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Ambient Coarse Particulate Matter and the Right Ventricle: The Multi-Ethnic Study of Atherosclerosis

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Background: Coarse particulate matter ($PM_{10–2.5}$) is primarily mechanically generated and includes crustal material, brake and tire wear, and biological particles. $PM_{10–2.5}$ is associated with pulmonary disease, which can lead to right ventricular (RV) dysfunction. Although RV characteristics have been associated with combustion-related pollutants, relationships with $PM_{10–2.5}$ remain unknown.

Objectives: To quantify cross-sectional associations between RV dysfunction and $PM_{10–2.5}$ mass and components among older adults and susceptible populations.

Methods: We used baseline cardiac magnetic resonance images from 1,490 participants (45–84 y old) from the Multi-Ethnic Study of Atherosclerosis and assigned 5-y residential concentrations of $PM_{10–2.5}$ mass, copper, zinc, phosphorus, silicon, and endotoxin, using land-use regression models. We quantified associations with RV mass, end-diastolic volume, and ejection fraction after control for risk factors and copollutants using linear regression. We further examined personal susceptibility.

Results: We found positive associations of RV mass and, to a lesser extent, end diastolic volume with $PM_{10–2.5}$ mass among susceptible populations including smokers and persons with emphysema. After adjustment for copollutants, an interquartile range increase in $PM_{10–2.5}$ mass ($2.2\ \mu g/m^3$) was associated with 0.5 g (95% CI: 0.0, 1.0), 0.9 g (95% CI: 0.1, 1.7), and 1.4 g (95% CI: 0.4, 2.5) larger RV mass among former smokers, current smokers, and persons with emphysema, respectively. No associations were found with healthy individuals or with ejection fraction.

Conclusions: Alterations to RV structure may represent a mechanism by which long-term $PM_{10–2.5}$ exposure increases risks for adverse respiratory and cardiovascular outcomes, especially among certain susceptible populations. https://doi.org/10.1289/EHP658

Introduction

Air pollution is a well-established risk factor for adverse respiratory outcomes, including chronic lung diseases (Andersen et al. 2011; Karakatsani et al. 2003; Lindgren et al. 2009; Schikowski et al. 2005; Sunyer 2001), hospitalizations (Chen et al. 2005) and death (Dockery et al. 1993; Pope et al. 2002). Most recently, it has been estimated that for 2013 worldwide ambient particulate matter (PM) pollution accounts for nearly 170,000 deaths and nearly 4 million disability-adjusted life years (DALYs) due to chronic respiratory disease (Forouzanfar et al. 2015; IHME 2016).

A common sequela of chronic lung disease is the development of pulmonary hypertension and impairments to the heart, including right ventricular (RV) dysfunction (Freixa et al. 2013). The right ventricle pumps blood through the lungs to allow for its oxygenation. Then the oxygen-rich blood flows to the left ventricle for subsequent distribution to all tissues of the human body. Changes in RV structure and function can therefore result in many similar clinical sequelae of left ventricular (LV) changes, including dyspnea, exercise intolerance, lower-extremity edema, and (at advanced stages) severe heart failure (Voelkel et al. 2006). Although the left ventricle is vulnerable to increased pressures during ejection due to systemic hypertension or valvular disease, reduced blood supply, and hypoxia, the right ventricle may be similarly affected by changes in lung function [e.g., chronic obstructive pulmonary disorder (COPD)], LV function, and hypoxia (e.g., sleep disordered breathing). The RV has been thought to respond to this increased load through structural changes such as hypertrophy (i.e., thickening of the ventricle leading to increased mass), chamber dilation leading to greater end-diastolic volume, and lowered pumping efficiency (i.e., reduced ejection fraction) (Polak et al. 1983; Shah et al. 1986). Although these three manifestations of RV dysfunction are most likely in severe stages of lung disease, the right ventricle can also be affected early in lung disease (Hilde et al. 2013). RV dysfunction has public health importance because it has been linked to poor outcomes among persons with and without preexisting disease, such as COPD and cardiovascular disease (Burgess et al. 2002; France et al. 1988; Kawut et al. 2012).

