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## **Particulate Matter Exposure and Cardiopulmonary Differences in the Multi-Ethnic Study of Atherosclerosis**

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## ABSTRACT

**Background:** Particulate matter (PM) exposure may directly affect the pulmonary vasculature. While the pulmonary vasculature is not easily measurable, differential associations for right ventricular (RV) and left ventricular (LV) mass may provide an indirect assessment of pulmonary vascular damage.

**Objectives:** To test whether long-term exposure to PM  $<2.5\mu\text{m}$  (PM<sub>2.5</sub>) is associated with greater RV mass and RV mass/end-diastolic volume ratio relative to the LV.

**Methods:** The Multi-Ethnic Study of Atherosclerosis performed cardiac magnetic resonance (CMR) imaging among participants 45-84 years old without clinical cardiovascular disease in 2000-02 in six U.S. cities. A fine-scale spatiotemporal model estimated ambient PM<sub>2.5</sub> exposure in the year before CMR; individually-weighted estimates account for indoor exposure to ambient PM<sub>2.5</sub>. Linear regression models were adjusted for demographics, anthropometrics, smoking status, cardiac risk factors and LV parameters, with additional adjustment for city.

**Results:** The 4,041 included participants were a mean of 61.5 years old and 47% were never smokers. The mean ambient PM<sub>2.5</sub> was 16.4  $\mu\text{g}/\text{m}^3$  and individually-weighted PM<sub>2.5</sub> was 11.0  $\mu\text{g}/\text{m}^3$ . PM<sub>2.5</sub> exposure was associated with a greater RV mass (ambient: 0.11 g per 5  $\mu\text{g}/\text{m}^3$ , 95% CI: -0.05, 0.27; individually-weighted: 0.20 g per 5  $\mu\text{g}/\text{m}^3$ , 95% CI: 0.04, 0.36) and a greater RV mass/end-diastolic volume ratio conditional on LV parameters. City-adjusted results for RV mass were of greater magnitude and statistically significant for both measures of PM<sub>2.5</sub>, while those for RV mass/end-diastolic volume ratio were attenuated.

**Conclusions:** Long-term PM<sub>2.5</sub> exposures were associated with greater RV mass and RV mass/end-diastolic volume ratio conditional on the LV, however additional adjustment for city attenuated the RV mass/end-diastolic volume findings. These findings suggest that PM<sub>2.5</sub> exposure may be associated with subclinical cardiopulmonary differences in this general population sample.

## INTRODUCTION

Exposure to ambient particulate matter (PM) has been linked to the occurrence of cardiovascular events (Brook et al. 2010; Pope et al. 2004). Although the causal mechanisms remain unclear, short and long-term exposure to ambient PM has been associated with systemic endothelial dysfunction and a secondary inflammatory response in the vasculature (Krishnan et al. 2012; Nurkiewicz et al. 2004; Tamagawa et al. 2008). Animals exposed to PM for even short time periods have increased muscularization of pulmonary arterioles (Lemos et al. 2006; Rivero et al. 2005), suggesting increased pulmonary arteriolar pressure; however, it is unknown whether PM exposure has a similar effect in humans.

While direct measurement of the pulmonary vasculature is not feasible in large epidemiologic studies, evaluation of cardiac structure can be used to indirectly assess chronic pulmonary vascular differences. We hypothesized that PM damages the pulmonary microvasculature, causing two distinct effects: increased right ventricular (RV) mass due to higher pulmonary artery pressure (Bogaard et al. 2009), and reduced blood flow to the left ventricle (LV), resulting in LV underfilling and reduced stroke work (due to Starling's Law), with consequent reduction of LV mass and myocyte atrophy (Hardziyenka et al. 2011). This process would be analogous to pulmonary capillary damage in emphysema, which may increase RV mass and reduce LV end-diastolic volume and LV mass (Vonk Noordegraaf 1997; Vonk Noordegraaf et al. 2005), and pulmonary hypertension, in which the ratio of RV to LV mass on cardiac magnetic resonance (CMR) predicts pulmonary artery pressure (Saba et al. 2002; Swift et al. 2013). Hence, we see the association of an exposure with RV mass after adjustment for LV mass as the best surrogate for pulmonary vascular damage (Figure S1).

Published results from the Multi-Ethnic Study of Atherosclerosis (MESA) have found that long-term traffic-related air pollution exposure, assessed by nitrogen dioxide (NO<sub>2</sub>), was associated with a greater RV mass after adjustment for LV mass (Leary et al. 2014), and that exposure to PM <2.5µm in diameter (PM<sub>2.5</sub>) was associated with a lower LV mass in analyses without adjustment for city (Van Hee et al. 2009). However, whether differences in RV relative to LV mass, which may reflect pulmonary vascular damage and related cardiopulmonary differences, occur in humans in relation to long-term PM exposure has not been assessed. We therefore examined the relationships between PM<sub>2.5</sub> exposure and RV structure compared to LV structure on CMR in MESA, a large multi-ethnic cohort study. We hypothesized that greater PM<sub>2.5</sub> exposure would be associated with increased RV mass and mass/end-diastolic volume ratio conditional on the LV.

