Influence of air pollution on influenza-like illness in China: A nationwide time-series analysis

Jun Yang,[a,i,*] Zhou Yang,[b,i] Li Qi,[c,i] Mengmeng Li,[d] Di Liu,[a] Xiaobo Liu,[e] Shilu Tong,[f] Qinghua Sun,[g] Luzhao Feng,[h,**] Chun-Quan Ou,[b] and Qiyong Liu[e,***]

[a]School of Public Health, Guangzhou Medical University, Guangzhou, 511436, China
[b]State Key Laboratory of Organ Failure Research, Department of Biostatistics, Guangdong Provincial Key Laboratory of Tropical Disease Research, School of Public Health, Southern Medical University, Guangzhou, 510515, China
[c]Chongqing Municipal Center for Disease Control and Prevention, Chongqing, 400042, China
[d]Department of Cancer Prevention, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou, 510060, China
[e]State Key Laboratory of Infectious Disease Prevention and Control, Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, National Institute for Communicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, 102206, China
[f]Shanghai Children's Medical Center, Shanghai Jiao Tong University, Shanghai, 200127, China
[g]School of Public Health, Zhejiang Chinese Medical University, Hangzhou, 310053, China
[h]School of Population Medicine and Public Health, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, 100730, China

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Summary

Background Evidence concerning effects of air pollution on influenza-like illness (ILI) from multi-center is limited and little is known about how regional factors might modify this relationship.

Methods In this ecological study, ILI cases defined as outpatients with temperature ≥38 °C, accompanied by cough or sore throat, were collected from National Influenza Surveillance Network in China. We adopted generalized additive model with quasi-Poisson to estimate province-specific association between air pollution and ILI in 30 Chinese provinces during 2015–2019, after adjusting for time trend and meteorological factors. We then pooled province-specific association by using random-effect meta-analysis. Potential effect modifications of season and regional characteristics were explored.

Findings A total of 26, 004, 853 ILI cases and 777, 223, 877 hospital outpatients were collected. In general, effects of air pollutants were acute. An inter-quartile range increase of $PM_{2.5}$, SO_2, PM_{10}, NO_2 and CO at lag0, and O_3 at lag0-2 was associated with 3.08% (95% CI: 1.91%, 4.27%), 3.00% (1.86%, 4.16%), 6.46% (4.71%, 8.25%), 7.21% (5.73%, 8.71%), 4.37% (3.05%, 5.70%), and −9.26% (−11.32%, −7.14%) change of ILI at national level, respectively. Associations between air pollutants and ILI varied by season and regions, with higher effect estimates in cold season, eastern and central regions and provinces with more humid condition and larger population.

Interpretation This study indicated that most air pollutants increased the risk of ILI in China. Our findings might provide implications for the development of policies to protect public health from air pollution and influenza.

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Keywords: Air pollution; Influenza-like illness; Short-term effect; Season; Socioeconomic factors

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*Corresponding author.
**Corresponding author.
***Corresponding author.
E-mail addresses: yangjun@gzhmu.edu.cn (J. Yang), fengluzhao@cams.cn (L. Feng), liuqiyong@icdc.cn (Q. Liu).
[i]These authors contributed equally to this work.

Research in context

Evidence before this study

Air pollution and influenza are the dual challenges to human health. Previous studies have attempted to link the associations between air pollutants and influenza-like illness. We searched PubMed with the MeSh terms ("air pollution", "air pollutant", "particulate matter", "PM", "$PM_{2.5}$", "PM_{10}", "sulfur dioxide", "SO_2", "nitrogen dioxide", "NO_2", "carbon monoxide", "CO", "ozone", "O_3") and ("influenza", "flu", "influenza-like illness", "ILI"). Our literature review shows that the current epidemiological studies were mainly conducted in single study site with controversial results. Furthermore, whether the associations between air pollution and influenza-like illness would be modified by regional characteristics remains uncertain.

Added value of this study

We conducted a time-series analysis of 30 Chinese provinces from 2015 to 2019, with a total of 26, 004, 853 ILI cases and 777, 223, 877 hospital outpatients, to examine the associations between air pollutants and ILI. We found that most air pollutants (i.e., PM_{10}, $PM_{2.5}$, NO_2, CO and SO) increased the risk of ILI in China, but a negative association for O_3. In addition, the associations between air pollutants and ILI significantly varied by season, and regional characteristics (gross domestic product per capita, population, proportion of the elderly, temperature, humidity and latitude).

Implications of all the available evidence

The available evidence is important for the development of evidence-based public health policies on protecting the susceptible population from the double threat of air pollution and influenza.

Introduction

As a common respiratory syndrome, influenza-like illness (ILI) poses a great challenge to human health and socioeconomic development around the world, which causes a substantial number of mortality and morbidity annually.[1,2] A wide range of respiratory viruses can cause ILI, such as influenza viruses, parainfluenza viruses and respiratory syncytial virus. Nevertheless, the incidence of ILI has always fluctuated over the past few years despite numerous efforts (e.g. vaccination and non-pharmaceutical interventions) in the prevention of respiratory virus infections. This suggests the importance of identifying other preventable/modifiable risk factors to further manage and reduce the burden of ILI.

