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Quantifying the adverse effect of excessive heat on children: An elevated risk of hand, foot and mouth disease in hot days

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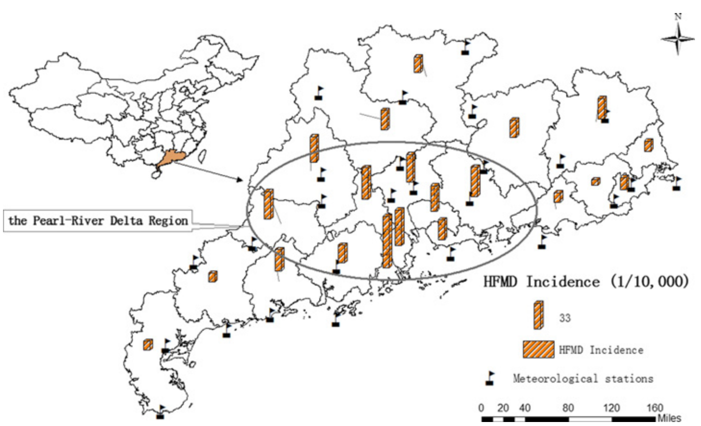
HIGHLIGHTS

- The facilitating effect of excessive heat on HFMD was verified and quantified.
- The impact of excessive heat varied across socio-economic status and age groups.
- *RR*s in developed areas were higher and persisted longer.
- Children aged 3–6 were the most sensitive to excessive heat.
- Relative effect of two kinds of conditions of excessive heat varied across regions.

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 such as temperature and relative humidity in HFMD development. However, no studies have specifically quantified the impact of another major environmental agent, excessive heat, on HFMD. The current study was designed to help address this research gap.
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. Distributed lag nonlinear models were applied to assess the impact of excessive heat on HFMD and its variability across social-economic status and age groups.
Results: After controlling the effects of several potential confounders, the commonly hot days were found to positively affect the HFMD burdens with the relative risk (*RR*) peaking at around 6 days of lag. The *RR* of HFMD in the Pearl-River Delta Region was generally higher and persisted longer than that in the remaining developing areas. Regarding the inter-age group discrepancy, children aged 3–6 years old had the highest risk of HFMD under conditions of excessive heat whereas those greater than 6 years old had the lowest. The lag structure of the impact of

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the extremely hot days was quite similar to that of the commonly hot days, although the relative effect of these two kinds of conditions of excessive heat might vary across regions.
Conclusions: This study indicated significantly facilitating effects of excessive heat on HFMD especially among those aged 3–6 and from developed areas. Results from the current study were particularly practical and important for developing area-and-age-targeted control programs in the context of climate change and urbanization.

1. Introduction

Hand, foot and mouth disease (HFMD), a common childhood infection, is normally self-limiting but can cause fatal complications such as myocarditis, aseptic meningitis and pulmonary edema (Kumar et al., 2015; Zhu et al., 2011). It has become a public health priority in China since its first large-scale epidemic in Fuyang City, Anhui Province in 2008 (Zhang et al., 2010). Both the reported numbers of cases and deaths of HFMD have been topping the list of category C infectious diseases in China thereafter (China, 2014). It is a particular concern in Guangdong Province where the incidence is higher than four times the national average and exceeds 30 cases per 10,000 (Deng et al., 2013; Zhang et al., 2014).

Meteorological predictors such as temperature, relative humidity and precipitation are the most commonly reported environmental agents which may have significant effects on childhood HFMD epidemics (Chen et al., 2015; Deng et al., 2013; Huang et al., 2013; Li et al., 2014; Urashima et al., 2003; Xing et al., 2014). Some of these studies were particularly interested in the correlation between HFMD and temperature which was treated as a continuous variable in the most cases, and calculated the relative risk (*RR*) or the average change rate in the incidence of HFMD (Chen et al., 2014; Chen et al., 2015; Huang et al., 2013). The significantly facilitating effect of temperature on HFMD has been well documented, with evidence suggesting that higher temperature may lead to a higher risk of being infected (Song et al., 2015; Urashima et al., 2003). A recent research (our recently submitted work) focusing on the impacts of humidex, a comprehensive index combining the effects of temperature and humidity and reflecting the human perceived heat, have further strengthened prior speculations of an adverse effect of excessive heat upon children, with the relative risk of HFMD observed increasing with humidex.

