Measuring the Effects of Mouse Allergen and Black Carbon Exposure on Children Living in New York City with Allergic Diseases

Medina Samira Jackson-Browne

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Abstract

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Background: Exposure to allergens and combustion by-products are risk factors for allergic health outcomes in children. The connection between exposure to allergens and allergic diseases such as asthma, in some children, is through the development of a biological condition known as allergic sensitization. In susceptible children, sensitization may occur when early-life exposure to an allergen causes the production of immunoglobulin E (IgE) antibodies. In asthmatic children, repeated exposures to this allergen may lead to clinical manifestations including airway inflammation, airway mucous production, bronchospasms, and bronchial hyper-responsiveness.

Sensitization and repeated exposure to allergens may, therefore, be important risk factors for asthma morbidity in children. Findings from a cross-sectional asthma study of children living in NYC published previously by our group found a positive association between cockroach and dust-mite allergens measured in bed dust and sensitization risk to these allergens consistent with other studies. However, contrary to previously published research, no association was observed between mouse allergen measured in bed dust and mouse sensitization risk in our study.

In urban areas such as New York City (NYC), exposure to combustion by-products, including black carbon (BC), has been shown to be associated with both asthma development and asthma morbidity. BC has been proposed to exacerbate asthma symptoms directly through

airway irritation or by behaving as an adjuvant, enhancing the production of IgE antibodies following exposure to an allergen in sensitized individuals. Our group previously observed an association between indoor measured BC concentrations and airway inflammation, however no association was found between BC and asthma symptoms for children living in NYC.

In the present study, we sought to address some of the limitations of the previous work. These limitations included a singular measurement of mouse allergen exposure, a shorter-term BC exposure measurement, and a cross-sectional study design for asthma symptom risks. My overarching hypothesis for this dissertation is that exposures to mouse allergen and BC are significant risk factors for allergic sensitization and asthma morbidity, respectively, for children living in NYC. I tested these hypotheses in three separate manuscripts by assessing multiple mouse exposure measurements with the risk for mouse sensitization (Chapter 2), testing the correlation between 7-day measured indoor BC and particulate matter smaller than 2.5 microns ($PM_{2.5}$) concentrations with annual modeled outdoor BC and $PM_{2.5}$ concentrations (Chapter 3), and determining whether annual modeled outdoor BC concentration is associated with persistent asthma symptoms, over a three-year period, for asthmatic children in NYC (Chapter 4).

Methods: For all manuscripts, data from an asthma case-control cohort of children (age 7-8 years) previously established by our group, the NYC Neighborhood Asthma and Allergy Study (NAAS), was utilized for analysis (n=350). Kitchen floor and bed settled dust samples were collected from the children's home during the initial home visit. Mouse allergen concentrations were quantified from both kitchen floor and bed dust samples using an enzyme-linked immunosorbent assay (ELISA). Blood samples were also collected during this visit. IgE antibodies to mouse allergens were measured by ImmunoCAP (Phadia, Uppsala, Sweden) from these blood samples. Information on the frequency of mouse sightings in the previous 12 months

was extracted from a questionnaire administered to parents of NAAS children. Neighborhood and school mouse sightings were collected from reports from the NYC Department of Health and Mental Hygiene (DOHMH). Indoor $PM_{2.5}$ and BC samples were collected from air samplers placed in NAAS children's home for an average of 7 days. In collaboration with the NYC DOHMH, we were given access to 2-year averaged modeled outdoor $PM_{2.5}$ and BC concentrations collected from air monitors at 124 street-level locations throughout NYC from 2008-2010. After the initial home visit, asthmatic NAAS children were followed-up annually for asthma symptoms. The questionnaire data collected from the asthmatics followed were used to evaluate the persistence or remittance of asthma symptoms over the 3-years following the initial home visit.

Results: In our mouse study we found that increasing mouse allergen measured from kitchen floor dust and children whose parents reported greater than weekly mouse sightings in the previous 12 months has an increased risk of mouse sensitization (prevalence risk (PR) = 1.09 [1.02-1.17], p=0.04 and PR= 3.84 [1.95-6.97], p=0.001 respectively). Neither mouse allergen measured from settled bed dust (PR = 1.06 [0.95-1.19], p=0.46) nor neighborhood rodent reports (PR = 1.25 [0.94-1.68], p=0.16) were significantly associated with an increased risk of sensitization to mouse. Exposure to mouse at school was also not associated with an increased risk of mouse sensitization (PR=0.66 [0.35-1.26], p=0.30). Results from the correlation study indicated both annual modeled outdoor $PM_{2.5}$ and BC concentrations were weakly correlated with 7-day measured indoor $PM_{2.5}$ and BC concentrations ($r = 0.21$ and 0.39, respectively, $p < 0.01$). However, annual modeled outdoor BC concentrations predicted almost 20% of the variability of 7-day measured indoor BC (R^2=0.19, p<0.001) compared to only 4% of the variability of 7-day indoor $PM_{2.5}$ explained by annual modeled outdoor $PM_{2.5}$, which predicted

measured indoor $PM_{2.5}$ ($R^2 = 0.04$, $p < 0.001$). Our regression analysis of the asthma morbidity study found no significant association between longer-term neighborhood modeled BC concentrations at study participant's home (PR = 0.87 [0.58-1.29, p=0.49] and school addresses (PR =1.09 [0.77-1.56], p=0.60) and persistent asthma symptoms.

Conclusions: My findings suggest that mouse allergen measured from kitchen floor dust and parent reported mouse sightings are important risk factors of mouse sensitization for children living in urban areas such as NYC. The results of the BC analysis indicate a moderate correlation between annual modeled outdoor BC concentrations and 7-day measured indoor BC concentrations. The annual modeled outdoor BC also predicted 20% of the variability in 7-day measured indoor BC. Conversely, $PM_{2.5}$ analysis indicate that annual modeled outdoor $PM_{2.5}$ is not correlated with 7-day measured indoor $PM_{2.5}$ concentrations. Finally, regression analysis of BC exposure and asthma morbidity indicate that annual modeled outdoor BC is not predictive of persistent asthma symptoms in our cohort.

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Preface

Dissertation Structure

This dissertation consists of an introduction, three self-contained original research papers, and a conclusion. The introduction provides background on the health effects of allergen and black carbon exposure. Chapters 2 through 4 are comprised of three research manuscripts, each of which corresponds to one of my three hypotheses. Each chapter is structured as a scientific paper with its own introduction, description of methods, results, and discussion sections. The three research papers are in preparation for publication. The chapter following the last manuscript summarizes findings from Chapters 2 through 4. Finally, Chapter 6 includes the overall conclusions of this dissertation and recommendations for future directions in asthma research.

Chapter 1: Introduction

Childhood asthma in urban areas

Over the last half of the 20th century, the prevalence of childhood asthma and allergic diseases has increased greatly in westernized countries, specifically in urban areas (Eder et al., 2006). Increased environmental exposure to aeroallergens, combustion by-products and environmental tobacco smoke, in conjunction with decreased microbial exposure have been shown to be the main drivers of increased childhood asthma and allergic disease prevalence in urban communities (Eder, 2006). New York City's (NYC) childhood asthma prevalence increased at a higher rate compared to other communities in New York and the US in general. The NYC Department of Health and Mental Hygiene (DOHMH) reported that childhood asthma prevalence ranged from 3% to 19% throughout the city in 2003 (Garg et al., 2003). In some NYC areas, there are large differences in prevalence of asthma found between geographically adjacent (boarding) neighborhoods. These differences in prevalence have also been shown to be unevenly distributed throughout the city, with poorer neighborhoods with larger African-American and Hispanic populations bearing the greatest childhood asthma prevalence burden.

Allergic sensitization and asthma

Allergen exposure is a risk factor for asthma in children living in urban communities (Eder, 2006; Illi et al., 2006; Lau et al., 2000; T. a Platts-Mills et al., 1997). The pathway in which a child exposed to allergens and subsequently develops asthma is thought to occur through the development of allergic sensitization (Ker et al., 2009; Spergel, 2010). This allergic pathway to disease is known as the allergic or atopic march. The atopic march refers to the natural progression of allergic diseases, including asthma, that usually begins in early childhood (Ker, 2009; T. a E. Platts-Mills, 2007; Spergel, 2010). This progression is characterized by a

immunoglobulin E (IgE) antibody production from B-cells of the immune system specific to a known allergen and clinical symptoms associated with exposure to that specific allergen. This production of specific-IgE following allergen exposure is the defining characteristic of allergic sensitization (Holt et al., 2005; Matricardi et al., 2009). Sensitization development usually occurs early in life and can persist into adulthood, however, sensitization and/or the associated clinical symptoms often remit during early or late adolescence. Since the incidence of immune related diseases is much higher during early childhood (Ker, 2009; Spergel, 2010; Wahn, 2007), the first decade of life is unique compared to later ages.

Mouse allergen and sensitization

Exposure to indoor allergens has been shown to be an important environmental exposure risk for allergic sensitization and most allergic diseases. In particular, cockroach allergen exposure is strongly associated allergic sensitization and asthma for children living in urban northeastern US communities. Other indoor allergens associated with allergic sensitization and asthma include allergens such as dust mite, and allergens from mammals including dogs, cat, rat, and mouse allergens (Matthew S. Perzanowski et al., 1999; T. a Platts-Mills, 1997; Sporik et al., 1999). Interventions to reduce allergens in urban homes have been difficult to sustain over long periods of time (Gergman et al., 1999), which may contribute to the increasing prevalence of allergic sensitization for children living in urban areas (Eder, 2006).

In a previously established asthma cohort from our group, the NYC Neighborhood Asthma and Allergy Study (NAAS), we found an association between allergen concentrations in children's homes and neighborhood asthma prevalence. Homes in areas with high asthma prevalence had higher cockroach, cat, and mouse allergen concentrations compared to homes in areas with low asthma prevalence (Olmedo et al., 2011). High cockroach, dust mite, and cat

allergen concentrations were also associated with allergic sensitization to those allergens. However, mouse allergen concentration was not associated with sensitization to mouse. Even so, studies have consistently found mouse allergen, which is prevalent in urban homes, to be an independent risk factor for asthma morbidity (Moncrief et al., 2012; Peters et al., 2007; Wanda Phipatanakul et al., 2000, 2005). Most studies exploring the relationship between indoor allergen exposure and sensitization in asthmatic children living in urban areas include mouse allergen as an important exposure measure.

Mouse exposure and measurement

The main mouse allergen measured in asthma epidemiological studies is mouse urinary protein (MUP), specifically Mus m 1. The sampling method is either from air samplers or settled dust. Both sample sources have been shown to be valid for detecting mouse allergen (G L Chew et al., 2005). Airborne Mus m 1 allergen measured from urban homes of school aged children in Baltimore, Maryland (USA) was only moderately correlated with settled dust measurements, however the concentrations of mouse allergen in the settled dust was 10 orders of magnitude higher compared to airborne mouse allergen concentrations (Matsui et al., 2005). This finding indicates that mouse allergen measured from settled dust may be high enough to trigger clinical symptoms.

Early mouse allergen research was concentrated in research facilities that used mice in their experiments. The main focus of these studies was to address the possible adverse health outcomes of facility workers from mouse allergen exposure. One such study found significantly greater Mus m 1 concentrations in the air of rooms where mice were housed compared to other rooms within the research facility (Ohman et al., 1994). In this study, Mus m 1 was also detected in research areas which did not house research mice. This finding indicates the possibility of

passive transfer of mouse allergens by facility workers or through air ducts connecting rooms within the facility. The lack of association between mouse allergen concentrations measured from bed dust in the NYC NAAS may have been due to the low concentration of mouse allergen in bed dust resulting from passive transfer from a primary source in a different area of the home. Matsui (2005) reported Mus m 1 concentrations could be detected in most of the homes in their study, with the highest levels collected from the kitchen (Matsui, 2005).

School-aged children often spend at least six hours per day in school, five days a week for 9-10 months a year. In studies investigating cockroach and mouse allergen levels in northeastern US schools, Chew (2005) detected mouse allergen in up to 81% of the schools (G L Chew, 2005). Similarly, Amr (2003) also found Mus m 1 in settled dust collected from Baltimore area schools (Amr et al., 2003). Low levels were observed in classrooms and offices, whereas the highest levels were found in the schools' cafeteria. The NYC DOHMH conducts annual school cafeteria inspections via the Bureau of Environmental Surveillance and Policy department. At least once every year, every public and private school's cafeteria in NYC is inspected and reports can be made available via Freedom of Information Act requests. In addition to school inspections, the NYC DOHMH also administers community health surveys (CHS) as well. Published results from the 2003 CHS revealed vast differences in the frequency of rodent sightings by neighborhood (Kass et al., 2005). In addition to measuring mouse allergen from settled dust, other measurements of exposure to mouse in children can be ascertained from results of the NYC CHS and school cafeteria food inspection reports.

Particulate matter and asthma

Exposure to particulate matter is associated with risk of respiratory and cardiovascular diseases (Cornell et al., 2012; Diaz-sanchez et al., 1997; Kinney et al., 2002; McCreanor et al.,

2007; Nadeau et al., 2010; Patel et al., 2010). Particulate matter smaller than 2.5 microns ($PM_{2.5}$) is directly emitted from combustion processes or formed in the atmosphere through chemical processes. $PM_{2.5}$ includes a mixture of compounds including sulfate, nitrate, elemental (black) carbon, organic carbon, and crustal material (Nino Künzli, Laura Perez, 2011). PM smaller than 10 microns (PM_{10}) can penetrate into the respiratory system through the nose and smaller particles such as $PM_{2.5}$ can reach down into the lower airways.

BC comprises between 4-11% of $PM_{2.5}$ from all sources however, BC comprises up to 75% of $PM_{2.5}$ from the incomplete combustion of diesel and other carbon containing fuel sources (Lall et al., 2006; Matte et al., 2013). High concentrations of BC has been shown to be associated with a higher risk of respiratory diseases including asthma (Cornell, 2012; Diaz-sanchez, 1997; Nadeau, 2010; Patel, 2010). Asthma prevalence in urban areas has also been shown to be associated with emissions from diesel truck traffic (Diaz-sanchez, 1997).

In general, the proposed mechanisms by which exposure induces asthma symptoms include airway irritation following inhalation of BC or $PM_{2.5}$ particles, increased epithelial permeability from oxidative stress caused by inhalation of BC and $PM_{2.5}$ particles , and adjuvant activity by inhaled BC attaching to antigen presenting cells concurrently with allergens enhancing T cell activation following allergen exposure (Gowers et al., 2012; Guarnieri et al., 2014). Studies have found BC exposure to be associated with FeNO, a marker of airway inflammation, among both sensitized and non-sensitized asthmatics (Cornell, 2012; Delfino et al., 2006).

Exposure and measurement

According to the US Environmental Protection Agency (EPA) the national annual average $PM_{2.5}$ concentrations decreased 24% from 2001 to 2010. Furthermore, total $PM_{2.5}$

emissions have declined by more than 50% since 1990 (EPA, 2010). NYC saw a 16% decline in $PM_{2.5}$ from 2008-2013. The main sources attributed to $PM_{2.5}$ concentrations in NYC are due to traffic density, building density, density of residual oil burning boilers, and industrial processes (NYC Department of Mental Health and Hygiene, 2015). In addition to $PM_{2.5}$, roadways designated as truck routes are major sources of BC in NYC. Proximity to truck routes have been shown to be associated with asthma morbidity (McConnell et al., 2010; McCreanor, 2007; Morgenstern et al., 2008). Another source of BC in NYC are buildings that burn residual oil for space and water heating. Residual oils #4 and #6 are of particular concern due to their high sulfur and nitrogen oxide concentrations (NYC Department of Mental Health and Hygiene, 2015). According to the NYC DOHMH, only 1% of all buildings in the city produces 86% of the total BC pollution from buildings (NYC Department of Mental Health and Hygiene, 2015). Buildings burning these oils are unevenly distributed throughout the city and contribute to the variations in BC concentrations by neighborhood (Matte, 2013; Patel, 2010).

Although both $PM_{2.5}$ and BC exposure are associated with asthma in children, the level of personal exposure to a particular pollutant in childhood may differ by pollutants (Götschi et al., 2002; Kheirbek et al., 2013; Tunno et al., 2015). Though most people, including children, spend approximately 85% of their time indoors, the majority of indoor $PM_{2.5}$ concentrations (50-70%) originate from outdoor sources that penetrate through doors and windows (Götschi, 2002; LaRosa et al., 2002; Long et al., 2000). A study in Boston found better correlation between indoor and outdoor $PM_{2.5}$ concentrations compared to BC (Clougherty, Wright, et al., 2008) indicating a difference in source or penetrance of these air pollutants. Other studies suggest that outdoor concentrations of BC are a better predictor of individual exposure compared to $PM_{2.5}$, since $PM_{2.5}$ varies more gradually over space compared to BC (Hochadel et al., 2006; Ross et al.,

2007). In NYC, approximately 50% of $PM_{2.5}$ concentrations are from distant sources but over 90% of BC concentrations are from local sources (Lall, 2006). Traffic-associated BC has shown to rapidly decrease at distances greater than 300 meters(m) from a major road, while risk for asthma morbidity is greatest for individuals living within 75-100m from a major highway (Jung et al., 2010; McConnell et al., 2006; Venn et al., 2002). The NYC NAAS also found positive correlations between BC concentrations and both the number of buildings burning residual oil and the density of truck routes (Cornell, 2012).

Summary

Measuring mouse allergen and BC exposure from multiple locations can help inform intervention strategies to reduce exposure and prevent symptoms related to allergy and asthma for children living in urban areas. BC and $PM_{2.5}$ concentrations vary over space and time, therefore assessing their associated respiratory health effects may also be influenced by when and where their measurement occurs. The main goals of this dissertation were to (1) examine the relationship between mouse exposure with the risk of sensitization to mouse, (2) compare longer-term neighborhood modeled BC and $PM_{2.5}$ concentrations to shorter-term indoor measured BC and $PM_{2.5}$ concentrations, and (3) determine the association, if any, between longer-term neighborhood modeled BC exposure and asthma morbidity.

Statement of Hypothesis

This molecular epidemiologic study contributes to the growing literature investigating the effects of environmental allergens and particulate matter exposure on allergic disease morbidity for children living in urban communities. We previously measured the risk of sensitization in children age 7-8 years living in NYC. We found that allergens from cockroach, dust mite, and cat, settled bed dust to be associated with sensitization but mouse allergen was not. We also found associations between indoor BC exposure and airway inflammation, but not asthma symptoms. As our mouse and BC exposure results were not consistent with previous epidemiological findings, this study will seek to address these inconsistency, thereby enhancing the body of knowledge in the field of asthma research. We focused on the following three main areas of interest:

(1) The impact of mouse exposure from multiple locations on mouse sensitization. Exposure was assessed using:

(a) settled dust from the kitchen floor and bed of children participants;

(b) parent reported mouse sightings inside of the participant's home;

(c) from neighborhood level rodent reports from NYC surveys; and

(d) school cafeteria inspection reports of mouse infestation

(2) To assess longer term $PM_{2.5}$ and BC exposure by measuring the correlation between modeled outdoor $PM_{2.5}$ and BC concentrations and measured indoor $PM_{2.5}$ and BC concentrations.

(3) To measure the effect of BC exposure on the persistence of asthma symptoms in children from age 7-8 to 11-12 years.

My overarching hypothesis is that **exposure to mouse allergen and black carbon are significant risk factors of sensitization and asthma morbidity, respectively, for children living in New York City.**

Hypothesis 1a:

We hypothesized that mouse allergen concentration in settled kitchen floor dust would be a better representation of indoor mouse exposure versus mouse allergen measured from settled bed dust and therefore associated with an increased risk for mouse sensitization.

Specific Aim 1a:

We compared the risk of mouse sensitization associated with mouse allergen concentrations measured from settled kitchen floor dust to mouse sensitization risk associated with mouse allergen concentration measured from settled bed dust.

Hypothesis 1b:

We hypothesized that longer-term mouse exposure measurements both inside and outside of the home would be associated with an increased risk of mouse sensitization.

Specific Aim 1b:

We determined whether parent-reported mouse sightings in the past 12-months, neighborhood reported rodent sightings in the past 90 days, and signs of mouse in school cafeterias from the prior school year would all be associated with an increased risk of sensitization to mouse.

Hypothesis 2a:

We hypothesized that 7-day measured indoor $PM_{2.5}$ and BC concentrations would be positively associated with annual modeled outdoor $PM_{2.5}$ and BC concentrations.

Specific Aim 2a:

We measured the correlation coefficient between annual modeled outdoor $PM_{2.5}$ and BC concentrations and 7-day measured indoor $PM_{2.5}$ and BC concentrations.

Hypothesis 2b*:*

We hypothesized that temporally adjusting the annual modeled outdoor $PM_{2.5}$ and BC concentrations would explain a greater proportion of the variability of the 7-day measured indoor $PM_{2.5}$ and BC concentrations compared to unadjusted modeled outdoor $PM_{2.5}$ and BC concentrations.

Hypothesis 3:

We hypothesized that annual modeled outdoor BC outdoor exposure would be associated with persistence of asthma symptom in children from age 7-8 to 11-12 years.

