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The influence of temperature and humidity on the incidence of hand, foot, and mouth disease in Japan

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ABSTRACT

Background: The increasing evidence for rapid global climate change has highlighted the need for investigations examining the relationship between weather variability and infectious diseases. However, the impact of weather fluctuations on hand, foot, and mouth disease (HFMD), which primarily affects children, is not well understood.

Methods: We acquired data related to cases of HFMD and weather parameters of temperature and humidity in Fukuoka, Japan between 2000 and 2010, and used time-series analyses to assess the possible relationship of weather variability with pediatric HFMD cases, adjusting for seasonal and interannual variations.

Results: Our analysis revealed that the weekly number of HFMD cases increased by 11.2% (95% CI: 3.2–19.8) for every 1 °C increase in average temperature and by 4.7% (95% CI: 2.4–7.2) for every 1% increase in relative humidity. Notably, the effects of temperature and humidity on HFMD infection were most significant in children under the age of 10 years.

Conclusions: Our study provides quantitative evidence that the number of HFMD cases increased significantly with increasing average temperature and relative humidity, and suggests that preventive measures for limiting the spread of HFMD, particularly in younger children, should be considered during extended periods of high temperature and humidity.

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1. Introduction

Hand, foot, and mouth disease (HFMD) is a common viral infection whose main clinical symptoms include fever, mouth ulcers, and vesicles on the hands, feet, and mouth. Although the infection occurs most frequently in children, adolescents and occasionally adults can also acquire HFMD. In most cases, the disease is mild and self-limiting, but more severe clinical symptoms, including neurological abnormalities such as meningitis, encephalitis, and polio-like paralysis, may occur. HFMD is most frequently caused by coxsackievirus A16 (CA16) and enterovirus 71 (EV71) (Melnick, 1996; Tunnessen, 1992; Chen et al., 2007); however, EV71 is more commonly linked with severe symptoms, including central nervous system disorders, and even fatality resulting from pulmonary edema in a small proportion of children, particularly those aged 5 years and younger (Cohen, 1998).

The incidence of HFMD has been reported to exhibit seasonal variation in a number of different areas. For example, a bimodal seasonal pattern has been detected in the United Kingdom, which is characterized by peaks in HFMD incidence in the summer and late autumn/early winter (Bendig and Fleming, 1996). In Belgium, HFMD infections are typically present throughout the year, showing small peaks in summer and autumn (Druyts-Voets, 1997), while the incidence of HFMD is highest in summer in Taiwan (Chen et al., 2007). In Hong Kong, it has been suggested that the changing epidemiology (an occurrence of winter peak) was due to increase in winter temperature (Ma et al., 2010a). The incidence frequency also appears to be influenced by the infectious agent. For example, when CA16 was the predominant circulating enterovirus in Singapore, a single epidemic peak was observed, whereas two peaks were detected in other epidemic years (Ang et al., 2009). In Malaysia, outbreaks occurred in a cyclical pattern every 3 years involving the co-circulation of CA16 and EV71, with sporadic increases in activity observed between large outbreaks (Podin et al., 2006). The observed seasonality of HFMD suggests that its incidence may be influenced by weather factors and indicates the existence of multiple functional pathways leading to infection and subsequent outbreaks. Despite this speculation, the impact of weather variability on the incidence of HFMD with adjustment for the mutual confounding between weather and other seasonal factors has only been investigated in a limited number of studies.

Abbreviations: CA16, coxsackievirus A16; CI, confidence interval; EV71, enterovirus 71; HFMD, hand, foot, and mouth disease; RR, relative risk.

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Here, we examined the possible relationship of temperature and humidity variability with the incidence of pediatric HFMD cases using surveillance data collected in Fukuoka, Japan, from 2000 to 2010.

2. Methods

2.1. Data sources

In Fukuoka Prefecture, which is located in the southwest of Japan, the number of HFMD patients is reported on a weekly basis from 120 sentinel medical institutions (Onozuka et al., 2010). HFMD was defined by clinical factors, which included vesicular lesions on hands, feet, mouth (which were often ulcerated), and, frequently, buttocks, in accordance with the Act on Prevention of Infectious Diseases and Medical Care for Patients Suffering Infectious Diseases (Ministry of Health, Labour and Welfare, 2011). We obtained clinical data that were recorded and reported by sentinel volunteers to the Fukuoka Institute of Health and Environmental Sciences, the municipal public health institute of the Fukuoka Prefectural Government. In addition, we also obtained data on daily average temperature and relative humidity in Fukuoka Prefecture from the Japan Meteorological Agency. Weekly means for temperature and relative humidity were calculated from the daily records.