## **METHODS**

### **Multi-Ethnic Study of Atherosclerosis**

MESA is a multicenter prospective cohort study designed to investigate the prevalence, correlates and progression of subclinical cardiovascular disease in whites, Hispanics, African and Chinese-Americans (Bild et al. 2002). In 2000-02, MESA recruited 6,814 participants 45-84 years old from six U.S. communities. Multiple racial/ethnic groups were recruited at all sites in order to reduce site-by-race confounding. Exclusion criteria included clinical cardiovascular disease, weight over 300 lbs., pregnancy or other impediment to long-term participation. The MESA Air Pollution Study was a large ancillary study funded by the Environmental Protection Agency (EPA) to add air pollution exposure assessments for each participant (Kaufman et al. 2012). The MESA-RV Study was an ancillary study funded by the National Heart Lung and

Blood Institute (NHLBI) to characterize RV structure and function by CMR in the MESA population. The protocols of MESA and all studies described herein were approved by the Institutional Review Boards of all collaborating institutions and the NHLBI. All participants provided informed consent.

### **Cardiac Magnetic Resonance Imaging**

Participants underwent CMR in 2000-02, as previously described (Natori et al. 2006). All imaging was performed on 1.5 T magnets with electrocardiographic gating. Methods for interpretation of LV and RV parameters have been previously reported (Bluemke et al. 2008; Chahal et al. 2010).

Briefly, all RV image analysis was performed at one site by two independent analysts on Windows workstations using QMASS software (Medis). The endocardial and epicardial borders of the RV were traced manually on short axis cine images at end-systole and end-diastole. RV end-diastolic volume and end-systolic volume were calculated using Simpson's rule. RV mass was determined at end-diastole as the difference between the epicardial and endocardial volumes multiplied by the specific gravity of myocardium (1.05 g/mL) (Natori et al. 2006). RV stroke volume was calculated by subtracting RV end-systolic volume from end-diastolic volume. RV ejection fraction was calculated as RV stroke volume divided by end-diastolic volume. The intra-reader intraclass correlation coefficients (ICCs) were 0.89-0.99 and inter-reader ICCs from random blinded re-reads were 0.80-0.96 for RV mass, end-diastolic volume and ejection fraction (Kawut et al. 2011).

## **PM<sub>2.5</sub> Exposure Estimates**

The MESA Air Pollution Study generated prediction models of long-term exposure to ambient PM<sub>2.5</sub> based on each participant's reported home address starting 1 year prior to the participant visit in 2000-02 (Kaufman et al. 2012). The maximum likelihood predictions incorporate spatiotemporal modeling, which has been described previously (Keller et al. 2015; Sampson et al. 2011). Briefly, the model leverages all available PM<sub>2.5</sub> concentrations collected from the U.S. EPA's Air Quality System monitors, 1-5 supplemental stationary monitors within each city, and monitoring at the homes of a subset of MESA participants (Cohen et al. 2009). The model also includes geographic variables such as land use (e.g. industrial, residential, water), distance to various features including airports and coastlines, traffic volumes incorporated via dispersion models, as well as population density and urban topography (Cohen et al. 2009; Keller et al. 2015). Using concentrations predicted in 2-week averages at each participant's home, we computed the annual average concentrations in the year prior to study visit and used this measure as a proxy of long-term exposure. Estimated exposures for ambient PM<sub>2.5</sub> in Los Angeles are shown in Figure 1.

A secondary exposure, individually-weighted PM<sub>2.5</sub>, was estimated using reported time spent indoors and the estimated infiltration fraction of ambient PM<sub>2.5</sub>. The infiltration fraction of ambient PM<sub>2.5</sub> was estimated based on indoor and outdoor measurements of PM<sub>2.5</sub>, performed at a small sample of participants' homes using particulate sulfur as a tracer of outdoor particulates, and models incorporating home characteristics and behaviors (Allen et al. 2012; Kaufman et al. 2012; Spalt et al. 2015). These variables required completion of a home characteristics

questionnaire at a follow-up visit in 2006-08; thus, individually-weighted PM<sub>2.5</sub> is available only for a subset.

Estimates for PM<sub>2.5</sub> exposures were weighted for time at each address if participants moved during the year.

### **Covariate Information**

Age, gender, race/ethnicity, educational attainment, income, smoking status, pack-years of smoking and medical history were self-reported in 2000-02. Height, weight, resting blood pressure, fasting serum glucose, C-reactive protein, total cholesterol and high-density lipoproteins (HDL) were measured using standard techniques (MESA Manual of Procedures 2008). Hypertension was defined as blood pressure  $\geq$  140/90 mmHg or self-reported hypertension and use of antihypertensive medications. Diabetes was defined as fasting glucose  $\geq$  7.0 mmol/L ( $\geq$  126 mg/dL), use of hypoglycemic medication or self-reported physician diagnosis. Current smoking status was verified using urine cotinine assay (Rodriguez et al. 2010). Participant questionnaires included self-report of trouble breathing at night, and the intensity and duration of typical physical activity, which was quantified as metabolic equivalent (MET) minutes per week (Bertoni et al. 2009). The neighborhood socioeconomic status (SES) index represents six U.S. Census variables identified as unique contributors to neighborhood SES (Hajat et al. 2013). Ambient NO<sub>2</sub> exposures were estimated using a similar model to that described for PM<sub>2.5</sub> (Keller et al. 2015), and weighted for time at each address if the participant moved.

