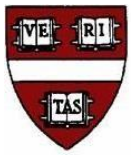
The Effects of Ambient Air Pollution and Particle Radioactivity on Cardiovascular Health

HARVARD UNIVERSITY

Graduate School of Arts and Sciences



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The undersigned, appointed by the
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"The Effects of Ambient Air Pollution and Particle Radioactivity on Cardiovascular Health"

presented by

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Date: August 28, 2020

THE EFFECTS OF AMBIENT AIR POLLUTION AND PARTICLE RADIOACTIVITY ON CARDIOVASCULAR HEALTH

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A Dissertation Submitted to the Faculty of

The Graduate School of Arts and Sciences

in Partial Fulfillment of the Requirements

for the Degree of Doctor of Philosophy

in the Department of Environmental Health

Harvard University

Boston, Massachusetts.

August 2020

Dissertation Advisor: Dr. Petros Koutrakis Adjani Antonela Peralta

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ABSTRACT

Exposure to ambient air pollution is a well-recognized risk factor for cardiovascular morbidity and mortality. Studies have shown that air pollution, especially acute exposure to traffic and industrial sources, can influence the autonomic nervous system and in turn affect heart rate variability leading to arrhythmias. While some studies examine acute air pollution effects on ventricular arrhythmias or heart rate corrected QT interval (QTc), few have explored both acute and long-term effects in a mixture of components. Studies tend to focus on fine particulate matter, which can penetrate deep into the lungs due to its smaller size and deposit a large spectrum of organic and inorganic elements[1]. However, fewer studies have examined which specific elements of fine particulate matter can contribute to cardiovascular toxicity. This dissertation investigates how multiple components of ambient air pollution can impact cardiovascular health. We hypothesized that different components of fine particulate matter may have a direct impact on arrythmias and ventricular repolarization. In particular, we theorized that all the $PM_{2.5}$ components would either increase the risk for ventricular arrythmias or prolong QT interval, but we expected $PM_{2.5}$ mass, lead, nickel and elemental carbon to have the largest adverse effects based on past literature.

In our first study, we assessed the association of the onset of ventricular arrhythmias with 0-21 day moving averages of $PM_{2.5}$ and particle radioactivity using time-stratified case-crossover analyses among 176 patients with dual-chamber implanted cardioverter-defibrillators in Boston, Massachusetts. We found that in this high-risk population, independently of particle radioactivity, 21-day $PM_{2.5}$ exposure was associated with higher odds of a ventricular arrhythmia event onset among patients with known cardiac disease and indication for ICD implantation.

In our second study, we utilized time-varying linear mixed-effects regressions with a random intercept for each participant to analyze associations between QTc interval and moving averages (0 to 7 day moving averages) of 24-hour mean concentrations of $PM_{2.5}$ metal components (vanadium, nickel, copper, zinc and lead) in the Normative Aging Study. We found that exposure to metals (especially lead and copper) contained in $PM_{2.5}$ were associated with acute changes in ventricular repolarization as indicated by prolonged QT interval length.

Finally, we utilized time-varying linear mixed-effects regressions to examine associations between acute (0-3 day), intermediate (4-28 day) and long-term (1 year) exposure to components of fine particulate air pollution ($PM_{2.5}$ mass, elemental carbon, organic carbon, nitrate, sulfate, ozone), temperature and heart-rate corrected QT interval (QTc). We also evaluated whether diabetic status would modify the association between the $PM_{2.5}$ components and QTc interval. We found consistent results that higher sulfate levels were associated with significant longer QTc across all moving averages and that organic carbon also increased QTc interval, but for different time periods depending on the model. We found that diabetic status could amplify the association between certain $PM_{2.5}$ components (elemental carbon, nitrate, organic carbon and sulfate) and QTc interval.

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ACKNOWLEDGMENTS

The completion of my dissertation would not have been possible without the support and help from many individuals. I would first like to thank my advisor, Dr. Petros Koutrakis, for his mentorship throughout my doctoral program. Each of my committee members provided not only their guidance, but also their full-hearted support for which I am grateful. Dr. Joel Schwartz adopted me into his research group and provided guidance on epidemiological topics while Dr. Brent Coull provided vital assistance with statistical analyses and questions. Dr. Diane Gold provided an invaluable clinical perspective that guided me towards cardiovascular epidemiology. I would also like to highlight the support from fellow PhD and SD students throughout the whole PhD process. In particular, I would like to highlight Mahdieh Danesh Yazdi (work wife extraordinaire) and Geetha Iyer for not only their friendship, but also the bubble tea breaks and epidemiological squabbles. Finally, I could not have completed this degree without the love and encouragement of my friends and family. Thank you, Mom/the alhe4 crew (Adjani, Lucia, Hazel and Estrella = 4) for helping me to follow my dreams. Thank you to all of the Donkers for encouraging me from the other side of the Atlantic.

I would specifically like to dedicate this dissertation to my mami, Estrella Rochelli, for her endless love, support, and encouragement.

INTRODUCTION

Exposure to ambient air pollution is a well-recognized risk factor for cardiovascular morbidity and mortality[2–5]. Acute exposure to traffic and industrial sources of particulate matter have been linked to the onset of myocardial infarctions[6] and markers of autonomic function such as lower heart rate variability[7], increased heart rates[8] and a greater risk of cardiac arrhythmias[9]. Studies estimate that chronic exposure to air pollution increases all-cause mortality by 2-4% for each 10 $\mu g/m^3$ increase in particulate matter[10,11] and that the majority of air pollution related deaths occur via cardiovascular disease[12]. In 2016, the World Health Organization (WHO) estimated that ambient air pollution caused 4.2 million premature deaths worldwide and that 58% of the deaths were due to ischemic heart disease and strokes[13].

Studies have shown that air pollution can influence the autonomic nervous system and in turn affect heart rate variability leading to arrhythmias. While some studies examine acute air pollution effects on ventricular arrhythmias or heart rate corrected QT interval (QTc), few have explored both acute and long-term effects in a mixture of components. Among elderly men without any clinically apparent heart disease, detection of asymptotic ventricular arrythmias was associated with a two-fold increase in the risk for all-cause mortality and myocardial infraction or death from coronary heart disease[14]. The QT interval measured from electrocardiograms (ECG) provides a non-invasive method to assess for the risk of ventricular arrhythmias. Prolongation of the QT interval can prompt an individual to experience torsades de pointes a potentially fatal type of ventricular arrythmia[15]. Studies tend to focus on fine particulate matter ($PM_{2.5}$), which can penetrate deep into the lungs due to its smaller size and deposit an a large spectrum of organic and inorganic elements[1]. However, fewer studies have examined which specific elements of $PM_{2.5}$ that can contribute to cardiovascular toxicity.

Particle radioactivity is an often-disregarded component of fine particulate matter. Exposure to this natural radiation can occur externally from cosmic or terrestrial radiation or internally through inhalation or ingestion. The National Council on Radiation Protection and Measurements found that individuals in the U.S. received 73% of their average annual dose of natural radiation through the inhalation of radon and thoron and their progeny[16,17]. Radon and thoron formed by the decay of radium and thorium diffuse through the ground, enter the atmosphere, and decay to solid progeny. These can attach to existing aerosol particles to form radioactive aerosols. Studies have shown that the majority of radioactive progeny attach to fine particles (particulate matter $\leq$2.5 μm aerodynamic diameter; $PM_{2.5}$)[18–20]. Since $PM_{2.5}$ can penetrate deep into the lung and enter circulation[21,22], these radioactive aerosols may deposit ionizing radiation into the bronchial passages and alveoli and induce adverse health effects.

Studies have highlighted the increased risk of cardiovascular diseases and mortality related to high levels of ionizing radiation from the nuclear spills and occupational hazards at nuclear power plants or uranium mining[23–28]. Radiation therapy for the treatment of benign or cancerous tumors has also been associated with the incidence and progression of cardiovascular morbidity[29–31]. A few studies have looked at the potential cardiovascular effects of low-level radiation associated with air pollution particles[32,33]. None of these studies, however, have looked at arrhythmias specifically.

The chemical components of $PM_{2.5}$ can be found both inside and on the surface of the particle. While there are both natural and anthropogenic sources for these chemical components, anthropogenic sources consist of auto vehicle emissions, industrial activity, fossil fuel combustion, burning of fuel oil and smoking byproducts[34–37]. Past studies have found that the chemical composition of $PM_{2.5}$ could contribute to daily average mortality. A study conducted in New York

City found that vanadium and nickel, associated with burning of fuel oils, increased the daily average mortality[38]. Furthermore, a study conducted in 26 U.S. cities found that nickel significantly modified that association between $PM_{2.5}$ mass and daily cardiovascular hospital admissions[39].

$PM_{2.5}$ components can either be directly emitted into the atmosphere (primary components) or are particles that are generated through chemical reactions in the atmosphere (secondary components)[40]. A previous study found that exposure to black carbon in the previous hour was associated with an increased QTc (2.54 ms; 95% CI: 0.28, 4.80) while no association was found between QTc and $PM_{2.5}$ mass, sulfur dioxide and ozone[41]. Furthermore, a separate study found that temperature was associated with a longer QTc interval for moving averages between 4 to 28 days[42]. However, these studies utilized central site monitoring data as a proxy for personal exposure.

Irregularities in cardiac repolarization significantly contribute to the production of cardiac arrhythmias[43]. ECG measurements of repolarization such as QT interval provide non-invasive indicators for possible cardiac arrhythmias and help identify patients susceptible to sudden cardiac death[44,45]. A previous study conducted in the NAS found a positive association between sub-chronic and long-term $PM_{2.5}$ exposure and QTc interval, but did not assess how the individual metal components of $PM_{2.5}$ could impact cardiac repolarization[46].

The underlying mechanisms of the association between ambient air pollution and cardiovascular morbidity are only partly understood, particularly for mixtures of air pollution components. Here we perform three different analyses, to assess which contributions of $PM_{2.5}$ exposure lead to cardiovascular toxicity. First, we explore particle radioactivity as a contributing component in the association of air pollution with ventricular arrhythmias. Second, we focus on a mixture of $PM_{2.5}$ metal components to determine which metals can cause adverse effects on

ventricular repolarization. Third, we focus on geocoded $PM_{2.5}$ components to explore which components can lead to a prolonged QTc interval, a risk factor for arrythmias.

CHAPTER 1: Exposure to air pollution and particle radioactivity with the risk of ventricular arrhythmias

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Short title: Air Pollution's Impact on Ventricular Arrhythmias

Non-standard Abbreviations and Acronyms

ICDs Implanted cardioverter-defibrillators

VA ventricular arrhythmias

$PM_{2.5}$ fine particulate matter

IQR interquartile range

AF atrial fibrillation

VT ventricular tachycardia

VF ventricular fibrillation

NSVT non-sustained ventricular tachycardia

NSVF non-sustained ventricular fibrillations

TSP total suspended particles

BMI body mass index

CHF congestive heart failure

Abstract

Background: Individuals are exposed to air pollution and ionizing radiation from natural sources through inhalation of particles. This study investigates the association between cardiac arrhythmias and short-term exposures to fine particulate matter ($PM_{2.5}$) and particle radioactivity.

Methods: Ventricular arrhythmic events were identified among 176 patients with dual-chamber implanted cardioverter-defibrillators (ICDs) in Boston, Massachusetts between September 2006 and June 2010. Patients were assigned exposures based on residential addresses. Daily $PM_{2.5}$ level was estimated at 1-km×1-km grid cells from a previously validated prediction model. Particle gross β activity was used as a surrogate for particle radioactivity and was measured from several monitoring sites by the U.S. Environmental Protection Agency's monitoring network. The association of the onset of ventricular arrhythmias (VA) with 0-21 day moving averages of $PM_{2.5}$ and particle radioactivity (two single-pollutant models and a two-pollutant model) prior to the event were examined using time-stratified case-crossover analyses, adjusted for dew point and air temperatures.

Results: A total of 1,050 VA were recorded among 91 patients, including 123 sustained VA among 25 of these patients. In the single-pollutant model of $PM_{2.5}$, each interquartile range (IQR) increase in daily $PM_{2.5}$ levels for a 21-day moving average was associated with 39% higher odds of a VA event (95% CI: 12% to 72%). In the single-pollutant model of particle radioactivity, each IQR increase in particle radioactivity for a 2-day moving average was associated with 13% higher odds of a VA event (95% CI: 1% to 26%). In the two-pollutant model, for the same averaging window of 21-days, each IQR increase in daily $PM_{2.5}$ was associated with an 48% higher odds of a VA event (95% CI: 15 to 90%), and each IQR increase of particle radioactivity with a 10% lower odds

of a VA event (95% CI: -29% to 14%). We found that with higher levels of particle radioactivity, the effect of $PM_{2.5}$ on ventricular arrhythmias is reduced.

Conclusions: In this high-risk population, intermediate (21-day) $PM_{2.5}$ exposure was associated with higher odds of a ventricular arrhythmia event onset among patients with known cardiac disease and indication for ICD implantation independently of particle radioactivity.

Clinical Perspective

1) What is new?

- Study found that radioactive properties of particle matter and total fine particle mass were associated with cardiovascular health (ventricular arrhythmias) in patients with implanted cardioverter-defibrillators.
- Study population consisted of patients at high risk for ventricular arrhythmias.
- To address combined associations, study includes a dual pollutant model.

2) What are the clinical implications?

- Particle air pollution and its radioactive components contribute significantly to the risk of acute clinically relevant electrophysiologic cardiac outcomes in high risk patients.
- Cardiovascular patients and those at high risk for cardiovascular events should be informed about the risks associated with air pollution and the onset of arrhythmias.

Introduction

Both short and long-term exposure to particulate air pollution have been associated with cardiovascular morbidity[2,47,48] and mortality[3,4]. Studies have shown that air pollution can influence the autonomic nervous system and in turn affect heart rate variability leading to arrhythmias[49–52]. While some studies examine acute air pollution effects on ventricular arrhythmias, few have explored both short and intermediate effects.

More recent research has tried to identify the relevant toxic components of particulate matter, which lead to cardiovascular events. Here we perform a novel analysis, assessing particle radioactivity as a contributing component in the association of air pollution with ventricular arrhythmias.

Individuals receive exposure to ionizing radiation from a variety of natural sources: decay products of radon (^{222}Rn) and thoron (^{220}Rn), cosmic radiation and natural radioactivity found in soil and food[53,54]. Exposure to this natural radiation can occur externally from cosmic or terrestrial radiation or internally through inhalation or ingestion. The National Council on Radiation Protection and Measurements found that individuals in the U.S. received 73% of their average annual dose of natural radiation through the inhalation of radon and thoron and their progeny[16,17]. Radon and thoron formed by the decay of radium and thorium diffuse through the ground, enter the atmosphere, and decay to solid progeny. These can attach to existing aerosol particles to form radioactive aerosols. Studies have shown that the majority of radioactive progeny attach to fine particles (particulate matter $\leq$2.5 μm aerodynamic diameter; $PM_{2.5}$)[18–20]. Since $PM_{2.5}$ can penetrate deep into the lung and enter circulation[21,22], these radioactive aerosols may deposit ionizing radiation into the bronchial passages and alveoli and induce adverse health effects.

