Science of the Total Environment 713 (2020) 136623

Contents lists available at ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

Spatial heterogeneity of the association between temperature and hand, foot, and mouth disease risk in metropolitan and other areas

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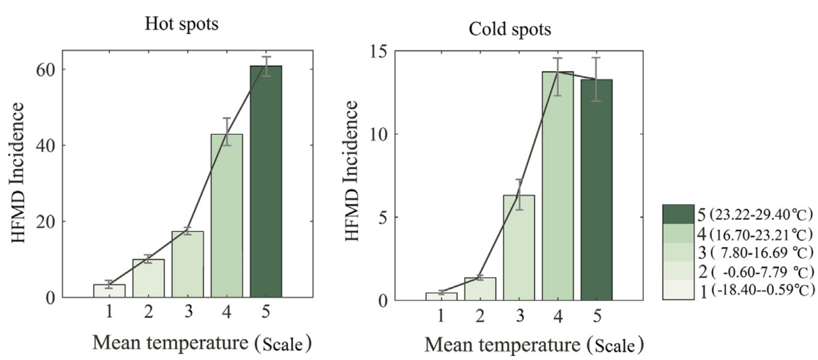
HIGHLIGHTS

- Spatial heterogeneity of HFMD
- The hot/cold spots were detected using Bayesian space-time hierarchy model.
- The effect of average temperature on HFMD were different in metropolitan and other areas.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 23 September 2019
Received in revised form 8 January 2020
Accepted 8 January 2020
Available online 10 January 2020

Editor: SCOTT SHERIDAN

Keywords:
Hand foot mouth disease
Spatial patterns
Average temperature
GeoDetector
Bayesian space-time hierarchy model

ABSTRACT

Interest in assessing the effects of temperature on hand, foot, and mouth disease (HFMD) has increased. However, little evidence is available on spatial heterogeneity in relationship to temperature and HFMD in metropolitan (capital city and municipal districts) and other areas where economic levels are significantly different. In this study, the Bayesian space-time hierarchy model was applied to identify the spatiotemporal heterogeneity of HFMD. GeoDetector was then used to quantify the determinant power of temperature to the disease in regions where the economic level has significant spatial heterogeneity. There was significant spatial heterogeneity in the influence of temperature on the incidence of HFMD in metropolitan and other areas. In metropolitan areas, where the disease risk is higher (hot spots), the HFMD incidence was higher alongside an increase in average temperature. However, in non-metropolitan areas, where the disease risk is lower (cold spots), there was an approximately S-shaped relationship between the temperature and the HFMD risk. More specifically, when the temperature was >25 °C, the HFMD incidence no longer increased monotonically with the increasing temperature. There was significant spatial heterogeneity in the effects of temperature on the HFMD incidence in metropolitan and non-metropolitan areas. This finding may serve as a suggestion and basis for the surveillance and control of this disease and it is conducive to the rational allocation of medical resources in different areas.

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https://doi.org/10.1016/j.scitotenv.2020.136623

1. Introduction

Hand, foot, and mouth disease (HFMD) is a common childhood infectious disorder, mainly caused by enterovirus 71 (EV71) and Coxsackie virus A16 (CV-A16) (Ooi et al., 2010; Schmidt et al., 1974). Since the early 1970s, many countries in the Asia-Pacific region have reported HFMD epidemics, such as Singapore (Ang et al., 2009), Vietnam (Van Tu et al., 2007), Thailand (Puenpa et al., 2011), Japan (Onozuka and Hashizume, 2011), Australia (Burry et al., 1968), and China (Xing et al., 2014). Although extensive studies have been conducted to identify the causative agent of HFMD, its pathogenesis is still completely unclear and no specific curative treatment for HFMD has been found. Therefore, HFMD remains a global public health concern (Chan et al., 2003; Ho et al., 1999).

