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Residential Roadway Proximity and Lung Function Decline in Pediatric Cystic Fibrosis

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Abstract

Residential Roadway Proximity and Lung Function Decline in Pediatric Cystic Fibrosis

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Introduction

Cystic fibrosis (CF) is a genetic disease that causes ongoing decline in lung function until patients ultimately experience respiratory failure. Air pollution exposure is thought to be detrimental to anyone with lung disease, and this is particularly true for people with CF. Research indicates that environmental factors account for about half of variations in lung function of CF patients. To ensure better outcomes for this group, there is a need to quantify the effect of air pollution exposure on rate of decline in lung function.

Methods

Demographic and clinical data were collected from pediatric patients of the Emory University + Children's Healthcare of Atlanta CF Care Center (n = 98). Data were collected from the period between 2013-2017. Residential distance to the closest major roadway was used as a proxy for air pollution exposure. Spirometry test results were used to calculate each subject's annual baseline lung function scores by finding the mean of the highest percent predicted value of forced expiratory volume in one second (FEV_1) result from each quarter. Annual rates of decline (ROD) in FEV_1 for each subject were determined by calculating the differences between subsequent baseline values. Linear regression, one-way non-parametric analysis (ANOVA), linear mixed models, Pearson correlation coefficients, and Chi-square tests were used to examine the association between residential roadway proximity and ROD. Other characteristics known to influence CF disease progression were included in the analysis, such as gender, race, insurance status, income, bacterial acquisition status, and CF-related diabetes (CFRD) status.

Results

No linear correlations were observed among raw or transformed roadway proximity and ROD data. In a mixed-model analysis utilizing a Chi-square test, living within 570 meters of a major roadway were observed to experience a mean annual ROD of -2.87% (95% CI: -4.21, -1.53) while subjects residing further away had a mean ROD of -0.94% (95% CI: -1.53, -0.36) ($p=0.011$). Using mixed-model and non-parametric one-way analyses respectively, chronic infection with methicillin-resistant *S. aureus* (MRSA) ($p=0.006$) and diagnosis of CFRD ($p=0.037$) were also observed to have statistically significant associations with ROD. Self-reported income levels were found to be significant for residential roadway proximity ($p=0.048$) but not ROD. Sex, race, insurance status, and *P. aeruginosa* infection status did not have a significant association with residential roadway proximity or ROD.

Conclusions

Pediatric patients with CF who live within a region observed to have increased levels of airway pollution experience an annual ROD in lung function that is 3.05 times greater than that of children living in areas where roadway air pollution exists at background levels. This vulnerability ultimately will affect their quality of life and increase the burden of care. Further research amongst a larger cohort and multiple centers is warranted to better understand this effect, and support public policy that guides air quality measures.

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Table of Contents

Introduction/Statement of Problem

Cystic fibrosis (CF) is a genetic disease caused by defects in the cystic fibrosis transmembrane conductance regulator (CFTR) (Akabas, 2000). While the gene influences gastrointestinal and pancreatic processes, the most consequential problem for patients with CF is lung disease characterized by the triad of decreased clearance of airway secretions, intense neutrophilic airway inflammation, and polymicrobial bacterial infection. This combination leads to progressive decline in lung function, and ultimately death in early adulthood due to respiratory failure (Breuer et al., 2018; Forrest et al., 2019; Foundation, 2017; Khan, Ali, Sweezey, Grasemann, & Palaniyar, 2019; Pilewski & Frizzell, 1999).

Due to advances in understanding the pathology and treatment of CFTR, the median life expectancy for someone born with CF has increased to the age of 46.2 in 2017, from 31.9 in 1990 (Foundation, 2017; Stephenson, Stanojevic, Sykes, & Burgel, 2017). However, patients must adhere to a demanding and complex course of therapies to maintain their health. Therapeutic actions must be performed multiple times within a day and include mechanical airway clearance, ingesting pancreatic enzymes to facilitate food digestion, inhalation of medications to clear debris from the airways, and use of oral or aerosolized antibiotics (Rowe, Hoover, Solomon, & Sorscher, 2016). Despite adherence to treatments, the bacteria can flourish to the point of causing repetitive episodes in which lung function declines and patients experience excessive respiratory symptoms. These periods are known as acute pulmonary exacerbations (APE) and require treatment with oral or intravenous antibiotics to restore pulmonary capacity to the greatest extent possible (Pieter C. Goeminne et al., 2013; Rowe et al., 2016). This often requires hospitalization for several days to a few weeks. It is not unusual for patients to require multiple hospitalizations per year as their disease progresses. In approximately 25% of APEs, lung function will not recover to

baseline. Following treatment, these patients have a new, lower level of lung function (Sanders et al., 2010).