Previous studies have reported that individual characteristics, such as age, underlying chronic disease, obesity and smoking status, may influence the severity of the symptoms.[3,4] In addition, adverse meteorological factors, such as temperature, humidity, solar radiation and precipitation, have been reported to be associated with an elevated risk of ILI.[5,6]

Ambient air pollutants could also lead to elevated incident of respiratory infections in general.[7–9] For example, Chen and colleagues reported that $PM_{2.5}$ was associated with elevated risk of influenza incidence in 47 Chinese cities; and in 24 Canadian cities,[9] Shin and co-authors observed higher effect estimates of O_3 and $PM_{2.5}$ on influenza/pneumonia hospitalizations among the males than the females during warm season.[10] However, the association between exposure to air pollution and ILI remains controversial. Several previous investigations reported positive associations between air pollution and ILI, but others found non-significant or even negative association.[11,12] For instance, Su and colleagues reported that O_3 was negatively associated with ILI [relative risk (RR) = 0.986; 95% CI: 0.979–0.994] in Jinan, China[12]; and in Hefei, China, Liu and co-workers found that PM_{10} was negatively associated with risk of ILI.[13] Previous studies with discrepant results were mainly conducted in a single city, or focused on single air pollutant and used different methodology, which has limited generalizability of these findings.[13–17]

Thus, this study aimed to assess the relationships between six major air pollutants ($PM_{2.5}$, PM_{10}, SO_2, NO_2, CO and O_3) and ILI in 30 Chinese provinces, and to test the modification effect of provincial-level socioeconomic factors and season.

Methods

Study sites and data sources

This was a nationwide ecological study covering 30 (out of total 31) provinces in mainland China. The Tibet Autonomous Region was excluded due to its high proportion (65.9%) of missing data on ILI. The data missing rates for the included provinces were all below 0.32%. Based on different meteorological characteristics/and background, the included provinces were further categorized/grouped into seven regions: northern, northeast, northwest, eastern, central, southern, and southwest (Fig. 1 & Table 1).

Data on the outpatients of influenza-like illness

Weekly number of provincial ILI cases from 2015 to 2019, defined as the outpatients who had acute respiratory infection with body temperature more than 38 °C and either cough or sore throat, were collected from the

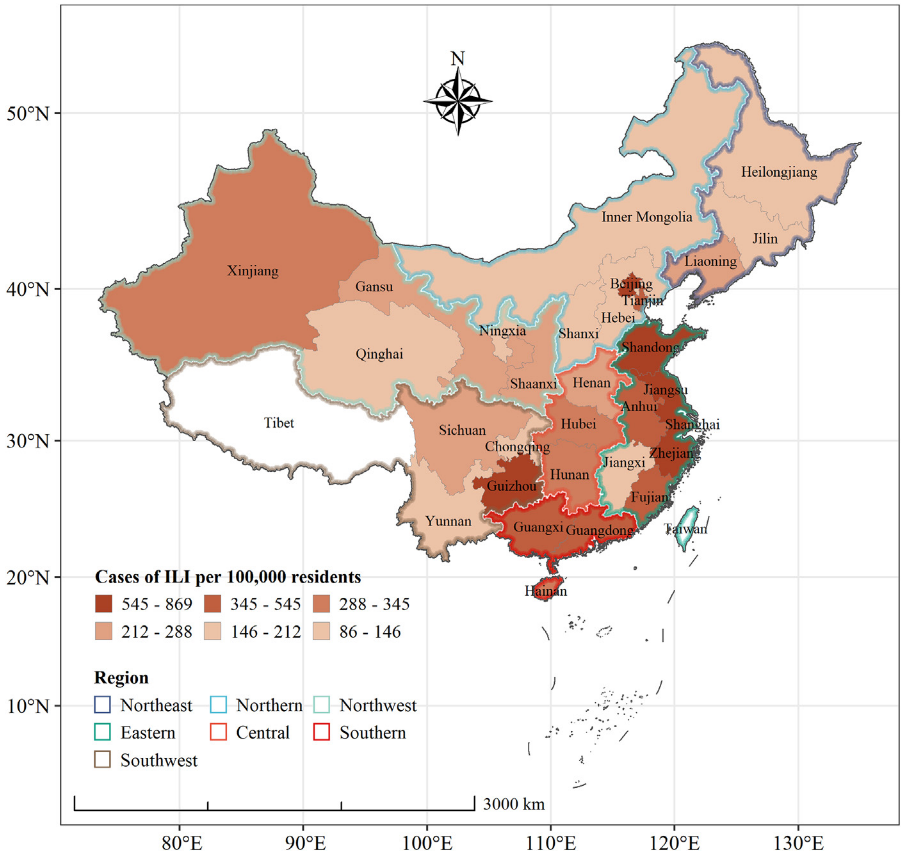

Fig. 1: Geographical distribution of the average weekly numbers of influenza-like illness cases per 100,000 residents in China. The 30 Chinese provinces were divided into seven regions. Tibet Autonomous Region was excluded from our analysis due to its high proportion (65.9%) of missing data on influenza-like illness.

National Influenza Surveillance Network,[18] which is managed by the Chinese Center for Disease Control and Prevention (CDC). National Influenza Surveillance Network has 554 sentinel hospitals distributed around mainland China. The ILI surveillance was carried out in the internal medicine outpatient service, internal medicine emergency service, fever outpatient service, pediatric outpatient service and pediatric emergency service. Based on the ILI definition, the medical staff in the consulting room of sentinel hospitals should register the number of ILI cases and total number of outpatient and emergency cases each day, and then report the weekly data to the National Influenza Surveillance Network.

All the ILI cases were registered in the sentinel hospitals distributed in each Chinese province.[19] Weekly number of all the hospital outpatients during 2015–2019 was also obtained from the China CDC. In addition, the provincial annual population size and annual number of outpatients were collected for each province during the same period from Chinese National Bureau of Statistics.

