DEDICATION

This work is dedicated to all families who have lost a child to asthma.

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LIST OF ABBREVIATIONS

A-A........................................................................African-American
BMI.......................................................................Body Mass Index
CDC.................................................................Centers for Disease Control
CI.........................................................................Confidence Interval
ED.........................................................................Emergency Department
EMS.................................................................Emergency Medical Services
ICD-10...........................................................International Classification of Disease, 10th Revision
ICU.................................................................Intensive Care Unit
LABA.......................................................................Long-Acting Beta Agonist
ME.........................................................................Medical Examiner
NC........................................................................North Carolina
NC DETECT............. NC Disease Event Tracking and Epidemiologic Collection Tool
NHIS............................................................National Health Interview Survey
NVSR.............................................................National Vital Statistics Report
OCME.............................................................Office of the Chief Medical Examiner
PICU.................................................................Pediatric Intensive Care Unit
PrEMIS...........................................................Pre-hospital Medical Information System
RUCC..............................................................Rural-Urban Continuum Code
SABA.......................................................................Short-Acting Beta Agonist
SES.......................................................................Socioeconomic status
SUDDEN.....................................................Sudden Unexpected Death in North Carolina
US ........................................................................United States
Asthma is chronic reversible obstruction of the small- and medium-sized airways of the lung. It is caused by inflammation of the airway mucosa coupled with spasm of the circumferential smooth muscles that may be triggered by viral infections, environmental allergens, or other irritants. Early in the disease process, this leads to airway obstruction and impaired airflow, which can be reversed with medical therapy. With exacerbations of asthma, the goblet cells of the airway mucosa also release mucous secretions into the airways, which can further obstruct the airway lumen. Severe exacerbations of asthma with significantly reduced airflow can potentially compromise gas exchange in the alveoli. Over time, remodeling of the airway occurs with more chronic inflammation, and irreversible obstructive changes can occur. Once these changes have taken place, the disease may be less responsive to treatment.

Asthma is treated by two broad categories of medications – anti-inflammatories and bronchodilators. Anti-inflammatories include corticosteroids as well as other classes of medications that act to decrease the underlying inflammation of the airways. These drugs may be administered in inhaled, oral, or parenteral forms and are used both on a daily basis to help prevent symptoms, and at higher doses to treat acute exacerbations. Bronchodilators are typically administered by the inhalational route and are used to relax the smooth muscle spasm of the airways. Short-acting beta agonists (SABAs) are generally used as “rescue” therapy to relieve acute symptoms, whereas long-acting beta-agonists (LABAs) are generally used as part of a maintenance or preventive regimen.
The clinical diagnosis of asthma is generally made by observing a pattern of recurrent bronchospasm that responds to asthma medication. The diagnosis is supported by pulmonary function testing, which can show airflow limitation that improves with administration of a bronchodilator. Asthma can be a challenging diagnosis to make in children, who are less able to accurately report symptoms. Additionally, children under 6 years of age may have difficulty performing standard pulmonary function testing. Therefore, diagnosis in children is often made based on parentally-reported history of recurrent symptoms consistent with asthma that respond to asthma medications.

Asthma is the most common chronic medical condition of childhood. Between 1980 and the mid-1990s, the period prevalence of asthma steadily increased among children [1]. Because of a redesign of the National Health Interview Survey (NHIS), estimates from this time moving forward are not comparable to earlier figures [2]. In 2003, North Carolina (NC) was in the second-highest quartile of US states for current asthma prevalence (8.7-10%) [1]. According to the 2010 report *The Burden of Asthma in North Carolina*, current asthma prevalence among the state’s children decreased from 11.5% to around 8% from 2005 through 2008, but then increased to over 10% in the years leading up to 2010 [3]. The asthma prevalence among NC children in 2010 was 15.5% for those with public insurance and 7.6% for those with private coverage [3].

Despite the relatively high prevalence of asthma, fatalities are a rare occurrence, especially among children. Asthma fatalities rates have generally followed trends seen in asthma prevalence over the past several decades. Using cause-of-death data, the
asthma fatality rate in the US increased from 1980 to 1995 and began to decline from 1996 to 1998 [4-7]. With the 1999 implementation of the tenth revision of the International Classification of Disease (ICD-10) as the means for categorizing cause of death, a sudden downward shift of approximately 10% was observed in the reporting of asthma mortality [5, 8, 9]. Thereafter the decline has continued through the early twenty-first century. According to the National Vital Statistics Report (NVSR) published by the Centers for Disease Control and Prevention (CDC), during the period of 1999-2012, the overall rate for all ages and races in the US has gradually decreased from 1.7 to 1.1 per 100,000 individuals [8, 10-22]. The asthma death rate among children has mirrored this pattern, with an increase thought the mid-1990s and decrease thereafter [1, 23]. Overall asthma mortality rates in NC generally exceeded national rates for 2000-2010, but followed a general trend of decrease [3].

Most death rate calculations use only individuals for whom asthma is listed as the primary cause of death. McCoy et al utilized both primary and contributing causes of death in their study of US asthma deaths from 1990-2001, and reported that use of only the primary cause of death may underestimate the incidence of asthma-related mortality [5]. This discrepancy was more pronounced with older age at death. They report that using just the primary cause will capture only 65-80% of the deaths in those under 24 years of age in which asthma is listed among all causes. These data must be interpreted with caution, however, as the listing of asthma as a contributing cause does not give any information about the extent to which asthma contributed to the death. The authors also note that temporal trends and disparities observed in their approach mirror those seen when using only primary cause of death data, suggesting that the standard approach is sufficient for identifying relevant risk factors [5].
The primary focus of the proposed study is a descriptive analysis of fatal asthma cases among children, with the goal of identifying important covariates for future research. Few studies exist which specifically address asthma mortality in children. As fatal asthma is an uncommon event, most of the data regarding autopsy findings are from single case reports and small series, mostly including adults. Often the numbers of young decedents in combined series are too small to make any meaningful conclusions about risk factors that may be unique to children. Because of their retrospective nature, these studies are subject to unavoidable biases. Nonetheless, existing data will be reviewed below, with limitations noted.

This review will first address specific potential risk factors for asthma death as determined in previous studies. It will then briefly describe factors associated with referral of asthma deaths for autopsy, and will describe typical findings on autopsy in asthma fatalities. The focus will mainly be on data from studies published from 1999 onward, which is the time frame that will be used for our proposed study. As ICD-10 was implemented in 1999 for recording causes of death, comparisons across this time point may be subject to systematic bias [5, 9]. As the number of effective therapies for asthma has increased over time, older studies may not be clinically relevant to asthmatics today. The pharmacotherapy of asthma has improved greatly with the more regular use of inhaled corticosteroids, which have been associated with reductions in mortality [24]. Finally, the review will focus on data from US populations, as these will be most comparable to our study population of children in NC. International studies will be cited when data from the US are sparse, or to highlight key differences.
General Clinical Characteristics

A 1996 study explored 108 cases of sudden death due to asthma among children and young adults through medical and autopsy records, as well as interviews with next-of-kin. The authors found that, in most cases, the fatal attack was associated with an identifiable trigger, delay in seeking medical attention, and rapidly worsening clinical status [25]. The fatal asthmatic was typically one with disease onset early in life, severe disease requiring systemic corticosteroids, and history of prior hospitalizations [25]. Increased bronchial reactivity, incomplete response to treatment, and reduced perception of impairment may be important risk factors for asthma death [26]. A small case-control study from 1986 found that cases of fatal asthma in childhood were more likely to have disregard of wheezing, more complicated and/or severe asthma, and a number of psychological and social risk factors [27]. Similarly, a case-control study of asthma deaths in individuals aged 5-50 years in Canada found poor symptom control, recent cold symptoms, and depressive symptoms to be more common in fatal than non-fatal asthma [28]. Hyzy et al found that patients who died of a rapid-onset fatal exacerbation had less healthcare utilization in the last year of life compared to cases in which the symptom onset was more gradual [29]. Self-denial or poor self-care was also cited commonly in a small case series by Hannaway [30].

