Impact of PM$_{2.5}$ and ozone on incidence of influenza in Shijiazhuang, China: a time-series study

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Abstract
Most of the studies are focused on influenza and meteorological factors for influenza. There are still few studies focused on the relationship between pollution factors and influenza, and the results are not consistent. This study conducted distributed lag nonlinear model and attributable risk on the relationship between influenza and pollution factors, aiming to quantify the association and provide a basis for the prevention of influenza and the formulation of relevant policies. Environmental data in Shijiazhuang from 2014 to 2019, as well as the data on hospital-confirmed influenza, were collected. When the concentration of PM$_{2.5}$ was the highest (621 μg/m$^3$), the relative risk was the highest ($RR$: 2.39, 95% CI: 1.10–5.17). For extremely high concentration PM$_{2.5}$ (348 μg/m$^3$), analysis of cumulative lag effect showed statistical significance from cumulative lag0–1 to lag0–6 day, and the minimum cumulative lag effect appeared in lag0–2 ($RR$: 0.760, 95% CI: 0.655–0.882). In terms of ozone, the RR value was 2.28(1.19,4.38), when O$_3$ concentration was 310 μg/m$^3$, and the RR was 1.65(1.26,2.15), when O$_3$ concentration was 0 μg/m$^3$. The RR of this lag effect increased with the increase of lag days, and reached the maximum at lag0–7 days, RR and 95% CI of slightly low concentration and extremely high concentration were 1.217(1.108,1.337) and 1.440(1.012,2.047), respectively. Stratified analysis showed that there was little difference in gender, but in different age groups, the cumulative lag effect of these two pollutants on influenza was significantly different. Our study found a non-linear relationship between two pollutants and influenza; slightly low concentrations were more associated with contaminant-related influenza. Health workers should encourage patients to get the influenza vaccine and wear masks when going out during flu seasons.

Keywords Attribution risk · Distributed lag nonlinear model · Influenza · Ozone · PM$_{2.5}$ · Relative risk · Time-series study

Introduction
Influenza is an acute infectious disease caused by influenza virus, many environmental factors that will influence the pathogenesis of infectious diseases (Chen et al. 2017). For influenza, there have been several global pandemics, all of which have caused great losses and economic burden (Morales et al. 2017; Somayaji et al. 2020). In China, especially in this extraordinary period, the flu virus has not been effectively controlled; the 2019 novel coronavirus has become a pandemic, so we should pay more attention to this disease to prevent it from causing a wider epidemic.

In recent years, the global climate is complex and changeable (Kalkstein et al. 2018; Wu et al. 2021). However, there is no clear conclusion about the influence of various complex weather conditions on diseases, and it is still being explored gradually. The same is true for infectious diseases. For influenza, some scholars at home and

Abbreviations
RR Relative risk
CI Confidence interval
DLNM Distributed lag nonlinear model
AR Attributable risk
abroad have carried out relevant studies, but these studies are also limited to regional studies. For different regions, the climate varies greatly, and the research conclusions on the relationship between influenza and pollution factors are not completely consistent (Zhang et al. 2021). For example, in southern China, there may be two peaks of influenza in a year, one in summer and one in winter (Meng et al. 2016; Saha et al. 2016), while in northern China, there is only one peak in the alternate seasons of winter and spring. Over the past several decades, various studies have assessed the impact of meteorological parameters on the transmission of influenza viruses in tropical and temperate regions, such as humidity, temperature, and wind speed (Dai et al. 2018; Qi et al. 2020; Lu et al. 2021), which have important effects on the transmission of influenza viruses. There are few studies on the relationship between pollution factors and influenza, and the results are varied, and the lag of research for pollutants also lacks a consistent conclusion.

For example, a recent study in Beijing clarified that PM$_{2.5}$ was significantly associated with a decrease in outpatient visits for influenza-like cases, while outpatient visits for influenza-like cases were associated with an increase in ozone concentration, not PM$_{10}$ concentration (Li et al. 2021). A similar study in Hefei showed a negative correlation between PM$_{2.5}$ and clinical influenza-like cases (Huang et al. 2016a, b; Liu et al. 2019), while in the study in Jinan, exposure to ozone had a negative impact on influenza-like cases (Su et al. 2019). Li et al. did not find a correlation between ozone and children’s respiratory diseases (Hwang & Chan, 2002; Li et al. 2018), which may be related to the different sensitivity of people in different cities to pollutants. As for pollutants, the pollution situation in Shijiazhuang was also serious in the past few years, and the air quality was also poor. Inhalable particulate matter has been concerned by people because it contains a large number of toxic and harmful substances. It can be suspended in the air for a long time, and the particle size is small (Feng et al. 2016), which can be directly inhaled by people, and has great harm to human health (Guo et al. 2013). In addition, according to the changes in the concentrations of six kinds of atmospheric pollutants routinely monitored in China from 2013 to 2020, it can be found that compared with 2013, the kind of atmospheric pollutant nationwide that decreased least in 2020 is O$_3$, which is only 1 μg/m$^3$. Moreover, in 2017, O$_3$ concentration in the country has increased rather than decreased compared with 2013. By 2020, O$_3$ concentration in the Beijing-Tianjin-Hebei region will still be 5.9 percentage points higher than that in 2013, and 42 μg/m$^3$ higher than that in the whole country during the same period. Ozone is gradually becoming the pollutant with the biggest impact on air quality besides fine particles. Therefore, we chose Shijiazhuang, the capital city of Hebei Province, and conducted a series of analysis on the incidence of influenza and the concentration of those two pollutants in Shijiazhuang.