CF disease progression is assessed through regular pulmonary function testing by spirometry during patients' clinic visits, which are expected to occur every three months when well and more frequently when sick (Konstan et al., 2017). The standard indicator of the degree of airway obstruction on the spirometric test is forced expiratory volume (FEV_1). Longitudinal data informs clinical decisions and provides a standardized mode of tracking disease severity (Kulich et al., 2005). The FEV_1 value is expressed as the percentage of the predicted or expected value for a healthy person, incorporating parameters of age, sex, height, and race (Konstan et al., 2017). Lung function, as measured by FEV_1, remains stable in CF until about 8-10 years, then declines progressively through the teen and adult years (CF Foundation Patient Registry Annual Report, 2016; Kulich et al., 2005). The rate of decline can be predictive of a patient's quality of life and the need for various clinical treatments. For example, the rate of decline influences when a patient begins to consider lung transplantation (Rosenbluth, Wilson, Ferkol, & Schuster, 2004).

Historically, a variety of reference equations have been used to convert the raw value of FEV_1, measured in liters, to an expected percentage of predicted lung function. In 2013, the CF Foundation (CFF) began utilizing the Global Lung Function Initiative (GLI) in their national patient registry (Konstan et al., 2017). The new equations standardize lung function tests by ethnicity, enabling test results to be easily evaluated across all ages of patients across the globe (Quanjer et al., 2012). Subsequently, the GLI became the "endorsed" global reference equation for spirometry of six international respiratory societies (Quanjer et al., 2012).

While air pollution exposure is detrimental to people without pre-existing lung disease, people with CF belong to a vulnerable population that is particularly susceptible to the health-related effects of air pollution (Pieter C. Goeminne et al., 2013; Goss, Newsom, Schildcrout, Sheppard, & Kaufman, 2004; Psoter, De Roos, Wakefield, Mayer, & Rosenfeld, 2017; Kevin J. Psoter et al., 2015). Research indicates that environmental factors account for about half of variations in lung function amongst CF patients (J. M. Collaco, Blackman, McGready, Naughton, & Cutting, 2010). However, there is a lack of research that examine rates of decline in the specific context of roadway air pollution. To ensure better outcomes for patients with CF, it is extremely important to understand the ways in which environmental influences affect disease progression.

Problem Statement

There is a need to quantify the effect that air pollution exposure has on rate of decline in lung function within patients with CF, in order to inform public policy for air quality standards, prevent pulmonary exacerbations, provide better treatment, and improve the clinical knowledge base for these patients.

Purpose of the Study

By assessing the longitudinal FEV_1 values for CF patients, and correlating the rates of decline over time with individuals' exposure to air pollution via roadway proximity, we can 1) quantify the effect of air pollution on lung function, 2) guide clinical decision-making around the specific healthcare needs of cystic fibrosis patients, 3) improve the clinical knowledge base, and 4) inform public policy decision-making for air quality standards.

Review of the Literature

Roadway Proximity

In 2002, approximately 146 million people in the United States lived in areas where presence of controlled components were not in compliance with National Ambient Air Quality Standards (Trasande & Thurston, 2005). One large contributor to air pollution is traffic-related emissions (Trasande & Thurston, 2005). These are produced not just by tailpipes, but from gasoline pumping, exhaust, and road dust stirred up by moving vehicles(Trasande & Thurston, 2005). Vehicles such as trucks, cars, and buses contribute benzene, particulate matter (PM), and gases such as nitrogen dioxide (NO_2), sulfates (SO_2), and O_3 (Trasande & Thurston, 2005). Concentrations of these pollutants are highest on roadways. Research indicates that carbon monoxide levels measured on a roadway are 20 times greater than typical atmospheric levels (Karner, Eisinger, & Niemeier, 2010). Yet pollutant concentration levels can persist and disperse to influence nearby air quality. Studies indicate that most decay to background within 160-570 meters from the source roadway (Karner et al., 2010). However, the air quality within that distance can vary tremendously depending on factors such as wind. Within 570 meters of major roadways, people are at risk for increased exposure to roadway pollutants. The typical pathway for exposure is inhalation(Trasande & Thurston, 2005).

Accordingly, residential roadway proximity can represent pollution exposure, serving as a proxy for individual monitoring devices or modeling exposures collected from outdoor air quality monitoring stations (Downs et al., 2007; Sarnat, Schwartz, Catalano, & Suh, 2001). An increasingly large body of evidence indicates that exposure to roadway pollutants creates a major burden to population health. This has been shown to begin early in life, even prior to birth. A Boston study of mothers and their children found an association between

roadway pollution exposure during pregnancy and higher risks of respiratory infections through infancy and the toddler years (Rice et al., 2015). It is also linked to effects in the pediatric population, such as hindered lung development and increase in allergic symptoms. European researchers discovered that children who had been exposed to higher levels of air pollution experienced reduced lung function and greater incidence of airway obstruction by the time they reached sixteen years of age (Milanzi et al., 2018). Similar effects were observed in a study in Southern California, where residential proximity to freeways was associated with decreased lung function in children aged 18 years and younger, particularly when pertaining to ambient concentrations of PM and O_3 (Urman et al., 2014). In Poland, researchers found that children living closer to major roadways experienced greater incidence of asthma-related symptoms, as well as allergic rhinitis (Porebski, Wozniak, & Czarnobilska, 2014).

