Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Long-term air pollution and COVID-19 mortality rates in California: Findings from the Spring/Summer and Winter surges of COVID-19☆

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ABSTRACT

A growing number of studies report associations between air pollution and COVID-19 mortality. Most were ecological studies at the county or regional level which disregard important local variability and relied on data from only the first few months of the pandemic. Using COVID-19 deaths identified from death certificates in California, we evaluated whether long-term ambient air pollution was related to weekly COVID-19 mortality at the census tract-level during the first ~12 months of the pandemic. Weekly COVID-19 mortality for each census tract was calculated based on geocoded death certificate data. Annual average concentrations of ambient particulate matter <2.5 μm ($PM_{2.5}$) and <10 μm (PM_{10}), nitrogen dioxide (NO_2), and ozone (O_3) over 2014–2019 were assessed for all census tracts using inverse distance-squared weighting based on data from the ambient air quality monitoring system. Negative binomial mixed models related weekly census tract COVID-19 mortality counts to a natural cubic spline for calendar week. We included adjustments for potential confounders (census tract demographic and socioeconomic factors), random effects for census tract and county, and an offset for census tract population. Data were analyzed as two study periods: Spring/Summer (March 16-October 18, 2020) and Winter (October 19, 2020–March 7, 2021). Mean (standard deviation) concentrations were 10.3 (2.1) $\mu g/m^3$ for $PM_{2.5}$, 25.5 (7.1) $\mu g/m^3$ for PM_{10}, 11.3 (4.0) ppb for NO_2, and 42.8 (6.9) ppb for O_3. For Spring/Summer, adjusted rate ratios per standard deviation increase were 1.13 (95% confidence interval: 1.09, 1.17) for $PM_{2.5}$, 1.16 (1.11, 1.21) for PM_{10}, 1.06 (1.02, 1.10) for NO_2, and 1.09 (1.04, 1.14) for O_3. Associations were replicated in Winter, although they were attenuated for $PM_{2.5}$ and PM_{10}. Study findings support a relation between long-term ambient air pollution exposure and COVID-19 mortality. Communities with historically high pollution levels might be at higher risk of COVID-19 mortality.

1. Introduction

Since the emergence of severe acute respiratory syndrome coronavirus 2 (SAR-CoV-2), the virus that causes the novel human coronavirus disease 2019 (COVID-19), there have been over 4.1 million reported deaths worldwide with over 600,000 in the United States, as of July 2021 (Dong et al., 2020). In the first year of the COVID-19 pandemic, multiple surges of COVID-19 cases and deaths have occurred (Dong et al., 2020). In the United States, the late Fall and Winter months (November through March) witnessed the highest rates of COVID-19 mortality (Dong et al., 2020). It is important to understand how risk factors associated with COVID-19 disease severity and mortality may change over the course of the pandemic and during different points in the year. This could reflect differences in weather and human behavioral patterns as well as intervention policies, testing accessibility, hospital conditions, available treatments and vaccinations, and virus variants. Such data are necessary in preparing for the next surge and mitigating the adverse impact of COVID-19 mortality risk factors, especially in the case where this becomes an endemic disease.

Among modifiable environmental risk factors, long-term exposure to

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air pollution has risen as a possible risk factor for increased COVID-19 disease severity and mortality (Katoto et al., 2021; Ali and Islam, 2020; Wu et al., 2020; Lopez-Feldman et al., 2021; Tchicaya et al., 2021; Liang et al., 2020; Konstantinoudis et al., 2021; Hutter et al., 2020; Dettori et al., 2021; Copat et al., 2020; Domingo et al., 2020). Associations between long-term exposure to air pollution and mortality are well documented (United States Environmental Protection Agency, 2020; United States Environmental Protection Agency, 2019) and there are several proposed mechanisms by which long-term air pollution exposure may increase the risk of COVID-19 mortality, including alterations in inflammatory and immune response and contributing to the development of chronic diseases that leave individuals more vulnerable to COVID-19 disease (Domingo et al., 2020; Bourdrel et al., 2021; Woodby et al., 2021; Comunian et al., 2020). Due to a needed rapid response to the global public health emergency most of the early publications assessed only correlation between long-term air pollution exposure and COVID-19 mortality without consideration of important potentially confounding factors—such as population size and density and socioeconomic variables (Copat et al., 2020). Confounding factors that relate with air pollution exposure and are also risk factors for COVID-19 mortality (e.g., through mechanisms effecting disease incidence, severity, and mortality) and are a concern because they can lead to spurious associations between exposure and outcome. There have been a few studies that do try to control for potential confounding factors. Among these higher COVID-19 mortality has been associated with long-term nitrogen dioxide (NO_2) (Liang et al., 2020; Konstantinoudis et al., 2021; Hutter et al., 2020), and particulate matter <2.5 μm ($PM_{2.5}$) (Wu et al., 2020; Lopez-Feldman et al., 2021; Tchicaya et al., 2021; Liang et al., 2020; Konstantinoudis et al., 2021) and <10 μm (PM_{10}) (Hutter et al., 2020; Dettori et al., 2021) in studies from across the globe. Most studies, however, were conducted using data from the first few months of the pandemic or relied on county or regional level aggregate death which disregard important local variability.

