#### **ORIGINAL PAPER**



# The impacts of precipitation patterns on dengue epidemics in Guangzhou city

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#### Abstract

Some studies have demonstrated that precipitation is an important risk factor of dengue epidemics. However, current studies mostly focused on a single precipitation variable, and few studies focused on the impact of precipitation patterns on dengue epidemics. This study aims to explore optimal precipitation patterns for dengue epidemics. Weekly dengue case counts and meteorological data from 2006 to 2018 in Guangzhou of China were collected. A generalized additive model with Poisson distribution was used to investigate the association between precipitation patterns and dengue. Precipitation patterns were defined as the combinations of three weekly precipitation variables: accumulative precipitation (Pre\_A), the number of days with light or moderate precipitation (Pre\_LMD), and the coefficient of precipitation variation (Pre\_CV). We explored to identify optimal precipitation patterns for dengue epidemics. With a lead time of 10 weeks, minimum temperature, relative humidity, Pre\_A, and Pre\_LMD were positively associated with dengue, while Pre\_CV was negatively associated with dengue. A precipitation pattern with Pre\_A of 20.67–55.50 mm per week, Pre\_LMD of 3–4 days per week, and Pre\_CV less than 1.41 per week might be an optimal precipitation pattern for dengue epidemics in Guangzhou. The finding may be used for climate-smart early warning and decision-making of dengue prevention and control.

Keywords Dengue · Weather · Precipitation patterns · Generalized additive model

## Background

Dengue is transmitted to humans by Aedes mosquitoes, which thrive in tropical and subtropical regions (Kraemer et al. 2015). In China, the areas affected by dengue have expanded and dengue incidence has increased since 2012 (Lai et al. 2015). Guangdong Province is the hardest-hit province by dengue due to subtropical climate, rapid urbanization, rising international and domestic trade, and population movement.

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In 2014, the number of dengue cases was the highest on record in Guangdong in the past 25 years, and Guangzhou, the capital city of the province, had the highest cases, accounting for 82.7% of all cases in Guangdong province (Xiao et al. 2016). Therefore, dengue is a major public health concern in Guangzhou, especially in the context of climate change and rapid globalization.

As a mosquito-borne infectious disease, dengue is highly sensitive to weather factors (Liao et al. 2015; Lu et al. 2009; Phaijoo and Gurung 2017; Xiang et al. 2017). Temperature and precipitation were the two most important meteorological factors associated with dengue. They may impact survival, maturation, and breeding of Aedes and ecology of dengue virus (DENV) (Chen et al. 2010; Iguchi et al. 2018; Lowe et al. 2018). Minimum temperature (Tmin) was found to be closely related to dengue epidemics, with a certain lag impact (Shen et al. 2015). Precipitation can influence mosquito population densities by providing or destroying breeding sites of mosquitoes (Benedum et al. 2018; Chen et al. 2010). Accumulative precipitation (Pre\_A) represents the intensity of precipitation during a certain period (Dibo et al. 2008;

Guhathakurta and Rajeevan 2008; Pappachan et al. 2004). Light and moderate precipitation do not destroy breeding sites and may increase the usage of water containers, which may be conducive to breeding sites for mosquitoes (Eastin et al. 2014; Hii et al. 2009). As observed in a previous study, the number of dengue cases increased sharply with the increase of 24-h precipitation below 11.9 mm; but instead, a negative association was observed above that (Xiang et al. 2017). The number of rainy days represents the frequency of precipitation and was significantly associated with dengue epidemics (Kong et al. 2019; Xu et al. 2017). For instance, in Kong et al.'s study, the number of rainy days was considered the greatest factor among potential climatic factors (Kong et al. 2019). In addition, a recent research used coefficient of precipitation variation (Pre CV) as an indicator to develop a prediction model of dengue epidemics (Jácome et al. 2019).

However, current studies mostly focused on a single precipitation variable, and how precipitation patterns impact dengue epidemics remains unclear. The combination of accumulative precipitation (Pre\_A), number of precipitation days, and coefficient of precipitation variation (Pre\_CV) represents precipitation patterns. Several studies have reported that precipitation pattern may be a better risk indicator for mosquitovector diseases, such as malaria and dengue (Pappachan et al. 2004; Wu et al. 2017). Hence, it is important to identify optimal precipitation patterns of dengue epidemics, which can provide deep insights for dengue early warning and timely control.

