Vanadium in Fine Particulate Matter and its Association with Blood Pressure in the Multi-Ethnic Study of Atherosclerosis Cohort

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Abstract

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BACKGROUND: Associations between estimates of long-term population exposure to fine airborne particulate matter (PM2.5) and cardiovascular endpoints, especially mortality, have now been reported in several population cohort studies. More recently, several studies have linked PM2.5 with increases in blood pressure, but the components of PM2.5 primarily responsible for these changes in blood pressure are not well studied. Although a few studies have linked trace elements such as copper, zinc, and nickel with elevations in blood pressure, the effects of ambient vanadium on blood pressure are unknown. The purpose of this study is to determine if estimated PM2.5 vanadium exposure is associated with systolic and diastolic blood pressure.

METHODS: The primary outcomes were cross-sectional measurements in 2005-2007 of seated systolic and diastolic blood pressure from 5517 participants aged 45-84 in the Multi-Ethnic

Study of Atherosclerosis (MESA). Individual-level ambient exposure to vanadium was estimated using existing geospatial modeling predictions developed by MESA Air and the National Particle Components Toxicity (NPACT) Initiative. Incrementally richer regression models were used to adjust for the following covariates: age, gender, race/ethnicity, educational level, income, smoking status, alcohol use, blood lipids, body mass index, blood glucose, city region, and anti-hypertensive usage. Sensitivity analyses were conducted by restricting analysis to those not taking anti-hypertensive medications, and to those who had lived at one address since 1980. Additionally some of the models included adjustment variables for other PM2.5 metals.

RESULTS: In our primary model with adjustment for city region, mean systolic blood pressure (SBP) increased by 0.4 mm Hg per interquartile range (IQR) increase in vanadium (V) concentration, 95% CI [-1.1, 1.8]. There was no effect on mean diastolic blood pressure (DBP). The effect estimate for SBP was in the negative direction when there was no adjustment for city region. The effect estimates for SBP and DBP became larger (1.4 mm Hg [-0.5, 3.3] and 1.1 mm Hg [0.1, 2.0]), respectively, in city-adjusted analyses after excluding study subjects taking anti-hypertensive medications. The findings were somewhat sensitive to adjustment for other PM2.5 metals, depending on the metal.

CONCLUSION: These results indicate that exposure to vanadium may be associated with increases in both SBP and DBP. Because the findings were primarily seen in those not taking anti-hypertensive medications and were somewhat model-dependent, these findings need to be interpreted cautiously and replicated in other cohorts. Investigating potential effects of other PM2.5 components will also be of interest.

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Chapter I: Introduction and Background

Hypertension is a leading risk factor for developing stroke and ischemic heart disease. It is estimated that 7.6 million premature deaths worldwide are attributed to hypertension.[1,2] Hypertension is known as the "silent killer" because over long periods of time increased peripheral vascular resistance leads to arterial wall damage, making an individual more susceptible to plaque accumulation and vessel narrowing. Ultimately this places a person at high risk of myocardial infarction, stroke, and kidney disease.[2,3] The most common known modifiable risk factors for hypertension are high-salt diet, smoking, lack of physical activity, and obesity.[2] However, many researchers have questioned whether there are extrinsic risk factors in our environment. In its 2002 World Health Report, the WHO estimated that 2% of cardiopulmonary mortality and 3 million premature deaths annually are attributed to air pollution.[4,5] Investigation of ambient particulate matter in air pollution and its relationship to cardiovascular disease may further lead to changes in environmental policy, affecting the health status of millions of people that reside in cities with high air pollutant concentrations.

In recent years associations have been made between fine particulate matter (PM2.5) and adverse cardiovascular outcomes.[6-9] Several studies serve to demonstrate a pathophysiological mechanism in which the toxicity of PM2.5 results in oxidative stress, ultimately leading to atherosclerosis and other cardiovascular dysfunction.[10,11] A proposed mechanism is that nitric oxide synthase may become down regulated by inhaled particles, thus having effects on the autonomic nervous system and ultimately leading to vascular stiffening and changes in cardiac output, thereby linking pulmonary inflammation to oxidative stress and atherosclerosis.[12] However, there have been very few large enough epidemiological studies to demonstrate that individuals exposed to high levels of PM2.5 have higher mean systolic or diastolic blood

pressure than those exposed to lower levels. A meta-analysis of nearly 114,000 participants from 15 cohort studies participating in the European Study of Cohorts for Air Pollution Effects (ESCAPE), showed that particulate matter from traffic exposure within 100 miles of a participant's residence was associated with small increases in systolic and diastolic blood pressure, with an estimated odds ratio of 1.05 [95% CI: 0.99, 1.11] for hypertension.[13] Schwartz et al. found that statistically significant associations between 1-year average black carbon exposure and elevated systolic and diastolic blood pressures.[14] Studies utilizing data from the Multi-Ethnic Study of Atherosclerosis (MESA) and the MESA Air cohort have served to develop possible biological pathways linking pollutant exposure to adverse cardiac outcomes.[11,15-19] Auchincloss et al. was the first to look at blood pressure outcomes up to 90 days after exposure to PM2.5, by conducting a cross-sectional study using MESA cohort data. She and her colleagues found that short-term exposure to PM2.5 was positively associated with increased systolic blood pressure and pulse pressure in individuals between 45-84 years of age.[17] Stronger evidence for an association between PM2.5 and elevated systolic blood pressure arise from a double blinded randomized control trial of 45 nonsmoking individuals that were divided into a filtered air verses diesel exhaust arm. Diesel exhaust is known to be a large source of PM2.5 exposure. It was found that subjects exposed to diesel exhaust had mean elevations in systolic blood pressure of 3.8 and 5.1 mm Hg 30 and 60 minutes after exposure, respectively, but no statistically significant change in diastolic blood pressure or heart rate.[20] Another study showed that exposure to concentrated ambient particles leads to increases in both systolic and diastolic blood pressure in individuals with pre-existing heart disease.[21]

Very little is known about the toxicity of the individual components of PM2.5 and their effect on the vasculature. Historically trace metals such as lead are associated with

hypertension.[22] Very few scientific studies have investigated the cardiovascular effects of ambient vanadium exposure, whose primary source is residual oil burning. One study by Bell et al. found that residency in particular geographic locations, during seasons when PM2.5 had higher fractions of nickel, vanadium, and elemental carbon, was associated with higher rates of respiratory and cardiovascular hospitalizations, leading to another study by the same authors to look at vanadium exposure specifically and its relationship to respiratory and cardiovascular admissions. In their follow-up study, one IQR increase in vanadium was associated with a 2.75% [1.76, 3.75] and 1.16% [0.43, 1.89] increase in respiratory and cardiovascular admissions respectively.[23,24]

