Association Between Air Pollutants and Acute Exacerbation of Chronic Obstructive Pulmonary Disease: A Time Stratified Case-Crossover Design With a Distributed Lag Nonlinear Model

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Abstract  Acute exacerbation of chronic obstruction pulmonary disease (AECOPD) as a respiratory disease, is considered to be related to air pollution by more and more studies. However, the evidence on how air pollution affect the incidence of AECOPD and whether there are population differences is still insufficient. Therefore, we select PM10, PM2.5, SO2, NO2, CO, and O3 as representatives combined with daily AECOPD admission data from 1 January 2015 to 26 June 2016 in the rural areas of Qingyang, northwestern China to explore the associations of air pollution with AECOPD. Based on a time-stratified case-crossover design, we constructed a distributed lag nonlinear model to qualify the single and cumulative lagged effects of air pollution on AECOPD. Stratified related risks by sex and age were also reported. The cumulative exposure-response curves were approximately linear for PM2.5, “V”-shaped for PM10, “U”-shaped for NO2 and inverted-“V” for SO2, CO and O3. Exposure to high-PM2.5 (42 μg/m3), high-PM10 (91 μg/m3), high-SO2 (58 μg/m3), low-NO2 (12 μg/m3), and high-CO (1.55 mg/m3) increased the risk of AECOPD. Females aged 15–64 were more susceptible under extreme concentrations of PM2.5, SO2, CO, and low-PM10 than other subgroups. In addition, adults aged 15–64 were more sensitive to extreme concentrations of NO2 compared with the elderly ≥65 years old, while the latter were more sensitive to high-PM10. High-SO2, high-CO, and extreme concentrations of PM2.5 had the greatest effects on the day of exposure, while low-SO2 and low-CO had lagged effects on AECOPD. Precautionary measures should be taken with a focus on vulnerable subgroups, to control hospitalization for AECOPD associated with air pollutants.

Plain Language Summary  Acute exacerbation of chronic obstruction pulmonary disease (AECOPD) as a respiratory disease, is considered to be related to air pollution. However, we still don’t know how air pollution affect the incidence of AECOPD and whether there is different effects on different groups of people. Therefore, we select PM10, PM2.5, SO2, NO2, CO, and O3 as representatives combined with daily AECOPD data to explore the associations of air pollution with AECOPD. By fitting the model, we found that in the cases of high-PM2.5, high-PM10, high-SO2, low-NO2, and high-CO, the incidence of AECOPD were higher. Females aged 15–64 were more vulnerable under extreme concentrations of PM2.5, SO2, CO and low-PM10 than other people. In addition, adults were more sensitive to extreme concentrations of NO2 compared with the old people >64 years old, while the latter were more sensitive to high-PM10. It was the day of high-SO2, high-NO2, and extreme concentrations of PM2.5 had the highest incidence of AECOPD. However, in the case of low-SO2 and low-CO, the incidence of AECOPD gradually increased with time until a certain day. Therefore, we must take preventive measures to control the occurrence of AECOPD during extreme air pollution, especially for those who are more sensitive.

1. Introduction

Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is an important clinical event characterized by an aggravation of the patient’s respiratory symptoms whose degree exceeds the range of daily variation, leading to changes in the drug treatment regimen; it is the main cause of death from chronic obstructive pulmonary disease (COPD) on a global scale (Shen & Wang, 2020). The Global Burden of Disease study pointed...
out that there were approximately 3.17 million deaths from COPD globally in 2015, while the number of people suffering from COPD worldwide reached 251 million in 2016, with the WHO predicting that COPD would become the third leading cause of death in 2030 worldwide (Murray et al., 2018). As the most populous developing country in the world, China has a heavier burden of COPD than developed countries (Zhu et al., 2018). Chen et al. showed that patients with AECOPD account for 13% of all COPD cases, and the average hospitalization cost per person for AECOPD hospitalizations is as high as 11,600 yuan (Y. H. Chen et al., 2008). In September 2018, Wang et al. predicted that the number of COPD patients in China would be about 100 million, indicating that it has become a chronic disease of the same importance as hypertension and diabetes (C. Wang et al., 2018).

With the rapid development of the society and economy, air pollution is increasingly serious, and its impact on human health has gradually become a great concern. Air pollutants mainly include particulate pollutants (PM$_{2.5}$ and PM$_{10}$) and gaseous pollutants (NO$_2$, SO$_2$, CO, and O$_3$). In recent years, mounting evidences show that exposure to air pollutants is related to COPD development (Shin et al., 2021; X. R. Yang et al., 2021). KO & Hui showed that outdoor air pollution is a significant environmental trigger of AECOPD, which leads to increased symptoms, emergency department visits, hospital admissions and even mortality (Ko & Hui, 2012). In 2016, a meta-analysis by Li et al. pointed out that short-term exposure to both gaseous and particulate pollutants could increase the burden of AECOPD significantly (J. H. Li et al., 2016). Therefore, it is of great significance to explore the impact of air pollutants on AECOPD.

