Short-term effects of air pollutants and meteorological factors on daily outpatient visits for urticaria in Shijiazhuang, Hebei Province, China

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Abstract

Objective: The associations of air pollutants and meteorological factors with the outpatient visits of urticaria remain poorly studied. This study aimed to assess the short-term effects of air pollutants and meteorological factors on daily outpatient visits for urticaria in Shijiazhuang, China, during 2014-2019.

Methods: Daily recordings of air pollutants concentrations, meteorological data, and the outpatient visits data for urticaria were collected during the 6 years. Descriptive research methods were used to describe the distribution characteristics and demographic features of urticaria. A combination of the generalized linear regression model (GLM) and distribution lag nonlinear model (DLNM) was used to evaluate the lag effect of environmental factors on daily outpatient visits for urticaria.

Results: The dose-response relationship between daily urticaria visits and CO, NO_2, O_3, temperature, and relative humidity was nonlinear. High concentrations of CO, NO_2, O_3, and high temperatures increased the risk of urticaria outpatient visits. The maximum cumulative effect of high concentrations of CO, NO_2, and O_3 was lag 0-14 days (CO: RR = 1.10, 95%CI: 1.06, 1.31; NO_2: RR = 1.09, 95%CI: 1.01, 1.08; O_3: RR = 1.16, 95%CI: 1.08, 1.25), and high temperatures was lag 0-7 days (RR = 1.27, 95%CI: 1.14, 1.41). Low concentrations of NO_2, O_3, and high humidity, on the other hand, act as protective factors for the urticaria outpatient. The maximum cumulative effect of low concentrations of NO_2 was the 0-day lag (RR = 0.97, 95%CI: 0.95, 0.99), O_3 was lag 0-5 days (RR = 0.94, 95%CI: 0.88, 0.99), and high humidity was lag 0-10 days (RR = 0.93, 95%CI: 0.89, 0.98).

Conclusions: In conclusion, we found that the development of urticaria in Shijiazhuang has a distinct seasonal and cyclical nature. Air pollutants and meteorological factors had varying degrees of influence on the risk of urticaria outpatient visits.

1. Introduction

Urticaria is one of the common allergic diseases seen in dermatology clinics. The main lesions are characterized by rash, angioedema, or both. Urticaria is classified according to its duration as acute urticaria (≤ 6 weeks) and chronic urticaria (≥ 6 weeks). In addition to this, we can also classify urticaria into induced urticaria (involving triggering factors) and spontaneous urticaria (not involving triggering factors) depending on whether triggering factors are involved (Zuberbier et al., 2018). The disease is intensely pruritic and seriously affects people's family and social life, as well as patients' performance at school and at work (Gonçalo et al., 2021; Saini and Kaplan, 2018). A Polish study showed that the lifetime prevalence of urticaria in the general population is 15%-20%, placing a significant burden on social and medical resources (Hay et al., 2014; Mazur et al., 2020). Several studies have reported that multiple risk factors can trigger urticaria, including genetic background, food intake, lifestyle, and social and economic status (Brzoza et al., 2017; Kim et al., 2018). However, there is no specific medicine for urticaria. Clinically, patients rely on antihistamines and hormonal drugs for symptomatic relief, but the urticaria will recur after the effect of the drugs has worn off (Schaefer, 2011). Therefore, identifying the environmental factors that influence the development of urticaria is important for improving the lives of patients and relieving the pressure on social and medical resources.

In recent years, air pollution has become a major global public health problem. Air pollution seriously affects people's health, causing up to 7 million premature deaths and even more hospitalizations each year. Moreover, climate change may alter the dispersion of major pollutants and exacerbate the formation of minor pollutants (Orru et al., 2017). In 2015, air pollution accounted for 7.6% of all deaths worldwide (Cohen et al., 2017). As a developing country, air pollution is responsible for more than 1 million deaths annually in China and has become a public health priority (Hong et al., 2019). Previous studies have confirmed the adverse effects of climate change and air pollutants on respiratory diseases and cardiovascular diseases (D'Amato and Akdis, 2020; D'Amato et al., 2016; Eguiluz-Gracia et al., 2020; Hansel et al., 2016; M et al., 2018; Rajagopalan et al., 2018). Epidemiological studies have confirmed that short-term exposure to air pollutants increases the risk of developing skin diseases (Araviiskaia et al., 2019; Krutmann et al., 2017; Mancebo and Wang, 2015; Puri et al., 2017). A study in Beijing showed that increased concentrations of particulate matter with an aerodynamic diameter less than 2.5μm ($PM_{2.5}$), particulate matter with an aerodynamic diameter less than 10μm (PM_{10}), and nitrogen dioxide (NO_2) were significantly associated with increased numbers of outpatient visits for acne vulgaris over the 2 years (Liu et al., 2018). In a German study, exposure to NO_2 was associated with an increased incidence of eczema (Morgenstern et al., 2008). Several studies have also examined the relationship between air pollutants and atopic dermatitis (Baek et al., 2021; Wang et al., 2021). However, so far, little evidence has directly assessed the relationship between air pollutants, meteorological factors, and urticaria, and the existing evidence was inconsistent. A Canadian study showed that NO_2, ozone (O_3), and $PM_{2.5}$ are associated with the incidence of urticaria (Kousha and Valacchi, 2015). A Beijing study found a positive correlation between sulfur dioxide (SO_2), and NO_2, and increased urticaria emergency room visits, but no relationship was found between particulate matter, O_3, and urticaria (Wang et al., 2021c). Future climate change may exacerbate the adverse effects on human health (Hong et al., 2019). It has been shown that exposure to cold leads to the development of urticaria and angioedema (Işk et al., 2014; Maltseva et al., 2021; Mari and Banks, 2020). There are also studies that confirm a significant relationship between a short period of skin heat exposure and urticaria (Pezzolo et al., 2016; White et al., 2017). A study in Lanzhou found that high temperature will increase the risk of urticaria for people at the age of 0–14 years and 15–59 years, while the low temperature will increase the risk of urticaria for people above 60 years (Zhang et al., 2021). Hence, there are sufficient reasons to investigate the effects of air pollutants and meteorological factors on urticaria in Shijiazhuang.

The study was carried out in Shijiazhuang, China because air pollution levels have been constantly quite high during recent years. Shijiazhuang became the second most polluted city in China after the severe haze event in northern China in 2013 (Song et al., 2018). This provides a natural venue for exploring the relationship between environmental factors and adverse health outcomes, but few studies have been conducted to analyze the influencing factors of urticaria and the evaluation of the lagging response relationship. Therefore, we aimed to describe the distribution characteristics and demographic features of urticaria in Shijiazhuang over 6 years, explore the potential relationship between air pollutants, meteorological factors, and daily outpatient visits for urticaria by constructing a distribution lag nonlinear model, screen for environmental factors that may affect urticaria, and quantify the effects of environmental factors on urticaria. The findings of this study could provide the scientific basis to help reduce the occurrence of urticaria, and improve the understanding of urticaria prevention.

2. Methods

2.1 Study area

Shijiazhuang (37°27' ~ 38°47' N, 113°30' ~ 115°20' E) is the capital of Hebei Province and one of the important central cities in the Beijing-Tianjin-Hebei region. As of 2019, Shijiazhuang has a resident population of about 1,103,100 and a total area of about 14,665 square kilometers. Shijiazhuang has a temperate monsoon climate with four distinct seasons, particularly distinct dry and wet periods, with a high temperature and heavy rain in summer and cold and dry winter. Shijiazhuang has developed heavy industry and air pollution mainly comes from the burning of fossil fuels and the emission of automobile exhaust. Especially in winter, the increasing amount of coal burning causes large emissions of air pollutants. Around 86.7 million tons of standard coal were reportedly burned in 2016 (Yang et al., 2018). In addition, there are a large number of construction sites in Shijiazhuang, some of which have not developed appropriate dust control measures. National highways, provincial roads, and other traffic roads, especially in the western counties (districts) the main coal transport channel secondary dust is still heavy, resulting in serious air pollution problems. Therefore, Shijiazhuang has become a natural place to study the relationship between environmental factors and urticaria. The specific location of Shijiazhuang City can be seen in Fig. 1.

