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Association between Air Pollution Exposure and Daily Outpatient Visits for Dry Eye Disease: A Time-Series Study in Urumqi, China

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Abstract: The potential effects of air pollution on the ocular surface environment have not been fully evaluated, and even fewer studies have been conducted on the lagged effects of air pollution on dry eye disease (DED). The data of 9970 DED outpatients between 1 January 2013 and 31 December 2020, and data for six air pollutants, including PM₁₀, PM_{2.5}, carbon monoxide (CO), sulfur dioxide (SO₂), nitrogen dioxide (NO₂), and ozone (O₃), were obtained from 11 standard urban background stationary air quality monitors in Urumqi, Xinjiang, China. Time series analysis design and quasi-Poisson generalized linear regression models combined with distributed lagged nonlinear models (DLNM) were used. Single- and multi-pollutant model results suggest that each additional per 10 µg/m³ of PM₁₀, NO₂, and SO₂ is associated with an increased risk of outpatient DED on lag day 0 and PM_{2.5}, NO₂, and SO₂ with other cumulative lag days; R software version 4.0.4 (15 February 2021) was used for the analysis. We conducted first time series analysis with a large sample size in northwest China (Xinjiang) and confirmed, for the first time, the impact of air pollution including particulate pollutants (PM₁₀, PM_{2.5}) and acidic gasses (SO₂, NO₂) on DED risk in the Urumqi region, and suggested the potential lagged effects of PM_{2.5}, SO₂, and NO₂.

Keywords: dry eye disease; air pollution; time-series analysis; outpatient visits

1. Introduction

Air pollution is known to be associated with cardiovascular disease, stroke [1], asthma [2], and some ocular diseases [3–5]. These diseases have attracted significant societal attention. However, the potential effects of air pollution on the ocular surface environment are often overlooked. At the same time, studies on the lagged effects of air pollution on ocular diseases are limited, with insufficient sample size and time span.

Dry eye disease (DED) is a common ocular surface disorder with clinical manifestations, such as redness, increased discharge, and visual fatigue. Clinical manifestations are exacerbated in environments such as high winds and is thought to be related to ocular

surface damage and impaired tear film stability [6,7]. DED prevalence has increased every year in recent years, with approximately 7.8% (3.23 million) of American women and 4.7% (1.68 million) of American men over 50 years of age reported to be affected [8], and it is even higher in Asia [9]. Another survey in Canada that included all age groups found that approximately 60.7% of DED patients were women, and women also made up most of the severe DED population [10]. The prevalence of DED in China is 17–21% [11], and it is even higher in outpatients (61.57%) [11,12]. Yu Donghui et al. published a new national survey on the prevalence of outpatient DED in China in 2019. They surveyed 23,922 eligible patients with DED registered in outpatient ophthalmology clinics in 32 cities in China and discovered that the prevalence of DED among outpatients was 61.57%, with 57.64% in men and 65.32% in women [12]. A systematic review and meta-analysis reported that the prevalence in western and northern China was significantly higher than in the southeastern area, which strongly suggests the potential importance of regional factors. DED has become a growing public health problem worldwide, particularly in China, due to its impact on daily activities and quality of life [6,13].

Previous research has linked some risk factors with DED, such as age, gender, and smoking status, as well as the prevalence of electronic devices, such as smartphones and computers. Chronic lack of sleep and fatigued eye use also contribute to the development of DED [13,14]. However, research on air pollution is still limited [11,15,16] because the corneal and conjunctival epithelia are separated from the air by a superficial tear film. Penetrating air pollutants can cause conjunctival dysfunction and imbalance in the ocular environment through this specific structure, and recent studies have also supported that air pollution can cause subclinical changes in the ocular surface [17–19]. There has been evidence suggesting that air pollution appears to be strongly associated with DED; this may be related to the type of pollutant as well as the lagged effect. However, until now, there have been relatively few relevant studies [17,18,20,21].

Urumqi is the capital of Xinjiang Uyghur Autonomous Region (hereinafter referred to as “Xinjiang”), which is in northwest China. Urumqi is characterized by large temperature differences between day and night, dryness, and extreme weather, such as sand-dust storms. The harsh climatic conditions have resulted in Urumqi covering a vast area, but with few habitable sites, showing a dotted distribution and a vast uninhabited area. In recent decades, as the world’s farthest inland city from the ocean and the political, economic, cultural, scientific, educational, and transportation center of Xinjiang, Urumqi has become one of the most rapidly growing large cities in western China. The high proportion of road transport and local industrial pollution has significantly increased in Urumqi, exacerbating the region’s poor air quality. To our knowledge, there have been no studies examining the relationship between air pollution and eye health in Urumqi, not to mention DED. The limited research evidence has been mainly concentrated on eastern cities, but the central and western regions should receive more attention due to their special climatic conditions and population distribution characteristics [22].

In this study, we aimed to systematically investigate the relationship between six major air pollutants and DED outpatient visits in the Urumqi region. We investigated the types of different air pollutants and their lagged effects of DED over a long period of time. We also analyzed the effects of individual characteristics through a time-series design with separate tests of the distribution of factors, such as patient gender, age, and season. We conducted these researches in order to further understand and address this growing public health problem.

2. Materials and Methods

2.1. Study Site

This study was conducted in the city of Urumqi, in the central part of Xinjiang province in northwest China and the center of the Asia-Europe continent. There are seven districts and one county with a total area of 13,800 square kilometers. With a resident population of 4.07 million in 2021, Urumqi has a medium-temperate continental arid climate. The hottest

months are July and August, when the average temperature is 25.7 °C, and the coldest month is January, when the average temperature is −15.2 °C. Coal carbon energy utilization and high proportions of road transport are the main sources of local air pollution.

2.2. Study Population

We conducted this retrospective time-series analysis study in the ophthalmology department of the First Affiliated Hospital of Xinjiang Medical University (Urumqi, Xinjiang, China), which is the largest and most popular medical institution in Xinjiang. We obtained clinical outpatient data from 1 January 2013 to 31 December 2020 in this hospital. The hospital has the largest and most modern ophthalmology clinic in Xinjiang province. As a hospital under the supervision of the Chinese Ministry of Health, it is considered “one of the top ten in China and the first in Northwest China” and has received many awards and general recognition from medical colleagues. It is the leader in the treatment of ocular surface diseases such as DED in Xinjiang province, and it has conducted many epidemiological surveys of eye diseases in the province. As a result, it has become the preferred and most favored medical institution for patients with eye diseases in Xinjiang and surrounding areas, including Urumqi.

Outpatient visit information was extracted from the electronic medical record system, including date of visit, diagnosis, and basic details such as gender, age, and current and permanent residence (zip codes). We prioritized the inclusion of the current address for follow-up studies when there were discrepancies in the above location information. Our study only focused on primary care patients, excluding emergency patients and those who had lived in Urumqi for less than 6 months, to reduce potential bias.

The International Classification of Diseases standard code [ICD-10] ophthalmology section was used for diagnosis, and H11.103 represents DED. In addition, we examined the diagnostic entries for DED in the outpatient medical records and the corresponding chief complaints, as well as ophthalmologic examinations. The final diagnostic information included was reviewed by physicians with intermediate or higher qualifications in the department or by the corresponding attending physicians to ensure the accuracy of the diagnosis and data classification. The geographical location of the hospital is shown in Figure 1 and Supplementary Material B.

2.3. Atmospheric Pollutants and Meteorological Data

All public meteorological data including daily average temperature (°C), relative humidity (%), and atmospheric pressure (hPa) were obtained from the China Meteorological Data Sharing Service (<http://data.cma.cn>, accessed on 10 December 2022). PM_{2.5} (daily 24-h average), PM₁₀ (daily 24-h average), CO (daily 24-h average), NO₂ (daily 24-h average), SO₂ (daily 24-h average), and O₃ (maximum daily 8-h average) were obtained from 11 standard urban background fixed-point air quality monitoring stations in Urumqi. Shoufusho (SFS), Sanshi Yizhong (SHYZ), Wenquan (WQ), Hongguang Mountain (HGS), Green Valley (LG), Xinjiang Nongken (XJNK), Jianshishan (JCZ), Railway Residence (TLJ), and Midong Baohuju (MDBHJ). Daban Baoju (DBBHJ), Peixun Jidi (PXJD), and the latitude, longitude, and distribution of each site are shown in Figure 1 and Supplementary Material B.

