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The exposure–response relationship between temperature and childhood hand, foot and mouth disease: A multicity study from mainland China



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ABSTRACT

Background: Hand, foot and mouth disease (HFMD) is a rising public health issue in the Asia-Pacific region. Numerous studies have tried to quantify the relationship between meteorological variables and HFMD but with inconsistent results, in particular for temperature. We aimed to characterize the relationship between temperature and HFMD in various locations and to investigate the potential heterogeneity.

Methods: We retrieved the daily series of childhood HFMD counts (aged 0–12 years) and meteorological variables for each of 143 cities in mainland China in the period 2009–2014. We fitted a common distributed lag nonlinear model allowing for over dispersion to each of the cities to obtain the city-specific estimates of temperature–HFMD relationship. Then we pooled the city-specific estimates through multivariate meta-regression with city-level characteristics as potential effect modifiers.

Results: We found that the overall pooled temperature–HFMD relationship was shown as an approximately inverted V shape curve, peaking at the 91th percentile of temperature with a risk ratio of 1.30 (95% CI: 1.23–1.37) compared to its 50th percentile. We found that 68.5% of the variations of city-specific estimates was attributable to heterogeneity. We identified rainfall and altitude as the two main effect modifiers.

Conclusions: We found a nonlinear relationship between temperature and HFMD. The temperature–HFMD relationship varies depending on geographic and climatic conditions. The findings can help us deepen the understanding of weather–HFMD relationship and provide evidences for related public health decisions.

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1. Introduction

Hand, foot and mouth disease (HFMD) is a worldwide childhood infectious disease caused by Enterovirus. Although HFMD is normally characterized by mild symptoms of febrile illness and rashes (World Health Organization, 2011), some patients can develop severe central nervous system complications and even fatal cardiopulmonary failure (Sabanathan et al., 2014). Over the last few decades, a series of large HFMD epidemics, accompanied by abnormally high rates of severe

and fatal cases, have occurred in countries of the Asia-Pacific region (Chan et al., 2003; Ho et al., 1999; Van Tu et al., 2007; Zhang et al., 2010). In mainland China, HFMD is one of the leading infectious diseases in children and is also responsible for hundreds of reported deaths every year since it has been made statutorily notifiable in May 2008 (Xing et al., 2014). Given its threat to children and the potential for its emergence as a leading cause of enterovirus-related CNS disease after poliomyelitis, HFMD has raised huge public health concerns in the Asia-Pacific region (Regional Emerging Diseases Intervention Center, 2009).

It is well accepted that weather plays an important role in the transmission of many infectious diseases (Kuhn et al., 2005). Epidemiologists have performed a large amount of studies trying to quantify the relationships between meteorological variables and HFMD. Among them, the temperature–HFMD relationship is the most controversial one. Earlier studies normally assumed a simple linear relationship. A study in Northern Thailand (Samphutthanon et al., 2014) showed that the relationship with temperature was negative, whereas studies in Hong

Abbreviations: HFMD, hand, foot and mouth disease; TSR, time series regression; DOW, day of week; LR, likelihood ratio; AIC, Akaike information criterion.

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Kong (Ma et al., 2010) and mainland China (Chen et al., 2015; Feng et al., 2014; Li et al., 2014; Wei et al., 2015; Wu et al., 2014; Zhang et al., 2016) found a positive relationship. More recent studies relaxed the linear assumption to allow for non-linear relationship. A study in Singapore (Hii et al., 2011) suggested the presence of a threshold and a J-shape relationship; by contrast, studies in Japan (Onozuka and Hashizume, 2011), Taiwan (Chang et al., 2012), South Korea (Kim et al., 2016) and mainland China (Xu et al., 2015; Zhu et al., 2015) showed that the risk of HFMD increased below moderately hot temperature but declined at extremely hot temperatures, with an approximately inverted V shape. The inconsistency of findings can be partly attributable to the diversity of methodologies and data sources, but it also implies that the temperature-HFMD relationship might be modified by some location-specific variables. The heterogeneity across studies is still poorly understood which hinder a more comprehensive characterization of the temperature-HFMD relationship.

The majority of previous studies are based on single-site analysis, which prevent the modelling and assessment of heterogeneous relationships. A more sophisticated approach is the use of two-stage multisite study (Dominici, 2002) in which data from multiple sites are analyzed, and then the site-specific results are pooled and evaluated potential effect modifiers. To the best of our knowledge, there are only three published papers focusing on the heterogeneity of temperature-HFMD relationship (Zhu et al., 2016; Zhu et al., 2015). However, all of them were conducted on a small scale, with limited between-site variability, and very few variables were studied to explain the heterogeneity.