It is widely accepted that temperature plays an important role in the transmission of many infectious diseases (Stanton et al., 1977). The researches of many studies have indicated there is a most suitable temperature for survival, reproduction, and transmission of the virus. For example, results from a previous study demonstrated that when the temperature is higher than 25 °C, the infectivity and activity of EV71 is restricted (Arita et al., 2005). Moreover, the leaders of an in-vitro experiment reported that compared to the replication rate at 37 °C, enterovirus replication is inhibited by nearly 90% at 39 °C (Stanton et al., 1977). Similarly, some researchers have pointed out that, in a certain range, the higher the temperature, the faster the virus reproduces and causes a higher incidence of HFMD. However, if the temperature is too high or too low, the viral activity is restrained, with an approximately inverted V shape (Xu et al., 2015; Zhu et al., 2016). Verified by virology evidence, it has been reported that there is a close temperature-sensitive nature of enteroviruses and other human enteric viruses (Kung et al., 2010; Rzezutka and Cook, 2004).

Additionally, over the past 30 years, the original ecological environment and people's life conditions have undergone great changes influenced by rapidly increasing global urbanization. The suitable survival environment of the virus may be also unavoidably further affected to some extent; this will likely continue to exert subtle effects on public health (Biadgilign et al., 2019; Gong et al., 2012; Lee et al., 2018) as it has in the past and as it is currently doing. As more megacities and urban agglomerations emerge, human activities are generating a tendency to be concentrated in these areas. This, in turn, may be causing some regions with higher economic levels and greater population densities to contribute to the accelerated transmission of these viruses (Gong et al., 2012; Lee et al., 2018). For example, Hu et al. demonstrated that the child population density explains 56% of the variance in the cumulative monthly HFMD incidences in 2912 counties in China (Hu et al., 2012). Yan et al. also showed that the HFMD incidence was higher in urban areas compared to rural areas, further demonstrating that the distance to the nearest freeway and per capita gross domestic product (GDP) are both risk factors associated with HFMD incidence (Yan et al., 2014).

These findings imply that both the natural and socioeconomic environment, to some extent, make transmission of the virus possible and effective. The leaders of some previous studies have examined the association between meteorological factors and HFMD incidence while also considering socioeconomic factors. However, to our knowledge, few researchers have explored the heterogeneity of temperature related to the highest HFMD risk while considering variations in urban conditions where economic conditions have significant heterogeneity. Therefore, this study was designed to assess and capture the heterogeneity of temperature related to the highest HFMD risk among regions where economic conditions differ. The objectives of this study were to: (1) identify the county-level spatiotemporal heterogeneity of HFMD risks in the Beijing-Tianjin-Hebei area of China from 2009 to 2013; (2) detect the hot/cold spots (higher/lower disease risk areas, respectively); and (3) quantify the effects of temperature on the HFMD incidence between metropolitan and non-metropolitan regions, then capture the heterogeneity of temperature related to the highest HFMD risk among these regions.

2. Data and methods

2.1. Study area

The Beijing-Tianjin-Hebei area, located in the northern part of the North China Plain, is one of the most densely populated regions of China. The region has a continental monsoon climate with an average annual temperature of 12 °C and, on average, 460 mm of annual precipitation. This area includes Beijing, Tianjin City, and the Hebei province in which Beijing and Tianjin are international megalopolises and together serve as the center of politics, the economy, and transportation in China (Fig. 1). Additionally, a large number of travelers move in and out of the region every day. Therefore, it is significant to prevent and control infectious diseases (e.g., HFMD) in the Beijing-Tianjin-Hebei area.

2.2. Data sources

Monthly data on HFMD cases were collected from January 2009 to December 2013 in each county from the Chinese Centre for Disease Control and Prevention for use in this study, with a total of 598,835 cases. The month-scale's temperatures and relative humidity data from the selected time period in each county were acquired from the China Meteorological Data Sharing Service System, as shown in Fig. 3. City socioeconomic variables such as the yearly-scale household electricity consumption, GDP, and population density from 2009 to 2013 were also collected (Table S1).

2.3. Statistical analysis

In this study, a Bayesian space-time hierarchy model (BSTHM) was first introduced to explore the spatiotemporal heterogeneity of HFMD risks and to classify the study area in terms of hot spots and cold spots. GeoDetector was then used to quantify the association between temperature and the HFMD incidence. Hereafter, the heterogeneity in the temperature that related to the highest epidemiological risks in hot and cold spots was captured.

