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Boosted regression tree model-based assessment of the impacts of meteorological drivers of hand, foot and mouth disease in Guangdong, China

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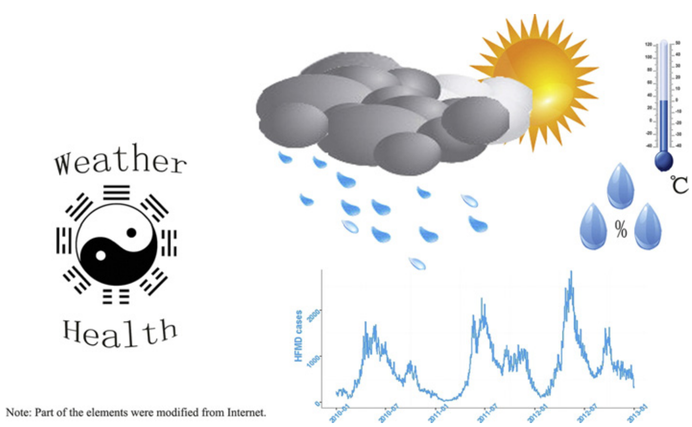
HIGHLIGHTS

- Variance of HFMD cases was explained most by meteorological factors about 1 week ago.
- The optimal lag at which the variance of HFMD cases was most explained was determined.
- The facilitating effects of meteorological factors were verified and quantified.
- Threshold points for each meteorological factor were identified.
- The contribution of each meteorological factor to the epidemic of HFMD was assessed.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Hand, foot and mouth disease (HFMD) is a common childhood infection and has become a major public health issue in China. Considerable research has focused on the role of meteorological factors in HFMD development. Nonlinear relationship, delayed effects and collinearity problems are key issues for achieving robust and accurate estimations in this kind of weather-health relationship explorations. The current study was designed to address these issues and assess the impact of meteorological factors on HFMD in Guangdong, China.
Methods: Case-based HFMD surveillance data and daily meteorological data collected between 2010 and 2012 was obtained from China CDC and the National Meteorological Information Center, respectively. After a preliminary variable selection, for each dataset boosted regression tree (BRT) models were applied to determine the optimal lag for meteorological factors at which the variance of HFMD cases was most explained, and to assess the impacts of these meteorological factors at the optimal lag.
Results: Variance of HFMD cases was explained most by meteorological factors about 1 week ago. Younger children and those from the Pearl-River Delta Region were more sensitive to weather changes. Temperature had the largest contribution to HFMD epidemics (28.99–71.93%), followed by precipitation (6.52–16.11%), humidity (3.92–17.66%), wind speed (3.84–11.37%) and sunshine (6.21–10.36%). Temperature between 10 °C and 25 °C,

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as well as humidity between 70% and 90%, had a facilitating effect on the epidemic of HFMD. Sunshine duration above 9 h and wind speed below 2.5 m/s also contributed to an elevated risk of HFMD. The positive relationship between HFMD and precipitation reversed when the daily amount of rainfall exceeded 25 mm.

Conclusions: This study indicated significantly facilitating effects of five meteorological factors within some range on the epidemic of HFMD. Results from the current study were particularly important for developing early warning and response system on HFMD in the context of global climate change.

1. Introduction

Hand, foot and mouth disease (HFMD) is a common childhood infection and has become a major public health issue in China, affecting over two million children annually (China NHAF, 2014; Zhu et al., 2011). It is a particular concern in Guangdong Province, with an incidence higher than four times the national average and exceeding 30 cases per 10,000 in 2012 (Deng et al., 2013; Zhang et al., 2014). Because of the absence of HFMD-targeted vaccination or specific treatments, quantification of the driving effects of environmental agents is essential for the early warning and response system on HFMD (Xu et al., 2015). Recently, there has been an increasing interest to assess the impacts of meteorological factors on HFMD (Chen et al., 2014; Feng et al., 2014; Li et al., 2014; Liu et al., 2015; Urashima et al., 2003; Wei et al., 2015; Zhuang et al., 2014).