Trained readers performed percent emphysema measurements on cardiac CT scans obtained between 2000-02 using modified Pulmonary Analysis Software Suite (PASS) software (Hoffman et al. 2009). Percent emphysema was defined as the percentage of voxels in the lung below -950 Hounsfield units, adjusted for the attenuation of air outside the chest. Emphysema was defined as percent emphysema above the upper limit of normal calculated using reference equations (Hoffman et al. 2014). Spirometry was conducted on a subset between 2004-07 in accordance with American Thoracic Society-European Respiratory Society guidelines (Miller et al. 2005) and following the MESA Lung protocol; all exams were reviewed by one investigator (Hankinson et al. 2010). Airflow limitation was defined as FEV<sub>1</sub>/FVC below 0.7.

### **Statistical Analyses**

The sample was stratified by quintile of ambient PM<sub>2.5</sub> exposure for descriptive purposes; levels of categorical variables and means of continuous variables are shown in Table 1. Linear regression models were used to estimate the associations between PM exposures and RV parameters conditional on LV parameters. Adjustment for the corresponding LV parameter was performed in order to indirectly assess pulmonary vascular differences (Figure S1). LV adjustment also accounts for other potential associations of LV with RV structure (e.g., greater LV mass causing elevated LV end-diastolic pressure leading to pulmonary venous hypertension and greater RV mass) and to reduce confounding related to body size. Additionally, the multivariable model adjusted for parameters thought to be associated with RV mass *a priori* (age, sex, race/ethnicity, height, weight, smoking status, pack-years, total cholesterol, HDL, hypertension, systolic blood pressure, fasting glucose, diabetes, and C-reactive protein) and confounders of air pollution exposure (education, income, neighborhood SES index). We present

these multivariable models prior to and after adjustment for city, the latter being treated as the primary analysis in order to address unmeasured confounding by study site. Linear relationships were confirmed in generalized additive models by visual inspection (data not shown). We present all results and 95% confidence intervals, as recommended by Rothman (Rothman 1990). In the primary analysis, effect modification of the PM and RV mass association on an additive scale was assessed using interaction terms by sex, race/ethnicity, age (above and below 60 years), smoking status (ever or never smoker), airflow limitation (yes/no), emphysema (yes/no) and city. Sensitivity analyses were performed limiting the sample to those who had lived at the same residence for more than 5 years prior to the study visit and adjusted for factors that may be associated with RV function or exposure to PM including percent emphysema, lung function (FEV<sub>1</sub>, FEV<sub>1</sub>/FVC), reported trouble breathing at night and self-reported physical activity (with the exception of percent emphysema, these variables were available only for a subset). Sensitivity analyses were also performed adjusting for NO<sub>2</sub> exposure and using a random intercept for city. Analyses were performed in SAS 9.3 (SAS Institute).

## RESULTS

MESA included 6,814 participants, of whom 5,098 underwent CMR with 5,004 being interpretable for the LV. Of the 4,634 participants selected for RV evaluation, reads were attempted in 4,484 before reaching a total of 4,204 interpretable scans (94% of attempted reads). PM<sub>2.5</sub> exposure estimates were available for 4,057 of these participants, of whom 4,041 also had complete covariate data (Figure S2). The 4,204 participants included in the MESA RV Study did not differ from other MESA participants except that they were on average younger, had a lower BMI and lower prevalence of diabetes, former and current smoking (Kawut et al. 2011). The

mean ( $\pm$  SD) age of the sample was  $61.5 \pm 10$  years, 52% were female, 47% were never smokers, 39% were white, 22% were Hispanic, 27% were African, and 12% were Chinese-American. Mean ambient  $PM_{2.5}$  exposure was  $16.4 \pm 3.4 \mu\text{g}/\text{m}^3$ , and mean individually-weighted  $PM_{2.5}$  exposure was  $11.0 \pm 3.7 \mu\text{g}/\text{m}^3$ . City-specific correlations of  $PM_{2.5}$  and  $NO_2$  exposures were moderate to high (0.53-0.81 for ambient and 0.32-0.55 for individually-weighted  $PM_{2.5}$ , Table S1).

Compared to participants in the highest quintile of ambient  $PM_{2.5}$  exposure, those in the lowest quintile were more likely to be white and ever-smokers, to have at least a high school education, a greater height, weight, and  $FEV_1$  and a lower percent emphysema (Table 1). Participants in the lowest quintile were more likely to be in St. Paul, MN, while those in the highest quintile were more likely to be in Los Angeles, CA. RV mass, RV end-diastolic volume, stroke volume, LV mass, LV end-diastolic volume and LV mass/end-diastolic volume ratio were greater, while RV mass/end-diastolic volume ratio, RV and LV ejection fraction were lower in the lowest quintile compared to the highest quintile of exposure (Table 2). The correlation between RV and LV mass was 0.62, end-diastolic volume 0.82, stroke volume 0.79 and ejection fraction 0.47 (all p-values  $<0.001$ ).

### **Ambient $PM_{2.5}$ Exposure**

Table 3 shows the associations of ambient  $PM_{2.5}$  with RV parameters conditional on LV parameters. In the multivariable model, ambient  $PM_{2.5}$  exposure was associated with a greater RV mass ( $0.11 \text{ g}/5\mu\text{g}/\text{m}^3$ , 95% CI: -0.05, 0.27) and mass/end-diastolic volume ratio, and with a lower RV end-diastolic volume and stroke volume conditional on LV parameters. With adjustment for city, the relationship between  $PM_{2.5}$  and RV mass became stronger (0.37

$\text{g}/5\mu\text{g}/\text{m}^3$ , 95% CI: 0.03, 0.71), while associations for RV mass/end-diastolic volume ratio, end-diastolic volume and stroke volume were weakened (Table 3).