When environmental epidemiology explores the effects of air pollutants and meteorological factors on human health, the most commonly used method is time series analysis (Dominici et al., 2002; Goldsmith et al., 2010; Joel, 1993; Krishnan et al., 2013; Souza et al., 2016; Yin et al., 2013). In recent years, case-crossover studies have been increasingly used in environmental epidemiology, which compare the exposure of the same research object during a certain period of time before the occurrence of an event and the time when the event did not occur (Guo et al., 2011; H. Liu et al., 2017; Lubczyńska et al., 2015; Zheng et al., 2012). So, it could eliminate the effects of some potential factors such as gender, age and personal lifestyle (Z. Zhang & Zhan, 2001), and more widely as an alternative method in time series analysis. As a case-crossover design, the time-stratified case-crossover design has been widely used to explore the impacts of environmental pollutants, meteorological factors, and extreme weather events on population health (B. Wang et al., 2021; J. Lu et al., 2021; Lee et al., 2019, 2020; Liang et al., 2021). The principle is to stratify the time by matching case and control days in a relatively short time, for example, calendar months, so that the case and control periods are in the same year, the same month and the same day of the week (Z. H. Wang et al., 2020). Distributed lag nonlinear models (DLNMs) consider the lagged effect of exposure factors and the nonlinear relationship between exposure and response at the same time (J. Yang et al., 2012). In 2006, Armstrong introduced a DLNM to a study of the health effects of temperature and proposed the model idea (Armstrong, 2006). In 2010, Gasparini and Armstrong further elaborated on the theory of DLNM based on the idea of traditional models such as generalized linear models and generalized additive models, using the cross-basis process (Gasparini et al., 2010). At present, this method is increasingly applied (F. Lu et al., 2018).

In this study, daily AECOPD admission data of individuals aged 15 or over in the rural areas of Qingyang, northwestern China, were collected from 1 January 2015 to 26 June 2016. Air pollutants and meteorological data were obtained over the same period. After adjusting for meteorological factors, such as temperature, relative humidity and air pressure, the time-stratified case-crossover design combined with a DLNM model was used to investigate the effects of PM$_{2.5}$, PM$_{10}$, SO$_2$, NO$_2$, CO, and O$_3$ on AECOPD in Qingyang’s rural areas by gender and age. The results provide theoretical support for the assessment of related environmental factors and AECOPD as well as guidance for local public health policy formulations and responses to air pollution.

2. Data

2.1. Study Area

Qingyang, a prefecture-level city under the jurisdiction of Gansu Province, is located at the intersection of the three provinces of Gansu, Shaanxi, and Ningxia in northwestern China. It is a gully area on the Loess Plateau in the middle and lower reaches of the Yellow River. Its altitude is between 885 and 2,082 m. It has a temperate continental monsoon climate, with an annual average temperature of 9.5°C–10.7°C, and annual sunshine of 2,213.4–2,540.4 hr. The overall climate is drought, mild, and light-rich.
2.2. AECOPD and Environmental Data

This study covered 1.48 million individuals in the rural areas of Qingyang, and the data (A. Liu, 2022) of all admission cases aged 15 or over diagnosed with AECOPD in 155 local medical institutions of Qingyang were obtained for the period between 1 January 2015 and 26 June 2016. Patient data, including gender, age, admission date and diagnosis at discharge, were also included. Daily admission data of AECOPD cases were identified by the 10th version of the International Classification of Diseases with codes J44.1, and sorted according to the frequency division of the admission date.

Air pollutant data (A. Liu, 2022) were collected from the Qingyang Environmental Monitoring Center between 1 January 2015 and 26 June 2016, including particulate and gaseous pollutants. Particulate pollutants included PM$_{2.5}$ ($\mu$g/m$^3$) and PM$_{10}$ ($\mu$g/m$^3$), as 24-hr averages. Gaseous pollutants included SO$_2$ ($\mu$g/m$^3$), NO$_2$ ($\mu$g/m$^3$), CO (mg/m$^3$), and O$_3$ (mg/m$^3$), of which SO$_2$, NO$_2$, and CO were 24-hr averages, while O$_3$ was the daily maximum 8-hr average. Meteorological data (A. Liu, 2022) were obtained from the China’s surface climate database of the China Meteorological Data Sharing Service Platform during the period of 1 January 2015 to 26 June 2016, including daily average temperature (°C), relative humidity (%), air pressure (hPa), and wind velocity (m/s).

