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Short-term effects of meteorological factors on hand, foot and mouth disease among children in Shenzhen, China: Non-linearity, threshold and interaction

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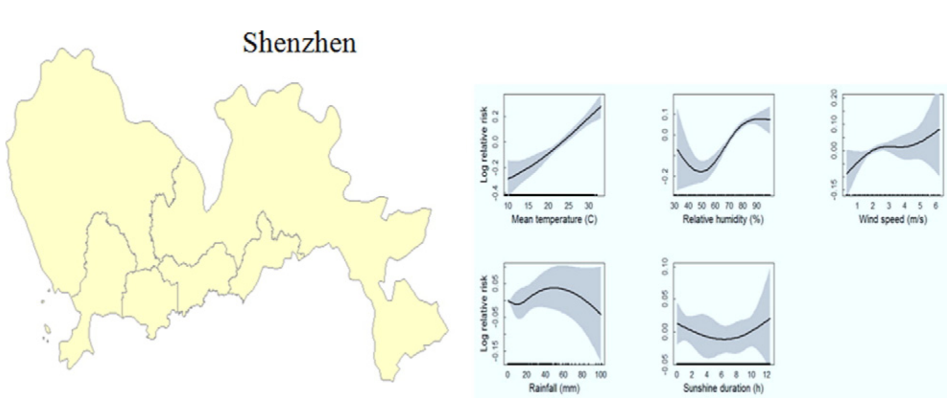
HIGHLIGHTS

- Temperature and wind are positively associated with hand, foot and mouth disease.
- There were thresholds for the effects of relative humidity.
- Low and high thresholds of relative humidity were found at 45% and 85%.
- There was non-significant interaction between weather variables on HFMD.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Various meteorological factors have been associated with hand, foot and mouth disease (HFMD) among children; however, fewer studies have examined the non-linearity and interaction among the meteorological factors.
Methods: A generalized additive model with a log link allowing Poisson auto-regression and over-dispersion was applied to investigate the short-term effects daily meteorological factors on children HFMD with adjustment of potential confounding factors.
Results: We found positive effects of mean temperature and wind speed, the excess relative risk (ERR) was 2.75% (95% CI: 1.98%, 3.53%) for one degree increase in daily mean temperature on lag day 6, and 3.93% (95% CI: 2.16% to 5.73%) for 1 m/s increase in wind speed on lag day 3. We found a non-linear effect of relative humidity with thresholds with the low threshold at 45% and high threshold at 85%, within which there was positive effect, the ERR was 1.06% (95% CI: 0.85% to 1.27%) for 1 percent increase in relative humidity on lag day 5. No significant effect was observed for rainfall and sunshine duration. For the interactive effects, we found a weak additive interaction between mean temperature and relative humidity, and slightly antagonistic interaction between mean temperature and wind speed, and between relative humidity and wind speed in the additive models, but the interactions were not statistically significant.

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Conclusions: This study suggests that mean temperature, relative humidity and wind speed might be risk factors of children HFMD in Shenzhen, and the interaction analysis indicates that these meteorological factors might have played their roles individually.

1. Introduction

Hand, foot and mouth disease (HFMD) has become an important public health concern in China and has attracted an increasing research interest in recent years (Wang et al., 2013). It is most common among infants and children aged younger than 5 years (Goksugur and Goksugur, 2010; Lin et al., 2014). The main clinical presentation includes fever, mouth ulcers, and vesicles mainly on the hands, feet, and mouth (Jiang et al., 2012). In most cases, the disease is mild and self-limiting, but more severe clinical symptoms with neurological abnormalities such as meningitis, encephalitis, and polio-like paralysis may occur (Chen et al., 2007). Currently, there is no vaccine or specific antiviral treatment available for HFMD.

Asian countries have experienced an increasing trend of HFMD outbreaks in the past decades, resulting in thousands of deaths among children due to severe complications (Xing et al., 2014). Particular public health concerns have been raised especially since the severe outbreaks in Malaysia and Taiwan in 1997 and 1998 (Ho et al., 1999). Several outbreaks have also been observed in mainland China in recent years, for example, a total of 1,619,706 new HFMD cases were reported in the year of 2011, resulting in 509 deaths (Jin et al., 2012).

