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Nonlinear effect of temperature on hand, foot, and mouth disease in Lanzhou, China

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Abstract

To examine the effects of temperature on the daily cases of hand, foot, and mouth disease (HFMD).

Data on the daily cases of HFMD in Lanzhou from 2008 to 2015 were obtained, and meteorological data from the same period were collected. A distributed lag nonlinear model was fitted to reveal the relationship between the daily mean temperature and the daily cases of HFMD.

From 2008 to 2015, 25,644 cases were reported, of which children under 5 years of age accounted for 78.68% of cases. The highest peak of HFMD cases was usually reported between April to July each year. An inverse V-shaped relationship was observed between daily mean temperature and HFMD cases; a temperature of 18°C was associated with a maximum risk of HFMD. The relative risk (RR) was 1.57 (95% confidence interval: 1.23–1.23), and boys and children aged 3 to 5 years were populations with the highest risk. The cumulative risks of high temperature (20.2°C and 25.2°C) in the total, age-specific, and gender-specific groups peaked on lag 14 days; RR was higher in girls than in boys and in children aged 1 to 2 years than in other age groups. However, the effects of low temperature (−5.3°C, 2.0°C, and 12.8°C) were not significant for both gender-specific and age-specific patients.

High temperature may increase the risk of HFMD, and boys and children aged 3 to 5 years were at higher risks on lag 0 day; however, the cumulative risks in girls and children aged 1 to 2 years increased with the increasing number of lag days.

Abbreviations: CI = confidence interval, CV-A16 = Coxsackie virus A16, DLNM = distributed lag non-linear model, HFMD = hand, foot, and mouth disease.

Keywords: hand-foot-mouth disease, lag effect, meteorological factors

1. Introduction

Hand, foot, and mouth disease (HFMD), a common childhood infectious disease, is mostly caused by Enterovirus 71 (EV-A71) or Coxsackievirus A16 (CV-A16) and frequently occurs in East and Southeast Asia including China.[1] HFMD poses a significant threat to public health and was classified as a C-class notifiable communicable disease in China in 2008. The main patient groups susceptible to HFMD are infants and children under 5 years of age.[2] The disease incidence peaks during the warm season, with a slight increase in the number of cases in the cold season each year.[3] The mild form of HFMD is thought to be a self-limiting disease. The typical clinical characteristics of patients with HFMD are usually mild and include fever, painful sores, blistering spots, ulcers, and skin rashes. However, a small number of children with HFMD are subject to more complicated diseases, such as myocarditis, pulmonary edema, aseptic meningitis, and even death.[4] To date, there are still no specific vaccines and effective treatments for clinical application. Therefore, there is an urgent need to identify the risk factors for HFMD to forecast the short-term trend of HFMD incidence for early disease surveillance and prevention.

Meteorological factors have been recognized as risk factors for HFMD epidemics. A study by Wang et al[5] reported that the incidence of HFMD in Shandong Province, China, was significantly associated with the average temperature, relative humidity, vapor pressure, and wind speed. Kim et al[6] found that average temperature and relative humidity are related to the incidence of HFMD in South Korea. Among the weather factors, average temperature had the greatest effect on the incidence of HFMD in Beijing, China.[7] Several studies have been conducted to explore the nonlinear relationship between temperature and HFMD. For instance, an inverse V-shaped relationship between the reported number of HFMD cases and temperature was observed in Japan and mainland China.[8,9] While in Wuhan, China, the association between temperature and HFMD incidence showed an approximate "M" shape.[10] The results of the abovementioned studies were not consistent, which may be

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JW and SL contributed equally to this work.

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All procedures involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

The authors have no conflicts of interests to disclose.

Supplemental Digital Content is available for this article.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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due to the significant spatial heterogeneity in the effects of temperature on HFMD incidence.[11–13] However, most previous studies were only conducted in the coastal cities or economically developed areas,[14–17] and none were performed in Lanzhou City, a semi-arid area in Northwest China.

In this study, we collected meteorological and HFMD onset data from January 2008 to December 2015 in Lanzhou, China. The distributed lag nonlinear model was used to analyze the association between temperature and HFMD incidence by controlling for the effects of average daily pressure and daily precipitation.[18] We reported both single-day lag effects and cumulative effects of temperature on the incidence of HFMD in Lanzhou. We also estimated the extreme effects of temperature including the 5th, 25th, 50th, 75th, and 95th percentiles. Moreover, we compared the effects of temperature in gender- and age-specific groups. A better understanding of the effect of temperature on HFMD incidence would help identify high-risk periods and sensitive populations that require health care. Moreover, the results can provide scientific evidence for establishing an early warning system and intervention strategies for HFMD.