Specific Aim 3:

We measured the association between annual modeled outdoor BC exposure among asthmatics at age 7-8 years and asthma symptoms within the same asthmatics at age 11-12 years.

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Chapter 2: Domestic Mouse Allergen and Reported Mouse Infestation in homes and Neighborhoods and Sensitization to Mouse Allergen Among Middle-income Children Living in New York City.

Medina S. Jackson-Browne, MS, MPhil[1], Gina S. Lovasi, PhD[2], Adnan Divijan[1] Andrew G. Rundle, Dr.PH[2], Luis Acosta, MD[1], Omar Olmedo, BS[1], Judith S. Jacobson, DrPH[2], Inge F. Goldstein, DrPH[2,] Rachel L. Miller, MD[1, 3,5]Matthew S. Perzanowski, PhD[1]

[1]Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York, NY
[2]Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY
[3]Department of Pediatrics, Columbia University College of Physicians and Surgeons, New York, NY
[4] Institute for Social and Economic Research and Policy, Columbia University, New York, NY
[5] Division of Pulmonary, Allergy, Critical Care Medicine, Department of Medicine, Columbia University College of Physicians and Surgeons, New York, NY

Corresponding author: Medina S. Jackson-Browne, MS, MPhil
Department of Environmental Health Sciences,
Mailman School of Public Health,
Columbia University
722 West 168th Street, 11th floor
New York, New York 10032
e-mail: msj2126@cumc.columbia.edu

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ABSTRACT

Rationale: The New York City Neighborhood Asthma and Allergy Study (NYC NAAS) previously reported no association between mouse allergen concentration measured in settled bed dust and mouse sensitization risk (Olmedo, 2011). In this present study, we hypothesized that mouse allergen concentration in settled kitchen floor dust would be a better indicator for risk of sensitization to mouse allergen compared to mouse allergen concentration in settled bed dust. We also hypothesized that in-home-parent and neighborhood reports of rodent and/or mouse sightings would be associated with mouse allergen concentrations from both bed and kitchen floor dust and that these reports would be associated with increased risk of sensitization to mouse.

Methods: The NYC NAAS is an asthma case-control study of 7-8 year-old children living in NYC. Serum and dust samples were collected during a home visit. A questionnaire about the child's health was also administered to the parent during this visit. The frequency of residents reporting rodent sightings by neighborhood and mouse sightings from school cafeteria inspections were obtained from the NYC Department of Health and Mental Hygiene. Modified Poisson Regression analysis was used to determine the prevalence risk (PR) for mouse sensitization.

Results: Among 332 children, 12% (40) were sensitized to mouse. The frequency of parent reported mouse sightings within the home and neighborhood reported rodent sightings were associated with Mus m 1 allergen concentrations from both kitchen floor and bed dust ($p < 0.001$ respectively for both). After adjusting for confounders, for every doubling of Mus m 1 allergen concentration in kitchen floor dust there was an associated 9% increased risk for sensitization to mouse (PR=1.09, p= 0.04) and there was a 6% increased risk for mouse sensitization (PR= 1.06,

p = 0.46) associated with Mus m 1 allergen from bed dust. Children living in homes where parents reported greater than weekly mouse sightings were almost four times more likely to be sensitized to mouse (PR= 3.84, $p < 0.001$) compared to children in homes no mouse sightings. Neighborhood rodent sighting frequencies and school mouse sightings from cafeteria reports were both not significantly associated with increase mouse sensitization risk after controlling for co-variates ($p = 0.16$ and $p=0.30$, respectively).

Conclusions: Unlike bed dust, Mus m 1 allergen concentration from kitchen floor settled dust was associated with an increased risk of sensitization to mouse. Greater-than-weekly parent reported mouse sightings in the home and the frequency of residents in the neighborhood sighting rodents were both associated with Mus m 1 concentrations from bed and kitchen floor settled dust, but only parent-reported mouse sightings was associated with increased risk of sensitization to mouse.

INTRODUCTION

From the late 20th century into the 21st, there was a steady increase in the prevalence of asthma among children living in urban areas of the United States. NYC's childhood asthma burden has increased at a higher rate compared to those of other US cities (Garg et al., 2003). The NYC DOHMH (2003) indicated that childhood (age 5) asthma prevalence was almost 3 times as high in some areas of NYC versus nearby NYC neighborhoods (Kass, 2005). These variations in asthma prevalence have been attributed to differences in pre- and postnatal exposure to environmental tobacco smoke (ETS), indoor and outdoor allergen exposure, and air pollution (Eder, 2006; Garg, 2003). Environment characteristics common to urban neighborhoods, such as close living quarters, poor geographic infrastructure, greater amount of tree canopy, increased exposure to indoor allergens (such as dust mite and cockroach), and air pollution may contribute to higher allergen exposure and may explain higher asthma prevalence among children living in cities. Allergen exposure is of particular interest to the study of asthma onset because allergic sensitization is strongly associated with asthma morbidity in some asthmatics (Ahluwalia et al., 2013; Amr, 2003; Garg, 2003; Kass, 2005; Lau, 2000; Matsui, 2009; Matsui et al., 2006, 2007). However, there have been few population-based studies on sensitization prevalence.

Many studies exploring indoor allergen exposure include mouse allergen as a risk factor for sensitization and asthma prevalence (Ahluwalia, 2013; Matsui, 2009, 2006, 2007; Matsui, Krop, et al., 2004; Matsui, Wood, et al., 2004; W Phipatanakul et al., 2000; Wanda Phipatanakul et al., 2007; Wanda Phipatanakul, 2000; Wanda Phipatanakul et al., 2004; Wanda Phipatanakul, 2005). We previously observed that in 7-8 year-old children living in middle-income New York City (NYC) homes, mouse allergen measured in bed dust was not associated with increased risk

of mouse sensitization. This finding was inconsistent with previously published mouse allergen studies (Matsui, 2009, 2007, 2004; W Phipatanakul, 2000). Studies measuring mouse allergen in the home found higher concentrations of mouse allergen in the kitchen floor dust compared to bed dust and other areas of the home (Salo et al., 2009). We hypothesized that the concentration of mouse allergen in kitchen floor dust would be associated with an increased risk of sensitization to mouse for children living in NYC. We also examined associations between parent-reported mouse sightings with both mouse allergen concentrations from both bed and kitchen floor dust and determined if these sightings were associated with an increased risk of sensitization to mouse. Since children at this age (7-8 years) spend a portion of their day in school during most of the year, we also hypothesized that cafeteria inspection reports of mouse infestation in schools and sightings of rodents reported in population surveys at the neighborhood level would also be associated with increased risk of sensitization to mouse.

METHODS

Cohort design

The New York City Neighborhood Asthma and Allergy Study (NYC NAAS) is an asthma case-control study that has previously been described (Olmedo, 2011). Briefly, children aged 7-8 years were recruited through a health insurance plan (HIP) that serves primarily a middle-income population. Neighborhoods were selected based on asthma prevalence among 5 year-olds as reported by the NYC DOHMH in 2000. Children from both high and low asthma prevalence neighborhoods.

Questionnaire data

A Previously validated asthma questionnaire ("International Study of Asthma and Allergies in Childhood (ISAAC)," n.d.) were administered in either English or Spanish to parents of participating children during a home visit. This questionnaire identified demographic characteristics; child's history of asthma, wheeze, cough, and allergies; and environmental factors including features of the indoor and outdoor environment, residential history, tobacco smoke exposure since birth, as well as detailed information about pet ownership and pest sightings within the home during the initial home visit. The initial home visits for all participants included in the study occurred between 2008-2011.

Mouse exposure

Home mouse exposure (Kitchen floor and Bed Dust)

From the questionnaire, we were able to determine how often, if ever, parents of study participants saw mice in their homes within the 12 months previous to the home visit. During the home visit, dust samples were collected from the child's bed and the kitchen floor by vacuum using a Dustream® collector (Indoor Biotechnologies, Charlottesville, VA). For the bed sample, dust from the fitted sheet on the upper-half of the bed and both sides of the pillows were collected for 3 minutes. Kitchen floor dust was collected from the floor perimeter for 3 minutes. Kitchen samples were extracted after sieving to remove particles larger than 400um in diameter. Bed dust samples were extracted without sieving. The extracted dust was diluted with PBS 0.05% Tween, ph. 7.4, at a concentration of 50 mg/mL. All dust samples were stored at -20°C before and after extraction. Mouse allergen (Mus m 1) in bed dust was measured using Multiplex® (Indoor Biotechnologies, Charlottesville, VA) as described previously.(Olmedo, 2011). Mouse allergen, specifically Mus m 1 a mouse urinary protein allergen, from kitchen

floor samples were measured by ELISA (Indoor Biotechnologies, Charlottesville, VA) in duplicate. In order to compare the bed dust Mus m 1 concentrations to kitchen floor levels, we set the lower limit of detection of bed dust mouse allergen to the kitchen floor sample results since it was higher. Of the 350 study participants, one kitchen floor was not sampled due to construction during the home visit and two other kitchen floor samples were also not collected for unknown reasons reducing the number of dust samples to 347.

Neighborhood Exposure

Rodent sighting frequencies by neighborhood (zipcode), as reported by the NYC Community Health Survey (CHS), were implemented in this study (Kass, 2005). This data was collected from approximately 10,000 adults age 18 and older and represented every neighborhood of NYC in 2003. Individuals were contacted via telephone and asked questions about their health, family health, living and building conditions. CHS participants were asked "In the past 90 days, have you seen mice or rats in your building?" Neighborhood frequencies were calculated by dividing the number of adults that answered "yes" and by the total number of CHS participating adults living in their neighborhood. This survey did not differentiate between mice and rats. The neighborhood residential rodent sighting frequency was then matched to the NYC NAAS participants' United Hospital Fund's neighborhood designation (UHF – a combination of several zip codes).

School Exposure

The NYC Bureau of Environmental Surveillance & Policy, a department within the NYC DOHMH, performs annual food service inspections in all NYC school cafeterias (public and private). These reports have detailed location and conditions where mice and/or signs of mice are observed by inspectors in and around school cafeterias. Every school was inspected at least

once every school year. We used cafeteria inspection reports for the year prior to the initial home visit for analysis. Missing mouse cafeteria reports were considered negative for signs of mice (based on personal communication with Bureau of Environmental Surveillance and Policy in June 2012).

Mouse sensitization (Serum IgE)

A blood specimen was collected during the home visit. Allergen-specific immunoglobulin E (IgE) for inhalant allergens, including mouse urinary protein (Mus m 1), were measured using ImmunoCAP® (Phadia, Uppsala, Sweden) to determine sensitization. Children with Mus m 1 IgE greater or equal to 0.35IU/mL were considered sensitized to mouse for this study.

Statistical Methods

All data analyses were performed using R statistical software version 3.13 (R Core Team, 2013) Exploratory analyses were completed to uncover distribution patterns in the data. The outcome variable, sensitization to mouse allergen (Mus m 1), was dichotomized; specific IgE levels greater than or equal to 0.35IU/mL were considered positive. Based on previously published studies and subsequent sensitivity analysis, regression models were adjusted for sex, Black race, cockroach and dust mite sensitization, neighborhood asthma prevalence, and living in an apartment building higher than the eighth floor. (Olmedo, 2011; M S Perzanowski et al., 2008; Wilson et al., 2010). Parent-reported mouse sightings were labeled in figures as “none” for no reported mouse sightings, “low” for less than weekly sightings, and “high” for at greater than weekly sightings. School cafeteria reports of signs of mice were also dichotomized for both

figures and regression analysis as no evidence of mice in the school's cafeteria, or evidence of mice in the school's cafeteria.

Pearson's correlation was used to determine the correlation coefficients for linear relationships between continuous variables. Modified Poisson regression with robust standard errors was used to measure the prevalence risk (PR) of mouse sensitization for each independent variable of mouse allergen exposure examined. The distribution of Mus m 1 concentrations measured from kitchen floor and bed dust were explored and subsequently log-transformed due to skewness for figures and analysis. For further clarity in interpreting the beta coefficient from regression results, we transformed the beta coefficient to reflect a doubling of mouse allergen (see equation 1) for both bed and kitchen floor Mus m 1 in regression models. The resulting interpretation would be "for every doubling in Mus m 1 concentration, there was an associated change (increase or decrease) in the risk for risk of mouse sensitization."

Equation1.

slope: e ^ ln(n)*β = PR for an "n"-fold change in x

slope: e ^ ln (2) *β = PR for a doubling of x

RESULTS

Study population

The number of participants enrolled in this study contained an equal distribution of lower and higher asthma prevalence neighborhoods. The sex of children in each of these neighborhood groups was also equally distributed. Serum was obtained from 332 (95%) of 350 children in the study (refer to Table 1 for summary of cohort characteristics). Of the 332 children, 169 (51%) had IgE levels >0.35 IU/ml to at least one of the allergens tested (*D. farinae*, cockroach, mouse,

cat, dog, tree mix, ragweed, and grass pollen), including 40 children (12%) whose levels of IgE to mouse allergen extract (MUP) was $\geq$ 0.35 IU/mL (Table 1.5).

There were significantly more male children with atopy compared to females ($p< 0.03$). Children who were atopic were more likely to have allergic rhinitis, asthma, and eczema compared to non-atopic children ($p<0.001$, respectively). Children with a father with a history of asthma were also more likely to be atopic compared to those whose father did not have a history of asthma ($p = 0.007$). A greater percentage of children with mouse sensitization lived in high asthma prevalence neighborhoods compared to children who are not sensitized to mouse ($p=0.04$). Children with mouse sensitization were more likely to have a mother with a history of asthma ($p<0.001$). Children with sensitization were also more likely to live in homes with parent reported mouse sightings and in neighborhoods with greater frequencies of rodent sighting as well (Table 1.5).

Table 1. Demographic and clinical characteristics of children in the New York City						
	Neighborhood Asthma and Allergy Study					
		Atopic		**Non-atopic**		
Characteristics		**N**	**%**	**N**	**%**	
Total	N = 332	169	50.9	163	49.1	
						P-value
Mean age in years (SD)			**7.4**		**7.4**	
Gender						**0.03**
	Male	105	62.1	82	50.3	
	Female	64	37.9	81	49.7	
Race/ethnicity						**0.14**
	Black	90	53.3	68	41.7	**0.035**
	Hispanic	60	35.5	56	34.4	**0.74**
	Other	37	21.9	41	25.2	**0.48**
Residence						**0.77**
	Apartment building	94	55.6	88	54.0	
	House (<4 apartments)	75	44.4	75	46.0	
Neighborhood asthma prevalence						**0.83**
	<9%	83	49.1	81	49.7	
	>11%	86	50.9	80	49.1	
	Other/missing/unknown	0	0.0	2	1.2	
Allergic rhinitis						**<0.001**
	Yes	93	55.0	55	33.7	
	No	76	45.0	108	66.3	
Asthma						**<0.001**
	Yes	119	70.4	77	47.2	
	No	50	29.6	86	52.8	
Eczema						**<0.001**
	Yes	67	39.6	29	17.8	
	No	102	60.4	134	82.2	
Maternal allergic rhinitis						**0.34**
	Yes	29	17.2	22	13.5	
	No	140	82.8	141	86.5	
Maternal asthma						**0.29**
	Yes	37	21.9	27	16.6	
	No	132	78.1	136	83.4	

Paternal allergic rhinitis						**0.18**
	Yes	29	17.2	19	11.7	
	No	140	82.8	144	88.3	
Paternal asthma						**0.007**
	Yes	33	19.5	15	9.2	
	No	136	80.5	148	90.8	
Lives with a smoker						**0.93**
	Yes	35	20.7	34	20.9	
	No	134	79.3	129	79.1	
Kitchen floor mouse allergen concentration			0.0		0.0	**0.3**
	Quartile 1 (lowest)	52	30.8	40	24.5	
	Quartile 2	32	18.9	41	25.2	
	Quartile 3	45	26.6	38	23.3	
	Quartile 4	38	22.5	44	27.0	
Bed dust allergen concentration						**0.73**
	Quartile 1 (lowest)	43	25.4	40	24.5	
	Quartile 2	46	27.2	37	22.7	
	Quartile 3	39	23.1	44	27.0	
	Quartile 4	41	24.3	42	25.8	
Parent weekly mouse sightings						**0.21**
	None	110	65.1	90	55.2	
	Low	47	27.8	57	35.0	
	High	12	7.1	15	9.2	
Neighborhood rodent sighting frequency						**0.12**
	Quartile 1 (lowest)	38	22.5	52	31.9	
	Quartile 2	53	31.4	35	21.5	
	Quartile 3	35	20.7	36	22.1	
	Quartile 4	43	25.4	39	23.9	

Table 1.5. Demographic and clinical characteristics of atopic children with and without mouse seroatopy						
		Mouse atopy		Other atopy		
Characteristics		**N**	**%**	**N**	**%**	**P-value**
Total	N = 169	40	12.0	129	38.9	
Mean age in years (SD)		7.4				
Gender						**0.75**
	Male	24	60.0	81	62.8	
	Female	16	40.0	48	37.2	
Race/ethnicity						
	Black	24	60.0	66	51.2	**0.33**
	Hispanic	15	37.5	46	35.7	**0.83**
	Other	16	40.0	63	48.8	**0.03**
Residence						**0.32**
	Apartment building	25	62.5	69	53.5	
	House (<4 apartments)	15	37.5	60	46.5	
Neighborhood asthma prevalence						**0.04**
	<9%	14	35.0	69	53.5	
	>11%	26	65.0	60	46.5	
Allergic rhinitis						**0.16**
	Yes	26	65.0	67	52.3	
	No	14	35.0	61	47.7	
Asthma						**0.26**
	Yes	31	77.5	88	68.2	
	No	9	22.5	41	31.8	
Eczema						**0.5**
	Yes	18	45.0	49	38.3	
	No	22	55.0	79	61.7	
Maternal allergic rhinitis						**0.62**
	Yes	6	15.0	23		
	No	34	85.0	102	81.6	
Maternal asthma						**< 0.001**
	Yes	17	42.5	20	15.5	
	No	23	57.5	105	81.4	
Paternal allergic rhinitis						**0.7**
	Yes	6	15.0	22	17.6	
	No	34	85.0	103	82.4	

Paternal asthma						**0.36**
	Yes	10	25.0	23	18.4	
	No	30	75.0	102	81.6	
Lives with a smoker						**0.29**
	Yes	6	15.0	29	22.8	
	No	34	85.0	98	77.2	
Kitchen floor mouse allergen concentration						**0.14**
	Quartile 1 (lowest)	7	17.5	45	35.4	
	Quartile 2	8	20.0	24	18.9	
	Quartile 3	12	30.0	33	26.0	
	Quartile 4	13	32.5	25	19.7	
Bed dust allergen concentration						**0.17**
	Quartile 1 (lowest)	9	22.5	34	26.4	
	Quartile 2	9	22.5	37	28.7	
	Quartile 3	7	17.5	32	24.8	
	Quartile 4	15	37.5	26	20.2	
Parent weekly mouse sightings						**0.001**
	None	20	50.0	90	69.8	
	Low	12	30.0	35	27.1	
	High	8	20.0	4	3.1	
Neighborhood rodent sighting frequency						**0.002**
	Quartile 1 (lowest)	5	12.5	33	25.6	
	Quartile 2	6	15.0	47	36.4	
	Quartile 3	13	32.5	22	17.1	
	Quartile 4	16	40.0	27	20.9	

Kitchen vs. bed mouse allergen exposure

The concentration of Mus m 1 allergen measured from bed dust positively correlated ($r = 0.44$, $p < 0.001$) with Mus m 1allergen concentration measured from kitchen floor dust (Figure 1). Children living in homes where parents reported greater than weekly mouse sightings in the past 12 months had higher concentrations of Mus m 1 allergen in their kitchen floor dust compared to homes where parents reported less than weekly and no mouse sightings (Figure 2A). Similar to Mus m 1 in kitchen floor dust, parents reporting greater than weekly mouse sightings had higher Mus m 1 allergen concentrations in their children's bed dust compared to the other two groups

(Figure 2B). Neighborhood rodent sighting frequencies were positively correlated with Mus m 1 allergen concentrations measured from both kitchen floor and bed dust (Figure 3A-B). However, the correlation between neighborhood rodent sighting frequencies and Mus m 1 allergen concentrations and bed dust was higher compared to the correlation between neighborhood rodent sightings and kitchen floor dust ($r = 0.22$ vs. $r = 0.12$, $p < 0.01$, respectively). School reports of mouse sightings were not associated with home kitchen floor or bed dust Mus m 1 allergen concentrations (Supplementary Figures 1A-B).

Figure 1. Correlation between Mus m 1 Allergen Concentrations from Kitchen floor and Bed Dust (N=347).

