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RESEARCH ARTICLE

Effect of temperature and its interactions with relative humidity and rainfall on malaria in a temperate city Suzhou, China

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Abstract
Malaria is a climate-sensitive infectious disease. Many ecological studies have investigated the independent impacts of ambient temperature on malaria. However, the optimal temperature measures of malaria and its interaction with other meteorological factors on malaria transmission are less understood. This study aims to investigate the effect of ambient temperature and its interactions with relative humidity and rainfall on malaria in Suzhou, a temperate climate city in Anhui Province, China. Weekly malaria and meteorological data from 2005 to 2012 were obtained for Suzhou. A distributed lag nonlinear model was conducted to quantify the effect of different temperature measures on malaria. The best measure was defined as that with the minimum quasi-Akaike information criterion. GeoDetector and Poisson regression models were employed to quantify the interactions of temperature, relative humidity, and rainfall on malaria transmission. A total of 13,382 malaria cases were notified in Suzhou from 2005 to 2012. Each 5 °C rise in average temperature over 10 °C resulted in a 22% (95% CI: 17%, 28%) increase in malaria cases at lag of 4 weeks. In terms of cumulative effects from lag 1 to 8 weeks, each 5 °C increase over 10 °C caused a 175% growth in malaria cases (95% CI: 139%, 216%). Average temperature achieved the best performance in terms of model fitting, followed by minimum temperature, most frequent temperature, and maximum temperature. Temperature had an interactive effect on malaria with relative humidity and rainfall. High temperature together with high relative humidity and high rainfall could accelerate the transmission of malaria. Meteorological factors may affect malaria transmission interactively. The research findings could be helpful in the development of weather-based malaria early warning system, especially in the context of climate change for the prevention of possible malaria resurgence.

Keywords Malaria · Temperature · Interaction · China · Distributed lag nonlinear model

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Introduction

Malaria, a recognized global public health priority, is caused by the infection of *Plasmodium* parasite, which is transmitted to humans through the bite of *Anopheles* mosquitoes (Josling and Llinas 2015). In 2000, more than 1 million people died from malaria all over the world, posing a great threat to population health (World Health Organization (WHO) 2015). Due to the implementation of effective measures since 2000, considerable achievements had been made by the global society in the efforts of eliminating malaria (WHO 2015). Although the morbidity and mortality of malaria had declined dramatically in the past decades, there were still 228 million cases and 405,000 deaths reported worldwide in 2018 (WHO 2019a). It should be noted that malaria control and eradication are stagnant and experiencing a bottleneck period in recent years, especially in the developing countries due to antimalarial drug resistance, increased population movement, and reduced financial support (WHO 2018; Feachem et al. 2019).

China has made great success in malaria control due to decades of large-scale national continuous efforts, with a dramatic reduction in malaria incidence from 30 million cases each year in the 1940s to zero indigenous case since 2017 (WHO 2019b). Currently, China is in a malaria elimination stage aiming to become malaria-free by 2020. However, the resurgence of malaria in the early twenty-first century along Huanghuai River Basin challenges the elimination of malaria in China (Gao et al. 2012). For example, Anhui Province almost achieved the goal of malaria elimination in 1999 with an incidence of 1.3 cases per 100,000 population. However, in 2006, its average incidence rate rebounded to 57.16 per 100,000 population and ranked the 1st in all provinces of China (Data Center for Public Health in China (DCFPH) 2019).

The seasonality of malaria incidence indicates that malaria is a climate-sensitive infectious disease (Gunda et al. 2017; Bai et al. 2013; Wu et al. 2017). Climatic factors, especially for ambient temperature, play an important role in malaria transmission by affecting the life cycle of an *Anopheles* mosquito, the duration of the extrinsic phase of *Plasmodium* parasites, and human behavior (Teklehaimanot et al. 2004; Ren et al. 2015). To date, some ecological studies have investigated the independent impacts of temperature indicators (e.g., average temperature, maximum temperature, and minimum temperature) on malaria, which were characterized as lagged effect and nonlinearity (Zhao et al. 2014a; Guo et al. 2015; Hundessa et al. 2017). Yin et al. introduced a new indicator called most frequent temperature (MFT) to reflect how humans adapt to ambient temperature (Yin et al. 2019). It is yet to be determined which temperature indicator could be the most suitable one for its impact on malaria transmission. In addition, evidence from experimental studies has shown that the interactions between temperature and relative humidity (or rainfall) could change the metabolism of *Anopheles* mosquito, influencing its growth and reproduction for malaria transmission (Lyons et al. 2014; Kristan et al. 2008). However, limited epidemiological studies have quantified the interactive effects of different meteorological factors on malaria transmission.

In this study, we aim to identify the best temperature measure to reflect the impacts of ambient temperature on malaria and quantify its interactions with relative humidity and rainfall. Results of this study will enable a better understanding of the interactive effects of meteorological factors on malaria transmission, which may contribute to the development of malaria control and prevention strategies in the context of climate change.

Materials and methods

Study location and period

Suzhou, a prefecture-level city in the northeast of Anhui Province in China, locates between 116° 09′–118° 10′ E longitude and 33° 18′–34° 38′ N latitude (Fig. 1). In 2016, Suzhou had a population of 5.59 million and a land area of 9787 km^2. The city features a semi-humid monsoon climate with an annual average temperature of 15.8 °C and an annual mean rainfall of 898 mm. Suzhou is a historical malaria epidemic area in China with an incidence rate of 33 per 100,000 population from 2005 to 2012 (Xiang et al. 2018).

Data collection

Disease surveillance data

Weekly surveillance data of malaria in Suzhou from 2005 to 2012 was extracted from the National Notifiable Disease Surveillance System which was launched in 2004. The study period was selected to ensure data accuracy and exclude increased imported cases after 2012 (DCFPH 2019; Feng and Xia 2014). Malaria has been listed as a statutory notifiable category-B infectious disease in China since 1978. All malaria cases were confirmed according to the national diagnostic criteria for malaria (GB15989-1995). Both clinically diagnosed and laboratory-confirmed cases were included in the data analysis. The surveillance data included variables such as age, gender, occupation, date of onset, and site. During 2004 to 2012, the vast majority (99.66%) of malaria cases in Anhui Province were indigenous (Feng and Xia 2014).

