Does air pollution explain COVID-19 fatality and mortality rates? A multi-city study in São Paulo state, Brazil

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Abstract Since air pollution compromise the respiratory system and COVID-19 disease is caused by a respiratory virus, it is expected that air pollution plays an important role in the current COVID-19 pandemic. Exploratory studies have observed positive associations between air pollution and COVID-19 cases, deaths, fatality, and mortality rate. However, no study focused on Brazil, one of the most affected countries by the pandemic. Thus, this study aimed to understand how long-term exposure to PM_{10}, $PM_{2.5}$, and NO_2 contributed to COVID-19 fatality and mortality rates in São Paulo state in 2020. Air quality data between 2015 and 2019 in 64 monitoring stations within 36 municipalities were considered. The COVID-19 fatality was calculated considering cases and deaths from the government's official data and the mortality rate was calculated considering the 2020 population. Linear regression models were well-fitted for $PM_{2.5}$ concentration and fatality ($R^2 = 0.416$; $p = 0.003$), NO_2 concentration and fatality ($R^2 = 0.232$; $p = 0.005$), and NO_2 concentration and mortality ($R^2 = 0.273$; $p = 0.002$). This study corroborates other authors' findings and enriches the discussion for having considered a longer time series to represent long-term exposure to the pollutants and for having considered one of the regions with the highest incidence of COVID-19 in the world. Thus, it reinforces measures to reduce the concentration of air pollutants which are essential for public health and will increase the chance to survive in future respiratory disease epidemics.

Keywords $PM_{2.5}$ · NO_2 · PM_{10} · Health impact · Long-term exposure

Introduction

The current coronavirus disease (COVID-19) pandemic through the spreading of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has triggered serious consequences to global health, healthcare systems, and economics, resulting in millions of human lives losses and huge social costs. As of December 31st, 2021, COVID-19 has caused more than 5.4 million deaths worldwide, with an average case fatality of 1.8%, varying by region (López-Feldman et al., 2021; WHO, 2021a; Worldometers, 2021).

At the beginning of the COVID-19 pandemic, human-to-human transmission was set as the main form of contagion. As the disease spread around the world and data from the most affected locations were studied, it was possible to note the great contribution of weather conditions and also of air pollution in the spread of the SARS-CoV-2 virus. Low wind

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speed associated with elevated concentrations of air pollutants favors the virus permanence in the air, so cities with these conditions are more likely to present high transmission rates (Coccia, 2021a, b). According to Coccia (2020), the analysis of 55 Italian cities reveals that air pollution-to-human transmission (airborne viral infectivity) seemed to be more relevant than human-to-human transmission. Besides wind speed and air pollutants concentration, the SARS-CoV-2 infectivity has already been related to temperature, relative humidity, and precipitation (Srivastava, 2021). In this sense, higher temperatures and relative humidity reduce the virus viability, and lower temperatures, the presence of drew or frost points, and precipitation increase the virus infectivity (Sarkodie & Owusu, 2020).

COVID-19 symptoms differ among patients and may include fever, cough, breathing difficulties, loss of smell, multiple organ dysfunction, and asymptomatic cases may also occur, according to the World Health Organization (WHO, 2021b). Moreover, older age, obesity, immunodeficiency, pre-existing chronic non-communicable diseases, and respiratory disorders are the major risk factors for mortality (Noor & Islam, 2020; Rothan & Byrareddy, 2020; Simonnet et al., 2020). Given the complexity of this new disease, it is challenging to understand the multiple factors involved in its development and spread.

Ambient air pollution is a well-known threat to global health. Many previous studies support the close relationship between exposure to air pollutants and several adverse health impacts, such as morbidity and mortality related to neurodevelopmental and neurodegenerative disorders, heart disease, stroke, asthma, bronchitis, chronic obstructive pulmonary disease, and lung cancer (Chen et al., 2017; Gharibvand et al., 2016; Landrigan et al., 2018; Lim et al., 2018). Moreover, it is important to highlight the association with infectious diseases and ambient air pollutants, observed in epidemic events, such as influenza seasons (Feng et al., 2016; Liang et al., 2014) and the 2003 Severe Acute Respiratory Syndrome (SARS) outbreak (Cui et al., 2003), in China. Besides SARS-CoV-2 being highly transmissible, COVID-19 is primarily a respiratory disease; therefore, understanding how air pollution might be either a contributing factor to this disease outcome or susceptibility is a topic of growing interest for this current global health crisis.

The influence of air pollution on public health can be understood from two different perspectives: short-term and long-term exposure. The health effects resulting from short-term exposure were described first, often associated with acute episodes of air pollution in the initial decades of the twentieth century. A classical description of these health effects occurred after the London Smog in 1952 (Wilkins, 1954). Currently, in this type of study, models such as Generalized Linear or Generalized Additive Models (GLM and GAM) are fitted to associate the increase in health outcomes such as death or hospitalization with episodes of worsening air quality. More recently, the long-term exposure effects of air pollution (i.e., living for years in an urban center) have been widely described. For instance, long-term exposure to air pollutants from vehicles (living near to traffic roads) has already been associated with lung cancer death, increased mediators of systemic inflammation in the bloodstream of adults, lower cognitive development in primary school children, and a higher probability of developing dementia (in the elderly) and asthma (in children) (Bidoli et al., 2016; Lanki et al., 2015; McConnell et al., 2010; Sunyer et al., 2015).

The relationship between air quality and COVID-19 was first described by Conticini et al. (2020) in Northern Italy and, according to the authors, the high levels of air pollution in Lombardy and Emilia Romagna might explain why these regions registered the highest level of virus fatality in the world at the beginning of the pandemic. After this study, similar ones were conducted in different regions of the world (Table 1). The effects of air pollution in the COVID-19 pandemic have been described both in terms of short-term exposure (using air quality data from the epidemic period) and long-term exposure (using air quality data from past periods).

