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ORIGINAL RESEARCH

ISCHEMIC HEART DISEASE

Particulate Matter Air Pollution and Long-Term Outcomes in Patients Undergoing Percutaneous Coronary Intervention

Issam Motairek, MD,[a,*] Salil V. Deo, MD,[b,c,*] Yakov Elgudin, MD, PhD,[b,c] David A. McAllister, MD,[d] Robert D. Brook, MD,[e] Zhuo Chen, PhD,[a] Jason Su, PhD,[f] Sunil V. Rao, MD,[g] Sanjay Rajagopalan, MD,[a,c] Sadeer Al-Kindi, MD[a,c,*]

ABSTRACT

BACKGROUND Fine particulate matter ($PM_{2.5}$) promotes atherosclerosis progression and plaque vulnerability. Consequently, patients with a high atherosclerotic burden may be at especially increased risk when exposed to air pollution.

OBJECTIVES The purpose of this study was to examine the relationship between chronic ambient $PM_{2.5}$ exposure and adverse outcomes after percutaneous coronary interventions (PCI).

METHODS Baseline clinical and procedural data from U.S. veterans undergoing elective PCI (2005-2018) were linked to annual ambient $PM_{2.5}$ exposure. The association between $PM_{2.5}$ exposure and major adverse cardiovascular events (MACEs) (myocardial infarction, stroke, or all-cause mortality) was determined using time-varying Cox regression models. Using flexible parametric models, we also evaluated the average life months lost for specific $PM_{2.5}$ levels over the 15-year period.

RESULTS In the 73,425 veterans that underwent an elective PCI, the mean annual $PM_{2.5}$ exposure was 8.4 ± 1.8 $\mu g/m^3$ (median follow-up 6.75 years). The incidence of MACE was 28%, 48%, and 65% at 5, 10, and 15 years, respectively. In adjusted models, each 1-$\mu g/m^3$ increase in $PM_{2.5}$ exposure was associated with an 8.7% (95% CI: 8.4%-8.9%; $P < 0.001$) increase in MACE. Compared to patients exposed to 5 $\mu g/m^3$, those exposed to 10 $\mu g/m^3$ lost 1.1, 3.8, and 7.6 months of life at 5, 10, and 15 years of exposure, respectively.

CONCLUSIONS Veterans undergoing elective PCI are at increased risk of MACE and significant life years lost with long-term exposure to fine particulate matter pollution, even at the current low levels in the United States. These findings emphasize the need for improved air quality standards and patient interventions to better protect vulnerable populations. (JACC Adv 2023;2:100285) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

From the [a]Harrington Heart and Vascular Institute, University Hospitals, Cleveland, Ohio, USA; [b]Department of Cardiovascular Surgery, Louis Stokes Cleveland VA Medical Center, Cleveland, Ohio, USA; [c]School of Medicine, Case Western Reserve University, Cleveland, Ohio, USA; [d]School of Health and Wellbeing, University of Glasgow, Glasgow, United Kingdom; [e]Department of Cardiology, Wayne State University, Detroit, Michigan, USA; [f]Division of Environmental Health Sciences, School of Public Health, University of California-Berkeley, Berkeley, California, USA; and the [g]Department of Cardiovascular Medicine, NYU Grossman School of Medicine, New York, New York, USA. *Drs Deo and Al-Kindi contributed equally to this paper.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

CVD = cardiovascular disease

MACE = major adverse cardiovascular events

MI = myocardial infarction

PCI = percutaneous coronary intervention

PLY = potential life years

$PM_{2.5}$ = fine particulate matter air pollution

VA-CART = Veterans Affairs Clinical Assessment, Reporting and Tracking program

Cardiovascular disease (CVD) remains the largest contributor to mortality in the world.[1] Over the past 2 decades, CVD-prevention guidelines have been focused almost exclusively on individual and metabolic risk factors while overlooking crucial social and environmental risk factors. Globally, environmental pollution is one of the largest contributors to premature disability and deaths.[2] The global burden of disease study estimates that at least 9 million deaths annually are attributable to air pollution alone,[2] and air pollution is among the main modifiable factors of CVD globally.[3] Robust literature supports that fine particulate matter ≤2.5 μm in diameter ($PM_{2.5}$) contributes to the majority of air pollution's impact on CV morbidity and mortality.[4] Animal studies have shown that long-term exposure to $PM_{2.5}$ promotes atherosclerosis progression and components of plaque vulnerability, with large human studies indeed confirming that patients exposed to higher $PM_{2.5}$ levels are at increased risk of adverse CVD events.[5-7]

Patients with prior heart disease, including ischemic heart disease, may be more susceptible to adverse effects of acute and chronic $PM_{2.5}$ exposure.[5,8] Individuals with coronary artery disease who undergo percutaneous coronary interventions (PCIs) may be particularly susceptible given the high atherosclerotic burden. Veterans in the United States are a vulnerable population who experience higher rates of CVD and are also more likely to engage in risky health behaviors associated with CVD such as tobacco use than nonveterans. Therefore, we sought to investigate the association between chronic $PM_{2.5}$ exposure and cardiovascular risk in a large longitudinal cohort of U.S. veterans after undergoing PCI over a 15-year follow-up period. We hypothesized that patients undergoing PCI are particularly susceptible to harmful effects of air pollution, and particulate matter exposure would be associated with significant increases in major adverse cardiovascular events (MACEs).

