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Traffic Related Air Pollution and the Right Ventricle: The Multi-Ethnic Study of Atherosclerosis

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Title: Traffic Related Air Pollution and the Right Ventricle: The Multi-Ethnic Study of Atherosclerosis

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At a glance commentary:

Scientific knowledge on the subject

Exposure to traffic-related air pollution has been linked to left ventricular hypertrophy, heart failure, and death. The lungs have substantial exposure to traffic-related pollutants; however, relationships between traffic-related air pollutants and right ventricular morphology have not been established.

What the study adds to the field

Higher levels of traffic-related air pollution, estimated by exposure to oxides of nitrogen, are associated with greater right ventricular mass and larger volumes. This relationship was not dependent on differences in left ventricular mass or volumes, systemic inflammation, roadway noise or lung disease.

Data supplement: This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org.

Abstract

Rationale: Right heart failure is a cause of morbidity and mortality in common and rare heart and lung diseases. Exposure to traffic-related air pollution is linked to left ventricular hypertrophy, heart failure and death. Relationships between traffic-related air pollution and right ventricular (RV) structure and function have not been studied.

Objective: To characterize the relationship between traffic-related air pollutants and RV structure and function.

Methods: We included men and women with magnetic resonance imaging (MRI) assessment of RV structure and function and estimated residential outdoor nitrogen dioxide (NO_2) concentrations from the Multi-Ethnic Study of Atherosclerosis, a study of individuals free of clinical cardiovascular disease at baseline. Multivariable linear regression estimated associations between NO_2 exposure (averaged over the year prior to MRI) and measures of RV structure and function after adjusting for demographics, anthropometrics, smoking, diabetes mellitus and hypertension. Adjustment for corresponding left ventricular (LV) parameters, traffic-related noise, markers of inflammation and lung disease were considered in separate models. Secondary analyses considered oxides of nitrogen (NO_x) as the exposure.

Measurements and Main Results: The study sample included 3,896 participants. In fully adjusted models, higher NO_2 was associated with greater RV mass and larger RV end-diastolic volume with or without further adjustment for corresponding LV parameters, traffic-related noise, inflammatory markers, or lung disease (all $p < 0.05$). There was no association between NO_2 and RV ejection fraction. Relationships between NO_x and RV morphology were similar.

Conclusion: Higher levels of NO_2 exposure were associated with greater RV mass and larger RV end-diastolic volume.

Word count: 250; **MeSH Terms:** Air pollutants, pulmonary circulation, heart ventricles, pulmonary hypertension

Introduction

Right heart failure is a cause of morbidity and mortality in obstructive and restrictive lung disease, left ventricular dysfunction, and pulmonary arterial hypertension.[1-3] Right ventricular (RV) hypertrophy is also associated with increased risk for heart failure and cardiovascular death in community dwelling adults without known cardiac disease at baseline.[4] Despite important epidemiologic and clinical roles of the RV, little is known about modifiable determinants of RV structure and function.[5]

Traffic-related air pollution is linked to left ventricular hypertrophy, heart failure and cardiovascular death.[6,7] Air pollution may affect the left ventricle through inflammation, oxidative stress, and autonomic dysfunction and these mechanisms could also affect the RV.[8-10] The lungs have substantial exposure to traffic-related air pollution and inhalants, which may directly increase RV afterload and lead to disproportionately greater changes in the RV compared to the left ventricle.[11,12] The impact of traffic-related air pollution on the RV, however, is not well-studied.

We examined the relationship between nitrogen dioxide (NO_2), a surrogate for traffic-related air pollution, and magnetic resonance imaging (MRI) measures of RV structure and function in a multi-ethnic cohort of adults free of clinical cardiovascular disease. We hypothesized that increased exposure to NO_2 would be independently associated with greater RV mass and larger RV end-diastolic volume. Some of the results in these studies have been previously reported in the form of an abstract.[13]

Methods

The Multi-Ethnic Study of Atherosclerosis (MESA) is a multicenter prospective cohort study designed to investigate subclinical cardiovascular disease in whites, African-Americans, Hispanics and Chinese-Americans.[14] Exclusion criteria included clinical cardiovascular disease (physician diagnosed heart attack, stroke, transient ischemic attack, heart failure, angina, current atrial fibrillation, any cardiovascular procedure), weight >136kg (300 lbs.), pregnancy, or impediment to long-term participation. The Environmental Protection Agency funded a large ancillary study to MESA, the Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA Air), which added cohort-specific air pollution monitoring and modeling.[15] The MESA-RV study was an ancillary study funded to interpret cardiac MRIs for RV function. Individual participants gave informed consent and the Institutional Review Boards of participating institutions approved the protocols of MESA and all studies described herein.

Traffic-related air pollution exposure

Participants' residential address was assigned geographic coordinates using ArcGIS 9.1 software (ESRI, Redlands, CA) in conjunction with Dynamap/2000 street network and geocoding database (Tele Atlas, Boston, MA). Using weighted averages of residential addresses over the year prior to cardiac MRI, individual outdoor home exposure to NO_2 and NO_x were estimated using spatio-temporal modeling and maximized via maximum likelihood (Figure 1).[16,17] Estimates were fit using monitoring data from the Environmental Protection Agencies Air Quality System database and extensive cohort-specific air monitoring including home-based monitoring conducted as part of MESA Air.[18] Geographical variables incorporated into the model included information on land use (e.g., industrial, residential), vegetative index, distance

to various features (e.g., airports, coastline), road density, population density, elevation, urban topography, emissions sources, and dispersion model outputs integrating road position, traffic volume, diurnal traffic patterns and meteorology.

Cardiac magnetic resonance imaging measures

Methods for acquisition and interpretation of LV and RV MRI parameters have been previously reported.[19,20] Endocardial and epicardial borders of the RV were manually traced on short axis cine images at end-systole and end-diastole. The outflow tract was included in RV volume. Papillary muscle and trabeculae were included in RV volumes and excluded from RV mass, as is commonly done for LV mass.[21,22] RV end-systolic volume and RV end-diastolic volume (RVEDV) were calculated using Simpson's rule by summation of areas on each slice multiplied by the sum of slice thickness and image gap. RV mass was determined at end-diastole as the difference between RV free wall end-diastolic epicardial and endocardial volumes multiplied by the specific gravity of the heart (1.05g/mL). RVEF was calculated by subtracting RV end-systolic volume from RVEDV and dividing this difference by RVEDV.

Covariables

Covariables including age, sex, race/ethnicity, height, weight, education, income, presence of hypertension or diabetes mellitus, fasting plasma glucose, cholesterol, systolic blood pressure, smoking status and pack-years, percent emphysema (obtained by chest CT), and self-reported lung disease (asthma and/or emphysema) were measured as previously described.[23] Because levels of air pollution within a neighborhood are correlated over time, self-reported time a participant lived in the index neighborhood (the residential neighborhood used to determine one

year pollutant estimates) was used as a surrogate for exposure duration.[8] Participants reported roadway noise as a: "very serious problem", "somewhat serious problem", "minor problem", or "not really a problem."

Statistical Analysis

We used linear regression to characterize relationships between NO_2 and RV parameters. All models were adjusted for height and weight, so it was not necessary to index RV parameters to account for differences in body size. Covariables were chosen *a priori* on the basis of known associations with ventricular size, heart disease and comorbidities. In limited models, we adjusted for age, sex, race/ethnicity, height and weight.[24] In fully adjusted models, we also included MESA field center, markers of socioeconomic status (self-reported income and education), and cardiovascular risk factors including smoking status, smoking pack-years, hypertension, cholesterol, diabetes mellitus, and impaired glucose tolerance. In pre-specified models, we further adjusted for LV parameters, self-reported roadway noise, markers of inflammation (C-reactive protein and interleukin-6), or lung structure (% emphysema) and self-reported lung disease in separate models.

The primary analysis examined the relationship between RV parameters and NO_2 averaged over the year prior to cardiac MRI. Sensitivity analyses used fixed-year estimates of NO_2 in 2000, 2001 and 2002 to ensure there was no artifice in timing of the MRI in relation to secular exposure trends. Secondary analyses in limited and fully adjusted models used NO_x as the exposure of interest, which includes other components of the traffic-related air pollutant mix.

Several exploratory models further evaluated the relationship between NO_2 and RV metrics. Duration and timing of exposure were considered using a sliding time window

analysis.[25] We estimated associations between NO_2 and RV parameters in 5-year 'time windows' (e.g. participants who lived in the index neighborhood for between 1 and 6 years). The time window was then shifted by one year (e.g. participants who lived in the neighborhood between 2 and 6 years) and new estimates of association and 95% confidence intervals were calculated. Overlapping 5-year periods avoid unstable estimates based on sparse data for a single calendar year and may more appropriately characterize the biologically relevant duration of exposure. Further exploratory models evaluated whether age, sex, or study site modified the association between NO_2 and RV parameters. We performed sensitivity analyses adjusting for body mass index category (normal weight and category 1 – 3 overweight) instead of height and weight to evaluate for residual confounding by obesity. Analyses were performed using STATA 12.0 (StataCorp, College Station, TX, USA).

Results

There were 6,814 men and women enrolled in MESA (see Figure E1 in the online supplement) of whom 5,098 underwent cardiac MRI and 5,004 (98%) had interpretable exams for the LV. Of 4,634 participants selected for MESA-RV, MRI reads were attempted in 4,484 participants before achieving the study goal of 4,204 participants (94% of attempted reads). Outdoor exposure to NO_2 was estimated in 4,095 of these participants (97%). One hundred ninety-nine participants were excluded for missing covariables leaving 3,896 in the study sample. Table 1 shows characteristics of the study sample compared with those excluded. The mean age of the study sample was 61.4 years and 52.6% were women. Mean RV mass in the study sample was 21.1 ± 4.4 g, mean RVEDV was 124.2 ± 30.8 mL and mean RVEF was 70.5 ± 6.4 %. Mean NO_2 was 21.8 ± 10.3 ppb with an interquartile range (IQR) from 13.9 to 31.0 ppb.

For individual cities the mean NO_2 ranged from 10.1 to 32.7 ppb and the city-specific IQR ranged from 3.1 to 5.0 ppb (Figure E2 in the online supplement).

