

Original Article



The Impacts of Mosquito Density and Meteorological Factors on Dengue Fever Epidemics in Guangzhou, China, 2006-2014: a Time-series Analysis*

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Abstract

Objective To explore the associations between the monthly number of dengue fever (DF) cases and possible risk factors in Guangzhou, a subtropical city of China.

Methods The monthly number of DF cases, Breteau Index (BI), and meteorological measures during 2006-2014 recorded in Guangzhou, China, were assessed. A negative binomial regression model was used to evaluate the relationships between BI, meteorological factors, and the monthly number of DF cases.

Results A total of 39,697 DF cases were detected in Guangzhou during the study period. DF incidence presented an obvious seasonal pattern, with most cases occurring from June to November. The current month's BI, average temperature (T_{ave}), previous month's minimum temperature (T_{min}), and T_{ave} were positively associated with DF incidence. A threshold of 18.25 °C was found in the relationship between the current month's T_{min} and DF incidence.

Conclusion Mosquito density, T_{ave} , and T_{min} play a critical role in DF transmission in Guangzhou. These findings could be useful in the development of a DF early warning system and assist in effective control and prevention strategies in the DF epidemic.

Key words: Breteau index; Dengue fever; Meteorological factors; Negative binomial regression model

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INTRODUCTION

Dengue fever (DF) is an acute viral disease transmitted by *Aedes* mosquitoes and ranks as the most important mosquito-borne viral disease worldwide^[1]. An

estimated 392 million unapparent infections and 96 million apparent dengue infections occurred globally in 2010^[2]. About 2.5 billion people live in over 100 endemic countries and areas with high risk of dengue virus (DENV) transmission^[3]. Infection with one of the four closely related but antigenically

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distinct DENV types (serotypes 1, 2, 3, and 4) may result in an infection with a varying severity of clinical symptoms and even death^[4].

Epidemics of DF in China were reported before 1940 and remained unreported during 1940-1977^[5]. In 1978, the first reported DF outbreak due to DENV type 4 occurred in Foshan (adjacent to Guangzhou), a city in Guangdong Province, where the spread of DF had started in the southern provinces of China^[6]. Since August 1978, relatively sporadic yearly outbreaks initiated through imported cases have been reported in Guangzhou; the most severe DF outbreak, thus far, was reported in 2014, with the number of cases reported in the first 11 months of 2014 (with an incidence peak between May and November) accounting for 70.57% of the total number of cases since 1978. Studies of Guangzhou's *A. albopictus* population show that the vector present peaks concurrently^[7]. In China, *A. aegypti* is found only in the coastal regions south of 22°N, but *A. albopictus* is much more widespread and considered to be the primary vector since DENV has been frequently isolated from it. Despite *A. aegypti* being the most important DF vector, *A. albopictus* is likely to be important in the maintenance of the infection^[7]. In Guangzhou, *A. albopictus* is the only vector for DF and dengue hemorrhagic fever^[8]. Global warming, widespread vectors, frequent population migration, and population growth have contributed to the spread of DF, making it a serious threat to public health in China^[9].

The distinct seasonal fluctuations of DF in most tropical areas appear to be largely influenced by meteorological factors. Meteorological factors were found to strongly impact the vector populations and DENV both directly and indirectly^[10]. Several previous studies have demonstrated that climate conditions can affect the breeding, maturation period, virus replication, density, and life cycle of mosquitos^[11-13]. It has been proposed that meteorological variables could increase the predictive power of DF models^[14]. The relationship between the meteorological factors and DF has been assessed in multiple settings using several statistical methods, including mathematical models, cross correlation analyses, and time-series analyses^[15-19]. The time-series analysis is particularly useful in modeling the temporal dependence structure as they explicitly assume temporal dependence between observations^[20]. Previous studies have commonly examined the linear or log-linear relationships between DF incidence and meteorological factors. A recent study noted a

strong relationship to a minimum temperature threshold between DF cases and meteorological factors for the semi-arid, tropical city of Cali, Colombia^[21]. However, some studies indicated that the effects of different ranges of temperatures on DF occurrence are distinct^[16,22-24]. There is a need to determine the mechanism on how meteorological factors influence the development of DF epidemics.

The current study aims to explore the association of DF incidence with mosquito density and meteorological factors in Guangzhou, China, during 2006-2014.

