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Addressing gaps in the age-specific evidence used for United States air pollution policy

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Addressing gaps in the age-specific evidence used for United States air pollution policy

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Abstract

Addressing gaps in the age-specific evidence used for United States air pollution policy

By Heather Strosnider

Introduction

Substantial and consistent evidence supports the conclusion that short-term exposure to ambient concentrations of ozone and fine particulate matter (PM2.5) is associated with increases in mortality and morbidity; however, the evidence for morbidity outcomes in populations under 65 is limited. This gap is due to the lack of a centralized, readily accessible database of emergency department (ED) visits and hospitalizations for populations under 65 for air pollution epidemiology. To address this gap, we leveraged the infrastructure of the Centers for Disease Control and Prevention National Environmental Public Health Tracking Program to gather data for respiratory ED visits and conducted a multi-county study.

Methods

We requested daily, county-level data aggregated by respiratory outcome, age group, and sex from thirty states. We conducted a descriptive analysis of respiratory ED visits to evaluate annual and daily rates. Then, we conducted a two-stage multi-county analysis of the association between short-term exposure to ambient ozone and PM2.5 and respiratory ED visits for each age-outcome group. Lastly, we evaluated the between county heterogeneity of the results from our two-stage analysis and explored the contribution of various county-level covariates to that heterogeneity for the association between PM2.5 and asthma among children.

Results

Seventeen states submitted the requested data, resulting in a database of almost 50 million respiratory ED visits covering over 40% of the United States population. The median rate of ED visits per 10,000 population per year for all respiratory ED visits combined was 410 with an interquartile range of 276. We observed variation in the rates by state, county, outcome, age group, and sex. Ozone and PM2.5 were associated with respiratory ED visits among all ages with variation in magnitude by age group and outcome. State, region, and percent of population without health insurance explained 50% of the between-county heterogeneity for the association between PM2.5 and asthma among children.

Conclusion

Our work addresses an important gap in air pollution epidemiology for respiratory morbidity for populations under 65 and suggests that effect estimates from multi-city studies of populations over 65 may not be transportable to younger age groups.

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Chapter 1 - Introduction

Substantial and consistent evidence supports the conclusion that short-term exposure to ambient concentrations of ozone and fine particulate matter ($PM_{2.5}$) is associated with increases in mortality and morbidity [1, 2]. In their 2013 Integrated Science Assessment (ISA), the U.S. Environmental Protection Agency (EPA) determined ozone to have a causal relationship with respiratory health effects and a likely causal relationship with cardiovascular health effects and non-accidental and cardiopulmonary-related mortality [2]. Ozone also has a suggestive causal relationship with central nervous system effects such as alterations in neurotransmitters, motor activity, short and long-term memory, sleep patterns, and histological signs of neurodegeneration. EPA concluded in their 2009 ISA for particulate matter (the update to which is currently under review) that $PM_{2.5}$ has a causal relationship with cardiovascular health effects and mortality and a likely causal relationship with respiratory health effects [1]. $PM_{10\text{-}2.5}$ and ultrafine particles have a suggestive causal relationship with cardiovascular health effects, respiratory health effects, and mortality. EPA's causal determinations are based on results from controlled human exposure, toxicological, and epidemiological studies reviewed as part of the process for setting national air pollution policy. While the depth of published literature is substantial, evidence is limited or inconsistent for some pollutants and health effects, such as the relationship between asthma and $PM_{2.5}$ among children and the relationship between respiratory infections and ozone. Further, questions remain regarding the shape of the concentration response (C-R) functions, the potential for health effects at lower concentrations, the effects of multi-pollutant exposures, and the protection of sensitive sub-populations.

Ozone is not directly emitted into the atmosphere. It is a secondary air pollutant generated by a reaction between ultraviolet radiation from the sun and precursor pollutants from anthropogenic and natural sources [2]. In the stratosphere, naturally occurring ozone plays a beneficial role by absorbing ultraviolet radiation from the Sun. Tropospheric or ground-level ozone is harmful to living organisms and the environment. Precursor pollutants include carbon monoxide (CO), nitrogen oxides (NOx), and volatile organic compounds (VOCs) largely generated from the combustion of fossil fuels. Temporal and spatial variation in ozone levels are influenced by concentration of precursor pollutant sources, meteorological patterns, and topography. However, ozone molecules have an atmospheric lifetime of a few weeks and, as such, are transported regionally and globally. As a secondary pollutant, ozone is more spatially homogeneous than other primary pollutants. Ambient concentration of ozone in the US has been declining since the implementation of the NOx State Implementation Plan Call rule in 2003 and the subsequent reduction of NOx emissions. Regionally, concentrations tend to be highest in the southwest, particularly southern California, and in the mid-Atlantic extending to the Atlanta metro area. Ozone levels are typically higher during the warm season, which varies regionally. Ozone itself reacts with NO and therefore levels are lower in urban areas where NO sources are concentrated and higher in neighboring suburban areas. In urban areas, ozone exhibits a strong diurnal pattern and varies spatially though the degree of spatial variability is different between urban areas. Ozone levels in rural areas are uniform and more persistent.

Whereas ozone is a specific chemical compound, particulate matter (PM) is a mixture of chemically and physically diverse particles and liquid droplets of varying sizes [1]. PM can include anions (sulfate, nitrate), cations (ammonium, sodium, potassium), trace elements, total

carbon (organic, elemental), gaseous pollutants (CO, NO2, SO2, O3), and biologic components. PM is classified according to its aerodynamic diameter. Fine particulate matter ($PM_{2.5}$) refers to those particles with a mean aerodynamic diameter less than or equal to 2.5 micrograms per meter. Such particles are of greater concern in regards to health, because of their ability to penetrate the lungs and their tendency to contain components with higher toxicity. Both finer and courser particles are more readily exhaled and thus do not penetrate the lungs as well. Standards for PM were established first for total suspended particles in 1971 and then transitioned to PM_{10} in 1987. $PM_{2.5}$ was first regulated in 1997 after health effects were observed in areas meeting the PM_{10} standard. Ambient concentrations of $PM_{2.5}$ have since declined. Regional differences have also declined though levels are higher in southern California and major urban areas, especially in the east. Over 24 hours, $PM_{2.5}$ peaks twice corresponding to morning and evening rush hour. $PM_{2.5}$ is spatially more homogeneous than smaller or larger PM or other primary pollutants due to the formation of secondary $PM_{2.5}$, a longer atmospheric lifetime, and increased transportability. $PM_{2.5}$ and ozone are correlated with positive correlation in the summer and negative correlation in the winter.

Both natural and anthropogenic sources contribute to $PM_{2.5}$. Primary $PM_{2.5}$ is directly emitted into the atmosphere and is largely generated by the combustion of fossil fuels. Secondary $PM_{2.5}$ is formed within the atmosphere through the transformation of gaseous pollutants such as sulfur oxides, nitrogen oxides, and volatile organic compounds. $PM_{2.5}$ varies chemically and physically over both time and space due to differences in meteorology, sources, and topography. While over fifty chemical components can contribute to $PM_{2.5}$, fewer than five typically account for the majority of the total mass [3]. Organic carbon, sulfate, and nitrate contribute the most to total

$PM_{2.5}$ mass, almost 40% [3, 4]. These components are emitted by multiple sources and are associated with secondary $PM_{2.5}$. The major source categories of primary $PM_{2.5}$ are metal industry, crustal/soil particles, motor vehicle traffic, steel industry, coal combustion, oil combustion, salt particles, and biomass burning [4]. Motor vehicle traffic accounts for more than 30% of $PM_{2.5}$ mass. While traffic and soil sources are more geographically ubiquitous, other sources are geographically concentrated: steel and metal processing in industrialized cities, biomass burning in northwest, residual oil combustion in northeast cities and cities with major seaports, and coal combustion in Ohio River Valley [4]. Elemental carbon, a tracer for traffic-related PM, shows less seasonal variation but is typically higher in west coast and lower northeast [3]. Organic carbon is highest in the west where it peaks in the fall and winter and in the southeast where it peaks in the spring and fall. Sulfate is higher in the east and has greater seasonal variation than other components with peaks in the summer. Nitrate is highest in the winter across the US with highest levels in California.

Under the Clean Air Act, EPA is required to set national primary and secondary ambient air quality standards that are protective of public health and welfare for common air pollutants [5]. National Ambient Air Quality Standards (NAAQS) have been set by EPA for six criteria air pollutants: particulate matter, ozone, sulfur dioxide, nitrogen dioxide, carbon monoxide, and lead. States are required to comply the standards and provide an enforceable state implementation plan. Standards are developed and periodically reviewed based on the latest science in peer-reviewed literature about each pollutant and its impact on public health and welfare. EPA's process includes an ISA, a risk/exposure assessment (REA), and a policy assessment (PA). An ISA synthesizes and evaluates the policy-relevant scientific evidence

including information on exposure, physiological mechanisms, toxicology, and epidemiology including information on reported C-R relationships with consideration of effects on susceptible populations [1, 2]. In an ISA, EPA evaluates the evidence of the relationship between each pollutant and various health outcomes and makes a causal judgement. When selecting studies to include in an ISA, EPA considers the quality, adequacy, and comparability of the study population, statistical methods, air quality data, and effect measurements used. Information from the ISA is used in development of the REA which is a quantitative assessment of pollutant exposure and the associated risks to human health or the environment based on current air quality levels, current standards, and proposed standards [6, 7]. Human health risk assessments require an estimate of the C-R relationship as well as data on ambient air pollutant concentrations, baseline rates of health effects, and the population. A C-R function is generally estimated from one or more epidemiologic studies used in the ISA. Specifically, the beta of a time-series or case-crossover regression analysis can be transformed to provide an estimate of the number of increased health effects per short-term increase in air pollution concentration. Such risk assessments typically focus on ED visits, hospitalizations, or deaths because of data availability.

Robust epidemiologic evidence and, subsequently, C-R functions exist for mortality among all ages and for hospitalizations among adults 65 and older due in large part to the availability of national vital statistics data and Medicare data. These data have enabled many multi-city analyses, which have been instrumental in setting the current NAAQS [8-15]. Estimates from multi-city studies provide strong evidence for determining causality between air pollution and health, for evaluating potential health benefits of proposed policies across a large portion of the

US, and for establishing ambient concentration standards that provide adequate protection for the US population. In selecting C-R functions for a REA, estimates of effect from multi-city studies are preferred because they (1) use the same study design over each city making city results comparable, (2) have more statistical power and provide effect estimates with relatively greater precision, (3) leverage the statistical power from data across all cities to detect an effect in any given city, and (4) avoid the problem of publication bias [6].

The evidence base for morbidity outcomes for US populations not covered by Medicare (i.e., <65 years) often come from single-city studies or international multi-city studies [16-21]. No single US study of respiratory or cardiovascular ED visits or hospitalizations among people under 65 covers more than a few cities or counties. This is because a national data source with the necessary data elements is not readily available and many states only recently began centralizing data for ED visits. The labor-intensive process for accessing, assembling, and managing hospital ED data from multiple states has deterred the execution of such studies. While informative, single-city studies have limitations for national policy setting due to between-city differences in air pollution composition and population characteristics as well as differences in study methodology. These differences make it difficult to synthesize results from single-city studies and resolve inconsistencies in evidence they produce. Further, they limit the ability of EPA to conduct human health risk assessments. For the current ozone and PM standards, EPA conducted national-scale mortality risk assessments using results from multi-city studies. For morbidity outcomes, EPA conducted similar risk assessments for hospital admissions among all ages in only 12 cities for ozone and 15 cities for PM where epidemiologic study results and necessary data were available. For respiratory related ED visits among all ages, their assessment

was only conducted in Atlanta and New York City, indicating a strong need for a multi-city study.

Among the outcomes not covered by a multi-city study, respiratory ED visits among people under 65 are an important health outcome. The majority of all respiratory ED visits occur among people under 65 [22]. Further, respiratory ED visits are more common among people under 65 than respiratory hospitalizations, cardiovascular ED visits, or cardiovascular hospitalizations. Diseases of the respiratory system (ICD-9-CM codes 460-519) are the primary diagnosis for approximately 10% of all ED visits annually, ranking as the third highest disease category. Multiple specific respiratory diseases such as acute upper respiratory infection (AURI) (ICD-9-CM 460, 461, 463-466), asthma (ICD-9-CM 493), and pneumonia (ICD-9-CM 480-486) rank in the top twenty primary diagnoses for people under 65. Diseases of the circulatory system (ICD-9-CM codes 390-459) are the primary diagnosis for 4.7 million (3.4%) ED visits annually. Circulatory system diseases in the top twenty primary diagnoses include heart disease (excluding ischemic), ischemic heart disease, essential hypertension (ICD-9-CM 401), and cerebrovascular disease for people 65 and over. No circulatory system diseases appear in the top twenty for people under 65. The top twenty primary diagnoses for emergency or unscheduled hospitalizations includes circulatory diseases of heart disease (excluding ischemic), ischemic heart disease, and cerebrovascular disease and respiratory diseases of pneumonia and chronic or unspecified bronchitis. These are conditions typically observed in older adults, with the exception of pneumonia hospitalizations, which is also common among young children.

Respiratory ED visits are often due to either exacerbations of chronic respiratory diseases, such as asthma or chronic obstructive pulmonary disease (COPD), or a worsening of respiratory symptoms associated with respiratory infections. AURI is the second highest primary diagnosis and asthma is the sixteenth representing 4% and 1.5% of ED visits each year [22]. Approximately 10% of ED patients report having asthma with hypertension as the only chronic disease found more frequently among ED patients. Five percent of ED patients report having COPD. Specific respiratory diseases in the top 20 primary diagnoses for ED visits vary by age. Children younger than 15 years of age are frequently diagnosed with AURI, acute pharyngitis (462), asthma, influenza (487, 488), and pneumonia. Individuals 15 to 64 years are diagnosed with AURI, acute pharyngitis, asthma, and chronic and unspecified bronchitis (490, 491) while adults 65 years and older are diagnosed with AURI, chronic and unspecified bronchitis, and pneumonia.

The primary route of exposure for air pollution is inhalation. Air pollution is absorbed via the respiratory tract (RT) with uptake dependent upon: (1) the morphology and physiochemical properties of the RT; (2) the route, volume, and frequency of breathing; and (3) the physicochemical properties of the pollutant(s) [1, 2]. For example, larger surface to volume ratio in smaller lungs (i.e. children versus adults) reduces distal penetration. Additionally, increased breathing in terms of frequency and volume, like during exercise, can increase distal penetration. The extracellular lining fluid (ELF) of the RT is a complex mixture of phospholipids, proteins, and antioxidants, which can vary though the RT and from person to person. It is the first barrier against air pollution through both its ability to react and transform an air pollutant and its

thickness. The physicochemical properties of a pollutant and the specific mixture of the ELF influences how the pollutant moves and interacts with the RT.

Ozone is highly reactive, has low water solubility, and is a gas at physiological temperature [2]. These characteristics influence its movement and absorption in the RT. Ozone reaches the underlying tissue of the RT by diffusing through the ELF. Ozone absorption gradually decreases with distal progression into the RT resulting in the greatest proportion, as much as half, absorbed in the URT. The ELF is thicker in the nasal cavity than the rest of the RT to the point where its thickness prevents ozone from reaching the underlying tissue. Ozone also reacts with the soluble ELF components to form range of secondary oxidation products, which tend to limit the tissue dose and distal penetration of ozone itself. Ozone and ELF components have different reaction rates and the formed secondary products have different reactivity. As substrates in the ELF are depleted, the amount of ozone reaching the underlying tissue increases. Ozone not absorbed or transformed in the URT penetrates further into the RT. Ozone dose to the lung tissue is greatest at the junction of the conducting airway and the gas exchange region known as the cetriacinar region.

Uncertainty remains regarding the mechanism(s) by which ozone leads to adverse health outcomes [2]. However, it is clear that exposure to ozone leads to decreased pulmonary function, airways inflammation, and increased bronchial reactivity. Evidence implicates the initiation of numerous cellular responses by the secondary oxidation products. These products can activate the neural reflexes, which can lead to decrements in pulmonary function. They can also alter the epithelial barrier function leading to increased permeability and potentially allergic sensitization

and airway hyper-responsiveness. They can modify innate or adaptive immunity that may lead to AHR and immune system dysfunction. Secondary oxidation products can also lead to sensitization of the bronchial smooth muscle and airways remodeling. They also directly initiation inflammation.

In addition to the previously described factors, the movement and absorption of PM specifically is further complicated by variability in PM size, shape, and composition [1]. Particles are exhaled or deposited in the RT predominately via diffusion, impaction, and sedimentation. Size of the particle also plays an important role. The primary mechanism for deposition is diffusive for particles <0.1 μm, aerodynamic and diffusive for particles 0.1 to 1 μm, and aerodynamic for particles >1 μm. Aerodynamic processes lead to deposition by impaction and sedimentation. Mid-range particles from 0.1 to 1.0 μm are subject to the least deposition. Where particles are deposited is highly variable, even for particles of the same size. Like ozone, the nasal passages acts a first line of defense, especially for larger particles where 100% are deposited in the nose. Where a particle is deposited determines how long the particles are retained and how they are cleared. Poorly soluble particles deposited in the tracheobronchial region are cleared in 24 to 48 hours via the mucociliary escalator while those deposited in the alveolar regions take months to years to clear via macrophage phagocytosis and migration to terminal bronchioles. Soluble particles can be absorbed through the epithelium either by dissolving on the RT surface or within phagolysomes depending on their size, shape, and composition. Absorbed particles are retained in the lungs or enter the bloodstream and distribute systemically.

Like ozone, the specific mechanisms and pathways leading from exposure to adverse health effects is unresolved [1]. Broadly, deposited particles can initiate pathways for cellular injury and inflammation. One possible mechanism may be initiation of these pathways by reactive oxygen species (ROS) for which PM is either a direct source or the stimulation for cellular production of ROS. Additional specific components of soluble PM may directly initiate pathways for cellular injury and inflammation by disrupting receptors or enzymes. The cellular injury or inflammation can lead to airway hyperresponsiveness, airway remodeling, allergic immune responses, impaired host defense and infections, progression of pre-existing lung disease, and DNA damage.

EPA concludes in its most recent integrated science assessments that current evidence from toxicological, controlled human exposure, and epidemiological studies indicates a positive association between short-term exposure to ozone and to $PM_{2.5}$ and respiratory ED visits [1, 2]. Fewer epidemiological studies have evaluated the effects of air pollutants on ED visits compared to hospitalizations. EPA reviewed eight ED studies in their 2013 ISA for ozone and five ED studies for 2009 PM. Overall, these studies indicate a positive association with ED visits for all respiratory outcomes combined as well as specific respiratory outcomes including asthma, COPD, and respiratory infections. However, the consistency, magnitude, and precision of estimated effects vary between studies for specific pollutants, outcomes, and age groups. Studies completed more recently contribute to the evidence base providing effect estimates across multiple age groups.

Strong epidemiologic evidence of a positive association between ozone and all respiratory ED visits among all ages is provided by several Atlanta studies [17, 20, 23, 24]. These studies consistently observed a larger magnitude of association during the warm season. Peel et al evaluated the associations for multiple respiratory diseases using a 3-day moving average lag and found significant positive associations with all respiratory outcomes combined and upper respiratory infections [17]. Associations with asthma, pneumonia, and COPD were elevated but consistent with the null. The Atlanta based studies along with studies in New York and Seattle provide evidence of a positive association between ozone and asthma ED visits among all ages, again with strongest associations seen in warm season [16, 25]. The Seattle study found effects of higher magnitude in children younger than 18 compared to adults 18 and older [16]. Similarly, a study in Alberta, Canada found stronger associations between ozone and asthma ED visits among the age groups 5 to 14 and 15 to 44 compared with all other age groups [21]. A seven-city study in Canada found positive associations between COPD ED visits and ozone, again with strongest associations seen in warm season, but no association for respiratory infection ED visits at the lags evaluated (lags 0, 1, or 2) [26].

Relatively large studies conducted since EPA's ISA provide further evidence to support a positive association between ozone and respiratory ED visits. A study of asthma ED visits in three US cities found positive associations with ozone among age groups under 40 but not age groups 40 and older with the strongest associations among 5-18 age group [27]. The largest study to date evaluated multiple respiratory ED visits among multiple age groups in California [28]. Significant, positive associations were observed for all ages for all respiratory diseases, ARI, and asthma and a slight association for pneumonia and COPD. The associations varied by age group

with the strongest magnitude frequently observed for children 0 to 4 and adults 19 to 64. An Indianapolis study of asthma ED visits found positive associations with ozone during the warm season for the 5-17 age group but not for other age groups [29]. In St. Louis, ozone was associated with respiratory and asthma/wheeze ED visits among all ages but not with pneumonia or COPD.[30] In Atlanta, ozone was associated with pneumonia and upper respiratory infection ED visits among children 0 to 4 but not with bronchiolitis/bronchitis [31].

Evidence of an association between $PM_{2.5}$ and respiratory ED visits is less substantiated. As with ozone, however, strong evidence of the respiratory effects of $PM_{2.5}$ was generated from Atlanta-based studies [17, 24]. These studies found an elevated but consistent with the null association between $PM_{2.5}$ and all respiratory diseases combined. Peel et al found similar elevated but non-significant associations between $PM_{2.5}$ and the specific diseases of upper respiratory infections, asthma, pneumonia, and COPD. Similar null associations were observed in Spokane, Washington for respiratory diseases combined, asthma, or COPD in all ages [19]. In contrast, two studies in New York City found significant, positive associations between $PM_{2.5}$ and asthma among all ages but not children [25, 32].

Recent studies provide more contrasting results with a null association observed in Indianapolis, Indiana but a positive association in St. Louis, Missouri for asthma ED visits in all ages [29, 30]. Null associations were also observed in St. Louis for all respiratory diseases combined, pneumonia, and COPD. Positive associations were observed in Atlanta for asthma and upper respiratory infection among children [31, 33]. Two additional large studies also observed strong association between $PM_{2.5}$ and asthma among children [27, 34]. The three-city study did not

found any association for asthma among adults [27]. The large California study found positive associations for not only asthma among adults but also for all respiratory diseases, ARI, and COPD with the strongest effects generally observed for children 5 to 18 and adults 19 to 64 [34]. Conversely, a seven-city Canadian study found positive association between $PM_{2.5}$ and asthma ED visits during the warm season and no association with COPD or respiratory infection [26].

The studies conducted since EPA's current ISA for ozone add to the evidence supporting an association between ozone and respiratory ED visits, specifically asthma ED visits among children. Single-city studies evaluating the effects of $PM_{2.5}$ continue to find conflicting results. However, two small US multi-city studies provide strong evidence of an association between $PM_{2.5}$ and asthma ED visits especially among children [27, 34]. These findings are consistent with two recent studies in Atlanta [31, 33]. For both pollutants, the evidence base is still lacking a nationally relevant multi-city study of respiratory ED visits covering all age groups and multiple outcomes. It is difficult to reconcile, qualitatively or quantitatively, the disparate results of these studies for reasons previously stated including methodological differences and potential publication bias. Further, differences in the estimated effects from these studies could be due to between city differences in factors that modify the relationship between pollutant and outcome. Population, pollutant, and community characteristics have been shown to be effect modifiers for mortality and morbidity outcomes in 65 and older population and may partially explain the heterogeneity seen for respiratory ED visits [35, 36]. Understanding which factors increase or decrease susceptibility is important in ensuring adequate protection of sensitive populations. Large, multi-city studies that analyze each city using the same model provide an opportunity to evaluate remaining risk heterogeneity.

Effect modification in epidemiological studies can be evaluated by comparing effect estimates for sub-populations within a study provided sufficient number of cases are available for each sub-population. A common approach is to examine how study or city variables explain between study or city risk heterogeneity. While useful, this type of evaluations are challenged by high correlation between potential factors and a lack of data for key factors. Evaluations for mortality and for hospitalizations among adults 65 and older have identified potential factors that increase risk, but heterogeneity often remains [35, 36]. Still some factors identified may help explain the disparate results between studies of respiratory ED visits and should be evaluated.

For the association between ozone and mortality, Bell et al found higher relative rates in communities with higher percent of population African American, unemployed, and taking public transportation [35]. However, significant heterogeneity remained and only percent taking public transportation was robust to inclusion of other city variables. For the association between $PM_{2.5}$ and hospitalizations among adults 65 and older, Bell et al found significant heterogeneity across seasons and regions for cardiovascular hospitalizations but season only for respiratory hospitalizations [36]. Bell et al also conducted meta-analyses evaluating the results across multiple studies [37, 38]. For ozone, studies provided strong evidence of higher risks among older populations and communities with lower employment and weak evidence of higher risks among non-white populations and communities with lower education and higher poverty [38]. One study reviewed found higher risk for non-white populations for asthma and pneumonia ED room admissions and higher risk for whites for COPD [39].

For $PM_{2.5}$, strong evidence indicated higher risks of death in older populations [37]. Weak or suggestive evidence indicated higher risks among women and communities with lower educational level, lower income level, and lower employment. Few studies evaluated associations of $PM_{2.5}$ by race. Two recent studies evaluated risk heterogeneity by county urbanization [40, 41]. Among adults 65 and older, researchers found higher magnitude associations between $PM_{2.5}$ and cardiovascular hospitalization in urban counties and respiratory hospitalizations in rural counties [40]. In New York, New Jersey, and Connecticut counties, researchers found a higher magnitude association between ozone and mortality in rural counties [41]. They also found the magnitude of the association increased as poverty or population density decreased or the percent of population 65 and older increased.

