RACIAL DISPARITIES IN ASTHMA SEVERITY: A COMPARISON BETWEEN BLACK AND WHITE ADULT ASTHMATICS IN THE SEVERE ASTHMA RESEARCH PROGRAM

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Asthma is a complex respiratory disease that has been increasing in prevalence in the United States since 1980 despite advances in treatment. Approximately 32.6 million Americans have had asthma at one point in their lives; while 22.2 million Americans are currently diagnosed with asthma. Severe asthma occurs in approximately 10% of those asthmatics. A distinct racial disparity exists within the severe asthma population, with Blacks having a greater likelihood of having poorly controlled disease compared to their White counterparts. The factors that contribute to this disparity are not truly known; however, it has been suggested that genetics, the environment, and socioeconomics play a role in the disparity.

This dissertation focused on the role that biologic, genetic, and socioeconomic factors play in the development of severe asthma using data from the Severe Asthma Research Program (SARP). The overall hypothesis was that Blacks are predisposed to an allergic, early onset asthma phenotype, which fundamentally differs from the asthma observed in Whites on the basis of biologic/genetic differences in disease process. The overall aim of this study is to assess the extent to which the racial disparity in asthma is attributable to the differences in the pathobiology of asthma. The first paper sought to assess the extent to which racial disparities between Black and White adult asthmatics with severe asthma are attributable to physiologic, immunoinflammatory, and sociodemographic variables. The second paper, utilizing the results

from paper 1, examined the factors that drive the increased production of immunoglobulin E (IgE) in Blacks, as well as the primary factors that contribute to severe asthma in Blacks with high IgE. The third paper presents some of the policy issues that affect the racial disparity seen in severe asthma and five recommendations that will aid in the reduction of the widening gap between Black and White asthmatics. IgE, along with family history of asthma, were shown to be a strong predictors of severe asthma in Blacks, while comorbidities were predictors for Whites. The public health significance of this study is that different interventions can now be created to effectively treat asthma in Blacks versus Whites.

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1.0 DISSERTATION OVERVIEW AND OBJECTIVES

Asthma is a complex respiratory disease that has been increasing in prevalence in the United States since 1980 despite advances in treatment. It is estimated that 32.6 million people (1 in 10 Americans) in the United States has had asthma at one point in their lives; while 22.2 million people (1 in 14 Americans) are currently diagnosed with asthma[1]. Among the over 20 million people with asthma, over 12 million have had an asthma attack within the past 12 months. Asthma is associated with high morbidity and mortality. In the United States, about 30,000 people a day have an asthma attack, while 5,000 people have an emergency department visit and 1,000 people are admitted to the hospital due to their asthma. Almost 11 Americans die each day due to their asthma, while 4,000 die annually from complications related to asthma. Due to these statistics, asthma has become an increasing burden on the individual diagnosed with asthma and the American health care system, costing $19.7 billion annually[1].

Asthma has become a topic of interest and research due to the complexity of the disease and the need to understand the impact that the disease has on patients. Currently, there is no standard or universal definition for asthma that is pathophysiologically and clinically applicable[2]. Asthma is typically identified in a person complaining of difficulty in breathing, paroxysmal cough and wheezing, and chest tightness which is due to the intermittent narrowing or blockage of the airways. There is no cure for asthma but some individuals do not experience any symptoms until there is an asthma episode. These episodes are often characterized by the

swelling of the lining of the airways with the muscles tightening around these airways[1]. Over a period time, repeated episodes may lead to chronic, irreversible airway changes. In more severe asthma attacks, the cells of the ciliated lining become so damaged that they contribute to the obstruction of the airways through the production of mucus[1]. In 1962, the American Thoracic Society (ATS) first defined asthma as "a disease characterized by increased responsiveness of the trachea and bronchi to various stimuli and manifested by the narrowing of the airways that changes in severity either spontaneously or as a result of therapy" [2]. Due to recent research proving that asthma also involves inflammation and hyper-responsiveness of the airways to the lungs, the definition of asthma has evolved. The National Institutes of Health and National Heart Lung and Blood Institute defined asthma as a disease which increased airway hyper-responsiveness and inflammation that often leads to coughing, wheezing, shortness of breath, and tightness in the chest with obstruction to the airways[2]. Along with there being no cure for asthma, there is also no concrete evidence to what causes asthma. Past research has suggested many risk factors or triggers for the development of asthma such as indoor and outdoor allergens (i.e., tobacco smoke or pollen), family history of asthma, obesity, and viral infections[1].

More women than men are affected by asthma, and minorities, mainly Blacks, have a higher prevalence of asthma compared to Whites. Blacks are disproportionately affected by asthma and have the higher asthma morbidity and mortality rates. The prevalence of asthma for Black children in 2004 was reported to be 12.5% compared to 7.5% in White children[2]. Children are twice as likely and are more vulnerable to developing asthma than adults. There are over 5 million children in the United States affected by asthma which results in an increase in the number of days of school missed (absenteeism)[1]. It has been shown in past studies that socioeconomic status is associated with the risk of developing asthma. People living in poor or

urban neighborhoods tend to be exposed to the allergens that affect asthma sufferers such as cockroach dust, mold, and dust mites[1]. Black children from poor urban neighborhoods have some of the highest risk for developing asthma[2].

As the prevalence of asthma increases, the costs associated with asthma increase. Annually, direct costs of health care for asthma are $10 billion, while indirect costs are $8 billion[1]. Direct costs include hospitalizations, emergency room visits, and doctor's office visits. Indirect costs include lost wages and transportation costs.

This dissertation aims to identify factors associated with asthma severity in two different racial groups, Blacks and Whites. A cross-sectional analysis in a sample of Blacks and Whites will examine risk factors for severe asthma in each group to see if they differ. Another study will examine the predictors of high IgE and asthma severity in Blacks. The last study focuses on the policy issues that affect the racial disparity seen in severe asthma and recommendations on overcoming those issues. The overall aim of this study is to assess the extent to which the racial disparity in asthma is attributable to differences in the pathophysiology of asthma. ***We, therefore, hypothesize that African Americans are predisposed to an allergic, early onset asthma phenotype, which fundamentally differs from the asthma observed in Caucasians on the basis of biologic/genetic differences in the disease process***.

2.0 INTRODUCTION

2.1 EPIDEMIOLOGY OF SEVERE ASTHMA

2.1.1 Severe Asthma Phenotype

Although there are treatments that can control asthma, there are still a small number of asthmatics (about 10%) that are not able to control their asthma despite the use of the highest treatment level (i.e., high dose of inhaled corticosteroids (ICS)) [3-5]. They define the severe asthma phenotype. There are several names for this type of asthma: chronic severe asthma (CSA), severe asthma, and refractory asthma. Individuals with severe asthma are characterized by their inability to have their asthma controlled with current available medications; however, severe asthma should not be mistaken as "poorly controlled" asthma. They have persistent daily symptoms, daily bronchodilator use, asthma-related nocturnal symptoms at least once a week, and a force expiratory volume in 1 second of less than 75% predicted for their age, height, sex, and race[4]. Asthma phenotypes help distinguish subgroups of asthma. Phenotype is defined as "the visible characteristics of an organism resulting from the interaction between its genetic makeup and the environment"[6]. Dr. Sally Wenzel states that there are three categories for asthma phenotypes: clinical or physiological phenotypes; phenotypes related to triggers such as aspirin, environmental allergens, menses, exercise, and occupational allergens; and inflammatory

phenotypes[6]. The severity-defined phenotype is classified under the clinical phenotypes. Having lower lung function, a history of pneumonia, less atopy, and being Black has been shown to be associated with having more severe and frequent exacerbations, hence suggesting their contribution to the development of severe asthma[6, 7]. Asthma severity can be measured according to the potential for frequent exacerbations and the degree of airway obstruction (disease severity) measured as baseline forced expiratory volume in one second (FEV_1)[8]. Currently, there is no way to determine if a patient with asthma is at risk of developing severe asthma. A reduction in FEV_1 does not necessarily explain everything about disease progression; therefore, additional risk factors may contribute to the risk of developing severe asthma[9].

In 2004, a study at National Jewish Medical Center with 80 individuals with severe asthma detailed the differences between early and late onset severe asthma. There were several differences between the two groups. In the early onset group, there was more of a genetic influence and response to allergens. On the contrary, in the late onset group, it tended to vary among individuals with results showing both allergic and non-allergic responses. Almost all of the individuals with early onset severe asthma (98%) had positive skin allergen tests, whereas, only 76% of the late onset group had positive skin tests. Pulmonary function (FEV_1 and FVC) was noticeably worse for those with late onset severe asthma compared to the early onset group. Late onset severe asthmatics were also shown to have higher numbers of eosinophils, whereas, the early onset severe asthmatics had higher numbers of tissue lymphocytes[9]. Table 1 below displays the differences between the early onset and late onset severe asthma groups.

Table 1 Distinguishing Features of Early- and Late-Onset Asthma[9]

	Early	***Late***
Atopy	Very High	Moderate
Allergic Symptoms	Very High	Moderate
Evidence for Th2 immunity	High	Moderate
Family History	High	Low
History of atopic dermatitis	High	Low
Persistent eosinophilia	Moderate	High
Urinary cysteinyl leukotrienes	Moderate	High
History of initiating infection	Moderate	High

2.1.2 Prevalence of asthma and severe asthma

Asthma has been increasing in prevalence and severity despite the availability of effective medications and treatments. The National Center for Health Statistics has frequently reported on the prevalence of asthma since 1980 through the use of the National Health Interview Survey (NHIS). From 1980-1996 the prevalence of asthma in the United States was reported through the use of questionnaires. Having at least one asthma attack episode within the past 12 months was considered to be a self-report of asthma. In 1980, 31.4 per 1000 population (69 million people) reported having asthma, whereas, in 1996, 54.6 per 1000 population (14.6 million people) reported having asthma. From 1980-1996, the prevalence of asthma rose by 74% according to

NHIS reports. However, in 1997 the NHIS was revised to accurately determine whether individuals truly had asthma. The questionnaire was revised to include a question that asked "Have you ever been told by a health care professional that you have asthma?" and the individual was followed for one year to capture any episodes of asthma. With the revisions, the prevalence of asthma decreased slightly from the previous year to 40.7 per 1000 population (11.1 million)[2]. Having a stricter definition of asthma ensured that individuals with asthma were being captured and not just individuals who may have had asthma symptoms such as wheezing but do not have clinical asthma as defined by medical professionals.

There are several reasons that may explain the increase in the prevalence of asthma in the United States over the past two decades. Americans are living more sedentary lifestyles, thus, the rates of obesity and other diseases have been steadily increasing. Obesity has been linked to asthma as a possible risk factor for its development. Along with the sedentary lifestyle comes more time spent indoors by children and adults, which has become increasingly popular behavior. Exposure to allergens has been shown to be related to atopy, which is linked to the development of asthma. Spending more time indoors increases an individual's chances of being exposed to indoor allergens such as dust mites, cockroach dust, and mold, which have all been linked to the development of asthma. Also, over the years industrialization has become more prevalent, thus, increasing the amount of pollution in the environment or environmental triggers. Airway hyperresponsiveness is a result of this exposure to environmental triggers, thus increasing the risk of developing asthma[2].

The prevalence of asthma is different among the races and age groups. The prevalence of asthma is higher among children aged 5-14; however, Black children have a higher prevalence of asthma compared to their White counterparts, 12.5% and 7.5% respectively, as shown in 2004.

This could be partially due to the increased exposure to allergens at an earlier age due to urban and poorer living environments. In 2004, Black adults were, also, shown to have a higher prevalence of asthma compared to White adults, 8.1% and 7.4%, respectively[2]. It is not known whether this number includes individuals who were diagnosed with asthma as a child and their asthma persisted into adulthood because age of onset was not collected. It can be hypothesized that the disparity between Blacks and Whites would be more pronounced with a larger gap between the two numbers; Blacks having many more diagnoses of asthma compared to Whites.

In contrast to general asthma, approximately 10% of the asthma population suffers from severe asthma, as previously described. Little is known about why and how severe asthma develops. Genetics, environmental factors, the combination of the genetics and the environment, or the occurrence of an acute event at the onset of asthma that results in a structural change in the lungs have not been ruled out as possible causes for the development of severe asthma[9].

2.1.3 Morbidity and mortality of asthma and severe asthma

Increasing morbidity is associated with more severe asthma. Individuals with severe asthma tend to visit the emergency room more frequently, have more hospitalizations, lower quality of life and high functional impairments or limitations[10]. Health care utilization is high for individuals with asthma and higher for those with severe asthma. A marker for severe asthma is typically the use of the emergency room.

Racial differences in asthma morbidity and mortality have frequently been studied. Morbidity and mortality in asthma are disproportionately higher in Blacks compared to Whites, despite the fact that asthma prevalence and asthma-related deaths have been decreasing overall[11]. Blacks have been shown to not only have higher prevalence rates for asthma, but

they are four times more likely to be hospitalized due to asthma and five times more likely to die as a result of asthma[12]. Gupta et al examined the morbidity and mortality rates in the United States from 1980-2002 by age and race. Annually, an average of 438,700 hospitalizations and 20 hospital discharges per 10,000 were due to asthma between the years of 1980 and 2002. Whites decreased from 9.0 to 6.1 discharges per 10,000 population between 1980 and 2002. Blacks hospitalization rates slightly decreased from 25.2 to 24.6 discharges per 10,000 population. Blacks had much higher rates of asthma hospitalizations compared to Whites during the same time period. The rate difference between Blacks and Whites increased from 1980 to 2002, 16.3 to 18.5 discharges per 10,000 population. Much of the increase seen in the racial rate differences was seen in children (aged 5-18 years old). White children hospitalization rates decreased from 11.5 to 8.1 discharges per 10,000 population; whereas, the hospitalization rates for Black children increased from 34.3 to 36.5 discharges per 10,000 population between 1980 to 2002[12].

Ginde et al used emergency room visits as the benchmark for asthma morbidity in a population and used the National Hospital and Ambulatory Medical Care Survey to describe trends in asthma morbidity for Blacks and Whites[13]. In 1998, the rate of asthma-related emergency room visits peaked at 7.6 per 1000 persons but decreased to 6.0 per 1000 persons by 2005 indicating some progress has been made to decrease asthma morbidity with respect to emergency room visits. However, when looking at the race-specific rates of emergency room visits, it appears that progress is not seen in both races. Whites decreased their rate of asthma-related emergency room visits by 25% from 1998 to 2005; whereas, the rates for Blacks steadily increased since 2000. The rate difference between Blacks and Whites increased from 2.5 per 1000 persons to 4.5 per 1000 persons[13]. The CDC's National Surveillance for Asthma from

1980 to 2004 showed similar racial disparities in emergency room visits for children and adults together. Black children and adults had higher asthma-related emergency room visits compared to White children and adults, 21.0 per 100 and 7.0 per 100, respectively.

Death as a result of asthma is rare; however, it can occur[2]. The mortality rate for asthma was 1.31 deaths per 1,000,000 population (218 deaths) in 5 to 34 year olds between 1980 and 2001 in the United States. In Whites, the mortality rate increased from 2.1 to 2.6 deaths per 1,000,000 population from 1980 to 2001. In contrast, the mortality rate for Blacks increased from 9.9 to 13.2 per 1,000,000 population during the same time period. The rate difference between Blacks and Whites during this time period increased from 7.8 to 10.6 deaths per 1,000,000 population. Interestingly, the rate difference for Black and White young adults (aged 19-34 year old) was 14.7 deaths per 1,000,000 population[12].

Some studies speculate that the cause of the racial gap in mortality rates is related to the lack of access to care, high prevalence rates, and more severe asthma among Blacks. In a study by Zoratti et al, Blacks were shown to have more visits to the emergency room, more hospitalizations, fewer visits to an asthma specialist, fewer inhaled corticosteroid use, and more oral corticosteroids prescribed[2]. Incorrect diagnosis of a severe asthma attack or physicians underestimating the severity of asthma symptoms along with no early intervention my also be contributing to the increased mortality rate among Blacks compared to Whites[2, 15].

2.1.4 Economic burden of asthma and severe asthma

Due to asthma being a chronic condition, use of daily medication is needed to control the disease; however, despite effective prophylactic therapy available to asthmatics, the prevalence and severity are steadily increasing. Asthmatics not properly managing their asthma by under-

using medications have resulted in the health systems incurring substantial costs[16]. In addition, severe asthma continues to excessively contribute to the economic burden and costs of asthma due to the difficult nature of the disease[9]. In 2005, 1% of the total health care cost for the United States was attributed to asthma costs. Treating uncontrolled and severe asthma accounted for the majority of these costs[16].

Individuals with asthma tend to acquire a considerable financial burden because of their asthma[2]. Direct, indirect, and intangible costs to asthma care can negatively affect the individual with asthma and their family. Direct costs consist of costs associated with physician costs, hospital costs, and drug costs. Physician costs account for the smallest amount of asthma costs. Typically, 20-25% of the direct costs for asthma is for hospital care such as in-patient care or emergency room care. Patients with more severe asthma tend to incur these hospital costs. Drug costs are the most expensive component of direct costs for asthma making up 37% of the total asthma direct cost. Poor compliance with asthma medication results in an increase in asthma morbidity, thus, resulting in an increase in the costs associated with asthma[16].

Indirect costs consist of resources that are lost due to the disease such as premature retirement, time off of work, absenteeism, or death. These costs occur only when asthma has become intrusive into the lifestyle of the individual. These costs vary depending on the severity of the asthma and age of the individual[16]. Hospitalizations and urgent care have resulted in almost $20 billion in annual asthma health care costs, direct and indirect included[1]. Absenteeism is a common problem associated with asthma morbidity. Every year, over three million days of work and ten million days of school are lost due to asthma[17]. In a study with over 2500 caregivers for children with asthma and adults with asthma, approximately 50% of children with asthma and 25% of adults with asthma reported missing school or work due to their

asthma. Being hospitalized, visiting the emergency room, or visiting an urgent care facility for their asthma was the reason why 41% of adults and 54% of children missed school or work[2].

Intangible costs occur when the quality of the individual's life is impaired. These costs also vary depending on the age of the individual and severity of the asthma[16]. Individuals with asthma may become depressed or feel as though their lives are very restricted or limited due to their asthma, thereby, resulting in a decrease in their quality of life.

The more severe the asthma, the higher the costs associated with asthma care18].

2.1.5 Management of asthma and severe asthma

A small fraction of asthma cases exhibit severe exacerbations and severe episodes of asthma. It is imperative that individuals with severe asthma receive optimal care that avails additional attention and care to their condition. Management of asthma can reduce the morbidity that is associated with severe asthma and increase quality of life[17]. According to the Global Initiative for Asthma (GINA) global guidelines, achieving and maintaining control of asthma symptoms in the long-term is the primary goal of asthma treatment[19, 20]. An assessment of each individual with asthma should occur to initially to determine the individual's current treatment plan, level of control, and compliance and adherence to the treatment regimen[19]. One study concluded that although management can improve asthma care, full asthma control is not always the result in all individuals[21].