2. Data and methods

2.1. Data

Data on the incidence of HFMD from January 2008 to December 2015 were obtained from the National Infectious Disease Report Information Management System from Lanzhou Center for Disease Control. The meteorological data, including daily average values of temperature, air pressure, wind speed, relative humidity, and daily precipitation, in the same period were acquired from the Gansu Provincial Meteorological Bureau.

2.2. Statistical analysis methods

The correlation between various meteorological factors and number of HFMD cases was determined using Spearman correlation test; the degree of correlation between various meteorological factors was also examined. The meteorological factors associated with HFMD onset were included in the model, with an inspection level of 0.05. A cross-basis matrix was developed to present the HFMD onset data and meteorological data. The average daily number of HFMD cases was used as a dependent variable, and a quasi-Poisson model was selected to fit our data. Based on the controlling season, long-term trend, and weekly effect, meteorological factors and HFMD were linked using distributed lag non-linear model. The average daily temperature was used, and the hybrid effect of average daily pressure and daily precipitation was controlled to analyze the relationship between the number of HFMD cases and average daily temperature. A two-dimensional matrix was established to determine the time lag and research lag effects of the average daily temperature on the number of HFMD cases using the following formula:

$$log[E(Y_t)] = \alpha + \beta TEM_{t,l} + ns(press_t, df = 3) + ns(rain_t, df = 3) + ns(Time_t, df = 7/year) + \gamma DOW_t$$

Where Y_t is the number of HFMD cases on t day, α is the constant, $TEM_{t,l}$ is the two-dimensional matrix, β is the variation coefficient, ns ($press_t$, df=3) is the influence of pressure (df=3), time is time ordinal variables, ns ($rain_t$, df=3) is the influence of precipitation (df=3), ns ($Time_t$, df=7) is the influence of seasonal and long-term trends (df=7), and DOW_t is the dummy variable on t day. Based on the relevant study, the maximum lag time was 30 days, with the mean temperature of 11.11°C as the reference value. The different temperatures P_5 (−5.3°C), P_{25} (2.00°C), P_{50} (12.80°C), P_{75} (20.2°C), and P_{95} (25.2°C) at different time lags of the relative risk (RR) values were obtained. The RR was calculated as follows: If β was the explanatory variable in the regression model, the temperature in the lag time of the relative risk of HFMD incidence can be calculated as exp (β). The effect of low temperature and high temperature on the daily incidence of HFMD after stratification of different gender and age groups and the effect of temperature on the incidence of daily HFMD were analyzed. A sensitivity analysis was performed by changing the df for time (6, 7, 8) per year (see Supplemental Materials Fig. S1, http://links.lww.com/MD/F93).

3. Results

A total of 25,644 cases of HFMD were reported from 2008 to 2015 in Lanzhou, and the average daily number of cases was 11.01. A total of 15,729 male children and 9,915 female children had HFMD, and the sex ratio was 1.29:1. A total of 20,177 (78.68%) children under 5 years of age acquired HFMD. The average daily pressure, temperature, relative humidity, rainfall, and wind speed were 848.38 hPa, 11.11°C, 49.90%, 0.83 mm, and 1.27 m/s, respectively (Table 1).

As presented in Table 2, the daily cases of HFMD were positively associated with temperature, relative humidity, amount of precipitation, and wind speed but negatively with

Table 1

Descriptive statistics of meteorological factors and the number of HFMD cases from 2008 to 2015 in Lanzhou city.

Variable	$\bar{x} \pm S$	min	P_{25}	P_{50}	P_{75}	max
Cases of HFMD	11.01±9.51	0.00	1.00	2.00	4.00	25.00
Male	7.36±7.34	0.00	1.00	2.00	4.00	25.00
Female	5.00±4.76	0.00	2.00	4.00	9.00	61.00
Aged < 1 yr	3.26±3.03	0.00	1.00	2.00	3.00	17.00
Aged 1–2 yrs	2.92±2.49	0.00	3.00	7.00	16.00	100.00
Age 3–5 yrs	6.48±6.04	0.00	2.00	5.00	11.00	75.00
Aged 6–14 yrs	2.44±1.92	0.00	2.00	3.00	7.00	42.00
Daily mean pressure (hPa)	848.38±5.54	820.79	842.53	846.12	850.35	888.42
Daily mean temperature (°C)	11.11±10.23	-16.80	2.00	12.79	20.20	31.88
Daily mean relative humidity (%)	49.90±15.48	13.85	38.52	50.31	60.70	100.00
Daily mean precipitation (mm)	0.83±0.36	0.00	0.00	0.00	0.01	44.00
Daily mean wind speed (m/s)	1.27±0.37	0.00	1.00	1.13	1.50	3.00

Table 2

Spearman correlation coefficients of meteorological factors and number of HFMD.