MATERIALS AND METHODS

Study Area

The study city, Guangzhou, is located at latitude 23.17, longitude 113.23, and is the largest metropolis in southern China. It has a population of 12.7 million and a population density of 1708 inhabitants/km². It has a typical subtropical climate and an average annual temperature of 21.9 °C, with the highest mean temperature (33.0-34.9 °C) observed between July and August and the lowest mean temperature (6.5-12.1 °C) observed between January and February. The annual average rainfall ranges from 1370-2353 mm and exhibits a seasonal cycle with wet and dry periods.

Data Collection

DF Data DF has been a legally notifiable communicable disease in China since 1989. Monthly autochthonous DF cases in Guangzhou during the period of January 2006 to November 2014 were retrieved from the Notifiable Infectious Disease Report System, China Centre for Disease Control and Prevention. The reported DF cases included clinical (57%) and laboratory (43%) diagnoses. An autochthonous case is defined according to the absence of evidence for the case being imported^[25].

Mosquito Density *A. albopictus* is the dominant transmission vector in Guangzhou city^[8]. Conventional surveillance methods for *Aedes* larval indices, used to describe the mosquito density, have been used systematically in Guangzhou since 2002. Herein, the Breteau Index (BI) surveillance data, considered the best index for *Aedes* density surveillance, was collected from 12 districts in Guangzhou city. From each district, three streets were selected as the BI monitoring points and water containers and mosquito larvae were checked from 100 houses through monthly door interviews. BI is

calculated according to the number of positive containers per 100 houses inspected.

Meteorological Data Monthly meteorological data, including minimum temperature (T_{min}), maximum temperature (T_{max}), average temperature (T_{ave}), rainfall, and average relative humidity (Hum) were obtained from the China Meteorological Data Sharing Service System.

Statistical Analysis Current and previous months' BI and meteorological factors were considered in the analyses. DF incidence, BI, and meteorological variables are highly auto-correlated, partly due to their trend and seasonality^[26], which may bias their correlations; therefore, the trend and seasonality were removed from these time-series before examining their associations. The Seasonal-Trend Decomposition Procedure based on Loess (STL), a filtering procedure used to decompose a time series into additive components of variation (i.e., trend, seasonality, and the remainder) by applying the Loess smoothing model and widely used in several disciplines, including environmental science, ecology, epidemiology, and public health, was used herein. Li et al.^[27] provided further description of the applications of this method. The number of points for the filtered time-series was the same as for the original time-series. Spearman correlation coefficients of filtered DF incidence, BI, and meteorological factors were then calculated. Subsequently, Spearman correlation coefficients between filtered variables that were significantly correlated with filtered DF incidence were further calculated. If some of these variables were highly correlated, then they were separately incorporated into the multivariate models.

A negative binomial regression model was used to examine the associations of BI and meteorological factors with DF incidence. The model was specified as follows:

$$Y_t \sim NB(r, p_t)$$

$$E(Y_t) = \mu_t = \frac{r(1-p_t)}{p_t} \quad \text{var}(Y_t) = \mu_t + \frac{1}{r} \mu_t^2$$

$$\begin{aligned} \text{Log}(\mu_t) &= \alpha + \eta \text{season} + s(\text{year}_t) + \\ & s(\text{cases}_{\text{lag1t}}) + \sum s_j(\text{var}_{it}) \\ & = \alpha + \text{COVs} + \sum s_j(\text{var}_{it}) \end{aligned} \quad (1)$$

Where t is the corresponding month of observation; r and p_t are parameters of the negative binomial distribution; Y_t is the observed monthly number of DF cases in month t ; μ_t is the expectation of Y_t ; α is the intercept; and COVs are covariates. To control for the seasonality of DF incidence, seasonal factors were introduced into the model and η is their

coefficient vector. Cubic regression splines [i.e., $s(\cdot)$] were used for year, DF cases of previous month (i.e., $\text{cases}_{\text{lag1t}}$), and selected variables (var_{it}). Generalized cross validation was used to find the appropriate smoothness for these splines. The exposure-response curves were first presented, followed by parametric terms for selected variables being accordingly incorporated into the model. The Akaike Information Criterion (AIC) was used to select the parametric terms for the selected variables. The effects of selected variables, shown as linear terms, were presented as the percent change in DF incidence associated with 1-increase in the selected variables. All analyses were performed using R software version 3.1.2 with its 'mgcv' package.