2.4. Statistical Analysis

Correlation analysis between air pollutants and meteorological factors in the Urumqi region was performed by Spearman correlation coefficient analysis with the R package. The “seasons” package was used to set alternative values for the control groups in the model. “Day of the week (DOW)” was used as an indicator variable to reconcile long-term trends, seasonal pattern effects, and day-of-the-week effects. To assess potential lagged effects of air pollutants, lags of up to 7 days were included in the model for cumulative and non-cumulative exposures, similar to the methodology of similar previously published studies. For example, cumulative effects were the average concentration effect for lags 0–n days and non-cumulative effects defined as the exposure effect for lags 0 to lags n days

before [22,23]. The maximum value of relative risk (RR) and the minimum value of p were used to calculate the optimal lag date for each lag model.

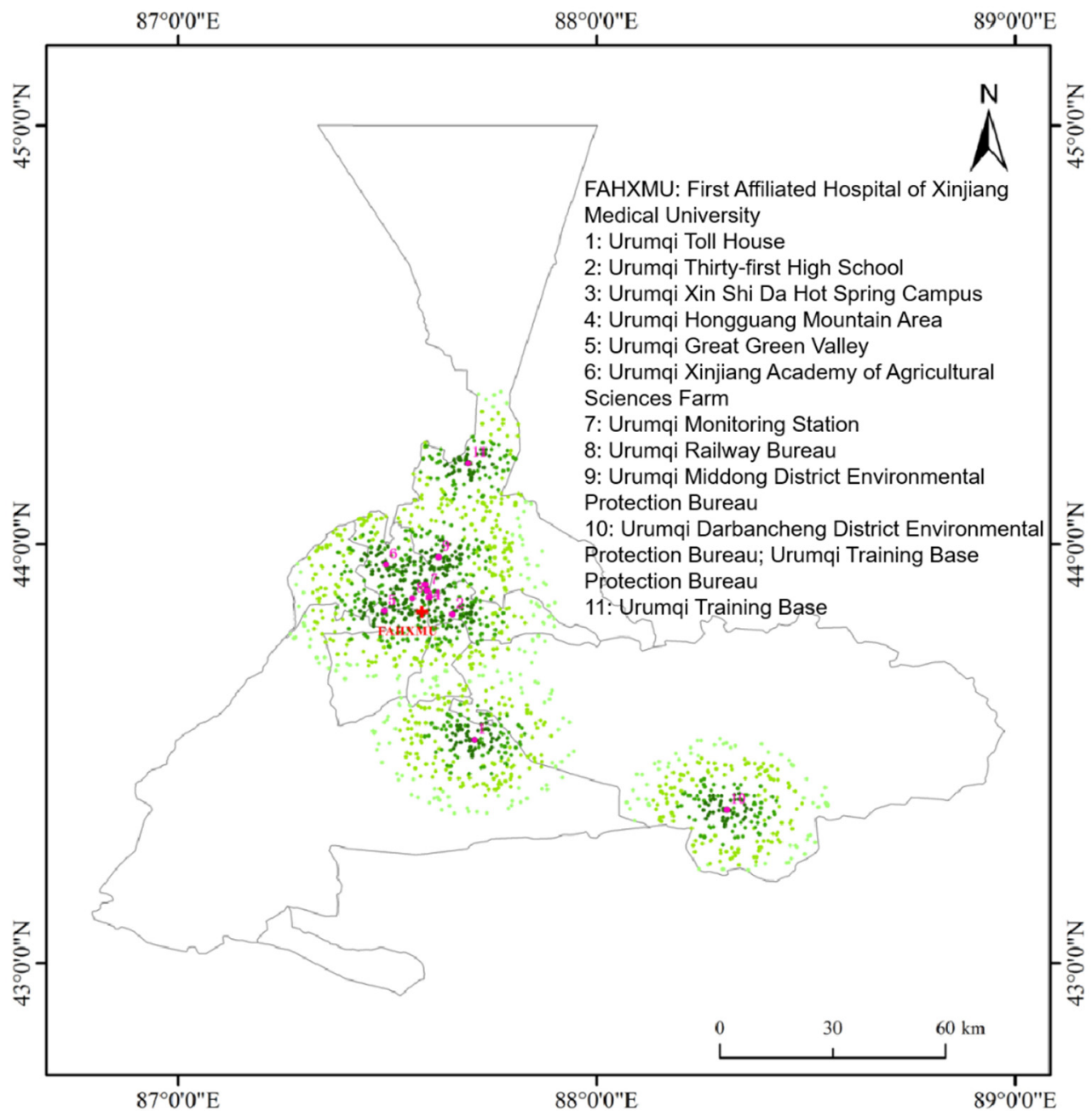


Figure 1. Location of environmental monitoring stations and hospital in Urumqi, Xinjiang. The location of each air quality monitor is marked with a pink dot; the location of the hospital is marked with a red cross; the home address of each recruited patient is marked with a green dot.

Considering that daily outpatient visits for DED are considered rare events that approximate a quasi-Poisson distribution, we used a quasi-Poisson generalized linear regression model with a distributed lagged nonlinear model (DLNM) to fit the effect of exposure to air pollutants on DED visits. Our research hypothesis is based on a few similar studies of the same type that have been published, in which the type and level of air pollution were associated with the onset of DED. Increased levels of six major air pollutants (PM_{10} , $PM_{2.5}$, SO_2 , NO_2 , O_3 , and CO) may increase the risk of DED outpatient visits, and this correlation has lag effects, while meteorological factors were one of the important confounding factors. Previous studies have suggested that meteorological factors such as

temperature (T) and relative humidity (RH) influence the stability of the tear film and the incidence of DED, so the effect of confounding variables of meteorological factors (T, RH, AP) was controlled by smoothing the natural cubic spline curve (ns) with three degrees of freedom (df). The choice of df was determined as the minimum of the sum of the absolute values of the partial autocorrelation function (PACF), which were based on the residuals of the underlying model consistent with the residual independence principle [22,24].

DED diagnostic records with no missing information ($n = 64,613$) were screened first, followed by those with permanent residents living within 20 km of the nearest air quality monitoring site on average ($n = 64,613$), according to the Baidu Map 0.2 package in the R software. The meteorological factors were used as covariates and the final model is shown below:

$$Y_t \sim \text{quasiPoisson}(\mu_t) \quad (1)$$

$$\begin{aligned} \text{Log}[E(Y_t)] = & \beta Z_t + \text{factor}(\text{DOW}) + \text{ns}(\text{time}, \text{df} = 7/\text{year}) \\ & + \text{ns}(T, \text{df} = 3) + \text{ns}(\text{RH}, \text{df} = 3) + \text{ns}(\text{AP}, \text{df} = 3) \\ & + \text{ns}(\text{NO}_2, \text{df} = 3) + \text{ns}(\text{O}_3, \text{df} = 3) + \text{ns}(\text{SO}_2, \text{df} = 3) \\ & + \text{ns}(\text{CO}, \text{df} = 3) + \text{ns}(\text{PM}_{2.5}, \text{df} = 3) + \text{ns}(\text{PM}_{10}, \text{df} = 3) + \text{intercept} \end{aligned} \quad (2)$$

where $E(Y_t)$ denotes the expected number of DED outpatients on day t , Z_t is the concentration of certain pollutants on day t , and β is the exposure coefficient; ns is the natural cubic spline function; df is the degree of freedom; DOW denotes the day of the week, RH, and AP represent the mean air temperature, relative humidity, and atmospheric pressure, respectively. We report the RRs and 95% confidence intervals (CIs) for continuous exposure (per 10 units increase compared to the average background exposure level).

