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Effects and interaction of temperature and relative humidity on the trend of influenza prevalence: A multi-central study based on 30 provinces in mainland China from 2013 to 2018

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ABSTRACT

Background: Evidence is inefficient about how meteorological factors influence the trends of influenza transmission in different regions of China.

Methods: We estimated the time-varying reproduction number (R_t) of influenza and explored the impact of temperature and relative humidity on R_t using generalized additive quasi-Poisson regression models combined with the distribution lag non-linear model (DLNM). The effect of temperature and humidity interaction on R_t of influenza was explored. The multiple random-meta analysis was used to evaluate region-specific association. The excess risk (ER) index was defined to investigate the correlation between R_t and each meteorological factor with the modification of seasonal and regional characteristics.

Results: Low temperature and low relative humidity contributed to influenza epidemics on the national level, while shapes of merged cumulative effect plots were different across regions. Compared to that of median temperature, the merged RR (95%CI) of low temperature in northern and southern regions were 1.40(1.24,1.45) and 1.20 (1.14,1.27), respectively, while those of high temperature were 1.10(1.03,1.17) and 1.00 (0.95,1.04), respectively. There were negative interactions between temperature and relative humidity on national (SI = 0.59, 95%CI: 0.57–0.61), southern (SI = 0.49, 95%CI: 0.17–0.80), and northern regions (SI = 0.59, 95%CI: 0.56,0.62). In general, with the increase of the change of the two meteorological factors, the ER of R_t also gradually increased.

Conclusions: Temperature and relative humidity have an effect on the influenza epidemics in China, and there is an interaction between the two meteorological factors, but the effect of each factor is heterogeneous among regions. Meteorological factors may be considered to predict the trend of influenza epidemic.

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1. Introduction

According to the statistics of the World Health Organization (WHO), influenza results in about 650,000 deaths yearly (WHO, 2023). It is estimated that influenza infection can cause a hospital stay of 81,536,000 days across the world (Collaborators, 2019). China is undertaking a huge burden of influenza (Li et al., 2022). In 2010–2015, an annual average of 88,100 influenza-associated excess deaths were reported in China, accounting for 8.2% of respiratory deaths (Li et al., 2019).

Previous studies have shown that influenza transmission depends on appropriate temperature and relative humidity (Lowen et al., 2007), which may modulate host intrinsic, innate, and adaptive immune responses to viral infections in the respiratory tract(Moriyama et al., 2020). In addition, there are non-independent associations between meteorological factors. Some studies have identified significant interactions between temperature and relative humidity, but the effects of these interactions often vary across geological regions and influenza subtypes (Chong et al., 2020; Zhou et al., 2022).

The seasonality of influenza takes on climate-specific differences (Azziz Baumgartner et al., 2012). Meteorological factors can partly explain the seasonality of influenza, but the association of temperature or humidity with influenza may differ with regions (Park et al., 2020; Tamerius et al., 2011). Low temperature and low humidity enhance the survival and transmissibility influenza viruses, whereas high humidity in tropical and subtropical regions favor influenza outbreaks (Sooryanarain & Elankumaran, 2015). The correlation between influenza and meteorological factors in different regions should be further detailed.

However, most of the previous studies have focused on a single, rather than multiple regions or meteorological factors in China. In this study, we used the time-varying reproduction number (R_t, defined as the average number of secondary infections caused by a typical single infectious individual at time t) to characterize the time-varying transmissibility of influenza. The associations of two meteorological factors (temperature and the relative humidity) with R_t, as well as the interaction between these two meteorological factors were evaluated in 30 provinces of China by a distributed lag non-linear model (DLNM) and generalized additive model (GAM). The results were meta-analyzed in the whole nation and its southern and northern regions.

2. Methods

2.1. Data collection

Data about influenza in 2010–2018 were collected from a total of 30 provinces in China's mainland. Meteorological data between 2013 and 2018 were collected for analysis, as those before 2013 were incomplete. The Tibet Autonomous Region was excluded because of lacked meteorological information and a high rate of missing influenza-like illness (ILI) data (up to 73.08%). The 30 provinces were divided into two regions divided by the Qinling Mountains and the Huaihe River. The northern region contained Heilongjiang, Jilin, Xinjiang, Inner Mongolia, Liaoning, Beijing, Tianjin, Hebei, Shanxi, Ningxia, Qinghai, Shandong, Gansu, Henan, and Shaanxi. The southern region contained Jiangsu, Anhui, Shanghai, Hubei, Sichuan, Zhejiang, Chongqing, Jiangxi, Hunan, Guizhou, Fujian, Yunnan, Guangdong, Guangxi, and Hainan.