This study aims to achieve the following objectives: (1) to investigate the seasonal variation and long-term trend of daily influenza cases in Shijiazhuang with a warm temperate continental monsoon climate from 2014 to 2019; (2) understand the correlation between PM$_{2.5}$ and ozone pollution factors and influenza according to the daily influenza monitoring data; (3) explore the susceptible population by grouping cases by sex and age, and further determine whether the association between the two pollutants and influenza varies by population; (4) air pollution in Shijiazhuang was serious in the past few years. Is this distinct from the research results in other areas?

**Materials and methods**

**The study location**

Shijiazhuang is the capital city of Hebei Province, located in the central and southern part of Hebei Province in North China, with coordinates between 37°27′–38°47′ north latitude and 113°30′–115°20′ east longitude. Shijiazhuang City straddles the Taihang Mountains and the North China Plain. Low in the northwest and high in the northwest, the landform is complex, which is not conducive to transfer for pollutants. The climate type is warm temperate continental monsoon climate, with distinct seasons and distinct dry and wet periods. In 2019, the resident population of Shijiazhuang was 11.0312 million.

**Data sources**

**Case data**

The daily incidence data of influenza from January 2014 to December 2019 were provided by Shijiazhuang Center for Disease Control and Prevention. A total of 43,435 influenza cases were obtained through screening. These cases were clinically diagnosed as influenza by hospitals in Shijiazhuang and reported to the Shijiazhuang Center for Disease Control and Prevention. We only included confirmed cases of influenza, and patients with suspected influenza were not included in statistical studies. For each patient, we collected information about gender, age, occupation, date of visit (day, month, year), and name of diagnosis.

**Environmental data**

Pollution data came from the real-time release platform of national urban air quality (www.aqistudy.cn). The environmental monitoring site in Shijiazhuang city provides hourly air...
The specific statistical model is as follows:

\[
\log\left( E(Y_t) \right) = a + cb(M_t, df) + \sum_{i=1}^{n} \text{ns}(X_i, df) + \text{ns}(\text{time}, 7) + \text{ns}(\text{year}, 1) + \beta^*\text{dow}
\]

where \(Y_t\) is the daily number of influenza cases on \(t\) day, and \(cb\) stands for Cross basis. \(M_t\) is the pollution factors to be studied. \(X\) represents other meteorological factors that can be included in the model, and the natural cubic spline function (ns) is used to control the long-term trend of time. The degrees of freedom of various meteorological factors included in the model were selected according to the criterion of AIC minimum. The df of temperature is 9, the df of humidity is 2, and the df for wind speed is 8. “Time” as a time variable (from 1 to 2191 days) is used to control long-term trends with “7 * year” degree of freedom. In addition, “dow” represents a day of the week and is included in the model as a co-variable of the day of the week to control the impact of a day of the week.

**Statistical methods**

**Descriptive statistical analysis**

We made statistical description on the case data from different sources, including the number of influenza cases in each day, month and year, and the incidence of influenza cases in different ages and genders. In meteorological factors and pollution factors, we carried out statistical description respectively.

**Distributed lag nonlinear model**

Spearman correlation analysis was first used to analyze the correlation between various pollution factors and influenza, as well as the correlation between various meteorological factors and pollution factors. The test level \(\alpha\) was set at 0.05, and the \(p\) value of double-tailed was selected. The correlation coefficient of two factors greater than 0.7 was considered a strong correlation and could not be included in the model at the same time. Secondly, the cross basis matrix of pollution factors and influenza was established, and the daily number of influenza cases was taken as the dependent variable. Since the daily number of influenza cases could be a statistical data with low incidence, we used a quasi-Poisson function as the connection function, and controlled the long-term trend of time. As the incubation period of influenza is relatively short, usually about a week or even only a few hours, and the lag effect of various meteorological factors and pollution factors on influenza is also short, we chose the longest lag period of 7 days. We conducted a series of statistical descriptions of the daily incidence of influenza. The detailed results were shown in the Table 1: the minimum number of influenza cases was 0. The maximum number was 499, and the average number of hospital visits was 12 per day. According to different sexual distinction, there were at least 0 and at most 245 visits per day for women, with an average of 5 visits per day. For man,
there were at least 0 visits per day, and at most 260 visits per day, average daily visit number was seven.