Furthermore, we performed subgroup analyses for sex (male, female) and age (0–1, 2–5, 6–18, 19–64, and ≥ 65 years) to further explore potential moderating factors. Differences between the warm season (April to September) and the cool season (January to March and October to December) were statistically analyzed by using packages including “season”, “dlnm”, and “splines” in R software version 4.0.4 (15 February 2021). Statistical tests were all two-sided, and p values less than 0.05 were considered statistically significant. The Medical Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University approved and supervised the study in its entirety, and the process was conducted in accordance with the Declaration of Helsinki (No. K202205-08).

3. Results

Final data from 9970 eligible cases were included in the current study, and Table 1 describes the basic characteristics of patients with DED included from 2013 to 2020, similar to the results of previous studies. Final data described that the number of female patients remained in the majority, approximately three times the number of males (72.63%), and patients aged 19–64 years (78.13%) made up the majority of the total age group; the prevalence of DED was as well slightly higher in the warm season than in the cold season (50.84%). In general, during this eight-year period, there appears to be an annual cyclical trend for the six regional air pollutants and DED outpatient visits, with CO, SO₂, and O₃ falling below China’s national ambient air quality standards, but NO₂, PM_{2.5}, and PM₁₀ exceeding these standards. Please see Table 1 for more information. The main meteorological factors also presented cyclical variations during the period 2013–2020, with temperature variations ranging from -26.0 to 35.1 °C, humidity from 6.0 to 100.0%, air pressure from 842.0 to 934.0 hPa, and wind speed from 0.0 to 14.8 m/s, with mean values of 8.4 °C, 55.5%, 912.7 hPa, and 2 m/s, respectively. Details of the remaining descriptive analysis indicators (standard deviation (SD), minimum, 25th and 75th percentiles, median, and maximum) and cycle variation characteristics are shown in Figures 2 and S1.

Table 1. Characteristics of outpatients for dry eye disease (DED) in the First Affiliated Hospital of Xinjiang Medical University (1 January 2013 to 31 December 2020).

Variables	Number of Measurements	Mean $\pm$ SD	Min	P25	Median	P75	Max
Air pollutant concentration							
PM _{2.5} ($\mu\text{g}/\text{m}^3$)	2921	64.5 $\pm$ 61.9	6	23	39	84	397
PM ₁₀ ($\mu\text{g}/\text{m}^3$)	2921	120.2 $\pm$ 90.8	10	62	98	153	1766
SO ₂ ($\mu\text{g}/\text{m}^3$)	2921	16 $\pm$ 15.2	2	8	10	17	177
NO ₂ ($\mu\text{g}/\text{m}^3$)	2921	48.5 $\pm$ 21	7	33	44	60	141
CO (mg/m^3)	2921	1.2 $\pm$ 1	0.01	0.6	0.9	1.5	6
O ₃ ($\mu\text{g}/\text{m}^3$)	2921	68.2 $\pm$ 37.7	2	35	67	99	182
Meteorological factors							
Mean temperature ($^{\circ}\text{C}$)	2921	8.4 $\pm$ 13.7	−26	−4.5	10.7	20.6	35.1
Relative humidity (%)	2921	55.5 $\pm$ 21.3	6	37	54	74	100
Wind speed (m/s)	2921	2 $\pm$ 1.1	0	1.4	1.9	2.4	14.8
Atmospheric pressure (hpa)	2921	912.7 $\pm$ 7.8	842	908	913	918	934
Number of dry eye disease outpatient visits (n)							
Total	9970	3.4 $\pm$ 3.6	0	1	2	5	24
Gender							
Male	2729	1 $\pm$ 1.3	0	0	0	1	9
Female	7241	2.5 $\pm$ 2.7	0	0	2	4	20
Age (years)							
0–5	68	0 $\pm$ 0.2	0	0	0	0	2
6–18	211	0 $\pm$ 0.3	0	0	0	0	3
19–64	7790	2.7 $\pm$ 2.8	0	0	2	4	20
≥ 65	1901	0.7 $\pm$ 1.1	0	0	0	1	16
Season							
Warm (April to September)	5069	3.5 $\pm$ 3.7	0	1	2	5	24
Cold (October to March)	4901	3.4 $\pm$ 3.4	0	1	2	5	21

Abbreviations: SD, standard deviation; Min, minimum, P25, 25th percentile; P75, 75th percentile; Max, maximum. PM₁₀, fine particulate matter with a median aerometric diameter of less than 10 μm ; PM_{2.5}, fine particulate matter with a median aerometric diameter of less than 2.5 μm ; SO₂, sulfur dioxide; NO₂, nitrogen dioxide; CO, carbon monoxide; O₃, ozone. Mean temperature represents the daily mean air temperature. Please refer to the figure/table before presenting the data/writup.

As shown in Figure 3, we reported correlations between the four main meteorological factors and six air pollutants by Spearman analysis, with the strongest correlation between PM_{2.5} and CO ($r = 0.86$, p -value < 0.0001) and a high correlation with NO₂ ($r = 0.82$, p -value < 0.0001). The results showed that correlations between particulate matter and other gaseous pollutants or between different air pollutants were also present to varying degrees (p -value < 0.0001).

In the single-day lagged effects model for exposure to single pollutants, we reported RRs with 95% CIs for each 10-unit increase in six air pollutants with the risk of DED. CO and O₃ were not significantly associated with the risk of DED outpatient visits, while the remaining four air pollutants were revealed to have a weak positive association with the risk of DED. Specifically, on day 0 increases in PM₁₀, SO₂, and NO₂ per 10 units were statistically significantly correlated with rising DED outpatient visits (1.01, 1.09, and 1.08, respectively). Cumulative lagged results suggested that increases in DED outpatient visits from lag 0–1 day to 0–7 days were positively and statistically correlated with increased NO₂ per 10 $\mu\text{g}/\text{m}^3$ increase (RR values range from a minimum of 1.06 to a maximum of 1.07, and all were statistically significant correlations). Similar results were found for PM_{2.5}; RR values ranged from a minimum of 1.04 to a maximum of 1.06 at lags 0–4 to 0–7 days, and all were statistically significant correlations. For SO₂ (RR = 1.09, 95% CI: 1.01–1.19),

it was statistically significantly associated with DED at lags 0–2 days. In addition, there appeared to be no detectable correlation between other pollutants and DED outpatient visits in the single pollutant model (Table 2).