Project Proposal

The lack of strong evidence for the associations between ozone and $PM_{2.5}$ and respiratory ED visits includes a clear need for multi-city or county study. To conduct such a study, data accessibility must be addressed. The Centers for Disease Control and Prevention's National Environmental Public Health Tracking Program (Tracking Program) is uniquely positioned to produce nationally relevant estimates of the short-term association between ambient ozone and $PM_{2.5}$ and respiratory morbidity for all age groups. The Tracking Program and its partners have built the Tracking Network, a web-based, distributed surveillance system of secure and public portals at federal, state, and local levels. Through the Tracking Network infrastructure, the Tracking Program can process, share, and publish health, environmental, and exposure data. Utilizing this infrastructure, the Tracking Program and its partners can pool data from multiple states and conduct a county level analysis on the associations between daily air pollution

concentrations and ED visits respiratory related outcomes including asthma, pediatric asthma, and COPD. Results from such an analysis would be extremely useful in clarifying the impact of ozone and $PM_{2.5}$ on ED visits for respiratory outcomes.

To build a national database, we will submit a data request for respiratory ED data to both tracking and non-tracking states where ED data are centralized and readily available. State health department or data organization staff will extract data for ED visits with a primary diagnosis of respiratory disease, based on International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes 460 – 519, from state inpatient and outpatient databases according to instructions provided in the data request. To increase the number of accepted data requests, data will be aggregated by date of admission, county of residence, sex, age group (children 0 to less than 19 years, adults 19 to less than 65 years, and older adults 65 years and over), and disease group (Table 1-1).

Traditionally, data from air pollution monitors are used to capture daily concentrations for studying the effects of air pollution on health. These monitors are part of various air monitoring networks maintained by EPA, state, and local agencies for regulatory purposes. Data on air pollution concentrations are necessary to ensure compliance with regulations, to evaluate policies and track progress, and to extend our understanding of air pollution. While the monitoring data offer the most accurate measurement of air pollution at the monitor location, gaps exist in the data. Monitors cover at most 20% of all US counties. Temporal gaps exist because monitors may sample once every three or six days, depending on the pollutant. Ozone monitors typically only operate during local ozone season, which is generally May through September with variation

across the US. These spatial gaps, along with population density, has resulted in most studies typically conducted in urban cities or counties. The temporal and spatial gaps in air monitoring data limit the data's applicability to public health surveillance and research.

To address the gap, EPA and its partners developed modeled data from a Bayesian space-time downscaling (DS) fusion modeling approach, as part of an interagency agreement between CDC and EPA [42]. This approach fuses available monitoring data and Community Multi-Scale Air Quality Model (CMAQ) model data in non-monitored areas. CMAQ combines meteorological, emission, and air chemistry-transport models to predict gridded, hourly concentration and deposition values for several pollutants including $PM_{2.5}$ and ozone. The fusion of monitoring and modeled data addresses temporal and spatial gaps in the air monitoring data and adjusts for any calibration bias in the CMAQ data. The process involves downscaling the gridded CMAQ data to the point-level air monitoring data using a linear regression with bias coefficients that vary in time and space under a Bayesian framework [43]. This process statistically addresses the "change of support" problem due to the spatial misalignment between the monitoring and CMAQ data.

The DS model provides predictions of daily maximum 8-hour average ozone concentrations in parts per billion ozone and daily 24-hour average $PM_{2.5}$ at census-tract centroids for the contiguous US. These data should be used with caution and an understanding of the potential measurement error or bias introduced by either the original input data or the modeling process itself. However, the nature of ozone and $PM_{2.5}$ make them more suitable candidates for modeling than other air pollutants. Ozone is a secondary pollutant, generated by a reaction between

ultraviolet radiation from the sun and precursor pollutants such as those emitted by the combustion of fossil fuels. $PM_{2.5}$ is both primary and secondary pollutant generated by the transformation of primary pollutants such as sulfur oxides, nitrogen oxides, and volatile organic compounds. Because of the formation process, secondary pollutants are more spatially smoothed than primary pollutants. For example, measurements from two monitors remain correlated over much larger distances for ozone and $PM_{2.5}$ compared to other pollutants like sulfur oxides, nitrogen oxides, and volatile organic compounds [44]. When developing these models, a common method is to build the model using a subset of the air monitoring data and then use the remaining data for calibrating and validating the model. For ozone, this modeling approach outperformed two alternatives, a Bayesian melding method and ordinary kriging, providing better-calibrated predications and predictive intervals with better empirical coverage [45]. Additional improvements are gained when modeling ozone and $PM_{2.5}$ together using a bivariate model to exploit the natural correlation between the pollutants [46]. As such, the DS model is a reasonable solution to the temporal and spatial gaps in available air pollution data and will be our choice of air pollution data for this work.

Historically, several epidemiologic study types including cross-sectional, cohort, and time-series have been used to evaluate the association between air pollution concentrations and adverse health outcomes [47-50]. Today, cross-sectional studies are challenged methodologically by the relatively low levels of air pollution exposure experienced in the US. Cohort studies are typically expensive and currently difficult financially to establish. While early time-series studies were challenged methodologically, time-series analyses are now frequently used to evaluate the association between air pollution concentrations and adverse health outcomes [47]. The

abundance of time-series analyses is due to (1) the statistical and computational advancements since the 1990s; (2) the availability of health outcome data, including vital statistics and Medicare data; and (3) the ease with which results can be incorporated into the regulatory process.

A time-series analysis assesses the association between day-to-day fluctuations in air pollution concentrations and day-to-day fluctuations in a health outcome in a single, geographically defined population such as a city or county. These analyses are implemented as regression models linking daily counts of the health outcome and daily concentrations of air pollution. Generally, administrative or vital statistics databases provide the daily counts of a health outcome by county or ZIP code. Outcomes are typically assumed to follow an overdispersed Poisson distribution given that the daily count within a county is relatively small in comparison to the size of the population at risk and it varies substantially. Air pollution concentration data, as discussed above, are either observational from monitoring sites or modeled using a variety of input data and statistical techniques. These data are either point level or grid based and must be assigned to the areal unit represented in the health outcome data. Several sources of potential measurement error exist including instrument imprecision in the monitoring data and calibration bias in the modeled data. Another source includes spatial error introduced by assigning one or more point or grid concentration levels to a larger areal unit. In both cases, several studies have shown that a population-weighted approach produces a robust metric for time-series analyses especially for spatially homogenous air pollutants such as ozone and $PM_{2.5}$ [51-53]. Lastly, while city or county air pollution metrics are not measures of personal exposure, they are relevant

metrics for air pollution policy and can produce robust and unbiased results for ozone and $PM_{2.5}$ [52].

Generalized linear models (GLM) and generalized additive models (GAM) are two types of regression models are frequently used in time-series analyses. GLM assumes a linear relationship between daily counts of a health outcome and air pollution concentration while GAM allows for non-linear relationship. As such GLM use parametric splines, while GAM uses nonparametric splines for estimating the short-term associations. Additionally they used different statistical methodology to generate that estimate. Results from these models, using the same data and similar specifications, can vary but still produce the same conclusion [20, 54]. The degree to which the results vary may relate to both model specifications and characteristics of the data such as the degree of adjustment for confounding factors and the unknown underlying nonlinear functions of time, weather, and seasonality [47, 54].

When conducting time-series analyses, the researcher must specify the lag relationship between the outcome and air pollution to be modeled. Substantial evidence indicates that air pollution on a single day can lead to adverse health outcomes on the same day and several days following (ISA Ozone, ISA PM). This effect can be modeled either by investigating single lag days one at a time, by averaging air pollution over multiple days, or by including multiple lag days in the same model (a distributed lag). Which single lag day best captures the effect can vary by outcome, pollutant, and even city [55]. Further, a single lag day or even 2 or 3 day average may underestimate the total effect of air pollution on a single day. A challenge in the distributed lag

approach is adjusting for the high correlation between day-to-day air pollution concentrations, which can be done by putting constraints on the distributed lag [56].

Time-series analyses require control of potential confounding by factors that vary on similar timescales as the pollution or health outcome [47, 57]. Because this method compares daily fluctuations in air pollution within a county, the population serves as its own control as it moves through time and thus individual level confounders do not need additional control. Potential confounders that may need controlled include population characteristics that fluctuate over short time periods, weather, day of the week, holidays, and seasonal or long-term trends in pollution or health outcomes. The inclusion of a spline function on time is a common approach to control for potential confounding by unmeasured factors that vary gradually over time. In this way, the model controls for long-term trends related to changes in population size, characteristics, health status, and health care access and short-term trends related to seasonality and influenza epidemics. Decisions must be made regarding how much control to exert on time [58]. By increasing the number of knots or degrees of freedom on the spline function, the research can increase the flexibility of the function and the control of time. However, too much flexibility can mask the daily fluctuations of interest. These models also include variables for temperature or humidity to control for the confounding effects of weather. Here, two decisions must be made: which variables to include and how much control to exert. A comprehensive sensitivity analysis of the association between PM_{10} and mortality supports that inclusion of smooth functions of current-day and average temperature and dew point from the past few days to control for weather effects [59]. The applicability of these results to other pollutants and outcomes is uncertain. Lastly, researchers must also consider confounding of the association between the outcome and

the air pollutant of interest by other pollutants. Air pollutants tend to be highly correlated both spatially and temporally. This is especially true if the pollutants are generated by the same source or if one is a pre-cursor to another. The inclusion of other pollutants in the model can produce adjusted estimates of the association for the pollutant.

An alternative, yet similar, approach to a time-series analysis is a case-cross over analysis where a case, or single ED visit, serves as its own control [60]. While a time-series analysis requires control of confounders through model specifications, a case-cross over analysis controls confounders by comparing air pollution levels on the day of a case or ED visit to air pollution levels on a reference day near in time to the case day and typically matched on factors such as day of the week. Under certain model specifications, these approaches are nearly equivalent [60]. In choosing between time-series and case-cross over analysis, researchers may consider the attributes of both the available data and the specific association under investigation. Additionally, researchers may use the approach not selected for the primary analysis as a sensitivity analysis [20].

With all these modeling decisions, building the right model can be challenging. The available modeling techniques and specifications have various pros and cons, which must be weighed against the characteristics of the data and the association under investigation. Traditional GLM or GAM evaluation techniques, such as evaluating the Akaike information criteria and residual diagnostics, but not without limitations. For example, these techniques are not helpful in setting the level of control for any smoothed parameters. A common approach is to a priori select a

model based on expert opinion and then to conduct a sensitivity analysis evaluating the robustness of a model's results to alternative model specifications.

Synthesizing the results of multiple time-series analyses, either quantitatively or qualitatively, is necessary to gain a more complete understanding of the relationship between air pollution and health. It is also an important part of process for establishing and evaluating air pollution policies. This synthetization of published, independent time-series analyses is challenged by the spectrum of model specifications used by different researchers. Further, the results of this process are subject to publication bias as single analyses with negative results are less likely to be published. The power of multi-city studies comes from pooling results of city or county specific time-series analyses conducted using the same methodology. Researchers first conduct a time-series analysis using daily, county level data to fit a log-linear regression for each city or county and then used a statistical approach to pool the rate ratio (RR) of mortality or morbidity associated with specific pollutants. This two-stage approach was used by investigators at John Hopkins University to obtain national effect estimates of air pollution on mortality across multiple cities and has been replicated by researchers to investigate additional health outcomes and pollutants [8-14, 61]. It has been formally evaluated as a result of the scrutiny these studies received having influenced air pollutions standards and found to be robust to spectrum of model specifications, specifically for mortality [54, 57, 59]. Pooling results for outcomes with greater city or county variability, such as asthma ED visits, may require slightly different model specifications or pooling techniques.

Multiple meta-analysis techniques are available to pool results, either from independent time-series analyses or as stage two of a multi-city analysis. A meta-analysis mathematically combines the effect estimates from single cities and provides an overall effect estimate with increased precision. A simple fixed effect model is a weighted average of estimated effects with inverse-variance as the weights. This model assumes effect of air pollution on respiratory ED visits is the same in every county, which is arguably hard to justify. A random effect model is essentially a two-level random intercept model and allows for the assumption that the effect is not the same in every county. Here the county-specific effect is a random variable with a mean and a variance. With this approach, it is difficult to obtain an unbiased estimate of that variance. A Bayesian approach, similar to the one used by JHU, can produce a better estimate of the true overall effect estimate, accounting for within-city statistical error and for heterogeneity of the true effect estimates between counties.

We will use the two-stage approach to generate nationally relevant effect estimates of the associations between short-term exposure to ozone and $PM_{2.5}$ and respiratory ED visits. In stage one, we will conduct county-specific time-series analyses to evaluate the short-term association between each air pollutant and respiratory ED visits for each combination of disease group (all respiratory, asthma, pediatric asthma, and COPD), age group (all ages, children 0 to <19, adults 19 to <65, and older adults 65+) and air pollutant (ozone and $PM_{2.5}$). Our outcome variable will be daily number of ED visits as the outcome variable (Y_t). We will assume Y_t follows an overdispersed Poisson distribution given that the daily number respiratory ED visits within a county are relatively rare in comparison to the size of the population at risk and it varies substantially. We will also assume the relationship between number of ED visits and unit

increase in air pollution to be multiplicative and non-linear. Therefore, we will fit Poisson generalized linear models (GLM), accounting for overdispersion (equation 1).

Equation 1:

$$Y_t \sim Poisson(\mu_t)$$

$$\log(y_t) = \beta_0 + \sum_{k=0}^{6} \beta_{t-k} X_{t-k} + Confounders + \epsilon$$

$$\epsilon \sim N(0, \sigma^2)$$

where: y_t = number of ED visits on day t, X_{t-k} = air pollution levels on day t-k

We will model an unconstrained distributed lag for lag days 0 through 6 to capture the cumulative association of exposures over the past week. For each set of county results, we will sum each β_{t-k} for lag days 0 through 6 to obtain the cumulative effect estimate for county i ($\hat{\beta}_i$) and calculate the variance ($\hat{\sigma}_i^2$) by summing the variance for each β_{t-k} and the covariance of each pair of β_{t-k}. $\hat{\beta}_i$ corresponds to change in daily number of ED visits per unit increase in air pollution on the log scale. The exponent of $\hat{\beta}_i$ can be interpreted as a RR because the population is essentially considered constant. We will include: (1) non-linear functions of one or more variables for temperature or humidity as natural cubic splines with 3 degrees of freedom; (2) a non-linear function of calendar date as a natural cubic spline with 8 degrees of freedom per year of county data; and (3) indicator variables for day of week and for holidays. We will fit single-

pollutant models for ozone and PM2.5 and two-pollutant models with both. We will conduct sensitivity analyses to evaluate the robustness and stability of our effect estimates.

In stage two, we will use a two-level Bayesian hierarchical model to pool $\hat{\beta}_i$ across all counties for each air pollutant, age group, and disease group to produce a national estimate of effect (Equation 2) [61, 62].

Equation 2:

$\hat{\beta}_i \sim N(\theta_i, \epsilon_i)$

$\theta_i \sim N(\mu, \tau^2)$

$\epsilon_i \sim N(0, \hat{\sigma}_i^2)$

$\hat{\beta}_i$ = estimated effect from county i

θ_i = unobserved true effect in county i

ϵ_i = county-specific random deviation that is independent across counties

μ = overall pooled effect

τ^2 = between-county heterogeneity

$\hat{\sigma}_i^2$ = estimated county-specific variance

We assume $\hat{\beta}_i$ to be a combination of the county-specific unobserved true effect (θ_i) and county-specific random error (ϵ_i) that is independent across all counties and is normally distributed with a mean of zero and a county-specific variance. In using a Bayesian approach to pool the observed county-specific effect estimates, we assume that θ_i varies between counties following a

normal distribution with a mean μ and variance of τ2. μ and τ2 are random variables for which we use non-informative priors. This approach provides us with an unbiased estimate of τ2 that represents the between-county heterogeneity. Subsequently, we will add various county level covariates for factors that may modify the effect and therefore explain the between-county heterogeneity. Potential covariates include urbanization, region, primary care access, and population demographics. The resulting information could be used to target at-risk populations and to ensure adequate protection of vulnerable populations.

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Table 1-1: Respiratory Emergency Department Data Requested from State Health Departments

Temporal Scale and Scope	Daily, all years available between 2001 and 2012
Spatial Scale	County
Age Group	0-<19 19-<65 65+
Sex	Male, female, unknown
Outcomes	1 = Asthma (ICD-9 code 493) 5 = COPD (ICD-9 codes 491, 492, 496) 6 = Acute respiratory infections (ICD-9 codes 460 – **466.0***) 7 = Pneumonia (ICD-9 codes 480 – 486) 8 = All other respiratory outcomes (ICD-9 codes 460-519 not included in 1, 5, 6, or 7) • 466 excluding 466.0 • 467-479 • 487-490 • 494-495 • 497-519 *note this is 466.0 not 466

Chapter 2 - Environmental public health tracking of respiratory emergency department visits

Abstract

Problem/Condition: Respiratory diseases are a frequent cause of emergency department (ED) visits in the United States (US). These visits are often precipitated by exacerbations of chronic respiratory diseases or a worsening of respiratory symptoms associated with respiratory infections. Exacerbations or worsening of symptoms can be triggered by exposure to indoor and outdoor environmental factors such as air pollution, pollen, pet dander, and environmental tobacco smoke. The prevention of respiratory ED visits is a target of public health interventions, including both individual and community interventions, aimed at reducing exposure to environmental triggers. Effective interventions require scientific evidence of the association between specific triggers and respiratory ED visits as well as an understanding of the individual or community factors that increase susceptibility to ensure adequate protection of sensitive populations. Surveillance of respiratory ED visits across all ages in the US is limited spatially and temporally by the lack of a readily accessible, centralized database of respiratory ED visits with the necessary data elements. The routine collection and analysis of such data are needed to generate evidence to inform public health interventions.

Reporting Period: 2000 to 2014

Description of System: Since 2002, CDC's National Environmental Public Health Tracking Program has collaborated with federal, state, and local partners to gather standardized

environmental health data by creating national data standards, collecting available data, and disseminating data for the development of public health actions. The National Environmental Public Health Tracking Network (i.e., the tracking network) collects data provided by national, state, and local partners and includes 23 health outcomes, exposures, and environmental hazards. Utilizing the tracking network, CDC received daily, county-level data for respiratory (ICD-9-CM codes 460-519) ED visits from seventeen states. State health department or data organization staff exacted data from state-based outpatient and inpatient databases and aggregated data by day, county of residence, age group, sex, and disease group.

Results: Part 1: The median of the rates of respiratory ED visits per 10,000 population per year across all counties (median rate) was 410 (IQR: 276). Approximately 43% of these visits were for acute respiratory infection (excluding pneumonia), which was 3.5 to 6 times more frequent then visits for pneumonia, asthma, and chronic obstructive pulmonary disease (COPD). Median rates varied by age and sex, with males having higher rates of respiratory ED visits among children 0 to 18 and adults 65 and over, and females having higher rates among adults 19 to 64. The median of the rates per 100,000 population per day (median daily rate) across all counties for all respiratory ED visits combined and for each specific disease group followed similar seasonal patterns, with the highest rates in the winter dropping steadily to the lowest rates in the summer and rising again in the fall. Median daily rates of asthma peaked in September whereas the other diseases peaked in February. The seasonal patterns of some diseases varied slightly by age and sex group. Part 2: The median of the age-adjusted rates per 10,000 population per year (median age-adjusted rate) by state ranged from 236 (IQR: 211) in Colorado (CO) to 661 (IQR: 249) in Maine (ME). The median age-adjusted rate of all respiratory ED visits was lower in

counties that were urban and in the West and had lower percent of population living in poverty, lower percent of population identifying as black, and fewer hospitals and urgent care centers. Median age-adjusted rates were lower in counties with higher percent of population identifying as Hispanic, higher percent of population without health insurance, and more primary care physicians and pulmonologists. The observed patterns by age, sex, state, and county characteristics varied by specific respiratory disease.

Interpretation:

The rate of respiratory ED visits and the specific respiratory disease identified as the primary diagnosis differs by sex and age group. The rate of respiratory ED visits varies by county. State contributes heavily to the county level variation in the rate of respiratory ED visits for each disease while the contribution of the county characteristics varied by disease. These county characteristics alone do not explain the observed variation in county rates. Data at a finer temporal and spatial scale can inform interventions aimed at preventing respiratory ED visits.

Public Health Actions:

These data can be linked with datasets for various environmental, social, and policy factors to provide evidence to inform public health interventions and are especially important for addressing gaps in the current understanding of the association between respiratory ED visits and air pollution. More investigation is needed to understand the factors driving county variation in respiratory ED visits. Any investigation should evaluate specific respiratory diseases by age and sex as the drivers may differ.

Introduction

Diseases of the respiratory system (ICD-9-CM codes 460-519) are the primary diagnosis for approximately 10% of emergency department (ED) visits annually in the United States (US), ranking as the third highest disease category [22]. These visits are often due to either exacerbations of chronic respiratory diseases, such as asthma or chronic obstructive pulmonary disease (COPD), or a worsening of respiratory symptoms associated with respiratory infections. Approximately 10% of ED patients report having asthma, making it the second most common chronic disease reported by ED patients [22]. Five percent of patients report having COPD. Specific respiratory diseases in the top 20 primary diagnoses for ED visits vary by age [22]. Children younger than 15 years of age are frequently diagnosed with acute upper respiratory infection (ICD-9-CM: 460, 461, 463-466), acute pharyngitis (ICD-9-CM: 462), asthma (ICD-9-CM: 493), influenza (ICD-9-CM: 487, 488), and pneumonia (ICD-9-CM: 480-486). Individuals 15 to 64 years are diagnosed with acute upper respiratory infection, acute pharyngitis, asthma, and chronic and unspecified bronchitis (ICD-9-CM: 490, 491) while adults 65 years and older are diagnosed with acute upper respiratory infection, chronic and unspecified bronchitis, and pneumonia. Primary diagnoses also differ by age and sex; for example, the rate of ED visits for asthma is higher among males in children under 15, but among individuals age 15 to 64 years it is higher for females [22]. Variation in the rate of respiratory ED visits by age and sex largely reflects the variation in disease prevalence [63-65].

Exposure to indoor and outdoor environmental factors including air pollution, aeroallergens, and environmental tobacco smoke can trigger exacerbations leading to respiratory ED visits. Air

pollutants including ozone, fine particulate matter, nitrogen dioxide, and carbon monoxide have been positively associated with respiratory ED visits in various age groups [17, 20, 24, 27, 31, 66]. Respiratory ED visits, largely asthma ED visits specifically, have been associated with exposure to pollen [66-68] and to indoor allergens such as dust mites, pet dander, and mold [69, 70]. Weather, including high temperatures and humidity, has also been linked to increases in asthma ED visits and other respiratory ED visits [71-73]. Increases in asthma ED visits have also been linked to thunderstorms, potentially due to increased exposure to pollen following a storm [74, 75].

The prevention of respiratory ED visits by reducing exposure to environmental triggers is an important part of public health interventions. At the individual level, avoidance of environmental triggers is an important part of disease management to reduce negative health outcomes and improve quality of life [76-78]. Community level interventions to reduce respiratory ED visits include efforts to prevent or mitigate exposure to ambient air pollution. Effective air pollution policy requires scientific evidence of the association between specific pollutants and health outcomes as well as an understanding of which factors increase susceptibility to ensure adequate protection of sensitive populations [1, 2]. Much of the evidence used to develop national air pollution standards is limited to studies of mortality or of morbidity outcomes among adults 65 years of age or older. The available evidence for respiratory ED visits among persons younger than 65 is largely limited to studies of asthma specifically within a limited number of cities. The generalizability of such evidence to other respiratory outcomes and other cities or the nation as a whole is not well characterized.

Cities and counties vary in their composition of individual and community factors that increase the risk of respiratory ED visits. In addition to age and sex, other individual factors such as low socio-economic status (SES), poor health literacy, smoking, and obesity are associated with ED visits for respiratory infections, asthma, and COPD [64, 79-84]. Rates of ED visits for asthma and COPD are higher among black persons [63, 85]. For individuals with chronic respiratory diseases, like asthma and COPD, poor adherence to a management plan can increase the risk of exacerbations and ED visits [86]. Counties with high racial segregation, low SES, poor primary care access, and rural status are more likely to have increased rates of asthma ED visits among children enrolled in Medicaid [87]. County level socioeconomic factors and primary care access have also been associated with ED use in general and could influence rates of ED visits for respiratory diseases [88, 89]. These factors not only influence risk of respiratory ED visits but they may also increase individual susceptibility to the effects of air pollution [37, 38].

Continued surveillance and research are needed to increase the evidence base and available data necessary for effective public health interventions for reducing respiratory ED visits. As such, the Centers for Disease Control and Prevention's (CDC) National Environmental Public Health Tracking Program (Tracking Program) requested data on daily, county level counts of respiratory ED visits from thirty state health departments. The motivation for collecting these data is to provide evidence to inform public health interventions and specifically to address gaps in the current understanding of the association between respiratory ED visits and air pollution. Seventeen states were able to meet the data request and submitted between three and twelve years of data for 2000 to 2014. This report summarizes daily, county level counts of nearly 50 million respiratory ED visits from those seventeen states and describes the data by sex, age

group, and disease group to provide additional insight on the variation of respiratory ED visits by demographics, season, and geography.

Methods

Data for ED visits with a primary diagnosis of respiratory disease, based on International Classification of Diseases, 9th Revision (ICD-9) codes 460 – 519, were extracted from state inpatient and outpatient databases according to instructions provided in the data request. Data were aggregated by date of admission, county of residence, sex, age group (children 0 to less than 19 years, adults 19 to less than 65 years, and older adults 65 years and over), and disease group (acute upper respiratory infection (ARI) (460 – 466.0) [in this analysis acute bronchitis and bronchiolitis are included as upper respiratory infections] , asthma (493), COPD (491, 492, or 496), pneumonia (480 – 486), and all other respiratory outcomes with ICD-9 codes 460 – 519 not included in the previous four disease groups).

Part 1: Rates by year and rates by day

Rates of respiratory ED visits were calculated per year and per day for each county by age group, sex, and disease group. First, the rate of ED visits per 10,000 population per year was calculated by county using the bridged-race Vintage 2016 postcensal estimates by single-year age group from CDC's National Center for Health Statistics (NCHS) as the denominator. Stratified rates per 10,000 population per year were calculated by disease group, including all respiratory diseases, age group, and, sex. The median and interquartile range (IQR) of county average rates were calculated by disease group, age group, and sex. Second, to view daily fluctuations in ED

visits, the rate of ED visits per 100,000 population per day was calculated by day of the year and by county using the NCHS data as the denominator. Average rates were calculated for all respiratory ED visits and for each specific disease by age group and sex. The median and IQR of the county average rates by day of the year were calculated by month, disease group, age group, and sex.