Blacks have a higher prevalence of asthma than Whites and this disparity is also evident with respect to the management of asthma. This may be the reason why more Blacks have emergency room visits compared to Whites[22]. Black children have been shown to have a higher prevalence of uncontrolled asthma compared to White children. Besides the possibility

that they may have more exposure to indoor allergens and poverty, lack of access to quality care and the inability to afford medication is a cause for the disparity seen in childhood asthma[2].

White children were more likely to have a codiagnosis of asthma and allergies (68%)[23]. Also, children with public insurance and children who use the emergency department as their primary source of care had the lowest prevalence of diagnosed allergies[23]. Children that reported being tested for allergies were less likely to report exposure to household allergens, more likely to receive allergy education and treatment, and less likely to report an episode of wheezing in the past two weeks compared to children who did not receive allergy testing[24].

Blacks tend to rate their doctor-patient communication as poor[24], thus, suggesting the need for better communication between physicians and Black patients. Studies have, as well, shown that physicians may not effectively manage the asthma of a Black patient nor communicate effectively with Blacks. This could be the result of the presence of ecological fallacies[25] or a provider bias due to stereotypes or clinical uncertainty [24]. It is important for clinicians not to stereotype each Black patient based on results from past studies or personal feelings about race. Disparities in education and income paired with the past legacy of racial discrimination can contribute to the disparity in health care. “The manner in which societal and historical factors influence the experience of the health care process are complex and not readily summarized numerically[26].” Managing asthma is a complex and challenging issue; however, there are ways to effectively do it. Asthma can be successfully managed with patient education[26], patient adherence to medications, good physician-patient communication[24], early diagnosis, and understanding patient’s belief[27, 14, 28]. Management of asthma can, in essence, improve an individual’s quality of life.

2.2 PATHOPHYSIOLOGY OF SEVERE ASTHMA

It is important to look at the pathophysiology of asthma and immuno-inflammatory characteristics of asthma. FEV_1 is a sensitive measure of airflow obstruction (and is associated with risk of exacerbations) and can be used to monitor lung function changes over time. To identify airway hyper-responsiveness a metacholine inhalation challenge test is used to determine the sensitivity of the smooth muscle to spasm[29]. It is also very important to consider exposure and sensitivity to allergens such as cat dander, dust mites, and ragweed as possible risk factors[29]. Among the phenotypes that Dr. Wenzel mentioned, the exacerbation-prone phenotype and eosinophilic phenotype are important to study when discussing asthma pathophysiology. Exacerbation-prone asthmatics are characterized by their frequency to have moderate to severe exacerbations which can be described as severe asthma if the frequency and severity of the exacerbations is high[6]. Some of the risk factors for severe exacerbations are: Black race, low FEV_1, early age of onset, low provocation concentration 20 (PC_{20}) and bronchodilation responsiveness, and a high percentage of sputum eosinophils[6]. The more common and prominent exacerbating phenotype is the eosinophilic inflammatory phenotype. Results have shown that eosinophils are not found in all asthma tissues[30] but decreasing them will decrease asthma exacerbations[31]. Asthmatics who did not have the presence of eosinophils in airway tissues were more likely to have airway obstruction; in contrast, those with eosinophils had more airway remodeling[31]. Two clinical trials concluded that eosinophils may be involved in the pathogenesis of asthma but may not be the main “player” in the development and progression of the disease[31].

2.3 RACIAL HEALTH DISPARITIES AND SEVERE ASTHMA

2.3.1 Racial health disparities

Racial and ethnic health disparities exist in the United States and result in the health status of minorities being different than their White counterparts. These disparities are mainly driven by social inequities that were initially observed by W.E.B. DuBois in 1906[32]. Minorities disproportionately suffer from the burden of disease. In 2005, it was reported that racial and ethnic health disparities resulted in approximately 83,000 deaths annually [33]. Health disparities for racial and ethnic minorities result in financial burdens due to the loss of income or work as a result of poor health. A large proportion of minorities tend to be underinsured or uninsured; therefore, causing them to pay high premiums or deductibles (if insured) or enduring discriminatory pricing (if uninsured)[32]. Uninsured patients oftentimes pay nearly double or triple what insured patients pay for hospital services[34]. Racial and ethnic minorities are often apart of publicly funded health programs are more likely to receive low quality health care which results in the worsening of an untreated disease and the "greater reliance on the health care system"[35]. Despite the arguments of those who do not believe that disparities in health care exist, the Institute of Medicine has shown that racial and ethnic disparities exist at every income level[35]. The Centers for Disease Control and the Morehouse School of Medicine have both made efforts to eliminate racial and ethnic health disparities; however, politicians have not made the elimination of health disparities a high priority[32]. Healthy People 2000 included the elimination of health disparities for all groups as one of their goals to be accomplished by 2010 which resulted in $3 billion in funding from the National Institutes of Health for health

disparities research[25]. In 2003, the Panel on Racial and Ethnic Disparities in Medical Care determined that each year Blacks have excess attributable mortalities of 100,000-150,000[25].

Access to quality care, personal health beliefs and behaviors, and patient education are all factors associated with health disparities but access to quality medical care is linked to access to health insurance[25]. Blacks are more likely to receive low quality care that is not consistent with practice or clinical guidelines compared to Whites. The insurance for Blacks is more likely to be Medicaid and Medicare has been associated with an increased risk of visiting the emergency department[36]. When comparing White and Black children in Medicaid, Black children, still, received less preventive care than White children[36]. However, a study conducted with asthmatic children of active duty military personnel showed that equal access to care can eliminate racial health disparities[37].

2.3.2 Disparities in lung disease

Lung disease is one area of health that has been shown to have health disparities. Asthma has been shown to have higher morbidity and mortality rates in Blacks than Whites[25]. Blacks, also, have four times the risk of hospitalization and five times the risk of mortality than Whites[12]. Black children visiting a private practice were less likely to report receiving a controller or receiver medications than White children[27]. However, Black children were less likely to receive care from a specialist compared to White children[38].

2.3.3 Disparities in physiologic measures

Disparities in physiologic measures have also been studied. One result showed that when compared to White children, Black children were more responsive to metacholine which is indicative of a higher level of asthma severity[39]. Also, it has been suggested that Blacks have smaller lung capacities and their predicted FVC and FEV_1 values are 15% lower than Whites [39]. These values are derived from the Hankinson equation. However, these values are still significantly lower in Blacks[39].

The Hankinson equation was based on 7429 nonsmoking participants from the third National Health and Nutrition Examination Survey (NHANES III). It provides spirometric reference values for three major racial groups, Whites, Blacks, and Mexicans[40]. Although this was a fairly large sample of people, the accuracy of the equation for non-White individuals may be limited due to the very small sample size of individuals in the higher age groups for the other races. In particular, after the age of 50 years, the sample size for Blacks drastically decreases. The Hankinson equation appears to be more accurate for individuals who are younger than 50 years of age for Blacks (and Mexicans).

Blacks have been shown to have smaller lung capacities but is the Hankinson equation the most accurate equation to base reference spirometric values for all races. It is important to note that when FEV1 is not adjusted for race, the FEV in liters is much higher for Blacks compared to Whites. There is nothing in the literature to suggest that one value is better to use than the other; however, most studies do present on the percent predicted pulmonary scores instead of the absolute pulmonary scores. A study with Black and White adults did reveal that the variability between subject in pulmonary function was larger than the difference between races suggesting the need for better predictive models for lung function[39]. It is not known

whether smaller lung capacities lead to the development of severe asthma. Nor it is known that the there is no other equation that is more accurate to calculate pulmonary function in Blacks, as well as Whites.

2.3.4 Disparities in Severe Asthma

In 2002, it was reported by the Centers for Disease Control and Prevention (CDC) that the prevalence of asthma in Blacks was approximately 38% higher than Whites. The CDC also reported that the asthma morbidity was drastically higher in Blacks than Whites. Compared to Whites, Blacks had 225% higher hospitalization rates, a 200% higher asthma death rate, 30% higher frequency of asthma attacks, and a 380% higher rate of visits to the emergency room[41]. The cause for this disparity in asthma between Blacks and Whites is unknown, however, several studies have suggested a possible biological or genetic reason for the increased prevalence and severity of asthma in the Black population. The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study investigated the differences in asthma severity between Blacks and Whites. In their study, they were able to show that Blacks were more likely to have severe asthma and use three or more long-term controllers, despite the fact that no differences in disease management were found. Black participants were also more likely to report not using their medication or taking medication on some days but not on all days resulting in Blacks having more asthma control problems. Blacks were also more likely to report having visited the emergency room as a result of their asthma compared to Whites, 19.6% and 6.1%, respectively. Blacks were also shown to significantly lower quality of life scores than Whites[41].

Some studies have suggested that there is a genetic difference between Blacks and Whites that may account for Blacks having more severe asthma. This genetic difference could result in a compromised response to certain asthma medications in Blacks[41]. Other research has shown that mortality in Blacks is increased with the use of long-acting beta agonists (LABA) compared to Whites[41].

Past studies have shown that Blacks with asthma report their asthma symptoms differently than their White counterparts. Blacks primarily report upper respiratory symptoms; whereas, Whites report lower airway symptoms which is associated with asthma-related symptoms[36, 42, 43]. This is likely to lead to asthma in blacks being undiagnosed.

2.4 RISK FACTORS AND CORRELATES FOR SEVERE ASTHMA

2.4.1 Demographic and Socioeconomic Factors

Female sex has been shown to be associated with asthma and adult females tend to have a more severe form of asthma. Some studies have shown that females have difficulty controlling their asthma, resulting in more hospitalizations and longer hospital stays related to their asthma[44].

Black race has been shown to be associated with a higher prevalence of asthma and are more severe asthma. It is currently unknown why Blacks have more severe asthma, although genetics have been suggested to play a role. Phenotype according to ancestry appears to play a role in the development of asthma. Individuals with African ancestry have been shown to have higher levels of immunoglobulin E (IgE), higher airway hyperresponsiveness, and have different patterns of allergic sensitization compared to those of European ancestry[11].

Lower income level and lower education has been shown to be associated with the increased prevalence of asthma[2]. Individuals living in poverty may not be as educated about asthma or exposure to allergens[45]. Exposure to certain indoor allergens that are suspected to cause asthma (cockroach dust, dust mites, mold, and cat dander) are more likely to occur in urban areas or inner cities which is where most low-income individuals reside.

A study in 1997 showed that the prevalence of asthma in Black children from a low-income family (income less than half the federal poverty level) was significantly different than White children. The increase in asthma prevalence among low income individuals, mainly Blacks, may be due to the environmental exposures that occur in urban rather than rural neighborhoods that increase the risk of airway hyperresponsiveness and, therefore, the development of asthma[2].

Lower socioeconomic status may be a surrogate measure for other factors that may truly be associated with severe asthma such as poor housing, indoor allergen sensitization, occupational exposure[10, 25].

2.4.2 Pulmonary Function Tests

Declining pulmonary function or FEV_1 is associated with the risk for severe asthma. One of the American Thoracic Society's minor characteristics for defining severe asthma is that an individual have persistent airway obstruction, which is typically demonstrated by having a FEV_1 of less than 80%. Although having a low FEV_1 score contributes to severe asthma, there are other factors that may also contribute to the development of severe asthma especially in the different races (e.g., Black and White race)[9].

The higher the percentage of reversibility of airways in response to bronchodilator use, the more severe the asthma.

2.4.3 Genetics

The etiology of asthma is unknown; however, studies have shown that asthma cannot be fully explained by environmental, social, cultural, or economic factors. With the availability of genetic mapping and the increasing popularity of genetic epidemiology in the past two decades, genetics has been shown to play a role in the development of asthma[11].

Having a family history of asthma is associated with the development of asthma; however, it is unclear as to whether having a family history of severe asthma is associated with the development of severe asthma. The population-based twin study in Norway was able to conclude that genetics played more of a role in the development of asthma than environmental factors[2]. This could possible indicate that genetics may play a role in the development of severe asthma. Liu et al examined NHANES data from 1999-2004 to determine the association of family history and the prevalence of asthma in adults. The three-tired familial risk methodology[46] was used to determine the whether an individual had average, moderate or high familial risk. Liu found that when compared to adults with average familial risk, the prevalence of asthma for adults with moderate familial risk was two times higher and six times higher for adults with high familial risk[46].

The Collaborative Study on the Genetics of Asthma (CSGA) was able to produce findings that support the claim that maternal asthma or allergy diagnosis is a risk factor for asthma development in children[27,46]. Also, their data suggested possible racial differences in the occurrence of family history of asthma with Blacks having a higher number of relatives other

relatives with asthma. One explanation suggested is the idea that there are different frequencies of various alleles associated with asthma in the different racial/ethnic groups[47].

Unfortunately, there were a limited number of studies that have looked at the genetic link to asthma; therefore, it is unknown how much genetic susceptibility contributes to the development of asthma and the disparities in asthma[11]. The limited studies have, however, shown that individuals of African descent have more severe asthma than those of European descent[11]. It is difficult to completely understand the role that genetics plays in the development of asthma for Blacks due to most of the genetic studies being underpowered and the variety of environmental factors that are unique to Blacks. These environmental factors further support the theory of there being a gene-by-environment interaction associated with asthma, especially in Blacks. Studies have also shown that certain genes suggest this gene-by-environment interaction.

A meta-analysis of almost 500 studies was carried out by Ober and Hoffjan was able to identify approximately 79 genes that were associated with asthma or its phenotypes in two or more racial/ethnic groups[11]. It also shows that the vast amount of genetic studies were done in a European population (60%) and Asian population (28%); therefore, limiting the generalizability of these studies to diverse populations which suffer disproportionately from asthma morbidity and mortality. Unfortunately, only 3% of the genetic studies were based on African populations.

Genetic studies have suggested that certain genetic polymorphisms may be associated with airway hyperresponsiveness and more rapid declines in pulmonary function[2, 9]. Studies have shown that polymorphisms of the B2-adrenergic receptor affect bronchodilator response. In particular these polymorphisms have been described as homozygous pairs Arg 16 Arg, Gln 27

Gln, and Glu 27 Glu[2]. The arginine (Arg) pair at position 16 is a polymorphism present in approximately 25% of Blacks and 15% of Whites[9]. There has also been studies that reported mutations at the interleukin 4 (IL-4) gene or the coding regions of the IL-4 receptor being associated with the loss of pulmonary function or near-fatal events[9].

CGSA was one of the first groups to screen for asthma using genome wide linkage data. They were also the first and only, to date, to include a population of African descent. The group examined the genes of families from three racial/ethnic groups: Whites, Blacks, and Hispanics. The study was able to show that each group had distinct genes involved with asthma and they did not overlap. This finding was able to provide more evidence to the genetic-by-environment interaction. One explanation is that there are genes unique to each race/ethnicity that contribute to asthma and act differently in regards to asthma development. The chromosomal regions involved in each group are: for Blacks (5p15, 17p11.1-q11.2), Whites (11p15,19q13), and Hispanics (2q33, 21q21). Another explanation is that the groups have the same polymorphisms but the frequency of the genes involved in asthma development is varies according to the racial/ethnic group[11]. The two loci unique to the Black population have been shown to be significantly linked to asthma: 5p15 ($p=0.0008$) and 17p11.1-q11.2 ($p=0.0015$). The 5p15 locus has continued to be a unique locus in just Blacks.

Due to the mixing of various populations, including African and European ancestry, special attention has been paid to admixture mapping. Although availability of admixture panels is limited, there is still technology available to determine the risk of asthma for admixture populations called mapping by admixture linkage disequilibrium (MALP). The idea behind MALP is that when two populations are joined together that have already been isolated separately and due to differences in risk allele frequencies an ancestral population is

disproportionately affected by a specific disease, determining "genomic regions where individuals with the trait of interest will have a higher proportion of ancestry from the parental population more likely to be affected by the trait" is feasible[11]. This method is utilized to identify susceptible genes by mapping distortions of ancestry. However, this process is more successful when the differences in disease prevalence and gene susceptibility between the two parental populations is very large

2.4.4 Environmental Exposure

Exposure to allergens is known to be associated with increased airway hyperresponsiveness, asthma symptoms, and severe asthma. Cockroaches, dust mites, mold, cat dander, and Alternaria are examples of indoor exposures that have been shown to be associated with severe asthma [45]. Dust mites have been shown to trigger asthma attacks and more so, in urban neighborhoods. Positive allergen skin tests to cockroaches have also been linked to development of severe asthma with a higher incidence of positive skin tests in Blacks[45]. Togias et al suggested that there may be genetic factors that are involved with the higher sensitivity to cockroaches in the Black population, mainly Black population in inner cities; hence, signifying a strong association to environmental exposures for Blacks[47].

Tobacco smoke or exposure to secondhand smoke is also a risk factor for severe asthma. In a prospective cohort study of 451 nonsmoking adults with asthma, it was shown that individuals with exposure to secondhand smoke had more hospitalizations, more emergency room visits, and higher asthma severity scores[2]. Individuals with asthma who smoke are at an increased risk of developing asthma and severe asthma, as well as individuals whose mothers smoked during pregnancy. Smoking during pregnancy was shown to decrease infant lung

function and lead to more asthma symptoms for the infant[45]. Cigarette smoking limits the effectiveness of corticosteroids which are used to treat asthma[9]; therefore, increasing the risk of developing severe asthma.

2.5 COMORBIDITIES AND SEVERE ASTHMA

2.5.1 Gastroesophageal Reflux Disease (GERD)

Gastroesophageal reflux disease (GERD) occurs when gastric acid and contents become backed up in the stomach and the esophagus becomes inflamed due to this back up. The lower esophageal sphincter (LES) prevents the flow of gastric acid; however, some asthmatics have a dysfunctional LES that allows the gastric acid to flow back into the esophagus thus creating the symptoms associated with this condition. Over half of all asthmatics suffer from symptoms associated with GERD. Although this number is high, many people are misdiagnosed or do not receive treatment for this condition. Asthma becomes difficult to manage in an individual with GERD due to the condition exacerbating asthma symptoms.

GERD can exacerbate asthma symptoms in two different ways. First, bronchoconstriction is encouraged by the flow of gastric acid into the esophagus through vagal stimulation. Vagal stimulation is also linked to chronic cough, which is commonly associated with GERD. Second, the microaspiration of gastric acid promotes airway inflammation and resistance. This leads to asthma exacerbations due to the narrowing of the airways and initiation of bronchospasms.

Most asthmatics suffer from atypical symptoms associated with GERD such as chronic cough and are not aware that they are suffering from GERD but assume that it is a symptom of

asthma. The use of over-the-counter medication antitussive is often utilized by asthma patients to relieve the symptoms associated with GERD. Also, physicians are frequently not aware of the underlying GERD that an asthmatic patient may have due to the fact that the patient may be complaining about symptoms related to asthma such as a cough. An individual with severe or hard to control asthma is more than likely going to present with atypical symptoms of GERD.

Various lifestyle modifications have to occur to reduce GERD symptoms, which will eventually reduce asthma exacerbations. Individuals with GERD should reduce their weight, avoid tobacco smoking and alcohol, and elevate their heads 15 degrees while sleeping[48].