However, the assessment of the relationship between HFMD and meteorological factors is complicated by two major issues. First, meteorological factors tend to have nonlinear impacts on the HFMD burden. There may exist some threshold points on two sides of which the weather-HFMD relationship can be substantially different (Chen et al., 2014; Huang et al., 2013; Lin et al., 2013; Wu et al., 2014). Second, interaction is a common issue among meteorological predictors (Huang et al., 2014; Lin et al., 2009; Zhang et al., 2016). Results may be biased if the collinearity problem is not reasonably addressed (Wang et al., 2010). Predictor selection procedures including the traditional stepwise method can reduce the influence of collinearity but simultaneously sacrifice information on those removed predictors.

The current study was designed to address these issues with a novel modeling technique and assess the impact of meteorological factors on HFMD in Guangdong, China.

Boosted regression tree (BRT) model is a recently developed technique, combining the advances of the traditional regression models and the machine-learning methods (Tonkin et al., 2015). It accommodates complex linear and nonlinear responses to multiple categorical and continuous predictors while is relatively insensitive to collinearity problems (Elith et al., 2008; Main et al., 2015). The BRT model was particular suitable for this case, therefore, was the major statistical method of the current study.

Results were also stratified by areas and age groups to study the difference and consistence of the meteorological factor-HFMD relationship across subpopulations.

2. Materials and methods

2.1. Study settings

Guangdong is one of the biggest provinces in Southern China, with an area of 179,800 km^2 and a population of 104 million (from 2010 census data). It can be generally divided into two parts: the Pearl River Delta Region and the Non-Pearl River Delta Region. According to statistical yearbooks of Guangdong, the Pearl River Delta Region has a much higher level of social-economic development, accounting for 80% GDP of the whole province with <50% population (Province SBOG, 2012).

2.2. Data sources

HFMD surveillance data collected between 2010 and 2012 was obtained from China Center for Disease Control and Prevention (China CDC). Information including birth date, onset time and ZIP code for the current address was reported to the real-time surveillance system once a patient was diagnosed with HFMD according to the National Clinic Guide (Version 2010) (China THMO, 2009). According to our data, over 99.5% HFMD cases were children under 15 years old who therefore was the study population of the current research. Children were further classified into 4 groups (<1, 1–3, 3–6, and >6 years) since children of different age groups tended to differ in daily activities, as well as in susceptibility and forms of being cared (Huang et al., 2013).

Daily meteorological data was obtained from the National Meteorological Information Center (http://cdc.nmic.cn/). Originally, eleven meteorological factors including mean vapor, precipitation, maximum wind speed, mean air pressure, mean wind speed, mean temperature, mean humidity, minimum temperature, sunshine duration, maximum temperature and minimum humidity were considered for the analysis.

2.3. Statistical analyses

Correlation between the eleven meteorological factors was examined to evaluate the collinearity problems. While boosted regression tree models were robust towards collinear predictors, to aid interpretability, we only retained those previously reported in literatures when predictors were highly correlated ($r > 0.75$) (Tonkin et al., 2015).

Boosted regression tree (BRT) model with Poisson distribution was used to explore the impacts of climate parameters on HFMD. BRT model combines algorithms of regression trees that use recursive binary splits to eliminate interactions among the predictors and boosting that built a large ensemble of small regression trees to display the nonlinear relationship between the response and its predictors as well as improve predictive performance (Ayanu et al., 2015; Tonkin et al., 2015). For this boosting method, 10-fold cross validation was used to select the best model - determining the optimal number of trees that should be included in the model to achieve the best predictive performance. The gbm.step procedure in *dismo* package in R (3.1.2) takes a stepwise approach to model selection (Elith and Leathwick, 2015).

BRT models require the specification of three parameters: the learning rate, tree complex and bag fraction. The learning rate shrinks the contribution of each tree as it is added to the growing model. The tree complex determines the maximum order of interaction in each tree, and bag fraction specifying the proportion of the training set that is used for model building in each step. Three parameters in the present study were specified at 0.005, 5, and 0.5, respectively, as recommended (Elith et al., 2008).