The objective of this study was to examine the association between COVID-19 mortality rates and estimates of long-term exposure to $PM_{2.5}$, PM_{10}, NO_2, and ozone (O_3) at the census tract level for California—a state with amongst the highest number of COVID-19 deaths in the United States. Use of census tracts as the geographical unit allowed for more careful control of potentially confounding factors and thus better inference, compared with, for example, county-level analyses. Most census tracts are less than 2 square miles (52 ha) in size and have 2500 to 8000 residents. The study was conducted using data from March 2020 to March 2021, separated into two study periods bisected in mid-October before the large Winter surge. This enabled us to evaluate whether air pollution findings could be replicated in both study periods. We chose as the outcome weekly census tract COVID-19 mortality, which were aggregated from death certificate data. Use of weekly mortality rates allowed us to more carefully take into account and control for different temporal patterns in the pandemic trajectory across the state (e.g., steeper or flatter epidemic curves, different overall pandemic trajectory patterns, etc.). Differences in pandemic trajectory patterns were important to account for since factors for these differences may also relate to long-term air pollution levels and confound pollution effect estimates. Potential confounding variables at the census tract and county level were also considered in our models and a number of sensitivity analyses were conducted.

2. Methods

2.1. Research setting, sample, and data

We examined COVID-19-related mortality in the state of California. We used the California Comprehensive Death Files from the California Department of Public Health, Center for Health Statistics and Informatics for 2020 and 2021. Data were updated weekly, and the last date of data export used in this analysis was May 15, 2021. To improve completeness of mortality data, we applied a nine-week buffer, given the usual lag in administrative mortality files. As such, the latest death date in this analysis was March 7, 2021. Data on causes of death and decedent's residential information, including census tract, were used in this analysis. This study was approved by the Committee for the Protection of Human Subjects of the state of California.

2.2. Assessment of COVID-19 mortality

Details of our COVID-19 mortality assessment method have been previously published (Garcia et al., 2021). Briefly, we used an internally developed algorithm to identify COVID-19-related deaths using the new International Statistical Classification of Diseases and Related Health Problems code for COVID-19 (U07.1) and a keyword search of variables related to immediate and underlying causes of death or other significant conditions that contributed to death. We applied this algorithm to all deaths occurring after February 1, 2020. Residential data on death certificates were used to assign residential census tracts for decedents. COVID-19 deaths occurring among residents in each census tract were aggregated to the weekly level. To align with the onset of the COVID-19 pandemic in California, we began our analyses on March 16, 2020, the first week when a county had either five deaths or 0.5 deaths per 100,000 population within a seven-day window.

2.3. Assessment of air pollution

Ambient $PM_{2.5}$, PM_{10}, NO_2, O_3 for all California census tracts were based on data from the ambient air quality monitoring system obtained from the US Environmental Protection Agency's Air Quality System for January 1, 2014–December 31, 2019. The air monitoring network in California is one of the most extensive in the U.S. with over 200 locations. 24-hour average $PM_{2.5}$, PM_{10}, and NO_2 concentrations and daily maximum 8-h average O_3 concentrations were included. Daily pollutant concentrations at the center of census tracts were estimated using inverse distance-squared weighting of observations from up to four nearby (<50 km) monitoring locations (Wong et al., 2004). Annual mean concentrations were calculated for each year, and then averaged across all six years (2014–2019) as an estimate of long-term air pollution exposure. All Federal Reference Method and Federal Equivalent Method data were included except those collected at near-road sites (located within 50 m of a freeway) which represent very small areas. Leave-one-out evaluation of the method in California indicated small biases (<0.7 ppb and <0.5 $\mu g/m^3$) and acceptable mean errors (<35%) (Eckel et al., 2016).

2.4. Covariates

Census tract sociodemographic characteristics were obtained from the American Community Survey 2014–2018 5-year Estimates, including: race/ethnicity (non-Hispanic Black, non-Hispanic Asian, and Hispanic any race), age (percent over age 65 years), sex (percent male), population, population density (persons per square mile), public transit use for commuting (percent of workers 16 years and over taking public transportation to work), housing with severe overcrowding (percent of housing units with over 1.5 persons per room (Blake et al., 2007)). We included the 2015 Social Deprivation Index (SDI) to account for differences in neighborhood socioeconomic variability that may affect COVID-19 mortality risk. SDI utilizes seven demographic characteristics from the American Community Survey to reflect social inequalities by census tract (I at the County Level., 2015).

County-level data on COVID-19 test positivity was used to reflect infection levels and spread. Testing data was obtained from the California Department of Public Health (StatewideD-19 Cases, 2021). Test positivity was calculated based on the number of positive tests out of the total administered tests recorded by county. Daily values were averaged to produce mean weekly test positivity values to match the temporal

resolution of our analysis. We applied a 2-week lag to reflect test positivity two weeks prior to when the COVID-19 deaths occurred. In the United States starting in December 2020, COVID-19 vaccines (first Pfizer and later Moderna, and Johnson & Johnson) became available to select individuals including healthcare and frontline employees, and then became increasingly available to various at-risk groups through March 2021 (National Center for Immun, 2021). Daily cumulative county-level vaccination data were obtained from the California Department of Public Health (StatewideD-19 Vaccin, 2021). Cumulative counts of people with at least one vaccine dose and fully vaccinated individuals were used in tandem with total county populations to produce two variables quantifying percent of county population with vaccine administration. For days in which no doses were administered in a given county, the last cumulative vaccination value was carried forward. Prior to December 15, 2020 (the first day of vaccination data), we assumed zero vaccinations. Measures of cumulative vaccination were matched using the day immediately prior to the start of the index week of COVID-19 deaths.