In this paper we fill this research gap by characterizing in more details the relationship between temperature and HFMD across various locations, and more importantly, exploring the reasons for the potential heterogeneity. Specifically, we conducted a two-stage multisite time series analysis based on data from 143 cities all across mainland China between 2009 and 2014. City-specific characteristics on multiple aspects, including geographic and climatic differences, social-economic status, health sources and other factors, were incorporated to study their modification effects on temperature-HFMD relationship.

2. Material and methods

2.1. Data sources

2.1.1. Daily series of HFMD counts and meteorological variables

We retrieved the surveillance data of reported clinical HFMD cases and meteorological variables in mainland China between 1 January 2009 and 31 December 2014.

We collected the reported clinical cases of HFMD from China Information System for Disease Control and Prevention. A clinical HFMD case is defined as a patient with papular or vesicular rashes on hands, feet, mouth or buttocks, with or without fever. All clinical cases were reported online within 24 h of diagnosis by use of a standardized form. More details of the surveillance data of HFMD have been described elsewhere (Xing et al., 2014). As over 99% of cases occurred among children under the age of 12 years (i.e. children in elementary school and below) according to our preliminary analysis, in this study we focused on the incidence of HFMD among children aged 0–12 years. The daily counts of HFMD clinical cases based on the date of onset of symptom were then aggregated at each of 293 cities in mainland China (Chen, 2009–2014). A city is defined as the main central urban area in each of the prefectures (i.e. prefectural-level city). A prefecture is an administration division ranking below a province and above a county in China's administrative structure, and a prefectural-level city corresponds to a middle to large size city in China.

We collected the daily monitoring data of meteorological variables, including mean temperature, mean relative humidity, mean air pressure, accumulated rainfall and sunshine hours, from China

Meteorological Data Sharing Service System. We included 646 national ground meteorological stations which have daily records in the period 2009–2014. The missing values in the daily records were filled by different approaches depending on the nature of each meteorological variable. Specifically, for temperature, humidity and air pressure, the missing values were filled by the polynomial interpolation (Zeileis and Grothendieck, 2005); for sunshine hours and rainfall, the missing values were replaced by zero. However, the missing issue should be negligible given that the missing proportion is very small (<0.1%).

By matching, we finally restricted the analysis to the 143 cities for which data from a meteorological station within the city administrative boundaries was available. For two cities with multiple meteorological stations, the station which is closest to the city center was chosen.

2.1.2. City-specific characteristics

We collected the geographic, climatic and social characteristics for each of the 143 cities. We used the coordinates of city/station to represent their differences in geographic locations, and we calculated the arithmetic mean of daily monitoring data of meteorological variables (including temperature, relative humidity, air pressure, rainfall and sunshine hours) at each city/station to represent their climatic differences. We collected the city-specific social characteristics from the China city statistical yearbook (Chen, 2009–2014), including demographic variables (population density and population increase rate), economic variables (GDP per person and GDP increase), health resources (licensed physicians and hospital beds per 1000 persons), traffic (total travel passengers a year) and number of elementary school students per 1000 persons. Besides, an indicator variable based on the national standard of meteorological and geographic division (China Meteorological Administration, 2006) was also used to group the 143 cities into eight regions.

2.2. Statistical analysis

We implemented a two-stage multisite time series analysis to first obtain the city-specific estimates of temperature-HFMD relationship, and then to pool the multicity estimates and study the heterogeneity.

2.2.1. First-stage analysis

In the first-stage analysis, we fitted a common time series regression (TSR) (Peng and Dominici, 2008) to each of the 143 cities to relate the daily series of HFMD counts and mean temperature. Given that multiple previous studies suggest that the temperature-HFMD relationship can be nonlinear and also their association can be delayed because of the incubation period of infectious disease, we incorporated distributed lag nonlinear model (Gasparrini et al., 2010) into the TSR to allow for bi-dimensional exposure-lag-response relationship. We determined our specific model parameters based on prior knowledge, followed by a systematic sensitivity analysis to further evaluated our choices. See more technical details and discussions of our model choices and related sensitivity analysis in Appendix, Text A.1.

In summary, a quasi-Poisson regression model was adopted to allow for over dispersion. The bi-dimensional exposure-lag-response relationship between temperature and HFMD was described through a cross-basis function (Gasparrini et al., 2010), using natural cubic splines with 5 degrees of freedom (*df*) for the exposure-response relationship and natural cubic splines with 4 *df* for the lag-response relationship. The lag range of 4 to 14 days was used to represent the lag structure of temperature-HFMD relationship. The start lag and the lag interval were informed by the median incubation period of HFMD infections (4 days) (Ministry of Health of China, 2009) and a preliminary analysis (see Appendix, Text A.1, Section 4), respectively. To control for the unmeasured time-varying

confounding, we used the natural cubic splines of calendar time with 8 *df* per year to remove the long-term trends and seasonality. To control for the measured time-varying confounding, we incorporated the exponentially weighted moving average of relative humidity, air pressure, rainfall and sunshine hours in the same lag range of temperature. We also adjusted for the effect of day of week (DOW) and holidays (including the vacations for elementary school and national public holidays) as indicator variables. To account for autocorrelations in the residuals, we included the autoregressive terms of HFMD daily counts at lag 1 and 2 into the model based on the autocorrelation plot of residuals. The autoregressive terms were incorporated on the logarithm scale to better match the mechanism of infectious disease transmission (Imai et al., 2015).

