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Short-term effects of meteorological factors and air pollution on childhood hand-foot-mouth disease in Guilin, China

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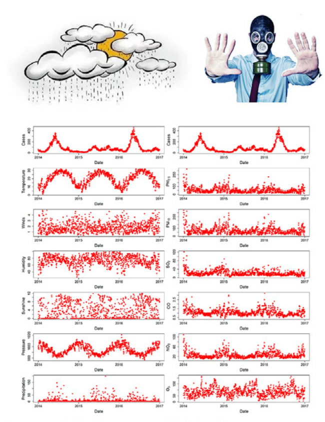
HIGHLIGHTS

- A total of 88,742 HFMD cases, daily weather and air pollution data during 2014-2016 were included in the analysis;
- Extreme temperature, precipitation and wind speed can affect the HFMD incidence;
- Extremely low values of $PM_{2.5}$ and high values of O_3 showed certain protective effects.
- Male children and children aged 0-3 year are vulnerable groups to extreme environment.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Previous studies have always focused on the impact of various meteorological factors on Hand–foot–mouth disease (HFMD). However, only few studies have investigated the simultaneous effects of climate and air pollution on HFMD incidence.
Methods: Daily HFMD counts among children aged 0–14 years in Guilin city were collected from 2014 to 2016. Distributed lag nonlinear models (DLNM) were used to assess the effects of extreme meteorological factors and air pollution indicators, as well as the effects of different lag days on HFMD incidence. Furthermore, this study explored the variability across gender and age groups.
Results: Extreme temperatures, high precipitation and low-O_3 concentration increased the risk of HFMD. Hot effect was stronger and longer lasting than cold effect. Risks of rainy effect and low-O_3 effect continued to increase as lag days extended, with the maximum RR values: 1.60 (1.38, 1.86) (90th vs median) and 1.48 (1.16, 1.89) (1th vs median) at 0–14 lag days, respectively. By contrast, extremely high wind speed, low precipitation, low $PM_{2.5}$ and high O_3 exerted a certain protective effect on HFMD incidence. The corresponding minimum RR values were: 0.85 (0.74, 0.98) (90th vs median) at 0–14 lag days, 0.98 (0.97, 0.99) (10th vs median) at 0–14 lag days, 0.73 (0.61, 0.88) (1th vs median) at 0–14 lag days and 0.81 (0.73, 0.90) (99th vs median) at 0–7 lag days, respectively.

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Male children and children aged 0–1 years (followed by 1–3 years) were the most susceptible subgroups to extreme climatic effects and air pollution.

Conclusions: Our results indicated that daily meteorological factors and air pollution exert non-linear and delayed effects on pediatric HFMD, and such effects vary depending on gender and age. These findings may serve as a reference for the development of an early warning system and for the adoption of specific interventions for vulnerable groups.

1. Introduction

Hand–foot–mouth disease (HFMD) is an acute infectious disease caused by enteroviruses, such as human enterovirus 71 (EV-71) and Coxsackievirus A group 16(Ang et al., 2009). HFMD is prevalent among preschoolers, and severe cases are mostly caused by EV-71 infection. This disease is self-limiting and mainly spreads through fecal-oral transmission or through close contact. Although its typical clinical symptoms are mild (such as rashes on hands, feet, and hip, as well as oral mucosal herpes), it occasionally causes severe complications, such as meningitis and encephalitis, which may lead to death. No effective vaccines and specific antiviral therapies for HFMD have been developed (Mao et al., 2016).

HFMD was first reported in New Zealand in 1957, and it has become an urgent issue in global public health (Zhuang et al., 2015). Frequent HFMD outbreaks were experienced in the Asia-Pacific region in the past decades. In the spring of 2008, a large, unprecedented HFMD outbreak was experienced in Fuyang City (China), wherein 6049 cases and 22 deaths were recorded (Yan et al., 2010). Large-scale HFMD outbreaks also occurred in South Korea and Hong Kong in 2009 and 2011, respectively (Lee et al., 2013; Song et al., 2015). Followed by vast HFMD cases and local outbreaks being observed in Vietnam and Thailand (Nguyen et al., 2014; Puenpa et al., 2014), as well as in Malaysia and India (Nmn et al., 2016; Palani et al., 2016). In addition, mainland China has been suffering from a huge burden caused by HFMD due to its large population base. The incidence of HFMD in 2014 was 203.16/100,000 and the mortality was 18.03/100,000, exceeding those in most East Asian countries (Zhuang et al., 2015). Hence, identification of the risk factors for HFMD and establishment of a targeted early warning system are crucial to the control of HFMD outbreak and reduction of the burden caused by this disease common among children.

HFMD incidence shows a remarkable seasonality (Wang et al., 2011). Studies have suggested that the incidence of HFMD is closely related to meteorological factors (Sumi et al., 2017; Wang et al., 2016a, 2016b; Wei et al., 2015). However, results obtained from different regions and findings on the effects of different meteorological factors are not entirely consistent. A Japanese study has shown that HFMD cases increase by 11.2% for every 1 °C increase in average temperature and by 4.7% for every 1% increase in relative humidity (Onozuka and Hashizume, 2011). Studies conducted in Gansu (China) have reported that a 1 °C increase in average temperature increases the weekly HFMD incidence counts by 5.9% in Tianshui, 2.8% in Lanzhou, and 1.8% in Jiuquan. Moreover, a 1% increase in relative humidity increases the weekly HFMD incidence count by 2.47% in Lanzhou and 1.11% in Tianshui (Gou et al., 2018). Cheng, et al. speculated that extreme rainfall increases the incidence of HFMD, whereas the opposite pattern was reported by another study conducted in Singapore (Cheng et al., 2014; Hii et al., 2011). Moreover, studies have found that relative humidity, sunshine, and wind speed influence the risk of HFMD (Huang et al., 2013; Wang et al., 2016a, 2016b; Yang et al., 2017). However, this result is inconsistent with the findings obtained in Huainan and Hong Kong (Ma et al., 2010; Zhao et al., 2017). Therefore, studies must be conducted in more cities to elucidate these controversial results.

Researches concerning the adverse health effect of air pollution were mostly concentrated on the relationship between air pollution and chronic non-communicable diseases. However, recent studies indicated that air pollution may mediate and promote the incidence of infectious diseases. Chen et al. found that measles is associated with exposure to ambient $PM_{2.5}$, which can be modified by meteorological factors (Chen et al., 2017a). Air pollution was also found to be significantly associated with the prevalence of influenza-like illness and avian influenza, whose effects varied among different age groups (Chen et al., 2010; Feng et al., 2016; Huang et al., 2016a, 2016b). In addition, Ye et al. found that haze can play an important role in the spread of intestinal infectious diseases such as rotavirus caused diarrhea (Ye et al., 2016). The adhesion of virus to gaseous particulate matter and the inflammatory reaction caused by the dissolution of O_3, SO_2, NO_2, etc. in the respiratory tract may promote the incidence of infectious diseases to some extent (Gralton et al., 2011; Sun et al., 2016). Nonetheless, researches on the relationship between air pollution and other enteric diseases such as hand, foot and mouth disease are very limited. To our knowledge, only two studies had investigated the effect of PM_{10} on HFMD incidence, and the results were inconsistent (Huang et al., 2016a, 2016b; Huang et al., 2018). Thus, exploring the impact of meteorological factors and air pollution on HFMD incidence can help clarify the potential factors and deepen our understanding of HFMD incidence.