Meteorological data

Daily meteorological data during the study period were downloaded from the China Meteorological Data Sharing Service System (www.data.cma.cn) and aggregated into

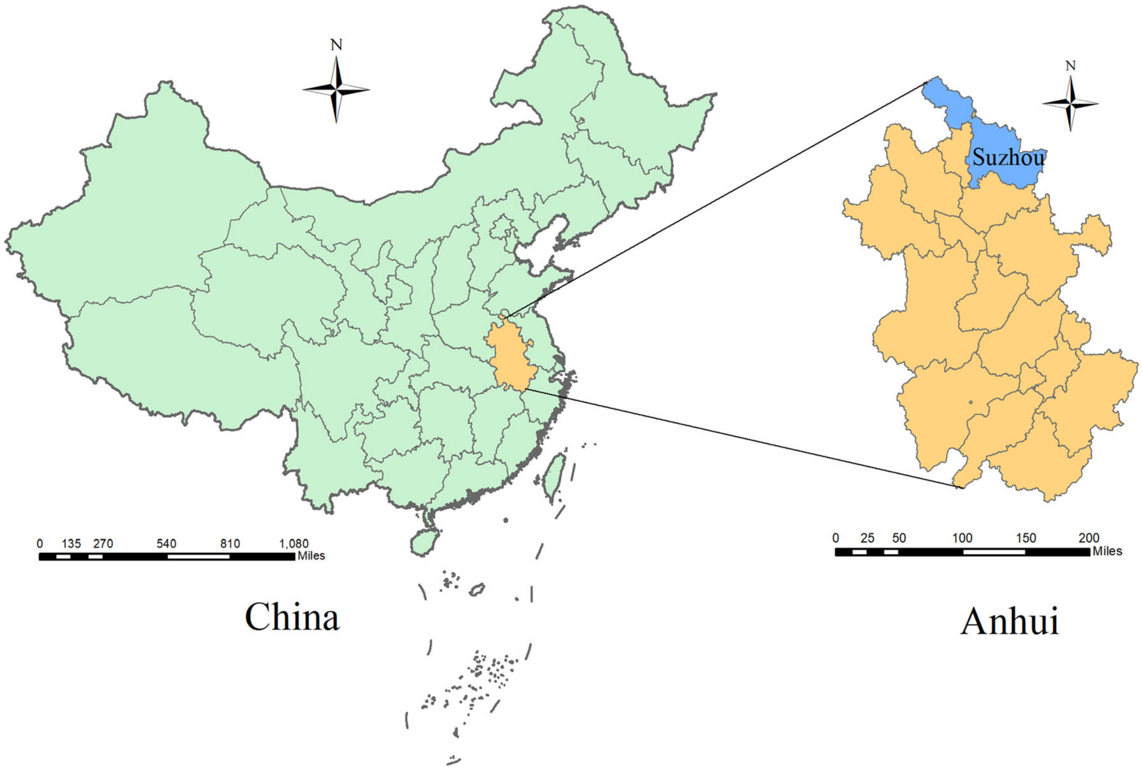

Fig. 1 Geographical location of Suzhou, Anhui Province in China

weekly data, including weekly average temperature, maximum temperature, minimum temperature, relative humidity, and rainfall. A new indicator called weekly MFT was also introduced to our analysis, which was obtained by calculating the most frequent daily average temperature during the week. Specifically, it is the mode of daily average temperature during the week (Yin et al. 2019). If daily temperature occurred with the same frequency at the week, the means of daily temperature were applied to fill the values. A meteorological station (33° 38′ N, 116° 59′ E) was selected to represent Suzhou.

Statistical analysis

Relationships between meteorological factors and malaria

Descriptive analysis was performed to describe the temporal distribution characteristics of malaria and meteorological factors in Suzhou. A generalized additive model (GAM) with quasi-Poisson family for over-dispersed data was used to estimate the exposure-response relationships between meteorological factors and malaria. Degrees of freedom of spline for meteorological and time variables in GAM were chosen on the basis of generalized cross-validation (GCV) rules (Simon 2006).

To determine which temperature indicator can best reflect the ambient temperature on malaria transmission, a two-stage analytical approach was applied to obtain robust comparisons among different temperature indicators. In the first-stage analysis, the distributed lag nonlinear model (DLNM) was applied to quantify the delayed and cumulative effects of different temperature variables on malaria (Gasparrini 2010), respectively, including average temperature, maximum temperature, minimum temperature, and MFT. A cross-basis function of temperature was established with a single linear threshold function chosen based on the previous research (Ding et al. 1991; Mukhtar et al. 2019). Previous studies have reported that relative humidity and rainfall were associated with the number of malaria cases (Guo et al. 2015; Zhao et al. 2014a; Xiang et al. 2018). Therefore, weekly relative humidity and weekly rainfall were also controlled in the models. The natural cubic splines with 3 degrees of freedom were used to control these confounding factors (Guo et al. 2015). To adjust for the long-term trend and seasonality, stratified factors of calendar year and month were incorporated into the model (Liu et al. 2018). The delayed effect of temperature on malaria was explored for 1–8 weeks based on the incubation period of malaria in humans (Teklehaimanot et al. 2004). The model can be specified as:

$$\log[E(Y_t)] = \beta + cb(\text{tem}) + ns(hum, 3) + ns(rain, 3) + factor(strata) \quad (1)$$

where Y_t is the weekly total number of malaria cases at time t; β is the intercept; cb(tem) indicates cross-basis for weekly average temperature, maximum temperature, minimum temperature, and MFT, respectively; *ns*() denotes a natural cubic spline function; *hum* and *rain* represent relative humidity and rainfall; *factor(strata)* is a dummy variable to adjust long-term trend and seasonality.

In the second-stage analysis, quasi-Akaike information criterion (QAIC) for each specific DLNM was used to compared the goodness of fits to determine which temperature variable can best represent the effect of ambient temperature on malaria transmission (Peng et al. 2006; Fan et al. 2020).

Stratified analyses

Stratified analyses were conducted to identify subpopulation's susceptibility to temperature effects by gender and age group. Differences in effect estimates between groups were tested using Eq. 2, as shown below. If the nominal 95% interval contains 0, the difference between two estimates is statistically insignificant (Nathaniel and Jane 2001).

$$z = \left(\widehat{Q}_1 - \widehat{Q}_2\right) / \sqrt{\widehat{\mathrm{SE}_1} + \widehat{\mathrm{SE}}_2} \qquad (2)$$

where $\widehat{Q}_1$ and $\widehat{Q}_2$ represent the estimates in the two subgroups, and $\widehat{\mathrm{SE}_1}$ and $\widehat{\mathrm{SE}}_2$ are standard errors.