Many studies have highlighted the increased risk of cardiovascular diseases and mortality related to both short- and long-term exposure to high levels of ionizing radiation from the atomic bomb, nuclear spills, and occupational hazards at nuclear power plants or uranium mining[23–28]. Radiation therapy for the treatment of benign or cancerous tumors has also been associated with the incidence and progression of cardiovascular disease[29–31]. In particular, radiation therapy for breast cancer and Hodgkin's lymphoma have been implicated in the development of cardiovascular disease, even though the targeted organs did not include the heart[55–57]. Recently, a few studies have looked at the potential cardiovascular effects of low-level radiation associated with air pollution particles[32,33]. None of these studies, however, has looked at arrhythmias specifically.

We examined the associations of short- and medium-term $PM_{2.5}$ and particle radioactivity with the odds of ventricular arrhythmias both independently and together in a two-pollutant model. We used the detected ventricular arrhythmic onset events from dual-chamber implanted cardioverter-defibrillators (ICDs) from a longitudinal study of cardiac patients in Massachusetts. This is the first study to assess the effects of radioactive properties of particle matter on cardiovascular health through increases in ventricular arrhythmias and the first to report the effects of fine particulate matter in the ICD cohort.

Methods

Patient Population

Our patient population has been previously described[58]. In brief, patients were recruited from the Tufts Medical Center's Cardiac Arrhythmia Center in Boston, Massachusetts

between September 2006, and March 2010. The study included patients with prior implantation of a dual (atrial and ventricular) chamber ICD and who were older than 18 years of age. Patient exclusion criteria included chronic atrial fibrillation (AF), diagnosis of a terminal disease, or the inability to provide informed consent.

During their first study visit, after obtaining informed consent, patients participated in an interview-administered questionnaire collecting individual characteristics and sociodemographic factors. To obtain a complete medical history, information from each of the patient's medical records was recorded on a form based on the National Cardiovascular Disease Data ICD Registry form[58]. Authors will not make their data available to other researchers due to the sensitive nature of the data collected for this study. The Institutional Review Boards at Tufts Medical Center and at the Harvard T.H. Chan School of Public Health approved the study protocol.

Ventricular arrhythmias

Information was collected from the implanted ICD devices beginning at a patient's enrollment until June 30, 2010. The ICD provided an arrhythmia logbook and electrograms by direct download during a follow-up visit at the clinic or wirelessly via trans-telephonic transmission[58]. These records recorded information of any detected atrial or ventricular arrhythmic event and classified each episode as sustained or non-sustained. The treating physician programmed each device to detect and respond to certain heart rate thresholds according to the patient's needs[58].

Once clinicians downloaded the information, an electrophysiologist blinded to the particle radioactivity and air pollution data reassessed any suspected arrhythmia. Each confirmed ventricular arrhythmia was classified as a ventricular tachycardia (VT) or ventricular fibrillation (VF) that was treated by the ICD (sustained), non-sustained VT or VF (not treated by the ICD),

sinus tachycardia, atrial fibrillation (AF), atrial arrhythmia other than AF, or not an arrhythmia. Sinus tachycardia events, noise, or oversensing recordings were disregarded following previous study protocols that also utilized the same cohort[58]. Further information about the classification of arrhythmias for this cohort can be found in Link et al. (2013).

The primary endpoint was all detected ventricular arrhythmias (sustained and non-sustained ventricular arrhythmias) and our secondary endpoint was sustained ventricular arrhythmias that required intervention by the ICD. The study excluded events that arose during the first 6 weeks after implantation of the ICD or events when the individual was admitted to a health care facility. Multiple events could occur on the same calendar day, but were only included if they were separated by a period of at least 60 minutes. An event day was characterized as a calendar day when one or more ventricular arrhythmias occurred.

Individuals were assigned exposures by linking their residential addresses to the closest $PM_{2.5}$ or meteorological grid cell or the nearest particle radiation monitoring station.

$PM_{2.5}$ and meteorological variables

We retrieved daily $PM_{2.5}$ predictions at 1-km × 1-km grid cells in the continental U.S. using a well-validated model incorporating land use, meteorology, chemical transport models, and satellite remote sensing. Three models were trained using a neural network model, a random forest, and gradient boosting, and then ensemble averaged using a geographically weighted regression[59]. To obtain daily $PM_{2.5}$ predictions, we linked each patient's residential zip code to the nearest center of a 1-km × 1-km grid cell for their exposure estimate.

Dew point and air temperatures were obtained from the National Center for Environmental Prediction (NCEP) and the National Center for Atmospheric Research (NCAR) Reanalysis project

at 32 km × 32 km grid cells in the continental US[60]. Values for these variables were assigned to each patient by linking their residential zip code to the closest 32 km × 32 km grid cell.

Particle radioactivity

The study utilized particle gross β activity as a proxy for total particle radioactivity. Hernández et al. (2005) found a significant linear correlation of R=0.72 between gross β and gross α activity[61]. The strong correlation between β and α radiation suggests that gross β activity can represent all long-lived radon progeny (including α emitter ^{210}Po, not just ^{210}Pb). Previous studies using methods similar to RadNet have shown that levels of gross β activity are a good qualitative indicator of radiation activity for particles collected on air sampling, and specifically radiation due to ^{210}Pb, a long-lived radon progeny[33,62].

The Environmental Protection Agency (EPA)'s RadNet monitoring network, which includes approximately 140 radiation air monitors around the United States, provided the information on gross β activitity[63]. RadNet started collecting data on radioactivity in 1973 when several different radiation systems were consolidated into one network. Current RadNet stationary sampling stations use a high-volume air sampler to collect total suspended particles (TSP) on 10-cm-diameter synthetic fiber filters[63,64]. Integrated samples are collected by monitor operators over 5 to 7 days and are then sent to the National Analytical Radiation Environmental Laboratory (NAREL) for analysis. Measurement occurs several days after sample collection, which allows time for short-lived radon progenies (including ^{214}Pb and ^{214}Bi) to decay[64]. Outlier values, identified as values greater than 1.5 times the IQR from the median after log-transforming beta concentrations to ensure normality, were excluded from the dataset. All days within each sampling period were assigned to the β gross activity measured for that sample. This created a pseudo-daily

time series. On days where one sample was completed and another sample began, the daily value was calculated as the mean of the two measured concentrations.

This study improved upon earlier studies of beta radiation[33,62] by assigning particle radioactivity exposure based on each participant's closest RadNet monitoring station, rather than using a regional particle gross β activity exposure. Each participant was matched to their closest RadNet site and was assigned the corresponding daily measurement. Data was obtained from the following three RadNet stations that encompassed the possible range of residential locations for the participants: Boston, MA (83%); Worcester, MA (14%) and Providence, RI (3%). Missing values at each monitor were imputed using random forest models based on nearby monitors and meteorological variables. Prediction results were cross-validated using ten-fold cross validation and showed good predictive ability (CV- R^2 between 0.77 and 0.85).

Statistical analysis

We examined whether same-day and moving average of $PM_{2.5}$ and particle radioactivity (single pollutant models) and then $PM_{2.5}$ and particle radioactivity together (two-pollutant model) were associated with ventricular arrhythmias using a time-stratified case-crossover analysis adjusted for temperature and dew point. Case-crossover designs have been used to study various ambient air pollutant effects on acute cardiovascular events[58,65–67]. Case days occur on a calendar day when a patient experiences one or more VA event. Control days where chosen to match the cases' by day of the week within the matching calendar month. In this study design, time invariant variables that do not vary daily such as race, sex, age, smoking status, diabetic status and other chronic conditions are eliminated as potential confounders. Matching by day of the week within the same calendar month helped control for potential confounding that

varied within week and seasonality by month. The bi-directional selection of control days before and after the case day helped eliminate potential bias induced by long-term time trends[68].

We estimated odds ratios assessing the association of ventricular arrhythmias with the exposure of interest using conditional logistic regression, controlling for the matched sets. A matched-set in this study is defined as a single case-day with all its matched controls. It was possible for a single individual to have multiple matched sets. Based on previous studies with the same population, all models were adjusted for dew point and air temperature. The effect estimates are reported as odds ratios of an event for an interquartile range (IQR) increase in $PM_{2.5}$ or particle radioactivity[58].

In sensitivity analyses, we included an indicator variable for multiple events on the same day to evaluate whether patients with multiple events on the same day are more susceptible to ventricular arrhythmias. The first event in that 24-hour period was given a value of 0, while following events within that one calendar day were assigned a value of 1. In the two-pollutant model ($PM_{2.5}$ and particle radioactivity) to investigate the combined exposure of $PM_{2.5}$ and particle radioactivity, we utilized multiplicative interactions terms.

Data management and all statistical analyses were conducted using SAS software version 9.4 (SAS Institute, Cary, NC, 2013) and R version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient Population

Descriptions of the participants included in this analysis have previously been published[58]. Briefly, 1,143 patients were screened and 843 were excluded due to either implantation of a single chamber ICD and/or chronic AF. From the 300 eligible patients, 200 enrolled and 176 subjects were followed for at least 90 days. The mean follow-up time in the final cohort was 1.9 years. The study population that experienced any type of VA was mostly male (77%) and Caucasian (91%) with a median age of 65 years and the median body mass index of 27.7 kg/m^2 (Table 1-1). Only 4% reported different residential zip codes during their one year follow up. Patients reported spending a median of 6 hours per weekend (range: 0-48 hours) and 6 hours in the last 48 hours away (range: 0-40 hours) from their homes.

Their median left ventricular ejection fraction was 25%, while 60% had a history of congestive heart failure. The subset of the study population that experienced a sustained VA event (>30 seconds) had similar demographic characteristics to the general ICD population that experienced any type of ventricular arrhythmic event. Seven individuals experienced more than one event per day for all VAs accounting for 18% of all events while two individuals experienced more than one event per day for sustained VAs accounting for 17% of sustained VAs.

Table 1-1*: Patient Population (91 subjects that experienced an event and were followed for at least 90 days) in the ICD cohort during the study period from September 1, 2006 until June 30, 2010*

	Subjects with any type of VA		Subjects with sustained VA	
	N (Total)	**N (with characteristics)**	**N (Total)**	**N (with characteristics)**
Age (years)	91	65.0 (33-89)	25	62.0 (37-86)
Gender (male)	91	70 (77%)	25	21 (84%)
Race	91		25	
White		83 (91%)		23 (92%)
Black		7 (8%)		2 (8%)
Other		1 (1%)		
BMI (kg/m^2)	91	27.7 (15.6-56.7)	25	29.6 (21.7-55.6)
Structural heart disease	91		25	
Ischemic		57 (63%)		18 (72%)
Nonischemic		26 (29%)		6 (24%)
Other		9 (10%)		2 (8%)
Left ventricular ejection fraction (%)	90	25.0 (10-70)	25	25 (10-55)
History of congestive heart failure	91	55 (60%)	25	15 (60%)
CHF class I		13 (14%)		4 (16%)
II		19 (21%)		5 (20%)
III		23 (25%)		6 (24%)
IV				
Co-morbidities				
Pulmonary Disease	91	17 (19%)	25	4 (16%)
Diabetes	89	28 (46%)	24	7 (29%)
Hypertension	88	52 (59%)	25	18 (72%)
Medications				
Beta blocker	88	84 (95%)	25	24 (96%)
Antiarrhythmic agents: (Amiodarone, sotalol, or others not including beta blockers)	88	10 (11%)	25	5 (20%)
Platelet Aggregation Inhibitors	88	66 (75%)	25	19 (76%)
Smoking				
Current	86	10 (12%)	25	3 (12%)
Former	73	46 (63%)	21	11 (52%)
Never	82	56 (68%)	24	14 (58%)
Lived with Smoker	91	57 (63%)	25	17 (68%)

Values are median (range) or n (%). Values may not always add up to 91 or 25 because of missing data. VA= ventricular arrhythmias; BMI= body mass index; CHF= congestive heart failure

Arrhythmias

During the study period, twenty-five patients had 123 sustained ventricular arrhythmia events categorized as ventricular tachycardia (VT) (n=112) and ventricular fibrillation (VF) (n=11). Ninety-one patients had 1050 sustained or non-sustained ventricular arrhythmias events categorized as non-sustained ventricular tachycardia (NSVTs) (n=913) and non-sustained ventricular fibrillations (NSVFs) (n=14).

Air quality and weather covariates

Table 1-2 presents the daily mean air pollution concentrations and weather covariates, as well as the estimated daily particle radioactivity levels during the study period. During this time, the median $PM_{2.5}$ was 8.42 μg/m^3 and the median particle radioactivity was 0.19 mBq/m^3. None of the air quality or weather covariates were highly correlated (Pearson correlation <0.5). $PM_{2.5}$ was positively correlated with particle radioactivity, dew point and air temperature. On the other hand, particle radioactivity was negatively correlated with dew point and air temperature.

Table 1-2*: Summary statistics and Pearson's correlation coefficient of daily mean air pollutant concentrations, particle radioactivity levels and meteorological variables in Boston, USA, during the study period from September 1, 2006 until June 30, 2010.*

	Summary statistics						**Pearson's correlation coefficient**	
	# Days	**Min**	**25th percentile**	**50th percentile**	**75th percentile**	**Max**	**$PM_{2.5}$**	**PR**
$PM_{2.5}$ (μg/m^3)	1128	2.23	6.27	8.42	12.52	55.21	1	0.35
PR (mBq/m^3)	1128	0.06	0.14	0.19	0.23	0.56	0.35	1
Temperature (°C)	1128	-12.74	1.94	11.35	18.62	28.05	0.20	-0.11
Dew point temperature (°C)	1128	-20.08	-1.37	6.22	14.31	23.57	0.24	-0.14

Single-pollutant models

Exposure to higher levels to $PM_{2.5}$ was associated with higher odds of any ventricular arrhythmic event with 4, 5, or 21-day moving average prior to the event, in models adjusted for dew point and temperature (Figure 1-1A). For the 4 and 5-day moving averages, the increased odds were very similar. The strongest increased odds was for the 21-day moving average, odds 39% higher (95% CI: 12 to 72%) for each IQR (3.37 $\mu g/m^3$) increase in $PM_{2.5}$. In a sensitivity analysis, we included a multiple event indicator to test whether patients with multiple events on a given day are more susceptible to $PM_{2.5}$. We did not see evidence of an interaction with the 4- or 5-day moving averages. However, for the 21-day average, the interaction reported a nominally larger association for subsequent events (75% higher odds; 95% CI: -2% to 214%).

Higher exposure to particle radioactivity was associated with higher odds of any ventricular arrhythmic event with same-day exposure and 2-day moving average prior to the event, in models adjusted for dew point and temperature (Figure 1-1B). For the 0, 2 and 3-day moving average, the increased odds were similar, except the 3-day moving average did not meet the threshold for statistical significance. Specifically, for the 2-day moving average there was a 13% higher odds of ventricular arrhythmic events (95% CI: 1% to 26%) for each IQR (0.08 mBq/m^3) increase in particle radioactivity. We did not see evidence that patients with multiple events on a given day are more susceptible to particle radioactivity.