For pollution factors, the fluctuation range was large, especially for particles; the concentration of PM$_{2.5}$ was the lowest 6 μg/m$^3$, the highest 621 μg/m$^3$, the fluctuation range of PM$_{10}$ was 17 ~ 866 μg/m$^3$, and the fluctuation range of NO$_2$ was 9 ~ 183 μg/m$^3$. For SO$_2$, the lowest concentration was about 4 μg/m$^3$, and the highest could reach 297 μg/m$^3$. The average concentration of O$_3$ in 8 h also fluctuated in a large range, and the difference between the maximum and

| Table 1 Summary statistics of daily influenza cases and atmospheric factors in Shijiazhuang from 2014 to 2019 |
|----------------------------------|--------|-------|-------|-------|-------|-------|-------|
|                                  | Mean   | SD    | Min   | P$_{25}$ | P$_{50}$ | P$_{75}$ | Max   | IQR   |
|----------------------------------|--------|-------|-------|----------|----------|----------|-------|-------|
| Total                            | 19.82  | 38.99 | 0.00  | 7.00     | 12.00    | 20.00    | 499.00| 13.00 |
| Male                             | 10.93  | 20.49 | 0.00  | 4.00     | 7.00     | 12.00    | 260.00| 8.00  |
| Female                           | 8.90   | 18.79 | 0.00  | 3.00     | 5.00     | 9.00     | 245.00| 6.00  |
| Age                              |        |       |       |          |          |          |       |       |
| 0–17                             | 7.38   | 32.52 | 0.00  | 0.00     | 2.00     | 4.00     | 438.00| 4.00  |
| 18–65                            | 10.12  | 8.77  | 0.00  | 4.00     | 8.00     | 13.00    | 72.00 | 9.00  |
| Above 65                         | 2.32   | 2.97  | 0.00  | 0.00     | 1.00     | 3.00     | 34.00 | 3.00  |
| Meteorological factors           |        |       |       |          |          |          |       |       |
| Temperature (°C)                 | 13.64  | 11.10 | -11.58 | 2.79     | 15.08    | 23.79    | 32.58 | 21.00 |
| Humidity (%)                    | 85.73  | 16.12 | 25.00 | 75.00    | 93.00    | 100.00   | 100.00| 25.00 |
| Wind speed (m/s)                | 4.67   | 1.96  | 1.00  | 3.00     | 4.00     | 6.00     | 17.00 | 3.00  |
| Pressure (mmHg)                 | 764.63 | 7.85  | 748.50 | 757.70   | 764.30   | 771.10   | 784.60| 13.40 |
| Pollution factors               |        |       |       |          |          |          |       |       |
| PM$_{2.5}$ (μg/m$^3$)           | 86.75  | 73.90 | 6.00  | 38.00    | 63.00    | 109.00   | 621.00| 71.00 |
| PM$_{10}$ (μg/m$^3$)            | 151.86 | 102.36| 17.00 | 82.00    | 127.00   | 189.00   | 866.00| 107.00|
| NO$_2$ (μg/m$^3$)               | 50.36  | 24.87 | 9.00  | 33.00    | 46.00    | 64.00    | 183.00| 31.00 |
| SO$_2$ (μg/m$^3$)               | 37.29  | 36.38 | 4.00  | 14.00    | 26.00    | 45.00    | 297.00| 31.00 |
| CO (mg/m$^3$)                   | 1.32   | 1.06  | 0.10  | 0.70     | 1.00     | 1.50     | 10.40 | 0.80  |
| O$_3$-8 h (μg/m$^3$)            | 93.38  | 59.94 | 0.00  | 47.00    | 84.00    | 130.00   | 310.00| 83.00 |

SD standard deviation, IQR interquartile range.

| Table 2 Annual distribution characteristics of influenza in Shijiazhuang from 2014 to 2019 |
|----------------------------------|-------|-------|-------|-------|-------|-------|-------|
|                                  | 2014  | 2015  | 2016  | 2017  | 2018  | 2019  | Total |
|----------------------------------|-------|-------|-------|-------|-------|-------|-------|
| Case                             | 3723  | 4383  | 4769  | 4518  | 6018  | 20,024| 43,435|
| 0–17                             | 724   | 642   | 836   | 842   | 887   | 12,245| 16,176|
| 18–65                            | 2688  | 3317  | 3163  | 2968  | 4033  | 6005  | 22,174|
| Above 65                         | 311   | 424   | 770   | 708   | 1098  | 1774  | 5085  |
| Gender                           |       |       |       |       |       |       |       |
| Male                             | 2259  | 2696  | 2726  | 2548  | 3282  | 10,428| 23,939|
| Female                           | 1464  | 1687  | 2043  | 1970  | 2736  | 9596  | 19,496|
| Month                            |       |       |       |       |       |       |       |
| January                          | 414   | 510   | 562   | 515   | 1371  | 2750  | 6122  |
| February                         | 324   | 358   | 601   | 451   | 589   | 1570  | 3893  |
| March                            | 304   | 533   | 595   | 423   | 548   | 1658  | 4061  |
| April                            | 262   | 383   | 360   | 326   | 424   | 1554  | 3309  |
| May                              | 248   | 306   | 307   | 279   | 328   | 718   | 2186  |
| June                             | 218   | 246   | 226   | 251   | 289   | 532   | 1762  |
| July                             | 179   | 191   | 185   | 193   | 210   | 489   | 1447  |
| August                           | 175   | 219   | 209   | 208   | 255   | 499   | 1565  |
| September                        | 236   | 295   | 224   | 314   | 324   | 597   | 1990  |
| October                          | 321   | 382   | 357   | 332   | 324   | 483   | 2199  |
| November                         | 367   | 417   | 479   | 376   | 680   | 712   | 3031  |
| December                         | 675   | 543   | 664   | 850   | 676   | 8462  | 11,870|
the minimum was approximately 310 μg/m³. The lowest concentration of CO was 0.10 mg/m³, and the maximum concentration was 10.4 mg/m³.

