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Nationwide assessment of ambient monthly fine particulate matter ($PM_{2.5}$) and the associations with total, cardiovascular and respiratory mortality in the United States

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Abstract

High air pollution events spanning multiple months and caused by environmental perturbations such as droughts and wildfires are increasing in frequency, intensity and duration due to climate change. While both daily and annual exposure to fine particulate matter ($PM_{2.5}$) have regulatory standards in the United States, mid-scale exposure at the monthly interval remains unregulated and the public health impacts of mid-duration ambient air pollution exposure are poorly understood. These present a new public health challenge in mitigating harmful effects of persistent ambient air pollution on community health. We executed an ecological study of the associations between monthly mean $PM_{2.5}$ exposure with total, cardiovascular and respiratory mortality counts, stratified by age, sex and race, in 698 counties in the conterminous United States from 1999 to 2018. A two-stage model was used to estimate the risk and number of deaths associated with this exposure timescale reported as incidence rate ratios (IRRs) and absolute risk differences per million persons (ARDs). Increased mortality of all types was positively associated with a 10 μg m^{-3} monthly change in $PM_{2.5}$ exposure (total mortality IRR: 1.011, 95% confidence interval (CI): (1.009, 1.013), ARD: 8.558, 95% CI: (6.869, 10.247); cardiovascular mortality IRR: 1.014, 95% CI: (1.011, 1.018), ARD: 3.716, 95% CI: (2.924, 4.509); respiratory mortality IRR: 1.016, 95% CI: (1.011, 1.023), ARD: 1.676, 95% CI: (1.261, 2.091)). Our results suggest elderly, non-black minorities and males to be the most impacted subgroups along with metropolitan and highly socially vulnerable communities. Heterogeneities in the magnitude and direction of association were also detected across climate regions of the United States. These results elucidate potential effects of monthly $PM_{2.5}$ on mortality and demonstrate a need for future health policies for this currently unregulated interval of ambient air pollution exposure.

1. Introduction

Ambient air pollution is a ubiquitous environmental exposure impacting global population health. Both acute and chronic ambient air pollution exposure are associated with numerous health conditions involving the respiratory [1], cardiovascular [1, 2], renal [3, 4], metabolic [5, 6], neurologic [7, 8] and reproductive systems [9]. Besides air pollution sourced from industrial and commercial activities, increased frequencies of extreme weather events including droughts [10] and wildfires [11] may contribute to elevated periods of ambient air pollution lasting for several months and leading to potential social, economic and environmental damages [12–14].

While considerable work has evaluated acute [15–20] and chronic [20–26] exposure to ambient air pollution, comparatively fewer studies exist on mid-duration exposure to air pollution at a monthly interval [27–29]. Ambient air quality standards in the United States exist at both the daily and annual scales but there is a gap with no established monthly regulatory thresholds. Exploring the consequences of mid-duration exposure is becoming more relevant as extreme weather events, which are becoming increasingly frequent and intense, are causing longer durations of elevated ambient air pollution periods [12, 30] as has been seen with recent wildfire seasons in the American West and agricultural burning events in other countries [31]. It is unclear if exposure to extended periods of air pollution present different magnitudes of risk from more familiar daily or annual air pollution measures.

There is an additional dearth of nationwide studies that evaluate ambient air pollution in the general population, including effects in younger adult populations who while traditionally healthier may show adverse consequences when exposed to longer duration environmental hazards. Most nationwide assessments of ambient air pollution focus on specific strata of the population, such as older adults (e.g. Medicare population) [15, 16, 22, 32] or occupational cohorts [33]. Therefore, the magnitude of risk due to ambient air pollution is poorly understood in younger adult populations and the general population as a whole.

We completed an ecological study to examine mortality events in the conterminous United States from 1999 to 2018 and estimate mortality risk and number of deaths associated with mid-duration exposure to fine particulates with an aerodynamic diameter of 2.5 μg or less ($PM_{2.5}$). We evaluated risk in the general population and specific population strata defined by person and place-based identifiers. The results of this study will elucidate the magnitude of association monthly $PM_{2.5}$ has on human health and will serve as a springboard for future work investigating mid-duration intervals of ambient air pollution health effects.

2. Materials and methods

2.1. Study population

Using uncompressed cause specific mortality files from the National Center for Health Statistics (NCHS) from 1999 to 2018 [34, 35], we generated monthly county level counts of total mortality and mortality by cardiovascular (International Classification of Diseases 10th revision (ICD-10 codes I00–I99) and respiratory (ICD-10 codes J09–J98) causes for the conterminous United States. We stratified these monthly aggregations into four age groups (0–19, 20–39, 40–64 and 65+ years), three race groups (White, Black, non-black) and two sex groups (male, female). Additional race categories were not evaluated due to low populations in finer race strata. Underlying county level annual population estimates were obtained from the surveillance, epidemiology, and end results program [36] and were aggregated for each population subgroup in our study based on age, sex and race. We assigned year-specific annual population estimates to all the months in a given year.

2.2. Outcome

This study evaluated total, cardiovascular and respiratory mortality counts at the county level and monthly temporal resolution from January 1999 to December 2018 in the conterminous United States.

2.3. Environmental data

Monthly average ambient levels of daily 24 h mean $PM_{2.5}$ ($\mu g\ m^{-3}$) were obtained from the Environmental Protection Agency (EPA) Air Quality System monitoring networks [37]. Monitor events that failed to meet the EPA minimum daily summary criteria were excluded from the study (1.4% of data days). We averaged daily pollutant levels within each calendar month and averaged multiple monitors within a county to generate an overall monthly mean $PM_{2.5}$ value. Data on time-varying confounders included mean monthly temperature (Celsius) and total monthly precipitation (millimeters) from the National Oceanic and Atmospheric Association's (NOAAs) Nclimgrid product at a 5 km grid cell resolution [38]. We calculated a monthly county level exposure for temperature and precipitation using zonal averages of all grid cells falling within a county boundary.

