



OPEN

# Acute effects of air pollutants on influenza-like illness in Hangzhou, China

Ye Lv<sup>1</sup>, Hong Xu<sup>1</sup>, Zhou Sun<sup>1</sup>, Muwen Liu<sup>1</sup>, Shanshan Xu<sup>1</sup>, Jing Wang<sup>1</sup>, Chaokang Li<sup>1</sup>, Hui Ye<sup>2</sup> & Xuhui Yang<sup>1</sup>✉

At present, with increasing awareness of the relationship between respiratory disease and air pollution, it is critical to assess the environmental risk factors for influenza. This study aimed to estimate the associations between ambient air pollution and the number of influenza-like illness (ILI) cases in Hangzhou, China, from 2015 to 2021. Weekly meteorological data, including average ambient temperature and average relative humidity, from December 29, 2014 to January 2, 2022 were collected from the Hangzhou Meteorological Service Center, and air pollutants, including nitrogen dioxide (NO<sub>2</sub>), sulfur dioxide (SO<sub>2</sub>), ground-level ozone (O<sub>3</sub>), particulate matter (PM) with aerodynamic diameter ≤ 2.5 μm (PM<sub>2.5</sub>), and PM with aerodynamic diameter ≤ 10 μm (PM<sub>10</sub>), were collected from National Ambient Air Quality Automatic Monitoring Stations in Hangzhou. The number of weekly ILI cases was collected from 15 influenza surveillance sentinel hospitals in Hangzhou. A generalized linear model (GLM) with quasi-Poisson regression was adopted to estimate the association between air pollution and ILI. After adjusting for the effects of average temperature, relative humidity, and seasonal and long-term trends, PM<sub>2.5</sub>, PM<sub>10</sub>, NO<sub>2</sub>, and SO<sub>2</sub> were found to be significantly associated with the number of ILI cases, with relative risk (RR) values of 1.018 (95% CI 1.001–1.036), 1.016 (1.005–1.028), 1.063 (1.067–1.364), and 1.207 (1.067–1.364), respectively. In the two-pollutant model, putting PM<sub>2.5</sub>, PM<sub>10</sub>, NO<sub>2</sub>, or SO<sub>2</sub> into the model separately with O<sub>3</sub> produced results similar to those of the single-pollutant model. PM<sub>2.5</sub>, PM<sub>10</sub>, and NO<sub>2</sub> have statistical significance in cold seasons, with the RR values of 1.020 (95% CI 1.001–1.038), 1.012 (95% CI 1.000–1.024), and 1.060 (95% CI 1.031–1.090), respectively. In summary, our study found that most air pollutants (PM<sub>10</sub>, PM<sub>2.5</sub>, NO<sub>2</sub>, and SO<sub>2</sub>) have a significant association with the risk of ILI cases in Hangzhou. These findings can serve as a reference for the formulation of effective protective measures.

**Keywords** Air pollution, Influenza-like illness, Generalized linear model, Environmental epidemiology

ILI cases are defined as outpatients having “acute respiratory infection with body temperature more than 38°C and either cough or sore throat”<sup>1</sup>. ILI is a common and nonspecific marker of influenza, belonging to symptom monitoring<sup>2</sup>, which can reflect the epidemic trends of influenza and be used to explore the relationship between influenza and influencing factors.

Many respiratory viruses can cause ILI, including influenza viruses, parainfluenza viruses, adenovirus, respiratory syncytial virus, etc. Influenza is the first infectious disease for which global monitoring has been implemented. The majority of influenza epidemics are caused by serotypes A and B<sup>3</sup>, and the illness has large morbidity, mortality, and economic costs per year<sup>4,5</sup>. It is estimated that up to 1 billion infections, 3–5 million severe cases, and 0.29–0.65 million deaths worldwide were caused by influenza every year<sup>6</sup>.

It is estimated that air pollution contributes to the premature deaths of 7 million people and poor health in millions more every year, and the burden of disease caused by air pollution is on a par with that of other major global health risks<sup>7</sup>. The short-term effects of air pollution manifest mainly in the increased morbidity and mortality of respiratory diseases. Hu et al.<sup>8</sup> found significant lagged and non-linear effects of meteorological factors and PM exposure on childhood asthma by Distributed lag non-linear models (DLNM) analyses. Besides, both time-series and case-crossover analyses revealed a positive association between air pollutants and mortality in Wuhan<sup>9</sup>.

<sup>1</sup>Hangzhou Center for Disease Control and Prevention (Hangzhou Health Supervision Institution), Hangzhou, Zhejiang, China. <sup>2</sup>Ecological and Environmental Monitoring Center of Hangzhou, Hangzhou, Zhejiang, China. ✉email: yangxh0420@163.com

Air pollutants are considered potential drivers of influenza transmissibility. The association between air pollutants and influenza incidence is nonlinear and spatially heterogeneous<sup>10,11</sup>. Strong positive relationships have been identified between PM<sub>2.5</sub> and ILI during flu season<sup>12</sup>. There was an exponential relationship between PM<sub>2.5</sub> and clinical ILI as well as laboratory-confirmed ILI, which remain significant after adjusting for temperature and long-term trends, while PM<sub>10</sub> was negatively correlated, respectively<sup>13,14</sup>. Besides, Yang et al.<sup>15</sup> demonstrated a significant association between ozone (O<sub>3</sub>) and influenza transmissibility, which tends to display a U-shaped pattern.

There have been many studies on environmental factors and influenza in various cities. However, insufficient studies have quantified the acute effects of all air pollutants on ILI cases. We gathered data on weekly meteorological factors, air pollutants, and the number of ILI cases in Hangzhou city from 2015 to 2021 and applied a GLM with a quasi-Poisson regression to assess the effects of air pollution on ILI cases. In addition, two-pollutant models are presented to assess the stability and consistency of the estimated effects of each pollutant.