2.5. Data analysis

Data were analyzed as two study periods: Spring/Summer (March 16 - October 18, 2020) and Winter (October 19, 2020–March 7, 2021). The introduction of vaccine administration and differences between Winter 2020–2021 and Spring/Summer 2020 mortality motivated the partition of study periods. A negative binomial mixed model was used to assess the relationship between weekly census tract COVID-19 mortality and pollutants $PM_{2.5}$, PM_{10}, NO_2, and O_3, adjusting for potential confounding variables, with each exposure being modeled separately. Mortality was modeled through weekly census tract COVID-19 deaths offset by census-tract population. Census tracts with zero total population were excluded from analysis. Pollutants were mean-centered and scaled to a one standard deviation change so that estimated effects were for a one standard deviation change in long-term pollution exposure. The variable for calendar week was centered at the mode of the weeks with the highest numbers of deaths at the county-aggregated level: July 27 - Aug 2, 2020 for Spring/Summer and Jan 4 - Jan 10, 2021 for Winter. To account for differences in deaths over time, a natural cubic spline for calendar week was included. Optimal number of degrees of freedom in the natural cubic spline were assessed separately for each study period and determined by AIC and BIC, resulting in 7° for Spring/Summer and 6° for Winter. To model differences in the pandemic trajectory across the state random intercepts were included at the county- and census tract-level. To allow for greater flexibility in the modeled pandemic trajectory by county, we applied uncorrelated random slopes on time, using spline basis functions, at the county-level. Continuous covariates were mean-centered and scaled to a one standard deviation change, with the exception of two covariates: SDI remained on its original scale and population density was log-transformed. Models generally followed the form of:

$$\ln E(y_{ijk}) = \beta_0 + u_{0i} + u_{0ij} + \beta_1 Pollutant_{ij} + \sum_{k=1}^{w} \times \sum_{b=1}^{df} \{(\gamma_b + u_{1i,\,b}) \times ns_{b,k}\} + \ldots + \ln(population_{ij})$$

where.

y_{ijk} is the COVID-19 death count for county i, census tract j, week k,

u_{0i} and u_{0ij} are random intercepts at the county and census tract-level, respectively,

$ns_{b,k}$ represents the basis functions for natural cubic splines on time, with b indexing a specific basis function (from 1 to the degrees of freedom [df] specified) evaluated at week k.

" …" represents additional terms for covariates, to control for confounding.

Inclusion of the offset for census tract population, $\ln(population_{ij})$, produces a model for the rate of mortality rather than mortality count.

We first present a crude analysis of pollution and COVID-19 mortality, and then a fully adjusted analysis that controls for additional potentially confounding variables. Crude models include the pollutant, a fixed effect of time (smooth), random intercepts for county and census tract, random slopes on time by county, and a census tract population offset. Fully adjusted models additionally include the following census-tract covariates: percent aged 65 years and over, percent non-Hispanic Black, non-Hispanic Asian, and Hispanic individuals of any race, SDI, and a log-transformed population density variable. Several sensitivity analyses were then conducted: inclusion of additional census-tract covariates as potential confounders, stricter classification of COVID-19 death, internal geocoding of residential census tract, varying windows of long-term pollutant exposure profiles, and the addition of a zero-inflation component to models. Additional census-tract covariates investigated in sensitivity analyses include percent male, a categorical fixed effect for contiguous counties grouped into 11 regions, percent taking public transit for work, percent living in housing with severe overcrowding, and 2-week lag county COVID-19 test positivity rate. Sensitivity analyses for the Winter also included further adjustment for county vaccination percentages. Stricter classification of COVID-19 deaths excluded any deaths where COVID-19 was only recorded under "other significant condition" and was not listed as an immediate or underlying cause of death. We also reran mortality models using internally geocoded census tract information, geocoded using the Texas A&M University geocoder (https://geoservices.tamu.edu/Services/Geocode/), in lieu of the census tract reported on death certificates. In addition to 6-year pollutant concentration averages, 4-year, 2-year, and 1-year averages were also analyzed. To evaluate zero inflation, we examined the ratio of predicted to observed zeros and found no evidence for excess zeros (ratios were: ~1.00001 for Spring/Summer models and ~0.997 for Winter models). Nonetheless, we included in the sensitivity analysis a model allowing for zero-inflation as a smooth function of time. All analyses were conducted in R version 4.0.4 (R Core Team, 2021) (R: A language and environ, 2021).

3. Results

There were 8012 census tracts with non-zero populations with weekly mortality data available for analysis. Among these census tracts, there were a total of 58133 COVID-19 deaths, including 16133 in the Spring/Summer and 42000 in the Winter. Due to missing pollutant exposure assessment information, 7940 census tracts were included in the analysis for $PM_{2.5}$, 7012 for PM_{10}, 7763 for NO_2, and 7956 for O_3. Distribution of sociodemographic characteristics among census tracts are shown in Table 1.

Distributions for estimated long-term air pollution concentrations are shown in Fig. 1. Mean (standard deviation) concentrations were 10.3 (2.1) μg/m^3 for $PM_{2.5}$, 25.5 (7.1) μg/m^3 for PM_{10}, 11.3 (4.0) ppb for NO_2, and 42.8 (6.9) ppb for O_3.

Plots of observed versus predicted weekly census tract COVID-19 mortality aggregated to the county (Fig. 2 and S1) demonstrate the distinct temporal patterns of the pandemic's progression across the state. Fig. 2 shows only the 10 counties with the highest COVID-19 mortality for more decipherability; all counties are shown in Figure S1. Predicted mortality were based on models with smooth of calendar week, random intercepts for county and for census tract, and random slope on smooth of calendar week for county, with an offset for census tract population.

Results for crude and fully adjusted models for the Spring/Summer study period are shown in Table 2. Crude models indicated positive relations between weekly census tract COVID-19 mortality and long-term $PM_{2.5}$, PM_{10}, and NO_2 concentrations. Effect estimates remained positive, but were attenuated, in fully adjusted models accounting for potentially confounding variables. Per each standard deviation increase

Table 1
Distribution of sociodemographic characteristics among 8012 California census tracts under study.

