

Relationship between meteorological factors, air pollutants and hand, foot and mouth disease from 2014 to 2020

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Research Article

Keywords: Hand, foot, and mouth disease, Meteorological factors, Air pollutants, Vaccination, COVID-19

Posted Date: February 1st, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1202274/v1>

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Abstract

Background: Meteorological factors and air pollutants have been reported to be associated with hand, foot, and mouth disease (HFMD) epidemics before the introduction of vaccine. However, there is limited evidence from studies with long-term dimensions.

Methods: We collected the daily HFMD counts, weather and air pollution data from 2014 to 2020 in Chengdu. Distributed lag non-linear models (DLNM) were used to assess the associations of meteorological factors and air pollutants on HFMD cases.

Results: From 2014-2020, high relative humidity and precipitation and extremely high and low levels of PM₁₀, O₃, SO₂ and CO increased the risk of HFMD. In pre-vaccination period, extreme high and low temperatures, PM₁₀ and NO₂, low precipitation and high concentrations of PM_{2.5} and O₃ significantly increase the risk of HFMD; In post-vaccination period, low temperature and high relative humidity, O₃, NO₂ and CO can significantly increase the incidence of HFMD; During the period of COVID-19, only low temperature will significantly increase the risk of HFMD; Low concentration of air pollutants has the greatest impact on the 6-14 age group, while the high concentration of air pollutants has the greatest impact on the 0-1 age group.

Conclusions: Our study suggest that high relative humidity and precipitation and extremely high and low levels of PM₁₀, O₃, SO₂ and CO increased the risk of HFMD from 2014 to 2020. The results of this study provide a reference for local authorities to formulate intervention measures and establish an environment-based disease early warning system.

1. Introduction

Hand food and mouth disease (HFMD) poses a substantial burden to health in mainland China and there is no specific treatment for it. During 2013 to 2016 prior to the introduction of Enterovirus 71 (EV71) vaccine, the incidence and mortality of HFMD have been leading the type C notifiable infectious diseases, affecting an average of more than 2.2 million children every year in China (<http://www.nhc.gov.cn/>). Three inactivated monovalent EV71 vaccines had been licensed in China in 2016, the efficacy against EV71-associated HFMD reached 98.8%. Nevertheless, there is no consensus on the cross-protection of vaccines against non-EV71-associated HFMD [1-4]. Although vaccination has been promoted on a large scale after 2016, the average number of reported cases of HFMD in China still remains high during the period from 2017 to 2019, about 2 million per year, dominated by coxsackievirus A16 (CVA16), coxsackievirus A6 (CVA6) and coxsackievirus A10 (CVA10) (<http://www.nhc.gov.cn/>). Whereas the pandemic of Coronavirus disease 2019 (COVID-19) further complicates the situation. During the pandemic, the incidence of most notifiable infectious diseases in China showed a downward trend, including HFMD [5-7].

Environmental factors, such as temperature, relative humidity, wind speed, precipitation, and air pollutants, have been reported to play an important role in the transmission of HFMD before the introduction of vaccine [8-11]. Climatic factors have been recognized to have effects on the reproduction of the virus, while pollutants are thought to affect the susceptibility of individuals resulting in increased number of HFMD cases [11-13]. A role for vaccination in these associations was hypothesized in previous study, which speculate that the human defense mechanism may regard some particles as a virus, and virus vaccination may have a beneficial effect on these particles [14]. Several epidemiological studies have also demonstrated that vaccine might modify the adverse effects of pollutants on some disease [14, 15]. In addition, due to COVID-19, governments have imposed restrictions on the movement of people, vehicles, and suspended industrial activities, resulting in a significant reduction in pollution levels [16]. Accordingly, we postulated that the relationship between environment factors and HFMD may be different in post-vaccination and COVID-19 epidemic periods. The evidence of the positive association between HFMD and environment factors have been cumulated these years. However, the relationship between environmental factors and HFMD after the introduction of vaccine subject to further proved. Therefore, we analyzed the incidence of HFMD and environmental factors from 2014-2020.