Higher NO_2 was associated with greater RV mass (0.4 g for an interquartile increase in NO_2)(Table 2, Figure 2). This relationship became stronger after adjustment for city (0.9 g for an interquartile increase in NO_2) and after full adjustment for cardiovascular risk factors (1.0 g for an interquartile increase in NO_2). This amounted to ~5% increase in RV mass per interquartile increase in NO_2. This significant association did not change with further adjustment for LV mass, traffic-related noise, inflammatory markers, or lung disease (Table 2 & E1 in the online supplement).

Higher NO_2 was associated with larger RVEDV (2.9 mL for an interquartile increase in NO_2)(Table 2, Figure 2). This relationship became stronger after full adjustment for potential confounding by cardiovascular risk factors (4.1 mL for an interquartile increase in NO_2). This amounted to ~3% increase in RVEDV per interquartile increase in NO_2. The significant association remained with further adjustment for LV end-diastolic volume, traffic-related noise, inflammatory markers, or lung disease (Table 2 & E1 in the online supplement). NO_2 was not associated with RVEF (Table 2, Figure 2).

Secondary analyses using NO_x as the exposure of interest suggested relationships similar to those for NO_2 but were in all cases modestly attenuated compared to NO_2 (Table E3 in the online data supplement). RVEDV was not consistently associated with NO_x.

For participants with residential stability estimates (3,892 of 3,896 participants), sliding time window analyses indicated that participants who lived in the neighborhood several years before the MRI had incrementally stronger associations between NO_2 and RV mass then did those who lived in the neighborhood for a shorter duration (Figure 3 and Table E2 in the online

supplement). An incremental increase in RVEDV with participant duration in the neighborhood was less clear (Figure 3 and Table E2 in the online supplement). Choice of the NO_2 reference period (calendar year 2000, 2001 or 2002) did not meaningfully impact the relationship between NO_2 and RV parameters (Table E4 in the online data supplement).

Participant age did not modify relationships between NO_2 and RV parameters. The relationships of NO_2 with RV mass may have been stronger in men (1.3 g [95% CI: 0.4 to 2.2 g] per interquartile increase in NO_2) then women (0.6 g [95% CI: -0.1 to 1.3 g] per interquartile increase in NO_2)(p for interaction=0.03). Similarly, the relationship of NO_2 with RVEDV may have been stronger in men (5.5 mL [95% CI: -0.3 to 11.2 mL] per interquartile increase in NO_2) than women (2.1 mL [95% CI: -2.2 to 6.5 mL] per interquartile increase in NO_2)(p for interaction=0.04).

Participant city modified the relationship between NO_2 and RV mass (p for interaction <0.001), but not RVEDV (p for interaction=0.33). Qualitative associations between NO_2 and RV mass were in the same direction as the main association in St. Paul (6.4 g [95% CI: 4.1 to 8.8 g] per interquartile increase in NO_2), Los Angeles (0.9 g [95% CI: -0.1 to 1.9 g] per interquartile increase in NO_2), Baltimore (0.4 g [95% CI: -1.2 to 1.9 g] per interquartile increase in NO_2) and Chicago (0.3 g [95% CI: -1.0 to 1.6 g] per interquartile increase in NO_2). Qualitative associations were in the opposite direction as the main association in New York (-0.2 g [95% CI: -1.5 to 1.1 g] per interquartile increase in NO_2) and Winston-Salem (-0.4 g [95% CI: -2.6 to 1.8 g] per interquartile increase in NO_2). Because of the strong associations for St. Paul, we then excluded participants in cities with the greatest (St. Paul) and smallest (Winston-Salem) estimates of association between NO_2 and RV mass. The estimate of association in this four–city sample was smaller but qualitatively similar to the main analysis (0.5 g [95% CI -0.1 to 1.1 g] increase per

interquartile increase in NO_2, n=2738). Restricting this four-city sample to the sliding time window with the strongest association strengthened the relationship (1.3 g [95% CI -0.1 to 2.7 g] increase per interquartile increase in NO_2, n=476).

A sensitivity analysis adjusting for body mass index category, instead of the standard adjustment by height and weight, did not change the results of any analysis.

Discussion

We have shown that higher estimates of long-term outdoor residential NO_2 exposure are associated with greater RV mass and larger RVEDV in a multiethnic, multicity cohort of adults without clinical cardiovascular disease. MESA participants had a 1.0 g (5%) increase in RV mass and 4.1 mL (3%) increase in RVEDV with an interquartile increase in NO_2. This difference in RV mass is quantitatively similar to that seen in LV mass in MESA participants with diabetes (2.4%) and in current smokers (5.3%), supporting clinical and biologic relevance.[26,27] RV hypertrophy in MESA participants is associated with a three-fold increased risk for heart failure or cardiovascular death.[4] This is the first report to suggest traffic-related air pollutants, of which NO_2 is a well-recognized surrogate for the pollutant mix, is associated with morphologic changes in the right ventricle of the heart.

Our study provides initial insight into timing of this association. Duration of exposure to traffic-related air pollutants appears to be important. Participants who lived in the same neighborhood for several years had the strongest associations between NO_2 and RV mass. This suggests a dose-response, may provide insight for duration of necessary exposure, and supports a causal relationship.

The finding of both increased RV mass and RVEDV may suggest that the exposure of interest increased RV afterload.[28] Previous studies have suggested air pollution increases endothelin-1, a potent pulmonary vasoconstrictor,[29] which could lead to increased pulmonary vascular resistance, increased RV afterload and ultimately RV hypertrophy and dilation. Alternatively, air pollutants can irritate the respiratory epithelium and lead to heterogeneous ventilation with decreased regional ventilation.[30] Regional hypoxia can cause hypoxic pulmonary vasoconstriction, increased resistance and RV enlargement.[31] Increases in afterload may compound oxidative stress and autonomic dysfunction, which have been implicated in the relationship between air pollution and LV mass and could directly contribute to RV pathology.[8-10,32]

Other mechanisms are possible as well. Air pollution may up-regulate myocardial inflammatory genes and proteins in the RV.[33] While it is not feasible to study myocardial gene and protein profiles in such a large study of the general population, our findings remained after adjustment for C-reactive protein and interleukin-6 blood levels, which suggests that our findings were independent of systemic inflammation. Roadway noise, which accompanies traffic-related air pollution and may disrupt sleep, could mediate some aspects of the relationship between roadway proximity and heart disease.[34] Adjusting for traffic-related noise did not attenuate relationships between NO_2 and RV morphology in our analyses.

Air pollution has also been linked to obstructive lung disease severity, which could increase RV afterload leading to increased RV mass.[35,36] However, we have previously shown that increasing airflow obstruction is associated with decreased RVEDV in MESA.[37] In addition, adjustment for structural or self-reported lung disease did not change relationships between NO_2 and RV morphology in this analysis. Finally, LV mass may increase with traffic-related air

pollution and LV hypertrophy can contribute to diastolic dysfunction and increased RV afterload, potentially explaining our results.[6,38] However, adjusting for the LV did not affect the results.

Relationships between NO_x and RV morphology were similar, but mildly attenuated compared to those with NO_2. In addition, the relationship between NO_x and RVEDV was sensitive to adjustment. The NO_x analyses reinforce that the observed relationships are consistent with associations of a pollutant mix, not a specific pollutant, and that relationships between these pollutants and RV mass is stronger than relationships with RVEDV.

The association between NO_2 and RV mass was modified by city of residence. For example, participants in New York City did not appear to have a relationship between NO_2 and RV mass despite the highest exposure to NO_2. Heterogeneity by city is very common in air pollution research and was also seen in studies of LV mass and endothelial dysfunction.[6,39] Two key factors may contribute to city-specific heterogeneity. First, the validity of outdoor assessment of NO_2 as a surrogate for individual exposure to traffic-related pollutants depends on the degree to which outdoor pollution contributes to indoor pollution (e.g. home infiltration coefficient, indoor sources) and the proportion of time a participant spends indoors, outdoors, and in different micro-environments.[40] These complex relationships vary between cities as a function of culture, climate, cooking/ventilation patterns, and average building age, among other factors. Second, our estimates of NO_2 are best conceptualized as a pattern of spatial decay consistent with some but not all traffic-related pollutants. For example, participants' exposure to NO_2 also reflects exposure to other hazardous air pollutants such as benzene and several volatile organic compounds, levels of which may vary by city.[41]

This study has limitations. While we consider our exposure models to be a significant improvement over roadway proximity and nearest monitor analyses, measurement error and misclassification are likely present. Because error in exposure assignments is unlikely to be dependent on RV measurements, these errors may be non-differential with bias toward the null, so actual relationships may even be stronger than we have shown. Residual or unmeasured confounding, particularly at the neighborhood level, could contribute to the results. This may be especially true in the adjustment for exposure duration as neighborhood residents with long-term stability may differ from short-term residents. In the adjustment for road noise, measured or modeled noise would have been preferable to self-reports, but were not available. Furthermore, our study was cross-sectional and causality cannot be confirmed. Finally, measurement of invasive pulmonary hemodynamics, which may have informed the mechanism underlying our results, was not feasible in almost 4,000 community dwelling participants free of cardiovascular disease.

Summary

Higher estimated exposure to NO_2 is associated with greater RV mass and larger RVEDV. This relationship is independent of markers of socioeconomic status, cardiovascular risk factors, left sided cardiovascular disease, markers of inflammation and lung disease. This is the first report to implicate traffic-related air pollution with changes in right ventricular morphology. Air pollution may therefore play a role determining the RV response and outcomes in cardiopulmonary disease.

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Figure Legends

Figure 1 Representative map of Winston-Salem showing coarse and fine details of nitrogen dioxide predictions in parts per billion (ppb) from the spatio-temporal model including approximate MESA participant locations (jittered for privacy).

Figure 2. Multivariable non-parametric smoothed relationship between nitrogen dioxide (NO_2) in parts per billion (ppb) and right ventricular (RV) parameters with adjustment for age, sex, race/ethnicity, height, weight, city, education, income, smoking, pack-years, hypertension, diabetes, cholesterol, and impaired glucose tolerance. Grey lines represent 95% confidence bounds.

Figure 3. Relationship between the number of years a participant lived in their neighborhood and the difference in right ventricular (RV) mass or end-diastolic volume (EDV) per interquartile increase in nitrogen dioxide (NO_2): a sliding time window analysis of the full model (* $p \leq 0.05$).