From 2014 to 2019, we also made a simple analysis on the annual number of influenza cases and the situation of each month. According to the overall statistical results in Table 2, there were 23,939 males and 19,496 females, including 16,176 minors aged 0–17, 22,174 aged 18–65, and 5085 patients aged over 65 years. The number of influenza cases showed an increasing trend year by year, with only a slight decline in 2017. In terms of different months, November to February of the following year was the peak season of influenza illness. In different sex stratification, we can find that the number of cases in men was slightly higher than that in women each year.

From spearman correlation coefficient matrix (Fig. 1), there were many meteorological and pollution factors that were correlated with the number of influenza cases which included temperature ($r = -0.292$, $P < 0.05$), dew point temperature ($r = -0.282$, $P < 0.05$), humidity ($r = -0.088$, $P < 0.05$), pressure, and others.
We found from the correlation coefficient matrix that the 24 h average temperature has a high correlation coefficient with dew point temperature, atmospheric pressure, and the average concentration of O$_3$ in 8 h; the correlation coefficient is 0.927, −0.898, and 0.772 respectively. In addition, there was a strong correlation between CO concentration and NO$_2$ concentration ($r = 0.821, P < 0.05$), PM$_{2.5}$ concentration, and PM$_{10}$ concentration ($r = 0.963, P < 0.05$). In order to exclude the influence of model multicollinearity on the results, the above factors can be not listed in the model for analysis at the same time.

For various meteorological and pollution factors from 2014 to 2019, we can see from the time sequence diagram (Fig. 2) that the annual fluctuations of various meteorological factors were roughly similar, while for pollutants, ozone pollution was roughly similar every year and has not been effectively controlled. In terms of other pollution factors, especially in 2017, 2018, and 2019, the fluctuation range
had a decreasing trend, which indicated that Shijiazhuang had a good control over air pollution in recent years due to the proposal of blue sky protection and the implementation of relevant national policies, and the air pollution situation has been improved. From the time sequence diagram of influenza, the annual incidence curve of influenza presents a “U” shape, and there was a peak in the alternating winter and spring every year, which is consistent with the results of previous studies (Song et al. 2021).

**Distributed lag nonlinear model**

In different pollutant models, we graphically described the relationship between various pollution factors and the number of influenza cases per day after controlling for relevant meteorological factors. For different pollution factors, they have different effects on influenza. The following results can be found from the 3D diagram of the relative risks of influenza caused by pollution factors and different lag days (Fig. 3). For pollution factors, as for PM$_{2.5}$, when the concentration of particulate matter was high, the risk of influenza was high, and there was a certain lag effect. With the increase of lag days, RR fluctuation showed a “W” shape, and the relative risk was high at the 0, 4, and 7 days of lag. As far as O$_3$ was concerned, the relative risk of influenza was higher at low concentration (0–75 μg/m$^3$) and high concentration (230–310 μg/m$^3$). At low concentration, the risk of influenza reached the maximum on lag7 day, while for high-concentration O$_3$, the lag risk of influenza reached a higher level on lag0 to lag5 days.

*Fig. 3 3D graph of pollution factors effect on influenza in different lag days*

*Fig. 4 The dose–response relationship between pollution factors and the incidence of influenza*
Fig. 5 Relative risk curves of different lag days and different PM$_{2.5}$ concentrations in influenza (A lag0, B lag2, C lag4, D lag6, E PM$_{2.5}$ concentrations $= 6$ μg/m$^3$, F PM$_{2.5}$ concentrations $= 38$ μg/m$^3$, G PM$_{2.5}$ concentrations $= 109$ μg/m$^3$, H PM$_{2.5}$ concentrations $= 621$ μg/m$^3$)

From Fig. 4, in the 7-day lag effect study, we can find that the relationship between various pollution factors and the relative risk of influenza was non-linear (Somayaji et al. 2020). The dose–response relationship between PM$_{2.5}$ and the incidence of influenza presented a curve. When the concentration of PM$_{2.5}$ was the highest, the relative risk was the highest, which was 2.39 (1.10, 5.17). For O$_3$, when O$_3$ concentration was low and high, the RR values were both high. When O$_3$ concentration was 310 μg/m$^3$, its RR value was up to 2.28 (1.19, 4.38). In addition, when O$_3$ concentration was 0 μg/m$^3$, its relative risk was also high, which was 1.65 (1.26, 2.15).

In terms of the risk of influenza-like cases caused by different concentrations of PM$_{2.5}$ in a single day (Fig. 5), the RR value of the protective effect at the minimum concentration was the smallest when the lag was 0 days, and the RR value of the risk effect at the maximum concentration was the largest; however, there was no statistical significance in the risk effect compared with the median concentration of PM$_{2.5}$. For ozone, as we can see in Fig. 6, the relative risk between ozone concentration and influenza was u-shaped. Both low and high concentrations of ozone were risk factors for influenza. Only when ozone concentration was around 140 μg/m$^3$, the occurrence of influenza will be reduced.

