Air Pollution and Outpatient Visits for Cardiovascular and Cerebrovascular Diseases: A Time-Series Analysis in Luoyang, China

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1 **Air pollution and outpatient visits for cardiovascular and cerebrovascular diseases: a time-series**
2 **analysis in Luoyang, China**

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13 **Abstract:**

14 **Background:** Previous studies have shown that air pollution has a great impact on cardiovascular
15 and cerebrovascular diseases (CCD), but there is a lack of research on low and medium pollution areas.
16 This study was the first time to explore the effects of air pollutants on the outpatient visits of CCD in
17 Luoyang, which is located in low and medium pollution areas.

18 **Methods:** In this study, the Generalized Additive Model (GAM) was used to establish a single
19 pollutant model, a multi-pollutant model and stratified modes of age, sex and season to evaluate the
20 effects of PM_{2.5}, PM₁₀, SO₂, NO₂, CO and O₃ on the outpatient visits of CCD within a week.

21 **Results:** The results of single pollutant model showed that PM_{2.5}, PM₁₀, SO₂, NO₂, CO and O₃ all
22 had significant effects on the outpatient visits of CCD with a lag effect, interquartile range (IQR)
23 increased in their concentration, the outpatient visits with CCD increased by 2.8%(95%CI:1.7%-4.0%),
24 3.0%(95%CI:1.8%-4.1%), -4.2% (95%CI: -5.5%- -2.9%), 20.5%(95%CI:18.2%-22.7%),
25 10.4%(95%CI:8.8%-12.1%), 2.3%(95%CI:0.8%-3.9%). The multi-pollutant model showed that there
26 may be complex interactions among pollutants. The results of stratified model showed that there was
27 no significant difference in the effects of different pollutants on different genders and ages, and the
28 results of seasonal stratification showed that PM_{2.5}, PM₁₀, SO₂ and CO had a greater influence on the
29 outpatient visits of CCD in spring and summer, while NO₂ and O₃ had a greater influence on the
30 outpatient visits of CCD in autumn and winter.

31 **Conclusion:** The results showed that air pollutants significantly affected the outpatient visits of CCD,
32 among which NO₂ had the greatest influence, and seasonal effects and the combined effects of various
33 pollutants should be considered in the prevention of CCD.

34 **Keywords:** air pollution; cardiovascular and cerebrovascular diseases; generalized additive model;

35 daily outpatient visits; analysis of time series

36 **1. Background**

37 It has been reported globally that air pollution is the fourth leading risk factor for death. [1].
38 According to statistics, in 2015, China was the country with the largest number of deaths caused by
39 environmental pollution among the world's 10 most populous countries. CCD was the leading cause of
40 death and loss of life in the world in 2016 and 2017. In 2019, 12% of the global deaths were attributed
41 to outdoor and household air pollution, and 50% of the deaths caused by air pollution were caused by
42 cardiovascular diseases (CVD). [2-5]. With the characteristics of high incidence, high disability rate, high
43 mortality rate, high recurrence rate and many complications, CCD led to high medical cost for the
44 treatment, which seriously affects the quality of life of residents and the development of national
45 economy. Thus, how to carry out in-depth research on the influencing factors of CCD and get effective
46 control decision-making has been concerned by relevant scholars all over the world.

47 A large number of epidemiological studies in the past few years have shown that the outpatient visits
48 is the most sensitive indicator of health outcomes caused by air pollution, and it can better reflect the true
49 health effects of air pollution [6, 7]. The occurrence of cardiovascular diseases and cerebrovascular
50 diseases has the same or similar causes, biological risk factors (blood lipids, blood pressure, blood sugar,
51 obesity), lifestyle risk factors (smoking, alcohol, diet, physical activity), environmental risk factors
52 (meteorology, air pollution and indoor air pollution) are closely related to the increase in outpatient rate
53 and risk of death of CCD, and the two kinds of diseases are often related to each other[8]. Many studies
54 have found that there are differences in the effects of different concentrations of pollutants on people of
55 different genders and ages in different seasons. Among the many influencing factors, only environmental
56 risk factors can be improved to a certain extent through the formulation of relevant public policies and

planning [9]. Therefore, it is of great significance to study the harm of air pollutants to the CCD of residents.

At present, it is considered that air pollutants mainly exist in the complex mixed form of particulate pollutants ($PM_{2.5}$, PM_{10}) and gaseous pollutants (NO_2 , SO_2 , O_3 , CO)[1]. It was confirmed that $PM_{2.5}$ and PM_{10} are harmful to CCD, but the mechanism of the effect of gaseous pollutants on human CCD is still under further exploration[10-16]. Previous studies focused more on the study of heavily polluted or economically developed areas, and seldom discussed the relationship between pollutants and CCD in areas with lower levels of air pollution and economic development [17-19]. In addition, only some particulate or gaseous pollutants have been considered in previous studies, while the impact of multiple particulate and gaseous pollutants in different seasons on people with CCD of different ages and genders have been less studied[18, 20-22]. Different regions have different natural, cultural, economic conditions, industrial structure and industrial layout, and the composition of pollutants is different, and the research results will be different [23].

This study took Luoyang as the study area. Luoyang belonged to the third-tier city in China. Because the industry with high energy consumption and high pollutants belongs to its pillar industry, and the industrial layout is unreasonable (the factory is too close to the city), urban construction produces a large amount of dust, so there is moderate pollution, and Luoyang is basin topography, so, the air mobility is poor, pollutants are not easy to spread, and it is easier to have serious effects on the health of residents. This study aimed to explore the following contents: (1) to explore the relationship between the concentration of $PM_{2.5}$, PM_{10} , NO_2 , SO_2 , O_3 , CO and the outpatient visits with CCD in areas with lower levels of pollution and economic development in the single pollutant model. (2) to establish the model of double pollutants, three pollutants, four pollutants and total pollutants, to discuss the

relationship between the concentration of each pollutant and the outpatient visits of CCD after the introduction of other pollutants, and also to discuss the interaction among various pollutants. (3) to establish a stratified model of season, sex and age to discuss the effects of each pollutant on the outpatient visits of CCD in different seasons, genders and ages. (4) to test the multicollinearity of the model.