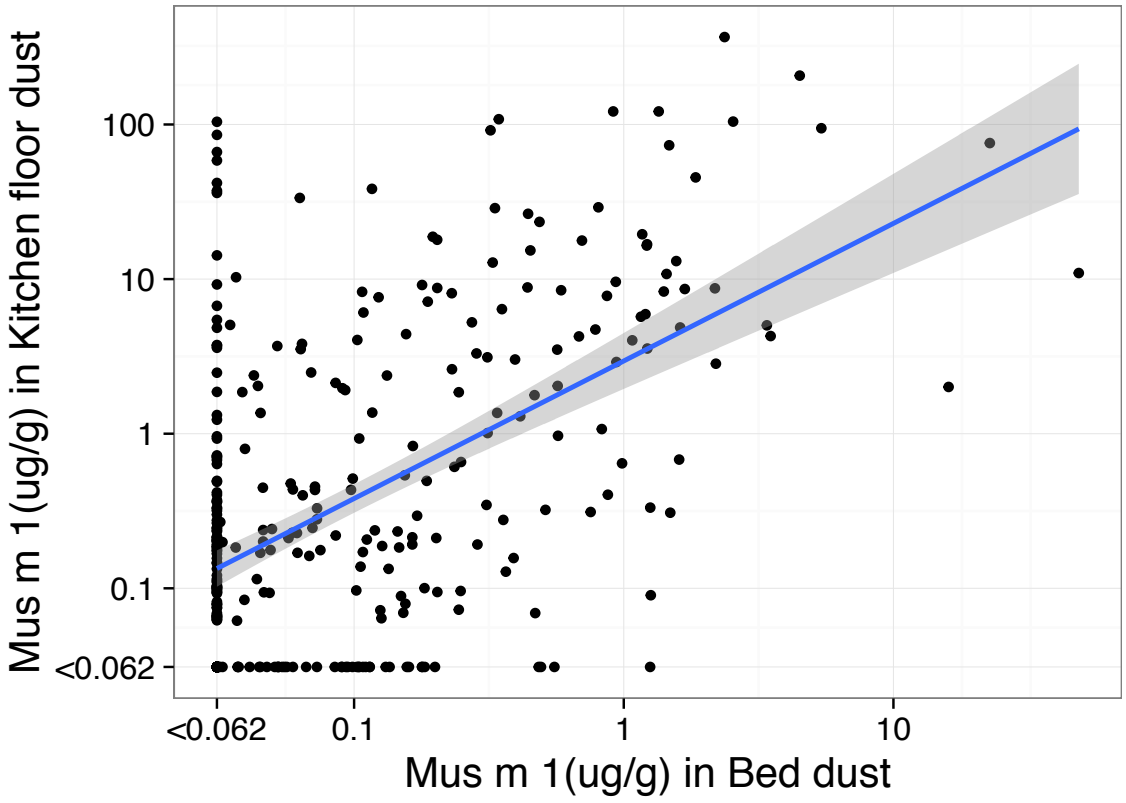

Figure 1. Mus m 1 allergen concentrations from bed dust were positively correlated with Mus m 1allergen concentrations from kitchen floor dust ($r = 0.44$, $p < 0.001$).

Figure 2A. Comparison Between Parent Reported Mouse Sightings and Mus m 1 Concentrations in Settled Dust from the Kitchen floor (N=347).

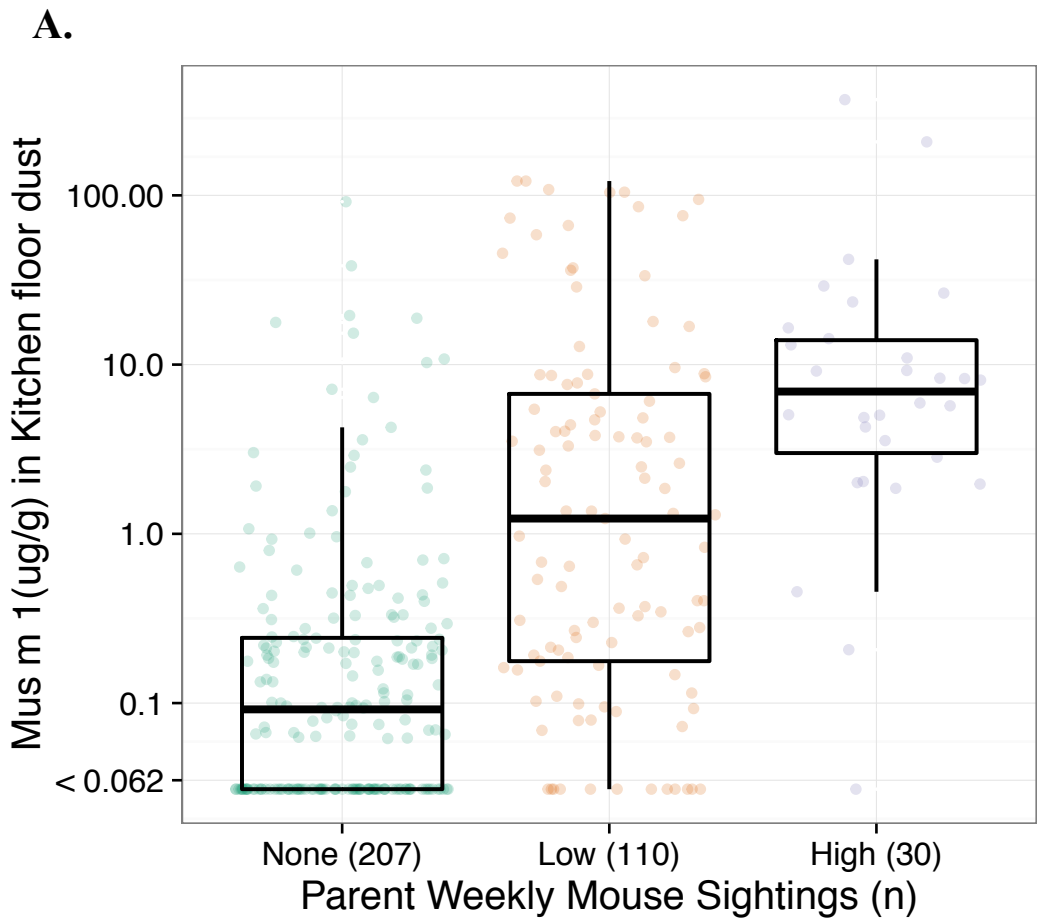

Figure 2A. Increasing parent reported mouse sightings were associated with increasing concentrations of Mus m 1 allergen in kitchen floor dust ($p < 0.001$).

Figure 2B. Comparison Between Parent Reported Mouse Sightings and Mus m 1 Concentrations in Settled Dust from the Bed (N=347).

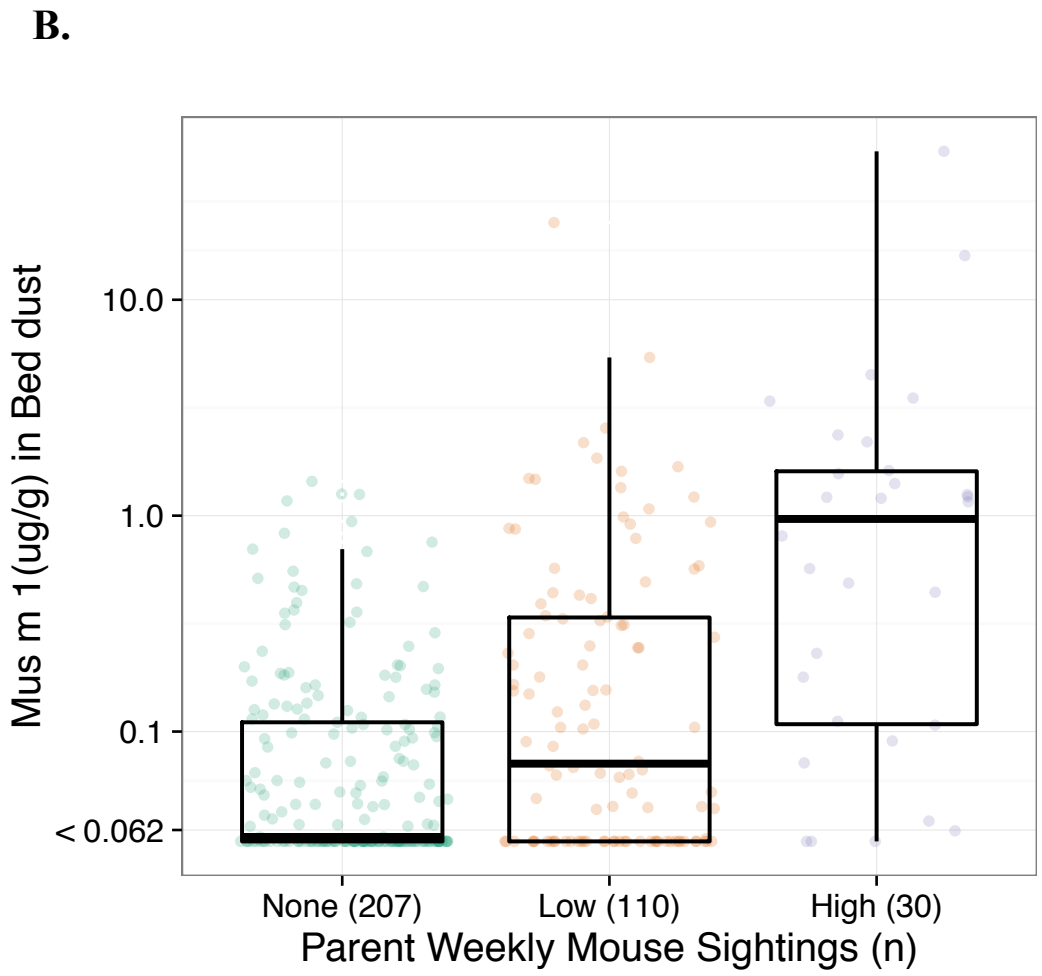

Figure 2B. Increasing parent reported mouse sightings are associated with increasing concentrations of Mus m 1 allergen in bed dust ($p < 0.001$).

Figure 3A. Comparison Between Neighborhood Rodent Sighting Frequencies and Mus m 1 Concentrations in Settled Dust from the Kitchen floor (N=347).

A.

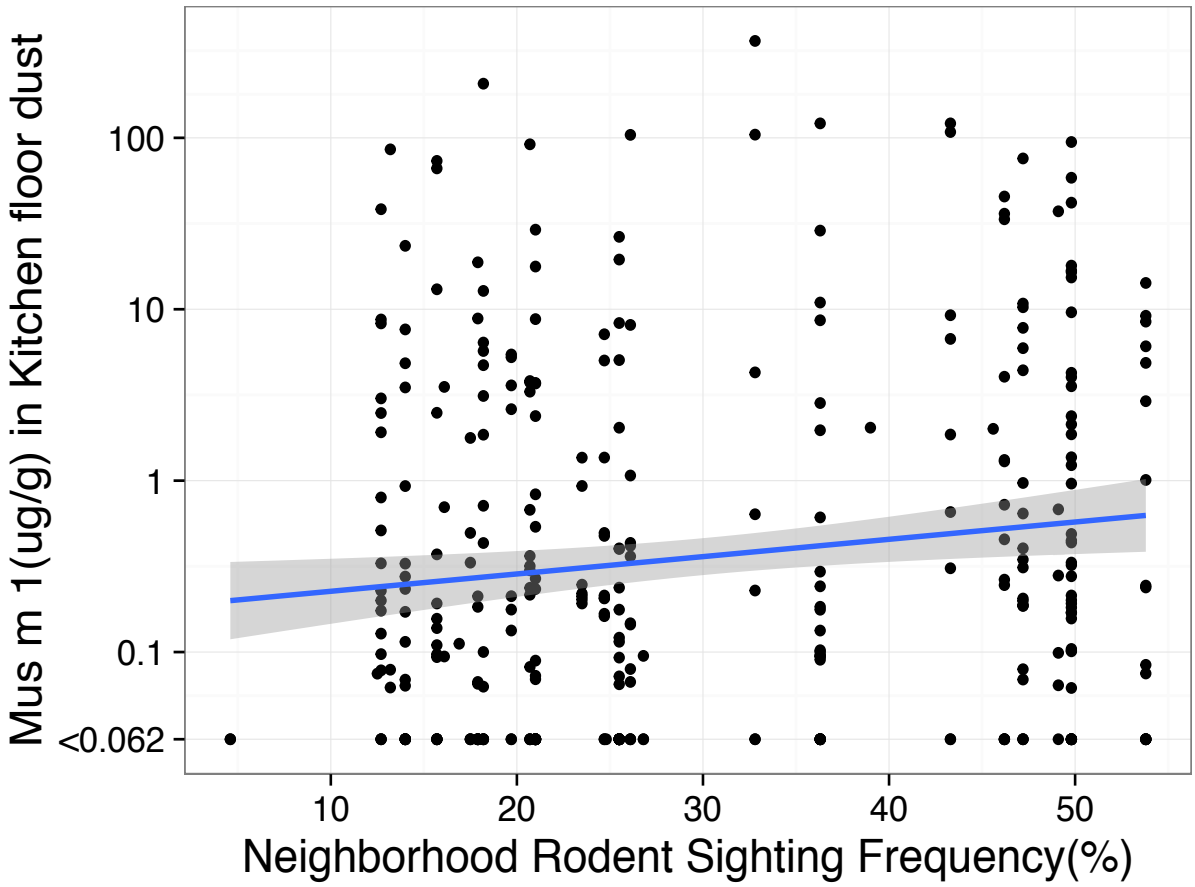

Figure 3A. Increasing neighborhood rodent sighting frequency is correlated with increasing concentrations of Mus m 1 allergen in kitchen floor dust ($r = 0.12$, $p < 0.001$).

Figure 3B. Comparison Between Neighborhood Rodent Sighting Frequencies and Mus m 1 Concentrations in Settled Dust from the Bed (N=347).

B.

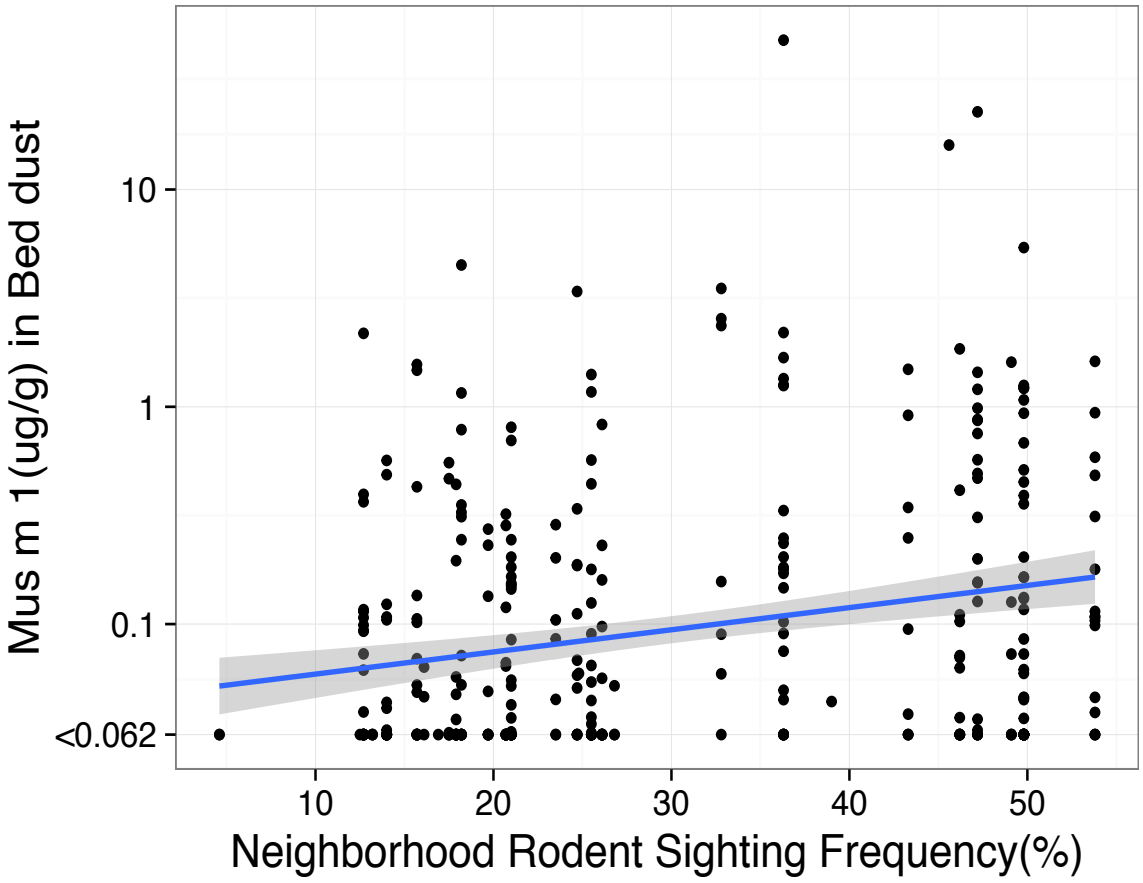

Figure 3B. Increasing neighborhood rodent sighting frequency is correlated with increasing concentrations of Mus m 1 allergen in bed dust ($r = .22$, $p < 0.001$).

Mouse sensitization prevalence risk

We found for every doubling of Mus m 1 allergen concentration from kitchen floor dust, there was an associated 9% increased risk for sensitization (Table 2) compared with an associated 6% increased risk for sensitization with mouse allergen measured in the bed dust, (Table 2). Bed dust Mus m 1 allergen concentrations were not significantly associated with mouse sensitization risk. Children whose parents reported greater than weekly mouse sightings had almost four times the risk of mouse sensitization compared with those whose parents reported no mouse sightings in the home (Table 3). For every 10% increase in frequency of neighborhood rodent sighting there was a 25% increased risk of sensitization to mouse among children living in that area, this association was also not statistically significant (Table 4).

Table 2. Mus m 1 allergen concentration from kitchen floor and bed dust and prevalence risk for mouse sensitization.

Mus m 1 μg/g (n= 332)	Kitchen Floor PR (95% CI)	P-value	Bed PR (95% CI)	P-value
Unadjusted	1.11 (1.03-1.20)	0.01	1.11 (0.99-1.27)	0.10
Adjusted#	1.09 (1.02-1.17)	0.04	1.06 (0.95-1.19)	0.46

adjusted for sex, Black race, floor of building, cockroach and dust mite sensitization, and neighborhood asthma prevalence.

Table 3. Parents reported mouse sightings and prevalence risk for mouse sensitization.

Parent mouse report (n= 332)	ref*	Less than weekly PR (95% CI)	P-value	Greater than weekly PR (95% CI)	P-value
Unadjusted	1.0	1.15 (0.59-2.27)	0.69	3.0 (1.4-6.1)	0.009
Adjusted#	1.0	0.98 (0.53-1.79)	0.95	3.8 (2.0-7.0)	0.001

* reference group = no reported mouse sightings in previous 12 months
# adjusted for sex, Black race, floor of building, cockroach and dust mite sensitization, and neighborhood asthma prevalence.

Table 4. Neighborhood rodent sighting frequency and prevalence risk for mouse sensitization.

Neighborhood frequency (n= 332)	PR (95% CI)	P-value
Unadjusted	1.41 (1.16-1.72)	0.003
Adjusted#	1.25 (0.94-1.68)	0.16

adjusted for sex, Black race, floor of building, cockroach and dust mite sensitization, and neighborhood asthma prevalence.

DISCUSSION

Consistent with previous studies, there a positive correlation of Mus m 1 allergen concentrations between settled kitchen floor dust and bed dust (Figure 1). Children with at least weekly reported mouse sightings in their homes had greater Mus m 1 allergen concentrations in both kitchen floor and bed dust compared to homes with less-than-weekly mouse sightings (Figure 2A-B). Increasing neighborhood rodent sighting frequencies was also associated with increasing Mus m 1 allergen concentrations in both kitchen floor and bed dust (Figure 3A-B). However, the correlation between neighborhood rodent sighting frequency and Mus m 1 allergen concentration from bed dust was stronger compared to the correlation with Mus m 1 concentrations from kitchen floor dust. Based on these results both neighborhood rodent and parent mouse reports appear to be consistent with in home measured mouse allergen concentration therefore can be used as proxies for mouse allergen exposure at home. Similarly, the unadjusted models for neighborhood rodent and parents reported mouse sightings were both associated with an increased risk of sensitization to mouse. However, only parent reporting greater than weekly mouse sightings were significantly associated with mouse sensitization risk in the adjusted models. Of all of the mouse exposures tested, parents reporting greater than

weekly mouse sightings were the strongest predictor of mouse sensitization risk for the children in our study.

In studies exploring risk factors for allergic sensitization, allergen concentrations have historically been measured inside the home (Ginger L. Chew et al., 2003; Matsui, 2005, 2006; Olmedo, 2011; Rosenfeld et al., 2011; Salo et al., 2008; Salo, 2009). Because such sensitization develops and manifests in early childhood, it is plausible that the indoor home environment may be the primary source of exposure. However, as children grow older, they may spend a significant amount of time in other indoor environments as well. By age 7, children living in NYC can spend up to 7 hours a day for 10 months in school per year. A study conducted in low income urban areas detected mouse allergen in 78% of settled dust samples from classrooms (G L Chew, 2005). However, our analysis found no association between school mouse exposure and mouse sensitization risk (Supplemental Table 2). Since previous studies have found varying detectable levels of mouse allergen in schools (Amr, 2003), we wanted to see how well the reported mouse sightings in school cafeterias correlated with mouse allergen concentrations in the children's homes. School mouse exposure was also not associated with either kitchen floor or bed dust mouse allergen concentrations (Supplemental Figures 2A-B). The school cafeteria may not be an ideal location within schools to explore the effect of mouse allergen exposure with sensitization. Also, a previous study compared allergen levels from different areas within urban area schools found the highest mouse allergen concentrations in the school's cafeteria (Amr et al. ,2003). We did not sample settled dust from the school's cafeteria which would explain our lack of significant finings. Assessing mouse exposure from settled dust from school cafeterias instead of using food inspection reports may be a better exposure measure and may yield different results than what we found.

