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_____ _____

Dongni Ye Date

Estimating acute cardiorespiratory effects of ambient air pollution mixtures

By

Dongni Ye
Doctor of Philosophy
Environmental Health Sciences

_____

Stefanie Ebelt Sarnat, ScD
Advisor

_____

Howard H. Chang, PhD
Committee Member

_____

Mitchel Klein, PhD
Committee Member

_____

James A. Mulholland, PhD
Committee Member

_____

Jeremy A. Sarnat, ScD
Committee Member

Accepted:

_____

Lisa A. Tedesco, Ph.D.
Dean of the James T. Laney School of Graduate Studies

_____

Date

Estimating acute cardiorespiratory effects of ambient air pollution mixtures

By

Dongni Ye
MPH, Yale University, 2012
BS, Tsinghua University, 2010

Advisor: Stefanie Ebelt Sarnat, ScD

An abstract of
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Abstract

Estimating acute cardiorespiratory effects of ambient air pollution mixtures

By Dongni Ye

Introduction

There is an ongoing effort to identify health-relevant components of ambient air pollution and to estimate combined effects of air pollution mixtures. For Aim 1 and Aim 2, we estimated acute cardiorespiratory effects of a broad range of pollutants that were not well-studied previously, as an attempt to gain a better understanding of causal agents in air pollution. In Aim 3, we estimated joint effects of multiple pollutants on pediatric asthma and compared across cities.

Methods

In a time-series framework, we estimated associations between daily ambient concentrations of air pollutants and daily counts of emergency department (ED) visits using Poisson regression. For Aim 1, daily concentrations of volatile organic compounds (VOCs) and daily counts of ED visits for cardiovascular diseases and asthma were obtained in Atlanta during 1998-2008. To seek coherence in understanding health effects of a large number of VOCs, we grouped VOCs based on chemical structure and compared different analytic approaches in estimating VOC group effects. For Aim 2, ambient concentrations of $PM_{2.5}$ metals and daily counts of ED visits for cardiovascular diseases were obtained in Atlanta during 1998-2013. We estimated cardiovascular associations for $PM_{2.5}$ metals and assessed co-pollutant confounding. For Aim 3, we estimated and compared joint effects of muliple pollutants on pediatric asthma ED visits across four cities (Atlanta, Dallas, Pittsburgh, and St. Louis).

Results

Findings in Aim 1 further support the link between incomplete combustion pollutants and cardiovascular health, and between atmospheric oxidation products and respiratory health. Findings in Aim 2 suggest that certain water-soluble metals (particularly water-soluble iron), or species from roadway emissions, impact cardiovascular health. In Aim 3, joint effects of major pollutants were generally similar across cities.

Conclusions

To understand health effects of pollution mixtures is challenging, given that multiple pollutants could affect a health outcome, pollutants are correlated, and only a subset of pollutants could be measured. Findings in Aim 1 and Aim 2 inform future directions in identifying health-relevant components in air pollution. Aim 3 evaluated the homogeneity of multi-pollutant joint effects across cities, and our findings advance the understanding of the combined effects of air pollution mixtures.

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INTRODUCTION

The Great London Smog of 1952 drew attention of the scientific community to the health impacts of ambient air pollution. Since then, numerous epidemiologic and toxicological studies have been conducted to understand acute and chronic effects of air pollution.[1] Evidence indicates that even at moderate-to-low levels, air pollution contributes to the development of cardiorespiratory conditions (e.g., asthma, chronic obstructive pulmonary diseases), exacerbation of symptoms among individuals with these conditions, and deaths from cardiovascular diseases.[1-4] Recent studies also suggest effects of air pollution on reproductive (e.g., preterm delivery, low birthweight) and neurological health (e.g., cognitive impairment).[3, 5-7]

Ambient air pollution is a mixture of gaseous pollutants and particulate matter (PM). Pollutants in the gas phase include carbon monoxide, nitrogen oxides, sulfur oxides, ozone, and various volatile organic compound. PM are solid or liquid particles varying in size and composition suspended in the air. The size distribution of total suspended particles is tri-modal, including coarse, fine, and ultrafine particles. Fine particulate matter, or particles with aerodynamic diameter less than 2.5 micrometer ($PM_{2.5}$), has received most attention in health studies, as these particles are small enough to be breathed in to the lung and deposit in the alveolar region. $PM_{2.5}$ consists of various chemical components. Among them, carbonaceous components (organic carbon and elemental carbon) and secondary ions (nitrate, sulfate, and ammonium) contribute the majority of total $PM_{2.5}$ mass, while metals and metalloids are present in trace amounts.

One perspective in investigating health effects of air pollution mixtures is to identify which pollutants or groups of pollutants are harmful. Traditionally, air pollution

epidemiologic studies considered a limited number of pollutants that are routinely measured at the ambient level. These include pollutants regulated by the U.S. Environmental Protection Agency (EPA) – carbon monoxide (CO), nitrogen oxides (NO_X), sulfur dioxides (SO_2), ozone (O_3), lead, and particulate matter ($PM_{2.5}$, PM_{10}), as well as $PM_{2.5}$ major components – organic carbon (OC), elemental carbon (EC), nitrate (NO_3), sulfate (SO_4), and ammonium (NH_4). Health effects of other co-existing pollutants, for example, volatile organic compounds (VOCs) and $PM_{2.5}$ metals and metalloids, are not well studied due to lack of routine measurements at the ambient level.

Ambient volatile organic compounds (VOCs) are organic pollutants that primarily exist in the gas phase. There is increasing evidence on the health effects of organic aerosols.[8] Epidemiologic studies have suggested cardiorespiratory effects of mixtures from fossil fuel combustion, which contain large fractions of organic pollutants.[8] Ambient organic carbon and its constituents have been associated with cardiorespiratory health outcomes in previous studies.[8-17] VOCs may also have an impact on health. Previous epidemiologic studies have suggested respiratory effects of indoor VOCs.[18] Controlled human exposure studies have suggested inflammatory effects of VOCs.[19, 20] However, epidemiologic evidence on cardiorespiratory effects of ambient VOCs is sparse.[21-29] Most previous studies considered only a limited number of species and are not representative of the wide range of VOCs found in urban air. This knowledge gap motivates Aim 1 of this dissertation.

In addition to trace pollutants in the gas phase, trace pollutants in the particle phase may also have an impact on health. In particular, transition metals, which contribute trace amounts of total $PM_{2.5}$ mass, have been suggested as toxic components of $PM_{2.5}$ due to

their potential for generating reactive oxygen species in living systems, leading to oxidative stress.[30-32] The Chemical Speciation Network (CSN), established by U.S. EPA in 1999, provides measurements of $PM_{2.5}$ metals and metalloids in 192 counties across the country. However, these CSN measurements are only operated every one-in-three or one-in-six days, which limits the power and the assessment of lag structure for studies based on temporal comparisons. In addition, metals exist in different forms, with some being more water-soluble and thus more biologically accessible than others.[33-36] However, due to lack of measurements, few epidemiologic studies have considered water-soluble fractions of metals in their attempt to identify health-relevant components of $PM_{2.5}$.[37, 38] This knowledge gap motivates Aim 2 of this dissertation.

Another perspective in investigating health effects of air pollution mixtures is to estimate joint effects of multiple pollutants. Traditionally, epidemiologic studies estimate health associations for individual pollutants using single-pollutant models.[39-41] However, the observed health associations of a given pollutant could differ across study locations (e.g., cities) due to several reasons: 1) co-pollutant confounding where pollutant co-variations differ by city; 2) effect modification by other pollutants where levels of modifying pollutants differ by city; 3) non-linear dose-response where pollution levels differ by city; 4) effect modification by factors other than pollution (e.g., population characteristics, meteorological conditions) where these factors differ by city; 5) differential measurement error across cities; and 6) random error. These issues complicate the interpretation and generalizability of health associations of individual pollutants across cities. In recent years, various multi-pollutant approaches have been employed to estimate combined effects of air pollution mixtures.[39, 40, 42, 43] Considering a hypothetical joint effect of all

pollutants changing from one set of concentrations to another provides a way to conceptualize health effects of the total pollution mixture, although it is not achievable in reality given that only a limited number of pollutants could be identified and measured. And even such a hypothetical joint effect could depend on factors other than pollution (e.g., population characteristics, meteorological conditions). Nonetheless, perhaps joint effects of multiple pollutants could be similar across cities given that: 1) a joint effect would not be confounded by pollutants that are part of the joint effect and 2) a joint effect could account for potential pollutant interactions and non-linear dose-response in the estimation to reflect health impacts of simultaneous exposures to multiple pollutants. The estimation and comparison of joint effects across cities motivates Aim 3 of this dissertation.

DISSERTATION AIMS

The three aims of this dissertation are as follows. **Aim 1**: To estimate acute cardiorespiratory effects of ambient volatile organic compounds. **Aim 2**: To estimate acute cardiovascular effects of ambient $PM_{2.5}$ metals. **Aim 3**: To estimate joint effects of multiple pollutants on pediatric asthma and compare across cities

To address these aims, we conducted three studies in a time-series framework. We used counts of emergency department visits as indicators for morbidity, and ambient concentrations of pollutants as exposures. Poisson generalized linear models were used to estimate associations between daily counts of emergency department visits and daily ambient concentrations of pollutants. Aim 1 and Aim 2 were conducted in Atlanta, Georgia, U.S., utilizing up to 15 years of data on ambient air pollution and emergency department visits. Aim 3 was conducted across four metropolitan areas in the U.S.:

Atlanta, Georgia; Dallas-Fort Worth, Texas; Pittsburgh, Pennsylvania; and St. Louis, Missouri/Illinois.

In Aim 1 and Aim 2, we estimated health effects of air pollutants that were not well studied previously. Specifically, in Aim 1, we estimated acute cardiorespiratory effects of a large number of ambient volatile organic compounds (VOCs) in a coherent manner by grouping these VOCs *a priori* by chemical structure and comparing different analytic approaches of defining and estimating VOC group effects. In Aim 2, we estimated acute cardiovascular effects of $PM_{2.5}$ components, including water-soluble fractions of a suite of metals that are not routinely measured at the ambient level. Our findings in Aim 1 and Aim 2 contribute to the ongoing effort to identify health-relevant components in air pollution mixtures. In Aim 3, we estimated joint effects of multiple pollutants as an attempt to better understand health impacts of air pollution mixtures. We explored different specifications of dose-response (i.e., pollution interactions and non-linearity) in the estimation and compared joint effect estimates across cities.

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Chapter 1

Estimating acute cardiorespiratory effects of ambient volatile organic compounds

Dongni Ye, Mitchel Klein, Howard H. Chang, Jeremy A. Sarnat, James A. Mulholland, Eric S. Edgerton, Andrea Winquist, Paige E. Tolbert, Stefanie Ebelt Sarnat

Ye, D., et al., *Estimating Acute Cardiorespiratory Effects of Ambient Volatile Organic Compounds*. Epidemiology, 2017. **28**(2): p. 197-206.

ABSTRACT

Background

The health effects of ambient volatile organic compounds (VOCs) have received less attention in epidemiologic studies compared to other commonly measured ambient pollutants. In this study, we estimated acute cardiorespiratory effects of ambient VOCs in an urban population.

Methods

Daily concentrations of 89 VOCs were measured at a centrally-located ambient monitoring site in Atlanta and daily counts of cardiovascular and asthma emergency department (ED) visits in the 5-county Atlanta area were obtained for the 1998-2008 period. To seek coherence in understanding the health effects of the large number of species, we grouped these VOCs *a priori* by chemical structure and estimated the associations between VOC groups and daily counts of ED visits in a time-series framework using Poisson regression. We applied three analytic approaches to estimate the VOC group effects: an indicator pollutant approach, a joint effect analysis, and a random effect meta-analysis, each with different assumptions. We performed sensitivity analyses to evaluate co-pollutant confounding.

Results

Hydrocarbon groups, particularly the alkene and alkyne groups, were associated with cardiovascular ED visits, while the ketone group was associated with asthma ED visits.

Conclusions

The associations between cardiovascular ED visits and the alkene and alkyne groups may reflect the effect of traffic exhaust, while the association between asthma ED visits and the ketone group may reflect the effect of secondary organics. The different patterns of associations we observed for cardiovascular and asthma ED visits suggest different modes of action of these pollutants or pollution mixtures they represent.

INTRODUCTION

Ambient air pollution is a complex mixture of particulate matter varying in size and composition and gaseous pollutants. Health effects of particulate matter, its constituents, and criteria gases have been frequently investigated.[1, 2] Other coexisting pollutants, for example, the volatile organic compounds (VOCs), have received less attention in epidemiologic studies.

Organic pollutants include a variety of compounds, such as hydrocarbons, halocarbons, and oxygenates. These compounds reside in the vapor phase, particle phase, or both, depending on organic equilibrium properties (e.g., vapor pressure) and particle surface composition (e.g., water content). There is a dynamic continuum among VOCs, semi-volatile organic compounds (SVOCs), and particle phase organics, and together they constitute the total organic aerosol.[3, 4] There is increasing evidence on the health effects of organic aerosols. Epidemiologic studies have suggested cardiorespiratory effects of mixtures from fossil fuel combustion, which contain large fractions of organic pollutants.[4] Ambient fine particle organic carbon ($PM_{2.5}$ OC) and its constituents have been associated with various cardiorespiratory health outcomes in previous epidemiologic studies.[4-13] VOCs may also have an impact on health. Previous epidemiologic studies have suggested respiratory effects of indoor VOCs.[14] Controlled human exposure studies have suggested inflammatory effects of VOCs.[15, 16] However, epidemiologic evidence on cardiorespiratory effects of ambient VOCs is sparse.[17-25] Most previous studies considered only a limited number of species and are not representative of the wide range of compounds found in urban air.

To advance our understanding of the health relevance of ambient VOCs, we estimated their acute cardiorespiratory effects in the Atlanta, Georgia, metropolitan population. This analysis capitalizes on our ongoing Study of Particles and Health in Atlanta (SOPHIA) that has information on ambient air pollution, including a wide range of VOCs, and emergency department (ED) visits.[26-29] To seek coherence in understanding the health effects of a large number of VOCs, we grouped VOCs *a priori* by chemical structure and estimated the group effects. Grouping by chemical structure was motivated by several considerations: 1) as chemical structure determines the reactivity of a compound, pollutants sharing a common chemical structure may be similar in toxicity, so grouping by chemical structure may enhance the understanding of their health associations from a biological perspective; and 2) pollutants sharing a common chemical structure may be generated from common emission sources or atmospheric chemical processes, so grouping by chemical structure may suggest health effects of these sources or processes.

While we grouped these VOCs by commonalities, pollutants within a group may still differ in their health associations and be subject to different levels of measurement error. As there is little understanding of the nature of these variations, we applied three analytic approaches to estimate the group effects, each with different assumptions concerning the variations within a group.

METHODS

VOC measurements and formation of VOC groups

Daily 24-hour average concentrations of VOCs were measured at the Atlanta Jefferson Street ambient monitoring site during 8/14/1998-12/31/2008 as part of the Aerosol

Research and Inhalation Epidemiology Study (ARIES). Sampling details were previously published by Hansen *et al*.[30] Briefly, 24-hour samples were collected in evacuated 6-L passivated stainless canisters and then analyzed via gas-chromatography with flame ionization detection. Data included daily concentrations of 89 identified individual species (77 hydrocarbons and 12 oxygenates), total identified hydrocarbons, and total identified oxygenates (Supplement, eTable 1.1). Concentrations were reported in part per billion, as carbon (ppb-C), and the limit of detection (LOD) for all species was 0.1 ppb-C.

We grouped individual VOCs *a priori* by chemical structure. Groups among the 77 hydrocarbons included alkanes, alkenes, alkynes, and aromatic hydrocarbons, and among the 12 oxygenates included aldehydes, acids, ketones, and ethers. We further divided the alkanes into four groups (n-alkane, iso/anteiso-alkane, other branched alkane, cycloalkane) based on branching. For this analysis, we only included species with concentrations above the LOD on at least 90% of days. This left 46 species in 7 hydrocarbon groups (n-alkane, iso/anteiso-alkane, other branched alkane, cycloalkane, alkene, alkyne, and aromatic) and 3 oxygenate groups (aldehyde, acid, and ketone) (Table 1.1). Observations below LOD were replaced with half the detection limit (0.05 ppb-C).

Emergency department visits

We obtained daily counts of cardiovascular and asthma ED visits for patients living within the 5-county Atlanta area (Clayton, Cobb, DeKalb, Fulton, and Gwinnett) during 8/14/1998-12/31/2008. Daily counts of ED visits were aggregated from individual-level billing records from metropolitan Atlanta hospitals as part of SOPHIA.[26-29] We identified cardiovascular ED visits as those with primary International Classification of Diseases, 9th Revision (ICD-9) diagnosis codes for ischemic heart disease (410-414),

cardiac dysrhythmias (427), congestive heart failure (428), or peripheral vascular and cerebrovascular disease (433-437, 440, 443-445, 451-453). Asthma ED visits were identified as those with primary ICD-9 diagnosis codes for asthma (493) or wheeze (786.09, before 10/1/1998; 786.07, after 10/1/1998).

Analytic approaches

We first estimated the effects of total identified hydrocarbons and total identified oxygenates, and then estimated VOC group effects using three analytic approaches. All analyses were conducted in a time-series framework, in which we estimated the associations between daily levels of VOCs and daily counts of ED visits using Poisson regression accounting for over-dispersion. Based on our previous research on ambient air pollution and ED visits in Atlanta,[26-29] and studies on ambient VOC health effects in other cities,[22, 24] we used same-day (lag 0) pollution levels in models predicting cardiovascular ED visits and 3-day moving average (of lags 0, 1, and 2) pollution levels in models predicting asthma ED visits. All models included the same covariate control for temporal trends and meteorology: time splines with monthly knots, cubic function of same-day maximum temperature, cubic function of lag 1-2-day moving average minimum temperature (when using 3-day moving average pollution levels), cubic function of mean dew point temperature (same-day or 3-day moving average, matching the temporal metric of the pollution term), day of week, indicators for holidays, seasons, season-maximum temperature interaction, season-day of week interaction, and indicators for hospital participation periods. The estimated associations were reported as rate ratios per interquartile range (IQR) increase in pollutant concentrations.

Analyses of cardiovascular ED visits included all ages. For asthma ED visits, we performed analyses among all ages, and analyses stratified by age category (5-18 and 19+ years old), given our previous work suggesting that effects of air pollution on asthma may differ for children.[31]

Estimation of total VOC effects

We used single-pollutant models to estimate the effect of total identified hydrocarbons and total identified oxygenates, as follows:

Log[E(Y)] = $\beta_0 + \beta_1 * (total)$ + covariate control

Eq. 1

where Y was the daily count of ED visits for cardiovascular disease or asthma, and *total* was the daily concentration of the total identified hydrocarbons or the total identified oxygenates.

Estimation of VOC group effects

We estimated VOC group effects using three analytic approaches: an indicator pollutant approach, a joint effect analysis, and a random effect meta-analysis.

1. Indicator pollutant approach

Pollutants in the same group may not be equally well measured. To minimize the impact of instrument measurement error on health effect estimation, we selected the pollutant with the highest median/LOD ratio as the indicator pollutant for each group, and considered the effect of the indicator pollutant as the group effect. This approach is based on the assumption that the pollutant with the concentration distribution furthest from the

LOD is less prone to instrument-related measurement error. The effects of indicator pollutants were estimated using single-pollutant models as follows:

Log[E(Y)] = $\beta_0 + \beta_g * (indicator\ pollutant\ of\ group_g)$ + covariate control

Eq 2.

where $indicator\ pollutant\ of\ group_g$ was the concentration of the indicator pollutant for group g.

2. Joint effect analysis

The effect of a given indicator pollutant may not fully represent the effect of its group if pollutant effects within a group differ. To capture the contribution of different pollutants within a group, we estimated a joint effect per IQR increase in all pollutants of a group as follows:

Log[E(Y)] = $\beta_0 + \sum_{i=1}^{i=n_g} \beta_i * (pollutant_i)$ + covariate control

Eq 3.

where n_g is the number of pollutants in group g, and $pollutant_i$ represented the concentration of each pollutant in group g. The estimated joint effect of group g was calculated as $e^{\sum_{i=1}^{i=n_g} IQR_i * \widehat{\beta}_i}$, where IQR_i was the interquartile range of $pollutant_i$ in group g. [32]

3. Random effect meta-analysis

In the joint effect analysis, we considered the individual pollutant effects as fixed, and estimated a combined effect per increase in all pollutants in a group. In this random effect meta-analysis, we considered pollutant effects within a group as random (normally

distributed) and estimated the group mean as the group effect. We applied a two-stage regression to estimate the group means and the within-group variance. [33-35]

In the first stage, we included all 46 VOCs in the Poisson model as follows:

$\text{Log}[E(Y)] = \beta_0 + \sum_{i=1}^{i=46} \beta_i * (pollutant_i)$ + covariate control

Eq 4.

where $pollutant_i$ represented the concentration of each of the 46 VOCs. We obtained the estimated pollutant effects and their estimated variance-covariance matrix from the first stage model.

Let $\widehat{\boldsymbol{\beta}}$ denote the vector of the estimated pollutant effects per IQR increase in pollutant concentrations, and let $\widehat{\boldsymbol{V}}$ denote the corresponding variance-covariance matrix. In the second stage, we regressed the first stage estimates against indicator variables representing the groups:

$\widehat{\boldsymbol{\beta}} = Z\boldsymbol{\alpha} + \boldsymbol{\theta} + \boldsymbol{\varepsilon}$

Eq 5.

where $\mathbf{Z}$ is the design matrix indexing the grouping; $\boldsymbol{\alpha}$ is a vector of the group means; $\boldsymbol{\theta}$ is a vector of pollutant-specific deviation from its group mean with $\boldsymbol{\theta} \sim N(0, \tau^2 \boldsymbol{I})$, where τ^2 is within group variance, and $\boldsymbol{\varepsilon}$ is the estimation error with $\boldsymbol{\varepsilon} \sim N(0, \widehat{\boldsymbol{V}})$.

We estimated the group means and within-group variance under a Bayesian framework using Markov chain Monte Carlo. Prior distributions for the group means and the within-group variance τ^2 were Normal with dispersed variance and inverse-gamma (0.001, 0.001), respectively.

Sensitivity analyses

We performed a series of sensitivity analyses for the indicator pollutant approach, using ED visits among all ages. First, we evaluated model misspecification by estimating the associations between tomorrow's pollutant levels (lag negative 1) and today's ED visits, controlling for today's pollutant and covariate levels. Tomorrow's pollutant levels should not be associated with today's ED visits in the absence of confounding, measurement error, or other model misspecification, as cause must precede effect.[36] Second, we evaluated potential confounding by VOCs, where we estimated the effect of each VOC group conditioning on others by including the 10 VOC indicator pollutants in one model. Third, we evaluated potential confounding by selected major pollutants by controlling for them one at a time in each VOC indicator pollutant model. The major pollutants considered in this analysis included 24-hour average $PM_{2.5}$ OC, one-hour maximum carbon monoxide (CO), one-hour maximum nitrogen dioxide (NO_2), and eight-hour maximum ozone (O_3). These pollutants were also measured at the Atlanta Jefferson Street ambient monitor during the study period.[30]

RESULTS

Descriptive statistics and grouping information for the 46 VOCs included in the analysis are listed in Table 1.1, and their Pearson correlations are listed in Supplementary eTable 1.2. Hydrocarbons had moderate-to-strong positive correlations with one another (r from 0.48 to 0.98, with mean of 0.82). Oxygenates had weak-to-moderate positive correlations with one another (r from 0.20 to 0.64, with mean of 0.42). Correlations between hydrocarbons and oxygenates were weak-to-moderate (r from -0.32 to 0.67, with mean of 0.28).

Descriptive statistics of the major pollutants ($PM_{2.5}$ OC, CO, NO_2, and O_3) considered in the sensitivity analysis are listed in Table 1.1, and their correlations with the 46 VOCs are listed in the Supplementary eTable 1.3. Hydrocarbons had moderate-to-strong positive correlations with $PM_{2.5}$ OC, CO, and NO_2 (r from 0.40 to 0.76, with mean of 0.60), while weak correlations with O_3 (r from -0.26 to 0.23, with mean of 0.10). Oxygenates had weak-to-moderate correlations with these major pollutants (r from -0.03 to 0.57, with mean of 0.22).

During the study period, there were 251,030 cardiovascular ED visits (66 per day) and 233,121 asthma ED visits (61 per day overall; 18 per day among 5-18 year olds; and 27 per day among 19+ year olds).

Primary analysis

We first estimated associations between total VOCs and ED visits using single-pollutant models. For cardiovascular ED visits, $\widehat{RR}$ (95% CI) per IQR increase in total hydrocarbons and in total oxygenates were 1.005 (1.001, 1.009) and 1.004 (0.996, 1.013), respectively. For asthma ED visits among all ages, the association for total oxygenates was stronger than that for total hydrocarbons, with $\widehat{RR}$s (95% CI) of 1.008 (1.001, 1.015) and 1.024 (1.007, 1.041), respectively. We observed this pattern among 5-18 and 19+ year olds as well (Supplement, eTable 1.4).

We then estimated VOC group effects using the three analytic approaches (Table 1.2). Note that the alkyne, acid, and ketone groups included only one pollutant, and thus their joint effect estimates were the same as their indicator pollutant effect estimates. For cardiovascular ED visits, $\widehat{RR}s$ per IQR increase in hydrocarbon groups were generally

similar with one another when estimated using the indicator pollutant approach and the joint effect analysis. However, in the random effect meta-analysis, only the alkyne group was associated with cardiovascular ED visits, with a $\widehat{RR}$ (95% CI) of 1.007 (1.001, 1.012). Among oxygenates, associations with cardiovascular ED visits were generally consistent with the null except for the aldehyde group in the joint effects analysis (Table 1.2).

For asthma ED visits among all ages, the association with the ketone group was the largest, with $\widehat{RR}s$ per IQR increase of 1.026 (1.004, 1.048), 1.026 (1.004, 1.048), and 1.024 (1.000, 1.049), using the indicator pollutant approach, the joint effect analysis, and the random effect meta-analysis, respectively. The association for the aldehyde group was also large in the joint effect analysis, with a $\widehat{RR}$ (95% CI) of 1.021 (1.004, 1.037). In comparison, the associations for hydrocarbon groups were weaker (Table 1.2). We observed this pattern of associations within the 5-18 and 19+ year age categories as well (Supplement, eTable 1.5). The biggest difference between these two age categories was that the association for the acid group was stronger among 5-18 than 19+ year olds.

Sensitivity analysis

We performed sensitivity analyses using ED visits among all ages.

For the indicator pollutant approach, we found associations between cardiovascular ED visits and tomorrow's levels for the acid and ketone groups, and between asthma ED visits and tomorrow's levels for the alkyne group, suggesting possible model misspecification when estimating these associations. Other associations with tomorrow's pollutant levels were consistent with the null, as expected under a well-specified model (Table 3).

We estimated the association for each VOC group conditioning on others by including the 10 VOC indicator pollutants in one model. The estimated associations between cardiovascular ED visits and the alkene and alkyne groups had little change compared to those in the primary analysis using the indicator pollutant approach, while the estimated associations for other hydrocarbon groups were closer to the null (Table 1.3). For asthma ED visits, results of this sensitivity analysis appeared to be unstable.

We estimated the association for each VOC indicator pollutant controlling for major pollutants one at a time in two-pollutant models. The estimated associations between cardiovascular ED visits and hydrocarbon groups were weaker when controlling for CO; the associations for CO were also weaker in two-pollutant models with the alkene or alkyne groups, compared to its estimated association in a single-pollutant model (Table 1.4). The estimated associations between asthma ED visits and the oxygenate groups had little change when controlling for any of these major pollutants, and $\widehat{RR}s$ per IQR increase in the ketone group were the largest ($\widehat{RR}$s from 1.025 to 1.027). The associations between asthma ED visits and hydrocarbon groups, on the other hand, were weaker when controlling for OC, CO, or NO_2 (Table 1.5).

DISCUSSION

In this study, we estimated acute cardiorespiratory effects of ambient VOCs by grouping these compounds based on chemical structure and estimating VOC group effects. As few epidemiologic studies have examined the health effect of ambient VOCs, there is little understanding on the variation of pollutant effects and measurement error within a group, confounding by VOCs, and confounding by other fractions of air pollution. Because of

these challenges, we applied multiple analytic approaches to estimate VOC group effects, and performed a range of sensitivity analyses.

We used the indicator pollutant approach as an attempt to minimize the instrument measurement error by using what we believed to be the best-measured pollutant. In the joint effect analysis, we considered individual pollutant effects as fixed and estimated a combined effect per increment of all pollutants in a group. In the random effect meta-analysis, we considered individual pollutant effects as random (normally distributed within a group) and estimated the group mean effect. Any inconsistency among group effect estimates using these approaches does not necessarily indicate that any of the estimates are wrong, but could reflect that these approaches define the group effects differently.

In our primary analysis of cardiovascular ED visits, we observed similar associations across hydrocarbon groups when using the indicator pollutant approach (Table 1.2). We performed a sensitivity analysis to estimate the effect of each group conditioning on others, and the results suggested that many of the hydrocarbon groups might be surrogates of the alkene and the alkyne groups (Table 1.3). The finding of alkyne being associated with cardiovascular ED visits conditioning on other VOC groups agreed with the random effect meta-analysis results in the primary analysis, in which the estimated associations of each group was adjusted for others (Table 1.2).

However, it is also possible that these VOC groups are surrogates of other pollutants in the ambient air, and that the alkene and the alkyne groups in our analysis were merely better surrogates compared to other VOCs. To understand what the VOCs might be surrogates of, we performed an additional sensitivity analysis controlling for selected

major pollutants one at a time in each VOC indicator pollutant model. When controlling for CO, the estimated associations between cardiovascular ED visits and the alkene and the alkyne groups were weaker, and the CO association was also weaker (Table 1.4). The alkene and the alkyne groups may be part of a causal mixture with CO, or, these pollutants could all be surrogates of other unmeasured pollutants in the causal mixture. Considering that pollutants in the alkene and alkyne groups are mainly generated from combustion, among which acetylene (the pollutant in the alkyne group) is a tracer of automobile emission, and CO is a classic traffic marker, their associations with cardiovascular ED visits may reflect the effect of traffic exhaust.

In our primary analysis of asthma ED visits, we observed relatively strong associations with the ketone group among all ages (Table 1.2) and among specific age categories (Supplement, eTable 1.5). We performed sensitivity analyses on asthma ED visits of all ages, and found that the estimated associations for the ketone group had little change after controlling for any of the major pollutants (Table 1.5). While certain ketones are byproducts of ozone formation, and the pollutant in our ketone group is moderately correlated with ozone in this analysis, the association between ketone and asthma ED visits had little change after controlling for ozone. The association between ketone and asthma ED visits could reflect something beyond the effect of ozone, perhaps, the effect of other secondary organics that are also generated through atmospheric oxidation processes.

Overall, we found that hydrocarbon groups, particularly the alkene and alkyne groups, were associated with cardiovascular ED visits, while the ketone group was associated with asthma ED visits. Some hydrocarbon groups were associated with asthma ED visits,

however, the magnitudes of their associations were smaller compared to the ketone group. The different patterns of associations we observed for the cardiovascular ED visits and the asthma ED visits suggest there could be different modes of action of these pollutants or the pollution mixtures they represent. The hydrocarbons included in our analysis are primarily emitted from traffic or other combustion sources, while oxygenates such as ketones are largely secondary. Previous studies of particle-phase pollutants have suggested that secondary organics are more related to respiratory inflammation, as they are hydrophilic and thus more readily react with constituents in the respiratory tract,[6] while primary organics are more related to systemic inflammation.[6, 7, 37] Our results on vapor-phase organics are consistent with these previous findings on particle-phase pollutants.

Previous epidemiologic studies reported positive associations between cardiovascular health outcomes and ambient hydrocarbons.[23, 25] Our finding of the alkyne group being associated with cardiovascular health outcomes has not been reported previously, although Suh *et al.* combined alkyne with other VOCs in a combustible category and reported its positive association with cardiovascular hospital admission.[35] Our findings on asthma ED visits and ambient VOCs are supported by existing evidence in general. Previous epidemiologic studies reported positive associations between respiratory health outcomes and ambient hydrocarbons, aldehydes, and ketones.[17-19, 21, 22, 24] Among them, Delfino *et al.* showed in a panel of asthmatic children that aldehyde (formaldehyde) and ketone (acetone) were associated with severe asthma symptoms with greater magnitudes compared to hydrocarbons (benzene, toluene, and xylenes),[19] similar to the pattern we observed here.