2.2. Influenza data

ILI was defined as acute respiratory infection with fever (body temperature higher than 38 °C), cough or sore throat. The weekly outpatients and emergency consultations due to ILI and the weekly sentinel specimens tested positive for influenza viruses in each province from 2013 to 2018 were obtained from the National Influenza Surveillance Network, which is managed by the Chinese Center for Disease Control and Prevention (CDC). Besides, the annual population size of each province in the corresponding period was collected from Chinese National Bureau of Statistics(http://www.stats.gov.cn/).

2.3. Meteorological and pollutant data

Daily meteorological parameters including ambient mean temperature (°C) and relative humidity (%) from 2013 through 2018 were obtained from the 0.25° × 0.25° resolution dataset (http://data.cma.cn/) established by the National Meteorological Information Center. During the same period, hourly average concentrations of major air pollutants, including PM2.5 (μg/m3), PM10 (μg/m3), NO2 (g/m3), SO2 (μg/m3), O3 (μg/m3), and CO (mg/m3), were obtained from the China National Environmental Monitoring Center (http://106.37.208.233:20035/) supported by 1628 air pollution monitoring stations. Daily air pollution indexes were calculated by averaging the hourly value of each meteorological variable in each monitoring station. Then we averaged daily pollution values and daily meteorological data from cities within each province to obtain provincial-level data.

2.4. Statistical analysis

We combined weekly ILI outpatient and emergency department visit rates and the proportions of influenza-positive specimens to define a weekly "proxy" incidence of influenza, referred to ILI + rates, to measure influenza activity. Then, ILI + rates were multiplied by the population size of the corresponding period in each province to obtain a time series of weekly ILI + counts. Using spline interpolation and weekly ILI + counts, the daily influenza counts were obtained. Then we used the estimate of serial interval provided by Ali ST et al.(Ali et al., 2022) to fit the value of the serial interval following a Gamma distribution, with a mean of 2.6 days and a standard deviation (SD) of 1.5 days. "EpiEstim" package was used to estimate R_t of influenza from January 8, 2013 to December 24, 2018.

The influenza epidemic trend approximately follows a quasi-Poisson distribution, while the relationship of influenza and meteorological factors is generally nonlinear and has a lag effect. We used generalized additive quasi-Poisson regression models combined with DLNM to explore the influence of meteorological factors on the R_t, with air pollutants as confounding factors. We built a "cross-basis" matrix of each meteorological factor, through the minimum Akaike information criterion for quasi-likelihood models (QAIC). The maximum lag time was set as 14 days. The formula of the model is:

$$\begin{aligned} Y_t \sim quasiPoisson(\mu_t)\ Log[E(\mu_t)] = \beta^*(Z_{t,l}) + ns\left(time_t, df = 14^*\frac{6}{year}\right) + ns(NO2_t, df = 3) \\ + ns(SO2_t, df = 3) + ns(PM10_t, df = 3) + ns(CO_t, df = 3) + ns(O3_t, df = 3) + ns(PM2.5_t, df = 3) + a \end{aligned} \tag{1}$$

where $E(\mu_t)$ denotes the R_t on Day t; β is the regression coefficient value for the effect of meteorological factors on Rt; $Z_{t,l}$ is the cross and function of the each meteorological factor (temperature and the relative humidity) level at day t and $lagl$, and the basis function is used for the function"poly"and the natural spline function with a degree of freedom of 3 is used for the lag dimension; ns is the natural spline basis function; df is the degree of freedom; $time_t$ is the day t time variable, with a degree of freedom of 14, which is used to control seasonal and long-term trends; NO2, SO2, PM10,CO,O3, and PM2.5 were taken as the confounding factors with $df = 3$ at corresponding $time_t$.

The multiple random-effect meta-analysis was used to estimate the overall (on the national level) effect of temperature and relative humidity on R_t based on the DLNM of 30 provinces. The relative risk (RR) and 95% confidence interval (95% CI) of influenza R_t was calculated, suggesting the impact of each meteorological factor.

