Environmental factors and immune related outcomes in the United States

HARVARD
Kenneth C. Griffin

GRADUATE SCHOOL
OF ARTS AND SCIENCES

THESIS ACCEPTANCE CERTIFICATE

The undersigned, appointed by the
Department of Population Health Sciences,
have examined a dissertation, entitled,

"Environmental Factors and Immune-related Outcomes in the United States"

presented by

YIJING FENG

candidate for the degree of Doctor of Philosophy
and hereby certify that it is worthy of acceptance.

Dr. Joel D. Schwartz, Ph.D., Committee Chair, Harvard T.H. Chan School of Public Health

Brent A Coull
Brent A Coull (Dec 4, 2025 09:44:54 EST)

Dr. Brent A. Coull, Ph.D., Harvard T.H. Chan School of Public Health

Murray A. Mittleman
Murray A. Mittleman (Dec 4, 2025 14:32:43 EST)

Dr. Murray A. Mittleman, D.Ec., Dr.P.H., M.D., Harvard T.H. Chan School of Public Health

Date: 21 November 2025

Environmental factors and immune related outcomes in the United States

A dissertation presented by

Yijing Feng

to

The Department of Population Health Sciences

The Graduate School of Arts and Sciences

in partial fulfillment of the requirements for the degree of

Doctor of Philosophy in the subject of

Epidemiology

Harvard University

Cambridge, Massachusetts

November, 2025

Environmental factors and immune related outcomes in the United States

ABSTRACT

Environmental factors have been found to be important risk factors of human health. Previous studies suggested that PM2.5 could perturb the immune system. PM2.5 is complex mixture of multiple constituents, and each of these constituents could have varying impact on health. However, most existing studies treated PM2.5 as a single exposure. How each of the constituents affects the immune system is less clear. Non-optimal temperature is another environmental factor that could potentially impair the immune function of human body. While the effects of mean temperature have been extensively studied, the influence of temperature variability—particularly over longer time periods—remains insufficiently explored.

In this dissertation, we attempted to address these gaps. We began by studying the association between long-term exposure to PM2.5, PM2.5 constituents, source-specific PM2.5 and hospital admissions from non-respiratory infections among the Medicare beneficiaries in the US between 2000-2016. We found that PM2.5 was associated with increased risk of hospital admissions from total non-respiratory infections and its subtypes including intestinal infections, urinary tract infections and septicemia. Sulfate, nickel and copper contributed the largest weights in the association between PM2.5 and non-respiratory infections. Anthropogenic sources of PM2.5 were found to have the largest impact on the exposure-outcome associations.

In chapter II, we studied the association between seasonal temperature variability, seasonal temperature and hospital admissions from infections using an adapted difference-in-difference analysis among the Medicare beneficiaries. We found that increased temperature variability in both warm and cold season, higher mean temperature in warm season and lower mean temperature in cold season were associated with increased admissions from infections.

In the last chapter, we shifted our focus from the older population to an immunocompromised group—kidney transplant recipients. Here we investigated the association between exposure to PM2.5 constituents prior to kidney transplant (KT) and post-KT outcomes including acute rejection, delayed-graft function, graft failure and mortality. We found that sulfate contributed the larges weight in the association between the PM2.5 mixture and long-term post-KT outcomes (graft failure and mortality) while lead, organic carbon and nickel contributed the largest weights in the short-term outcomes (delayed graft function and acute rejection).

This dissertation contributes to the growing body of evidence on the impact of environmental exposures on the immune system. It further demonstrates that the health effects of PM2.5 can vary depending on its chemical constituents and specific sources. Overall, this work provides important insights into the broader health implications of air pollution and climate change on human populations.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ACKNOWLEDGEMENTS

I would like to express my deepest gratitude to my advisor, Professor Joel Schwartz, for his exceptional mentorship and unwavering support throughout my research. His guidance, encouragement, and insightful feedback have been invaluable in helping me navigate both scientific challenges and broader issues in my research career.

I am also sincerely grateful to my committee members, Dr. Murray Mittleman and Dr. Brent Coull, for their professional guidance, constructive suggestions, and generous support of my work. Their expertise and thoughtful feedback have greatly strengthened this thesis.

I would also like to thank my fellow lab mates, Mahdieh Danesh Yazdi, Yaguang Wei, Bryan Vu, Edgar Castro, Tingfan Jin, Xinye Qiu, Adjani Peralta, Alexandra Shtein, Anna Kosheleva and James Healy for creating such a supportive, collaborative, and stimulating environment. Their help, encouragement, and camaraderie have made this journey both productive and enjoyable.

I would like to give a special thank to Shuxin Dong, who supported me through the worst moment during the past few years. I would also like to thank the friends I met at tennis courts, Yingshan Zhao, Ziying Cao, Hanzhao Wu and Ganxin Lei, who had made my life in Boston really enjoyable.

I also want to thank my husband, Wuicheung Li for supporting me during the past seven years. And of course, our 11-month-old Adrian, who has brought us so much joy.

Finally, and most importantly, I would like to thank my parent for providing the unconditional love and support during the past 32 years. I would not have been able to get here without the

INTRODUCTION

The health of populations worldwide is profoundly and extensively influenced by a diverse range of environmental risk factors. These factors extend far beyond simple physical surroundings, encompassing exposure to pollutants like air and water contamination, chemical hazards, and the rapidly escalating impacts of climate change. Collectively, these environmental determinants are linked to a significant portion of the global disease burden, contributing to both noncommunicable diseases—including respiratory illnesses, cardiovascular disease, and cancers—as well as infectious diseases. For effective policymaking and significant public health improvement, it is essential to fully grasp the complex link between environmental factors and health.

Fine particulate matter (PM2.5) exposure is a well-recognized risk factor for health and has been found to be associated with multiple adverse health outcomes, and is potentially modifiable by change in policies and personal behaviors(1). It's estimated that PM2.5 had led to more than 4.2 million annual deaths and ranked the fifth among the global risk factors(2). Previous studies suggested that PM2.5 could lead to harm in multiple system in human body. PM2.5 exposure was associated with increased risk of respiratory diseases, cardiovascular diseases, dementia, etc.(3-5). Animal experiments indicate that reactive oxygen species (such as hydrogen peroxide, superoxide, etc.), which have established relevance in the pathogenesis of cardiovascular disease and aging,(6) are affected by particles,(7-10) which represent one pathway for their cardiovascular and lung effects. Particles, and particularly the metals on particles, have also been associated with an increased production of 8-OHdG.(11-17) Sigaud and coworkers and reported that exposure of animals to particles reduced resistance to bacterial pneumonia.(18) Consistent with this, concentrated ambient particle exposure reduced the ability of macrophages in the lung to kill streptococcal bacteria.(19) Despite the adverse health impact, having a more stringent standard for air pollution requires the consideration of both health benefit and economic costs.

Most of the previous study treated PM2.5 as a single exposure to evaluate the effect. However, PM2.5 is a complex mixture of different constituents which has diameters <2.5μm. Each of these constituents could potentially have different impacts on health(20). Identifying the specific constituents which cause the most harm could provide information for further experimental studies and elucidate the mechanism behind the adverse effect of PM2.5. Moreover, different standards and pollution control strategy target different components and sources. PM2.5 come from multiple sources including traffic, coal burning, fuel oil, dust and biomass burning, etc. PM2.5 from each of these sources include different constituents and potentially leads to different health impacts(20). Results from studies focusing on particulate constituents and source-specific PM2.5 could inform air pollution reduction strategies which brings large health benefit while not spending too much on reducing the emissions from irrelevant sources.

Inflammation and oxidative stress are leading hypotheses for the mode of action for PM2.5. and may studies have examined the association of PM2.5 with biomarkers of inflammation and immune activation(21). However, studies of immunological responses have tended to focus on respiratory responses such as Asthma or respiratory infections. The impact of PM2.5 on other immune responses in underdeveloped. Furthering our understanding of the full health impacts of PM2.5 can provide more evidence for policy makers and potentially advocate for lower standards for air pollution and thus could potentially protect the health of the population.

Temperature is another environmental factor that is closely linked to human health. A previous multi-country study estimated that 7.7% of the total mortality were attributable to non-optimum temperature(22). Extreme temperatures are also known to be an important risk factor for multiple health outcomes including cardiovascular diseases and mental disorders(23, 24).
Temperature also affects immune system, both innate and adapted immunity. Exposure to heat could impair the function of immune cells and increase the production of signaling molecules that leads to

inflammations(25). Temperature fluctuations can impact adaptive immune response in multiple aspects including immune cell mobilization, antigen processing and presentation, lymphocyte activation, as well as the function of B and T cells(26). Temperature also affects epithelial barriers. Changes in temperature can modify epithelial composition, weaken epithelial integrity, and trigger both microbial imbalance and immune dysregulation(26). Both extreme high and low temperature are associated with inflammations (27-29) Previous studies suggested that mean temperature was associated with risk of infections(30). However, less is known about whether temperature variability also affects the risk of infections, especially variability across longer periods.

Chronic diseases have accounted for the majority of the health burden in recent years; however, infectious diseases continue to pose a significant threat to human health. In 2021, upper respiratory infection caused 8.16 million disability-adjusted life years globally(31). in 2015, it was estimated that the healthcare expenditure for intestinal infection was $6.4 billion in the United States(32). There were around 10.5 million office visits for urinary tract infection, causing $3.5 billion in societal costs per year(33, 34). The cost of sepsis management ranks the highest among all of the disease in the US hospitals. In 2013, it was estimated that sepsis accounted for more than $24 million in hospital expenses(35). More importantly, sepsis is a leading cause of hospital death. Previous experimental and epidemiological studies have demonstrated that PM2.5 has potential immunotoxicity and increase the risk of infection(36-38). Many studies have found a positive association between PM2.5 exposure and risk for respiratory infections(39-41). However, fewer studies have investigated the effect of PM2.5 on non-respiratory infections with conflicting results(42-44). Due to the lack of consistent evidence, further study is required in this field.

Kidney transplant is the most performed solid organ transplantation. The number of kidney transplants performed in the US has been steadily increasing during the past years. In 2022, 26,310 kidney transplants were performed in the US(45). With 5-year survival of over 86%, there are large number of kidney transplant recipients in the US(45). In 2018, it was estimated that graft failure has led to an

incremental cost of $1.38 billion in the US(46). It's likely that KT recipients have higher vulnerability to the effect of PM2.5 than the general population. KT recipients are on chronic immunosuppression which leads to alterations in immune system, which could potentially increase their risk of infections and malignancy induced by air pollution(47, 48). Moreover, PM2.5 could increase oxidative stress and systematic inflammation response(36), which are risk factors for adverse post-KT outcomes such as DGF and acute rejection. While this population has potentially higher vulnerability, KT recipients are not currently recognized as a vulnerable group to air pollution, thus the potential harm of air pollution is not communicated to this group of people regularly. Understand the impact of different air pollution among KT recipients could potentially improve the overall health among this population and reduce the health cost among the group. Previous studies suggested that PM2.5 was associated with increased risk of adverse health outcomes among KT-recipients(49, 50). However, it's still unclear which component and source of PM2.5 have the most impact among this population.

In this dissertation, we tried to address these research gaps and try to provide high-quality evidence for the association between environmental factors and immune related outcomes. In chapter I, we investigated the association between long-term exposure to total PM2.5, PM2.5 constituents, source-specific PM2.5 and hospital admissions from non-respiratory infections among Medicare beneficiaries aged 65 or older. We began by evaluating the association between annual PM2.5 level at the ZIP code of residence and admissions from total non-respiratory infections and its subtypes including intestinal infections, urinary tract infection, central nervous system infections and septicemia using a quasi-Poisson regression model. Then, using the weighted quantile sum regression, we estimated how each of the 15 PM2.5 constituents contributed to the observed association between PM2.5 and non-respiratory infection. We also identified the sources of PM2.5 across different time periods and regions in the US by using Ward's hierarchical clustering and non-negative matrix factorization. Using the source-factors identified from the PM2.5 constituent data, we investigated the association between source-specific PM2.5 and hospital admissions from non-respiratory infections. We found that long-term exposure to PM2.5 was

associated with increased admissions from total non-respiratory infections, intestinal infections, urinary tract infections and septicemia while sulfate, nickel and copper contributed the largest weights in the observed associations. PM2.5 sourced from oil combustion, coal burning and traffic had the strongest associations with admissions from non-respiratory infections.

In chapter II, we evaluated the impact of seasonal temperature variability on hospital admissions from different infections including respiratory, intestinal, urinary tract, CNS infections and septicemia. In this chapter, an adapted difference-in-difference (DID) method was used to estimate the causal association between the exposure and outcome. DID allowed us to control for the between-ZIP code confounding which changed slowly over time, including unmeasured confounders. To explore the potential effect measure modifications, we further conducted stratified analysis by age, sex, race, and Medicaid eligibilityWe found that higher temperature variability in both warm and cold season, higher mean temperature in warm season and lower mean temperature in cold season were associated with increased hospital admissions from total infections. However, the impact of temperature variability varied across different sub-types of infections.

While chapter I and II focused on a more general population, the final chapter shifts attention to kidney transplant recipients, who were likely to be more vulnerable to immunotoxicities. In this chapter, we evaluated the association between long-term exposure to PM2.5 constituents prior to KT and long-term (graft failure and all-cause mortality) and short-term (delayed graft function, acute rejection) outcomes after transplant among kidney transplant recipients in the US between 2000-2016. In addition, effect measure modification by age, sex, race/ethnicity, donor type and cold-ischemia time were also explored. Here we found that sulfate had the highest importance in the association between the PM2.5 mixture and long-term post-KT outcomes, while lead, organic carbon, nickel and nitrates contributed the largest weights in the association for short-term outcomes. Recipients who were non-white or received a kidney

with cold ischemia time>12hr were more vulnerable to the adverse impacts of PM2.5 when compared to their counterparts.

Overall, this dissertation demonstrated that exposure to environmental stressors including PM2.5, high temperature variability and non-optimal temperature are associated with increased risk of immune-related health outcomes. Additionally, we found that certain chemical constituents within PM2.5 contribute more significantly to adverse health effects than others. The findings of this dissertation highlight the importance of air pollution control strategies that focus on the most harmful constituents and sources. Additionally, addressing climate change is also crucial for improving population health.

1 CHAPTER I

Long-term Exposure to Ambient PM2.5, Particulate Constituents and Hospital Admissions from Non-respiratory Infection

Yijing Feng, Edgar Castro, Yaguang Wei, Tingfan Jin, Xinye Qiu, Francesca Dominici, Joel Schwartz

1.1 ABSTRACT

The association between PM2.5 and non-respiratory infections is unclear. Using data from Medicare beneficiaries and high-resolution datasets of PM2.5 and its constituents across 39,296 ZIP codes in the U.S between 2000-2016, we investigated the associations between annual PM2.5, PM2.5 constituents, source-specific PM2.5, and hospital admissions from non-respiratory infections. Each standard deviation (3.7-μg m^{-3}) increase in PM2.5 was associated with a 10.8% (95%CI 10.8-11.2%) increase in rate of hospital admissions from non-respiratory infections. Sulfates (30.8%), Nickel (22.5%) and Copper (15.3%) contributed the largest weights in the observed associations. Each standard deviation increase in PM2.5 components sourced from oil combustion, coal burning, traffic, dirt, and regionally transported nitrates was associated with 14.5% (95% CI 7.6-21.8%), 18.2% (95% CI 7.2-30.2%), 20.6% (95% CI 5.6-37.9%), 8.9% (95% CI 0.3-18.4%) and 7.8% (95% CI 0.6-15.5%) increases in hospital admissions from non-respiratory infections. Our results suggested that non-respiratory infections are an under-appreciated health effect of PM2.5.

1.2 INTRODUCTION

It is estimated that 15% of all the deaths across the world are directly attributable to infectious disease each year(51). While respiratory infections draw the most attention, non-respiratory infections are also an important health burden. For example, in 2015, it was estimated that the healthcare expenditure for intestinal infections was $6.4 billion in the United States(32). There were around 10.5 million office visits for urinary tract infection, causing $3.5 billion in societal costs per year(33, 34).

Fine particulate matter (PM2.5) is a well-recognized risk factor for health and has been found to be associated with multiple adverse health outcomes such as cardiovascular disease and respiratory disease(1, 52). Previous studies suggested that PM2.5 has potential immunotoxicity and could be a risk factor for infection(38, 53, 54). Various studies have found a positive association between PM2.5 exposure and risk for respiratory infections(39-41, 55). However, only limited studies have investigated the effect of PM2.5 on non-respiratory infections and there were conflicting results(42-44, 56). Due to the lack of consistent evidence, further study is required in this field.

PM2.5 is a complex mixture of multiple constituents that come from different sources(20). Different chemical constituents likely have different immunotoxic profiles which could lead to different health impacts. Identifying the constituent-specific effects could help us understand the underlying pathways by which different components and sources of PM2.5 lead to adverse health outcomes and provide information for targeted interventions.

In this study, we investigated the associations between long-term exposure to PM2.5 and hospital admissions from non-respiratory infections among older adults in the US and identified the constituents and source specific PM2.5 which contribute most to the adverse health effects.

Here, we show that ZIP codes with higher PM2.5 concentration had higher rates of hospital admissions from non-respiratory infections. Across the 15 PM2.5 constituents we examined, sulfates, Nickel and Copper contributed most to the observed association between PM2.5 and the outcome. PM2.5 sourced

from oil combustion, coal burning, traffic, dirt, and regionally transported nitrates had the strongest associations with admissions from different non-respiratory infection.

1.3 METHODS

Study population

We included all beneficiaries who enrolled in Medicare fee for service and were aged 65 and older between 2000-2016. Medicare is a national health insurance program in the U.S. which provides coverage mainly for those who are 65 years of age or older(57). Beneficiaries entered the open cohort on January 1st 2000 or the first January 1st after their enrollment, which ever came later, and were followed until the date of death, or December 31st, 2016, whichever came earlier. This study is approved by the IRB of the Harvard T.H. Chan School of Public Health. Informed consent was waived because this study conducted secondary analysis of deidentified data.

Outcome

The outcomes of this study were hospital admissions from non-respiratory infections, and its subtypes including central nervous system (CNS) infections, intestinal infections, urinary tract infections and septicemia. Data on hospital admissions including ICD (International Classification of Diseases) Diagnosis codes at discharge and date of admissions among Medicare beneficiaries between 2000-2016 were extracted from the Medicare Provider Analysis and Review (MEDPAR) data file. Hospital admission data could include multiple diagnosis codes for each admission record. In this study, we defined the outcome as having a principal discharge diagnosis code of non-respiratory infections.

For hospital admission records with ICD-9 diagnosis codes, we applied the categorizing scheme from the Clinical Classification Software for ICD-9-CM (CCS) to categorize over 14,000 ICD-9 diagnosis codes into 280 clinically meaningful and mutually exclusive diagnosis groups(58). For hospital admission

records with ICD-10 diagnosis code, we applied the categorizing scheme from the Clinical Classification Software Refined for ICD-10-CM (CCSR) to categorize over 70,000 ICD-10 diagnosis codes into 530 clinically meaningful diagnosis groups(59). Based on CCS and CCSR, ICD diagnosis from hospital admission records were categorized into total non-respiratory infections, CNS infections, intestinal infections, urinary tract infections and septicemia.

For admission records with ICD-9 diagnosis codes, non-respiratory infection was defined as diagnosis code being within one of group 2-9, 76-78, 90, 135, 159, 197, 201 and 248 of CCS scheme; CNS infection was defined as diagnosis code being within one of group 76-78; intestinal infection was defined as diagnosis code being within group 135; urinary tract infection was defined as diagnosis code being within group 159; septicemia was defined as diagnosis code being within group 2.

For CCSR scheme, each ICD-10 diagnosis code could exist in more than one diagnosis group. Therefore, for admission records with ICD-10 diagnosis codes, non-respiratory infection was defined as being in group INF002-004, INF006-011, MUS001-002, MUS027, NVS001-NVS003, GEN001, SKN001 and DIG001 but not in group RSP002-006. CNS infection was defined as diagnosis code being within either one of group NVS001-003; intestinal infection was defined as diagnosis code being in group DIG001; urinary tract infection was defined as diagnosis code being in group GEN001; septicemia was defined as diagnosis group being in group INF002.

The number of hospital admissions from non-respiratory infections and its subtypes were calculated for each year within each ZIP code.

Environmental exposure data

Levels of ambient PM2.5 and its constituents across the contiguous US between 2000-2016 were estimated from validated ensemble machine learning models developed by our grouped previously. Details of the exposure modeling are described elsewhere[47,48,49]. Daily PM2.5 at a 1km*1km grid cell

level was estimated by combining predictions from random forest, gradient boosting, and neural network models in a geographically weighted regression ensemble. Predictors of the model for PM2.5 included aerosol optical depth, meteorology data, chemical transport model simulations and land-use data(60). The cross-validated (CV) R^2 of the annual PM2.5 prediction model was 0.89.

Annual mean levels of 15 PM2.5 constituents [elemental carbon (EC), ammonium ($NH4^+$), nitrate (NO_3^-), organic carbon (OC), and sulfate (SO_4^{2-}), bromine (Br), calcium (Ca), copper (Cu), iron (Fe), potassium (K), nickel (Ni), lead (Pb), silicon (Si), vanadium (V), and zinc (Zn)] were estimated at a 50m*50m grid cell level in urban areas and at a 1km*1km level in rural areas. The estimates incorporated predictions from multiple machine-learning models including random forest (RF), stochastic gradient boosting (GBM), extreme gradient boosting (XGB), cubist, and K-nearest neighbors (KNN) models. These were ensembled using a support vector machine (SVM). Like the prediction models for PM2.5, models for PM2.5 constituents included a large number of predictors which included satellite observations, meteorology data and novel land use covariates(61, 62). The CV R^2 ranged from 0.80 to 0.96 across different constituents. The constituents predicted comprise most, but not all of the total mass of PM2.5.

Grid cell level PM2.5 and constituent concentrations were then aggregated to the ZIP code level based on previously described methods(63). The coefficient of variation for each of the exposure within ZIP codes are provided in Appendix A supplementary table 1.

Covariates

We obtained demographic information (age, sex, race), ZIP code of residence and Medicaid eligibility of the Medicare beneficiaries from the Medicare denominator file. Sex information in Medicare data was obtained from multiple sources including self-reported at enrollment, claims data or Electronic Health Records. Information on beneficiaries' ZIP code, age, and Medicare eligibility were updated annually. ZIP code level socioeconomic status (SES) data including percentage of Hispanics, percentage of population

that had less than high school education, median household income, percentage of population who were on public assistance and percentage of population living in poverty were directly obtained from American Community Survey 5-year estimates between 2011-2016 (64) or linearly interpolated from the 2000 and 2010 US Decennial Census(65). Data on the percentage of smokers within a ZIP code was obtained from Behavioral Risk Factor Surveillance System. Annual percent of Medicare enrollees having at least one ambulatory visit to a primary care clinician and distance to nearest hospital at ZIP code level were obtained or calculated from data from the Dartmouth Atlas of Healthcare website(66). ZIP code-level maximal daily temperature in the summer and maximal daily temperature in the winter was calculated from the Gridded Surface Meteorological (gridMET) Dataset(67). To account for potential temporal trends, we also included indicatory variables of calendar year as covariates.

Statistical analysis

Individual level data of Medicare beneficiaries were first aggregated to counts of events by ZIP code and year and merged with the ZIP code-level covariates. Within each ZIP code-year stratum, we calculated the total counts of non-respiratory infections as well as its subtypes, total number of Medicare beneficiaries, percent of female beneficiaries, percent of Black beneficiaries, and percent of beneficiaries who were also eligible for Medicaid. In our analysis, we only included ZIP codes which had more than 100 beneficiaries.

Associations between PM2.5 and the admission rates of our five outcomes, namely total non-respiratory infections, central nervous system (CNS) infections, intestinal infections, urinary tract infections, and septicemia were investigated using multivariable quasi-Poisson regression models below.

$$log\big(admission\ count_{ijk}\big) = \beta_0 + \beta_1 PM2.5 + \beta' \boldsymbol{Z} + log(beneficiary\ count_{ij}) + \varepsilon_{ijk}$$

Where i indicates the ith ZIP code, j indicates the j^{th} year, k indicates the k^{th} outcome (total non-respiratory infection and its subtypes), $\boldsymbol{Z}$ indicates the matrix of covariates mentioned above. Admission counts indicate the number of hospital admissions for the corresponding outcome while beneficiary count

indicates the number of Medicare beneficiaries aged 65 or older who were alive on January 1st of the corresponding year within the ZIP code. Quasi-Poisson regression was used because the outcome of the study was count data and the variance of the outcome was larger than the mean of the outcome.

The US Environmental Protection Agency is considering lowering the standard of annual PM2.5 to 9-10 $\mu g\ m^{-3}$. To evaluate the effect of PM2.5 at levels below the proposed standards, we conducted the same analysis restricted to ZIP code-years where PM2.5 $\leq 9\ \mu g\ m^{-3}$.

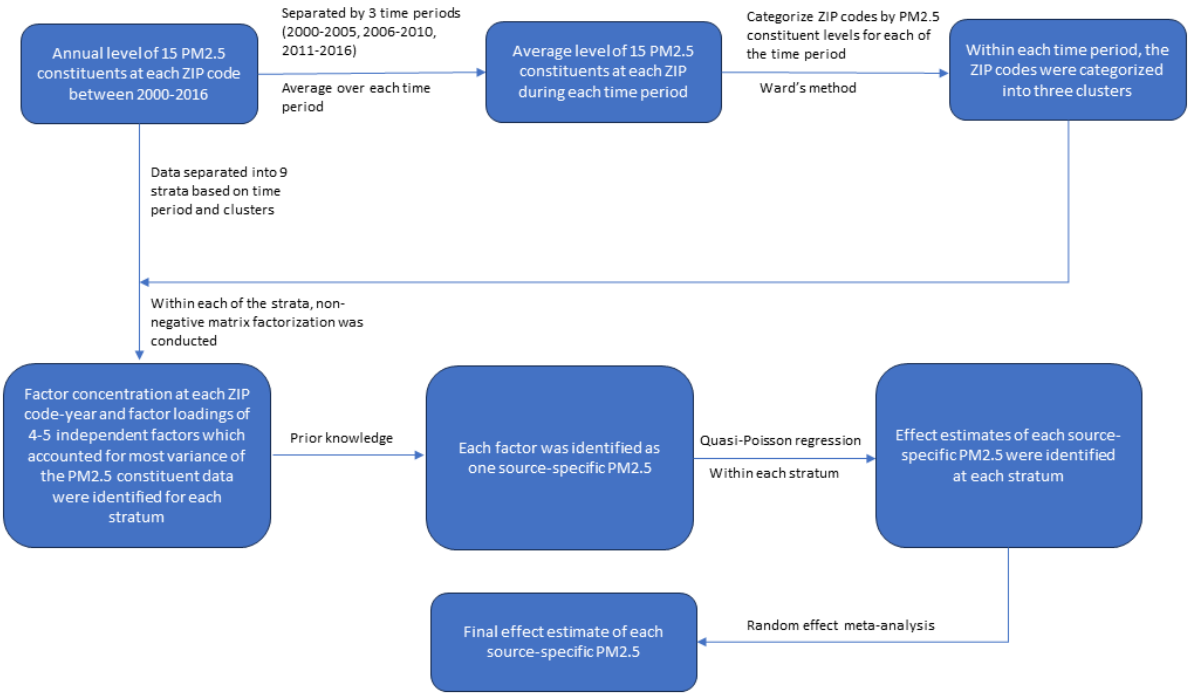
Given that PM2.5 is a mixture of multiple constituents, within which correlations exist, we used weighted quantile sum regression to investigate the mixture effects of the different constituents. Weighted quantile sum regression is a modeling technique which can identify the association between mixtures and the outcome of interest while reducing the impact of high collinearity. A detailed description of the weighted quantile sum method is provided in the appendix A. Briefly, weighted quantile sum regression estimates the relative contribution of each constituent and generates a mixture index as a linear combination of different constituents. It assumes each quantile increase in the mixture index is linearly and unidirectionally associated with the outcome(68). Using weighted quantile sum regression with a quasi-Poisson link, we estimated the association between each one decile increase in the PM2.5 mixture and our five outcomes of interest while estimating the relative contribution from each of the components within the PM2.5 mixture. The weighted quantile sum regression was run with 100 bootstrap samples and all the weights were constrained to be positive.