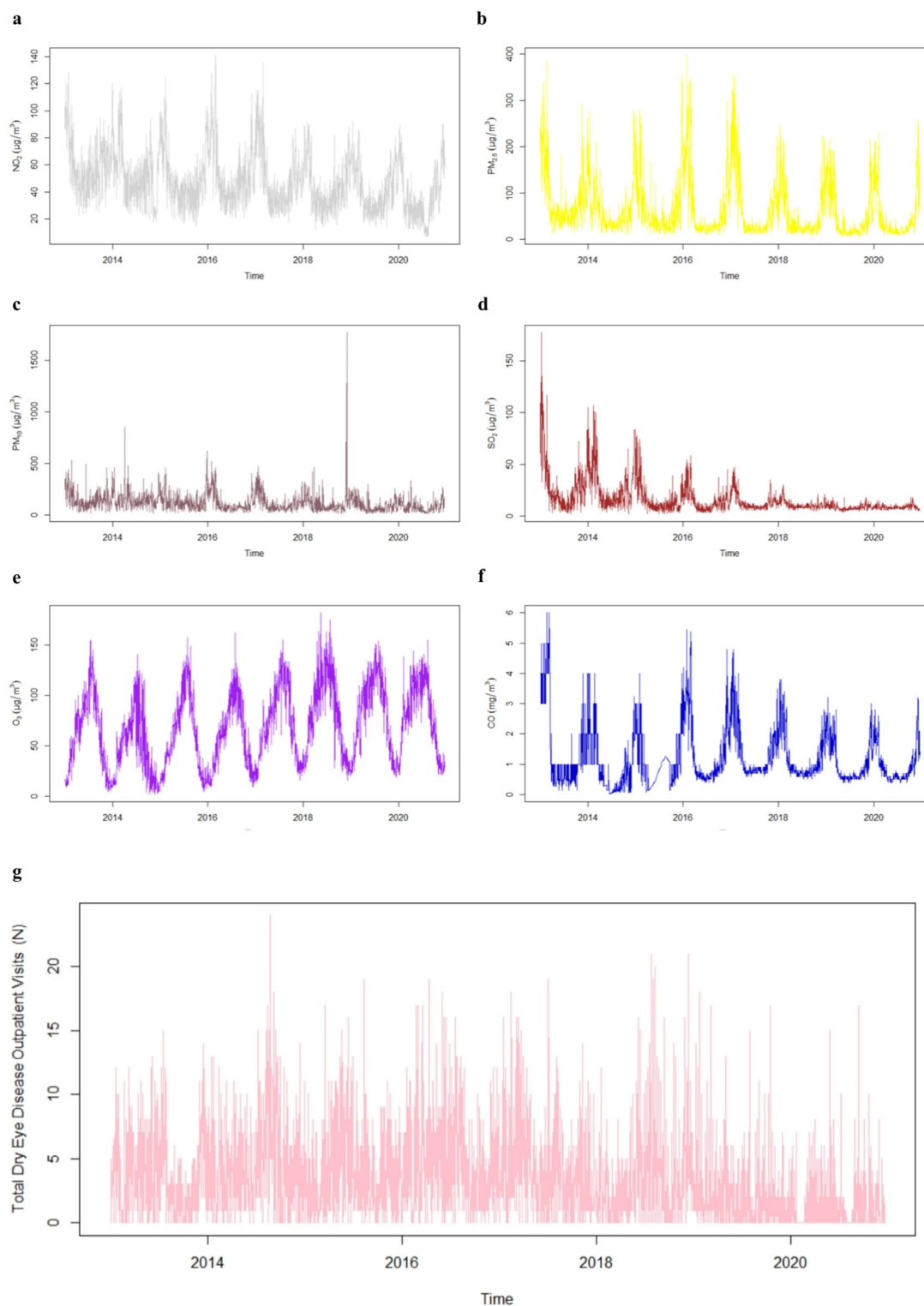


Figure 2. Distribution of exposure to NO₂ (a), PM_{2.5} (b), PM₁₀ (c), SO₂ (d), O₃ (e), CO (f), and outpatient visits for dry eye disease (DED) (g) over time in Urumqi, Xinjiang, 1 January 2013 to 31 December 2020. Different colors represent different types of air pollutants/number of DED outpatient visits, gray (NO₂), bright yellow (PM_{2.5}), brown (PM₁₀), rufous (SO₂), purple (O₃), blue (CO) and red (DED outpatient visits).

Table 2. The relative risks (RRs) of per 10 units increase in air pollutants on DED outpatient visits at various lag days: Single-pollutant model.

Lag Effects	PM _{2.5} (µg/m ³)	PM ₁₀ (µg/m ³)	CO (mg/m ³)	SO ₂ (µg/m ³)	NO ₂ (µg/m ³)	O ₃ (µg/m ³)
Single lag effects RRs (95% CI)						
Lag 0	1.02 (0.99–1.04)	1.01 (1.00–1.02) *	1.08 (0.93–1.25)	1.09 (1.01–1.18) *	1.08 (1.04–1.13) **	1.00 (0.96–1.04)
Lag 1	1.01 (0.98–1.04)	1.00 (0.99–1.01)	1.04 (0.89–1.22)	1.00 (0.92–1.08)	0.99 (0.95–1.03)	0.99 (0.96–1.03)
Lag 2	1.00 (0.98–1.02)	1.00 (0.99–1.00)	0.96 (0.86–1.08)	1.01 (0.95–1.06)	0.99 (0.97–1.02)	1.00 (0.97–1.02)
Lag 3	1.01 (0.99–1.02)	1.00 (0.99–1.00)	0.99 (0.92–1.06)	0.99 (0.95–1.02)	1.00 (0.98–1.02)	1.00 (0.98–1.02)
Lag 4	1.01 (1.00–1.02)	1.00 (1.00–1.01)	1.03 (0.95–1.1)	0.97 (0.94–1.01)	1.00 (0.98–1.02)	1.00 (0.98–1.02)
Lag 5	1.01 (1.00–1.02)	1.00 (0.99–1.01)	1.03 (0.96–1.10)	0.97 (0.94–1.00)	1.00 (0.99–1.02)	1.00 (0.98–1.02)
Lag 6	1.01 (1.00–1.02)	1.00 (0.99–1.00)	1.00 (0.96–1.05)	0.98 (0.95–1.00)	1.00 (0.99–1.01)	1.00 (0.99–1.01)
Lag 7	1.00 (0.98–1.02)	1.00 (0.99–1.01)	0.97 (0.87–1.08)	0.99 (0.94–1.05)	1.00 (0.97–1.03)	1.00 (0.97–1.02)
Cumulative lag effects RRs (95% CI)						
Lag 0–1	1.02 (1.00–1.05)	1.01 (1.00–1.02)	1.12 (0.96–1.32)	1.09 (1.00–1.18)	1.07 (1.02–1.11) **	0.99 (0.94–1.03)
Lag 0–2	1.02 (1.00–1.05)	1.01 (1.00–1.01)	1.08 (0.93–1.26)	1.09 (1.01–1.19) *	1.06 (1.02–1.11) **	0.98 (0.94–1.03)
Lag 0–3	1.03 (1.00–1.06)	1.01 (1.00–1.02)	1.07 (0.91–1.26)	1.08 (0.99–1.18)	1.06 (1.01–1.11) *	0.98 (0.93–1.03)
Lag 0–4	1.04 (1.01–1.07) *	1.01 (1.00–1.02)	1.10 (0.93–1.3)	1.05 (0.96–1.15)	1.06 (1.01–1.11) *	0.98 (0.93–1.04)
Lag 0–5	1.05 (1.02–1.09) **	1.01 (1.00–1.02)	1.13 (0.94–1.35)	1.02 (0.92–1.12)	1.06 (1.01–1.12) *	0.99 (0.93–1.04)
Lag 0–6	1.06 (1.02–1.09) **	1.01 (1.00–1.02)	1.13 (0.95–1.35)	0.99 (0.90–1.10)	1.06 (1.01–1.12) *	0.99 (0.93–1.04)
Lag 0–7	1.06 (1.02–1.10) **	1.01 (1.00–1.02)	1.10 (0.92–1.30)	0.98 (0.89–1.09)	1.06 (1.01–1.13) *	1.06 (1.01–1.13) *

*, $p < 0.05$; **, $p < 0.01$. PM₁₀, fine particulate matter with a median aerometric diameter of less than 10 mm; PM_{2.5}, fine particulate matter with a median aerometric diameter of less than 2.5 mm; SO₂, sulfur dioxide; NO₂, nitrogen dioxide; CO, carbon monoxide; O₃, ozone.