The incidence of HFMD has exhibited seasonality in a number of areas, indicating that weather factors might have played an important role (Wang et al., 2011). A few studies have investigated the effects of meteorological factors on HFMD with inconsistent findings. For example, one study reported that maximum temperature above 32 °C was associated with increased HFMD incidence in Singapore (Hii et al., 2011); one study in Beijing, China found a non-linear and positive effect of temperature within the range of 25.0–27.5 °C (Xu et al., 2014); and studies from a few Chinese cities also supported the positive association (Huang et al., 2013; Chen et al., 2014); whereas another study from Japan found that the number of days per week with the average temperature above 25 °C was negative associated with HFMD incidence (Urashima et al., 2003). In addition, non-significant association between rainfall and HFMD was observed in Japan and Rizhao City, China (Onozuka and Hashizume, 2011; Wu et al., 2014), which was contrary to the findings from Singapore (Hii et al., 2011) and Guangzhou, China (Chen et al., 2014). Moreover, wind speed was found to be a risk factor for HFMD in Hong Kong (Ma et al., 2010), which was not observed in other studies (Deng et al, 2013; Huang et al., 2013).

Most of the previous studies examined the linear association between weather factors and HFMD without checking linear assumption (Huang et al., 2008; Zhang et al., 2008). Two recent studies in China suggested that most of the meteorological factors had an approximate linear relationship with HFMD (Chen et al., 2014; Lin et al., 2014; Wu et al., 2014); however, their exposure–response curves suggested that there seemed thresholds for the some meteorological variables, such as relative humidity. Another study from Singapore found non-linear effects of temperature and rainfall on HFMD, with the threshold being 32 °C for maximum temperature and 75 mm for rainfall (Hii et al., 2011). And another study from Japan found that the number of days per week with the average temperature above 25 °C was negative associated with HFMD incidence (Urashima et al., 2003).

At the same time, most studies only examined the effects of the individual meteorological factor; no study has explored the interactive effects of different meteorological factors yet, though the impact of weather variables depends on combined effects of the various meteorological factors.

Shenzhen City in south China has experienced serious epidemics of HFMD in recent year; according to the surveillance data, this city had four-fold HFMD epidemic of the national average (Deng et al., 2013). The current study aimed to examine the relationship of daily variation in meteorological factors with the occurrence of HFMD based on the exposure–response relationships, and we further examined the interactions of the effects of meteorological factors on HFMD.

2. Materials and methods

2.1. Setting

Shenzhen is a city in the south of Guangdong Province, adjacent to Hong Kong. It has a typical monsoon-influenced climate with wet and hot summers and dry and cool to mild winters. The annual mean temperature is around 22 °C. The mean temperature ranges from 28 °C to 30 °C in summer, and from 15 °C to 16 °C in winter. It has an area of 1997 km^2 and is home to 10.5 million residents. Fig. 1 showed the geographical distribution and elevation of Shenzhen, the average elevation ranges 70–120 m.

2.2. Data sources

Data on daily count of HFMD during the period 2010–2013 were obtained from the local Center for Disease Control and Prevention. HFMD was diagnosed by clinical symptoms, which included vesicular lesions on hands, feet, mouth (which were often ulcerated), and, frequently, buttocks, in accordance with the National Guideline on Diagnosis and Treatment of Hand Foot Mouth Disease (Chinese Ministry of Health). According to China's notifiable infectious disease regulation, all HFMD cases were required to be reported to the infectious disease surveillance system via the web-based surveillance system with standardized format, including the information of name, sex, age, address, date of symptom onset, etc. A recent data quality survey demonstrated that the data were of high quality, especially in the eastern regions of China, with reporting completeness of 99.84% and accuracy of the information reported of 92.76% (Ji et al., 2011). As most of the HFMD cases (91%) occurred among children younger than 5 years, we restricted our analysis to children aged 0–5 years.

Daily meteorological data including daily mean, minimum and maximum temperatures (°C), relative humidity (%), rainfall amount (mm), wind speed (m/s) and duration of sunshine (h) were obtained from National Weather Data Sharing System (http://cdc.cma.gov.cn/home.do), which was publicly accessible.