Ethics Statement The present study was reviewed by the research institutional review board of Southern Medical University and Guangzhou Center for Disease Control and Prevention. Patient data used in the study were de-identified and therefore the study did not require ethics clearance.

RESULTS

The total number of DF cases reported in Guangzhou during the study period was 39,697. From January 2006 to November 2014, there were three epidemic years in which the number of annual DF cases reached more than 700 (i.e., 777 cases in 2006, 1262 cases in 2013, and 37,305 cases in 2014; Figure 1). DF incidence presented an obvious seasonal pattern with most cases occurring from June to November. BI and meteorological variables showed apparent seasonal patterns, with BI and rainfall peaking from April to September and T_{min} , T_{max} , and T_{ave} peaking from June to September. The seasonal pattern of Hum was less obvious (Figure 2).

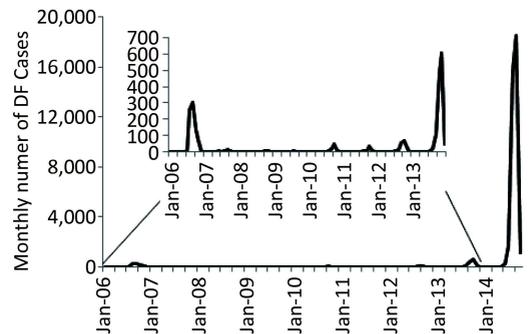


Figure 1. Monthly number of dengue fever (DF) cases in Guangzhou, China, between January 2006 and November 2014 (inset represents the 2006-2013 epidemic curve).

Results of Spearman correlation analyses indicate that the correlations between filtered DF incidence and the current month's BI, T_{min} , and T_{ave} , and the previous month's T_{min} and T_{ave} were statistically significant at 10% level (Table 1). Because the filtered current month's T_{min} and T_{ave} , and the previous month's T_{min} and T_{ave} were highly correlated (Table 2), they were further incorporated into the negative binomial regression models separately with the current month's BI, and the models were called Models 1, 2, 3, and 4, respectively. Figure 3 presents

the exposure-response curves for current month's BI, T_{min} , and T_{ave} and previous month's T_{min} and T_{ave} . DF incidence generally increased with current month's BI and T_{ave} and previous month's T_{min} and T_{ave} . There was an apparent threshold in the relationship between DF incidence and current month's T_{min} . Overall, the DF incidence initially increased with current month's T_{min} , and then, when T_{min} was larger than the threshold, the exposure-response curve slope was nearly 0. Cubic regression splines of current month's BI (Model 1: $\chi^2=10.824$, $P=0.004$;

