Long-Term Air Pollution in Relation to Cardiac Structure, Function, and Supraventricular Arrhythmias

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Abstract

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Background: Air pollution is an important contributor to cardiovascular morbidity, including risk of heart failure. Acute exposure is associated with inflammation, elevation of blood pressure, and episodes of atrial fibrillation (AF). However, less is understood about how long-term exposures may influence measures of atrial and ventricular structure and function, including supraventricular arrhythmias. No large longitudinal analyses have investigated these associations.

Methods: In the setting of the Multi-Ethnic Study of Atherosclerosis (MESA), we investigated associations of participant-specific, spatiotemporal model-estimated concentrations of fine particulate matter ($PM_{2.5}$), oxides of nitrogen (NO_X), and ozone (O_3) with both cardiac magnetic resonance imaging-derived measures of left atrial (LA) and left ventricular (LV) structure and function, as well as with supraventricular arrhythmias identified from 14-day ambulatory electrocardiography (ECG) monitors worn by participants. Multivariable linear regression and generalized estimating equations were used, adjusting for potential confounders including MESA study site.

Results: Among 2,250 participants at MESA Exam 5 (2010-2012), five-year average exposure to $PM_{2.5}$, NO_X, and O_3 was not significantly associated with measures of left atrial structure and

contractility. Among 1,324 MESA participants with ambulatory ECG monitoring at MESA Exam 6 (2016–2018), five-year average concentration of pollutants was not associated with supraventricular arrhythmias, though high two-week average concentration of $PM_{2.5}$ was associated with increased rates of supraventricular tachycardia (23% higher per 5ug/m^3, 95% CI: 4%-46%). Higher one-year average pollutant concentration prior to MESA Exam 1 (2000-2002) was associated with greater left-ventricular mass index (LVMI) for NO_X (1.8% per 40 parts per billion [ppb] NO_X, 95% CI: 0.3, 3.3) and $PM_{2.5}$ (1.6% per 5ug/m^3 higher $PM_{2.5}$, 95% CI: 0.3, 2.9), and lower LVMI for O_3 (-3.5% per 10ppb O_3). Greater ten-year average NO_X concentration between Exams 1 and 5 was associated with reduced LV contractility as measured by left-ventricular circumferential strain, though this association was only marginally significant. All analyses were sensitive to adjustment for MESA study site.

Conclusions: Our study offers mixed evidence for an association of long-term concentrations of $PM_{2.5}$, NO_X, and O_3 with cardiac structure and function. We did not find evidence of associations between pollutants and LA structure, and the association of $PM_{2.5}$ with supraventricular tachycardia was minimal and confined to two-week pollutant concentrations. We identified significant associations between long-term pollutant concentrations and cross-sectional LVMI in the direction hypothesized for $PM_{2.5}$ and NO_X, and opposite that hypothesized for O_3, though the strong inverse correlation between O_3 and both $PM_{2.5}$ and NO_X may influence this finding. These findings suggest a role for NO_X, $PM_{2.5}$, and O_3 in influencing cardiac structure in MESA. Additional work is needed to clarify that role and better understand the biological underpinnings of these associations.

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Dedication

For my Mom and Dad, and for Kate Berry, who is more supportive and encouraging than any reasonable person could hope for.

CHAPTER 1: **The association of long-term air pollution exposure with left atrial structure and function in the Multi-Ethnic Study of Atherosclerosis**

Abstract:

Rationale: Air pollution exposure is an important risk factor for cardiovascular morbidity. Acute exposure is associated with episodes of atrial fibrillation (AF), and long-term exposure may influence ventricular mass and volume. However, little is understood about the relationship between long-term pollution exposure and atrial structure and function, which may influence the risk of AF and heart failure.

Objectives: Determine the association of long-term exposure to fine particulate matter ($PM_{2.5}$), oxides of nitrogen (NO_X), and ozone (O_3) with left atrial structure (LA) and function, as measured by LA volume index, LA emptying fraction (EF), and LA global longitudinal strain.

Methods: In the Multi-Ethnic Study of Atherosclerosis (MESA), we used estimated five-year average concentrations of $PM_{2.5}$, NO_X, and O_3 at participant addresses from validated hierarchical spatio-temporal models developed from extensive monitoring of MESA participants. Left atrial measures were calculated from cardiac magnetic resonance imaging completed between 2010 and 2012. Linear regression was used, adjusting for MESA study site and potential confounding characteristics.

Measurements and main results: In 2,250 MESA participants, five-year average concentration of $PM_{2.5}$, NO_X, and O_3 was not significantly associated with LA volume index, LA EF, or LA global longitudinal strain. Results were very sensitive to adjustment for MESA study site.

Conclusions: Using recently developed study-specific exposure estimation and highly accurate imaging, we did not find evidence to suggest an association between long-term exposure to

several common pollutants and measures of LA structure and function. Additional analyses in areas of higher pollution may be useful in determining whether associations are consistent across exposure levels.

INTRODUCTION

Air pollution exposure is an established risk factor for cardiovascular morbidity [1, 2] and may contribute to risk of atrial fibrillation (AF) [3-5]. Previous studies have demonstrated associations of same-day exposure to ozone (O_3) and fine particulate matter ($PM_{2.5}$) with AF episodes, as well as an association of acute nitrogen dioxide (NO_2) exposure with hospitalization for all arrhythmias, though the mechanisms through which air pollution might affect risk of AF are not fully understood [3-5].

One possible mechanism for AF development is atrial remodeling resulting from sustained local and systemic inflammation [6]. Multiple studies have demonstrated associations between proximity of residence to traffic [7] or long-term NO_2 and $PM_{2.5}$ exposure and *ventricular* size and structure [8, 9]. Atrial remodeling can occur parallel to ventricular remodeling and lead to functional changes. Independent of left ventricular structural measures, higher left atrial (LA) volume and low LA myocardial strain (percent shortening between two points on the atrial myocardium) are associated with AF [10, 11] and help predict heart failure (HF) in those with cardiomyopathy [12, 13]. An understanding of the association of long-term pollution exposure with functional measures that reflect atrial remodeling is critical to understanding the mechanisms through which air pollution acts on the heart and may inform prevention efforts.

In the Multi-Ethnic Study of Atherosclerosis (MESA) and Air Pollution (MESA Air), detailed information derived from study-specific spatio-temporal modeling of individual exposure is available on participants' long-term exposure to several important pollutants, including $PM_{2.5}$, oxides of nitrogen (NO_X), and O_3. As little is known about the effect of air pollution on measures of left atrial (LA) structure and function, we examined the association of

well-characterized long-term air pollution exposures with cardiac magnetic resonance (CMR)-derived LA minimum volume index, LA emptying fraction (EF), and LA strain. We hypothesized that higher levels of long-term air pollution would be associated with greater LA volume index, lower LA EF, and lower LA strain values.

METHODS

MESA is a multi-ethnic longitudinal study of 6,814 participants 45 to 84 years of age free of clinically-recognized cardiovascular disease at baseline (2000-2002) in six United States communities. Details of MESA have been previously reported [14]. Participant characteristics were collected at study Exams 1 (2000-2002) through 5 (2010-2012), including height, weight, blood pressure, diabetes status, high-density lipoprotein (HDL) cholesterol, glucose, and self-reported age, sex, race/ethnicity, exercise habits, highest attained education level, household income, smoking history and status, and antihypertensive medication use. Neighborhood socioeconomic status was calculated using principal factor analysis of 16 variables and has been described elsewhere [15]. Clinical presentations with myocardial infarction, heart failure, and AF after baseline but before the Exam 5 CMR were identified as previously described [16, 17]. Each study site obtained Institutional Review Board approval, and all participants provided written informed consent.

Our analysis used long-term $PM_{2.5}$, NO_X, and O_3 concentrations derived from MESA-specific spatiotemporal exposure prediction models, which have been described previously in detail [18, 19]. MESA Air [20] uses monitoring data from US Environmental Protection Agency Air Quality System, supplementary monitoring of MESA participants and, in New York City, data from the New York City Community Air Study. Geographic covariates from MESA sites were used in the development of the spatio-temporal models, with partial least squares scores

used to reduce dimensionality of the >300 geographic covariates. A hierarchical spatio-temporal model was developed in MESA Air that incorporates a spatially-varying long-term mean, smooth time trends, spatially-varying coefficients for time trends, and a spatiotemporal residual. Cross-validation of these models has been described previously and suggests good predictive accuracy [18, 19].

Cardiac MR imaging was conducted on 3,015 participants during the Exam 5 study visit with 1.5-T scanners at each site, using Signa LX or CVi (GE Medical Systems, Waukesha, WI) or Symphony or Sonata (Siemens Medical Systems, Erlangen, Germany) and a steady-state free precession sequence [21]. These images were subsequently re-read by for LA minimum and maximum volume, global longitudinal LA strain, and LA EF. Measurement of LA volume and strain used Multimodality Tissue Tracking software (MTT, version 5.0, Toshiba, Japan). The software tracks reader-defined endocardial and epicardial boarders over the course of the cardiac cycle. LA minimum volume is defined as the LA volume at the end of ventricular diastole immediately following mitral valve closure. LA volume is indexed to body surface area in our analysis and presented in units of ml/m^2. Global longitudinal strain measures the average maximum percent shortening between two tracked points relative to end-diastolic length and was measured by averaging global longitudinal strain of all segments of the LA over the cardiac cycle. Total LA EF measures the proportion of maximal LA volume ejected from the LA by the end of atrial systole and was calculated as follows: (LA Maximum Volume – LA Minimum Volume)/LA Maximum volume.

Statistical Analysis

Continuous data are presented as mean (standard deviation, SD) and categorical data as frequencies (percentages). The study sample included MESA participants for whom CMR

imaging was performed at MESA Exam 5 and for whom LA measurements were made from CMR. This analysis used linear regression to assess the relationship of five-year average modeled concentrations of $PM_{2.5}$, NO_X, and O_3 prior to MESA Exam 5 with LA measurements. Covariates were chosen *a priori* based on their hypothesized associations with air pollution and with atrial structure and function. These covariates included age, height, weight, race/ethnicity, sex, MESA study site, self-reported household income, census tract-level socioeconomic status, educational attainment, and known cardiovascular risk factors including smoking history and current smoking status, diabetes, low-density lipoprotein (LDL) cholesterol, lipid-lowering medication, and physical activity. Hypertension is known to be associated with LA structure but was not included in our primary analysis list of covariates because it was potentially in the pathway between air pollution and LA structure and function.

In sensitivity analyses, we explored the association of interest when adjusting for antihypertensive medication use, systolic and diastolic blood pressure, and when not including MESA study site as a covariate. While our main analysis used LA minimum volume index as a primary outcome, we additionally investigated LA maximum volume indexed to body surface area and percent-predicted LA minimum volume using an allometric approach described previously in MESA [22]. Because results when using these measures did not differ from results seen using LA minimum volume index, they are not reported here. Finally, to explore the possibility that shorter exposure windows are more important to differences in LA structure and function, we re-ran the analysis using one-year average yearly exposure to $PM_{2.5}$, NO_X, and O_3.

RESULTS

From a total of 4,600 participants who completed MESA Exam 5, complete data on exposure, outcome, and covariates were available for 2,250 (Figure 1.1). Characteristics of these

2,250 participants are displayed in Table 1.1. At MESA Exam 5, included participants had a mean age of 69, a mean body mass index of 27.9, and 54% were women. The final analysis population included 43% white, 25% African-American, 20% Hispanic, and 13% Chinese-American individuals.

Air pollution exposure varied greatly by MESA study site for $PM_{2.5}$, NO_X, and O_3 (Figure 1.2). Participants in Minneapolis, MN had the lowest levels of $PM_{2.5}$ exposure, followed by those in Baltimore, MD, Winston-Salem, NC, and Chicago, IL. New York, NY and Los Angeles, CA had the highest five-year average concentrations of both $PM_{2.5}$ and NO_X. Long-term O_3 exposure was highest among participants in Winston-Salem and lowest among participants in New York City and Los Angeles.

Table 1.1 shows participant characteristics overall and by $PM_{2.5}$ exposure quartiles. In MESA, different clinic sites recruited participants from different race/ethnic groups. Between-site pollution exposure variability was much larger than within-site variability. Therefore, race/ethnic group was differentially distributed across pollutant quartiles. White participants were over-represented in the lowest $PM_{2.5}$ exposure quartile (corresponding roughly to levels in Minnesota and Winston-Salem), African-Americans were over-represented in quartiles 2 and 3, and Chinese-Americans were over-represented in the highest exposure quartile (corresponding roughly to $PM_{2.5}$ levels in Los Angeles).

Table 1.2 shows the distribution of participant characteristics by quartiles of LA global longitudinal strain, with higher strain among women than among men, and significant differences in strain by race/ethnicity. Systolic blood pressure was lower with increasing quartiles of LA strain, as was the prevalence of antihypertensive medication use. Prevalence of history of AF was substantially higher in the lowest quartile of LA strain.

The results for the linear regression analyses are shown in Figure 1.3. In fully adjusted analyses (Model 2) there was no significant association of $PM_{2.5,}$ NO_X, or O_3 with LA minimum volume index (Figure 1.3A). Analysis of long-term pollutant exposures in relation to LA EF (Figure 1.3B) and to LA strain (Figure 1.3C) yielded similar results. Higher levels of $PM_{2.5}$ and NO_X were associated with higher LA EF, and higher levels of $PM_{2.5}$ and NO_X were associated with higher LA strain, but the 95% confidence intervals for the adjusted models all overlapped with 0.

In analyses restricted to participants with no history of AF, heart failure, or MI before the CMR imaging, results were not markedly different from those seen in main analyses. Analyses additionally adjusting for hypertension medication, systolic and diastolic blood pressure did not differ from main regression results. Sensitivity analyses where MESA study site was not included as a regression covariate yielded substantially different results than the main analysis (Supplementary Figure 1.1). After full adjustment in Model 2, higher $PM_{2.5}$ was associated with higher LA strain (2.46% per 5μg/m^3 $PM_{2.5}$, 95%CI: 0.70 – 4.22%). Higher NO_X was associated with significantly higher LA minimum volume index (1.79 ml/m^2 per 40ppm NO_X, 95%CI: 0.86, 2.72 ml), and significantly lower LA EF (-1.56% per 40ppm NO_X, 95%CI: -2.72, -0.39%) and LA strain (-2.04% per 10ppm NO_X, 95%CI: -3.48, -0.60%). Finally, higher O_3 exposure was significantly and strongly associated with lower LA minimum volume index (-3.76 ml per 40ppm NO_X, 95%CI: -5.71, -1.81ml), and higher LA EF (4.64% per 10ppm O_3, 95%CI: 2.19, 7.09%) and LA strain (6.48% per 10ppm, 95%CI: 3.48 – 9.49%).

DISCUSSION

In a multi-ethnic setting with extensive data on air pollution exposure and high-quality LA measures, we found no significant evidence of an association of long-term exposure to $PM_{2.5}$,

NO_X, or O_3 with atrial structure and function. Results were strongly influenced by adjustment for MESA study site. Air pollution is a known risk factor for cardiovascular and ischemic heart disease, and acute pollution exposure likely influences risk of arrhythmia and AF episodes [2, 3]. Air pollution is hypothesized to act partially through inflammatory pathways, which may influence atrial structure and function [1]. Very little work has been done to investigate the relationship between long-term air pollution exposure and measures of atrial structure and function, and none has included atrial strain as an outcome.

Previous studies have reported associations between greater LA volume and presence of fibrosis, incident AF, and incident CVD [21, 23-25]. Air pollution exposure may influence risk of these outcomes through progressive changes in LA structure and function. As such, we hypothesized that higher pollution levels, particularly $PM_{2.5}$ and NO_X, would be associated with greater LA volume index. Our primary analysis results do not support this hypothesis. Both LA strain and EF measure contractility of the atrial walls, and lower values are associated with cardiovascular events, morbidity, and mortality [21, 23-25]. Therefore, we hypothesized that the studied pollutants would be associated with lower EF and LA strain, indicating lower contractile function, potentially due to atrial remodeling. Our results do not support this hypothesis, with no statistically significant relationships between measured pollutants and LA EF and LA strain.

These results were very sensitive to adjustment for MESA study site, as shown in Supplementary Table 1.1, suggesting that there may be substantial unmeasured confounding that adjustment for site addresses. While it is common to adjust for site in analyses involving air pollution in MESA, adjustment greatly limits the variability in exposure in our analysis, as MESA study site and pollutant concentrations are strongly correlated and most of the variability in pollution is seen between rather than within study site (Figure 1.2). It is possible that

adjustment for site is unnecessary and that residual confounding is not a particular concern, in which case our results without site adjustment in Supplementary Figure 1.1 would warrant consideration as evidence of an association between greater NO_X and $PM_{2.5}$ concentrations and increased LA volume index, as well as greater O_3 concentrations and decreased LA volume index. However, study site continues to be strongly associated with both exposure and outcome in models including all covariates, and its inclusion in regression models appears important in minimizing confounding.