2. Study area and Methods

2.1 Study area

Luoyang City, as shown in figure 1, located at $112^{\circ}16'-112^{\circ}37'E$ and $34^{\circ}32'-34^{\circ}45'N$, in the northwest of Henan Province, China. The topography in Luoyang is complex, of which mountain areas account for 45.5%, hills account for 40.7%, and plains account for 13.8%. Luoyang has a warm temperate continental monsoon climate, which is relatively mild and has four distinct seasons. According to statistics, the population of permanent residents in Luoyang reached 6.888 million in 2018, the gender and age structure of the population showed a good development trend, including a males-to-females ratio of 1:1. The total GDP of Luoyang in 2018 reached 464.08 billion yuan, and the speed of industrial development was also rising steadily, and as an important industrial base in Henan, the added value of the secondary industry in Luoyang in 2018 was 206.76 billion yuan.

Figure1. the sketch map of study area

2.2 Methods

2.2.1 Data collection

The daily outpatient data of CCD came from the hospital information system of Luoyang Central Hospital and Luoyang first people's Hospital. We only kept outpatient data that did not contain personal privacy (only included the information of patients' disease type, date of visit, age and gender). According to the classification standard of ICD-10 (10th edition of International Classification of Diseases), the statistics of CCD were carried out from January 1, 2016 to December 31, 2018, with a total of 208355 CCD outpatient data. This research project was approved by the ethics committee of Zhengzhou University, and the procedures used in this study adhere to the tenets of the Declaration of Helsinki.

The air pollutant concentration data in Luoyang from January 1, 2016 to December 31, 2018 came from China Environmental Monitoring Centre (<http://www.cnemc.cn/>) and the China Air quality online Monitoring and Analysis platform (<https://www.aqistudy.cn/>). The data types of air quality included $PM_{2.5}$ ($\mu g / m^{-3}$), PM_{10} ($\mu g / m^{-3}$), SO_2 ($\mu g / m^{-3}$), NO_2 ($\mu g / m^{-3}$), O_3 ($\mu g / m^{-3}$) and CO (mg / m^{-3}). The meteorological data were obtained from the China Meteorological data Network (<http://data.cma.cn/>), including daily minimum temperature ($^{\circ}C$), daily maximum temperature ($^{\circ}C$), daily mean temperature ($^{\circ}C$), daily mean relative humidity (%), daily mean pressure (hpa), wind speed (m / s^{-1}).

2.2.2 Statistical analysis

This study used the average (Mean), Standard Deviation (SD), percentile (P_{25} , P_{50} , P_{75}), maximum and minimum values (MAX, MIN) to describe meteorological data, pollutant concentration data, outpatient data of different ages, genders and seasons.

The statistical distribution of daily outpatients in Luoyang from January 1, 2016 to December 31, 2018 approximately obeyed Poisson distribution, so this study chose the semiparametric generalized

additive model (GAM) and time-series method to estimate the relationship between PM_{2.5}, PM₁₀, NO₂, SO₂, O₃, CO and the number of outpatient visits with CCD, control variables such as time trend, meteorological factors, the “week effect” and “holiday effect” were introduced to ensure the stability of the model. The specific GAM models are as follows:

$$\text{Log}[E(Y_t)] = a + \beta_t X_t + ns(\text{time}, 9) + ns(Z_t, df) + DOW + Holiday \quad (1)$$

In the model, Log[] is the connection function of Poisson distribution; Y_t is the actual number of outpatients on day t ; $E(Y_t)$ is the expected number of outpatients on day t ; a is intercept; β_t is the coefficient of exposure response; X_t is the concentration of atmospheric particulate pollutants on day t ; ns is cubic regression spline; Z_t is the meteorological confounding factor of day t ; DOW and Holiday are dummy variables to control "week effect" and "holiday effect" respectively.

The GAM model was established by calling the "mgcv" package in R3.6.2, and the best model was determined by the minimum principle of Akaike information criterion (AIC). The excess risk (ER) and its 95% confidence interval (CI), for every IQR increase of PM_{2.5}, PM₁₀, SO₂, NO₂, CO and O₃ concentration were calculated as the short-term effect evaluation index of the effect of pollutants on CCD. Test level $\alpha = 0.05$, ER and its 95%CI calculation formula are as follows:

$$ER = e^{a*\beta} \times 100\% \quad (2)$$

$$CI = e^{(\beta \pm 1.96SE)*a} \quad (3)$$

Where ER is the relative risk; a is the IQR for each pollutant; β is the regression coefficient; CI is 95% confidence interval.

In order to evaluate the delayed and cumulative effects between air pollution and the outpatient visits with CCD, we introduce Single-day lag data (lag0-lag7) and Multi-day lag data (lag0-lag07) within a week to establish a lag model, in which the Multi-day lag data were obtained by calculating the moving

average. The best lag days of each pollutant was determined according to the principle of maximum effect value.

We established single-pollutant model and multi-pollutant model respectively, and the multi-pollutant model was used to test the interaction between pollutants. The stability of the model was tested according to the variance expansion coefficient (VIF) of each pollutant in the model. A stratified study was conducted according to sex, age and season, and Z test was used to test whether the differences between groups were statistically significant, and the formula for Z-value is as follows:

$$Z = \frac{(\hat{Q}_1 - \hat{Q}_2)}{\sqrt{S\hat{E}_1^2 + S\hat{E}_2^2}} \quad (3)$$

Where $\hat{Q}_1$ and $\hat{Q}_2$ are the estimated values of different groups of models, and $S\hat{E}_1^2$, $S\hat{E}_2^2$ are the standard errors respectively.