Over the last decade, NYC has led the nation in collecting and distributing local environmental exposure and public health data (Clougherty et al., 2009; Clougherty, Johnson, et al., 2008). City officials have also collaborated with many research groups to help analyze and publish results to local and global communities (Garg, 2003). The use of a neighborhood exposure level collected by the NYC DOHMH was both a strength and limitation of this study. Due to inconsistencies in sensitization literature, in regards to exposure level, the inclusion of a neighborhood level exposure variable strengthens our study design. Also, the lack of association between the neighborhood rodent sighting frequency and mouse sensitization risk may have been due to misclassification of exposure from the inclusions of rats in its measurement. However, one drawback of analyzing the association of the neighborhood rodent frequencies, a group-level exposure, with individual health outcomes is that group-level data may be an inaccurate proxy for individual exposure level (ecologic fallacy). Other limitations were the cross-sectional selection and case-control design of the study, which prevented us from assessing temporality or directionality between mouse exposure and sensitization. However, there is a large body of evidence that exposure to allergens precedes the production of specific-IgE in sensitized individuals (Illi, 2006) . However, we cannot be sure that the mouse allergen concentrations we measured are the same as those that were present at the time when the children became sensitized. Given the positive association observed in this study between Mus m 1 allergen concentrations from the kitchen floor dust and mouse sensitization risk, it is possible that the current exposure levels are reasonable proxies for those in the past and should be further explored.

In conclusion, Mus m 1 allergen concentration measured from kitchen floor dust were associated with mouse sensitization risk while concentrations from bed dust were not. The

frequency of parent reported mouse sightings within the home and neighborhood reported rodent sightings were associated with Mus m 1 allergen concentrations from both kitchen floor and bed dust ($p < 0.001$ respectively for both). The in-home parent mouse and neighborhood rodent sighting reports may be a less expensive way to assess exposure to mouse allergen compared to home sampling techniques. Mouse sightings in school cafeterias were not associated with risk of sensitization to mouse in this study, perhaps because these food inspection reports are not capturing the child's personal mouse exposure at school. As such, mouse allergen concentrations from settled dust samples from school cafeterias may be more predictive of mouse sensitization risk than cafeteria sightings. These findings can help inform intervention strategies to prevent mouse sensitization associated adverse health outcomes such as allergic rhinitis and asthma. Targeting interventions for the reduction of mouse allergen in children's homes, specifically their kitchens may reduce the risk of exacerbation of allergic symptoms in children sensitized to mouse and. This reduced exposure may also in turn reduce the risk of exacerbation of asthma symptoms triggered by mouse allergen exposure for asthmatic children living in urban communities as well.

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Supplemental Section

We found no significant association for school cafeteria mouse sightings after adjusting for sex, cockroach and dust mite sensitization, and neighborhood asthma prevalence (table S1). The results of the full adjusted mouse sensitization for kitchen floor and bed dust are shown in supplementary tables 2 and 3. Both models included parent mouse sighting reports, neighborhood rodent sightings, school mouse reports, race, sex, neighborhood asthma prevalence, and both cockroach and dust mite sensitization. Both cockroach and dust mite sensitization were associated with mouse sensitization in both kitchen floor and bed dust full models adjusted for where the floor of the child's bedroom is located within the home. School cafeteria mouse sightings was not associated with mouse allergen concentrations from the kitchen floor or bed dust in the child's home (figure S1A-B).

Supplementary Tables

Supplemental Table 1. School Cafeteria Food Inspection Reports and Prevalence risk for mouse sensitization

School Cafeteria (N= 328)	PR (95% CI)	P-Value
Unadjusted	0.74 (0.36-1.55)	0.46
Adjusted #	0.66 (0.35-1.26)	0.30

* reference group = no evidence of mouse in school cafeteria
# adjusted for sex, Black race, cockroach and dust mite sensitization, and neighborhood asthma prevalence.

Supplemental Table 2. Prevalence risk for mouse sensitization: Full Kitchen floor dust Model

N=332	PR (95% CI)#	P-value
Kitchen Floor (Mus m 1 µg/g)	1.07 (0.96-1.19)	0.21
Parent mouse sighting (less than weekly)*	0.67 (0.31-1.47)	0.32
Parent mouse sighting (greater than weekly)*	2.49 (1.02-6.12)	0.04
Neighborhood rodent sighting (10%)	1.24 (0.90-1.71)	0.18
School Cafeteria inspection report	0.60 (0.32-1.11)	0.11
Black race	1.59 (0.85-2.99)	0.15
Sex	0.71 (0.42-1.19)	0.19
Neighborhood asthma prevalence	0.87 (0.42-2.11)	0.76
Cockroach sensitization	3.24 (1.71-6.15)	0.003
Dust mite sensitization	3.49 (1.49-6.85)	0.003

* reference group= parent reporting no mouse sightings
#adjusted for floor of building

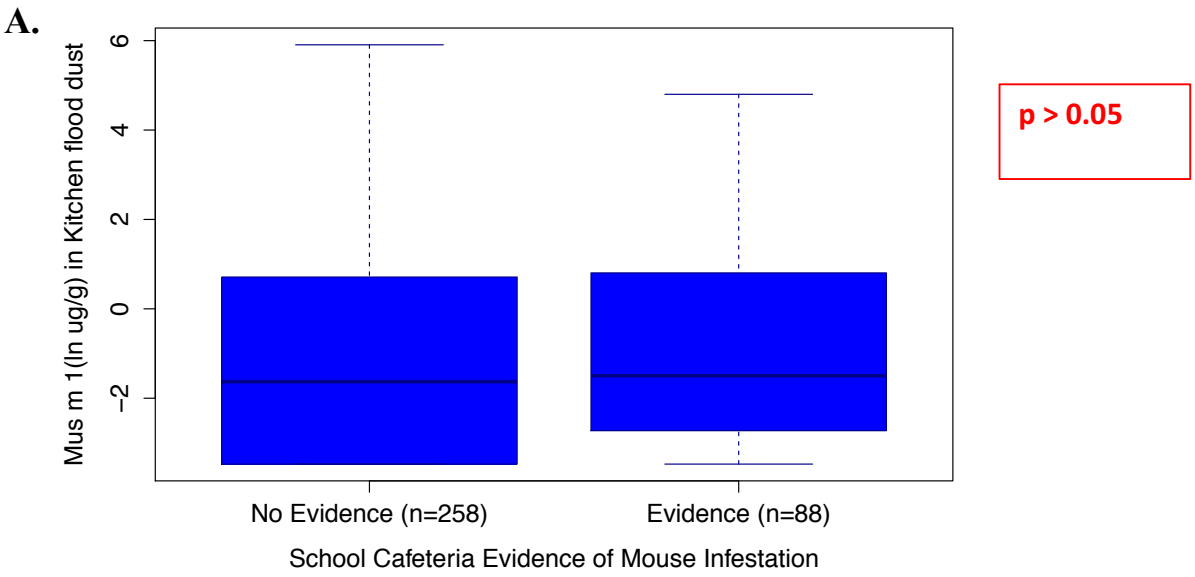
Supplemental Table 3. Prevalence risk for mouse sensitization: Full Bed dust Model

	PR (95% CI)#	P-value
Bed (Mus m 1 µg/g)	0.97 (0.89-1.06)	0.05
Parent mouse sighting (less than weekly)*	0.92 (0.52-1.64)	0.08
Parent mouse sighting (greater than weekly)*	3.8 (2.0-7.2)	< 0.001
Neighborhood rodent sighting (10%)	1.25 (0.94-1.67)	0.12
School Cafeteria inspection report	0.58 (0.30-1.12)	0.10
Black race	1.66 (0.89-3.06)	0.10
Sex	0.67 (0.38-1.17)	0.16
Neighborhood asthma prevalence	0.89 (0.39-2.01)	0.78
Cockroach sensitization	3.3 (1.6-6.3)	< 0.001
Dust mite sensitization	3.6 (1.8-7.0)	< 0.001

* reference group= parent reporting no mouse sightings
#adjusted for floor of building

Supplemental Figures

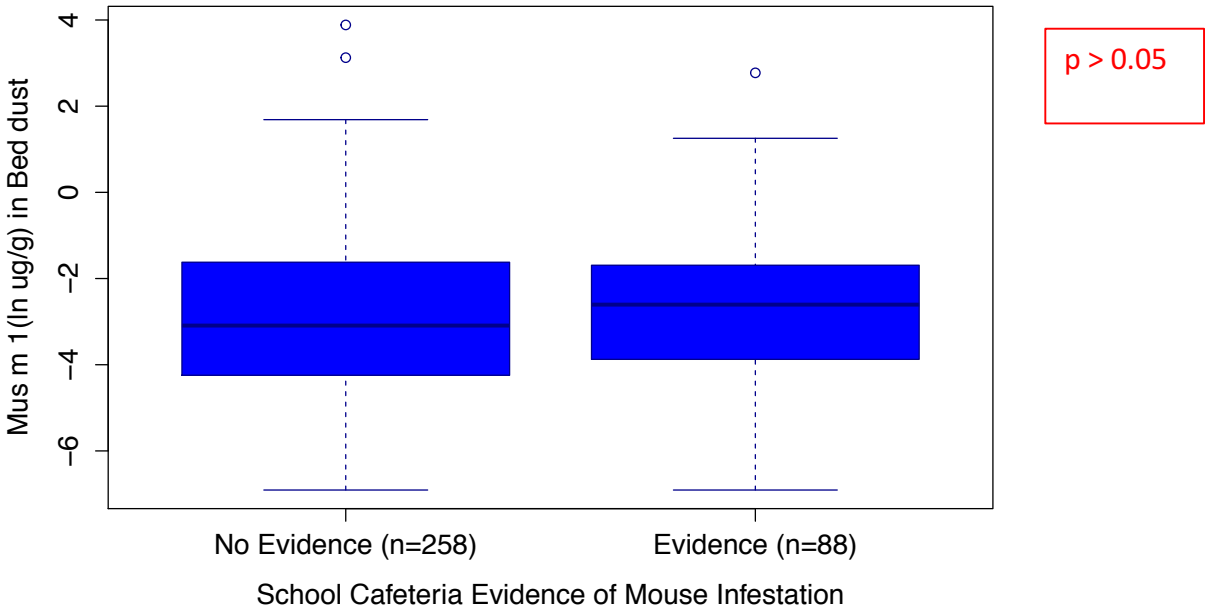
Supplemental Figure 1A. Comparison Between School Cafeteria Mouse Reports and Mus m 1 Concentrations in Settled Dust from the Kitchen Floor (N=346).



Supplemental Figure 1A. No association between mouse reports from school cafeterias and Mus m 1 allergen concentrations from participant's kitchen floor dust.

Supplemental Figure 1B. Comparison Between School Cafeteria Mouse Reports and Mus m 1 Concentrations in Settled Dust from the Bed (N=346).

B.



Supplemental Figure 1B. No association between mouse reports from school cafeterias and Mus m 1 allergen concentrations from participant's bed dust.

Chapter 3: Prediction of Indoor $PM_{2.5}$ and Black Carbon Concentrations from Modeled Outdoor Measurements in New York City.

Authors: Medina S. Jackson-Browne, MS, Luis Acosta MD, Andrew Rundle DrPhD, Beizhan Yan, Daniel Sheehan, Thomas Matte MD, Matthew S. Perzanowski, PhD, Steven Chilrud, PhD

Abstract

Background: The associations between particulate matter $\leq$ 2.5 microns ($PM_{2.5}$) and black carbon (BC) and adverse respiratory health outcome have inconsistent findings. This may be due to outdoor air monitors and shorter-term air monitoring not adequately reflecting individual, longer-term exposure. Recently, researchers at New York City (NYC) Department of Health and Mental Hygiene (DOHMH) and Queens College developed a model to estimate annual, street-level concentrations of ambient $PM_{2.5}$ and BC for the New York City Community Air Survey (NYCCAS) study. This land use regression model uses street side 14-day mean concentrations measures collected in each season at 124 locations. In this study, we aimed to use our measured, 7-day, indoor concentrations of $PM_{2.5}$ and BC to gain confidence in the modeled, outdoor levels for locations away from the model's calibration nodes.

Methods: We compared 2-year averaged street side levels of $PM_{2.5}$ and BC estimated from NYCCAS models to 7-day $PM_{2.5}$ and BC concentrations measured by indoor air monitors. We also tested for improvements in the model by adjusting the modeled 2-year average outdoor $PM_{2.5}$ and BC concentrations using ambient NYC $PM_{2.5}$ and BC concentrations measured during the 7-day indoor measurement time.

Results: The modeled outdoor $PM_{2.5}$ concentrations predicted 4% of the variability in indoor measured $PM_{2.5}$ concentrations ($p < 0.001$). The modeled outdoor BC concentrations predicted 20% of the variability in the measured indoor BC concentrations ($p < 0.001$). The ambient-adjustment of the modeled outdoor $PM_{2.5}$ and BC concentrations did not significantly improve the correlation or R^2 values between outdoor modeled and indoor measured $PM_{2.5}$ and BC concentrations.

Conclusions: The annual modeled outdoor and ambient-adjusted outdoor $PM_{2.5}$ concentration models both poorly predicted indoor $PM_{2.5}$ concentrations. However, the models for annual outdoor BC were modestly predictive of measured indoor BC concentrations. These findings suggest that the NYCCAS model of BC could be useful in estimating domestic BC exposure in NYC homes.

Introduction

High particulate matter (PM) exposure has been shown to be hazardous to human health and is therefore monitored by every state in the country (EPA, 2010). High concentrations of $PM_{2.5}$ are associated with risk of respiratory and cardiovascular disease (Cornell, 2012; Diaz-sanchez, 1997; Kinney, 2002; McCreanor, 2007; Nadeau, 2010; Patel, 2010). Increased childhood asthma prevalence in urban communities has also been shown to be associated with high $PM_{2.5}$ concentrations from combustion sources such as emissions from diesel trucks and buildings burning residual oil for heat (Cornell, 2012; Kheirbek, 2013; Patel, 2010; Patel et al., 2011). PM with a diameter of 2.5 microns and smaller ($PM_{2.5}$) can reach the lower airways and cause clinical manifestations within the blood and airways (Guarnieri, 2014). Black carbon (BC) is a main component of $PM_{2.5}$ from combustion sources such as diesel and other carbon-containing sources. BC can represent up to 75% of $PM_{2.5}$ in direct diesel exhaust emissions (Lall, 2006; Matte, 2013).

In general, a major fraction of NYC's $PM_{2.5}$ comes from upwind regions and include natural, industrial and combustion sources of fine particulate matter (Lall, 2006). Conversely, NYC's BC originates largely from local sources driven by high traffic density, high building density (space heating), with some local industrial facilities (NYC Department of Mental Health and Hygiene, 2015). A significant fraction of the space heating source of local BC in NYC are buildings that burn residual oil (#4 and #6) for space and water heating. Buildings that burn residual oil are distributed unevenly throughout NYC and may also contribute to variations in BC concentration by neighborhood (Clougherty et al., 2013; DOHMH, 2005).

Spatial Variability of Ambient $PM_{2.5}$ and BC, Penetration Indoors, and Indoor Sources

A previous study found that for urban communities in the Netherlands, Germany, and Sweden, between 50-70% of the variability in outdoor $PM_{2.5}$ concentrations can be explained by traffic-related variables (Brauer et al., 2003). A follow-up to that study also noted that outdoor $PM_{2.5}$ concentrations may underestimate exposure from traffic-related sources compared to BC measurements (Cyrys et al., 2003).

Ratios of measurements of air pollutants made both indoors and outdoors (I/O) shed light on the penetration of outdoor species indoors and whether there are significant indoor sources. Kinney et al measured I/O ratios of both VOCs, PM2.5 and components of PM2.5 for non-smoking apartments in NYC. Many VOCs show large I/O ratios with values often between 2 and 10 indicating the importance of indoor sources for these VOCs. In contrast, the I/O ratios observed for BC have a median of 0.8 with relatively few homes showing ratios above 1 indicating a general lack of indoor BC sources and good penetration outdoor BC into residential apartments through doors, windows, and other openings. (Kinney et al 2002); the I/O ratios observed for $PM_{2.5}$ are typically between 1 and 2 suggesting some weak indoor sources of PM2.5 which add to the $PM_{2.5}$ coming from the outdoors (Kinney et al. 2002). Other cities/studies have seen similar results. For example, 50-70% of indoor $PM_{2.5}$ was found to originate from outdoor sources (Götschi, 2002; LaRosa, 2002; Long, 2000). Furthermore, it has been estimated that between 69% to 84% of indoor BC concentrations came from penetration of ambient sources (LaRosa, 2002), suggesting less indoor sources of BC as compared to that for $PM_{2.5}$..

However, some studies have seen opposite results to those discussed above. A study in Boston evaluating the correlation between indoor and outdoor $PM_{2.5}$ and BC concentrations found a better correlation between indoor and outdoor concentrations of $PM_{2.5}$ ($R^2 = 0.68$) compared to BC ($R^2 = 0.08$) (Clougherty, 2008). Other studies found outdoor BC concentration

are a better predictor of exposure at the local level compared to $PM_{2.5}$ and that $PM_{2.5}$ concentrations varied over greater distances compared to BC (Hochadel, 2006; Ross, 2007).

Health effects of BC and impact of time period of measurements

High concentrations of BC have been shown to be associated with a higher risk of respiratory diseases (Cornell, 2012; Diaz-sanchez, 1997; Nadeau, 2010; Patel, 2010). Major roadways designated as truck routes are one of the primary sources of BC in NYC (Cornell, 2012; Matte, 2013). Many NYC homes are located close to several of these roadways and may contribute to differences neighborhood childhood asthma prevalence. In a previous published study from our group exploring neighborhood differences in childhood asthma prevalence, we did not observe any differences in BC concentrations measured indoors and lung function between asthmatic and non-asthmatic children (Cornell, 2012). These BC measurements were collected inside the study participants' homes for only an average of 7 days and air pollution concentrations are less variable over longer averaging time periods (Brauer, 2003; Clougherty, 2013; Götschi, 2002; LaRosa, 2002; Long, 2000). A longer-term estimate of exposure may better predict adverse respiratory health outcomes associated with air pollution versus a shorter-term estimate for children living in NYC.

In this study, we aim to use our measured, 7-day indoor concentrations of $PM_{2.5}$ and BC to gain confidence in the modeled, outdoor levels for locations away from the model's calibration nodes. Specifically, we tested for a significant association between longer-term exposure modeled concentrations and the 7-day indoor concentrations to see whether the model would be predictive of indoor levels for our study subjects and measured how much variability of our indoor measurements of $PM_{2.5}$ and BC concentrations could be explained by the variations in outdoor ~annual concentrations. Based on previously published findings of roughly similar

penetration rates of ambient $PM_{2.5}$ and BC and more prevalent indoor sources of $PM_{2.5}$ compared to BC, we hypothesized that modeled long-term outdoor BC concentrations would do a better job at predicting the 7-day indoor levels of BC than modeled outdoor long-term $PM_{2.5}$ concentrations would for 7-day indoor levels of $PM_{2.5}$.

Methods

The New York City (NYC) Neighborhood Asthma and Allergy Study (NAAS) is an asthma case-control study described previously (Olmedo, 2011) exploring neighborhood differences of asthma prevalence in children living in NYC. Children were recruited through a middle-income health insurance plan (HIP). Children aged 7-8 years were selected based on neighborhood asthma prevalence among 5 year-olds as reported by the NYC DOHMH (Department of Health and Mental Hygiene) in 2000. From 2008-2011 home visits were conducted for 350 NYC NAAS participants. Comprehensive questionnaires were administered to parents in either English or Spanish during the home visit which included the child's residential history, building type, and tobacco smoke exposure.

During the home visit, a small air-sampling pump was placed at a location in the living room of the apartment for an average of 7 days, but specific samples could be collected over as little as two days to a maximum of 14 days. The pumps were relatively quiet, ran on alternating current with a sample rate of 0.5 liter per minute (L/min). These size selective inlets (BGI's Triplex cyclone) to these pumps were held at approximately 5 ft , with $PM_{2.5}$ collected onto Teflo filters that were then weighed on a microbalance inside of an environmentally controlled Hepa filtered chamber (Jung, Artigas, et al., 2011b). These filters were also used to quantify black carbon ($\mu g/m^3$) using a multi-wavelength optical absorption technique, described previously (Yan et al., 2011). The optical device is composed of a balanced deuterium tungsten

halogen light source, an integrating sphere, a filter holder, and a miniature fiber-optic spectrometer (Cornell, 2012). These concentrations will be identified as "measured indoor" ($PM_{2.5}$ or BC) concentrations throughout this manuscript.

