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Mapping the long-term associations between air pollutants and COVID-19 risks and the attributable burdens in the continental United States☆

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ABSTRACT

Numerous studies have investigated the associations between COVID-19 risks and long-term exposure to air pollutants, revealing considerable heterogeneity and even contradictory regional results. Studying the spatial heterogeneity of the associations is essential for developing region-specific and cost-effective air-pollutant-related public health policies for the prevention and control of COVID-19. However, few studies have investigated this issue. Using the USA as an example, we constructed single/two-pollutant conditional autoregressions with random coefficients and random intercepts to map the associations between five air pollutants ($PM_{2.5}$, O_3, SO_2, NO_2, and CO) and two COVID-19 outcomes (incidence and mortality) at the state level. The attributed cases and deaths were then mapped at the county level. This study included 3108 counties from 49 states within the continental USA. The county-level air pollutant concentrations from 2017 to 2019 were used as long-term exposures, and the county-level cumulative COVID-19 cases and deaths through May 13, 2022, were used as outcomes. Results showed that considerably heterogeneous associations and attributable COVID-19 burdens were found in the USA. The COVID-19 outcomes in the western and northeastern states appeared to be unaffected by any of the five pollutants. The east of the USA bore the greatest COVID-19 burdens attributable to air pollution because of its high pollutant concentrations and significantly positive associations. $PM_{2.5}$ and CO were significantly positively associated with COVID-19 incidence in 49 states on average, whereas NO_2 and SO_2 were significantly positively associated with COVID-19 mortality. The remaining associations between air pollutants and COVID-19 outcomes were not statistically significant. Our study provided implications regarding where a major concern should be placed on a specific air pollutant for COVID-19 control and prevention, as well as where and how to conduct additional individual-based validation research in a cost-effective manner.

1. Introduction

Since the first case of Coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2, was identified in Wuhan, China in December 2019 (WHO, 2020), the disease has spread to over 200 countries and regions. As of February 21, 2023, the world had recorded a total of 757,264,511 confirmed cases and 6,850,594 deaths (WHO, 2022). Due to its high infectiousness, COVID-19 has incurred and continues to incur substantial economic and disease costs.

As the greatest environmental risk factor, air pollution is responsible for approximately four million deaths annually (Landrigan et al., 2018). Prior research (Forman and Finch, 2018; Tsai et al., 2019) has demonstrated that exposure to high levels of air pollutants significantly impairs the respiratory, cardiovascular, nervous, and immune systems, thereby exacerbating viral respiratory infections and increasing susceptibility. Viruses can also attach to particulate matter, which aids in their dissemination (van Doremalen et al., 2020). Numerous epidemiologic studies (Katoto et al., 2021; Yates et al., 2022) have indicated that long-term exposure to air pollutants preceding the COVID-19 epidemic has a negative effect on COVID-19 outcomes, such as rising incidence and mortality. Different studies, however, produce notably divergent and even opposite results. For instance, the study by Stieb et al. (2021)

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in Toronto, Canada demonstrates that long-term exposure to $PM_{2.5}$ is positively associated with the incidence of COVID-19. The research conducted by Huang and Brown (2021) in Germany reveals no significant association. The research conducted in the United Kingdom by Travaglio et al. (2021) demonstrates a negative association between $PM_{2.5}$ and COVID-19 incidence. In addition, the most recent systematic review (Carballo et al., 2022) shows that in Europe and North America, approximately 63.8% of studies demonstrate positive long-term associations between air pollutants and COVID-19 cases and 54% between air pollutants and COVID-19 deaths. The remains exhibit irrelevant or even negative associations. The distinction is intuitively clarified by the summary in Table 1of representative studies examining the long-term associations between air pollutants and COVID-19 outcomes. This distinction (or heterogeneity) may be the result of different analysis methods, but it is more likely due to the unique natural conditions, pollution levels, medical resources, and cultural characteristics of the different regions. For example, the study by Deguen and Kihal-Talantikite (2021) indicates a stronger association between NO_2 and COVID-19 cases in regions with higher levels of overcrowding. Moreover, the study by Cazzolla Gatti et al. (2020) indicates a stronger association between $PM_{2.5}$ and COVID-19 cases in the most polluted regions.

Due to the heterogeneous associations between air pollution and COVID-19 between regions, examining the overall associations across a large-scale area, such as a country or even a continent, would ignore the local variation, which may lead to inaccurate region-specific associations and even false public health implications in local regions. As of February 21, 2023, the United States of America (USA) is the nation with the highest number of confirmed COVID-19 cases and deaths, with 101,752,396 cases and 1,106,783 deaths, respectively (WHO, 2022). With a large landmass of ~9.37 million square kilometers and the federal system, the air-pollutant-COVID-19 associations may vary considerably between states. Determining the spatial distribution of associations between COVID-19 and long-term exposure to air pollutants in the USA is crucial for the development of region-specific and cost-effective pollutant-related public health interventions and the estimation of attributable burdens. Currently, few studies have been conducted on this topic.

In this study, we used the 2017–2019 county-level concentrations of air pollutants as the long-term exposure and the county-level cumulative COVID-19 cases and deaths as the COVID-19 outcomes. Due to the spatial dependence, conditional autoregression models with random intercepts and random coefficients were developed to estimate the state-level spatial distributions of associations between five major air pollutants ($PM_{2.5}$, O_3, SO_2, NO_2, and CO) and COVID-19 outcomes (incidence and mortality), and then the count-level spatial distributions of attributable burdens were mapped using these associations and county-level air pollutant concentrations.

2. Materials and methods

2.1. Data

This study covered 3108 counties in 48 states and one special district (the District of Columbia) in the continental USA. Each state was denoted by two capital letters derived from its full name, and the District of Columbia was treated as a special state for the sake of clarity. The matched table listing the location and abbreviated name of each state is available in the supplementary materials (Table S1 and Fig. S1).

The website of the National Centers for Disease Control and Prevention (https://covid.cdc.gov/covid-data-tracker/#trends_dailycases) was used to obtain the county-level numbers of cumulative confirmed COVID-19 cases and deaths from the date of the first confirmed COVID-19 case until May 13, 2022. The website https://www.census.gov/was used to retrieve county-level population data representing the most recent census of the USA, conducted in 2021. Based on the guidelines

Table 1
Long-term associations between air pollutants and COVID-19 outcomes in several representative studies.