To identify source specific effects of PM2.5, we used non-negative matrix factorization (NMF) to conduct source apportionment on our ZIP code-level PM2.5 constituent data. Similar to principal component analysis, NMF is a method for dimensionality reduction which explains the observed multidimensional data using limited number of bases(69). However, NMF constrains the matrix components and the mixture coefficients to non-negative values, which is more appropriate for mass concentrations(70). The regulations for the sources of air pollution varied differently over time, and hence the proportion of each component's contribution to each source was likely to also vary over time. Therefore, we conducted

source apportionment separately by time periods. To ensure enough sample size for NMF, we separated our data by three time periods (2000-2005, 2006-2010 and 2011-2016). The contribution of different sources of PM2.5 also vary across regions. Therefore, within each time period, we summarized the ZIP code mean concentration for each constituent. Using Wards hierarchical clustering, the contiguous US was categorized into three clusters with similar patterns of PM2.5 constituents for each of the time periods. Within each of the nine stratum (3 clusters * 3 time periods), NMF was conducted to identify 4-5 independent factors which accounted for most of variance of the PM2.5 constituent data and the source factors levels for each observation(71). Based on the factor loadings of the constituents and our prior knowledge on the trace elements of PM2.5, we identified the source for each factor (72) (details are provided in the appendix A). The units of source factor levels were first converted to $\mu g\ m^{-3}$ and rescaled by the standard deviation of each source factor (see Appendix A supplementary methods). Within each stratum, associations between source specific factors and non-respiratory infection outcomes were estimated using quasi-Poisson regression models, and all the source factors were mutually adjusted. The total effect for each source was estimated by combining the stratum specific effects using random effect meta-analysis (flowchart is shown in figure 1). Details of the random effect meta-analysis are provided in the appendix A.

All the analyses were adjusted for the confounders listed in the covariate section. To account for the autocorrelations within ZIP codes across years, we incorporated robust standard error in all of the effect estimates. Statistical analyses were conducted using R 4.1.3(73).

Figure 1.1 Flowchart for identify source specific effects of PM2.5.



1.4 RESULTS

ZIP code-level characteristics

Hospital admissions of non-respiratory infections from 39,296 ZIP codes between 2000-2016 were included in the analysis. In total, 13,724,218 admissions from non-respiratory infections were identified. This study included data from 67,005,279 Medicare beneficiaries, among whom 37,037,978 (55.3%) were female, 56,700,531 (84.6%) were White, 5,788,605 (8.6%) were Black and 11,837,647 (17.6%) were ever eligible for Medicaid. Among the 436,577 included ZIP code-years, the median number of beneficiaries was 536, while the median percentage of beneficiaries younger than 75 years-old was 55.2%, the median percentage of female beneficiaries was 55.6%, median percentage of White beneficiaries was 95.9%. Other ZIP code-level characteristics controlled for in the analysis, including percentage of smokers, SES, and meteorology are summarized in Table 1.1.

Table 1.1 Characteristics of the included ZIP codes between 2000-2016.

	Overall
ZIP code-years	436,577
Number of beneficiaries per ZIP code	536 [222, 1530]
Characteristics of Medicare beneficiaries (median percentage [IQR])	
Female	55.59 [52.55, 58.37]
Aged between 65-74	55.24 [50.33, 59.88]
Aged between 75-84	32.07 [28.83, 35.30]
White	95.86 [86.13, 98.60]
Black	0.90 [0.00, 5.81]
Eligible for Medicaid	10.03 [5.93, 17.26]
ZIP code-level contextual characteristics (median [IQR])	
Hispanic (%)	2.87 [1.04, 8.84]
Poverty (%)	8.46 [5.21, 13.27]
Education below high-school (%)	25.62 [16.06, 37.69]
Median Household income ($)	44575 [35537, 57417]
Smoker (%)	46.76 [42.22, 51.47]
Percent beneficiaries had ambulatory visit (%)	80.35 [76.65, 83.22]
Distance to the nearest hospital (Km)	8.73 [3.04, 17.09]
Population density	127.38 [35.87, 1110.00]
Winter maximal daily temperature (℃)	6.88 [2.17, 13.37]
Summer maximal daily temperature (℃)	29.51 [27.04, 32.25]

PM2.5 and non-respiratory infection

Across all the included ZIP code-years, the median level of PM2.5 was 9.7μg m^{-3} (IQR 7.7-11.8). The median admission rate of non-respiratory infections was 25.1 (IQR 16.3-35.2) per 1000 person-years. The distribution of PM2.5 levels and rate of admission from non-respiratory infections in 2008 are shown in Figures 2 and 3. After adjusting for the covariates, each standard deviation (3.7-μg m^{-3}) increase in PM2.5 was associated with a 10.8% (95%CI 10.8-11.2%) increase in the admission rate from non-respiratory infection. PM2.5 was also significantly associated with increased admission rates for three sub-types of non-respiratory infection. The increases in admission rate associated with each standard deviation

increase in PM2.5 were 6.8% (95% CI, 6.4-7.2%), 12.0% (95% CI, 11.6-12.0%) and 12.8% (95% CI, 12.4-13.2%) for intestinal infections, urinary tract infections and septicemia respectively (Table 1.2). When we restricted the analysis to ZIP code-years with PM2.5 ≤ 9 $\mu g\ m^{-3}$, a standard deviation increase in PM2.5 was associated with 21.5% (95%CI 20.6-22.8%) increase in rate of hospital admissions from non-respiratory infections (Table 1.2).

Figure 1.2 ZIP code-level PM2.5 in the US in 2008.

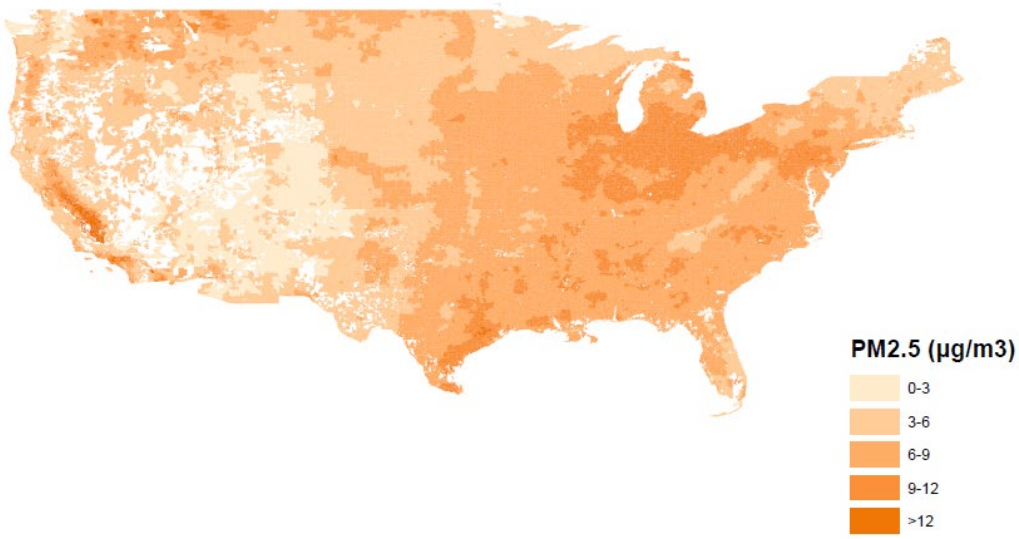


Figure 1.3 Rate of hospital admissions from non-respiratory infections in the US in 2008

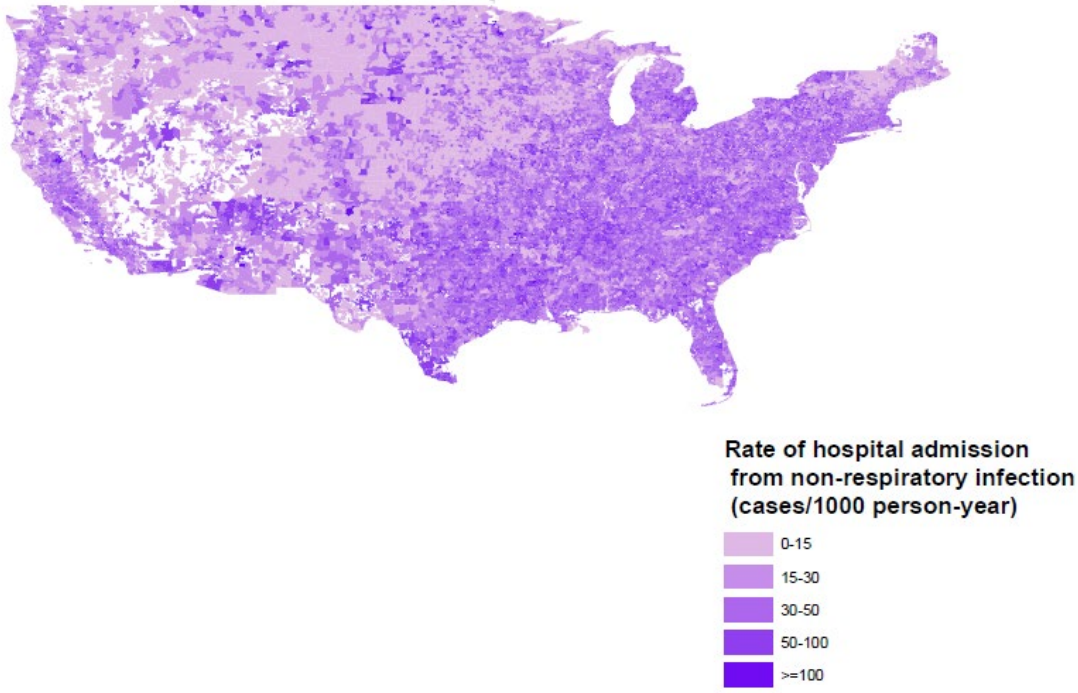


Table 1.2 Association between PM2.5 and rate of hospital admissions from non-respiratory disease among Medicare beneficiaries between 2000-2016.

Outcome	Admission rate ratio (95%CI)	
	All ZIP code-years	ZIP code-years with PM2.5 ≤ 9 μg m^{-3}
Non-respiratory infection	1.108 (1.108-1.112)	1.215 (1.206-1.228)
CNS infection	1.007 (0.996-1.022)	0.949 (0.921-0.982)
Intestinal infection	1.068 (1.064-1.072)	1.189 (1.173-1.206)
Urinary tract infection	1.120 (1.116-1.12)	1.236 (1.223-1.245)
Septicemia	1.128 (1.124-1.132)	1.228 (1.215-1.241)

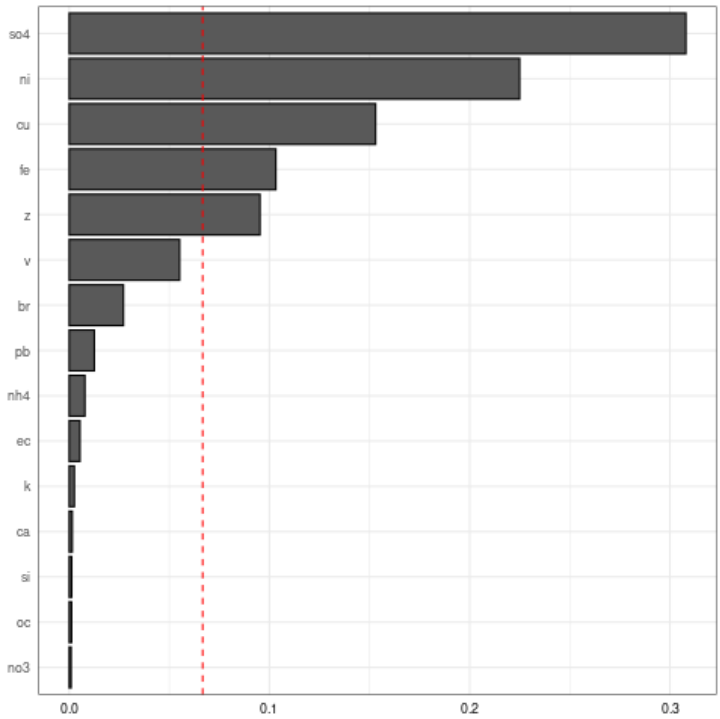
Admission rate ratio was calculated for each standard deviation (3.7μg m^{-3}) increase in PM2.5. All the associations were adjusted for percentage of beneficiaries who were female, percentage of beneficiaries who were aged between 65 and 74, percentage of beneficiaries who were aged above between 75 and 84, percentage of beneficiaries who were White, percent of beneficiaries who were Black, percentage of beneficiaries who were eligible for Medicaid, percentage of population living in poverty, percentage of population having education less than high school, percent smokers, median household income, percentage of population who were on public assistance, average annual percent of Medicare enrollees having at least one ambulatory visit to a primary care clinician, distance to nearest hospital, population density, summer maximal daily temperature, winter maximal daily temperature at ZIP code-level and calendar year.

Mixture effect of PM2.5 constituents

Each decile increase in the mixture was associated with a 10.3% (95%CI 10.2-10.4%) increase in admission rate of non-respiratory infection, while the constituents with the highest relative importance were SO_4 (30.8%), Ni (22.5%) and Cu (15.3%) (Figure 4). Similarly, each decile increase in the mixture was associated with 10.2% (95%CI 10.1-10.4%), 12.7% (95%CI 12.4-13.0%), and 12.0% (95%CI 11.8-12.3%) increases in admission rate for septicemia, intestinal infections and urinary tract infections,

respectively. The constituents with the highest relative importance were Ni (19.7%), SO_4 (17.4%) and Cu (15.6%) for septicemia; Cu (37.3%), Ni (20.0%) and SO_4 (18.4%) for intestinal infections and SO_4 (34.2%), Ni (14.2%), Fe (13.5%) for urinary tract infections. Each decile increase in the mixture was associated with 4.2% (95%CI 3.2-5.2%) increase in admission rate of CNS infections while the constituents with highest relative importance were Si (25.2%), OC (16.2%) and Ca (14.4%). Detailed relative importance of constituents for the four sub-types of non-respiratory infections are shown in Appendix A supplementary figure S1-4. All the results were adjusted for covariates mentioned above.

Figure 1.4 Weights of PM2.5 constituents in the mixture index for the association between the particle mixture and non-respiratory infections.



The dash line indicated the suggested threshold for the most influential constituents. Source data are provided as a Source Data file.

Source specific PM2.5 and non-respiratory infections

Geographical distributions for the clusters within which we conducted separate NMF are shown in Appendix A figure S5-S7. The major sources of PM2.5 identified from our constituent data were coal burning, traffic, oil combustion, soil, biomass burning and regionally transported nitrates. Coal burning was identified in all of the nine strata while oil combustion was identified in eight strata; soil and traffic were identified in seven strata. Detailed results from NMF are shown in Appendix A (figure s8-s16).

After summarizing over all the strata, PM2.5 from five out of the six identified sources was significantly associated with increased admission rate from non-respiratory infections. The estimated increases in admission rate from non-respiratory infections for each one standard deviation increase in source specific PM2.5 were 14.5% (95%CI 7.6-21.8%), 18.2% (95%CI 7.2-30.2%), 20.6% (95%CI 5.6-37.9%), 8.9% (95%CI 0.3-18.4%), and 7.8% (95%CI 0.6-15.5%) for oil combustion, coal burning, traffic, soil and regionally transported nitrate respectively. PM2.5 from oil combustion and coal burning were associated with increased hospital admissions from intestinal infections, urinary tract infections and septicemia; while PM2.5 from traffic was associated with increased admission from all four subtypes of non-respiratory infections. Detailed effect estimates of each of the source-specific PM2.5 are shown in table 1.3.

Table 1.3 Association between source-specific PM2.5 and rate of hospital admissions from non-respiratory infections among Medicare beneficiaries between 2000-2016.

	Admission Rate Ratio				
	Non-respiratory infection	CNS infection	Intestinal infection	Urinary tract infection	Septicemia
Oil combustion	1.145 (1.076-1.218)	1.004 (0.988-1.02)	1.171 (1.085-1.264)	1.148 (1.051-1.255)	1.135 (1.074-1.199)
Soil, dirt	1.089 (1.003-1.184)	1.112 (1.065-1.162)	1.105 (0.962-1.27)	1.153 (0.99-1.343)	1.032 (0.99-1.075)
Coal burning	1.182 (1.072-1.302)	1.007 (0.988-1.026)	1.161 (1.013-1.332)	1.226 (1.076-1.397)	1.154 (1.068-1.248)
Traffic	1.206 (1.056-1.379)	1.056 (1.011-1.103)	1.239 (1.038-1.479)	1.278 (1.042-1.567)	1.187 (1.067-1.321)
Biomass	1.089 (0.996-1.192)	1.059 (1.012-1.109)	1.091 (0.966-1.234)	1.088 (0.942-1.256)	1.135 (1.075-1.199)
Regionally transported nitrate	1.078 (1.006-1.155)	0.987 (0.943-1.034)	0.992 (0.981-1.003)	1.051 (1.017-1.085)	1.112 (1-1.236)

Admission rate ratio was calculated for each standard deviation increase in source-specific PM2.5. All the associations were adjusted for percentage of beneficiaries who were female, percentage of beneficiaries who were aged above between 65 and 74, percentage of beneficiaries who were aged between 75 and 84, percentage of beneficiaries who were White, percent of beneficiaries who were Black, percentage of beneficiaries who were eligible for Medicaid, percentage of population living in poverty, percentage of population had education less than high school, percent smoker, median household income, percentage of population who were on public assistance, average annual percent of Medicare enrollees having at least one ambulatory visit to a primary care clinician, distance to nearest hospital, population density, summer maximal daily temperature, winter maximal daily temperature at ZIP code-level and calendar year.

1.5 DISCUSSION

In this study among older adults across the contiguous US, we observed that ZIP codes with higher PM2.5 concentrations had increased admission rates from total and different subtypes of non-respiratory infections including intestinal infections, urinary tract infections and septicemia. The associations were observed even at lower levels of PM2.5 including levels below the US EPA's recently proposed standards, after adjusting for multiple confounders. When we examined PM2.5 constituents, SO_4, Ni and Cu contributed most to the association between the constituent mixture and hospital admissions from non-respiratory infections. Based on our source apportionment analysis, PM2.5 sourced from oil combustion, coal burning and traffic had the strongest associations with admissions from different non-respiratory infections, which is generally consistent with the loadings in the mixture analyses, since Ni is a tracer for oil combustion, SO_4 for coal combustion, and Cu for traffic particles.

Positive associations between PM2.5 and infections have been found in many studies, most of which focused on respiratory infections such as pneumonia and bronchiolitis(49, 52, 55, 74, 75). However, associations between PM2.5 and non-respiratory infections have also been observed. A previous study among the US Medicare population found that each 1μg m^{-3} increase in short-term PM2.5 was associated with 0.41%, 0.39%, 0.13% and 0.09% increases in hospital admission rates from septicemia, urinary tract infections, skin and subcutaneous tissue infections and intestinal infections(75). However, that study examined short-term exposures to PM2.5 and not long-term exposures as we have done. A study from China observed that each 1μg m^{-3} increase in short-term PM2.5 was associated with a 0.93% increase in rate of hospital admissions from bacterial infections of unspecified site and a 0.97% increase in the rate of hospital admissions from intestinal infections(44). Our study further supports that PM2.5 is a risk factor for non-respiratory infections and is the first we know of to examine long-term exposures to particles, particle components, and particle sources. The potential pathways through which PM2.5 affects non-respiratory infections have not been thoroughly studied yet. An animal study suggested that exposure to PM2.5 down-regulated IL-1β and IFN-β, which led to increased susceptibility to viral infections(76).

Moreover, chronic exposure to PM2.5 could alter phagocytic activity and superoxide dismutase (SOD) activity, which affects immune response to pathogens(77). The immunotoxicity potentially plays a key role in the observed association between PM2.5 and non-respiratory infections.

We observed that sulfate, Ni and Cu had the largest contribution to the effect of PM2.5 mixture on hospital admissions from non-respiratory infections. Ni is a heavy metal with high immunotoxicity. Previous studies suggested Ni exposure could increase production of reactive oxygen species, reduce the activity of SOD and catalase, and induce mitochondrial dysfunction, which are all interrelated with the function of the immune system(78). Airborne Ni is predominantly from the combustion of heavy fuel oil, but other sources include metallurgy, stainless steel production and other industrial sources. An animal study found that the soluble Ni component could alter the immune defense in rats and increase their vulnerability to bacterial infections(79). Similar to Ni, Cu is also a divalent cation that could affect the immune system and oxidative stress, including through Fenton chemistry. Exposure to high levels of Cu increases the production of pro-inflammatory cytokines and ROS(80). An in vitro study found that copper could induce the apoptosis of monocytes. Airborne Cu is primarily a non-tailpipe traffic emission, primarily from brake wear. Other sources include industry and smelters. Sulfate particles derive primarily from coal combustion and have been observed to have the strongest association with mortality across different PM2.5 constituents in a number of studies(81, 82). However, evidence on the association between sulfate and infections is still lacking. A recent study observed that exposure to sulfate particles was associated with increased length of stay from hand-foot-mouth disease(83). One potential mechanism for the observed effect could be that acidic sulfates turn the metal oxides from PM2.5 into metal ions which are soluble in the lung lining fluid, producing oxidative compounds and ultimately perturb the immune system(84-86). It is plausible that sulfate interplays with metals such as nickel and copper and leads to the observed association between these PM2.5 constituents and non-respiratory infections.

PM2.5 sourced from coal burning, oil combustion, and traffic was identified in most of the strata and significantly associated with increased admission rate from total non-respiratory infections and most

subtypes. These results are in accordance with our mixture analysis, given that sulfates, Nickel and Copper are the main constituents of PM2.5 sourced from coal burning, oil combustion and non-exhaust traffic. It was estimated that more than 80% of the PM2.5 in the US was from fossil fuel combustion including coal, petrol, and diesel and 0.36 million excess deaths in the country during 2012 were attributable to these sources(87). Previous epidemiological studies suggested that, when compared to natural sources, PM2.5 from fossil fuel combustion has a greater adverse effect on mortality(81, 82, 88). Thurston et al observed that coal combustion PM2.5 was associated with increased mortality from ischemic heart disease and that it showed a larger effect than overall PM2.5 in general(82). Moreover, PM2.5 sourced from fossil fuel burning has also been found to be associated with multiple diseases including pneumonia, psychiatric disorders, and cancer(71, 87, 89). Road traffic is another major contributor to the PM2.5 and has been found to be associated with many adverse health outcomes(90-92). Traffic related PM can be categorized as exhaust and non-exhaust sources. Exhaust particles mainly come from tailpipe emissions while non-exhaust particles mainly come from the wear of tires and brakes, and also the abrasion of road surface(93). A recent meta-analysis suggested that air pollution sourced from traffic emissions were associated with multiple adverse health outcomes including low birthweight, asthma onset, cardiovascular events, and mortality from multiple causes(94). The results from our study provide further evidence for the harmful effect of PM2.5 sourced from fossil fuel and traffic on health, suggesting that regulations on PM2.5 could potentially focus on these sources.

The observed association between PM2.5 and its constituents and the outcomes were consistent across different subtypes of non-respiratory infections. However, the association between PM2.5 and CNS infection was much weaker when compared to other subtypes. One plausible explanation would be that the blood-brain barrier provides unique protection to the CNS and thus may be less affected by the environmental risk factors such as air pollution(95). Related evidence is still sparse and, therefore, more studies are needed in order to elucidate the observed difference between CNS infections and other subtypes of non-respiratory infections.

This study has several strengths. First, this is the first study to comprehensively evaluate the impact of PM2.5 on non-respiratory infections. Second, using the data of PM2.5 constituents across the contiguous US, the study was able to identify the constituents and source-specific PM2.5 which had the strongest associations with different non-respiratory infection outcomes. These results could potentially help elucidate the potential mechanisms behind the immunotoxicity of PM2.5 and its constituents. Moreover, the results from mixture and source specific analysis are informative for targeted prevention strategies and policy making. Third, this study included more than 60 million participants, and most of the Medicare fee-for-service beneficiaries between 2000-2016 in the analysis, which is a representative sample of the older adults across the US, therefore, the results are likely to be generalizable to older population. The large sample size also provided enough power for us to evaluate the association between the exposures and multiple subtypes of non-respiratory infections.

The study also has limitations. First, the exposure data in this study are at ZIP code level instead of individual level. The participants' individual exposure level within a same ZIP code could vary due to different factors. The exposure data were aggregated from grid cell level to ZIP code level. Therefore, the measurement error of the exposure could be affected by the size of ZIP code area and population, which is potentially non-differential. However, the within ZIP code coefficients of variation of the exposure data are small for the major PM2.5 components, suggesting that the potential measurement error arising from the aggregation was small. Moreover, previous studies suggested that ZIP code level air pollution is a valid proxy for individual level exposure and could avoid some of the impact of personal level confounding (96). Second, the ZIP code level total PM2.5 and PM2.5 constituents in this study are not weighted by population. However, population-weighted exposure estimates could potentially lead to larger measurement error and further bias the result estimates. Third, the outcomes of this study were hospital admissions, which only captures the cases that were hospitalized or the most severe non-respiratory infection cases. It is unclear whether these results also apply to the milder cases. Further study which captures the outpatient cases are needed in the field. Fourth, this study was limited to Medicare

beneficiaries who were 65 or older. Considering that older adults are more vulnerable to the adverse effect of air pollution, the results from this study might not be generalized to younger population. Moreover, since the metal components had substantial weights in contributing to the weighted quantile sum, but very small mass concentrations, the effect size estimate per weighted decile of the mixture cannot be directly compared to the effects per unit mass of PM2.5. However, these small mass components also contributed importantly to the source apportionment study, which may partially explain the larger effect size for sources, while this may also reflect the unimportance of other components of PM2.5 that were not included in our component mixture. Lastly, we are only able to obtain limited data on individual level confounders in this study. To reduce residual confounding, confounders such as smoking and SES were controlled at the contextual level.

In conclusion, higher ZIP code level PM2.5 exposure was associated with increased rate of hospital admissions from non-respiratory infections and the association remained robust even in areas with lower PM2.5, continuing below PM2.5 concentrations of 9 $\mu g\ m^{-3}$. Sulfates, Nickel, and Copper play the most important role in the effect of the PM2.5 mixture on non-respiratory infections. PM2.5 sourced from fuel oil combustion, coal burning and traffic had larger effects on admission from non-respiratory infections when compared to PM2.5 from other sources. PM2.5 effects on non-respiratory infections has been understudied and this study provides evidence that this pathway could be an important additional impact from PM2.5 and should be considered in evaluating the adequacy of current PM2.5 standards.

2 CHAPTER II

Seasonal Temperature Variability and Hospital Admissions from Infections among Older Persons in the US

Yijing Feng, James Healy, Mahdieh Danesh Yazdi, Yaguang Wei, Francesca Dominici, Joel Schwartz

2.1 ABSTRACT

BACKGROUND

Mean temperature has been found to be associated with multiple types of infections. The impact of long-term temperature variability on infections is largely unknown. Due to climate change, long-term temperature variability is expected to increase in multiple regions worldwide. We investigated the association between seasonal temperature variability and the risk of hospital admissions from infections in the elderly.

METHODS

We studied Medicare beneficiaries over 65 in the contiguous US between 2000-2016. The exposures were the annual standard deviation (SD) of cold season (Jan-Mar, Oct-Dec) temperature (cold SD) and warm season (Apr-Sep) temperature (warm SD) and average temperature of cold (cold temperature) and warm season (warm temperature). The outcomes were hospital admissions from infections (respiratory, intestinal, urinary tract, central nervous system infections, septicemia, and other infections). An adapted difference-in-difference method was used to evaluate the exposure-outcome association

RESULTS

Each one °C increase in cold SD was associated with 2.59 (95%CI 1.91, 3.30) additional admissions from infections per 10,000 person-years among Medicare beneficiaries; the corresponding effects for one °C increase in warm SD and warm temperature were 2.73 (95%CI 1.52, 3.99) and 3.08 (95%CI 2.58, 3.58) additional admissions from infections per 10,000 person-years respectively. Each one °C increase in cold temperature was associated with a 0.89 (95%CI 0.57, 1.23) per 10,000 person-years decrease in hospital admission rate from infections.

CONCLUSIONS

Increased seasonal temperature variability was associated with increased hospital admission rate from infections among older adults in the US. Climate change could affect human health through changes in temperature variability.

2.2 INTRODUCTION

Although chronic diseases such as cardiovascular disease and cancer have drawn more attention in recent years, infections are still a significant health burden. It was estimated that around 15% of deaths around the globe are directly attributable to infectious diseases every year(51). Based on the estimates from The Global Burden of Disease, more than 2 million deaths were caused by lower respiratory infections in 2016(97). In the United States (US), it was estimated that the health expenditure for intestinal infections was $6.4 million in 2015(33).

Temperature is known to be an essential factor for the risk of infection. The survival, activities, and the spread of pathogens are highly influenced by ambient temperature(98, 99). Moreover, temperature could also affect the immune system and thus increase the vulnerability to infections. At low temperature, much of the energy in the body is directed to heat generation, which leads to decreased energy availability for the immune system(100). Experimental study suggested that exposure to extreme temperature was associated with change in levels of proinflammatory and anti-inflammatory cytokine response and increased level of cortisol(101). Epidemiological studies have found that increased daily temperature was associated with increased risk of multiple types of infections including respiratory, intestinal, and urinary tract infections(102-104). However, most of these studies focused on the impact of mean temperature and short-term exposure(102, 105). This leaves uncertain how much of, e.g., acute hospitalizations for infections associated with temperature were merely brought forward by a few days or weeks. It also needs to be clarified the cumulative effects of temperature over a season. Besides mean temperature, the variability of temperature is a significant risk factor for health. It was observed that short-term temperature variability was associated with increased hospital admissions from respiratory infections(106). The impact of long-term temperature variability on annual infection rates is largely unknown.