Characteristic	Mean	Standard Deviation	Median	25th – 75th percentile
Percent over age 65 years	14.4	8.1	12.9	9.2, 17.8
Percent non-Hispanic Asian	13.5	15.4	8.0	2.9, 17.8
Percent non-Hispanic Black	5.6	8.7	2.6	0.8, 6.6
Percent Hispanic any race	37.9	26.5	30.8	15.4, 57.9
Social Deprivation Index	58.8	29.2	63	35, 85
Population	4886.3	2210.9	4618	3481.75, 5915.5
Population density	8718.0	9709.2	6458.5	2730.6, 11095.1
Percent male	49.7	5.0	49.4	47.4, 51.5
Percent of workers 16 years and over taking public transportation to work (n = 7992)	5.1	7.8	2.3	0.7, 5.9
Percent of housing units with over 1.5 persons per room (n = 7981)	3.2	4.6	1.6	0.4, 4.3

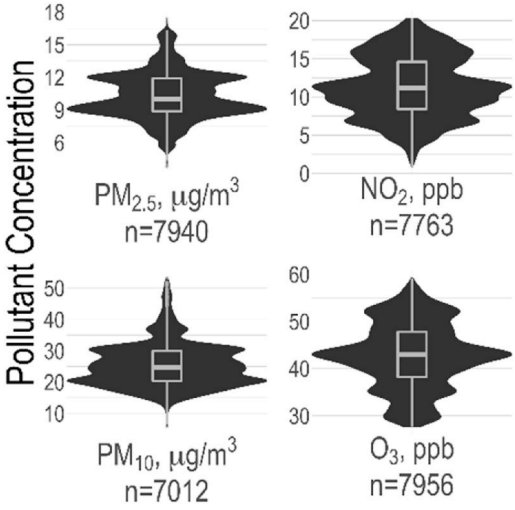

Fig. 1. Violin plots demonstrating distributions of 2014–2019 mean annual concentrations for $PM_{2.5}$, PM_{10}, NO_2, and O_3 across California census tracts included in the study. The width of the curve corresponds to the frequency of the data across pollutant concentrations. Each violin plot also contains a box plots showing the median (bar), interquartile range (box), and outlier (dots) concentrations for each pollutant.

in long-term air pollutant concentration, the adjusted rate ratios (aRR) for weekly COVID-19 mortality during the Spring/Summer study period were 1.13 (95% confidence interval [CI]: 1.09, 1.17) for $PM_{2.5}$, 1.16 (95%CI: 1.11, 1.21) for PM_{10}, and 1.06 (95%CI: 1.02, 1.10) for NO_2. This means, for example, a census tract that was otherwise similar but had 2.1 $\mu g/m^3$ higher $PM_{2.5}$ (one standard deviation) was estimated to have a 13% (95%CI: 9%, 17%) higher COVID-19 mortality rate. Results for O_3 indicated an inverse association in the crude model, but after accounting for potentially confounding variables in the fully adjusted model a positive association was observed (aRR = 1.09; 95%CI: 1.04, 1.14)—this change in effect estimate was largely driven by adjustment for SDI. For all pollutants, results of the sensitivity analyses—including additional adjustment for potential confounding variables, a stricter definition of COVID-19 mortality, internal geocoding, and zero-inflated models—were generally similar to those observed for the fully adjusted models (Table S1). To resolve convergence issues for zero-inflated models, the negative binomial (conditional) models did not include random slopes for time in both study periods; main model results were similar when random slopes were not included (data not shown). Results for Spring/Summer analyses using four-, two-, and one-year annual average pollution concentrations were also generally similar to the fully adjusted model results (Table S1). The robust positive associations for the four pollutants were replicated in the Winter study period analysis, although the effect estimates for $PM_{2.5}$ and PM_{10} were attenuated (Table 2). Per each standard deviation increase in long-term air pollutant concentration, the aRR for weekly COVID-19 mortality during the Winter study period was 1.06 (95%CI: 1.03, 1.08) for $PM_{2.5}$, 1.07 (95%CI: 1.04, 1.10) for PM_{10}, 1.05 (95%CI: 1.02, 1.08) for NO_2, and 1.09 (95%CI: 1.06, 1.13) for O_3. Effect estimates for the Winter study period were generally similar to the fully adjusted model results for all sensitivity analyses, including adjustment for county-level population vaccination percentage (Table S2).

4. Discussion

In this study of COVID-19 mortality and long-term air pollution exposure, we found weekly census tract COVID-19 mortality rates to be associated with long-term exposure to $PM_{2.5}$, PM_{10}, NO_2, and O_3 during both the Spring/Summer and Winter study periods. Associations were similar for NO_2 and O_3 in both study periods but were attenuated for $PM_{2.5}$ and PM_{10} in the Winter analysis compared with the Spring/Summer results. Findings were robust in sensitivity analyses.