However, no studies have specifically assessed the impacts of conditions of excessive heat relative to common conditions on HFMD. The current study was designed to help address this research gap.

Generally, the assessment of the impacts of meteorological conditions may be complicated by several factors. First, the most significant effect of excessive heat may not occur at the day of the event but a couple of days afterward (Lin et al., 2009; Lin et al., 2012). Recently, there have been increasing interests for the research to quantify the delayed effects of meteorological conditions (Chen et al., 2014; Huang et al., 2013; Lin et al., 2012). Distributed lag nonlinear model, a recently developed time series modeling technique, was proved effective in assessing delayed impacts without collinearity problems, and was particularly suitable for this case. Therefore, it was the main statistical method carried out in the current study. Second, socio-economic status and demographical characteristics such as age may be potential confounders (Pacific, 2011; Xing et al., 2014). Developed areas and developing areas differ in various aspects including population density, infrastructure, sanitary conditions and living standard of the population. The impact of excessive heat on HFMD may vary across different regions, although no comparative studies have addressed this issue which is considered particularly important for a vast province with unbalanced regional development. Children of different age groups tend to have different susceptibility, life styles and social contacts. Therefore, their responses to meteorological conditions may be significantly different (Deng et al., 2013; Huang et al., 2013). When stratified by potential confounders, results may vary substantially.

This study aimed to quantify the impact of excessive heat on childhood HFMD in Guangdong Province, China, from 2010 to 2012, and to assess its variability across social-economic status and age groups.

2. Materials and methods

2.1. Study settings and data sources

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 (areas within the ellipse, as shown in Fig. 1) 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 less than 50% population (Province, 2014).

Year-round case-based HFMD surveillance data collected between 2010 and 2012 was obtained from China Center for Disease Control and Prevention (China CDC). Both the clinically diagnosed and the laboratory-confirmed cases were reported to the case-based surveillance system (CBSS). According to the National Clinic Guide, a clinically diagnosed case was defined as a patient with papular or vesicular rash on hands, feet, mouth, or buttocks, with or without fever, while a laboratory-confirmed case was defined as a clinically diagnosed case with laboratory evidence of enterovirus infection detected by RT-PCR, real-time PCR, or virus isolation (Health, 2009; Xing et al., 2014). Information including birth date, onset time and ZIP code for the current address was reported to the CBSS when a patient was diagnosed with HFMD. The quality of the data was assessed and assured by the China CDC. With high reporting completeness and high accuracy of the information reported, the surveillance data of HFMD was of high quality (Huang et al., 2013).

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. The form of child care may affect HFMD infection. In China, children under 3 years old are usually cared for at home, 3–6 years attend kindergartens, and above 6 years go to school. Children under 1 year old obviously differ from those aged 1–3 years in daily activities. To assess the variability of the impact of excessive heat across age groups, analyses were stratified accordingly (<1, 1–3, 3–6, and >6 years) (Huang et al., 2013). Population data was obtained from Statistical Yearbooks of Guangdong (Province, 2014).

Daily meteorological data was obtained from the National Meteorological Information Center (http://cdc.nmic.cn/). Then, humidex was calculated based on relative humidity and temperature with a calculator provided by CSGNetwork (http://www.csgnetwork.com/) in California. Humidex, rather than temperature, was used in this study because it directly reflected the heat that human truly perceived (Chebana et al., 2013; Masterton and Richardson, 1979). A day with a mean humidex greater than 30 was defined as a day of excessive heat in this study since it was reported that a humidex over 30 would cause human discomfort (Canada, 2014). Conditions of excessive heat were further classified into two categories: the commonly hot days with a humidex ranging from 30 to 40, and the extremely hot days with a humidex greater than 40 (Canada, 2014).

