Short-term Effects of Multiple Ozone Metrics on Outpatient Visits For Urticaria in Lanzhou

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Abstract

Background Although mounting evidence suggests that short-term exposure to ozone increases the risk of respiratory disease, cardiovascular disease and mortality, there are few studies comparing the effects of ozone in relation to urticaria in China.

Objective To evaluate the risks for urticaria exacerbations related to ambient ozone measured as 1-h maximum (O_3-1 h max), maximum 8-h (O_3-8 h max) and 24-h average (O_3-24 h avg) concentrations.

Methods We calculated three metrics of ozone, 1-h maximum, maximum 8-h and 24-h average based on the hourly data. Generalized additive models with poisson regression incorporating natural spline functions were used to investigate short-term effects on urticaria associated with ambient ozone pollution in Lanzhou, China, using 5 years of daily data (2013-2017). We also examined the association by sex, age and season.

Results In all-year analyses, a 10 μg/m^3 increase in daily average, O_3-1 h max, O_3-8 h max and O_3-24 h avg at lag2 corresponded to an increase of 0.58%(95%CI：0.26%~0.90%), 0.82% (95%CI：0.47%~1.16%) and 2.17% (95%CI：1.17%~2.79%), respectively. The elderly populations and females were susceptible to O_3, and the associations between ozone and urticaria appeared to be more evident during warm season than in the cold season.

Conclusion In conclusion, these results indicated that ozone, as a widespread pollutant, affects outpatient visits for urticaria in Lanzhou.

Key word: Ambient Ozone; Urticaria; Excess Risk; Metric

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Conflict of interest None declared.

Ethics approval This study was approved by the Ethics Committee of the First Hospital of Lanzhou University (the Ethics number：LDYYLL2019-35).

Availability of data and materials Weather data are available from: http://data.cma.cn/site/index.html. Outpatient data were obtained from the three major tertiary hospitals through the Health Information System, which has not deposited in publicly available repositories. Therefore, it is available from the corresponding author on reasonable request. Air quality data are obtained form 4 monitoring stations interspersed in study areas.

1. Introduction

In recent years, with the development of the economy and science and technology, the concentration of atmospheric particulate matter in China has been gradually controlled, and the type of air pollution has begun to change from traditional soot pollution to photochemical smog pollution. Among them, O_3 is the most toxic component of photochemical smog pollution, and the concentration of O3 in the near-surface atmosphere is increasing year by year (Huang et al. 2018).

It has been reported that an increase in O_3 concentration can cause a series of acute health hazards, such as increased risk of skin disease, upper respiratory tract infections and cardiovascular disease (Gryparis et al. 2004; Bell et al. 2006; Jerrett et al. 2009; Zhang et al. 2006).

In the human body, the skin is the part that comes into most frequent and extensive contact with the external environment, and it serves as a defense barrier, constantly exposed to air pollutants and sensing changes in the environment. Urticaria is a common allergic disease with recurring symptoms and pronounced itching, and the prevalence of urticaria has been increasing worldwide over the past decade (Zuberbier et al. 2010; Lapi et al. 2016), placing a heavy burden on patients' quality of life, workability, mental health and socio-economic well-being (Maurer et al. 2016; Broder et al. 2015; Graham et al. 2016). The etiology of urticaria is unknown, but there are a number of risk factors, both endogenous (e.g. genetic) and exogenous (e.g. environmental), including indoor environmental conditions, ambient air pollutants and other meteorological factors. Particulate matters (PM), which are representative of ambient air pollutants, have been shown to have an effect on urticaria (Kousha et al. 2015). As the second most important air pollutant in China, O_3 has been little studied in relation to urticaria disease. Only Xu Feng (2011) et al. in Shanghai found a correlation between the maximum daily 8-h concentration of O_3 and the number of emergency room visits for urticaria. Since the mechanism of O_3 production is influenced by solar radiation, temperature and humidity (Wang et al. 2017), and ozone concentrations vary widely over a 24-hour period, three commonly used concentration monitoring measures are used. According to the methods of US EPA (Darrow et al. 2011), which included O_3-1 h max (the highest hourly value recorded in a given day), O_3-8 h max (the maximum running or moving 8-hr values among all 24 h in a day) and O_3-24 h avg (the mean of 24 individual hourly concentrations measured from midnight to midnight). Therefore, when studying the health effects of O_3, it is difficult to obtain accurate and comprehensive results on the health effects of O_3 in a population if the concentration of a single measure is used without considering the variation of concentrations in other measures (Li et al. 2015).