One study that tracked use of inhaled corticosteroids showed a trend towards a protective effect against fatalities [31], and of the 22 patients in one fatal asthma cohort, few were on inhaled corticosteroids [32]. Nonetheless, those who die of asthma are frequently on multiple medications, which may be interpreted as a marker for increased
disease severity. A systematic review of papers published 1960-2004 found that increased use of asthma medications was associated with increased risk of both near-fatal and fatal asthma [31]. Hannaway reported 20 cases of fatal asthma among adults and children, 16 (75%) of whom were taking inhaled corticosteroids [30]. More than half of the total cohort were described as having excellent or good compliance with medications, but overuse of inhaled beta agonists was reported in nine (45%) [30]. An inverse association has been reported between death from asthma and prescriptions filled for antibiotics and oral steroids in asthmatics under 45 years of age [33]. Approximately 19% of decedents in one series had adrenal cortical abnormalities, presumably due to chronic use of corticosteroids [25]. Large decreases in steroid dosing may put children with asthma at increased risk for death [27].

Psychological comorbidities likely increase the risk for asthma fatality, and they are often part of a complex milieu [27, 34]. A case-control study of childhood and adult asthma deaths in Canada found depressive symptoms to be more common in fatal than non-fatal asthma [28]. Depression may affect medication adherence and perception of symptoms. Additionally, Miller et al have proposed a physiological mechanism whereby airway obstruction may be worsened in depressed children; children with both asthma and depressive symptoms may show more “vagal bias” when stressed, thus predisposing to increased airway resistance [35].

“Near Fatal” Asthma

The term “near fatal” or “potentially fatal” asthma has been used in many studies to describe severe asthma with exacerbations requiring intensive management. These are
often considered to be cases that came very close to resulting in fatality. No consistent
definition exists across studies of what constitutes a near or potentially fatal asthma
attack, but the terms generally indicate an episode in which the patient receives care in
an intensive care unit (ICU). In these cases, the patient may or may not require
intubation and mechanical ventilation. Although such patients are often studied to
examine risk factors for asthma fatality, it is unclear whether patients who experience
near fatal events are more likely to ultimately have a fatal event, and whether fatal and
near fatal attacks have the same risk factors.

Intubation, or the use of a breathing tube inserted to facilitate mechanical ventilation, is
generally thought to be a marker for a life-threatening asthma exacerbation. It is unclear,
however, if intubation, either with a current or prior episode, indicates increase risk of
mortality. A study examining 261 pediatric ICU (PICU) admissions for asthma over eight
centers noted that 96% of patients intubated for severe asthma exacerbation survived to
discharge; most who died had experienced cardiac arrest prior to PICU admission [36].
In comparing near-fatal to fatal asthma cases among both adults and children, Strunk et
al found only two statistically significant predictors for fatal events: rapid progression of
symptoms and lack of a history of prior intubation [37]. In a case series of five adult
subjects with sudden-onset fatal asthma (within one hour of onset of symptoms), two
were considered to be mild, while one had a previous near-fatal attack requiring
mechanical ventilation [38]. Hannway reported that half of fatal and near fatal attacks
occurred in younger, stable, and reportedly compliant asthmatics [30]. Taken together,
these studies indicate that prior history of a near fatal event is far from universal in
asthma fatalities. Furthermore, they suggest that a subset of patients exists with more
mild asthma, or at least whose asthma severity is underestimated, at the time of the fatal attack.

**Age**

Asthma death rates increased through the 1980s and early 1990s with the fastest increases seen among those ages 5 to 14 years of age [6, 23]. Despite this increase, asthma death is rare even among children, even though the morbidity of childhood asthma is high [1]. Only 8% of the total number of 2012 US asthma deaths occurred in individuals 24 years old or younger, and only half of those occurred in those 15 years old or younger [22]. In the period from 1999-2012, the rates were consistently lowest among individuals 1-4 years of age and only slightly higher in the 5-14 year old and 15-24 year old age groups. From 1999-2012, the National Vital Statistics Report (NVSR) reported rate per 100,000 for all races and sexes combined has remained relatively stable at 0.2 for ages 1-4 years and 0.3 for 5-14 years. The rate per 100,000 has decreased from 0.5 to 0.3 for 15-24 years over the same time period [8, 10-20, 22]. As noted previously, national asthma death rates are generally not reported for those under one year of age due to unstable estimates. Age-based rates were roughly comparable in NC over the same time period. The average rate for NC children aged 5-14 years was approximately 0.3 per 100,000 over the time period 2000-2010. Rates were not reported in children 0-4 years due to small numbers, and the rate for ages 15-34 years was approximately 0.4 per 100,000 [3].
Sex

McCoy et al reported higher rates of asthma death among females from 1990-2001 [5] and this trend continued in the following decade [8, 10-20, 39-42]. This is likely largely due to higher asthma prevalence among females when considering all ages [39]. Asthma prevalence is higher among males until around the age of puberty, then higher in females for the remainder of the life span [43].

Race/Ethnicity and Socioeconomic Status

Blacks have historically had higher asthma death rates than whites [44] and this trend continued through the first decade of this century [8, 10-20, 39-42]. According to the NVSR, non-Hispanic blacks consistently had had the highest overall asthma death rates of any racial/ethnic group reported in all years from 1999-2012 [8, 10-20, 22]. Combining all ages and both sexes, the asthma death rate has been about twice as high in blacks as compared to whites over the same time period, while the death rates among non-Hispanics have generally been about twice as high as among Hispanics [8, 10-20, 22, 45].

Race and socioeconomic status (SES) are highly related and may be a source of confounding. A study of asthma fatalities in the Philadelphia area found that asthma death rates from 1985-1991 were highest in census tracts that had both high levels of poverty and larger numbers of minorities [46]. Although SES and race are often correlated, black race also appears to an independent risk factor [47], possibly due to biological factors that predispose to more severe disease [48]. Genetic data suggest
that percentage of African genetic ancestry directly correlates with asthma severity [49] and this may, in part, be due to rare genetic variants in the beta-2 receptor gene [50].

It is possible that a systematic bias exists towards reporting asthma as the primary cause of death in blacks as compared to other groups, and that this accounts for at least some of the racial differences in asthma death rates. McCoy et al examined all deaths in the US from 1999-2001 in which asthma was listed as either a primary or contributing cause of death. They reported that among this group, whites were less likely to have asthma reported as a primary cause of death as compared to blacks [5]. Without a more detailed comparison of cases in which asthma is listed as a primary instead of a secondary cause, this remains a hypothetical issue.