Climate change has led to more extreme weather in recent years. Studies suggest that long-term temperature variability is expected to increase in multiple regions across the world(107, 108). Elucidating

the associations between temperature variability and annual health measures is essential for understanding the health impacts of climate change.

This study aims to investigate the causal relationship between seasonal temperature variability, seasonal mean temperature, and hospital admissions from infections among older Medicare beneficiaries in the US using an adapted difference-in-difference (DID) analysis.

2.3 METHODS

Study population

The research cohort included individuals enrolled in the Medicare fee-for-service program aged 65 or older from 2000 to 2016. Medicare, a nationwide health insurance initiative, primarily caters to individuals aged 65 and above in the United States(57). For this investigation, we followed these beneficiaries from either January 1st, 2000 or the first January 1st following their enrollment, whichever occurred later, until their date of demise, or December 31st, 2016, whichever was earlier. Only beneficiaries who resided in ZIP codes with over 100 Medicare beneficiaries were included in the analysis.

Outcome

The primary outcome of this study was total hospital admission from infections. The secondary outcomes were hospital admissions from different sub-categories of infections including respiratory, intestinal, central neural system (CNS), urinary tract, and septicemia. Hospital admission data among the Medicare beneficiaries were obtained from the Medicare Provider Analysis and Review (MEDPAR) data file. Information on the primary International Classification of Disease (ICD) diagnosis code at discharge and date of admission were available for each admission. Diagnosis of the hospital admissions were either recorded with ICD-9 or ICD-10 codes. We applied the categorizing scheme from the Clinical Classification Software for ICD-9-CM (CCS) (58)to the hospital admissions with ICD-9 diagnosis codes.

We applied the categorizing scheme from the Clinical Classification Software Refined for ICD-10-CM (CCSR)(59). Detailed categorizations of the ICD codes are shown in Appendix B.

Exposure data

Details of the temperature exposure are described elsewhere(109). Briefly, the exposures of this study were, for each calendar year, the standard deviation (SD) of cold season temperature (cold SD), SD of warm season temperature (warm SD), average temperature of cold season (cold temperature) and average temperature of warm season (warm temperature) in the US between 2000-2016. The exposure data was derived from the gridMET data, which provided high-resolution estimates of daily meteorological variables across the US at the 4 km*4 km grid cell level(67). Warm season was defined as April-September, while cold season was defined as January-March and October-December. Seasonal average and SD were calculated from daily temperature across the season in each grid cell. We assigned the ZIP code level exposures by averaging all the values for grid cells whose centroids were within the ZIP code area.

Other covariates

Age, sex, race, ZIP code of residence, and Medicaid eligibility among the beneficiaries were obtained from the Medicare denominator file. Age, ZIP code, and Medicaid eligibility were updated annually. The ages of the beneficiaries were categorized into three groups: 65-74, 75-85, and 85 or older. Data of ZIP code level socioeconomic status (SES), including percentage of the elderly population who lived in poverty, the percentage of the population who had less than a high school education, the percentage of the Hispanic population, median house value, and median household income were obtained from American Community Survey 5-year survey between 2011-2016 or linearly interpolated from the 2000 and 2010 US census(64). Information on access to healthcare at the ZIP code level, including percentage of Medicare

beneficiaries who had at least one ambulatory visit in a year, percentage of female beneficiaries who had mammograms over two years, percentage of beneficiaries who had an eye examination in a year, and percentage of beneficiaries who had a lipid panel test in a year were obtained from the Dartmouth Atlas of Healthcare website(66). We also calculated the distance to the nearest hospital from the ZIP code centroid using data from ESRI in 2010(110). Percentage of the population who were ever smokers and the mean body mass index were obtained from the Behavioral Risk Factor Surveillance System(111).

Statistical analysis

In primary analysis, individual-level data of the beneficiaries were aggregated to counts of events (admissions from infection and its sub-categories) and beneficiaries by year and ZIP code, then merged with ZIP code-level variables. Hospital admission rate for each ZIP code-year was calculated by the number of admissions divided by the number of beneficiaries. Within each stratum defined by ZIP code and year, we also calculated percentage of beneficiaries within each age group, percentage of beneficiaries who were female, who were black and who were eligible for Medicaid.

This study used an adapted difference-in-difference (DID) analysis (112) to evaluate the change in the rate of hospital admissions from infection across different years within each ZIP code, conditional on the exposures of interest and other covariates. By conditioning on each ZIP code, DID controls for between-ZIP code confounding which changes slowly over time. The common temporal trend of the outcomes across ZIP codes was accounted for by including a natural spline time term in the outcome model. DID assumes that the temporal trends of the outcomes are the same across different ZIP codes, conditioning on the covariates. To relax this assumption, we first included the time-varying demographics and socioeconomic and population density covariates to account for the difference in the temporal trends of the outcome between ZIP codes driven by these variables. To further relax the assumption, we grouped the ZIP codes into clusters and allowed different temporal trends between them. We assumed that ZIP

codes with similar SES levels and access to healthcare would have similar trends of the outcome. Using Ward's hierarchical clustering, we grouped the ZIP codes into five clusters based on the SES and access to healthcare. The linear probability model we used was:

$$E(AR_{ij}) = \beta_0 + \beta_1\, cold\ SD + \beta_2\, cold\ temperature + \beta_3\, warm\ SD + \beta_4\, warm\ temperature + \boldsymbol{\beta_5}'covariates + \delta_i + ns(year, 4) + ns(year, 4) * as.factor(clusters)$$

Where AR_{ij} is the rate of admission from infection in ZIP code *i* and year *j*, the exposures are the four temperature variables, δ_i is the indicator variable for ZIP code *i*, ns(year, 4) is the natural spline term for year with 4 degrees of freedom. In this study, the admission rates were presented as cases/10,000 person-year. The coefficients $\beta_1, \beta_2, \beta_3, \beta_4$ will be estimating the absolute increase in rate of admission for each 1 unit increase in the four exposures (cold SD, warm SD, cold temperature, warm temperature). To obtain the confidence interval of the effect estimates, we used bootstrap method with 1000 iterations.

We conducted stratified analyses to investigate the potential effect of measure modifications (EMM) by age, sex, race, and Medicaid eligibility. For each stratified analysis, we aggregated the individual beneficiary data to strata by ZIP code, year, and one of the stratification factors. EMM by sex, race, and Medicaid eligibility were evaluated using a bootstrap method. For each iteration, we generated a bootstrap sample of the dataset and stratified the bootstrap sample by one of the stratification factors. We conducted a similar analysis within each stratum as our primary analysis while removing the stratification factor from the regression model. From each bootstrap sample, we obtained the stratum-specific effect estimates of temperature exposure and the difference in effect between strata. The heterogeneity of effect estimates was defined by 95%CI of the effect difference not covering zero. Cochran's Q test evaluated EMM by age group.

2.4 RESULTS

Population and ZIP code-level characteristics

In this study, we included 67,005,279 beneficiaries of the Medicare FFS program, among whom 37,037,978 (55.3%) were female, 56,700,531 (84.6%) were white, and 5,788,605 (8.6%) were ever eligible for Medicaid. In total, 21,328,883 admissions between 2000-2016 from infection were included in our analysis, among which 7,825,674 were respiratory infections, 998,777 were intestinal infections, 95,721 were CNS infections, 3,643,771 were urinary tract infections and 5,772,883 were septicemia. The rate of hospital admissions from infections was 452.3/10,000 person-years among Medicare beneficiaries across the study period. Individual data were aggregated to 436,594 strata defined by ZIP code and years. Characteristics of the ZIP code years are shown in Table 2.1.

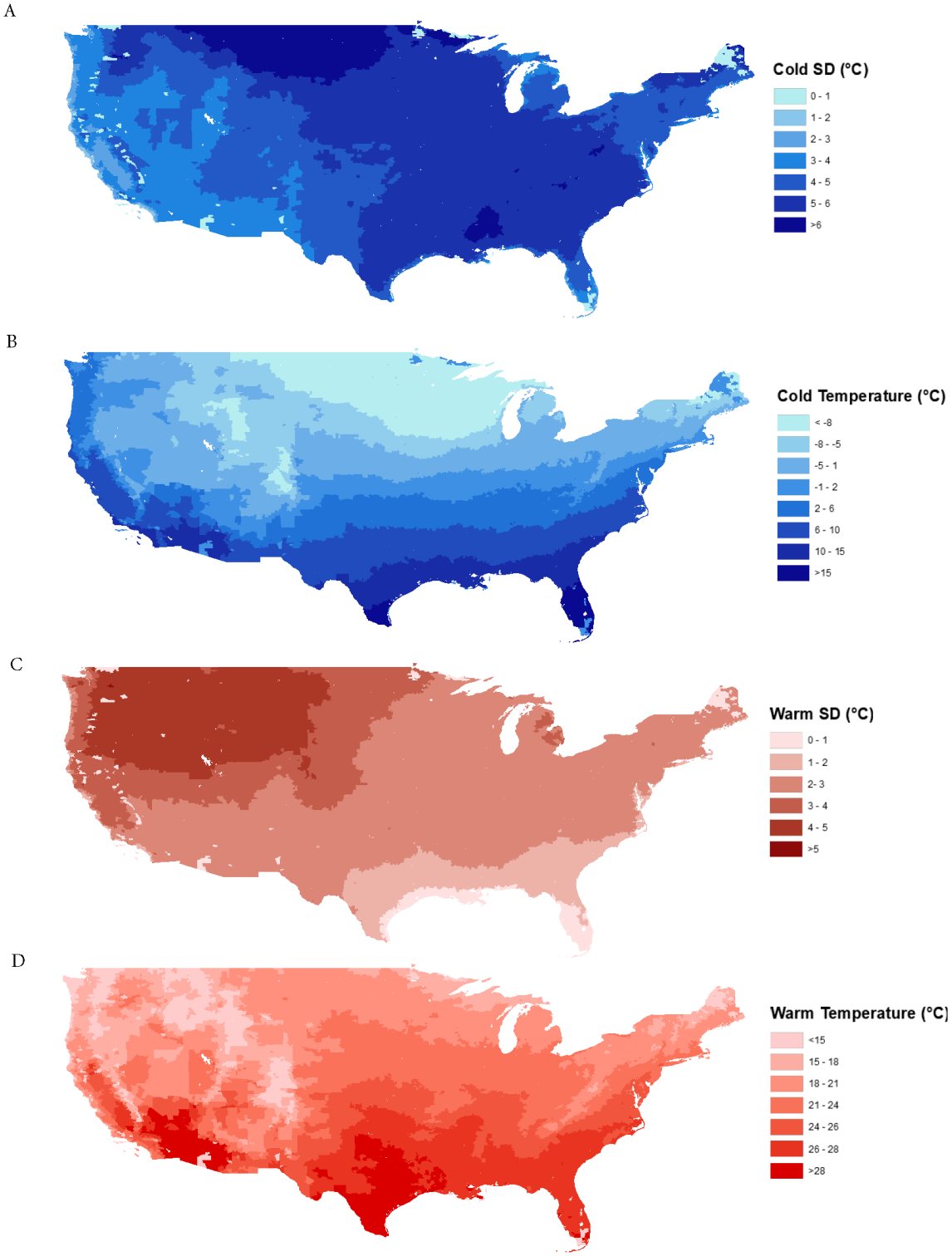
Table 2.1 Characteristics of the included ZIP codes between 2000-2016.

	Overall
ZIP code-years	436594
Number of beneficiaries per ZIP code	536 [222, 1530]
Characteristics of Medicare beneficiaries (median percentage [IQR])	
Female	0.56 [0.53, 0.58]
Aged between 65-74	0.55 [0.50, 0.60]
Aged between 75-84	0.32 [0.29, 0.35]
White	95.86 [86.13, 98.60]
Black	0.90 [0.00, 5.81]
Eligible for Medicaid	10.03 [5.93, 17.26]
ZIP code-level contextual characteristics (median [IQR])	
Distance to the nearest hospital (Km)	8.73 [3.04, 17.09]
% beneficiaries had an eye examination	67.08 [63.10, 71.34]
% beneficiaries had an lipid panel test	79.48 [75.16, 83.10]
% female beneficiaries had an mammogram	64.15 [59.18, 68.81]
% beneficiaries had ambulatory visit	80.35 [76.65, 83.22]
Poverty (%)	0.08 [0.05, 0.13]
Hispanic (%)	0.03 [0.01, 0.09]
Education below high-school (%)	0.26 [0.16, 0.38]
Median House Value ($)	118257.14 [81225.42, 188200.00]
Median Household income ($)	44575.63 [35536.91, 57416.92]
Smoker (%)	0.47 [0.42, 0.51]
Mean BMI	27.59 [26.91, 28.35]
Population density	127.39 [35.87, 1109.87]

Temperature exposures and admissions from infections

Across all the ZIP code-years, the median cold SD, warm SD, cold temperature, and warm temperature were 5.0°C, 2.8°C, 1.5°C and 23.4°C respectively. Detailed distributions of the exposures are shown in Figure 1.

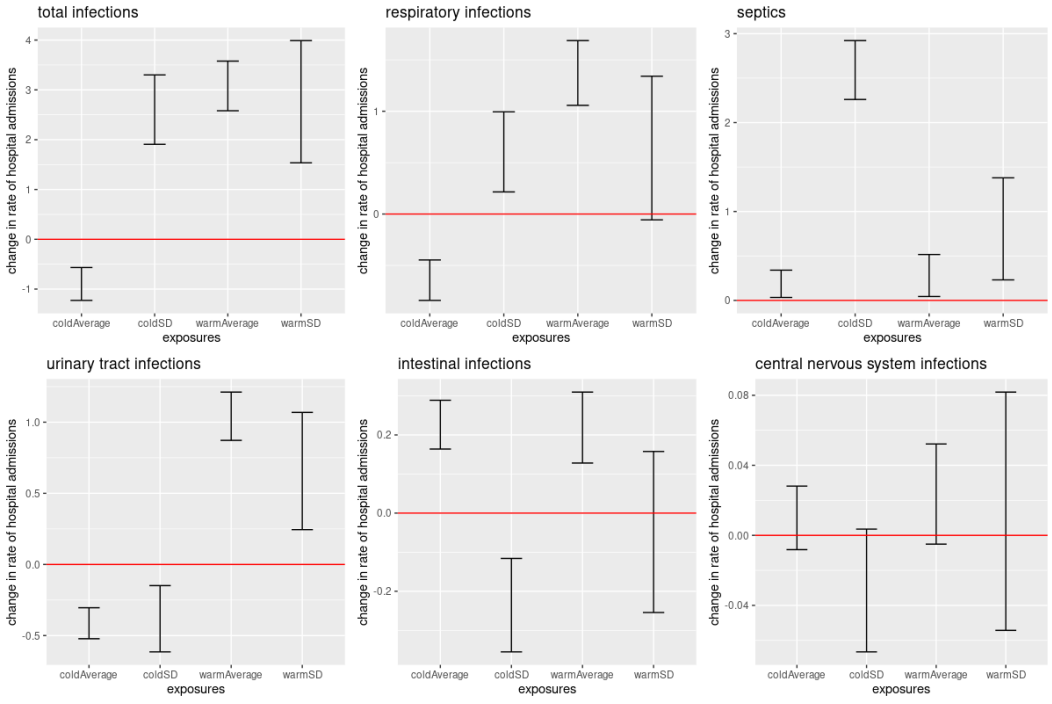
Figure 2.1 Distribution of Cold SD, Cold temperature, Warm SD and Warm temperature across the contiguous US in 2008.



Each one °C increase in cold SD was associated with 2.59 (95%CI 1.91, 3.30) additional admissions from infections per 10,000 person-years among Medicare beneficiaries; the corresponding effects for one °C increase in warm SD and warm temperature were 2.73 (95%CI 1.52, 3.99) and 3.08 (95%CI 2.58, 3.58) additional admissions from infections per 10,000 person-years respectively. A negative association was observed between cold temperature and admission from infection. Each one °C increase in cold temperature was associated with a 0.89 (95%CI 0.57, 1.23) per 10,000 person-years decrease in the rate of hospital admission from infections.

Each one °C increase in cold SD was associated with 0.91/10,000 person-years (95%CI 0.39, 1.36) and 2.70/10,000 person-years (95%CI 2.29, 3.12) increase in admission rate from respiratory infections and septicemia. In contrast, each one °C increase in cold SD was associated with 0.37/10,000 person-years (95%CI 0.15, 0.61) and 0.23/10,000 person-years (95%CI 0.12, 0.36) decrease in the rate of admission from urinary tract infections and intestinal infections (figure 2).

Figure 2.2 Association between seasonal temperature, seasonal temperature variability, and hospital admissions from infections among Medicare beneficiaries between 2000-2016.



Each one °C increase in warm SD was associated with 0.81/10,000 person-years (95%CI 0.23, 1.38) and 0.68/10,000 person-years (95%CI 0.24, 1.07) increase in rate of admission from septicemia and urinary tract infections. Similar to the total infection, a one °C increase in cold temperature resulted in 0.65/10,000 person-years (95%CI 0.45, 0.84) and 0.43/10,000 person-years (95%CI 0.30, 0.52) decrease rate of hospital admission from respiratory infection and urinary tract infection. However, the cold temperature was positively associated with admissions from septicemia and intestinal disease, and the corresponding effect size for a one °C increase in cold temperature was 0.19/10,000 person-years (95%CI 0.03, 0.34) and 0.22/10,000 person-years (95%CI 0.16, 0.29) respectively.

Positive associations were observed between warm temperatures and most of the infections. Each one °C increase in warm temperature was associated with 1.34/10,000 person-years (95%CI 1.06-1.69), 0.29/10,000 person-years (95%CI 0.04, 0.52), 1.05/10,000 person-years (95%CI 0.87, 1.21) and 0.22/10,000 person-years (95% 0.13, 0.31) increase rate of admission from respiratory infections, septicemia, urinary tract infections and intestinal infections respectively (figure 2).

Stratified analysis

The effects of the cold SD, cold temperature, and warm temperature on hospital admissions from infections were consistent between males and females (table 2.2). However, each one °C increase in warm SD was associated with 4.26/10,000 person-years (95%CI 2.66, 6.17) among males while that was 1.43/10,000 person-years (95%CI 0.02, 3.02) among females. We estimated that the effect of warm SD was 2.87 /10,000 person-years (95%CI 0.46, 5.38) larger among males than females. When we stratified the study population by age, the largest effect estimate of cold SD, warm SD, and warm temperature were observed among the oldest group (age ≥85) where each one °C increase in cold SD, warm SD and warm temperature were associated with 9.89/10,000 person-years (95%CI 7.61, 12.55), 4.38/10,000 person-years (95%CI -0.37, 8.94) and 7.75/10,000 person-years (95%CI 5.57, 9.61) increase in admissions.

Significant effects of cold temperature were only observed among the youngest group (aged 65-74), and each one °C increase in cold temperature was associated with 1.35/10,000 person-years (95%CI 1.01, 1.70) decrease in admission rates from infections. Significant effect heterogeneity was observed for cold SD ($Q = 73.8$, $df = 2$, $p < 0.01$) and warm temperature ($Q = 30.2$, $df = 2$, $p < 0.01$) between age groups. Each 1one °C increase in cold SD, warm SD, warm temperature, and cold temperature were associated with absolute increases of 2.69/10,000 person-years (95%CI 1.93-3.51), 2.82/10,000 person-years (95%CI 1.39-4.25), 3.00/10,000 person-years (95%CI 2.36-3.55) and decrease of 1.03/10,000 person-years (95%CI 0.58-1.46) in the rate of hospital admissions from infections among Whites. Significant association was only observed for warm SD among Blacks; each one °C increase in the exposure was associated with 13.54/10,000 person-years (95%CI 2.88, 24.57) absolute increase in hospital admission rate from infections. The direction of the estimated effects was the same between those who identify as black and those who identify as white (table 2.2). Significant effect heterogeneities were observed between beneficiaries who were eligible for Medicaid versus those who weren't. Effect sizes of warm SD (effect difference: 7.79/10,000 person-years; 95%CI 1.87, 13.93), cold temperature (effect difference: -1.70/10,000 person-years; 95%CI -3.31, -0.03) and warm temperature (effect difference: 4.23/10,000 person-years; 95%CI 1.65, 6.59) were significantly more prominent among those who were eligible for Medicaid than those who were not eligible (2). Detailed results of the stratified analysis for different subtypes of infections are shown in Appendix B table s1-s5.

Table 2.2 Association between seasonal temperature, seasonal temperature variability, and hospital admissions from all infections among Medicare beneficiaries across different strata between 2000-2016

		Effect estimates			
		Cold SD	Warm SD	Cold Temperature	Warm Temperature
Sex	Female	2.87 (1.89,3.82)	1.43 (0.02,3.02)	-0.79 (-1.22,-0.33)	3.18 (2.48,3.82)
	Male	2.47 (1.5,3.48)	4.26 (2.66,6.17)	-0.99 (-1.47,-0.51)	2.88 (2.2,3.54)
	Effect difference	0.36 (-0.99,1.67)	-2.87 (-5.38,-0.46)	0.21 (-0.52,0.86)	0.28 (-0.67,1.26)
Race	Black	0.11 (-5.9,5.71)	13.54 (2.88,24.57)	-2.09 (-5.09,1.12)	1.57 (-3.44,6.39)
	White	2.69 (1.93,3.51)	2.82 (1.39,4.25)	-1.03 (-1.46,-0.58)	3.00 (2.36,3.55)
	Effect difference	-2.56 (-8.54,3.1)	10.66 (-0.42,22.41)	-1.01 (-4.05,2.1)	-1.46 (-6.44,3.24)
Medicaid eligibility	Medicaid eligible	3.88 (0.51,6.81)	9.31 (3.34,15.14)	-2.14 (-3.67,-0.52)	6.84 (4.2,9.15)
	Medicaid non-eligible	2.41 (1.7,3.09)	1.3 (0.12,2.47)	-0.45 (-0.75,-0.12)	2.6 (2.12,3.15)
	Effect difference	1.42 (-2.05,4.67)	7.97 (1.87,13.93)	-1.7 (-3.31,-0.03)	4.23 (1.65,6.59)
Age	65-74	-0.14 (-0.78,0.54)	2.52 (1.4,3.69)	-1.35 (-1.7,-1.01)	1.95 (1.49,2.48)
	75-84	3.6 (2.06,4.81)	3.82 (1.79,6.21)	-0.55 (-1.26,0.1)	2.48 (1.57,3.54)
	>=85	9.89 (7.61,12.55)	4.38 (-0.37,8.94)	-1.13 (-2.5,0.2)	7.75 (5.57,9.61)

2.5 DISCUSSION

In this study, we used an adapted difference-in-difference analysis among Medicare beneficiaries over 65 across the contiguous US to evaluate the causal associations between seasonal temperature, seasonal temperature variability, and hospital admissions from infections. We found that higher cold SD, warm SD, warm temperature, and lower cold temperature resulted in increased annual rates of hospital admissions from infections. Older people who were eligible for Medicaid were more vulnerable to temperature exposures when compared to those who were not eligible. Moreover, the impacts of temperature exposures varied across different subtypes of infections.

To the best of our knowledge, this is the first study to comprehensively evaluate the impact of seasonal temperature variability on the risk of different types of infections. Most previous studies on seasonal temperature variability focused on outcomes such as mortality, cardiovascular disease, and respiratory diseases(109, 113). A study among the elderly population in Hong Kong found that temperature

variability during wintertime was associated with an increased risk of hospital admission from respiratory diseases, while no association was observed for temperature variability during summer(114). These results are consistent with our observed association between temperature variability and respiratory infections. These studies of the effects of seasonal exposure on annual rates avoid short-term displacement effects that are possible in daily time series studies and capture cumulative effects of temperature variability across entire seasons.

Some studies have observed that short-term temperature variability was associated with an increased risk of infections. Xu et al. observed that each three °C decrease in temperature between neighboring days was associated with a 10% increase in the daily incidence of hand, foot, and mouth diseases(106). Another study in Japan found that each one °C in the diurnal temperature range was associated with a 3.3-fold increase in the risk of respiratory syncytial virus infection(115). Our study adds to the current evidence regarding the adverse impacts of temperature variability on infections, suggesting that temperature variability also affects infections on a longer time scale. The pathway through which temperature variability affects infections is still unclear. Temperature variability could potentially perturb the immune system. Hung et al. observed that, when compared to stable weather conditions, larger between-day temperature changes were associated with changes in white blood cell counts(116). Variability in temperature impedes adaptation to a prevailing temperature, which may also play a role. It's also likely that the observed effect of temperature variability was driven by the increased number of extreme temperature conditions. At very low temperature, the energy required for maintaining body temperature increased, which could lead to decrease in the energy availability for immune system, and thus decrease the immunity(100). In vivo study found that exposure to extreme temperature resulted in higher plasma cortisol level, which could suppress the immune response to pathogens(101).

The impact of temperature variability varied across different types of infections. While increased cold SD was associated with increased hospital admissions from total infection, we observed a slight protective effect of cold SD on urinary tract infections and intestinal infections. One potential reason could be that

the ideal temperature varies across pathogens(117). Therefore, higher temperature variability may interrupt the life cycles of some pathogens while facilitating the spread of others. Moreover, temperature may affect the activities of vectors and intermediate hosts differently across different pathogens(118). However, our results also suggested complicated associations between temperature variability and infections. More experimental studies are needed to fully elucidate the mechanisms behind the observed associations.

Effect sizes among those eligible for Medicaid were larger than those who were not eligible for Medicaid. People eligible for Medicaid are more likely to have lower socioeconomic status when compared to their counterparts. Similar to our results, Sun et al(114). found that older adults with lower SES were more vulnerable to wintertime temperature variability than people with higher SES. The low SES population is more likely to have sub-optimal living and working conditions, which may facilitate the spread of infectious diseases and offer limited protection against the rigors of extreme temperatures(119). Moreover, this populations limited access to health care and poor health conditions could also potentially increase their vulnerability to temperature exposures(120).

"J"-shaped exposure-outcome relationship has been found between ambient temperature and multiple health outcomes, including cardiovascular disease, respiratory disease, and mortality(121, 122). Consistent with previous findings, we observed that lower cold temperatures and higher warm were associated with increased risk of hospital admissions from infections. The cold temperature could affect infections by multiple pathways, including inducing pathophysiological changes in the mucosa, suppressing of immune response, and affecting outdoor activities(100, 123, 124). At high temperatures, the activities of vectors and pathogens are usually increased, which may facilitate the spread of infections(118). Additional research is required to clarify the pathway through which mean temperature affects infections comprehensively.

This study has several strengths. Firstly, this study included data from more than 60 million Medicare beneficiaries between 2000-2016, a general population of older adults in the US. Secondly, we used a

difference-in-difference method to investigate the effects of temperature exposures, which could eliminate the measured and unmeasured ZIP code-level confounding, which were time-invariant or changed slowly over time. Thirdly, the models used in this study were at additive scales, which estimated the rate changes for each unit increase in the exposure. Compared to relative-scale estimates, our results could be easily interpreted and reflected the actual effect sizes.

Our study also has limitations. First, the difference-in-difference method relies on the parallel trend assumption, which could not be verified empirically. However, we clustered the ZIP codes by contextual SES and access to healthcare and allowed different temporal trends between clusters, making the parallel trend assumptions more plausible. Second, our data only captures the hospital admissions from infections. Therefore, our results may only apply to severe infections. Third, although the exposures in this study were derived from validated algorithms, there could be measurement errors that could bias our effect estimates. Fourth, this study only included beneficiaries who were 65 or older. Considering that the older population was likely to be more vulnerable to extreme temperatures and infections, our results might not apply to the younger population.

In conclusion, increased temperature variability in both warm and cold seasons, lower mean temperature in cold season, and higher mean temperature in warm season were associated with an increased rate of hospital admission from infections among older adults in the US. Our findings indicate that climate change could affect human health through change in temperature variability, highlighting the intricate interplay between climatic factors and human health outcomes.

3 CHAPTER III

Particulate constituents and post-transplant outcomes among kidney transplant recipients in the US

Yijing Feng, Yiting Li, Sunjae Bae, Babak Orandi, Mara McAdams-Demarco, Joel Schwartz

3.1 ABSTRACT

Total $PM_{2.5}$ has been found to be associated with adverse post-transplant outcomes among kidney transplant (KT) recipients. However, $PM_{2.5}$ is a complex mixture of multiple constituents and those constituents have different toxicity. It's unclear which constituents are most harmful to KT recipients. In this study, we aimed to investigate the associations between $PM_{2.5}$ constituents and post-KT outcomes among KT recipients.

We included KT recipients who received a kidney transplant between 2001-2016 and were recorded in the Scientific Registry of Transplant Recipients. The exposures were fifteen $PM_{2.5}$ constituents at the ZIP code of residence prior to KT estimated from ensembled machine learning models. We included short-term [delayed graft function (DGF), acute rejection] and long-term outcomes [all-cause mortality, death-censored graft failure (DCGF)] in this study. The association between $PM_{2.5}$ constituents and short-term outcomes were evaluated using a weighted quantile sum logistic regression, while the associations for the long-term outcomes were evaluated using a weighted quantile sum pooled-logistic regression.