In the present study, we combined dengue and weather data during 2006–2018 in Guangzhou of China to investigate the association between precipitation and dengue, and further explore optimal precipitation patterns for dengue epidemics. Our findings would be helpful to develop dengue early warning system in Guangzhou.

# Methods

## Study site

Guangzhou, the capital of Guangdong province, is the political, economic, cultural, technological, and transportation center of southern China. At the end of 2018, the population in Guangzhou reached 14.94 million. The humid subtropical climate with heavy precipitation and high temperature in Guangzhou makes it one of the most suitable cities for dengue epidemics in China (Guo et al. 2014).

#### **Dengue data**

Dengue case counts in Guangzhou from 1 January 2006 to 31 December 2018 were retrieved from the Chinese National Notifiable Infectious Disease Reporting Information System (NNIDRIS). All dengue cases were confirmed according to the unified diagnosis criteria (National Health Commission of the People's Republic of China 2018). Information of dengue cases included age, gender, occupation, date of onset, clinic-confirmed or laboratory-confirmed cases, local case, or imported case. The criteria of local or imported cases used in the study are from Lai's report (Lai et al. 2015). In our study, we only investigated the association between weather factors and local dengue cases. All local cases were anonymized and finally arranged into weekly time-series data.

#### Meteorological data

Daily meteorological data was obtained from the China Meteorological Data Service Center (http://data.cma.cn/) and arranged into weekly time-series data. There were five weather monitoring stations in Guangzhou, and we used the average value of the five stations in the study. Weather variables included weekly average minimum temperature (Tmin, °C), weekly average relative humidity (Rh, %), weekly accumulative precipitation (Pre A, mm), number of days with light or moderate precipitation per week (Pre LMD, days), and coefficient of precipitation variation per week (Pre CV). The light or moderate precipitation is defined as 24-h accumulative precipitation ranging from 0.1 to 25 mm according to the national standard of precipitation grade (China Meteorological Administration 2013). In our initial analyses, we observed that the model incorporating Pre LMD showed a lower generalized cross validation (GCV) score than that incorporating number of precipitation days (see Table S1), so we used the Pre LMD to represent the precipitation frequency in our study. Pre CV is the coefficient of precipitation variation in a certain week, which is calculated as the ratio of the standard deviation (SD) and mean (x) of precipitation, and used as a measurement of fluctuation of precipitation in a week.

#### **Statistical analysis**

We implemented a three-stage analysis in the study. First, we described the distribution of dengue and weather variables. Then, we estimated the impacts of weather variables on dengue. Finally, we investigated the association between precipitation patterns and dengue.

Spearman correlation analysis was firstly used to identify the correlation between dengue and meteorological variables. Previous studies conducted in Guangzhou reported lag time of weather variables on dengue varying from 8 to 12 weeks (Li et al. 2017a; Li et al. 2017b; Lowe et al. 2018). In our study, similar trends were observed in 8–12-week lag for each meteorological variable in a preliminary analysis (see Fig. S1). Thus, we considered weather variables with 10-week lag, which is consistent with the sum time of development time (days from hatching to adult ecdysis) of Aedes albopictus around 2 weeks (Costanzo et al. 2015; Ezeakacha and Yee 2019), survival time of adult female Aedes albopictus under field conditions around 6 weeks (Brady et al. 2013), and incubation time around 2 weeks (Chan and Johansson 2012; Li et al. 2019).

Second, we applied generalized additive models (GAM) to study the impacts of weather variables on dengue (Li et al. 2017b; Maindonald 2006). Quasi-Poisson distribution was used in model because the Cullen and Frey graph indicated the observed number of dengue cases followed a Poisson distribution (see Fig. S2), and the test for over-dispersion was statistically significant (Delignette-Muller and Dutang 2015). The model can be specified as follows:

$$Log(\mu_{t}) = \beta_{0} + s(Pres_{t-10}, df) + s(Tmin_{t-10}, df) + s(Rh_{t-10}, df) + s\{log(cases)_{t-10}, df\} + s(time, df)$$
(1)

where  $u_t$  represents predicted local cases during week t;  $\beta_0$  represents intercept; *Pres<sub>t-10</sub>* denotes three precipitation factors (Pre\_A, Pre\_LMD, Pre\_CV) in the previous 10 weeks; *Tmin<sub>t-10</sub>* represents minimum temperature in the previous 10 weeks; log  $(cases)_{t-10}$  indicates auto-regressive term for local dengue cases; *time* is used to control long-term trend; and *s* and *df* indicate spline smoothing function and degree of freedom, respectively. Given the overfittings observed when *df* was above three, a *df* of three was used in the model that was also used in a previous study (Xiao et al. 2018; Limper et al. 2016).