**Obesity**

Obesity-related asthma has been associated with decreased responsiveness to treatment and poor disease control [51]. Despite a fairly robust literature about the effects of excess weight on asthma, very few studies have specifically looked at obesity as a risk factor for asthma death. Obesity, defined using age-adjusted body mass index (BMI), was present in half of fatal asthma cases in one case series including both children and adults, and was equally prevalent in both slow- and rapid-onset fatalities [29]. Furthermore, obesity was found to be the most common comorbidity in a 22-case series of 17 adult and 5 pediatric asthma fatalities, although it is not stated whether this was seen equally in both the adult and childhood cases [32]. Obesity was found to be a risk factor for recurrent near fatal asthma exacerbations in a strictly pediatric study [52].
Urbanicity/ Rurality

Inner city residence has been studied as a risk factor for increased asthma severity, as it may be associated with crowded living conditions, increased exposure to pulmonary irritants, and poor access to care. It is unclear if inner city residence also increases risk of asthma mortality, but some data suggest that this is a possibility. For the period of 1981-1985, three large metropolitan areas – New York City, Chicago, and Phoenix – were found to have asthma mortality rates significantly in excess of expected [6]. Multiple case series from inner city Philadelphia, Milwaukee, and Baltimore have identified similar risk factors for death, including black race and poverty [32, 46, 53, 54]. Conversely, as delayed medical care has been identified as a risk factor, distance from a hospital may increase risk for mortality. This has not been well-studied among US populations, although residence in a rural or remote location was found to be risk factor for asthma death in a study from Australia examining data from 2005-2009 [55].

Time and Location of Death

Asthma symptoms and morbidity often vary with seasonal triggers. Very young children often experience exacerbations triggered by exposure to viral respiratory infections, which are more common in the fall and winter months. A well-documented upswing in asthma exacerbations occurs yearly in September among preschool and school-age children in the US, but this so-called “September spike” is not as pronounced in older asthmatics [56-58]. Data suggest that asthma mortality may also be seasonal, although following a slightly different pattern. The authors of a 1984 study of asthma deaths in England and Wales found that these occurred most frequently between July and
September, with a peak in August, and this effect was most pronounced among 5-14 year olds [59]. A similar trend was observed in a 1993 study of asthma deaths among 5-34 year olds in Seattle [60]. In the Milwaukee inner city cohort which included >75% adults, most deaths occurred during the summer months [32]. Conversely, McCoy et al reported more deaths in the winter months among those for whom asthma was listed as either the primary or a contributing cause of death, using data from across the US [5]. This may reflect more frequent deaths from respiratory infections, to which asthmatics may be more susceptible or have more severe courses, during the winter months.

As delay in seeking care may be a factor in asthma fatality, fatal events often occur at home and during weekends and evenings when access to medical care may be more limited. In a case series from South Africa, most deaths occurred outside of a healthcare facility and deaths occurred at a higher rate on weekends as compared to weekdays [61]. McCoy et al reported an increase in out-of-hospital deaths both among those in whom asthma was listed as a primary cause as well as a contributing cause [5]. This increase was more pronounced among individuals 35 years and older [5]. In 50% of the Hannaway case series from New England, the site of the fatal attack was the decedent’s home, and symptom onset of the fatal episode occurred in under 3 hours in 80% of cases [30]. In the Milwaukee cohort, more than 75% of asthma deaths occurred during sleep or shortly after awakening [32]. Asthma symptoms are often increased at night due to the trough in endogenous cortisol production that occurs in the early morning hours, as well as the potential for patients to be less aware of worsening symptoms while sleeping.
**Precipitating Activity**

Fatal daytime attacks in children and adolescents may occur while participation in sporting activities [62, 63]. A study conducted by the Temple Sports Asthma Research Center identified 61 cases of asthma deaths during or after sporting activities from 1993-2000 [62]. Of these, 51% had their fatal event during an organized practice or competitive event. Basketball and track were the most common activities, and the decedents were most likely to be white males between the ages of 10-20 years old with a history of mild intermittent or persistent asthma.

**Toxicology**

Illicit drug use is a well-documented risk factor for asthma death in adults in multiple series [32, 53] but data on childhood asthma deaths are much more limited. In the Milwaukee county case series, one of the cases under 18 years of age had a positive history of marijuana use, but negative toxicology report at the time of death [32].

**Factors Associated with Referral for Autopsy**

Not all asthma deaths are referred for autopsy by a medical examiner (ME). Although practices vary geographically, referral of a case to the ME is more common when the death occurs under questionable or unusual circumstances. A study in Maryland found that 17% of total asthma deaths from 1988-1992 had been referred for autopsy. Those referred for autopsy were more likely to be black male inner-city residents between 15-50 years of age, and were more likely to have a history of drug abuse and with a fatal
episode that started at home. Approximately 10% of the ME cases were children 4 years and younger who were found at home unresponsive [54].

A follow-up study of asthma deaths in Maryland from 1998-2002 found an increase in the proportion of ME-reviewed cases, with 74% of deaths in under 14-year olds, and 83% of the deaths in 15-34 years old being referred for autopsy [53]. As seen previously, males were much more likely to be referred to ME although females were more likely to die from asthma. While the total asthma deaths were nearly equally distributed between whites and blacks, the latter were much more likely to be referred for medical examiner review.

Similarly, in a case series of 22 fatal asthma case from inner city Milwaukee cases examined by the Milwaukee County Medical Examiner from 2004-2008, five individuals (23%) were under 19 years of age, and all of these were African-Americans. These data reflect a possible bias towards referral to a ME for younger, black decedents, as well as for children who die at home.

**Findings on Autopsy**

Fatal attacks may be the result of unusually extensive inflammation resulting in diffuse obstruction of the airways. Carroll *et al* noted structural changes in the walls of both large and small airways in fatal asthma, but primarily only in small airways in nonfatal cases [64]. Mucus hyper-secretion may also contribute to partial or complete obstruction of the airways in fatal attacks. A New Zealand study of 93 cases of fatal asthma, 20% of
whom were under 18 years of age, partial to complete airway luminal obstruction by a combination of mucus and cells was found to be common [65]. This finding may vary depending upon age. Bai et al found that airway narrowing was more common in older individuals who died of asthma (19-40 years) as compared to those who died at a younger age (17-23 years of age) [66]. The inflammation may not be limited to the airways themselves and has been observed extending into the pulmonary vasculature as well. Inflammatory infiltration of the muscular pulmonary arteries was seen in fatal asthma cases, and noted to be most pronounced at sites adjacent to airways [67]. Several studies have examined the types of inflammatory cells seen in rapid-onset versus more slow-onset fatal asthma cases.

Whereas eosinophils are thought to be the predominant inflammatory cell type in slow-onset cases, some data suggest that neutrophils may play a role in the development of rapid-onset fatalities. A 1993 case series found increased number of eosinophils in cases of slow-onset fatal asthma (defined as >2.5 hours from symptoms onset to death) as compared to sudden-onset fatal asthma (defined as <1 hour from symptom onset to death) [68]. In the sudden-onset cases, numbers of neutrophils were found to exceed those of eosinophils, whereas the opposite was seen in the slow-onset cases. Carroll et al found that the numbers of neutrophils were increased with decreased eosinophils, and mucus gland area was also increased in short-duration cases (<2 hours) as compared to long-duration (>5 hours) [69]. James et al reported that in 10 cases with a course of 3 hours or less, there was more muscle shortening, higher ratios of neutrophils to eosinophils, and less mucus as compared to 6 cases that had a course of greater than 8 hours [70]. Not all authors have observed increased neutrophils in rapid-onset cases. Hyzy et al compared autopsy findings in 21 cases where time from symptom onset to
death was greater than 6 hours versus 16 cases where death occurs less than 6 hours after symptom onset in subjects was between 2-34 years of age at death. They found that bronchial eosinophils and bronchiolar basement membrane thickening were more common in more rapid-onset cases, while neutrophils were uncommonly seen in both types [29].

