RESEARCH ARTICLE

Associations of acute exposure to airborne pollutants with COVID-19 infection: evidence from China

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Abstract

The outbreak of COVID-19, caused by SARS-CoV-2, has spread across many countries globally. Greatly, there are limited studies concerned with the effect of airborne pollutants on COVID-19 infection, while exposure to airborne pollutants may harm human health. This paper aimed to examine the associations of acute exposure to ambient atmospheric pollutants to daily newly COVID-19 confirmed cases in 41 Chinese cities. Using a generalized additive model with Poisson distribution controlling for temperature and relative humidity, we evaluated the association between pollutant concentrations and daily COVID-19 confirmation at single-city level and multicity levels. We observed a 10-μg/m^3 rise in levels of $PM_{2.5}$ (lag 0−14), O_3 (lag 0−1), SO_2 (lag 0), and NO_2 (lag 0−14) were positively associated with relative risks of 1.050 (95% CI: 1.028, 1.073), 1.011 (1.007, 1.015), 1.052 (1.022, 1.083), and 1.094 (1.028, 1.164) of daily newly confirmed cases, respectively. Further adjustment for other pollutants did not change the associations materially (excepting in the model for SO_2). Our results indicated that COVID-19 incidence may be susceptible to airborne pollutants such as $PM_{2.5}$, O_3, SO_2, and NO_2, and mitigation strategies of environmental factors are required to prevent spreading.

Keywords Air pollution · COVID-19 · Novel coronavirus pneumonia · Generalized additive model

Introduction

COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread across the world and many countries are experiencing ongoing local transmission (Ghinai et al. 2020; Götzinger et al. 2020). The World Health Organization (WHO) reported the novel coronavirus pneumonia has afflicted over 110,749,023 people in more than 221 countries throughout the world and killed over 2,455,131 people as of 21 February 2021. In China, COVID-19 started in Wuhan and spread rapidly across the whole country, and an initial public restriction has played an important role in limiting the spread of infection (Chinazzi et al. 2020). The government has strictly restricted the movement of people and transportation; industrial and economic activities have been greatly reduced. However, restrictions may be less effective once the outbreak is more widespread.

Early studies showed that SARS-CoV-2 has a pathogenic mechanism analogous to the SARS coronavirus, causing potential damage to vital organs including the heart, lungs, liver, and kidneys (Qiu et al. 2020). Many solid observation evidences confirmed the important role of airborne transmission in the spread of COVID-19 (Van Doremalen et al. 2020; Liu et al. 2020). Also, air pollution has been recognized to exacerbate the transmission and severity of respiratory viral infections such as MERS and SARS (Domingo and Rovira 2020; Singh 2016, Yin and Wunderink 2018). The recent literature described the potential associations between atmospheric pollutants and the outbreak of COVID-19 (Contini and Costabile 2020; Dutheil et al. 2020). In some Northern Italian areas, the high propagation capacity of SARS-CoV-2 may be related to an elevated level of ambient particulate matter (Martelletti and Martelletti 2020). A study in 3122 US counties observed that urban air pollution is likely to increase COVID-19 case fatality and mortality rates (Liang et al. 2020). In China, more viral infections were found in the areas afflicted by high PM, nitrogen dioxide, carbon monoxide, and formaldehyde (Pansini

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and Fornacca 2021). The viruses attach to air pollutants (Reche et al. 2018) and pollutants actually act as the airborne medium of SARS-CoV-2 (Contini and Costabile 2020)

We have long known that acute to chronic exposure to atmospheric pollutants such as $PM_{2.5}$, PM_{10}, nitrogen dioxide (NO), ozone (O_3), sulfur dioxide (SO_2), and carbon monoxide (CO) may cause inflammation with systemic effects, usually in the lung, and induce oxidative stress (Al-Kindi et al. 2020; Bind et al. 2012; Newbury et al. 2019). Past work has suggested that exposure to ambient ground-level atmospheric pollutants, such as $PM_{2.5}$ and O_3, can impose a huge burden on the respiratory and cardiovascular system and thus cause many diseases, including stroke, chronic obstructive pulmonary disease (COPD), myocardial infarction, asthma, and congestive heart conditions (Ho et al. 2019; Lelieveld et al. 2019; Schraufnagel et al. 2019). In in vitro studies, NO_2 has also been reported to correlate with cellular inflammation, bronchial hyperresponsiveness, and increased risk of infection (Koenig 2000). SO_2 may contribute to respiratory symptoms in both healthy patients and patients with potential pulmonary disease, particularly causing changes in airway physiology (Chen et al. 2007).

Since SARS-CoV-2 could survive and remain infectious in aerosols for several hours, and may have a significant effect on human morbidity and mortality throughout the world (Van Doremalen et al. 2020), it is crucial to probe the associations between atmospheric pollutants and COVID-19 incidence. The current studies have evaluated the relationship between the individual pollutants and COVID-19 morbidity or mortality in Italy (Zoran et al. 2020), England (Travaglio et al. 2021), the Netherlands (Andree 2020), and America (Wu et al. 2020). However, few studies have focused on the impact of acute atmospheric pollutant exposure on daily COVID-19 incidence in China. For example, Zhu et al. evaluated cumulative lag effects of ambient airborne pollutants with daily COVID-19 confirmed cases using generalized additive models (Zhu et al. 2020). This paper aims to discuss the impacts of airborne pollutants on COVID-19 morbidity in 41 cities in China (excepting Wuhan), controlling for meteorological variables. To evaluate the impacts of these factors on COVID-19 fast diffusion and fatality, time-series values of selected atmospheric and weather variables over the period January 20−February 29, 2020, together with daily newly COVID-19 confirmed cases have been examined.

Methods

Data collection

We performed a daily time-series study of the correlations between daily newly COVID-19 confirmed cases and air pollutants exposures. The analysis included COVID-19 confirmed cases that occurred among people of the 41 Chinese cities from January 20 to February 29, 2020, of which the cumulative number of which exceeds 100 and the environmental data are available (excepting Wuhan). Since Wuhan with the largest outbreaks and lack of available test may have under-reported cases, we did not take Wuhan into account in our data. Data on daily newly COVID-19 confirmed cases for each city over the study period was obtained from the records kept in the local health commissions and reviewed by the National Health Commission of the People's Republic of China.