2.5.2 Obesity

Obesity has become a growing public health problem with approximately 1.6 billion adults and 20 million children being overweight and 400 million adults being obese, globally[49]. Obesity is defined as having a body mass index (BMI) of 30 or more. There are also three subtypes of obesity: I (BMI=30.0-34.0), II (BMI=35.0-39.9), and III (BMI>40).

Medical costs associated with obesity consist of almost 8.4% of the national healthcare expenditure with up to 100 billion dollars being spent annually to treat obesity related illnesses. Obesity causes morbidity and premature mortality in individuals by causing several other conditions such as cardiovascular disease, type 2 diabetes, gout, and cancer. Quality of life is also diminished in obese individuals[49].

Obesity can cause or lead to changes in respiratory function. Respiratory mechanics, respiratory muscle strength, breathing patterns, and lung volumes are some of the functions that are disturbed by obesity[49]. Some of the lung function changes are increased respiratory rate,

reduced tidal volume, reduced forced vital capacity, increased airway resistance, reduced total lung capacity, and increased residual volume.

The increased prevalence of concomitant asthma and obesity has led to the suggestion that the two may be associated with one another[49]. There have been several studied carried out in children and adults and retrospectively and prospectively to determine the relationship between asthma and obesity. The first study to suggest an association between asthma and obesity was released in 1984. This cross-sectional study was done in Great Britain in 1977 in a population of children ages 5 to 11. Several retrospective studies followed this study and majority of these studies showed an association between obesity and asthma in children. The first study to report this finding in adults was published in 1986. Several studies were able to show that obese adults had an increased odd of having asthma compared to those with normal BMIs. Surprisingly, many of the studies showed an association between obesity and asthma exclusively, which reveals a possible confounding effect of gender.

In 1999, the first prospective study examining the relationship between obesity and asthma was published[49]. Nurses from the Nurses' Health Study II were screened and followed for 4 years (1991-1995). The results of the study showed a dose-response relationship between BMI and the relative risk of incident asthma. The relative risk was incident asthma was 2.7 for obese nurses even after adjusting for confounding factors. This study was the very first study to state that obesity precedes or antecedes asthma. Majority of the prospective studies examining the relationship between obesity and asthma reported that obesity preceded the incidence of asthma. Eventually a prospective study in children was carried out and provided the same results as the adult study: obesity preceded the development of asthma. As with the retrospective studies, the prospective studies showed a gender bias in the relationship between obesity and

asthma. Females were shown to have a greater effect than men; however, this gender confounding has not been studied fully to definitively state a true association[49].

2.6 ALLERGIC SENSITIZATION AND SEVERE ASTHMA

2.6.1 Atopy

Allergies have been shown to play a major role in the development of asthma. Asthma has been often described as an atopic disease, with atopy being defined as skin prick test (SPT) positivity or the development of IgE in response to environmental allergens. Pearce et al describes the paradigm between asthma and allergies as the exposure to allergen causing sensitization and continued exposure leading to clinical asthma[50]. A meta-analysis carried out by Pearce et al showed that on average there were approximately 37% of asthma cases that were attributable to atopy in adults[50].

2.6.2 Immunoglobulin E

Since IgE has been shown to be a good proxy measure of the allergic component in asthma, it is important to look at atopy in terms of IgE. The same meta-analysis showed that the 33% of asthma cases were attributable to atopy when using different cutoff levels for serum IgE[50]. Although atopy and asthma have been frequently studied, the relationship and its influence on asthma severity are complex and not well understood. In a population of only females, the results showed that the mean total IgE levels increased with asthma severity; however, this was not

statistically significant[51]. Inouye et al[52] and Siroux et al[53] also showed that there was no relationship between asthma severity and allergic sensitization.

2.6.3 Racial differences in allergic sensitization

Several studies have shown that Blacks have higher IgE levels compared to their White counterparts[41, 47, 36]. Black race has been highly associated with reactivity to indoor and outdoor allergens[41]. Blacks tend to have higher reactivity to cockroach[47, 54]. It has been suggested that this higher sensitization may be the result of Blacks living in inner city environments; therefore, there appears to be an environmental influence on the relationship between Blacks and allergen sensitization[47, 36]. Blacks have also been shown to be highly allergic to dust mite, mold, dog, cat, and rodent, which are all indoor allergens associated with living in urban environments[54]. Outdoor allergens such as ragweed and grass have been associated with Black asthmatics. Sensitization to these allergens is associated with an increased risk for asthma[36].

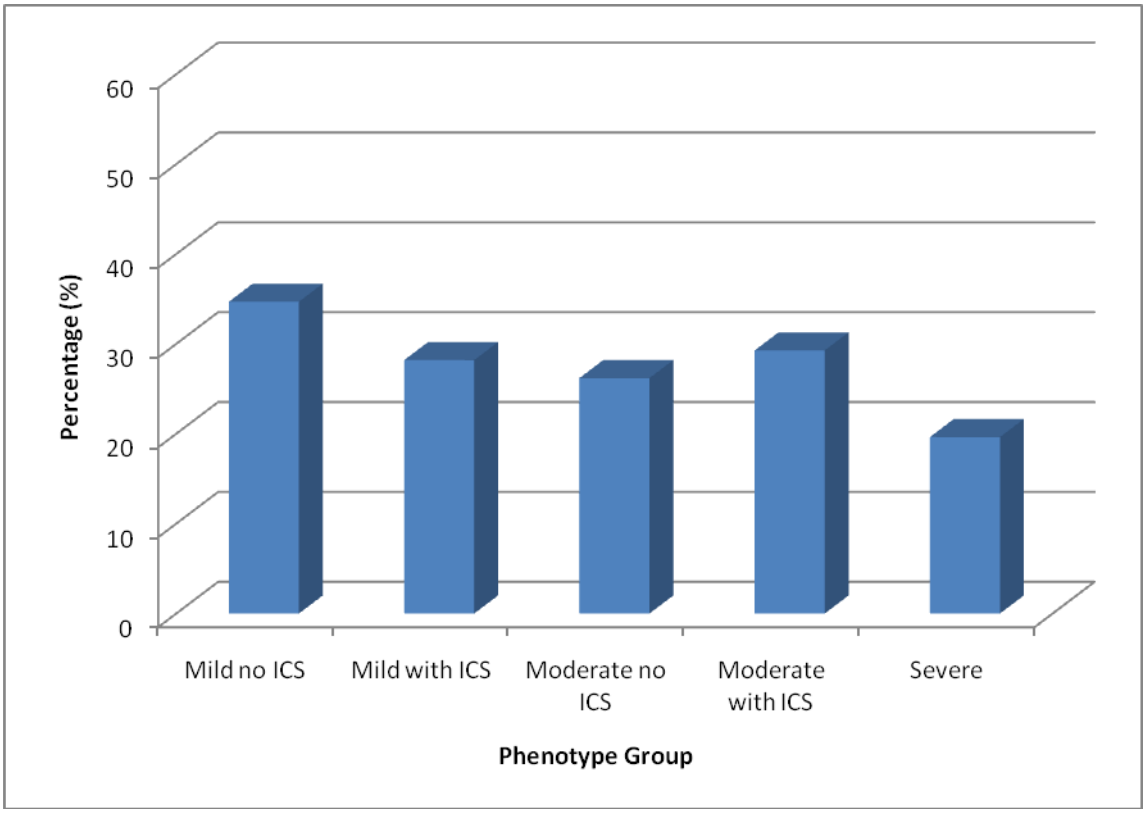

Figure 1 Percentage of Phenotype Group with Five or More Positive Skin Allergen Tests in White Participants of the Severe Asthma Research Program

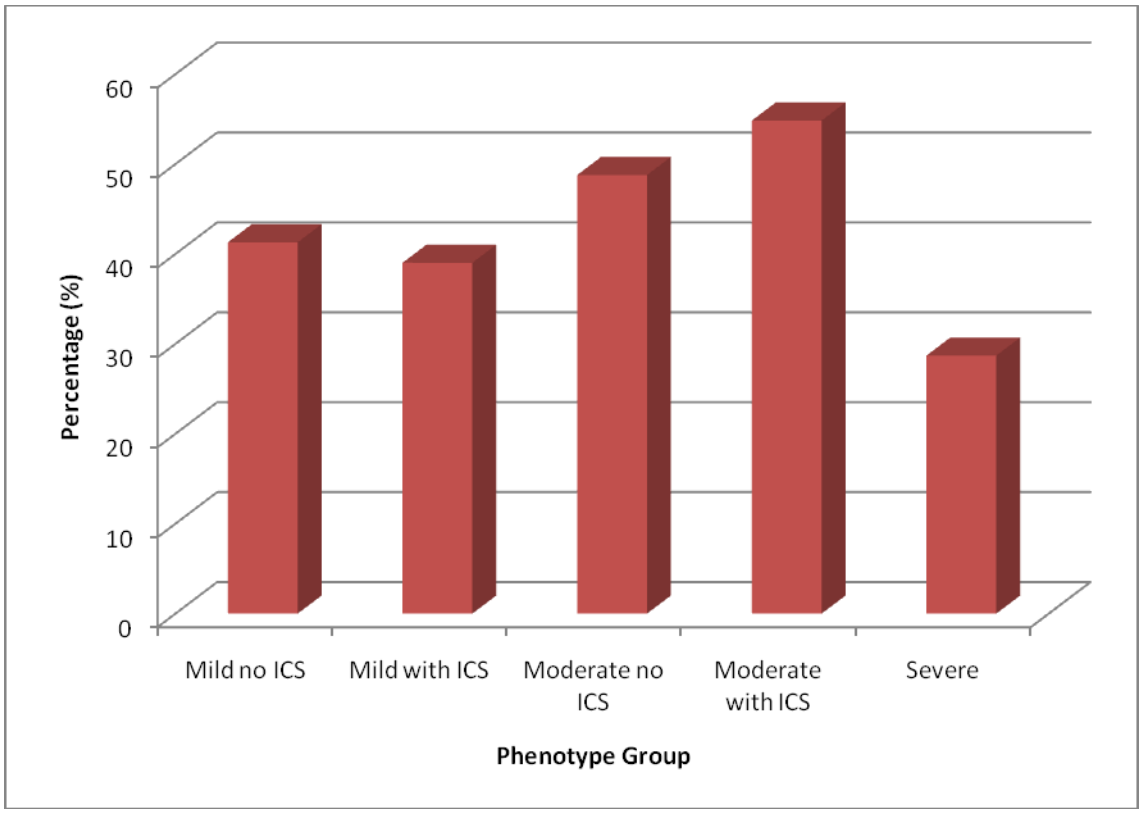

Figure 2 Percentage of Phenotype Group with Five or More Positive Skin Allergen Tests in Black Participants of the Severe Asthma Research Program

2.7 SPECIFIC AIMS

The overall aim of this study is to assess the extent to which the racial disparity in asthma is attributable to differences in the pathobiology of asthma.

The first aim is to determine the relative contribution of differences in immunoinflammatory processes and environmental factors such as socioeconomic status (SES) to health outcome disparities in asthma between Blacks and Whites.

The second aim is to determine the contribution of immunoinflammatory processes and environmental factors to the development of high IgE, and the factors beyond IgE that contribute to severe asthma in Blacks.

The third aim is to determine the policy implications of the widening racial gap in asthma between Black and White adult asthmatics.

We used cross-sectional data from the Severe Asthma Research Program (SARP) to perform analyses for the first two research aims.

2.8 SEVERE ASTHMA RESEARCH PROGRAM (SARP)

In 2001, the Severe Asthma Research Program (SARP) was established by the National Heart, Lung, and Blood Institute to characterize and differentiate individuals with severe asthma from those with mild to moderate asthma. SARP initially consisted of eight funded sites- the University of Pittsburgh, the University of Virginia (subsites at Cleveland and Emory University), Brigham and Women's Hospital, Imperial College, National Jewish Medical and Research Center, Wake Forest University, Washington University, and the University of Wisconsin, however the number of sites was reduced to 4: University of Pittsburgh, Cleveland Clinics (the University of Virginia and Emory included), University of Wisconsin, and Wake Forest University. From August 2003 until February 2010, 1391 subjects aged 18-79 years were recruited and enrolled.

2.8.1 Defining severe asthma

The American Thoracic Society's (ATS) criteria were used to determine whether individuals had severe/refractory asthma. Table 2 below shows the major and minor criteria required to define severe/refractory asthma. As a note, it requires that other conditions have been excluded, exacerbating factors have been treated, and patient is generally compliant.

Table 2 ATS workshop consensus for definition of severe/refractory asthma[9]

Major criteria (need ≥ 1)
Treatment with continuous or near continuous (≥ 50% of year) OCSs
Requirement for treatment with high-dose ICSs
Minor criteria (need ≥ 2)
Requirement for additional daily treatment with a controller medication (e.g., LABA, theophylline, or leukotriene antagonist)
Asthma symptoms requiring SABA use on a daily or near-daily basis
Persistent airway obstruction (FEV1 < 80% predicted, diurnal peak expiratory flow variability > 20%)
One or more urgent care visits for asthma per year
Three or more oral steroid bursts per year
Prompt deterioration with a ≤ 25% reduction in oral or inhaled corticosteroid dose
Near-fatal asthma event in the past

2.8.2 SARP measurements

To determine each subject's phenotype they completed multiple allergen skin testing evaluations for atopy, standardized questionnaires, collection of blood, pulmonary function testing, sputum induction and measurement of exhaled nitric oxide. Any subject that met one of the two major

criteria and two of the seven minor criteria were identified as severe asthmatics. However, subjects determined to have mild to moderate (not severe) disease remained in the study to be used as the reference group for comparisons/analyses. These subjects were classified as having mild asthma if they had a prebronchodilator FEV_1 greater than 80% predicted and were on no or low to moderate doses of ICS; whereas, a subject was considered moderate if they had a prebronchodilator FEV_1 of less than 80% predicted on low to moderate doses of ICS[15]. Current smokers or individuals with five or more pack-years of tobacco use were excluded from being in SARP[15].

Along with testing for 14 common allergens, subjects were all given standardized questionnaires administered by clinical staff that included demographic information, medical history, comorbidities, family history, smoking history, and frequency of asthma symptoms such as wheezing, nocturnal symptoms and shortness of breath. Medical resource or health care utilization was assessed by the subject's recollection of emergency room visits, hospital and ICU visits, asthma ventilation procedures, and other near fatal events that may have occurred in the past year (12 months) or in their lifetime. Pulmonary function testing was also carried out for each subject. Each subject had a variety of tests to quantify FEV_1 and FVC values. In addition, subjects with an FEV1 of >55% predicted underwent a methacholine challenge test to determine bronchial reactivity (airway twitchiness). The PC_{20} was determined as the interpolated dose of methacholine (from the last two doses) required to cause a 20% fall in FEV1.

Self-administered Asthma Quality of Life Questionnaires (AQLQ) were completed by the subjects in SARP. This 32-item questionnaire is a disease specific quality of life instrument used in adults with asthma to test four domains (activity limitations, symptoms, emotional function

and exposure to environmental stimuli). For each domain, the total score is the mean of the items within the domain; whereas, the overall AQLQ score is the mean of all 32 items.

Sputum induction was performed on about one-third of the subjects using hypertonic saline. Total inflammatory cell numbers were obtained. Cell differentials were performed and expressed as the percentage of total inflammatory cells. Bronchoscopy was conducted and additional pathology samples were collected.

2.8.3 Description of Dependent and Independent Variables

The dependent variable of interest was asthma severity (phenotype group) in both paper 1 and 2, but was high IgE in paper 2. Phenotype group was defined within the SARP study as mild, moderate, and severe. The mild and moderate groups were combined for this project; therefore, there are only two phenotypes being analyzed in this study, mild/moderate and severe. Participants with a phenotype of 1-4 were considered mild or moderate; whereas, participants with a phenotype of 5 were considered severe. The severe group was defined by the ATS workshop definition of severe or refractory asthma.

The main independent variable of interest is racial background for paper 1. Only two racial groups were analyzed in the first study, Blacks and Whites.

Several other variables were used as independent variables in the analyses: socioeconomic status, comorbidities, pulmonary function measures, immunoinflammatory markers, genetic measures, and medication use. Socioeconomic status was measured by age of asthma onset, employment status, exposure to secondhand smoke, pet ownership, and type of pet. The comorbidities in this study were diabetes, hypertension, GERD, and BMI or obesity. Pulmonary function measures that were used in this study were baseline predrug FEV_1 %

predicted, baseline predrug FVC % predicted, FEV_1/FVC, baseline predrug absolute FEV_1 in liters, and maximum FEV_1 reversal. Immunoinflammatory markers of interest were $\log_{10}$ immunoglobulin E, presence of atopy, five or more positive allergen skin tests, type of allergen, area of allergen wheal, $\log_{10}$ eosinophils count, and $\log_{10}$ basophil count. Genetic measures were also used such as family history of asthma (no family history, one family member with asthma, or two or more family members with asthma) and family history of allergies (no family history, one family member with allergies, or two or more family members with allergies). Corticosteroid use (no/inhaled corticosteroid use or high dose corticosteroid/oral and injected corticosteroids) was used to determine medical use.

The confounders that were adjusted for in these studies were age of enrollment or current age, gender and clinical center.

3.0 RACIAL DIFFERENCES IN BIOLOGIC PREDICTORS OF SEVERE ASTHMA: DATA FROM THE SEVERE ASTHMA RESEARCH PROGRAM

Christy Gamble[5], Evelyn Talbott[5], Ada Youk[5], Fernando Holguin[5], Bruce Pitt[5], Lori Silveira[4], Eugene Bleecker[9], William Busse[7], William Calhoun[6], Mario Castro[8], Kian Fan Chung[3], Serpil Erzurum[2], Elliot Israel[1], and Sally Wenzel[5].

Boston, MA[1], Cleveland, OH[2], London, UK[3], Denver, CO[4], Pittsburgh, PA[5], Galveston, TX[6], Madison, WI[7], St. Louis, MO[8], Winston-Salem, NC[9]

3.1 ABSTRACT

Background: Biologic factors are known to contribute to asthma severity. It is unknown whether these factors differentially contribute to asthma severity in Blacks compared to Whites.

Objective: We sought to assess the extent to which racial disparities in severe asthma between Blacks and Whites are attributable to physiologic, immunoinflammatory, and sociodemographic variables.

Methods: Black and White asthmatic adults enrolled in a cross-sectional study focused on severe asthma were evaluated. Severe asthma was identified using the American Thoracic Society definition. Following initial univariable analyses, unconditional logistic regression models were used to estimate the probability of having severe asthma for Blacks and Whites.

Results: Differences in severe asthma in Blacks compared to Whites were observed. In univariable analysis, IgE was not associated with severe asthma in Blacks or Whites, while in multivariable analysis IgE was significantly associated with severe asthma for Blacks (p=0.014) but not in Whites. The odds of having severe asthma more than doubled for Blacks with 2 or more family members with asthma (p=0.026), while the odds of severe asthma for White participants with a strong family history of asthma decreased by almost half (p=0.05). Atopy was negatively associated with severe asthma in both races in univariable analysis, but remained significant only in Blacks, while co-morbidities were associated with severe asthma in Whites.