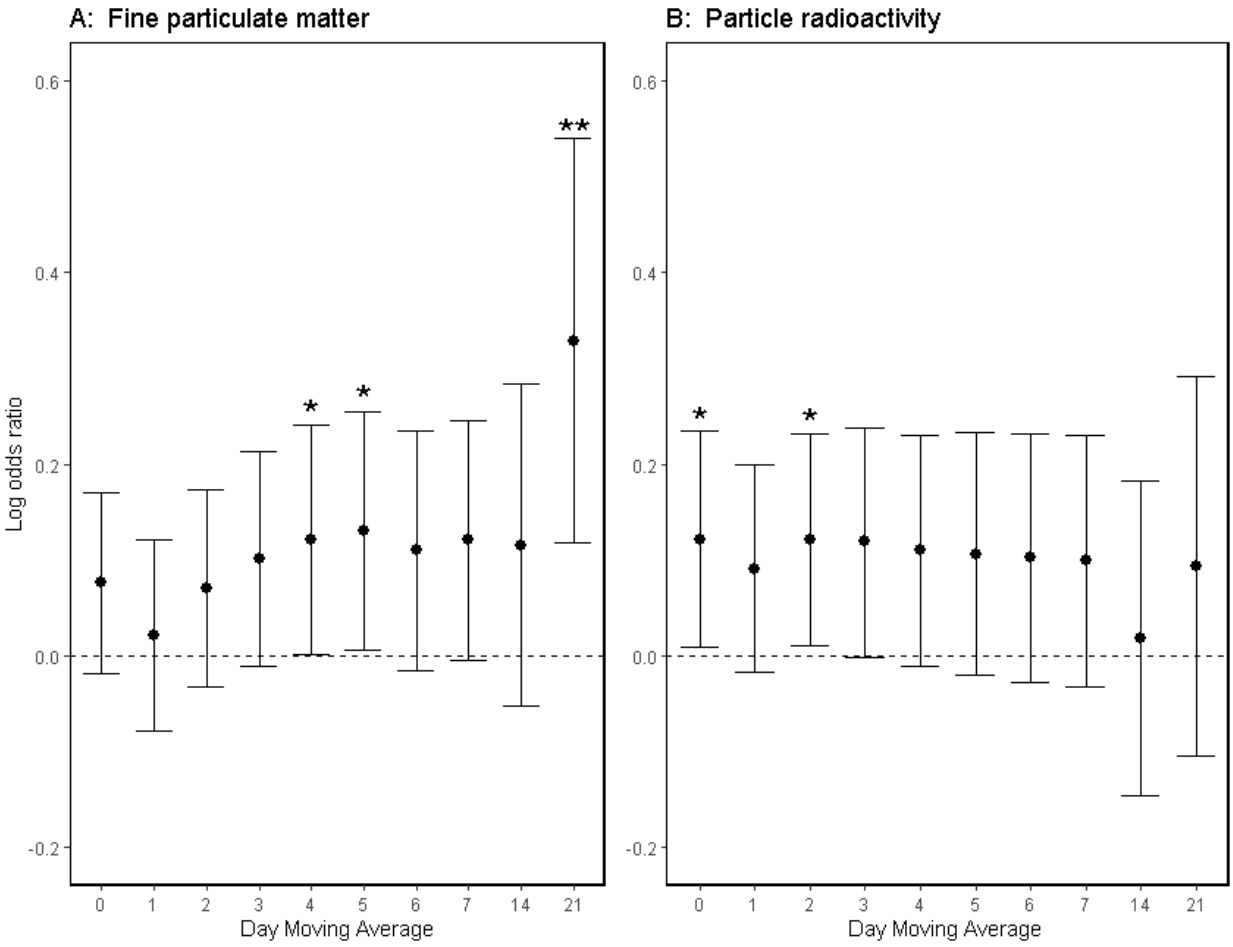

Figure 1-1: Log odds ratios of ICD Detected Ventricular Arrhythmias Associated with Each Interquartile Range Increase in Mean (A) Fine Particulate Matter ($PM_{2.5}$) or (B) Particle radioactivity 0-21 days prior to the Arrhythmic Event, Adjusted for Temperature and Dew Point in the ICD cohort from September 1, 2006 to June 30, 2010. * $p<0.05$; ** $p<0.01$

$PM_{2.5}$ and particle radioactivity (Two-pollutant models)

In models including both $PM_{2.5}$ and particle radioactivity, only the 21-day moving average of $PM_{2.5}$ remained statistically significant for any of the time windows (Table 1-3**Error! Reference source not found.**). For each 3.37 $\mu g/m^3$ increase in daily mean $PM_{2.5}$ levels for a 21-day moving average, the odds of a ventricular arrhythmic event 48% higher (95% CI: 15 to 90%) when adjusted for particle radioactivity, dew point and air temperature. In sensitivity analyses, we included an interaction term between the multiple event indicator and the 21-day $PM_{2.5}$ moving average. The interaction reported a stronger association for subsequent events (76% higher odds; 95% CI: -2% to 215).

To assess whether particle radioactivity modified the effects of $PM_{2.5,}$ we added an interaction term between 21-day $PM_{2.5}$ and 21-day particle radioactivity. We found a significant interaction between 21-day $PM_{2.5}$ and 21-day particle radioactivity (estimate -0.28; 95% CI: -0.45 to -0.11).

We did not find any significant association between $PM_{2.5}$ or particle radioactivity with sustained ventricular arrhythmias that required intervention by the ICD implant, our secondary endpoint (Table 1-4).

Table 1-3: *Odds ratios of ICD Detected Ventricular Arrhythmias Associated with*

*Each Interquartile Range Increase in Mean Exposure levels ($PM_{2.5}$ and PR) 0-21 days prior to the Arrhythmic Event, Model includes both $PM_{2.5}$ and PR, and is adjusted for Temperature and Dew Point in the ICD cohort from September 1, 2006 to June 30, 2010 . * p<0.01*

Moving average (day)	**$PM_{2.5}$ (95% CI)**	**Particle radioactivity (95% CI)**
0	1.04 (0.94-1.16)	1.11 (0.98-1.25)
1	0.99 (0.88-1.10)	1.10 (0.98-1.24)
2	1.03 (0.91-1.15)	1.12 (0.99-1.26)
3	1.07 (0.94-1.21)	1.09 (0.95-1.25)
4	1.10 (0.96-1.25)	1.07 (0.93-1.23)
5	1.11 (0.96-1.28)	1.06 (0.92-1.22)
6	1.09 (0.94-1.25)	1.07 (0.92-1.23)
7	1.10 (0.96-1.27)	1.06 (0.91-1.22)
14	1.15 (0.95-1.40)	0.95 (0.79-1.15)
21	1.48* (1.15-1.90)	0.90 (0.71-1.14)

Table 1-4: *Odds ratios of ICD Detected Sustained Ventricular Arrhythmias Associated with Each Interquartile Range Increase in Mean Exposure levels ($PM_{2.5}$ and PR) 0-21 days prior to the Arrhythmic Event, Adjusted for Temperature and Dew Point in the ICD cohort from September 1, 2006 to June 30, 2010.*

Moving average (day)	**$PM_{2.5}$ (95% CI)**	**Particle radioactivity (95% CI)**
0	1.14 (0.76-1.69)	0.95 (0.65-1.39)
1	1.20 (0.82-1.76)	0.84 (0.59-1.19)
2	1.19 (0.80-1.77)	0.89 (0.60-1.32)
3	1.21 (0.78-1.88)	0.82 (0.53-1.27)
4	1.22 (0.78-1.91)	0.78 (0.49-1.25)
5	1.17 (0.72-1.87)	0.83 (0.51-1.37)
6	1.05 (0.64-1.71)	0.98 (0.61-1.59)
7	1.07 (0.65-1.74)	0.98 (0.61-1.57)
14	1.43 (0.78-2.62)	1.00 (0.54-1.83)
21	1.17 (0.52-2.62)	1.33 (0.53-3.29)

Discussion

This is the first study that we know of to explore the association of $PM_{2.5}$ and particle radioactivity with ventricular arrhythmias and finds a direct correlation between them. We found that in the single $PM_{2.5}$ pollutant models that were individually adjusted for dew point and air temperature, higher exposure was associated with a higher odds of ventricular arrhythmias during 4, 5 and 21 days prior. On the other hand, the single pollutant particle radioactivity models found an association between higher exposure and higher odds of ventricular arrhythmias on the day of exposure and 2 days prior.

In the two-pollutant models including both $PM_{2.5}$ and particle radioactivity, only the 21-day moving average exposure of $PM_{2.5}$ was independently associated with a higher odds of a ventricular arrhythmic event (48% higher odds; 95% CI: 15 to 90%). However, the associations in the two-pollutant models for the 4 and 5-day moving averages of $PM_{2.5}$ remain very similar in magnitude to the estimates in the single pollutant models of $PM_{2.5}$, but with slightly wider confidence intervals. This suggests that $PM_{2.5}$ has an effect on the risk of VA, which is independent of particle radioactivity for both an acute and intermediate effect (4, 5 and 21-day exposure).By conducting a sensitivity analysis with a multiple event indicator, we found that having multiple events on the same calendar day $PM_{2.5}$ could potentially have a nominally larger effect on subsequent events.

Although particle radioactivity did not cross the significance threshold in the two-pollutant models, the effect estimates for the 0, 2 and 3-day moving averages were very similar to the one-pollutant models, but with slightly wider confidence intervals. Indicating that $PM_{2.5}$ could have an intermediate effect (21-day) while particle radioactivity could have a more acute impact (<3 days) on ventricular arrhythmias.

While many studies have found that air pollution factors into mortality and morbidity rates across the globe[10,11,69–71], instead of focusing exclusively on $PM_{2.5}$ as a single exposure, our study included particle radioactivity. The significant interaction between 21-day $PM_{2.5}$ and 21-day particle radioactivity suggests that the risk of ventricular arrhythmias due to $PM_{2.5}$ increases at a steeper rate at lower concentrations of particle radioactivity after adjusting for dew point and temperature. Thus, there is a weaker effect of $PM_{2.5}$ in the presence of higher levels of particle radiation. This provides evidence that particle radioactivity modifies the association between $PM_{2.5}$ and the risk of ventricular arrhythmias. So far, no study has investigated how the combined exposure to both particulate matter and particle radiation affects this high-risk population and how they interact, although this could have important implications for cardiac health and preventative strategies.

The World Health Organization (WHO) estimates that in 2016 ambient air pollution caused 4.2 million premature deaths across the globe[72]. From these premature deaths, cardiovascular disease accounts for the majority of deaths from air pollution[72,73]. Since this is the first study to examine how particle radioactivity affects the risk of ventricular arrhythmias, we are unable to directly compare our particle radioactivity results with other studies. Nevertheless, epidemiological studies have found evidence of a positive association between circulatory disease mortality and low doses of ionizing radiation[74]. A recent longitudinal study in the Normative Aging cohort employed the same exposure metric of gross β activity as a surrogate of particle radioactivity and found a positive association with an increase in both diastolic and systolic blood pressure[33]. While this study did not find an independent effect of particle radioactivity on VA, these scientific studies support the growing literature looking at the association between cardiovascular diseases, fine particle mass and particle radioactivity[24,33].

Biological Mechanism

While inhaled radon gas has been associated with higher lung cancer risk, few studies have explored the association between low background levels of ionizing radiation and cardiovascular disease[75,76]. Radioactive aerosols emit α and β particles and transmit γ and X-rays. The deposition of radioactive materials inside the human body can cause biophysical harm depending on the dose, deposition site and the different types of radiation emitted throughout the decay process[77–79].

Many studies have reported on possible biological mechanisms associated with the effects of radiation on cardiovascular morbidity and mortality[25,80,81]. Radiation therapy utilizes high doses of ionizing radiation which can induce cardiovascular toxicity through radiation induced fibrosis, microvascular injury and neovascularization, and atherosclerosis[82,83]. At lower doses, pro-inflammatory markers are upregulated after exposure to radiation[25,84]. Specifically, a recent study found moderate associations of regional mean particle β radioactivity with several oxidative stress and inflammatory biomarkers after adjusting for $PM_{2.5}$ concentrations in The Framingham Heart Study[62]. The literature supports the theory that low background levels of ionizing radiation contribute to cardiovascular disease through a heightening of the immune response and systemic inflammation.

Strengths and Limitations

Our study had several limitations. We did not find an association between sustained ventricular arrhythmias and $PM_{2.5}$, but this could be due to insufficient power. There is potential for non-differential measurement error in our exposure assessment, which has previously been described[33,62]. Since measurements of particle gross β activity were measured on samples collected over a period of several days and then used to create a pseudo-daily time series, we may not have

enough temporal resolution to estimate short-term exposures at windows of less than five days. This study improves upon earlier studies of particle gross β activity[33,62] by assigning particle radioactivity exposure based on each participant's closest RadNet site, rather than using a regional beta value. This reduces exposure misclassification and improves the spatial and temporal variability of our particle radioactivity exposures. It is unlikely that any measurement error in either particle radioactivity or $PM_{2.5}$ is associated with the participant's VA events since the exposure was measured independently from the ventricular arrhythmic events.

This study also improves on previous air pollution measurements and weather covariate information utilized for this ICD cohort population. Instead of using a single monitoring site like previous studies,[58,85] this study assigned exposures based on patients' residential address using spatio-temporal models for $PM_{2.5}$, particle radioactivity, dew point temperature and air temperature, which reduced the amount of potential measurement error. The assigned exposures do not take into account a patient's mobility outside of their residential zip code. This potential misclassification is nondifferential because patients with lower exposure are not likely to have more misclassification error than patients with higher exposure. This suggests that adjusting for the nondifferential measurement error would result in a larger effect estimate with smaller confidence intervals.

The implantable ICD devices allow for accurate diagnosis and timing of events (all VAs and sustained VAs). Precise time measurements were recorded for every event, which were independently verified by an electrophysiologist increasing the accuracy of the outcome measurement. The study assessed the temporal association of ventricular arrhythmias captured by implantable defibrillators with fine particulate matter and particle radioactivity. By including

patients with dual-chambered ICD, we reduce the potential for outcome misclassification by distinguishing between ventricular and atrial arrhythmias.

Whether the association of radiation and $PM_{2.5}$ with arrhythmias is a direct arrhythmogenic response to these agents or whether the arrhythmias are secondary to radiation- or particle-induced myocardial ischemia or heart failure is not addressed by this study. Many of the patients had a history of coronary artery disease and congestive heart failure. These patients characterize an at-risk population because their previous history of cardiovascular disease could make them more susceptible to air pollution. By utilizing a case-crossover method, the self-matching design eliminates confounding by time invariant or relatively constant characteristics such as a patient's chronic or average risk factors[68]. Nevertheless, the generalizability of the results is limited by the characteristics of a high-risk patient population for subclinical and clinical cardiac events. It is uncertain whether the associations would be the same among younger, non-white, or less at-risk patients.

Conclusions

In this high-risk population, intermediate (21-day) $PM_{2.5}$ exposure was associated with higher odds of a ventricular arrhythmia event onset among patients with known cardiac disease and indication for ICD implantation independently of particle radioactivity. For shorter term associations (less than 7 days), we may not be able to distinguish the effect of $PM_{2.5}$ from particle radioactivity, but in models only accounting for $PM_{2.5}$, associations between fine particulate matter and ventricular arrhythmias were significant for 4 and 5 day moving averages.

We found that exposure to fine particulate matter independent of low levels of background radiation contributes to the risk of ventricular arrhythmias. Furthermore, particle radioactivity

reduces the effect of fine particulate matter in the presence of higher levels of particle radiation on ventricular arrhythmias.

Funding Sources

This publication was made possible by the United States Environmental Protection Agency (USEPA) grant RD-835872 and the National Institute of Environmental Health Sciences (NIEHS) P01ES009825. Its contents are solely the responsibility of the grantee and do not necessarily represent the official views of the USEPA or NIEHS. Further, USEPA and NIEHS does not endorse the purchase of any commercial products or services mentioned in the publication. This publication was also funded by the National Institutes of Health grant T32ES007069 and ES000002.

Disclosures

The authors have no conflict of interests.