2.3.1. Bayesian space-time hierarchy model

The BSTHM is used to reveal spatial and temporal information implied in spatiotemporal data, based on Bayesian statistical thoughts. In our method, the number of cases y_{it} and the risk population n_{it} were modeled by Poisson regression with the log link function (Li et al., 2014), as follows:

$$\begin{aligned} & y_{it} \sim Poisson(n_{it}u_{it}) \\ & log(u_{it}) = \alpha + s_i + (b_0 t^* + v_t) + b_{1i} t^* + \varepsilon_{it} \end{aligned} \tag{1}$$

in which u_{it} indicated the potential risk of HFMD in the i ($i = 1, 2, \ldots, 208$) county and months t ($t = 1, 2, \ldots, 60$). The term α was used to denote the fixed effect of the overall disease risk in the study region during the selected period (Li et al., 2014). The spatial term s_i, during the selected period, described the spatial heterogeneity of the disease risk. Similarly, $(b_0 t^* + v_t)$ represented the overall time evolution of the disease risk with the random effect $v_t \sim N(0, \sigma_v^2)$ (Gelman, 2006). The term t^* *was* used to express the time span relative to the midpoint t_{mid}. The term b_{1i}, quantified the deviation from the overall temporal variation b_0 (Li et al., 2014). ε_{it} was chosen to denote the Gaussian noise following the normal distribution $N(0, \sigma_\varepsilon^2)$ (Gelman, 2006).

Hereafter, all counties were divided into hot, cold, and neither hot nor cold spots, following the classification principle proposed by Richardson et al. (2004). Specifically, if the county's posterior probability p [exp (s_i) > 1|data] ≥ 0.975, it was defined as a hot spot, whereas <0.025 was considered a cold spot; the other counties were regarded as neither hot nor cold spots, in which all calculations were implemented in WinBUGS (Lunn et al., 2000).