2. Material And Methods

2.1 Study area

Chengdu is the capital city of Sichuan, located in the Sichuan Basin in Southwest China, has a subtropical monsoon humid climate. The geographical location is between 102°54' – 104°53' E and 30°05' – 31°26' N.

2.2 Data sources

We retrieved the daily counts of HFMD cases from the infectious disease surveillance systems of Chengdu Disease Control and Prevention Center (CDC) from January 1, 2014 to December 31, 2020. Considering that the vast majority of HFMD cases involve children, this study only includes patients below 15 years old, which account for 99.32% of the total number of cases. The number of people vaccinated for each dose of EV71 vaccine in Chengdu were extracted from the Chengdu Immunization Planning Information Management System at the Chengdu CDC. And we collected daily data of meteorological data, including temperature, relative humidity, wind speed and precipitation and air pollution indicators, namely, PM_{2.5}, PM₁₀, O₃, SO₂, CO and NO₂ from the publicly accessible China National Weather Data Sharing System and the Sichuan Environmental Monitoring Center, respectively.

2.3 Statistical analyses

According to previous studies[13, 17, 18], we used a quasi-Poisson regression model combined with distributed lag nonlinear models (DLNM) to estimate the effects of meteorological factors and air pollutants on HFMD incidence according to the basis of data distribution and the relationship between variables.

$$Y_t = \alpha + NS(X; df; lag; df) + NS(\text{Time}; df) + \sum NS(X_i) + \beta DOW_t \quad \text{--- [13]}$$

where α is an intercept and Y_t refers to the daily counts of HFMD cases onset on day t ; NS reference a natural cubic spline modeling the nonlinear lagged relationship between meteorological factors or air pollutants and HFMD incidence; X is the examined meteorological or air pollution variables that we want to research; X_i represents the several other meteorological and air pollution variables that should be controlled due to their modifying effect on HFMD incidence [13].

In this model, degrees of freedom (df) was 4 for mean temperature, relative humidity, wind speed, precipitation, SO_2 , $PM_{2.5}$, PM_{10} , NO_2 , CO and O_3 , as well as lag spaces with 3 df based on the Akaike information criterion for quasi-Poisson (Q-AIC); Accordingly, the maximum lag days were set to 14 according to the incubation period and previous studies [13, 19]. Time is the indicator variable used to control long-term trends and seasonality; and DOW stands for day of week. We set $df=7$ for time variable because 7 per year has been justified as a balance between providing adequate control for seasonality and other confounding by trends in time, while leaving sufficient information from which to estimate exposure effects [20]. In this study, the effects of extreme meteorological factors and air pollutants on HFMD were examined and presented as relative risk (RR) by comparing 5th and 95th percentiles with their median values.

Subgroup analysis was conducted by gender (male and female) and age group ($\leq 1y$, 2–3y, 4–5y, 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.

3. Result

3.1. Summary statistics for HFMD cases, meteorological factors, and air pollutants

A total of 315,441 HFMD cases were included in our study, including 182,331 of males and 133,110 of females, and the male-to-female ratio is 1.37:1. Table.1 presents the daily average number of HFMD cases was 125 from January 2014 to December 2020. The peak age of HFMD is 2-3 years old, the daily average number of cases was 65 and the maximum number was 410. Of the three time periods (Table.S1-3), pre-vaccination period had the highest average incidence of 141 cases per day and the maximum number of HFMD cases is up to 784. After the introduction of the vaccine, an average of 475 people were given the first dose every day, and 401 people received the second dose.

From 2014 to 2020, the average values of temperature, relative humidity, wind speed, precipitation, $PM_{2.5}$, PM_{10} , O_3 , NO_2 , SO_2 and CO were 18.14°C, 3.74m/s, 75.45%, 2.89mm, 60.27 $\mu\text{g}/\text{m}^3$, 91.92 $\mu\text{g}/\text{m}^3$, 74.10 $\mu\text{g}/\text{m}^3$, 51.47 $\mu\text{g}/\text{m}^3$, 10.88 $\mu\text{g}/\text{m}^3$ and 0.89 mg/m^3 , respectively. Of the three time periods, the average value of air pollutants was the largest in 2014-2016, climate factors except relative humidity was the largest in 2020 and the average value of relative humidity was the largest in 2017-2019 (Table.2).