CHAPTER 2: Associations between $PM_{2.5}$ metal components and QT interval length

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Abstract

Background/Objective: Several studies have found associations between increases in QT interval length, a marker of cardiac electrical instability, and short-term fine particulate matter ($PM_{2.5}$) exposures. To our knowledge, this is the first study to examine the association between specific $PM_{2.5}$ metal components and QT interval length.

Methods: We measured heart-rate corrected QT interval (QTc) duration among 630 participants in the Normative Aging Cohort (NAS) based in Eastern Massachusetts between 2000 to 2011. We utilized time-varying linear mixed-effects regressions with a random intercept for each participant to analyze associations between QTc interval and moving averages (0 to 7 day moving averages) of 24-hour mean concentrations of $PM_{2.5}$ metal components (vanadium, nickel, copper, zinc and lead) measured at the Harvard Supersite monitoring station. Models were adjusted for daily $PM_{2.5}$ mass estimated at a 1 km x 1 km grid cell from a previously validated prediction model and other covariates. Bayesian kernel machine regression (BKMR) was utilized to assess the overall joint effect of the $PM_{2.5}$ metal components.

Results: We found consistent results with higher lead (Pb) associated with significant higher QTc intervals for both the multi-pollutant and the two pollutant ($PM_{2.5}$ mass and a $PM_{2.5}$ component) models across the moving averages. The greatest effect of lead on QTc interval was detected for the 4-day moving average lead exposure. In the multi-pollutant model, each 2.72 ng/m^3 increase in daily lead levels for a 4-day moving average was associated with an 8.77 ms (95% CI: 4.25, 13.29) increase in QTc interval. In the two-pollutant models with $PM_{2.5}$ mass and lead, each 2.72 ng/m^3 increase in daily lead levels for a 4-day moving average was associated with

a 9.19 ms (95% CI: 5.09, 13.30) increase in QTc interval. We found that 4-day moving average of copper has a negative association with QTc interval when compared to the other $PM_{2.5}$ metal components. In the multi-pollutant model, each 1.81 ng/m^3 increase in daily copper levels for a 4-day moving average was associated with an -3.88 ms (95% CI: -7.13, -0.63) increase in QTc interval. Copper's essential function inside the human body could mediate its cardiotoxicity on cardiac conductivity and explain why we found that copper in comparison to the other metals was less harmful for QTc interval.

Conclusions: Exposure to metals contained in $PM_{2.5}$ are associated with acute changes in ventricular repolarization as indicated by QT interval characteristics.

Funding: USEPA Grant RD 83479801 & RD 83587201; NIH grant T32ES007069

Introduction

Epidemiological studies have reported a consistent association between exposure to particulate air pollution and cardiovascular morbidity and mortality[4,5]. Increases in ambient air pollution have been associated with increases in markers of autonomic function such as lower heart rate variability[7], increased heart rates[8] and a greater risk of cardiac arrhythmias[9]. Many of these studies focus on fine particulate matter ($PM_{2.5}$), which can penetrate deep into the lungs due to its smaller size and deposit an a large spectrum of organic and inorganic elements[1]. However, fewer studies have examined which specific elements of $PM_{2.5}$ contribute to cardiovascular toxicity.

Irregularities in cardiac repolarization significantly contribute to the production of cardiac arrhythmias[43]. Electrocardiogram (ECG) measurements of repolarization such as QT interval provide non-invasive indicators for possible cardiac arrhythmias and help identify patients susceptible to sudden cardiac death[44,45]. A previous study conducted in the NAS found a positive association between sub-chronic and long-term $PM_{2.5}$ exposure and QTc interval, but did not assess how the individual metal components of $PM_{2.5}$ could impact cardiac repolarization[46].

The chemical components of $PM_{2.5}$ can be found both inside and on the surface of the particle. While there are both natural and anthropogenic sources for these chemical components, anthropogenic sources consist of auto vehicle emissions, industrial activity, fossil fuel combustion, burning of fuel oil and smoking byproducts[34–37]. Past studies have found that the chemical composition of $PM_{2.5}$ could contribute to daily average mortality. Lippmann et al. (2006)[38] found that vanadium and nickel, associated with burning of fuel oils, increased the daily average mortality in New York City. Furthermore, Zanobetti et al. (2008)[39] found that nickel significantly modified that association between $PM_{2.5}$ mass and daily cardiovascular hospital admissions in 26 U.S. cities.

Only a few studies have examined how $PM_{2.5}$ metal components could affect cardiovascular markers[86,87]. Jacobs et al. (2012)[86] found that among older individuals taking antihypertensive medication, vanadium, iron and nickel content in $PM_{2.5}$ was significantly associated with systolic blood pressure and pulse pressure. Another study on a non-smoking longitudinal adult cohort in Detroit, Michigan reported a positive association with $PM_{2.5}$ metal components and brachial artery diameter and a negative association with $PM_{2.5}$ metal components, blood pressure and heart rate. Lead is well known to have toxic effects on the cardiovascular system including increase in blood pressure and the risk of left ventricular hypertrophy[88], as well as neurotoxic effects[89], which may extend to the autonomic nervous system. However, the underlying mechanisms of the association between ambient air pollution and cardiovascular morbidity are only partly understood, particularly for mixtures of air pollution components.

We evaluate whether short-term exposures to $PM_{2.5}$ metal components are associated with associated with heart rate corrected QT interval (QTc) duration, which is a marker of ventricular repolarization, in the Normative Aging Study cohort. We hypothesize that exposure to a mixture of $PM_{2.5}$ metal components (vanadium, nickel, copper, zinc and lead) elevates QTc interval and that each individual $PM_{2.5}$ metal component will increase QTc interval, a marker of ventricular repolarization, among the 551 men living in Eastern Massachusetts. To our knowledge, this is the first study to assess the effects of $PM_{2.5}$ metal components on ventricular repolarization through changes in QTc interval.

Methods

Study population

The participants in this study included 551 elderly men living in Eastern Massachusetts who are part of the Veterans Affairs Normative Aging Cohort with up to four visits during the period 2000-2012. Inclusion criteria for the initial cohort required no previous history of chronic disease and the ability to participate in at least one onsite physical examination and questionnaire every 3 to 5 years. Previous studies have reported the enrollment and inclusion requirements in more detail[41,90]. In brief, physical examinations and interviews provided information on the participants height and weight to calculate their Body Mass Index (BMI), current medication use and fasting blood samples to assess cholesterol levels[91]. Smoking and drinking status were obtained from physician administered questionnaires. Diabetic status was assigned based on a physician's diagnosis of type II diabetes or the reported use of diabetic medication during a study visit. Mean atrial pressure (MAP) was calculated from the systolic and diastolic blood pressures (SBP and DBP) measured by the physician during a site visit.

While there were 630 total participants during this time with at least one QTc measurement, only 551 of them had all the necessary covariates for this analysis. The study was missing information on fifty-one participants on their temperature or relative humidity and five on $PM_{2.5}$. One participant was missing information on cholesterol and another on race. Four were missing information on education and two on smoking status. We also excluded 15 participants with no information on $PM_{2.5}$ metal exposure. Between November 14, 2000 and December 21, 2011, these 551 participants came in for a total of 967 study visits.

The Institutional Review Boards of participating institutions, Harvard T.H. Chan School of Public Health, and the Veteran Administration, approved the study protocol and all participants provided written informed consent.

ECG measurement and analysis

QTc measurements were obtained from electrocardiogram measurements (ECG). These measurements were obtained at the exam site (VA Boston Healthcare System, Boston, MA) for 5 to 10 min between 05:30 and 14:00 hours with a two-channel (five lead) ECG monitor (Trillium 3000; Forest Medical, Inc., East Syracuse, NY) using a sampling rate of 256 Hz per channel[92]. An earlier study provides more detailed report on how the ECG measurements were processed to attain the corrected QT interval values[42]. Briefly, the ECG recordings were processed using the Trillium 3000 software to create a Mathcad (Parametric Technology Corporation, Needham, MA) file that includes the QT interval values. Corrected QT values were calculated using Bazett's formula by only measuring the start of a normal or supraventricular beat to the end of a T wave with sufficient amplitude[42,93]. QTc measurements were expressed in milliseconds (ms).

Air pollution and meteorology variables

We retrieved daily $PM_{2.5}$ predictions at 1 km × 1 km grid cells in the continental U.S. using a well-validated model incorporating land use, meteorology, chemical transport models, and satellite remote sensing. Three models were trained using a neural network model, a random forest, and gradient boosting, and then ensemble averaged using a geographically weighted regression[59]. Each patient's residential address was linked to the nearest center of a 1 km × 1 km grid cell for their exposure estimate. The National Center for Environmental Prediction (NCEP) and the National Center for Atmospheric Research (NCAR) Reanalysis project provides meteorological information at 32 km × 32 km grid cells in the continental U.S.[60]. These meteorological variables

were assigned to each patient by linking their residential zip code to the nearest 32 km × 32 km grid cell.

PM metal components

Daily ambient concentrations of the $PM_{2.5}$ metal components were collected at the Harvard Supersite in Boston, MA during the study period 2000-2011. The Supersite is located on the roof of the Countway library of the Harvard Medical School, which is approximately one mile from the VA examination site where the ECG measurements took place (VA Boston Healthcare System, Boston, MA). The study focused on five $PM_{2.5}$ metal components chosen *a priori*: vanadium, nickel, copper, zinc, and lead based on previous literature. Daily $PM_{2.5}$ samples were collected on Teflon filters utilizing Harvard Impactors[94] and the $PM_{2.5}$ elements were evaluated with an Energy Dispersive X-ray Fluorescence Spectrometer (Epsilon 5, PANalytical, Almelo, The Netherlands).

Statistical Analysis

We utilized time-varying linear mixed-effects regressions with a random intercept and Bayesian kernel machine regression (BKMR) to analyze associations between QTc interval and moving averages (0 to 7 day moving averages) of 24-hour mean concentrations of $PM_{2.5}$ metal components (vanadium, nickel, copper, zinc and lead) measured at the Harvard Supersite monitoring station. We report the changes in QTc interval in milliseconds and 95% CI in QTc interval for an interquartile range (IQR) increase in zero to seven-day moving average for each individual $PM_{2.5}$ metal component.

Bayesian kernel machine regression (BKMR) is a Bayesian approach that uses a regression kernel to consider high order nonlinearities (squares, cubes, etc.) and interactions among a mixture of exposures, and evaluate which form best explains the outcome[95,96]. This method controls for multicollinearity, non-linear and non-additive effects while adjusting for any relevant covariates

and potential confounders. The model parameters are treated as random variables which help identify a) the most relevant components in a mixture, b) dose-response curves for those components, and c) the overall effect of that mixture and interactions between each component. The BKMR results were reported with the 95% posterior credible interval (PCI) with the other exposures fixed at their 50^{th} percentile. Prior to data analysis for the BKMR model, all the continuous variables were logged, centered, and standardized. We utilized 50,000 iterations for the Markov Chains and to generate the predictions and burned the first half of the iterations.

Three different models were used to examine the association between $PM_{2.5}$ metal components and QTc interval. The first model was a multi-pollutant model where all the individual metal components were included, the second model was a two-pollutant model that consisted of each individual $PM_{2.5}$ metal components and $PM_{2.5}$ mass and the third model was the BKMR analysis that included all of the individual metal components. All models were adjusted for daily $PM_{2.5}$ mass estimated at a 1 km x 1 km grid cell from a previously validated prediction model and other covariates: age (years), race, maximum years of education, BMI (kg/m^2), total cholesterol (mg/dL), mean arterial pressure (mmHg), diabetic status, use of beta blocker medication, alcohol intake (2 or more drinks per day or less than 2 drinks per day as reference), smoking status (current, former or never as reference), census tract percent of population age 25 years or older with less than a high school diploma, air temperature (°C), relative humidity (%) and seasonality (sine and cosine).

We performed two sensitivity analysis. First, we examined if season would alter the association between the $PM_{2.5}$ metal components and QTc interval with stratification in the multipollutant model. Second, to further explore the issue of multicollinearity, we assessed if the

effect estimates reported in the multipollutant model would change if we excluded $PM_{2.5}$ metal components that were highly correlated with each other (excluded vanadium and zinc).

Data management and all statistical analyses were conducted using R version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

The study included 551 VA Normative Aging Study participants who had all the relevant covariates for this analysis. The participants were older males with a mean age (± SD) of 74.1 years ± 6.8 years who were mostly white (96.6%). *Table 2-1* presents other characteristics of the study patients. Table 2-2 presents the summary statistics and Spearman's correlations between the $PM_{2.5}$ metal components and meteorological measurements for the study period. During this time, the median $PM_{2.5}$ mass concentration was 8.3 $\mu g/m^3$ and the highest correlation between $PM_{2.5}$ metal components was between nickel and vanadium (Spearman correlation coefficient, $\rho = 0.84$). The $PM_{2.5}$ metal components were positively correlated with each other while temperature and relative humidity was negatively correlated with some of the $PM_{2.5}$ metal components (temperature: vanadium, nickel, zinc and lead; relative humidity: copper, zinc and lead). The highest negative correlation existed between temperature and nickel (Spearman correlation coefficient, $\rho = -0.19$).

Table 2-1: Baseline characteristics of the 551 study participants in the VA Normative Aging Study during the study period between November 14, 2000 and December 21, 2011

Characteristics	Mean (SD)	N (%)
Age (years)	74.1 (6.8)	
Race		
White		532 (96.6)
Black		13 (2.4)
Hispanic (White)		5 (0.9)
Hispanic (Black)		1 (0.2)
Body mass index (kg/m^2)	27.8 (4.1)	
Total cholesterol (mg/dL)	182.9 (37.5)	
Mean arterial pressure (mmHg)	86.7 (11.1)	
Diabetes		
Yes		112 (19.7)
No		456 (80.3)
Beta blocker medication		
Yes		217 (39.4)
No		334 (60.6)
Maximum years of education	15.1 (3.0)	
Alcohol intake		
<2 drinks per day		99 (18.0)
2+ drinks per day		452 (82.0)
Smoking status		
Never smoker		163 (29.6)
Current smoker		28 (5.1)
Former smoker		360 (65.3)

Table 2-2: *Summary statistics and Spearman's correlation coefficients of $PM_{2.5}$ metal components and meteorological measurements in the VA Normative Aging Study between November 14, 2000 and December 21, 2011*

	Summary Statistics		Spearman's correlation coefficients							
	Mean (SD)	**Median (IQR)**	**V**	**Ni**	**Cu**	**Zn**	**Pb**	**$PM_{2.5}$**	**Temp**	**RH**
V (ng/m^3)	3.1 (2.9)	2.3 (3.3)	1.00	0.84	0.28	0.54	0.38	0.41	-0.06	0.15
Ni (ng/m^3)	2.8 (3.2)	1.8 (3.0)		1.00	0.31	0.59	0.36	0.35	-0.19	0.07
Cu (ng/m^3)	3.6 (2.9)	3.4 (3.6)			1.00	0.30	0.26	0.27	0.10	-0.09
Zn (ng/m^3)	13.2 (12.8)	10.2 (9.1)				1.00	0.35	0.39	-0.10	-0.01
Pb (ng/m^3)	5.5 (3.7)	5.0 (4.2)					1.00	0.32	-0.04	-0.10
$PM_{2.5}$ ($\mu g/m^3$)	10.1 (6.3)	8.2 (6.8)						1.00	0.19	0.10
Temp (°C)	11.6 (5.3)	11.9 (8.2)							1.00	0.16
RH (%)	68.1 (17.0)	67.0 (27.0)								1.00

Abbreviations: SD- standard deviation; IQR- interquartile range; V- vanadium; Ni- nickel; Cu- copper; Zn- zinc; Pb- lead; $PM_{2.5}$- fine particulate matter mass; Temp- temperature; RH- relative humidity.