## Materials and methods

### Study area

Hangzhou, the provincial capital and a sub-provincial city of Zhejiang province, which is located on the southeast coast of China at the lower reaches of the Qiantang River, is one of China's most important e-commerce centers. It is also a new first-tier city with an area of 16,850 square kilometers and a population of 12 million. The air quality in Hangzhou improved from 2015 to 2021, with the average concentration of PM<sub>2.5</sub> decreasing from 54.7 µg/m<sup>3</sup> to 27.8 µg/m<sup>3</sup> and PM<sub>10</sub> decreasing from 81.1 µg/m<sup>3</sup> to 56.3 µg/m<sup>3</sup>, which puts both below the national standard (GB3095-2012 "Environmental Air Quality Standard"). However, there were still 44 days when the air quality index (AQI) exceeded the third level limit of the national standard. Winter in Hangzhou runs from late November to early December<sup>16</sup>, with a season length of 103 days, and the average winter temperature is 6.1 °C<sup>17</sup>.

### Data collection

Daily meteorological factors, including average ambient temperature and average relative humidity, from December 29, 2014, to January 2, 2022, were obtained from the Hangzhou Meteorological Service Center. The concentration of air pollutants, including SO<sub>2</sub>, NO<sub>2</sub>, O<sub>3</sub>, PM<sub>2.5</sub>, and PM<sub>10</sub>, for the same period were collected from National Ambient Air Quality Automatic Monitoring Stations in Hangzhou. We determined the weekly mean of the concentration of each pollutant for Hangzhou by averaging the daily data from the following 10 monitoring stations: Binjiang, Hemu Primary School, Zhejiang Agricultural University, Wolong Bridge, Xixi, Yunqi, Fire Brigade, Xiasha, Chengxiang Town, and Linping Town.

The influenza surveillance system of Hangzhou is composed of 15 sentinel hospitals, which included 1 children's hospital and 14 general hospitals. ILI cases were defined as the outpatients who had an acute respiratory infection with a body temperature higher than 38 °C, and cough or sore throat. The surveillance departments included internal medicine out-patient emergency, pediatric internal medicine out-patient emergency, and fever clinics. The ILI cases were identified by physicians in the surveillance unit of the sentinel hospital. Based on the ILI definition, the numbers of total visits and ILI cases were reported to the influenza surveillance system every week. A total of 895,363 ILI cases were included in this study from 2015 to 2021. The influenza surveillance was conducted in accordance with the National influenza surveillance protocol<sup>1</sup>. The influenza surveillance has been approved by the National Health Commission of China and Hangzhou Municipal Health Commission. The study was conducted following Declaration of Helsinki, and the research protocol was approved by Ethics Committee of Hangzhou Center for Disease Control and Prevention (2022-26). The need to obtain informed consent was waived by Ethics Committee of Hangzhou Center for Disease Control and Prevention, as it only uses quantitative data from the influenza surveillance system without individual case information. If a sentinel hospital encounters a case of acute respiratory infection that meets the definition of ILI, the patients will be informed to report and register as an ILI case.

### Study design and statistical analysis

Descriptive statistical analyses were conducted using mean ± standard deviation (SD), range, and percentiles, as appropriate. Spearman correlations were performed for the independent and response variables. Weekly visits to the influenza sentinel hospital for influenza-like symptoms were small probability events relative to that of Hangzhou overall, with a distribution approximating the Poisson distribution. The data were cleaned and pre-analyzed, and a GLM with a quasi-Poisson regression was used to analyze the effect of pollutant concentrations on the number of ILI cases. Most existing studies have considered the influence of mean temperature and relative humidity on ILI. Thus, the confounding effects of meteorological conditions were adjusted by incorporating the weekly average of mean temperature and humidity, which was smoothed by a natural cubic spline function (*ns*). Additionally, time variables smoothed by *ns* were used to adjust for the unmeasured long-term trends and seasonality of weekly ILI cases<sup>8,10,18,19</sup>.

The formula of the model is shown below:

$$\log[E(Y_t)] = + (\text{Pollutant}_t) + ns(\text{time, df*year}) + ns(\text{Temp}_t, 3) + ns(\text{Rhum}_t, 3)$$

where  $Y_t$  denotes the weekly number of ILI cases at  $t$  ( $t = 1, 2, \dots, 366$ ) week,  $\alpha$  is the model intercept,  $\text{Pollutant}_t$  is the concentration of air pollutant,  $ns(\text{time, df*year})$  is a time variable,  $\text{Temp}_t$  is the weekly average temperature, and  $\text{Rhum}_t$  is the weekly average relative humidity. According to the approaches used in previous studies, the degrees of freedom (df) of meteorological factors, such as temperature and relative humidity, were taken as 3, and the degrees of freedom of time variables were taken as 7/year<sup>18–20</sup>. The partial autocorrelation function (PACF) was used to test the goodness of fit of the model. We used both single-pollutant model and double-

Variables	Mean	SD	Min	Percentile			Max
				25	50	75	
ILI cases (N)	2446.35	1013.60	800.00	1828.50	2231.00	2813.00	7979.00
Meteorological parameters							
Mean temperature (°C)	17.72	8.4	-1.14	10.10	18.17	24.74	33.79
Relative Humidity (%)	73.33	9.70	41.71	66.33	73.78	81.00	95.29
Weekly average concentration							
PM <sub>2.5</sub> (µg/m <sup>3</sup> )	40.88	19.80	9.16	26.77	35.62	49.79	118.27
PM <sub>10</sub> (µg/m <sup>3</sup> )	68.96	28.81	23.43	47.61	64.87	82.77	182.96
SO <sub>2</sub> (µg/m <sup>3</sup> )	9.59	4.63	3.71	6.18	8.45	11.91	32.29
NO <sub>2</sub> (µg/m <sup>3</sup> )	42.46	14.03	11.49	31.38	42.27	52.06	84.14
O <sub>3</sub> (µg/m <sup>3</sup> )	95.67	40.34	19.57	63.37	93.68	123.41	198.33

**Table 1.** Distribution of ILI cases, air pollutants and meteorological parameters in Hangzhou from 2015 to 2021. *SD* standard deviation, *Min* minimum, *P*<sub>25</sub> the 25th percentile, *P*<sub>75</sub> the 75th percentile, *Max* maximum.