3.2. Time series analysis for HFMD cases, meteorological factors, and air pollutants

The time-series analysis illustrates the trends in daily HFMD cases and environmental factors from 2014 to 2020. We observed a significant seasonal variation for total cases, temperature, precipitation, PM_{2.5}, PM₁₀ and O₃ from Fig. 1. Two significant peak was observed during late spring and early summer (from May to July) and late autumn and early winter (from October to December) except 2018 and 2020.

3.3. Distributed lag non-linear models

We use the overall picture to visualize the effect for different meteorological and air pollutants variables at different lag days. All 3-D graph of the relative risk (RR) compared with their median value.

See as Fig. 2, from 2014-2020, there was a non-linear association between meteorological factors and HFMD incidence. The effect of temperature on HFMD reached its maximum at 32 °C at lag 0 days and the association between wind speed and HFMD have a different lag structure. The number of HFMD cases increased with the increase of relative humidity. The relationship between precipitation and HFMD was strongest at 70-80mm, then gradually decreased and reached the lowest value at 150mm. Similarly, we found that the effects of different air pollutants on HFMD varied with the lag days and pollutant concentrations, as shown in the Fig. 3. In addition, The 3D plot of the pre-vaccination, post-vaccination and COVID-19 period showed that the lag structure of environmental factors and HFMD in different periods was different. (see Fig. S1-6).

Different climatic variables and pollutants exerted varied extreme effects on HFMD. It is worth noting that the lag structure of the overall analysis results from 2014 to 2020 shows differences from the three periods, as shown in Table.S4 and Figures S7-10.

From 2014 to 2020, high relative humidity and precipitation will increase the risk of HFMD among the meteorological factors, and the cumulative effect was 1.63 (95%CI: 1.39-1.91) and 1.05 (95%CI: 0.84-1.29), respectively. The rest of the studied meteorological factors showed a protective effect, but this protective effect was only statistically significant at low wind speed and relative humidity. Among air pollutants, extreme levels of PM₁₀, O₃, SO₂ and CO will significantly increase the risk of HFMD, extremely high concentration of PM_{2.5} will significantly increase the incidence of HFMD after lag 6 days, but the cumulative RR is not statistically significant. In addition, we also observed that low level of NO₂ had a protective effect against HFMD, but this protective effect became weaker as the lag days increased.

In pre-vaccination period (Fig.S7), extremely high and low temperature and low precipitation can significantly increase the risk of HFMD, the cumulative effect was 5.19 (95%CI: 3.37-8.10), 1.90 (95%CI: 1.42-2.56) and 1.15 (95%CI: 1.04-1.27), respectively (Table.S4). Low wind speed and relative humidity and high precipitation played a protective role in HFMD incidence and the cumulative effects were 0.63 (95%CI: 0.51-0.77), 0.59 (95%CI: 0.48-0.73) and 0.64 (95%CI: 0.46-0.88), respectively. We found that extremely high concentrations of all air pollutants increased the incidence of HFMD. In addition,

extremely high concentrations of $PM_{2.5}$, PM_{10} , O_3 and NO_2 are significantly associated with the incidence of HFMD and the overall estimated RR was 2.00(95%CI: 1.51-2.64), 2.61 (95%CI: 2.09-3.26), 1.54 (95%CI: 1.23-1.94) and 1.63 (95%CI: 1.20-2.21), respectively. Low levels of PM_{10} and NO_2 will also significantly increase the incidence of HFMD while other air pollutants at low concentrations showed protective effects.

In post-vaccination period, low temperatures, high relative humidity and high concentration of O_3 , NO_2 and CO will increase the risk of HFMD. Low wind speed and relative humidity and high temperature showed protective effect to HFMD and the cumulative effect was 0.41 (95%CI: 0.29-0.57), 0.09 (95%CI: 0.05-0.15) and 0.42 (95%CI: 0.25-0.71), respectively. In COVID-19 period, low temperature and high concentration of $PM_{2.5}$ will increase the incidence of HFMD. Wind speed, $PM_{2.5}$, PM_{10} , NO_2 , O_3 and CO at low level will significantly reduce the risk of HFMD.