Stratified heterogeneity q statistic estimated from the GeoDetector model was employed to measure and attribute the stratified heterogeneity (Wang et al. 2010; Wang and Hu 2012; Wang et al. 2016). Continuous meteorological variables were converted to categorical variables using different discretization methods, including equal breaks, natural breaks, quantile breaks, geometric breaks, and standard deviation breaks (Cao et al. 2013). Default values of break numbers ranging from 3 to 7 were selected (Song et al. 2020). The optimal discretization method and break number were determined by the maximum q value. Percentage of heterogeneity explained by temperature in each subgroup equaled to 100q% (Wang et al. 2016). The larger the q value was, the stronger the influence of temperature on malaria cases.

Interactions of meteorological factors on malaria

Three methods were employed to test the possible interactions of meteorological factors on malaria transmission. First, a non-parametric bivariate response model based on GAM was then employed to explore the patterns of both temperature and humidity on malaria transmission by using a thin-plate function without linear assumptions (Roberts 2004; Breitner et al. 2014). This model could provide a three-dimensional diagram to observe whether or not there are potential interactive patterns between the two continuous predictors on malaria transmission. We also explored the interactive patterns between temperature and rainfall. Degrees of freedom for thin-plate spline were chosen using GCV rules (Simon 2006). The optimal lag period from the DLNM was used.

$$\log[E(Y_t)] = \beta + s(tem, hum) + s(rain) + s(time) \qquad (3)$$

where s (*tem, hum*) denotes the two-dimensional thin-plate spline function to model the interaction of temperature and relative humidity on malaria transmission. $s(tem, hum) = \sum_{i=1}^{I}\sum_{l=1}^{L} \delta_{il}\, d_l(tem) a_i(hum)$, where δ_{il} is the parameter, $d_l(tem)$ and $a_i(hum)$ are the smoothing functions. This formula will allow each of temperature parameters to vary smoothly with humidity. There was a simple relationship between the model matrix X: $X_i = X_{temi} \otimes X_{humi}$, where X_i indicates the ith row of X, and $\otimes$ is the Kronecker product (Simon 2006). S (*rain*) is the spline of rain to control for confounding factors. S (*time*) is the spline of time to control for long-term trend and seasonality.

Second, the interaction detector was used for identifying the interactions of meteorological variables on malaria cases (Wang et al. 2010; Wang and Hu 2012). Five possible types of interaction effects were explored, including nonlinear-weaken ($q_{u\cap v} < \min[q_u,q_v]$), uni-variable weaken ($\min[q_u,q_v] \le q_{u\cap v} \le \max[q_u,q_v]$), bi-variable enhance ($\max[q_u,q_v] < q_{u\cap v} < [q_u + q_v]$), independent ($q_{u\cap v} = [q_u + q_v]$) and nonlinear-enhanced ($q_{u\cap v} > [q_u + q_v]$) (Wang et al. 2010; Song et al. 2020), where q_u and q_v are the q values of variable u and v, respectively, and $q_{u\cap v}$ is the q value of the interaction between variable u and variable v.

Third, a Poisson regression model was fitted to quantify the interactions. Each of the weather variables was divided into two groups cut by the possible turning point, which was observed from the three-dimensional diagram above (Roberts 2004). Specifically, temperature, humidity, and rainfall were divided into $T = 0$ (if temperature lower than turning point) and $T = 1$ (if temperature higher than turning point), $H = 0$ and $H = 1$, and $R = 0$ and $R = 1$. The model was as follows:

$$\log[E(Y_t)] = \beta + T + H/R + T : H/R + \mathrm{COV} \qquad (4)$$

where T, H, and R are the new binary variables to represent the average temperature, humidity and rainfall, respectively. COV are other confounding factors, which was the same as model 1.

Through model 4, RR_{01} ($T = 0$, $H/R = 1$), RR_{10} ($T = 1$, $H/R = 0$), and RR_{11} ($T = 1$, $H/R = 1$) for average temperature and humidity (or rainfall) were obtained. Possible multiplication and additive interaction were assessed by the following indexes: the interaction relative risk (IRR), relative excess risk due to interaction (RERI), and the attributable proportion due to interaction (AP) (Andersson et al. 2005; Pan et al. 2020; Du et al. 2019). Synergistic interaction was observed when IRR > 1 or RERI > 0; and antagonistic interaction when IRR < 1 or RERI < 0.

$$\mathrm{IRR} = \mathrm{RR}_{11} / (\mathrm{RR}_{01} + \mathrm{RR}_{10}) \qquad (5)$$

$$\mathrm{RERI} = \mathrm{RR}_{11} - \mathrm{RR}_{01} - \mathrm{RR}_{10} + 1 \quad (6)$$

$$\mathrm{AP} = \mathrm{RERI}/\mathrm{RR}_{11} \quad (7)$$

Sensitivity analysis

Finally, we performed additional sensitivity analyses to assess the model fitness and performance. The sensitivity of model was tested by changing the threshold value of temperature, adjusting the confounding factors, and varying the lag period.

All data analyses were conducted in R 3.5.2 with "mgcv," "dlnm," and "GD" packages (Simon 2006; Gasparrini 2011; Song et al. 2020). All statistical tests were two-sided, and $p < 0.05$ was considered statistically significant.

Results

Descriptive analysis of the meteorological variables and malaria cases

A total of 13,382 malaria cases were notified in Suzhou over the study period, with a weekly number of 32 malaria cases. The main characteristics of malaria cases and meteorological variables were summarized in Table 1. The weekly mean values for average temperature, maximum temperature, minimum temperature, MFT, relative humidity, and rainfall were 15.8 °C, 20.7 °C, 11.8 °C, 15.8 °C, 66.6%, and 2.5 mm, respectively.

The time series plot of weekly malaria cases in Suzhou is shown in Fig. S1. There was a downward trend in malaria cases from 2005 to 2012. Seasonal pattern in malaria was observed with a peak in summer and a bottom in winter, corresponding to the patterns of meteorological factors (Fig. S2).

As shown in Table 2, the correlation coefficients between the number of weekly malaria cases and weekly average temperature, maximum temperature, minimum temperature, MFT, relative humidity, and rainfall at lag 4 weeks were 0.49 ($p < 0.05$), 0.48 ($p < 0.05$), 0.50 ($p < 0.05$), 0.49 ($p < 0.05$), 0.32 ($p < 0.05$), and 0.22 ($p < 0.05$), respectively. There were strong correlations (> 0.90) between temperature measures.