	PM <sub>2.5</sub>	PM <sub>10</sub>	NO <sub>2</sub>	SO <sub>2</sub>	O <sub>3</sub>	Mean temperature	Relative Humidity
PM <sub>2.5</sub>		0.944*	0.775*	0.773*	- 0.329*	- 0.663*	- 0.162*
PM <sub>10</sub>	0.944*		0.835*	0.703*	- 0.292*	- 0.644*	- 0.315*
NO <sub>2</sub>	0.775*	0.835*		0.641*	- 0.481*	- 0.658*	- 0.112*
SO <sub>2</sub>	0.773*	0.703*	0.641*		- 0.188*	- 0.436*	- 0.180*
O <sub>3</sub>	- 0.329*	0.292*	0.481*	0.188*		0.737*	- 0.362*
Mean temperature	- 0.663*	- 0.644*	- 0.658*	- 0.436*	0.737*		0.030
Relative humidity	- 0.162*	- 0.315*	- 0.112*	- 0.180*	- 0.362*	0.030	

**Table 2.** Correlations among air pollutants and meteorological parameters in Hangzhou from 2015 to 2021. \*Indicates *P* < 0.05.

pollutant model to explore the effects of air pollutants on risk of ILI. When constructing a model, the presence of multicollinearity can lead to model distortion or inaccurate estimation. In order to reduce the effect of collinearity between pollutants, the variance inflation factor (VIF) and correlation coefficients were used to illuminate the multi collinearity in the models. Variables with VIF values greater than 5 or correlation coefficients greater than 0.7 could not be included in the model simultaneously<sup>21,22</sup>. In addition, we analyzed the effects of different pollutants on the risk of influenza in the warm season (April-September) and the cold season (October-March).

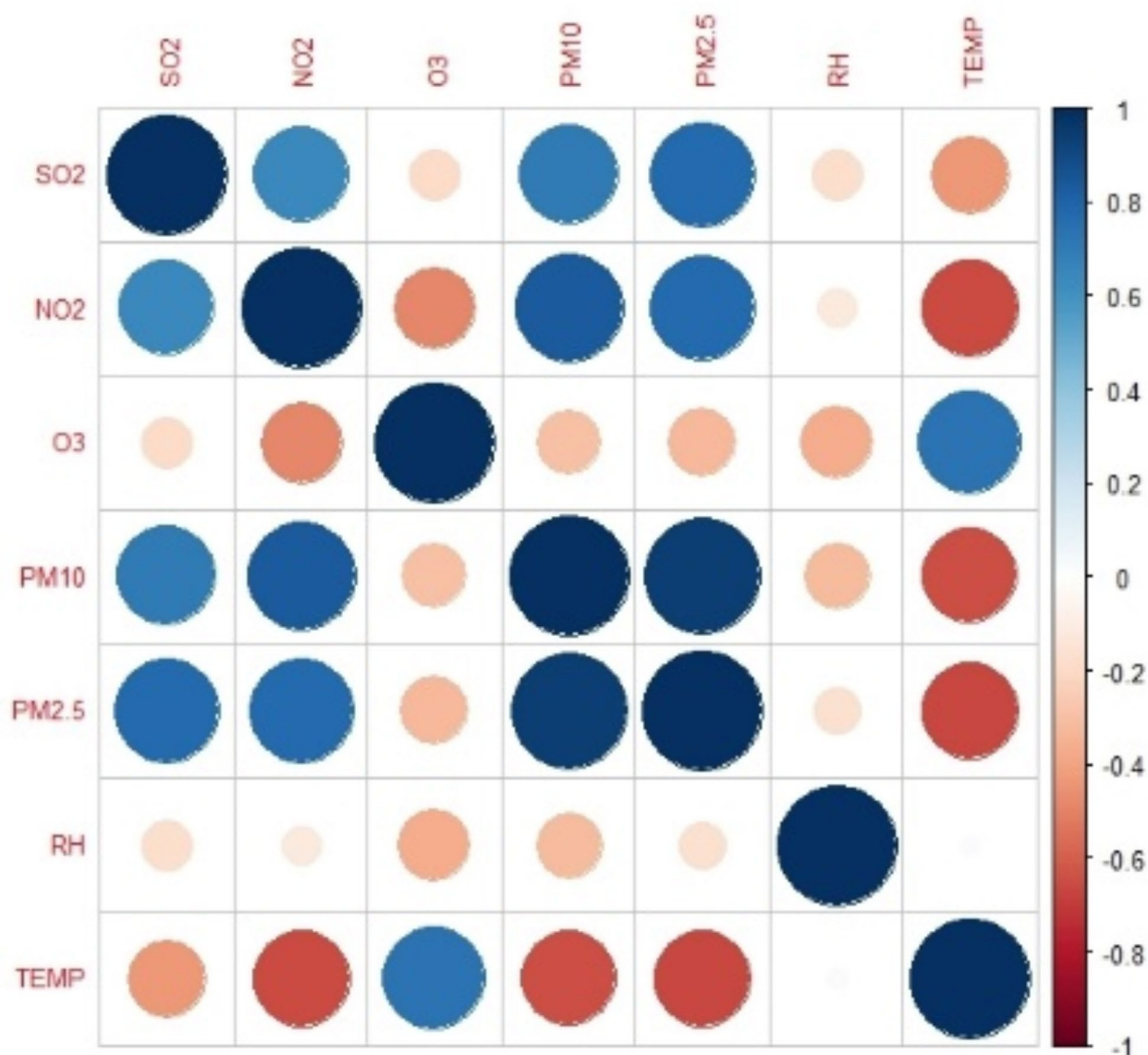
Excel software was used to create a database. Statistical analyses were conducted using R4.4.3 software with the “tsModel” and “splines” packages to fit a time-series model, and a *p* value less than 0.05 was considered to be statistically significant (two tailed).