2.4. Community characteristics data

We considered several place-based stratification variables as effect modifiers on the causal pathway between monthly $PM_{2.5}$ exposure and mortality. Place-based modifiers included: NOAA climate regions [39], urbanicity status and social vulnerability index (SVI) categories. All nine NOAA climate regions were represented in our study including the Northwest, Northern Rockies and Plains, Upper Midwest, Ohio Valley, Northeast, Southeast, South, Southwest, and West (figure S1). The NCHS 2006 and 2013 binary urban/rural classification codes were used to classify counties into metropolitan and nonmetropolitan categories with the 2013 categorization being used in our primary analysis and the 2006 categorization being

used for sensitivity purposes [40, 41]. In the binary NCHS urban/rural definition, metropolitan counties were those that fell under the categories of: large central metro, large fringe metro, medium metro, and small metro. Nonmetropolitan counties were those that were classified as micropolitan and noncore. The county level SVI for 2018 was used as an overall measure of socio-economic vulnerability of a community [42]. The Centers for Disease Control and Prevention's SVI is a composite index meant to capture community resiliency to external stressors such as natural disasters and is built using Census derived data on socio-economic status, demographic composition (e.g. race, age, disability status), household composition and transportation infrastructure [43]. SVI was categorized into tertiles based on the study population's distribution of total SVI scores with the highest tertile representing the most socially vulnerable counties and the lowest tertile representing the least socially vulnerable counties.

2.5. Study design

We estimated the association between mean monthly levels of exposure to $PM_{2.5}$ and total, cardiovascular and respiratory mortality using an ecological study design. For our primary analysis which evaluated the association between mortality, mortality by type and stratification by place-based modifiers with mean monthly $PM_{2.5}$, we included counties whose monthly population was >25 000 people for the duration of the study period and had $\geqslant$25% valid data-months of $PM_{2.5}$ during the study period ($N = 698$ counties). In our sub analysis of person-based effect modifiers (age, sex and race) for total and cardiovascular mortality only, we restricted our study population threshold to counties with >100 000 people ($N = 446$ counties). We imposed a stricter population threshold for our sub analysis to avoid model convergence issues with the lower population subgroups. We did not analyze person-based effect modifiers for respiratory mortality or the youngest age group (0–19) due to a sparsity of mortality events among this population.

2.6. Statistical analysis

We used a two-stage modeling approach commonly employed in ecological environmental epidemiology research [17, 44, 45] to estimate the association between mean monthly $PM_{2.5}$ and mortality. In the first stage, an over dispersed Poisson regression model was fit to each county adjusting for mean monthly temperature, total monthly precipitation and for temporal confounding using a Fourier term with a single sine–cosine pair on elapsed time (1–240 months) along with an indicator variable for calendar year. Adjusting for time in this manner controls for long term and seasonal trends in mortality due to events such as seasonal respiratory epidemics and non-infectious disease epidemics (e.g. opioids), or changes in population growth unrelated to air pollution exposure [46]. By modeling each county independently, we made within-county comparisons by comparing each county to itself at a monthly interval, eliminating the need to adjust for other potential confounding variables that we did not expect to vary from month to month [47]. Strategies to adjust for time and the rationale behind this approach have been described elsewhere [46]. In the second stage, we pooled the county level estimates from the first stage models using a random effects meta-analysis estimated via restricted maximum likelihood using the *metafor* package [48] to allow for between-county heterogeneity to estimate an overall association between mean monthly $PM_{2.5}$ and mortality.

Our measures of association were presented for a 10 μg m^{-3} increase in mean monthly $PM_{2.5}$ and were reported on the IRR and ARD scales. The ARD was calculated following Di *et al* (2017) [15] and was given by

$$\mathrm{ARD} = \alpha * \frac{(\exp(\beta * 10) - 1)}{(\exp(\beta * 10))}$$

$$SE_{\mathrm{ARD}} = \propto * \exp(-\beta * 10) * se(10 * \beta)$$

where α is the baseline monthly mortality rate for all counties in the study area which was calculated as the mean monthly mortality rate per mortality type and effect modification strata (i.e. sub analyses) and β is the regression coefficient for $PM_{2.5}$.

To investigate effect modification by place and person-based effect characteristics, we stratified the original data into sub evaluations for each modification level. For example, to analyze effect modification by NOAA climate region, we grouped the first stage county-specific effect estimates into their respective NOAA climate region and completed the meta-analysis approach on each subset separately. In calculating ARD, we estimated monthly baseline mortality rates for each effect modifier subset giving each strata its own baseline mortality rate. Following Di *et al* (2017) [15] we assessed the statistical significance of effect modification by race, sex, age, urbanicity and social vulnerability by choosing a referent category for each modifier and using a Z test with an α level of 0.05 to determine statistical significance. We did not apply statistical tests for NOAA climate region since there was no clear choice of a referent category to use.

2.7. Sensitivity analyses

We evaluated the sensitivity of our model to the temporal construct of county-month-time outcome and exposure, which is less documented compared to daily or annual time series approaches. Informed by Bhaskaran *et al* [46], our evaluations included: (a) time stratified approach with a categorical variable for year and a numeric variable for elapsed month (1–240), (b) Fourier approach with four4 sine–cosine pairs and a categorical variable for year, (c) Fourier approach with one sine–cosine pair and a linear term for elapsed time (1–240 months) and a squared term for elapsed time, (d) Fourier approach with a single sine–cosine pair, a categorical term for year, a linear term for elapsed time, a squared term for elapsed time and a cubed term for elapsed time, and (e) Cubic *B* splines with 3, 4 and 5 degrees of freedom per year. All approaches using cubic *B*-splines had some counties that failed to converge in the stage 1 approach. We qualitatively evaluated the fit of each approach using data from a single county by plotting model residuals over time and by plotting fitted values for the outcome (total mortality) and exposure (monthly $PM_{2.5}$) over time to evaluate potential over/under smoothing in the time series. We further tested the model for the (a) inclusion of a population offset and (b) comparison of effect estimates from negative binomial against quasi-Poisson family models. An additional model was run for total mortality excluding the cardiovascular and respiratory mortality events to examine if the measures of associations had large changes for total mortality when cardiovascular and respiratory causes were excluded. Finally, we tested for potential confounding by lagged meteorological variables by evaluating models using mean temperature and total precipitation from the previous month as covariates and a model using the rolling average of mean monthly temperature and total precipitation from the current month and the previous month's values.

All statistical analysis was completed using R statistical software [49] (version 4.1).