3. Result

The statistical results of air pollutants, meteorological factors and outpatient visits of CCD were shown in Table 1. From January 1, 2016 to December 31, 2018, there were 208,355 outpatients with CCD in Luoyang, with an average of 190 cases per day. After grouping, it showed that the average daily outpatient visits were 95.8 for males, 93.8 for females, 2.8 for < 41 years old, 84 for 41-65 years old and 102 for > 65 years old, and the average daily outpatient visits in spring, summer, autumn and winter were 202.9, 189.3, 180.1 and 190.12 respectively.

The average concentrations of air pollutants PM_{2.5}, PM₁₀, SO₂, NO₂ and O₃ were 69.70µg/m³, 19.65µg/m³, 26.65µg/m³, 43.32µg/m³, 63.0 µg/m³ and CO were 1.58mg/m³, respectively. The daily average temperature, relative humidity, pressure and wind speed were 15.5 °C, 58.2%, 978hpa, 2.8 m/s, respectively.

Table 1 Data for air pollutants, meterological factors, and outpatient visits of CCD in Luoyang

	Mean	SD	Min	P25	P50	P75	Max	IQR
PM _{2.5} ($\mu\text{g}/\text{m}^3$)	69.8	54.5	7.9	36.7	53.7	81.3	487.3	44.6
PM ₁₀ ($\mu\text{g}/\text{m}^3$)	124.3	78.3	21.2	70.6	105.3	151.1	599.3	80.5
SO ₂ ($\mu\text{g}/\text{m}^3$)	26.6	17.5	4.3	14.8	21.9	33.0	142.0	18.3
NO ₂ ($\mu\text{g}/\text{m}^3$)	43.3	18.5	11.8	29.0	39.7	54.4	109.4	25.3
O ₃ -8h($\mu\text{g}/\text{m}^3$)	63.0	37.5	3.8	33.0	53.4	89.2	189.6	56.2
CO (mg/m ³)	1.6	0.6	0.5	1.2	1.4	1.8	6.3	0.7
Temperature (°C)	15.5	9.8	-7.5	7.2	16.5	24.2	32.0	17.0
RH (%)	58.2	21.0	11.0	42.0	58.0	75.0	98.0	33.0
Windspeed(m/s)	2.8	1.1	0.1	2.0	2.6	3.4	8.3	1.4
Pressure(hpa)	978.2	8.8	960.0	971.0	978.0	985.0	1003.0	14.0
Gender								
Male	95.8	60.1	5.0	31.0	102.0	137.0	304.0	106.0
Female	93.8	60.4	4.0	29.0	99.0	135.0	288.0	106.0
Age group(year)								
<41	2.8	2.8	0	0	2.0	4.0	18.0	4.0
41-65	84.0	55.5	4.0	24.0	89.0	121.0	308.0	97.0
>65	102.8	63.4	6.0	36.0	107.0	147.0	302.0	111.0
Season								
Spring	202.9	143.5	28.0	59.8	177.0	331.3	575.0	271.5
Summer	189.3	113.8	15.0	47.8	223.5	271.3	387.0	223.5
Autumn	180.1	99.8	15.0	64.0	216.0	251.0	403.0	187.0
Winter	190.1	119.6	26.0	66.0	180.0	267.5	526.0	201.5

162 Abbreviations: PM_{2.5}: particulate matter < 2.5 μm in aerodynamic diameter, PM₁₀: particulate matter
163 < 10 μm in aerodynamic diameter, SO₂: sulfur dioxide, NO₂: nitrogen dioxide, O₃-8h: daily 8-h mean
164 concentration of ozone, CO: carbon monoxide, RH: relative humidity.

165 3.1 Single pollutant model

As shown in figure 2, the increase in the concentration of SO_2 resulted in a reduction in the risk of outpatient visits for CCD, and at lag06, an IQR increases in the concentration of SO_2 reduced the risk of outpatient visits by 16.8%. The increased concentrations of $\text{PM}_{2.5}$, PM_{10} , NO_2 , CO and O_3 were significantly correlated with the increased risk of outpatient visits for CCD. With IQR increase of concentration, the highest risk and 95%CI of outpatient visits were 0.028 (0.017-0.040), 0.030 (0.018-0.041), 0.205 (0.182-0.227), 0.104 (0.088-0.121) and 0.023 (0.008-0.039), respectively. NO_2 was the pollutant that has the greatest impact on outpatients with CCD.

Figure 2 Effects of an IQR increased of pollutants' concentration on outpatient visits of CCD

3.2 Multiple collinearity test

The model's Variance Inflation Factor (VIF) can be used to test the multicollinearity of models. Experience has shown that when the VIF value is greater than or equal to 5, indicating that there is a serious multicollinearity between independent variables, and this multicollinearity may excessively affect the least square estimates. In this study, all pollutants were added to the model (model), and it was found that the VIF value of $\text{PM}_{2.5}$ and PM_{10} were more than 5. It was considered that there was a serious collinearity between $\text{PM}_{2.5}$ and PM_{10} . After removing $\text{PM}_{2.5}$ (model1) or PM_{10} (model2) on the basis

of the total pollutant model (model), it was found that the VIF values of all influencing factors were less than 5. The results of collinearity test were shown in Table 2.

To avoid multicollinearity, PM_{2.5} and PM₁₀ are not introduced into the multi-pollutant model at the same time.

