II.* Retrieved 10 Sept 2004,from http://www.healthypeople.gov/Document/pdf/Volume2/24Respiratory.pdf

United States Environmental Protection Agency. (2005). *What are the six common air pollutants.* Retrieved June 26, 2005, from http://www.epa.gov/ebtpages/pollairpocriteriaairpollutants.html

Varraso, R., Siroux, V., Maccario, J., Pin, I., & Kauffmann, F. (2005). Asthma severity is associated with body mass index and early menarche in women. *Am J Respir Crit Care Med, 171*(4), 334-339.

Villeneuve, P. J., Leech, J., & Bourque, D. (2005). Frequency of emergency room visits for childhood asthma in ottawa, canada: The role of weather. *Int J Biometeorol*.

Weiss, K. B., & Sullivan, S. D. (2001). The health economics of asthma and rhinitis. I. Assessing the economic impact. *J Allergy Clin Immunol, 107*(1), 3-8.

Wenzel, S., Balzar, S., Chu, H. W., Silkoff, P., Cundall, M., Trudeau, J. B., et al. (2005). Severe asthma in adults. The pathology of difficult asthma. *Am J Respir Crit Care Med, 172*(2), 149-160.

Wenzel, S. E., Szefler, S. J., Leung, D. Y., Sloan, S. I., Rex, M. D., & Martin, R. J. (1997). Bronchoscopic evaluation of severe asthma. Persistent inflammation associated with high dose glucocorticoids. *Am J Respir Crit Care Med, 156*(3 Pt 1), 737-743.

Wilson, A. M., Wake, C. P., Kelly, T., & Salloway, J. C. (2005). Air pollution, weather, and respiratory emergency room visits in two northern new england cities: An ecological time-series study. *Environ Res, 97*(3), 312-321.

APPENDIX A
Distribution Tables and Results of Univariate Analysis from Chapter 3

Factors assessed for risk of disease severity

Category of factor	Examples
Personal characteristics	Age, gender , BMI
Biomarkers of respiratory infection	Mycoplasma pneumonia and Chlamydia pneumonia seropositivity, Mycoplasma pneumonia and Chlamydia pneumonia infection classification (ie current, past, chronic)
Allergy (atopy) history	Age of onset, causes breathing problems, seasonal symptom frequency, atopy score
Allergy skin test	Mold, vegetation, cat, dog, allergen positivity score
Asthma history	Yrs with asthma, age of onset
Asthma quality of life measurements	Scores for symptoms, activity, emotions, environment and overall
Asthma symptoms	Frequency of cough, sputum, chest tightness, wheeze, shortness of breath, nocturnal breathing difficulty, use of rescue inhaler; duration of asthma attacks
Blood analysis	White blood cell differentials, Hemoglobin, Hematocrit
Family history	Asthma, allergies, eczema (father, mother, sibling, child)
For women only	Pre-menstrual symptoms, ovarian or uterine surgery
Lung function test (Spirometry)	Measurements of obstructive lung disorder (FEV, FVC, PEF, FEF)
Medical care utilization	Doctor office visits, ED or hospitalization, ICU
Medication use	In general, patterns of ICS and B-agonist use
Non-respiratory co-morbidities	GERD, osteoporosis, diabetes
Pet ownership	Cat, dog, rodent, bird
Provoking factors	Animal, activity, exercise, aspirin
Respiratory co-morbidities	Pneumonia, acute and chronic bronchitis, sinusitis, sinus surgery, nasal polyps, polyp surgery
Tobacco use and exposure	Smoking status, including length and beginning age; exposure to environmental tobacco smoke

Personal characteristics

1. Distribution

	Normal N = 18	**Mild/moderate asthma N = 152**	**Severe asthma N = 63**
Gender # (%)			
Male	7 (39)	43 (28.3)	23 (36.5)
Female	11 (61)	109 (71.7)	40 (63.5)
Age # (%)			
All median (range)	25.9 (18.9 – 49.0)	30.8 (13.0 – 63.2)	44.1 (16.7 – 68.1)
By gender			
Male	25.9 (22.5 – 42.4)	28.4 (13.2 – 57.7)	44.9 (22.1 – 66.5)
Female	24.3 (18.9 – 48.0)	32.9 (13.0 – 63.2)	43.8 (16.7 – 68.1)
BMI # (%)			
All median (range)	26.7 (20.6 – 47.6)	28.0 (17.4 – 63.9)	30.0 (19.8 – 55.7)
By gender			
Male	26.4 (23.9 – 47.6)	26.4 (17.4 – 41.2)	28.7 (20.1 – 45.0)
Female	27.0 (20.6 – 37.6)	28.2 (17.8 – 63.9)	31.3 (19.8 – 55.7)

2. Univariate analysis personal characteristics.

	Odds ratio (CI)	Global p value
Gender	0.686 (0.368 - 1.279)	0.238
Age	1.070 (1.041 - 1.010)	<0.001
BMI	1.028 (0.992 - 1.065)	0.134

Biomarkers of respiratory infection specific from Mycoplasma pneumonia (Mpn) and Chlamydia pneumonia (Cpn)

1. Distribution

	Normal N = 18	**Mild/moderate asthma N = 152**	**Severe asthma N = 63**
Asthma provoked by respiratory infection # (%)	0	134 (91)	60 (95)
Mycoplasma pneumonia + subjects # (%)	9 (56.2)	89 (61.8)	31 (45.6)
By degree of infection			
Current	1 (5.6)	3 (2.0)	3 (4.8)
Past	5 (27.8)	49 (32.5)	19 (30.2)
Chronic	0	9 (5.9)	0
Borderline	2 (11.1)	18 (11.8)	9 (14.3)
Current / past	2 (11.1)	11 (7.2)	0
Past / chronic	1 (5.6)	8 (5.3)	3 (4.8)
Current / past / chronic	0	4 (2.6)	2 (3.2)
Chlamydia pneumonia + subjects # (%)	10 (62.5)	72 (50)	36 (52.9)
By degree of infection			
Current	1 (5.6)	1 (0.7)	1 (1.6)
Past	4 (22.2)	26 (17.1)	14 (22.2)
Chronic	1 (5.6)	10 (6.6)	0
Borderline	0	0	1 (1.6)
Current / past	0	3 (2.0)	0
Past / chronic	5 (27.8)	33 (21.7)	18 (28.6)
Current / past / chronic	1 (5.6)	4 (2.6)	0

2. Univariate analysis

Factor	Odds ratio (CI)	Global p value
Asthma provoked by respiratory infection	2.090 (0.579 - 7.542)	0.230
Mpn +	0.518 (0.289 - 0.928)	0.027
Cpn +	1.140 (0.674 - 1.928)	0.625
Mpn+ by category		
Current	2.162 (0.426 – 10.968)	0.352
Past	0.728 9 0.397 – 1.334)	0.300
Chronic	0.408 (0.087 – 1.909)	0.215
Borderline	1.003 (0.431 – 2.333)	0.994
Current / past	0.182 (0.023 – 1.434)	0.106
Past / chronic	0.785 (0.202 – 3.046)	0.727
Current / past / chronic	1.060 (0.190 – 5.916)	0.947
Cpn+ by category		
Current	2.000 (0.123 – 32.377)	0.629
Past	1.391 (0.727 – 2.663)	0.323
Chronic	0.189 (0.024 – 1.503)	0.115
Borderline	--------	-------
Current / past	--------	-------
Past / chronic	1.325 (0.725 – 2.421)	0.363
Current / past / chronic	-------	-------

Allergy (atopy) history

1. Distribution

	Normal N = 18	**Mild/moderate asthma N = 152**	**Severe asthma N = 62**
Allergy symptoms w/o cold or flu # (%)	3 (16.6)	146 (96)	58 (93.6)
Age allergy onset median (range)	3 (0 – 41)	9 (1 – 53)	11 (0 - 48)
Still symptomatic # (%)	2 (25)	140 (97)	56 (98.3)
Allergies make you breath worse # (%)	0	130 (90.9)	58 (98.3)

2. Distribution of seasonal frequency of allergy symptoms

	Normal N=18	**Mild/moderate asthma N = 152**	**Severe asthma N = 62**
Spring allergies # (%)			
None	15 (83.3)	9 (6.0)	13 (4.8)
Mild	2 (11.1)	45 (29.6)	12 (19.3)
Moderate	1 (5.6)	60 (39.5)	27 (43.5)
Severe	0	38 (25.0)	20 (32.3)
Summer allergies # (%)			
None	15 (83.3)	19 (12.5)	8 (12.9)
Mild	2 (11.1)	63 (41.5)	19 (30.7)
Moderate	1 (5.6)	55 (36.2)	22 (35.5)
Severe	0	15 (9.9)	13 (21.0)
Fall allergies # (%)			
None	15 (83.3_	13 (8.6)	5 (8.1)
Mild	3 (16.7)	45 (29.6)	14 (22.6)
Moderate	0	67 (44.1)	23 (37.1)
Severe	0	27 (17.8)	20 (32.3)
Winter allergies # (%)			
None	17 (94.4)	37 (24.3)	10 (16.1)
Mild	1 (5.6)	60 (39.5)	20 (32.3)
Moderate	0	36 (23.7)	16 (25.8)
Severe	0	19 (12.5)	16 (25.8)
Total seasonal atopy score median (range)	4 (4 – 9)	10 (4 – 16)	11.5 (4 – 16)

3. Univariate analysis

	Odds ratio (CI)	Global p value
Allergy symptoms w/o cold or flu	0.596 (0.162 – 2.189)	0.444
Age allergy onset	1.032 (1.005 – 1.061)	0.021
Still symptomatic	2.0 (0.228 – 17.504)	0.502
Allergies make you breath worse	5.8 (0.741 – 45.386)	0.064
Spring allergies		
Mild	0.0571 (0.278 – 1.172)	0.116
Moderate	1.183 (0.650 – 2.151)	0.583
Severe	1.429 (0.748 – 2.728)	0.284
Summer allergies		
Mild	0.624 (0.333 – 1.171)	0.137
Moderate	0.970 (0.524 – 1.797)	0.923
Severe	2.423 (1.077 – 5.453)	0.035
Fall allergies		
Mild	0.693 (0.348 – 1.382)	0.291
Moderate	0.748 (0.408 – 1.372)	0.346
Severe	2.205 (1.122 – 4.333)	0.023
Winter allergies		
Mild	0.730 (0.391 – 1.363)	0.319
Moderate	1.121 (0.567 – 2.214)	0.744
Severe	2.435 (1.156 – 5.127)	0.021
Total seasonal atopy score	1.151 (1.026 – 1.291)	0.014

