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Comparisons of Combined Oxidant Capacity and Redox-Weighted Oxidant Capacity in Their Association with Increasing Levels of COVID-19 Infection

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Abstract: Background: Ozone (O_3) and nitrogen dioxide (NO_2) are substances with oxidizing ability in the atmosphere. Only considering the impact of a single substance is not comprehensive. However, people's understanding of "total oxidation capacity" (O_x) and "weighted average oxidation" ($O_x{}^{wt}$) is limited. Objectives: This investigation aims to assess the impact of O_x and $O_x{}^{wt}$ on the novel coronavirus disease (COVID-19). We also compared the relationship between the different calculation methods of O_x and $O_x{}^{wt}$ and the COVID-19 infection rate. Method: We recorded confirmed COVID-19 cases and daily pollutant concentrations (O_3 and NO_2) in 34 provincial capital cities in China. The generalized additive model (GAM) was used to analyze the nonlinear relationship between confirmed COVID-19 cases and O_x and $O_x{}^{wt}$. Result: Our results indicated that the correlation between O_x and COVID-19 was more sensitive than $O_x{}^{wt}$. The hysteresis effect of O_x and $O_x{}^{wt}$ decreased with time. The most obvious statistical data was observed in Central China and South China. A 10 μg m^{-3} increase in mean O_x concentrations were related to a 23.1% (95%CI: 11.4%, 36.2%) increase, and a 10 μg m^{-3} increase in average $O_x{}^{wt}$ concentration was related to 10.7% (95%CI: 5.2%, 16.8%) increase in COVID-19. In conclusion, our research results show that O_x and $O_x{}^{wt}$ can better replace the single pollutant research on O_3 and NO_2, which is used as a new idea for future epidemiological research.

Keywords: oxidants; COVID-19; air pollution; GAM; ozone; nitrogen dioxide

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1. Introduction

Previous epidemiological studies have shown that the components of the atmosphere are complex and diverse, and many of them have oxidizing properties, for instance, ozone (O_3) and nitrogen dioxide (NO_2), which affect the normal operation of the respiratory system [1]. In addition, some studies have also confirmed that the effects of O_3 or NO_2 on the respiratory system and cardiovascular diseases can be observed [2,3]. However, these studies have certain limitations. Ozone (O_3) is unstable in the atmosphere and reacts with NO_2 and other oxides of nitrogen under light conditions to form secondary pollutants that are harmful to the human body [4]. Their relationships are as follows:

$$NO_2 + \text{UV photons } (hv) \rightarrow O + NO \tag{1}$$

$$O + O_2 \rightarrow O_3 \tag{2}$$

$$O_3 + NO \rightarrow NO_2 \tag{3}$$

The instability between O_3 and NO_2 makes it impossible to accurately determine their respective contributions to human health.

Previous research targeted the calculation of the dual pollutant model but ignored the chemical conversion between NO_2 and O_3 [5,6]. Only a few reports pay attention to the potential risks to human health caused by the dynamic changes between NO_2 and O_3 [7]. In the above formula, the conversion between NO_2 and O_3 is rapid and continuous [6]. Under normal circumstances, the sum of NO_2 and O_3 is regarded as a constant by us, so we define the "total oxidation capacity" as O_x [8]. Chardon et al. used the O_x method to calculate and quantify the correlation between ozone concentration and respiratory diseases [9]. However, this method is still imperfect. Ozone and NO_2 do not have equivalent oxidizing power. Ozone is an oxidant with stronger oxidizing power than NO_2, so the concept of weighted average oxidation ($O_x{}^{wt}$) is introduced [10]. The improved method can more accurately determine the redox effect produced by the combined action of O_3 and NO_2. Values of $O_x{}^{wt}$ were used in previous studies to explore the impact of environmental factors on COPD [11].