Data on air pollution and meteorology

Daily average concentrations of major air pollutants, including $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO, and O_3, were obtained for 2024 air pollution monitoring stations (Fig. S1) during 2015–2019 from the China National Environmental Monitoring Centre (http://106.37.208.233:20035/). Daily meteorological data, including ambient mean temperature (°C) and relative humidity (%), were derived from the National Meteorological Information Center (http://data.cma.cn/site/index.html). The quality of environmental data from these monitoring stations was assured by a series of regulations and criteria carried out by the Chinese government.[20]

We first aggregated weekly mean values of air pollutants and meteorological factors from the daily level data in each monitoring station. We then averaged weekly mean values from all monitoring stations in each city to derive city-specific weekly variables. Finally, the provincial-level air pollution data and meteorological factors were calculated as the population-weighted average of city-specific factors. The city-specific

Province	ILI[a]±SD	Weekly average concentration[b]						Temperature (°C)	Humidity (%)
		$PM_{2.5}$	PM_{10}	SO_2	NO_2	CO	O_3		
Northern									
Inner Mongolia	209 ± 84	33.2	73.6	20.9	25.9	0.8	63.9	6.0	49.5
Beijing	769 ± 336	60.0	90.8	8.2	42.6	1.0	61.5	12.1	53.5
Tianjin	482 ± 282	61.9	101.4	18.0	45.8	1.2	59.9	13.6	57.2
Hebei	184 ± 98	65.4	117.0	28.7	45.5	1.3	63.9	12.5	59.5
Shanxi	96 ± 38	56.9	105.6	47.5	36.7	1.5	62.2	11.0	56.9
Northeast									
Heilongjiang	106 ± 40	38.0	63.3	18.0	26.5	0.7	53.5	4.4	65.2
Jilin	142 ± 60	41.2	71.3	19.0	28.5	0.9	59.8	6.3	63.6
Liaoning	280 ± 80	44.4	77.7	28.0	31.2	1.0	65.2	9.6	60.7
Northwest									
Xinjiang	307 ± 111	70.3	191.3	14.2	31.2	1.2	61.6	9.8	50.2
Ningxia	87 ± 40	40.6	98.9	29.0	28.0	0.9	65.5	9.6	51.7
Qinghai	187 ± 146	38.6	84.7	19.7	29.2	1.1	66.9	6.2	54.0
Gansu	214 ± 91	37.2	86.5	20.5	29.3	0.9	64.7	9.5	58.2
Shaanxi	287 ± 165	52.3	98.4	16.0	36.6	1.1	54.6	12.3	65.3
Eastern									
Shandong	602 ± 307	60.6	113.0	26.0	37.8	1.1	70.8	13.9	64.3
Jiangsu	712 ± 365	49.3	84.1	17.1	36.7	0.9	68.4	16.4	74.2
Anhui	350 ± 91	53.5	83.5	15.4	34.0	0.8	64.2	16.3	76.4
Shanghai	289 ± 127	42.2	59.8	11.9	43.0	0.7	73.0	17.5	73.6
Zhejiang	714 ± 337	38.8	63.6	11.4	35.4	0.8	60.2	18.2	77.6
Jiangxi	146 ± 58	40.5	65.3	20.7	23.6	1.0	56.8	18.7	77.1
Fujian	441 ± 136	25.4	45.8	8.7	22.7	0.7	58.7	19.4	80.2
Central									
Henan	278 ± 97	67.4	117.7	21.5	37.3	1.2	67.0	15.8	65.7
Hubei	317 ± 108	53.2	85.4	13.2	31.5	1.1	59.5	17.1	76.0
Hunan	343 ± 115	45.2	71.6	14.8	24.8	1.0	57.3	17.8	77.8
Southern									
Guangdong	533 ± 172	31.0	49.8	10.6	28.2	0.8	57.8	22.9	79.8
Guangxi	365 ± 136	37.2	58.8	14.1	22.8	0.9	51.4	21.4	78.9
Hainan	290 ± 94	19.2	35.7	5.4	12.8	0.6	56.3	25.0	81.6
Southwest									
Sichuan	269 ± 97	45.0	70.9	13.4	32.7	0.9	53.0	16.6	76.4
Chongqing	152 ± 125	45.6	70.8	11.4	42.5	0.9	42.2	17.8	78.2
Guizhou	650 ± 126	29.6	50.4	14.3	21.8	0.8	50.7	16.0	79.0
Yunnan	146 ± 28	26.5	47.2	13.6	17.9	0.8	59.7	16.2	72.7

[a]ILI: Influenza-like illness per 1000 hospital outpatient visits; SD: standard deviation. [b]The concentrations of $PM_{2.5}$, PM_{10}, SO_2, NO_2, O_3 were measured as μg/m^3 and CO was measured as mg/m^3.

Table 1: **Summary of weekly influenza-like illness, air pollution, and meteorological variables in 30 Chinese provinces from 2015 to 2019.**

population were collected from the Sixth National Population Census of China (http://www.stats.gov.cn/).

Statistics

A two-stage analytic strategy was used to assess the impacts of air pollutants on ILI.[9,21,22] The quasi-Poisson regression was firstly used to derive province-specific relative risk (RR) of ILI related to each single air pollutant. Then, we pooled the province-specific association by using the multivariable random effect meta-analysis approach, to get an overall estimate for the entire country. In addition, stratification analysis was also conducted to assess modification effects of season and region. And effect modifications of provincial-level characteristics were explored by fitting meta-regression.