Our results are subject to spatial misalignment and instrument measurement error. The degree of these sources of error likely differs by VOC group, and thus the estimated group effects should be compared in light of these limitations. Compared to oxygenates, hydrocarbons as primary pollutants may be more subject to spatial misalignment, due to larger spatially heterogeneity. If this is the case, the estimated associations for hydrocarbon groups may be more biased towards the null compared to those for the oxygenate groups. Additionally, pollutants with a lower ambient concentration (e.g., the cycloalkane and aldehyde groups) may be more subject to instrument measurement error leading to underestimation of effects.

We chose to group pollutants based on *a prior* knowledge (chemical structure) rather than the statistical relationships among them (e.g., factor analysis, principle components analysis, etc). In doing so, the group definition is not specific to the data, and will allow for replication in future studies. Collinearity could be a concern when including multiple correlated pollutants in the same model (eq. 3 and eq. 4). One consequence of collinearity is that it could lead to inflation of the variances for individual pollutant effect estimates. However, in our approaches where multiple pollutants were included in the same model, our interest was not in estimating individual pollutant effects, but rather, the group effects. Specifically, in the random effect meta-analysis, the second stage regression accounted for this variance inflation by estimating the group effect as a weighted-average of the first stage estimates, with the inverse variance-covariance matrix of the first stage estimates serving as the weights. In the joint effect analysis, the variance of the joint effect estimate incorporates negative co-variances between individual pollutant estimates, and thus could be more modest compared to the variances of individual pollutant

estimates. In addition, our relatively long time-series (over 10 years) with relatively large counts of outcome events allow for a high degree of collinearity with less impact on the estimates than would be the case for a study with fewer observations.[32]

We grouped these VOCs by chemical structure with the idea that this grouping may enhance the understanding of their health associations from commonalities that are related to their structures, such as toxicity, source, and atmospheric process. However, pollutants sharing a common chemical structure may still differ in these factors, and the estimated group effect may not be easily generalized to pollutants that fall into the same group but are not included in our analysis. For example, alkenes included in our analysis were mainly anthropogenic, as biogenic alkenes measured at Jefferson St. were lower in concentration and thus excluded from the analysis due to >10% of measurements being below detection (Supplement, eTable 1.1). Biogenic alkenes, such as isoprene, are important in the generation of ozone and secondary organics; these pollutants may exert health effects through pathways that are different from the anthropogenic alkenes included in this analysis.

Nonetheless, our approach allowed us to compare and understand the health associations of a large number of species in a coherent manner. Our findings further support the link between incomplete combustion and cardiovascular health, and the link between atmospheric oxidation products and respiratory health.

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Table 1.1. Summary statistics of daily 24-hour average ambient air pollutants measured at the Atlanta Jefferson Street monitoring site during 8/14/1998-12/31/2008: total hydrocarbons, total oxygenates, 46 individual VOCs grouped by chemical structure, and four major pollutants that are included in analyses.[a]

VOC GROUPS	INDIVIDUAL VOCs	50th (25th, 75th) percentiles
	TOTAL HYDROCARBONS[b]	92.7 (63.2, 159.3)
	TOTAL OXYGENATES[b]	19.3 (11.8, 27.6)
HYDROCARBONS:		
N-ALKANE	Ethane	6.9 (4.9, 10.2)
	Propane[c]	**10.3 (6.5, 19.5)**
	n-Butane	6.2 (3.5, 11.0)
	n-Pentane	3.2 (2.2, 5.4)
	n-Hexane	1.5 (1.0, 2.6)
	n-Heptane	0.9 (0.6, 1.5)
	n-Octane	0.5 (0.3, 0.8)
	n-Nonane	0.6 (0.4, 0.9)
	n-Decane	0.7 (0.5, 1.3)
ISO/ANTEISO-ALKANE	i-Butane	2.3 (1.4, 4.2)
	i-Pentane[c]	**6.7 (4.3, 12.4)**
	2-Methylpentane	1.9 (1.2, 3.4)
	3-Methylpentane	1.2 (0.8, 2.1)

	2-Methylhexane	0.8 (0.5, 1.5)
	3-Methylhexane	1.1 (0.7, 1.9)
	2-Methylheptane	0.3 (0.2, 0.6)
OTHER ALKANE	2,2-Dimethylbutane	0.5 (0.3, 1.0)
	2,3-Dimethylbutane	0.6 (0.4, 1.1)
	2,3-Dimethylpentane	0.5 (0.3, 1.0)
	2,4-Dimethylpentane	0.3 (0.2, 0.7)
	2,2,4-Trimethylpentane[c]	**2.0 (1.2, 3.9)**
	2,3,4-Trimethylpentane	0.6 (0.3, 1.2)
	3-Ethylhexane	0.3 (0.2, 0.6)
CYCLOALKANE	Cyclopentane	0.3 (0.2, 0.5)
	Methylcyclopentane[c]	**0.8 (0.5, 1.4)**
	Methylcyclohexane	0.5 (0.3, 0.8)
ALKENE	**Ethylene[c]**	**3.1 (2.0, 5.4)**
	Propene	1.4 (0.9, 2.6)
ALKYNE	**Acetylene[c]**	**4.2 (2.7, 7.6)**
AROMATIC	Benzene	2.4 (1.8, 3.8)
	Toluene[c]	**7.1 (4.7, 12.5)**
	Ethylbenzene	1.4 (0.9, 2.4)
	n-Propylbenzene	0.4 (0.2, 0.7)
	m-Xylene & p-Xylene	3.7 (2.2, 6.9)
	o-Xylene	1.5 (0.9, 2.8)
	m-Ethyltoluene	0.6 (0.3, 1.0)

	p-Ethyltoluene	1.3 (0.8, 2.2)
	1,2,4-Trimethylbenzene[d]	1.7 (1.0, 3.0)
	1,3,5-Trimethylbenzene	0.7 (0.4, 1.2)
OXYGENATES:		
ALDEHYDE	Hexanal	0.8 (0.5, 1.1)
	Heptanal	0.6 (0.4, 0.8)
	Octanal	1.2 (0.7, 1.8)
	Decanal	0.7 (0.4, 1.1)
	Benzaldehyde[c]	**1.7 (1.2, 2.5)**
ACID	**Acetic Acid[c]**	**3.6 (1.5, 7.2)**
KETONE	**2-Butanone[c]**	**1.7 (1.0, 2.9)**

	MAJOR POLLUTANTS	**50th (25th, 75th) percentiles**
	24-hr $PM_{2.5}$ OC ($\mu g/m^3$)	3.6 (2.6, 5.0)
	1-hr max CO (ppm)	0.69 (0.43, 1.27)
	1-hr max NO_2 (ppb)	39.3 (29.5, 50.0)
	8-hr max O_3 (ppb)	39.5 (25.7, 56.7)

[a]There were 3793 days during 08/14/1998-12/31/2008. Hydrocarbons were available for 3233 of these days, while oxygenates were available for 3231 of these days. The unit is ppb-C and the limit of detection (LOD) is 0.1 ppb-C for all VOCs. VOC concentrations below 0.1 ppb-C were replaced with 0.05 ppb-C in all analyses.

[b]Total hydrocarbons denotes total identified non-methane hydrocarbons. Total oxygenates denotes total identified oxygenated hydrocarbons.

[c]Species in bold text are the indicator pollutants for each VOC group.

[d]1,2,4-Trimethylbenzene & sec-Butylbenzene

Table 1.2. Estimated associations between VOC groups and cardiovascular and asthma ED visits using three analytic approaches.[a]

VOC GROUPS	INDICATOR POLLUTANT APPROACH[b]	JOINT EFFECT ANALYSIS[c]	RANDOM EFFECT META-ANALYSIS[d]
	CARDIOVASCULAR ED VISITS AMONG ALL AGES		
HYDROCARBONS			
N-ALKANE	1.002 (1.000, 1.005)	1.006 (1.001, 1.011)	0.999 (0.997, 1.001)
ISO/ANTEISO-ALKANE	1.004 (1.001, 1.008)	1.005 (1.000, 1.010)	1.000 (0.997, 1.003)
OTHER ALKANE	1.005 (1.001, 1.008)	1.006 (1.001, 1.011)	1.000 (0.997, 1.002)
CYCLOALKANE	1.005 (1.001, 1.009)	1.005 (1.001, 1.010)	1.002 (0.997, 1.007)
ALKENE	1.006 (1.002, 1.009)	1.006 (1.002, 1.009)	1.001 (0.997, 1.006)
ALKYNE	1.006 (1.003, 1.010)	1.006 (1.003, 1.010)	1.007 (1.001, 1.012)
AROMATIC	1.006 (1.002, 1.010)	0.998 (0.992, 1.005)	1.000 (0.999, 1.001)
OXYGENATES			
ALDEHYDE	1.001 (0.998, 1.004)	1.008 (1.000, 1.016)	1.000 (0.998, 1.002)
ACID	1.002 (0.995, 1.010)	1.002 (0.995, 1.010)	1.001 (0.993, 1.009)
KETONE	1.005 (0.995, 1.014)	1.005 (0.995, 1.014)	1.003 (0.993, 1.013)
	ASTHMA ED VISITS AMONG ALL AGES		
HYDROCARBONS			
N-ALKANE	1.004 (1.000, 1.009)	1.005 (0.995, 1.014)	0.999 (0.994, 1.003)

VOC GROUPS	INDICATOR POLLUTANT APPROACH[b]	JOINT EFFECT ANALYSIS[c]	RANDOM EFFECT META-ANALYSIS[d]
ISO/ANTEISO-ALKANE	1.006 (1.000, 1.013)	1.010 (1.000, 1.019)	1.006 (0.999, 1.013)
OTHER ALKANE	1.006 (1.000, 1.013)	1.007 (0.999, 1.016)	0.999 (0.993, 1.004)
CYCLOALKANE	1.009 (1.002, 1.016)	1.009 (1.002, 1.016)	0.995 (0.986, 1.007)
ALKENE	1.005 (0.998, 1.011)	1.005 (0.998, 1.011)	0.992 (0.983, 1.003)
ALKYNE	1.006 (0.999, 1.012)	1.006 (0.999, 1.012)	1.000 (0.987, 1.014)
AROMATIC	1.009 (1.002, 1.017)	1.008 (0.995, 1.021)	1.002 (0.998, 1.005)
OXYGENATES			
ALDEHYDE	0.998 (0.991, 1.005)	1.021 (1.004, 1.037)	1.000 (0.995, 1.006)
ACID	1.008 (0.991, 1.026)	1.008 (0.991, 1.026)	1.003 (0.983, 1.021)
KETONE	1.026 (1.004, 1.048)	1.026 (1.004, 1.048)	1.024 (1.000, 1.049)

[a]This analysis included 3224 days on which all VOCs were available during 8/14/1998-12/31/2008. VOC concentrations below the limit of detection (LOD) of 0.1 ppb-C were replaced with 0.05 ppb-C in all analyses. We used same-day (lag 0) pollution levels in models predicting cardiovascular ED visits and 3-day moving average (of lags 0, 1, and 2) pollution levels in models predicting asthma ED visits. All methods included the same covariate control for temporal trends and meteorology: time splines with monthly knots, cubic function of same-day maximum temperature, cubic function of lag 1-2-day moving average minimum temperature (when using 3-day moving average pollution levels), cubic function of mean dew point temperature (same-day or 3-day moving average, matching the temporal metric of the pollution term), day of week, indicators for holidays, seasons, season-maximum temperature interaction, season-day of week interaction, and

indicators for hospital participation periods. The estimated associations are expressed as rate ratios (95% confidence interval) per interquartile range (IQR) increase in pollutant concentrations (listed in Table 1).

[b]The "indicator pollutant approach" estimated the effect of each indicator pollutant increasing by its IQR in single-pollutant models.

[c]The "joint effect analysis" estimated the effect of all pollutants in a group jointly increasing by their IQRs in multi-pollutant models that included all pollutants of the group. The joint effect estimates for VOC groups comprised of only one pollutant were the same as the estimates obtained from the indicator pollutant approach.

[d]The "random effect meta-analysis" estimated the mean effect of any of the pollutants in a group increasing by its IQR in a two-stage regression, where the 46 individual pollutant effects were estimated simultaneously in the Poisson model in the first stage, and the mean of each group was estimated under a Bayesian framework using Markov chain Monte Carlo in the second stage. The estimated rate ratio (95% CI) for the random effect meta-analysis is median (2.5^{th}, 97.5^{th} percentiles) from the posterior distribution.

Table 1.3. Sensitivity analyses evaluating model misspecification and confounding by VOCs.[a]

VOC GROUPS	PRIMARY ANALYSIS[b]	LAG NEGATIVE 1[c]	CONTROL FOR OTHER VOC GROUPS[d]
		CARDIOVASCULAR ED VISITS AMONG ALL AGES	
HYDROCARBONS			
N-ALKANE	1.002 (1.000, 1.005)	1.002 (0.999, 1.005)	1.000 (0.997, 1.003)
ISO/ANTEISO-ALKANE	1.004 (1.001, 1.008)	1.003 (0.999, 1.007)	0.996 (0.985, 1.008)
OTHER ALKANE	1.005 (1.001, 1.008)	1.002 (0.998, 1.006)	0.994 (0.981, 1.007)
CYCLOALKANE	1.005 (1.001, 1.009)	1.003 (0.999, 1.007)	1.002 (0.988, 1.016)
ALKENE	1.006 (1.002, 1.009)	1.002 (0.998, 1.005)	1.005 (0.998, 1.011)
ALKYNE	1.006 (1.003, 1.010)	1.002 (0.998, 1.006)	1.005 (1.000, 1.011)
AROMATIC	1.006 (1.002, 1.010)	1.002 (0.997, 1.006)	1.005 (0.988, 1.021)
OXYGENATES			
ALDEHYDE	1.001 (0.998, 1.004)	0.999 (0.996, 1.002)	1.000 (0.997, 1.003)
ACID	1.002 (0.995, 1.010)	1.010 (1.002, 1.018)	1.001 (0.993, 1.009)
KETONE	1.005 (0.995, 1.014)	1.012 (1.002, 1.021)	1.003 (0.993, 1.013)
		ASTHMA ED VISITS AMONG ALL AGES	
HYDROCARBONS			
N-ALKANE	1.004 (1.000, 1.009)	1.000 (0.997, 1.003)	1.001 (0.995, 1.007)

VOC GROUPS	PRIMARY ANALYSIS[b]	LAG NEGATIVE 1[c]	CONTROL FOR OTHER VOC GROUPS[d]
ISO/ANTEISO-ALKANE	1.006 (1.000, 1.013)	1.000 (0.996, 1.005)	0.986 (0.963, 1.010)
OTHER ALKANE	1.006 (1.000, 1.013)	1.002 (0.998, 1.007)	0.985 (0.961, 1.009)
CYCLOALKANE	1.009 (1.002, 1.016)	1.001 (0.996, 1.006)	1.027 (0.999, 1.056)
ALKENE	1.005 (0.998, 1.011)	1.002 (0.998, 1.007)	0.993 (0.979, 1.006)
ALKYNE	1.006 (0.999, 1.012)	1.004 (1.000, 1.008)	1.001 (0.990, 1.013)
AROMATIC	1.009 (1.002, 1.017)	1.002 (0.997, 1.007)	1.019 (0.987, 1.052)
OXYGENATES			
ALDEHYDE	0.998 (0.991, 1.005)	1.002 (0.998, 1.006)	0.994 (0.987, 1.001)
ACID	1.008 (0.991, 1.026)	0.998 (0.987, 1.010)	1.001 (0.984, 1.020)
KETONE	1.026 (1.004, 1.048)	1.003 (0.990, 1.017)	1.027 (1.003, 1.050)

[a]These analyses included 3224 days on which all VOCs were available during 8/14/1998-12/31/2008. VOC concentrations below the limit of detection (LOD) of 0.1 ppb-C were replaced with 0.05 ppb-C in all analyses. We used same-day (lag 0) pollution levels in models predicting cardiovascular ED visits and 3-day moving average (of lags 0, 1, and 2) pollution levels in models predicting asthma ED visits. All methods included the same covariate control for temporal trends and meteorology: time splines with monthly knots, cubic function of same-day maximum temperature, cubic function of lag 1-2-day moving average minimum temperature (when using 3-day moving average pollution levels), cubic function of mean dew point temperature (same-day or 3-day moving average, matching the temporal metric of the pollution term), day of week, indicators for holidays,

seasons, season-maximum temperature interaction, season-day of week interaction, and indicators for hospital participation periods. The estimated associations are expressed as rate ratios (95% confidence interval) per interquartile range (IQR) increase in pollutant concentrations (listed in Table 1).

[b]The "primary analysis" is the indicator pollutant approach in the primary analysis. It estimated the effect of each indicator pollutant increasing by its IQR in single-pollutant models.

[c]The "lag negative 1" is based on indicator pollutant approach. It estimated the associations between tomorrow's indicator pollutant level (lag negative 1) and today's ED visits, controlling for today's indicator pollutant and covariate levels. We reported the estimates of the lag negative 1 pollutant levels in this column.

[d]The "control for other VOC groups" included all indicator pollutants in one model simultaneously.

Table 1.4. Sensitivity analysis controlling for selected major pollutants one at a time in each VOC indicator pollutant model predicting cardiovascular ED visits among all ages.[a]

		$PM_{2.5}$ OC	CO	NO2	O3
SINGLE-POLLUTANT MODELS OF MAJOR POLLUTANTS: →		1.006 (1.000, 1.012)	1.009 (1.003, 1.015)	1.004 (0.995, 1.013)	1.001 (0.985, 1.017)
SINGLE-POLLUTANT MODELS OF VOC INDICATOR POLLUTANTS: ↓		**TWO-POLLUTANT MODELS: MAJOR POLLUTANT (TOP OF CELL). VOC INDICATOR POLLUTANT (BOTTOM OF CELL).**			
N-ALKANE	1.001 (0.999, 1.004)	1.006 (0.999, 1.012) 1.001 (0.998, 1.003)	1.009 (1.003, 1.016) 1.000 (0.997, 1.003)	1.003 (0.994, 1.013) 1.001 (0.998, 1.004)	1.001 (0.984, 1.017) 1.001 (0.999, 1.004)
ISO/ANTEISO-ALKANE	1.003 (0.999, 1.007)	1.005 (0.998, 1.012) 1.001 (0.996, 1.006)	1.011 (1.003, 1.019) 0.998 (0.993, 1.004)	1.002 (0.993, 1.012) 1.002 (0.998, 1.007)	1.000 (0.984, 1.017) 1.003 (0.999, 1.007)
OTHER ALKANE	1.003 (0.999, 1.007)	1.005 (0.998, 1.012) 1.001 (0.996, 1.006)	1.011 (1.003, 1.019) 0.998 (0.992, 1.004)	1.002 (0.993, 1.012) 1.003 (0.998, 1.007)	1.000 (0.984, 1.017) 1.003 (0.999, 1.007)

		$PM_{2.5}$ OC	CO	NO2	O3
		1.004 (0.997, 1.012)	1.010 (1.002, 1.018)	1.002 (0.992, 1.011)	1.000 (0.984, 1.017)
CYCLOALKANE	1.004 (0.999, 1.008)	1.002 (0.997, 1.007)	0.999 (0.994, 1.005)	1.004 (0999, 1.008)	1.004 (0.999, 1.008)
		1.001 (0.994, 1.009)	1.006 (0.998, 1.014)	1.000 (0.991, 1.010)	1.001 (0.985, 1.017)
ALKENE	1.006 (1.002, 1.010)	1.005 (1.001, 1.010)	1.003 (0.998, 1.008)	1.006 (1.002, 1.010)	1.006 (1.002, 1.010)
		1.002 (0.995, 1.010)	1.007 (0.999, 1.014)	1.001 (0.992, 1.010)	1.001 (0.985, 1.017)
ALKYNE	1.005 (1.001, 1.008)	1.004 (1.000, 1.008)	1.002 (0.998, 1.007)	1.005 (1.001, 1.008)	1.005 (1.001, 1.008)
		1.004 (0.996, 1.011)	1.009 (1.001, 1.018)	1.001 (0.992, 1.011)	1.000 (0.984, 1.017)
AROMATIC	1.005 (1.000, 1.009)	1.003 (0.998, 1.009)	1.000 (0.994, 1.006)	1.004 (0.999, 1.009)	1.005 (1.000, 1.009)
		1.006 (1.000, 1.012)	1.009 (1.003, 1.015)	1.004 (0.995, 1.013)	1.001 (0.985, 1.017)
ALDEHYDE	1.000 (0.991, 1.008)	1.000 (0.997, 1.003)	1.000 (0.997, 1.003)	1.000 (0.997, 1.003)	1.000 (0.997, 1.003)
		1.006 (1.000, 1.012)	1.009 (1.003, 1.015)	1.004 (0.995, 1.013)	1.001 (0.985, 1.017)
ACID	1.000 (0.991, 1.008)	0.999 (0.991, 1.008)	0.999 (0.991, 1.008)	1.000 (0.991, 1.008)	1.000 (0.991, 1.008)

		$PM_{2.5}$ OC	CO	NO2	O3
		1.006 (0.999, 1.012)	1.009 (1.003, 1.015)	1.004 (0.995, 1.013)	1.001 (0.985, 1.017)
KETONE	1.006 (0.996, 1.016)	1.005 (0.995, 1.015)	1.005 (0.995, 1.015)	1.005 (0.996, 1.015)	1.006 (0.996, 1.016)

[a]This analysis included 2997 days during 8/14/1998-12/31/2008 for which both data on major pollutants and VOCs were available. VOC concentrations below the limit of detection (LOD) of 0.1 ppb-C were replaced with 0.05 ppb-C in all analyses. We used same-day (lag 0) pollution levels in models predicting cardiovascular ED visits. All methods included the same covariate control for temporal trends and meteorology: time splines with monthly knots, cubic function of same-day maximum temperature, cubic function of mean dew point temperature (lag 0), day of week, indicators for holidays, seasons, season-maximum temperature interaction, season-day of week interaction, and indicators for hospital participation periods. The estimated associations are expressed as rate ratios (95% confidence interval) per interquartile range (IQR) increase in pollutant concentrations (listed in Table 1).

Table 1.5. Sensitivity analysis controlling for selected major pollutants one at a time in each VOC indicator pollutant model predicting asthma ED visits among all ages.[a]

		$PM_{2.5}$ OC	CO	NO2	O3
SINGLE-POLLUTANT MODELS OF MAJOR POLLUTANTS: →		1.019 (1.007, 1.030)	1.018 (1.007, 1.030)	1.031 (1.014, 1.049)	1.037 (1.009, 1.066)
SINGLE-POLLUTANT MODELS OF VOC INDICATOR POLLUTANTS: ↓		**TWO-POLLUTANT MODELS: MAJOR POLLUTANT (TOP OF CELL). VOC INDICATOR POLLUTANT (BOTTOM OF CELL).**			
N-ALKANE	1.006 (1.001,1.011)	1.015 (1.002, 1.028) 1.003 (0.998, 1.009)	1.015 (1.001, 1.029) 1.003 (0.997, 1.009)	1.027 (1.009, 1.046) 1.004 (0.998, 1.009)	1.033 (1.004, 1.062) 1.005 (1.000, 1.010)
ISO/ANTEISO-ALKANE	1.012 (1.004, 1.020)	1.012 (0.997, 1.028) 1.007 (0.996, 1.017)	1.012 (0.994, 1.030) 1.006 (0.994, 1.018)	1.024 (1.005, 1.044) 1.007 (0.998, 1.016)	1.030 (1.001, 1.059) 1.010 (1.002, 1.018)
OTHER ALKANE	1.011 (1.003, 1.020)	1.014 (0.999, 1.030) 1.005 (0.994, 1.016)	1.015 (0.997, 1.034) 1.003 (0.990, 1.016)	1.026 (1.007, 1.046) 1.006 (0.997, 1.015)	1.030 (1.002, 1.060) 1.010 (1.001, 1.018)

		$PM_{2.5}$ OC	CO	NO2	O3
		1.010 (0.994, 1.025)	1.008 (0.990, 1.026)	1.023 (1.003, 1.042)	1.029 (1.001, 1.058)
CYCLOALKANE	1.014 (1.006, 1.022)	1.009 (0.999, 1.020)	1.009 (0.997, 1.022)	1.009 (1.000, 1.018)	1.012 (1.004, 1.021)
		1.019 (1.003, 1.034)	1.021 (1.004, 1.039)	1.029 (1.010, 1.048)	1.034 (1.005, 1.063)
ALKENE	1.008 (1.000, 1.015)	1.000 (0.990, 1.010)	0.998 (0.987, 1.009)	1.003 (0.995, 1.011)	1.007 (0.999, 1.014)
		1.015 (1.001, 1.030)	1.017 (1.000, 1.035)	1.027 (1.008, 1.046)	1.033 (1.005, 1.063)
ALKYNE	1.009 (1.002, 1.016)	1.003 (0.994, 1.012)	1.001 (0.990, 1.012)	1.005 (0.997, 1.012)	1.008 (1.001, 1.015)
		1.012 (0.996, 1.028)	1.012 (0.994, 1.031)	1.024 (1.005, 1.044)	1.030 (1.002, 1.059)
AROMATIC	1.013 (1.004, 1.022)	1.007 (0.995, 1.019)	1.006 (0.992, 1.020)	1.007 (0.998, 1.017)	1.011 (1.003, 1.020)
		1.019 (1.007, 1.032)	1.019 (1.007, 1.031)	1.032 (1.014, 1.050)	1.037 (1.009, 1.066)
ALDEHYDE	1.000 (0.993, 1.007)	0.997 (0.990, 1.004)	0.998 (0.991, 1.005)	0.998 (0.991, 1.005)	0.999 (0.992, 1.006)
		1.018 (1.006, 1.030)	1.018 (1.006, 1.030)	1.031 (1.013, 1.049)	1.036 (1.007, 1.065)
ACID	1.011 (0.990, 1.032)	1.009 (0.989, 1.030)	1.009 (0.988, 1.030)	1.008 (0.988, 1.029)	1.008 (0.987, 1.029)

		$PM_{2.5}$ OC	CO	NO2	O3
		1.017 (1.005, 1.029)	1.017 (1.005, 1.028)	1.029 (1.011, 1.047)	1.033 (1.004, 1.062)
KETONE	1.030 (1.007, 1.054)	1.025 (1.001, 1.049)	1.025 (1.001, 1.050)	1.025 (1.001, 1.049)	1.027 (1.003, 1.051)

[a]This analysis included 2997 days during 8/14/1998-12/31/2008 for which both data on major pollutants and VOCs were available. VOC concentrations below the limit of detection (LOD) of 0.1 ppb-C were replaced with 0.05 ppb-C in all analyses. We used 3-day moving average (of lags 0, 1, and 2) pollution levels in models predicting asthma ED visits. All methods included the same covariate control for temporal trends and meteorology: time splines with monthly knots, cubic function of same-day maximum temperature, cubic function of lag 1-2-day moving average minimum temperature, cubic function of mean dew point temperature (3-day moving average), day of week, indicators for holidays, seasons, season-maximum temperature interaction, season-day of week interaction, and indicators for hospital participation periods. The estimated associations are expressed as rate ratios (95% confidence interval) per interquartile range (IQR) increase in pollutant concentrations (listed in Table 1).

SUPPLEMENT

eTable 1.1. Summary statistics of daily 24-hr average ambient VOC concentrations (in ppb-C) measured at the Atlanta Jefferson Street monitoring site during 8/14/1998-12/31/2008: total hydrocarbons, total oxygenates, and 89 identified individual species grouped by chemical structure.[a]

VOC GROUPS	INDIVIDUAL VOCs[b]	MEAN (SD)	50th (25th, 75th) percentiles	% < LOD
	TOTAL HYDROCARBONS[c]	143.7 (148.3)	92.7	-
	TOTAL OXYGENATES[c]	20.9 (12.3)	19.3	-
HYDROCARBONS:				
N-ALKANE	Ethane	9.0 (7.4)	6.9 (4.9, 10.2)	0
	Propane[d]	**18.0 (25.6)**	**10.3 (6.5, 19.5)**	**0**
	n-Butane	10.8 (14.2)	6.2 (3.5, 11.0)	<1
	n-Pentane	4.8 (4.8)	3.2 (2.2, 5.4)	<1
	n-Hexane	2.3 (2.5)	1.5 (1.0, 2.6)	<1

VOC GROUPS	INDIVIDUAL VOCs[b]	MEAN (SD)	50th (25th, 75th) percentiles	% < LOD
	n-Heptane	1.3 (1.4)	0.9 (0.6, 1.5)	<1
	n-Octane	0.7 (0.7)	0.5 (0.3, 0.8)	6
	n-Nonane	0.8 (0.9)	0.6 (0.4, 0.9)	3
	n-Decane	1.1 (1.2)	0.7 (0.5, 1.3)	1
ISO/ANTEISO-	i-Butane	3.8 (4.6)	2.3 (1.4, 4.2)	0
ALKANE	**i-Pentane[d]**	**11.1 (12.7)**	**6.7 (4.3, 12.4)**	**0**
	2-Methylpentane	3.1 (3.6)	1.9 (1.2, 3.4)	0
	3-Methylpentane	1.9 (2.2)	1.2 (0.8, 2.1)	<1
	2-Methylhexane	1.3 (1.4)	0.8 (0.5, 1.5)	1
	3-Methylhexane	1.6 (1.5)	1.1 (0.7, 1.9)	<1
	2-Methylheptane	0.5 (0.7)	0.3 (0.2, 0.6)	7
OTHER ALKANE	2,2-Dimethylpropane	<0.1	<0.1	99
	2,2-Dimethylbutane	0.8 (1.3)	0.5 (0.3, 1.0)	7

VOC GROUPS	INDIVIDUAL VOCs[b]	MEAN (SD)	50th (25th, 75th) percentiles	% < LOD
	2,3-Dimethylbutane	1.0 (1.1)	0.6 (0.4, 1.1)	3
	2,3-Dimethylpentane	0.9 (1.1)	0.5 (0.3, 1.0)	1
	2,4-Dimethylpentane	0.6 (0.8)	0.3 (0.2, 0.7)	7
	2,2,4-Trimethylpentane[d]	**3.5 (4.4)**	**2.0 (1.2, 3.9)**	**<1**
	2,3,4-Trimethylpentane	1.1 (1.5)	0.6 (0.3, 1.2)	2
	2,3-Dimethylhexane	0.3 (0.5)	<0.1 (<0.1, 0.3)	52
	2,4-Dimethylhexane	0.6 (0.8)	0.3 (<0.1, 0.7)	32
	2,5-Dimethylhexane	0.5 (0.6)	0.3 (<0.1, 0.6)	32
	3-Ethylhexane	0.5 (0.6)	0.3 (0.2, 0.6)	7
	2,2,4-Trimethylhexane	0.3 (0.5)	<0.1 (<0.1, 0.4)	58
	2,2-Dimethylheptane	<0.1	<0.1	>99
CYCLOALKANE	Cyclopentane	0.4 (0.4)	0.3 (0.2, 0.5)	6
	Cyclohexane	0.2 (0.5)	<0.1 (<0.1, 0.2)	73

VOC GROUPS	INDIVIDUAL VOCs[b]	MEAN (SD)	50th (25th, 75th) percentiles	% < LOD
	Methylcyclopentane[d]	**1.3 (1.3)**	**0.8 (0.5, 1.4)**	**<1**
	Methylcyclohexane	0.7 (0.9)	0.5 (0.3, 0.8)	9
	Ethylcyclohexane	<0.1	<0.1	100
ALKENE	**Ethylene[d]**	**4.9 (5.8)**	**3.1 (2.0, 5.4)**	**0**
	Propene	2.5 (3.2)	1.4 (0.9, 2.6)	<1
	1-Butene	0.5 (0.7)	0.3 (0.2, 0.6)	12
	cis-2-Butene	0.3 (0.4)	0.1 (<0.1, 0.3)	45
	trans-2-Butene	0.4 (0.6)	0.2 (<0.1, 0.5)	33
	1-Pentene	0.3 (0.5)	<0.1 (<0.1, 0.3)	66
	cis-2-Pentene	0.3 (0.5)	0.1 (<0.1, 0.3)	39
	trans-2-Pentene	0.6 (0.9)	0.3 (0.2, 0.6)	18
	1-Hexene	0.1 (0.3)	<0.1 (<0.1, <0.1)	92
	cis-2-Hexene	<0.1 (0.1)	<0.1 (<0.1, <0.1)	83

VOC GROUPS	INDIVIDUAL VOCs[b]	MEAN (SD)	50th (25th, 75th) percentiles	% < LOD
	trans-2-Hexene	0.2 (0.4)	<0.1 (<0.1, <0.1)	77
	i-Butene	0.8 (1.0)	0.5 (0.3, 0.9)	12
	2-Methyl-1-butene	0.5 (0.8)	0.3 (<0.1, 0.6)	27
	2-Methyl-2-butene	0.7 (1.3)	0.3 (<0.1, 0.8)	33
	3-Methyl-1-butene	0.1 (0.2)	<0.1 (<0.1, 0.1)	70
	2-Methyl-1-pentene	0.1 (0.2)	<0.1 (<0.1, <0.1)	92
	4-Methyl-1-pentene	<0.1	<0.1	99
	2-Methyl-2-pentene	0.2 (0.4)	<0.1 (<0.1, <0.1)	78
	cis-4-methyl-2-Pentene	<0.1	<0.1	>99
	2,4,4-Trimethyl-1-pentene	<0.1	<0.1	98
	2,4,4-Trimethyl-2-pentene	<0.1	<0.1	100
	Cyclopentene	0.1 (0.2)	<0.1 (<0.1, <0.1)	78
	1,3-Butadiene	0.4 (0.5)	0.2 (0.1, 0.4)	25

VOC GROUPS	INDIVIDUAL VOCs[b]	MEAN (SD)	50th (25th, 75th) percentiles	% < LOD
	Isoprene	2.3 (3.3)	0.8 (0.1, 3.4)	21
	alpha-Pinene	1.7 (1.9)	1.2 (0.6, 2.1)	11
	beta-Pinene	0.1 (0.5)	<0.1 (<0.1, <0.1)	94
	delta 3-Carene	<0.1	<0.1	>99
	d-Limonene	0.4 (1.1)	<0.1 (<0.1, <0.1)	86
ALKYNE	**Acetylene[d]**	**7.1 (8.2)**	**4.2 (2.7, 7.6)**	**0**
AROMATIC	Benzene	3.4 (3.1)	2.4 (1.8, 3.8)	0
	Toluene[d]	**10.9 (11.0)**	**7.1 (4.7, 12.5)**	**<1**
	Ethylbenzene	2.2 (2.6)	1.4 (0.9, 2.4)	0
	n-Propylbenzene	0.6 (0.6)	0.4 (0.2, 0.7)	5
	i-Propylbenzene	<0.1 (0.2)	<0.1 (<0.1, <0.1)	92
	m-Xylene & p-Xylene	6.5 (9.0)	3.7 (2.2, 6.9)	0
	o-Xylene	2.5 (3.1)	1.5 (0.9, 2.8)	0

VOC GROUPS	INDIVIDUAL VOCs[b]	MEAN (SD)	50th (25th, 75th) percentiles	% < LOD
	m-Ethyltoluene	0.9 (1.1)	0.6 (0.3, 1.0)	3
	p-Ethyltoluene	1.9 (2.2)	1.3 (0.8, 2.2)	2
	o-Ethyltoluene	0.8 (1.1)	0.5 (<0.1, 1.1)	27
	1,2,3-Trimethylbenzene	0.6 (1.4)	<0.1 (<0.1, 0.4)	75
	1,2,4-Trimethylbenzene[e]	2.7 (3.2)	1.7 (1.0, 3.0)	<1
	1,3,5-Trimethylbenzene	1.0 (1.3)	0.7 (0.4, 1.2)	4
	Styrene	0.7 (0.8)	0.5 (<0.1, 0.9)	26
OXYGENATES:				
ALDEHYDE	Pentanal	0.3 (0.3)	0.1 (<0.1, 0.4)	50
	Hexanal	0.9 (0.6)	0.8 (0.5, 1.1)	3
	Heptanal	0.7 (0.5)	0.6 (0.4, 0.8)	7
	Octanal	1.4 (1.0)	1.2 (0.7, 1.8)	6
	Nonanal	0.9 (0.9)	0.8 (0.3, 1.3)	22

VOC GROUPS	INDIVIDUAL VOCs[b]	MEAN (SD)	50th (25th, 75th) percentiles	% < LOD
	Decanal	0.9 (0.8)	0.7 (0.4, 1.1)	8
	Benzaldehyde[d]	**2.2 (2.2)**	**1.7 (1.2, 2.5)**	**1**
ACID	**Acetic Acid[d]**	**5.3 (5.6)**	**3.6 (1.5, 7.2)**	**6**
KETONE	Acetone	6.4 (6.2)	4.8 (1.9, 9.1)	10
	2-Butanone[d]	**2.1 (1.6)**	**1.7 (1.0, 2.9)**	**3**
	2-Octanone	<0.1	<0.1	>99
ETHER	MTBE	<0.1	<0.1	>99

[a] There were 3793 days during 08/14/1998-12/31/2008. Hydrocarbons were available for 3233 of these days, while oxygenates were available for 3231 of these days. The limit of detection (LOD) was 0.1 ppb-C for all VOCs. VOC concentrations below 0.1 ppb-C were replaced with 0.05 ppb-C in all analyses.