3. Methods

Given that daily admission for AECOPD is a small-probability event, Quasi-Poisson regression was used to address over-dispersion in count data. To investigate the nonlinear and lagged effects of air pollutants on daily admissions for AECOPD in the rural areas of Qingyang, we combined a DLNM with a time-stratified case-crossover design. The model is described below:

\[ Y_t \sim \text{Poisson}(\mu_t) \]

\[ g(\mu_t) = \alpha + \beta X_{it} + COV_S + \lambda Strata + \eta DOW_t + \theta Holiday_t \]

where \( g(\mu_t) \) refers to the connection function, and \( t \) represents the date of observation; \( Y_t \) is the number of admissions for AECOPD on day \( t \); \( \alpha \) is the intercept; \( X_{it} \) refers to the cross-basis of the independent variable and the lag, where \( i \) represents the number of lag days and \( \beta \) is the coefficient vector. The natural cubic spline function was selected to construct the cross basis function, whose degree of freedom was selected according to the minimum generalized cross validation; \( COV_S \) represents the matrix of all meteorological factors covariates in the model using natural cubic spline function, and their optimal degree of freedom were selected according to the Akaike information criterion; \( strata \) is the time-level factor in the time-stratified case-crossover design to control the long-term trend and seasonality, and \( \lambda \) represents the parameter; \( DOW_t \) is the “week effect” of the day \( t \), where \( \eta \) represents the parameter; \( Holiday_t \) is the “holiday effect” of the day \( t \), where \( \theta \) represents the parameter. Totally 27 days were selected as the maximum number of lag days according to related study (Luo et al., 2013) to reveal the lagged effects of air pollutants on AECOPD.

Descriptive analysis was performed to assess air pollutants and meteorological variables, as well as AECOPD data in Qingyang’s rural areas by calculating means, standard deviations, maximum values, minimum values, and quartiles. As all indicators were non-normally distributed, Spearman’s correlation analysis was used to determine correlation coefficients between daily admissions, air pollutants and meteorological variables. The effects of air pollutants on AECOPD were measured by the relative risk (RR). The median (P$_{50}$) of air pollutant concentration was used as the reference value, and the P$_{25}$ and P$_{75}$ percentiles were used as the high and low concentration nodes, respectively, to analyze the impact on AECOPD. We assessed single-day and cumulative (lag0–2, lag0–7, lag0–15, lag0–20, and lag0–27) lagged effects to effectively depict the characteristics of the associations of air pollutants with AECOPD. Further analysis was conducted through stratification by gender and age groups (adults, 15–64 years old and the elderly, ≥65 years old). Sensitivity analyses were performed to test the robustness of the selected model by changing the df for air pollutants (df = 2–5 or df = 1–4).

All statistical tests were two-sided, with \( P < 0.05 \) considered statistically significant. The R software (Version 4.0.4) was used for data analysis, with “psych,” “splines,” “lubridate,” “dlnm,” and “mgcv” packages (R Core Team, 2021).
4. Results

The descriptive statistics of daily AECOPD admissions, air pollutants and meteorological variables are presented in Table 1. A total of 9,897 AECOPD cases in the rural areas of Qingyang were reported from 1 January 2015 to 26 June 2016, with a median of 16.00. Of these cases, males aged 15–64 totaled 1970, with a median of daily admission of 3, while those ≥65 years old were 2,841, with a median of 4; females aged 15–64 totaled 2,170, with a median of daily admission of 3, while those ≥65 years were 2,916, with a median of 4.

The daily average air concentrations of PM2.5, PM10, SO2, NO2, CO, and O3 in the rural areas of Qingyang were 34.48 μg/m3, 75.98 μg/m3, 34.62 μg/m3, 18.41 μg/m3, 1.25 mg/m3, and 88.15 μg/m3, respectively; and daily average temperature, air pressure, relative humidity and wind velocity were 9.48°C, 867.21 hPa, 56.38% and 21.59 m/s, respectively.

The time-series of AECOPD admissions, air pollutants and meteorological indicators from 1 January 2015 to 26 June 2016 are shown in Figure 1. AECOPD admissions in each subgroup in Qingyang’s rural areas had seasonal fluctuations. The changes of PM2.5 and PM10 amounts had no characteristics, and CO, NO2, SO2, and O3 changes showed obvious fluctuation trends.

The associations of air pollutants and meteorological factors with AECOPD admissions are presented in Table S1 in Supporting Information S1. Daily concentrations of PM2.5, PM10, SO2, NO2, and CO were positively correlated with AECOPD admissions, with correlation coefficients of 0.21, 0.23, 0.45, 0.10, and 0.26, respectively (P < 0.05). O3 was negatively correlated with AECOPD admissions, with a correlation coefficient of −0.29 (P < 0.05).