**Attribution risk analysis**

The association between the two pollutants and the incidence of influenza was presented in the results of attributable risk analysis (Fig. 7). According to the pollutant concentration $x_0$, which corresponds to the lowest risk of influenza, as the best choice, PM$_{2.5}$ and ozone concentrations were set at 217 μg/m$^3$ and 140 μg/m$^3$ respectively. As can be seen from Table 3, 22.85% of the total number of influenza cases were attributed to PM$_{2.5}$ concentration and 23.40% to ozone concentration during the study period. The backward attribution risk of low-concentration PM$_{2.5}$ was 22.27%, and that of high-concentration PM$_{2.5}$ was 0.64%. The backward attribution risk of low ozone concentration was 21.92%, and that of high ozone concentration was 1.49%. In terms of the contribution of different concentrations of the two pollutants, low ozone concentration was more correlated with contaminant-related influenza. Although the estimation of the ascription score calculated forward was affected by a certain degree of negative bias, the difference was not significant.

In order to further determine the contribution of different concentrations of the two pollutants, we divided the two pollution factors into four grades according to the cutoff values of 1 and 99th percentile and centered on $x_0$, extremely low concentration pollutants, slightly low concentration pollutants, slightly high concentration pollutants, and extremely high concentration pollutants. As is shown in Table 3, among the contributions of low concentration of pollutants, the contribution of extremely low concentration of pollutants to the incidence of influenza was small in Shijiazhuang. 0.20% of the total number of cases of influenza were attributed to extremely low PM$_{2.5}$ concentration, while 22.15% were attributed to slightly low PM$_{2.5}$ concentration. For ozone, extremely low ozone concentration only accounted for a small part of the burden of influenza, about 1.39%, while the contribution of slightly low ozone concentration could reach 21.15%. Possibly, this result was due to the definition of slightly low concentrations of these two pollutants covered most of the time in the city, so the attributable risk result was larger and more likely to attract our attention.

**Stratification analysis**

The above analysis results indicate that slightly low concentrations of PM$_{2.5}$ and ozone are important factors for influenza, and the maximum concentrations of PM$_{2.5}$ and ozone are also risk factors for influenza. Therefore, we stratified influenza caused by both slightly low and extremely high concentrations by sex and age. Pollutant concentrations corresponding to the 25th percentile were selected for slightly low concentrations, 38 μg/m$^3$ for PM$_{2.5}$ and 47 μg/m$^3$ for ozone. Extremely high concentrations were selected for pollutant concentrations corresponding to the 99th percentile, 348 μg/m$^3$ for PM$_{2.5}$ and 250 μg/m$^3$ for ozone. From the 7-day cumulative lag risk chart (Table 4), it can be found that both slightly low concentration ozone and extremely high concentration ozone were greater than 1, both of which were risk factors for influenza. For PM$_{2.5}$, the cumulative lag effect was no statistical significance between slightly low concentration PM$_{2.5}$ and daily cases of influenza, while for extremely high concentration PM$_{2.5}$, analysis of cumulative lag effect showed statistical significance from cumulative lag0–1 to lag0–6 day, and the minimum cumulative lag effect appeared in lag0–2 (RR: 0.760, 95% CI: 0.655–0.882). In terms of ozone, there was a significant correlation between ozone and influenza. No matter the concentration of the ozone was slightly low or extremely high, the RR of this lag effect increased with the increase of lag days, and reached the maximum at lag0–7 days; RR and 95% CI of slightly low concentration and extremely high concentration were 1.217 (1.108, 1.337) and 1.440 (1.012, 2.047), respectively.

As can be seen from the stratified analysis results (Table 4), there was a little difference between those two pollution factors and daily influenza cases in gender. The
The cumulative lag effect of extremely high concentration PM$_{2.5}$ on the two genders had statistical significance in certain lag days. Specifically, the cumulative lag effect of extremely high concentration PM$_{2.5}$ on women from lag0–1 to lag0–6 was statistically significant, and the $RR$ value was the smallest in lag0–6 days ($RR$: 0.732, 95% CI: 0.571–0.939). Analysis of cumulative lag effect between extremely high concentrations of PM$_{2.5}$ and the incidence of male influenza showed statistical significance from cumulative lag0–1 to cumulative lag0–4 day, and the minimum cumulative lag effect appeared in lag0–2 ($RR$: 0.775, 95% CI: 0.659–0.911). For women, there was a significant correlation between slightly low concentrations of ozone and influenza from cumulative lag0–4 days to cumulative lag0–7 days. The $RR$ of this lag effect was increased with the increase of lag days, and reached the maximum cumulative lag effect at lag0–7 days ($RR$: 1.194, 95% CI: 1.074–1.327). The cumulative lag between slightly low concentrations of ozone and the incidence of influenza in men was statistically significant from lag0–3 days to lag0–7 days, and the maximum $RR$ was lag0–7 days ($RR$: 1.236, 95% CI: 1.117–1.367). For extremely high concentrations of ozone, the cumulative lag effect of different lag days was significant for women from lag0–1 to lag0–5, and $RR$ reached the maximum at lag0–5 days ($RR$: 1.405, 95% CI: 1.007–1.959); for males, there was no statistical significance between extremely high concentrations of ozone and influenza.