[b]Species in black text were the 46 species included in the analysis, selected as those with concentrations above detection on at least 90% of days. Species in grey text had concentrations below detection on greater than 10% of days during the study period and were thus excluded from the analysis.

[c]Total hydrocarbons denotes total identified non-methane hydrocarbons. Total oxygenates denotes total identified oxygenated hydrocarbons.

[d]Species in bold black text are the indicator pollutants for each VOC group.

[e]1,2,4-Trimethylbenzene & sec-Butylbenzene

eTable 1.2. Pearson correlations among the 46 VOCs included in the primary analysis.[a]

	Ethane	Propane	n-Butane	n-Pentane	n-Hexane	n-Heptane	n-Octane	n-Nonane	n-Decane	i-Butane	i-Pentane	2-Methylpentane	3-Methylpentane	2-Methylhexane	3-Methylhexane	2-Methylheptane
Ethane	1.00	0.76	0.82	0.64	0.63	0.61	0.57	0.51	0.48	0.80	0.61	0.61	0.61	0.57	0.54	0.60
Propane		1.00	0.78	0.75	0.80	0.78	0.73	0.68	0.66	0.83	0.78	0.79	0.78	0.77	0.72	0.75
n-Butane			1.00	0.74	0.73	0.68	0.65	0.58	0.55	0.90	0.75	0.72	0.72	0.67	0.60	0.68
n-Pentane				1.00	0.90	0.88	0.81	0.79	0.78	0.82	0.94	0.92	0.91	0.88	0.84	0.86
n-Hexane					1.00	0.92	0.85	0.82	0.81	0.80	0.93	0.96	0.96	0.93	0.88	0.90
n-Heptane						1.00	0.85	0.83	0.80	0.76	0.89	0.92	0.91	0.93	0.89	0.90
n-Octane							1.00	0.80	0.78	0.72	0.84	0.86	0.85	0.85	0.82	0.87
n-Nonane								1.00	0.87	0.66	0.82	0.84	0.83	0.84	0.81	0.83
n-Decane									1.00	0.65	0.81	0.83	0.82	0.82	0.80	0.82
i-Butane										1.00	0.83	0.80	0.79	0.75	0.71	0.76
i-Pentane											1.00	0.96	0.94	0.91	0.87	0.89
2-Methylpentane												1.00	0.97	0.94	0.90	0.92
3-Methylpentane													1.00	0.93	0.88	0.90
2-Methylhexane														1.00	0.90	0.90
3-Methylhexane															1.00	0.88
2-Methylheptane																1.00

	2,2-Dimethylbutane	2,3-Dimethylbutane	2,3-Dimethylpentane	2,4-Dimethylpentane	2,2,4-Trimethylpentane	2,3,4-Trimethylpentane	3-Ethylhexane	Cyclopentane	Methylcyclopentane	Methylcyclohexane	Ethylene	Propene	Acetylene	Benzene	Toluene	Ethylbenzene
Ethane	0.56	0.58	0.52	0.55	0.52	0.54	0.61	0.62	0.61	0.53	0.74	0.66	0.72	0.73	0.56	0.56
Propane	0.68	0.76	0.71	0.72	0.73	0.74	0.76	0.76	0.78	0.69	0.77	0.79	0.74	0.81	0.75	0.77
n-Butane	0.64	0.69	0.60	0.64	0.61	0.64	0.69	0.70	0.72	0.61	0.75	0.70	0.75	0.80	0.64	0.65
n-Pentane	0.79	0.89	0.85	0.85	0.86	0.87	0.86	0.88	0.90	0.77	0.80	0.83	0.71	0.88	0.87	0.83
n-Hexane	0.80	0.92	0.89	0.89	0.90	0.90	0.90	0.89	0.95	0.82	0.81	0.85	0.74	0.89	0.92	0.88
n-Heptane	0.77	0.89	0.89	0.87	0.90	0.89	0.89	0.86	0.92	0.83	0.80	0.84	0.72	0.87	0.91	0.86
n-Octane	0.75	0.83	0.82	0.82	0.83	0.84	0.87	0.81	0.85	0.77	0.75	0.79	0.66	0.81	0.85	0.82
n-Nonane	0.70	0.82	0.80	0.79	0.82	0.82	0.82	0.79	0.84	0.73	0.72	0.77	0.62	0.77	0.83	0.82
n-Decane	0.70	0.81	0.80	0.79	0.82	0.82	0.81	0.78	0.82	0.72	0.69	0.75	0.59	0.76	0.82	0.82
i-Butane	0.72	0.77	0.71	0.73	0.71	0.74	0.77	0.78	0.79	0.69	0.80	0.77	0.76	0.85	0.74	0.75
i-Pentane	0.82	0.93	0.89	0.89	0.91	0.91	0.89	0.90	0.94	0.80	0.81	0.85	0.73	0.89	0.90	0.87
2-Methylpentane	0.84	0.96	0.92	0.92	0.94	0.94	0.92	0.92	0.96	0.83	0.84	0.87	0.74	0.91	0.93	0.91
3-Methylpentane	0.82	0.94	0.89	0.90	0.92	0.92	0.90	0.89	0.95	0.81	0.81	0.85	0.73	0.90	0.92	0.88
2-Methylhexane	0.78	0.91	0.93	0.88	0.92	0.91	0.90	0.87	0.93	0.82	0.79	0.84	0.71	0.87	0.92	0.87
3-Methylhexane	0.78	0.89	0.91	0.89	0.91	0.89	0.87	0.85	0.89	0.83	0.78	0.83	0.68	0.83	0.88	0.88
2-Methylheptane	0.79	0.90	0.88	0.88	0.90	0.91	0.96	0.86	0.90	0.82	0.81	0.84	0.72	0.87	0.89	0.88
2,2-Dimethylbutane	1.00	0.85	0.80	0.82	0.81	0.83	0.80	0.84	0.81	0.71	0.75	0.75	0.64	0.79	0.79	0.79
2,3-Dimethylbutane		1.00	0.91	0.92	0.93	0.93	0.90	0.93	0.92	0.81	0.82	0.85	0.72	0.88	0.90	0.89

	2,2-Dimethylbutane	2,3-Dimethylbutane	2,3-Dimethylpentane	2,4-Dimethylpentane	2,2,4-Trimethylpentane	2,3,4-Trimethylpentane	3-Ethylhexane	Cyclopentane	Methylcyclopentane	Methylcyclohexane	Ethylene	Propene	Acetylene	Benzene	Toluene	Ethylbenzene
2,3-Dimethylpentane			1.00	0.92	0.92	0.92	0.89	0.86	0.90	0.81	0.79	0.82	0.68	0.84	0.89	0.87
2,4-Dimethylpentane				1.00	0.91	0.92	0.89	0.88	0.91	0.80	0.80	0.83	0.70	0.85	0.88	0.87
2,2,4-Trimethylpentane					1.00	0.95	0.90	0.87	0.91	0.82	0.80	0.86	0.70	0.86	0.91	0.90
2,3,4-Trimethylpentane						1.00	0.92	0.88	0.91	0.81	0.82	0.86	0.71	0.88	0.91	0.91
3-Ethylhexane							1.00	0.87	0.91	0.81	0.82	0.85	0.72	0.88	0.89	0.88
Cyclopentane								1.00	0.89	0.79	0.80	0.82	0.70	0.86	0.87	0.85
Methylcyclopentane									1.00	0.81	0.81	0.85	0.73	0.89	0.92	0.88
Methylcyclohexane										1.00	0.72	0.76	0.66	0.80	0.82	0.81
Ethylene											1.00	0.86	0.84	0.88	0.79	0.80
Propene												1.00	0.73	0.87	0.84	0.85
Acetylene													1.00	0.84	0.70	0.70
Benzene														1.00	0.87	0.87
Toluene															1.00	0.89
Ethylbenzene																1.00

	n-Propylbenzene	m-Xylene & p-Xylene	o-Xylene	m-Ethyltoluene	p-Ethyltoluene	1,2,4-Trimethylbenzene	1,3,5-Trimethylbenzene	Hexanal	Heptanal	Octanal	Decanal	Benzaldehyde	Acetic Acid	2-Butanone
Ethane	0.55	0.57	0.58	0.55	0.54	0.56	0.56	0.08	0.22	0.04	0.35	0.02	-0.23	-0.32
Propane	0.70	0.78	0.77	0.71	0.72	0.74	0.72	0.29	0.30	0.27	0.50	0.18	-0.02	-0.06
n-Butane	0.62	0.67	0.68	0.63	0.63	0.65	0.64	0.11	0.23	0.14	0.39	0.05	-0.17	-0.31
n-Pentane	0.81	0.83	0.83	0.82	0.84	0.84	0.81	0.42	0.40	0.39	0.58	0.34	0.11	0.10
n-Hexane	0.83	0.88	0.88	0.84	0.86	0.87	0.84	0.46	0.40	0.43	0.60	0.34	0.12	0.12
n-Heptane	0.82	0.86	0.86	0.83	0.86	0.86	0.83	0.46	0.42	0.42	0.60	0.37	0.12	0.14
n-Octane	0.79	0.82	0.82	0.79	0.81	0.81	0.79	0.46	0.42	0.39	0.56	0.35	0.10	0.11
n-Nonane	0.80	0.82	0.83	0.81	0.82	0.83	0.81	0.49	0.44	0.44	0.59	0.41	0.19	0.20
n-Decane	0.83	0.82	0.82	0.84	0.85	0.86	0.85	0.51	0.43	0.47	0.61	0.42	0.20	0.20
i-Butane	0.70	0.76	0.76	0.72	0.72	0.73	0.73	0.23	0.32	0.21	0.48	0.15	-0.09	-0.17
i-Pentane	0.83	0.88	0.88	0.85	0.87	0.87	0.84	0.46	0.43	0.42	0.61	0.36	0.13	0.13
2-Methylpentane	0.87	0.91	0.91	0.88	0.90	0.90	0.88	0.48	0.45	0.44	0.62	0.36	0.15	0.14
3-Methylpentane	0.85	0.89	0.88	0.86	0.88	0.88	0.86	0.46	0.41	0.43	0.61	0.35	0.13	0.13
2-Methylhexane	0.83	0.88	0.87	0.84	0.87	0.86	0.84	0.47	0.41	0.44	0.61	0.37	0.13	0.15
3-Methylhexane	0.83	0.88	0.88	0.85	0.85	0.86	0.84	0.58	0.47	0.46	0.62	0.39	0.15	0.20
2-Methylheptane	0.86	0.89	0.88	0.87	0.88	0.88	0.86	0.48	0.46	0.42	0.61	0.35	0.13	0.11
2,2-Dimethylbutane	0.78	0.79	0.79	0.79	0.79	0.79	0.79	0.40	0.44	0.35	0.54	0.29	0.11	0.09
2,3-Dimethylbutane	0.86	0.89	0.89	0.88	0.88	0.89	0.87	0.47	0.44	0.43	0.61	0.35	0.14	0.13
2,3-Dimethylpentane	0.84	0.87	0.87	0.86	0.86	0.88	0.85	0.52	0.45	0.45	0.64	0.37	0.15	0.17
2,4-Dimethylpentane	0.85	0.88	0.88	0.87	0.87	0.88	0.86	0.48	0.45	0.43	0.62	0.34	0.14	0.14

	n-Propylbenzene	m-Xylene & p-Xylene	o-Xylene	m-Ethyltoluene	p-Ethyltoluene	1,2,4-Trimethylbenzene	1,3,5-Trimethylbenzene	Hexanal	Heptanal	Octanal	Decanal	Benzaldehyde	Acetic Acid	2-Butanone
2,2,4-Trimethylpentane	0.86	0.90	0.89	0.87	0.90	0.89	0.87	0.53	0.46	0.47	0.64	0.41	0.20	0.22
2,3,4-Trimethylpentane	0.88	0.92	0.91	0.89	0.91	0.91	0.89	0.50	0.47	0.45	0.62	0.37	0.17	0.17
3-Ethylhexane	0.86	0.89	0.88	0.87	0.88	0.88	0.87	0.45	0.45	0.40	0.59	0.34	0.11	0.09
Cyclopentane	0.83	0.85	0.85	0.84	0.84	0.85	0.84	0.44	0.41	0.40	0.58	0.31	0.11	0.08
Methylcyclopentane	0.85	0.89	0.89	0.86	0.88	0.88	0.86	0.46	0.43	0.43	0.61	0.36	0.14	0.13
Methylcyclohexane	0.77	0.81	0.81	0.78	0.78	0.79	0.78	0.48	0.38	0.42	0.56	0.32	0.10	0.09
Ethylene	0.77	0.81	0.81	0.80	0.78	0.80	0.79	0.32	0.40	0.29	0.52	0.21	-0.01	-0.05
Propene	0.80	0.85	0.85	0.82	0.83	0.83	0.81	0.44	0.44	0.38	0.56	0.37	0.11	0.12
Acetylene	0.66	0.71	0.71	0.68	0.68	0.71	0.69	0.22	0.28	0.22	0.46	0.12	-0.11	-0.17
Benzene	0.82	0.87	0.87	0.84	0.85	0.86	0.84	0.38	0.41	0.34	0.58	0.26	0.02	-0.01
Toluene	0.84	0.89	0.88	0.86	0.88	0.87	0.85	0.49	0.44	0.44	0.62	0.37	0.16	0.17
Ethylbenzene	0.87	0.98	0.97	0.89	0.89	0.89	0.88	0.54	0.48	0.46	0.64	0.37	0.16	0.16
n-Propylbenzene	1.00	0.87	0.87	0.94	0.93	0.91	0.94	0.50	0.47	0.45	0.64	0.37	0.16	0.14
m-Xylene & p-Xylene		1.00	0.98	0.89	0.89	0.90	0.88	0.51	0.46	0.44	0.63	0.34	0.15	0.13
o-Xylene			1.00	0.89	0.89	0.90	0.88	0.51	0.48	0.44	0.63	0.35	0.14	0.13
m-Ethyltoluene				1.00	0.95	0.93	0.96	0.50	0.48	0.46	0.64	0.36	0.16	0.13
p-Ethyltoluene					1.00	0.94	0.94	0.51	0.47	0.49	0.65	0.42	0.19	0.19
1,2,4-Trimethylbenzene[b]						1.00	0.93	0.49	0.45	0.47	0.67	0.37	0.16	0.12
1,3,5-Trimethylbenzene							1.00	0.47	0.46	0.44	0.63	0.35	0.14	0.11

	n-Propylbenzene	m-Xylene & p-Xylene	o-Xylene	m-Ethyltoluene	p-Ethyltoluene	1,2,4-Trimethylbenzene	1,3,5-Trimethylbenzene	Hexanal	Heptanal	Octanal	Decanal	Benzaldehyde	Acetic Acid	2-Butanone
Hexanal								1.00	0.48	0.64	0.54	0.52	0.40	0.47
Heptanal									1.00	0.40	0.41	0.42	0.22	0.26
Octanal										1.00	0.53	0.49	0.42	0.36
Decanal											1.00	0.39	0.24	0.20
Benzaldehyde												1.00	0.39	0.50
Acetic Acid													1.00	0.57
2-Butanone														1.00

[a]There were 3793 days during 08/14/1998-12/31/2008. The correlations in this table are based on 3224 days for which data on all VOCs were available.

[b]1,2,4-Trimethylbenzene & sec-Butylbenzene

eTable 1.3. Pearson correlations between 46 VOCs and selected major pollutants included in the sensitivity analysis.[a]

VOC GROUPS	INDIVIDUAL VOCS	$PM_{2.5}$ OC	CO	NO_2	O_3
HYDROCARBONS:					
N-ALKANE	Ethane	0.46	0.56	0.40	-0.17
	Propane[b]	**0.56**	**0.67**	**0.48**	**-0.02**
	n-Butane	0.48	0.63	0.41	-0.26
	n-Pentane	0.64	0.68	0.48	0.12
	n-Hexane	0.65	0.72	0.52	0.14
	n-Heptane	0.64	0.71	0.54	0.16
	n-Octane	0.59	0.65	0.47	0.12
	n-Nonane	0.61	0.63	0.47	0.20
	n-Decane	0.60	0.61	0.44	0.21
ISO/ANTEISO-ALKANE	i-Butane	0.55	0.68	0.46	-0.12
	i-Pentane[b]	**0.67**	**0.72**	**0.52**	**0.16**
	2-Methylpentane	0.67	0.75	0.52	0.16

VOC GROUPS	INDIVIDUAL VOCS	$PM_{2.5}$ OC	CO	NO_2	O_3
	3-Methylpentane	0.65	0.73	0.51	0.15
	2-Methylhexane	0.65	0.72	0.54	0.18
	3-Methylhexane	0.64	0.70	0.50	0.22
	2-Methylheptane	0.64	0.71	0.50	0.13
OTHER ALKANE	2,2-Dimethylbutane	0.57	0.65	0.45	0.08
	2,3-Dimethylbutane	0.66	0.73	0.50	0.15
	2,3-Dimethylpentane	0.65	0.70	0.51	0.20
	2,4-Dimethylpentane	0.64	0.71	0.49	0.17
	2,2,4-Trimethylpentane[b]	**0.67**	**0.72**	**0.51**	**0.23**
	2,3,4-Trimethylpentane	0.67	0.73	0.51	0.18
	3-Ethylhexane	0.64	0.72	0.51	0.11
CYCLOALKANE	Cyclopentane	0.63	0.70	0.47	0.13
	Methylcyclopentane[b]	**0.65**	**0.72**	**0.53**	**0.15**
	Methylcyclohexane	0.56	0.65	0.43	0.13

VOC GROUPS	INDIVIDUAL VOCS	$PM_{2.5}$ OC	CO	NO_2	O_3
ALKENE	**Ethylene[b]**	**0.59**	**0.72**	**0.47**	**-0.07**
	Propene	0.61	0.69	0.46	0.07
ALKYNE	**Acetylene[b]**	**0.53**	**0.71**	**0.50**	**-0.10**
AROMATIC	Benzene	0.65	0.76	0.51	0.01
	Toluene[b]	**0.64**	**0.72**	**0.51**	**0.18**
	Ethylbenzene	0.65	0.71	0.48	0.14
	n-Propylbenzene	0.63	0.67	0.47	0.15
	m-Xylene & p-Xylene	0.65	0.72	0.49	0.12
	o-Xylene	0.64	0.71	0.48	0.12
	m-Ethyltoluene	0.62	0.68	0.46	0.13
	p-Ethyltoluene	0.63	0.68	0.47	0.15
	1,2,4-Trimethylbenzene[c]	0.63	0.69	0.47	0.13
	1,3,5-Trimethylbenzene	0.62	0.68	0.47	0.11
OXYGENATES:					

VOC GROUPS	INDIVIDUAL VOCS	$PM_{2.5}$ OC	CO	NO_2	O_3
ALDEHYDE	Hexanal	0.40	0.29	0.18	0.40
	Heptanal	0.34	0.34	0.27	0.17
	Octanal	0.30	0.26	0.11	0.23
	Decanal	0.50	0.44	0.33	0.21
	Benzaldehyde[b]	**0.27**	**0.20**	**0.18**	**0.34**
ACID	**Acetic Acid[b]**	**0.10**	**-0.02**	**-0.03**	**0.36**
KETONE	**2-Butanone[b]**	**0.17**	**-0.02**	**0.05**	**0.57**

[a]There were 3793 days during 08/14/1998-12/31/2008. The correlations in this table are based on 2997 days for which both data on major pollutants and VOCs were available.

[b]Species in bold black text are the indicator pollutants for each VOC group.

[c]1,2,4-Trimethylbenzene & sec-Butylbenzene

eTable 1.4. Estimated associations between total VOCs and asthma ED visits by age category using single-pollutant models.[a]

TOTAL VOCs	5-18 YEAR OLDS	19+ YEAR OLDS	ALL AGES
Total hydrocarbons[b]	1.006 (0.994, 1.018)	1.009 (0.999, 1.019)	1.008 (1.001, 1.015)
Total oxygenates[b]	1.039 (1.009, 1.071)	1.020 (0.997, 1.044)	1.024 (1.007, 1.041)

[a]This analysis included 3224 days on which all VOCs were available during 8/14/1998-12/31/2008. We used 3-day moving average (of lags 0, 1, and 2) pollution levels in models predicting asthma ED visits. All methods included the same covariate control for temporal trends and meteorology: time splines with monthly knots, cubic function of same-day maximum temperature, cubic function of lag 1-2-day moving average minimum temperature, cubic function of mean dew point temperature (3-day moving average), day of week, indicators for holidays, seasons, season-maximum temperature interaction, season-day of week interaction, and indicators for hospital participation periods. The estimated associations are expressed as rate ratios (95% confidence interval) per interquartile range (IQR) increase in pollutant concentrations (listed in Table 1).

[b]Total hydrocarbons denotes total identified non-methane hydrocarbons. Total oxygenates denotes total identified oxygenated hydrocarbons.

eTable 1.5. Estimated associations between VOC groups and asthma ED visits by age category using three analytic approaches.[a]

VOC GROUPS	INDICATOR POLLUTANT APPROACH[b]	JOINT EFFECT ANALYSIS[c]	RANDOM EFFECT META-ANALYSIS[d]
	ASTHMA ED VISITS AMONG 5-18 YEAR OLDS		
HYDROCARBONS			
N-ALKANE	1.009 (1.001, 1.018)	1.000 (0.983, 1.017)	0.998 (0.984, 1.009)
ISO/ANTEISO-ALKANE	1.002 (0.990, 1.014)	1.010 (0.993, 1.027)	1.016 (1.000, 1.034)
OTHER ALKANE	0.998 (0.987, 1.010)	1.004 (0.988, 1.020)	0.991 (0.975, 1.004)
CYCLOALKANE	1.007 (0.995, 1.020)	1.004 (0.991, 1.017)	0.993 (0.969, 1.022)
ALKENE	0.998 (0.987, 1.009)	0.998 (0.987, 1.009)	0.989 (0.967, 1.021)
ALKYNE	1.001 (1.089, 1.012)	1.001 (0.989, 1.012)	0.997 (0.963, 1.035)
AROMATIC	1.002 (0.988, 1.015)	1.003 (0.981, 1.026)	1.002 (0.991, 1.013)

VOC GROUPS	INDICATOR POLLUTANT APPROACH[b]	JOINT EFFECT ANALYSIS[c]	RANDOM EFFECT META-ANALYSIS[d]
OXYGENATES			
ALDEHYDE	0.999 (0.987, 1.011)	1.021 (0.993, 1.051)	1.001 (0.986, 1.016)
ACID	1.036 (1.004, 1.070)	1.036 (1.004, 1.070)	1.029 (0.986, 1.075)
KETONE	1.043 (1.003, 1.085)	1.043 (1.003, 1.085)	1.033 (0.981, 1.087)
	ASTHMA ED VISITS AMONG 19+ YEAR OLDS		
HYDROCARBONS			
N-ALKANE	1.003 (0.996, 1.009)	1.011 (0.997, 1.024)	0.998 (0.992, 1.003)
ISO/ANTEISO-ALKANE	1.008 (0.999, 1.018)	1.010 (0.997, 1.024)	0.997 (0.988, 1.006)
OTHER ALKANE	1.010 (1.001, 1.020)	1.012 (1.000, 1.025)	1.001 (0.995, 1.008)

VOC GROUPS	INDICATOR POLLUTANT APPROACH[b]	JOINT EFFECT ANALYSIS[c]	RANDOM EFFECT META-ANALYSIS[d]
CYCLOALKANE	1.010 (1.000, 1.020)	1.012 (1.001, 1.022)	1.005 (0.991, 1.019)
ALKENE	1.008 (0.999, 1.017)	1.008 (0.999, 1.017)	0.997 (0.984, 1.009)
ALKYNE	1.008 (0.999, 1.017)	1.008 (0.999, 1.017)	1.003 (0.986, 1.021)
AROMATIC	1.013 (1.003, 1.024)	1.018 (1.000, 1.036)	1.003 (0.999, 1.008)
OXYGENATES			
ALDEHYDE	1.002 (0.993, 1.010)	1.027 (1.004, 1.050)	1.002 (0.996, 1.009)
ACID	0.989 (0.966, 1.012)	0.989 (0.966, 1.012)	0.979 (0.954, 1.004)
KETONE	1.029 (1.000, 1.060)	1.029 (1.000, 1.060)	1.031 (1.001, 1.065)

[a]This analysis included 3224 days on which all VOCs were available during 8/14/1998-12/31/2008. VOC concentrations below the limit of detection (LOD) of 0.1 ppb-C were replaced with 0.05 ppb-C in all analyses. We used 3-day moving average (of lags 0, 1, and 2) pollution levels in models predicting asthma ED visits. All methods included the same covariate control for temporal trends and meteorology: time splines with monthly knots, cubic function of same-day maximum temperature, cubic function of lag 1-2-day moving average minimum temperature, cubic function of mean dew point

temperature (3-day moving average), day of week, indicators for holidays, seasons, season-maximum temperature interaction, season-day of week interaction, and indicators for hospital participation periods. The estimated associations are expressed as rate ratios (95% confidence interval) per interquartile range (IQR) increase in pollutant concentrations (listed in Table 1).

[b]The "indicator pollutant approach" estimated the effect of each indicator pollutant increasing by its IQR in single-pollutant models.

[c]The "joint effect analysis" estimated the effect of all pollutants in a group jointly increasing by their IQRs in multi-pollutant models that included all pollutants of the group. The joint effect estimates for VOC groups comprised of only one pollutant were the same as the estimates obtained from the indicator pollutant approach.

[d]The "random effect meta-analysis" estimated the mean effect of any of the pollutants in a group increasing by its IQR in a two-stage regression, where the 46 individual pollutant effects were estimated simultaneously in the Poisson model in the first stage, and the mean of each group was estimated under a Bayesian framework using Markov chain Monte Carlo in the second stage. The estimated rate ratio (95% CI) for the random effect meta-analysis is median (2.5^{th}, 97.5^{th} percentiles) from the posterior distribution.

Chapter 2

Estimating acute cardiovascular effects of ambient $PM_{2.5}$ metals

Dongni Ye, Mitchel Klein, James A. Mulholland, Armistead G Russell, Rodney Weber, Eric S. Edgerton, Howard H. Chang, Jeremy A. Sarnat, Paige E. Tolbert, Stefanie Ebelt Sarnat

ABSTRACT

Background

Few epidemiologic studies have estimated health effects of water-soluble fractions of $PM_{2.5}$ metals, the more biologically accessible fractions of metals, in their attempt to identify health relevant components of ambient $PM_{2.5}$.

Objective

In this study, we estimate acute cardiovascular effects of $PM_{2.5}$ components in an urban population, including a suite of water-soluble metals that are not routinely measured at the ambient level.

Methods

Ambient concentrations of criteria gases, $PM_{2.5}$, and $PM_{2.5}$ components were measured at a central monitor in Atlanta during 1998-2013, with some $PM_{2.5}$ components only measured during 2008-2013. In a time-series frame work using Poisson regression, we estimated associations between these pollutants and daily counts of emergency department visits for cardiovascular diseases in the 5-county Atlanta area.

Results

Among the $PM_{2.5}$ components we examined during 1998-2013, water-soluble Fe had the strongest estimated effect on cardiovascular outcomes. The associations for $PM_{2.5}$ and other $PM_{2.5}$ components were consistent with the null when controlling for water-soluble Fe. Among $PM_{2.5}$ components that were only measured during 2008-2013, water-soluble V was associated with cardiovascular ED visits.

Discussion

Transition metals, such as water-soluble Fe and water-soluble V, could be biologically relevant components of $PM_{2.5}$ due to their ability to generate reactive oxygen species in living systems. In addition, as water-soluble Fe is mainly from roadway emissions, the observed associations with water-soluble Fe may also point to certain aspects of traffic pollution as a mixture harmful for cardiovascular health.

Conclusions

Our study suggests cardiovascular effects of certain water-soluble metals that have not been well-studied previously. Our findings further elucidate the link between traffic emissions and cardiovascular health, and contribute to the ongoing effort to identify causal mixtures in air pollution.