Where	Air pollutants	COVID-19 outcome	Methods	Results
Canada (Stieb et al., 2020)	$PM_{2.5}$	Cases	Negative binomial regression	No associations
Toronto, Canada (Stieb et al., 2021)	$PM_{2.5}$	Cases	Negative binomial regression	Positive associations
107 Italian provinces (Bontempi and Coccia, 2021)	$PM_{2.5}$	Cases	Pearson's (partial) correlation coefficient	Positive associations
United Kingdom (Travaglio et al., 2021)	NO_2, O_3, $PM_{2.5}$	Cases and deaths	Negative binomial regression	NO_2 is positively associated with both cases and deaths. $PM_{2.5}$ are negatively associated with cases and not associated with deaths. O_3 is negatively associated with both cases and deaths.
Germany (Huang and Brown, 2021)	$PM_{2.5}$, NO_2, SO_2	Cases	Poisson model with a spatial random effect.	Positive associations in both NO_2 and SO_2. No association in $PM_{2.5}$
Italy (Perone, 2021)	$PM_{2.5}$, NO_2, O_3	Deaths	OLS multivariate analysis; cluster analysis	Positive associations in $PM_{2.5}$, NO_2, and O_3.
New York (Magazzino et al., 2021a)	$PM_{2.5}$ and NO_2,	Deaths	Deep machine learning	Positive associations
United States of America (Liang et al., 2020)	NO_2, O_3, $PM_{2.5}$	Deaths	Negative binomial models	No association in both O_3 and $PM_{2.5}$. Positive association in NO_2
401 European regions (Hass and Jokar Arsanjani, 2021)	$PM_{2.5}$, NO_2	Cases	OLS; geographically Weighted Regression	Negative association in NO_2. Positive association in $PM_{2.5}$
Catalonia, Spain (Zaldo-Aubanell et al., 2021)	NO_2	Cases and deaths	Generalized linear binomial model	Positive association in deaths. Negative association in cases
Paris, Lyon and Marseille (Magazzino et al., 2020; Mele et al., 2021)	$PM_{2.5}$, NO_2	Deaths	Neural networks	Positive association
Hubei in China (Magazzino et al., 2021b)	$PM_{2.5}$	Death	Neural networks	Positive association
United States (Liu and Li, 2020)	O_3, NO_2, CO, SO_2	Deaths	Pearson correlation tests; multivariate regression	Positive association in O_3. No association in NO_2, SO_2, and CO

Note: The negative and positive associations mentioned in this table are statistically significant.

specified by the Environmental Protection Agency, five criteria air pollutants were selected for the study: SO_2, NO_2, $PM_{2.5}$, CO, and O_3. In addition, the daily concentrations at $0.75^\circ \times 0.75^\circ$ grids for each air pollutant were retrieved from the fourth-generation ECMWF global reanalysis of atmospheric composition (EAC4) (Inness et al., 2019) using https://ads.atmosphere.copernicus.eu/cdsapp#!/dataset/cams-global-reanalysis-eac4?tab=overview. The long-term exposure concentrations at $0.75^\circ \times 0.75^\circ$ grids were calculated by averaging the daily concentrations from 2017 to 2019. The concentration resolution was then reduced from $0.75^\circ \times 0.75^\circ$ grids to $0.1^\circ \times 0.1^\circ$, using the ordinary kriging interpolation. By averaging the grid values in each county, the concentrations of air pollutants were calculated at the county level. The detailed procedure flowchart for the analysis is available in the supplementary materials (Fig. S2).

2.2. Methods

A descriptive analysis was used to present the spatial distributions of air pollutant concentrations and COVID-19 outcomes. The Pearson correlation coefficients were used to demonstrate the collinearity of air pollutants. Without adjusting for confounding variables, the Kendall rank correlation (Abdi, 2007) was used to evaluate the marginal associations between air pollutants and COVID-19 outcomes.

For each air pollutant, single-pollutant conditional autoregression models with county-level random intercepts were developed to examine the overall linear association between air pollutants and COVID-19 incidence and mortality. Twelve common confounding variables were taken into account, including the number of hospital beds and active medical doctors per 1000 people, median house value, median house income, population density, mean body mass index, mean temperature, the percentage of those with less than a high school education, the percentage of those $\geq$65 years old, the smoking rate, the percentage of black race, and the percentage of those living in poverty (data obtained from https://data.hrsa.gov/topics/health-workforce/ahrf and https://www.census.gov/). The population at the county level was adjusted for as an offset term. The commonly used spatial prior by Leroux et al. (2000), hereafter referred to as Leroux prior, was used to characterize the random county-level intercepts due to its adaptability in incorporating both spatial structure and unstructured effects. Incorporating Leroux prior can not only account for heterogeneity in intercepts but also adjust for unobserved confounding variables with spatial autocorrelation. Due to the overdispersion, a likelihood function based on the negative binomial distribution was chosen (Venables and Ripley, 2013). To investigate the heterogeneity of associations, state-level random coefficients based on the Leroux prior were incorporated into the model to estimate the state-specific associations between air pollutants and COVID-19 outcomes, i.e., the spatial distribution of associations. Due to the collinearity of air pollutants, two-pollutant models were developed to determine if the association was confounded or mediated by another air pollutant. On the basis of the estimated associations from the single-pollutant models, the attributable cases and deaths of COVID-19 were calculated for each air pollutant. The detailed flowchart for the analysis is available in Fig. S2. Notably, the decision to characterize the state-level rather than county-level heterogeneous associations was for the reason that the latter would yield an unstable result due to the estimation of 3108 coefficients under 3108 samples.

To conduct a sensitivity analysis, we removed 1% of counties with extreme incidences or mobilities, i.e., >99.5% quantile and <0.5% quantile (sensitivity analysis 1). In addition, the intensity of nucleic acid detection and medical resources were insufficient at the onset of the COVID-19 epidemic, which may have affected the results. Therefore, we eliminated the cases and deaths before April 30, 2020 to make a second sensitivity analysis (sensitivity analysis 2).

3. Results

To keep the associations between various air pollutants and COVID-19 outcomes on a consistent scale, the relative risk (RR) per interquartile range (IQR) increase was used to quantify the impact of each air pollutant. When calculating the attributable burdens, the background concentration 0 was used as the reference level, as air pollutant concentrations at extremely low levels continue to have adverse health effects (Weichenthal et al., 2022). These orientation words (e.g., east, northeast, western) in our study indicate only a general orientation, and there is no clear boundary because the region position related to our findings does not conform to the common region categorization. The precise positions of the regions must be determined by combining the mentioned figures.