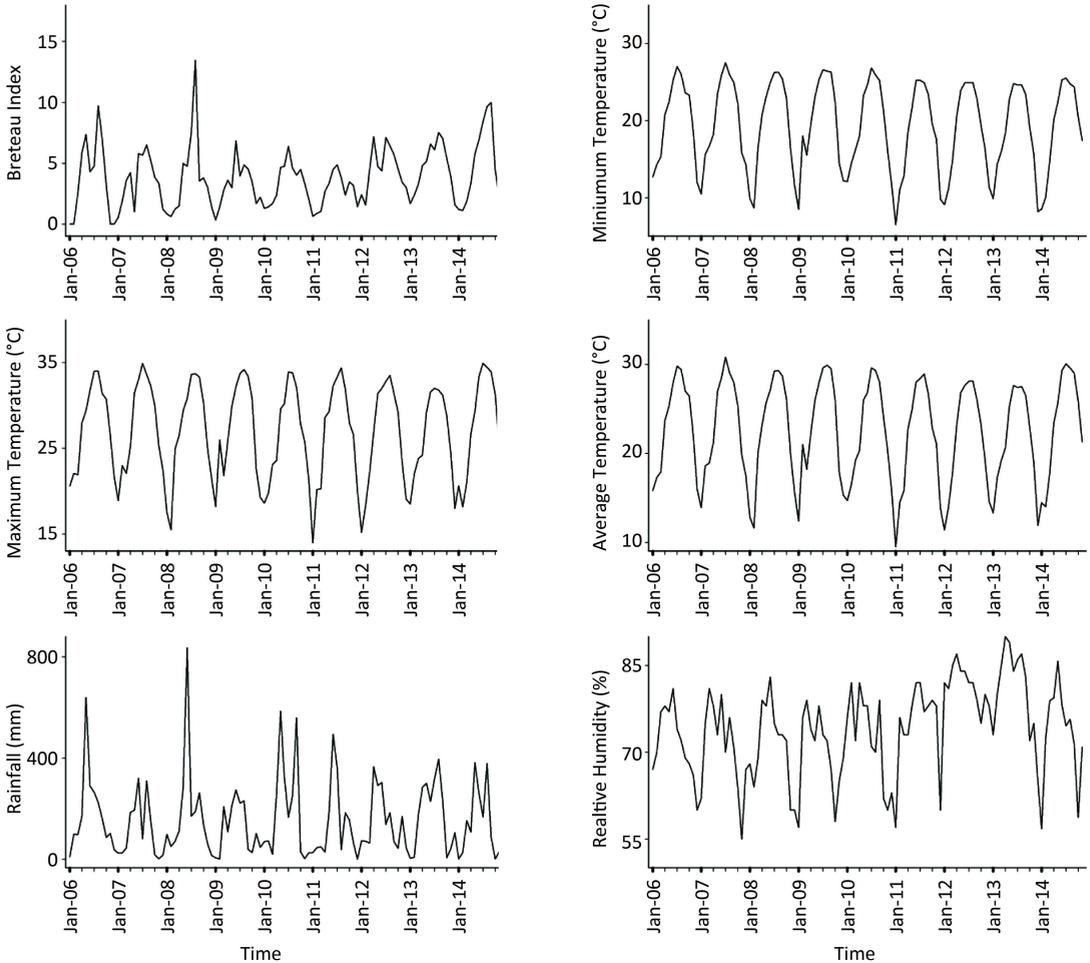


Figure 2. Monthly Breteau Index (BI) and meteorological measurements in Guangzhou, China, between January 2006 and November 2014.

Table 1. Spearman Correlation Coefficients of Monthly Number of Dengue Fever Cases and Candidate Variables

Lag-time (month)	BI	T_{min}	T_{max}	T_{ave}	Rainfall	Hum
0	0.197*	-0.199*	-0.098	-0.164*	-0.014	0.099
1	0.144	-0.180*	-0.154	-0.181*	-0.041	0.101

Note. BI, Breteau Index; T_{min} , minimum temperature; T_{max} , maximum temperature; T_{ave} , average temperature; Hum, average relative humidity; * means $P < 0.1$.

Model 2: $\chi^2=10.937$, $P<0.001$; Model 3: $\chi^2=8.181$, $P=0.004$; Model 4: $\chi^2=12.301$, $P=0.041$, T_{min} ($\chi^2=25.060$, $P<0.001$), and T_{ave} ($\chi^2=19.800$, $P<0.001$), and previous month's T_{min} ($\chi^2=30.349$, $P<0.001$) and T_{ave} ($\chi^2=25.383$, $P<0.001$) were statistically significant

(Table 3). A new model was thus built with a linear term for current month's BI and T_{ave} , previous month's T_{min} and T_{ave} , and piecewise linear terms for current month's T_{min} assuming that the exposure-response curve slope was 0 when T_{min} was