INTRODUCTION

Epidemiologic studies have indicated acute cardiovascular effects of fine particulate matter ($PM_{2.5}$; particulate matter with aerodynamic diameter ≤ 2.5 μm).[1-4] As $PM_{2.5}$ is a complex mixture of various chemical species, there is an ongoing effort to identify its health-relevant components. Nation-wide multi-site studies in the U.S. have examined whether the associations between $PM_{2.5}$ and cardiovascular morbidity and mortality are modified by $PM_{2.5}$ chemical composition.[5-7] Other time-series studies have estimated associations between cardiovascular morbidity and mortality and individual $PM_{2.5}$ components directly.[8-17] Although the specific components that are associated with health outcomes vary across studies, there is growing evidence on the acute cardiovascular effects of metals/metalloids and carbonaceous components of $PM_{2.5}$.[18-20]

Metals/metalloids exist in $PM_{2.5}$ in different forms, with some forms being more water-soluble and thus more biologically accessible than others.[21-24] However, most ambient air pollution monitoring networks only measure these components in total elemental concentrations, and not in water-soluble concentrations. As a result, few epidemiologic studies have estimated health associations with water-soluble fractions of $PM_{2.5}$ metals in their attempts to identify health-relevant components of $PM_{2.5}$.[25, 26]

To advance our understanding of acute cardiovascular effects of $PM_{2.5}$ and its components, we conducted a time-series study in Atlanta, Georgia, to estimate the associations between daily counts of cardiorespiratory emergency department (ED) visits and daily concentrations of $PM_{2.5}$ components, including a suite of $PM_{2.5}$ water-soluble metals/metalloids that are not routinely measured at the ambient level. This analysis

utilized up to 15 years of data on ambient air pollution and ED visits obtained as part of our ongoing Study of Particles and Health in Atlanta (SOPHIA).[27-29]

METHODS

Air pollution data

Ambient concentrations of criteria gases, $PM_{2.5}$, and $PM_{2.5}$ components were measured at the Atlanta Jefferson Street ambient monitoring site during 8/14/1998-12/15/2013 as part of the South Eastern Aerosol Research and Characterization (SEARCH) network and the Aerosol Research and Inhalation Epidemiology Study (ARIES).[30] Criteria gases were measured daily, including one-hour maximum carbon monoxide (CO), one-hour maximum nitrogen dioxide (NO_2), one-hour maximum sulfur dioxide (SO_2), and eight-hour maximum ozone (O_3). $PM_{2.5}$ and its major components, including organic carbon (OC), elemental carbon (EC), ammonium (NH_4), nitrate (NO_3), and sulfate (SO_4), were measured daily using filter-based 24-hour integrated Federal Reference Methods. Total elemental concentrations of $PM_{2.5}$ metals and metalloids (henceforth all referred to as metals), including titanium (Ti), manganese (Mn), iron (Fe), cupper (Cu), zinc (Zn), aluminum (Al), lead (Pb), silicon (Si), calcium (Ca), sodium (Na), and potassium (K), were analyzed from the daily $PM_{2.5}$ filters using X-ray fluorescence. X-ray fluorescence analyses were conducted by Desert Research Institute on filters collected through 3/22/2008, and by Atmospheric Research & Analysis Inc. on filters collected after 3/23/2008; different limits of detection (LOD) were reported before and after the laboratory change for each species. Water-soluble concentrations of $PM_{2.5}$ metals, including water-soluble vanadium (WS V), water-soluble chromium (WS Cr), water-soluble manganese (WS Mn), water-soluble iron (WS Fe), water-soluble nickel (WS Ni),

and water-soluble cupper (WS Cu), were analyzed using inductive-coupled plasma optical emission spectrometry (ICP-OES) during 8/14/1998 – 4/6/2008. Starting from 4/7/2008, these water-soluble fractions were analyzed using inductive-coupled plasma mass spectrometry (ICP-MS); again, different LODs were reported before and after the analytical change for these species. Additional water-soluble species, including water-soluble zinc (WS Zn), water-soluble cadmium (WS Cd), water-soluble lead (WS Pb), water-soluble selenium (WS Se), water-soluble arsenic (WS As), water-soluble barium (WS Ba), and water-soluble lanthanum (WS La), were reported starting in 4/7/2008 from ICP-MS analyses. All water-soluble measures were available daily before 2009 and one-in-three day after 2009.

The LODs of all $PM_{2.5}$ metals are listed in Supplementary eTable 2.1. We calculated the percent of samples below LOD over the full time period, and over the time periods before and after measurement/laboratory changes separately. For this analysis, we included $PM_{2.5}$ metals whose concentrations were above LOD on at least 85% of days. Ultimately, six $PM_{2.5}$ metals (Si, K, Ca, Fe, Zn, WS Fe) were included in the analysis over the full time period (8/14/1998 – 12/15/2013), along with criteria gases (CO, NO_2, SO_2, and O_3), $PM_{2.5}$ mass, and $PM_{2.5}$ major components (OC, EC, NO_3, and SO_4). We did not include NH_4 in epidemiologic analyses since this component mainly exists as NH_4NO_3 or NH_4SO_4. Fifteen additional $PM_{2.5}$ metals were included in the analysis over the later time period (4/7/2008 – 12/15/2013): Al, Na, Cu, Ti, WS Cr, WS Cu, WS Mn, WS Ni, WS V, WS As, WS Ba, WS Se, WS Zn, WS Cd, and WS Pb. For species included in the analysis, any observations below LOD were assigned a value of LOD/2.

Emergency department visits

We obtained daily counts of cardiovascular ED visits for patients living within the 5-county Atlanta area (Clayton, Cobb, DeKalb, Fulton, and Gwinnett) during 8/14/1998 – 12/15/2013. Daily ED visit counts were aggregated from individual-level billing records from metropolitan Atlanta hospitals as part of SOPHIA.[28, 29, 31] We identified cardiovascular ED visits as those billing records with primary International Classification of Diseases, 9th Revision (ICD-9) diagnosis codes for ischemic heart disease (410-414), cardiac dysrhythmias (427), congestive heart failure (428), or peripheral vascular and cerebrovascular disease (433-437, 440, 443-445, 451-453).

Analytic approach

In a time-series framework, we estimated the associations between daily levels of air pollutants and daily counts of cardiovascular ED visits using Poisson regression accounting for over-dispersion. Based on our previous research of ambient air pollution and cardiovascular ED visits in Atlanta, we used the same-day (lag 0) pollution level.[27-29, 32]

All models included the same covariate control for temporal trends and meteorology: time splines with monthly knots, cubic function of same-day maximum temperature, cubic function of lag 1-2-day moving average minimum temperature, cubic function of lag 0-1-2-day moving average mean dew point temperature, day of week, indicators for holidays, seasons, season-maximum temperature interaction, season-day of week interaction, indicators for hospital participation periods, and indicator for changes in air pollution measurement. The estimated associations were reported as rate ratios (RR) per interquartile range (IQR) increase in pollutant concentrations.

Primary analysis

We included criteria gases (CO, NO_2, SO_2, and O_3), $PM_{2.5}$ mass, $PM_{2.5}$ major components (OC, EC, NO_3, and SO_4), and $PM_{2.5}$ metals (Si, K, Ca, Fe, Zn, WS Fe) in the analysis over the full time period (8/14/1998 – 12/15/2013). Fifteen additional $PM_{2.5}$ metals (Al, Na, Cu, Ti, WS Cr, WS Cu, WS Mn, WS Ni, WS V, WS As, WS Ba, WS Se, WS Zn, WS Cd, and WS Pb) were included in the analysis over the later time period (4/7/2008 – 12/15/2013).

For pollutants included in the analysis over the full time period (1998-2013), we first estimated their associations with cardiovascular ED visits using single-pollutant models. Based on the results, we applied multi-pollutant models to assess co-pollutant confounding. As previous studies have suggested stronger cardiovascular effects of particulate matter in the cold than warm days, we then performed analyses in the warm and cold seasons separately to see if the patterns of associations across pollutants were similar. We defined the warm season as May to October, and the cold season as November to April.

For pollutants included in the analysis over the later time period (2008-2013), we estimated their associations with cardiovascular ED visits using single-pollutant models. As this time period was shorter and water-soluble species were only measured every one-in-three days after 2009, we did not perform multi-pollutant or season-specific analysis due to concerns of sparse data.

For comparability, we restricted the analyses in each time period to days on which all pollutants were available. Thus, over the full time period (1998-2013), year-round analyses included 3303 days, warm season analyses included 1737 days, and cold season

analyses included 1566 days. Over the later time period (2008-2013), year-round analyses included 631 days.

Sensitivity analyses

We evaluated model misspecification by estimating the associations between tomorrow's pollutant levels and today's ED visits, controlling for today's (lag 0 day) pollutant and covariate levels. Tomorrow's pollutant levels should not be associated with today's ED visits in the absence of confounding, measurement error, or other model misspecification, as cause must precede effect.[33] To accommodate pollutants with 1-in-3 day measurements, we defined "tomorrow" as the third day since today (negative lag 3 day). We restricted the primary analysis to days on which all pollutants were available so that the health associations of different pollutants were estimated on the same set of days (n=3303 for the year-round analysis). However, this led to reduced statistical power. As a sensitivity analysis, we performed the same set of analyses without this restriction by using all available days to see if the estimated associations were similar to those in the primary analysis.

RESULTS

Criteria gases (CO, NO_2, SO_2, O_3), $PM_{2.5}$ mass, $PM_{2.5}$ major components (OC, EC, NO_3, SO_4), and $PM_{2.5}$ metals (Si, K, Ca, Fe, Zn, WS Fe) were included in the analysis over the full time period (8/14/1998 – 12/15/2013). Fifteen additional $PM_{2.5}$ metals were included in the analysis over the later time period (4/7/2008 – 12/15/2013). We calculated descriptive statistics of these pollutants over all seasons (Table 2.1), in the warm season (Supplement, eTable 2.2a), and in the cold season (Supplement, eTable 2.2b). OC, EC, NH_4, SO_4, and NO_3 together contributed about 80% of the $PM_{2.5}$ mass, while the

concentrations of metals were much lower. Among metals, Si and Fe were most abundant. Water-soluble Fe had the highest average concentration among water-soluble species (as commonly seen in other studies [21, 23, 24, 34, 35]). Secondary pollutants such as O_3 and SO_4 had higher concentrations in the warm than in the cold season, while primary pollutant such as CO had higher concentrations in the cold than in the warm season. The concentrations of metals were generally similar in the warm and cold season, while water-soluble Fe was higher in the warm than in the cold season.

Pearson correlations of these pollutants were also calculated over all seasons (Supplement, eTable 2.3), in the warm season (Supplement, eTable 2.4a), and in the cold season (Supplement, eTable 2.4b). Over all seasons, $PM_{2.5}$ was most correlated with SO_4 (r=0.80), OC (r=0.74), EC (r=0.67), and WS Fe (r=0.65). Water-soluble Fe was most correlated with SO_4 (r=0.61) and Fe (r=0.69). OC and EC were highly correlated with one another (r=0.79), and their correlations with other $PM_{2.5}$ components were weak-to-moderate (r from 0.17 to 0.58). $PM_{2.5}$ was more strongly correlated with SO_4 and O_3 in the warm season, and with EC, OC, and metals in the cold season.

During the full time period (8/14/1998 – 12/15/2013), there were 426,252 cardiovascular ED visits (an average of 76 visits per day).

Primary analysis

We estimated the associations between cardiovascular ED visits and pollutants available during the full time period (8/14/1998 – 12/15/2013) using single-pollutant models. The estimated RRs were positive for a number of pollutants, including criteria gases, $PM_{2.5}$ mass, and $PM_{2.5}$ components (OC, EC, NO_3, Si, Ca, Fe, Zn, water-soluble Fe) (Figure

2.1). Among them, the estimated RR per IQR increase in water-soluble Fe was the highest [RR (95% CI) of 1.012 (1.005, 1.019)].

To assess if the association for water-soluble Fe was confounded by other pollutants, we estimated the associations between cardiovascular ED visits and water-soluble Fe controlling for each of the other measured pollutants in two-pollutant models. The associations for water-soluble Fe changed little when controlling for any of the pollutants. In contrast, the associations for $PM_{2.5}$ mass and $PM_{2.5}$ components (OC, EC, NO_3, Si, Ca, Fe, Zn) were weaker and consistent with the null when controlling for water-soluble Fe (Figure 2.2).

We performed analyses in the warm (May-October) and cold (November-April) seasons separately to see if the patterns of associations were similar. In the warm season, the estimated RR per IQR increase in water-soluble Fe was the highest. The associations for $PM_{2.5}$ and a number of $PM_{2.5}$ components (OC, EC, SO_4, K) were consistent with the null (Figure 2.3). While the estimated RRs for CO, Si, Ca, Fe, and Zn were positive in single-pollutant models, they were lower in two-pollutant models with water-soluble Fe (Figures 2.3 and 2.4).

In the cold season, the estimated associations across pollutants were generally higher than those in the warm season (Figures 2.3 and 2.5). Among $PM_{2.5}$ components, the estimated RR for water-soluble Fe was still the highest (Figure 2.5).The associations for CO, $PM_{2.5}$, OC, EC, NO_3, SO_4, Si, K, and Ca were weaker and consistent with the null when controlling for water-soluble Fe. The association for water-soluble Fe was weaker in two-pollutant models with Fe (Figures 2.5 and 2.6).

Measurements of an additional fifteen $PM_{2.5}$ metals were only available during the later time period (4/7/2008 – 12/15/2013). We estimated their associations with cardiovascular ED visits using single-pollutant models. The estimated RRs were the highest for water-soluble V [RR (95% CI) of 1.012 (1.000, 1.025)] and Na [RR (95% CI) of 1.008 (0.998, 1.017)] (Figure 2.7).

Sensitivity analyses

For single-pollutant models in the year-round analysis, we evaluated model misspecification by estimating the associations between tomorrow's pollutant levels and today's ED visits, controlling for today's pollutant and covariate levels. We found associations between cardiovascular ED visits and tomorrow's levels of WS Mn, suggesting possible model misspecification when estimating this association (Supplement, eFigures 2.1 and 2.2). All other associations with tomorrow's pollutant levels were consistent with the null, as expected under a well-specified model.

We restricted the primary analysis to days on which all pollutants were available. However, this led to reduced statistical power. We performed the same set of analyses without this restriction as a sensitivity analysis. We observed patterns of associations similar to those in the primary analysis, except that the association for SO_4 in the cold season was stronger in this sensitivity analysis than in the primary analysis (Supplement, eFigures 2.3-2.9).

DISCUSSION

In this study, we estimated acute cardiovascular effects of $PM_{2.5}$ and its components, including a suite of water-soluble metals that are not routinely measured at the ambient

level. We performed multi-pollutant analysis to account for co-pollutant confounding, and compared the patterns of associations across pollutants in the warm and cold season. Among the $PM_{2.5}$ components we examined during the full time period (1998-2013), water-soluble Fe had the strongest estimated effect in both the warm and cold seasons. The associations for $PM_{2.5}$ and other $PM_{2.5}$ components were generally weak and consistent with the null when controlling for water-soluble Fe. Among $PM_{2.5}$ components that were only measured during the later time period (2008-2013), water-soluble V was associated with cardiovascular ED visits.

Oxidative stress has been suggested as a central mechanism by which particulate matter affect health.[36] Transition metals can generate reactive oxygen species (ROS) in living systems, leading to oxidative stress.[36, 37] Redox-active transition metals, such as Fe, Cu, Mn, and V, can act as catalysts of Fenton or Fenton-like reactions, facilitating the conversion of superoxide anion and hydrogen peroxide to hydroxyl radical.[37, 38] As particle-bound metals need to dissolve and become metal ions to participate in these reactions, the water-soluble fractions of metals are thought to be more biologically relevant than total metals.[24, 39] Recent studies have used cellular and cell-free assays to measure oxidative potential of ambient particulate matter, and suggested that water-soluble metals, especially water-soluble Fe, water-soluble Cu, and water-soluble Mn, contribute to the ROS generation of particulate matter.[40-44] In our analysis, however, we observed positive associations with water-soluble Fe, but not with water-soluble Cu or water-soluble Mn. One reason could be that these species are less abundant than water-soluble Fe in the ambient air and thus could be more subject to measurement error, resulting in more underestimated health associations.

The observed associations with metals could also indicate cardiovascular effects of certain pollution mixtures. Metals are released to the atmosphere from various sources, including natural process acting on crustal minerals, re-suspension of road dust and brake/tire wear abrasion during traffic, combustion of fossil fuels and wood, industrial process, and waste incineration.[21, 23, 24, 34, 45-48] Crustal species such as silicon, iron, calcium, sodium, aluminum, and potassium are largely found in re-suspension of road dust; meanwhile, copper, barium, manganese, iron, zinc, and chromium are commonly related to brake/tire wear debris; Nickel and vanadium are often attributed to residual oil combustion.[21, 23, 24, 34, 45-48] The water-soluble fractions of these metals are partly from direct emission and partly from secondary processing of the primary insoluble metals by acid dissolution. A recent study in Atlanta investigated source contributions of a suite of water-soluble metals.[23] Roadway emissions, such as brake/tire wear debris and re-suspension of road dust, as well as secondary processing by acid were suggested as major contributors of a number of water-soluble metals, including water-soluble Fe, water-soluble Cu, water-soluble Mn, and water-soluble Zn. For water-soluble Fe, over 30% was attributed to mechanical abrasion of automobile brakes/tires and another 50% were thought to be formed secondarily through acid dissolution of insoluble Fe, which is primarily from resuspension of road dust.[23] Thus, the association we observed with water-soluble Fe could point to certain aspects of roadway emissions as a mixture harmful for cardiovascular health. Other co-emitted roadway pollutants may also have an impact. In our analysis, however, associations with other brake/tire-related species, such as water-soluble Cu, water-soluble Mn, water-soluble Zn, and water-soluble Ba, were consistent with the null. Again, these species are less abundant than water-soluble Fe in

the ambient air and thus could be more subject to measurement error, resulting in more underestimated health associations. Other road dust-related species, such as Si and Ca, had positive associations with cardiovascular ED visits in single-pollutant models; however, their associations were consistent with the null when controlling for water-soluble Fe. Compared to these species, water-soluble Fe could be part of the causal mixture or a better surrogate of the mixture.

Fe (i.e., total Fe) and water-soluble Fe were both included in our analysis over the full time period, and their associations with cardiovascular ED visits were similar in single-pollutant models. In the warm season, the association with total Fe was consistent with the null when controlling for water-soluble Fe, suggesting that the water-soluble fraction was driving the association of Fe. This is expected if iron is a causal agent and its water-soluble fraction is more biologically accessible. However, we did not observe this pattern of associations in the cold season.

In fact, in the cold season, other $PM_{2.5}$ components, such as EC and OC had stronger associations with cardiovascular ED visits than in the warm season. While the associations for EC and OC were weaker when controlling for water-soluble Fe, and the association of water-soluble Fe was also slightly weaker in two-pollutant models with these pollutants. EC and OC are partly from tailpipe emissions; together with road dust and brake/tire-related species such as total Fe and water-soluble Fe, these pollutants may all contribute to cardiovascular effects of traffic pollution.

Epidemiologic evidence on cardiovascular effects of water-soluble metals is sparse. Heal et al., in a time-series study in Edinburgh, Scotland, estimated the associations between cardiovascular hospital admissions and a number of $PM_{2.5}$ total and water-soluble metals,

including Cu, Fe, Ni, V, and Zn. However, direct measurements of these species were only available for one year, during which they did not find significant associations with total or water-soluble metals, nor with $PM_{2.5}$ mass.[25] Huang et al. exposed a panel of 38 healthy adults to concentrated ambient particles (CAP) from Chapel Hill, NC, and reported that water-soluble metals in CAP (the V/Cu/Zn factor by principal component analysis) was associated with increased blood fibrinogen levels.[26]

A number of studies have provided general evidence for adverse cardiovascular effects of $PM_{2.5}$ metals, although they only considered total elemental concentrations, not water-soluble fractions of metals.[9, 10, 12, 13, 15, 26, 39, 49-53] Suh et al. combined Cu, Mn, Zn, Ti, and Fe in a transition metal category and reported positive associations with cardiovascular hospital admissions in a time-series study in Atlanta.[10] Ito et al., in a time-series study in New York City, reported positive associations between cardiovascular hospital admissions and a number of $PM_{2.5}$ components (OC, EC, SO_4, Ni, V, Zn, Se, Br). Lippmann et al., in a time-series study of 64 U.S. counties, found positive associations between cardiovascular hospital admissions and OC, EC, SO_4, Fe, V, and Zn.[12] Zhang et al. reported that short-term exposures to transition metals (Cr, Fe, Cu, Mn, and Ni) in the ambient air were associated with decreased microvascular function in a panel of adults in Los Angeles.[50] Morishita et al. found that a number of $PM_{2.5}$ metals (As, Ca, Ce, Fe, Mg, Mn, S, Se, Ti) were associated with heart rate in a panel of adults in Dearborn, Michigan.[53]

Some studies reported stronger associations of carbonaceous components than metals.[13, 14] Sarnat et al., in a time-series study in St. Louis, found positive associations between cardiovascular ED visits and carbonaceous constituents (OC, EC, and certain hopanes),

but not with metals (Si, K, Ca, Fe, Cu, Zn, and Pb).[14] Bell et al., in a time-series study in four New England counties, observed positive associations between cardiovascular hospital admissions and black carbon, Ca, Zn, and V, where the association with black carbon was stronger than the metals and was robust to co-pollutant adjustment of these metals.[13] The inconsistencies between our study and these previous studies may be due to a number of factors, including the specific components being examined, co-pollutant confounding, pollutant interactions, non-linear dose-response, differences in population susceptibility, and measurement error. In particular, these studies only considered total elemental but not water-soluble metals; besides, as OC is itself a mixture of organic compounds, its health effects also depend on its composition, which likely varies by study location. In addition, previous studies have suggested synergism between organic compounds and metals in generating reactive oxygen species.[36, 54] Health associations of organic pollutants could depend on the levels of metals, and vice versa, which further complicates the comparison of health effects across PM components.

There are several limitations to our study. Our results are subject to spatial misalignment and instrument measurement error, and the degree of these sources of error likely differs by pollutant. Compared to pollutants dominated by secondary origins (e.g., O_3, $PM_{2.5}$, NO_3, SO_4, water-soluble metals), primary pollutants (e.g., EC, Fe, Cu, Zn) are likely more subject to spatial misalignment due to greater spatiotemporal heterogeneity, and thus their estimated associations may be more biased towards the null. Additionally, pollutants with a lower ambient concentration may be more subject to instrument measurement error leading to underestimation of effects.

Overall, our study suggests cardiovascular effects of certain water-soluble metals that have not been well studied previously. Our findings further elucidate the link between traffic emissions and cardiovascular health, and contribute to the ongoing effort to identify causal mixtures in air pollution.

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Table 2.1. Summary statistics of ambient air pollutants measured at the Atlanta Jefferson Street monitoring site[a].

POLLUTANTS	UNIT	N	MEAN (SD)	50th (25th, 75th) PERCENTILES
		8/14/1998 – 12/15/2013		
Criteria gases				
CO	ppm	5458	0.86 (0.83)	0.56 (0.36, 1.02)
NO_2	ppb	5321	37.2 (15.2)	35.9 (26.4, 46.3)
SO_2	ppb	5465	13.4 (14.7)	8.1 (3.2, 18.7)
O_3	ppb	5490	42.1 (19.9)	39.6 (27.2, 54.9)
$PM_{2.5}$				
$PM_{2.5}$ mass	$\mu g/m^3$	5588	14.46 (7.69)	12.81 (8.93, 18.21)
OC	$\mu g/m^3$	5546	3.67 (2.08)	3.22 (2.31, 4.47)
EC	$\mu g/m^3$	5515	1.26 (0.98)	0.98 (0.63, 1.58)
NH_4	$\mu g/m^3$	5563	1.39 (1.00)	1.10 (0.72, 1.73)
NO_3	$\mu g/m^3$	5569	0.81 (0.77)	0.55 (0.31, 1.06)
SO_4	$\mu g/m^3$	5572	3.88 (2.96)	2.94 (1.88, 4.87)
Si	$\mu g/m^3$	4932	0.0945 (0.1124)	0.0682 (0.0398, 0.1108)
K	$\mu g/m^3$	4932	0.0638 (0.0838)	0.0508 (0.0353, 0.0755)
Ca	$\mu g/m^3$	4932	0.0364 (0.0297)	0.0293 (0.0183, 0.0447)
Fe	$\mu g/m^3$	4921	0.0765 (0.0594)	0.0603 (0.0396, 0.0951)
Zn	$\mu g/m^3$	4880	0.0114 (0.0112)	0.0088 (0.0057, 0.0133)
water-soluble Fe	ng/m^3	4085	24.22 (20.63)	18.67 (10.81, 31.28)

POLLUTANTS	UNIT	N	MEAN (SD)	50th (25th, 75th) PERCENTILES
		4/7/2008 – 12/15/2013		
Na	$\mu g/m^3$	1930	0.0389 (0.0393)	0.0260 (0.0147, 0.0471)
Al	$\mu g/m^3$	1931	0.0460 (0.0595)	0.0318 (0.0174, 0.0561)
Ti	$\mu g/m^3$	1931	0.0045 (0.0039)	0.0036 (0.0023, 0.0054)
Cu	$\mu g/m^3$	1916	0.0053 (0.0104)	0.0038 (0.0024, 0.0057)
water-soluble V	ng/m^3	805	0.20 (0.19)	0.14 (0.07, 0.26)
water-soluble Cr	ng/m^3	805	0.14 (0.17)	0.10 (0.06, 0.15)
water-soluble Mn	ng/m^3	796	1.20 (0.98)	0.94 (0.57, 1.54)
water-soluble Ni	ng/m^3	805	0.30 (0.68)	0.15 (0.09, 0.25)
water-soluble Cu	ng/m^3	790	2.83 (4.56)	1.84 (1.10, 3.06)
water-soluble Zn	ng/m^3	682	8.99 (6.14)	7.32 (4.69, 11.16)
water-soluble As	ng/m^3	805	0.68 (0.53)	0.56 (0.36, 0.80)
water-soluble Se	ng/m^3	805	0.72 (0.59)	0.55 (0.33, 0.92)
water-soluble Cd	ng/m^3	805	0.08 (0.08)	0.06 (0.04, 0.09)
water-soluble Ba	ng/m^3	805	3.24 (3.23)	2.45 (1.36, 4.10)
water-soluble Pb	ng/m^3	803	1.39 (2.98)	0.87 (0.56, 1.42)

[a]Criteria gases were measured daily, including one-hour maximum carbon monoxide (CO), one-hour maximum nitrogen dioxide (NO_2), one-hour maximum sulfur dioxide (SO_2), and eight-hour maximum ozone (O_3). $PM_{2.5}$ and its major components, including organic carbon (OC), elemental carbon (EC), ammonium (NH_4), nitrate (NO_3), and sulfate (SO_4), were measured daily using filter-based 24-hour integrated Federal Reference Methods. Total elemental concentrations of $PM_{2.5}$ metals and metalloids (henceforth all referred to as metals), including titanium (Ti), manganese (Mn), iron (Fe),

cupper (Cu), zinc (Zn), aluminum (Al), lead (Pb), silicon (Si), calcium (Ca), sodium (Na), and potassium (K), were analyzed from the daily $PM_{2.5}$ filters using X-ray fluorescence. X-ray fluorescence analyses were conducted by Desert Research Institute on filters collected through 3/22/2008, and by Atmospheric Research & Analysis Inc. on filters collected after 3/23/2008. Water-soluble concentrations of $PM_{2.5}$ metals, including water-soluble vanadium (WS V), water-soluble chromium (WS Cr), water-soluble manganese (WS Mn), water-soluble iron (WS Fe), water-soluble nickel (WS Ni), and water-soluble cupper (WS Cu), were analyzed using inductive-coupled plasma optical emission spectrometry (ICP-OES) during 8/14/1998 – 4/6/2008. Starting from 4/7/2008, these water-soluble fractions were analyzed using inductive-coupled plasma mass spectrometry (ICP-MS). Additional water-soluble species, including water-soluble zinc (WS Zn), water-soluble cadmium (WS Cd), water-soluble lead (WS Pb), water-soluble selenium (WS Se), water-soluble arsenic (WS As), water-soluble barium (WS Ba), and water-soluble lanthanum (WS La), were reported starting in 4/7/2008 from ICP-MS analyses. All water-soluble measures were available daily before 2009 and one-in-three day after 2009.

Figure 2.1. Estimated associations between cardiovascular ED visits and pollutants available during 1998-2013 using single-pollutant models, year-round analysis (3303 days), Atlanta, GA.

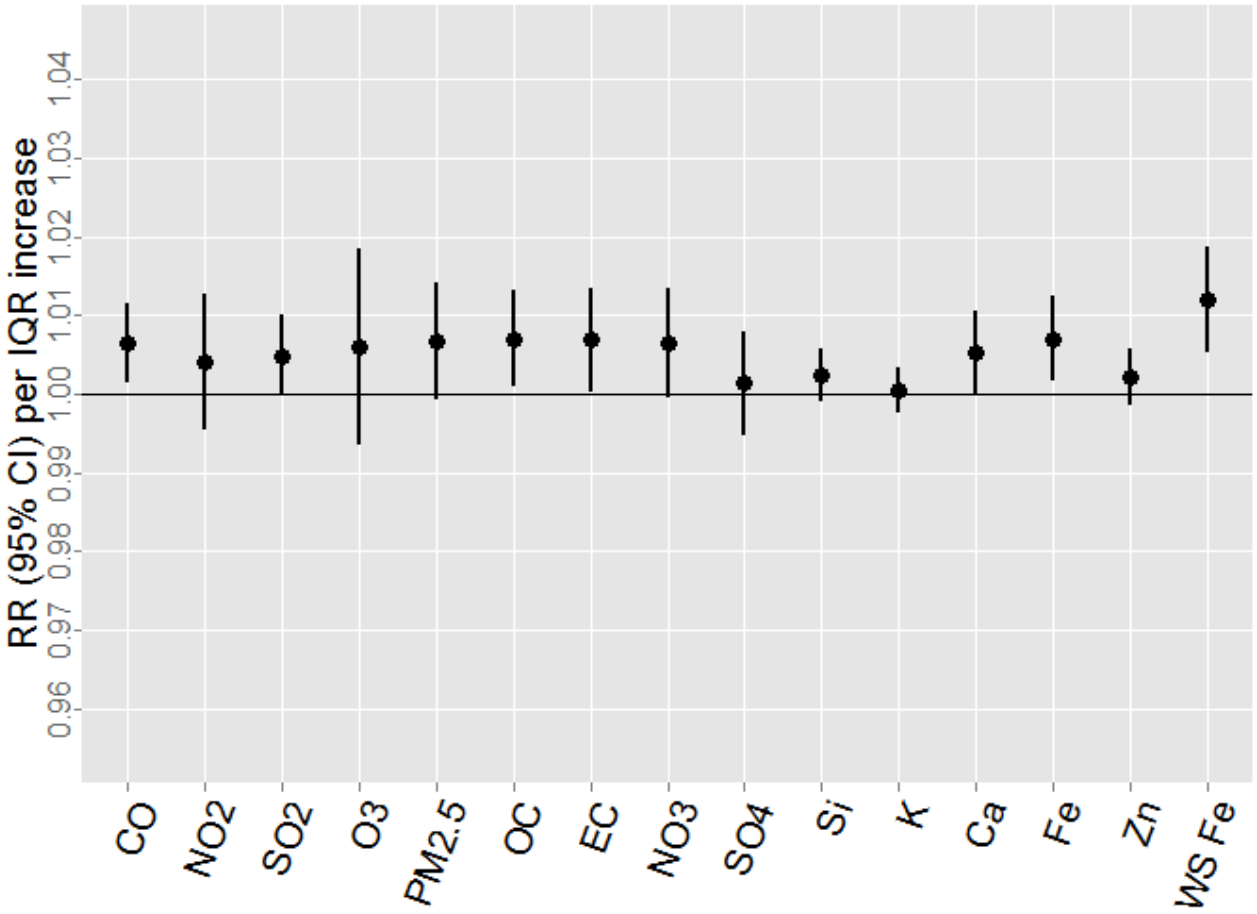


Figure 2.2. Estimated associations between cardiovascular ED visits and water-soluble Fe controlling for each of the other pollutants, 1998-2013 year-round analysis (3303 days), Atlanta, GA.