There was no evidence for statistically significant effect modification of the relationship between  $\text{PM}_{2.5}$  and RV mass conditional on LV mass by gender, age, smoking status, airflow limitation or emphysema (Figure 2). However, there was significant interaction by race/ethnicity in the city-adjusted model (P-interaction=0.003), and results were positive among whites (0.70  $\text{g}/5\mu\text{g}/\text{m}^3$ , 95% CI: 0.25, 1.14) and Hispanics (0.84  $\text{g}/5\mu\text{g}/\text{m}^3$ , 95% CI: 0.42, 1.26), and negative among African-Americans (-0.46  $\text{g}/5\mu\text{g}/\text{m}^3$ , 95% CI: -0.97, 0.06) (Figure 2). Associations were largely unchanged when limited to the 82% who had been at the same residence for more than 5 years, and after adjusting for percent emphysema,  $\text{FEV}_1$ ,  $\text{FEV}_1/\text{FVC}$ , reported trouble breathing at night or self-reported physical activity in the subsets with these measures (Figure 2).

There was significant effect modification for RV mass conditional on LV mass by city (P-interaction <0.001) with large variation between the extremes of St. Paul, MN (3.86  $\text{g}/5\mu\text{g}/\text{m}^3$ , 95% CI: 2.56, 5.16) and Forsyth County, NC (-0.84  $\text{g}/5\mu\text{g}/\text{m}^3$ , 95% CI: -2.20, 0.51) (Table S2). City-adjusted results were similar using a random intercept for city (Table S3).

In models including  $\text{NO}_2$ , the multivariable association between ambient  $\text{PM}_{2.5}$  and RV mass conditional on LV mass was in the opposite direction (-0.12  $\text{g}/5\mu\text{g}/\text{m}^3$ , 95% CI: -0.32, 0.09), and the city-adjusted association was attenuated (0.09  $\text{g}/5\mu\text{g}/\text{m}^3$ , 95% CI: -0.34, 0.52). However, results were of a greater magnitude (with less precision) in the multivariable and city-adjusted models for RV mass/end-diastolic volume ratio, end-diastolic volume (multivariable model -4.01  $\text{mL}/5\mu\text{g}/\text{m}^3$ , 95% CI: -5.05, -2.96; city-adjusted model -2.53  $\text{mL}/5\mu\text{g}/\text{m}^3$ , 95% CI: -4.74, -0.32) and stroke volume compared to the main results (Table S4).

### **Individually-weighted PM<sub>2.5</sub> Exposure**

Participants with measures of individually-weighted PM<sub>2.5</sub> did not appreciably differ from the overall sample (Table S5). Individually-weighted PM<sub>2.5</sub> exposure was associated with greater RV mass (0.20 g/5μg/m<sup>3</sup>, 95% CI: 0.04, 0.36) and mass/end-diastolic volume ratio, as well as a lower end-diastolic volume (-1.51 mL/5μg/m<sup>3</sup>, 95% CI: -2.32, -0.70) and stroke volume conditional on LV parameters in the multivariable model (Table 3). The association for RV mass was of greater magnitude after adjustment for city (0.30 g/5μg/m<sup>3</sup>, 95% CI: 0.01, 0.59), while that of mass/end-diastolic volume ratio was attenuated, and associations for end-diastolic volume and stroke volume were no longer present (Table 3).

Sensitivity analyses for individually-weighted PM<sub>2.5</sub> are shown in Figure S3. Similar to ambient PM<sub>2.5</sub>, there were significant interactions by race/ethnicity (with positive associations for whites and Hispanics, and a negative association for African-Americans), but no interaction by sex, age, smoking status, airflow limitation or emphysema. For individually-weighted PM<sub>2.5</sub> there was also significant interaction of the association with RV mass by city (P-interaction <0.001, data not shown).

Further adjustment for NO<sub>2</sub> exposure resulted in attenuated associations between individually-weighted PM<sub>2.5</sub> and RV mass (multivariable model 0.04 g/5μg/m<sup>3</sup>, 95% CI: -0.19, 0.26; city-adjusted model 0.21 g/5μg/m<sup>3</sup>, 95% CI: -0.06, 0.47). Additionally, after adjustment for NO<sub>2</sub> in the multivariable model there were greater magnitude associations with less precision for mass/end-diastolic volume ratio, end-diastolic volume (-2.66 mL/5μg/m<sup>3</sup>, 95% CI: -3.80, -1.51), and stroke volume, while city-adjusted results remained null (Table S4).

## DISCUSSION

This study demonstrates that in a large cohort free of clinical cardiovascular disease, higher ambient and individually-weighted PM<sub>2.5</sub> exposures were associated with greater RV mass conditional on LV mass in models with and without adjustment for city. In addition, PM<sub>2.5</sub> exposures were associated with greater RV mass/end-diastolic volume ratio and lower end-diastolic volume and stroke volumes conditional on LV parameters before adjustment for city. These findings provide evidence in the general population that PM<sub>2.5</sub> exposure is associated with differences in cardiac structure, possibly reflecting pulmonary vascular differences.