Subgroup analysis was conducted to examine the potential effect in terms of gender and age. Consistent with the main analysis, similar associations were observed in both male and female subgroups (Fig.S13). But difference associations were obvious in different age groups (Fig.S11-12). See as Table.S5, we found that the cumulative effect of O_3 and NO_2 are greatest in children aged 0-1 years old at both extremely low and high concentrations. The effects of low concentrations of SO_2 , PM_{10} and CO on children aged 6-14 were greater than those of other age groups. Low concentration of $PM_{2.5}$ only had a significant effect on the age group of 6-14 years old, and its cumulative RR was 1.82 (95%CI: 1.56-2.13) while the effect of high concentration of $PM_{2.5}$ on all age groups was not statistically significant. Overall, in addition to high relative humidity and rainfall, the rest of the meteorological factors have a protective effect to the risk of HFMD for all age groups.

The results obtained were similar to those obtained in sensitivity analyses, which were conducted by adding vaccination population to the model.

4. Discussion

In this study, We applied the distributed lag nonlinear model (DLNM) to explore the relationship between climate, air pollution and HFMD incidence in terms of variables and lag days. The results suggest that high relative humidity, high precipitation and extremely high and low levels of PM_{10} , O_3 , SO_2 and CO will increase the risk of HFMD from 2014 to 2020. And high concentration of air pollutants has the greatest impact on 0-1-year-old children.

In the overall analysis we don't find an association between extremely level of temperature and HFMD. The relationship between temperature and HFMD before the introduction of EV71 vaccine has been explored by many studies and they agreed that temperature changed the incidence of HFMD by affecting the survival and transmission of pathogen as well as human activities and behaviors [21-23]. A study in Guilin [13] found that an extremely low wind speed exerted certain protective effect which were consistent with our research in pre-vaccination period and overall analysis. But study conducted in Hefei indicated that wind speed can increase the risk of HFMD while Huang et. al [24] found no statistically significant

association between wind speed and HFMD. This discrepancy may be attributed to the possible confounding effects caused by geographic and socioeconomic distribution. In analyses before vaccination and throughout the study period, we found that high relative humidity increased the incidence of HFMD, but this effect was not statistically significant. Numbers of previous studies have found this effect to be meaningful [25-27]. On the one hand, under the condition of high relative humidity, HFMD-related pathogens may be able to thrive depending on humidity, resulting in longer survival times, and have stronger infectiousness [28]. On the other hand, high relative humidity can also limit sweating and then affect the metabolism of children [27]. The correlation between rainfall and HFMD was not found in the overall analysis which is consistent with a study in Huainan [29], but low rainfall before vaccination would increase the risk of HFMD which were contradictory to previous findings [9, 30-32]. But our results in pre-vaccination period is still interpretable. On the one hand, low precipitation increases host outdoor activity and effective contacts between susceptible and infectious individuals, which may subsequently promote the spread of HFMD infection [30]. moreover, unlike temperature and humidity, rainfall's values at most days were zero, which could further cause the estimation of exposure-response relationship to progress toward a null value, therefore, different reference values will lead to changes in the impact of precipitation.

Our study found that almost all air pollutants are associated with the risk of HFMD, especially at an extremely high concentration from 2014-2020. Study results show PM₁₀ increases risk of HFMD while PM_{2.5} is not associated with the development of HFMD, which was supported by many studies [13, 19, 33, 34]. The mechanism to explain this relationship between PM₁₀ and HFMD is that HFMD is mainly spreads through fecal-oral transmission or through close contact and exposure to air pollution makes children more vulnerable to intestinal infections by hand contact. Thus, HFMD viruses attached to ambient particles may be transported over long distances under favorable weather condition [12, 13]. Gu et al [15]. found that both moderate and high concentrations of ozone increased the risk of HFMD, and we found that high and low concentration of ozone increased the risk of HFMD from 2014-2020. However, Yu et al [13]. found that high concentration of O₃ has a certain protective effect on foot and mouth disease. Thus, we need more research to explore the real relationship between them. Studies in Shenzhen and Ningbo found a significant association between NO₂ and the incidence of HFMD [15, 35] which demonstrated the reliable of our result in pre-vaccination. The possible mechanism is as follows: NO₂ dissolves in water on the surface of the digestive tract and forms acidic substances, which can induce inflammation of the digestive tract mucosa through physical and chemical interactions and weaken immunity and increase the risk of enterovirus infection [36]. We find a significant association between SO₂ and HFMD from 2014-2020 which supposed by a study in Hefei found that SO₂ increases the risk of HFMD [11, 37]. Our overall analysis suggests that CO increased the risk of HFMD, but studies on CO and HFMD are limited. Yan et al. found a positive effect of CO but insignificant [35]. Although there is no evidence prove that CO is related to the incidence of HFMD, the effect of health is well known. A number of studies demonstrated that chronic CO exposure appears to impart adverse health effects, especially with cardiovascular events [38].