Table 2 Test results of model collinearity

		PM _{2.5}	PM ₁₀	SO ₂	NO ₂	CO	O ₃
Model	VIF	10.63	7.58	3.38	3.20	3.60	3.71
Model1			2.45	3.38	3.08	3.15	3.52
Model2		3.44		3.38	3.17	3.57	3.67

3.3 Multi-pollutant model

The results of the two-pollutant, three-pollutant, four-pollutant and five-pollutant model were shown in Table 3. The results showed that there were complex interactions between pollutants. It was worth noting that there was almost no change in the results after the pollutants except NO₂ were introduced into O₃ alone or at the same time, while the ER value of O₃ increased only after the introduction of NO₂, and the ER value was almost unchanged after the introduction of PM_{2.5}, PM₁₀, SO₂ and CO alone or at the same time. The ER value of PM_{2.5} and PM₁₀ increased after the introduction of SO₂, and decreased after the introduction of CO and NO₂; the ER value decreased when SO₂ introduced any pollutants alone or at the same time; The ER value of NO₂ decreased only after the introduction of CO alone or at the same time, while the ER value of CO decreased only after the introduction of NO₂ alone or at the same time.

3.4 stratification analysis

3.4.1 stratified analysis of gender

The results of gender stratification were shown in figure 3, there was a significant correlation between each pollutant and the number of outpatients of different genders. For both men and women,

the increase of SO_2 concentration was related to the decrease of the risk of outpatient visits of CCD, while the increase of $\text{PM}_{2.5}$, PM_{10} , NO_2 , CO and O_3 concentration was related to the increase of that risk. For an IQR increased in the concentrations of $\text{PM}_{2.5}$, PM_{10} , NO_2 , CO and O_3 , the maximum ER and 95%CI of male were 0.035 (0.018, 0.051), 0.030 (0.014, 0.047), 0.194 (0.163, 0.226), 0.115 (0.092, 0.139), 0.022 (0.000, 0.044), respectively, and the maximum ER and 95%CI of female were 0.018 (0.002), 0.027 (0.011), 0.208 (0.176), 0.090 (0.067) and 0.036 (0.014), respectively. There was no significant difference in the effect of each pollutant on the outpatient visits of CCD among different genders.

Figure 3 Effects of an IQR increased of pollutants' concentration on outpatient visits of CCD in different genders

3.4.2 stratified analysis of age

The results of age stratification were shown in figure 4. There was no significant correlation between PM_{10} , SO_2 and the outpatient visits with CCD in people under 41 years old. $PM_{2.5}$, NO_2 , CO , O_3 were significantly correlated with the outpatient visits with CCD in all age groups. O_3 and SO_2 were only positively correlated with the risk of CCD outpatient visits in people over 65 years old. An IQR increase in $PM_{2.5}$, NO_2 and CO , the maximum ER and 95%CI of < 41-year-old group were 0.109 (0.009, 0.219), 0.323 (0.126, 0.555) and 0.250(0.099, 0.422), respectively. The concentrations of $PM_{2.5}$, PM_{10} , NO_2 and CO increased by IQR, the maximum excess risk and 95%CI of 41-64 age group were 0.034 (0.017, 0.052), 0.029 (0.012, 0.046), 0.203 (0.169, 0.238) and 0.092(0.068, 0.118), while in the >65 age group the corresponding ER and 95%CI were 0.018(0.007,0.030),0.027(0.012,0.043),0.195(0.165,0.225),0.108(0.085,0.131) respectively. The effect of other pollutants except O_3 on the outpatient visits of CCD showed no statistical significance among the three age groups. The effect of O_3 on the outpatient visits of CCD in people aged 41-64 was higher than that in people under 40.

Figure 4 Effects of an IQR increased of pollutants' concentration on outpatient visits of CCD in different ages

3.4.3 stratified analysis of season

The seasonal stratification results were shown in Figure 5. PM_{2.5}, PM₁₀, SO₂, NO₂, CO, O₃ had significant correlation with outpatient visits of CCD in four seasonal groups. The effects of PM_{2.5} and PM₁₀ were consistent, and their maximum ER was greater than 0 in spring and summer, and less than 0 in autumn and winter. The maximum ER of SO₂ was greater than 0 only in spring. The maximum ER of NO₂ was greater than 0 in spring and winter, and less than 0 in summer and autumn. The maximum ER of CO and O₃ was less than 0 only in autumn and winter. The effects of pollutants on outpatient

visits of CCD were statistically different in some seasons: the risk of $PM_{2.5}$ and PM_{10} on CCD was higher in spring and summer, the risk of CO was greater in summer, and SO_2 , NO_2 and O_3 had the greatest influence on the outpatient visits of CCD in spring, winter and autumn respectively.

Figure 5 Effects of an IQR increased of pollutants' concentration on outpatient visits of CCD in different seasons

4. Discussion

In this study, the time-series analysis of the effect of air pollutants on the outpatient visits of CCD in Luoyang from January 1, 2016 to December 31, 2018 showed that all the six pollutants had a significant effect on the outpatient visits of CCD, and there was a lag effect. Wang et al [24] studied the

relationship between air pollution and markers of CVD in China, and found that higher exposure to air pollutants is associated with increased levels of CVD markers such as C-reactive protein and coronary artery calcification. Riggs et al [25] found that exposure to particulate pollutants can cause oxidative stress and inflammation, resulting in vascular function damage, and eventually lead to atherosclerosis.

In this study, the single pollutant model found that the concentration of $PM_{2.5}$ and PM_{10} increased by an IQR ($44.6 \mu\text{g}/\text{m}^3$, $80.5 \mu\text{g}/\text{m}^3$), and the outpatient visits of CCD increased by 2.8% (95% CI: 1.7%-4.0%) and 3.0% (95% CI: 1.8%-4.1%), respectively. Zhong et al. studied the effect of PM on CCD in Beijing and found that $PM_{2.5}$ and PM_{10} increased IQR ($71.7 \mu\text{g}/\text{m}^3$, $87.6 \mu\text{g}/\text{m}^3$), the relative risk (RR) of CCD was 1.038 (1.035-1.041) and 1.035 (1.033-1.037), respectively [26]. Liu et al. [27] conducted a study on the effect of air pollutants on hospitalization of heart failure in 26 cities in China, it was found that the concentration of $PM_{2.5}$ and PM_{10} increased by a quartile ($47.5 \mu\text{g}/\text{m}^3$, $76.9 \mu\text{g}/\text{m}^3$), and the admission rate of CVD increased by 1.2% (95% CI: 0.5% -1.8%) and 1.3% (95% CI: 0.5%-2.0%) respectively. The differences between the results of different studies might be mainly due to the different concentrations of pollutants in the study area.