Figure 2-1 shows the results from the multi-pollutant linear mixed-effects regression model with all the $PM_{2.5}$ metal components included in the same model adjusted for $PM_{2.5}$ mass (Multi-pollutant), the two-pollutant models including each $PM_{2.5}$ metal component and $PM_{2.5}$ mass (Two-pollutant) and BKMR which included all five $PM_{2.5}$ metal components. All models consistently showed that lead had the highest statistically significant effect on QTc interval across all moving averages except for the 1-day lag.

The greatest effect of lead on QTc interval was detected for the 4-day moving average lead exposure across all models. In the multi-pollutant model, each 2.7 ng/m^3 increase in daily lead levels for a 4-day moving average was associated with an 8.77 ms (95% CI: 4.25, 13.29) increase in QTc interval. In the two-pollutant models with lead and $PM_{2.5}$ mass, each 2.7 ng/m^3 increase in daily lead levels for a 4-day moving average was associated with a 9.19 ms (95% CI: 5.09, 13.30) increase in QTc interval. In the BKMR model, each geometric IQR increase in daily lead levels for a 4-day moving average was associated with a 22.72 ms (95% CI: 11.76, 33.68) increase in QTc interval. The results were similar across all models with Pb providing the most consistent findings.

The multi-pollutant model and the BKMR model both suggest that 4-day moving average of copper has statistically significant negative association with QTc interval when compared to the other $PM_{2.5}$ metal components.

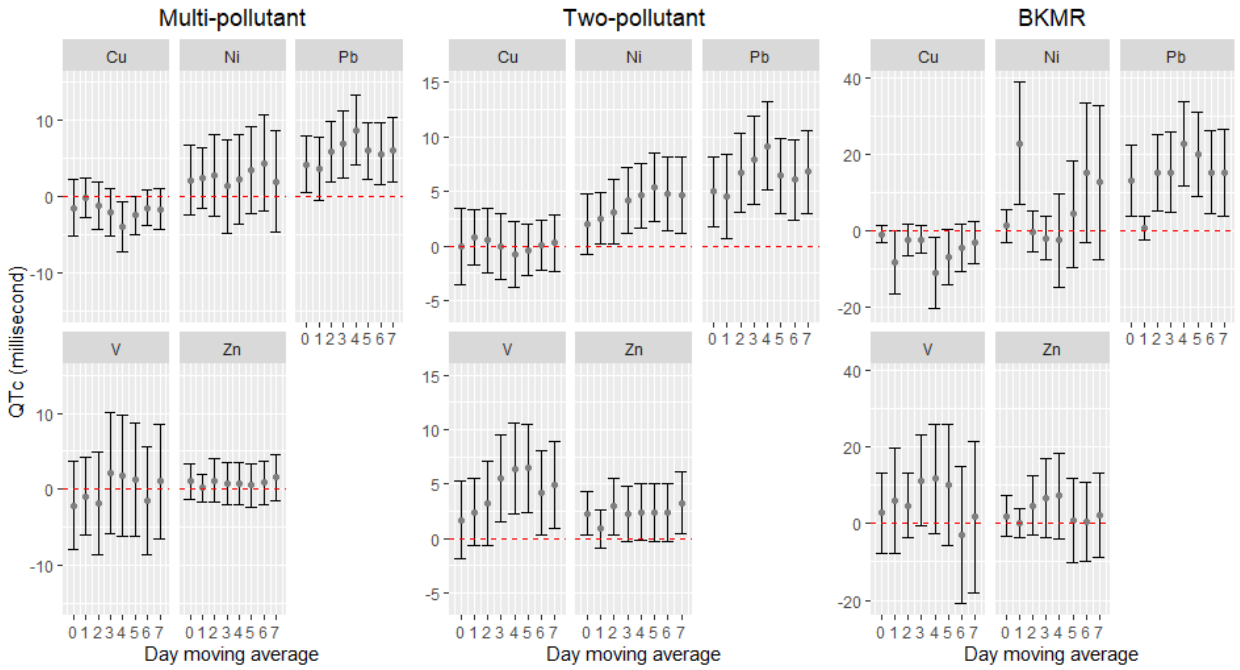

Figure 2-1: Changes in milliseconds and 95% CI in QTc interval for an IQR increase in zero to seven day moving average of each $PM_{2.5}$ metal component. The results are presented in a multi-pollutant model where all the metal components are included in the same model, the two-pollutant model which includes each individual $PM_{2.5}$ metal component and $PM_{2.5}$ mass and the BKMR model. The results for BKMR are reported with the 95% posterior credible interval (PCI) with the other exposures fixed at their 50th percentile. All models are adjusted for $PM_{2.5}$ mass, age (years), race, maximum years of education, BMI (kg/m2), total cholesterol (mg/dL), mean arterial pressure (mmHg), diabetic status, use of beta blocker medication, alcohol intake (2 or more drinks per day or less than 2 drinks per day as reference), smoking status (current, former or never as reference), census tract percent of population age 25 years or older with less than a high school diploma, air temperature (°C), relative humidity (%) and seasonality (sine and cosine).

Figure 2-2 shows the estimated joint effect of the $PM_{2.5}$ metal mixture on QTc interval length when all the predictors are fixed to different percentiles, as compared with when they are all fixed to the 50th percentile, supporting a strong and linear positive association of the whole mixture with increasing QTc interval length across all the moving averages.

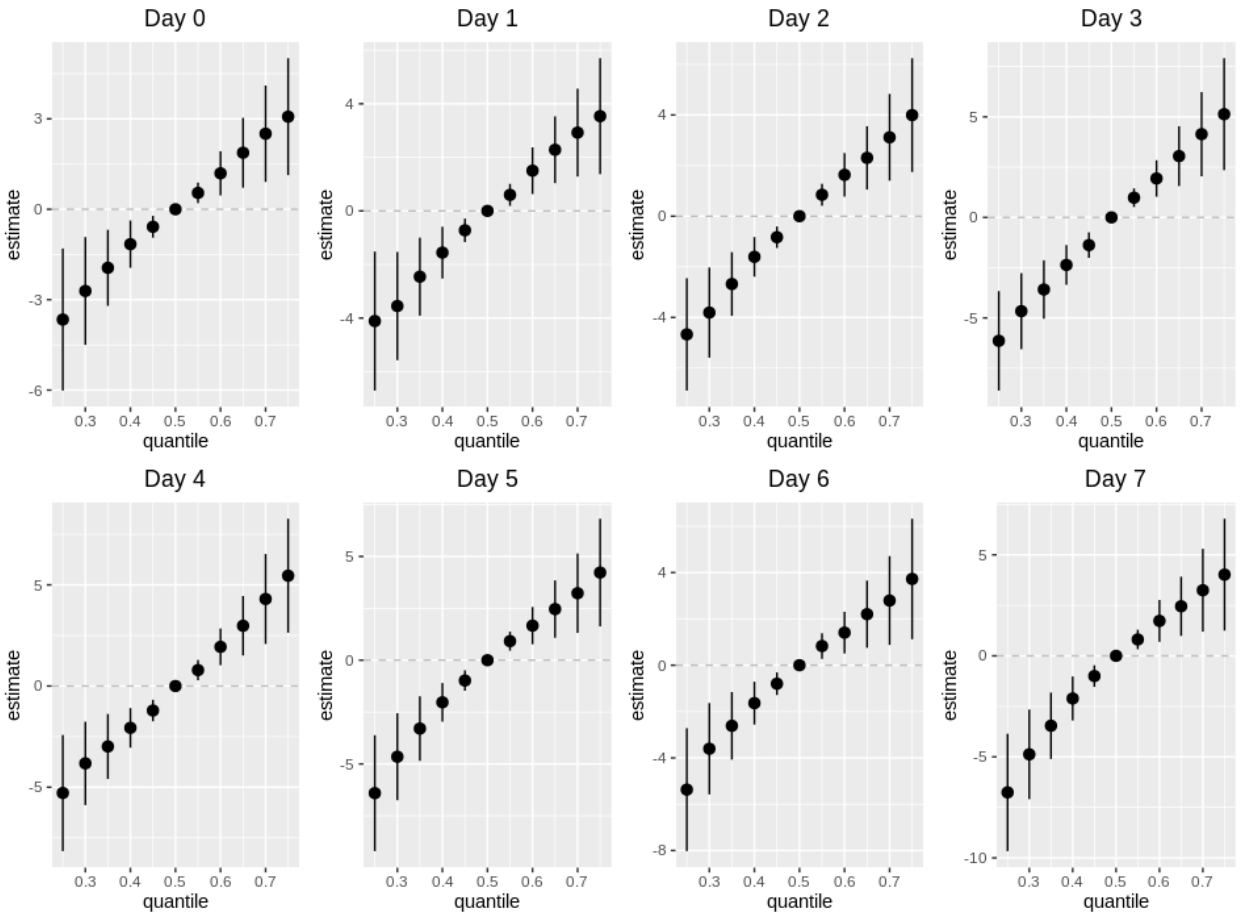

Figure 2-2: Overall joint effect of the $PM_{2.5}$ metal mixture for 0 to 7 day moving averages with QTc interval length estimated by Bayesian Kernel Machine Regression (BKMR). This figure compares the estimated change in QTc interval length when all predictors are at a certain quantile with the value when all of them are at their 50th percentile. BKMR models were adjusted for $PM_{2.5}$ mass, age (years), race, maximum years of education, BMI (kg/m2), total cholesterol (mg/dL), mean arterial pressure (mmHg), diabetic status, use of beta blocker medication, alcohol intake (2 or more drinks per day or less than 2 drinks per day as reference), smoking status (current, former or never as reference), census tract percent of population age 25 years or older with less than a high school diploma, air temperature (°C), relative humidity (%) and seasonality (sine and cosine).

For the sensitivity analysis, we found that season could alter the association between $PM_{2.5}$ metal components and QTc interval (Figure 2-3). In the fall, we found that lead continues to consistently have a statistically significant association with QTc interval across the 2 to 7 day moving averages and reports the largest $PM_{2.5}$ lead association with QTc interval on the 5-day moving average (15.55 ms, 95% CI: 6.99, 24.12). Furthermore, nickel also showed a statistically

significant association with QTc interval in the fall and reported the largest effect size for any $PM_{2.5}$ metal component on the 6-day moving average (21.00 ms, 95% CI: 5.31, 36.69).

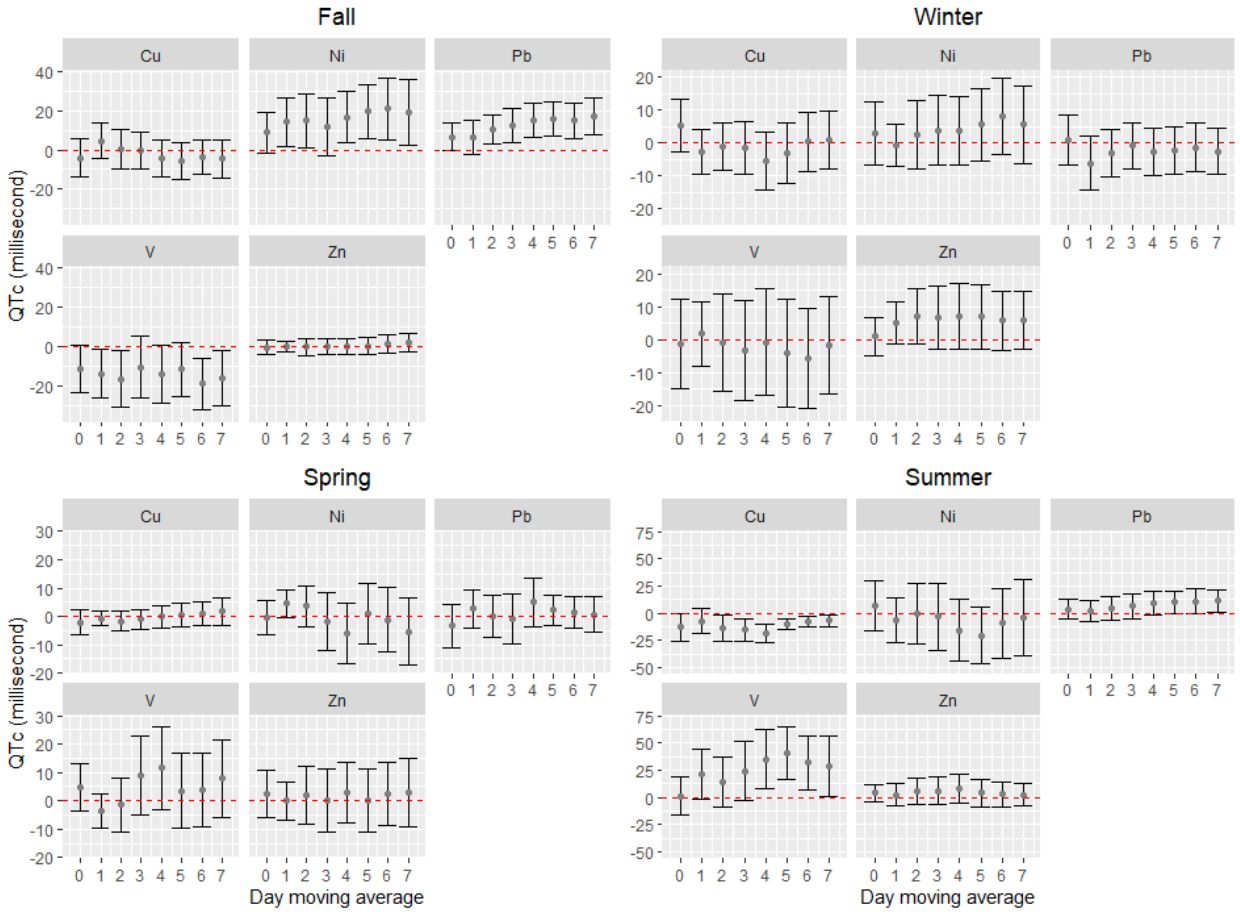

Figure 2-3: Change in QTc interval length and 95% CI for an IQR increase in 0 to 7 day moving average of each $PM_{2.5}$ metal component in the multi-pollutant model stratified by season. Model was adjusted for $PM_{2.5}$ mass, age (years), race, maximum years of education, BMI (kg/m2), total cholesterol (mg/dL), mean arterial pressure (mmHg), diabetic status, use of beta blocker medication, alcohol intake (2 or more drinks per day or less than 2 drinks per day as reference), smoking status (current, former or never as reference), census tract percent of population age 25 years or older with less than a high school diploma, air temperature (°C), relative humidity (%) and seasonality (sine and cosine).

In the summer, we found a statistically significant negative association between QTc interval and copper for the 2 to 6 day moving averages and a statistically significant positive association between QTc interval and vanadium for the 4 to 7 day moving averages. We also found

a suggestive positive association between QTc interval and $PM_{2.5}$ lead exposure for 4 to 7 day moving average. We did not find any statistically significant associations between any $PM_{2.5}$ metal component and QTc interval for the winter or spring seasons.

In our second sensitivity analysis, we removed zinc and vanadium to assess if the results were due to multicollinearity with copper and nickel and the results remained consistent (Figure 2-4).