Guilin City was taken as our research area based on the following reasons. First, HFMD incidence in Guilin City is relatively high, basically more than three times the national average. Second, Guilin City is characterized by ethnic minorities and numerous mountains and rivers, and the geographical environment and lifestyle in this city are quite different from those in plain and coastal areas. DLNM was utilized to quantify the association of climate and air pollution with HFMD incidence. This study aimed to identify the risk factors of HFMD and the populations susceptible to this disease, thereby providing a reference for establishing an early warning system and for formulating target intervention policies to prevent and control infectious diseases.

2. Data and methods

2.1. Study settings and data sources

Guilin City is a famous tourist destination in southern China, and ethnic minorities live in this city. Guilin has an area of 27,667 km^2 and a population of 5.1 million (in 2016). This city is located in a subtropical monsoon climate zone with mild climate and abundant rainfall and sunshine. The annual average temperature is 20 °C, and the average relative humidity is 73%. Northeast wind is the dominant wind direction throughout the year. Fig. 1 shows the geographical location of Guilin City.

Daily data on HFMD incidence from 2014 to 2016 were obtained from the Infectious Disease Reporting System of the Guangxi Center for Disease Prevention and Control. Clinical diagnosis of HFMD is based on the National Guideline on Diagnosis and Treatment of Hand Foot Mouth Disease issued by the Chinese Ministry of Health. Symptoms of typical cases include acute onset, fever, rashes on hands, feet, and buttocks; HFMD is also frequently characterized by scattered herpes in the oral mucosa and pharyngeal isthmus, which may be accompanied by cough, runny nose, loss of appetite, and diarrhea. HFMD is listed as a category C infectious disease in China. Health departments require that infected patients, patients with suspected infection, or carriers of the

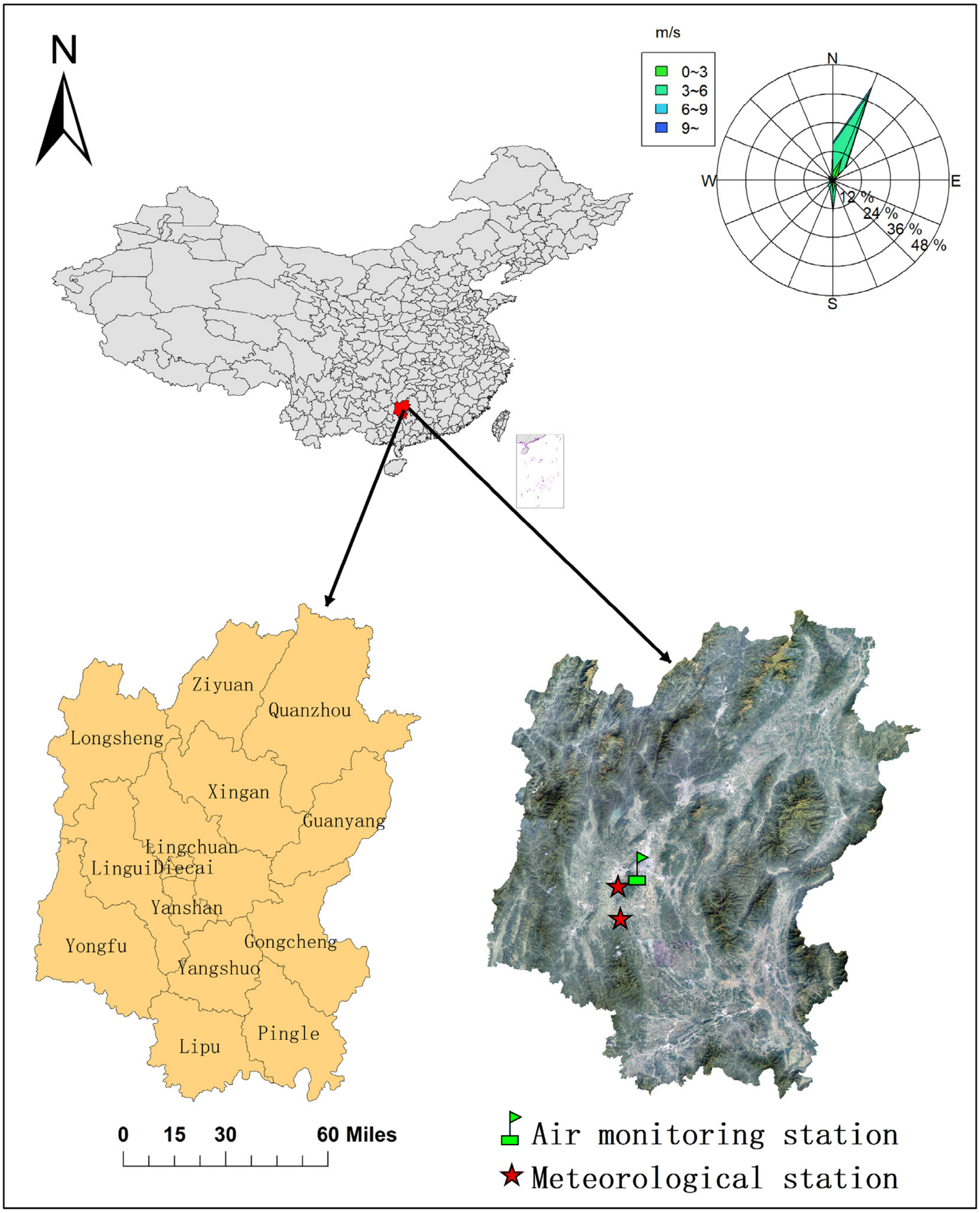

Fig. 1. Geographical location of Guilin City, China.

infectious pathogen be classified under this category; such cases must be reported online within 24 h upon diagnosis or must be reported by means of a network report card filled out by trained health personnel and sent within 24 h if the medical institution does not have Internet access. All reported data are reviewed by professionals to ensure their accuracy and reliability. Considering that the vast majority of HFMD cases involve children, this study only includes patients below 14 years old, which account for 99.68% of the total number of cases.

Daily meteorological data, including minimum, mean, and maximum temperature, atmospheric pressure, relative humidity, sunshine duration, wind speed, and precipitation, for the same time period were downloaded from the publicly accessible China National Weather Data Sharing System (http://data.cma.cn/site/index.html). A small proportion of missing rainfall data, approximately 5.93%, is filled in by data from another weather monitoring station located in the same city; this concrete step taken to obtain a complete dataset will not cause bias in the results of this study. Data on air pollution were obtained from the local environmental protection station. Six air pollution indicators, namely, $PM_{2.5}$, PM_{10}, SO_2, CO, NO_2, and O_3, were included in this study, and no data were missing during the study period.