METHODS

OVERVIEW OF THE DATA SOURCE AND STUDY COHORT. The primary source of data for this study was the Veterans Affairs Clinical Assessment, Reporting and Tracking (VA-CART) program. The VA-CART program is a national quality-improvement initiative for all the cardiac catheterization laboratories at the Department of VA medical centers. The VA-CART includes prospectively collected patient baseline clinical characteristics, extent of coronary artery disease, and procedural details. This was further supplemented by inpatient, outpatient, and laboratory electronic health record information available in the Corporate Data Warehouse, a central data repository of the VA. The geospatial information in the Corporate Data Warehouse is stored in PSSG files, which are updated annually. We used the year of each patient's PCI procedure and linked this to the corresponding PSSG tables to obtain their zip code at the time of their procedure. The particulate air pollution exposure was then obtained using this zip code information.

Initially 75,096 patients who underwent elective PCI between January 2005 and December 2018 were identified. From these, 1,671 patients with missing zip code information were removed, leaving 73,425 patients in the study cohort (CONSORT diagram) (Supplemental Figure 1).

MAIN EXPOSURE. The main exposure of interest in our study was the annual $PM_{2.5}$ particulate air pollution reported at the zip code level. Validated $PM_{2.5}$ exposure estimates developed by the Atmospheric Composition Analysis Group were utilized.[9] These estimates combine information from satellite remote sensing, chemical transport modeling, and calibration to ground-based observations to generate concentration estimates. Data are provided in 1 × 1-km grids, which we imported to an open-source geographical information system software, QGIS v. 3.16 (Open Source Geospatial Foundation), and mapped to the 2018 zip code boundaries from the U.S. Census Bureau. The mean ZIP $PM_{2.5}$ exposures were calculated using zonal statistics in QGIS. Each veteran in our cohort was assigned the level of exposure in ZIP of residence at the time of PCI and annually thereafter.

COVARIATES. We obtained demographic, clinical, laboratory, and pharmacy data prior to their procedure for patients from the CART tables; when this information was not directly available in CART, we obtained these data using the International Classification of Diseases 9th and 10th edition or Common Procedure Terminology codes, from the outpatient visit closest to the procedure date. Demographics included age at PCI, sex, and self-reported race and ethnicity. Clinical factors obtained were hypertension, diabetes mellitus, dyslipidemia, obesity (body mass index ≥30 kg/m^2), heart failure, chronic kidney disease (estimated glomerular filtration rate <60 mL/min/m^2), smoking status, and prior myocardial infarction (MI). We obtained procedural data including the extent of coronary artery disease (number of vessels with >70% stenosis), number of

coronary vessels stented, number of stents used, type of stent (bare metal vs drug eluting), and the use of antiplatelet agents after the procedure. We additionally included area-level socioeconomic variables. The community deprivation index[10] is a validated composite metric derived at the census level to evaluate the socioeconomic position. It is derived from the following variables obtained at the census tract level: percentage of individuals with less than a high-school degree (25 years and over); percentage of individuals living below the poverty level; percentage of female-headed households with children younger than 18 years; percentage of individuals in management, science, and arts occupation; percentage of individuals in crowded households (>1 occupant per room); percentage of individuals with public assistance or food stamps; percentage of unemployed individuals (16-64 years old in labor force); and percentage of individuals with an annual household income of <30,000. The score ranges between 0 and 1, with higher numbers indicating higher deprivation (lower socioeconomic position). Additional details of community deprivation index are available in Supplemental Item 1.

ENDPOINTS. Data were modeled to analyze 2 coprimary endpoints: MACEs and all-cause mortality after PCI. MACE was defined as a composite of the first occurrence of MI, stroke, or death assince CVD-specific death was not available.