To date, epidemiological studies of O3 using various indicators have only focused on developed cities in China, such as Beijing (Li et al. 2015), Shanghai and Guangzhou (Sun et al. 2017) etc, and it is difficult to compare the results from these regions. Lanzhou is a landlocked city in China, with a unique geographical location and meteorological conditions, and photochemical pollution has been one of the problems affecting air pollution in the city (Wiwatanadate et al. 2014). Therefore, we consider the Lanzhou region as an ideal area to evaluate the effect of O3 on urticaria disease.

In this study, a Generalised Additive Model (GAM) based on Poisson distribution is proposed to quantitatively evaluate the near-surface O_3 monitoring data of municipality Lanzhou from 2013 to 2017, using various measures of O_3 concentration, including O_3-1 h max, O_3-8 h max and O_3-24 h avg to explore the acute health effects of different O_3 concentrations on the urticaria population. The results of this study may provide clues or evidence for further research on the effects of environmental ozone on dermatological diseases，and ultimately provide useful information for our environmental regulatory policies.

2. Materials and Methods

2.1. Data collection

The clinical data of urticaria were obtained from the medical records of three Grade-A general hospitals in Lanzhou city. The data were selected from January 1, 2013 to December 31, 2017, and were exported by the hospital information system (HIS). According to the first four area codes and the ID number of the home address, the local residents in Lanzhou were screened out. The cases were coded according to the International Classification of Disease, tenth revision (ICD-10) for urticaria (code: L50) by the clinicians in a division of Dermatology.

Hourly concentrations of ambient air pollutants including Ozone (O_3), Nitrogen dioxide (NO_2), Sulfur dioxide (SO_2), Particulate Matter (with an aerodynamic diameter $\leqslant$2.5 μm, $PM_{2.5}$) and Crbon monoxide (CO) were obtained from Lanzhou Municipal Environmental Monitoring Center. There were four fixed-site monitoring stations in our study, and the location of the four monitoring stations and the three tertiary hospitals were shown in the Supplemental Material (Fig. S.1). Hourly meteorological data (including temperature and relative humidity) measured by national environmental monitoring stations were collected from China Meteorological Administration. We calculated the following three O_3 exposure metrics for daily O_3 concentrations on an hourly basis including O_3-1 h max, O_3-8 h max and O_3-24 h avg.

2.2. *Statistical Methods*

Spearman's correlation coefficients were used to analyze the relationships between air pollutants and meteorological factors. As the number of urticaria outpatient visits approximately obeyed an overdispersion Poisson distribution, a generalized additive model (GAM) with Poisson chain as the core analysis was used to estimate the relationship between ambient air pollution and the number of daily visits to the urticaria outpatient clinic. In this model, we incorporated a days of week (DOW) categorical variable to control for variation in weekly outpatient visits. We also used a penalized smoothing spline function incorporating calendar time, daily temperature and relative humidity to adjust for the effects of seasonal patterns, long-term trends, and meteorological factors and to exclude their potential nonlinear confounding effects. The A cubic smoothing function is used to control for the confounding effects of long-term trends, Sunday numbers, and weather factors (temperature and relative humidity). The model is as following:

GAM is shown below (Equation (1)):

$$\log E\ (y_t\ ) = \beta Z_t + ps\ \ (time, df = 7) + ps\ \ (temp, df = 3) + ps(rhum, df = 3) + factor\ \ (dow) + \alpha \quad (1)$$