Since the delayed effects of climate parameters on HFMD are well documented (Wang et al., 2013; Zhang et al., 2015), lag selection is essential for the assessment of weather-HFMD relationships. The optimal lag of climate predictors was defined as the lag at which the variance of HFMD case numbers was most explained in the cross validation. The maximum lag was set at 14 days which was previously reported to be the upper bound of the incubation of HFMD (Ministry of Health, 2014). Then the relationship between the climate parameters at the optimal lag and HFMD cases were quantified with BRT models. Correlation between the observed HFMD case numbers and the predicted ones in the test set was calculated to indicate the model performance. And the contribution of each predictor was calculated to measure its relative importance in HFDM development. Partial dependence plots were produced to show the association between each meteorological variable and the HFMD cases after accounting for the average effects of all other variables in the model (Thanapongtharm et al., 2014).

All the analyses were accomplished with R (3.1.2).

3. Result

3.1. Potential predictors

Five daily meteorological predictors including mean temperature (0.1 °C), precipitation (0.1 mm), relative humidity (%), sunshine (0.1 h), and average wind speed (0.1 m/s) were incorporated into final BRT models (Table 1). Two indicators, holiday and the day of week, were controlled as common potential confounders.

3.2. Lag selection and the overview of the impacts of meteorological factors

Lag selection results from verification and cross validation indicated that the variance of the HFMD case series could be explained most by meteorological factors about 1 week ago (Table 2). According to the cross validation results, 44.42%–66.92% of the variance of HFMD case series could be explained by meteorological factors at the optimal lag. A larger proportion of the variance of HFMD case series in the Pearl-River Delta Region [total (range in subgroups): 57.46% (48.64%–65.21%)] was explained than that in the remaining areas [54.30% (44.42%–62.13%)] ($P < 0.001$).

In terms of intra-age group discrepancy, the proportion of variance explained decreased with age, with children under 1 year old having the largest interpreting rate (PRDR: 65.21%; NPRDR: 62.13%) while those >6 years old having the smallest (PRDR: 48.64%; NPRDR: 44.42%) (Table 2).

3.3. The relationship between HFMD case series and meteorological factors at the optimal lag

Correlation between the observed and the BRT-predicted HFMD case numbers was evaluated for each dataset. As a variant of the proportion of variance explained, these correlation coefficients revealed similar degree of association between HFMD case series and meteorological factors, as well as intra-age group discrepancies (Table 3). Temperature had the largest relative contribution to the epidemic of HFMD in Guangdong Province (28.99%–71.93%), followed by precipitation (6.52%–16.11%), humidity (3.92%–17.66%), wind speed (3.84%–11.37%) and sunshine (6.21%–10.36%).

There existed two threshold points on the temperature-fitted function curves. One was between 10 and 15 °C and the other between 25 and 30 °C. When the temperature was above the first threshold, the risk of HFMD was increasing until the second threshold point after which the trend was flattened or even slightly downward. As the whole province panel and the Pearl-River Region panel showed, the curve for children under 1 year old tended to be steeper than that for other age groups (Fig. 1).

Precipitation was observed to facilitate the development of HFMD until a threshold point around 25 mm. When the daily amount of rainfall exceeded the first threshold point, the risk of HFMD began to decrease and became constant above the second threshold point (37.5 mm). The relative contribution of precipitation was between 6.52% and 16.11% for each dataset.

In the current study, the humidity-fitted function curves were similar to temperature-fitted function curves. The risk of HFMD did not increase until 70% of humidity. When the humidity approached 90%, the trend of the curves also began to be flattened or even slightly downward, as what was observed in temperature-fitted function curves. In addition, curves for the Pearl-River Delta Region tended to be steeper than that for the non-Pearl-River Delta Region, as Fig. 1 showed. In terms of intra-age group discrepancy, the slope of the curve for children under 1 year old was the smallest whereas that for children between 3 and 6 years old was the largest.

This study observed that wind speed and sunshine duration may also facilitate the epidemic of HFMD in Guangdong within some range. There are positive trends existed in predictor-fitted function curves, when the value of the predictor was under some threshold point (about 2.5 m/s) for wind speed and above some threshold point (about 9 h/day) for sunshine.