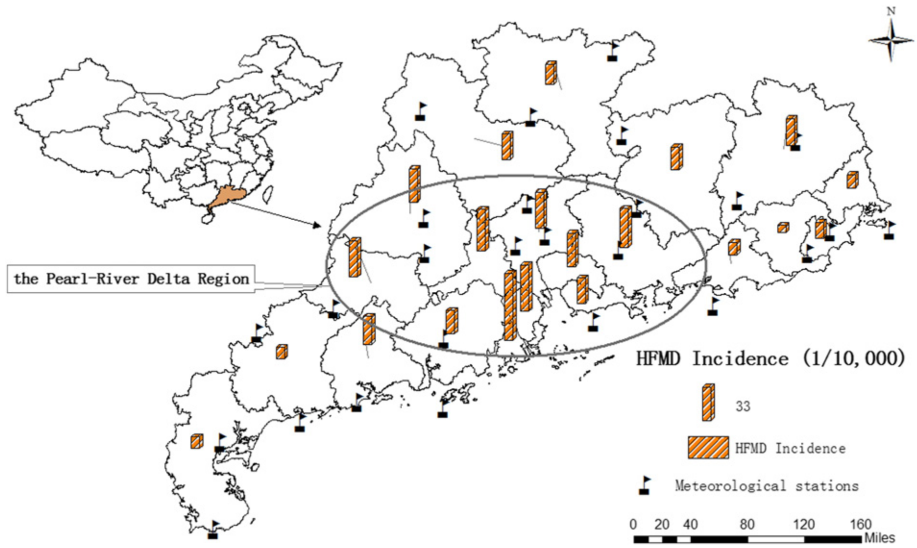

Fig. 1. Spatial distribution of meteorological stations and the average incidence of HFMD in Guangdong during 2010–2012. The HFMD burden in the Pearl-River Delta Region was much higher than that in the remaining areas.

2.2. Statistical analysis

For each subset of analysis, we applied a distributed lag nonlinear model with quasi-Poisson distribution to quantify the effect of excessive heat on childhood HFMD, with daily counts of HFMD cases as the dependent variable and an indicator of the day type as the predictor of interest.

To correct for the seasonality and long-term trend, a natural spline fit to time was incorporated into the model. An indicator of whether or not it was a holiday and a series of dummy variables representing the day of week were also incorporated to control the impacts of holidays and the day of week. Three natural spline fits to sunshine, rainfall and wind speed, all with 3 degrees of freedom (df), were used to control the potential confounding effects of these factors. Relative humidity and temperature were excluded to avoid collinearity problems.

Based on previous studies, we specified the delayed effect of excessive heat up to two weeks of lag (minimum lag equal to 0 by default) (Huang et al., 2013; Xu et al., 2015). Df for the natural spline fit to time was specified within 5–10, and for the space of the lag dimension of excessive heat within 3–6. Sensitivity analyses were conducted to evaluate the robustness of assessments and select the “best parameters” according to Akaike's Information Criterion for quasi-Poisson (Q-AIC).

Data manipulation and analyses were accomplished with R packages including “data.table”, “ggplot2” and “dlnm”. Mapping was carried out with ArcGIS10.0 (ESRI).

3. Result

3.1. Descriptive statistics

There were totally 827,911 cases under 15 years old reported to the CBSS during the period of 2010–2012 in Guangdong province (Table 1). The average provincial incidence during the study period was 26.26 per 10,000. Incidence in the Pearl-River Delta Region (34.17 per 10,000) was higher than twice that in the remaining areas (17.07 per 10,000) (Fig. 1, Table 1).

There were 530 days during the study period in Guangdong Province experiencing excessive heat. Among these days, 416 were commonly hot days with an average humidex of around 36, while 114 were extremely hot days with an average humidex over 40 (Table 1).

3.2. Relationship between excessive heat and the risk of HFMD

When analyzed as a whole (top-left panel, Fig. 2), the impact of commonly hot days on HFMD was insignificant until 3 days after the event. The risk of HFMD peaked at Lag 6 with a relative risk of 1.08 (1.07, 1.09) and thereafter decreased. Most of the lag-specific *RR*s were significantly elevated, suggesting significantly facilitating effects of the commonly hot days on HFMD. As a result, when the impact was cumulated over lags, the relative risk of HFMD increased to 1.99 (1.79, 2.20) (Table 2).

In examining subsets of analysis, the highest risk of HFMD in the commonly hot days for children under 6 years old typically occurred at 5–7 days after the event, whereas the *RR* peaked as late as 10–11 days of lag for children greater than 6. Regarding the 14-day cumulative effects of the commonly hot days (Table 2), *RR* was highest among children between 3 and 6 years old [the Pearl-River Delta Region: 2.52 (2.16, 2.93), the remaining areas: 1.81 (1.54, 2.13)] and lowest among those greater than 6 [the Pearl-River Delta Region: 1.23 (1.03, 1.45), the remaining areas: 1.34 (1.03, 1.75)].