Table 1 summarizes the most relevant results discussed in the systematic review published by Copat et al. (2020), as well as including more recent studies that were published until August 2021. Most authors focused their attention to examine the effects of air pollution on COVID-19 outcomes, in terms of $PM_{2.5}$, PM_{10}, and NO_2 exposures. $PM_{2.5}$ was the most explored pollutant, as it was the object of investigation in all studies. These studies support

Table 1 Summary of evidence on air pollution exposure and COVID-19 events

Reference	Study location	COVID-19 outcome	Air pollutants' data	Main findings
Páez-Osuna et al. (2021)	Mexico	Accumulated mortality rate from Feb. 2020 to Apr.JULY 2021	$PM_{2.5}$ (past period)	• Significant relationship between cumulative mortality rates and $PM_{2.5}$ emissions from vehicles ($r = 0.616$, $p < 0.005$) and $PM_{2.5}$ emissions from anthropogenic sources ($r = 0.746$, $p < 0.005$)
Yu et al. (2021)	Worldwide basis (251 countries)	Cases and deaths per million population until 31 Jan. 2021	$PM_{2.5}$ (past period)	• Deaths display a moderate positive correlation with $PM_{2.5}$ ($r = 0.419$, $p < 0.01$), GDP per capita ($r = 0.445$, $p < 0.01$), population density ($r = 0.521$, $p < 0.01$), and the number of hospital beds ($r = 0.409$, $p < 0.01$)
Travaglio et al. (2021)	England	Cumulative cases and deaths count between Feb. 1, 2020, and Apr. 8, 2020	$PM_{2.5}$, PM_{10}, NO_2, NO, and O_3 (past period)	• In total, 1 µg/m³ increase in NO_2 was associated with 3.1% more deaths • A total of 1 µg/m³ increase in $PM_{2.5}$ and PM_{10} was associated with 12% and 8% more cases, respectively
Konstantinoudis et al. (2021)	England	Cumulative deaths reported until Jun. 30, 2020	$PM_{2.5}$ and NO_2 (past period)	• In total, 1 µg/m³ increase in $PM_{2.5}$ and NO_2 were associated with 1.4% and 0.5% increase in mortality risk, respectively
López-Feldman et al. (2021)	Mexico City metropolitan area	Confirmed cases and deaths available on 7 Oct. 2020	$PM_{2.5}$ (past period)	• $PM_{2.5}$ increases the probability of dying, even with including municipal and individual levels covariates • Its effect is monotonically increasing with age and reaches a maximum at around 80 years of age
Vasquez-Apestegui et al. (2021)	Peru	Cases and deaths occurred until Jun. 12, 2020	$PM_{2.5}$ (past period)	• PM2.5 was associated with the number of cases ($\beta = 0.07$; 95% CI: 0.034–0.107) and deaths ($\beta = 0.0014$; 95% CI: 0.0006–0.0.0023) but not with case fatality rate

Table 1 (continued)

Reference	Study location	COVID-19 outcome	Air pollutants' data	Main findings
Wu et al. (2020)	USA	Death counts up to Jun. 18, 2020	$PM_{2.5}$ (past period)	• A total of 1 µg/m³ in the long-term average $PM_{2.5}$ was associated with a statistically significant 11% (95% CI, 6 to 17%) increase in the county's COVID-19 mortality rate
Borro et al. (2020)	Italy	Cases and deaths between Feb. 20, 2020, and Mar. 30, 2020	$PM_{2.5}$ (past period)	• Positive correlations between $PM_{2.5}$ and incidence ($r = 0.67$, $p < 0.0001$), mortality rate ($r = 0.65$, $p < 0.0001$) case fatality rate ($r = 0.7$, $p < 0.0001$)
Frontera et al. (2020)	Italy	Total cases, hospitalized cases, ICU admissions and deaths available on Mar. 31, 2020	$PM_{2.5}$ (past period)	• Significant relationship between the mean $PM_{2.5}$ concentration and COVID-19 outcomes (total number cases: $r = 0.64$; $p = 0.0074$; ICU admissions per day: $r = 0.65$; $p = 0.0051$; deaths: $r = 0.53$; $p = 0.032$; hospitalized cases: $r = 0.62$; $p = 0.0089$)
Liang et al. (2020)	USA	Daily county-level confirmed cases and deaths occurred between Jan. 22, 2020, and Jul. 17, 2020	$PM_{2.5}$, NO_2, and O_3 (past period)	• An increase in NO_2 (4.6 ppb) was associated with an increase 11.3% of case-fatality (95% CI 4.9–18.2%) and 16.2% of mortality (95% CI 8.7–24.0%) • An increase in $PM_{2.5}$ (2.6 µg/m³) was marginally associated, with a 14.9% (95% CI 0.0–31.9%) increase in mortality
Hendryx and Luo (2020)	USA	Confirmed cases and deaths as of May 31, 2020	$PM_{2.5}$, diesel PM and O_3 (past period)	• Prevalence was associated with $PM_{2.5}$ [23.5 (10.3), 0.02] and diesel PM [253 (50.7), 0.001] • Deaths were associated with $PM_{2.5}$ [1.08 (0.54) 0.05] and diesel PM [14.3 (2.54) 0.001] by linear multiple regression models [estimate (SE), p-value]

Table 1 (continued)

Reference	Study location	COVID-19 outcome	Air pollutants' data	Main findings
Yao et al. (2020)	China	CFR (cumulative death counts divided by cumulative confirmed cases) as of Mar. 22, 2020	$PM_{2.5}$ and PM_{10} (past period)	• A 10-μg/m^3 increase in $PM_{2.5}$ and PM_{10} concentrations, fatality rate increased by 0.61% (0.09–1.12%) and 0.33% (0.03–0.64%), respectively
Chakraborty et al. (2020)	India	Total number cases total number of deceased on Jun. 15, 2020	$PM_{2.5}$, PM_{10}, NO_2, NO_X and SO_2 (past period)	• Positive correlation between NO_2 and both the absolute number of deaths ($r = 0.79$, $p < 0.05$) and case fatality rate ($r = 0.74$, $p < 0.05$) • $NO_2/PM_{2.5}$ ratio increased the fatality rate by ~ 7.2% ($R^2 = 0.44$)
Dales et al. (2021)	Santiago, Chile	Cases and deaths between Mar. 16, 2020, and Aug. 31, 2020	$PM_{2.5}$, NO_2, CO, and O_3 (epidemic period)	• Approx. 6% increase in daily deaths related to an IQR increase in CO, NO_2, and $PM_{2.5}$, with cumulative RR of 1.061, 1.067, and 1.058, respectively • IQR increase in NO_2 was associated with a 12.7% increase in daily mortality, in the > 85 years old group
Zhu et al. (2020)	China	Daily confirmed cases from Jan. 23, 2020, to Feb. 29, 2020	$PM_{2.5}$, PM_{10}, SO_2, CO, NO_2 and O_3 (epidemic period)	• A 10-μg/m^3 increase (lag0–14) in $PM_{2.5}$, PM_{10}, NO_2, and O_3 was associated with a 2.24% (95% CI: 1.02 to 3.46), 1.76% (95% CI: 0.89 to 2.63), 6.94% (95% CI: 2.38 to 11.51), and 4.76% (95% CI: 1.99 to 7.52) more cases, respectively
Bolaño-Ortiz et al. (2020)	LAC cities	Cases and deaths from Apr. 1, 2020, to May 31, 2020	$PM_{2.5}$, PM_{10}, and NO_2 (epidemic period)	• Significant correlation tests for mortality $PM_{2.5}$, PM_{10}, and NO_2: Mexico City (lag 6) – 0.28**, – 0.49***, – 0.23**/ São Paulo (lag 0) 0.30**, 0.32**, 0.51*/Santiago (lag 14) 0.47***, 0.40***, 0.56*** • Significant correlation tests for mortality PM_{10} and NO_2: Buenos Aires (lag 0) 0.25*, 0.32***