Index	Pressure (h Pa)	Temperature (°C)	Relative humidity (%)	Precipitation (mm)	Wind speed (m/s)	Cases of HFMD
Pressure (h Pa)	1.000					
Temperature (°C)	−0.645*	1.000				
Relative humidity (%)	0.145*	−0.146*	1.000			
Precipitation (mm)	−0.184*	0.211*	0.382*	1.000		
Wind speed (m/s)	−0.230*	0.258*	−0.251*	0.112*	1.000	
Cases of HFMD	−0.335*	0.528*	0.094*	0.139*	0.094*	1.000

HFMD = hand, foot, and mouth disease.
* $P<0.05$.

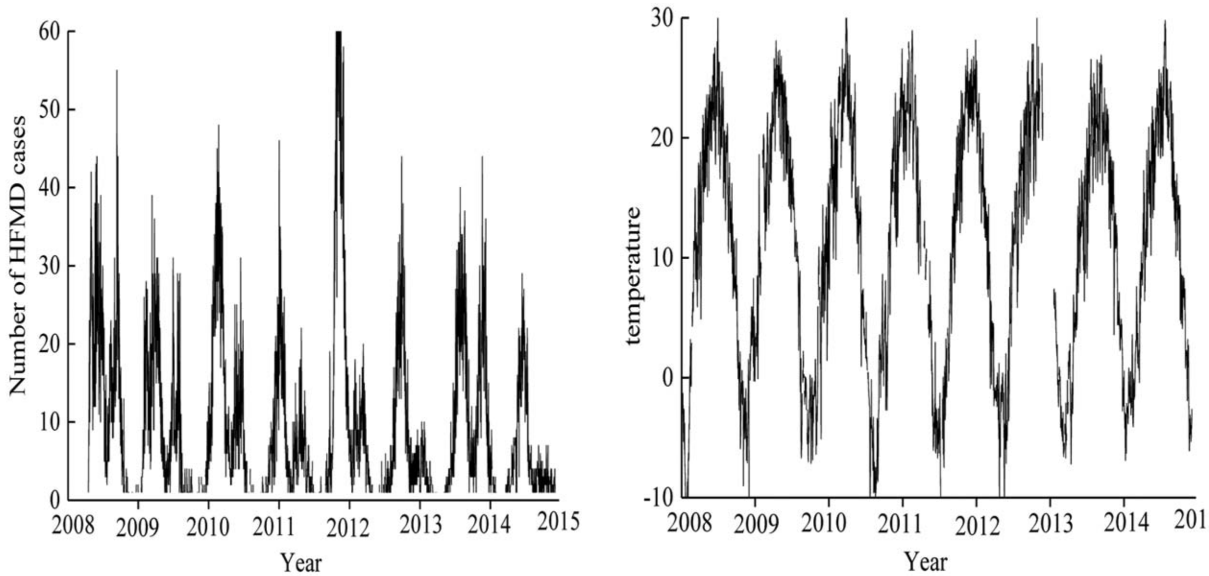

Figure 1. Daily distribution of meteorological variables and hand, foot, and mouth disease cases from 2008 to 2015.

air pressure. Moreover, temperature was the major factor associated with HFMD ($r=0.528$, $P<.05$).

Figure 1 describes the time sequence of HFMD cases and temperature changes during the study period. The incidence of HFMD had a seasonal pattern, with a relatively major peak in late spring and early summer (April to July) and a relatively minor peak in late autumn (October to November).

Figure 2 depicts three-dimensional associations of the entire exposure-lag-response between temperature change and HFMD allowing for a maximum lag of 30 days. A nonlinear relationship was shown. A strong and immediate association of high temperature with HFMD was observed, and the maximum value of RR was 1.38 (95% confidence interval [CI]: 1.08–1.75) when the temperature was 23°C on lag 0 day. A low temperature showed a weaker impact on HFMD, and the maximum value of RR was 1.14 (95% CI: 1.03–1.25) when the temperature was 8°C on lag 1 day.