2.2 Data collection

We collected the number of daily outpatient visits for urticaria as a data source from medical records of three hospitals from January 1, 2014, to December 31, 2019 (a total of 2191 days), the First Hospital of Hebei Medical University, Hebei Children's Hospital, and Shijiazhuang First Hospital, all of which are tertiary care hospitals located in the central city of Shijiazhuang, with good representativeness and authority. Moreover, the patients' sex and age in Shijiazhuang City were included, and patients living outside Shijiazhuang City were excluded according to recorded home addresses. International Classification of Diseases, Tenth Revision (ICD-10) code L50 was used to identify patients with a diagnosis of urticaria.

We obtained daily air quality report data from the Shijiazhuang City Air Quality Online Monitoring and Analysis Platform (https://www.aqistudy.cn/). The daily air pollutant concentrations come from seven fixed monitoring stations in Shijiazhuang. All seven stations are located away from major roads, industrial sources, high buildings, or residential sources of emission from the burning of coal, to ensure those monitoring data are not be intervened by local sources of traffic or industrial combustion pollution. Thus, these monitoring data reflect the real urban background air pollution level. The air pollutants in this study include $PM_{2.5}$, PM_{10}, Carbon monoxide (CO), NO_2, SO_2, and O_3, and the median was used to fill in the missing data of air pollutants on a particular day. We used the 24-hour average concentrations of $PM_{2.5}$, PM_{10}, CO, NO_2, and SO_2 as the daily pollutant exposure concentrations in Shijiazhuang. The maximum 8-hour moving average of ozone calculated from our national control system was used as the daily ozone concentration.

Meteorological data for the same period were obtained from the China Meteorological Data Sharing Service of the National Meteorological Administration of China (http://data.cma.cn), including 24-hour average temperature (℃), 24-hour maximum wind speed (m/s), 24-hour maximum relative humidity (%), and 24-hour maximum air pressure (Pa). The missing meteorological data for one day was filled with the average of the two adjacent days.

2.3 Statistical analysis

2.3.1 Descriptive statistical methods

Descriptive statistical analysis was used to explore the temporal trends and demographic characteristics of daily outpatient visits for urticaria. We also described the temporal trends and distribution characteristics of meteorological factors and air pollutants. We performed normality tests for urticaria daily outpatient visits, air pollutant concentrations, and meteorological factors, respectively, and found that none of them obeyed a normal distribution. Therefore, Spearman's rank correlation coefficient was used to estimate the relationship between daily outpatient visits for urticaria and environmental factors.

2.3.2. Construction of statistical models

Daily outpatient visits for urticaria were combined with meteorological factors and air pollutants and linked by date. Time series analysis was used to estimate the overall associations over the whole study period (2014–2019). The population of Shijiazhuang city did not vary significantly throughout the study period, and daily urticaria outpatient visits approximately obeyed a Poisson distribution. The standard Poisson approach may lead to greater errors when deviations in the estimates of the effects of ambient air pollutants and meteorological factors on daily urticaria outpatient visits violate the assumption of constant overdispersion, so the quasi-Poisson distribution was used instead of the Poisson distribution in this study (Bouche et al., 2009; Liao et al., 2016; Pan et al., 2018). Many studies have shown nonlinearity and lags in the effects of environmental factors on human health outcomes (Hu et al., 2020; Wang et al., 2021a; Wang et al., 2021b). Hence, we used a generalized linear regression model combined with a distributional lag nonlinear model (with a quasi-Poisson distribution for the family of functions) to investigate the lagged effect of environmental factors on daily outpatient visits for urticaria. Previous studies have confirmed the existence of a large number of complex correlations between meteorological factors and air pollutants (Analitis et al., 2018; Ulpiani et al., 2021). To avoid the effect of multicollinearity on model stability, we constructed models that included only CO, NO_2, O_3, temperature, and relative humidity, respectively. In addition, we apply penalized cubic smoothing spline functions to some variables with complex nonlinear relationships, such as calendar time, daily wind speed, and daily air pressure, to adjust for long-term trends, seasonal effects, and the effects of meteorological factors. We choose the degrees of freedom (df) for calendar time (df = 7), wind speed (df = 3), and air pressure (df = 3) according to Akaike's information criterion for quasi-Poisson (Q-AIC). In addition, we incorporated a categorical variable for the day of the week (DOW) to control for the variation in daily urticaria clinic visits within each week. The model equation was as follows:

$$Log\left[E\left(Y_t\right)\right] = a + W_x^n? + ns(time, 7 * year) + ns(WS, df) + ns(AP, df) + as.factor(dow)$$

Y_t is the number of daily outpatient visits for urticaria on day t, $E\left(Y_t\right)$ is the mathematical expectation of the number of daily outpatient visits for urticaria on day t; α is the intercept of the model; $W_x^n\eta$ denotes the cross-basis function, which is used to assess the nonlinear and lagged relationships among air pollutants, meteorological factors and daily urticaria visits by constructing a cross basis matrix. A quadratic B spline function with three degrees of freedom was chosen for the basis function of the exposure dimension and a quadratic polynomial function for the lagging dimension; we used natural cubic spline functions to control for seasonal variation, long-term trends, meteorological factors. Dow is a categorical variable indicating the day of the week effect and was included in the model as a dummy variable to control for the effect of a particular day of the week (Gasparrini et al., 2010). We used Akaike's quasi-Poisson information criterion(Q-AIC) to determine the degrees of freedom for each variable in the model (Portet, 2020). Based on the latency period of urticaria and a review of previous literature, we set the maximum lag days to 14 days (Bedford, 2004; Gisondi et al., 2021; Sharma and Dhar, 1995; Stock, 2009; Tanaka et al., 2017; Végh et al., 2017).

In this study, the effects of extreme meteorological factors and air pollution indicators on daily outpatient visits for urticaria were analyzed and obtained relative risk (RR) by comparing the 90th above or 10th below percentiles of the meteorological variables and air pollution indicators to their median values. The incubation period of urticaria is 0–14 days (average: 7 days), we described the characteristics of the cumulative lag effect with lag days of lag 0, lag 0–3, lag 0–5, lag 0–7, lag 0–10, and lag 0–14 respectively. Finally, we perform a sensitivity analysis to evaluate the robustness of the results by changing the degrees of freedom of the time trends (6–8 dfs/year). All statistical analyses were performed with the "DLNM" and "Spline" packages in R software (version 4.1.0). All P values were two-tailed distributions, and the difference was statistically significant if $P < 0.05$.

3. Results

3.1 Descriptive statistical analysis

From January 1, 2014, to December 31, 2019 (a total of 2191 days), a total of 54,950 outpatient visits were recorded because of urticaria. The characteristics of daily outpatient visits for urticaria, air pollutants, and meteorological factors are shown in Table 1. The average number of daily outpatient visits for urticaria was 25 cases (range: 1–53 cases). The statistical descriptions of air pollutants were as follows: $PM_{2.5}$ daily average concentration was 86.59 μg/m^3 (range: 0-621 μg/m^3). PM_{10} daily average concentration was 151.10 μg/m^3 (range: 0-866 μg/m^3). SO_2 daily average concentration was 37.29 μg/m^3 (range: 4-297 μg/m^3). CO daily average concentration was 1.32 mg/m^3 (range: 0.1–10.4 mg/m^3). NO_2 daily average concentration was 50.36 μg/m^3 (range: 9-183 μg/m^3). O_3 daily average concentration was 93.38 μg/m^3 (range: 0-310 μg/m^3). Statistical descriptions of meteorological factors are as follows: The average daily temperature was 13.65 ℃ (range: -12.22-34.14°C). The average value of daily maximum relative humidity was 85.62% (range: 25.00%-100.00%). The average value of daily maximum wind speed was 10.34 m/s (range: 2.00 m/s ~ 38.00 m/s). The average value of daily maximum air pressure was 30.08 Pa (range: 29.06 Pa ~ 30.89 Pa).