2.2.2. Second-stage analysis

In the second-stage analysis, we meta-analyzed estimates of the exposure-lag-response association reduced to the unidimensional overall cumulative exposure-response by the application of multivariate meta-regression (Gasparrini and Armstrong, 2013; Gasparrini et al., 2012). To pool the exposure-response relationship, the exposure (i.e. temperature) should be distributed in a similar range in all sites, otherwise a common analysis will leave some parameters inestimable (Gasparrini et al., 2012). However, in our study the temperature ranges vary widely across cities. To address above issue, we adopted two separate approaches for different purposes.

In the first approach, we adopted a relative scale measurement of temperature by transforming temperatures to the related city-specific percentile, so that we can unify the temperature ranges across cities. Our main purpose is to combine all the city-specific estimates under the same model and provide us a better opportunity to capture the potential effect modifiers. We first fitted a multivariate meta-regression model with intercept only allowing for heterogeneity modelled through random effects (denote as intercept-only model). Then, we ran a single meta-predictor analysis by incorporating city-specific characteristics into the model separately (denote as single meta-predictor models) and compared it to the intercept-only model, in which we allowed the heterogeneity to be partly explained by meta-variables and modelled as fixed effects. Because different meta-predictors can be correlated with each other, we further ran a forward stepwise analysis to identify the optimum subset of meta-predictors.

To avoid the potential distortion of the above percentile-based approach, we also adopted another approach based on the absolute temperature measurement. In the second approach, we grouped the 143 cities into eight regions so that the temperature ranges can be similar within the subgroup. Our main purpose is to obtain the region-specific estimates of temperature-HFMD relationship while retaining the original measurement of temperature, which may be more interested by public health practitioners. Because the city-specific characteristics were also similar after grouping, we pooled the city-specific estimates by regions without incorporating meta-predictors except intercept. The region-specific estimates were further combined with geographic maps for better interpretation. Although the second approach is limited in identifying effect modifiers directly, the indicator of regions can be seen as a categorized proxy variable of potential effect modifiers. Thus we compared the pooled estimates of temperature-HFMD relationship and the distributions of related effect modifiers between regions as a verification for the first approach.

For the second-stage analysis, we used the maximum likelihood estimation to obtain estimates and a multivariate extension of likelihood ratio (LR) test to test the significance of meta-predictors and differences between models (Gasparrini et al., 2012). Akaike information criterion (AIC) was used to measure the goodness of model fits. The residual heterogeneity was measured and tested by the multivariate extension of I^2 statistics and Cochran Q test (Gasparrini et al., 2012).

We did all statistical analysis with R software (version 3.2.3) using the packages *dlm* and *mvmeta*. The geographic maps were made by ArcGIS software (version 10.2.1, authorization number: EFL734321752).

3. Results

From 2009 to 2014, a total of 3,060,450 clinical cases of HFMD under 12 years of age were collected in the 143 cities of mainland China. Our study covered the majority of big cities in mainland China with the geographic region distributed from latitude 18.1° to 50.2° north, and longitude 84.5° to 130.6° east (Fig. 1). The western part is the least urbanized and sparsely populated area in China, thus only few data obtained from that area. The disease burden of HFMD (measured as the total number of clinical cases during our study period) varied geographically, with most cases occurring in densely populated large cities (Fig. 1). Shenzhen, Beijing, and Guangzhou were the top 3 cities in terms of the total number of HFMD cases reported. See Appendix, Table A.1 for the full lists of cities included and Table A.2 for the summary statistics of the city-specific characteristics.

Based on the relative scale measurement of temperature, the overall pooled estimates (i.e. intercept-only model) suggested a nonlinear relationship between temperature and HFMD with an approximately inverted V shape (Fig. 2a). We found a gradual increase in risk of HFMD until it peaked at 91th percentile of temperature with reference to 50th percentile (RR = 1.30, 95% CI: 1.23–1.37). Afterward, there was suggestive evidence of a dropping down of risk at extremely hot temperatures. Although all the cities were analyzed by a common time series model, the city-specific estimates still exhibited substantial variability (Fig. 2a). The residual heterogeneity indicated that 68.5% of the variation was attributable to true differences across cities (p -value of Q test < 0.001) (Table 1).