Prior literature on this topic in humans is limited, likely due to difficulty quantifying long-term individual exposures and measuring the pulmonary vasculature. One study, which directly evaluated this relationship in 81 healthy children in Mexico, found that long-term ambient PM exposure was associated with higher mean pulmonary arterial pressure on transthoracic echocardiography and that acute PM exposures were associated with higher serum endothelin (ET)-1 levels (Calderon-Garciduenas et al. 2007).

In experimental settings, PM<sub>2.5</sub> has various effects on the pulmonary vasculature including increased levels of vasoconstrictive proteins such as ET-1 (Matsumoto et al. 2010), pulmonary and systemic inflammation, oxidative stress and platelet activation (Emmrechts et al. 2012; Marchini et al. 2014; Nurkiewicz et al. 2006). In animal studies, exposure to PM has been associated with reduced endothelial-derived vasodilation (Nurkiewicz et al. 2004; Tamagawa et al. 2008) and increased muscularization of pulmonary arterioles (Lemos et al. 2006; Rivero et al. 2005). While some studies suggest these findings also occur in humans (Delfino et al. 2009;

Peretz et al. 2008; Zhang et al. 2013), it remains unclear whether this is due to local inflammation caused by inhaled particles or particle translocation into the circulation.

Our finding of a greater RV mass, conditional on LV mass, with greater PM<sub>2.5</sub> exposure suggests adaptation to an elevated RV afterload (i.e. increased pulmonary vascular resistance). The associations between PM<sub>2.5</sub> and greater mass/end-diastolic volume ratio and lower RV end-diastolic volume and stroke volume are consistent with compensatory remodeling to reduce wall stress in response to higher pressures, as has been proposed to explain LV concentric remodeling in systemic hypertension (Ganau et al. 1992). While the described changes in RV structure are of a small magnitude (1-2% increase per 5 µg/m<sup>3</sup>), they may reflect important pulmonary vascular differences in this general population sample without significant cardiopulmonary disease.

We evaluated for confounding and effect modification by emphysema and airflow obstruction. Importantly, percent emphysema has been associated with a lower proportion of small pulmonary vessels (Estepar et al. 2013), a lower RV and LV end-diastolic volume (Barr et al. 2010; Kawut et al. 2014), and greater PM<sub>2.5</sub> exposure in this cohort (Adar et al. 2015). The observed associations were largely unchanged in those with and without emphysema and airflow obstruction, and after adjusting for percent emphysema, FEV<sub>1</sub> and FEV<sub>1</sub>/FVC.

Given the recently published association between NO<sub>2</sub> exposure and greater RV mass and end-diastolic volume in MESA (Leary et al. 2014), we presented results for PM<sub>2.5</sub> adjusted for NO<sub>2</sub> exposure. Findings for ambient PM<sub>2.5</sub> and RV mass in the NO<sub>2</sub> and city-adjusted model were attenuated (and in the multivariable model were in the opposite direction), but those for end-diastolic volume, stroke volume and mass/end-diastolic volume ratio in the multivariable model were of greater magnitude. As the correlations between 1-year ambient PM<sub>2.5</sub> and NO<sub>2</sub>

exposures in this study were moderate to high (likely due to overlapping sources and similar modeling of exposure), and NO<sub>2</sub>-adjusted results do not isolate PM-specific findings, these results should be interpreted cautiously.

The strengths of this study include the advanced PM<sub>2.5</sub> exposure modeling at six cities across the U.S., the use of CMR measures of ventricular structure and function and the multi-ethnic general population sample. However, there are a number of limitations that should be discussed.

First, the city-specific results were highly variable. Adjustment for city was performed in order to account for potential unmeasured confounders, and these results are preferred. However, differences in both the levels of exposure and variation in exposure by city may contribute to differences among the within-city estimates. In addition, the smaller sample size for each city may have led to unstable effect estimates within each city. Planned differences in the recruitment of racial/ethnic groups may have contributed to the effect modification seen by city (Hispanic participants were recruited in New York, St. Paul, and Los Angeles; Chinese-Americans in Chicago and Los Angeles). Additionally, results varied by race/ethnicity with stronger direct associations between RV mass and PM<sub>2.5</sub> for whites and Hispanics. While this may be related to residual confounding by site, it should be evaluated further. Second, there is inevitably some misclassification of PM exposure. PM<sub>2.5</sub> exposure was estimated using a complex spatiotemporal model to estimate exposure at each participant's home, but exposures at other locations were not assessed. Our primary exposure of interest was ambient PM<sub>2.5</sub> due to potential measurement error in the variables used to estimate individually-weighted PM<sub>2.5</sub> (infiltration fraction and time spent indoors), and the assumption that participants' behaviors and home characteristics did not

change significantly in the five years between measurement of endpoints and questionnaire completion. While a small number of participants moved or retired over this time, results were consistent in those living at the same residence for at least five years. Exposure measurement error could impact our ability to make inferences, and beyond efforts to characterize exposure accurately we did not correct for potential measurement error in this analysis (Sheppard et al. 2012). Third, we used CMR measures of the RV and LV as proxies for the pulmonary vasculature; however the ratio of RV to LV mass has been found to be a major predictor of mean pulmonary arterial pressure on right heart catheterization (Saba et al. 2002; Swift et al. 2013). Future studies may also provide direct assessment of the pulmonary vasculature using recently developed non-invasive measures (Estepar et al. 2013; Hueper et al. 2013).