3. Results

3.1. Descriptive statistics

The average total study population was approximately 228 million people and covered a broad geographic range of the conterminous United States. The study population and total mortality events ($n = 38.3$ million) remained similar across the two population thresholds used in the primary and sub analyses (table 1). For person-based effect modifiers, the oldest age group (65+) composed the majority of mortality cases with greater than 70% representation across all types. The youngest age group (0–19 years) had the smallest percentage of mortality events (table 1). For race, most deaths were in White individuals with approximately 16% of the sample represented by non-black and Black minorities (table 1). Mortality by sex was nearly evenly split for all mortality types (table 1).

Mortality events were observed across all NOAA climate regions with the Northeast, Southeast and Ohio Valley regions representing over half of mortality counts while the Northern Rockies and Plains and Southwest regions contributed only 6.5% of mortality events (table 1). A total of 33.6% of mortality events occurred in counties within the high SVI tertile while the lowest SVI tertile had 25.9% of mortality events (table 1). For urbanicity status, metro counties had close to 95% of the reported mortality events compared to nonmetro counties (table 1).

There was a decreasing trend in mean monthly $PM_{2.5}$ exposure over the past 20 years with a decline from a 13 $\mu g\ m^{-3}$ mean in the early 2000s to about 7 $\mu g\ m^{-3}$ in 2018 (figure 1). The spatial distribution of $PM_{2.5}$ displayed exposure heterogeneities with southern California, the Pacific Northwest and Rocky Mountains areas having higher mean monthly $PM_{2.5}$ compared to the rest of the country. The Great Plains were the least sampled region in our study (figure 2).

Mean monthly $PM_{2.5}$ summaries over the entire study period stratified by inclusion criteria demonstrated the 100 000-population cutoff had higher concentrations of $PM_{2.5}$ compared to the 25 000-population threshold used in the primary analysis (table 2). Stratification by NOAA climate region indicated the Northeast, Ohio Valley, South, Southeast and West to have higher levels of mean monthly $PM_{2.5}$ compared to other regions (table 2). Levels of mean monthly $PM_{2.5}$ exposure declined with tertiles of SVI and going from metro to nonmetro counties (table 2).

3.2. Baseline associations between $PM_{2.5}$ and mortality

All three mortality types (total, cardiovascular and respiratory) demonstrated a positive association with a 10 $\mu g\ m^{-3}$ increase in mean monthly $PM_{2.5}$ exposure (figure 3) with all IRR estimates being relatively precise (i.e. narrow confidence intervals) (table S1). We estimated an IRR for each 10 $\mu g\ m^{-3}$ of $PM_{2.5}$ of 1.011 (95% CI: 1.009, 1.013) for total mortality, 1.014 (95% CI: 1.011, 1.018) for cardiovascular mortality, and 1.016 (95% CI: 1.001, 1.023) for respiratory mortality. The ARD for a 10 $\mu g\ m^{-3}$ increase in mean monthly $PM_{2.5}$ was largest for total mortality ARD: 8.558 (95% CI: 6.869, 10.247) and also had the widest 95% confidence interval compared to cardiovascular ARD: 3.716 (95% CI: 2.924, 4.509) and respiratory mortality ARD:

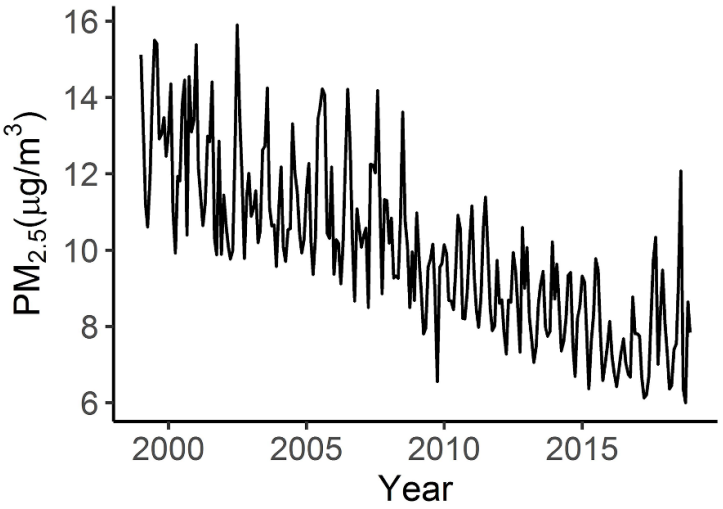

Figure 1. Mean monthly $PM_{2.5}$ for primary study population, 1999–2018 ($N = 698$ United States counties with >25 000 persons).

Table 1. Baseline characteristics of study population (1999–2018).

Category	Stratification Variable	Total mortality	Cardiovascular mortality	Respiratory mortality
Inclusion criteria	Total (25 000 pop threshold)	38 302 705	12 799 061	3644 670
	Total (100 000 pop threshold)	35 477 198	11 864 976	3335 762
Person-based variables[a]	Age (years)[b]			
	0–19	770 778 (2.2%)	25 630 (0.2%)	23 026 (0.70%)
	20–39	1434 953 (4.1%)	151 024 (1.3%)	33 863 (1.0%)
	40–64	7607 096 (21.4%)	2008 122 (16.9%)	443 352 (13.3%)
	65+	25 664 371 (72.3%)	9680 200 (81.6%)	2835 521 (85.0%)
	Race			
	White	29 616 027 (83.5%)	9930 435 (83.7%)	2947 982 (88.4%)
	Non-black	1013 736 (2.9%)	324 816 (2.7%)	80 968 (2.4%)
	Black	4847 435 (13.6%)	1609 725 (13.6%)	306 812 (9.2%)
	Sex			
	Male	17 740 684 (50.0%)	5785 870 (48.8%)	1595 042 (47.8%)
	Female	17 736 514 (50.0%)	6079 106 (51.2%)	1740 720 (52.2%)
Place-based variables[c]	NOAA climate region			
	Northeast ($n = 118$)	9026 988 (23.5%)	3170 915 (24.8%)	829 755 (22.8%)
	Northern Rockies and Plains ($n = 31$)	489 207 (1.3%)	147 356 (1.1%)	54 754 (1.5%)
	Northwest ($n = 49$)	1662 603 (4.3%)	507 701 (4.0%)	160 121 (4.4%)
	Ohio Valley ($n = 125$)	6358 591 (16.6%)	2113 936 (16.5%)	634 437 (17.4%)
	South ($n = 91$)	4290 770 (11.2%)	1395 047 (10.9%)	400 767 (11.0%)
	Southeast ($n = 127$)	6624 935 (17.3%)	2155 833 (16.8%)	612 999 (16.8%)
	Southwest ($n = 47$)	1984 264 (5.2%)	582 736 (4.6%)	200 280 (5.5%)
	Upper Midwest ($n = 60$)	2674 222 (7.0%)	888 238 (6.9%)	247 325 (6.8%)
	West ($n = 50$)	5191 125 (13.6%)	1837 299 (14.4%)	504 232 (13.8%)
	SVI[d]			
	High ($n = 232$)	12 881 632 (33.6%)	4395 737 (34.3%)	1208 769 (33.2%)
	Medium ($n = 232$)	15 477 895 (40.4%)	5148 345 (40.2%)	1468 626 (40.3%)
	Low ($n = 233$)	9937 406 (25.9%)	3253 565 (25.4%)	966 823 (26.5%)
	Urbanicity			
	Metro ($n = 530$)	36 551 863 (95.4%)	12 218 917 (95.5%)	3452 241 (94.7%)
	Nonmetro ($n = 168$)	1750 842 (4.6%)	580 144 (4.5%)	192 429 (5.3%)