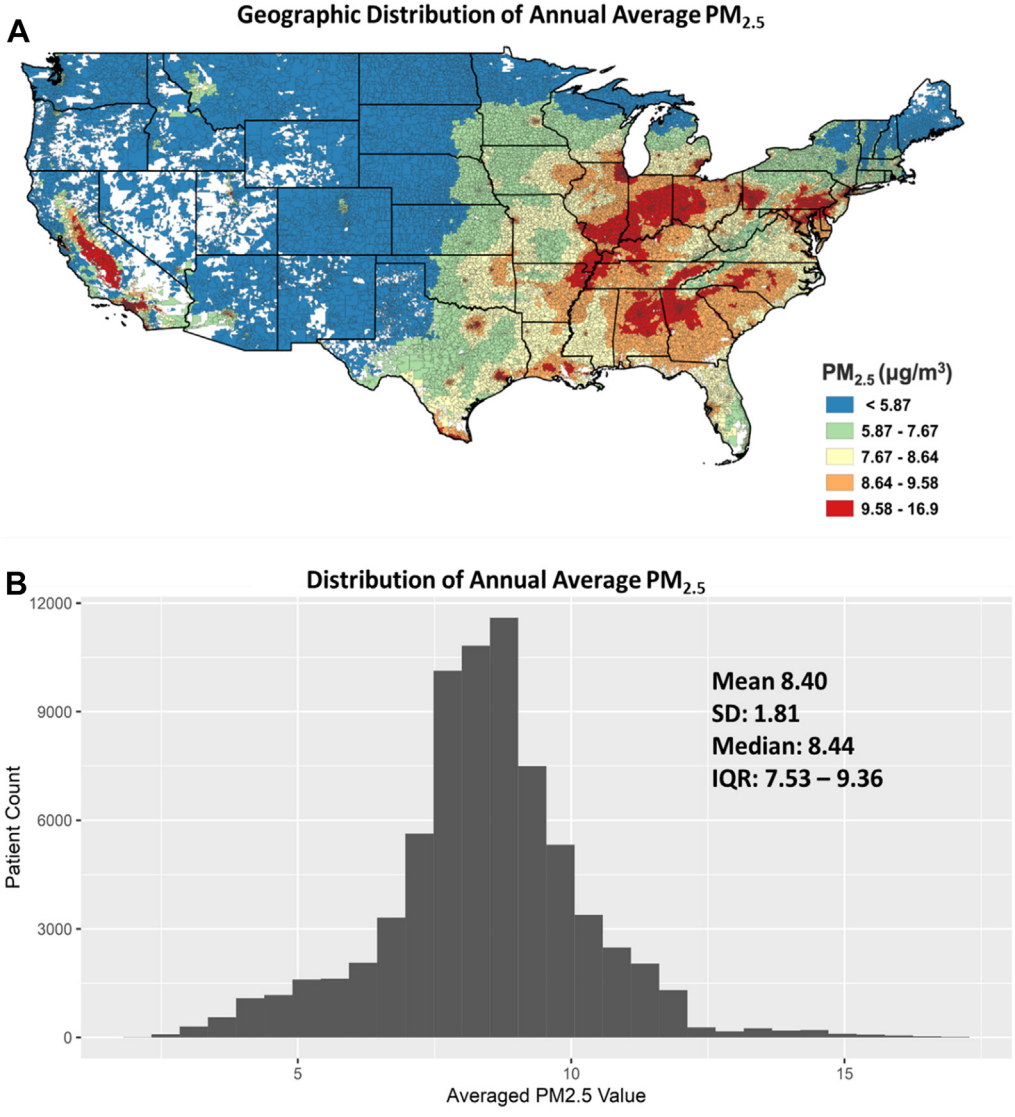
STATISTICAL ANALYSIS. The analysis presents categorical and continuous data as frequency (percentage) and mean (standard deviations), respectively. To study coprimary endpoints, proportional hazard Cox models were fit using the annual $PM_{2.5}$ (as a time varying covariate) as the main exposure and the hospital identifier as a random effect in the model. Three sequential models were fit with increasing levels of covariate adjustments: 1) model 1 (M1): unadjusted; 2) model 2 (M2): M1 + adjusted for age + sex + race + ethnicity + community deprivation index and for the fully adjusted model; 3) model 3 (M3): in addition to variables in M2, the following covariates were included: a) patient clinical characteristics: anemia, hypertension, chronic obstructive pulmonary disease, obesity, heart failure, diabetes, atrial fibrillation, preprocedural frailty, chronic kidney disease, dialysis dependence, smoking, peripheral arterial disease, and cerebrovascular disease; b) procedural details: extent of coronary artery disease, preprocedural left ventricular ejection fraction, presence of a chronic total occlusion, presence of calcified coronary vessels, and presence of bifurcation stenosis; c) socioeconomic characteristics (derived from the residential zip code): area deprivation index, median household income, percentage with high-school education, percentage receiving assisted income, percentage without health insurance, percentage below the poverty limit, percentage of vacant housing, and U.S. region. Additionally, the average ozone exposure for the residential zip code was included in the analysis using a restricted cubic spline with knots at the 25th and 75th quantiles.[11] Missing data were addressed through the use of multiple imputation (Supplemental Table 1). Results for these models are presented as hazard ratios (HRs) (with 95% confidence intervals [CI]). As sensitivity analyses, we also fit model M3 using only complete cases without missing data (Supplemental Table 2).

Further analysis was conducted using parametric survival models to evaluate the potential life years (PLY) gained after PCI due to the baseline $PM_{2.5}$ exposures, with all-cause mortality being the endpoint. Null models were initially fit to different standard parametric distributions; using the Akaike information criterion and graphical visualization, the Gompertz distribution was observed to be the best fit for our data (Supplemental Figure 2). Therefore, Gompertz parametric model was utilized with the $PM_{2.5}$ (averaged over the study period) as the main exposure, with race, ethnicity, and deprivation index as the covariates. The PLYs lost were calculated by simulating specific case scenarios using the parameters and covariate coefficients obtained from the model fit, with age as the time scale. Follow-up time was extended until the survival probability reached zero, allowing for the estimation of PLY lost (and its 95% CI using the delta method). Additional information on the methods used to estimate life lost is provided in Supplemental Methods (Supplemental Figure 3).