We found that each decile increases in the $PM_{2.5}$ constituent mixture was associated with a 6.8% (95% confidence interval [CI] 5.8-7.8%) and 3.6% (95%CI 2.1-5.1%) increase in the odds of DGF and acute rejection. Organic carbon and Nickel contributed the largest weights to the observed association between $PM_{2.5}$ mixture and DGF while lead had the largest impact on acute rejection. Each decile increases in $PM_{2.5}$ constituent mixture was associated with a 4.7% (95%CI 3.3-6.3%) and 3.9% (95%CI 2.5-5.2)

increase in the hazard of DCGF and all-cause mortality. The constituent that contributed the largest weight to the observed association between $PM_{2.5}$ mixture and long-term post-KT outcomes was sulfate.

$PM_{2.5}$ mixture was associated with an increased risk of adverse post-transplant outcomes among KT recipients. Of all the $PM_{2.5}$ constituents included in this study, sulfate had the largest impact on long-term outcomes, while lead, organic carbon and Nickel were more related to short-term outcomes.

3.2 INTRODUCTION

$PM_{2.5}$ is a risk factor for kidney health. Previous epidemiology studies suggest that $PM_{2.5}$ is associated with increased risk of chronic kidney disease and kidney function decline(125). Kidney transplant (KT) recipients are likely to be vulnerable to the harmful effect of $PM_{2.5}$. Previous studies suggested that $PM_{2.5}$ has potential immunotoxicity(36, 126). Because of the chronic immunosuppression medications necessary for successful KT, alterations in the immune system may render recipients particularly susceptible to the infections and malignancy induced by air pollution(47, 48). Moreover, $PM_{2.5}$ could increase oxidative stress and systematic inflammatory responses(36), which are risk factors for adverse post-KT outcomes.

Emerging evidence suggests that $PM_{2.5}$ is a risk factor for adverse post-transplant outcomes among KT recipients(49, 50). However, these studies have generally treated $PM_{2.5}$ as a single, uniform exposure, assuming that its harmful effects are the same across regions with similar total $PM_{2.5}$ levels. In reality, $PM_{2.5}$ is a complex mixture of constituents with varying toxicities and health impacts(20). These constituents are emitted from different sources, which also vary geographically(72), meaning that even areas with identical total $PM_{2.5}$ levels may experience different health effects due to differences in composition. The impact of individual $PM_{2.5}$ constituents on post-KT outcomes remains unclear. Identifying the most harmful constituents could guide air pollution control strategies that specifically target these constituents or their primary sources. Such targeted approaches are likely to be more effective in reducing the adverse health impacts of $PM_{2.5}$ compared to broad strategies aimed at reducing total $PM_{2.5}$ levels. Moreover, the results from this study could also provide important information for kidney transplant recipients and kidney transplant candidates who seek to optimize their outcome by living in less polluted areas or installing HEPA filters. Therefore, understanding how $PM_{2.5}$ constituents influence post-KT outcomes is critical for improving the health of KT recipients. In this study, we aimed to evaluate effect of particulate constituents on adverse post-KT outcomes including delayed graft function (DGF), acute rejection, all-cause mortality and death-censored graft failure.

3.3 METHODS

Data Source

This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donors, wait-listed candidates, and transplant recipients in the US, submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration (HRSA), US Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors. This dataset has previously been described elsewhere(127).

Study population

We utilized SRTR data to identify adults who received their first KT between 2001 and 2016. To ensure consistency, we limited our analysis to participants with a residential ZIP code within the contiguous United States, excluding those with missing demographic, educational, recipient, or donor data. Follow-up started from the transplant date and ended on the date of loss to follow-up, death, or five years post-transplant, whichever occurred first. This study was approved by the IRB at New York University Grossman School of Medicine and was exempt under s22-00535, as the study participants could not be identified.

Exposure data

Mean annual levels of 15 $PM_{2.5}$ constituents (including Elemental carbon (EC), Ammonium ($NH4+$), Nitrate ($NO3^-$), Organic carbon (OC), Sulfate ($SO4^{2-}$), Bromine (Br), Calcium (Ca), Copper (Cu), Iron (Fe), Potassium (K), Nickel (Ni), Lead (Pb), Silicon (Si), Vanadium (V), and Zinc (Zn)) were estimated at a resolution of 50m x 50m in urban areas and 1km x 1km in rural areas(61, 128). The concentrations of

the 15 $PM_{2.5}$ constituents were estimated using advanced ensemble machine learning methods. These models integrated predictions from various machine learning algorithms and were then combined using either a geographically weighted generalized additive model, or super-learning. Predictive models for $PM_{2.5}$ constituents were developed using information from numerous predictors, including satellite data, meteorological information, and land use factors. The cross-validated R-squared values ranged from 0.80 to 0.96 for different constituents, which indicated strong model performance. Subsequently, the $PM_{2.5}$ constituent concentrations at the grid cell level were aggregated to the ZIP code level(63). These environmental exposures were then linked to the participants based on their year of KT and residential ZIP codes.

The exposure in this study was defined as the moving average of PM constituents during the 1-year period prior to KT. If a recipient received KT in July of 2006, then the exposure would be calculated as $\frac{7}{12} \times PM\ component\ level_{2006} + \frac{5}{12} \times PM\ component\ level_{2005}$.

Outcome

The outcomes of this study were post-KT outcomes including delayed graft function (DGF), acute rejection, graft failure, and all-cause mortality. DGF was defined as the need for dialysis during the first week after KT. Acute rejection was defined as having any acute rejections episodes within the first year after transplantation. Graft failure was defined as returning to dialysis or transplant. Information on mortality in SRTR was obtained from multiple sources including the National Technical Information Service's Death Master File, End-stage kidney disease (ESKD) Death Notification Form from Centers For Medicare& Medicaid Services and the follow-up reports from transplant programs(127).

Other covariates

In this study, we included individual factors and contextual factors as covariates. Individual level factors included age at transplant, sex, race/ethnicity, education (high school graduate or above/below high school graduate), body mass index (BMI), cause of end-stage kidney disease (ESKD) (diabetes, hypertension, glomerulonephritis and other), insurance type (public, private and other), years on dialysis, donor type (deceased/living), and cold ischemia time (CIT). Individual factors and donor factors were obtained from SRTR. Contextual factors included median household income, percentage of population who lived in poverty, percent of residents who were black, percentage of Medicare beneficiaries had at least 1 ambulatory visit in a year and annual mean temperature at the ZIP code of residence. Contextual variables were obtained from the American Community Survey (64) , the Dartmouth Atlas of Healthcare website (66) and DAYMET database(129). The year of KT was also included as a covariate to account for potential temporal trends in both the particulate constituent levels and the practice of kidney care and KT.

Statistical analysis

We used weighted quantile sum regressions to evaluate the association between PM constituent mixtures and post-KT outcomes. Weighted quantile sum regression is a statistical method for estimating the effects of a mixture with correlated constituents, it assumes each quantile increase in the mixture index is linearly and unidirectionally associated with the outcome(68). The method allowed us to estimate the overall effect of the mixture and the relative contribution of each constituent in the total effect while accounting for the correlation between different constituents. The regression process was separated into two stages. Data was first separated into a test set and a validation set. In the first stage, constituents were transformed into quantiles (we chose deciles), and the relative importance of each constituent was estimated in the test set. To ensure robustness in estimating the weights (relative importance) for individual constituents, 100 bootstrap samples were taken of the training set and the weights were fit in each sample. The mean weight for each constituent was then used in the second stage. All the weights for each constituent in the mixture were constrained to be positive and sums up to 1. In the second stage, a

mixture index was calculated by $\sum_i^j w_i d_i$, where w_i was the relative importance of the i^{th} constituent estimated from the first stage and d_i was the level ((in quantiles)) of the i^{th} constituent. Then the effect of the mixture index was estimated using a generalized linear model regression model in the validation set. The estimated effect of the mixture index evaluates the impact when the mixture index increased by one decile (The total effect when each of the constituents increased by one decile).

DGF and acute rejections were binary outcomes, therefore, we used a weighted quantile sum regression with a logit link to investigate the exposure-outcome associations. In our primary analysis for graft failure, people who died before having an event was censored at the time of death. For the two time-to-event outcomes (graft failure and all-cause mortality), we used the pooled logistic regression model, which has been shown to well approximate an Cox model, to evaluate the exposure-outcome associations. For each participant, we separated the follow-up period by months and created a new variable that indicates the number of months since transplantation. For example, if a participant censored that 24 months post-KT, this person would have 24 observations in the analysis and were excluded from the risk set after 24 months. In our primary analysis, we assumed non-informative censoring. The model below was used

$$logit\big(p(Y_t = 1|Y_{t-1} = 0)\big) = \beta_0 + \beta_1 \times wqs + \beta_z' Z + \beta_t' \, splines(t)$$

wqs indicates the mixture index, *Z* indicates the confounders; *t* indicates months since transplantation (time variable). In order to allow for a flexible baseline hazard, we included a natural spline for the time variable.

To identify vulnerable subgroups, we evaluated the effect measure modification by age at transplant (<55/ 55 or older), sex, race (White/non-White), donor type (deceased/living) and CIT (<=12hr/>12hr) by including the interaction term into the WQS model.

We conducted three sensitivity analysis: 1) restricting the analysis for DCGF and mortality to first year post-KT; 2) further controlling for NO2 and Ozone in the model; 3) running a Cox proportional hazard

model and another Fine and Gray's competing risk model with total $PM_{2.5}$ as the exposure to evaluate whether that competing risk had large impact on the observed association between the exposure and graft failure.

All of the regression models were adjusted for recipient factors, donor factors and contextual variables. The analysis was conducted using R 4.1.3 and Stata 17(130, 131).

3.4 RESULTS

In total, 192,587 KT recipients were included in the analysis. Of all the included KT recipients, 16,187 (8.4%) recipients experienced acute rejection, 35,793 (18.6%) had delayed graft function, 18,969 (9.7%) developed graft failure and 21,750 (11.3%) died during the follow-up. Detailed baseline characteristics are shown in table 3.1. Detailed distributions of the exposures are shown in table 3.2. The correlations between particulate constituents are shown in Appendix C figure S1.

Table 3.1 Baseline characteristics of the 192,587 kidney transplant recipients who received transplant in the US between 2001-2016.

	Overall
n	192,587
Age at transplant (mean (SD))	51.56 (13.47)
Female (%)	75,021 (39.0)
Race/ethnicity (%)	
White	97,927 (50.8)
Black	51,455 (26.7)
Hispanic/latino	28,586 (14.8)
*Other	14,619 (7.6)
BMI (mean (SD))	27.91 (5.50)
Cause of ESKD (%)	
Diabetes	68,556 (35.6)
Hypertension	42,985 (22.3)
Glomerulonephritis	39,994 (20.8)
Other	41,052 (21.3)
Education level below high school graduate	87,261 (45.3)
Insurance (mean (SD))	
Public	121,871 (63.3)
Private	70,571 (36.6)
Other	145 (0.1)
Year on dialysis (mean (SD))	2.91 (3.08)
Deceased donor(%)	117,145 (60.8)
Cold ischemia time (hr, mean (SD))	12.84 (10.79)
Median household income (mean (SD))	52,595.30 (21383.19)
Percent below poverty (mean (SD))	14.70 (9.09)
Percent Black (mean (SD))	17.04 (23.19)
Percent had at least 1 ambulatory visit (mean (SD))	76.81 (6.71)

SD: standard error; ESKD: end-stage kidney disease

Continuous variables are presented as mean (standard deviation) and categorical variables are presented as count(percentage)

*Other race/ethnicity included American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, Arab or Middle Eastern, Indian Sub-continent, Unknown, Multi-Racial

Table 3.2 ZIP code level PM2.5 constituent concentration during the year prior to transplant among the 192,587 kidney transplant recipients who received transplant in the US between 2001-2016.

Constituent	Median (IQR)
Total $PM_{2.5}$ (µg/m3)	9.9 (8.2-11.9)
Br (ng/m3)	3.0 (2.6-3.4)
Ca (ng/m3)	40.1 (30.1-58.2)
Cu (ng/m3)	2.7 (1.7- 4.0)
EC (µg/m3)	0.57 (0.44-0.74)
Fe (ng/m3)	65.8 (50.7-84.7)
k (ng/m3)	58.5 (51.9-67.2)
NH4 (µg/m3)	0.91 (0.60-1.33)
Ni (ng/m3)	0.59 (0.39-0.93)
NO3 (µg/m3)	1.13 (0.68-1.69)
OC (µg/m3)	1.84 (1.53-2.27)
Pb (ng/m3)	1.87 (1.34-2.91)
Si (ng/m3)	85.4 (61,7-129.4)
SO4 (µg/m3)	2.13 (1.52-3.11)
V (ng/m3)	0.77 (0.41-1.47)
Zn (ng/m3)	8.1 (5.9-10.9)

After adjusting for the potential confounders, each one decile increased in the mixture of particulate constituents was associated with a 6.8% (95%CI 5.8-7.8%) increase in the odds of DGF among KT recipients. The particulate constituents with the highest relative importance were OC (35.6%), Ni (34.4%) and NO3 (21.3%).

Each one decile increased in the mixture of particulate constituents was associated with a 3.6% (95%CI 2.1-5.1%) increase in the odds of acute rejections. 75% of the observed effect of particulate constituent mixture on acute rejection was contributed by Pb (figure 1).

Each decile increase in the mixture index was associated with a 4.7% (95%CI 3.3-6.3%) increase in the hazard of graft failure after KT. The constituent which contributed the largest weight to the observed associations was SO4, with the relative importance of 51.3%. Detailed distributions of the relative importance are shown in figure 1.

Each decile increase in the mixture index was associated with a 3.9% (95%CI 2.5-5.2) increase in the hazard of all-cause mortality among KT recipients within 5 years post-KT. Similar to graft failure, the constituents which contributed the largest weights to the observed associations were SO4 (30.1%) and NH4 (22.1%). In addition, Pb also contributed to the observed outcome, with an estimated importance of 13.3%.

Figure 3.1 The estimate contribution of each PM2.5 constituent in the association between PM2.5 mixture and post-transplant outcomes among kidney transplant recipients.

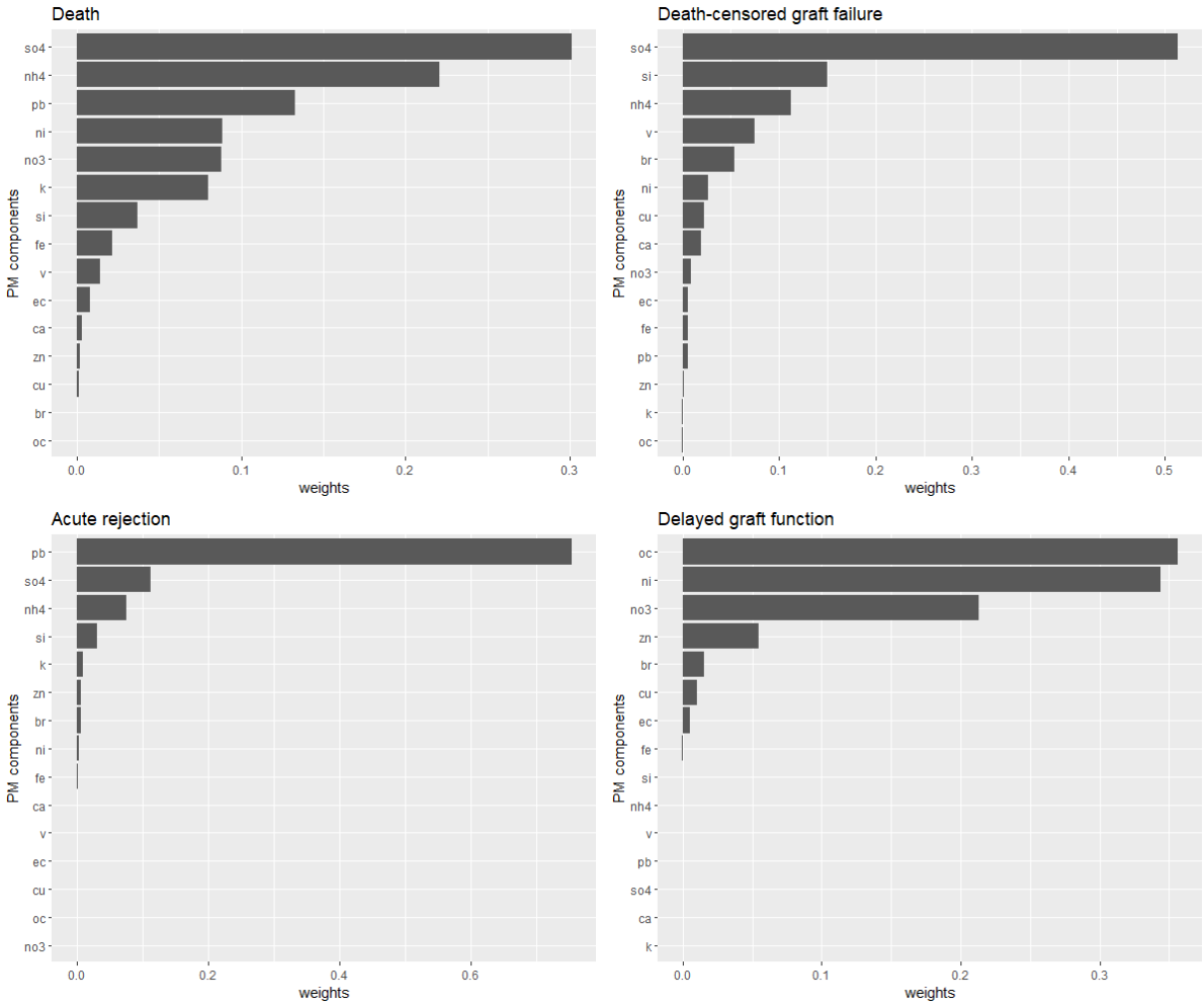


Table 3.3 Estimated effect of each decile increase in PM2.5 mixture on post-transplant outcomes among 192,587 kidney transplant recipients who received transplant in the US between 2001-2016.

		Death		Death-censored graft failure		Acute rejection		Delayed graft function	
		aHR (95%CI)	$p_{interaction}$	aHR (95%CI)	$p_{interaction}$	aOR (95%CI)	$p_{interaction}$	aOR (95%CI)	$p_{interaction}$
Age	<55	**1.060 (1.040,1.081)**	**0.038**	1.048 (1.029,1.067)	0.435	1.031 (1.019,1.05)	0.498	**1.075 (1.061,1.090)**	**0.015**
	>=55	**1.038 (1.000,1.076)**		1.058 (1.021,1.095)		1.032 (0.998,1.066)		**1.096 (1.068,1.125)**	
Sex	male	1.050 (1.035,1.066)	0.772	1.049 (1.032,1.065)	0.17	1.026 (1.015,1.038)	0.062	1.080 (1.066,1.093)	0.122
	female	1.047 (1.016,1.079)		1.034 (1.002,1.067)		1.038 (1.015,1.061)		1.094 (1.067,1.122)	
Race	non-White	1.049 (1.033,2.76)	0.091	**1.075 (1.058,1.093)**	**0.014**	**1.051 (1.038,1.068)**	**0.008**	**1.081 (1.066,1.096)**	**0.04**
	White	1.034 (1.004,1.064)		**1.051 (1.019,1.084)**		**1.013 (0.968,1.061)**		**1.061 (1.031,1.091)**	
Donor Type	living	1.038 (1.019,1.058)	0.644	1.068 (1.038,1.098)	0.736	**1.014 (1.005,1.02)**	**<0.001**	**1.133 (1.106,1.16)**	**<0.001**
	deceased	1.033 (0.996,1.072)		1.073 (1.02,1.128)		**1.047 (1.03,1.063)**		**1.085 (1.035,1.137)**	
CIT	<12hr	1.046 (1.03,1.062)	0.521	1.074 (1.051,1.097)	0.13	**1.012 (1.005,1.017)**	**<0.001**	**1.071 (1.053,1.09)**	**0.002**
	>=12hr	1.040 (1.009,1.072)		1.055 (1.015,1.098)		**1.047 (1.025,1.07)**		**1.102 (1.067,1.138)**	

aHR: adjusted hazard ratio for each decile increases in the mixture index; aOR: adjusted odds ratio for for each decile increases in the mixture index; CIT: cold-ischemia time

The rankings of the relative importance of each constituent did not change significantly after including the interaction terms in the model (Appendix B table S1-S4). The effect exposure-outcome associations were larger for acute rejection, DGF, and DCGF among KT recipients who were non-White than those who were White (table 3). Significant effect measure modification was also observed for cold ischemia time in our analysis of the short-term outcomes and larger effects were observed among those who had longer CIT. Detailed results for the interaction analysis are shown in table 3.3.

The results of the sensitivity analysis are shown in Appendix B (table S5-S9).

3.5 DISCUSSION

In this national study among all adult KT recipients among the US between 2001-2016, we observed that higher levels of particulate constituent mixtures were associated with increased risk of adverse post-KT outcomes. For long-term outcomes, SO4 contributed most to the observed effect. Pb was the most important particulate constituent on the associations between particulate constituent mixture and acute rejection. Ni and OC had the highest relative importance in the association between the $PM_{2.5}$ mixture and DGF. To the best of our knowledge, this is the first study to investigate the impact of different $PM_{2.5}$ constituents on post-KT outcomes.

We observed that SO4 had the largest contributions to the association between the particulate constituent mixture and long-term outcomes among KT recipients. The majority of the SO4 in $PM_{2.5}$ came from coal burning, resulting from the secondary formation of SO4 from SO2 emissions. Coal-related $PM_{2.5}$ has been decreasing in the US during the past decades due to new technology and policy changes, but it remains a large environmental concern in many developing countries(132, 133). Previous studies found that SO4 in $PM_{2.5}$ was associated with increased risk of multiple diseases including cancers and infections(134, 135), suggesting that SO4 could potentially affect the immune system of human body. A panel study suggested

that Sulfates could increase oxidative stress and coagulation in human body, which poses great risk to KT recipients(136). Coagulation could lead to tissue hyperfusion, ischemia and necrosis, which leads to kidney damage(137). Moreover, oxidative stress induced by Sulfate particles could also lead to inflammation and potentially lead to immunothrombosis, which is another important risk factor for graft failure(138).

Over ¾ of the observed effect of $PM_{2.5}$ mixture on acute rejection was attributable to Lead in our study. The Lead in air pollution significantly decreased after the banning of leaded gasoline in the US in 1996(139). However, Lead continues to be emitted from industrial sources such as ore and metal processing(140). Lead is also higher near roads because of the use of Lead weights to balance tires, which fall off and are ground down by subsequent traffic. Thus, Lead could be serving as a proxy for other unmeasured components of traffic particles. Previous studies suggested that Lead is a heavy metal with potential nephrotoxicity(141, 142). Higher exposure to Lead has also been found to be associated with worse long-term outcomes among KT recipients. Sotomayor et.al observed that higher plasma Lead level was associated with increased risk of graft failure among a cohort of Dutch KT recipients(143). The observed impact of Lead on acute rejection could be due to its effect on immune system. Experimental studies suggested that Lead induced changes in the activity of T cells, decreased the production of IFN-γ, a cytokine which prevents early thrombosis, congestion and necrosis after KT(144, 145). Moreover, exposure to Lead could also lead to increased oxidative stress in the system, which is another risk factor for acute rejection(146, 147).

OC and Nickel were the top contributors in the association between $PM_{2.5}$ mixtures and delayed graft function. This result suggested that the adverse effect of $PM_{2.5}$ on delayed function is likely to be driven by $PM_{2.5}$ which sourced from fuel oil combustion, vehicle emissions and biomass burning. Environmental risk factors are believed to be less important in the development of DGF(148). However, environmental factors could potentially induce some predisposed conditions among KT recipients which leads to higher

vulnerability and thus increase the risk of DGF. In our interaction analysis, we observed that KT recipients with longer CIT experienced higher $PM_{2.5}$ mixture related risk of DGF, which also suggest that environmental risk factors and transplant factors could potentially interplay and lead to worse outcomes among the patients.

Our study found that the primary contributing constituents to the observed association between $PM_{2.5}$ and post-KT outcomes differ depending on the specific outcome. The association between SO4 and long-term outcomes suggested that it may affects kidney transplant recipients mainly through long-term systematic process like chronic inflammation(149). In contrast, Pb might more directly target immune cell function and antigen presentation(144, 145). The association of OC and Ni, a potent inducer of oxidative stress, with delayed graft function (DGF) aligns mechanistically with their potential to cause intense oxidative damage during the critical peri-transplant ischemia-reperfusion phase, impairing initial recovery and function(78, 150). Our results suggested that $PM_{2.5}$ affects KT recipients through multiple mechanisms and that the toxicity of its constituents varies. $PM_{2.5}$ is currently regulated as a single air pollutant in the US and many other countries, with most existing studies treating it as a uniform exposure that assumes all constituents and sources of $PM_{2.5}$ have the same level of toxicity(49, 50). Findings from this study and an increasing body of evidence suggested that the toxicity and health impacts of $PM_{2.5}$ can vary significantly based on its different constituents and sources.

This study has several strengths. First, this study included nearly all of the KT recipients in the US who received transplant during the study period, which allowed sufficient power in our analysis and good generalizability of the results. Second, SRTR collects data on a large number of recipient and donor related factors, which allowed us to control for important confounders in the study. Moreover, this study used the weighted quantile sum regression to investigate the associations between $PM_{2.5}$ constituents and post-KT outcomes, which allowed us to handle the high correlation between different constituents.

This study is also limited in the following aspects. First, because of confidentiality concerns, we had to use ZIP code level exposures instead of individual level exposures in this study. The actual exposure level

could be influenced by different individual factors and therefore leads to measurement error. However, a previous study suggested that ambient $PM_{2.5}$ exposure level is a valid proxy for individual exposure and could help avoid some confounding from individual level confounders(96). PM2.5 constituent levels could vary over short distances, therefore, the process of aggregating exposures to ZIP code level could also lead to measurement error. However, the aggregation process is independent of the outcome status and the measurement of the outcome. Therefore, the measurement is likely to be independent and non-differential and bias the estimates towards to null. Second, we were only able to obtain ZIP code information at the year of KT, which may not reflect the real area that the recipient spent most of their time prior to KT. However, the ZIP code information from SRTR has successfully served as proxies of physical locations in multiple studies. Third, given that the ZIP code information was not updated during the study period, we were not able to use time-varying exposure in this study, which may bias the estimates for long-term outcomes. However, the results remained consistent when we limited the follow-up time to first year post-KT. Lastly, although we try to include all the potential confounders that are available to our model, given the observational nature of the study, residual confounding is always possible.

In conclusion, $PM_{2.5}$ mixture was associated with increased risk of adverse post-transplant outcomes among KT recipients. Of all the $PM_{2.5}$ constituents included in this study, SO4 had the largest impact on long-term outcomes, while Pb, OC and Ni were more related to short-term outcomes. It's likely that KT recipients would be benefit from a more targeted $PM_{2.5}$ control strategy than a universal one. Future regulations on $PM_{2.5}$ should consider focusing on the major sources of the $PM_{2.5}$ constituents with larger health impact. KT recipients/candidates could consider moving to areas with lower levels of harmful constituents or to use HEPA particle filters to optimize post-transplant outcomes.

CONCLUSION

This dissertation evaluated the link between environmental exposures (PM2.5, mean temperature and temperature variability) and immune related outcomes among large population settings. In the first study, using non-negative matrix factorization and weighted-quantile sum regression, we addressed the collinearity between PM2.5 constituents, and evaluated the association between long-term PM2.5 constituents, source specific PM2.5, and admissions from non-respiratory infections among Medicare beneficiaries. W found that higher PM2.5 was associated with increased hospital admissions from total non-respiratory infections and its sub-types including intestinal infections, urinary tract infection and septicemia. Sulfates, Nickel and Copper were the most important constituents in the observed associations between the PM2.5 mixture and non-respiratory infections. Anthropogenic sources of PM2.5 including coal burning, fuel oil combustion and traffic were the sources that associated with the largest effect.

In the second study, using an adapted DID method, we evaluated the association between seasonal temperature variability and admissions from infections among older population in the US. By using the adapted DID, we were able to control for the between-ZIP code confounding that changed slowly over time. We found that higher temperature variability, higher mean temperature in warm season and lower mean temperature were associated with increased hospital admissions from infections. The result suggested that extreme and unstable temperature conditions could lead to adverse health impact, which highlighted the importance of controlling for climate change.

In the third study, we switched our focus to KT recipients, an immunocompromised population. Using weighted quantile sum regression, we evaluated the association between PM2.5 constituent exposures prior to KT and adverse post-KT outcomes. We observed that sulfate, lead, organic carbon and nickel contributed the highest weights in the association between PM2.5 and adverse outcomes post-KT. Moreover, recipients who were non-white and received a kidney with longer CIT were likely to be more vulnerable to the harmful impact of PM2.5.

