Published in final edited form as:

Environ Res. 2016 February ; 145: 9–17. doi:10.1016/j.envres.2015.10.026.

Association between Satellite-based Estimates of Long-term PM_{2.5} Exposure and Coronary Artery Disease

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Abstract

Background—Epidemiological studies have identified associations between long-term PM_{2.5} exposure and cardiovascular events, though most have relied on concentrations from central-site air quality monitors.

Methods—We utilized a cohort of 5,679 patients who had undergone cardiac catheterization at Duke University between 2002–2009 and resided in North Carolina. We used estimates of daily PM_{2.5} concentrations for North Carolina during the study period based on satellite derived Aerosol Optical Depth (AOD) measurements and PM_{2.5} concentrations from ground monitors, which were spatially resolved with a 10 × 10 km resolution, matched to each patient's residential address and averaged for the year prior to catheterization. The Coronary Artery Disease (CAD) index was used to measure severity of CAD; scores >23 represent a hemodynamically significant coronary artery

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Competing Financial Interests: None.

Disclaimer: The research described in this article has been reviewed by the Environmental Protection Agency and approved for publication. The contents of this article do not necessarily represent Agency policy nor does mention of trade names or commercial products constitute endorsement or recommendation for use.

Human Study Approval (from page 6 of the manuscript): All subjects received and signed informed consent forms prior to enrollment, and CATHGEN has been approved by and follows all Duke University Institutional Review Board policies.

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lesion in at least one major coronary vessel. Logistic regression modeled odds of having CAD or an MI with each 1 $\mu\text{g}/\text{m}^3$ increase in annual average $\text{PM}_{2.5}$, adjusting for sex, race, smoking status and socioeconomic status.

Results—In adjusted models, a 1 $\mu\text{g}/\text{m}^3$ increase in annual average $\text{PM}_{2.5}$ was associated with an 11.1% relative increase in the odds of significant CAD (95% CI: 4.0%-18.6%) and a 14.2% increase in the odds of having a myocardial infarction (MI) within a year prior (95% CI: 3.7% -25.8%).

Conclusions—Satellite-based estimates of long-term $\text{PM}_{2.5}$ exposure were associated with both coronary artery disease (CAD) and incidence of myocardial infarction (MI) in a cohort of cardiac catheterization patients.

Keywords

coronary disease; epidemiology; myocardial infarction; $\text{PM}_{2.5}$; spatiotemporal analyses

1. Introduction

Air pollution is associated with several adverse health outcomes. Specifically, ambient fine particulate matter 2.5 $\mu\text{g}/\text{m}^3$ ($\text{PM}_{2.5}$) is associated with increased mortality and increased risk for respiratory and cardiovascular disease (Brook et al., 2010; Ruckerl et al., 2011). The Global Burden of Disease Study 2010 estimates that worldwide over 3.2 million premature deaths and over 74 million years of healthy life lost were attributable to ambient particulate matter pollution, making it one of the top global health risk factors (Lim et al., 2012). Further, an estimated 22% of disability-adjusted life-years for heart disease are attributable to ambient particulate matter pollution. Recently, a World Health Organization report estimated that air pollution exposure contributed to about 6% (3.7 million) of all deaths in 2012, with 40% of those coming from coronary artery disease (CAD) (World Health Organization, 2014). Populations particularly susceptible to the health effects of air pollution include infants and children, older adults, and those with underlying disease, particularly diabetes and cardiovascular disease (Pope, 2014).

A great deal of research has focused on the short-term variation in air pollution exposure, with fewer studies focusing on long-term $\text{PM}_{2.5}$ exposure. More than 100 time-series and case-crossover analyses have demonstrated associations with short term $\text{PM}_{2.5}$ exposure with myocardial infarctions (MIs) and increased risk for hospitalizations and mortality (EPA., 2009). Cohort studies have also identified associations between long-term $\text{PM}_{2.5}$ exposure and MIs (Cesaroni et al., 2014), mortality, increased susceptibility to progression of disease (EPA., 2009; Hoek et al., 2013), and overall reduced life expectancy (Correia et al., 2013). Recent studies have assessed associations between $\text{PM}_{2.5}$ and biomarkers of atherosclerosis (Rivera et al., 2013; Sun et al., 2013). One limitation of these studies is a reliance on exposure estimates based on single, central site monitors within a community.

The CATHeterization GENetics (CATHGEN) cohort described in this manuscript is a large, sequential cohort with participants selected from patients primarily from North Carolina presenting to the Duke University Medical Center Cardiac Catheterization Clinic between 2001 and 2011. In addition to clinical information collected during the catheterization visit

and subsequent visits for follow-up treatment or physical examinations, an extensive set of biological information was collected in this cohort (Kraus et al., 2015). This includes genetic, and epigenetic analysis, RNA transcriptomic and micro-RNA analysis, frozen blood samples that are available for extensive screening of soluble vascular biomarkers including metabolomics, and electrocardiographic data for defining cardiac electrophysiology. The large cohort size and rich biologic database make it feasible to associate long-term exposure to PM_{2.5} with biomarkers that may define pathways by which air pollution contributes to the progression of CAD.

