Estimating the influence of high temperature on hand, foot, and mouth disease incidence in China

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Abstract
The burden of disease caused by ambient high temperature has become a public health concern, but the associations between high temperature and hand, foot, and mouth disease (HFMD) remain indistinct. We used distributed lag non-linear model (DLNM) to estimate the burden of disease attributable to high temperature, adjusting for long-term trend and weather confounders. Total 18,167,455 cases were reported in 31 Chinese provinces, the incidence of HFMD showed a gradually increasing trend from 2008 to 2017 in China. Minimum morbidity temperature (MMT) was mainly concentrated at 17 to 23 °C in ≤5 years old group, 18 to 25 °C in 6~10 years old group and 19 to 27 °C in >10 years old group. The greatest relative risk (RR) in age group ≤5 years old was 2.06 (95% CI: 1.85~2.30) in Heilongjiang, and the lowest RR was 1.02 (95% CI: 1.00~1.05) in Guangdong; the greatest RR in age group 6~10 years old was 2.24 (95% CI: 1.72~2.91) in Guizhou, and the lowest RR was 1.01 (95% CI: 0.97~1.12) in Tianjin; the greatest RR in the age group >10 years old was 2.53 (95% CI: 1.66~3.87) in Heilongjiang, and the lowest RR was 1.02 (95% CI: 0.71~1.46) in Henan. We found the positive association between high temperature and HFMD in China.

Keywords High temperature · Hand, foot, and mouth disease · Minimum morbidity temperature · China

Introduction
Hand, foot, and mouth disease (HFMD) is a common infectious disease mainly occurring in children under 5 years old. It is mainly caused by Coxsackievirus A16 (CV-A16) and Enterovirus 71 (EV71) (Saguil et al. 2019). HFMD is mainly characterized by respiratory symptoms such as fever, runny nose, and sores in hands, feet, and mouth. Some severe patients will have meningitis, encephalitis, encephalomyelitis, pulmonary edema, and circulatory disorders, which will leave sequelae and even lead to death (Cox and Levent 2018). At present, there is no effective vaccine to completely prevent HFMD. Finding risk factors and improving prevention strategies are very important for children’s health.

As a consequence of global climate change, extreme high temperature has a serious impact on human health. High temperature has become a common meteorological disaster, which has a certain impact on people’s daily life, health, and various departments of the national economy (Royé et al. 2020). As we know, high temperature will increase the death and morbidity of diseases to a certain extent, especially cardiovascular diseases, respiratory diseases, and so on (Luan et al. 2017; Song et al. 2018). However, there are few studies on the association between high temperature and infectious diseases, which has not attracted enough attention. In order to cope with the heat weather in the future, we should not only pay attention to the impact of high temperature on mortality but also pay more attentions to its impact on infectious diseases.

Current studies (Caminade et al. 2019; Dennis and Fisher 2018) indicate that the emergence and recurrence of infectious diseases are also affected by climate factors in addition to human, biological, and ecological determinants. Understanding the link between climate change and ecological change is a decisive factor in mastering the law of disease change.
occurrence and redistribution, which will eventually help to optimize prevention strategies. The correlations between meteorological factors and HFMD have been confirmed by relevant studies, but there is a lack of research on the temperature early warning threshold of HFMD.

China has a vast territory. From south to north, there are tropical, subtropical, warm temperate, temperate, and cold temperate regions. Tibet and Qinghai belong to special plateau climate regions. From west to east, the altitude gradually decreases. Due to different climatic zones and altitudes, the temperature varies greatly between different provinces in China. The average temperature difference between the northern and southern regions is more than 20 °C, and the average temperature difference can exceed 10 °C even at the same latitude. Therefore, it is of great significance to study the impact of temperature on the incidence of HFMD according to the actual situation in different regions.

Based on meteorological and HFMD incidence data in 31 provinces of China, this study wants to evaluate the differences of the impact of high temperature on HFMD in province level, and to explore the minimum morbidity temperature (MMT), which can be used as a reference for formulating temperature early warning. We integrate the high temperature with the HFMD incidence and put forward early warning information, which is very important to reduce the adverse impact of current and future diseases on health, especially the health protection of children.