In adult populations, other negative outcomes have been observed. $PM_{2.5}$ exposure has been linked to increasing incidence rates of aerodigestive cancers (Raaschou-Nielsen, Ketzel, Harbo Poulsen, & Sorensen, 2016; Weinmayr et al., 2018). A study in the Netherlands determined that living close to major roadways is related to increases in deaths from cardiovascular disease, pulmonary disease, and lung cancer, as well as non-disease-specific mortality rates (Brunekreef et al., 2009).

These observations amongst the general public make air pollution a particular concern for vulnerable populations, such as people with pre-existing lung disease. A panel study published in 2012 indicated that most peer-reviewed research published between 2000-2011 found that air pollution exposure was negatively associated with respiratory health in all children, but particularly those with asthma (Li, Williams, Jalaludin, & Baker, 2012). Among children diagnosed with asthma, those living in near proximity to major roadways were more likely to experience symptoms of greater severity than those living further away, and had

increased use of medications, increased hospitalizations, decreased airway function, and increased inflammation (Brown et al., 2012). The effects may be more dramatic among adults with lung disease. One study of non-CF bronchiectasis patients in Belgium concluded that residential proximity to a major roadway correlated with a significant increase in mortality within their cohort (Goeminne, Bijnens, Nemery, Nawrot, & Dupont, 2014).

Air Pollution Exposure and Cystic Fibrosis

Air pollution exposure levels have been shown to correlate with increased acquisition of bacteria within CF patients and acute, therapeutic use of antibiotics. Children exposed to higher levels of $PM_{2.5}$ show positive associations with acquisition of *Pseudomonas aeruginosa* (K. J. Psoter et al., 2015) and methicillin-resistant *Staphylococcus aureus* (MRSA) (Psoter et al., 2017). These are the two main respiratory pathogens in CF and are associated with worse health outcomes.

Exposure to air pollution has also been linked to exacerbations in CF patients. One study of CF patients within the United States determined that exposure to $PM_{2.5}$, as estimated by residential zip code, is linked to having more than two APEs within a year (Goss et al., 2004). The same research also identified a linear relationship between FEV_1 values and air pollution values for particulate matter. Each additional exposure to 10 $\mu g/m^3$ exposure to $PM_{2.5}$ correlated to 24 mL of decreased value in FEV_1. When modeled in terms of percent predicted lung function, every 10 $\mu g/m^3$ was associated with a decrease in 0.5 percent predicted value of FEV_1 (Goss et al., 2004). In a 12-year study conducted in Belgium, increased ambient levels of nitrogen dioxide (NO_2), ozone (O_3), and PM_{10} correlated to increased antibiotic therapy in people with CF, particularly in summer months (P. C.

Goeminne et al., 2013). This is representative of increased rates of infections in the study population.

Similarly, in Brazil, researchers found evidence of increased risk of pulmonary exacerbation after increases in the interquartile range of O_3 concentrations (Farhat et al., 2013). During the one-year study period, atmospheric levels of air pollutants were largely within acceptable standards as determined by the World Health Organization, with ozone levels considered "higher than acceptable" on eight days (Farhat et al., 2013).

While PM and other air pollutants have a demonstrated impact on pulmonary health, research directly linking residential roadway proximity to decline in lung function is extremely limited. Only one study has shown that patients with CF who live near major roadways were more likely to experience two or more pulmonary exacerbations within their study period (Jassal, Yu, Bhatia, Keens, & Davidson Ward, 2013). Using longitudinal data from a cohort of pediatric CF patients receiving care at the Children's Hospital Los Angeles, Jassal et al. did not find an association between exacerbation frequency and ambient levels of particulate matter or ozone. However, they discovered an association between residential proximity and major arterial roadways as calculated by geospatial mapping of patient home addresses as procured from the EMR (Jassal et al., 2013). This study relied upon outdoor air monitoring stations to quantify air pollution exposure to the subjects, a method that can serve as a proxy for exposure but is not considered extremely accurate (*Air Pollution, the Automobile, and Public Health*, 1988; Moschandreas et al., 2002). Furthermore, the power of Jassal et al.'s analysis was likely limited by its cohort of 145 subjects.

There is limited research to explain the mechanisms driving roadway proximity's effect on outcomes in patients with cystic fibrosis. Preliminary research indicates that pollution exposure modifies cellular behavior and gene expression. Laboratory models have

demonstrated that PM can cause toxicological reactions in the lungs of rats by altering ATP production and energy metabolism (Jin, Su, Ding, Sun, & Li, 2019). Other laboratory research demonstrated that PM exposure seems to induce oxidative stress within the epithelium of the airway, driving cytotoxic effects on the cellular level (Jeannet et al., 2016). This phenomenon was observed to be more profound within a population of mice with CF than wild-type mice (Jeannet et al., 2016; Kamdar et al., 2008). From a biological standpoint, this may be due to CF itself causing oxidant stress due to defects in the CFTR protein that limit the export of the major antioxidant in the lung: glutathione (Kettle et al., 2014).