We defined the excess risk (ER), that is, the proportion of the change of R_t to the change of each study factor explained by the corresponding factor, which can be calculated by

$$\left(e^{b^*x} - 1\right)^*100 \tag{2}$$

b refers the coefficient of each studying factor, and x refers to the changing unit size. For the study of temperature and humidity, we explored the impact of each change in temperature by 1 °C, 5 °C and 10 °C, and each change in relative humidity by 10%, 25% and 50% on the change of R_t, according to the northern and southern regions combined with seasonal factors.

Finally, we explored the interaction between temperature and relative humidity on the risk of influenza based on a GAM. The model is expressed as:

$$Log[E(\mu_t)] = \beta_1 + s_1(k, x) + strata \tag{3}$$

β_1 denotes intercept, k and x represent the meteorological factors (temperature and the relative humidity), $s_1(k, x)$ denotes the interaction between variables k and x.

The effect of the interaction between temperature and relative humidity on influenza was quantitatively explored. With the median as the standard, the meteorological factors were divided into "low" and "high". All combinations are calculated and compared to obtain RR values. Then the meta analysis was used to calculate the merged interaction of the northern, southern and overall regions.

3. Results

Fig. 1 depicts the weekly laboratory positive rates from 2010 to 2018, representing the activity intensity of influenza virus. Influenza viruses were distributed throughout the year in the southern China at low latitudes, and in some provinces in the northern region, such as Shandong, Shanxi, and Beijing. The influenza viruses were highly prevalent in winter and spring. Fig. 2 presents the total laboratory detection rate of influenza virus in China. The activity intensity of influenza virus in the southeast coastal areas of China was high, as well as the positive rate of laboratory detection. Along a line connecting the Qinling Mountain and the Huai River, the 30 provinces were divided into southern region and northern region (Fig. 3).

We analyzed the effect of temperature and relative humidity on R_t in 30 provinces using DLNM. The 3D plots showed exposure-lag-response association between meteorological factors (temperature and relative humidity) and R_t at 0–14 lag days (Figure A.1-2). For temperature, we analyzed the associations of high and low temperature with R_t at different specific lag days (Figure A.3). Besides, the relative risk contour map of meteorological factors and R_t at 0–14 lag days was plotted (Figure A. 4–5). Furthermore, we added the description about the merged effect of temperature. Fig. 4 is the forest plots of the merged effect of high and low temperature in northern and southern regions, and compared it to that of the median temperature. The merged RR (95%CI) of low temperature were 1.40(1.24,1.45) in the northern region and 1.20 (1.14,1.27) in the southern region. And the merged RR (95%CI) of high temperature were 1.10(1.03,1.17) in the northern region and 1.00 (0.95,1.04) in the southern region.

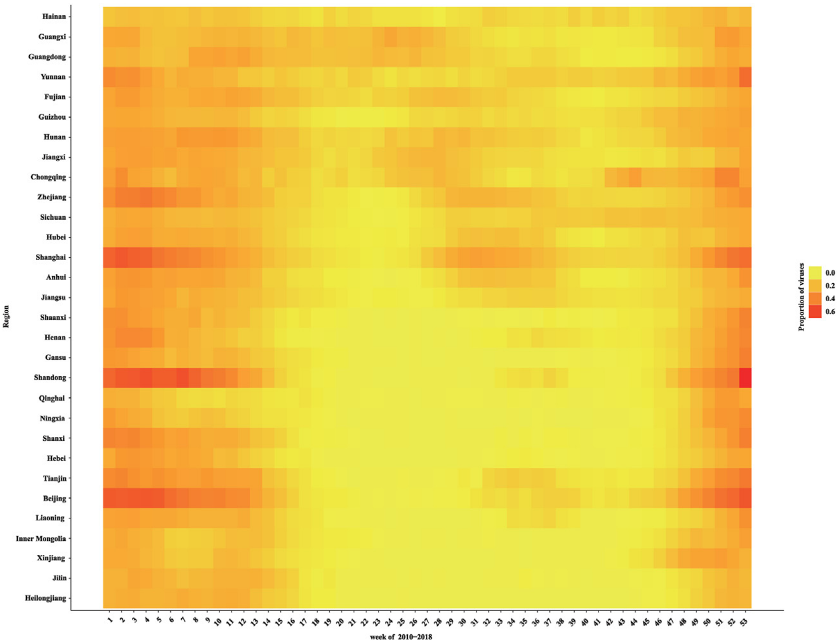

Fig. 1. Heatmap of the weekly laboratory detection positive rate from 2010 to 2018.