2.3. Statistical analysis

As daily count of HFMD typical followed a Poisson distribution, a generalized additive model (GAM) with a log link and allowing Poisson auto-regression and over-dispersion was applied to investigate the short-term effects daily meteorological factors on HFMD (Villeneuve et al., 2003). We controlled for day of the week (DOW) and public holidays using categorical indicator variables. In addition, we used penalized smoothing splines (Kan et al., 2007) to adjust for long-term and seasonal trends in daily morbidity with degree of freedom (df) selected a priori based on previous studies (Bell et al., 2009; Peng et al., 2009). For the smooth function of calendar time, 6 df per year was chosen so that we could filter out the information at time scales of 2 months (Lin et al., 2013a). The model for temperature can be

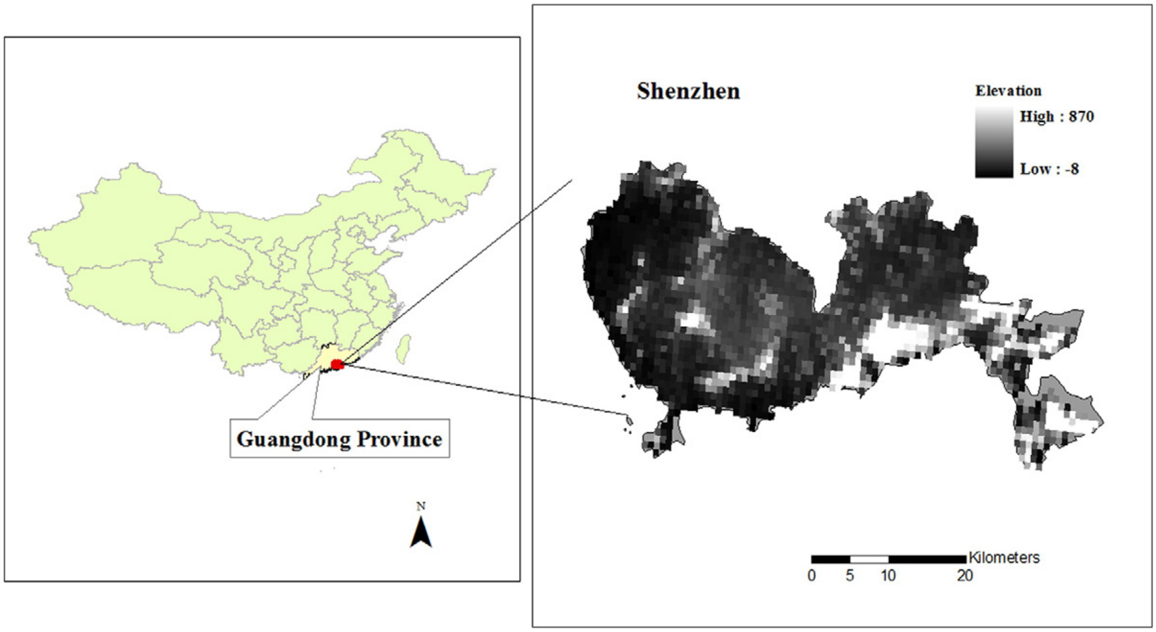

Fig. 1. Geographical location of Shenzhen in China (left picture shows the location of Guangdong Province in China, right shows the elevation map of Shenzhen).

specified as:$\log[E(Yt)] = \alpha + \text{temperature} + s(t, df = 6 / \text{year}) + \beta_1 * DOW + \beta_2 * PH$,where E(Yt) is the expected number of HFMD on day t, α is the intercept, s() indicates a smoother based on penalized smoothing splines, df is the degree of freedom, DOW is an indicator for day of week, PH presents a binary variable for the public holiday, and β is the regression coefficient.

To examine the shape of the association between the logarithm of daily HFMD count and the weather variables, we firstly graphically examined the exposure–response curves derived using a smoothing function (Hong et al., 2002; Kan et al., 2003). The initial analysis suggested that there was threshold for relative humidity; the exposure–response curve showed that there was no significant effect below and above a certain value and an approximately linear effect within certain range of values. We used the Akaike Information Criterion (AIC) to determine that thresholds. Briefly, in the model multiple thresholds were tested based on minimal AIC value of model (Li et al., 2015). For example, by visual inspection of the exposure–response curve, we may identify that the potential threshold might be within 40% to 50%, and we then fitted two models with the thresholds from 40% to 50% (by 1%) to identify the threshold with minimum sum of the AIC of the two models.