In previous literature reports, the relationship between O_3 and acute respiratory infection (ARI) and upper respiratory tract inflammation (URTI) has been clearly observed, which helps to assess the potential risks of O_3 to the human body [12]. A small part of the formation of NO_2 comes from nature, which is mainly due to fuel combustion and automobile exhaust emissions [13]. Therefore, an experiment that selected people living next to the highway as the research object found that for every 17.9 ppb (2 SD) increase in NO_x, the probability of having a forced vital capacity (FVC) defect increased by 1.6% (p = 0.005) [14]. In addition, the discussion that the joint action of NO_2 and O_3 can cause a series of respiratory diseases has also been mentioned in the previous literature [15]. However, the acute respiratory infectious disease caused by novel coronavirus disease (COVID-19) that broke out at the end of 2019 [16] has swept the world in a short period of time and has brought a great impact on production and, more generally, life in human society [17]. Most of the patients showed symptoms of fever, dry cough, and fatigue. Critically ill patients have symptoms of dyspnea, multiple organ failure and even death [18]. And COVID-19 has been confirmed to be spread through three methods: direct transmission, aerosol transmission and contact transmission [19]. Aerosol transmission may be a result of the fact that droplets mix in the air to form aerosols and cause infection after inhalation. Therefore, we have reason to guess that changes in NO_2 and O_3 concentrations will have an influence on the spread of COVID-19.

In this study, we studied the causes of the global spread of COVID-19 from an environmental perspective. We selected the oxidative air pollutants O_3 and NO_2 as the study objects and performed a traditional analysis of the single-pollutant model. Also, we optimized the traditional method and the O_x and $O_x{}^{wt}$ methods are used to evaluate the COVID-19 infection rate. In addition, this study also reflects the lagged effects of O_3 and NO_2 on COVID-19 to assess the adverse health effects. This study is expected to be of great importance for comprehending the oxidative capacity of dual pollutants and human health prediction.

2. Materials and Methods

2.1. Study Location

This study selected 34 provincial capital cities in China from 73°33′ to 135°05′ east longitude and 3°51′ to 53°33′ north latitude. The selected 34 cities have developed economies, high population densities, and complete medical facilities, which will help to obtain more complete data. In addition, these cities have a wide range of regional distribution, so the statistical data has a certain degree of representativeness.

2.2. Data Collection

We collected data on daily confirmed cases of COVID-19 in 34 provincial capital cities in China from 1 September 2020 to 31 December 2020, which were obtained from the National Health Commission of China "COVID-19 cases. Available online: http://www.nhc.gov.cn (accessed on 1 September 2020)". Data on air pollutants (O_3 and NO_2) were obtained from the online air quality monitoring and analysis platform "Pollutant concentration. Available online: https://www.aqistudy.cn (accessed on 1 September 2020)".

2.3. Statistical Analysis

Previous reports have shown that environmental pollutants play a great role in respiratory diseases [20,21]. The Generalized Additive Model (GAM) can help analyze the possible link between environmental pollutants and COVID-19 [22,23]. We analyzed the potential impact of a single pollutant. However, the two pollutants selected in this study have oxidative properties and cannot exist stably in the air [24]. Therefore, the "total oxidation capacity" concept O_x and the "weighted average oxidation" concept $O_x{}^{wt}$ are introduced in the analysis. The specific formula is expressed as:

$$O_x = O_3 + NO_2$$

$$O_x{}^{wt} = (1.07volts\ (V) \times NO_2 + 2.075volts\ (V) \times O_3)/3.145$$

To study the short-term effects of O_3 and NO_2 on COVID-19 more comprehensively, we analyzed and compared the mixed effects of O_3 and NO_2. The relationship model is established by a bivariate smoothing spline [25].

The hysteresis of oxidizing species (O_2 and NO_2) was also considered in this study. The 1–7 days after pollutant discharge is selected as the lag period of this study. The reason for this choice was that the incubation period of COVID-19 reported by researchers is mostly 1–7 days [26,27]. Similarly, GAM is applied to analyze the relationship between COVID-19 and the hysteresis effect of pollutants in different regions and to calculate the influence of O_x and $O_x{}^{wt}$ on COVID-19 in the hysteresis model.

Finally, this study explored the potential impact of changes in pollutant concentration. We conducted a regional study on O_x and $O_x{}^{wt}$, divided into four regions: North China, East China, Central China and South China, and other regions. We adjusted the concentration of O_x and $O_x{}^{wt}$ with combined oxidation ability to calculate the relative risk (RR) of COVID-19. The specific formula is as follows:

$$RR = \exp\,(\beta \times IQR)$$

where β is the coefficient of the pollutant in the model calculations, and IQR is the interquartile range of the pollutant during model calculation (P(75%)–P(25%)) [28]. The health effects of pollutants are characterized by the RR coefficient.

In this study, the original data is huge, involving four months of observational data in 34 cities. Based on this, we first used Microsoft Excel to preprocess the data, and then the GAM analysis was completed by R software, which can be used to deal with the relationship between O_3, NO_2, O_x, $O_x{}^{wt}$ and COVID-19. The software uses the mgcv and hmisc extension packages [29]. The estimations were expressed as their 95% confidence intervals (95% CI).