New approaches to assessing daily PM_{2.5} values use a fusion of satellite-derived aerosol optical density (AOD) data and ground monitoring stations measurements (Chudnovsky et al., 2012; Lee et al., 2012; Lee et al., 2011). In this paper the model was used to estimate daily PM_{2.5} values throughout NC from 2002-2009, in 10 × 10 km grids. Using this approach, we investigate the association between long-term PM_{2.5} exposure and CAD severity and recent MIs using a cardiovascular cohort enriched with individuals having coronary artery disease. Because the population at hand is high risk our findings will help identify subgroups that are particularly susceptible to the health effects of air pollution.

2. Methods

2.1 Study population

The CATHGEN cohort is a group of 9334 patients who underwent cardiac catheterization at Duke University from 2001-2011. Participants came primarily from North Carolina and underwent a cardiac catheterization and coronary angiography in order to diagnose and treat coronary artery disease. Participants underwent catheterization procedures on referral from their referring physician and/or were admitted with an appropriate condition, such as a recent MI. Therefore, all CATHGEN participants had a clinical indication for a cardiac catheterization. Clinical information was obtained from an intake questionnaire at the time of catheterization as well as medical records. All subjects received and signed informed consent forms prior to enrollment, and CATHGEN has been approved by and follows all Duke University Institutional Review Board policies. Ground PM_{2.5} concentration and satellite AOD data were obtained from 2002-2009 and a yearly average was created for each participant using the 365 days of exposure prior to each participant's catheterization date. Therefore, patients were included in the current analysis only if they resided in North Carolina and their catheterization procedure was performed after January 1, 2003 and before December 31, 2009.

Residential addresses were obtained from medical records and geocoded by the Children's Environmental Health Initiative (CEHI) for 8017 (86%) of the 9334 study participants. Of these 8017 individuals, 7118 (76%) resided in North Carolina, and 5679 (61%) had a catheterization that occurred between 2003 and 2009 (thus having complete exposure data available for the year prior to catheterization). Figure 1 shows the residential locations of these individuals. Participants resided in 91 of the 100 NC counties, with Durham County containing the highest percentage (21%).

2.2 Outcome classification

The Coronary Artery Disease (CAD) index was used to measure severity of coronary artery disease. The index ranges from 0 to 100 and is a risk indicator of events due to coronary atherosclerosis. The CAD index takes into consideration the number of diseased coronary vessels (0-3), left anterior descending CAD, number of coronary vessels with 95% occlusion, 75% and 95% proximal left anterior descending coronary artery stenosis, and 75% and 95% left main coronary artery stenosis (Bart et al., 1997).

A binary measure of CAD was constructed and individuals with a CAD index >23 represent a population with at least one hemodynamically significant lesion (>75% luminal stenosis) in one epicardial coronary artery. A CAD index score was not given to 610 study participants because they underwent a therapeutic intervention that precluded a full catheterization (not all coronary arteries were imaged). Therefore, 5069 study participants had complete PM_{2.5} and CAD outcome data available. We additionally assessed whether participants experienced an MI within a year prior to their catheterization. Participants were considered to be cases for the MI analyses if they had a documented MI in their medical records within a year prior to their catheterization visit. There were 5,679 study participants who had complete exposure and MI outcome data available.

2.3 Exposure assessment

Daily PM_{2.5} concentrations were predicted at a 10 × 10 km spatial resolution for the state of North Carolina from 2002-2009 using recently developed statistical prediction models (Chudnovsky et al., 2012; Lee et al., 2012; Lee et al., 2011). These models estimate exposure using two main stages. First, satellite-based AOD data that reflect particle abundance in the atmospheric column were used to predict ground-level PM_{2.5} concentrations for days when satellite data were available (Chudnovsky et al., 2012; Lee et al., 2011). A daily calibration approach using a mixed effects model was then applied to control for the inherent day-to-day variability in the AOD-PM_{2.5} relationship that depends on a number of time-varying parameters such as particle optical properties, vertical and diurnal concentration profiles and ground surface reflectance. Second, a cluster analysis approach was applied that uses AOD and PM_{2.5} ground monitoring data to predict PM_{2.5} concentrations on days when satellite data are not available due to the presence of clouds or snow (Lee et al., 2012). Cluster analysis was applied to every third day data and because cluster assignment was done every third-day, the same cluster classification was applied to the adjacent two days, assuming an identical spatial pattern for three consecutive days. In addition, cluster analysis was performed on PM_{2.5} concentration differences obtained by subtracting the daily regional PM_{2.5} concentrations from the respective PM_{2.5} concentrations. Finally, a cluster-specific PM_{2.5} prediction model using a generalized additive model (GAM) was developed. For each cluster PM_{2.5} concentration, values were regressed on the regional PM_{2.5} levels and the spatial smooth function of latitude and longitude. For both stages model performance was examined by comparing the measured and predicted PM_{2.5} concentrations using R² and % mean relative error (MRE) estimates. More detailed information on the prediction model has been described previously (Chudnovsky et al., 2012; Lee et al., 2012; Lee et al., 2011). Satellite PM_{2.5} exposures were

estimated for 1233 10×10 km grid cells, and data from 52 EPA air quality monitors in NC were used.