Values of daily 24-h average levels of ambient $PM_{2.5}$, PM_{10}, SO_2, NO_2, and CO as well as daily 8-h mean levels of O_3 for each city were obtained from https://www.aqistudy.cn/. We averaged the valid monitoring data of selected airborne pollutants in each city, and obtained the daily mean levels of the pollutants. Meanwhile, we gathered daily average temperature and average relative humidity data for each city from http://pm.kksk.org/ to control for the miscellaneous effects of weather conditions.

Statistical analysis

We assessed the detrimental effects of airborne pollutants on COVID-19 incidence using a two-stage analysis strategy which has been widely applied in multicity time-series research (Chen et al. 2017; Liu et al. 2018). To be specific, the relationship between daily COVID-19 confirmation and pollutants ($PM_{2.5}$, O_3, SO_2, and NO_2) was assessed in separate models for each city using generalized additive Poisson models (GAM) at first stage. At second stage, a random-effects meta-analysis was undertaken to pool the effect estimates at the multicity level. The models were applied to each pollutant separately.

In stage 1, GAM were used in the scope of distributed lag linear modeling framework to approximate city-specific effects of pollutants on COVID-19 morbidity. The model includes the following explanatory variables: (1) log (the number of people newly infected with SARS-CoV-2 every day); (2) the day of the week, which takes into account possible variations within a week; (3) smooth functions of elapsed time to adjust for time varying influences on COVID-19 morbidity; and (4) smooth functions of mean temperature and mean relative humidity on the same day to correct for possible nonlinear and lagged confounding effects of weather conditions. The basic model was shown by Eq. (1):

$$\log E(Y_n) = \beta Z_n + s(time_n, df) + s(TEMP_n, df)$$
$$+ s(RH_n, df) + DOW_n \qquad (1)$$

where $E(Y_n)$ is the expected count of daily newly COVID-19 confirmed cases on day n; β is the regression coefficient; Z_n is

the level of selected pollutants on the day n; time$_n$ is the variable for time with a df natural cubic spline on day n to control for long-term trends; TEMP and RH are the mean temperature and mean relative humidity on day n with a df natural cubic spline; and DOW$_n$ is the variable for the day n. The df value of smooth functions of elapsed time, mean temperature, and mean relative humidity have an effect on parameter estimation and the stability of the model. Using minimum the residual partial autocorrelation function plots (PACF) and lower generalized cross-validation (GCV) values, the appropriate df value was selected (Amini et al. 2019). This model was applied to each city and air pollutants separately. In this stage, we set 14 as maximum lag day of air pollutants because the incubation period of COVID-19 can vary from 2 to 14 days, mostly 3−7 days (Lauer et al. 2020; Lin and Li 2020).

In stage 2, a meta-analysis of random effects was performed to combine the city-specific effect estimates; thus, we obtained the estimates of the immediate effects of air pollutants at the multicity average level. We calculated the delayed and cumulative effects of airborne pollutants on daily new COVID-19 incidence and presented as relative risks (RRs) and corresponding 95% confidence intervals (CIs) associated with a 10-$\mu g/m^3$ rise in levels of the pollutants. The following formulas were used:

$$RR = \exp(\beta) \tag{2}$$

$$RR(95\%CI) = \exp(\beta \pm 1.96 std) \tag{3}$$

where β is the predicted regression coefficient of the model; std is the standard error of the model.

Further to the primary model, we also fitted two-pollutant models which each included adjustment to one other pollutant. The correlation between airborne pollutants concentrations and COVID-19 morbidity was considered valid if there is no significant difference between the effect estimates of the single-pollutant and two-pollutant models. We also conducted stratified analyses to evaluate the feasible the pollutants — COVID-19 incidence association by case location. The location of cases was categorized into cities in Hubei and cities outside Hubei.

All statistical analyses were completed using the R3.6.3 software. Two-sided statistical tests were used, and the statistical significance was set at p-value <0.05.

Results

Figure 1 shows the positions of the 41 cities studied in the PRC and the descriptive statistics on cumulative COVID-19 confirmed cases are shown in Table S1. From January 20 to February 29, 2020, there was a total of 22,970 confirmed cases for COVID-19 in the 41 cities, 16,687 (72.6%) of cases were detected in cities in Hubei, and 6283 (27.4%) were

reported in other provinces. Xiaogan was the highest of the 12 cities in Hubei with about 3451 COVID-19 confirmed cases, while Enshi was the lowest city with 258 confirmed cases. Among the 21 cities outside Hubei included in this study, Chongqing had the highest number of confirmed cases ($n = 576$), whereas the lowest confirmed cases were observed in Shaoyang ($n = 136$). According to the National Bureau of Statistics, despite the population of cities outside Hubei studied (approximately 145.1 million in 2019) is 2.5 times higher than that in cities in Hubei (approximately 59.3 million in 2019), the number of COVID-19 confirmed cases in Hubei is 2.6 times higher than that in cities outside Hubei, which elucidates the weak association between population and COVID-19 spread. Drastic control measures implemented are likely to have helped reduce the spread of the virus by decreasing contact and increasing the physical distance between those who have COVID-19 and those who do not, which may imply the role of case importation in transmission in cities across China (Kraemer et al. 2020).

Table 1 provides a description of all atmospheric and weather variables recorded over the period covered by this research, and the pollutants in each city can be seen in Table S2. The daily mean PM$_{2.5}$ level was 51.0 $\mu g/m^3$, which has exceeded the daily concentration limit set in the Ministry of Ecology and Environment of China on ambient air quality of 35 $\mu g/m^3$ and > 2 times above than the WHO guideline of 25 $\mu g/m^3$. Analogously, the mean value of PM$_{10}$ (62.4 $\mu g/m^3$) was higher than the Chinese standard and the WHO guideline of (50 $\mu g/m^3$). The levels of other pollutants were lower than the Chinese standards and the WHO guideline. The mean values of O$_3$, NO$_2$, SO$_2$, and CO were 75.9 $\mu g/m^3$, 18.8 $\mu g/m^3$, 7.7 $\mu g/m^3$, and 0.9 mg/m^3, respectively. As a response to COVID-19 lockdown and declining economic activity, NO$_2$, SO$_2$, and CO declined sharply, while O$_3$ kept steady or even increased (Chu et al. 2021; Pei et al. 2020). The average daily temperature was 7.6 °C, varying from −22.5 to 23.0 °C (interquartile range of 5.3 °C); for relative humidity, the average was 74.7%, with interquartile range (IQR) of 21.5%. On account of the contagion of COVID-19, most industrial activities were prohibited, and nearly all avoidable outdoor human activities stopped during the study period. However, severe air pollution episodes still occurred in China, especially in the North China Plain, illustrating large emissions reduction in transportation and industries may not improve severe air pollution, since unfavorable meteorology is inevitable (Wang et al. 2020b).