The three-dimensional curves for RRs of AECOPD admissions associated with air pollutants over 27 lag days are shown in Figure 2. It was evident that air pollutants had nonlinear relationships with AECOPD. The correlation strength between pollutant concentrations and AECOPD admissions changed with the number of lag days.

To better summarize the aforementioned relationships, unidimensional specific summaries were generated, and the cumulative exposure-response curves are shown in Figure 3. The cumulative exposure-response curves for PM2.5 was approximately linear, and the effect was enhanced with the increasing concentration. The curves for PM10, SO2, and CO were complicated. But if only the statistically significant part was considered, PM10 was a “V”-shaped, SO2 and CO were inverted-“V” shaped. The cumulative exposure-response curves were “U”-shaped.

Table 1

<table>
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<tr>
<th>Variable</th>
<th>Mean ± SD</th>
<th>Min</th>
<th>P25</th>
<th>P50</th>
<th>P75</th>
<th>Max</th>
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<td>Total AECOPD cases</td>
<td>18.22 ± 11.14</td>
<td>0.00</td>
<td>10.00</td>
<td>16.00</td>
<td>23.00</td>
<td>64.00</td>
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<td>Male 15–64 years old</td>
<td>3.57 ± 2.61</td>
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<td>3.00</td>
<td>5.00</td>
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<td>≥65 years old</td>
<td>5.18 ± 3.76</td>
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<td>2.00</td>
<td>4.00</td>
<td>7.00</td>
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<td>Female 15–64 years old</td>
<td>3.96 ± 3.20</td>
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<td>5.00</td>
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<td>≥65 years old</td>
<td>5.33 ± 3.82</td>
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<td>3.00</td>
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<td>7.00</td>
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<td>PM2.5 (μg/m3)</td>
<td>34.48 ± 24.01</td>
<td>6.00</td>
<td>20.00</td>
<td>28.00</td>
<td>42.00</td>
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<td>PM10 (μg/m3)</td>
<td>75.98 ± 52.87</td>
<td>10.00</td>
<td>42.00</td>
<td>60.00</td>
<td>91.00</td>
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<td>SO2 (μg/m3)</td>
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<td>8.00</td>
<td>12.00</td>
<td>58.00</td>
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<tr>
<td>NO2 (μg/m3)</td>
<td>18.41 ± 8.04</td>
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<td>12.00</td>
<td>16.00</td>
<td>23.00</td>
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<td>CO (mg/m3)</td>
<td>1.25 ± 0.69</td>
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<td>0.80</td>
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<td>O3 8h (μg/m3)</td>
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<td>11.00</td>
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<td>111.00</td>
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<td>Mean temperature (°C)</td>
<td>9.48 ± 9.55</td>
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<td>10.10</td>
<td>18.18</td>
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<td>Air pressure (hPa)</td>
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<td>Relative humidity (%)</td>
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<td>42.00</td>
<td>54.50</td>
<td>69.25</td>
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<td>Wind velocity (m/s)</td>
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<td>10.50</td>
<td>18.00</td>
<td>20.50</td>
<td>24.50</td>
<td>51.50</td>
</tr>
</tbody>
</table>

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for NO\textsubscript{2} and inverted-“V” for O\textsubscript{3}. However, a statistically significant interval of NO\textsubscript{2} was only observed from 4 μg/m\textsuperscript{3} (minimum) to 16 μg/m\textsuperscript{3} (median), while O\textsubscript{3} was from 103 μg/m\textsuperscript{3} (more than median) to 172 μg/m\textsuperscript{3} (maximum). Therefore, within a statistically significant range, the effects of NO\textsubscript{2} and O\textsubscript{3} decreased as the concentration increased.

The statistically significant single-day lagged effects of extreme air pollutants on AECOPD admissions in each subgroup are shown in Figure 4. PM\textsubscript{2.5} only affected elderly males and adult females, with the greatest effect for NO\textsubscript{2} and inverted-“V” for O\textsubscript{3}. However, a statistically significant interval of NO\textsubscript{2} was only observed from 4 μg/m\textsuperscript{3} (minimum) to 16 μg/m\textsuperscript{3} (median), while O\textsubscript{3} was from 103 μg/m\textsuperscript{3} (more than median) to 172 μg/m\textsuperscript{3} (maximum). Therefore, within a statistically significant range, the effects of NO\textsubscript{2} and O\textsubscript{3} decreased as the concentration increased.