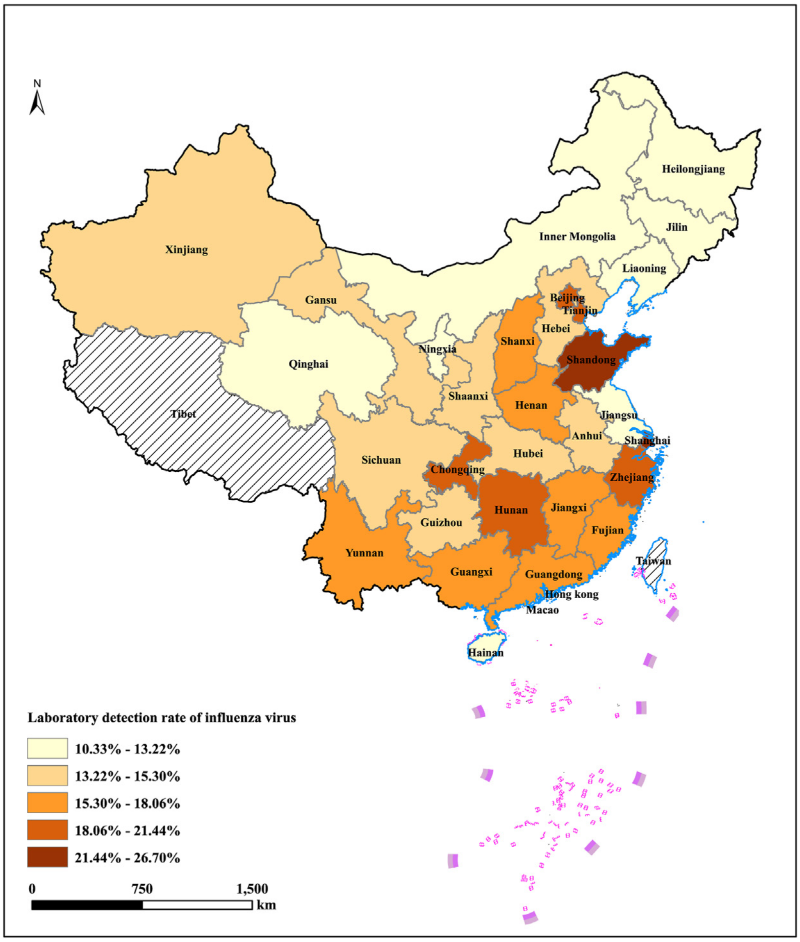

Fig. 2. The distribution of 30 provinces consisting of influenza detection rate in China.

Fig. 3. Map of China's northern and southern regions (bounded by Qinling Mountain and Huai River).

Fig. 5 illustrates the merged cumulative effects of temperature in the whole, northern and southern regions. The cumulative effect curves in the whole country and the northern region presented a two-way pattern, while that in the southern region presented a negative correlation between RR and temperature. Low temperature was related to high RR at all the three levels. Fig. 6 depicts the merged cumulative effect of relative humidity in the whole country, northern region and southern region respectively. In the southern region, the merged cumulative effect curve showed a "N" shape, and the relative humidity values with minimum RR were about 40% and 80%. While in northern region, the curve showed negative correlation with RR, and the minimum RR was located in the biggest relative humidity value. The cumulative effect curve at the national level showed two-way pattern, and the minimum risk reached when the relative humidity was 80%. Both higher and lower relative humidity was associated with higher RR.

Tables 1 and 2 lists the ER values of R_t under the influence of meteorological factors. In the sensitivity analysis, we defined ER and analyzed the impact of temperature and relative humidity in different seasons. We set the reference points of temperature at 1 °C,5 °C, and 10 °C. Both in southern and northern region, the greater the range of temperature change, the greater the impact on R_t, that is, the greater the impact on the epidemic trend of influenza. The influence of temperature change amplitude on R_t in the northern region was greater than that in the south. We explored the impact on R_t when relative humidity reached 10%, 25% and 50%, respectively. The northern region was more affected by the change of relative humidity than the southern region in all the four seasons.