3.1. Descriptive analysis

In the continental USA, as of May 13, 2022, 78,266,160 cases of COVID-19 and 945,079 deaths had been reported. As shown in Fig. 1a–d, the majority of COVID-19 cases and deaths occurred in the east and southwest. The incidence and mortality rates of COVID-19 were also unevenly distributed among counties. Cases and fatalities were distributed similarly. $PM_{2.5}$, O_3, SO_2, NO_2, and CO had respective mean concentrations of 11.1, 68.0, 3.3, 8.2, and 192.6 μg/m^3 across the continental USA (see Table 2). As depicted in Fig. 1e–i, the five air pollutants were most prevalent in the eastern USA. In addition, $PM_{2.5}$ and CO concentrations were also elevated in the west. Fig. 1j reveals that the Pearson correlations between SO_2 and NO_2, $PM_{2.5}$ and CO, and NO_2 and CO were moderately robust and exceeded 0.6. Without adjusting for confounding variables, Kendall rank correlations showed that the five air pollutants were positively associated with COVID-19 incidence, but negatively associated with COVID-19 mortality, with the exception of O_3.

3.2. Associations and attributable burdens on COVID-19 incidence

Fig. 2 depicts the mean associations between air pollutants and COVID-19 incidence. The red lines in Fig. 2 indicate that $PM_{2.5}$, NO_2, and CO were significantly associated with an increased incidence of COVID-19, with a 2.8% (95% CI: 1.4%–4.3%), 3.7% (95% CI: 1.8%–5.6%), and 2.7% (95% CI: 1.1%–4.3%) risk increase per IQR increase, respectively, in the absence of other pollutants. The associations between O_3 and SO_2 and COVID-19 incidence were not statistically significant. As shown in Fig. 2 by the black lines, NO_2 maintained a stable positive association even when other pollutants were controlled for. The associations for $PM_{2.5}$ and CO were also stable except for those under the control of a pollutant with strong collinearity, i.e., the association for CO under controlling for $PM_{2.5}$ or NO_2 and the association for $PM_{2.5}$ under controlling for CO. The associations for O_3 and SO_2 were insignificant after controlling for other air pollutants. In sensitivity analysis 1 involving the exclusion of counties with extreme incidences, the association of NO_2 became insignificant in both single-pollutant and two-pollutant models. Other significant findings from sensitivity analyses, which can be found in the supplementary materials (Figs. S8–13), were not changed.

The spatial distributions of associations between air pollutants and COVID-19 incidence at the state level are shown on the left side of Fig. 3. In general, the associations exhibited considerable heterogeneity between states and even opposite results. The majority of states exhibited positive associations for $PM_{2.5}$, SO_2, NO_2, and CO; in particular, the positive associations for CO and $PM_{2.5}$ were statistically significant. For O_3, the majority of states exhibited negative associations, particularly in the western states where the negative associations were statistically significant. In the western and northeastern states, none of the five air pollutants appeared to have a negative effect on the incidence of COVID-19. Several states, including New Jersey (NJ), WI (Wisconsin), and IL

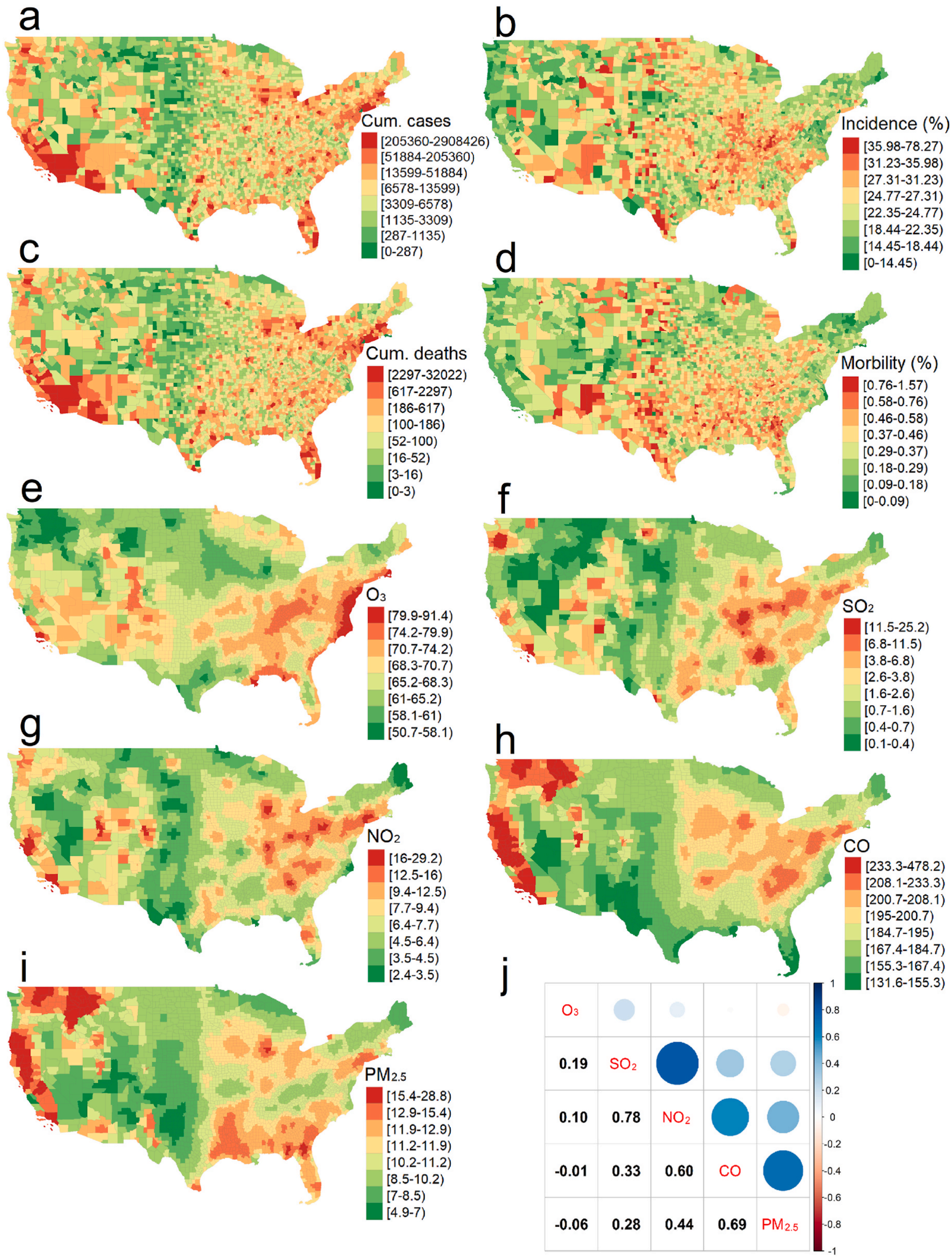

Fig. 1. Descriptive analyses for air pollutants and COVID-19 outcomes.

(Illinois), consistently exhibited significantly positive associations for the five air pollutants. Two-pollutant models produced comparable results, with the exception that fewer states exhibited significant associations when a pollutant with strong collinearity was controlled for.