Table 1. Characteristics of the study sample compared with the non-study subjects

	Study Sample (n=3896)	Non-Study Sample (n=2918)
Age (years)	61.4 ± 10.1	63.2 ± 10.4
Female (%)	52.6	53.2
Race (%)		
White	39.9	36.6
Chinese	12.5	10.8
African-American	25.6	30.6
Hispanic	22.0	22.0
Height (cm)	166.4 ± 9.9	166.3 ± 10.2
Weight (kg)	77.4 ± 16.2	80.3 ± 18.6
Body mass index (kg/m^2)	27.8 ± 5.0	29.0 ± 6.0
Educational attainment (%)		
No high school degree	15.8	21.1
High school degree	18.1	18.3
Some college	16.1	16.7
Bachelor's Degree	18.5	15.5
Higher than bachelor's degree	19.1	16.5
Cigarette smoking status (%)		
Never	52.6	47.3
Former	35.1	38.7

Current	12.4	14.0
Pack-years of smoking	10.8 ± 22.8	12.3 ± 21.4
Hypertension (%)	42.5	48.4
Systolic blood pressure (mmHg)	125.3 ± 20.9	128.3 ± 22.1
Diabetes mellitus (%)	12.3	15.3
Fasting plasma glucose (mg/dL)	95.9 ± 28.2	99.3 ± 32.8
Study Site (%)		
St. Paul	16.0	15.2
Los Angeles	18.2	20.9
Baltimore	17.7	13.6
Chicago	14.1	21.1
New York City	20.3	10.7
Winston-Salem	13.8	18.5
Stable residential neighborhood (%)		
> 5 years	79.8	76.0
> 10 years	63.8	61.8
NO_2 (ppb)	22.6 ± 10.3	22.2 ± 9.2*
NO_x (ppb)	50.5 ± 26.9	50.4 ± 26.7*

Abbreviations: NO_2=nitrogen dioxide, cm=centimeters, kg=kilograms, m^2=meters squared, mmHg=millimeters of mercury, ppb=parts per billion

**1055 participants with NO_2 and NO_x estimates not included in the study sample because of missing MRI or covariates*

Table 2. Multivariable linear regression estimating the associations between NO_2 exposure and right ventricular structure and function

Model	per interquartile increase in NO_2		
	difference	95% CI	p-value
RV mass, g (Limited model*)	0.4	0.2, 0.7	<0.001
RV mass, g (Limited model* + city)	0.9	0.3, 1.4	0.002
RV mass, g (Full Model†)	1.0	0.4, 1.5	0.001
RV mass, g (Full Model† + LV mass)	0.9	0.3, 1.4	0.001
RVEDV, mL (Limited model*)	2.9	1.4, 4.7	<0.001
RVEDV, mL (Limited model* + city)	2.7	-0.9, 6.2	0.14
RVEDV, mL (Full Model†)	4.1	0.5, 7.7	0.03
RVEDV, mL (Full Model† + LVEDV)	2.7	0.0, 5.4	0.05
RVEF, % (Limited model*)	-0.1	-0.5, 0.5	0.80
RVEF, % (Limited model* + city)	-0.2	-1.2, 0.8	0.69
RVEF, % (Full Model†)	-0.2	-1.2, 0.8	0.72
RVEF, % (Full Model† + LVEF)	0.0	-1.0, 0.9	0.92

Abbreviations: NO_2=nitrogen dioxide, CI=confidence interval, RV=right ventricular, LV= left ventricular, RVEDV= right ventricular end-diastolic volume, LVEDV= left ventricular end-diastolic volume, RVEF= right ventricular ejection fraction, LVEF= left ventricular ejection fraction

**Adjusted for age, sex, race/ethnicity, height and weight*

[†]Adjusted for age, sex, race/ethnicity, height, weight, city, education, income, smoking, pack-years, hypertension, diabetes, cholesterol, and impaired glucose tolerance

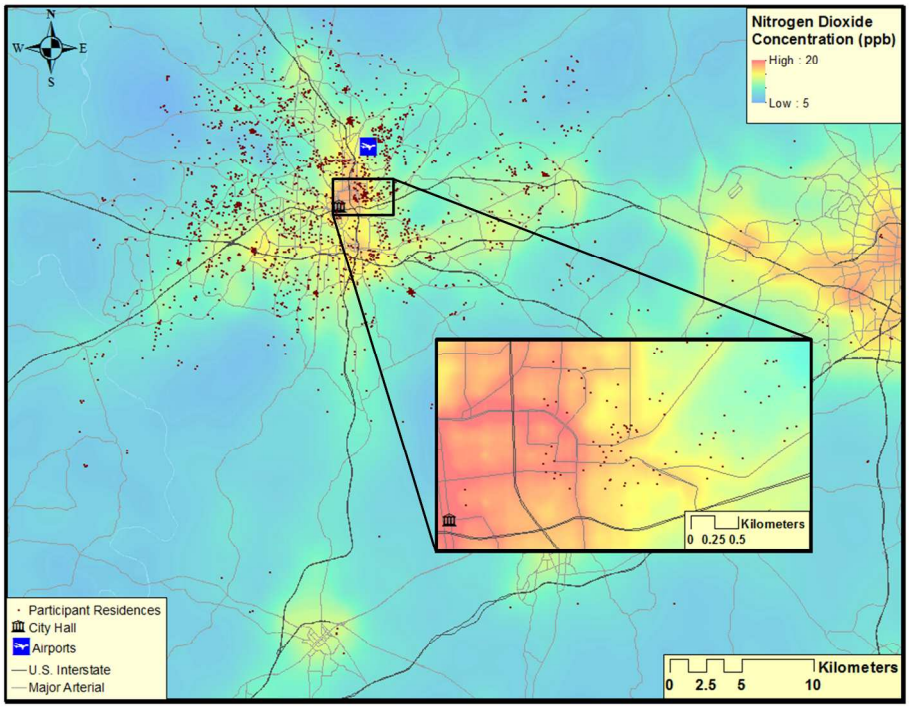

Figure 1 Representative map of Winston-Salem showing coarse and fine details of nitrogen dioxide predictions in parts per billion (ppb) from the spatio-temporal model including approximate MESA participant locations (jittered for privacy).
279x215mm (279 x 279 DPI)

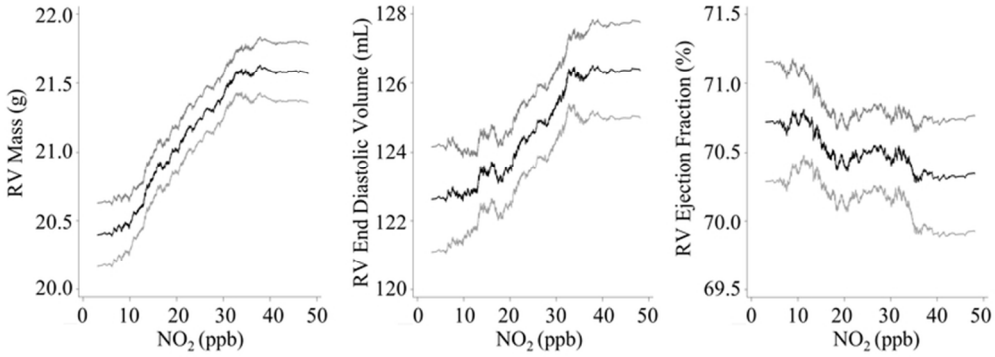

Figure 2. Multivariable non-parametric smoothed relationship between nitrogen dioxide (NO2) in parts per billion (ppb) and right ventricular (RV) parameters with adjustment for age, sex, race/ethnicity, height, weight, city, education, income, smoking, pack-years, hypertension, diabetes, cholesterol, and impaired glucose tolerance. Grey lines represent 95% confidence bounds.
69x26mm (300 x 300 DPI)

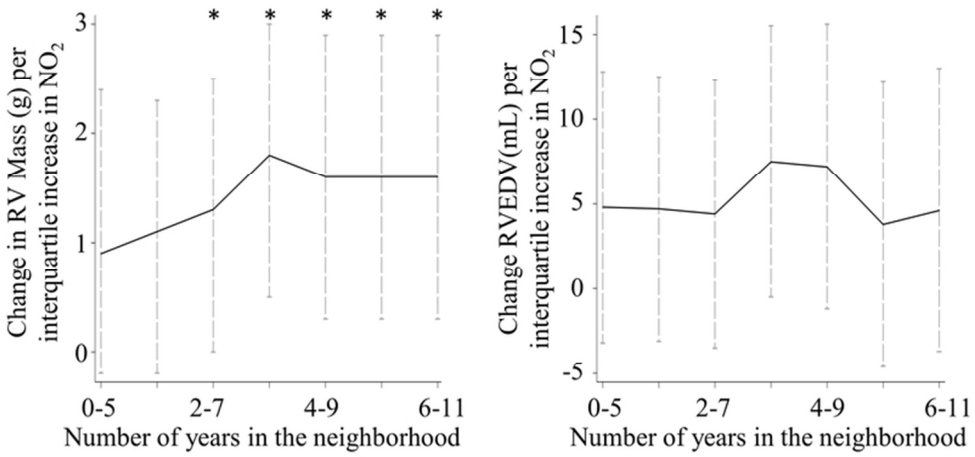

Figure 3. Relationship between the number of years a participant lived in their neighborhood and the difference in right ventricular (RV) mass or end-diastolic volume (EDV) per interquartile increase in nitrogen dioxide (NO2): a sliding time window analysis of the full model (* $p \leq 0.05$).
69x33mm (300 x 300 DPI)

Title: Traffic Related Air Pollution and the Right Ventricle: The Multi-Ethnic Study of Atherosclerosis

Authors: Peter J Leary, Joel D Kaufman, R. Graham Barr, David A Bluemke, Cynthia L Curl, Catherine L Hough, Joao A Lima, Adam A Szpiro, Victor C Van Hee, Steven M Kawut