Part 2: Rates by year and county characteristics

The age-adjusted rate of ED visits per 10,000 population per year was calculated by county using the NCHS population data where the case count was greater than 15. Age-adjusted was implemented using the three age groups in the ED data (children 0 to <19, adults 19 to <65, and older adults 65 and older) and the NCHS population data. The median and IQR of the county age-adjusted rates were calculated for each disease group by state and by several county level factors previously found to be associated with respiratory diseases or adverse outcomes [63, 81, 87-91]. The county level factors included (1) urbanization, (2) geographic region, (3) percent of population living in poverty, (4) percent of population identifying as black or African American, (5) percent of population identifying as Hispanic, (6) percent of population without health insurance, (7) number of hospitals per 100,000 population, (8) number of urgent care centers, (9) number of primary care physicians per 100,000 population, and (10) number of pulmonologists per 100,000 population. Counties were categorized by urbanization using NCHS's 2013 urban-rural classification scheme consisting of four metropolitan categories (large central metropolitan, large fringe metropolitan, medium metropolitan, and small metropolitan) and two nonmetropolitan categories (micropolitan and noncore) [92]. Geographic region was assigned using the U.S. Census Bureau designations of Northeast, South, Midwest, and West. The percent

of population living in poverty was calculated using U.S. Census Bureau, Small Area Income and Poverty Estimates. The percent of population black and percent of population Hispanic was calculated using NCHS's bridged-race Vintage 2016 postcensal estimates. The percent of population without health insurance was calculated using the U.S. Census Bureau, Small Area Health Insurance Estimates. The number of hospitals and number of urgent care centers were calculated using the Homeland Infrastructure Foundation – Level Data 2017-05-19. Hospitals were excluded if they were specific to cancer, psychiatric, addiction, substance abuse, maternity, orthopedic, or rehabilitation. The number of primary care physicians and number of pulmonologist were calculated using the Health Resources and Services Administration Area Health Resources File (AHRF) 2016-2017 Release. For each continuous measure, counties were grouped based on tertile classification scheme.

Results

Part 1

Variation in county level rates per year by age and sex

Across all counties and years, the median of the rates of ED visits per 10,000 population per year (median rate) for all respiratory ED visits combined was 410 (IQR: 276) (Table 2-1A). By disease group, the median rate for ARI at 178 (IQR: 138) was 3.5 to 6 times higher than the median rates for pneumonia, asthma, and COPD. By age group, the median rate for all respiratory ED visits combined was 301 (IQR: 231) for adults, 455 (IQR: 301) for older adults, and 611 (IQR: 481) for children (Table 2-1A). For children and adults, the disease group with the highest median rate was ARI while the disease group with the highest median rate for older

adults was pneumonia. The median rates for ARI and asthma decreased by age group while the median rates for COPD increased. The median rate of pneumonia among older adults was 3 times the rate among children and almost 5 times the rate among adults. By sex, the median rate was slightly higher among females compared to males overall and for ARI and asthma (Table 2-1A). Rates for COPD and pneumonia were nearly equivalent for females and males. By age group and sex, males had slightly higher median rates of respiratory ED visits among children and older adults but females had a much higher rate among adults (Table 2-1B). Females had higher median rates for ARI than males across all age groups. Among adults, females had higher median rates than males across all disease groups. The median rate for asthma was higher for males among children and higher for females among adults and older adults. Median rates for COPD and pneumonia were higher in females among adults and higher in males among older adults. Males also had higher median rates for pneumonia among children.

Variation in county level rates per day by age and sex

The median of the rates of respiratory ED visits per 100,000 population per day (median daily rate) exhibited a seasonal pattern with the highest rates in the winter dropping steadily to the lowest rates in the summer and rising again in the fall (Figure 2-1). For all respiratory ED visits combined, ARI, COPD, and pneumonia, the median daily rates peaked in February while asthma median daily rates peaked in September (Table 2-2). By age group and sex, ARI shows a pronounced season pattern among children (Figure 2-1). Male children, female children, and female adults show a similar seasonal pattern for asthma with flat rates from January to May, a drop in June, and a sharp increase between August and September (Figure 2-1). This pattern,

which was particularly pronounced among male children, differed from the pattern for other age-sex groups and other diseases.

Part 2

Variation in county level rates per year by state and county characteristics

For all respiratory ED visits combined, the median rate by state ranged from 236 (IQR: 211) in Colorado (CO) to 661 (IQR: 249) in Maine (ME) (Table 2-3). CO had the lowest median rate for ARI and pneumonia while UT had the lowest median rate for asthma and COPD. Across all outcomes, COPD had the greatest variation by state followed by asthma (Figure 2-2). ME had the highest median rate for ARI and was among the highest for asthma, COPD, and pneumonia. Massachusetts (MA) had the highest median rate for asthma while Illinois (IL) had the highest for both COPD and pneumonia.

The median rate for all respiratory ED visits combined was lowest in the urban counties classified as large fringe metro followed by large central metro counties (Table 2-4; Figure 2-3). The rates were highest in rural micropolitan and small metro counties. The median rates for ARI followed a similar pattern. The median rate for asthma was highest in large central metro counties, consistent across less urban counties and micropolitan counties, and lowest in noncore counties. Median rates for COPD and pneumonia generally increased from the most urban to the most rural counties. Except for asthma, micropoliatan counties had the highest rates. The median rate for all respiratory ED visits combined ranged from 300 (IQR: 196) in West counties to 449 (IQR: 300) in Midwest counties. West counties also had the lowest rates for ARI, COPD, and pneumonia. The lowest rates for asthma were in both West and Midwest counties. Counties in

the South had the highest rates of ARI while counties in the Northeast had the highest rates for the other outcomes.

The median rate for all respiratory ED visits combined increased from 340 (IQR: 205) in the first tertile of percent of population living in poverty to 476 (IQR: 307) in the third tertile. The median rate increased as poverty increased for ARI and asthma and to a lesser extend for COPD. Rates remained consistent for pneumonia. The median rates exhibited the same pattern for percent of the population identifying as black. The median rates for all respiratory ED visits combined, ARI, COPD, and pneumonia decreased as the percent of population Hispanic increased whereas rates for asthma increased. For all respiratory ED visits combined, COPD, and pneumonia, median rates decreased as percent of population without health insurance increased. Rates of ARI were highest in the second tertile and rates for asthma did not vary. For all outcomes, median rates were lowest in counties with the fewest hospitals and lowest in counties with the most urgent care centers. Rates were highest in the second tertile for number of physicians or pulmonologists but were lowest in the third tertile representing counties with the greatest number of doctors. For asthma, however, rates were lowest in the counties with the fewest physicians or pulmonologists.

Discussion

Data were analyzed for 47.1 million respiratory ED visits from seventeen states and used to evaluate the occurrence of respiratory ED visits by age, sex, state, and county level characteristics. The results are consistent with previous analyses or surveillance efforts, where

available, and offer new information useful for actions aimed at reducing respiratory ED visits. These results provide a comprehensive view of annual and daily rates of ED visits for specific respiratory diseases and elucidate specific age and sex trends that can inform future interventions. Further, previous analyses were often limited spatially either to a specific jurisdiction or were based on a national survey. These results include all respiratory ED visits in seventeen states at the county level and reveal important spatial variation that should be further examined.

Part 1

Overall, males and females had similar rates for all respiratory ED visits per 10,000 population per year among children and older adults (Table 2-1). Conversely, the rate for adult females under 65 was approximately 1.5 times more than the rate for adult males (Table 2-1). While these findings align with the male and female rates of ED visits for any reason or diagnosis [22], this analysis of more spatially and temporally resolved data provides additional insight on different patterns by sex and age for specific respiratory diseases. First, females experienced higher rates of ED visits for ARI across all three age groups and adult females had almost twice the rate over adult males. Second, the biggest difference in rates between males and females for each age group was observed for asthma ED visits. Rates of asthma ED visits were higher among males in children and higher among females in adults and older adults, corresponding to the change in higher male prevalence in childhood and higher female prevalence in adulthood [93]. Last, differences were also observed between males and females for each specific respiratory disease, which warrant further investigation. While the rate for all respiratory ED visits was

similar between males and females in adults 65 and older, females had higher rates of ED visits for ARI and asthma and males had higher rates of ED visits for COPD and pneumonia. This information highlights the important respiratory diseases for specific sex and age groups and can be used to further investigate or target specific at-risk populations.

Rates of ED visits in general are highest in the spring and similar in winter, summer, and fall. Overall, the rate of respiratory ED visits per 100,000 population per day exhibited seasonal variation with higher rates in the winter and lower rates in the summer (Table 2-2; Figure 2-1). Reports have shown that asthma ED visits peak in September and that the peak varies by age with the fall peak strongest among children [94, 95]. This analysis shows that the seasonal pattern of asthma varies not only by age but also by sex. The greatest fall peak was observed among male children and adult females under 65 showed trends similar to children. The seasonal variation appeared stronger for the infectious outcomes of ARI and pneumonia and weakest for COPD. In general, the pattern of daily fluctuations was similar between sex and age groups with the greater seasonal variation observed for children. Variation in daily and seasonal patterns provide further insight into the observed differences by sex and age groups. Future analyses should evaluate the spatial variation in seasonal patterns in both respiratory ED visits and potential risk factors such as air pollution and weather.

Part 2

This is the first analysis evaluating county level rates for respiratory ED visits. For all disease groups, county rates per 10,000 population per year increased two-fold between the 25^{th} and 75^{th} percentile. Rates of COPD had the greatest differences between the 25^{th} and 75^{th} percentile with

the greatest variation observed among adults and among females. Large variation was also observed for asthma among older adults, for ARI among adults, and for pneumonia among older adult males. This variation could be due to differences or challenges in diagnostics or to differences in county characteristics such as respiratory disease prevalence, socio-economic status, health literacy, or health care access. Strong variation in county rates was found by state indicating that the variation by county may be partially explained by factors that vary state to state such as health care policies (Table 2-3; Figure 2-2). These results emphasize the role of place as a social determinant of health and illustrate the importance of spatially resolved data for guiding public health actions.

Variation in county age-adjusted rates per 10,000 population per year was observed by several of the county characteristics evaluated with different patterns for specific respiratory disease (Table 2-4; Figure 2-3). For context, the rate of ED visits for any reason is typically higher in non-metropolitan statistical areas, highest in the Midwest and lowest in the West, and twice as high among persons identifying as black versus white or Hispanic [22]. However, the largest source of payment (34.9%) is Medicaid or equivalent program. In this analysis, the rates of respiratory ED visits were also highest in the Midwest and lowest in the West. Rates for asthma, COPD, and pneumonia were highest in the Northeast, corresponding to previous publication showing highest rates of asthma in the Northeast [64]. Rates of ARI were highest in the South. Rates for all outcomes except asthma were highest in rural micropolitan counties but rates varied within categories of urban and rural. For all outcomes rates were higher in rural micropolitan counties compare to rural noncore counties. Rate were lower in large fringe or large central metro counties compared to medium and small metro counties. Rates of asthma ED visits exhibited a

different pattern from the other outcomes with the highest rates in the most urban counties and lowest rates in the most rural counties. Rates for all outcomes except pneumonia increased as percent of population living in poverty and percent of population identifying as black increased. While this may contribute to the urban-rural variation for asthma, a recent analysis showed higher rates of asthma ED visits and hospitalizations among children in urban areas after adjusting for race, ethnicity, and poverty [96]. Rates of asthma prevalence and ED use are generally lower among Hispanic persons, except Puerto Ricans, yet this analysis shows are increase in asthma ED rates as percent of population identifying as Hispanic increases.

Interpreting variation in ED rates is complicated by differences in ED utilization driven by multiple factors that influence when or if someone seeks treatment or is able to seek treatment. Medicare, Medicaid, or Children's Health Insurance Program (or state equivalent) is the largest source of payment with only about 15% of ED visits for people without insurance [22]. Several studies have shown higher rates of ED utilization among individuals on such public insurance largely driven by barriers to health care [97, 98]. Another study showed higher rates of ED utilization because of recent changes in insurance status specifically among those adults recently changing from uninsured to insured by Medicaid [99]. In California, rates of ED visits higher in counties with poorer residents and at the same income level, rates were higher in counties with more insured and more highly education residents [89]. Among children enrolled in Medicaid, living in poor, urban areas did not increase the risk of asthma prevalence but did increase the risk of asthma ED visit or hospitalization [96]. Another study found asthma ED visits among asthmatic children enrolled in Medicaid increased as the number of primary care physicians and hospital beds increased but decreased as the number of pulmonary physicians increased [87]. In

this analysis, rates decreased as insurance coverage decreased, increased as number of hospitals increased, and decreased as number of urgent care centers decreased. For both number of primary care and pulmonology physicians rates were highest in the second tertile and lowest in the third tertile representing the highest number of physicians.

Limitations

While the results are nationally relevant, they are based only on data from seventeen states. However, the overall rates by sex, age group, and disease are comparable to rates generated using national surveys. Classification of specific respiratory disease groups based on primary diagnosis and ICD-9-CM codes could potentially lead to misclassification. Additionally, asthma and COPD are diseases consisting of heterogeneous phenotypes including some of which may overlap [100]. Only three states were able to provide data for residents visiting ED visits outside of their state. Including these cases is important for border counties where the nearest ED may be in the neighboring state. The years of data provided for each state varied and ranged from one to fourteen. Temporal trends could influence the county annual mean rate depending on the years of data available. While patterns were observed by comparing median county rates, the range of county rates overlapped across categories for each county characteristic analyzed. Additional analyses are needed to determine which factors result in rates that are statistically different and how they potentially interact with consideration to how they are correlated. Additional factors may contribute to the variation in county annual mean rates and should be further investigated in order to effectively prevent respiratory ED visits.

Conclusion

This report provides the first nationally relevant review of county level rates of respiratory emergency department visits and provides insight into the variation of these rates by specific disease group, age, sex, and county level characteristics. Further investigation is needed to identify causes of county variation in rates and such analysis should evaluate differences between respiratory disease, age, and sex. These data can be linked with datasets for various environmental and social factors to provide evidence to inform public health interventions. Future efforts include linking these data to daily concentrations of air pollutants to examine the association between short-term air pollution exposure and respiratory ED visits and to address an important gap in the evidence of this association for people under the age of 65. These data and the results of the air pollution analysis will be used to calculate the morbidity benefits associated with reductions in air pollution concentration. These morbidity benefits will be disseminated via the tracking network. Future efforts may also include the collection of additional daily ED data for diseases with possible environmental etiology to support additional analyses and data dissemination.

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Table 2-1: Median and interquartile range (IQR) of county rate per 10,000 population per year by outcome, age, and sex

A. Median (IQR) of county rate per 10,000 population per year

Age	Sex	All	ARI	Asthma	COPD	Pneumonia
All	All	410 (276)	178 (138)	40 (27)	30 (26)	50 (30)
0-<19	All	610 (481)	369 (301)	60 (40)	*	47 (33)
19-<65	All	301 (231)	125 (112)	37 (28)	22 (21)	29 (19)
65+	All	455 (301)	57 (47)	22 (18)	112 (89)	137 (109)
All	Female	446 (312)	199 (161)	46 (33)	32 (28)	49 (31)
All	Male	371 (238)	155 (113)	35 (24)	28 (24)	50 (32)

B. Median (IQR) of county rate per 10,000 population per year

Age	Sex	All	ARI	Asthma	COPD	Pneumonia
0-<19	Female	599 (476)	377 (319)	50 (36)	*	42 (32)
	Male	625 (480)	367 (291)	70 (49)	*	51 (35)
19-<65	Female	374 (297)	165 (152)	49 (38)	24 (26)	30 (21)
	Male	227 (165)	87 (76)	23 (19)	19 (18)	28 (18)
65+	Female	448 (294)	63 (54)	27 (23)	102 (84)	126 (97)
	Male	464 (309)	49 (42)	15 (14)	122 (94)	148 (126)

Table 2-2: Median and interquartile range (IQR) of county rate per 10,000 population per month by outcome, age, and sex

	All	ARI	Asthma	COPD	Pneumonia
Total	10.7 (8.8)	4.6 (4.6)	1.0 (1.4)	0.7 (1.2)	1.2 (1.4)
January	13.6 (10.1)	6.0 (5.3)	1.1 (1.4)	0.8 (1.2)	1.6 (1.5)
February	***15.2 (11.2)****	***6.7 (6.0)***	1.2 (1.4)	***0.9 (1.2)***	***1.8 (1.6)***
March	13.3 (9.7)	5.7 (5.1)	1.1 (1.3)	0.8 (1.2)	1.6 (1.5)
April	10.9 (7.7)	4.5 (4.0)	1.1 (1.3)	0.7 (1.2)	1.3 (1.4)
May	9.9 (7.1)	4.2 (3.8)	1.1 (1.3)	0.7 (1.1)	1.2 (1.2)
June	8.0 (5.8)	3.3 (3.0)	0.8 (1.4)	0.6 (1.2)	1.0 (1.1)
July	**7.0 (5.2)**	**2.9 (2.7)**	**0.7 (1.2)**	0.6 (1.1)	0.8 (1.1)
August	7.4 (5.7)	3.1 (3.0)	0.9 (1.2)	**0.6 (1.1)**	**0.8 (1.0)**
September	10.5 (8.2)	4.6 (4.4)	***1.3 (1.5)***	0.7 (1.1)	1.0 (1.1)
October	11.3 (8.4)	4.9 (4.4)	1.3 (1.4)	0.7 (1.1)	1.2 (1.3)
November	12.1 (9.1)	5.5 (4.9)	1.2 (1.4)	0.7 (1.1)	1.3 (1.3)
December	13.6 (11.0)	6.1 (5.7)	1.1 (1.4)	0.8 (1.2)	1.5 (1.5)

***Bold = highest median rate; *bold and italic* = lowest median rate**

Table 2-3: Median and interquartile range (IQR) of age-adjusted rates per 10,000 population per year

State	Counties	Years Covered	All	ARI	Asthma	COPD	Pneumonia
CA	58	2006 - 2013	365 (151)	156 (75)	45 (22)	25 (18)	52 (23)
CO	64	2013	**236 (211)**	**108 (122)**	27 (15)	15 (16)	**23 (17)**
FL	67	2005 - 2014	543 (268)	273 (165)	54 (24)	38 (21)	53 (18)
IL	102	2009 - 2014	625 (249)	239 (120)	46 (25)	***52 (27)***	***73 (31)***
IA	13	2005 - 2012	465 (243)	208 (193)	41 (8)	32 (18)	57 (8)
LA	64	2010 - 2012	429 (367)	183 (217)	37 (27)	32 (18)	54 (34)
ME	16	2001 - 2011	***661 (249)***	***283 (101)***	60 (25)	48 (20)	70 (28)
MA	14	2002 - 2012	494 (162)	205 (108)	***76 (39)***	32 (9)	67 (21)
MN	87	2007 - 2013	310 (153)	115 (69)	29 (14)	21 (11)	49 (17)
MO	115	2001 - 2012	410 (222)	211 (147)	32 (21)	24 (17)	36 (17)
NH	10	2000 - 2009	544 (191)	265 (129)	59 (10)	33 (8)	59 (6)
NM	33	2010 - 2013	362 (271)	166 (153)	39 (26)	22 (16)	35 (17)
NY	62	2005 - 2013	395 (155)	163 (88)	49 (21)	36 (17)	49 (17)
NC	100	2008 - 2014	337 (186)	151 (94)	45 (29)	28 (17)	35 (18)
SC	46	2000 - 2013	613 (233)	267 (94)	67 (31)	34 (13)	61 (25)
UT	29	2001 - 2013	263 (174)	115 (61)	**23 (13)**	**11 (10)**	47 (26)
VT	14	2003 - 2012	359 (136)	153 (83)	36 (8)	29 (18)	61 (10)

***Bold = highest median rate; *bold and italic* = lowest median rate**

Table 2-4: Median and interquartile range (IQR) of age-adjusted rates per 10,000 population per year

	Category	Counties	All	ARI	Asthma	COPD	Pneumonia
Urban	Large Central Metro	31	406 (150)	174 (93)	***61 (36)***	**18 (11)**	**43 (10)**
	Large Fringe Metro	111	**346 (193)**	**155 (92)**	42 (20)	25 (18)	44 (22)
	Medium Metro	147	415 (206)	185 (82)	46 (24)	28 (19)	47 (22)
	Small Metro	102	450 (292)	201 (166)	44 (25)	29 (24)	48 (27)
	Micropolitan	187	***453 (318)***	***208 (166)***	45 (31)	***33 (26)***	***54 (31)***
	Noncore	316	411 (330)	194 (171)	**38 (27)**	32 (25)	52 (33)
Region	Midwest	317	***449 (300)***	194 (155)	**36 (22)**	28 (25)	50 (32)
	Northeast	116	430 (205)	204 (114)	***53 (27)***	***36 (16)***	***56 (18)***
	South	277	448 (300)	***208 (162)***	49 (30)	32 (19)	48 (27)
	West	184	**300 (196)**	**144 (102)**	37 (23)	**19 (18)**	**42 (28)**
% living below poverty	[3.65, 12.91]	298	**340 (205)**	**145 (102)**	**36 (22)**	**24 (18)**	48 (22)
	(12.91, 17.45]	298	437 (275)	204 (142)	44 (25)	32 (24)	50 (30)
	(17.45, 47.5]	298	***476 (307)***	***218 (154)***	***49 (34)***	***33 (23)***	49 (33)
% black	[0.24, 1.24]	298	**363 (286)**	**164 (142)**	**32 (24)**	**27 (24)**	48 (32)
	(1.24, 8.13]	298	410 (245)	181 (139)	41 (21)	29 (22)	50 (26)
	(8.13, 73.1]	298	***454 (295)***	***211 (150)***	***54 (31)***	***31 (20)***	49 (26)
% Hispanic	[0.56, 2.12]	298	***475 (323)***	***213 (164)***	**40 (28)**	***33 (26)***	***55 (40)***
	(2.12, 6.18]	298	409 (291)	179 (157)	44 (26)	31 (21)	50 (26)
	(6.18, 81.1]	298	**374 (228)**	**166 (113)**	***45 (28)***	**25 (18)**	**44 (22)**
% w/out health insurance	[4.9, 13.95]	298	***432 (292)***	**174 (142)**	42 (26)	***33 (27)***	***56 (30)***
	(13.95, 19.4]	297	418 (262)	***200 (137)***	43 (26)	28 (20)	44 (26)
	(19.4, 36]	299	**401 (299)**	183 (159)	42 (29)	29 (18)	45 (26)
# hospitals per 10K	[0 ,1.55]	299	**335 (196)**	**146 (107)**	**38 (24)**	**24 (17)**	**41 (24)**
	(1.55, 3.93]	298	***469 (268)***	***211 (135)***	***47 (27)***	33 (20)	53 (24)
	(3.93, 71.6]	297	458 (347)	208 (180)	40 (27)	33 (27)	***55 (35)***
# urgent care centers per 10K	0	487	429 (332)	***194 (174)***	40 (27)	***33 (25)***	***52 (34)***
	[0.1,1.66]	133	***431 (192)***	189 (115)	***53 (27)***	30 (17)	50 (20)
	(1.66, 2.76]	133	400 (227)	175 (100)	45 (21)	**25 (15)**	44 (22)
	(2.76, 44.4]	134	**364 (228)**	**168 (126)**	**39 (27)**	27 (20)	**42 (26)**
# PC physicians per 10K	[0, 42.1]	299	402 (276)	178 (142)	**38 (25)**	32 (24)	48 (32)
	(42.1, 68.8]	297	***467 (298)***	***213 (147)***	45 (30)	33 (22)	***52 (28)***
	(68.8, 353]	298	**378 (231)**	**166 (124)**	45 (29)	**26 (17)**	**47 (22)**
# Pulmonologists per 10K	0	529	408 (315)	183 (165)	**38 (26)**	31 (25)	50 (36)
	[0.3,2.03]	120	421 (215)	187 (116)	47 (25)	31 (17)	***53 (22)***
	(2.03, 3.55]	117	***435 (243)***	***195 (138)***	49 (27)	30 (16)	49 (20)
	(3.55,34.6]	118	**401 (229)**	**176 (130)**	***51 (30)***	**26 (15)**	**44 (21)**