This study adds to the growing body of evidence indicating that the health effects of PM2.5 are not uniform but vary depending on its specific chemical constituents and sources. PM2.5 emitted from different origins can have distinct impacts on human health, suggesting that the toxicity of PM2.5 is closely tied to its composition. Despite this, current regulatory standards focus solely on the total mass concentration of PM2.5, which may not be the most effective approach for protecting public health. Targeted PM2.5 control strategies that address the most harmful constituents or emission sources have the potential to achieve greater improvements in population health outcomes. Moreover, our results also highlight that the change in temperature associated with climate change pose a significant threat to human health. These findings underscore the urgent need to implement effective strategies to slow down climate change, in order to protect public health and mitigate future health risks associated with a warming climate.

REFERENCE

1. U.S. EPA. Integrated Science Assessment (ISA) for Particulate Matter (Final Report, Dec 2019). U.S. Environmental Protection Agency, Washington, DC.; 2019.
2. Cohen AJ, Brauer M, Burnett R, Anderson HR, Frostad J, Estep K, et al. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. Lancet. 2017;389(10082):1907-18.
3. Brook RD, Rajagopalan S, Pope CA, 3rd, Brook JR, Bhatnagar A, Diez-Roux AV, et al. Particulate matter air pollution and cardiovascular disease: An update to the scientific statement from the American Heart Association. Circulation. 2010;121(21):2331-78.
4. Xing YF, Xu YH, Shi MH, Lian YX. The impact of PM2.5 on the human respiratory system. J Thorac Dis. 2016;8(1):E69-74.
5. Shi L, Steenland K, Li H, Liu P, Zhang Y, Lyles RH, et al. A national cohort study (2000-2018) of long-term air pollution exposure and incident dementia in older adults in the United States. Nat Commun. 2021;12(1):6754.
6. Dhalla NS, Temsah RM, Netticadan T. Role of oxidative stress in cardiovascular diseases. J Hypertens. 2000;18(6):655-73.
7. Brook RD, Urch B, Dvonch JT, Bard RL, Speck M, Keeler G, et al. Insights into the mechanisms and mediators of the effects of air pollution exposure on blood pressure and vascular function in healthy humans. Hypertension. 2009;54(3):659-67.
8. Sun Q, Yue P, Ying Z, Cardounel AJ, Brook RD, Devlin R, et al. Air pollution exposure potentiates hypertension through reactive oxygen species-mediated activation of Rho/ROCK. Arterioscler Thromb Vasc Biol. 2008;28(10):1760-6.
9. Brook RD, Franklin B, Cascio W, Hong Y, Howard G, Lipsett M, et al. Air pollution and cardiovascular disease: a statement for healthcare professionals from the Expert Panel on Population and Prevention Science of the American Heart Association. Circulation. 2004;109(21):2655-71.
10. Nel A. Atmosphere. Air pollution-related illness: effects of particles. Science. 2005;308(5723):804-6.
11. Arimoto T, Yoshikawa T, Takano H, Kohno M. Generation of reactive oxygen species and 8-hydroxy-2 -deoxyguanosine formation from diesel exhaust particle components in L1210 cells. Jpn J Pharmacol. 1999;80(1):49-54.
12. Ren C, Vokonas PS, Suh H, Fang S, Christiani DC, Schwartz J. Effect modification of air pollution on Urinary 8-Hydroxy-2 -Deoxyguanosine by genotypes: an application of the multiple testing procedure to identify significant SNP interactions. Environ Health. 2010;9:78.
13. Tokiwa H, Sera N, Nakanishi Y, Sagai M. 8-Hydroxyguanosine formed in human lung tissues and the association with Diesel exhaust particles. Free Radic Biol Med. 1999;27(11-12):1251-8.
14. Prahalad AK, Inmon J, Ghio AJ, Gallagher JE. Enhancement of 2 -deoxyguanosine hydroxylation and DNA damage by coal and oil fly ash in relation to particulate metal content and availability. Chem Res Toxicol. 2000;13(10):1011-9.
15. Prahalad AK, Inmon J, Dailey LA, Madden MC, Ghio AJ, Gallagher JE. Air pollution particles mediated oxidative DNA base damage in a cell free system and in human airway epithelial cells in relation to particulate metal content and bioreactivity. Chem Res Toxicol. 2001;14(7):879-87.

16. Knaapen AM, Shi T, Borm PJ, Schins RP. Soluble metals as well as the insoluble particle fraction are involved in cellular DNA damage induced by particulate matter. Mol Cell Biochem. 2002;234-235(1-2):317-26.
17. Kim JY, Mukherjee S, Ngo LC, Christiani DC. Urinary 8-hydroxy-2 -deoxyguanosine as a biomarker of oxidative DNA damage in workers exposed to fine particulates. Environ Health Perspect. 2004;112(6):666-71.
18. Sigaud S, Goldsmith CA, Zhou H, Yang Z, Fedulov A, Imrich A, et al. Air pollution particles diminish bacterial clearance in the primed lungs of mice. Toxicol Appl Pharmacol. 2007;223(1):1-9.
19. Zhou H, Kobzik L. Effect of concentrated ambient particles on macrophage phagocytosis and killing of Streptococcus pneumoniae. Am J Respir Cell Mol Biol. 2007;36(4):460-5.
20. Kelly FJ, Fussell JC. Size, source and chemical composition as determinants of toxicity attributable to ambient particulate matter. Atmospheric environment. 2012;60:504-26.
21. Cervellati F, Benedusi M, Manarini F, Woodby B, Russo M, Valacchi G, et al. Proinflammatory properties and oxidative effects of atmospheric particle components in human keratinocytes. Chemosphere. 2020;240:124746.
22. Gasparrini A, Guo Y, Hashizume M, Lavigne E, Zanobetti A, Schwartz J, et al. Mortality risk attributable to high and low ambient temperature: a multicountry observational study. Lancet. 2015;386(9991):369-75.
23. Alahmad B, Khraishah H, Roye D, Vicedo-Cabrera AM, Guo Y, Papatheodorou SI, et al. Associations Between Extreme Temperatures and Cardiovascular Cause-Specific Mortality: Results From 27 Countries. Circulation. 2023;147(1):35-46.
24. Thompson R, Lawrance EL, Roberts LF, Grailey K, Ashrafian H, Maheswaran H, et al. Ambient temperature and mental health: a systematic review and meta-analysis. Lancet Planet Health. 2023;7(7):e580-e9.
25. Liu JF, Chen PC, Ling TY, Hou CH. Hyperthermia increases HSP production in human PDMCs by stimulating ROS formation, p38 MAPK and Akt signaling, and increasing HSF1 activity. Stem Cell Res Ther. 2022;13(1):236.
26. Imberti L, Tiecco G, Logiudice J, Castelli F, Quiros-Roldan E. Effects of Climate Change on the Immune System: A Narrative Review. Health Sci Rep. 2025;8(4):e70627.
27. Geng Y, Li R, He SX, Yang HH, Deng QT, Shao XY, et al. Dexmedetomidine Attenuates Acute Lung Injury Induced by Heatstroke and Improve Outcome. Shock. 2019;52(5):532-9.
28. Hsieh YC, Chen RF, Yeh YS, Lin MT, Hsieh JH, Chen SH. Kynurenic acid attenuates multiorgan dysfunction in rats after heatstroke. Acta Pharmacol Sin. 2011;32(2):167-74.
29. Cai J, Meng X, Wang C, Chen R, Zhou J, Xu X, et al. The cold effects on circulatory inflammation, thrombosis and vasoconstriction in type 2 diabetic patients. Sci Total Environ. 2016;568:271-7.
30. Manchal N, Young MK, Castellanos ME, Leggat P, Adegboye O. A systematic review and meta-analysis of ambient temperature and precipitation with infections from five food-borne bacterial pathogens. Epidemiol Infect. 2024;152:e98.
31. Collaborators GBDURIOM. Global, regional, and national burden of upper respiratory infections and otitis media, 1990-2021: a systematic analysis from the Global Burden of Disease Study 2021. Lancet Infect Dis. 2025;25(1):36-51.
32. Peery AF, Crockett SD, Murphy CC, Lund JL, Dellon ES, Williams JL, et al. Burden and Cost of Gastrointestinal, Liver, and Pancreatic Diseases in the United States: Update 2018. Gastroenterology. 2019;156(1):254-72 e11.

33. Schappert SM, Rechtsteiner EA. Ambulatory medical care utilization estimates for 2007. Vital Health Stat 13. 2011(169):1-38.
34. Flores-Mireles AL, Walker JN, Caparon M, Hultgren SJ. Urinary tract infections: epidemiology, mechanisms of infection and treatment options. Nat Rev Microbiol. 2015;13(5):269-84.
35. Paoli CJ, Reynolds MA, Sinha M, Gitlin M, Crouser E. Epidemiology and Costs of Sepsis in the United States-An Analysis Based on Timing of Diagnosis and Severity Level. Crit Care Med. 2018;46(12):1889-97.
36. Calderon-Garciduenas L, Solt AC, Henriquez-Roldan C, Torres-Jardon R, Nuse B, Herritt L, et al. Long-term air pollution exposure is associated with neuroinflammation, an altered innate immune response, disruption of the blood-brain barrier, ultrafine particulate deposition, and accumulation of amyloid beta-42 and alpha-synuclein in children and young adults. Toxicol Pathol. 2008;36(2):289-310.
37. Dai L, Mehta A, Mordukhovich I, Just AC, Shen J, Hou L, et al. Differential DNA methylation and PM(2.5) species in a 450K epigenome-wide association study. Epigenetics. 2017;12(2):139-48.
38. Fossati S, Baccarelli A, Zanobetti A, Hoxha M, Vokonas PS, Wright RO, et al. Ambient particulate air pollution and microRNAs in elderly men. Epidemiology. 2014;25(1):68-78.
39. Liang Y, Fang L, Pan H, Zhang K, Kan H, Brook JR, et al. PM2.5 in Beijing - temporal pattern and its association with influenza. Environ Health. 2014;13:102.
40. Zhi W, Xu Q, Chen Z, Jiang W, Wang T, Zhou Y, et al. Respiratory syncytial virus infection in children and its correlation with climatic and environmental factors. J Int Med Res. 2021;49(9):3000605211044593.
41. Chen MJ, Yang PH, Hsieh MT, Yeh CH, Huang CH, Yang CM, et al. Machine learning to relate PM2.5 and PM10 concentrations to outpatient visits for upper respiratory tract infections in Taiwan: A nationwide analysis. World J Clin Cases. 2018;6(8):200-6.
42. Wang Y, Liu Z, Yang L, Zhou J, Li J, Liao HL, et al. Sepsis-related hospital admissions and ambient air pollution: a time series analysis in 6 Chinese cities. BMC Public Health. 2021;21(1):1182.
43. Honda TJ, Kazemiparkouhi F, Henry TD, Suh HH. Long-term PM(2.5) exposure and sepsis mortality in a US medicare cohort. BMC Public Health. 2022;22(1):1214.
44. Gu J, Shi Y, Zhu Y, Chen N, Wang H, Zhang Z, et al. Ambient air pollution and cause-specific risk of hospital admission in China: A nationwide time-series study. PLoS Med. 2020;17(8):e1003188.
45. OPTN. OPTN: Organ Procurement & Transplantation Network 2023 [Available from: https://optn.transplant.hrsa.gov/data/.
46. Sussell J, Silverstein AR, Goutam P, Incerti D, Kee R, Chen CX, et al. The economic burden of kidney graft failure in the United States. Am J Transplant. 2020;20(5):1323-33.
47. Fishman JA. Infection in Organ Transplantation. Am J Transplant. 2017;17(4):856-79.
48. Au E, Wong G, Chapman JR. Cancer in kidney transplant recipients. Nat Rev Nephrol. 2018;14(8):508-20.
49. Feng Y, Jones MR, Ahn JB, Garonzik-Wang JM, Segev DL, McAdams-DeMarco M. Ambient air pollution and posttransplant outcomes among kidney transplant recipients. Am J Transplant. 2021;21(10):3333-45.

50. Chang SH, Merzkani M, Murad H, Wang M, Bowe B, Lentine KL, et al. Association of Ambient Fine Particulate Matter Air Pollution With Kidney Transplant Outcomes. JAMA Netw Open. 2021;4(10):e2128190.
51. World Health Organization. Deaths by Cause, Age, Sex, by Country and by Region, 2000-2016.2018. Available from: https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates.
52. Pun VC, Kazemiparkouhi F, Manjourides J, Suh HH. Long-Term PM2.5 Exposure and Respiratory, Cancer, and Cardiovascular Mortality in Older US Adults. Am J Epidemiol. 2017;186(8):961-9.
53. Calderon-Garciduenas L, Solt AC, Henriquez-Roldan C, Torres-Jardon R, Nuse B, Herritt L, et al. Long-term air pollution exposure is associated with neuroinflammation, an altered innate immune response, disruption of the blood-brain barrier, ultrafine particulate deposition, and accumulation of amyloid beta-42 and alpha-synuclein in children and young adults. Toxicol Pathol. 2008;36(2):289-310.
54. Dai L, Mehta A, Mordukhovich I, Just AC, Shen J, Hou L, et al. Differential DNA methylation and PM2.5 species in a 450K epigenome-wide association study. Epigenetics. 2017;12(2):139-48.
55. Chen PC, Mou CH, Chen CW, Hsieh DPH, Tsai SP, Wei CC, et al. Roles of Ambient Temperature and PM(2.5) on Childhood Acute Bronchitis and Bronchiolitis from Viral Infection. Viruses. 2022;14(9).
56. Sarmiento EJ, Moore JX, McClure LA, Griffin R, Al-Hamdan MZ, Wang HE. Fine Particulate Matter Pollution and Risk of Community-Acquired Sepsis. Int J Environ Res Public Health. 2018;15(4).
57. Hoffman ED, Jr., Klees BS, Curtis CA. Overview of the Medicare and Medicaid programs. Health Care Financ Rev Stat Suppl. 2002:1-378.
58. Healthcare Cost and Utilization Project (HCUP). HCUP CCS, March 2017. [Available from: www.hcup-us.ahrq.gov/toolssoftware/ccs/ccs.jsp.
59. Healthcare Cost and Utilization Project (HCUP). Clinical Classifications Software Refined (CCSR). December 2022. [Available from: www.hcup-us.ahrq.gov/toolssoftware/ccsr/ccs_refined.jsp.
60. Di Q, Amini H, Shi L, Kloog I, Silvern R, Kelly J, et al. An ensemble-based model of PM(2.5) concentration across the contiguous United States with high spatiotemporal resolution. Environ Int. 2019;130:104909.
61. Amini H, Danesh-Yazdi M, Di Q, Requia W, Wei Y, AbuAwad Y, et al. Annual Mean PM2.5 Components (EC, NH4, NO3, OC, SO4) 50m Urban and 1km Non-Urban Area Grids for Contiguous U.S., 2000-2019 v1. Palisades, New York: NASA Socioeconomic Data and Applications Center (SEDAC); 2023.
62. Amini H, Danesh-Yazdi M, Di Q, Requia W, Wei Y, AbuAwad Y, et al. Hyperlocal super-learned PM2.5 components across the contiguous US. 2022 [Available from: Research Square [https://doi.org/10.21203/rs.3.rs-1745433/v2].
63. Wei Y, Wang Y, Wu X, Di Q, Shi L, Koutrakis P, et al. Causal Effects of Air Pollution on Mortality Rate in Massachusetts. Am J Epidemiol. 2020;189(11):1316-23.
64. American Community Survey (ACS) [Available from: https://www.census.gov/programs-surveys/acs.
65. Census Bureau Data [Available from: https://data.census.gov/.
66. The Dartmouth Atlas of Health Care [Available from: https://www.dartmouthatlas.org/.

67. Abatzoglou JT. Development of gridded surface meteorological data for ecological applications and modelling. International Journal of Climatology. 2013;33(1):121-31.
68. Carrico C, Gennings C, Wheeler DC, Factor-Litvak P. Characterization of Weighted Quantile Sum Regression for Highly Correlated Data in a Risk Analysis Setting. J Agric Biol Environ Stat. 2015;20(1):100-20.
69. Wang YX, Zhang YJ. Nonnegative Matrix Factorization: A Comprehensive Review. IEEE Transactions on Knowledge and Data Engineering. 2013;25(6):1336-53.
70. Gaujoux R, Seoighe C. A flexible R package for nonnegative matrix factorization. BMC Bioinformatics. 2010;11:367.
71. Qiu X, Wei Y, Amini H, Wang C, Weisskopf M, Koutrakis P, et al. Fine particle components and risk of psychiatric hospitalization in the U.S. Sci Total Environ. 2022;849:157934.
72. Thurston GD, Ito K, Lall R. A Source Apportionment of U.S. Fine Particulate Matter Air Pollution. Atmos Environ (1994). 2011;45(24):3924-36.
73. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing. 2022.
74. Guo C, Yu T, Lin C, Chang LY, Bo Y, Wong MCS, et al. Habitual Exercise, Air Pollution, and Pneumonia Mortality: A Longitudinal Cohort Study of Approximately 0.4 Million Adults. Am J Epidemiol. 2022;191(10):1732-41.
75. Wei Y, Wang Y, Di Q, Choirat C, Wang Y, Koutrakis P, et al. Short term exposure to fine particulate matter and hospital admission risks and costs in the Medicare population: time stratified, case crossover study. BMJ. 2019;367:l6258.
76. Tao RJ, Cao WJ, Li MH, Yang L, Dai RX, Luo XL, et al. PM2.5 compromises antiviral immunity in influenza infection by inhibiting activation of NLRP3 inflammasome and expression of interferon-beta. Mol Immunol. 2020;125:178-86.
77. Lee A, Kinney P, Chillrud S, Jack D. A Systematic Review of Innate Immunomodulatory Effects of Household Air Pollution Secondary to the Burning of Biomass Fuels. Ann Glob Health. 2015;81(3):368-74.
78. Genchi G, Carocci A, Lauria G, Sinicropi MS, Catalano A. Nickel: Human Health and Environmental Toxicology. Int J Environ Res Public Health. 2020;17(3).
79. Roberts JR, Young SH, Castranova V, Antonini JM. The soluble nickel component of residual oil fly ash alters pulmonary host defense in rats. J Immunotoxicol. 2009;6(1):49-61.
80. Figliuzzi M, Tironi M, Longaretti L, Mancini A, Teoldi F, Sangalli F, et al. Copper-dependent biological effects of particulate matter produced by brake systems on lung alveolar cells. Arch Toxicol. 2020;94(9):2965-79.
81. Crouse DL, Philip S, van Donkelaar A, Martin RV, Jessiman B, Peters PA, et al. A New Method to Jointly Estimate the Mortality Risk of Long-Term Exposure to Fine Particulate Matter and its Components. Sci Rep. 2016;6:18916.
82. Thurston GD, Burnett RT, Turner MC, Shi Y, Krewski D, Lall R, et al. Ischemic Heart Disease Mortality and Long-Term Exposure to Source-Related Components of U.S. Fine Particle Air Pollution. Environ Health Perspect. 2016;124(6):785-94.
83. Li W, Wang J, Zhou K, Tian Y, Wei F, Zhang M, et al. Association of PM(2.5) and its components with lengths of hospital stay for hand foot and mouth disease in children. Environ Sci Pollut Res Int. 2022;29(33):50598-607.

84. Meng X, Hang Y, Lin X, Li T, Wang T, Cao J, et al. A satellite-driven model to estimate long-term particulate sulfate levels and attributable mortality burden in China. Environ Int. 2023;171:107740.
85. Brehmer C, Lai A, Clark S, Shan M, Ni K, Ezzati M, et al. The Oxidative Potential of Personal and Household PM2.5 in a Rural Setting in Southwestern China. Environ Sci Technol. 2019;53(5):2788-98.
86. Fang T, Guo H, Zeng L, Verma V, Nenes A, Weber RJ. Highly Acidic Ambient Particles, Soluble Metals, and Oxidative Potential: A Link between Sulfate and Aerosol Toxicity. Environ Sci Technol. 2017;51(5):2611-20.
87. Vohra K, Vodonos A, Schwartz J, Marais EA, Sulprizio MP, Mickley LJ. Global mortality from outdoor fine particle pollution generated by fossil fuel combustion: Results from GEOS-Chem. Environ Res. 2021;195:110754.
88. Chen Y, Chen R, Chen Y, Dong X, Zhu J, Liu C, et al. The prospective effects of long-term exposure to ambient PM(2.5) and constituents on mortality in rural East China. Chemosphere. 2021;280:130740.
89. Dherani M, Pope D, Mascarenhas M, Smith KR, Weber M, Bruce N. Indoor air pollution from unprocessed solid fuel use and pneumonia risk in children aged under five years: a systematic review and meta-analysis. Bull World Health Organ. 2008;86(5):390-8C.
90. Fan ZT, Meng Q, Weisel C, Laumbach R, Ohman-Strickland P, Shalat S, et al. Acute exposure to elevated PM2.5 generated by traffic and cardiopulmonary health effects in healthy older adults. J Expo Sci Environ Epidemiol. 2009;19(5):525-33.
91. Hart JE, Spiegelman D, Beelen R, Hoek G, Brunekreef B, Schouten LJ, et al. Long-Term Ambient Residential Traffic-Related Exposures and Measurement Error-Adjusted Risk of Incident Lung Cancer in the Netherlands Cohort Study on Diet and Cancer. Environ Health Perspect. 2015;123(9):860-6.
92. Heck JE, Wu J, Lombardi C, Qiu J, Meyers TJ, Wilhelm M, et al. Childhood cancer and traffic-related air pollution exposure in pregnancy and early life. Environ Health Perspect. 2013;121(11-12):1385-91.
93. Thorpe A, Harrison RM. Sources and properties of non-exhaust particulate matter from road traffic: a review. Sci Total Environ. 2008;400(1-3):270-82.
94. Boogaard H, Patton AP, Atkinson RW, Brook JR, Chang HH, Crouse DL, et al. Long-term exposure to traffic-related air pollution and selected health outcomes: A systematic review and meta-analysis. Environ Int. 2022;164:107262.
95. Mastorakos P, McGavern D. The anatomy and immunology of vasculature in the central nervous system. Sci Immunol. 2019;4(37).
96. Weisskopf MG, Webster TF. Trade-offs of Personal Versus More Proxy Exposure Measures in Environmental Epidemiology. Epidemiology. 2017;28(5):635-43.
97. Collaborators GBDLRI. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory infections in 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Infect Dis. 2018;18(11):1191-210.
98. Ianevski A, Zusinaite E, Shtaida N, Kallio-Kokko H, Valkonen M, Kantele A, et al. Low Temperature and Low UV Indexes Correlated with Peaks of Influenza Virus Activity in Northern Europe during 2010(-)2018. Viruses. 2019;11(3).
99. Alto BW, Bettinardi D. Temperature and dengue virus infection in mosquitoes: independent effects on the immature and adult stages. Am J Trop Med Hyg. 2013;88(3):497-505.

100. Vialard F, Olivier M. Thermoneutrality and Immunity: How Does Cold Stress Affect Disease? Front Immunol. 2020;11:588387.
101. Kox M, Stoffels M, Smeekens SP, van Alfen N, Gomes M, Eijsvogels TM, et al. The influence of concentration/meditation on autonomic nervous system activity and the innate immune response: a case study. Psychosom Med. 2012;74(5):489-94.
102. Chua PLC, Ng CFS, Tobias A, Seposo XT, Hashizume M. Associations between ambient temperature and enteric infections by pathogen: a systematic review and meta-analysis. Lancet Planet Health. 2022;6(3):e202-e18.
103. Elser H, Rowland ST, Tartof SY, Parks RM, Bruxvoort K, Morello-Frosch R, et al. Ambient temperature and risk of urinary tract infection in California: A time-stratified case-crossover study using electronic health records. Environ Int. 2022;165:107303.
104. Moriyama M, Ichinohe T. High ambient temperature dampens adaptive immune responses to influenza A virus infection. Proc Natl Acad Sci U S A. 2019;116(8):3118-25.
105. Zhao Q, Li S, Coelho M, Saldiva PHN, Huxley RR, Guo Y. High ambient temperature and risk of hospitalization for gastrointestinal infection in Brazil: A nationwide case-crossover study during 2000-2015. Sci Total Environ. 2022;849:157836.
106. Xu J, Zhao D, Su H, Xie M, Cheng J, Wang X, et al. Impact of temperature variability on childhood hand, foot and mouth disease in Huainan, China. Public Health. 2016;134:86-94.
107. Tamarin-Brodsky T, Hodges K, Hoskins BJ, Shepherd TG. Changes in Northern Hemisphere temperature variability shaped by regional warming patterns. Nature Geoscience. 2020;13(6):414-21.
108. Bathiany S, Dakos V, Scheffer M, Lenton TM. Climate models predict increasing temperature variability in poor countries. Sci Adv. 2018;4(5):eaar5809.
109. Healy JP, Danesh Yazdi M, Wei Y, Qiu X, Shtein A, Dominici F, et al. Seasonal Temperature Variability and Mortality in the Medicare Population. Environ Health Perspect. 2023;131(7):77002.
110. USA Geographic Names Information System Hospitals 2010 [Available from: https://www.arcgis.com/home/item.html?id=f114757725a24d8d9ce203f61eaf8f75.
111. Behavioral Risk Factor Surveillance System 2024 [Available from: https://www.cdc.gov/brfss/index.html.
112. Wang Y, Kloog I, Coull BA, Kosheleva A, Zanobetti A, Schwartz JD. Estimating Causal Effects of Long-Term PM2.5 Exposure on Mortality in New Jersey. Environ Health Perspect. 2016;124(8):1182-8.
113. Rahman MM, Garcia E, Lim CC, Ghazipura M, Alam N, Palinkas LA, et al. Temperature variability associations with cardiovascular and respiratory emergency department visits in Dhaka, Bangladesh. Environ Int. 2022;164:107267.
114. Sun S, Laden F, Hart JE, Qiu H, Wang Y, Wong CM, et al. Seasonal temperature variability and emergency hospital admissions for respiratory diseases: a population-based cohort study. Thorax. 2018;73(10):951-8.
115. Onozuka D. The influence of diurnal temperature range on the incidence of respiratory syncytial virus in Japan. Epidemiol Infect. 2015;143(4):813-20.
116. Hung SC, Yang CC, Liu CF, Kung CT, Lee WH, Ho CK, et al. The Association Pattern between Ambient Temperature Change and Leukocyte Counts. Int J Environ Res Public Health. 2021;18(13).
117. Bisht K, Te Velthuis AJW. Decoding the Role of Temperature in RNA Virus Infections. mBio. 2022;13(5):e0202122.

118. El-Sayed A, Kamel M. Climatic changes and their role in emergence and re-emergence of diseases. Environ Sci Pollut Res Int. 2020;27(18):22336-52.
119. ONeill MS, Zanobetti A, Schwartz J. Modifiers of the temperature and mortality association in seven US cities. Am J Epidemiol. 2003;157(12):1074-82.
120. Crosby R, Wendel ML, Vanderpool RC, Casey BR. Rural populations and health: Determinants, disparities, and solutions: John Wiley & Sons; 2012.
121. Yang C, Meng X, Chen R, Cai J, Zhao Z, Wan Y, et al. Long-term variations in the association between ambient temperature and daily cardiovascular mortality in Shanghai, China. Sci Total Environ. 2015;538:524-30.
122. Chen R, Yin P, Wang L, Liu C, Niu Y, Wang W, et al. Association between ambient temperature and mortality risk and burden: time series study in 272 main Chinese cities. Bmj. 2018;363:k4306.
123. Larsson K, Tornling G, Gavhed D, Muller-Suur C, Palmberg L. Inhalation of cold air increases the number of inflammatory cells in the lungs in healthy subjects. Eur Respir J. 1998;12(4):825-30.
124. Graudenz GS, Landgraf RG, Jancar S, Tribess A, Fonseca SG, Fae KC, et al. The role of allergic rhinitis in nasal responses to sudden temperature changes. J Allergy Clin Immunol. 2006;118(5):1126-32.
125. Rasking L, Vanbrabant K, Bove H, Plusquin M, De Vusser K, Roels HA, et al. Adverse Effects of fine particulate matter on human kidney functioning: a systematic review. Environ Health. 2022;21(1):24.
126. Zelikoff J, Nadziejko C, Fang T, Gordon C, Premdass C, Cohen M. Short term, low-dose inhalation of ambient particulate matter exacerbates ongoing pneumoncoccal infections in Streptococcus Pneumoniae-infected rats. In: Phalen R, Bell Y, editors. Proceedings of the third Colloquium on Particulate Air Pollution and Human Health. Irvine CA: University of California; 1999. p. 8-94 – 8-101.
127. Massie AB, Kucirka LM, Segev DL. Big data in organ transplantation: registries and administrative claims. Am J Transplant. 2014;14(8):1723-30.
128. Amini H, Danesh-Yazdi M, Di Q, Requia W, Wei Y, AbuAwad Y, et al. Annual Mean PM2.5 Components Trace Elements (TEs) 50m Urban and 1km Non-Urban Area Grids for Contiguous U.S., 2000-2019, v1. Palisades, New York: NASA Socioeconomic Data and Applications Center (SEDAC); 2023.
129. DAYMET: Daily Surface Weather and Climatological summaries 2024 [Available from: https://daymet.ornl.gov/.
130. StataCorp. Stata: Release 17. Statistical Software. College Station, TX: StataCorp LLC. 2021,.
131. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing. 2024.
132. McDuffie EE, Martin RV, Spadaro JV, Burnett R, Smith SJ, ORourke P, et al. Source sector and fuel contributions to ambient PM(2.5) and attributable mortality across multiple spatial scales. Nat Commun. 2021;12(1):3594.
133. Henneman L, Choirat C, Dedoussi I, Dominici F, Roberts J, Zigler C. Mortality risk from United States coal electricity generation. Science. 2023;382(6673):941-6.
134. Feng Y, Castro E, Wei Y, Jin T, Qiu X, Dominici F, et al. Long-term exposure to ambient PM2.5, particulate constituents and hospital admissions from non-respiratory infection. Nat Commun. 2024;15(1):1518.