Table 1 (continued)

Reference	Study location	COVID-19 outcome	Air pollutants' data	Main findings
Jiang et al. (2020)	China	Cases between Jan. 25, 2020, and Feb. 29, 2020	$PM_{2.5}$, PM_{10}, SO_2, CO, NO_2, and O_3 (epidemic period)	• Air pollution was positively associated with incidence. RRs in Wuhan: $PM_{2.5}$ 1.036 (95% CI, 1.032–1.039); CO 1.932 (95% CI, 1.763–2.118); NO_2 1.056 (95% CI, 1.053–1.059). RRs in XiaoGan: $PM_{2.5}$ 1.059 (95% CI, 1.046–1.072); SO_2 1.199 (95% CI, 1.166–1.233); NO_2 1.115 (95% CI, 1.095–1.136). RRs in HuangGang $PM_{2.5}$ 1.144 (95% CI, 1.12 – 1.169); SO_2 1.051 (95% CI, 1.018–1.085); O_3 1.016 (95% CI, 1.012–1.02)

GDP gross domestic product, *IQR* interquartile-range, *RR* relative risk, *CFR* case fatality rates, *ICU* intensive care unit, *SE* standard error, *CI* confidence interval; 1% (***), 5% (**), and 10% (*) level of significance

the evidence that exposure to $PM_{2.5}$ and NO_2 exerts a greater influence on COVID-19 outcomes, such as case, fatality rate, and mortality rate. The contribution of PM_{10} seems to be less significant and other pollutants, such as O_3, show controversial results. China, the USA, Italy, and some locations of the Latin America and the Caribbean (LAC) Region were the main explored areas. However, studies that specifically investigated Brazilian data were not found.

In 2020, Brazil was the 2nd country with more COVID-19 deaths (194,149 deaths) and the 23rd considering deaths per population rate (917 deaths per million) (Our world in data, 2021). Despite this being a tragic scenario, it makes Brazil a propitious place to study the COVID-19 disease. According to Rosario et al. (2020), Brazilian solar radiation is a climatic factor that suppresses the spread of COVID-19. Even so, Brazil was one of the countries that stood out the most during the first year of the pandemic (including placing the emergence of new variants of the SARS-COV-2 virus). Brazil was analyzed in two previous studies mentioned in Table 1. Neither Yu et al. (2021) nor Bolaño-Ortiz et al. (2020) investigated the air pollution influence on COVID-19 fatality or mortality rates, focusing on the number of cases and deaths separately. Yu et al. (2021) studied the effects of long-term exposure to $PM_{2.5}$ in a global analysis. They noticed that there is a positive correlation between deaths per million population and $PM_{2.5}$ concentration. However, it cannot be understood as higher COVID-19 fatality since they also found a positive correlation between cases per million population and $PM_{2.5}$ concentration (Yu et al., 2021). Bolaño-Ortiz et al. (2020) studied the effects of short-term exposure to $PM_{2.5}$, PM_{10}, and NO_2 pollutants and found a positive correlation between these pollutants and COVID-19 cases and mortality in São Paulo, Brazil.

Considering that long-term exposure to air pollutants may have a significant influence on COVID-19 fatality and mortality rates since it compromises the respiratory system and that this association has not been yet demonstrated in Brazil, which is one of the pandemic hotspots, this study aimed to understand how long-term exposure to air pollutants contributed to COVID-19 fatality and mortality rates in São Paulo, the most populous Brazilian state.

Materials and methods

Study area

Brazil is the 5th largest country in the world with 8.36 million km^2 and has 212 million inhabitants (The World Bank, 2021). In this study, only São Paulo state was considered, because it is the only Brazilian state with a robust air quality monitoring network, with 64 automatic stations and 22 manual monitoring points across the 248,209 Km^2 state area (Fig. 1) (CETESB, 2021).

The first case of COVID-19 in Brazil was registered in the city of São Paulo (capital of the state) in a person who had been in Italy. As the main Brazilian airport is located in the São Paulo state, people from different areas pass through the region. This fact has favored both the spread of the disease at the beginning of the pandemic and the spread of new variants

of SARS-CoV-2. In 2020, 24% of all COVID-19 deaths registered in Brazil occurred in São Paulo state. If São Paulo state was a country, it would be the 12th country with more COVID-19 deaths in 2020 (Our world in data, 2021; SEADE, 2021a).

São Paulo state occupies only 2.9% of the Brazilian area. However, it is the most populous, presenting 22% of its population. The projection based on the last Brazilian census estimates that 44.9 million people are living in the 645 municipalities of São Paulo state (SEADE, 2021b). In 2020, São Paulo's Gross Domestic Product (GDP) was about US$ 447,447 million, representing 31% of Brazilian GDP (SEADE, 2021c).