Allergy Skin Test

1. Allergens applied during the skin test

Histamine 1 mg/ml (+ control)
50% glycerin in 50% saline (- control)
Dermatophagoides pteronyssinus
Cat
Dog
American cockroach
Alternaria
Cladosporium
Aspergillus mix
Timothy grass (or grass mix)
Short ragweed
Common weed mix: cocklebur, lambs quarter, pigweed, English plantain, Russian thistle
Eastern 7-tree mix: white ash, American beech, red birch, American elm, shagbark hickory, red oak, cottonwood

2. Distribution

Allergen	**Normal N = 18**	**Mild/ moderate asthma N = 149**	**Severe asthma N = 57**
Alternaria # positive (%)	0	47 (31.5)	14 (24.6)
Aspergillus	0	15 (10.1)	5 (8.8)
Cat	2 (11.1)	69 (46.3)	23 (40.4)
Cladosporium	0	9 (6.0)	5 (8.8)
Cockroach	0	48 (32.2)	10 (17.5)
D. farinae	2 (11.1)	101 (67.8)	29 (50.9)
D. pteronyssinus	3 (16.7)	103 (69.1)	34 (59.7)
Dog	0	37 (24.8)	6 (10.5)
Grass mix	0	68 (45.6)	18 (31.6)
Ragweed	0	73 (49.3)	20 (36.4)
Tree mix	0	46 (30.1)	12 (21.1)
Weed mix	0	55 (36.9)	9 (15.8)
Total allergy score median (range)	0 (0 – 3)	4 (0 – 12)	3 (0 – 12)

3. Univariate analysis

	Odds ratio (CI)	Global p-value
Alternaria	0.706 (0.353 – 1.416)	0.321
Aspergillus	0.859 (0.297 – 2.483)	0.777
Cat	0.784 (0.422 – 1.457)	0.441
Cladosporium	1.496 (0.479 – 4.670)	0.496
Cockroach	0.448 (0.208 – 0.961)	0.031
D. farinae	0.492 (0.264 – 0.917)	0.026
D. pteronyssinus	0.660 (0.350 – 1.243)	0.201
Dog	0.356 (0.141 – 0.897)	0.017
Grass mix	0.550 (0.288 – 1.048)	0.064
Ragweed	0.587 (0.310 – 1.110)	0.098
Tree mix	0.597 (0.289 – 1.233)	0.153
Weed mix	0.320 (0.156 – 0.703)	0.002
Total allergy score	0.848 (0.751 – 0.957)	0.005

Asthma history

1. Distribution

	Mild/moderate asthma (n= 145)	**Severe asthma (n=61)**
Age of diagnosis with breathing problems median (range)	12 (0 -50)	20 (0 – 58)
Age of diagnosis with asthma	12 (0 – 50)	20 (0 – 58)
Length of disease	15 (1 – 53)	18 (1-59)

2. Univariate analysis

	Odds ratio (CI)	**Global p value**
Age of diagnosis with breathing problems	1.029 (1.008 – 1.050)	0.006
Age of diagnosis with asthma	1.025 (1.007 - 1.044)	0.007
Length of disease	1.018 (0.995 - 1.042)	0.117

Asthma quality of life measurements

1. Distribution

*****AQL measurements are interpreted as lowest possible score = 1, highest possible score = 7******

	Normal N = 18	**Mild/moderate asthma N= 152**	**Severe asthma N = 62**
Symptom score Median (range)	7 (6.83 – 7)	5.25 (1.083 – 7)	4.29 (1 – 6.58)
Activity score	7 (6.81 – 7)	5.09 (1 – 7)	4.185 (1.545 – 6.545)
Emotional score	7 (7-7)`	5.2 (1 – 7)	4.4 (1 – 7)
Environmental score	7 (7 – 7)	4.75 (1.25 – 7)	4 (1 – 7)
Overall AQL score	7 (6.89 – 7)	5.15 (1.125 – 6.938)	4.17 (1.187 – 6.5)

2. Univariate analysis

	Odds ratio (CI)	**Global p-value**
Symptom score	1.494 (1.185 - 1.884)	0.0005
Activity score	1.691 (1.310 - 2.181)	< 0.0001
Emotional score	1.251 (1.040 - 1.505)	0.017
Environmental score	1.376 (1.119 - 1.692)	0.002
Overall AQL score	1.598 (1.246 - 2.049)	0.0001

Asthma symptoms

1. Distribution of symptom frequency

	Mild/ moderate asthma N= 152	**Severe asthma N = 63**
Cough frequency		
Never	23 (15.1)	4 (6.3)
1x per month	43 (28.3)	11 (17.5)
Weekly but < 1x per day	29 (19.1)	13 (20.6)
2x per week but < 1x per day	24 (15.8)	10 (15.9)
Daily	19 (12.5)	9 (14.3)
At least 2x per day	14 (9.2)	16 (25.4)
Sputum frequency		
Never	39 (25.7)	8 (12.7)
1x per month	41 (27.0)	12 (19.1)
Weekly but < 1x per day	22 (14.5)	11 (17.5)
2x per week but < 1x per day	23 (15.1)	7 (11.1)
Daily	22 (14.5)	13 (20.6)
At least 2x per day	5 (3.3)	12 (19.1)
Chest tightness frequency		
Never	26 (17.1)	4 (6.4)
1x per month	44 (29.0)	8 (12.7)
Weekly but < 1x per day	28 (18.4)	24 (38.1)
2x per week but < 1x per day	27 (17.8)	11 (17.5)
Daily	21 (13.9)	13 (20.6)
At least 2x per day	6 (4.0)	3 (4.8)

1. Distribution of symptom frequency (continued)

	Mild/ moderate asthma N= 152	**Severe asthma N = 63**
Wheeze frequency		
Never	19 (12.5)	5 (7.9)
1x per month	43 (28.3)	12 (19.1)
Weekly but < 1x per day	39 (25.7)	21 (33.3)
2x per week but < 1x per day	24 (15.8)	9 (14.3)
Daily	22 (14.5)	10 (15.9)
At least 2x per day	5 (3.3)	6 (9.5)
Shortness of breath frequency		
Never	17 (11.2)	2 (3.2)
1x per month	38 (25.0)	7 (11.1)
Weekly but < 1x per day	41 (27.0)	22 (34.9)
2x per week but < 1x per day	27 (17.8)	9 (14.3)
Daily	26 (17.1)	15 (23.8)
At least 2x per day	3 (2.0)	8 (12.7)
Nocturnal symptom frequency		
Never	58 (38.2)	15 (23.8)
1x per month	36 (23.7)	14 (22.2)
Weekly but < 1x per day	16 (10.5)	8 (12.7)
2x per week but < 1x per day	15 (9.9)	10 (15.9)
Daily	22 (14.5)	12 (19.1)
At least 2x per day	5 (3.3)	4 (6.4)

2. Distribution for overall measures of asthma symptoms

	Mild/ moderate asthma N= 152	**Severe asthma N = 63**
Duration of asthma attacks		
< 1 hour	93 (61.2)	29 (46.0)
1-6 hours	37 (24.3)	14 (22.2)
6-48 hours	15 (9.9)	11 (17.5)
> 2 days	7 (4.6)	9 (14.3)
Overall symptom frequency score		
Median (range)	16.5 (6 – 36)	20 (9-36)
** Minimum possible score = 6 Maximum possible score = 36****		

3. Univariate analysis

	Odds ratio (CI)	**Global p-value**
Cough frequency	1.373 (1.136 – 1.660)	0.0008
Sputum frequency	1.142 (1.170 – 1.704)	0.0002
Chest tightness frequency	1.314 (1.062 – 1.626)	0.011
Wheeze frequency	1.223 (0.988 – 1.514)	0.064
Shortness of breath frequency	1.494 (1.189 – 1.878)	0.0004
Nocturnal symptom frequency	1.229 (1.026 – 1.472)	0.025
Overall symptom frequency score	1.091 (1.042 – 1.142)	0.0001
Duration of asthma attacks	1.560 (1.155 – 2.107)	0.004

Blood analysis

1. Distribution of blood elements

Element median (range)	**Reference values for adults *(source: AHS)***	**Mild/moderate asthma (n= 149)**	**Severe asthma (n=63)**
WBC ct ($x10^9$/L)	4.0 - 11.0	6.55 (2.3 – 12.9)	6.8 (3.9 – 13.5)
Neutrophil ct ($x10^9$/L)	2.0 - 7.5	3.8 (0.7 – 9.5)	4.1 (1.8 – 11.9)
Lymphocyte ct ($x10^9$/L)	1.0 - 4.0	2.0 (1.0 – 4.5)	1.8 (0.2 – 3.6)
Monocyte ct ($x10^9$/L)	0.0 - 0.8	0.4 (0.1 – 1.1)	0.4 (0 – 1)
Eosinophil ct ($x10^9$/L)	0.0 - 0.5	0.2 (0 – 1.3)	0.2 (0 – 1.3)
Basophil ct ($x10^9$/L)	0.0 - 0.2	0 (0 - .2)	0 (0 – 0.1)
Neutrophil %	48 - 73	59 (29 – 82)	61 (34 – 95)
Lymphocyte %	18 - 48	30.7 (13 – 60)	27 (1.4 – 52)
Monocyte %	0 - 9	7 (1 – 14)	6 (0 – 11)
Eosinophil %	0 - 5	3.35 (0 – 16)	3.1 (0 – 14)
Basophil %	0 - 2	0 (0 – 2)	0 (0 -1)
Hb concentration male female	 130 - 180 g/L 115 - 160 g/L	13.8 (6.5 – 17)	14.15 (9.7 – 16.4)
IgE For individuals > 15 years	0-158 IU/ ml	158 (2 – 2822)	119 (0 – 1325)
Hematocrit male female	 0.38 - 0.52 0.35 - 0.47	0.41 (0.25 – 0.49)	42 (31 – 48)

2. Univariate analysis

	Odds ratio (CI)	Global p value
WBC ct	1.033 (0.885 – 1.205)	0.685
Neutrophil ct	1.156 (0.964 – 1.387)	0.117
Lymphocyte ct	0.635 (0.398 – 1.013)	0.048
Monocyte ct	0.169 (0.026 – 1.111)	0.058
Eosinophil ct	1.444 (0.382 – 5.461)	0.591
Basophil ct	0.002 (0 – 1.481)	0.057
Neutrophil %	1.029 (1.0 – 1.059)	0.047
Lymphocyte %	0.972 (0.941 – 1.004)	0.079
Monocyte %	0.850 (0.734 – 0.984)	0.026
Eosinophil %	1.007 (0.909 – 1.115)	0.899
Basophil %	0.552 (0.301 – 1.014)	0.048
Hb concentration	1.115 (0.911 – 1.364)	0.282
IgE	0.999 (0.998 – 1.000)	0.080
Hematocrit	1.058 (0.979 – 1.143)	0.151