Online Supplement

Figure E1 Study sample

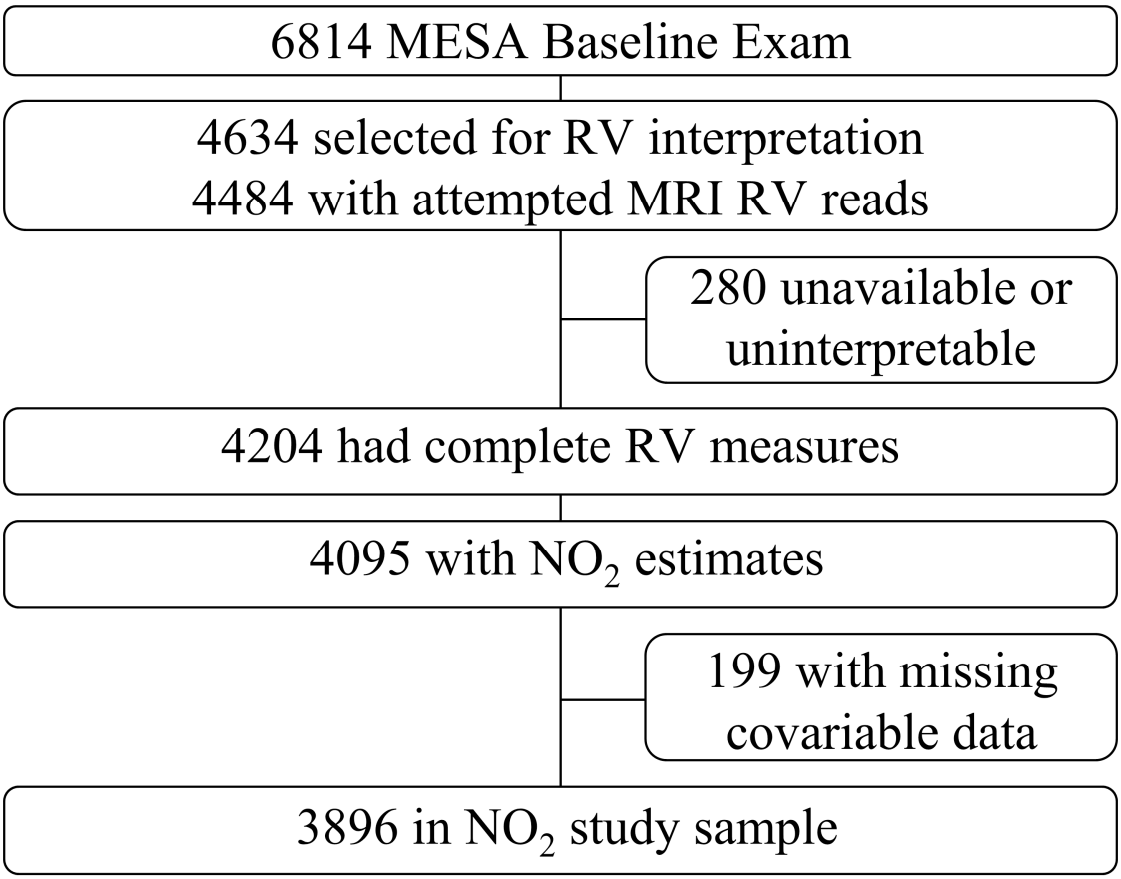

Figure E2. Box plot of between and within city gradients of nitrogen dioxide (NO_2) in parts per billion (ppb) for participants in the year prior to their MRI in the Multi-Ethnic Study of Atherosclerosis and Air Pollution.

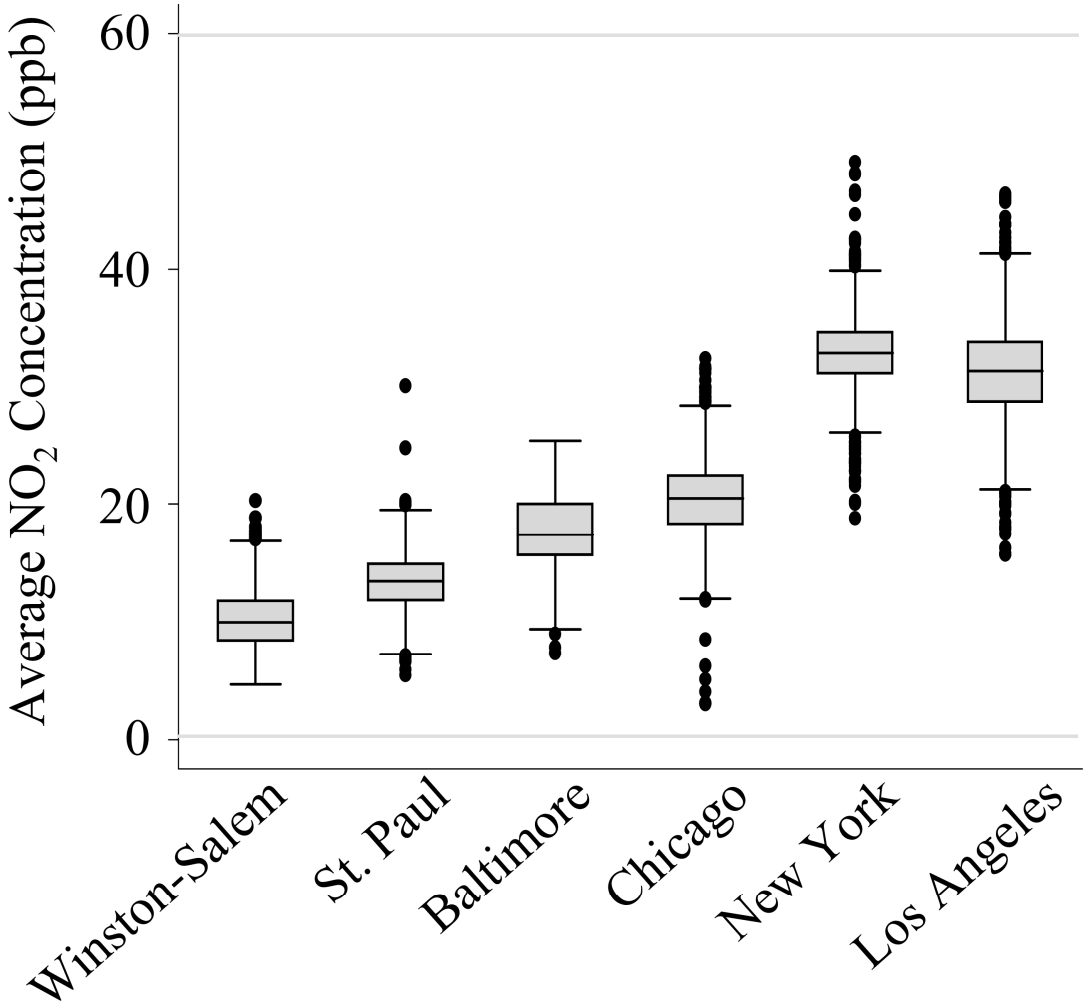

Table E1. Multivariable linear regression estimating the associations between NO_2 exposure and right ventricular structure and function in the full model* with further adjustment for differences in roadway noise, inflammation, and lung disease

Model	per interquartile increase in NO_2		
	difference	95% CI	p-value
RV Mass, g, Full Model (n=3,896)	**1.0**	**0.4, 1.5**	**0.001**
Full + roadway noise (n=3,890)	1.0	0.4, 1.5	0.001
Full + CRP and IL-6 (n=3,804)	1.1	0.5, 1.6	<0.001
Full + % emphysema (Chest CT) & self reported asthma or emphysema (n=3,893)	0.9	0.4, 1.5	0.001
RVEDV, mL, Full Model (n=3,896)	**4.1**	**0.5, 7.7**	**0.03**
Full + roadway noise (n=3,890)	3.9	0.3, 7.6	0.04
Full + CRP and IL-6 (n=3,804)	4.2	0.5, 7.8	0.03
Full + % emphysema (Chest CT) & self reported asthma or emphysema (n=3,893)	3.7	0.1, 7.3	0.04

Abbreviations: NO_2=nitrogen dioxide, CI=confidence interval, RV= right ventricular, CRP=c-reactive protein, IL-6=interleukin-6, CT=computed tomography, RVEDV= right ventricular end-diastolic volume

**Adjusted for age, sex, race/ethnicity, height, weight, city, education, income, smoking, pack-years, hypertension, diabetes, cholesterol, and impaired glucose tolerance*

Table E2. Residential stability as a proxy for the timing of exposure to traffic related air pollution: a sliding time window analysis of the full model*

Number of years lived in the same neighborhood	n	RV mass (g)	per interquartile increase in NO_2 95% CI	p-value
0 to 5 years	785	1.0	(-0.2, 2.4)	0.09
1 to 6 years	834	1.1	(-0.2, 2.3)	0.09
2 to 7 years	848	1.3	(0.0, 2.5)	0.04
3 to 8 years	816	1.8	(0.5, 3.0)	0.005
4 to 9 years	743	1.6	(0.3, 2.9)	0.02
5 to 10 years	773	1.6	(0.3, 2.9)	0.02
6 to 11 years	727	1.6	(0.3, 2.9)	0.01
All years	**3,896**	**1.0**	**(0.4, 1.5)**	**0.001**
	n	RVEDV (mL)	95% CI	p-value
0 to 5 years	785	4.8	(-3.2, 12.8)	0.24
1 to 6 years	834	4.7	(-3.1, 12.5)	0.24
2 to 7 years	848	4.4	(-3.5, 12.3)	0.28
3 to 8 years	816	7.5	(-0.5, 15.5)	0.07
4 to 9 years	743	7.2	(-1.2, 15.6)	0.10
5 to 10 years	773	3.8	(-4.6, 12.2)	0.37
6 to 11 years	727	4.6	(-3.7, 13.0)	0.28
All years	**3,896**	**4.1**	**(0.5, 7.7)**	**0.03**

Abbreviation: NO_2=nitrogen dioxide, CI=confidence interval, RV=right ventricular, RVEDV=right ventricular end-diastolic volume

**Adjusted for age, sex, race/ethnicity, height, weight, city, education, income, smoking, pack-years, hypertension, diabetes, cholesterol, and impaired glucose tolerance*

Table E3. Multivariable linear regression estimating the associations between NO_x exposure and right ventricular structure and function