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Figure 1. Time-series diagram of daily acute exacerbation of chronic obstruction pulmonary disease admissions by subgroup and air pollutants from 1 January 2015 to 26 June 2016.
occurring on the day of exposure. Low-PM$_{2.5}$ had a protective effect, and the minimum RRs for elderly males and adult females were 0.986 (95% CI: 0.975–0.997) and 0.980 (95% CI: 0.968–0.993), respectively. High-PM$_{2.5}$ had a harmful effect, and the largest RRs for elderly males and adult females were 1.016 (95% CI: 1.001–1.031) and 1.025 (95% CI: 1.008–1.043), respectively. Low-PM$_{10}$ only affected adult females at lag0-1 day. High-PM$_{2.5}$ had most harmful effects in males on the last day of lag27 days, with RRs of 1.027 (95% CI: 1.004–1.051) and 1.036 (95% CI: 1.016–1.056) for adults and elderly, respectively. In females, the effect was greatest on the day of exposure, with RRs of 1.036 (95% CI: 1.006–1.069) and 1.039 (95% CI: 1.012–1.066) for adults and elderly, respectively. The effects of low-SO$_2$ in males decreased with time until lag19 days. They started and peaked at lag11 days with an RR of 0.989 (95% CI: 0.978–0.999) for adults and lag1 day with an RR of 0.983 (95% CI: 0.967–0.999) for elderly. While in females, the effects of low-SO$_2$ increased with time and get the largest RRs at lag27 days of 0.978 (95% CI: 0.962–0.994) and 0.983 (95% CI: 0.969–0.997) for adults and elderly, respectively. High-SO$_2$ only had effects in elderly males and adults females, and its effects were greatest on the day of exposure with RRs of 1.046 (95% CI: 1.008–1.087) and 1.056 (95% CI: 1.009–1.104), respectively. No statistically significant effect of NO$_2$ was observed in elderly females (Figure S1 in Supporting Information S1). In other subgroups, low-NO$_2$ showed a harmful effect. In adult males and females, the effect began at lag4 days and gradually increased until lag27 days, with maximum RRs of 1.030 (95% CI: 1.009–1.051) and 1.026 (95% CI: 1.006–1.046), respectively. The hazard to elderly males was greatest on the day of exposure, with an RR of 1.016 (95% CI: 1.001–1.032), and disappeared at lag21 days. High-NO$_2$ showed a protective effect at the beginning, and had the greatest effect on the day of exposure. The minimum RRs for adult males, elderly males and adult females were 0.924 (95% CI: 0.887–0.963), 0.963 (95% CI: 0.930–0.997), and 0.915 (95% CI: 0.879–0.951), respectively. However, it had a harmful effect after a period of time, with maximum RRs at lag27 days of 1.052 (95% CI: 1.012–1.095) on elderly males and 1.063 (95% CI: 1.017–1.112) on adult females. There was no effect of CO on the day of exposure, and the greatest RRs were reached at lag27 days. Low-CO had a protective effect, with
the minimum RRs of 0.970 (95% CI: 0.943–0.997), 0.948 (95% CI: 0.926–0.971), 0.939 (95% CI: 0.913–0.965),
and 0.967 (95% CI: 0.945–0.990) for adult males, elderly males, adult females and elderly females, respectively.
While high-CO only did harm to adult females with a maximum RR of 1.029 (95% CI: 1.002–1.057). No statistically
significant effect of low-O3 was observed. And high-O3 only had a protective effect in elderly males and
adult females at lag0–8 and lag13–16 days, respectively. The protective effect in elderly males was strongest at
the day of exposure, with an RR of 0.978 (95% CI: 0.957–0.999), while in adult females was strongest at lag16 days,
with an RR of 0.981 (95% CI: 0.962–0.999).

According to the DLNM fitting model, the forest plot for the statistically significant cumulative lagged effects of
extreme air pollutants on AECOPD at different lags in each subgroup in Qingyang’s rural areas from 1 January
2015 to 26 June 2016 are shown in Figure 5. Low-PM2.5, low-PM10, low-SO2, and low-CO showed protective
effects, all of which were greatest in adult females, with strongest RRs at lag0–15 days of 0.718 (95% CI: 0.618–
0.833), 0.8 (95% CI: 0.673–0.952), 0.697 (95% CI: 0.534–0.911), and 0.343 (95% CI: 0.213–0.552), respectively.
High-PM2.5, high-PM10, high-SO2, and high-CO showed harmful effects. At the same time, adult females
were also the most sensitive individuals, with strongest RRs of 1.537 (95% CI: 1.228–1.924) at lag0–20 days,
2.666 (95% CI: 1.627–4.367) at lag0–27 days, 2.64 (95% CI: 1.605–4.343) at lag0–15 days, and 1.489 (95% CI:
1.102–2.012) at lag0–20 days, respectively. Adults were more sensitive to extreme concentrations of NO2 than the
elderly. The former had greater RRs of low-NO2 than the latter, which were largest at lag0–27 days, and no effects
of high-NO2 were observed for the elderly (Figure S2 in Supporting Information S1). It also means that low-NO2
showed a harmful effect, while high-NO2 showed a protective effect. Low-O3 had a harmful effect only in elderly
males, with maximum RR of 1.354 (95% CI: 1.027–1.785) at lag0–20 days. Meanwhile, high-O3 had protective
effects in elderly males and adult females, with minimum RRs of 0.778 (95% CI: 0.614–0.987) at lag0–20 days
and 0.627 (95% CI: 0.468–0.814) at lag0–27 days, respectively.