Material and methods

Data sources

HFMD cases were collected from the National Population and Health Science Data Sharing Platform (https://www.ncmi.cn/). These data were obtained through the Data-center of China Public Health from May 2008 to December 2017. The study covered 31 Chinese provinces including Anhui, Beijing, Fujian, Gansu, Guangdong, Guangxi, Guizhou, Hainan, Hebei, Henan, Heilongjiang, Hubei, Hunan, Jilin, Jiangsu, Jiangxi, Liaoning, Inner Mongolia, Ningxia, Qinghai, Shandong, Shanxi, Shaanxi, Shanghai, Sichuan, Tianjin, Tibet, Xinjiang, Yunnan, Zhejiang, and Chongqing.

We collected mean temperature, pressure, relative humidity, rainfall, and sunshine for the same period, and meteorological data was collected from the China Meteorological Data Sharing Service System (http://data.cma.cn/).

Statistical analysis

Current studies widely used distributed lag non-linear model (DLNM) to assess the effect of ambient temperature on health, and the formula was illustrated as follows (Gasparrini 2011; Gasparrini et al. 2010):

\[
Y_t = \alpha + NS(T, T \ast 7) + NS(Humidity, 3) \\
+ NS(Pressure, 3) + NS(Rainfall, 3) + NS(Sunshine, 3) \\
+ \gamma \text{ Dow} + \eta \text{ Holiday} + \beta \text{ Temperature}
\]

where \( \alpha \) was the intercept; \( \gamma, \eta, \) and \( \beta \) represented coefficients; \( \text{df} \) was the degrees of freedom; the model adopted natural cubic spline curve, \( \text{NS(Time)} \) was used to control effects of long-term trend and seasonality, \( T \) was the number of years and the \( \text{df} \) was 7 per year; \( \text{NS(Humidity)} \) was used to control the effect of relative humidity, \( \text{NS(Pressure)} \) was used to control the effect of pressure, \( \text{NS(Rainfall)} \) was used to control the effect of rainfall, \( \text{NS(Sunshine)} \) was used to control the effect of sunshine, and the \( \text{df} \) was 3. Dow represented day of the week and Holiday represented public holidays, these two categorical variables in the model were used to stand for their confounding effects. Considering the cumulative effect and the lag effect, we choose the lag days at 7. We choose the 10th, 75th, and 90th percentiles distribution of mean temperature as three internal knots to estimate the exposure–response relationship in the model.

Referring to previous relevant studies (Gasparrini et al. 2015; Luan et al. 2018), we defined high temperature as the 95th percentile of temperature higher than the mean temperature in this research. MMT represented the temperature corresponding to the point with the lowest relative risk, which can be regarded as the optimal temperature. The effective range of the mean temperature was defined between the 1st percentile (P1) and the 99th percentile (P99) of the time series. The basis of MMT was the best linear unbiased prediction for cumulative exposure response associations for each province, namely the lowest percentile morbidity between 1st and 99th percentiles.

Sensitivity analyses were presented at Supplementary Fig. S1. R software (version 4.1.1) was used to analyze the data, and DLNM package was applied.

Results

From 2008 to 2017, the HFMD incidence showed a gradually increasing trend in China, with less incidence in winter and a peak in summer (Fig. 1).

Table 1 presented the summary of HFMD cases and weather conditions during the study period. A total of 18,167,455 cases were reported in 31 Chinese provinces. Guangdong had the largest number of cases (2,910,068 cases), other provinces and cities with a large number of cases included Guangxi (1,907,353 cases), Hunan (1,255,729 cases), Zhejiang (1,143,235 cases), and Jiangsu
Fig. 1 The HFMD incidence in China during 2008 to 2017