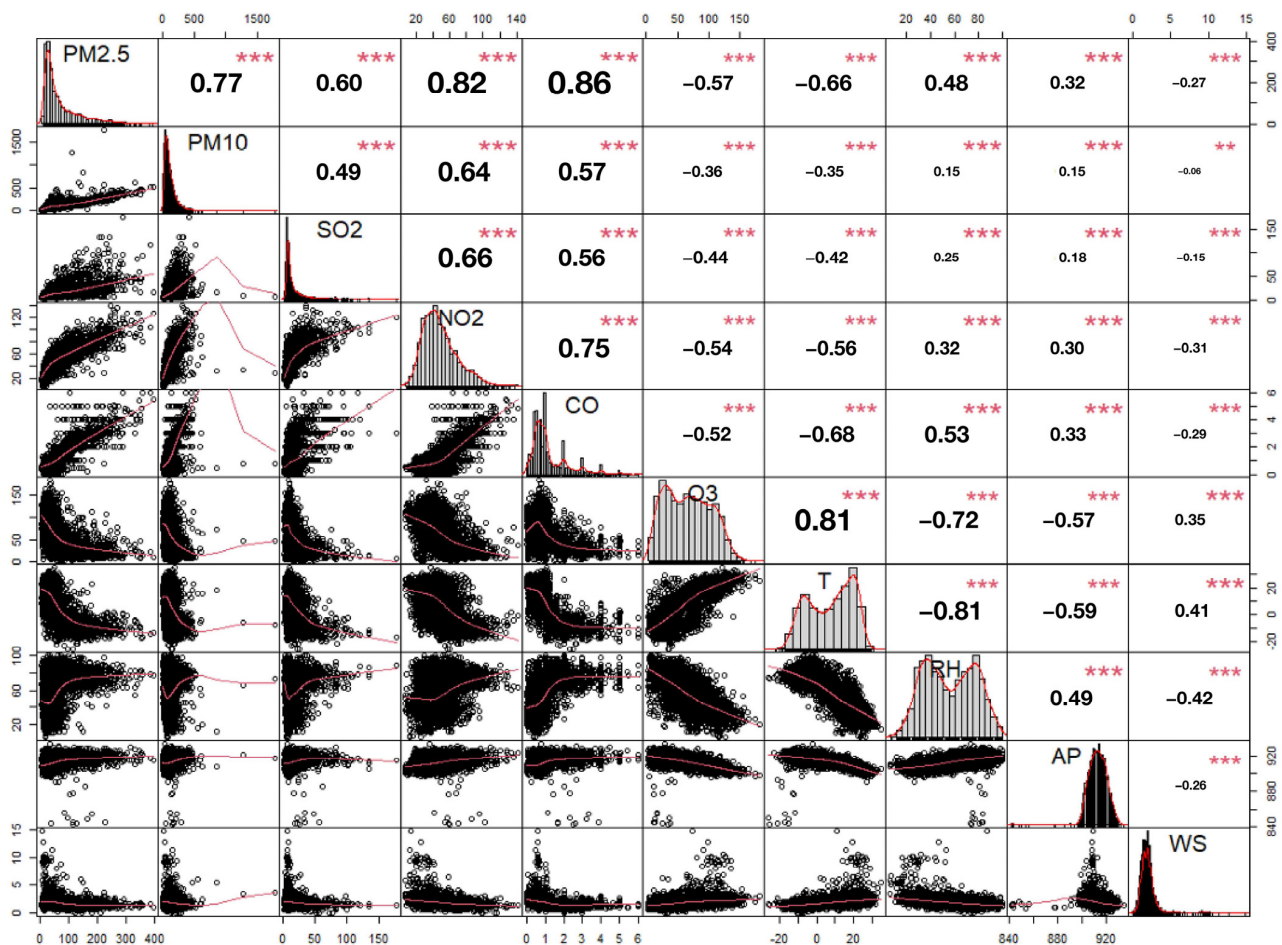


Figure 3. Spearman correlation between different air pollutants and meteorological factors. T: Mean temperature; RH: Relative humidity; AP: Atmospheric pressure; WS: Wind speed; **: $p < 0.01$; ***: $p < 0.001$.

Combining the results of the multi-pollutant model (Table 3), we failed to find significant correlations between CO and O₃ and the risk of DED outpatient visits, but NO₂, SO₂, and PM_{2.5} showed statistically significant correlations between per 10 µg/m³ increase and outpatient visits of DED patients. Furthermore, because the findings in single and multi-pollutant models were inconsistent, it was unclear whether there was a statistically significant correlation between increased PM₁₀ exposure and DED outpatient visits. In addition, we conducted a sensitivity analysis on the data for different years (2013–2017, 2013–2018, and 2013–2019), the results suggest that these findings remained stable (Supplementary Materials B).

Results of subgroup analysis based on individual patient characteristics showed no gender differences between air pollutants except NO₂ and increased DED outpatient visits. In the age subgroup, the ≥65 years age group did not correlate with any air pollutant, while NO₂ showed statistically significant correlations in the DED age groups 0–5 years, 6–18 years, and 19–64 years. Similar results were found for PM_{2.5}. However, it was noteworthy that per 10-unit increase in SO₂ showed the strongest correlation (RR = 2.57, 1.17–5.65) with a statistically significant rise in DED outpatient visits at age 0–5 years. In addition, O₃ also showed a statistically significant correlation in DED in 6–18 years (RR = 1.09, 1.02–1.15) and the opposite effect was found in CO (19–64 years) versus PM_{2.5} (6–18 years). Moreover, increased DED outpatient visits during the warm season exhibited significant positive correlations with PM₁₀ and CO per 10-unit increase, while significant correlations were found with all other air pollutants except for SO₂ during the cold season, and the opposite effect was found in O₃ (cold season). Details are shown in Table 4.

Considering the evidence of health effects of the association between long-term O₃ concentrations and total mortality, 2021 WHO Global Air Quality Guidelines (AQG 2021) provided seasonal average O₃ peak recommendations (60 µg/m³) [25]. Our results suggested that the annual average value of O₃ in Urumqi (68.2 µg/m³) was slightly above this criterion, and our results failed to find a significant correlation between O₃ and DED in both the single-pollutant and multi-pollutant models, but a significant correlation between O₃ and the decline in DED outpatient visits during the cold season can be seen in the results of the subgroup analysis. This may be explained by the decrease in O₃ levels during the cold season and the specific “U”-shaped dose response in the 5% to 95% dose range of O₃ that we found in Figure 4.

Table 3. Correlation of per 10 units increase in air pollutants and outpatients for DED: Multipollutant model.

	PM _{2.5} (µg/m ³)		PM ₁₀ (µg/m ³)		CO (mg/m ³)		NO ₂ (µg/m ³)		SO ₂ (µg/m ³)		O ₃ (µg/m ³)	
	Lag effect		Lag effect		Lag effect		Lag effect		Lag effect		Lag effect	
	Single	Cumulative	Single	Cumulative	Single	Cumulative	Single	Cumulative	Single	Cumulative	Single	Cumulative
Adjusted for PM _{2.5}			1.00 (1.00–1.01)	1.01 (0.99–1.02)	1.03 (0.96–1.10)	1.04 (0.85–1.28)	1.08 (1.03–1.13) **	1.06 (1.01–1.12) *	0.97 (0.94–1.01)	1.05 (0.96–1.15)	1.00 (0.97–1.02)	0.98 (0.94–1.03)
Adjusted for PM ₁₀	1.01 (1.00–1.02)	1.04 (1.00–1.08)			1.02 (0.96–1.10)	1.06 (0.88–1.27)	1.07 (1.02–1.12) **	1.05 (1.00–1.10) *	0.97 (0.94–1.00)	1.05 (0.96–1.15)	0.99 (0.95–1.03)	0.98 (0.94–1.03)
Adjusted for CO	1.01 (1.00–1.02)	1.05 (1.01–1.09) **	1.01 (1.00–1.02)	1.01 (1.00–1.02)			1.09 (1.04–1.15) **	1.08 (1.03–1.14) **	0.97 (0.93–1.00)	1.06 (0.97–1.15)	0.99 (0.96–1.03)	0.98 (0.92–1.03)
Adjusted for NO ₂	1.01 (1.00–1.02)	1.04 (1.00–1.08) *	1.00 (1.00–1.01)	1.00 (0.99–1.02)	0.96 (0.87–1.07)	0.95 (0.77–1.15)			0.97 (0.93–1.00)	0.91 (0.81–1.02)	0.99 (0.97–1.02)	0.99 (0.94–1.04)
Adjusted for SO ₂	1.01 (1.00–1.02)	1.05 (1.02–1.09) **	1.01 (1.00–1.02)	1.01 (1.00–1.02)	1.03 (0.96–1.10)	1.09 (0.91–1.31)	1.07 (1.02–1.12)	1.05 (1.00–1.11) *			0.99 (0.95–1.03)	0.98 (0.94–1.03)
Adjusted for O ₃	1.01 (1.00–1.02)	1.06 (1.02–1.10) **	1.00 (1.00–1.01)	1.01 (1.00–1.02)	1.03 (0.96–1.11)	1.10 (0.92–1.31)	1.07 (1.02–1.11)	1.08 (1.02–1.15) **	1.07 (0.99–1.16)	1.11 (1.02–1.20) *		
Adjusted for the other 5 pollutants	1.01 (1.00–1.02)	0.97 (0.94–1.01)	1.00 (1.00–1.01)	1.01 (1.00–1.03)	0.84 (0.70–1.01)	0.84 (0.70–1.01)	1.07 (1.02–1.11) **	1.10 (1.03–1.18) **	0.97 (0.94–1.01)	1.06 (0.96–1.17)	0.99 (0.95–1.03)	0.98 (0.92–1.04)