Table 3 lists the meta effects of temperature and relative humidity on R_t in the whole country, southern region, and northern region. Temperature and relative humidity were divided in accordance with the median to study the effect of different meteorological factors on R_t of influenza. SI, as the interaction indicator of additive scale, showed that there was negative interaction between temperature and relative humidity in the whole country (SI = 0.59, 95%CI: 0.57–0.61), southern (SI = 0.49, 95%CI: 0.17–0.80), and northern (SI = 0.59, 95%CI: 0.56,0.62) regions. In the whole country, compared with high temperature and high relative humidity, the RR of other three situations reduced (RR = 0.83, 95%CI: 0.76–0.89 for low temperature and high relative humidity; RR = 0.84, 95%CI: 0.79–0.90 for high temperature and low relative humidity; RR = 0.78, 95%CI: 0.71–0.86 for low temperature and low relative humidity, respectively), which was as the same in northern region. However, in the southern region, only the low temperature and low relative humidity were associated with a reduction in influenza epidemic (RR = 0.97, 95%CI: 0.95–1.00). Table A.1 lists the effects of above two meteorological factors on influenza epidemic and the additive interaction indexes in 30 provinces.

4. Discussion

The impact of climate change on the transmission of infectious diseases is a research hotspot (Wang et al., 2018). In this study, we systematically elucidated the association between meteorological factors (temperature and relative humidity) and influenza activity using a six-year dataset from 30 provinces of China. In addition, the interaction between the two meteorological factors was further analyzed. Different from other studies, we used R_t, instead of the number of influenza cases, to measure influenza activity, which provided a clearer view into the correlations between meteorological factors and influenza prevalence ($R_t > 1$). In brief, our study found that low temperature and low relative humidity were related to high RR at the national level, while the effect between temperature and relative humidity was negative. In general, the greater the change of the two meteorological factors, the greater the impact on R_t.

A systematic review concluded that temperature was a significant predictor of influenza virus persistence over an environmentally relevant range (Marr et al., 2019). Studies have reported that viral particles can persist longer outside human body at a lower temperature (Lofgren et al., 2007), which might be one of the reasons for the increase of influenza transmission intensity in low-temperature regions (Du et al., 2022). This is consistent with our study for the larger R_t at a low