135. Song Y, Yang L, Kang N, Wang N, Zhang X, Liu S, et al. Associations of incident female breast cancer with long-term exposure to PM(2.5) and its constituents: Findings from a prospective cohort study in Beijing, China. J Hazard Mater. 2024;473:134614.
136. Chuang KJ, Chan CC, Su TC, Lee CT, Tang CS. The effect of urban air pollution on inflammation, oxidative stress, coagulation, and autonomic dysfunction in young adults. Am J Respir Crit Care Med. 2007;176(4):370-6.
137. Suarez-Alvarez B, Liapis H, Anders HJ. Links between coagulation, inflammation, regeneration, and fibrosis in kidney pathology. Lab Invest. 2016;96(4):378-90.
138. Iba T, Helms J, Maier CL, Levi M, Scarlatescu E, Levy JH. The role of thromboinflammation in acute kidney injury among patients with septic coagulopathy. J Thromb Haemost. 2024;22(6):1530-40.
139. Dignam T, Kaufmann RB, LeStourgeon L, Brown MJ. Control of Lead Sources in the United States, 1970-2017: Public Health Progress and Current Challenges to Eliminating Lead Exposure. J Public Health Manag Pract. 2019;25 Suppl 1, Lead Poisoning Prevention(Suppl 1 LEAD POISONING PREVENTION):S13-S22.
140. United States Environmental Protection Agency. Lead (Pb) Air Pollution 2024 [Available from: https://www.epa.gov/lead-air-pollution.
141. Nan Y, Yang J, Yang J, Wei L, Bai Y. Associations Between Individual and Combined Metal Exposures in Whole Blood and Kidney Function in U.S. Adults Aged 40 Years and Older. Biol Trace Elem Res. 2024;202(3):850-65.
142. Park Y, Lee SJ. Association of Blood Heavy Metal Levels and Renal Function in Korean Adults. Int J Environ Res Public Health. 2022;19(11).
143. Sotomayor CG, Giubergia F, Groothof D, Ferreccio C, Nolte IM, Navis GJ, et al. Plasma Lead Concentration and Risk of Late Kidney Allograft Failure: Findings From the TransplantLines Biobank and Cohort Studies. Am J Kidney Dis. 2022;80(1):87-97 e1.
144. Halloran PF, Afrouzian M, Ramassar V, Urmson J, Zhu LF, Helms LM, et al. Interferon-gamma acts directly on rejecting renal allografts to prevent graft necrosis. Am J Pathol. 2001;158(1):215-26.
145. Fenga C, Gangemi S, Di Salvatore V, Falzone L, Libra M. Immunological effects of occupational exposure to lead (Review). Mol Med Rep. 2017;15(5):3355-60.
146. Lopes AC, Peixe TS, Mesas AE, Paoliello MM. Lead Exposure and Oxidative Stress: A Systematic Review. Rev Environ Contam Toxicol. 2016;236:193-238.
147. Wen N, Wu J, Li H, Liao J, Lan L, Yang X, et al. Immune landscape in rejection of renal transplantation revealed by high-throughput single-cell RNA sequencing. Front Cell Dev Biol. 2023;11:1208566.
148. Siedlecki A, Irish W, Brennan DC. Delayed graft function in the kidney transplant. Am J Transplant. 2011;11(11):2279-96.
149. Han B, Xu J, Zhang Y, Li P, Li K, Zhang N, et al. Associations of Exposure to Fine Particulate Matter Mass and Constituents with Systemic Inflammation: A Cross-Sectional Study of Urban Older Adults in China. Environ Sci Technol. 2022;56(11):7244-55.
150. Lodovici M, Bigagli E. Oxidative stress and air pollution exposure. J Toxicol. 2011;2011:487074.
151. Higgins JP, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. J R Stat Soc Ser A Stat Soc. 2009;172(1):137-59.

APPENDIX A

Methods

Weighted quantile sum regression

The generalized linear weighted quantile sum regression proceeds in steps. The original data is divided into two groups. Then each of the exposures is converted into a categorical variable representing the quantiles (in our case deciles) of that exposure. In the first group a regression (in our case quasi-Poisson) is fit relating the outcome to the quantiles of all of the exposures. Since all exposures are on the same scale (deciles) the coefficients of each exposure can be interpreted as the relative weight of a 1 decile increase in that exposure in predicting the outcome. The weights are scaled to sum to one. Then, using those weights, in the held-out data set a new variable is computed that is the weighted sum of each of the exposures (as deciles). This single variable is then used as the exposure in a regression (quasi-Poisson, in our case) predicting the outcome. Both regression control for all covariates. In weighted quantile sum regression, the threshold for the most influential components was defined as weight > (1/number of species) (68)

Rescaling the source factors

For each ZIP code in each year, we first calculated a total PM2.5 mixture level by adding up the concentration of the 15 constituents. Within each of the 9 strata defined by time period and mixture pattern, we obtained the concentration of source factors (either 4 or 5 factors within each stratum) for the ZIP code-year. For a typical stratum with 4 factors, we run the regression model below

$$\textit{total PM2.5 mixture} = \beta_0 + \beta_1 \times factor1 + \beta_2 \times factor2 + \beta_3 \times factor3 + \beta_4 \times factor4$$

The concentration of each source factor was multiple by its corresponding β and converted to concentration with unit as $\mu g/m^3$. After the conversion, we compiled all the source factor data across

strata and calculated the standard deviation for each of the source-specific PM2.5. Concentration of source-specific PM2.5 was rescaled by dividing by the source-specific standard deviation. The standard deviation for PM2.5 sourced from oil combustion, soil, coal burning, traffic, biomass burning, and regionally transported nitrates were 0.72, 0.68, 1.91, 1.37, 1.03 and 1.37 respectively.

Random effect meta-analysis

We used random effect meta-analysis to combine the stratum-specific effect estimates of the source-specific PM2.5(151). In random effect analysis, we assume that the mean effects are different across strata defined by time and region. Within each of the strata, the effect estimated is assumed to be

$$\hat{\theta}_i = \mu + \gamma_i + \epsilon_i$$

$$\hat{\theta}_i \sim N(0, \tau^2 + \hat{\sigma}_i^2)$$

Where μ is the population effect; γ_i is the random effects for each stratum and follow the distribution below;

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

While ϵ_i is the statistical error in the estimates of stratum-specific effect and follows

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

The population effect of each source-specific PM2.5 $\hat{\mu}$ is estimated by

$$\hat{\mu} = \frac{\sum_{i=1}^{k} \frac{1}{\hat{\tau}^2 + \hat{\sigma}_i^2} \hat{\theta}_i}{\sum_{i=1}^{k} \frac{1}{\hat{\tau}^2 + \hat{\sigma}_i^2}}$$

Where $\hat{\tau}^2$ and $\hat{\sigma}_i^2$ are the maximum likelihood estimator of the random effects and statistical error.

Identification of source factors

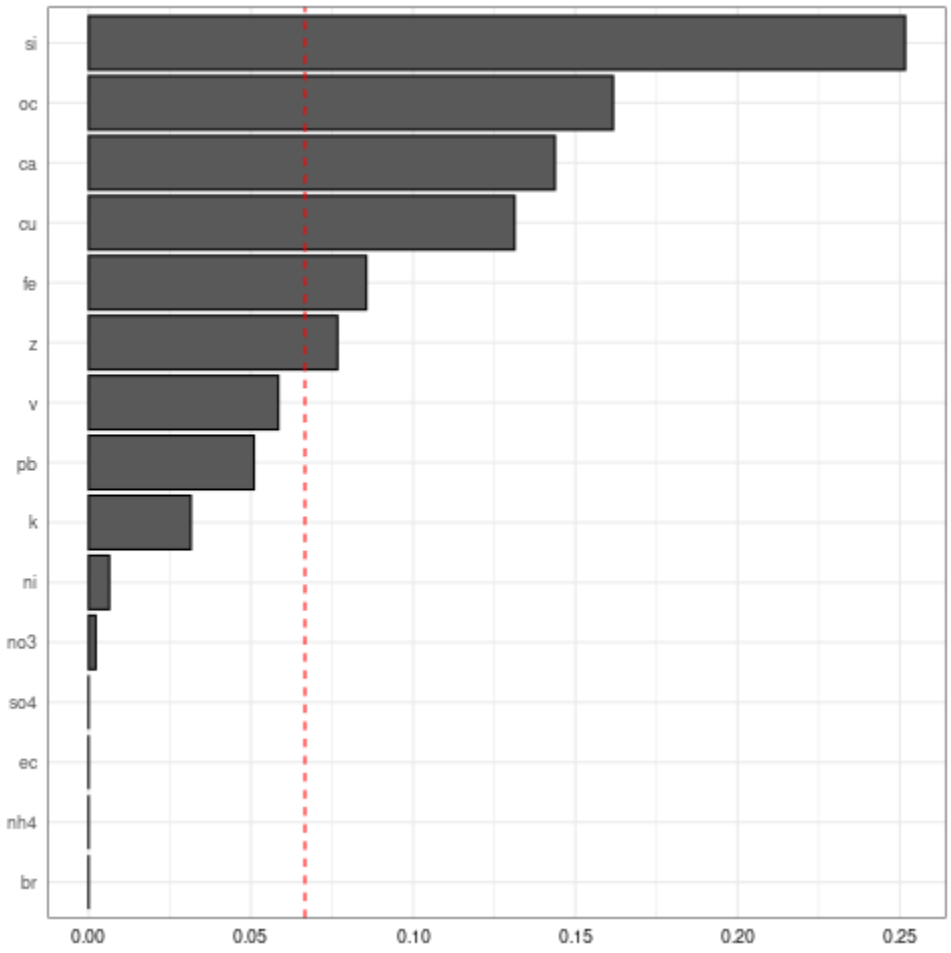
The elemental components of PM2.5 mass usually originated from different sources. Specific elements or groups of elements that are highly associated with a source of air pollution could be serve as tracers and help us identify the sources of air pollution(72). From non-negative matrix factorization, we obtain the loadings of each element (constituent) within each factor and the results are shown in Appendix C figure S6-S14. We identified the source of each factor based on the loadings of tracer elements. For example, if a factor A has high loadings of Ni and V, then factor A is identified as oil combustion. The tracer elements for each source of air pollution are listed below:

Sources	Tracers
Oil combustion	Ni, V
Soil, dirt	Ca, Si
Coal burning	SO4
Traffic	EC, Zn, Pb, Cu, Fe
Biomass	K
Regionally transported nitrate	NH4

Supplementary table 1. Distribution of coefficient of variation of air pollution data for each ZIP code across the study period.

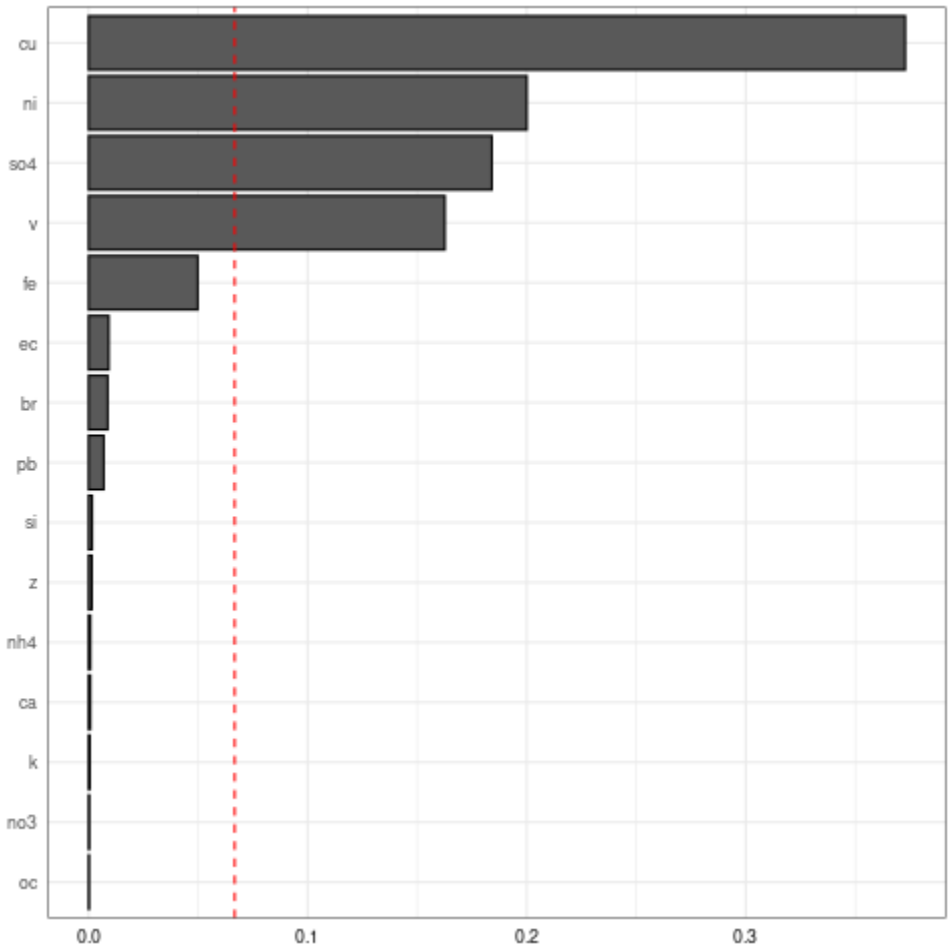
	Coefficient of variation
	Median (2.5th%, 97.5th%)
PM2.5	5.5% (3.6%, 8.6%)
Br	3.5% (2.5%, 4.9%)
Ca	6.9% (5.3%, 9.2%)
Cu	14.1% (8.9%, 21.6%)
EC	9.6% (6.9%, 13.4%)
Fe	7.0% (5.0%, 10.0%)
K	5.8% (3.9%, 8.7%)
NH4	6.2% (4.8%, 8.4%)
Ni	20.9% (13.6%, 33.6%)
NO3	8.1% (5.6%, 12.0%)
OC	6.3% (4.3%, 9.1%)
Pb	10.3% (7.7%, 13.9%)
Si	6.9% (4.9%, 8.2%)
SO4	3.8% (2.8%, 5.0%)
V	11.9% (8.0%, 18.0%)
Zn	8.4% (6.1%, 11.9%)

Supplementary Figure S1. Weights of PM2.5 constituents in the mixture index for the association between the mixture and central nervous system infections.



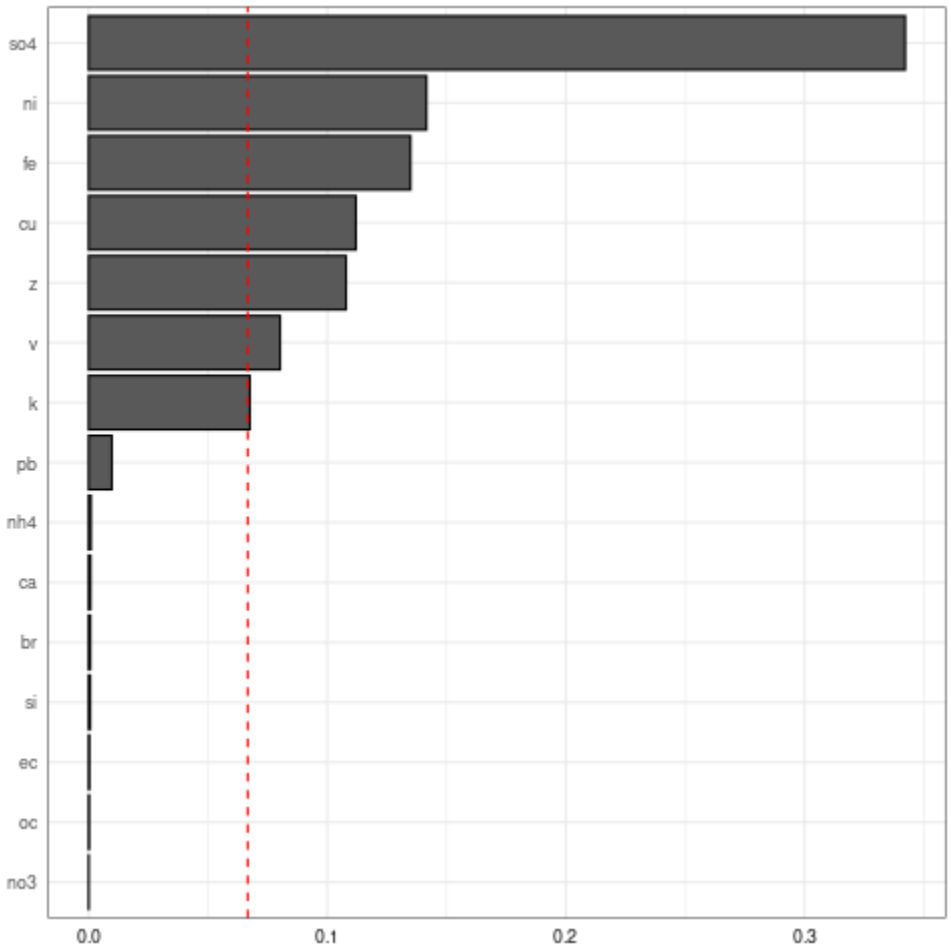
The dash line indicated the threshold for the suggested threshold for the most influential constituents. Source data are provided as a Source Data file.

Supplementary Figure S2. Weights of PM2.5 constituents in mixture index for the association between mixture and intestinal infections.



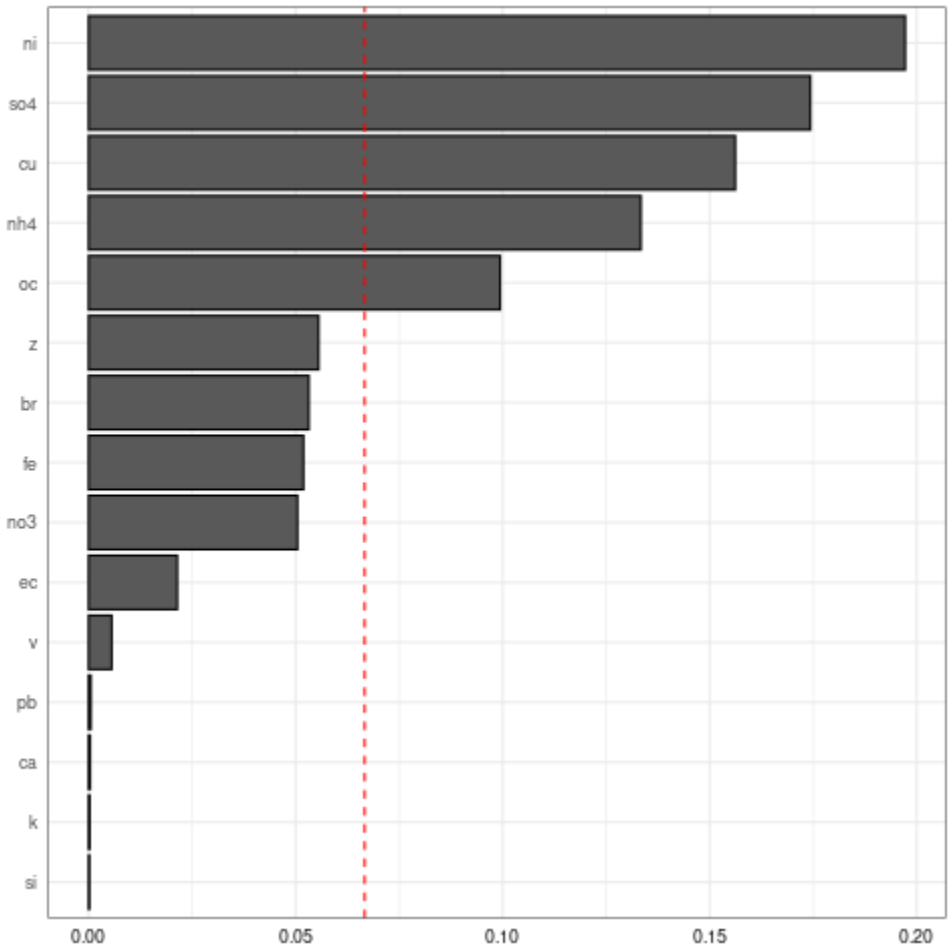
The dash line indicated the suggested threshold for the most influential constituents. Source data are provided as a Source Data file.

Supplementary Figure S3. Weights of PM2.5 constituents in the mixture index for the association between the mixture and urinary tract infections.



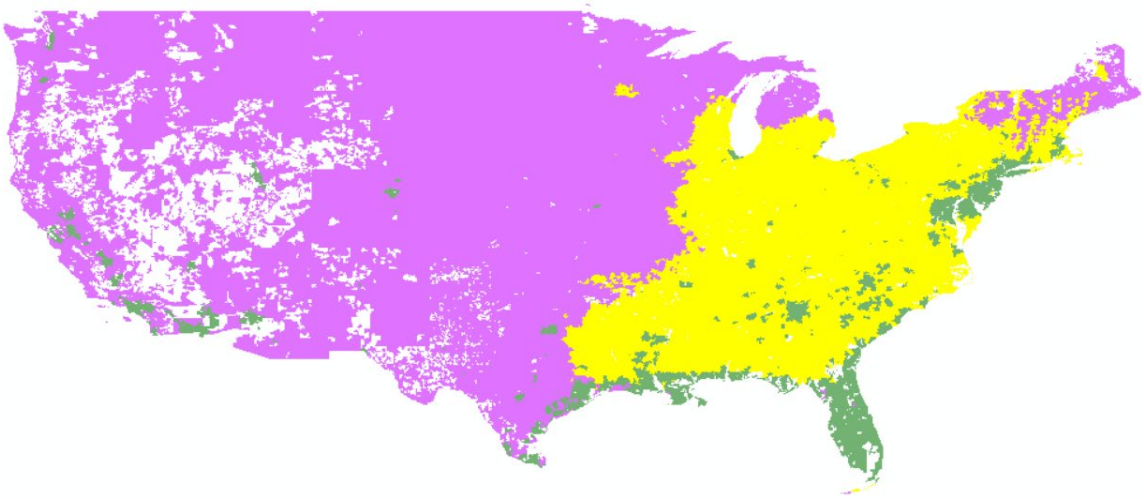
The dash line indicated the suggested threshold for the most influential constituents. Source data are provided as a Source Data file.

Supplementary Figure S4. Weights of PM2.5 constituents in the mixture index for the association between the mixture and septicemia.



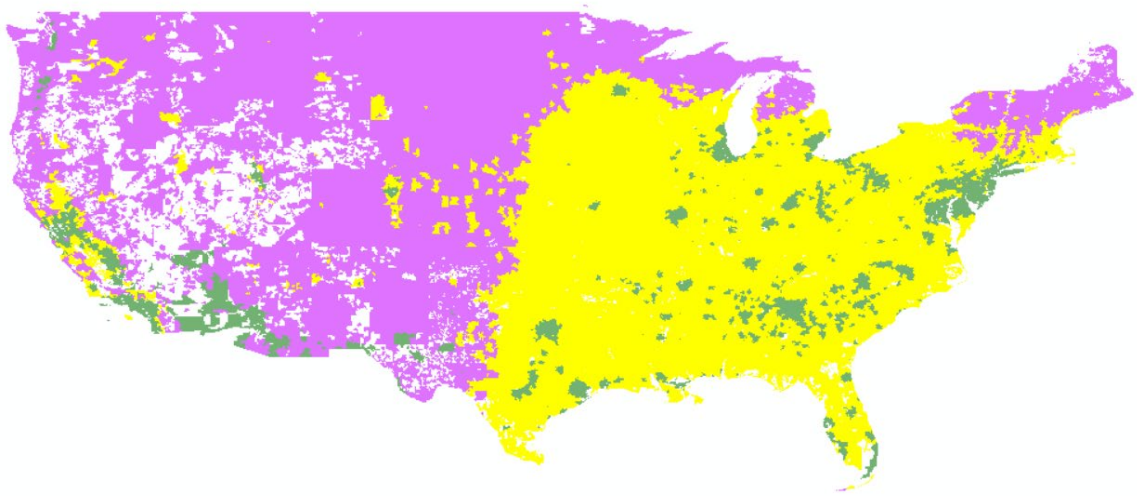
The dash line indicated the suggested threshold for the most influential constituents. Source data are provided as a Source Data file.

Supplementary Figure S5. Clusters of ZIP codes within which separated non-negative matrix factorizations were conducted for the PM2.5 constituent data between 2000-2005.



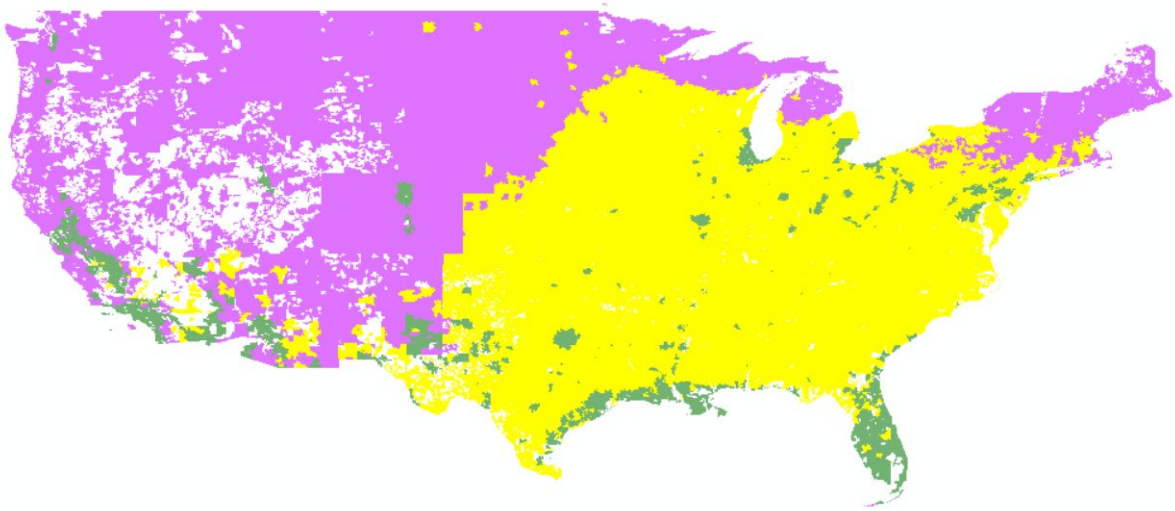
Purple area indicates the regions included in Cluster 1 between 2000-2005; yellow area indicates the regions included in Cluster 2 between 2000-2005; green area indicates the regions included in Cluster 3 between 2000-2005. Source data are provided as a Source Data file. The figure was created from ArcMap 10.7.

Supplementary Figure S6. Clusters of ZIP codes within which separated non-negative matrix factorizations were conducted for the PM2.5 constituent data between 2006-2010.