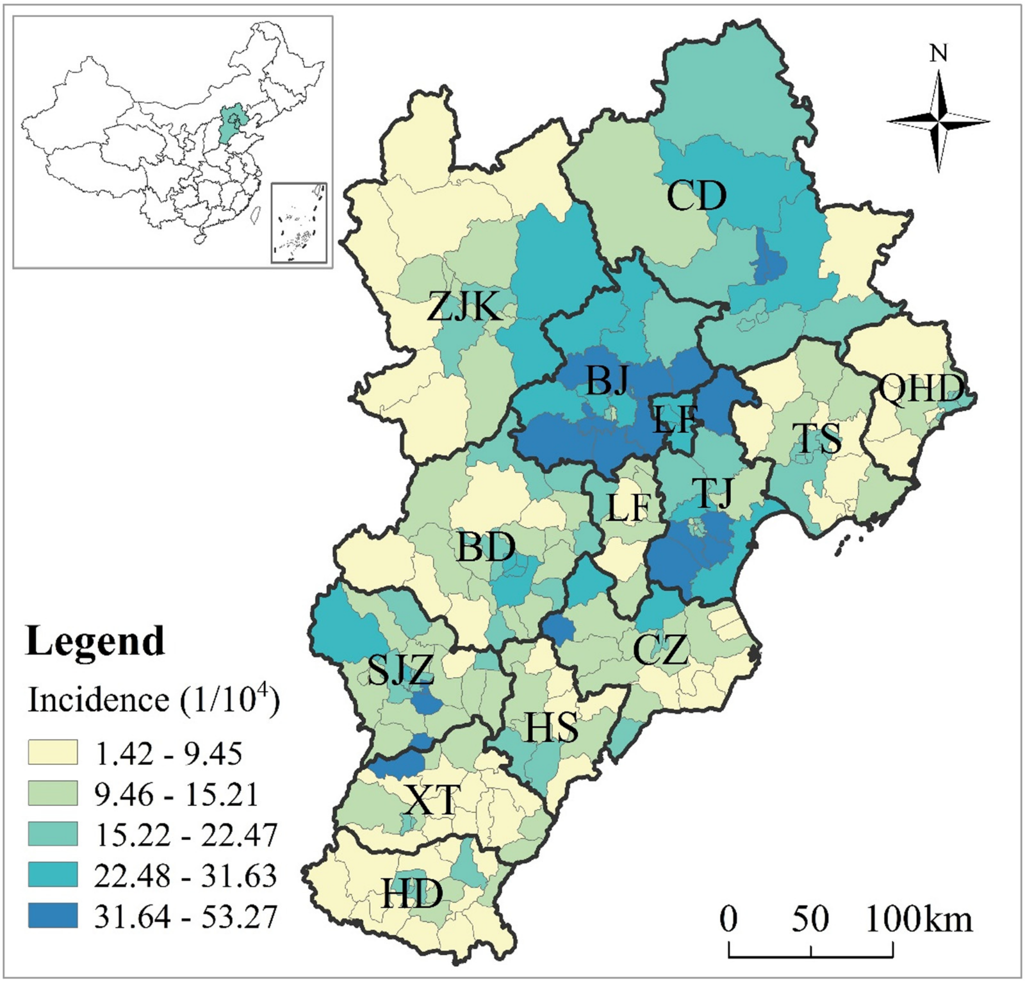

Fig. 1. The geographic location of the Beijing-Tianjin-Hebei area in China with the average monthly incidence of HFMD in each county in children from 2009 to 2013. Note: CD: Chengde city; ZJK: Zhangjiakou; BJ: Beijing; LF: Langfang; TS: Tangshan; QHD: Qinhuangdao; BD: Baoding; TJ: Tianjin; CZ: Cangzhou; SJZ: Shijiazhuang; HS: Hengshui; XT: Xingtai; HD: Handan.

2.3.2. GeoDetector

The GeoDetector model both could quantify the stratified heterogeneity of a responding variable (i.e., HFMD risk) and the determinant power of an impact factor (i.e., average temperature) on a dependent variable under the assumption that if the two variables were associated, their spatial stratified heterogeneity tended to be consistent (Wang et al., 2010; Wang and Xu, 2017). This included four modules: the factor detector, the interaction detector, the risk detector, and the ecological detector. The factor detector and the risk detector are introduced in this study.

The factor detector can quantify the spatial and temporal heterogeneity of HFMD risk according to the BSTHM's results and examine the determinant power of driving factors (Xs) to Y by the q statistic value (Wang and Hu, 2012). In this study, its input data included an explanatory variable and hierarchical information of an impact factor. Then, the statistic significant indicator p-values were calculated through a non-central F-distribution (Wang and Xu, 2017). The q value was calculated as below:

$$q = 1 - \frac{\sum_{h=1}^{L} N_h \sigma_h^2}{N\sigma^2} \quad (2)$$

where q was the determinant power of the risk factor and also quantified the spatiotemporal stratified heterogeneity for the target variable (i.e., HFMD risk), ranging from 0 to 1, indicating the determinant power of a risk factor or a target variable's heterogeneity. N_h and N were used to represent the number of samples in sub-region h and the whole region, respectively; $h = 1, 2, \ldots, L$ was the stratification of impact factor X. Similarly, σ^2 and σ_h^2 were chosen to represent the total variance of Y across the entire study area and the sub-region h.

The spatial heterogeneity of an impact factor has different effects on Y in different regions. The risk detector can determine whether there is a significant difference in the effect of X's different categories on Y in two sub-regions by a t-test so as to capture the temperature that relates to the highest epidemiological risks, as follows:

$$t_{\overline{y}_{h=1}-\overline{y}_{h=2}} = \frac{\overline{Y}_{h=1} - \overline{Y}_{h=2}}{\left[\frac{Var\left(\overline{Y}_{h=1}\right)}{n_{h=1}} + \frac{Var\left(\overline{Y}_{h=2}\right)}{n_{h=2}}\right]^{\frac{1}{2}}} \quad (3)$$

where $\overline{Y}_h$ and n_h represent the average value of Y (i.e., the HFMD incidence) and the number of samples in the sub-region h, respectively; Var denotes the variance. All of the above processes were implemented in GeoDetector which was downloaded from www.geodetector.cn.

3. Results

3.1. Spatiotemporal variation of HFMD

The results showed that geographically, the HFMD risk had significant spatial heterogeneity with a q value of 0.67 as calculated using GeoDetector. Notably, areas with the highest spatial relative risk (hot spots) were mainly concentrated in large cities like Beijing and Tianjin that have developed economies, high population densities, and mixed socio-human environments (Chang et al., 2016; Xu et al., 2017). Conversely, areas with the lowest spatial relative risk (cold spots) were mainly scattered in the non-metropolitan regions; these have underdeveloped economic levels and lower population densities (Fig. S1) (Chang et al., 2016; Xu et al., 2017). As shown in Fig. 2, 63 and 63 counties classified as hot and cold spots corresponded to metropolitan and non-metropolitan areas, respectively, while another 82 counties were identified as neither hot nor cold spots.