In terms of the interregional discrepancy, the relative risk of HFMD in the Pearl-River Delta Region was generally higher and persisted longer than that in the Non-Pearl-River Delta Region (Fig. 2).The cumulative relative risk for the Pearl-River Delta Region was 2.21 (1.97, 2.48) and significantly higher than the figure for the remaining areas [1.56 (1.40, 1.73)].

Table 1
Descriptions of HFMD cases (case numbers and incidence) and weather conditions (number of days and the description of humidex).

	HFMD cases		Humidex [N (mean ± SD)]		
	Case numbers	Incidence (1/10,000)	Common conditions[a]	Commonly hot days	Extremely hot days
The whole province	827,911	26.26	566 (19.33 ± 7.06)	416 (36.27 ± 3.00)	114 (40.88 ± 0.63)
The Pearl-River Delta Region	579,032	34.17	535 (19.65 ± 6.91)	404 (36.07 ± 3.04)	157 (40.98 ± 0.73)
The Non-Pearl-River Delta Region	248,879	17.07	574 (19.12 ± 7.09)	417 (36.23 ± 3.00)	105 (40.83 ± 0.61)

[a] Common conditions: Days with a humidex below 30.

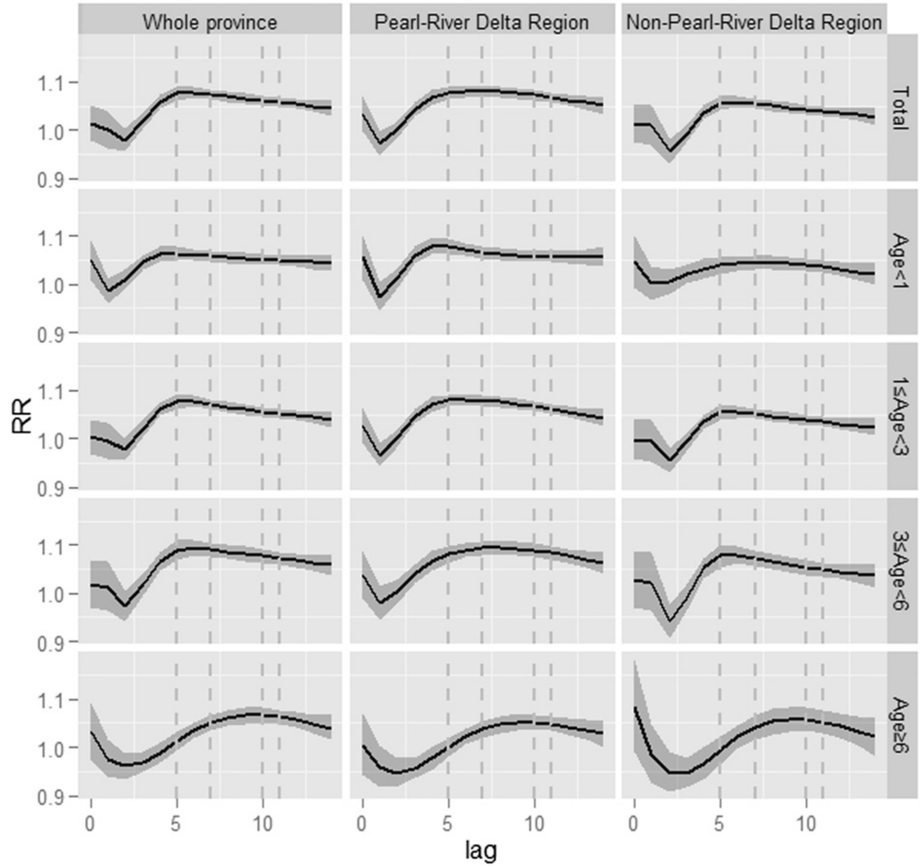

Fig. 2. The lag structure of the impact of the commonly hot days on HFMD. The risk of HFMD in the commonly hot days typically peaked at 5–7 days of lag and thereafter decreased. Most of the lag-specific *RRs* were significantly elevated, suggesting significantly positive impacts of the commonly hot days on HFMD. The relative risk of HFMD in the Pearl-River Delta Region was generally higher and persisted longer than that in the Non-Pearl-River Delta Region. The highest risk of HFMD for children greater than 6 years old occurred as late as 10–11 days after the heat event.