As these findings are cross-sectional, reverse causality and selection bias must be considered. Reverse causality is unlikely because PM exposure is not plausibly altered by an individual's cardiac structure. Selection bias is also unlikely as participants were recruited from the general population. Finally, while confounding is a concern in any observational study, we attempted to minimize residual confounding by adjusting for many factors, carefully measured in MESA, that can affect cardiac structure. Further studies to confirm these findings in longitudinal analyses and to evaluate potential mechanisms are warranted.

## **CONCLUSION**

Greater ambient and individually-weighted ambient-derived PM<sub>2.5</sub> exposures were associated with greater RV mass conditional on changes in the LV, and in non-city adjusted models a greater RV mass/end-diastolic volume ratio. These findings suggest that PM<sub>2.5</sub> exposure may contribute to subclinical pulmonary vascular differences in the general population.

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**Table 1:** Characteristics of MESA participants with right and left ventricular parameters on cardiac magnetic resonance imaging and air pollution estimates in 2000-02, by quintile of ambient PM<sub>2.5</sub> exposure (n=4,041)

Characteristic	Q1 (n=808)	Q2 (n=808)	Q3 (n=809)	Q4 (n=808)	Q5 (n=808)
<b>Age, years</b>	60.5±10.2	61.7±10.1	61.8±9.9	61.4±9.8	62.3±10.3
<b>Male, %</b>	50.1	50.2	44.5	42.2	51.1
<b>Race, %</b>					
White	51.1	41.7	46.0	41.1	14.7
Black	13.0	43.4	36.1	30.2	12.0
Hispanic	32.4	9.3	11.5	22.5	33.4
Chinese	3.5	5.6	6.4	6.2	39.9
<b>Educational attainment, %<sup>a</sup></b>					
Incomplete High School	13.9	11.5	11.1	17.0	26.5
Complete High School	20.9	17.8	18.8	16.1	19.2
Some college	33.0	29.3	29.4	26.2	24.3
Complete college	16.7	18.7	18.7	17.9	17.9
Graduate school	15.3	22.0	21.6	22.3	12.1
<b>Gross Family Income, %<sup>b</sup></b>					
Below \$12,000	9.3	7.6	8.8	9.4	15.5
\$12,000 - \$24,999	15.4	13.6	14.6	19.2	30.9
\$25,000 - \$34,999	13.7	10.8	12.4	15.5	14.4
\$35,000 - \$49,999	18.3	16.3	16.7	14.6	12.5
\$50,000 - \$99,999	29.5	31.3	29.5	23.6	14.7
\$100,000 and above	10.5	14.4	14.8	15.1	10.6
<b>Neighborhood SES Index<sup>c</sup></b>	-0.8 ± 4.3	-1.4 ± 5.7	-1.0 ± 6.0	-1.6 ± 7.6	-0.9 ± 7.1
<b>Height, cm</b>	166.9±9.9	168.1±10.2	167.0±9.8	166.1±9.7	164.1±9.5
<b>Weight, kg</b>	79.7±15.1	80.0±16.5	78.8±16.8	77.8±16.0	71.7±15.4
<b>Body mass index, kg/m<sup>2</sup></b>	28.5±4.8	28.2±5.0	28.1±5.0	28.1±5.2	26.4±4.6
<b>Smoking, %</b>					
Never	44.2	46.2	42.2	44.9	56.4
Former	41.6	39.2	42.9	40.8	33.0
Current	14.2	14.5	15.0	14.2	10.5
<b>Pack-years<sup>d</sup></b>	23.4±23.7	23.9±23.2	25.5±25.9	26.1±26.3	22.2±22.7
<b>Diabetes, %<sup>e</sup></b>	11.0	9.3	12.4	11.0	14.2

<b>Fasting glucose, mg/dL</b>	101.6±26.2	101.8±22.9	102.9±29.3	102.2±29.0	108.2±35.6
<b>Hypertension, %<sup>f</sup></b>	35.5	47.0	44.7	46.3	42.6
<b>Systolic blood pressure, mmHg</b>	122.3±20.0	127.8±21.9	125.5±20.4	126.4±20.4	125.9±22.0
<b>U.S. City, %</b>					
Forsyth County, North Carolina	7.9	26.9	24.7	14.5	-
New York, New York	4.2	21.0	24.4	43.8	7.8
Baltimore, Maryland	11.1	33.3	32.3	14.2	-
St. Paul, Minnesota	71.9	3.2	-	-	-
Chicago, Illinois	4.8	15.6	18.7	27.0	2.7
Los Angeles, California	-	-	-	0.5	89.5
<b>C-reactive protein, mg/L</b>	3.4±4.9	3.6±5.5	3.6±5.4	4.0±6.7	3.1±5.5
<b>HDL cholesterol, mg/dL</b>	49.8±14.9	50.9±14.7	52.1±15.7	53.3±15.7	49.9±14.2
<b>Total cholesterol, mg/dL</b>	198.9±37.2	191.7±35.2	195.1±33.1	193.1±35.0	192.5±34.4
<b>FEV<sub>1</sub>, L<sup>g</sup></b>	2.65±0.75	2.40±0.69	2.37±0.73	2.31±0.70	2.37±0.72
<b>FEV<sub>1</sub>/FVC ratio<sup>h</sup></b>	0.75±0.08	0.75±0.08	0.75±0.09	0.74±0.09	0.75±0.08
<b>Airflow limitation, %<sup>h,i</sup></b>	19.0	22.0	24.2	24.8	20.2
<b>Percent emphysema-950, median (IQR)<sup>j</sup></b>	2.37	2.87	2.84	3.00	3.43
	(1.09, 4.64)	(1.28, 5.71)	(1.24, 5.59)	(1.27, 6.03)	(1.46, 6.26)
<b>Emphysema above ULN, %<sup>k</sup></b>	8.5	9.6	8.1	6.9	4.5
<b>Reported trouble breathing at night, %<sup>l</sup></b>	11.0	9.0	9.6	11.1	9.1
<b>Reported physical activity, MET-min/week<sup>m</sup></b>	6306±5508	5246±4443	5288±4455	5358±4528	4345±4531
<b>Ambient PM<sub>2.5</sub>, µg/m<sup>3</sup></b>	12.5±1.4	14.7±0.4	15.7±0.3	17.0±0.6	22.1±1.7
<b>Individually-weighted PM<sub>2.5</sub>, µg/m<sup>3</sup></b>	7.4±1.5	9.2±1.7	9.9±1.9	11.4±2.0	16.5±2.4
<b>Ambient NO<sub>2</sub>, ppm</b>	13.7±3.9	17.8±7.9	20.0±8.4	25.8±8.2	31.5±4.7