Vanadium is a heavy metal that is found naturally in the Earth's crust at concentrations of 100-150 ppm.[25] Vanadium is always in a bound state and is found in about 65 different minerals among which are patronite, vanadinite, carnotite and bauxite. It is often used as a catalyst in commercial processes such as in the production of sulfuric acid. The most common use for vanadium is for the addition to steel and iron alloys for increased durability and resistance to rusting. Occupational exposures to aerosolized vanadium-containing compounds occur in steel manufacturing, ceramic and fabric-printing industries (due to vanadium compounds used as a colorant and mordant), and boiler manufacturing or repair.[25,26] Most environmental pollution from vanadium is as a result of aerosolized byproducts from oil and coal combustion that contain this metal. The general populations' ambient exposure to vanadium mainly arises from residual oil fly ash from combustion of fuel oils originating from oil refineries, coal-burning power plants, vehicles, and marine vessels, but also can be from dust near steel manufacturing plants.[25,27,28] Crude oil has a wide range of vanadium concentration (3-257 ppm) depending on

the specific type and source of crude oil. Particulate matter from coal ash tends to have vanadium concentrated on its outer surface, with an overall vanadium concentration of 19-126 ppm.[25,29]

There are several known adverse effects of vanadium to human health. Inhalation of air containing vanadium can cause lung irritation, sore throat, wheezing, chest pain, rhinorrhea, and asthma.[29] Of the organ tissues, lungs have the highest concentration of vanadium, reflecting that inhalation is the primary route of exposure that may induce long-term adverse health effects. Inhaled vanadium from PM2.5 is highly water soluble, and therefore may easily produce systemic effects.[27] Exposure to vanadium also may result in neurological symptoms to include headache and tremors. Contact with the skin can cause localized irritation and dermatitis. Animal toxicology studies have demonstrated that high doses of vanadium resulted in arrhythmias, ECG changes and elevations in systolic and diastolic blood pressure.[26] Changes in cardiac physiology were evident through studies by Jackson in the early 1900s showing that intravenous administration of vanadium to dogs leads to marked vasoconstriction of the visceral arteries.[25] However, long-term effects of vanadium in humans are not well studied.

Based on preliminary studies by Bell et al. and Ostro et al., it is hypothesized that increased exposure to vanadium is associated with elevations in both systolic and diastolic blood pressure. To explore this hypothesis, we conducted a cross-sectional analysis to determine if there is an association between estimated $PM_{2.5}$ vanadium concentrations and two continuous outcome measures: systolic blood pressure and diastolic blood pressure. By determining what role vanadium in PM2.5 plays in regards to hypertension, we can contribute to characterizing how individual components in PM2.5 are related to adverse cardiovascular effects.

Chapter II: Methods

Study Setting

The Multi-Ethnic Study of Atherosclerosis (MESA) began in July 2000 to investigate the prevalence, correlates, and progression of subclinical cardiovascular disease (CVD). MESA contains 6,814 men and women between 45 and 84 years of age. Approximately 38% of the cohort is White, 28% African-American, 23% Hispanic, and 11% Asian (of Chinese descent). Women make up 52% of the cohort. The participants are selected from six different US cities to include: Forsyth County, NC, Northern Manhattan and the Bronx, NY, Baltimore City and Baltimore County, MD, St. Paul, MN, Chicago, IL, and Los Angeles County, CA. Clinical examinations were conducted on these individuals in order to obtain comprehensive data on cardiovascular-related endpoints such as body mass index, blood pressure, and blood lipid levels. Data collection on the participants was divided into five exams of 18-24 months duration, with Exam 1 beginning in 2000, and Exam 5 completed in December 2011. For the purpose of this research study, only Exam 4 data, collected from September 2005-May 2007, was analyzed.

Built upon MESA, the MESA Air cohort, supported by the Environmental Protection Agency (EPA), currently includes 6226 subjects: 5479 of which are enrolled in the parent MESA study; 257 recruited specifically MESA Air and 490 recruited from the MESA Family study. The MESA Air cohort began in 2004, and has been followed over a 10-year project period for the occurrence of cardiovascular disease events and many other outcomes.

Study sample and outcome data

All diastolic and systolic blood pressures from Exam 4 MESA cohort participants with vanadium exposure data available were included in the analysis (5,517 out of 5,698 Exam 4

participants). For each participant the average of the second and third diastolic and systolic blood pressure readings out of three seated blood pressures taken 2 minutes apart were used.

Exposure Estimates

Exposure to vanadium from $PM_{2.5}$ was quantified through geospatial modeling predictions that were developed from 2009-2010 annual averages, as measured by the Interagency Monitoring for Protected Visual Environments (IMPROVE) and Chemical Speciation Network (CSN) of the U.S. EPA. The model from which vanadium exposure is predicted is a spatial statistical model using land use regression methods and geostatistical smoothing to estimate long-term pollutant concentrations. Some of the 600 geographic covariates measured included distance to roadways, airports, ports, railways, industrial sites, or commercial centers. Additionally, land use and population density within a given buffer, and the level of vegetation within a monitor's vicinity were included in model development. Partial least squares (PLS) methods were used to address co-linearity of geographic information system (GIS) data.[30] Geocoding based on each MESA Exam 4 participant's address was used to assign an exposure estimate to each subject (from national spatial models developed by MESA Air).[16] Each subject's annual ambient vanadium exposure estimate from the year prior to their specific exam time (2005-2007) was used to estimate long-term exposure.

Exclusion Criteria

Individuals that were included in the prior Exams of the MESA Cohort were recruited for Exam 4. Ineligibility from participating in Exam 4 of the MESA cohort is based on self-report of the following criteria: Age younger than 45 or older than 84 years, physician-diagnosed heart

attack, physician-diagnosed angina or taking nitroglycerin, physician-diagnosed stroke or transient ischemic attack, physician-diagnosed heart failure, current atrial fibrillation, history of procedures related to cardiovascular disease (CABG, angioplasty, valve replacement, pacemaker or defibrillator implantation, any surgery on the heart or arteries), active treatment for cancer, pregnancy, any serious medical condition which would prevent long-term participation, weight >300 pounds, cognitive inability as judged by the interviewer, living in a nursing home or on the waiting list for a nursing home, plans to leave the community within five years, language barrier (speaks other than English, Spanish, Cantonese or Mandarin), and chest CT scan in the past year. Additionally any Exam 4 individuals for whom geocoding data was not available were not included in our analysis.