Relationships between meteorological factors and malaria

Figure 2 illustrates the crude relationships between meteorological factors and the number of malaria cases at lag of 4 weeks. A positive linear relationship was observed for temperature, relative humidity, and rainfall. The relationships between different temperature measures and malaria cases were consistently observed (Fig. 3). Results showed that when ambient temperature exceeded 10 °C, each 5 °C increase in average temperature, maximum temperature, minimum temperature, and MFT was associated with an approximately 22% (95% CI: 17%, 28%), 20% (95% CI: 16%, 25%), 23% (95% CI: 17%, 28%), and 19% (95% CI: 15%, 24%) increase in the number of malaria cases at lag of 4 weeks, respectively. Cumulative effects were plotted to show that each 5 °C increase in average temperature, maximum temperature, minimum temperature, and MFT above 10 °C was associated with about 175.0% (95% CI: 139%, 216%), 169.0% (95% CI: 130%, 214%), 157.0% (95% CI: 126%, 193%), and 169.0% (95% CI: 133%, 209%) increase in the cumulative number of malaria cases from 1 to 8 weeks, respectively.

The average temperature obtained the best performance with QAIC values of 2465.18, followed by minimum temperature (QAIC = 2468.98), MFT (QAIC = 2486.58), and maximum temperature (QAIC = 2558.32).

Stratified analyses

Males were at a similar temperature-related risk of malaria as females (Table 3). When comparing the differences between age groups, the effects of temperature on young-aged group (0–14 years old, RR: 1.28, 95% CI: 1.21, 1.36) and middle-aged group (15–59 years old, RR: 1.24, 95% CI: 1.18, 1.31)

Table 1 Summary statistics for malaria cases and weekly meteorological variables in Suzhou, Anhui Province, China, 2005–2012

	Mean	SD	Min	Percentiles			Max
				25%	50%	75%	
Malaria cases	32.0	57.0	0.0	1.0	4.0	34.0	314.0
Average temperature (°C)	15.8	9.7	− 2.1	6.8	17.5	24.5	32.2
Maximum temperature (°C)	20.7	9.8	0.0	11.9	23.1	28.9	37.2
Minimum temperature (°C)	11.8	9.7	− 6.1	3.1	12.6	20.7	28.1
Most frequent temperature (°C)	15.8	9.8	− 3.2	7.0	17.9	24.7	32.9
Relative humidity (%)	66.6	12.6	30.3	57.4	67.0	75.7	93.0
Rainfall (mm)	2.5	5.1	0.0	0.0	0.6	2.7	47.7

SD, the standard deviation; *Min*, the minimum of variables; *Max*, the maximum of variables

Table 2 Cross-correlation analysis of meteorological variables and malaria cases at lag 4 weeks

	Malaria cases	Average temperature	Maximum temperature	Minimum temperature	Most frequent temperature	Relative humidity
Average temperature (°C)	0.49 [a]					
Maximum temperature (°C)	0.48 [a]	0.99 [a]				
Minimum temperature (°C)	0.50 [a]	0.99 [a]	0.97 [a]			
Most frequent temperature (°C)	0.49 [a]	0.99 [a]	0.99 [a]	0.99 [a]		
Relative humidity (%)	0.32 [a]	0.33 [a]	0.24 [a]	0.41 [a]	0.32 [a]	
Rainfall (mm)	0.22 [a]	0.41 [a]	0.34 [a]	0.47 [a]	0.40 [a]	0.63 [a]

[a] $p < 0.05$

appeared larger than those on old-aged group at lag 4 weeks (≥ 60 years old, RR: 1.14, 95% CI: 1.07, 1.22). Results of stratified heterogeneity q statistic showed that temperature explained 29% ($p < 0.05$), 31% ($p < 0.05$), 26% ($p < 0.05$), 30% ($p < 0.05$), and 30% ($p < 0.05$) of heterogeneity for male, female, young-aged (0–14 years old), middle-aged (15–59 years old), and old-aged group (≥ 60 years old), respectively (Table 4).

Interactions of temperature with relative humidity and rainfall on malaria transmission

Figure 4 displayed the joint effects of temperature and humidity/rainfall on malaria transmission. Results showed that the association between temperature and malaria changed with humidity. High temperature and high humidity led to a higher risk of malaria transmission. Interaction between