Data sources and considerations

To investigate the association between previous exposure to air pollutants and COVID-19, it was
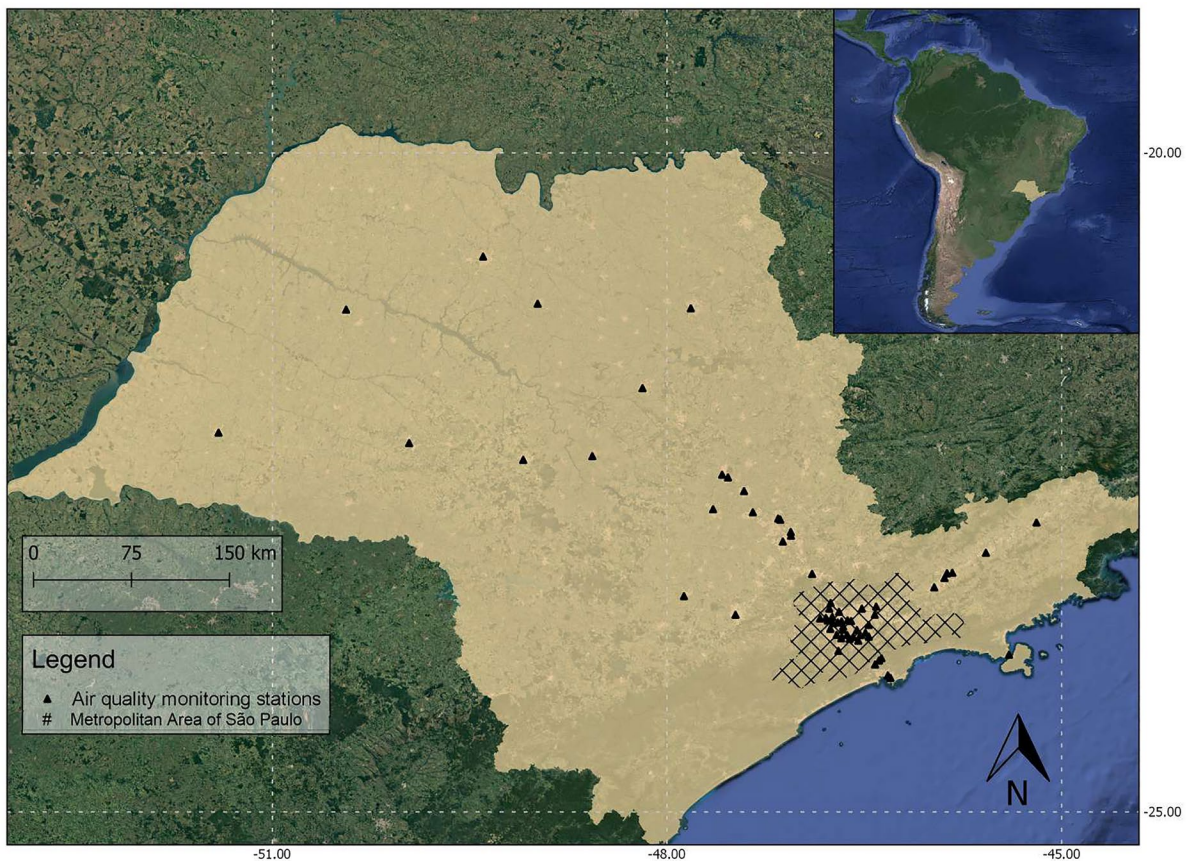

Fig. 1 Map of São Paulo state presenting the location of the 64 automatic air quality monitoring stations

considered air quality data from 2015 to 2019. The air quality in 2020 was not considered because social isolation implied lower levels of air pollution in some regions and these lower levels are uncharacteristic of the population's daily exposure through the years (Debone et al., 2020).

The pollutants considered were the particulate matter with less than 10 μm of diameter (PM_{10}), particulate matter with less than 2.5 μm of diameter ($PM_{2.5}$), and nitrogen dioxide (NO_2). These are the pollutants more frequently considered in the previous studies conducted in other countries (see Table 1) and they are also consistently monitored in the state. Between 2015 and 2019, PM_{10} was monitored at 36 municipalities (60 monitoring stations), $PM_{2.5}$ at 19 municipalities (31 monitoring stations), and NO_2 at 32 municipalities (51 monitoring stations). The annual mean concentration of each pollutant was consulted on the São Paulo's environmental agency database (named QUALAR). When there was more than one monitoring station in the same city, the annual air quality was considered as the mean. The population exposure to the pollutants through the years was considered as the mean concentration between 2015 and 2019 in each municipality.

COVID-19 data (cases and deaths) were consulted in the official São Paulo state report of December 31st, 2020. The COVID-19 fatality was considered as the rate between all death registered in each city until December, 31st and all cases in the same period. The mortality rate was defined as the ratio between all deaths registered in 2020 and the official estimated population for the same year. The year 2021 was not considered, because Brazilian Health System collapsed. There was a list of patients who needed hospitalization with people from all over the state and they were transported according to the availability of lays. So, deaths registered in one city were not necessarily of inhabitants of this specific city. Another consequence of the collapse was that there were deaths as a result of lack of medical care, which considerably increased the COVID-19 fatality and mortality rates.

Statistical analysis

Six independent linear regression analyses were performed in order to investigate the association between fatality rate and the previous exposure to PM_{10}, $PM_{2.5}$ and NO_2 and between mortality rate and the exposure to these three pollutants. The dependent variable was considered as the COVID-19 fatality or mortality rate in each city and the independent variable was considered as the mean pollutant concentration in the previous years. The linear regression model is presented in Eq. (1).

$$Y_i = \beta_0 + \beta_1 X_1 + \varepsilon_i \tag{1}$$

In which Y_i is the response variable; β_0 is the intercept; β_1 is the inclination; X_1 is the predictor variable; and ε_i is the aleatory error.

Besides the regression model, a Pearson coefficient analysis was performed to measure the extent of the relationship between the variables.

Both analyses were performed in the IBM SPSS Statistics 20 Software and p-value < 0.05 was considered as statistically significant.

Results

The municipalities considered in this study and the descriptive data about the COVID-19 fatality and mortality rates, air quality, population, and GDP are presented in Table 2. The 36 cities altogether summed more than 925,000 cases and almost 32,000 deaths in 2020. The population of these cities varied from 26,572 to 11,914,851 inhabitants, representing 66% of the state population, performing a GDP from US$340,193,079 to US$137,439,108,165, about 66% of the state production, evidencing the relevance and representativeness of the chosen municipalities. The average fatality rate in these municipalities was 2.9%. The COVID-19 disease was the least lethal in Araraquara city (1.15%) and the most lethal in Guarulhos (6.10%). The average mortality rate was 110.9 deaths per 10^5 inhabitants. The highest mortality rate was registered in Santos city (210.6 deaths per 10^5 inhabitants) and the lowest was registered in Araraquara (39.3 deaths per 10^5 inhabitants). Regarding air quality, the mean annual concentrations of PM_{10} ranged between 19.7 and 53.0 μg/m³ (average $= 28.7 \pm 7.4$), $PM_{2.5}$ between 10.0 and 22.0 μg/m³ (average $= 15.6 \pm 2.8$), and NO_2 between 9.0 and 46.4 μg/m³ (average $= 22.4 \pm 9.5$).

