ORIGINAL RESEARCH

Ambient Air Pollution Is Associated With the Severity of Coronary Atherosclerosis and Incident Myocardial Infarction in Patients Undergoing Elective Cardiac Evaluation

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***Background*—**The effect of air pollution exposure on atherosclerosis severity or incident clinical events in patients with coronary artery disease is not known.

***Methods and Results*—**We conducted a prospective longitudinal cohort study of 6575 Ohio residents undergoing elective diagnostic coronary angiography. Multinomial regression and Cox proportional hazards models were used to assess the relationship between exposure to fine particulate matter <2.5 μm in diameter ($PM_{2.5}$) and nitrogen dioxide on coronary artery disease severity at baseline and risk of myocardial infarction, stroke, or all-cause mortality over 3 years of follow-up. Among participants with coronary artery disease, exposure to $PM_{2.5}$ levels was associated with increased likelihood of having coronary atherosclerosis that was mild (odds ratio 1.43, 95% CI 1.11–1.83, P=0.005) and severe (odds ratio 1.63, 95% CI 1.26–2.11, P<0.0001), with the effect on severe coronary artery disease being significantly increased compared with mild disease (P_{trend}=0.03). Exposure to higher $PM_{2.5}$ levels was also significantly associated with increased risk of incident myocardial infarction (hazard ratio 1.33, 95% CI 1.02–1.73, P=0.03) but not stroke or all-cause mortality. The association of $PM_{2.5}$ with incident myocardial infarction was not affected after adjustment for Framingham Adult Treatment Panel III (ATP III) risk score or statin therapy. In comparison, there were no significant associations between nitrogen dioxide levels and all-cause mortality or risk of stroke after adjustment for Framingham ATP III risk score.

***Conclusions*—**Exposure to $PM_{2.5}$ increased the likelihood of having severe coronary artery disease and the risk of incident myocardial infarction among patients undergoing elective cardiac evaluation. These results suggest that ambient air pollution exposure may be a modifiable risk factor for risk of myocardial infarction in a highly susceptible patient population. **(*J Am Heart Assoc*. 2016;5:e003947 doi: 10.1161/JAHA.116.003947)**

Key Words: air pollution • coronary atherosclerosis • myocardial infarction

A large body of epidemiological evidence has shown consistent associations between exposure to ambient air pollution and risk of cardiovascular disease (CVD),[1] with the majority of studies conducted in population-based cohorts from the general population. These studies reported associations of various CVD-related phenotypes, including coronary artery disease (CAD), myocardial infarction (MI), and stroke, with both short- and long-term exposure to pollutants such as fine particulate matter with aerodynamic diameter ≤2.5 μm ($PM_{2.5}$), ozone, and nitrogen dioxide (NO_2).[1–3] Although experimental data from animal models also support the notion that ambient air pollution promotes the development of atherosclerosis and related risk factors,[4–7] few studies have investigated the relationship between ambient air pollution exposure and the extent of coronary atherosclerosis in humans because this phenotype usually requires invasive procedures such as coronary angiography. Moreover, the underlying biological processes for these associations are not fully understood, although multiple plausible mechanisms have been proposed, including systemic inflammation, oxidative stress, endothelial dysfunction, thrombosis, and arrhythmia.[8–10]

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Accompanying Tables S1 through S6 and Figure S1 are available at http://jaha.ahajournals.org/content/5/7/e003947/DC1/embed/inline-supplementary-material-1.pdf

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Despite previous evidence linking air pollution with CVD, many questions remain to be answered, particularly with respect to clinical management of highly susceptible populations. Patients with CAD, for example, still have a 50% increased risk of incident events even in the contemporary era of high-potency statin therapy.[11] In this regard, it is not known whether prolonged exposure to air pollution increases risk of incident clinical events and whether the increased risk depends on the presence or extent of coronary atherosclerosis or is attenuated by statin therapy. To address these gaps in knowledge that may inform future prevention strategies, we investigated whether exposure to ambient air pollutants, such as $PM_{2.5}$ and NO_2, was associated with the degree of coronary stenosis and the prospective risk of MI, stroke, or all-cause mortality in a cohort of patients undergoing elective diagnostic coronary angiography.

Methods

Study Population

The Cleveland Clinic GeneBank study is a single-site sample repository generated from consecutive patients undergoing elective diagnostic coronary angiography or elective cardiac computed tomographic angiography with extensive clinical and laboratory characterization and longitudinal observation. Participant recruitment occurred between 2001 and 2007, and all patients provided written informed consent prior to being enrolled. Ethnicity was self-reported, and information regarding demographics, medical history, and medication use was obtained by patient interviews and confirmed by chart reviews at baseline enrollment. Assessment of functional capacity, as a measure of physical activity, was estimated at enrollment based on the self-administered Duke Activity Status Index questionnaire.[12] All clinical outcome data were verified by source documentation. At baseline, CAD was defined as adjudicated diagnoses of stable or unstable angina, MI (adjudicated definition based on defined electrocardiographic changes or elevated cardiac enzymes), angiographic evidence of ≥50% stenosis in ≥1 major epicardial vessel, and/or a history of known CAD (documented MI, CAD, or history of revascularization). Coronary atherosclerosis severity at baseline was defined as the number of major epicardial vessels with ≥50% stenosis. All quantitative determinations of coronary stenosis were adjudicated by a cardiologist blinded to participant identity. Prospective cardiovascular risk was assessed by the incidence of all-cause mortality or nonfatal MI or stroke during 3 years of follow-up from the time of enrollment. Participants were contacted annually either directly in person, by telephone follow-up, or by other means. In the case of a participant being deceased, a preidentified and pre–agreed upon proxy was contacted. Nonfatal events were defined as MI or stroke in patients who survived at least 48 hours following the onset of symptoms, and all adjudicated outcomes were confirmed using source documentation. The GeneBank Study has been used previously for discovery and replication of novel genes and risk factors for CAD.[13–20] The present study was approved by the institutional review boards of the Cleveland Clinic and the University of Southern California Keck School of Medicine.

Clinical Laboratory Measurements

Samples were collected from overnight fasted participants on the day of elective cardiac catheterization. Plasma aliquots were isolated from whole blood collected into EDTA tubes, maintained at 0 to 4°C immediately following phlebotomy, processed within 4 hours of blood draw, and stored at −80°C until analysis. Plasma levels of total cholesterol, low- and high-density lipoprotein cholesterol, triglycerides, and high-sensitivity C-reactive protein were measured on the Architect platform (Abbott Diagnostics).