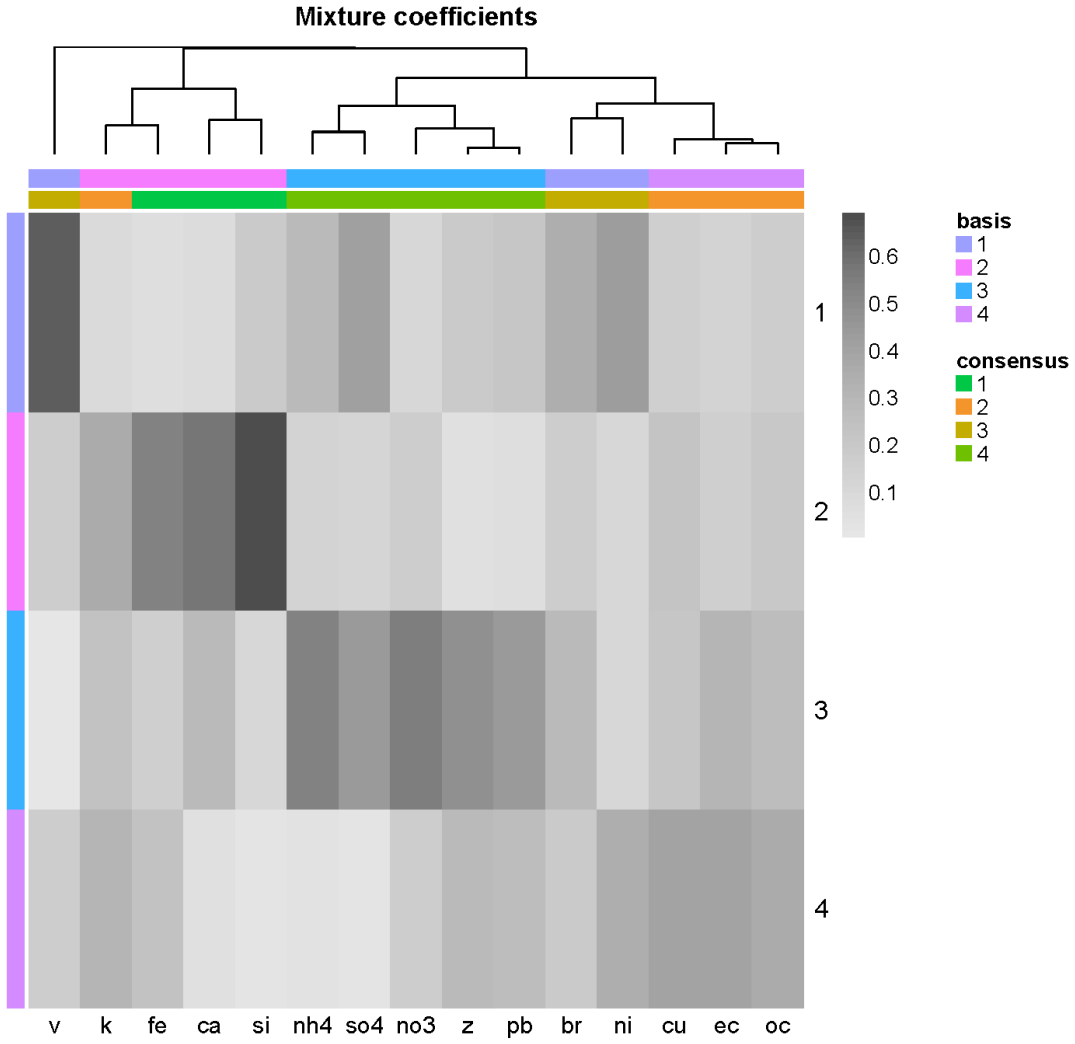
Purple area indicates the regions included in Cluster 1 between 2006-2010; yellow area indicates the regions included in Cluster 2 between 2006-2010; green area indicates the regions included in Cluster 3 between 2006-2010. Source data are provided as a Source Data file. The figure was created from ArcMap 10.7.

Supplementary Figure S7. Clusters of ZIP codes within which separated non-negative matrix factorizations were conducted for the PM2.5 constituent data between 2011-2016.



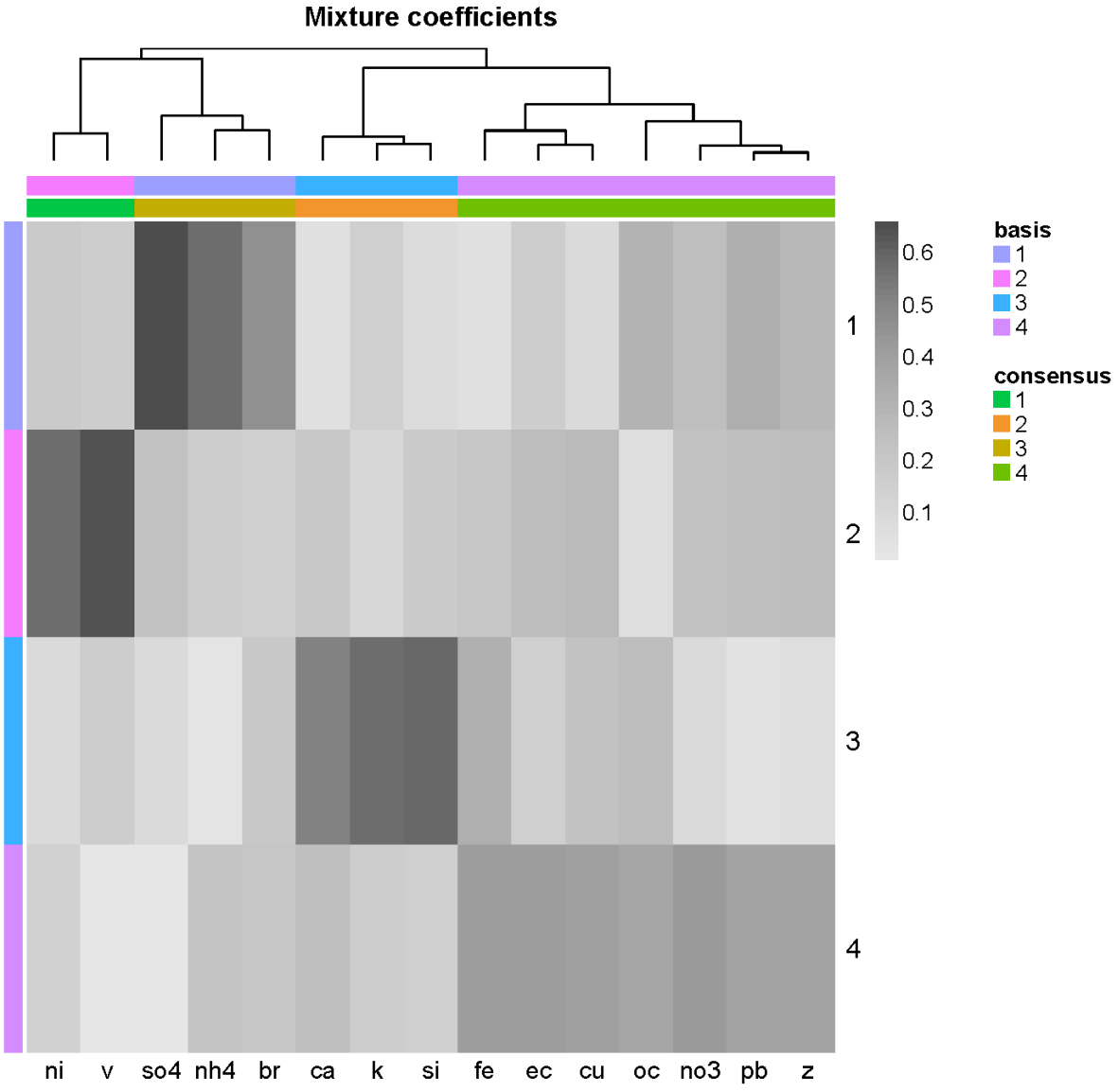
Purple area indicates the regions included in Cluster 1 between 2011-2016; yellow area indicates the regions included in Cluster 2 between 2011-2016; green area indicates the regions included in Cluster 3 between 2011-2016. Source data are provided as a Source Data file. The figure was created from ArcMap 10.7

Supplementary Figure S8. The heatmap of loadings of each PM2.5 constituents on each factor obtained from non-negative matrix factorization in cluster 1 between 2000-2005. Basis 1 was identified as oil combustion; basis 2 was identified as dirt; basis 3 was identified as coal burning; basis 4 was identified as traffic.



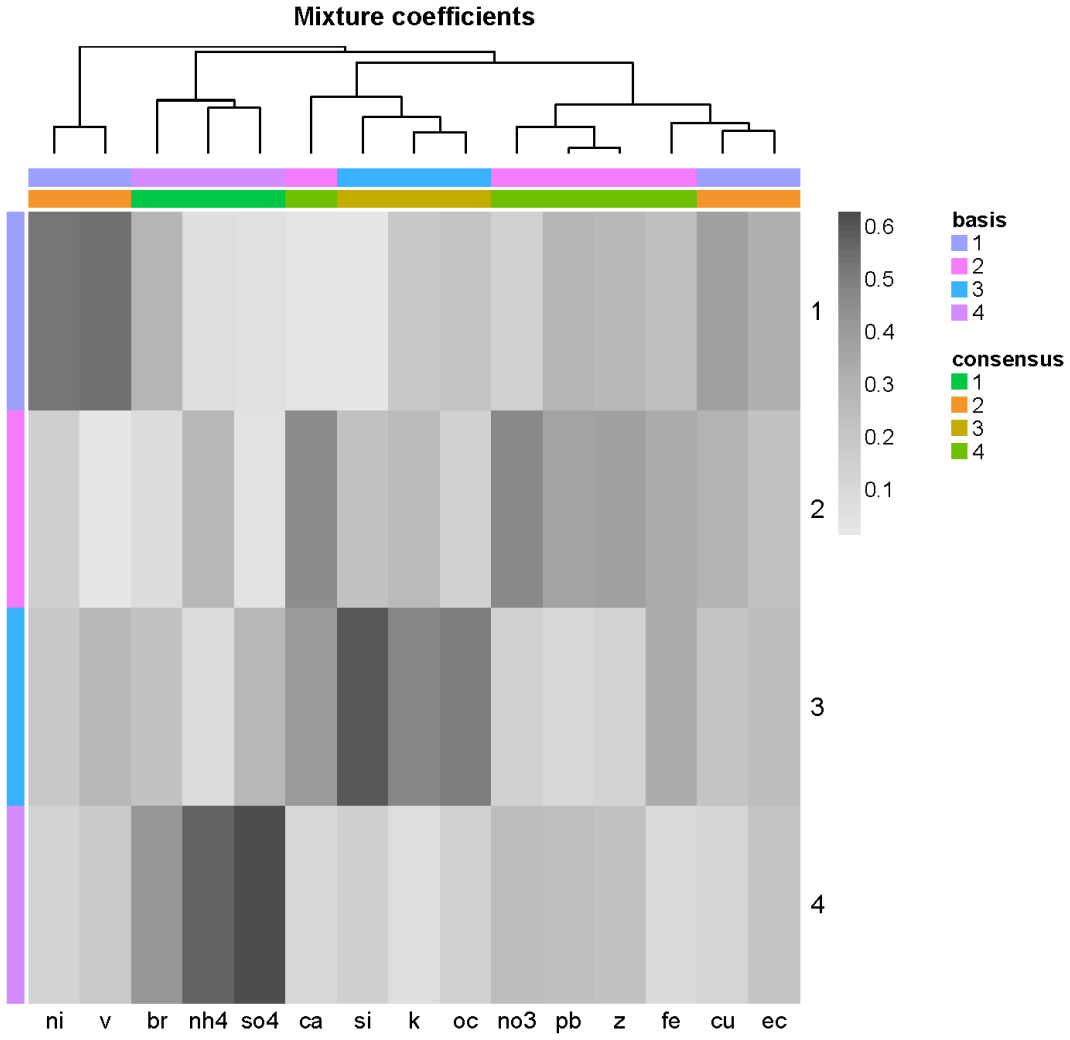
The numbers (1-4) on the Y axis indicates each of the source factors while the grey scale indicates the loading of each component in each source factor. Basis indicates the number of factors identified from non-negative matrix factorization (NMF). Consensus indicates the consensus across multiple runs of NMF. Source data are provided as a Source Data file.

Supplementary Figure S9. The heatmap of loadings of each PM2.5 constituents on each factor obtained from non-negative matrix factorization in cluster 2 between 2000-2005. Basis 1 was identified as coal burning; basis 2 was identified as oil combustion; basis 3 was identified as dirt; basis 4 was identified as traffic.



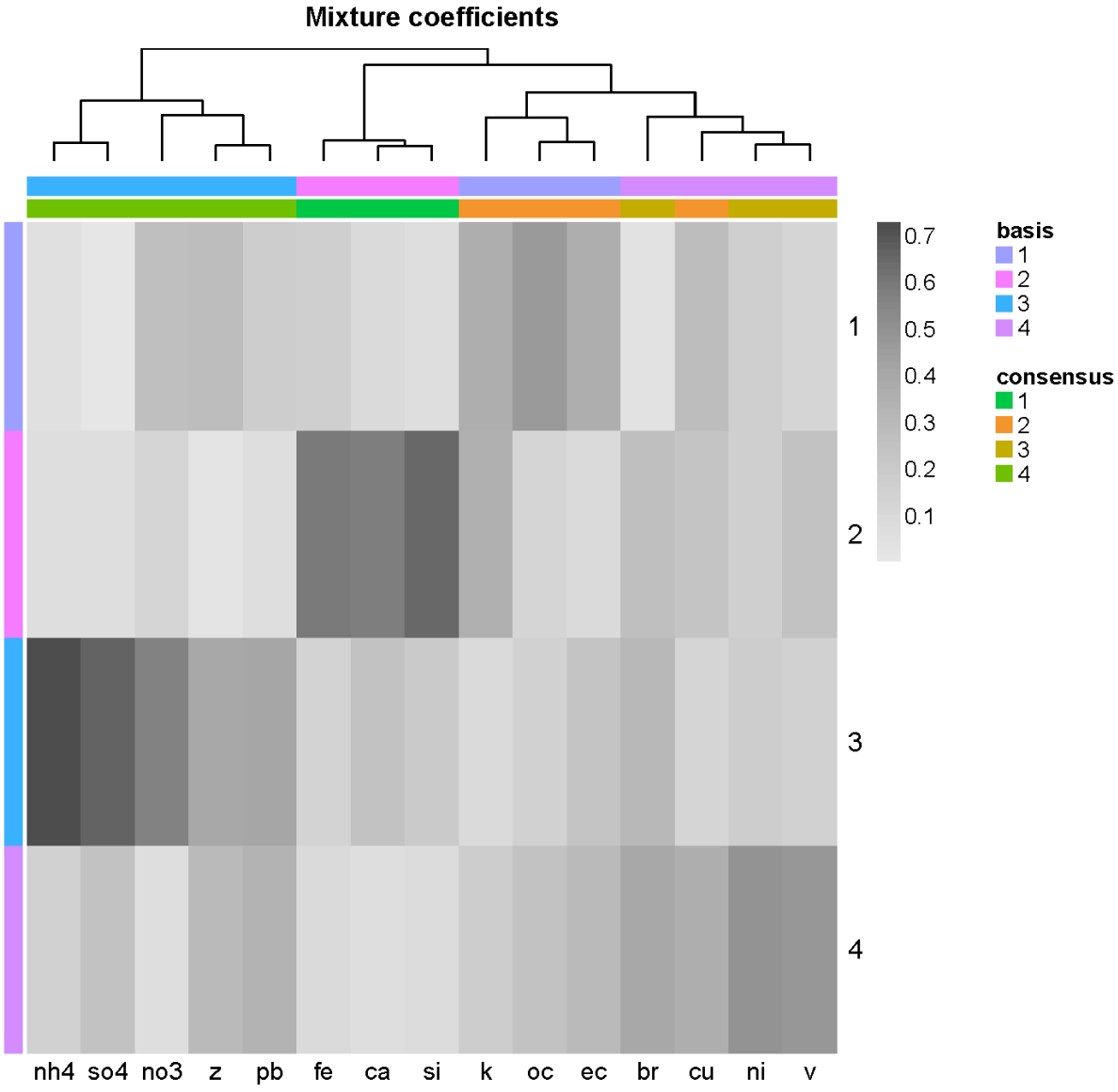
The numbers (1-4) on the Y axis indicates each of the source factors while the grey scale indicates the loading of each component in each source factor. Basis indicates the number of factors identified from non-negative matrix factorization (NMF). Consensus indicates the consensus across multiple runs of NMF. Source data are provided as a Source Data file.

Supplementary Figure S10. The heatmap of loadings of each PM2.5 constituents on each factor obtained from non-negative matrix factorization in cluster 3 between 2000-2005. Basis 1 was identified as oil combustion; basis 2 was identified as traffic; basis 3 was identified as biomass burning; basis 4 was identified as coal burning.



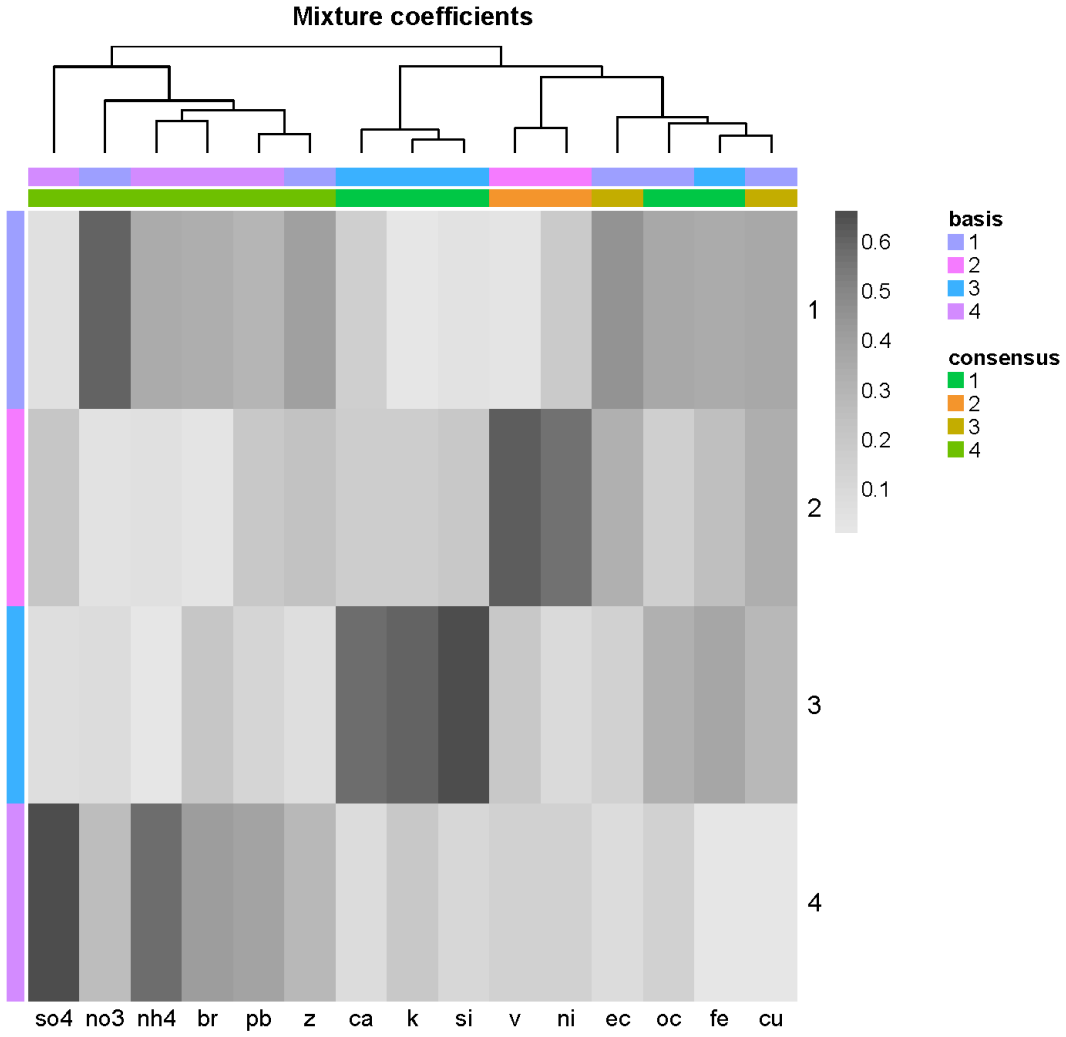
The numbers (1-4) on the Y axis indicates each of the source factors while the grey scale indicates the loading of each component in each source factor. Basis indicates the number of factors identified from non-negative matrix factorization (NMF). Consensus indicates the consensus across multiple runs of NMF. Source data are provided as a Source Data file.

Supplementary Figure S11. The heatmap of loadings of each PM2.5 constituents on each factor obtained from non-negative matrix factorization in cluster 1 between 2006-2010. Basis 1 was identified as mix of biomass burning and traffic; basis 2 was identified as dirt; basis 3 was identified as coal burning; basis 4 was identified as oil combustion.



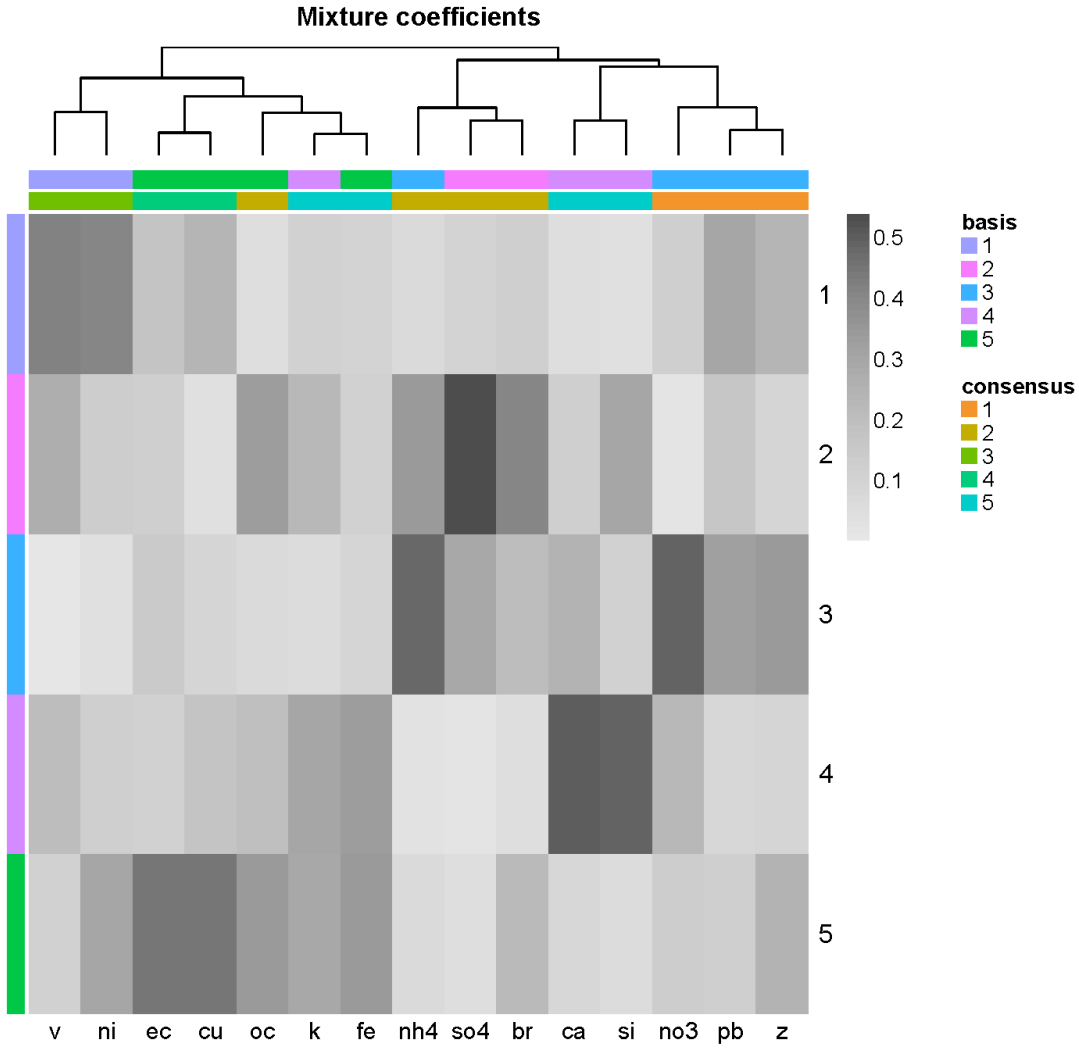
The numbers (1-4) on the Y axis indicates each of the source factors while the grey scale indicates the loading of each component in each source factor. Basis indicates the number of factors identified from non-negative matrix factorization (NMF). Consensus indicates the consensus across multiple runs of NMF. Source data are provided as a Source Data file.

Supplementary Figure S12. The heatmap of loadings of each PM2.5 constituents on each factor obtained from non-negative matrix factorization in cluster 2 between 2006-2010. Basis 1 was identified as traffic; basis 2 was identified as oil combustion; basis 3 was identified as dirt; basis 4 was identified as coal burning.



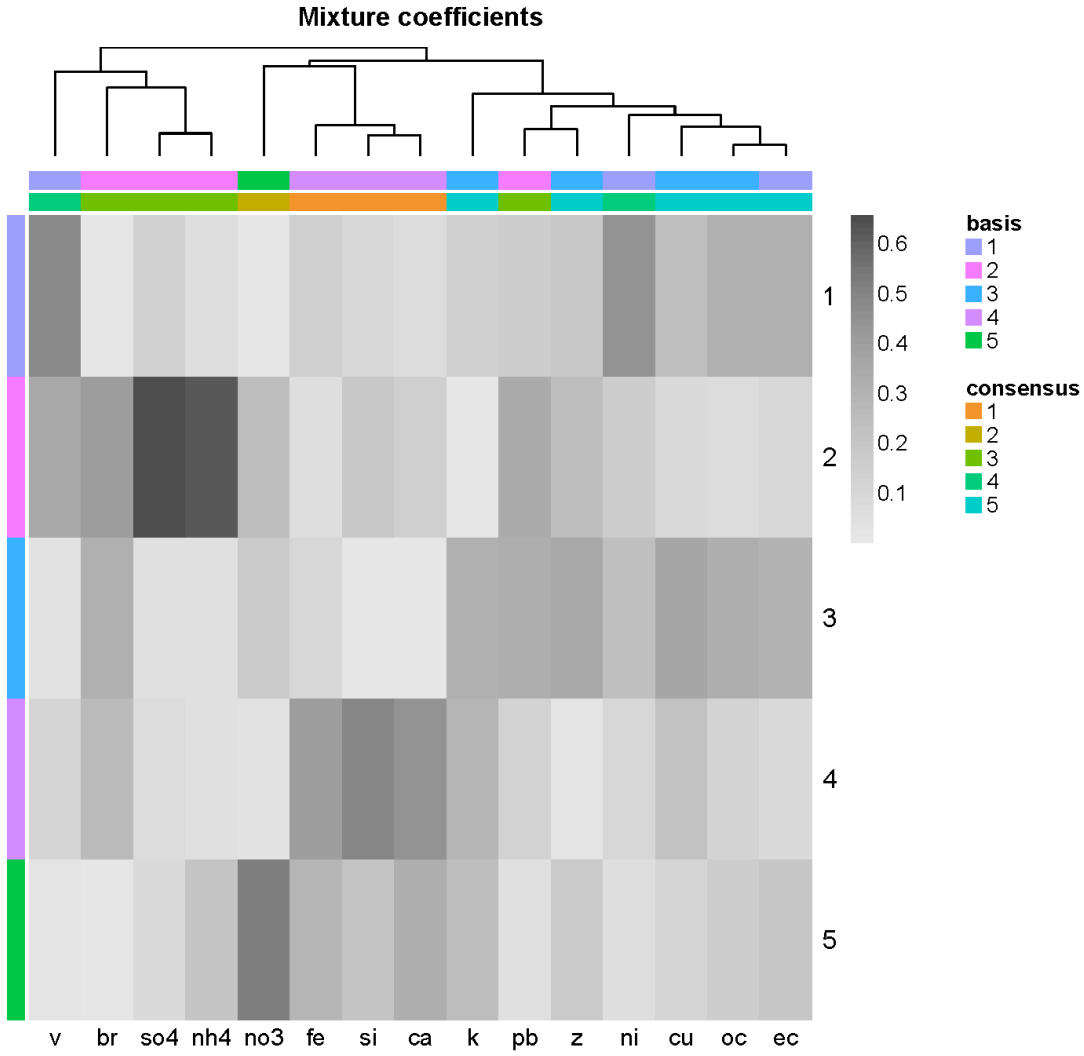
The numbers (1-4) on the Y axis indicates each of the source factors while the grey scale indicates the loading of each component in each source factor. Basis indicates the number of factors identified from non-negative matrix factorization (NMF). Consensus indicates the consensus across multiple runs of NMF. Source data are provided as a Source Data file.