2.2. Statistical analysis

We examined the relationship between the number of weekly HFMD cases and temperature and humidity using negative binomial regression to account for over-dispersion in the data (McCullagh and Nelder, 1989). To account for the seasonality of HFMD cases that were not directly due to the weather, the model included Fourier terms up to the sixth harmonic. Fourier terms can be used to re-create any periodic signal, such as a consistent seasonal pattern, using a linear combination of sine and cosine waves of varying wavelength (Stolwijk et al., 1999). The number of harmonics defines the lowest wavelength reproduced (i.e., the level of seasonal adjustment), with six harmonics corresponding to a wavelength of 9 weeks (one-sixth of a year). Indicator variables for the years of the study were incorporated into the model to allow for long-term trends and interannual variations. Rainfall was also initially considered, but as no evidence of an association with the number of cases was detected ($p>0.1$), it was not included in the final analysis. To allow for autocorrelations, an autoregressive term of order one was incorporated into the models (Brumback et al., 2000). Plots of model residuals, predicted and observed time-series plots, and the partial autocorrelation function of the residuals (Supplementary Data, Fig. S1) suggested that this was an adequate adjustment for seasonal trends.

Based on the results of exploratory analyses with the lowest deviance of the above-described models, we considered lags (delays in effect) of up to 3 weeks when analyzing the influence of temperature and humidity on the number of HFMD cases. In initial analyses designed to identify the broad shape of any association, we fitted a natural cubic spline (3 *df*) (Durrleman and Simon, 1989) to the average temperature and humidity over lags of 0 to 3 weeks. We then fitted the data to linear models to quantify the change in disease risk associated with the change in each weather variable. The choice of model (i.e., linear or threshold) (Armstrong, 2006) was based on our comparison of deviance among the models derived from likelihood ratio tests (Daniels et al., 2000); models with lower deviance

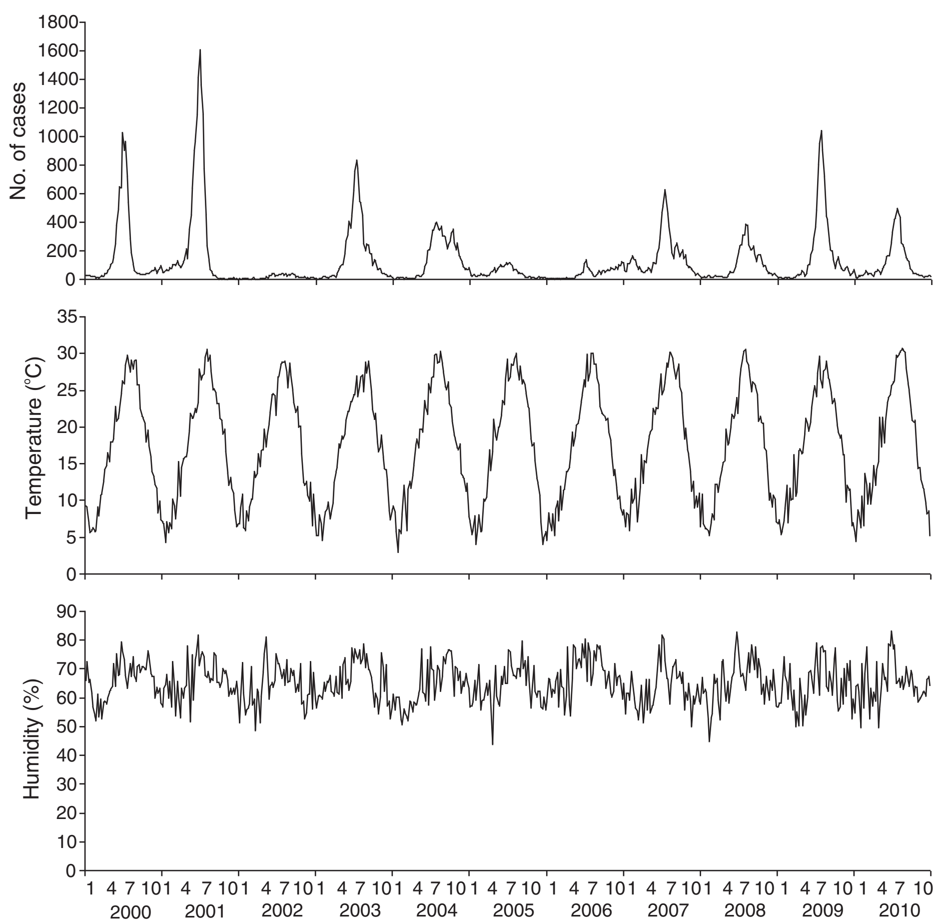

Fig. 1. Seasonal variation in the weekly number of HFMD cases by temperature and relative humidity in Fukuoka, Japan, between 2000 and 2010.