Air Pollution Exposure Assessment

Daily concentrations of $PM_{2.5}$ and NO_2 in the United States from 1998 through 2010 were downloaded from the US Environmental Protection Agency's (EPA) Air Quality System (AQS) database (https://www.epa.gov/aqs). This national database contains hourly and daily outdoor air pollution concentration data back to the late 1970s, and the network has remained fairly stable since 2000 for $PM_{2.5}$ and NO_2. Data for $PM_{2.5}$ and NO_2 were primarily limited to those collected with Federal Reference Method samplers and Federal Equivalent Method monitors. Non–Federal Reference Method $PM_{2.5}$ and NO_2 data were used only when Federal Reference or Equivalent Method measurement data were not available for a location. Because ozone was not routinely monitored across the year in many locations, it was not included in this study. Automated quality control checks on the concentration ranges and persistence were applied to the AQS data. Because the national air-monitoring networks began measuring $PM_{2.5}$ and NO_2 in 1999, few data exist prior to that date. The hourly $PM_{2.5}$ and NO_2 data were averaged into standard daily exposure metrics, and monthly averages were calculated from the daily average pollutant data. A 75% data completeness criterion was used in determining monthly averages. Because the historical daily $PM_{2.5}$ measurements were often made once every third or sixth day rather than daily, the completeness criterion was applied based on the expected completeness for a 1-in-6-day sampling schedule. Monthly air-quality exposure values were spatially interpolated from the air-quality monitoring locations of the residential ZIP code coordinates (based on geographic centroid) of each

participant at the time of enrollment into the GeneBank study. The station-specific monthly air-quality data were spatially interpolated using inverse distance-squared weighting. The data from up to 4 air-quality measurement stations were included in each interpolation. Because of the regional nature of $PM_{2.5}$ and NO_2 concentrations, a maximum interpolation radius of 50 km was used; however, when a residence was located within 5 km of ≥1 station with valid observations, the interpolation was based solely on the concentrations from the stations within 5 km. The same 75% completeness criteria were applied to the estimates of average exposures for each exposure period. Estimated levels of $PM_{2.5}$ and NO_2 were based on 46 and 4 monitoring sites, respectively.

Land Use Assignment

The National Land Cover Database (NLCD) for 2011 was used to assess the extent of industrial development near each participant's reported residence.[21] The NLCD provides many categories of land cover at the native 30-m resolution of the Landsat Thematic Mapper. Specifically, we used the land cover class (class 24: developed, high intensity) that combines commercial, industrial, high-density residential, and transportation land use and is characterized by 80% to 100% impervious surfaces. The percentage of industrial-like land cover in the postal ZIP code area, defined by the 2010 5-digit ZIP code boundaries, of each participant's residence was computed in a geographic information system (ArcGIS version 10.3; Esri). This measure was significantly correlated with levels before and after enrollment of $PM_{2.5}$ (r=0.25 and r=0.29, respectively; P<0.0001) and NO_2 (r=0.22 and r=0.20, respectively; P<0.0001).

Statistical Analyses

Primary outcomes included the degree of coronary atherosclerosis severity at baseline (0, 1–2, or ≥3 epicardial vessels with ≥50% stenosis) and prospective incident events (nonfatal MI, stroke, all-cause mortality) over 3 years of follow-up. Participants who experienced an event within 14 days of enrollment were excluded from the analyses to omit acute events during the initial baseline period. Air pollution variables for each participant included estimated levels of exposure to $PM_{2.5}$ (in $\mu g/m^3$) and NO_2 (in parts per billion) during the 36 months prior to baseline enrollment and the 36 months after enrollment for cross-sectional and prospective analyses, respectively. Multinomial logistic regression was applied to evaluate the effect of air pollution on coronary atherosclerosis severity among participants with CAD at baseline. Cox proportional hazards models were used to estimate the effect of ambient air pollution on prospective events among all participants and in a subset with CAD at baseline. To test for confounding after adjustment for a priori covariates (age, sex, smoking, and education), we performed sensitivity analyses with the following variables: obesity (body mass index <30 versus ≥30), statin therapy use (yes or no), high-sensitivity C-reactive protein, and coronary atherosclerosis severity (0, 1–2 or ≥3 epicardial vessels with ≥50% stenosis). In addition, we tested whether cardiovascular risk factors modified the effects of air pollution on CAD outcomes by further adjusting for Framingham Adult Treatment Panel III (ATP III) risk score (including total and high- and low-density lipoprotein cholesterol levels, presence of atherosclerosis, family history of premature coronary heart disease, smoking, hypertension, diabetes mellitus, and age). None of the above potential covariates changed the estimates considerably (>10%); therefore, the final model included the a priori selected covariates of age, sex, current smoking (yes or no), and education level (college or higher, high school, less than high school) as adjusting variables. To assess potential residual confounding, physical activity and commercial/industrial land use were included in the models to test their influence on the effect estimates. Multipollutant models were further adjusted for the other respective copollutant. Additional analyses for association of $PM_{2.5}$ levels with incident MI were performed after stratifying by the presence of coronary atherosclerosis (≥1 epicardial vessel with ≥50% stenosis) and/or statin therapy use and by median age (≥64 years), sex, education level, current smoking, or obesity (body mass index ≥30). Adjusted hazard ratios or odds ratios with 95% CIs are reported with 2-sided P values. Interaction P values were obtained from likelihood ratio tests. All analyses were performed using SAS 9.3 (SAS Institute Inc).

Results

Clinical Characteristics of GeneBank Participants

The clinical characteristics of the GeneBank participants in this study are described in Table 1 and Table S1. To avoid the potential for referral bias, only those participants whose residential ZIP codes were reported as being in Ohio (n=6575) were included. As expected for a patient population undergoing elective coronary angiography for clinical evaluation, the majority of participants at enrollment were male, had prevalent CAD, and were using statin therapy. In addition, a significant fraction of participants were obese or had diabetes, and most had attained at least a high school level of education (Table 1 and Table S1).

Description of Air Pollutants

Air pollution variables included average estimated daily exposure levels of $PM_{2.5}$ and NO_2 during the 36 months prior to enrollment and the 36 months after enrollment for

Table 1. Clinical Characteristics of GeneBank Participants Residing in Ohio

Trait	n=6575
Age, y	64±11
Male	4462 (68)
CAD at baseline	4904 (77)
Number of epicardial vessels with stenosis ≥50%	
0 vessels	1961 (30)
1 or 2 vessels	2503 (38)
≥3 vessels	2111 (32)
MI	288 (4)
Stroke	127 (2)
All-cause mortality	590 (9)
CRP, mg/L*	2.6 (1.1–6.3)
Total cholesterol, mg/dL	171±41
HDL cholesterol, mg/dL	40±13
LDL cholesterol, mg/dL	100±34
Triglycerides, mg/dL	155±110
Framingham ATP III risk score†	
Male	7.9±3.0
Female	10.9±4.8
BMI category, kg/m^2	
<30	3848 (59)
≥30	2727 (41)
Diabetes mellitus	2485 (38)
Current smokers	916 (14)
Using statin therapy	3857 (59)
Education‡	
College or higher	2812 (43)
High school	2809 (43)
Less than high school	951 (15)
DASI score§	37.7±15.9
Commercial/industrial land use development‖	3.2±4.0