Some data suggest that T-lymphocytes may play a role in asthma fatalities. The ratio of T-lymphocytes to B-lymphocytes was elevated in fatal asthma cases as compared to cystic fibrosis cases or age- and sex-matched cases of non-asthmatic sudden death [71]. Faul et al found increased numbers of CD8-positive T-cells in five cases of sudden asthma death [38]. Cells expressing glucocorticoid receptors were found to be increased in number in lung specimens from slow-onset asthma fatalities as compared to controls, suggesting that insensitivity to steroids may play a role in the development of fatal asthma [72]. While these cells consisted of eosinophils, macrophages, and neutrophils, the majority were T-cells [72].

Mast cells play an important role in inflammation by release of pro-inflammatory mediators which are stored in their cytoplasmic granules. Increased numbers of granulated and degranulated mast cells were seen in fatal cases as compared to controls in one small study [73]. Massive degranulation of mast cells may play a role in the pathogenesis of rapid-onset asthma death. Although total numbers were comparable between rapid and slower onset fatalities, a greater proportion of mast cells were degranulated in shorter-duration cases [74]. More muscle contraction was also observed in the short-duration cases suggesting that the mast cell degranulation led to severe
bronchospasm [74]. A few studies have also suggested a possible role for basophils in the pathogenesis of fatal asthma [75, 76].

The contraction of airway smooth muscles contribute significantly to the pathogenesis of an asthma attack [77] and cause additional luminal obstruction in addition to mucus plugging and inflammation [78]. Increased thickness of the airway smooth muscle layer suggests recurrent bronchospasm and appears to be related to severity but not duration of asthma [78]. This increased thickness may occur by increases in cell size, number, or both. In one study, hypertrophy, or increased size of airway smooth muscle cells, was seen in both the large airways of both fatal and non-fatal asthma, whereas hyperplasia, or increased numbers of these cells, was seen only in fatal cases [79].
CHAPTER 2: MAIN RESULTS

ABSTRACT

Background: Although asthma is the most common chronic disease of childhood, accounting for significant morbidity, asthma-related deaths are rare among children. Data are limited on what risk factors are associated with death from asthma among children. This study was designed to examine features of recent asthma deaths among children in North Carolina (NC) and identify patient-, time-, and location-specific potential risk factors.

Methods: Using publicly-available records, we collected data on all deaths that occurred in children under 19 years of age in NC between January 1, 1999 and December 30, 2012 and in which asthma was listed as the primary cause of death on the official state-issued death certificate. For cases in which the Office of the Chief Medical Examiner (OCME) issued a report, we obtained additional details, including clinical details of the fatal attack as provided, the height and weight of the decedent, and toxicology results if available. If autopsy was performed, we reviewed the gross and microscopic findings described on the report. We used generalized linear modeling based on a Poisson distribution to project future rates, mean ages of death, and race-stratified risk ratio with 95% confidence intervals (CI).

Results: A total of 84 deaths were attributed to asthma in the period studied. Two of these occurred in children under one year of age, and were excluded from further analysis, leaving a final cohort of 82. Of these, 46 decedents (56%) were male and 62 (76%) were African-American. The mean and median ages at death were 10.7 and 11.2 years respectively in the entire cohort, and were slightly higher among A-A decedents.
as compared to whites (9.7 and 6.5 years). Linear regression modeling based on the Poisson distribution projects an average age at death of 10.7 years (95% CI: 9.6, 11.9). Asthma death rates for NC children aged 1 to <19 years were fairly stable around a mean of 2.7 deaths per million, and Poisson linear regression models predicts a future annualized rate of 2.4 per million (95% CI: 1.9, 3.1) based on current trends. The death rate for A-A children over the study period was over eight times higher than that for white children. Based on trends observed, a Poisson linear regression model predicts A-A children have 8.3 times the risk of asthma death as compared to children of all other races combined (95% CI: 5.0, 13.9). Modeling further indicates no increased risk by sex when accounting for either race ($p = 0.29$) or age ($p = 0.91$). Most deaths in the cohort occurred in the fall (28%), and fewest in the summer (21%), while the average age of decedents was highest in the spring (12.8 years) and lowest in the fall (9.4 years). Approximately 40% of deaths occurred in the Eastern region of NC, with a higher estimated rate than in the Western or Piedmont regions. The seasonal distribution of deaths occurring in the Piedmont exhibited a similar pattern to that seen in the overall cohort, whereas those occurring in the Eastern region showed virtually no seasonal variability. As compared to the entire cohort, cases referred to the Office of the Chief Medical Examiner (OCME) were more predominantly A-A (86%) and female (51%), and had lower mean and median ages at death. Among those cases with an autopsy report on record, mucus plugging, eosinophils, and airway basement membrane thickening were the most commonly seen features on examination of the lungs. Neutrophilic infiltrates were not described in any reports. Among those cases where height and weight were available, obesity (defined as body mass index $\geq 95^{th}$ percentile for age) was seen in 24% of females, but not in any males.
Conclusions: Asthma deaths among children, although rare, represent an area of significant racial disparity in NC, and statistical modeling results suggest that this will continue into the future. Differing age distributions across the seasons potentially reflects a shift in triggers for fatal exacerbations that occurs with increased age. Eastern NC appears to have been disproportionately affected compared to other parts of the state. The lack of seasonal variability seen for deaths occurring in this region may reflect climate differences and/or perennial triggers in that area. While eosinophils and mucus plugging were commonly seen on autopsies in our cohort, neutrophilic infiltrates were not. The role of obesity as a risk factor for asthma death may vary by sex.
INTRODUCTION

Asthma is the most common chronic disease of children in the United States (US), responsible for significant morbidity and health care expenditures. Deaths from asthma are rare among children, but may be preventable as many effective therapies exist. The population-adjusted rates of asthma deaths are highest among blacks and females, regardless of age. This difference still exists when correcting for the higher prevalence of asthma in these groups [39]. The identification of specific risk factors for death from asthma has been challenging. Because it is a rare event, it is not practical to study prospectively, and studies examining this phenomenon are subject to biases inherent in retrospective data. Often, studies of asthma fatalities also examine mixed cohorts of both adults and children, making it difficult to separate out child-specific risk factors. These studies are often conducted in specific geographic areas, decreasing the generalizability of results. Finally, time-related cohort effects further complicate analysis, as environmental conditions, therapeutic options, and practice standards vary over time.

Asthma prevalence among North Carolina (NC) children under 18 years of age has been estimated at approximately 8%, and tracks roughly with race and indicators of poverty, with prevalence being highest among A-A children and those on public insurance [3]. These figures generally reflect national trends and averages. Our study was designed to describe characteristics of children who died as a direct result of an asthma exacerbation in NC from 1999 through 2012. The objectives of this study are to (1) track population-based asthma death rates for children in NC over the time period, (2) describe patient- and event-level features of these fatalities, (3) compare cases with a report from the Office of the Chief Medical Examiner (OCME) versus those in which a
report was not completed, and (4) describe pathology findings in those cases where an autopsy was performed.

METHODS

The study was approved by the Wake Forest Health Sciences Institutional Review Board. Because only data pertaining to deceased individuals were collected, informed consent was not required. We selected January 1, 1999 as the starting point for our study because this was the date on which International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) was implemented as the standard system for classifying cause of death on official government records in the US. Although this change did not appear to significantly affect US childhood asthma death rates [1], we elected to use this cutoff to ensure that our cases were as similar across time as possible, given our expected relatively small cohort size. We included all deaths in which the primary cause of death was listed as asthma (ICD-10 code J45) or status asthmaticus (J 46). We selected the age range of less than 19 years, as this roughly reflects the ages for which a patient would be seen by a pediatric provider, although different practices may transition patients to adult providers anywhere between 18 to 22 years of age.