Patients' geocoded addresses were matched to the centroid of the nearest 10×10 km grid location based on spatial location and date. The average number of participants assigned to each 10×10 km grid cell was 9 (Min=1, Max=423). Study participants provided detailed address history upon study enrollment and addresses for the year prior to the catheterization date were used. PM_{2.5} predictions were averaged for the year prior to each patient's catheterization date. There were 15 individuals who moved during the year prior to their catheterization visit. For these individuals a weighted average was computed using exposure data from both residential locations. Some participants underwent multiple catheterization events during the study period. For those individuals the most recent catheterization visit was linked with exposure data. We chose the most recent catheterization visit because we had better residential address data for this visit. Figure 2 shows the average of each of the eight annual averages for each 10×10 km grid throughout the state.

2.4 Confounders and effect measure modifiers

We made use of a directed acyclic graph (DAG) in order to create a least biased estimate (Greenland et al., 1999). Covariates of interest include: age, sex, race/ethnicity (non-Hispanic White, African American, and other race/ethnicity), body mass index (BMI), smoking status, median home value, area level attained education, urban/ rural status, county of residence, history of hypertension, and history of diabetes. History of diabetes was defined as a previous physician diagnosis of either type I or type II diabetes. History of hypertension was ascertained during the health and physical exam administered prior to the catheterization procedure by a physician or physician's assistant.

Data from the 2000 U.S. Census was used to characterize each participant's socioeconomic status (SES) and urban/rural status. Participants were assigned to block groups based on their address at catheterization visit. Block-group level educational attainment was defined as the percentage of males and females in the block group without a high school education. Educational attainment was dichotomized for interaction analyses with 25% representing low attainment and <25% representing high educational attainment. Block group-level median home value was considered as another potential measure of socioeconomic status. Finally, participants were defined as living in an urban block group if the block group was 50% urban.

2.5 Statistical analyses

Logistic regression analysis was used to estimate odds ratios (OR) and 95% confidence intervals (CI) associated with a CAD index >23 or MI for each $1 \mu\text{g}/\text{m}^3$ increase in annual average PM_{2.5}. Models were adjusted for sex, race/ethnicity, smoking status, and area level attained education.

We examined whether associations with PM_{2.5} were modified by select covariates by including an interaction term between continuous levels of PM_{2.5} and the potential modifiers of interest. We compared these models with the main effects model without interaction terms. The Likelihood Ratio Test (LRT) was used to assess potential effect modification and

a cutoff of $p < 0.05$ was used for significance and $p < 0.10$ was used to indicate potential presence of modification. Modifiers of interest included: age, sex, race, smoking history, BMI, history of diabetes or hypertension, education rank, and urban/rural status.

We performed sensitivity analyses to address potential sources of bias by restricting analyses to those individuals with an annual $PM_{2.5}$ average below the current EPA annual $PM_{2.5}$ National Ambient Air Quality Standard (NAAQS) of $12.0 \mu\text{g}/\text{m}^3$ to determine if effects could be seen at levels below the current standard. Additional sensitivity analyses were performed by comparing the results when choosing the first vs. most recent catheterization visit for the 174 individuals who had multiple catheterization visits. We also performed sensitivity analyses by including county of residence, BMI, age at time of catheterization, and median home value in the adjusted models. Finally, additional sensitivity analyses were conducted for the 610 individuals with only a catheterization on select arteries (were not assigned a CAD index score) and examined the $PM_{2.5}$ -MI associations with this subset of participants who had a clinical indication for an immediate intra-coronary artery intervention at the time of catheterization. Statistical analyses were performed using SAS version 9.3 (Cary, NC).

3. Results

The study population was comprised of 5679 participants in total, and 5069 patients who underwent a cardiac catheterization. Study participants were aged 20-93 (mean age 60.8 ± 12.1 years). Catheterization visits were evenly spaced from 2002 to 2009. Table 1 shows the distribution of the study population characteristics. Those patients who were assigned a CAD score >23 represent 44% of the study population and those who had an MI in the year preceding the catheterization visit represent 12% of the population. The majority of the study population was male (61%), non-Hispanic white (73%), and had a history of hypertension (68%). More than 77% of the study participants were either overweight or obese. Demographic and clinical characteristics were similar within the CAD and MI outcome groups.