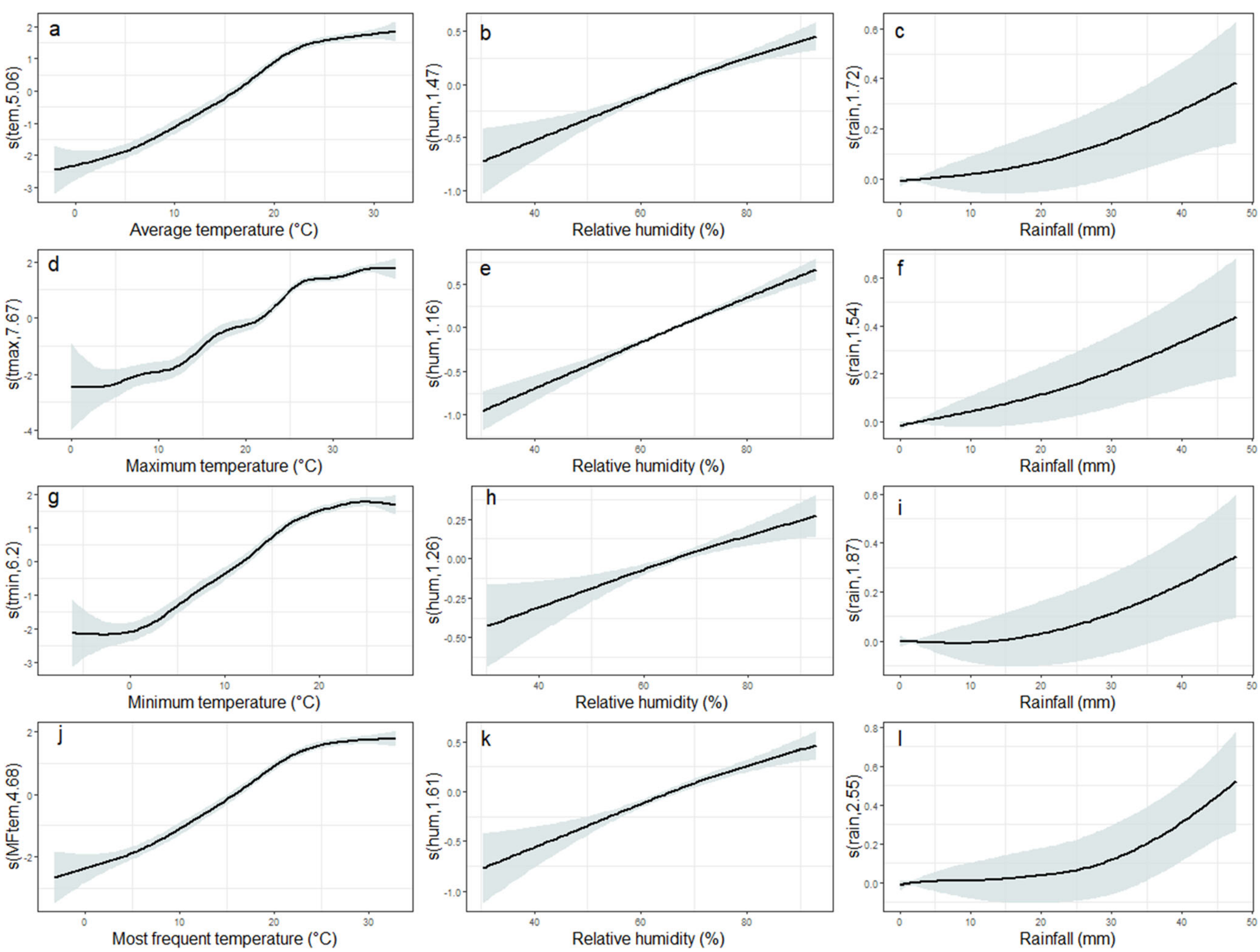

Fig. 2 Relationships between meteorological factors and the number of malaria cases at lag 4 week. $s()$ denotes the smoothing spline functions of independent variables. The numbers in $s()$ denote smoothness of curve

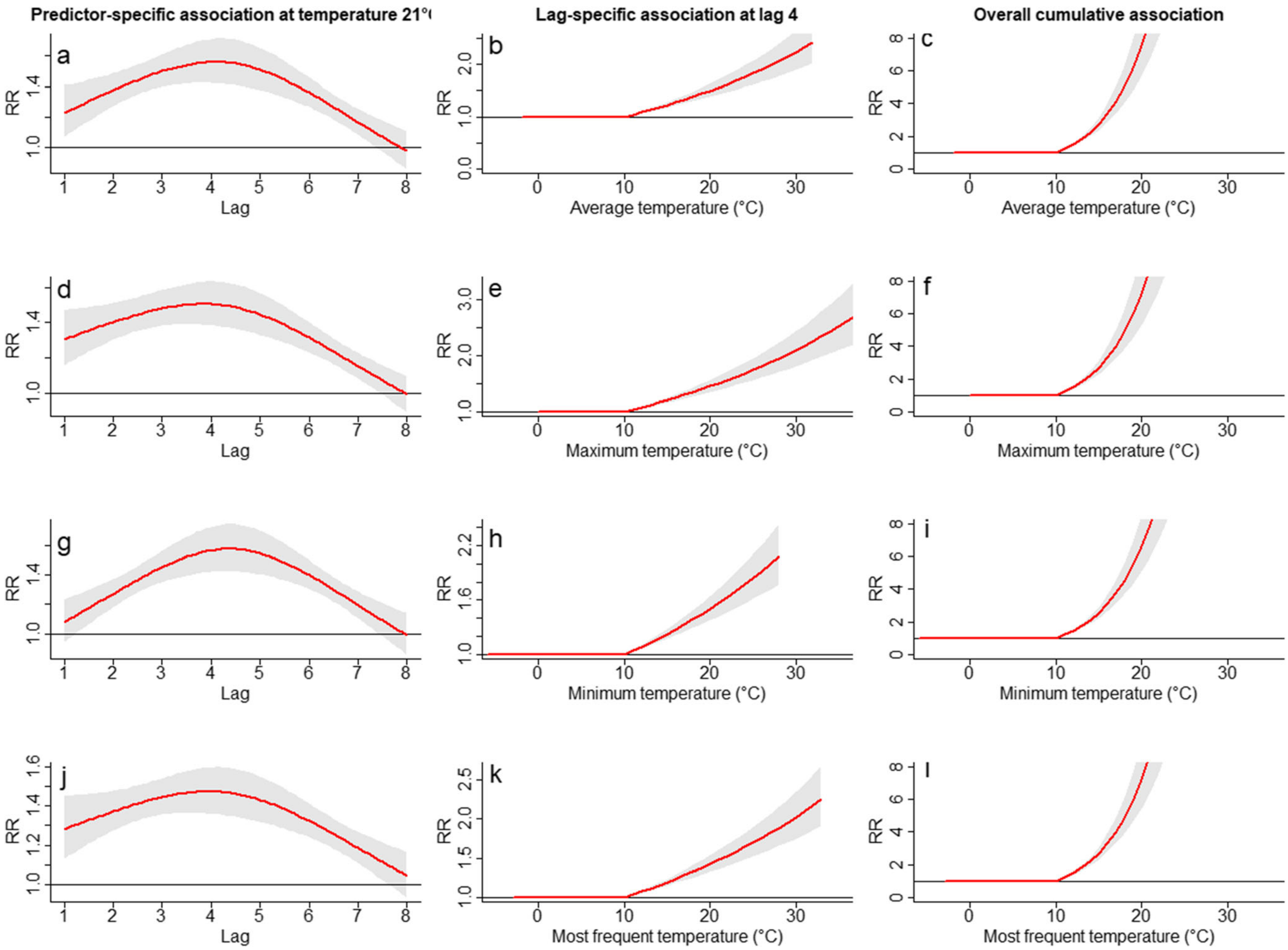

Fig. 3 The lagged and cumulative effects of different temperature measures on malaria at lag 1–8 weeks

average temperature and humidity has greater explanatory power (q = 0.46) than the single factor, indicating that the interaction is bi-variable enhancement (Table 4). The IRR (1.42, 95% CI: 1.09, 1.84), RERI (0.36, 95% CI: 0.13, 0.59), and AP (0.30, 95% CI: 0.09, 0.50) also indicated a significant synergistic interaction between temperature and humidity (Table 5). Similar synergistic interaction between temperature and rainfall was also observed with explanatory power which was 38%, IRR was 1.28 (95% CI: 1.06, 1.53), RERI was 0.31 (95% CI: 0.10, 0.52), and AP was 0.21 (95% CI: 0.08, 0.35). In addition, as shown in Fig. 5, Table 4 and Table 6, there was weak synergistic interaction between temperature and humidity (or rainfall) in different gender and age groups. The turning point for temperature, humidity, and rainfall in all groups was 25 °C, 60%, and 5 mm, respectively (Fig. S3).

Sensitivity analysis

When changing the threshold temperatures from 10 °C to 15 °C or 5 °C (Fig. S4), adjusting the confounding variables (e.g., included humidity only, set the splines with 4 degrees of freedom) (Figs. S5–6), and varying different lag period (Fig. S7), the effect of temperature on malaria transmission was similar with original results, indicating the model was robust.

Discussion

The effect of ambient temperature on malaria transmission has received increasing attentions in recent years due to the likely increasing malaria burden in a warming climate. In this study, we quantified the lagged and cumulative effects of different temperature measures on malaria from 2005 to 2012 in Suzhou, using a generalized additive model and a distributed lag nonlinear model. Our results revealed the effect of temperature and its interactions with humidity and rainfall on malaria transmission in a temperate city in China.