Long-term exposures to air pollution are believed to affect the same biological mechanisms that lead to COPD and

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cardiovascular disease. There is evidence that air pollution is associated with greater inflammation (Adar et al. 2015b) and reduced vessel compliance (Brook et al. 2014; Krishnan et al. 2013; Mills et al. 2005); such evidence suggests a plausible link to RV function. In fact, two studies from the Multi-Ethnic Study of Atherosclerosis (MESA) recently linked long-term exposures to two combustion-related air pollutants: nitrogen dioxide (NO_2) (Leary et al. 2014) and fine PM (aerodynamic diameter <2.5 μm, $PM_{2.5}$) (Aaron et al. 2016) to greater RV hypertrophy and lower function. Although PM in the coarse fraction (aerodynamic diameter between 2.5 and 10 μm, $PM_{10–2.5}$) has also been associated with adverse respiratory end points (Adar et al. 2014; Brunekreef and Forsberg 2005), no study has investigated associations between $PM_{10–2.5}$ and RV characteristics. Understanding the health impacts of $PM_{10–2.5}$ independent of other pollutants, including $PM_{2.5}$ and NO_2 has importance, given that the U.S. Environmental Protection Agency (EPA) is interested in regulating $PM_{10–2.5}$ levels but has struggled with insufficient data in the general population as well as among susceptible individuals (U.S. EPA 2009). Because $PM_{10–2.5}$ is generated by very different diverse processes, ranging from crustal material to brake and tire wear, a lack of information on associations between health and indicators of different $PM_{10–2.5}$ sources represents another important gap in the literature.

To expand the literature on the health implications of $PM_{10–2.5}$ and to better understand environmental risk factors of RV dysfunction, we aimed to quantify cross-sectional associations between $PM_{10–2.5}$ and measures of RV function among older adults and susceptible subpopulations. We approached this goal using individual-level long-term estimates of $PM_{10–2.5}$ mass and selected source-specific components with multiple measures of RV structure (mass, end-diastolic volume) and function (ejection fraction) in participants of MESA. Some of these results have been previously reported in the form of an abstract (Adar et al. 2015a).

Methods

Study Population

Initiated in 2000, MESA is a multicenter, prospective study examining the progression of subclinical cardiovascular disease among an ethnically diverse population of 6,814 subjects (45–84 y old) who were free of known cardiovascular disease at baseline (Bild et al. 2002). In this analysis, we restricted reporting to participants from Chicago, Illinois, St. Paul, Minnesota, and Winston-Salem, North Carolina, who were part of the MESA Coarse ancillary study ($n = 3{,}295$). The MESA Coarse study conducted intensive sampling of $PM_{10–2.5}$ concentrations in three of the MESA sites chosen to reflect $PM_{10–2.5}$ variability. We further restricted to those who had cardiac magnetic resonance images (MRI) interpreted for RV morphology as part of the MESA RV ancillary study ($n = 1{,}851$). After excluding those with missing exposures and covariates, our final sample was 1,490 persons (Figure S1).

All protocols described herein received approval from local and national institutional review boards. Participants also provided informed consent.

Right Ventricle Characteristics

The MESA RV study obtained measures of RV function using cardiac MRIs performed at the baseline exam (Natori et al. 2006). These measures include RV mass at end-diastole, end-diastolic volume, and ejection fraction (Bluemke et al. 2008; Chahal et al. 2010). These measures were estimated by two independent analysts using QMASS software (version 4.2; Medis), is described elsewhere (Chahal et al. 2010). Based on random, blinded rereads from approximately 230 scans, the inter-reader intraclass correlation coefficients were 0.89, 0.96, and 0.80 for RV mass, end-diastolic volume, and ejection fraction, respectively (Kawut et al. 2011).

Exposure Assessment

We used site-specific land-use regression spatial prediction models derived from project-specific $PM_{10–2.5}$ measurements and geographic data to predict concentrations of $PM_{10–2.5}$ at subjects' residences. Details of these models have been previously published (Zhang et al. 2014). Briefly, we conducted two spatially intensive 2-wk monitoring campaigns of integrative PM_{10} and $PM_{2.5}$ samples using paired Harvard Personal Exposure Monitors (HPEMs) in each of three MESA Coarse sites. In each city, approximately 60 locations were targeted to cover the greatest geographic space. Additionally, the locations were selected to capture the variability of hypothesized characteristics associated with $PM_{10–2.5}$ mass and components (e.g., vegetation, distance to roads). All samples were weighed in a temperature- and relative humidity-controlled chamber, analyzed for elements by X-ray fluorescence spectroscopy, and total $PM_{10–2.5}$ mass and that of chemical components were calculated by difference (U.S. EPA 2009). The specific components of interest were copper, zinc, phosphorus, and silicon as consistent indicators for motor vehicle brake wear, tire wear, fertilized soil/agriculture, and crustal material across all study sites, respectively (Sturtz et al. 2014). We also examined a fifth component of $PM_{10–2.5}$, endotoxin, a major component of the outer membrane of Gram-negative bacteria. Endotoxin was chosen due to its capability to induce inflammation and modulate immune responses (Hadina et al. 2008) and its association with airway disease (Schwartz et al. 1995). We separately derived spatial prediction models for $PM_{10–2.5}$ mass and each component using many geographic variables, including land use, population density, vegetation, impervious surface, roadways, railways, and airports, as well as spatial correlation. The cross-validated (CV) R^2 for the site-specific models of $PM_{10–2.5}$ and chemical species ranged from 0.3 to 0.9. As described elsewhere (Zhang et al 2014), the models performed best for copper (CV R^2, 0.5–0.9) and generally worse for endotoxin (CV $R^2 = 0.3–0.4$). For our statistical modeling, we selected 5–y average concentrations weighted according to subjects' residential history preceding subjects' MRI.