***Bold = highest median rate; *bold and italic* = lowest median rate**

Figure 2-1: Median county rate per 100,000 population per day

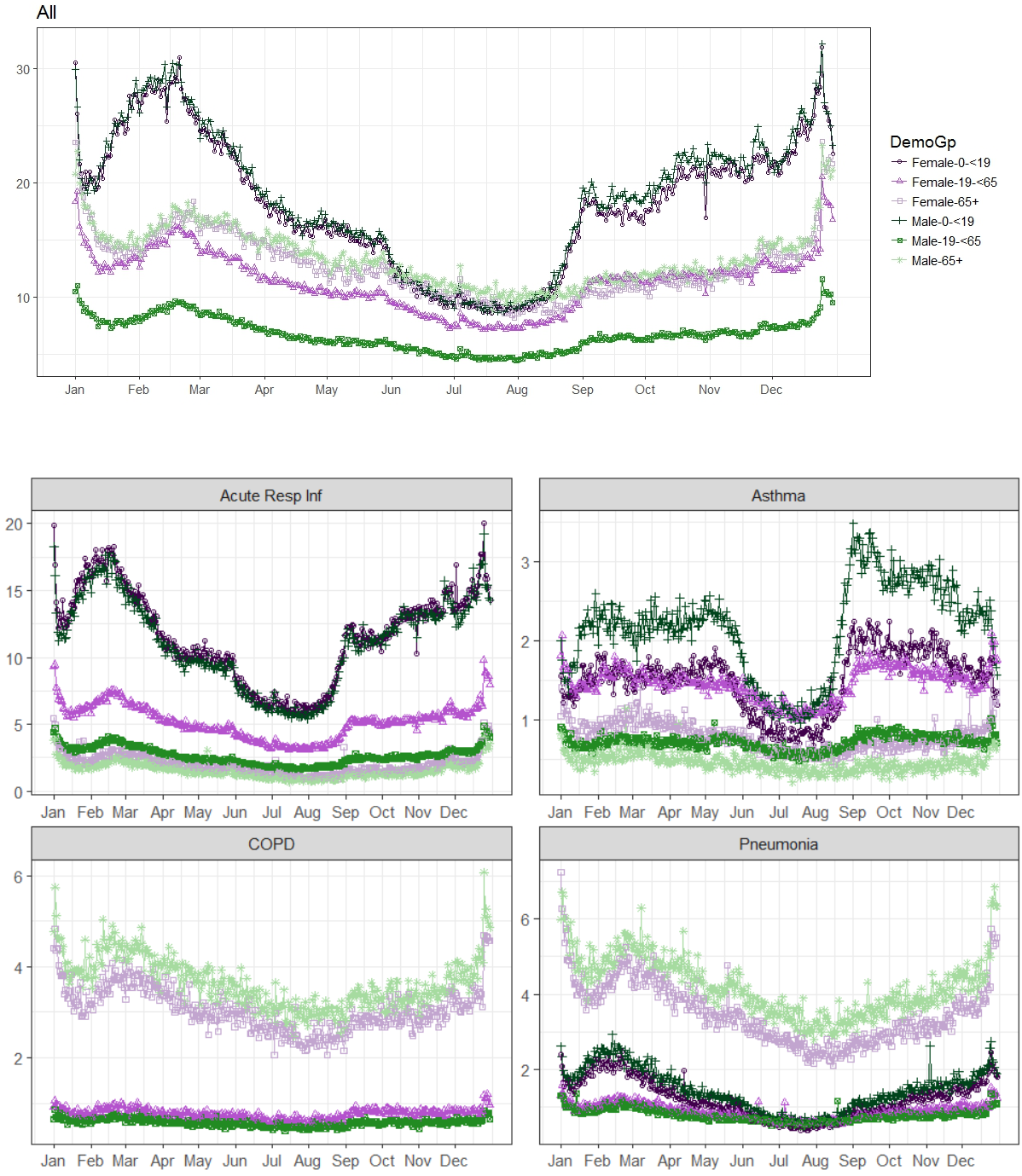

Figure 2-2: Median and interquartile range (IQR) of age-adjusted rates per 10,000 population per year

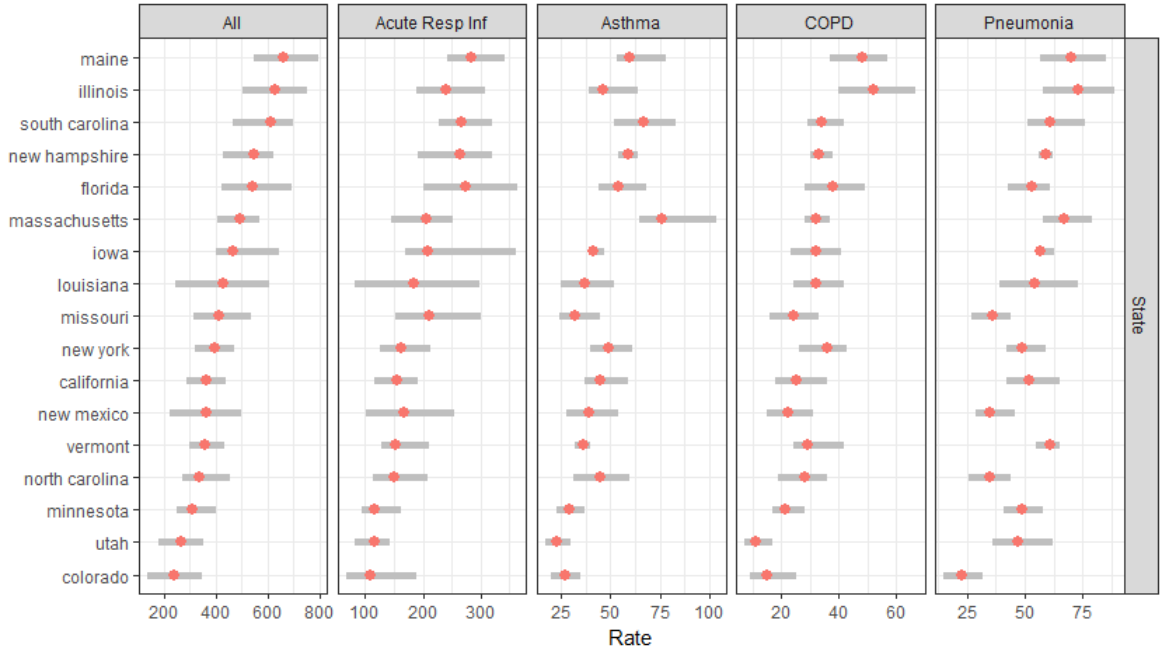

Figure 2-3: Median and interquartile range (IQR) of age-adjusted rates per 10,000 population per year

Chapter 3 - Age-specific associations between ambient air pollution concentrations and respiratory emergency department visits in the United States

Abstract

Background

While associations between air pollution and respiratory morbidity for adults 65 and older are well-documented in the United States, evidence is limited for people under 65. To address this gap, the Centers for Disease Control and Prevention's National Environmental Public Health Tracking Program collected emergency department (ED) data from 17 states and generated the first nationally-relevant effect estimates for respiratory ED visits for all ages.

Methods

With 47.4 million respiratory ED visits, data included 894 U.S. counties for 2001–2012 (with 3 to 12 years per county). County-specific time-series analyses using quasi-Poisson log-linear models were conducted to estimate associations between air pollution and respiratory ED visits among children 0-<19, adults 19-<65, and adults 65 and older. We used ozone and fine particulate matter (PM2.5) concentration estimates from a Bayesian space-time downscaling fusion model. Overall health effect estimates were generated using a Bayesian approach to pool the county effect estimates.

Results

The association between $PM_{2.5}$ and respiratory ED visits was elevated among children, slightly elevated among adults <65, and consistent with the null among adults 65 and older. Associations between $PM_{2.5}$ and asthma were elevated and similar among all age groups. $PM_{2.5}$ was

associated with ARI among children and to a lesser extent ARI and pneumonia among adults <65. In contrast, the association between ozone and respiratory ED visits was elevated among both adult groups but not among children. However, the association among children was sensitive to choice of temporal control. Asthma and ozone were associated among adults <65 and slightly among children. Associations were elevated for ARI and COPD among both adult groups. Associations were elevated for pneumonia among all age groups.

Conclusions and Relevance

Ozone and $PM_{2.5}$ were associated with respiratory ED visits among all ages with variation in magnitude and strength of the evidence by age group and outcome. These results address a gap in the evidence used to ensure adequate public health protection under national air pollution policy.

Introduction

Substantial and consistent evidence supports the conclusion that short-term exposure to ambient ozone and fine particulate matter ($PM_{2.5}$) is associated with increases in mortality and morbidity [1,2]. Robust evidence exists for mortality and for hospitalizations among adults 65 and older due to the availability of national vital statistics data and Medicare data. These data have enabled many multi-city analyses, which have been instrumental in setting National Ambient Air Quality Standards (NAAQS) for the Clean Air Act [3-10]. Estimates from multi-city studies provide strong evidence for determining causality between air pollution and health, for evaluating potential health benefits of proposed policies across the United States (US), and for establishing ambient air quality standards that provide adequate protection for the US population.

Because national datasets are lacking, the evidence base for morbidity outcomes for populations not covered by Medicare (i.e., <65 years) often come from single-city studies [11-14]. This is particularly important for respiratory emergency department (ED) visits since the vast majority are from people under age 65 [15]. Collectively, the evidence from single-city studies indicates positive associations between air pollution and ED visits for all respiratory diseases combined, and for asthma, chronic obstructive pulmonary disease (COPD), and respiratory infections [9,16-21]. While informative, these studies have limitations with respect to nationwide generalizability due to between-city differences in air pollution composition and population characteristics as well as differences in study methodology. For the current ozone and particulate matter (PM) standards, the Environmental Protection Agency (EPA) conducted national-scale mortality risk assessments using results from multi-city studies [22,23]. For morbidity outcomes, EPA

conducted similar risk assessments for hospital admissions among all ages in only 12 cities for ozone and 15 cities for PM where epidemiologic study results and necessary data were available. For respiratory related ED visits among all ages, their assessment was only conducted in Atlanta and New York City, indicating a strong need for a multi-city study.

In response to a Pew Commission report, the Centers for Disease Control and Prevention's (CDC) National Environmental Public Health Tracking Program (Tracking Program) was launched to integrate health, exposure, and environmental hazard data to inform environmental health programs and policies [24]. The National Environmental Public Health Tracking Network (Tracking Network) is a web-based system with components at national, state, and local levels (ephtracking.cdc.gov). It is used to collect, integrate, analyze, and disseminate health and environmental data that drive actions to improve the health of communities. We invited 30 states known to have ED data centralized within their state to participate in the project. Using the Tracking Network, we collected daily, county respiratory ED data for all ages from 17 states representing 45% of the US population (138.5 million individuals). We used these data to perform the first nationally relevant study to estimate associations between ozone and $PM_{2.5}$ and respiratory ED visits among all ages in the US.

Methods

We obtained data for daily, county ED visits with a primary diagnosis of respiratory disease, based on International Classification of Diseases, 9th Revision (ICD-9) codes 460 – 519, from 17 states (California, Colorado, Florida, Illinois, Iowa, Louisiana, Maine, Massachusetts,

Minnesota, Missouri, New Hampshire, New Mexico, New York, North Carolina, South Carolina, Utah, and Vermont) for 2000 through 2014 with 3 to 13 years per state (data availability varied by state). We created 19 age-specific outcomes by aggregating the data into four age groups by five outcome groups, excluding COPD among children. The age groups included all ages combined, children 0 to less than 19 years (children), adults 19 to less than 65 years (adults), and adults 65 years and older (older adults). The outcome groups included all respiratory outcomes combined (460 – 519), acute respiratory infection (ARI) including upper respiratory infections, bronchitis, and bronchiolitis (460 – 466.0), asthma (493), chronic obstructive pulmonary disease (COPD) (491, 492, or 496), and pneumonia (480 – 486).

For ambient air pollution concentrations, we used data from the Bayesian space-time downscaling (DS) fusion modeling approach, developed by the U.S. Environmental Protection Agency (EPA) and its partners [25]. Predictions of daily maximum 8-hr average ozone concentrations in parts per billion ozone and daily 24-hr average $PM_{2.5}$ from the DS model were generated at census-tract centroids for the contiguous US as part of an interagency agreement between CDC and EPA. The Downscaler model development process and validation of results have been published previously [25-27]. For this study, we generated daily, population-weighted county-level estimates of ozone and $PM_{2.5}$, for years 2001 through 2012 [28-29]. Daily, county-level estimates of maximum temperature and dew point temperature in degrees Fahrenheit (°F) were generated from the North American Land Data Assimilation System (NLDAS) model [30]. We converted predictions from NLDAS model from a grid resolution of 14-km X 14-km to county using a previously cited geo-imputation approach [31]. We used SAS v9.3, Python v3.3.2 and ArcGIS 9.3 for preparing the environmental datasets.

We used a two-stage model to obtain nationally relevant estimates of short-term associations between ozone and $PM_{2.5}$ and respiratory ED visits. In the first stage, we fit time-series models (n = 17880) for each combination of county (n = 894) and age-specific outcome (n = 20). To minimize issues with model convergence, we excluded those counties where more than 90% of days had zero ED visits for a given age-specific outcome (n = 5575). We modeled an unconstrained distributed lag for lag days 0 through 6 to capture the cumulative association of exposures over the past week using a Poisson log-linear model that accounted for overdispersion. We fit single-pollutant models for ozone and $PM_{2.5}$ and two-pollutant models with both. We included: (1) non-linear functions of same day maximum temperature, same day maximum dew point temperature, and previous six-day average maximum temperature as natural cubic splines with 3 degrees of freedom; (2) a non-linear function of calendar date as a natural cubic spline with 8 degrees of freedom per year of county data; and (3) indicator variables for day of week and for holidays. For the second stage, two-level Bayesian hierarchical models with non-informative priors were fit to combine county-specific effect estimates for each age-specific outcome to obtain nationally relevant effect estimates for ozone and $PM_{2.5}$ [32]. We evaluated the sensitivity of our results by running the models with various degrees of freedom on calendar date (6, 8, 10, and 12 per year) and with three combinations of weather variables: 1) temperature, 2) temperature and dew point temperature, and 3) temperature, dew point temperature, and previous six-day average temperature. We also ran the models with lag day –1 (pollution on the following day) as a negative control exposure to estimate the association with ozone and $PM_{2.5}$ on the day after the ED visit [33]. All models were implemented using R statistical software (version 3.3.2; R Foundation for Statistical Computing).

Results

Our analysis included 38.4 million respiratory ED visits from 869 counties including 480 non-metropolitan counties (Table 3-1) [34]. Children and adults had approximately 16 million visits each while older adults had about 6 million visits. The mean daily rates of respiratory ED visits per 10,000 people was 1.20 for all ages combined, 1.94 for children, 0.91 for adults, and 1.37 for older adults. Rates of ARI and asthma were highest among children, while the rates for COPD and pneumonia were highest among older adults (Figure 3-1). We calculated the interquartile range (IQR) of each pollutant for each county for the specific years of data used in that county's time-series analysis. The 869 county-specific IQR for daily 8-hour maximum ozone varied from 8.0 parts per billion (ppb) to 34.0 ppb with a mean IQR of 16.54 ppb (Figure 3-2). For 24-hour average $PM_{2.5}$ levels, the mean county IQR was 5.26 micrograms per cubic meter ($\mu g/m^3$) and ranged from 1.9 to 9.8 $\mu g/m^3$.

We observed statistically significant positive associations between ozone and all respiratory ED visits combined in both single and two-pollutant models for all age groups, except for children in the two-pollutant model where the association estimate was null (Figure 3-3). The rate ratios (RRs) shown indicate the increase in rate of ED visits for a 20 ppb increase in ozone concentration on lag days 0 through 6. In the two-pollutant models, the association between all respiratory ED visits and ozone was strongest among adults and elevated for older adults. In contrast, $PM_{2.5}$ was associated with all respiratory ED visits in both single and two-pollutant models for all ages combined, children, and adults and consistent with the null among older adults (Figure 3-4). The RRs shown indicate the increase in rate of ED visits for a 10 $\mu g/m^3$

increase in $PM_{2.5}$ concentration on lag days 0 through 6. The RRs between all respiratory ED visits combined and $PM_{2.5}$ was higher among children than adults.

For both pollutants, the associations with specific outcomes varied in significance and magnitude by age group. For ozone, we observed significant and positive associations with asthma, ARI, COPD, and pneumonia among all ages combined in both single-pollutant and two-pollutant models (Figure 3-3). For adults, we also observed significant, positive associations between ozone and all four outcomes. Ozone was associated with ARI, COPD, and pneumonia among older adults but was consistent with the null for asthma. For children, ozone was only associated with pneumonia and, to a lesser extent, asthma. The highest magnitude RR for ozone was asthma among adults followed by ARI among older adults and pneumonia among adults. For $PM_{2.5}$ and all ages combined, we observed positive, significant associations for asthma and ARI in single and two-pollutant models and pneumonia in single-pollutant models (Figure 3-4). In contrast to our ozone results, we observed an association between $PM_{2.5}$ and ARI among children and an elevated RR for asthma among children but no association for pneumonia. $PM_{2.5}$ was associated with ARI, asthma, and pneumonia among adults and with asthma only among older adults. The highest RR observed was for asthma among children followed by the RRs for asthma among adults and older adults. We found little evidence of an association between $PM_{2.5}$ and COPD among any age group in either single or two-pollutant models.

In our sensitivity analyses, the RR increased slightly as the number of degrees of freedom per year of data increased for ozone; association estimates for $PM_{2.5}$ changed little (Figure 3-5). It is notable that, for children, many RRs for ozone increase in magnitude from a negative or null

association to positive association as we increase temporal control (Figure 3-5 A and B). The RR for ozone and ARI among children was 1.000 (95% CI: 0.993, 1.007) with the *a priori* 8 degrees of freedom, but was 1.015 (95% CI: 1.010, 1.023) with 12 degrees of freedom. Further, the RR for ozone and asthma among children was only slightly elevated with 8 degrees of freedom but increased in magnitude and was statistically significant with 10 and 12 degrees of freedom. We choose 8 degrees of freedom *a priori* based on work completed by previous multi-city studies which generally used 6 to 8 degrees of freedom per year and generally found their effect estimates to be robust to the degrees of freedom used [3-5,9]. Previous Atlanta-based studies of respiratory ED visits or hospitalizations among all ages or children have generally used 12 degrees of freedom [12,14]. It is plausible that the most valid degree of temporal control may vary by outcome and age group in relation to the degree of seasonality. Given the strong seasonality of respiratory ED visits among children especially, the necessary degree of control may be higher than what is needed for outcomes and age groups studied by previous multi-city studies. An alternative approach would be to allow the degrees of freedom to vary by outcome and age group, and possibly county, using a fit criterion, such as the Akaike Information Criterion (AIC) [Katsouyanni]. For the three combinations of weather variables we evaluated, our results fluctuated slightly for ozone but were robust for $PM_{2.5}$ with overlapping 95% credible intervals (Figure 3-6). The associations observed between ozone or $PM_{2.5}$ concentrations on lag day -1 (the following day's pollution) and ED visits for asthma, COPD, and pneumonia were consistent with the null supporting our model specifications (Figure 3-7).

Discussion

Our nationally relevant study, based on nearly 40 million respiratory ED visits representing all ages, addresses an important gap in air pollution epidemiology and is a valuable reference for future national air pollution policy risk assessments. Our results support the EPA's determination of a likely causal relationship between $PM_{2.5}$ and respiratory effects and a causal relationship between ozone and respiratory effects [1,2]. However, our results highlight important variation in magnitude across age groups, outcomes, and pollutants. $PM_{2.5}$ and respiratory ED visits were strongly associated among children, moderately associated among adults, and not associated among older adults. While the associations with $PM_{2.5}$ were elevated and similar among all age groups for asthma, they varied by age group for ARI and pneumonia. Conversely, ozone was strongly associated with respiratory ED visits among both adult groups. The association among children was elevated with increased temporal control, though the magnitude remained lower than both adult groups. The association between ozone and asthma varied by age group with the highest magnitude among adults. Associations varied by age group for ARI but were similar across age groups for COPD and pneumonia. These findings indicate that multi-city studies of populations over 65 may not be a good proxy of acute respiratory impacts on younger age groups, and that reliance on such studies could underestimate population respiratory health impacts of $PM_{2.5}$ or ozone that were stronger in our study for younger age groups.

Few single-city studies have estimated associations of ozone or $PM_{2.5}$ across different age groups for ED visits or hospitalizations. Those that have looked specifically at asthma and generally found a greater impact on children [11,16,35]. We observed stronger associations for

$PM_{2.5}$ on asthma among children compared to adults and older adults, and a stronger association for ozone on asthma among adults and older adults compared to children. Based on the few studies evaluating hospital admissions and ED visits for respiratory outcomes, EPA found consistent evidence of positive associations for asthma and COPD [2]. While EPA found strong toxicological evidence supporting an association between ozone and respiratory infections and pneumonia, the epidemiologic evidence was inconsistent. We observed positive associations between ozone and ARI, asthma, COPD, and pneumonia for all age groups with the only exceptions being ARI among children and asthma among older adults after adjusting for $PM_{2.5}$. In our results, the greatest ozone association observed was for asthma among adults younger than 65, an age group previously not included in other multi-city studies of morbidity. For $PM_{2.5}$, EPA's review of available studies produced stronger and more consistent evidence for COPD and respiratory infections effects than for asthma effects including both ED visits and hospitalizations. In contrast, we observed significant, positive associations between $PM_{2.5}$ and asthma across all age groups and between $PM_{2.5}$ and acute respiratory infections for children and adults. Pneumonia was associated with $PM_{2.5}$ among adults only while COPD was not associated with $PM_{2.5}$ in any age group analyzed. These disparate results could be due to differences in study methodology or between city differences in air pollution composition, exposure patterns, choice of environmental data, or population characteristics. Additionally, the diagnosis of asthma in children under five is difficult and could result in more outcome measurement error when included in the analysis.

The differences in magnitude across associations of outcomes, age groups, and pollutants are consistent with differences in disease pathology, respiratory tract physiology, pollutant

chemistry, exposure patterns, or a combination thereof. The specific respiratory diseases leading to ED visits varies by age group with ARI, asthma, and pneumonia prominent in children; asthma and COPD in adults; and COPD and pneumonia in older adults [15]. The pathology of these diseases and their impact on the respiratory tract also varies by age. Small airway obstruction related to COPD is often observed in the smallest airways, where gas exchange occurs, compared to a more proximal location among individuals with asthma [36]. Similarly, among those with asthma, hyperresponsiveness tends to be more proximally located in younger individuals versus more peripherally located in older individuals [36]. Age also influences respiratory tract morphology, breathing patterns, physiochemical properties of the extracellular lining fluid, immunologic responses, and mechanical properties of the lung [1,2,36]. These differences can influence not only disease pathology but also pollutant uptake, dose, and effect on the respiratory tract. The impact of these differences on our results is further complicated by the differing physiochemical properties of ozone and $PM_{2.5}$ [1,2]. For example, ozone is a gas that can penetrate deep into the lower respiratory tract with more distal penetration in larger lungs [2]. Conversely, evidence suggests that children may receive a larger dose of particulate matter in the lower respiratory tract compared to adults [1]. Together, these differences lend biological plausibility to our results.

Limitations

Although our statistical model is well established and has been evaluated extensively [32,37-40], model misspecification is nevertheless a concern. Our county time-series analyses could be biased by an unmeasured or inadequately modeled predictor or confounder if that confounder fluctuates over time in a manner similar to ozone or $PM_{2.5}$. Our sensitivity analyses, which

include modeling time trend and meteorology in various ways and estimating associations with a negative control exposure, suggest that such a bias is unlikely [33]. One possible exception is the results for ozone and ARI and asthma among children, which were sensitive to the number of degrees of freedom included in the time control. Classification of specific respiratory diseases based on primary diagnosis and ICD-9 codes could potentially lead to misclassification. Such misclassification would not affect the results for all respiratory diseases combined. While county air pollution metrics are not measures of personal exposure, they are relevant metrics for air pollution policy and can produce robust and unbiased results for ozone and $PM_{2.5}$ that tend to be more spatially homogenous than other air pollutants [41]. Modeled air pollution data may introduce additional measurement error into our analyses; however, evaluation of the Downscaler model has shown it to be a reasonable solution to the temporal and spatial gaps in available air pollution data [26,27]. While our study provides estimates to inform national environmental health policy by combining the local estimates, we average across the local variation in the short-term associations between air pollution and respiratory ED visits that exists.

Conclusion

Both ozone and $PM_{2.5}$ were associated with respiratory ED visits among all ages combined, and we observed variation in the magnitude of these associations across age, respiratory outcome, and pollutant. Our results provide the first nationally comprehensive risk estimates for ARI, asthma, COPD, pneumonia, and all respiratory outcomes combined for children, adults younger than 65, older adults, and all ages combined. Prior to our study, US multi-city estimates were only available for mortality or for morbidity among older adults due to limitations in nationally

standardized and accessible health data. Such gaps in available data, and consequently our gaps in understanding of the relationship between health and environmental hazards, were the primary motivation for the creation of CDC's Tracking Network. By examining associations with ozone and $PM_{2.5}$ for people of all ages across hundreds of counties in the US, we address a key gap in the evidence used to inform national ambient air pollution policy.