American air pollution levels have decreased greatly in the past several decades, and average $PM_{2.5}$ exposure levels in the US of ~8μg/m^3 are 6-11 times lower than those estimated for China and India and are 39% lower than US levels in 2000. The relatively low pollutant concentrations at MESA sites could influence the ability of this analysis to identify true associations. Adjustment for study site as a potential confounder limits our focus to within-study site variability. Though it is common to report regression results per 5μg/m^3 of $PM_{2.5}$, for instance, the interquartile range of $PM_{2.5}$ at each study site was less than 2 μg/m^3, making the magnitude of comparisons less interpretable.

It is possible that long-term pollution is not associated with LA structure, and the MESA findings support this conclusion. Previous studies have demonstrated associations between acute pollution exposure (<2 hours) and atrial and ventricular arrhythmias, but our study was not designed to identify acute effects. Our results agree with findings from a recent UK Biobank study that did not identify associations between long-term pollutant concentrations and measures of LA structure [26], but the two studies differ in the population and pollution profiles, and our analysis adjusts for city of residence and incorporates detailed address-level exposure estimates using well-validated exposure estimation models.

Our analysis was restricted to LA measurements at a single time point and was unable to assess changes in LA structure and function. Additionally, pollutant concentrations were estimated for participants' home addresses and did not include more personalized estimates based on individual commute/work exposure or indoor infiltration of air pollutants. We analyzed five-year average concentrations of pollutants, but it is possible that this time window is not large enough to capture exposures relevant to atrial remodeling. It should be noted that, although MESA is a diverse and well-phenotyped cohort, participants were free of prior known cardiovascular disease at enrollment, and thus may represent a relatively healthy population not entirely representative of others in their age cohort with respect to air pollution effects. If pollution exposure does influence cardiovascular disease risk, people in whom this association is most pronounced may not have been selected into our cohort sample.

In an analysis using state-of-the-art pollution modeling developed specifically for MESA participants and high quality CMR-derived outcomes, we did not find evidence of an association between long-term air pollution exposure and LA structure and function. Additional studies investigating longitudinal changes in LA volume and in areas with higher pollutant exposure will be useful next steps in increasing our understanding of the effects of air pollution on cardiac structure and function.

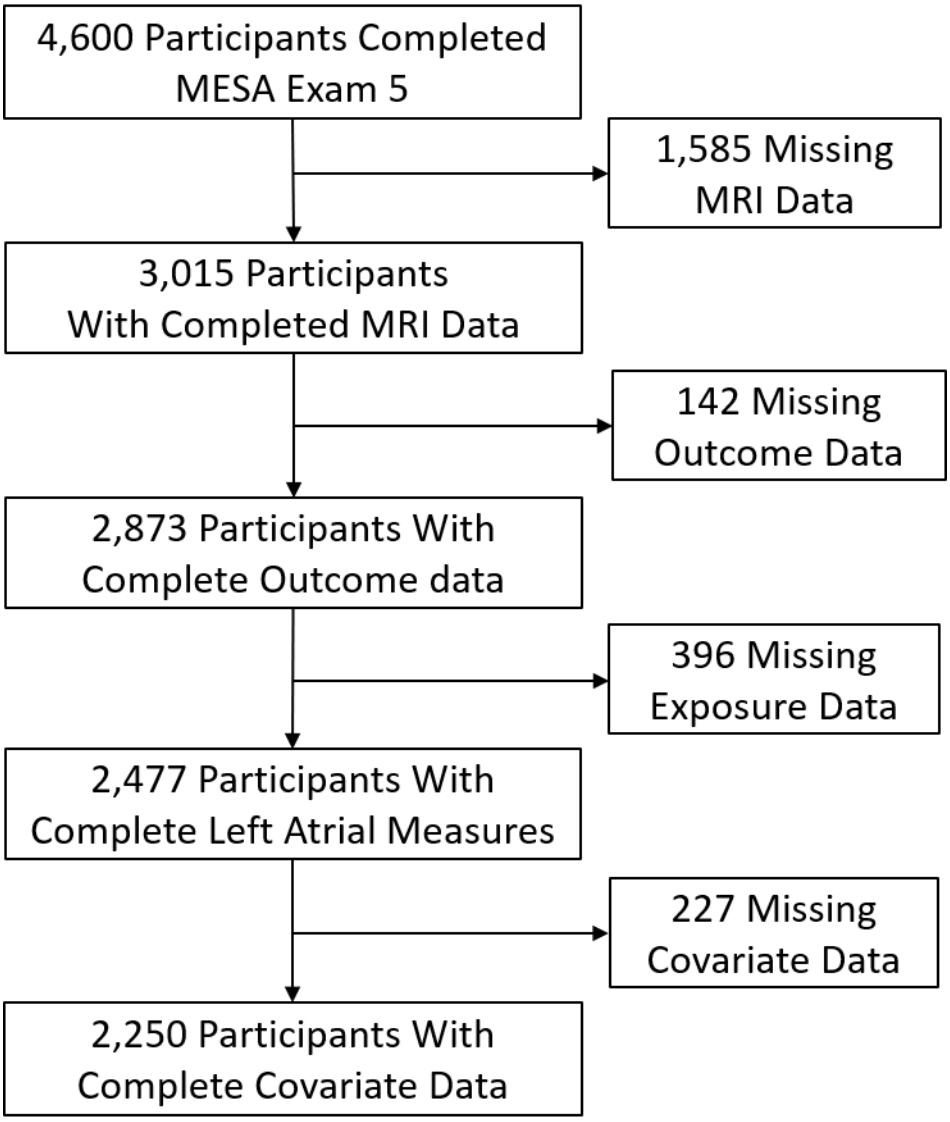
Table 1.1: MESA participant characteristics, by quartile of five-year average concentration of fine particulate matter

		Five-year average fine particulate matter ($PM_{2.5}$) quartiles ($\mu g/m^3$)			
	Total	**Q1 (8.0 - 11.4)**	**Q2 (11.5 - 12.3)**	**Q3 (12.4 - 13.5)**	**Q4 (13.6 +)**
N	2250	562	563	562	563
Female (%)	54	50	55	56	55
Age (years), mean (SD)	69 (9)	68 (10)	69 (9)	70 (9)	70 (9)
Body Mass Index, mean (SD)	28 (5)	29 (5)	28 (5)	28 (5)	27 (5)
Race/Ethnicity (%)					
White	43	58	41	48	23
Chinese-American	13	4	12	10	26
African-American	25	8	44	32	14
Hispanic	20	30	3	10	36
Current Smoker (%)	5.9	6.9	5.5	6.8	4.3
Systolic Blood Pressure (mmHg), mean (SD)	123 (20)	121 (19)	124 (20)	123 (20)	124 (21)
Diastolic Blood Pressure (mmHg), mean (SD)	68 (10)	68 (9)	68 (10)	68 (11)	68 (10)
LDL Cholesterol (mg/dL), mean (SD)	107 (33)	106 (32)	108 (32)	106 (34)	107 (33)
HDL Cholesterol (mg/dL), mean (SD)	56 (17)	53 (16)	57 (17)	58 (16)	57 (18)
Fasting Blood Glucose (mg/dL), mean (SD)	100 (25)	102 (27)	99 (25)	98 (22)	102 (27)
Diabetes (%)	17	14	17	17	20
Hypertension (%)	57	50	52	58	70
History of Atrial Fibrillation (%)	4.6	3.4	4.3	5.9	4.8
History of Myocardial Infarction (%)	3.2	3.9	3.4	3.2	2.1
History of Heart Failure (%)	2.7	2.5	2.5	3.9	2.0
LA Minimum Volume Index (ml/m^2), mean (SD)	17 (9)	16 (8)	17 (9)	17 (9)	17 (10)
LA Peak Longitudinal Strain (%), mean (SD)	32 (14)	30 (13)	31 (13)	32 (15)	34 (16)
LA Emptying Fraction (%)	55 (12)	54 (11)	54 (12)	55 (12)	56 (13)

Table 1.2: MESA participant characteristics, by quartile of left atrial global longitudinal strain

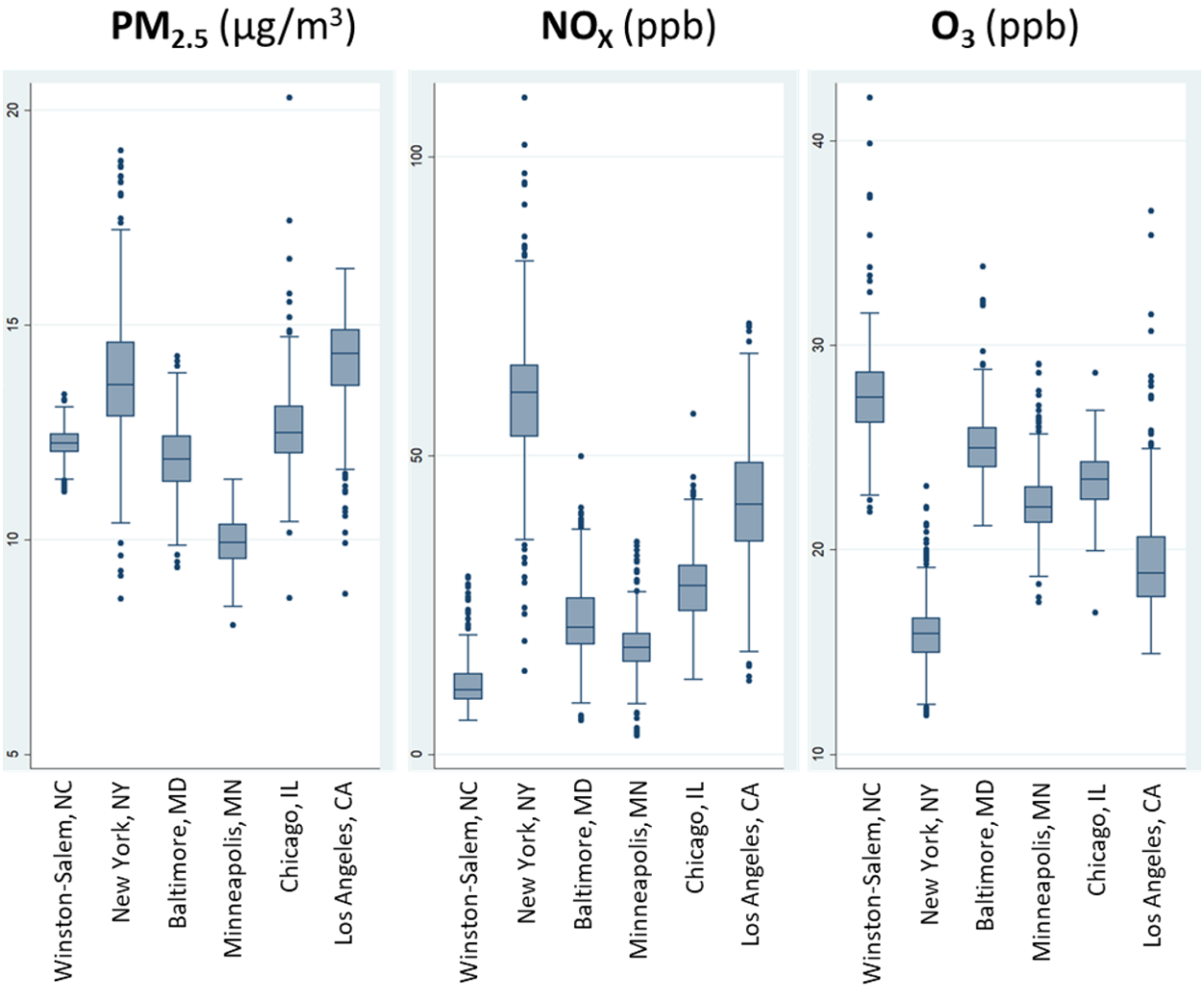
		Left atrial global longitudinal strain quartiles (%)			
	Total	**Q1 (2.3 - 22.8)**	**Q2 (22.9 - 29.8)**	**Q3 (29.9 - 37.5)**	**Q4 (37.6 +)**
N	2250	562	562	563	563
Female (%)	54	38	53	61	64
Age (years), mean (SD)	69 (9)	73 (9)	69 (9)	68 (9)	67 (9)
Body Mass Index, mean (SD)	28 (5)	29 (5)	29 (5)	28 (5)	26 (5)
Race/Ethnicity (%)					
White	43	44	45	44	38
Chinese-American	13	4	7.1	14	27
African-American	25	30	27	24	17
Hispanic	20	21	21	18	18
Current Smoker (%)	5.9	6.7	6.4	5.9	4.4
Systolic Blood Pressure (mmHg), mean (SD)	123 (20)	126 (21)	123 (20)	123 (20)	120 (19)
Diastolic Blood Pressure (mmHg), mean (SD)	68 (10)	69 (10)	67 (10)	68 (10)	68 (10)
LDL Cholesterol (mg/dL), mean (SD)	107 (33)	102 (33)	108 (34)	107 (32)	109 (32)
HDL Cholesterol (mg/dL), mean (SD)	56 (17)	55 (16)	55 (16)	58 (17)	57 (18)
Fasting Blood Glucose (mg/dL), mean (SD)	100 (25)	103 (27)	100 (27)	99 (23)	98 (24)
Diabetes (%)	17	21	17	17	12
Hypertension (%)	57	58	58	51	62
History of Atrial Fibrillation (%)	4.6	10.6	3.6	2.5	2
History of Myocardial Infarction (%)	3.2	6.6	2.3	1.8	2
History of Heart Failure (%)	2.7	7.9	1.8	0.5	0.7

Figure 1.1: Flow diagram of MESA participant inclusion



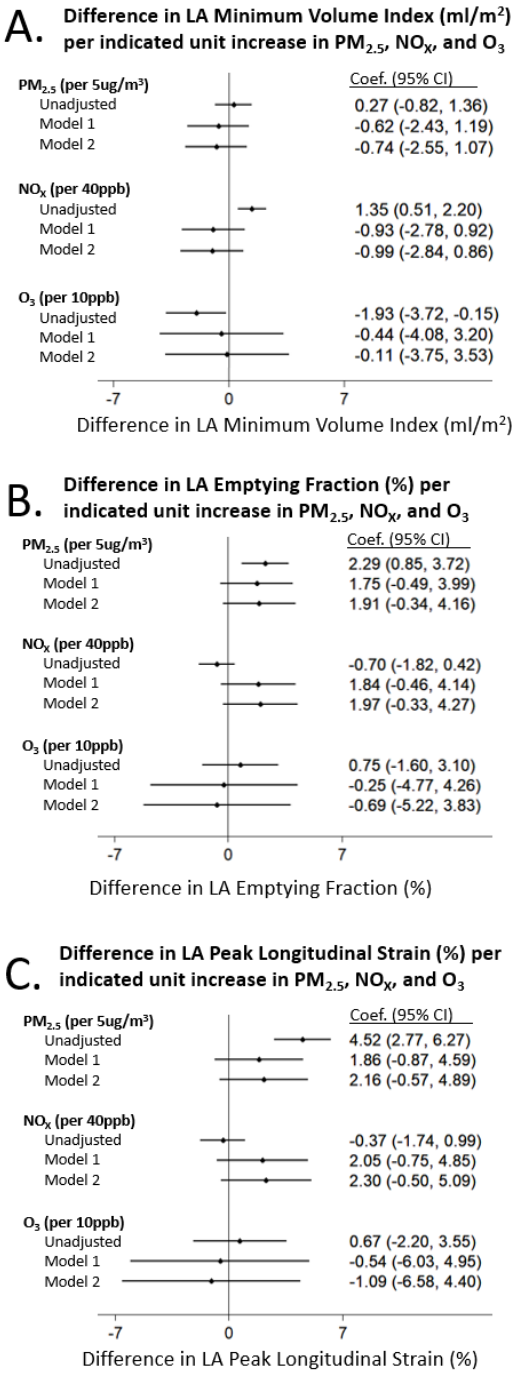
MESA = Multi-Ethnic Study of Atherosclerosis
MRI = magnetic resonance imaging

Figure 1.2: Box plots of modeled five-year average concentration of fine particulate matter ($PM_{2.5}$), oxides of nitrogen (NO_X), and ozone (O_3), in the Multi-Ethnic Study of Atherosclerosis and Air Pollution, by study site



$PM_{2.5}$ = particulate matter smaller than 2.5 microns in size; NO_X = oxides of nitrogen; O_3 = ozone; ppm = parts per million

Figure 1.3: Associations of five-year average fine particulate matter ($PM_{2.5}$), oxides of nitrogen (NO_X), and ozone (O_3) concentrations with LA minimum volume (A), LA emptying fraction (B), and LA global longitudinal strain (C)



LA = left atrial; ppm = parts per million
Model 1 includes: age, height, weight, race/ethnicity, sex, study site, self-reported household income, census tract-level socioeconomic status, educational attainment
Model 2 includes: Model 1 + smoking history, diabetes, LDL cholesterol, lipid-lowering medication, and physical activity

CHAPTER 2**: The association of long-term air pollution exposure with supraventricular arrhythmia in the Multi-Ethnic Study of Atherosclerosis**

Abstract:

Background/Aim: Acute air pollution exposure is associated with supraventricular arrhythmias, including atrial fibrillation (AF). Studies investigating longer-term exposures on AF risk have shown mixed results, and additional work clarifying the role of pollutants on atrial electrophysiology is needed.