Exposures to $PM_{2.5}$ and NO_2 were also estimated for each participant using spatiotemporal models derived from project-specific measurements, land-use characteristics, as well as regulatory monitoring data in the MESA Air study (Gill et al. 2011; Szpiro et al. 2010).

Covariates

All covariates, with the exception of airflow limitation, were assessed at baseline. These included sociodemographic and behavior information obtained via interview, and anthropometric measurements, left ventricle function, and laboratory data from the clinical exam. Comorbidities of hypertension and diabetes were also defined based on blood pressure or glucose measurements, respectively, self-reported medication use, and doctor diagnosis (Genuth et al. 2003; JNC 1997). Through the MESA Lung ancillary study, we had data on percent emphysema from computed tomography (CT) scans (Hoffman et al. 2009) and spirometry (Hankinson et al. 2010). The MESA Neighborhood Study developed a neighborhood socioeconomic scale (NSES) for each participant based on a principal components analysis of

2000 census tract data (U.S. Census Bureau 2002), including median household income, percent of persons in tract with at least a high school degree and median home value (Hajat et al. 2013).

Statistical Analysis

Multivariable linear regression models were used to quantify adjusted cross-sectional associations between $PM_{10-2.5}$ and continuous measures of our RV outcomes. All models were adjusted for age, race/ethnicity (White, Chinese, Black, and Hispanic), sex, education (less than high school, high school/some college, college or more), NSES, height, weight, cigarette smoking history (never, former, current), pack-years of smoking (0 pack-y, $0 < \text{pack-y} \leq 10$, $10 < \text{pack-y} \leq 20$, greater than 20), second-hand smoke exposure, hypertension (JNC 1997), diabetes (according to the 2003 American Diabetes Association Fasting Criteria Algorithm: normal, impaired fasting glucose, untreated diabetes, treated diabetes), cholesterol, study site, and an interaction of study site with NSES. Age, height, weight, NSES, and cholesterol were modeled as continuous; all other variables were modeled as categorical. In secondary models, we examined the linearity of these associations using splines and the robustness of our results to adjustment for $PM_{2.5}$ and NO_2 in two pollutant models. In secondary models of the chemical species of $PM_{10-2.5}$ we also adjusted for total mass as a covariate using a constituent residual model (Mostofsky et al. 2012). We used interaction terms to assess effect modification by age, sex, race/ethnicity, smoking status, emphysema (defined as percent of emphysema-like lung based on CT scans that were greater than the upper limit of normal (Hoffman et al. 2014)), and airflow limitation ($FEV_1/FVC < 0.7$). All reported estimates were scaled to the interquartile range (IQR) for each pollutant/species: $PM_{10-2.5}$ ($2.2\,\mu g/m^3$), copper ($4\,ng/m^3$), zinc ($11\,ng/m^3$), phosphorous ($6\,ng/m^3$), silicon ($0.13\,\mu g/m^3$), endotoxin ($0.08\,EU/m^3$), NO_2 (7.0 ppb), and $PM_{2.5}$ ($3.8\,\mu g/m^3$).

In sensitivity analyses, we restricted our analyses to participants who were residentially stable (lived at their current residence for 10 y or longer) and examined additional control for hypertension, diabetes, and cholesterol, as well as measures of LV function and lung disease as potential mediators.

The data analysis for this paper was generated using SAS (version 9.4; SAS Institute Inc.) and R (version 3.3.2; R Development Core Team).

Results

The mean age of the sample at baseline was 61 y; nearly 9% had physician-diagnosed asthma, and 7% had emphysema based on their CT scans (Table 1). Although participants in this sample were more likely to be Chinese, less likely to be black, and more likely to have a graduate degree than the full MESA Coarse cohort, these individuals were otherwise quite similar. Importantly, they did not differ with respect to their air pollution levels for all pollutants except zinc, which was approximately 10% lower in the study sample (Table S1).