The single meta-predictor models showed that the geographic and climatic characteristics could explain part of the heterogeneity, whereas the social characteristics seemed to have no significant modification effects, except a borderline impact of economic variables (Table 1). Similar modification effects were found between temperature, relative humidity, sunshine hours, latitude and rainfall, so did that between air pressure and altitude, mainly because they had similar geographic distributions and were highly correlated (see Appendix, Figs. A.1 and A.2 and Table A.3, which compared the results of different meta-predictors). For the sake of simplicity, we only displayed the modification effects of rainfall (p -value of LR test < 0.001) and altitude (p -value = 0.008) (Table 1) because they have the largest impact in their own category and have a more sensible interpretation. Rainfall had the best ability to explain the heterogeneity with the related I^2 statistic dropping from 68.5% (intercept-only model) to 66.5% (Table 1). We found that rainfall could strongly elevate the association between temperature and HFMD, especially at hot temperatures (Fig. 2b). For altitude, we found that the temperature-HFMD relationship at hot temperatures changed from an inverted V shape to an approximately straight line by comparing low and high altitude (Fig. 2c). By incorporating both rainfall and altitude into the model, we could decrease the residual heterogeneity to 66.1% (p -value < 0.001) (Table 1).

The region-specific analysis can further confirm the modification effects of rainfall and altitude (Fig. 3). First, we found an upward trend of the temperature-HFMD relationship from northwest to southeast, with nearly null association in Inner Mongolia region, Northwestern and Northern China (Fig. 3a–b). The spatial variation of the temperature-HFMD relationship was highly in agreement with the geographic distribution of rainfall (Fig. 3a–c). Besides, we found the nonlinear behavior of temperature-HFMD curves can be explained by the distribution of accumulated rainfall at different temperatures as well (Fig. 3b and d). The turning points of temperature-HFMD curves were very close to those temperature points where rainfall changed rapidly, and the temperature-HFMD relationship elevated with the rising of rainfall. The exceptions were

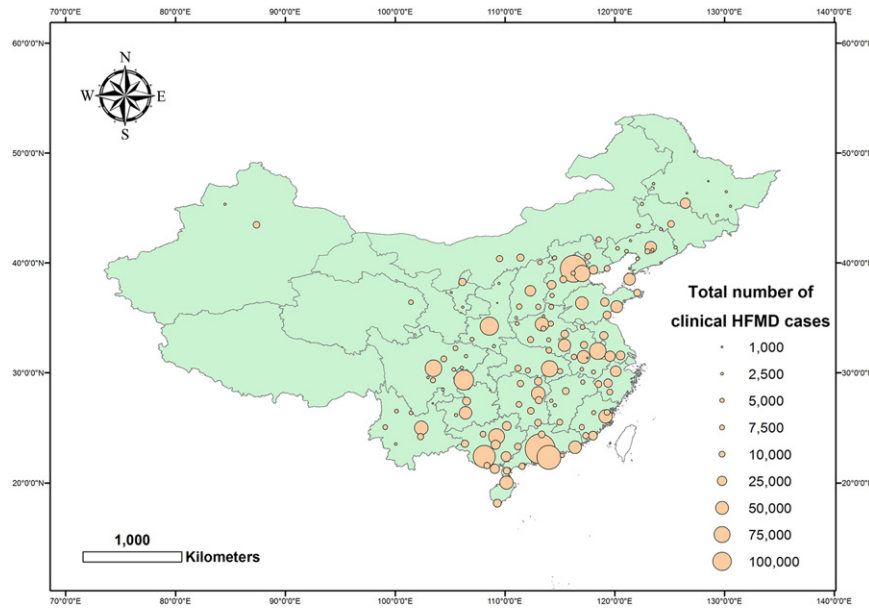


Fig. 1. Geographic locations and disease burdens of HFMD for the 143 cities of mainland China, 2009–2014.

found in Northeast, Southwest and Southern China, where the risk of HFMD went up continually with increasing of temperature, although substantial drop of rainfall was seen at extremely hot temperatures (Fig. 3b and d). In contrast, an approximately inverted V shape were estimated in Huang-Huai-Yangtze river basin and Jiangnan region. As the single meta-predictor model suggested, we found altitudes might play a role in explaining the discrepancy. In Huang-Huai-Yangtze river basin and Jiangnan region, the distribution of altitudes is positively skewed to zero (Fig. 3d) with plain as the dominant terrain (Fig. 3c) (most areas belong to the alluvial plain created by Huang, Huai and Yangtze rivers). Whereas, in the other three regions, the altitudes are distributed around a relatively high mean value (Fig. 3d) with mountains or hills as the dominant terrain

(Fig. 3c). By applying region-specific intercept-only models, the residual heterogeneity varied from 41.5% to 66.4% with *p*-value ranging from <0.001 to 0.008 (Table 2).