Though slightly different, trends of predictor-fitted function curves were mainly consistent across regions and age groups.

Table 2
Lag selection results.

Group	Verification		Cross validation	
	Optimal lag	Variance explained (%)	Optimal lag	Variance explained (%)
Whole province				
Total	lag.8	73.37	lag.6	57.76
Age < 1	lag.8	78.31	lag.6	66.92
1 ≤ age < 3	lag.5	72.98	lag.6	59.26
3 ≤ age < 6	lag.12	71.13	lag.6	49.17
Age ≥ 6	lag.8	71.74	lag.8	50.97
Pearl-River Delta region				
Total	lag.8	71.31	lag.6	57.46
Age < 1	lag.7	73.88	lag.5	65.21
1 ≤ age < 3	lag.8	71.80	lag.6	59.71
3 ≤ age < 6	lag.6	68.13	lag.7	48.89
Age ≥ 6	lag.8	64.53	lag.7	48.64
Non-Pearl-River Delta region				
Total	lag.9	70.32	lag.7	54.30
Age < 1	lag.8	72.34	lag.8	62.13
1 ≤ age < 3	lag.9	68.03	lag.7	52.95
3 ≤ age < 6	lag.10	68.23	lag.6	44.76
Age ≥ 6	lag.8	61.11	lag.9	44.42

Table 1
Description of HFMD case (N) and potential predictors [M (IR)][a].

		Whole province	The Pearl River Delta region	The non-Pearl River Delta region
Case numbers (N)	Total	827,911	579,032	248,879
	Age < 1	127,594	81,098	46,496
	1 ≤ age < 3	429,504	298,356	131,148
	3 ≤ age < 6	234,400	174,360	60,040
	Age ≥ 6	36,413	25,218	11,195
Weather conditions M (IR)[a]	Mean temperature (0.1 °C)	232.06 (169.33, 272.36)	238.70 (175.7, 274.60)	230.19 (166.54, 271.50)
	Precipitation (0.1 mm)	12.75 (0.24, 58.24)	5.61 (0.00, 53.10)	13.38 (0.23, 61.33)
	Relative humidity (%)	77.29 (70.72, 83.58)	76.75 (69.60, 83.40)	77.44 (71.31, 83.65)
	Sunshine (0.1 h)	46.57 (15.75, 76.58)	45.50 (10.3, 78.2)	46.19 (17.15, 75.88)
	Average wind speed (0.1 m/s)	20.53 (17.86, 24.89)	21.10 (18.00, 26.00)	20.35 (17.73, 24.50)

[a] M (IR): median (interquartile range).

Table 3
Model performance and the relative importance of predictors (at the optimal lags).

Group	Correlation		Contribution (%)				
	Verification	Cross validation	RF	Sun	Wind	RH	Temp
Whole province							
Total	0.86	0.74 (se = 0.02)	14.45	8.70	8.14	10.18	44.97
Age < 1	0.88	0.80 (se = 0.01)	10.11	7.96	4.94	5.37	64.23
1 ≤ age < 3	0.86	0.75 (se = 0.01)	13.72	8.85	7.91	8.94	49.33
3 ≤ age < 6	0.86	0.67 (se = 0.03)	16.11	9.57	10.45	15.10	29.65
Age ≥ 6	0.81	0.68 (se = 0.02)	13.05	7.88	11.37	13.33	42.98
Pearl-River Delta region							
Total	0.83	0.72 (se = 0.02)	11.65	8.25	7.55	10.50	47.32
Age < 1	0.85	0.78 (se = 0.01)	8.53	6.21	3.84	3.92	70.79
1 ≤ age < 3	0.83	0.74 (se = 0.02)	10.94	7.91	6.65	9.22	53.51
3 ≤ age < 6	0.84	0.64 (se = 0.03)	11.70	10.14	9.81	17.66	28.99
Age ≥ 6	0.79	0.64 (se = 0.03)	11.00	9.38	11.30	13.93	41.05
Non-Pearl-River Delta region							
Total	0.81	0.72 (se = 0.02)	10.75	7.45	8.15	8.85	53.79
Age < 1	0.83	0.77 (se = 0.01)	6.52	7.47	4.93	3.92	71.93
1 ≤ age < 3	0.79	0.71 (se = 0.02)	9.98	7.74	7.33	6.82	58.05
3 ≤ age < 6	0.80	0.62 (se = 0.03)	12.72	8.33	10.46	13.96	36.29
Age ≥ 6	0.80	0.63 (se = 0.01)	12.04	10.36	10.71	11.75	42.60

