JACC: ADVANCES VOL. 3, NO. 8, 2024

ORIGINAL RESEARCH

OUTCOMES AND QUALITY

Particulate Matter 2.5 Pollution Impact on Comorbid Cancer and Cardiovascular Disease Mortality in the U.S.

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ABSTRACT

BACKGROUND Evidence regarding the effect of long-term exposure to particulate matter (PM) 2.5 and comorbid cancer and cardiovascular disease (CVD) mortality is limited.

OBJECTIVES In this study, the author report the association between long-term exposure to PM 2.5 and CVD mortality, cancer mortality and comorbid cancer and CVD mortality in the U.S. population.

METHODS The Centers for Disease Control and Prevention (CDC) WONDER (Wide-Ranging Online Data for Epidemiologic Research) multiple-cause-of-death database was used to obtain U.S. county-level mortality and population estimates from 2016 to 2020. Data on average daily density of PM 2.5 were abstracted from the 2018 CDC's National Environmental Public Health Tracking system. Counties were divided into quartiles with Q1 representing counties with least average daily density and Q4 representing counties with maximum average daily density of PM 2.5. Age-adjusted mortality rates were abstracted for each quartile, for the overall population and subgroups of population.

RESULTS The age-adjusted mortality rates for CVD, cancer, and comorbid cancer and CVD mortality were 505.3 (range: 505.0-505.7), 210.7 (range: 210.5-210.9), and 62.0 (range: 61.8-62.1) per 100,000 person-years, respectively. CVD mortality had the highest percentage excess mortality in Q4 compared with Q1, followed by comorbid cancer and CVD. Cancer had the least percentage excess mortality. A disproportionate effect of PM 2.5 exposure was noted on vulnerable and minority groups, based on Social Vulnerability Index and race stratification, respectively.

CONCLUSIONS Higher levels of long-term PM 2.5 exposure reported increased CVD mortality, cancer mortality and comorbid cancer and CVD disease mortality, with a pronounced detrimental effect in vulnerable and minority population. (JACC Adv. 2024;3:101106) © 2024 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/).

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ISSN 2772-963X https://doi.org/10.1016/j.jacadv.2024.101106

ABBREVIATIONS AND ACRONYMS

AAMR = age-adjusted mortality rate

CVD = cardiovascular disease

NCHS = National Center for Health Statistics

PM = particulate matter

SVI = Social Vulnerability Index

The Global Burden of Disease report estimated ~9 million deaths attributable to pollution and ~6.7 million deaths attributable to air pollution in 2019, specifically ~5 million deaths of the total ~9 million being cardiovascular disease (CVD) related.[1] This risk is higher than that attributed to common CVD risk factors including diabetes, hypertension, hyperlipidemia, and smoking.[2] In addition, these results are based on only a small set of environmental risk factors and hence are an under estimation of the actual magnitude of the problem.[3] Among air pollutants, ambient particulate matter (PM) 2.5 defined by the particle size being <2.5 μm have been studied extensively in the current literature, with respect to CVD.[4,5] Furthermore, reports have suggested a disproportionate risk from air pollution among individuals with comorbidities.[6,7] Until recently, guidelines have failed to address the management of pollution as a way to prevent CVD. In 2020, the American Heart Association issued a policy statement that provided guidance on reducing the CVD burden of ambient air pollutants.[8] Although substantial progress has been made in terms of understanding and preventing ambient air pollution-related CVD burden, a lot remains unknown, specifically related to PM 2.5 exposure and comorbid cancer and CVD mortality. In this study, we report the association between long-term exposure to PM 2.5 and CVD mortality, cancer mortality and comorbid cancer and CVD mortality in the U.S. population. Furthermore, we examine whether PM 2.5 has a disproportionate effect on vulnerable patients and minority groups.

METHODS

DATA SOURCE. Mortality and population data. For the present analysis, we used the Centers for Disease Control and Prevention (CDC) WONDER (Wide-Ranging Online Data for Epidemiologic Research) multiple-cause-of-death database to obtain the U.S. county-level mortality and population estimates from 2016 to 2020. The data in WONDER are based on death certificates for the U.S. residents. Each death certificate documents one underlying cause of death and up to 20 multiple causes of death, in addition to demographic data. Deaths of nonresidents (eg, nonresident aliens, nationals living abroad etc) and fetal deaths are excluded from the database. The underlying cause-of-death is defined by the World Health Organization as "the disease or injury which initiated the train of events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury." Mortality data from the death certificates are provided by the States to the National Center for Health Statistics (NCHS) through the Vital Statistics Cooperative Program. The U.S. Census Bureau data at the national, state, and county levels are used for population estimates.