Ozone exposure has been noted to down-regulate the expression of CFTR in rats, which likely results in more significant symptoms of the disease (Qu et al., 2009). A dearth of research in this area limits the understanding of how pollution exposure functions to cause harm in humans. However, inflammatory responses are likely involved. Pulmonary inflammation with neutrophils is one of the earliest findings in CF, occurring in the youngest of patients and as early as a few weeks of age (Khan et al., 2019). Toxic products of these neutrophils in the first few months of life are the best predictors of airway damage and progression of lung disease in later childhood (Cohen-Cymberknoh, Kerem, Ferkol, & Elizur, 2013; Margaroli & Tirouvanziam, 2016; Perrem & Ratjen, 2019). The inflammation is intense, life-long, and exacerbated by the presence of bacterial pathogens like Pseudomonas aeruginosa. As discussed above, exposure to air pollutants significantly increase inflammation in asthma. No known studies have assessed the relationship between exposure to pollutants and inflammation in CF. Since an exaggerated inflammatory response is a hallmark of CF, it is reasonable to speculate that like asthma, CF inflammation may worsen with exposure to pollutants, thus accelerating lung function decline. Further exploration is necessary to understand these links between CF and air pollution exposure.

Methodology

Subject Selection and Data

This was a retrospective cohort study that used data from the Cystic Fibrosis Patient Registry from the Emory University + Children's Healthcare of Atlanta (Emory + Children's) CF Care Center. Data from January 1, 2013-December 31, 2017 were incorporated into the study. Only patients who had been followed at the Pediatric CF Clinic for the duration of the study period and had consented to enrollment in the national cystic fibrosis registry were enrolled. Because spirometry is generally considered to be more reliable in patients after the age of seven years, patients who were at least seven at the beginning of the study period were included. Spirometry data from 2013 and later was utilized for consistency with the Global Lung Function Initiative (Quanjer et al., 2012).

Exclusion criteria were: patient was under the age of 12 at the conclusion of the study period (indicating potentially unreliable spirometry data), patient's spirometry data for the study period were incomplete (missing one or more years of data), or the subject was known to have moved residences or lived in multiple residences during the study period. A total of 110 patients met age criteria for the study. Ultimately, 12 were excluded, and 98 subjects were included in the study.

Address of residence data was collected from the electronic health record. Patients who lived outside the state of Georgia, who had lung transplants during the observational window, and those who were known to have moved more than one time during the study window, were excluded. In addition to demographic information, CF genotype, type of insurance, income, CF-related diabetes status, oral glucose tolerance test results, and hemoglobin A1c, if tested and available, were collected. In addition, for the duration of the

study period, if the person's clinical laboratory testing had indicated airway cultures positive for *Pseudomonas* and *MRSA*, this information was recorded along with spirometry test results including FEV1 in liters and FVC. To ensure that all spirometry results were standardized, a publicly available Microsoft Excel macro published by the Global Lung Function Initiative was used to convert raw results to GLI. Spirometry test results were used to calculate each subject's annual baseline lung function scores by finding the mean of the highest percent predicted value of forced expiratory volume in one second (FEV_1) result from each quarter. Annual ROD in FEV_1 for each subject were determined by calculating the yearly differences in baseline values for each year of the study.

The study was approved by Emory University's Institutional Review Board. Identifiable data was utilized so that results extracted from the Registry could be validated in Children's electronic health record.

Geomapping

Texas A&M University Geoservices were used to geocode the list of patient addresses using the USCGeocoder source. The program ArcGIS 10.5.1 (Esri, Inc., Redlands, California) and the publicly available 2013 TIGER/Line Shapefiles were used to generate maps of primary and secondary roadways in Georgia. The included roadways were defined by the United States Census Bureau (2013) as "generally divided, limited-access highways within the interstate highway system or under State management, and are distinguished by the presence of interchanges," or "main arteries, usually in the U.S. Highway, State Highway, or County Highway system" with "one or more lanes of traffic in each direction." With ArcGIS 10.5.1, the distance was calculated from each subject's home to the nearest roadway as a direct line.

Statistical Analysis

Subjects were divided into two groups based on their residential proximity to a major highway. Since research indicates that levels of airborne pollutants generated from roadways return to background levels after approximately 570 meters, the groups were divided accordingly into patients who lived within 570 meters of a primary or secondary roadway and those who were outside of that range. Analyses were designed to assess associations between residential roadway proximity and patient demographic characteristics, including sex, race, income level, and type of insurance. Residential roadway proximity and conditions that are predictive of more drastic decline in lung function were also assessed for associations, including CF diabetes status, and microbiological cultures for MRSA and *Pseudomonas aeruginosa* (Sanders et al., 2010). In instances where spirometry results were calculated using formulas other than the Global Lung Index (GLI), subjects' sex, age, height, FEV_1 in liters, and FVC in liters were utilized to convert to GLI with a macro for Microsoft Excel publicly made available by the European Respiratory Society.