Abbreviation: RF: rainfall, Sun: sunshine, Wind: wind speed, RH: relative humidity, and Temp: temperature.

4. Discussion

The current study has quantified the impacts of a set of meteorological factors on the epidemic of HFMD in Guangdong Province, with boosted regression tree (BRT) models. This tree-based modeling technique can in nature eliminate the effect of collinearity which is quite common among meteorological factors, and achieve robust estimations. However, this research also stands out from prior tree model-based studies by taking the delayed effect of predictors into account and carrying out an optimal lag selection procedure prior to modeling.

According to the result of lag selection, we found that the HFMD incidence in Guangdong was most likely affected by the weather about 1 week ago. It was consistent with prior findings that HFMD commonly had an incubation of 1 week (Huang et al., 2013; Zhang et al., 2015). We also found that a larger proportion of variance of HFMD case series for the Pearl-River Delta Region could be explained by meteorological factors which indicated that children in this area tend to be more sensitive to weather changes than those in the remaining areas. The developed Pearl-River Delta Region is more densely populated and children in this area have more social contacts and outdoor activities, which is supposed to be an important reason for this intraregional discrepancy (Zhang et al., 2015). We also found that younger children were more influenced by the weather. Considerable research has provided epidemiological evidence that HFMD is a common childhood infection that mainly attacks children under 5 years old (Gui et al., 2015; Zou et al., 2012). For the same reason, this study found that children >6 years old were the least susceptible.

The susceptibility of younger children and those from the Pearl-River Delta Region was well documented in our previous studies (Deng et al., 2013; Zhang et al., 2015; Zhang et al., 2014). For each analysis, we linked the HFMD surveillance data to the meteorological data at the optimal lag to achieve a better goodness of fit and a more accurate assessment of the impacts of meteorological factors on HFMD.

This study assessed the relative importance of weather variables in the development of HFMD. Three dominant factors were temperature, precipitation and humidity. This result is quite expected since not only can these factors influence human activities and susceptibility but they also have potential impact on the activity and spread of HFMD-