The effect of temperature on malaria transmission

Similar to our results, the positive role of temperature in a certain range for malaria transmission has been reported in

Table 3 The effect of average temperature on malaria cases along the lag weeks

Subgroup	Lag 1	Lag 4	Lag 6	Lag 8	Lag 1–8
Total	1.10 (1.03, 1.17)[a]	1.22 (1.17, 1.28)[a]	1.15 (1.11, 1.19)[a]	0.99 (0.93, 1.05)	2.75 (2.39, 3.16)[a]
Gender					
Male	1.11 (1.03, 1.19) [a]	1.25 (1.19, 1.31)[a]	1.16 (1.12, 1.20)[a]	0.98 (0.92, 1.04)	2.93 (2.49, 3.45)[a]
Female	1.08 (1.01, 1.17) [a]	1.19 (1.14, 1.25)[a]	1.14 (1.10, 1.18)[a]	1.01 (0.94, 1.08)	2.51 (2.13, 2.96)[a]
Cochran's Q value	0.26	2.01	0.50	0.44	1.71
Age (years)					
Young (0–14 years)	1.11 (1.01, 1.21) [a]	1.28 (1.21, 1.36)[a]	1.16 (1.11, 1.22)[a]	0.92 (0.82, 1.00)	2.96 (2.43, 3.62)[a]
Middle (15–59 years)	1.09 (1.01, 1.17) [a]	1.24 (1.18, 1.31)[ab]	1.16 (1.12, 1.21)[a]	0.98 (0.92, 1.05)	2.84 (2.41, 3.36)[a]
Old (≥ 60 years)	1.12 (1.02, 1.24) [a]	1.14 (1.07, 1.22)[ab]	1.11 (1.06, 1.17)[a]	1.06 (0.97, 1.17)	2.41 (1.93, 3.00)[a]
Cochran's Q value	0.22	6.52[a]	1.95	4.62	2.05

[a] $p < 0.05$

[b] The difference was significant when comparing with the old group

previous studies (Hundessa et al. 2017; Gunda et al. 2017; Kim et al. 2012; Li et al. 2013). The underlying biological mechanisms may be attributed to the following two ways. First, higher temperature, at an optimum range, could shorten the time of the multiplication of the *Plasmodium* within mosquitoes (Ren et al. 2015), accelerate sporogony cycle of parasite (Teklehaimanot et al. 2004; Mordecai et al. 2019), and lengthen the survival of mosquitoes (le Sueur and Sharp 1991; Mukhtar et al. 2019), which may subsequently increase the probability of malaria transmission. Second, the behavior of human would be changed during hot days such as wearing less clothing and spending more time outdoors. This may increase the risk of mosquito biting.

Moreover, our study indicated that each 5 °C rises of ambient temperature (e.g., average temperature) resulted in a 22% increase in malaria cases. However, effect estimates in different regions were not consistent according to previous studies. For example, a study from Guangzhou, south China, showed that a 1 °C rise in average temperature was associated with a 0.9% increase in the monthly number of malaria cases from 2006 to 2012 (Li et al. 2013). A study from South Korea found that the number of malaria cases increased by 16.1% for each 1 °C rise in weekly average temperature for the years 2001–2009 (Kim et al. 2012). The differences in geographical and climate variations, statistical methods, and other non-climatic factors may be the reasons leading to the regional discrepancies. A multi-city study in China found that cities in a cool climate zone were more sensitive to the increase of ambient temperature than that in a warm climate (Xiang et al. 2018). Thus, increasing temperature in a cooler climate area may lead to a higher risk of malaria resurgence in the future (Chua 2012; Song et al. 2016; Zhao et al. 2014b). Our study also found that young- and middle-aged individuals may be more vulnerable to temperature attributable malaria than elder individuals. This may be because young people were more likely to have more outdoor activities, which potentially increases the risk of infection.

Table 4 q values of meteorological variables on malaria cases at lag 4 weeks

Variable	q_T	q_H	q_R	$q_{T \cap H}$	$q_{T \cap R}$
Total	0.30[a]	0.18[a]	0.21[a]	0.46[b]	0.38[b]
Male	0.29[a]	0.19[a]	0.20[a]	0.46[b]	0.37[b]
Female	0.31[a]	0.17[a]	0.21[a]	0.45[b]	0.38[b]
Young	0.26[a]	0.16[a]	0.17[a]	0.40[b]	0.33[b]
Middle	0.30[a]	0.19[a]	0.21[a]	0.47[b]	0.38[b]
Old	0.30[a]	0.18 [a]	0.21[a]	0.46[b]	0.38[b]

T, average temperature; *H*, humidity; *R*, rainfall; $T \cap H$, the interaction between average temperature and humidity; $T \cap R$, the interaction between average temperature and rainfall

[a] $p < 0.05$

[b] Bi-variable enhance

In addition, our results demonstrate that average temperature may be marginally superior to other temperature measures in terms of model fitting. A study in European cities also reported the important role of average temperature in ambient temperature-mortality association, which could better reflect complete heat exposure compared to other heat measures (Hajat et al. 2006). However, in practice, a large number of missing values may influence the use of temperature measures. As suggested by Barnett et al., the selection of temperature indicator should be based on practical feasibility such as the accessibility and completeness of the data (Barnett et al. 2010).

Interactive effects of relative humidity and rainfall on temperature-malaria association

Our study indicated that the number of malaria cases would increase under the condition of high temperature and high humidity. Some studies illustrated the critical role of humid conditions in malaria transmission especially in arid region

Table 5 Interactive analysis between average temperature and humidity/rainfall on malaria cases at lag 4 weeks

Variable	Group	Regressor	RR (95% CI)	IRR	RERI	AP
Temperature	Humidity	$T = 0, H = 0$	Ref	1.42 (1.09–1.84) [a]	0.36 (0.13–0.59) [a]	0.30 (0.09–0.50) [a]
		$T = 0, H = 1$	0.93 (0.78–1.12)			
		$T = 1, H = 0$	0.91 (0.69–1.19)			
		$T = 1, H = 1$	1.20 (0.96–1.51)			
	Rainfall	$T = 0, R = 0$	Ref	1.28 (1.06–1.53) [a]	0.31 (0.10–0.52) [a]	0.21 (0.08–0.35) [a]
		$T = 0, R = 1$	0.98 (0.85–1.13)			
		$T = 1, R = 0$	1.15 (0.98–1.36)			
		$T = 1, R = 1$	1.44 (1.19–1.75) [a]			