The lag structure of the impact of the extremely hot days (not shown) was quite similar to that of the commonly hot days described above. But as Table 2 shows, when analyzed as a whole, the commonly hot days tended to have greater impacts than the extremely hot days although discrepancies might not be significant because of the overlap of confidence intervals. In stratified analyses, there existed a similar pattern in the Pearl-River Delta Region. However, for the Non-Pearl-River Delta Region, the impact of the extremely hot days was greater, suggesting a variability in the relative effects of different levels of excessive heat across regions.

4. Discussion

The current study has quantified the impact of excessive heat on childhood HFMD from perspectives of both the predictor and its lag, using Guangdong Province as the study area from 2010 to 2012. Because of the absence of HFMD-targeted vaccination or specific treatments, quantification of the adverse effects of environmental agents is essential for the early warning and response system on HFMD (Xu et al., 2015). This study stands out from prior studies by highlighting the critical role of excessive heat in facilitating the transmission of childhood HFMD.

Table 2
The 14-day cumulative relative risk for excessive heat and its 95% confidence interval, *RR* (95%*CI*).

	Whole province	Pearl-River Delta Region	Non-Pearl-River Delta Region
Total			
Commonly hot days	1.99 (1.79, 2.20)	2.21 (1.97, 2.48)	1.56 (1.40, 1.73)
Extremely hot days	1.94 (1.70, 2.21)	2.07 (1.79, 2.39)	1.66 (1.45, 1.90)
Age < 1			
Commonly hot days	1.95 (1.73, 2.19)	2.19 (1.91, 2.50)	1.60 (1.37, 1.87)
Extremely hot days	1.86 (1.61, 2.15)	2.03 (1.72, 2.38)	1.59 (1.32, 1.91)
1 ≤ age < 3			
Commonly hot days	1.88 (1.70, 2.08)	2.11 (1.89, 2.36)	1.45 (1.30, 1.63)
Extremely hot days	1.87 (1.64, 2.12)	2.01 (1.74, 2.31)	1.58 (1.37, 1.81)
3 ≤ age < 6			
Commonly hot days	2.32 (2.01, 2.66)	2.52 (2.16, 2.93)	1.81 (1.54, 2.13)
Extremely hot days	2.23 (1.85, 2.69)	2.33 (1.90, 2.86)	2.03 (1.64, 2.50)
Age ≥ 6			
Commonly hot days	1.52 (1.28, 1.80)	1.23 (1.03, 1.45)	1.34 (1.03, 1.75)
Extremely hot days	1.46 (1.19, 1.79)	1.07 (0.85, 1.34)	1.39 (1.01, 1.91)

An elevated risk of HFMD was observed under conditions of excessive heat. This finding supported most previous studies which suggested that temperature could positively affect HFMD epidemics, with higher temperature leading to a higher risk of being infected (Chen et al., 2015; Deng et al., 2013; Urashima et al., 2003; Xing et al., 2014). We also found that the highest risk of HFMD under conditions of excessive heat occurred at 6 days of lag when analyzed as a whole, suggesting that the incubation period of HFMD might be within 6 days. This finding was also consistent with previous studies. Considerable literatures have reported an incubation period of HFMD ranging from 2 days to 2 weeks (Huang et al., 2013; Ministry of Health, 2014). HFMD development may result from comprehensive function of multiple factors including excessive heat, individuals' susceptibility and virus activities. However, more data was needed to further identify the predominant ones.

Our results also demonstrated the variability in the impact of excessive heat on HFMD across regions and age groups. In terms of the interregional discrepancy, the relative risk of HFMD in the Pearl-River Delta Region was generally higher and persisted longer, which suggested that children in the Pearl-River Delta Region were more sensitive to the effect of excessive heat. Several reasons may be used to explain this phenomenon. First, the Pearl-River Delta Region was much more densely populated than the remaining areas, which tended to facilitate the spread of HFMD in this area (Fabre and Rodwin, 2011). Second, air conditions were widely used in the Pearl-River Delta Region, which might weaken children's thermal adaptability (Yu et al., 2012). In the other hand, public places in this developed area were better-equipped and children tended to have more outdoor activities, as compared with the remaining developing areas. These above two points may be potential predictors of the elevated risk of HFMD in the Pearl-River Delta Region under conditions of excessive heat. Last but not least, the Pearl-River Delta Region, where China initialized its opening up and reform policies, had a particularly higher proportion of migrant children who generally had high mobility but limited access to local medical insurance or government-funded medical assistance programs (Fabre, 2015; Liao and Liao, 1990; Zhang et al., 2011). It was reported that migrant children had a 100% higher risk of being infected with HFMD (Xu et al., 2014). It also indicated that the policy makers should pay more attention to this special group of population.