Conclusion: Biologic factors were distinctly associated with severe asthma only in Blacks. Studies which incorporate comprehensive evaluation of biologic factors associated with asthma may lead to the development of therapies that target biologic abnormalities in Blacks.

Key Messages: Severe asthma in Blacks is strongly associated with traditional markers of allergic and genetic patterns of disease. These same patterns are not seen in Whites.

Capsule Summary: The results of this study show racial differences in the pathobiology of severe asthma. Compared to their White counterparts, the predisposition to more severe asthma, as defined by evidence for lack of control despite maximal therapy, in Blacks appears to be more strongly attributable to both genetic and allergic factors. These differences could lead to the identification of distinctly different management options for Black as compared to White asthmatic patients.

3.2 INTRODUCTION

Although standard treatments can control most asthma, a small number of asthmatics (about 10%) require treatment with the highest level of inhaled corticosteroids (ICS), often in combination with other drugs, including systemic corticosteroids(1-2). Despite these high medication doses, these patients often never achieve adequate disease control and continue to have frequent and/or severe exacerbations, daily symptoms and bronchodilator use, as well as persistent airway obstruction (3). Although lower lung function, a history of pneumonia, less atopy, and lower blood basophils have all been shown to be independently associated with the presence of this more severe asthma, much remains to be determined regarding the factors which either associate or predict its development (4).

Asthma in Blacks has long been associated with higher morbidity and mortality rates than Whites(5). Blacks have four times the risk of hospitalization and five times the risk of mortality than Whites(6). Although Blacks have been reported to be more likely to have severe asthma, particularly in relation to asthma exacerbations(7), concerns have generally focused on contribution from limited access to appropriate medical care, adherence to medications and related socioeconomic factors to this severe form of disease(8).

However, in addition to SES, biologic factors likely also contribute to asthma severity in both racial groups. Whether there are differences in the contribution of biologic factors to asthma severity in Blacks compared to Whites has not been specifically addressed. For instance, immunoglobulin E (IgE) levels are well known to be significantly higher in Blacks than Whites in both asthmatic and non-asthmatic populations(9-16). In addition to total IgE, specific IgE also differs by race with higher levels of grass and cockroach specific IgE associated with asthma and more poorly controlled asthma in Blacks(15, 17). Higher total IgE levels have been shown to be

associated with lower lung function with the relationship stronger in some racial and ethnic group than others (18). Finally, substantial differences in Th2 related gene allele frequencies have been described in Blacks compared to Whites suggesting that hereditary/genetic differences could explain some of the potential severity differences(19).

The objective of this paper was to determine the extent to which the racial health disparities in asthma, particularly severe asthma, are attributable to physiologic, immunoinflammatory and/or sociodemographic variables. ***We hypothesized that the contribution of immunoinflammatory predictors to asthma severity would differ by race.*** To address this hypothesis, clinical, immunologic, and physiologic data from the cross sectional National Heart Lung and Blood Institutes' sponsored Severe Asthma Research Program (SARP) database were analyzed to determine whether there were differences in the factors associated with severe asthma in Black compared to White asthmatic participants.

3.3 METHODS

3.3.1 Subjects

The data in this study was obtained from subjects enrolled in the Severe Asthma Research Program, a network established to identify and characterize severe asthmatic subjects in relation to milder asthmatics to better understand mechanisms for their disease. The baseline characteristics of this population were recently published(4). SARP initially consisted of eight funded sites- the University of Pittsburgh, the University of Virginia (subsites at Cleveland and Emory University), Brigham and Women's Hospital, Imperial College, National Jewish Medical

and Research Center, Wake Forest University, Washington University, and the University of Wisconsin. The number of sites was reduced to 4 in 2006: University of Pittsburgh (including National Jewish), Cleveland Clinics (including the University of Virginia and Emory University), the University of Wisconsin, and Wake Forest University.

From August 2003 until February 2010, 1391 subjects aged 18-79 years were recruited and enrolled. Current smokers or individuals with five or more pack-years of tobacco use were excluded from SARP(4). The American Thoracic Society's (ATS) definition was used to determine whether individuals had severe/refractory asthma(20). Severe asthma subjects were required to meet one of 2 major criteria (high dose inhaled or oral corticosteroid [CS] use) and at least 2 of 7 minor criteria. All subjects who did not meet criteria for severe asthma were classified as "not severe". There were no specific requirements for the subjects other than a confirmed diagnosis of asthma based on symptoms, bronchodilator response or airway hyperresponsiveness.

3.3.2 Data collection/Measures at interview

All subjects completed multiple (14) allergen skin testing evaluations for atopy, standardized and SARP specific questionnaires, collection of blood for complete blood counts and differentials and total IgE, exhaled nitric oxide and pulmonary function testing as previously described(4). Questionnaires were administered by clinical staff and included information on demographics, medical history, comorbidities, family history, smoking history, and frequency of asthma symptoms such as wheezing, nocturnal symptoms and shortness of breath. Medical resource or health care utilization was assessed by the subject's recollection of emergency room visits, hospital and ICU visits, and asthma ventilation procedures. Baseline pre-bronchodilator

spirometry testing was carried out for each subject. In addition, a maximal bronchodilator response was calculated as the greatest percent change from the prebronchodilator FEV_1 following 4-8 puffs of albuterol. A variety of other procedures were done on subpopulations of SARP subjects (methacoline, sputum induction, and bronchoscopy), but are not included in this study due to incomplete data primarily based on site specific testing (sputum) or exclusions on the basis of FEV1% predicted (sputum, methacholine) or subject preference (bronchoscopy).

3.3.3 Statistical Analysis

Statistical analyses were conducted using SAS software (SAS Institute Inc. 2008. *SAS Statistical Software: Version 9.2.*Cary, North Carolina) and STATA software (StataCorp. 2009. *Stata Statistical Software: Release 11*. College Station, TX). Categorical variables were examined using cross-tabulations and frequencies, [expressed as n (%)]. Chi-square (χ^2) or Fisher's exact test were performed for racial comparisons of categorical variables in the severe asthma group. The Wilcoxon-Mann-Whitney test was performed for racial comparisons of continuous variables in the severe asthma group [expressed as median (25^{th}-75^{th} percentiles)].

3.3.4 Univariable models

Unconditional logistic regression was used to calculate the crude and adjusted odds ratios to estimate the probability of having severe asthma. Race specific (Black and White) models were used for this study. Univariable models were used to determine which variables to include for model selection and exclude during the model building process, with only the variables with a p-value of less than 0.15 included.

3.3.5 Multivariable models

Variables that had a p-value of less than 0.15 in the univariable models were included for model selection. In addition, variables deemed of clinically significance regardless of statistical significance were included in the full model. The likelihood ratio (LR) test p-value was used to determine if variables should remain in the model. Goodness of fit of the model was assessed using Pregibon's Dbeta and Hosmer and Lemeshow's delta-d. Models were adjusted for age of enrollment and clinical center.

3.4 RESULTS

3.4.1 Baseline demographics

General demographics. Of the 1391 total enrolled in SARP, 916 participants met inclusion criteria for this analysis. This analysis included only adult participants (18 years of age and older). Participants with a racial background classified as nonblack and nonwhite, as well as participants considered normal (not asthmatic) were excluded (n=475). There were more White (71%) than Black participants (29%). More female participants were included compared to males, and there were slightly more mild/moderate asthmatics compared to severe asthmatics. Forty percent of Blacks and 42% of Whites were categorized as severe asthmatics. The median age at enrollment for Blacks was almost 5 years younger than the age for Whites in the severe asthma group (p=0.011) with 65% of Blacks enrolling into SARP at 45 years of age or younger (Figure 1). While the age that the participants were first diagnosed with asthma was not

significantly different between Blacks and White severe asthmatics; 10% more of the Black compared to the White population were diagnosed younger than three years of age (Appendix 1). Body mass index (BMI) in Blacks was also higher than in Whites.

Socioeconomic related factors. White severe asthmatics were more likely to be employed compared to their Black counterparts. Almost 32% of Black severe asthmatics were exposed to secondhand smoke compared to 23% of White severe asthmatics (p=0.049). Pet ownership within the severe asthma group was significantly less in Blacks than Whites, with 22% of Blacks and 47% of Whites owning pets.

Pulmonary function. When pulmonary function was corrected for race, height, and age Black asthmatics had higher median baseline predrug FEV_1 and FVC % predicted values compared to Whites; however, absolute FEV_1 (in liters) was lower for Blacks compared to Whites. Bronchodilator reversibility was not significantly different for Blacks and Whites.

Immunoinflammatory markers. The mean IgE level for severe asthmatics was 174±5 IU/ml in Blacks and 85±5 IU/ml in Whites (p=0.003). While there was no difference in overall prevalence of atopy in the population, Blacks were more likely to have a high number of ($\geq$5) positive skin tests compared to Whites. Blood eosinophils did not differ by race.

3.4.2 Participants younger than age 40

As Black subjects had a lower median age at enrollment, a secondary comparison was done between White and Black asthmatics enrolled in SARP above and below age 40. Even in those under 40, the mean age at enrollment for Blacks remained slightly (but not significantly) younger compared to Whites, 29.6 ± 6.3 and 28.7 ± 6.7, respectively. Similar to the total group, gender did not differ. In contrast to the total dataset, there was no significant difference in employment.

Even in the lower age group, BMI remained significantly and substantially higher in Blacks (Median=33.9; 25^{th}-75^{th} percentiles=30.1-45.0) than Whites (Median=27.5; 25^{th}-75^{th} percentiles=23.8-24.5). Comorbidities such as diabetes, hypertension, and GERD were not significantly different between races and most participants were atopic. The median IgE level in Black asthmatics was higher compared to Whites but the levels did not differ in the severe asthma subgroup. Using percent predicted values, FEV1 did not differ across the races, however, the absolute FEV_1 (in liters) was significantly and markedly lower in Blacks (Median=1.91 liters; 25^{th}-75^{th} percentiles=1.53-2.23) compared to Whites (Median=2.28 liters; 25^{th}-75^{th} percentiles=1.65-3.00), despite Blacks being younger in this subset. There was no difference in bronchodilator reversibility.

3.4.3 Participants age 40 and above

Among older asthmatics, Black severe asthmatics were significantly younger and younger at diagnosis than White severe asthmatics. Greater than 10% more Black severe asthmatics were female than Whites, p=0.07. Current employment again did not differ among the races. White asthmatics were more likely to report a diagnosis of GERD compared to Blacks (45% and 33%, respectively) despite the higher BMI in the older Black severe asthmatics. There were no differences in atopic/allergic markers across the two races.

Similar to the younger age group, baseline pre drug FEV_1, FVC % predicted and the FEV_1 /FVC were significantly higher in Blacks compared to Whites. The absolute FEV_1 (in liters) did not differ between Blacks and Whites in this age group, but was likely confounded by

the higher percentage of females and lower overall age in the Black participants. Bronchodilator reversibility did not differ between the races.

3.4.4 Univariable models: Black participants

In the univariable models for Blacks, current age and pulmonary function (baseline predrug FEV_1 in liters, baseline predrug FEV_1 %predicted) were highly associated with asthma severity. BMI, GERD, and current employment were also associated with severe asthma, but no other co-morbidity was associated, including exposure to second hand smoke. Interestingly, the presence (atopy yes/no) and degree of atopy (% of participants with five or more positive allergen skin tests) were negatively associated with severe asthma, while 2 or more family members with asthma was positively associated. In the univariable analysis, IgE was not associated with severe asthma in Blacks.

3.4.5 Univariable models: White participants

The results from the White univariable models differed substantially from the Black univariable models. While current age, BMI, GERD and pulmonary function (baseline pre drug FEV_1 in liters and percent predicted) were statistically significant in these models, in Whites, other co-morbidities, such as diabetes and hypertension, were highly associated with asthma severity. However, similar to Blacks, second hand smoke exposure was not associated. In contrast to Blacks, older age when first diagnosed with asthma and increasing degree of bronchodilator responsiveness were also highly associated with asthma severity. Similar to Blacks, the presence and degree of atopy were also negatively predictive of severe asthma.

Unlike Blacks, owning a pet was marginally associated with decreased odds for severe asthma in Whites. Family history of asthma was not associated with asthma severity in Whites.

3.4.6 Multivariable models: Black participants

For every 10% decrease in baseline FEV_1 % predicted the odds of having severe asthma increased 40% ($p<0.0001$).Although bronchodilator responsiveness was of borderline significance ($p=0.058$), the odds for severe asthma decreased by 2% with an increase of one percent in reversibility after bronchodilator suggesting that those Black asthmatics with more fixed airflow limitation were at highest risk of severe asthma.

In contrast to the univariable analysis, IgE was strongly associated with severe asthma in Blacks ($p=0.014$). For every $\log_{10}$ increase in IgE the risk of severe asthma more than doubled. The odds of having severe asthma also more than doubled for Blacks who had 2 or more family members diagnosed with asthma ($p=0.026$). Despite the association with total IgE and family history, having five or more positive skin tests to allergens was negatively associated with severe asthma ($p=0.05$).

Blacks with GERD have more than three times the odds of having severe asthma compared to Blacks without GERD ($p=0.002$). While employment was marginally associated with severe asthma in the univariable models, it was not significant in the multivariate analyses ($p=0.366$).

After adjusting for confounders, baseline predrug FEV_1 % predicted, GERD, total IgE, and having two or more family members with asthma remained significantly associated with asthma severity. Given the relatively smaller sample size of Black participants, lower

bronchodilator responsiveness and having less than five positive skin tests may also be considered significant in this model.

3.4.7 Multivariable models: White participants

Similar to Blacks, baseline FEV_1% predicted was highly associated with severe asthma, with every 10% percent decrease in baseline FEV_1 increasing the odds of having severe asthma by 60% ($p<.0001$). Additionally, GERD remained highly associated with severe asthma (doubling the odds of severe asthma) ($p=0.009$), while in contrast to Blacks, diabetes remained marginally associated with asthma severity ($p=0.114$). Current pet ownership decreased the odds of severe asthma by 35% ($p=0.05$). In contrast to Black severe asthmatics, the odds of severe asthma for White participants who had 2 or more family members diagnosed with asthma decreased by almost half ($p=0.05$) and IgE (and measures of atopy) did not enter the final model. The final model for Whites after adjusting for age and site included baseline FEV_1 percent predicted, GERD, lack of pet ownership and having no or a weak family history of asthma as positive predictors of asthma severity.

3.5 DISCUSSION

In this cross sectional analysis of over 900 Black and White asthmatic subjects, striking differences were found in the factors associated with severe asthma. While baseline FEV_1 % predicted and GERD were important factors for both racial groups, biologic factors including IgE, skin test reactivity and family history were distinctly associated with severe asthma in

Blacks. Although socioeconomic factors almost certainly impact the high health care utilization and associated morbidity of asthma in Blacks, the results from this analysis suggest biologic/genetic factors related to atopy/allergy are, also, of substantial, if not even greater importance. These results underline the importance of understanding differences in pathobiologic mechanisms driving asthma and its severity in different racial groups.

Asthma has often been described as an atopic disease, with atopy defined as the development of specific IgE in response to environmental allergens. However, the association of allergies with asthma severity has been more difficult to confirm. Indeed, in the initial SARP demographic study, the presence of atopy was a strong negative predictor for severe asthma(4). Therefore, the finding that increasing IgE levels were strongly predictive of severe asthma in Blacks (and not at all in Whites) was surprising. While IgE was not a significant predictor of severity in the univariable model for Blacks ($p=0.717$); it became a strong predictor of severity in the multivariate model, suggesting that when numerous confounding factors were controlled for IgE remained as a predictive variable ($p=0.016$). Black asthmatics were again confirmed to have a much higher total IgE compared to White asthmatics, irrespective of severity. These results extend the findings of Naqvi et al who demonstrated that higher IgE levels were associated with more severe asthma in Black, Mexican, and Puerto Rican patients(18). However, unlike the study by Naqvi, SARP used a rigidly predefined and validated definition of severity, which supports the relevance of this biologic difference to disease severity. Naqvi utilizes frequency of symptoms and FEV1 % predicted scores to categorize a participant as moderate-to-severe; whereas, SARP requires that a participant be continuously using an oral or high dose inhaled corticosteroid.

While IgE was a significant positive predictor of asthma severity in Blacks, having five or more positive skin tests was a significant negative predictor of severe asthma. It is still unclear why two measures of atopy have apparently opposing effects on asthma severity within the Black SARP population. Serum IgE, which is a sum of all the circulating systemic IgE, would appear to be measuring something additional to the presence or absence of the 14 specific IgEs measured by skin testing in SARP. Interestingly, a subsequent post hoc univariate model also did not find a positive skin test for cockroaches to be associated with severe asthma in Blacks ($p=0.60$). While further pathobiologic studies of this relationship are needed, the data suggest that it may not be the number of positive skin tests, rather the amount of specific IgE made to each or any allergen or the presence of a specific, yet unidentified IgE. In future studies, the total wheal size to each allergen can also be included in the analyses. Additionally, robust measures of allergen exposure were not included in these studies, which could also contribute to these differences.

A well known risk factor for asthma is having a first degree relative with asthma(21). Atopy and allergy are also known to be contributed to by hereditary/genetic factors. Therefore, while it might be expected that family history would be predictive for asthma, studies on the hereditary relationship to severity in specific racial groups (as opposed to presence) have been limited. Perhaps more surprisingly, a reasonably strong family history of asthma in White participants was negatively associated with severe asthma. Given the generally later age at onset in the White participants (especially in those >40 yrs old), these results suggest that severe asthma in Whites specifically includes a different, non-atopic/allergic, late onset disease subset/phenotype with less genetic elements, as has been previously identified(22). This specific subtype/phenotype of severe asthma is not being identified in Blacks either because it is less

likely to occur or it is not being identified possibly for socioeconomic related reasons. In any case, studies of Black asthmatic populations may be more likely to produce genetic links to severity as compared to studies of White populations.

Numerous studies have pointed to the critical role that socioeconomic factors and health disparities play in asthma in the Black community. In the current study, factors related to SES, including current employment and pet ownership, were not related to severe asthma in Blacks. However, this lack of relationship to SES may be related to the limited data collected in SARP related to SES. As SARP expands, the questionnaires have added educational, marital status and zip code, which should improve the ability to assess the role of SES in the severity of asthma. Interestingly, while employment status was not associated with severity in either Blacks or Whites, as has been noted previously, pet ownership was associated with protection from severe asthma in Whites(23). Black participants in SARP, in general, had significantly lower pet ownership than Whites in SARP. It is unclear whether increasing pet ownership would improve asthma outcomes in Blacks (as seen in Whites), even without substantial changes in SES, but requires further study.