Covariate Data

Covariates adjusted for in this data analysis, due to their potential independent associations with blood pressure or use as precision variables, include: age, gender, race/ethnicity, socioeconomic status (highest educational level and family income), body mass index, smoking status, alcohol use, blood lipids (HDL and LDL cholesterol), blood glucose, anti-hypertensive medication use, and city region. The following co-pollutants were adjusted for in this data analysis (see Sensitivity Analysis): elemental carbon (EC), organic carbon (OC), sulfate, nitrate, silicon, sulfur, nickel, copper, arsenic, chromium, and sulfur dioxide. The participants' annual exposure estimates of PM2.5 and co-pollutant exposures for the year prior to their exam were developed through MESA Air and NPACT.[16,31]

Statistical Analysis

For individual i, the primary model was the multiple linear regression model shown below. Systolic and diastolic blood pressure data were analyzed in their native scale, given assumption of normal distribution of data.

$Y_i = \beta_0 + X_i\beta + Z_i\gamma + \varepsilon_i$, where:

Y_i = outcome variables: systolic BP and diastolic BP

X_i = estimate of long-term exposure to vanadium in ng/m^3

Z_i = vector of adjustment variables (covariates)

β is the parameter of interest

errors, ε_i, are independent and identically distributed within areas and individuals

Incrementally richer covariate models were built *a priori*. The base model (Model 1) includes age, gender, and race/ethnicity. Model 2 includes all the variables in the base model and added highest education level completed, income, smoking status, alcohol use, and body mass index (BMI). Model 3 includes all variables in Model 2 with the addition of lipid levels (both HDL and LDL), anti-hypertensive medication usage, and blood glucose levels. Model 4 includes all variables in Model 2 and adjusts for $PM_{2.5}$ exposure. Model 5 is essentially a within-city region analysis, and therefore includes all variables in Model 2 with adjustment for city region. Models 2 and 5 were considered our primary models in this analysis.

Sensitivity analyses

i. Residence stability: This secondary analysis was restricted to study participants who lived at one address since 1980, as was done by Diez Roux et al. using the large subset of the cohort with 20 years of geocoded residential history.[15]

ii. Co-pollutant model: Two-pollutant models were fitted that included vanadium with each of the co-pollutant variables (see Covariate Data above) and $PM_{2.5}$. This allowed us to determine the effect of vanadium adjusted for these other pollutants.

iii. Exclusion of Exam 4 participants that are taking anti-hypertensive medications for Models 1-5 to remove the variable effects of anti-hypertensive medication use on blood pressure.

Power calculations

For this multiple regression analysis, for the largest model using 13 predictors with a desired power of 90%, α of 0.05, and a sample size of 5,517 after Exam 4 participants without vanadium exposure data were excluded, the smallest detectable effect size (f^2) is 0.0041, corresponding to an approximate 0.4% increase in model R^2 with inclusion of the vanadium variable (Stata IC/12.1). Power is therefore excellent.

Chapter III: Results

A total of 5,698 individuals aged 45-84 participated in MESA Exam 4 from September 2005-May 2007, of which 5,517 were included in this data analysis due to availability of vanadium exposure data. Demographic characteristics and mean systolic and diastolic blood pressure by variable subcategory are shown in Table 1. As shown in Table 1, SBP was associated with gender, age, race, gross income in last 12 months, highest education level achieved, smoking status, alcohol use, and anti-hypertensive medication use. Although there was not an association between SBP and site location across all cities, the mean SBP among New York City (NYC) residents was statistically lower than the mean SBP among Los Angeles (LA) and Forsyth Co., NC residents ($p<0.0001$). Additionally, the mean SBP among Forsyth Co., NC residents was statistically higher than the mean SBP of residents in all other cities ($p<0.0001$-$p=0.025$). DBP was associated with race, gross income in the last 12 months, and smoking status (Table 1).

Ambient vanadium exposure among the participants ranged from 0.26-4.76 ng/m^3 with a mean of 1.50 ± 0.98 ng/m^3 (Fig. 1). The interquartile range for vanadium concentration is 0.802 ng/m^3, which was the incremental unit of vanadium concentration used in this analysis. Vanadium concentration stratification by study site showed that participants living in NYC had the highest average exposure annually of 3.51 ± 0.56 ng/m^3 followed by LA residents with 1.63 ± 0.24 ng/m^3 (Fig. 2). Residents living in Baltimore, Chicago, St. Paul, and Forsyth Co., NC were exposed to lower average vanadium concentrations annually (1.17 ± 0.25, 0.90 ± 0.12, 0.86 ± 0.12, and 0.86 ± 0.18 ng/m^3 respectively).

In our primary model with adjustment for city region (Model 5), mean systolic blood pressure (SBP) increased by 0.4 mm Hg per interquartile range (IQR) increase in vanadium (V)

concentration, 95% CI [-1.1, 1.8] (Fig. 3A). The effect estimate for SBP was in the negative direction when there was no adjustment for city region in Models 1-4 (Fig. 3A). There was no effect on mean diastolic blood pressure (DBP) in all models (Fig. 3B). The effect estimates for SBP and DBP became larger (1.4 mm Hg [-0.5, 3.3] and 1.1 mm Hg [0.1, 2.0] per IQR increase in V), respectively, in city-adjusted analyses after excluding study subjects taking anti-hypertensive medications (Fig. 4). However, the effect estimates for SBP and DBP in the analyses unadjusted for city region remained similar to the primary unrestricted analyses, with SBP negatively associated with an increase in V concentration, and no effect on DBP.