Modeled outdoor ($PM_{2.5}$ and BC) neighborhood measurements

Air was monitored by the NYC DOHMH for the New York City Community Air Survey (NYCCAS) at 124 street-level locations, 10-12 feet above the ground, throughout NYC for only 2 weeks, 4 times (once each season) per year (Matte, 2013) from 2008-2010. There were also 5 reference monitors, one in each borough, continuously collecting daily samples by the New York State Department of Environmental Conservation (DEC). Land-use regression incorporating variables associated with land-use and the reference monitor measurements was performed by NYCCAS from years 2008-2010 previously described by (Clougherty, 2009) to create concentration models for both $PM_{2.5}$ and BC. Concentrations from these models were then geocoded to the NYC NAAS participant home addresses as described in the projects data dictionary report (Sheehan et al., n.d.).

$PM_{2.5}$ concentrations from the NYCCAS and DEC air monitors were reported in the same units used in the NYC NAAS study ($\mu g/m^3$). The BC concentrations from the NYCCAS air monitors were quantified using a validated reflectance analysis that reports units in abs but which are then converted over to units in $\mu g/m^3$ (Matte, 2013). However, this method was different than the that used by the real time DEC stations (which use aethalometers) and the NYC NAAS study which uses a multi-wavelength absorbance method (Yan et al. 2011). However, BC data measured by all these methods have been shown to be very consistent in NYC (Yan, 2011). The outdoor modeled $PM_{2.5}$ and BC concentrations created by NYCCAS will be identified as "modeled outdoor" ($PM_{2.5}$ or BC) concentrations throughout this manuscript.

Both $PM_{2.5}$ and BC concentrations collected at one of the reference sites by the DEC (on the roof of Intermediate School 52 located in Bronx, NY) previously described was used as a source of daily ambient $PM_{2.5}$ and BC exposure from March 2008-December 2010 (Clougherty, 2009). These daily ambient measurements were used to adjust the modeled outdoor $PM_{2.5}$ and BC concentrations for the exact calendar dates in which the measured indoor $PM_{2.5}$ and BC were collected (see equation 1). This adjustment has been previously used in studies assigning exposure for health outcome (Ross et al., 2013). These concentrations will be identified as "adjusted modeled outdoor" ($PM_{2.5}$ or BC) concentrations throughout this manuscript.

Equation 1:

$$\text{Modeled outdoor } (PM_{2.5} \text{ or BC}) \text{ conc.} \times \left[\frac{\text{(7-day) avg. DEC conc.)}}{\text{(2- year avg. DEC conc.)}}\right]$$

Statistical Methods

R (version 3.1.3) statistical programming was used for all data analysis and data visualization (R Core Team, 2013). DEC data was available from 3/1/08 to 6/1/10 which corresponded to approximately 2/3 the home visits. Consequently, we restricted our analyses to homes during this time period, resulting in n=237. Exploratory data analysis was completed to examine distribution patterns in the data. All $PM_{2.5}$ and BC variables were log-transformed for graphs and analysis. Sensitivity analysis was performed to identify the best neighborhood modeled $PM_{2.5}$ and BC buffer (100m, 250m, 500m, or 1000m). Based on these results and previously published findings (Ross, 2007), the 500m buffer length for all NYCCAS analyses was chosen. Pearson's Correlation coefficient was used to measure the linear relationships between modeled outdoor and measured indoor $PM_{2.5}$ and BC concentrations. We used linear

regression model results to assess predictability of measured indoor $PM_{2.5}$ and BC concentrations from modeled outdoor $PM_{2.5}$ and BC concentrations.

Results

$PM_{2.5}$ Results

Table 1. $PM_{2.5}$ Concentration Summary

$PM_{2.5}$ ($\mu g/m^3$) n=237	**Median**	**Minimum**	**Maximum**
Measured Indoor	12.90	0.035	291
Modeled Outdoor	10.50	8.81	13.64
Adjusted Modeled Outdoor	10.63	4.31	26.40

Descriptions for $PM_{2.5}$ concentrations are summarized in Table 1. The median concentration of measured indoor $PM_{2.5}$ was significantly greater than both modeled outdoor and adjusted modeled outdoor $PM_{2.5}$ concentrations. The modeled outdoor $PM_{2.5}$ was weakly (Evans, 1996) positively correlated ($r = 0.21$) with measured indoor $PM_{2.5}$ concentrations (Figure 1). Modeled outdoor $PM_{2.5}$ concentrations only predicted 4% of the variability in measured indoor $PM_{2.5}$ concentrations (Table 2). Adjusted modeled outdoor $PM_{2.5}$ concentrations predicted 8% of the variability in measured indoor $PM_{2.5}$ concentrations (Table 3). The correlation between adjusted modeled outdoor $PM_{2.5}$ concentrations and measured indoor $PM_{2.5}$ concentrations was slightly higher ($r = 0.28$) compared to outdoor modeled $PM_{2.5}$ (Figure 2). Increases in both outdoor modeled and adjusted outdoor modeled $PM_{2.5}$ concentrations were positively associated with increases in indoor measured $PM_{2.5}$ concentrations ($\beta = 2.30$ and 0.74, respectively).

Table 2. Indoor $PM_{2.5}$ and Modeled Outdoor $PM_{2.5}$ Regression Results

Measured $PM_{2.5}$ Indoor	**β**	**95% CI**	**p-value**
Modeled Outdoor $PM_{2.5}$ ($\mu g/m^3$)	2.30	0.90, 3.60	< 0.01
R-Squared	0.04		
Model *p-value*	< 0.01		

Table 3. Indoor $PM_{2.5}$ and Adjusted Modeled Outdoor $PM_{2.5}$ Regression Results

Measured Indoor $PM_{2.5}$	**β**	**95% CI**	**p-value**
Adjusted Modeled Outdoor $PM_{2.5}$ ($\mu g/m^3$)	0.74	0.43, 1.01	< 0.01
R-Squared	0.08		
Model *p-value*	< 0.01		

Figure 1. Measured Indoor and Modeled Outdoor $PM_{2.5}$ Concentrations (N=237).

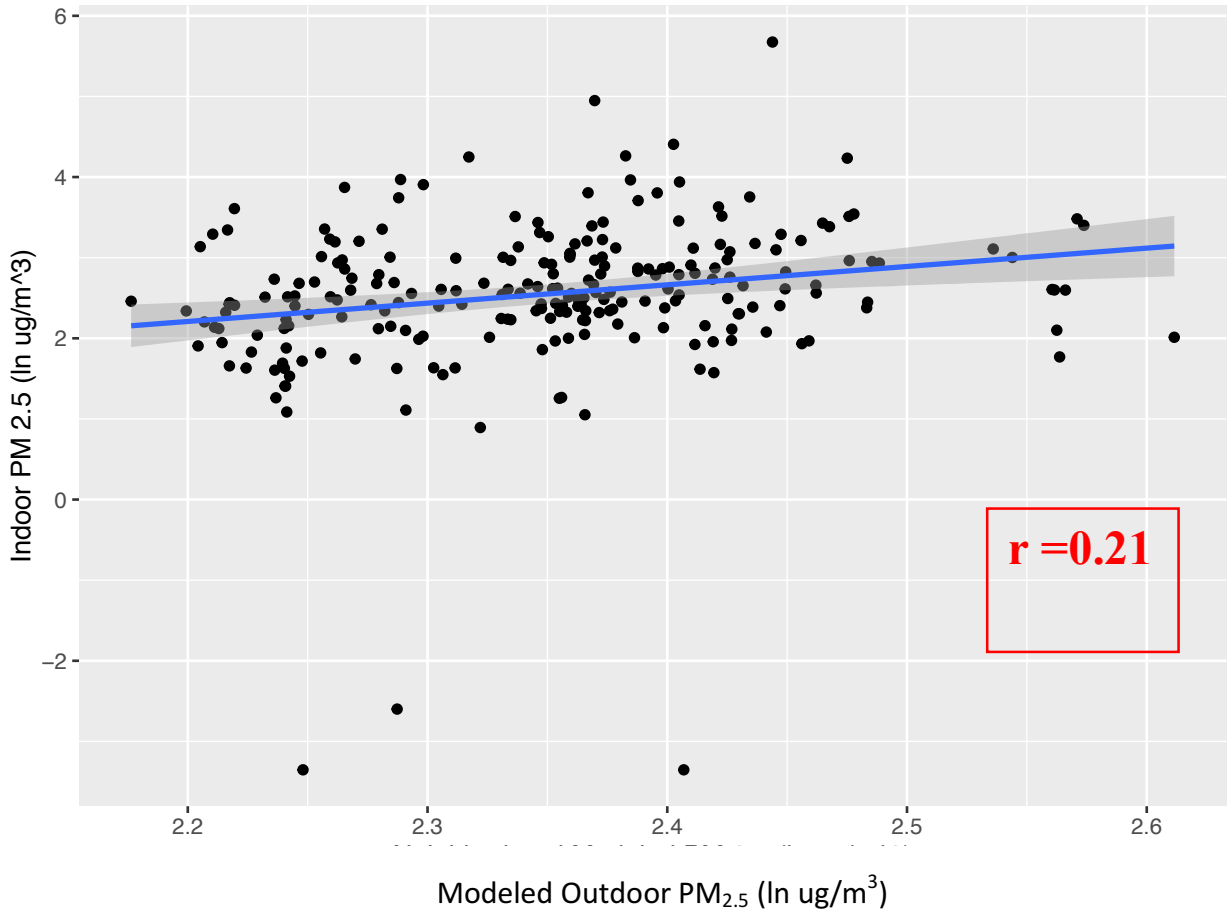


Figure 1. Pearson's correlation results of measured indoor $PM_{2.5}$ and modeled outdoor $PM_{2.5}$ ($p < 0.001$). Blue line represents linear regression line with 95% CI in grey.

Figure 2. Measured Indoor and Adjusted Modeled Outdoor $PM_{2.5}$ Concentrations (N=237).

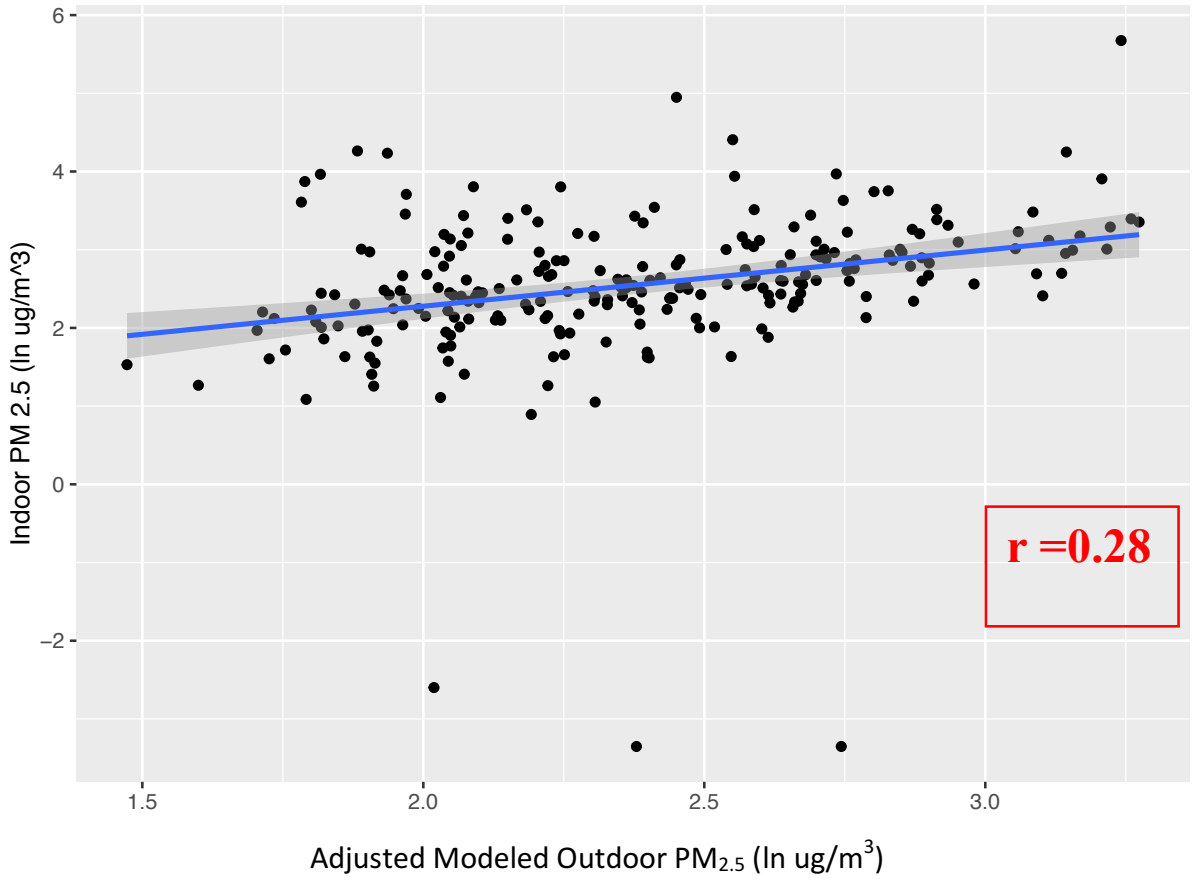


Figure 2. Pearson's correlation results of measured indoor $PM_{2.5}$ and adjusted modeled outdoor $PM_{2.5}$ ($p < 0.001$). Blue line represents linear regression line with 95% CI in grey.

BC Results

Descriptions of BC concentrations are summarized in Table 4. The median BC concentrations were similar for both measured indoor levels and both modeled and adjusted modeled outdoor levels. Similarly, to $PM_{2.5}$, there was greater range in 7-day indoor measured BC concentrations compared to the annual modeled outdoor levels, consistent with the much shorter averaging time of the indoor levels as compared to the modeled outdoor levels. The modeled outdoor BC concentrations were moderately (Evans, 1996) positively correlated (r = 0.44) with measured indoor BC concentrations (Figure 3). Modeled outdoor BC concentrations predicted 20% of the variability in measured indoor BC concentrations (Table 5). The adjusted modeled outdoor levels show the same r (Figure 4) and r^2 (Table 6) with measured indoor levels as the unadjusted model. Increases in both modeled outdoor and adjusted modeled outdoor BC concentrations were positively associated with increases in measured indoor BC concentrations (β = 1.31 and 0.82, respectively).

Table 4. BC Concentration Summary

BC (n=237)	Median	Minimum	Maximum
Measured Indoor ($\mu g/m^3$)	1.31	0.04	8.30
Modeled Outdoors ($\mu g/m^3$)	1.13	0.72	1.82
Adjusted modeled outdoor modeled ($\mu g/m^3$)	1.23	0.49	2.88

Figure 3. Measured Indoor and Modeled Outdoor BC Concentrations (N=237).

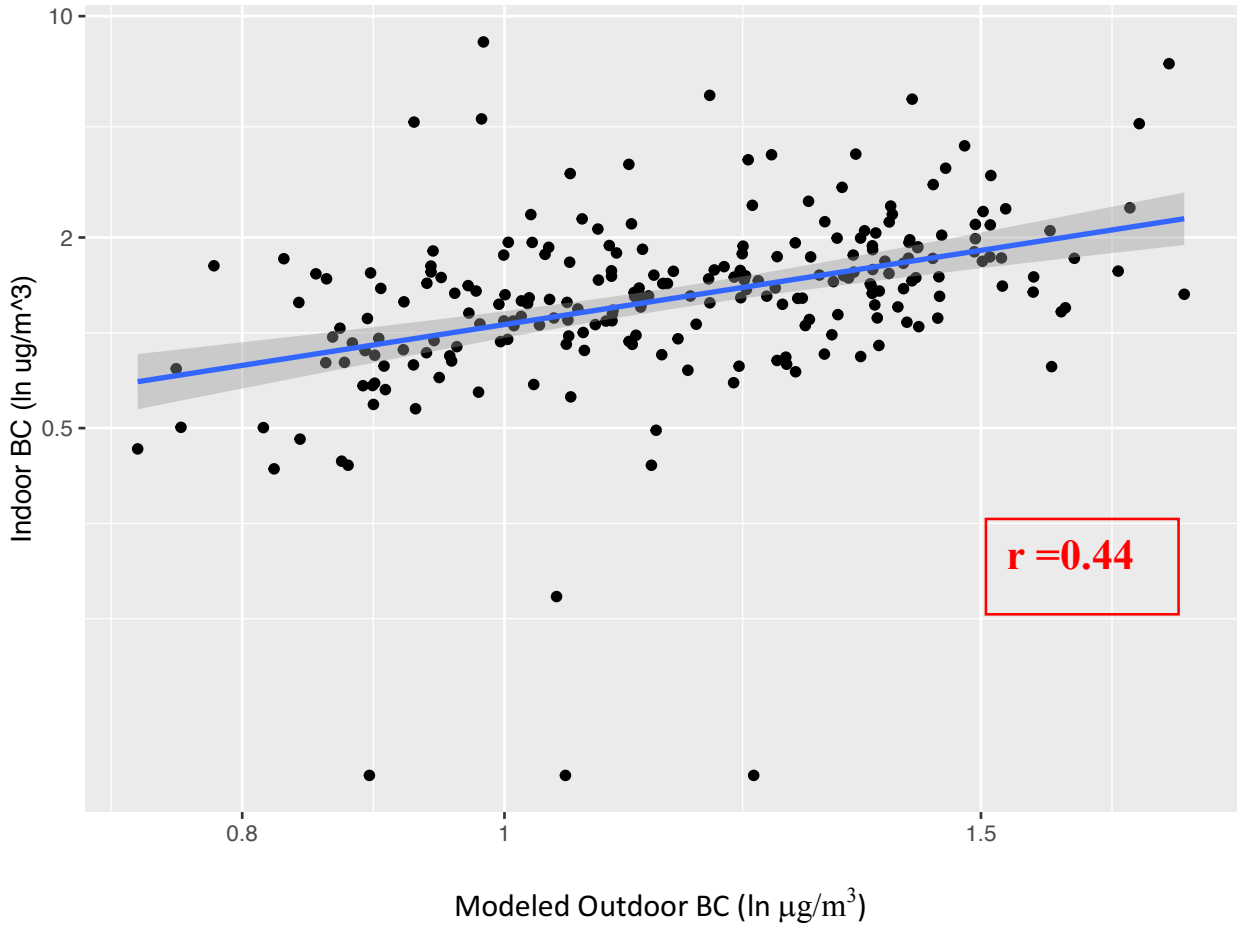


Figure 3. Pearson's correlation results of measured indoor BC and modeled outdoor BC ($p < 0.001$). Blue line represents linear regression line with 95% CI in grey.

Table 5. Measured Indoor BC and Modeled Outdoor BC Regression Results

Measured Indoor BC ($\mu g/m^3$)	**β**	**95% CI**	**p-value**
Modeled Outdoor ($\mu g/m^3$)	1.31	0.88, 1.67	< 0.01
R-Squared	0.19		
Model *p-value*	< 0.01		

Figure 4. Measured Indoor and Adjusted Modeled Outdoor BC Concentrations (N=237).

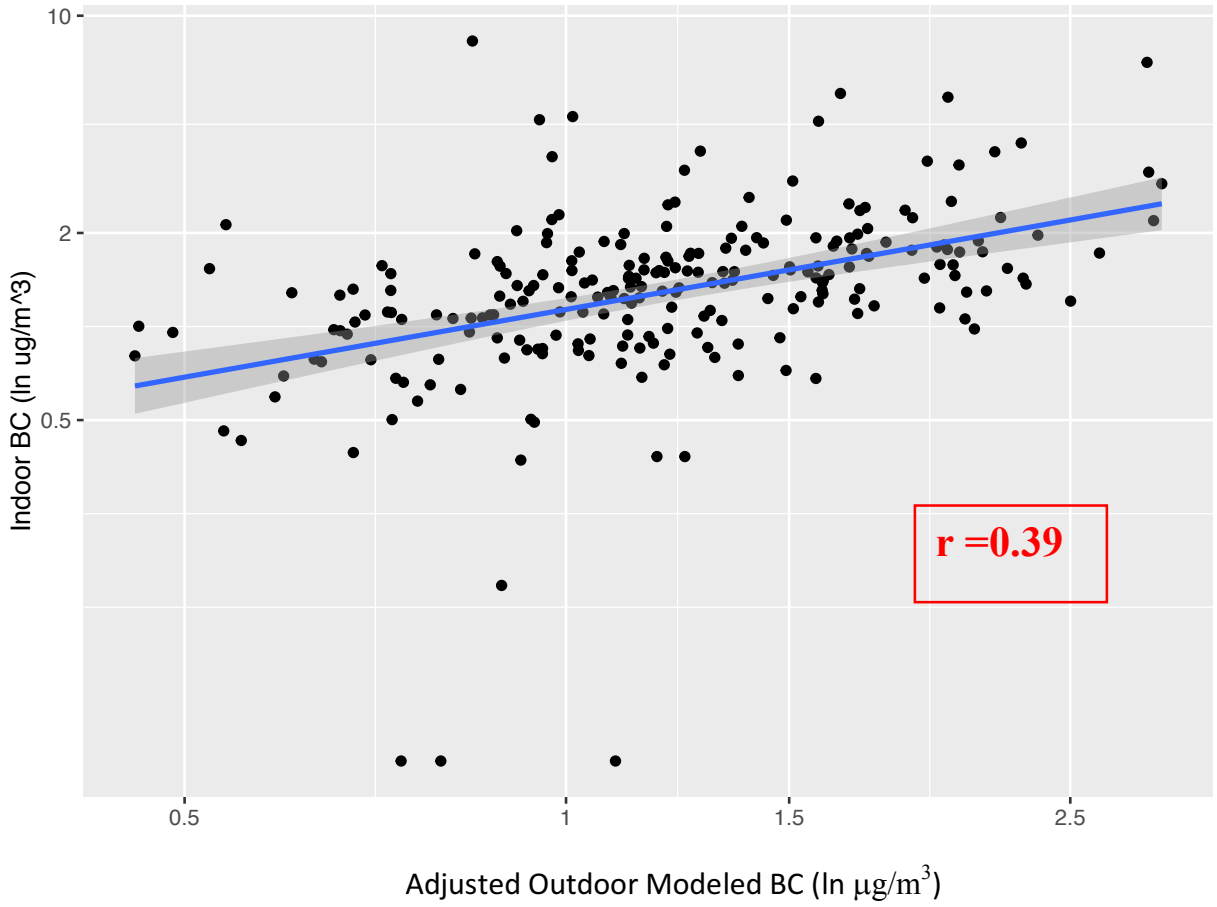


Figure 4. Pearson's correlation results of measured indoor BC and adjusted modeled outdoor BC ($p < 0.001$). Blue line represents linear regression line with 95% CI in grey.