In terms of different age groups, the cumulative lag effects of ozone and PM$_{2.5}$ on influenza were significantly different. With the condition of slightly low concentration of PM$_{2.5}$, for minors, aged 0–17 years, this effect was significant from lag0–6 to lag0–7; the $RR$ of this lag effect increased with the increase of lag days, and reached the maximum at lag0–7 days ($RR$: 1.178, 95% CI: 1.040–1.335). The cumulative lag effect of slightly low concentration of PM$_{2.5}$ for people aged 18–65 years was not statistically significant. For the...
elderly over 65 years old, there were significant differences in the cumulative lag0–2 and lag0–6 days, and the cumulative lag effect was the lowest in the cumulative lag0–6 days (RR: 0.887, 95% CI: 0.791–0.994). Under extremely high concentration PM$_{2.5}$ weather conditions, there was no statistical significance in the cumulative lag effect analysis results of people aged 18–65 years old and over 65 years old at different cumulative lag days, while for minors aged 0–17 years old, the cumulative lag effect was significant from lag0 day to lag0–7 days. Moreover, RR value reached the minimum in lag0–6 days (RR: 0.428, 95% CI: 0.306–0.599). For ozone, with low ozone concentration, the cumulative lag effect analysis results of minors 0–17 years old in different cumulative lag days were not significant, but for adults 18–65 years old, this effect was significant from 0–3 days to 0–7 days of cumulative lag, and the RR value kept rising. The cumulative effect reached the maximum at lag0–7 days (RR: 1.241, 95% CI: 1.129–1.366). For the elderly over 65 years old, this effect was also statistically significant from lag0–3 days to lag0–7 days. Its RR was the highest in 0–6 days lag (RR: 1.231, 95% CI: 1.082–1.401). Under extremely high concentration ozone weather conditions, the cumulative lag effect analysis results of people aged 18–65 had no statistical significance at different cumulative lag days, while for minors aged 0–18, this effect was significant from lag0–1 days to lag0–7 days. Moreover, the RR reached the maximum value in lag0–5 days of accumulation (RR: 2.261, 95% CI: 1.298–3.941). As for the people aged over 65 years old, the cumulative lag effect showed statistical significance only in 0–2 days lag (RR: 1.390, 95% CI: 1.004–1.925).

### Sensitivity analysis

By changing the degree of freedom (6 to 9) for the long-term trend of the time variable (Duan et al. 2019), and observing every increase of 10 units of PM$_{2.5}$ and 1 unit of ozone (Fig. 8), we can find that the change of influenza incidence risk in different lag days was very small, and the results were robust, proving that our results were relatively reliable.

## Discussion

Influenza is an acute infectious disease caused by influenza virus; its occurrence and spread are affected by pathogens, human society, natural environment, and many other factors (Lu et al. 2020). It has the following features: first, the variability is strong; this is because the subtype influenza virus surface antigen is more, according to the different combination of virus antigen of surface of particles, and can form various subtypes; in addition, the transmission route is diverse, and the population is generally susceptible; there is no cross immunity between subtypes, so it is easy to cause seasonal epidemic. Although China has been developing and inoculated influenza vaccine since 1998, influenza vaccine has not been included in China’s national immunization program, and the vaccination rate is low, only about 2% (Zhang et al. 2019). Therefore, compared with developed countries abroad, the influenza control in China is not good, which still needs to be paid attention to. As for influenza, there have been several global pandemics, all of which have caused great losses and economic burden (Huang et al. 2016a, b), especially in this special period; the influenza virus has not been effectively controlled and the novel coronavirus has emerged. We should pay more attention to influenza disease in order to prevent a wider epidemic.

In terms of the time distribution of influenza-like cases, influenza tends to occur in the months of winter and spring each year (Song et al. 2021), especially in December and January, which is similar to the results of previous studies in some areas. But we can see that in December 2019, there was a sharp increase in the number of cases of influenza. On the one hand, this may be related to the slight overlap in the onset of the transmission of the novel coronavirus. As the pneumonia caused by the novel coronavirus has similar symptoms to influenza in the initial stage, in order to control the transmission of the novel coronavirus, our country has carried out a series of screening and control for the source of infection, the route of transmission, and the relevant treatment drugs in pharmacies, so there will be a greater number of influenza screening and reporting. On the other hand,
most of the influenza cases collected by us were based on clinical diagnosis, and there were also some asymptomatic infected persons who were difficult to detect. There were some patients with mild influenza symptoms who went to pharmacies or small clinics on their own. Therefore, the number of influenza cases we collected may be lower than the actual number (Aman et al. 2021). Other studies have shown that extremely high particles, which can react with the body to produce reactive oxygen species and promote lipid peroxidation (Woody et al. 2021; Toczyłowski et al. 2021). This is related to the transition metal components contained in fine particles, which can react with the body to produce reactive oxygen species and promote lipid peroxidation (Woody et al. 2021). Other studies have shown that extremely high