[a] Percentages for person-based variables used the 100 000-population threshold ($N = 446$ counties).

[b] Age group 0–19 was not assessed in our sub analysis of age.

[c] N is the number of counties in each place-based strata and percentages are based on 25 000-population threshold.

[d] One county was not included in SVI analysis because it lacked a total overall SVI score. Percentages will not add up to 100%. Higher values of SVI correspond with higher levels of social vulnerability.

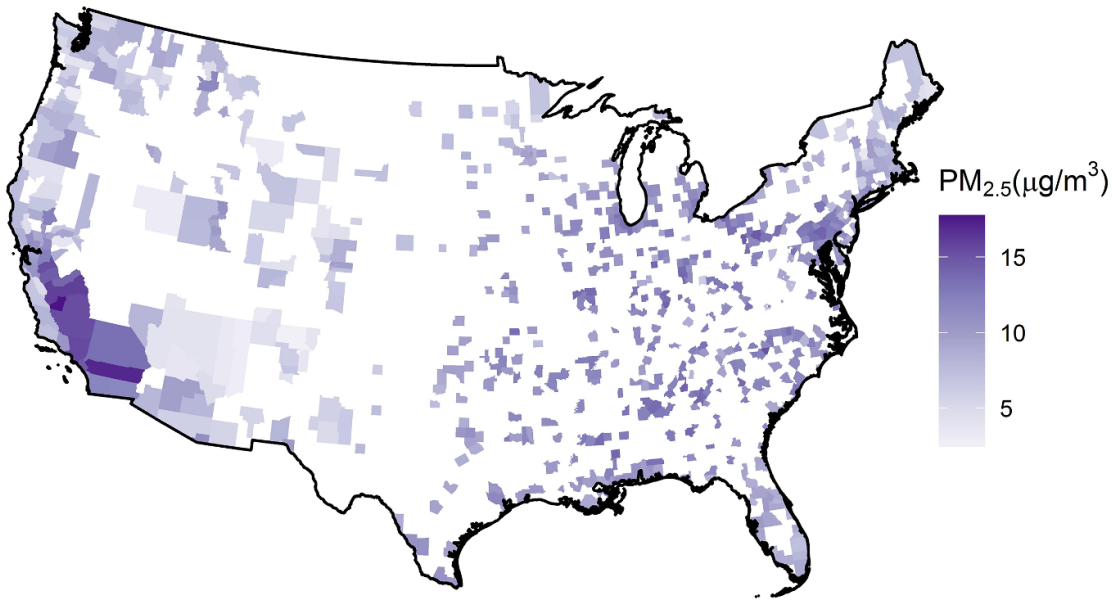

Figure 2. Mean monthly $PM_{2.5}$ ($\mu g\ m^{-3}$), 1999–2018 for primary study population (>25 000 persons). Unshaded areas are counties not included in analysis.

Table 2. Baseline characteristics (percentiles) of mean monthly $PM_{2.5}$ concentrations ($\mu g\ m^{-3}$) for study population (1999–2018).

Stratification variable	5th	25th	50th	75th	95th
Inclusion criteria					
25 000 pop threshold	3.81	6.93	9.34	12.24	18.06
100 000 pop threshold	4.60	7.43	9.70	12.50	18.20
NOAA climate region					
Northeast	4.19	6.99	9.39	12.3	17.82
Northern Rockies and Plains	2.37	4.67	6.56	8.93	13.88
Northwest	2.76	4.39	6.05	8.66	15.02
Ohio Valley	6.33	8.84	11.19	14.16	19.65
South	5.97	8.18	10.03	12.11	16.13
Southeast	6.08	8.12	10.15	12.84	18.66
Southwest	2.02	4.11	5.84	7.93	13.14
Upper Midwest	4.84	7.32	9.31	11.88	16.21
West	2.67	5.78	8.35	12.15	22.64
SVI					
High	3.77	7.17	9.60	12.49	18.50
Medium	4.08	7.19	9.55	12.40	18.10
Low	3.68	6.51	8.88	11.83	17.50
Urbanicity					
Metro	4.51	7.39	9.70	12.53	18.30
Non-metro	2.55	5.20	7.87	10.97	16.70

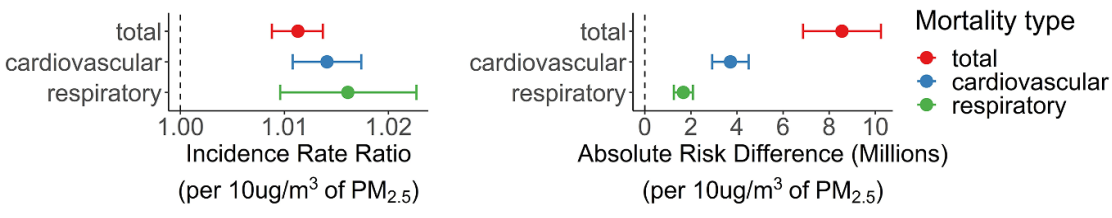

Figure 3. Incidence rate ratios and absolute risk differences per million individuals for total, cardiovascular and respiratory mortality associated with a 10 $\mu g\ m^{-3}$ increase in mean monthly $PM_{2.5}$.