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Table 3-1: Overall mean and variance of county level mean daily counts and rates per 10,000 population of respiratory emergency department visits for counties analyzed by outcome and age group

Outcome	Age Group	ED Visits	Counties	Mean Daily Count	Variance Daily Count	Mean Daily Rate	Variance Daily Rate
All	All	39,975,411	869	17.26	2383.55	1.20	0.313
All	0-<19	16,096,443	836	7.34	523.19	1.94	0.914
All	19-<65	16,398,438	836	7.50	400.90	0.91	0.206
All	65+	5,884,333	789	2.78	51.35	1.37	0.296
ARI	All	18,169,816	836	8.13	498.03	0.57	0.090
ARI	0-<19	9,534,546	812	4.48	189.91	1.22	0.400
ARI	19-<65	7,176,147	774	3.49	68.61	0.42	0.058
ARI	65+	701,212	419	0.61	1.16	0.21	0.014
Asthma	All	5,761,712	691	3.10	100.70	0.14	0.005
Asthma	0-<19	2,265,810	517	1.64	22.15	0.23	0.014
Asthma	19-<65	2,717,781	594	1.76	30.87	0.13	0.004
Asthma	65+	379,423	206	0.68	1.65	0.09	0.002
COPD	All	2,385,148	678	1.32	7.19	0.10	0.003
COPD	0-<19	NA	NA	NA	NA	NA	NA
COPD	19-<65	896,808	506	0.69	1.43	0.08	0.002
COPD	65+	1,342,479	571	0.88	2.96	0.38	0.027
Pneumonia	All	4,659,863	749	2.31	35.25	0.16	0.004
Pneumonia	0-<19	1,294,844	467	1.04	6.02	0.16	0.005
Pneumonia	19-<65	1,425,621	566	0.97	4.55	0.09	0.001
Pneumonia	65+	1,660,353	589	1.04	5.27	0.46	0.036

Figure 3-1: Distribution of county level means for daily rate of respiratory emergency department visits per 10,000 population

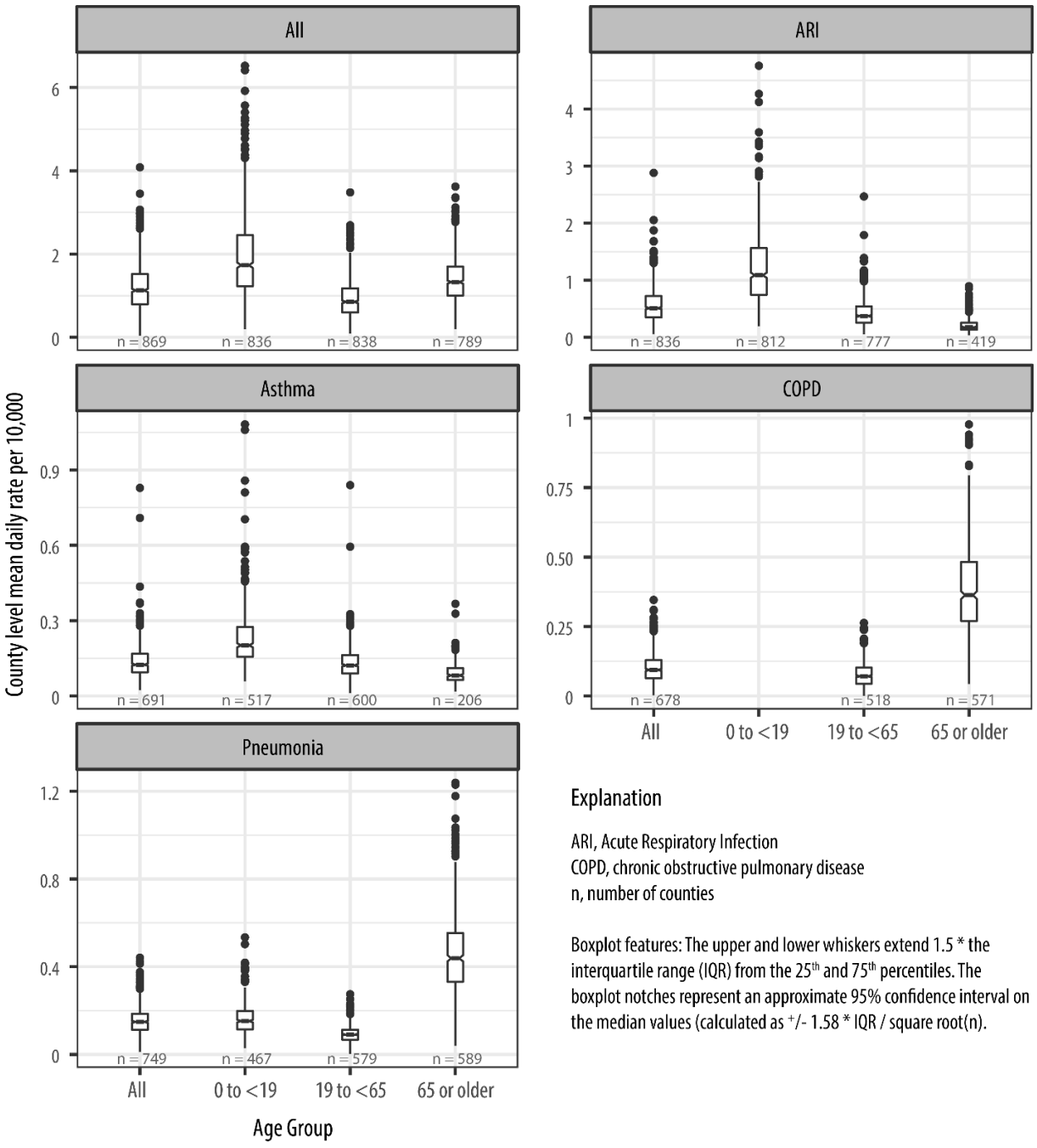
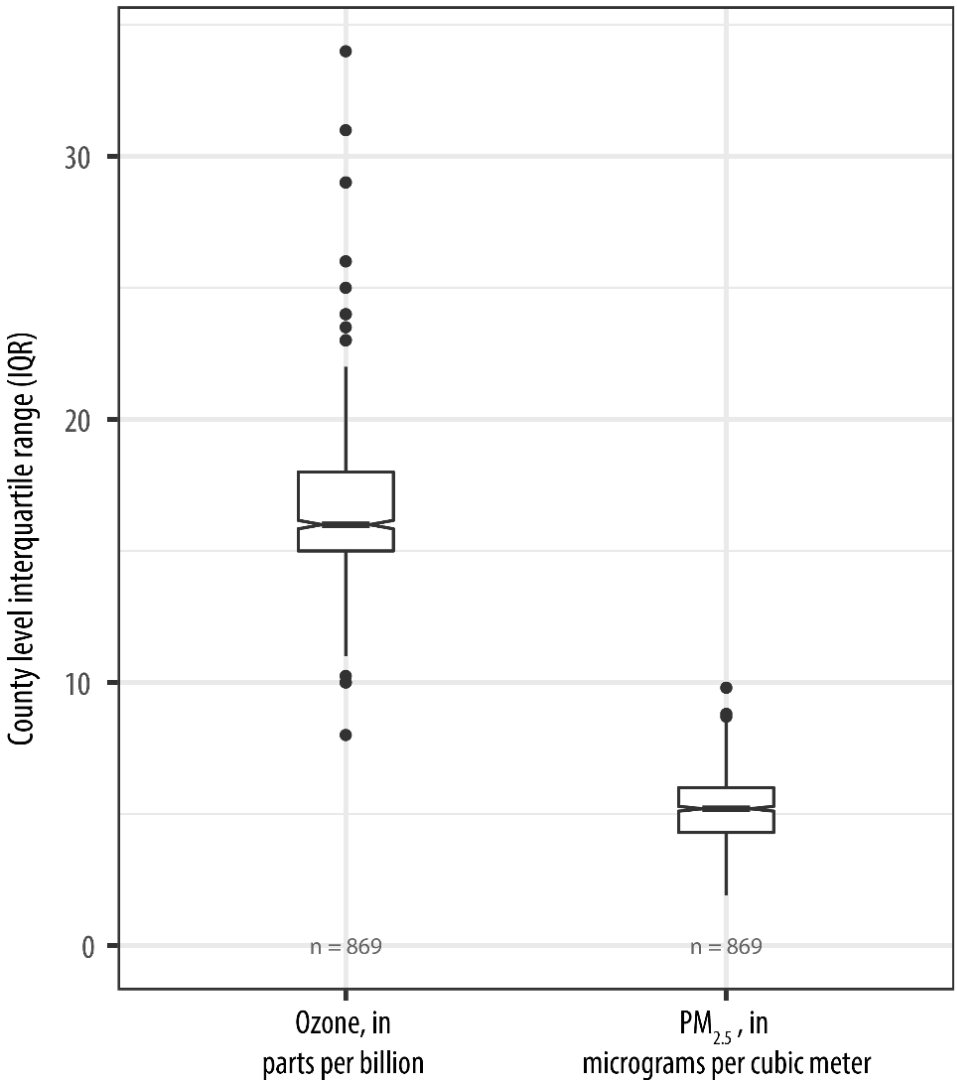


Figure 3-2: Distribution of county level interquartile ranges for daily 8-hour maximum ozone and 24-hour average $PM_{2.5}$



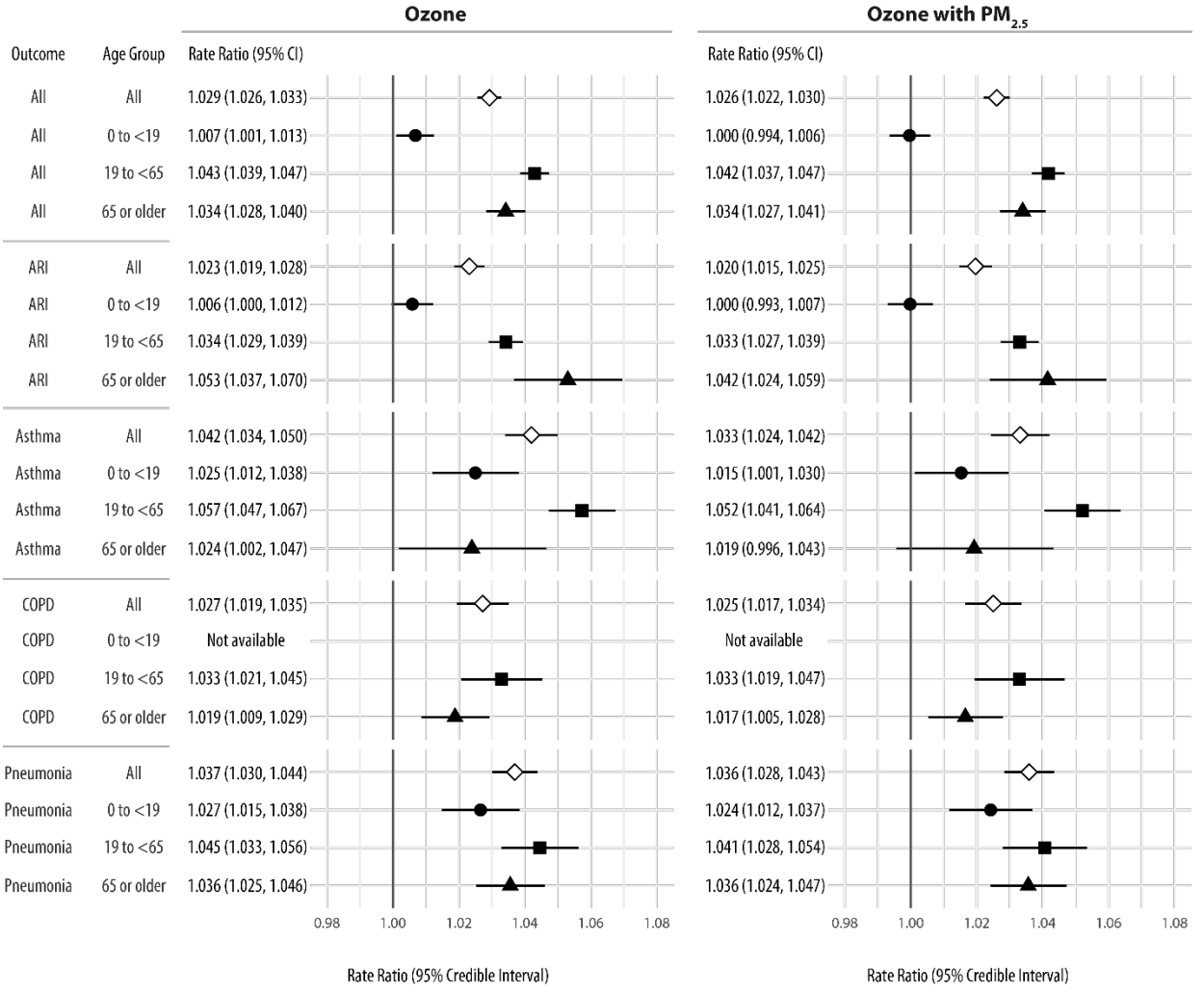
Explanation

n, Number of counties

$PM_{2.5}$, Fine particulate matter (2.5 micrometers in diameter or less)

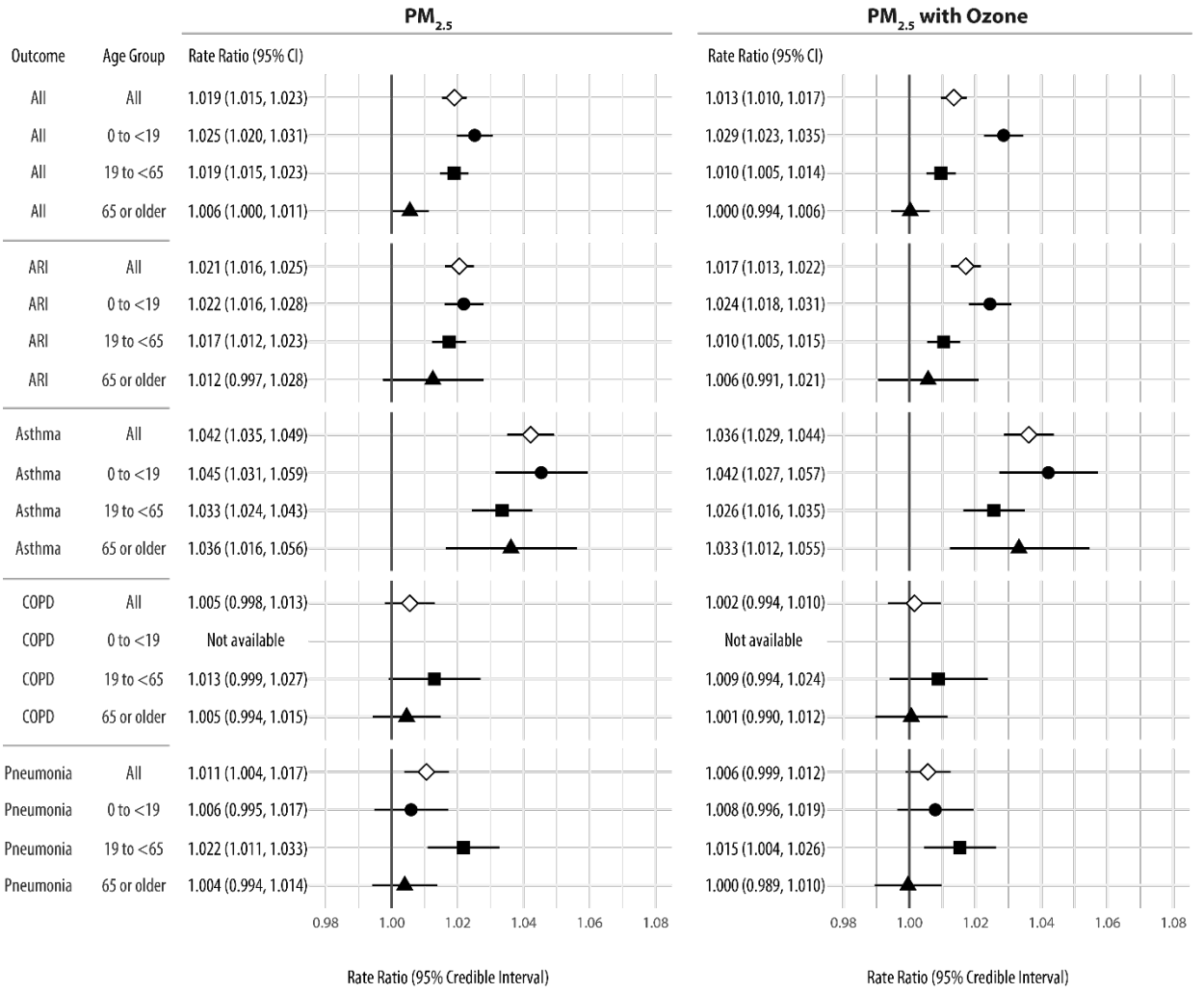
Boxplot features: The upper and lower whiskers extend 1.5 * the interquartile range (IQR) from the 25th and 75th percentiles. The boxplot notches represent an approximate 95% confidence interval on the median values [calculated as +/- 1.58 * IQR / square root(n)].

Figure 3-3: Rate ratio & 95% credible interval for a 20 parts per billion increase in daily 8-hour maximum ozone from an unconstrained, distributed lag model (lags 0 – 6) (unadjusted and $PM_{2.5}$ adjusted)



Abbreviations: $PM_{2.5}$, Fine Particulate Matter (2.5 micrometers in diameter or less); 95% CI, 95% Credible Interval; ARI, Acute Respiratory Infection; COPD, Chronic Obstructive Pulmonary Disease

Figure 3-4: Rate ratio & 95% credible interval for a 10 microgram per cubic meter increase in 24-hour average $PM_{2.5}$ from an unconstrained, distributed lag model (lags 0 – 6) (unadjusted and ozone adjusted)

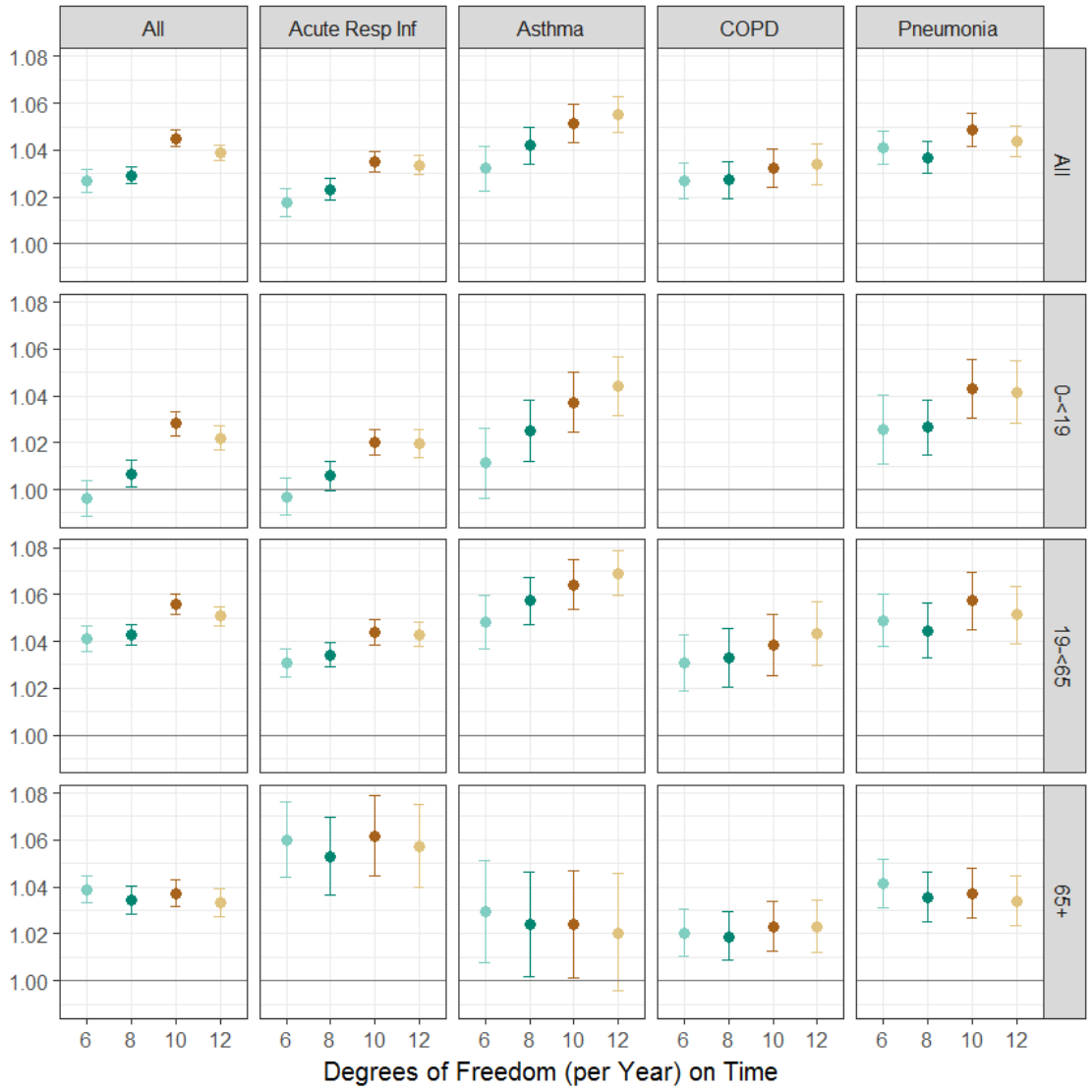


Abbreviations: $PM_{2.5}$, Fine Particulate Matter (2.5 micrometers in diameter or less); 95% CI, 95% Credible Interval; ARI, Acute Respiratory Infection; COPD, Chronic Obstructive Pulmonary Disease

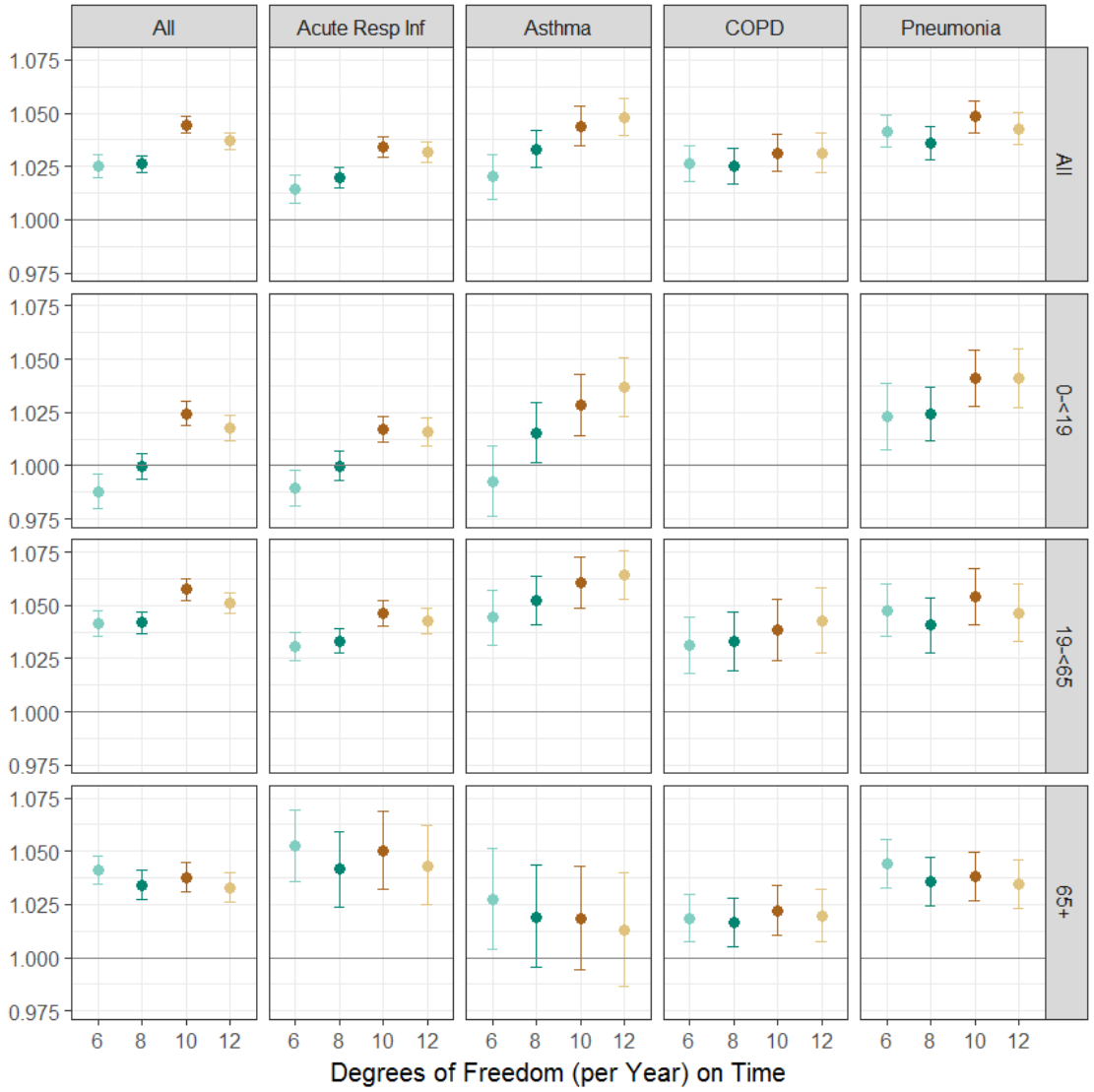
Sensitivity Analysis

Figure 3-5: Evaluation of different degrees of freedom per year as alternative specifications for control of temporal trend (8 degrees of freedom per year were selected a priori for the primary analysis.)