2.2. Statistical analysis

On the basis of data distribution and the relationship between variables, we used a quasi-Poisson regression model combined with DLNM to estimate the effects of meteorological conditions and air pollution on HFMD incidence. The results of the initial analysis utilizing a univariate model indicate that four meteorological variables (mean temperature, relative humidity, wind speed, and precipitation) and three air pollution variables ($PM_{2.5}$, PM_{10}, and O_3) are significantly associated with HFMD incidence. Considering the consistent impact of $PM_{2.5}$ and PM_{10} on HFMD incidence, we only included $PM_{2.5}$ in the subsequent multivariate model analysis. A Poisson regression model that allows overdispersion of data was built as follows:

$$Y_t \sim Poisson(u) = \alpha + NS(M, df, lag, df) + \sum NS\ (X_i) + NS(Time, df) + \beta DOW_t + \gamma Holiday_t$$

where t is the day of observation; Y_t is the observed HFMD cases on t; α is an intercept; *NS* is a natural cubic spline used to model the nonlinear relationship between meteorological or air pollution variables and HFMD incidence; *M* is the examined meteorological or air pollution variable that was closely related to the incidence of mumps; X_i represents the several other meteorological and air pollution variables that should be controlled due to their modifying effect on HFMD incidence; *M* and X_i are the matrices obtained by applying cross-basis functions to each of them; *Time* is the indicator variable used to control long-term trends, seasonality, and differences in the annual at-risk population; *DOW* stands for day of week; and *Holiday* is a covariate used to control the effect of public holidays. In this model, the degrees of freedom (*df*) per year for time variable was set to 7. We defined natural cubic spline bases with 4 df for mean temperature, relative humidity, wind speed, precipitation, $PM_{2.5}$, and O_3, as well as lag spaces with 3 df. Accordingly, the maximum lag days were set to 14 based on the incubation period and on previous studies (Xiao et al., 2017; Zhang et al., 2016a, 2016b). *df* determination was based on the Akaike information criterion for quasi-Poisson (Q-AIC), which can produce the optimal model. In addition, residual analysis was conducted to check the autocorrelation feature of the model. All knots were placed by default in the space allotted for each of the meteorological and air pollution variables, and they were equally spaced. The knots for the spline for lags were also placed at equally spaced values on the log scale of lags.

In this study, the effects of extreme meteorological factors on childhood HFMD were examined and presented as relative risk (RR) by comparing the 90th above or 10th below percentiles of the meteorological variables to their median values; moreover, the effects of extreme air pollution indicators were examined by comparing the 99th above or 1th below percentiles of pollution indicators to the median values. Considering that the incubation period of HFMD is 2–10 days (average: 3–5 days), we divided the lag days of the study variables into six categories (lag0, lag0–3, lag0–5, lag0–7, lag0–10, and lag0–14) to effectively depict the characteristics of the cumulative effect. Stratified analysis was conducted to investigate the impact of extreme climate and environmental conditions on different populations according to gender (male and female) and age group (0–1y, 1–3y, 3–6y, and 6–14y). The criteria for age grouping are based on differences in the outdoor activities and environmental exposures of the children belonging to different age groups. Children aged 0–1 years old show less activity and rarely go out, 1–3 years old are more active and mainly stay with their parents, 3–5 years old attend kindergarten school, and 6–14 years old go to school.

2.3. Sensitivity analysis

Sensitivity analyses were performed to determine the selected model and specified parameters. We conducted the sensitivity analysis as follows: (1) The maximum lag days (10–20 days) for meteorological and air pollution variables were extended. (2) df (4–13) for seasonality and long-term trend, df (3–7) for meteorological and air pollution variables, and df (2–7) for lag space were changed. (3) The comparison indicators (90th, 95th, 99th, 10th, 5th, and 1th vs. median value) were varied to assess extreme conditions effects.

This study was approved by the Ethics Committee of Guangxi Medical University. All data included in the analysis were anonymized.

3. Results

A total of 88,742 children aged 0–14 years with HFMD were included in our study. A greater number of the patients are male, and the male-to-female ratio is 1.38:1. Table 1 summarizes the information regarding the cases and the meteorological and air pollution factors. The daily average number of HFMD cases was 81 (range: 4–460) in the study area. The daily average values for meteorological factors, namely, mean temperature, wind velocity, relative humidity and precipitation were 20.1 °C (range:1.2 °C–31.9 °C), 1.85 m/s (range: 0.4–4.8 m/s), 73.47% (range: 25%–99%), and 6.68 mm (range: 0–198 mm), respectively. The daily average values for the air pollution indicators, namely, $PM_{2.5}$ and O_3, were 52.80 μg/m^3 (range: 4–322 μg/m^3) and 85.12 μg/m^3 (range: 4–216 μg/m^3), respectively. The time-series analysis of HFMD cases and meteorological and air pollution factors indicated that HFMD incidence showed an obvious seasonality (Fig. 2). A significant peak was observed during late spring and early summer (from May to July), and another seasonal peak appeared in the late autumn and early winter, although it was not obvious. Meteorological factors (mean temperature, relative humidity, and atmospheric pressure) and air pollution indicators ($PM_{2.5}$, NO_2, and O_3) also showed significant periodicity, and their patterns were relatively stable. No statistically significant difference in the HFMD incidence of different genders and age groups was found ($P < 0.001$) (Table S6).

Different climatic and environmental variables exerted varied extreme effects on HFMD, and this difference was also observed between subgroups in the population. Table 2 showed the cumulative effects of extreme values of various variables on HFMD at lag day 14. Studies have found that extremely high temperature can significantly increase the risk of HFMD, and the cumulative effect was RR value: 2.04 (1.81, 2.29) (90th vs median). Extreme heat has a stronger effect on males than females, with their RR values: 2.08 (1.79, 2.43) (90th vs median) and 1.97 (1.64, 2.36) (90th vs median), respectively. All age groups besides those aged 6–14 years were susceptible to extreme heat and the most sensitive age group was 0–1 years, with RR value: 2.42 (1.70, 3.44) (90th vs median). No remarkable cumulative effect of extremely

Table 1
Description of HFMD cases and meteorological and air pollution factors in Guilin from 2014 to 2016.