Since the beginning of the COVID-19 pandemic, there have been several studies published on the associations between long-term air pollution and COVID-19 mortality; however, many of these studies did not control for potential confounding factors, such as population size or demographics (Katoto et al., 2021; Ali and Islam, 2020; Copat et al., 2020; Domingo et al., 2020). Among studies with some consideration of potentially confounding variables, several have reported positive associations between COVID-19 mortality and long-term air pollution concentrations, primarily $PM_{2.5}$ and NO_2. In a U.S. county-level study using mortality data through June 18, 2020, Wu and colleagues reported 2000–2016 average concentrations of $PM_{2.5}$ to be associated with COVID-19 mortality rates: mortality rate ratio = 1.11 (1.06, 1.17) per 1 $\mu g/m^3$ in a model adjusting for 20 county-level covariates (Wu et al., 2020). In another U.S. county-level study, using data through July 17, 2020 and evaluating multiple air pollutants, Liang and colleagues reported positive associations for COVID-19 mortality with 2010–2016 average concentrations of $PM_{2.5}$ (effect estimate = 1.19 [1.04, 1.37] per 2.6 $\mu g/m^3$) and NO_2 (effect estimate = 1.17 [1.10, 1.25] per 4.6 ppb), and null associations for O_3 (effect estimate = 1.00 [0.93, 1.08] per 3.3 ppb) (Liang et al., 2020). In models with all three pollutants, the effect estimate for NO_2 remained similar (1.16 [1.09, 1.24]) while the $PM_{2.5}$ effect estimate slightly attenuated (1.15 [1.00, 1.32]). These analyses adjusted for state- and county-level covariates and included a random intercept for each state (Liang et al., 2020). A study based in England using data through June 30, 2020 reported associations with 2014–2018 average concentrations of NO_2 and $PM_{2.5}$ (Konstantinoudis et al., 2021). The associated increase in COVID-19 mortality risk was 0.5% (95% credible interval: −0.2%, 1.2%) per 1 $\mu g/m^3$ (0.487 ppb) NO_2 and 1.4% (95% credible interval: 2.1%, 5.1%) per 1 $\mu g/m^3$ $PM_{2.5}$, in models adjusting for confounding and spatial autocorrelation (Konstantinoudis et al., 2021). A study from Mexico City using individual-level data through October 7, 2020 reported the probability of dying from COVID-19 increased by 0.77 percentage points per increase of 1 $\mu g/m^3$ in 2000–2018 average $PM_{2.5}$ concentration, adjusting for individual- and municipal-level covariates (Lopez-Feldman et al., 2021). In Vienna, Austria using data through April 21, 2020, increased COVID-19 mortality was associated with high levels of 2019 annual average NO_2 (hazard ratio = 1.72 [1.02, 2.90] for pollution above 30 $\mu g/m^3$ [14.6 ppb]) and PM_{10} (hazard ratio = 1.49 [0.73 3.08] for pollution above 20 $\mu g/m^3$) (Hutter et al., 2020). A study from Italy using data through June 3, 2020 found PM_{10}, but not $PM_{2.5}$ or NO_2, to be associated with provinces' Standardize Mortality Ratios (coefficient = 0.15 [0.06–0.23]) (Dettori et al., 2021). A recent study from France using data through

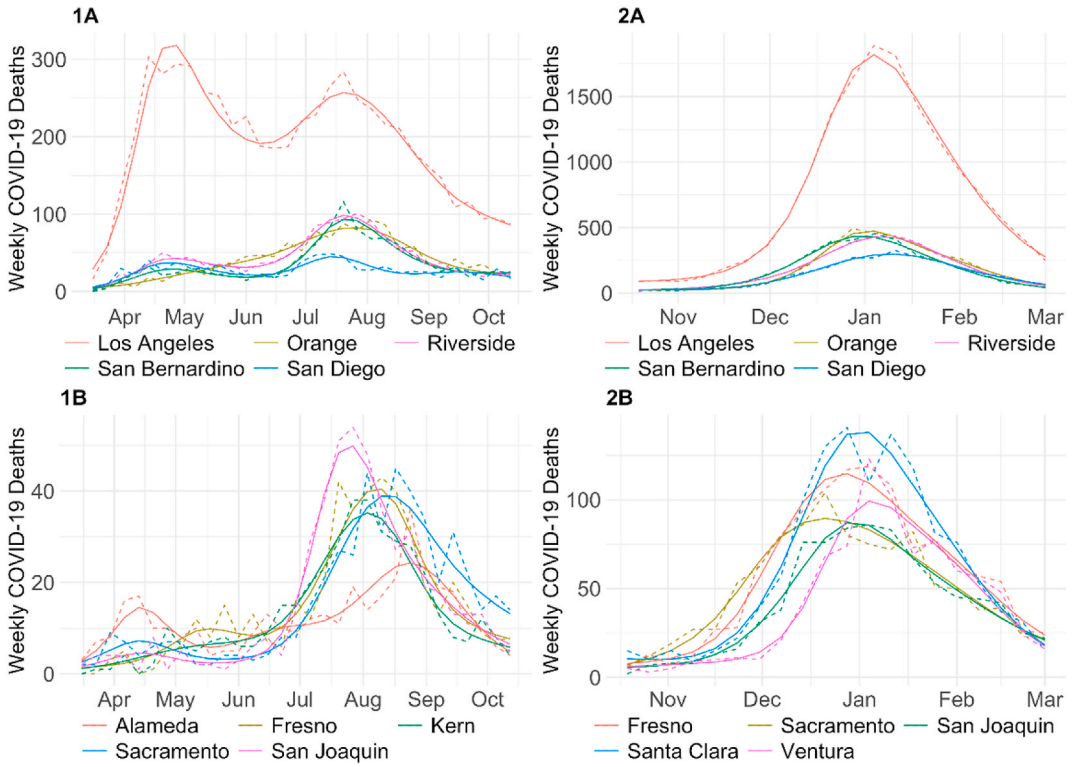

Fig. 2. Observed (dashed lines) versus predicted (solid line) weekly COVID-19 mortality for selected counties during the Spring/Summer (panels 1 A and 1 B) and Winter (panels 2 A and 2 B) study periods. Counties shown are those with the highest COVID-19 mortality. Predictions were based on models of weekly census tract COVID-19 mortality as a function calendar week (natural spline with degrees of freedom = 7 [Spring/Summer] or 6 [Winter]), random intercepts for county and for census tract, and random slope on smooth of calendar week for county, with an offset for census tract population. Census tract predictions were then aggregated to the county. Models were fitted separately for the two study periods.

Table 2
Estimated weekly census tract COVID-19 mortality rate ratios (95% confidence intervals) associated with a standard deviation[a] increase in long-term (2014–2019 annual average) air pollutant concentration during the Spring/Summer study period, California, March 16 – Oct 18, 2020.