We found that low temperatures, high relative humidity, and high concentrations of O₃, NO₂ and CO have adverse effect on HFMD in post-vaccination period. This suggests that even after vaccination, we should pay attention to living hygiene especially toy and hand hygiene, under adverse weather conditions. The independent effects of air pollution and influenza vaccination on childhood HFMD have been extensively investigated, but no study have investigated potential effect modification by vaccination for the relationship between environmental factors and HFMD. A case-crossover study conducted in Taiwan, China [14] and Liu et al [15]. demonstrated that vaccine might modify the adverse effects of pollutants on some disease. Although the previous studies have different study designs, participant' characteristics, vaccine types, and health outcomes with our study, they provide indirect support for our findings that vaccine might modify the adverse effects of environmental factors on HFMD. It should be mentioned that we include the number of vaccinations in the sensitivity analysis to consider the effect of collinearity between vaccination and environmental factors. The results suggest that this effect has little effect on the results, which further proves the reliability of our results. Overall, our findings provided the new evidence on supporting the increase in vaccine use for HFMD in Chinese children and adolescents who expose to ambient air pollution.

During the COVID-19 epidemic period, the number of HFMD cases in Chengdu decreased significantly, and the impact of environmental factors on the incidence was not significant. Aside from suspending classes, the government, also took other measures such as closing management in the community, isolating at home and closing all kinds of leisure places, which may reduce contact and airborne diseases [7, 39]. In addition, extremely weather factors and air pollutants have no significant impact on HFMD because of the lack of outdoor activities. It is worth noting that although our results show that there is a correlation between the incidence of HFMD during COVID-19 's period, due to the broad confidence interval and limited sample size, this findings should be interpreted with caution.

In conclusion, our study can only demonstrated that the relationship between HFMD and environmental factors after the introduction of vaccine and COVID-19 epidemic is different from that before vaccine introduction. But whether the relationship was altered by the vaccine and COVID-19 needs to be confirmed by more studies.

The results of stratified analysis showed that Children aged 0–1 years is more affected by high relative humidity due to their immune system is not yet well developed. In addition, the low concentration of air pollutants has the greatest impact on the 6-14 age group, while the high concentration of air pollutants has the greatest impact on the 0-1 age group. Since the age group is analyzed from the overall data, the impact of low concentrations of air pollutants on the 6-14 age group may be attributed to a lack of vaccine protection and more outdoor activities to increase the risk of infection. High concentrations of air pollutants are more likely to attack young children with immature immune mechanisms, thus increasing the risk of the disease. As mentioned above, the goverment should pay more attention to the sensitive group of children when making policies.

There are several limitations to this study. First, cases of negative infection or asymptomatic symptoms may not be included in passive surveillance data, leading to an underestimate of the impact. Second, this study is essentially an ecological study and ecological fallacies are inevitable.

5. Conclusion

High relative humidity, high precipitation and extremely levels of PM₁₀, O₃, SO₂ and CO will increase the risk of HFMD from 2014-2020 and this relationship are different among different ages. The relationship between environmental factors and HFMD after vaccine introduction and during the COVID-19 epidemic was different from that before vaccine introduction. The results of this study provide a reference for local authorities to formulate intervention measures and establish an environment-based disease early warning system.