Data are shown as mean±SD or numbers of participants (%). ATP III indicates Adult Treatment Panel III; BMI, body mass index; CAD, coronary artery disease; CRP, high sensitivity C-reactive protein; DASI, Duke Activity Status Index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MI, myocardial infarction.
*CRP levels were available for 3572 participants and are shown as median (IQR).
†Framingham ATP III risk scores were available for 6395 participants. Sex-specific risk scores were calculated according to ATP III guidelines using total and LDL- and HDL cholesterol levels, presence of atherosclerosis, smoking status, hypertension, diabetes mellitus, and age.
‡≥College indicates 2–4 years of college or postgraduate education.
§DASI (measure of physical activity) was available for 5509 participants.
‖Commercial/industrial land development indicates the percentage of commercial/industrial land use in current ZIP code boundaries.

cross-sectional and prospective analyses, respectively. As shown in Figure 1, GeneBank participants who reported their residential ZIP codes as being located in Ohio were clustered in metropolitan regions, particularly in the area surrounding Cleveland. Estimated exposure levels for $PM_{2.5}$ in the 36 months before and after enrollment were available for ≈6100 Ohio residents and ranged from 10 to 21 μg/m^3, whereas NO_2 levels were available for ≈4600 participants and ranged from 5 to 23 parts per billion (Figure 2). Exposure levels of each pollutant during the 36 months before and after enrollment were strongly correlated with each other, with comparable means, whereas $PM_{2.5}$ and NO_2 levels were only weakly correlated with each other regardless of exposure period (Figure S1). Based on data from the EPA, $PM_{2.5}$ levels in Ohio during the pre- and postenrollment periods (1998–2010) were comparable to US national and regional trends, whereas NO_2 levels were lower. This may have been caused by the small number of monitoring sites for NO_2, which led to fewer participants receiving assignments for this pollutant compared with $PM_{2.5}$ and limiting exposure contrast.

Effect of Air Pollution Exposure on Severity of Coronary Atherosclerosis

We determined the association of air pollution levels before study entry with the extent of coronary atherosclerosis among patients with CAD, defined based on angiographic evidence at baseline or a positive history of CAD. After adjustment for age, sex, education level, and smoking, a 2-SD (2.2-μg/m^3) increase in exposure to $PM_{2.5}$ over the 36 months preceding enrollment was associated with significantly increased likelihood (odds ratio 1.43, 95% CI 1.11–1.83; P=0.005) of having mild coronary disease, defined as 1 to 2 vessels with ≥50% stenosis, compared with patients with a history of CAD but no vessels with ≥50% stenosis at baseline (Table 2). The association of $PM_{2.5}$ with severe coronary atherosclerosis, defined as ≥3 vessels with ≥50% stenosis, was even more pronounced (odds ratio 1.63, 95% CI 1.26–2.11; P<0.001) (Table 2). A test of heterogeneity demonstrated that the effect of $PM_{2.5}$ on severe coronary atherosclerosis was significantly different from the effect on mild disease (heterogeneity P=0.03) (Table 2). Additional adjustment for the Framingham ATP III risk score, which captures several other CVD risk factors, did not appreciably change the effect estimates (Table 2). The magnitude and significance of the association of $PM_{2.5}$ with the extent of coronary atherosclerosis were also not markedly affected after further adjustment for additional potential covariates (Table S2). In comparison, increased NO_2 levels (2 SD; 4.1 parts per billion) were not associated with the likelihood of having mild or severe atherosclerotic disease (Table 3).

Effect of Air Pollutants on Incident Clinical Events

We next investigated whether air pollution levels were associated with prospective risk of incident MI, stroke, and

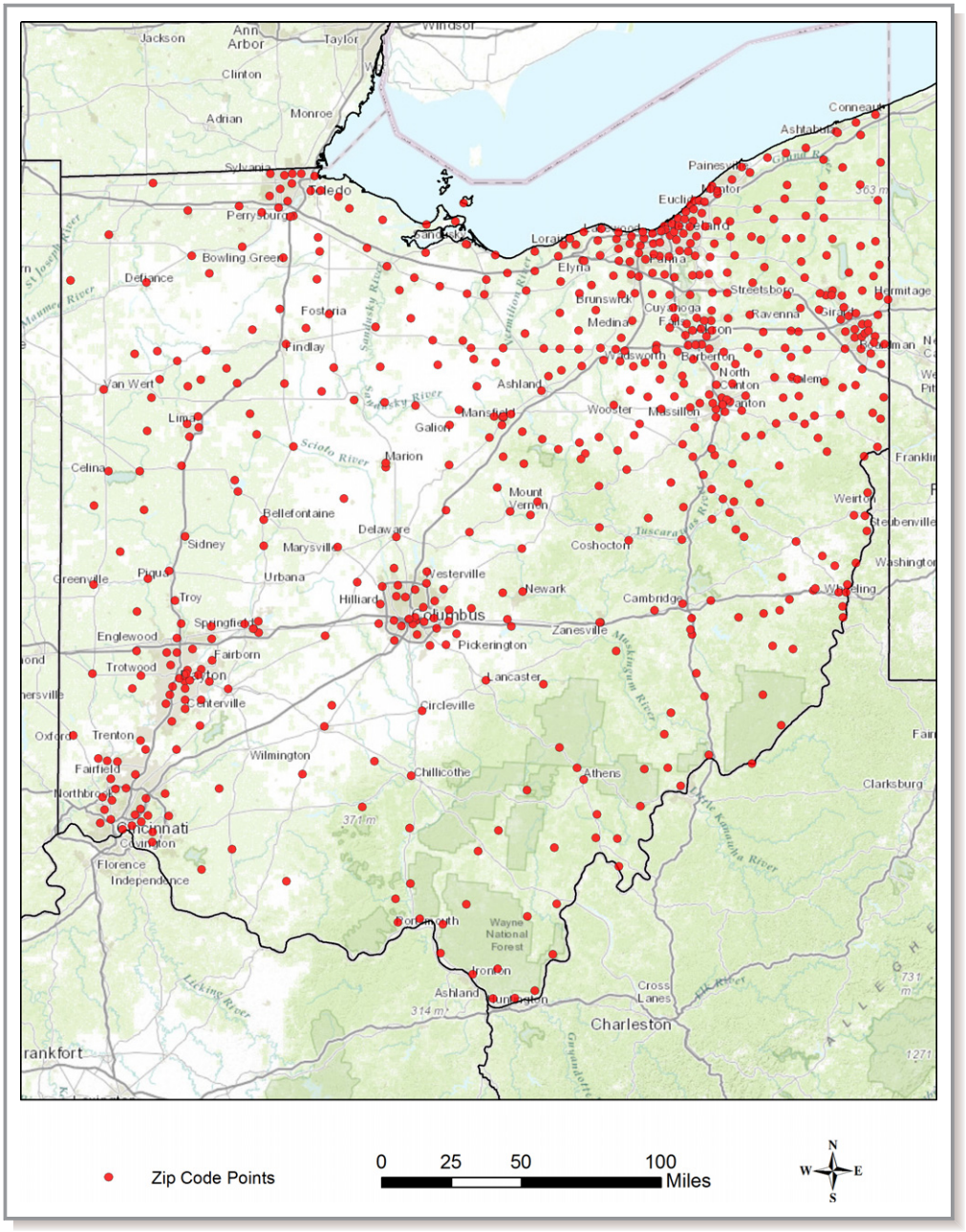

Figure 1. Distribution of residential ZIP codes in the GeneBank cohort. The geographic locations of the residential ZIP codes reported by GeneBank participants residing in Ohio are denoted by red dots. Most participants were clustered in metropolitan regions, particularly the surrounding Cleveland area, although there are also relatively high-density clusters in the northeast, central, and southwest regions of Ohio.