Particulate pollutants were recognized as risk factors, but the mechanism of the effect of gaseous pollutant exposure on CCD risk is not clear [28-30]. In this study, the single pollutant model found that an IQR ($18.3 \mu\text{g}/\text{m}^3$, $25.3 \mu\text{g}/\text{m}^3$, $0.7 \text{mg}/\text{m}^3$, $56.2 \mu\text{g}/\text{m}^3$) increase in SO_2 , NO_2 , CO and O_3 concentrations was associated with a -4.2% (95% CI: -5.5%-2.9%), 20.5% (95% CI: 18.2%-22.7%), 10.4% (95% CI: 8.8%-12.1%) and 2.3% (95% CI: 0.8%-3.9%) increase in outpatient visits of CCD, respectively. Except for SO_2 , the influence of the other three gaseous pollutants on CCD was higher than previous studies, which might be caused by the lower economic and medical level of local residents in developed areas. Zhong et al. found that the concentration of SO_2 , NO_2 , CO and O_3 increased by an

IQR($10.9\mu\text{g}/\text{m}^3$, $28.2\mu\text{g}/\text{m}^3$, $0.73\text{mg}/\text{m}^3$, $50.6\mu\text{g}/\text{m}^3$) in Beijing, the admission rate of CVD increased by 3.17% (95% CI: 2.93% -3.41%), 1.38% (95% CI: 1.26% -1.50%), 3.78% (95% CI: 3.51% -4.05%), 2.07% (95% CI: 1.96% -2.18%)[26], while Liu et al. found that the concentration of SO_2 , NO_2 and CO increased by an IQR($22.2\mu\text{g}/\text{m}^3$, $24.1\mu\text{g}/\text{m}^3$, $0.56\text{mg}/\text{m}^3$), the admission rate of CVD increased by 1.2% (95% CI: 0.5% -1.8%), 1.6% (95% CI: 0.6% -2.5%), 1.2% (95% CI: 0.5% -1.9%)[27]. Tan et al. found that SO_2 , O_3 and NO_2 had less influence on CVD outpatient visits than CO, $\text{PM}_{2.5}$ and PM_{10} [31]. In this study, it was also found that SO_2 and O_3 had less impact on outpatient visits of CCD than CO, $\text{PM}_{2.5}$ and PM_{10} , but NO_2 was the most harmful among the six pollutants. The results of this study showed that O_3 concentration was related to the increased risk of outpatient visits for CCD, which was consistent with some research results [31-33]. However, many studies had shown that O_3 had nothing to do with CVD or had a negative correlation [34, 35]. Due to the different concentration and composition of pollutants in different regions, there were differences in natural conditions, human factors and social factors, these potential factors might affect the research results.

The results of the multi-pollutant model in this study revealed the possible interaction between various pollutants. Consistent with a study of 272 cities in China, similar results were obtained for $\text{PM}_{2.5}$ and PM_{10} [36]. The ER values of $\text{PM}_{2.5}$, PM_{10} , SO_2 and CO were almost unchanged after the introduction of O_3 alone or at the same time, while the ER of O_3 were also not significantly changed after the introduction of $\text{PM}_{2.5}$, PM_{10} , SO_2 and CO alone or at the same time. It indicated that there might be independent effects between O_3 and $\text{PM}_{2.5}$, PM_{10} , SO_2 , CO. However, this study found that when $\text{PM}_{2.5}$ and PM_{10} were introduced separately or at the same time, the influence of NO_2 on the outpatient visits of CCD decreased, it was also found that when NO_2 and CO were introduced into each other alone or at the same time, the ER decreased significantly, while the ER value increased after

NO₂ and O₃ introduced into each other alone or at the same time, indicating that there may be antagonism between NO₂ and CO, while there was a synergistic effect between NO₂ and O₃. The ER of PM_{2.5} and PM₁₀ increased after the introduction of SO₂, while the value of ER decreased after the introduction of CO and NO₂, but the ER of SO₂ decreased after the introduction of PM_{2.5} and PM₁₀, and the ER of NO₂ and CO increased after the introduction of PM_{2.5} and PM₁₀, indicating that the health effect relationship between PM_{2.5}, PM₁₀ and other gaseous pollutants was not simple superposition, and there might be complex interactions [37].

The results of gender stratification study in this study showed that there was no significant difference in the effect of air pollutants on male and female, which was consistent with some previous studies[38-40]. In terms of the maximum lag effect in this study, NO₂ was the most harmful pollutant, and the estimated value of the effect of outpatient visits in males was generally greater than that in females. Ma Yuxia et al.'s study [41] on the relationship between PM_{2.5} and CVD in Beijing found that there are more women than men with ischemic heart disease or hypertension caused by the increase of PM_{2.5} concentration. However, the incidence of arrhythmia in men was usually higher than that in women. Studies in different regions showed that the differences in research results were related to the concentration of local pollutants, but the differences between genders were mainly caused by differences in physiological structure and living habits between male and female [42, 43].