Family history

1. Distribution

	Normal N = 18	**Mild/moderate asthma N= 152**	**Severe asthma N = 63**
Father			
Asthma	1 (5.56)	31 (21.38)	5 (8.20)
Allergies	1 (5.56)	45 (32.37)	17 (28.81)
Eczema	0	14 (9.66)	1 (1.64)
Mother			
Asthma	2 (11.11)	36 (24.83)	11 (18.03)
Allergies	3 (16.67)	61 (42.96)	29 (48.33)
Eczema	1 (5.56)	9 (6.04)	3 (4.92)
Siblings			
Asthma	2 (11.11)	49 (38.89)	21 (37.50)
Allergies	3 (16.67)	61 (50.00)	30 (57.69)
Eczema	2 (11.11)	17 (12.98)	7 (12.50)
Child (ren)			
Asthma	0	22 (2821)	13 (30.95)
Allergies	2 (18.18)	41 (50.62)	24 (54.55)
Eczema	2 (18.18)	8 (9.52)	7 (15.91)
# of siblings			
Median (range)	2 (0 -8)	2 (0 – 7)	2 (1 – 9)
# of children			
Median (range)	0 (0– 2)	0 (0 – 4)	0 (0 – 5)

2. Univariate analysis

	Odds ratio (CI)	Global p-value
Father		
Asthma	0.328 (0.121 – 0.890)	0.016
Allergies	0.845 (0.434 – 1.646)	0.620
Eczema	0.156 (0.020 – 1.213)	0.022
Mother		
Asthma	0.666 (0.313 – 1.415)	0.281
Allergies	1.242 (0.678 – 2.276)	0.483
Eczema	0.805 (0.210 – 3.079)	0.747
Siblings		
Asthma	0.943 (0.493 – 1.804)	0.859
Allergies	1.364 (0.708 – 2.624)	0.352
Eczema	0.958 (0.974 – 2.457)	0.929
Child (ren)		
Asthma	1.141 (0.503 – 2.589)	0.753
Allergies	1.171 (0.561 – 2.444)	0.674
Eczema	1.798 (0.606 – 5.334)	0.295
# of siblings	1.199 (1.019 – 1.408)	0.028
# of children	1.672 (1.295 – 2.159)	< 0.0001

For women only

1. Distribution

	Normal N = 11	**Mild/moderate asthma N = 106**	**Severe asthma N = 39**
Respiratory symptoms during and around monthly menses	0	14 (13.21)	6 (15.79)
Hormone replacement therapy	0	2 (1.83)	8 (20.51)
Surgery uterus	0	10 (9.17)	8 (20.51)
Surgery ovaries	0	8 (7.34)	8 (20.51)

2. Univariate analysis

	Odds ratio (CI)	**Global p-value**
Respiratory symptoms about or during monthly menses	1.232 (0.437 – 3.477)	0.696
Hormone replacement therapy	13.806 (2.787 – 68.399)	0.002
Surgery uterus	2.555 (0.927 – 7.039)	0.076
Surgery ovaries	3.258 (1.130 – 9.398)	0.032

Lung function test (Spirometry)

1. Distribution

	Normal N = 18	**Mild/moderate asthma N = 151**	**Severe asthma N = 63**
FEV_1 baseline median (range)	3.82 (2.77 – 4.9)	2.66 (0.88 – 6.22)	2 (0.68 – 4.51)
Pre-bronchodilator FEV_1 predicted	3.81 (2.56 (4.94)	3.16 (2.15 – 5.33)	3.24 (1.99 – 5.01)
FEV_1 percent predicted	100.5 (83 – 123)	84 (27 – 121)	68 (24 – 110)
FVC baseline	4.46 (3.28 – 6.25)	3.59 (1.58 – 7.93)	3.15 (0.95 – 5.78)
Pre-bronchodilator FVC predicted	4.15 (3.16 – 5.98)	3.79 (2.59 – 6.57)	3.98 (2.62 – 6.31)
Pre-bronchodilator FEF	3.93 (2.59 – 6.07)	2.17 (0.40 – 5.32)	1.13 (0.22 – 4.18)
Pre-bronchodilator FEF predicted	3.82 (2.63 – 5.07)	3.5 (2.11 – 5.27)	3.19 (1.47 – 4.65)
Pre-bronchodilator PEF	8.27 (5.69 – 11.31)	6.75 (1.43 – 14.57)	5.62 (2.04 – 10.68)
Pre-bronchodilator PEF predicted	7.35 (5.44 – 11.05)	7.09 (2.61 – 11.65)	7.41 (5.27 – 11.5)
Post-bronchodilator FEV_1	3.86 (3.01 – 4.94)	2.84 (1.37 – 6.3)	2.27 (0.7 – 4.36)
Post-bronchodilator FEV_1 predicted	104 (86 – 125)	92 (42 – 124)	73 (24 – 119)
Post-bronchodilator FVC	4.51 (3.44 – 6.3)	3.68 (1.67 – 8.11)	3.32 (0.93 – 5.33)
Percent difference FEV_1	3.2 (0 – 54)	7.15 (-1.6 – 68.2)	8.6 (-3.3 – 91.1)
Post-bronchodilator FEF	4.14 (2.59 – 5.95)	2.75 (0.64 – 6.34)	1.39 (0.26 – 5.67)
Post-bronchodilator PEF	8.08 (4.8 – 11.27)	7.28 (3.23 – 14.7)	6.21 (2.36 – 11.22)

2. Univariate analysis

	Odds ratio (CI)	**Global p-value**
FEV_1 baseline	0.359 (0.236 – 0.547)	< 0.0001
FEV_1 percent predicted	0.951 (0.934 – 0.968)	< 0.0001
FVC baseline	0.578 (0.423 – 0.789)	0.0002
Pre-bronchodilator FEF	0.393 (0.269 – 0.574)	< 0.0001
Pre-bronchodilator PEF	0.702 (0.589 – 0.837)	< 0.0001
Post-bronchodilator FEV_1	0.341 (0.221 – 0.525)	< 0.0001
Percent difference FEV_1	1.015 (0.993 – 1.037)	0.185
Post-bronchodilator FVC	0.654 (0.484 – 0.884)	0.004
Post-bronchodilator FEF	0.418 (0.301 – 0.581)	< 0.0001
Post-bronchodilator PEF	0.730 (0.612 – 0.871)	0.0002

Medical care utilization

1. Distribution

	Mild/moderate asthma N = 152	**Severe asthma N = 63**
One or more urgent care visits in the last 12 months	37 (22.16)	37 (44.05)
Frequency of these visits		
No more than 2x per year	23 (62.16)	9 (25.71)
At least 2x per year but no more than 4	10 (27.03)	16 (45.71)
More than 4x but less than 1x per month	4 (10.81)	9 (25.71)
More than 1x per month	0	1 (2.86)
Seen a doctor in the last 12 months due to breathing problems	73 (48.03)	55 (87.30)
ER ever for breathing problems	90 (59.60)	48 (76.19)
ER last 12 months for breathing problems	21 (20.00)	16 (30.19)
Hospitalization ever for breathing problems	45 (30.00)	39 (61.90)
Hospitalization last 12 months for breathing problems	3 (4.29)	9 (19.57)
ICU ever for breathing problems	10 (6.62)	17 (27.42)
ICU for asthma	7 (77.78)	5 (38.46)
Intubation due to asthma attack	3 (75.00)	4 (44.44)

2. Univariate analysis

	Odds ratio (CI)	Global p-value
One or more urgent care visits in the last 12 months	2.766 (1.572 – 4.865)	0.0004
Frequency of these visits		For model: 0.008
No more than 2x per year	Base category	
At least 2x per year but no more than 4	4.089 (1.356 – 12.329)	0.012
More than 4x but less than 1x per month	5.75 (1.407 – 23.492)	0.015
More than 1x per month	n/a	
Seen a doctor in the last 12 months due to breathing problems	7.440 (3.320 – 16.675)	< 0.0001
ER ever for breathing problems	2.169 (1.116 – 4.216)	0.018
ER last 12 months for breathing problems	1.730 (0.812 – 3.686)	0.159
Hospitalization ever for breathing problems	3.792 (2.046 – 7.026)	< 0.0001
Hospitalization last 12 months for breathing problems	5.432 (1.385 – 21.313)	0.008
ICU ever for breathing problems	5.327 (2.276 – 12.464)	0.0001
ICU for asthma	0.178 (0.026 – 1.228)	0.063
Intubation due to asthma attack	0.267 (0.019 – 3.653)	0.298

Medication use (asthma-specific)

1. Distribution

	Mild/moderate asthma N = 167	**Severe asthma N = 83**
Frequency of rescue inhaler use		
Never	42 (27.63)	8 (12.70)
1x per month	59 (38.82)	21 (33.33)
Weekly but < 2x per week	28 (18.42)	16 (25.40)
More than 2x per week	23 (15.13)	18 (28.57)
Use of oral corticsteriods	1 (0.60)	18 (21.43)
Use of inhaled corticosteroids	6 (3.59)	80 (96.39)
Daily use of β-agonist inhaler	52 (31.14)	77 (91.67)
Additional	76 (45.51)	57 (67.86)

2. Results of univariate analysis.

	Odds ratio (CI)	**Global p-value**
Frequency of rescue inhaler use		
Never	------	------
1x per month	1.869 (0.756 – 4.651)	0.176
Weekly but < 2x per week	3.00 (1.132 – 7.946)	0.027
More than 2x per week	4.109 (1.549 – 10.901)	0.005
Use of oral corticsteriods	45.273 (5.924 – 345.95)	< 0.0001
Use of inhaled corticosteroids	715.555 (174.420 – 2935.569)	< 0.0001
Daily use of β-agonist inhaler	4.669 (2.659 – 8.198)	< 0.0001
Use of additional controller medication	13.171 (5.735 – 30.251)	< 0.0001

Pet ownership

1. Distribution

	Normal N = 18	**Mild/moderate asthma N = 152**	**Severe asthma N = 63**
Own cat	9 (50)	38 (25.00)	15 (23.81)
Own dog	2 (11.11)	42 (27.63)	22 (34.92)
Own birds	1 (5.56)	4 (2.63)	2 (3.17)
Own rodents	1 (5.56)	0	1 (1.59)
Own other pets	2 (11.11)	21 (13.82)	5 (7.94)

2. Univariate analysis.

	Odds ratio (CI)	**Global p-value**
Own cat	0.938 (0.472 – 1.862)	0.853
Own dog	1.405 (0.750 – 2.634)	0.291
Own birds	1.213 (0.216 – 6.798)	0.828
Own rodents	----------	----------
Own other pets	0.538 (0.193 – 1.496)	0.212

