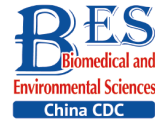


Letter to the Editor



Association and Prediction of Influenza-like Illness with Meteorological Factors in Mississippi, USA

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Seasonal influenza viruses have caused significant morbidity and mortality worldwide. Especially in the United States, influenza viruses spread during the winter, leading to a sharp increase in acute respiratory infections and hospitalizations. Influenza affects approximately 5% to 20% of the population each season^[1]. Influenza is a climate-related acute respiratory infectious disease with a seasonal trend. In temperate regions, influenza infection usually has an obvious annual peak, which mainly occurs in winter months. However, the seasonal patterns in tropical and subtropical regions seem to be more complex. In the tropics, influenza activity can occur throughout the year or as multiple epidemics, sometimes varying from year-to-year^[2].

Several meteorological factors are responsible for the seasonal outbreak of influenza. These include temperature, relative humidity, pressure, wind speed, precipitation, and other factors. The incidence and mortality of influenza rise with the reduction of temperature^[3]. The exposure-lag-response relationships between influenza virus activity and environmental factors, such as temperature, are not completely defined. Available evidence is often based on traditional statistical models, which do not reveal the cumulative or lag effects of environmental factors on influenza. Moreover, despite the increasing number of population-based estimates of influenza-associated excess deaths and hospitalizations, few studies of influenza-like illness (ILI) have been published. To address this shortcoming, we used distributed lagged nonlinear models (DLNMs) to explore the influence of meteorological factors on ILI.

The study site is the state of Mississippi in the southern USA. The state is located in a humid subtropical climate region, with an annual average temperature ranging from 17 °C in the north to 20 °C along the coast. Normal precipitation ranges from

approximately 1,270 to 1,650 mm, and is fairly evenly spread throughout the year. ILI epidemics of various magnitudes have plagued Mississippi annually for decades. The study utilized weekly data on ILI incidence from the United States Outpatient Influenza-like Illness Surveillance Network (ILINet). The data were from the first week of 2011 to week 29 of 2020. ILI is defined as “fever (temperature of 100 °F (37.8 °C) or greater) and a cough and/or a sore throat without a known cause other than influenza” (<https://www.cdc.gov/flu/weekly/overview.htm> accessed on November 24, 2021). Data of weekly meteorological variables, including mean temperature, mean wind speed, accumulated precipitation, mean atmospheric pressure, and mean relative humidity, were obtained from the National Oceanic and Atmospheric Administration. We also downloaded data of particulate matter $\leq 2.5 \mu\text{m}$ in diameter ($\text{PM}_{2.5}$) from the US Environmental Protection Agency. The data were selected based on previous studies about influenza and other respiratory diseases.

DLNMs were employed to determine the correlation between meteorological factors and ILI incidence. The Poisson regression was constructed with a quasi-Poisson function that allowed the excess dispersion in the weekly number of ILI cases to combine DLNMs. The weekly ILI incidence was calculated as:

$$E(Y_t) = \alpha + cb.x + \sum ns(\text{meteorological factors}, df) + ns(\text{PM}_{2.5}, df) + ns(\text{time}, df) + \text{factor}(\text{holiday})$$

where $E(Y_t)$ is the weekly ILI incidence; t is the week during the study period from 2011 through 2020; α is the intercept; cb represents the cross-basis matrix in the distributed lag models; x is the interest study factor; $ns()$ is the natural cubic spline; df is the

degree of freedom; time represents seasonality and long term trends with a degree of freedom of 7/year; and holiday refers to a binary variable of public holidays used to control the impact of public holidays. If one of the factors was studied, the remaining five variables were adjusted as covariates. Based on the potential lag effect and influenza incubation period reported in previous studies, the maximum time lag was selected as 4 weeks. To select the best model and evaluate the robustness of the model, df of each factor was determined based on previous studies and combined with Akaike Information Criterion for quasi-Poisson (Q-AIC). The optimal df of each factor was 3, except the temperature (df = 4). The “dlnm” package in R3.6.0 was used to create the DLNMs