Abbreviations: HDL, high density lipoprotein; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; IQR, interquartile range; ULN upper limit of normal.

Values are mean ± SD or %, except as noted

<sup>a</sup>13 participants did not report educational attainment.

<sup>b</sup>134 participants did not report income.

<sup>c</sup>Higher numbers reflect greater SES. The neighborhood SES index combines several neighborhood SES variables (Hajat et al.)

<sup>d</sup>Among 1,918 ever smokers; 233 did not report pack-years.

<sup>e</sup>Defined as fasting glucose ≥7.0 mmol/L (≥126 mg/dL) or hypoglycemic medication use.

<sup>f</sup>Defined as blood pressure ≥140/90 mmHg, or self-report and antihypertensive medication use.

<sup>g</sup>Among 2,657 spirometry grade A-D FEV<sub>1</sub>.

<sup>h</sup>Among 2,646 with spirometry grade A-D FEV<sub>1</sub> and FVC.

<sup>i</sup>Defined as FEV<sub>1</sub>/FVC ratio below 0.7.

<sup>j</sup>Not available for 1 participant.

<sup>k</sup>ULN defined by reference equations (Hoffman et al.), not available for 26 participants.

<sup>l</sup>33 did not report trouble breathing at night.

<sup>m</sup>209 did not report physical activity.

**Table 2:** Cardiac magnetic resonance imaging parameters for participants with air pollution measures, by quintile of ambient PM<sub>2.5</sub> exposure (n=4,041)

	Q1	Q2	Q3	Q4	Q5
Imaging Parameter	(n=808)	(n=808)	(n=809)	(n=808)	(n=808)
RV mass, g	21.8 ± 4.8	21.2 ± 4.4	20.8 ± 4.4	21.1 ± 4.2	20.2 ± 4.1
RV end diastolic volume, mL	130.2 ± 33.5	125.9 ± 31.3	122.3 ± 29.5	124.5 ± 29.8	117.3 ± 28.2
RV mass/end-diastolic volume ratio, g/mL	0.170 ± 0.02	0.171 ± 0.02	0.172 ± 0.02	0.172 ± 0.02	0.175 ± 0.02
RV stroke volume, mL	90.4 ± 22.3	87.6 ± 20.2	86.2 ± 20.3	87.4 ± 20.2	82.3 ± 18.7
RV ejection fraction, %	70.0 ± 6.4	70.2 ± 6.6	70.8 ± 6.6	70.6 ± 6.4	70.6 ± 6.2
LV mass, g	152.2 ± 38.4	148.2 ± 39.4	144.8 ± 37.8	147.0 ± 40.5	137.2 ± 38.4
LV end diastolic volume, mL	128.8 ± 31.6	126.3 ± 31.4	126.7 ± 32.3	128.5 ± 30.9	122.2 ± 30.2
LV mass/end-diastolic volume ratio, g/mL	1.20 ± 0.25	1.19 ± 0.26	1.17 ± 0.27	1.16 ± 0.25	1.13 ± 0.20
LV stroke volume, mL	86.5 ± 20.5	86.5 ± 19.9	86.2 ± 20.5	88.4 ± 19.5	84.6 ± 18.2
LV ejection fraction, %	67.7 ± 7.6	69.1 ± 7.4	68.7 ± 7.5	69.4 ± 6.9	70.0 ± 7.5

Values are mean ± SD

**Table 3:** Mean differences in RV mass, end-diastolic volume, mass/end-diastolic volume ratio, stroke volume and ejection fraction adjusted for LV parameters per 5  $\mu\text{g}/\text{m}^3$  increase in ambient  $\text{PM}_{2.5}$  (N=4,041) and individually-weighted  $\text{PM}_{2.5}$  exposure (N=3,379)