are preferred. When a difference in the values of deviance between the linear and best-fit threshold models was less than 3.84 (chi square value for one degree of freedom at the $P = 0.05$ level), the linear model was selected for simplicity. The observed values of deviances suggested that the deviance between the linear and threshold models changed little; thus, we assumed that linear models without a threshold were appropriate for assessing the associations between weather variability and the incidence of HFMD cases. In addition, to investigate which population sectors are likely to be most affected by HFMD, we also conducted the analyses for separate age groups (0–4, 5–9, 10–14, and over 15 years of age) using the identical methods.

We also examined weather-morbidity curves and lag effects in more detail using distributed lag non-linear models (Gasparrini et al., 2010). Distributed lag non-linear models that were fit to the morbidity data with a 3-df natural cubic spline for the weather-morbidity and coefficient-lag curves are illustrated in Figs. 4 and 5. As a sensitivity analysis, the weather-morbidity relationships were also estimated using different degrees of seasonal control (3rd and 12th harmonics). All statistical analyses were conducted using Stata 11.1 (Stata Corp., College Station, TX, USA) and R statistical software, version 2.12.2 (R Development Core Team, 2011) using the dlnm package, version 1.3.1 (Gasparrini et al., 2010).

3. Results

A total of 73,684 (100%) HFMD cases from 2000 to 2010 were included in our analyses, of which 61,736 (83.8%) were in children aged 0–4 years, 10,815 (14.7%) in those aged 5–9 years, 619 (0.8%) in those aged 10–14 years, and 514 (0.7%) in those aged over 15 years. Descriptive statistics for the number of patients based on age and weather variables are summarized in Table 1. From the analysis of the weekly reported number of HFMD cases, the seasonal peak in cases was found to differ from year to year, although it typically occurred during the summer months (Fig. 1). The 10-year data were then analyzed to identify relationships between the incidence of HFMD and temperature and humidity.

The relationship between the relative risk (RR) of HFMD and temperature is shown in Fig. 2. Analysis of the crude relationship revealed that the potential risk of HFMD increased as the temperature increased from the lowest recorded temperature level (Supplementary Data, Fig. S2). After adjusting for seasonal, inter-year, and humidity variations, it was confirmed that a significant increase in the risk of HFMD was associated with an increase in temperature. Notably, the

Table 1
Characteristics of the weekly number of HFMD cases by age and meteorological data in Fukuoka, Japan, between 2000 and 2010.

Characteristics	Data
No. of weeks	572
No. of HFMD cases	
No. (%)	
0–4 years	61,736 (83.8)
5–9 years	10,815 (14.7)
10–14 years	619 (0.8)
> 15 years	514 (0.7)
Mean no. of cases per week	
Mean (5th to 95th percentile)	
0–4 years	107.9 (4–441)
5–9 years	18.9 (0–92)
10–14 years	1.1 (0–5)
> 15 years	0.9 (0–4)
Weekly mean temperature (°C)	
Mean (5th to 95th percentile)	17.4 (6.0–29.1)
Weekly mean humidity (%)	
Mean (5th to 95th percentile)	65.1 (53.4–77.3)

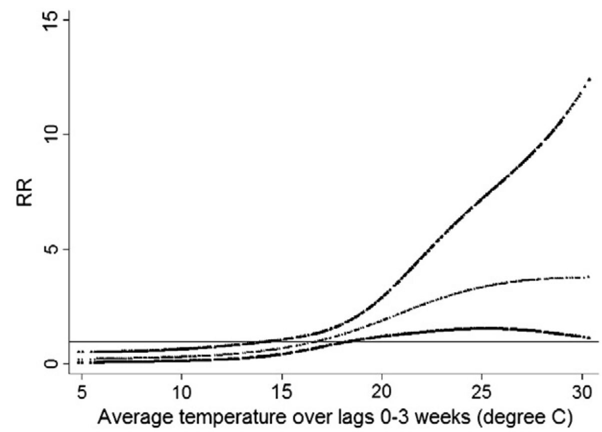

Fig. 2. Relationship between relative risk (RR) of HFMD scaled to mean weekly number of cases and temperature over lags of 0 to 3 weeks. The relationship was adjusted for relative humidity, seasonal variations, and inter-year variations. The center line in the graph shows the estimated spline curve, and the upper and lower lines represent the 95% confidence limits.