The overall temporal trend of HFMD risk from 2009 to 2013 was non-homogeneous (Fig. S2), demonstrated by the *q* value of GeoDetector at 0.51. Specifically, for each year, higher disease risks occurred in the late spring and summer (May to July) while lower disease risks occurred in the winter (December to February).

3.2. Spatial heterogeneity of the associations between HFMD and temperature

Using GeoDetector, the determinant powers of temperature were assessed. In hot spots, for temperature, the *q* value was 0.32 ($p < 0.01$). The incidence of HFMD increased along with the rise in average temperatures (Fig. 3), with the incidence of HFMD at $60.84/10^4$ and $3.34/10^4$ in high and low temperature conditions, respectively. The result for relative humidity was not statistically significant.

In cold spots, there was a converse relationship between HFMD risks and temperature, with a *q* value of 0.14. There was an approximately S-shaped relationship between temperature and the HFMD risk. When the temperature was lower than 25 °C, the HFMD risk increased with an increase in temperature and the incidence of HFMD no longer increased monotonically with increasing temperature (Fig. 3).

4. Discussion

In recent years, childhood HFMD has become increasingly recognized as a significant health problem (Huang et al., 2013; Xiao et al., 2017). Moreover, in areas with different economic conditions, the HFMD risk has introduced a significant difference. In this study, the BSTHM was used to classify the study area into hot and cold spots that corresponded to metropolitan and non-metropolitan areas, respectively. Then, the effects of temperature on childhood HFMD were