We classified each death into one of the four seasons (fall, winter, spring, or summer) based upon the cutoff dates for the given year. As we were only able to access OCME reports on decedents under 18 years of age, we compared the mean and median ages, racial and sex distributions of the OCME cases with the non-OCME cases under age 18 years. We obtained the following information from official death certificates: dates of birth
and death, time and place of death, sex, race, and address of primary residence of the
decedent. We determined the distribution of cases across the three geographic regions
of NC (Western, Piedmont, and Eastern), using boundaries as defined on the NC Public
Schools Elementary Social Studies Resources website
(http://www.ncpublicschools.org/curriculum/socialstudies/elementary/studentsampler/20geography). If an OCME report was available, we abstracted additional information which
may have included, as available, a clinical summary of the death, Hispanic ethnicity,
gross and microscopic findings on autopsy, height, weight, and results of toxicology
studies. The death certificate data were provided upon request by the State Center for
Health Statistics, Division of Public Health, NC Department of Health and Human
Services, and OCME report data were obtained upon request from the NC OCME.

We organized our data and calculated means and medians using Excel 2010 (Microsoft
Corporation, Seattle, WA). We determined age at death in days using the reported dates
of birth and death, using an online time calculator (http://www.timeanddate.com). We
generated linear regression models, based on the Poisson distribution, to project future
annualized asthma death rates and race-stratified risk ratio, using Statistical Analysis
Software version 9.4 (SAS Institute, Cary, NC). We calculated rates as number of deaths
per million individuals using 1990-2014 annual age-stratified population estimates from
the US Census Bureau and National Center for Health Statistics as provided on the CDC
Wonder website (http://wonder.cdc.gov/bridged-race-population.html). In census years,
these figures were drawn from the census report, and in intervening years, from
intercensal or postcensal estimates. We calculated rates for each calendar year,
determined mean and median rates for the period, then calculated 3- and 5-year rolling
averages. We calculated body mass index (BMI) in kilograms of body weight divided by
the square of height in meters. Age and sex-specific BMI percentiles were determined using the web-based CDC BMI calculator (https://www.cdc.gov/healthyweight/assessing/bmi/).

RESULTS

Basic Demographics

A total of 84 asthma deaths occurred among children under 19 years of age in NC between January 1, 1999 and December 31, 2012. During the study period, two asthma deaths were reported in children under one year of age. These cases were not reviewed by the OCME and there is no public record of an autopsy for either. We elected to exclude these from our analyses due to the difficulty of diagnosing asthma in children this young. Descriptive statistics of the remaining 82 cases are summarized in Table 1. Linear regression modeling based on the Poisson distribution suggests a future average of death of 10.7 years (95% CI: 9.6, 11.9). The mean and median number of cases per year were both seven, with a range of three to 11 cases per year. Males accounted for 46 deaths, representing 56%. As a group, the A-A decedents had higher mean and median ages at death, and were predominantly male, while 53% of white decedents were female (Table 2). Absolute numbers of deaths increased by increasing age bracket, as shown in Figure 1. We found OCME reports on 35 of the 82 total asthma deaths (43%), and autopsies were performed in 30 of these cases (88% of cases with an OCME report, 37% of all cases). As compared to the entire cohort, the OCME cases were more predominantly A-A (86%) and female (51%), and had lower mean and median ages at death.

Population-Based Rates of Asthma Deaths
The yearly rate of asthma deaths fluctuated over the time period, ranging between 1.0 and 5.1 per million, with a mean and median of 2.7 per million. The three- and five-year rolling averages more closely approximated the period mean and did not suggest a clear trend. Poisson linear regression modeling predicts a future annualized rate of 2.4 per million (95% CI: 1.9, 3.1) based on current trends. Rates for A-A children were several-fold higher throughout the study period, with a mean rate per million of 7.7, which was over eight times higher than the mean rate of 0.9 for whites. Year-to-year A-A to white rate ratios showed significant variability, ranging between 3.4 and 15.3, and could not be calculated in 2002 or 2009 due to no deaths among whites in those years. Based on these data, Poisson linear regression modeling projects a risk ratio of 8.3 for A-A children as compared to whites (95% CI: 5.9, 13.9). No difference in risk by gender is seen by Poisson regression modeling, when accounting for either age ($p = 0.91$) or race ($p = 0.29$).

**Month and Season of Death**

Significant variability was seen in month of death. June was the month in which most asthma deaths occurred, with 11 total cases (13%). Examining data across all years, the two consecutive months with the highest number were January and February, with 19 total cases (23%). The three-month period with the most number of deaths was November through January, which accounted for 25 total deaths (30%). The single month with the most number of cases was September 2012, with three. Overall, fall was the season with the most deaths, and the number of deaths decreased progressively through winter, spring, and summer (Figure 2). As also illustrated in Figure 2, the mean and median ages at death were highest among those that occurred in the spring (12.7 and 12.8 years, respectively), and lowest in winter (9.6 and 9.4 years, respectively). Table 3 shows that spring was the season in which the number of deaths increased...
most with increasing age group. By examining the mean and median ages of death by 4-month rolling periods, September through December had the lowest ages, while May through August had the highest (Figure 3).

Geographic Location of Death

We were able to ascertain a county of residence for 81 (99%) of the decedents aged 1 to less than 19 years. As illustrated in Figure 4, over half of the deaths occurred in the Piedmont, the most populous region of NC. The Eastern region accounted for over 40% of deaths, although only 30% of the total population of 1 to under 19-year olds resided in this region during the study period, based on cumulative population counts. Only six deaths (7%) occurred in the Western region, which was home to 11% of the population of interest during the study period. Although based on small numbers, the death rate in the Western region (1.7 per million) was less than half of the in the Eastern region (3.7 per million), while the Piedmont rate (2.3 per million) approximated overall period mean of 2.7 per million. Seasonal variability of deaths, mirroring the pattern seen in the overall cohort, was notable in Piedmont, but not in the Eastern region (Figure 5).

DISCUSSION

We found the population-based rates for asthma death among 1 to under 19-year olds in NC were variable from year-to-year between 1999-2012, but seem to fluctuate around the period mean of 2.7 per million. CDC does not report death rates for under 1 to under 19-year olds as a category, but the overall national rate of asthma death was fairly steady between 2.0 and 2.5 per million during the same time period for children aged 1-14 years [8, 10-22]. We found that A-A children had over eight times the risk of dying of
asthma as compared to white children for the study period. This mirrors a disparity that has been noted nationally.