Where, $E(y_t)$ defined as the expected number of outpatients visits for urticaria at day t; β represents the relative log rate of urticaria outpatients related to a unit increase of particulate matter; Z_t indicates the concentrations of O_3 (O_3-1 h max, O_3-8 h max and O_3-24 h avg) at day t; ps indicates penalized spline function for nonlinear variables, which is adapted to control for potential confounding of long-term trends and seasonality in daily outpatients visits; *df* is the degree of freedom; *temp* and *rhum* are the daily temperatures (℃) and relative humidity (%) at day *t*; *time* represents the calendar time; *dow* is the dummy variable for the date of the week; α is the intercept for the model (Li et al. 2015; Sun et al. 2017).

When the core model was established, we introduced air pollution variables into the single pollutant model to test for possible interactions between urticaria outpatients and air pollutants. Secondly, because of the delayed health effects of air pollutants, we also considered a moving average lag effect for the study (e.g., from the current day, lag0 to previous 7 days, lag7) and cumulative day lags (e.g., from the current day and the previous 1, lag01 to the previous 8 days, lag07). Third, we also assessed the robustness of the results in terms of the *df* values for calendar time (5, 6 and 8 *df* per year), and temperature (4-6), and by adjusting for other pollutants, including SO_2, NO_2, $PM_{2.5}$ and CO. Additionally, the associations stratified by sex (female and male), age (≤18 years, 19-64 years and ≥65 years) and season (spring, summer, autumn and winter) were examined. The statistical significance of subgroup differences was tested through Z-test: $(\hat{Q}_1 - \hat{Q}_2) \pm 1.96\sqrt{S\hat{E}_1^2 + S\hat{E}_2^2}$ (where $\hat{Q}_1$ and $\hat{Q}_2$ were the estimated for age and sex group, and $S\hat{E}_1^2$ and $S\hat{E}_2^2$ were respective standard errors.)

All analyses were conducted in R Programming Language (V.3.2.2, R Development Core Team) using the "mgcv" packages. The results of the statistical test were two-sided with *p*-values<0.05 considered statistically significant. The estimated effect is expressed as the percentage excess risk (ER%) and its 95% confidence interval (95% CI) for urticaria outpatients per 10 μg/m3 O3 component increase.

3. Results

The results of the descriptive analysis of O_3 concentration and meteorological factors and daily outpatient visits for urticaria are shown in Table 1 From 18 January 2013 to 31 December 2017, the average daily outpatient visits for urticaria in Lanzhou were 40.65±17.34, with slightly more male than female visits (23.07±10.58). The O_3-1 h max, O_3-8 h max and O_3-24 h avg values were (80.43±48.75) μg/m^3, (82.97±45.37) μg/m^3 and (40.14±26.82) μg/m^3 respectively. The average daily temperature and relative humidity are (11.20 ± 9.93) °C and (49.95 ± 15.57) %, respectively. Daily mean concentrations of SO_2, NO_2, $PM_{2.5}$ and CO were (23.41±15.73) μg/m^3, (48.09±22.29) μg/m^3, (56.54±31.86) μg/m^3 and (1.23±0.74) μg/m^3, respectively. The temporal trends of O_3 from urticaria outpatient visits and the different measures of O_3 showed a clear seasonal trend for O_3-1 h max, O_3-8 h max and O_3-24 h avg, with a peak in summer and autumn and a decrease in winter and spring. The trends in the pattern of urticaria outpatient attendances were generally similar in the Supplemental Material (Fig. S.2).

The Spearman correlation coefficients between air pollutants and meteorological factors are described in Table 2 The results show that O_3-1 h max, O_3-8 h max and O_3-24 h avg are highly positively correlated (p<0.01), with most of the different indicators for O_3 being positively correlated with temperature and relative humidity and only O_3-24 h avg being negatively correlated with relative humidity, r=-0.15 (p<0.01). Three indicators for O_3 are negatively correlated with SO_2 and CO and positively correlated with $PM_{2.5}$.