Third, to better catch the impact of precipitation on dengue. we investigated the association between precipitation patterns and dengue in warm temperature (see Fig. S3). Here, we defined 18 °C as the threshold of Tmin according to the previous studies (Fan et al. 2014; Shen et al. 2015). Due to that the fluctuation range of Pre A was almost same between years (Fig. 1), Pre A was divided into two levels (high and low) according to its median, as well as Pre LMD and Pre CV. We then created a new variable, group1, to represent different precipitation patterns of the combinations of the three precipitation variables. Here, the precipitation pattern of low Pre A level, low Pre LMD level, and high Pre CV level was selected as the reference group because the pattern was not conducive to dengue epidemics. Finally, group1 was taken as a categorical variable to incorporate into model. Tmin, Rh and dengue in the previous 10 weeks were used as control variables in the model. A new model can be specified as follows:

$$Log(\mu_t) = \beta_0 + \beta_1 G 1 + s(Tmin_{t-10}, df) + s(Rh_{t-10}, df) + s\{log(cases)_{t-10}, df\} + s(time, df)$$
(2)

where  $\beta_I$  is the regression coefficient; G1 represents the group1; the other components are the same as that in Eq. (1). Since the wide application of Pre\_A and number of precipitation days, we conducted stratified analyses to further study the impact of Pre\_A and Pre\_LMD by two levels of Pre\_CV, and the cutoff point of Pre\_CV was its median (see Fig. S3 and Fig. S4). Pre\_A and Pre\_LMD were then classified as low, medium, and high (26th–50th percentile; 51st– 75th percentile; 76th–100th percentile), respectively. As the



Fig. 1 Time-series of weekly dengue case counts and weather variables in Guangzhou during the period from January 2006 to December 2018. The dengue case counts were in logarithmic scale

25th percentile was often defined as a lower threshold in studies of meteorology (Kirono et al. 2017; Martínez et al. 2007), in our study, we excluded the lowest 25% of precipitation (below 4.27 mm/week) to avoid potential complexity resulting from too many combinations. In addition, very low precipitation is not a main driving force of dengue epidemics. Then, group2 was created to represent different precipitation patterns of the combinations of Pre\_A and Pre\_LMD. For the consistency of reference in the stratified analyses, we used the precipitation pattern of medium Pre\_A level and medium Pre\_LMD level as the reference group due to the fact that some precipitation patterns were not existing. Likewise, group2 was incorporated into the model as a categorical variable. A new model can be specified as follows:

$$Log(\mu_t) = \beta_0 + \beta_2 G2 + s(Tmin_{t-10}, df) + s(Rh_{t-10}, df) + s\{log(cases)_{t-10}, df\} + s(time, df)$$
(3)

where  $\beta_2$  is the regression coefficient; G2 represents the group2; the other components are the same as that in Eq. (1). Finally, to test the accuracy of the model, we classified the weekly dengue cases of each precipitation pattern for low and high levels (according to the median of case counts), then calculated the proportion of weeks of high level.

All statistical analyses were two-sided, and values of P < 0.05 were considered statistically significant. The "*mgcv*" package in the statistical software R (Version 3.6.1) was used to fit all models.

#### Sensitivity analysis

To test the robustness of our results, we changed lag time (from 8 to 12 weeks) and df of the smoothing function for all variables (from 3 to 5). We also conducted a sensitivity analysis controlling imported cases as a potential impact factor in the GAM. For different lag weeks, the reference is 10-week lag and we compared the results of 8-, 9-, 11-,and 12-week lag with 10-week lag, respectively; For df, the reference is df of 3, and we compared the results of df of 4 and 5 with that df of 3, respectively; we also compared the results of controlling imported cases.