Mortality in CDC WONDER secondary to comorbid cancer and CVD was identified using 4-digit International Classification of Diseases (ICD)-10 codes, CVD (ICD-10th Revision codes I00-I78), and malignant neoplasms (ICD-10th Revision codes C00-C97). Mortality secondary to CVD, cancer and comorbid cancer and CVD was reported separately. Furthermore, since multiple causes of death were used in the present analysis, the mortality reported may not be the underlying cause of death and are, therefore, not mutually exclusive with considerable overlap. Only mortality in individuals 15 years and older was included in the present analysis.

Cause-specific mortality at the county level was stratified based on age, sex, race/ethnicity, and urban-rural classification. Race was categorized as American Indian or Alaskan Native, Asian/Pacific Islander, Black or African American, and White. Ethnicity was categorized as Hispanic and non-Hispanic. The 2013 NCHS Urban-Rural Scheme for Counties was used for stratification of urbanization in the present analysis. Briefly, the 2013 NCHS divides counties into large metropolitan (≥1 million), medium or small metropolitan (50,000-999,999), and rural (micropolitan and noncore [nonmetropolitan counties that did not qualify as micropolitan; <50,000]) counties.

Air pollution-particulate matter. The average daily density of the fine PM 2.5 in counties across the United States was used for the present analysis. The data on fine PM 2.5 were abstracted from the CDC's National Environmental Public Health Tracking system. PM 2.5 average density data from the year 2018 were used for the present analysis. These data are collected using reference-grade air

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.

Manuscript received January 7, 2024; revised manuscript received June 8, 2024, accepted June 9, 2024.

quality monitors acquired from the U.S. Environmental Protection Agency Air Quality System. The steps involved in data collection and summarization include daily acquisition of PM 2.5 concentration and other supplemental data which include latitude, longitude, elevation etc. from designated Federal Reference Methods or equivalent Environmental Protection Agency's Air Quality System data mart. The maximum daily concentration at each monitoring site is retained and annual average measure estimates are created using the daily monitoring data. Furthermore, since not all U.S. counties have sufficient air quality monitoring to derive a PM 2.5 concentration estimates, data are supplemented with modeled estimates of PM 2.5 concentration derived from a Downscaler model. PM 2.5 across counties was presented as $\mu g/m^3$.

Social vulnerability index. Social Vulnerability Index (SVI) is a measure to identify counties prone to social vulnerability in general, initially designed to identify communities that may need support before, during, or after disasters. The SVI uses 16 U.S. census variables from the 5-year American Community Survey, namely, below 150% poverty, unemployed, housing cost burden, no high school diploma, no health insurance, aged 65 and older, aged 17 and younger, civilian with a disability, single-parent households, English language proficiency, racial and ethnic minority status, multiunit structures, mobile homes, crowding, no vehicle, and group quarters. These variables are broadly grouped under 4 categories, socioeconomic status, household characteristics, racial and ethnic minority status, and housing type and transportation. SVI percentile ranking values range from 0 to 1, with higher values indicating greater social vulnerability. SVI of year 2018 was used for the current analysis.

Institutional Review Board approval was not deemed necessary as the present study included deidentified data with prior ethics committee approval. We used the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guidelines to report results in the present study.

Statistical analysis. Central tendency of average fine PM 2.5 in $\mu g/m^3$ across PM 2.5 quartiles was presented as median and range. We reported county-level age-adjusted mortality rates (AAMRs) per 100,000 person-years with 95% CIs for CVD, cancer and comorbid cancer and CVD for the overall population and stratified by demographic variables (age, sex, race, and ethnicity) and urbanization. The 2000 standard population was used for age adjustment of the crude mortality rate.

The AAMRs were presented for the overall population and for individual quartile of counties based on the average fine PM 2.5 concentration. Quartiles were created by ascending order of counties based on the average fine PM 2.5 concentration, such that the 1st quartile would have counties with the least average fine PM 2.5 concentration, while the 4th quartile would have the highest average fine PM 2.5 concentration. Equal number of counties were assigned to each quartile. While reporting mortality overall and across each subgroup, <20 deaths were not reported to avoid potential identification and violation of data privacy. We reported excess mortality in the 4th quartile compared with the 1st quartile, overall and stratified by subgroups. Percentage excess mortality was calculated as the ratio of excess mortality to total mortality overall and by subgroups. To study the interplay between average PM 2.5 and SVI across counties, we further stratified PM 2.5 quartiles into SVI quartiles. All statistical analysis was carried out using R, version 4.0.3 (R Foundation for Statistical Computing). The statistical analysis was carried out between October and November 2022.

RESULTS

The median average fine PM 2.5 concentration in the PM 2.5 1st quartile was 6.4 [range: 3.0-7.7] ($\mu g/m^3$), in the PM 2.5 2nd quartile was 8.7 [range: 7.7-9.4] ($\mu g/m^3$), in the PM 2.5 3rd quartile was 9.9 [range: 9.4-10.4] ($\mu g/m^3$), and finally in the PM 2.5 4th quartile was 11.2 [range: 10.4-19.7] ($\mu g/m^3$).