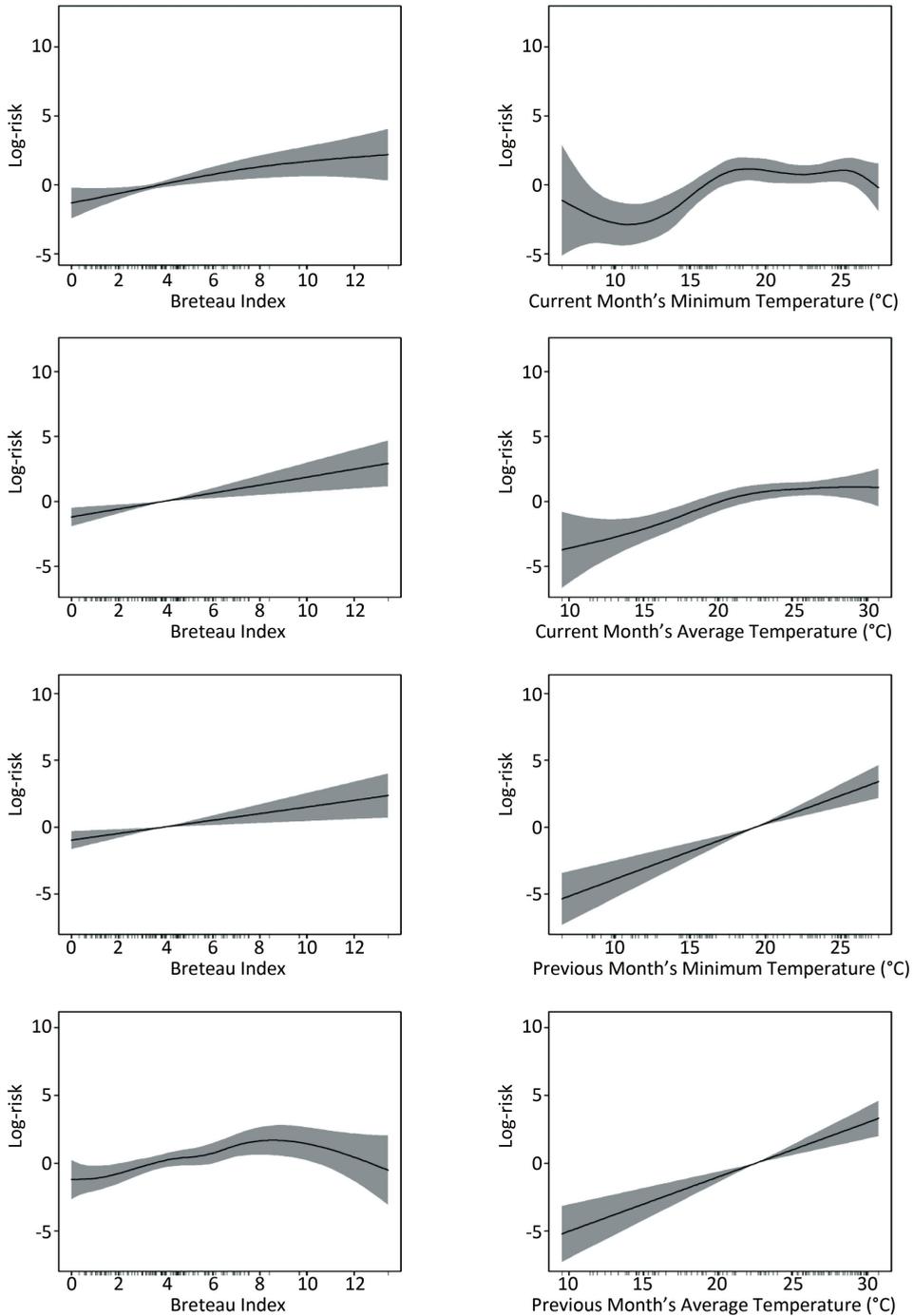


Figure 3. Exposure-response curves of current month's Breteau Index (BI), minimum temperature (T_{min}), average temperature (T_{ave}), and previous month's T_{min} and T_{ave} against dengue fever (DF) incidence in log scale. The solid lines are the estimates of the smooths for current month's BI, T_{min} , T_{ave} , previous month's T_{min} and T_{ave} , and the shaded regions are the confidence bands for the smooths.

larger than the threshold. Figure 3 indicates that the threshold was between 17.5 °C and 20.0 °C; therefore, models were constructed with thresholds ranging from 17.5 °C to 20.0 °C using 0.1 °C increments. The model for current month's T_{min} can be expressed as follows:

$$\log(\mu_t) = \alpha + \eta season + s(year_t) + s(cases_{log1t}) + \beta_1 BI + \beta_2 T_{min} - \beta_2(T_{min} - \psi) \quad (2)$$

Where β_1 is the coefficient for BI; ψ is the threshold and $(T_{min} - \psi)_+ = (T_{min} - \psi) \times I(T_{min} > \psi)$ being $I(A) = 1$ if A is true; β_2 is the slope of left line segment (that is, for $T_{min} \leq \psi$); and $-\beta_2$ is the 'difference-in-slopes' parameter, so 0 is the slope of the right line segment.