In the first-stage, the quasi-Poisson regression was fitted to capture the province-specific association between single air pollutant and ILI after adjusting for potential confounders. The formula of the model is:

$$Log[E(Y_{i,t})] = \alpha + log(Y_{i,t-1}) + \beta \text{ Pollutant}_{it} + ns\,(\text{Time}, 5 \times 2) + ns\,(\text{Temp}, 3) + ns\,(\text{Hum}, 3) + offset(log(Population_{i,t}))\quad(1)$$

where $Y_{i,t}$ denotes weekly number of ILI cases at t (t= 1, 2, ..., 261) week in province i and $Y_{i,t\text{-}1}$ is that of the previous week (to adjust for auto-correlation); $\text{Pollutant}_{i,t}$ is the concentration of a single air pollutant in different lag periods. Previous studies implied that impacts of air pollutants on influenza could persist up for more than one week.[17] Thus, to fully understand the lag structure, we modeled the effect of air pollutants in the current week (lag 0), the previous week (lag 1), and then up to lag 3. Additionally, we also fitted the model with moving average concentration of air pollutants, from the current and previous weeks (lag 0–1), up to lag 0–3. The optimal lag of the effect of air pollution was selected by minimizing the Akaike Information Criterion (AIC). Time trend smoothed by a natural cubic spline function (*ns*) with 2 degrees of freedom (df) for each year was used to adjust for the unmeasured long-term trend and seasonality of weekly ILI cases. Additionally, the confounding effects of meteorological conditions were adjusted by incorporating the two-week moving average of mean temperature and humidity, which was smoothed by *ns* with empirical 3 df.[23] Moreover, to consider the varying population size, a log product of the population size covered by sentinel hospitals for each province was included as offset, which was commonly applied in previous studies.[14,16] Since the outpatient consultation in these sentinel hospitals is assumed to have a good representativeness in each province,[24] the annual population size for the sentinel hospitals in each province was calculated as the product of the proportion of annual number of outpatients in the sentinel hospitals among the total provincial number of outpatients, and the corresponding provincial population size.[25] Further, the population size for each week was estimated by linear interpolation. The province-specific effects of air pollution were then estimated as the RR associated with per inter-quartile range (IQR) increase of air pollutant concentration for each province (Table S1), which was calculated as $\exp(\beta \times \text{IQR})$. The IQR was used to measure and compare the effects across provinces because the severity of air pollution varied greatly among the provinces and the effects per IQR change demonstrated significantly lower heterogeneity than the effects per 1 $\mu g/m^3$ or 1 mg/m^3 increase.[26]

In the second-stage, the random-effect meta-analysis was applied to estimate overall country-level effect of air pollution on ILI by pooling province-specific effect estimated in the first stage. The meta-analysis was evaluated by the restricted maximum likelihood method. The relative risk of ILI associated with per Impact of air pollution was indicated as the percentage change of ILI and its 95% confidence interval (95% CI) with per IQR increase in air pollution concentration, which was computed as (RR-1) × 100%.

To test whether effects of air pollution varied by different seasons, we divided the full year data into seasons (warm: April to September; cold: October to March of the next year) based on the average monthly temperature at national level (Fig. S2). Season-specific air pollution-ILI associations were estimated by fitting models in each season. Moreover, the regional difference of the effect was also investigated by pooling province-specific effects in the southern and northern region separately.

In addition, the effect modifications of provincial-level characteristics, including gross domestic product (GDP) per capita, illiterate rate, proportion of the elderly, temperature, and so on, were also explored by fitting meta-regression.

We performed multiple sensitivity analyses to validate the robustness of the main findings, including changing the df of time trend (2–4 df per year), temperature (2–4 df), and relative humidity (2–4 df). Additionally, the weekly average concentration of air pollution was replaced with the weekly maximum daily average concentration. And the offset term of population size covered by sentinel hospitals was replaced by the provincial total population or the number of hospital outpatients. Moreover, two-pollutant models were constructed to test the independent impact of air pollution on ILI. Finally, we pooled the effect estimates after excluding one province each time to test whether the main findings were influenced by one province.

Role of funders

The funders had no role in the study design, data collection, data analysis, data interpretation. JY, LF and QL had full access to study data, and were responsible for writing of the manuscript and for the decision to submit it.

Results

Table 1 presents summary statistics of weekly numbers of ILI cases per 100,000 residents, air pollution, and meteorological variables in 30 Chinese provinces, from 2015 to 2019. This study involved 26, 004, 853 ILI cases and 777, 223, 877 hospital outpatients (Table S2). The nationwide weekly average was 332 ILI cases per 100,000 residents, ranging from 87 per 100,000 in Ningxia Province to 769 per 100,000 in Beijing. Generally, eastern and southern China faced a higher incidence of ILI than other regions (Fig. 1), but the air pollution level was higher in the northern region. The weather in the low latitude regions like southern and eastern were warmer and more humid. And the Spearman's correlation between air pollution and meteorology is presented in Fig. S3.

Fig. 2 demonstrates monthly distribution of ILI cases in 30 provinces. Generally, the incidence of ILI showed