Univariable models revealed that comorbidities were highly associated ($p<0.0001$) with asthma severity in Whites. This association was much less in Blacks except for GERD, which, as previously shown in SARP, continued to be a positive predictor of severity for both Blacks and Whites. In contrast, hypertension and diabetes were highly significant predictors for Whites but not for Blacks, despite their higher prevalence in Blacks compared to Whites in the general population. It can be hypothesized that asthma itself may be affecting Blacks much more than Whites such that the severity of the asthma could be masking the effects of other diseases. Blacks may be focusing on the most severe ailments, while other diseases may not yet be

diagnosed. Blacks may have been diagnosed younger with asthma due to a better pediatric medical safety net, or because Black babies with asthma are substantially sicker than White babies with asthma. As they age, Blacks may not be going to the doctor regularly to get full checkups, which would allow diagnosis of comorbidities, such as diabetes. In support of this, Black severe asthmatics reported lower percentages of diagnosed diabetes and hypertension compared to Whites; while Blacks with mild/moderate asthma reported diabetes and hypertension twice as often as their White counterparts. Exposure to tobacco smoke has also been shown to increase the prevalence and severity of asthma. In a cohort of adult nonsmoking asthmatics, adults exposed to secondhand smoke at baseline had higher asthma severity scores compared to those without tobacco smoke exposure(24). However, in SARP, secondhand smoke was not a significant predictor of asthma severity for either race and was, therefore, not included within the final predictor model for both races.

Lower baseline predrug FEV_1 is well recognized as a predictor of severe asthma(3, 20, 25). In this study, the odds of severe asthma increased by 40% and 60% for Blacks and Whites, respectively, for every 10% decline in FEV_1 % predicted. While we used FEV_1 % predicted in the models, there are also striking differences in the absolute FEV_1 (in liters) in Blacks compared to Whites, which are "corrected" by the Hankinson equations used in SARP lung function testing. When racially corrected (and age/sex corrected) the mean/median FEV_1 % predicted is higher in Blacks compared to Whites. However, the absolute FEV_1 is significantly lower compared to Whites, despite the younger age of the Black asthmatics. Hankinson equations for FEV_1 % were built on disproportionate samples sizes in Blacks compared to Whites. White participants are equally distributed throughout the age groups; whereas, after the age of 50 years the number of Black participants drastically decreases compared to the number of younger Black

participants(25). As a Black participant ages and goes beyond the age of 50 years, the accuracy of the Hankinson equations may not be as valid as they are for the younger Black participants. Further, recent genetic studies suggest that being identified as "Black" in America is accompanied by a wide range of genetic racial admixture ranging from 100% African ancestry to 10% or less, such that predictive equations for "Blacks" may not apply to all "Black" participants(26). In any case, measuring lung function by FEV_1 % predicted could easily overestimate the lung capacity of many Black patients and lead to under recognition of the severity of the disease.

In Blacks, in addition to FEV_1 % predicted, maximum bronchodilator responsiveness was marginally associated with asthma severity in Blacks. However, for every % increase in bronchodilator responsiveness the odds for severe asthma decreased by 2%. The reasons for this inverse relationship are not clear but suggest that as asthma worsens in Blacks, the airways may stiffen/remodel such that the most commonly used treatment for asthma (beta agonists) becomes less effective. Whether these findings suggest a mechanism for the recent findings regarding increased severe asthma exacerbations and deaths in Blacks taking long acting beta agonists remains to be determined(27).

This study is not without limitations, certainly the biggest of which is the cross-sectional study design. It is difficult to confirm a temporal relationship in regards to severity and the variables of interest. Another limitation is the sample size differences for each race. The White SARP population consisted of over 70% of the data in this analysis, whereas, less than 30% of the data is from the Black SARP population. Having populations of similar sizes would aid in confirming the results from this study and possibly reveal stronger associations between predictors and severe asthma. Although the SARP database is one of the most extensive

databases of asthmatics from numerous geographic sites and includes the collection of lung inflammatory markers, such as sputum eosinophils, sputum induction was only performed on about 50% of the population. Therefore, sputum measures could not be used. However, genome wide association data and longitudinal participant information are being added to the database enabling even more complete studies on asthma severity in the future.

In conclusion, distinctly different factors appear to be associated with rigidly defined severity of asthma in Blacks compared to Whites, with allergic markers and strong family history much stronger positive predictors of severity for Blacks than for Whites. Thus in addition to socioeconomic factors, studies which incorporate comprehensive evaluation of biologic and genetic factors of relevance to asthma in Blacks in particular, may lead to the development of targeted therapies which improve overall asthma outcomes in the Black population.

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3.7 TABLES AND FIGURES

Table 3 Univariable Logistic Regression Models for Black Participants in SARP (n=267)

Variable	Coeff	SE	OR	95% CI	G	p
Age Onset	0.006	0.0090	1.01	0.99-1.02	0.45	0.503
Age	0.057	0.0119	1.06	1.03-1.08	22.63	<.0001
Female	0.176	0.2745	1.19	0.70-2.04	0.41	0.521
Center	-0.112	0.0462	0.89	0.82-0.98	5.83	0.016
BMI	0.033	0.0142	1.03	1.01-1.06	5.36	0.021
Employed	-0.376	0.2559	0.69	0.42-1.13	2.16	0.141
2nd Smoke	-0.205	0.2660	0.82	0.48-1.37	0.59	0.442
Pets	0.042	0.3008	1.04	0.58-1.88	0.02	0.889
GERD	0.977	0.2865	2.66	1.52-4.66	11.63	0.001
Diabetes	0.647	0.4681	1.91	0.76-4.78	1.91	0.167
HTN	0.409	0.2988	1.51	0.84-2.70	1.87	0.171
FEV1% pred	-0.031	0.0066	0.97	0.96-0.98	22.07	<.0001
FEV1 liters	-1.397	0.2312	0.25	0.16-0.39	36.54	<.0001
% Eosinophil	0.007	0.0351	1.01	0.94-1.08	0.04	0.849
Reversal	0.0067	0.0061	1.01	0.995-1.02	1.18	0.277
IgE	0.075	0.2077	1.08	0.72-1.62	0.13	0.717
≥5 skin tests	-0.486	0.2843	0.62	0.35-1.07	2.92	0.088
Atopy	-1.009	0.2855	0.37	0.21-0.64	12.50	0.0004
1 Fam Hx	-0.065	0.3090	0.94	0.51-1.72	0.04	0.834
2+ Fam Hx	0.511	0.3166	1.67	0.90-3.10	2.61	0.106

**Age Onset=Age when first diagnosed with asthma, Age=Age when enrolled into SARP, Center= clinical center site, 2nd hand smoke=exposure to secondhand smoke during day, Pets=own any pets, GERD=gastroesophogeal reflux disease, HTN=hypertension diagnosis, FEV1=forced expiratory volume in one second, % Eosinophil=% of eosinophils in the blood, Reversal=Max FEV1 reversal, IgE=Immunoglobulin E,≥5 skin tests= 5 or more positive skin tests, 1 Family Hx= Have 1 family member with asthma, 2+ Family Hx= Have 2 or more family members with asthma*

** IgE entered as continuous log-transformed variables in the model*

Table 4 Univariable Logistic Regression Models for White Participants in SARP (n=649)

Variable	Coeff	SE	OR	95% CI	G	p
Age Onset	0.015	0.0054	1.02	1.00-1.03	7.61	0.006
Age	0.057	0.0067	1.06	1.05-1.07	72.70	<.0001
Female	-0.261	0.1656	0.77	0.56-1.07	2.48	0.115
Center	-0.138	0.0289	0.87	0.82-0.92	22.68	<.0001
BMI	0.044	0.0115	1.05	1.02-1.07	14.64	0.0001
Employed	0.037	0.1660	1.04	0.75-1.44	0.05	0.823
2nd Smoke	0.106	0.1930	1.11	0.76-1.62	0.30	0.584
Pets	-0.309	0.1621	0.73	0.53-1.01	3.63	0.057
GERD	1.116	0.1827	3.05	2.13-4.37	37.30	<.0001
Diabetes	1.420	0.3793	4.14	1.97-8.70	14.02	0.0002
HTN	1.198	0.2319	3.31	2.10-5.22	26.67	<.0001
FEV1% pred	-0.066	0.0055	0.94	0.93-0.95	145.77	<.0001
FEV1 liters	-1.399	0.1264	0.25	0.19-0.32	122.56	<.0001
% Eosinophil	-0.010	0.0304	0.99	0.93-1.05	0.10	0.748
Reversal	0.029	0.0055	1.03	1.02-1.04	27.14	<.0001
IgE	-0.124	0.1399	0.88	0.67-1.16	0.79	0.374
≥5 skin tests	-0.488	0.1962	0.61	0.42-0.90	6.17	0.013
Atopy	-0.654	0.1734	0.52	0.37-0.73	14.25	0.0002
1 Fam Hx	-0.246	0.1874	0.78	0.54-1.13	1.72	0.190
2+ Fam Hx	-0.096	0.2103	0.91	0.60-1.37	0.21	0.648

**Age Onset=Age when first diagnosed with asthma, Age=Age when enrolled into SARP, Center= clinical center site, 2nd hand smoke=exposure to secondhand smoke during day, Pets=own any pets, GERD=gastroesophogeal reflux disease, HTN=hypertension diagnosis, FEV1=forced expiratory volume in one second, % Eosinophil=% of eosinophils in the blood, Reversal=Max FEV1 reversal, IgE=Immunoglobulin E,≥5 skin tests= 5 or more positive skin tests, 1 Family Hx= Have 1 family member with asthma, 2+ Family Hx= Have 2 or more family members with asthma*

** IgE entered as continuous log-transformed variables in the model*

Table 5 Final Model for Black Participants in SARP (n=267)

Variable	OR	95%CI	p>|z|
Age	1.06	1.02-1.09	0.002
Center	0.93	0.81-1.07	0.318
Employed	0.72	0.35-1.48	0.366
1 Family history	1.50	0.62-3.60	0.367
2+ Family history	2.79	1.13-6.87	0.026
GERD	3.59	1.62-7.97	0.002
Baseline FEV1% pred	0.96	0.94-0.98	<.0001
Max FEV1 Reversal	0.98	0.96-1.00	0.058
IgE	2.12	1.16-3.87	0.014
≥5 positive skin tests	0.46	0.21-1.01	0.053

** Age=Age when enrolled into SARP, Age Onset=Age when first diagnosed with asthma, Center= clinical center site, 1 Family History= Have 1 family member with asthma, 2+ Family History= Have 2 or more family members with asthma, GERD=gastroesophogeal reflux disease, FEV1=forced expiratory volume in one second, IgE=Immunoglobulin E*

** IgE entered as continuous log-transformed variable in the model*

**Adjusted for current age (age of SARP enrollment) & clinical center*

Table 6 Final Model for White Participants in SARP (n=649)

Variable	OR	95%CI	p>|z|
Age	1.02	1.00-1.04	0.046
Center	0.88	0.81-0.95	0.001
BMI	1.00	0.98-1.03	0.790
Age Onset	1.00	0.99-1.02	0.866
1 Family History	0.67	0.42-1.09	0.108
2+ Family History	0.57	0.32-1.00	0.051
Pets	0.65	0.42-1.00	0.051
GERD	1.92	1.18-3.13	0.009
Diabetes	2.27	0.82-6.29	0.114
Baseline FEV1% pred	0.94	0.93-0.95	<.0001

** Age=Age when enrolled into SARP, Center= clinical center site, Age Onset=Age when first diagnosed with asthma, 1 Family History= Have 1 family member with asthma, 2+ Family History= Have 2 or more family members with asthma, Pets=own any pets, GERD=gastroesophogeal reflux disease, FEV1=forced expiratory volume in one second*

**Adjusted for current age (age of SARP enrollment) & clinical center*

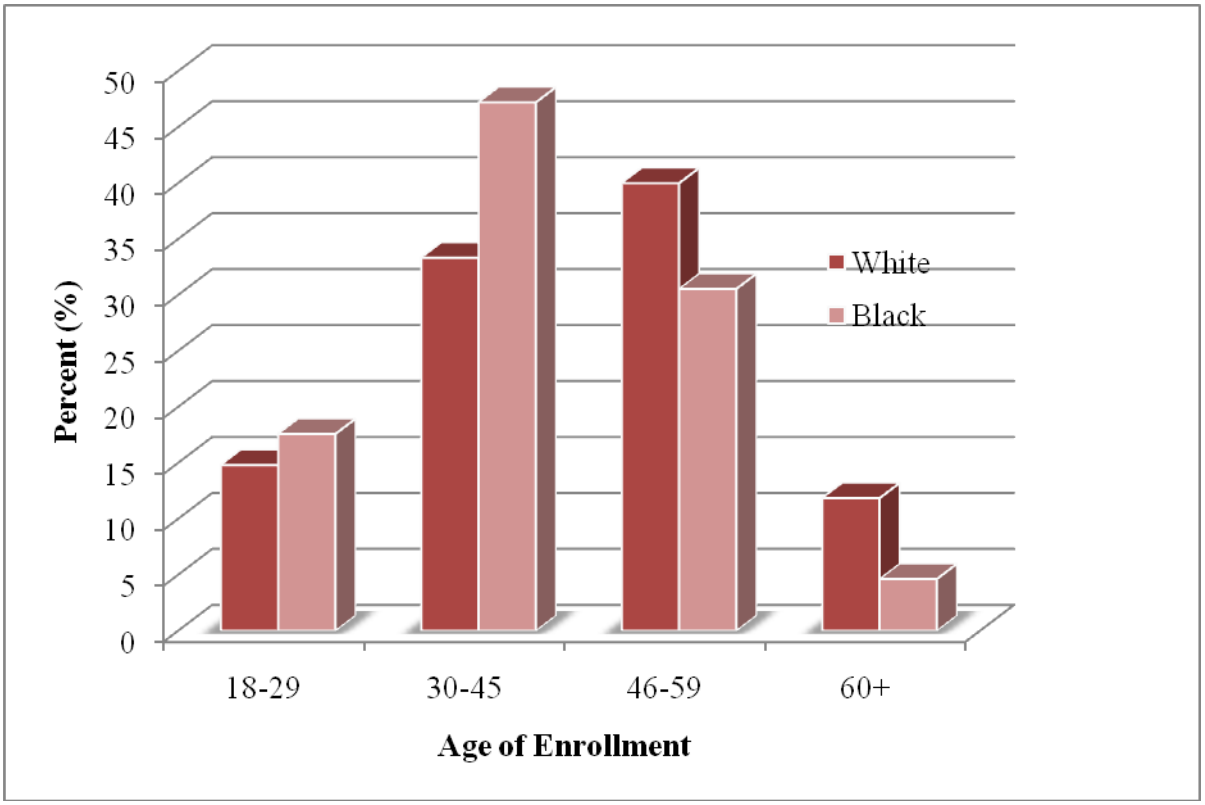

Figure 3 Percent of Black & White Participants enrolled into the Severe Asthma Research Program by age at enrollment

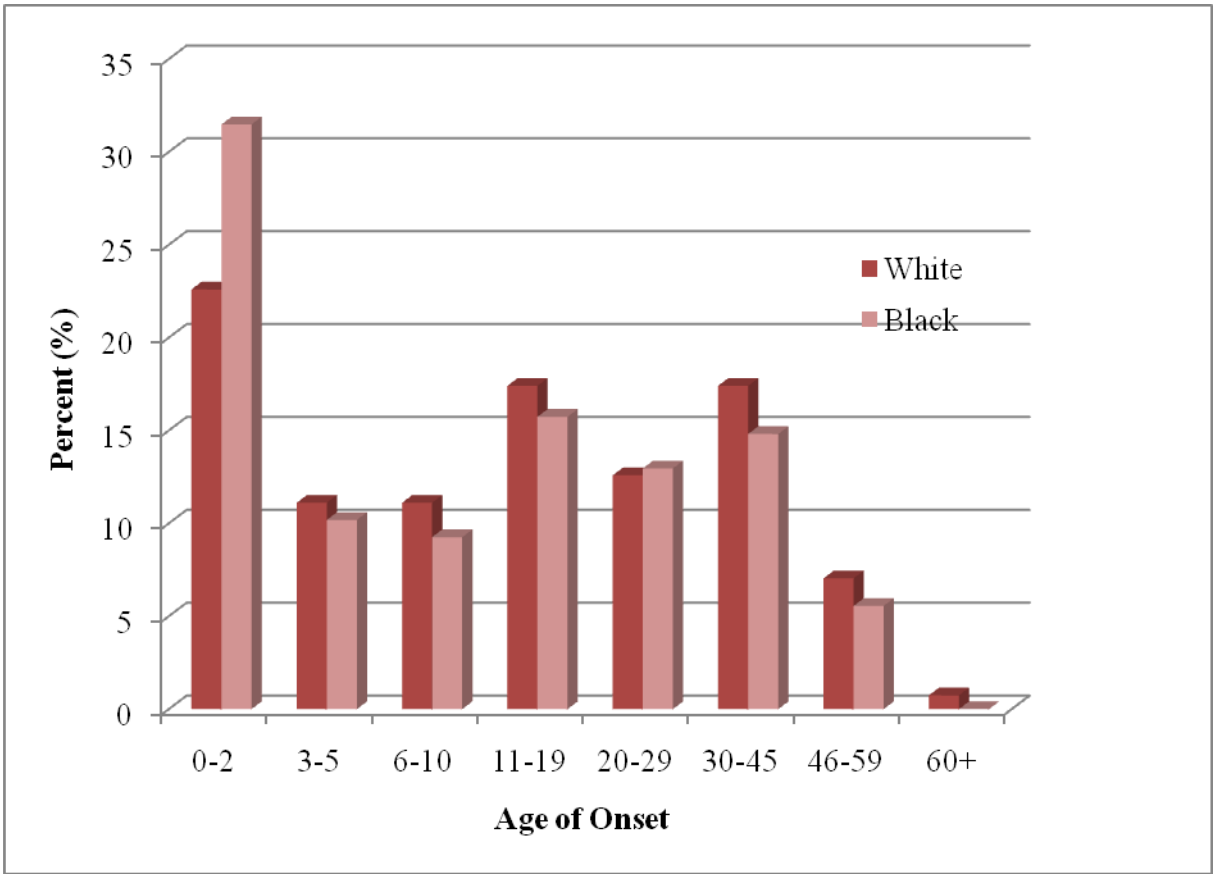

Figure 4 Percent of Black & White Population diagnosed with asthma in the Severe Asthma Research Program

4.0 THE PREDICTORS OF TOTAL SERUM IMMUNOGLOBULIN E IN BLACK ADULT ASTHMATICS IN THE SEVERE ASTHMA RESEARCH PROGRAM

4.1 INTRODUCTION

Severe asthma occurs in approximately 10% of those with asthma[1, 2]. Racial disparities appear to exist within the severe asthma population, Blacks often presenting with poorly controlled and more severe asthma as compared to their White counterparts[3]. Nationally, the mortality rates for asthma in Blacks range from two to five times those observed in Whites[4, 5]. It is very likely that a combination of genetics, the environment, and socioeconomics all play a role in this disparity[3, 5].