#### Results

From 1 January 2006 to 31 December 2018, a total of 41,932 local dengue cases were reported in Guangzhou. The descriptive summary for dengue cases and weather variables is shown in Table 1. There is a weekly average of 61 dengue cases over the study period. The weekly mean Tmin, Pre\_A, Pre\_LMD, Pre\_CV, and Rh were 19.15 °C, 40.06 mm, 3.34 days, 1.49, and 76.40%, respectively. Figure 1 depicts the

Table 1Basic information of weekly dengue cases and meteorologicalfactors in Guangzhou during the period 2006–2018

Variables	Min	P <sub>25</sub>	Median	P <sub>75</sub>	Max	$Mean \pm SD$
Dengue cases	0	0	0	2	8136	61 ± 519
Tmin (°C)	5.05	14.12	20.38	24.78	27.66	$19.15\pm5.96$
Pre_A (mm)	0.00	4.27	20.67	55.50	348.14	$40.06\pm50.84$
Pre_LMD (day)	0.00	2.00	3.00	5.00	7.00	$3.34\pm2.03$
Pre_CV	0.33	1.07	1.41	1.90	2.45	$1.49\pm0.54$
Rh (%)	44.14	71.64	77.31	82.86	95.79	$76.40\pm8.79$

time-series of weekly dengue case counts and weather conditions. The dengue epidemics fluctuated markedly during the study period with the highest peak in 2014. Figure S5 depicts the fluctuation of dengue cases and weather variables characterized by seasonal patterns. The peak Tmin period was from the 17th to the 37th week when Pre\_A and Pre\_LMD were medium and Pre\_CV was low. The peak dengue epidemic period was observed after 10 weeks (the 27th–47th weeks). Spearman correlation analyses indicated that the associations between dengue and Tmin, Pre\_A, and Pre\_LMD were all positive (Table 2), while there was a negative association between Pre\_CV and dengue.

The exposure-response associations between weather variables and dengue are shown in Fig. 2. Nonlinear positive associations were observed between weekly mean Tmin and Rh in the previous 10 weeks and dengue. Linear positive associations were found between Pre\_A and Pre\_LMD in the previous 10 weeks with dengue cases, and the association of Pre\_CV with dengue cases was nonlinear and negative. In Fig. 2b, the density of the distribution of the Pre\_A values on the X-axis dropped sharply when it rose above 200 mm. For the association between Rh and dengue, the slopes of exposureresponse curves seemed to be flattened at high Rh (above about 80%).

The associations between precipitation patterns (represented by group1 and group2) and dengue are presented in Fig. 3. There was a greater dengue risk 10 weeks after precipitation patterns with two or more high levels (i.e., when group1 is HHL, LHH, HLH and HHH in Fig. 3 a). Figure 3 b and c

**Table 2**Spearman correlation analyses between dengue andmeteorological factors (lag 10 weeks)

Variables	Cases	Tmin	Pre_A	Pre_LMD	Pre_CV
Tmin	0.64 <sup>a</sup>				
Pre_A	0.34 <sup>a</sup>	0.47 <sup>a</sup>			
Pre_LMD	0.22 <sup>a</sup>	0.33 <sup>a</sup>	0.63 <sup>a</sup>		
Pre_CV	-0.22 <sup>a</sup>	-0.31 <sup>a</sup>	-0.56 <sup>a</sup>	-0.65 <sup>a</sup>	
Rh	0.33 <sup>a</sup>	0.35 <sup>a</sup>	0.68 <sup>a</sup>	0.59 <sup>a</sup>	-0.53 <sup>a</sup>

 $^{a}P < 0.05$ 



**Fig. 2** Exposure-response curves between weekly weather variables (lag 10 weeks) and weekly dengue cases. Solid lines indicate the logarithmic value of relative risks (log RRs) of the weather variables on dengue epidemics, and the gray areas indicate the 95% CI of the weather

show the results of stratification analyses, and positive associations between precipitation patterns and dengue risk were found in low Pre\_CV level. The risk of dengue was the greatest (RR = 2.73, 95%CI: 1.20–6.20) 10 weeks after a precipitation pattern of medium Pre\_A and Pre\_LMD with low Pre\_CV (i.e., when group2 is MM in Fig. 3 b). Figure 3 c indicates that the associations between precipitation patterns and dengue risk were weak when Pre\_CV was high. And we found that estimates in "MM" (lag 8–12 weeks, see Table S2) were statistically significant or the lower limits of the confidence interval were close to 1. Table 3 showed that the numbers of weeks with high-level case counts were mostly in "MM", to some extent verifying this pattern's contribution to dengue epidemics.