The seasonal autoregressive integrated moving average with exogenous variables (SARIMAX) model is an extension of SARIMA model. The input series includes covariates, such as meteorological factors. In the resulting SARIMAX (p, d, q) (P, D, Q)_s (X), p, d, and q denote the order of autoregression, order of difference, and order of moving average, respectively; P, D, and Q denote the order of seasonal autoregression, order of difference, and order of moving average, respectively; and s is the specific value of cycle; s is the cycle of American influenza (52 weeks); and X is the vector of external variables. The data in the training set, from the first week of 2011 to week 52 of 2018, were used to construct the SARIMA model. The data in the validation set from the first week of 2019 to week 29 of 2020 were used to test the effect of model. The autocorrelation function (ACF) and partial autocorrelation function (PACF) used to estimate the model residuals were tested by the Ljung-Box Q test. The minimum Bayesian information criterion (BIC) was taken as the optimal SARIMAX model. The “TSA” package in R3.6.0 was used to create the SARIMAX model.

From the first week of 2011 to week 29 of 2020, a total of 280, 871 ILI cases were reported in Mississippi. The weekly ILI incidence fluctuated from 3.35 to 81.23 per 100,000 population (Supplementary Table S1, available in www.besjournal.com). ILI occurred throughout the year. The peaks of incidence were in winter months, but with temporal variations in the peaks among different years. The temperature and PM_{2.5} were negatively correlated with ILI incidence in Mississippi. Wind speed and pressure were positively correlated with ILI incidence. Temperature very strongly correlated with ILI incidence, and pressure

moderately strongly correlated. Correlation of the other factors was weakly or absent (Supplementary Table S2, Supplementary Figure S1, available in www.besjournal.com).

The DLNM analysis revealed that the duration of the effect of temperature and pressure on the ILI incidence was 4 weeks. The median temperature and pressure were 18.97 °C and 100.5 kpa, respectively, adjusted for wind speed, precipitation, humidity, and PM_{2.5}. The relationship between temperature and pressure and ILI incidence at different percentiles was analyzed using percentage points set as the 1st, 10th, 90th, and 99th percentiles.

The relative risk (RR) of ILI incidence was elevated as temperature decreased. RR was highest (1.60, 95% CI: 1.37–1.86) when the temperature decreased to 0.5 °C at 0-week lag (Figure 1A). The cumulative exposure of temperature from 0 to 4 weeks indicated an increased RR with decreased temperature. RR was highest when the temperature dropped to 0.5 °C (4.63, 95% CI: 3.63–5.90; Figure 1C). As shown in Figure 2, lower temperatures (P₁ = 2.85 °C, P₁₀ = 8.62 °C) could increase the risk of ILI incidence, while higher temperatures (P₉₀ = 27.52 °C, P₉₉ = 29.21 °C) could increase the risk of ILI incidence for lag 0 to 3 weeks (Supplementary Table S3, available in www.besjournal.com). Consistent with our findings, low temperature is reportedly a risk factor for influenza at different lag periods^[4]. Low temperature can promote the spread of influenza by prolonging the survival of the virus, increasing crowd contact, and affecting host immunity^[5]. In addition, experiments performed with guinea pigs at different temperatures demonstrated that low temperature enhanced the transmission efficiency of influenza virus in the air. Breathing cold air could slow mucociliary clearance and thereby encourage the transmission of influenza virus in the respiratory tract. Moreover, low temperature may make the host more susceptible to influenza virus infection or prolong the course of disease after infection^[6].

At 1–4 weeks lag, pressure had a positive effect on ILI incidence. The RR was highest in the second week (1.66, 95% CI: 1.36–2.02; Figure 1B). Data of the cumulative exposure to pressure from 0 to 4 weeks showed that the RR increased with the increment of pressure. Pressure > 100.5 kpa increased the risk of ILI incidence. RR was highest when the pressure was 102.0 kpa (6.64, 95% CI: 3.74–11.80; Figure 1D). Lower pressures (P₁ = 99.92 kpa, P₁₀ = 100.11 kpa) did not influence ILI incidence, while general high pressure (P₉₀ = 101.06 kpa) could increase the risk of ILI incidence

for lag 1 to 2 weeks (Figure 2). Extremely high pressure ($P_{99} = 101.42$ kpa) could increase the risk of ILI incidence for lag 1 to 4 weeks (Supplementary Table S4, available in www.besjournal.com). Very few studies have examined the effects of atmospheric pressure on influenza. Some studies found that high pressure is associated with influenza. Pressure is an important determinant of weather. High pressure during winter can result in contraction of local blood vessels in the nasal cavity and small cracks in the mucous membrane. These changes can allow respiratory viruses to easily invade the body. In addition, because the inverse temperature layer of the atmosphere is relatively stable, air pollutants do not easily diffuse and self-purify. This favors the replication and spread of viruses, resulting in numerous viruses in the atmosphere^[7]. High pressure often means a sunny day. The resulting increase in outdoor activities increases the risk of virus infection^[8].