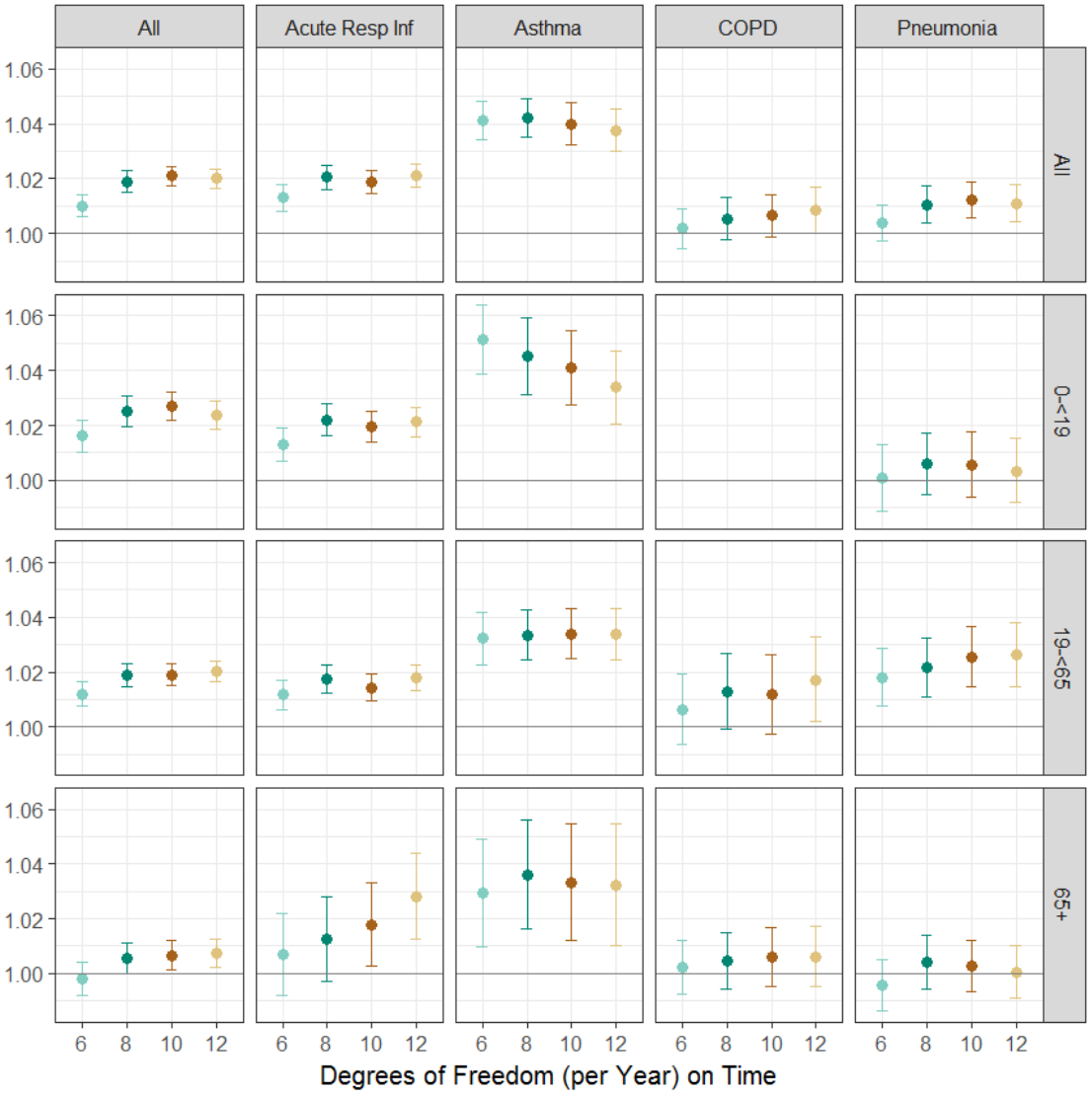
A: RR & 95% CI from an unconstrained, distributed lag model (lags 0 – 6) for a 20 ppb increase in 8-hour ozone



B: RR & 95% CI from an unconstrained, distributed lag model (lags 0 – 6) for a 20 ppb increase in 8-hour ozone, adjusted for $PM_{2.5}$



C: RR & 95% CI from an unconstrained, distributed lag model (lags 0 – 6) for a 10 µg/m^3 increase in 24 hour $PM_{2.5}$



D: RR & 95% CI from an unconstrained, distributed lag model (lags 0 – 6) for a 10 µg/m^3 increase in 24 hour $PM_{2.5}$, adjusted for ozone

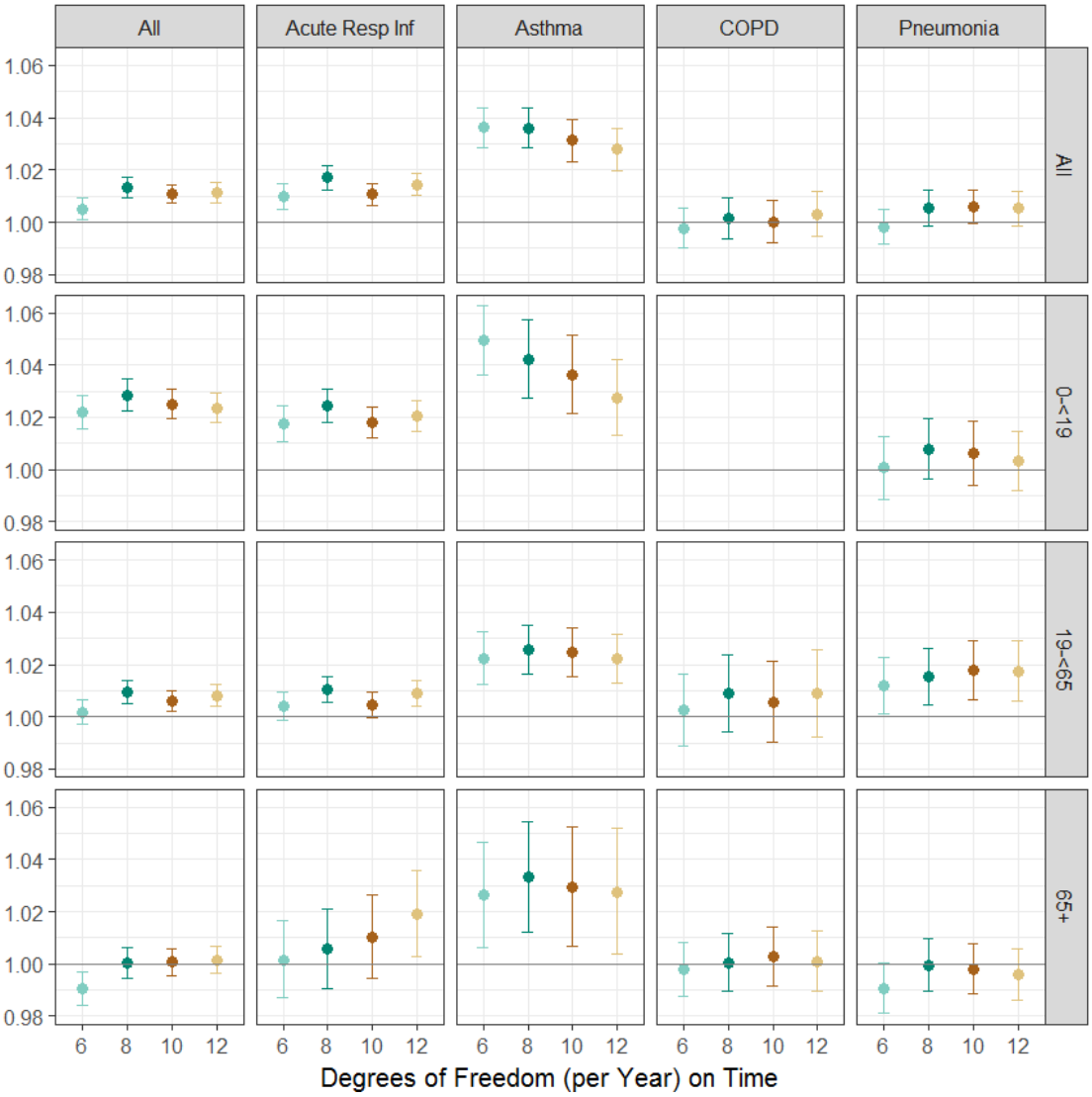
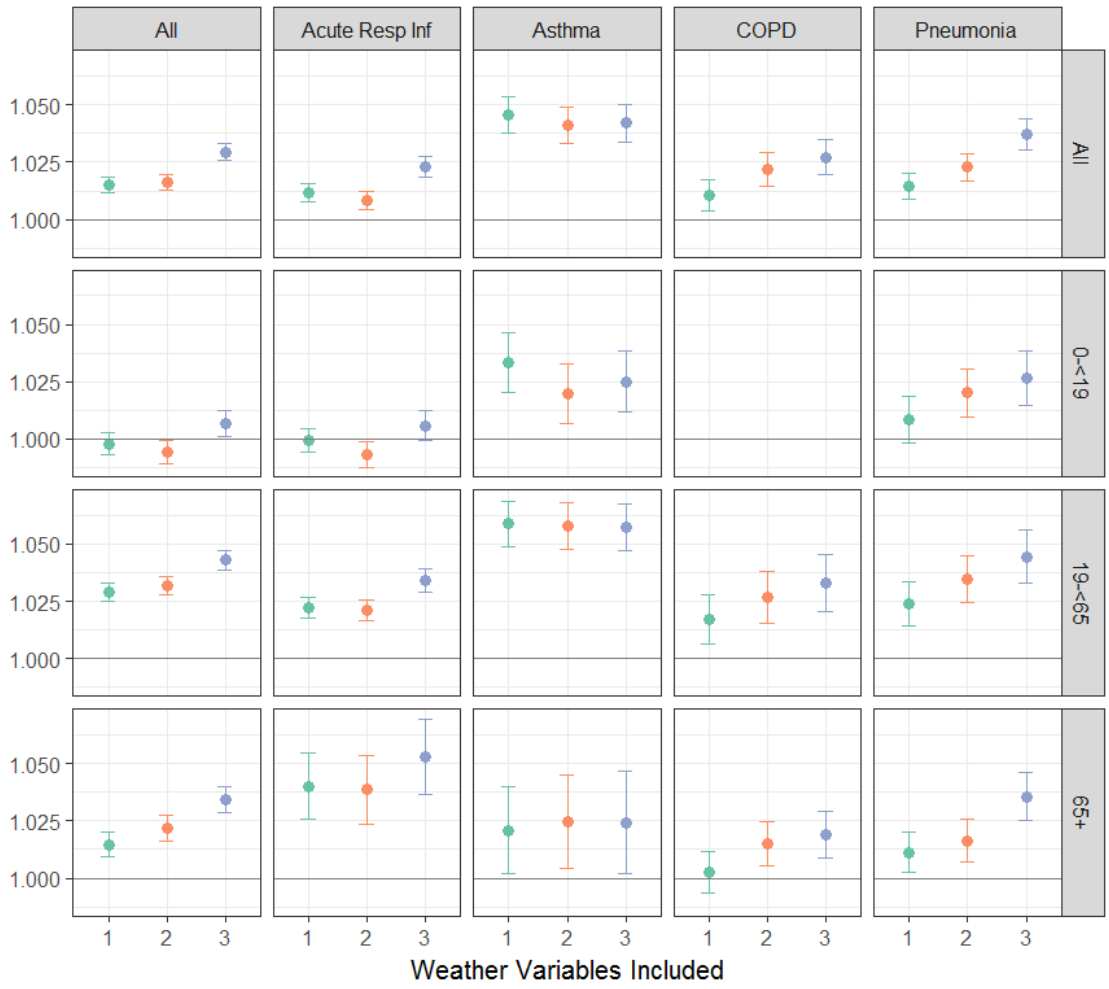


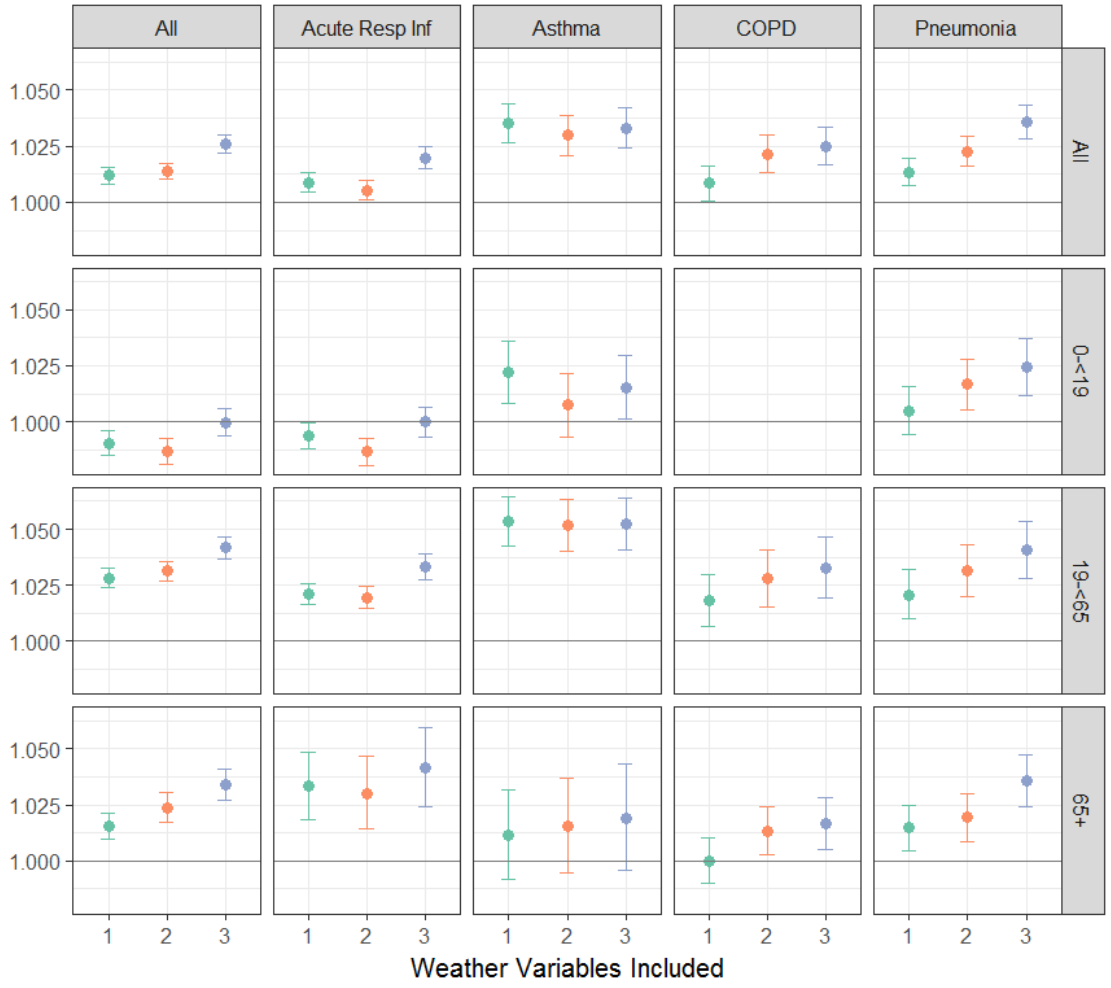
Figure 3-6: Evaluation of the effect of different variables to control for weather

Three combinations of weather variables analyzed: 1) same day maximum temperature, 2) same day maximum temperature and same day maximum dew point temperature, and 3) same day maximum temperature, same day maximum dew point temperature, and previous six-day average temperature. Combination 3 was used in the primary analysis.

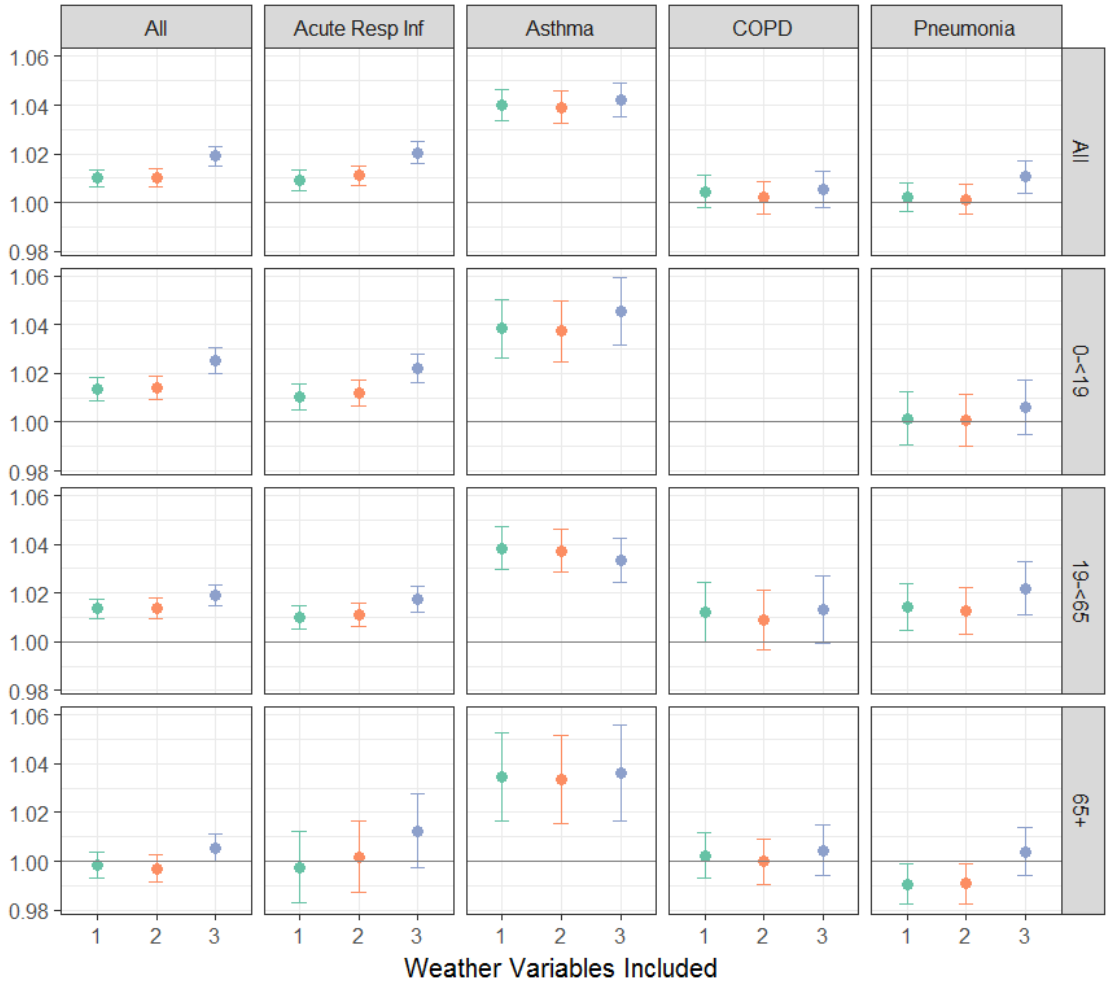
A: RR & 95% CI from an unconstrained, distributed lag model (lags 0 – 6) for a 20 ppb increase in 8-hour ozone



B: RR & 95% CI from an unconstrained, distributed lag model (lags 0 – 6) for a 20 ppb increase in 8-hour ozone, adjusted for $PM_{2.5}$



C: RR & 95% CI from an unconstrained, distributed lag model (lags 0 – 6) for a 10 µg/m^3 increase in 24 hour $PM_{2.5}$



D: RR & 95% CI from an unconstrained, distributed lag model (lags 0 – 6) for a 10 µg/m^3 increase in 24 hour $PM_{2.5}$, adjusted for ozone

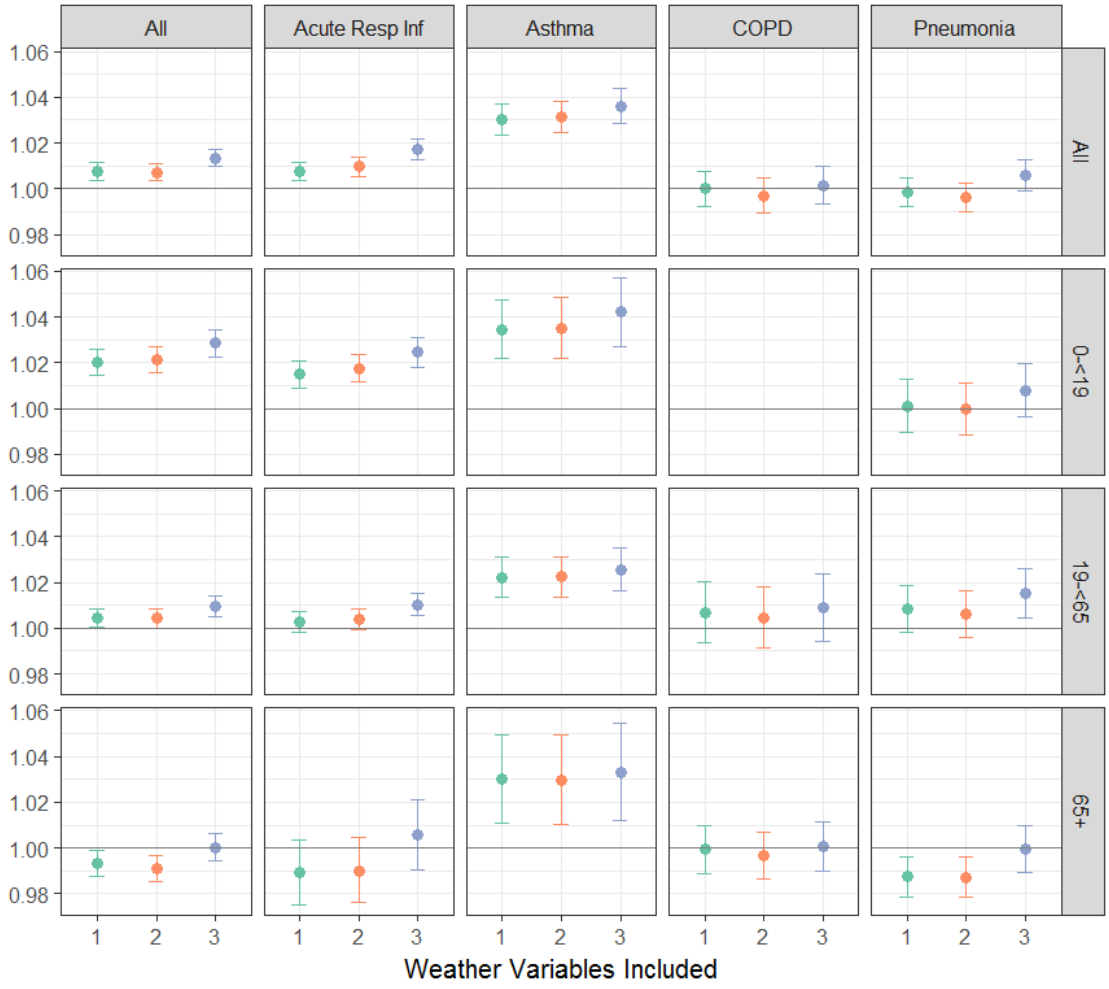
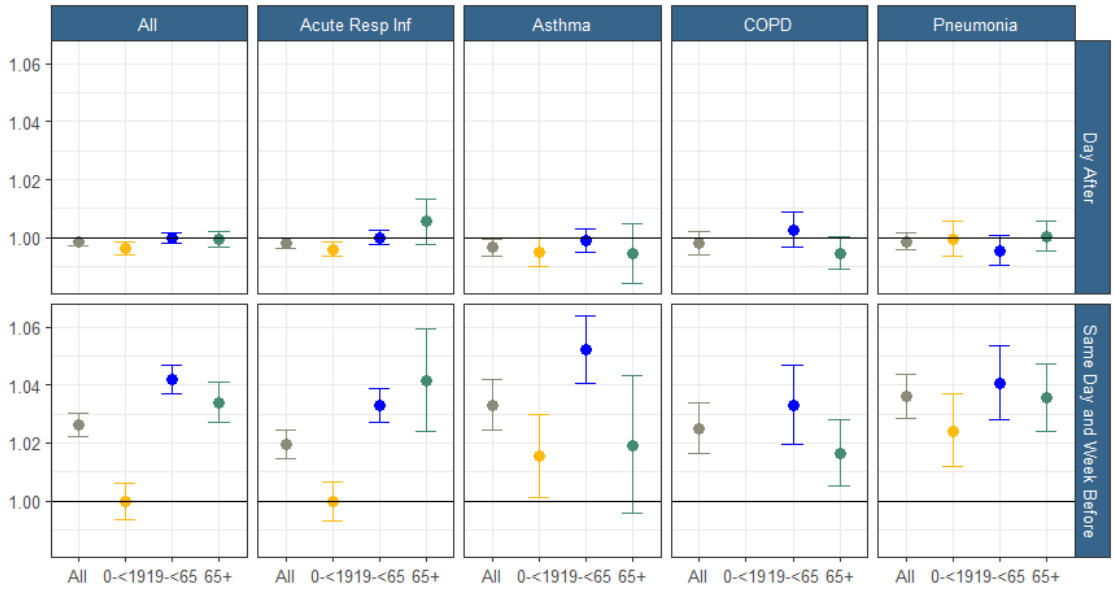
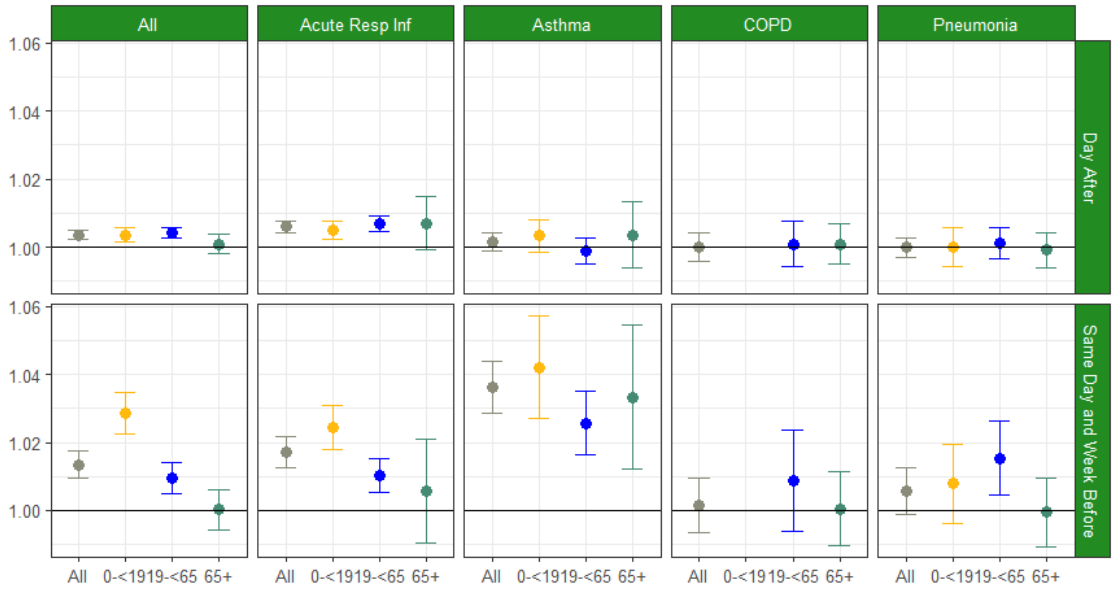


Figure 3-7: Evaluation of associations between respiratory ED visits and air pollution the day after the ED visit as a negative control exposure

A: RR & 95% CI for a 20 ppb increase in 8-hour ozone the day after an ED visit and the same day plus week before an ED visit (adjusted for $PM_{2.5}$)



B: RR & 95% CI for a 10 µg/m^3 increase in 24 hour $PM_{2.5}$ the day after an ED visit and the same day plus week before (adjusted for ozone)



Chapter 4 - Heterogeneity in the short-term association between fine particulate matter and asthma emergency department visits among children

Abstract

Introduction

Substantial evidence indicates a positive association between short-term exposure to fine particulate matter (PM2.5) and asthma emergency department (ED) visits among children. However, results from single city studies vary potentially due to methodological differences or between city differences in the air pollution mixture, exposure patterns, or underlying population. We observed between-county heterogeneity for this association as well as for other age groups, diseases, and pollutants in our recent multi-city study of respiratory ED visits across all ages. We applied the same methodology to each county and therefore, in this analysis, explored the potential contribution of various county-level covariates to the between-county heterogeneity.