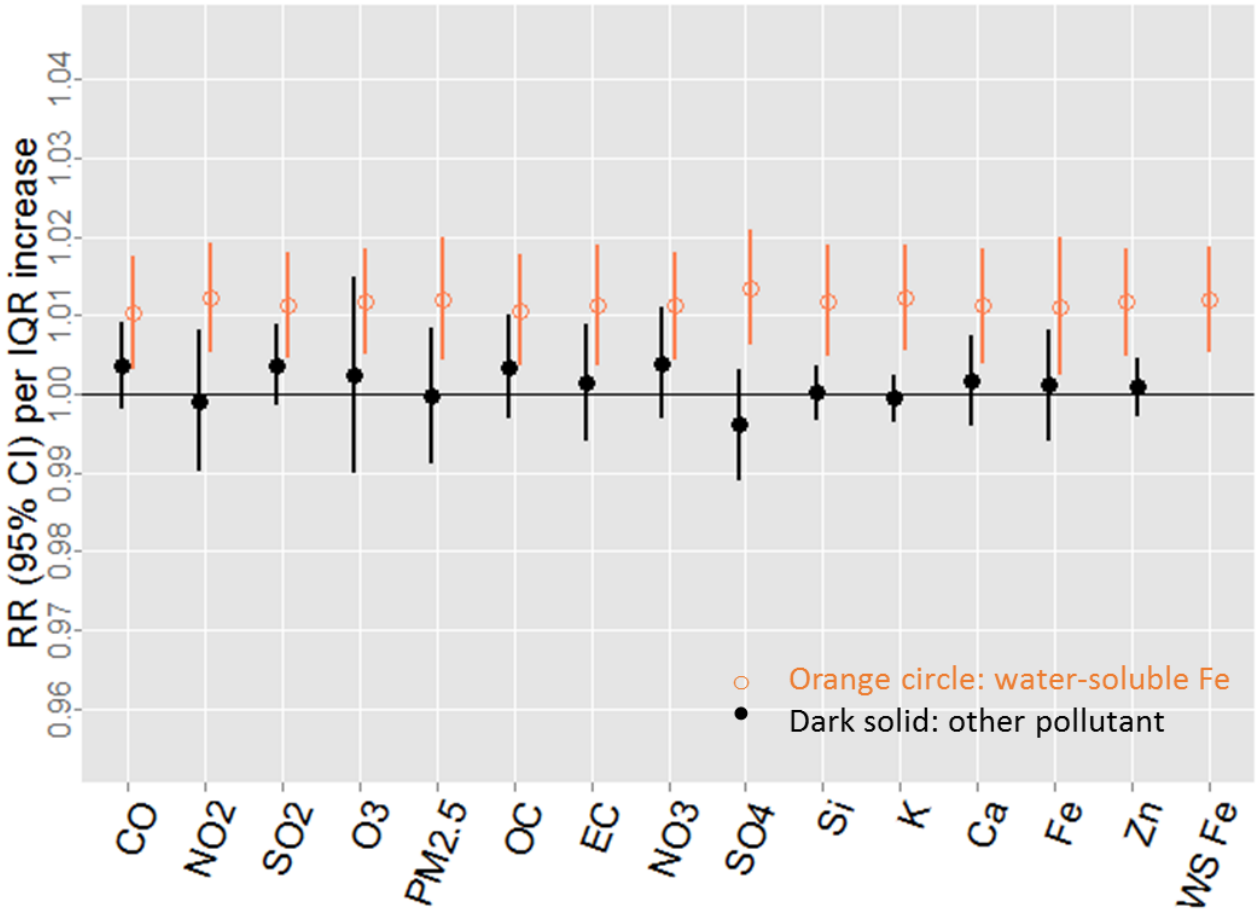


Figure 2.3. Estimated associations between cardiovascular ED visits and pollutants available during 1998-2013 using single-pollutant models, warm-season analysis (1737 days).

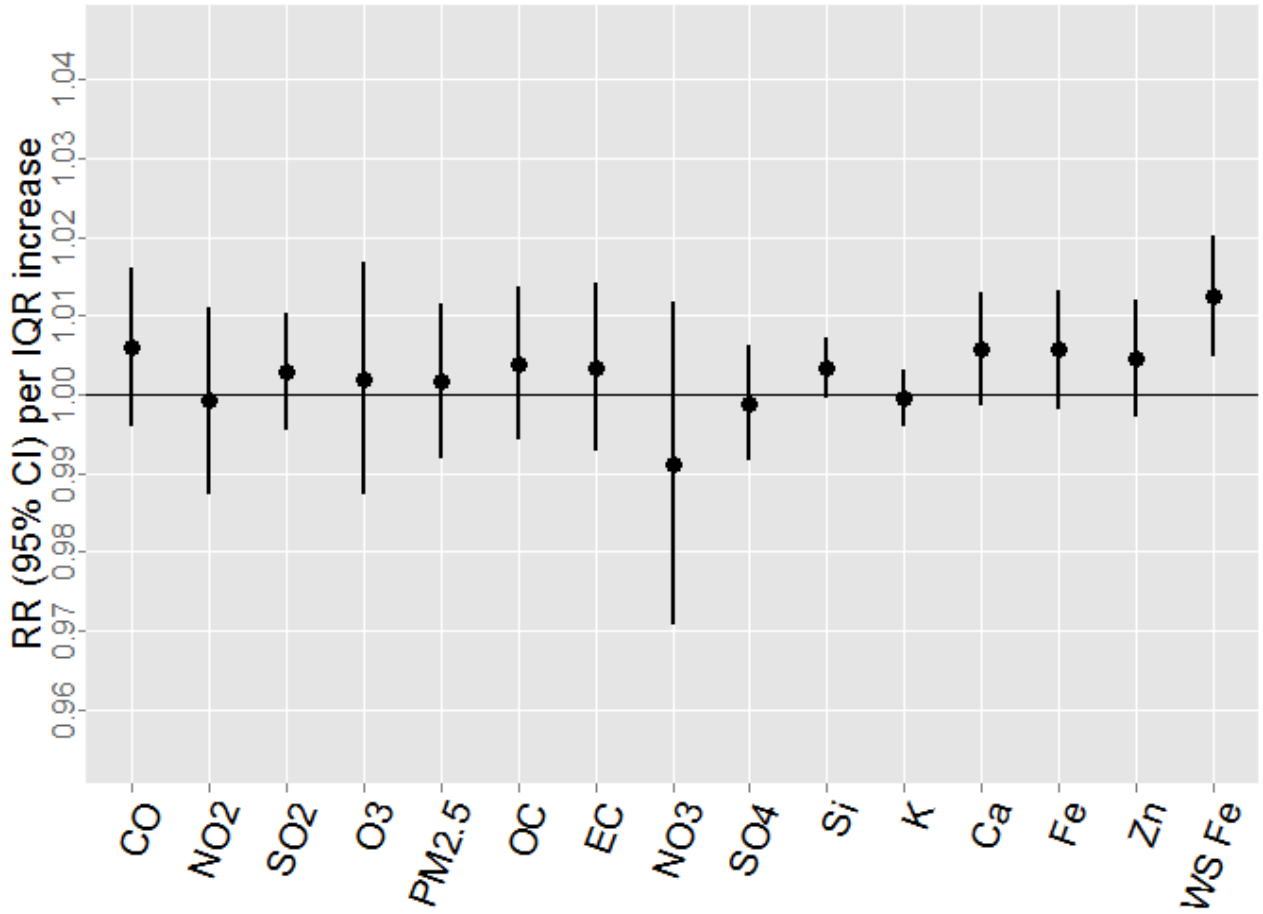


Figure 2.4. Estimated associations between cardiovascular ED visits and water-soluble Fe controlling for each of the other pollutants, 1998-2013 warm-season analysis (1737 days).

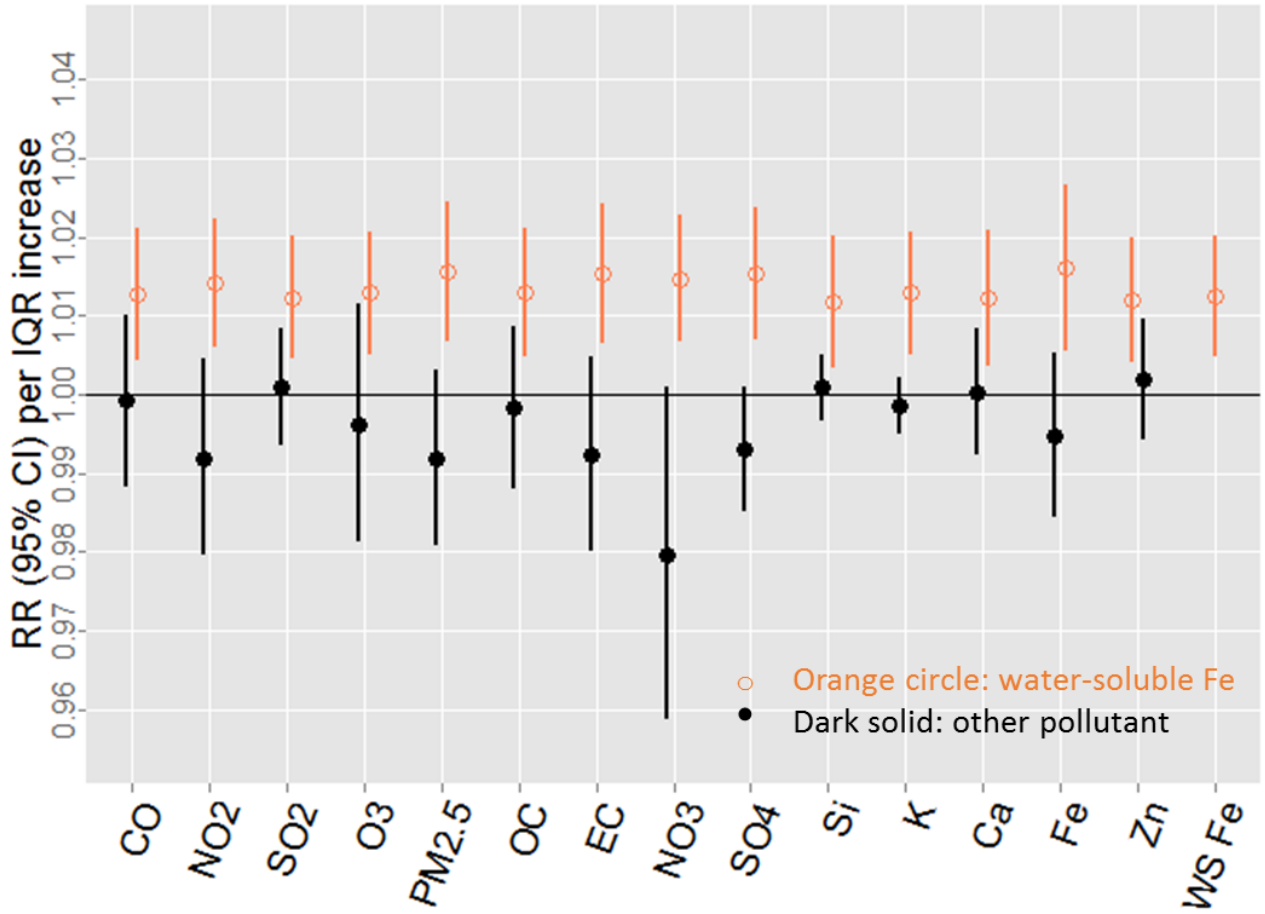


Figure 2.5. Estimated associations between cardiovascular ED visits and pollutants available during 1998-2013 using single-pollutant models, cold-season analysis (1566 days).

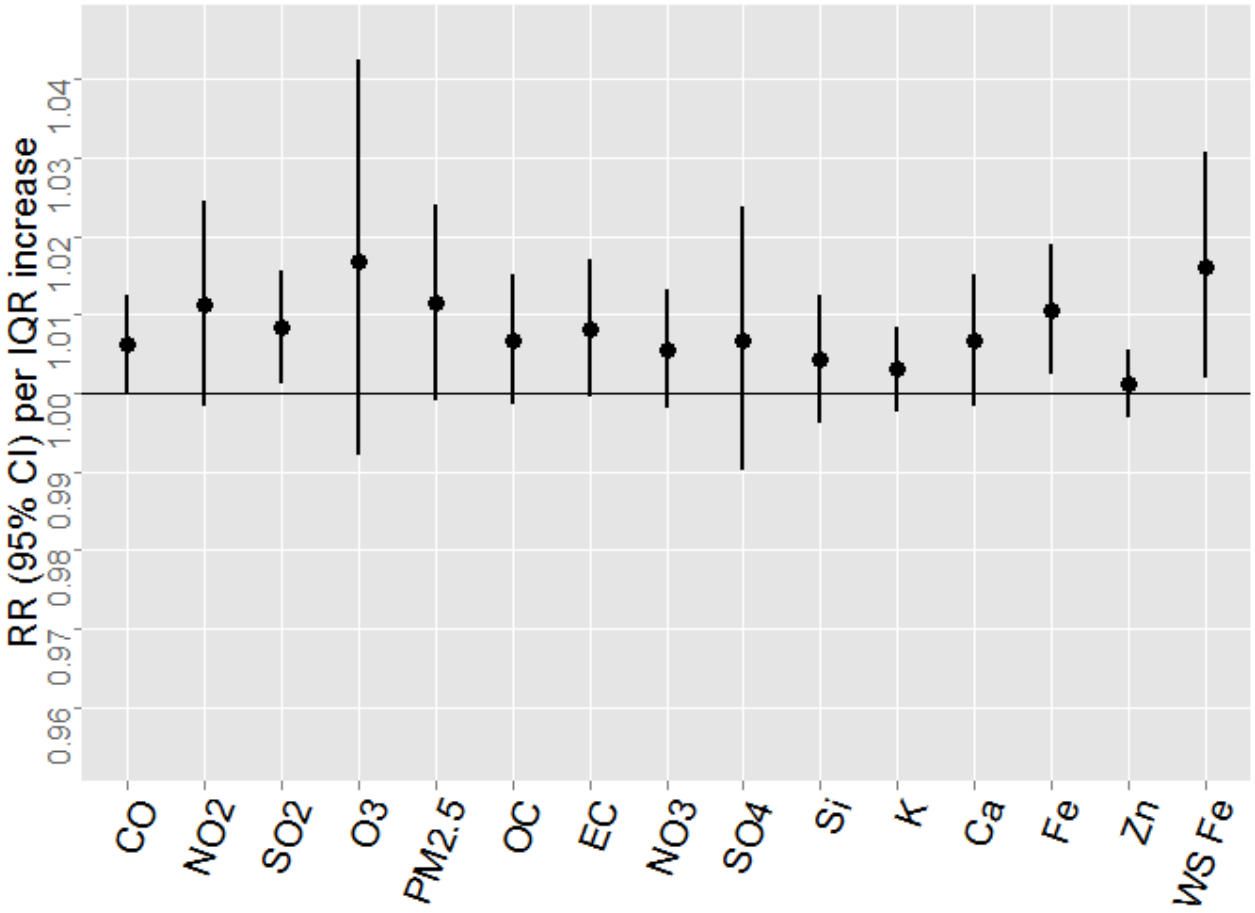


Figure 2.6. Estimated associations between cardiovascular ED visits and water-soluble Fe controlling for each of the other pollutants, 1998-2013 cold-season analysis (1566 days).

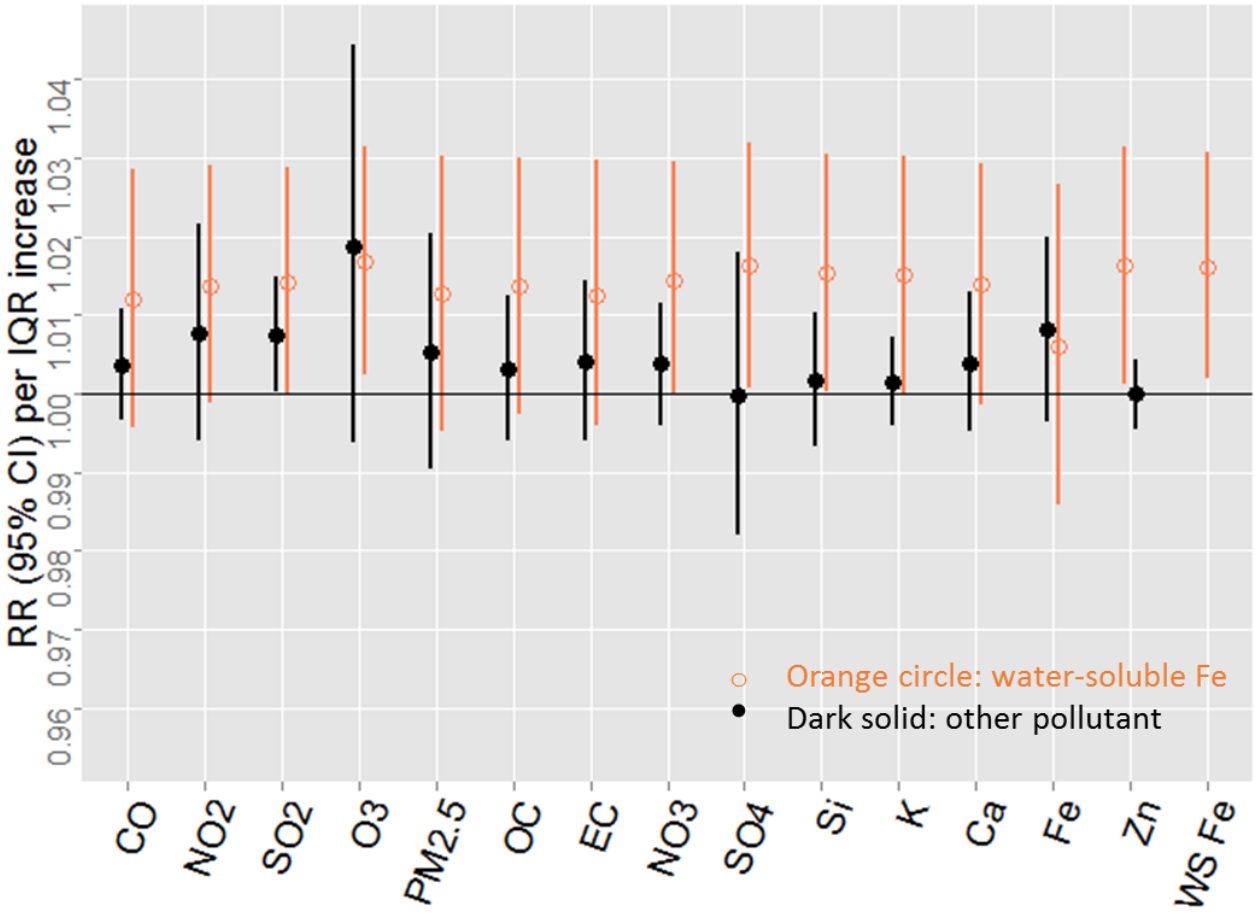
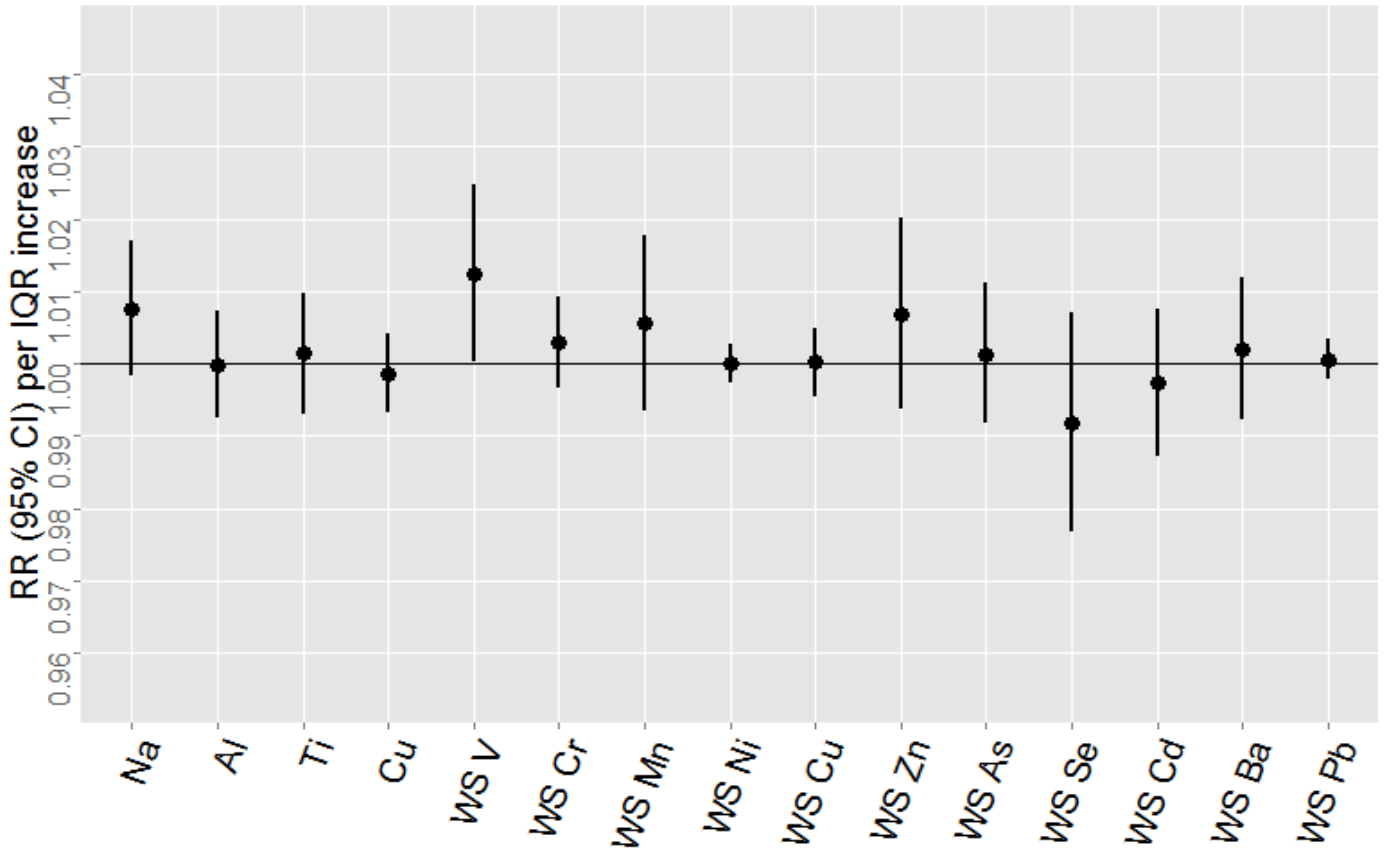


Figure 2.7. Estimated associations between cardiovascular ED visits and pollutants only available during 2008-2013 using single-pollutant models, year-round analysis (631 days).



SUPPLEMENT

eTable 2.1. Limits of detection (LOD) of $PM_{2.5}$ trace components measured at the Atlanta Jefferson Street monitoring site, and % of measurements below LOD, during 1998-2008 and 2008-2013.[a]

POLLUTANTS	UNIT	MEASUREMENT PERIOD	ANALYSIS PERIOD	LOD 1998-2008	LOD 2008-2013	%<LOD 1998-2008	%<LOD 2008-2013	%<LOD 1998-2013
Na	$\mu g/m^3$	2008-2013	2008-2013	n/a	0.0040	n/a	5	5
Al	$\mu g/m^3$	1998-2013	2008-2013	0.0064	0.0060	26	7	19
Si	$\mu g/m^3$	1998-2013	1998-2013	0.0037	0.0057	<1	2	1
S	$\mu g/m^3$	1998-2013	1998-2013	0.0010	0.0015	0	0	0
K	$\mu g/m^3$	1998-2013	1998-2013	0.0008	0.0007	<1	<1	<1
Ca	$\mu g/m^3$	1998-2013	1998-2013	0.0086	0.0037	3	1	2
Ti	$\mu g/m^3$	1998-2013	2008-2013	0.0043	0.0003	77	2	47
Mn	$\mu g/m^3$	1998-2013	excluded	0.0008	0.0012	41	31	37
Fe	$\mu g/m^3$	1998-2013	1998-2013	0.0049	0.0014	<1	<1	<1
Cu	$\mu g/m^3$	1998-2013	2008-2013	0.0012	0.0016	49	12	34
Zn	$\mu g/m^3$	1998-2013	1998-2013	0.0008	0.0007	<1	1	1
Pb	$\mu g/m^3$	1998-2013	excluded	0.0023	0.0019	55	38	48

POLLUTANTS	UNIT	MEASUREMENT PERIOD	ANALYSIS PERIOD	LOD 1998-2008	LOD 2008-2013	%<LOD 1998-2008	%<LOD 2008-2013	%<LOD 1998-2013
water-soluble V	ng/m^3	1998-2013	2008-2013	0.58	0.005	95	<1	77
water-soluble Cr	ng/m^3	1998-2013	2008-2013	1.04	0.014	87	1	70
water-soluble Mn	ng/m^3	1998-2013	2008-2013	0.29	0.023	65	0	50
water-soluble Ni	ng/m^3	1998-2013	2008-2013	1.04	0.046	97	7	79
water-soluble Fe	ng/m^3	1998-2013	1998-2013	2.63	0.698	1	<1	1
water-soluble Cu	ng/m^3	1998-2013	2008-2013	0.79	0.741	53	12	45
water-soluble Zn	ng/m^3	2008-2013	2008-2013	n/a	0.617	n/a	0	0
water-soluble As	ng/m^3	2008-2013	2008-2013	n/a	0.026	n/a	<1	<1
water-soluble Se	ng/m^3	2008-2013	2008-2013	n/a	0.024	n/a	0	0
water-soluble Cd	ng/m^3	2008-2013	2008-2013	n/a	0.004	n/a	<1	<1
water-soluble Ba	ng/m^3	2008-2013	2008-2013	n/a	0.118	n/a	0	0
water-soluble La	ng/m^3	2008-2013	excluded	n/a	0.007	n/a	51	51
water-soluble Pb	ng/m^3	2008-2013	2008-2013	n/a	0.025	n/a	0	0

[a] Total elemental concentrations of $PM_{2.5}$ metals/metalloids, including titanium (Ti), manganese (Mn), iron (Fe), cupper (Cu), zinc (Zn), aluminum (Al), lead (Pb), silicon (Si), calcium (Ca), sodium (Na), and potassium (K), were analyzed from the daily

$PM_{2.5}$ filters using X-ray fluorescence. X-ray fluorescence analyses were conducted by Desert Research Institute on filters collected through 3/22/2008, and by Atmospheric Research & Analysis Inc. on filters collected after 3/23/2008; different limits of detection (LOD) were reported before and after the laboratory change for each species. Water-soluble concentrations of $PM_{2.5}$ metals/metalloids, including water-soluble vanadium (WS V), water-soluble chromium (WS Cr), water-soluble manganese (WS Mn), water-soluble iron (WS Fe), water-soluble nickel (WS Ni), and water-soluble cupper (WS Cu), were analyzed using inductive-coupled plasma optical emission spectrometry (ICP-OES) during 8/14/1998 – 4/6/2008. Starting from 4/7/2008, these water-soluble fractions were analyzed using inductive-coupled plasma mass spectrometry (ICP-MS); again, different LODs were reported before and after the analytical change for these species. Additional water-soluble species, including water-soluble zinc (WS Zn), water-soluble cadmium (WS Cd), water-soluble lead (WS Pb), water-soluble selenium (WS Se), water-soluble arsenic (WS As), water-soluble barium (WS Ba), and water-soluble lanthanum (WS La), were reported starting in 4/7/2008 from ICP-MS analyses. All water-soluble measures were available daily before 2009 and one-in-three day after 2009.

eTable 2.2a. Summary statistics of ambient air pollutants measured at the Atlanta Jefferson Street monitoring site during the warm season (May - October), 1998-2013 and 2008-2013.

POLLUTANTS	UNIT	N	MEAN (SD)	50th (25th, 75th) PERCENTILES
		8/14/1998 – 12/15/2013		
Criteria gases				
CO	ppm	2755	0.74 (0.66)	0.53 (0.35, 0.88)
NO_2	ppb	2738	37.2 (15.2)	35.9 (26.4, 46.3)
SO_2	ppb	5465	13.4 (14.7)	8.1 (3.2, 18.7)
O_3	ppb	5490	42.1 (19.9)	39.6 (27.2, 54.9)
$PM_{2.5}$				
$PM_{2.5}$	$\mu g/m^3$	2839	16.11 (8.24)	14.64 (10.00, 20.56)
OC	$\mu g/m^3$	2820	3.63 (1.79)	3.28 (2.42, 4.39)
EC	$\mu g/m^3$	2811	1.27 (0.92)	1.01 (0.66, 1.59)
NH_4	$\mu g/m^3$	2831	1.69 (1.18)	1.37 (0.83, 2.22)
NO_3	$\mu g/m^3$	2831	0.47 (0.36)	0.36 (0.24, 0.58)

POLLUTANTS	UNIT	N	MEAN (SD)	50th (25th, 75th) PERCENTILES
SO_4	$\mu g/m^3$	5572	5.03 (3.47)	4.10 (2.48, 6.56)
Si	$\mu g/m^3$	2564	0.1168 (0.1360)	0.0821 (0.0505, 0.1324)
K	$\mu g/m^3$	2564	0.0624 (0.1014)	0.0474 (0.0343, 0.0681)
Ca	$\mu g/m^3$	2564	0.0393 (0.0318)	0.0316 (0.0204, 0.0482)
Fe	$\mu g/m^3$	2556	0.0825 (0.0597)	0.0673 (0.0455, 0.0997)
Zn	$\mu g/m^3$	2525	0.0098 (0.0087)	0.0079 (0.0051, 0.0116)
water-soluble Fe	ng/m^3	2104	31.72 (23.64)	25.83 (16.36, 40.63)
		4/7/2008 – 12/15/2013		
Na	$\mu g/m^3$	1050	0.0363 (0.0321)	0.0268 (0.0156, 0.0454)
Al	$\mu g/m^3$	1051	0.0574 (0.0738)	0.0395 (0.0224, 0.0658)
Ti	$\mu g/m^3$	1051	0.0050 (0.0055)	0.0040 (0.0027, 0.0057)
Cu	$\mu g/m^3$	1045	0.0053 (0.0104)	0.0038 (0.0024, 0.0057)
water-soluble V	ng/m^3	463	0.20 (0.17)	0.15 (0.09, 0.28)

POLLUTANTS	UNIT	N	MEAN (SD)	50th (25th, 75th) PERCENTILES
water-soluble Cr	ng/m^3	463	0.15 (0.21)	0.11 (0.07, 0.16)
water-soluble Mn	ng/m^3	463	1.31 (0.92)	1.08 (0.66, 1.70)
water-soluble Ni	ng/m^3	463	0.34 (0.69)	0.17 (0.11, 0.27)
water-soluble Cu	ng/m^3	457	2.83 (3.27)	2.04 (1.31, 3.22)
water-soluble Zn	ng/m^3	368	8.73 (5.90)	7.14 (4.59, 11.16)
water-soluble As	ng/m^3	463	0.62 (0.40)	0.54 (0.37, 0.74)
water-soluble Se	ng/m^3	463	0.75 (0.61)	0.60 (0.39, 0.94)
water-soluble Cd	ng/m^3	463	0.06 (0.05)	0.05 (0.03, 0.07)
water-soluble Ba	ng/m^3	463	3.24 (3.37)	2.61 (1.60, 4.34)
water-soluble Pb	ng/m^3	462	1.22 (1.25)	0.89 (0.59, 1.39)

eTable 2.2b. Summary statistics of ambient air pollutants measured at the Atlanta Jefferson Street monitoring site during the cold season (November - April), 1998-2013 and 2008-2013.

POLLUTANTS	UNIT	N	MEAN (SD)	50th (25th, 75th) PERCENTILES
		8/14/1998 – 12/15/2013		
Criteria gases				
CO	ppm	2703	0.97 (0.97)	0.61 (0.37, 1.19)
NO_2	ppb	2583	37.9 (14.4)	37.4 (27.7, 46.9)
SO_2	ppb	2694	15.2 (15.8)	9.9 (4.0, 21.0)
O_3	ppb	2704	31.9 (14.0)	30.4 (22.0, 40.6)
$PM_{2.5}$				
$PM_{2.5}$	$\mu g/m^3$	2749	12.77 (6.67)	11.39 (8.14, 15.93)
OC	$\mu g/m^3$	2726	3.72 (2.34)	3.15 (2.18, 4.57)
EC	$\mu g/m^3$	2704	1.26 (1.03)	0.96 (0.59, 1.56)
NH_4	$\mu g/m^3$	2732	1.07 (0.62)	0.93 (0.64, 1.34)
NO_3	$\mu g/m^3$	2738	1.17 (0.90)	0.93 (0.52, 1.57)

POLLUTANTS	UNIT	N	MEAN (SD)	50th (25th, 75th) PERCENTILES
SO_4	$\mu g/m^3$	2737	2.68 (1.60)	2.3 (1.58, 3.35)
Si	$\mu g/m^3$	2368	0.0704 (0.0719)	0.0542 (0.0324, 0.0886)
K	$\mu g/m^3$	2368	0.0652 (0.0594)	0.0557 (0.0367, 0.0820)
Ca	$\mu g/m^3$	2368	0.0333 (0.0270)	0.0268 (0.0166, 0.0411)
Fe	$\mu g/m^3$	2365	0.0701 (0.0584)	0.0527 (0.0344, 0.0876)
Zn	$\mu g/m^3$	2355	0.0131 (0.0131)	0.0101 (0.0066, 0.0153)
water-soluble Fe	ng/m^3	1981	16.25 (12.68)	13.31 (8.02, 20.29)
		4/7/2008 – 12/15/2013		
Na	$\mu g/m^3$	880	0.0419 (0.0463)	0.0253 (0.0140, 0.0490)
Al	$\mu g/m^3$	880	0.0322 (0.0302)	0.0248 (0.0130, 0.0455)
Ti	$\mu g/m^3$	880	0.0035 (0.0026)	0.0030 (0.0019, 0.0045)
Cu	$\mu g/m^3$	871	0.0057 (0.0142)	0.0035 (0.0022, 0.0057)
water-soluble V	ng/m^3	342	0.19 (0.21)	0.11 (0.06, 0.25)

POLLUTANTS	UNIT	N	MEAN (SD)	50th (25th, 75th) PERCENTILES
water-soluble Cr	ng/m^3	342	0.11 (0.10)	0.08 (0.05, 0.14)
water-soluble Mn	ng/m^3	333	1.04 (1.03)	0.76 (0.47, 1.29)
water-soluble Ni	ng/m^3	342	0.25 (0.67)	0.13 (0.07, 0.22)
water-soluble Cu	ng/m^3	314	9.30 (6.40)	7.60 (4.96, 11.15)
water-soluble Zn	ng/m^3	368	8.73 (5.90)	7.14 (4.59, 11.16)
water-soluble As	ng/m^3	342	0.76 (0.65)	0.60 (0.34, 0.93)
water-soluble Se	ng/m^3	342	0.66 (0.55)	0.47 (0.29, 0.85)
water-soluble Cd	ng/m^3	342	0.10 (0.10)	0.08 (0.05, 0.12)
water-soluble Ba	ng/m^3	342	3.00 (3.00)	2.12 (1.12, 3.83)
water-soluble Pb	ng/m^3	341	1.62 (4.33)	0.84 (0.54, 1.45)

eTable 2.3. Year-round Pearson correlations among pollutants, 1998-2013 and 2008-2013.