3. Results

Our study utilized data on pollutants and patients from 34 capital cities from 1 September 2020 to 31 December 2020. In this study, O_3 and NO_2 were selected as the research objects, and O_3, NO_2, O_x, and $O_x{}^{wt}$ were analyzed.

Table 1 shows the relationship between NO_2, O_3, O_x, $O_x{}^{wt}$ and COVID-19. A strong correlation between COVID-19 and O_3 was observed in Zhengzhou and Guiyang, which were 67% (95%CI: 30%, 114%) and 53% (95%CI: −6.8%, 153%) respectively. For NO_2, the populations in Changsha and Urumqi showed more obvious sensitivities of 70% (95%CI: 3.1%, 183%) and 67% (95%CI: −12%, 221%), respectively. During the study period, Zhengzhou observed the peaks of O_x and $O_x{}^{wt}$ regarding COVID-19 infection rates, which were 49% (95%CI: 25%, 79%) and 24% (95%CI: 12%, 37%), followed by Guiyang. The corresponding O_x and $O_x{}^{wt}$ results in Guiyang were 44% (95%CI: −7.4%, 124%) and 21% (95%CI: −3.4%, 51%). However, the correlation between O_x and $O_x{}^{wt}$ in Harbin and COVID-19 was only weakly detected, corresponding to 0.7% (95%CI: −10%, 13%) and 2.4% (95%CI: −4.1%, 9.5%), respectively. The infection rate of COVID-19 in Zhengzhou showed a good correlation with O_3, O_x, O_x^{wt}. The high population density and poor air quality in Zhengzhou are the possible reasons for this result. In addition, the government has implemented control measures to reduce the spread of COVID-19, which has reduced motor vehicle NOx emissions to a certain extent [30]. Also, the increase in O_3 concentrations is mainly correlated with NOx emissions reduction, so O_3 may be closely related to COVID-19 [31]. These results are consistent with other recent research [32,33].

Table 1. Single pollutant effect for COVID-19 in some China cities.

	O_3	NO_2	O_X	O_x^{wt}
Beijing	3.7% (−6.4%, 14%)	##	##	0.23% (−4.1%, 4.7%)
Tianjin	##	##	##	##
Shanghai	##	##	##	##
Chongqing	##	18% (−7.9%, 53%)	1% (−9%,13%)	##
Shenyang	##	8.5% (−24%, 56%)	##	##
Harbin	4.3% (−11%, 23%)	17% (−11%, 55%)	0.7% (−10%,13%)	2.4% (−4.1%, 9.5%)
Changchun	##	##	##	##
Shijiazhuang	##	##	##	##
Jinan	##	##	##	##
Nanjing	##	3.3% (−31%, 56%)	##	##
Hangzhou	##	##	##	##
Fuzhou	##	##	##	##
Zhengzhou	67% (30%, 114%)	##	49% (25%, 79%)	24% (12%, 37%)
Wuhan	4.5% (3.1%, 5.9%)	##	15% (13%, 16%)	4.9% (4.2%, 5.5%)
Changsha	3.2% (−7.9%, 15.9%)	70% (3.1%, 183%)	5.5% (−5.3%, 17%)	2.1% (−3.2%, 7.8%)
Hefei	##	##	2.3% (−18%, 17%)	##
Guangzhou	32% (19%, 46%)	32% (6%, 64%)	23% (13%, 33%)	12% (7.8%, 17%)
Nanning	##	40% (−58%, 370%)	##	##
Lanzhou	8.6% (−23%, 53%)	3.7% (−27%, 49%)	4.8% (−16%, 31%)	3.2% (− 9.9%,18%)
Yinchuan	##	##	##	##
Taiyuan	##	##	##	##
Huhehot	##	##	##	##
Xi'an	24% (−2.9%, 58%)	##	3% (−22%, 37%)	3.8% (−10%, 20%)
Urumqi	##	67% (−12%, 221%)	26% (−36%, 151%)	##
Xining	##	##	##	##
Lasa	##	##	##	##
Chengdu	1.1% (−14%, 20%)	45% (−8.1%, 129%)	4.8% (−10%, 22%)	1.6% (−6%, 9.9%)
Guiyang	53% (−6.8%, 153%)	##	44% (−7.4%, 124%)	21% (−3.4%, 51%)
Haikou	##	##	##	##
Kunming	8.6% (−34%, 81%)	##	5.1% (−38%, 81%)	3.3% (−19%, 33%)
Nanchang	##	##	11% (−1.5%, 25%)	6% (−0.4%, 13%)

Notes: ## Indicates no correlation.