The optimal SARIMA (1, 0, 0) (1, 1, 0)₅₂ structured on our previous research results were used to build the SARIMAX models with meteorological factors as covariates^[9]. The cross-correlation function was used to investigate relationships of meteorological factors and PM_{2.5} with ILI incidence. All the variables, except precipitation and relative humidity, were significantly correlated with ILI incidence (Supplementary Figure S2, available in www.besjournal.com). These findings were consistent with the preceding Spearman's correlation analysis results. A total of four SARIMAX model parameters with covariates were significant,

with decreased AIC values. The temperature lagged 1-week and 4-week ($\beta = -0.276$, $P = 0.008$; $\beta = 0.216$, $P = 0.038$), wind speed lagged 1-week ($\beta = -0.672$, $P = 0.013$), and pressure lagged 4-week ($\beta = -1.802$, $P = 0.002$) influenced ILI incidence (Table 1). SARIMAX (1, 0, 0) (1, 1, 0)₅₂ with temperature at lag 1-week, wind speed at lag 0-week, and pressure at lag 4-week was the optimal model with the lowest AIC and BIC values. The SARIMAX model displayed a good fitting effect on the prediction of ILI incidence (Supplementary Table S5, Supplementary Figure S3, available in www.besjournal.com).

Wind speed was also included in the model as a covariate, in addition to the temperature and pressure variables, which were most strongly correlated with ILI. Wind speed is a common meteorological variable. However, its correlation with disease has not been studied extensively. We observed that the *RR* of ILI incidence increased significantly with increased wind speed at the 0-week lag. However, the incidence gradually decreased at wind speeds above 4 m/s. Wind can resuspend bacteria from soil or plant surfaces^[10]. This increases the chances that the influenza virus will be redrawn into the respiratory tract. Based on common resuspension, higher wind speeds may dilute local bacterial concentrations^[7,10], thus reducing the infection of influenza.

DLNMs and a 10-year time-series with covariates were respectively adopted in the correlation analysis and prediction. This enabled the simultaneous evaluation of the real-time and delayed effect of

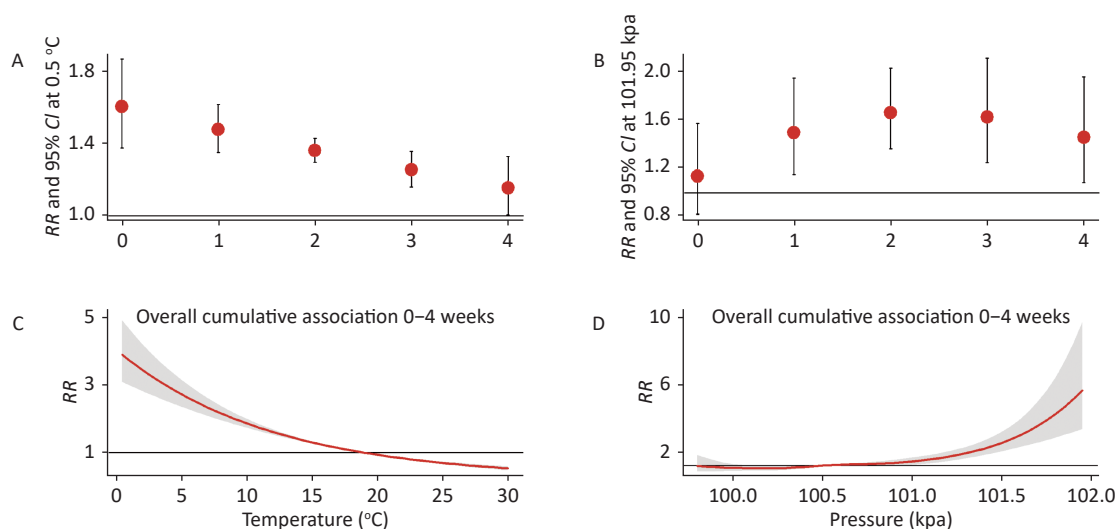


Figure 1. Associations of influenza-like illness (ILI) incidence with temperature and pressure. Lag-response associations of ILI incidence with temperature (A) and pressure (B). Cumulative associations of ILI incidence with temperature (C) and pressure (D).