| Table 4 Cumulative effect and 95% confidence intervals of ozone and PM$_{2.5}$ on influenza of different genders and ages at different cumulative lag days (compared with 50th pollution) |
|-----------------------------------------------|
| **PM$_{2.5}$ (25th)**                           |
| lag0  0.972(0.937,1.009)                      |
| lag0-1 0.966(0.926,1.007)                     |
| lag0-2 0.972(0.927,1.020)                     |
| lag0-3 0.982(0.931,1.035)                     |
| lag0-4 0.985(0.928,1.046)                     |
| lag0-5 0.981(0.919,1.049)                     |
| lag0-6 0.978(0.911,1.050)                     |
| lag0-7 1.005(0.931,1.085)                     |
| **PM$_{2.5}$ (99th)**                          |
| lag0  0.935(0.823,1.064)                      |
| lag0-1 0.816(0.714,0.932)*                    |
| lag0-2 0.760(0.655,0.882)*                    |
| lag0-3 0.768(0.652,0.903)*                    |
| lag0-4 0.796(0.662,0.957)*                    |
| lag0-5 0.800(0.655,0.977)*                    |
| lag0-6 0.775(0.621,0.968)*                    |
| lag0-7 0.807(0.634,1.028)                     |
| **Ozone (25th)**                              |
| lag0  0.991(0.959,1.024)                      |
| lag0-1 1.002(0.952,1.054)                     |
| lag0-2 1.030(0.970,1.094)                     |
| lag0-3 1.071(1.003,1.145)*                    |
| lag0-4 1.118(1.039,1.203)*                    |
| lag0-5 1.163(1.073,1.259)*                    |
| lag0-6 1.197(1.100,1.303)*                    |
| lag0-7 1.217(1.108,1.337)*                    |
| **Ozone (99th)**                              |
| lag0  1.109(0.979,1.257)                      |
| lag0-1 1.201(0.989,1.459)                     |
| lag0-2 1.271(1.011,1.595)                     |
| lag0-3 1.321(1.030,1.694)*                    |
| lag0-4 1.356(1.030,1.786)*                    |
| lag0-5 1.385(1.026,1.868)*                    |
| lag0-6 1.411(1.029,1.937)                     |
| lag0-7 1.440(1.012,2.047)*                    |

$*$P < 0.05.
Fig. 8 Sensitivity analysis (degrees of freedom for the time from 6 to 9)
concentrations of PM$_{2.5}$ can even promote remodeling of lung tissue and reduce lung function (Pinkerton et al. 2000; Toczyłowski et al. 2021). Influenza virus could attach to the surface of these particles to form aerosols, and people were susceptible to influenza virus through breathing or contact (Feng et al. 2016). In addition, environmental pollutants can damage the anti-infection immunity process. Studies have found that environmental pollutants (PM$_{2.5}$, NO$_2$) can affect the intake and phagocytosis of macrophages and NK cells on virus-infected cells, which can reduce the body’s immune ability, and increase the chance of infection (Meng et al. 2021; Woodby et al. 2021).

For ozone, although the spearman correlation coefficient between ozone and the daily number of influenza cases was negative (Song et al. 2021), the corresponding ozone concentration was higher in summer and autumn, but lower in winter and spring, while the incidence of influenza mostly occurred in winter and spring, but this did not prove that the higher ozone concentration was better. Ozone was a kind of air pollutant; high concentration of ozone will also irritate the eyes and respiratory mucosa and has other adverse effects on human health. Different concentrations of ozone had different effects on the incidence of influenza. A certain concentration of ozone could reduce the incidence of influenza, which was related to the fact that ozone itself was a strong oxidant and has a certain bactericidal effect (Song et al. 2021). In addition, some scholars have pointed out that a certain concentration of ozone can stimulate the immune response system in the body, enhance the innate immunity of the lungs, and resist viral infection (Ali et al. 2018). In mice, it has also been shown that 0.5-ppm ozone can redistribute influenza virus in the lungs of mice and activate the immune suppression mechanism, thus reducing the severity of influenza (Jakab and Hmielecki 1988). And below or above this concentration, the ozone will have a promoting role in the pathogenesis of influenza. As studies have found that long-term inhalation of ozone was also more likely to induce or aggravate the respiratory system disease (Yang et al. 2012, 2012; Ali et al. 2018, 2018), our research also shows that the extremely high concentrations of ozone also plays a promoting role in the pathogenesis of influenza, which is consistent with the results of our study. This may be related to ozone destroying the balance between protease and anti-protease (Kesic et al. 2012). Studies pointed out that exposure to a certain concentration of ozone can induce the expression of inflammatory markers, activate inflammatory response, and increase the susceptibility of influenza virus (Woodby et al. 2021). This is mainly because pollutants in the air such as ozone and NO$_2$ can directly react with the respiratory mucosal fluid, and produce oxidized substances, which can cause inflammatory reaction (Woodby et al. 2021; Loaiza-Ceballos et al. 2022).

In the attributable risk analysis results of this study, we can also see that for PM$_{2.5}$, the risk of influenza-like diseases is mainly attributed to the slightly low concentration of PM$_{2.5}$ pollution. On the one hand, the slightly low concentration we defined covers a wide range, from 14 to 217 $\mu$g/m$^3$, which included a large period of time in the city, which was the main reason. On the other hand, at slightly low concentrations of PM$_{2.5}$, people were more likely to work, play, and participate in activities outside, and were more likely to gather in large crowds, which also increased the spread of the flu during flu season. The risk of ozone on influenza-like diseases was also mainly attributed to mild low ozone pollution, which may be related to a certain range of ozone concentration that could reduce the incidence of influenza. Lower or higher ozone concentration will promote the onset of influenza. While high ozone concentration will cause a series of uncomfortable symptoms in human body, in order to reduce this discomfort, people take precautions in advance, which reduce the probability of the spread of influenza, so ozone pollution in slightly low concentrations is more likely to cause the onset of influenza-like illness.