Supplementary Figure S13. The heatmap of loadings of each PM2.5 constituents on each factor obtained from non-negative matrix factorization in cluster 3 between 2006-2010. Basis 1 was identified as oil combustion; basis 2 was identified as coal burning; basis 3 was identified as regionally transported nitrate; basis 4 was identified as biomass burning; basis 5 was identified as traffic



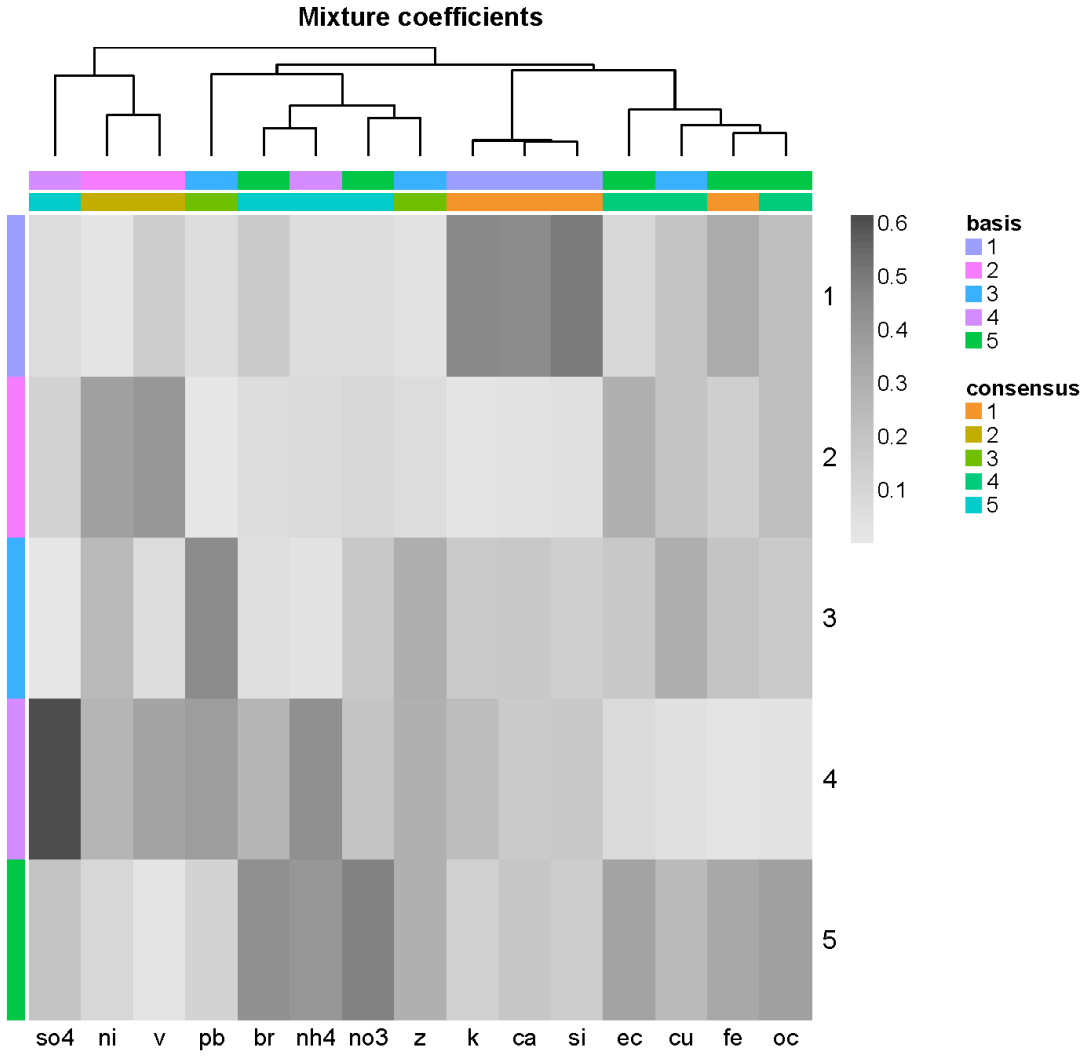
The numbers (1-5) on the Y axis indicates each of the source factors while the grey scale indicates the loading of each component in each source factor. Basis indicates the number of factors identified from non-negative matrix factorization (NMF). Consensus indicates the consensus across multiple runs of NMF. Source data are provided as a Source Data file.

Supplementary Figure S14. The heatmap of loadings of each PM2.5 constituents on each factor obtained from non-negative matrix factorization in cluster 1 between 2011-2016. Basis 1 was identified as oil combustion; basis 2 was identified as coal burning; basis 3 was identified as traffic; basis 4 was identified as dirt; basis 5 was identified as regionally transported nitrate.



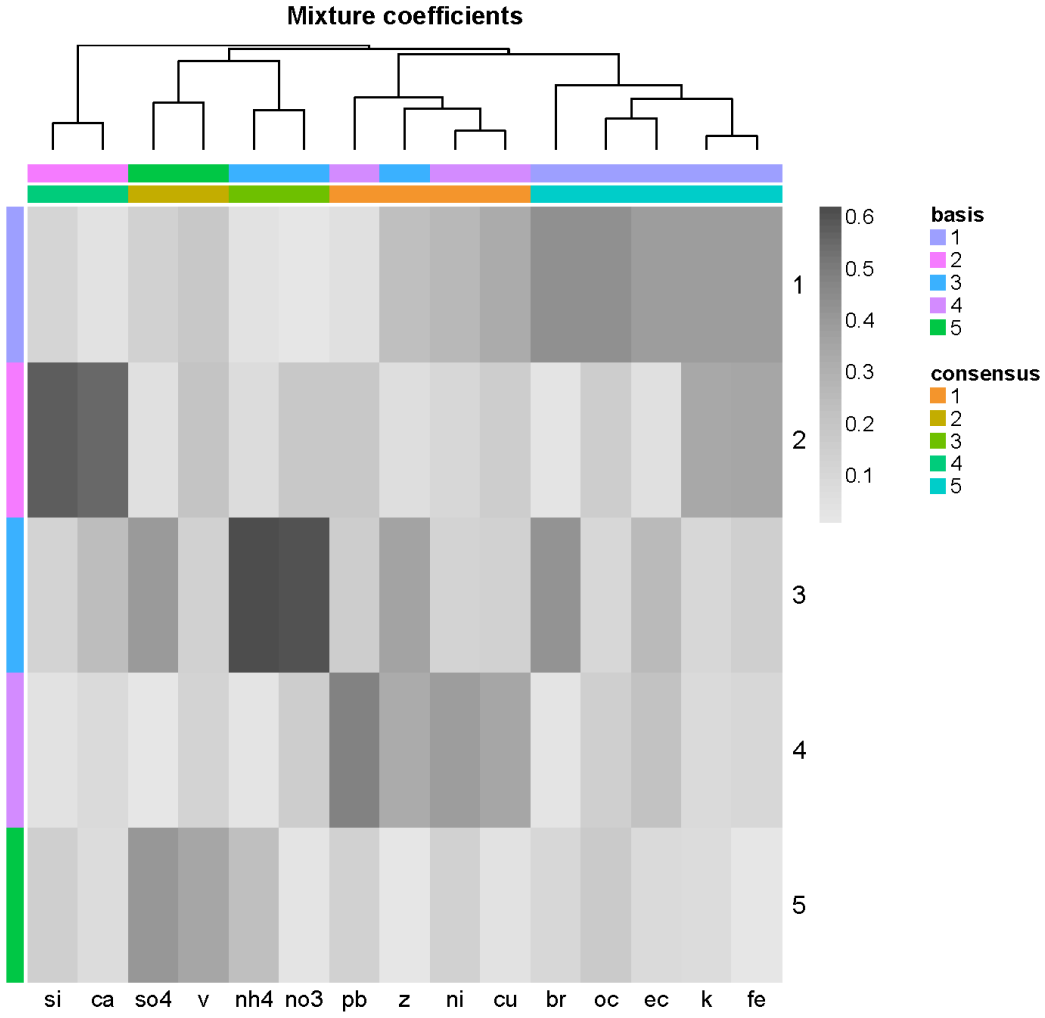
The numbers (1-5) on the Y axis indicates each of the source factors while the grey scale indicates the loading of each component in each source factor. Basis indicates the number of factors identified from non-negative matrix factorization (NMF). Consensus indicates the consensus across multiple runs of NMF. Source data are provided as a Source Data file.

Supplementary Figure S15. The heatmap of loadings of each PM2.5 constituents on each factor obtained from non-negative matrix factorization in cluster 2 between 2011-2016. Basis 1 was identified as dirt; basis 2 was identified as oil combustion; basis 3 was identified as non-tailpipe traffic; basis 4 was identified as coal burning; basis 5 was identified as tailpipe traffic.



The numbers (1-5) on the Y axis indicates each of the source factors while the grey scale indicates the loading of each component in each source factor. Basis indicates the number of factors identified from non-negative matrix factorization (NMF). Consensus indicates the consensus across multiple runs of NMF. Source data are provided as a Source Data file.

Supplementary Figure S16. The heatmap of loadings of each PM2.5 constituents on each factor obtained from non-negative matrix factorization in cluster 3 between 2011-2016. Basis 1 was identified as biomass burning; basis 2 was identified as dirt; basis 3 was identified as regionally transported nitrate; basis 4 was identified as traffic; basis 5 was identified as coal burning.



The numbers (1-5) on the Y axis indicates each of the source factors while the grey scale indicates the loading of each component in each source factor. Basis indicates the number of factors identified from non-negative matrix factorization (NMF). Consensus indicates the consensus across multiple runs of NMF. Source data are provided as a Source Data file.

APPENDIX B

Categorization of ICD diagnosis codes

ICD-9 diagnosis codes

Disease	CCS disease groups
Total infections	1-9; 76-78; 90; 122-126; 135; 159; 197; 201; 248
Respiratory infections	122-126
CNS infections	76-78
Intestinal Infections	135
Urinary tract infection	159
Septicemia	2

ICD-10 diagnosis codes

Disease	CCSR disease groups
Total infections	INF001-011; RSP002-006; MUS001-002; MUS027; NVS001-NVS003; GEN001; SKN001; DIG001
Respiratory infections	RSP002-006
CNS infections	NVS001-003
Intestinal Infections	DIG001
Urinary tract infection	gen001
Septicemia	INF002

Table S1. Association between seasonal temperature, seasonal temperature variability and hospital admissions from respiratory infections among Medicare beneficiaries across different strata between 2000-2016

			Effect estimates			
			coldSD	warmSD	Cold Temperature	Warm Temperature
sex	female		0.87 (0.36,1.4)	-0.09 (-0.89,0.8)	-0.48 (-0.75,-0.23)	1.16 (0.75,1.53)
	male		0.34 (-0.2,0.93)	1.68 (0.68,2.77)	-0.83 (-1.13,-0.52)	1.54 (1.11,1.99)
		effect difference	0.54 (-0.21,1.31)	-1.75 (-3.17,-0.43)	0.36 (-0.01,0.72)	-0.39 (-0.93,0.22)
race	black		0.63 (-0.51,1.76)	0.89 (-1.44,3.24)	0.06 (-0.55,0.64)	-0.9 (-1.91,-0.02)
	white		-0.11 (-0.28,0.05)	-0.04 (-0.42,0.38)	0.28 (0.2,0.35)	0.26 (0.14,0.4)
		effect difference	0.75 (-0.42,1.94)	0.92 (-1.42,3.3)	-0.21 (-0.83,0.39)	-1.17 (-2.21,-0.25)
Medicaid eligibility	Medicaid eligible		-0.62 (-1.25,0.02)	0.72 (-0.34,1.87)	0.18 (-0.09,0.52)	0.43 (-0.01,0.89)
	Medicaid non-eligible		-0.2 (-0.31,-0.08)	-0.12 (-0.35,0.13)	0.21 (0.15,0.28)	0.22 (0.13,0.31)
		effect difference	-0.42 (-1.03,0.25)	0.8 (-0.23,1.93)	-0.04 (-0.32,0.3)	0.22 (-0.24,0.68)
age	65-74		-0.42 (-0.78,-0.02)	0.92 (0.12,1.62)	-0.77 (-0.98,-0.54)	0.54 (0.24,0.82)
	75-84		0.6 (-0.14,1.38)	0.8 (-0.61,2.23)	-0.48 (-0.85,-0.07)	1.2 (0.63,1.8)
	>=85		3.55 (2.07,5.27)	-0.05 (-3.14,2.82)	-1.12 (-1.94,-0.29)	4.21 (3,5.59)

Table S2. Association between seasonal temperature, seasonal temperature variability and hospital admissions from septicemia among Medicare beneficiaries across different strata between 2000-2016

			Effect estimates			
			coldSD	warmSD	Cold Temperature	Warm Temperature
sex	female		-0.35 (-0.53,-0.17)	-0.1 (-0.43,0.2)	0.25 (0.15,0.34)	0.2 (0.04,0.35)
	male		-0.11 (-0.26,0.04)	0.02 (-0.25,0.28)	0.19 (0.11,0.27)	0.22 (0.11,0.33)
		effect difference	-0.23 (-0.47,0.01)	-0.12 (-0.53,0.28)	0.06 (-0.06,0.18)	-0.02 (-0.21,0.16)
race	black		-2.34 (-5.48,0.54)	0.88 (-4.67,7.95)	-1.35 (-3.02,0.39)	-0.61 (-3.51,1.94)
	white		0.63 (0.16,1.11)	0.51 (-0.29,1.32)	-0.72 (-0.97,-0.44)	1.12 (0.75,1.45)
		effect difference	-3.05 (-6.18,0.11)	0.45 (-5.42,7.72)	-0.6 (-2.34,1.09)	-1.68 (-4.59,0.96)
Medicaid eligibility	Medicaid eligible		0.81 (-1.08,2.57)	0.4 (-3.02,3.96)	-0.82 (-1.77,0.1)	2.86 (1.47,4.35)
	Medicaid non-eligible		0.56 (0.18,0.95)	1.04 (0.28,1.71)	-0.42 (-0.63,-0.25)	1.23 (0.94,1.5)
		effect difference	0.29 (-1.59,2.02)	-0.63 (-4.14,2.94)	-0.4 (-1.39,0.53)	1.66 (0.14,3.09)
age	65-74		0.93 (0.58,1.24)	0.45 (-0.11,1.04)	-0.12 (-0.28,0.05)	0.44 (0.18,0.71)
	75-84		3.61 (2.92,4.28)	1.61 (0.47,2.75)	0.12 (-0.21,0.41)	-0.12 (-0.59,0.36)
	>=85		6.39 (5.19,7.57)	1.41 (-0.88,3.52)	1.18 (0.52,1.78)	0.35 (-0.61,1.29)

Table S3. Association between seasonal temperature, seasonal temperature variability and hospital admissions from urinary tract infections among Medicare beneficiaries across different strata between 2000-2016

			Effect estimates			
			coldSD	warmSD	Cold Temperature	Warm Temperature
sex	female		-0.02 (-0.06,0.03)	-0.01 (-0.1,0.08)	0.01 (-0.02,0.03)	0 (-0.03,0.04)
	male		-0.04 (-0.1,0.02)	0.02 (-0.08,0.12)	0.02 (-0.01,0.05)	0.05 (0.01,0.1)
		effect difference	0.02 (-0.05,0.1)	-0.03 (-0.18,0.11)	-0.01 (-0.06,0.03)	-0.05 (-0.11,0.01)
race	black		-0.33 (-0.72,0.06)	-0.59 (-1.81,0.38)	0.12 (-0.09,0.37)	0.09 (-0.16,0.33)
	white		0.02 (-0.04,0.1)	0.02 (-0.07,0.13)	0 (-0.04,0.03)	0.04 (-0.01,0.13)
		effect difference	-0.35 (-0.75,0.04)	-0.59 (-1.82,0.38)	0.12 (-0.1,0.36)	0.05 (-0.21,0.29)
Medicaid eligibility	Medicaid eligible		-0.12 (-0.26,-0.01)	-0.07 (-0.32,0.2)	0.08 (0.01,0.15)	-0.06 (-0.15,0.05)
	Medicaid non-eligible		-0.02 (-0.06,0.02)	0.03 (-0.04,0.11)	0.01 (-0.01,0.03)	0.03 (0,0.06)
		effect difference	-0.1 (-0.25,0.02)	-0.1 (-0.37,0.2)	0.07 (0,0.15)	-0.09 (-0.19,0.02)
age	65-74		-0.37 (-0.56,-0.21)	0.39 (0,0.79)	-0.32 (-0.42,-0.21)	0.58 (0.42,0.74)
	75-84		-0.6 (-1.13,-0.17)	1 (0.25,1.78)	-0.46 (-0.71,-0.22)	1.25 (0.9,1.61)
	>=85		-0.15 (-1.08,1.02)	2.64 (0.5,4.45)	-0.93 (-1.47,-0.4)	2.31 (1.5,3.1)

Table S4. Association between seasonal temperature, seasonal temperature variability and hospital admissions from intestinal infections among Medicare beneficiaries across different strata between 2000-2016

		Effect estimates			
		coldSD	warmSD	Cold Temperature	Warm Temperature
sex	female	-0.41 (-0.77,-0.06)	0.76 (0.14,1.38)	-0.51 (-0.67,-0.33)	1.31 (1.05,1.59)
	male	-0.39 (-0.69,-0.12)	0.67 (0.13,1.13)	-0.28 (-0.43,-0.14)	0.66 (0.46,0.88)
	effect difference	-0.02 (-0.49,0.45)	0.1 (-0.75,0.86)	-0.23 (-0.46,0)	0.65 (0.31,0.99)
race	black	-0.94 (-3.38,1.68)	1.97 (-2.3,6.64)	-0.39 (-1.5,1.16)	1.67 (-0.7,4.13)
	white	-0.46 (-0.7,-0.2)	0.61 (0.12,1.11)	-0.49 (-0.63,-0.35)	1.08 (0.86,1.28)
	effect difference	-0.51 (-2.96,2.18)	1.38 (-2.92,6.09)	0.08 (-1.02,1.65)	0.61 (-1.85,3.06)
Medicaid eligibility	Medicaid eligible	-0.9 (-2.16,0.27)	3.11 (0.72,5.23)	-1.26 (-1.96,-0.69)	3.02 (2.04,3.97)
	Medicaid non-eligible	-0.4 (-0.61,-0.15)	0.26 (-0.12,0.64)	-0.23 (-0.34,-0.11)	0.78 (0.61,0.96)
	effect difference	-0.51 (-1.76,0.66)	2.85 (0.44,4.96)	-1.06 (-1.73,-0.44)	2.25 (1.28,3.21)
age	65-74	-0.16 (-0.28,-0.03)	0.17 (-0.06,0.36)	0.09 (0.02,0.15)	0.15 (0.05,0.24)
	75-84	-0.33 (-0.56,-0.07)	-0.3 (-0.7,0.19)	0.37 (0.24,0.5)	0.22 (0.03,0.41)
	>=85	-0.22 (-0.7,0.23)	0.07 (-0.73,0.93)	0.37 (0.16,0.64)	0.48 (0.1,0.85)

Table S5. Association between seasonal temperature, seasonal temperature variability and hospital admissions from central nervous system infections among Medicare beneficiaries across different strata between 2000-2016

		Effect estimates			
		coldSD	warmSD	Cold Temperature	Warm Temperature
sex	female	2.7 (2.32,3.1)	0.39 (-0.34,1.15)	0.11 (-0.07,0.33)	0.3 (0.01,0.63)
	male	2.57 (2.06,3.1)	1.29 (0.42,2.16)	0.25 (0.01,0.47)	0.25 (-0.09,0.6)
	effect difference	0.12 (-0.53,0.81)	-0.9 (-2.04,0.28)	-0.14 (-0.41,0.18)	0.04 (-0.43,0.53)
race	black	1.8 (-1.34,5.49)	8.4 (2.62,14.25)	-0.13 (-1.66,1.52)	0.25 (-2.06,2.76)
	white	2.66 (2.26,3.02)	1.05 (0.39,1.81)	0.11 (-0.07,0.29)	0.29 (-0.01,0.57)
	effect difference	-0.84 (-3.98,2.66)	7.31 (1.45,13.36)	-0.24 (-1.79,1.42)	-0.06 (-2.51,2.55)
Medicaid eligibility	Medicaid eligible	3.95 (2.27,5.51)	3.4 (0.44,6.45)	0.24 (-0.52,1.03)	0.62 (-0.67,1.77)
	Medicaid non-eligible	2.5 (2.19,2.81)	-0.21 (-0.69,0.38)	0.14 (-0.01,0.3)	0.2 (-0.03,0.44)
	effect difference	1.46 (-0.27,2.99)	3.53 (0.71,6.56)	0.11 (-0.68,0.88)	0.42 (-0.84,1.58)
age	65-74	-0.02 (-0.07,0.03)	-0.01 (-0.12,0.07)	0.02 (-0.01,0.05)	0.02 (-0.02,0.06)
	75-84	-0.04 (-0.11,0.03)	0.03 (-0.1,0.16)	0 (-0.04,0.04)	0.02 (-0.03,0.08)
	>=85	-0.04 (-0.13,0.04)	0.16 (-0.02,0.34)	-0.05 (-0.09,0)	-0.01 (-0.08,0.06)

APPENDIX C

Table S1. Relative contributions of $PM_{2.5}$ constituents in the association between the $PM_{2.5}$ mixture and all-cause mortality across models with interactions terms.

All-cause mortality									
Age		Sex		Race		Donor type		Cold ischemia time	
Component	weights	Component	weights	Component	weights	Component	weights	Component	weights
so4	0.344	so4	0.269	so4	0.652	nh4	0.329	nh4	0.503
nh4	0.260	nh4	0.197	nh4	0.169	so4	0.312	so4	0.201
k	0.138	v	0.103	no3	0.048	no3	0.149	ni	0.128
v	0.086	ni	0.095	fe	0.041	v	0.055	k	0.040
pb	0.049	no3	0.078	v	0.028	k	0.041	br	0.035
ni	0.043	ec	0.064	pb	0.024	si	0.035	fe	0.026
br	0.024	br	0.063	si	0.023	fe	0.034	no3	0.026
fe	0.022	fe	0.062	k	0.007	br	0.014	ec	0.016
no3	0.019	k	0.027	ca	0.003	pb	0.012	si	0.010
si	0.009	si	0.009	ec	0.003	ni	0.011	oc	0.005
ca	0.003	z	0.008	br	0.001	ca	0.007	v	0.005
ec	0.002	oc	0.008	cu	0.001	zn	0.000	cu	0.003
oc	0.000	ca	0.007	ni	0.001	oc	0.000	pb	0.001
cu	0.000	pb	0.006	zn	0.000	cu	0.000	ca	0.001
zn	0.000	cu	0.005	oc	0.000	ec	0.000	zn	0.000

Table S2. Relative contributions of $PM_{2.5}$ constituents in the association between the $PM_{2.5}$ mixture and death-censored graft failure across models with interactions terms.

Death-censored graft failure									
Age		Sex		Race		Donor type		Cold ischemia time	
Component	weights	Component	weights	Component	weights	Component	weights	Component	weights
so4	0.579	so4	0.409	so4	0.753	so4	0.323	so4	0.462
ca	0.122	nh4	0.299	si	0.131	si	0.254	si	0.162
si	0.104	si	0.073	v	0.076	v	0.140	v	0.125
fe	0.047	br	0.060	k	0.013	pb	0.119	nh4	0.088
ni	0.036	ca	0.039	pb	0.009	nh4	0.060	ni	0.067
pb	0.035	ni	0.035	ni	0.007	fe	0.038	ca	0.058
k	0.034	fe	0.028	ca	0.003	ca	0.035	pb	0.014
br	0.014	v	0.025	nh4	0.003	k	0.017	br	0.011
v	0.008	ec	0.013	fe	0.002	ec	0.005	fe	0.006
nh4	0.007	cu	0.007	cu	0.001	cu	0.004	ec	0.003
cu	0.006	pb	0.006	br	0.001	ni	0.002	k	0.002
no3	0.004	no3	0.005	no3	0.001	no3	0.002	cu	0.001
zn	0.001	k	0.001	ec	0.000	zn	0.001	no3	0.000
oc	0.001	zn	0.000	zn	0.000	oc	0.000	zn	0.000
ec	0.001	oc	0.000	oc	0.000	br	0.000	oc	0.000

Table S3. Relative contributions of $PM_{2.5}$ constituents in the association between the $PM_{2.5}$ mixture and acute rejection across models with interactions terms.

Acute rejection									
Age		Sex		Race		Donor type		Cold ischemia time	
Component	weights	Component	weights	Component	weights	Component	weights	Component	weights
pb	0.400	pb	0.591	pb	0.362	pb	0.638	pb	0.612
si	0.163	so4	0.124	so4	0.281	zn	0.117	so4	0.112
so4	0.143	si	0.082	nh4	0.206	so4	0.102	nh4	0.086
k	0.087	br	0.073	zn	0.092	nh4	0.058	zn	0.046
nh4	0.059	nh4	0.038	k	0.035	si	0.031	br	0.041
zn	0.049	zn	0.037	br	0.012	k	0.017	si	0.041
ca	0.044	k	0.036	si	0.010	ca	0.013	fe	0.017
br	0.042	fe	0.007	ca	0.001	br	0.011	k	0.016
fe	0.005	ni	0.006	ec	0.001	ni	0.009	ni	0.014
no3	0.004	ca	0.004	fe	0.000	fe	0.002	ec	0.010
ni	0.003	ec	0.003	ni	0.000	ec	0.001	ca	0.005
ec	0.001	oc	0.000	no3	0.000	oc	0.001	oc	0.000
oc	0.000	v	0.000	oc	0.000	no3	0.000	cu	0.000
cu	0.000	cu	0.000	v	0.000	cu	0.000	no3	0.000
v	0.000	no3	0.000	cu	0.000	v	0.000	v	0.000

Table S4. Relative contributions of $PM_{2.5}$ constituents in the association between the $PM_{2.5}$ mixture and delayed graft function across models with interactions terms.

Delayed graft function									
Age		Sex		Race		Donor type		Cold ischemia time	
Component	weights	Component	weights	Component	weights	Component	weights	Component	weights
oc	0.538	oc	0.420	oc	0.378	oc	0.471	oc	0.359
ni	0.282	ni	0.330	ni	0.174	v	0.193	ni	0.241
cu	0.111	cu	0.150	no3	0.173	ni	0.188	cu	0.214
v	0.064	br	0.088	br	0.132	cu	0.126	v	0.148
ec	0.002	v	0.008	ec	0.075	br	0.020	br	0.037
br	0.001	no3	0.002	zn	0.061	no3	0.002	ec	0.001
si	0.000	zn	0.001	nh4	0.003	ec	0.000	no3	0.000
no3	0.000	fe	0.001	cu	0.002	nh4	0.000	si	0.000
nh4	0.000	k	0.000	si	0.001	ca	0.000	ca	0.000
pb	0.000	nh4	0.000	pb	0.000	si	0.000	fe	0.000
zn	0.000	si	0.000	v	0.000	fe	0.000	pb	0.000
fe	0.000	so4	0.000	fe	0.000	k	0.000	k	0.000
ca	0.000	ca	0.000	ca	0.000	so4	0.000	so4	0.000
k	0.000	ec	0.000	so4	0.000	pb	0.000	zn	0.000
so4	0.000	pb	0.000	k	0.000	zn	0.000	nh4	0.000

Table S5. Relative contributions of $PM_{2.5}$ constituents in the association between the $PM_{2.5}$ mixture and time-to-event outcomes (death censored graft failure and mortality) during first year after kidney transplant.

Death		Death censored graft-failure	
Component	weights	Component	weights
so4	0.403	so4	0.482
si	0.225	v	0.169
v	0.165	si	0.113
fe	0.067	pb	0.077
pb	0.064	nh4	0.061
k	0.023	ni	0.053
oc	0.016	oc	0.021
cu	0.014	k	0.013
no3	0.008	ca	0.009
ca	0.003	fe	0.001
ec	0.003	ec	0.001
ni	0.003	cu	0.000
z	0.002	no3	0.000
nh4	0.002	br	0.000
br	0.001	z	0.000

Table S6. Estimated effect of each decile increase in $PM_{2.5}$ mixture on time-to-event outcomes (death censored graft failure and mortality) during first year after kidney transplant.

	aHR (95%CI)
Death	1.137 (1.111, 1.164)
Death censored graft failure	1.092 (1.070, 1.113)

Table S7. Relative contributions of $PM_{2.5}$ constituents in the association between the $PM_{2.5}$ mixture and post-KT outcomes when further adjusting for NO_2 and Ozone

Component	Weights	Component	Weights	Component	Weights	Component	Weights
pb	0.308	ni	0.436	so4	0.364	so4	0.246
z	0.171	oc	0.401	v	0.132	nh4	0.171
si	0.116	v	0.097	si	0.082	ni	0.095
so4	0.101	cu	0.059	pb	0.067	no3	0.089
br	0.096	br	0.007	nh4	0.066	v	0.088
k	0.073	no3	0.000	z	0.053	si	0.065
nh4	0.062	z	0.000	ec	0.040	pb	0.056
ca	0.039	nh4	0.000	ca	0.040	br	0.046
fe	0.020	ec	0.000	br	0.039	ec	0.038
ni	0.011	ca	0.000	cu	0.034	ca	0.035
ec	0.001	si	0.000	ni	0.031	k	0.034
cu	0.000	pb	0.000	no3	0.030	oc	0.014
oc	0.000	fe	0.000	fe	0.014	z	0.009
no3	0.000	k	0.000	k	0.007	fe	0.008
v	0.000	so4	0.000	oc	0.002	cu	0.007

Table S8. Estimated effect of each decile increase in $PM_{2.5}$ mixture on post-KT outcomes when further adjusting for NO_2 and Ozone

	Effect estimates (95%CI)
Acute rejection	1.051 (1.030, 1.074)
Delayed graft function	1.086 (1.072, 1.100)
Death	1.051 (1.035, 1.067)
DCGF	1.065 (1.033, 1.099)

DCGF: Death censored graft failure

For acute rejection and delayed graft failure, the effect estimates are odds ratio while for Death and DCGF, the effect estimates were hazard ratios

Table S9. Association between total PM2.5 and graft failure (treating death as censoring VS treating death as competing event)

	HR
Cox model	1.013 (1.007, 1.019)
Fine and Gray's model	1.012 (1.006, 1.017)

HR: hazard ratio for each 1μg/m^3 increase in PM2.5; Cox model estimated the association between PM2.5 and death-censored graft failure; Fine and Gray's estimated the association between PM2.5 and graft failure while treating death as a competing event.

Figure S1. Correlation plot between PM2.5 constituents in the US.