Data from the variables sex, income, insurance type, MRSA status, *Pseudomonas* status, and CFRD status were assessed for standard deviation and normalcy with Wilcoxon two-sample tests and Kruskal-Wallis tests. Sex, race, insurance, income, MRSA infection status, *Pseudomonas* infection status, and CFRD status were compared to residential proximity to major roadways using mixed model analyses and Wilcoxan signed-rank tests. Parametric and non-parametric analyses were used because some variables did not meet criteria for normal distribution. Both sets of results are reported. Data are presented as mean + 95% confidence interval, and median + interquartile range.

Logistic and linear regressions, including Spearman's, and Pearson's correlations, were performed on the crude data to assess for linear relationships between the residential distance from a major roadway and annual rate of decline.

One-way analysis of variance (ANOVA) and Kruskal-Wallis tests were performed to evaluate the relationships between the demographic and clinical characteristics of interest, and residential proximity to roadways (within or outside of 570 meters). Both sets of results are reported. Two-way ANOVA was performed to evaluate the cross-effects of MRSA and CFRD with roadway proximity.

Data analysis was performed with SAS 9.4 for Windows (SAS Institute).

Results

The major outcome variable was average ROD in baseline FEV_1 over the course of the study period. The relationships between ROD and subjects' demographic and clinical characteristics are found in Figure 1. Subjects living within 570 meters of a major roadway had a mean ROD of -2.87% (95% CI: -4.21, -1.53) while subjects living further away were found to have a mean ROD of -0.94% (95% CI: -1.53, -0.36). The p-value of this calculation was 0.011.

Of the demographic and clinical characteristics that were collected, two associations were found with ROD. One was MRSA status. Subjects with no history of chronic positive MRSA acquisition in their clinical laboratory cultures had a mean ROD of -0.79% (95% CI: -1.34, -0.24) while subjects with 1-2 or 3-5 years of chronic MRSA cultures experienced mean declines of -2.89% (-4.81, -0.98) and -4.30% (-6.61, -1.99) respectively. The p-value of this calculation was 0.006. Another association was found between CFRD status and ROD. Subjects whose oral glucose tolerance tests yielded normal results experienced a median

ROD of -0.73 (IQR: -2.22, 0.51) while subjects with CFRD diagnoses declined at a median rate of -1.95 (IQR: -5.85, -1.14). The associated p-value was 0.037.

Two-way ANOVA was performed to assess the cross-interactions between characteristics that had a statistically significant association with ROD. Neither MRSA infection (p=0.0549) or CFRD status (p=0.1492) were found to have significant interactions with residential roadway proximity.

Figure 2 illustrates the relationship between ROD and residential distance from a major roadway. Linear regressions, including Pearson's and Spearman's correlations with Fisher's z-transformations, did not find statistically significant relationships ($p = 0.0829$ and $p = 0.1473$, respectively).

In order to evaluate for potential confounders, the relationship between subjects' demographic and clinical characteristics and their residential proximity to a major roadway were analyzed by means of Chi-square tests and Fisher's exact tests (Figure 2). No associations were found between subject gender, race, insurance, self-reported income, MRSA infection status, or CFRD status. Only income levels were found to be statistically significant with a p-value of 0.048.

Conclusions

Children with cystic fibrosis who live within range of increased concentrations of airborne roadway pollutants demonstrate a higher rate of decline in lung function than patients who live in a range where the levels can be considered "background," to an order of approximately three times greater. This aligns with previously discussed research that demonstrates the deleterious effects of air pollutants on lung function in both healthy individuals and those with pre-existing lung disease. It also emphasizes that people with cystic fibrosis experience a unique vulnerability to air pollution.

There are some potential confounders. First, the analysis found an association between income levels and residential roadway proximity. This could indicate that low socioeconomic status is associated with living in closer proximity to a major roadway. However, 33.7% of subjects did not report their income status and were analyzed as a separate group of non-reporters. This is a large portion of the cohort and discredits the significance of the result. One-way ANOVA analysis found no statistically significant association between the rate of decline in lung function and income level, indicating that income level is not necessarily a confounder within this model regardless of its association with residential roadway proximity.

Additionally, there is a demonstrated association between chronic MRSA infection and rate of decline. This aligns with existing research indicating that MRSA acquisition corresponds to negative outcomes and more severe CF disease (J. M. Collaco et al., 2010; Pieter C. Goeminne et al., 2013; Psoter et al., 2017; Kevin J. Psoter et al., 2015). Similarly, as evidenced in the literature, CFRD status corresponds to higher rates of decline in people with CF (Bilodeau, Bardou, Maille, Berthiaume, & Brochiero, 2016; J. M. Collaco et al., 2010; Kerem, Viviani, Zolin, MacNeill, Hatziagorou, Ellemunter, Drevinek, Gulmans, Krivec, & Olesen, 2014). Additional research would be useful in determining the two-way effect of these variables and roadway proximity on ROD.