In the stratified analysis, we were able to find that slightly low concentration of PM$_{2.5}$ was a “protective factor” compared to median levels, except for minors aged 0–17. This may be due to the fact that when PM$_{2.5}$ concentration was low, particulate matter was less suspended in the air and aerosol formation was less, which was not conducive to the attachment of virus and further reduced the spread of influenza virus, so the occurrence of influenza was also reduced accordingly. On the contrary, in the case of extremely high concentration of PM$_{2.5}$, the air quality was very poor, so people mostly chose to stay indoors and seldom go out. In addition, with the progress of society, people’s awareness of health care is strengthened; when going out in the weather with poor air quality, people also choose to wear masks to protect themselves (Li et al. 2021), which also shows a certain degree of “protection effect.” However, this protective effect only applied to minors aged 0–17, and there was no statistical significance for people aged over 18 and elderly people aged over 65. The reason might be that people aged 65 and above are all elderly people. There were many basic diseases and their immunity is relatively low (Feng et al. 2016; Li et al. 2021). People aged between 18 and 65 were more likely to take medicine for treatment because they were busy with their work, so the frequency of seeing a doctor was relatively low.

In terms of ozone, compared with the median ozone concentration, both slightly low ozone concentration and extremely high ozone concentration were risk factors. The risk effect of mild low ozone concentration was more significant in adults over 18 years old, and there was no statistical significance for minors under 18 years old. In contrast, at
extremely high concentrations of ozone, the risk effect was statistically significant in minors aged 0–17 years; we suspect that this may be related to different ages of ozone which can reduce the influenza incidence of the best concentration of the range that was different. For minors, especially pre-school children and infants, their immune system was not fully developed, the immunity was still low (Li et al. 2020), and the ability to tolerate ozone was low, so for them, a certain concentration ozone range that can reduce the incidence of influenza was lower than adults. Previous studies have shown that the association between ozone and influenza-like cases varied by region, possibly due to differences in ozone sensitivity among populations living in areas with different levels of pollution.

Shijiazhuang, due to the particularity of the industrial structure and its geographical location, the pollution situation in the past few years has been serious. In 2017, due to the blue sky protection plan and the implementation of relevant policies, the concentration of air pollutants except ozone in the 3 years from 2017 to 2019 showed an obvious decreasing trend, but the actual annual incidence of influenza was not effectively alleviated, and even increased, which was mainly related to the following reasons. On the one hand, the concentrations of various meteorological factors and pollution factors measured in the atmosphere of Shijiazhuang could not accurately represent the concentration of pollutants actually exposed to different people, which was closely related to the actual indoor pollutants in different work units, different living places, and personal protection factors. On the other hand, there were many factors that affect the occurrence and prevalence of influenza (Fdez-Arróyabe et al. 2021). In addition to the variation of influenza virus itself, there were also the density of population, individual living standards, medical insurance policies, and vaccination, which will affect the occurrence and development of influenza disease (Liu et al. 2020).

Although there are some uncontrollable limitations of our research, it is both useful and necessary to further explore the link between air pollution and influenza in light of the current situation of influenza disease control and the novel coronavirus pandemic. Our study also has several advantages. We took Shijiazhuang, which is heavily polluted, as the research site to explore the relationship between two typical pollution factors in Shijiazhuang and influenza disease, and took the lag dimension of pollutants into consideration. At the same time, we also analyzed the attributable risk of pollutants, decomposed the dangerous effects of the two pollutants in more detail, and quantified the relationship between PM$_{2.5}$, ozone, and influenza, which provided evidence for the formulation of relevant policies for influenza-like diseases and the prevention of public health undertakings. In addition, this study also has some limitations. Our study included the association between influenza and pollution factors, but there are many factors affecting the occurrence of influenza (Liang et al. 2014), and confounding factors have not been completely excluded, so there are still some limitations. Second, the possibility of misdiagnosis and missed diagnosis cannot be ruled out because of the patients with mild symptoms of influenza even asymptomatic infected patients.

**Conclusion**

In summary, our study found a non-linear relationship between two pollutants (PM$_{2.5}$ and ozone) and influenza; slightly low concentrations were more associated with contaminant-related influenza. Stratified analysis showed that there was little gender difference in the incidence of influenza between the two pollutants; in terms of different age groups, the cumulative lag effect of these two pollutants on influenza was significantly different. Therefore, when formulating relevant policies, these air pollution factors should be taken into consideration. In fact, we encourage patients to get the influenza vaccine. This is more effective in preventing influenza. Moreover, in the months when the flu is more serious, we recommend people to minimize crowd gatherings, wear masks when going out, which can not only reduce the inhalation of particulate matter, but also reduce the spread of influenza.

**Author contribution** Xue Wang: software; formal analysis; writing—original draft; visualization. Jianing Cai: data curation, project administration, visualization. Xuehui Liu: investigation, writing—review and editing. Binhao Wang: software, investigation. Lina Yan: resources, investigation. Ran Liu: writing—review and editing. Xayiong Nie: writing—review and editing. Yaxiong Nie: writing—review and editing. Xiaolin Zhang: conceptualization, methodology, supervision, project administration.

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**Data availability** Our data is not public. The data comes from Shijiazhuang CDC; please contact the corresponding unit if necessary.

**Declarations**

**Ethics approval and consent to participate** This study has been approved by the ethics committee of Shijiazhuang Center for Disease Control.

**Consent to publish** Not applicable.

**Competing interests** The authors declare no competing interests.
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