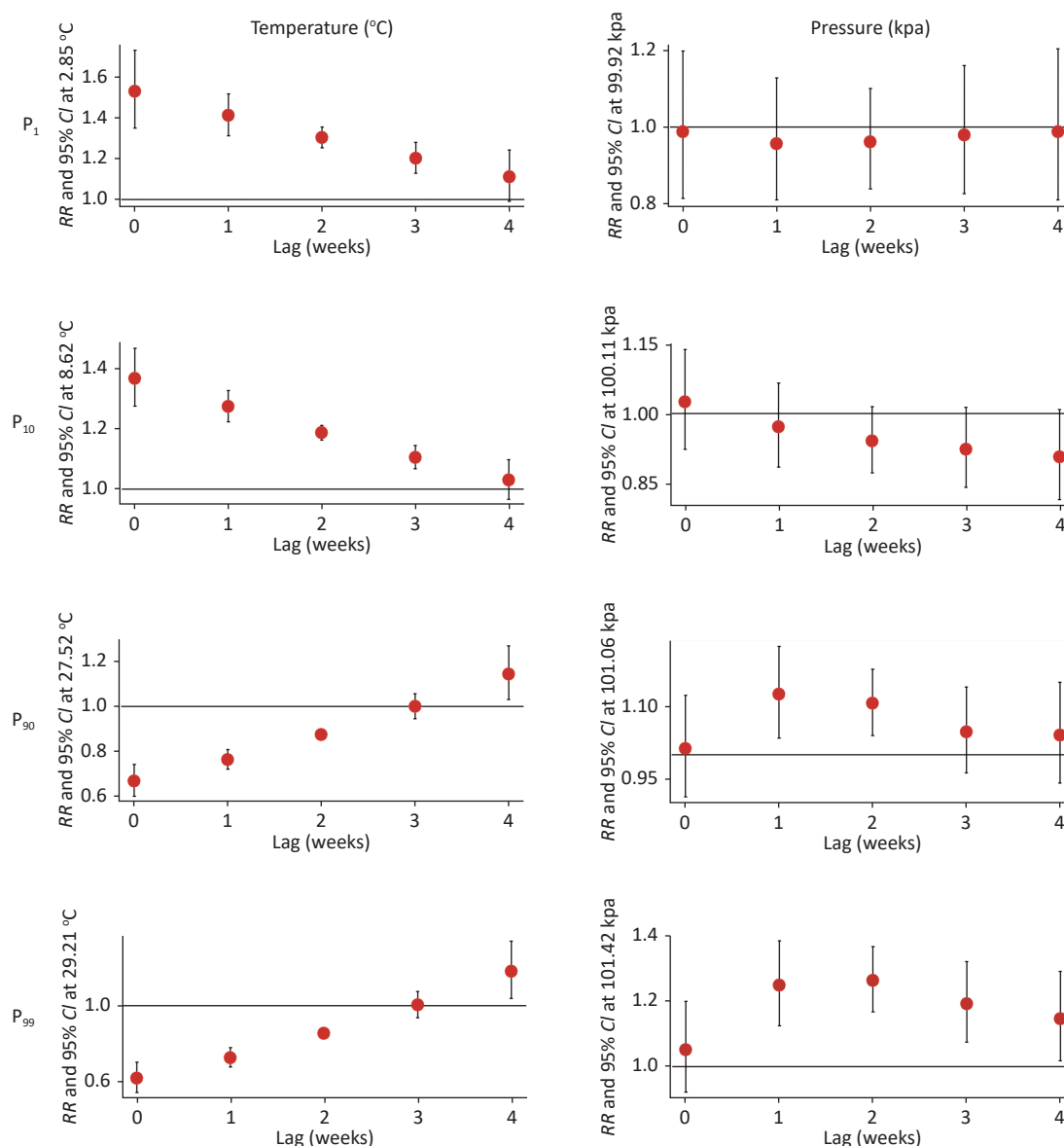


Figure 2. Effects of temperature (left) and pressure (right) on influenza-like illness (ILI) incidence estimated at the extreme values of P_1 , P_{10} , P_{90} , and P_{99} .

meteorological variation by capturing the true incidence of ILI incidence as much as possible. Nonetheless, several limitations need to be acknowledged. First, only the $PM_{2.5}$ air pollution factor was considered when controlling for confounding factors. In subsequent studies, more air pollution factors should be included in the model and more mixed effects of meteorological factors and air pollution factors should be assessed. Second, the study was performed in a single subtropical city. The findings may not be generalizable to the regions with different climatic conditions.