Table 1. Demographic Data of MESA Exam 4 Participants with Estimated Vanadium Exposure

Demographic	**Sample**		**Systolic Blood Pressure**	**ANOVA p value**	**Diastolic Blood Pressure**	**ANOVA p value**
	N	**%**				
Total	5517	--	123.4 ± 20.6		69.5 ± 10.0	
Gender				<0.0001		0.569
Male	2588	47	123.0 ± 19.1		72.4 ± 9.6	
Female	2929	53	124.3 ± 22.0		67.1 ± 9.7	
Age				<0.0001		0.763
45-54	748	13.6	114.5 ± 16.5		71.3 ± 10.1	
55-64	1730	31.3	120.1 ±18.9		71.2 ± 10.0	
65-74	1741	31.6	126.0 ± 20.2		69.3 ± 9.7	
75-84	1141	20.6	130.4 ± 23.0		67.2 ± 9.9	
85+	157	2.8	132.8 ± 21.4		65.3 ± 9.7	
Mean age	66.3	--	--		--	
Race				<0.0001		0.011
White	2224	40.3	120.5 ± 19.4		68.0 ± 9.7	
Chinese	634	11.5	123.0 ± 19.6		70.0 ± 9.4	
Black	1479	26.8	128.2 ± 21.7		71.9 ± 10.3	
Hispanic	1180	21.3	124.6 ± 21.3		69.5 ± 10.0	
Gross income in last 12 mo.				<0.0001		0.010
<$12,000	542	9.8	127.3 ± 22.6		68.5 ± 10.8	
$12,000-$29,999	1286	23.3	127.4 ± 22.4		69.2 ± 10.1	
$30,000-$49,999	1260	22.8	123.9 ± 20.6		69.5 ± 10.0	
$50,000-$74,999	933	16.9	121.1 ± 18.9		70.3 ± 10.0	
$75,000-$99,999	527	9.6	120.0 ± 17.1		70.3 ± 9.6	
$100,000+	782	14.2	118.5 ± 17.7		69.8 ± 9.4	
Not available	187	3.4	--		--	
Highest education level				<0.0001		0.636

No schooling	40	0.7	131.2 ± 22.7		68.9 ± 11.4	
Grades 1-8	474	8.6	128.9 ± 23.0		69.7 ± 10.2	
Grades 9-11	358	6.5	127.4 ± 21.2		69.1 ± 10.3	
Completed high school/GED	994	18.0	126.6 ± 21.3		69.2 ± 10.1	
Some college but no degree	900	16.3	124.2 ± 20.2		69.9 ± 9.9	
Technical school certificate	393	7.1	123.9 ± 21.2		70.0 ± 10.2	
Associate Degree	283	5.1	122.5 ± 19.3		69.2 ± 9.5	
Bachelor's Degree	998	18.0	120.6 ± 19.3		69.6 ± 10.0	
Graduate/Professional school	1065	19.3	119.9 ± 19.4		69.9 ± 10.0	
Not available	12	0.2	--		--	
Smoking status				0.004		0.003
Never smoked	2783	50.4	124.1 ± 21.1		69.3 ± 9.9	
Former smoker quit > 1 yr	2098	38.0	123.8 ± 20.0		69.6 ± 9.8	
Former smoker quit < 1 yr	89	1.6	122.0 ± 20.9		72.1 ± 11.4	
Current smoker	526	9.5	121.2 ± 20.9		70.9 ± 11.1	
Do not know	16	0.3	127.2 ± 32.4		72.9 ± 10.3	
Not available	5	0.1	--		--	
Presently drink alcohol				<0.0001		0.543
Yes	2458	44.6	122.0 ± 19.4		70.2 ± 10.0	
No	3052	55.3	125.1 ± 21.6		69.2 ± 10.1	
Not Available	7	0.1	--		--	
Anti-hypertensive Medication				<0.0001		0.149
Yes	2636	47.8	128.2 ± 21.2		69.5 ± 10.2	
No	2703	49.0	119.3 ± 19.2		69.6 ± 19.2	
Not Available	178	3.2	--		--	
Site Location				0.110		0.243
Forsyth County, NC	868	15.7	128.2 ± 20.5		70.3± 10.4	
New York, NY	930	16.9	120.9 ± 19.8		69.7 ± 9.9	
Baltimore, MD	845	15.3	123.9 ± 20.1		69.5 ± 9.7	
St. Paul, MN	877	15.9	122.4 ± 20.1		69.7 ± 10.3	
Chicago, IL	987	17.9	122.1 ± 20.1		69.4 ± 9.9	
Los Angeles, CA	1010	18.3	125.0 ± 21.7		69.2 ± 10.1	
Body mass index in kg/m^2 (mean)	28.4 ± 5.6		--		--	
LDL in mg/dL (mean)	110 ± 33.1		--		--	
HDL in mg/dL (mean)	52.8 ± 15.7		--		--	
Fasting blood glucose, mg/dL (mean)	101 ± 27.8		--		--	
PM2.5 exposure in µg/m^3 (mean)	13.7 ± 2.0		--		--	