Results

895,363 ILI cases were enrolled during the study period, and the average number of weekly ILI cases was 2446.35. The average concentrations of PM<sub>2.5</sub>, PM<sub>10</sub>, SO<sub>2</sub>, NO<sub>2</sub>, and O<sub>3</sub> were 40.88, 68.96, 9.59, 42.46, and 95.67 µg/m<sup>3</sup>, respectively. The mean values of air temperature and relative humidity were 17.72 °C and 73.33%, respectively (Table 1). The results of the statistical tests revealed that all pollutants correlated with temperature and humidity. PM<sub>2.5</sub>, PM<sub>10</sub>, SO<sub>2</sub>, and NO<sub>2</sub> negatively correlated with temperature and relative humidity, but O<sub>3</sub>, which positively correlated with air temperature, did not. There was also a correlation among air pollutants with correlation coefficients greater than 0.6, except for O<sub>3</sub> (Table 2; Fig. 1).

Figure 2 presents the time-series distributions of ILI cases, PM<sub>2.5</sub>, PM<sub>10</sub>, NO<sub>2</sub>, SO<sub>2</sub>, O<sub>3</sub>, mean temperature, and relative humidity for Hangzhou from 2015 to 2021. The concentrations of all pollutants showed seasonality, with PM<sub>2.5</sub>, PM<sub>10</sub>, NO<sub>2</sub>, and SO<sub>2</sub> gradually increasing in winter and peaking between the 48th and 5th week of the following year (winter), then gradually decreasing, reaching a minimum in the 28th to 33rd week (summer), and then gradually increasing again, and so on. However, the seasonality of O<sub>3</sub> was completely different from that of other pollutants, where the highest concentration occurred in summer, then gradually decreased, and reached the lowest concentration in winter. In addition, the weekly average concentration of SO<sub>2</sub> showed a continuous decreasing trend from 2015. The weekly average temperature in Hangzhou was regular, with high temperatures occurring from the 26th to the 35th week (summer) of the year and low temperatures from the 50th to the 6th week of the following year (winter). The weekly average relative humidity in Hangzhou did not show periodicity.

Table 3 shows the results of the single-and double-pollutant models. After controlling for the effects of average temperature, relative humidity, and seasonal and long-term trends, the weekly mean PM<sub>2.5</sub> concentration was significantly statistically associated with the number of ILI cases, and there was a 1.8% (RR: 1.018, 95% CI 1.001–1.036) increase in ILI cases for every 10 µg/m<sup>3</sup> increase in PM<sub>2.5</sub>. Additionally, PM<sub>10</sub>, NO<sub>2</sub>, and SO<sub>2</sub> were



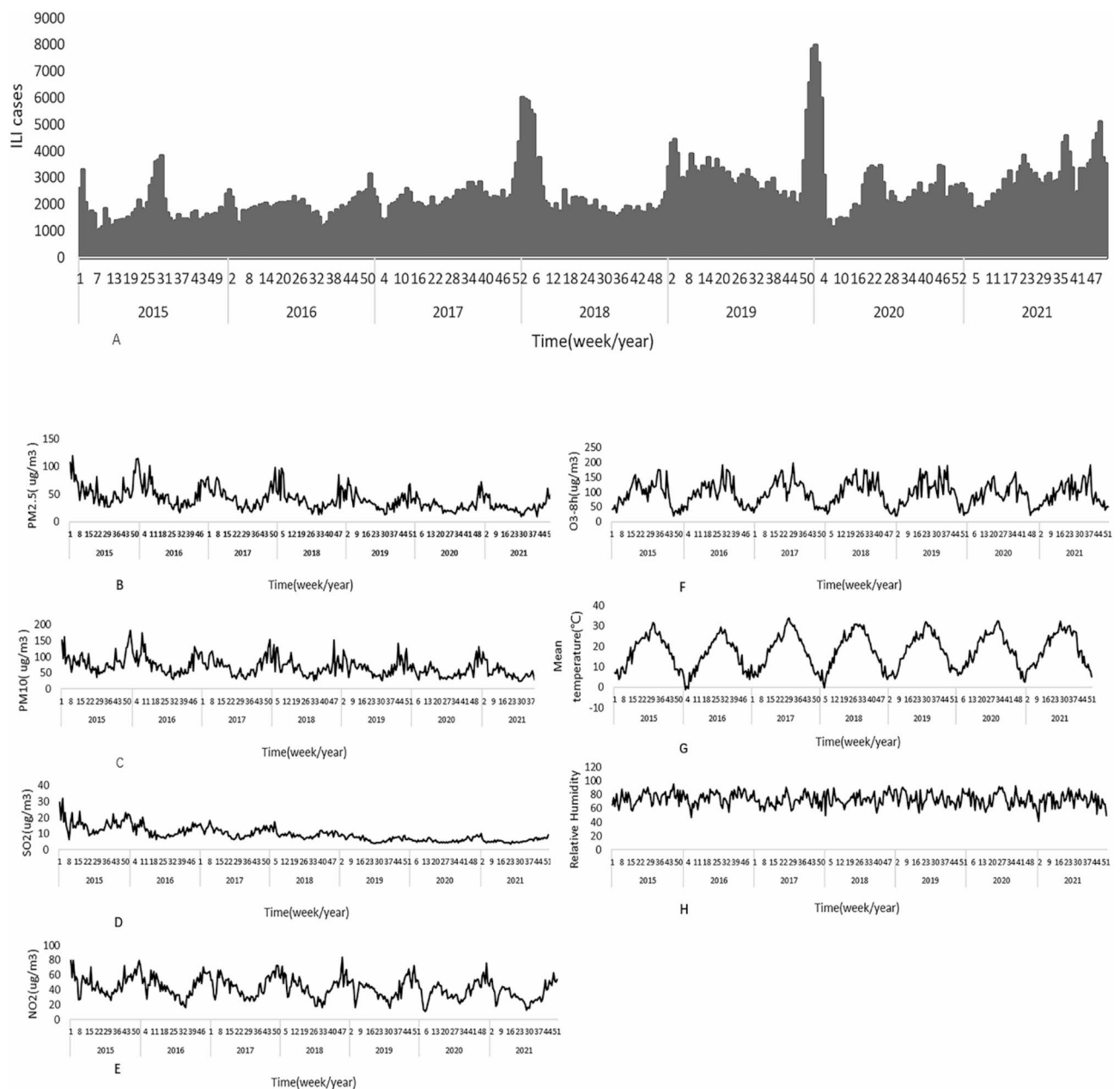
**Fig. 1.** Correlation Heat Map of air pollutants and meteorological parameters.