all-cause mortality among all GeneBank participants. A 2-SD increase in $PM_{2.5}$ levels over 36 months of follow-up after angiographic evaluation was associated with significantly increased risk of MI (hazard ratio 1.33, 95% CI 1.02–1.73; P=0.03) (Table 4). The effect estimates for the association of $PM_{2.5}$ and MI risk were not substantially changed in models that adjusted for Framingham ATP III risk score (Table 4) and other potential covariates (Table S3) or in a multipollutant model adjusting for NO_2 levels (Table S4). Restricting these analyses to only patients with angiographically determined CAD at baseline yielded similar effect estimates (Table S3). To address the potential for referral bias further, we also carried out an analysis that included only participants from the greater Cleveland metropolitan area (n=3437). The effect estimate obtained from this subanalysis with ≈2400 fewer participants (hazard ratio 1.12; 95% CI 0.96–1.30; P=0.15) was comparable and directionally consistent with the analysis that included all Ohio residents (Table 4). By comparison,

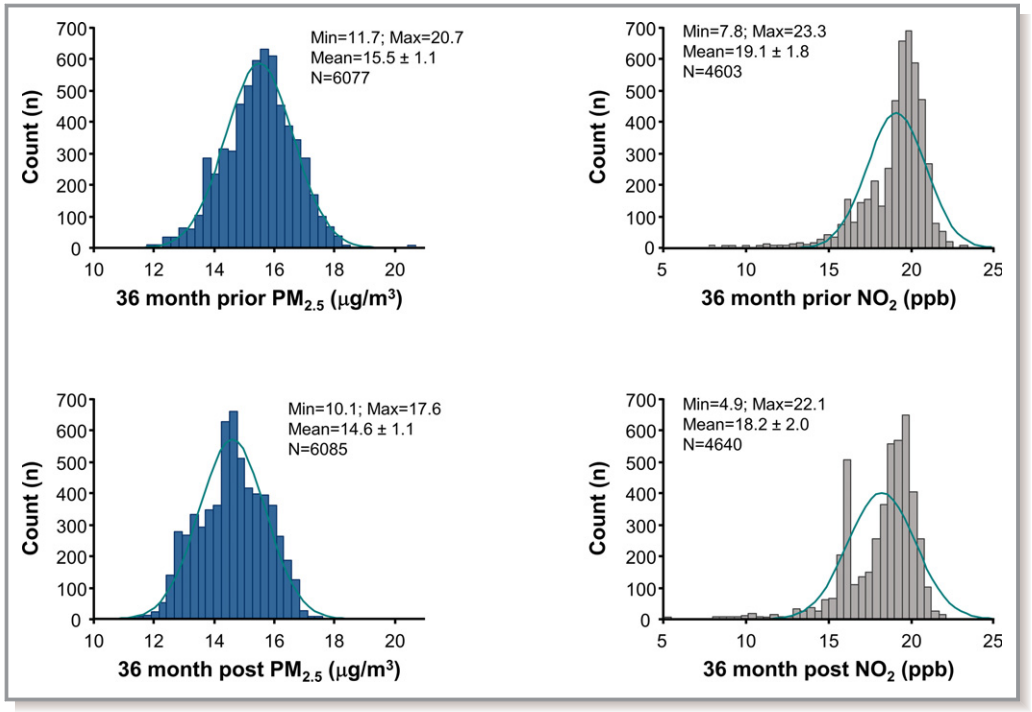

Figure 2. Distribution of ambient air pollution exposure levels. The distributions of $PM_{2.5}$ (blue) and NO_2 (gray) levels in the GeneBank cohort during the 36 months before and after enrollment are shown. For each time period, $PM_{2.5}$ and NO_2 levels (mean±SD) were estimated for ≈6100 and ≈4600 participants, respectively. max indicates maximum; min, minimum; NO_2, nitrogen dioxide; $PM_{2.5}$, fine particulate matter <2.5 μm in diameter; ppb, parts per billion.

there were no associations between $PM_{2.5}$ or NO_2 levels with risk of all-cause mortality (Tables 4 and 5), whereas a 2-SD increase in NO_2 levels was associated with elevated risk of stroke (hazard ratio 1.72, 95% CI 1.03–2.87; P=0.04) (Table 5); however, this association was no longer significant after adjustment for Framingham ATP III risk score (Table 5). It is possible that the lack or attenuation of significance in some of these analyses may have been due to reduced sample size. There were, for example, fewer numbers of participants for whom NO_2 levels or complete data on the full set of covariates were available (Tables S3 and S4).

Effect of $PM_{2.5}$ on Incident MI Stratified by the Presence of Coronary Atherosclerosis at Baseline and/or by Statin Therapy

We next performed stratified analyses and formal tests of interaction to determine whether the effect of $PM_{2.5}$ on incident MI was modulated by coronary atherosclerosis at baseline or by the use of statin therapy. Stratifying the analyses by participants who had coronary atherosclerosis at baseline, who used statin medications, or both did not reveal statistical evidence that the effects of $PM_{2.5}$ on MI risk were modulated by these factors (Table S5). There was also no significant statistical evidence that risk of MI was modulated by 3-way interactions among $PM_{2.5}$, coronary atherosclerosis, and statin therapy use (3-way interaction P=0.33). Last, we investigated whether any of the effects of $PM_{2.5}$ on risk of MI were modified by a priori covariates and performed analyses stratified by median age, sex, education level, smoking, coronary atherosclerosis severity, and obesity (body mass index ≥30), which also included formal tests of interaction. There were no significant effect modifications among these covariates, $PM_{2.5}$, and risk of MI (Table S6).