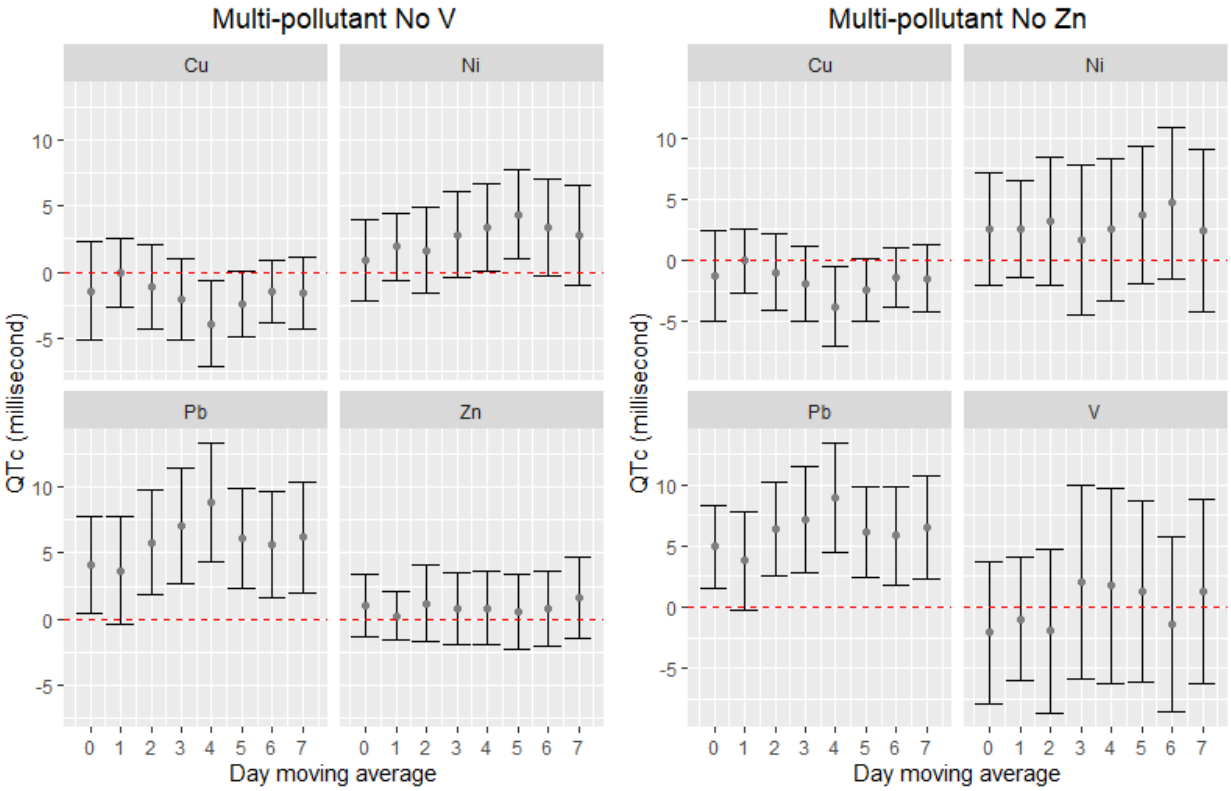

Figure 2-4: Changes in milliseconds and 95% CI in QTc interval for an IQR increase in zero to seven day moving average of each $PM_{2.5}$ metal component. The results are presented in a multi-pollutant model where all the metal components are included in the same model except for the indicated $PM_{2.5}$ metal component. The models were adjusted for $PM_{2.5}$ mass, age (years), race, maximum years of education, BMI (kg/m2), total cholesterol (mg/dL), mean arterial pressure (mmHg), diabetic status, use of beta blocker medication, alcohol intake (2 or more drinks per day or less than 2 drinks per day as reference), smoking status (current, former or never as reference), census tract percent of population age 25 years or older with less than a high school diploma, air temperature (°C), relative humidity (%) and seasonality (sine and cosine).

Discussion

To our knowledge, this is the first study to investigate the short-term effects of particle metal components on QT interval length. In the Normative Aging Study, an Eastern Massachusetts longitudinal cohort, we found that higher exposure to individual $PM_{2.5}$ metal components even after controlling for $PM_{2.5}$ mass was associated with QTc interval length, a marker for ventricular repolarization. Specifically, we found that lead was significantly associated with higher QTc interval length across most periods ranging from 0 to 7-day moving average (except 2-day moving averages) and that copper was associated with a lower QTc interval length. Since these analyses controlled for $PM_{2.5}$ mass, this finding indicates that per unit mass, Cu has a smaller effect on increasing QTc, not that it actually reduced QTc. Hence, in comparison to the other four $PM_{2.5}$ metal components, Cu is relatively less harmful for QT interval.

Our results further suggest that season, in particular the fall and summer, increases respectively the cardiovascular toxicity of nickel and vanadium. On the other hand, we found no significant associations with QT interval and zinc an indicator of traffic-related emissions. Zinc originates from zinc dithiophosphate which is an anti-wear and antioxidant produced by tire and brake wear and tailpipe emissions of motor oil[35,97,98].

Lead exposure arises from inhalation of lead particles and ingestion of polluted water and food sources[99]. While the two major sources of lead were phased out (1978, lead-based paint)[100] or banned (1986, gasoline)[101] in the United States, the resuspension of old lead particles from gas and exterior paint continue to release lead into the environment. Lead not only accumulates on the top layer of soil but will remain for generations due to its half-life of approximately 700 years[102]. Current motor vehicle sources of lead include brake wear[97], motor vehicle wheel weights[103],

vaporization from hot brake surfaces[97,104] and motor oil combustion[105]. Lead's bioavailability and presence in dust particles will have continued implications for public health.

Previous epidemiological studies on lead exposure mainly considered the cardiovascular effects of hypertension and blood pressure[106–109]. Navas-Acien et al. (2007) conducted a systematic review and concluded that a causal relationship between lead exposure and hypertension, but did not have sufficient evidence to deduce a causal relationship between lead exposure and other clinical cardiovascular outcomes[110]. In a study of the effects of bone and blood lead exposure on QTc interval length in the NAS, low-level cumulative exposure to bone lead was associated with a prolonged QTc interval, while no association was found with blood lead[111]. Specifically, individuals in the lowest tertile of tibia lead compared to the highest tertile had a 7.95 ms (95% CI: 1.42, 14.45) increase in QTc interval and no association was found for blood lead levels. While we cannot directly compare our results with these studies, they support our hypothesis that $PM_{2.5}$ lead can adversely impact cardiac conductivity through prolonged QT intervals.

Sources of nickel and vanadium include the burning of oil residual in office buildings and heavy fuel oil in marine engines[112,113]. In our study, V and Ni were highly correlated (ρ =0.84) most likely due to their joint production through oil combustion. Studies conducted in New York City found that during the fall and winter months higher nickel concentrations could be found due to residual fuel oil used for space heating[36] and that nickel could modify the association between $PM_{2.5}$ mass and daily cardiovascular hospital admissions[39]. Consistent with these findings we found a positive association between $PM_{2.5}$ nickel levels and QTc interval. Animal models have found adverse cardiovascular associations with $PM_{2.5}$ associated vanadium and nickel concentrations[38,114].

Sources of copper include brake wear and lining as well as copper additives in motor oil combustion[115,116]. Copper is an essential metal involved in the function of several enzymes and required for myocardial contractility[117]. Several studies have reported that copper deficiency impacts atherosclerosis and increases the risk of coronary heart disease[117,118]. Furthermore, both epidemiological[119–121] and animal[117,122,123] studies have reported associations between copper deficiency and blood pressure changes, hyperlipidemia, and abnormal electrocardiograms. A study in elderly individuals in South Korea found that blood pressure and heart rate variability measures were associated with lead and strontium, but did not find a statistically significant association with nickel, vanadium, zinc, or copper[124]. Although the association between copper and heart rate variability measures (Standard Deviation of Normal-to-Normal Intervals (SDNN), Root Mean Square of the Successive Differences (RMSSD), low frequency and high frequency) was not statistically significant, their analysis suggests a possible negative association with copper. However, copper is normally obtained by ingestion, not inhalation. On the other hand, inhaled copper and vanadium increased fibrinogen levels, and induced pulmonary vasoconstriction and phosphorylation of ERK1/2 and p38 in vivo[125,126]. Copper's essential function inside the human body could mediate its cardiotoxicity on cardiac conductivity and explain why we found that copper in comparison to the other metals was less harmful for QTc interval.

From a clinical perspective, the QTc interval provides a noninvasive assessment tool for ventricular repolarization. Prolonged QT intervals can predispose an individual to experience a life-threatening type of ventricular arrhythmia called torsades de pointes[15]. While a QTc interval greater than 500ms increases the risk for torsades de pointes, there is no predetermined threshold that is safe from proarrhythmic risk[15,93]. In controlled clinical trials, the US Food and Drug Administration (FDA) requires that pharmacologic medication not alter a patient's QTc interval

by more than 5 ms and warns that drugs that alter QTc between 5-20 ms have been associated with proarrhythmic risk[127]. Many of the effect estimates reported in this study are greater than 5ms and have the potential to increase the risk of arrhythmias.

Numerous biological mechanisms have been proposed to explain how acute exposure to air pollution can induce cardiovascular morbidity including elevated levels of reactive oxygen species[128], endothelial injury and systemic inflammation[129] and altered autonomic activation[92,130,131]. Several studies have reported associations between fine particle mass and cardiovascular outcomes representing these biological mechanisms, but none specifically address how $PM_{2.5}$ metal components could contribute to myocardial vulnerability (ventricular arrhythmias and repolarization dynamics).

Strengths and limitations

One limitation of our study is that the concentrations of the $PM_{2.5}$ metal components were assigned from the use of a single monitoring site. The $PM_{2.5}$ metal exposures capture temporal resolution but are not spatially resolved. There is potential for non-differential measurement error in our exposure assessment, which has been previously described[132]. It is unlikely that any measurement error in the $PM_{2.5}$ metal components concentrations is associated with the participant's ECG readings because the exposure was measured independently from the QTc interval measurements. This non-differential misclassification underestimates the observed associations and bias the results towards the null[133].

Our study minimized outcome misclassification because the ECG recordings were processed using a specific software (Trillium 3000) instead of relying on manually readings of beat labels and QT intervals. The automated processing reduced the potential of outcome differential measurement errors and inter-technician variability.

A major strength of this study is the use of multiple statistical approaches to deal with multicollinearity issues that arise from analyzing multiple exposures that are highly correlated. We were able to show the robustness of the association between lead and copper with QTc interval length with both BKMR and our sensitivity analysis. Use of BKMR, a novel flexible statistical method, allowed us to present the joint effect of the $PM_{2.5}$ metal mixtures and address multicollinearity and potential non-linear or non-additive effects. By including each individual $PM_{2.5}$ metal component and controlling for $PM_{2.5}$ mass, we gain insight into the differential toxicity of these $PM_{2.5}$ metal components. Thus, we conclude that lead on average has the most adverse impact on QTc interval length and that copper compared to the other four $PM_{2.5}$ metal components is less toxic towards ventricular repolarization.

Our inclusion of various potential confounders and use of both individual and census tract variables to control for socioeconomic status reduces the potential for residual confounding. Since the study population consists mainly of older white males, the results should be interpreted with caution if applying to others such as younger individuals, females, or other racial groups. Future studies could explore the effect of $PM_{2.5}$ metal components on QTc interval for these other populations.

Disclosures

The authors have no conflicts of interests.

CHAPTER 3: Associations between acute and long-term exposure to $PM_{2.5}$ components and temperature with QT interval length in The VA Normative Aging Study

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Abstract

Background/Objective: Our study adds to the sparse literature on the effect of multiple fine particulate matter ($PM_{2.5}$) components on QT interval length, an outcome with high clinical relevance in vulnerable populations. To our knowledge, this is the first study to examine the association between spatiotemporally resolved exposures to $PM_{2.5}$ components and QT interval length.

Methods: Among 568 men living in Eastern Massachusetts between 2000 to 2011, we utilized time-varying linear mixed-effects regressions with a random intercept for each participant to examine associations between acute (0-3 day), intermediate (4-28 day) and long-term (1 year) exposure to $PM_{2.5}$ components, temperature and heart-rate corrected QT interval (QTc). Each of the $PM_{2.5}$ components and temperature were geocoded to the participant's residential address using a validated hybrid exposure model and gridMET predictions, respectively. We also evaluated whether diabetic status modifies the association between $PM_{2.5}$ components and QTc interval.

Results: We found consistent results that higher sulfate levels and colder temperatures were associated with significant longer QTc across all moving averages except the day of exposure. The greatest effect of sulfate and temperature on QTc interval was detected for the 28-day moving average. In the multi-pollutant model, each 1.6 $\mu g/m^3$ IQR increase in daily sulfate levels was associated with a 15.4 ms (95% CI: 10.4, 20.4) increase in QTc interval and in the single-pollutant models a 15.5 ms (95% CI: 11.7, 19.3) increase in QTc interval. Other secondary particles such as nitrate and organic carbon also prolonged QT interval, while the primary particles of elemental

carbon decreased QT interval. We found that diabetic status could amplify the association between certain $PM_{2.5}$ components (elemental carbon, nitrate, organic carbon and sulfate) and QTc interval.

Conclusions: Both acute and long-term exposure to $PM_{2.5}$ components and temperature are associated with changes in ventricular repolarization as measured by QT interval length.

Funding: USEPA Grant RD83479801 & RD83587201; NIH grant T32ES007069

Introduction

Epidemiological studies have shown an association between exposure to air pollution and increased risks of cardiovascular mortality[134,135], arrhythmias[9,136], stroke[137], myocardial infarctions[138], and exacerbation of heart failure[139]. While many studies have demonstrated associations of higher fine particle pollution with electrophysiologic abnormalities, far fewer have evaluated which components of particles or meteorological variables might be responsible for these abnormalities. Moreover, relatively few studies have studied QT prolongation as an outcome, even though in vulnerable patients it can be a risk factor for ventricular arrhythmias with clinical import[41,46,140]. Studies have proposed that a prolonged QT interval and T-wave abnormalities are indicative for an increased risk of arrhythmias[141], cardiovascular heart disease and cardiovascular mortality[142].

Fine particulate air pollution ($PM_{2.5}$) includes particles of an aerodynamic diameter of less than 2.5 µm and consist of a mixture of multiple organic and inorganic compounds. Sources of $PM_{2.5}$ include both natural and anthropogenic sources such as auto vehicle emissions, fossil fuel combustion, industrial activities[34–36]. $PM_{2.5}$ components can either be directly emitted into the atmosphere (primary components) or they are formed through chemical reactions in the atmosphere (secondary components)[40]. A previous study in an elderly population found that exposure to black carbon, similar to organic carbon, in the previous hour was associated with an increased QTc (2.54 ms; 95% CI: 0.28, 4.80), while no association was found between QTc and $PM_{2.5}$ mass, sulfur dioxide and ozone[41]. Furthermore, a separate study in the same cohort found that temperature was associated with a longer QTc interval for moving averages between 4 and 28 days[42]. However, these studies utilized central site monitoring data as a proxy for personal exposure or only focused on one component of $PM_{2.5}$.

We hypothesized that both acute (0-3 day), intermediate (4-28 day) and long-term (1 year) exposure to $PM_{2.5}$ and its specific components would be related to an increase in heart rate corrected QT interval (QTc) among 568 men living in Eastern Massachusetts. Furthermore, we assessed whether this association was modified by the participant's diabetic status and whether the effect estimates remained stable if we excluded $PM_{2.5}$ components that were highly correlated with each other. To our knowledge, this is the first study to assess the effects of multiple $PM_{2.5}$ components and temperature on ventricular repolarization with geocoded exposures.