Average $PM_{10-2.5}$ mass concentrations were lowest for Winston-Salem ($3.7\,\mu g/m^3$) but similar in St. Paul ($5.3\,\mu g/m^3$) and Chicago ($5.5\,\mu g/m^3$). St. Paul had the largest intracity variation (standard deviation: $1.8\,\mu g/m^3$ in St. Paul vs. $1.2\,\mu g/m^3$ for Chicago and Winston-Salem). With respect to the chemical components, the highest average concentrations of the two traffic-related markers of copper and zinc were in Chicago, whereas Winston-Salem had the highest concentrations of phosphorus. Mean endotoxin levels were generally low ($\leq 0.1\,EU/m^3$) across all locations. In all locations, we observed modest to high correlations (0.46–0.89) between the traffic-related pollutants of copper, zinc, and NO_2. In addition, $PM_{2.5}$ and NO_2 were also correlated (>0.6) in all locations. Although the other pollutants did not demonstrate consistent patterns across sites, there were notable (>0.6) correlations between most pollutants in Chicago (Table S2).

Among all participants, RV mass was positively associated with $PM_{10-2.5}$ mass, copper, phosphorus, and silicon in single-pollutant models (Table 2). After controlling for $PM_{2.5}$ and NO_2, however, which were themselves associated with RV mass, the association with copper was eliminated and associations with $PM_{10-2.5}$ mass, phosphorus, and silicon were blunted. Apart from copper, adjustment for $PM_{10-2.5}$ mass did not strongly affect associations with any chemical components (Figure S2). Results were also robust to more and less control for potential intermediate factors such as hypertension, cholesterol, diabetes, emphysema, airflow limitation, and LV mass and function (Figure S3).

Analysis of effect modification suggested that associations between $PM_{10-2.5}$ and RV mass were present in several susceptible populations. These subgroups included: former and current smokers in comparison with nonsmokers (p-value for interaction $= 0.02$), persons with emphysema in comparison with persons without emphysema (p-value for interaction $= 0.02$), and residentially stable participants in comparison with participants who had lived at their residences for less than 10 y (p-value for interaction $= 0.15$). These associations remained even after adjustment for $PM_{2.5}$ and NO_2 concentrations (Figure 1) and after adjustment for emphysema (results not shown).

Although the size and direction of the associations between $PM_{10-2.5}$ mass and silicon with RV end-diastolic volume were consistent with RV mass, the confidence intervals were very wide and indistinguishable from no association (Table 2). As with RV mass, associations with RV end-diastolic volume were strongest among current smokers, participants with emphysema, and particpants who were residentially stable, although the precision of these estimates remained large (Figure S4). No associations were observed with ejection fraction in the full cohort or in any subpopulation evaluated.

Discussion

Among a population-based cohort from three U.S. metropolitan areas, we found suggestive evidence of associations between $PM_{10-2.5}$ and RV structure after adjustment for confounding by $PM_{2.5}$ and NO_2. Positive associations between total $PM_{10-2.5}$ mass concentrations and RV hypertrophy and, to a lesser extent, dilation were driven by relationships among former and current smokers, persons with advanced emphysema, and participants who were residentially stable. Associations were not found among other participants. No associations were found with RV ejection fraction among any group.

This study adds to the literature by expanding our understanding of the health implications of $PM_{10-2.5}$ and the environmental risk factors for RV dysfunction. After adjustment for other risk factors such as smoking, height, weight, and co-pollutants previously associated with RV dysfunction, we observed the most robust associations for $PM_{10-2.5}$ mass with a 1.4 g (95% CI: 0.4, 2.5) and 0.9 g (95% CI: 0.1, 1.7) larger RV mass among persons with emphysema and current smokers, respectively, per $2.2\,\mu g/m^3$. These associations were on the same order of magnitude as those reported for $PM_{2.5}$ in the full cohort (Aaron et al. 2016) and in the MESA Coarse cities. These differences are also comparable to differences in RV mass for participants $5\,kg/m^2$ apart in BMI (Chahal et al. 2012) and may be clinically relevant, given that MESA participants with RV hypertrophy have double to triple the risk of heart failure or cardiovascular death (Kawut et al. 2012).

Table 1. Descriptive characteristics of the MESA Coarse participants at the baseline examination (2000–2002), by study site.