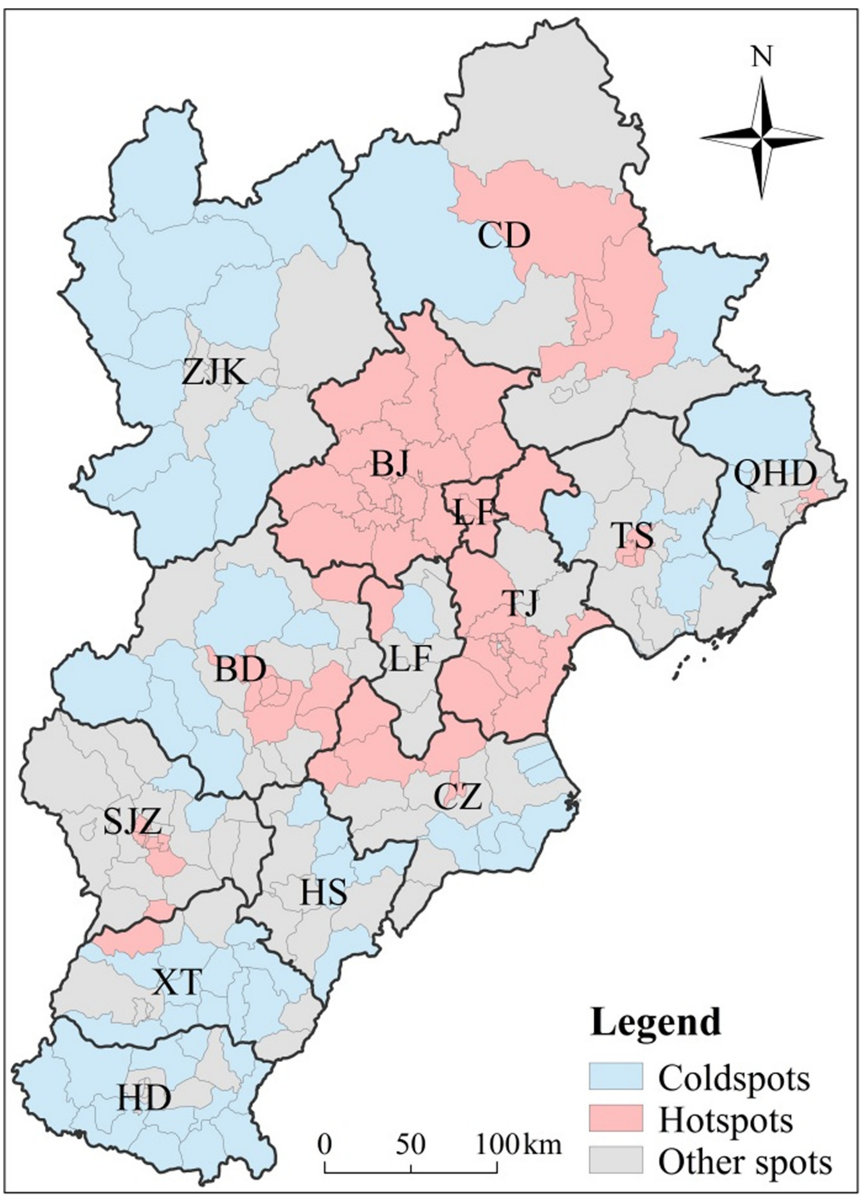

Fig. 2. Distribution of the hot spots and cold spots of HFMD in the study area.

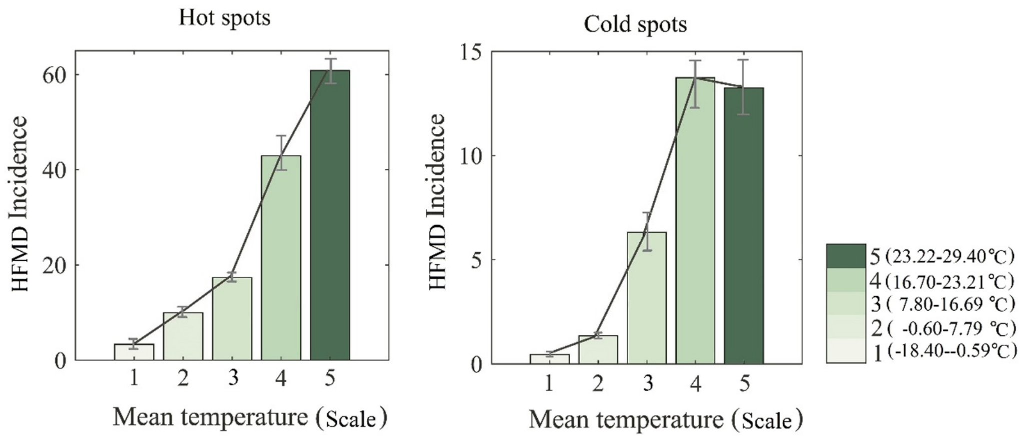

Fig. 3. Comparison of the effects of temperature on the incidence of HFMD in hot and cold spots.

quantified using GeoDetector. Notably, this study stands out from prior studies by revealing that, in regions with different economic levels, there is a significant heterogeneity in temperatures that relate to the highest epidemiological risks.

Alternatively, in areas where the economic level was different, the temperature that corresponded to the highest epidemiological risk was also different: Areas with a higher economic level tended to report a higher temperature related to the highest risk, which has been demonstrated in previous studies. For example, Zhu et al. conducted a time-series study to investigate the impacts of temperature on the HFMD incidence in 17 cities in the Shandong province in which the economic level was higher in the eastern large cities while lower in the western counties. The temperature that related to the highest epidemiological risk in the large eastern cities was higher than that in the western counties (Zhu et al., 2016). Similarly, Xiao et al. implemented a study in China in which the economic situation was high in southern China, converse in northern China. They demonstrated that in southern China, the temperature that related to the highest epidemiological risk was higher than that in northern China (Xiao et al., 2017). Furthermore, Xing et al. found that for patients who were infected with EV71, living in a rural area was a risk factor for severe disease (Xing et al., 2014). The potential reason may be that in metropolitan areas, the effect of economic levels cannot be ignored: A developed economy and complete infrastructure can protect the urbanized population from weather. For instance, the use of air conditioning and heaters, especially in the summer and winter, are so great that the living and working environments are far more comfortable than that in natural environments (Figs. S3 and S4).

Undoubtedly, in metropolitan regions, when the living and working environments are controlled by modern equipment, the temperature that restricts the growth or transmission the virus has not been reached. Alternatively, in non-metropolitan regions, underdeveloped economies with incomplete infrastructure make residents' lives less dependent on modern equipment, the temperature that restricts the growth or transmission the virus could be easily reached. Even though some families have installed air conditioning or heaters, they may be reluctant to use these devices because of their desire to save money due to the low incomes seen in non-metropolitan regions. These results can be demonstrated from selected proxy variables such as household electricity consumption and GDP (Figs. S3 and S4).