Table 1 Descriptive data on HFMD incidence and weather in 31 Chinese provinces

| Province    | Cases     | Mean temperature (°C) | Relative humidity (%) | Pressure (Kpa) | Rainfall (mm) | Sunshine (h) |
|-------------|-----------|-----------------------|-----------------------|----------------|---------------|--------------|
|             | Min       | Median                | Max                   | 75th           | 95th          | Mean         | SD           | Mean         | SD           | Mean           | SD           | Mean         | SD           |
| Anhui       | 920,505   | 0.7                   | 17.4                  | 30.0            | 24.4          | 28.1         | 16.2         | 9.0          | 72.8         | 7.8           | 1011.1        | 8.4          | 3.0          | 2.3           | 5.2          | 1.4          |
| Beijing     | 316,632   | -4.8                  | 15.0                  | 28.6            | 23.6          | 27.4         | 13.7         | 10.9         | 52.2         | 12.6          | 1012.4        | 8.8          | 1.7          | 2.2           | 6.7          | 1.5          |
| Chongqing   | 316,841   | 2.9                   | 17.4                  | 28.9            | 23.3          | 28.0         | 17.2         | 7.3          | 77.3         | 5.1           | 955.6         | 7.8          | 3.5          | 2.6           | 2.8          | 1.8          |
| Fujian      | 690,429   | 9.3                   | 22.4                  | 29.8            | 26.8          | 29.4         | 21.1         | 6.1          | 73.8         | 6.7           | 1001.3        | 6.1          | 4.1          | 3.3           | 4.7          | 1.8          |
| Gansu       | 100,403   | -9.3                  | 10.2                  | 22.8            | 18.6          | 21.1         | 9.1          | 9.2          | 57.1         | 8.8           | 834.1         | 3.4          | 1.1          | 1.0           | 6.8          | 1.1          |
| Guangdong   | 2,910,068 | 9.9                   | 23.5                  | 29.4            | 27.7          | 28.9         | 22.2         | 5.6          | 77.0         | 6.5           | 1006.0        | 5.8          | 5.4          | 4.7           | 5.0          | 1.8          |
| Guangxi     | 1,907,353 | 7.4                   | 23.3                  | 29.4            | 27.4          | 28.6         | 21.7         | 6.0          | 76.5         | 5.1           | 995.9         | 6.2          | 4.6          | 3.3           | 4.3          | 1.7          |
| Guizhou     | 373,593   | 15.5                  | 26.2                  | 30.3            | 28.6          | 29.7         | 25.1         | 3.9          | 79.9         | 3.4           | 1007.0        | 5.1          | 5.3          | 5.3           | 5.9          | 1.9          |
| Hebei       | 151,542   | -0.7                  | 16.9                  | 29.5            | 25.1          | 29.4         | 18.1         | 6.0          | 76.9         | 5.3           | 993.0         | 8.0          | 4.9          | 3.4           | 4.8          | 1.9          |
| Heilongjiang| 128,934   | 0.7                   | 17.5                  | 23.5            | 17.5          | 22.5         | 3.4          | 15.2         | 67.8         | 8.8           | 987.7         | 6.3          | 1.6          | 1.6           | 6.5          | 1.4          |
| Henan       | 814,822   | -1.3                  | 17.0                  | 29.5            | 25.1          | 28.1         | 15.8         | 9.3          | 65.1         | 10.2          | 1003.4        | 8.5          | 2.2          | 2.1           | 4.7          | 1.4          |