Our research had two main findings regarding the thermal response in different age groups. One was that the highest risk of HFMD for children greater than 6 years old occurred as late as 10–11 days of lag. And the other was that the relative risk of HFMD was highest among children aged 3–6 years old and lowest among those greater than 6.For children greater than 6 years old, the relatively longer incubation suggested a weaker sensitivity to hot days, which consisted with the fact that HFMD mainly occurred among children under 6 years old (Deng et al., 2013; Liu et al., 2015; Shah et al., 2003). One possible explanation for this discrepancy was that children greater than 6 years old had a better immunity to HFMD. Thus, more time was needed for HFMD-related enterovirus to get the load necessary for the onset of the disease. Children aged 3–6 years old were the most sensitive to conditions of excessive heat. As mentioned, children of this age group tended to attend kindergartens where large numbers of susceptible people gathered.

Another interesting finding of the current study was that children in the Non-Pearl-River Delta Region were more sensitive to the extremely hot days than to the commonly hot days. It was consistent with prior studies which suggested the harmfulness of extremely hot weather on human health (Bai et al., 2014; Lin et al., 2009; Lin et al., 2012; Sheridan and Lin, 2014). However, the situation in the Pearl-River Delta Region was the opposite. It seemed unexpected but justified since the reduced risk may be due to the reduced outdoor activities and the widespread use of air-conditioning systems in this developed area in extremely hot days.

This study has several strengths, including the fact that this is, to our knowledge, the first research examining the facilitating effect of excessive heat on HFMD, and further assessing its variability across social-economic status and age groups. Distributed lag nonlinear models were applied to evaluate the impact of excessive heat conditions from perspectives of both the predictor and its lag. Both the modeling method and analytic result of this study have a reference sense toward the control and prevention issues of infectious diseases.

Nevertheless, several limitations should be acknowledged with this study. First, the study period of this research was limited in 3 years which might be shorter than that of previous studies. To ensure enough sample size, analyses were conducted at a daily basis in this study, which was also considered to provide more accurate information on the excessive heat–HFMD relationships. Second, this study was ecological in design nature and bias due to exposure and/or outcome assessment were inevitable, although the categorization of humidex could reduce the problem of mismeasurement to some extent. Future research should be carried out to confirm our findings, particularly our speculation on the mechanism of interregional and/or inter-age group differences.

Since this is the first study incorporating heat as a categorical predictor, no other available literatures can be compared on risk magnitudes. However, this study can serve as reference for the future research on heat–HFMD relationships.

In conclusion, this study provided strong evidence that conditions of excessive heat had significantly facilitating effects on childhood HFMD. Children in the developed Pearl-River Delta Region, as well as those aged 3–6, were more sensitive to excessive heat. Results from the current study were particularly practical and important for developing area-and-age-targeted control programs in the context of climate change and urbanization.

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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References

Bai, L., et al., 2014. The effects of summer temperature and heat waves on heat-related illness in a coastal city of China, 2011–2013. Environ. Res. 132, 212–219.
Canada, G.O., 2014. Spring and Summer Weather Hazards.
Chebana, F., et al., 2013. A general and flexible methodology to define thresholds for heat health watch and warning systems, applied to the province of Quebec (Canada). Int. J. Biometeorol. 57, 631–644.
Chen, C., et al., 2014. Short-term effects of meteorological factors on children hand, foot and mouth disease in Guangzhou, China. Int. J. Biometeorol. 58, 1605–1614.
Chen, Z., et al., 2015. Epidemiological profiles of hand, foot, and mouth disease, including meteorological factors, in Suzhou, China. Arch. Virol. 160, 315–321.
China, N.H.A.F., 2014. National Report on Notifiable Diseases in 2014.
Deng, T., et al., 2013. Spatial–temporal clusters and risk factors of hand, foot, and mouth disease at the district level in Guangdong Province, China. PLoS One 8, e56943.
Fabre, G., 2015. The Chinese healthcare challenge: comment on "Shanghai rising: avoidable mortality as measured by avoidable mortality since 2000". Int. J. Health Policy Manag. 4, 195–197.