Table 3 Using the GAM model to control the effects of meteorological factors such as long-term and seasonal trends, temperature and relative humidity, the associations of O_3-1 h max, O_3-8 h max and O_3-24 h avg with urticaria outpatient visits were most significant on lag day 2 (lag2), with an increase in ER of 0.58%(95%CI：0.26%~0.90%), 0.82% (95%CI：0.47%~1.16%) and 2.17% (95%CI：1.17%~2.79%) for each 10 μg/m^3 increase in O_3-1 h max, O_3-8 h max and O_3-24 h avg, respectively. Therefore, the effect values for lag2 were chosen as the best lag times for O_3-1 h max, O_3-8 h max and O_3-24 h avg in this study. We also found that O_3-24 h avg always had the highest effect value when the effect values were compared in terms of increasing concentrations of the same unit (10 μg/m^3 or IQR) (see table 4).

Fig.1 shows the effect of lag2 on urticaria outpatient attendances for every 10 μg/m^3 increase in the O_3 exposure index for the different measurement methods. When stratified by gender, the effect of O_3 was greater in women than in men, with an increase of 0.52%, 0.63% and 1.25% for every 10 μg/m^3 increase in O_3-1 h max, O_3-8 h max and O_3-24 h avg, respectively, which were not statistically significant. When stratified by age, the effect of O_3 was more pronounced in those aged ≥65 years, but was not statistically significant.

In Fig.2, it is shown whether the relationship between O_3 and the number of urticaria outpatient visits varies with season for the different measures. We found that the effect values for O_3 were slightly higher in summer and autumn than in the other two seasons, but were not statistically significant.

As shown in Table 5, when SO_2 and CO are introduced into the model, the excess risk of different indicators O_3 are reduced but still have statistical significance (p<0.05). When $PM_{2.5}$ was introduced, the excess risk increased and it was also statistically significant. However, when NO_2 was introduced into the model, the results were significantly different. Among them, the effect value of O_3-1 h max increased to 1.26% (95%CI: 0.73%~1.79%) after adding pollutant NO_2, while the excess risk of O_3-8 h max and O_3-24 h avg showed a downward trend, respectively 1.15% and 2.63%, both of which were statistically significant.

By changing the *df* of time (*df*=5-8) and *df* of temperature trend (*df*=3-7) in the model, a new model fitting, compared with the results of the original model change is not obvious, is proved in our study to establish the model of daily average temperature, time, the two parameters had no obvious effect on results, the model established in this study is stable. (Table 6.)

4. Discussion

In this study, a statistical modelling approach was used and, after controlling for multiple confounding factors, it was found that elevated levels of O_3 pollution in Lanzhou had a significant effect on the increase in urticaria outpatient visits in the whole population. This result is similar to that of Xu Feng (2011) and Szyszkowicz et al (2012). In the exposure-response relationship between O_3 and urticaria outpatient visits (The figures were displayed in the Supplemental Material, Figure S3), a positive relationship was found between O_3-1 h max and O_3-8 h max at concentrations below 100 μg/m^3 and O_3-24 h avg below 40 μg/m^3, confirming that O_3 can cause damage to urticaria patients at low concentrations. The Chiang Mai study (Wiwatanadate et al. 2014), however, concluded that there was a negative correlation between O_3 concentration and the occurrence of rash. This inconsistency may be related to factors such as the climatic characteristics of the study area, socio-economic conditions, and the age distribution of the study population.

In this study, three measurement methods of O_3 exposure index increased by 10μg/m^3, and the number of urticaria outpatients increased to different degrees, which meant O_3-1 h max, O_3-8 h max and O_3-24 h avg increased by 0.58%, 0.82% and 2.17% for every 10μg/m^3 increase on lag2 day, suggesting that O_3 has a significant short-term impact on urticaria outpatient visits. By comparing the results of three different O_3 exposure indicators, it can be seen that O_3-24 h avg has the largest effect value, and O_3-1 h max has the smallest effect value. Therefore, although the O_3-8 h max concentration index is currently used as an index that can better represent the acute health effects of O_3 (Yang et al. 2012). However, in this study, the significance of the other two exposure indicators cannot be ignored.