1998-2013	**CO**	**NO_2**	**SO_2**	**O_3**	**$PM_{2.5}$**	**OC**	**EC**	**NO_3**	**SO_4**	**Si**	**K**	**Ca**	**Fe**	**Zn**	**WS Fe**
CO	1.00														
NO_2	0.55	1.00													
SO_2	0.32	0.30	1.00												
O_3	0.01	0.33	-0.04	1.00											
$PM_{2.5}$	0.47	0.50	0.24	0.44	1.00										
OC	0.64	0.53	0.21	0.22	0.74	1.00									
EC	0.73	0.58	0.28	0.12	0.67	0.79	1.00								
NO_3	0.26	0.18	0.21	-0.37	0.24	0.26	0.27	1.00							
SO_4	0.14	0.30	0.16	0.55	0.80	0.34	0.34	0.01	1.00						
Si	0.12	0.15	0.08	0.22	0.23	0.17	0.19	-0.11	0.13	1.00					
K	0.17	0.15	0.03	0.09	0.25	0.28	0.20	0.07	0.08	0.21	1.00				
Ca	0.38	0.43	0.28	0.27	0.44	0.38	0.47	0.08	0.28	0.62	0.20	1.00			
Fe	0.48	0.43	0.17	0.21	0.47	0.49	0.58	0.07	0.19	0.69	0.26	0.66	1.00		
Zn	0.49	0.33	0.20	-0.03	0.38	0.45	0.50	0.28	0.10	0.11	0.18	0.34	0.42	1.00	
WS Fe	0.27	0.37	0.13	0.46	0.65	0.39	0.48	-0.05	0.61	0.48	0.18	0.47	0.64	0.16	1.00

2008-2013	**CO**	**NO_2**	**SO_2**	**O_3**	**$PM_{2.5}$**	**OC**	**EC**	**NO_3**	**SO_4**	**Si**	**K**	**Ca**	**Fe**	**Zn**	**WS Fe**
Na	-0.03	-0.06	-0.12	-0.06	0.08	0.11	0.02	-0.09	-0.01	0.20	0.15	0.16	0.10	0.06	0.01
Al	-0.03	-0.02	-0.05	0.15	0.17	0.07	0.05	-0.16	0.06	0.94	0.26	0.59	0.53	-0.02	0.31
Ti	0.15	0.17	0.10	0.22	0.32	0.24	0.27	-0.10	0.16	0.87	0.28	0.70	0.70	0.18	0.43
Cu	0.26	0.24	0.07	0.07	0.21	0.25	0.27	0.06	0.05	0.09	0.23	0.21	0.26	0.21	0.23
WS V	-0.10	-0.11	-0.05	-0.01	0.21	0.10	-0.03	-0.09	0.25	0.23	0.15	0.14	0.07	0.00	0.17
WS Cr	0.21	0.17	0.02	0.16	0.26	0.21	0.25	-0.02	0.16	0.12	0.19	0.18	0.24	0.21	0.34
WS Mn	0.33	0.35	0.12	0.26	0.45	0.36	0.49	-0.05	0.28	0.31	0.31	0.41	0.60	0.39	0.52
WS Ni	0.01	-0.01	0.04	0.09	0.02	0.03	0.06	-0.08	0.02	0.04	0.07	0.01	0.06	0.03	0.07
WS Cu	0.27	0.26	0.07	0.10	0.24	0.27	0.30	0.01	0.09	0.06	0.24	0.15	0.26	0.22	0.27
WS Zn	0.51	0.45	0.13	0.07	0.44	0.45	0.58	0.18	0.24	0.05	0.19	0.27	0.39	0.80	0.37
WS As	0.50	0.30	0.07	-0.05	0.28	0.40	0.47	0.23	0.01	0.00	0.12	0.11	0.29	0.29	0.20

WS Se	0.16	0.24	0.42	0.13	0.46	0.27	0.26	0.14	0.46	0.07	0.08	0.26	0.20	0.18	0.41
WS Cd	0.48	0.34	0.16	-0.08	0.31	0.45	0.47	0.30	0.04	0.00	0.16	0.18	0.32	0.47	0.21
WS Ba	0.42	0.39	0.16	0.23	0.36	0.38	0.50	0.05	0.18	0.17	0.72	0.30	0.49	0.33	0.39
WS Pb	0.25	0.17	0.06	0.04	0.19	0.23	0.19	0.07	0.06	0.00	0.12	0.07	0.10	0.22	0.13

2008-2013	**Na**	**Al**	**Ti**	**Cu**	**WS V**	**WS Cr**	**WS Mn**	**WS Ni**	**WS Cu**	**WS Zn**	**WS As**	**WS Se**	**WS Cd**	**WS Ba**	**WS Pb**
Na	1.00														
Al	0.21	1.00													
Ti	0.19	0.83	1.00												
Cu	0.00	0.06	0.17	1.00											
WS V	0.48	0.21	0.21	-0.03	1.00										
WS Cr	0.04	0.11	0.15	0.17	0.09	1.00									
WS Mn	0.11	0.28	0.43	0.20	0.08	0.25	1.00								
WS Ni	0.13	0.05	0.08	0.04	0.09	0.04	0.16	1.00							
WS Cu	-0.03	0.05	0.12	0.92	-0.01	0.22	0.21	0.09	1.00						
WS Zn	-0.05	0.01	0.16	0.28	-0.02	0.29	0.40	0.00	0.28	1.00					
WS As	-0.07	-0.01	0.04	0.24	-0.07	0.17	0.13	-0.09	0.21	0.42	1.00				
WS Se	-0.01	0.01	0.10	0.10	0.15	0.18	0.11	-0.02	0.13	0.25	0.29	1.00			
WS Cd	0.02	-0.02	0.06	0.41	-0.04	0.14	0.19	-0.05	0.36	0.52	0.52	0.38	1.00		
WS Ba	0.02	0.19	0.31	0.34	-0.08	0.22	0.56	0.15	0.34	0.36	0.21	0.12	0.24	1.00	
WS Pb	-0.02	0.01	0.04	0.71	0.02	0.10	0.05	-0.01	0.73	0.26	0.27	0.18	0.39	0.15	1.00

eTable 2.4a. Pearson correlations among pollutants during the warm season (May - October), 1998-2013 and 2008-2013.

1998-2013	**CO**	**NO_2**	**SO_2**	**O_3**	**$PM_{2.5}$**	**OC**	**EC**	**NO_3**	**SO_4**	**Si**	**K**	**Ca**	**Fe**	**Zn**	**WS Fe**
CO	1.00														
NO_2	0.60	1.00													
SO_2	0.28	0.29	1.00												
O_3	0.18	0.52	0.14	1.00											
$PM_{2.5}$	0.45	0.57	0.31	0.59	1.00										
OC	0.55	0.58	0.21	0.48	0.74	1.00									
EC	0.72	0.63	0.31	0.30	0.64	0.71	1.00								
NO_3	0.48	0.41	0.17	0.09	0.48	0.46	0.55	1.00							
SO_4	0.26	0.43	0.30	0.54	0.88	0.49	0.45	0.40	1.00						
Si	0.09	0.10	0.10	0.06	0.14	0.11	0.14	0.04	0.03	1.00					
K	0.09	0.10	0.02	0.11	0.16	0.16	0.09	0.09	0.07	0.19	1.00				
Ca	0.40	0.44	0.28	0.29	0.43	0.38	0.49	0.31	0.29	0.59	0.17	1.00			
Fe	0.44	0.40	0.20	0.22	0.38	0.39	0.54	0.26	0.18	0.76	0.20	0.70	1.00		
Zn	0.46	0.37	0.22	0.17	0.39	0.39	0.51	0.34	0.24	0.10	0.13	0.40	0.39	1.00	
WS Fe	0.36	0.44	0.24	0.39	0.64	0.48	0.58	0.28	0.56	0.45	0.18	0.50	0.66	0.27	1.00

2008-2013	**CO**	**NO_2**	**SO_2**	**O_3**	**$PM_{2.5}$**	**OC**	**EC**	**NO_3**	**SO_4**	**Si**	**K**	**Ca**	**Fe**	**Zn**	**WS Fe**
Na	-0.12	-0.12	-0.11	-0.14	-0.02	-0.04	-0.09	-0.06	-0.06	0.32	0.13	0.20	0.17	-0.03	0.05
Al	-0.08	-0.07	-0.04	-0.02	0.11	0.01	-0.01	-0.02	-0.03	0.96	0.25	0.60	0.68	-0.03	0.30
Ti	0.07	0.11	0.07	0.10	0.25	0.15	0.18	0.07	0.09	0.90	0.26	0.71	0.79	0.13	0.39
Cu	0.30	0.28	0.04	0.20	0.26	0.29	0.31	0.18	0.14	0.09	0.50	0.28	0.27	0.19	0.30
WS V	-0.13	-0.12	-0.01	-0.09	0.21	0.08	-0.07	-0.01	0.21	0.33	0.12	0.20	0.19	0.01	0.22
WS Cr	0.25	0.18	0.00	0.12	0.21	0.16	0.21	0.17	0.11	0.09	0.17	0.15	0.20	0.17	0.26
WS Mn	0.31	0.40	0.12	0.29	0.46	0.38	0.43	0.21	0.31	0.36	0.33	0.53	0.58	0.38	0.53
WS Ni	0.01	-0.01	0.08	0.07	0.00	0.02	0.03	0.01	0.01	0.04	0.07	0.00	0.02	0.02	0.02

WS Cu	0.32	0.32	0.07	0.19	0.25	0.22	0.32	0.19	0.14	0.09	0.39	0.23	0.30	0.15	0.34
WS Zn	0.40	0.43	0.11	0.17	0.41	0.31	0.49	0.32	0.38	0.03	0.11	0.32	0.31	0.77	0.39
WS As	0.39	0.20	0.01	-0.01	0.18	0.21	0.40	0.27	0.05	-0.03	0.01	0.04	0.18	0.08	0.19
WS Se	0.20	0.27	0.43	0.19	0.47	0.25	0.27	0.21	0.48	0.05	0.05	0.26	0.18	0.14	0.40
WS Cd	0.48	0.41	0.09	0.07	0.28	0.30	0.45	0.36	0.16	0.02	0.12	0.24	0.31	0.34	0.26
WS Ba	0.35	0.33	0.09	0.30	0.33	0.37	0.42	0.28	0.20	0.18	0.83	0.33	0.38	0.21	0.34
WS Pb	0.31	0.32	0.09	0.19	0.27	0.15	0.24	0.24	0.21	0.01	0.17	0.19	0.21	0.18	0.32

2008-2013	**Na**	**Al**	**Ti**	**Cu**	**WS V**	**WS Cr**	**WS Mn**	**WS Ni**	**WS Cu**	**WS Zn**	**WS As**	**WS Se**	**WS Cd**	**WS Ba**	**WS Pb**
Na	1.00														
Al	0.32	1.00													
Ti	0.30	0.87	1.00												
Cu	0.02	0.09	0.16	1.00											
WS V	0.50	0.30	0.32	-0.02	1.00										
WS Cr	0.02	0.08	0.10	0.29	0.06	1.00									
WS Mn	0.09	0.32	0.43	0.30	0.09	0.22	1.00								
WS Ni	0.14	0.05	0.07	-0.01	0.08	0.02	0.12	1.00							
WS Cu	0.00	0.08	0.14	0.83	0.03	0.38	0.30	0.08	1.00						
WS Zn	-0.09	-0.01	0.10	0.24	-0.06	0.26	0.45	0.00	0.34	1.00					
WS As	-0.20	-0.02	0.00	0.10	-0.15	0.18	0.05	-0.15	0.07	0.20	1.00				
WS Se	-0.07	0.00	0.08	0.03	0.17	0.15	0.13	-0.03	0.08	0.20	0.36	1.00			
WS Cd	-0.12	-0.01	0.06	0.21	-0.07	0.20	0.31	-0.04	0.22	0.48	0.56	0.47	1.00		
WS Ba	0.07	0.22	0.28	0.50	-0.06	0.18	0.47	0.14	0.47	0.30	0.13	0.09	0.25	1.00	
WS Pb	-0.06	-0.01	0.08	0.60	0.02	0.23	0.21	0.03	0.64	0.24	0.17	0.21	0.37	0.25	1.00

eTable 2.4b. Pearson correlations among pollutants during the cold season (November - April), 1998-2013 and 2008-2013.

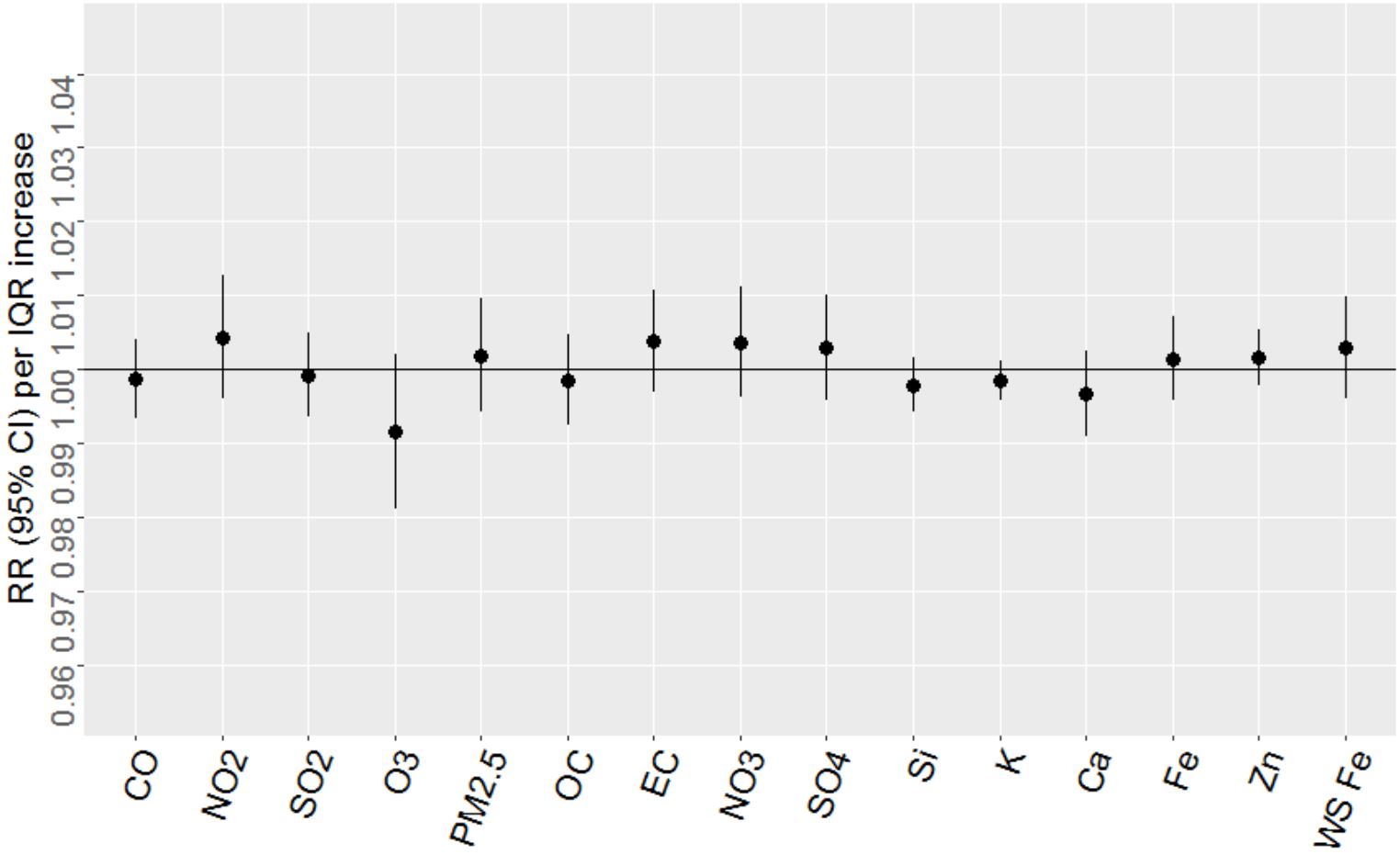
1998-2013	**CO**	**NO_2**	**SO_2**	**O_3**	**$PM_{2.5}$**	**OC**	**EC**	**NO_3**	**SO_4**	**Si**	**K**	**Ca**	**Fe**	**Zn**	**WS Fe**
CO	1.00														
NO2	0.54	1.00													
SO2	0.33	0.31	1.00												
O3	0.01	0.24	-0.12	1.00											
PM25	0.61	0.47	0.24	0.04	1.00										
OC	0.70	0.50	0.21	0.06	0.82	1.00									
EC	0.75	0.54	0.27	-0.06	0.75	0.86	1.00								
NO3	0.16	0.12	0.19	-0.40	0.42	0.24	0.24	1.00							
SO4	0.24	0.22	0.18	0.16	0.65	0.34	0.30	0.24	1.00						
Si	0.30	0.33	0.12	0.35	0.35	0.32	0.33	-0.08	0.17	1.00					
K	0.32	0.26	0.04	0.10	0.49	0.49	0.40	0.09	0.18	0.31	1.00				
Ca	0.42	0.44	0.31	0.17	0.43	0.40	0.45	0.07	0.21	0.74	0.28	1.00			
Fe	0.57	0.49	0.16	0.14	0.57	0.59	0.63	0.09	0.15	0.61	0.42	0.60	1.00		
Zn	0.49	0.32	0.18	-0.07	0.50	0.50	0.53	0.21	0.15	0.25	0.30	0.36	0.50	1.00	
WS Fe	0.44	0.39	0.14	0.18	0.60	0.49	0.52	0.11	0.47	0.44	0.29	0.40	0.67	0.28	1.00

2008-2013	**CO**	**NO_2**	**SO_2**	**O_3**	**$PM_{2.5}$**	**OC**	**EC**	**NO_3**	**SO_4**	**Si**	**K**	**Ca**	**Fe**	**Zn**	**WS Fe**
Na	-0.01	-0.03	-0.13	0.09	0.21	0.21	0.10	-0.17	0.14	0.14	0.34	0.15	0.06	0.10	0.05
Al	0.16	0.22	-0.10	0.41	0.25	0.22	0.19	-0.16	0.07	0.86	0.42	0.71	0.44	0.12	0.16
Ti	0.41	0.44	0.17	0.27	0.43	0.42	0.47	-0.01	0.13	0.72	0.50	0.76	0.71	0.43	0.40
Cu	0.26	0.25	0.10	0.06	0.24	0.26	0.28	0.04	0.04	0.15	0.19	0.21	0.27	0.23	0.23
WS V	-0.08	-0.10	-0.10	0.07	0.23	0.11	0.00	-0.12	0.40	0.07	0.26	0.07	-0.06	0.00	0.11
WS Cr	0.34	0.22	0.04	0.10	0.38	0.38	0.40	0.03	0.20	0.13	0.36	0.22	0.37	0.45	0.56
WS Mn	0.42	0.32	0.12	0.11	0.40	0.35	0.55	-0.03	0.16	0.18	0.38	0.25	0.62	0.44	0.48
WS Ni	0.03	0.01	-0.04	0.05	0.03	0.03	0.09	-0.09	-0.03	0.01	0.08	0.01	0.09	0.05	0.11
WS Cu	0.26	0.24	0.07	0.06	0.28	0.30	0.29	-0.01	0.08	0.03	0.16	0.11	0.24	0.29	0.27

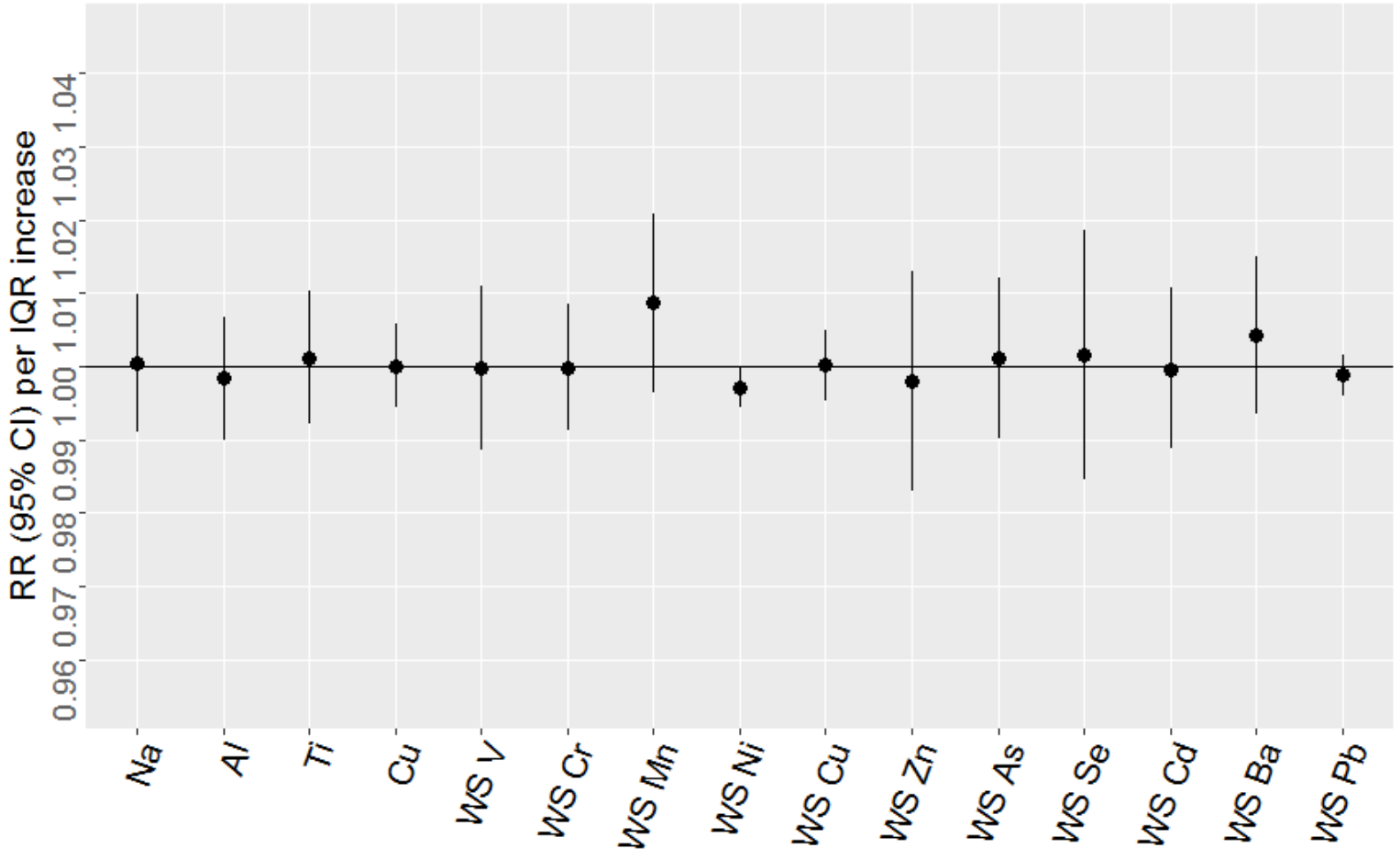
WS Zn	0.59	0.48	0.17	0.01	0.53	0.56	0.67	0.19	0.13	0.12	0.47	0.23	0.50	0.83	0.43
WS As	0.54	0.39	0.15	0.04	0.49	0.52	0.52	0.20	0.09	0.12	0.43	0.22	0.41	0.44	0.35
WS Se	0.17	0.22	0.40	-0.04	0.43	0.32	0.27	0.28	0.47	0.05	0.19	0.24	0.21	0.28	0.40
WS Cd	0.45	0.31	0.26	0.01	0.53	0.55	0.53	0.21	0.18	0.11	0.38	0.24	0.40	0.56	0.41
WS Ba	0.56	0.51	0.28	0.07	0.41	0.42	0.62	0.08	0.09	0.11	0.48	0.24	0.64	0.51	0.48
WS Pb	0.23	0.15	0.07	0.05	0.24	0.27	0.19	0.03	0.07	0.02	0.21	0.06	0.10	0.27	0.14

2008-2013	**Na**	**Al**	**Ti**	**Cu**	**WS V**	**WS Cr**	**WS Mn**	**WS Ni**	**WS Cu**	**WS Zn**	**WS As**	**WS Se**	**WS Cd**	**WS Ba**	**WS Pb**
Na	1.00														
Al	0.20	1.00													
Ti	0.13	0.62	1.00												
Cu	-0.01	0.12	0.30	1.00											
WS V	0.49	0.08	0.04	-0.04	1.00										
WS Cr	0.15	0.11	0.26	0.08	0.17	1.00									
WS Mn	0.15	0.17	0.46	0.14	0.06	0.37	1.00								
WS Ni	0.14	0.01	0.07	0.07	0.11	0.06	0.20	1.00							
WS Cu	-0.04	0.04	0.13	0.95	-0.03	0.11	0.16	0.10	1.00						
WS Zn	-0.03	0.11	0.34	0.32	0.01	0.46	0.36	0.00	0.27	1.00					
WS As	-0.02	0.13	0.21	0.31	-0.02	0.30	0.23	-0.04	0.27	0.57	1.00				
WS Se	0.07	-0.03	0.10	0.17	0.13	0.28	0.07	0.00	0.20	0.32	0.29	1.00			
WS Cd	0.04	0.14	0.25	0.51	-0.01	0.27	0.20	-0.04	0.43	0.58	0.49	0.43	1.00		
WS Ba	-0.02	0.11	0.40	0.25	-0.11	0.35	0.67	0.18	0.27	0.46	0.33	0.15	0.31	1.00	
WS Pb	-0.02	0.09	0.08	0.76	0.03	0.11	0.01	-0.01	0.78	0.31	0.30	0.23	0.40	0.15	1.00

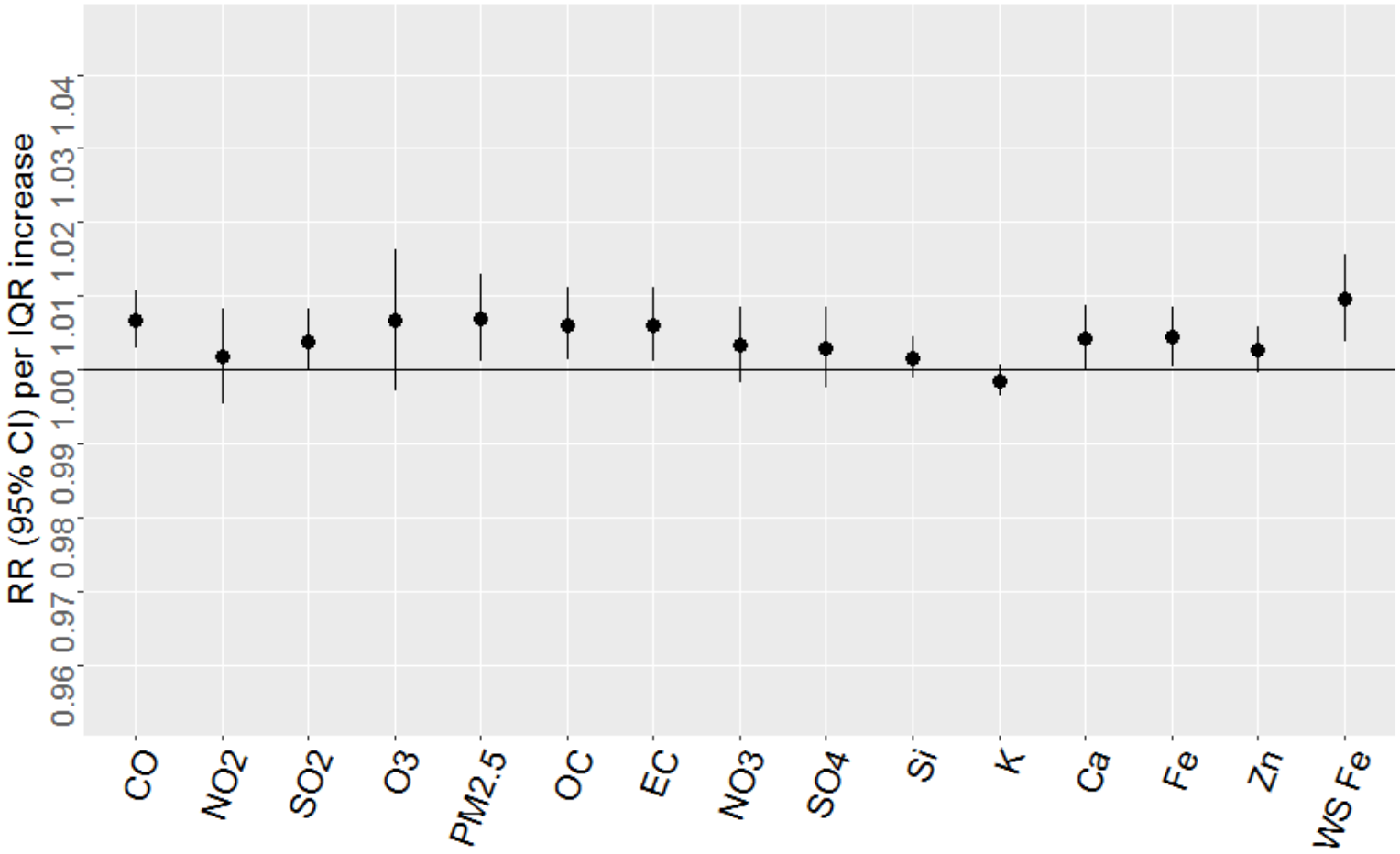
eFigure 2.1. Estimated associations between cardiovascular ED visits and tomorrow's pollutant levels, 1998-2013 year-round analysis (3303 days).