The Pearson correlation analyses revealed positive relationships between COVID-19 fatality rate and the concentrations of pollutants $PM_{2.5}$ and NO_2 ($p = 0.001$ and $p = 0.003$, respectively). The

Table 2 Descriptive data about COVID-19 disease (cases, deaths, fatality, and mortality rates) during 2020, pollutants mean concentrations between 2015 and 2019, population, and GDP of the 36 analyzed municipalities in the São Paulo state

Municipality	Population	COVID-19				Pollutant concentration (Mean of the years 2015–2019)			GDP[a] in 2020
		Cases	Deaths	Mortality (per 10^5 inhabitants)	Fatality (%)	PM_{10} (µg/m³)	$PM_{2.5}$ (µg/m³)	NO_2 (µg/m³)	(Billion US$)
1. Araraquara	228,792	7811	90	39.34	1.15	26.8		17.8	1.80
2. Paulínia	106,781	6487	91	85.22	1.40	31.1	15.0	20.0	6.28
3. Marília	232,599	6922	105	45.14	1.52	20.0		11.6	1.55
4. Bauru	365,523	18,289	301	82.35	1.65	26.2		16.2	2.81
5. Araçatuba	190,921	10,366	205	107.37	1.98	27.0			1.41
6. Santa Gertrudes	26,572	1137	23	86.56	2.02	53.0	17.0	33.0	0.34
7. São José dos Campos	716,688	25,853	545	76.04	2.11	22.1	11.8	19.0	7.63
8. Piracicaba	391,464	19,508	416	106.27	2.13	34.7	13.0	15.6	5.08
9. Presidente Prudente	221,938	8834	197	88.76	2.23	21.0		11.6	1.53
10. Jaú	148,613	4344	98	65.94	2.26	24.4		15.4	0.91
11. Sorocaba	663,739	23,03	563	84.82	2.44	24.8		18.8	6.73
12. Taubaté	309,483	8264	203	65.59	2.46	20.6	12.5	15.6	3.32
13. São José do Rio Preto	450,361	36,185	917	203.61	2.53	33.0	15.0	20.0	3.37
14. Tatuí	121,202	3793	99	81.68	2.61	19.8		9.0	0.76
15. Americana	235,075	8016	212	90.18	2.64	33.2			2.17
16. Limeira	297,662	10,899	289	97.09	2.65	31.5	16.0	19.7	2.53
17. Guaratinguetá	118,741	2379	64	53.90	2.69	19.6	10.0	12.3	1.09
18. Jundiaí	409,439	17,53	485	118.45	2.77	24.6	14.0	25.8	8.39
19. Santos	428,703	32,311	903	210.63	2.79	23.5	15.0	27.6	4.32
20. Cubatão	130,025	8122	229	176.12	2.82	48.0		38.2	2.53
21. Jacareí	229,163	6112	175	76.36	2.86	23.2		13.4	2.44
22. Santo André	694,681	27,983	855	123.08	3.06	28.6		27.0	5.57
23. Ribeirão Preto	688,894	30,865	953	138.34	3.09	29.5	13.3	10.0	6.60
24. Rio Claro	202,289	4923	164	81.07	3.33	39.0	19.0		1.88
25. Campinas	1,181,555	43,41	1474	124.75	3.40	24.1	17.6	19.4	11.80
26. Taboão da Serra	287,155	10,059	352	122.58	3.50	28.8		37.2	1.61
27. São Bernardo do Campo	815,109	33,828	1200	147.22	3.55	26.4	16.2	27.8	9.72
28. Carapicuíba	396,447	12,224	442	111.49	3.62	28.0		33.2	1.10
29. Catanduva	117,414	4957	180	153.30	3.63	33.4		15.6	0.80
30. São Paulo	11,914,851	401,718	15,679	131.59	3.90	28.6	16.8	34.6	137.43
31. Diadema	405,596	11,589	480	118.34	4.14	27.0			2.82
32. São Caetano do Sul	151,111	7608	316	209.12	4.15	32.2	17.0	36.6	2.58
33. Mauá	463,338	11,189	465	100.36	4.16	29.8	17.0	23.7	2.93
34. Mogi das Cruzes	436,883	11,571	547	125.20	4.73	21.0		16.5	2.95
35. Osasco	682,876	18,975	971	142.19	5.12	39.8	22.0	46.4	14.73
36. Guarulhos	1,361,862	27,979	1708	125.42	6.10	29.7	18.2	26.9	11.79

[a]GDP was collected in the official governmental platform and converted to US$ considering US$1 = R$5.20 (the exchange rate on December 31st, 2020)

correlation was stronger for $PM_{2.5}$ than NO_2 ($R^2 = 0.416$ and $R^2 = 0.232$, respectively). Between COVID-19 mortality rate and the pollutants' concentrations, the Pearson correlation was significant for the pollutants PM_{10} and NO_2 ($p = 0.03$ and $p = 0.001$, respectively). The relation was considered very low between PM_{10} exposure and mortality rate ($R^2 = 0.097$) and low between NO_2 exposure and mortality rate ($R^2 = 0.273$).

The linear regression models were well-fitted in the relationships between the fatality and $PM_{2.5}$ and NO_2 concentrations (ANOVA test $p = 0.003$ for $PM_{2.5}$ and $p = 0.005$ for NO_2) and between mortality rate and NO_2 concentration (ANOVA test $p = 0.002$). The model did not fit into the relationship between COVID-19 fatality and PM_{10} concentration (ANOVA test $p = 0.520$) and between COVID-19 mortality and PM_{10} and $PM_{2.5}$ concentrations (ANOVA test $p = 0.065$ for MP_{10} and $p = 0.202$ for $MP_{2.5}$). Figure 2 presents the graphs which illustrate each model.

Some municipalities presented fatality or mortality rates that could not be explained by the models (exceeding the 95% confidence interval). The fatality rate registered in Guarulhos city (6.10%) did not fit in any of the three performed models and the one registered in Mogi das Cruzes city (4.73%) did not fit into the NO_2 model. Regarding mortality rates, the cities of Santos and São José do Rio Preto (210.63 and 203.61 deaths per 10^5 inhabitants, respectively) did not fit into the NO_2 model.