Characteristics	Total	Winston-Salem	St. Paul	Chicago
n	1490	457	536	497
	61.1 ± 10.0	62.4 ± 9.6	59.4 ± 10.0	61.9 ± 10.1
Age (y, %)				
45–54	477 (32%)	124 (27%)	196 (37%)	157 (32%)
55–64	437 (29%)	128 (28%)	173 (32%)	136 (27%)
65–74	404 (27%)	150 (33%)	119 (22%)	135 (27%)
75–84	172 (12%)	55 (12%)	48 (9%)	69 (14%)
Female	795 (53%)	253 (55%)	278 (52%)	264 (53%)
Race/ethnicity				
White	828 (56%)	277 (61%)	327 (61%)	224 (45%)
Chinese	158 (11%)	0 (0%)	0 (0%)	158 (32%)
Black	293 (20%)	178 (39%)	0 (0%)	115 (23%)
Hispanic	211 (14%)	2 (0%)	209 (39%)	0 (0%)
Education				
<High school	400 (27%)	128 (28%)	205 (38%)	67 (13%)
High school/some college	440 (30%)	135 (30%)	191 (36%)	114 (23%)
≥College	650 (44%)	194 (42%)	140 (26%)	316 (64%)
Smoking status				
Never	744 (50%)	225 (49%)	255 (48%)	264 (53%)
Former	556 (37%)	171 (37%)	200 (37%)	185 (37%)
Current	190 (13%)	61 (13%)	81 (15%)	48 (10%)
≥10 y in neighborhood	1033 (69%)	281 (61%)	381 (71%)	371 (75%)
Health				
BMI (kg/m^2)	27.7 ± 5.0	28.2 ± 5.0	28.9 ± 4.9	26.0 ± 4.7
Cholesterol (mg/dl)	195.3 ± 36.0	189.1 ± 34.7	201.5 ± 38.9	194.2 ± 32.7
Hypertension	584 (39%)	232 (51%)	167 (31%)	185 (37%)
Diabetic	2.3 (1.0)	1.4 (1.0)	2.0 (1.0)	3.8 (1.0)
% Emphysema (−950 HU)[a]	81% (0)	37% (0)	71% (0)	134% (0)
Airflow limitation[b]	220 (22%)	66 (26%)	57 (19%)	97 (22%)
Emphysema	97 (7%)	15 (3%)	46 (9%)	36 (7%)
Asthma	130 (9%)	36 (8%)	51 (10%)	43 (9%)
Left Ventricular end-diastolic Mass (g)	147.5 ± 39.0	145.7 ± 38.5	154.6 ± 38.5	141.4 ± 38.8
RV Outcomes				
RV mass (g)	21.6 ± 4.7	21.2 ± 4.3	22.7 ± 4.9	20.8 ± 4.5
RV ejection fraction (%)	70.3 ± 6.7	69.1 ± 7.0	70.2 ± 6.3	71.4 ± 6.5
RV end-diastolic volume (mL)	127.6 ± 33.2	122.9 ± 30.5	135.1 ± 35.0	123.9 ± 32.2
Pollutants				
$PM_{10–2.5}$ ($\mu g/m^3$)	4.9 ± 1.6	3.7 ± 1.2	5.3 ± 1.8	5.5 ± 1.2
Copper (ng/m^3)	4.4 ± 2.5	2.5 ± 0.8	3.5 ± 0.8	7.1 ± 2.4
Zinc (ng/m^3)	9.0 ± 9.6	3.1 ± 1.6	5.1 ± 1.2	18.5 ± 11.5
Silicon ($\mu g/m^3$)	0.4 ± 0.1	0.4 ± 0.0	0.5 ± 0.1	0.4 ± 0.1
Phosphorous (ng/m^3)	15.9 ± 3.6	19.7 ± 2.2	12.9 ± 1.9	15.6 ± 2.7
Endotoxin (EU/m^3)	0.1 ± 0.1	0.0 ± 0.0	0.1 ± 0.0	0.0 ± 0.1
$PM_{2.5}$ ($\mu g/m^3$)	14.6 ± 2.1	15.5 ± 0.9	12.3 ± 1.4	16.1 ± 1.4
NO_2 (ppb)	14.7 ± 5.1	10.3 ± 2.5	13.5 ± 2.2	20.2 ± 4.1

Note: Values given as *n* (%) or mean ± standard deviation. BMI, body mass index; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter <2:5 μm in diameter; $PM_{10–2.5}$, particulate matter between 2.5 and 10 μm in diameter; RV, right ventricular.
[a]Emphysema is defined as the percent emphysema via computed tomography scan greater than the upper limit of normal.
[a]Airflow limitation is defined as an FEV_1/FVC <0.7 and was available on only 974 participants.