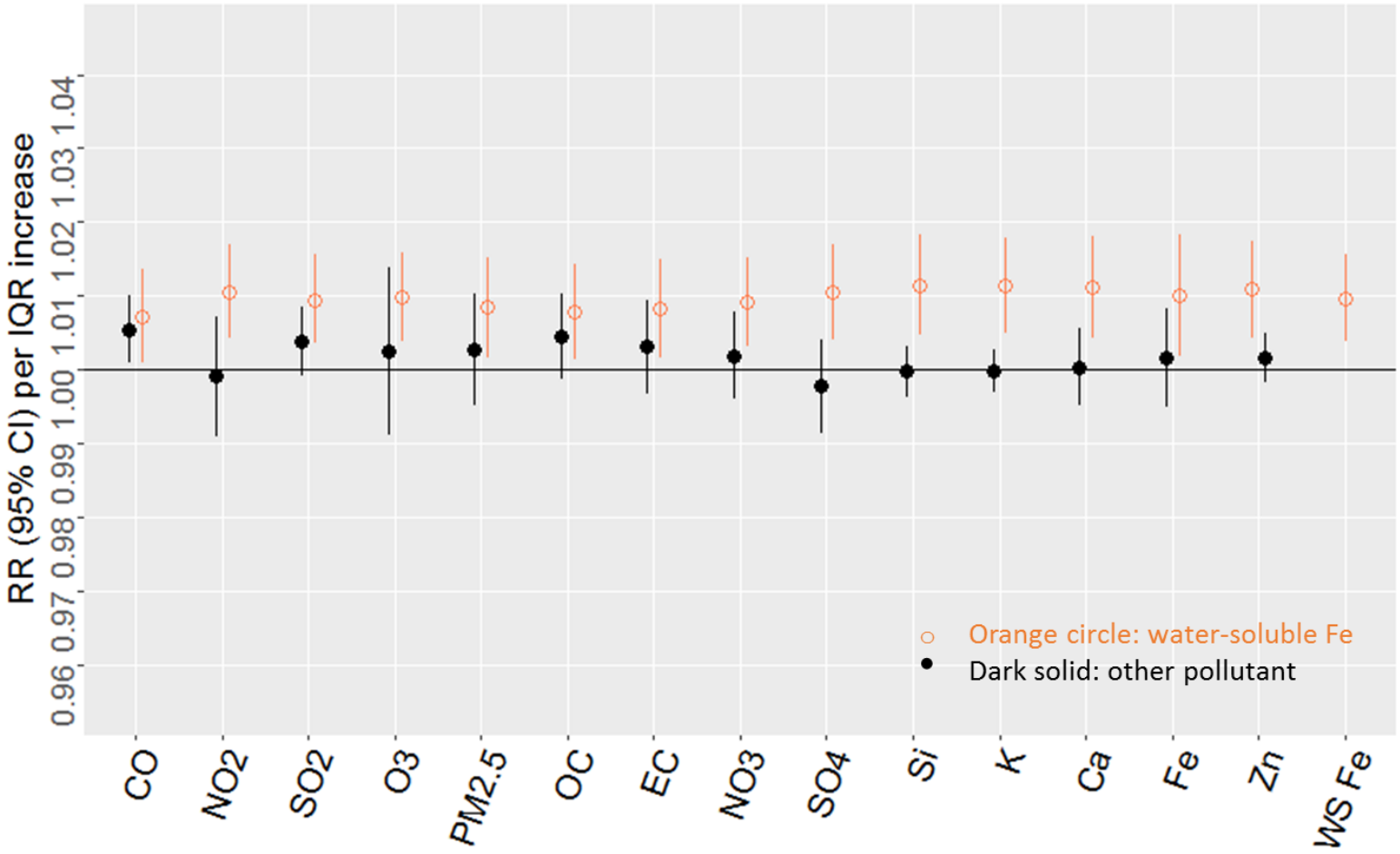
eFigure 2.2. Estimated associations between cardiovascular ED visits and tomorrow's pollutant levels, 2008-2013 year-round analysis (631 days).



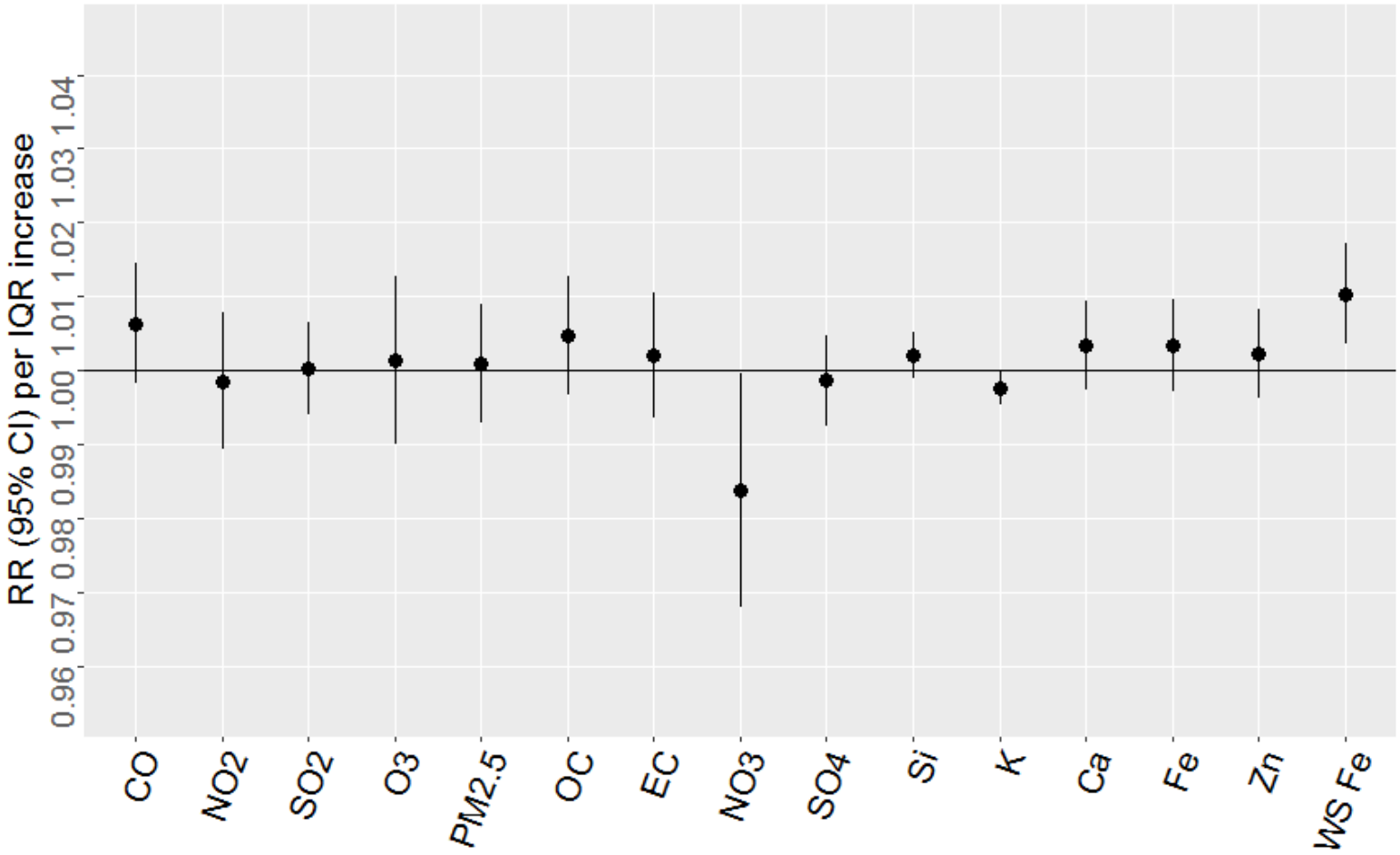
3Figure 2.3. Estimated associations between cardiovascular ED visits and pollutants available during 1998-2013 using single-pollutant models, year-round analysis including all days with data available for each pollutant.



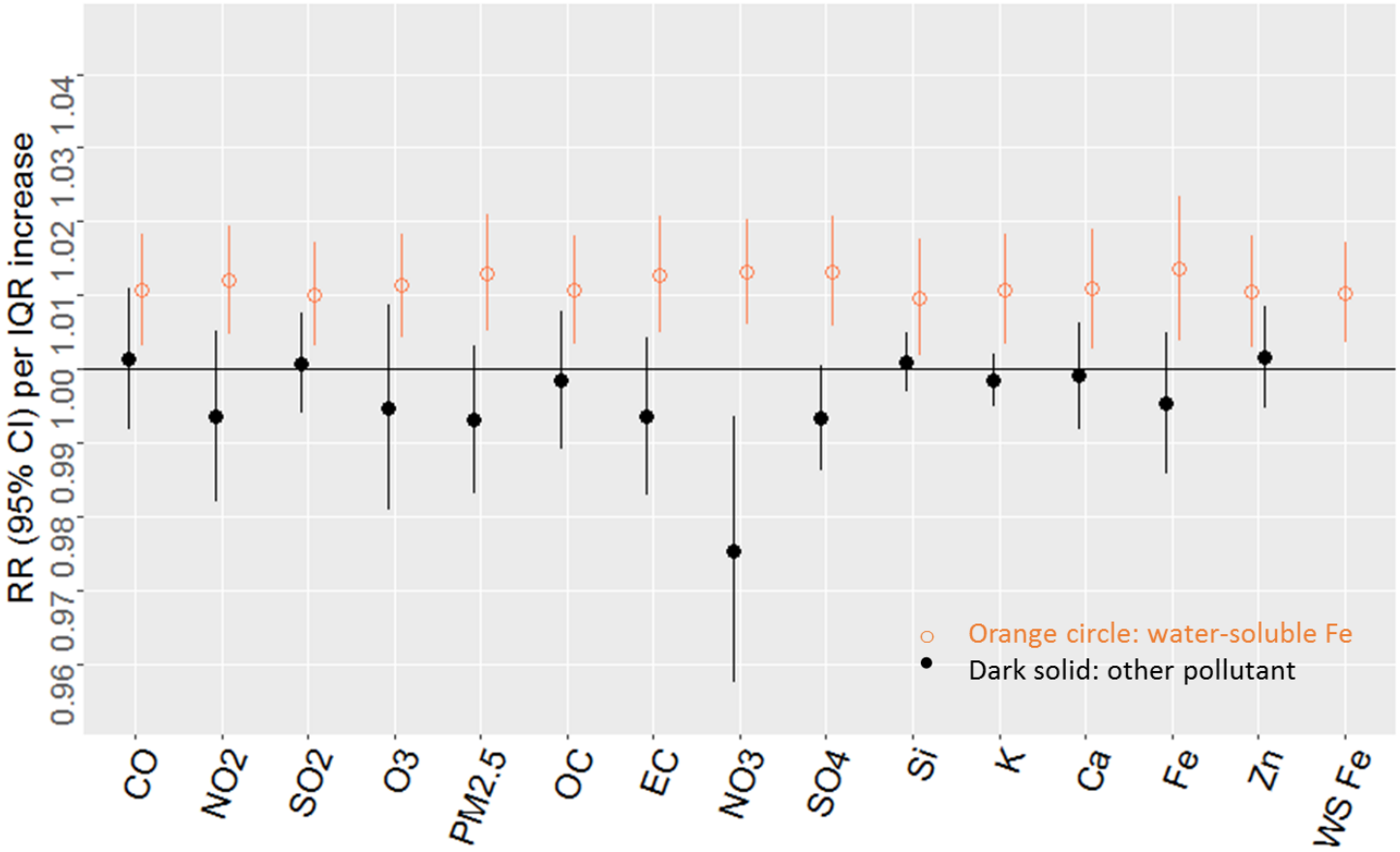
eFigure 2.4. Estimated associations between cardiovascular ED visits and water-soluble Fe controlling for each of the other pollutants, 1998-2013 year-round analysis including all days with data available for each pollutant.



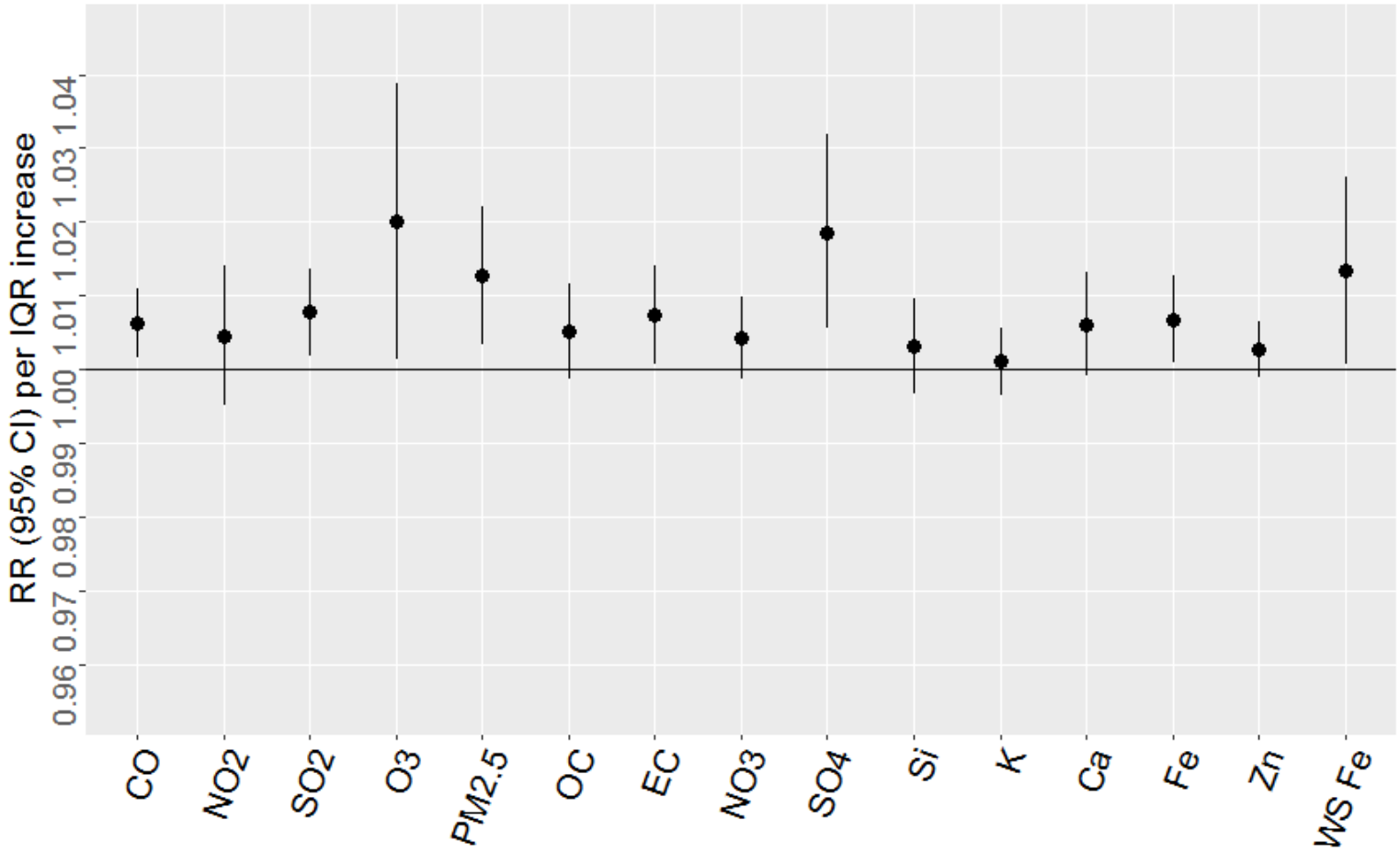
eFigure 2.5. Estimated associations between cardiovascular ED visits and pollutants available during 1998-2013 using single-pollutant models, warm-season analysis including all days with data available for each pollutant.



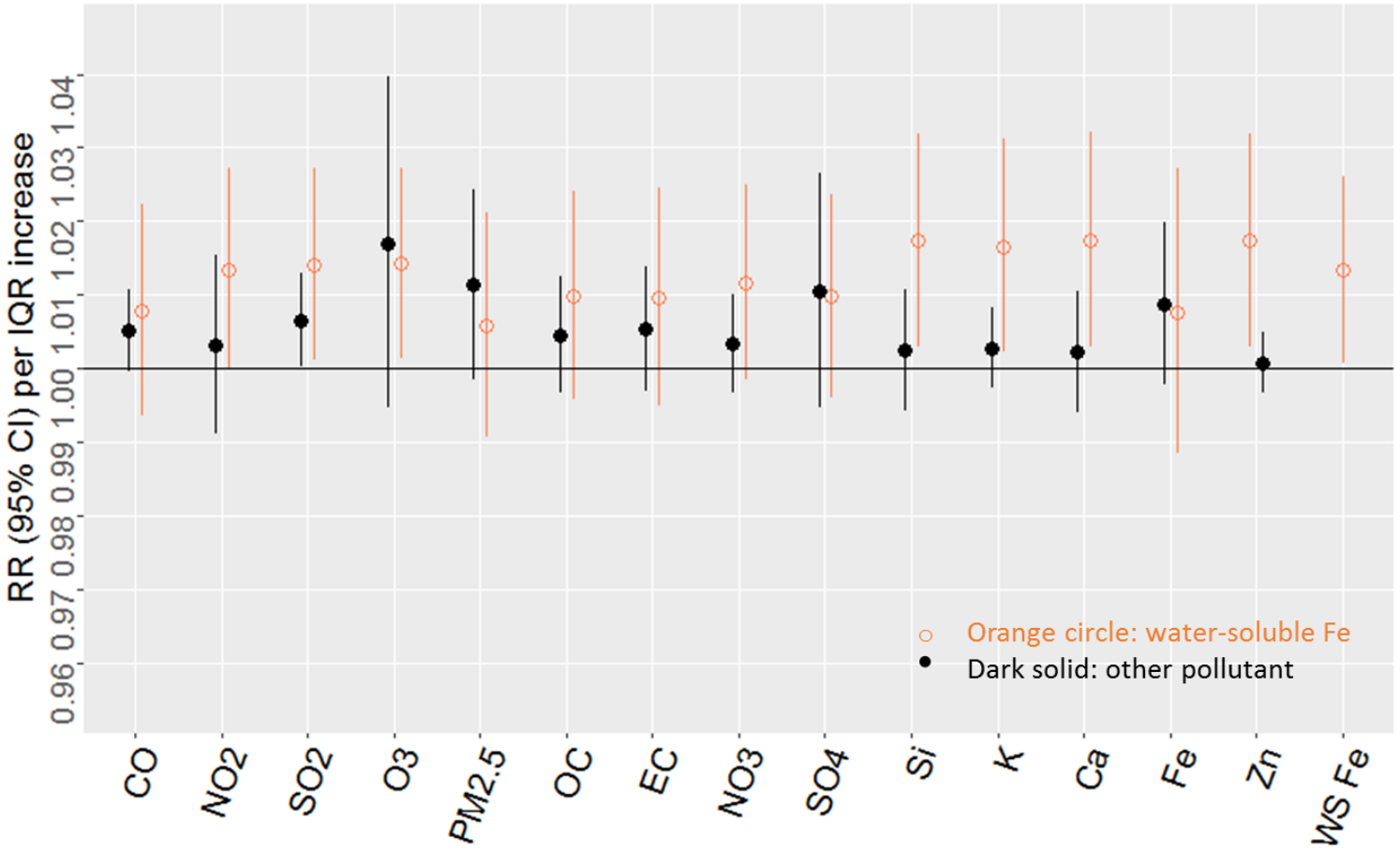
eFigure 2.6. Estimated associations between cardiovascular ED visits and water-soluble Fe controlling for each of the other pollutants, 1998-2013 warm-season analysis including all days with data available for each pollutant.



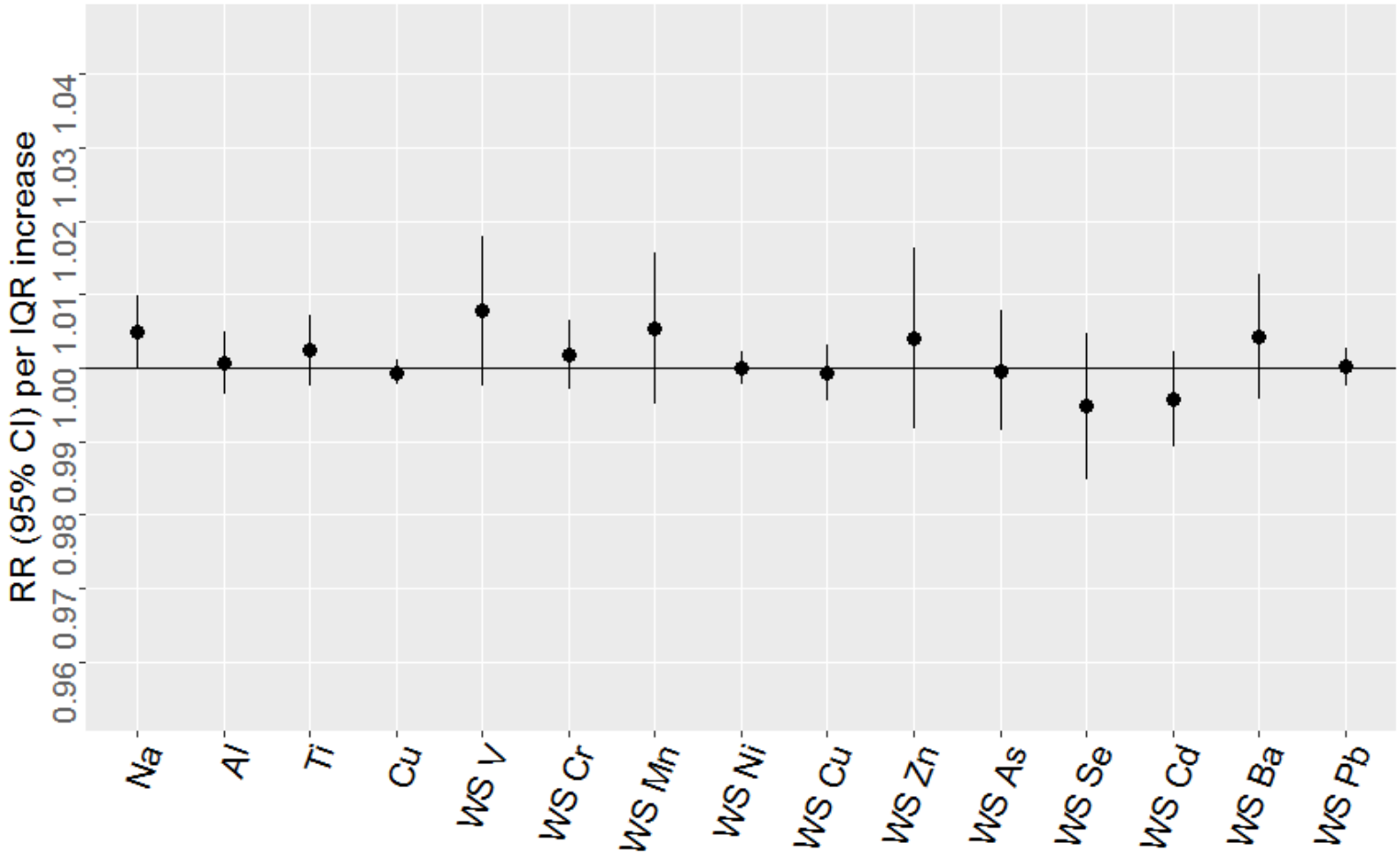
eFigure 2.7. Estimated associations between cardiovascular ED visits and pollutants available during 1998-2013 using single-pollutant models, cold-season analysis including all days with data available for each pollutant.



eFigure 2.8. Estimated associations between cardiovascular ED visits and water-soluble Fe controlling for each of the other pollutants, 1998-2013 cold-season analysis including all days with data available for each pollutant.



eFigure 2.9. Estimated associations between cardiovascular ED visits and pollutants only available during 2008-2013 using single-pollutant models, year-round analysis including all days with data available for each pollutant.



Chapter 3

Joint effects of ambient air pollutants on pediatric asthma in multiple U.S. cities

Dongni Ye, Mitchel Klein, Howard H. Chang, Jeremy A. Sarnat, James A. Mulholland, Stefanie Ebelt Sarnat

INTRODUCTION

Ambient air pollution is a complex mixture of gaseous pollutants and particulate matter varying in size and composition. While multiple pollutants may impact a health outcome, traditionally, epidemiologic studies estimate health associations of individual pollutants using single-pollutant models.[1] The observed health associations of a given pollutant could differ across study locations (e.g., cities) due to several reasons: 1) co-pollutant confounding where pollutant co-variations differ by city; 2) effect modification by other pollutants where pollution levels differ by city; 3) non-linear dose-response where pollution levels differ by city; 4) effect modification by factors other than pollution (e.g., population characteristics, meteorological conditions) where these factors differ by city; 5) differential measurement error across cities; and 6) random error. These issues complicate the interpretation and generalizability of health associations of individual pollutants across cities.

In recent years, various "multi-pollutant" approaches have been employed to estimate health effects of air pollution mixtures.[2-5] These approaches include the use of source apportionment metrics, principal components, broad indices of pollution (e.g., traffic intensity), air quality indices, and the sum of pollutant concentrations in replacement of the single-pollutant term in regression models; the estimation of joint effect of multiple pollutants in parametric and non-parametric models; and the application of statistical learning algorithms to identify pollutant combinations that could be responsible for health outcomes.[2-4, 6-11]

Considering a hypothetical joint effect of all pollutants changing from one set of concentrations to another provides a way to conceptualize health effects of the total

pollution mixture, although it is not achievable in reality given that only a limited number of pollutants could be identified and measured. And even such a hypothetical joint effect could depend on factors other than pollution (e.g., population characteristics, meteorological conditions). Nonetheless, perhaps joint effects of multiple pollutants could be similar across cities given that 1) a joint effect would not be confounded by pollutants that are part of the joint effect and that 2) a joint effect could account for potential pollutant interactions and non-linear dose-response in the estimation to reflect health impacts of simultaneous exposures to multiple pollutants.

In this study, we estimated joint effects of a set of ambient air pollutants on emergency department (ED) visits for pediatric asthma in a time-series framework. We considered criteria gases and major components of fine particulate matter as part of the joint effect because they dominate ambient air pollution, are routinely measured, and many of them are thought to impact respiratory health according to previous studies.[12] We estimated the joint effects in four cities to evaluate whether joint effect estimates are similar across cities. How well a joint effect estimate reflects the health impact of multiple pollutants also depends on the specification of pollutant interactions and dose-response shape. Here, we explored different specifications of pollutant interactions and the shape of dose-response in the joint effect estimation. This study builds on our prior research of ambient air pollution and emergency department visits conducted through the Study of Particles and Health in Atlanta (SOPHIA) and the Southeastern Center for Air Pollution and Epidemiology (SCAPE).[13-16]

METHODS

Emergency department visits

We obtained daily counts of emergency department (ED) visits of pediatric asthma (5-18 year-olds) for patients living in the following four metropolitan areas: 20-county Atlanta (years 2002-2008), 12-county Dallas (years 2006-2008), 16-county St. Louis (years 2002-2007), and 3-county Pittsburg (years 2002-2008). Daily counts of ED visits were aggregated from individual-level billing records from individual hospitals and the Georgia Hospital Association for Atlanta, from Dallas Fort Worth Hospital Council Foundation for Dallas, from the Missouri Hospital Association for St. Louis, and from individual hospitals in Pittsburg. We identified ED visits for pediatric asthma as those between 5-18 years old with primary ICD-9 diagnosis codes for asthma (493) or wheeze (786.07).

Air pollution data

Estimates of daily ambient air pollutant concentrations at 12-km spatial resolution were produced by fusing the Community Multi-Scale Air Quality (CMAQ) model simulations and the ground-level measurements using the approach developed by Friberg et al.[17-19] Daily population-weighted average exposures to ambient air pollutants were obtained based on the CMAQ-fused pollutant concentration estimates. Data include 1-hour maximum carbon monoxide (CO), 1-hour maximum nitrogen dioxide (NO_2), 1-hour maximum sulfur dioxide (SO_2), 8-hour maximum ozone (O_3), and 24-hour average fine particulate matter ($PM_{2.5}$, particulate matter with aerodynamic diameter of 2.5 μm or less) and its major components - organic carbon (OC), elemental carbon (EC), nitrate (NO_3), sulfate (SO_4), and ammonium (NH_4).

Analytic approach

In a time-series framework, we estimated the associations between daily concentrations of air pollutants and daily counts of ED visits for pediatric asthma in each city using Poisson generalized linear models accounting for over-dispersion. Based on our previous research of ambient air pollution and ED visits for asthma,[13, 14] we used the 3-day moving average (of lags 0, 1, and 2) pollution level.

All models included the same covariate control for temporal trends and meteorology: time splines with monthly knots, cubic function of same-day maximum temperature, cubic function of lag 1-2-day moving average minimum temperature, cubic function of lag 0-1-2-day moving average mean dew point temperature, day of week, indicators for holidays, seasons, season-maximum temperature interaction, season-day of week interaction, and indicators for hospital participation periods.

Estimation of individual pollutant associations

We used single-pollutant models to estimate the associations between asthma ED visits and individual pollutants in each city. The estimated associations were reported as rate ratios (RR) per interquartile range (IQR) increase in pollutant concentrations. To facilitate comparison across cities, we used the average IQR of pollutant concentrations across the four cities (Table 3.1).

Estimation of joint effects

We used multi-pollutant models to estimate joint effects of criteria gases and $PM_{2.5}$ components in each city (i.e., CO, NO_2, SO_2, O_3, OC, EC, and SO_4). We did not include NO_3 in the joint effect estimation because its associations with asthma in single-pollutant models were close to the null in all cities. We did not include NH_4 as NH_4 mainly exist as $(NH_4)_2SO_4$ and NH_4NO_3.

We first estimated the joint effect of the above seven pollutants, assuming linear dose-response for each pollutant and no pollutant interaction. To consider potential pollutant interactions, we estimated the joint effects of the seven pollutants including all pairwise multiplicative interactions in the model (using linear terms for pollutants). Because the inclusion of a large number of interaction terms could lead to model instability and interaction may not present for every pollutant pair, we then tried to identify a subset of pollutant interactions that may exist across cities. To identify pollutant interactions, we added 2-way multiplicative interaction of each pollutant pair one at a time to the 7-pollutant model, and selected interaction terms whose estimates were in the same direction in all cities (i.e., all positive or all negative), or in the same direction in three cities with at least one of them being significant at 0.1 level. We then estimated the joint effects of the seven pollutants with the identified interaction terms in the model. To consider potential non-linear dose-response, we estimated joint effects of the seven pollutants modeled as cubic polynomials.

The estimated joint effects were reported as rate ratios (RR) contrasting the seven pollutants at their 75^{th} to 25^{th} percentiles. We also plotted joint effect estimates contrasting all pollutants at their 15^{th}, 25^{th}, 35^{th}, 45^{th}, 55^{th}, 65^{th}, 75^{th}, 85^{th}, and 95^{th} percentiles to their 5^{th} percentiles. To facilitate comparison across cities, we use the averaged percentiles across the four cities (Table 3.1).

Sensitivity analysis

Previous studies have indicated that secondary organics are important for respiratory health.[20, 21] For a sensitivity analysis, we estimated joint effects of the seven pollutants plus a marker of secondary organics (2-butanone, a volatile organic compound) in

Atlanta. We chose this pollutant because a previous study found associations between 2-butanone and asthma ED visits in Atlanta.[22] We did not perform this analysis in the other three cities due to lack of measurements of volatile organic compounds.

RESULTS

Descriptive statistics of pollutants are listed in Table 3.1, and their Pearson correlations are listed in Supplementary eTable 3.1. Average concentrations of O_3 were generally similar across cities (mean percent difference=4%), while average concentrations of SO_2, EC, and NO_3 had greater variation across cities (mean percent differences are 31, 21, and 54%, respectively). Overall, during the respectively analytic time periods, Dallas had the lowest pollution level among four cities, especially for SO_2 and EC. Traffic-related primary pollutants such as CO, NO_2, and EC were moderate-to-high positively correlated with one another, while specific correlations differed across cities (r from 0.54 to 0.79). OC and EC are highly correlated (r from 0.62 to 0.78). SO_2 had weak-to-moderate positive correlations with other pollutants, with strongest correlations with EC. Among PM secondary ions, SO_4 and NH_4 are highly correlated with one another (r from 0.69 to 0.95). Pollutant correlations in Dallas are weak compared to other cities.

The average daily counts of emergency department visits for pediatric asthma were 24 in Atlanta 20-county area during 2002-2008, 25 in Dallas 12-county area during 2006-2008, 16 in St. Louis 16-county area during 2002-2007, and 7 in Pittsburgh 3-county area during 2002-2008.

We used single-pollutant models to estimate the associations between asthma ED visits and individual pollutants in each city (Figure 3.1). Most single-pollutant associations were positive. Associations of NO_3 were close to the null in all cities. The estimated

associations of O_3 and EC differ the most across cities – in St. Louis, O_3 had the highest estimated RR, while in Dallas, EC had the highest estimated RR.

We estimated joint effects of the seven pollutants – CO, NO_2, SO_2, O_3, OC, EC, and SO_4 – using linear terms for pollutants and without pollutant interactions. The joint effect estimates (contrasting 75^{th} to 25^{th} percentiles) were generally similar across cities (Table 3.2): $\widehat{RRs}$ (95% CIs) were 1.10 (1.04, 1.16) in Atlanta, 1.14 (1.03, 1.27) in Dallas, 1.16 (1.08, 1.24) in St. Louis, 1.08 (0.99, 1.18) in Pittsburgh.

We then estimated joint effects of the seven pollutants with all pairwise interactions. The estimated joint effects with all pairwise interactions (contrasting 75^{th} to 25^{th} percentiles) were weaker in Dallas and Pittsburgh compared to Atlanta and St. Louis (Table 3.2). In Dallas, $\widehat{RR}$ (using the 5^{th} percentiles as reference) increased as the contrast increased, peaked at the contrast of 65^{th} to 5^{th} percentiles, and decreased when the contrast increased further (Figure 3.2). As a result, the joint effect estimate contrasting 75^{th} to 25^{th} percentile was close to the null in Dallas (Table 3.2). Note that pollutant concentrations were relatively low in Dallas, especially for SO_2 and EC. For these two pollutants, concentrations equivalent to the four-city averaged percentiles of 75^{th} or above barely occurred in Dallas.