Discussion

Ambient air pollution is widely recognized as a risk factor for all-cause of deaths and cardiopulmonary diseases (Beelen et al., 2014; Gharibvand et al., 2016; Landrigan et al., 2018; Zhao et al., 2020; Zhu et al., 2019). However, the relationship between air pollutants exposure and viral respiratory infections has been poorly investigated. Cui et al. (2003) found that Chinese regions with a moderate long-term air pollution index (API) were related with a 126% case fatality rate higher than locations with low API, during the 2003 SARS outbreak. In a similar vein, Liang et al. (2014) and Feng et al. (2016) reported that $PM_{2.5}$ concentrations were significantly related to cases and influenza-like illness (ILI) risk, respectively, during the flu season of Beijing.

Fig. 2 Scatter plots showing the relation between COVID-19 ▶ fatality or mortality rates and PM_{10}, $PM_{2.5}$, and NO_2 concentrations in the previous years in the 36 Brazilian municipalities. The numbers signed in the graphs represent the municipalities presented in Table 2. Figure elaborated by the authors in the IBM SPSS Statistics 20 Software

Several works are now emerging, reporting close relation between air pollutants exposure and COVID-19 outcomes, such as deaths, fatality, and mortality rates (Table 1). $PM_{2.5}$ was the most explored among the authors. Furthermore, these studies support the evidence that the long-term exposure of $PM_{2.5}$ exerts an important influence on COVID-19 outcomes, as shown in Yu et al. (2021) that found that deaths per million population were positive correlated with $PM_{2.5}$ ($r = 0.419$, $p < 0.01$), using a satellite-derived $PM_{2.5}$ concentration of 251 countries, from 2016. Páez-Osuna et al. (2021) carried a study in Mexico and showed a significant relationship between cumulative mortality rates and $PM_{2.5}$ emissions from vehicles ($r = 0.616$, $p < 0.005$), considering data from the last 37 years. Borro et al. (2020) reported positive correlations between $PM_{2.5}$ and mortality rate ($r = 0.65$, $p < 0.0001$) and case fatality rate ($r = 0.7$, $p < 0.0001$), considering $PM_{2.5}$ data of days before the first reported cases in Italy. In opposite to what was found in our study, Vasquez-Apestegui et al. (2021) estimated a significant association between long-term exposure to $PM_{2.5}$ and COVID-19 mortality in Peru; however, they did not observe this relationship for the lethality rate. The discrepant results between the investigations suggest that the better variable (fatality or mortality rate) to have the relationship with long-term exposure to air pollutants depends on the specific characteristics as which are the analyzed cities, socioeconomic indicators, quality of healthcare services, etc.

In several instances, the results related to long-term exposure of NO_2 also has shown a close relation between COVID-19 outcomes, as evidenced by Travaglio et al. (2021) that reported that a 1-μg/m^3 increase in NO_2 was associated with 3.1% more deaths, but 1-μg/m^3 increase in $PM_{2.5}$ was associated with 12% more cases, considering air pollution data from 2018 of England. Konstantinoudis et al. (2021) found that a 1-μg/m^3 increase in $PM_{2.5}$ and NO_2 was associated with a 1.4% and 0.5% increase in mortality risk in England, respectively, considering air
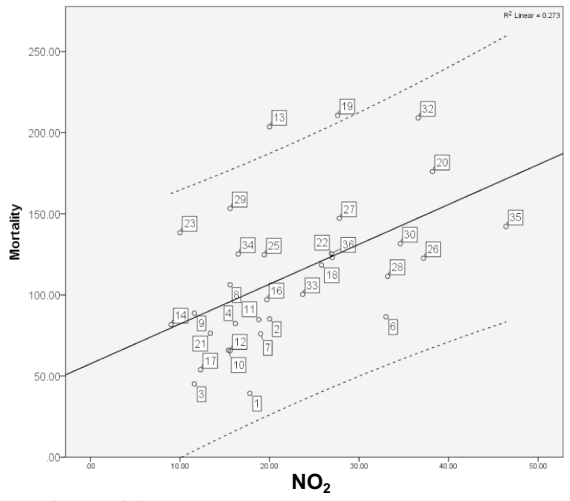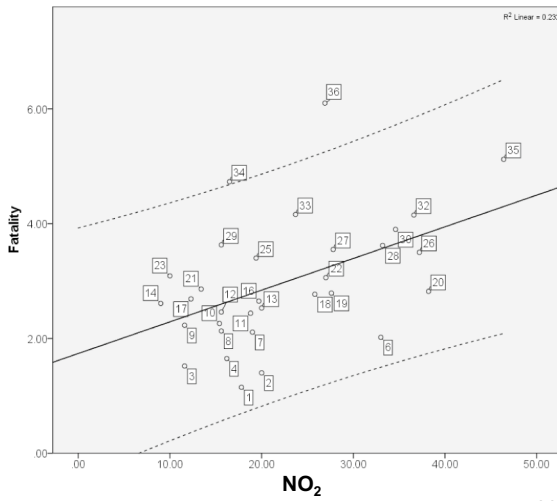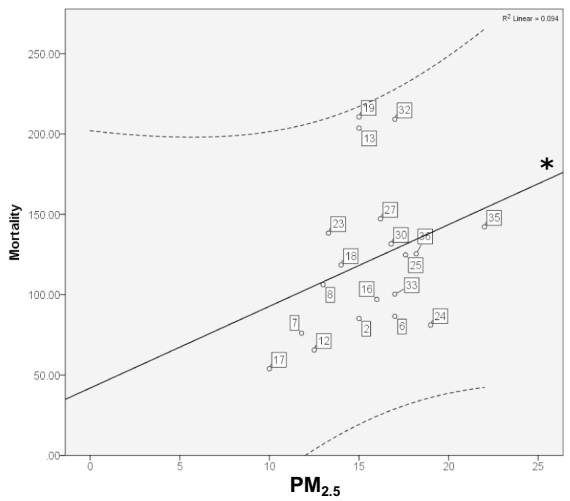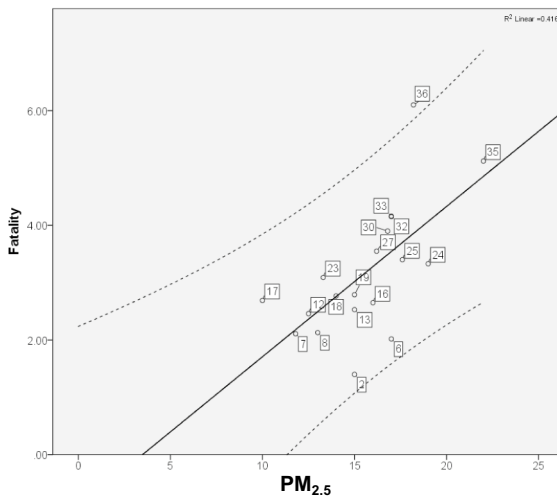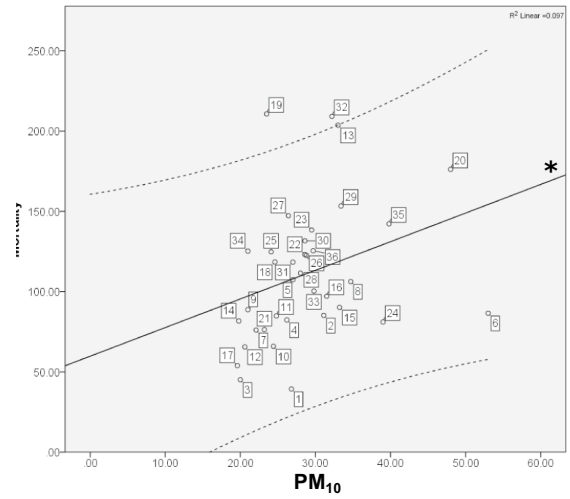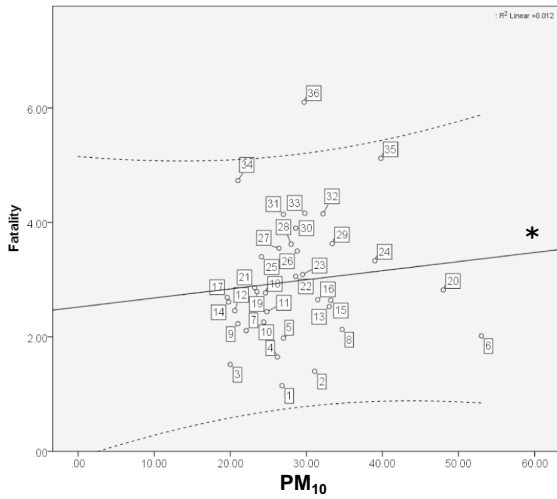
Linear regression model
95% Confidence interval
* p-value > 0.05