CVD MORTALITY. Between 2016 and 2020, the overall AAMR for CVD was 505.3 (95% CI: 505.0-505.7) per 100,000 person-years (Table 1). The distribution of PM 2.5-associated AAMRs for CVD across the U.S. counties is shown in Central Illustration. The AAMRs for CVD were higher in counties belonging to higher PM 2.5 quartiles; 1st quartile (449.9 [95% CI: 449.0-450.8] per 100,000 person-years) and 4th quartile (519.6 [95% CI: 519.1-520.2] per 100,000 person-years), accounting for 69.7 excess deaths per 100,000 person-years in the 4th compared with the 1st quartiles (Table 1). This pattern was present across stratifications but was more pronounced among individuals >45 years of age (340.3 excess mortality in the 4th quartile compared with the 1st quartile) and among Black or African American individuals (138.3 excess mortality in the 4th quartile compared with the 1st quartile). Further the disparity was higher in Medium small metro and Micropolitan/NonCore (Nonmetro) counties compared with Large Metro.

CANCER MORTALITY. Between 2016 and 2020, the overall AAMR for cancer was 210.7 [95% CI:

TABLE 1 AAMR per 100,000 Person-Years for Cardiovascular Disease, Overall, Stratified by Demographic Variables and Average Daily Density of Fine Particulate Matter in Micrograms per Cubic Meter (PM 2.5) Quartiles of Counties

	Total	1st Quartile	2nd Quartile	3rd Quartile	4th Quartile	Excess AAMR per 100,000 Person-Year in 4th Quartile Compared With 1st Quartile	Percentage Excess Mortality
Cardiovascular disease mortality	505.3 (505.0-505.7)	449.9 (449.0-450.8)	484.0 (483.3-484.8)	539.0 (538.2-539.7)	519.6 (519.1-520.2)	69.7	13.8
Age, y							
<45	34.4 (34.3-34.6)	30.1 (29.7-30.5)	30.8 (30.5-31.1)	38.7 (38.3-39.0)	50.0 (49.0-50.9)	19.9	57.8
>45	1,095.7 (1,094.9-1,096.5)	976.1 (974.2-978.0)	1,052.1 (1,050.5-1,053.7)	1,166.1 (1,164.5-1,167.8)	1,316.4 (1,312.2-1,320.5)	340.3	31.0
Sex							
Male	607.5 (606.9-608.1)	540.7 (539.2-542.2)	580.7 (579.4-581.9)	648.9 (647.6-650.2)	625.8 (624.8-626.7)	85.1	14.0
Female	421.5 (421.1-421.9)	372.1 (371.0-373.2)	403.6 (402.8-404.5)	449.5 (448.6-450.4)	434.4 (433.7-435.1)	62.3	14.8
Race							
White	498.8 (498.5-499.2)	446.3 (445.4-447.2)	483.5 (482.7-484.3)	530.6 (529.7-531.4)	511.7 (511.0-512.3)	65.4	13.1
Black or African American	643.9 (642.7-645.2)	525.5 (521.3-529.6)	603.3 (600.1-606.4)	666.9 (664.5-669.2)	663.8 (661.9-665.8)	138.3	21.5
Asian and Pacific Islander	297.7 (296.5-299.0)	266.3 (262.0-270.7)	280.6 (278.0-283.3)	286.0 (283.4-288.6)	308.4 (306.4-310.4)	42.1	14.1
American Indian or Alaska Native	395.7 (392.2-399.2)	527.2 (519.0-535.4)	402.6 (394.5-410.7)	401.7 (394.5-408.8)	246.5 (241.2-251.8)	−280.7	−70.9
Ethnicity							
Hispanic or Latino	402.8 (401.7-403.8)	383.9 (381.6-386.2)	389.9 (387.3-392.5)	399.9 (397.6-402.1)	417.0 (415.3-418.7)	33.1	8.2
Not Hispanic or Latino	515.2 (514.8-515.6)	459.4 (458.4-460.3)	489.6 (488.8-490.4)	552.1 (551.3-553.0)	530.1 (529.5-530.7)	70.7	13.7
Urbanization							
Large metro	475.2 (474.8-475.7)	431.0 (429.7-432.3)	450.1 (449.1-451.1)	489.4 (488.4-490.5)	489.8 (489.1-490.5)	58.8	12.4
Medium small metro	517.0 (516.4-517.7)	442.7 (441.1-444.2)	492.1 (490.9-493.3)	540.9 (539.6-542.2)	560.4 (559.2-561.6)	117.7	22.8
Micropolitan/ NonCore (Nonmetro)	584.4 (583.5-585.4)	493.3 (491.4-495.1)	557.7 (555.9-559.6)	663.6 (661.6-665.6)	611.9 (610.0-613.8)	118.6	20.3