Spearman correlation coefficients for pollutant and meteorological variable pairs for the study period are given in Table 2. Across the study period, PM$_{2.5}$ concentrations were closely correlated with PM$_{10}$ concentrations (Pearson's correlation coefficient $r = 0.793$), but less so with CO ($r = 0.563$) and even slightly correlated with NO$_2$ ($r = 0.414$), SO$_2$ (0.365), and O$_3$ ($r = 0.196$). O$_3$ was weakly correlated with

Fig. 1 Cumulative confirmed cases in 41 Chinese cities from January 20 to February 29, 2020
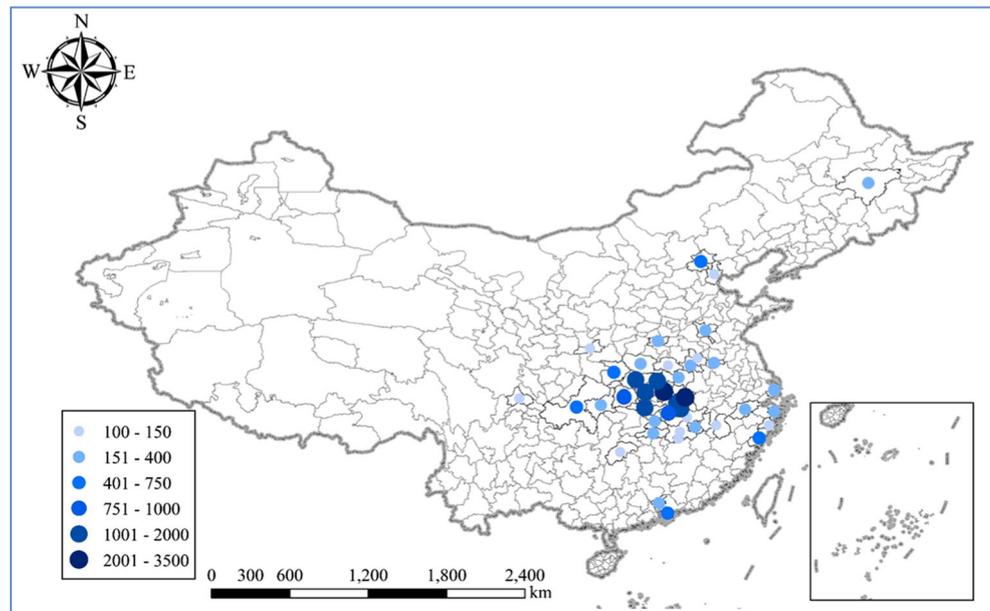
other pollutants, whereas the highest correlation coefficient of 0.196 with $PM_{2.5}$. For other pollutants (NO_2, SO_2, and CO), the pattern of correlations was broadly analogous to O_3. In addition, temperature and relative humidity were negatively correlated with all pollutants. Since the Spearman rank-order correlation analyses indicated a high correlation between temperature and relative humidity and several air pollutants, we incorporated these meteorological factors into the models to assess their underlying confounding effects.

Figure 2 gives the pooled relative risk in daily newly COVID-19 confirmed cases (and 95% CIs) associated with a 10-$\mu g/m^3$ rise in airborne pollutants for single-day lags from lag of 0 to 7. In the main model for $PM_{2.5}$, each 10 $\mu g/m^3$ elevation of exposure to $PM_{2.5}$ was observed to coincide a small increase in daily newly COVID-19 confirmed cases in the same day (lag 0), with RR (95% CI) of 1.005 (1.001, 1.011). For longer lags, the RR increased gradually until lag 4, reaching a maximum of 1.010 (1.004, 1.016) before

decreasing. We observed positive associations between O_3 and daily newly COVID-19 confirmed cases from lag of 0 to 5 with the strongest RR (95% CI) of 1.011 (1.007, 1.014) at lag 0. Fewer remarkable findings were observed in the model for SO_2, with significant positive associations of SO_2 and daily newly COVID-19 confirmed cases at lag 0 [1.052 (1.022, 1.083)], lag 1 [1.032 (1.001, 1.063)], and lag 3 [1.044 (1.007, 1.082)]. In addition, there was no association between increases in NO_2 and COVID-19 outcomes at any single-day lag. Generally, associations with daily newly COVID-19 confirmed cases tended to be positive for single-day lags, and the RRs were slightly higher for $PM_{2.5}$ than O_3, both less than SO_2.

Since prominent correlations between atmospheric pollutants and COVID-19 incidence were observed at several moving averages lags (Table 3), the cumulative effects were further examined. City-specific and the strongest pooled effect estimates of daily newly COVID-19 confirmed cases with increases in the 14−day average of $PM_{2.5}$ and NO_2 are presented in Fig. 3a and 3b. $PM_{2.5}$ and NO_2 significantly increased the risk of daily COVID-19 incidence at lag 0−14 [1.050 (1.028, 1.073) and 1.094 (1.028, 1.164), respectively]. For individual cities, the city-specific estimates of the relative risks in daily newly COVID-19 confirmed cases varied greatly, ranging from 0.230 (for Bozhou) to 1.386 (for Guangzhou) in $PM_{2.5}$ concentration and ranging from 0.578 (for Tianjin) to 3.880 (for Changsha) in NO_2 concentration. As shown in Fig. 3c, each 10 $\mu g/m^3$ increase in O_3 was associated with daily newly COVID-19 confirmed cases in lag 0−1 and the pooled RR (95% CI) was 1.011 (1.007, 1.015). In the city level, the highest RRs of O_3 were observed in Jingmen, Ezhou, and Taizhou, while the lowest RRs were observed in Shaoyang and Jiujiang.