In conclusion, lower temperatures and higher

pressures were risk factors of ILI incidence in Mississippi. Greater attention should be paid to ILI incidence during periods of cold and in the winter when the air pressure is high. These findings will be helpful for establishing an early warning system, strengthening active prevention and intervention of disease risk factors, and reducing the burden of disease in society.

Declarations of Interest None

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Table 1. SARIMAX models of ILI incidence with different meteorological factors and PM_{2.5}

Model	Meteorological factors					AIC	BIC
	Variables	Lag	β	SE (β)	P		
SARIMAX (1, 0, 0) (1, 1, 0) ₅₂	Temperature	0	0.042	0.105	0.688	2237.400	2252.990
SARIMAX (1, 0, 0) (1, 1, 0) ₅₂		1	-0.276	0.104	0.008*	2224.420	2240.000
SARIMAX (1, 0, 0) (1, 1, 0) ₅₂		2	0.023	0.104	0.826	2222.790	2238.360
SARIMAX (1, 0, 0) (1, 1, 0) ₅₂		3	-0.188	0.104	0.070	2214.520	2230.070
SARIMAX (1, 0, 0) (1, 1, 0) ₅₂		4	0.216	0.104	0.038*	2208.340	2223.880
SARIMAX (1, 0, 0) (1, 1, 0) ₅₂	Wind speed	0	-0.672	0.270	0.013*	2231.410	2247.000
SARIMAX (1, 0, 0) (1, 1, 0) ₅₂		1	0.057	0.272	0.835	2231.330	2246.910
SARIMAX (1, 0, 0) (1, 1, 0) ₅₂		2	-0.067	0.271	0.805	2222.780	2238.350
SARIMAX (1, 0, 0) (1, 1, 0) ₅₂		3	0.442	0.271	0.103	2215.150	2230.700
SARIMAX (1, 0, 0) (1, 1, 0) ₅₂		4	-0.361	0.275	0.189	2210.910	2226.450
SARIMAX (1, 0, 0) (1, 1, 0) ₅₂	Pressure	0	-0.059	0.594	0.921	2237.550	2253.140
SARIMAX (1, 0, 0) (1, 1, 0) ₅₂		1	0.424	0.602	0.481	2230.880	2230.880
SARIMAX (1, 0, 0) (1, 1, 0) ₅₂		2	1.101	0.589	0.062	2219.370	2234.930
SARIMAX (1, 0, 0) (1, 1, 0) ₅₂		3	-0.102	0.594	0.864	2217.760	2233.310
SARIMAX (1, 0, 0) (1, 1, 0) ₅₂		4	-1.802	0.586	0.002*	2203.300	2218.840
SARIMAX (1, 0, 0) (1, 1, 0) ₅₂	PM _{2.5}	0	0.122	0.083	0.143	2235.420	2251.010
SARIMAX (1, 0, 0) (1, 1, 0) ₅₂		1	-0.016	0.083	0.849	2231.340	2246.910
SARIMAX (1, 0, 0) (1, 1, 0) ₅₂		2	0.022	0.083	0.795	2222.770	2238.340
SARIMAX (1, 0, 0) (1, 1, 0) ₅₂		3	0.052	0.083	0.534	2217.400	2232.960
SARIMAX (1, 0, 0) (1, 1, 0) ₅₂		4	-0.103	0.083	0.214	2211.090	2226.640
SARIMAX (1, 0, 0) (1, 1, 0) ₅₂	Temperature	1	-0.195	0.109	0.074	2198.740	2225.950
		4	0.129	0.105	0.222	–	–
	Wind speed	0	-0.600	0.267	0.024*	–	–
	Pressure	4	-1.504	0.596	0.012*	–	–
SARIMAX (1, 0, 0) (1, 1, 0) ₅₂	Temperature	1	-0.211	0.109	0.049*	2198.230	2221.550
	Wind speed	0	-0.596	0.267	0.026*	–	–
	Pressure	4	-1.672	0.581	0.004*	–	–

Note. *: $P < 0.05$. AIC: Akaike Information Criterion; BIC: Bayesian information criterion.

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