In a stratified study by sex and age, it was found that outpatient visits for female urticaria were more affected by O_3 concentration than men. The increase in outpatient visits for people over 65 was related to O_3 concentration. Because there are few similar documents, the accuracy of the results has not been confirmed.

This study found in the seasonal stratification that the relationship between O_3 and urticaria outpatient visits is more prominent in summer and autumn. There is no statistical significance, but the possible reasons can be: 1. Ozone has prominent seasonal variability, with average maximum concentrations ranging from late May to around October, usually 119.1 μg/m^3, and declining significantly in winter (Wang et al. 2017). Changes in ozone concentrations also vary throughout the day and are usually characterised by low levels of concentration between 0:00 and 8: 00, slowly increasing to the peak between 8:00 and 16: 00, then maintaining high levels of concentration until 18:00, after which concentrations drop sharply, reaching low levels at 23:00 on the same day (Zhou et al. 2018). The change pattern of O_3 in a day or a year may be due to the high temperature in summer and strong solar radiation intensity, which are conditions conducive to the generation of O_3. 2. The influence of topographical factors in the valley of Lanzhou. Lanzhou is surrounded by mountains, with quiet wind all year round, and the transport and ventilation effects of pollutants are not significant (Li et al. 2020). 3. People often open windows for ventilation in warm seasons, resulting in increased penetration of outdoor air into the indoor space. In the cold season, people rarely go out, especially the elderly and the weak. These factors may increase exposure to ambient air pollutants in warm seasons.

In this study, it was found that ozone has a strong correlation with particulate matter and that the effect value of O_3 increases and is statistically significant after the introduction of $PM_{2.5}$ into the model. It has been shown that certain conditions are favourable for the rapid production of ozone and secondary particulate matter, leading to a complex superposition of ozone and fine particulate pollutants in the atmosphere. As particulate matter is a complex pollutant and its composition varies considerably depending on its regional origin, it is not possible to confirm whether particulate matter is a confounding factor for ozone or a modifying effect, and more research evidence is needed in the future.

It has long been recognized that environmental exposure to ozone affects skin health. By evaluating the skin of hairless mice exposed to ozone, Thiele et al (1997) found a decrease in vitamins C and E and the formation of malondialdehyde, a marker of lipid peroxidation, in the epidermis of hairless mice exposed to varying levels of ozone at increasing and decreasing doses. McCarthy et al (2013) exposed normal human epidermal keratinocytes (NHEKs) to environmentally-related ozone concentrations for 30 minutes, and observed that exposure to 0.8ppm ozone resulted in increased DNA damage and depletion of ATP and Sirtuin 3 levels. However, ozone is also used for its antibacterial and antioxidant effects in the treatment of various skin diseases such as chronic inflammation, allergic diseases and pruritic skin diseases etc (Bocci et al. 2015; Abeck et al. 2008). Therefore, the harmful or protective effects of ozone on the skin need to be explored in further studies.

5. Conclusions

In this study, it was found that an increase in atmospheric ozone concentrations in Lanzhou increased the number of urticaria outpatient visits, with a maximum lag time of lag1 for O_3-1 h maximum concentration, lag2 for O_3-8 h maximum concentration and lag2 for O_3-24 h mean concentration. There was significant differences in the three ozone exposure indicators for urticaria outpatient visits, and it could be seen that O_3-24 h avg had the largest effect value. Based on gender, age and seasonal analyses at different exposure levels, it was also found that there was a higher increase in urticaria outpatient visits when O_3 was applied to females, elder population, summer and autumn compared to the rest of the population. The results of the study provide richer evidence for a comprehensive assessment of the acute effects of ozone on dermatological diseases and can provide more technical support for policy makers to revise their public health policies accordingly.