Based on the threshold identified in the above procedure, we then estimated the linear effect of various weather variables according to different lag structures, including current day (lag0) up to 14 days before (lag14) as this infection usually has a short incubation period of 3–6 days (Wong et al., 2010). Univariate model was firstly fitted for each meteorological factor, and then multivariate model was used to control the influence of other meteorological factors.

To investigate the interaction between the meteorological factors in relation to HFMD, each of these meteorological factors was firstly classified into two categories using the median value as the cut-point, and a new variable was then created to represent the combination of two variables of interest (using temperature and humidity as an example) and could be classified into four categories: low temperature and low humidity, low temperature and high humidity, high temperature and low humidity, and high temperature and high humidity. Possible additive interaction was assessed following a method proposed by Andersson (Andersson et al., 2005), which calculated three measures of additive interactions: relative excess risk due to interaction (RERI), attributable proportion (AP) and synergy index (SI). When RERI and AP was equal to 0 and SI equal to 1, we considered absence of additive interaction; while additive interaction was present if RERI and AP did not equal 0 and SI exceeded unity. Furthermore, a RERI greater than 0 denoted a synergetic interaction, which implied that the joint effects of two factors in an additive model was greater than the sum of their individual effects. On the other hand, if RERI was smaller than 0, it implied an antagonistic interaction, indicating that in the presence of two exposures in an additive model, one factor decreased the effect of the other (Lundberg et al., 1996; Rothman et al., 2008).

2.4. Sensitivity analysis

As the risk estimates usually varied with the model specifications in time-series analysis (Peng et al., 2006; Gasparrini and Armstrong, 2010), we performed additional sensitivity analyses to test the robustness of our results: use of alternative degrees of freedom (5–9 df/year) for temporal adjustment. We also did similar analyses for daily minimum and maximum temperatures.

All statistical analyses were two-sided and values of $P < 0.05$ were considered statistically significant. The "mgcv" package in R software Version 3.1.0 (R Development Core Team, 2012) was used to fit all models and estimate the exact standard errors of regression coefficients. We reported the results as excess relative risk (ERR), which was defined as the percentage increase in daily HFMD count for each unit increase in each meteorological factor, with 95% confidence intervals (95% CI). The ERR was calculated by: $(RR\text{-}1) \times 100\%$, where RR was obtained from the GAM model (Lin et al., 2013b).

3. Results

Between 1 January 2010 and 31 December 2013, there were a total of 102,015 HFMD cases among children under 5 years old in Shenzhen. There were more male cases with a male-to-female sex ratio of 1.66:1 (63,694:38,321). The descriptive summary for HFMD cases and weather conditions was shown in Table 1. There was an average of 69.8 daily children HFMD cases over the study period. The mean temperature, relative humidity, rainfall, wind speed and duration of sunshine were 23.0 °C, 74.3%, 4.7 mm, 22.4 m/s and 5.1 h, respectively. Fig. 2 depicted the time series of daily HFMD counts and weather conditions in the study area. There were seasonal patterns in these factors; particularly,

Table 1
Summary statistics of daily HFMD count and weather condition in Shenzhen, 2010–2013.

Variables	No. of days	Mean ± SD	Min	P_{25}	Median	P_{75}	Max
Daily HFMD count	1461	69.8 ± 60.5	0.0	19.0	55.0	105.0	357.0
Tmean (°C)	1461	23.0 ± 5.6	5.4	19.0	24.4	27.8	32.0
Tmin (°C)	1461	20.5 ± 5.7	2.4	16.5	21.9	25.3	29.1
Tmax (°C)	1461	26.6 ± 5.7	7.2	22.8	27.8	31.3	36.4
Relative humidity (%)	1461	74.3 ± 13.4	24.0	68.0	76.0	84.0	100.0
Rainfall (mm)	1440	4.7 ± 13.1	0.0	0.0	0.0	1.0	152.3
Wind speed (m/s)	1461	2.2 ± 0.8	0.3	1.7	2.1	2.6	6.2
Sunshine (h)	1459	5.1 ± 3.8	0.0	1.1	5.6	8.5	12.5

Abbreviations: Tmean, mean temperature; Tmin, minimum temperature; Tmax, maximum temperature; SD, standard deviation; Min, minimum; Max, maximum; P_x, xth percentile.

there was obvious seasonality for the HFMD occurrence with the epidemic peaking in summer–autumn months.