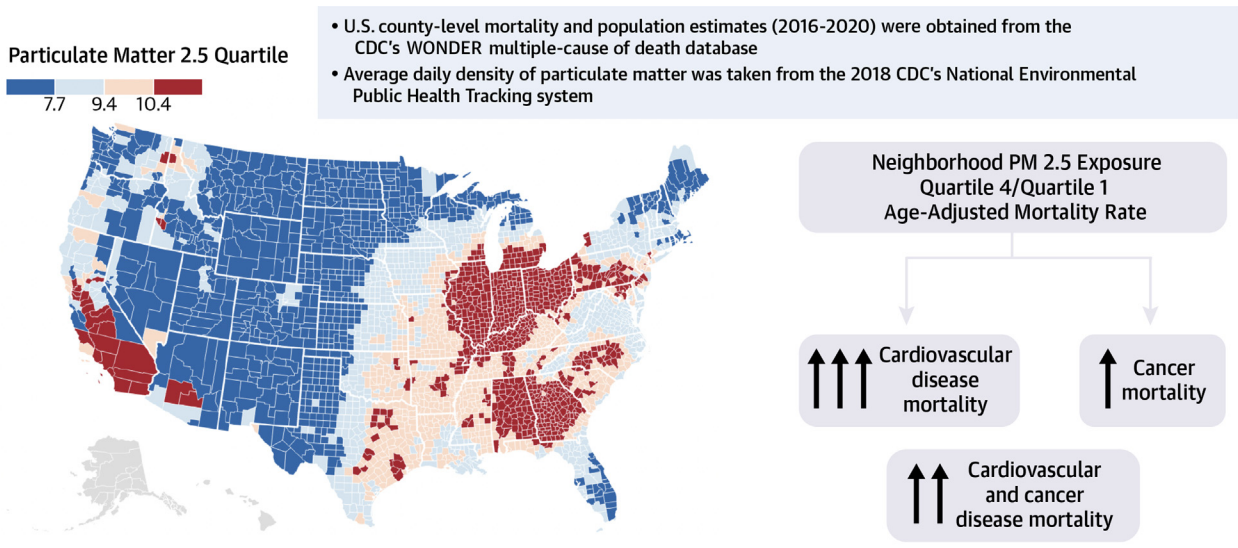
Values are median (95% CI).
AAMR = age-adjusted mortality rate.

210.5-210.9] per 100,000 person-years. Like CVD mortality, the AAMRs for cancer were higher in counties belonging to higher PM 2.5 quartiles; 1st quartile (199.5 [95% CI: 198.9-200.1] per 100,000 person-years) and 4th quartile (212.8 [95% CI: 212.4-213.2] per 100,000 person-years), accounting for 13.3 excess deaths per 100,000 person-years in the 4th quartile compared with the 1st quartile (Table 2). The AAMRs increased across age, sex, race/ethnicity, and urbanization from the lowest to highest PM 2.5 quartiles (Table 2). Overall, AAMRs for cancer mortality were highest in adults >45 years of age, men, Black or African American, and Micropolitan/NonCore counties (Nonmetro) (Table 2).

COMORBID CANCER AND CVD MORTALITY. Between 2016 and 2020, the AAMR was 62.0 (range: 61.8-62.1) per 100,000 person-years (Table 3). Figure 1 illustrates AAMRs for comorbid cancer and CVD across the U.S. counties. The AAMRs for comorbid cancer and CVD were higher in counties belonging to higher PM 2.5 quartiles; 1st quartile (55.6 [95% CI: 55.3-55.9] per 100,000 person-years) and 4th quartile (62.1 [95% CI: 61.9-62.3] per 100,000 person-years) (Table 3). This disparity was associated with 6.5 excess deaths per 100,000 person-years in the 4th compared with the 1st quartile (Table 3). Overall, AAMRs were higher for adults >45 years of age, men, Black or African American, and Medium small metro counties than their counterparts.

PERCENTAGE EXCESS MORTALITY. Based on the interpretation of the percentage excess mortality, CVD mortality increased the most with increasing PM

CENTRAL ILLUSTRATION **Particulate Matter 2.5 Pollution Impact on Comorbid Cancer and Cardiovascular Disease Mortality in the United States**



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2.5 levels, followed by comorbid cancer and CVD mortality and finally cancer mortality (13.8 vs 10.5 vs 6.3, respectively).

SVI AND PM 2.5 QUARTILE. As evident from the Figure 2, only PM 2.5 2nd, 3rd, and 4th quartiles were associated with increase in comorbid cancer and CVD mortality with increasing SVI quartile and minimal effect of SVI quartiles in counties belonging to the 1st PM 2.5 quartile.