| Hubei       | 2,910,068 | 1.4                   | 20.3                  | 30.9            | 26.8          | 30.2         | 19.3         | 8.0          | 75.2         | 5.9           | 1005.4        | 7.5          | 4.9          | 3.4           | 4.8          | 1.9          |
| Hunan       | 1,907,353 | 7.4                   | 23.3                  | 29.4            | 27.4          | 28.6         | 21.7         | 6.0          | 76.5         | 5.1           | 995.9         | 6.2          | 4.6          | 3.3           | 4.3          | 1.7          |
| Inner Mongolia | 174,363 | 15.5                  | 26.2                  | 30.3            | 28.6          | 29.7         | 25.1         | 3.9          | 79.9         | 3.4           | 1007.0        | 5.1          | 5.3          | 5.3           | 5.9          | 1.9          |
| Jiangsu     | 1,037,181 | 2.9                   | 20.3                  | 30.9            | 26.8          | 30.2         | 19.3         | 8.0          | 75.2         | 5.9           | 1005.4        | 7.5          | 4.9          | 3.4           | 4.8          | 1.9          |
| Jiangxi     | 397,794   | 8.3                   | 18.2                  | 24.3            | 18.9          | 23.2         | 6.4          | 13.4         | 64.0         | 9.5           | 987.1         | 6.6          | 1.8          | 1.8           | 6.6          | 1.2          |
| Jilin       | 3,131,966 | 7.4                   | 23.3                  | 29.4            | 27.4          | 28.6         | 21.7         | 6.0          | 76.5         | 5.1           | 995.9         | 6.2          | 4.6          | 3.3           | 4.3          | 1.7          |
| Liaoning    | 2,910,068 | 1.4                   | 20.3                  | 30.9            | 26.8          | 30.2         | 19.3         | 8.0          | 75.2         | 5.9           | 1005.4        | 7.5          | 4.9          | 3.4           | 4.8          | 1.9          |
| Ningxia     | 1,907,353 | 7.4                   | 23.3                  | 29.4            | 27.4          | 28.6         | 21.7         | 6.0          | 76.5         | 5.1           | 995.9         | 6.2          | 4.6          | 3.3           | 4.3          | 1.7          |
| Qinghai     | 1,907,353 | 7.4                   | 23.3                  | 29.4            | 27.4          | 28.6         | 21.7         | 6.0          | 76.5         | 5.1           | 995.9         | 6.2          | 4.6          | 3.3           | 4.3          | 1.7          |
| Shaanxi     | 1,037,181 | 2.9                   | 20.3                  | 30.9            | 26.8          | 30.2         | 19.3         | 8.0          | 75.2         | 5.9           | 1005.4        | 7.5          | 4.9          | 3.4           | 4.8          | 1.9          |
| Shandong    | 397,794   | 8.3                   | 18.2                  | 24.3            | 18.9          | 23.2         | 6.4          | 13.4         | 64.0         | 9.5           | 987.1         | 6.6          | 1.8          | 1.8           | 6.6          | 1.2          |
| Shanghai    | 399,091   | 1.7                   | 19.4                  | 32.0            | 24.5          | 30.1         | 17.7         | 6.4          | 13.4         | 64.0         | 9.5           | 987.1         | 6.6          | 1.8          | 1.8           | 6.6          | 1.2          |
(1,037,181 cases), and Tibet had the least number of cases (10,253 cases). The range of mean temperature was from 3.4 to 25.1 °C, the highest mean temperature was in Hainan and the lowest in Heilongjiang. The range of relative humidity, pressure, rainfall, and sunshine was from 46.5 to 80%, 671.1 to 1016.3 Kpa, 0.3 to 5.4 mm, and 2.8 to 7.9 h respectively.