Methods: In the Multi-Ethnic Study of Atherosclerosis (MESA), we used estimated five-year average ambient fine particulate matter ($PM_{2.5}$), oxides of nitrogen (NO_X), and ozone (O_3) from validated hierarchical spatio-temporal models and conducted two-week ambulatory electrocardiography (ECG) monitoring of participants. Supraventricular arrhythmia measures of interest were presence of AF during monitoring, average count of premature atrial contractions (PACs) per hour, and average number of runs per day of supraventricular tachycardia (SVT). Generalized estimating equations were used, adjusting for MESA study site and other a priori defined potential confounders. In secondary analyses, we repeated the analyses above using two-week exposure windows.

Results: In 1,324 MESA participants, five-year average ambient concentrations of $PM_{2.5}$, NO_X, and O_3 were not significantly associated with presence of AF, PACs per hour, or average runs per day of SVT during monitoring. In the analysis of two-week exposure windows, higher $PM_{2.5}$ was associated with more runs of SVT, higher O_3 with greater odds of AF, and higher NO_X with lower odds of AF.

Conclusions: Using recently developed study-specific exposure estimation and newly available ambulatory ECG monitoring, we found no evidence that five-year average yearly exposure to

$PM_{2.5}$, NO_X, and O_3 were associated with rates of supraventricular arrhythmias. Secondary analyses using two-week exposures suggested moderate associations, but these results are not robust and should be viewed with caution. Additional work is needed to further investigate the relationship of long-term pollution with supraventricular arrhythmias.

INTRODUCTION

Air pollution is a significant contributor to cardiovascular morbidity [1, 2]. Recent studies have demonstrated associations of acute exposure to high ozone (O_3) and fine particulate matter ($PM_{2.5}$) with episodes of atrial fibrillation (AF), as well as an association of high nitrogen dioxide (NO_2) exposure with same-day hospitalization for ventricular and supraventricular arrhythmias [3-5]. AF is associated with a 3- to 5-fold increase in risk of stroke and a doubling of risk for dementia and sudden cardiac death [27-31], and perturbation of cardiac rhythm may be an important pathway through which air pollution adversely affects cardiovascular health. One possible mechanism for AF development in the context of air pollution exposure is atrial remodeling—progressive change of atrial structure that may lead to changes in cardiac function, including arrhythmia, decreased myocardial strain, lower ejection fraction, and larger maximum and minimum size [6].

However, additional work clarifying the potential role of pollutants on atrial arrhythmias is needed [7, 8, 32-35]. Existing studies of air pollution and cardiac arrhythmia have used pollution data from population-level sources, and many have studied individuals with implanted cardiac monitoring devices. Newly developed ambulatory electrocardiographic (ECG) monitors can be used to detect subclinical atrial arrhythmias including AF, are useful in precisely characterizing AF/arrhythmia burden, and can be applied in a large general population sample. Additionally, studies of air pollution and arrhythmia have focused largely on short-term, often same day, exposure. Studies investigating longer-term exposures on risk of AF have shown mixed results [36, 37], and studies on these exposures and cardiac arrhythmias other than AF are largely absent.

In the current study, we used long-term individual-level pollutant exposure and long-term ambulatory electrocardiographic monitoring to investigate the association between air pollution exposure and atrial arrhythmias to elucidate potentially clinically-relevant mechanisms through which AF arises in the general population.

METHODS

MESA is a multi-ethnic longitudinal study with participants 45 to 84 years of age and free of clinically-detected cardiovascular disease at baseline (2000-2002) in six United States communities. Details of MESA have been previously reported [14]. Participant characteristics were collected at study Exam 1 (2000-2002), including height, weight, blood pressure, diabetes status, high- and low-density lipoprotein (HDL, LDL) cholesterol, lipid-lowering and antihypertensive medication use, fasting blood glucose, and self-reported age, sex, race/ethnicity, physical activity, highest attained education level, household income, and smoking history and status. Neighborhood socioeconomic status was calculated using principal factor analysis of 16 census-tract-level variables from the American Community Survey 2005-2009 estimates [38] reflecting education, employment, housing, household income and wealth, and has been described elsewhere [15]. Participants with a myocardial infarction or a clinical diagnosis of heart failure or AF before the cardiac monitoring at Exam 6 (2016-2018) were identified through study-specific methods that have been previously published [16, 17]. Each study site obtained Institutional Review Board approval, and all participants provided written informed consent.

Long-term ambulatory ECG monitoring was conducted on 1,557 individuals during the MESA Exam 6 study visit between 2016 and 2018 [39]. Participants were asked to wear one or two ECG patch monitors that each store up to 14 days of continuous rhythm (Zio Patch XT, iRhythm Technologies, Inc, San Francisco, CA). Among participants who wore two patches, the

median interval between patches was 36 days. Data from the monitors were processed and analyzed by the manufacturer, with duration of monitoring defined as the total time during which the ECG tracing was adequate to determine the cardiac rhythm. The continuous outcomes of interest were the average count of premature atrial contractions (PACs) per hour and the average number of runs per day (24 hours) of supraventricular tachycardia (SVT), defined as 4 or more consecutive PACs. Atrial fibrillation was identified as an irregularly irregular rhythm with absent P waves lasting at least 30 seconds; atrial flutter was also identified, and both atrial fibrillation and atrial flutter were included as AF for these analyses. Detected arrhythmias were independently verified by the Epidemiological Cardiology Research Center at Wake Forest University School of Medicine. Rates of PACs per hour and runs of SVT per day were highly right-skewed, with non-normal distributions. These rates were thus log-transformed for analysis.

Our analysis used spatio-temporal modeling-predicted values of ambient $PM_{2.5}$, NO_X, and O_3 for individual MESA participants based on residential address history [18, 19]. This modeling incorporated data from Environmental Protection Agency long-term monitoring equipment, study-specific monitoring stations, detailed community- and individual-level pollutant measurements in MESA, and geographic information system (GIS)-based geographic covariates [18, 19]. Partial least squares regression was used to reduce dimensionality of the large set of GIS-based covariates. The models for $PM_{2.5}$, NO_X, and O_3 used regression on geographical covariates with spatial smoothing by universal kriging. Cross-validation of these models has been described previously and suggests good predictive accuracy [18, 19].

Data were missing in fewer than 5% of participants for all covariates except household income, for which data were missing in 5.2% of participants. Missing covariate data were

imputed using multiple-imputation by chained equations (Stata release 14.2, StataCorp LP, College Station, TX) [40].

For the main analysis, we used generalized estimating equations (GEE) with a Gaussian distribution and independent correlation structure within participants to assess the relationship between five-year average modeled exposures to $PM_{2.5}$, NO_X, and O_3 and log-transformed PACs per hour and runs of SVT per day. This method allowed for the most efficient use of data from multiple monitors worn by some participants and the multiple pollution exposure windows. Associations generated using this model are presented as geometric mean ratios. These ratios may be interpreted as the percent difference in the outcome per increment of the exposure. Additionally, our analysis used GEE with a binomial distribution and logistic link function with independent correlation structure to assess the relationship between five-year average modeled exposures to $PM_{2.5}$, NO_X, and O_3 and presence of AF on the monitor. For each method, covariates were chosen *a priori* based on their hypothesized associations with air pollution and supraventricular arrhythmias. In the analyses of pollution exposures in relation to presence of AF on the monitor, we limited the number of covariates included because of concerns about over-fitting the model given the relatively small number of participants with those outcomes. The covariates included were age, height, weight, sex, race/ethnicity, and MESA study site. The analysis of PACs per hour and runs of SVT per day included the above covariates plus education, income, neighborhood socioeconomic status (SES), diabetes status, current smoking status, LDL and HDL cholesterol, and physical activity. In sub-group analyses, we stratified by history of AF, myocardial infarction (MI), and heart failure prior to Exam 6 to explore the effect of previously-diagnosed conditions known to be associated with risk of AF and supraventricular

arrhythmia. Because the results of these analyses did not differ materially from the primary analysis, they are not presented here.

In secondary analyses, we explored short-term associations of $PM_{2.5}$, NO_X, and O_3 exposure in the two weeks prior to monitoring with the previously described outcomes, using the same methods as above. In addition to previously listed covariates, we adjusted for participant address-specific average temperature and humidity in the two weeks prior to monitoring. In all analyses, we investigated additional adjustment for systolic blood pressure and hypertension medication, which may partially mediate any association between pollution and atrial arrhythmias. We additionally performed main analyses while including multiple pollutants in the model simultaneously.

RESULTS

Outcome information from cardiac monitors was available for a total of 1,557 participants who attended MESA Exam 6. Complete exposure and covariate information was available for 1,324 participants (Figure 2.1), who collectively completed 1,846 cardiac monitoring periods. Participant characteristics are shown in Table 2.1. The analysis population had a mean age of 74 years at MESA Exam 6, and 51% were women. The population was 43% white, 13% Chinese-American, 25% African-American, and 18% Hispanic.

Table 2.1 also shows the distribution of participant characteristics by quartiles of PACs per hour. Those in higher quartiles of PACs per hour were more likely to be men, older age, less physically active, and have a higher systolic blood pressure than participants in lower quartiles of PACs per hour. The proportion of white participants increased with increasing quartiles of PACs per hour, while the proportion of Chinese-American and Hispanic participants decreased. Participants in higher quartiles of PACs per hour had greater frequency of a history of MESA-

identified AF, with 2.5% in the lowest quartile, and 14.3% in the highest. During monitoring, AF was identified in 87 (6.6%) participants. Participants with monitor-detected AF tended to be older, less active, more likely to smoke, and have lower LDL cholesterol. SVT was detected on 1,465 (79%) patches. The distribution of runs of SVT per day was highly right-skewed, with a mean of 3.2 runs per day and a median of 0.36 runs per day. Distribution of PACs per hour was similarly right skewed, with a mean of 41 beats per hour and a median of 4.3 beats per hour.

Figure 2.2 illustrates the distribution of ambient concentrations of $PM_{2.5}$, NO_X, and O_3 in the five years prior to ECG monitoring by MESA study site among participants. Exposures differed greatly by site, with the highest levels of $PM_{2.5}$ and NO_X in New York, NY, and Los Angeles, CA, and the highest levels of O_3 in Winston-Salem, NC and Chicago, IL. Between-site exposure variability was much greater than within-site exposure variability for all pollutants estimated.

Our primary analysis results are reported in Table 2.2 as the fully adjusted model without inclusion of site (Model 1) and with additional adjustment for site (Model 2). In Model 2, there were no significant associations of five-year average ambient levels of $PM_{2.5}$, NO_X, and O_3 with monitor-derived rates of PACs or runs of SVT. In Model 2, for each 40 parts per billion (ppb) higher ambient NO_x exposure, the rate of PACs per hour was 53% higher, but this relationship did not reach statistical significance ($p = 0.15$). Associations of $PM_{2.5}$ and O_3 with PACs per hour and runs of SVT per day were also non-significant. Additionally, we observed no significant association between five-year average ambient levels of $PM_{2.5}$, NO_X, and O_3 and presence of AF on the monitor. Generally, inclusion of MESA site in the adjustment model strongly influenced the point estimates, often leading to results farther from the null. Additional adjustment for SBP and use of hypertension medication did not materially affect the results.

In our secondary analysis of two-week pollution exposure and atrial arrhythmias, greater $PM_{2.5}$ was significantly associated with greater runs of SVT per day in Model 2 (23% per 5μg/m^3 higher $PM_{2.5}$; 95% CI: 4% – 46%. Table 2.3). Additionally, greater ambient O_3 was associated with greater risk of AF detected on the monitor (odds ratio per 10 ppb higher O_3: 1.66; 95% CI: 1.15 – 2.41), while greater NO_X was associated with significantly lower odds of AF (odds ratio per 40 ppb higher NO_X: 0.28; 95% CI: 0.09 – 0.82). These associations were attenuated when including multiple pollutants simultaneously in the regression models (Supplementary Table 2.1).

DISCUSSION

In a multi-ethnic population with well-characterized air pollution exposure estimates and long-term cardiac monitoring, we found no evidence that five-year average yearly exposure to $PM_{2.5}$, NO_X, or O_3 were associated with rates of supraventricular arrhythmias or odds of AF. Ambient air pollution is an established cardiovascular disease risk factor, and short-term exposure to elevated pollutants has been associated with increased risk of arrhythmias and AF episodes in older individuals with implanted cardioverter-defibrillators, and hence established cardiovascular disease diagnosis. Despite this, little work has been done to investigate the relationship between long-term air pollution exposure and both clinical and subclinical arrhythmias, and prior work with ECG data has not been based in a general population sample.

Previous studies found associations of short-term exposure to $PM_{2.5}$ with ventricular and supraventricular arrhythmias [41, 42], and two recent studies suggested that long-term $PM_{2.5}$ and NO_2 pollution exposure is associated with incident AF [36, 37]. Based on this and additional information, we hypothesized that increased exposure to ambient levels of $PM_{2.5}$, NO_x, and O_3

would be associated with greater odds of monitor-detected AF and greater rates of subclinical atrial arrhythmias. Our primary analysis did not provide evidence supporting this hypothesis.

Our secondary analysis focusing on air pollution in the two weeks prior to monitoring demonstrated a significant association between $PM_{2.5}$ exposure and runs of SVT, but not AF. We have more confidence in our SVT results than those for AF, due to SVT being a common and continuous measure. Several recent studies have identified associations of high rates of supraventricular ectopy with greater risk of AF and other cardiovascular events [43-45] as well as greater risk of stroke beyond the risk conferred through AF [46]. Though previous studies have suggested an increased risk of AF associated with short-term pollution exposure, little information exists regarding other atrial arrhythmias that may precede AF, including SVT.

In addition, a strong and significant association was seen between two-week exposure to O_3 and presence of AF, in the direction hypothesized. However, these analyses also yielded a strong, statistically significant association of NO_X with AF (odds ratio: 0.28; 95% CI: 0.09 - 0.82) in the direction opposite to that hypothesized. Taken together with the sparse nature of the AF data, we believe these results most likely represent spurious, rather than true, associations. Alternatively, these findings could represent residual confounding by other pollutants. NO_X and O_3 concentrations are negatively correlated, and associations were attenuated in models including both pollutants (Supplementary Table 2.1).

In another recently completed analysis, we examined the association of long-term exposure to these same pollutants with cardiac MRI-derived measures of left atrial structure and function and did not observe statistically-significant relationships. Taken together, these results are more consistent with the hypothesis that air pollution primarily affects cardiac arrhythmias through triggering alterations in the autonomic nervous system than the hypothesis that these

effects are mediated through progressive cardiac remodeling from sustained exposure to elevated levels of $PM_{2.5}$, NO_X, and O_3 [47, 48]. However, this observational study cannot address this hypothesis directly.

It is possible, given our results, that long-term exposure to $PM_{2.5}$, NO_X, and O_3 do not influence atrial arrhythmias, and that these pollutants act on supraventricular rhythm solely through short-term mechanisms. However, the relatively low ambient concentrations of these pollutants in the United States (US) relative to historical US and contemporary levels in other countries may also mask our ability to precisely determine the true association. Mean $PM_{2.5}$ concentrations at all MESA sites in the five years prior to ambulatory monitoring was below the US standard of 12 ug/m^3, and 4-8 times lower than World Health Organization-estimated mean exposure levels seen in India (90.9 ug/m3) and China (52 ug/m^3) [49]. Finally, our estimates were very sensitive to adjustment for study site in our model, suggesting that there may be residual unmeasured confounding that we are beginning to address by the addition of study site. This suggests adjustment for site is important for minimizing confounding because the majority of variability in pollutant exposure was found between, rather than within, MESA sites. However, the strong associations between pollutant concentrations and study site also mean adjustment for study site limits between-participant variability and may affect our ability to identify true associations in the data.