Table 2 depicted the correlations between various weather variables. High correlations were found between mean, minimum and maximum temperatures, for easy interpretation, we examined the effect of mean temperature in the main model. All other weather variables (except between rainfall and wind speed) were significantly correlated with each other with low correlation coefficients, e.g., between daily mean temperature and relative humidity (r = 0.30), between relative humidity and rainfall (r = 0.39).

The exposure–response relationship for various meteorological factors with HFMD occurrence was shown in Fig. 3. An almost linear and positive effect of mean temperature and wind speed was observed; while the effect of rainfall and duration of sunshine appeared to be non-significant. However, for relative humidity, it seemed that there were lower and higher thresholds, our analysis suggested the best models with the lower threshold at 45% and higher threshold at 85% (Fig. s1), between which there was a positive and linear effect. So in the subsequent analyses, we examined the linear effect of relative humidity within the range from 45% to 85%.

The associations between various meteorological factors and children HFMD were presented in Fig. 4. In the univariate analyses, significant associations were observed for daily mean temperature, relative humidity and wind speed for some of the lag days. Consistent findings were observed in the multivariate models, daily mean temperature at lag of 4–14 days was significantly associated with increased HFMD (meaning that exposure to higher temperature was generally followed by increased HFMD 4–14 days later), with the largest effect being observed at lag day 6 (ERR = 2.75%, 95% CI: 1.98% to 3.53% for one degree increase in daily mean temperature); within the range of 45%–85% of relative humidity, a negative effect was found on the current day, with ERR being −0.31% (95% CI: −0.54% to −0.08% for 1% increase); and a positive effect was found for relative humidity at longer lag days of 3–14, with ERR at lag day 5 being 1.06% (95% CI: 0.85% to 1.27%); a positive effect was observed for wind speed at lag of 2–4 and 10 days, with the largest effect on lag day 3 (ERR = 3.93%, 95% CI: 2.16% to 5.73%). For the effect of rainfall and duration of sunshine, we only found a negative effect of rainfall and a positive effect of duration of sunshine at the current day in the univariate, and no significant association was found in the multivariate models.

Table 3 showed the interaction between the three meteorological factors (mean temperature, relative humidity and wind speed) which were significantly associated with HFMD. The results suggested that there was some weak additive interaction between mean temperature and relative humidity (RERI = 0.018, SI = 1.104); while there was slightly antagonistic interaction for the effects of mean temperature and wind speed (RERI = −0.023, SI = 1.872), relative humidity and wind speed (RERI = −0.007, SI = 0.968). However, all the interactions were not statistically significant.

In the sensitivity analyses, when the degrees of freedom for time trend were varied between 5 and 9 to control for seasonality and long-term trends, similar results were obtained. The analyses for daily minimum and maximum temperatures showed a similar result with that of mean temperature (as shown the exposure–response relationship in Fig. s2).

4. Discussion

Our results showed that the daily variation of meteorological factors was associated with day-to-day variation of children hand, foot and mouth disease in Shenzhen and suggested that mean temperature,