On the right side of Fig. 3, the spatial distributions of cases attributable to air pollutants at the county level are depicted based on the associations estimated from single-pollutant models. The regions encompassing at least three adjacent states with statistically significant positive associations were roughly denoted with blue ellipses; henceforth, this type of region will be referred to as a blue region. In these regions, the spatial aggregation of significant associations suggests that the calculated attributable numbers of cases may be statistically significant; that is, they did not appear to be the result of type-I error due to multiple tests and spatial random permutations in state-level

Table 2
Mean concentrations and Kendall rank correlations between air pollutants and COVID-19 outcomes.

Air pollutants	Mean ($\mu g/m^3$)	2.5% quantile ($\mu g/m^3$)	97.5% quantile ($\mu g/m^3$)	Incidence		Mortality	
				Kendall's tau	*P*	Kendall's tau	*P*
$PM_{2.5}$	11.1	7.1	14.8	0.012	0.325	−0.013	0.26
O_3	68.0	58.6	78.8	0.092	<0.001	0.093	<0.001
SO_2	3.3	0.4	10.8	0.087	<0.001	−0.007	0.561
NO_2	8.2	3.6	15.6	0.052	<0.001	−0.086	<0.001
CO	192.6	156.3	227.6	0.043	<0.001	−0.067	<0.001

associations. Results showed that $PM_{2.5}$ and CO presented a heavy attributable burden on cases in the vast majority of counties, most of which were located in the blue regions. NO_2 had a single blue region, whereas SO_2 and O_3 had none. For all five air pollutants, New Jersey had consistently high attributable burdens, whereas counties in the northeast of USA did not. As shown in Fig. 4, $PM_{2.5}$ and CO contributed the most cases to the 3108 counties, while SO_2 and NO_2 contributed the second most and O_3 the least. There were 7,432,104 cases attributable to $PM_{2.5}$ and 12,651,985 cases attributable to CO, which corresponded to proportions of 9.5% and 16.2%, respectively.

3.3. Associations and attributable burdens on COVID-19 mortality

The mean associations between air pollutants and COVID-19 mortality are depicted in Fig. 5. Without controlling for other pollutants, $PM_{2.5}$, SO_2, NO_2, and CO were significantly positively associated with COVID-19 mortality, whereas O_3 was significantly negatively associated. After controlling for other pollutants, the associations for $PM_{2.5}$, O_3, and CO became insignificant. Other than controlling for one another, the significantly positive associations for SO_2 and NO_2 remained unchanged. The single-pollutant models estimated that a IQR increase in SO_2 and NO_2 was associated with a 4.0% (95% CI: 1.6%–6.5%) and 6.1% (95% CI: 2.8%–9.6%) increase in COVID-19 mortality, respectively. All sensitivity analyses yielded comparable results, which can be found in the supplementary materials (Figs. S8–13).

The spatial distributions of the associations between air pollutants and COVID-19 mortality at the state level are shown on the left side of Fig. 6. Similar to the heterogeneous associations observed for incidence, it appeared that none of the five air pollutants had a significantly negative effect on COVID-19 mortality in the western and northeastern states. In the majority of states, the associations for $PM_{2.5}$, SO_2, NO_2, and CO were positive, whereas associations for O_3 were negative in almost every state. SO_2 and NO_2 had stronger positive associations with mortality than with incidence. Four neighboring states, namely New Jersey, PA (Pennsylvania), MD (Maryland), and DE (Delaware), always exhibited significantly positive associations for $PM_{2.5}$, SO_2, NO_2, and CO. In particular, New Jersey exhibited a significantly positive association for O_3 even after controlling for all other pollutants, as shown in the supplementary materials (Fig. S4).

The spatial distributions of cases attributable to air pollutants at the county level are depicted on the right side of Fig. 6. $PM_{2.5}$, SO_2, NO_2 and CO presented heavy attributable burdens on deaths in the vast majority of counties, whereas O_3 did so in a minority of counties. Two large blue regions were observed for CO and three small blue regions were observed for $PM_{2.5}$. A blue region in the east was discovered for SO_2. There was no blue region for O_3. Four states, namely New Jersey, Pennsylvania, Maryland, and Delaware, were in blue regions for $PM_{2.5}$, SO_2, NO_2, and CO. None of the five air pollutants had a negative impact on the northeastern counties of USA. The right side of Fig. 4 depicts the total number of attributable deaths in 3108 counties. The trend was comparable to that of the number of cases, but the percentage of deaths attributable to all pollutants, excluding O_3, was much higher than the percentage of cases.

4. Discussion

4.1. Main findings and interpretation

This is the first study to investigate the spatial distributions of long-term associations between air pollutants and COVID-19 outcomes and the attributable burdens, as far as we are aware. Remarkably spatially heterogeneous associations and attributable burdens were discovered in the USA. $PM_{2.5}$, SO_2, NO_2, and CO had positive associations in the majority of states, whereas O_3 had negative associations. None of the pollutants were statistically associated with COVID-19 outcomes in the westernmost and northeastern states. By averaging the associations across the USA, $PM_{2.5}$, and CO were significantly associated with COVID-19 incidence, whereas NO_2 and SO_2 were significantly associated with COVID-19 mortality. The remaining associations between air pollutants and COVID-19 outcomes were not statistically significant. Our findings may assist in identifying high-sensitivity regions in which air pollutants exacerbate COVID-19 outcomes to a greater degree, thereby allowing the government to develop a region-specific and cost-effective pollutant-related public health policy for COVID-19 control and prevention, such as i) prioritizing precautionary measures, such as hospital beds and personal protective equipment, in areas with high levels of air pollution and strong positive associations, ii) enhancing the control of air pollution in certain regional areas and iii) promoting the identification of the causes of the heterogeneity of associations to mitigate the adverse health effects of air pollution.

For the mean associations with COVID-19 incidence, single air-pollutant models exhibited statistically significant positive associations with $PM_{2.5}$ and CO. However, when controlling for each other in two-pollutant models, the associations were no longer significant, suggesting that the estimated effects of CO and $PM_{2.5}$ from single-pollutant models may overlap due to their high collinearity. By reviewing previous studies (De Angelis et al., 2021; Fang et al., 2021; Ingram et al., 2022; Mulder et al., 2021; Stieb et al., 2021) that demonstrated significantly positive long-term associations of $PM_{2.5}$ and CO with COVID-19 incidence, few of them controlled for the confounding from each other ($PM_{2.5}$ or CO). Therefore, our study suggests that additional research is necessary to disentangle the associations between CO and $PM_{2.5}$ and the incidence of COVID-19, or to investigate their combined associations. This type of overlap was also observed in the associations between SO_2 and NO_2 and COVID-19 mortality, indicating that similar research is also warranted for these associations. Single-pollutant models demonstrated significantly positive associations between $PM_{2.5}$ and CO and COVID-19 mortality, but when SO_2 and NO_2 were controlled for, the associations became insignificant, suggesting that the associations of $PM_{2.5}$, CO, and O_3 with mortality may be derived from the proxies of SO_2 and NO_2.