The spatio-temporal models employed in MESA Air do not permit us to investigate exposure windows shorter than two weeks for pollutant levels, and thus we could not confirm prior studies' findings that exposure to pollutants influences cardiac arrhythmias in the hours and days following elevated exposure levels. Monitor-detected AF was present on only 6.6% of monitors, providing limited power to identify associations of pollution with presence of AF.

Because of the small number of participants with AF, we used limited adjustment in our analysis. However, adjustment for both six-level categorical site and four-level race/ethnicity in the limited adjustment may still lead to spurious associations, likely including that seen for AF. Additionally, there were 12 tests for significance in the main analysis, and an additional 12 in the secondary analysis, and spurious results could arise due to multiple comparisons. As such, we are cautious in drawing conclusions based on those results that reached statistical significance, as they all arose from analyses that were not conceived as part of the original analysis plan.

In an analysis using sophisticated participant-specific exposure models and state-of-the-art ambulatory ECG monitors which collected up to 14 days of continuous tracing, we did not find evidence of an association of five-year exposure to $PM_{2.5}$, NO_X, and O_3 with supraventricular arrhythmias in the MESA cohort. There was suggestive evidence of a relationship between two-week pollutant exposures and supraventricular arrhythmias, but these results are secondary to our main analysis and should be interpreted with caution. Additional work is needed to further investigate the relationship of long-term pollution with cardiac arrhythmias, not only in populations with detailed exposure measurements, but also in populations with greater AF burden and higher average pollution levels.

Table 2.1: MESA Exam 6 (2016-2018) participant characteristics, by quartile of premature atrial contractions

		Quartiles of premature atrial contractions per hour			
Characteristic	Total	0.0 - 1.3	1.4 - 4.3	4.4 – 23.3	23.4 – 90.4
N	1324	331	331	331	331
Age, yrs (SD)	74 (8)	70 (7)	72 (8)	75 (8)	78 (8)
Female (%)	51	56	55	49	44
Height, cm (SD)	166 (10)	164 (9)	165 (10)	166 (10)	166 (10)
Systolic Blood Pressure, mmHg (SD)	127 (20)	126 (19)	127 (19)	127 (20)	130 (22)
Treated Hypertension (%)	62	59	59	63	66
Weight, lb (SD)	171 (38)	171 (38)	171 (36)	171 (37)	173 (41)
BMI (SD)	28 (5)	28 (6)	28 (5)	28 (5)	28 (6)
Current Smoking (%)	6.5	8.4	8.2	5.0	4.3
LDL Cholesterol, mg/dL (SD)	105 (35)	109 (37)	106 (34)	106 (35)	103 (33)
HDL Cholesterol, mg/dL (SD)	60 (18)	57 (18)	58 (17)	61 (19)	62 (19)
Lipid-Lowering Medication (%)	46	45	44	48	46
Physical Activity, MET-Mins/week (SD)	5362 (6232)	6109 (7752)	5416 (5782)	5367 (5558)	4619 (4894)
Diabetes (%)	23	24	22	20	23
Race/Ethnicity (%)					
White	43	29	48	49	47
Chinese-American	13	20	13	12	8
Black/African-American	25	27	20	24	30
Hispanic	18	24	18	15	15
History of Myocardial Infarction (%)	2.7	3.1	1.2	3.9	2.3
History of Heart Failure (%)	1.6	0.9	0.6	2.4	2.7
History of Atrial Fibrillation (%)	7.2	2.5	4.3	8.1	14.3

Table 2.2: Multivariable adjusted association of five-year average fine particulate matter ($PM_{2.5}$), oxides of nitrogen (NO_X), and ozone (O_3) concentrations with premature atrial contractions, runs of supraventricular tachycardia, and atrial fibrillation.

		$PM_{2.5}$ (per 5μg/m^3)		NO_X (per 40ppb)		O_3 (per 10ppb)	
		Geometric Mean Ratio (95% CI)	P-Value	Geometric Mean Ratio (95% CI)	P-Value	Geometric Mean Ratio (95% CI)	P-Value
PACs (beats per hour)	Model 1a*	1.05 (0.74 - 1.51)	0.78	0.98 (0.69 - 1.38)	0.90	0.99 (0.70 - 1.41)	0.97
	Model 2**	1.31 (0.83 - 2.07)	0.25	1.53 (0.85 - 2.76)	0.15	0.69 (0.44 - 1.09)	0.12
Runs of SVT (runs perday)	Model 1a*	1.18 (0.87 - 1.60)	0.28	1.03 (0.77 - 1.38)	0.83	1.04 (0.78 - 1.39)	0.80
	Model 2**	1.27 (0.85 - 1.91)	0.24	1.39 (0.86 - 2.24)	0.17	0.79 (0.54 - 1.15)	0.22

		Odds Ratio (95% CI)	P-Value	Odds Ratio (95% CI)	P-Value	Odds Ratio (95% CI)	P-Value
Atrial Fibrillation	Model 1b†	1.09 (0.47 - 2.53)	0.85	0.93 (0.42 - 2.08)	0.86	1.39 (0.59 - 3.31)	0.46
	Model 2**	0.40 (0.15 - 1.05)	0.06	0.33 (0.08 - 1.34)	0.12	1.13 (0.36 - 3.56)	0.83

* Model 1a: age, height, weight, sex, race/ethnicity, education, income, neighborhood SES, diabetes status, current smoking status, LDL & HDL cholesterol, and physical activity

† Model 1b: age, height, weight, sex, race/ethnicity

** Model 2: Model 1 + Study site

PAC = premature atrial contraction

SVT = supraventricular tachycardia

ppb = parts per billion

Table 2.3: Multivariable adjusted association of two-week average fine particulate matter ($PM_{2.5}$), oxides of nitrogen (NO_X), and ozone (O_3) with atrial fibrillation, premature atrial contractions, and runs of supraventricular tachycardia.

		$PM_{2.5}$ (per 5μg/m^3)		NO_X (per 40ppb)		O_3 (per 10ppb)	
		Geometric Mean Ratio (95% CI)	P-Value	Geometric Mean Ratio (95% CI)	P-Value	Geometric Mean Ratio (95% CI)	P-Value
PACs (beats per hour)	Model 1b†	1.00 (0.83 - 1.20)	0.98	0.98 (0.74 - 1.30)	0.89	1.01 (0.88 - 1.15)	0.94
	Model 2**	1.09 (0.90 - 1.32)	0.38	1.27 (0.87 - 1.85)	0.22	0.95 (0.82 - 1.10)	0.49
Runs of SVT (runs per day)	Model 1b†	1.18 (1.01 - 1.37)	0.04	1.08 (0.86 - 1.37)	0.51	1.03 (0.92 - 1.15)	0.65
	Model 2**	**1.23 (1.04 - 1.46)**	**0.02**	1.25 (0.92 - 1.68)	0.15	0.98 (0.87 - 1.10)	0.74
		Odds Ratio (95% CI)	P-Value	Odds Ratio (95% CI)	P-Value	Odds Ratio (95% CI)	P-Value
Atrial Fibrillation	Model 1a*	0.98 (0.63 - 1.52)	0.92	0.74 (0.37 - 1.45)	0.38	1.61 (1.16 - 2.22)	0.00
	Model 2**	0.69 (0.41 - 1.15)	0.15	**0.28 (0.09 - 0.82)**	**0.02**	**1.66 (1.15 - 2.41)**	**0.01**

* Model 1a: age, height, weight, sex, race/ethnicity

† Model 1b: age, height, weight, sex, race/ethnicity, education, income, neighborhood SES, diabetes status, smoking status, pack years, LDL & HDL cholesterol, physical activity

** Model 2: Model 1 + Study site

PAC = premature atrial contraction

SVT = supraventricular tachycardia

ppb = parts per billion

Figures:

Figure 2.1: Study participation and inclusion in analysis

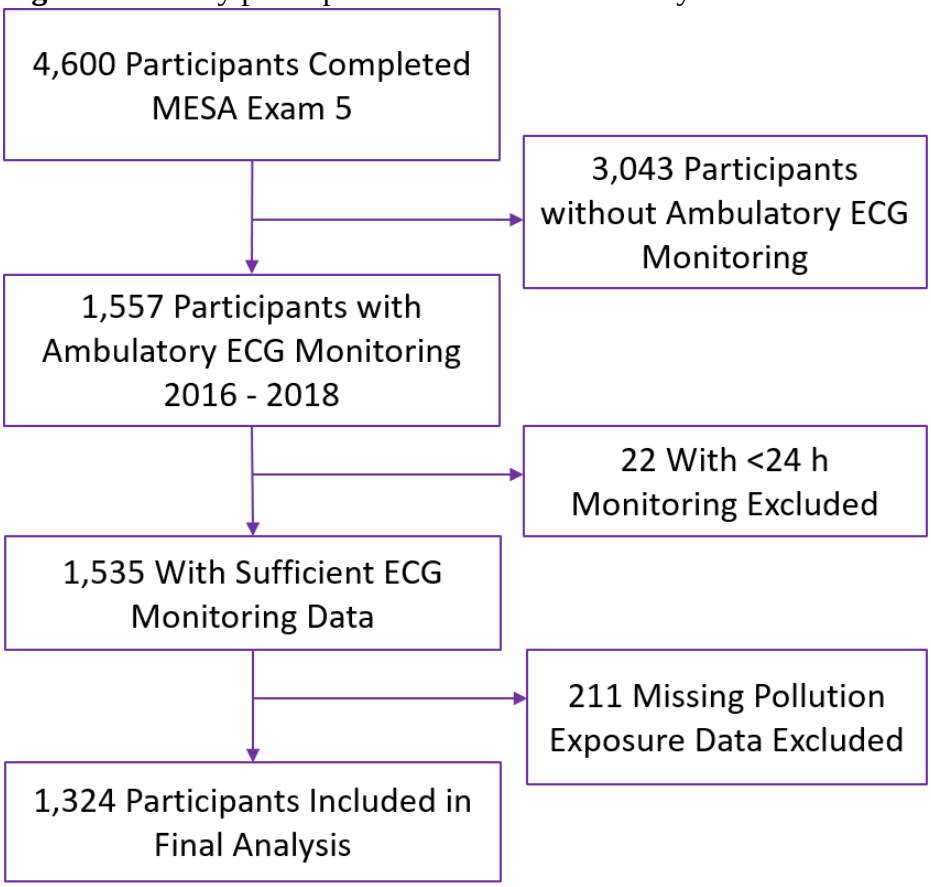
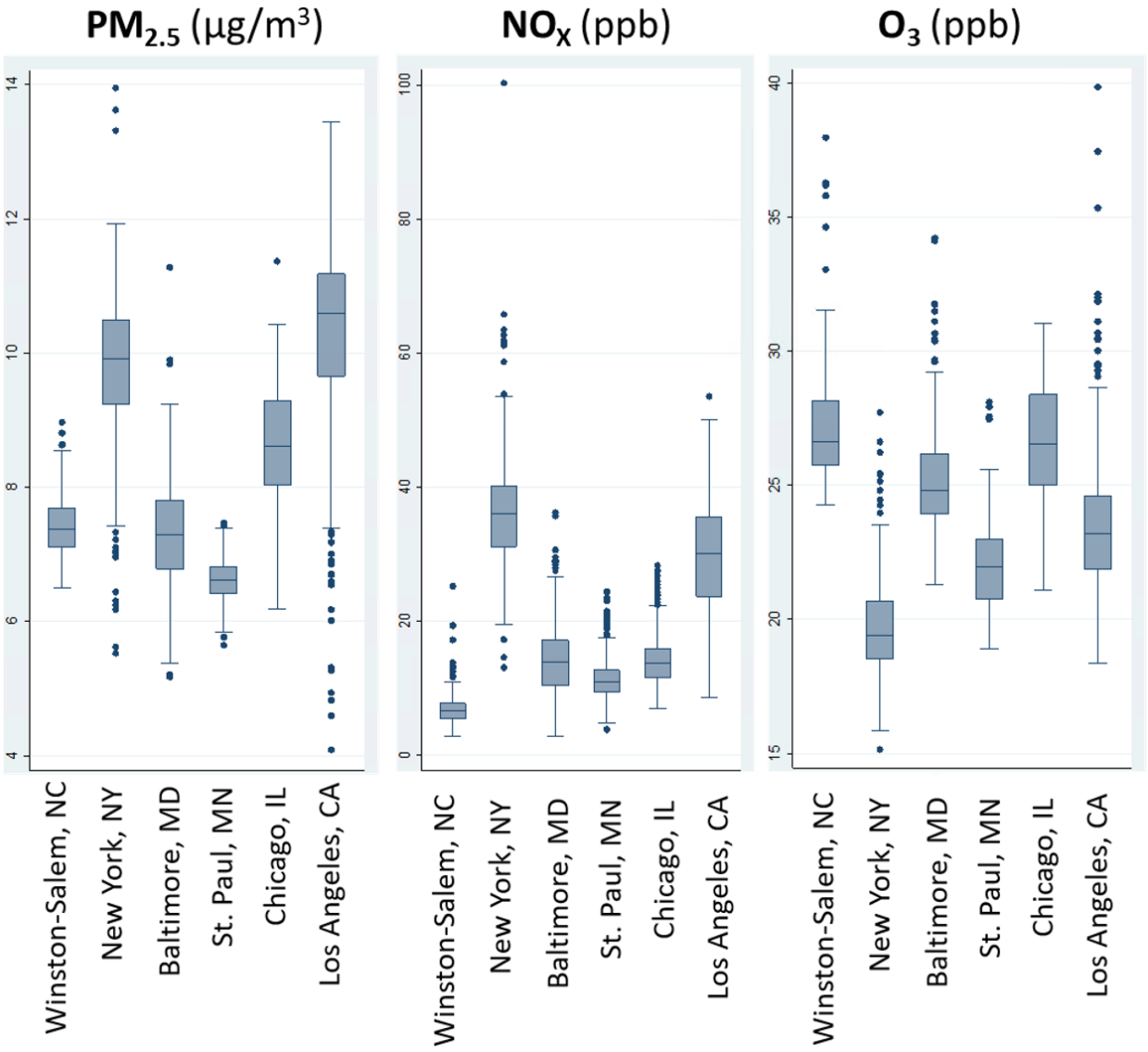


Figure 2.2: Box plots of modeled five-year average yearly concentrations of fine particulate matter ($PM_{2.5}$), oxides of nitrogen (NO_X), and ozone (O_3) in the Multi-Ethnic Study of Atherosclerosis and Air Pollution, preceding study Exam 6 (2016 – 2018), by study site



$PM_{2.5}$ = particulate matter smaller than 2.5 microns in size; NO_X = oxides of nitrogen; O_3 = ozone; ppb = parts per billion

CHAPTER 3**: The association of long-term air pollution exposure with left ventricular structure and function in the Multi-Ethnic Study of Atherosclerosis**

Abstract:

Background: Air pollution contributes to cardiovascular morbidity, including heart failure. Exposure to pollutants has been associated with hypertension and inflammation, which contribute to cardiac remodeling. Few studies have investigated long-term air pollution concentrations and measures of cardiac structure, and no large longitudinal analyses have investigated this association.

Methods: In the Multi-Ethnic Study of Atherosclerosis (MESA), we investigated cross-sectional and longitudinal associations between modeled fine particulate matter ($PM_{2.5}$), oxides of nitrogen (NO_X) and ozone (O_3) concentrations and left ventricular mass index (LVMI), mass to volume ratio, ejection fraction, and circumferential strain by cardiac magnetic resonance imaging (CMR) at two time points roughly 10 years apart. Multivariable linear regression was used to estimate the association between pollutants and both cross-sectional and longitudinal CMR measures.

Results: Higher concentrations of $PM_{2.5}$ and NO_X in the year prior to MESA Exam 1 (2000-2002) were associated with higher LVMI at Exam 1 (1.6% per 5ug/m^3 higher $PM_{2.5}$, 95% CI: 0.3, 2.9; 1.8% per 40 parts per billion [ppb] NO_X, 95% CI: 0.3, 3.3) and higher O_3 was associated with lower LVMI (-3.5% per 10ppb, 95% CI: -6.0, -1.0). In longitudinal analyses, higher NO_X was associated with a worsening of LV circumferential strain (-0.87% per 40ppb, 95% CI: -1.69, -0.05).