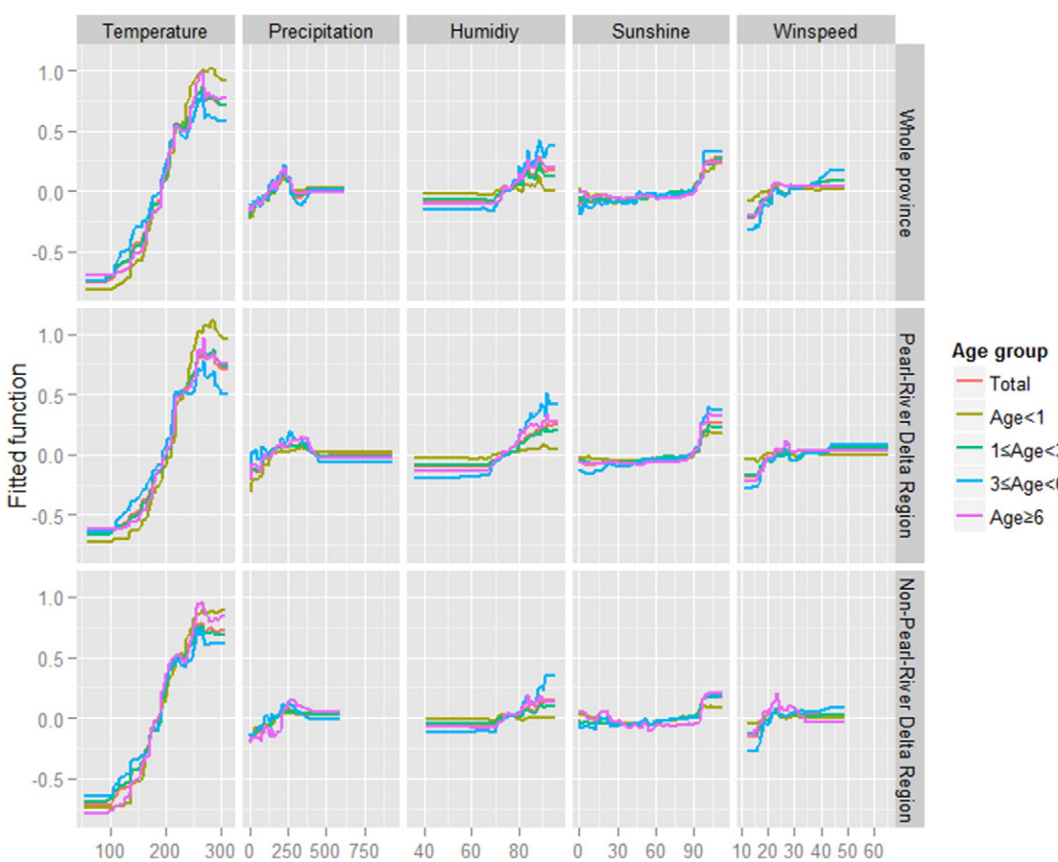

Fig. 1. Relationship between HFMD and meteorological factors at the optimal lag. Temperature between 10 °C and 25 °C, as well as humidity between 70% and 90%, had a facilitating effect on the epidemic of HFMD. An elevated risk was also observed when the value was above 9 h for sunshine duration or below 2.5 m/s for wind speed. The positive relationship between HFMD and precipitation reversed when the daily amount of rainfall exceeded 25 mm.

related virus (Huang et al., 2013; Zhang et al., 2015). Our results showed that the impact of temperature was negligible until it approached the first threshold point at 10 °C. In subtropical areas such as Guangdong, temperature under 10 °C only happened in winter or spring months when HFMD occurred at persistently low level. The possible reason may be that during those cold months, the activity of HFMD-related enterovirus was largely inhibited. Above the first threshold, the risk of HFMD increased with temperature. The facilitating effect of temperature on HFMD was widely reported in literatures (Huang et al., 2013; Zhang et al., 2015). However, when the temperature increased above the second threshold (about 25 °C), the risk did not continue to increase, but to be steady or even decrease instead. This was similar to a previous study from Japan which reported a negative association between the number of days per week of average temperature above 25 °C and HFMD incidence (Huang et al., 2013; Urashima et al., 2003). One of our previous research also demonstrated that the risk of HFMD would not continuously increase when the temperature exceeded 25 °C (Huang et al., 2013). The potential slightly downward trend existed in temperature-fitted function curves above 25 °C may be due to the reduced outdoor activities of children since the perceived heat may make them uncomfortable in humid subtropical conditions (Zhang et al., 2015). Another finding regarding the impact of temperature was that children under 1 year old seemed to be the most vulnerable.

Our research reinforced previous studies on the facilitating effect of rainfall in childhood HFMD development (Chen et al., 2015; Song et al., 2015). The elevated risk in rainy days maybe due to the increased contact rate of droplets which was the major carrier of HFMD-related virus (Government, 2015). However, when the amount of daily rainfall exceeded 37.5 mm, an opposite association was observed. Actually, the threshold effect of precipitation observed in the current study was expected since children tended to have fewer outdoor activities in heavily rainy days. This finding was consistent with a previous study from Singapore which reported a similar nonlinear relationship between risk of HFMD and precipitation (Hii et al., 2011).