Figure 3 shows the RR of HFMD, with 11.11°C (annual average temperature) as the reference temperature, based on lag day (lag 0, 7, 14, 21, and 30 days) and temperature (−5.3°C, 2.0°C, 12.8°C, 20.2°C, and 25.2°C). On lag 0 day, a strong association was observed between temperature and HFMD at a temperature range of 14°C to 26°C; the risk increased with an increase in temperature, and a temperature of 23°C was associated with a maximum number of HFMD cases. On lag

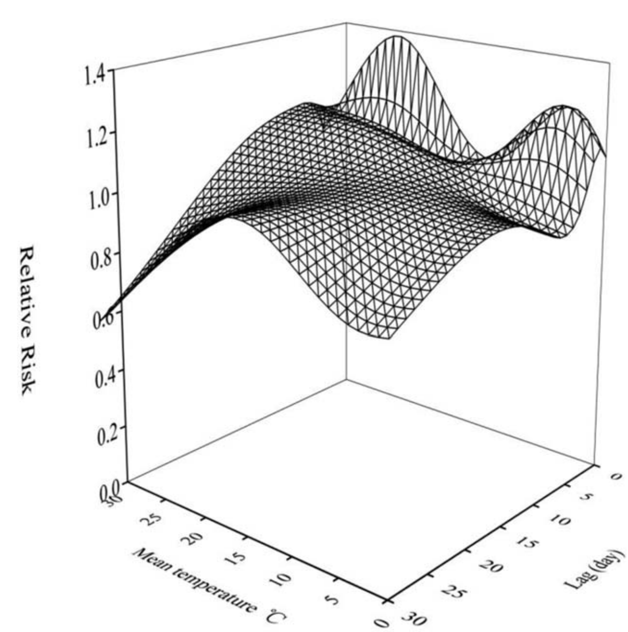

Figure 2. Three-dimensional plot of the relationship between the mean temperature and hand, foot, and mouth disease over 30 lag days.