In models with all pairwise pollutant interactions, the estimates of individual pollutant terms appeared to be unstable (Supplement, eFigure 3.1b). To identify pollutant interactions that may be present in all cities, we added 2-way multiplicative interactions of each pollutant pair one at a time to the 7-pollutant model, and selected interaction terms whose estimates were in the same direction in all cities, or in the same direction in three cities with at least one of them being significant at 0.1 level. The following six

interaction terms met our criteria: CO-NO_2, SO_2-O_3, O_3-EC, O_3-OC, O_3-SO_4, and OC-SO_4. We estimated joint effect of the seven pollutants including the six interaction terms mentioned above. The estimated joint effects with the six interaction terms were generally similar to those estimated in models with no interaction (Figure 3.2). The estimated joint effects with the six interaction terms were similar across cities (Table 3.2 and Figure 3.2).

We also estimated joint effects of the seven pollutants modeled as cubic polynomials. Again, in Dallas, $\widehat{RR}$ (using the 5th percentiles as the reference) decreased once pollutant concentrations were above the 65th percentiles (Figure 3.2). The joint effect estimates contrasting 75th to 25th percentiles were highest in Atlanta and St. Louis, while close to the null in Dallas (Table 3.2).

In the sensitivity analysis, the estimated joint effects of the seven pollutants plus 2-butanone was 1.10 (1.03, 1.18), similar to that without 2-butanone.

DISCUSSION

Because multiple pollutants in the ambient air could affect respiratory health, in this study we are interested in the combined effect of the air pollution mixture. We included criteria gases and major PM components as part of the joint effect because these pollutants dominate ambient air pollution, are commonly measured, and previous studies have indicated their respiratory effects.[12]

The joint effect estimates were generally similar across cities ($\widehat{RR}_{\boldsymbol{s}}$ from 1.08 to 1.16 using the model with no interaction, Table 3.2). In one of the cities, where additional data on volatile organic pollutants were available, we compared joint effects with and without adding a marker of secondary organics (which were thought to affect respiratory health)

and found similar joint effect estimates. This result suggested that health effects of secondary organics was "captured" by the seven pollutants included in the joint effect (which was expected as ozone and organic carbon were included as part of the joint effect) if secondary organics have an effect and 2-butanone is a good marker.

One challenge of estimating joint effects of multiple pollutants is the potential for pollutant interactions and non-linear dose-response. As multiple pollutants could impact the same health outcome, health effects of a pollutant likely depends on the levels of other pollutants. Biologically, it is also plausible that different pollutants influence the same biological pathway at different stages.[23] In our analysis, we first estimated the joint effect with all pairwise interactions. The estimates of individual pollutant terms in this model appeared to be unstable (Supplement, eFigure 3.1b), although the joint effect estimates were reasonable. As interaction may not be present between every pollutant pair, we attempt to identify pollutant interactions that may exist. To do this, we added a 2-way interaction for each pollutant pair in the 7-pollutant model one at a time, and selected interaction terms whose estimates were similar across cities (i.e., same direction, or same direction in three cities with at least one of them being significant at 0.1 level). We used these criteria instead of relying on p-value alone because with 21 interaction terms in 4 cities (i.e., 84 terms in total), we would expect a number of these terms being significant by chance. In addition, we considered that if an interaction is present between two pollutants, this should apply to multiple cities. However, because of the selection criteria we used, the joint effect estimates with the selected interactions could be arbitrarily similar across cities. It is possible that 2-way interactions are truly different

across cities when the interaction terms depend on other pollutants or non-pollution factors (i.e., there could be 3-way or multi-way interactions).

As mentioned above, one source of variations in joint effect estimates across cities is the presence of effect modification by non-pollution factors, such as population susceptibility and meteorological factors. We did not evaluate the impact of these factors in this analysis. We tried to limit the impact of population susceptibility by focusing on pediatric asthma as opposed to asthma of all ages.

Another concern when comparing health effect estimates across cities is the impact of differential measurement error across cities. Using ground-level measurements from ambient monitoring sites may lead to differential measurement error across cities as the patterns of monitoring site placement often differ across cities (e.g., close to major roads or industrial area in one city but not in the other city). To mitigate the impact of differential measurement error on health effect estimation, we used population-weighted average exposure derived from the CMAQ-fused pollution concentration estimates. The CMAQ model is a chemical transport model that provides air pollution concentration simulations at fine-scale spatial resolution, and the CMAQ air pollution simulations were then calibrated using ground level air pollution measurement to provide CMAQ-fused air pollution estimates.[17, 18] However, as the quality of CMAQ simulations and the coverage of ground level measurements likely varies across regions, we still expect some degree of differential measurement error across cities.

A limited number of previous studies have estimated health effects of pollution mixtures on pediatric respiratory outcomes using the joint effect approach. Schildcrout et al. estimated joint effect on asthma exacerbation among children in eight cities in North

America, but only focused on joint effects of pairs of air pollutants.[24] Winquist et al., in a time-series study in Atlanta, U.S., estimated joint effects of different combinations of air pollutants on ED visits of pediatric asthma;[15] and Xiao et al., in a time-stratified case-crossover study of pediatric respiratory ED visits in Georgia, U.S., estimated joint effects of similar combinations of pollutants as Winquist et al.[25] However, their work only considered joint effects in one location. Other studies have investigated health effect of pollution mixtures using different approaches, including classification and regression tree analysis,[8] self-organizing map,[9] and Bayesian kernel machine regression.[26]

An understanding of the combined effect of pollution mixture could potentially inform multi-pollutant regulation and risk assessment.[27, 28] It is possible that some pollutants included in a joint effect estimation are not causal but they reflect the health impact of the pollution mixture due to co-variation with the causal agents. This should be considered when applying joint effect results in pollution regulation.

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Table 3.1. Summary statistics of pollutants in four cities

	Unit	Mean (sd)	Percentiles		
			25^{th}	50^{th}	75^{th}
Atlanta (2002-2008)					
CO	ppm	0.65 (0.29)	0.45	0.59	0.78
NO_2	ppb	21.58 (6.97)	16.60	21.18	26.11
SO_2	ppb	10.05 (6.90)	4.78	8.33	13.54
O_3	ppb	42.15 (17.34)	28.11	40.50	55.15
$PM_{2.5}$	$\mu g/m^3$	15.41 (7.12)	10.13	14.32	19.12
OC	$\mu g/m^3$	2.99 (1.54)	1.92	2.71	3.66
EC	$\mu g/m^3$	1.10 (0.59)	0.69	0.98	1.37
NO_3	$\mu g/m^3$	0.63 (0.57)	0.25	0.43	0.85
SO_4	$\mu g/m^3$	4.50 (2.99)	2.29	3.71	5.81
NH_4	$\mu g/m^3$	1.42 (0.86)	0.80	1.22	1.81
Dallas (2006-2008)					
CO	ppm	0.39 (0.20)	0.25	0.33	0.48
NO_2	ppb	19.68 (8.23)	13.21	18.52	25.50
SO_2	ppb	5.41 (3.90)	2.52	4.89	6.96
O_3	ppb	41.79 (14.38)	31.24	39.68	51.25
$PM_{2.5}$	$\mu g/m^3$	10.85 (4.70)	7.39	10.00	13.28
OC	$\mu g/m^3$	2.50 (1.24)	1.63	2.28	3.14
EC	$\mu g/m^3$	0.48 (0.19)	0.35	0.46	0.58
NO_3	$\mu g/m^3$	0.54 (0.71)	0.18	0.33	0.73

	Unit	Mean (sd)	Percentiles		
SO_4	$\mu g/m^3$	2.81 (1.85)	1.48	2.36	3.62
NH_4	$\mu g/m^3$	1.02 (0.68)	0.56	0.86	1.31
Pittsburgh (2002-2008)					
CO	ppm	0.49 (0.22)	0.33	0.43	0.58
NO_2	ppb	26.53 (8.14)	20.57	25.94	31.87
SO_2	ppb	20.23 (9.45)	13.17	18.75	25.16
O_3	ppb	37.47 (18.61)	22.78	35.03	50.96
$PM_{2.5}$	$\mu g/m^3$	15.01 (8.57)	8.79	12.94	19.17
OC	$\mu g/m^3$	3.75 (1.97)	2.35	3.32	4.71
EC	$\mu g/m^3$	0.93 (0.45)	0.60	0.87	1.18
NO_3	$\mu g/m^3$	2.12 (2.04)	0.67	1.46	2.94
SO_4	$\mu g/m^3$	4.91 (3.36)	2.59	3.92	6.19
NH_4	$\mu g/m^3$	1.79 (0.95)	1.11	1.61	2.26
St. Louis (2002-2007)					
CO	ppm	0.47 (0.22)	0.33	0.41	0.56
NO_2	ppb	21.28 (6.31)	16.85	21.08	25.67
SO_2	ppb	11.56 (5.43)	7.77	10.96	14.52
O_3	ppb	38.45 (17.03)	24.95	36.45	50.29
$PM_{2.5}$	$\mu g/m^3$	13.80 (6.69)	9.07	12.45	17.22
OC	$\mu g/m^3$	3.34 (1.64)	2.20	3.03	4.14
EC	$\mu g/m^3$	0.69 (0.33)	0.47	0.63	0.84
NO_3	$\mu g/m^3$	2.12 (1.99)	0.65	1.46	3.02

	Unit	Mean (sd)	Percentiles		
SO_4	$\mu g/m^3$	3.37 (2.55)	1.69	2.66	4.09
NH_4	$\mu g/m^3$	1.69 (1.03)	0.96	1.43	2.21

Four-city

	Unit	Mean	% difference	Averaged percentiles		
				25th	**50th**	**75th**
CO	ppm	0.50	14%	0.34	0.44	0.60
NO_2	ppb	22.27	15%	16.78	21.68	27.29
SO_2	ppb	11.81	32%	7.06	10.73	15.04
O_3	ppb	39.96	5%	26.77	37.92	51.91
$PM_{2.5}$	$\mu g/m^3$	13.77	8%	8.85	12.43	17.20
OC	$\mu g/m^3$	3.14	15%	2.03	2.84	3.91
EC	$\mu g/m^3$	0.80	21%	0.53	0.73	0.99
NO_3	$\mu g/m^3$	1.35	54%	0.44	0.92	1.86
SO_4	$\mu g/m^3$	3.90	17%	2.01	3.16	4.92
NH_4	$\mu g/m^3$	1.48	15%	0.86	1.28	1.90

Table 3.2. Estimated joint effects of the seven pollutants on asthma ED visits (5-18 year-olds) in four cities, contrasting 75th to 25th percentiles[a]

$\widehat{RR}$ (95% CI)	Joint effect with no interaction[b]	Joint effect with all pairwise interactions[d]	Joint effect with six interactions[c]	Joint effect with pollutants modeled as cubic polynomials[e]
Atlanta	1.10 (1.04, 1.16)	1.13 (1.03, 1.24)	1.14 (1.06, 1.22)	1.22 (1.11, 1.33)
Dallas	1.14 (1.03, 1.27)	1.05 (0.78, 1.40)	1.11 (0.94, 1.30)	1.08 (0.82, 1.40)
Pittsburgh	1.08 (0.99, 1.18)	1.08 (0.95, 1.23)	1.12 (1.01, 1.25)	1.21 (1.06, 1.38)
St. Louis	1.16 (1.08, 1.24)	1.12 (1.10, 1.31)	1.16 (1.07, 1.26)	1.16 (1.05, 1.27)

[a]The seven pollutants include CO, NO_2, SO_2, O_3, OC, EC, and SO_4. Percentiles are averaged percentiles of the four cities

[b]Joint effect of the above seven pollutants, modeled using linear terms, no pollutant interaction.

[c]Joint effect of the above seven pollutants, modeled using linear terms, with the six selected interactions: CO-NO_2, SO_2-O_3, O_3-EC, O_3-OC, O_3-SO_4, and OC-SO_4.

[d]Joint effect of the above seven pollutants, modeled using linear terms, with all 21 pairwise interactions.

[e]Joint effect of the above seven pollutants, modeled using cubic polynomials.

Figure 3.1. Estimated associations between pediatric asthma ED visits (5-18 year-olds) and individual pollutants in four cities using single-pollutant models

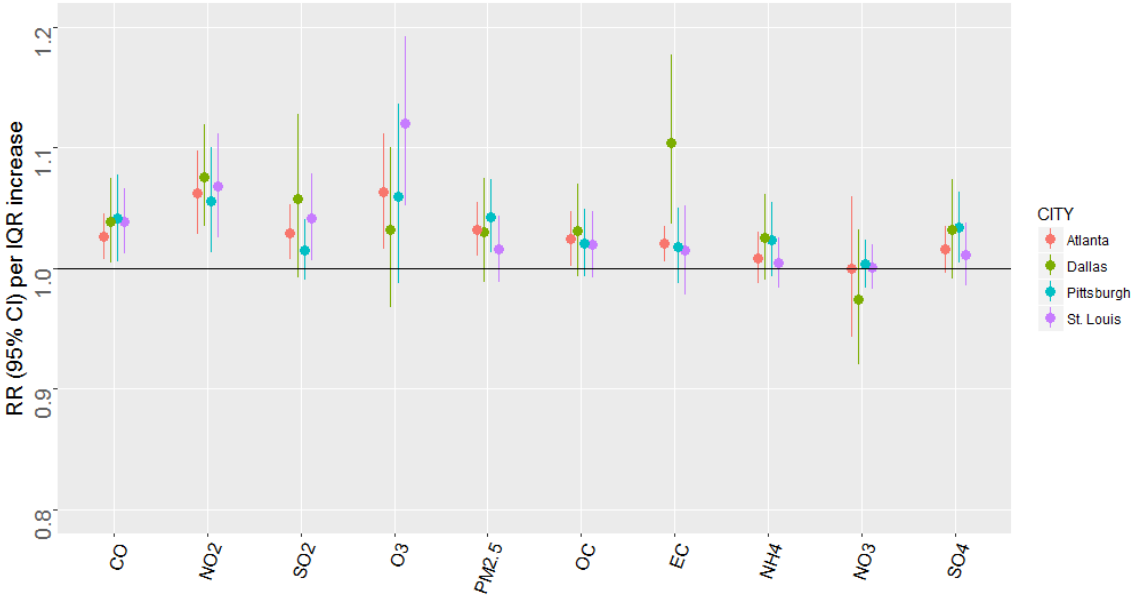
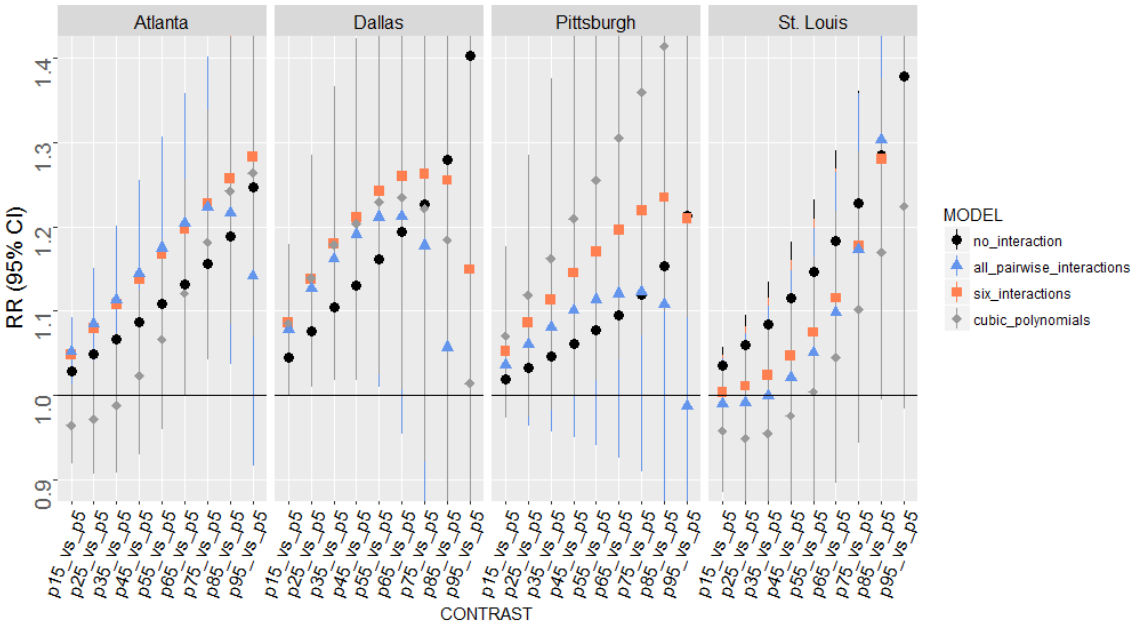


Figure 3.2. Estimated joint effects of the seven pollutants on asthma ED visits (5-18 year-olds) in four cities, contrasting pollutants at their 15th, 25th, 35th, 45th, 55th, 65th, 75th, 85th, and 95th percentiles to their 5th percentiles[a]



[a]The seven pollutants include CO, NO_2, SO_2, O_3, OC, EC, and SO_4. Percentiles are averaged percentiles of the four cities. The "no_interaction" model includes the above seven pollutants, using linear terms for pollutants and without pollutant interactions. The "all_pairwise_interactions" model includes the above seven pollutants, using linear terms for pollutants and with all pairwise pollutant interactions. The "six_interactions" model includes the above seven pollutants, using linear terms for pollutants and with the six selected pollutant interactions: CO-NO_2, SO_2-O_3, O_3-EC, O_3-OC, O_3-SO_4, and OC-SO_4. The "cubic_polynomials" model includes the above seven pollutants, modeled as cubic polynomials.

SUPPLEMENT

eTable 1. Pearson correlations among pollutants in four cities

Atlanta	CO	NO_2	SO_2	O_3	$PM_{2.5}$	OC	EC	NO_3	SO_4	NH_4
CO	1.00									
NO_2	0.79	1.00								
SO_2	0.26	0.39	1.00							
O_3	-0.11	0.02	0.02	1.00						
$PM_{2.5}$	0.28	0.26	0.07	0.61	1.00					
OC	0.61	0.57	0.15	0.32	0.68	1.00				
EC	0.77	0.73	0.22	0.07	0.50	0.76	1.00			
NO_3	0.40	0.44	0.27	-0.44	-0.03	0.20	0.29	1.00		
SO_4	0.01	-0.04	0.03	0.63	0.85	0.31	0.18	-0.23	1.00	
NH_4	0.05	0.02	0.04	0.55	0.86	0.35	0.23	-0.04	0.95	1.00

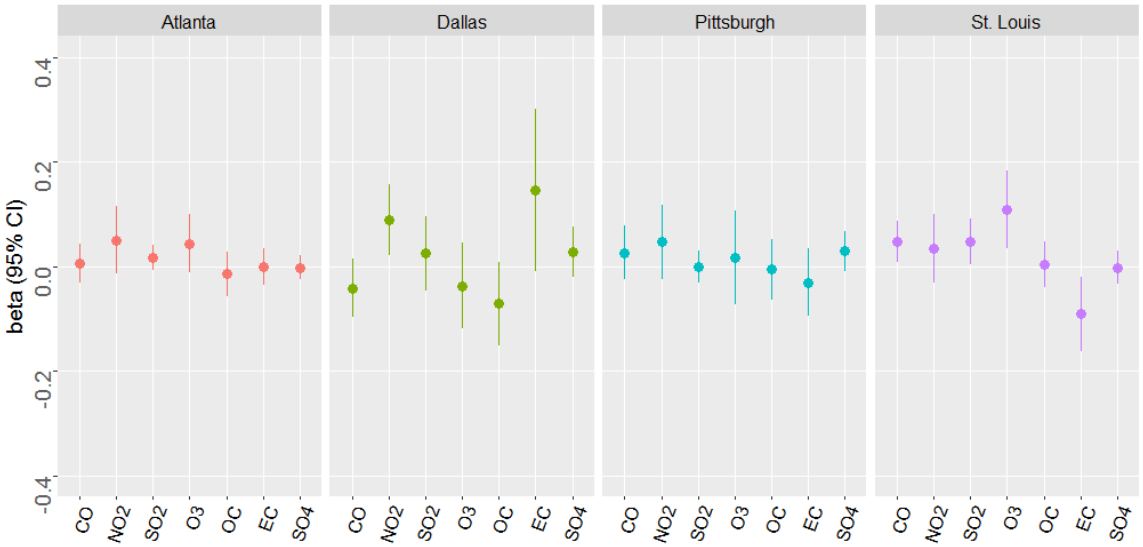
Dallas	CO	NO_2	SO_2	O_3	$PM_{2.5}$	OC	EC	NO_3	SO_4	NH_4
CO	1.00									
NO_2	0.79	1.00								
SO_2	0.35	0.33	1.00							
O_3	-0.07	0.12	0.09	1.00						
$PM_{2.5}$	-0.02	0.00	0.13	0.42	1.00					
OC	0.36	0.36	0.34	0.37	0.53	1.00				
EC	0.59	0.63	0.41	0.21	0.38	0.78	1.00			
NO_3	0.20	0.16	0.13	-0.39	0.07	0.12	0.16	1.00		
SO_4	-0.18	-0.14	-0.01	0.42	0.79	0.39	0.23	-0.01	1.00	
NH_4	-0.07	-0.01	0.03	0.28	0.73	0.42	0.28	0.35	0.88	1.00

Pittsburgh	CO	NO_2	SO_2	O_3	$PM_{2.5}$	OC	EC	NO_3	SO_4	NH_4
CO	1.00									
NO_2	0.71	1.00								
SO_2	0.47	0.50	1.00							
O_3	-0.11	0.17	0.02	1.00						
$PM_{2.5}$	0.45	0.51	0.46	0.47	1.00					
OC	0.43	0.54	0.44	0.42	0.79	1.00				
EC	0.55	0.54	0.49	-0.01	0.58	0.73	1.00			
NO_3	0.28	0.28	0.26	-0.33	0.11	0.20	0.41	1.00		
SO_4	0.20	0.30	0.32	0.57	0.81	0.62	0.39	-0.12	1.00	
NH_4	0.35	0.45	0.42	0.38	0.80	0.74	0.64	0.41	0.78	1.00

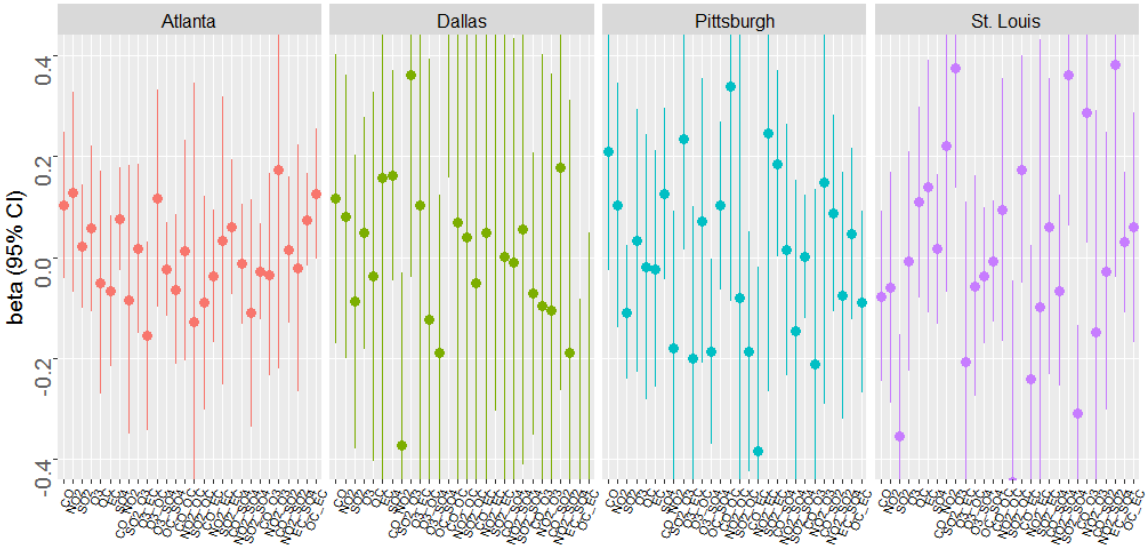
St. Louis	CO	NO_2	SO_2	O_3	$PM_{2.5}$	OC	EC	NO_3	SO_4	NH_4
CO	1.00									
NO_2	0.66	1.00								
SO_2	0.31	0.44	1.00							
O_3	-0.09	0.13	0.05	1.00						
$PM_{2.5}$	0.22	0.30	0.38	0.34	1.00					
OC	0.35	0.43	0.43	0.38	0.60	1.00				
EC	0.57	0.58	0.46	0.12	0.43	0.61	1.00			
NO_3	0.30	0.29	0.24	-0.40	0.30	0.09	0.26	1.00		
SO_4	0.05	0.15	0.22	0.51	0.82	0.43	0.32	0.02	1.00	
NH_4	0.23	0.31	0.33	0.07	0.77	0.37	0.37	0.65	0.69	1.00

eFigure 3.1. Beta estimates in the joint effect models in four cites

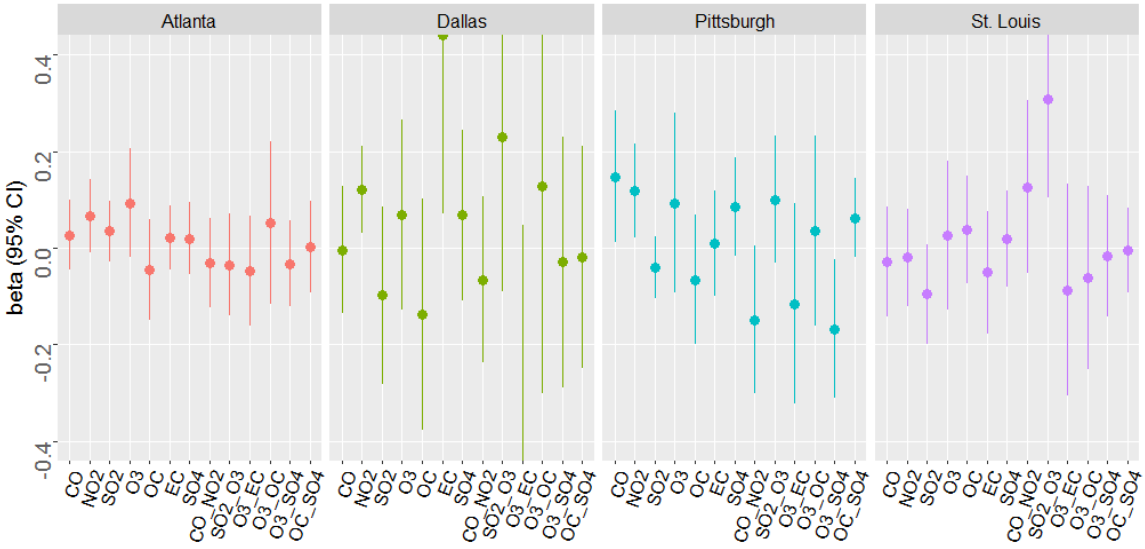
eFigure 3.1a. Beta estimates from the joint effect model in four cities, 75th vs. 25th percentiles, no interaction and using linear pollutant terms



eFigure 3.1b. Beta estimates from the joint effect model in four cities, 75th vs. 25th percentiles, including all pairwise interactions and using linear pollutant terms



eFigure 3.1c. Beta estimates from the joint effect model in four cities, 75th vs. 25th percentiles, including six interactions and using linear pollutant terms



eFigure 3.1d. Beta estimates from the joint effect model in four cities, 75th vs. 25th percentiles. Pollutants are modeled as cubic polynomials

CONCLUSION

As ambient air pollution is a complex mixture, there is an ongoing effort to identify its health-relevant components, and to estimate combined effects of the mixture. For Aim 1 and Aim 2, we investigated acute cardiorespiratory effects of a range of pollutants that were not well-studied previously, as an attempt to gain a better understanding of the causal agents in air pollution mixtures. For Aim 3, we estimated joint effects of multiple pollutants and compared joint effect estimates across cities.

Specifically, in Aim 1, we estimated acute cardiorespiratory effects of a large number of volatile organic compounds (VOCs) in a coherent manner by grouping them based on chemical structure and estimating VOC group effects. Our findings further support the link between incomplete combustion products and cardiovascular health, and between atmospheric oxidation products and respiratory health. In Aim 2, we estimated acute cardiovascular effects of ambient $PM_{2.5}$ components, including a suite of water-soluble metals that are not routinely measured at the ambient level. Our results suggest that certain water-soluble metals (particularly water-soluble iron) or species from roadway emissions have an impact on cardiovascular health. In Aim 3, we estimated joint effects of major pollutants in the ambient air and found that joint effect estimates were generally similar across cities.

To understand the health effects of a pollution mixture is challenging. For example, to identify causal agents in a mixture, we may start with the question, "what pollutants or groups of pollutants are harmful in a pollution mixture?" However, when an association is found between a specific pollutant and a health outcome, the question becomes, "Does the observed association with the pollutant represent the health effects of some

unmeasured pollutants in certain pollution mixtures?" This seemingly circular process largely arises from the fact that pollutants are correlated with one another and that individual pollutants cannot all be enumerated. And even if all pollutants could be measured, it would still be a challenge to handle a large number of pollutants in health effect estimation. Nonetheless, our work in Aim 1 and Aim 2 helped to advance the understanding of the health relevance of trace pollutants that were not well-studied previously, and our results point to future directions to better address this question. For example, we learned in Aim 1 that atmospheric oxidation products may affect respiratory health, and that ozone, the traditional marker for photochemical oxidants, may not fully represent the health effects of oxidation products – a follow-up question arising from our work is whether it would be helpful to monitor secondary organic pollutants and to understand their respiratory effects in order to better protect human health. We also learned in Aim 1 and Aim 2 that both organic pollutants from traffic exhaust and metals from mechanical abrasion during traffic appear to affect cardiovascular health – follow-up questions arising from our work include: 1) whether organics and metals are different surrogates of the traffic pollution or they both have an effect on cardiovascular health, and 2) whether there is synergism between organic pollutants and metals.

Another perspective in understanding the health impact of a pollution mixture is to estimate its combined effect. In Aim 3, we estimated joint effects of seven pollutants that dominate ambient urban pollution and that might have an impact on the health outcome (pediatric asthma). Given that only a limited number of pollutants were measured and included as part of the joint effect, a key question is what the joint effect of the seven pollutants represents. As it is unlikely that these seven pollutants contain all the causal

agents in the air pollution mixture, this 7-polluant joint effect may not represent health impact of the total pollution mixture. Rather, it could represent health effects of different mixtures in different cities, if co-variations among pollutants differ across cities. Thus, a following question is: if the joint effect estimates are similar across cities, does this suggest that the joint effect of the seven pollutants is close to the health impact of the total pollution mixture? Our work in Aim 3 is exploratory given the limited number of pollutants available and the limited number of cities for comparison. Another issue that underlies the understanding of the combined effects of pollution mixtures is the presence of potential interactions among pollutants, and the potential heterogeneity in the patterns of pollution interactions across cities. Further investigations would be needed to address these questions.

Because the magnitudes of effects of air pollution are relatively small, our conclusions could be easily influenced by sources of error (e.g., confounding, measurement error, and chance). Specifically, in Aim 1 and Aim 2, air pollution measurements were obtained from a single ambient monitor in Atlanta. Temporal variation of a pollutant at one location may not be representative of the variation in the entire city. Thus, our results are subject to spatial misalignment, and the degree of its impact likely differs by pollutant. Compared to secondary pollutants, primary pollutants are likely to be more subject to spatial misalignment due to greater spatiotemporal variability. In addition, pollutants with lower ambient concentrations are likely to be more subject to instrument measurement error. Thus, the comparison of health associations across pollutants should be made in light of these limitations.

Our long time-series of daily measurements of a broad range of air pollutants as well as the collection of emergency department visits data provide a unique opportunity to estimate health effects of pollutants that were not well-understood previously. The availability of speciated pollution measurements also raises the question of how to understand health effects of a large number of pollutants in a coherent manner. High-dimensionality is a key challenge in investigating health effect of pollution mixtures, and various dimension-reduction techniques have been developed to solve this problem. Our work for Aim 1 tackled this issue by grouping pollutants based on a priori knowledge rather than based on statistical relationships in the data. One advantage of our approach is that the group definition is not specific to the data, which allows for replications in future studies. Model instability could be a concern in our study when including multiple correlated pollutants in a single model. However, in our study, the long time-series of relatively abundant daily outcome events allows for a higher degree of collinearity with less impact on health effect estimates than would be the case for a study with fewer observations.

Ambient measurements of trace pollutants, while costly, allow further investigations of causal agents in air pollution mixtures. Our studies in Atlanta (Aims 1 and 2) advance the understanding of cardiovascular health effects of organic pollutants from incomplete combustion and metals from roadway emission, as well as respiratory effects of atmospheric oxidation products. As a future direction, it would be a benefit to have these findings validated in other cities. In Aim 3, we only considered major pollutants in the joint effect estimation. For the future, based on our findings, it would be interesting to include trace pollutants as part of the joint effect. In order to assess the homogeneity of

joint effects across cities, it would beneficial to include more cities than we currently have.

Overall, our work contributes to the ongoing effort to identify health-relevant components of ambient air pollution and to estimate combined effects of pollution mixtures. Our findings could potentially inform multi-pollutant regulation and health impact assessment.