Model	per interquartile increase in NO_x (48.1ppb)		
	difference	95% CI	p-value
RV mass, g (Limited model*)	0.2	(0.0, 0.4)	0.04
RV mass, g (Limited model* + city)	0.4	(0.0, 0.8)	0.04
RV mass, g (Full Model†)	0.5	(0.1, 0.8)	0.03
RVEDV, mL (Limited model*)	1.3	(0.0, 2.7)	0.05
RVEDV, mL (Limited model* + city)	0.8	(-1.7, 3.3)	0.52
RVEDV, mL (Full Model†)	1.7	(-0.9, 4.2)	0.20
RVEF, % (Limited model*)	0.0	(-0.4, 0.4)	0.98
RVEF, % (Limited model* + city)	0.1	(-0.6, 0.8)	0.78
RVEF, % (Full Model†)	0.1	(-0.6, 0.9)	0.72

Abbreviations: NO_x= oxides of nitrogen, CI= confidence interval, ppb= parts per billion, RV=right ventricular, LV= left ventricular, RVEDV= right ventricular end-diastolic volume, LVEDV= left ventricular end-diastolic volume, RVEF= right ventricular ejection fraction, LVEF= left ventricular ejection fraction

**Adjusted for age, sex, race/ethnicity, height and weight*

†Adjusted for age, sex, race/ethnicity, height, weight, city, education, income, smoking, pack-years, hypertension, diabetes, cholesterol, and impaired glucose tolerance

Table E4. Multivariable linear regression estimating the associations between NO_2 exposure by calendar year and right ventricular structure and function in the full model*

Model	per interquartile increase in NO_2		
	difference	95% CI	p-value
Calendar Year 2000 (NO_2 IQR 17.7ppb)			
RV mass, g	0.8	0.2, 1.3	0.005
RVEDV, mL	4.3	0.8, 7.8	0.02
RVEF, %	0.1	-0.9, 1.1	0.82
Calendar Year 2001 (NO_2 IQR 17.0ppb)			
RV mass, g	0.9	0.4, 1.4	0.001
RVEDV, mL	4.4	1.0, 7.8	0.01
RVEF, %	-0.1	-1.1, 0.8	0.77
Calendar Year 2002 (NO_2 IQR 17.5ppb)			
RV mass, g	0.9	0.3, 1.4	0.002
RVEDV, mL	4.1	0.6, 7.6	0.02
RVEF, %	-0.3	-1.3, 0.7	0.56

Abbreviations: NO_2=nitrogen dioxide, CI=confidence interval, IQR= interquartile range, RV=right ventricular, LV= left ventricular, RVEDV= right ventricular end-diastolic volume, LVEDV= left ventricular end-diastolic volume, RVEF= right ventricular ejection fraction, LVEF= left ventricular ejection fraction

**Adjusted for age, sex, race/ethnicity, height, weight, city, education, income, smoking, pack-years, hypertension, diabetes, cholesterol, and impaired glucose tolerance*

Title: Traffic Related Air Pollution and the Right Ventricle: The Multi-Ethnic Study of Atherosclerosis

Running head: Air pollution and the right ventricle

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Author Contributions: All authors participated in the conception and design of the research. JDK, CLC, AAS, VCVH developed the air pollution estimates. DAB and JAL oversaw the MRI interpretation of right ventricular metrics. PJL and SMK analyzed and interpreted the data and drafted the report. All authors reviewed, revised, and approved the final version of the manuscript.

Subject code: 6.1 Air pollution: Epidemiology

Word Count (Introduction to Acknowledgement): 3,007

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At a glance commentary:

Scientific knowledge on the subject

Exposure to traffic-related air pollution has been linked to left ventricular hypertrophy, heart failure, and death. The lungs have substantial exposure to traffic-related pollutants; however, relationships between traffic-related air pollutants and right ventricular morphology have not been established.

What the study adds to the field

Higher levels of traffic-related air pollution, estimated by exposure to oxides of nitrogen, are associated with greater right ventricular mass and larger volumes. This relationship was not dependent on differences in left ventricular mass or volumes, systemic inflammation, roadway noise or lung disease.

Data supplement: This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org.

Abstract

Rationale: Right heart failure is a cause of morbidity and mortality in common and rare heart and lung diseases. Exposure to traffic-related air pollution is linked to left ventricular hypertrophy, heart failure and death. Relationships between traffic-related air pollution and right ventricular (RV) structure and function have not been studied.

Objective: To characterize the relationship between traffic-related air pollutants and RV structure and function.

Methods: We included men and women with magnetic resonance imaging (MRI) assessment of RV structure and function and estimated residential outdoor nitrogen dioxide (NO_2) concentrations from the Multi-Ethnic Study of Atherosclerosis, a study of individuals free of clinical cardiovascular disease at baseline. Multivariable linear regression estimated associations between NO_2 exposure (averaged over the year prior to MRI) and measures of RV structure and function after adjusting for demographics, anthropometrics, smoking, diabetes mellitus and hypertension. Adjustment for corresponding left ventricular (LV) parameters, traffic-related noise, markers of inflammation and lung disease were considered in separate models. Secondary analyses considered oxides of nitrogen (NO_x) as the exposure.

Measurements and Main Results: The study sample included 3,896 participants. In fully adjusted models, higher NO_2 was associated with greater RV mass and larger RV end-diastolic volume with or without further adjustment for corresponding LV parameters, traffic-related noise, inflammatory markers, or lung disease (all $p < 0.05$). There was no association between NO_2 and RV ejection fraction. Relationships between NO_x and RV morphology were similar.

Conclusion: Higher levels of NO_2 exposure were associated with greater RV mass and larger RV end-diastolic volume.

Word count: 250; **MeSH Terms:** Air pollutants, pulmonary circulation, heart ventricles, pulmonary hypertension

Introduction

Right heart failure is a cause of morbidity and mortality in obstructive and restrictive lung disease, left ventricular dysfunction, and pulmonary arterial hypertension.[1-3] Right ventricular (RV) hypertrophy is also associated with increased risk for heart failure and cardiovascular death in community dwelling adults without known cardiac disease at baseline.[4] Despite important epidemiologic and clinical roles of the RV, little is known about modifiable determinants of RV structure and function.[5]

Traffic-related air pollution is linked to left ventricular hypertrophy, heart failure and cardiovascular death.[6,7] Air pollution may affect the left ventricle through inflammation, oxidative stress, and autonomic dysfunction and these mechanisms could also affect the RV.[8-10] The lungs have substantial exposure to traffic-related air pollution and inhalants, which may directly increase RV afterload and lead to disproportionately greater changes in the RV compared to the left ventricle.[11,12] The impact of traffic-related air pollution on the RV, however, is not well-studied.

We examined the relationship between nitrogen dioxide (NO_2), a surrogate for traffic-related air pollution, and magnetic resonance imaging (MRI) measures of RV structure and function in a multi-ethnic cohort of adults free of clinical cardiovascular disease. We hypothesized that increased exposure to NO_2 would be independently associated with greater RV mass and larger RV end-diastolic volume. Some of the results in these studies have been previously reported in the form of an abstract.[13]

Methods

The Multi-Ethnic Study of Atherosclerosis (MESA) is a multicenter prospective cohort study designed to investigate subclinical cardiovascular disease in whites, African-Americans, Hispanics and Chinese-Americans.[14] Exclusion criteria included clinical cardiovascular disease (physician diagnosed heart attack, stroke, transient ischemic attack, heart failure, angina, current atrial fibrillation, any cardiovascular procedure), weight >136kg (300 lbs.), pregnancy, or impediment to long-term participation. The Environmental Protection Agency funded a large ancillary study to MESA, the Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA Air), which added cohort-specific air pollution monitoring and modeling.[15] The MESA-RV study was an ancillary study funded to interpret cardiac MRIs for RV function. Individual participants gave informed consent and the Institutional Review Boards of participating institutions approved the protocols of MESA and all studies described herein.

Traffic-related air pollution exposure

Participants' residential address was assigned geographic coordinates using ArcGIS 9.1 software (ESRI, Redlands, CA) in conjunction with Dynamap/2000 street network and geocoding database (Tele Atlas, Boston, MA). Using weighted averages of residential addresses over the year prior to cardiac MRI, individual outdoor home exposure to NO_2 and NO_x were estimated using spatio-temporal modeling and maximized via maximum likelihood (Figure 1).[16,17] Estimates were fit using monitoring data from the Environmental Protection Agencies Air Quality System database and extensive cohort-specific air monitoring including home-based monitoring conducted as part of MESA Air.[18] Geographical variables incorporated into the model included information on land use (e.g., industrial, residential), vegetative index, distance

to various features (e.g., airports, coastline), road density, population density, elevation, urban topography, emissions sources, and dispersion model outputs integrating road position, traffic volume, diurnal traffic patterns and meteorology.

Cardiac magnetic resonance imaging measures

Methods for acquisition and interpretation of LV and RV MRI parameters have been previously reported.[19,20] Endocardial and epicardial borders of the RV were manually traced on short axis cine images at end-systole and end-diastole. The outflow tract was included in RV volume. Papillary muscle and trabeculae were included in RV volumes and excluded from RV mass, as is commonly done for LV mass.[21,22] RV end-systolic volume and RV end-diastolic volume (RVEDV) were calculated using Simpson's rule by summation of areas on each slice multiplied by the sum of slice thickness and image gap. RV mass was determined at end-diastole as the difference between RV free wall end-diastolic epicardial and endocardial volumes multiplied by the specific gravity of the heart (1.05g/mL). RVEF was calculated by subtracting RV end-systolic volume from RVEDV and dividing this difference by RVEDV.

Covariables

Covariables including age, sex, race/ethnicity, height, weight, education, income, presence of hypertension or diabetes mellitus, fasting plasma glucose, cholesterol, systolic blood pressure, smoking status and pack-years, percent emphysema (obtained by chest CT), and self-reported lung disease (asthma and/or emphysema) were measured as previously described.[23] Because levels of air pollution within a neighborhood are correlated over time, self-reported time a participant lived in the index neighborhood (the residential neighborhood used to determine one

year pollutant estimates) was used as a surrogate for exposure duration.[8] Participants reported roadway noise as a: "very serious problem", "somewhat serious problem", "minor problem", or "not really a problem."

