



# 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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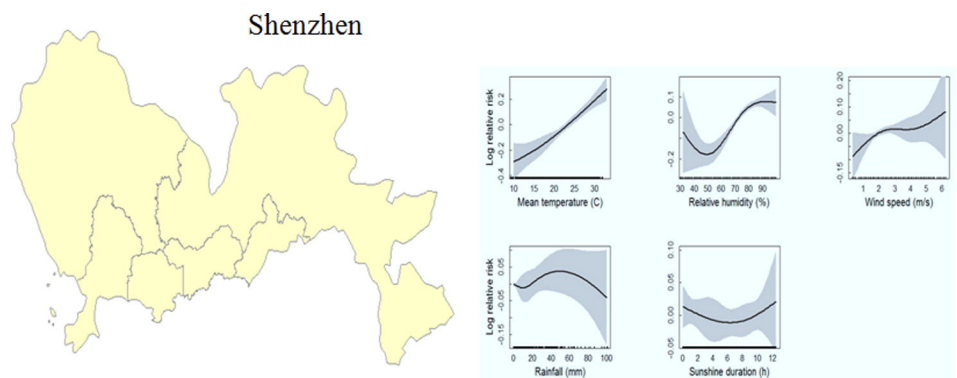
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## HIGHLIGHTS

- 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.

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## 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<sup>2</sup> 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

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