Provoking factors

1. Distribution

	Mild/moderate asthma N = 152	**Severe asthma N = 63**
Recent exposure causing asthma symptoms to worsen	14 (9.27)	8 (12.70)
Asthma provoked by an animal	100 (66.67)	35 (55.56)
Asthma provoked by a routine physical activity	74 (48.68)	47 (75.81)
Asthma provoked by exercise	117 (77.48)	53 (91.38)
Asthma provoked by aspirin	12 (8.22)	8 (13.79)

2. Univariate analysis

	Odds ratio (CI)	**Global p-value**
Recent exposure causing asthma symptoms to worsen	1.423 (0.565 – 3.583)	0.460
Asthma provoked by an animal	0.625 (0.342 – 1.141)	0.127
Asthma provoked by a routine physical activity	3.303 (1.703 – 6.406)	0.0002
Asthma provoked by exercise	3.080 (1.141 – 8.317)	0.014
Asthma provoked by aspirin	1.787 (0.690 – 4.628)	0.241

Respiratory and non-respiratory co-morbidities

1. Distribution

	Normal N = 18	**Mild/ moderate asthma N = 152**	**Severe asthma N = 63**
Pneumonia	2 (11.11)	53 (35.81)	39 (61.90)
Bronchitis w/ antibiotic treatment	2. (12.50)	59 (39.86)	33 (52.38)
Chronic bronchitis	0	12 (8.05)	6 (9.52)
Sinusitis w/ antibiotic treatment	0	59 (38.82)	40 (63.49)
Sinus surgery	0	17 (11.18)	19 (30.16)
Nasal polyps	0	9 (6.12)	14 (22.22)
Nasal polyp surgery	0	7 (4.64)	14 (22.22)
Gastroesophageal reflux disease (GERD)	0	25 (16.78)	28 (44.44)

2. Univariate analysis.

	Odds Ratio (CI)	**Global p-value**
Pneumonia	2.913 (1.583 – 5.358)	0.0005
Bronchitis w/ antibiotic treatment	1.659 (0.916 – 3.005)	0.094
Chronic bronchitis	1.202 (0.430 – 3.358)	0.728
Sinusitis w/ antibiotic treatment	2.741 (1.493 – 5.034)	0.0009
Sinus surgery	3.429 (1.640 – 7.169)	0.001
Nasal polyps	4.381 (1.784 – 10.760)	0.001
Nasal polyp surgery	5.878 (2.243 – 15.403)	0.0002
Gastroesophageal reflux disease (GERD)	3.968 (2.057 – 7.654)	< 0.0001

Tobacco use and exposure

1. Distribution

	Normal N = 18	**Mild/moderate asthma N = 152**	**Severe asthma N = 63**
Current smoker	1 (5.56)	23 (15.13)	9 (14.29)
Age onset smoking	38 (38 – 38)	16 (10 – 21)	19 (16 – 23)
Exposure to 2nd hand smoke	2 (11.11)	40 (26.32)	15 (23.81)

2. Univariate analysis.

	Odds ratio (CI)	Global p-value
Current smoker	0.935 (0.406 – 2.151)	0.874
Age onset smoking	1.617 (1.058 – 2.473)	0.008
Exposure to 2nd hand smoke	0.875 (0.442 – 1.732)	0.700

APPENDIX B
Supplemental Methods from Chapter 3

Study cohort

In September 2001, the Severe Asthma Research Project (SARP), a collaborative, multi-city study was commenced to obtain a more comprehensive understanding of severe asthma. One objective of the study was to investigate the prevalence of suspect risk factors for disease severity in adult asthmatics. Individuals recruited for the study were between the ages of 19-59 years. Each city worked under a standardized definition of severe asthma (as defined by the SARP steering committee) and uniform inclusion criteria for severe asthma. Patients who reported having been diagnosed with asthma were assessed for asthma severity based on the following criteria:

Major criteria (individual must satisfy at least one of the following):

- Treatment with continuous or near-continuous oral corticosteroids
- Treatment with continuous high-dose inhaled corticosteroids

Minor Criteria: (individual must satisfy at least two of the following)

- Require daily treatment with controller medication in addition to inhaled
- Asthma symptoms require short-acting β-agonist use on a daily or near daily basis
- Persistent airway obstruction, as determined by FEV1 < 80% predicted and diurnal PEF variability > 20%
- One or more urgent care visits for asthma per year
- Three or more oral corticosteroid bursts per year
- Prompt deterioration with reduction in oral or inhaled corticosteroid dose
- Near-fatal asthma event in the past

Asthmatic subjects who did not satisfy the above criteria for severe asthma were classified as not severe. The point-prevalence nature of this study did not accommodate for matching of subjects.

Data

General. All qualified subjects, upon enrollment into the SARP, were asked to sign a consent form which permits the sharing of their data and/or biological samples across the SARP study sites. Original samples and data collected from study subjects remained at the site of collection and were shared with other SARP sites upon approval by the SARP steering committee.

Screening. Prospective study subjects are screened for eligibility based on their smoking history, respiratory disease other than asthma (ie CF and VCD), diagnosis with asthma, length of disease, asthma medication and attack history, and satisfaction of the aforementioned major and minor criteria for severe asthma.

Questionnaire. Upon qualification for study enrollment, patient was asked to complete additional sections of the SARP questionnaire. These sections included:

- Asthma Quality of Life
- Atopy history
- Demographic information
- Environmental factors specific to pet ownership
- Family allergy and asthma history
- General symptoms of respiratory disease
- Medical history, including co-morbidities and health care utilization
- Medication history
- Provoking factor exposure specific to asthma symptoms
- Smoking and ETS exposure history
- Symptoms and exposures exclusive to women (i.e. reproductive, hormones).

Blood work. Blood was drawn from all study subjects either at screening for study eligibility or at a subsequent visit. Each Clinical Center is responsible for drawing blood from SARP subjects

in order to obtain blood counts and differentials, IgE, hematocrit, and hemoglobin. Labels for each subject's blood and serum tubes are uniformly labeled with the study subject's SARP ID# and blood draw date. The labeling is coordinated Dr. Doug Everett, SARP Data Collection Coordinator at the National Jewish Medical Center, Denver, CO. Site laboratories determine the blood counts and differentials, serum IgE, hematocrit, and hemoglobin. The results were entered on the SARP Blood Draw Form.

Allergy skin test. Skin testing will be done all adult SARP study subjects. Study subjects were screened for medication use, including certain over-the-counter medicines, taken within the preceeding 24 hours of testing. Percutaneous (puncture) skin testing was performed on the subject's forearm with at least 2-cm spacing between tests. The Multi-Test II device (Lincoln Diagnostics, Decatur, Illinois) was used to provide allergen to the study subject's forearm The Multi-Test II meets OSHA guidelines for technician protection, and has been reported to provide a lower coefficient of variation than similar devices. The allergens included in the skin test were as follows:

- Dermatophagoides pteronyssinus
- Dermatophagoides farinae
- Cat
- Dog
- American cockroach
- Alternaria
- Cladosporium
- Aspergillus mix
- Timothy grass (or grass mix)
- Short ragweed
- Common weed mix: cocklebur, lambs quarter, pigweed, English plantain, Russian thistle
- Eastern 7-tree mix: white ash, American beech, red birch, American elm, shagbark hickory, red oak, cottonwood

The core extracts were ordered by each Clinical Center from Greer Laboratories, Lenoir, NC. Negative controls consisted of 50% glycerin in 50% saline and positive controls consist of 1 mg/ml histamine base. Significant skin tests are those in which the application of an allergen produces a wheal with the largest diameter of 3 mm or more than the negative control AND a flare with the largest diameter of 10 mm or more. Values were then recorded on the SARP skin testing form.

In the event of a systemic-allergic reaction (anaphylaxis), injectable epinephrine (1:1000) was present for injection.

Lung function test. Spirometry is the timed-based measurement of the amount of air which can be forcefully exhaled from the lungs after a full inspiration. The SARP is concerned primarily with 4 measurements during spirometry:

- Peak flow (PEFR)- the maximum flow that occurs during the procedure
- Forced expiratory volume in 1 second (FEV1)- the volume of air that is blown out during peak flow is the 1st second of the procedure and
- Forced vital capacity (FVC)- the total amount of air that leaves the lung during the proceedure
- FEV1=FVC ratio-an additional useful calculation which is the fraction or percent of the total volume of air expired that can be exhaled in one second.

The SARP uses these measures to determine the severity of asthma in the study subjects. Prior to spirometry, subjects are screened for intake of certain drugs and substances within 48 hours of the lung function test. If asthma medication was withheld during lung function test, a post-bronchodilator test is administered and the 4 aforementioned measurements are re-collected.

Serological analysis for respiratory pathogens. Serum from study subjects was obtained for serological analysis. Of interest was the sero-prevalence of antibodies indicative of respiratory infection cause by *Mycoplasma pneumoniae (Mpn)* and *Chlamydia pneumoniae (Cpn).* An Enzyme-Linked Immunosorbent Assay (ELISA) specific for the detection of Mpn- and Cpn-specific IgM, IgG, and IgA was used (Savyon Diagnostics, Ashdod, Israel). The serological analysis was performed at University of Wisconsin under the direction of William H. Busse, M.D., SARP steering committee chair.

To test for infection with *Mpn,* the unit of measurement was an arbitrary binding unit (BU)/ ml of sample. Determinations of infection were as follows:

- < 10BU/ ml = negative (no indication of *Mpn* infection)
- 10 and $\leq$ 20 BU/ ml = borderline (Indicative of exposure but not of infection. A secondary analysis of an additional second serum sample taken 2-3 weeks later should be conducted; second borderline result should be interpreted as negative)
- 20 BU/ml = positive (indication of infection by *Mpn*)

To test for infection with *Cpn,* the unit of measurement was the absorbance (OD) of the sample. The reference value was the cut-off value (COV) that is calculated as follows:0

COV = NC x 2 (NC = the average absorbance at 450 nm of the Negative Control run in duplicate).

Determinations of infections were as follows:

- O.D. < COV = Negative (no indication of infection by *Cpn*)
- COV $\leq$ O.D. $\leq$ 1.1 x COV = Borderline (indicative of exposure but not of infection. Secondary analysis of an additional serum sample taken 2-3 weeks later should be conducted; second borderline result should be interpreted as negative)
- O.D. > 1.1 x COV = Positive (indication of infection by C*pn*).

Using the aforementioned determinations of infections, serum was analyzed for the prevalence of IgM (current infection), IgG (past infection) and IgA (chronic infection). The presence of IgA antibodies is also an indicator of chronic mucosal stimulation.