Table 1
Summary statistics of urticaria cases, air pollutants and meteorological factors in Shijiazhuang, 2014–2019

Variables	Mean ± SD	Min	P_{25}	P_{50}	P_{75}	Max	IQR
Daily urticaria count							
Total	25.08 ± 7.98	1.00	20.00	25.00	30.00	53.00	10.00
Male	12.75 ± 4.84	1.00	9.00	12.00	16.00	32.00	7.00
Female	12.32 ± 4.62	0.00	9.00	12.00	15.00	33.00	6.00
Age							
< 18	16.50 ± 6.47	1.00	12.00	16.00	21.00	41.00	9.00
18–39	4.73 ± 2.64	0.00	3.00	4.00	6.00	16.00	3.00
> 39	3.86 ± 2.24	0.00	2.00	4.00	5.00	13.00	3.00
Atmospheric pollutants (μg/m^3)							
$PM_{2.5}$	86.59 ± 73.93	0.00	38.00	64.00	108.50	621.00	70.50
PM_{10}	151.10 ± 102.91	0.00	81.00	27.00	189.00	866.00	108.00
SO_2	37.29 ± 36.38	4.00	14.00	26.00	45.00	297.00	31.00
CO (mg/m^3)	1.32 ± 1.06	0.10	0.70	1.00	1.50	10.40	0.80
NO_2	50.36 ± 24.87	9.00	33.00	46.00	64.00	183.00	31.00
O_{3}_8h	93.38 ± 59.94	0.00	47.00	84.00	130.00	310.00	83.00
Meteorological factors							
Temperature (℃)	13.65 ± 11.01	-12.22	3.33	15.00	23.87	34.14	20.54
Relative Humidity (%)	85.62 ± 16.17	25.00	75.00	93.00	100.00	100.00	25.00
Wind Speed (m/s)	10.34 ± 4.32	2.00	7.00	9.00	13.00	38.00	6.00
Air Pressure (Pa)	30.08 ± 32.22	29.06	29.83	30.07	30.33	30.89	0.50

We calculated the incidence rate of urticaria from 2014 to 2019 based on the annual average population obtained from the Shijiazhuang Statistical Yearbook. The yearly incidence of urticaria in Shijiazhuang shows an inverted "V" type trend. Starting in 2014, the incidence of urticaria increased year by year, peaking in 2017, and then began to decline year by year, see Figure S1. The highest number of outpatient cases of urticaria (10,487) with an incidence rate of 102.382/100,000 were reported in 2017 and the lowest number (7,503) with an incidence rate of 75.128/100,000 were reported in 2014, see Table 2. The average number of reported cases was highest in August (988 cases) and lowest in February (524 cases) (Figure S2.a). The monthly incidence trend was similar, with the peak incidence in June and August (Figure S2.b).

Table 2
Reported incidence of urticaria in Shijiazhuang from 2014 to2019

Year	Total population (100,000)	Cases	Incidence (1/100,000)
2014	99.87	7503	75.128
2015	100.71	9237	91.714
2016	101.51	9534	93.922
2017	102.43	10487	102.382
2018	103.15	9328	90.431
2019	109.91	8861	80.621

Of the 54,950 reported outpatient cases, 27,946 were male and 27,004 were female, with a gender ratio of 1.03:1. The incidence of urticaria was higher in males than in females, and the difference was statistically significant by a chi-square test ($P < 0.05$). The total number of male and female patients increased first during the 6 years period, reaching a maximum in 2017 and then decreasing (Figure S3.a). The average monthly number of outpatient visits for both males and females also showed a trend of increasing and then decreasing, reaching a maximum in August for both males and females (Figure S3.b).

The study population was divided into the following age groups: 0–4 years, 5–14 years, and then an age group of 10 years up to ≥ 85 years. We plotted the gender-age demographic pyramid of urticaria outpatients in Figure S4. We can see that the largest proportion of patients were in the 0–4 years age group and 5–14 years age groups. In addition to this, there were more male patients than female patients in the 0–4 years age group, 5–14 years age group, 75–84 years age group, and ≥ 85 years age group, while there were fewer male patients than female patients in all age groups between 15–74 years. This suggests that men are susceptible to urticaria in childhood and old age, while women are susceptible to urticaria in middle age. We stratified the patients into 3 age groups (< 18 years, 18–39 years, and > 39 years) for analysis. The age of the patients ranged from a few months to 94 years, with the majority concentrated in the < 18 years age group (approximately 65.77%). The number of patients in all three age groups first increased and then decreased from year to year. The difference is that the number of patients in the < 18 years age group peaked in 2017, and the peak in the remaining two age groups was in 2015. Compared to the < 18 years age group, the temporal trend plots were flat with little change in the 18–39 years and > 39 years age groups (Figure S5.a). The monthly trend plots for each age group showed that the number of urticaria outpatients in the < 18 years age group peaked in August, reminding us that summer is the peak season for childhood urticaria visits. In contrast, the other two age groups showed insignificant changes (Figure S5.b).

3.2 Correlation Analysis

Table 3 demonstrates the matrix of correlation coefficients between meteorological factors, air pollutant concentrations, and daily outpatient visits for urticaria. The correlations between each variable and daily urticaria visits reached the level of significance. Daily outpatient visits for urticaria were positively correlated with O_3 ($r = 0.40$), and negatively correlated with other pollutants ($PM_{2.5}$: $r = -0.28$; PM_{10}: $r = -0.30$; SO_2: $r = -0.37$; CO: $r = -0.26$; NO_2: $r = -0.23$). In addition, daily outpatient visits for urticaria were positively correlated with temperature ($r = 0.53$) and relative humidity ($r = 0.18$), and negatively correlated with wind speed ($r = -0.05$) and air pressure ($r = -0.43$). We considered the strong correlation between air pollutants and meteorological factors, so we constructed univariate models to avoid the generation of multicollinearity.

Table 3
Spearman rank correlation coefficients between daily air pollutant concentrations, meteorological factors and the number of urticaria outpatient cases reported daily in Shijiazhuang, 2014–2019

Variables	Cases	$PM_{2.5}$	PM_{10}	SO_2	CO	NO_2	O_3_8h	Tavg	Max RH	Max WS	Max AP
Cases	1.00										
$PM_{2.5}$	-0.28*	1.00									
PM_{10}	-0.30*	0.96*	1.00								
SO_2	-0.37*	0.61*	0.64*	1.00							
CO	-0.26*	0.88*	0.85*	0.66*	1.00						
NO_2	-0.23*	0.75*	0.77*	0.65*	0.82*	1.00					
O_3_8h	0.40*	-0.34*	-0.30*	-0.34*	-0.42*	-0.41*	1.00				
Tavg	0.53*	-0.41*	-0.39*	-0.47*	-0.51*	-0.49*	0.77*	1.00			
Max RH	0.18*	0.19*	0.12*	-0.17*	0.10*	0.02	0.07*	0.27*	1.00		
Max WS	-0.05*	-0.27*	-0.20*	-0.09*	-0.29*	-0.29*	0.17*	0.11*	-0.28*	1.00	
Max AP	-0.43*	0.29*	0.27*	0.37*	0.37*	0.39*	-0.70*	-0.88*	-0.27*	-0.08*	1.00

TAvg: 24-hour average temperature; Max RH: 24-hour maximum relative humidity

Max WS: 24-hour maximum wind speed; Max AP: 24-hour maximum air pressure

*$P < 0.05$

3.3 Seasonal distribution

As shown in Fig. 2, there is a clear seasonal pattern of daily outpatient visits for urticaria, meteorological factors, and air pollutants. The peak incidence of urticaria was observed from June to August each year. The air pollutants and meteorological factors have a clear cyclical pattern. For air pollutants, we found that the concentration of O_3 was low in winter and high in summer. While the seasonal distribution of other pollutants is exactly the opposite. For meteorological factors, we found that the temperatures gradually increase from January, reaching a maximum in June, and then gradually decrease. The relative humidity is lowest in March, reaching a peak in August. Wind speed reaches its maximum in April, and then gradually decreases. However, the range of air pressure is not obvious.