The results of age stratification in this study showed that there was no significant difference in the effects of PM₁₀, PM_{2.5}, SO₂, NO₂ and CO on CCD in different age groups, which was consistent with the results of many previous studies[38-40]. There were significant correlations between PM_{2.5}, NO₂, CO, O₃ and outpatient visits of CCD in all age groups. The increase of the concentration of PM_{2.5}, NO₂ and CO was positively correlated with the risk of CCD in all age groups. O₃ was only positively

correlated with the risk of CCD in people over 65 years old, and the study also found that under the influence of $PM_{2.5}$, the maximum lag effect appeared earlier in people over 65 years old. Similar to the results of this study, Ma Yuxia et al studied the relationship between $PM_{2.5}$ and CVD in Beijing and found that the lag effect was the shortest in the 60-75-year-old subgroup [41]. Compared with young people, elderly people have poorer physical fitness and more basic diseases, so people over 65 years old are more likely to be affected by the environment, and the maximum lag effect appears faster.

The results of seasonal stratification showed that the effect of $PM_{2.5}$ and PM_{10} on the outpatient visits of CCD in spring and summer was higher than that in autumn and winter. Wang et al [23] also found that the effect of $PM_{2.5}$ and PM_{10} on CCD in warm season (April to September) was greater than that in cold season (October to March). However, Nguyen et al [44] studied the relationship between ambient air pollutants and CVD hospitalization in Vietnam and found that air pollution has a stronger impact in cold seasons (November to March). In this study, the effect of CO on CCD in summer was greater than that in spring and autumn, while NO_2 and O_3 had the greatest effect on CCD in winter and autumn, respectively. SO_2 has the highest risk of outpatient visits to CCD in spring, which is consistent with the results of Su et al. [45]. In addition, it was also found that SO_2 was significantly positively correlated with the risk of outpatient visits for CCD only in spring, while in other seasons and other model studies, SO_2 was always negatively correlated with the increased risk of outpatient visits for CCD. Generally speaking, $PM_{2.5}$, PM_{10} , SO_2 and CO had a greater influence on the outpatient visits of CCD in spring and summer, and NO_2 and O_3 had a greater influence on the outpatient visits of CCD in autumn and winter. The differences between different research results might be caused by the division of seasons, local meteorological conditions and pollutant concentrations.

The influencing factors selected in this study are limited. The environmental risk factors affecting

CCD included not only meteorological factors and outdoor pollutant concentration, but also indoor air quality. Therefore, it was suggested that the relevant data which can directly or indirectly reflect indoor air quality should be added to the next study to enhance the accuracy of the research results. In addition, the research of Hamanaka and Zhong et al. [10, 19] showed that the climatic conditions and pollution sources were different in different regions, and the composition of pollutants was also different, so this study can be used as a reference for countries and regions similar to Luoyang in pollutant level, socio-economic level and geographical conditions, such as Thailand, North Korea and so on.

5. Conclusion

This study was one of the few studies on the effects of six kinds of air pollutants on the outpatient visits of CCD in low and medium pollution areas. It is found that $PM_{2.5}$, PM_{10} , SO_2 , NO_2 , CO and O_3 all have significant and delayed effects on the outpatient visits of CCD, among which NO_2 has the strongest effect. The results of multi-pollutant model suggested that there were complex interactions among pollutants, so in the formulation of relevant public health policies, not only one kind of harmful pollutant should be considered, but also the joint prevention of multiple pollutants should be considered. The results of stratified study showed that there was no significant difference in the effect of pollutants on different genders, but the effect of O_3 on the outpatient visits with CCD in people aged 41-65 was higher than that in people under 41 years old, and there was no significant difference between $PM_{2.5}$, PM_{10} , SO_2 , NO_2 , CO and outpatient visits of CCD in all age groups. There were significant differences in the effects of pollutants on CCD in different seasonal groups. the results showed that $PM_{2.5}$, PM_{10} , SO_2 and CO should be prevented in spring and summer. NO_2 and O_3 should be prevented in autumn and winter. the results of the study have important positive significance

353 in improving the management level of prevention and control of CCD for countries and regions where
354 the pollution level and social situation are similar to those in Luoyang.