Discussion

In the present study, we evaluated the effects of prolonged exposure to ambient air pollution on prevalent and incident risk of adverse clinical events in residents of Ohio who had undergone elective cardiac evaluation at the Cleveland Clinic. Our results demonstrated that a 2-SD increase in exposure to $PM_{2.5}$ levels during the 36 months preceding enrollment was associated with 43% to 63% increased likelihood of having angiographically determined coronary atherosclerosis at study entry. The effect estimates for these associations were fairly robust with adjustment for various covariates and potential confounders, such as Framingham ATP III risk score, obesity, smoking, physical activity, and land use development. Our results further demonstrated that the effect of $PM_{2.5}$

Table 2. Association of $PM_{2.5}$ Levels With Coronary Atherosclerosis Severity Among Participants With CAD at Baseline

Outcome	n (Rate)	OR (95% CI)		*P* Value*	*P* Value†
		1 μg/m³ $PM_{2.5}$	2 SD $PM_{2.5}$		
Model 1					
0 vessels	271 (0.06)	1.00	1.00	—	—
1 or 2 vessels	2324 (0.51)	1.17 (1.05–1.31)	1.43 (1.11–1.83)	0.005	—
≥3 vessels	1923 (0.43)	1.24 (1.11–1.40)	1.63 (1.26–2.11)	<0.001	0.03
Model 2					
0 vessels	256 (0.06)	1.00	1.00	—	—
1 or 2 vessels	2283 (0.52)	1.15 (1.03–1.29)	1.37 (1.06–1.77)	0.02	—
≥3 vessels	1887 (0.43)	1.22 (1.09–1.37)	1.56 (1.20–2.04)	<0.001	0.04

ORs, 95% CIs, and *P* values were obtained using multinomial logistic regression with 36-month prior-to-baseline exposure levels. Model 1 was adjusted for age, sex, education level (college or higher, high school, less than high school), and current smoking. Model 2 included model 1 plus adjustment for Framingham Adult Treatment Panel III risk score. CAD indicates coronary artery disease; OR, odds ratio; $PM_{2.5}$, fine particulate matter <2.5 μm in diameter.

*Multinomial test of effects of $PM_{2.5}$ levels on coronary atherosclerosis severity (defined as 1–2 or ≥3 epicardial vessels with ≥50% stenosis) compared with the reference group (no epicardial vessels with ≥50% stenosis).

†Test of heterogeneity for the effect of $PM_{2.5}$ levels on coronary atherosclerosis severity: 1- or 2-vessel disease vs ≥3-vessel disease.

significantly differed as a function of coronary atherosclerosis severity among patients with a history of CAD or documented angiographic evidence of CAD at enrollment. These observations are consistent with cross-sectional associations between $PM_{2.5}$ and subclinical atherosclerosis.[22–24]

Our study also represents one of the first analyses with ambient air pollution exposure and incident adverse clinical events in participants undergoing elective cardiac evaluation by angiography. In this highly susceptible patient population, we demonstrated that a 2.2-μg/m³ increase in $PM_{2.5}$ levels during 3 years of follow-up was specifically associated with increased risk of MI but not stroke or all-cause mortality. The effect estimates remained comparable when additional covariates, such as NO_2 levels, physical activity, or commercial/industrial land use, were included in the model, although the significance of the association was slightly attenuated. A possible explanation for this observation may be that the percentage of high-intensity land development served as a proxy for various unmeasured confounding variables, such as socioeconomic status, even after adjustment for education level. Furthermore, because the percentage of commercial/industrial land use was significantly correlated with $PM_{2.5}$ levels in our data set (r=0.29; P<0.0001), its inclusion in the models may have led to overadjustment. Last, the reduced

Table 3. Association of NO_2 Levels With Coronary Atherosclerosis Severity Among Participants With CAD at Baseline

Outcome	n (Rate)	OR (95% CI)		*P* Value*	*P* Value†
		1 ppb NO_2	2 SD NO_2		
Model 1					
0 vessels	211 (0.06)	1.00	1.00	—	—
1 or 2 vessels	1795 (0.52)	1.00 (0.92–1.09)	1.01 (0.75–1.35)	0.95	—
≥3 vessels	1471 (0.42)	0.98 (0.90–1.06)	0.92 (0.68–1.24)	0.58	0.20
Model 2					
0 vessels	200 (0.06)	1.00	1.00	—	—
1 or 2 vessels	1763 (0.52)	1.00 (0.92–1.09)	1.00 (0.74–1.34)	0.98	—
≥3 vessels	1441 (0.42)	0.97 (0.89–1.06)	0.90 (0.67–1.23)	0.52	0.19

ORs, 95% CIs, and *P* values were obtained using multinomial logistic regression with 36-month prior-to-baseline exposure levels. Model 1 was adjusted for age, sex, education level (college or higher, high school, less than high school), and current smoking. Model 2 included model 1 plus adjustment for Framingham Adult Treatment Panel III risk score. CAD indicates coronary artery disease; NO_2, nitrogen dioxide; OR, odds ratio; ppb, parts per billion.

*Multinomial test of effects of NO_2 levels on coronary atherosclerosis severity (defined as 1–2 or ≥3 epicardial vessels with ≥50% stenosis) compared with the reference group (no epicardial vessels with ≥50% stenosis).

†Test of heterogeneity for the effect of NO_2 levels on coronary atherosclerosis severity: 1- or 2-vessel disease vs ≥3-vessel disease.

Table 4. Association of $PM_{2.5}$ Levels With Incident Clinical Events Over 3 Years of Follow-up

Outcome	n (Rate)	HR (95% CI)		*P* Value
		1 μg/m^3 $PM_{2.5}$	2 SD $PM_{2.5}$	
Model 1				
MI	5854 (0.04)	1.14 (1.01–1.28)	1.33 (1.02–1.73)	0.03
Stroke	5875 (0.02)	1.07 (0.89–1.27)	1.15 (0.78–1.69)	0.48
All-cause mortality	5854 (0.08)	1.08 (0.99–1.18)	1.18 (0.98–1.43)	0.08
Model 2				
MI	5696 (0.04)	1.14 (1.01–1.28)	1.32 (1.02–1.17)	0.04
Stroke	5715 (0.02)	1.03 (0.86–1.23)	1.07 (0.73–1.59)	0.72
All-cause mortality	5696 (0.07)	1.07 (0.98–1.17)	1.16 (0.96–1.41)	0.13

HRs, 95% CIs, and *P* values were obtained using Cox proportional hazards models with 36-month postbaseline exposure levels. Model 1 was adjusted for age, sex, education level (college or higher, high school, less than high school), and current smoking. Model 2 includes model 1 plus adjustment for Framingham Adult Treatment Panel III risk score. HR indicates hazard ratio; MI, myocardial infarction; $PM_{2.5}$, fine particulate matter <2.5 μm in diameter

sample sizes in the fully adjusted models could have decreased the power and the level of significance for the association of $PM_{2.5}$ with risk of MI.

Other groups have reported that lipid-lowering therapies reduce the adverse effects of air pollution on CVD-related phenotypes.[25–28] In our patient population, we did not obtain evidence of differential effects of $PM_{2.5}$ on prospective risk of MI when participants were stratified by the use of statins. Information on statin use, however, was available only at baseline, and it is possible that patients had changes in medication use during the follow-up period that could have modulated the association between $PM_{2.5}$ and incident MI. The association of $PM_{2.5}$ with MI also did not vary as a function of other strata, such as sex, smoking status, education level, obesity, or the presence or severity of coronary atherosclerosis at baseline (≥50% stenosis in ≥1 major epicardial vessel). By comparison, a prospective analysis with >12 000 participants drawn from the Intermountain Heart Collaborative Study in Utah reported a modest 4.5% increased risk of MI and/or unstable angina for a 10-μg/m^3 increase in concurrent-day $PM_{2.5}$.[29] These participants were also recruited through coronary angiography, but in contrast to our results, the increased risk of an acute coronary event was evident in those with ≥1 severely diseased coronary vessel, defined as ≥70% stenosis. Notably, Pope et al evaluated acute exposure during the few days surrounding the coronary event, whereas we used estimates of exposure over the ensuing 36 months after angiography. Consequently, factors related to assessment and duration of exposure, geographic area, sample size, study populations, and/or disease phenotype definitions could potentially account for some of the differences between our results and those in the Intermountain Heart Collaborative Study.