Abbreviations

HFMD

hand foot and mouth disease

COVID-19

coronavirus disease 2019

DLNM

distributed lag non-linear models

EV71

enterovirus 71

CVA16

coxsackievirus A16

CVA6

coxsackievirus A6

CVA10

coxsackievirus A10

CDC

Disease Control and Prevention Center.

Declarations

Statement

We confirm that all methods were carried out in accordance with relevant guidelines and regulations.

Ethics approval and consent to participate

The database of environment factors is open. The hand foot and mouth disease data used in this study are from the Chengdu disease control and prevention, who granted the permission. All individual

information used in this study were anonymized before its use, which does not involve ethics approval and consent to participate.

Consent for publication

Not applicable

Availability of data and materials

Daily meteorological data can download from the publicly accessible China National Weather Data Sharing System (<http://data.cma.cn/site/index.html>). Daily data of air pollutants were collected from the Sichuan Environmental Monitoring Center (<http://sthjt.sc.gov.cn/>). The datasets of incidence of HFMD generated during and analyzed during the current study are not publicly available due to restrictions apply to the availability of these data but are available from the corresponding author on reasonable request.

Conflict of interest

The authors declared no competing interest.

Funding

This research was supported by grants from National Natural Science Foundation of China Young Scientists Fund (Grant No. 81903375), General Program of China Postdoctoral Science Foundation (Grant No. 2018M643509) and Technology Innovation R&D Project of Chengdu Science and Technology Bureau (Grant No. 2019-YF05-01080-SN).

Author Contributions Statement

All authors contributed to the conception and design of the research. HX Peng, ZH Chen and J Liao implemented the data analysis, interpreted the results and drafted this manuscript. L Long provided critical revision of the manuscript for important intellectual content. K Zheng and S Li did the preliminary analysis. XL Ren collated the results. XX Duan, XQ Tang, X Wang and CX Yang revised the manuscript. All authors read and approved the final manuscript.

Acknowledgements

Not applicable

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Tables

Table.1: Description of HFMD cases and Vaccination number in Chengdu from 2014 to 2020.

			Mean±SD	Min	P25	Median	P75	Max
Cases	Total		125±112	1	48	104	165	780
	Gender	female	53±47	1	20	44	71	337
		male	73±65	1	28	61	96	452
	Age	≤1	33±37	1	13	24	38	291
		2-3	65±56	1	26	55	65	410
		4-5	24±20	1	8	19	35	145
		6-14	7±7	1	2	5	10	49
		≥15	2±2	1	1	1	2	14
	Year	2014-2016	124±74	8	60	121	174	392
		2017-2019	141±139	2	54	105	158	780
2020		74±96	1	3	23	104	359	
vaccination	Dose	1	475±427	1	70	415	856	1464
		2	401±371	0	58	211	739	1291

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

Table2:Description of environmental factors in Chengdu from 2014 to 2020

Variables	Mean±SD	Min	P25	Median	P75	Max
temperature (°C)	18.14±7.28	1.39	11.39	18.89	24.44	32.33
Wind speed (m/s)	3.74±1.58	0.98	3.00	3.00	4.16	15.02
Relative humidity (%)	75.45±11.35	28.11	67.80	75.95	84.15	99.87
Precipitation (mm)	2.89±10.59	0	0	0	1.02	188.47
PM _{2.5} (ug/m ³)	60.27±40.52	3.60	35.50	48.09	72.93	371.21
PM ₁₀ (ug/m ³)	91.92±63.08	8.64	47.52	75.20	117.63	555.45
O ₃ (ug/m ³)	74.10±39.30	1.86	42.55	68.50	111.12	178.48
NO ₂ (ug/m ³)	51.47±20.75	2.07	37.12	49.28	64.44	126.49
SO ₂ (ug/m ³)	10.88±9.18	0	5.46	7.71	13.56	76.42
C0(mg/m ³)	0.89±0.42	0	0.61	0.81	1.07	2.90

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

Figures

Figure 1

Time-series results of HFMD incidence and environmental factors in Chengdu from 2014 to 2020. WS: wind speed; RH: relative humidity

Figure 2

3-D plot of RR along meteorological variables and lags from 2014-2020.