significantly associated with ILI cases, with RR values of 1.016 (95% CI 1.005–1.028), 1.063 (95% CI 1.067–1.364), and 1.207 (95% CI 1.067–1.364), respectively. According to the VIF and correlation coefficient between two pollutants, only variables without obvious collinearity were included in double-pollutant models. When PM<sub>2.5</sub>, PM<sub>10</sub>, NO<sub>2</sub>, or SO<sub>2</sub> was separately included into the model with O<sub>3</sub>, the results were similar to those of the single-pollutant model, but SO<sub>2</sub> was no longer statistically associated with ILI cases when it was adjusted with NO<sub>2</sub>. Compared with the single pollutant model, the effect of NO<sub>2</sub> was decreased after adjusting with SO<sub>2</sub>.

Table 4 shows the effects of different pollutants on the risk of ILI cases in the warm season and the cold season. PM<sub>2.5</sub>, PM<sub>10</sub>, and NO<sub>2</sub> have statistical significance in cold seasons, with the RR values of 1.020 (95% CI 1.001–1.038), 1.012 (95% CI 1.000–1.024), and 1.060 (95% CI 1.031–1.090), respectively. While the effects of pollutants on ILI cases were not statistically significant during the warm season.

## Discussion

Air pollution and influenza are dual challenges to human health. The 2019 Global Burden of Disease Report deemed air pollution to be the fourth largest Level 2 risk factor for attributable deaths, contributing to 2.92 million (2.53–3.33) or 11.3% (10.0–12.6) of all female deaths and 3.75 million (3.31–4.24) or 12.2% (11.0–13.4) of all male deaths in 2019<sup>23</sup>. Despite improvements in doses, adjuvants, and alternative administration routes for influenza vaccines, influenza remains a serious global public health problem with increasing morbidity and mortality. It is important to identify and analyze the environmental risk factors of influenza to understand how they influence respiratory virus infections. In our research, we investigated the short-term effects of air pollution



**Fig. 2.** The distribution of weekly ILI cases, air pollutant concentrations and meteorological factors, in Hangzhou, China during 2015–2021.

on ILI in Hangzhou, it showed that PM<sub>2.5</sub>, PM<sub>10</sub>, NO<sub>2</sub>, and SO<sub>2</sub> were found to be significantly associated with the number of ILI cases, and the two-pollutant model produced the similar results to those of the single-pollutant model.

For this, Yang et al.<sup>25</sup> built a novel integrated platform to realize the visualization of air quality for analyzing data together accurately and effectively. Chen et al.<sup>26</sup> updated the procedure of performing the extended convergent cross-mapping (CCM), and found the respiratory infection cases increased progressively with increased AQI. Various evaluating indicators such as the number of influenza cases and rates, have been used in studies<sup>27</sup>. In our study, we chose the number of ILI cases as the surveillance object. The application of symptom surveillance, such as ILI cases, can shorten the lag period of traditional monitoring and is conducive to monitoring the occurrence and development trends of diseases effectively<sup>28</sup>. Many prior studies have shown that elevated concentrations of air pollutants, such as NO<sub>2</sub>, SO<sub>2</sub>, PM<sub>10</sub>, and PM<sub>2.5</sub>, increase the relative risk of influenza or ILI, with effects generally limited to one week. This can be explained by the incubation period of acute respiratory diseases such as influenza, which is commonly in the range of 1–4 days, respiratory syncytial virus infection, which is usually in the range of 2–8 days, and human adenovirus infection, which is usually in the range of 3–8 days. In our study, the single-pollutant model suggested that concentrations of PM<sub>2.5</sub>, PM<sub>10</sub>, NO<sub>2</sub>, and SO<sub>2</sub> were positively associated with the number of ILI cases that week, which is similar to the results of several existing studies. After



Model			$\beta$	SE	Z	P	RRs(95%CI) <sup>a</sup>
Single-pollutant	PM <sub>2.5</sub>		0.001814	0.000862	2.104	0.036*	1.018(1.001–1.036)
	PM <sub>10</sub>		0.001621	0.000569	2.846	0.005*	1.016(1.005–1.028)
	NO <sub>2</sub>		0.006098	0.001250	4.879	<0.01*	1.063(1.067–1.364)
	SO <sub>2</sub>		0.018778	0.006265	2.997	0.003*	1.207(1.067–1.364)
	O <sub>3</sub>		0.000260	0.000570	0.456	0.648	1.003(0.991–1.014)
Two-pollutant	PM <sub>2.5</sub> +O <sub>3</sub>	PM <sub>2.5</sub>	0.001838	0.000896	2.052	0.041*	1.019(1.001–1.037)
		O <sub>3</sub>	–0.000060	0.000588	–0.103	0.918	0.999(0.988–1.011)
	PM <sub>10</sub> +O <sub>3</sub>	PM <sub>10</sub>	0.001649	0.000587	2.810	0.005*	1.017(1.005–1.028)
		O <sub>3</sub>	–0.000122	0.000580	–0.210	0.833	0.999(0.987–1.011)
	NO <sub>2</sub> +SO <sub>2</sub>	NO <sub>2</sub>	0.005950	0.001559	3.816	<0.01*	1.061(1.029–1.094)
		SO <sub>2</sub>	0.001226	0.007682	0.160	0.873	1.012(0.871–1.177)
	NO <sub>2</sub> +O <sub>3</sub>	NO <sub>2</sub>	0.006087	0.001255	4.850	<0.01*	1.063(1.037–1.089)
		O <sub>3</sub>	0.000065	0.000553	0.117	0.907	1.001(0.990–1.012)
	SO <sub>2</sub> +O <sub>3</sub>	SO <sub>2</sub>	0.018678	0.006282	2.973	0.003*	1.205(1.066–1.363)
		O <sub>3</sub>	0.000174	0.000564	0.309	0.757	1.002(0.991–1.013)

**Table 3.** Estimated relative risks (RRs) and 95% confidence intervals (CIs) of ILI cases for a 10 µg/m<sup>3</sup> increase of pollutant concentrations based on the single- and two-pollutant models. \*Indicates  $P < 0.05$ . <sup>a</sup>Estimated relative risks (RRs) and 95% confidence intervals (CIs) of ILI cases for a 10 µg/m<sup>3</sup> increase of pollutant concentrations.