Table 5. Association of NO_2 Levels With Incident Clinical Events Over 3 Years of Follow-up

Outcome	n (Rate)	HR (95% CI)		*P* Value
		1 ppb NO_2	2 SD NO_2	
Model 1				
MI	4490 (0.04)	0.99 (0.92–1.06)	0.94 (0.70–1.26)	0.68
Stroke	4504 (0.02)	1.14 (1.01–1.30)	1.72 (1.03–2.87)	0.04
All-cause mortality	4489 (0.08)	1.00 (0.95–1.06)	1.00 (0.81–1.25)	0.98
Model 2				
MI	4364 (0.04)	0.98 (0.91–1.05)	0.91 (0.68–1.21)	0.51
Stroke	4377 (0.02)	1.12 (0.98–1.27)	1.56 (0.93–2.61)	0.09
All-cause mortality	4363 (0.08)	1.00 (0.94–1.05)	0.99 (0.79–1.23)	0.92

HRs, 95% CIs, and *P* values were obtained using Cox proportional hazards models with 36-month postbaseline exposure levels. Model 1 was adjusted for age, sex, education level (college or higher, high school, less than high school), and current smoking. Model 2 included model 1 plus adjustment for Framingham Adult Treatment Panel III risk score. HR indicates hazard ratio; MI, myocardial infarction; NO_2, nitrogen dioxide; ppb, parts per billion.

We also note some limitations of our study. First, despite estimating exposure over 36 months, this time period may not be suitable for examining more long-term effects of ambient air pollution on adverse clinical events, even in high-risk populations. Second, the overall event rate for MI, stroke, or all-cause mortality over 36 months of follow-up was still relatively low, possibly rendering some of the analyses underpowered for detecting associations or prone to spurious associations. This may have been relevant for the analyses assessing $PM_{2.5}$ exposure and MI risk that were stratified by statin therapy use or presence of coronary atherosclerosis or the more fully adjusted statistical models because fewer participants had complete data for the additional covariates that were included. For similar reasons, the association of NO_2 with incident events may also have been underpowered because exposure estimates for this pollutant were available in 25% fewer participants than for $PM_{2.5}$. Third, this study included only patients from a single tertiary care center in Cleveland and restricted the analyses to residents of Ohio. We also did not have information on how long patients lived at the reported residential addresses. Consequently, the results may not be generalizable to other geographic locations or populations because the effects of ambient air pollution exposure may vary depending on the sources of pollution, the exposure period, and/or population characteristics. Last, there is the possibility of misclassification in exposure measurements, but these are likely to be nondifferential and would bias the results toward the null.

Conclusions

We demonstrated that exposure to $PM_{2.5}$ was associated with the extent of CAD severity and increased risk of incident MI among patients undergoing elective cardiac evaluation. These data suggest that reducing exposure to ambient air pollution is an environment-modifying strategy that may be especially relevant for patients with CAD who are at high risk for MI. The paucity of data on the relationship between ambient air pollution exposure and incident events in patients with CAD merits additional studies with larger study samples to address these questions, which may have important clinical implications for secondary prevention strategies in highly susceptible patients.

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Disclosures

None.

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Supplemental Material

Ambient Air Pollution is Associated with the Severity of Coronary Atherosclerosis and Incident Myocardial Infarction in Patients Undergoing Elective Cardiac Evaluation

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Table S1. Clinical Characteristics of GeneBank Subjects Residing in Ohio Stratified by Type of Incident Event.

Trait	No Events (n=5662)	MI (n=288)	Stroke (n=127)	Death (n=590)
Age (years)	63 ± 11	68 ± 11	70 ± 9	71 ± 10
Male (%)	3824 (68)	209 (73)	86 (68)	403 (68)
CAD at baseline (%)	4106 (75)	263 (92)	105 (86)	517 (90)
Number of epicardial vessels with stenosis ≥50%				
0 vessels (%)	1813 (32)	38 (13)	26 (20)	94 (16)
1 or 2 vessels (%)	2153 (38)	113 (39)	43 (34)	224 (38)
≥3 vessels (%)	1696 (30)	137 (48)	58 (46)	272 (46)
*CRP (mg/L)	2.4 ± 4.9	3.5 ± 7.2	3.0 ± 5.5	5.1 ± 1.07
Total cholesterol (mg/dl)	172 ± 41	172 ± 45	173 ± 43	162 ± 40
HDL cholesterol (mg/dl)	40 ± 13	38 ± 12	39 ± 12	39 ± 14
LDL cholesterol (mg/dl)	101 ± 33	99 ± 35	103 ± 36	93 ± 33
Triglycerides (mg/dl)	155 ± 112	171 ± 123	147 ± 85	142 ± 83
†Framingham ATP III risk score				
Male	7.8 ± 3.0	8.8 ± 2.8	9.6 ± 2.6	9.2 ± 2.8
Female	10.7 ± 4.9	12.4 ± 4.8	12.9 ± 4.5	12.4 ± 4.1
BMI category (kg/m^2)				
<30 (%)	3278 (58)	185 (64)	68 (54)	377 (64)
≥30 (%)	2384 (42)	103 (34)	59 (47)	213 (36)
Diabetics (%)	2020 (36)	139 (48)	62 (49)	315 (53)
Current smokers (%)	786 (14)	44 (15)	21 (17)	78 (13)
Using statin therapy (%)	3325 (59)	173 (60)	78 (61)	339 (57)
‡Education				
≥College (%)	2515 (44)	99 (34)	40 (32)	192 (32)
High School (%)	2385 (42)	132 (46)	68 (54)	265 (45)
<High school (%)	761 (13)	57 (20)	19 (49)	133 (23)
§DASI score	39.1 ± 15.5	30.3 ± 16.7	32.7 ± 14.9	26.3 ± 15.7
‖Commercial/industrial land use development	3.1 ± 4.0	3.8 ± 5.2	3.4 ± 3.9	3.6 ± 4.3

Data are shown as mean ± SD or numbers of individuals (%).
[*]CRP=high sensitivity C-reactive protein levels were available in 3572 subjects and are shown as median ± IQR.
[†]Framingham ATP III risk scores were available in 6395 subjects. Sex-specific risk scores were calculated according to ATP III guidelines using total-, LDL-, and HDL-cholesterol levels; presence of atherosclerosis; smoking status; hypertension; diabetes and age.
[‡]≥College=2-4 years of college or post graduate education.
[§]DASI=Duke Activity Status Index (measure of physical activity) was available in 5509 subjects.
[‖]Commercial/industrial land development: percentage of commercial/industrial land use in current zip code boundaries.