From the spatial distribution of associations on COVID-19 incidence, we identified an aggregation region in the western USA with significantly negative associations for O_3, consistent with a previous study (Travaglio et al., 2021) in the United Kingdom and possibly attributable to the decreased conversion of nitrogen oxide to O_3. Three states, namely New Jersey, Wisconsin, and Illinois, consistently exhibited positive associations for all five pollutants, indicating that a public health intervention related to air pollution is more warranted in these regions. Almost all states, excluding the northeastern states, exhibited

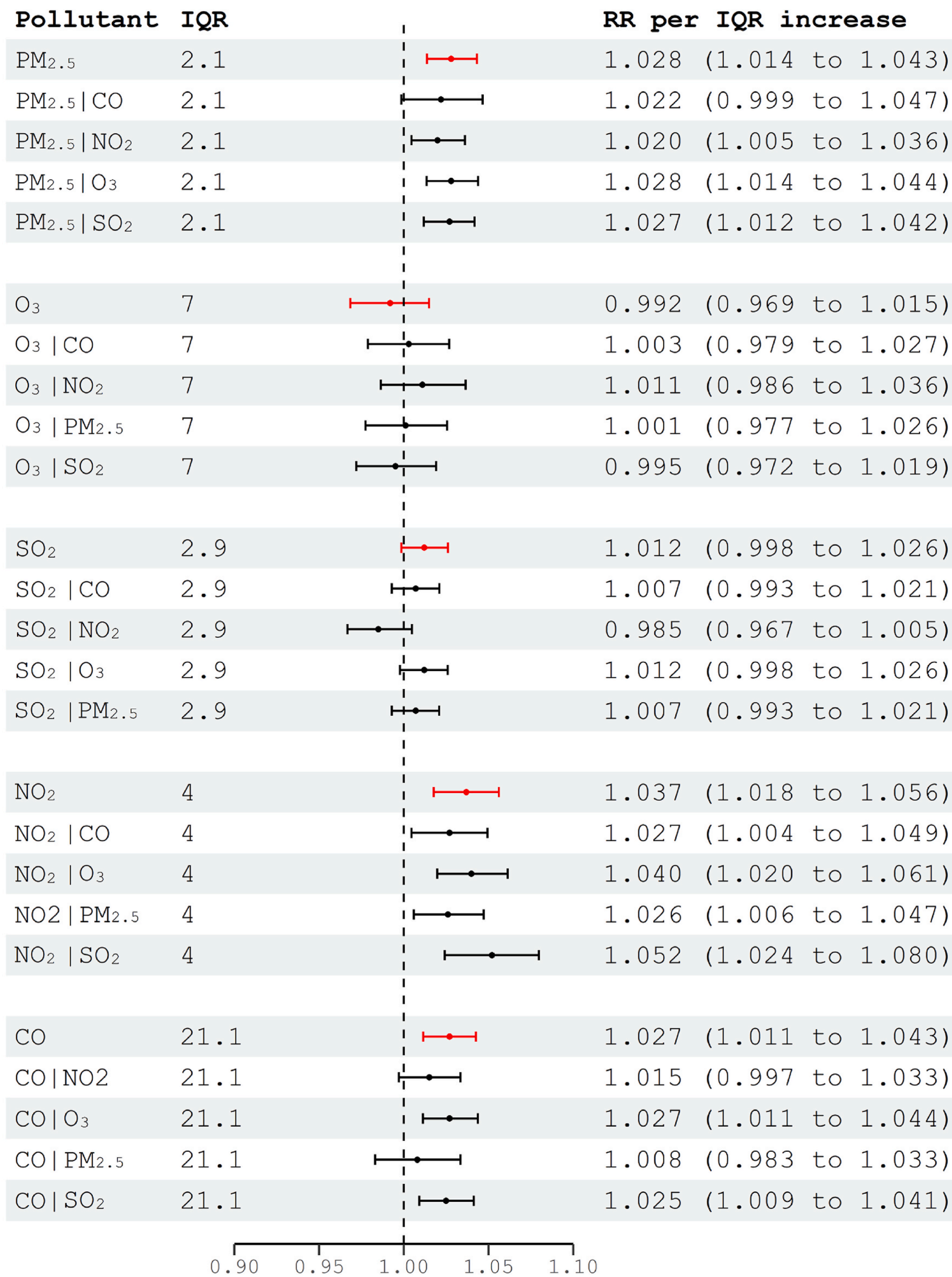

Fig. 2. Mean associations between air pollutants and COVID-19 incidences. IQR: interquartile range (μg/m^3). RR: relative risk. "Pollutant 1|Pollutant 2" indicates the association of Pollutant 1 under controlling for Pollutant 2, estimated from a two-pollutant model. Without "|", "Pollutant" indicates the association without controlling for any other pollutants, estimated from a single-pollutant model. The association between NO_2 and COVID-19 incidence becomes insignificant in sensitivity analysis 1.

positive associations between CO and $PM_{2.5}$ and COVID incidence, suggesting that $PM_{2.5}$ and CO should be the primary focus in preventing and controlling COVID-19 infection in the USA. Some states exhibited significantly positive associations for O_3 and SO_2, but due to their spatially nonadjacent locations, it is likely that these associations are due to type-I error resulting from multiple tests and random spatial permutations. Accordingly, O_3 and SO_2 did not appear to increase the incidence of COVID-19, which is consistent with prior research conducted in the USA (Hendryx and Luo, 2020; Hu et al., 2021). In terms of COVID-19 mortality, interesting results were also observed. For example, four neighboring states, New Jersey, Pennsylvania, Maryland, and Delaware, consistently exhibited significantly positive associations