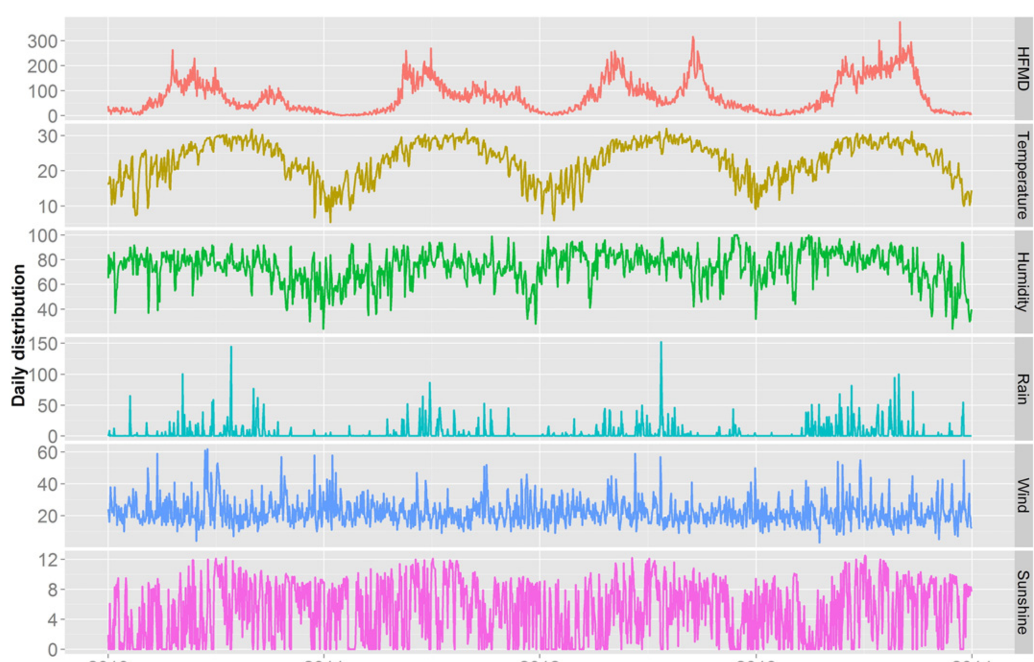

Fig. 2. The time series of daily children HFMD and weather factors in Shenzhen, 2010–2013 (unit: Temperature (°C), relative humidity (%), rainfall (mm), wind speed (m/s) and duration of sunshine (h)).

Table 2
Pearson correlations between daily weather variables in Shenzhen, 2010–2013.

	Tmean	Tmin	Tmax	Humidity	Rainfall	Wind velocity
Tmin	0.99**					
Tmax	0.98**	0.94**				
Humidity	0.30**	0.35**	0.21**			
Rainfall	0.12**	0.13***	0.06*	0.39**		
Wind velocity	−0.11**	−0.08**	−0.17**	−0.12**	0.01	
Sunshine	0.32**	0.28**	0.47**	−0.46**	−0.37**	−0.03*

Abbreviations: Tmean, mean temperature; Tmin, minimum temperature; Tmax, maximum temperature.
* $P < 0.05$.
** $P < 0.01$.

relative humidity and wind speed might be important determinants of transmission of HFMD in the study area. Our analysis further suggested there was no interaction between the meteorological factors on the risk of HFMD, which, to our knowledge, is the first study to report the interaction between meteorological factors on HFMD.

The present study showed a positive effect of daily mean temperature on HFMD incidence. Similar findings have been reported in Japan (Onozuka and Hashizume, 2011) and China (Bo et al., 2014; Chen et al., 2014; Lin et al., 2014; Wu et al., 2014). Our study found a log-linear exposure–response relationship between daily mean temperature and HFMD in Shenzhen, which was consistent with studies in other Chinese cities (Chen et al., 2014; Lin et al., 2014; Wu et al., 2014). On the contrary, some studies found that there was threshold of temperature, for example 25.0–27.5 °C in Beijing, China (Xu et al., 2014), 20 °C in Japan (Onozuka and Hashizume, 2011), and 32 °C in Singapore (Hii et al., 2011); this discrepancy might be due to the differing weather and demographic profiles in these different areas. The underlying mechanism for the relationship between temperature and HFMD remained unknown. It was possible that higher ambient temperature in the study area was more appropriate for the breeding and survival of the virus in the environment, and thus facilitate the transmission of the HFMD in the study population (Lin et al., 2013a).

For relative humidity, this study found that it was adversely associated with HFMD at shorter lag days, and it was positively associated with HFMD at longer lag days, which was similar with the findings from Rizhao, China (Wu et al., 2014 Due to the 3–6 days of incubation period of this infection and in light of previous findings (Huang et al., 2013; Deng et al., 2013), the positive effect at longer lag days were more biologically plausible, as the clinical symptoms were more likely to present several days after the exposure to higher relative humidity. We found that there were thresholds for the effects of relative humidity, which has not been reported in previous studies. It was possible that within certain range of relative humidity, higher humidity which could facilitate the attachment of the virus on the surface of objects or toys (Wong et al., 2010), which was also supported by experimental studies, where the viruses have a more rapid declining rate during dry seasons (Abad et al., 1994).

In this study, wind speed was found to be positively associated with HFMD, which was in accordance with one study in Hong Kong (Ma et al., 2010) and one spatial analysis in Shandong, China (Liao et al., 2015). In the study region, windy days are appropriate outdoor activities in most time of one year, so children are more likely to go outdoors when it is windy, and increase the opportunity of being infected through respiratory droplets or direct contacting with the contaminated toys and environmental surfaces (Ma et al., 2010).