Methods

We previously generated 114 county-specific regression coefficients (β), which represent the association of PM2.5 on asthma ED visits among children less than 19 years in each county. Here, we use a Bayesian hierarchical regression model to pool the county-specific βs from our two pollutant models with various county-level covariates included in the model. We then visualized the change in heterogeneity as measured by a mean estimate of $\tau 2$ and its 95% posterior interval (PI). We also visualized the impact of those covariates on the overall rate ratio (RR) and its 95% credible interval (CI). We evaluated county-level covariates related to county

demographics, socioeconomic status, and health care access as well as state, region, and urbanization.

Results

While each of the 12 covariates included resulted in at least a 25% decrease in heterogeneity, only state resulted in a 95% PI that did not overlap with the 95% PI for $\tau 2$ when no covariate was included in the model. Percent of the population without health insurance and region reduced heterogeneity by 50%. We also observed small differences in the RR across levels of the covariates for a 10 μg/m3 increase in PM2.5 with mostly overlapping 95% CI. Most notable was a decrease in RRs as percent of population without health insurance and the number of urgent care centers per 100,000 population increased. We observed significant, positive associations for eight out of the twelve states analyzed and observed the highest RR in the Northeast and the Midwest.

Conclusion

The strong results by state indicate the importance of a state-level or spatial covariate as a major driver for the between-county heterogeneity. Future analysis should explore the combined effect of these variables with consideration to their correlation and any spatial correlation in both the effect estimates and covariates. Pooling county-specific effect estimates using a meta-regression versus meta-analysis technique provides one method for exploring between-county heterogeneity in the association between air pollution and adverse health effects.

Introduction

Over fifty years of epidemiologic studies provide extensive evidence of the association between short-term exposure to ambient air pollutants and adverse health outcomes [1-7]. These studies are instrumental in setting national air pollution policy by providing evidence to establish causality between specific pollutants and outcomes and to quantify the association for risk assessments. While the depth of published literature is substantial, questions remain regarding the shape of the concentration response (C-R) functions, the potential for health effects at lower concentrations, the effects of multi-pollutant exposures, and the protection of sensitive sub-populations [8, 9]. Further, evidence is limited for some pollutants and health effects, such as the relationship between asthma and fine particulate matter ($PM_{2.5}$) among children. Uncertainty remains in part due to disparate results between individual studies which are largely time-series analyses in a single, geographically defined population such as a city (or county) [7, 10-16]. The heterogeneity could be due to methodological differences between studies, differences in the air pollution mixture or exposure patterns, or differences in the underlying population with regards to factors that modify the effect of air pollution on health [17].

Generally, air pollution time-series analyses are conducted using readily available hospital or vital statistics data and air monitoring data where sufficient information is not available for stratified analyses. An alternative approach is to examine how city variables explain between city risk heterogeneity. While this approach is limited regarding the evaluation of multiple, independent analyses, it is a natural extension of studies which cover multiple cities or counties [18-21]. These studies statistically pool the results of multiple, city (or county) specific time-series analyses conducted using the same methodology. They have more statistical power than

single city studies resulting in effect estimates with relatively greater precision and they avoid the problem of publication bias [22]. Meta-analysis techniques can be used to generate an overall effect estimate and to recover shrunken, and arguably better, estimates of individual city effects [23]. Heterogeneity of the individual city effects is accounted for in the heterogeneity variance of the mean estimate of effect. Exploring the shrunken individual county effects and pooling the effects by different factors using meta-regression techniques can be used to evaluate possible sources of the heterogeneity.

Few studies have evaluated potential sources of heterogeneity in the association between $PM_{2.5}$ and asthma ED visits among children specifically. Evidence more broadly suggests a number of potential individual or community factors that increase individual susceptibility or health care utilization. Effect modification of the association between $PM_{2.5}$ and asthma morbidity among children by neighborhood socioeconomic status (SES) was observed in California and Atlanta but not in New York City [24-26]. Another study in Atlanta found a higher risk for asthma ED visits associated with $PM_{2.5}$ among children who were born prematurely and to African American mothers [27]. Other studies suggest that race, ethnicity, sex, and insurance coverage do not modify the relationship between particulate matter and asthma morbidity [14, 28, 29]. A study in Seoul, Korea observed effect modification between asthma ED visits and coarse particulate matter by patient history of allergic rhinitis or atopic dermatitis [30]. Evidence also suggests that individual or community levels factors may alter exposure to ambient air pollution including use of air conditioning, home ventilation, and activity patterns [31-33]. Additionally, the composition of $PM_{2.5}$ itself can vary between cities [34, 35]. $PM_{2.5}$ is a complex mixture of chemically and physically diverse particles and liquid droplets, which varies spatially in relation

to variation in meteorology, sources, and topography [8]. Studies have shown variation in the association between $PM_{2.5}$ and respiratory morbidity by region of the United States but not by county urbanization [14, 36-38]. A study in California observed effect modification of the association between $PM_{2.5}$ and asthma morbidity among children by residential exposure to traffic pollution [29].

In a previous analysis, we used a two-stage approach to generate nationally relevant effect estimates for the short-term associations between ozone and PM2.5 and respiratory emergency department (ED) visits (chapter 2). First, we conducted county time-series analyses to estimate the short-term associations between ozone and PM2.5 and respiratory ED visits within each county. We evaluated the associations for each pollutant by outcome group: all respiratory outcomes combined (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM]: 460 – 519), acute respiratory infection (ARI) including upper respiratory infections, bronchitis, and bronchiolitis (460 – 466.0), asthma (493), chronic obstructive pulmonary disease (COPD) (491, 492, or 496), and pneumonia (480 – 486). We also evaluated these associations by age group (all ages combined, children 0 to less than 19 years, adults 19 to less than 65 years, and adults 65 years and older). Then, we pooled the county-specific βs by age and outcome group using a two-level Bayesian hierarchical model with non-informative priors to obtain nationally relevant effect estimates. While we found a significant, positive association between asthma and PM2.5 for all age groups, we observed the highest between-county heterogeneity as measured by $\tau 2$ for this association among older adults and among children (Figure 4-1). Because children are not included in other multi-city studies in the United States, we seek to evaluate heterogeneity in the association between PM2.5 and asthma

ED visits among children and which, if any, county level factors contribute to the between-county heterogeneity.

Methods

In stage one of our previous analysis we generated county-specific effect estimates (βs) with standard errors for ozone and $PM_{2.5}$. Our health data included daily counts of ED visits with a primary diagnosis of respiratory disease, based on International Classification of Diseases, 9th Revision (ICD-9) codes 460 – 519, from 894 counties in 17 states. We used ozone and $PM_{2.5}$ data from a Bayesian space-time downscaling (DS) fusion modeling approach, developed by the U.S. Environmental Protection Agency (EPA) and its partners [39]. We modeled an unconstrained distributed lag for lag days 0 through 6 to capture the cumulative association of exposures over the past week using a Poisson log-linear model that accounted for overdispersion. We fit single-pollutant and two-pollutant models controlling for long-term and seasonal trends, same day maximum temperature, same day maximum dew point temperature, previous six-day average maximum temperature, day of the week, and holidays.

The βs from each county-specific model is an estimated effect of air pollution in the county analyzed. From stage one, we have 114 county-specific βs which are exponentiated to generate the rate ratio (RR) indicating the increase in rate of ED visits per unit increase in $PM_{2.5}$ concentration on lag days 0 through 6 (Figure 4-2). We assume β to be a combination of the county-specific unobserved true effect and county-specific random error that is independent across all counties and is normally distributed with a mean of zero and a county-specific

variance. Here, we used a Bayesian hierarchical regression model to pool the county-specific βs from our two pollutant models with various county-level covariates:

$$\hat{\beta}_i = \alpha_0 + \alpha_1 \mathrm{X}_i + \eta_i + \epsilon_i$$

$$\epsilon_i \sim N(0, \hat{\sigma}_i^2)$$

$$\eta_i \sim N(0, \tau^2)$$

Priors:

$\tau^2 \sim Inv - Gamma(a_0, b_0)$, where a_0, b_0 are small (e.g. 0.01)

where,

$\hat{\beta}_i$ = estimated effect for county i from our previous analysis

α_0 = intercept log relative risk

α_1 = change in log relative risk per unit increase X_i

X_i = county-specific covariate that explains the unobserved true log relative risk

η_i = random effect describing the county-specific deviation from the distribution mean

τ^2 = residual between county heterogeneity

ϵ_i = county-specific random deviation that is independent across counties

$\hat{\sigma}_i^2$ = variance for county i from our previous analysis

In using this approach to pool the observed county-specific effect estimates, we assume that (1) the unobserved true effect varies between counties; (2) it's a combination of a intercept log

relative risk, change in log relative risk per unit increase in county-specific covariate, and a random effect; and (3) τ2 is a random variable for which we use non-informative priors. This approach provides us with an unbiased estimate of τ^2 that represents the between-county heterogeneity. To evaluate heterogeneity, we fit models with various county-level variables as X_i (e.g., county poverty level). We evaluated eight continuous variables as both a continuous variable in our model (Table 4-1) and a categorical variable based on tertiles (Table 4-2). We also evaluated four categorical variables (Table 4-3). Analyses were conducted using R statistical software (version 3.4.3; R Foundation for Statistical Computing) and the R-INLA package [40].

Results

Of the twelve covariates analyzed, inclusion of state, percent without health insurance as a continuous variable, and US Census region in the model resulted in a 50% decrease in the between county heterogeneity (Figure 4-3). The remaining seven continuous variables (Table 4-1) when included as a continuous variable in the model and EPA region resulted in at least a 25% decrease in the between county heterogeneity (Figure 4-3). Urbanization and percent of population without health insurance as a categorical variable also resulted in a slight decrease while inclusion of the eight continuous variables as categorical variables (Table 4-2) increased between county heterogeneity. Inclusion of state produced the largest decrease with posterior interval (PI) that do not overlap the PI for the national estimate of τ^2. All other PI for τ^2 overlapped with the PI for the national estimate of τ^2.

We also observed differences in the rate ratios (RR) and 95% credible intervals (CI) for a 10 $\mu g/m^3$ increase in $PM_{2.5}$ between counties as grouped based on these variables. We observed

small differences in the mean estimates for the RRs with overlapping 95% CIs for a 10 $\mu g/m^3$ increase in $PM_{2.5}$ between counties at the 20^{th} percentile and counties at the 80^{th} percentile for most of the eight continuous variables (Figure 4-4). The greatest difference in the mean estimate for RR was for percent without health insurance where we observed a higher RR in counties with fewer percent of the population without health insurance. While the CI for each estimate overlapped, the RR for counties with higher percent of the population without health insurance was consistent with the null. We also observed a difference in the RR for counties grouped by number of urgent care centers per 100,000 population where counties with a greater density of centers also had a RR consistent with the null. In evaluating these variables by tertile, we observed more variation but mostly overlapping CIs (Figure 4-5). The largest variation was again observed by percent uninsured and number of urgent care centers per 100,000 population. The counties with the lowest density of urgent care centers and the lowest percent of population without health insurance had RRs slightly elevated above the overall RR generated from the model without any covariates. The RRs decreased as the percent uninsured and the number of urgent care centers per 100,000 population increased. As either continuous or categorical, we observed slightly higher RRs as the number of primary care physicians per 100,000 population and number of pulmonologist per 100,000 population increased and slightly lower RRs as the number of hospitals per 100,000 population increased. Similarly, the RRs increased as percent of the population identifying as black increased and decreased as percent of the population identifying as Hispanic increased. The RRs showed little variation by percent of population living in poverty.

The greatest variation in the RRs was observed by the categorical variables of state, EPA region, and Census region (Figures 4-5 A, B, and C). This variation follows a similar pattern across all three variables as ordered from the US west coast to east coast. The RR was highest in NY followed by MO and MN and lowest in NH, FL, CA, and SC. We observed significant positive RRs in every state except NH, NC, SC, and UT where the RR was consistent with the null and in FL were the RR was negative. Following the same pattern, we observed significant positive associations in EPA regions 1, 2, 5, 7, and 9. The highest RRs were observed in EPA regions 2 and 7 overlapping with NY, MO, and IA. Similarly, RRs were elevated and significant in the Northeast and Midwest. EPA region 4 and Census region South both contained the same states of FL, NC, and SC. In these regions, the RRs were negative but consistent with the null. By urbanization, RRs were significant and positive in the most urban counties categorized as large central metro counties (Figure 4-5 D). The RRs generally decreased as urbanization decreased, though the results for both large fringe metro counties and the group of medium metro, small metro, and micropolitan counties were consistent with the null.

Discussion

From our original analysis, we had 114 county-specific effect estimates generated based on 1.8 million asthma ED visits among children. Overall, we found a significant, positive association between asthma ED visits among children and PM2.5 and observed between county heterogeneity. In this analysis, we were able to reduce heterogeneity by 50% with the inclusion of either state, percent of population without health insurance, or Census region in our Bayesian hierarchical regression model. While state, Census region, and EPA region reduce the between county heterogeneity, they do not offer a specific explanation for the heterogeneity. Either state-

specific covariates or factors that vary spatially may contribute to the reduction in heterogeneity. These variables may capture the effect of multiple county specific covariates, which could be explored by including more than one covariate in our model.

We observed a reduction in heterogeneity by percent of population without health insurance and a decrease in the RR for the association between $PM_{2.5}$ and asthma as the percent without health insurance increased. As either a continuous or categorical variable, we observed a significant, positive RR in the counties with the lowest percent of population without health insurance while the RR in the counties with the highest percent was consistent with the null. This finding indicate that counties with high percent of population without health insurance do not experience an increase in asthma ED visits among children as $PM_{2.5}$ increases. It is possible that children without health insurance experience an exacerbation of their asthma symptoms but not seek care in an emergency department. Overall, only about 15% of ED visits in general are made by individuals without health insurance [41]. Public insurance including Medicare, Medicaid, or Children's Health Insurance Program is the largest source of payment for ED visits followed by private insurance. Studies have shown increased ED utilization by children with asthma on Medicaid versus private insurance [42, 43]. Medicaid is implemented at a state level and therefore variation in implementation could partially explain the reduction in heterogeneity by state as a covariate. Other county or state variation in health care could contribute to the heterogeneity. We also observed a decrease in the RR as the number of urgent care centers increased. Urgent care centers may be providing care for patients that otherwise would have visited an emergency department. However, urgent care centers tend to be in urban areas with higher income levels and private insurance coverage, which suggest possible interaction between

these factors [44]. Additionally, in California, the risk of asthma ED visits among asthmatic children on Medicaid decreased as number of pulmonologists increased and increased as the number of primary care doctors and hospitals increased [45]. Evidence suggests that a future analysis should explore potential interaction between type of insurance, duration of coverage, poverty, and measures of health care access.

One possible explanation of the regional variation in effect from an air pollution perspective could be the regional variation in $PM_{2.5}$ driven by variation in sources, meteorology, and topography [8]. $PM_{2.5}$ is a mixture of chemically and physically diverse particles and liquid droplets of anions, cation, trace elements, total carbon, gaseous pollutants, and biologic components. While motor vehicle traffic is a large and ubiquitous source of primary $PM_{2.5}$, other sources are more geographically concentrated [35]. Residual oil combustion is a prominent source in northeast cities and cities with major seaports while coal combustion is prominent in the mid-Atlantic and biomass burning in the northwest [35]. Speciated $PM_{2.5}$ data shows higher concentrations of sulfate in the east and higher concentrations of nitrate, organic carbon, and elemental carbon in the west [34]. Other multi-city studies investigating respiratory hospital admissions among person 65 and older found little or no heterogeneity in risk but did find variation in the associations with individual PM components, specifically positive associations with organic carbon and elemental carbon [20, 46, 47]. In Peng et al, sulfate resulted in the second highest percent increase in respiratory emergency hospital admissions among persons 65 and older though the effect was not significant. Another multi-city study found that sulfur, but not other species including organic carbon and elemental carbon, was associated with respiratory related mortality [21]. The applicability of results for respiratory hospital admissions among

persons 65 and older and respiratory mortality to asthma ED visits among children is limited. Further, speciated $PM_{2.5}$ data are temporally and spatially sparse. However, these studies suggest that additional analysis with speciated $PM_{2.5}$ data may be warranted.

Limitations

In this analysis, we assumed that the county effect estimates were independent and identically distributed. These factors could be further explored assuming a spatial relationship between the county effect estimates or otherwise adjusting for region. Additionally, we assumed that the relationship between each factor and the RR was the same in every county. It may be that the importance of each factor varies by region or state and may explain some within region or state heterogeneity. Lastly, there are other factors that were not considered in this analysis largely due to the lack of data. For example, a study of respiratory mortality and $PM_{2.5}$ in 75 cities found higher effects in areas where people smoked more or had two or more drinks a day [21]. The portion of outdoor PM infiltrating indoors is influenced by building ventilation and use of air conditioning, which vary both regionally and seasonally [31, 33, 48]. Future analyses could evaluate surrogates for these factors or evaluate their effects for a subset of counties where necessary data are available. Future analyses could also evaluate the contribution of multiple factors simultaneously and potential interaction with consideration to correlation between factors.

Conclusion

Pooling county-specific effect estimates using a meta-regression versus meta-analysis technique, as implemented here, provides one method for exploring between county heterogeneity in the association between air pollution and adverse health effects. This analysis explores sources of the heterogeneity for the association between $PM_{2.5}$ and asthma among children but can be applied to additional pollutants, outcomes, and age groups. In this analysis, the spatial variables of US Census region and state largely accounted for the between county heterogeneity in the association. Across all three variables, we observed effect estimates of higher magnitude corresponding to the Northeast and Midwest compared to the West and to the South, where the effect estimate was consistent with the null. Additionally, the percent of population uninsured partially explained the heterogeneity where counties with higher percent uninsured had lower RR than counties with lower percent uninsured. While the other variables analyzed only slightly reduced heterogeneity, the magnitude of the effect estimates did vary by measures of minority population, socioeconomic status, and health care access. Most notable was a decline in the effect estimate as the number of urgent care centers increased. The combined effect of these variables on the heterogeneity should be explored by including multiple covariates in the model with consideration to their correlation and any spatial correlation in both the effect estimates and covariates. Further analysis is needed to understand the reasons for the heterogeneity in the effect estimates.

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Table 4-1: Description of covariates included in analysis

Covariate	Data Source	Processing	20th%	Median	80th%
Percent of population living in poverty	Census Bureau: Model-based Small Area Income & Poverty Estimates (SAIPE) for Counties and State.	Mean percent for years of health data analyzed for each county	9.7	13.5	17.1
Percent of population without health insurance	Census Bureau: Small Area Health Insurance Estimates (SAHIE).	Mean percent for years of health data analyzed for each county	11.2	16.2	20.3
Percent of population identifying as black or African American	CDC NCHS bridged-race Vintage 2016 postcensal estimates by single-year age group	Mean percent for years of health data analyzed for each county	4.2	10.5	21.3
Percent of population identifying as Hispanic	CDC NCHS bridged-race Vintage 2016 postcensal estimates by single-year age group	Mean percent for years of health data analyzed for each county	4.2	10.1	25.8
Number of primary care physicians per 100,000 population	HHS HRSA Area Health Resources File (AHRF) 2016-2017 Release. American Medical Association Physician Masterfiles	Sum doctors for "Phys,Primary Care, Hsp Resident 2010" (f1467610) and "Phys,Primary Care, Patient Care 2010" (f1467510); Calculatenumber per 10,000 population	538	831	1108
Number of pulmonologists per 100,000 population	HHS HRSA Area Health Resources File (AHRF) 2016-2017 Release. American Medical Association Physician Masterfiles	Select "Pulmonary Dis, Total Patn Care 2010" (f1111510); Calculatenumber per 10,000 population	15	31	45
Number of hospitals per 100,000 population	Homeland Infrastructure Foundation – Level Data. Published: 2017-05-19	Excluded hospitals that were limited to cancer, psychiatric, addiction, substance abuse, maternity, orthopedic, or rehabilitation; Calculated number per 10,000 population	9	14	19
Number of urgent care centers per 100,000 population	Homeland Infrastructure Foundation – Level Data. Published: 2009-07-17	Calculated number per 10,000 population	7	16	26

Table 4-2: Rate Ratio (RR) & 95% Credible Interval (CI) for asthma ED visits among children and 10 ug/m^3 increase in $PM_{2.5}$ for all counties analyzed in counties at the 20th percentile versus counties at the 80th percentile for each covariate

	RR (CI)		
Covariate	**20th%**	**80th%**	**Tau^2 (PI)***
Percent of population living in poverty	1.044 (1.00, 1.088)	1.042 (0.998, 1.086)	0.023 (0.013, 0.043)
Percent of population without health insurance	1.079 (1.039, 1.121)	1.019 (0.98, 1.058)	0.012 (0.006, 0.026)
Percent of population identifying as black or African American	1.032 (1.011, 1.054)	1.05 (1.028, 1.072)	0.021 (0.011, 0.040)
Percent of population identifying as Hispanic	1.06 (1.037, 1.083)	1.036 (1.013, 1.058)	0.020 (0.010, 0.038)
Number of primary care physicians per 100,000 population	1.024 (0.989, 1.06)	1.052 (1.016, 1.089)	0.020 (0.010, 0.038)
Number of pulmonologists per 100,000 population	1.029 (1.005, 1.054)	1.047 (1.023, 1.072)	0.021 (0.012, 0.040)
Number of hospitals per 100,000 population	1.048 (1.011, 1.085)	1.037 (1.001, 1.074)	0.023 (0.013, 0.042)
Number of urgent care centers per 100,000 population	1.064 (1.039, 1.09)	1.017 (0.993, 1.042)	0.018 (0.009, 0.035)
	RR (CI)		**Tau2 (PI)***
National	1.042 (1.057, 1.027)		0.033 (0.022, 0.054)

*** Tau-squared and its Posterior Interval (PI) is scaled by 1000 for visualization**

Table 4-3: Rate Ratio (RR) & 95% Credible Interval (CI) for asthma ED visits among children and 10 ug/m^3 increase in $PM_{2.5}$ in counties categorized has low (intercept), medium, and high for each continuous variable

Covariate	Tertile	RR (CI)	Tau^2 (PI)**
Percent of population living in poverty	[4.79,11.5]*	1.048 (1.022, 1.074)	0.039 (0.026, 0.062)
	(11.5,15.2]	1.040 (0.979, 1.104)	
	(15.2,29.1]	1.039 (0.979, 1.102)	
Percent of population without health insurance	[5.09,13.2]*	1.077 (1.053, 1.10)	0.030 (0.020, 0.047)
	(13.2,18.5]	1.071 (1.016, 1.128)	
	(18.5,32.6]	0.997 (0.947, 1.048)	
Percent of population identifying as black or African American	[0.776,6.32]*	1.028 (1.003, 1.054)	0.039 (0.026, 0.061)
	(6.32,14.2]	1.051 (0.990, 1.115)	
	(14.2,62.5]	1.047 (0.986, 1.111)	
Percent of population identifying as Hispanic	[1.42,6.35]*	1.065 (1.036, 1.094)	0.038 (0.026, 0.060)
	(6.35,18.4]	1.040 (0.975, 1.109)	
	(18.4,62.8]	1.031 (0.969, 1.097)	
Number of primary care physicians per 100,000 population	[237,712]*	1.020 (0.996, 1.046)	0.037 (0.025, 0.058)
	(712,973]	1.035 (0.975, 1.097)	
	(973,2290]	1.070 (1.009, 1.133)	
Number of pulmonologists per 100,000 population	[0,22.4]*	1.023 (0.998, 1.048)	0.038 (0.026, 0.060)
	(22.4,37.4]	1.042 (0.981, 1.106)	
	(37.4,143]	1.060 (1.000, 1.124)	
Number of hospitals per 100,000 population	[0,10.8]	1.052 (1.026, 1.078)	0.039 (0.026, 0.061)
	(10.8,16]	1.034 (0.975, 1.096)	
	(16,36.5]	1.042 (0.981, 1.107)	
Number of urgent care centers per 100,000 population	[0,10.2]*	1.075 (1.052, 1.098)	0.035 (0.024, 0.055)
	(10.2,21.8]	1.032 (0.978, 1.088)	
	(21.8,48.2]	1.014 (0.959, 1.071)	
National		1.042 (1.027, 1.057)	0.033 (0.022, 0.054)

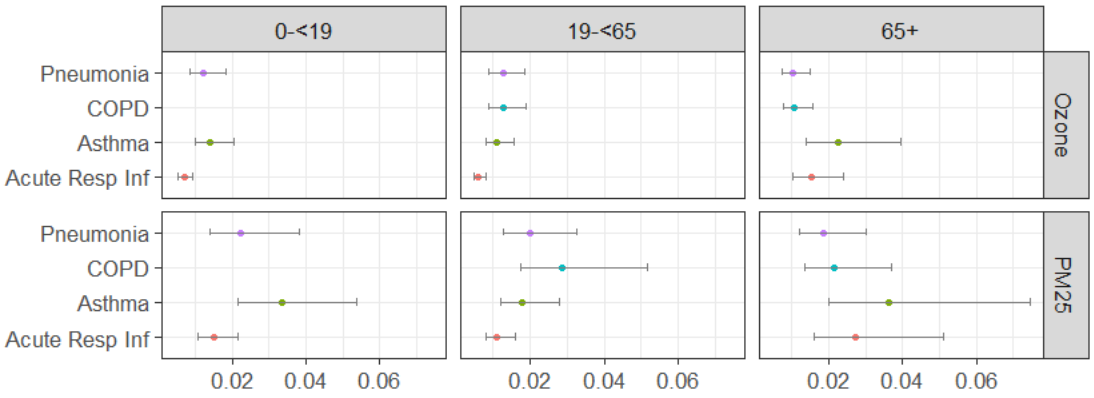
*** Intercept ** Tau-squared and its Posterior Interval (PI) is scaled by 1000 for visualization**