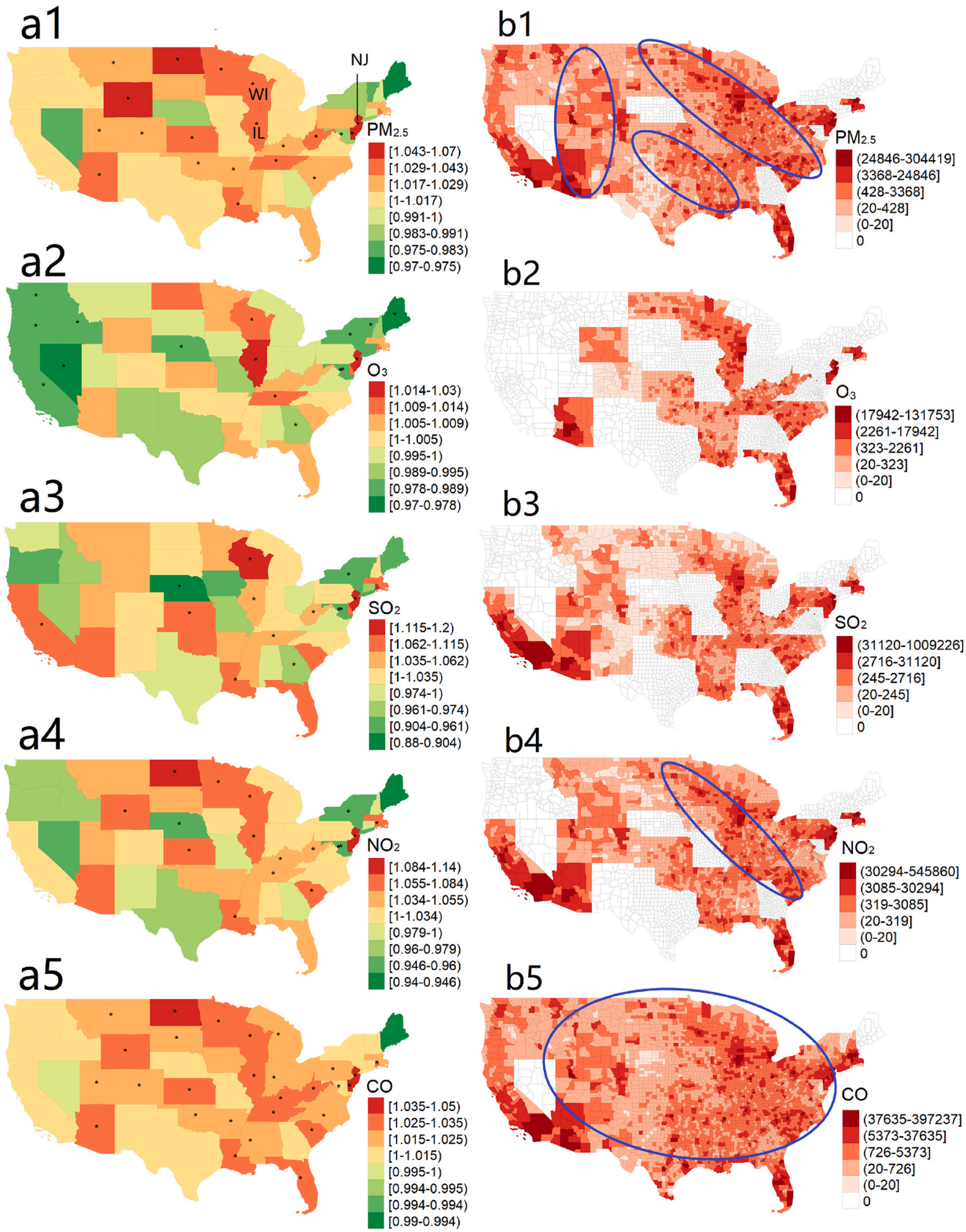

Fig. 3. Spatial distributions of the associations between air pollutants and COVID-19 incidences (a1–a5) and the attributable cases (b1–b5). The results are derived from the single-pollutant models. *indicates statistical significance with $P < 0.05$. The blue ellipses indicate the regions, which cover at least three adjacent states with significantly positive associations. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

for $PM_{2.5}$, SO_2, NO_2, and CO. These positive/negative associations did not appear to be the result of a type-I error, suggesting that a specific epidemiological mechanism and public health intervention related to pollutants may be necessary for these regions. Furthermore, with significantly divergent associations in the northeastern of the four states, further investigation into the underlying causes is required.

4.2. Comparison with the previous ecological studies in the USA

We compared our findings to previous ecological studies conducted in the USA. $PM_{2.5}$ is the air pollutant that has been investigated the most in these studies. Some studies (Hendryx and Luo, 2020; Donghai Liang et al., 2020) found an insignificant association between COVID-19 mortality and $PM_{2.5}$ after adjusting for other air pollutants, which is

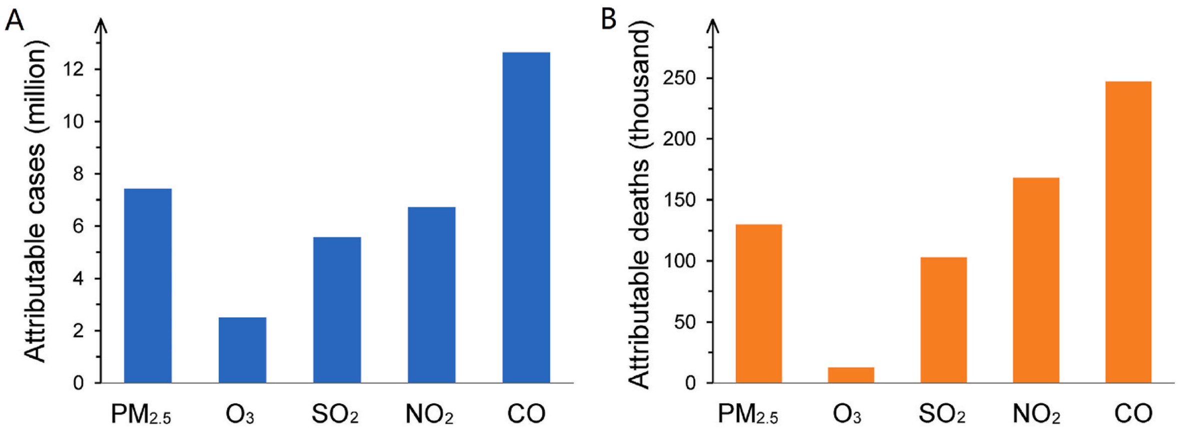

Fig. 4. Total COVID-19 burdens attributable to air pollutants. For $PM_{2.5}$, O_3, SO_2, NO_2, and CO, the attributable percentages of COVID-19 cases were 9.5%, 3.2%, 7.1%,8.6% and 16.2% respectively. The attributable percentage of COVID-19 deaths were 13.7%, 1.4%, 10.9%, 17.8% and 26.1%, respectively. Notably, the attributable burdens were calculated based on single-pollutant models, so they may overlap between two air pollutants, especially those with strong collinearity.

consistent with our findings. For NO_2 and O_3, the majority of previous studies in the USA found similar nationwide associations to ours, i.e., a positive association with NO_2 (Hu et al., 2021; Donghai Liang et al., 2020; Sarmadi et al., 2021) and an insignificant and even negative association with O_3 (Hendryx and Luo, 2020; Hu et al., 2021; Ingram et al., 2022; Liang et al., 2020; Petroni et al., 2020). For SO_2 and CO, there are relatively few relevant studies in the USA. Due to the lack of emphasis on the spatial distribution of associations between COVID-19 outcomes and air pollutants in prior research, we compared our findings to those regional studies conducted in the USA. An ecological study conducted in Illinois (Scannell Bryan et al., 2021) found no association between COVID-19 mortality and $PM_{2.5}$, NO_2, or O_3 levels. An ecological study (Terrell and James, 2022) conducted in Louisiana (LA) revealed a significant association between COVID-19 mortality and $PM_{2.5}$. Fig. 6 illustrates that the results of the two regional studies are comparable to ours.