The mean annual average $PM_{2.5}$ level for the study population was $12.4 \mu\text{g}/\text{m}^3$ (Table 1), which is slightly above the NAAQS annual $PM_{2.5}$ limit of $12.0 \mu\text{g}/\text{m}^3$. African American and other race/ethnicity, those living in urban areas, and those residing in low home value areas had slightly higher $PM_{2.5}$ concentrations. $PM_{2.5}$ concentrations did not vary significantly among the two outcome groups (Supplementary Table 1). The interquartile range (IQR) of the annual average $PM_{2.5}$ concentrations for the CATHGEN study population was $0.78 \mu\text{g}/\text{m}^3$ (Min: $8.6 \mu\text{g}/\text{m}^3$, Max: $14.4 \mu\text{g}/\text{m}^3$). Annual $PM_{2.5}$ averages in NC decreased over time from $12.5 \mu\text{g}/\text{m}^3$ in 2002 to $9.0 \mu\text{g}/\text{m}^3$ in 2009.

We used the CAD index as a measure of coronary atherosclerosis and MIs within the preceding year as effect outcomes. Table 2 presents the adjusted associations between each $1 \mu\text{g}/\text{m}^3$ increase in annual average $PM_{2.5}$ exposure for these outcomes. We observed an 11% relative increase in odds of having a CAD index >23 (95% CI: 1.04, 1.19) for each $1 \mu\text{g}/\text{m}^3$ increase in annual average $PM_{2.5}$ compared with a CAD index <23 . Associations between $PM_{2.5}$ and CAD remained when choosing the first catheterization visit instead of

the most recent visit for the 174 individuals who had multiple catheterization visits (OR: 1.12, 95% CI: 1.05, 1.20). For each 1 $\mu\text{g}/\text{m}^3$ increase in annual average $\text{PM}_{2.5}$ the odds of an MI occurring within the preceding year increased by 14% (95% CI: 1.04, 1.26).

The majority (78%) of the study population resided in an area that had an annual average $\text{PM}_{2.5}$ level slightly above the current NAAQS of 12.0 $\mu\text{g}/\text{m}^3$, with 1275 participants residing in an area with an annual average level below the limit. To determine whether effects could be seen at levels below the current EPA annual $\text{PM}_{2.5}$ standard, the analysis was restricted to these 1275 individuals. As seen in Table 2 the association between $\text{PM}_{2.5}$ and CAD index, and $\text{PM}_{2.5}$ and MI in the prior year, was significant at levels below the current NAAQS.

We conducted sensitivity analyses to assess potential sources of bias in the adjusted models. We assessed whether or not adjusting for county of residence, age at time of catheterization, BMI, median home value, or distance to Duke University altered any of the associations with each outcome. As seen in Table 3, the associations between long-term $\text{PM}_{2.5}$ exposure and outcomes did not change significantly after adjustment for these covariates.

There were 610 individuals who did not receive a CAD score to quantify the severity of atherosclerotic lesions because their CAD was found to be significant enough during catheterization to require immediate medical intervention. These individuals were not included in the CAD index analysis, but were included in the MI analysis. Because they had more severe CAD than the cohort as a whole, we performed a sensitivity analysis to determine whether this subpopulation was driving the MI association of the entire study cohort. Table 4 shows that when this population was removed from the analysis, there was still a significant positive association between those who had an MI in the prior year (OR 1.12, CI: 1.01, 1.23) with each 1 $\mu\text{g}/\text{m}^3$ increase in annual average $\text{PM}_{2.5}$ concentration. The odds of having an MI in the prior year increased by 22% (95% CI: 0.86, 1.72) with each 1 $\mu\text{g}/\text{m}^3$ in annual average $\text{PM}_{2.5}$, for those 610 individuals.

CATHGEN cohort consists of several thousand individuals, so it is possible to explore the contribution of various effect modifiers on the outcomes. Table 5 shows that participants aged 65 years old or greater had higher odds of having a CAD score >23 for each 1 $\mu\text{g}/\text{m}^3$ increase in annual average $\text{PM}_{2.5}$ (OR: 1.20, 95% CI: 1.08, 1.32) compared to those participants under the age of 65 (OR: 1.06, 95% CI: 0.97, 1.16), with $p=0.08$ for modification. The $\text{PM}_{2.5}$ -CAD association was also modified by race/ethnicity and history of hypertension.

Table 6 shows that participants in the underweight (OR: 1.81, 95% CI: 0.64, 5.15) and normal weight (OR: 1.41, 95% CI: 1.11, 1.79) BMI categories had stronger associations between long-term $\text{PM}_{2.5}$ exposure and having an MI in the year prior, though the interaction term did not reach significance. There was modification by diabetes status, with those without diabetes having a stronger association between long-term $\text{PM}_{2.5}$ exposure and having an MI in the year prior (OR: 1.21, 95% CI: 1.07, 1.36).