*: $p < 0.05$; **: $p < 0.01$. PM₁₀, fine particulate matter with a median aerometric diameter of less than 10 µm; PM_{2.5}, fine particulate matter with a median aerometric diameter of less than 2.5 µm; SO₂, sulfur dioxide; NO₂, nitrogen dioxide; CO, carbon monoxide; O₃, ozone.

Table 4. Correlation of per 10 units increase in air pollutants and outpatients for DED, and effect modification through stratified by patients' characteristics.

Characteristics	PM _{2.5} (µg/m ³)		PM ₁₀ (µg/m ³)		CO (mg/m ³)		NO ₂ (µg/m ³)		SO ₂ (µg/m ³)		O ₃ (µg/m ³)	
	Lag effect		Lag effect		Lag effect		Lag effect		Lag effect		Lag effect	
	Single	Cumulative	Single	Cumulative	Single	Cumulative	Single	Cumulative	Single	Cumulative	Single	Cumulative
Sex												
Male	1.04 (1.00–1.08)	1.03 (0.97–1.10)	1.01 (1.00–1.02)	1.02 (1.00–1.05)	1.14 (0.91–1.42)	0.93 (0.69–1.24)	1.01 (0.99–1.03)	1.15 (1.05–1.27) **	0.98 (0.93–1.03)	0.96 (0.81–1.13)	0.98 (0.94–1.02)	0.98 (0.92–1.05)
Female	1.01 (1.00–1.03)	1.03 (0.98–1.07)	1.00 (1.00–1.01)	1.01 (0.99–1.03)	1.04 (0.96–1.12)	0.83 (0.67–1.02)	1.09 (1.03–1.15) **	1.08 (1.01–1.16) *	0.97 (0.94–1.01)	1.08 (0.97–1.20)	0.99 (0.95–1.03)	0.98 (0.92–1.04)
Age (years)												
0–5	1.09 (1.02–1.17) *	1.17 (0.89–1.56)	1.02 (1.00–1.05)	1.03 (0.92–1.15)	1.77 (0.59–5.34)	0.75 (0.15–3.65)	1.16 (1.04–1.30) **	1.56 (0.95–2.54)	2.08 (1.00–4.33)	2.57 (1.17–5.65) *	0.94 (0.83–1.06)	0.77 (0.52–1.16)
6–18	0.95 (0.90–1.01)	0.77 (0.63–0.95) *	-	-	0.84 (0.59–1.18)	0.75 (0.26–2.20)	1.29 (1.01–1.64) *	1.50 (1.06–2.13) *	0.83 (0.54–1.28)	0.72 (0.45–1.15)	1.09 (1.02–1.15) **	0.86 (0.70–1.07)
19–64	1.01 (1.00–1.03) *	1.04 (0.99–1.08)	1.00 (1.00–1.01)	1.01 (0.99–1.03)	0.83 (0.69–0.99) *	0.80 (0.66–0.97) *	1.08 (1.02–1.14) **	1.10 (1.02–1.17) **	0.98 (0.95–1.01)	1.05 (0.95–1.16)	0.99 (0.96–1.02)	0.97 (0.92–1.03)
≥65	1.04 (1.00–1.07)	1.04 (0.96–1.12)	1.01 (1.00–1.01)	1.02 (0.99–1.05)	1.18 (0.86–1.61)	1.20 (0.79–1.82)	1.06 (0.96–1.17)	1.10 (0.98–1.24)	0.93 (0.87–1.00)	1.14 (0.93–1.38)	0.96 (0.90–1.03)	0.97 (0.89–1.05)
Season												
Warm (April to September)	0.98 (0.95–1.01)	1.03 (0.92–1.15)	1.03 (0.99–1.06)	1.05 (1.00–1.11) *	1.19 (1.01–1.4) *	1.75 (1.01–3.03) *	0.98 (0.94–1.01)	1.03 (0.92–1.15)	0.95 (0.89–1.02)	0.84 (0.62–1.14)	0.98 (0.95–1.02)	1.02 (0.95–1.11)
Cold (October to March)	1.01 (1.00–1.02) **	1.03 (0.99–1.07)	1.00 (1.00–1.01) *	1.02 (1.00–1.04) *	1.07 (1.02–1.12) ***	0.87 (0.74–1.02)	1.09 (1.02–1.17) *	1.16 (1.07–1.26) **	1.05 (1.01–1.09)	0.91 (0.81–1.01)	0.92 (0.86–0.98) **	0.87 (0.81–0.93) **

*: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$. PM₁₀, fine particulate matter with a median aerometric diameter of less than 10 µm; PM_{2.5}, fine particulate matter with a median aerometric diameter of less than 2.5 µm; SO₂, sulfur dioxide; NO₂, nitrogen dioxide; CO, carbon monoxide; O₃, ozone.