Conclusions: Our study offers mixed evidence of a cross-sectional association between higher $PM_{2.5}$ and NO_x concentrations and greater LVMI. We also found associations between greater O_3

concentration and lower cross-sectional LVMI, though this association may be confounded by other pollutants. These findings suggest a role for NO_X, $PM_{2.5}$, and O_3 and cardiac remodeling in MESA. Additional work is needed to clarify that role and better understand the biological underpinnings of these associations.

INTRODUCTION

Air pollution is a significant contributor to worldwide cardiovascular morbidity [1, 2] including risk of heart failure (HF). One potential mechanism through which pollution exposure may influence cardiovascular disease risk is cardiac remodeling—progressive structural and functional changes to the myocardium in response to acute or sustained perturbations, such as hypertension and inflammation. Greater short-term concentrations of fine particulate matter smaller than 2.5 microns in size ($PM_{2.5}$), oxides of nitrogen (NO_X), and ozone (O_3) have been associated with elevated blood pressure [50-52], increased inflammatory biomarkers, and arrhythmia [3, 33].

In the Multi-Ethnic Study of Atherosclerosis (MESA) baseline examination, residential proximity to major roadways was associated with greater left ventricular (LV) mass index (LVMI) [7], and higher long-term NO_2 concentration was associated with greater right ventricular (RV) mass and larger RV end-diastolic volume [8]. Additionally, a 2018 study of UK Biobank participants demonstrated associations between long-term $PM_{2.5}$ concentrations and larger LV end-diastolic and end-systolic volumes and RV end-diastolic volume [9]. In the same analysis, higher long-term NO_2 concentrations were associated with larger left and right ventricular volume. Research on the long-term effects of O_3 has focused primarily on mortality [53, 54]. Though recent literature has suggested an association between higher residential outdoor long-term O_3 concentrations and subclinical arterial disease [55], the relationship between long-term exposure and cardiovascular health is not clearly understood.

While these studies suggest a relationship of greater long-term pollutant concentrations with increased cardiovascular disease and impaired LV structure, no studies have investigated longitudinal changes in LV measures. Additionally, none of these studies investigated

myocardial strain as an outcome. Lower values of myocardial strain indicate impaired contractile performance [56] and are predictive of HF beyond LV ejection fraction (EF) [57], are associated with advanced age, male sex, hypertension, subclinical atherosclerosis, and LV hypertrophy, and may offer a more sensitive measure of cardiac remodeling prior to clinical manifestation [58-61].

In MESA, we investigated cross-sectional and longitudinal associations of long-term concentrations of $PM_{2.5}$, NO_X, and O_3, and cardiac magnetic resonance (CMR)-derived measures characterizing cardiovascular structure and function, including LVMI, LV mass-to-volume ratio (LVMVR), and LV EF. In a subset of this population, we also investigated associations of these pollutants with LV circumferential strain. Our hypothesis was that that long-term concentrations of all three pollutants would be associated with altered LV structure and impaired LV function as measured by CMR.

METHODS

Study Sample

MESA is a longitudinal study of 6,814 participants 45 to 84 years of age enrolled between 2000 and 2002 at six sites throughout the United States: Baltimore, MD; Chicago, IL; Winston Salem, NC; Los Angeles, CA; New York, NY; and Minneapolis, Minnesota. Participants in MESA were free of clinically recognized cardiovascular disease at enrollment and have been followed-up at five subsequent in-person examinations after baseline, with MESA Exam 5 taking place between 2010 and 2012. Details of MESA have been reported previously [14]. At baseline and at follow-up visits, height, weight, blood pressure, diabetes status, low-density lipoprotein (LDL) cholesterol, fasting blood glucose, physical activity habits, smoking status, second-hand smoke exposure, household income, and medication use were ascertained. Age, sex, race/ethnicity, and highest attained education level were self-reported at baseline. A

neighborhood disadvantage score was created using principal factor analysis of 16 census tract-level variables, including education, income, wealth, poverty, employment, and housing characteristics, using US Census and American Community Survey data, and has been described elsewhere [15]. Clinical presentations with myocardial infarction (MI), heart failure (HF), and atrial fibrillation (AF) after baseline but before Exam 5 were identified as previously described [16, 62]. For participants with missing values in any covariate of interest, values were imputed using multiple imputation with chained equations (Stata release 14.2, StataCorp LP, College Station, TX). Each study site obtained Institutional Review Board approval, and all participants provided written informed consent.

Air Pollution Concentrations

Our analysis used spatio-temporal modeling-predicted values of $PM_{2.5}$, NO_X, and O_3 for individual MESA participants based on the MESA Air Pollution (MESA Air) ancillary study. MESA Air built upon MESA by adding air pollution concentration measurements at the six MESA study sites through a series of cohort-specific measurements and integrated fixed-site monitoring, residential monitoring, "Snapshot" monitoring to develop traffic-gradients, and participant home monitoring with U.S. Environmental Protection Agency (EPA) Air Quality System air pollution data [63]. These data, along with geographic information system (GIS)-based geographic covariates, were used by MESA investigators to develop novel spatiotemporal models used to estimate participant-specific residential pollution concentration predictions [18, 19].

The spatiotemporal models for $PM_{2.5}$, NO_X, and O_3 have been described elsewhere in detail [18, 19]. Briefly, two-week average concentration of pollutants is calculated from the following model:

$$C(s,t) = \mu(s,t) + v(s,t) \quad (1)$$

Where $\mu(s,t)$ represents the spatiotemporal mean surface and $v(s,t)$ the spatiotemporal residual variation [18]. The spatiotemporal mean surface, $\mu(s,t)$, is comprised of a long-term mean at location *s*, time-trends estimated from EPA Air Quality System (AQS) and MESA specific monitoring, and spatially varying coefficients for time trends. The models for all three pollutants use regression on geographical covariates with spatial smoothing by universal kriging, as well as partial least squares regression to reduce dimensionality of the large set of GIS-based covariates. Cross-validation of these models has been described previously and suggests good predictive accuracy [18, 19]. Pollutant concentrations were predicted at each participant's home address for the period from January 1, 1999 through the date of MESA Exam 5.

To compare our analysis to formerly published results, we also calculated distance from participant homes to the nearest roadway at MESA Exams 1 and 5, which included interstate, state, or county highway or major arterial as defined by the US Census Feature Class Codes A1, A2, and A3. Distances were defined categorically as <50m, 50-100m, 101-150m, and >150m for consistency with prior analyses.

Cardiac MRI Measures

Cardiac magnetic resonance (CMR) imaging was performed for 5,003 participants upon enrollment in MESA (Exam 1, 2000–2002) using 1.5T scanners at each study location with an electrocardiographic-triggered fast spoiled gradient-echo pulse sequence, and has been described previously [16, 64]. Images were analyzed centrally at the study MR review center at Johns Hopkins University in Baltimore, MD, using MASS software, which semi-automatically traced endocardial and epicardial borders, from which LV mass and volume were calculated [65]. On a random sample of 1,773 of these participants, tagged short-axis slices were captured during

breath holds. Tagging applies spatial modulation of magnetization to superimpose a grid on the myocardium image, from which myocardial deformation can be tracked to calculate LV circumferential strain from four mid-wall segments from three LV short-axis slices. Additional details have been reported elsewhere [57, 66]

At MESA Exam 5 (2010-2012), CMR imaging was performed on 3,015 participants, 2,981 of whom had undergone CMR imaging at Exam 1. Imaging was again performed on 1.5T scanners [66]. Tagged CMR-derived LV circumferential strain as described above was available for a subset of 2,716 of these participants. Exam 5 CMR images were assessed using a cine steady-state free precession (SSFP) pulse sequence, which offers improved image quality and a faster examination compared to the fast gradient echo pulse sequence at Exam 1. To improve comparability of Exams 1 and 5 CMR measures, a central reading center applied calibration curves to participants' baseline LV mass and volume measurements, as described previously, to estimate SSFP-derived CMR measures at Exam 1 [66].

CMR-derived measures of interest included LVMI, LVMVR, LV EF, and LV circumferential strain. LV mass was indexed using a previously described allometric approach for body-size adjustment of LV mass based on height, weight, and sex in MESA [16]. Briefly, we identified a sample of 1,766 MESA participants at Exam 1 without obesity, hypertension, antihypertensive medication use, diabetes, impaired fasting glucose, or hypoglycemic medication use. We derived regression models from this population using a multiplicative model regressing log(LV mass) on log(height), log(weight), and sex. Based on this model, 100 × LV mass was divided by predicted LV mass based on height (in meters), weight (in kilograms), and sex as follows: $100 \times \text{LV mass} / (a \times \text{height}^{0.45} \times \text{weight}^{0.54})$, where a = 7.93 for women and 9.41 = men. Indexed mass is thus presented as % above or below the predicted mass, based on height,

weight, and sex. LVMVR was calculated as LV mass divided by LV end-diastolic volume. EF was calculated as (end-diastole LV volume – end-systole LV volume) divided by the LV volume at end-diastole. Peak circumferential LV strain measures the average maximum percent distance change between two tracked points relative to end-diastolic circumference and was measured by averaging all mid-LV segments.

Statistical Analysis

We carried out a cross-sectional analysis of the associations of average $PM_{2.5}$, NO_2, and O_3 residential concentrations in the year preceding MESA Exam 1 with LVMI, LVMVR, EF, and LV circumferential myocardial strain at MESA Exam 1. We used linear regression adjusted for covariates chosen *a priori* based on their hypothesized associations with both air pollution exposure and ventricular structure and function, including age, race/ethnicity, MESA site, education history, neighborhood socioeconomic status, and known cardiovascular risk factors such as smoking status, smoking pack-years, second-hand smoke exposure, alcohol use, systolic and diastolic blood pressure (SBP, DBP), treatment for hypertension, diabetes status, LDL cholesterol, and fasting glucose. Analyses of LVMVR, EF, and circumferential strain were additionally adjusted for height, weight, and sex. We also conducted a cross-sectional analysis of pollutant concentrations in the year preceding Exam 5 in relation to Exam 5 CMR-derived measures. We conducted sub-group analyses stratified by history of AF, MI, and HF prior to measurement at Exam 5.

Longitudinal analyses investigated the associations of average $PM_{2.5}$, NO_2, and O_3 concentrations during the 10-year period between Exams 1 and 5 with changes in LVMI, LVMVR, LVEF, and circumferential strain between Exams 1 and 5. These analyses used linear regression, adjusted for the Exam 1 CMR-derived measures and covariates described above.

Because we were concerned about potential selection bias due to nonrandom dropout between Exams 1 and 5, we used inverse probability weighting based on probability of participation in Exam 5.

We were wary of potential bias introduced through using the ratio measures, LVMVR and EF, as outcomes in our analyses [67]. As sensitivity analyses, we used non-indexed LV mass as our outcome of interest. We also analyzed associations of pollutant concentrations with LV mass indexed to body surface area to identify differences between this method and indexing to body size based on the allometric method described above. Because the results of both sensitivity analyses did not appreciably differ from our main findings, we are presenting results as initially proposed.

Observed cross-sectional and longitudinal associations were examined for possible effect modification by MESA site, age, sex, race/ethnicity, BMI, hypertension medication, and SBP. Observed associations were also analyzed in models omitting SBP, DBP, and hypertensive medication, which may mediate any potential association.

RESULTS

Complete exposure, LVMI, LVMVR, LV EF, and covariate data were available for 4,825 of the 5,003 participants who attended Exam 1 and had a cardiac MRI (Figure 3.1). Of these, 1,513 had complete LV circumferential strain data available. At Exam 5, complete exposure, LVMI, LVMVR, LV EF, and covariate data were available for 2,811 participants, 2,695 of whom also had complete Exam 1 data and were included in longitudinal analyses. LV strain data were available for 2,449 of these participants at Exam 5, and 688 were included in longitudinal analyses.

Ambient concentrations of $PM_{2.5}$, NO_X, and O_3 at participant homes differed considerably between MESA study sites and between MESA exams (Figure 3.2). Los Angeles, CA, and New York, NY had the highest levels of both ambient $PM_{2.5}$ and NO_X at Exams 1 and 5 and the lowest levels of O_3. At all sites, $PM_{2.5}$ and NO_X were substantially lower at Exam 5 than at Exam 1. Pollutant concentrations were strongly correlated, with O_3 inversely related to both NO_X and $PM_{2.5}$ (Pearson's correlation coefficients: -0.85 and -0.58, respectively), while NO_X and $PM_{2.5}$ were strongly positively correlated (Pearson's correlation coefficient: 0.62. Supplemental Figure 3.1). Ambient O_3, however, increased at all sites but one between 2000 and 2012 (Figure 3.2). Mean participant LVMI was 104% of predicted (SD=16) at Exam 1 and 106% of predicted (18) at Exam 5, with an average change of +3.0% for participants with measurements at both exams. LVMVR, LV EF, and mean circumferential strain did not differ substantially between Exams 1 and 5.

Participant characteristics at Exams 1 and 5 are shown in Table 3.1. Participants who completed Exam 5 were slightly younger and wealthier than those who dropped out before Exam 5. The median time between Exams 1 and 5 was 9.4 years, and participant characteristics at Exam 5 were largely similar to those at Exam 1, with but with higher diabetes prevalence and prevalence of use of lipid-lowering and hypertension medications.

Cross-Sectional Analyses

Results from cross-sectional analyses are displayed in Table 3.2. At Exam 1, after adjustment for Model 2 covariates described above, greater $PM_{2.5}$ was significantly associated with higher LVMI (1.6% per 5ug/m^3 higher $PM_{2.5}$, 95% CI: 0.3, 2.9), greater NO_X was significantly associated with higher LVMI (1.8% per 40ppb NO_X, 95% CI: 0.3, 3.3), and higher O_3 with lower LVMI (-3.5% per 10ppb higher O_3, 95% CI: -6.0, -1.0). None of the pollutants

were significantly associated with LVMVF, LVEF, or LV circumferential strain. Results were very sensitive to adjustment for MESA site, with regression estimates changing substantially and, in our analysis of $PM_{2.5}$ levels and LVMI, changing directions after removal of MESA site as a model covariate.

The direction and magnitude of these associations was mirrored in Exam 5 cross-sectional analyses. However, none of the significant associations seen at Exam 1 was statistically significant at Exam 5.

In our analysis of distance to major roadways (Table 3.3), participants living within 50 meters of a major road had higher LVMI at Exam 1 compared to those living >150 meters from a major road (0.9%, 95% CI: -0.4, 2.1), though this relationship was not significant.

Longitudinal Analysis

Results for the longitudinal analysis investigating exposure to NO_X, $PM_{2.5}$, and O_3 and changes in LV CMR measures are displayed in Table 3.4. After adjustment for all covariates of interest, 10ppb greater average yearly O_3 in the years between Exams 1 and 5 was associated with a greater decrease in LVMI over that period, though not significantly (-3.3%, p=0.059). NO_X was associated with lower LV circumferential strain (-0.87%, p=0.037). The longitudinal analysis was adjusted for baseline CMR values. When baseline adjustment was omitted, both associations were non-significant.

Sensitivity Analyses

Sensitivity analyses did not suggest effect modification by MESA site (Supplementary Figure 3.2), and results did not appear to be driven by a single MESA site, nor did individual covariates have substantial effects on our regression estimates. Evidence of effect modification was not identified by sex, blood pressure, BMI, or diabetes. Significant associations of all

pollutants with LVMI at Exam 1 were stronger among younger participants (Supplementary Figure 3.3) and showed significant p-values of an interaction term between pollutant concentration and continuous age in our model for $PM_{2.5}$ and NO_X (p=<0.001 and p=0.03, respectively). Associations between all pollutants and LVMI at Exam 1 also appeared stronger in African-American participants than in whites, Chinese-Americans, and Hispanics (Supplementary Figure 3.3). Simultaneous adjustment for multiple pollutants rendered the associations of $PM_{2.5}$, NO_X, and O_3 with LVMI non-significant, but the directions of the relationships remained (Supplementary Figure 3.4).

DISCUSSION

In the Multi-Ethnic Study of Atherosclerosis, with detailed air pollution exposure modeling and repeated CMR measurements, higher NO_X and $PM_{2.5}$ were associated with higher LVMI while higher O_3 was associated with lower LVMI in cross-sectional analyses. We found suggestive but not consistent evidence of a relationship between long-term pollution exposure and changes in LV circumferential strain. Regression models were very sensitive to adjustment for MESA study site. While our analyses identified a cross-sectional association between elevated O_3 exposure and reduced LVMI at Exam 1, this finding should be viewed cautiously in the context of the existing literature detailing associations of high O_3 with adverse respiratory and cardiovascular outcomes and the established inverse relationship of O_3 with $PM_{2.5}$ and NO_X at each site.