Immunoglobulin E (IgE) is a proxy measure of atopy and studies have shown that Blacks have higher IgE levels compared to Whites[3, 5, 6]. Total serum IgE was recently shown to be a risk factor for severe asthma in Blacks, but not in Whites. While total IgE has a hereditary component, multiple environmental and genetic factors are likely to contribute[7, 8]. Exposure to particular allergens, including D. pteronyssinus, cockroach, and Alternaria, has been strongly associated with the development of specific IgE. In Black children specific IgE to cockroach is known to be a risk factor for hospitalizations and days missed from school for asthma[9]. Its presence appears to require both a level of environmental exposure and genetic tendency to production of IgE[10]. However, whether specific IgE relate to severe asthma, as opposed to

poorly controlled (and perhaps undertreated) asthma is not yet clear[11-13]. Interestingly, sensitization to grass and ragweed have also been reported to be more likely in Black children[14]. These outdoor allergens in particular are often associated with extremely high levels of specific IgE that likely contribute substantially to the total measured IgE. However, whether they contribute to the total IgE associated with severe asthma in Blacks is not yet known.

In our previous study, family history of asthma was strongly predictive of severe asthma in association with IgE. Thus, in addition to IgE, genetics almost certainly plays a major role in the development of asthma, and more recently in Blacks with severe asthma[3, 5]. The Collaborative Study on the Genetics of Asthma (CSGA) revealed that Blacks, in particular, had a stronger family history of asthma as compared to Whites and concluded that the higher number of family members diagnosed with asthma in Blacks may reflect the "contribution of certain alleles with difference frequencies", as well as early exposures of Blacks to allergens[15].

As our previous study suggested that a higher IgE was a predictor of severe asthma in Blacks as compared to Whites[3], an analysis of the factors that predict a high IgE level in all Black asthmatics, as well as in those with severe disease was undertaken. As high IgE alone was not specific for severe asthma, a 2nd analysis was undertaken to identify the additional factors, which in the presence of high IgE associate with the development of severe asthma. To address these objectives, clinical, immunologic, and physiologic data from the cross-sectional National Heart Lung and Blood Institutes' sponsored Severe Asthma Research Program (SARP) database were analyzed in relation to IgE levels and asthma severity.

4.2 METHODS

4.2.1 Subjects

All data was obtained from subjects enrolled in the Severe Asthma Research Program, a network established to identify and characterize severe asthmatic subjects in relation to milder asthmatics to better understand mechanisms for their disease. The baseline characteristics of this population were recently published[3, 16]. SARP initially consisted of eight-funded sites- the University of Pittsburgh, the University of Virginia (subsites at Cleveland and Emory University), Brigham and Women's Hospital, Imperial College, National Jewish Medical and Research Center, Wake Forest University, Washington University, and the University of Wisconsin. The number of sites was reduced to 4 in 2006: University of Pittsburgh (including National Jewish), Cleveland Clinics (including the University of Virginia and Emory University), the University of Wisconsin, and Wake Forest University. Current smokers or individuals with five or more pack-years of tobacco use were excluded from SARP. This study was approved by the IRB affiliated with the University of Pittsburgh Medical Center.

From August 2003 until July 2010, 1391 subjects aged 18-79 years were recruited and enrolled, while 955 were White and Black participants had complete demographic and phenotypic information. The American Thoracic Society's (ATS) definition of severe asthma was used to determine whether individuals had severe/refractory asthma[1]. All subjects who did not meet criteria for severe asthma were classified as "not severe". Of the participants enrolled in SARP, 278 Black participants 18 yrs of age and older met criteria for not severe or severe asthma Participants with missing IgE data were excluded (n=69).

4.2.2 Data Collection/Measures at Interview

All subjects completed multiple (14) allergen skin testing evaluations for atopy, standardized and SARP specific questionnaires, collection of blood for complete blood counts and differentials and total IgE, exhaled nitric oxide and pulmonary function testing as previously described. Questionnaires were administered by clinical staff and included information on demographics, medical history, comorbidities, allergic exposures (own dog/cat, specific allergen sensitivity) family history, and smoking history, atopy (yes or no) was defined as a single positive reaction (consisting of a wheal at least 3mm in diameter and erythema of at least 10mm diameter) to any of 14 skin test allergens. The area of the wheal, calculated as the widest diameter of the wheal multiplied by the largest perpendicular wheal length for each allergen tested was calculated as an estimate of amount of specific IgE to a given allergen. Obesity was defined as participants with a body mass index (BMI) of greater than 30.

Baseline pre-bronchodilator spirometry testing was carried out for each subject. In addition, a maximal bronchodilator response was calculated as the greatest percent change from the prebronchodilator FEV_1 following 4-8 puffs of albuterol. A variety of other procedures were done on subpopulations of SARP subjects (methacoline, sputum induction, and bronchoscopy), but are not included in this study due to incomplete data primarily based on site specific testing (sputum) or exclusions on the basis of FEV1% predicted (sputum, methacholine) or subject preference (bronchoscopy).

4.2.3 Statistical Analysis

Statistical analyses were conducted using SAS software (SAS Institute Inc. 2008. *SAS Statistical Software: Version 9.2.*Cary, North Carolina) and STATA software (StataCorp. 2009. *Stata Statistical Software: Release 11*. College Station, TX). Categorical variables were examined using cross-tabulations and frequencies, [expressed as n (%)]. Chi-square (χ^2) or Fisher's exact test were performed for racial comparisons of categorical variables in the severe asthma group. The Wilcoxon-Mann-Whitney test was performed for racial comparisons of continuous variables in the severe asthma group [expressed as median (25^{th}-75^{th} percentiles)].

4.2.4 Univariable Models

Unconditional logistic regression was used to calculate the crude and adjusted odds ratios to estimate the probability of having a high IgE in general, and then having a high IgE in severe asthma. IgE group specific (low and high) models were used for this study. The median IgE for this population was used to determine the high and low IgE group. Participants with an IgE level below the median were classified as "low" while participants with an IgE level at or above the median were classified as "high". Univariable models were used to determine which variables to include for model selection and to exclude during the model building process, with only the variables with a p-value of less than 0.15 included. Variables with a p-value of less than 0.05 were considered highly significant.

4.2.5 Multivariate Models

Variables with a p-value of less than 0.15 in the univariable models were included for model selection. Forward stepwise model selection was used to determine the variables within the models. Goodness of fit of the model was assessed using Pregibon's Dbeta and Hosmer and Lemeshow's delta-d. Models were adjusted for age of enrollment (current age), clinical center, and gender. Variables with a p-value of less than 0.05 were considered significant.

4.3 RESULTS

4.3.1 Demographics

Demographics: All Black asthmatics by High and Low IgE (Table 1)

The median age at onset was lower in the high as compared to the low IgE group (p=0.017). Body mass index (BMI) was high for all Blacks, but higher in those with low IgE compared to those with high (p=0.058). There was a marginal difference in the diagnosis of diabetes between the IgE groups with the low IgE group tending to have more diabetes than the high group (p=0.051). Employment rates did not differ between the high and low IgE groups.

Demographics: Black Severe Asthmatics by High and Low IgE (Table 2)

Among the Black severe asthmatics, 47.4% were in the low IgE group and 52.6% were in the high IgE group. However, unlike the total population, there was no difference in age at onset between low and high IgE subgroups (p=0.462). Further, there was no difference in diabetes

diagnosis in severe asthmatics with and without high IgE. Similar to the total population, there was no difference in rates of employment in those high and low IgE.

Allergic Immune factors in All Asthmatics (Table 1)

Not surprisingly, participants in the high IgE group were more likely to be atopic and had more positive allergen skin tests compared to the low IgE group. Atopy was common in all Black asthmatic subjects, with nearly 90% of participants in the high IgE group atopic compared to almost 80% in the low IgE group ($p=0.016$). Asthmatic participants in the high IgE group were more likely to have multiple positive skin tests, including almost all the common indoor and outdoor allergens. 59% of all Black asthmatics with high IgE had 5 or more positive skin tests, while 28% of those in the low IgE group had 5 or more ($p<0.001$). The allergen that most significantly differed between high and low IgE subjects was grass mix (66% and 38% positive respectively, $p<0.0001$). In addition to "presence of a positive reaction", the median allergen wheal areas for multiple indoor and outdoor allergens were all significantly larger for the high IgE group compared to the low IgE group, with the largest wheals seen in response to grass and dust mite. Environmentally, pet ownership tended to be more likely in those with high IgE ($p=0.09$ for any pet, $p=0.02$ for furry pet other than cat or dog). Consistent with this more allergic phenotype, blood eosinophil counts were significantly higher in the high IgE group ($p=0.002$). Interestingly, while family history of allergies did not differ between the two group, the percentages of patients reporting this was numerically higher in the low IgE group (p-values <0.2). There were no differences in family history of asthma.

Allergic Immune factors in the Severe Asthma Population (Table 2)

As previously noted, atopy was less common in the Black severe asthmatics than in the total population irrespective of IgE. In contrast to all asthmatics, in severe asthmatics, there were

no differences with the presence of atopy by high or low IgE (p=0.497) and the percentage of participants with ≥5 positive skin tests was only marginally different (p=0.057). The high IgE severe asthma group was more likely to have positive skin tests for grass mix, ragweed, cockroach and D. pteronyssinus. Only the median areas for D. pteronyssinus and ragweed were greater in those asthmatics with high IgE, and all median wheal areas were markedly smaller than those in all Black asthmatics (for example, ragweed median in all asthmatics=38, median in severe asthmatics=0). In contrast to the total asthma population, there were no differences in pet ownership by IgE level. Similar to the differences in the total asthma population, blood eosinophil counts were also higher in the high IgE severe asthma group (p=0.045). In contrast to the total asthma population, there were no numeric or statistical differences between family history of allergies or asthma by level of IgE.

Pulmonary function in the All Asthmatics (Table 1)

While there were no differences in either FEV or FVC% predicted, the high IgE group had a significantly lower FEV_1 /FVC compared to the low IgE group (p=0.0003). Bronchodilator reversibility was also significantly higher in the high IgE group than in the low IgE group.

Pulmonary function in the Severe Asthma Population (Table 2)

Similar to all Black asthmatics, FEV_1/FVC and bronchodilator reversibility tended to be lower in the high IgE group (p=0.088 and p=0.072, respectively).

Corticosteroid use in the Severe Asthma Population (Table 2)

Systemic corticosteroid (CS) use was not significantly different between the high and low IgE group for Black severe asthmatics (p=0.1860). Half of the low IgE groups used systemic CS compared to 35% in the high IgE group.

4.3.2 Univariable Models

Factors predicting High IgE in All Asthmatics (Table 3a)

The presence of atopy or multiple positive skin tests (5 or more) each triples the risk of having high IgE in all Black asthma participants ($p<0.0235$, $p<0.0001$). Specific positive skin reactions to the outdoor allergens grass mix and ragweed in all Black participants increased the likelihood of being in the high IgE group by 3.5 fold and 3-fold respectively ($p<0.0001$ and $p=0.0002$). Positive allergen skin tests to indoor allergens such as cockroach and D. pteronyssinus, also increased the risk but to a smaller (2-fold) degree than outdoor allergens ($p=0.006$ and $p=0.0009$ respectively). Reactions to trees also doubled the risk, $p= 0.0110$. The area of the wheal for various allergens (Alternaria, grass mix, cat, dog, cockroach, D. pteronyssinus, tree, and ragweed) increased the odds of being in the high IgE group by about 1% for every 1 mm^2 change. Pet ownership tended to increase the odds of having a high IgE associated asthma ($p=0.09$), and having a furry pet, other than a dog or cat, increased the odds of having a high IgE more than 5-fold.

The diagnosis of diabetes marginally decreased the odds of being in the high IgE group by 70% ($p=0.061$), while obesity had no impact ($p=0.1792$). Family history of allergies tended to decrease the odds of having high IgE by about 40% (p-values<0.2) while family history of asthma was not significantly associated.

Factors predicting High IgE in the Severe Asthma Population (Table 3b)

Within the Black severe asthma group, allergic sensitization was still associated with being in the high IgE group, but in contrast to the total population, this was not significant ($p=0.3748$). In contrast, having five or more positive allergen skin tests more than doubled the odds of being in the high IgE group ($p=0.060$). Having a skin reaction to D. pteronyssinus or

ragweed also was associated with a high IgE in the Black severe asthmatic group (p=0.013 and p=0.014, respectively). The size of the ragweed and tree wheals increased the odds of being in the high IgE group by 2% for every 1mm^2 change (p=0.016 and p=0.05, respectively).

Pet ownership did not significantly impact the likelihood of having a high IgE in the Black severe asthmatic group. Neither obesity, diabetes, nor family histories of allergies or asthma were associated with IgE in severe asthmatics by univariable analysis.

Systemic corticosteroid use was not a significant predictor of high IgE in Black severe asthmatics (p=0.1879). However, the odds of having a high IgE were reduced by almost 50% when a severe asthmatic was using systemic corticosteroids.

Factors predicting severe asthma in those participants with High IgE (Table 4)

In the univariable models for participants in the high IgE group, lower FEV_1, FVC% predicted, FEV_1 /FVC, and obesity were all strongly and positively associated with severe asthma. Having diabetes, being unemployed, and having two or more family members with asthma were marginally associated with severe asthma. In contrast, 5 or more positive skin tests and many specific skin test reactions were negatively associated with severe asthma. Family history of allergies was not associated with severe asthma, while having several family members with a history of asthma greatly increased the odds of severe asthma (OR=2.75, p=0.06).

4.3.3 Multivariate Models

Factors predicting High IgE in All Asthmatic Population

After adjusting for age, clinical center, and gender, the amount and type of allergic sensitization were associated with having high IgE in Black asthmatics, while the presence or absence of atopy was not. Five or more positive skin tests increased the odds of having a high

IgE by 1.5 but it was not a significant predictor. Sensitization to D. pteronyssinus doubled the odds of having high IgE group for all asthmatics. Having a furry pet other than a dog or cat significantly increased the odds of having a high IgE by 5 (p=0.044).

Factors predicting High IgE in the Black Severe Asthma Population

In Black severe asthmatics, the presence of a positive skin test reaction to D. pteronyssinus increased the odds of having a high IgE by four (p=0.026), as compared to 2 in all asthmatics, The area of the ragweed allergen wheal also increased the odds of having a high IgE by 1% for every 1 mm^2 change in wheal size (p=0.036). Unlike the results in all asthma, having multiple (≥5) positive skin tests was not a predictor of high IgE.

Factors predicting severe asthma in those participants with High IgE

Participants in the high IgE group who had family members with asthma markedly increased the odds of having severe asthma, with the odds being four times higher if a participant in the high IgE group had one family member with asthma (p=0.056), and almost six times higher for 2 or more family members (p=0.014). A Black asthmatic in the high IgE group who is obese had nearly triple the odds of having severe asthma (p=0.045). Having a positive skin reaction to D. pteronyssinus lowered the odds of having severe asthma by over 60% but this was not significant (p=0.163). Interestingly, in the high IgE group, no lung function variable increased the risk for severe asthma.

4.4 DISCUSSION

In this study of Black asthmatics within the Severe Asthma Research Program, as expected, specific allergic sensitization is an important predictor of high IgE. In contrast, IgE itself, with

paradoxical protective effects of specific allergic sensitizations and positive contributions from genetics and obesity are the important predictors of severe asthma. While a stronger impact of total IgE to severe asthma than specific allergic skin reactions would not be surprising, the contradictory effects of the two clearly related factors remain difficult, but likely important, to understand.

Black race has been shown to be associated with increased sensitization to indoor and outdoor allergens[5]. Having a positive skin reaction to certain allergens is strongly associated with being in the high IgE group. Increasing area of the skin test reaction to ragweed increased the odds of being in the high IgE group for all asthmatics and for severe asthmatics, supporting the concept that ragweed specific IgE levels are contributing directly to the measureable total IgE. In Black severe asthmatics, D. pteronyssinus reactions produced a four-fold increase in the likelihood of being in the high IgE group, while in all asthmatics the increase was two-fold. In a post hoc analysis, reactivity to D. pteronyssinus increased the odds of being in the high IgE group by three in Black mild/moderate asthmatics after adjusting for confounders, compared to four in the severe group ($p=0.023$). This suggests a stronger influence of dust mite sensitivity to IgE levels in Black asthmatics, and perhaps particularly in severe asthma.

The protective effect D. pteronyssinus specific IgE to the development of severe asthma is particularly intriguing in Blacks with high IgE. On the one hand, high specific IgE to this dust mite allergen is associated with increased odds for high IgE in Black asthmatics, and severe asthmatics in particular. However, when predicting severe asthma in participants with high IgE, the D. pteronyssinus response is associated with decreased odds for severe asthma. The reasons for this paradox are not clear but may imply that although D. pteronyssinus specific IgE contributes greatly to the high total IgE, alternative (and not yet identified/measured in this

study) allergens contribute to the pathologic IgE. As all of our participants had asthma, we are unable to comment on the contribution of specific allergies or family history of allergies to asthma in general, rather only to severe asthma.

We previously showed that family history of asthma was an important predictor of severe asthma for Blacks, a relationship confirmed in the current analysis[3]. The results indicate that within the high IgE group, the additional factor of a strong family history of asthma greatly increased the odds of having severe asthma, which is apparently independent of IgE or allergies. The relationship of family history (and personal history) of allergies to the development of asthma has long been controversial, with the strongest predictors for asthma generally accepted to be a family history of asthma, as opposed to allergies[17, 18]. However, our data do support a "dose response" for asthma related genetic factors in that increasing the number of family members with asthma greatly increases the odds of having severe asthma in Blacks with high IgE.

This study clearly demonstrates an environmental contribution to high IgE levels. In all asthma, owning a furry pet other than a dog or a cat predicted having a high IgE level. Whether this is specific to a certain type of pet (i.e., rabbit) or is related to socioeconomic factors (more difficult to have a traditional pet in socioeconomically deprive households) remains to be addressed.

Over 50% of Black asthmatics in this study met criteria for obesity. Among Blacks in the high IgE group, obesity tripled the odds of having severe asthma compared to those who were not obese. The TENOR study of severe asthma also showed that Blacks were heavier and more likely to be severe[5]. A recent study of obesity in SARP began to tease out the relationship of obesity to severe asthma. In Black and White patients who developed asthma before the age of

12 (the majority of Black asthmatics), there was a linear relationship of increasing duration of disease with increasing obesity[19]. In this study, obesity (as opposed to duration of disease) was a predictive factor for severe asthma in Black asthmatics with high IgE levels. This would suggest that obesity per se, is more likely to be contributing to asthma severity as opposed to increasing duration of disease.

Surprisingly, in Black asthmatics with high IgE, no pulmonary function test predicted severe asthma. FEV_1 is generally one of the most robust predictors of severe asthma[20], such that the absence of these variables is particularly interesting. It suggests that IgE associated severe asthma in Blacks is more dependent on socioeconomic (obesity and employment) and immune factors (allergy) than lung function measures.

The results of this study suggest that systemic corticosteroids block the increased production of IgE in Black severe asthmatics, as the univariate results indicate that the use of systemic corticosteroids is more prevalent in Black severe asthmatics with low IgE levels. This would be consistent with systemic CS use decreasing allergic sensitization through effects on total IgE and the number of positive skin tests).

This study is not without limitations. The size of the total Black population in this study was small but as the group was further stratified into a severe asthmatic group or high IgE group, the numbers became even smaller. Approximately 25% of the Blacks within the original SARP dataset were excluded because they did not have reported IgE levels. Some important categorical variables, such as atopy and inhaled corticosteroid use, due to collinearity within the severe and high IgE group. Therefore, comparisons were limited.