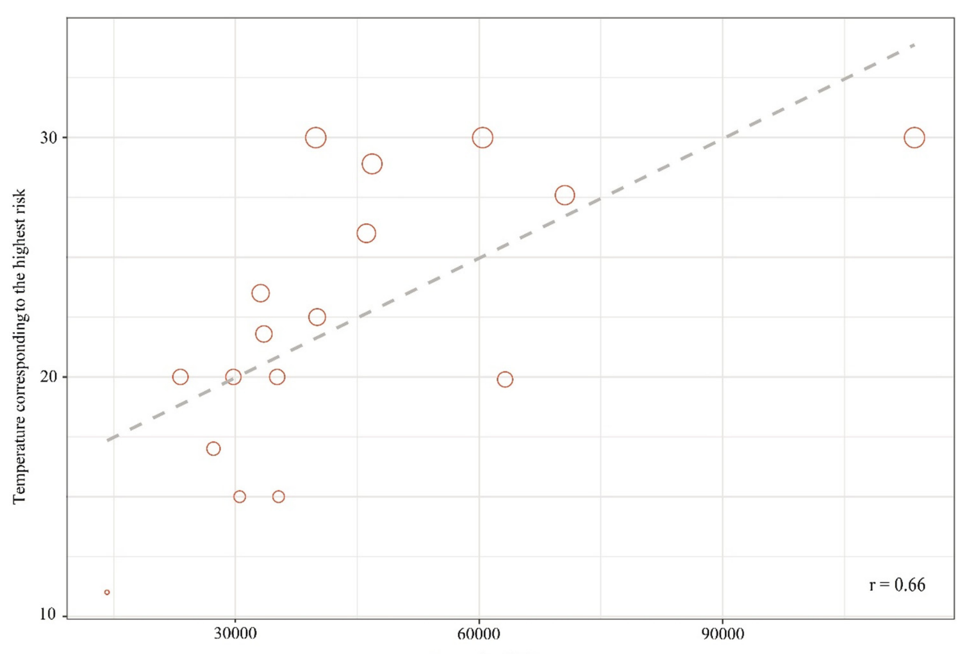

Fig. 4. The scatter plot of per capita GDP and temperature corresponded to the highest risk.

Ultimately, we analyzed the association of per capita GDP and the temperature that corresponded to the highest epidemiological risk in 17 cities of Shandong province, China, from one previous study, which can be used to support our results (Zhu et al., 2016). Fig. 4 shows that in regions with different economic levels, there is a significant heterogeneity in the temperature that related to the highest epidemiological risk; areas with a higher economic level tended to report a higher temperature related to the highest risk. Moreover, the Pearson's correlation coefficient between per capita GDP and the temperature that corresponded to the highest risk was introduced; the value was 0.66, which can be used to support our study.

One limitation of this study is that the micro-environments may have significantly influenced the HFMD incidence, including community and home environments and even educational levels. The spatial scale used in this study was at the county level, which may have obscured some factors through the ecological fallacy effect. It could also have introduced some uncertainties in the study.

5. Conclusions

This study described the detailed spatiotemporal dynamics of HFMD incidence from 2009 to 2013 in the Beijing-Tianjin-Hebei area, China. Then the high-risk areas (hot spots) were detected, which were mainly concentrated in metropolitan areas, while the low-risk areas (cold spots) were mainly distributed in non-metropolitan regions. Additionally, the study captured that, in the metropolitan and non- metropolitan areas with different economic levels, the temperature that related to the highest epidemiological risk was significantly different. These results provide a good illustration for the heterogeneity of the temperature's effect on the HFMD incidence. This information can serve as a point of reference and as a basis for the surveillance and control of this disease in practice. Both are conducive to informing the rational allocation of medical resources.

Declaration of competing interest

The authors declare that they have no competing interests.

Acknowledgements

This study was supported by the following grants: National Key Research and Development Program of China (2017YFC1602002, 2017YFC1601800); National Natural Science Foundation of China (41601419, 41531179, 41601478); Innovation Project of LREIS (O88RA205YA, O88RA200YA).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2020.136623.

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