T, average temperature; *H*, humidity; *R*, rainfall

[a] $p < 0.05$

Table 6 Subgroup analysis between average temperature and humidity/rainfall on malaria cases at lag 4 weeks

Subgroup	Variable	Regressor	RR (95% CI)	IRR	RERI	AP
Male	Humidity	$T = 0, H = 0$	Ref	1.41 (1.05–1.90) [a]	0.35 (0.10–0.60) [a]	0.30 (0.06–0.53) [a]
		$T = 0, H = 1$	0.93 (0.76–1.15)			
		$T = 1, H = 0$	0.89 (0.65–1.20)			
		$T = 1, H = 1$	1.17 (0.90–1.52)			
	Rainfall	$T = 0, R = 0$	Ref	1.18 (0.97–1.45)	0.22 (−0.01–0.45)	0.16 (0.00–0.32)
		$T = 0, R = 1$	1.03 (0.87–1.21)			
		$T = 1, R = 0$	1.16 (0.97–1.39)			
		$T = 1, R = 1$	1.41 (1.14–1.75) [a]			
Female	Humidity	$T = 0, H = 0$	Ref	1.42 (1.07–1.88) [a]	0.37 (0.12–0.63) [a]	0.30 (0.08–0.52) [a]
		$T = 0, H = 1$	0.93 (0.77–1.13)			
		$T = 1, H = 0$	0.95 (0.71–1.27)			
		$T = 1, H = 1$	1.25 (0.98–1.60)			
	Rainfall	$T = 0, R = 0$	Ref	1.31 (1.03–1.67) [a]	0.43 (0.20–0.66) [a]	0.29 (0.15–0.43) [a]
		$T = 0, R = 1$	0.92 (0.78–1.08)			
		$T = 1, R = 0$	1.15 (0.95–1.37)			
		$T = 1, R = 1$	1.49 (1.20–1.85) [a]			
Young	Humidity	$T = 0, H = 0$	Ref	1.18 (0.85–1.63)	0.15 (−0.16–0.45)	0.15 (−0.18–0.49)
		$T = 0, H = 1$	0.81 (0.64–1.02)			
		$T = 1, H = 0$	0.99 (0.71–1.38)			
		$T = 1, H = 1$	0.95 (0.71–1.27)			
	Rainfall	$T = 0, R = 0$	Ref	1.31 (1.03–1.67) [a]	0.35 (0.07–0.63) [a]	0.24 (0.06–0.42) [a]
		$T = 0, R = 1$	1.04 (0.86–1.26)			
		$T = 1, R = 0$	1.07 (0.87–1.32)			
		$T = 1, R = 1$	1.47 (1.14–1.87) [a]			
Middle	Humidity	$T = 0, H = 0$	Ref	1.36 (1.02–1.83) [a]	0.35 (0.08–0.62) [a]	0.27 (0.05–0.49) [a]
		$T = 0, H = 1$	0.97 (0.79–1.19)			
		$T = 1, H = 0$	0.98 (0.72–1.33)			
		$T = 1, H = 1$	1.30 (1.01–1.69) [a]			
	Rainfall	$T = 0, R = 0$	Ref	1.25 (1.02–1.53) [a]	0.30 (0.07–0.54) [a]	0.20 (0.05–0.35) [a]
		$T = 0, R = 1$	0.99 (0.84–1.17)			
		$T = 1, R = 0$	1.21 (1.01–1.45) [a]			
		$T = 1, R = 1$	1.51 (1.21–1.87) [a]			
Old	Humidity	$T = 0, H = 0$	Ref	1.83 (1.27–2.65) [a]	0.54 (0.28–0.81) [a]	0.47 (0.22–0.73) [a]
		$T = 0, H = 1$	0.93 (0.74–1.18)			
		$T = 1, H = 0$	0.68 (0.46–0.99) [a]			
		$T = 1, H = 1$	1.15 (0.84–1.57)			
	Rainfall	$T = 0, R = 0$	Ref	1.32 (1.02–1.71) [a]	0.30 (0.04–0.57) [a]	0.24 (0.04–0.44) [a]
		$T = 0, R = 1$	0.91 (0.74–1.11)			
		$T = 1, R = 0$	1.06 (0.83–1.34)			
		$T = 1, R = 1$	1.27 (0.97–1.67)			

T, average temperature; *H*, humidity; *R*, rainfall

[a] $p < 0.05$

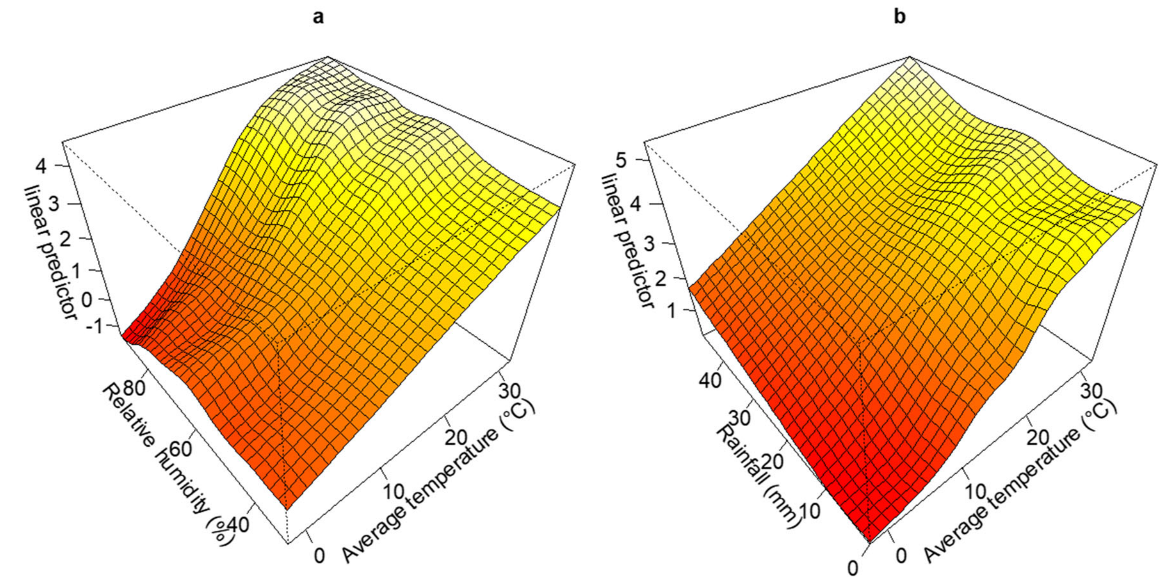

Fig. 4 Interaction of temperature with humidity (**a**) and rainfall (**b**) on malaria at lag 4 weeks in Suzhou, China, 2005–2012

(Zacarias and Andersson 2011; Yang et al. 2010). The possible mechanisms of the interaction between temperature and humidity are still under development. A laboratory study performed with African *Anopheles* mosquito at different combinations of temperature and humidity found that, during hot days, the survival rate of *Anopheles* was higher in the stratum of high humidity levels than low humidity levels (Lyons et al. 2014). Temperature combined with humidity could influence weight loss of mosquitoes via metabolism, influencing survival periods of *Anopheles* across all growth stages (Lyons et al. 2014).