Table 6. Indoor Measured BC and Adjusted Outdoor Modeled BC Regression Results

Indoor measured BC (µg/m^3)	β	**95% CI**	**p-value**
Adjusted outdoor modeled (µg/m^3)	0.67	0.47, 0.88	< 0.01
R-Squared	0.15		
Model *p-value*	< 0.01		

Discussion

As hypothesized, modeled outdoor BC performed better at predicting indoor BC concentrations, consistent with less indoor sources of BC as compared to $PM_{2.5}$; however, the adjusted model did not show any significant increase in predicting the variability than the unadjusted model. This better prediction is also consistent with BC being more sensitive to spatial heterogeneity (Kinney et al. 2005, Jung et al. 2010; Jung, Bernabé, et al. 2011) than temporal heterogeneity in NYC, in contrast to $PM_{2.5}$ (Kinney et al 2005; Clougherty et al. 2013). Furthermore, indoor $PM_{2.5}$ concentrations may be more influenced by indoor $PM_{2.5}$ sources compared to BC. Despite the low correlation coefficient and R^2 values, the large beta coefficient in Table 2 indicates a strong linear relationship between outdoor modeled $PM_{2.5}$ and indoor measured $PM_{2.5}$ concentrations. Long term (i.e. 2 yr average) modeled outdoor $PM_{2.5}$ levels poorly predicted 7-day measured indoor $PM_{2.5}$ concentrations. The adjusted modeled outdoor PM2.5 levels did slightly better at predicting short term measured indoor levels.

Many studies in the last decade have focused on identifying the best measurement methods for assessing the health effects of air pollution exposure (Cyrys, 2003; Götschi, 2002; Jung, Artigas, et al., 2011b; Jung, Bernabé, et al., 2011; LaRosa, 2002; Long, 2000). However, for chronic health outcomes in intra city health studies, it is still an open question whether the short term exposure measurements provided by personal and residential monitors, which have been shown to more accurately represent spatial variations observed within a city over short time scales of days to a week or two, are better for individualized exposure assessment than longer term averages available from ambient monitors. The NYCCAS model was designed to greatly improve the spatial representativeness of typical fixed site monitors but also provide long term average values. We compared ~7 day measured indoor levels of PM2.5 and BC to the modeled

2-year average values partly in order to assess whether we could have confidence in the modeled values and partly to explore this tension between short and long term measurements. In reality for chronic health issues, the question is how well does short term measured indoor measurements capture long term chronic exposures?

Previous studies indicate that there is greater variability in measured indoor $PM_{2.5}$ concentrations compared to measured outdoor levels even when both measurements are made over the same time period due to episodic indoor $PM_{2.5}$ sources (Long, 2000). These temporal variations in indoor $PM_{2.5}$ sources indicate that indoor short term measurements of $PM_{2.5}$ may be a better sampling method for assessing the risk for acute health effects attributed to its exposure. Although the annual modeled outdoor $PM_{2.5}$ was weakly correlated to 7-day indoor measured $PM_{2.5}$ concentrations, these two measurements differed greatly by time. The outdoor modeled concentration was a 2-year annual average, while the indoor was a shorter-term 7-day average.

The annual safe upper-limit $PM_{2.5}$ concentration is 15 $\mu g/m^3$ and the 24-hour upper-limit is 35 $\mu g/m^3$ (EPA, 2010). This difference indicates an importance in temporal variability of $PM_{2.5}$ concentrations and its relationship to human health. In an attempt to correct for the temporal discrepancy between these two measurements, we adjusted the modeled outdoor concentrations using daily ambient $PM_{2.5}$ concentrations. After adjusting for the exact indoor collection dates, there was a slight improvement in the correlation and R^2 between modeled outdoor and adjusted modeled outdoor $PM_{2.5}$ and measured indoor $PM_{2.5}$ concentrations.

The largest limitations for our study relate to timing differences, at least for the stated aim of the study was to gain confidence in the long term modeled levels for locations not within their own data set of 124 street side measurements was the mismatch in time, both the large differences in averaging time represented in the indoor measurements (2 to 14 days) the large

differences between the short term measured indoor samples and the 2 year averaging time of the modeled outdoor levels, and the fact that the indoor measurements were not made at all of the same time. Furthermore, the outdoor models were created using land-use regression and adjusted for daily ambient concentrations (from one of the same sources we used for temporally adjusting the outdoor modeled concentrations). This may have introduced bias in our regression analysis by over-fitting the adjusted modeled outdoor $PM_{2.5}$ and BC regression models.

Another limitation was that the vertical differences between the street-side modeled outdoor concentrations and the measured indoor levels which varied from ground floor to X floor. Though the mixing height in all seasons reaches higher than the buildings in NYC, the strong traffic emissions of BC especially along truck routes and major highways can result in vertical gradients. Another limitation to the present study was our small sample size. We were only able to analyze 237 samples due to missing ambient measured data.

The correlations between both modeled outdoor BC and measured indoor BC concentrations were noticeably greater than the correlations between modeled outdoor PM2.5 and measured indoor $PM_{2.5}$ concentrations. The modeled outdoor levels only predicted between 4% and 16% of the measured indoor sources of PM2.5 and BC, respectively. In conclusion, modeled outdoor $PM_{2.5}$ was poorly correlated with measured indoor $PM_{2.5}$ while modeled outdoor BC was moderately correlated with measured indoor BC concentrations in NYC concentrations.

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Chapter 4: Black carbon exposure and persistence of asthma symptoms in children from age 7-8 to 10-11 years living in New York City.

Authors: Medina Jackson-Browne, MS, Luis Acosta, Andrew Rundle, DrPH, Beizhan Yan, PhD, James Quinn, Daniel Sheehan, Thomas Matte, MD, Steven Chillrud, PhD, Matthew Perzanowski, PhD.

Abstract

Background: Exposure to black carbon (BC) has been shown to be associated with current asthma symptoms. There is limited evidence of its impact on the persistence of asthma symptoms over time. Previously, we have demonstrated a modest correlation between the New York City Community Air Survey (NYCCAS) modeled outdoor BC concentrations and indoor measured BC concentrations in New York City homes and thus consider it a marker of chronic BC exposure for NYC residents. We hypothesized that the NYCCAS outdoor BC model concentrations would be positively associated with persistent asthma symptom between ages 7-8 and 10-11 years among children living in NYC.

Methods: Children participating in a previously established asthma study were followed for 3 years. Asthma symptoms were assessed by questionnaire at baseline (age 7-8) and annually for three years (to age 10-11). Modeled outdoor BC concentration for the child's home and school addresses at baseline were used to estimate chronic exposure. We also used the density of truck routes and number of buildings burning residual oil around the child's home at baseline as other BC exposure predictors.

Results: Neither increasing BC exposure at home nor school were statistically significantly associated with persistent asthma symptoms (Prevalence Risk (PR) = 0.87, P = 0.49 and PR = 1.09, P = 0.6, respectively). The number of buildings burning residual oil was also not associated with persistent asthma symptoms (PR = 1.00, P = 0.26). Increasing density of truck routes at children's home address was inversely associated with persistent asthma symptoms (PR = 0.85, P = 0.001).

Conclusions: Modeled outdoor BC concentrations and number of buildings burning residual oil did not predict persistent asthma symptoms for the children in our study. Children living near densely populated truck routes had a decreased risk for persistent asthma symptoms.

Introduction

Particulate matter sized 2.5 microns or less ($PM_{2.5}$) is an air pollutant that has strict emission standards set by the US United State Environmental Protection Agency (EPA) for protection of human health and the environment (EPA, 2010). $PM_{2.5}$ and smaller ultra-fine particles can penetrate deep into the lungs and the associated health effects are of rising concern. $PM_{2.5}$ contains of a mixture of compounds with the abundance of $PM_{2.5}$ from diesel exhaust comprised of elemental carbon (EC) (EPA, 2012); if optically measured then the term black carbon (BC) is used instead of EC (EPA, 2012). BC contributes to the adverse impacts on human health associated with $PM_{2.5}$ (EPA, 2012). Some studies have identified BC as a possible contributor to the exacerbation of allergy and asthma symptoms. However, the cumulative research results of the role of BC in allergic diseases have yielded inconsistent results.

There is mounting evidence to suggest that exposure to BC causes asthma symptoms through airway inflammation. Studies measuring airway inflammation indicate a positive association between BC exposure and markers of airway inflammation such as FeNO (fractional exhaled nitric oxide) or EBC (exhaled breath condensate) (Delfino, 2006; Jansen et al., 2005; Rosa et al., 2014). An earlier pulmonary challenge study in rats found increased BAL (bronchial lavage) neutrophils with increasing levels of concentrated air particles, including $PM_{2.5}$ from diesel exhaust (Saldiva et al., 2002), toxicological evidence that BC, a major component of $PM_{2.5}$ from diesel exhaust, triggers airway inflammation in some individuals.

BC may also play a role in triggering asthma symptoms through an IgE-mediated pathway. Immunological studies have shown BC to behave as an adjuvant by binding to APC (antigen presenting cells) causing enhancement of T cell activation in the presence of an allergen

(Riedl et al., 2005). Previously published research have shown exposure to the ragweed allergen in conjunction to diesel exhaust particles enhances T cell production (Diaz-sanchez, 1997). A subsequent study by the same authors reported evidence of induction of primary sensitization by diesel exhaust in otherwise healthy subjects (Riedl, 2005). Although there is evidence of BC causing an immune response in the lungs, these responses do not always result in corresponding symptoms. This may explain why some studies measuring allergic and asthma symptoms as a result of BC exposure have yielded inconsistent results (McCreanor, 2007; Morgenstern, 2008; Ormstad, 2000; van Vliet et al., 1997). A study conducted in The Netherlands found BC exposure was positively associated with atopy but not with asthma, rhinitis, or symptoms of either (van Vliet, 1997).

Since BC is found at elevated levels in diesel exhaust, traffic patterns have been used as indicators of BC exposure. Studies comparing traffic routes with personal, indoor, outdoor, and ambient BC measurements have also yielded inconsistent results, with some studies reporting concordance between traffic sources and BC measurements while others reporting low correlations between traffic routes and BC concentrations. (Clougherty, 2008; Cornell, 2012; Fruin et al., 2004; Hankey et al., 2015; Hoek et al., 2008; Johnson et al., 2010; Lena et al., 2002; Patel, 2010). However, living in close proximity to vehicle traffic has been linked to asthma morbidity (Albino Barraza-Villarreal, 2008; Behndig, 2006; Mann, 2010).

A previously published study by our group found a significant correlation between indoor BC concentrations and number of nearby truck routes and with neighborhood asthma prevalence but not lung function (Cornell, 2012; Rosa, 2014). However, both BC exposure and asthma morbidity assessments were one-time, cross-sectional measurements and BC exposure was only measured inside of the child's home over a short period of time (7-days on average). In this

study, we aimed to measure the effect of an estimated measure of more chronic exposure at both the child's home and school on the persistence of asthma symptoms over a 4-year period. We hypothesized that asthmatic children with greater BC exposure would have a greater risk for asthma symptom persistence.

Methods

Study design

A previously establish asthma cohort (Olmedo, 2011) of children aged 7-8 years, were prospectively followed to ages 10-11 years. Asthma cases at age 7-8 were defined as a parent reporting that their child had at least one of the following in the previous 12 months by questionnaire:

(1) Wheeze

(2) Wheeze with exercise

(3) Being woken at night by cough without having a cold

(4) Asthma medication use.

Asthma Outcomes

Children classified as asthmatic at baseline were administered follow-up questionnaires at least once at 1, 2, and 3 year intervals after baseline. Asthma symptom persistence was defined as a child meeting the asthma case definition at baseline and again at the 3-year follow-up. Asthma symptom remission was defined as having asthma symptoms at baseline but not at the 3-year follow-up. Neighborhood asthma prevalence was dichotomized for figures where 11% or greater was defined as a higher asthma prevalence neighborhood (HAPN) and lower asthma prevalence neighborhood (LAPN) was 9% or less based on data for 5-year old school children from the NYC Department of Health and Mental Hygiene (DOHMH) in 2000 (Garg, 2003;

Olmedo, 2011). For regression analyses, neighborhood asthma prevalence was included as a continuous variable.

Black Carbon Exposure Variables

Outdoor air was monitored by the NYC DOHMH for the NYCCAS (New York City Community Air Survey) at 124 street level (12 feet above the ground) locations throughout NYC for 2 week monitoring periods during each season from 2008-2010 (Matte, 2013). There were also 5 reference monitors, one in each borough, collecting ambient daily samples. These measurements were used to adjust outdoor measurements for variation that occurred throughout the city over time due to weather conditions. Land-use regression modeling was performed by NYCCAS to generate a 2-year annual average BC concentration model spanning years 2008-2010 (Clougherty, 2008). Local concentrations from these models were then used to characterize 500 meter buffers around study participants baseline geocoded home and school addresses in GIS. BC was measured using a reflectance technique previously described (Matte, 2013) and then converted to equivalent EC levels in $\mu g/m^3$. The density of truck traffic routes and number of buildings burning residual oil were also used to characterize 500 meter buffers around study participants baseline geocoded home addresses (Cornell, 2012).

Seroatopy status

A blood specimen was collected during the baseline home visit. Allergen-specific immunoglobulin E (IgE) for inhalant allergens (German cockroach, mouse urine proteins, Dermatophagoides, farinae, cat dander, dog dander, common ragweed, mixed tree pollen) were measured by ImmunoCAP® (Phadia, Uppsala, Sweden) to determine seroatopy status. Children with specific IgE $\geq$ 0.35IU/mL to at least one of the allergens tested were considered seroatopic.

Statistical Methods

All data analyses and figures were performed using R (version 3.1.3) (R Core Team, 2013). Exploratory analyses were completed to uncover distribution patterns in the data. The outcome variables, asthma symptom persistence and neighborhood asthma prevalence were both dichotomized (yes/no and HAPN/LAPN, respectively. Modeled outdoor BC concentrations were log-transformed for analyses. Chi-squared test of independence was performed on study characteristics to measure differences between the baseline and followed-up asthmatics and also for differences between children with and without asthma symptom persistence. Modified Poisson regression with robust standard errors was used to measure the prevalence risk-ratio (PR) of asthma persistence and neighborhood asthma prevalence. For further clarity in interpretation of the magnitude of the associations observed with the regression analyses, the resulting PR was determined by transforming β to reflect a doubling of "x" (Equation 1) for outdoor BC concentrations in regression models.

Equation1.

$$\log(\hat{y} = 1) = \text{constant} + \beta * \log(x)$$

slope: $e \wedge \ln(2) * \beta = PR$ for a doubling of x

Results

At baseline there were 206 children classified as asthmatic, and of those, n=153 completed the 3-year follow-up questionnaire. Among these 153 children, 5 were missing neighborhood modeled BC exposure concentrations or blood serum samples leaving 148 children for final analyses (Table 1). The baseline characteristics did not differ statistically between the children recruited for the study and the subset that remained in the study 3 years later (Table 1). A majority of the asthmatic children at baseline and at the 3-year follow-up

were male (60% for both), seroatopic (60% and 58%, respectively), and had a baseline home visit during the heating season (60% for both).

There was a similar percent of male children with and without persistent asthma symptoms (Table 2). There was a greater percent of children with a smoker in the home with persistent symptoms compared to without, however this difference was not statistically significant. Children with persistent asthma symptoms were also more likely to be African-American, Hispanic and seroatopic ($p = 0.03$) compared to children without symptoms. There was no statistically significant difference in median measured indoor BC concentrations between children with persistent symptoms and those without. However, children without persistent asthma symptoms were more likely to have their baseline visit during the heating season ($p < 0.001$) than those with remission of symptoms.

Modeled outdoor home BC was not significantly associated with risk of persistent asthma symptoms (Figure 1A). Similar to modeled outdoor BC concentrations at the home address results, no association was found between increasing modeled outdoor BC at the child's school address and persistent asthma symptoms (Figure 1B). Increasing density of truck routes was associated with risk of persistent asthma symptoms (Figure 1C). The number of buildings burning residual oil around the participants' home address was not associated with the risk of asthma symptom persistence (Figure 1D).

Discussion

The main goal of this study was to determine the effect BC exposure has on the risk for asthma symptom persistence among school age children in NYC. We did not find a significant association between modeled outdoor BC exposure and asthma symptom persistence in our cohort. Neither modeled outdoor home nor modeled outdoor school BC concentrations were

positively associated with asthma symptom persistence in our study. The number of buildings burning residual oil and the density of trucks routes also did not positively predict persistent asthma symptoms.

Exposure to diesel exhaust particles, including BC, is associated with increased risk for both allergic sensitization and exacerbation of asthma symptoms (A. Barraza-Villarreal et al., 2011; Casillas, 1997; Delfino et al., 2002, 2013; Diaz-sanchez, 1997; Eder, 2006). There was a significantly larger percentage of seroatopic children with (68%) asthma symptom persistence compared to those without (35%) persistent symptoms (Table 2). After adjusting for seroatopy status and heating season, only the density of truck routes was significantly associated with the risk of asthma symptom persistence in our models (Supplemental Table 1). This association was in the opposite direction of what we expected (RR = 0.81). However, previously published findings from children in this cohort also observed an inverse association between BC exposure and airway inflammation but only in non-seroatopics, it is possible that the non-seroatopic children in the study are driving the overall inverse association seen in our results (Cornell, 2012).

Black carbon concentrations increase during the heating season in NYC (Clougherty, 2013; Jung, 2010). Heating season has also been shown to be positively associated with wheeze in children (Bastien et al., 2015; Clougherty, 2013, 2008; Jung, 2010). There was a greater number of asthmatic children without symptom persistence when the baseline assessment was conducted during the heating season compared to children with persistent asthma symptoms. Due to these associations with heating season, it is possible that the symptoms observed at baseline in some of the asthmatics were due to the season of the home visit causing misclassification of disease. Sensitivity analysis resulted in no significant association between

heating season and modeled outdoor BC at participants' home or at school addresses. The number of buildings burning residual oil and the density of truck routes surrounding the study participants home were also not associated with modeled outdoor BC (Supplemental Table 1).

Measured BC in home has been shown to be most influenced by traffic within 100-400 m buffer (Eder, 2006; Zhou et al., 2007) and risks for asthma morbidity have also been found to be greatest for individuals living within 75-100 meters of a major road or highway (Jung, 2010; McConnell, 2006; Venn, 2002). Densities of truck routes and the number of buildings burning residual oil surrounding the children's homes were characterized at a 500 meter(m) buffer and the latter was not significantly associated with asthma symptom persistence (Figure 1 B and C). We used a 500m buffer for consistency with the outdoor modeled BC buffers, however sensitivity analysis using a 250m buffer for both truck route densities and buildings burning residual oil resulted in no association with asthma symptom persistence (Supplemental Table 2). However, after controlling for heating season and seroatopy status, the density of truck routes around the participants' home address was negatively associated with persistent asthma symptoms (Supplemental Table 1).

There was a significantly larger percentage of seroatopic children with (68%) asthma symptom persistence compared to those without (35%) persistent symptoms (Table 2). Higher prevalence of childhood asthma has also been noted in urban areas particularly in poorer neighborhoods among African-American and Hispanic populations. African-American children are 7 times more likely to die due to complications from asthma than White children (Akinbami et al., 2012; Togias et al., 2010). Poorly controlled asthma is also more common among urban African-American and Hispanic children than among urban White children (Akinbami, 2012; Crocker et al., 2009). More than half of the children with persistent asthma symptoms are

African-American and close to 40% are Hispanic (Table 2). Although there were no statistically significant differences between baseline and follow-up, African-American and Hispanic children represent the majority of children with asthma symptom persistence and therefore may represent the greatest groups at risk for asthma morbidity.