Data analysis

Coding and format of variables. The outcome of interest is the phenotype of "severe" asthma. Although the hypothesis of this study tests whether the prevalence of atypical pathogens contributes to asthma severity is adults, data collected from the questionnaires and clinical tests is also tested for their relationship to severe asthma. Most of the data from the questionnaire and all of the data from the skin test are formatted as binary responses (0=no, 1=yes). Data from the serological analysis was sorted into 2 sets: data coded as binary responses (ie – or + for infection) and data coded as categorical responses (ie. current, past or chronic infection). These 2 sets of responses were analyzed separately for their relationship to severe asthma. Data from the blood work and lung function test retained their original continuous format.

The 5 confounding variables to be controlled for. Based on the recent literature regarding risk factors for adult asthma severity, current age and female gender were selected as variables that will be controlled for. Since recent evidence suggests that a person's body mass index (BMI) may contribute to poor health outcomes in those with chronic disease, BMI was also controlled for. Finally, since the influence of age of asthma onset and years with asthma on disease severity is poorly understood, these variables were also selected for controlling.

Logistic regression. The goal of logistic regression is to find the best fitting (yet biologically reasonable) model to describe the relationship between the dichotomous characteristic of interest (dependent variable = response or outcome variable) and a set of independent (predictor or explanatory) variables Logistic regression generates the coefficients (and its standard errors and significance levels) of a formula to predict a *logit transformation* of the probability of presence of the characteristic of interest:

$$\text{logit}(p) = b_0 + b_1 X_1 + b_2 X_2 + b_3 X_3 + \ldots + b_k X_k$$

where p is the probability of presence of the characteristic of interest. The logit transformation is defined as the logged odds:

$$\text{odds} = \frac{p}{1-p} = \frac{\textit{probability of presence of characteristic}}{\textit{probability of absence of characteristic}}$$

and

$$\text{logit}(p) = \ln\left[\frac{p}{1-p}\right]$$

Univariate analysis. The outcome of interest is binary: 0= mild/moderate asthma and 1=severe asthma. Using logistic regression, all variables are assessed individually for their relationship to severe asthma. Those with a p-value $\leq$ 0.20 are extracted and retained for further analysis.

Stepwise "backward" regression analysis and severe asthma model. The goal of logistic regression is to correctly predict the category of outcome (ie asthma severity) for individual cases. Stepwise regression is a form of logistic regression that tests the fit of the model after

individual variables are added or deleted and is used to explore the relationship of predictor variables to the outcome of interest. Backward stepwise regression is the analysis that begins with a full or saturated model and variables are deleted from the model in an iterative process. The fit of the model is tested after the elimination of each variable to ensure that the model still adequately fits the data. When no further variables can be eliminated from the model, the analysis has been completed. However in all cases, the p value criteria for entry into the model must be less than removal. Standard practice in epidemiology and biostatistics is p= 0.15 for entry of a predictor variable into the stepwise elimination model and p= 0.20 for removal.

BIBLIOGRAPHY

Abu-Hasan, M., Tannous, B., & Weinberger, M. (2005). Exercise-induced dyspnea in children and adolescents: If not asthma then what? *Ann Allergy Asthma Immunol, 94*(3), 366-371.

Adamko, D., Lacy, P., & Moqbel, R. (2002). Mechanisms of eosinophil recruitment and activation. *Curr Allergy Asthma Rep, 2*(2), 107-116.

Adams, R. J., Weiss, S. T., & Fuhlbrigge, A. (2003). How and by whom care is delivered influences anti-inflammatory use in asthma: Results of a national population survey. *J Allergy Clin Immunol, 112*(2), 445-450.

Adler, A., Tager, I., & Quintero, D. R. (2005). Decreased prevalence of asthma among farm-reared children compared with those who are rural but not farm-reared. *J Allergy Clin Immunol, 115*(1), 67-73.

Akerman, M. J., Calacanis, C. M., & Madsen, M. K. (2004). Relationship between asthma severity and obesity. *J Asthma, 41*(5), 521-526.

Alford, S. H., Zoratti, E., Peterson, E. L., Maliarik, M., Ownby, D. R., & Johnson, C. C. (2004). Parental history of atopic disease: Disease pattern and risk of pediatric atopy in offspring. *J Allergy Clin Immunol, 114*(5), 1046-1050.

Allacci, M. S. (2005). Identifying environmental risk factors for asthma emergency care" a multilevel approach for ecological study. *J Ambul Care Manage, 28*(1), 2-15.

Apelberg, B. J., Buckley, T. J., & White, R. H. (2005). Socioeconomic and racial disparities in cancer risk from air toxics in maryland. *Environ Health Perspect, 113*(6), 693-699.

Apter, A. J. (2003). Clinical advances in adult asthma. *J Allergy Clin Immunol, 111*(3 Suppl), S780-784.

Apter, A. J., Boston, R. C., George, M., Norfleet, A. L., Tenhave, T., Coyne, J. C., et al. (2003). Modifiable barriers to adherence to inhaled steroids among adults with asthma: It's not just black and white. *J Allergy Clin Immunol, 111*(6), 1219-1226.

Arif, A. A., Delclos, G. L., Lee, E. S., Tortolero, S. R., & Whitehead, L. W. (2003). Prevalence and risk factors of asthma and wheezing among us adults: An analysis of the nhanes iii data. *Eur Respir J, 21*(5), 827-833.

Aron, Y., Busson, M., Polla, B. S., Dusser, D., Lockhart, A., Swierczewski, E., et al. (1999). Analysis of hsp70 gene polymorphism in allergic asthma. *Allergy, 54*(2), 165-170.

Arruda, L. K., Sole, D., Baena-Cagnani, C. E., & Naspitz, C. K. (2005). Risk factors for asthma and atopy. *Curr Opin Allergy Clin Immunol, 5*(2), 153-159.

Arshad, S. H., Kurukulaaratchy, R. J., Fenn, M., & Matthews, S. (2005). Early life risk factors for current wheeze, asthma, and bronchial hyperresponsiveness at 10 years of age. *Chest, 127*(2), 502-508.

Bacharier, L. B., Strunk, R. C., Mauger, D., White, D., Lemanske Jr, R. F., & Sorkness, C. A. (2004). Classifying asthma severity in children-mismatch between symptoms, medication use and lung function. *Am J Respir Crit Care Med*.

Bai, T. R., & Knight, D. A. (2005). Structural changes in the airways in asthma: Observations and consequences. *Clin Sci (Lond), 108*(6), 463-477.

Baker, K. M., Brand, D. A., & Hen, J., Jr. (2003). Classifying asthma: Disagreement among specialists. *Chest, 124*(6), 2156-2163.

Bang, K. M., Hnizdo, E., & Doney, B. (2005). Prevalence of asthma by industry in the us population: A study of 2001 nhis data. *Am J Ind Med, 47*(6), 500-508.

Barr, R. G. (2004). Propective study of postmenopausal hormone use and newly diagnosed asthma and chronic obstructive pulmonary disease. *Archives of Internal Medicine, 164*(February 23,2004), 379-386.

Barr, R. G., & Camargo, C. A., Jr. (2004). Hormone replacement therapy and obstructive airway diseases. *Treat Respir Med, 3*(1), 1-7.

Barr, R. G., Cooper, D. M., Speizer, F. E., Drazen, J. M., & Camargo, C. A., Jr. (2001). Beta(2)-adrenoceptor polymorphism and body mass index are associated with adult-onset asthma in sedentary but not active women. *Chest, 120*(5), 1474-1479.

Basagana, X., Sunyer, J., Kogevinas, M., Zock, J. P., Duran-Tauleria, E., Jarvis, D., et al. (2004). Socioeconomic status and asthma prevalence in young adults: The european community respiratory health survey. *Am J Epidemiol, 160*(2), 178-188.

Basehore, M. J., Howard, T. D., Lange, L. A., Moore, W. C., Hawkins, G. A., Marshik, P. L., et al. (2004). A comprehensive evaluation of il4 variants in ethnically diverse populations: Association of total serum ige levels and asthma in white subjects. *J Allergy Clin Immunol, 114*(1), 80-87.

Bel, E. H. (2004). Clinical phenotypes of asthma. *Curr Opin Pulm Med, 10*(1), 44-50.

Bertorelli, G., Bocchino, V., Zhuo, X., Chetta, A., Del Donno, M., Foresi, A., et al. (1998). Heat shock protein 70 upregulation is related to hla-dr expression in bronchial asthma. Effects of inhaled glucocorticoids. *Clin Exp Allergy, 28*(5), 551-560.

Betsou, F., Sueur, J. M., & Orfila, J. (2003). Anti-chlamydia pneumoniae heat shock protein 10 antibodies in asthmatic adults. *FEMS Immunol Med Microbiol, 35*(2), 107-111.

Blakey, J., Halapi, E., Bjornsdottir, U. S., Wheatley, A., Kristinsson, S., Upmanyu, R., et al. (2005). Contribution of adam33 polymorphisms to the population risk of asthma. *Thorax, 60*(4), 274-276.

Blasi, F., Allegra, L., & Tarsia, P. (1998). Chlamydia pneumoniae and asthma. *Thorax, 53*(12), 1095.

Bloom, J. W., Chacko, J., Lohman, I. C., Halonen, M., Martinez, F. D., & Miesfeld, R. L. (2004). Differential control of eosinophil survival by glucocorticoids. *Apoptosis, 9*(1), 97-104.

Blumenthal, M. N. (2005). The role of genetics in the development of asthma and atopy. *Curr Opin Allergy Clin Immunol, 5*(2), 141-145.

Boffetta, P. (2002). Molecular epidemiology: A tool for understanding mechanisms of disease. *Eur J Surg Suppl*(587), 62-69.

Boudreaux, E. D., Emond, S. D., Clark, S., & Camargo, C. A., Jr. (2003). Acute asthma among adults presenting to the emergency department: The role of race/ethnicity and socioeconomic status

race/ethnicity and asthma among children presenting to the emergency department: Differences in disease severity and management. *Chest, 124*(3), 803-812.

Briggs, D. (2005). The role of gis: Coping with space (and time) in air pollution exposure assessment. *J Toxicol Environ Health A, 68*(13-14), 1243-1261.

Brisbon, N., Plumb, J., Brawer, R., & Paxman, D. (2005). The asthma and obesity epidemics: The role played by the built environment-a public health perspective. *J Allergy Clin Immunol, 115*(5), 1024-1028.

Brogger, J., Bakke, P., Eide, G. E., Johansen, B., Andersen, A., & Gulsvik, A. (2003). Long-term changes in adult asthma prevalence. *Eur Respir J, 21*(3), 468-472.