4. Discussion

In this paper, we conducted a multisite two-stage time series analysis including 143 cities in mainland China to examine the relationship between temperature and HFMD and related effect modifiers. As some previous studies suggested, we found that the surveillance data could be better explained by a nonlinear relationship between temperature and HFMD. The nonlinear behavior of the temperature-HFMD relationship implies that the impact of temperature on HFMD may involve with

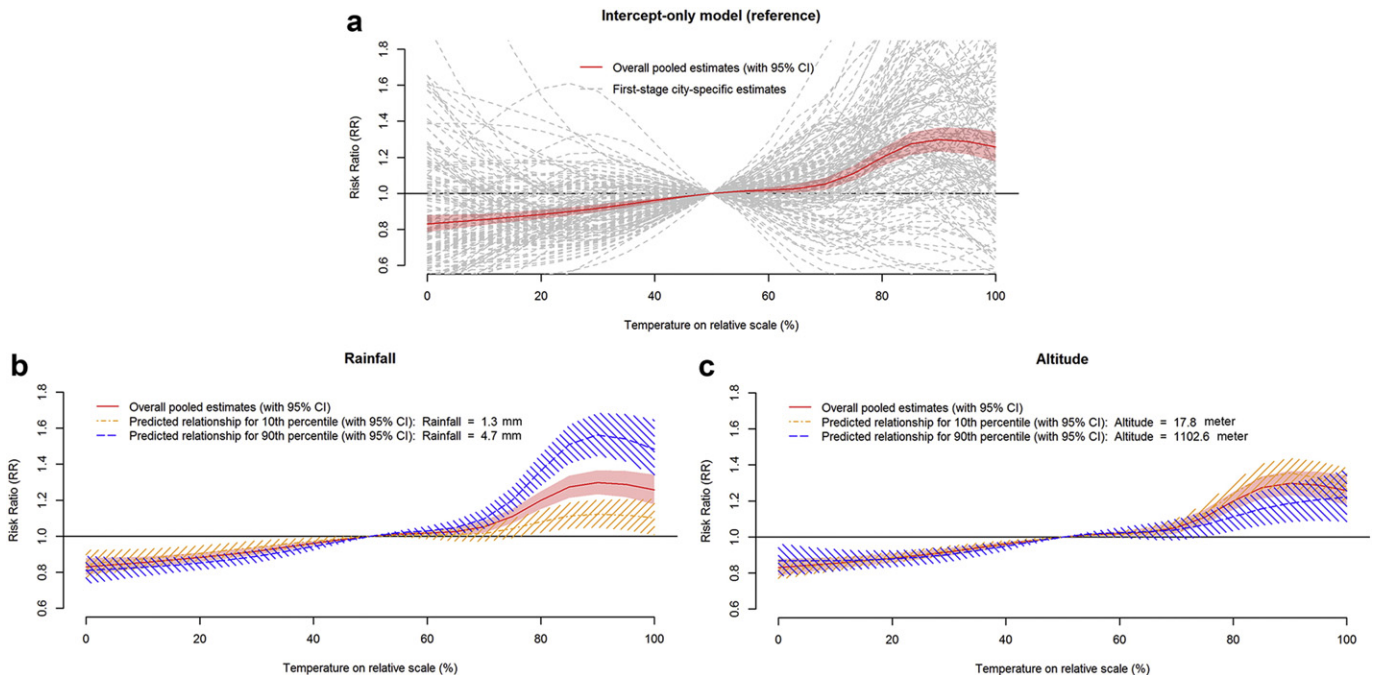


Fig. 2. Estimated temperature-HFMD relationships in relative risk. (a) intercept only, (b) rainfall and (c) altitude. All the estimations were based on the relative scale measurement of temperature with reference at 50th percentile of temperature.

Table 1
Multivariate meta-regression models for meta-predictors.