As shown in the Fig. 2, HFMD cases mainly occurred from April to July, which accounting for 58% of the total number of cases. From August to December, the incidence of HFMD was relatively stable, accounting for about 34% of the total cases. From January to March, the incidence of HFMD was the least, accounting for about 18% of the total incidence. The incidence of HFMD was the highest in June, and the lowest in February.

Figure 3 showed the distribution of HFMD cases in different age groups. The incidence of HFMD was mainly concentrated in ≤5 years old group, especially in 1~2 years old group, which accounted for 30% of all the incidence. Other age groups with more incidence were 2~3 years old (23.1%), 3~4 years old (17.5%), 4~5 years old (9.5%), and 0~1 years old (9.5%). In the age group over 5 years old, the number of cases gradually decreased with the increase of age. We divided the study into three age groups in the subsequent study: ≤5 years old, 6~10 years old, and >10 years old.

The optimum temperature of HFMD in 31 provinces is presented in Table 2. In the age group ≤5 years old, the lowest MMT in Qinghai was 13.4 °C, Hainan had the highest MMT, which was 25.8 °C. In the age group 6~10 years old, Henan had the highest MMT, which was 28.0 °C, and also the lowest MMT in Qinghai was 14.0 °C. In the age group >10 years old, Chongqing had the highest MMT, which was 28.9 °C, the lowest MMT was still in Qinghai, which was 14.3 °C. MMT increased gradually with the increase of age. MMT was mainly concentrated at 17 to 23 °C in ≤5 years old group, 18 to 25 °C in 6~10 years old group and 19 to 27 °C in >10 years old group respectively (Supplementary Fig. S2, Fig. S3, Fig. S4).

Table 3 showed the relative risk and 95% confidence interval of high temperature on HFMD in 31 Chinese provinces. The greatest impact of high temperature on HFMD cases in ≤5 years old was 2.06 (95% CI: 1.85~2.30) in Heilongjiang, and the lowest impact was 1.02 (95% CI: 1.00~1.05) in Guangdong. The greatest relative risk in 6~10 years old was 2.24 (95% CI: 1.72~2.91) in Guizhou, and the minimum relative risk was 1.01 (95% CI: 0.97~1.12) in Tianjin. In the age group >10 years old, Heilongjiang and Henan had the maximum and minimum relative risk, the RR was 2.53 (95% CI: 1.66~3.87) and 1.02 (95% CI: 0.71~1.46). The effect of high temperature
on HFMD at different age groups had no obvious law, but on the whole, the effect of high temperature on northern provinces was higher than that in southern provinces to a certain extent.

**Discussion**

Using the time series data of HFMD incidence in 31 provinces in China from 2008 to 2017, this study confirmed the correlation between high temperature and HFMD, which was consistent with the previous research results (Xu et al. 2020; Pearson et al. 2020). However, different from other studies, we found that there had threshold differences in the impact of high temperature on the incidence of HFMD in different provinces and age groups, which can be used as a reference for early warning and guide the public health protection of HFMD.

HFMD is a high incidence infectious disease in infants, which has the characteristics of high incidence rate, difficulty in diagnosis, and rapid progress (Aswathyraj et al. 2016). The first outbreak of HFMD was reported in Canada in 1957 (Chong et al. 2015). Since then, many studies on HFMD have been widely published all over the world. Asia has the largest outbreak of HFMD in the world, which has been reported in Japan, Singapore, India, and other countries (Koh et al. 2016; Gonzalez et al. 2019; Kua and Pang 2020; Rao et al. 2017; Huang et al. 2018). A study from China’s infectious disease surveillance system showed that there were 720,092 cases of HFMD from 2008 to 2012 (Xing et al. 2014), the highest incidence rate of HFMD in the northern region was in May, or in September and October respectively.

Over the past 50 years, the national average high-temperature days have decreased first and then increased. The number of high-temperature days decreased from the 1950s to the early 1980s and began to increase significantly in the early 1980s. There was a linear increasing trend in the number of high temperature days in Northwest and North China, especially in North China. In midsummer, Tianjin, Jinan, Chongqing, Fuzhou, Changsha, Nanchang, Wuhan, Nanjing, and other places had high temperature under the control of the Western Pacific subtropical high. High temperature makes the human body unable to adapt to the environment, exceeding the tolerance limit of the human body, resulting in the occurrence or aggravation of diseases and even death (Liu et al. 2015). The association between the incidence rate of HFMD and meteorological variables is corresponding to the biological rationality. Laboratory studies (Arita et al. 2005) have shown that the effect of temperature on enterovirus depends on whether the circulating strains are temperature sensitive or resistant, and the survival
rate of enterovirus may be improved at higher temperature (Kung et al. 2010). Summer heat will change human contact behavior. More people may be in crowded air-conditioned environment, which may lead to increased incidence rate of children’s contact frequency and HFMD. MMT varied in different area and population, climate, geographical factors, and social economic factors. Our research results showed that the optimum temperature in China was mainly concentrated at 17~27 °C, and there were differences in MMT among different age groups. MMT increased gradually with the increase of age. Under the action of high temperature, the thermoregulation mechanism was temporarily blocked, resulting in heat storage in the body, especially in children under 10 years old, because children had poor adaptability to high temperature.