355 **Abbreviations**

356 PM_{2.5}: Particulate matter with aerodynamic diameter less than 2.5 µm

357 PM₁₀: Particulate matter with aerodynamic diameter less than 10 µm

358 SO₂: Sulfur dioxide

359 NO₂: Nitrogen dioxide

360 O₃: Ozone

361 CO: Carbon monoxide

362 CCD: Cardiovascular and Cerebrovascular Diseases

363 GAM: Generalized Additive Model

364 ER: Excess Risk

365 RR: Confidence Interval

366 CI: Confidence Interval

367 AIC: Akaike Information Criterion

368 VIF: Variance Inflation Factor

369 IQR: InterQuartile Range

370 SD: Standard Deviation

371 SE: Standard Errors

372 RH: Relative Humidity

PM _{2.5}		PM ₁₀	
	<i>ER (95%CI)</i>		<i>ER (95%CI)</i>
Before adjustment	0.028(0.017,0.040) *	Before adjustment	0.030(0.018,0.041) *
Double-pollutant model		Double-pollutant model	
PM _{2.5} + SO ₂	0.045(0.033,0.057) *	PM ₁₀ + SO ₂	0.047(0.036,0.059) *
PM _{2.5} + NO ₂	-0.034(-0.046, -0.021) *	PM ₁₀ + NO ₂	-0.027(-0.039, -0.015) *
PM _{2.5} + CO	-0.035(-0.050, -0.021) *	PM ₁₀ + CO	-0.015(-0.028, -0.002) *
PM _{2.5} + O ₃	0.028(0.016,0.040) *	PM ₁₀ + O ₃	0.030(0.018,0.042) *
Three-pollutant model		Three-pollutant model	
PM _{2.5} + SO ₂ + NO ₂	-0.023(-0.035, -0.010) *	PM ₁₀ + SO ₂ + NO ₂	-0.014(-0.027, -0.001) *
PM _{2.5} + SO ₂ + CO	-0.03(-0.045, -0.016) *	PM ₁₀ + SO ₂ + CO	-0.006(-0.019,0.008)
PM _{2.5} + SO ₂ + O ₃	0.046(0.034,0.058) *	PM ₁₀ + SO ₂ + O ₃	0.050(0.038,0.062) *
PM _{2.5} + NO ₂ + CO	-0.069(-0.083, -0.054) *	PM ₁₀ + NO ₂ + CO	-0.046(-0.059, -0.032) *
PM _{2.5} + NO ₂ + O ₃	-0.035(-0.048, -0.023) *	PM ₁₀ + NO ₂ + O ₃	-0.026(-0.038, -0.013) *
PM _{2.5} + CO + O ₃	-0.036(-0.050, -0.021) *	PM ₁₀ + CO + O ₃	-0.015(-0.029, -0.002) *
Four-pollutant model		Four-pollutant model	
PM _{2.5} + SO ₂ + NO ₂ + CO	-0.068(-0.082, -0.054) *	PM ₁₀ + SO ₂ + NO ₂ + CO	-0.04(-0.053, -0.027) *
PM _{2.5} + SO ₂ + NO ₂ + O ₃	-0.025(-0.037, -0.012) *	PM ₁₀ + SO ₂ + NO ₂ + O ₃	-0.011(-0.023,0.002)
PM _{2.5} + SO ₂ + CO + O ₃	-0.029(-0.044, -0.015) *	PM ₁₀ + SO ₂ + CO + O ₃	-0.004(-0.017,0.010)
PM _{2.5} + NO ₂ + CO + O ₃	-0.068(-0.083, -0.054) *	PM ₁₀ + NO ₂ + CO + O ₃	-0.043(-0.057, -0.030) *
Five-pollutant model		Five-pollutant model	
PM _{2.5} + SO ₂ + NO ₂ + CO + O ₃	-0.068(-0.082, -0.053) *	PM ₁₀ + SO ₂ + NO ₂ + CO + O ₃	-0.035(-0.048, -0.021) *
SO ₂		NO ₂	
	<i>ER (95%CI)</i>		<i>ER (95%CI)</i>
Before adjustment	-0.042(-0.055, -0.029) *	Before adjustment	0.205(0.182,0.227) *
Double-pollutant model		Double-pollutant model	
SO ₂ + PM _{2.5}	-0.046(-0.006, -0.032) *	NO ₂ + PM _{2.5}	0.239(0.213,0.266) *
SO ₂ + PM ₁₀	-0.045(-0.058, -0.031) *	NO ₂ + PM ₁₀	0.231(0.205,0.257) *
SO ₂ + NO ₂	-0.063(-0.077, -0.048) *	NO ₂ + SO ₂	0.261(0.236,0.285) *
SO ₂ + CO	-0.056(-0.070, -0.042) *	NO ₂ + CO	0.179(0.154,0.205) *
SO ₂ + O ₃	-0.042(-0.055, -0.029) *	NO ₂ + O ₃	0.224(0.200,0.249) *
Three-pollutant model		Three-pollutant model	
SO ₂ + PM _{2.5} + NO ₂	-0.061(-0.075, -0.047) *	NO ₂ + PM _{2.5} + SO ₂	0.284(0.256,0.312) *
SO ₂ + PM _{2.5} + CO	-0.054(-0.068, -0.040) *	NO ₂ + PM _{2.5} + CO	0.212(0.185,0.239) *
SO ₂ + PM _{2.5} + O ₃	-0.046(-0.060, -0.032) *	NO ₂ + PM _{2.5} + O ₃	0.262(0.234,0.291) *
SO ₂ + PM ₁₀ + NO ₂	-0.061(-0.076, -0.047) *	NO ₂ + PM ₁₀ + SO ₂	0.274(0.247,0.302) *