3.4 Analysis of lag effect

We used contour plots to demonstrate the lagged effect of environmental factors on daily urticaria visits, as shown in Fig. 3. Each 1 mg/m^3 increase in CO concentration resulted in an increased risk of urticaria outpatient visits, with the risk reaching a maximum at 14 days lag (RR = 1.03, 95%CI: 1.00, 1.05). Each 10 μg/m^3 increase in NO_2 and O_3 resulted in the greatest risk of urticaria outpatient visits at 0-day lag (NO_2: RR = 1.01, 95%CI: 1.00, 1.03; O_3: RR = 1.01, 95%CI: 1.00, 1.01). Each 1°C increase in temperature was associated with the risk of outpatient visits for urticaria, with the greatest risk occurring at 0-day lag (RR = 1.01, 95%CI: 1.00, 1.02). The relative humidity was a protective factor for urticaria outpatient visits, with the smallest risk at 0-day lag (RR = 0.99, 95%CI: 0.98, 0.99).

We plotted the dose-response relationship between meteorological factors, air pollutants, and daily urticaria visits using the median as the reference value, as shown in Fig. 4. We found the relationship between meteorological factors, air pollutants, and daily urticaria visits was non-linear. The dose-response curve between CO and daily urticaria visits was approximately inverted "V" type, with the risk peaking at 6 mg/m^3 (RR = 1.39, 95%CI: 1.09, 1.76). We observed that the risk of urticaria outpatient visits increased with increasing NO_2 concentrations, the risk was greatest when NO_2 concentrations reached a maximum of 183 μg/m^3 (RR = 2.27, 95%CI: 1.20, 4.28). Low concentrations of O_3 can reduce the risk of outpatient visits for urticaria. The high concentration of O_3 is a risk factor for the urticaria outpatient, with the highest risk at concentrations up to 181 μg/m^3 (RR = 1.16, 95%CI: 1.08, 1.25). We observed an approximate "M" type dose-response curve for temperature and urticaria outpatient with two peaks at 1°C (RR = 1.05, 95%CI: 0.90, 1.23) and 25°C (RR = 1.22, 95%CI: 1.06, 1.40), the first peak was not statistically significant. For relative humidity, we found that low humidity presents a protective effect. In contrast, high humidity increased the risk of urticaria outpatient visits. The relative risk was greatest at a relative humidity of 78% (RR = 1.05, 95%CI: 1.00, 1.10).

Figure 5 shows the effect of extreme meteorological factors and pollutant concentrations at different lags on daily outpatient visits for urticaria. We observed a protective effect of low concentrations of CO on daily outpatient visits for urticaria throughout the lag period. High concentrations of CO corresponded to a higher risk of daily outpatient visits for urticaria, with the relative risk reaching a maximum at 14 days lag. We observed that low concentrations of NO_2 significantly reduced the risk of urticaria outpatient visits at 0-day lag. The effect of high concentrations of NO_2 approximated a "U" type, it could decrease the risk of urticaria outpatient visits, with minimal risk at 9 days lag, and then begins to increase gradually again as the lag period increases. Low concentrations of O_3 significantly reduced the risk of urticaria visits, while the effect of high concentrations of O_3 showed the opposite result. The high temperature was significantly associated with the risk of daily outpatient visits for urticaria, with the largest effect being at 0-day lag. We failed to find any significant association between low temperature and the risk of daily outpatient visits for urticaria. High humidity reduced the risk of daily outpatient visits for urticaria, it has the largest protective effect at 0-day lag. However, the effect of low humidity was not statistically significant throughout the lag period.

Table 4 demonstrates the cumulative risk of extreme air pollution and meteorological factors on urticaria outpatient visits at different lag periods. We observed that high concentrations of CO, NO_2, O_3, and high temperature increased the cumulative risk of urticaria clinic visits. The cumulative risk of CO, NO_2, and O_3 increased with the increase of lag days and reached the maximum at lag 0–14 days. The cumulative risk of high temperature was the largest at lag 0–7 days (RR = 1.27, 95%CI: 1.14, 1.41). On the contrary, low concentrations of NO_2, O_3, and high humidity decreased the cumulative risk of urticaria clinic visits. Low concentrations of NO_2 were associated with the lowest RR at 0-day lag (RR = 0.76, 95%CI: 0.66, 0.88). The cumulative effects for the low concentrations of NO_2 between lag 0–3 days (RR = 0.95, 95%CI: 0.89, 0.99) to lag 0–5 days (RR = 0.94, 95%CI: 0.88, 0.99) were statistically significant. High humidity corresponded to the lowest risk at lag 0–10 days (RR = 0.93, 95%CI: 0.89, 0.98).

Table 4
The cumulative effect of pollution factors and climate factors on urticaria outpatient visits

Variables	Lag0	Lag0-3	Lag0-5	Lag0-7	Lag0-10	Lag0-14
CO						
P_{10} = 0.5	0.98(0.96,1.00)	0.97(0.94,1.00)	0.96(0.92,1.00)	0.96(0.91,1.00)	0.95(0.90,1.01)	0.95(0.83,1.01)
P_{90} = 2.6	1.02(0.99,1.05)	1.04(0.99,1.10)	1.05(0.99,1.12)	1.07(0.99,1.15)	1.09(1.00,1.20)*	1.10(1.06,1.31)*
NO_2						
P_{10} = 23	0.97(0.95,0.99)*	0.97(0.94,1.01)	0.98(0.94,1.02)	0.97(0.93,1.01)	0.96(0.91,1.01)	0.98(0.92,1.04)
P_{90} = 84	1.03(1.00,1.05)*	1.07(1.03,1.12)*	1.08(1.03,1.13)*	1.08(1.02,1.14)*	1.09(1.00,1.14)*	1.09(1.01,1.18)*
O_3						
P_{10} = 20	0.99(0.96,1.03)	0.95(0.89,0.99)*	0.94(0.88,0.99)*	0.95(0.89,1.02)	0.96(0.88,1.04)	0.92(0.83,1.02)
P_{90} = 180	1.04(1.02,1.07)*	1.08(1.04,1.13)*	1.10(1.05,1.16)*	1.13(1.08,1.20)*	1.15(1.09,1.23)*	1.16(1.08,1.25)*
Temperature						
P_{10}=-1.6	0.94(0.85,1.05)	0.92(0.82,1.03)	0.93(0.82,1.06)	0.94(0.81,1.07)	0.94(0.80,1.09)	1.02(0.85,1.22)
P_{90} = 27.2	1.17(1.08,1.25)*	1.12(1.04,1.22)*	1.24(1.12,1.36)*	1.27(1.14,1.41)*	1.24(1.09,1.40)*	1.21(1.03,1.41)*
Humidity						
P_{10} = 62	0.99(0.96,1.03)	0.99(0.93,1.05)	1.01(0.93,1.08)	1.02(0.94,1.10)	1.03(0.94,1.13)	1.03(0.92,1.15)
P_{90} = 100	0.98(0.96,0.99)*	0.97(0.95,1.00)	0.96(0.92,0.98)*	0.94(0.91,0.98)*	0.93(0.89,0.98)*	0.95(0.90,1.00)
*P < 0.05						

3.6 Sensitivity analysis

Sensitivity analysis showed that the effects of air pollutants and meteorological factors on both the single-day lag and the cumulative lag of daily outpatient visits for urticaria were robust when we changed the degrees of freedom for time trends (6−8 dfs/year), as shown in Figure S6-S7.