After adjusting for meteorological factors, pollutants with the strongest cumulative lagged effects in the single
pollutant model and other pollutants at the same time period were included in the two-pollutant model (Figure 6).
Regardless of adjustment status, the cumulative lagged effects of PM2.5 in females decreased or even disappeared.
And after adjusting for SO2, the effects disappeared in all subgroups. While the effects increased in males, after
adjusting for NO2 and O3. After adjusting for CO, the effects in elderly males was enhanced, but disappeared
in other subgroups. For cumulative lagged effects of PM10 and SO2, the adjustments for other pollutants had
irregular impacts. After adjusting for SO2 and CO, the cumulative lagged effects of NO2 in all subgroups were
Figure 4. Statistically significant single-day lagged effect curves of extreme air pollutants for acute exacerbation of chronic obstruction pulmonary disease (AECOPD) in each subgroup at different lags in Qingyang’s rural areas from 1 January 2015 to 26 June 2016. The effects were expressed by the relative risk of AECOPD. The high-concentration effects were estimated by comparing the 75th percentile of daily air pollutants to the median value, whereas the low-concentration effects were estimated by comparing the 25th percentile of daily air pollutants to the median value. Elderly and adult patients were sub-grouped according to age (adult, 15–64 years old; the elderly, ≥65 years old).

Figure 4. (Continued)
enhanced, while were weakened after adjusting for PM$_{10}$ and O$_3$. Before adjustment, CO only had effects in females, which was enhanced after adjusting for SO$_2$ and NO$_2$. Adjustment for PM$_{10}$ could make the effects in males statistically significant. Before adjustment, O$_3$ only had an effect in elderly males, which was enhanced after adjusting for PM$_{2.5}$ and CO. Adjustment for NO$_2$ could make the effect in adult females statistically significant.

Sensitivity analysis revealed that the effects were robust when the degrees of freedom were altered. Adjusting for the degrees of freedom for PM$_{2.5}$, PM$_{10}$, SO$_2$, NO$_2$, CO, and O$_3$ did not alter the main results, as shown in Figures S3 and S4 in Supporting Information S1. Considering that the maximum lag time set in this study was long enough, it was not changed.

Figure 5. Forest plots for statistically significant cumulative lagged effects of extreme air pollutants on acute exacerbation of chronic obstruction pulmonary disease (AECOPD) at different lags in each subgroup in Qingyang’s rural areas from 1 January 2015 to 26 June 2016. The effects were expressed by the relative risk of AECOPD. The high-concentration effects were estimated by comparing the 75th percentile of daily air pollutants to the median value, whereas the low-concentration effects were estimated by comparing the 25th percentile of daily air pollutants to the median value. Elderly and adult individuals were sub-grouped according to age (adult, 15–64 years old and the elderly, ≥65 years old).
5. Discussion