Just over half of the deaths (57%) occurred in the six-month period from September through February, which generally represents the bulk of the respiratory viral season in NC. Respiratory viruses are most prevalent during fall and winter, and are a major trigger for wheezing episodes in preschool and early school-age children. The “September spike” of asthma exacerbations occurring in the early fall in school-age children has been well-described in the US [56-58]. Using data from 2008, Lich and colleagues have described a September peak in ED visits for asthma in NC among 0-15 year olds that is not seen in older individuals [80]. While the mean and median ages of those who died in the fall and winter were less than 10 years, they exceeded 12 years of age in the spring. The younger mean and median ages of decedents during fall and winter supports a role for respiratory viruses as a potential trigger for fatal exacerbations in younger children. The increase in mean and median age in the spring did not occur due to fewer deaths among the youngest children occurring during the spring, but also to increased numbers of deaths among teens. This finding suggests a potential driver other than simply the decreased prevalence of respiratory viral infections seen in the spring. Older children and adolescents may be more likely to have an allergic trigger for their asthma, as they become more sensitized with age, and spring when environmental allergies typically peak in NC. The older average age of decedents in the spring is therefore potentially due, at least in part, to environmental allergies as an increasingly more important trigger for fatal exacerbations with advancing age.
A disproportionate number of childhood asthma deaths occurred in the Eastern geographical region of NC. This finding is consistent with other reports of increased childhood asthma burden in this area. In 2008, some of the highest rates of ED visits for asthma among children, especially boys under 17 years of age, occurred in counties in this part of the state [80]. Deaths occurring in the Piedmont region showed the same pattern of seasonality seen in the overall cohort -- greatest numbers in the fall, decreasing with each subsequent season to lowest numbers in the summer. By contrast, deaths occurring in the Eastern region of NC showed much less seasonal variability, suggesting the presence of perennial risk factors, which may be environmental and/or patient-related. Because so few deaths occurred in the Western region, it was difficult to determine any seasonal affect. The distribution of deaths in urban and rural areas roughly mirrored the general population distribution, with two-thirds occurring in large metro areas.

Cases in which an OCME report was issued were more likely to involve a female decedent and the average age of death was slightly younger among these cases as compared to the entire cohort. The percentage of A-A children was even higher among the OCME subset (86%) than it was. It appears that most of the decedents referred for OCME evaluation were declared dead outside the hospital or shortly after arrival. Because the circumstances of such deaths are more questionable, it is consistent that these cases would be referred to the medical examiner. We do not have clinical or autopsy data regarding those deaths in which an OCME report was not issued, and therefore cannot draw conclusions about specific clinical circumstances in those deaths beyond the date and time of death. It is possible that these deaths occurred in patients who were admitted to a hospital for a period of time prior to death being declared.
The most common finding on microscopic examination at autopsy was the presence of eosinophils, with no report specifically noting neutrophils. This seems to confirm the role of eosinophilic inflammation in the pathogenesis of fatal exacerbations, while also suggesting that neutrophilic inflammation likely does not play a prominent role. It is possible that the presence of eosinophils in high number may prompt the pathologist to consider asthma as a cause of death, while increased numbers of neutrophils may prompt consideration of other diagnoses. Mucus plugging was noted, either on gross or microscopic examination, in two-thirds of the reports. Other authors have hypothesized that extensive plugging of the airways may be a mechanism by which death occurs in fatal exacerbations. Diffuse obstruction of the airways from mucus plugs could lead to massive ventilation-perfusion mismatching, resulting in profound hypoxemia that may be slower to resolve and less responsive to bronchodilators than bronchospasm associated with less mucus plugging. Some of the reports either did not report mucus plugging, or specifically documented the lack thereof. This suggests that mucus plugging may not play a significant role in all deaths, even those with sudden and rapid decompensation. Alternatively, it is possible that airway mucus, at least in some instances, may be partially or completely washed out in the preparation of lung histology material, giving the false impression of decreased or absent plugging.

The data presented here allow for the generation of several hypotheses about possible risk factors for having a fatal asthma exacerbation in childhood, but further research is needed to test these. While our study represents one of the largest to date on fatal childhood asthma, it is limited by its retrospective nature. The amount and quality of data
available are limited to those included in the public record. Data points that may be highly relevant, such as use of medications, and prior exacerbation history, were unfortunately not available for analysis. Real-time data collection would allow for more detailed characterization of cases but is not practical with rare outcomes such as childhood asthma deaths, which occur infrequently in even the most populous areas. A case-control approach would be a useful next step in evaluating the role of race, sex, season, and obesity, among others.
ADDITIONAL ANALYSES

Rurality/Urbanicity

We used the home county to determine the Rural-Urban Continuity Code (RUCC) as a measure of rural versus urban residence. We obtained these data from the US Department of Agriculture Economic Research Service website (http://www.ers.usda.gov/data-products/rural-urban-continuum-codes.aspx). The RUCC (1-9) is determined every ten years (1993, 2003, 2013) based on overall county population density, and can be collapsed into the general grouping of 1-3 (large metro areas), 4-7 (non-metro urban areas), and 8-9 (completely rural areas). Because of the relatively small sample size, we used these three groupings, rather than the individual codes, to provide a general measure of the urbanicity or rurality of the decedent’s county of residence at the time of death. For deaths that occurred in 2003 we used the grouping for that year. For deaths that occurred between years, we examined the grouping from both the previous and subsequent grouping (1993 and 2003 for deaths occurring in 1999-2002, and 2003 and 2013 for death occurring in 2004-2012). We did not encounter any situations where the previous and subsequent groupings were different for a county, so these were used to assign a categorization to the home address of each decedent.

We were able to determine a RUCC classification for 75 cases (94%). A county of residence was not listed for one decedent. For five additional cases, the classification was different in the preceding and subsequent assessment, Of those in which RUCC could be determined, 51 decedents (66%) resided in large metro areas, 25 decedents
(30%) resided in non-metro urban areas, and only 1 (1%) resided in an area designated as completely rural. For comparison, based on 2013 RUCC and 2010 population estimates, 77% of the total state population resided in large metro areas, 20% in non-metro urban areas, and 3% in rural areas. Based on 2003 RUCC and 2000 population estimates, 68% of the total state population resided in large metro areas, 28% in non-metro urban areas, and 4% in rural areas.

POTENTIAL FUTURE DIRECTIONS

Expansion of Sample Size

Although our study describes fairly recent deaths, in a relatively homogenous age group and geographic area, one of the most significant limitations remains the relatively small sample size. Data on asthma deaths from the years 2013 through 2015 should now be available through the NC State Center for Health Statistics. We would like to expand our cohort to include these years to have the most recent data possible, and to expand our sample size. Expanding the age range is also a potential approach to increase the sample size. One option would be to increase the upper age limit to 24 years of age to correspond to the age categories used by CDC in reporting mortality data. This might allow us to more closely examine differences between childhood, adolescent, and young adult cases.

Real-Time Data Collection

One of the drawbacks of the data we had available for our study is the lack of depth and detail regarding the decedents’ clinical histories, including severity of disease and medications. Real-time collection of data from cases as they occur may allow for more
complete information to be collected, as is the approach used in the Sudden Unexpected Death in NC (SUDDEN, https://www.med.unc.edu/medicine/cardiology/sudden) that is currently ongoing in several NC counties. As childhood asthma deaths are rare, however, it would take a significant amount of time to collect a substantial number of more well-characterized cases. Collection of adult cases would be more feasible, but given that adult asthmatics are more likely to have additional comorbidities, teasing out the role played by these would be challenging.

**Case Control Approach**

A case-control study of fatal asthma would be a logical next step for the further examination of potential risk factors identified from our study, including age, race, season, and obesity. Non-fatal exacerbations could be matched to fatal ones, and this could be done to control for a number of factors such as race, gender, age, or time of year. The optimal controls for a case-control study are individuals as much like the cases as possible, except for the absence of the outcome, i.e. asthma fatality. Optimal power is generally achieved at a ratio of around 4-5 controls per case [81]. Given that asthma exacerbations among children are among the most common reason for accessing health care services, such controls should be fairly easily obtained.