SO ₂ + PM ₁₀ + CO	-0.055(-0.069, -0.041) *	NO ₂ + PM ₁₀ + CO	0.204(0.177,0.231) *
SO ₂ + PM ₁₀ + O ₃	-0.045(-0.058, -0.031) *	NO ₂ + PM ₁₀ + O ₃	0.249(0.222,0.276) *
SO ₂ + NO ₂ + CO	-0.065(-0.080, -0.051) *	NO ₂ + SO ₂ + CO	0.216(0.190,0.242) *
SO ₂ + NO ₂ + O ₃	-0.068(-0.082, -0.054) *	NO ₂ + SO ₂ + O ₃	0.299(0.273,0.327) *
SO ₂ + CO + O ₃	-0.056(-0.070, -0.042) *	NO ₂ + CO + O ₃	0.200(0.174,0.228) *
Four-pollutant model		Four-pollutant model	
SO ₂ + PM _{2.5} + NO ₂ + CO	-0.065(-0.079, -0.05) *	NO ₂ + PM _{2.5} + SO ₂ + CO	0.249(0.222,0.278) *
SO ₂ + PM _{2.5} + NO ₃ + O ₃	-0.066(-0.081, -0.052) *	NO ₂ + PM _{2.5} + SO ₂ + O ₃	0.326(0.295,0.357) *
SO ₂ + PM _{2.5} + CO + O ₃	-0.054(-0.068, -0.041) *	NO ₂ + PM _{2.5} + CO + O ₃	0.233(0.205,0.262) *
SO ₂ + PM ₁₀ + NO ₂ + CO	-0.065(-0.079, -0.051) *	NO ₂ + PM ₁₀ + SO ₂ + CO	0.237(0.210,0.265) *
SO ₂ + PM ₁₀ + NO ₃ + O ₃	-0.067(-0.081, -0.053) *	NO ₂ + PM ₁₀ + SO ₃ + O ₃	0.309(0.280,0.339) *
SO ₂ + PM ₁₀ + CO + O ₃	-0.055(-0.069, -0.041) *	NO ₂ + PM ₁₀ + CO + O ₃	0.221(0.193,0.250) *
SO ₂ + CO + O ₃ + SO ₂	-0.071(-0.085, -0.056) *	NO ₂ + CO + O ₃ + SO ₂	0.254(0.226,0.283) *
Five-pollutant model		Five-pollutant model	
SO ₂ + PM _{2.5} + NO ₂ + CO + O ₃	-0.069(-0.084, -0.055) *	NO ₂ + PM _{2.5} + SO ₂ + CO + O ₃	0.289(0.259,0.320) *
SO ₂ + PM ₁₀ + NO ₂ + CO + O ₃	-0.069(-0.083, -0.055) *	NO ₂ + PM ₁₀ + SO ₂ + CO + O ₃	0.271(0.242,0.301) *
CO		O ₃	
	<i>ER (95%CI)</i>		<i>ER (95%CI)</i>
Before adjustment	0.104(0.088,0.121) *	Before adjustment	0.023(0.008,0.039) *
Double-pollutant model		Double-pollutant model	
CO + PM _{2.5}	0.140(0.117,0.163) *	O ₃ + PM _{2.5}	0.023(0.008,0.039) *
CO + PM ₁₀	0.117(0.097,0.137) *	O ₃ + PM ₁₀	0.024(0.008,0.040) *
CO + SO ₂	0.146(0.129,0.165) *	O ₃ + SO ₂	0.023(0.007,0.038) *
CO + NO ₂	0.037(0.019,0.055) *	O ₃ + NO ₂	0.046(0.030,0.063) *
CO + O ₃	0.104(0.088,0.121) *	O ₃ + CO	0.026(0.010,0.041) *
Three-pollutant model		Three-pollutant model	
CO + PM _{2.5} + NO ₂	0.092(0.070,0.115) *	O ₃ + PM _{2.5} + NO ₂	0.057(0.040,0.075) *
CO + PM _{2.5} + SO ₂	0.178(0.154,0.202) *	O ₃ + PM _{2.5} + SO ₂	0.023(0.008,0.039) *
CO + PM _{2.5} + O ₃	0.140(0.118,0.163) *	O ₃ + PM _{2.5} + CO	0.026(0.011,0.042) *
CO + PM ₁₀ + NO ₂	0.065(0.045,0.085) *	O ₃ + PM ₁₀ + NO ₂	0.048(0.032,0.065) *
CO + PM ₁₀ + SO ₂	0.151(0.130,0.173) *	O ₃ + PM ₁₀ + SO ₂	0.026(0.010,0.041) *
CO + PM ₁₀ + O ₃	0.117(0.097,0.137) *	O ₃ + PM ₁₀ + CO	0.023(0.008,0.039) *
CO + NO ₂ + SO ₂	0.070(0.051,0.089) *	O ₃ + SO ₂ + NO ₂	0.064(0.046,0.081) *
CO + NO ₂ + O ₃	0.032(0.014,0.050) *	O ₃ + NO ₂ + CO	0.045(0.029,0.063) *
CO + SO ₂ + O ₃	0.148(0.128,0.168) *	O ₃ + SO ₂ + CO	0.027(0.011,0.043) *
Four-pollutant model		Four-pollutant model	
CO + PM _{2.5} + NO ₂ + SO ₂	0.126(0.103,0.150) *	O ₃ + PM _{2.5} + NO ₂ + SO ₂	0.072(0.054,0.090) *
CO + PM _{2.5} + SO ₂ + O ₃	0.178(0.154,0.202) *	O ₃ + PM _{2.5} + CO + SO ₂	0.027(0.012,0.043) *
CO + PM _{2.5} + NO ₂ + O ₃	0.087(0.065,0.110) *	O ₃ + PM _{2.5} + CO + NO ₂	0.054(0.036,0.071) *

CO + PM ₁₀ + NO ₂ + SO ₂	0.094(0.074,0.116) *	O ₃ + PM ₁₀ + NO ₂ + SO ₂	0.065(0.048,0.082) *
CO + PM ₁₀ + SO ₂ + O ₃	0.151(0.130,0.172) *	O ₃ + PM ₁₀ + SO ₂ + CO	0.025(0.009,0.041) *
CO + PM ₁₀ + NO ₂ + O ₃	0.059(0.039,0.079) *	O ₃ + PM ₁₀ + CO + NO ₂	0.045(0.028,0.062) *
CO + SO ₂ + NO ₂ + O ₃	0.064(0.046,0.083) *	O ₃ + SO ₂ + NO ₂ + CO	0.060(0.043,0.078) *
Five-pollutant model		Five-pollutant model	
CO + PM _{2.5} + NO ₂ + SO ₂ + O ₃	0.120(0.097,0.143) *	O ₃ + PM _{2.5} + NO ₂ + CO + SO ₂	0.068(0.051,0.086) *
CO + PM ₁₀ + NO ₂ + SO ₂ + O ₃	0.086(0.065,0.107) *	O ₃ + PM ₁₀ + NO ₂ + CO + SO ₂	0.060(0.042,0.077) *

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P.S. please put the “table 3” in the section 3.3 below the texts.

Declarations

Ethics approval and consent to participate

Ethics License of the present study was acquired from the Ethics Committee of Zhengzhou University (Code of ethics: ZZUIRB 2020-50).

Consent for publication

Consent for publication has been obtained from all of the authors.

Availability of data and material

The datasets created and analyzed during the current study are available from the corresponding author by reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All authors contributed to the study conception and design. X.-Y. Gong and H.-T. Wei acquired the data; M.-F. Wang, X.-Y. Gong and H Yang analyzed and interpreted the data; H.-L. Guo, M.-F. Wang and H.-T. Wei wrote and revised the paper; All of the authors have read and approved the final version of the manuscript.

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