Based on the literature and previous research, a lack of association between *Pseudomonas* acquisition and ROD is unexpected (Kevin J. Psoter et al., 2015). Greater prevalence of *Pseudomonas* infection has been observed in correlation with roadway pollution exposure (Psoter et al., 2017) and variations in local climate (Joseph M. Collaco et al., 2011). This may be due to the age of the pediatric cohort. While some young children with CF acquire *Pseudomonas* prior to six years of age (Kerem, Viviani, Zolin, MacNeill, Hatziagorou,

Ellemunter, Drevinek, Gulmans, Krivec, Olesen, et al., 2014), infection in this age group often is not chronic. To the corollary, the incidence of this bacteria increases with adulthood. An older cohort might have provided a more accurate representation of *Pseudomonas*'s longitudinal effects on lung function.

No linear relationship between rate of decline and residential distance from a major roadway was observed in the data set as a whole. The stratified analysis addresses this issue. As previously discussed, concentrations of pollutants are highest closer to roadways. The composition of traffic-related emissions is heterogeneous, with different components decreasing in concentration at variable rates (Karner et al., 2010). Children living very close to a major roadway and very far away trended towards higher rates of decline than those located centrally, indicating a potential protective factor in living between about 1000m-2000m from roadways. This may be caused by limited access to care experienced by children in extremely rural areas. Living very far from their CF care center might discourage them from scheduling or attending clinic visits when they are feeling well. These patients' records might be limited to FEV_1 values that are recorded only at times when they felt ill enough to make the long trip to clinic, and would be artificially low as a result. Alternatively, the lack of a linear relationship might be explained by the small size of the cohort lacking enough analytical power to demonstrate a significant effect.

A potential confounder that was not considered is local climate in the state of Georgia. Meteorological effects, such as humidity and temperature, have been shown to play a role in bacterial acquisition. Research has demonstrated negative associations between extreme climate features, such as heat and humidity, and bacterial acquisition in the CF population (J. M. Collaco, Raraigh, Appel, & Cutting, 2016; Knibbs, Williams, Sims, & Bell, 2017). This study cohort resides in Georgia, a region of the United States that is

characterized by prolonged heat and humidity. Further research into the links between climate and CF disease markers is necessary.

Other limitations exist in this research. While utilizing roadway proximity as a proxy for airway pollution can be useful, it is not an exact measurement of pollution exposure, nor is it the best available (Moschandreas et al., 2002). Gathering data about residential addresses was challenging. Although the IRB granted permission to contact patients and verify their residential information, including changes in address, many did not answer their telephones or respond to researcher emails. Address data from medical records was utilized in order to standardize the collection. While Children's Healthcare of Atlanta verifies that information with patients at every clinic visit and there is reasonable certainty of accuracy, the addresses were not all verified by the subjects.

The size of the study cohort was also a limiting factor. When the cohort was assessed for exposures such as income or insurance level, the group sizes become small enough to limit the power of the analysis. It is likely that similar analysis of a larger study population would yield greater significance in some of the areas of interest.

Lastly, the analysis could have included additional clinical variables such as CF genotype, pancreatic sufficiency status, and otherwise; there are a multitude of factors that are shown to correspond with FEV_1 decline in this population (Kerem, Viviani, Zolin, MacNeill, Hatziagorou, Ellemunter, Drevinek, Gulmans, Krivec, Olesen, et al., 2014). Further research would be valuable in elucidating the roles of all of these factors within the complex model of air pollution exposure and cystic fibrosis lung function decline.

In conclusion, this research has shown a significant association between residential roadway proximity – a surrogate for exposure to air pollutants - and rate of decline in lung function. While there is room for more exploration within this subject, the existing data

serves as compelling evidence to guide policy-making towards limiting roadway emissions. It also serves to educate clinicians and people fighting cystic fibrosis about environmental factors that increase the burden of care and challenge quality of life.

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Appendices

List of Definitions
Baseline Lung Function In the Atlanta Care Center clinics, the average of the best values of each quarter for spirometry testing including FEV_1 and percent predicted FEV_1, as calculated with GLI equations.
Rate of Decline Rate of decline in lung function is the difference in a patient's baseline percent predicted FEV_1 values between two consecutive calendar years.
FEV_1 Forced expiratory volume in the first second.
Chronic Pseudomonas Chronic *Pseudomonas* infection is defined as ≥ 50% of all respiratory cultures during one year of the study period demonstrate growth of *Pseudomonas aeruginosa* (Lee et al., 2003).
Chronic MRSA Chronic *MRSA* infection is defined as ≥ 50% of all respiratory cultures during one year of the study period demonstrate growth of *MRSA*