Methods

Study population

The participants in this study included 568 elderly men living in Eastern Massachusetts who are part of the Veterans Affairs Normative Aging Cohort with up to four visits during the period 2000-2012. Inclusion criteria for the initial cohort required no previous history of chronic disease and the ability to participate in at least one onsite physical examination and questionnaire every 3 to 5 years. Previous studies have reported the enrollment and inclusion requirements in more detail[41,90]. In brief, physical examinations and interviews provided information on the participants height and weight to calculate their Body Mass Index (BMI), current medication use and fasting blood samples to assess cholesterol levels[91]. Smoking and drinking status were obtained from physician administered questionnaires. Diabetic status was assigned based on a physician's diagnosis of type II diabetes or the reported use of diabetic medication during a study visit. Mean atrial pressure (MAP) was calculated from the systolic and diastolic blood measured by the physician during a site visit.

While there were 581 total participants during this time with at least one QTc measurement, only 568 of them had all the necessary covariates for this analysis. Two participants were missing information on their smoking status and four were missing information on their education level. One was missing information on their race and another one their cholesterol level. Furthermore, five participants were excluded with no information on one of the six $PM_{2.5}$ components. Between November 14, 2000 and December 21, 2011, these 568 participants came in for a total of 1040 study visits.

The Institutional Review Boards of participating institutions, Harvard T.H. Chan School of Public Health, and the Veteran Administration, approved the study protocol and all participants provided written informed consent.

ECG measurement and analysis

QTc measurements were obtained from electrocardiogram measurements (ECG). These measurements were obtained at the exam site (VA Boston Healthcare System, Boston, MA) for 5 to 10 min between 05:30 and 14:00 hours with a two-channel (five lead) ECG monitor (Trillium 3000; Forest Medical, Inc., East Syracuse, NY) using a sampling rate of 256 Hz per channel[92]. An earlier study provides more detailed report on how the ECG measurements were processed to attain the corrected QT interval values[42]. Briefly, the ECG recordings were processed using the Trillium 3000 software to create a Mathcad (Parametric Technology Corporation, Needham, MA) file that includes the QT interval values. Corrected QT values were calculated using Bazett's formula by only measuring the start of a normal or supraventricular beat to the end of a T wave with sufficient amplitude[42,93]. QTc measurements were expressed in milliseconds (ms).

$PM_{2.5}$ components and meteorological data

We retrieved daily $PM_{2.5}$ predictions at 1 km × 1 km grid cells in the continental U.S. using a well-validated model incorporating land use, meteorology, chemical transport models, and satellite remote sensing. Three models were trained using a neural network model, a random forest, and gradient boosting, and then ensemble averaged using a geographically weighted regression[59]. Each participant's residential address was linked to the nearest center of a 1 km × 1 km grid cell for their exposure estimate. The study focused on five $PM_{2.5}$ components and temperature chosen *a priori*: $PM_{2.5}$ mass, elemental carbon, organic carbon, sulfate, and nitrate based on previous literature. Each of the $PM_{2.5}$ components were geocoded to the participant's residential address using a validated hybrid exposure model, which has previously been described in detail[143].

We obtained daily minimum and maximum surface meteorological data for temperature and relative humidity at a spatial resolution of 4 km x 4 km from gridMET for the continental U.S.[144]. The minimum and maximum daily measurement was averaged to create a daily temperature or daily relative humidity value. Afterwards, each participant's residential address was lined to the nearest center of a 4 km x 4 km grid cell for their exposure estimate. To evaluate the effect of both short and long-term $PM_{2.5}$ exposure, we focused on 0-28 days and 1 year moving averages of exposure before the participant's study visit.

Statistical analysis

We utilized time-varying linear mixed-effects regressions with a random intercept to analyze associations between QTc interval and moving averages (0 to 365 day moving averages) of 24-hour mean concentrations of geocoded $PM_{2.5}$ component mixtures ($PM_{2.5}$ mass, elemental carbon, organic carbon, sulfate and nitrate) and temperature. We report the changes in QTc interval

in milliseconds and 95% CI in QTc interval for an interquartile range (IQR) increase in 0 to 365 day moving average for each individual $PM_{2.5}$ component.

Two different models were used to examine the association between $PM_{2.5}$ geocoded components and temperature with QTc interval. The first model was a multi-pollutant model where all the individual components were included, and the second model was a single-pollutant model that consisted of each individual $PM_{2.5}$ components and temperature. All models were adjusted for the following covariates: age (years), race, maximum years of education, BMI (kg/m^2), total cholesterol (mg/dL), mean arterial pressure (mmHg), diabetic status, use of beta blocker medication, alcohol intake (2 or more drinks per day or less than 2 drinks per day as reference), smoking status (current, former or never as reference), census tract percent of population age 25 years or older with less than a high school diploma, relative humidity (%) and seasonality (sine and cosine).

We also evaluated whether diabetic status would modify the association between the $PM_{2.5}$ components and QTc interval in the multi-pollutant model. The participants were classified into two groups by a history of diabetes (diabetic versus not diabetic). We included interaction terms between the possible effect modifier and each $PM_{2.5}$ component and temperature. In addition, we performed a sensitivity analysis to assess if the effect estimates reported in the multi-pollutant model would change when excluding $PM_{2.5}$ mass, which was highly correlated to the other $PM_{2.5}$ components.

Data management and all statistical analyses were conducted using R version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

The study included 568 VA Normative Aging Study participants who had all the relevant covariates for this analysis. The participants were older males with a mean age (± SD) of 75.7 years ± 6.9 years who were mostly white (96.7%). Table 3-1 presents other characteristics of these study participants. Among the study participants between November 14, 2000 and December 21, 2011, the mean QTc interval (± SD) was 385.3 ms ± 51.8 ms. Among the diabetic participants, the mean QTc interval was 385.9 ms ± 61.1 ms while the mean QTc interval among non-diabetics was 385.2 ± 49.1 ms

Table 3-1: Baseline characteristics of the 568 study participants in the VA Normative Aging Study during the study period between November 14, 2000 and December 21, 2011

Characteristics	**Mean (SD)**	**N (%)**
Age (years)	75.7 (6.9)	
Race		
White		549 (96.7)
Black		13 (2.3)
Hispanic (White)		5 (0.9)
Hispanic (Black)		1 (0.2)
Body mass index (kg/m^2)	27.8 (4.1)	
Total cholesterol (mg/dL)	182.9 (37.5)	
Mean arterial pressure (mmHg)	89.6 (11.1)	
Diabetes		
Yes		112 (19.7)
No		456 (80.3)
Beta blocker medication		
Yes		222 (39.1)
No		346 (60.9)
Maximum years of education	15.1 (3.0)	
Alcohol intake		
<2 drinks per day		452 (79.6)
2+ drinks per day		99 (17.4)
Smoking status		
Never smoker		169 (29.8)
Current smoker		28 (4.9)
Former smoker		371 (65.3)

Table 3-2 presents the summary statistics and Spearman's correlations between the $PM_{2.5}$ components and temperature for the study period. During this time, the median $PM_{2.5}$ mass

concentration was 8.5 μg/m^3 and the highest correlation between $PM_{2.5}$ components was between $PM_{2.5}$ mass and sulfate (Spearman correlation coefficient, $\rho = 0.69$). The $PM_{2.5}$ components were positively correlated with each other except. Temperature was negatively correlated with elemental carbon and nitrate and positively correlated with the other $PM_{2.5}$ components. The highest negative correlation existed between temperature and nitrate (Spearman correlation coefficient, $\rho = -0.38$).

Table 3-2: Summary statistics and Spearman's correlation coefficients of $PM_{2.5}$ components and meteorological measurements in the VA Normative Aging Study between November 14, 2000 and December 21, 2011

	Summary Statistics		Spearman's correlation coefficients					
	Mean (SD)	**Median (IQR)**	**$PM_{2.5}$**	**EC**	**OC**	**Sulfate**	**Nitrate**	**Temp**
$PM_{2.5}$ (μg/m^3)	10.3 (6.4)	8.5 (6.8)	1.00	0.45	0.59	0.69	0.49	0.20
EC (μg/m^3)	0.56 (0.27)	0.52 (0.30)		1.00	0.55	0.36	0.34	-0.01
OC (μg/m^3)	2.95 (1.58)	2.67 (1.79)			1.00	0.47	0.26	0.21
Sulfate (μg/m^3)	2.96 (2.49)	2.29 (2.09)				1.00	0.48	0.18
Nitrate (μg/m^3)	1.19 (1.11)	0.82 (0.98)					1.00	-0.38
Temp (°C)	11.5 (5.3)	11.8 (8.2)						1.00

Abbreviations: SD- standard deviation; IQR- interquartile range; $PM_{2.5}$- fine particulate matter mass; EC- elemental carbon; OC- organic carbon; Temp- temperature.

Figure 3-1 shows the results from the multi-pollutant linear mixed-effects regression model with all the $PM_{2.5}$ components and temperature included in the same model (Multi-pollutant) and the single-pollutant models including each $PM_{2.5}$ component and temperature (Single-pollutant). The two models consistently showed that sulfate had a statistically significant effect on QTc interval across all moving averages except for the day of exposure (day 0). The greatest effect of sulfate on QTc interval was detected for the 28-day moving average sulfate exposure for both the multi-pollutant and single-pollutant model. In the multi-pollutant model, each 1.6 μg/m^3 IQR increase in daily sulfate levels for a 28-day moving average was associated with a 15.4 ms (95%

CI: 10.4, 20.4) increase in QTc interval. In the single-pollutant models with sulfate, each 1.6 $\mu g/m^3$ increase in daily sulfate levels for a 28-day moving average was associated with a 15.5 ms (95% CI: 11.7, 19.3) increase in QTc interval. The results for sulfate were the most robust across the different $PM_{2.5}$ components and moving averages.

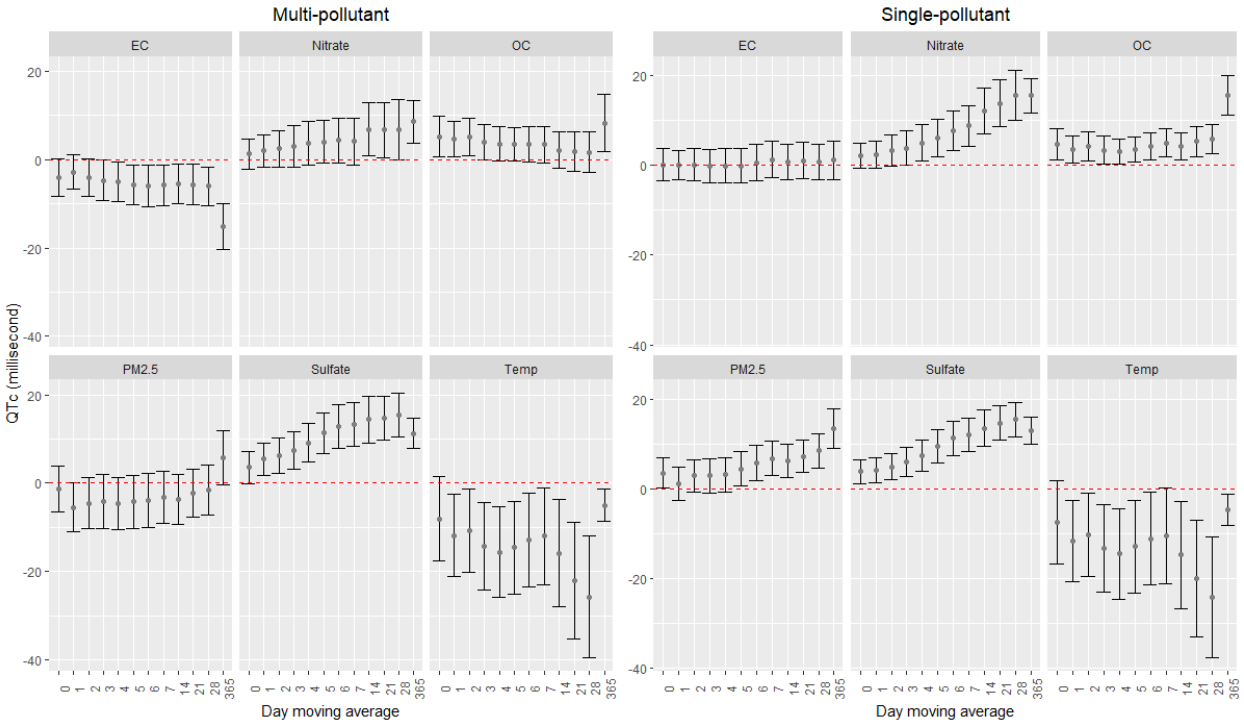

Figure 3-1: Changes in milliseconds and 95% CI in QTc interval for an IQR increase in 0 to 28 day moving average and 1 year moving average of each $PM_{2.5}$ component. The results are presented in a multi-pollutant model where all the $PM_{2.5}$ components and temperature are included in the same model and the single-pollutant model, which includes each individual $PM_{2.5}$ component or temperature. The models are adjusted for age (years), race, maximum years of education, BMI (kg/m^2), total cholesterol (mg/dL), mean arterial pressure (mmHg), diabetic status, use of beta blocker medication, alcohol intake (2 or more drinks per day or less than 2 drinks per day as reference), smoking status (current, former or never as reference), census tract percent of population age 25 years or older with less than a high school diploma, relative humidity (%), and seasonality (sine and cosine).

Furthermore, the two models consistently reported that increases in temperature were associated with decreasing QTc interval. The greatest effect of temperature occurred on the 28-day moving average for both the multi-pollutant model and the single-pollutant model. In the

multi-pollutant model, each 15.4 C increase in daily temperature for a 28-day moving average was associated with a 25.8 ms (95% CI: -39.6, -12.0) decrease in QTc interval. In the single-pollutant models with temperature, each 15.4 C decrease in daily temperature for a 28-day moving average was associated with a 24.2 ms (95% CI: -37.7, -10.6) increase in QTc interval. Thus, colder temperatures significantly prolong QTc interval.

There is also evidence that organic carbon increased QTc interval. Both the multi-pollutant model and the single-pollutant model suggest that long-term exposure (1-year moving average) was the most relevant. In the multi-pollutant model, each 1.3 $\mu g/m^3$ IQR increase in daily organic carbon levels for a 1-year moving average was associated with a 8.3 ms (95% CI: 1.9, 14.8) increase in QTc interval and in the single-pollutant model a 1-year moving average exposure of organic carbon was associated with 15.7 ms (95% CI: 11.1, 20.2) increase in QTc interval (see Figure 3-1).

The multi-pollutant model illustrates that elemental carbon has a statistically significant negative association with QTc interval. In particular, the multi-pollutant model showed that each IQR increase for a 1-year moving average of elemental carbon was associated with a -15.1 ms (95% CI: -20.4, -9.9) decrease in QTc interval. Focusing on nitrate, the multi-pollutant model suggested that nitrate had a positive association with QTc interval for intermediate and long-term exposures (14, 21, 28 and 1-year moving averages), but not for shorter time periods.

For our sensitivity analysis, we removed $PM_{2.5}$ mass to assess if the results were due to multicollinearity with the other $PM_{2.5}$ components and the results remained consistent (Figure 3-2).