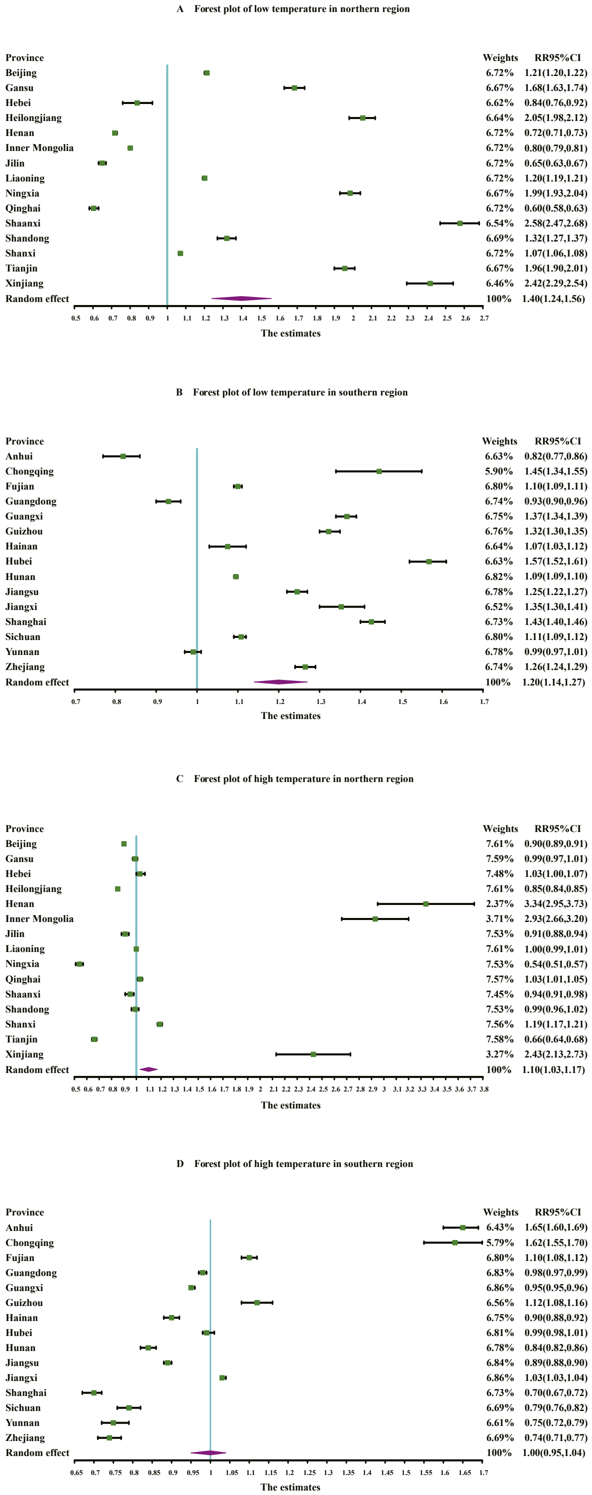

Fig. 4. Forest plots of the merged effect of high and low temperature in northern and southern region (A. low temperature in northern region B. low temperature in southern region C. high temperature in northern region D. high temperature in southern region).

temperature. In addition, the lower levels of several monocyte-derived cytokines in winter (Ter Horst et al., 2016), and the respiratory defenses inhibited by cold air, such as mucociliary clearance (Eccles, 2002), might weaken the immune function

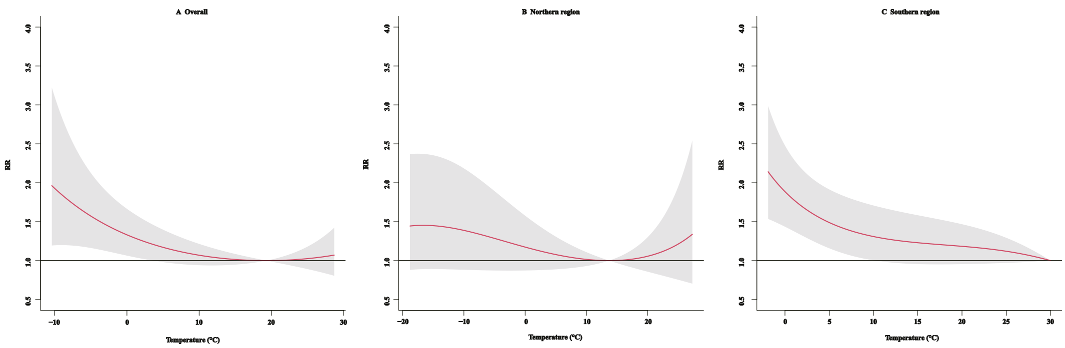

Fig. 5. Merged cumulative effect curve of temperature in the (A) national, (B) northern, and (C) southern regions.

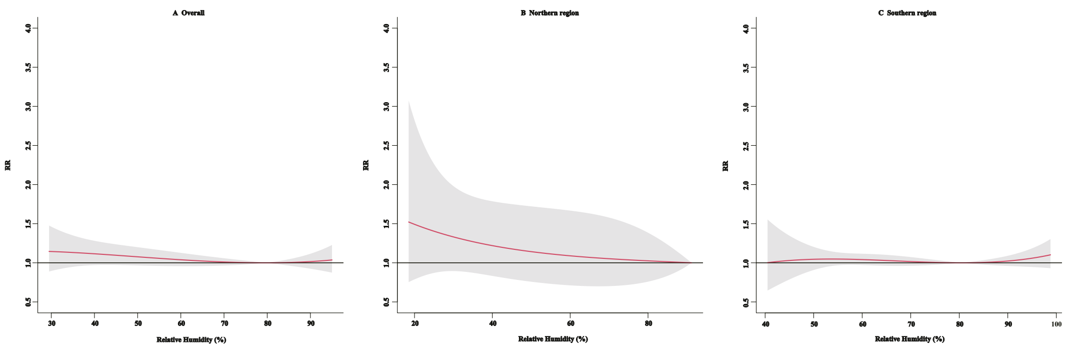

Fig. 6. Merged cumulative effect curve of relative humidity in the (A) national, (B) northern, and (C) southern regions.