Table 1: Summary of Background Normalized Data

TABLE 1. Summary of Background Normalized Data

group	pollutant	approximate multiplier above background concentration at edge-of-road	approximate distance required to reach background concentration (m)[a]
rapid: >50% drop by 150 m	CO	21[b]	—[c]
	metal deposition	2.9	161
	UF1 particle no.	4.0	189
less rapid or gradual decay/change	benzene	2.1	280
	EC	1.7	420[d]
	NO	3.3	565[e]
	NO_2	2.9	380[f]
	NO_X	1.8	570[e]
	PM_{10}	1.3	176
	UF2 particle no.	4.8	910[e]
	VOC1	2.0	270

[a] The approximate distances were derived from an expanded version of Figure 2; the distance point at which the smoothed line reached a value of one on the *y*-axis is cited here as background. [b] Near-road CO concentrations extended outside of the range plotted in Figure 2. [c] CO concentrations did not reach background within the 285 m for which data were measured. [d] Background normalized concentrations attained an approximate minimum value of 1.1 at this distance from the road. [e] Reached background concentrations outside of the range plotted in Figure 2. [f] Background normalized concentrations attained an approximate minimum value of 1.08 at this distance from the road.

From: (Karner et al., 2010)

Figure 1: Average Rate of Decline in Lung Function

Characteristic	Parametric Results		Non-Parametric Results	
	Average Rate of Decline Mean (95% CI)	***p*-Value**	**Average Rate of Decline Median (IQR)**	***p*-Value**
Residential location				
Within 570m	-2.87 (-4.21, -1.53)	**0.011**	-2.18 (-5.38, -0.09)	**0.028**
Greater than 570m	-0.94 (-1.53, -0.36)		-1.13 (-2.24, 0.33)	
Gender				
Male	-1.32 (-2.12, -0.52)	0.459	-1.13 (-3.00, 0.25)	0.780
Female	-1.76 (-2.66, -0.86)		-1.22 (-2.27, 0.17)	
Race				
White	-1.46 (-2.09, -0.83)	0.523	-1.15 (-2.54, -0.01)	0.502
Other	-2.10 (-4.12, -0.06)		-1.85 (-4.80, 0.28)	
Insurance				
Private	-0.86 (-1.50, -0.22)	0.12	-1.10 (-2.58, 0.56)	0.20
Medicaid	-2.76 (-4.14, -1.40)		-1.50 (-5.94, -0.41)	
Private + Medicaid	-1.93 (-5.02, 1.16)		-1.70 (-1.92, -1.14)	
Other	-1.78 (-3.34, -0.21)		-1.68 (-2.58, -0.97)	
Income				
No report	-1.72 (-2.58, -0.86)	0.654		0.915
$0-29,999	-2.95 (-7.72, 1.81)		-2.02 (-6.74, 1.85)	
$30,000-59,999	-1.39 (-2.51, -0.28)		-1.13 (-2.94, 0.36)	
$60,000-89,999	-2.11 (-5.92, 1.70)		-1.88 (-5.56, 1.92)	
$90,000+	-0.96 (-1.81, -0.10)		-1.05 (-2.29, -0.01)	
MRSA Status				
No chronic MRSA infection	-0.79 (-1.34, -0.24)[a]	0.006	-0.90 (-2.18, 0.48)[a]	**0.003**
1-2 years of chronic MRSA	-2.89 (-4.81, -0.98)[b]		-2.63 (-4.36, -1.14)[b]	
3-5 years of chronic MRSA	-4.30 (-6.61, -1.99)[b]		-4.23 (-6.35, -1.25)[b]	
Pseudomonas Status				
No chronic Pseudomonas infection	-1.31 (-2.15, -0.48)	0.519	-1.16 (-2.66, 0.50)	0.462

1-2 years chronic Pseudomonas	-1.57 (-3.20, -0.06)		-1.10 (-2.22, -0.11)	
3-5 years chronic Pseudomonas	-2.03 (-2.98, -1.07)		-1.65 (-2.97, -0.26)	
CFRD Status				
Normal glucose tolerance	-0.85 (-1.69, -0.01)	0.0740	-0.73 (-2.22, 0.51)[a]	**0.037**
Impaired glucose tolerance	-1.17 (-2.84, 0.51)		-1.17 (-2.25, 0.98)[a,b]	
CF-related diabetes	-3.1 (-4.91, -1.29)		-1.95 (-5.85, -1.14)[b]	