Meta-predictors	LR test ^a			Model fits AIC	Cochran Q test ^b			I ² (%)
	Stat	df	p		Stat	df	p	
<i>Intercept-only model</i>								
Intercept only	–	–	–	527.9	2253.3	710	<0.001	68.5
<i>Single meta-predictor models</i>								
Latitude	23.2	5	<0.001	514.8	2136.7	705	<0.001	67.0
Longitude	10.9	5	0.053	527.0	2217.7	705	<0.001	68.2
Altitude	15.5	5	0.008	522.4	2180.3	705	<0.001	67.7
Temperature	23.6	5	<0.001	514.3	2130.4	705	<0.001	66.9
Relative humidity	22.8	5	<0.001	515.1	2140.0	705	<0.001	67.1
Air pressure	16.3	5	0.006	521.6	2175.5	705	<0.001	67.6
Rainfall	36.7	5	<0.001	501.3	2106.1	705	<0.001	66.5
Sunshine hours	14.8	5	0.011	523.2	2177.5	705	<0.001	67.6
Population increase	1.6	5	0.905	536.4	2238.7	705	<0.001	68.5
Population density	6.5	5	0.265	531.5	2243.5	705	<0.001	68.6
GDP per person	11.2	5	0.047	526.7	2230.1	705	<0.001	68.4
GDP increase	10.5	5	0.061	527.4	2230.2	705	<0.001	68.4
Licensed physicians	2.9	5	0.719	535.1	2244.0	705	<0.001	68.6
Hospital beds	2.4	5	0.785	535.5	2243.1	705	<0.001	68.6
Travel passengers	5.4	5	0.370	532.5	2242.5	705	<0.001	68.6
Number of students	2.9	5	0.718	535.0	2215.0	705	<0.001	68.2
<i>Multiple meta-predictors model</i>								
Rainfall + altitude	46.7	10	<0.001	501.2	2065.1	700	<0.001	66.1

All models were based on the relative scale measurement of temperature with reference at 50th percentile of temperature.

^a LR test was used to test the significance of meta-predictors with the Intercept-only model as reference.

^b Cochran Q test was used to test the significance of residual heterogeneity with the null hypothesis as no heterogeneity.

complex mechanisms. HFMD can be transmitted either by exposure to infectious individuals or contaminated environmental reservoir (Wang et al., 2011). It is believed that temperature can affect the transmission of HFMD. Previously proposed theories mainly fall into two categories, which have opposite impacts on the transmission of HFMD (Chen et al., 2014). First, there is evidence for the positive associations between temperature and the host activity (Bélangier et al., 2009) and also the host excretion of enterovirus (Fong and Lipp, 2005), thereby hot temperature may increase the chances that susceptible individuals contact with infectious individuals or contaminated environment. Second, temperature and ultraviolet radiation are known as two main factors leading to enterovirus inactivation (Bertrand et al., 2012). Therefore, extremely hot temperature may shorten the survival time of enterovirus in the environment, and then decrease its chances for transmission back to the host. This can explain the dropping down of risk at very hot temperatures. However, previous theories cannot fully explain the nonlinear behavior of temperature-HFMD relationship, especially why they differ across studies.

After ruling out the diversity of methodologies by analyzing multi-city data through a common time series model, we still found considerable heterogeneity among city-specific estimates. Our region-specific estimates of the temperature-HFMD curve are consistent with previous single-site studies in the same region. For instances, studies in Shandong (Zhu et al., 2015) (located at the Huang-Huai-Yangtze river basin) also suggest an inverted V relationship between temperature and HFMD; whereas an approximately linear relationship was identified in Guangdong (Huang et al., 2013) (located in Southern China). Our findings imply that it is very likely that the heterogeneity across regions is due to true differences rather than random variations. Thus, for

those single-site time series studies, it should be very cautious to generalize their results.

We found geographic and climatic variables, especially rainfall, can explain part of heterogeneity in the temperature-HFMD relationship, not just the different magnitude in different regions but also its nonlinear behavior. The modification effects of rainfall may be attributable to its impact on the enterovirus survival. Water environment is known as the main natural reservoir for enterovirus (Rajtar et al., 2008). In the water environment, enterovirus is able to tolerate various factors leading to virus inactivation, such as temperature, salinity, pH and etc. (Salo and Cliver, 1976). By providing water in the environment, rainfall may directly weaken the negative impact of temperature (i.e. virus inactivation) so that its positive impact (i.e. increasing contacts) can hold a leading position. In the contrary, we would expect the temperature-HFMD relationship decline if the rainfall dropped. It is interesting to note that the decrease of the temperature-HFMD relationship with the dropping of rainfall at extremely hot temperatures cannot be seen in areas where the terrain was dominated by mountains or hills. One possible reason might be that mountain or hills have a better ability to protect the natural reservoirs of enterovirus, such as providing more shelters to keep water from evaporating and keep the natural reservoirs from being exposure to the ultraviolet radiation. Therefore, the drop of rainfall may have less impact in those areas. However, further studies are needed to verify this hypothesis.