Season		$\beta$	SE	Z	P	RRs(95%CI) <sup>a</sup>
Cold	PM <sub>2.5</sub>	0.001980	0.000913	2.168	0.032*	1.020(1.001–1.038)
	PM <sub>10</sub>	0.001205	0.000594	2.031	0.044*	1.012(1.000–1.024)
	NO <sub>2</sub>	0.005824	0.001429	4.074	<0.01*	1.060(1.031–1.090)
	SO <sub>2</sub>	0.008109	0.006846	1.184	0.238	1.084(0.948–1.240)
	O <sub>3</sub>	0.0005474	0.0010973	0.499	0.618	1.005(0.984–1.027)
Warm	PM <sub>2.5</sub>	0.0015970	0.0014590	1.094	0.276	1.016(0.987–1.046)
	PM <sub>10</sub>	0.0005499	0.0010129	0.543	0.588	1.006(0.986–1.027)
	NO <sub>2</sub>	0.0037720	0.0020840	1.810	0.073	1.038(0.997–1.082)
	SO <sub>2</sub>	–0.005901	0.0111300	–0.530	0.596	0.943(0.758–1.172)
	O <sub>3</sub>	0.0000899	0.000503	0.179	0.859	1.001(0.991–1.011)

**Table 4.** Estimated relative risks (RRs) and 95% confidence intervals (CIs) of ILI cases for a 10 µg/m<sup>3</sup> increase of pollutant concentrations in the warm (April to September) and cold (October to March) seasons. \*Indicates  $P < 0.05$ . <sup>a</sup>Estimated relative risks (RRs) and 95% confidence intervals (CIs) of ILI cases for a 10 µg/m<sup>3</sup> increase of pollutant concentrations.

adjusting for the effects of average temperature, relative humidity, and seasonal and long-term trends, PM<sub>10</sub>, PM<sub>2.5</sub>, NO<sub>2</sub>, and SO<sub>2</sub> were found to be significantly associated with the number of ILI cases. In the two-pollutant model, any pair of pollutants with a correlation coefficient larger than 0.7 were not included. We put PM<sub>2.5</sub>, PM<sub>10</sub>, NO<sub>2</sub>, or SO<sub>2</sub> into the model separately with O<sub>3</sub> produced results similar to those of the single-pollutant model, in agreement with some previous studies. PM was considered to be a vector for the transport of different respiratory pathogens, and it could enhance the probability for the inhalation of these pathogens<sup>29</sup>. The observed results in our study were consistent with previous epidemiology studies. In Guangzhou, PM<sub>1</sub>, PM<sub>2.5</sub>, and PM<sub>10</sub> were found to be risk factors for ILI, and the health impacts of PM pollutants varied by particle size<sup>30</sup>.

While some studies reported a negative or no association between pollutants and ILI, no significant effect of NO<sub>2</sub> was observed in Jinan<sup>22</sup>. Nor did we find a significant association between O<sub>3</sub> and ILI, which is consistent with Sun's research<sup>31</sup>. Ali et al. reported the reduced transmissibility of influenza associated with O<sub>3</sub> in Hong Kong, China<sup>32</sup>. In a study conducted in Brisbane, O<sub>3</sub> and PM<sub>10</sub> were found to be positively associated with pediatric seasonal influenza<sup>33</sup>, this is consistent with the research findings from Ningbo<sup>34</sup>. While O<sub>3</sub> was found to be negatively associated with ILI and reproduction number (Rt) in a nationwide study in China, and it might be attributable to the virucidal activity of O<sub>3</sub> and its effect on host defense mechanism<sup>15,22</sup>. The discrepancies in these results are attributable to the geographical location, socio-demographic characteristics, sources of pollutants, or statistical methods used. It might also be related to different exposure concentration levels and durations of O<sub>3</sub>.

Among the five main air pollutants, PM<sub>2.5</sub>, PM<sub>10</sub>, and NO<sub>2</sub> exhibit strong collinearity, so we only include pollutant variables without obvious collinearity in the two-pollutant models. After correcting for the possible

confounding effects of O<sub>3</sub>, the RR of other air pollutants did not change significantly. It indicated that O<sub>3</sub> had little effect on the other four pollutants. However, SO<sub>2</sub> was no longer statistically associated with ILI cases when it was adjusted with NO<sub>2</sub>, which was the same as the results of Wuhan, researchers concluded that NO<sub>2</sub> may be a potential confounder for co-pollutants in the multi-pollutant model<sup>21</sup>.

It's suggested that the cold season has a greater impact on ILI cases than the warm season, which is consistent with other studies<sup>21,29</sup>. PM<sub>2.5</sub> could increase the prevalence of influenza in cold weather, after adjusting for potential variables, there were a strong positive relationship between PM<sub>2.5</sub> and ILI risk during the flu season<sup>12</sup>. The reasons may be that the concentration of pollutants in cold season is higher than that in warm season, and the low temperature makes it more comfortable for influenza viruses to survive, what's more, the respiratory mucosa is more fragile in winter. The results of this study suggest certain potential mechanisms that might be involved in the relationship between air pollution and influenza risk<sup>35</sup>. A possible reason is that oxidative stress may cause air pollutants to produce free radicals, which are bad for the lungs<sup>36</sup>. Second, air pollutants can reduce the ability of macrophages to phagocytize or inactivate viruses, which may lead to changes in a host's susceptibility. A previous study found evidence that PM<sub>10</sub> exposure may interfere with the replication of viruses<sup>37</sup>. In addition, air pollutions can decrease the expression of surfactant proteins, which may lead to increased inflammation and decreased phagocytosis<sup>38</sup>. Some researchers have contended that polluting particles in the air can provide "condensation nuclei" to which virus droplets attach, increasing the risk of various infectious diseases<sup>12</sup>.