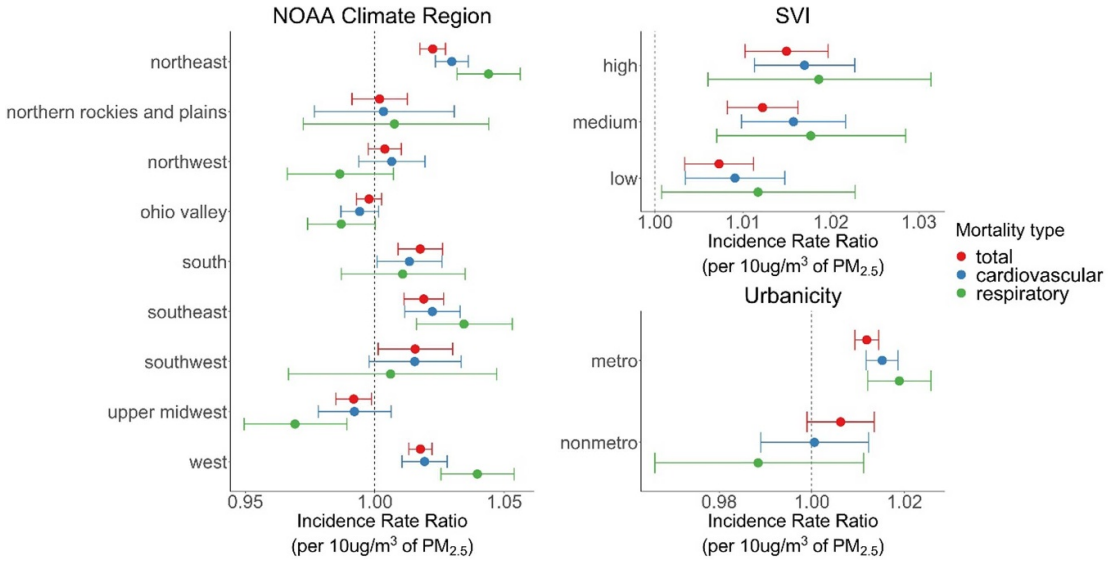

Figure 4. Incidence rate ratios associated with a 10 μg m^{-3} increase in mean monthly $PM_{2.5}$ for total, cardiovascular and respiratory mortality stratified by NOAA climate region, urbanicity status, and SVI.

1.676 (95% CI: 1.261, 2.091) (table S1). This is a by-product from how the standard error for the ARD was calculated since it involved multiplying by the baseline mortality rate which is higher for total mortality compared to other mortality types.

3.3. Place-based effect modifiers

Place-based stratification by NOAA climate region indicated heterogeneities in the strength and direction of association between monthly $PM_{2.5}$ exposure and mortality (figure 4, tables S2–S4). Positive associations between monthly $PM_{2.5}$ exposure and mortality were detected for the Northeast, Northwest, South, Southeast, Southwest and West regions (figure 4). The Northeast and Southeast regions had the strongest positive associations with mean monthly $PM_{2.5}$ and mortality (IRR for total mortality: 1.022, 95% CI: 1.018, 1.027 and 1.019, 95% CI: 1.011, 1.027 respectively). Negative associations were detected for the Ohio Valley and Upper Midwest regions (figure 4). Model results stratified on SVI displayed a trend of increasing risk in the most socially vulnerable counties (IRR for total mortality: 1.015, 95% CI: 1.010, 1.020) and lowered risk in the least socially vulnerable counties (IRR for total mortality: 1.007, 95% CI: 1.003, 1.011) (figure 4, tables S2–S4). Mortality risk was significantly higher in the highest SVI tertile compared to the lowest SVI tertile (table S2). One county did not have a measure for total SVI and was excluded from the analysis for SVI. Stratified analysis for urbanicity suggested positive associations with mean monthly $PM_{2.5}$ and mortality for metro counties (IRR for total mortality: 1.012, 95% CI: 1.009, 1.014) and marginal positive associations for nonmetro counties (IRR for total mortality: 1.006, 95% CI: 0.999, 1.014) albeit mortality risk was not significantly different comparing metro to nonmetro counties (figure 4, table S2). All results were relatively precise (tables S2–S4).

Results presented on the ARD scale for place-based effect modifiers followed the same directional pattern as the IRR scale. The Northeast, South, Southeast, Southwest and West regions had large ARDs from increased monthly $PM_{2.5}$ exposure particularly for total mortality (figure 5, table S2). ARD estimates ranged from −5.234 (95% CI: −10.308, −0.161) per million in the Upper Midwest up to 16.308 (95% CI: 12.851, 19.764) per million in the Northeast region for total mortality. An ARD of respiratory mortality could not be estimated for the Northern Rockies and Great Plains region due to convergence issues. The ARD for SVI was close to double when comparing the most socially vulnerable to the least socially vulnerable counties (ARD: 11.405, 95% CI: 8.189, 14.621 per million vs ARD: 5.259, 95% CI: 2.697, 7.820 per million) for total mortality (figure 5, table S2). Finally, ARD estimates for metro and nonmetro counties were mostly similar and not significantly different from each other with metro counties having slightly higher ARDs (ARD: 8.698, 95% CI: 6.917, 10.480 per million for total mortality and ARD: 7.503, 95% CI: 2.028, 12.978 per million respectively) (figure 5, tables S2–S4).

3.4. Person based effect modifiers

Person-based effect modification was only assessed for total and cardiovascular mortality due to unstable estimates with respiratory mortality from low sample sizes. Mortality events in the youngest age group