Our finding of an association of higher one-year average NO_X with LVMI at Exam 1 (1.8% greater LVMI per 40ppb greater NO_X, p=0.019) is consistent with previous work by Van Hee et al. in MESA that reported greater LVMI associated with living within 50 meters of a major road (1.4g/m^2 greater LVMI, p=0.01) [7]. Similarly, our finding of a significant

association between long-term NO_X concentrations and decreases in LV circumferential strain correspond to worsening contractility over time in high-NO_X concentrations. In our analysis, living within 50 meters of a major road was suggestively associated with greater LVMI (1.1%, p=0.080), but fell short of statistical significance. The difference between our results and those reported in Van Hee et al. may be due to more recent recalibration of Exam 1 CMR measures to improve accuracy, or our use of a slightly different method with which to index LV mass to body size [16]. Proximity to a major road was intended to be used as a surrogate for traffic-based pollution exposure; however, this metric does not consider actual traffic volumes on major roads, wind direction, or other variables influencing dispersions and concentrations of pollutants at participant addresses. We now use NO_X models from advanced spatio-temporal models in MESA to more directly estimate traffic-related air pollutant concentrations and better characterize the relationship between these pollutants and study outcomes.

We additionally identified a strong association between greater long-term ambient $PM_{2.5}$ in the year preceding Exam 1 and higher LVMI (1.6% higher than predicted per 5ug/m^3 $PM_{2.5}$, p=0.017), similar in magnitude and significance to that seen for NO_X in our study. Though recent studies have focused on heart failure and cardiac morphology [26, 35], the degree to which $PM_{2.5}$ and NO_X are associated with development of cardiac remodeling and heart failure is still unclear, and results presented here are the first to identify a cross-sectional relationship of NO_X and $PM_{2.5}$ with LVMI. In the setting of the UK Biobank Study, Aung et al recently reported associations between greater $PM_{2.5}$ and larger end-diastolic and end-systolic volumes measures by echocardiography, but found no such relationship with LV mass for either $PM_{2.5}$ or NO_2 [26].

In our analysis, greater O_3 was associated with lower cross-sectional LVMI and greater decreases in LVMI over follow-up, though the latter association fell short of a 0.05 threshold for

statistical significance. This was unexpected, as it could suggest a potential beneficial effect of O_3 on cardiac morphology. Sensitivity analyses suggest that these associations were not driven by a single MESA site, nor were any individual covariates having substantial effects on our regression estimates. Though models are sensitive to adjustment for study site, even models omitting site showed similar direction, magnitude, and significance of the O_3 LVMI relationship (Tables 3.2, 3.3).

Interpretation of differences in LVMI may not be straightforward, as different pathologic processes can differentially influence LVMI. While hypertension and increased vascular resistance can lead to concentric remodeling of the LV and increase LVMI, frailty (with sarcopenia) and acute injury, such as MI, can decrease LVMI. While this study is not the first to counterintuitively suggest "protective' effects of increased O_3 pollution [68], the biological processes through which this might occur are not known, and interpretation of these findings should be done extremely cautiously given the evidence of detrimental effects of O_3 in prior studies [69]. Finally, at most MESA sites O_3 concentration is strongly inversely correlated with both $PM_{2.5}$ and NO_X. It is possible that associations observed between O_3 and LVMI are confounded by the strong relationships of $PM_{2.5}$ and NO_X with LVMI, and that high O_3 in our model instead represents lower concentration of these other pollutants. In sensitivity analyses, additional adjustment for $PM_{2.5}$ and NO_X render the association of O_3 with LVMI non-significant, but the direction of the relationship remains. Finally, outdoor ozone concentrations may be poorly correlated with indoor concentrations, and MESA participants spend most time indoors [70].

While strong cross-sectional associations existed at Exam 1, there were no significant associations between ambient pollution and CMR measures at Exam 5. There may be several

reasons for this. Our sample size is smaller by 41% at Exam 5 compared to baseline, which reduced study power to identify associations. Additionally, NO_X and $PM_{2.5}$ pollution decreased markedly between 2000 and 2012 in the US broadly, and MESA study sites specifically, as a result of continued national and local regulation of transportation and point-sources of primary pollutants. In our sample, for instance, mean NO_x exposure was 46% lower (27.8 vs. 51.2ppb), and mean $PM_{2.5}$ was 36% lower (10.9 vs 17.0ug/m^3) at Exam 5 than Exam 1. Though we used a linear model to describe the pollutant-CMR-measure association, it is possible that there is a threshold above which these associations occur, or that the relationship is more complicated. We found evidence of possible effect modification of the association of pollutants with LVMI at Exam 1 by age, with weaker associations with increasing age. Our sample is older at Exam 5, and it is possible that its age distribution suggests a weaker association with LVMI. Further, selection bias may be an issue, if those participants who died or dropped out between Exams 1 and 5 represented a population in which the association was particularly strong.

There was strong evidence of effect modification by race/ethnicity, with stronger associations between Exam 1 pollutants and LVMI seen among African-American participants than among other race/ethnic groups. The burden of CV risk factors is higher in African-Americans than in whites in the US [71], and exposure to air pollutants was higher for African-American participants than white participants and higher for those living in census tracts with high African-American populations [72]. While previous studies have investigated effect modification by race/ethnicity of the association between air pollution and health outcomes, there does not appear to be consistent evidence of it [73]. Additional work will be needed to replicate or further explore these results.

Despite the careful measurement of pollutants and cardiac structure and function, this study has several limitations. As Figure 3.2 illustrates, a large proportion of the variability in air pollution concentrations existed between, rather than within, MESA sites. Because of this, adjustment for study site in regression models significantly limits the pollutant comparison range, which may decrease power to detect associations. Also, though we analyzed change in CMR measures between Exams 1 and 5, we did so at only two time points, as opposed to more frequent serial CMR measurements that might help us better understand rates of change in CMR measures. Our study is also subject to potential bias if participants selectively dropped out of the cohort due to death or frailty. Participants who did and those who did not drop out before Exam 5 had similar values of CMR measures, but those who returned to Exam 5 tended to be younger and healthier than those who did not.

In a large multi-ethnic cohort with pollutant exposure modeled from sophisticated, study-specific spatio-temporal models, we found mixed evidence of a cross-sectional association of higher $PM_{2.5}$ and NO_x concentrations with greater LVMI, and of higher NO_X with greater decrease in LV circumferential strain. We also demonstrated an association between greater O_3 exposure and lower cross-sectional LVMI. These findings suggest a role for NO_X, $PM_{2.5}$, and O_3 and cardiac remodeling in MESA, and additional work is needed to clarify that role and better understand the biological underpinnings of these associations.

Table 3.1: Characteristics at MESA Exams 1 (2000-2002) and 5 (2010-2012) of participants included in cross-sectional analyses.

	Exam 1 Participants	**Exam 5 Participants**	
	Exam 1 Values	Exam 1 Values	Exam 5 Values
N	4,825	2,811	2,811
Age, years, mean (SD)	61 (10)	60 (9)	69 (9)
Female, %	53	53	53
Height, cm, mean (SD)	167 (10)	167 (10)	166 (10)
Weight, lb, mean (SD)	170 (35)	171 (36)	169 (37)
Systolic Blood Pressure, mmHg, mean (SD)	125 (21)	123 (20)	123 (20)
Diastolic Blood Pressure, mmHg, mean (SD)	72 (10)	72 (10)	68 (10)
LDL Cholesterol, mg/dL, mean (SD)	117 (31)	118 (31)	107 (32)
Any Current Alcohol use, %	58	61	45
Smoking Status, %			
Never	53	53	47
Former	36	36	46
Current	12	11	7
Smoking Pack-Years, mean (SD)	11 (20)	10 (20)	10 (21)
Physical Activity, MET-min/wk, mean (SD)	4895 (4480)	4949 (4456)	4447 (4603)
Fasting Glucose, mmol/L, mean (SD)	95 (27)	94 (25)	100 (25)
Race/Ethnicity, %			
White	40	42	42
Chinese-American	13	13	13
African-American	25	25	25
Hispanic	21	20	20
Education, %			
< High School	15	12	12
Completed High School	17	16	16
Some College/Associates Degree	28	28	28
Bachelor's/Graduate/Professional Degree	40	43	20
Income <$25,000, %	28	23	25
Diabetes, %	11	9	17
Lipid-lowering medication, %	16	15	37
Hypertension medication, %	34	32	53
LV Mass Index, % predicted, mean (SD)	104 (16)	103 (16)	106 (18)
LV Mass to Volume Ratio, g/ml mean (SD)	0.9 (0.2)	0.9 (0.2)	1.0 (0.2)
LV Ejection Fraction, %, mean (SD)	63 (6)	63 (6)	62 (7)
LV Mean Circumferential Strain, %, mean(SD)	18 (3)	18 (3)	18 (3)
Δ LV Mass Index, % predicted, mean (SD)	N/A	N/A	3.0 (15.9)
Δ LV Mass to Volume Ratio, g/ml mean (SD)	N/A	N/A	0.1 (0.2)
Δ LV Ejection Fraction, %, mean (SD)	N/A	N/A	-0.7 (7.5)
Δ LV Mean Circumferential Strain, %, mean (SD)	N/A	N/A	0.2 (3.6)

LDL = low-density lipoprotein

MET-min = metabolic equivalent minutes
LV = left ventricular

Table 3.2: Estimated cross-sectional associations of fine particulate matter ($PM_{2.5}$), oxides of nitrogen (NO_X), and ozone (O_3), with cardiac magnetic resonance-derived measures at MESA Exams 1 (2000-2002) and 5 (2010-2012).

			Model 1*		Model 2**	
	Exposure	**Outcome**	**Coef. (95% CI)**	**P-Value**	**Coef. (95% CI)**	**P-Value**
Exam 1	$PM_{2.5}$ (per 5 ug/m^3)	LVMI (%)	-1.7 (-2.3, -1.0)	≤0.005	**1.6 (0.3, 2.9)**	**0.02**
		Mass/Volume Ratio (g/ml)	-0.03 (-0.03, -0.02)	≤0.005	-0.01 (-0.02, 0.00)	0.11
		Ejection Fraction (%)	0.35 (0.12, 0.58)	≤0.005	0.38 (-0.11, 0.88)	0.13
		LV Circumferential Strain (%)	-0.04 (-0.2, 0.12)	0.62	0.18 (-0.20, 0.55)	0.36
	NO_X (per 40ppb)	LVMI (%)	1.0 (0.2, 1.7)	0.01	**1.8 (0.3, 3.3)**	**0.02**
		Mass/Volume Ratio (g/ml)	-0.03 (-0.03, -0.02)	≤0.005	0.00 (-0.01, 0.02)	0.67
		Ejection Fraction (%)	0.36 (0.08, 0.64)	0.01	-0.31 (-0.88, 0.25)	0.28
		LV Circumferential Strain (%)	-0.40 (-0.60, -0.20)	≤0.005	0.19 (-0.21, 0.59)	0.35
	O_3 (per 10ppb)	LVMI (%)	-2.7 (-3.8, -1.5)	≤0.005	**-3.5 (-6.0, -1.0)**	**0.01**
		Mass/Volume Ratio (g/ml)	0.04 (0.03, 0.06)	≤0.005	0.02 (-0.01, 0.05)	0.15
		Ejection Fraction (%)	-0.86 (-1.30, -0.42)	≤0.005	-0.30 (-1.25, 0.64)	0.53
		LV Circumferential Strain (%)	0.67 (0.27, 1.06)	≤0.005	-0.30 (-1.15, 0.54)	0.48

LVMI = Left Ventricular Mass Index, NO_X = oxides of nitrogen, O_3 = ozone, $PM_{2.5}$ = particulate matter < 2.5um, ppb = parts per billion

*Model 1 includes height, weight, & sex (except for LVMI), race/ethnicity, income, education, LDL cholesterol, lipid-lowering medication use, physical activity, current smoking and pack-year history of smoking, second-hand smoke exposure, diabetes status by fasting glucose criteria, use of diabetes medications, SES, alcohol use, and systolic blood pressure

**Model 2 includes Model 1 + MESA study site

			Model 1*		Model 2**	
	Exposure	**Outcome**	**Coef. (95% CI)**	**P-Value**	**Coef. (95% CI)**	**P-Value**
Exam 5	$PM_{2.5}$ (per 5 ug/m^3)	LVMI (%)	4.9 (2.4, 7.3)	≤0.005	2.0 (-1.1, 5.0)	0.21
		Mass/Volume Ratio (g/ml)	-0.04 (-0.07, -0.02)	≤0.005	-0.03 (-0.06, 0.01)	0.14
		Ejection Fraction (%)	-0.84 (-1.81, 0.13)	0.09	-0.66 (-1.87, 0.55)	0.28
		LV Circumferential Strain (%)	1.13 (0.73, 1.53)	≤0.005	0.36 (-0.13, 0.85)	0.15
	NO_X (per 40ppb)	LVMI (%)	5.0 (3.2, 6.9)	≤0.005	2.4 (-0.8, 5.6)	0.14
		Mass/Volume Ratio (g/ml)	-0.01 (-0.03, 0.01)	0.34	-0.00 (-0.04, 0.04)	0.88
		Ejection Fraction (%)	-1.00 (-1.73, -0.28)	0.01	-0.71 (-1.98, 0.55)	0.27
		LV Circumferential Strain (%)	0.95 (0.65, 1.25)	≤0.005	-0.08 (-0.59, 0.44)	0.78
	O_3 (per 10ppb)	LVMI (%)	-5.2 (-7.1, -3.2)	≤0.005	-2.6 (-5.4, 0.2)	0.07
		Mass/Volume Ratio (g/ml)	-0.00 (-0.03, 0.02)	0.75	0.01 (-0.02, 0.04)	0.55
		Ejection Fraction (%)	0.89 (0.12, 1.66)	0.02	0.37 (-0.75, 1.48)	0.52
		LV Circumferential Strain (%)	-0.86 (-1.18, -0.54)	≤0.005	-0.16 (-0.61, 0.30)	0.50

LVMI = Left Ventricular Mass Index, NO_X = oxides of nitrogen, O_3 = ozone, $PM_{2.5}$ = particulate matter < 2.5um, ppb = parts per billion

*Model 1 includes height, weight, & sex (except for LVMI), race/ethnicity, income, education, LDL cholesterol, lipid-lowering medication use, physical activity, current smoking and pack-year history of smoking, second-hand smoke exposure, diabetes status by fasting glucose criteria, use of diabetes medications, SES, alcohol use, and systolic blood pressure

**Model 2 includes Model 1 + MESA study site

Table 3.3: Estimated associations of distance from participant residential addresses to major roads with cardiac magnetic resonance-derived measures at MESA Exams 1 (2000-2002) and 5 (2010-2012)

		Exam 1 (2000 – 2002)		Exam 5 (2010 – 2012)	
	Distance to Major Road	**Coef. (95% CI)***	**P-Value**	**Coef. (95% CI)***	**P-Value**
LVMI (%)	>150	Ref.	N/A	Ref.	N/A
	100-149	0.9 (-0.5, 2.2)	0.21	1.7 (-0.4, 3.8)	0.11
	50-99	0.3 (-1.0, 1.6)	0.68	0.0 (-2.0, 2.1)	0.97
	<50	1.1 (-0.1, 2.2)	0.08	1.0 (-0.8, 2.8)	0.28
Mass/Volume Ratio (g/ml)	>150	Ref.	N/A	Ref.	N/A
	100-149	-0.00 (-0.02, 0.01)	0.82	0.01 (-0.01, 0.04)	0.24
	50-99	-0.00 (-0.02, 0.01)	0.50	0.02 (-0.01, 0.04)	0.15
	<50	0.01 (-0.00, 0.02)	0.16	0.02 (-0.00, 0.04)	0.06
Ejection Fraction (%)	>150	Ref.	N/A	Ref.	N/A
	100-149	-0.13 (-0.64, 0.38)	0.61	-0.05 (-0.88, 0.79)	0.92
	50-99	-0.11 (-0.60, 0.38)	0.66	0.08 (-0.73, 0.89)	0.85
	<50	0.21 (-0.24, 0.66)	0.37	0.24 (-0.47, 0.96)	0.50
LV Circumferential Strain (%)	>150	Ref.	N/A	Ref.	N/A
	100-149	0.01 (-0.37, 0.39)	0.96	0.04 (-0.28, 0.37)	0.79
	50-99	-0.01 (-0.38, 0.37)	0.97	0.16 (-0.16, 0.47)	0.33
	<50	0.15 (-0.20, 0.49)	0.40	0.01 (-0.27, 0.29)	0.93