Mechanisms through which $PM_{10–2.5}$ exposures might likely affect the right ventricle (Voelkel et al. 2006) include the restructuring of the pulmonary vasculature, increases in RV load (Zangiabadi et al. 2014), hypoxia, inflammation (Chaouat et al. 2009), and autonomic dysfunction (Wensel et al. 2009; Wrobel et al. 2012). Support for these mechanisms comes from a previous study of healthy Mexican children that reported greater pulmonary arterial pressures and serum levels of the vasoconstrictive protein endothelin-1 with larger long-term PM concentrations (Calderón-Garcidueñas et al. 2007). Toxicological research has similarly demonstrated enhanced vasoconstriction and impaired vasodilation of pulmonary arterioles in healthy animals and in animals with chronic bronchitis exposed to PM (Faustini et al. 2012; Peel et al. 2005). Interestingly, the associations with RV mass were robust to control for hypertension, emphysema, airflow limitation, and LV mass and function, suggesting that these factors may not be critical intermediates of our observed associations. However, it is difficult to conclusively assess mediation in this study given our cross-sectional design and the possibility that only advanced cases of emphysema or airflow limitation are critical intermediates, which are limited in number in this population. Our overall null associations with RV ejection fraction were similar to findings in a previous analysis (Kawut et al. 2012) where only RV mass was independently associated with cardiovascular death. These data could suggest that RV hypertrophy is an earlier indicator of increased pressure in the RV than RV ejection fraction, though this has yet to be clearly demonstrated.

Although the observed association between $PM_{10–2.5}$ and RV appeared to be independent of $PM_{10–2.5}$-associated lung damage, the interaction with emphysema suggests that individuals with preexisting lung damage may be more susceptible to long-term $PM_{10–2.5}$ exposures. This susceptibility is plausible, given that persons with COPD have greater deposition and less mucociliary clearance of particles from their lungs relative to healthy individuals (Bennett et al. 1997; Brown et al. 2002). It is also consistent

Table 2. Associations between $PM_{10-2.5}$ mass and RV structure and function in single and multipollutant models.

	Mass (g)			Volume (mL)			Ejection Fraction (%)		
Model	Difference	95% CI	*p*–Value	Difference	95% CI	*p*–Value	Difference	95% CI	*p*–Value
$PM_{10-2.5}$									
Single Pollutant Model	0.3	0.0, 0.5	0.06	0.4	−1.3, 2.2	0.63	−0.1	−0.6, 0.4	0.75
+ $PM_{2.5}$	0.2	−0.1, 0.5	0.14	0.3	−1.5, 2.2	0.74	−0.1	−0.6, 0.4	0.76
+ NO_2	0.2	−0.1, 0.5	0.22	0.4	−1.5, 2.3	0.68	−0.1	−0.6, 0.4	0.72
Cu									
Single Pollutant Model	0.3	−0.2, 0.8	0.20	0.6	−2.5, 3.6	0.71	0.1	−0.7, 1.0	0.75
+ $PM_{2.5}$	0.0	−0.5, 0.5	0.93	0.0	−3.4, 3.3	0.99	0.5	−0.5, 1.4	0.32
+ NO_2	−0.2	−0.8, 0.5	0.56	−0.1	−4.3, 4.1	0.96	0.4	−0.8, 1.6	0.56
Zn									
Single Pollutant Model	0.0	−0.3, 0.3	0.90	−0.6	−2.6, 1.3	0.51	−0.1	−0.6, 0.5	0.81
+ $PM_{2.5}$	−0.2	−0.5, 0.1	0.16	−1.1	−3.2, 0.9	0.27	0.1	−0.5, 0.6	0.85
+ NO_2	−0.3	−0.7, 0.0	0.09	−1.4	−3.6, 0.9	0.24	−0.1	−0.7, 0.6	0.81
P									
Single Pollutant Model	0.5	0.0, 1.0	0.03	0.5	−2.6, 3.6	0.75	−0.1	−0.9, 0.8	0.87
+ $PM_{2.5}$	0.2	−0.3, 0.7	0.41	−0.4	−3.6, 2.9	0.83	0.0	−0.9, 1.0	0.93
+ NO_2	0.3	−0.2, 0.8	0.25	0.0	−3.4, 3.4	0.99	−0.1	−1.0, 0.9	0.91
Si									
Single Pollutant Model	0.4	0.1, 0.7	0.01	0.8	−1.1, 2.8	0.41	−0.2	−0.7, 0.4	0.54
+ $PM_{2.5}$	0.2	−0.2, 0.5	0.36	0.2	−2.0, 2.4	0.86	0.0	−0.6, 0.6	0.95
+ NO_2	0.3	−0.1, 0.6	0.19	0.7	−1.8, 3.1	0.59	−0.2	−0.9, 0.4	0.49
Endotoxin									
Single Pollutant Model	−0.1	−0.5, 0.2	0.49	−0.2	−2.4, 1.9	0.82	−0.1	−0.7, 0.5	0.67
+ $PM_{2.5}$	0.1	−0.3, 0.4	0.64	0.1	−2.1, 2.4	0.91	−0.4	−1.0, 0.3	0.26
+ NO_2	0.0	−0.4, 0.3	0.89	−0.1	−2.4, 2.1	0.90	−0.2	−0.8, 0.5	0.59
NO_2									
Single Pollutant Model	0.5	0.1, 0.9	0.01	0.8	−1.8, 3.5	0.54	0.0	−0.8, 0.7	0.93
+ $PM_{10-2.5}$	0.4	0.0, 0.9	0.06	0.6	−2.2, 3.5	0.66	0.0	−0.8, 0.8	0.96
+ $PM_{2.5}$	0.2	−0.3, 0.8	0.38	0.3	−3.1, 3.8	0.84	0.3	−0.7, 1.3	0.53
$PM_{2.5}$									
Single Pollutant Model	1.0	0.4, 1.6	0.001	1.8	−2.0, 5.6	0.36	−0.6	−1.7, 0.4	0.25
+ $PM_{10-2.5}$	0.9	0.3, 1.5	0.003	1.7	−2.3, 5.6	0.41	−0.6	−1.7, 0.5	0.28
+ NO_2	0.8	0.0, 1.5	0.043	1.5	−3.4, 6.4	0.56	−0.9	−2.3, 0.5	0.19