Fabre, G., Rodwin, V.G., 2011. Public health and medical care for the world's factory: China's Pearl River Delta Region. BMC Med. 9, 110.
Health, C.M.O., 2009. Hand, Foot and Mouth Disease Clinic Guide.
Huang, Y., et al., 2013. Effect of meteorological variables on the incidence of hand, foot, and mouth disease in children: a time-series analysis in Guangzhou, China. BMC Infect. Dis. 13, 134.
Kumar, V.S., et al., 2015. Clinical profile of hand, foot, and mouth disease and its associated complications among children in Shimoga City, southern Karnataka: a hospital-based study. Indian J. Public Health 59, 141–144.
Li, T., et al., 2014. Hand-foot-and-mouth disease epidemiological status and relationship with meteorological variables in Guangzhou, southern China, 2008–2012. Rev. Inst. Med. Trop. Sao Paulo 56, 533–539.
Liao, S., Liao, S., 1990. Trends and directions of population migration in Guangdong province. Chin. J. Popul. Sci. 2, 139–145.
Lin, S., et al., 2009. Extreme high temperatures and hospital admissions for respiratory and cardiovascular diseases. Epidemiology 20, 738–746.
Lin, S., et al., 2012. Excessive heat and respiratory hospitalizations in New York State: estimating current and future public health burden related to climate change. Environ. Health Perspect. 120, 1571–1577.
Liu, S.L., et al., 2015. Comparative epidemiology and virology of fatal and nonfatal cases of hand, foot and mouth disease in mainland China from 2008 to 2014. Rev. Med. Virol. 25, 115–128.
Masterton, J.M., Richardson, F.A., 1979. Humidex: A Method of Quantifying Human Discomfort Due to Excessive Heat and Humidity.
Ministry of Health, 2014. Hand, foot & mouth disease. (Available from: https://www.moh.gov.sg/content/moh_web/home/diseases_and_conditions/h/hfmd.html).
Pacific, W.R.O.F., 2011. A Guide to Clinical Management and Public Health Response for Hand, Foot and Mouth Disease. Philippines, Manila.
Province P.G.O.G., 2014. Statistical Yearbook of Guangdong Province (2013).
Shah, V.A., et al., 2003. Clinical characteristics of an outbreak of hand, foot and mouth disease in Singapore. Ann. Acad. Med. Singap. 32, 381–387.
Sheridan, S.C., Lin, S., 2014. Assessing variability in the impacts of heat on health outcomes in New York city over time, season, and heat-wave duration. EcoHealth 11, 512–525.
Song, Y., et al., 2015. Time series analyses of hand, foot and mouth disease integrating weather variables. PLoS One 10, e0117296.
Urashima, M., et al., 2003. Seasonal models of herpangina and hand-foot-mouth disease to simulate annual fluctuations in urban warming in Tokyo. Jpn. J. Infect. Dis. 56, 48–53.
Xing, W., et al., 2014. Hand, foot, and mouth disease in China, 2008–12: an epidemiological study. Lancet Infect. Dis. 14, 308–318.
Xu, Z., et al., 2014. The population-based health effect of hand, foot and mouth disease in children in Shanghai. Pediatr. Infect. Dis. J. 33, 448–452.
Xu, M., et al., 2015. Non-linear association between exposure to ambient temperature and children's hand-foot-and-mouth disease in Beijing, China. PLoS ONE 10, e0126171.
Yu, J., et al., 2012. A comparison of the thermal adaptability of people accustomed to air-conditioned environments and naturally ventilated environments. Indoor Air 22, 110–118.
Zhang, Y., et al., 2010. An emerging recombinant human enterovirus 71 responsible for the 2008 outbreak of hand foot and mouth disease in Fuyang city of China. Virol. J. 7, 94.
Zhang, D., et al., 2011. Public health services in Shenzhen: a case study. Public Health 125, 15–19.
Zhang, W., et al., 2014. Epidemiological features and trends of hand, foot and mouth disease in Guangdong Province, 2009–2012. Journal of Sun Yat-sen University (Medical Sciences) 35, 607–613.
Zhu, Q., et al., 2011. Surveillance of hand, foot, and mouth disease in mainland China (2008–2009). Biomed. Environ. Sci. 24, 349–356.