Statistical Analysis

We used linear regression to characterize relationships between NO_2 and RV parameters. All models were adjusted for height and weight, so it was not necessary to index RV parameters to account for differences in body size. Covariables were chosen *a priori* on the basis of known associations with ventricular size, heart disease and comorbidities. In limited models, we adjusted for age, sex, race/ethnicity, height and weight.[24] In fully adjusted models, we also included MESA field center, markers of socioeconomic status (self-reported income and education), and cardiovascular risk factors including smoking status, smoking pack-years, hypertension, cholesterol, diabetes mellitus, and impaired glucose tolerance. In pre-specified models, we further adjusted for LV parameters, self-reported roadway noise, markers of inflammation (C-reactive protein and interleukin-6), or lung structure (% emphysema) and self-reported lung disease in separate models.

The primary analysis examined the relationship between RV parameters and NO_2 averaged over the year prior to cardiac MRI. Sensitivity analyses used fixed-year estimates of NO_2 in 2000, 2001 and 2002 to ensure there was no artifice in timing of the MRI in relation to secular exposure trends. Secondary analyses in limited and fully adjusted models used NO_x as the exposure of interest, which includes other components of the traffic-related air pollutant mix.

Several exploratory models further evaluated the relationship between NO_2 and RV metrics. Duration and timing of exposure were considered using a sliding time window

analysis.[25] We estimated associations between NO_2 and RV parameters in 5-year 'time windows' (e.g. participants who lived in the index neighborhood for between 1 and 6 years). The time window was then shifted by one year (e.g. participants who lived in the neighborhood between 2 and 6 years) and new estimates of association and 95% confidence intervals were calculated. Overlapping 5-year periods avoid unstable estimates based on sparse data for a single calendar year and may more appropriately characterize the biologically relevant duration of exposure. Further exploratory models evaluated whether age, sex, or study site modified the association between NO_2 and RV parameters. We performed sensitivity analyses adjusting for body mass index category (normal weight and category 1 – 3 overweight) instead of height and weight to evaluate for residual confounding by obesity. Analyses were performed using STATA 12.0 (StataCorp, College Station, TX, USA).

Results

There were 6,814 men and women enrolled in MESA (see Figure E1 in the online supplement) of whom 5,098 underwent cardiac MRI and 5,004 (98%) had interpretable exams for the LV. Of 4,634 participants selected for MESA-RV, MRI reads were attempted in 4,484 participants before achieving the study goal of 4,204 participants (94% of attempted reads). Outdoor exposure to NO_2 was estimated in 4,095 of these participants (97%). One hundred ninety-nine participants were excluded for missing covariables leaving 3,896 in the study sample. Table 1 shows characteristics of the study sample compared with those excluded. The mean age of the study sample was 61.4 years and 52.6% were women. Mean RV mass in the study sample was 21.1 ± 4.4 g, mean RVEDV was 124.2 ± 30.8 mL and mean RVEF was 70.5 ± 6.4 %. Mean NO_2 was 21.8 ± 10.3 ppb with an interquartile range (IQR) from 13.9 to 31.0 ppb.

For individual cities the mean NO_2 ranged from 10.1 to 32.7 ppb and the city-specific IQR ranged from 3.1 to 5.0 ppb (Figure E2 in the online supplement).

Higher NO_2 was associated with greater RV mass (0.4 g for an interquartile increase in NO_2)(Table 2, Figure 2). This relationship became stronger after adjustment for city (0.9 g for an interquartile increase in NO_2) and after full adjustment for cardiovascular risk factors (1.0 g for an interquartile increase in NO_2). This amounted to ~5% increase in RV mass per interquartile increase in NO_2. This significant association did not change with further adjustment for LV mass, traffic-related noise, inflammatory markers, or lung disease (Table 2 & E1 in the online supplement).

Higher NO_2 was associated with larger RVEDV (2.9 mL for an interquartile increase in NO_2)(Table 2, Figure 2). This relationship became stronger after full adjustment for potential confounding by cardiovascular risk factors (4.1 mL for an interquartile increase in NO_2). This amounted to ~3% increase in RVEDV per interquartile increase in NO_2. The significant association remained with further adjustment for LV end-diastolic volume, traffic-related noise, inflammatory markers, or lung disease (Table 2 & E1 in the online supplement). NO_2 was not associated with RVEF (Table 2, Figure 2).

Secondary analyses using NO_x as the exposure of interest suggested relationships similar to those for NO_2 but were in all cases modestly attenuated compared to NO_2 (Table E3 in the online data supplement). RVEDV was not consistently associated with NO_x.

For participants with residential stability estimates (3,892 of 3,896 participants), sliding time window analyses indicated that participants who lived in the neighborhood several years before the MRI had incrementally stronger associations between NO_2 and RV mass then did those who lived in the neighborhood for a shorter duration (Figure 3 and Table E2 in the online

supplement). An incremental increase in RVEDV with participant duration in the neighborhood was less clear (Figure 3 and Table E2 in the online supplement). Choice of the NO_2 reference period (calendar year 2000, 2001 or 2002) did not meaningfully impact the relationship between NO_2 and RV parameters (Table E4 in the online data supplement).

Participant age did not modify relationships between NO_2 and RV parameters. The relationships of NO_2 with RV mass may have been stronger in men (1.3 g [95% CI: 0.4 to 2.2 g] per interquartile increase in NO_2) then women (0.6 g [95% CI: -0.1 to 1.3 g] per interquartile increase in NO_2)(p for interaction=0.03). Similarly, the relationship of NO_2 with RVEDV may have been stronger in men (5.5 mL [95% CI: -0.3 to 11.2 mL] per interquartile increase in NO_2) than women (2.1 mL [95% CI: -2.2 to 6.5 mL] per interquartile increase in NO_2)(p for interaction=0.04).

Participant city modified the relationship between NO_2 and RV mass (p for interaction <0.001), but not RVEDV (p for interaction=0.33). Qualitative associations between NO_2 and RV mass were in the same direction as the main association in St. Paul (6.4 g [95% CI: 4.1 to 8.8 g] per interquartile increase in NO_2), Los Angeles (0.9 g [95% CI: -0.1 to 1.9 g] per interquartile increase in NO_2), Baltimore (0.4 g [95% CI: -1.2 to 1.9 g] per interquartile increase in NO_2) and Chicago (0.3 g [95% CI: -1.0 to 1.6 g] per interquartile increase in NO_2). Qualitative associations were in the opposite direction as the main association in New York (-0.2 g [95% CI: -1.5 to 1.1 g] per interquartile increase in NO_2) and Winston-Salem (-0.4 g [95% CI: -2.6 to 1.8 g] per interquartile increase in NO_2). Because of the strong associations for St. Paul, we then excluded participants in cities with the greatest (St. Paul) and smallest (Winston-Salem) estimates of association between NO_2 and RV mass. The estimate of association in this four–city sample was smaller but qualitatively similar to the main analysis (0.5 g [95% CI -0.1 to 1.1 g] increase per

interquartile increase in NO_2, n=2738). Restricting this four-city sample to the sliding time window with the strongest association strengthened the relationship (1.3 g [95% CI -0.1 to 2.7 g] increase per interquartile increase in NO_2, n=476).

A sensitivity analysis adjusting for body mass index category, instead of the standard adjustment by height and weight, did not change the results of any analysis.

Discussion

We have shown that higher estimates of long-term outdoor residential NO_2 exposure are associated with greater RV mass and larger RVEDV in a multiethnic, multicity cohort of adults without clinical cardiovascular disease. MESA participants had a 1.0 g (5%) increase in RV mass and 4.1 mL (3%) increase in RVEDV with an interquartile increase in NO_2. This difference in RV mass is quantitatively similar to that seen in LV mass in MESA participants with diabetes (2.4%) and in current smokers (5.3%), supporting clinical and biologic relevance.[26,27] RV hypertrophy in MESA participants is associated with a three-fold increased risk for heart failure or cardiovascular death.[4] This is the first report to suggest traffic-related air pollutants, of which NO_2 is a well-recognized surrogate for the pollutant mix, is associated with morphologic changes in the right ventricle of the heart.

Our study provides initial insight into timing of this association. Duration of exposure to traffic-related air pollutants appears to be important. Participants who lived in the same neighborhood for several years had the strongest associations between NO_2 and RV mass. This suggests a dose-response, may provide insight for duration of necessary exposure, and supports a causal relationship.

The finding of both increased RV mass and RVEDV may suggest that the exposure of interest increased RV afterload.[28] Previous studies have suggested air pollution increases endothelin-1, a potent pulmonary vasoconstrictor,[29] which could lead to increased pulmonary vascular resistance, increased RV afterload and ultimately RV hypertrophy and dilation. Alternatively, air pollutants can irritate the respiratory epithelium and lead to heterogeneous ventilation with decreased regional ventilation.[30] Regional hypoxia can cause hypoxic pulmonary vasoconstriction, increased resistance and RV enlargement.[31] Increases in afterload may compound oxidative stress and autonomic dysfunction, which have been implicated in the relationship between air pollution and LV mass and could directly contribute to RV pathology.[8-10,32]

Other mechanisms are possible as well. Air pollution may up-regulate myocardial inflammatory genes and proteins in the RV.[33] While it is not feasible to study myocardial gene and protein profiles in such a large study of the general population, our findings remained after adjustment for C-reactive protein and interleukin-6 blood levels, which suggests that our findings were independent of systemic inflammation. Roadway noise, which accompanies traffic-related air pollution and may disrupt sleep, could mediate some aspects of the relationship between roadway proximity and heart disease.[34] Adjusting for traffic-related noise did not attenuate relationships between NO_2 and RV morphology in our analyses.

Air pollution has also been linked to obstructive lung disease severity, which could increase RV afterload leading to increased RV mass.[35,36] However, we have previously shown that increasing airflow obstruction is associated with decreased RVEDV in MESA.[37] In addition, adjustment for structural or self-reported lung disease did not change relationships between NO_2 and RV morphology in this analysis. Finally, LV mass may increase with traffic-related air

pollution and LV hypertrophy can contribute to diastolic dysfunction and increased RV afterload, potentially explaining our results.[6,38] However, adjusting for the LV did not affect the results.

Relationships between NO_x and RV morphology were similar, but mildly attenuated compared to those with NO_2. In addition, the relationship between NO_x and RVEDV was sensitive to adjustment. The NO_x analyses reinforce that the observed relationships are consistent with associations of a pollutant mix, not a specific pollutant, and that relationships between these pollutants and RV mass is stronger than relationships with RVEDV.