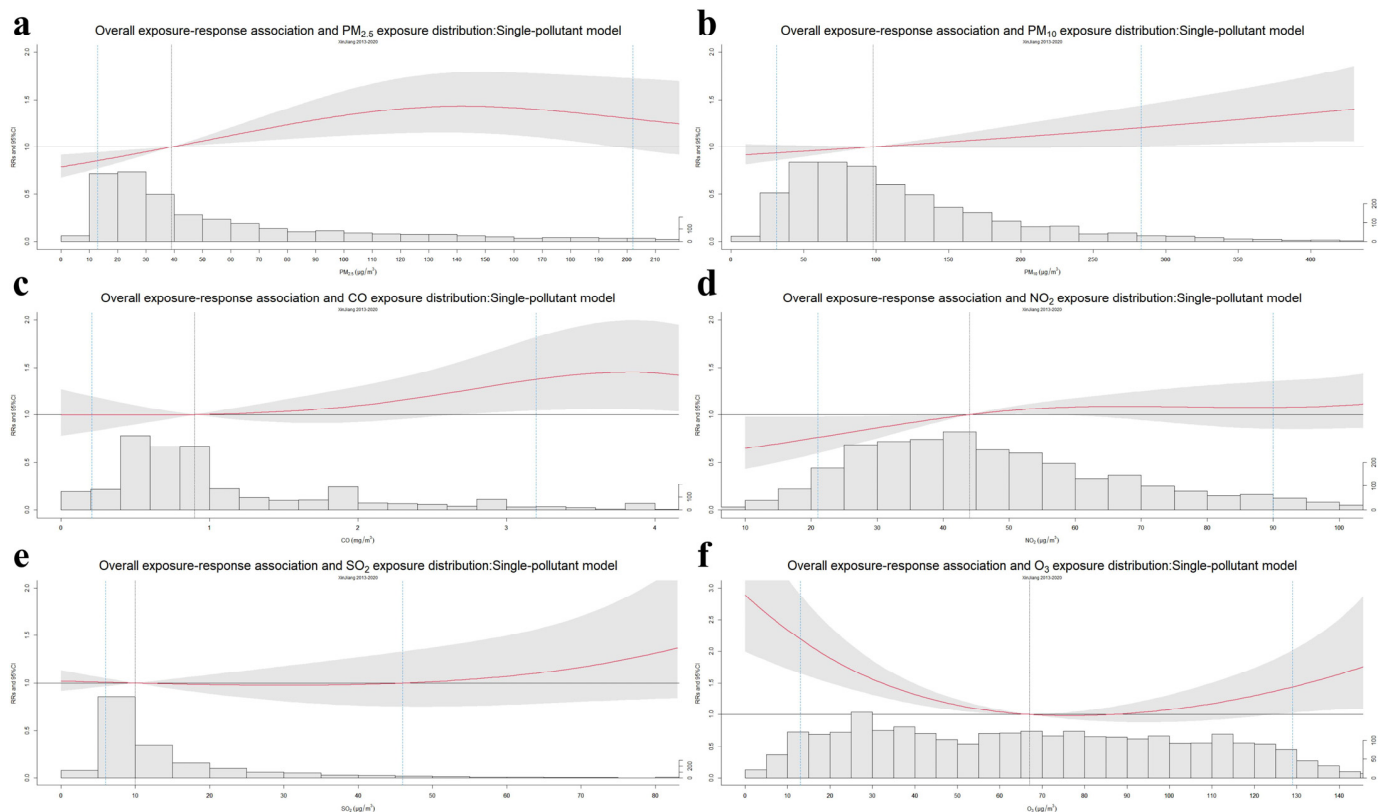


Figure 4. Overall exposure-response association for outpatient visits for DED and air pollutants: PM_{2.5} (a), PM₁₀ (b), CO (c), NO₂ (d), SO₂ (e), O₃ (f) in single-pollutant model.

4. Discussion

In this study, significant associations were found between air pollutants (PM₁₀, PM_{2.5}, SO₂, NO₂) and outpatient visits for DED, with NO₂ exhibiting the most significant effect in both the single-pollutant and multi-pollutant models, which was consistent with previous findings from similar studies on DED and air pollution in other regions [21]. Subgroup analysis results suggested stronger effects, with SO₂ demonstrating the strongest effect in children aged 0–5 years; O₃ only impacted the DED population aged 6–18 years. The most susceptible group was females (72.6% of the total number of patients were female). For PM₁₀ and CO, the association between air pollutants and the number of DED outpatient visits was stronger in the warm season than in the cold season, while it was reversed for NO₂ and PM_{2.5}.

There was growing evidence indicating that air pollution was associated with DED [17,18,21]. Mu et al. reported that RRs for DED increased with levels of pollutants PM_{2.5}, PM₁₀, NO₂, CO, SO₂, and O₃ in a time-series study investigating the relationship between air pollution exposure and daily pediatric visits for DED in Shenzhen [20]. Hwang et al., on the other hand, conducted a population-based cross-sectional study with 16,824 participants from 1 January 2010 to 31 December 2012, and discovered that symptoms and diagnosis of DED were significantly associated with increased O₃ and NO₂ exposure [21]. This was consistent with the results of a prospective observational study conducted between 2016 and 2018 by Kim et al. [26], which found no correlation between increased PM₁₀ exposure and DED. Furthermore, Galor et al. discovered that environmental factors influenced DED risk in the U.S. veteran population, with air pollution emerging as the most influential predictor [27]. Similarly, in a case-crossover design and data from 25,818 eligible DED subjects in Taiwan from 2004 to 2013, Zhong et al. demonstrated that CO and NO₂ were positively associated with DED visits ($p < 0.05$) [17]. Different study sites, air pollution levels, and study populations limited our integration of these findings. However, as the first study conducted in the largest city in northwest China, our findings

provided new evidence in the field. We confirmed for the first time the effects of PM₁₀, PM_{2.5}, SO₂, and NO₂ on DED risk in Urumqi, and pointed out the potential lagged effects of PM_{2.5}, SO₂, and NO₂. Sensitivity analyses for different years checked this conclusion. However, limitations due to the lack of validation must be considered.

As previously stated, the Urumqi region's unique geographical characteristics of being far from the coast and climatic characteristics of frequent extreme weather, particularly the arid climate and coal-based energy consumption, have caused air pollutants to be poorly dispersed in the natural environment [28,29]. Therefore, it was critical to investigate local air-pollution-related health issues, considering policy development and disease prevention, etc. According to the Chinese Ministry of Ecology and Environment 2022's interannual spatial distribution trends of six major air pollutants for 2013–2020 in 74 key cities, including Urumqi, all five air pollutants were higher in the northwest than in other regions (east and southwest), except for O₃, and our results confirmed this (Table 1 and Figure 2). However, studies on the health risks of air pollution in this region, particularly ocular surface diseases, were scarce. A time-series study published in 2017 by China's National Center for Chronic and Noncommunicable Disease Prevention and Control investigated the effects of major air particulate pollution in 38 of the largest cities (total population >200 million) in 27 Chinese provinces, revealing that Urumqi, Xinjiang (with daily average PM₁₀ concentrations as high as 136.0 g/m³), was the most polluted city [30]. Particulate pollutant concentrations had decreased in most parts of China as a result of environmental and energy-saving policies, but PM₁₀ pollution remained a major issue in the northwest, particularly in Xinjiang [31]. Our results similarly confirm that the average PM₁₀ value in Urumqi (120.2 µg/m³) was much higher than the average value in northwest China (67.73 µg/m³). Considering the correlation between PM₁₀ and DED risk was observed, further PM₁₀ detection and environmental cleanup and protection measures should be carried out in the region.

Long-term high concentrations of PM_{2.5} and PM₁₀ may be attributed to high tailpipe emissions from the developed local transportation industry, or to the suspended accumulation of particulate matter caused by frequent dust storm weather [32]. Kenji Kashiwagi et al. and Zihan Xu et al. both found that the strong association between short-term exposure to PM₁₀ and DED diagnosis may be attributed to the direct reaction of small molecules of particulate matter with ocular surface tissues, impairing tear film function [33,34]. A large amount of dust and particulate matter can also enter the eye with tears to produce the subsequent chain reaction, as reflected in the cumulative lag effect of PM_{2.5} (cumulative lag of 0–4 to 0–7 days), which was consistent with the results of a previously published study from Taiwan [17].

In addition, NO₂ has been widely demonstrated in other time-series studies to be significantly associated with an increasing incidence of ocular diseases, such as conjunctivitis [23]. Our results suggested that NO₂ (48.5 µg/m³) concentrations in the Urumqi region are still higher than in other regions (38.1 µg/m³ in Hefei, Anhui; 47.9 µg/m³ in Hangzhou, Zhejiang; and 21 µg/m³ in Taiwan), not to mention being higher than the WHO annual average NO₂ target (10 µg/m³) during most of the year. Significant associations of NO₂ with the cumulative lags of DED from 0–1 to 0–7 days were observed in both single-pollution and multi-pollution models, and the results of our correlation analysis suggested that NO₂ is highly correlated with particulate matter (PM_{2.5} and PM₁₀). It was probably because they both derive from road traffic pollution generated by incomplete combustion of fuel inside engines [17]; it is worth noting that traffic emissions in Urumqi are mainly diesel exhaust containing potent oxidants, which may mediate the production of stress inflammation on the ocular surface. Usually, high concentrations of NO₂ in direct contact with the ocular surface can acidify tears, and thus, lead to the reduction of tears, all of which are typical symptoms of DED [35].

Notably, our research found that the annual average SO₂ concentration in Urumqi had been decreasing for eight consecutive years (Figure 1), with an annual decrease of more than 40%, possibly due to the local industrial desulfurization and “coal to gas” projects that began in 2010 [36]. However, our findings showed that SO₂ was significantly associated

with the risk of DED and had a cumulative lag effect of 0–2 days, which was strongest for children aged 0–5 years; this may be related to children's increased exposure to outdoor air pollution [37], implying that additional local pollution control measures, such as coal combustion, are still needed.