Figure 2: Average Rate of Decline vs. Residential Roadway Proximity

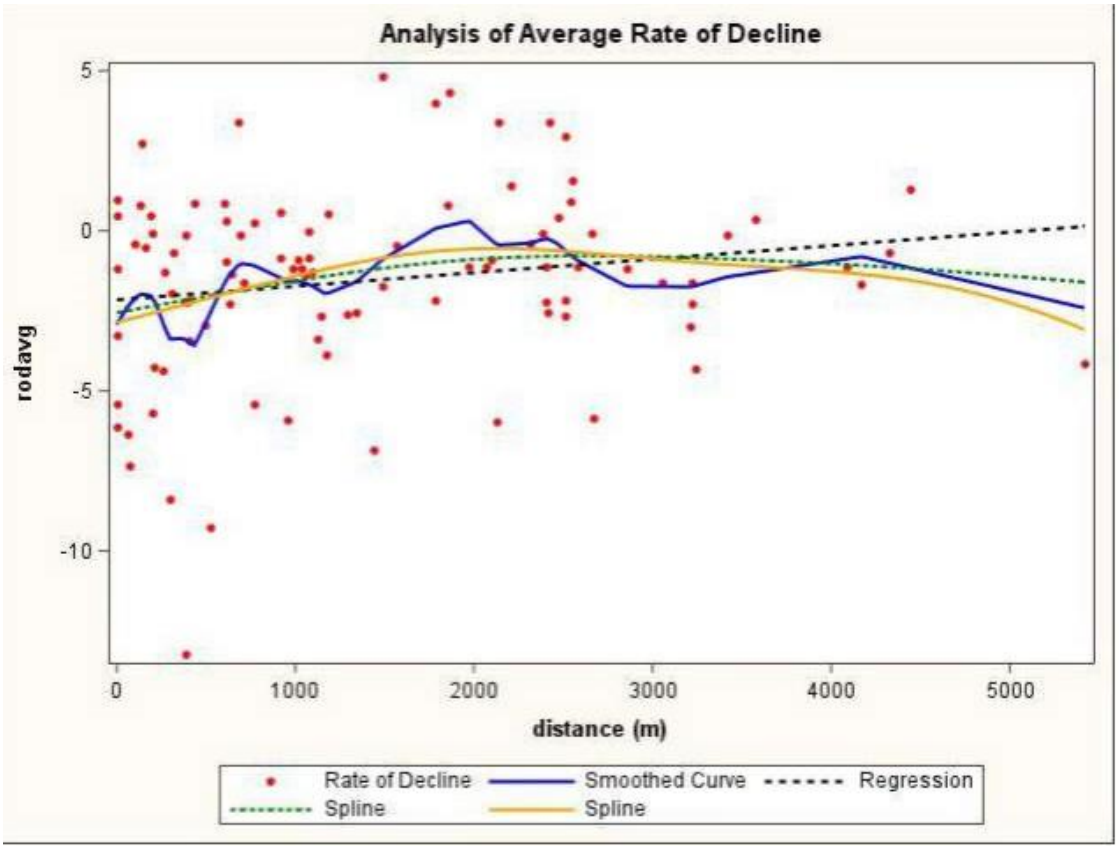

Figure 3: Rate of Decline and Distance from Major Roadway

Residential Proximity to Major Roadway	**N = 98**	**Within 570m (n = 30)**	**570m or Greater (n = 68)**	**Parametric *p*-value**	**Non-parametric *p*-value**
Age (mean, SD)	16 (2.55)				
Gender				0.893	1.00
Male	50 (51%)	15 (40%)	35 (51.5%)		
Female	48 (49%)	15 (50%)	33 (48.5%)		
Race				0.652	0.751
White	86 (87.8%)	27 (90%)	59 (86.8%)		
Other	12 (12.2%)	3 (10%)	9 (13.2%)		
Insurance				0.771	0.775
Private	59 (60.2%)	16 (53.3%)	43 (63.2%)		
Medicaid	30 (30.6%)	11 (36.7%)	19 (27.9%)		
Private + Medicaid	5 (5.1%)	2 (6.7%)	3 (4.4%)		
Other	4 (4.1%)	1 (3.3%)	3 (4.4%)		
Income					
No report	33 (33.7%)	7 (23.3%)	26 (38.2%)	**0.044**	0.053
$0-29,999	8 (8.2%)	6 (20%)	2 (2.9%)		
$30,000-59,999	15 (15.3%)	6 (20%)	9 (13.2%)		
$60,000-89,999	9 (9.2%)	2 (6.7%)	6 (8.8%)		
$90,000+	34 (34.7%)	9 (30%)	25 (36.8%)		
Chronic MRSA				0.093	0.083
No chronic infection	72 (73.5%)	18 (60%)	54 (79.4%)		
1-2 years chronic MRSA	13 (13.3%)	5 (16.7%)	8 (11.8%)		
3-5 years chronic MRSA	13 (13.3%)	7 (23.3%)	6 (8.8%)		
Chronic Pseudomonas				0.462	0.482
No chronic infection	55 (56.1%)	18 (60%)	37 (54.4%)		
1-2 years chronic Pseudomonas	19 (19.4%)	7 (23.3%)	12 (17.7%)		
3-5 years chronic Pseudomonas	24 (24.5%)	5 (16.7%)	19 (27.9%)		

CFRD Status				0.318	0.327
Normal Glucose Tolerance	48 (49.0%)	17 (56.7%)	31 (45.6%)		
Impaired Glucose Tolerance	30 (30.6%)	6 (20%)	24 (35.3%)		
CF-related Diabetes	20 (20.4%)	7 (23.3%)	13 (19.1%)		