One of the major limitations of this study was sample size. A larger cohort of children living throughout NYC may increase the power to assess the main effect of BC exposure and any interaction with seroatopy and BC exposure on risk of asthma symptom persistence. Early life BC exposure measurements and multiple blood sampling (to measure seroatopy) would also provide a stronger design to more efficiently measure the association between BC exposure and seroatopy earlier in life and subsequently asthma development. Previous studies have hypothesized that early life exposure to combustion-by products may be involved in the development of allergic sensitization (Matthew S. Perzanowski et al., 2013). There were two major strengths of this study design; the use of longer-term BC exposure models and the prospective following of asthmatics. In addition, the ages of the study participants are optimal for assessing risk factors for the persistent asthma symptoms. During adolescence, remission of asthma symptoms will occur for many asthmatic children (Spahn et al., 2008; Taussig et al., 2003).

In addition to our previously published findings (Cornell, 2012), the lack of association between BC exposure and asthma symptom persistence are indicators that the decreased risk found in modeled outdoor BC results may be a consequence of how BC was measured in this study. The modeled outdoor BC concentrations used here were 2-year annual average estimates of BC exposure and may be more of a chronic exposure model which has less variability than shorter-term BC measurements. This reduced variability may underestimate the risk of asthma

symptom persistence from acute BC exposure. In addition, we were only able to follow 143 asthmatics during the time the neighborhood modeled BC concentrations were measured. This small sample size may have diminished our power to detect an association between neighborhood modeled BC and asthma symptom persistence.

The results from this study did not support our hypothesis that increased BC exposure is associated with asthma symptom persistence in children from age 7-8 to 10-11 years of age. However, among asthmatics with symptoms that persisted, we did observe more seroatopic children compared to children whom symptoms remitted. Given the racial demographic children with asthma symptoms that persist, African-American and Hispanic children are a particularly vulnerable group and further research assessing the health effects of BC with asthma should focus on these children. These children may also be more susceptible to the development of allergic sensitization from BC exposure early in life, which may increase their risk to developing asthma. Further research examining the effects of early life BC exposure and the development of allergic sensitization in African-American and Hispanic populations could lead to a better understanding of the effect of BC exposure in seroatopic asthmatics.

Tables and Figures

Table 1. Characteristics of Baseline Compared to Follow-up Study Participants.

	Baseline (n=206)	Follow-up at 3 years (n=148)
Male (%)	**57**	**61**
African-American race (%)	**49**	**49**
Hispanic ethnicity (%)	**36**	**36**
Home visit during heating season (%)	**60**	**60**
Smoker in the home (%)	**20**	**19**
Seroatopy (%)	**60**	**58**
Mean Indoor airborne black carbon ($\mu g/m^3$[SD])	**1.5 (1.0) (n=188)**	**1.5 (1.0) (n=142)**
Neighborhood Characteristics		
Live in HAPN (%)	**51.3**	**50.3**
Truck route density (km/km^2)	**1.9**	**1.8**
Mean Residential buildings burning residual oil (#)	**4.2**	**4.0**

None statistically significantly different (i.e., all $p > 0.05$)

Table 2. Baseline characteristics of Follow-up Study Participants.

	Asthma Persistence (n=105)	No Asthma Persistence (n=43)
Male (%)	**61**	**61**
African-American race (%)	**51**	**44**
Hispanic ethnicity (%)	**39**	**28**
Home visit during heating season (%)	**55**	**72***
Smoker in the home (%)	**21**	**14**
Seroatopy (%)	**68**	**35***
Median Indoor airborne black carbon ($\mu g/m^3$)	**1.3**	**1.4**
Neighborhood Characteristics		
Live in HAPN (%)	**51**	**48**
Truck route density (km/km^2)	**1.7**	**2.2**
Mean Residential buildings burning residual oil (#)	**3**	**6**

*$p < 0.05$

Figure 1A. Home Modeled Outdoor Black Carbon and Asthma Symptom Persistence Risk (N=146).

A.

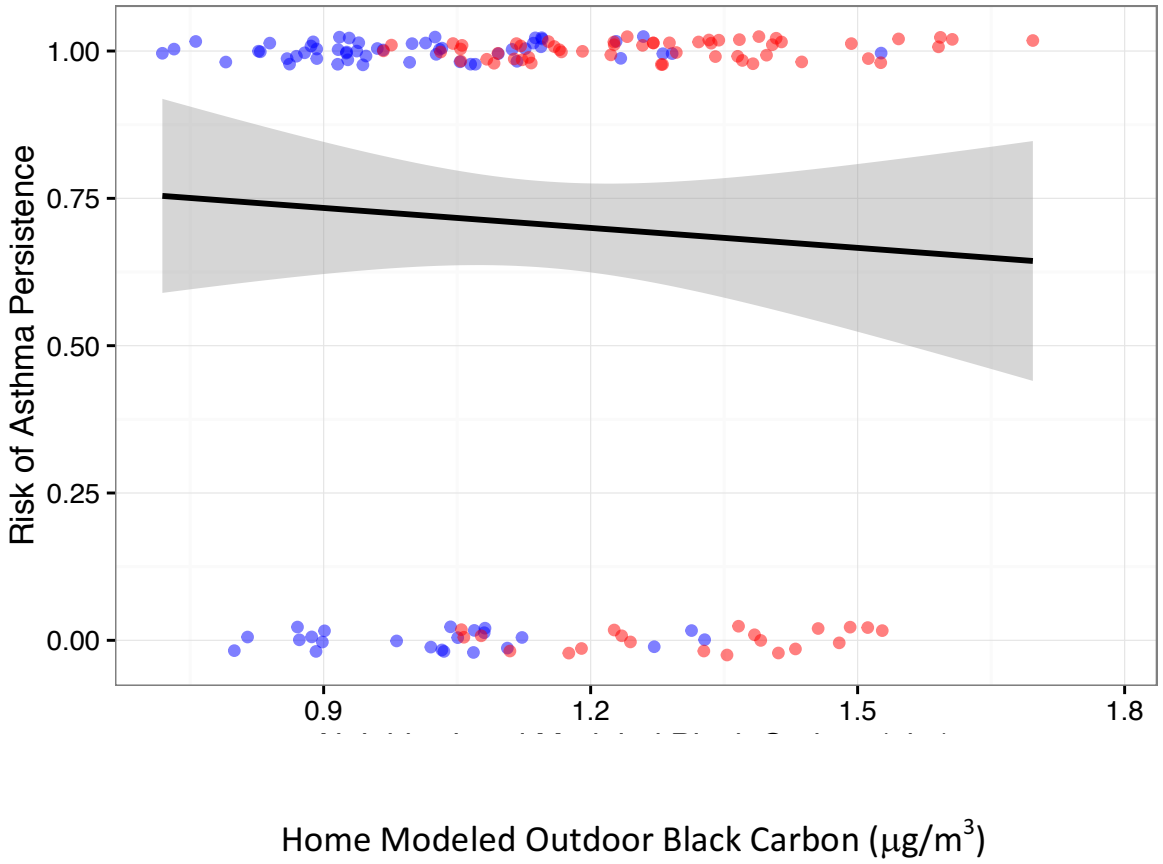

Figure 1A. Modeled outdoor BC at baseline home address is not associated with risk of persistent asthma symptoms (PR = 0.87, 95%CI (0.58-1.29), p = 0.49). Red points represent high asthma prevalence neighborhoods and blue points represent low asthma prevalence neighborhoods.

Figure 1B. School Modeled Outdoor Black Carbon and Asthma Symptom Persistence Risk (N=146).

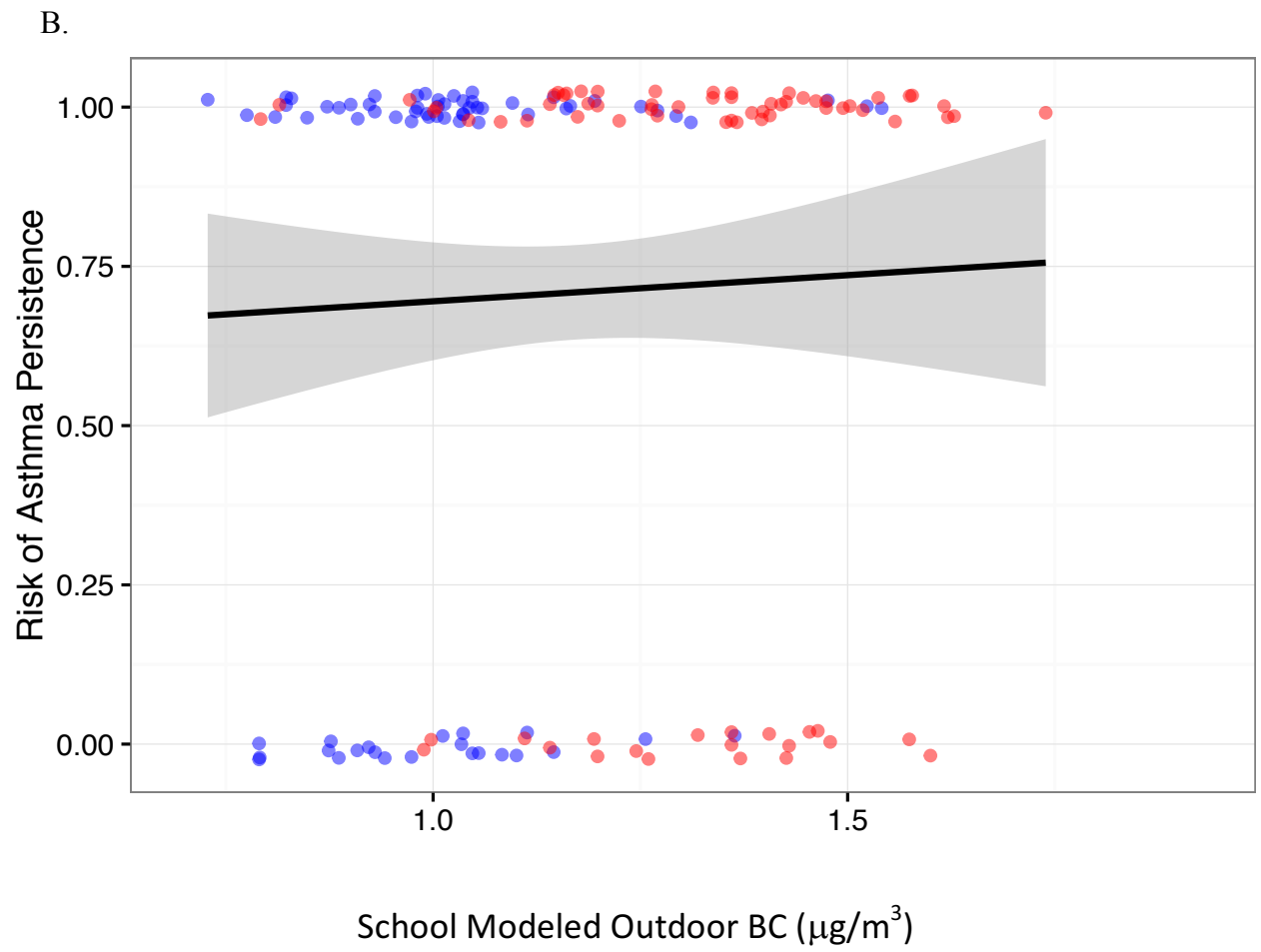

Figure 1B. Modeled outdoor BC at baseline school address (n=146) is not associated with risk of persistent asthma symptoms (PR = 1.09, 95% CI (0.77-1.56), p = 0.60). Red points represent high asthma prevalence neighborhoods and blue points represent low asthma prevalence neighborhoods.

Figure 1C. Density of Truck Routes and Asthma Symptom Persistence Risk (N=146).

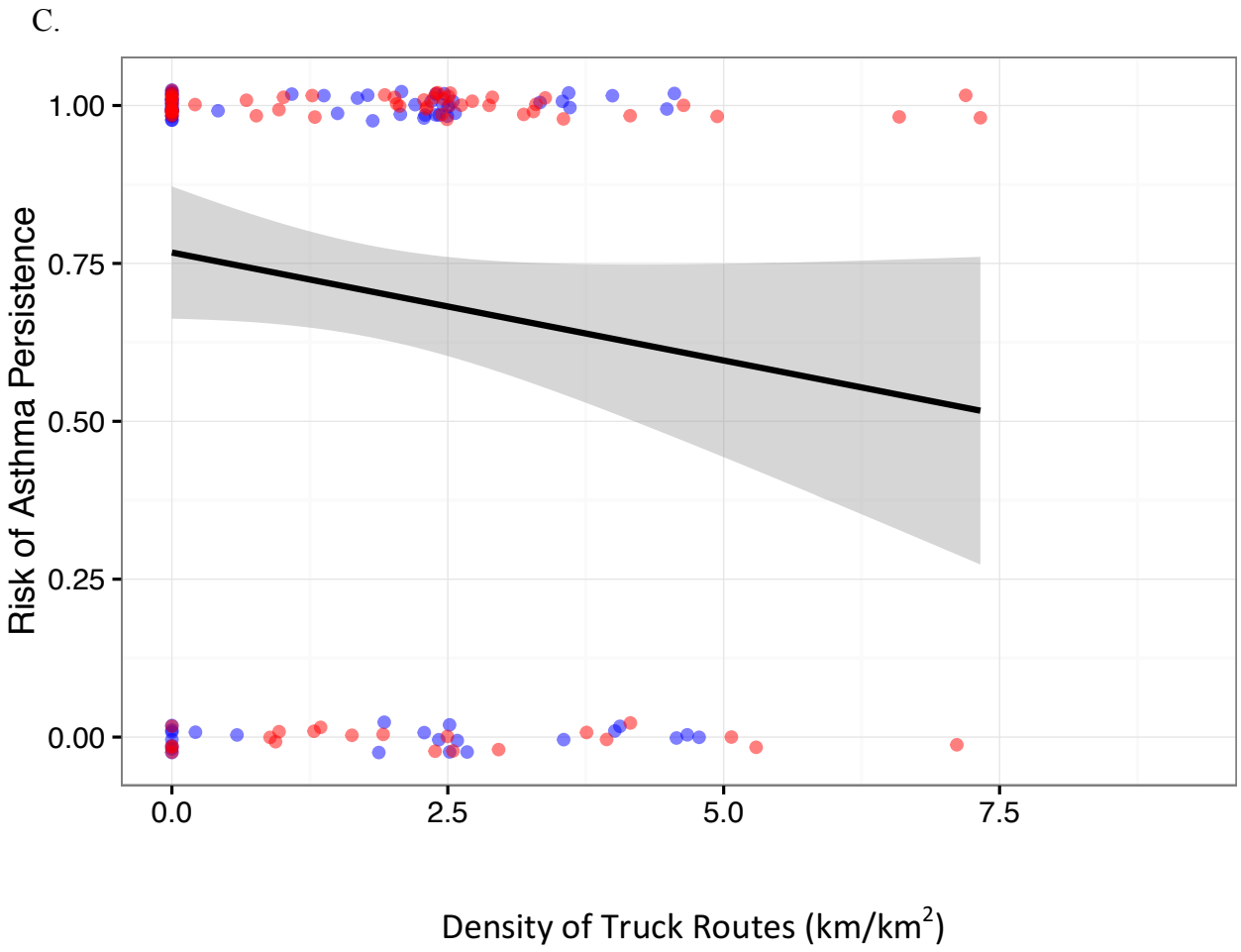

Figure 1C. Density of truck routes around participants' home address (n=146) is inversely associated with risk of persistent asthma symptoms (PR = 0.85, 95% CI (0.77-0.94), $p < 0.001$). Red points represent high asthma prevalence neighborhoods and blue points represent low asthma prevalence neighborhoods.

Figure 1D. Buildings Burning Residual Oil and Asthma Symptom Persistence Risk (N=146).

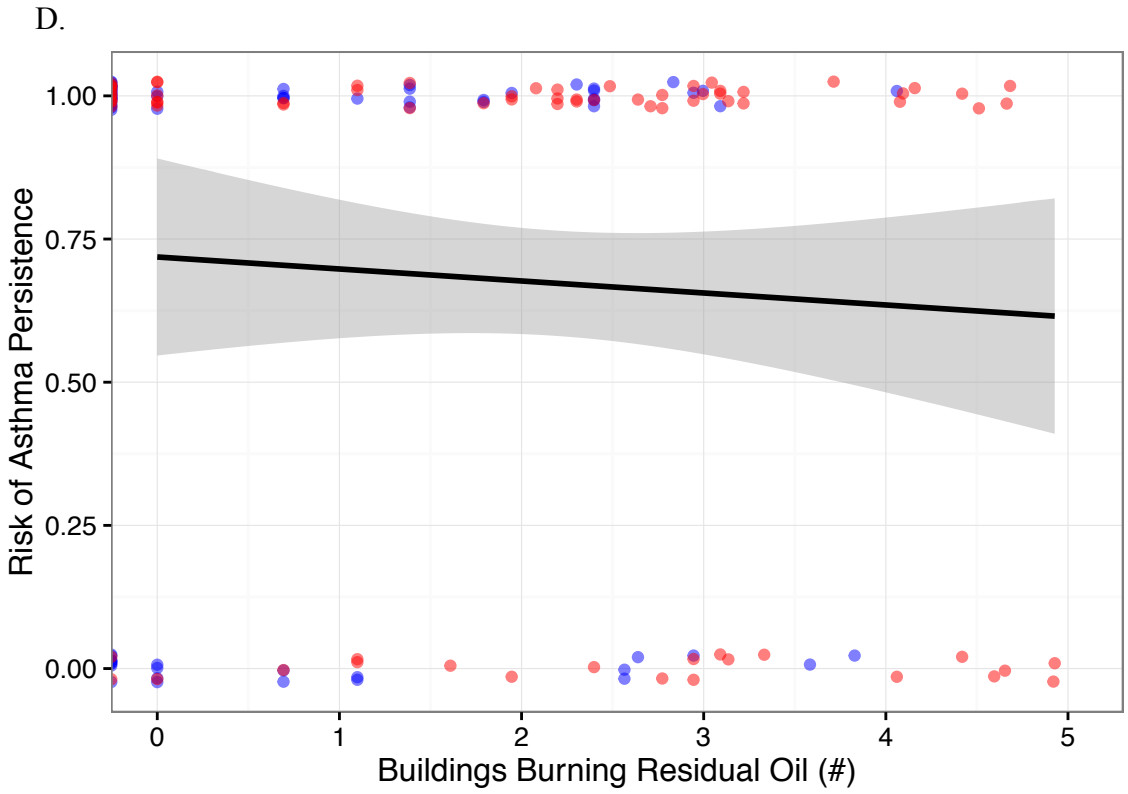

Figure 1D. Number of buildings burning residual oil at baseline home address (n=146) is not associated with risk of persistent asthma symptoms (PR = 1.00, 95% CI (0.99-1.002), p = 0.26). Red points represent high asthma prevalence neighborhoods and blue points represent low asthma prevalence neighborhoods.

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Supplemental Section

The regression model including all possible BC exposure variables and confounders are shown in supplemental table 1. Outdoor modeled BC at school, density of truck routes, heating season at baseline, and seroatopy were associated with asthma symptoms persistence (Supplemental Table 1). After adjusting for season, we found that increasing truck routes around participants' home address was significantly associated with risk of seroatopy.

Supplemental Table 1. Full BC exposure and asthma symptom persistence regression model.

Persistent Asthma Symptoms	PR (95% CI)	p-value	Adjusted PR[#] (95% CI)	p-value
Home Outdoor Modeled BC	0.92 (0.42-2.02)	0.84	0.93 (0.44-1.96)	0.85
School Outdoor Modeled BC	2.12 (1.16-3.86)	0.01	2.07 (1.19-3.58)	0.009
Density of Truck Routes	0.81 (0.72-0.91)	< 0.001	0.81 (0.71-0.92)	< 0.001
Buildings Burning Residual Oil	1.00 (0.99-1.001)	0.31	1.00 (0.99-1.002)	0.19
Heating Season	1.10 (1.00-1.23)	0.53	1.12 (1.01-1.24)	0.03
		Seroatopy	1.49 (1.16-1.91)	0.002

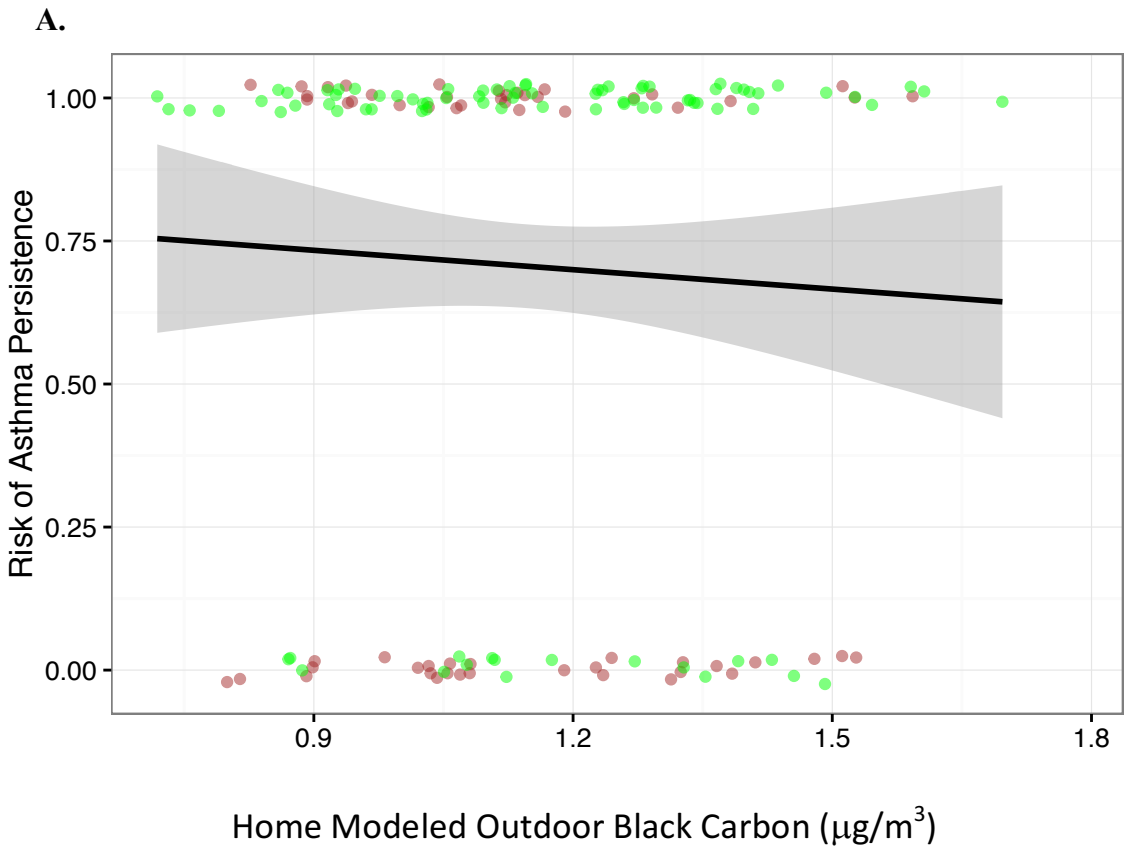
 # Adjusted for Seroatopy status

Supplemental Table 2. Sensitivity analysis of Truck route and buildings burning residual oil 250m buffers.