Variables	Min	Max	Mean ± SD	P1	P10	Median	P90	P99
Case	4.0	460.0	81.2 ± 78.8	9.0	18.5	55.0	204.5	352.2
Mean temperature (°C)	1.2	31.9	20.1 ± 7.6	4.0	9.3	21.9	29.3	31.3
Wind velocity (m/s)	0.4	4.8	1.9 ± 0.7	0.5	0.9	1.7	3.1	4.3
Relative humidity (%)	25.0	99.0	73.5 ± 13.6	35.0	55.0	75.0	90.0	97.1
Sunshine duration (h)	0.0	12.0	3.6 ± 3.8	0.0	0.0	2.2	9.3	11.2
Atmospheric pressure (hPa)	977.0	1020.8	994.7 ± 7.8	981.6	985.0	994.0	1006.1	1010.8
Precipitation (mm)	0.0	198.0	6.7 ± 17.7	0.0	0.0	0.1	19.3	94.3
$PM_{2.5}$ (ug/m^3)	4.0	322.0	52.8 ± 35.3	12.0	20.0	44.0	95.0	202.1
PM_{10} (ug/m^3)	8.0	333.0	72.0 ± 45.2	17.0	30.0	61.0	128.5	246.1
SO_2 (ug/m^3)	3.0	122.0	21.1 ± 12.2	5.0	10.0	18.0	37.0	58.1
CO (mg/m^3)	0.4	3.2	1.1 ± 0.3	0.6	0.7	1.0	1.5	2.2
NO_2 (ug/m^3)	6.0	109.0	25.5 ± 12.6	11.0	14.0	22.0	41.0	70.1
O_3 (ug/m^3)	4.0	216.0	85.1 ± 36.8	18.0	42.0	80.0	135.0	186.0

SD: standard deviation; Px: percentile of the data.

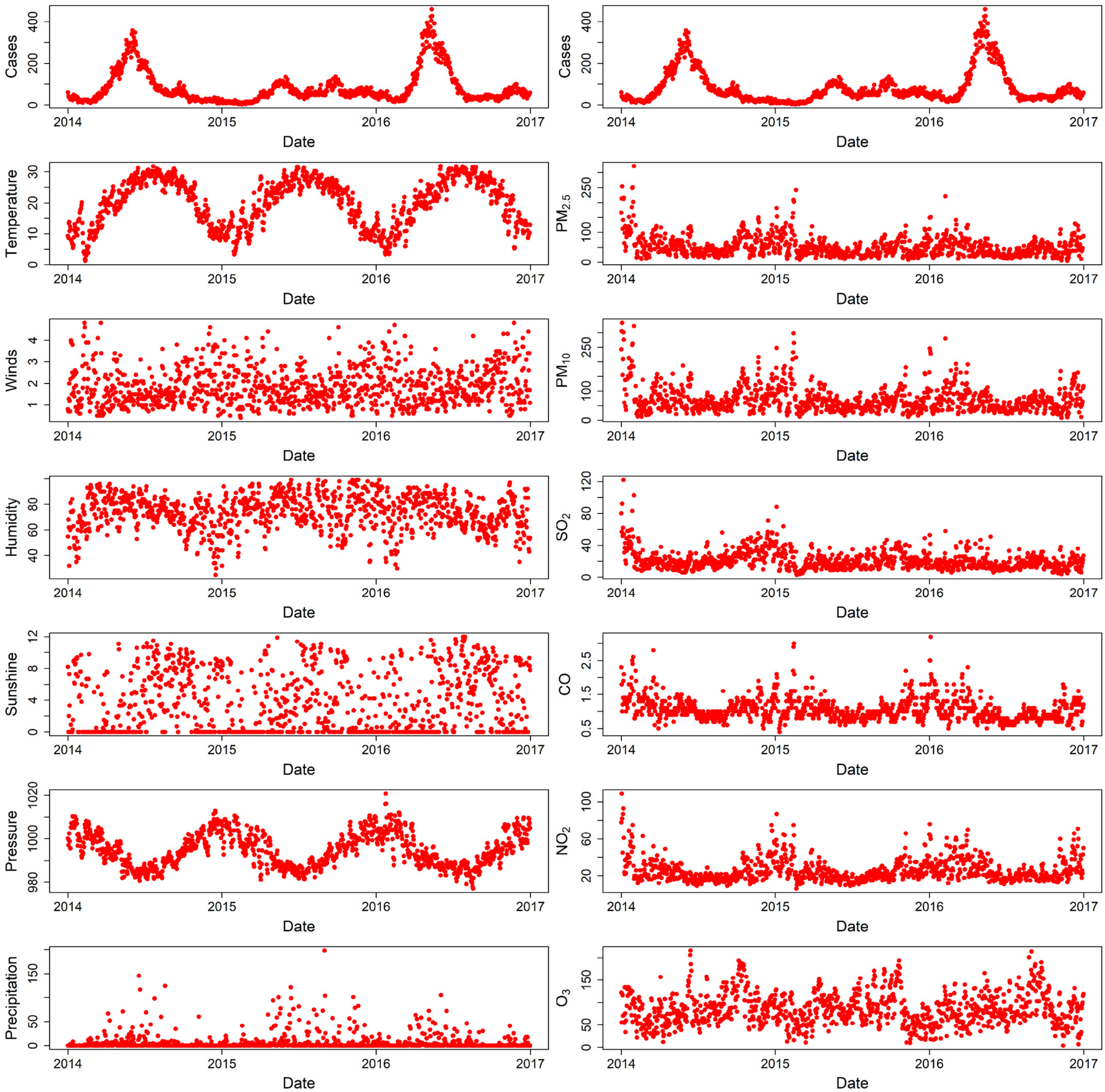

Fig. 2. Time-series results regarding the association of HFMD incidence with meteorological factors and air pollution indicators in Guilin from 2014 to 2016.

Table 2
Extreme effect analysis of different meteorological and air pollution factors from 2014 to 2016. Relative risk (RR) and 95% confidence interval were used to estimate the effect of the above factors in different subgroups.

Variables	Total case	Male	Female	0–1 y	1–3 y	3–6 y	6–14 y
Hot effect	2.04(1.81,2.29)	2.08(1.79,2.43)	1.97(1.64,2.36)	2.42(1.70,3.44)	1.93(1.66,2.25)	2.28(1.79,2.91)	1.33(0.70,2.53)
Cold effect	0.94(0.80,1.11)	0.94(0.76,1.17)	0.94(0.73,1.21)	0.73(0.43,1.24)	0.97(0.79,1.20)	1.01(0.73,1.40)	0.57(0.23,1.41)
Wet effect	0.90(0.77,1.05)	0.77(0.63,0.94)	1.12(0.88,1.41)	0.84(0.53,1.32)	0.88(0.72,1.07)	0.94(0.69,1.29)	1.26(0.54,2.95)
Dry effect	0.76(0.67,0.87)	0.75(0.63,0.89)	0.78(0.64,0.96)	1.17(0.78,1.75)	0.69(0.58,0.82)	0.80(0.61,1.05)	0.72(0.35,1.50)
Windy effect	0.85(0.74,0.98)	0.88(0.73,1.05)	0.82(0.66,1.02)	0.78(0.50,1.20)	0.79(0.66,0.95)	0.97(0.73,1.29)	1.30(0.59,2.87)
Windless effect	0.84(0.74,0.95)	0.85(0.72,1.00)	0.82(0.68,0.99)	0.58(0.40,0.86)	0.81(0.69,0.95)	0.92(0.72,1.19)	1.49(0.75,2.96)
Rainy effect	1.60(1.38,1.86)	1.83(1.51,2.23)	1.33(1.06,1.67)	2.80(1.77,4.42)	1.47(1.21,1.77)	1.62(1.20,2.19)	1.12(0.50,2.52)
Rainless effect	0.98(0.97,0.99)	0.98(0.97,0.99)	0.99(0.97,1.01)	0.94(0.91,0.97)	1.00(0.98,1.01)	0.96(0.94,0.99)	1.07(1.00,1.14)
High-$PM_{2.5}$ effect	1.01(0.70,1.46)	1.12(0.69,1.82)	0.87(0.50,1.52)	2.28(0.70,7.38)	1.10(0.69,1.74)	0.47(0.21,1.04)	0.23(0.04,1.53)
Low-$PM_{2.5}$ effect	0.73(0.61,0.88)	0.71(0.56,0.90)	0.77(0.58,1.02)	0.49(0.28,0.84)	0.74(0.58,0.94)	0.82(0.57,1.20)	0.99(0.37,2.68)
High-O_3 effect	1.06(0.90,1.26)	1.10(0.88,1.37)	1.01(0.78,1.31)	0.36(0.21,0.61)	0.94(0.75,1.16)	2.02(1.44,2.82)	2.38(0.95,5.98)
Low-O_3 effect	1.48(1.16,1.89)	1.70(1.23,2.35)	1.22(0.84,1.78)	2.40(1.11,5.19)	1.68(1.23,2.30)	1.05(0.64,1.72)	0.67(0.17,2.62)