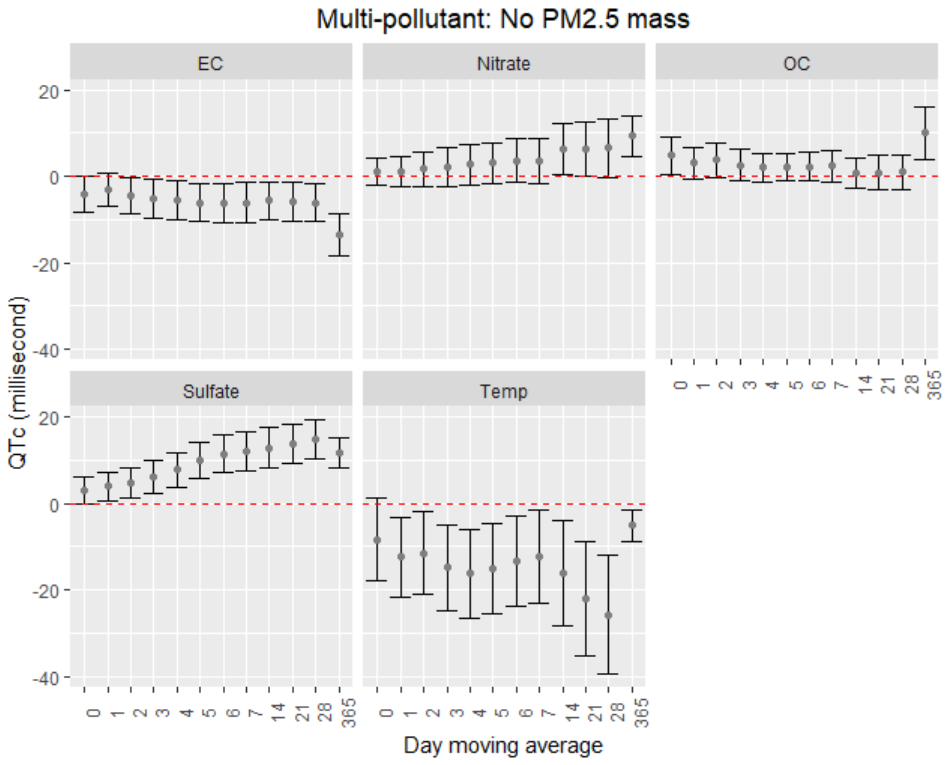

Figure 3-2: Change in QTc interval length and 95% CI for an IQR increase in 0 to 28 day and 1-year moving averages of each $PM_{2.5}$ component and temperature, but not including $PM_{2.5}$ mass. The results are presented in a multi-pollutant model where all the $PM_{2.5}$ components and temperature are included in the same model except for the indicated $PM_{2.5}$ component. The model was adjusted for age (years), race, maximum years of education, BMI (kg/m^2), total cholesterol (mg/dL), mean arterial pressure (mmHg), diabetic status, use of beta blocker medication, alcohol intake (2 or more drinks per day or less than 2 drinks per day as reference), smoking status (current, former or never as reference), census tract percent of population age 25 years or older with less than a high school diploma, relative humidity (%), and seasonality (sine and cosine).

We found that diabetic status modified the association between certain $PM_{2.5}$ components and QTc interval (see Figure 3-3). Specifically, diabetic status amplified the associations seen in the multi-pollutant model between QTc interval and elemental carbon, organic carbon, nitrate, and sulfate. Thus, diabetic individuals experienced a greater change in QTc interval in comparison to non-diabetics for these four $PM_{2.5}$ components. Among non-diabetic individuals, long-term exposure to $PM_{2.5}$ mass was positively associated with QTc interval. In particular, the multi-pollutant model among non-diabetics showed that each 2.3 $\mu g/m^3$ IQR increase for a 1-year

moving average of $PM_{2.5}$ mass was associated with an 8.9 ms (95% CI: 2.6, 15.6) increase in QTc interval. We did not have an association between temperature and QTc interval among diabetics. However, we did find similar associations from the main multi-pollutant model (Figure 3-1) between temperature and QTc interval among the non-diabetics. The greatest association between temperature and QTc interval continued to be on the 28-day moving average of temperature among the non-diabetics.

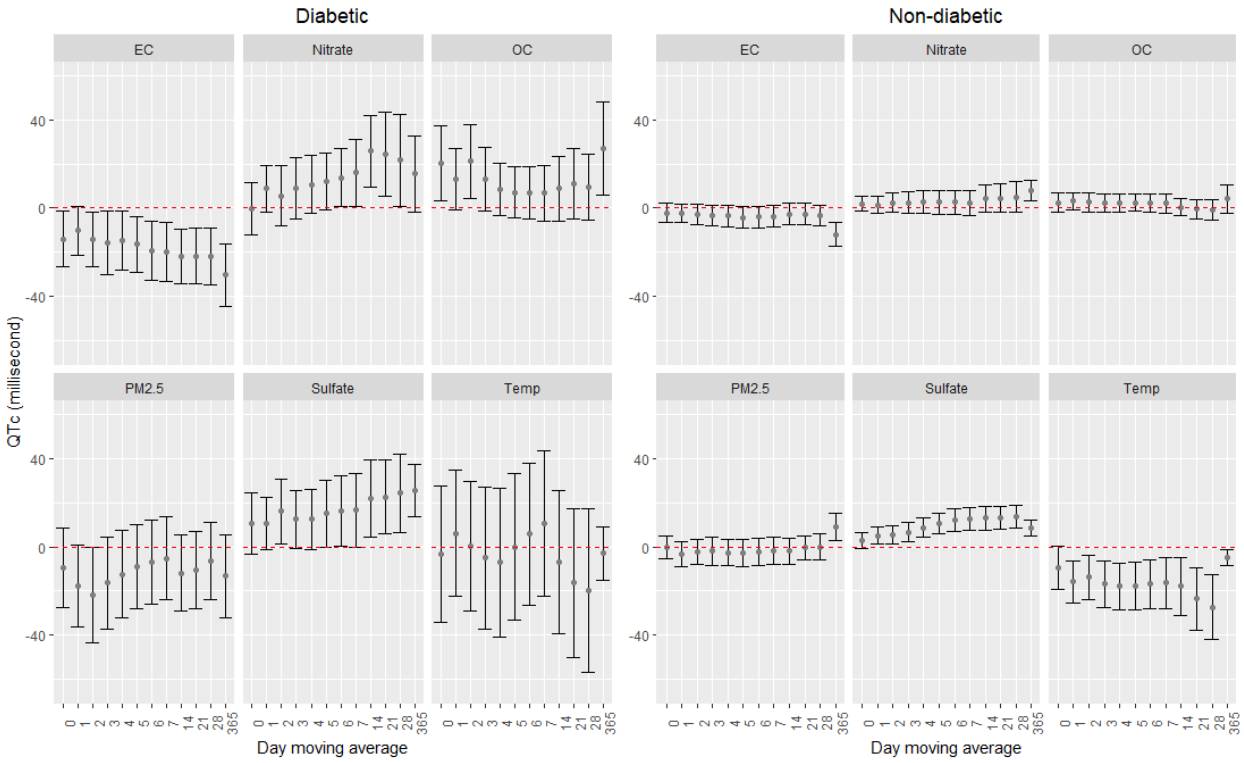

Figure 3-3: Change in QTc interval length and 95% CI for an IQR increase in 0 to 28 day and 1-year moving for each $PM_{2.5}$ component and temperature in the multi-pollutant model among diabetic and non-diabetic individuals. The model was adjusted for the main effects of each $PM_{2.5}$ component and temperature, the interaction term between the $PM_{2.5}$ component and the dichotomous indicator variable for diabetic status, age (years), race, maximum years of education, BMI (kg/m^2), total cholesterol (mg/dL), mean arterial pressure (mmHg), diabetic status, use of beta blocker medication, alcohol intake (2 or more drinks per day or less than 2 drinks per day as reference), smoking status (current, former or never as reference), census tract percent of population age 25 years or older with less than a high school diploma, relative humidity (%), and seasonality (sine and cosine).

Discussion

Our study adds to the sparse literature on the effect of multiple $PM_{2.5}$ air pollutant components on QT interval length, an outcome with high clinical relevance in vulnerable populations. In the Normative Aging Study, a longitudinal cohort of older men, we found that increased levels of $PM_{2.5}$ components were associated with both prolonged and decreased QT interval length. We detected that sulfate and temperature were significantly associated with elevated QTc interval length across all the moving averages except for the day of exposure. In particular, colder temperatures were associated with prolonged QTc interval length. We also found that organic carbon was associated with prolonged QTc interval length for both acute time periods (0 to 2-day moving averages) and long-term exposure (1-year moving average).

On the other hand, elemental carbon showed a negative association with QTc interval for intermediate and long-term exposures (3 day to 1-year moving averages). Our findings suggest that secondary $PM_{2.5}$ (sulfate, nitrate, and organic carbon) can increase QTc interval, while a primary component (elemental carbon) can have decrease effect on QTc interval. Further studies are needed to evaluate these associations.

We observed evidence of effect measure modification by diabetic status in the associations between certain $PM_{2.5}$ components (elemental carbon, nitrate, organic carbon, and sulfate) and QTc interval. Our results suggest that that diabetic status can cause individuals to be more vulnerable to the effects of these four $PM_{2.5}$ components by prolonging their QTc interval. Diabetic individuals tend to have a longer QTc interval compared to others without diabetes possibly due to a variety of autonomic abnormatlities[145]. Furthermore, diabetic individuals experience elevated biomarkers of oxidative stress especially among more vulnerable populations such as the elderly[146,147]. Several studies have shown that diabetic status can modify the association between

$PM_{2.5}$ exposure and cardiac conduction abnormalities[148–150]. These results are supported by evidence from the same cohort that showed that the association between QTc interval and black carbon was stronger among diabetic participants[41]. We also found that non-diabetic status amplified the association between long-term $PM_{2.5}$ mass exposure and temperature. Further studies are needed to examine these associations.

From a clinical perspective, the QTc interval provides a noninvasive assessment tool for ventricular repolarization. Abnormally prolonged QTc intervals and wide T waves are associated with increased risks of arrhythmias[151]. A QTc interval greater than 450 ms is considered irregular[127]. In controlled clinical trials, the US Food and Drug Administration (FDA) requires that pharmacologic medication not alter a patient's QTc interval by more than 5 ms and warns that drugs that alter QTc between 5-20 ms have been associated with proarrhythmic risk[127]. Thus, our reported effect sizes that are greater than 5 ms all fall within the associated proarrhythmic risk.

Numerous biological mechanisms have been proposed to explain how acute exposure to air pollution can induce cardiovascular morbidity including elevated levels of reactive oxygen species[128], endothelial injury and systemic inflammation[129] and altered autonomic activation[92,130,131]. Several studies have reported associations between fine particle mass and cardiovascular outcomes representing these biological mechanisms, but none specifically address how a mixture of $PM_{2.5}$ components and temperature could contribute to repolarization dynamics.

Strengths and limitations

This study improves on previous air pollution measurements and meteorological information utilized for this longitudinal cohort population. Rather than utilizing central site monitoring data like previous studies[41,42], this study assigned exposure based on participants' residential address using a validated hybrid exposure model, which has previously been described

in detail[143]. The use of a spatiotemporal model for $PM_{2.5}$ components and temperature reduce the potential for measurement error. However, the assigned exposures do not consider a participant's mobility outside their residential address. Nevertheless, this potential misclassification is nondifferential because participants with lower exposure are not likely to have more misclassification error than participants with higher exposure. We would expect reducing this nondifferential error would produce greater effect estimates and narrower confidence intervals.

A major strength of this study is the use of multiple models and sensitivity analysis to address possible multicollinearity issues that arise from analyzing multiple exposures that are highly correlated. A previous study in the same cohort[46], reported positive associations between sub-chronic and long-term $PM_{2.5}$ mass exposure and QTc interval, but only included $PM_{2.5}$ mass and temperature in their models. We were able to show that a robust positive association between secondary particles (sulfate, nitrate, and organic carbon) and QTc interval and a robust negative association for primary particles of elemental carbon and QTc interval with our analysis.

By including multiple $PM_{2.5}$ components and assessing acute-, intermediate-, and long-term exposure, we were able to better understand the differential toxicity of these components across various time windows. Finally, this study also consists of older men who are predominantly white, thus the observed findings may not be generalizable to women, younger individuals, or to other racial and ethnic groups. Further studies are needed to see if the results would be consistent across other vulnerable and high-risk populations.

We conclude that exposure to colder temperature and secondary particles on average prolongs QTc interval length and elemental carbon compared to the other components is less toxic towards QTc interval, a marker of ventricular repolarization.

DISCLOSURES

The authors have no conflicts of interests.

CONCLUSIONS

In this dissertation, we have applied a variety of study designs to better understand the associations between the components of fine particulate air pollution and cardiovascular health. First, we applied a time-stratified case-crossover analyses to demonstrate that intermediate (21-day) $PM_{2.5}$ exposure was associated with higher odds of a ventricular arrhythmia event onset among patients with known cardiac disease and indication for ICD implantation independently of particle radioactivity. We found evidence that particle radioactivity modifies the association between $PM_{2.5}$ and the risk of ventricular arrhythmias. It was the first study to investigate how joint exposure to both fine particulate matter and particle radiation affects high-risk populations, which could have important implications for cardiac health and prevention strategies.

In our second study, we applied a longitudinal cohort study design and found that exposure to metals contained in $PM_{2.5}$, particularly lead and copper, were associated with acute changes in ventricular repolarization as indicated by increased QTc intervals. We employed Bayesian kernel machine regression (BKMR), a novel flexible statistical method, that allowed us to present the joint effect of the $PM_{2.5}$ metal mixtures and address multicollinearity and potential non-linear or non-additive effects. By including each individual $PM_{2.5}$ metal component and controlling for $PM_{2.5}$ mass, we gain insight into the differential toxicity of these metal components. We concluded that lead on average has the most adverse impact on QTc interval length and that copper compared to the other four $PM_{2.5}$ metal components was less toxic towards ventricular repolarization. Since the $PM_{2.5}$ metal components (vanadium, nickel, copper, zinc, and lead) measured at the Harvard Supersite monitoring station, we wanted to explore how other $PM_{2.5}$ components that were geocoded to residential addresses could impact QTc interval.

In our final study, we utilized time-varying linear mixed-effects regressions to examine associations between acute (0-3 day), intermediate (4-28 day) and long-term (1 year) exposure to

components of fine particulate air pollution, temperature and heart-rate corrected QT interval. Each of the $PM_{2.5}$ components were geocoded to the participant's residential address using a validated hybrid exposure model. We found consistent results that higher sulfate levels and colder temperatures were associated with significant higher QTc across all moving averages except for the day of exposure (day 0). We also found that organic carbon was associated with prolonged QTc interval length for both acute time periods (0 to 2-day moving averages) and long-term exposure (1-year moving average). On the other hand, elemental carbon showed a negative association with QTc interval for intermediate and long-term exposures (3 day to 1-year moving averages).

Our findings suggest that secondary air pollution particles (sulfate, nitrate, and organic carbon) can increase QTc interval while some primary air pollution particles (elemental carbon) can have decrease effect on QTc interval. We also found that diabetic status could modify the association between certain $PM_{2.5}$ components and QTc interval.

While this thesis contributes to the field of cardiovascular and air pollution epidemiology, it also emphasizes the need for further studies. The results from the three studies have certain limitations when applied to not at risk or elderly populations. Further studies are needed to explore if these associations persist in healthier, younger, and more diverse populations across different regions of the U.S. Studies should focus on improving models of personal exposure to different $PM_{2.5}$ components including metals. Further studies are needed to explore if associations between different markers of ventricular repolarization and mixtures of both acute and longer-term pollutants exist among other high-risk populations.

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