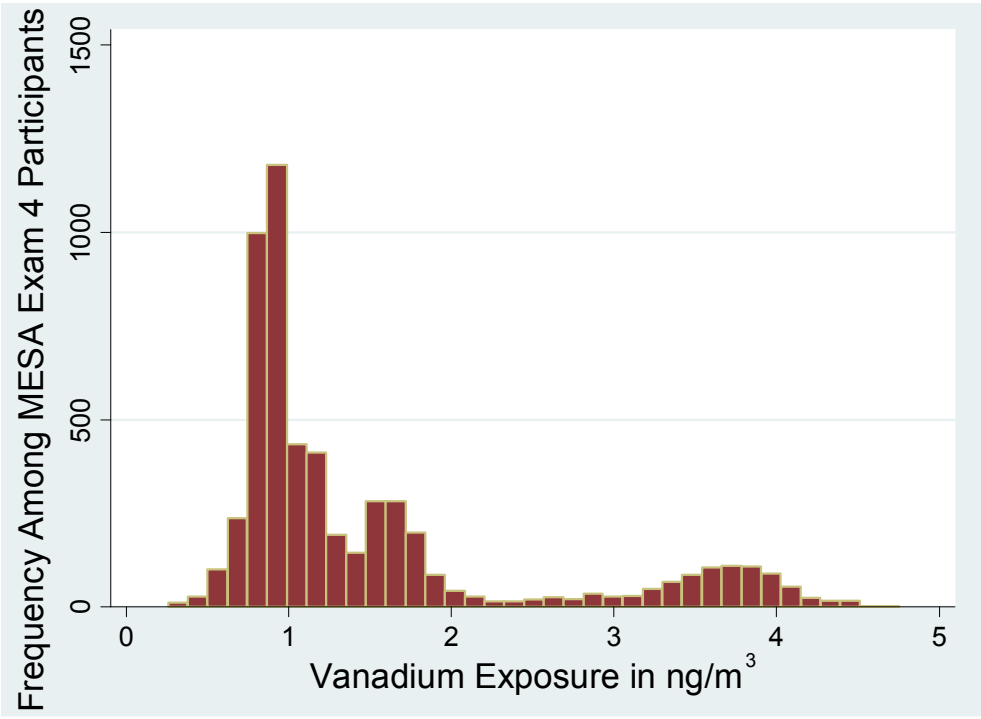


Figure 1. Distribution of Vanadium Concentrations among MESA Exam 4 Participants

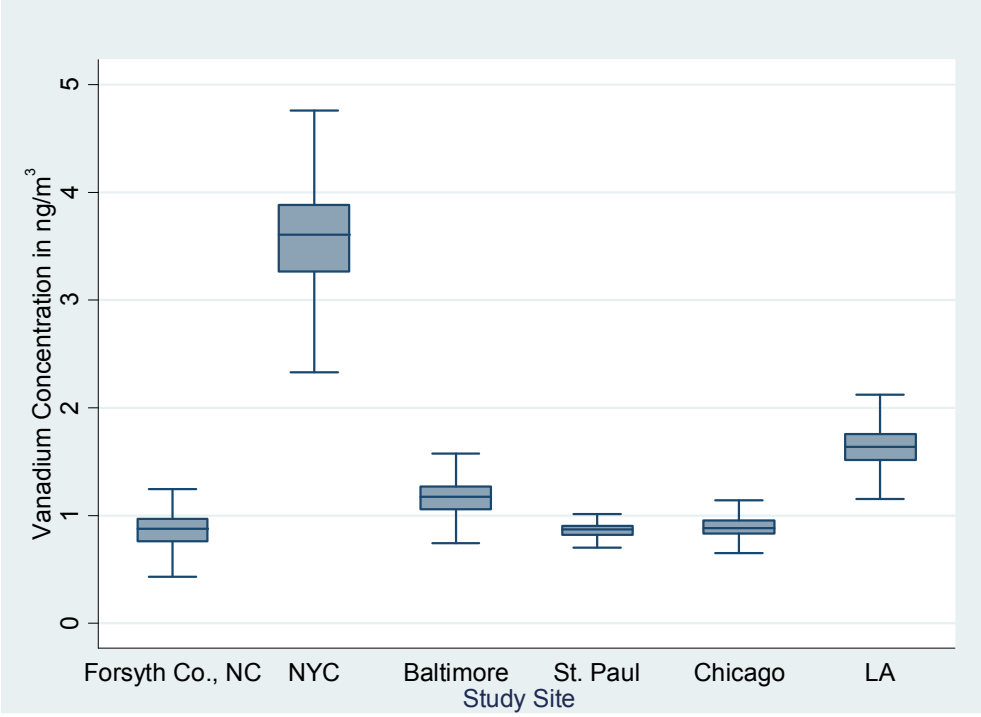
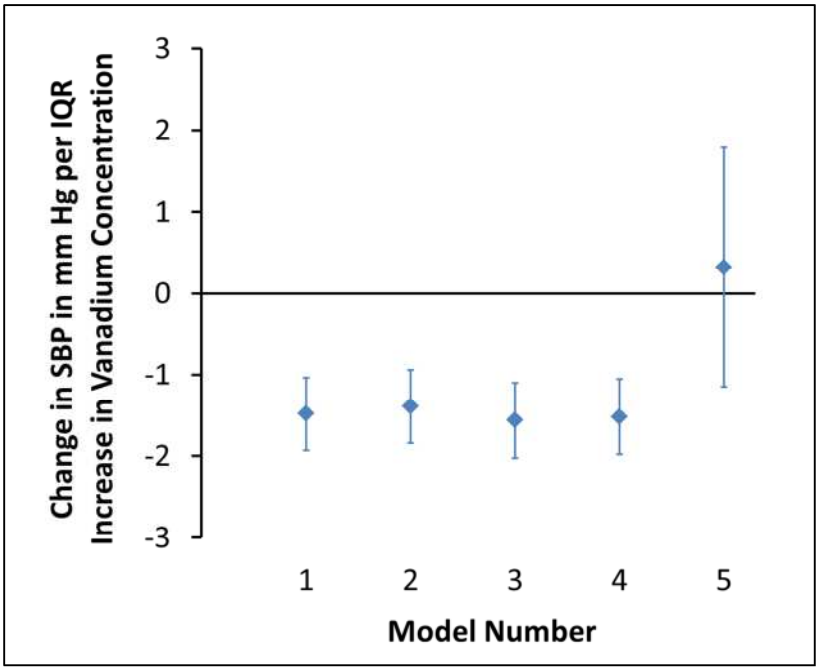


Figure 2. Vanadium Concentration by Study Site

A.



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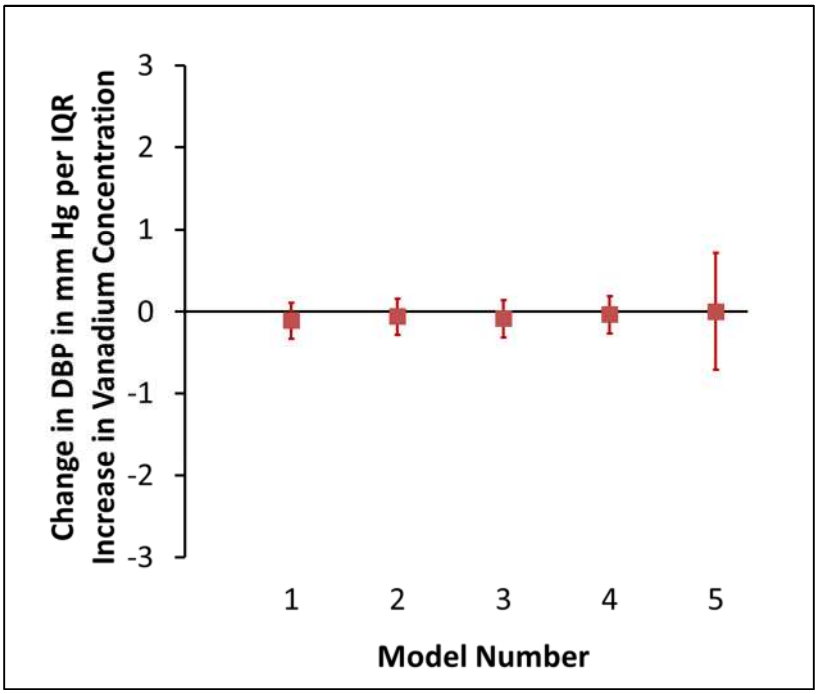
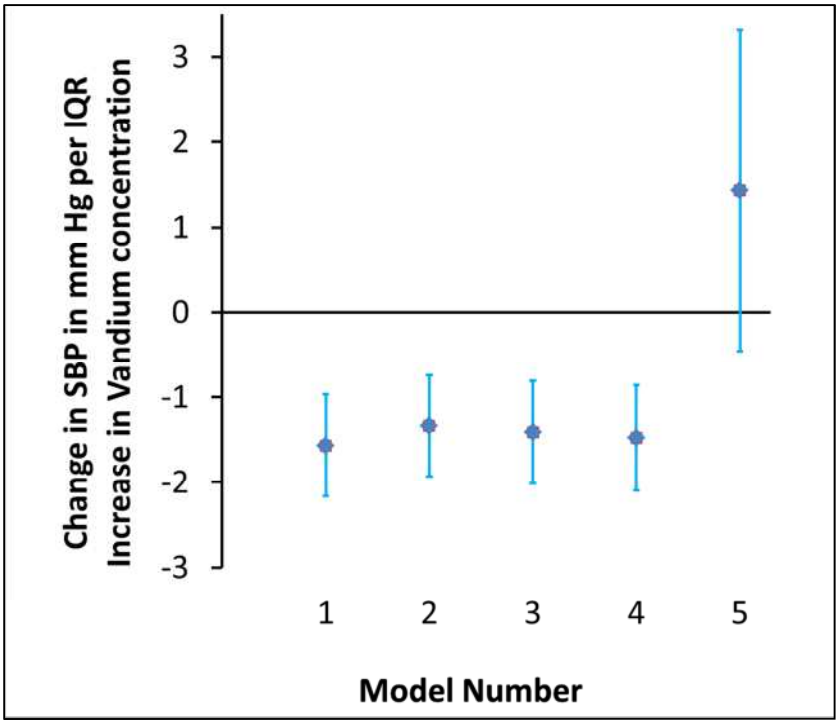