Persistent Asthma Symptoms	PR (95% CI)	p-value	Adjusted PR[#] (95% CI)	p-value
Density of Truck Routes	0.95 (0.89-1.01)	0.09	0.95 (0.89-1.02)	0.12
Buildings Burning Residual Oil	0.99 (0.97-1.00)	0.09	0.98 (0.96-1.00)	0.15

 # Adjusted for Seroatopy status

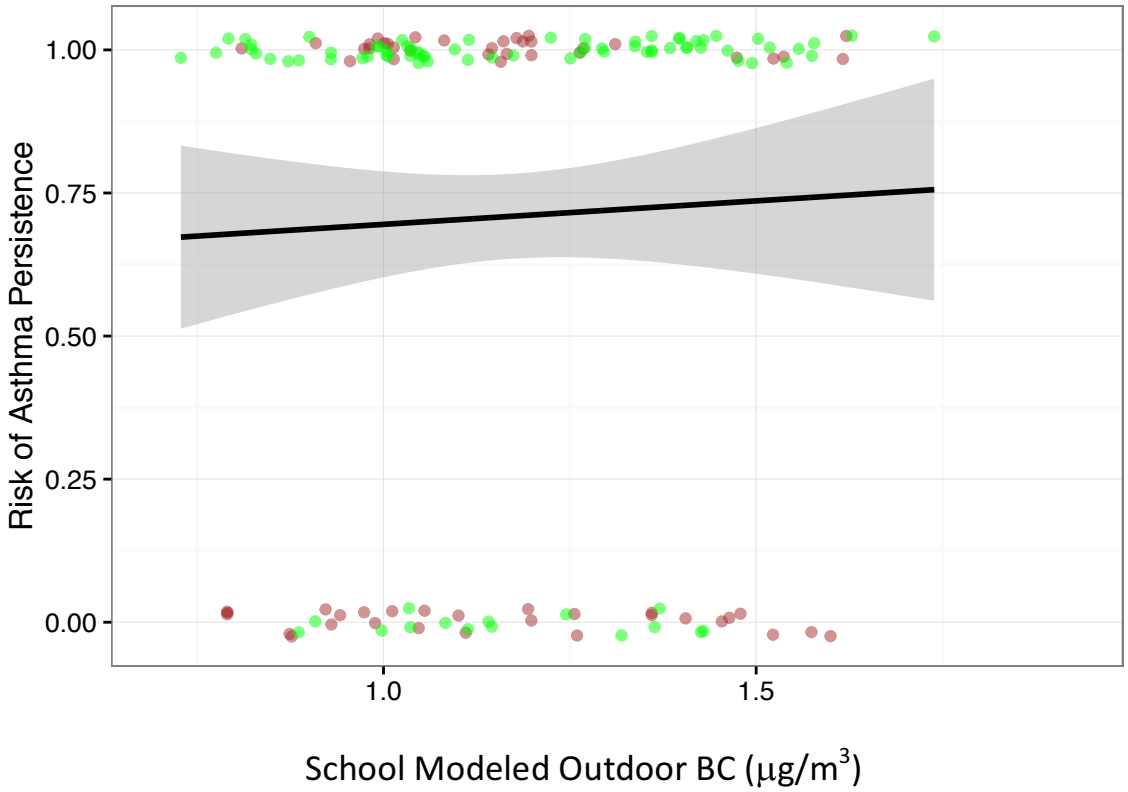
Supplemental Figure 1A. Home Modeled Outdoor Black Carbon and Asthma Symptom Persistence Risk by Seroatopy Status (N=146).



Supplemental Figure 1A. Modeled outdoor BC at baseline home address (n=146) is not associated with risk of persistent asthma symptoms (PR = 1.00, 95%CI (0.99-1.001), p = 0.18). Brown points represent seroatopics and green points non-seroatopics.

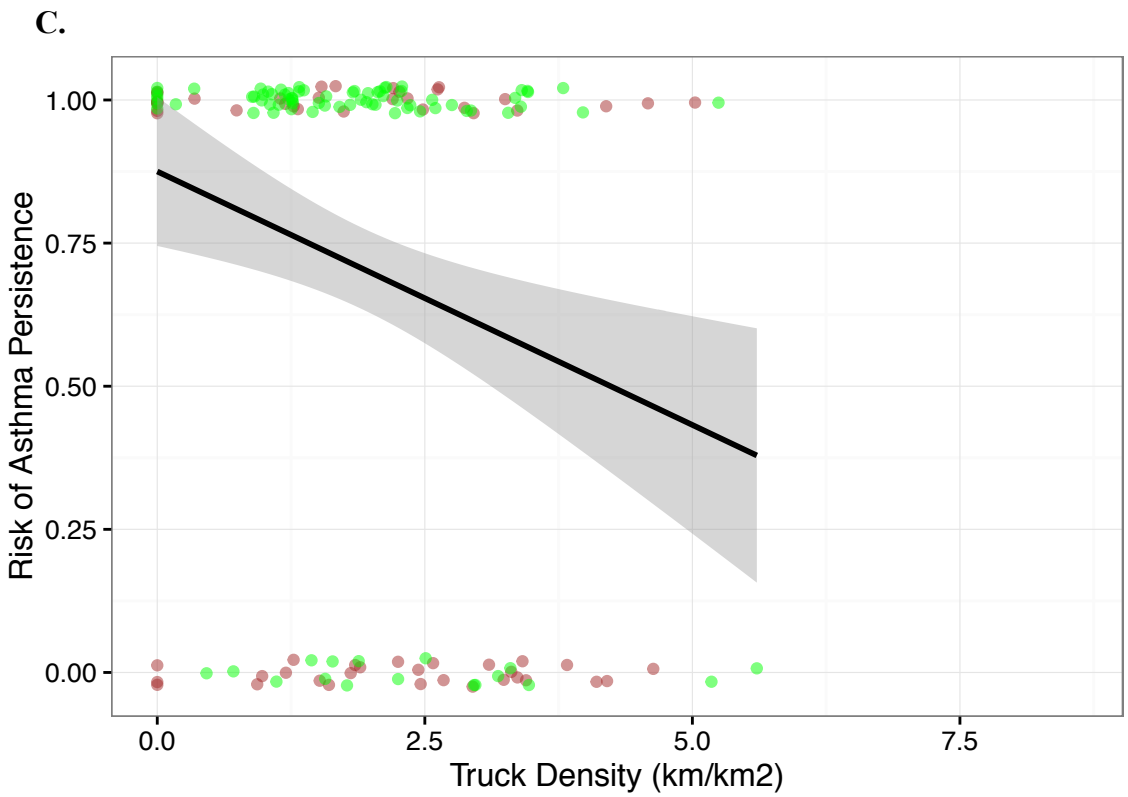
Supplemental Figure 1B. School Modeled Outdoor Black Carbon and Asthma Symptom Persistence Risk by Seroatopy Status (N=146).

B.



Supplemental Figure 1B. Modeled outdoor BC at baseline school address (n=146) is not associated with risk of persistent asthma symptoms (PR = 1.10, 95% CI (0.99-1.24), p = 0.07). Brown points represent seroatopics and green points non-seroatopics.

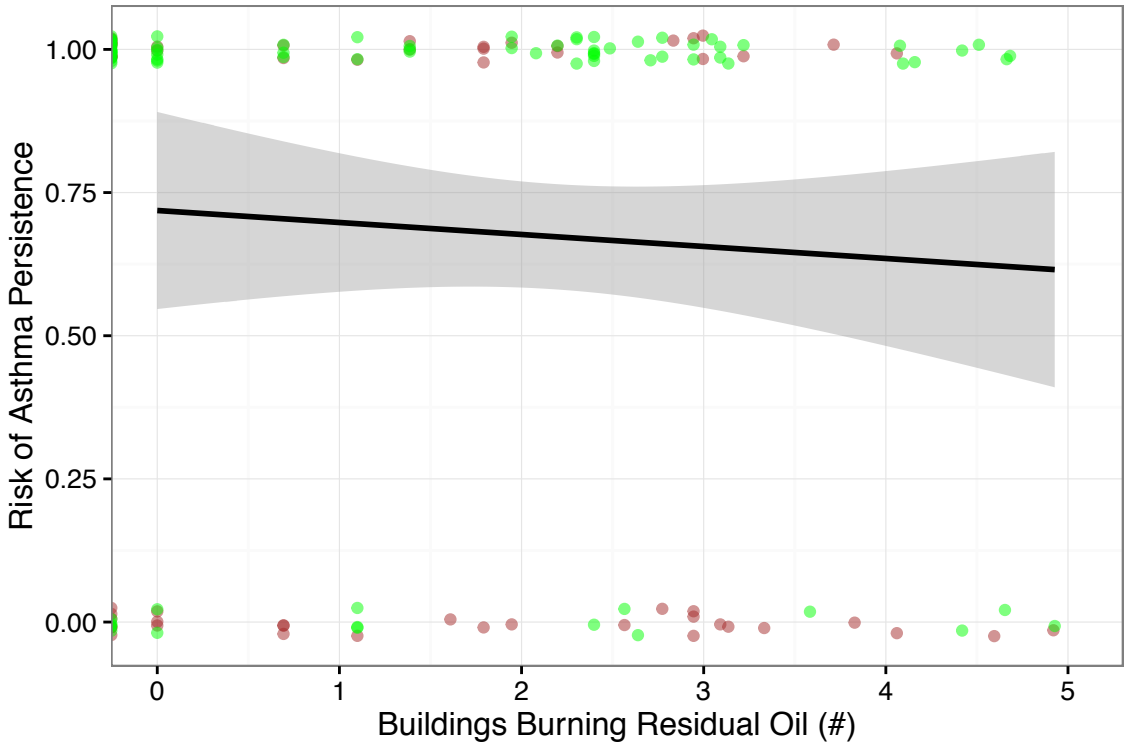
Supplemental Figure 1C. Density of Truck Routes and Asthma Symptom Persistence Risk by Seroatopy Status (N=146).



Supplemental Figure 1C. Density of truck routes around participants' home address (n=146) is negatively associated with risk of persistent asthma symptoms (PR = 0.85, 95% CI (0.78-0.95), p = 0.003). Brown points represent seroatopics and green points non-seroatopics.

Supplemental Figure 1D. Buildings Burning Residual Oil and Asthma Symptom Persistence Risk by Seroatopy Status (N=146).

D.



Supplemental Figure 1D. Number of buildings burning residual oil at baseline home address (n=146) is not associated with risk of persistent asthma symptoms (PR = 1.00, 95% CI (0.99-1.01), p = 0.18). Brown points represent seroatopics and green points non-seroatopics.

Chapter 5: Summary of Major Findings

The three manuscripts contained in this dissertation were designed to address the overarching hypothesis that exposure to mouse allergen and black carbon are significant risk factors of allergic sensitization and asthma morbidity, respectively, for children living in NYC. By testing three working hypotheses, outlined below we address the main components of the overarching hypothesis.

Hypothesis 1a: We hypothesized that mouse allergen concentration in settled kitchen floor dust would be a better representation of indoor mouse exposure versus mouse allergen measured from settled bed dust and therefore associated with an increased risk for mouse sensitization.

Principle findings from Specific Aim 1a:

Increasing mouse allergen concentrations measured from settled kitchen dust was positively associated with an increased risk of mouse sensitization for the children in our study. Mouse allergen from settled bed dust was not significantly associated with an increased risk of sensitization to mouse. Our findings support our hypothesis that mouse allergen concentration measured from settled kitchen floor dust is a better representation of mouse exposure inside of the home and mouse sensitization risk compared to mouse allergen concentrations from settled bed dust.

Hypothesis 1b: We hypothesized that longer-term mouse exposure measurements both inside and outside of the home would be associated with an increased risk of mouse sensitization.

Principle findings from Specific Aim 1b:

The strong association between parents reporting greater than weekly mouse sightings in the past 12 months supports our hypothesis that longer-term mouse exposure measures are

associated with risk of mouse sensitization. There was no significant association between neighborhood rodent sights in the past 90 day and school cafeteria mouse reports and mouse sensitization risk.

Hypothesis 2a:

We hypothesized that 7-day measured indoor $PM_{2.5}$ and BC concentrations would be positively associated with annual modeled outdoor $PM_{2.5}$ and BC concentrations.

Principle findings from Specific Aim 2a:

Annual modeled outdoor $PM_{2.5}$ was weakly positively correlated ($r = 0.21$) with 7-day measured indoor $PM_{2.5}$. We also found annual modeled outdoor BC values better predicted 7-day measured indoor BC concentrations compared to annual outdoor modeled $PM_{2.5}$ concentrations predicting 7-day indoor measured $PM_{2.5}$ concentrations.

Hypothesis 2b*:*

We hypothesized that temporally adjusting the annual modeled outdoor $PM_{2.5}$ and BC concentrations would explain a greater proportion of the variability of the 7-day measured indoor $PM_{2.5}$ and BC concentrations compared to unadjusted annual modeled outdoor $PM_{2.5}$ and BC concentrations.

Principle findings from Specific Aim 2b:

After temporally adjusting annual modeled outdoor $PM_{2.5}$, we observed only a slight increase in the strength of the correlation with 7-day measured indoor $PM_{2.5}$ compared to unadjusted annual modeled outdoor $PM_{2.5}$ (r changed from 0.2 to 0.3). We did observe greater variability explained in the 7-day measured indoor $PM_{2.5}$ by the temporal adjustment compared to the unadjusted model. The temporal adjustment of annual modeled outdoor BC did not change the correlation with 7-day measured indoor BC compared to unadjusted annual modeled outdoor

BC and also did not explain more variability in 7-day measured indoor BC compared to the unadjusted longer-term neighborhood modeled BC. The limitations discussed at length in chapter 4 helped explain the overall observation that modeled outdoor $PM_{2.5}$ was poorly correlated with measured indoor $PM_{2.5}$ while modeled outdoor BC was moderately correlated with measured indoor BC concentrations in NYC concentrations.

Hypothesis 3:

We hypothesized that annual modeled outdoor BC outdoor exposure would be associated with persistence of asthma symptom in children from age 7-8 to 11-12 years.

Principle findings from Specific Aim 3:

In contrast to our hypothesis, annual modeled outdoor BC concentrations at both home and school was not associated with persistent asthma symptoms in children from age 7-8 to 10-11 years.

Chapter 6: Conclusions and Future Directions

Conclusions

The NYC NAAS was the first to examine asthma persistence prospectively among children living in neighborhoods that differ in rates of asthma prevalence. Other unique features of the study population are 1) similar access to health care (same health insurance), 2) overlapping socio-demographic characteristics (race and income) between high and low asthma prevalence neighborhoods and 3) a substantial proportion of African-Americans living in both low and high asthma prevalence neighborhoods.

The associations between mouse allergen in kitchen floor dust and mouse sensitization risk as well as the lack of association with concentrations from bed dust suggests that mouse allergen is not evenly distributed throughout the home. This finding is consistent with other studies but emphasizes the importance of sampling kitchens over an earlier focus on sampling bed dust. Furthermore, significant associations were not detected between neighborhood rodent reports and school cafeteria mouse reports with mouse sensitization risk. However, the neighborhood rodent report did not differentiate between rat and mouse. This generalization may have introduced exposure misclassification in our analysis and biased the association. Therefore, the neighborhood rodent reports may not accurately measure mouse exposure for children in NYC. In reference to the non-significant association between school cafeteria inspection reports and mouse sensitization risk, the inspection report results were not collated in a standardized manner. Schools were randomly selected to be inspected throughout the school year therefore schools inspected during the winter months may have had more evidence of mice compared to schools inspected in warmer months which may have also introduced misclassification of exposure in our study. Also, school cafeterias may not represent where most students are

exposed to mouse allergens. Sampling settled dust or air from classrooms environments may better predict mouse sensitization risk in children (Amr, 2003).

There is overwhelming evidence of an association between mouse allergen exposure and mouse sensitization in asthmatic children living in urban communities (Boulet et al., 2011; Donohue et al., 2008; Matsui, 2009, 2005, 2007). The findings from our mouse study demonstrate the importance of domestic exposure to mouse allergen to the development of sensitization in children. Reducing exposure to mouse allergen should be an important component of plans for the management of asthma. The implementation of intensive, multicomponent mouse exposure-reduction strategies should be evaluated as a method of reducing morbidity due to asthma in urban populations.

The results from our PM correlation study show a difference between how much modeled outdoor $PM_{2.5}$ concentrations influences measured indoor $PM_{2.5}$ compared to the influence modeled outdoor BC concentrations has on measured indoor BC concentrations. These differences may be due to the spatial and temporal variability associated with each respective particle. $PM_{2.5}$ has been shown to have greater spatial variability compared to greater temporal variability in BC (Jung, 2010; Patel, 2010; Ross, 2013). We found weak and moderate correlations between both modeled outdoor $PM_{2.5}$ and BC concentrations and measured indoor $PM_{2.5}$ and BC concentrations consistent with previously published findings and the limitations of the study. Adjusting the modeled outdoor concentrations temporally in an attempt to improve the overall relationship between outdoor and indoor concentrations. After adjusting for temporal variability, we found little to no change in correlation between outdoor modeled $PM_{2.5}$ and BC concentrations and indoor measured $PM_{2.5}$ and BC concentrations. Our findings suggest both $PM_{2.5}$ and BC outdoor models are not strongly predictive of indoor measured concentrations,

however outdoor modeled BC concentrations predicted greater variability in indoor measured BC concentrations compared to $PM_{2.5}$.

We previously found no significant association between shorter-term indoor measured BC concentration and asthma morbidity for children living in NYC (Cornell, 2012). We then hypothesized that longer-term BC exposure estimates would be associated with asthma morbidity for the same children in NYC (Hypothesis 3). However, the results with the longer term exposure estimates from our asthma study also found no association. However, the cohort size in this asthma study was smaller than the previous since we only analyzed the asthmatics. Also, there were significantly more atopic children with asthma symptoms that persisted compared to those whose symptoms remitted. This finding suggests an increased risk for asthma morbidity from childhood into pre-teen years for atopic children.

Future directions

The development of asthma in children is a complex phenomenon. As a result, it is difficult to determine whether mouse allergen or BC exposure are direct causative agents. Studies have identified mouse allergen and BC as potential triggers of symptom exacerbation of asthma and other allergic conditions. However, the results of the effect of exposure on sensitization and subsequent asthma development and/or morbidity have been inconsistent. Taken together, our finding suggests that both mouse allergen and BC exposure may be associated with adverse allergic health outcomes.

Our results can be used by local public health officials for mitigating mouse exposure in homes and school. Mouse intervention resources may have a greater impact on reducing allergic-related conditions and diseases if the intervention is focused first in the kitchen and then in the child's bedroom (Wanda Phipatanakul, 2004; Rosenfeld, 2011) and classrooms in schools

(Amr, 2003). The neighborhood modeled $PM_{2.5}$ and BC concentrations analyzed in our study may not reflect personal exposure and therefore underestimate the effect of these pollutants on the risk for asthma morbidity for children in NYC. Repeated measures of personal exposure may result in positive associations between BC and asthma morbidity for children in NYC. Also, larger prospective cohorts could be used to give greater statistical power to allow for further exploration of possible modifying effects of seroatopy status in the association between BC and asthma morbidity for children living in NYC. In conclusion, how, when, and where these environmental exposure measures are taken are instrumental in assessing allergy-related health morbidities.

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