pollution data from 2014 to 2018. Chakraborty et al. (2020), using the pollution data from the year before the COVID-19 pandemic, found a positive correlation between NO_2 and both the absolute number of deaths ($r = 0.79$, $p < 0.05$) and case fatality rate ($r = 0.74$, $p < 0.05$), in India.

Our findings are consistent with previous studies, since we also showed a significant positive correlation between COVID-19 fatality rate and air pollutants long-term exposure, considering $PM_{2.5}$ and NO_2 concentrations ($R^2 = 0.416$ and $R^2 = 0.232$, respectively) and between COVID-19 mortality rate and previous exposure to NO_2 ($R^2 = 0.273$). Specifically, our model for $PM_{2.5}$ resulted in metrics with a similar range of values to those presented by Borro et al. (2020). Regarding the association between NO_2 concentration and COVID-19 fatality rate, our results were more moderate than those presented by Chakraborty et al. (2020); however, it is important to highlight that India has one of the highest rates of air pollution in the world and the authors had data available from 207 air quality monitoring stations in 128 cities, which may justify a lower value metric for our model.

The relationship between PM_{10} concentration and COVID-19 (cases, deaths, or fatalities) was explored by fewer authors (Table 1). Since this pollutant penetrates less deeply into the airways than smaller diameter PM and gases, the concentration of PM_{10} is often used in models that assess the health effects of short-term exposure. In this context, the increase in the concentration of this pollutant is especially associated with an increase in daily hospitalizations or deaths of people with chronic diseases or those affecting the cardiorespiratory system (Anderson et al., 2012). In this vein, Zhu et al. (2020) and Bolaño-Ortiz et al. (2020) noted the effects of short-term exposure to PM_{10} on the number of COVID-19 cases and mortality, respectively. The analysis of health effects resulting from long-term exposure to PM_{10} is present in the bibliography, although it is not included in the main models recommended by the WHO (Ostro, 2004; Pascal et al., 2011). Positive associations between prior and systemic exposure to PM_{10} and the increase in COVID-19 cases and fatality were described by Travaglio et al. (2021) and Yao et al. (2020), respectively. However, these associations were lower than those found between the exposure to $PM_{2.5}$ and the same outcomes. It is noteworthy that the concentration of

$PM_{2.5}$ is usually between 50 and 70% of the concentration of PM_{10} (Ostro, 2004; Pascal et al., 2011); thus, given the existence of a relationship between $PM_{2.5}$ long-term exposure and health outcomes, it is also possible to have similar results concerning PM_{10}, even if such outcomes are not a direct consequence of this pollutant, but rather of $PM_{2.5}$. In the present study, neither the Pearson correlation nor the regression model fitted the relationship between COVID-19 fatality and previous exposure to PM_{10}. Regarding the COVID-19 mortality rate, it was found an almost insignificant Pearson correlation with previous PM_{10} exposure ($R^2 = 0.097$; $p = 0.033$) and the linear regression model did not fit into the variables (ANOVA test $p = 0.065$).

Moreover, it is important to point out that the effect of exposure to air pollutants on COVID-19 outcomes varied within regions. Several factors can explain the divergences, such as differences in lockdown policies and strategies, socioeconomic indicators, quality of healthcare services, geographical location, and meteorological parameters (Ali et al., 2021). For instance, a comparative study among China, England, Germany, and Japan indicated that the population density and absolute humidity influence both the SARS-COV-2 spread and the decay duration of the pandemic (Diao et al., 2021).