Note: All models adjusted for age, race, gender, height, weight, neighborhood socioeconomic scale (NSES), NSES, education, smoking status, pack-years, second-hand smoke exposure, hypertension, diabetes, total cholesterol, study site, and site by NSES interaction. Associations scaled to interquartile range (IQR) IQR of pollutant: $PM_{10-2.5}$ (2.2 $\mu g/m^3$), Cu (4 ng/m^3), Zn (11 ng/m^3), P (6 ng/m^3), Si (0.13 $\mu g/m^3$), endotoxin (0.08 EU/m^3), $PM_{2.5}$ (3.8 $\mu g/m^3$), NO_2 (7.0 ppb). CI, confidence interval; Cu, copper; NO_2, nitrogen dioxide; P, phosphorous; $PM_{2.5}$, particulate matter $<2{:}5$ μm in diameter; $PM_{10-2.5}$, particulate matter between 2.5 and 10 μm in diameter; Si, silicon; Zn, zinc.

with epidemiological evidence of enhanced vulnerability of persons with respiratory conditions to short-term air pollution exposures (Faustini et al. 2012; Peel et al. 2005; Sacks et al. 2011), though the findings of the few studies to examine chronic lung disease as an effect modifier of long-term exposures to air pollution have been mixed (Andersen et al. 2012; Jerrett et al. 2009).

We also observed positive associations between RV mass and $PM_{10-2.5}$ concentrations among participants who smoke or who have a history of smoking, independent of their emphysema status. One possible explanation may be that individuals who smoke or have smoked are more susceptible to the effects of air pollution because of smoking's ability to increase inflammation and vasoconstriction (Akishima et al. 2007) and alter immune function, among other effects. However, epidemiologic evidence has also been mixed regarding the interaction between smoking and air pollution (Pope et al. 2011), suggesting that more research is necessary to understand this relationship. In addition, some caution is warranted about the generalizability of these findings as the smokers in MESA are generally healthier than the average smoking population due to our restriction to older adults without cardiovascular disease at baseline.

Our study is not without limitations. First, due to its cross-sectional design, our findings only provide evidence of potential associations that warrant further evaluation. Reverse causality is unlikely, however, and we have adjusted our models for a rich set of personal characteristics to account for between-person differences. Second, despite the highly innovative exposure assessment used, our exposure models are entirely spatial in nature and are assumed to capture the key differences in concentrations across space at different times. Our finding that associations were larger and more precise among persons living at their residences for >10 y may, however, suggest that our overall results may be biased towards the null due to inaccuracies in long-term exposures for some participants. On the other hand, compared with individuals who lived in their neighborhood for <10 y, residentially stable participants were more likely to be older, have hypertension, and have advanced emphysema, suggesting that these individuals may have been susceptible for other reasons. Another issue is that our models varied in predictive power by pollutant. Thus, differences in the observed strength of association between pollutants may be causal or could simply reflect different measurement errors. For example we found significant associations with $PM_{2.5}$ and NO_2, which, compared with $PM_{10-2.5}$, had substantially better predictive ability due to a greater number of measurements that were collected over a longer period of time. In contrast, no associations were found with endotoxin, which had the lowest CV R^2 in our prediction models. This finding may be the result of smaller errors for $PM_{2.5}$ and NO_2 that make them less likely to be biased toward the null in individual pollutant and multipollutant models. Finally, although the exposure estimation methods used in this study allow for individual assessment of outdoor concentrations, we do not have estimates of indoor or personal concentrations.