low temperature on the HFMD incidence was observed at 14 lag days. Extremely low relative humidity showed a certain protective effect. Males and children aged 1–3 were the most sensitive people, with RR values: 0.75 (0.63, 0.89) (10th vs median) and 0.69 (0.58, 0.82) (10th vs median), respectively. Windy and windless effects both played a protective role in HFMD incidence in this study. The corresponding RR values of the total cases were 0.85 (0.74, 0.98) (90th vs median) and 0.84 (0.74, 0.95) (10th vs median), respectively. RR value was more pronounced in the effect of precipitation. Rainy effect could remarkably increase the risk of HFMD incidence, while rainless effect showed the opposite trend. Males and children aged 1–3 years shared the most significant RR values, with 1.83 (1.51, 2.23) (90th vs median) and 2.80 (1.77, 4.42) (90th vs median) for rainy effect, and 0.98 (0.97, 0.99) (10th vs median) and 0.94 (0.91, 0.97) (10th vs median) for rainless effect, respectively. Results showed that the extremely low $PM_{2.5}$ concentration corresponded to the low RR value: 0.73 (0.61, 0.88) (1th vs median). Whereas the extremely low O_3 concentration corresponded to the high RR value: 1.48 (1.16, 1.89) (1th vs median). Both males and children aged 1–3 years owned more prominent cumulative effects than other subgroups. Effects of extremely high $PM_{2.5}$ and O_3 were not significant at 14 lag days.

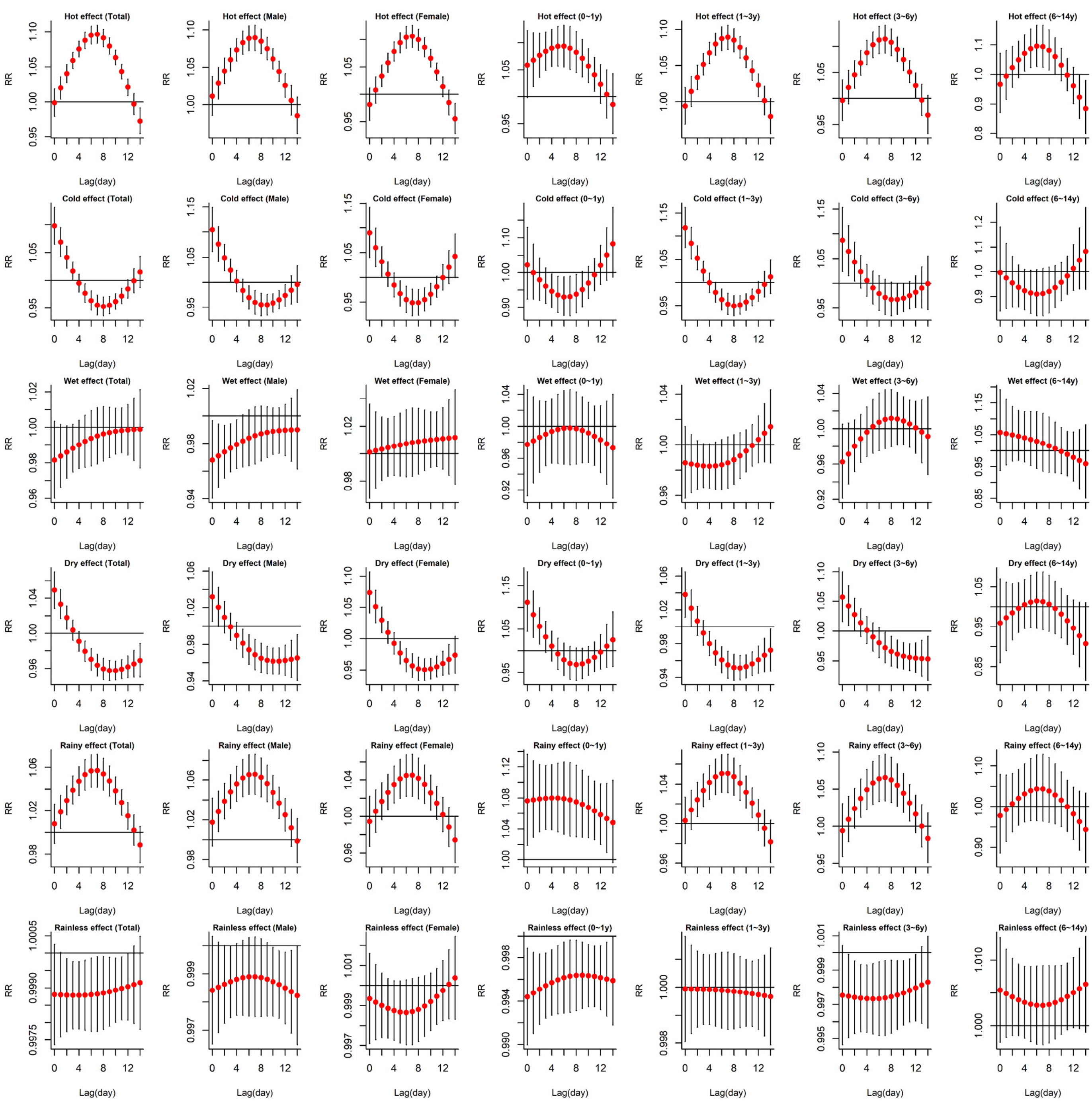

Fig. 3. Summary of overall cumulative associations between HFMD incidence and extreme weather conditions for mean temperature (hot effect, cold effect), relative humidity (wet effect, dry effect), and precipitation (rainy effect, rainless effect) for all groups at different lag days from 2014 to 2016. The extreme conditions effects were estimated by the RR of HFMD by comparing the 90th percentile of daily meteorological value to the median value, whereas the low values of extreme effects were estimated by comparing the 10th percentile of daily meteorological value to the median value.