LVMI = Left Ventricular Mass Index

***** All models adjusted for height, weight, & sex (except for LVMI), race, site, income, education, LDL cholesterol, lipid-lowering medication use, physical activity, current smoking and pack-year history of smoking, second-hand smoke exposure, diabetes status by fasting glucose criteria, use of diabetes medications, SES, alcohol use, and systolic blood pressure

Table 3.4: Estimated associations of average concentrations of fine particulate matter ($PM_{2.5}$), oxides of nitrogen (NO_X), and ozone (O_3), in the 10 years between MESA Exams 1 (2000-2002) and 5 (2010-2012) with changes in cardiac magnetic resonance-derived measures

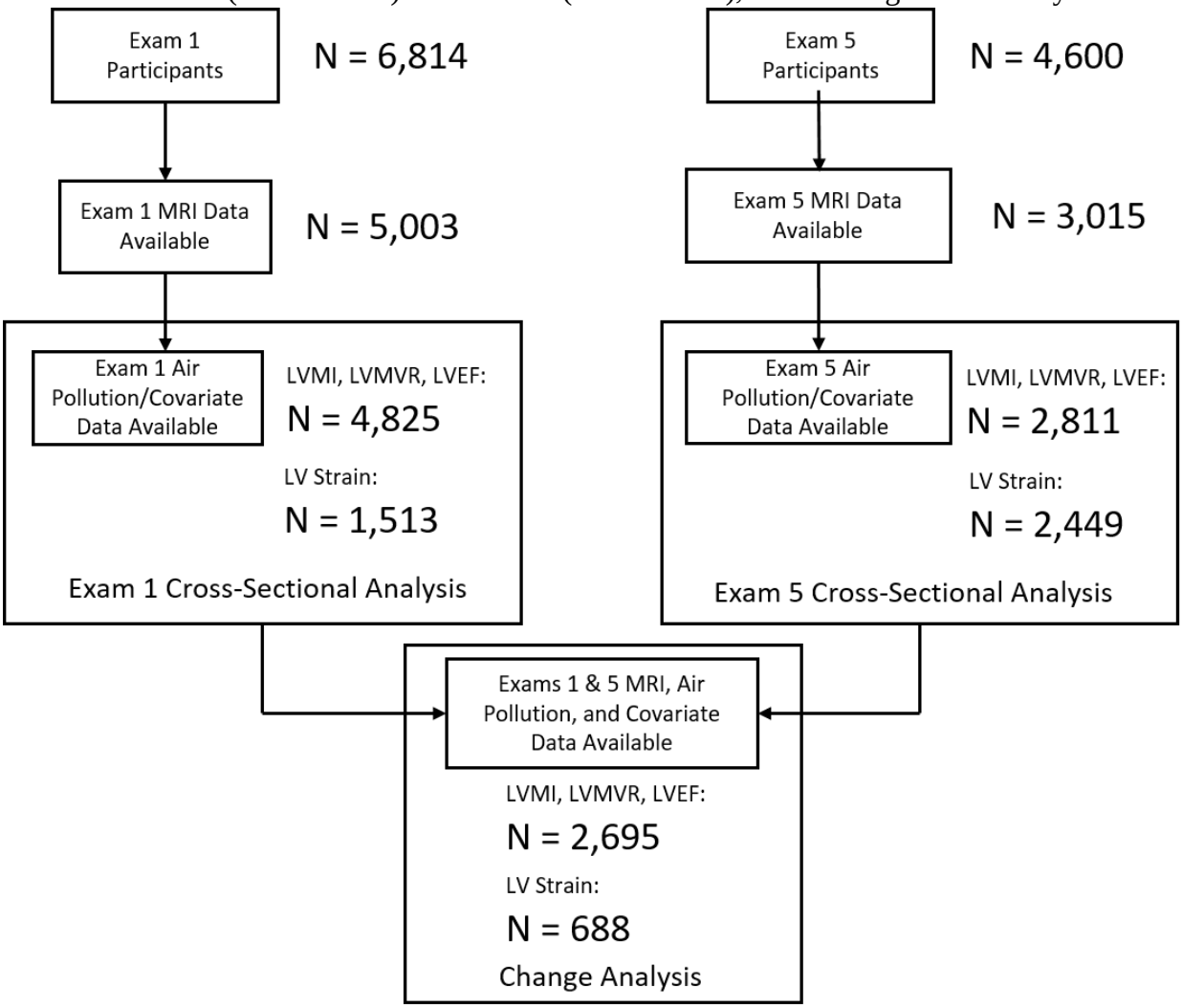
		Model 1*		Model 2**	
Exposure	**Outcome**	**Coef. (95% CI)**	**P-value**	**Coef. (95% CI)**	**P-value**
$PM_{2.5}$ (per 5 ug/m^3)	Δ LVMI (%)	3.75 (2.40, 5.11)	≤0.005	-0.73 (-3.32, 1.85)	0.58
	Δ Mass/Volume Ratio (g/ml)	-0.03 (-0.05, -0.01)	≤0.005	-0.03 (-0.06, 0.01)	0.12
	Δ Ejection Fraction (%)	-0.43 (-1.03, 0.18)	0.17	-0.86 (-2.00, 0.29)	0.14
	Δ LV Circumferential Strain (%)	0.77 (0.22, 1.32)	0.01	-0.44 (-1.39, 0.52)	0.37
NO_X (per 40ppb)	Δ LVMI (%)	3.01 (1.61, 4.42)	≤0.005	-0.16 (-3.06, 2.74)	0.91
	Δ Mass/Volume Ratio (g/ml)	0.00 (-0.02, 0.02)	0.86	0.00 (-0.03, 0.04)	0.89
	Δ Ejection Fraction (%)	-0.99 (-1.56, -0.41)	≤0.005	-0.36 (-1.47, 0.75)	0.53
	Δ LV Circumferential Strain (%)	0.61 (0.16, 1.07)	0.01	**-0.87 (-1.69, -0.05)**	**0.04**
O_3 (per 10ppb)	Δ LVMI (%)	-4.17 (-6.16, -2.18)	≤0.005	-3.30 (-6.72, 0.13)	0.06
	Δ Mass/Volume Ratio (g/ml)	-0.02 (-0.05, 0.00)	0.08	-0.02 (-0.07, 0.02)	0.32
	Δ Ejection Fraction (%)	1.70 (0.82, 2.58)	≤0.005	0.64 (-0.86, 2.15)	0.40
	Δ LV Circumferential Strain (%)	-1.17 (-1.86, 0.48)	≤0.005	0.58 (-0.60, 1.77)	0.33

LVMI = Left Ventricular Mass Index, NO_X = oxides of nitrogen, O_3 = ozone, $PM_{2.5}$ = particulate matter < 2.5um, ppb = parts per billion

*Model 1 includes height, weight, & sex (except for LVMI), baseline outcome measure, race/ethnicity, income, education, LDL cholesterol, lipid-lowering medication use, physical activity, current smoking and pack-year history of smoking, second-hand smoke exposure, diabetes status by fasting glucose criteria, use of diabetes medications, SES, alcohol use, and systolic blood pressure

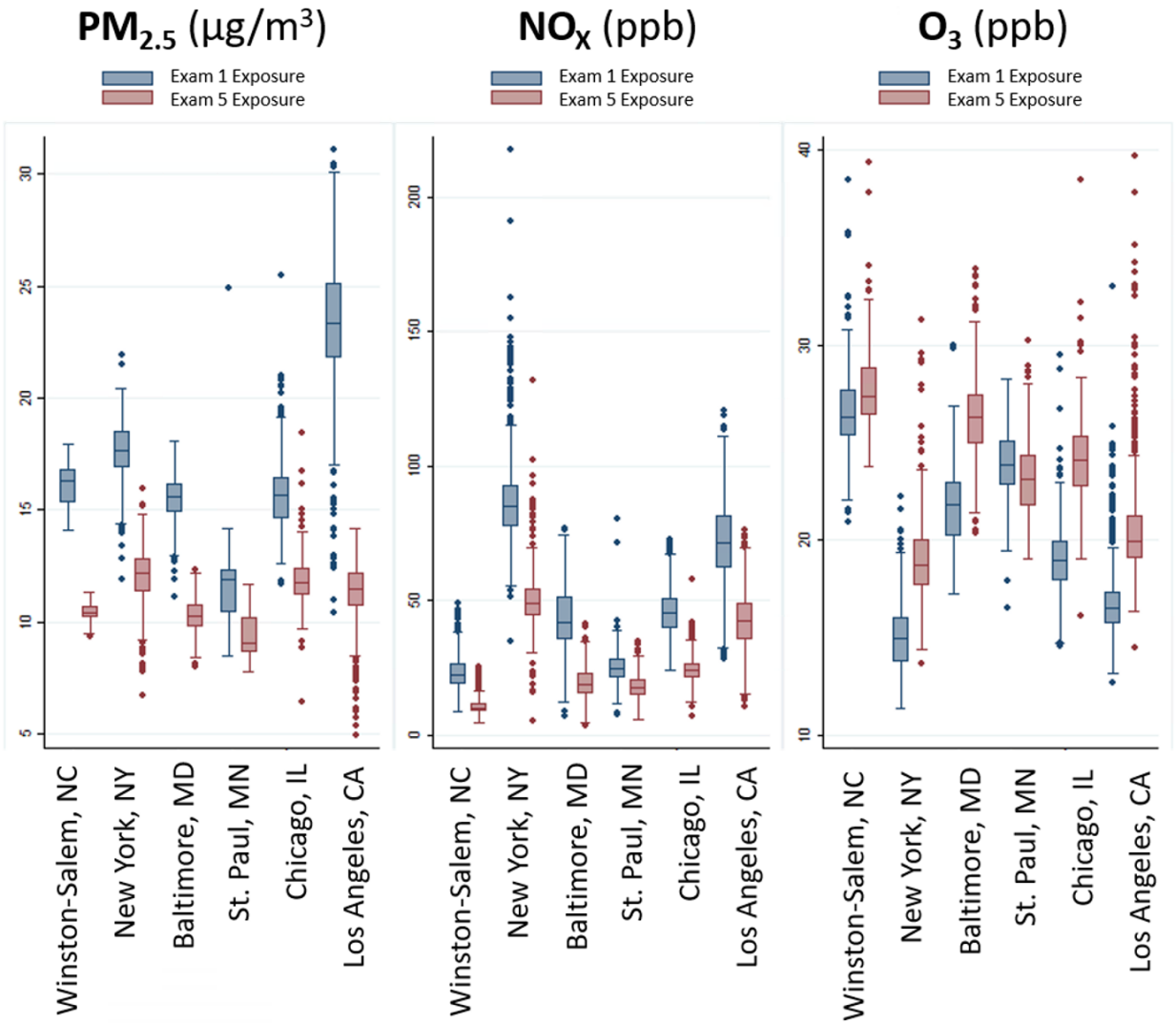
**Model 2 includes Model 1 + MESA study site

Figure 3.1: Flow chart indicating available data and analysis sample for cross-sectional analyses at MESA Exam 1 (2000 – 2002) and Exam 5 (2010 – 2012), and for longitudinal analyses.



LVMI = Left Ventricular Mass Index
LVMVR = Left Ventricular Mass-to-Volume Ratio
LVEF = Left Ventricular Ejection Fraction
MRI = Magnetic Resonance Imaging

Figure 3.2: Ambient concentrations of fine particulate matter ($PM_{2.5}$), oxides of nitrogen (NO_X), and ozone (O_3) at MESA participant addresses in the year preceding Exam 1 (2000 – 2002) and the year preceding Exam 5 (2010 – 2012), by MESA study site



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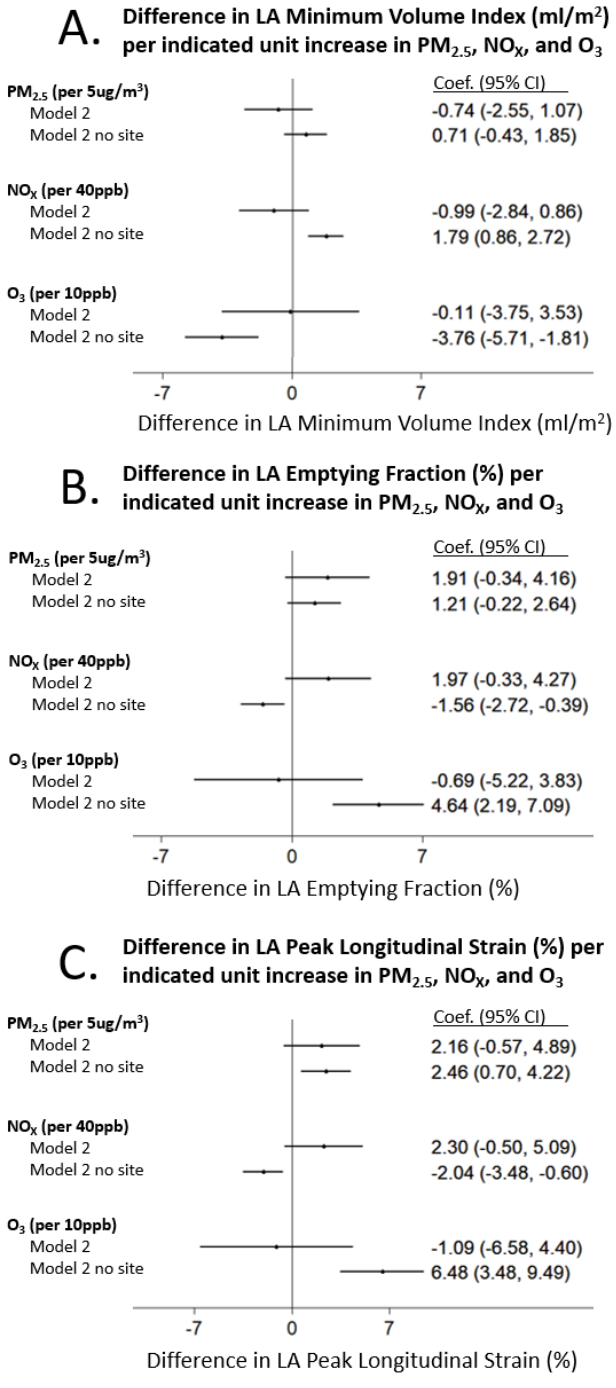
Supplementary Material:

Supplementary Table 2.1: Multi-pollutant modeled regression results for associations of fine particulate matter ($PM_{2.5}$), oxides of nitrogen (NO_X), and ozone (O_3) with presence of atrial fibrillation during monitoring.