Our study quantified the interaction effect of high temperature and high rainfall on malaria. Consistent with our findings, interactions between temperature and rainfall have previously been detected in some regions but without the estimation of interactive effect (Luo et al. 2012; Zhou et al. 2004). From a biological perspective, rainfall may provide available breeding sites for vectors such as pool, puddle, and river, increasing the transmission of malaria (Nath and Mwchahary 2012). The observed interaction between temperature and rainfall might be due to that rainfall enlarges the breeding site of mosquitoes and high temperature accelerates the development of mosquitoes at aquatic stages before rain puddles dry up, enriching the density of mosquitoes (Kristan et al. 2008). However, some studies pointed that the flush-out effect of heavy rainfall is associated with a negative effect on malaria transmission (Wardrop et al. 2013; Wu et al. 2017), which was not observed in our study. The inconsistent results

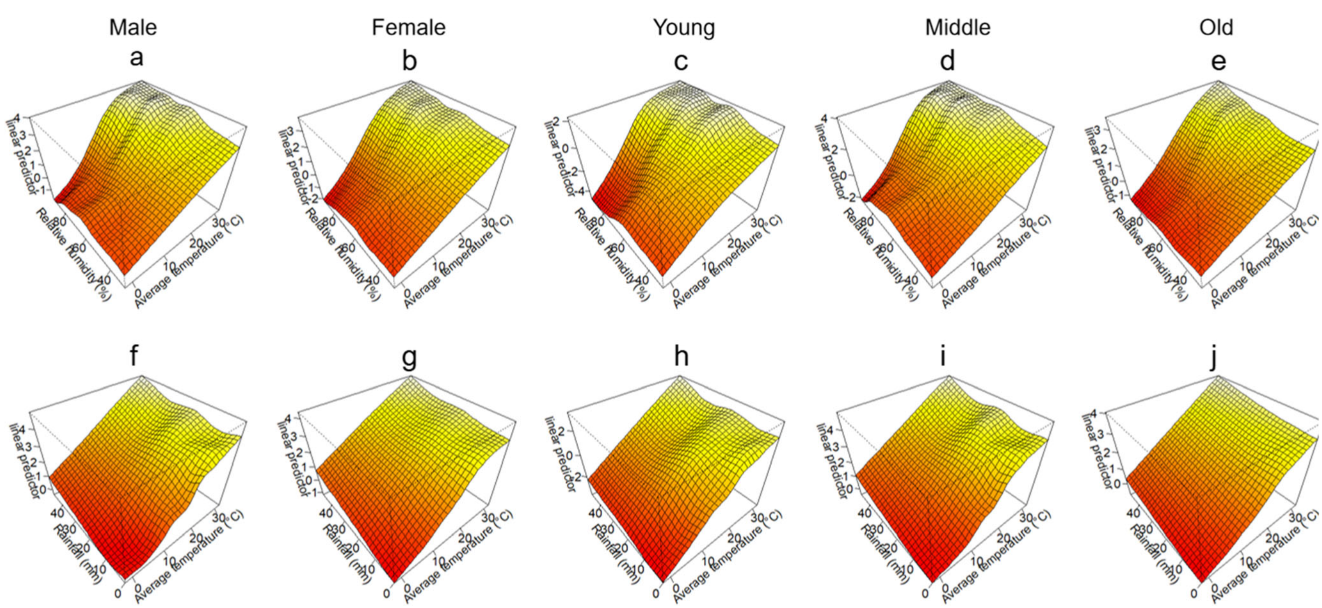

Fig. 5 Subgroup analysis of temperature with humidity and rainfall on malaria at lag 4 weeks in Suzhou, China, 2005–2012

could be explained by the range of rainfall and socioeconomic status (e.g., sanitary condition) in different regions and warrants further research.

Our results highlight the importance of incorporating the interactions of meteorological factors into the early warning system for malaria control and prevention, which could better predict the risk of malaria. China has made great success in malaria elimination (WHO 2019a). Drug spraying, insecticide treated nets, and patriotic public health campaigns conducted in a hotspot region played important roles in malaria prevention (National Health Commission of the People's Republic of China (NHC) 2010). In addition, the high efficiency of surveillance system, which detected and responded to malaria timely and accurately, contributed to the reduction of malaria in China.

Limitations of this study should be acknowledged. Firstly, underreporting bias from infectious disease surveillance data was inevitable. We are, therefore, unable to include the patients without seeking formal medical treatment. Secondly, only one city was included in our analysis. Thus, the result might be subject to local climatic conditions and demographical characteristics. Finally, different types of malaria, socioeconomic status, and other environmental variables (e.g., land cover, the distance to water bodies) were not controlled in this study. Nevertheless, this study has several strengths. To our best knowledge, this is the first study to quantify the interactive effects of meteorological factors on malaria transmission in China. Moreover, the advanced statistical method of DLNM, which could deal with lagged and nonlinear effects of temperature on malaria simultaneously, was used for our analyses.

Conclusion

Ambient temperature above a certain threshold is positively associated with malaria transmission, characterized by a lagged effect in regions with a temperate climate. Relative humidity and rainfall have an interactive effect on the temperature-malaria association. Higher risk of malaria occurred in weeks with higher average temperature together with high relative humidity and high rainfall. Such factors need to be considered in future malaria control and prevention strategies.

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Authors' contributions All authors contributed to the study conception and design. Data analysis and writing of the first draft of the manuscript were performed by LZD and WSZ. LQY, SSY, XJJ, and TM provided assistance for data acquisition, data analysis, and statistical analysis. BP, JBF, and ZY participated in the coordination of the study and reviewed the manuscript. GQ and ZYW carried out literature searching and manuscript editing. All authors commented on previous versions of the manuscript and approved the final manuscript.

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Data availability The authors do not have permission to share data.

Compliance with ethical standards

Competing interests The authors declare that they have no competing interests.

Ethics approval and consent to participate Ethical approval for analysis of this de-identified data was granted by the Ethics Review Committee, School of Public Health, Shandong University (20120501).

Consent for publication Not applicable

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