4.3. Limitations and further research implications

Due to the ecological design, certain limitations must be acknowledged (Villeneuve and Goldberg, 2020; Weaver et al., 2022; Wu et al., 2020), such as: 1) the region-level air pollutant concentrations cannot reflect the real individual exposure, which may lead to the misclassification of exposure; 2) the county-level adjustment factors cannot reflect the characteristics of the COVID-19 vulnerable population and COVID-19 patients; 3) the lack of nucleic acid detection may lead to the misclassification of COVID-19 outcomes; and 4) other unobserved determinants of COVID-19 mortality may confound the results. We used Leroux-prior-based random intercepts to control for potential unobserved confounders, which may also mitigate the first three limitations, as they can be assumed to be associated with unobserved confounders. The Moran's I statistic presented in the supplementary materials (Table S3) demonstrated that the Leroux prior can substantially reduce the spatial autocorrelation of residuals. However, the simple spatial prior cannot adequately account for these limitations, and ecological fallacies may still exist in our study. In addition, SARS-CoV-2 infections struck different regions of the USA at different times, suggesting that the causes of COVID-19 infections and deaths in 2020 may differ from those in 2021–2022. Consequently, the associations between air pollutants and COVID-19 outcomes may be time-dependent, similar to the short-term associations between temperature and COVID-19 incidence (Wang et al., 2022). Thus, it may be necessary to conduct additional spatiotemporal ecological studies. Moreover, we only examined the heterogeneity of associations at the state level, which is another limitation. Kimberly (2022) showed that even within the same state, counties present vastly different attributes, which may lead to different associations between counties. Therefore, additional research based on individual or higher-resolution aggregation data should be conducted to examine the higher-resolution heterogeneity of associations and to obtain more accurate count-level attributable burdens.

Due to the possibility of ecological fallacies, additional validation research based on quasi-experimental or individual data is necessary. On the other hand, it is difficult to conduct large-scale validation research due to the high cost. Our research may shed light on where and how future research can be conducted in a cost-effective manner. For example, additional research conducted in the west and northeast of the USA could help to explain why O_3 is negatively associated with COVID-19 outcomes, but would not be conducive to examining the positive effects of air pollutants on COVID outcomes. Additional research conducted in the eastern USA, particularly in New Jersey, Pennsylvania, Maryland, and Delaware, has a higher probability of validating the adverse impact of pollutants on COVID outcomes. Further research simultaneously conducted in the west and the east is helpful to confirm the existence of heterogeneous associations and investigate the causes of such heterogeneity.

5. Conclusion

The associations between COVID-19 outcomes, long-term exposure to air pollutants, and COVID-19 burdens were mapped in the continental USA, which exhibited substantial heterogeneity. $PM_{2.5}$, SO_2, NO_2, and CO had positive associations in the majority of states, whereas O_3 had negative associations. In the westernmost and northeasternmost states, none of the pollutants had significantly positive associations with COVID-19 outcomes. Attributable burdens exhibited mainly in the east of the USA and $PM_{2.5}$ and CO contribute the most. On average across 49 states, $PM_{2.5}$ and CO were significantly positively associated with COVID-19 incidence; NO_2 and SO_2 were significantly positively associated with COVID-19 mortality; and the remaining associations between air pollutants and COVID-19 outcomes were not statistically significant. Our findings may aid in the identification of high-sensitivity regions where air pollutants exacerbate COVID-19 outcomes to a greater extent, enabling the government to develop a region-specific and cost-effective pollutant-related public health policy for COVID-19 control and prevention; for example, New Jersey, Pennsylvania, Maryland, and Delaware have a greater need to control air pollution. Furthermore, our study has implications for where and how to conduct future research based on individual data in a cost-effective manner; for example, future research conducted in the west and northeast of the USA may help to explain why O_3 is negatively associated with COVID-19 outcomes, but will not be conducive to studying the positive effects of air pollutants on COVID outcomes.