Pollutants in Model*	Pollutant	Odds Ratio for Atrial Fibrillation (95%CI)	P-Value
$PM_{2.5}$, NO_X	$PM_{2.5}$ (per 5ug/m^3)	0.98 (0.55, 1.74)	0.94
	NO_X (per 40ppb)	**0.28 (0.09, 0.94)**	**0.04**
$PM_{2.5}$, O_3	$PM_{2.5}$ (per 5ug/m^3)	0.81 (0.47, 1.38)	0.44
	O_3 (per 10ppb)	**1.61 (1.11, 2.36)**	**0.01**
NO_X, O_3	NO_X (per 40ppb)	0.50 (0.15, 1.66)	0.26
	O_3 (per 10ppb)	1.41 (0.91, 2.19)	0.12
$PM_{2.5}$, NO_X, O_3	$PM_{2.5}$ (per 5ug/m^3)	0.91 (0.51, 1.64)	0.76
	NO_X (per 40ppb)	0.55 (0.15, 2.00)	0.36
	O_3 (per 10ppb)	1.43 (0.92, 2.21)	0.11

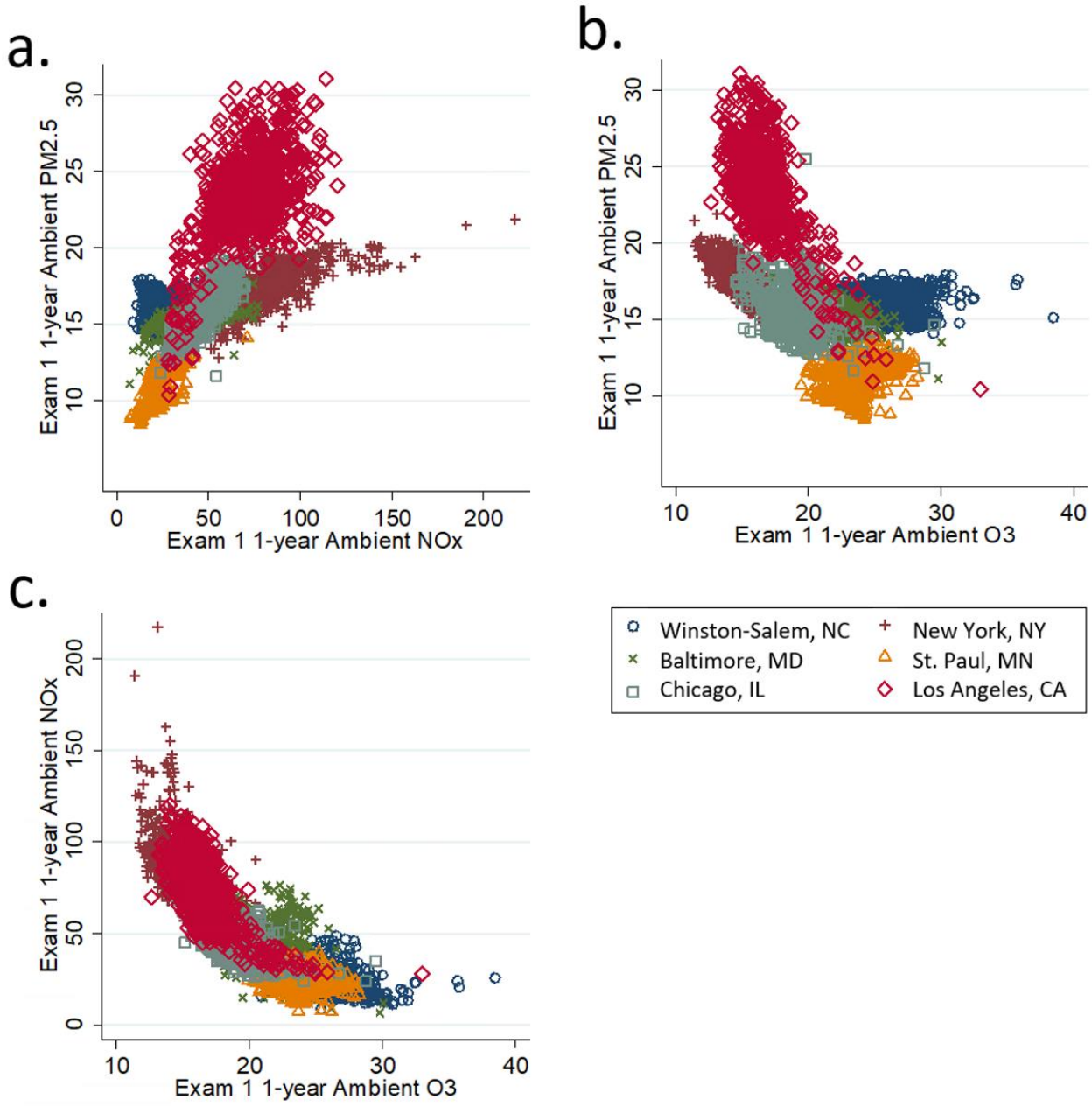
*Models include age, height, weight, sex, race/ethnicity, and MESA study site, and indicated pollutant concentrations
ppb = parts per billion

Supplementary Figure 1.1: Associations of fine particulate matter ($PM_{2.5}$), oxides of nitrogen (NO_X), and ozone (O_3), with LA minimum volume (A), LA emptying fraction (B), and LA global longitudinal strain (C) with and without study site adjustment

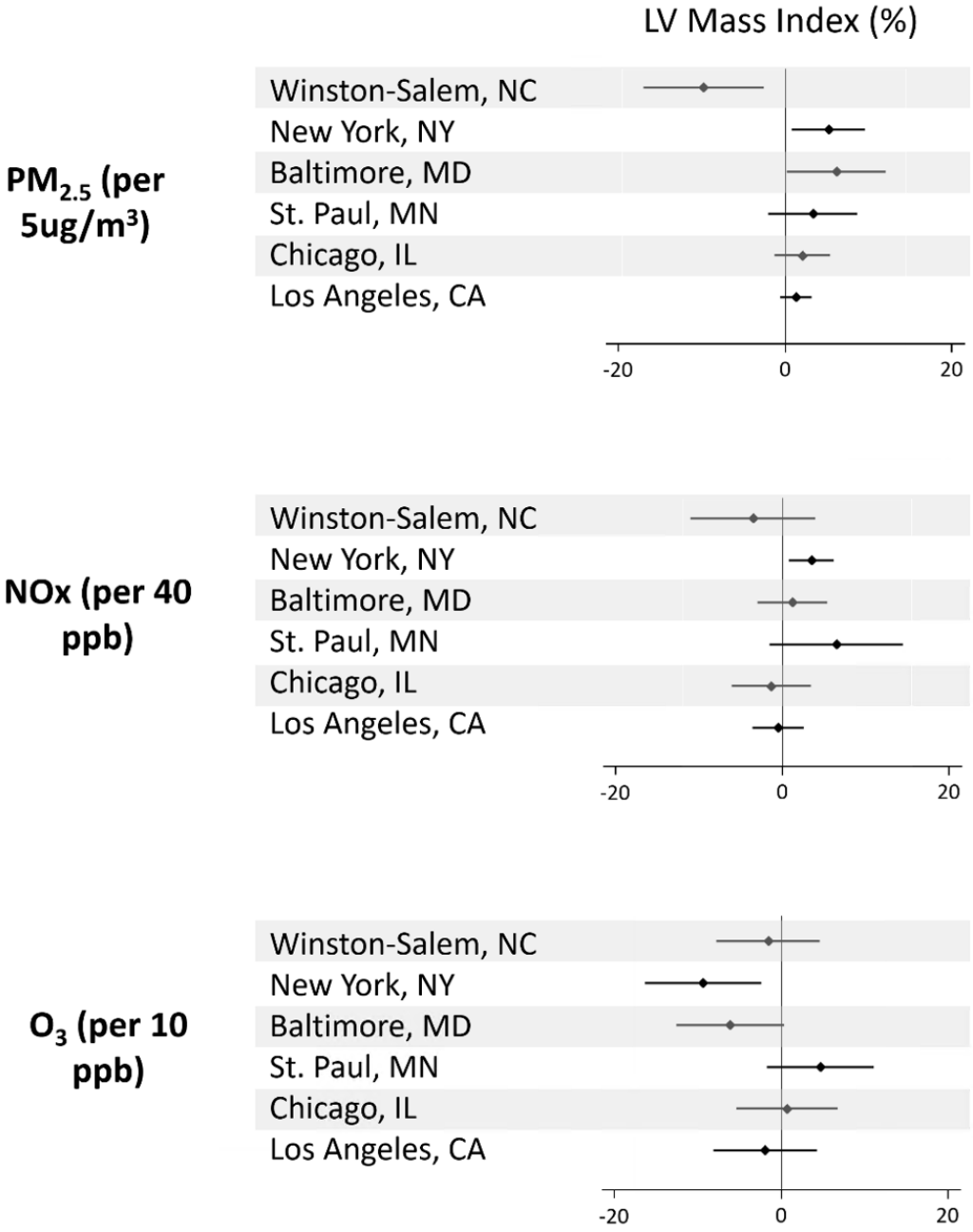


LA = left atrial; ppm = parts per million
Model 2 includes: age, height, weight, race/ethnicity, sex, study site, self-reported household income, census tract-level socioeconomic status, educational attainment, smoking history, diabetes, LDL cholesterol, lipid-lowering medication, and physical activity

Supplementary Figure 3.1: Scatterplots indicating relationships between ambient concentrations of (a) fine particulate matter ($PM_{2.5}$) and oxides of nitrogen (NO_X), (b) $PM_{2.5}$ and ozone (O_3), and (c) NO_X and O_3 in the year prior to MESA Exam 1 (2000 – 2002)

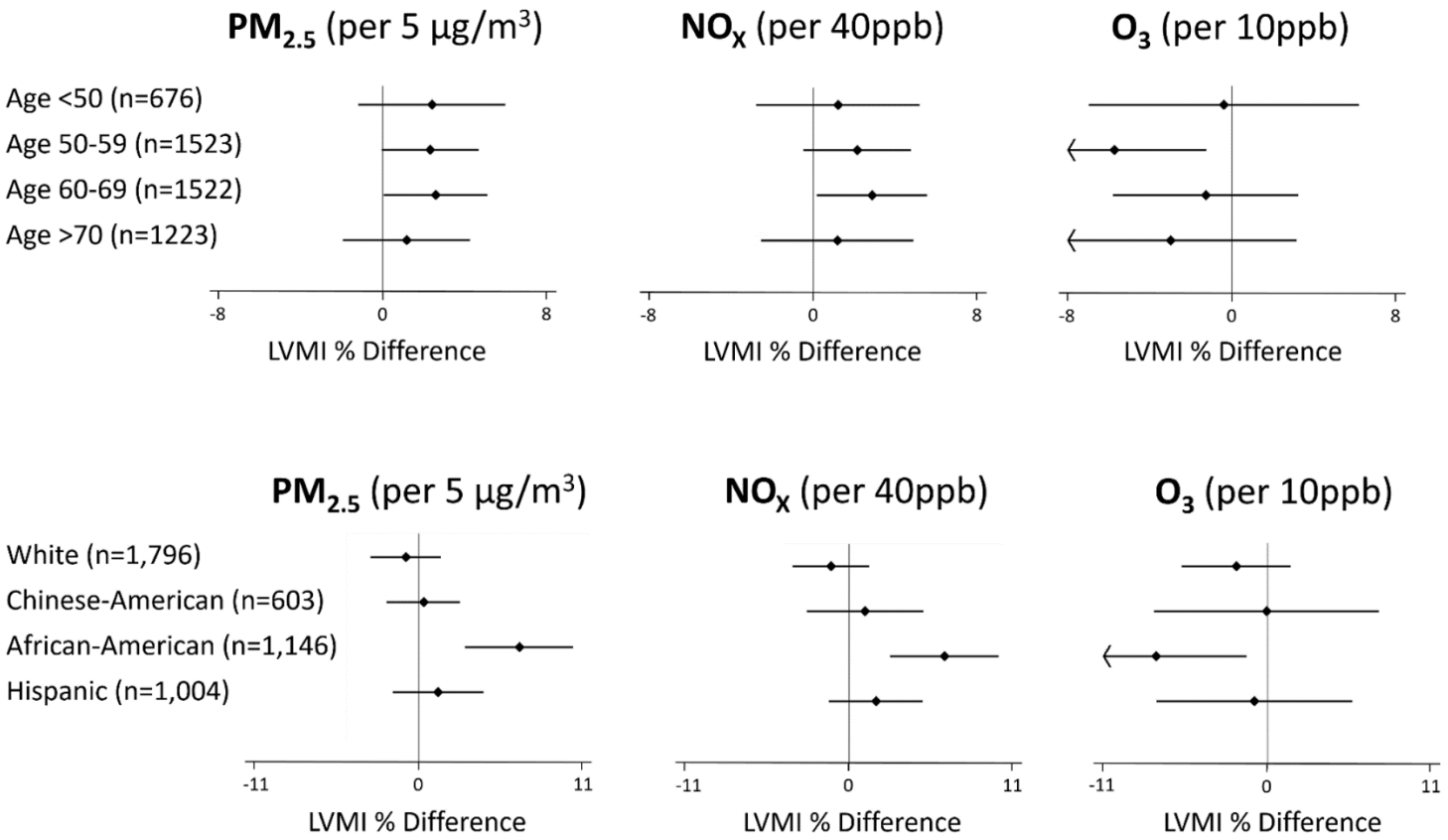


Supplementary Figure 3.2: Associations of fine particulate matter ($PM_{2.5}$), oxides of nitrogen (NO_X), and ozone (O_3), with cardiac magnetic resonance-derived measures at MESA Exam 1* (2000-2002) stratified by study site



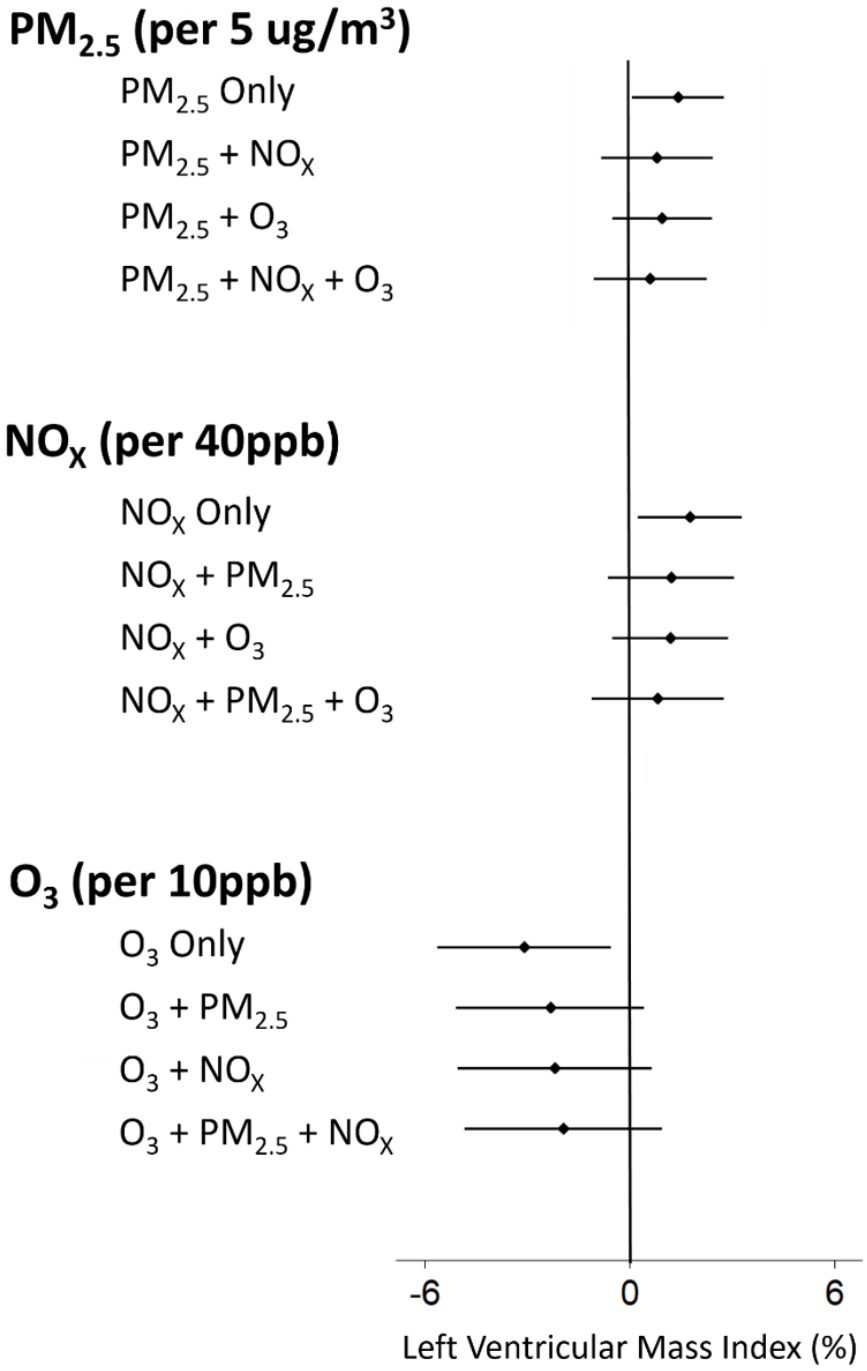
*All models adjusted for age, race/ethnicity, systolic & diastolic blood pressure, LDL cholesterol, smoking status & pack-years, second-hand smoke exposure, physical activity, fasting blood glucose, alcohol use, education history, income, lipid-lowering medication, hypertension medication, diabetes, and indicated pollutant concentrations

Supplementary Figure 3.3: Exam 1 cross-sectional associations of fine particulate matter ($PM_{2.5}$), oxides of nitrogen (NO_X), and ozone (O_3), with left ventricular mass index* by age and race/ethnicity strata



*All models adjusted for age, race/ethnicity (except race/ethnicity-stratified results), systolic & diastolic blood pressure, LDL cholesterol, smoking status & pack-years, second-hand smoke exposure, physical activity, fasting blood glucose, alcohol use, education history, income, lipid-lowering medication, hypertension medication, diabetes, MESA site, and indicated pollutant concentrations

Supplementary Figure 3.4: Associations of fine particulate matter ($PM_{2.5}$), oxides of nitrogen (NO_X), and ozone (O_3) with left ventricular mass index at Exam 1 (2000 – 2002), when including multiple pollutants simultaneously in regression models*



*All models adjusted for age, race/ethnicity, systolic & diastolic blood pressure, LDL cholesterol, smoking status & pack-years, second-hand smoke exposure, physical activity, fasting blood glucose, alcohol use, education history, income, lipid-lowering medication, hypertension medication, diabetes, MESA site, and indicated pollutant concentrations