Table 1 Descriptive statistics of daily airborne pollutants and weather variables in 41 Chinese cities from January 20 to February 29, 2020

Variables	Min	Q25	Median	Q75	Max	Mean	SD
$PM_{2.5}$ ($\mu g/m^3$)	2.0	26.0	42.0	65.0	270.0	51.0	35.9
PM_{10} ($\mu g/m^3$)	5.0	34.0	53.0	80.0	338.0	62.4	39.8
NO_2 ($\mu g/m^3$)	3.0	11.0	16.0	23.0	116.0	18.8	11.8
SO_2 ($\mu g/m^3$)	2.0	5.0	6.0	9.0	56.0	7.7	5.3
CO (mg/m^3)	0.2	0.6	0.8	1.0	2.3	0.9	0.3
O_3 ($\mu g/m^3$)	5.0	58.0	76.0	94.0	150.0	75.9	23.4
Temperature (°C)	−22.5	5.0	7.6	10.3	23.0	7.6	5.5
Relative humidity (%)	9.3	65.2	75.8	86.8	100	74.7	15.2

Table 2 Spearman correlations between airborne pollutants and meteorological variables in all cities during the study period

| Factors	$PM_{2.5}$	PM_{10}	NO_2	SO_2	CO	O_3	TEMP
PM_{10}	0.793**						
NO_2	0.414**	0.331*					
SO_2	0.365*	0.244	0.355*				
CO	0.563**	0.390*	0.302	0.364*			
O_3	0.196	0.193	0.056	0.068	-0.118		
TEMP	-0.834**	-0.677**	-0.328*	-0.307	-0.576**	-0.278	
RH	-0.388*	-0.327*	-0.448*	-0.012	-0.155	-0.531**	0.452**

Note: TEMP and RH indicate ambient temperature and relative humidity, respectively; * and ** indicate $P < 0.05$ and $P < 0.01$, respectively

We analyzed two-pollutant models for air pollutants to test interdependences of the pollutants. In such models with $PM_{2.5}$ as one thereof, the RRs were generally unchanged or increased except adjusting for PM_{10}, compared with the value in the single-pollutant models (Fig. 4a). Similarly, in models with O_3 as one of the pollutants, the RRs were generally unchanged or slightly increased compared with its value in the single-pollutant model (Fig. 4b). However, the associations between SO_2 (Fig. 4c) or NO_2 (Fig. 4d) and risk of COVID-19 incidence were no longer significant at some lags in two-pollutant models (except for O_3 and NO_2). The effects of SO_2 were stronger after adjusting for NO_2 but were non-significant after adjusting for other pollutants ($PM_{2.5}$, PM_{10}, O_3, and CO). Each 10 μg/m³ rise in concentration of SO_2 at lag 0 coincided

with an increase of 2.6% [95% CI (1.5, 3.9)] risk of COVID-19 incidence after adjusting for NO_2. Similarly, each 10-μg/m³ rise in concentration of NO_2 at lag 0−14 coincided with an exacerbation of 0.6% [95% CI (−0.9, 2.3)] risk of COVID-19 incidence after adjusting for O_3. Overall, $PM_{2.5}$ had the most robust association with daily newly COVID-19 confirmed cases when adjusted for confounding by other pollutants.

Stratified analysis by regions showed that relative risks in cities in Hubei were larger than those in cities outside Hubei because Hubei was the province with the most severe COVID-19 outbreak (Table S3). In cities in Hubei, the associations remained positive and significant for most pollutants. Notably, positive associations were also founded for O_3 at lag 0−1 for cities outside Hubei, while no prominent effects were

Fig. 2 Pooled relative risks of daily newly COVID-19 confirmed cases associated with (**a**) $PM_{2.5}$, (**b**) O_3, (**c**) SO_2, and (**d**) NO_2. Note: Error bars are 95% CIs
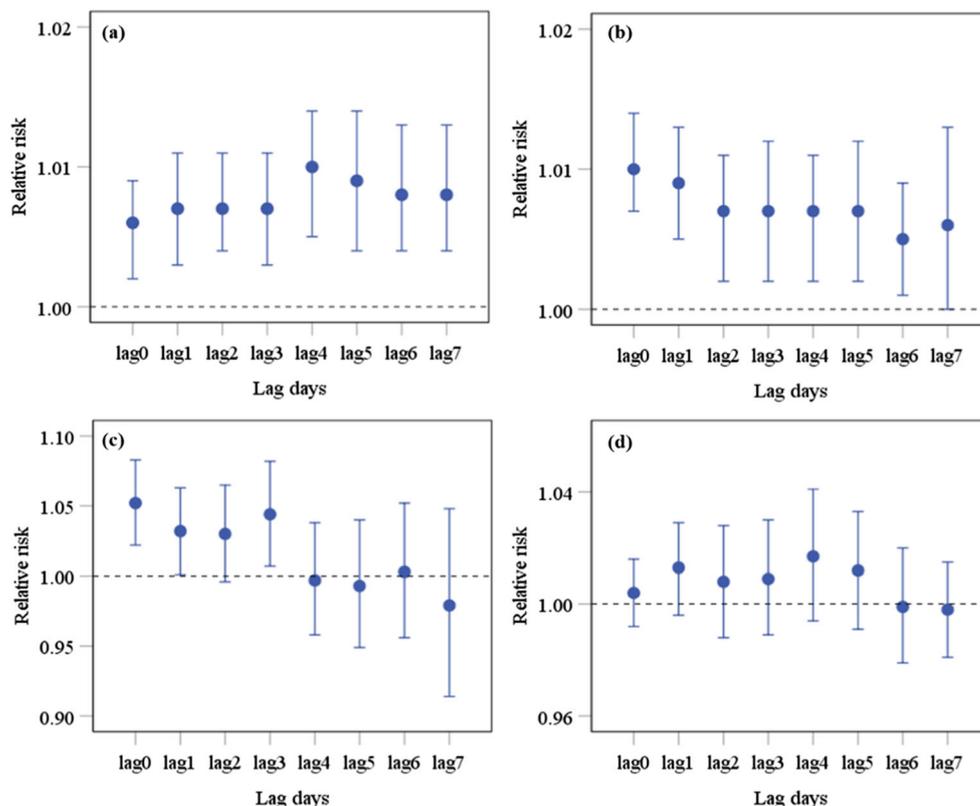
Table 3 Cumulative effect estimates on different lag days of airborne pollutants in all cities