In this study, the time-stratified case-crossover design combined with a DLNM was used to examine the impacts of air pollutants on AECOPD in the rural areas of Qingyang from 1 January 2015 to 26 June 2016. We found significant associations of PM$_{2.5}$, PM$_{10}$, SO$_2$, NO$_2$, CO, and O$_3$ with AECOPD admissions. Exposure to high-PM$_{2.5}$ of 42 μg/m$^3$, high-PM$_{10}$ of 91 μg/m$^3$, high-SO$_2$ of 58 μg/m$^3$, low-NO$_2$ of 12 μg/m$^3$, and high-CO of 1.55 mg/m$^3$ could increase the risk of AECOPD, while low-PM$_{2.5}$ of 20 μg/m$^3$, low-PM$_{10}$ of 42 μg/m$^3$, low-SO$_2$ of 8 μg/m$^3$, high-NO$_2$ of 23 μg/m$^3$, low-CO of 0.8 mg/m$^3$, and high-O$_3$ of 111 μg/m$^3$ were protective factors. A meta-analysis by Li et al., in 2016 pointed out that short-term exposure to both gaseous and particulate pollutants could significantly increase the exacerbation risk of COPD (J. H. Li et al., 2016). In 2017, a study in Shanghai found that exposure to high-PM$_{2.5}$ of 75–250 μg/m$^3$ is an important cause of AECOPD (X. W. Sun et al., 2017). Khaniabadi et al. pointed out that every increase of 10 μg/m$^3$ for PM$_{10}$, O$_3$, SO$_2$, and NO$_2$ could explain 5.9%, 4.1%, 1.2%, and 1.9% of daily hospitalizations for COPD in 2011, versus 6.6%, 1.9%, 2.3%, and 2.1% in 2012, respectively (Khaniabadi et al., 2018). These results are consistent with the present study, except for NO$_2$. This may related to the fact that the NO$_2$ levels in this study area (mean of 18.41 μg/m$^3$ and maximum of 46 μg/m$^3$) are lower than other area (mean of 67.3 μg/m$^3$ and maximum of 621 μg/m$^3$) in aforementioned study (Khaniabadi et al., 2018), and also lower than ambient air quality standards (Ministry of Environmental Protection of the People’s Republic of China, 2012) of daily average of 80 μg/m$^3$. Therefore, the actual concentration level of high-NO$_2$ in this study
is also very low, and the effect of “high-NO\textsubscript{2}” is differ from other studies. What's more, since the geographic, demographic are different from the areas in which the risk relationships were developed and not evaluated here, further investigations will be needed to fully quantify other health impacts of NO\textsubscript{2} and other air pollutants.

The effects of exposures to high-concentration and low-concentration air pollutants were not concerted in subgroups based on gender and age. Adult females were most affected by extreme concentrations of PM\textsubscript{2.5}, SO\textsubscript{2}, CO, and low-PM\textsubscript{10}. In addition, elderly ≥65 years old were more sensitive to high-PM\textsubscript{10} compared with the adults. These findings corroborated a study by Cao Yu et al., using data collected in 2017. In the latter study, particulate pollutants increased the risk of AECOPD hospitalization, and the risk was higher for women and the elderly (Cao et al., 2017). Differences by sex may exist for deposition patterns of particulate matter, diet, and other air pollution exposures (e.g., cooking, transportation), which could be the reason why females are more susceptible (Bell et al., 2015). A study in Hong Kong also found that CO is negatively correlated with the number of daily hospital admissions for respiratory diseases, with the negative correlation being stronger in adults than in the elderly and children (Tian et al., 2013). This may be related to the varying intake fractions in subgroups, as a study investigated the time-activity patterns of representative residents in Lanzhou City showing that adults spend more time outdoors than the elderly due to work or other reasons (Wu et al., 2020). A investigation on indoor and
outdoor time of Chinese adults also indicated that the average outdoor time for 18–44, 45–59, 60–79, and more than 80 years old residents were 219, 235, 210, and 150 min/d, respectively (B. B. Wang et al., 2014). High-SO₂, high-NO₂, and extreme concentrations of PM₂.₅ had the greatest impacts on the day of exposure, and these effects lasted for a period of time. This indicated that the immediate effects of these air pollutants were stronger than the lagged effects. Moreover, the protective effects of low-SO₂ and low-CO have hysteresis on AECOPD, which gradually increased with time until lag 27 days. A study in Shanghai in 2018 pointed out that the effects of PM₂.₅ and PM₁₀ on COPD death have both immediate and cumulative lagged types (Y. C. Chen et al., 2019). A study by Gao et al., in 2019 also showed that the cumulative lagged effect on COPD in Beijing residents per 10 μg/m³ increase in NO₂ and SO₂ amounts reached the maximum hospitalization rates of 3.03% (95% CI: 1.82%–4.26%) at lag0–6 days and 2.07% (95% CI: 1.00%–3.15%) at lag0–1 day, respectively (Gao et al., 2019). These results corroborate the present study, as they show the same lagged effects. However, there is no relevant research on the hysteresis of protective effects of low-SO₂ and low-CO, so it needs further researches.