4. Discussion

Shijiazhuang city has serious air pollution and chronically poor air quality due to its geographical location and production capacity structure. In this paper, we have obtained relatively complete distribution characteristics of urticaria by describing and analyzing the time trends and demographic characteristics of urticaria in Shijiazhuang in recent years. A time-series study was used to investigate the relationship between environmental factors and urticaria outpatient visits in Shijiazhuang city from 2014 to 2019. Previous studies have shown that temperature and humidity are important meteorological factors affecting urticaria (Konstantinou et al., 2011; Maltseva et al., 2021; Pezzolo et al., 2016; Zhang et al., 2021; Zhou et al., 2018). However, studies on the association between pollution factors and urticaria are scarce and the findings are inconsistent. Liu et al. showed that $PM_{2.5}$, PM_{10}, and NO_2 were significantly associated with an increase in the number of urticaria outpatient visits, but no relationship was found between SO_2 and the number of urticaria clinic visits (Liu et al., 2018). Wang et al. found that SO_2 increased the risk of urticaria outpatient visits (Wang et al., 2021c). We used a distributed lag nonlinear model to explore the effects of air pollutants and meteorological factors on urticaria outpatient visits. We found that high concentrations of CO, NO_2, O_3, and high temperatures increased the risk of urticaria outpatient visits, while low concentrations of NO_2, O_3, and high humidity would act as a protective factor. Therefore, more research is needed in the future to investigate the effects of air pollutants on outpatient visits for urticaria.

The seasonal distribution suggests that the peak number of outpatient visits for urticaria is concentrated between June and August each year, with a certain seasonality and periodicity, a finding that is consistent with previous studies (Banerjee et al., 2010; Kim et al., 2013; Konstantinou et al., 2011). Multiple factors, both biotic and abiotic, may be responsible for this trend. In summer, high temperatures provide an environment for fleas, rodents, and mites to thrive. In particular, children are more susceptible to their bites leading to urticaria (Howard and Frieden, 1996). In addition, high ultraviolet light radiation in summer is more likely to impair the function of the immune system, leading to the development of urticaria (Kim et al., 2013).

We used a distributed lagged nonlinear model to investigate the relationship between CO and daily outpatient visits for urticaria. We found that the dose-response curve was approximately inverted "V" type, with the risk peaked at $6 mg/m^3$ (RR = 1.388, 95%CI: 1.093, 1.761). High concentrations of CO increased the risk of daily outpatient visits for urticaria compared with low concentrations, with the greatest risk occurring at 0-day lag. In addition, the cumulative effect increased progressively with increasing lag period. A study in Taiwan found a positive correlation between CO and the number of daily urticaria patient visits, especially for male patients (RR = 2.06, 95%CI: 1.48, 2.87) and older patients (RR = 4.67, 95%CI: 1.63, 13.37) (Tseng et al., 2021). A Korean study showed that each 100 ppb increase in CO was associated with a 5.00% (95% CI: 1.10%, 8.80%) increase in the number of daily outpatient visits for patients with atopic dermatitis (Oh et al., 2018). A Canadian study found that exposure to high concentrations of CO significantly increased the risk of daily emergency room visits for patients with urticaria, which is consistent with our findings (Kousha and Valacchi, 2015). CO is an odorless, colorless, and tasteless gas produced from the incomplete combustion of carbon compounds (Huang et al., 2021). High concentrations of CO exposure may lead to unconsciousness or death. Meanwhile, CO is strong oxidizing agent, triggering oxidative stress and skin barrier dysfunction could be reasons for this relationship (Abolhasani et al., 2021).

In terms of NO_2, we found that the risk of urticaria outpatient visits increased with increasing NO_2 concentration. Low concentrations of NO_2 were protective factors against urticaria, whereas high concentrations of NO_2 increased the risk of urticaria outpatient visits. Studies have found that environmental NO_2 exposure may cause a range of skin diseases through the interaction of air pollutants with the immune system (Abolhasani et al., 2021). A Japanese study showed that the prevalence of urticaria among elementary school students attending urban schools was 12.4%, second only to atopic dermatitis, due to higher levels of NO_2 in cities (Guo et al., 2019; Hu et al., 2022). In addition, positive associations of NO_2 with urticaria visits were found in a study in Beijing, China (Wang et al., 2021). A study in Taiwan showed that the women were particularly susceptible to higher concentrations of NO_2 on the visit day (Tseng et al., 2021). A Canadian study also reported that higher values of NO_2 led to higher visit numbers for urticarial patients (Kousha and Valacchi, 2015). More and more epidemiological evidence showed that NO_2 exposure has adverse effects on various skin diseases, but the exact mechanisms are mainly unclear (Kathuria and Silverberg, 2016). An epidemiological study in Germany found that human epidermal barrier function was disrupted when short-term exposed to low concentrations of NO_2 (Eberlein-König et al., 1998). However, our study did not find a significant association between low concentrations of NO_2 and urticaria. The inconsistency of the results might be due to the difference in study designs, exposure levels, along with individual confounders (such as age, gender, and socioeconomic status). Some studies have found that NO_2 exposure may affect the skin by indirect inflammation or oxidative stress injury (Araviiskaia et al., 2019; Furue et al., 2019). A study in Chengdu, China suggests that dissolved NO_2 in water may stimulate the skin microbiota and then disrupt immune function, facilitating the development of diseases (Li et al., 2018). There are too few studies on the relationship between NO_2 and urticaria, a large number of studies are still needed to demonstrate these relationships in the future.

We found an "S" type dose-response curve for O_3 and urticaria outpatient visits, with low concentrations of O_3 being protective against urticaria and high concentrations of O_3 increasing the risk of outpatient visits for urticaria. The cumulative effect of O_3 on urticaria outpatient visits was greatest at 14 days lag. A Canadian study also confirmed that exposure to O_3 environments increases the risk of developing urticaria (Kousha and Valacchi, 2015). Furthermore, if ground-level O_3 concentrations increase, the number of emergency department visits for skin conditions such as urticaria and eczema increases in Shanghai (Xu et al., 2011). This is consistent with the results of our study. It is known that worldwide, O_3 causes hundreds of thousands of premature deaths and tens of millions of dermatology-related emergency room visits each year (Zhang et al., 2019). Previous studies have demonstrated that O_3 is a strong oxidant present in the air that induces antioxidant depletion and lipid peroxidation, causing oxidative stress in the skin, leading to chronic skin tissue damage and aggravating skin diseases such as contact dermatitis and urticaria (Fuks et al., 2019; Petracca et al., 2021). O_3 cannot penetrate human skin, but O_3 oxidizes biomolecules through the formation of free radicals and reactive intermediates. In particular, the reaction of O_3 with polyunsaturated fatty acids (PUFA), which are surfactants present at the air-cell interface, results in the formation of reactive oxygen species such as peroxyl radicals, malondialdehyde (MDA) (Petracca et al., 2021; Pryor et al., 1995). These bioactive products can act as signaling molecules that penetrate into the subcutaneous layers and cause further damage (McDaniel et al., 2018). It has also been shown that low concentrations of O_3 are protective factors against skin diseases, and ozone water therapy, topical ozone oil, and ozone autologous blood therapy have been widely used to treat various skin diseases (Zeng and Lu, 2018). Moreover, emerging evidence suggests that O_3 also plays an important role in the management and prevention of various skin diseases, including infectious skin diseases, skin-related allergic diseases, erythroderma scales, wound healing, and ulcer recovery (Wang, 2018). Therefore, different concentrations of O_3 can exhibit dual beneficial or harmful effects, with moderate O_3 concentrations acting as a protective agent for humans. However, long-term exposure to high concentrations of O_3 can trigger a range of allergic reactions. The effect of different concentrations of O_3 is complex, and further studies are needed to investigate this issue.