Lag days	RR (95% CI)			
Pollutants	PM$_{2.5}$	O$_3$	SO$_2$	NO$_2$
Lag 0	1.006 (1.002–1.009)	1.010 (1.007–1.014)	1.052 (1.022–1.083)	1.004 (0.992–1.016)
Lag 1	1.007 (1.003–1.011)	1.009 (1.005–1.013)	1.032 (1.001–1.063)	1.013 (0.996–1.029)
Lag 2	1.007 (1.004–1.011)	1.007 (1.002–1.011)	1.030 (0.996–1.065)	1.008 (0.988–1.028)
Lag 3	1.007 (1.003–1.011)	1.007 (1.002–1.012)	1.044 (1.007–1.082)	1.009 (0.989–1.030)
Lag 4	1.010 (1.005–1.014)	1.007 (1.002–1.011)	0.997 (0.958–1.038)	1.017 (0.994–1.041)
Lag 5	1.009 (1.004–1.014)	1.007 (1.002–1.012)	0.993 (0.949–1.040)	1.012 (0.991–1.033)
Lag 6	1.008 (1.004–1.013)	1.005 (1.001–1.009)	1.003 (0.956–1.052)	0.999 (0.979–1.020)
Lag 7	1.008 (1.004–1.013)	1.006 (1.000–1.013)	0.979 (0.914–1.048)	0.998 (0.981–1.015)
Lag 0–1	1.003 (1.000–1.007)	1.011 (1.007–1.015)	0.999 (0.961–1.038)	0.995 (0.984–1.007)
Lag 0–3	1.005 (1.000–1.011)	1.009 (1.004–1.015)	1.039 (0.982–1.100)	1.004 (0.991–1.018)
Lag 0–7	0.998 (0.988–1.007)	1.009 (1.001–1.017)	0.938 (0.852–1.033)	0.986 (0.968–1.006)
Lag 0–14	1.050 (1.028–1.073)	1.021 (0.994–1.049)	0.812 (0.632–1.043)	1.094 (1.028–1.164)

observed for other pollutants. Overall, the maximum cumulative RRs were found in cities in Hubei, which were 1.094 (95% CI: 1.064, 1.124) for PM$_{2.5}$ at lag 0–14; 1.016 (95% CI: 1.011, 1.021) for O$_3$ at lag 0–1; 1.080 (95% CI: 1.045, 1.117) for SO$_2$ at lag 0; and 1.213 (95% CI: 1.085, 1.356) for NO$_2$ at lag 0–14, respectively. Our result is consistent with the findings of the study by Wang et al., who found that the correlations between COVID-19 and ambient PM were stronger for cities inside Hubei than those outside Hubei, and had the highest RR at lag 0–14 for PM$_{2.5}$ (Wang et al. 2020a).
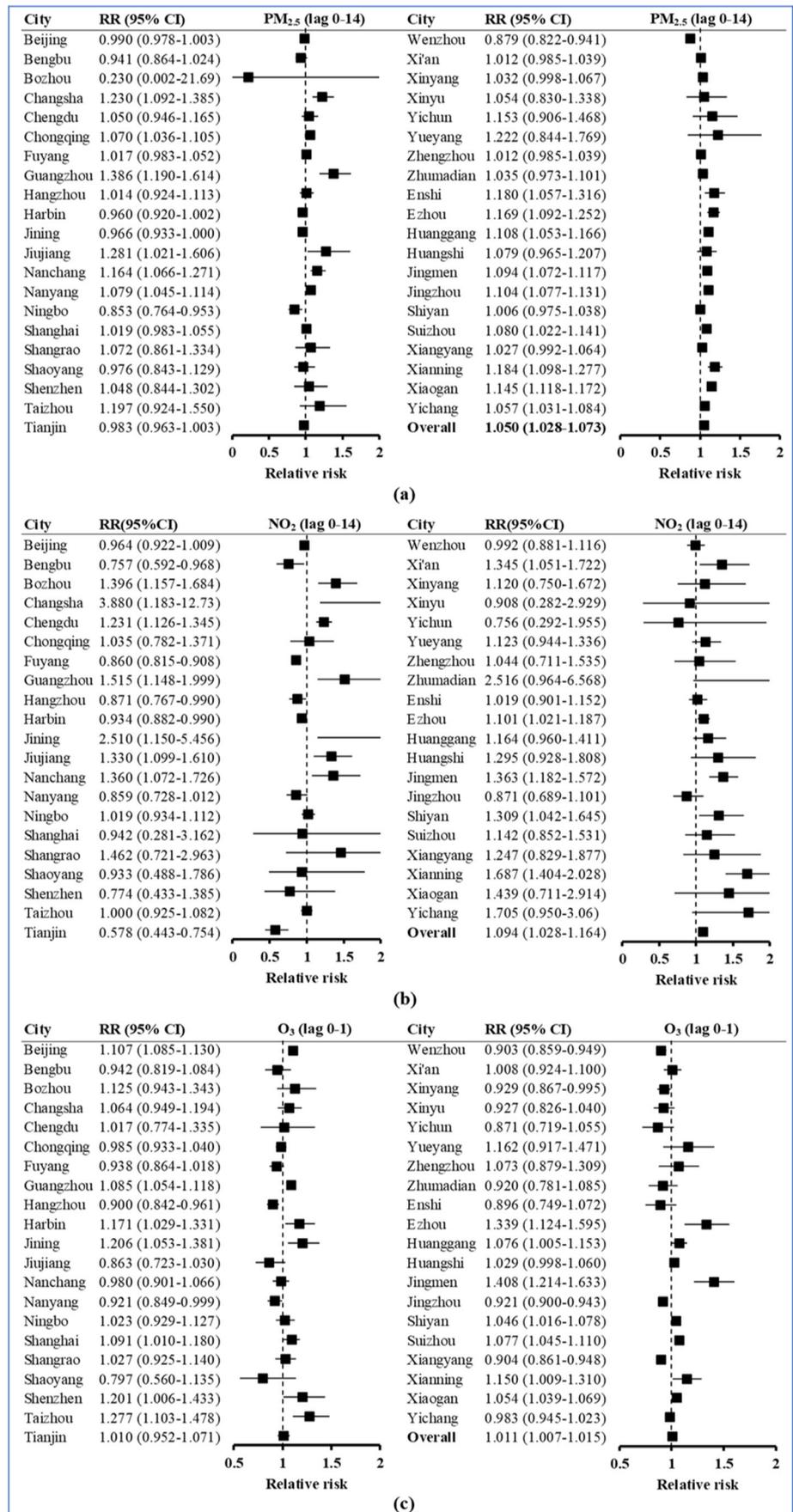
Discussion