A number of potential NC sources for controls could be considered. The Pre-hospital Medical Information System (PrEMIS, https://www.emspic.org/applications/premis) is a database that collects information about utilizations of Emergency Medical Services (EMS) in NC. While a number of variables are reported, diagnosis is not among these. It would therefore be difficult to determine for certain whether a child taken by ambulance to the hospital has respiratory distress due to asthma exacerbation or another cause.
Also, as many asthma exacerbations do not require EMS services, use of this source of controls might result in having an unusually severe degree of disease among the controls. The North Carolina Disease Event Tracking and Epidemiologic Collection Tool (NC DETECT, http://www.ncdetect.org) is a statewide database that tracks the majority of ED visits since 2008. This dataset includes diagnostic information, but does not record race as a variable. Given that race is perhaps the most significant risk factor for asthma deaths that we identified, this limitation would be significant. The Carolinas Collaborative (https://carolinascollaborative.org) is a newly-established data repository that combines the medical records system of the three major academic medical centers in the state: Duke University Health System, the University of NC Health Care, and Wake Forest Baptist Health. Efforts are being taken to ensure the data are robust and well-harmonized. As the population of patients seen in academic medical centers may differ from those seen in community hospitals or other venues are likely systematically different, however, this source of controls may also be sub-optimal. Furthermore, all three of the academic centers involved are in the Piedmont region, limiting the geographic representation of the controls.

National-level datasets could be considered, with the caveat that non-NC controls may not be optimal for NC cases. The Virtual PICU System (VPS) collects data from Pediatric Intensive Care Units (PICUs) at over 100 hospitals. As only a fraction of asthma exacerbations require PICU admission, controls obtained from this source would likely be biased towards much higher severity. Other national-level data repositories are being created, and may offer other potential sources for controls.
Case Crossover Approach

Another approach to consider is the case-crossover design. A case-crossover study uses an individual’s history prior to an event occurring as the control period. This approach allows for determination of potential environmental and/or time-related risk factors, such as age or time of year. It does not allow for determination of risk factors related to more fixed individual characteristics, such as gender or sex. This approach would allow for the possibility to examine the role of weather and/or environmental risk factors in causing fatal asthma exacerbations. Various types of geocoded data are available regarding temperature, air quality, and other environmental measures that could be examined as potential risk factors. These data could be obtained for the time around an individual’s prior non-fatal exacerbations and then compared to the fatal exacerbation. This novel approach is appealing as it can attempt to address the hypothesis that environmental triggers may be important in triggering severe and fatal exacerbations.

The primary factor that would limit the feasibility of this approach, however, is likely to be sample size. Asthma deaths are a rare event. Even when data can be obtained on a fatal exacerbation from hospital records, previous events may not be well-characterized or captured, and the quality of such data is likely to be highly variable. Geocoded data are plentiful, but deciding which parameters to study is likely to be challenging. Similarly, determining the time period to study around a given exacerbation is unclear. The problem of missing data, and variable data quality, are also likely to limit the feasibility of a case crossover approach.
Examination of Asthma as Secondary Cause of Death

Some authors have compared cases in which asthma is the primary cause of death, versus those where it is listed as a secondary or contributing cause. Their findings have suggested that whites may be more likely to have asthma listed as a secondary cause whereas A-A individuals may be more likely to have it listed as the primary cause. We did not analyze cases in our study where asthma was listed as a secondary cause, as we felt that this would represent a more heterogeneous cohort. These data are publicly available, however, and could be readily obtained and analyzed.

Analysis of Mucus from Fatal Exacerbations

The extensive mucus plugging seen in many of the fatal cases examined, suggests the hypothesis that such individuals may have mucus that is qualitatively (as well as simply quantitatively) different from that which is usually seen in asthma exacerbations or other respiratory illnesses. Many laboratories are currently studying difference in mucus composition and physical properties that are seen in a wide array of adult and pediatric respiratory disorders. If specific features of the compositional components or physical properties of the mucus obtained from decedents could be identified, this could suggest potential genetic risk factors, as many genes are known that encode components of normal respiratory mucus. It may also allow for the identification of individuals at risk for sudden, massive mucus plugging in the setting of an asthma exacerbation.

Exploration of Rare Genetic Risk Factors

Our study identified eight-fold increased rates of asthma deaths in A-A as compared to white children. While some of this may be driven by SES, the possibility of A-A race as an independent risk factor has been proposed by other authors. Recently, Ortega, et al. showed that rare variants in the beta-2 receptor genes, the site of action for beta agonist
medications, which are more common in the African Ancestral background, may be associated with adverse asthma events in asthmatics taking LABA drugs [50]. These variants may modulate response to such drugs and could plausibly play a role in fatal exacerbations. Because the variants of interest are rare, if their presence was confirmed among fatal cases at a rate above the expected, it would offer compelling evidence for a genetic predisposition for fatal exacerbations.

**Evaluation of Risk and Development of Interventions to Prevent Asthma Deaths**

The ultimate purpose of studying risk factors for a rare but catastrophic event such as asthma death is to prospectively identify at-risk individuals and intervene to prevent fatality. Because asthma deaths are rare, however, identifying those at highest risk, and proving the effectiveness of any intervention is methodologically challenging. Use of standard regression models for outcomes in which there are few events but many potential predictors can result in underestimation of probability in low-risk individuals, but overestimation of probability in those at high-risk [82]. The use of prediction models that have been successfully applied to other rare diseases may prove useful [83].
### TABLE 1: Demographics of the Study Population Aged 1 to <18 Years by OCME Status (n = 80).

<table>
<thead>
<tr>
<th></th>
<th>OCME</th>
<th>Non-OCME</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>19/34 (51%)</td>
<td>16/46 (35%)</td>
<td>35/80 (44%)</td>
</tr>
<tr>
<td>African-American</td>
<td>29/34 (86%)</td>
<td>32/46 (70%)</td>
<td>61/80 (76%)</td>
</tr>
<tr>
<td>Mean Age</td>
<td>9.6 yrs</td>
<td>11.2 yrs</td>
<td>10.7 yrs</td>
</tr>
<tr>
<td>Median Age</td>
<td>9.1 yrs</td>
<td>11.7 yrs</td>
<td>11.2 yrs</td>
</tr>
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</table>

### TABLE 2: Demographics of the Study Population by Race (n=82). One subject identified as American Indian is included in the total count. The 95% CIs were calculated using Poisson linear regression modeling.

<table>
<thead>
<tr>
<th></th>
<th>African-American</th>
<th>White</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>26/62 (42%)</td>
<td>10/19 (53%)</td>
<td>36/82 (44%)</td>
</tr>
<tr>
<td>Mean Age</td>
<td>11.1 yrs (95% CI: 9.9, 12.4)</td>
<td>9.7 yrs (95% CI: 6.9, 12.5)</td>
<td>10.7 yrs (95% CI: 9.6, 11.9)</td>
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<tr>
<td>Median Age</td>
<td>11.6 yrs</td>
<td>6.5 yrs</td>
<td>11.2 yrs</td>
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### Table 3: Number of Deaths by Season and Three-Year Age Category. Numbers of absolute events shown with row percentages in parentheses.