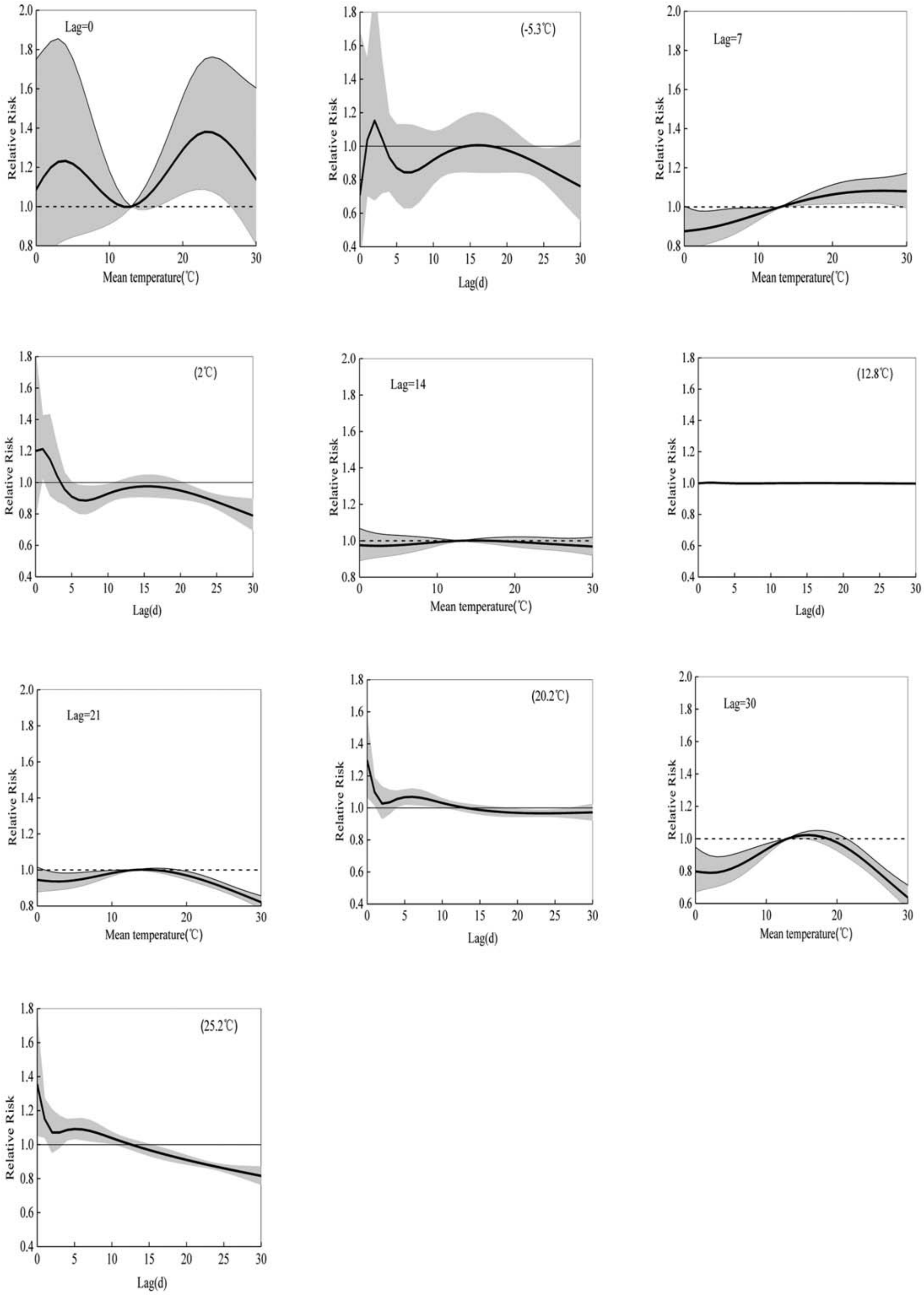

Figure 3. Plot of RR by temperature at specific lags, and RR by lag at specific temperatures. RR = relative risk .

7 days, a weaker association was observed between temperature and HFMD at a temperature range of 14°C to 29°C. However, no significant association was observed between temperature change and HFMD on lag 14 days, 21 days, or 30 days. At temperatures 20.2°C and 25.2°C, strong associations were found on lag 0 day, whereas weaker associations were observed on lag 2 to 9 days. However, no significant risks were noted on lag 30 days and at temperatures −5.3°C, 2.0°C, and 12.8°C.

Figure 4 shows the overall relative risks of the mean temperature for total HFMD cases during lag 30 days. The exposure-response curve showed an inverted V shape, and an 18°C temperature was associated with the maximum number of HFMD cases; the RR was 1.57 (95% CI: 1.23–1.23). In Figure 5, the exposure-response curve shows an inverted V shape for both age-specific and gender-specific groups; boys and children aged 3 to 5 years were the population with the highest risk at the mean temperature during lag 30 days.

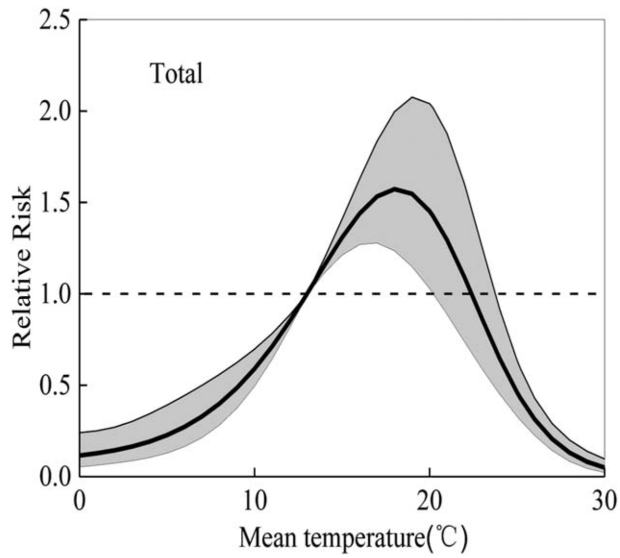

Figure 4. Overall relative risks of mean temperature for the total hand, foot, and mouth disease cases over 30 days.

Table 3 shows the cumulative RRs of different temperatures for age-specific and gender-specific HFMD cases. At temperatures 20.2°C and 25.2°C, the values of RR for the total, age-specific, and gender-specific groups peaked on lag 14 days; the RR was higher in girls than in boys and was higher in children aged 1 to 2 years than in other age groups. Temperature had no significant cumulative effect on the daily cases of HFMD when the temperatures were at 5.3°C, 2.0°C, and 12.8°C (these RR values are not displayed in Table 3).