Figure 3. Difference in Mean Systolic (A) and Diastolic (B) Blood Pressure per IQR Increase in Vanadium Concentration

A.



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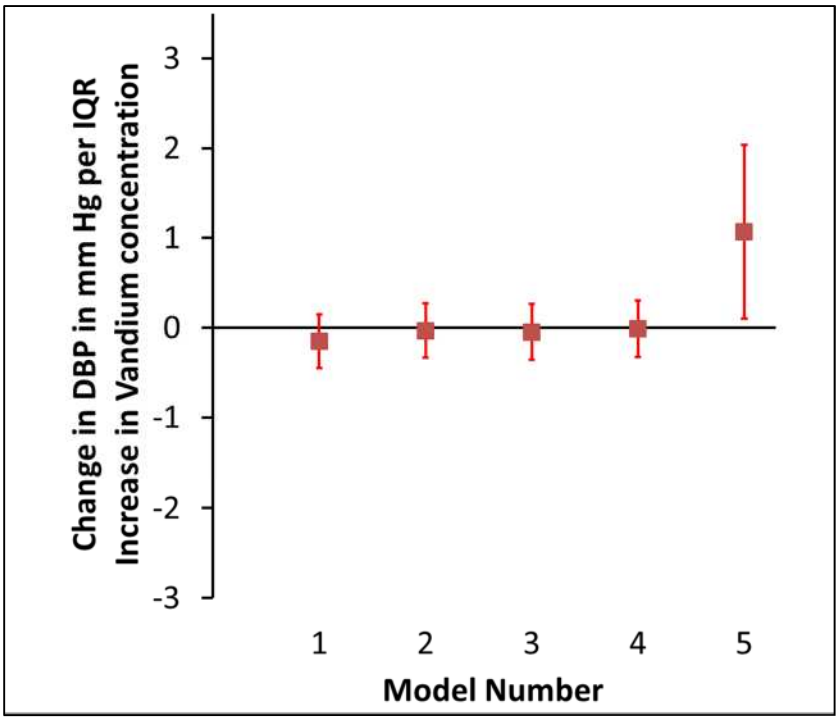

Figure 4. Difference in Mean Systolic (A) and Diastolic (B) Blood Pressure per IQR Increase in Vanadium Concentration in Participants Not Taking Anti-hypertensive Medications

Given that there was a small V effect estimate for SBP in Model 5 of the primary analysis, further stratification by site location demonstrated that Forsyth Co., NC, Chicago, Baltimore, and LA had the largest positive V effect estimates for SBP, though not statistically significant (Table 2). Stratification of Model 2 by site location among participants not taking anti-hypertensive medications showed larger V effect estimates for both SBP and DBP in Forsyth Co., NC and Baltimore than in the unrestricted Model 5 analysis. However, the V effect estimates for SBP were smaller for Chicago and LA as compared to the unrestricted Model 5 analysis (Table 3). The V effect estimate for DBP in Chicago demonstrated the only negative association among all cities in Table 3.

Table 2. Difference in Mean Systolic and Diastolic Blood Pressure per IQR increase in Vanadium Exposure: Model 2 Stratified by City

Site Location	Vanadium Effect Estimate for SBP (95% CI)	Vanadium Effect Estimate for DBP (95% CI)
Forsyth Co., NC	3.31 (-3.04, 9.65)	-0.56 (-3.66, 2.54)
New York, NY	-1.05 (-2.83, 0.72)	-0.14 (-1.03, 0.75)
Baltimore, MD	2.39 (-2.15, 6.92)	0.68 (-1.44, 2.80)
St. Paul, MN	-5.23 (-14.37, 3.91)	-3.56 (-8.11, 0.98)
Chicago, IL	6.80 (-1.82, 15.41)	-1.42 (-5.62, 2.77)
Los Angeles, CA	2.26 (-2.12, 6.63)	0.86 (-1.26, 2.98)

Table 3. Difference in Mean Systolic and Diastolic Blood Pressure per IQR increase in Vanadium Exposure: Model 2 Stratified by City in Participants Not Taking Anti-Hypertensive Medications

Site Location	Vanadium Effect Estimate for SBP (95% CI)	Vanadium Effect Estimate for DBP (95% CI)
Forsyth Co., NC	5.72 (-3.57, 15.03)	0.35 (-4.31, 5.01)
New York, NY	0.01 (-2.28, 2.30)	1.05 (-0.20, 2.31)
Baltimore, MD	*7.46 (1.70, 13.23)	2.31 (-0.63, 5.25)
St. Paul, MN	1.03 (-9.06, 11.12)	0.63 (-4.43, 5.67)
Chicago, IL	3.53 (-6.92, 13.98)	-1.13 (-6.39, 4.13)
Los Angeles, CA	1.13 (-4.04, 6.31)	1.29 (-1.37, 3.96)

*denotes $p \leq 0.05$

Further sensitivity analyses conducted among MESA Exam 4 participants not taking anti-hypertensive medications restricted to those that lived at a single address since 1980 (n=828) showed a decrease in V effect estimates for SBP and DBP as compared to the unrestricted analysis of the same group (Table 4).