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Figures

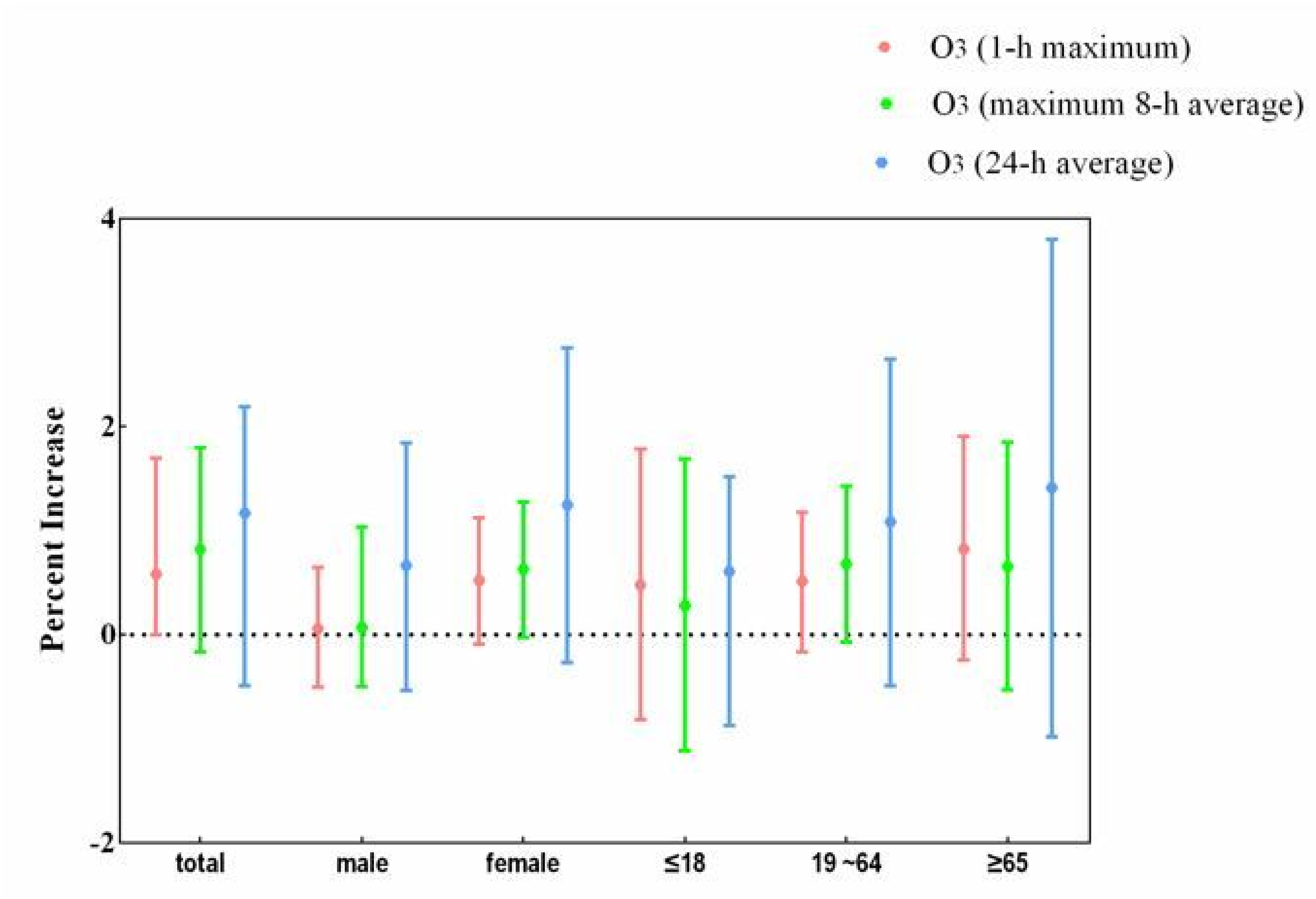

Figure 1

Results of grouped analyses by gender and age on the association between a 10μg/m3 increases in the average concentration of O3-8h and daily outpatient visits for urticaria