Brulle, R. J., & Pellow, D. N. (2005). Environmental justice: Human health and environmental inequalities. *Annu Rev Public Health.*

Burchard, E. G., Avila, P. C., Nazario, S., Casal, J., Torres, A., Rodriguez-Santana, J. R., et al. (2004). Lower bronchodilator responsiveness in Puerto Rican than in Mexican subjects with asthma. *Am J Respir Crit Care Med, 169*(3), 386-392.

Busse, W., Banks-Schlegel, S., Noel, P., Ortega, H., Taggart, V., & Elias, J. (2004). Future research directions in asthma: An nhlbi working group report. *Am J Respir Crit Care Med.*

Busse, W., Banks-Schlegel, S. P., & Larsen, G. L. (1995). Childhood- versus adult-onset asthma. *Am J Respir Crit Care Med, 151*(5), 1635-1639.

Busse, W. W., Banks-Schlegel, S., & Wenzel, S. E. (2000). Pathophysiology of severe asthma. *J Allergy Clin Immunol, 106*(6), 1033-1042.

Busse, W. W., Rosenwasser, L. J., Lenfant, C., Lemanske, R. F., Jr., Banks-Schlegel, S., & Wenzel, S. E. (2003). Mechanisms of asthma. *J Allergy Clin Immunol, 111*(3 Suppl), S799-804.

Cantani, A., & Micera, M. (2005). Epidemiology of passive smoke: A prospective study in 589 children. *Eur Rev Med Pharmacol Sci, 9*(1), 23-30.

Castro, M., Zimmermann, N. A., Crocker, S., Bradley, J., Leven, C., & Schechtman, K. B. (2003). Asthma intervention program prevents readmissions in high healthcare users. *Am J Respir Crit Care Med, 168*(9), 1095-1099.

Centers for Disease Control. (2005a). *Asthma: Behavioral risk factor surveillance survey*. Retrieved Aug 19, 2005, from http://www.cdc.gov/asthma/brfss/default.htm

Centers for Disease Control. (2005b). *The Morbidity and Mortality Weekly Report: Know what matters.* Retrieved Sept 4, 2005, from http://www.cdc.gov/mmwr/about.html

Cesaroni, G., Farchi, S., Davoli, M., Forastiere, F., & Perucci, C. A. (2003). Individual and area-based indicators of socioeconomic status and childhood asthma. *Eur Respir J, 22*(4), 619-624.

Chan-Yeung, M., Zhan, L. X., Tu, D. H., Li, B., He, G. X., Kauppinen, R., et al. (2002). The prevalence of asthma and asthma-like symptoms among adults in rural beijing, china. *Eur Respir J, 19*(5), 853-858.

Chaudhuri, R., Livingston, E., McMahon, A. D., Thomson, L., Borland, W., & Thomson, N. C. (2003). Cigarette smoking impairs the therapeutic response to oral corticosteroids in chronic asthma. *Am J Respir Crit Care Med, 168*(11), 1308-1311.

Chauhan, A. J., Inskip, H. M., Linaker, C. H., Smith, S., Schreiber, J., Johnston, S. L., et al. (2003). Personal exposure to nitrogen dioxide (NO_2) and the severity of virus-induced asthma in children. *Lancet, 361*(9373), 1939-1944.

Chen, L. L., Tager, I. B., Peden, D. B., Christian, D. L., Ferrando, R. E., Welch, B. S., et al. (2004a). Effect of ozone exposure on airway responses to inhaled allergen in asthmatic subjects. *Chest, 125*(6), 2328-2335.

Chen, Y., Stewart, P., Dales, R., Johansen, H., Scott, G., & Taylor, G. (2004b). Ecological measures of socioeconomic status and hospital readmissions for asthma among canadian adults. *Respir Med, 98*(5), 446-453.

Chinen, J., & Shearer, W. T. (2003). Basic and clinical immunology. *J Allergy Clin Immunol, 111*(3 Suppl), S813-818.

Cole Johnson, C., Ownby, D. R., Havstad, S. L., & Peterson, E. L. (2004). Family history, dust mite exposure in early childhood, and risk for pediatric atopy and asthma. *J Allergy Clin Immunol, 114*(1), 105-110.

Contoli, M., Caramori, G., Mallia, P., Johnston, S., & Papi, A. (2005). Mechanisms of respiratory virus-induced asthma exacerbations. *Clin Exp Allergy, 35*(2), 137-145.

Cook, D. N., Pisetsky, D. S., & Schwartz, D. A. (2004). Toll-like receptors in the pathogenesis of human disease. *Nat Immunol, 5*(10), 975-979.

Cook, P. J., Davies, P., Tunnicliffe, W., Ayres, J. G., Honeybourne, D., & Wise, R. (1998). Chlamydia pneumoniae and asthma. *Thorax, 53*(4), 254-259.

Corne, J. M., Marshall, C., Smith, S., Schreiber, J., Sanderson, G., Holgate, S. T., et al. (2002). Frequency, severity, and duration of rhinovirus infections in asthmatic and non-asthmatic individuals: A longitudinal cohort study. *Lancet, 359*(9309), 831-834.

Corvalan, C., Amigo, H., Bustos, P., & Rona, R. J. (2005). Socioeconomic risk factors for asthma in chilean young adults. *Am J Public Health, 95*(8), 1375-1381.

Costa, C. P., Kirschning, C. J., Busch, D., Durr, S., Jennen, L., Heinzmann, U., et al. (2002). Role of chlamydial heat shock protein 60 in the stimulation of innate immune cells by chlamydia pneumoniae. *Eur J Immunol, 32*(9), 2460-2470.

Crain, E. F., Walter, M., O'Connor, G. T., Mitchell, H., Gruchalla, R. S., Kattan, M., et al. (2002). Home and allergic characteristics of children with asthma in seven u.S. Urban communities and design of an environmental intervention: The Inner-City Asthma Study. *Environ Health Perspect, 110*(9), 939-945.

Cundall, M., Sun, Y., Miranda, C., Trudeau, J. B., Barnes, S., Wenzel, S. E., et al. (2003). Neutrophil-derived matrix metalloproteinase-9 is increased in severe asthma and poorly inhibited by glucocorticoids mechanisms of severe asthma *J Allergy Clin Immunol, 112*(6), 1064-1071.

Davies, D. E. (2001). The bronchial epithelium: Translating gene and environment interactions in asthma. *Curr Opin Allergy Clin Immunol, 1*(1), 67-71.

de Marco, R., Pattaro, C., Locatelli, F., & Svanes, C. (2004). Influence of early life exposures on incidence and remission of asthma throughout life. *J Allergy Clin Immunol, 113*(5), 845-852.

Delfino, R. J., Gong, H., Jr., Linn, W. S., Pellizzari, E. D., & Hu, Y. (2003). Asthma symptoms in hispanic children and daily ambient exposures to toxic and criteria air pollutants. *Environ Health Perspect, 111*(4), 647-656.

Delfino, R. J., Sioutas, C., & Malik, S. (2005). Potential role of ultrafine particles in associations between airborne particle mass and cardiovascular health. *Environ Health Perspect, 113*(8), 934-946.

Douglass, J. A., & O'Hehir, R. E. (2000). What determines asthma phenotype? Respiratory infections and asthma. *Am J Respir Crit Care Med, 161*(3 Pt 2), S211-214.

Eder, W., & von Mutius, E. (2004). Hygiene hypothesis and endotoxin: What is the evidence? *Curr Opin Allergy Clin Immunol, 4*(2), 113-117.

Ellman, M. S., Viscoli, C. M., Sears, M. R., Taylor, D. R., Beckett, W. S., & Horwitz, R. I. (1997). A new index of prognostic severity for chronic asthma. *Chest, 112*(3), 582-590.

Emre, U., Sokolovskaya, N., Roblin, P. M., Schachter, J., & Hammerschlag, M. R. (1995). Detection of anti-chlamydia pneumoniae ige in children with reactive airway disease. *J Infect Dis, 172*(1), 265-267.

ENFUMOSA. (2003). The enfumosa cross-sectional european multicentre study of the clinical phenotype of chronic severe asthma. European network for understanding mechanisms of severe asthma. *Eur Respir J, 22*(3), 470-477.

Farhat, S. C., Paulo, R. L., Shimoda, T. M., Conceicao, G. M., Lin, C. A., Braga, A. L., et al. (2005). Effect of air pollution on pediatric respiratory emergency room visits and hospital admissions. *Braz J Med Biol Res, 38*(2), 227-235.

Federico, M. J., Covar, R. A., Brown, E. E., Leung, D. Y., & Spahn, J. D. (2005). Racial differences in t-lymphocyte response to glucocorticoids. *Chest, 127*(2), 571-578.

Ford, E. S. (2005). The epidemiology of obesity and asthma. *J Allergy Clin Immunol, 115*(5), 897-909.

Ford, E. S., & Mannino, D. M. (2005). Time trends in obesity among adults with asthma in the united states: Findings from three national surveys. *J Asthma, 42*(2), 91-95.

Ford, E. S., Mannino, D. M., Homa, D. M., Gwynn, C., Redd, S. C., Moriarty, D. G., et al. (2003). Self-reported asthma and health-related quality of life: Findings from the behavioral risk factor surveillance system. *Chest, 123*(1), 119-127.

Ford, E. S., Williams, S. G., Mannino, D. M., & Redd, S. C. (2004). Influenza vaccination coverage among adults with asthma: Findings from the 2000 behavioral risk factor surveillance system. *Am J Med, 116*(8), 555-558.

Ford, J. G., Iqbal, J., & Sunmonu, Y. (2002). Beta2-agonists: Friend or foe? *Semin Respir Crit Care Med, 23*(4), 369-376.

Friese and Long. (2003). *Regression models for categorical dependent variables using stata, revised edition*: STATA Press.

Fuhlbrigge, A., Jackson, B., & Wright, R. (2002). Gender and asthma. *Immunology and Allergy Clinics of North America, 22*(4).

Galan, I., Tobias, A., Banegas, J. R., & Aranguez, E. (2003). Short-term effects of air pollution on daily asthma emergency room admissions. *Eur Respir J, 22*(5), 802-808.

Gee, G. C., & Payne-Sturges, D. C. (2004). Environmental health disparities: A framework integrating psychosocial and environmental concepts. *Environ Health Perspect, 112*(17), 1645-1653.

Gencay, M., Rudiger, J. J., Tamm, M., Soler, M., Perruchoud, A. P., & Roth, M. (2001). Increased frequency of chlamydia pneumoniae antibodies in patients with asthma. *Am J Respir Crit Care Med, 163*(5), 1097-1100.