4. Discussion

We investigated the association between long-term PM_{2.5} exposure and select cardiovascular disease outcomes using a cardiovascular cohort enriched with prevalent coronary artery disease. We used satellite-based predictions to assess long-term PM_{2.5} exposure for NC residents of the cohort. We observed positive associations between long-term PM_{2.5} exposure and CAD and measures of prior MI. These associations remained after adjusting for other covariates in sensitivity analyses. We additionally observed effect modification of the PM-CAD index relationship by age, race, and history of hypertension. Future studies will take advantage of the richness of the CATHGEN cohort that includes a large number of CAD events, extensive clinical information, genetic/epigenetic data, and biological phenotyping from blood which can potentially shed light on the how both short- and long-term air pollution exposure contributes to CAD.

Other large population-based cohorts such as ARIC (Kan et al., 2008), WHI (Miller et al., 2007), Nurses Health Study (Puett et al., 2009) and MESA Air (Kaufman et al., 2012) have reported a positive association between air pollutant exposures and clinically important cardiovascular outcomes or increases in biomarkers of atherosclerosis. Yet, in each of these studies the population was free from overt coronary heart disease at the time of enrollment. By contrast the CATHGEN cohort is highly enriched with research subjects with coronary artery disease. Thus, the high prevalence of CAD in this cohort as well as spatial distribution of the cohort offers a unique opportunity to investigate the effect modification of the PM_{2.5}-CAD relation by community characteristics and social stressors. Knowledge of such relationships might be important in understanding some drivers of health disparities and crafting more effective environmental health literacy messaging to public health officials, health care providers and the public to mitigate the public health burden of particulate air pollution, particularly among at-risk populations.

Many of the previous studies on long-term PM_{2.5} exposure and CVD morbidity have used pollution data from air quality monitoring networks to assign study participants' PM_{2.5} exposure. Using only data from ground-based monitors can potentially introduce bias because it assumes that everyone residing within a certain radius of a monitor has the same PM_{2.5} exposure. Further, counties without air pollution monitors tend to be predominantly rural, have greater percentage of older adults, and more poverty than counties with air pollution monitors (Bravo et al., 2012; Miranda et al., 2011) and are therefore not as well studied as urban areas with more monitors. In contrast, satellite data expand spatial coverage to an entire state or region of the country, enhancing the ability to estimate location- and/or subject-specific exposure PM_{2.5}. In this analysis we used PM_{2.5} concentration data generated by previously developed and published models that fused satellite data with ground based monitoring to create daily measurements of PM_{2.5} throughout the entire state of NC, with a resolution of 10km × 10km. There was high predictability between modeled and monitored values at sites where monitors were located, which ensures less uncertainty in the resulting estimates (Lee et al., 2012). For this study annual averages were obtained by averaging the individual daily exposures for the 12 months prior to a person's catheterization procedure in the 10 × 10 km grid in which that person resided. Satellite derived predictions can reduce measurement error and exposure misclassification (Kloog et al., 2011; Zeger et

al., 2000), and have recently been used in epidemiological studies of air pollution exposure and mortality (Lee et al., 2015), birth outcomes (Hyder et al., 2014; Lakshmanan et al., 2015), and incidence of acute MIs (Madrigano et al., 2013).

By using satellite-derived predictions combined with a diverse population and clinical phenotyping we were able to conduct stratified analyses and assess the effect of potential modifiers of the air pollution-CAD associations. We observed associations between long-term PM_{2.5} exposure and increased prevalence of CAD and MI in non-Hispanic whites, but not in African Americans. One possible explanation for this finding is that the prevalence of CAD tends to be greater in non-Hispanic whites compared to African Americans (Budoff et al., 2002), while African Americans tend to have higher blood pressure and incidence of strokes than non-Hispanic whites (Gutierrez and Williams, 2014). Additional research is needed to see if there is an association between long-term PM_{2.5} exposure and more strokes in African Americans.

We also observed stronger differences in PM_{2.5} associations for CAD among those aged 65 and above. This finding is consistent with previous research that shows stronger associations with PM_{2.5} exposure for older adults (Shumake et al., 2013). Surprisingly, we observed stronger associations with PM_{2.5} among individuals without diabetes. A few studies have found similar results (Wilker et al., 2013), though most have found individuals with diabetes to be more susceptible to the effects from air pollution (Dubowsky et al., 2006; O'Neill et al., 2005; Schneider et al., 2010). Finally, we observed stronger associations between PM_{2.5} and CAD and the MI outcome among underweight individuals, although the interaction term did not reach significance. Previous studies have found underweight individuals to potentially be more susceptible to experiencing severe cardiovascular disease and mortality (Sharma et al., 2014), with a slightly elevated BMI being protective in some cases (Romero-Corral et al., 2006).