DISCUSSION

This study using the CDC WONDER mortality data and the CDC's National Environmental Public Health Tracking system PM 2.5 data found an incremental association between higher PM 2.5 levels and county-level mortality secondary to CVD, cancer, and comorbid cancer and CVD. The study observed that adults >45 years, men, Black or African American individuals, medium small metro/micropolitan/Non-Core had a higher relative increase in mortality related to CVD, cancer, and comorbid cancer and CVD, with increasing PM 2.5 exposure. Furthermore, higher PM 2.5 levels had highest impact on CVD mortality, followed by comorbid cancer and CVD mortality and finally cancer mortality. Finally, only higher PM 2.5 quartile was associated with higher comorbid cancer and CVD mortality with increasing SVI quartile, pointing toward possible potentiation of SVI adverse outcomes with worsening average PM 2.5 density in counties. This was the first nationally representative study reporting the effect of long-term exposure of PM 2.5 on CVD, cancer, and comorbid cancer and CVD mortality. The data obtained from the current study will add further to the evidence on the role of environmental factors in CVD mortality/comorbid cancer and CVD mortality and help plan targeted preventive and treatment strategies among patients with comorbid cancer and CVD mortality.

Though significant strides have been made with respect to addressing conventional CVD risk factors, CVD mortality remains one of the leading cause of mortality worldwide.[9,10] Considering this, the attention has now expanded to address nontraditional risk factors in totality, also termed as "exposome." The exposome is defined as a highly variable and dynamic entity, evolving throughout the individual lifetime, with components in individuals natural, built, and social environments.[11]

Prior studies have reported a hazardous effect of PM 2.5 both pathologically and clinically. At the cellular level, PM 2.5 causes a determinantal effect because of activation of various signaling pathways, mainly adenosine monophosphate-activated protein kinase catalytic subunit α1, mitogen-activated protein kinase, nuclear factor-κB, and (signal transducer and

TABLE 2 AAMR per 100,000 Person-Years for Cancer, Overall, Stratified by Demographic Variables and Average Daily Density of Fine Particulate Matter in Micrograms per Cubic Meter (PM2.5) Quartiles of Counties

	Total	1st Quartile	2nd Quartile	3rd Quartile	4th Quartile	Excess AAMR per 100,000 Person-Year in 4th Quartile Compared With 1st Quartile	Percentage Excess Mortality
Cancer mortality	210.7 (210.5-210.9)	199.5 (198.9-200.1)	208.3 (207.8-208.8)	216.9 (216.4-217.4)	212.8 (212.4-213.2)	13.3	6.3
Age, y							
<45	13.9 (13.8-14.0)	13.2 (12.9-13.5)	13.3 (13.1-13.5)	14.4 (14.2-14.6)	14.2 (14.0-14.3)	1.0	7.2
>45	457.4 (456.9-457.9)	433.1 (431.8-434.4)	452.8 (451.8-453.9)	470.8 (469.7-471.8)	461.8 (461.0-462.6)	28.7	6.3
Sex							
Male	253.8 (253.4-254.2)	238.3 (237.3-239.2)	249.8 (249.0-250.6)	262.5 (261.7-263.3)	257.3 (256.7-258.0)	19	7.5
Female	179.0 (178.7-179.3)	169.5 (168.7-170.2)	177.3 (176.7-177.9)	183.6 (183.0-184.2)	180.9 (180.4-181.3)	11.4	6.4
Race							
White	212.5 (212.3-212.8)	201.9 (201.2-202.5)	211.1 (210.6-211.6)	219.1 (218.5-219.6)	213.9 (213.5-214.3)	12.0	5.6
Black or African American	238.3 (237.5-239.0)	196.3 (193.8-198.8)	231.4 (229.5-233.4)	239.3 (237.9-240.6)	247.4 (246.2-248.5)	51.1	21.4
Asian and Pacific Islander	128.4 (127.6-129.2)	123.6 (120.7-126.5)	124.5 (122.8-126.2)	124.7 (123.0-126.4)	126.9 (125.7-128.1)	3.3	2.6
American Indian or Alaska Native	139.3 (137.3-141.4)	176.6 (172.0-181.3)	147.6 (142.8-152.4)	142.3 (138.1-146.4)	86.6 (83.5-89.6)	−90.0	−64.6
Ethnicity							
Hispanic or Latino	149.1 (148.5-149.8)	153.1 (151.6-154.5)	147.6 (146.1-149.1)	145.8 (144.5-147.2)	149.0 (148.0-150.0)	−4.1	−2.7
Not Hispanic or Latino	216.8 (216.6-217.1)	206.2 (205.6-206.9)	212.6 (212.1-213.1)	223.8 (223.3-224.3)	219.5 (219.1-219.9)	13.3	6.1
Urbanization							
Large metro	200.3 (200.0-200.6)	190.8 (189.9-191.7)	199.0 (198.3-199.7)	199.0 (198.3-199.7)	203.5 (203.1-204.0)	12.7	6.3
Medium small metro	215.4 (214.9-215.8)	199.8 (198.8-200.9)	209.3 (208.5-210.1)	221.7 (220.9-222.5)	224.3 (223.5-225.0)	24.5	11.4
Micropolitan/NonCore (Nonmetro)	236.8 (236.2-237.4)	214.0 (212.8-215.2)	231.8 (230.6-233.0)	253.8 (252.6-255.1)	244.9 (243.7-246.1)	30.9	13.0