Results of extreme effect analysis for different meteorological and environmental variables at different lag days indicated that the adverse health effect of a hot condition occurs relatively slower and lasts longer than that of cold condition (Fig. 3). Hot effect presented an inverted V-shaped curve under different lag days, while the cold effect curved the reversed trend. RR of hot effects peaked on the sixth lag day and then decreased, whereas the largest RR value of cold effects was achieved on the current day and only lasted about 4 days. Although the curves of the above two effects are basically similar among the subgroups, children aged 1–3 years remain the most affected population and gender differences were not obvious. The cumulative RR value of the dry effect showed an inverted J type. Relative humidity could increase the risk of HFMD at the first four days when exposure to dry effect, and then showed a certain protective effect. No significant associations between wet effect and HFMD incidence were observed at different lag days. As the lag days increased, the risk of rainy effects rose first and then decreased, reaching a maximum on 6–7 lag days and lasting about 10 days. Males and children aged 0–1 years were more affected by the wet effect. In contrast, RR values of rainless effect indicated a certain protective role and children aged 1–3 years was the most remarkable subgroup. Fig. 4 indicated that windy effect could reduce the risk of HFMD, which was more pronounced during the first four days when

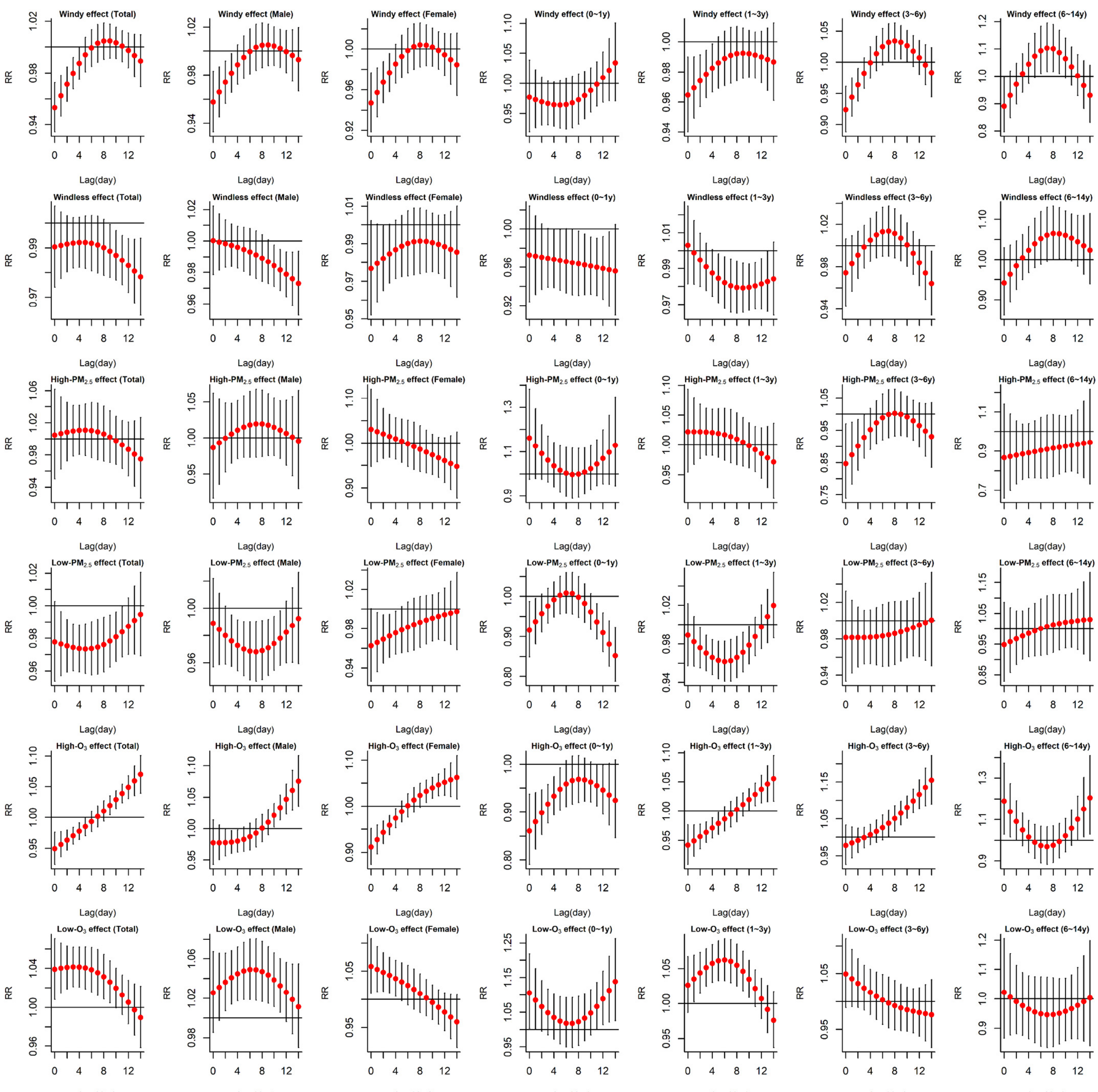

Fig. 4. Summary of overall cumulative associations between HFMD incidence and meteorological and air pollution factors (Wind velocity, $PM_{2.5}$, O_3) for all groups at different lag days from 2014 to 2016. Similarly, the extreme effects of wind speed were calculated by comparing the 90th percentile of daily wind speed value to the median value and 10th percentile of which to the median. The extreme effects of air pollution indicators ($PM_{2.5}$, O_3) were estimated by comparing the 99th percentile of daily value to the median and the 1th percentile of which to the median.

Table 3
Extreme effect analysis of different meteorological and air pollution factors from 2014 to 2016. The relative risk (RR) and 95% confidence interval were used to estimate the cumulative effect of different lag days.