To date, epidemiologic evidence regarding the underlying relationships of ambient atmospheric pollutants on COVID-19 outbreak is insufficient. In this study, we analyzed multisite data on airborne pollutants and daily newly COVID-19 confirmed cases in 41 Chinese cities, although Wuhan (the worst affected city of China) was not included. We observed modest correlations between daily newly COVID-19 confirmed cases and acute exposure to NO$_2$, and to a lesser extent, with PM$_{2.5}$, O$_3$, and SO$_2$. In the analysis of main models for pollutants, we observed that the RRs (95% CI) for the associations between

daily newly COVID-19 confirmed cases and PM$_{2.5}$, O$_3$, SO$_2$, and NO$_2$ were 1.050 (1.028, 1.073) at lag 0–14, 1.011 (1.007, 1.015) at lag 0–1, 1.052 (1.022, 1.083) at lag 0, and 1.094 (1.028, 1.164) at lag 0–14 per each 10-μg/m^3 increment, respectively. The finding suggests that air pollution is an important factor in COVID-19 infection. To be specific, our results indicate that an air pollution with high PM$_{2.5}$, O$_3$, SO$_2$, and NO$_2$ likely favor the COVID-19 transmission.

Some research has shown that acute exposure to air pollutants is correlated with COVID-19 prevalence or fatality. Study conducted carried out in 120 cities across China revealed increases in daily counts of confirmed cases of 2.24%, 4.76%, −7.79%, and 6.94% each 10-μg/m^3 increment in PM$_{2.5}$, O$_3$, SO$_2$, and NO$_2$ as well (Zhu et al. 2020). Comparing our results to the aforementioned analysis, our findings for SO$_2$ and COVID-19 incidence are completely opposite to their results. It is not clear why the correlations between air pollution and daily COVID-19 morbidity would be different in our study from associations reported by different studies, but it might be explained by factors such as the different scale of the study city and amount of data, fewer considered meteorological variables, and relative higher concentrations and big fluctuation of pollutants during study

Fig. 3 Forest plot for cumulative RRs (95% CI) of daily newly COVID-19 confirmed cases associated with a 10-ug/m^3 increase in (**a**) PM$_{2.5}$ at lag 1-14; (**b**) NO$_2$ at lag 0-14; (**c**) O$_3$ at lag 0–1

City	RR (95% CI)	PM$_{2.5}$ (lag 0-14)	City	RR (95% CI)	PM$_{2.5}$ (lag 0-14)
Beijing	0.990 (0.978-1.003)		Wenzhou	0.879 (0.822-0.941)	
Bengbu	0.941 (0.864-1.024)		Xi'an	1.012 (0.985-1.039)	
Bozhou	0.230 (0.002-21.69)		Xinyang	1.032 (0.998-1.067)	
Changsha	1.230 (1.092-1.385)		Xinyu	1.054 (0.830-1.338)	
Chengdu	1.050 (0.946-1.165)		Yichun	1.153 (0.906-1.468)	
Chongqing	1.070 (1.036-1.105)		Yueyang	1.222 (0.844-1.769)	
Fuyang	1.017 (0.983-1.052)		Zhengzhou	1.012 (0.985-1.039)	
Guangzhou	1.386 (1.190-1.614)		Zhumadian	1.035 (0.973-1.101)	
Hangzhou	1.014 (0.924-1.113)		Enshi	1.180 (1.057-1.316)	
Harbin	0.960 (0.920-1.002)		Ezhou	1.169 (1.092-1.252)	
Jining	0.966 (0.933-1.000)		Huanggang	1.108 (1.053-1.166)	
Jiujiang	1.281 (1.021-1.606)		Huangshi	1.079 (0.965-1.207)	
Nanchang	1.164 (1.066-1.271)		Jingmen	1.094 (1.072-1.117)	
Nanyang	1.079 (1.045-1.114)		Jingzhou	1.104 (1.077-1.131)	
Ningbo	0.853 (0.764-0.953)		Shiyan	1.006 (0.975-1.038)	
Shanghai	1.019 (0.983-1.055)		Suizhou	1.080 (1.022-1.141)	
Shangrao	1.072 (0.861-1.334)		Xiangyang	1.027 (0.992-1.064)	
Shaoyang	0.976 (0.843-1.129)		Xianning	1.184 (1.098-1.277)	
Shenzhen	1.048 (0.844-1.302)		Xiaogan	1.145 (1.118-1.172)	
Taizhou	1.197 (0.924-1.550)		Yichang	1.057 (1.031-1.084)	
Tianjin	0.983 (0.963-1.003)		**Overall**	**1.050 (1.028-1.073)**	

Relative risk (0 0.5 1 1.5 2)   Relative risk (0 0.5 1 1.5 2)

(a)

City	RR(95%CI)	NO$_2$ (lag 0-14)	City	RR(95%CI)	NO$_2$ (lag 0-14)
Beijing	0.964 (0.922-1.009)		Wenzhou	0.992 (0.881-1.116)	
Bengbu	0.757 (0.592-0.968)		Xi'an	1.345 (1.051-1.722)	
Bozhou	1.396 (1.157-1.684)		Xinyang	1.120 (0.750-1.672)	
Changsha	3.880 (1.183-12.73)		Xinyu	0.908 (0.282-2.929)	
Chengdu	1.231 (1.126-1.345)		Yichun	0.756 (0.292-1.955)	
Chongqing	1.035 (0.782-1.371)		Yueyang	1.123 (0.944-1.336)	
Fuyang	0.860 (0.815-0.908)		Zhengzhou	1.044 (0.711-1.535)	
Guangzhou	1.515 (1.148-1.999)		Zhumadian	2.516 (0.964-6.568)	
Hangzhou	0.871 (0.767-0.990)		Enshi	1.019 (0.901-1.152)	
Harbin	0.934 (0.882-0.990)		Ezhou	1.101 (1.021-1.187)	
Jining	2.510 (1.150-5.456)		Huanggang	1.164 (0.960-1.411)	
Jiujiang	1.330 (1.099-1.610)		Huangshi	1.295 (0.928-1.808)	
Nanchang	1.360 (1.072-1.726)		Jingmen	1.363 (1.182-1.572)	
Nanyang	0.859 (0.728-1.012)		Jingzhou	0.871 (0.689-1.101)	
Ningbo	1.019 (0.934-1.112)		Shiyan	1.309 (1.042-1.645)	
Shanghai	0.942 (0.281-3.162)		Suizhou	1.142 (0.852-1.531)	
Shangrao	1.462 (0.721-2.963)		Xiangyang	1.247 (0.829-1.877)	
Shaoyang	0.933 (0.488-1.786)		Xianning	1.687 (1.404-2.028)	
Shenzhen	0.774 (0.433-1.385)		Xiaogan	1.439 (0.711-2.914)	
Taizhou	1.000 (0.925-1.082)		Yichang	1.705 (0.950-3.06)	
Tianjin	0.578 (0.443-0.754)		**Overall**	**1.094 (1.028-1.164)**	