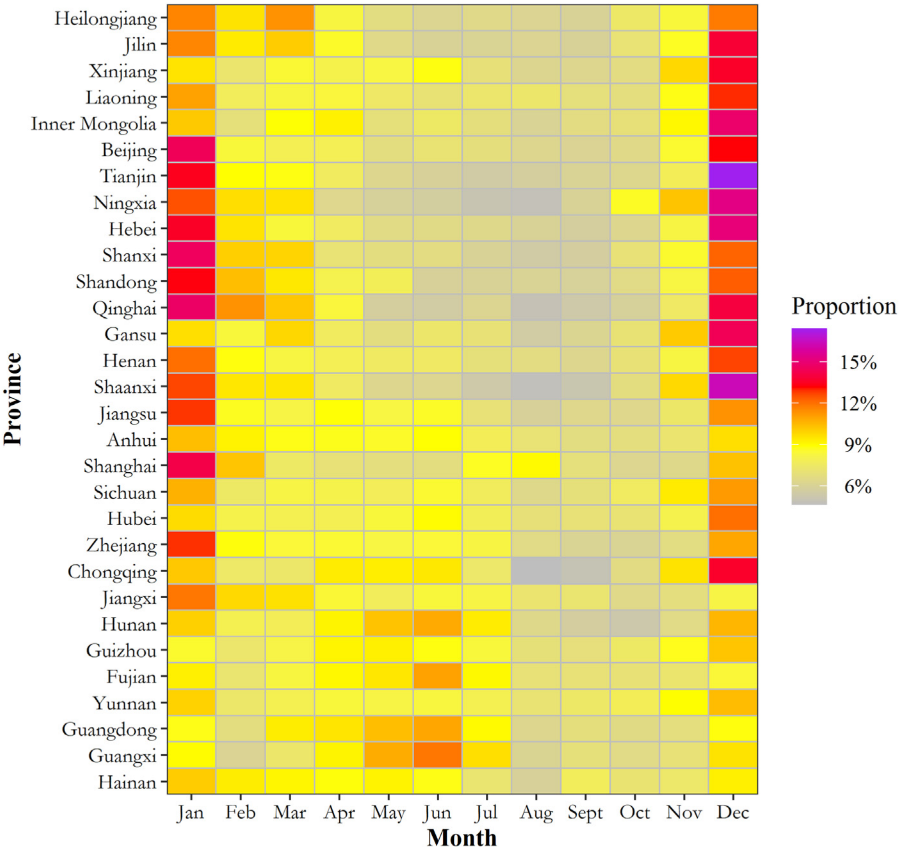

Fig. 2: Monthly distribution of influenza-like illness per 1000 outpatients. Provinces were sorted by latitude from high to low.

significant seasonal variation, which was peaked in the winter, especially in the high latitude regions. However, some provinces in the low latitude regions like southern China had a second peak of ILI in late spring and early summer.

Fig. 3 presents the effect estimation of air pollution on ILI in different lag periods. Overall, we observed significantly positive associations between ILI and all major air pollutants studied, except for O_3. The lag structure varied across air pollutants: positive effects of $PM_{2.5}$, PM_{10} and CO were generally only observed in the current week, with harvesting effects existed in lagged periods; whereas the impact of SO_2, NO_2, and O_3 demonstrated a delayed effect, especially for O_3, which could persist for three weeks. Moreover, the models using concentrations of $PM_{2.5}$, PM_{10}, SO_2, NO_2, and CO at the current week (lag 0) produced the lowest AIC, while O_3 fitted the models best at lag 0–2 week. Thus, our subsequent results for each air pollutant were all based on their optimal lag time. Specifically, an IQR increase of $PM_{2.5}$ at lag 0, PM_{10} at lag 0, SO_2 at lag 0, NO_2 at lag 0, CO at lag 0, and O_3 at lag 0–2 was associated with 3.08% (95% CI: 1.91%, 4.27%), 3.00% (95% CI: 1.86%, 4.16%), 6.46% (95% CI: 4.71%, 8.25%), 7.21% (95% CI: 5.73%, 8.71%), 4.37% (95% CI: 3.05%, 5.70%), and –9.26% (95% CI: –11.32%, –7.14%) change of ILI at the national level, respectively (Table S3). And similar tendency was observed when calculating the effect estimates of air pollution on ILI by per 10 μg/m^3 (1 mg/m^3 for CO) (Table S4).

Fig. 4 displays the seasonal and regional differences in the impact of air pollutants on ILI. Compared with warm season, higher effects of all the pollutants were found in cold season. From regional perspective, people living in the eastern and central regions in China were affected more severely by air pollution, while the highest effects of CO and O_3 were detected in the northwest region.

Table 2 shows the effect modifications of provincial-level characteristics on the impact of air pollution on ILI. People living in low-latitude provinces with warmer and more humid meteorological conditions were more sensitive to PM and NO_2. In addition, the provinces with a higher proportion of the young (below 14 years of age) and the elderly (above 64 years of age) tend to be suffered more from air pollution, although not statistically significant. The impact of PM_{10} was stronger in the provinces with higher GDP per capita, while the effects

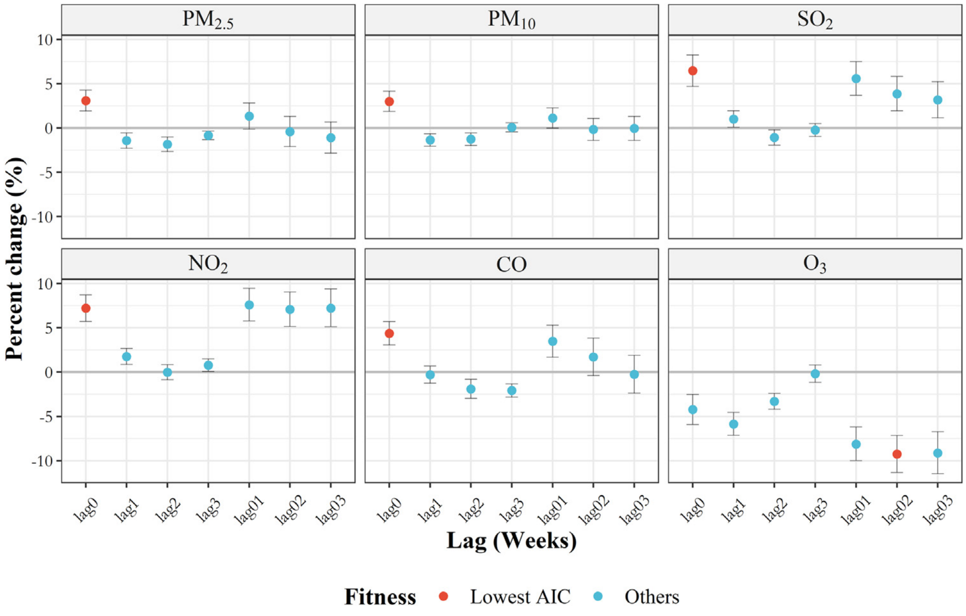

Fig. 3: Estimated percentage changes (95% CI) of influenza-like illness per IQR increase of weekly average concentrations of air pollutants. The dots along with the error bars indicate point estimates with their 95% CIs; and red dots present the effect estimates of optimal lag for air pollutants, which are selected by the performance of the model fitness (the lower the AIC value, the better the model fitness). IQR denotes inter-quartile range.

of $PM_{2.5}$, PM_{10}, and SO_2 were greater in the regions with larger population.