We found that the dose-response curve of temperature and urticaria outpatient visits is approximate "M" type. It has two peaks, the first of which is not statistically significant. High temperature increases the risk of urticaria outpatient visits. The cumulative effect was greatest at lag 0. The effect of low temperature on urticaria, on the other hand, was not statistically significant. The mechanisms for the increased risk of urticaria due to high temperature are unclear, but it may be that increased temperature favors the proliferation of fungi and bacteria and that the body is more easily exposed to allergens, causing oxidative stress in the body and thus increasing the risk of urticaria (Demain, 2018; Gonçalves et al., 2021). It has also been shown that temperature changes alter allergen exposure and may also disrupt the immune system's specific tolerance to allergens, compromising the body's immune system and causing an increased risk of urticaria (Ray and Ming, 2020). This reminds us to reduce the risk of urticaria by going out less in hot weather. In addition to this, warmer climates can lead to an expansion of the distribution of the processional moth, which carries urticarial bristles that can more easily cause urticaria in humans and other warm-blooded animals (Battisti et al., 2017; Vasseur et al., 2022). A study in Poland showed a direct correlation between temperature and daily Artemisia pollen levels, with higher temperatures leading to a longer Artemisia pollen season and a significant increase in human exposure to allergens, causing chronic urticaria in 14.3% of patients (Stach et al., 2007). It has also been shown that cold exposure causes the development of allergic reactions such as urticaria and angioedema, and its pathophysiology is believed that cold exposure leads to the formation of IgE from auto allergens, which can stimulate the release of pro-inflammatory mediators from skin mast cells, causing the development of cold urticaria and a series of allergic reactions (Işk et al., 2014; Maltseva et al., 2021). Our study did not find an effect of low temperature on urticaria, and the effect of temperature on urticaria remains to be explored because of the small number of relevant studies.

For relative humidity, we found that the dose-response curve between humidity and urticaria outpatient visits was close to the "S" type. High humidity is a protective factor for urticaria outpatient visits compared to low humidity. An interesting German study found that a complex syndrome of urticaria and allergic reactions induced by strenuous exercise could be prevented in humid and warm weather (von Vigier et al., 1995). In contrast, a Croatian study showed that higher air humidity was a predisposing factor for exercise-type allergic reactions (Plavec and Vuljanko, 2010). The results of the two studies may be inconsistent due to geographical reasons and individual differences. A European epidemiological study elucidated that acute childhood urticaria showed similar epidemiological patterns in Northern and Southern Europe regardless of expected differences in genetic, geographical, and environmental background, with humidity significantly and negatively associated with the incidence of acute urticaria (Konstantinou et al., 2011). This is consistent with the results of our study.

The present study has several advantages. First, Shijiazhuang is one of the representative cities in northern China with severe pollution, which provides a natural site for us to study the relationship between air pollutants, meteorological factors, and urticaria. Second, this study explores the distribution characteristics and demographic features of urticaria for the first time, and it helps us to keep abreast of current disease patterns. Finally, we used a distributed lag nonlinear model to quantify the effects of air pollutants and meteorological factors on daily outpatient visits for urticaria, and examined in depth the effects of extreme air pollutants concentrations and meteorological factors on daily outpatient visits for urticaria. The robustness of the results was evaluated by changing the degrees of freedom for time trends (6–8 dfs/year), and the results were found to be stable and reliable.

However, our study has several limitations. First, we collected data from only three hospitals in Shijiazhuang for outpatient visits for urticaria, which may lead to information bias in the study results due to insufficient study population, and the findings still need to be validated on a larger population. In addition, the air pollutant data were obtained from seven fixed monitoring sites in Shijiazhuang, and we assumed that the population in each area of Shijiazhuang was exposed to the same level of air pollutant concentrations. In fact, the exposure levels varied in each area of the population, which introduced measurement bias. Previous studies have shown that indoor air pollutants and meteorological factors have a certain impact on urticaria. Individual exposure levels differed indoors and outdoors, and we only examined the effects of outdoor air pollutants and meteorological factors on urticaria outpatient visits. Finally, due to limitations in data availability, we did not assess the effects of other confounding factors on urticaria outpatient visits, such as health status, occupation, marital status, and educational status.

5. Conclusions

In conclusion, we found that the development of urticaria is characterized by apparent seasonal fluctuations. Air pollutants and meteorological factors had varying degrees of influence on the risk of urticaria outpatient visits. High concentrations of CO, NO_2, O_3, and high temperatures increase the risk of urticaria outpatient visits. Low concentrations of NO_2, O_3, and high humidity, on the other hand, act as protective factors. Our findings undoubtedly provide evidence of the association between air pollutants, meteorological factors, and urticaria, which could help to assess the likely impacts of future climate change on health and provide a scientific basis for relevant departments to take preventive measures, especially in the heavily polluted northern China.

Declarations

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Contributions

Yaxiong Nie: Software, Formal analysis, Writing - Original Draft, Visualization, Data Curation. Shilin Xue: Software, Visualization. Lina Yan: Resources, Investigation. Ning Ma: software, Investigation. Xuehui Liu: Investigation, Writing – Review & Editing. Ran Liu: Writing - Review & Editing. Xue Wang: Writing - Review & Editing. Yameng Wang: Writing - Review & Editing. Xinzhu Zhang: Writing - Review & Editing. Xiaolin Zhang: Conceptualization, Methodology, Supervision, Project administration. Lijuan Lu: Data Curation, Project administration.

Data Availability Statement

Our data are not publicly available. Data were obtained from the First Hospital of Hebei Medical University, Hebei Children's Hospital and the First Hospital of Shijiazhuang. Please contact the appropriate unit if needed.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the First Hospital of Hebei Medical University.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Figures