| Province       | ≤5 years old (°C) | 6~10 years old (°C) | >10 years old (°C) |
|----------------|------------------|---------------------|-------------------|
| Anhui          | 20.3             | 22.6                | 24.5              |
| Beijing        | 24.3             | 24.8                | 26.3              |
| Chongqing      | 22.3             | 26.7                | 28.9              |
| Fujian         | 22.7             | 23.4                | 26.3              |
| Gansu          | 15.5             | 16.9                | 19.8              |
| Guangdong      | 23.8             | 26.5                | 27.8              |
| Guangxi        | 22.1             | 23.9                | 25.7              |
| Guizhou        | 18.7             | 22.0                | 22.8              |
| Hainan         | 25.8             | 27.5                | 28.3              |
| Hebei          | 19.0             | 22.3                | 23.9              |
| Heilongjiang   | 17.8             | 20.0                | 20.3              |
| Henan          | 23.0             | 28.0                | 28.7              |
| Hubei          | 17.3             | 18.5                | 21.8              |
| Hunan          | 17.5             | 20.6                | 22.7              |
| Inner Mongolia | 22.1             | 22.6                | 22.8              |
| Jiangsu        | 20.5             | 25.2                | 26.6              |
| Jiangxi        | 21.7             | 22.9                | 23.2              |
| Jilin          | 19.1             | 20.2                | 23.5              |
| Liaoning       | 18.1             | 19.2                | 20.6              |
| Ningxia        | 17.3             | 19.6                | 20.6              |
| Qinghai        | 13.4             | 14.0                | 14.3              |
| Shaanxi        | 18.4             | 20.6                | 20.8              |
| Shandong       | 21.8             | 23.0                | 24.9              |
| Shanghai       | 21.4             | 23.3                | 24.5              |
| Shanxi         | 20.7             | 22.7                | 22.8              |
| Sichuan        | 16.1             | 18.3                | 19.9              |
| Tianjin        | 21.8             | 22.6                | 24.3              |
| Tibet          | 15.1             | 16.2                | 16.8              |
| Xinjiang       | 18.6             | 19.1                | 20.5              |
| Yunnan         | 18.6             | 19.6                | 20.5              |
| Zhejiang       | 21.3             | 21.9                | 22.3              |

| Province       | ≤5 years old (°C) | 6~10 years old (°C) | >10 years old (°C) |
|----------------|------------------|---------------------|-------------------|
| Anhui          | 1.05             | (1.02,1.09)*        | 1.34 (1.00,1.80)* |
| Beijing        | 1.33             | (1.22,1.45)*        | 1.56 (1.16,2.02)* |
| Chongqing      | 1.10             | (1.06,1.14)*        | 1.43 (1.05,1.94)* |
| Fujian         | 1.23             | (1.05,1.43)*        | 1.25 (0.71,1.96)* |
| Gansu          | 1.45             | (1.43,1.48)*        | 1.53 (1.42,1.66)* |
| Guangdong      | 1.02             | (1.00,1.05)*        | 1.21 (1.07,1.36)* |
| Guangxi        | 1.06             | (1.01,1.12)*        | 1.13 (0.86,1.48)* |
| Guizhou        | 1.96             | (1.88,2.05)*        | 2.24 (1.72,2.91)* |
| Hainan         | 1.25             | (1.18,1.33)*        | 1.70 (1.35,2.09)* |
| Hebei          | 1.08             | (1.05,1.12)*        | 1.28 (1.03,1.59)* |
| Heilongjiang   | 2.06             | (1.85,2.30)*        | 2.03 (1.39,2.84)* |
| Henan          | 1.28             | (1.23,1.33)*        | 1.19 (0.96,1.48)* |
| Hubei          | 1.07             | (1.04,1.10)*        | 1.11 (0.95,1.30)* |
| Hunan          | 1.30             | (1.08,1.52)*        | 1.81 (1.26,2.49)* |
| Inner Mongolia | 1.26             | (1.23,1.30)*        | 1.23 (1.09,1.38)* |
| Jiangsu        | 1.04             | (0.99,1.10)*        | 1.03 (0.73,1.45)* |
| Jiangxi        | 1.42             | (1.26,1.59)*        | 1.08 (0.50,1.75)* |
| Jilin          | 1.88             | (1.75,2.01)*        | 1.74 (1.42,2.11)* |
| Liaoning       | 1.48             | (1.23,1.77)*        | 1.57 (0.76,2.75)* |
| Ningxia        | 1.98             | (1.53,2.53)*        | 2.08 (1.07,4.03)* |
| Qinghai        | 1.53             | (1.46,1.60)*        | 1.85 (1.54,2.19)* |
| Shaanxi        | 1.27             | (1.16,1.39)*        | 1.69 (1.20,2.28)* |
| Shandong       | 1.74             | (1.67,1.81)*        | 1.74 (1.42,2.12)* |
| Shanghai       | 1.03             | (0.98,1.08)*        | 1.05 (0.88,1.25)* |
| Shanxi         | 1.18             | (1.14,1.23)*        | 1.39 (1.10,1.75)* |
| Sichuan        | 1.77             | (1.59,1.96)*        | 1.73 (1.21,2.36)* |
| Tianjin        | 1.10             | (0.88,1.40)*        | 1.01 (0.97,1.12)* |
| Tibet          | 1.58             | (1.33,1.86)*        | 1.69 (0.94,2.74)* |