Sensitivity analyses were conducted to validate the robustness of our main findings. With additional adjustment for another pollutant, the associations of ILI with each pollutant generally remained statistically significant after adjusting for other pollutants (Table 3). However, effect estimates of pollutants except O_3 became insignificant or negative after controlling for NO_2, and were similar for $PM_{2.5}$ after adjusting for SO_2 or CO. The percentage change in ILI associated with air pollution did not vary substantially when changing the df of time trend, temperature, and relative humidity (Table S5). When using weekly maximum air pollution concentrations, we found very similar effects of air pollutants (Table S6). And our main results were generally robust when changing the offset term of the main model (Table S7). In addition, the pooled effect estimates were similar when we excluded one province each time (Fig. S4).

Discussion

In this nationwide study, we systematically evaluated the impact of air pollutants on ILI in 30 Chinese provinces, covering 26, 004, 853 ILI cases. We found statistically significant and positive relationships of ILI with $PM_{2.5}$, PM_{10}, SO_2, NO_2, and CO, but a negative association for O_3. The effects of $PM_{2.5}$, PM_{10}, and CO were acute but effects of NO_2, SO_2, and O_3 lasted from one to three weeks. The relationships of air pollutants with ILI varied greatly by season and socioeconomic characteristics. Our findings may be useful for understanding impact of air pollution on respiratory infectious disease and for identifying prevention strategies against ILI.

The present study demonstrated statistically significant associations between air pollutants and ILI in 30 Chinese provinces, which is in line with previous studies (Table S8).[12–15] The mechanisms underlying the association between air pollution and ILI incidence are less elucidated. One possible explanation may be that air pollution exposure could induce oxidative stress, impair the activation of macrophage dependent invasive pathogens, and aggravate inflammation.[27] These, in turn, could damage respiratory system and reduce the resistance to viral and bacterial infections. In addition, PM in smaller diameters that could be suspended in the air for a longer period of time has been suggested to be a vector for the transport of different respiratory pathogens.[28] Thus, high PM concentrations could enhance the probability for the inhalation of these pathogens and promote respiratory infection development, such as ILI, rhinoviruses and adenoviruses. Interestingly, negative association was found between O_3 and ILI in the present study, which is consistent with several previous investigations. For instance, Su et al. (2019) reported a negative effect of O_3 on ILI in the city of Jinan, China,[12] and Ali et al. (2018) found that O_3 was associated with reduced transmissibility of influenza virus in Hong Kong, China.[29] Jakab and colleagues found that exposure

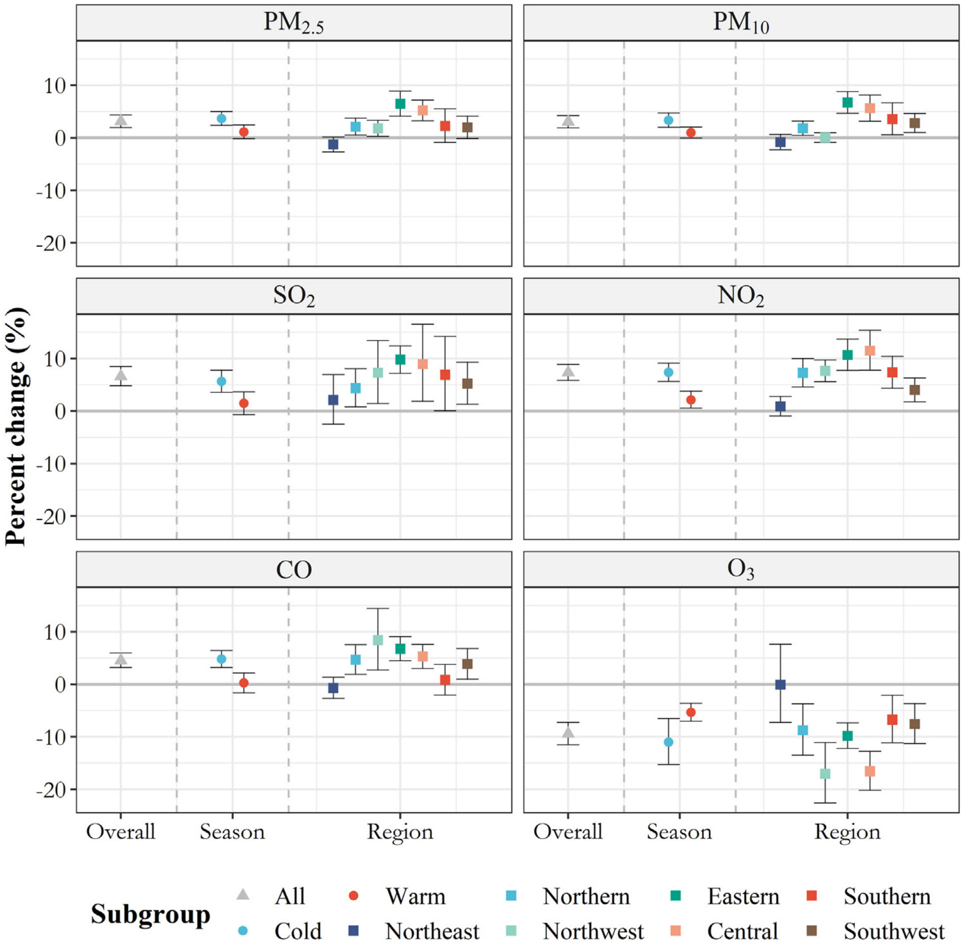

Fig. 4: Seasonal and regional difference in the impact of air pollutants on influenza-like illness. The dots along with the error bars indicate point estimates with their 95% CIs.