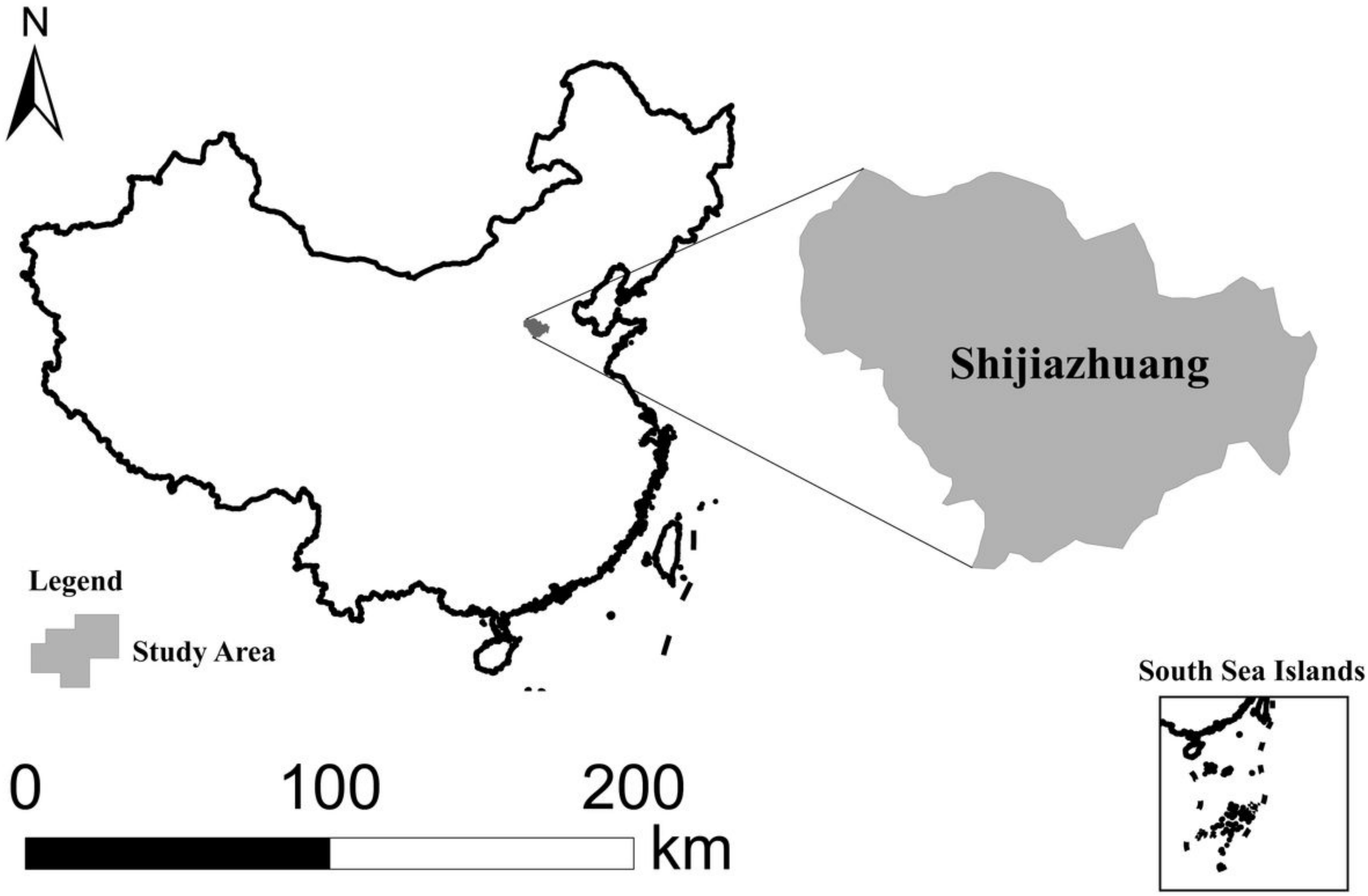

Figure 1

The location information of Shijiazhuang

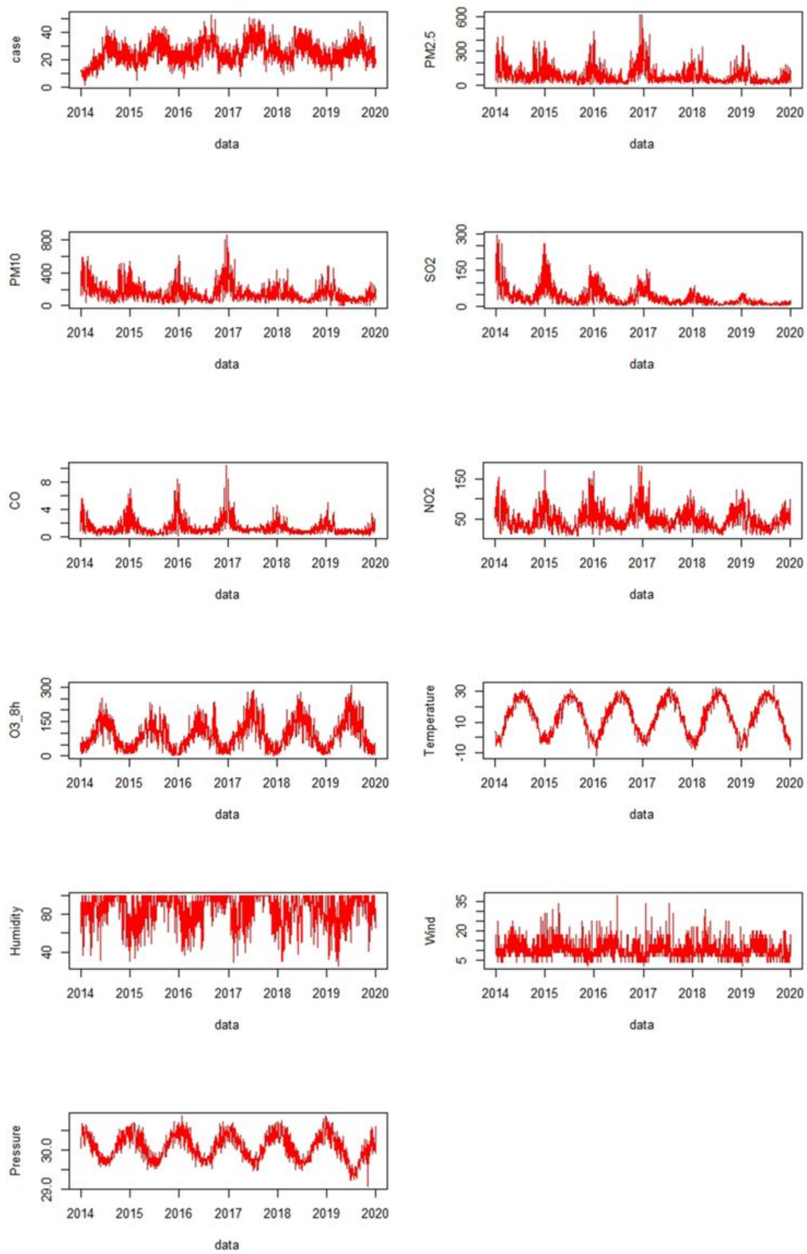

Figure 2

Time series analysis in air pollutants, meteorological factors, and urticaria outpatient visits in Shijiazhuang, 2014-2019

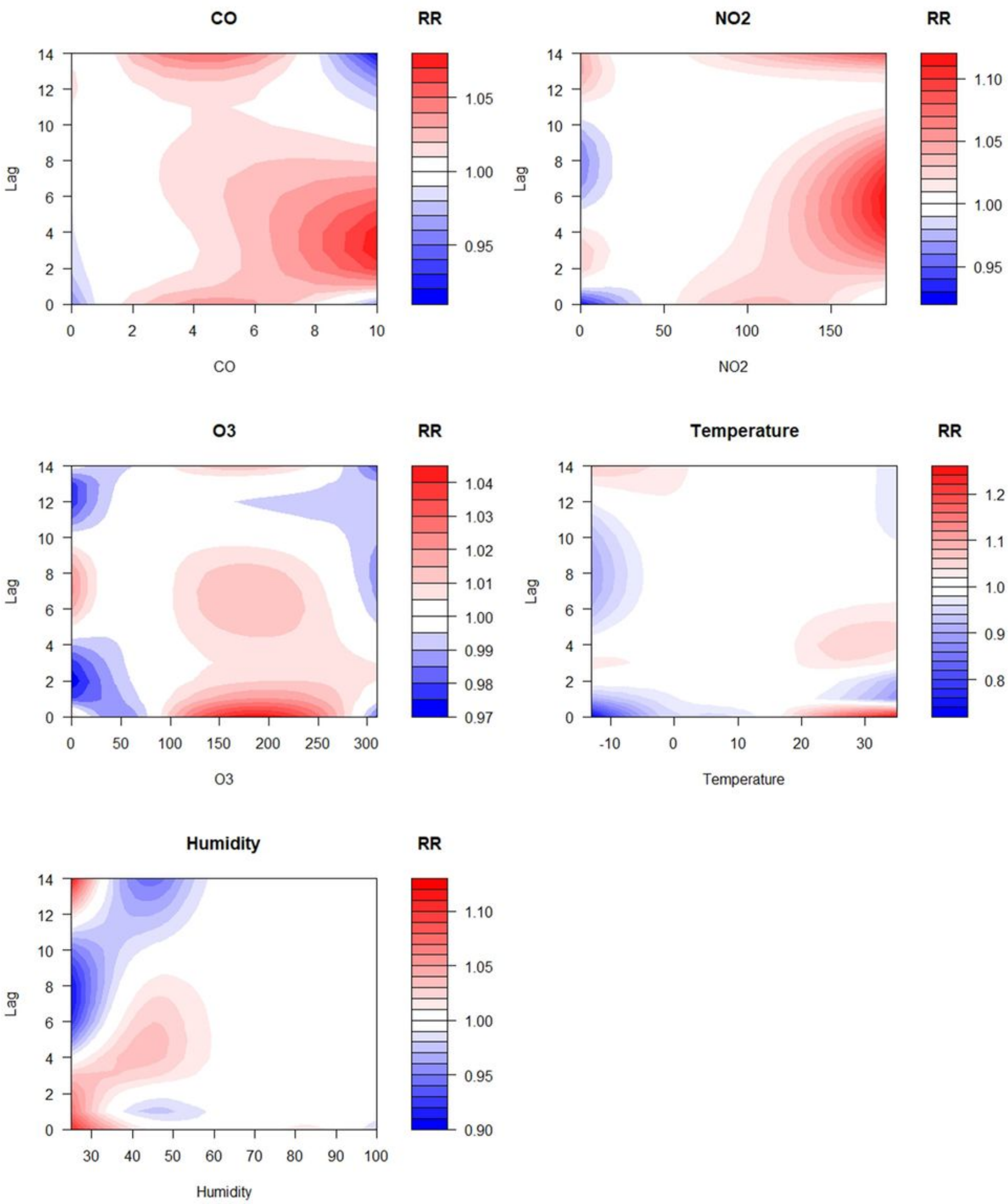

Figure 3

Contour plots of the single-day lagged effects of air pollutants and meteorological factors on daily urticaria visits