According to the results of this study, the relationship between humidity and the risk of HFMD was similar to the scenario of temperature. Different from a previous study carried out in Guangzhou which reported a linearly positive relationship between the risk of HFMD and humidity (Huang et al., 2013), the current study identified two thresholds, one was 70% and the other 90%. Results of this study should be more reasonable and accurate. According to the meteorological data of Guangdong, the condition of humidity under 70% also mainly occurred in cold months when the incidence of HFMD was persistently low. So the finding of the negligible impact of low humidity on HFMD was expected. In addition, high humidity can lead to a higher-than-recorded perceived heat and a feeling of being uncomfortable (Zhang et al., 2015). Thus, a steady or even decreased risk of HFMD under highly humid condition was expected as a result of reduced social contacts (actually schools may be shut during these extreme-weather days). Besides study area and period, the discrepancy between this study and the previous one may be due to the different models used. The study from Guangzhou built a generalized additive model (GAM) which incorporated a couple of meteorological predictors and their lags simultaneously into the same model (Huang et al., 2013). Estimations may be biased since the collinearity problem was inevitable for GAM. In contrast, estimations from the BRT model in the current study were considered to be more robust. This study indicated that children in the developed Pearl-River Delta Region tended to be more sensitive to humidity changes since the slope of humidity-fitted function curves for this developed area was larger than that for the remaining areas. Regarding the intra-age group discrepancy, we found that children between 3 and 6 years old were the most susceptible to humidity changes while those under 1 year old were the least.

As the current research identified, the contribution of wind speed and daily sunshine duration to the development of HFMD in Guangdong was smaller relative to other three factors. Although conclusions on the impact of wind speed varied across literatures, our finding was consistent with most previous research which demonstrated a positive relationship between HFMD and wind speed (Liu et al., 2015; Ma et al., 2010; Zhang et al., 2016). The potential reason is that wind facilitates the spread of droplet which is one of the major vectors of enterovirus. However, in terms of the impact of sunshine, no significant trend was observed on sunshine-fitted function curves until 9 h. When the daily sunshine duration was longer than 9 h, the risk of HFMD increased. Although a previous study conducted in Shenzhen, a city in Guangdong Province, demonstrated that no significant association was observed for sunshine duration (Zhang et al., 2016), with the BRT method we found a positive relationship when the daily sunshine duration was above 9 h. The possible reason may be that conditions with a daily sunshine duration longer than 9 h tended to happen in warm months when the incidence of HFMD was relatively high. And a longer duration of sunshine was considered to lead to a higher temperature, more outdoor activities and, finally, a higher risk of HFMD.

This study has several strengths, including the fact that this is, to our knowledge, the first research combining the advantages of the boosted regression tree model which can obtain robust estimations even if collinearity and nonlinearity problems exist and the lag selection procedure which is common and essential in weather-health relationship explorations. Both the results and methods of the current study have a reference sense towards the prevention and control issues of infectious disease including HFMD.

Nevertheless, a couple of limitations should be acknowledged with this study. First, the research period of this study was limited in 3 years which may be shorter than that of previous studies. To ensure enough sample size, analysis was conducted at a daily basis, which was also considered to provide more accurate assessments of the impacts of meteorological factors. Second, ecological fallacy was inevitable for surveillance data-based studies. This research was no exception. Results from the current study which were obtained at aggregate level may not be effective in predicting individual outcomes, although a lot of times a speculation made for population is of more importance on public health.

In conclusion, this study has assessed the impacts of five meteorological factors on childhood HFMD, and displays the relationship between the risk of HFMD and these predictors at the optimal lags. Temperature may be the most influential factor, and has an apparent facilitating effect on HFMD development. Children under 1 year old were the most sensitive to temperature changes but the least sensitive to humidity changes. The risk of HFMD increased in rainy days but decreased when the amount of rainfall exceeded 25 mm. Sunshine duration above 9 h, as well wind speed below 2.5 m/s, leads to an elevated risk of HFMD, although its contribution was smaller relative to other predictors. Results from the current study were particularly important for developing early warning and response system on HFMD in the context of global climate change.

Competing interests

We declare that we have no conflicts of interest.

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Ethical approval

No confidential information was involved in this research. We obtained ethical approval from the Ethical Review Committee of the School of Public Health, Sun Yat-sen University (No. 201415).

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