Subgroup analysis suggested that the effect of air pollution on DED was influenced by gender, age, and cold and warm season, which were reflected to varying degrees in different types of air pollutants (see Table 4). It has been reported that the incidence of DED is significantly higher in women than in men [38]. DED affected women twice as much as men over the age of 50; in addition, it was diagnosed 6 years earlier in women than in men, which may be due to some female-specific factors unrelated to tear production, but the mechanism was unknown [39]. Estrogen may play a role in effectively inducing DED by antagonizing androgens' protective effect on levator gland function [40]. Furthermore, it may be related to women's lower resistance to external stimuli compared to men, as well as the type and composition of their different air exposure (e.g., cooking fumes) [41]. High sensitivity to NO₂ in infants and young adults may be related to the excessive use of electronic devices in modern society [42], or the habit of wearing contact lenses in youths [43]. In addition, during the cold season, more frequent use of fuel combustion, such as coal, led to increased emissions of harmful substances, such as particulate matter (PM_{2.5} and PM₁₀), and may cause high concentrations of environmental pollutants and increased DED cases [44].

Regarding the mechanism of effects of different air pollutants on DED, previous studies have reported a variety of potential mechanisms. NO₂ and O₃ were both oxidants with strong oxidizing properties, which can lead to a massive increase of some inflammatory cytokines in the tear fluid, such as IL-6, IL-1 β , IFN- γ , and IL-17, and further cause an inflammatory response in the ocular surface [21,45]. This was also considered to be the core mechanism of DED [46]. In addition, some animal studies have shown that particulate matter (including PM_{2.5} and PM₁₀) had similar properties, which caused ocular surface damage through oxidative stress and destabilization of the tear film [47]. Furthermore, SO₂ and NO₂, which are acidic gasses, can cause acidification of tears and alter the pH environment of the inner epidermal cells when they enter the eye, thereby irritating the ocular surface and causing inflammation [48,49]. Air pollutants also possessed the ability to alter the anterior corneal tear film, especially NO₂ and CO, which are combustion products with aerosol properties that can invade the outermost lipid layer of the anterior corneal tear film; PM_{2.5} and PM₁₀, which interfere with the structure of the anterior corneal tear film on direct contact, can easily cause ocular discomfort [50]. Moreover, previous animal experiments and clinical studies have shown that O₃ and PM_{2.5} can reduce the density of conjunctival cupped cells [51]. The increase in PM_{2.5} concentration can also increase tear osmolarity and cause apoptosis of corneal epithelial cells, which can lead to dysfunction of ocular surface cells and eventually develop into dry eye disease [52,53].

In summary, this study has several strengths. First, we conducted the first time-series analysis design with a large-scale sample size in the largest city in northwest China. Second, our study provided new evidence in the field, confirming, for the first time, the effect of air pollution including PM₁₀, PM_{2.5}, SO₂, and NO₂ on DED risk in Urumqi, and suggesting the potential lagged effect of PM_{2.5}, SO₂, and NO₂. Third, we analyzed the effects of different types of air pollutants on DED in detail and detected the differences in the effects of gender and age, as well as cold and warm seasonal factors among local DED patients in Urumqi by subgroup analysis.

There were undeniably some limitations of our study:

First, although the Ophthalmology Department of the First Affiliated Hospital of Xinjiang Medical University is the largest ophthalmology clinic in Xinjiang, and it attracted more than 50% of outpatient visits for DED patients as the preferred provider for patients with ophthalmic diseases in the surrounding area, it must be taken into account that there were several other ophthalmology clinics in the city, and, therefore, the omission of patients who visited other hospitals for proximity or other reasons must be taken into account.

Second, although we used both current and permanent postal addresses in the medical records to determine exposure addresses, and multiple procedures were also used to screen as many patients as possible who lived in the major areas of Urumqi, the data from fixed monitoring stations were closest to the individual's residence. However, due to misregistration of information, there may still be postal address zip codes that differ from the actual area of residence and other occurrences that may undermine the validity of the study, and individual-level exposure and indoor contamination cannot be examined in detail. In addition, given the inherent limitations of the perspective retrospective ecological time-series design in investigating causality, especially since estimates of air pollutants and other measured parameters were not based on precise individual exposures, a time-to-event (TTE) study design may be a better alternative, because it not only takes into account the occurrence of the event but can also include the time of the event. Future designs based on mobile monitoring systems will be expected to provide accurate individual-level exposures, as well as indoor pollution, which are currently unavailable for detailed examination.

Third, the diagnosis of DED relied on electronic medical record information systems, and although appropriate review procedures were adopted, these data may be associated with misclassification bias due to errors when entering the data into the system. On the other hand, electronic medical record systems lacked some valuable information, such as socioeconomic status, education level or occupation, and DED subtypes, thus preventing us from further analyzing those effects of individual differences.

Fourth, multiple lifestyle factors, such as sleep status and electronic device use, as well as some occupational exposures, such as night shift workers and visual display terminal workers, may affect the estimated effect sizes. In addition, UV exposure, allergens such as pollen, atmospheric suspended particles or solvents (e.g., volatile chemicals) may also act as potential confounders in this study. As a result, future studies should take these difficult-to-measure confounding factors into full account.

Fifth, as previously stated, the quasi-Poisson generalized linear regression model with DLNM that we utilized allows the application of numerous parameters to account for effects at different lags, thus it flexibly characterizes the relationship of potential nonlinearities and lagged effects in time series data. Although this method is widely accepted and used in environmental-related health studies, different statistical models may influence the results. For example, as described in Zhang et al. [54], generalized linear regression can provide a simple relationship between single chemicals and outcomes, thus distributing the effects of individual exposure events over specific time periods. WQS models can explore the effects of mixed exposure burdens on outcomes in one direction at a time. The BKMR model can explore the exposure-response function of each chemical at a certain level and investigate the interaction between any two chemicals. Therefore, different models can assess different aspects. Further research should consider the collaborative use and interpretation of appropriate models to fully reveal their strengths and limitations in order to achieve functional complementarity.

Sixth, as previously discussed, although limited studies on air pollution and DED have been published, since our study was the first research conducted in Urumqi, there was a lack of validation based on this region. Furthermore, large-scale and long-term multi-center studies are still needed to analyze in detail the association in different populations in the wider region.

5. Conclusions

We conducted the first large sample size time series analysis in northwest China (Xinjiang), covering 9970 DED patients in Urumqi from 1 January 2013 to 31 December 2020, and analyzed in detail the association of six major air pollutants with DED outpatient visits, as well as single-day lag and cumulative lag effects in Urumqi by constructing single-pollutant and multi-pollutant models. Our study confirmed, for the first time, the effect of air pollution, including PM₁₀, PM_{2.5}, SO₂, and NO₂, on the risk of DED in Urumqi, and suggested the potential lag effect of PM_{2.5}, SO₂, and NO₂, which provided new evidence

for research in this area. The results of the subgroup analysis suggested that the effects of air pollution on DED were influenced by gender, age, and cold/warm seasons. Considering the impact of particulate pollutants and acid gasses (SO₂, NO₂) in this rapidly growing economic and industrial region, it highlights the persistence of further implementation of local pollution control measures, related to the combustion of fossil fuels such as coal, as well as the need for special population protection policies.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/atmos14010090/s1>. Supplementary Materials A: Figure S1 shows the dose concentration distribution over time for meteorological conditions in Urumqi, Xinjiang. Supplementary Materials A: Figures S2–S192 show the exposure-response association between dry eye disease outpatient visits and six air pollutants exposure, the relative risks (RRs) of per 10 µg/m³ increase on dry eye disease outpatient visits at various lag days, 3D graph and contour map of their exposure on dry eye disease outpatient visits. Supplementary Material B shows the location of the First Affiliated Hospital of Xinjiang Medical University (Urumqi, Xinjiang, China) and the location of 11 monitoring stations.

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Institutional Review Board Statement: The Medical Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University approved and supervised the whole process of the study, and the process was conducted in accordance with the Declaration of Helsinki (No. K202205-08).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient(s) to publish this paper.

Data Availability Statement: Access to any dataset used can be obtained by contacting the corresponding author.

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Conflicts of Interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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