Despite these limitations, this work has many important strengths. The MESA cohort is an extremely well-characterized population with detailed and standardized measures of outcomes and covariates. The availability of RV measures is unique in such a large sample. Another distinction in this study is our exposure

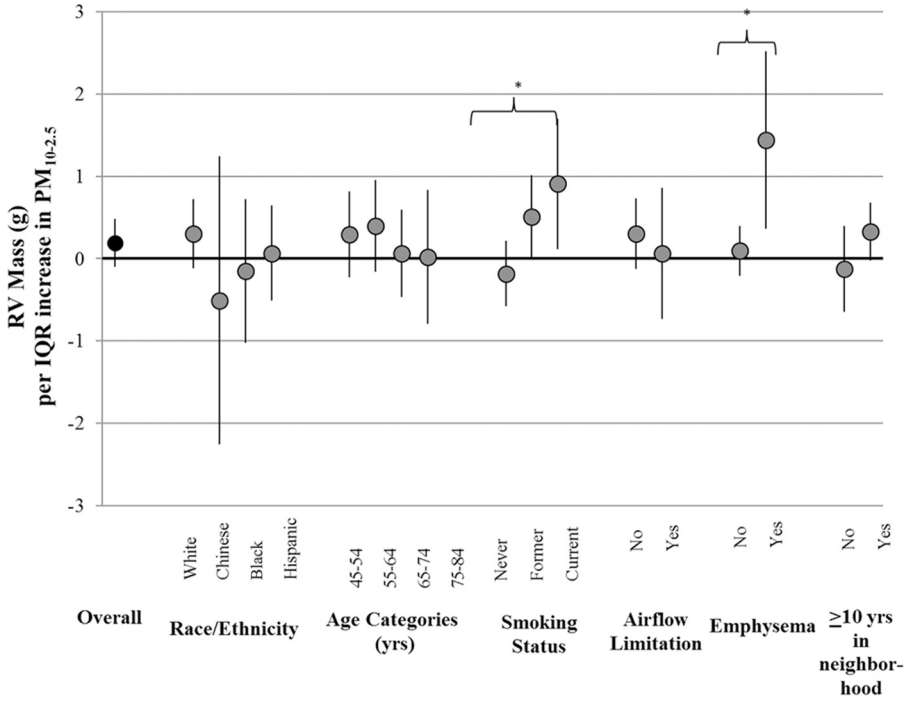

Figure 1. Effect modification of associations between $PM_{10–2.5}$ concentrations and RV end-diastolic mass after control for $PM_{10–2.5}$ and NO_2 [g per interquartile range (IQR) of pollutant, 95% confidence interval (CI)].

*Interaction was statistically significant ($p < 0.05$). Note: $PM_{2.5}$, particulate matter with aerodynamic diameter between 2.5 and 10 μm; NO_2, nitrogen dioxide.

assessment, which improves on existing epidemiology studies of long-term exposures to $PM_{10–2.5}$ in the United States. Our model predicts fine-scale spatial variability in exposures using a model derived from intensive air pollution monitoring campaigns in each study community. This methodology is in contrast to previous studies that have relied exclusively on data from relatively sparse national monitoring networks to estimate exposures to $PM_{10–2.5}$ (Lipfert et al. 2006; McDonnell et al. 2000; Pope et al. 2002; Puett et al. 2009; Puett et al. 2011). We were also able to control for copollutants ($PM_{2.5}$ and NO_2) and demonstrated independent associations with $PM_{10–2.5}$. The availability of chemical component data has particularly important implications for regulatory purposes, given that $PM_{10–2.5}$ is generated by both natural and anthropogenic sources. This inclusion has important implications for regulatory purposes, given that $PM_{10–2.5}$ is generated by both natural and anthropogenic sources.

Conclusion

This cross-sectional study provided some evidence of a positive association between long-term residential $PM_{10–2.5}$ concentrations and RV mass among persons with a history of tobacco-smoke exposures and persons with severe emphysema. If replicated by future work, our findings could suggest a possible mechanism for observed associations between $PM_{10–2.5}$ exposures and mortality from respiratory disease.

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