Table S2. Association of $PM_{2.5}$ Levels (1μg/m^3) with Coronary Atherosclerosis Severity Among Subjects with CAD at Baseline and with Adjustment for Potential Covariates.

	OR (95% CI)					
Model	**0 vessels**	**1-2 vessels**	***p-value**	**≥3 vessels**	***p-value**	**†p-value**
1	1.00 (n=271)	1.17 (1.05-1.31) (n=2324)	$5.2x10^{-3}$	1.24 (1.11-1.40) (n=1923)	<0.001	0.03
2	1.00 (n=271)	1.17 (1.05-1.31) (n=2324)	$5.5x10^{-3}$	1.24 (1.11-1.39) (n=1923)	<0.001	0.03
3	1.00 (n=271)	1.17 (1.04-1.30) (n=2324)	$6.8x10^{-3}$	1.25 (1.11-1.40) (n=1923)	<0.001	0.02
4	1.00 (n=134)	1.18 (1.01-1.39) (n=1380)	0.04	1.27 (1.08-1.50) (n=1090)	.004	0.05
5	1.00 (n=266)	1.15 (1.02-1.29) (n=2306)	0.02	1.22 (1.09-1.38) (n=1914)	<0.001	0.02
6	1.00 (n=245)	1.19 (1.05-1.38) (n=2084)	$4.6x10^{-3}$	1.25 (1.11-1.41) (n=1754)	<0.001	0.10

Odds ratios (ORs), 95% confidence intervals (CIs) obtained using multinomial logistic regression with 36-month prior-baseline exposure levels. Coronary atherosclerosis severity was defined as having 1-2 or ≥3 epicardial vessels with ≥50% stenosis.
Model 1: Adjusted for age, sex, education level (≥college, high school, <high school), and current smoking (yes/no).
Model 2: Model 1 plus adjustment for obesity (BMI ≥30).
Model 3: Model 1 plus adjustment for statin therapy (yes/no).
Model 4: Model 1 plus adjustment for C-reactive protein (CRP).
Model 5: Model 1 plus adjustment for percentage of high intensity land development (commercial/industrial land use).
Model 6: Model 1 plus adjustment for physical activity.
*Multinomial test of effects of $PM_{2.5}$ levels on coronary atherosclerosis severity (defined as 1-2 or ≥3 epicardial vessels with ≥50% stenosis) compared to reference group (positive history of CAD but with 0 vessels with ≥50% stenosis at enrollment).
†Test of heterogeneity for the effect of $PM_{2.5}$ levels on coronary atherosclerosis severity: 1-2 vessel disease vs. ≥3 vessel disease.

Table S3. Association of $PM_{2.5}$ (1μg/m^3) with MI over 3 Years of Follow-up with Adjustment for Potential Covariates.

	All Subjects			With CAD		
Model	**N (Rate)**	**HR (95% CI)**	**p-value**	**N (Rate)**	**HR (95% CI)**	**p-value**
1	5854 (0.04)	1.14 (1.01-1.28)	0.03	4348 (0.05)	1.13 (1.00-1.27)	0.06
2	5854 (0.04)	1.14 (1.01-1.28)	0.03	4348 (0.05)	1.13 (1.00-1.27)	0.06
3	5854 (0.04)	1.14 (1.01-1.28)	0.03	4348 (0.05)	1.13 (1.00-1.27)	0.06
4	3202 (0.04)	1.09 (0.94-1.28)	0.26	2518 (0.05)	1.09 (0.93-1.28)	0.30
5	5854 (0.04)	1.11 (0.99-1.26)	0.08	4348 (0.05)	1.12 (0.99-1.27)	0.07
6	5818 (0.04)	1.09 (0.97-1.24)	0.16	4316 (0.05)	1.07 (0.94-1.22)	0.28
7	5307 (0.04)	1.11 (0.98-1.26)	0.10	3935 (0.05)	1.11 (0.97-1.26)	0.12

Hazard ratios (HRs), 95% confidence intervals (CIs) obtained using Cox regression with 36-month post-baseline exposure levels. Results are reported for all study subjects and for those with CAD at baseline.
Model 1: Adjusted for age, sex, education level (≥college, high school, <high school), and current smoking (yes/no).
Model 2: Model 1 plus adjustment for obesity (BMI ≥30).
Model 3: Model 1 plus adjustment for statin therapy (yes/no).
Model 4: Model 1 plus adjustment for C-reactive protein (CRP).
Model 5: Model 1 plus adjustment for coronary atherosclerosis severity (0, 1-2, ≥3 epicardial vessels with ≥50% stenosis).
Model 6: Model 1 plus adjustment for percentage of high intensity land development (commercial/industrial land use).
Model 7: Model 1 plus adjustment for physical activity.

Table S4. Multipollutant Model for Association of $PM_{2.5}$ Exposure Levels with MI over 3 Years of Follow-up.

			HR (95% CI)		
Exposure	**N (Rate)**	**Co-pollutant**	**1μg/m^3 or ppb**	**2 SD**	**p-value**
$PM_{2.5}$	5854 (0.04)	-	1.14 (1.01-1.28)	1.33 (1.02-1.73)	0.03
	4489 (0.04)	NO_2	1.13 (0.97-1.31)	1.30 (0.94-1.79)	0.12

Hazard ratios (HRs), 95% confidence intervals (CIs) and p-values obtained using Cox proportional hazard models with 36-month post-baseline exposure levels, after adjustment for age, sex, education level (≥college, high school, <high school), current smoking (yes/no), and indicated co-pollutant.

Table S5. Association of $PM_{2.5}$ Levels (1μg/m^3) with MI over 3 Years of Follow-up Stratified by the Presence of Coronary Atherosclerosis at Baseline and Statin Therapy Use.

All Subjects			
Strata	**N (Rate)**	**HR (95% CI)**	**p-interaction**
No Coronary Atherosclerosis	1762 (0.01)	0.97 (0.69-1.38)	0.47
Coronary Atherosclerosis	4092 (0.05)	1.13 (1.00-1.29)	
No Statin Therapy	2417 (0.04)	1.05 (0.87-1.27)	0.89
On Statin Therapy	3437 (0.04)	1.19 (1.03-1.39)	
[*]No Statin Therapy			
Strata	**N (Rate)**	**HR (95% CI)**	**p-interaction**
No Coronary Atherosclerosis	1058 (0.01)	0.70 (0.40-1.22)	0.35
Coronary Atherosclerosis	1359 (0.06)	1.06 (0.86-1.30)	
[a]On Statin Therapy			
Strata	**N (Rate)**	**HR (95% CI)**	**p-interaction**
No Coronary Atherosclerosis	704 (0.02)	1.22 (0.77-1.93)	0.98
Coronary Atherosclerosis	2733 (0.05)	1.18 (1.00-1.39)	

Hazard ratios (HRs) and 95% confidence intervals (CIs) obtained using Cox proportional hazard models with 36-month post-baseline exposure levels by coronary stenosis and statin therapy, after adjustment for age, sex, education level (≥college, high school, <high school), and current smoking (yes/no). Presence of coronary atherosclerosis was defined as ≥1 epicardial vessels with ≥50% stenosis.