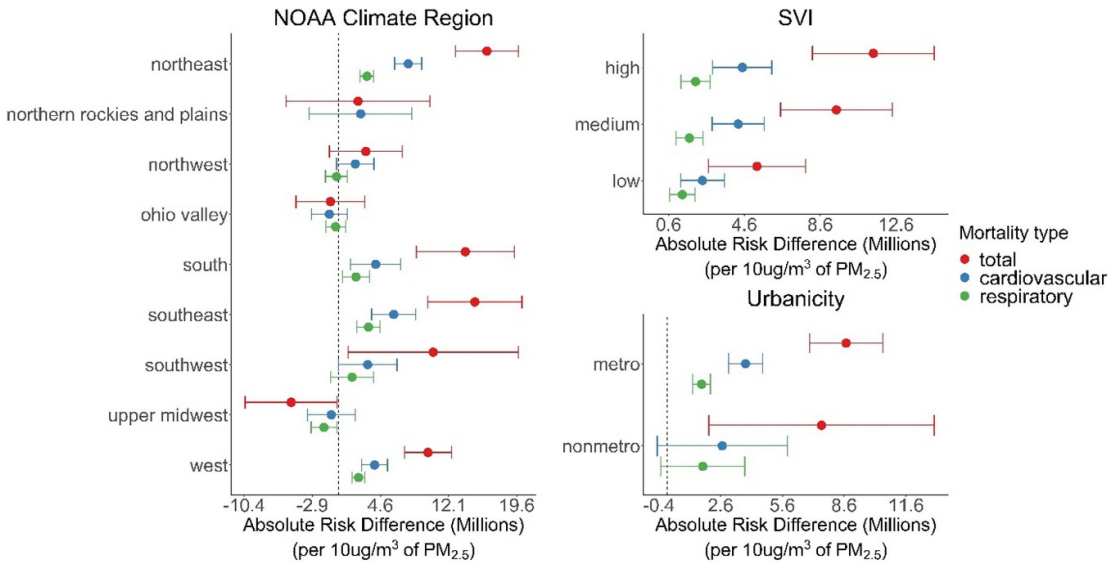

Figure 5. Absolute risk differences per million individuals for total, cardiovascular and respiratory mortality associated with a 10 μg m^{-3} increase in mean monthly $PM_{2.5}$ stratified by NOAA climate region, urbanicity status, and SVI.

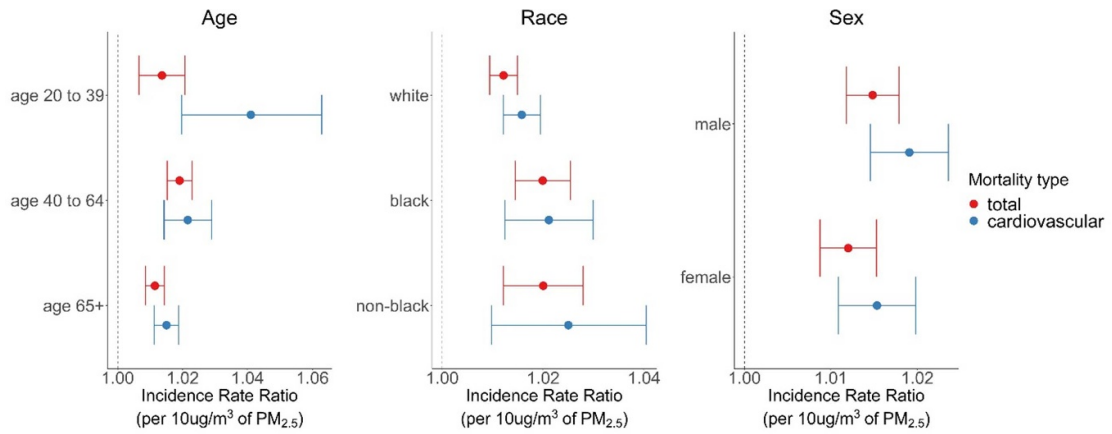

Figure 6. Incidence rate ratios associated with a 10 μg m^{-3} increase in mean monthly $PM_{2.5}$ for total and cardiovascular mortality stratified by age, race and sex groups.

(0–19) was also not analyzed due to scarcity of events. The IRRs for age-based stratification demonstrated that younger adults (20–39) had the strongest associated risk for cardiovascular mortality (IRR 1.041, 95% CI: 1.020, 1.063) and that the age 40–64 group had the highest risk with total mortality (IRR 1.019, 95% CI: 1.015, 1.023) albeit this risk was not statistically significantly different from the younger adult (20–39) group (figure 6, tables S5 and S6). The oldest age group had the smallest positive association with mean monthly $PM_{2.5}$ exposure and mortality (IRR for total mortality 1.012, 95% CI: 1.009, 1.014). Race based stratification indicated the non-black race category had the strongest association with mean monthly $PM_{2.5}$ and cardiovascular mortality (IRR 1.025, 95% CI: 1.001, 1.041) followed by Black and White (figure 6, tables S5 and S6). The IRRs for the Black race category was significantly different than White for total mortality but not cardiovascular mortality. Risk of total and cardiovascular mortality was not significantly different comparing non-black to White categories. For the cardiovascular model, the non-black race category had one county that did not converge and was excluded from the pooled results. Finally, sex-based stratification suggested a higher risk in males (IRR for total mortality 1.015, 95% CI: 1.012, 1.018) (figure 6, tables S5 and S6). All estimates were relatively precise (tables S5 and S6).

ARD estimates for age-based stratification demonstrated a large, significant effect in the oldest age group (age 65+) (ARD: 47.404 per million for total mortality, 95% CI: 35.693, 59.114) with smaller impacts on the younger age strata (ARD: 2.142 per million for age 20–39 and ARD: 9.619 per million for age 40–64 for total mortality) (figure 7, tables S5 and S6). Race based stratification had varied results with similar ARDs across race groups albeit non-black and Black had slightly higher ARD estimates than White populations (figure 7,

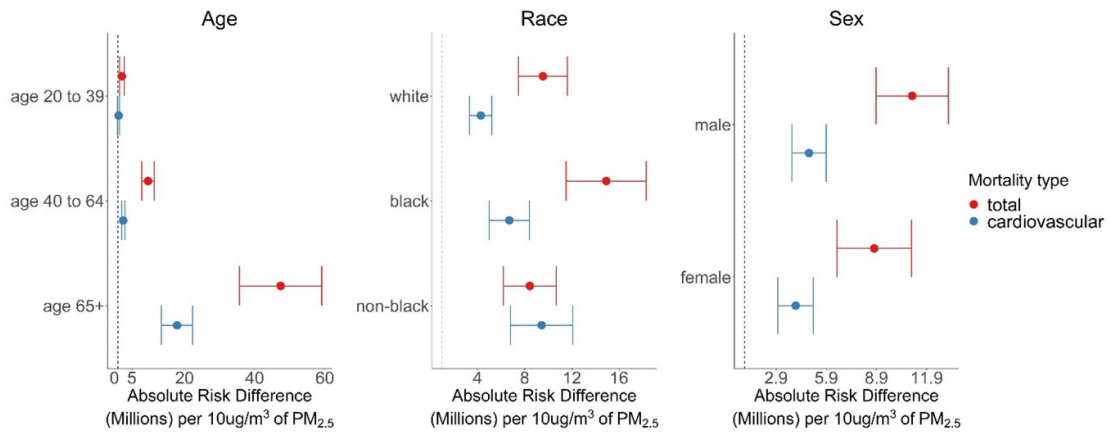

Figure 7. Absolute risk differences per million individuals for total and cardiovascular mortality associated with a 10 μg m^{-3} increase in mean monthly $PM_{2.5}$ stratified by age, race and sex groups.