In our analysis, Guarulhos city presented the higher COVID-19 fatality rate, which could not be explained either by $PM_{2.5}$ or NO_2 previous exposure. However, the COVID-19 mortality rate did not configure an outlier in the COVID-19 mortality rate models. It suggests that Guarulhos inhabitants were less tested for the disease in 2020. In this sense, the major tests were performed in people which needed medical care, so the observed fatality rate was very higher than the predicted one. Furthermore, the mortality rate in Santos and São José do Rio Preto municipalities could not be explained by NO_2 previous exposure. Despite presenting a lower population density compared to the others (1494 and 945 inhabitants per km^2 in Santos and São José do Rio Preto respectively), these cities are, respectively, the 1st and the 3rd cities with the higher proportion of elderly people in the population. In Santos, 21.50% of the inhabitants are older than 60 years; in São José do Rio Preto, the proportion is 15.40%. So, the elevated mortality rate registered in these cities is probably related to their population age structure. According to

Coccia ([2021c](#)), high expenditures in the health sector (> 7.5% of GDP) may reduce the fatality rates even in places with a great percentage of elderly people.

Climatic and meteorological factors seem to be less related to the high rates described for these municipalities. Santos, for example, is a coastal city with high averages of temperature, relative humidity, and wind speed throughout the year. São José do Rio Preto is among the three cities with the highest annual thermal average.

Besides small airborne particulate matter being widely recognized as more dangerous to human health since it can penetrate deeply into the respiratory tract, chronic exposure to $PM_{2.5}$ has been related to overexpression of the angiotensin-converting enzyme 2 (ACE-2) in mice (Aztatzi-Aguilar et al., [2015](#); Lin et al., [2018](#)). ACE-2 was reported as an important entry receptor for SARS-CoV-2 since the S1 subunit of the viral spike (S) protein binds to human ACE-2 in the alveoli (Babadaei et al., [2020](#); Beyerstedt et al., [2021](#)). Considering that the alveolar level only can be reached by small airborne particulate matter, the link between chronic exposure to air pollution and COVID-19 fatality can be explained, since high levels of $PM_{2.5}$ could overexpress ACE-2 facilitating viral penetration (Frontera et al., [2020](#)).

The effects of the air pollution on the COVID-19 pandemic may go beyond the increased fatality rate due to pulmonary impairment, especially in the most susceptible population. Recent studies have been demonstrating that aerosols are capable of carrying the SARS-CoV-2 virus (Asadi et al., [2020](#); Greenhalgh et al., [2021](#)). In this way, in regions with high local levels of aerosols in the atmosphere, disease transmission can be optimized. In Mexico, during June 2020 Saharan dust event, it was possible to find a positive association between PM levels and the daily number of COVID-19 cases and deaths (Kutralam-Muniasamy et al., [2021](#)).

Furthermore, in predominantly urban regions, such as most municipalities analyzed in this study, exposure to $PM_{2.5}$ is accompanied by NO_2, as they are generally positively correlated, emitted from a common source. In Sao Paulo, vehicles are responsible for 62.5% of nitrogen oxides and 37% of $PM_{2.5}$ emissions (CETESB, [2021](#)). Considering that NO_2 is a deep lung irritant with high oxidative potential, that increases inflammatory response and cellular injury, chronic exposure to this pollutant may promote viral activity due to the lung defense disruption and tissue damage caused by oxidative stress, increasing the COVID-19 patients' vulnerability (Frontera et al., [2020](#)).

The present study corroborates the main findings on the relationship between long-term exposure to $PM_{2.5}$ and NO_2 and COVID-19. It also reveals that, in São Paulo state (Brazil), the fatality rate is a better variable to explore its association with air pollutants' exposure than mortality rate and that $PM_{2.5}$ is the best pollutant for such model. The study relevance is highlighted by the use of statistical models, which support the first descriptive associations on the theme (such as that by Conticini et al. in [2020](#)), by using a longer time series to demonstrate the long-term exposure and by the studied area, which has consolidated among the regions with the highest incidence of COVID-19 in the world. Despite this, some limitations should be mentioned. The first is the scarcity of air quality monitoring stations in Brazil. This limited the area of analysis to the state of São Paulo. The second limitation is the evident underreporting of COVID-19 cases and deaths. At the beginning of the pandemic, tests to detect the disease were scarce and they were used only in hospitalized patients. The fact that only patients with complications were tested may have resulted in a generally overestimated fatality. We suppose that Guarulhos city presented the higher fatality rate because, in the city, the tests were applyed mostly in hospitalized people. This supposition could not be verified, because Brazilian Health Ministry does not disclose the number of tested people per city. Even among the deceased, underreporting throughout 2020 is evident. The lack of tests and the government's pressure to minimize the severity of the COVID-19 pandemic led many health professionals to attribute deaths that were possibly due to COVID-19 to other causes. In the state of São Paulo, deaths due to respiratory distress syndrome (ICD-10 J80) between 2017 and 2019 were 71, 106, and 94 and, in 2020, they increased to 377 (DATASUS, [2021](#)). Regarding deaths from acute respiratory failure (ICD-10 J96), they were 359, 334, 327 in 2017, 2018, and 2019 respectively, and, in 2020, they increased to 643 (DATASUS, [2021](#)). The historical series of deaths from severe acute respiratory syndrome (SARS; ICD-10 U04) were hidden from the official platform of the Ministry of Health of Brazil, revealing the lack of government transparency about the pandemic.

Considering the notary's office data, deaths registered by SARS in Brazil jumped from 293 in 2019 to 2422 in 2020 (Cartórios de Registro Civil do Brasil, 2021). The National Council of Health Departments estimates that, in 2020, there were 275,587 exceed deaths in Brazil probably due to COVID-19, but reported due to other causes (CONASS, 2021).

Our work, by presenting a significant correlation between COVID-19 fatality and long-term exposure to air pollutants, reinforces the relevant debate on the urgency of improving strategies for sustainable practices in urban centers, especially regarding air pollution control measures, since it can bring direct benefits to human health, especially in the context of this current global health crisis.

Conclusion

The COVID-19 pandemic is bringing a lot of learning to the world. In the search for an understanding of how the disease behaves and what are the associated risk factors, one more harmful effect of air pollution is perceived. The present study found a positive correlation between long-term exposure to $PM_{2.5}$ and NO_2 pollutants in the 5 years previous to the pandemic and COVID-19 fatality rate ($R^2 = 0.416$ and $R^2 = 0.232$, respectively). It was also found a positive correlation between long-term exposure to NO_2 pollutant in the 5 years previous to the pandemic and COVID-19 mortality rate ($R^2 = 0.273$). These results reinforce that measures to reduce the concentration of pollutants are essential for public health and will increase the chance of survival in future epidemics of respiratory diseases.

Declarations

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