[*]P-value for 3-way interaction between $PM_{2.5}$ levels, coronary atherosclerosis and statin therapy was not significant (p=0.33).

Table S6. Association of $PM_{2.5}$ Levels (1μg/m^3) with MI over 3 Years of Follow-up Stratified by Potential Effect Modifiers.

Model	Strata	N (Rate)	HR (95% CI)	p-interaction
1	Age <64	2850 (0.03)	1.05 (0.87-1.27)	0.27
	Age ≥64	3004 (0.05)	1.20 (1.03-1.39)	
2	Females	1893 (0.03)	1.31 (1.05-1.64)	0.16
	Males	3961 (0.04)	1.08 (0.93-1.24)	
3	Not Current Smoker	5042 (0.04)	1.15 (1.01-1.31)	0.65
	Current Smoker	812 (0.05)	1.09 (0.83-1.44)	
4	≥College	2563 (0.03)	1.12 (0.91-1.38)	0.63
	High School	2469 (0.04)	1.24 (1.04-1.49)	
	<High School	822 (0.06)	1.01 (0.79-1.28)	
5	0 diseased vessels	1762 (0.01)	0.97 (0.69-1.38)	0.96
	1-2 diseased vessels	2240 (0.04)	1.16 (0.96-1.40)	
	≥3 diseased vessels	1852 (0.06)	1.10 (0.93-1.31)	
5	BMI <30	3400 (0.04)	1.15 (0.98-1.34)	0.85
	BMI ≥30	2454 (0.04)	1.12 (0.93-1.35)	

Hazard ratios (HRs), 95% confidence intervals (CIs) obtained using Cox regression with 36-month post-baseline exposure levels.
Coronary atherosclerosis severity defined as 0, 1-2 or ≥3 epicardial vessels with ≥50% stenosis.
Model 1: Adjusted for sex, current smoking (yes/no), and education level (≥college, high school, <high school).
Model 2: Adjusted for age, current smoking (yes/no), and education level (≥college, high school, <high school).
Model 3: Adjusted for age, sex, and education level (≥college, high school, <high school).
Model 4: Adjusted for age, sex, and current smoking (yes/no).
Model 5: Adjusted for age, sex, current smoking (yes/no), and education level (≥college, high school, <high school).

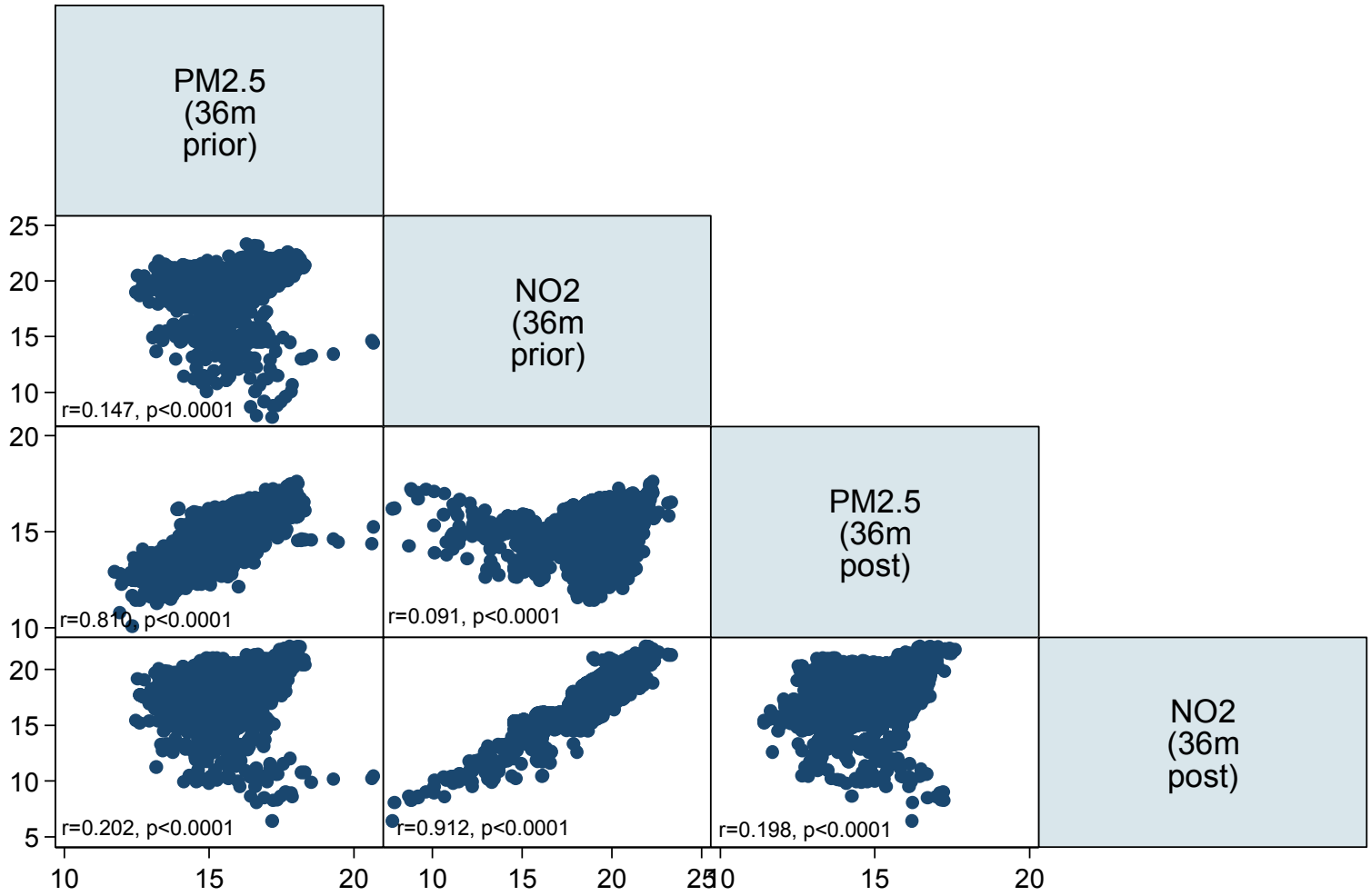

Figure S1. Correlation of Exposure Levels 36 Months Prior to and Post Enrollment. Pairwise Pearson's correlations between ambient air pollutant levels show that $PM_{2.5}$ ($\mu g/m^3$) and NO_2 (ppb) are weakly related regardless of time period, whereas the levels of each pollutant 36 months prior to and after enrollment are highly correlated.