Models	$PM_{2.5}$	PM_{10}	NO_2	O_3
Spring/Summer (March 16 – Oct 18, 2020)				
Crude model[b]	1.22 (1.18, 1.27)	1.36 (1.31, 1.42)	1.27 (1.22, 1.32)	0.92 (0.87, 0.97)
Fully adjusted[c]	1.13 (1.09, 1.17)	1.16 (1.11, 1.21)	1.06 (1.02, 1.10)	1.09 (1.04, 1.14)
Winter (Oct 19, 2020 – March 7, 2021)				
Crude model[b]	1.14 (1.11, 1.17)	1.26 (1.22, 1.29)	1.22 (1.18, 1.26)	0.93 (0.89, 0.96)
Fully adjusted[c]	1.06 (1.03, 1.08)	1.07 (1.04, 1.10)	1.05 (1.02, 1.08)	1.09 (1.06, 1.13)

Abbreviations: nitrogen dioxide, NO_2; ozone, O_3; particulate matter <2.5 μm, $PM_{2.5}$; particulate matter <10 μm, PM_{10}.
Note: Effect estimates where 95% confidence interval exclude the null (i.e., 1) are considered statistically significant at the p-value <0.05 level.
[a] Pollutant standard deviation: 2.1 μg/m^3 $PM_{2.5}$; 7.1 μg/m^3 PM_{10}; 4.0 ppb NO_2; 6.9 ppb O_3.
[b] Negative binomial mixed model adjusted for smooth of calendar week, random intercepts for county and for census tract, and random slope on smooth of calendar week for county, with an offset for census tract population.
[c] Model additionally adjusted for percent over age 65 years, percent Hispanic any race, percent Black, percent Asian, social deprivation index, and population density.

December 2020 reported long-term (1999–2016) $PM_{2.5}$ concentration to be associated with increased COVID-19 mortality, but effect estimates attenuated in later Fall/early Winter months (Nov–Dec) (Tchicaya et al., 2021)—similar to the attenuated $PM_{2.5}$ associations observed in our study during the Winter study period. It is important to note that some studies have also reported null or mixed mortality associations for long-term air pollution (Valdés Salgado et al., 2021; Berg et al., 2021). Overall, the present study provide additional evidence—consistent with the growing body of literature—of associations between COVID-19 mortality with $PM_{2.5}$ and NO_2 and provide support for novel associations with PM_{10} and O_3, not only during the first few months of the pandemic, but also during the larger third Winter wave experienced in California.

Studies have reviewed possible mechanisms by which air pollution exposure may affect COVID-19 severity and mortality (Bourdrel et al., 2021; Woodby et al., 2021; Comunian et al., 2020). Mechanisms for short-term versus long-term air pollution exposure are likely different, and we focus our discussion on possible mechanisms relating to long-term exposure. It is well-documented that exposure to ambient air pollution increases the risk of several chronic health conditions, including respiratory, cardiovascular, and metabolic diseases (Hoek et al., 2013; Feigin et al., 2016; Cohen et al., 2017; Yang et al., 2019; Eze et al., 2015; Chen et al., 2014), and individuals with these co-morbidities are at higher risk of severe COVID-19 disease and mortality (Singh et al., 2020; Ssentongo et al., 2020; Goodman et al., 2020). Thus air pollution may affect COVID-19 mortality risk by contributing to health conditions that then increase an individual's risk of mortality. Exposure to air pollution can induce oxidative stress, increasing systemic inflammation and effect inflammatory and adaptive immune response (Bourdrel et al., 2021; Woodby et al., 2021). Altered inflammatory and immune response, including suppressed antiviral adaptive responses, may then promote COVID-19 incidence and increase risk of disease severity and mortality (Bourdrel et al., 2021; Woodby et al., 2021). Air pollution is associated with chronic rhinitis and rhinosinusitis—conditions which might allow for easier penetration of the SARS-CoV-2 virus by increasing airway mucosal permeability (Bourdrel et al., 2021; London et al., 2018;

Annesi-Maesano et al., 2012). Further supporting biological plausibility, air pollution has been associated with increased risk of morbidity and mortality for other viral respiratory infections (Ciencewicki and Jaspers, 2007), including influenza (Ciencewicki and Jaspers, 2007; Pope et al., 2004) and lower respiratory tract infections (Estimates of the global, 2017).

The future of the COVID-19 pandemic is unknown. It will likely continue and evolve into the future, possibly becoming endemic. It is of public health importance to understand risk factors associated with adverse outcomes of COVID-19 to mitigate disease impact. Evidence, including this study, suggests long-term air pollution concentrations to be associated with COVID-19 mortality rates in an area (region, county, census tract, etc.), indicating that communities with historically higher levels of ambient air pollution have a disproportionate burden of COVID-19 death (Katoto et al., 2021; Ali and Islam, 2020; Wu et al., 2020; Lopez-Feldman et al., 2021; Liang et al., 2020; Konstantinoudis et al., 2021; Hutter et al., 2020). These communities likely face additional stressors, including exposure to higher levels of other risk factors for COVID-19 severity and mortality (Singh et al., 2020; Ssentongo et al., 2020; Goodman et al., 2020). Targeting of communities with increased vulnerabilities by public health campaigns is an essential component of pandemic response for COVID-19 as well as future public health emergencies. Further, the results from this study underscore the health benefits of continued air pollution regulation. Decreased air pollution presents the potential for reduction in the burden of COVID-19 and possibly other viral respiratory infections (Ciencewicki and Jaspers, 2007; Pope et al., 2004; Estimates of the global, 2017), with the co-benefit of also reducing the many other adverse health outcomes linked with long-term air pollution exposure (Hoek et al., 2013; Feigin et al., 2016; Cohen et al., 2017; Yang et al., 2019; Eze et al., 2015; Chen et al., 2014).