Some have suggested that health effects from long-term PM_{2.5} exposure may differ for urban and rural residents (Correia et al., 2013). Few studies, however, take rural residents into consideration when examining air pollution and CVD outcomes, primarily because of lack of PM_{2.5} monitors in rural locations. For this analysis we used US Census data to classify participants as rural and urban, depending on which block group they resided in. The use of satellite data allows inclusion of both urban and rural residents. We found stronger associations between PM_{2.5} and having an MI in the prior year among rural residents, although the interaction term did not reach significance. This finding is consistent with a recent analysis of short-term PM_{2.5} exposure and hospital admissions (Kloog et al., 2014), which reported associations in rural but not urban residents. Future studies should make an increased effort to include rural residents when considering health effects from air pollution.

The current annual PM_{2.5} NAAQS is 12.0 µg/m³, but the shape of the dose-response curve near the standard is uncertain. To partially address this issue we removed from the study all measurements that were above the current standard. The findings between long-term PM_{2.5} exposure and each of the select CVD outcomes remained when restricting the study population to those exposed to long term PM_{2.5} levels below 12.0 µg/m³.

During the catheterization procedure, 610 individuals underwent a therapeutic catheterization only rather than a complete diagnostic catheterization. Thus, not all of their coronary arteries were imaged and scored, and they were not assigned a CAD index score. We observed stronger associations for the MI outcomes for these 610 individuals. This population is likely at a more critical stage of their disease and it may not be surprising that environmental influences might be stronger.

In the present study, we found positive associations between long-term PM_{2.5} exposure and severity of atherosclerosis as measured by the CAD index. Our positive findings between long-term PM_{2.5} exposure and severity of atherosclerosis and measures of MI are broadly consistent with previous studies which have reported associations between long-term PM_{2.5} and CVD mortality, incidence of MIs, and increased susceptibility to progression of atherosclerosis (Brook et al., 2010; Newman et al., 2015). Previous research has identified associations between long-term PM_{2.5} exposure and subclinical measures of atherosclerosis such as carotid intima medial thickness (CIMT) and aortic calcification (Allen et al., 2009; Brook and Rajagopalan, 2010; Diez Roux et al., 2008; Kunzli et al., 2005). Although previous findings on long-term PM_{2.5} exposure and incidence of MIs are inconsistent (Bhaskaran et al., 2009), a recent epidemiological analysis using satellite derived predictions found an association between long-term PM_{2.5} exposure and incidence of MI (Madrigano et al., 2013).

The current analysis has both strengths and limitations. One of them is the generalizability of the CATHGEN cohort to other clinical settings and geographic regions. CATHGEN was selected from patients at a cardiac catheterization laboratory at Duke University Medical Center. Most individuals were referred for catheterization because of suspected CAD, although about 30% of the CATHGEN participants were not found to have clinically significant CAD. In sensitivity analyses we found that adjusting for county of residence did not alter the associations, thus there was likely not strong bias due to subject selection into the cohort. However, there may be residual confounding present, particularly since we were unable to obtain information on several individual level socioeconomic indicators. Another limitation is that we did not have complete residential history for each participant. We did, however, have a full address history for each participant for the year prior to his or her catheterization, and studies have shown that exposure during the prior year is an adequate surrogate of long-term exposure associated with cardiovascular disease. A final limitation is the relatively coarse spatial resolution of 10 × 10 km. Higher spatial resolution will become available in the near future (1 × 1 km) and reduce exposure error as well produce daily exposure estimates within micro-environments in urban and rural areas (Chudnovsky et al., 2014; Chudnovsky et al., 2013). Finally, analysis of those below the regulatory limit may be mixing secular trends with low pollution areas. Despite these limitations, the current study has several strengths including the large sample size of the CATHGEN cohort, the predictive ability of the CAD index, and the reduction in exposure error due to the satellite-derived predictions.

5. Conclusions

Our findings indicate that long-term PM_{2.5} exposure was associated with both coronary artery disease and prevalence of MIs in a cohort of cardiac catheterization patients. We have demonstrated that our AOD-based exposure model can be successfully applied to estimate spatially resolved PM_{2.5} exposures for individual addresses. Since individuals with cardiovascular disease are known to be especially vulnerable to air pollution, understanding the relationship between exposure and adverse events and disease risk in this population would have a greater impact on public health than a similarly-sized study of the general population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding Sources: This research was supported by intramural research funding by the US EPA. The Health Effects Institute (Research Agreement #4946-RFPA10-3/14-7) and the NIEHS (award number T32ES007018) provided additional funding.

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Highlights

- The research looked at long-term PM_{2.5} exposure and select cardiovascular outcomes.
- We utilized a cohort of cardiac catheterization patients who resided in NC.
- Long-term PM_{2.5} exposure was characterized using satellite-derived estimates.
- PM_{2.5} exposure was associated with coronary artery disease and having a recent MI.

Figure 1.
Residential location of CATHGEN participants.

Figure 2. Annual average PM_{2.5} (µg/m³) predictions averaged from 2002 to 2009. Dots represent EPA PM_{2.5} monitoring stations.