In this study, we evaluated the relationship between air pollution and ILI by GLM, which helps provide insight into the health effects of air pollution on ILI. However, this study also has several limitations. Firstly, the study used the daily mean values of air pollutants as monitored by 10 stations located in nine districts of Hangzhou rather than individual exposure, which would have involved measuring indoor microclimate and exposure time, this may lead to the measurement error. Future studies should incorporate personal monitoring to improve exposure estimates<sup>18</sup>. Secondly, this study focused on pollutants and did not analyze socio-demographic characteristics, lifestyle and habits, pollutant sources, and other factors that might influence the incidence of ILI. Thirdly, the data used in this study were collected in a single city, which limits extrapolation of the conclusions. However, the results are relevant for cities with similar geography and economic conditions. Future multi-regional studies are needed to validate the results of this work. In summary, this is the first study to quantify the acute effects of multiple air pollutants on the number of ILI cases in Hangzhou, China. The study found that air pollutants (PM<sub>10</sub>, PM<sub>2.5</sub>, NO<sub>2</sub>, and SO<sub>2</sub>) have a significant association with the risk of influenza in Hangzhou. Controlling the air pollution levels may reduce the opportunity of exposure, thereby decreasing the transmission of influenza and other respiratory viruses in China<sup>29</sup>. Our finding also provided additional urban evidence regarding the impact of air pollutants on ILI in China. The quantitative evaluation of the health effects of air pollution on the number of ILI cases can provide epidemiological evidence for future mechanism research and can act as a reference for developing effective protective measures. Besides, timely release the warning information for vulnerable groups to remind them of pollution situations and preventive measures. This study also emphasized that the effect of ozone cannot be ignored.

## Data availability

The datasets generated and analysed during the current study are not publicly available due to the monitoring data of ILI are non open data, and there are available from the corresponding author upon reasonable request.

Received: 8 July 2024; Accepted: 19 March 2025

Published online: 26 March 2025

## References

1. National Health Commission of China. Notice on printing and distributing the national influenza surveillance Program. (2017).
2. Sosin, D. Draft framework for evaluating syndromic surveillance systems. *J. Urb. Health.* **80** (2 Suppl 1), i8–13. <https://doi.org/10.1007/pl00022309> (2003).
3. Javanian, M. et al. A brief review of influenza virus infection. *J. Med. Virol.* **93**, 4638–4646. <https://doi.org/10.1002/jmv.26990> (2021).
4. Stamboulia, D., Bonvehí, P., Nacinovich, F., Cox, N. & Influenza *Infect. Dis. Clin. N. Am.* **14**(1):141–166. doi: [https://doi.org/10.1016/s0891-5520\(05\)70222-1](https://doi.org/10.1016/s0891-5520(05)70222-1). (2000).
5. Feng, L. et al. Burden of influenza-associated outpatient influenza-like illness consultations in China, 2006–2015: A population-based study. *Influenza Other Respir. Viruses.* **14**, 162–172. <https://doi.org/10.1111/irv.12711> (2019).
6. Clayville, L. Influenza update: A review of currently available vaccines. *Pharm. Ther.* **36** (10), 659–684 (2011).
7. WHO global air quality guidelines. *Particulate matter (PM<sub>2.5</sub> and PM<sub>10</sub>), ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide* (World Health Organization, 2021).
8. Hu, Y. et al. Interactive effects of meteorological factors and particulate pollutants on childhood asthma: A time series analysis in Shanghai, China. *Res. Square.* <https://doi.org/10.21203/rs.3.rs-842165/v1> (2021).
9. Ren, M. et al. The short-term effects of air pollutants on respiratory disease mortality in Wuhan, China: comparison of time-series and case-crossover analyses. *Sci. Rep.* **7**, 40482. <https://doi.org/10.1038/srep40482> (2017).
10. Yang, J. et al. Influence of air pollution on influenza-like illness in China: A nationwide time-series analysis. *E Bio Med.* **87**, 104421. <https://doi.org/10.1016/j.ebiom.2022.104421> (2023).
11. Tang, S. et al. Measuring the impact of air pollution on respiratory infection risk in China. *Environ. Pollut.* **232**, 477–486. <https://doi.org/10.1016/j.envpol.2017.09.071> (2018).
12. Feng, C., Li, J., Sun, W., Zhang, Y. & Wang, Q. Impact of ambient fine particulate matter (PM<sub>2.5</sub>) exposure on the risk of influenza like-illness: a time-series analysis in Beijing, China. *Environ. Health.* **15**, 17. <https://doi.org/10.1186/s12940-016-0115-2> (2016).
13. Toczyłowski, K., Wietlicka-Piszc, M., Grabowska, M. & Sulik, A. Cumulative effects of particulate matter pollution and meteorological variables on the risk of Influenza-Like illness. *Viruses* **13** (4), 556. <https://doi.org/10.3390/v13040556> (2021).
14. Liu, X. et al. Effects of air pollutants on occurrences of influenza-like illness and laboratory-confirmed influenza in Hefei, China. *Int. J. Biometeorol.* **63** (1), 51–60. <https://doi.org/10.1007/s00484-018-1633-0> (2019).
15. Yang, J. et al. Association between Ozone and influenza transmissibility in China. *BMC Infect. Dis.* **23** (1), 763. <https://doi.org/10.1186/s12879-023-08769-w> (2023).