In conclusion, our study suggests substantial differences in the factors that predict high IgE in all Black asthmatics compared to the severe asthmatics, with degree of allergic response

and environmental exposures more contributory in all asthmatics, and dust mite/ragweed reaction more specific to severe asthmatics. It provides intriguing clues that, in fact, certain allergens and a family history of allergies, as opposed to asthma, may protect against severe asthma or high levels of IgE. This study again highlights the need for genetic studies conducted within the Black population to identify the genes that make Blacks susceptible to severe asthma, among other diseases. Finally, the impact of obesity and employment on the presence of severe asthma in Blacks with high IgE continue to underline an additional (and theoretically addressable) contribution of socioeconomic factors to severe asthma in Blacks, thus which should be carefully included in all genetic studies.

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4.6 TABLES

Table 7 Baseline Characteristics of Low and High IgE Groups in Black SARP Population

Variable	Low n=103	High N=106	Pvalue
Female	80 (77.7%)	65 (61.3%)	**0.0104**
Age of onset (yrs)	12 (4,26)	7 (2,18)	**0.0174***
Current Age (yrs)	36.6 (29.1,43.0)	32.6 (24.6,45.3)	0.1942
Duration (yrs)	18.5 (10.6,29.8)	22.3 (14.4,29.7)	**0.1192**
BMI	32.5 (27.4,38.6)	30.1 (25.0,36.5)	**0.0582**
Currently employed	65 (63.1%)	65 (61.3%)	0.7901
Presence of atopy	80 (77.7%)	94 (88.7%)	**0.0164***
≥5 positive skin tests	29 (28.2%)	61 (59.2%)	**<0.0001***
Alternaria positive test	31 (30.1%)	42 (39.6%)	0.1942
Grass Mix positive test	39 (37.9%)	70 (66.0%)	**<0.0001***
Cat positive test	31 (30.1%)	48 (45.3%)	**0.0239***
Dog positive test	17 (16.5%)	26 (24.5%)	0.1604
Roach positive test	28 (27.2%)	48 (45.3%)	**0.0053***
Pteryn positive test	48 (46.6%)	74 (69.8%)	**0.0007**
Tree positive test	24 (23.3%)	43 (40.6%)	**0.0103**
Ragweed positive test	35 (34%)	63 (59.4%)	**0.0002**
Alternaria, area	0 (0,30)	0 (0,49)	**0.0598**
Grass Mix, area	0 (0,42)	49 (0,112)	**<0.0001***
Cat, area	0 (0,25)	8.5 (0,54)	**0.0105***
Dog, area	0 (0,0)	0 (0,20)	**0.1041**
Roach, area	0 (0, 20)	9 (0,55)	**0.0010***
Pteryn, area	9 (0,42)	48.5 (0,99)	**0.0004***
Tree, area	0 (0,12)	0 (0,36)	**0.0028**
Ragweed, area	0 (0,35)	37.5 (0,90)	**<0.0001***
Owns any pet	20 (19.4%)	31 (29.2%)	**0.0899**
Owns a cat	6 (5.8%)	8 (7.5%)	0.5927
Owns a dog	12 (11.7%)	18 (17.0%)	0.2474
Owns an “other” pet	2 (1.9%)	10 (9.4%)	**0.0173***
Log Eosinophil	-0.68 (-0.96,-0.51)	-0.60 (-0.96,-0.39)	**0.0023**
Diabetes	11 (10.7%)	4 (3.8%)	**0.0505**
Obese	62 (60.2%)	54 (50.9%)	0.1785
2ndhand smoke	33 (32.0%)	40 (37.7%)	0.3864
1 family member with asthma	33 (32%)	40 (37.7%)	0.3585
2+ family members with asthma	33 (32%)	31 (29.2%)	0.8741
1 family member with allergies	39 (37.9%)	34 (32.1%)	0.1895
2+ family members with allergies	44 (42.7%)	38 (35.8%)	0.1724
FEV1, liters	2.23 (1.75,2.58)	2.18 (1.71,2.71)	0.9756
FEV1 % predicted	77 (65,89)	75 (57,90)	0.2832
FVC % predicted	86 (77,99)	91.1 (76,103)	0.2836
FEV1/FVC	0.76 (0.67,0.81)	0.68 (0.59,0.76)	**0.0003***
Max FEV1 Reversal	11.7 (5.7,20.7)	17.7 (9.4,27.8)	**0.0041***

Table 8 Baseline Characteristics of Low and High IgE Groups in Black Severe SARP Population

Variable	Severe N=76		Pvalue
	Low N=36	High N=40	
Female	27 (75.0%)	26 (65.0%)	0.3434
Age of onset, yrs	13 (3.2, 28)	9 (1.5, 27)	0.4619
Current Age, yrs	41.0 (35.1, 47.7)	41.5 (30.9,48.2)	0.9875
Duration, yrs	25.0 (11.9,34.7)	23.8 (15.3,36.3)	0.6584
BMI	33.0 (29.3,41.6)	32.8 (26.9,36.7)	0.2816
Currently employed	22 (61.1%)	21 (52.5%)	0.4495
Presence of atopy	25 (69.4%)	31 (77.5%)	0.4965
≥5 positive skin tests	8 (22.2%)	17 (42.5%)	**0.0571**
Alternaria positive test	9 (25.0%)	12 (30.0%)	0.6474
Grass Mix positive test	13 (36.1%)	22 (55.0%)	**0.0892**
Dog positive test	7 (19.4%)	10 (25.0%)	0.5314
Roach positive test	8 (22.2%)	16 (40.0%)	**0.0762**
Pteryn positive test	9 (25%)	21 (52.5%)	**0.0110**
Tree positive test	9 (25%)	15 (37.5%)	0.2439
Ragweed positive test	7 (19.4%)	18 (45%)	**0.0114**
Alternaria, area	0 (0,24)	0 (0,32.5)	0.8421
Grass Mix, area	0 (0,39)	28 (0,80)	**0.0820**
Cat, area	0 (0,41.5)	0 (0,51)	0.4755
Dog, area	0 (0,75)	0 (0,4.5)	0.7727
Roach, area	0 (0,7.5)	0 (0,52.5)	0.1827
Pteryn, area	0 (0,7.5)	20 (0,71)	**0.0277***
Tree, area	0 (0,10)	0 (0,47)	0.3926
Ragweed, area	0 (0,45)	0 (0,84)	**0.0101**
Owns any pet	6 (16.7%)	12 (30.0%)	0.1725
Owns a cat	2 (5.6%)	1 (2.5%)	0.5999
Owns a dog	4 (11.1%)	8 (20.0%)	0.2898
Owns an “other” pet	1 (2.8%)	3 (7.5%)	0.6145
Log Eosinophil	-0.82 (-0.96,-0.68)	-0.54 (-0.96,-0.44)	**0.0450***
Diabetes	4 (11.1%)	3 (7.5%)	0.7041
Obese	26 (72.2%)	27 (67.5%)	0.6546
2ndhand smoke	9 (25.0%)	16 (40.0%)	0.2220
Systemic Corticosteroid use	18 (50%)	14 (35%)	0.1860
1 family member with asthma	11 (30.6%)	14 (35.0%)	0.3017
2+ family members with asthma	11 (30.6%)	16 (40.0%)	0.2012
1 family member with allergies	12 (33.3%)	10 (25.0%)	0.4434
2+ family members with allergies	13 (36.1%)	16 (40.0%)	0.8898
FEV1, liters	1.75 (1.43,2.23)	1.74 (1.35,2.18)	0.6967
FEV1 % pred	69.5 (58.5,80.5)	62 (47.5,80.5)	0.5121
FVC % pred	78 (72.6,97)	83.4 (68,95)	0.7279
FEV1/FVC	0.71 (0.61,0.79)	0.63 (0.53,0.72)	**0.0880**
Max FEV1 Reversal	12.4 (6.2,18.1)	17.7 (9.4,31.5)	**0.0719**

Table 9 Univariable Models for Black SARP Participants: Predicting the Odds of Having High IgE

Variable	OR	95% CI	Pvalue
Age of onset	0.977	0.956-0.998	**0.0294**
Currently Employed	0.927	0.530-1.622	0.7901
Presence of Atopy	3.819	1.198-12.177	**0.0235**
≥5 positive skin tests	3.638	1.998-6.624	**<0.0001**
Alternaria positive test	1.478	0.819-2.669	0.1951
Grass Mix positive test	3.461	1.897-6.316	**<0.0001**
Roach positive test	2.321	1.278-4.217	**0.0057**
Dog positive test	1.637	0.820-3.269	0.1625
Cat positive test	1.347	0.450-4.031	0.5939
Pteryn positive test	2.882	1.546-5.374	**0.0009**
Tree positive test	2.215	1.200-4.089	**0.0110**
Ragweed positive test	3.109	1.714-5.639	**0.0002**
Alternaria, area	1.006	0.999-1.013	**0.0893**
Grass Mix, area	1.005	1.001-1.009	**0.0094**
Cat, area	1.005	1.000-1.011	**0.0734**
Dog, area	1.011	0.998-1.025	**0.1070**
Roach, area	1.008	1.001-1.016	**0.0311**
Pteryn, area	1.006	1.002-1.010	**0.0050**
Tree, area	1.015	1.005-1.026	**0.0044**
Ragweed, area	1.012	1.006-1.018	**0.0001**
Own any pets	1.741	0.914-3.317	**0.0918**
Own cat	1.347	0.450-4.031	0.5939
Own dog	1.588	0.722-3.494	0.2500
Own “other” pet	5.439	1.161-25.485	**0.0316**
Log Eosinophil	1.340	0.750-2.395	0.3235
Diabetes	0.324	0.100-1.054	**0.0610**
Obese	0.687	0.397-1.188	0.1792
2ndhand smoke	1.289	0.725-2.291	0.3868
1 Family member with asthma	1.364	0.703-2.646	0.3590
2+ family members with asthma	1.057	0.534-2.093	0.8741
1 Family member with allergies	0.604	0.283-1.286	0.1909
2+ family members with allergies	0.598	0.285-1.255	0.1739
FEV1 % predicted	0.994	0.981-1.007	0.3728
FVC % predicted	1.009	0.993-1.025	0.2752
FEV1, liters	1.015	0.693-1.486	0.9396
FEV1/FVC	0.026	0.002-0.296	**0.0032**
Max FEV1 Reversal	1.025	1.007-1.044	**0.0074**

Table 10 Univariable Models for Black SARP Participants in the Severe Phenotype Group: Predicting the Odds of Having High IgE

Variable	OR	95% CI	Pvalue
Age of onset	0.989	0.960-1.020	0.4905
Currently Employed	0.703	0.282-1.753	0.4501
Presence of Atopy	1.860	0.472-7.323	0.3748
≥5 positive skin tests	2.715	0.957-7.699	**0.0604**
Alternaria positive test	1.275	0.449-3.620	0.6477
Grass Mix positive test	2.343	0.871-6.303	**0.0917**
Roach positive test	2.555	0.895-7.296	**0.0797**
Dog positive test	1.429	0.466-4.376	0.5323
Cat positive test	0.434	0.038-5.009	0.5038
Pteryn positive test	3.769	1.328-10.698	**0.0127**
Tree positive test	1.833	0.658-5.107	0.2462
Ragweed positive test	3.943	1.327-11.712	**0.0135**
Alternaria, area	1.002	0.991-1.014	0.6910
Grass Mix, area	1.005	0.998-1.011	0.1741
Cat, area	1.000	0.990-1.011	0.9346
Dog, area	0.995	0.971-1.019	0.6660
Roach, area	1.002	0.994-1.009	0.7040
Pteryn, area	1.007	0.998-1.016	**0.1480**
Tree, area	1.017	1.000-1.035	**0.0503**
Ragweed, area	1.015	1.003-1.027	**0.0155**
Own any pets	2.148	0.707-6.526	0.1776
Own cat	0.434	0.038-5.009	0.5038
Own dog	2.000	0.545-7.333	0.2958
Own “other” pet	3.000	0.297-30.345	0.3521
Log Eosinophil	1.548	0.655-3.659	0.3193
Diabetes	0.667	0.139-3.207	0.6129
Obese	0.799	0.298-2.138	0.6548
2ndhand smoke	1.855	0.684-5.027	0.2245
1 Family member with asthma	1.838	0.576-5.865	0.3036
2+ family members with asthma	2.101	0.668-6.604	0.2039
1 Family member with allergies	0.625	0.187-2.085	0.4445
2+ family members with allergies	0.923	0.297-2.865	0.8898
Systemic corticosteroid use	0.538	0.214-1.353	0.1879
FEV1 % predicted	0.997	0.976-1.018	0.7653
FVC % predicted	1.003	0.976-1.030	0.8438
FEV1, liters	1.008	0.470-2.162	0.9841
FEV1/FVC	0.079	0.002-2.998	0.1711
Max FEV1 reversal	1.039	1.002-1.076	**0.0366**

Table 11 Univariable Models for Black SARP Participants in the High IgE Group: Predicting the Odds of Having Severe Asthma

Variable	OR	95% CI	P-value
Age of onset	1.021	0.99-1.052	0.183
Employed	0.553	0.247-1.235	**0.148**
≥5 positive skin tests	0.408	0.174-0.958	**0.040**
Alternaria positive test	0.557	0.236-1.312	0.181
Grass Mix positive test	0.529	0.215-1.298	0.164
Roach positive test	0.833	0.361-1.926	0.670
Dog positive test	1.224	0.483-3.104	0.670
Cat positive test	1.032	0.448-2.377	0.941
Pteryn positive test	0.305	0.116-0.802	**0.016**
Tree positive test	0.938	0.407-2.158	0.879
Ragweed positive test	0.480	0.200-1.153	**0.101**
Alternaria, area	0.994	0.984-1.004	0.248
Grass Mix, area	0.997	0.992-1.002	0.230
Cat, area	0.995	0.987-1.003	0.198
Dog, area	0.981	0.960-1.003	**0.090**
Roach, area	0.998	0.989-1.007	0.706
Pteryn, area	0.992	0.986-0.999	**0.024**
Tree, area	1.001	0.991-1.010	0.860
Ragweed, area	0.999	0.994-1.003	0.499
Own any pets	1.076	0.453-2.555	0.868
Own cat	0.214	0.025-1.813	0.157
Own dog	1.394	0.498-3.901	0.527
Own “other” pet	0.753	0.182-3.111	0.695
Log Eosinophil	0.837	0.406-1.724	0.6288
Diabetes	5.417	0.543-54.0	**0.149**
Obese	3.000	1.316-6.837	**0.009**
2ndhand smoke	1.159	0.514-2.618	0.722
1 Family member with asthma	1.376	0.502-3.770	0.535
2+ family members with asthma	2.725	0.959-7.742	**0.060**
1 Family member with allergies	0.486	0.167-1.413	0.185
2+ family members with allergies	0.848	0.311-2.317	0.749
Systemic corticosteroid use	6.461	2.108-19.803	**0.001**
FEV1 % predicted	0.972	0.952-0.992	**0.0056**
FVC % predicted	0.970	0.948-0.992	**0.008**
FEV1, liters	0.233	0.111-0.489	**0.0001**
FEV1/FVC	0.010	<0.001-0.411	**0.015**
Max FEV1 Reversal	1.004	0.986-1.023	0.672

Table 12 Multivariate Model for Black SARP Participants: Predicting the Odds of Having High IgE

Variable	OR	95% CI	Pvalue
Age of onset	0.985	0.958-1.01	0.295
Have "other" pet	5.263	1.049-26.414	0.044
≥ 5 positive tests	1.584	0.732-3.425	0.243
Pteryn positive test	2.191	1.037-4.628	0.040
Ragweed, area	1.008	1.001-1.015	0.011

Table 13 Multivariate Model for Black SARP Participants in the Severe Phenotype Group: Predicting the Odds of Having High IgE

Variable	OR	95% CI	Pvalue
Ragweed, area	1.014	1.001-1.028	0.036
Pteryn positive test	3.896	1.174-12.930	0.026

Table 14 Multivariate Model for Black SARP Participants in the High IgE Group: Predicting the Odds of Having Severe Asthma

Variable	OR	95% CI	Pvalue
Obesity	2.784	1.021-7.589	0.045
Employed	0.393	0.141-1.096	0.074
Pteryn positive test	0.429	0.131-1.409	0.163
1 family member with asthma	3.850	0.965-15.354	0.056
2+ family members with asthma	5.704	1.425-22.841	0.014

5.0 POLICY RECOMMENDATIONS FOR REDUCING THE DISPARITY BETWEEN BLACK AND WHITE SEVERE ASTHMATICS

5.1 INTRODUCTION

Asthma is a complex respiratory disease that has been increasing in prevalence in the United States since 1980 despite advances in treatment. It is estimated that 32.6 million people (1 in 10 Americans) in the United States has had asthma at one point in their lives; while 22.2 million people (1 in 14 Americans) are currently diagnosed with asthma[1]. Among the over 20 million people with asthma, over 12 million have had an asthma attack within the past 12 months[1]. Asthma is associated with high morbidity and mortality. In the United States, about 30,000 people a day have an asthma attack, while 5,000 people have an emergency department visit and 1,000 people are admitted to the hospital due to their asthma[1]. Almost 11 Americans die each day due to their asthma, while 4,000 die annually from complications related to asthma[1]. Due to these statistics, asthma has become an increasing burden on the individual diagnosed with asthma and the American health care system, costing $19.7 billion annually[1].

5.1.1 Severe Asthma

Although there are treatments that can control asthma, there are still a small number of asthmatics (about 10%) that are not able to control their asthma despite the use of the highest

treatment level (i.e., high dose of inhaled corticosteroids (ICS))[2-4]. Individuals with severe asthma are characterized by their inability to have their asthma controlled with current available medications. They have persistent daily symptoms, daily bronchodilator use, asthma-related nocturnal symptoms at least once a week, and a force expiratory volume in 1 second of less than 75% predicted for their age, height, sex, and race[3].

Having lower lung function, a history of pneumonia, less atopy, and being Black has been shown to be associated with having more severe and frequent exacerbations, hence suggesting their contribution to the development of severe asthma[5,6]. Currently, there is no way to determine if a patient with asthma is at risk of developing severe asthma.

5.1.2 Economic Burden

Due to asthma being a chronic condition, use of daily medication is needed to control the disease; however, despite effective prophylactic therapy available to asthmatics, the prevalence and severity are steadily increasing. Asthmatics not properly managing their asthma by under-using medications have resulted in the health systems incurring substantial costs[7]. In addition, severe asthma continues to excessively contribute to the economic burden and costs of asthma due to the difficult nature of the disease[8]. In 2005, 1% of the total health care cost for the United States was attributed to asthma costs. Treating uncontrolled and severe asthma accounted for the majority of these costs[7].