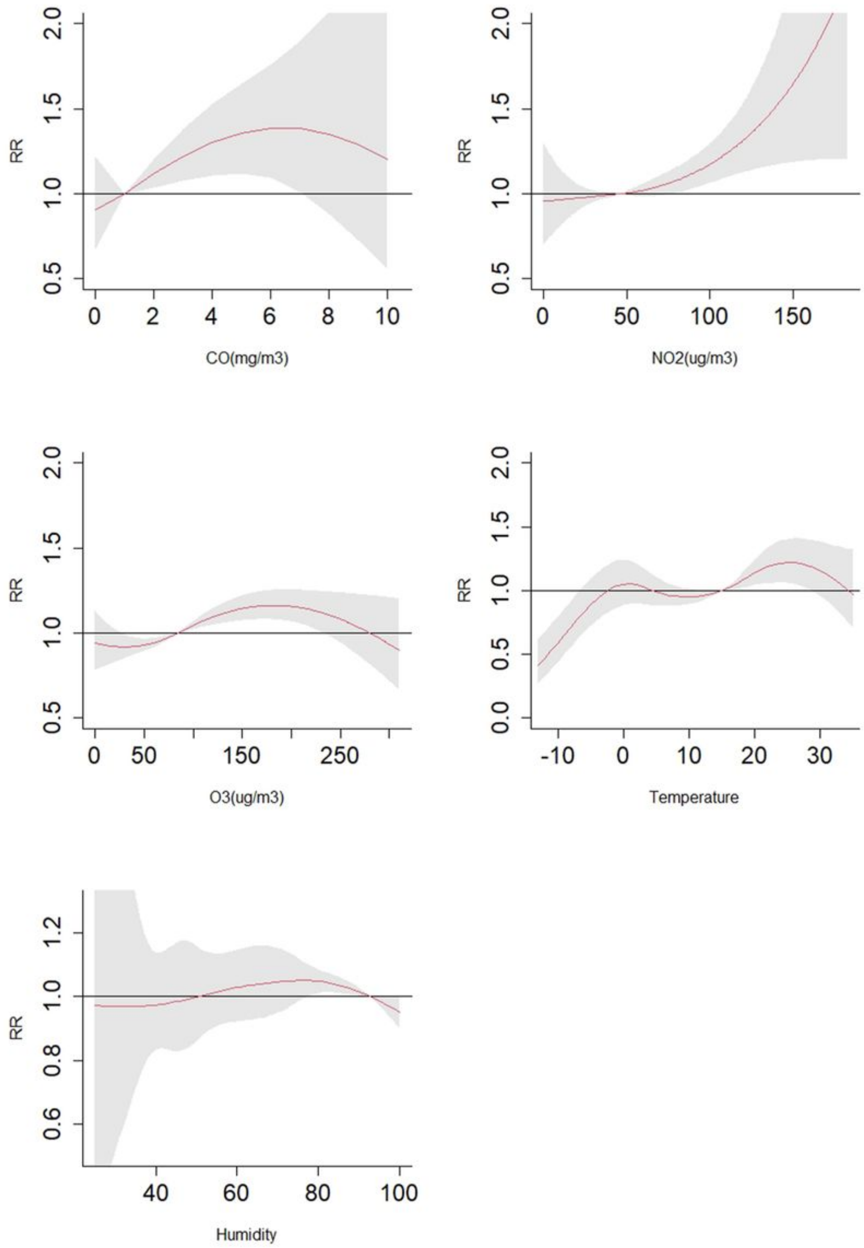

Figure 4

Impacts of meteorological factors and air pollution concentrations on daily outpatient visits for urticaria within 14 days

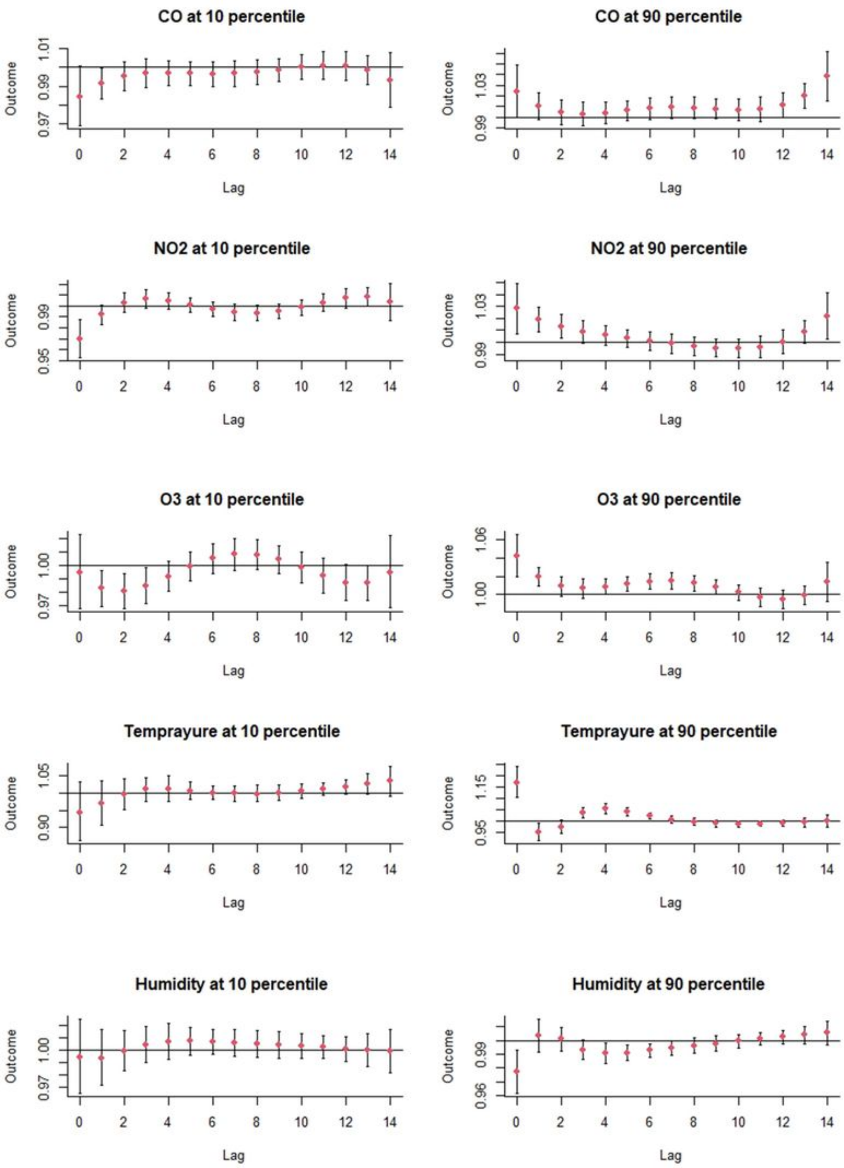

Figure 5

Lag effects of extreme air pollutant concentrations and meteorological factors on daily outpatient visits for urticaria

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementaryinformation.doc