to O_3 could alleviate the severity of influenza among mice with less infection transmission and reduced pulmonary syndrome.[30] However, other studies reported nonsignificant or positive association between O_3 and ILI.[31,32] The discrepancies might be related to the different levels of O_3 and duration of the exposure.

The lag structure of the association between air pollution and ILI can provide crucial evidence on the development of surveillance system for the control and prevention of influenza. We found that the impact of air pollution on the risk of ILI were generally limited to one week, which is broadly in concordant with previous findings and could be explained by the incubation period of influenza virus (ranging from one to four days).[8,12,15]

Our study also found that the effects of air pollutants on ILI were stronger in cold season than in hot season, which is in accordance with previous study.[14] However, the exact underlying mechanisms of higher risk of air pollutants on ILI during cold season are not entirely articulated. Prolonged exposure to low temperature and low humidity during cold season may induce desiccation of nasal mucosa, cause epithelial damage and reduce mucociliary clearance capacity in the respiratory tract, which could play an important role in aggravating the vulnerability of the host to respiratory disease,[33–35] such as ILI, influenza, and pneumonia. In addition, cold weather and low humidity during cold season could increase transmission efficiency of the respiratory infection by extending the survivability of virus and bacteria.[33] Experimental evidence suggested that viral transmission was more frequent at 5 °C than at 30 °C.[36] However, further studies are still warranted before a clearer inference can be obtained.

Previous investigations have estimated modification effects of city- or provincial-level characteristics on the relationships between air pollutants and health,[37–40] but the evidence on ILI is limited. In the present research, we found that the relationships between air pollutants and ILI were modified by GDP per capita, population,

Effect modifier	IQR	Percentage change of the effect of air pollutants (%)					
		$PM_{2.5}$	PM_{10}	SO_2	NO_2	CO	O_3
GDP per capita[a]	23944.75	0.78 (−0.15,1.72)	**0.98 (0.09,1.88)**	0.19 (−1.20,1.60)	1.08 (−0.04,2.20)	0.10 (−0.95,1.17)	−0.87 (−2.74,1.03)
Population[b]	3651.25	**1.56 (0.19,2.94)**	**2.11 (0.88,3.36)**	**2.42 (0.48,4.41)**	1.37 (−0.35,3.13)	0.64 (−0.96,2.25)	−1.66 (−4.46,1.23)
Unemployment (%)	0.95	−0.58 (−2.26,1.13)	−0.54 (−2.18,1.12)	0.94 (−1.44,3.39)	−0.70 (−2.74,1.38)	0.12 (−1.73,2.01)	0.62 (−2.80,4.16)
Illiterate (%)	0.03	0.99 (−0.45,2.46)	0.18 (−1.23,1.61)	1.14 (−0.94,3.27)	−0.16 (−1.89,1.61)	1.35 (−0.30,3.03)	−1.21 (−4.12,1.79)
Hospital beds[c]	11.05	−0.51 (−2.22,1.23)	−1.15 (−2.77,0.50)	0.28 (−2.18,2.79)	−0.96 (−3.03,1.16)	0.65 (−1.29,2.62)	−2.28 (−5.49,1.05)
Age (%)							
0–14	0.06	0.49 (−1.18,2.19)	0.24 (−1.40,1.90)	0.35 (−2.06,2.83)	0.40 (−1.67,2.52)	0.81 (−1.07,2.72)	−1.18 (−4.48,2.23)
15–64	0.06	−1.42 (−3.53,0.74)	−1.36 (−3.45,0.76)	−1.80 (−4.93,1.43)	−0.73 (−3.42,2.04)	−1.57 (−3.89,0.80)	3.20 (−1.25,7.84)
>64	0.03	0.65 (−0.95,2.27)	1.02 (−0.52,2.57)	1.22 (−1.03,3.51)	0.06 (−1.89,2.06)	0.34 (−1.48,2.19)	−1.23 (−4.30,1.93)
Weather							
Temperature (°C)	7.64	**1.78 (0.13,3.46)**	**3.02 (1.64,4.41)**	1.69 (−0.85,4.29)	**2.20 (0.19,4.25)**	0.01 (−2.01,2.07)	−1.06 (−4.47,2.46)
Relative humidity (%)	18.53	1.76 (−0.21,3.77)	**3.26 (1.62,4.93)**	2.06 (−0.82,5.02)	1.37 (−1.15,3.95)	−0.35 (−2.70,2.05)	1.09 (−3.31,5.69)
Geography							
Longitude (°)	10.19	0.21 (−1.24,1.68)	0.89 (−0.48,2.27)	0.19 (−1.88,2.31)	−0.02 (−1.86,1.85)	−1.38 (−3.12,0.38)	2.95 (−0.16,6.15)
Latitude (°)	9.49	−1.50 (−2.99,0.01)	**−2.30 (−3.59,−0.98)**	−1.84 (−4.02,0.39)	−1.58 (−3.45,0.33)	−0.15 (−1.97,1.71)	0.76 (−2.43,4.05)

Note. IQR: inter-quartile range. The bolded estimates correspond to P-value <0.05. [a]GDP: Gross domestic product, measured as 1000 Chinese Yuan. [b]Ten thousand. [c]Hospital beds per 10,000 residents.