16. Yu, Z., Wu, L., Gao, D. & Fan, G. Discussion on the method of dividing four seasons in Zhejiang Province. *Meteorological Sci. Technol.* **42** (3), 474–481 (2014).
17. Hu, Y. & Chen, B. Analysis of climate change characteristics in four seasons in Hangzhou. *J. Zhejiang Meteorol.* **41** (02), 1–5 (2020).
18. Wu, K. et al. Effects of fine particulate matter and its chemical constituents on influenza-like illness in Guangzhou, China. *Ecotoxicol. Environ. Saf.* **doi:16**, 290 (2024).
19. Lu, F. et al. Application of time series analysis in the field of air pollution and health and its R software implementation. *Chin. J. Health Stat.* **35** (04), 622–625 (2018).
20. Liu, C. et al. Ambient particulate air pollution and daily mortality in 652 cities. *N Engl. J. Med.* **381** (8), 705–715. <https://doi.org/10.1056/NEJMoa1817364> (2019).
21. Meng, Y., Lu, Y., Xiang, H. & Liu, S. Short-term effects of ambient air pollution on the incidence of influenza in Wuhan, China: A time-series analysis. *Environ. Res.* **192**, 110327. <https://doi.org/10.1016/j.envres.2020.110327> (2021).
22. Su, W. et al. The short-term effects of air pollutants on influenza-like illness in Jinan, China. *BMC Public Health.* **19** (1), 1319. <https://doi.org/10.1186/s12889-019-7607-2> (2019).
23. GBD 2019 Risk Factors Collaborators. Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the global burden of disease study 2019. *Lancet* **396** (10258), 1223–1249. [https://doi.org/10.1016/S0140-6736\(20\)30752-2](https://doi.org/10.1016/S0140-6736(20)30752-2) (2020).
24. Buchy, P. & Badur, S. Who and when to vaccinate against influenza. *Int. J. Infect. Disease.* **93**, 375–387. <https://doi.org/10.1016/j.ijid.2020.02.040> (2020).
25. Yang, C. et al. An implementation of real-time air quality and influenza-like illness data storage and processing platform. *Comput. Hum. Behav.* **100**, 266–274. <https://doi.org/10.1016/j.chb.2018.10.009> (2019).
26. Chen, D., Sun, X. & Cheke, R. Robert A cheke, inferring a causal relationship between environmental factors and respiratory infections using convergent Cross-Mapping. *Entropy (Basel).* **25** (5), 807. <https://doi.org/10.3390/e25050807> (2023).
27. Lu, B. et al. Epidemiological and genetic characteristics of influenza virus and the effects of air pollution on laboratory-confirmed influenza cases in Hulunbuir, China, from 2010 to 2019. *Epidemiol. Infect.* **148**, e159. <https://doi.org/10.1017/S0950268820001387> (2020).
28. Shi, M. *Analysis on the Relationship between Influenza and Meteorology in Hangzhou and Establishment of Early Warning Models* [D] Zhejiang University. 1–83 (Department of epidemiology and Health Statistics School of Public Health, 2013).
29. Yang, J. et al. The association between ambient pollutants and influenza transmissibility: A nationwide study involving 30 provinces in China. *Influenza Other Respiratory Viruses.* **17** (7), e13177. <https://doi.org/10.1111/irv.13177> (2023).
30. Lu, J. et al. Short-term effects of ambient particulate matter (PM<sub>1</sub>, PM<sub>2.5</sub> and PM<sub>10</sub>) on influenza-like illness in Guangzhou, China. *Int. J. Hyg. Environ Health.* **247**, 114074. <https://doi.org/10.1016/j.ijheh.2022.114074> (2023).
31. Sun, R. et al. Air Pollution and Influenza: A Systematic Review and Meta-Analysis. *Iran J Public Health* **53**(1), 1–11. <https://doi.org/10.18502/ijph.v53i1.14678> (2024).
32. Ali, S. T. et al. Ambient ozone and influenza transmissibility in Hong Kong. *Eur. Respir. J.* **51**(5), 1800369. <https://doi.org/10.1183/13993003.00369-2018> (2018).
33. Xu, Z. et al. Air pollution, temperature and pediatric influenza in Brisbane, Australia. *Environ. Int.* **59**, 384–388. <https://doi.org/10.1016/j.envint.2013.06.022> (2013).
34. Zhang, R. et al. The modification effect of temperature on the relationship between air pollutants and daily incidence of influenza in Ningbo, China. *Respir. Res.* **22**(1), 153. <https://doi.org/10.1186/s12931-021-01831-8> (2021).
35. Cieniewicz, J. & Jaspers, I. Air pollution and respiratory viral infection. *Inhalation Toxicol.* **19** (14), 1135–1146. <https://doi.org/10.1080/08958370701665434> (2007).
36. Dellinger, B. et al. Role of free radicals in the toxicity of airborne fine particulate matter. *Chem. Res. Toxicol.* **14** (10), 1371–1377. <https://doi.org/10.1021/tx010050x> (2001).
37. Kaan, P. & Hegele, R. Interaction between respiratory syncytial virus and particulate matter in Guinea pig alveolar macrophages. *Am. J. Respir. Cell Mol. Biol.* **28** (6), 697–704. <https://doi.org/10.1165/rcmb.2002-0115OC> (2003).
38. LeVine, A., Hartshorn, K., Elliott, J., Whitsett, J. & Korfhagen, T. Absence of SP-A modulates innate and adaptive defense responses to pulmonary influenza infection. *Am. J. Physiology-Lung Cell. Mol. Physiol.* **82** (3), L563–L572. <https://doi.org/10.1152/ajplung.00280.2001> (2002).

# Author contributions

All authors contributed to the study conception and design. Lv Ye and Yang Xuhui designed and supervised the study, and wrote the main manuscript; Lv Ye, Yang Xuhui, Xu Hong, Sun Zhou and Ye Hui prepared material preparation, data collection and data analysis; Liu Muwen and Wang Jing prepared Table 2; Fig. 1; Xu shanshan and Li chaokang prepared Fig. 2; All authors interpreted the results and reviewed the manuscript.

# Funding

This research was supported by the Medical and Health Technology Project of Zhejiang Province (2023KY1000) and Health Science and Technology Program Key Projects of Hangzhou (ZD20230031).

# Declarations

# Competing interests

The authors declare no competing interests.

# Additional information

**Correspondence** and requests for materials should be addressed to X.Y.

**Reprints and permissions information** is available at [www.nature.com/reprints](http://www.nature.com/reprints).

**Publisher's note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.



**Open Access** This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc-nd/4.0/>.

© The Author(s) 2025