Table 1
Characteristics of the CATHGEN study population

	PM _{2.5} (µg/m ³) ^a	Total cohort	CAD ^b	MI in prior year ^c
Total	12.4	5,679	2,491	704
Age at time of enrollment in years (mean ± SD)		60.8 ± 12.1	63.3 ± 11.2	59.8 ± 12.4
Gender				
Male	12.4	3,471 (61)	1,798 (72)	467 (66)
Female	12.4	2,208 (39)	693 (28)	237 (34)
Body mass index (kg/m ²)				
<18.5 (Underweight)	12.5	80 (1)	38 (2)	14 (2)
18.5-24.9 (Normal weight)	12.4	1,187 (21)	485 (20)	151 (21)
25.0-29.9 (Overweight)	12.4	1,987 (35)	967 (39)	258 (37)
30.0 (Obese)	12.3	2,399 (42)	991 (40)	281 (40)
Missing		26	10	0
Race ^d				
Non-Hispanic white	12.3	4,146 (73)	1,940 (78)	489 (69)
African American	12.5	1,204 (21)	409 (16)	161 (23)
Other	12.5	329 (6)	142 (6)	54 (8)
History of smoking				
Yes	12.4	2,664 (47)	1,364 (55)	398 (57)
No	12.4	3,015 (53)	1,127 (45)	306 (43)
History of diabetes				
Yes	12.4	1,660 (29)	846 (34)	212 (30)
No	12.4	4,019 (71)	1,645 (66)	492 (70)
History of hypertension				
Yes	12.4	3,882 (68)	1,894 (76)	510 (72)
No	12.4	1,797 (32)	597 (24)	194 (28)
Urban/ rural status ^e				
Urban	12.5	3,110 (55)	1,299 (52)	360 (51)
Rural	12.2	2,569 (45)	1,192 (48)	344 (49)
Educational attainment ^f				
Low	12.4	2,290 (40)	1,032 (41)	338 (48)
High	12.4	3,389 (60)	1,459 (59)	366 (52)
Median home value (\$)				
<82,700	12.5	1,400 (25)	675 (27)	248 (35)
82,700-118,000	12.4	1,403 (25)	613 (25)	166 (24)
118,000-166,500	12.3	1,436 (25)	638 (26)	159 (23)
166,500	12.3	1,414 (25)	561 (23)	127 (18)
Missing		26	4	4

Numbers in parentheses are the percent of each group (Total Cohort, CAD, MI in prior year) represented by each characteristic.

^a Annual average PM_{2.5} level (µg/m³) is based on the average of each participants' PM_{2.5} exposure for the year prior to their catheterization visit.

^b Binary measure of CAD index (>23 CAD index). The total sample size for the CAD outcome is 5,069.

^c MI in prior year includes those that experienced a MI in the year prior to their catheterization visit.

^d Other race/ethnicity includes Native American, Hispanic, Asian, and unknown.

^e Urban status was defined as living in a block group that was 50% urban.

^f Low educational attainment includes those who live in block groups where 25% of males and females have less than a high school education.

Association between 1 $\mu\text{g}/\text{m}^3$ increase in annual average $\text{PM}_{2.5}$ ^a exposure and measures of CAD and MI for the total cohort and those with an annual average $\text{PM}_{2.5}$ exposure of $<12.0 \mu\text{g}/\text{m}^3$

Table 2

Outcome	Total cohort				<12.0 $\mu\text{g}/\text{m}^3$			
	N		Events		N		Events	
			Odds Ratio ^b	95% CI			Odds Ratio ^b	95% CI
CAD Index	5,069	2,491	1.11	1.04, 1.19	1,079	501	1.15	1.01, 1.31
MI in prior year	5,679	704	1.14	1.04, 1.26	1,275	124	1.65	1.29, 2.11

^aInterquartile range of annual average $\text{PM}_{2.5}$: $0.78 \mu\text{g}/\text{m}^3$.

^bModels are adjusted for race, area level education, gender, and smoking status.

Table 3
Sensitivity analyses for the addition of select covariates^a

	CAD Index	MI in prior year
Crude Model	1.07 (1.00, 1.14)	1.14 (1.03, 1.25)
Model 0 (Gender, smoking, race)	1.10 (1.03, 1.18)	1.13 (1.02, 1.24)
Model 1 (Added educational attainment)	1.11 (1.04, 1.19)	1.14 (1.04, 1.26)
Model 2 (Added county of residence)	1.11 (1.03, 1.19)	1.17 (1.05, 1.30)
Model 3 (Added age)	1.12 (1.05, 1.20)	1.14 (1.04, 1.26)
Model 4 (Added BMI)	1.11 (1.04, 1.18)	1.14 (1.03, 1.25)
Model 5 (Added median home value)	1.11 (1.04, 1.18)	1.12 (1.02, 1.24)
Model 6 (Added distance to Duke)	1.11 (1.04, 1.19)	1.14 (1.04, 1.26)

^aTotal N for the CAD outcome is 5069, and 5679 for the MI outcome.