The association between NO_2 and RV mass was modified by city of residence. For example, participants in New York City did not appear to have a relationship between NO_2 and RV mass despite the highest exposure to NO_2. Heterogeneity by city is very common in air pollution research and was also seen in studies of LV mass and endothelial dysfunction.[6,39] Two key factors may contribute to city-specific heterogeneity. First, the validity of outdoor assessment of NO_2 as a surrogate for individual exposure to traffic-related pollutants depends on the degree to which outdoor pollution contributes to indoor pollution (e.g. home infiltration coefficient, indoor sources) and the proportion of time a participant spends indoors, outdoors, and in different micro-environments.[40] These complex relationships vary between cities as a function of culture, climate, cooking/ventilation patterns, and average building age, among other factors. Second, our estimates of NO_2 are best conceptualized as a pattern of spatial decay consistent with some but not all traffic-related pollutants. For example, participants' exposure to NO_2 also reflects exposure to other hazardous air pollutants such as benzene and several volatile organic compounds, levels of which may vary by city.[41]

This study has limitations. While we consider our exposure models to be a significant improvement over roadway proximity and nearest monitor analyses, measurement error and misclassification are likely present. Because error in exposure assignments is unlikely to be dependent on RV measurements, these errors may be non-differential with bias toward the null, so actual relationships may even be stronger than we have shown. Residual or unmeasured confounding, particularly at the neighborhood level, could contribute to the results. This may be especially true in the adjustment for exposure duration as neighborhood residents with long-term stability may differ from short-term residents. In the adjustment for road noise, measured or modeled noise would have been preferable to self-reports, but were not available. Furthermore, our study was cross-sectional and causality cannot be confirmed. Finally, measurement of invasive pulmonary hemodynamics, which may have informed the mechanism underlying our results, was not feasible in almost 4,000 community dwelling participants free of cardiovascular disease.

Summary

Higher estimated exposure to NO_2 is associated with greater RV mass and larger RVEDV. This relationship is independent of markers of socioeconomic status, cardiovascular risk factors, left sided cardiovascular disease, markers of inflammation and lung disease. This is the first report to implicate traffic-related air pollution with changes in right ventricular morphology. Air pollution may therefore play a role determining the RV response and outcomes in cardiopulmonary disease.

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Figure Legends

Figure 1 Representative map of Winston-Salem showing coarse and fine details of nitrogen dioxide predictions in parts per billion (ppb) from the spatio-temporal model including approximate MESA participant locations (jittered for privacy).

Figure 2. Multivariable non-parametric smoothed relationship between nitrogen dioxide (NO_2) in parts per billion (ppb) and right ventricular (RV) parameters with adjustment for age, sex, race/ethnicity, height, weight, city, education, income, smoking, pack-years, hypertension, diabetes, cholesterol, and impaired glucose tolerance. Grey lines represent 95% confidence bounds.

Figure 3. Relationship between the number of years a participant lived in their neighborhood and the difference in right ventricular (RV) mass or end-diastolic volume (EDV) per interquartile increase in nitrogen dioxide (NO_2): a sliding time window analysis of the full model (* $p \leq 0.05$).

Table 1. Characteristics of the study sample compared with the non-study subjects

	Study Sample (n=3896)	Non-Study Sample (n=2918)
Age (years)	61.4 ± 10.1	63.2 ± 10.4
Female (%)	52.6	53.2
Race (%)		
White	39.9	36.6
Chinese	12.5	10.8
African-American	25.6	30.6
Hispanic	22.0	22.0
Height (cm)	166.4 ± 9.9	166.3 ± 10.2
Weight (kg)	77.4 ± 16.2	80.3 ± 18.6
Body mass index (kg/m^2)	27.8 ± 5.0	29.0 ± 6.0
Educational attainment (%)		
No high school degree	15.8	21.1
High school degree	18.1	18.3
Some college	16.1	16.7
Bachelor's Degree	18.5	15.5
Higher than bachelor's degree	19.1	16.5
Cigarette smoking status (%)		
Never	52.6	47.3
Former	35.1	38.7

Current	12.4	14.0
Pack-years of smoking	10.8 ± 22.8	12.3 ± 21.4
Hypertension (%)	42.5	48.4
Systolic blood pressure (mmHg)	125.3 ± 20.9	128.3 ± 22.1
Diabetes mellitus (%)	12.3	15.3
Fasting plasma glucose (mg/dL)	95.9 ± 28.2	99.3 ± 32.8
Study Site (%)		
St. Paul	16.0	15.2
Los Angeles	18.2	20.9
Baltimore	17.7	13.6
Chicago	14.1	21.1
New York City	20.3	10.7
Winston-Salem	13.8	18.5
Stable residential neighborhood (%)		
> 5 years	79.8	76.0
> 10 years	63.8	61.8
NO_2 (ppb)	22.6 ± 10.3	22.2 ± 9.2*
NO_x (ppb)	50.5 ± 26.9	50.4 ± 26.7*

Abbreviations: NO_2=nitrogen dioxide, cm=centimeters, kg=kilograms, m^2=meters squared, mmHg=millimeters of mercury, ppb=parts per billion

**1055 participants with NO_2 and NO_x estimates not included in the study sample because of missing MRI or covariates*

Table 2. Multivariable linear regression estimating the associations between NO_2 exposure and right ventricular structure and function

Model	per interquartile increase in NO_2		
	difference	95% CI	p-value
RV mass, g (Limited model*)	0.4	0.2, 0.7	<0.001
RV mass, g (Limited model* + city)	0.9	0.3, 1.4	0.002
RV mass, g (Full Model†)	1.0	0.4, 1.5	0.001
RV mass, g (Full Model† + LV mass)	0.9	0.3, 1.4	0.001
RVEDV, mL (Limited model*)	2.9	1.4, 4.7	<0.001
RVEDV, mL (Limited model* + city)	2.7	-0.9, 6.2	0.14
RVEDV, mL (Full Model†)	4.1	0.5, 7.7	0.03
RVEDV, mL (Full Model† + LVEDV)	2.7	0.0, 5.4	0.05
RVEF, % (Limited model*)	-0.1	-0.5, 0.5	0.80
RVEF, % (Limited model* + city)	-0.2	-1.2, 0.8	0.69
RVEF, % (Full Model†)	-0.2	-1.2, 0.8	0.72
RVEF, % (Full Model† + LVEF)	0.0	-1.0, 0.9	0.92

Abbreviations: NO_2=nitrogen dioxide, CI=confidence interval, RV=right ventricular, LV= left ventricular, RVEDV= right ventricular end-diastolic volume, LVEDV= left ventricular end-diastolic volume, RVEF= right ventricular ejection fraction, LVEF= left ventricular ejection fraction

**Adjusted for age, sex, race/ethnicity, height and weight*

[†]Adjusted for age, sex, race/ethnicity, height, weight, city, education, income, smoking, pack-years, hypertension, diabetes, cholesterol, and impaired glucose tolerance

Title: Traffic Related Air Pollution and the Right Ventricle: The Multi-Ethnic Study of Atherosclerosis

Authors: Peter J Leary, Joel D Kaufman, R. Graham Barr, David A Bluemke, Cynthia L Curl, Catherine L Hough, Joao A Lima, Adam A Szpiro, Victor C Van Hee, Steven M Kawut

Online Supplement

Figure E1 Study sample

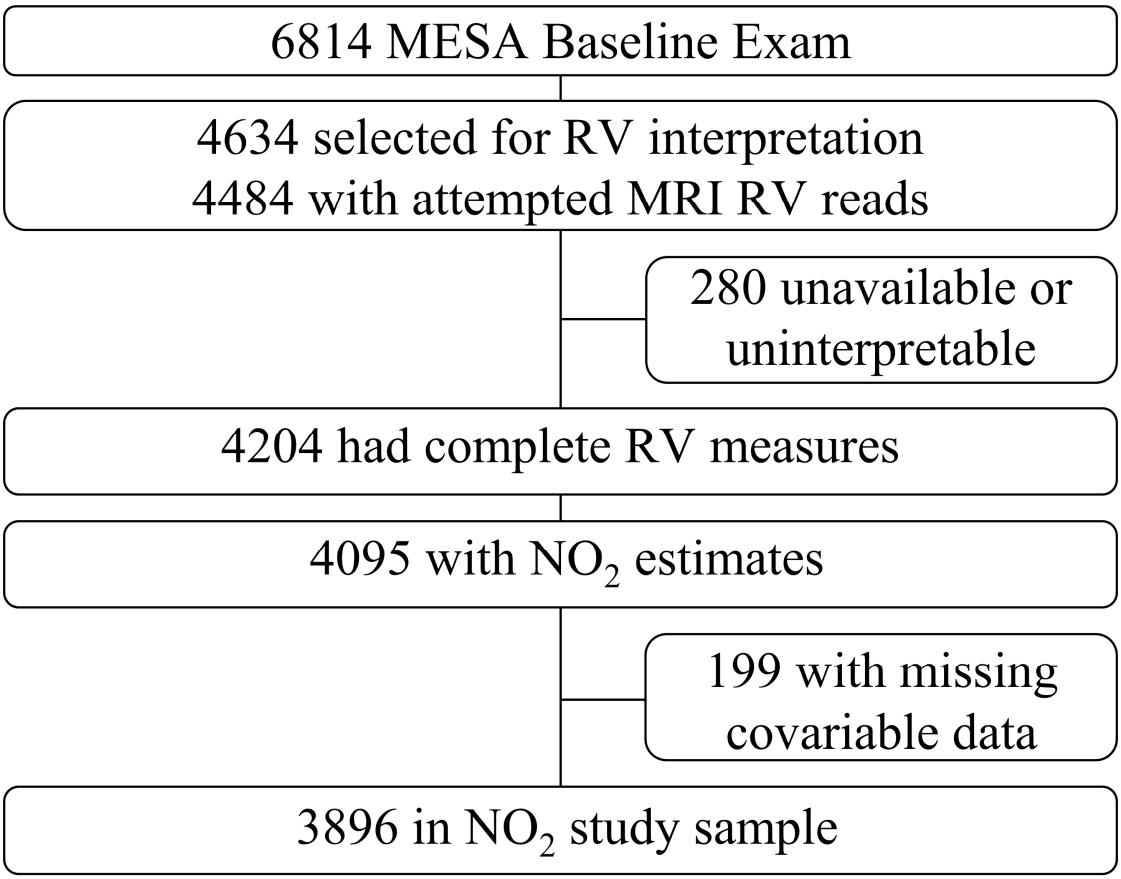

Figure E2. Box plot of between and within city gradients of nitrogen dioxide (NO_2) in parts per billion (ppb) for participants in the year prior to their MRI in the Multi-Ethnic Study of Atherosclerosis and Air Pollution.