Sensitivity analyses found that the impact estimates were relatively robust when we used different lags for weather variables (see Table S2 and Fig. S6 a). In addition, when df varied, or imported cases were incorporated as a confounding factor in the model, the results did not change substantially (see Fig. S6 b).

# Discussion

In this study, we employed GAM to fit the associations between precipitation variables and dengue epidemics. The results indicated that a weekly precipitation pattern with Pre\_A of 20.67–55.50 mm, Pre\_LMD of 3–4 days per week, and Pre\_CV less than 1.41 with a lead time of 10 weeks might be an appropriate weather condition for dengue epidemics in Guangzhou.

variables. Low dengue risks were seen at low Pre\_A, low Pre\_LMD, and high Pre\_CV level so that a corresponding precipitation pattern was selected as the reference group in the following process

Our research showed that the peak of dengue epidemic was observed at the 10th week after favorable meteorological variables (see Fig. S5). For instance, the average weekly Tmin over the 13 years (2006–2018) reached 18 °C at about the 13th week, and the dengue occurred at about the 23rd week, which is consistent with the setting of 10-week lag in several previous studies, where the lag time was usually within 3 months (Kakarla et al. 2019; Kong et al. 2019; Li et al. 2017a; Xu et al. 2019). For example, Kakarla et al. found that, for precipitation, a higher transmission risk of dengue was observed between 8 and 15 weeks of lag (Kakarla et al. 2019). Li et al.'s study in Guangzhou also reported that precipitation in the previous 3 months and temperature in the previous 2 months were strongly related to dengue (Li et al. 2017a). The reason for varied length of lag time may be due to the changes in the biology of mosquitoes and the incubation period of dengue viruses (Hii et al. 2012).

We observed that the exposure-response associations between weather variables and dengue are similar to the reports of several previous studies (Benedum et al. 2018; Li et al. 2017b; Lu et al. 2009). There was a wide confidence interval of dengue risk in high-level Pre\_A. Specifically, the density of the distribution of the Pre\_A values on the X-axis dropping sharply indicated uncertainty of the effect of heavy precipitation on dengue, and caution is needed in explaining its impact. Some researchers reported "flushing" events following excessive precipitation, directly destroying breeding sites, and leading to larvae death (Benedum et al. 2018). While other researchers in Taiwan found the relative risk of dengue increased when the maximum 24-h precipitation exceeds approximately 50 mm (Chien and Yu 2014). A probable reason



**Fig. 3** The impacts of different precipitation patterns on dengue at 10week lag (Tmin > 18 °C). Group1: combinations of three precipitation variables (Pre\_A, Pre\_LMD, and Pre\_CV), for example, LHL, represent the combination of low Pre\_A level, high Pre\_LMD level, and low Pre\_ CV level; group2: combinations of two precipitation variables (Pre\_A and Pre\_LMD) by two levels of Pre\_CV; for example, LM represents

for the discrepancy might be that the influence of precipitation depends not only on the precipitation, but also on human

 Table 3
 The proportion of weeks with high dengue epidemic level

Group 2 (Rain_CV < median)	Lag 8 weeks	Lag 9 weeks	Lag 10 weeks	Lag 11 weeks	Lag 12 weeks
LL <sup>a</sup>	_			_	_
LM <sup>b</sup>	0.44	0.50	0.38	0.31	0.31
LH <sup>a</sup>		_	_		_
ML	0.60	0.40	0.40	0.20	0.00
MM	0.64	0.69	0.62	0.74	0.68
MH	0.57	0.57	0.54	0.49	0.54
HL	0.56	0.56	0.44	0.56	0.61
HM	0.60	0.60	0.52	0.52	0.54
HH	0.57	0.57	0.47	0.50	0.40

<sup>a</sup> Groups with no results because the corresponding precipitation patterns were not existing