RESULTS

COHORT CHARACTERISTICS. A total of 73,425 Veterans (mean age 66.2 years, females 1.7%, White 85.6%, Hispanic ethnicity 3.7%) who underwent elective PCI (January 1, 2005-December 31, 2018) were included in this study. The averaged mean $PM_{2.5}$ exposure was 8.4 ± 1.8 (**Figure 1**), with 1,573 (2.1%) patients living in census tracts with $PM_{2.5}$ levels greater than or equal to the recommended threshold of 12 $\mu g/m^3$. Almost one-half the veterans lived in the Southern region, while 26.3% resided in the Midwest. Average $PM_{2.5}$ levels were highest in the Midwest (median 8.9, IQR: 7.8-10.1) and lowest in the West (median 6.9, IQR: 5.0-9.4). Patients living at the highest tertile of $PM_{2.5}$ levels (IQR: 9.0-16.9) were

FIGURE 1 Distribution of $PM_{2.5}$ in the Study Cohort



(A) Histogram of the averaged $PM_{2.5}$ exposure (μg/m^3) observed in our cohort. **(B)** Distribution of the averaged $PM_{2.5}$ (μg/m^3) observed by study patients in each U.S. region. $PM_{2.5}$ = fine particulate matter air pollution.

more likely to be non-Whites and had a higher prevalence of diabetes mellitus, chronic kidney disease, and heart failure (Table 1).

$PM_{2.5}$ AND MACE. Over a median 6.75 (maximum 17.31) years, 32,581 MACEs were observed. The cumulative incidence of MACE in the whole cohort at 5, 10, and 15 years was 28% (IQR: 27.67%-28.33%), 48.03% (IQR: 47.60%-48.46%), and 65.56% (IQR: 64.48%-66.27%), respectively. At 15 years, the cumulative incidence of MACEs in the first, second, and third tertiles of $PM_{2.5}$ was 63.36% (IQR: 62%-64.59%), 65.85% (IQR: 64.58%-67.07%), and 67.50% (IQR: 66.25%-68.71%), respectively. In unadjusted analysis, compared to the first tertile for $PM_{2.5}$, the risk of MACEs was higher in the second (HR: 1.069 [95% CI: 1.04-1.098]) and third tertile (HR: 1.160 [95% CI: 1.130-1.191]). In models fitted using $PM_{2.5}$ as a continuous exposure, every 1 μg/m^3 was associated with 8.8% (95% CI: 8.5-9.1) relative increase in the risk of MACE (Table 2).

$PM_{2.5}$ AND POTENTIAL LIFE LOST. For the entire cohort, on average, patients residing in areas with

TABLE 1 Characteristics of the Study Cohort Stratified by Average Annual $PM_{2.5}$ Levels

		$PM_{2.5}$ ($\mu g/m^3$)		
	Overall (N = 73,425)	**Tertile 1 (1.96, <7.84) (n = 24,475)**	**Tertile 2 (7.85, <8.98) (n = 24,476)**	**Tertile 3 (8.99, 16.93) (n = 24,474)**
Age, y	66.18 ± 8.7	66.63 ± 8.6	65.90 ± 8.7	66.00 ± 8.8
Males	72,174 (98)	24,103 (98)	24,055 (98)	24,016 (98)
Self-reported race				
White	59,324 (80.8)	21,487 (87.8)	20,274 (82.8)	17,563 (71.8)
Black	8,698 (11.8)	953 (3.9)	2,572 (10.5)	5,173 (21.1)
Others	1,258 (1.7)	435 (1.8)	386 (1.6)	437 (1.8)
Missing	4,145 (5.6)	1,600 (6.5)	1,244 (5.1)	1,301 (5.3)
Ethnicity				
Hispanic	2,649 (3.6)	960 (3.9)	741 (3.0)	948 (3.9)
Missing	2,637 (3.6)	997 (4.1)	808 (3.3)	832 (3.4)
Hypertension	71,625 (97.5)	23,787 (97.2)	23,906 (97.7)	23,932 (97.8)
Diabetes mellitus	46,075 (62.8)	14,804 (60.5)	15,602 (63.7)	15,669 (64.0)
Chronic kidney disease	14,472 (19.7)	4,457 (18.2)	4,808 (19.6)	5,207 (21.3)
Dialysis dependence	3,256 (4.4)	881 (3.6)	1,082 (4.4)	1,293 (5.3)
Anemia	33,195 (45.2)	10,525 (43.0)	11,090 (45.3)	11,580 (47.3)
Atrial fibrillation	21,852 (29.8)	7,413 (30.3)	7,201 (29.4)	7,238 (29.6)
Chronic obstructive pulmonary disease	42,640 (58.1)	14,097 (57.6)	14,464 (59.1)	14,079 (57.5)
Peripheral arterial disease	37,886 (51.6)	12,109 (49.5)	12,743 (52.1)	13,034 (53.3)
Cerebrovascular disease	26,992 (36.8)	8,598 (35.1)	9,110 (37.2)	9,284 (37.9)
History of cancer	25,167 (34.3)	8,484 (34.7)	8,381 (34.2)	8,302 (33.9)
Heart failure	34,706 (47.3)	10,911 (44.6)	11,350 (46.4)	12,445 (50.8)
Obese	29,982 (40.8)	10,052 (41.1)	9,871 (40.3)	10,059 (41.1)
Smoker	44,224 (60.2)	14,772 (60.4)	14,457 (59.1)	14,995 (61.3)
Median household income	$45,764 (37,678-57,109)	$45,880 (38,805-56,104)	$44,645 (36,982-55,936)	$46,848 (37,517-59,879)
Preprocedural frailty score (range 0-1)	0.23 (0.16-0.32)	0.23 (0.16-0.32)	0.23 (0.16-0.32)	0.23 (0.16-0.32)
Community deprivation index (range 0-1)	0.39 (0.33-0.45)	0.39 (0.33-0.44)	0.40 (0.34-0.46)	0.39 (0.33-0.46)
U.S. region				
Midwest	19,302 (26.3)	5,202 (21.3)	5,206 (21.3)	8,894 (36.3)
Northeast	5,844 (8.0)	2,921 (11.9)	1,297 (5.3)	1,626 (6.6)
South	36,412 (49.6)	9,357 (38.2)	16,579 (67.7)	10,476 (42.8)
West	11,867 (16.2)	6,995 (28.6)	1,394 (5.7)	3,478 (14.2)
Average ozone exposure	40.22 (38.17-42.20)	40.61 (37.67-43.67)	40.08 (38.38-41.80)	40.20 (38.23-41.86)
PCI procedural characteristics				
Bifurcation stenosis				
Yes	5,474 (7.5)	1,969 (8.0)	1,749 (7.1)	1,756 (7.2)
No	49,338 (67.2)	16,282 (66.5)	16,141 (65.9)	16,915 (69.1)
Information missing	18,613 (25.3)	6,224 (25.4)	6,586 (26.9)	5,803 (23.7)
Chronic total occlusion				
Yes	4,280 (5.8)	1,467 (6.0)	1,391 (5.7)	1,422 (5.8)
No	50,322 (68.5)	16,712 (68.3)	16,416 (67.1)	17,194 (70.3)
Information missing	18,823 (25.6)	6,296 (25.7)	6,669 (27.2)	5,858 (23.9)
Calcified coronary stenosis				
Yes	12,948 (17.6)	4,351 (17.8)	4,216 (17.2)	4,381 (17.9)
No	43,348 (59.0)	14,359 (58.7)	14,189 (58.0)	14,800 (60.5)
Information missing	17,129 (23.3)	5,765 (23.6)	6,071 (24.8)	5,293 (21.6)
Extent of coronary stenosis ≥70%				
Single vessel disease	58,414 (79.6)	19,530 (79.8)	19,323 (78.9)	19,561 (79.9)
Double vessel disease	9,060 (12.3)	2,995 (12.2)	3,037 (12.4)	3,028 (12.4)
Triple vessel disease/left main disease	2,785 (3.8)	962 (3.9)	924 (3.8)	899 (3.7)
Missing information	3,166 (4.3)	988 (4.0)	1,192 (4.9)	986 (4.0)
Medications after procedure				
Beta-blockers	23,554 (32.1)	7,491 (30.6)	7,959 (32.5)	8,104 (33.1)
Statins	22,174 (30.2)	7,086 (29.0)	7,426 (30.3)	7,662 (31.3)
ARB/ACEI	20,758 (28.3)	6,541 (26.7)	7,047 (28.8)	7,170 (29.3)
Diuretics	10,770 (14.7)	3,222 (13.2)	3,693 (15.1)	3,855 (15.8)