and increase the susceptibility of the host. Moreover, temperature may affect influenza viruses at the molecular level. For example, Lipid ordering of virus envelope at low temperature contributes to virus stability (Polozov et al., 2008). A high temperature might have a negative effect on virus survival by affecting the molecular stability of hemagglutinin (Sooryanarain & Elankumaran, 2015). Paynter S. (Paynter, 2015) have found that a high temperature may discourage aerosol transmission of influenza virus, and our study found that the southern region had the minimum risk corresponding to the cumulative curve at the highest temperature. However, we also found a "U" shape of temperatures with transmission at the northern and whole country, which has also been reported in other studies(Lau et al., 2021; Wang et al., 2023). The large-scale infection of influenza epidemic at a high temperature might be explained by that the adaptive immune responses against influenza infection are impaired by a high temperature (Moriyama & Ichinohe, 2019). Besides, a sharp change in temperature brings about a large change in R_t, especially in the autumn of the northern region, suggesting that in the autumn of northern China, where the temperature fluctuates largely, more attention should be paid to the possibility of influenza outbreaks.

Many airborne viruses are sensitive to ambient humidity(Yang & Marr, 2012), which affects not only the stability of virus but also respiratory droplet size(Pica & Bouvier, 2012). At a low relative humidity, water in the aerosol evaporates rapidly, leading to the formation of droplet nuclei that remain in the air for a longer period of time, thereby increasing the chance of influenza transmission due to pathogen-carrying aerosol (Moriyama et al., 2020). In addition, a lower humidity slows the flow of mucus along the cilia of the epithelial-cell layer, which results in a delay in virus clearance, cilia loss on airway epithelial cells and detachment of epithelial cells, thereby weakening the first line of defense against viral infection(Neumann & Kawaoka, 2022). Our study found that the minimum risk of relative humidity in the southern region and across the country was around 80%, with a biphasic pattern in the latter that is similar to the results of in vitro studies of influenza virus in guinea pigs, ferrets and mice (Lester, 1948; Lowen et al., 2007). A study has also found that the highest relative humidity yields the highest risk of A(H3N2) infection, whereas A(H1N1) is observed at the lowest relative humidity(Zhou et al., 2022), and the discovery of A(H3N2) is consistent with that in the northern region of our study. For example, at a higher relative humidity, the RR of R_t increased, and the northern region might face a higher risk of influenza outbreak at this time. Compared with that in the southern region, the air in the northern region is drier and the relative humidity is lower, and R_t is more sensitive to the change of relative humidity, especially in summer and autumn. Thus, influenza occurs more frequently in the winter and spring in northern China(Qi et al., 2022; Yu et al., 2013). We should take caution when environmental humidity suddenly changes in the summer and autumn.

In this study, temperature and relative humidity showed a negative interaction. Although our study found that separate low temperature or low relative humidity conditions are beneficial for the spread of influenza, there has been also a study

Table 1
Estimated percent change (95% CI) in Rt for each 1 °C,5 °C, and 10 °C increase in temperature in four seasons.

Region	Season	1°	5°	10°
Northern	Spring	2.10(1.24,2.95)	10.08(5.92,14.24)	18.62(10.49,26.75)
	Summer	7.35(3.54,11.15)	29.75(6.33,53.16)	52.63(3.33,101.92)
	Autumn	21.03(13.27,28.79)	78.71(58.88,98.54)	97.33(84.11,110.56)
	Winter	13.72(8.29,19.16)	49.42(26.28,72.57)	67.21(41.72,92.70)
Southern	Spring	1.18(0.63,1.74)	5.70(2.93,8.48)	10.89(5.33,16.46)
	Summer	6.44(4.16,8.73)	30.12(19.24,41.00)	50.70(32.42,68.98)
	Autumn	8.89(5.41,12.37)	38.88(22.12,55.64)	59.81(32.86,86.76)
	Winter	2.62(1.28,3.96)	12.70(5.96,19.44)	25.27(12.07,38.48)

Table 2
Estimated percent change (95% CI) in Rt for each 10%, 25% and 50% increase in relative humidity in four seasons.