Values are median (95% CI).
Abbreviation as in Table 1.

activator of transcription)Stat-1, transforming growth factor-β/Smad, increased endothelial cell apoptosis, and systemic inflammation.[12,13] Studies have reported a higher PM 2.5 level to be associated with higher leukopoietic activity, as well as arterial inflammation, even after adjusting for traditional risk factors.[14] This has been attributed to a higher efflux of monocytes from the bone marrow migrating to adipose tissue and arterial wall.[15] Additionally, long-term PM 2.5 exposure has been attributed to be associated with higher coronary plaque vulnerability.[16] At the population level, long-term exposure to increased PM 2.5 concentration has been reported to increase the emergency room visits for respiratory distress, increased mortality due to lung cancer, chronic obstructive pulmonary disease, stroke, and ischemic heart disease.[17] However, limited studies have reported the disproportionate impact of PM 2.5 on minority subgroups and in patients with comorbid cancer and CVD.

As reported above long-term exposure to increased PM 2.5 concentration has been reported to be associated with increased all-cause and cardiopulmonary mortality.[18-24] Studies have reported the strongest association of the determinate effect of long-term exposure to PM 2.5 as pollutant for CVD mortality, specially mortality secondary to ischemic heart disease.[23-27] The Harvard Six Cities Study from 1974 to 2009 reported a 14% increased risk of all-cause death and a 26% increase in CVD mortality with 10-μg/m3 increase in PM 2.5.[24] The Rome longitudinal study reported a 4% increase in all-cause mortality and 10% increase in ischemic heart disease mortality with 10-μg/m3 increase in PM 2.5.[25] Reports of the California Teachers Study and the Women's Health Initiative all reported similar results.[20,28] The results of our study report similar findings with the percentage excess mortality highest for CVD mortality, with increasing PM 2.5 concentration. This pathogenesis for predilection in CVD-specific mortality is unclear and needs to be further explored. The Rome longitudinal study and the Harvard Six Cities Study also reported an association between long-term exposure with PM 2.5 and lung cancer.[24,25] Furthermore, a nationwide study in Brazil between 2010 and 2018 reported a significant association between each 10 $\mu g/m^3$ increase in concentrations of PM 2.5 and the risk of oral, nasopharynx, esophagus, and stomach, colon, rectum, liver, gallbladder, larynx, lung, bone, skin, female breast, cervix, prostate, brain, and leukemia.[29] Our study found percentage excess mortality to be higher for comorbid cancer and CVD than cancer

TABLE 3 AAMR per 100,000 Person-Years for Comorbid Cancer and Cardiovascular Disease, Overall, Stratified by Demographic Variables and Average Daily Density of Fine Particulate Matter in Micrograms per Cubic Meter (PM2.5) Quartiles of Counties

	Total	1st Quartile	2nd Quartile	3rd Quartile	4th Quartile	Excess AAMR per 100,000 Person-Year in 4th Quartile Compared With 1st Quartile	Percentage Excess Mortality
Comorbid cancer and cardiovascular disease mortality	62.0 (61.8-62.1)	55.6 (55.3-55.9)	62.0 (61.8-62.3)	66.1 (65.8-66.4)	62.1 (61.9-62.3)	6.5	10.5
Age, y							
<45	2.4 (2.4-2.5)	2.0 (1.9-2.1)	2.1 (2.0-2.2)	2.6 (2.5-2.7)	2.6 (2.5-2.6)	0.6	25.0
>45	136.6 (136.4-136.9)	122.7 (122.0-123.4)	137.1 (136.6-137.7)	145.7 (145.1-146.3)	136.6 (136.2-137.1)	13.9	10.8
Sex							
Male	80.7 (80.5-80.9)	72.6 (72.0-73.1)	80.7 (80.3-81.2)	85.9 (85.4-86.4)	81.1 (80.7-81.4)	8.5	10.5
Female	48.2 (48.1-48.4)	42.5 (42.1-42.9)	48.1 (47.8-48.4)	51.7 (51.4-52.0)	48.5 (48.3-48.7)	6.0	12.4
Race							
White	61.8 (61.6-61.9)	55.9 (55.6-56.3)	62.9 (62.6-63.2)	65.3 (65.0-65.6)	61.5 (61.3-61.7)	5.6	9.1
Black or African American	74.0 (73.6-74.5)	59.0 (57.6-60.4)	68.3 (67.2-69.3)	81.0 (80.1-81.8)	74.0 (73.4-74.7)	15.0	20.3
Asian and Pacific Islander	39.5 (39.1-40.0)	31.5 (30.0-32.9)	34.5 (33.6-35.5)	36.4 (35.5-37.3)	45.2 (44.4-45.9)	13.7	34.7
American Indian or Alaska Native	44.3 (43.1-45.5)	51.8 (49.2-54.3)	45.7 (43.0-48.5)	50.5 (48.0-53.0)	29.5 (27.7-31.3)	−22.3	−50.3
Ethnicity							
Hispanic or Latino	48.7 (48.4-49.1)	41.8 (41.1-42.6)	43.7 (42.9-44.6)	46.0 (45.3-46.8)	55.7 (55.0-56.3)	13.9	28.5
Not Hispanic or Latino	63.0 (62.9-63.2)	57.4 (57.1-57.8)	63.1 (62.9-63.4)	67.8 (67.5-68.1)	62.5 (62.3-62.7)	5.1	8.1
Urbanization							
Large metro	59.1 (58.9-59.3)	52.6 (52.1-53.1)	59.1 (58.7-59.5)	62.7 (62.3-63.1)	59.2 (58.9-59.4)	6.6	11.2
Medium small metro	62.2 (62.0-62.4)	54.1 (53.5-54.6)	60.7 (60.3-61.2)	64.4 (64.0-64.9)	66.5 (66.0-66.9)	12.4	19.9
Micropolitan/NonCore (Nonmetro)	70.7 (70.4-71.0)	62.6 (61.9-63.2)	72.1 (71.5-72.8)	77.7 (77.1-78.4)	69.6 (69.0-70.3)	7.0	9.9