Figure 3

3-D plot of RR along air pollutants and lags from 2014-2020.

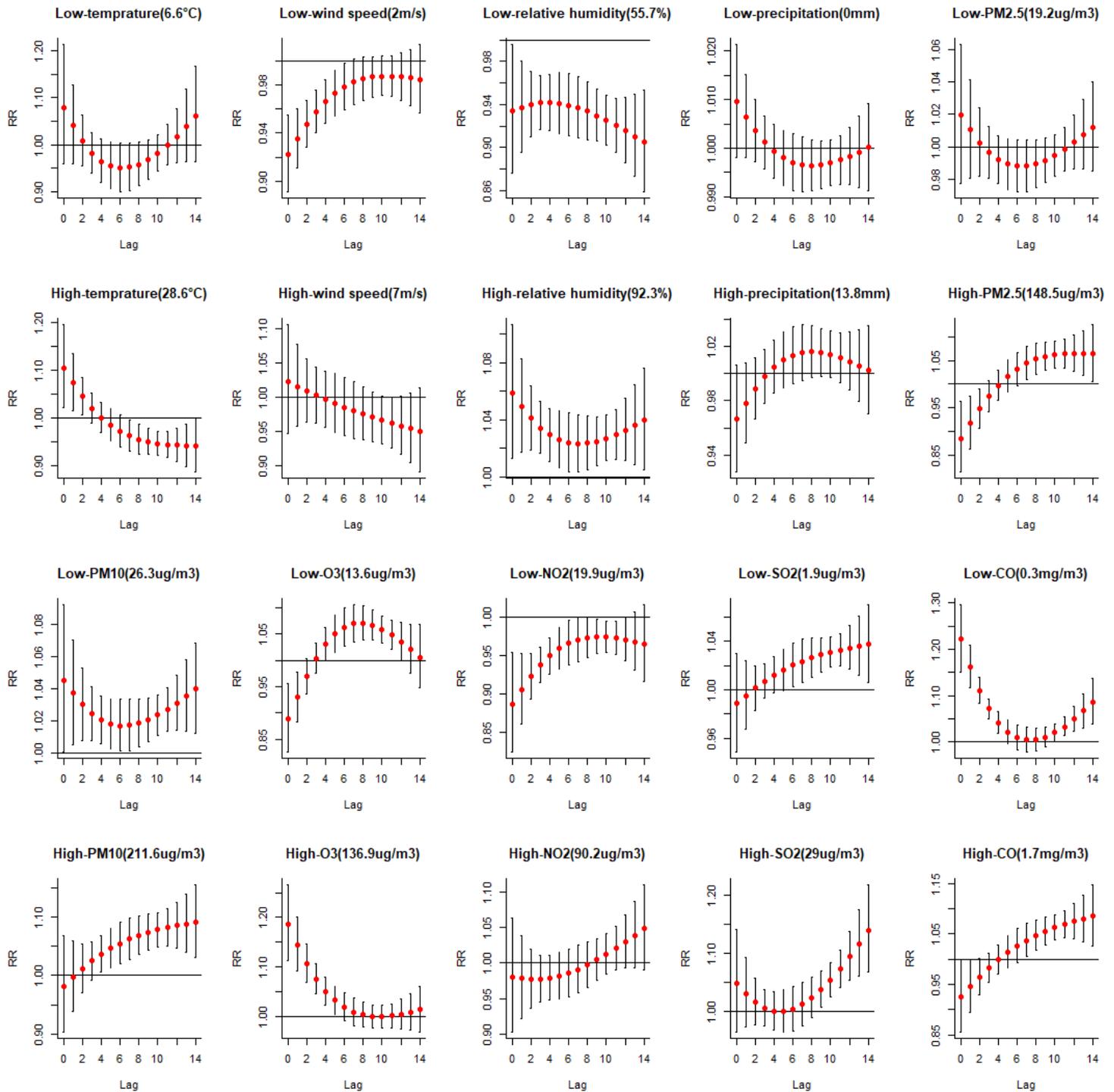


Figure 4

Extreme meteorological and pollutants variables with HFMD incidence from 2014-2020.

Supplementary Files

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