<b>RV parameter adjusted for LV parameter</b>	<b>Ambient <math>\text{PM}_{2.5}</math> (95% CI)</b>	<b>Individually-weighted <math>\text{PM}_{2.5}</math> (95% CI)</b>
<b>RV mass, g</b>		
Multivariable model	0.11 (-0.05, 0.27)	0.20 (0.04, 0.36)*
Multivariable model + city	0.37 (0.03, 0.71)*	0.30 (0.01, 0.59)*
<b>RV end-diastolic volume, mL</b>		
Multivariable model	-2.57 (-3.38, -1.76)*	-1.51 (-2.32, -0.70)*
Multivariable model + city	-0.57 (-2.31, 1.17)	0.05 (-1.46, 1.56)
<b>RV mass/end-diastolic volume ratio, g/mL</b>		
Multivariable model	0.003 (0.002, 0.004)*	0.002 (0.001, 0.003)*
Multivariable model + city	0.002 (-0.0002, 0.004)	0.001 (-0.001, 0.003)
<b>Stroke volume, mL</b>		
Multivariable model	-2.20 (-2.78, -1.62)*	-1.20 (-1.80, -0.61)*
Multivariable model + city	-0.72 (-1.97, 0.54)	0.28 (-0.82, 1.39)
<b>RV ejection fraction, %</b>		
Multivariable model	-0.28 (-0.57, -0.001)*	-0.11 (-0.40, 0.17)
Multivariable model + city	-0.18 (-0.80, 0.43)	0.15 (-0.39, 0.69)

Multivariable model: adjusted for age, sex, race/ethnicity, height, weight, education, income, neighborhood SES index, smoking status, pack-years, total cholesterol, HDL, hypertension, systolic blood pressure, fasting glucose, diabetes, C-reactive protein and respective left ventricular parameter

\*P-value < 0.05

## Figure Legends

**Figure 1:** A map of 2000-02 mean outdoor residential PM<sub>2.5</sub> concentrations for Los Angeles Basin, CA including the location of stationary monitoring sites operated by the South Coast Air Quality Management District (“AQSD”), fixed sites operated by the MESA Air Study, and MESA Air participants’ homes where monitoring was conducted (jittered to protect privacy)

**Figure 2:** Sensitivity analyses for the multivariable association of ambient PM<sub>2.5</sub> exposure and RV mass adjusted for LV mass and city. Shown are the mean differences (■) and 95% confidence limits for a 5 µg/m<sup>3</sup> change in PM<sub>2.5</sub>. The size of the square reflects the relative number of participants in each group. Multivariable model: adjusted for age, sex, race/ethnicity, height, weight, education, income, neighborhood SES index, smoking status, pack-years, total cholesterol, HDL, hypertension, systolic blood pressure, fasting glucose, diabetes, C-reactive protein, left ventricular mass and city. P-interactions: sex 0.91, race/ethnicity 0.003, age group 0.43, smoking status 0.54, airflow limitation 0.41, emphysema 0.84.

Figure 1.

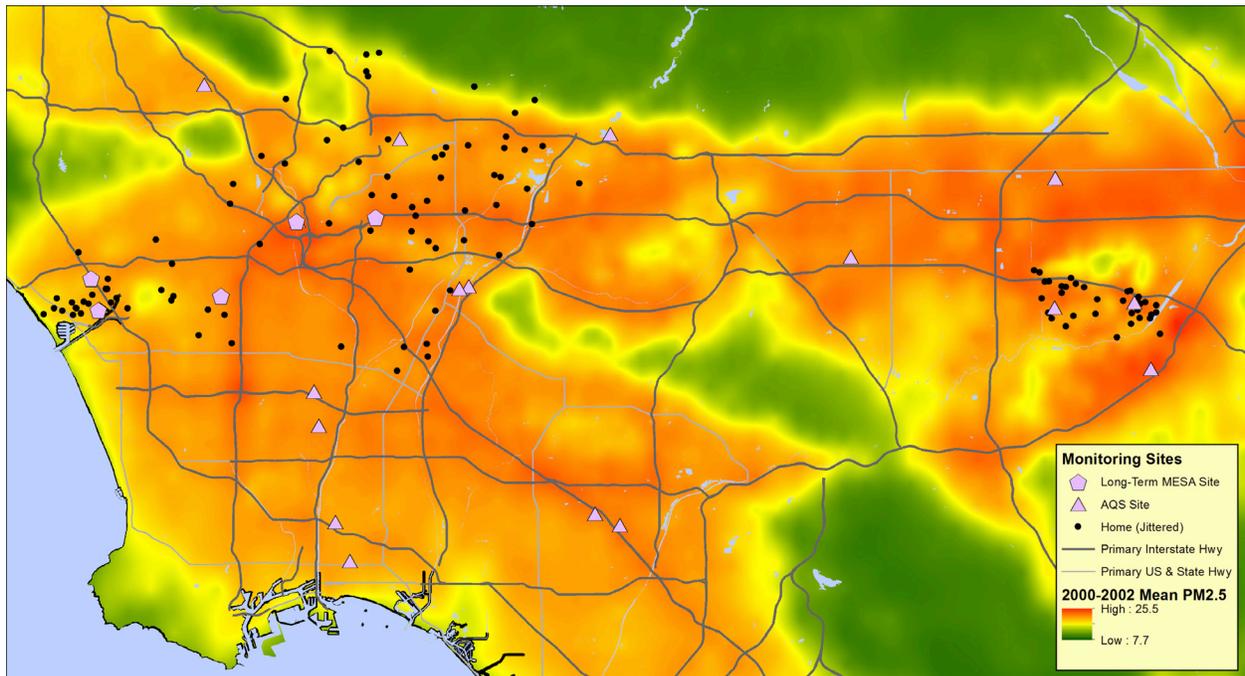


Figure 2.