<sup>b</sup> Reference group

the combination of low Pre\_A level and medium Pre\_CV level, and the cutoff point of Pre\_CV is its median value;  $Pre_CV = NA$ : weeks with no rainfall; ref: reference group. LL/LH of b and LH/HH of c: groups with no results were due to that the corresponding precipitation patterns were not existing

activities, such as water usages and city drainage systems (Chien and Yu 2014). A positive impact of Pre\_LMD on dengue was also found in our study, which is consistent with Xu's study in Guangzhou. They found that adult mosquito density was closely related to the number of days with precipitation in the previous month (Xu et al. 2017), and our study further verified that the number of precipitation days plays an important role in dengue epidemics. We found a positive effect of Rh on dengue below about 80%, which was consistent with a previous study which reported a positive effect of low humidity (below 76%) on dengue (Wu et al. 2018).

In the present study, we used Pre\_CV as a measurement of fluctuation of precipitation in a specific week. The fluctuation in weather was associated with dengue transmission (Campbell et al. 2013). Results of Spearman's correlation analysis and exposure-response analysis both showed Pre\_CV had a negative impact on dengue epidemics. Liao et al. also found a negative association between dengue incidence and coefficient of variation of precipitation at 2-month and 3-month lags (Liao et al. 2015). In terms of precipitation patterns, the highest risks of dengue epidemic were observed at medium levels of Pre\_A and Pre\_LMD (i.e., when group2 is MM in Fig. 3 b). The result was consistent with the fact that an excessive amount of precipitation combined with too many rainy days was unfavorable to dengue epidemics, highlighting the impacts of light and moderate precipitation (Eastin et al. 2014; Iguchi et al. 2018). In addition, though precipitation patterns of HM and HH with low Pre\_CV had a relatively high risk of dengue, we should also be cautious about greater uncertainty of the actual dengue risk at heavy precipitations.

Our study illustrated the weather variables less fluctuated than dengue epidemics, while the latter displayed wide interannual variation in seasonal epidemic size, especially in 2014. Vector-borne diseases may present complex dependence on environmental conditions and other factors. Oidtman's research suggested that dengue epidemics in most years were limited by unfavorable conditions concerning one or more factors; the epidemic in 2014 was made possible by the combination of favorable conditions for all factors (Oidtman et al. 2019). Based on the assumption, we mainly focused on the impacts of meteorological variables on dengue with controlling some covariables in this study.

To our knowledge, there is less knowledge about the impact of combinations of several weather factors on dengue epidemics. This is the first study to explore the associations between dengue and precipitation patterns in Guangzhou after controlling temperature and humidity, which may more precisely reflect the impact of precipitation on dengue. Findings from this study may set an example for further study on the precipitation-dengue association.

The current study has some limitations. First, this was an ecological study and it was not able to provide a causal inference. Second, due to the unavailability of long-term and weekly scale mosquito surveillance data, our study did not evaluate the direct impact of weather variables on mosquitoes. But the association between meteorological variables and dengue epidemics may indirectly reflect the influence on vectors. Research based on weekly vector surveillance data would further confirm the association of weather-dengue epidemics. Moreover, this study only focused on one study area. Nevertheless, Guangzhou, due to its specific features in climate and socio-economy, is the area with the most dengue cases in China, and has continuous time-series dataset of dengue, which made Guangzhou is an ideal study area in China.

# Conclusions

This study provided a more nuanced understanding of dengue epidemics influenced by precipitation and identified optimal precipitation patterns for dengue epidemics in Guangzhou. Results may be helpful for climate-smart early warning and decision-making of dengue prevention and control practice in the future.

Abbreviations DENV, dengue virus; GAM, generalized additive models; GCV, generalized cross validation; Log RR, logarithmic value of relative risk; NNIDRIS, National Notifiable Infectious Disease Reporting Information System; Pre\_A, accumulative precipitation; Pre\_CV, the coefficient of precipitation variation; Pre\_LMD, the number of days with light or moderate precipitation; Rh, relative humidity; SD, standard deviation; Tmin, minimum temperature

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s00484-021-02149-2.

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**Data availability** The dengue data that support the findings of this study are available from Chinese National Notifiable Infectious Disease Reporting Information System, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Chinese Center for Disease Control and Prevention. The meteorological datasets supporting the conclusions of this article are available in China Meteorological Data Service Center repository (http://data.cma.cn/).

#### Declarations

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

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

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