Region	Season	10%	25%	50%
Northern	Spring	4.15(2.34,5.95)	9.87(5.49,14.25)	18.36(10.10,26.62)
	Summer	41.83(32.25,51.40)	85.94(73.09,98.79)	98.88(93.74,104.03)
	Autumn	40.51(17.42,63.61)	98.24(90.46,106.01)	99.99(99.09,100.89)
	Winter	13.51(5.68,21.35)	34.46(15.90,53.01)	69.17(47.56,90.78)
Southern	Spring	3.08(1.96,4.21)	7.38(4.81,9.95)	14.11(9.76,18.46)
	Summer	19.52(10.99,28.06)	40.33(18.50,62.17)	59.63(28.72,90.55)
	Autumn	26.23(12.09,40.36)	44.76(17.34,72.18)	72.82(54.48,91.15)
	Winter	11.71(6.63,16.79)	30.16(15.52,44.80)	48.65(15.75,81.55)

Table 3
Merged effects of temperature (temp) and relative humidity (RH) on Rt.

	Overall	Southern	Northern
	RR (95%CI)	RR (95%CI)	RR (95%CI)
High temp and high RH	Ref	Ref	Ref
Low temp and High RH	0.83(0.76,0.89) *	1.00(0.97,1.01)	0.70(0.59,0.75) *
High temp and low RH	0.84(0.79,0.90) *	0.99(0.97,1.01)	0.69(0.62,0.76) *
Low temp and low RH	0.78(0.71,0.86) *	0.97(0.95,1.00) *	0.60(0.53,0.68) *
SI (95%CI) [a]	0.59(0.57,0.61) *	0.49(0.17,0.80)	0.59(0.56,0.62) *

[a] When meta merging SI, Zhejiang province was excluded.

indicating that influenza risk goes up when temperature rises across different relative humidity levels in Hongkong (Wang et al., 2017). In addition, another study has observed the risk of A(H3N2) infection increases with temperature at a higher relative humidity (Zhou et al., 2022). An animal model study shows that high humidity and temperature could reduce intestinal barrier function and increase the expression of inflammatory cytokines, thus interfering with the immune response to influenza (Deng et al., 2020). The specific mechanism is worth further exploration.

Our study has several strengths. First, this study explored the impact of meteorological factors on R_t of influenza in multiple regions. Second, we combined weekly ILI data with the activity intensity of influenza virus for better understanding of the influenza epidemic trend. The weekly ILI + counts were calculated by multiplying the population size of each province, then daily ILI + counts were obtained for further estimation of R_t. Third, compared with weekly ILI data, R_t can more intuitively demonstrate the transmissibility of influenza.

However, some disadvantages existed in our study. This study did not evaluate the effect of influenza subtypes, which have been confirmed associated with meteorological factors (Zhang, Chen, et al., 2022). The quantity and quality of influenza data may vary from city to city; for example, the reported cases in southern cities were more than in northern cities, which may affect the accuracy of the analysis(Zhang, Peng, et al., 2022). The mechanisms responsible for interactions between meteorological factors discussed may require further studies. We plan to explore the impact of pollutants on influenza transmission and conduct a more comprehensive and systematic analysis of China's influenza-related meteorological or pollution factors at the national level.

In conclusion, this study systematically and quantitatively described the association between meteorological factors and influenza activity in China at the provincial and national level. We found a positive contribution of low temperature and low relative humidity to influenza epidemics at the national level, while there was a negative interaction between temperature and relative humidity. Our findings suggest that meteorological factors should be absorbed into the current influenza surveillance systems to prevent epidemics or outbreaks.

Ethics approval

The research design and methodology used only anonymized data sets. This means that no ethical approval is required.

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Author contributions

Z.P. conceived the study. Z.C., and X.J. organized and cleaned the data. Y.Y., M.L., and S.Z. carried out data analysis, programming and wrote the paper. Z.P., L.W., and Z.L. reviewed and edited the paper. All authors gave final approval for publication.

Data and availability

The meteorological data, pollutant data, and population data used in this study can be downloaded from http://data.cma.gov.cn, http://106.37.208.233:20035/, and http://www.stats.gov.cn/. Influenza data can be requested from the Chinese Center for Disease Control and Prevention.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.idm.2023.07.005.

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