In our study, social characteristics were not significant in explaining the heterogeneity. By contrast, a recent similar study in Shandong province (China) including 17 cities (Zhu et al., 2016) suggested that number of healthcare institutions and household income could modify the temperature-HFMD relationship (geographic and climatic variables

Fig. 3. The region-specific analysis combined with geographic maps. (a) Geographic distributions of eight meteorological and geographic regions in mainland China. (b) Region-specific estimates of temperature-HFMD relationship. The continuous colored lines represent the regional pooled temperature-HFMD curves (95% CI as shaded area), whereas the long-dashed grey lines are the city-specific estimates. All the estimations were based on the absolute scale measurement of temperature. Separate temperature ranges and reference were used in different regions. (c) Geographic distributions of rainfall for the 143 cities of mainland China on the base map of world terrain (the shaded relief imagery representing terrain). Different regions have been separated by bold black lines. (d) The distribution of accumulated rainfall (at different temperatures) and altitude by regions. The continuous colored lines are the predicted smooth line based on the distribution of accumulated rainfall.

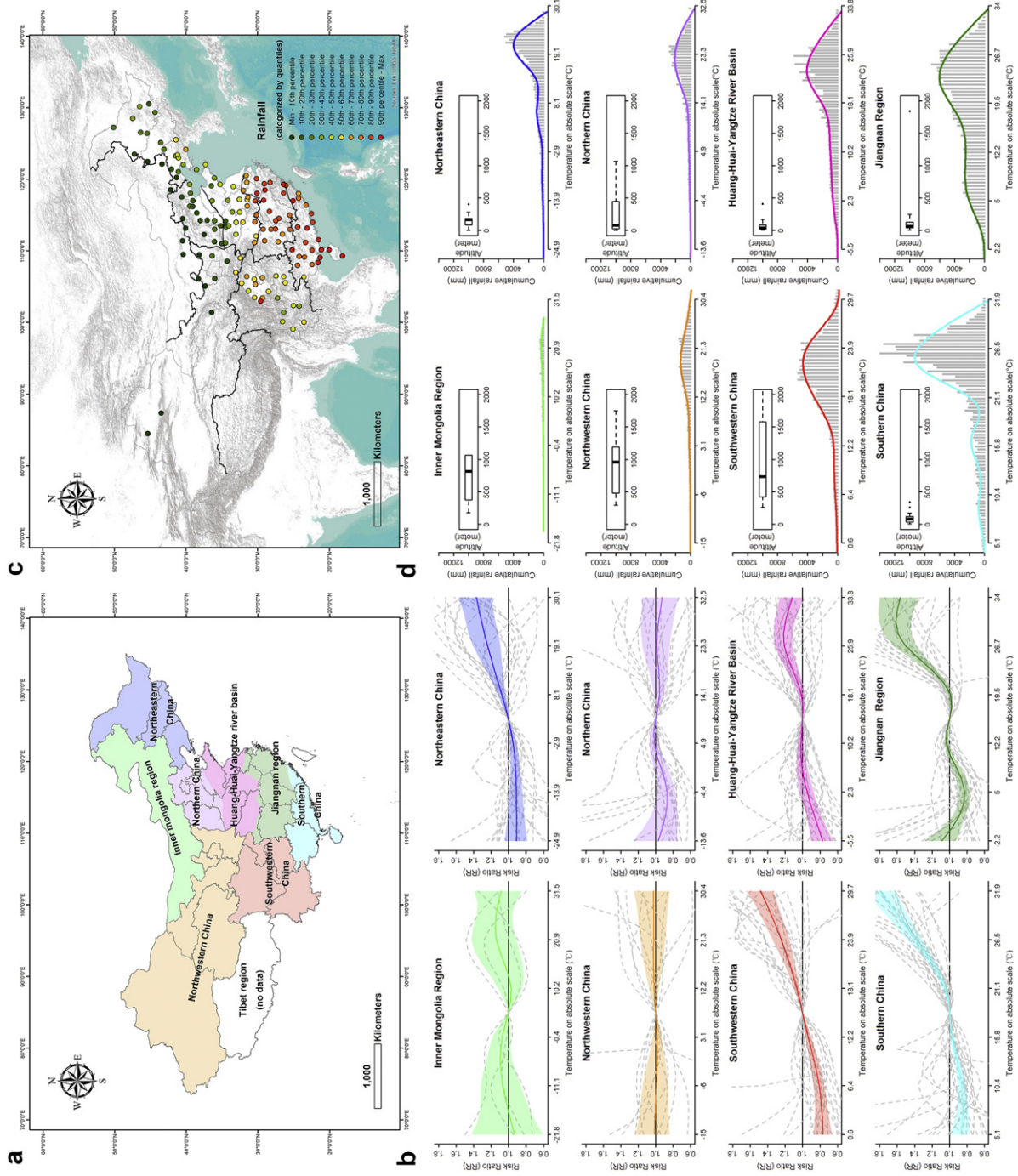


Table 2
Multivariate meta-regression models for regions.