Table 2: **Estimated percentage change of the association between air pollution and influenza-like illness with per IQR increase in provincial-level predictors.**

	$PM_{2.5}$	PM_{10}	SO_2	NO_2	CO	O_3
Not adjusted	**3.08 (1.91,4.27)**	**3.00 (1.86,4.16)**	**6.46 (4.71,8.25)**	**7.21 (5.73,8.71)**	**4.37 (3.05,5.70)**	**−9.26 (−11.32,−7.14)**
Adjusted for $PM_{2.5}$	–	–	**5.43 (3.65,7.25)**	**8.80 (7.33,10.28)**	**3.92 (2.46,5.40)**	**−9.58 (−11.69,−7.42)**
Adjusted for PM_{10}	–	–	**5.07 (3.34,6.84)**	**8.06 (6.54,9.59)**	**3.27 (1.80,4.75)**	**−9.34 (−11.40,−7.24)**
Adjusted for SO_2	1.06 (−0.13,2.26)	**1.29 (0.30,2.29)**	–	**7.16 (5.47,8.87)**	**2.52 (1.27,3.79)**	**−7.96 (−9.72,−6.17)**
Adjusted for NO_2	−1.81 (−2.84,−0.77)	−0.96 (−1.66,−0.26)	−0.22 (−1.60,1.17)	–	−0.93 (−2.23,0.40)	**−6.88 (−8.51,−5.21)**
Adjusted for CO	0.56 (−0.68,1.82)	**1.33 (0.27,2.40)**	**4.19 (2.48,5.92)**	**8.02 (6.40,9.67)**	–	**−8.84 (−10.77,−6.86)**
Adjusted for O_3	**3.37 (2.16,4.60)**	**3.09 (1.89,4.31)**	**5.82 (4.24,7.42)**	**6.61 (5.24,8.00)**	**4.26 (3.06,5.49)**	–

The bolded estimates correspond to P-value <0.05.

Table 3: **Estimated percentage change of the associations between air pollutants and influenza-like illness in the two-pollutant model.**

proportion of population aged 65 or above, temperature, humidity and latitude. The regions with high GDP per capita and large population are generally the hotspots for air pollution, and have high population density and rapid population movement, which could facilitate the transmission of respiratory viral and bacterial infections. This phenomenon is further confirmed by the finding of stronger effects of air pollutants in eastern and central regions in China that have high population density and GDP per capita.[41] With weak immune system and higher prevalence of comorbidity, the elderly with respiratory tract infections, pneumonia or influenza are more likely to be affected by air pollution.[38,42,43] Therefore, it is reasonable that higher proportion of the elderly could contribute to the vulnerability of local population to air pollution. The worsen effect of air pollution in the regions with high temperature and low latitude may be partly explained by personal exposure patterns, i.e., people who live in warmer areas typically spend more time outdoors, and are more prone to using natural ventilation in the buildings,[38,42] favoring ambient air pollution effect.

This study has important strengths and public health implications. Firstly, with rapidly economic development and urbanization, air pollution has posed a major health risk to residents in China.[44] Our findings add to the multi-center evidence about the impact of air pollutants on ILI in China. The persistent control measures on reducing air pollution levels, including PM_{10}, $PM_{2.5}$, NO_2 and SO_2, could be beneficial to alleviating air pollution exposure opportunity and thereby lowering the transmission of influenza and other respiratory viruses in China. Community-based protective actions should target the vulnerable population, particularly the elderly, during the period of polluted days. In addition, given the low vaccination rate (9.4%) in the general population of China,[45] the present results underscore urgent need to strengthen the awareness of raising the vaccination rate among vulnerable populations.

Several limitations should be acknowledged in the present study. Firstly, the air pollution data were derived from stationed outdoor monitoring sites and the indoor exposure was not measured, which may lead to measurement error. Secondly, the ILI cases might be underreported, because not every patient visited the sentinel hospitals and those with mild influenza symptoms tended to go to local hospitals or stay at home. But this bias is likely to be random and have non-differential impacts on the modelling outcomes. Thirdly, due to limited data, some climatic factors, such as solar radiation and absolute humidity, were not included in the time-series model. As the association between air pollution and ILI could be modified by socioeconomic status, caution needs to be taken when generalizing our findings to other regions with different population structure and socioeconomic profiles. In addition, we did not further explore the potential variations in the effect of air pollution on influenza-like diseases within each province due to data unavailability. Future studies using more granular data (such as at city- or county-level) are warranted. Finally, the ecological design of this study refrains us from making casual inference on the association between air pollution and ILI. Further laboratory research is in great need to articulate possible mechanisms underlying the association between air pollution and ILI.

In conclusion, we found that most air pollutants (i.e., PM_{10}, $PM_{2.5}$, NO_2, CO and SO_2) increased the risk of ILI in China. The associations between air pollutants and ILI varied greatly by season and socioeconomic characteristics, including GDP per capita, proportion of the elderly and weather conditions. These findings may have important implications for the development of effective public health interventions and comprehensive warning systems on air pollution and influenza.

Contributors

JY, LF and QL conceived and initiated the study. JY, ZY, LQ, LF and QL collected the data. JY and ZY verified the underlying data, performed statistical analysis and drafted the manuscript. QL, ML, LF, QL, DL, XL CQO, ST and QS revised the manuscript. All authors read and approved the final manuscript.

Data sharing statement

The data that support this work are available from the corresponding author upon reasonable request.

Declaration of interests

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ebiom.2022.104421.

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