This study has strengths. First, this study investigated air pollution effects during the Spring and Summer (March 2020–October 2020) waves as well as the more recent Winter (October 2020–March 2021) wave, for which fewer studies have been conducted. Elevated pollution effect estimates were replicated in the two study periods, albeit with some attenuation for $PM_{2.5}$ and PM_{10}. Second, our estimate of COVID-19 mortality was based on statewide death certificate data which reduces the possibility of selection bias, since these data capture all deaths including those that occurred at home. Third, pollution effect estimates were robust to sensitivity analyses assessing a range of study features, including outcome definition, modelling assumptions, and additional possible confounding variables including test positivity rates and population vaccination percentages. Last, the study setting of California is well-suited for this analysis given the large range of air pollution levels across the states and its large and diverse population.

This study has limitations. First, long-term air pollution exposure assessment was based on the census tract in which decedents were reported to have been living prior to death. This 6-year annual average may not reflect decedents' actual exposure histories since it does not take into account residential mobility in the years prior to death. However, pollution effect estimates were similar between 6-year annual average exposures and more recent exposure variables (e.g., 1-year and 2-year annual averages)—which should reduce exposure misclassification resulting from decedents moving. Second, given our study design we were unable to control for possible confounding variables at the individual level. We do control for important area covariates, including an index for social deprivation and population density, that may confound the relation between long-term air pollution and census tract COVID-19 mortality rates. Further, our unit of analysis (census tract) is among the finest scale for current studies of long-term air pollution and COVID-19 mortality. Nonetheless, inferences based on this study can only be made for ecological (census tract-level) associations and not directly for individual-level associations. Third, our modelling approach does not completely control for spatiotemporal autocorrelation. Our models account for the temporal correlation through the complex smooth for calendar week, spatial correlation through random intercepts for county and census tract, and spatiotemporal correlation though random slopes for county. This approach, however, does not take into account distance between census tracts and could lead to spatial autocorrelation of residuals.

5. Conclusion

This study supports the hypothesis that long-term exposure to ambient air pollutants increases the risk of COVID-19 mortality. Positive associations with COVID-19 mortality rates were observed for $PM_{2.5}$, PM_{10}, NO_2, and O_3 during both the Spring/Summer and Winter study periods. Public health programs might consider communities with historically high pollution levels for interventions as the pandemic continues.

Author statement

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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.

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Appendix A. Supplementary data

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References

Ali, N., Islam, F., 2020. The effects of air pollution on COVID-19 infection and mortality—a review on recent evidence. Frontiers in public health 8 (779).

Annesi-Maesano, I., Hulin, M., Lavaud, F., et al., 2012. Poor air quality in classrooms related to asthma and rhinitis in primary schoolchildren of the French 6 Cities Study. Thorax 67 (8), 682–688.

Berg, K., Romer Present, P., Richardson, K., 2021. Long-term air pollution and other risk factors associated with COVID-19 at the census tract level in Colorado. Environ. Pollut. 287, 117584.

Blake, K.S., Kellerson, R.L., Simic, A., 2007. Measuring Overcrowding in Housing. U.S. Department of Housing and Urban Development, Office of Policy Development.

Bourdrel, T., Annesi-Maesano, I., Alahmad, B., Maesano, C.N., Bind, M.-A., 2021. The impact of outdoor air pollution on COVID-19: a review of evidence from in vitro, animal, and human studies. Eur. Respir. Rev. 30 (159), 200242.