Values are mean ± SD, n (%), or median (IQR).

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; PCI = percutaneous coronary interventions; $PM_{2.5}$ = fine particulate matter air pollution.

TABLE 2 Risk of Major Adverse Cardiovascular Events Based on $PM_{2.5}$ Exposure

Model	HR (95% CI) per 1 μg/m³ Increase in the $PM_{2.5}$ Concentration	*P* Value
Model 1: unadjusted	1.085 (1.083-1.087)	<0.001
Model 2: model 1 + age at coronary revascularization + sex + race + ethnicity + deprivation index	1.086 (1.084-1.088)	<0.001
Model 3: fully adjusted model (variables included listed in the method section)	1.088 (1.085-1.091)	<0.001

All models include the hospital identifier as a random effect.
$PM_{2.5}$ = fine particulate matter air pollution.

$PM_{2.5}$ of 10 μg/m³ (compared to those in areas of $PM_{2.5}$ of 5 μg/m³) lost 0.64 (IQR: 0.54-0.74) years over a 15-year time period after their PCI procedure. The **Central Illustration** shows the estimated life lost across age at PCI in patients living at high and low social deprivation. The absolute life lost decreases with age at PCI, with no difference between patients living at high or low social deprivation. If we consider 2 60-year White, non-Hispanic men residing in a region with a sample mean deprivation index (0.39), compared to the person exposed to a $PM_{2.5}$ of 10 μg/m³, over a 35-year time period (lifetime), the individual exposed to a $PM_{2.5}$ of 10 μg/m³ lost 1.31 (1.02, 1.60) years (Supplemental Figure 4A). If these same patients had PCI at 50 years of age, the lifetime years lost are even higher at 1.51 (IQR: 1.01-2.02) years (Supplemental Figure 4B).

SUBGROUP ANALYSES. Increasing $PM_{2.5}$ exposures were associated with MACEs across all studied subgroups. The association between $PM_{2.5}$ and MACE was generally stronger in patients without a comorbid disease than in those with a comorbid disease, namely those with pre-existing heart failure, chronic kidney disease, and diabetes. **Figure 2** shows the forest plot of the association between $PM_{2.5}$ and MACE within subgroups.