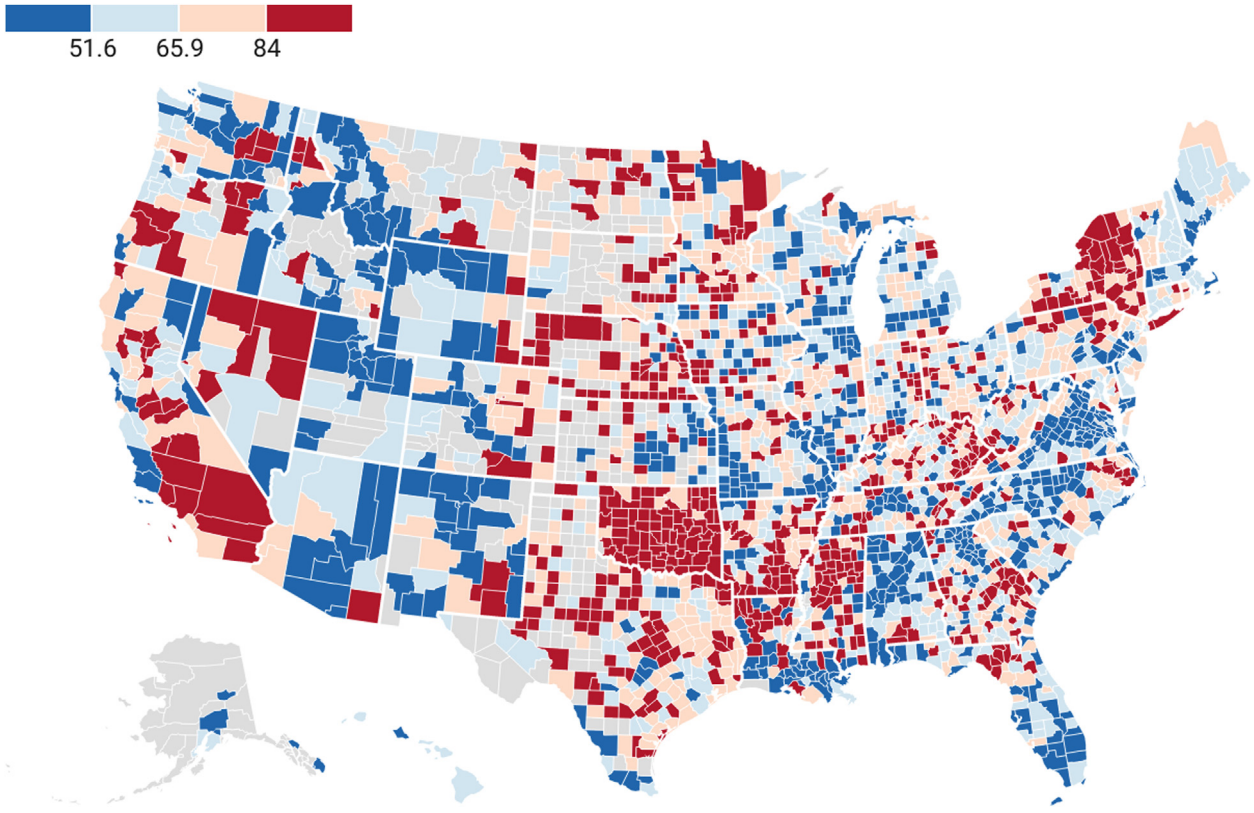
Values are median (95% CI).
Abbreviation as in Table 1.

mortality with increasing PM 2.5 concentration. Our study is one of the first reports of the effect of PM 2.5 long-term exposure on comorbid cancer and CVD mortality.