Sensitivity analyses were conducted by varying the df (6–8 per year) for time (Supplemental Materials Fig. S1, http://links.lww.com/MD/F93), and the main conclusions of the study remained unchanged.

4. Discussion

Many epidemiologic studies have increasingly recognized that temperature plays an important role in the occurrence of HFMD, and children are the most vulnerable group.[5–17] In this study, the first to report on this topic, we examined the association of temperature with age- and gender-specific HFMD among children in Lanzhou, China, during 2008 to 2015.

In our study, the descriptive analysis of temporal trends showed that the incidence of HFMD peaked twice a year. The major peak occurred between April and July, along with a minor peak between October and November. These seasonal patterns were similar to those found in other areas in China (Chongqing, Guangxi, and Guangdong Province) as well as Vietnam.[4,10,13,15] However, other regions have different seasonal patterns. In Korea, a single peak was reported in late June.[6] This inconsistency might be due to various environmental factors such as climatic, geographic, and socioeconomic factors.

The results of our analysis of the association between temperature and pediatric HFMD cases displayed an approximate inverted V-shaped exposure-response curve. A temperature of 18°C was associated with the maximum number of HFMD cases, which is consistent with the findings of the multi-city studies conducted in mainland China and Japan.[8,9] Previous studies have suggested that a possible temperature threshold causes the outbreak of HFMD, which may be related to the mechanism of HFMD transmission. By contrast, the thermal effect played an important role in the infectivity of enterovirus. An experimental study found that infectivity and activity of EV71 could be inhibited at temperatures higher than 25°C because of the potential properties of the circulating strains.[19] Stanton et al[20] also found that the replication of enterovirus was restricted by approximately 90% at a temperature of 39°C, compared with the replication rate at a temperature of 37°C. Additionally, serological antibody levels may be adjusted using temperature. An experimental study in mice had shown that the antibody against EV71 increased with temperature by accelerating DNA replication,[21] suggesting that high ambient temperature may limit the occurrence of HFMD. However, cold conditions could favor virus transmission and maintain virus activity, thereby increasing the possibility of transmission and the incidence of HFMD in children.[22,23] Conversely, outdoor activity levels decrease during the cold seasons and increase during the warm seasons. Thus, temperature was related to the behaviors of the host population. Some temperature ranges may increase children's risk of encountering individuals with an infection or a contaminated environment, thereby increasing the incidence of HFMD.[24]

Our gender-specific analyses revealed that boys seemed to be more sensitive to the effects of temperature on lag 0 day, perhaps because boys engage in more physical activities than girls, thereby leading to more contact and aiding the spread of HFMD. However, the cumulative risks for girls increased with increasing lag days; the RR values for girls were higher than those for boys after lag 7 days. This may be related to gender differences in physiology or cause, which warrants an in-depth study in the future.

In terms of age-specific HFMD, children aged 3 to 5 years were more sensitive to temperature on lag 0 day than other age groups. For this reason, the following 3 aspects should be considered. First, a high contact rate was associated with a rapid increase in the daily number of HFMD cases, especially at the beginning of the school semester.[25] Second, indoor ventilation in kindergarten (the education level of most children within this age group) classes was inadequate, which promoted the transmission of HFMD via the respiratory pathway.[26] Third, preschool children showed low levels of antibodies against the virus, and most children younger than 5 years of age lacked effective antibodies against EV-A71 and Coxsackievirus A16 (CV-A16), making them more sensitive to an increase in temperature as a response to an unprotected and immature immune system.[27] However, the cumulative risks of children aged 1 to 2 years increased with the increasing lag days; the RR values of children aged 1 to 2 years were higher than those of other groups after lag 7 days, which might be due to a decrease in immune function or other causes. Further studies are needed to validate this finding.