Individuals with asthma tend to acquire a considerable financial burden because of their asthma[9]. Direct, indirect, and intangible costs to asthma care can negatively affect the individual with asthma and their family. Direct costs consist of costs associated with physician costs, hospital costs, and drug costs. Physician costs account for the smallest amount of asthma

costs. Typically, 20-25% of the direct costs for asthma are for hospital care such as in-patient care or emergency room care. Patients with more severe asthma tend to incur these hospital costs. Drug costs are the most expensive component of direct costs for asthma making up 37% of the total asthma direct cost. Poor compliance with asthma medication results in an increase in asthma morbidity, thus, resulting in an increase in the costs associated with asthma[7].

Indirect costs consist of resources that are lost due to the disease such as premature retirement, time off of work, absenteeism, or death. These costs occur only when asthma has become intrusive into the lifestyle of the individual. These costs vary depending on the severity of the asthma and age of the individual[7]. Hospitalizations and urgent care have resulted in almost $20 billion in annual asthma health care costs, direct and indirect included[1]. Absenteeism is a common problem associated with asthma morbidity. Every year, over three million days of work and ten million days of school are lost due to asthma[10].

Intangible costs occur when the quality of the individual's life is impaired. These costs also vary depending on the age of the individual and severity of the asthma[7]. Individuals with asthma may become depressed or feel as though their lives are very restricted or limited due to their asthma, thereby, resulting in a decrease in their quality of life. The more severe the asthma, the higher the costs associated with asthma care[7].

5.2 BACKGROUND

5.2.1 Racial Disparities

In 2002, it was reported by the Centers for Disease Control and Prevention (CDC) that the prevalence of asthma in Blacks was approximately 38% higher than Whites. The CDC also reported that the asthma morbidity was drastically higher in Blacks than Whites. Compared to Whites, Blacks had 225% higher hospitalization rates, a 200% higher asthma death rate, 30% higher frequency of asthma attacks, and a 380% higher rate of visits to the emergency room[11]. In 2008, the American Lung Association reported that 105.5 per 1000 Blacks had asthma compared to 782 per 1000 Whites[12] The cause for this disparity in asthma between Blacks and Whites is unknown, however, several studies have suggested a possible biological or genetic reason for the increased prevalence and severity of asthma in the Black population. The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study investigated the differences in asthma severity between Blacks and Whites[13]. In their study, they were able to show that Blacks were more likely to have severe asthma and use three or more long-term controllers. Black participants were also more likely to report not using their medication or taking medication on some days but not on all days resulting in Blacks having more asthma control problems.

Past studies have shown that Blacks with asthma report their asthma symptoms differently than their White counterparts. Blacks primarily report upper respiratory symptoms; whereas, Whites report lower airway symptoms which is associated with asthma-related symptoms[14]. This is likely to lead to asthma in blacks being undiagnosed.

5.2.2 Genetics

The etiology of asthma is unknown; however, studies have shown that asthma cannot be fully explained by environmental, social, cultural, or economic factors. With the availability of genetic mapping and the increasing popularity of genetic epidemiology in the past two decades, genetics has been shown to play a role in the development of asthma[15, 9, 16].

Unfortunately, there were a limited number of studies that have looked at the genetic link to asthma; therefore, it is unknown how much genetic susceptibility contributes to the development of asthma and the disparities in asthma[15]. The limited studies have, however, shown that individuals of African descent have more severe asthma than those of European descent[15]. It is difficult to completely understand the role that genetics plays in the development of asthma for Blacks due to most of the genetic studies being underpowered and the variety of environmental factors that are unique to Blacks[16]. These environmental factors further support the theory of there being a gene-by-environment interaction associated with asthma, especially in Blacks[14].

5.2.3 Allergic sensitization

Allergies have been shown to play a major role in the development of asthma. Asthma has been often described as an atopic disease, with atopy being defined as skin prick test (SPT) positivity or the development of IgE in response to environmental allergens. Pearce et al describes the paradigm between asthma and allergies as the exposure to allergen causing sensitization and continued exposure leading to clinical asthma[17]. A meta-analysis carried out by Pearce et al showed that on average there were approximately 37% of asthma cases that were attributable to

atopy in adults[17]. Although atopy and asthma have been frequently studied, the relationship and its influence on asthma severity are complex and not well understood.

Exposure to allergens is known to be associated with increased airway hyperresponsiveness, asthma symptoms, and severe asthma. Cockroaches and dust mites are examples of indoor exposures that have been shown to be associated with asthma severity[18]. Dust mites have been shown to trigger asthma attacks and increase asthma symptoms, more so among those living in the inner city. Positive allergen skin tests to cockroaches have also been linked to asthma severity with a higher incidence of positive skin tests in Blacks[18, 14]. Togias et al suggested that there may be genetic factors that are involved with the higher sensitivity to cockroaches in the Black population, mainly Black population in inner cities; hence, signifying a strong association to environmental exposures for Blacks[19].

5.3 PRE-EXISTING POLICY

There is currently no existing legislation regarding severe asthma nor asthma in adults. Most pending legislation or policy regards the management of asthma within children in schools. It can be inferred that legislation or policies concerning the management of asthma in adults would not be effective because of the difficulty in changing the attitudes and behaviors of adults. However, there has been legislation related to risk factors for developing severe asthma, such as smoking. The introduction of smoking bans have decreased the amount of secondhand smoke that asthmatics have to encounter during their daily lives[20]. The smoking legislation prohibits smoking in public places, as well as in the workplace.

5.4 RECOMMENDATIONS

Reducing racial disparities in severe asthma, and asthma in general, has been difficult to accomplish. The gap between White and Black asthmatics still exists; therefore, I present five recommendations that would lead to closing the gap between the races. The recommendations focus on both the asthmatic and the health care system.

1. Improve and increase asthma education among Black asthmatics.

Asthma has become a disease that is common and underestimated; hence, lowering the importance of being educated about the disease and its possible deadly effects. Asthmatics must be educated about the disease process to completely understand the disease that they are dealing with and how to effectively manage the disease. Asthmatics must be taught how to correctly use their inhalers and what are the appropriate emergency procedures that must occur in the instance of an exacerbation. Asthmatics, mainly severe asthmatics, must have access to a primary care physician who is familiar with their medical history and can monitor their disease and make changes as deemed necessary. Also, asthmatics must be made aware of the allergens that have the potential to cause exacerbations or worsen their asthma. Because it is unclear as to how severe asthma develops or if individuals with mild or moderate asthma will develop severe asthma, asthmatics must be educated on the risk factors associated with severe asthma.

Community education fairs, hospital educational sessions, or trained community advocates can be utilized to help disseminate the information that will educate asthmatics about their asthma. This information is very important to severe asthmatics and should be provided at each visit to a medical facility, including the emergency department.

2. Improve asthma management for Black asthmatics.

According to the American Lung Association, “adequate healthcare is integral to reducing the burden of asthma”[12]. Black asthmatics, including severe asthmatics, must have access to proper preventive care and treatment, so that they can no longer use the emergency department as their primary care when an asthmatic episode occurs[12]. Management of asthma is essential to reducing the prevalence of asthma in Blacks. Research has shown that children with a management plan are less likely to have asthma symptoms; however, Black children were less likely to have a management plan compared to their White counterparts[12]. There is a need for this population to improve adherence and compliance when it comes to their asthma, such as adhering to scheduled appointments or prescribed medical regimens. The Halm study revealed that low-income, inner-city patients believed that they only had asthma when they were symptomatic, which was associated with lower inhaled corticosteroid use (ICS)[21]. Similarly, the Lee study showed that Black adults were less likely to use their ICS inhaler compared to White adults due to the negative beliefs associated with ICS therapy in Black patients[22]. Black patients felt that there was less of a need to use a controller for their asthma if their asthma symptoms did not occur frequently or daily. This contributes to poor asthma control, which in turn leads to the delay in diagnosing severe asthma and the increased use of emergency department care due to the prolonged treatment of asthma[23].

Studies have shown that allergy testing is not a routine component of treatment for asthma; therefore, individuals do not have specific documentation as to their allergic status that may motivate them to take positive steps to improving or managing their health[24]. The TENOR study revealed that there needs to be more of an emphasis on allergy testing within the Black population to better manage the asthma in this population[13].

Lung function is correlated to asthma severity. Asthma severity can be measured according to the potential for frequent exacerbations and the degree of airway obstruction (disease severity) measured as baseline forced expiratory volume in one second (FEV_1)[13]. In Gamble et al, pulmonary function was highly associated with severe asthma [25]. This fact illustrates the need for mandatory spirometry testing for every patient who displays the symptoms of asthma and those who have been diagnosed previously with asthma.

Health care providers must be trained and educated on the racial differences in asthma to effectively treat the disease in the Black population. Blacks have been shown to describe their asthma problems differently than their White counterparts[14]; therefore, providers must be proactive in testing Black patients who present any breathing problems for asthma. Providers must also be aware of the National Asthma Education Prevention Program (NAEPP) guidelines and adhere to them. Referrals of Black asthmatics to pulmonologists and allergists by primary care providers must be routinely done to ensure the patient is getting the appropriate care to manage their asthma.

3. Utilize racial and ethnic disparities in severe asthma to develop appropriate health care interventions.

Access to quality medical care is correlated with access to health insurance. While the number of Black asthmatic children having access to health care has increased due to the creation of the State Children's health Insurance Program, the number of Black adult asthmatics having access to health care has steadily decreased[26]. This issue has contributed to the racial disparity seen in asthma.

A report by the Institute of Medicine revealed that there are systemic health care factors, such as stereotyping, bias, and clinical uncertainty, which contribute to the racial disparity in

asthma[23]. The Okelo study showed that physicians often underestimate asthma severity in minority patients. Studies have shown that Black asthmatic children received fewer controller and reliever medications compared to White asthmatic children[27]. Also, Black adults reported having fewer medication recommendations from providers than White adults. In regards to asthma management, fewer Black adult asthmatics reported receiving education on self-management of asthma. Providers must adhere to NAEPP guidelines, which lead to a reduction in health care utilization (emergency department visits, hospitalizations, etc) by asthmatics. Also, communication between physicians and Black asthmatic patients is critical to improving asthma care in Blacks and reducing the racial disparity[27].

Increasing the number of physicians working in low-income areas will help to reduce the racial disparity seen in asthma and severe asthma. Medical students, medical residents, and physicians should be given incentives to work in neighborhoods that do not provide access to quality health care. Underdiagnosis of asthma contributes to the racial disparity; hence, the increased access to medical care can aid in reducing the disparity.

Due to the differences in the genetics of Black and White asthmatics, there is a need to differentiate between the medications used to treat asthma in the two populations. The TENOR study has suggested that there be customized treatment regimens and education strategies specifically for Black asthmatics[13]. This is preferred due to recent study results showing the increase in mortality of Blacks using LABA[13].

4. Conduct more research studies, mainly genetic studies, with Black participants.

Studies have shown that there may be an environment-genetic interaction occurring in the development and severity of asthma. To effectively study the disease in Blacks, researchers must be cognizant of the fact that Blacks tend to be exposed to different environmental factors

compared to their White counterparts. Black race is associated with more exposure to indoor and outdoor pollution such as secondhand smoke, diesel emissions, and lead. Also, studies have shown that Blacks may have genes that make them susceptible to more severe asthma[13, 16]. The American Lung Association has suggested that due to the complexity of asthma and the varying levels of genetic and environmental factors that are influential in the asthma process, researchers must conduct large studies on Black populations[12]. In order to properly treat and manage severe asthma in Blacks, there needs to be an increase in the amount of studies conducted with Black participants. Most studies either do not have Black participants or there is a dismal amount of Black participants, which result in a very low, if any, external validity[12, 16]. Relatively few genetic studies have included Blacks, as well as other minorities. This is disappointing given the "potential impact of genetic studies on reducing disparities in the prevention and treatment of asthma"[16]. There is also a need to not only have more asthmatic Black participants but also more Black healthy controls to determine the true effect of the environment and genetics on the Black asthmatic population.

One possible solution to this problem is for researchers to make a presence in Black communities and to use these resources to recruit healthy and asthmatic Blacks. Due to the Black community having distrust with the medical system, this is an important step to ensure that asthma is Blacks is well studied and, eventually, managed. Properly training investigators and using investigators who are highly motivated to study asthma in the Black population can overcome the issue of low recruitment of Blacks.

5. Introduce more legislation regarding risk factors for asthma and severe asthma in adults.

Due to the growing number of lawyers being trained in public health law, there has been an increase in the introduction of more regulations or legislation focused on improving the public's health. The smoking ban is one success in the field of public health law that has aided in reducing the detrimental effects of air pollution on asthmatics; however, there is a need for more legislation or policies regarding risk factors associated with severe asthma. Possible legislation can focus on the reduction of diesel emission in urban neighborhoods, the increase of city parks that are conducive for physical activity, creation of funds for low-income or uninsured individuals with chronic diseases to help pay for preventive and disease management services, and mandatory allergy testing for every asthmatic treated at a medical facility. The American Lung Association continues to publish the "State of Lung Disease in Diverse Communities" but it is not published every year, unlike their numerous tobacco reports. This report should be used by local, state, and federal governments to ascertain future directions for legislation, policies, and regulations to eliminate asthma, as well as other lung diseases. Robert Wood Johnson Foundation's Allies Against Asthma coalition was created primarily to reduce the racial and economic disparities within childhood asthma through the use of policy to change the current state of asthma[28]. Creating a similar coalition focused on adult asthmatics, mainly severe asthmatics, would aid in creating effective legislation to reduce the racial disparities in adult asthma.

5.5 CONCLUSION

In conclusion, these recommendations will have a tremendous effect upon the life of the asthmatics and the health care system. The cost of health care is very high for asthmatics and even higher for severe asthmatics [7]. Education, asthma management plans, research studies with large Black populations, and asthma regulations will decrease the costs of health care for the asthmatic and health care system dramatically if they are followed; therefore, it is imperative that these recommendations be implemented to reduce the racial disparity seen in asthma and severe asthma.

5.6 REFERENCES

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6.0 DISSERTATION WORK LIMITATIONS

The cross-sectional study design is a limitation of this study. It is difficult to confirm a temporal relationship in regards to severity and the variables of interest. Did the severity result in high BMI, low quality of life, or breathing problems or is this relationship the reverse? Were some individuals categorized as mild or moderate before they became severe or did they always have severe asthma? Another concern is the lack of incident data that could strengthen the data. Only prevalent cases can be studied in this project. There are many questions that cannot be answered due to the disadvantages of this study design.

Another limitation is the lack of data on the subject's type of health care insurance, marital status, education, and income. The first aim of this study focuses on health care utilization. The disparity that may be seen once this aim is analyzed may be explained more if an insurance variable were added. Including an insurance variable could have strengthened the analysis for this aim. To effectively look at the racial disparity in health care utilization, it is important to see the role of insurance in this relationship. Also, demographic and socioeconomic variables such as education and income have been shown to influence the relationship between race and asthma severity. This study was not able to analyze the impact of these variables on that relationship. Marital status would have been an interesting variable to analyze since there are no known studies that have looked at this variable in relation to asthma severity in Blacks and Whites. It is better to have a complete "picture" of the disparity among individuals in the severe

phenotype group and these variables would have provided more information on the disparity in severe asthma.

Lack of power may be an additional limitation in this project for the last specific aim, comparing mild/moderate and severe asthma groups among Blacks in SARP. This analysis would be important to look at to determine if there is more to the disparity between the two severe groups (Blacks and Whites) than race. There could be additional factors that add to the disparity seen in asthma and severe asthma for Blacks. There is the possibility that another variable within the dataset explains some of the disparity seen in many studies and possibly this study.

The number of Black participants was significantly smaller than the White participants. In paper two, the small number of Black participants got smaller when breaking the group down into Black severe asthmatics and Black asthmatics with high IgE.

7.0 FUTURE RESEARCH DIRECTIONS

This research has led to the suggestion of several possible studies and analyses in the future. First, due to the low number of Black participants in genetic studies and the clear disparity between Black and White severe asthmatics, a genetic epidemiology study must be conducted with Black participants. Second, an analysis should be carried out to look at the influence of socioeconomic variables on asthma severity in Black and White asthmatics. Third, pet ownership was shown to be a predictor of high IgE in Blacks. This association should be looked into further to determine the true effects of the variable. Fourth, a seasonal allergen study should be conducted. Blacks have been shown to be highly sensitized to indoor and outdoor allergens. Looking at the month of birth and allergens to determine if there is a certain time of year when severe asthmatics were born is another suggested future study. Lastly, Blacks have more severe asthma, more health care utilization due to their asthma, and disparate treatment of their asthma compared to Whites. Quality of life are affected by these variables and more so it would be important to look at the effect of severe asthma on a Black asthmatics life compared to their White counterpart. The SARP study is steadily increasing their Black population to carry out some of these suggested studies.

8.0 PUBLIC HEALTH SIGNIFICANCE

Asthma has a financial and emotional burden on asthmatics and their families, especially if they have the severe form of this disease. If severe asthma is controlled, the financial burden to the individual and family will be reduced; therefore, increasing their income[18]. Asthma control is imperative to the management of asthma, especially in Blacks and low-income individuals. There are several public health implications that can arise out of this project and future projects based on these analyses. The results of this project show a racial difference in asthma pathophysiology, which can result in the need for different treatment and management of asthma in Blacks and Whites. Compared to their White counterparts, Blacks may be predisposed to more severe asthma and frequent asthma exacerbations. Due to the link between atopy and asthma, it is important to ensure that asthmatics are tested for allergies; however, the relationship between positive SPTs and severe asthma is not conclusive. This study could raise the possibility that there is an association between the two, mainly in Blacks. The role that eosinophils play in asthma pathogenesis has been a topic of debate. This study may provide more information about eosinophils, SPTs, and asthma severity. Past studies have, also, shown that Blacks have a smaller lung capacity than Whites. This result, combined with others, led to the introduction of a race corrected FEV_1. The results from this study can also have a similar impact on clinical care. GINA guidelines and pocket references have been updated and in use around the world; however, the control and management of asthma has continued to be a challenge for asthma care,

mainly for Blacks and other minorities. The results from this study can help to inform and reiterate the need for the training of clinicians in the area of physician-patient communication and cultural/racial beliefs. Clinicians need to actively listen and communicate with patients, especially Black patients, to ensure that they are educated about their asthma (health literacy), diagnosed earlier to avoid severity, and receiving quality and equitable care. The management of asthma can lead to the improvement of the quality of life of patients, decrease absenteeism at work or school, and decrease the prevalence of severe exacerbations. A decrease in the amount of dollars used to pay for the excess of medical resources that are used by asthmatics is also another result of effectively managing asthma. This project will add to the current knowledge about the racial differences in asthma severity.

This study also highlights the need for the important role that IgE plays in Black asthmatics and the needs for genetic studies to further understand its role in the development of severe asthma in Blacks. The role of sensitization to specific allergens such as dust mite and cockroach in Blacks was highlighted in this study. Also, this study eludes to the fact that there could be possible ways to identifying severe asthma in Blacks and Whites, which could aid in the early detection and treatment of problems associated with asthma severity. Genetics, mainly family history of asthma, and allergic sensitization were shown to be predictors of severe asthma in Blacks; while comorbidities, such as diabetes and hypertension, were predictors of severe asthma in Whites.

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