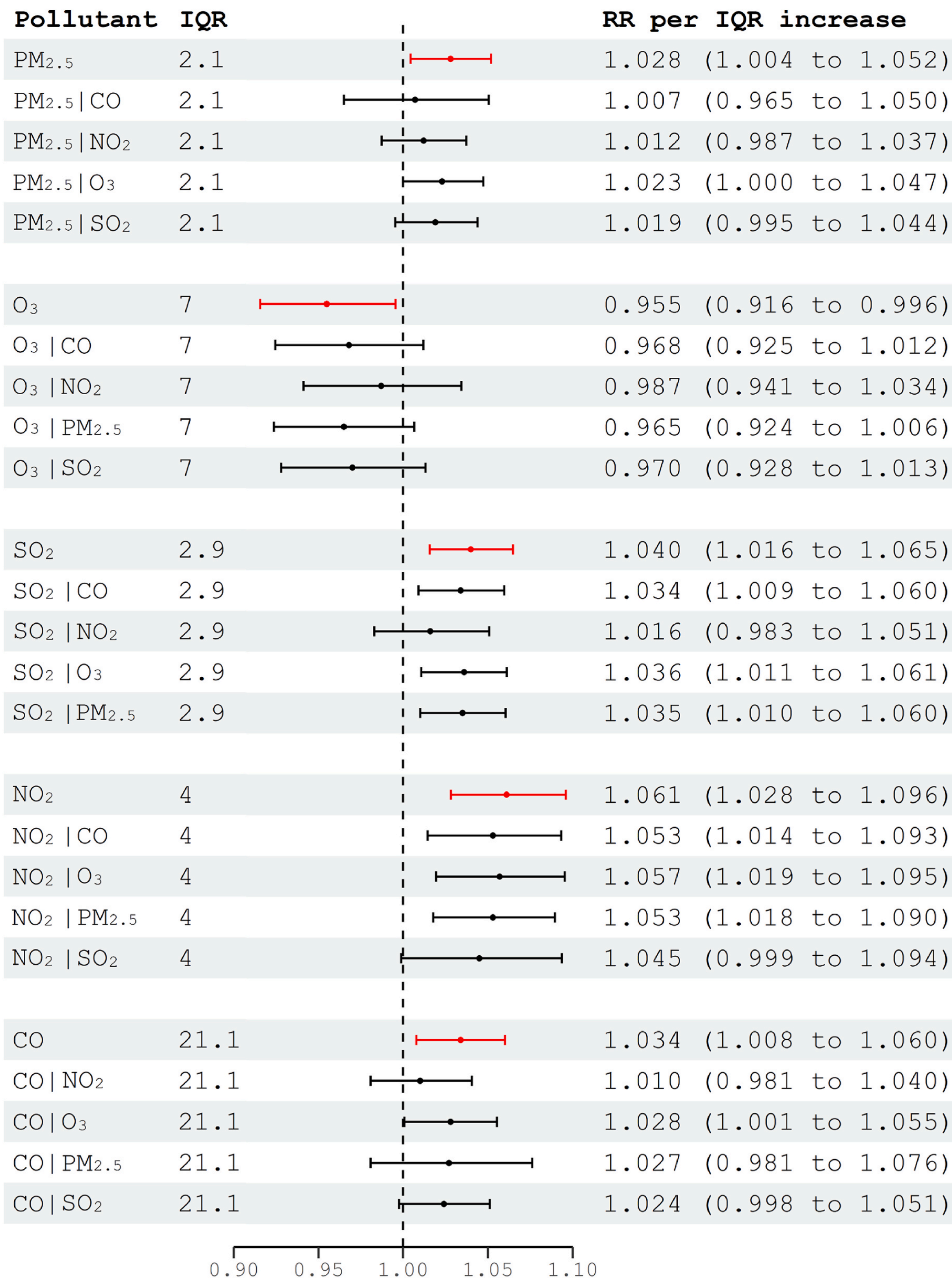

Fig. 5. Mean associations between air pollutants and COVID-19 mortality. IQR: interquartile range (μg/m^3). RR: relative risk. "Pollutant 1|Pollutant 2" indicates the effect of Pollutant 1 after controlling for Pollutant 2, estimated from a two-pollutant model. Without "|", "Pollutant" indicates the effect without controlling for any other pollutants, estimated from a single-pollutant model. Sensitivity analyses remain a stable result.

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Credit author statement

Conceptualization: BF, WW, FL; Methodology: WW, FL; Investigation: BF, WW; Data collection: YZ, JW; Supervision: BZ; Original draft: BF, WW; Review & editing: BZ, FL. BF and WW contributed equally to

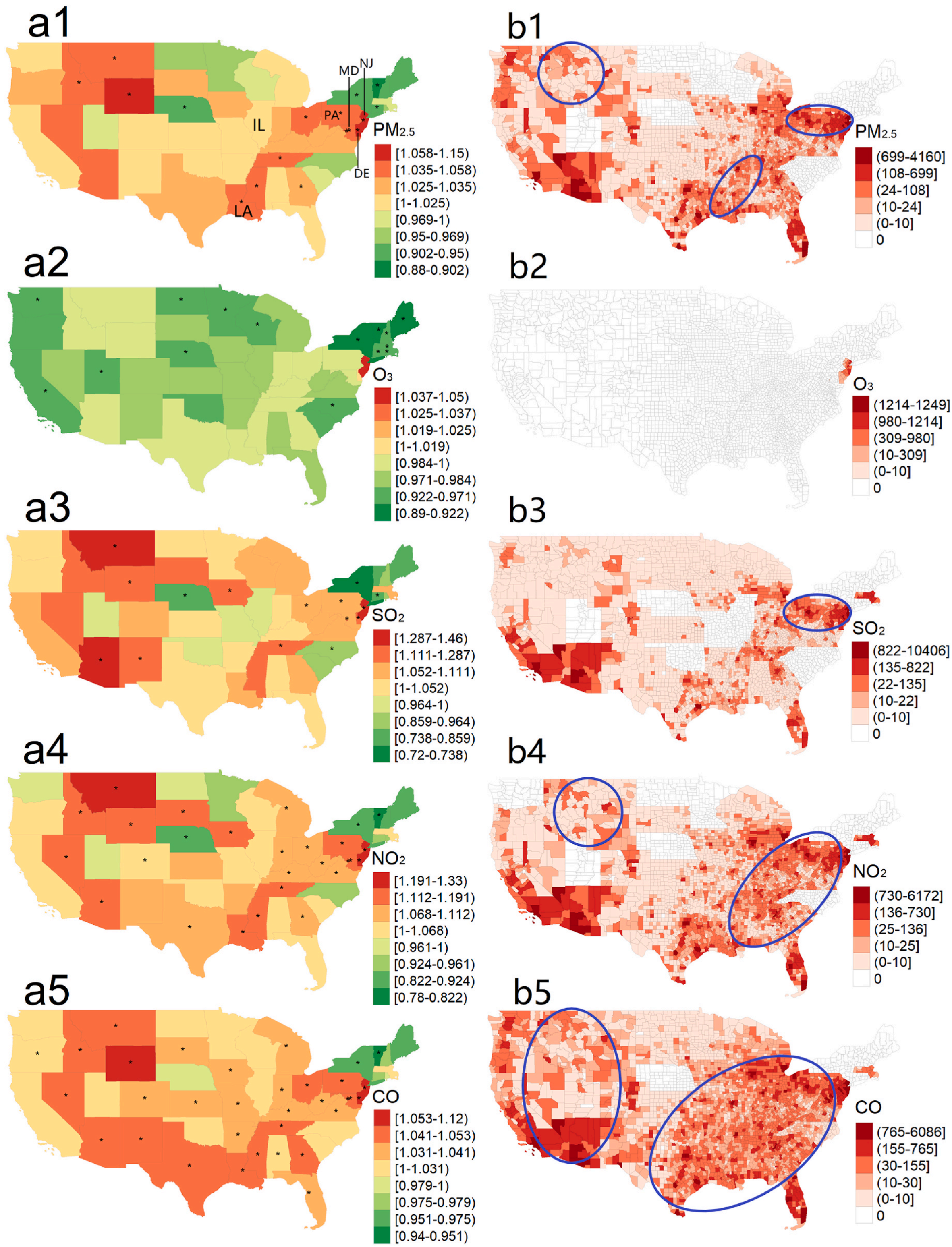

Fig. 6. Spatial distributions of the associations between air pollutants and COVID-19 mortality (a1–a5) and the attributable deaths (b1–b5). The results come from the single-pollutant models. *indicates statistical significance with $P < 0.05$. The blue ellipses indicate the regions covering at least three adjacent states with significantly positive associations. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

this work.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

I have shared the link to my data and code in the main text

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envpol.2023.121418.

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