table S5 and S6). Yet, the ARDs for Black and non-black were statistically significantly different from the White ARD. Sex based stratification indicated males had a higher number of deaths associated with mean monthly $PM_{2.5}$ exposure than females, although this difference was not statistically significant (ARD: 11.0 per million for total mortality, 95% CI: 8.872, 13.208) (figure 7, tables S5 and S6).

3.5. Sensitivity analyses

Evaluation of our temporal smoothers indicated that a Fourier approach with a single sine–cosine pair and a categorical variable for year struck a good balance of smoothing for the outcome time series and had statistical parsimony compared to other approaches. A comparison of effect estimates reveals robust inference across the approaches considered (table S7).

Models were robust to the inclusion of a monthly population offset and comparisons of negative binomial vs overdispersed Poisson models yielded negligible differences in the effect estimates. For the effect modification analysis by urbanicity status, we compared the meta-analysis effect estimates using the 2006 instead of the 2013 binary definition of urban/rural by NCHS and found little difference between the two definitions so we proceeded with the most recent urban/rural classification. Lastly, we executed a model for total mortality excluding cardiovascular and respiratory mortality events and observed an essentially identical IRR (IRR: 1.010, 95% CI: 1.008, 1.013) with an ARD about half the value presented in our main results (ARD: 4.762, 95% CI: 3.800, 5.730) which was anticipated as nearly half the total mortality counts were classified as cardiovascular or respiratory events. Our models were robust to the inclusion of lagged meteorological variables (including the previous month's temperature and precipitation or a rolling average of the current and previous month's temperature and precipitation) with minimal change to our effect estimates.

4. Discussion

Our findings demonstrate monthly mean exposure to $PM_{2.5}$ showed positive associations with the incidence rate and number of deaths associated with mortality events in the conterminous United States. Additional heterogeneities in risk were detected across NOAA climate regions and by strata of age, race, sex, urbanicity and social vulnerability. The use of NCHS cause specific mortality data allows for the exploration of risks across a wide age spectrum, while simultaneously evaluating an exposure characteristic of moderate duration air pollution intervals. Our results are some of the first for a large nationwide study to report the associations of ambient air pollution with mortality in the general population and provides insight into the impact of mid-duration ambient air pollution which is currently an unregulated interval of exposure.

Our estimates for monthly air pollution exposure detected an increased risk for total mortality similar to previously reported studies evaluating daily $PM_{2.5}$ exposure in the Medicare population[15]. Specifically, acute daily $PM_{2.5}$ had an increase in risk for total mortality in the Medicare population of 1.05% and an ARD of 1.42 per million people per 10 μg m^{-3} increase in daily $PM_{2.5}$ [15]. We found a similar percent increase in risk of 1.1% but estimated a higher ARD of 8.6 per million people per 10 μg m^{-3} increase in mean monthly $PM_{2.5}$ for total mortality in the general population. The higher ARD estimate was anticipated given the monthly interval is a longer period of time and an increase in mean monthly $PM_{2.5}$ of 10 μg m^{-3} is a greater cumulative increase in ambient air pollution against the daily interval. Compared to findings on chronic

annual exposures, our study estimated lower risk from changes in monthly $PM_{2.5}$. One study that evaluated chronic annual exposure to $PM_{2.5}$ in the Medicare population reported a 10 $\mu g\ m^{-3}$ increase in average annual $PM_{2.5}$ increased the risk for total and cardiovascular disease mortality by 5% and 8.8% respectively [23]. These were higher than our estimates for monthly exposure which were a 1.2% and 1.5% increase in risk respectively.

We identified the elderly, racial minorities, metropolitan and highly socially vulnerable communities to be the most impacted strata of the study population similar to findings using the Medicare population [21, 50]. Unlike in other studies, the data from NCHS facilitated estimation of mortality risk in age groups that are typically overlooked such as younger adults. We reported relatively high risk from monthly $PM_{2.5}$ suggesting that even younger adults who are typically healthier are still at an increased risk of mortality due to mid-duration ambient air pollution exposure. Causes for increased risk are unknown but may be a result of behavior that places individuals at risk for increased air pollution exposure such as outdoor occupations or recreation which may also explain potential sex differences as we observed males had higher overall risk than females across mortality types. One study investigating the associations between ozone and chronic kidney disease also found younger adults to have a higher risk compared to older adults [51]. However, we did estimate a lower absolute risk for younger adults measured by ARDs. This observation was intuitive since younger adults as a population are expected to have a lower baseline mortality rate than older adults who are frailer and may suffer from comorbidities which predispose them to mortality. Thus, even though younger adults may have a slightly higher risk of mortality as reported by our IRRs, the public health impacts are still lower than the impact in the elderly population when expressed in absolute terms. Elderly populations should still be prioritized in public health interventions as a vulnerable subgroup.

Our findings reinforce the importance of estimating additive risk measures that are better at capturing environmental health impacts by representing risk in terms of individuals affected. This approach facilitates targeted public health interventions to protect the most vulnerable subgroups. Indeed, the results of our statistical hypothesis testing of effect modification by person and place-based effect modifiers suggested that effect modification may be present on one scale but not the other and may vary based on disease. Specifically, age and race IRRs in our study were typically not significantly different from the referent category chosen. However, ARD estimates showing the potential public health impact of ambient air pollution on these communities did achieve statistical significance reinforcing the need to utilize absolute measures of effect.