Our study provided the first evidence of possible interaction of various meteorological factors on the risk of HFMD. Previous studies have illustrated the effects of individual meteorological factor on HFMD; ambient weather is a complex combination of many meteorological variables, it is important to better understand the complex relationship between these meteorological factors and their interactive effects on HFMD. This study observed some weak interactive effects among mean temperature, relative humidity and wind speed, which was not statistical significant, suggesting that these meteorological factors have played their roles individually. On the other hand, the observed weak antagonistic interaction between wind speed and relative humidity might be due to that, during humid days, the virus could be easily attached to the surface of the environment, but high wind speed might not be appropriate for this attachment.

This study had two major strengths. Firstly, this study calls for consideration of linearity, threshold and interaction between various meteorological factors in future studies. Our study examined the association between meteorological factors and HFMD occurrence based on the exposure–response relationships, and found a non-linear effect of relative humidity and presence of thresholds, which has not been reported. Secondly, this study investigated the interactive effects of various meteorological factors on the risk of HFMD, which improved our understanding of the association between weather and HFMD. More importantly, findings from this study have some important public health implications. The linear effects of mean temperature and wind

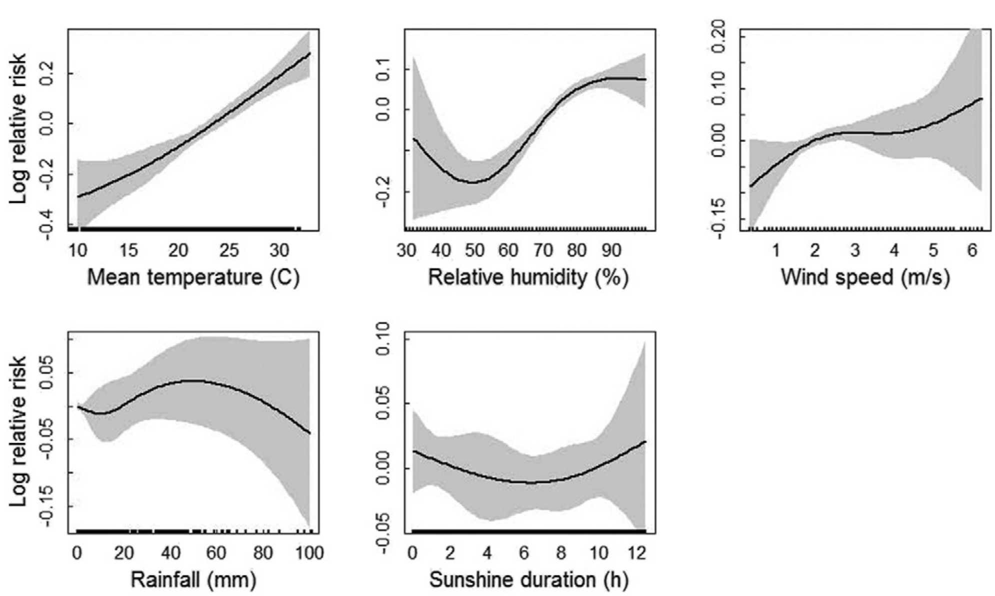

Fig. 3. Smoothing plots of daily weather variables against children HFMD in Shenzhen, 2010–2013. Confounding factors included time trend, day of week and public holidays.