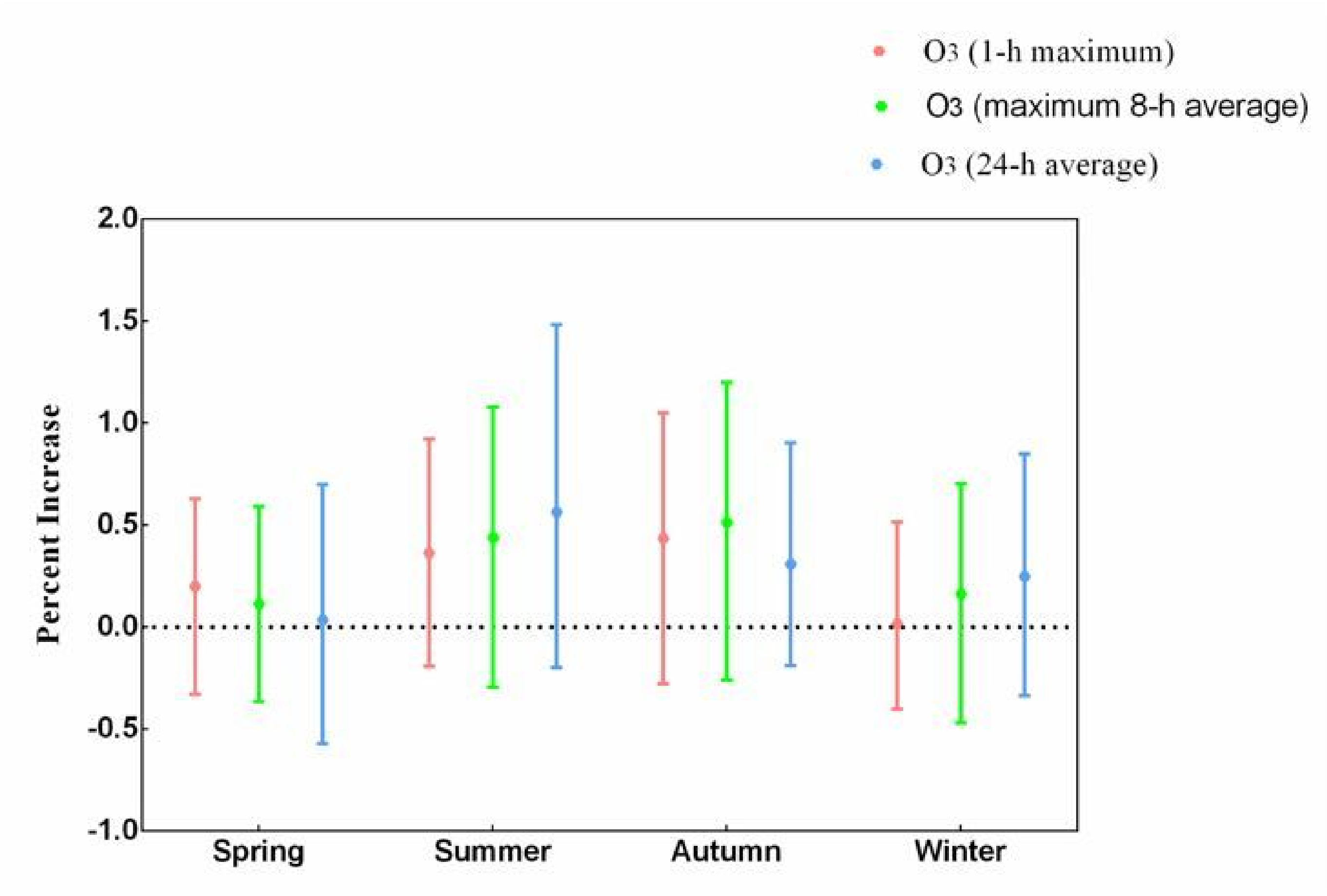

Figure 2

Shows the season-stratified results from a single-day lag and a multi-day cumulative lag.