Our results also showed that cumulative and lagged effects differed with changes in temperature. For all patients, that is, age-specific and gender-specific HFMD cases, compared with those at 11.11°C (annual average temperature), the cumulative risks of 20.2°C and 25.2°C (95th percentile annual average temperature) on the incidence of HFMD were the highest on lag 14 days. Yang et al[28] found that the typical incubation period of HFMD ranged from 4 to 7 days; however, the incubation period of HFMD was longer than 10 days in some children. Therefore, our results may be owing to the role of the incubation period of

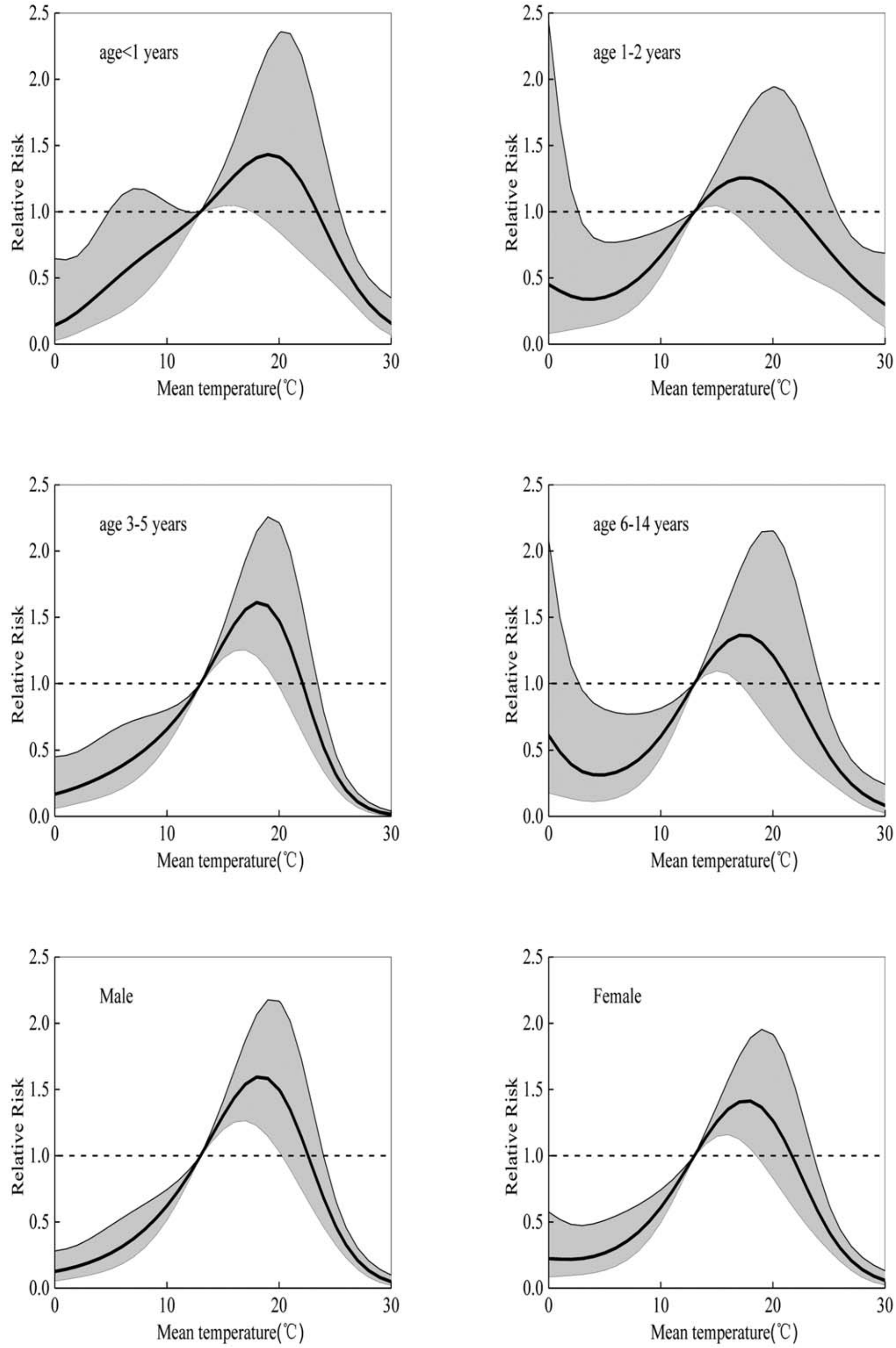

Figure 5. Overall relative risks of mean temperature for age- and gender-specific hand, foot, and mouth disease cases over 30 days.

HFMD. Interestingly, compared with 25.2°C, the lag effects of 20.2°C on the incidence of HFMD were longer for different groups. The thermal effect played an important role on the infectivity of enterovirus. As previously mentioned, a possible temperature threshold could cause an outbreak of HFMD, and as reported in our study, that temperature threshold was 18°C. When the temperature was above 18°C, the effect of temperature on pediatric HFMD decreased with increasing temperature; this may explain our interesting results.