Table S1 lists the impact of O_3, NO_2, O_x, and O_x^{wt} on the infection rate of COVID-19 within 7 days of lag. In Zhengzhou and Changsha, the impact of pollutants on COVID-19 had gradually weakened over time. Compared with Zhengzhou, the lag effect in Changsha on the third day is negligible. For every 10μg m^{-3} increase of O_x, the COVID-19 infection rate increases by 0.06% (95%CI: −10%, 11%), with a 3-day lag, and 0.5% (95%CI: −4%, 6%) increase of COVID-19 corresponding to a 10 μg m^{-3} increase in the 3-day lag average concentrations of O_x^{wt}. In addition, we have observed that the lag effect of NO_2 in Urumqi had caused the COVID-19 infection rate to continue to rise, except for a decrease on the 7th day. The peak on day 6 was 68% (95%CI: −43%, 404%). However, the lagging effects of pollutants in Guiyang showed an overall upward trend, except for the phenomenon of falling back on the 4th day after the lag. For a 10 μg m^{-3} increase in O_x, the infection rate of COVID-19 was 8% (95%CI: −18%, 44%), 24% (95%CI: −12%, 78%), and 31% (95%CI: −16%, 106%) on the 2nd, 5th, and 7th days of the lag, respectively.

Further, we have observed that under the combined effects of O_3 and NO_2 in Zhengzhou, the infection rate of COVID-19 was as high as 125% (95%CI: 16.4%, 336%), far exceeding the 83.6% (95%CI: −25.4%, 352%) in Changsha. At the same time, Urumqi had an 83.1% (95%CI: −25.2%, 348%) infection rate close to that of Changsha. In addition, the data we collected showed that O_3 and NO_2 did not have a significant impact in some areas, such as Kunming, where an increase in the concentration of 10 μg m^{-3} was related to an increase in COVID-19 by 1.9% (95%CI: −24.5%, 37.7%). Overall, the lag effects of pollutants were weak for COVID-19 at a 7-day lag.

Figures S1–S4 show the relative risk of COVID-19 infection in the four regions of China (East China, North China, Central China and South China, and other regions) with changes in Ox concentration. For Shanghai in East China, the infection rate of COVID-19 had been increasing with the increase of O_x concentration. Similarly, in Taiyuan and Tianjin in North China, O_x and COVID-19 showed an approximately linear growth relationship. However, no definite causality had been observed in Beijing. Obviously, COVID-19 and O_x in Guangzhou in South China were showing a J-shaped growth trend. Finally, both Guiyang and Urumqi have shown a weak growth trend, which shows that the increase in O_x concentration has a positive effect on the increase in the COVID-19 infection rate. High O_x concentration greatly increases the risk of people suffering from COVID-19.

The relative risks of the relationship between $O_x{}^{wt}$ and COVID-19 in different regions of China (from Supplementary Materials Figures S5–S8). Comparing and analyzing Figures S1 and S5, it can be found that the curve trends of O_x and $O_x{}^{wt}$ in the same area have a high degree of similarity. Taking Shanghai in East China as an example, the relative risk of disease in the population was increasing when $O_x{}^{wt}$ was in the concentration range of 0–15 μg m^{-3}, which has obvious statistical significance. The same rising result was shown in the O_x analysis in Figure S1. Therefore, the pathogenic risk of COVID-19 can be analyzed in the characterization of O_x and $O_x{}^{wt}$.

4. Discussion

We analyzed the link between oxidizing pollutants (O_3 and NO_2) and COVID-19 by using GAM. Our results showed: (1) The increase in COVID-19 infection rate is related to the increase in O_3 and NO_2 concentrations in the short term; (2) In the joint analysis of O_3 and NO_2, the sensitivity of O_x is higher than that of $O_x{}^{wt}$; (3) In the hysteresis model, the hysteresis effect of O_x and $O_x{}^{wt}$ is constantly weakening.

As evidenced by previous epidemiological studies, O_3 and NO_2 are related to the health of the human respiratory system [34]. However, most studies only consider the effects of O_3 or NO_2 on the human body, and few reports consider both O_3 and NO_2. For example, a study showed that O_3 has obvious harm to children and has a negative impact on human health [3]. The report did not mention the role of pollutant NO_2. A study in Tehran demonstrated that O_3 and NO_2 contribute to a range of respiratory diseases such as COPD [35]. This is consistent with our results that O_3 and NO_2 have caused an increasing number of confirmed cases of COVID-19.