Relative risk (0 0.5 1 1.5 2)   Relative risk (0 0.5 1 1.5 2)

(b)

City	RR (95% CI)	O$_3$ (lag 0-1)	City	RR (95% CI)	O$_3$ (lag 0-1)
Beijing	1.107 (1.085-1.130)		Wenzhou	0.903 (0.859-0.949)	
Bengbu	0.942 (0.819-1.084)		Xi'an	1.008 (0.924-1.100)	
Bozhou	1.125 (0.943-1.343)		Xinyang	0.929 (0.867-0.995)	
Changsha	1.064 (0.949-1.194)		Xinyu	0.927 (0.826-1.040)	
Chengdu	1.017 (0.774-1.335)		Yichun	0.871 (0.719-1.055)	
Chongqing	0.985 (0.933-1.040)		Yueyang	1.162 (0.917-1.471)	
Fuyang	0.938 (0.864-1.018)		Zhengzhou	1.073 (0.879-1.309)	
Guangzhou	1.085 (1.054-1.118)		Zhumadian	0.920 (0.781-1.085)	
Hangzhou	0.900 (0.842-0.961)		Enshi	0.896 (0.749-1.072)	
Harbin	1.171 (1.029-1.331)		Ezhou	1.339 (1.124-1.595)	
Jining	1.206 (1.053-1.381)		Huanggang	1.076 (1.005-1.153)	
Jiujiang	0.863 (0.723-1.030)		Huangshi	1.029 (0.998-1.060)	
Nanchang	0.980 (0.901-1.066)		Jingmen	1.408 (1.214-1.633)	
Nanyang	0.921 (0.849-0.999)		Jingzhou	0.921 (0.900-0.943)	
Ningbo	1.023 (0.929-1.127)		Shiyan	1.046 (1.016-1.078)	
Shanghai	1.091 (1.010-1.180)		Suizhou	1.077 (1.045-1.110)	
Shangrao	1.027 (0.925-1.140)		Xiangyang	0.904 (0.861-0.948)	
Shaoyang	0.797 (0.560-1.135)		Xianning	1.150 (1.009-1.310)	
Shenzhen	1.201 (1.006-1.433)		Xiaogan	1.054 (1.039-1.069)	
Taizhou	1.277 (1.103-1.478)		Yichang	0.983 (0.945-1.023)	
Tianjin	1.010 (0.952-1.071)		**Overall**	**1.011 (1.007-1.015)**	

Relative risk (0.5 1 1.5 2)   Relative risk (0.5 1 1.5 2)

(c)

period. Furthermore, uncontrolled residual confounding or chance as possible explanations should also be considered.

Moreover, several multicity studies about individual pollutants have also been reported. A multicity study (Wang et al. 2020a) in 72 cities (excluding Wuhan) reported a summary estimate for daily COVID-19 confirmed cases of 1.016 (1.015, 1.018) per 10 μg/m³ rise in the level of $PM_{2.5}$ at lag 0 −14. A national American analysis observed a significant increment of 7.1% (1.2%, 13.4%) and 11.2% (3.4%, 19.5%) in COVID-19 case fatality and mortality per IQR in NO_2 (Liang et al. 2020). In England, studies also reported increases in COVID-19 incidence in addition to mortality alongside rises in NOx or SO_2, meaning that regional variations in the two pollutants may predict the numbers of COVID-19 cases and death (Travaglio et al. 2021). A study conducted in 120 Chinese cities (excluding Wuhan) by multivariate negative binomial regression implicated that the increased number of COVID-19 confirmed cases was accompanied by acute exposure to elevated levels of $PM_{2.5}$ and O_3 and reduced levels of SO_2 (Zhou et al. 2021). It should be noted that some studies summarized above reported a negative significant association between SO_2 and COVID-19 incidence; this may be due to the relatively low levels of SO_2. Our two-pollutant models found a non-significant association between SO_2 and COVID-19 incidence after adjusting for other pollutants such as $PM_{2.5}$ and O_3, suggesting that the mechanism of the interaction between SO_2 and other pollutants should be explored in future studies.

Whether the observed correlations between air pollutants are independent of other pollutants is a significant issue for air quality control and health risk assessment. In the present study, although the degree of the correlation between $PM_{2.5}$ and O_3 has changed in two-pollutant models, the correlation between the two remained mostly significant, which provides evidence supporting the independent health impacts of $PM_{2.5}$ and O_3. It is remarkable that the estimates of relative risk of COVID-19 incidence per 10-μg/m³ rise with the decrease of $PM_{2.5}$ levels have no significant effects, a finding that may reflect the close correlations of $PM_{2.5}$ with PM_{10} caused by similar sources. As for SO_2, the two-pollutant models indicated that the estimated effect of SO_2 on COVID-19 incidence was attributable to confounding by other air pollutants (except NO_2). In addition, although NO_2 are key O_3 precursors (Naja and Lal 2002), the two-pollutant model indicated that NO_2 has a strong and independent influence on COVID-19 incidence, meaning that the influence of NO_2 may not be mediated by O_3.