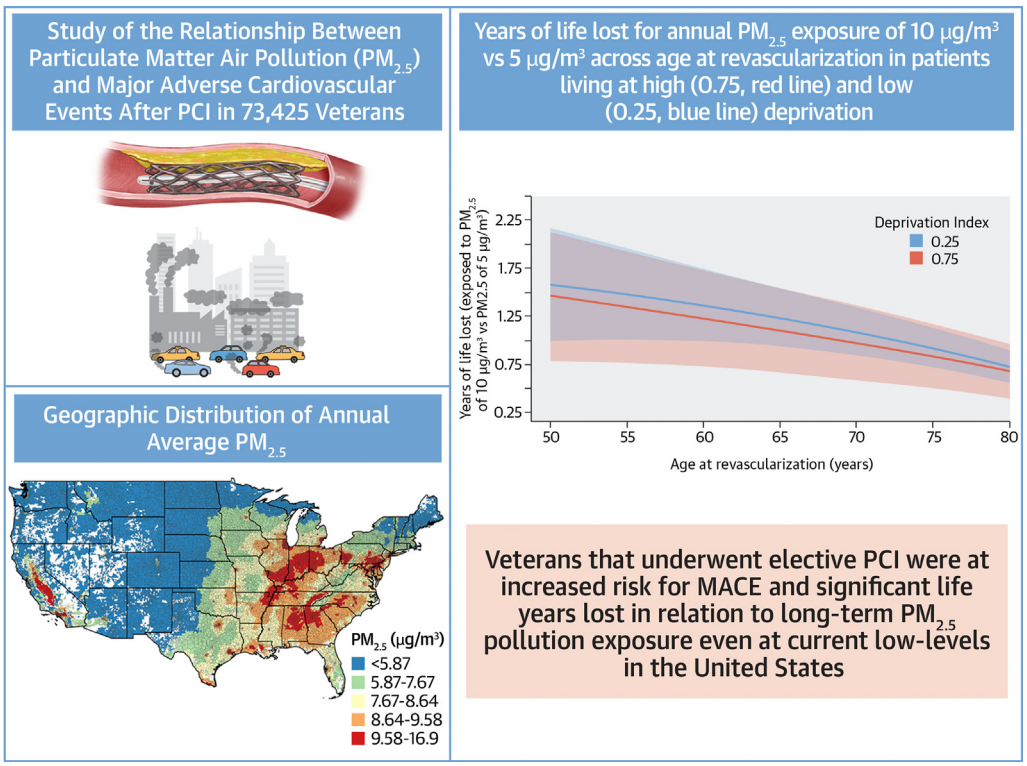
DISCUSSION

In this nationwide study of predominantly men undergoing PCI in the VA health system, higher $PM_{2.5}$ exposures were associated with an increased relative risk of adverse cardiac events. Additionally, we found that over a lifetime, patients who live in areas with higher exposure ($PM_{2.5}$ 10 μg/m³, corresponding with the 2005 World Health Organization [WHO] threshold) had significantly shorter estimated lifespan (1-2 years) than those living in areas with lower exposure ($PM_{2.5}$ of 5 μg/m³, corresponding to the 2021 WHO threshold), with the effect size more pronounced in patients who underwent PCI at younger ages. Increasing $PM_{2.5}$ was associated with MACEs across all studied subgroups. The association between PM2.5 and MACE was generally stronger in patients without comorbidities, namely those without pre-existing heart failure, chronic kidney disease, and diabetes.

A number of cohort studies and case cross-over studies from large cohorts across the world have demonstrated a strong link between both acute and chronic exposure to ambient $PM_{2.5}$ levels and acute MI/cardiovascular mortality.[7,12,13] However, studies that have examined this in a high-risk population presenting to the cardiac catheterization laboratory are limited.[5] Additionally, studies that have examined this at lower contemporary levels of air pollution in vulnerable populations are nearly nonexistent. A study from the Intermountain Healthcare hospitals of Utah's Wasatch Front including patients presenting to the cardiac catheterization laboratory found that in those with angiographic evidence of coronary artery disease, a 10-μg/m³ increase in concurrent-day fine particulate matter air pollution >25 μg/m³ was associated with a HR of 1.06 (95% CI: 1.02-1.11) for all acute coronary syndromes, 1.15 (95% CI: 1.03-1.29) for ST-segment elevation MI, and 1.09 (95% CI: 1.02-1.17) for unstable angina.[14] In the CATHGEN Cohort in the United States from Duke University, proximity to major roadways as a proxy for traffic exposure was associated with higher prevalence of peripheral arterial disease and hypertension. Neither MI nor the number of diseased coronary vessels was, however, associated with traffic exposure.[15]

To our knowledge, the current study is the first large national contemporary analysis of $PM_{2.5}$ and long-term outcomes in patients after PCI. This cohort has a significant burden of coronary atherosclerosis and concurrent risk factors. Our study adds important information to the available literature. First, this analysis shows that patients undergoing PCI are highly susceptible to air pollution exposure, with each 10 μg/m³ increase in annual updated $PM_{2.5}$ being associated with HR of 1.39 for MACE. In comparison, a meta-analysis of prior cohorts without preexisting

CENTRAL ILLUSTRATION **Years of Life Lost Based on $PM_{2.5}$ Exposure Were Modeled Using Gompertz Parametric Model Which Provided the Best Fit**