**Figure 6.** Forest plots for cumulative lagged effects on acute exacerbation of chronic obstruction pulmonary disease (AECOPD) in each subgroup using the two-pollutant model in Qingyang’s rural areas from 1 January 2015 to 26 June 2016. The effects were expressed by the relative risk of extreme concentrations for AECOPD development, with the median concentration as a reference. Elderly and adult individuals were sub-grouped according to age (adult, 15–64 years old and the elderly, ≥65 years old).
The results of two-pollutant model analyses showed that adjusting for CO or SO₂ could reduce or eliminate the effects of PM₂.₅ and PM₁₀ while enhance the effect of NO₂ in all subgroups. And the adjustment for PM₁₀ could enhance the effect of CO, while reduce the effect of NO₂ in all subgroups. A 2017 study showed that in a multi-pollutant model, after controlling for SO₂ alone, the effect of PM₁₀ on COPD admissions was not statistically significant (W. Y. Zhang et al., 2017). A study in Shanghai pointed out that after adjusting for SO₂, the effects of PM₂.₅ and PM₁₀ are not significant (Y. C. Chen et al., 2019). It was proposed that the negative association between CO and hospital admissions for respiratory tract infections became stronger when PM₁₀ was adjusted for in two-pollutant models (Tian et al., 2013). A study in Zhangjiakou city (J. L. Yang, 2017) showed that after adjusting for PM₁₀ and CO, for every 10 μg/m³ increase in NO₂, the daily admission rate of COPD increased by 5.2 (95% CI: 2.2%–8.5%) and 6.7% (95% CI: 2.5%–11%), respectively, while the rate increased by 6.4% (95% CI: 3.7%–9.2%) before the adjustment. These results corroborate the present study, and indicate that there may be some connections between the pathogenic mechanism of air pollutants to AECOPD.

Relevant studies have explored the biological mechanisms of air pollutants affecting AECOPD, showing that deficiency of α-antitrypsin (alpha1-antitrypsin) can increase the risks of COPD, liver disease and several other...
diseases (Silverman & Sandhaus, 2009). Substances such as polycyclic aromatic hydrocarbons and transition metals carried on the surface of PM$_{2.5}$ can cause an accumulation of reactive oxygen species in cells (Z. L. Sun et al., 2016). This process may cause the imbalance of protease-antitrypsin by inducing defects in antitrypsin function, weakening the ability to protect cell integrity and inhibit neutrophils, and subsequently triggering the pathogenesis of COPD through a series of mechanisms (Z. J. Li et al., 2009).

There were limitations in the present study. First, the associations of air pollutants with AECOPD were examined based on group-level data, and the study did not control for indoor exposure level; therefore, the data could not reflect actual individual exposures. Further studies should associate the individual’s exposure to air pollutants with the incidence. Second, when exploring the associations of air pollutants with AECOPD, the time span of the data included was relatively short. In addition, this study was based on a rural area in northwest China, and the results may not be generalized to other areas with different air pollution patterns, meteorological conditions, economic levels. Further studies should expand the research area and the time span, in order to examine the general and long-term effects of exposure to air pollutants. Finally, the date of admission, rather than the time of AECOPD, was used in the current analysis, which may result in temporal misalignment between exposure to air pollutants and AECOPD, underestimating exposure effects. However, as AECOPD requires immediate hospitalization and treatment, we estimate that time misalignment has limited effects on the current results. Since admission or diagnosis may occur within a few days after the onset of symptoms, the lagged effects of air pollutants on AECOPD should be explained with caution.

Despite the above limitations, this study presents several advantages. The time-stratified case-crossover design controls for seasonal effects and long-term trends by matching the number of days in the case and control in a relatively short time (such as a calendar month). The DLNM considers both the lagged effects of exposure factors and the nonlinear relationship between exposure and response. Therefore, this study combined the time stratified case crossover design and the DLNM to make use of the advantages of both approaches. It is certain that the present findings could help understand the associations of air pollutants with AECOPD, providing novel insights into assessing the potential impacts of air pollution on health, determining public health priorities and taking preventive measures for susceptible subgroups in the future.

6. Conclusion
In conclusion, exposure to PM$_{10}$, PM$_{2.5}$, SO$_2$, NO$_2$, CO, and O$_3$ exerts nonlinear and lagged effects on AECOPD in Qingyang district. Females aged 15–64 were more vulnerable under extreme concentrations of PM$_{2.5}$, SO$_2$, CO, and low-PM$_{10}$ than other subgroups. In addition, adults aged 15–64 were more sensitive to extreme concentrations of NO$_2$ compared with the elderly≥65, while the latter were more sensitive to high-PM$_{10}$. Precautionary measures should be taken with a focus on vulnerable subgroups, to control hospitalization for AECOPD associated with air pollutants.

Conflict of Interest
The authors declare no conflicts of interest relevant to this study.

Data Availability Statement
Version 4.0.4 of the R software as well as “psych,” “splines,” “lubridate,” “dlnm,” and “mgcv” packages which are used for constructing the distributed lag nonlinear model (DLNM) are publicly available at https://cran.r-project.org/. The incidence data and environmental data used in this analysis can be accessed at https://doi.org/10.7910/DVN/QLAJIF.

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