Our study reported a differential effect of long-term exposure PM 2.5 across vulnerable subgroups and minorities. This differential effect has not been reported frequently in environmental pollution studies. The reason for this effect may include mainly inequitable burden of pollutants, with a major brunt borne by communities of color and other minorities.[30] For instance, the redlining of the U.S. neighborhood in the 1930s mostly deemed Black communities as being hazardous, leading to financial disinvestment, poor air quality, heat-island effect, and minimal green space.[30] The reasons for medium small metro/micropolitan/NonCore urbanization level associated with a higher relative increase in mortality related to CVD, cancer, and comorbid cancer and CVD, compared with large metro remains unknown. We hypothesize a possible higher outdoor time, lower resources for mitigating ill effects of air pollutants and scarce health care resources as the possible explanation for this observed difference. These results further highlight complex pathological processes and the need for public health policy changes to target these vulnerable groups of the society.

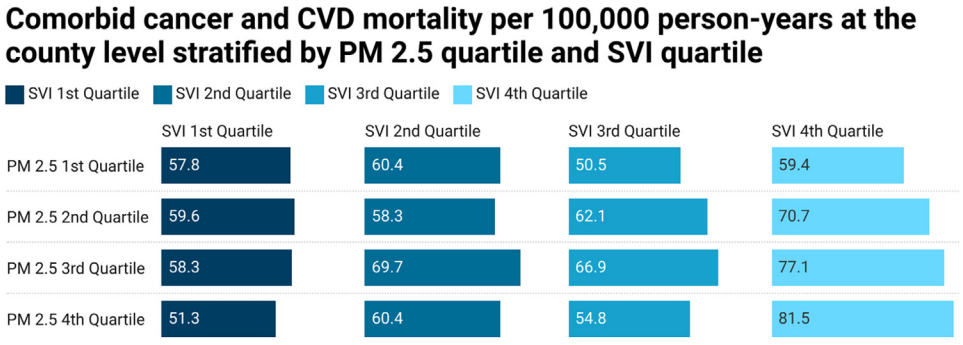
STUDY LIMITATIONS. The study is with limitations. This study does not account for other air pollutants like ozone, nitrogen oxides, sulfur dioxide, carbon monoxide, lead, benzene, and polycyclic aromatic hydrocarbons that could have potential adverse health impacts. We cannot draw causal relationships between county-level characteristics and mortality due to the cross-sectional nature of our analysis. We report AAMRs without adjusting for individual risk factors, and this important limitation should be considered while interpreting the results. Annual income and educational qualification which can be an important factor in determining PM 2.5 exposure was not accounted for in the current study. Furthermore, as mentioned in the methods section, the modeled PM 2.5 levels for few countries can misclassify counties across the quartile group generated for the present study. Considering the limitation of the database, we could not account for cancer stage or specific cancer therapies on outcomes. Finally, the exclusion of

FIGURE 1 Heat Map of the United States Representing Comorbid Cancer and CVD Mortality per 100,000 Person-Years at the County Level From 2016 to 2020



No specific regional predilection was noted for comorbid cancer and CVD mortality. CVD = cardiovascular disease.

FIGURE 2 Comorbid Cancer and CVD Mortality per 100,000 Person-Years at the County Level Stratified by PM 2.5 Quartile and SVI Quartile



Increase in SVI quartile was associated with higher comorbid cancer and CVD mortality in the 2nd, 3rd, and 4th PM 2.5 quartile. PM = particulate matter; SVI = Social Vulnerability Index; other abbreviation as in Figure 1.

nonresidents in the WONDER database may result in undercounting a large number of undocumented U.S. immigrants who are likely to be vulnerable minority with significant exposure to PM 2.5 pollution.

CONCLUSIONS

In a nationally representative sample of the U.S. population, counties with higher long-term PM 2.5 exposure exhibited increased mortality rates from CVD, cancer, and comorbid cancer and CVD. This association was most pronounced among vulnerable and minority populations. There is a critical need to evaluate targeted preventive and treatment interventions based on the available evidence regarding the role of environmental variables in patients with comorbid cancer and CVD.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Long-term exposure to PM 2.5 exhibited increased CVD mortality, cancer mortality, and comorbid cancer and CVD mortality in the U.S. population. Furthermore, higher PM 2.5 levels have a disproportionate impact on mortality in vulnerable and minority.

TRANSLATIONAL OUTLOOK: Future studies should aim to delineate the pathophysiologic mechanisms by which PM 2.5 increases cardiovascular and cancer mortality to inform strategies for prevention.

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KEY WORDS **cardio-oncology, cardiovascular disease, cancer, PM 2.5 exposure**