<table>
<thead>
<tr>
<th></th>
<th>1 to &lt;7 yrs</th>
<th>7 to &lt;13 yrs</th>
<th>13 to &lt;18 yrs</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fall</strong></td>
<td>8 (35%)</td>
<td>9 (39%)</td>
<td>6 (26%)</td>
<td>23</td>
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<tr>
<td><strong>Winter</strong></td>
<td>7 (32%)</td>
<td>7 (32%)</td>
<td>8 (36%)</td>
<td>22</td>
</tr>
<tr>
<td><strong>Summer</strong></td>
<td>6 (35%)</td>
<td>4 (24%)</td>
<td>7 (41%)</td>
<td>17</td>
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<tr>
<td><strong>Spring</strong></td>
<td>3 (15%)</td>
<td>7 (35%)</td>
<td>10 (50%)</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>27</td>
<td>31</td>
<td>82</td>
</tr>
</tbody>
</table>

### Table 4: Number of Deaths by Sex and BMI Category

<table>
<thead>
<tr>
<th></th>
<th>Boys (n=15)</th>
<th>Girls (n=17)</th>
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<tbody>
<tr>
<td><strong>Obese</strong></td>
<td>0 (0%)</td>
<td>4 (24%)</td>
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<tr>
<td>(BMI ≥95&lt;sup&gt;th&lt;/sup&gt; percentile)</td>
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<tr>
<td><strong>Overweight</strong></td>
<td>3 (20%)</td>
<td>2 (12%)</td>
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<tr>
<td>(BMI 85 to &lt;95&lt;sup&gt;th&lt;/sup&gt; percentile)</td>
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<tr>
<td><strong>Normal weight</strong></td>
<td>11 (73%)</td>
<td>9 (52%)</td>
</tr>
<tr>
<td>(BMI 5 to &lt;85&lt;sup&gt;th&lt;/sup&gt; percentile)</td>
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<tr>
<td><strong>Underweight</strong></td>
<td>1 (7%)</td>
<td>2 (12%)</td>
</tr>
<tr>
<td>(BMI &lt;5&lt;sup&gt;th&lt;/sup&gt; percentile)</td>
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Figure 1: Number of Deaths 1 to <19 Years of Age by 3-Year Age Bracket and Sex (n = 82)
Figure 2: Number of Deaths with Mean and Median Ages at Death by Season (n=82)
Figure 3: Mean and Median Ages of Death by Four-Month Rolling Intervals (n = 82)
Figure 4: Number of Deaths per County and Geographic Region of NC (n = 81)
Figure 5: Number of Deaths with Mean and Median Ages by Season and Geographic Region of NC
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                  M.S. candidate

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              Baltimore, MD

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              Johns Hopkins University School of Medicine
              Baltimore, MD
2006-2007 **Chief Resident**, Department of Pediatrics, Johns Hopkins University School of Medicine Baltimore, MD

2007-2010 **Post-Graduate Fellow**, Eudowood Division of Pediatric Respiratory Sciences Johns Hopkins University School of Medicine Baltimore, MD

PROFESSIONAL LICENSURE

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<thead>
<tr>
<th>Year</th>
<th>Specialty Certification</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005-present</td>
<td>Diplomate, American Board of Pediatrics General Pediatrics</td>
</tr>
<tr>
<td>2010-present</td>
<td>Diplomate, American Board of Pediatrics Pediatric Pulmonology</td>
</tr>
</tbody>
</table>

EMPLOYMENT

**Academic Appointments**

**Wake Forest School of Medicine, Wake Forest University**

<table>
<thead>
<tr>
<th>Year</th>
<th>Position</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010-present</td>
<td>Assistant Professor, Department of Pediatrics</td>
</tr>
</tbody>
</table>

**Professional Experience**

<table>
<thead>
<tr>
<th>Year</th>
<th>Position</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td><strong>Consultant Physician (locum tenens)</strong> Paediatric Respiratory Department Starship Children’s Hospital Auckland District Health Board Auckland, New Zealand.</td>
</tr>
</tbody>
</table>

OTHER PROFESSIONAL APPOINTMENTS AND INSTITUTIONAL SERVICE

**Departmental Committee Service**

<table>
<thead>
<tr>
<th>Year</th>
<th>Position</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003-2007</td>
<td>Johns Hopkins Pediatrics Residency Program Curriculum Committee</td>
</tr>
<tr>
<td>2005-2007</td>
<td>Johns Hopkins Pediatrics Residency Program Intern Selection Committee (Voting</td>
</tr>
</tbody>
</table>
2006-2007  Johns Hopkins Department of Pediatrics Morbidity and Mortality Committee
2006-2007  Josie King Patient Safety Committee of Johns Hopkins Children’s Center
2013-2015  Wake Forest Department of Pediatrics Grand Rounds Committee (Co-Chair)
2015-present  Wake Forest Department of Pediatrics Grand Rounds Committee (Chair)
2015-present  Brenner Children’s Hospital Faculty Council (Elected Member)

EXTRAMURAL APPOINTMENTS AND SERVICE

Journal Reviewer

BMC Pulmonary Medicine
Clinical Transplantation
Family and Community Health
Journal of Neonatal-Perinatal Medicine
Journal of Pediatrics
Orphanet Journal of Rare Diseases
Pediatric Pulmonology

Funding Agency Reviewer

Physicians’ Services Incorporated Foundation (Toronto, Canada)
Research Grant Reviewer, 2013

PROFESSIONAL MEMBERSHIPS

2015-present  American Thoracic Society
Member, Rare Lung Disease Working Group
2007-present  Member, American Thoracic Society
2012-present  Member, North Carolina Medical Society
2012-present  Fellow, American Academy of Pediatrics
2012-present  Fellow, American College of Chest Physicians
HONORS AND AWARDS

1999 Holderness Medical Research Fellow
UNC School of Medicine

2000 John B. Graham Student Research Society
UNC School of Medicine

2001 Eugene S. Mayer Community Service Honor Society
UNC School of Medicine

2001 Heusner Pupil Award
UNC School of Medicine

2013-present Elected Member
Society for Pediatric Research

INVITED PRESENTATIONS AND SEMINARS

PUBLIC OUTREACH

04/04/14 Challenges of Pediatric Asthma – in North Carolina and Globally
School Nurse Association of North Carolina, Southwest Chapter Meeting (Gastonia, NC)

11/12/14 Childhood Asthma
Friends of Brenner Children's Hospital meeting

GRANTS

CURRENT AND PENDING

Current

Duke Endowment Grant (Role: Co-Investigator; PI: Helga Rippen, MD)
08/2015-present
The Carolinas Collaborative: Expanding a Learning Health Care System

Pending

N/A
PAST GRANT HISTORY

**NIH T32 HL072748-04**
Role: Trainee; PI: Pamela Zeitlin, MD, PhD
Multidisciplinary Training Program in Pediatric Pulmonary

**Hartwell Foundation Biomedical Research Fellowship**
Role: PI
07/2008-06/2010
Analysis of Candidate Genes for Surfactant Dysfunction

**Arricale Family Research Fund for Pediatric ILD Pilot Grant**
Role: PI
01/2009-06/2010
A Genetic Hypothesis for Neuroendocrine Cell Hyperplasia of Infancy (NEHI)

**NIH 1K12 HL089992**
Role: Trainee; PI: Deborah Meyers, PhD
02/2011-08/2013
Center for Genomics and Personalized Medicine Training Grant

**Wake Forest Center for Bioethics, Health, and Society Pilot Grant**
Role: PI
01/2013-10/2014
Exploring Attitudes and Beliefs Regarding Genetic Research Among Lumbee Indians of North Carolina

**NIH R21 NR013272**
Role: Co-investigator; PI Savithri Nageswaran, MD
07/2014-06/2015
The Role of Health Care Providers in Decision Making for Life-Sustaining Treatments in Children with Complex Chronic Conditions

BIBLIOGRAPHY

**Peer-Reviewed Journal Articles**


**Invited Book Chapters/Reviews**


**Miscellaneous**


**Abstracts/Scientific exhibits/Presentations at national meetings:**


GRADUATE STUDENTS/RESIDENTS/FELLOWS ADVISED

Resident and Fellows

2012-2015

Katherine Cleveland Gilbert, MD
Pediatric Resident (2012)
Allergy/Immunology Fellow (2013-2015)
Wake Forest School of Medicine