Previous experiments on coronaviruses in controlled conditions show that it can survive at around 4 °C and a relative humidity of 20−80%, and inactivates rapidly above 20 °C (Casanova et al. 2010). It seems that specific climate conditions, especially ambient temperature and humidity, modulate the survival and spread of SARS-CoV-2. A systematic review suggested that warm and humid climates seem to weaken the transmission of COVID-19, while the certainty of the evidence produced was graded as low (MecenasI et al. 2020). Analogously, a time-series analysis in mainland China found with a relative humidity of 67−85.5%, every 1 °C elevation in temperature resulted in a decrease in the daily confirmed cases of 36−57% (Qi et al. 2020). Contrary to the above conclusion, a study across China suggests that the spread speed of the COVID-19 outbreak is independent of temperature, while the temperature dependence of the propagation reported in earlier related work was likely to be an artifact since the temperature dependence blurred with a prevailing zonal pattern of

Fig. 4 Pooled RRs (95% CI) of daily newly COVID-19 confirmed cases associated with a 10-ug/m³ rise in (a) $PM_{2.5}$ at lag 1-14; (b) O_3 at lag 0-1; (c) SO_2 at lag 0, and (d) NO_2 at lag 0-14, with and without adjustment for other airborne pollutants
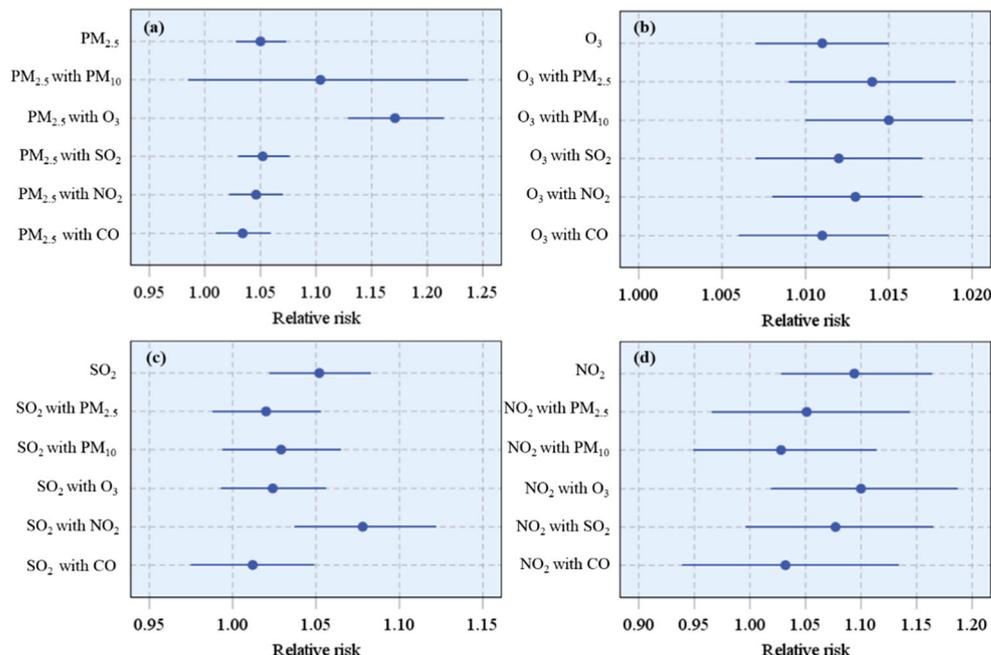
spread across the north-temperature zone, reflecting the primary patterns of human activities (Jamil et al. 2020). In addition, ultraviolet photons have also been considered to play the possible role in the modulation of COVID-19 epidemiology (Nicastro et al. 2020).

The underlying pathophysiological mechanism for developing COVID-19 is perplexing and very few toxicological literature on biological plausibility have been published. It has been reported (Frontera et al. 2020) that chronic exposure to $PM_{2.5}$ leads to overexpression of alveolar angiotensin-converting enzyme 2 (ACE-2) receptor, which is crucial in protecting the lung from air pollution (Alifano et al. 2020; Lin et al. 2018), as well as the main receptor of SARS-CoV-2 (Zhou et al. 2020). This may increase the viral load in a body exposed to pollutants, thus occupying ACE-2 receptors and weakening host defenses. Furthermore, exposure to NO_2 may bring a second hit after exposure to $PM_{2.5}$, causing severe forms of SARS-CoV-2 to appear in the lungs where ACE-2 depleted, leading to worse results. The current toxicology literature suggests that exposure to ambient ground-level ozone is pertinent to the emergence of respiratory diseases such as asthma, influenza, and SARS (Zoran et al. 2020). O_3 is a potential oxidizer and may induce oxidative stress, which may harm the immune systems and organs such as the lung and heart, by changing the host's resistance to viral and bacterial infections (Ciencewicki and Jaspers 2007). A study in northern Italy (Conticini et al. 2020) has shown that an over-expression of interleukin-8(IL-8), interleukin-7 (IL-17), and tumor necrosis factor-α (TNF-α), induced by O_3, contributes to prolonged systemic and respiratory system inflammation and eventually leads to an innate immune system hyperactivation. Compared to $PM_{2.5}$ and O_3, fewer research has studied the biological pathways of harmful effects of NO_2 and SO_2. The virological explanation might be that NO_2 causes the reactions of components in the airway surface fluids (ASF) of the respiratory tract and lungs, resulting in highly reactive proteins and lipid oxidation products that can cause inflammation by subsequently damaging epithelial cells through secondary reactions (Gamon and Wille 2016). Another study by Chauhan et al. (2003) has done research on the relation between NO_2 exposure and respiratory disease caused by proven respiratory viral infections including coronavirus.

Our study indicates that air pollutants are important in analyzing the pathogenesis of COVID-19 and that the effect of air pollutants on the disease deserves more attention. It is also subject to some limitations. Primarily, the correlations between air pollutants and COVID-19 confirmation were affected by many other factors, such as strict prevention measure and population migration. Secondly, as the definitions of COVID-19 cases changed at different stages of the epidemic, the number of COVID-19 confirmed cases may be affected. Next, we only focused on cities across China where the cumulative COVID-19 confirmed cases exceed 100 and the environmental data are available (except Wuhan) during the study period, so the estimate of air pollutant effects cannot be generalized to other countries. Finally, stratified analyses by gender or age on were not analyzed in our study due to a lack of detailed information on each infectious case. Future studies should be developed to overcome these limitations, and the mechanisms of the impact on COVID-19 risk deserve further study.

Conclusion

In conclusion, our data show that daily COVID-19 confirmed cases are positively correlated with short-term exposure to atmospheric pollutants, such as $PM_{2.5}$, O_3, SO_2, and NO_2 in 41 cities across China, and the robust associations between $PM_{2.5}$ or O_3 and daily newly COVID-19 confirmed cases were not complicated by the other air contaminants assessed. Exposure to NO_2 for the 14-day average concentration exhibited the most obvious cumulative lagged effect on daily COVID-19 confirmed cases. These results can lay the foundation for the study of correlations between airborne pollutant exposure and potential health risks of COVID-19. The effects of atmospheric pollutants on COVID-19 incidence exhibited a positive variation, suggesting that not only extensive public health control measures but also the lag effect of ambient air pollutants should be considered for curbing COVID-19 infection.

Declarations

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