Chen, H., Burnett, R.T., Kwong, J.C., et al., 2014. Spatial association between ambient fine particulate matter and incident hypertension. Circulation 129 (5), 562–569.
Ciencewicki, J., Jaspers, I., 2007. Air pollution and respiratory viral infection. Inhal. Toxicol. 19 (14), 1135–1146.
Cohen, A.J., Brauer, M., Burnett, R., et al., 2017. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. Lancet 389, 1907–1918, 10082.
Comunian, S., Dongo, D., Milani, C., Palestini, P., 2020. Air pollution and covid-19: the role of particulate matter in the spread and increase of covid-19's morbidity and mortality. Int. J. Environ. Res. Publ. Health 17 (12).
Copat, C., Cristaldi, A., Fiore, M., et al., 2020. The role of air pollution (PM and NO2) in COVID-19 spread and lethality: a systematic review. Environ. Res. 191, 110129.
Dettori, M., Deiana, G., Balletto, G., et al., 2021. Air pollutants and risk of death due to COVID-19 in Italy. Environ. Res. 192, 110459.
Domingo, J.L., Marquès, M., Rovira, J., 2020. Influence of airborne transmission of SARS-CoV-2 on COVID-19 pandemic. A review. Environ. Res. 188, 109861.
Dong, E., Du, H., Gardner, L., 2020. An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect. Dis. 20 (5), 533–534.
Eckel, S.P., Cockburn, M., Shu, Y.H., et al., 2016. Air pollution affects lung cancer survival. Thorax 71 (10), 891–898.
Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory tract infections in 195 countries: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Infect. Dis. 17 (11), 2017, 1133–1161.
Eze, I.C., Hemkens, L.G., Bucher, H.C., et al., 2015. Association between ambient air pollution and diabetes mellitus in Europe and North America: systematic review and meta-analysis. Environ. Health Perspect. 123 (5), 381–389.
Feigin, V.L., Roth, G.A., Naghavi, M., et al., 2016. Global burden of stroke and risk factors in 188 countries, during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet Neurol. 15 (9), 913–924.
Garcia, E., Eckel, S.P., Chen, Z., Li, K., Gilliland, F.D., 2021. COVID-19 mortality in California based on death certificates: disproportionate impacts across racial/ethnic groups and nativity. Ann. Epidemiol. 58, 69–75.
Goodman, K.E., Magder, L.S., Baghdadi, J.D., et al., 2020. Impact of Sex and Metabolic Comorbidities on COVID-19 Mortality Risk across Age Groups: 66,646 Inpatients across 613 U.S. Hospitals. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.
Hoek, G., Krishnan, R.M., Beelen, R., et al., 2013. Long-term air pollution exposure and cardio- respiratory mortality: a review. Environ. Health 12 (1), 43.
Hutter, H.P., Poteser, M., Moshammer, H., et al., 2020. Air pollution is associated with COVID-19 incidence and mortality in Vienna, Austria. Int. J. Environ. Res. Publ. Health 17 (24).
SDI at the County Level, 2015. Robert Graham Center. https://www.graham-center.org/rgc/maps-data-tools/sdi/social-deprivation-index.html. (Accessed 15 December 2020), 2015, Accessed.
Katoto, P.D.M.C., Brand, A.S., Bakan, B., et al., 2021. Acute and chronic exposure to air pollution in relation with incidence, prevalence, severity and mortality of COVID-19: a rapid systematic review. Environ. Health 20 (1), 41.
Konstantinoudis, G., Padellini, T., Bennett, J., Davies, B., Ezzati, M., Blangiardo, M., 2021. Long-term exposure to air-pollution and COVID-19 mortality in England: a hierarchical spatial analysis. Environ. Int. 146, 106316.
Liang, D., Shi, L., Zhao, J., et al., 2020. Urban air pollution may enhance COVID-19 case-fatality and mortality rates in the United States. Innovation 1 (3), 100047.
London, N.R., Lina, I., Ramanathan, M., 2018. Aeroallergens, air pollutants, and chronic rhinitis and rhinosinusitis. World Journal of Otorhinolaryngology - Head and Neck Surgery 4 (3), 209–215.
Lopez-Feldman, A., Heres, D., Marquez-Padilla, F., 2021. Air pollution exposure and COVID-19: a look at mortality in Mexico City using individual-level data. Sci. Total Environ. 756, 143929.
National Center for Immunization and Respiratory Diseases (NCIRD), Division of Viral Diseases, 2021. How CDC Is Making COVID-19 Vaccine Recommendations. In: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations-process.html. (Accessed 21 July 2021). Accessed.
Pope, C.A., Burnett, R.T., Thurston, G.D., et al., 2004. Cardiovascular mortality and long-term exposure to particulate air pollution. Circulation 109 (1), 71–77.
R: A Language and Environment for Statistical Computing [computer Program], 2021. R Foundation for Statistical Computing, Vienna, Austria, Version 4.0.4.
Singh, A.K., Gillies, C.L., Singh, R., et al., 2020. Prevalence of co-morbidities and their association with mortality in patients with COVID-19: a systematic review and meta-analysis. Diabetes Obes. Metabol. 22 (10), 1915–1924.
Ssentongo, P., Ssentongo, A.E., Heilbrunn, E.S., Ba, D.M., Chinchilli, V.M., 2020. Association of cardiovascular disease and 10 other pre-existing comorbidities with COVID-19 mortality: a systematic review and meta-analysis. PLoS One 15 (8), e0238215.
Statewide COVID-19 Cases Deaths Tests, 2021. California Health and Human Services Open Data Portal. https://data.chhs.ca.gov/dataset/covid-19-time-series-metrics-by-county-and-state/resource/046cdd2b-31e5-4d34-9ed3-b48cdbc4be7a. (Accessed 24 May 2021). Accessed.
Statewide COVID-19 Vaccines Administered by County, 2021. California Health and Human Services Open Data Portal. https://data.chhs.ca.gov/dataset/vaccine-progress-dashboard/resource/130d7ba2-b6eb-438d-a412-741bde207e1c. (Accessed 24 May 2021).
Tchicaya, A., Lorentz, N., Omrani, H., de Lanchy, G., Leduc, K., 2021. Impact of long-term exposure to PM(2.5) and temperature on coronavirus disease mortality: observed trends in France. Environ. Health 20 (1), 101.
United States Environmental Protection Agency, 2019. Integrated Science Assessment for Particulate Matter. Office of Research and Development, National Center for Environmental Assessment, Research Triangle Park, NC. EPA/600/R-19/188.
United States Environmental Protection Agency, 2020. Integrated Science Assessment for Ozone and Related Photochemical Oxidants. Office of Research and Development, Center for Public Health & Environmental Assessment, Research Triangle Park, NC. EPA/600/R-20/012.
Valdés Salgado, M., Smith, P., Opazo, M.A., Huneeus, N., 2021. Long-term exposure to fine and coarse particulate matter and COVID-19 incidence and mortality rate in Chile during 2020. Int. J. Environ. Res. Publ. Health 18 (14).
Wong, D.W., Yuan, L., Perlin, S.A., 2004. Comparison of spatial interpolation methods for the estimation of air quality data. J. Expo. Anal. Environ. Epidemiol. 14 (5), 404–415.
Woodby, B., Arnold, M.M., Valacchi, G., 2021. SARS-CoV-2 infection, COVID-19 pathogenesis, and exposure to air pollution: what is the connection? Ann. N. Y. Acad. Sci. 1486 (1), 15–38.
Wu, X., Nethery, R.C., Sabath, M.B., Braun, D., Dominici, F., 2020. Air pollution and COVID-19 mortality in the United States: strengths and limitations of an ecological regression analysis. Science advances 6 (45).
Yang, B.-Y., Guo, Y., Markevych, I., et al., 2019. Association of long-term exposure to ambient air pollutants with risk factors for cardiovascular disease in China. JAMA network open 2 (3) e190318-e190318.