Table 4

Association between 1 $\mu\text{g}/\text{m}^3$ increase in annual average $\text{PM}_{2.5}$ and measures of myocardial infarction for those with and without a CAD index

Outcome	With CAD index			Without CAD index		
	Events	Odds Ratio ^a	95% CI	Events	Odds Ratio ^a	95% CI
MI in prior year	666	1.12	1.01, 1.23	38	1.22	0.86, 1.72

^aModels are adjusted for race, area level education, gender, and smoking status.

Table 5
Effect modification of the PM_{2.5}-CAD index (>23) association by select covariates

	Subjects (%)	Odds ratio	95% CI	LRT <i>p</i> -value
Age (years)				
<65	3066 (60.5)	1.06	0.97, 1.16	0.08
65	2003 (39.5)	1.20	1.08, 1.32	
Gender				
Male	3145 (62.0)	1.12	1.03, 1.21	0.77
Female	1924 (38.0)	1.10	0.98, 1.23	
Race ^a				
Non-Hispanic White	3703 (73.1)	1.19	1.10, 1.28	0.001
African American	1071 (21.1)	0.87	0.75, 1.00	
Other	295 (5.8)	1.10	0.76, 1.59	
History of smoking				
Yes	2475 (48.8)	1.16	1.06, 1.27	0.21
No	2594 (51.2)	1.07	0.97, 1.17	
Body mass index (kg/m ²)				
<18.5 (Underweight)	68 (1.4)	1.66	0.89, 3.13	0.21
<25 (Under/ normal weight)	1030 (20.4)	1.09	0.94, 1.26	
25.0-29.9 (Overweight)	1802 (35.7)	1.18	1.06, 1.32	
30.0 (Obese)	2144 (42.5)	1.05	0.95, 1.16	
History of diabetes				
Yes	1523 (30.0)	1.06	0.94, 1.19	0.28
No	3546 (70.0)	1.14	1.05, 1.24	
History of hypertension				
Yes	3575 (70.5)	1.08	1.00, 1.17	0.04
No	1494 (29.5)	1.26	1.11, 1.45	
Urban/ rural status ^b				
Urban	2743 (54.1)	1.13	1.03, 1.23	0.79
Rural	2326 (45.9)	1.11	1.00, 1.22	
Educational attainment ^c				
Low	2057 (40.6)	1.10	0.98, 1.23	0.86
High	3012 (59.4)	1.11	1.02, 1.20	

^a Other race/ethnicity includes Native American, Hispanic, Asian, and unknown.

^b Urban status was defined as living in a block group that was 50% urban.

^c Low educational attainment includes those who live in block groups where 25% of males and females have less than a high school education.

Table 6Effect measure modification of the PM_{2.5}-MI in prior year association by select covariates

	Subjects (%)	Odds ratio	95% CI	LRT <i>p</i> -value
Age (years)				
<65	3442 (60.6)	1.12	0.99, 1.26	0.55
65	2237 (39.4)	1.19	1.01, 1.40	
Gender				
Male	3471 (61.1)	1.13	1.00, 1.27	0.67
Female	2208 (38.9)	1.18	0.99, 1.39	
Race				
Non-Hispanic White	4146 (73.0)	1.18	1.05, 1.33	0.38
African American	1204 (21.2)	1.02	0.84, 1.23	
Other ^d	329 (5.8)	1.25	0.77, 2.02	
History of smoking				
Yes	2664 (46.9)	1.22	1.07, 1.40	0.15
No	3015 (53.1)	1.06	0.92, 1.22	
Body mass index (kg/m ²)				
<18.5 (Underweight)	80 (1.4)	1.81	0.64, 5.15	0.15
<25 (Under/ normal weight)	1187 (21.0)	1.41	1.11, 1.79	
25.0-29.9 (Overweight)	1987 (35.2)	1.05	0.91, 1.23	
30.0 (Obese)	2399 (42.4)	1.10	0.95, 1.28	
History of diabetes				
Yes	1660 (29.2)	1.02	0.87, 1.20	0.09
No	4019 (70.8)	1.21	1.07, 1.36	
History of hypertension				
Yes	3882 (68.4)	1.14	1.02, 1.27	0.81
No	1797 (31.6)	1.17	0.97, 1.41	
Urban/ rural status				
Urban	3110 (54.8)	1.09	0.96, 1.24	0.18
Rural	2569 (45.2)	1.25	1.07, 1.45	
Educational attainment ^c				
Low	2290 (40.3)	1.10	0.95, 1.28	0.65
High	3389 (59.7)	1.15	1.02, 1.30	

^a Other race/ethnicity includes Native American, Hispanic, Asian, and unknown.^b Urban status was defined as living in a block group that was 50% urban.^c Low educational attainment includes those who live in block groups where 25% of males and females have less than a high school education.