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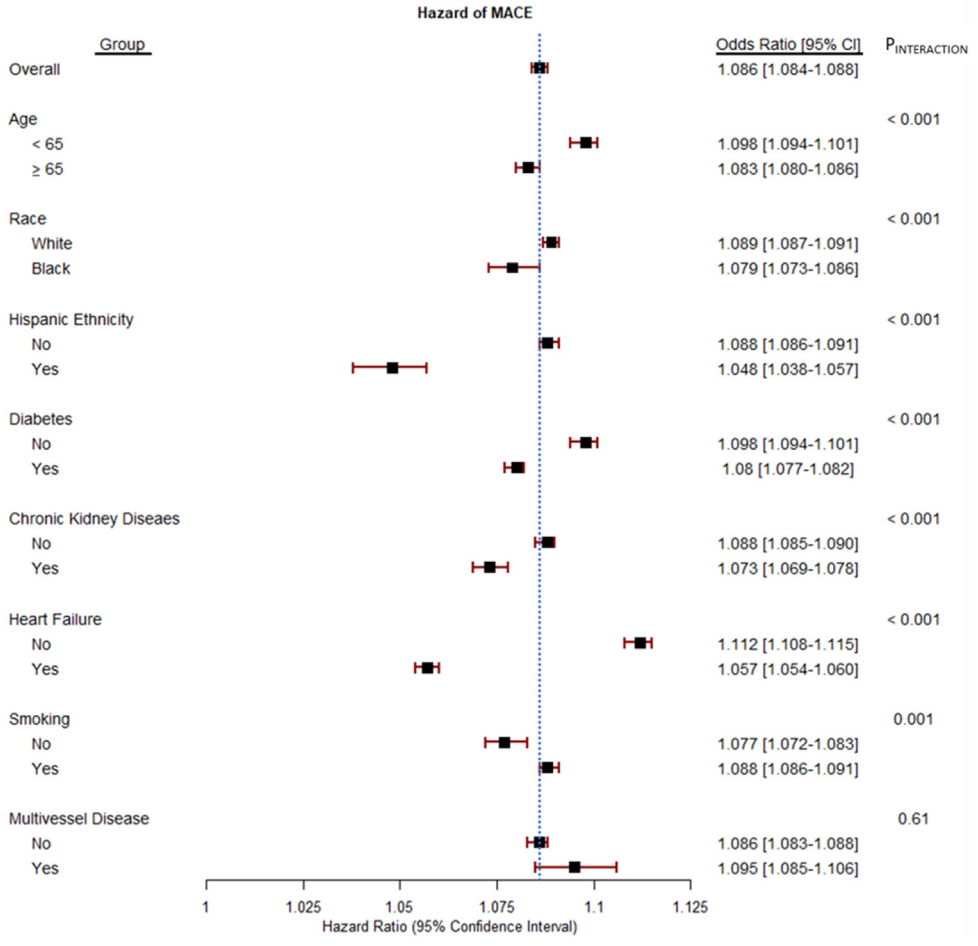
The **shaded areas** show the 95% confidence interval of the estimate at age groups. MACE = major adverse cardiovascular events; PCI = percutaneous coronary interventions; $PM_{2.5}$ = fine particulate matter air pollution.

CVD showed that 10 μg/m³ increase in CVD is associated with an HR of 1.09 for mortality. This large difference may partly be due to the fact that exposure-response curves are curvilinear, with steep increases in mortality at lower exposures (such as those observed in our U.S.-based cohort).[16] The size of this association, however, seems to be high even when compared with other contemporaneous North American cohorts notable for their high risk, such as those with solid organ transplantation.[17] In a cohort of patients surviving MI in Canada with a mean $PM_{2.5}$ of 10.7 μg/m³, each 10 μg/m³ increase in $PM_{2.5}$ exposure was associated with an HR of 1.64 (95% CI: 1.13-2.40) in death from MI.[18] A prior study also showed that $PM_{2.5}$ exposure, but not ozone, is associated with 5-year mortality (HR: 1.13 per +1 SD [95% CI: 1.07-1.20]) in patients with MI enrolled in 2 registries.[19] These studies are in line with our estimates. Together with prior studies, our findings add key evidence to support that patients with pre-existing coronary artery disease are at much higher risk of MACE due to $PM_{2.5}$ exposures (ie, a susceptible population).

This study also makes an important contribution by expressing the results as PLYs lost due to $PM_{2.5}$ exposure, which are intuitively easy to understand, interpret, and convey to policy makers. The results show that reducing $PM_{2.5}$ exposure levels in accordance with the recent WHO guidelines (10 to 5 μg/m³) was associated with significant improvement in life expectancy and was also dependent on age at PCI/exposure time. Importantly, the difference in life expectancy was independent of social deprivation, suggesting that $PM_{2.5}$ affects susceptible patients (those undergoing PCI) independent of their socioeconomic status.

$PM_{2.5}$ has been associated with atherosclerosis formation, progression, and plaque vulnerability. Controlled animal studies have clearly demonstrated a causal role of $PM_{2.5}$ exposure in the development of atherosclerosis via multiple mechanistic

FIGURE 2 **Forest Plot of Hazard Ratio for MACEs per 1 μg/m³ Annual $PM_{2.5}$ Exposure According to Subgroups Cox Regression Models Adjusted for Demographic Risk Factors (Model 1) With $PM_{2.5}$ as the Main Exposure (per 1 μg/m³ of Annual Exposure, Annual Time-Updated Covariate) and Major Adverse Cardiovascular Events as the Dependent Outcome**



Interaction tests are performed between the subgroups, and *P* value for the interaction is shown. Hazard ratios for the association between $PM_{2.5}$ and MACE within subgroups are shown. MACE = major adverse cardiovascular events; $PM_{2.5}$ = fine particulate matter air pollution.