Variables	Lag0	Lag0–3	Lag0–5	Lag0–7	Lag0–10	Lag0–14
Hot effect	1.00(0.98,1.02)	1.12(1.06,1.19)	1.31(1.22,1.41)	1.58(1.45,1.71)	1.97(1.79,2.18)	2.04(1.81,2.29)
Cold effect	1.10(1.07,1.13)	1.24(1.14,1.35)	1.21(1.09,1.34)	1.11(0.98,1.26)	0.97(0.84,1.13)	0.94(0.80,1.11)
Wet effect	0.98(0.96,1.00)	0.94(0.88,1.00)	0.92(0.85,1.01)	0.91(0.82,1.01)	0.91(0.79,1.03)	0.90(0.77,1.05)
Dry effect	1.05(1.03,1.07)	1.11(1.05,1.17)	1.07(1.00,1.16)	1.00(0.92,1.10)	0.88(0.79,0.98)	0.76(0.67,0.87)
Windy effect	0.95(0.93,0.97)	0.87(0.82,0.93)	0.86(0.79,0.93)	0.86(0.78,0.94)	0.87(0.77,0.98)	0.85(0.74,0.98)
Windless effect	0.99(0.97,1.01)	0.97(0.92,1.01)	0.95(0.89,1.01)	0.93(0.86,1.01)	0.90(0.82,1.00)	0.84(0.74,0.95)
Rainy effect	1.01(0.99,1.03)	1.10(1.04,1.16)	1.21(1.12,1.31)	1.35(1.23,1.49)	1.55(1.37,1.76)	1.60(1.38,1.86)
Rainless effect	1.00(1.00,1.00)	1.00(0.99,1.00)	0.99(0.99,1.00)	0.99(0.98,1.00)	0.99(0.98,1.00)	0.98(0.97,0.99)
High-$PM_{2.5}$ effect	1.00(0.95,1.06)	1.03(0.88,1.21)	1.05(0.86,1.29)	1.07(0.85,1.36)	1.08(0.80,1.45)	1.01(0.70,1.46)
Low-$PM_{2.5}$ effect	0.98(0.95,1.00)	0.91(0.84,0.98)	0.86(0.78,0.94)	0.82(0.73,0.91)	0.76(0.66,0.88)	0.73(0.61,0.88)
High-O_3 effect	0.95(0.92,0.98)	0.85(0.79,0.92)	0.82(0.75,0.90)	0.81(0.73,0.90)	0.86(0.76,0.98)	1.06(0.90,1.26)
Low-O_3 effect	1.04(1.01,1.07)	1.17(1.07,1.28)	1.27(1.12,1.43)	1.37(1.17,1.59)	1.47(1.21,1.79)	1.48(1.16,1.89)

exposure to extremely high wind velocity. Children aged 3–6 years were the most obvious beneficiary group, and gender differences were not apparent. In addition, we observed a slight protective effect on males and children aged 1–3 years at 8 lag days. The risk of HFMD maintained a low level when exposure to low $PM_{2.5}$ concentration during the first 10 days while low O_3 concentration showed the opposite effect. Males and children aged 1–4 years were more affected when compared to other subgroups. The risk of HFMD was low when exposure to high O_3 concentration at the first 4–5 lag days and then increased after nearly 9–10 lag days. Table 3 shows the cumulative effects of the extreme values for meteorological and environmental variables at different lag days. Overall, hot effect, rainy effect and low-O_3 effect could increase the HFMD incidence, and the cumulative effects increased with lag days extending. The maximum RR values all appeared at 0–14 lag days. Windy effect and low-$PM_{2.5}$ effect could lower the risk of HFMD, which would become more pronounced as the lag days increased. Effects of 0–14 lag days corresponded to the minimum RR value. Cold effect could also increase the HFMD incidence and the duration was short, with a maximum RR value: 1.24 (1.14, 1.35) (10th vs median) at 0–3 lag days. The dry effect acted as a risk factor in the first three days of lag, while played a protective role after 10 lag days. RR values of rainless effect and high-O_3 effect remained low level and showed no obvious trend under different lag days. The minimum RR of high-O_3 effect was 0.81 (0.73, 0.90) (99th vs median) at 0–7 lag days.

The results obtained were similar to those obtained in sensitivity analyses, which were conducted by changing the df for meteorological and air pollution indicators from 2 to 7 and the df for lag space from 3 to 7 and also by changing the maximum lag days from10 days to 20 days. Results of model parameter specification and sensitivity analysis can be saw in Table S1–S5 and Fig. S1–S6.

4. Discussion

The impact of climate change and air pollution on health has increasingly received attention in recent years. Extreme weather and $PM_{2.5}$ may induce the onset of cardiovascular and cerebrovascular diseases (Chafe et al., 2014; Ngo and Horton, 2016), premature birth (Schifano et al., 2016), and the spread of insect- (Lu et al., 2009) and waterborne diseases (Sterk et al., 2013). Moreover, climatic conditions are increasingly recognized as important factors influencing HFMD incidence as HFMD displays a remarkable seasonality; Environmental particulate matter is thought to be likely to mediate the spread of viral infections through air (Ijaz et al., 2016). additionally, HFMD has been a public health burden (Cheng et al., 2018). In this study, we applied the distributed lag nonlinear model to explore the relationship between climate, air pollution and HFMD incidence in terms of variables and lag days. The results suggest that mean temperature, wind speed, precipitation, $PM_{2.5}$, and O_3 are significantly associated with HFMD incidence, and their effects differ on different lag days and in different subgroups. Such association of climate and air pollution with HFMD incidence may serve as a reference for local governments to formulate targeted disease prevention policies and establish an early warning system for diseases.

Our study has found that both extremely high and low temperatures increase the risk of HFMD, with hot effect being stronger and lasting longer than cold effect. This finding validates most previous findings, suggesting an optimal temperature range in temperature-related incidence and that the exposure–response curve has an approximately V-shape (Chang et al., 2012; Liao et al., 2016; Zhu et al., 2016), similar to the effect of extreme temperatures on death (Ma et al., 2015). By contrast, other studies have suggested a positive effect of daily mean temperature on HFMD incidence, wherein the higher the temperature, the greater the disease incidence. A significant effect was not observed at low temperatures (Sumi et al., 2017; Zhang et al., 2016a, 2016b). This discrepancy may be attributed to differences in climatic, environmental, and socioeconomic factors and in differences in prevention policies among the regions included in these analyses (Xiao et al., 2017; Zhu et al., 2016). People in the tropical region are more affected by extreme heat, whereas those who live in the subtropical and temperate regions may be affected by both high and low temperatures (Gasparrini et al., 2015; Zhang et al., 2016a, 2016b). In addition, the use of air-conditioning and heating units is an important factor affecting temperature-related health effects (Potera, 2017). Temperature may influence HFMD incidence in two ways. On the one hand, temperature affects the body's immunity and adaptability, especially among children, pregnant women, and elderly (Averett, 2016; Hess et al., 2014). On the other hand, temperature affects the viability and replication of enterovirus in the external environment, as well as affects the living habits of people, especially children, thereby increasing the risk of infection. The infectivity of enteroviruses increases with increasing temperature within an appropriate temperature range (Hagiwara et al., 1983; Yeager and O'Brien, 1979). Meanwhile, a comfortable temperature promotes the outdoor activities of children, increasing their chances of contact with other people (e.g., toy sharing); as a result, their risk of infection increases (Edwards et al., 2014). This suggested us that measures should be took to cool down and keep warm, and also pay attention to living hygiene when encountering extreme temperatures.