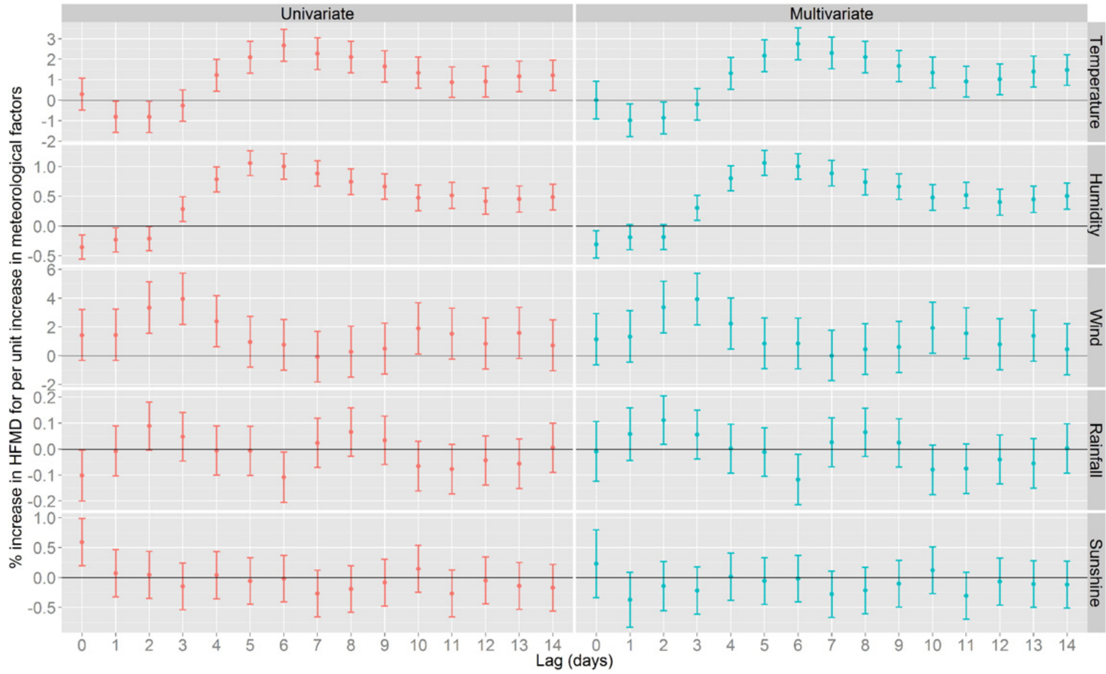

Fig. 4. The univariate and multivariate analyses for the association between daily meteorological factors and children HFMD in Shenzhen, 2010–2013 (the effect estimates were excessive relative risk for one unit increase in the weather variables).

speed, and non-linear effect of relative humidity should be considered in the future disease control and prevention measures to combat HFMD. Though this study did not find significant interaction of various meteorological factors, we suggest more studies to investigate possible interactions and control measures to consider these results.

A few limitations should be noted. Firstly, this study was ecological in study design, which has limited our capacity for causal inference. Secondly, we used meteorological data from only one national weather monitoring station, presenting concern in terms of representativeness and exposure estimate. Thirdly, being a preliminary and exploratory study, our analysis could not provide exact mechanism to explain the observed association, particularly for the interaction between various meteorological factors, and we could not exclude the possibility that unmeasured confounding factors might have affected our finding to some extent.

Table 3
The interactive effects between mean temperature, relative humidity and wind speed on HFMD in Shenzhen, 2010–2013.

Models	No. of days	ERR (%)	Lower (%)	Upper (%)
Temperature–humidity				
Low–low	290	0	–	–
Low–high	264	10.7	0.0	22.6
High–low	174	6.4	−0.35	17.2
High–high	391	18.9	7.7	31.3
RERI	0.018 (95% CI: −0.092, 0.128)			
AP	0.015 (95% CI: −0.078, 0.108)			
Synergy index	1.104 (95% CI: 0.566, 2.156)			
Temperature–wind				
Low–low	411	0	–	–
Low–high	222	9.2	0.5	18.6
High–low	520	9.1	1.8	16.9
High–high	302	15.9	8.1	24.3
RERI	−0.023 (95% CI: −0.121, 0.075)			
AP	−0.020 (95% CI: −0.104, 0.064)			
Synergy index	0.872 (95% CI: 0.511, 1.488)			
Humidity–wind				
Low–low	360	0	–	–
Low–high	194	8.7	2.0	15.8
High–low	361	12.1	6.6	17.9
High–high	204	20.1	13.5	27.1
RERI	−0.007 (95% CI: −0.095, 0.082)			
AP	−0.006 (95% CI: −0.079, 0.068)			
Synergy index	0.968 (95% CI: 0.632, 1.483)			

Abbreviations: RERI, relative excess risk due to interaction; AP, attributable proportion.

5. Conclusion

In summary, our study suggests that high mean temperature, wind speed, and relative humidity might be risk factors of HFMD in Shenzhen, and the interaction analysis indicates that these meteorological factors might have played their roles individually.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.scitotenv.2015.09.027.

Conflicts of interest

None.

Ethics statement

Data were collected as part of government mandated health surveillance and analyzed anonymously so ethical approval was not needed.

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