Gern, J. E., & Lemanske, R. F., Jr. (2003). Infectious triggers of pediatric asthma. *Pediatr Clin North Am, 50*(3), 555-575, vi.

Gern, J. E., Rosenthal, L. A., Sorkness, R. L., & Lemanske, R. F., Jr. (2005). Effects of viral respiratory infections on lung development and childhood asthma. *J Allergy Clin Immunol, 115*(4), 668-674; quiz 675.

Gilliland, F. D., Berhane, K., Islam, T., McConnell, R., Gauderman, W. J., Gilliland, S. S., et al. (2003). Obesity and the risk of newly diagnosed asthma in school-age children. *Am J Epidemiol, 158*(5), 406-415.

Godard, P., Chanez, P., Siraudin, L., Nicoloyannis, N., & Duru, G. (2002). Costs of asthma are correlated with severity: A 1-yr prospective study. *Eur Respir J, 19*(1), 61-67.

Gold, D. R., & Wright, R. (2005). Population disparities in asthma. *Annu Rev Public Health, 26*, 89-113.

Guerra, S., Sherrill, D. L., Martinez, F. D., & Barbee, R. A. (2002). Rhinitis as an independent risk factor for adult-onset asthma. *J Allergy Clin Immunol, 109*(3), 419-425.

Gunnbjornsdottir, M. I., Omenaas, E., Gislason, T., Norrman, E., Olin, A. C., Jogi, R., et al. (2004). Obesity and nocturnal gastro-oesophageal reflux are related to onset of asthma and respiratory symptoms. *Eur Respir J, 24*(1), 116-121.

Hammerschlag, M. R. (2000). Chlamydia pneumoniae and the lung. *Eur Respir J, 16*(5), 1001-1007.

Hammerschlag, M. R. (2001). Mycoplasma pneumoniae infections. *Curr Opin Infect Dis, 14*(2), 181-186.

Hammerschlag, M. R. (2003). Pneumonia due to chlamydia pneumoniae in children: Epidemiology, diagnosis, and treatment. *Pediatr Pulmonol, 36*(5), 384-390.

Hawkins, G. A., Amelung, P. J., Smith, R. S., Jongepier, H., Howard, T. D., Koppelman, G. H., et al. (2004). Identification of polymorphisms in the human glucocorticoid receptor gene (nr3c1) in a multi-racial asthma case and control screening panel. *DNA Seq, 15*(3), 167-173.

Holgate, S. (2001). Mechanisms of allergy and adult asthma. *Curr Opin Allergy Clin Immunol, 1*(1), 47-50.

Holgate, S. T. (1999). Genetic and environmental interaction in allergy and asthma. *J Allergy Clin Immunol, 104*(6), 1139-1146.

Holgate, S. T., Holloway, J., Wilson, S., Bucchieri, F., Puddicombe, S., & Davies, D. E. (2004). Epithelial-mesenchymal communication in the pathogenesis of chronic asthma. *Proc Am Thorac Soc, 1*(2), 93-98.

Hoppin, J. A., Umbach, D. M., London, S. J., Alavanja, M. C., & Sandler, D. P. (2004). Diesel exhaust, solvents, and other occupational exposures as risk factors for wheeze among farmers. *Am J Respir Crit Care Med*.

Hosmer Jr. and Lemeshow. (2000). *Applied logistic regression* (2nd ed.): Wiley.

Huittinen, T., Hahn, D., Anttila, T., Wahlstrom, E., Saikku, P., & Leinonen, M. (2001). Host immune response to *Chlamydia Pneumoniae* heat shock protein 60 is associated with asthma. *Eur Respir J, 17*(6), 1078-1082.

Ilowite, J., Webb, R., Friedman, B., Kerwin, E., Bird, S. R., Hustad, C. M., et al. (2004). Addition of montelukast or salmeterol to fluticasone for protection against asthma attacks: A randomized, double-blind, multicenter study. *Ann Allergy Asthma Immunol, 92*(6), 641-648.

Jaakkola, J. J., Hwang, B. F., & Jaakkola, N. (2005). Home dampness and molds, parental atopy, and asthma in childhood: A six-year population-based cohort study. *Environ Health Perspect, 113*(3), 357-361.

Jatakanon, A., Uasuf, C., Maziak, W., Lim, S., Chung, K. F., & Barnes, P. J. (1999). Neutrophilic inflammation in severe persistent asthma. *Am J Respir Crit Care Med, 160*(5 Pt 1), 1532-1539.

Jenkins, H. A., Cherniack, R., Szefler, S. J., Covar, R., Gelfand, E. W., & Spahn, J. D. (2003). A comparison of the clinical characteristics of children and adults with severe asthma. *Chest, 124*(4), 1318-1324.

Johnston, S. L., & Martin, R. J. (2005). *Chlamydophila pneumoniae and mycoplasma pneumoniae:* A role in asthma pathogenesis? *Am J Respir Crit Care Med*.

Jongepier, H., Boezen, H. M., Dijkstra, A., Howard, T. D., Vonk, J. M., Koppelman, G. H., et al. (2004). Polymorphisms of the ADAM 33 gene are associated with accelerated lung function decline in asthma. *Clin Exp Allergy, 34*(5), 757-760.

Kabesch, M., Hoefler, C., Carr, D., Leupold, W., Weiland, S. K., & von Mutius, E. (2004). Glutathione s transferase deficiency and passive smoking increase childhood asthma. *Thorax, 59*(7), 569-573.

Kappos, A. D., Bruckmann, P., Eikmann, T., Englert, N., Heinrich, U., Hoppe, P., et al. (2004). Health effects of particles in ambient air. *Int J Hyg Environ Health, 207*(4), 399-407.

Kedda, M. A., Shi, J., Duffy, D., Phelps, S., Yang, I., O'Hara, K., et al. (2004). Characterization of two polymorphisms in the leukotriene c4 synthase gene in an australian population of subjects with mild, moderate, and severe asthma. *J Allergy Clin Immunol, 113*(5), 889-895.

Kelley, C. F., Mannino, D. M., Homa, D. M., Savage-Brown, A., & Holguin, F. (2005). Asthma phenotypes, risk factors, and measures of severity in a national sample of us children. *Pediatrics, 115*(3), 726-731.

Kim, J. J., Smorodinsky, S., Lipsett, M., Singer, B. C., Hodgson, A. T., & Ostro, B. (2004a). Traffic-related air pollution near busy roads: The east bay children's respiratory health study. *Am J Respir Crit Care Med*.

Kim, J. J., Smorodinsky, S., Lipsett, M., Singer, B. C., Hodgson, A. T., & Ostro, B. (2004b). Traffic-related air pollution near busy roads: The East Bay children's respiratory health study. *Am J Respir Crit Care Med, 170*(5), 520-526.

King, M. E., Mannino, D. M., & Holguin, F. (2004). Risk factors for asthma incidence. A review of recent prospective evidence. *Panminerva Med, 46*(2), 97-110.

Kinnunen, A., Paavonen, J., & Surcel, H. M. (2001). Heat shock protein 60 specific T-cell response in chlamydial infections. *Scand J Immunol, 54*(1-2), 76-81.

Kraft, M. (2000). The role of bacterial infections in asthma. *Clin Chest Med, 21*(2), 301-313.

Kraft, M., Hamid, Q., Chrousos, G. P., Martin, R. J., & Leung, D. Y. (2001). Decreased steroid responsiveness at night in nocturnal asthma. Is the macrophage responsible? *Am J Respir Crit Care Med, 163*(5), 1219-1225.

Kunzli, N. (2005). Unifying susceptibility, exposure, and time: Discussion of unifying analytic approaches and future directions. *J Toxicol Environ Health A, 68*(13-14), 1263-1271.

Kunzli, N., McConnell, R., Bates, D., Bastain, T., Hricko, A., Lurmann, F., et al. (2003). Breathless in Los Angeles: The exhausting search for clean air. *Am J Public Health, 93*(9), 1494-1499.

Kupczyk, M., Kuprys, I., Gorski, P., & Kuna, P. (2004). Aspirin intolerance and allergy to house dust mites: Important factors associated with development of severe asthma. *Ann Allergy Asthma Immunol, 92*(4), 453-458.

Lawson, J. A., & Senthilselvan, A. (2005). Asthma epidemiology: Has the crisis passed? *Curr Opin Pulm Med, 11*(1), 79-84.

Lazarus, R., Raby, B. A., Lange, C., Silverman, E. K., Kwiatkowski, D. J., Vercelli, D., et al. (2004). Toll-like receptor 10 (tlr10) genetic variation is associated with asthma in two independent samples. *Am J Respir Crit Care Med*.

Lemanske, R. F., Jr. (2000). Inflammatory events in asthma: An expanding equation. *J Allergy Clin Immunol, 105*(6 Pt 2), S633-636.

Lemanske, R. F., Jr. (2003). Is asthma an infectious disease? Thomas a. Neff lecture. *Chest, 123*(3 Suppl), 385S-390S.

Lemanske, R. F., Jr., & Busse, W. W. (2003). 6. Asthma. *J Allergy Clin Immunol, 111*(2 Suppl), S502-519.

Leung, T. F., Tang, N. L., Wong, G. W., & Fok, T. F. (2005). Cd14 and toll-like receptors: Potential contribution of genetic factors and mechanisms to inflammation and allergy. *Curr Drug Targets Inflamm Allergy, 4*(2), 169-175.

Lieberman, D., Printz, S., Ben-Yaakov, M., Lazarovich, Z., Ohana, B., Friedman, M. G., et al. (2003). Atypical pathogen infection in adults with acute exacerbation of bronchial asthma. *Am J Respir Crit Care Med, 167*(3), 406-410.

Liou, A., Grubb, J. R., Schechtman, K. B., & Hamilos, D. L. (2003). Causative and contributive factors to asthma severity and patterns of medication use in patients seeking specialized asthma care. *Chest, 124*(5), 1781-1788.

Little, S. A., MacLeod, K. J., Chalmers, G. W., Love, J. G., McSharry, C., & Thomson, N. C. (2002). Association of forced expiratory volume with disease duration and sputum neutrophils in chronic asthma. *Am J Med, 112*(6), 446-452.

Liu, L., Jarjour, N. N., Busse, W. W., & Kelly, E. A. (2004). Enhanced generation of helper t type 1 and 2 chemokines in allergen-induced asthma. *Am J Respir Crit Care Med, 169*(10), 1118-1124.

Lwebuga-Mukasa, J. S., Oyana, T. J., & Johnson, C. (2005). Local ecological factors, ultrafine particulate concentrations, and asthma prevalence rates in buffalo, new york, neighborhoods. *J Asthma, 42*(5), 337-348.