Some limitations of this study should be acknowledged. First, the data on HFMD were collected through passive monitoring; therefore, the actual numbers of HFMD cases may have been underestimated. Second, we used the mean values of HFMD cases after monitoring the temperature to present personal exposure,

Table 3

The relative risks of different temperatures for age-specific and gender-specific HFMD cases in Lanzhou.

Variables	Temperature (°C)	RR (95%CI)				
		Lag 0 d	Lag 7 d	Lag 14 d	Lag 21 d	Lag 30 d
Total	20.2	1.30 (1.07–1.58)	1.95 (1.50–2.52)	2.26 (1.71–3.00)	1.90 (1.40–2.59)	1.43 (1.01–2.02)
	25.2	1.36 (1.05–1.75)	2.50 (1.80–3.48)	2.95 (2.11–4.12)	1.81 (1.29–2.55)	0.43 (0.31–0.59)
Male	20.2	1.44 (1.14–1.84)	1.88 (1.37–2.57)	1.92 (1.37–2.7)	1.71 (1.18–2.48)	1.24 (0.81–1.89)
	25.2	1.64 (1.19–2.24)	2.52 (1.68–3.78)	2.53 (1.69–3.80)	1.71 (1.13–2.59)	0.4 (0.27–0.59)
Female	20.2	1.25 (1.02–1.54)	1.95 (1.48–2.57)	2.42 (1.79–3.28)	2.02 (1.44–2.81)	1.47 (1.01–2.15)
	25.2	1.25 (0.95–1.63)	2.32 (1.64–3.29)	2.96 (2.07–4.24)	1.82 (1.26–2.63)	0.44 (0.31–0.63)
< 1 yr	20.2	1.06 (0.83–1.36)	1.49 (1.04–2.13)	1.98 (1.35–2.89)	1.86 (1.19–2.9)	1.40 (0.82–2.39)
	25.2	0.99 (0.72–1.36)	1.5 (0.96–2.35)	2.13 (1.38–3.29)	1.58 (0.99–2.53)	0.68 (0.43–1.08)
1–2 yrs	20.2	1.25 (0.94–1.67)	2.28 (1.55–3.36)	2.44 (1.62–3.67)	2.23 (1.41–3.53)	1.16 (0.69–1.94)
	25.2	1.30 (0.89–1.89)	2.79 (1.72–4.52)	3.10 (1.9–5.04)	2.41 (1.45–3.99)	0.68 (0.43–1.10)
3–5 yrs	20.2	1.37 (1.08–1.74)	1.86 (1.36–2.54)	2.11 (1.49–2.99)	1.72 (1.18–2.51)	1.44 (0.95–2.18)
	25.2	1.53 (1.11–2.1)	2.33 (1.56–3.48)	2.53 (1.68–3.8)	1.47 (0.98–2.22)	0.30 (0.20–0.44)
6–14 yrs	20.2	1.32 (0.97–1.80)	1.46 (0.96–2.21)	1.71 (1.05–2.76)	1.54 (0.93–2.56)	1.19 (0.66–2.14)
	25.2	1.17 (0.79—1.74)	1.38 (0.81–2.33)	1.77 (0.98–3.19)	1.29 (0.73–2.29)	0.43 (0.25–0.74)

HFMD = hand, foot, and mouth disease.

which may result in misclassification bias. Third, modifications from other socioeconomic factors, such as household income and the use of air conditioning, were not considered because of the lack of detailed individual information, which might have affected our findings.

5. Conclusion

This study examined the association of temperature with age- and gender-specific HFMD among children in Lanzhou, China, during 2008 to 2015. The association between temperature and pediatric HFMD cases was shown as an inverted V-shaped exposure-response curve, and 18°C was the temperature at which the maximum number of HFMD cases occurred. The cumulative risks of different temperatures on the incidence of HFMD were highest on lag 14 days. Boys and children aged 3 to 5 years were found to be the population most susceptible to HFMD.

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Funding acquisition: Sheng Li.
Investigation: Jinyu Wang, Sheng Li.
Methodology: Sheng Li.
Project administration: Jinyu Wang, Sheng Li.
Resources: Sheng Li.
Software: Jinyu Wang.
Supervision: Sheng Li.
Writing – original draft: Jinyu Wang, Sheng Li.
Writing – review & editing: Jinyu Wang, Sheng Li.

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