Region	Reference	Temperature range	Model fits	Cochran Q test ^a			I ² (%)
	(°C)	(°C)	AIC	Stat	df	p	
Inner Mongolia Region	4.9	(−21.8, 31.5)	40.1	31.2	15	0.008	51.9
Northeastern China	2.6	(−24.9, 30.1)	126.9	297.8	100	<0.001	66.4
Northwestern China	7.7	(−15.0, 30.4)	79.3	85.5	50	0.001	41.5
Northern China	9.5	(−13.6, 32.5)	122.6	228.5	80	<0.001	65.0
Southwestern China	15.2	(0.6, 29.7)	96.4	208.1	95	<0.001	54.4
Huang-Huai-Yangtze River Basin	14.1	(−5.5, 33.8)	119.3	328.0	120	<0.001	63.4
Southern China	18.5	(5.1, 31.9)	72.4	257.0	110	<0.001	57.2
Jiangnan Region	15.9	(−2.2, 34.0)	96.0	249.1	105	<0.001	57.8

All models were based on the absolute scale measurement of temperature with intercept-only model being fitted, and separate temperature range and reference were used for different regions (shown in the table).

^a Cochran Q test was used to test the significance of residual heterogeneity with the null hypothesis as no heterogeneity.

were not considered in their study). However, the proportion of heterogeneity they could explain was limited, with the related I² decreasing from 98.31% to 98.09% and 98.07%, respectively. Although we also found a borderline impact of GDP, the modification effects of social characteristics were negligible compared to that of geographic and climatic variables. Another study in Guangdong province (China) including 8 cities (Guo et al., 2016) agrees with our conclusions. They found that the city's latitude and longitude were the most two important effect modifiers.

It is worth noting that there is still substantial heterogeneity that cannot be explained by the identified effect modifiers. The unexplained heterogeneity can be attributable to several reasons. First, the way how the city-specific characteristics were modelled may be not sufficient to fully represent their modification effects. Taking rainfall as example, both the mean and distributions of rainfall may have impact on the temperature–HFMD curve. However, we only incorporated the city-specific mean of rainfall into the meta-model. Second, there might exist some other important effect modifiers that we failed to take into account. City-specific variables like vegetation coverage, features of soil, local customs, public-health intervention, differences in data quality and etc. may have the potential to explain some part of heterogeneity, but we do not have the related information. Third, the relative scale analysis can induce heterogeneity by itself because various temperature ranges were forced to be on the same scale. A comparative study (Gasparrini et al., 2012) showed that, given the identical data and meta-predictor, the decrease of residual heterogeneity was much higher in the absolute scale analysis than that in the relative scale analysis. However, our findings can still explain the major discrepancies seen in previous single-site studies.

This study has three main limitations. The first one is to do with the intrinsic nature of time series analysis and ecological study. It should always bear in mind that what we really captured is the short-term associations at the population level before any further inference is made. The second limitation is related to the data quality. The weaknesses of surveillance data of HFMD in mainland China have been described elsewhere (Xing et al., 2014). The most relevant one is the potential bias caused by under-reporting. However, because time series analysis used its own previous observations as reference and removed the long-term trends and seasonality, the impact of under-reporting bias should be limited. The third limitation is to do with the spatial correlation. Spatial correlation is normally an issue which needs to be considered in pooling the multisite estimates (Peng and Dominici, 2008). In the context of pooling nonlinear relationship, incorporation of the spatial correlation will increase the complexity of models dramatically. Related methodologies are still under development which is far beyond the scope of this study. However, we believe that the spatial correlation may not have a significant impact on our conclusions for three main reasons. First, the main consequence of spatial autocorrelation is to bias the variances rather than the estimators (Dubin, 1998). Thus, we believe

that the pooled estimates of temperature–HFMD relationship are still valid. Besides, for the identified effect modifiers, their *p* values of LR test are far away from the significant level. So, it is very unlikely that our conclusions will change substantially after the incorporation of spatial correlation. Second, the identified effect modifiers can be confirmed by both the overall relative scale analysis and the region-specific absolute analysis, which implies our conclusions are robust. Third, because the meta-predictors have also shown spatial correlation, therefore we expect that the spatial correlations can be partly explained by the meta-predictors.

5. Conclusions

In conclusion, our study provides estimates of temperature–HFMD relationship based on a large dataset including 143 cities of mainland China. We found the temperature–HFMD relationships varied from region to region. Rainfall and altitude may play an important role in modifying the temperature–HFMD relationship. Our findings can help deepen the understanding of how meteorological variables affect the transmission of HFMD. Furthermore, this evidence can provide implications for the related public-health decision, such as the establishment of weather-based disease early warning systems.

Conflict of interest

The authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.envint.2016.11.021>.

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