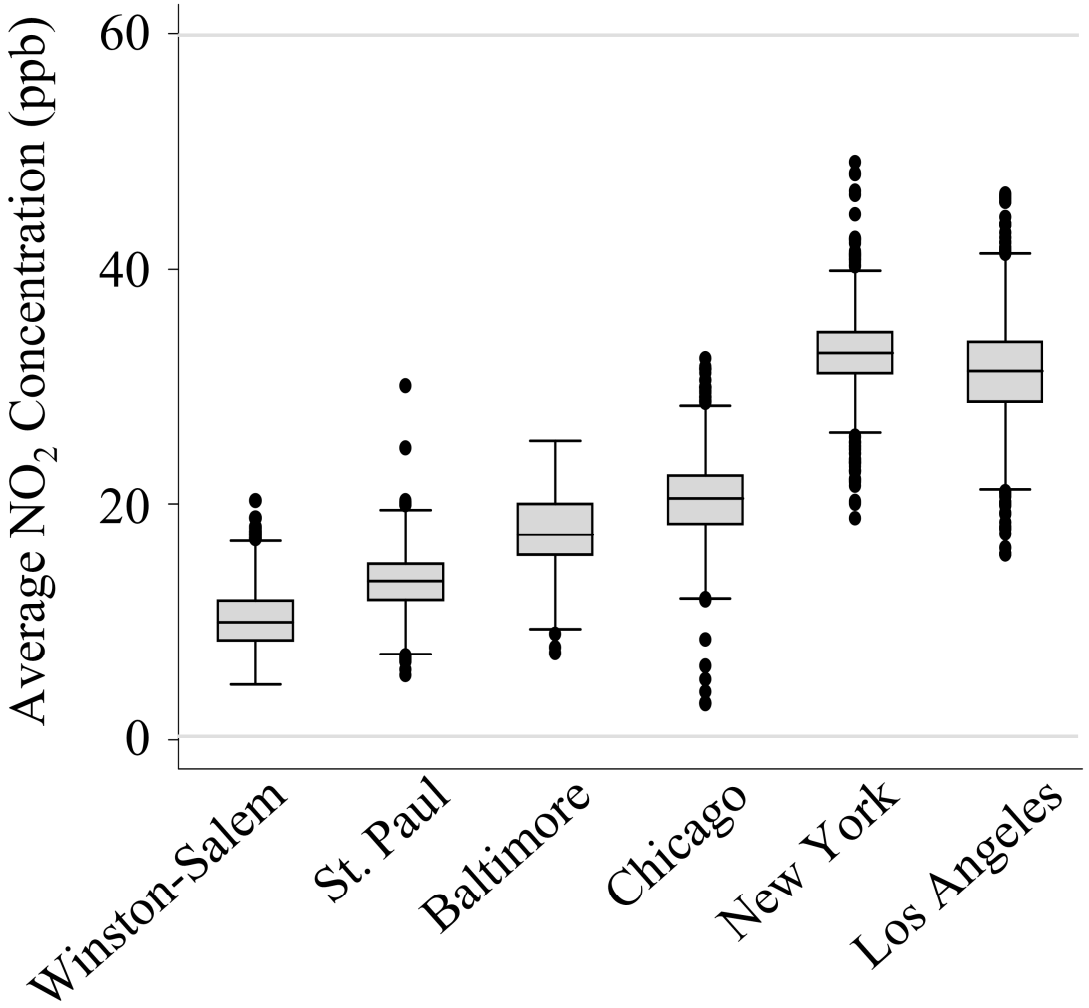

Table E1. Multivariable linear regression estimating the associations between NO_2 exposure and right ventricular structure and function in the full model* with further adjustment for differences in roadway noise, inflammation, and lung disease

Model	per interquartile increase in NO_2		
	difference	95% CI	p-value
RV Mass, g, Full Model (n=3,896)	**1.0**	**0.4, 1.5**	**0.001**
Full + roadway noise (n=3,890)	1.0	0.4, 1.5	0.001
Full + CRP and IL-6 (n=3,804)	1.1	0.5, 1.6	<0.001
Full + % emphysema (Chest CT) & self reported asthma or emphysema (n=3,893)	0.9	0.4, 1.5	0.001
RVEDV, mL, Full Model (n=3,896)	**4.1**	**0.5, 7.7**	**0.03**
Full + roadway noise (n=3,890)	3.9	0.3, 7.6	0.04
Full + CRP and IL-6 (n=3,804)	4.2	0.5, 7.8	0.03
Full + % emphysema (Chest CT) & self reported asthma or emphysema (n=3,893)	3.7	0.1, 7.3	0.04

Abbreviations: NO_2=nitrogen dioxide, CI=confidence interval, RV= right ventricular, CRP=c-reactive protein, IL-6=interleukin-6, CT=computed tomography, RVEDV= right ventricular end-diastolic volume

**Adjusted for age, sex, race/ethnicity, height, weight, city, education, income, smoking, pack-years, hypertension, diabetes, cholesterol, and impaired glucose tolerance*

Table E2. Residential stability as a proxy for the timing of exposure to traffic related air pollution: a sliding time window analysis of the full model*

Number of years lived in the same neighborhood	n	RV mass (g)	per interquartile increase in NO_2 95% CI	p-value
0 to 5 years	785	1.0	(-0.2, 2.4)	0.09
1 to 6 years	834	1.1	(-0.2, 2.3)	0.09
2 to 7 years	848	1.3	(0.0, 2.5)	0.04
3 to 8 years	816	1.8	(0.5, 3.0)	0.005
4 to 9 years	743	1.6	(0.3, 2.9)	0.02
5 to 10 years	773	1.6	(0.3, 2.9)	0.02
6 to 11 years	727	1.6	(0.3, 2.9)	0.01
All years	**3,896**	**1.0**	**(0.4, 1.5)**	**0.001**
	n	RVEDV (mL)	95% CI	p-value
0 to 5 years	785	4.8	(-3.2, 12.8)	0.24
1 to 6 years	834	4.7	(-3.1, 12.5)	0.24
2 to 7 years	848	4.4	(-3.5, 12.3)	0.28
3 to 8 years	816	7.5	(-0.5, 15.5)	0.07
4 to 9 years	743	7.2	(-1.2, 15.6)	0.10
5 to 10 years	773	3.8	(-4.6, 12.2)	0.37
6 to 11 years	727	4.6	(-3.7, 13.0)	0.28
All years	**3,896**	**4.1**	**(0.5, 7.7)**	**0.03**

Abbreviation: NO_2=nitrogen dioxide, CI=confidence interval, RV=right ventricular, RVEDV=right ventricular end-diastolic volume

**Adjusted for age, sex, race/ethnicity, height, weight, city, education, income, smoking, pack-years, hypertension, diabetes, cholesterol, and impaired glucose tolerance*

Table E3. Multivariable linear regression estimating the associations between NO_x exposure and right ventricular structure and function

Model	per interquartile increase in NO_x (48.1ppb)		
	difference	95% CI	p-value
RV mass, g (Limited model*)	0.2	(0.0, 0.4)	0.04
RV mass, g (Limited model* + city)	0.4	(0.0, 0.8)	0.04
RV mass, g (Full Model†)	0.5	(0.1, 0.8)	0.03
RVEDV, mL (Limited model*)	1.3	(0.0, 2.7)	0.05
RVEDV, mL (Limited model* + city)	0.8	(-1.7, 3.3)	0.52
RVEDV, mL (Full Model†)	1.7	(-0.9, 4.2)	0.20
RVEF, % (Limited model*)	0.0	(-0.4, 0.4)	0.98
RVEF, % (Limited model* + city)	0.1	(-0.6, 0.8)	0.78
RVEF, % (Full Model†)	0.1	(-0.6, 0.9)	0.72

Abbreviations: NO_x= oxides of nitrogen, CI= confidence interval, ppb= parts per billion, RV=right ventricular, LV= left ventricular, RVEDV= right ventricular end-diastolic volume, LVEDV= left ventricular end-diastolic volume, RVEF= right ventricular ejection fraction, LVEF= left ventricular ejection fraction

**Adjusted for age, sex, race/ethnicity, height and weight*

†Adjusted for age, sex, race/ethnicity, height, weight, city, education, income, smoking, pack-years, hypertension, diabetes, cholesterol, and impaired glucose tolerance

Table E4. Multivariable linear regression estimating the associations between NO_2 exposure by calendar year and right ventricular structure and function in the full model*

Model	per interquartile increase in NO_2		
	difference	95% CI	p-value
Calendar Year 2000 (NO_2 IQR 17.7ppb)			
RV mass, g	0.8	0.2, 1.3	0.005
RVEDV, mL	4.3	0.8, 7.8	0.02
RVEF, %	0.1	-0.9, 1.1	0.82
Calendar Year 2001 (NO_2 IQR 17.0ppb)			
RV mass, g	0.9	0.4, 1.4	0.001
RVEDV, mL	4.4	1.0, 7.8	0.01
RVEF, %	-0.1	-1.1, 0.8	0.77
Calendar Year 2002 (NO_2 IQR 17.5ppb)			
RV mass, g	0.9	0.3, 1.4	0.002
RVEDV, mL	4.1	0.6, 7.6	0.02
RVEF, %	-0.3	-1.3, 0.7	0.56

Abbreviations: NO_2=nitrogen dioxide, CI=confidence interval, IQR= interquartile range, RV=right ventricular, LV= left ventricular, RVEDV= right ventricular end-diastolic volume, LVEDV= left ventricular end-diastolic volume, RVEF= right ventricular ejection fraction, LVEF= left ventricular ejection fraction

**Adjusted for age, sex, race/ethnicity, height, weight, city, education, income, smoking, pack-years, hypertension, diabetes, cholesterol, and impaired glucose tolerance*