Table 4. Difference in Mean Systolic and Diastolic Blood Pressure per IQR increase in Vanadium Exposure in Participants with One Address Since 1980 among Those Not Taking Anti-hypertensive Medications

	Vanadium Effect Estimate for SBP (95% CI)	Vanadium Effect Estimate for DBP (95% CI)
MODEL 1	*-2.40 (-3.34, -1.46)	-0.16 (-0.60, 0.35)
MODEL 2	*-2.12 (-3.07, -1.17)	-0.08 (-0.56, 0.41)
MODEL 3	*-2.22 (-3.19, -1.25)	-0.12 (-0.62, 0.38)
MODEL 4	*-2.27 (-3.24, -1.30)	-0.07 (-0.57, 0.43)
MODEL 5	0.54 (-3.18, 4.26)	0.42 (-1.50, 2.34)

*denotes $p \leq 0.05$

In the city-adjusted analysis restricted to participants not taking anti-hypertensive medications, adjustment for copper and elemental carbon, two traffic-related pollutants, changed the V effect estimate for SBP from a positive to a negative direction. Additionally, the V effect estimate for SBP was sensitive to adjustment for chromium and PM2.5. However, adjustment for nickel led to a much larger V effect estimate. The V effect estimate for DBP was the most sensitive to adjustment for copper, PM2.5 and nitrate (Table 5). In order to determine how closely vanadium is related to potential confounding co-pollutants in this analysis, correlation coefficients for nickel, copper, and PM2.5 for each study site were determined (Table 6). Correlations were very strong, except for the PM2.5-V correlation in Chicago.

Formal testing of effect modification by anti-hypertensive use was done by addition of an interaction term between BP and an indicator variable of medication use. The interaction terms for SBP in Models 2 and 5 were not found to be statistically significant (p=0.79 and p=0.89

respectively). Similarly, the interaction terms for DBP in Models 2 and 5 were not statistically significant (p= 0.90 and p=0.83 respectively).

Table 5. Difference in Mean SBP and DBP per IQR Increase in Vanadium Exposure: Model 5 Adjusted for Co-Pollutants Restricted to Participants Not Taking Anti-hypertensive Medications

Co-pollutant	Vanadium Effect Estimate for SBP (95% CI)	Vanadium Effect Estimate for DBP (95% CI)
ARSENIC	1.21 (-0.71, 3.12)	*1.13 (0.14, 2.11)
COPPER	-0.85 (-3.75, 2.05)	0.69 (-0.80, 2.18)
ELEMENTAL CARBON	-0.19 (-2.87, 2.50)	0.91 (-0.47, 2.29)
NICKEL	3.15 (-1.55, 7.85)	1.18 (-1.23, 3.59)
ORGANIC CARBON	1.10 (-0.83, 3.03)	*1.10 (0.12, 2.09)
SILICON	1.11 (-0.85, 3.07)	*1.18 (0.18, 2.19)
SULFUR	1.47 (-0.67, 3.62)	*1.10 (0.002, 2.20)
SULFUR DIOXIDE	1.23 (-0.73, 3.21)	*1.03 (0.018, 2.04)
NITRATE	1.26 (-0.70, 3.23)	0.83 (-0.18, 1.84)
CHROMIUM	0.71 (-1.58, 3.00)	1.1 (-0.067, 2.26)
PM2.5	0.84 (-1.28, 2.97)	0.72 (-0.37, 1.81)

*denotes p≤0.05

Table 6. Correlation Coefficients of Nickel, Copper, and PM2.5 with Vanadium

Co-pollutant by Site Location	**Correlation with Vanadium**	**p value**
NICKEL		
Forsyth Co., NC	0.96	<0.0001
New York, NY	0.96	<0.0001
Baltimore, MD	0.97	<0.0001
St. Paul, MN	0.90	<0.0001
Chicago, IL	0.74	<0.0001
Los Angeles, CA	0.93	<0.0001
COPPER		
Forsyth Co., NC	0.93	<0.0001
New York, NY	0.84	<0.0001
Baltimore, MD	0.97	<0.0001
St. Paul, MN	0.90	<0.0001
Chicago, IL	0.79	<0.0001
Los Angeles, CA	0.94	<0.0001
PM2.5		
Forsyth Co., NC	0.72	<0.0001
New York, NY	0.55	<0.0001
Baltimore, MD	0.64	<0.0001
St. Paul, MN	0.66	<0.0001
Chicago, IL	0.12	0.004
Los Angeles, CA	0.77	<0.0001

Chapter IV: Discussion and Conclusion

These results indicate that vanadium may be a key component of PM2.5 that is contributing to increased blood pressure, although the findings of our primary analysis do not support our research hypothesis, as associations with increased SBP and DBP were primarily observed in those not taking anti-hypertensive medications. Additionally, these findings were somewhat sensitive to adjustment for PM2.5 and some PM2.5 components. In our primary unrestricted analysis, only SBP was shown to be positively associated with higher V exposure in our city-adjusted model. There was no association between V exposure and DBP; this is consistent with other research findings that have found an association between increased PM2.5 and SBP, but not with DBP.[17,20]

A priori, we believe that adjusting for the use of anti-hypertensive medications in Model 3 and including this covariate as an interaction term with vanadium in our sensitivity analyses would account for any effect modification. However, given that an association with vanadium was seen in this restricted population group rather than the adjusted group (Model 3), future studies should consider including only medication-naïve individuals in their primary analysis, since a small increase in blood pressure due to ambient vanadium in PM2.5 could be modulated by the use of anti-hypertensive medication. Although there may be an interest in determining which classes of anti-hypertensive medications are potential effect modifiers, this was not the main purpose of the restricted analysis; instead its intent was to estimate an association between V exposure and blood pressure that is not contaminated by medication effects. Moreover, there was not adequate power to adjust for use of each medication class.