The model with the minimum AIC was then selected. The results indicate that current month's BI (Model 1: $Z = 3.403$, $P < 0.001$; Model 2: $Z = 3.039$, $P = 0.002$; Model 3: $Z = 2.860$, $P = 0.004$; Model 4: $Z = 3.135$, $P = 0.002$) and T_{ave} ($Z = 4.024$, $P < 0.001$), and previous month's T_{min} ($Z = 5.513$, $P < 0.001$) and T_{ave} ($Z = 5.824$, $P < 0.001$) were significantly associated with DF incidence. The threshold for current month's T_{min} was 18.3 °C. Current month's T_{min} ($Z = 4.868$, $P < 0.001$) was also significantly correlated with DF incidence (Table 4). An increase of 1 in current month's BI was associated with a 35.8% [95% confidence interval (CI), 13.9%-62.0%], 34.2% (95% CI, 11.0%-62.3%), 28.0% (95% CI, 8.1%-51.7%), and 30.1% (95% CI, 10.4%-53.4%) increase of DF incidence based on Models 1, 2, 3, and 4, respectively. An increase of 1.0 °C in current month's T_{ave} and previous month's T_{min} and T_{ave} was related to a 29.0% (95% CI, 13.9%-46.0%), 51.8% (95% CI, 30.9%-76.1%), and 52.8% (95% CI, 32.5%-76.3%) increase of DF incidence, respectively, and an increase of 1.0 °C in current month's T_{min} was related to a 64.9% (95% CI, 34.8%-101.7%) increase of DF incidence when

current month's T_{min} was smaller than 18.3 °C (Table 4).

Table 2. Spearman Correlation Coefficients of Selected Variables

Variables	T_{min}	T_{ave}	T_{min1}	T_{ave1}
BI	-0.020	-0.084	-0.002	-0.094
T_{min}	-	0.838*	0.996*	0.850*
T_{ave}	-	-	0.846*	0.998*
T_{min1}	-	-	-	0.845*

Note. BI, current month's Breteau Index; T_{min} , current month's minimum temperature; T_{ave} , current month's average temperature; T_{min1} , previous month's minimum temperature; T_{ave1} , previous month's average temperature; * means $P < 0.001$.

Table 3. Results of the Negative Binomial Regression Model with Cubic Regression Splines for Selected Variables

Model	Variables	edf	χ^2	P
Model 1	BI	1.585	10.824	0.004
	T_{min}	5.088	25.060	<0.001
Model 2	BI	1.000	10.937	<0.001
	T_{ave}	2.729	19.800	<0.001
Model 3	BI	1.000	8.181	0.004
	T_{min1}	1.000	30.349	<0.001
Model 4	BI	4.647	12.301	0.041
	T_{ave1}	1.000	25.383	<0.001

Note. BI, current month's Breteau Index; T_{min} , current month's minimum temperature; T_{ave} , current month's average temperature; T_{min1} , previous month's minimum temperature; T_{ave1} , previous month's average temperature; edf, effective degree of freedom.

Table 4. Results of the Negative Binomial Regression Model with Parametric Terms for Selected Variables

Model	Variables	β	Z	P	Percentage Change 95% CI
Model 1	BI	0.306	3.403	<0.001	35.8 (13.9-62.0)
	T_{min}	0.500	4.868	<0.001	64.9 (34.8-101.7)
Model 2	BI	0.295	3.039	0.002	34.2 (11.0-62.3)
	T_{ave}	0.255	4.024	<0.001	29.0 (13.9-46.0)
Model 3	BI	0.247	2.860	0.004	28.0 (8.1-51.7)
	T_{min1}	0.418	5.513	<0.001	51.8 (30.9-76.1)
Model 4	BI	0.263	3.135	0.002	30.1 (10.4-53.4)
	T_{ave1}	0.424	5.824	<0.001	52.8 (32.5-76.3)

Note. BI, current month's Breteau Index; T_{min} , current month's minimum temperature; T_{ave} , current month's average temperature; T_{min1} , previous month's minimum temperature; T_{ave1} , previous month's average temperature.

DISCUSSION

Time-series analysis has been extensively used to study the effects of meteorological factors on DF incidence^[16,28-30]. In the current study, negative binomial regression models were used to examine the effects of meteorological measures on the monthly number of DF cases in Guangzhou between 2006 and 2014. The results indicated that current month's BI and average temperature (T_{ave}) and previous month's minimum temperature (T_{min}) and T_{ave} were positively associated with DF incidence. A threshold of 18.3 °C was discovered in the relationship between current month's T_{min} and DF incidence.