In terms of precipitation, we found that extremely high precipitation increases HFMD incidence among children, and the rainy effect gradually strengthens with the extension of accumulated lag days. This result is supported by previous findings (Chen et al., 2015; Cheng et al., 2014; Dong et al., 2016). Chen et al. reported that the effect of extreme precipitation on childhood HFMD is greatest on the sixth lag day. A study in Guangzhou found that rainfall is positively associated with HFMD incidence, but the relationship is weak (Chen et al., 2014). In addition, most studies have used a simple correlation analysis or spatial regression to explore the relationship between HFMD and rainfall based on weekly or monthly incidence counts (Jiang et al., 2016; Wang et al., 2016a, 2016b; Wang et al., 2015). These studies used different study designs and model specifications; thus, comparison of results across cities is limited. Laboratory results showed that the geographical distribution of human enterovirus strains in surface water is similar to that of enterovirus found in human fecal samples, and soil moisture content affects the activity and infectivity of the enterovirus; this finding suggests that the water cycle plays a role in HFMD incidence (Hsu et al., 2007; Ooi et al., 2002; Yeager and O'Brien, 1979). The specific correlation mechanism between rainfall and HFMD incidence requires further study. It is crucial to prevent water and food being contaminated by pathogens and viruses in rainy weather, and guide children to notice personal health and safe drinking. The present study found that an extremely high wind speed exerted certain protective effect and no stable relationship was found between extreme relative humidity and HFMD incidence, which were contradictory to previous findings (Lin et al., 2013; Qi et al., 2018; Yang et al., 2018). Studies conducted in Hefei and Shenzhen indicated that extremely high humidity values and wind speed can increase the risk of HFMD, which may be attributed to the conducive attachment of the virus on surfaces of various objects (e.g., toys) in a high-humidity environment and to the dissemination of particulates containing enteroviruses by wind (Wong et al., 2010). By contrast, studies in Huainan and Guangzhou found no association between HFMD incidence and wind speed and relative humidity (Huang et al., 2013; Zhao et al., 2017). This discrepancy may be attributed to the possible confounding effects caused by differences in socioeconomic and environmental factors (Xiao et al., 2017). The short research period and the collinearity problem between variables in this study may be other possible causes of such discrepancy.

In addition to the climatic factors, two air pollution indicators were included in the DLNM to explore their potential effects on HFMD incidence. To our best knowledge, this study is the first to explore the simultaneous impact of multiple climatic and air pollution indicators on HFMD incidence. Huang et al. found no significant correlation between PM_{10} and HFMD incidence and a certain relationship between PM_{10} and female HFMD cases in studies conducted in Ningbo (China) (Huang et al., 2016a, 2016b; Huang et al., 2018). However, the degree of air pollution varies between Guilin and Ningbo as the former is a tourist city with good air quality. The values for air pollution indicators are high during spring and will not affect individuals who frequent the outdoors. By contrast, the latter is an industrial city with no obvious seasonality for air pollution. Our study showed that $PM_{2.5}$ and O_3 remarkably influence HFMD incidence. An extremely low $PM_{2.5}$ level decreases the risk of HFMD, whereas a high $PM_{2.5}$ level exerts the opposite effect, though it is not significant. This $PM_{2.5}$-HFMD association may be explained by two mechanisms. First, enterovirus attached to ambient particles may be transported over long distances under favorable weather conditions (Cao et al., 2014; Chen et al., 2017b). Second, $PM_{2.5}$ can reduce the body's antioxidant capacity, mediate inflammatory reactions, and even cause mutations, thereby increasing the body's susceptibility to infectious diseases (Jaspers et al., 2005; Nel, 2005; Okada, 2014). Moreover, high concentration of ozone exerts a protective effect against HFMD. Although numerous lines of evidence have shown that ambient ozone causes adverse effects on certain chronic diseases (Karakatsani et al., 2017; Lanzinger et al., 2014), research on the relationship between ambient ozone and infectious diseases remains limited. Ambient ozone affects the progression of chronic diseases through oxidative stress or inflammatory reactions; by contrast, ozone affects infectious diseases possibly through its inhibitory effect on the ability of bacteria or viruses to survive or replicate in the external environment. An experimental study has found that exposure to ambient levels of ozone can alter the pathogenesis of respiratory infection after aerosol infection of mice with influenza A virus (Wolcott et al., 1982). EV-71 inactivation by ozone is related to the kinetics of ozone solubility, and appropriate ozone concentration restricts virus production, prolongs the survival time of cells, and suppresses cytokine production related to EV-71 infection (Lin and Wu, 2006; Lin et al., 2007). This result suggests that the combination of ambient ozone and suitable climate may affect the incidence of HFMD. Parents and caregivers should take necessary protective measures to reduce children's exposure to heavy air pollution.

The cumulative effects of extreme weather and air pollution are inclined to become significant on the third day after exposure and can last for two weeks or so, consistent with previous findings (Lin et al., 2013; Wu et al., 2014). Taking into account the average incubation period of HFMD of 3–5 days, the emergence of this trend is more consistent with biological rationality. The results of stratified analysis showed that male children and those aged 1–3 years (followed by children aged 0–1 years) are the most susceptible group to HFMD. This gender-related discrepancy in the effects of extreme conditions may be attributed to the differences in metabolism, physiology, and environmental exposure between males and females. Females usually have stronger congenital and adaptive immune responses and resistance against various infections than males (Bouman et al., 2005; Klein and Roberts, 2015). Children aged 0–1 years and 1–3 years are more affected by extreme climatic and air pollution factors, and this finding may be attributed to two reasons. First, children in these age groups usually have poor sanitation and are prone to contact food or toys contaminated with feces. The immune system of children at these ages is not yet well developed and is sensitive to changes in the external environment. In addition, in China, children aged 3–6 years generally begin to attend kindergarten school and come into contact with more susceptible children. The risk of infection thus increases accordingly. This pattern is possibly the reason why children in this age group also have high RR to specific extreme effects. As mentioned above, the policy makers should pay more attention to the sensitive group of children.

The present study has several limitations. First, passive surveillance data do not include all HFMD cases. Negative infections or cases with insignificant clinical symptoms may have been overlooked, leading to underestimation. The adoption of clinical diagnostic methods rather than laboratory diagnosis in most cases is another source of reported bias. Second, this study only analyzed data collected for 3 years. Data in specific age group were limited, and a certain degree of collinearity among the analysis variables was observed. Both factors reduce the stability of the model. Third, this study is essentially an ecological study that can only detect the association of climate and air pollution with HFMD incidence and cannot explore the possible pathogenesis from the perspectives of social economy, behaviors, and physiology.

Despite these limitations, the present study had two major strengths. First, this study, to our knowledge, is the first to incorporate multiple air pollution indicators into the examination of the effects on climate related HFMD incidence. Second, this study explored the association of climate and air pollution with HFMD incidence on different lag days and in different population subgroups, thereby deepening our understanding of extreme effects and identifying the vulnerable populations.

5. Conclusions

This study confirmed that meteorological and air pollution factors influence HFMD incidence. However, the specific effects can vary depending on gender and age. The extreme and delayed effects of mean temperature, precipitation, as well as $PM_{2.5}$ and O_3, are associated with HFMD incidence. Male children and those aged 0–3 years are more susceptible to extreme external conditions than the other subgroups. The present results are of substantial practical importance to local authorities for the formulation of targeted disease interventions and for the construction of environment-based early warning systems for diseases.

Conflict of interest

The authors declare no competing interests.

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Appendix A. Supplementary data

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