Environmental Science and Pollution Research (2023) 30:1477–1484
adaptability of the body to meteorological conditions was limited, especially for vulnerable children. When the temperature was higher or lower than the threshold, the thermal balance regulatory mechanism was easy to be disturbed, and the burden of physiological temperature regulation increased, resulting in physical discomfort and disease invasion (Tyler et al. 2016).

There were also differences between different provinces. MMT in different regions showed a trend of increasing from north to south and from west to east. When making relevant health policies, it should consider to break the concept of national unity or geographical area, and to develop the policy according to local conditions. MMT in low latitude and coastal areas was higher than that in other areas. This was mainly due to the long duration of hot summer in low latitude areas, and local residents’ adaptation to high temperature was affected by physiological and behavioral adaptation. When a person lived in specific climatic conditions for a long time, he might adapt to the environment (Lee et al. 2019).

In the northern provinces, such as Heilongjiang and Tianjin, high temperature had a high impact on HFMD, while the southern provinces, such as Guangzhou and Guizhou, high temperature had a low impact on HFMD. There were regional differences in the impact of high temperature on the HFMD, which might be due to the large change of temperature difference in northern regions, especially non-coastal regions, under the influence of continental climate during the change of seasons, especially the alternation of spring and summer, while the temperature difference in southern regions was relatively small under the influence of marine climate. In addition, the population in the south has high adaptability to high temperature compared to the population in the north.

There had some limitations in our study. Because we could not measure individual exposure dose, we used meteorological monitoring data to evaluate the impact, which inevitably has an ecological fallacy. We only considered meteorological variables. Other major environmental risk factors of HFMD were not included, such as seasonal life in cities or suburbs, accumulated ultraviolet radiation, socioeconomic conditions, and air pollution. These factors should be considered or adjusted in future research.

### Conclusion

In summary, there are correlations and regional differences between high temperature and HFMD. Based on the study of MMT, we can formulate personalized threshold early warning for different regions and age group, and take targeted protection strategies for the population, especially children, to reduce the disease burden of HFMD.

### Supplementary Information

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### Author contribution

Guijie Luan and Hongyan Yao conceived and designed studies; Shaonian Liu, Weiyan Zhang, Yingjie Zhang, and Liang Sun collected the data; Guijie Luan analyzed the data and wrote the paper; Long Zhai revised the methods and manuscript.

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### Data availability

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

### Declarations

#### Ethics approval and consent to participate

Not applicable.

#### Consent for publication

Not applicable.

#### Competing interests

The authors declare no competing interests.

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