pathways.[7,13] The initiating events are likely in the lungs and systemic vasculature and include local inflammation, ion channel activation, and oxidative stress. Systemic release of biologically active molecules (eg, cytokines, oxidized lipids, endothelin, and immune cells), autonomic imbalance of the hypothalamic-pituitary-adrenal axis, as well as translocation of particulate matter through the lung interface to reach blood circulation all contribute as well.[7] Ultimately, these pathways may converge to cause end-organ damage including but not limited to vascular dysfunction,[6] plaque instability, and thrombosis.[20] A chronic window of sustained exposure to $PM_{2.5}$ facilitates atherosclerosis formation, which ultimately premeditates plaque rupture and erosions, resulting in acute coronary syndrome.[21,22] A recent study utilizing optical coherence tomography, and intravascular imaging tool, found that higher exposure to $PM_{2.5}$ was associated with the presence of vulnerable plaque features such as macrophages and thin-cap fibroatheroma, as well as plaque rupture, as the culprit of acute coronary syndrome.[23]

With advances in cardiovascular interventions over the past decade, there is an ever-increasing number of patients undergoing PCI for whom $PM_{2.5}$ may pose a threat even at low exposure levels. Mean levels of 8.4 mg/m³ were well within the National Ambient Air Quality Standards limits of <12 mg/m³ and add to the body of evidence continuing

to demonstrate robust effects even to levels below 5 mg/m^3.[21,22,24-26] The reported mean survival time models between higher and lower $PM_{2.5}$ exposure groups describe the added benefit of improved air quality standards in terms of a time interval free from an event after PCI. Studies have utilized these statistical approaches to evaluate lifetime treatment effect of drugs, but ours is likely the first to use this to study $PM_{2.5}$ exposure.[27]

Strict policy that includes transitioning into clean energy may provide a more definitive measure for $PM_{2.5}$ adverse impacts; however, these solutions are rather longer-term. To mitigate the negative impacts of wildfire emissions on air quality and human health, including triggering clinical cardiovascular events, alternative policy decisions may be necessary. These could include promoting clean energy implementing innovative and cooperative actions on the part of federal, state, local, and tribal governments; nonprofits and landowners to adopt land-management practices to mitigate wildfire risk; and investing in technologies to reduce risk and improve air quality. Policy makers should consider the health impacts of wildfire emissions and take action to address this significant public health concern. Furthermore, personal protection strategies may allow for a more immediate solution. For example, interventional trials showed that air filtration with N95 masks demonstrate as much as 2 to 7 mm Hg decrease in systolic blood pressure.[7] Other studies illustrated that home air filtration strategies decrease inflammation and thrombotic markers while improving endothelial function and blood pressure.[28-30] These strategies may have potentiated protective effects in vulnerable populations such as those undergoing PCI.

STUDY LIMITATIONS. Patients undergoing PCI within the VA often have advanced disease with a high prevalence of risk factors as evidenced by the patients in this cohort (>60% with smoking and diabetes mellitus, >50% with peripheral artery disease, and 20% with chronic kidney disease). Moreover, PCI itself is associated with accentuation of this inherent risk. This same high comorbidity burden also constitutes a circumstance where these results may not necessarily be generalizable to other populations. Furthermore, this cohort consists of predominantly males, adding another limitation which may hinder generalizability. Nonetheless, the VA cohort has been widely used in many epidemiological studies and provides a valuable and reliable source of knowledge and hypothesis testing. Another limitation is the modeled nature of $PM_{2.5}$ concentrations as well as the utilization of zip-level rather than residential-level exposures which may make it prone to exposure mischaracterization and measurement bias. However, large studies have validated the reliability of these estimates given that $PM_{2.5}$ was relatively stable spatially and temporally.

CONCLUSIONS

In this study, we found that air pollution was associated with poor outcomes after PCI. The study highlights the crucial need to improve air quality in the United States to protect vulnerable populations from adverse CVD health effects of particulate matter air pollution. Susceptible individuals with CVD may consider taking steps to reduce their exposure to air pollution, including staying indoors on days when $PM_{2.5}$ concentrations are high, using home air purifiers, and considering the use of masks when outdoors in areas with high levels of $PM_{2.5}$.

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ADDRESS FOR CORRESPONDENCE: Prof Sadeer Al-Kindi, Case Western Reserve University, Swetland Center for Environmental Health, Harrington Heart and Vascular Institute, University Hospitals Cleveland Medical Center, 11100 Euclid Avenue, Cleveland, Ohio 44106, USA. E-mail: sadeer.al-kindi@uhhospitals.org. OR Dr Salil V. Deo, Louis Stokes Cleveland VA Medical Center, Northeast Ohio VA Healthcare System, 10701 East Boulevard, Cleveland, Ohio 44139, USA. E-mail: Salil.Deo@va.gov.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Exposure to particulate matter pollution is associated with adverse long-term outcomes and years of life lost in patients undergoing percutaneous coronary interventions.

TRANSLATIONAL OUTLOOK: Further research is warranted to unravel whether air pollution intervention strategies can prevent plaque vulnerability in populations undergoing coronary interventions.

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KEY WORDS air pollution, coronary artery disease, mortality, risk, years of life lost

APPENDIX For supplemental tables and figures, please see the online version of this paper.