While our results show similar risk of mortality between race groups when expressed with a multiplicative measure of association, our ARD estimates do better at illustrating the disparities in the absolute number of mortality events associated with ambient air pollution exposure demonstrating people of color having significantly larger ARDs than White populations. This is due to the higher overall baseline mortality rates in communities of color which propagate into higher realized ARDs associated with ambient air pollution exposure. Our observations are similar to past work and reflect the impacts of environmental racism on community health. A recent systematic review concluded strong evidence that areas with higher social and economic deprivation were linked to higher levels of ambient air pollution and race-based disparities in exposure [52]. Other studies in North America suggested racial minorities and lower socio-economic status communities shared an undue burden of exposure to ambient air pollution exposure compared to White and higher socio-economic status communities [53, 54]. Despite declines in ambient air pollution concentrations over time in the United States, the benefits of these declines continue to be inequitable across sub-populations with racial minority communities having persistent associations with higher levels of $PM_{2.5}$ and lagging in terms of achieving meaningful gains in decreased levels of $PM_{2.5}$ concentrations over time [55]. Indeed, historical practices such as redlining continue to have modern day impacts on the inequitable distribution of air pollution and contribute to disparities in health effects with communities of color being most impacted [56]. Efforts to promote environmental justice and address the effects of systemic racism are needed to combat racial disparities in mortality risk due to ambient air pollution exposure. Metropolitan counties continue to have greater risk of mortality due to ambient air pollution compared to nonmetropolitan counties as has been reported in other research [50, 53]. Continued policy, energy and business changes are needed to reduce ambient air pollution emissions in urban areas.

Heterogeneities in the mortality risk across NOAA climate regions present a complex landscape of mortality hazards associated with monthly $PM_{2.5}$ exposure. In our analysis, some NOAA climate regions had seemingly protective associations with monthly air pollution exposure, while other regions had harmful or null associations. Regional differences in the associations of ambient air pollution and health are notoriously difficult to tease apart and may be driven by multiple factors including differences in PM composition which is known to vary both regionally and seasonally [57]. Other posited explanations for disparate regional health effects include seasonal or regional variation in human behavior, weather conditions or unmeasured confounders [58]. However not all studies identified regional differences in health effects when examining

specific PM constituents which may indicate other agents are involved in this phenomenon [59]. Identifying sources of between region variability is further complicated by the possibility of within region health effects variability which may be driven not only by constituents of PM but by groups of gaseous pollutants [60]. Future research is needed to better understand the underlying drivers of observed regional differences in health effects of ambient air pollution.

This research highlights the need for reevaluating air pollution policy and considering a monthly level ambient air quality standard to monitor and protect against mid-duration exposures to ambient air pollution. These moderate exposure events will likely become more frequent as extreme weather events such as wildfires and droughts that produce increased and lasting volumes of particulates including smoke and dust are suspected to become more common due to climate change [61]. By overlooking mid-duration exposures, we may potentially propagate disparities in mortality risk in socially and demographically vulnerable communities. Our study revealed mid-duration air pollution exposure risk which demonstrates the need for investigative and policy consideration for this exposure timescale.

Future research is needed to explore the effects of mid-duration ambient air pollution exposure on specific health conditions such as respiratory, neurological, reproductive and cardiovascular diseases. Given that we evaluated the most severe health outcome there are likely less severe effects (e.g. hospitalizations, emergency department visits, outpatient visits, medication prescriptions) that may be associated with mid-duration ambient air pollution exposure that we overlooked. Additional work should also investigate climatic heterogeneities in the impact of ambient air pollution on community health. This study was one of the first to consider NOAA climate regions as an effect modifier on the causal pathway between ambient air pollution exposure and mortality risk, but more research is needed to understand heterogeneities in risk across geographic space bounded by climatic regimes.

The primary limitation of our work is the ecological study design subject to the ecological fallacy where we cannot ascribe individual level risk based on estimates for aggregated units nor can we adjust for individual level confounders. However, ecological research still proves useful for providing community-wide estimates and for hypothesis generation informing future individual level analyses. Another limitation is potential exposure misclassification as air monitors are not evenly distributed spatially and are typically located in dense urban areas. Nonmetro and rural counties are likely under-sampled due to lack of air monitors. Yet for a county level analysis, air monitor data can be seen as a useful measure of exposure for a large portion of the population. Finally, we were limited in not being able to analyze person-based modifiers for respiratory related mortality and the youngest age group (0–19) for all mortality types due to small population with insufficient statistical power.

The strengths of our study include the use of uncompressed cause specific mortality files which capture all reported events for the United States population during the nearly two-decade study period. Few research studies on air pollution utilized the uncompressed cause specific mortality data files which allowed us to study the entire general population. Many previous nationwide assessments of air pollution studied population strata (e.g. Medicare population [15, 22, 23, 32] and occupational cohorts [33]), whose association with air pollution may not be representative of the general population. Additionally, this study was among some of the first and largest studies to evaluate monthly ambient air pollution exposure with mortality at a national scale. Our emphasis is to highlight a need for policy that fills the gap between daily and annual air quality standards and provide a more complete regulatory architecture to minimize public health impacts.

5. Conclusions

In the general population, mean monthly levels of $PM_{2.5}$ were associated with an increased risk and number of deaths of total, cardiovascular and respiratory mortality events. These associations persisted within person and place-based strata of the population particularly impacting the elderly, non-black and male individuals and people living in the most socially vulnerable and metropolitan counties. This study demonstrated evidence of risk at an unregulated temporal interval of exposure which should be considered as needing future public health action to mitigate and reduce harm.

Data availability statement

The data that support the findings of this study are available upon reasonable request from the authors. However, mortality data must be directly obtained from the Centers for Disease Control and Prevention (CDC) at the following URL www.cdc.gov/nchs/nvss/nvss-restricted-data.htm. Restrictions apply to the availability of these data, which were provided under a data use agreement for the current investigation.

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Conflict of interest

The authors declare no conflict of interest.

Contribution statement

Data collection: A Rau, A Abadi, J E Bell, J D Berman; *Study design*: A Rau, J D Berman; *Data analysis*: A Rau, J D Berman, M B Fiecas; *Original manuscript draft*: A Rau; *Manuscript review*: A Abadi, J E Bell, J D Berman, M B Fiecas, Y Gwon; *Funding acquisition*: J E Bell, J D Berman. All authors have reviewed and agreed to the final version of the manuscript.

Ethics statement

This study was approved by the institutional review board at the University of Nebraska Medical Center and was classified as exempt and does not constitute human subject research as defined at 45CFR46.102.

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