The density of vector mosquitoes can be expressed through several indices, including BI and/or positive house index, number of indoor resting *Aedes* females, etc.^[31]. Among these indices, BI is the most widely used index due to its high correlation with adult mosquito density^[32]. A previous study indicated that, when BI is equal to or greater than 9.5, there may be a high risk of DF epidemic. If BI increases to 20-30, DF outbreaks may occur at any time. The previous outbreaks were effectively controlled after BI fell below 5 for 3 weeks. Consistent with results of studies, which found that mosquito density was positively correlated with DF outbreak^[33-35], the present study showed that the monthly number of DF cases was positively associated with BI of the current month. Likewise, Pham et al.^[36] also found that the monthly number of DF cases was positively associated with BI in Vietnam. One case-control study supported the findings of the current study and verified that the relationship between mosquito density and DF infection is dynamic^[37]. In 2014, the DF pandemic in several communities and blocks also verified this correlation. The present study further indicated that BI is an objective indicator to predict and evaluate the state of a DF epidemic.

Meteorological variables, such as temperature, have been identified as an important factor involved in the transmission of DF^[16,38-39]. Temperature affects the spread of DENV at each stage of the mosquito's life cycle. Research has indicated that the extrinsic incubation period and viral development rate can be shortened with higher temperatures^[39]. The present study found that current month's T_{ave} and T_{min} at 1-month lag and T_{ave} at 1-month lag were positively associated with DF incidence. These findings are supported by other studies discussing the expected

time lag between meteorological factors and DF cases. In Brazil, positive associations were found between the minimum temperatures and DF transmission at lag-0^[30]. A retrospective ecological study conducted in Mexico from 1995 to 2003 showed that increases in weekly T_{min} were a significant factor in the increase in the reported DF cases^[40]. Lu et al.^[41] also reported that minimum temperature at lag-1 month was positively associated with DF incidence in Guangzhou during 2001-2006. In Taiwan, Wu et al.^[22] found that, with every 1.0 °C increase of monthly average temperature, there was a 1.95-fold increased risk for DF transmission, as well as positive associations between the minimum temperature at lag 1-3 months and DF cases.

Interestingly, the current study identified a threshold of 18.3 °C in the relationship between T_{min} and DF incidence- T_{min} had a significantly positive effect on the monthly number of DF cases when T_{min} was smaller than 18.3 °C. This finding is in general agreement with another study in which T_{min} was reported to be positively associated with DF incidence. A recent study documenting the relationship between DF cases and meteorological factors in Cali, Colombia, is particularly relevant to the findings herein because it also noted a strong correlation with the minimum temperature threshold of 18.0 °C^[21]. Further, the authors also revealed that the lagged mean daily temperature range was the strongest local predictor of DF incidence, thus paving the way for further research.

The present study has the following strengths. Firstly, it explored the log non-linear relationship between temperatures and DF incidence and further provided a T_{min} threshold of 18.35 °C for the relationship, which helps to better understand the impact of T_{min} on DF incidence. Secondly, to the best of the authors' knowledge, this is the first study to analyze the causes for the high incidence in the DF pandemic of Guangzhou between 2006 and 2014.

The major limitation of this study is that fact that only the effects of BI, T_{ave} , and T_{min} on DF incidence were analyzed despite other factors, such as change in urbanization status, population density, and vector control measures, also possibly affecting DF incidence; nevertheless, it is difficult to obtain relevant data of these factors. Further study is needed to take these factors into consideration.

CONCLUSIONS

Mosquito density, T_{ave} , and T_{min} were found to be statistically associated with DF incidence in Guangzhou, China. These findings elucidate how mosquito density and temperatures influence the development of DF epidemics. Such information could be useful in the development of a DF early warning system and assist in effective control strategies and decision making in DF epidemics and public health prevention.

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DECLARATION OF CONFLICTING INTERESTS

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

AUTHORS' CONTRIBUTIONS

SHEN Ji Chuan, LUO Lei, CHEN Xiao Guang, and YANG Zhi Cong initiated the study. LUO Lei, JING Qin Long, and SHEN Ji Chuan collected the data. SHEN Ji Chuan, LI Li, and OU Chun Quan analyzed the data. SHEN Ji Chuan, LI Li, CHEN Xiao Guang, and YANG Zhi Cong wrote the paper. All authors contributed to and approved the submitted version of the manuscript.

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