Table 4-4: Rate Ratio (RR) & 95% Credible Interval (CI) for asthma ED visits among children and 10 ug/m^3 increase in $PM_{2.5}$ for counties categorized by each covariate

Covariate	States	Counties	RR (CI)	Tau^2 (PI)**
National	12	114	1.042 (1.027, 1.057)	0.033 (0.022, 0.054)
State	**States**	**Counties**		0.006 (0.003, 0.014)
California (CA)*	1	27	1.013 (1.001, 1.025)	
Florida (FL)	1	15	0.946 (0.906, 0.987)	
Illinois (IL)	1	7	1.055 (1.005, 1.107)	
Iowa (IA)	1	4	1.079 (1.003, 1.16)	
Massachusetts (MA)	1	8	1.055 (1.011, 1.101)	
Minnesota (MN)	1	3	1.095 (1.013, 1.183)	
Missouri (MO)	1	9	1.113 (1.07, 1.157)	
New Hampshire (NH)	1	2	0.926 (0.807, 1.062)	
New York (NY)	1	17	1.128 (1.092, 1.166)	
North Carolina (NC)	1	4	1.043 (0.953, 1.141)	
South Carolina (SC)	1	12	1.014 (0.961, 1.070)	
Utah (UT)	1	6	1.038 (0.995, 1.082)	
EPA Region	**States**	**Counties**		0.018 (0.011, 0.030)
1 (NH, ME)	2	10	1.048 (1.004, 1.094)	
2 (NY)	1	17	1.128 (1.091, 1.167)	
3	0	0	na	
4 (FL, NC, SC)	3	31	0.974 (0.938, 1.012)	
5 (IL, MN)	2	10	1.064 (1.016, 1.114)	
6	0	0	na	
7 (IA, MO)	2	13	1.100 (1.066, 1.152)	
8 (UT)	1	6	1.038 (0.994, 1.084)	
9 (CA)*	1	27	1.013 (1.001, 1.026)	
10	0	0	na	
Census Region	**States**	**Counties**		0.016 (0.010, 0.029)
Midwest (IL, IA, MN, MO)	4	23	1.092 (1.049, 1.137)	
Northeast (MA, NH, NY)	3	27	1.103 (1.061, 1.144)	
South (FL, NC, SC)	3	31	0.975 (0.935, 1.017)	
West (CA, UT)*	2	33	1.018 (1.004, 1.033)	
Urbanization Category	**States**	**Counties**		0.026 (0.016, 0.046)
Large Central Metro*	9	29	1.051 (1.026, 1.076)	
Large Fringe Metro	10	35	1.051 (0.989, 1.115)	
Medium Metro	11	40	1.028 (0.971, 1.088)	
Small Metro	5	9		
Micropolitan or Noncore	1	1		

*** Intercept ** Tau-squared and its Posterior Interval (PI) is scaled by 1000 for visualization**

Figure 4-1: Heterogeneity (Tau^2 and 95% PI) in the association between ozone and $PM_{2.5}$ and respiratory ED visits by outcome and age group



*** Tau-squared and its Posterior Interval (PI) is scaled by 1000 for visualization**

Figure 4-2: Pooled and county-specific Rate Ratio (RR) & 95% Credible Interval (CI) for asthma ED visits among children and 10 ug/m^3 increase in $PM_{2.5}$

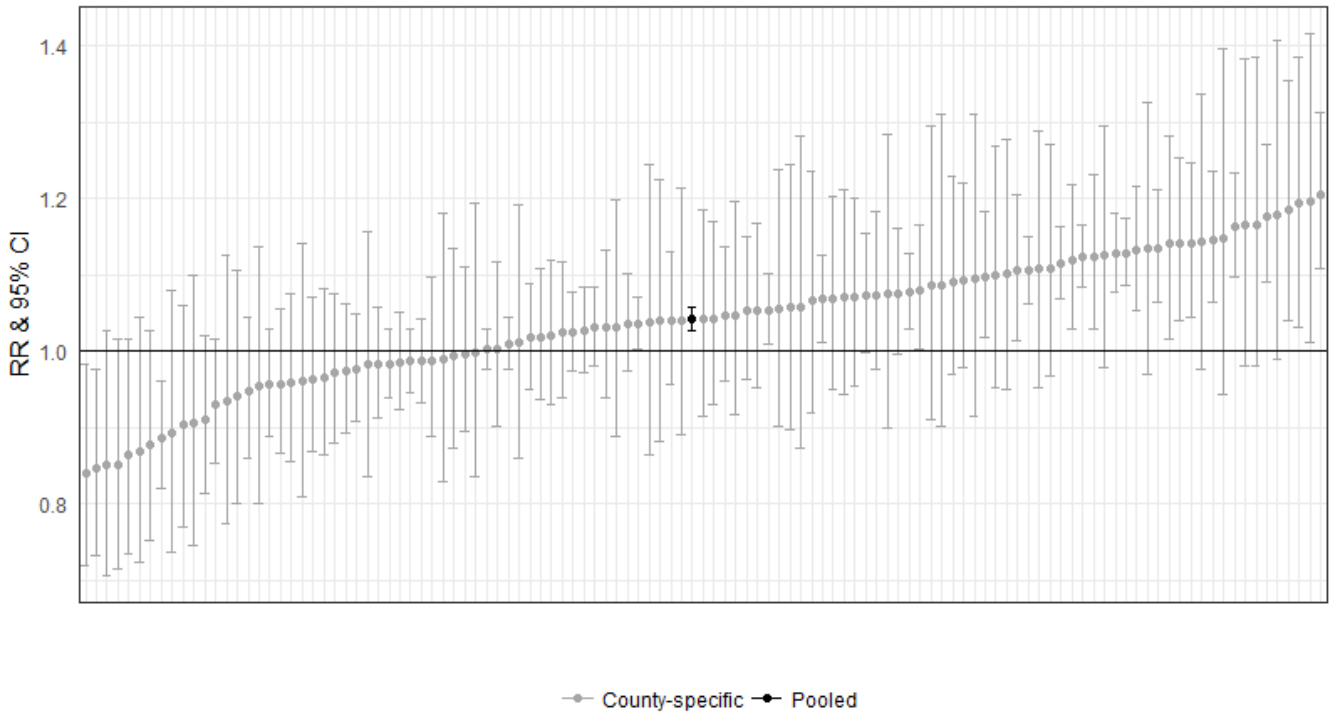
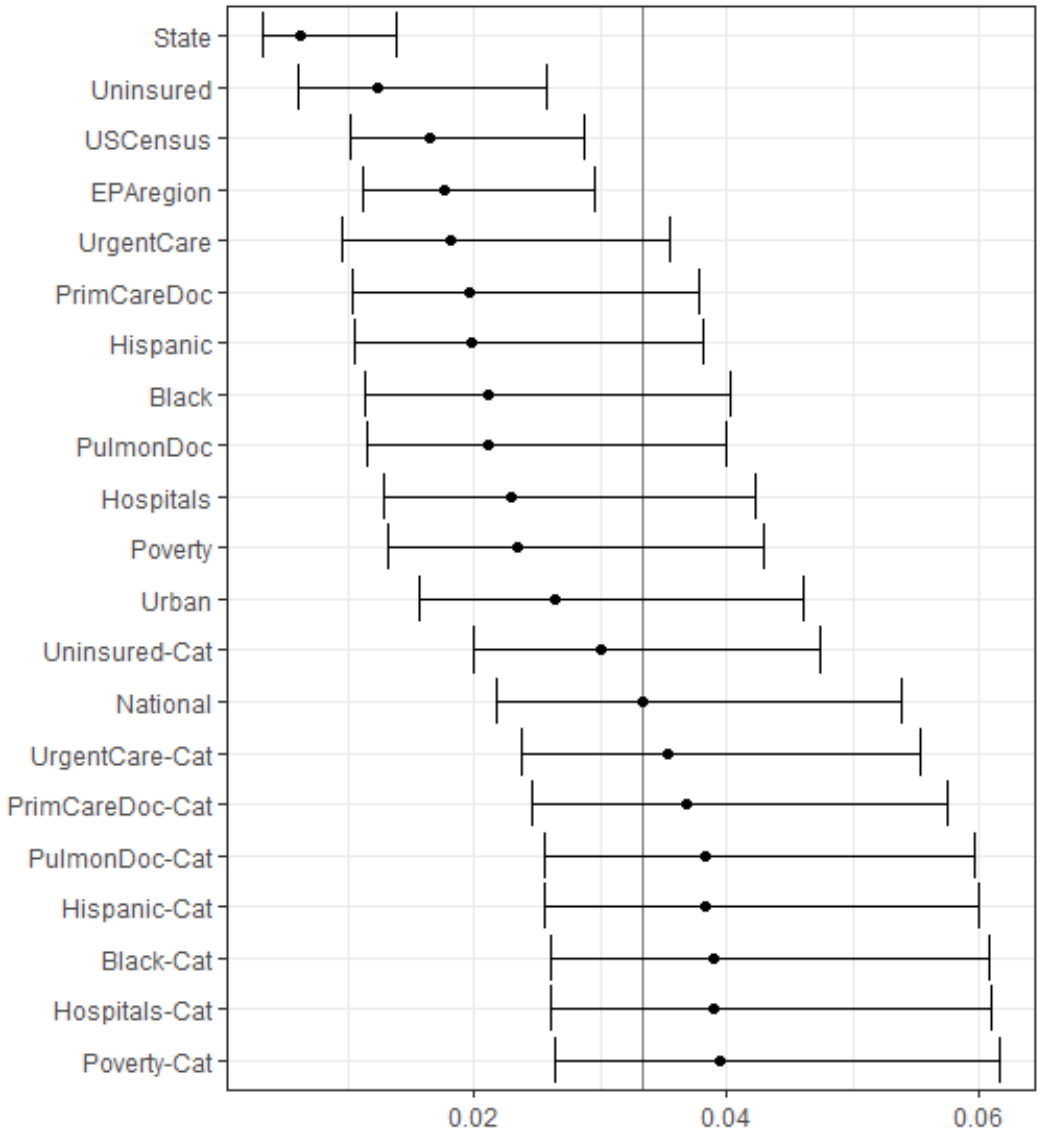


Figure 4-3 Tau2 and 95% Posterior Interval by asthma ED visits among children and $PM_{2.5}$ for overall model (National) and models containing each covariate



*** Tau-squared and its Posterior Interval (PI) is scaled by 1000 for visualization**

Figure 4-4: Rate Ratio (RR) & 95% Credible Interval (CI) for asthma ED visits among children and 10 ug/m^3 increase in $PM_{2.5}$ for all counties analyzed (National) and in counties at the 20th percentile versus counties at the 80th percentile for each covariate

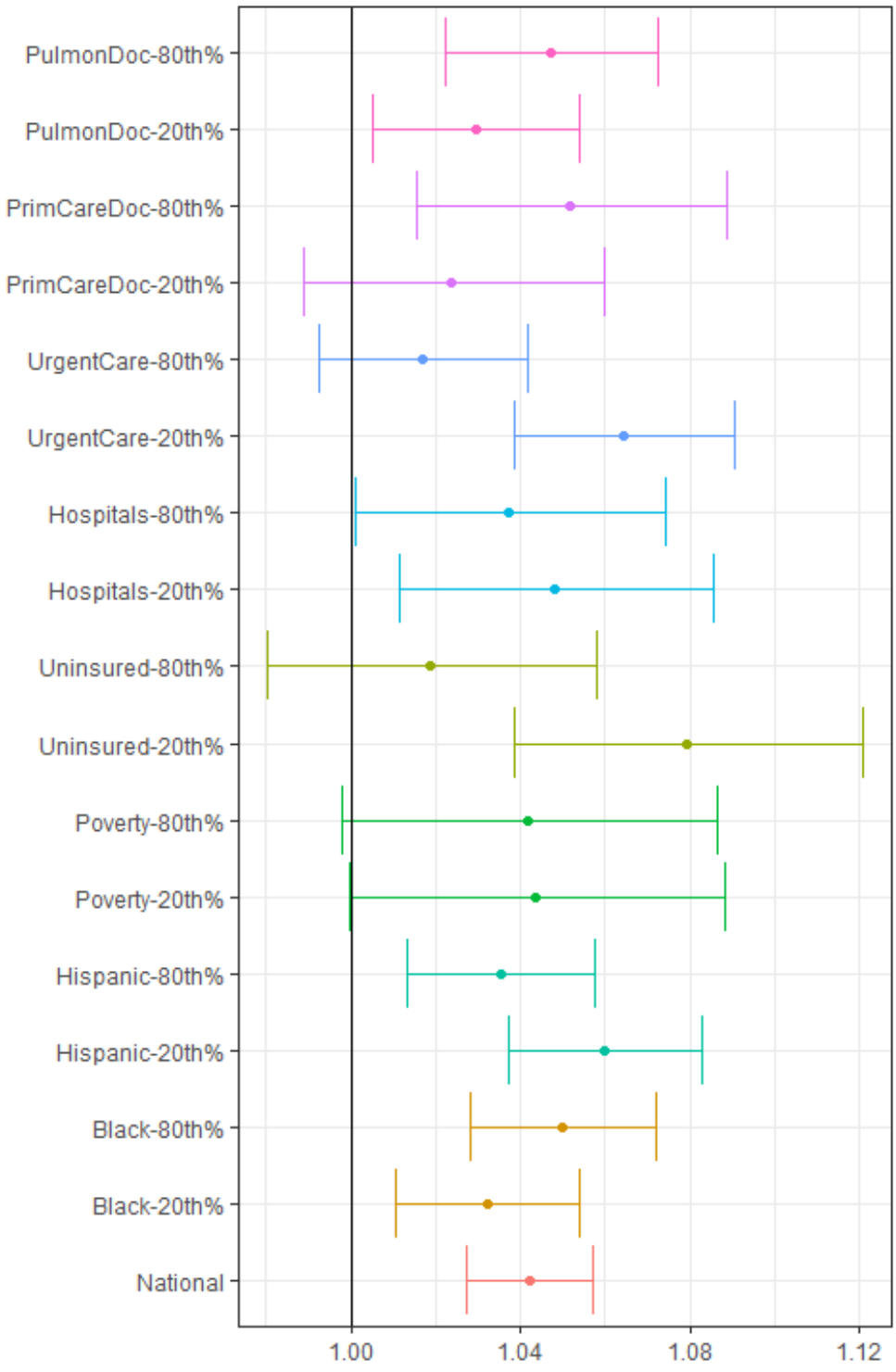


Figure 4-5: Rate Ratio (RR) & 95% Credible Interval (CI) for asthma ED visits among children and 10 ug/m^3 increase in $PM_{2.5}$ for all counties analyzed (National) and in PM2.5 in counties categorized has low (intercept), medium, and high for each continuous variable

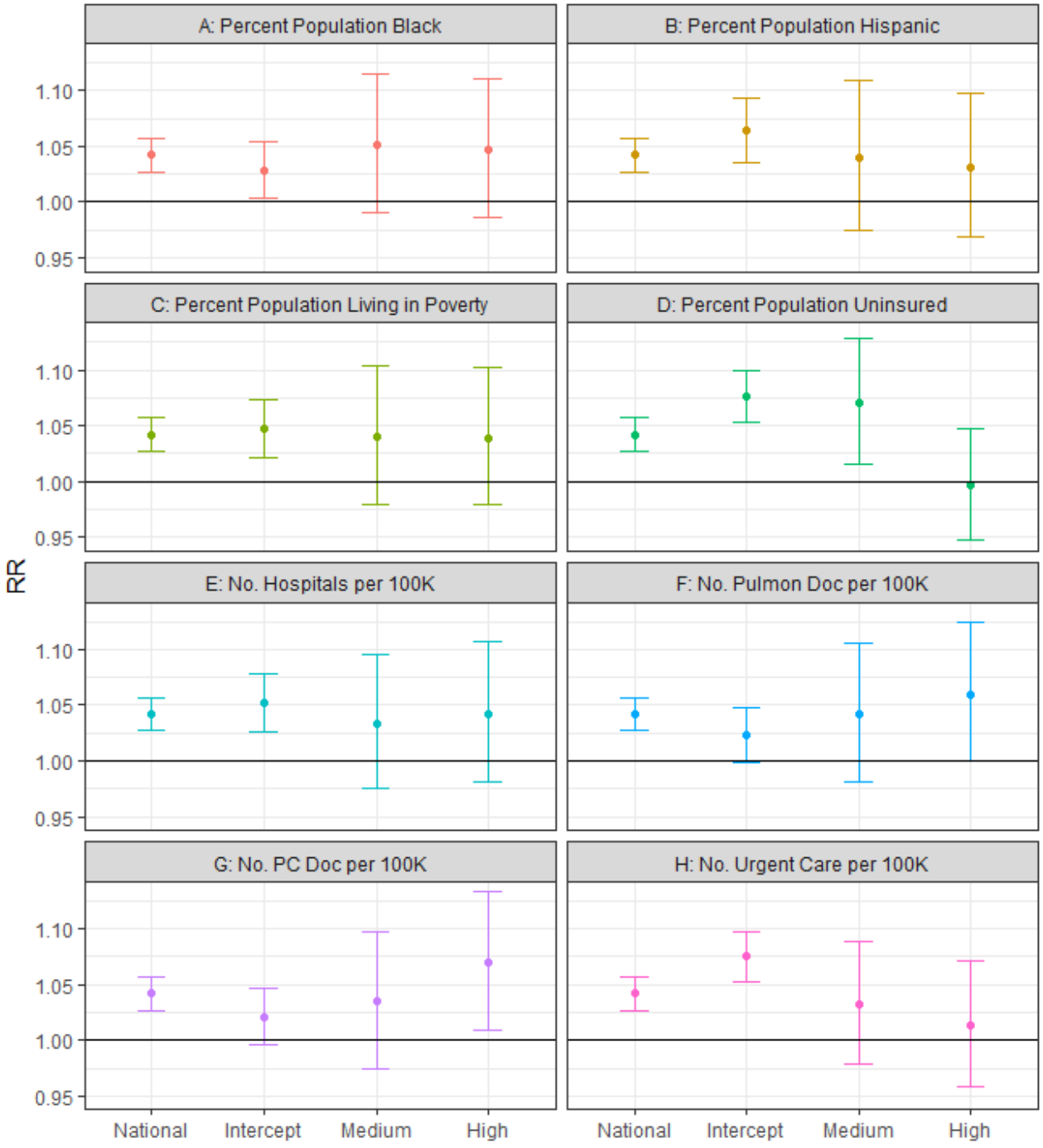
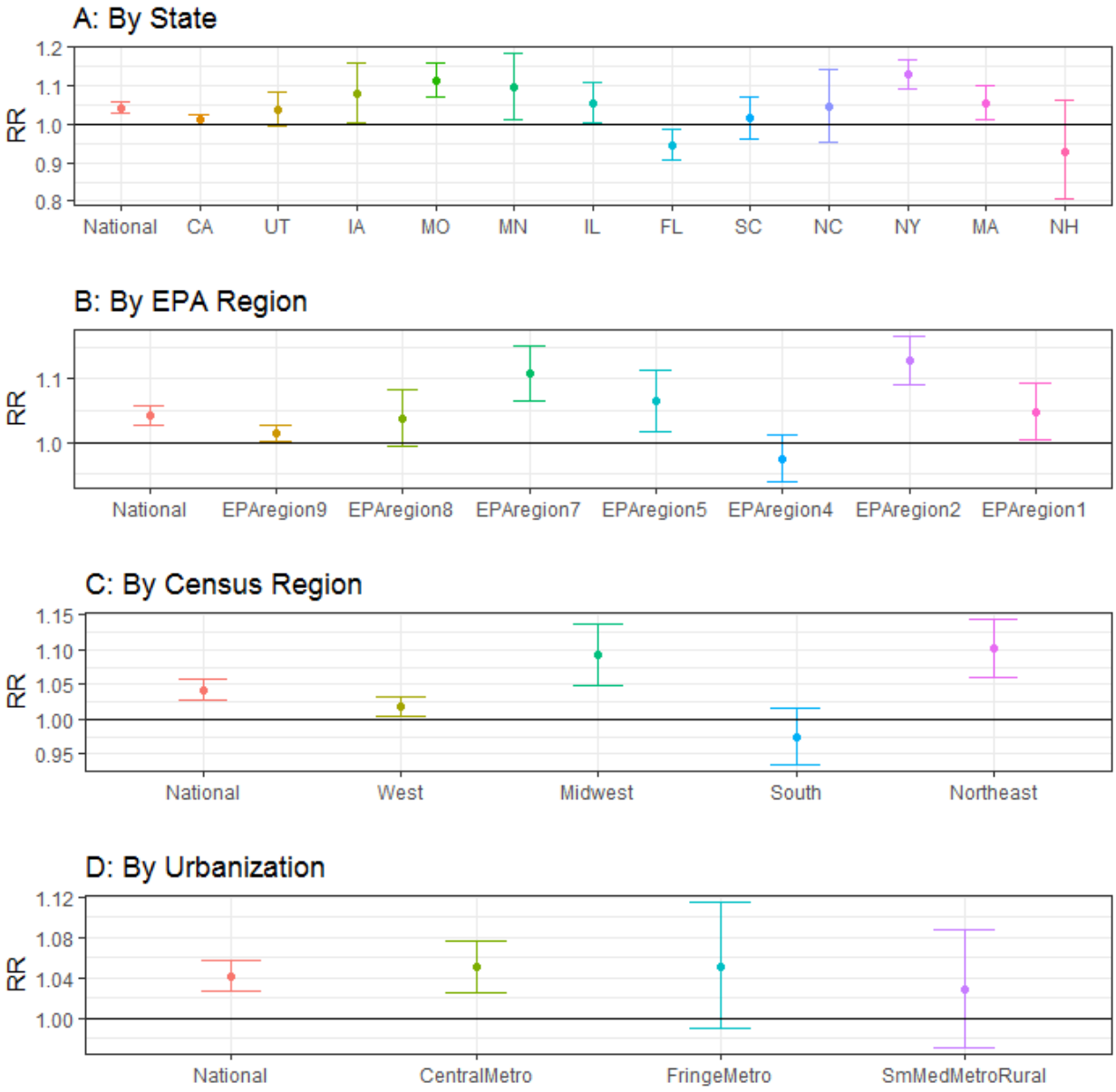


Figure 4-6: Rate Ratio (RR) & 95% Credible Interval (CI) for asthma ED visits among children and 10 ug/m^3 increase in $PM_{2.5}$ for counties analyzed (National) and counties categorized by each covariate



*Figures A, B, and C are orientated west to east from left to right.

Chapter 5 - Conclusion

In this work, we address an important gap in the epidemiologic evidence regarding the short-term association between air pollution and respiratory morbidity among persons younger than 65. This gap existed because of the lack of a central, readily accessible database with the necessary data elements for respiratory ED visits among people younger than 65. Leveraging the infrastructure and partnerships of CDC's Tracking Program, we were able to obtain daily, county level ED data from 17 states. The inclusion of specific date of the health event, a necessary element for air pollution research on acute health effects, in the data request increases the sensitivity of the dataset. In working with the Tracking Program's partners, we were able to construct a data request that provided the data necessary for our analyses and minimized any data sharing concerns from most states. Further, daily, county level data from 17 states (902 counties) amounted to 18 million rows of data representing 48.3 million respiratory ED visits. The Tracking Program infrastructure provided us a systematic and manageable approach for data extraction from the original database, transportation to CDC, validation, and storage. Lastly, the computing time for conducting time-series analyses on this volume of data was reduced from over 150 days on a single computer to less than five using CDC's high performance computing Linux cluster. Analyses such as this will be easier with continued computational advancements and the adoption of electronic health records, provided that data sharing issues are also addressed.

Diseases of the respiratory system are the primary diagnosis for approximately 10% (over 14 million) of all ED visits annually. The vast majority of these ED visits are for persons under 65

with the highest rate among children less than 19. By outcome, rates for ARI and asthma were highest among children while rates for COPD and pneumonia were highest among adults 65 and older. The rate of respiratory ED visits varied considerably between counties and appears to be driven in part by state and region. We observed minor variation in county rates by county urbanization, minority population, poverty, and measures of health care access. However, no clear explanation of this variation was identified. Further analysis is needed to identify statistically significant spatial trends and to better elucidate the reason for such variation in county rates.

We found significant, positive associations between both ozone and $PM_{2.5}$ with respiratory ED visits among all ages combined. Our results support the EPA's causal determinations and highlight important variation in magnitude across age groups, outcomes, and pollutants. $PM_{2.5}$ was associated with asthma among all age groups, ARI among children and adults 65 and older, and pneumonia among adults 65 and older. Ozone was associated with asthma among adults 65 and older and children, ARI and chronic obstructive pulmonary disease (COPD) among adults under 65 and adults 65 and older, and pneumonia among all age groups. Our analysis is the first nationally relevant, multi-city study to include respiratory morbidity across all age groups. Our results suggest that multi-city studies of populations over 65 may not be a good proxy of acute respiratory impacts on younger age groups, and that reliance on such studies could underestimate population respiratory health impacts of PM2.5 or ozone that were stronger in our study for younger age groups.

We observed between county heterogeneity in our county specific effect estimates with greater heterogeneity in results for children versus adults, $PM_{2.5}$ versus ozone, and asthma versus the other outcomes. The highest heterogeneity was observed for the association between $PM_{2.5}$ and asthma among children. This heterogeneity was largely explained by the spatial variables of US Census region, EPA region, and state. Further analysis is needed to understand what factors are driving this regional heterogeneity in the association between asthma ED visits among children and $PM_{2.5}$. While the other variables analyzed did not explain much heterogeneity, we did observe variation in the effect estimates by measures of minority population, socioeconomic status, and health care access. The effect estimates decreased as the percent of population uninsured and the number of urgent care centers increased.

Establishing effective air pollution policy and control requires an understanding of the impact of air pollution across all age groups and especially among sensitive subpopulations. This work begins to address an important gap in air pollution epidemiology for respiratory morbidity among persons under 65.