Mannino, D. M., Homa, D. M., Akinbami, L. J., Moorman, J. E., Gwynn, C., & Redd, S. C. (2002). Surveillance for asthma--united states, 1980-1999. *MMWR Surveill Summ, 51*(1), 1-13.

Martin, R. J., Kraft, M., Chu, H. W., Berns, E. A., & Cassell, G. H. (2001). A link between chronic asthma and chronic infection. *J Allergy Clin Immunol, 107*(4), 595-601.

Matsumoto, H., Niimi, A., Takemura, M., Ueda, T., Minakuchi, M., Tabuena, R., et al. (2005). Relationship of airway wall thickening to an imbalance between matrix metalloproteinase-9 and its inhibitor in asthma. *Thorax, 60*(4), 277-281.

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

Merchant, J. A., Naleway, A. L., Svendsen, E. R., Kelly, K. M., Burmeister, L. F., Stromquist, A. M., et al. (2005). Asthma and farm exposures in a cohort of rural iowa children. *Environ Health Perspect, 113*(3), 350-356.

Miranda, C., Busacker, A., Balzar, S., Trudeau, J., & Wenzel, S. E. (2004). Distinguishing severe asthma phenotypes: Role of age at onset and eosinophilic inflammation. *J Allergy Clin Immunol, 113*(1), 101-108.

Morwood, K., Gillis, D., Smith, W., & Kette, F. (2005). Aspirin-sensitive asthma. *Intern Med J, 35*(4), 240-246.

Mosmann, T. R., Cherwinski, H., Bond, M. W., Giedlin, M. A., & Coffman, R. L. (1986). Two types of murine helper t cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins. *J Immunol, 136*(7), 2348-2357.

Mudway, I. S., & Kelly, F. J. (2004). An investigation of inhaled ozone dose and the magnitude of airway inflammation in healthy adults. *Am J Respir Crit Care Med, 169*(10), 1089-1095.

Nagy, A., Kozma, G. T., Keszei, M., Treszl, A., Falus, A., & Szalai, C. (2003). The development of asthma in children infected with chlamydia pneumoniae is dependent on the modifying effect of mannose-binding lectin. *J Allergy Clin Immunol, 112*(4), 729-734.

National Center for Environmental Health, C. D. C. (2003). *Asthma.* Retrieved 7 Sept 2004, from http://www.cdc.gov/nceh/airpollution/asthmaataglance/asthmaAAG.pdf

National Center for Environmental Health, C. f. D. C. (2005). *Environmental Public Health Indicators Project.* Retrieved July 10, 2005, from http://www.cdc.gov/nceh/indicators/default.htm

National Center for Health Statistics, C. f. D. C. (2005). *Asthma prevalence, health care use, and mortality, 2002*. Retrieved June 14, 2005, from http://www.cdc.gov/nchs/products/pubs/pubd/hestats/asthma/asthma.htm

National Center for Health Statsitics, C. f. D. C. (2005). *National hospital discharge and ambulatory surgery data*. Retrieved May 10, 2005, from http://www.cdc.gov/nchs/about/major/hdasd/nhdsdes.htm

National Institutes of Health Asthma Education and Prevention Program. (2002). *Expert panel report 2: Guidelines for the diagnosis and management of asthma.* Retrieved 10 Sept 2004, from http://www.nhlbi.nih.gov/guidelines/asthma/

Neidell, M. J. (2004). Air pollution, health, and socio-economic status: The effect of outdoor air quality on childhood asthma. *J Health Econ, 23*(6), 1209-1236.

Ngoc, P. L., Gold, D. R., Tzianabos, A. O., Weiss, S. T., & Celedon, J. C. (2005). Cytokines, allergy, and asthma. *Curr Opin Allergy Clin Immunol, 5*(2), 161-166.

Nieves, A., Magnan, A., Boniface, S., Proudhon, H., Lanteaume, A., Romanet, S., et al. (2005). Phenotypes of asthma revisited upon the presence of atopy. *Respir Med, 99*(3), 347-354.

Nuckols, J. R., Ward, M. H., & Jarup, L. (2004). Using geographic information systems for exposure assessment in environmental epidemiology studies. *Environ Health Perspect, 112*(9), 1007-1015.

Olden, K., & White, S. L. (2005). Health-related disparities: Influence of environmental factors. *Med Clin North Am, 89*(4), 721-738.

Peled, R., Friger, M., Bolotin, A., Bibi, H., Epstein, L., Pilpel, D., et al. (2005). Fine particles and meteorological conditions are associated with lung function in children with asthma living near two power plants. *Public Health, 119*(5), 418-425.

Pennsylvania Health Care Cost Containment Council. (2005). *About Us.* Retrieved July 15, 2005, from http://www.phc4.org/

Peters, S. P. (2004). Asthma treatment in the 21st century: What's next? *Clin Rev Allergy Immunol, 27*(3), 197-205.

Romanet-Manent, S., Charpin, D., Magnan, A., Lanteaume, A., & Vervloet, D. (2002). Allergic vs nonallergic asthma: What makes the difference? *Allergy, 57*(7), 607-613.

Romieu, I., Sienra-Monge, J. J., Ramirez-Aguilar, M., Moreno-Macias, H., Reyes-Ruiz, N. I., Estela del Rio-Navarro, B., et al. (2004). Genetic polymorphism of gstm1 and antioxidant supplementation influence lung function in relation to ozone exposure in asthmatic children in mexico city. *Thorax, 59*(1), 8-10.

Rona, R. J., Smeeton, N. C., Bustos, P., Amigo, H., Diaz, P. V., Corvalan, C., et al. (2005). The early origins hypothesis with an emphasis on growth rate in the first year of life and asthma: A prospective study in Chili, socioeconomic risk factors for asthma in chilean young adults. *Thorax, 60*(7), 549-554.

Rosner, B. (2005). *Fundamentals of biostatistics* (6th ed.): Brooks/ Cole.

Ruidavets, J. B., Cassadou, S., Cournot, M., Bataille, V., Meybeck, M., & Ferrieres, J. (2005). Increased resting heart rate with pollutants in a population based study. *J Epidemiol Community Health, 59*(8), 685-693.

Schatz, M., & Camargo, C. A., Jr. (2003). The relationship of sex to asthma prevalence, health care utilization, and medications in a large managed care organization. *Ann Allergy Asthma Immunol, 91*(6), 553-558.

Stemmler, S., Arinir, U., Klein, W., Rohde, G., Hoffjan, S., Wirkus, N., et al. (2005). Association of interleukin-8 receptor alpha polymorphisms with chronic obstructive pulmonary disease and asthma. *Genes Immun, 6*(3), 225-230.

Storms, W. W. (2003). Review of exercise-induced asthma. *Med Sci Sports Exerc, 35*(9), 1464-1470.

Szczeklik, W., Sanak, M., & Szczeklik, A. (2004). Functional effects and gender association of cox-2 gene polymorphism g-765c in bronchial asthma. *J Allergy Clin Immunol, 114*(2), 248-253.

ten Brinke, A., van Dissel, J. T., Sterk, P. J., Zwinderman, A. H., Rabe, K. F., & Bel, E. H. (2001). Persistent airflow limitation in adult-onset nonatopic asthma is associated with serologic evidence of chlamydia pneumoniae infection. *J Allergy Clin Immunol, 107*(3), 449-454.

Thomsen, S. F., Ulrik, C. S., Kyvik, K. O., Larsen, K., Skadhauge, L. R., Steffensen, I., et al. (2005). The incidence of asthma in young adults. *Chest, 127*(6), 1928-1934.

Thurston, G. D., & Bates, D. V. (2003). Air pollution as an underappreciated cause of asthma symptoms. *JAMA, 290*(14), 1915-1917.

U.S. Department of Commerce. (2002). *US Census 2000.* Retrieved Nov 10, 2004, from http://www.census.gov/

U.S. Department of Health and Human Services. (2000). *Healthy People 2010: Respiratory diseases (goal 24). Conference edition, Vol II.* Retrieved 10 Sept 2004, from http://www.healthypeople.gov/Document/pdf/Volume2/24Respiratory.pdf

U.S. Environmental Protection Agency. (2005a). *Air and radiation: Basic information.* Retrieved May 5, 2005, from http://www.epa.gov/air/basic.html

U.S. Environmental Protection Agency. (2005b). Toxic release inventory program. Retrieved May 10, 2005, from http://www.epa.gov/tri/

U.S. Environemntal Protection Agency (2005). *What are the six common air pollutants.* Retrieved June 26, 2005, from http://www.epa.gov/ebtpages/pollairpocriteriaairpollutants.html

Umetsu, D. T., Akbari, O., & Dekruyff, R. H. (2003). Regulatory t cells control the development of allergic disease and asthma. *J Allergy Clin Immunol, 112*(3), 480-487; quiz 488.

Varraso, R., Siroux, V., Maccario, J., Pin, I., & Kauffmann, F. (2005). Asthma severity is associated with body mass index and early menarche in women. *Am J Respir Crit Care Med, 171*(4), 334-339.

Villeneuve, P. J., Leech, J., & Bourque, D. (2005). Frequency of emergency room visits for childhood asthma in ottawa, canada: The role of weather. *Int J Biometeorol*.

Vine, M. F., Degnan, D., & Hanchette, C. (1997). Geographic information systems: Their use in environmental epidemiologic research. *Environ Health Perspect, 105*(6), 598-605.

Weiss, K. B., & Sullivan, S. D. (2001). The health economics of asthma and rhinitis. I. Assessing the economic impact. *J Allergy Clin Immunol, 107*(1), 3-8.

Wenzel, S. (2003). Mechanisms of severe asthma pathology of difficult asthma. *Clin Exp Allergy, 33*(12), 1622-1628.

Wenzel, S., Balzar, S., Chu, H. W., Silkoff, P., Cundall, M., Trudeau, J. B., et al. (2005). Severe asthma in adults *Am J Respir Crit Care Med, 172*(2), 149-160.

Wenzel, S. E., Szefler, S. J., Leung, D. Y., Sloan, S. I., Rex, M. D., & Martin, R. J. (1997). Bronchoscopic evaluation of severe asthma. Persistent inflammation associated with high dose glucocorticoids. *Am J Respir Crit Care Med, 156*(3 Pt 1), 737-743.

White, M. C., Berger-Frank, S. A., Middleton, D. C., & Falk, H. (2002). Addressing community concerns about asthma and air toxics. *Environ Health Perspect, 110 Suppl 4*, 561-564.

Wilson, A. M., Wake, C. P., Kelly, T., & Salloway, J. C. (2005). Air pollution, weather, and respiratory emergency room visits in two northern new england cities: An ecological time-series study. *Environ Res, 97*(3), 312-321.