The results of this study were model-dependent, with a positive association between vanadium and blood pressure only seen in city-adjusted analyses. This may be due to

uncontrolled confounding in the negative direction due to uncontrolled factors that vary across city. For example, there was not an equal distribution of racial groups recruited between the six sites (i.e. St. Paul, MN with no Black or Chinese participants). New York City residents had a lower mean systolic blood pressure than the other cities. Additionally, compared to the other five study sites, NYC had a substantially higher mean vanadium exposure among their study participants, likely due to residual oil burning in its port and use of residential space heating in old buildings.[28] This may explain why there was a negative V effect estimate for SBP in Models 1-4 in the primary analysis. Conducting a city-adjusted analysis as a primary regression model in the future allows one to control for these significant variations between locations.

There are numerous research studies supporting the association between PM2.5 and adverse cardiovascular outcomes, as discussed earlier. In our primary unrestricted analysis, Model 4 was not markedly affected by the addition of the PM2.5 variable, but the V effect estimate for both SBP and DBP was somewhat sensitive to adjustment for PM2.5 in our Model 5 co-pollutant sensitivity analysis among participants not taking anti-hypertensive medications. This lends us to believe that some of the positive effect estimate for vanadium is due to a "mass-effect" from PM2.5. Additionally, PM2.5 and vanadium are strongly correlated in five out of six analyzed cities, with the exception of Chicago, IL, which had a weak correlation.

Results from the co-pollutant sensitivity analyses indicate that even among the population restricted to those not on anti-hypertensive medications, the V effect estimates may be confounded by other components of PM2.5. Of all the PM2.5 components, adjustment for copper had the greatest effect on the V effect estimate for both SBP and DBP. Other PM2.5 components that also affected the V effect estimate included: elemental carbon, nickel, nitrate, and chromium. Copper, a traffic-related pollutant that is associated with brake wear, was found to

have a strong correlation with vanadium at all study sites, despite their understood separate sources. Copper was also positively associated with carotid intima-media thickness (CIMT) in the Women's Health Initiative-Observational Study and MESA.[31] In toxicological studies, copper has been found to be an important pulmonary pro-inflammatory metal.[32] Elemental carbon is another traffic-related pollutant that is associated with diesel emissions.[9,31,33] In our study, elemental carbon may be a potential confounder since it greatly modified the V effect estimate for SBP and for DBP to a lesser degree. This finding is corroborated by a longitudinal study, which found an IQR increase in 1-year average EC exposure to be associated with a 2.64 mm Hg increase in SBP and a 2.41 mm Hg increase in DBP.[14] Additionally, EC has been associated with increased hospitalizations and mortality due to coronary artery disease.[24,34]

Interestingly, the effect estimate for V was actually larger once nickel was adjusted for in the co-pollutant analysis, which implies that nickel may be a potential confounder in this analysis. Nickel was shown to be strongly correlated with vanadium at all study sites, signifying the likelihood of vanadium and nickel being co-varying pollutants, as both arise from residual oil burning.[28] Bell et al. found an association between nickel and adverse cardiovascular outcomes in her study showing that nickel and vanadium content within PM2.5 explained 37% of the heterogeneity in cardiac hospitalizations associated with PM2.5.[23] Other studies have shown nickel and vanadium concentrations to positively modify the association between the previous day's particulate matter with diameter < 10μm (PM10) and mortality from all causes.[8,35]

In our analysis, the V effect estimate for SBP was moderately sensitive to adjustment for chromium, but the V effect estimate for DBP was only mildly sensitive. Inhalation of ambient chromium is mainly associated with carcinogenic effects of the respiratory tract rather than adverse cardiovascular outcomes.[36] The distance-to-road variables from the national model were

modified after the chromium model was developed and therefore some of the participants' exposure predictions were not readjusted, leaving 4,754 out of 5,517 participants with annual ambient chromium estimates. The unavailability of a substantial percentage of participants may have led to a V effect estimate for DBP that was not statistically significant as well as a smaller observed V effect estimate for SBP.

Nitrate may also be confounding our V effect estimate for DBP in our Model 5 restricted analysis. Large components of PM2.5 are nitrate aerosols generated by the rapid oxidation of NO to NO_2.[37] Exposure to nitrate has been associated with increased plaque formation in aortic tissue of mice.[38] Although epidemiological studies linking nitrate with adverse cardiovascular outcomes are limited, Ostro et al. reported an association between nitrate and mortality induced by ischemic heart disease.[9,31]

There are several limitations of this study, with the primary one being that it is a cross-sectional study, which makes it more difficult to infer cause and effect. A longitudinal study would allow us to better assess the effects of long-term exposure to ambient vanadium on blood pressure. Based on this analysis, it is difficult to determine whether vanadium is the toxic agent, or a surrogate of exposure to a source that is not accounted for in the data we had available in this study. There may be co-varying agents of interest in addition to those discussed earlier that cannot be determined within the confines of available data. Additionally, given that PLS methods were used to incorporate GIS data into the national spatial models, it is difficult to analyze which particular geographic covariates are good predictors of within-city gradients of vanadium exposure. Another limitation is that the national spatial models used to estimate each participant's annual pollutant exposure was developed two years after the conclusion of Exam 4. However, the models are believed to generate exposure estimates that are stable over time, so the

estimated annual V exposure for each participant in the year prior to their clinical exam is believed to be similar to those generated using data sampling from 2008-2009. Furthermore, the models from which MESA Air exposure estimates are derived are under constant refinement to better capture each individual's ambient pollutant exposure.[39] Therefore, this study may be repeated in the future when more refined exposure estimates are available. Although the multi-ethnic aspect of our research population improves the generalizability of this study, the analysis is limited to participants in the six cities chosen for the MESA cohort, which have very different racial demographic makeup. Ideally the effects of vanadium on blood pressure should be studied in port cities, given the association with marine vessels, or in occupational settings that have high vanadium concentrations such as in boiler repair work. Lastly, as changes in blood pressure are multi-factorial in etiology, it is difficult to control for all intrinsic factors that may impact its outcome.

Conclusion

The findings of this study add to the scientific literature on the association between PM2.5 and increased blood pressure by determining whether a specific PM2.5 component, in this case vanadium, plays a role in this association. Since the association between ambient vanadium and increased SBP and DBP was found primarily in restricted analyses for those not on anti-hypertensive medications, further studies need to be conducted to validate these findings. Additionally, other trace metals and PM2.5 components should be evaluated independently to advance our understanding of which particular PM2.5 component(s) are responsible for adverse cardiovascular effects. Ultimately, this knowledge may translate into development of environmental policies that promote public health.

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