However, the monitoring data of O_3 and NO_2 may be one-sided, which is caused by the dynamic chemical relationship between O_3 and NO_2 [36]. Measurements of O_3 and NO_2 show differences due to variations in weather or measurement region [37]. In warm areas, with sufficient sunlight, the diffusion capacity of pollutants is limited at this time because of the stable conditions formed under the high-pressure system [38]. Therefore, a large number of photochemical reactions that contribute to the formation of O_3 are carried out [39]. However, most NO_2 comes from automobile exhaust emissions and the combustion of coal and fossil fuels At this time, NO_2 is the dominant substance and has a negative correlation with O_3. Therefore, the monitoring of a single pollutant cannot accurately reflect the relationship between COVID-19 and pollutants, so we considered using joint analysis [40].

O_x is the sum of O_3 and NO_2 [41], and the calculation method is simple and quick. However, its shortcomings are also obvious. The oxidation capacity of O_3 may be underestimated because the different oxidation potentials of O_3 and NO_2 are not taken into account [42]. The formula for $O_x{}^{wt}$ describes the weighted average oxidation capacity [43].

In the process of using $O_x{}^{wt}$ for analysis, we assigned the oxidation potential of O_3 to 2.075 V and the oxidation potential of NO_2 to 1.07 V to better evaluate the oxidative capacity of O_3 and NO_2 [44]. In the joint analysis, we found that the correlation between O_x and COVID-19 is more sensitive than $O_x{}^{wt}$. There are many reasons for this result, and sampling time in autumn and winter may be one of the main influencing factors. This photochemical reaction is no longer active, so the role of O_3 may be overestimated. For example, previous studies have shown that the $O_x{}^{wt}$ value in winter is less than that in summer, and the effect of photochemistry seems to be very important [45]. It is undeniable that $O_x{}^{wt}$ has improved the metric for the oxidation reaction. Our research also confirmed this result, $O_x{}^{wt}$ can be used to determine the adverse effects of O_3 and NO_2 on human respiratory diseases (such as COVID-19).

In addition, we have analyzed the hysteresis effects of pollutants, and the results show that the hysteresis effects of O_x and $O_x{}^{wt}$ have been declining over time. In the regional study of $O_x{}^{wt}$ and O_x, we observed that the increase in the concentration of pollutants increased the relative risk of COVID-19 disease. The reasons for this phenomenon are complex, including regional differences, concentration-response functions, and so on.

This study has the following two advantages. We studied the combined effects of pollutants with oxidizing properties and explored the connection with the current world pandemic (COVID-19); then, the potential risks to human health brought by the hysteresis effect of pollutants were detected. But our research inevitably has some limitations. First, the time period we selected for the study is relatively short, and changes in factors such as seasons interfered with the research results; second, the relevant literature that has been published is relatively scarce, and there is not enough supporting literature to be consulted in the process of this research.

5. Conclusions

Our research shows that the chemical changes of O_3 and NO_2 as two oxidizing substances cannot be ignored. Therefore, the research model of a single pollutant cannot effectively reflect the true impact on COVID-19. Based on this, this research introduces two concepts, O_x and $O_x{}^{wt}$. The O_x parameter solves the errors caused by the traditional single pollutant model or double pollutant model statistics. Moreover, the value of O_x comes from the addition of O_3 and NO_2, which is simple and convenient to calculate. Values for $O_x{}^{wt}$ take into account the oxidation ability of different substances more accurately, which provides support for further research. Finally, the results of this study provide directions for epidemiological research, and the interaction of pollutants (such as O_3 and NO_2) should be considered. In addition, the single pollutant parameter has been adopted when the national policy is formulated, and at the same time, the impact of pollutant interaction on human health should also be evaluated.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/atmos13040569/s1, Figure S1. O_X values in eastern China; Figure S2. O_X values in Northern China; Figure S3. O_X value in southern China; Figure S4. O_X values in other cities of China; Figure S5. $O_x{}^{wt}$ values in eastern China; Figure S6. $O_x{}^{wt}$ values in northern China; Figure S7. $O_x{}^{wt}$ values in southern China; Figure S8. $O_x{}^{wt}$ values in other cities of China; Table S1. Lag effect for China cities.

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