time between the temperature increase and the occurrence of HFMD involved lag periods between 0 and 3 weeks, as indicated by the positive linear slope with increasing temperature (Fig. 2). Our analysis revealed that an increase of 1 °C in the mean weekly temperature resulted in an increase in the number of HFMD cases for all age groups by 11.2% (95% CI: 3.2–19.8), and by 12.1% (95% CI: 3.9–20.8) in those aged 0–4 years, 9.6% (95% CI: 0.0–20.1) in those aged 5–9 years, 12.7% (95% CI: −3.3 to 31.2) in those aged 10–14 years, and 16.5% (95% CI: −2.2 to 38.8) in those aged over 15 years.

We also examined the relationship between the RR of HFMD and humidity (Fig. 3). In the analysis of the crude relationship, the potential risk of HFMD tended to increase with increasing relative humidity (Supplementary Data, Fig. S3). However, following adjustment for seasonal and inter-year variations, a significant increase was observed in the number of HFMD cases with increasing relative humidity, with lag periods between 0 and 3 weeks, as indicated by the positive linear slope with high humidity (Fig. 3). For each 1% increase in humidity, the number of HFMD cases increased by 4.7% (95% CI: 2.4–7.2) for all age groups, and by 4.7% (95% CI: 2.3–7.1) in those aged 0–4 years, 5.5% (95% CI: 2.8–8.3) in those aged 5–9 years, 3.1%

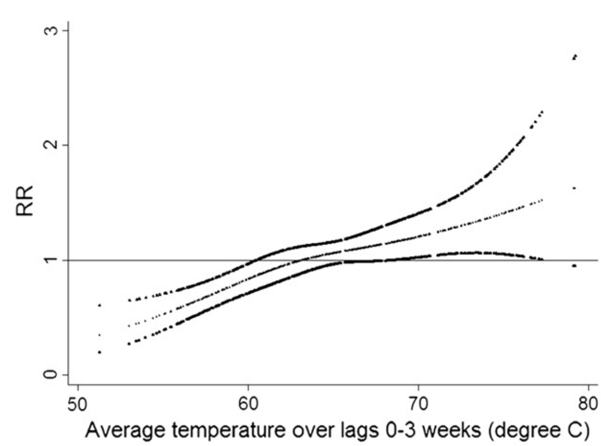

Fig. 3. Relationship between relative risk (RR) of HFMD scaled to the mean weekly number of HFMD cases and relative humidity over lags of 0 to 3 weeks. The relationship was adjusted for temperature, seasonal variations, and inter-year variations. The center line shows the estimated spline curve, and the upper and lower lines the 95% confidence limits.

(95% CI: −0.8 to 7.2) in those aged 10–14 years, and 8.7% (95% CI: 3.7 to 13.8) in those aged over 15 years.

The RR of HFMD by temperature at specific lag periods (0, 2, 4, and 6 weeks) and by lag at specific temperatures (6, 11, 24, and 29 °C), which corresponded to approximately the 5th, 25th, 75th, and 95th percentiles, respectively, of temperature distribution, were also determined (Fig. 4). High temperature effects were more prominent over shorter lag periods and diminished over time, whereas the effects in low temperature ranges were persistent over longer lag periods. We also analyzed the RR of HFMD by humidity at specific lag periods (0, 2, 4, and 6 weeks) and by lag at specific humidity (53%, 60%, 70%, and 77%), which corresponded to approximately to the 5th, 25th, 75th, and 95th percentiles, respectively, of humidity distribution (Fig. 5). As was observed for temperature, high humidity effects were also more prominent in shorter lag periods and diminished over time, whereas effects in low humidity ranges were persistent over longer lag periods.

To investigate whether the results were sensitive to the levels of control for seasonal patterns, the analyses were repeated using different degrees of seasonal control. Halving (3 harmonics) or doubling (12 harmonics) the degree of seasonal control in sensitivity analyses only minimally changed the estimated effects of temperature and humidity. Specifically, the temperature model yielded increases of 10.8% (95% CI: 3.0–19.3) with 3 harmonics and 11.2% (95% CI: 3.3–19.8) with 12 harmonics with respect to the incidence of HFMD. The humidity model yielded increases of 5.0% (95% CI: 2.7–7.3) with 3 harmonics and 4.7% (95% CI: 2.4–7.1) with 12 harmonics with respect to the incidence of HFMD.

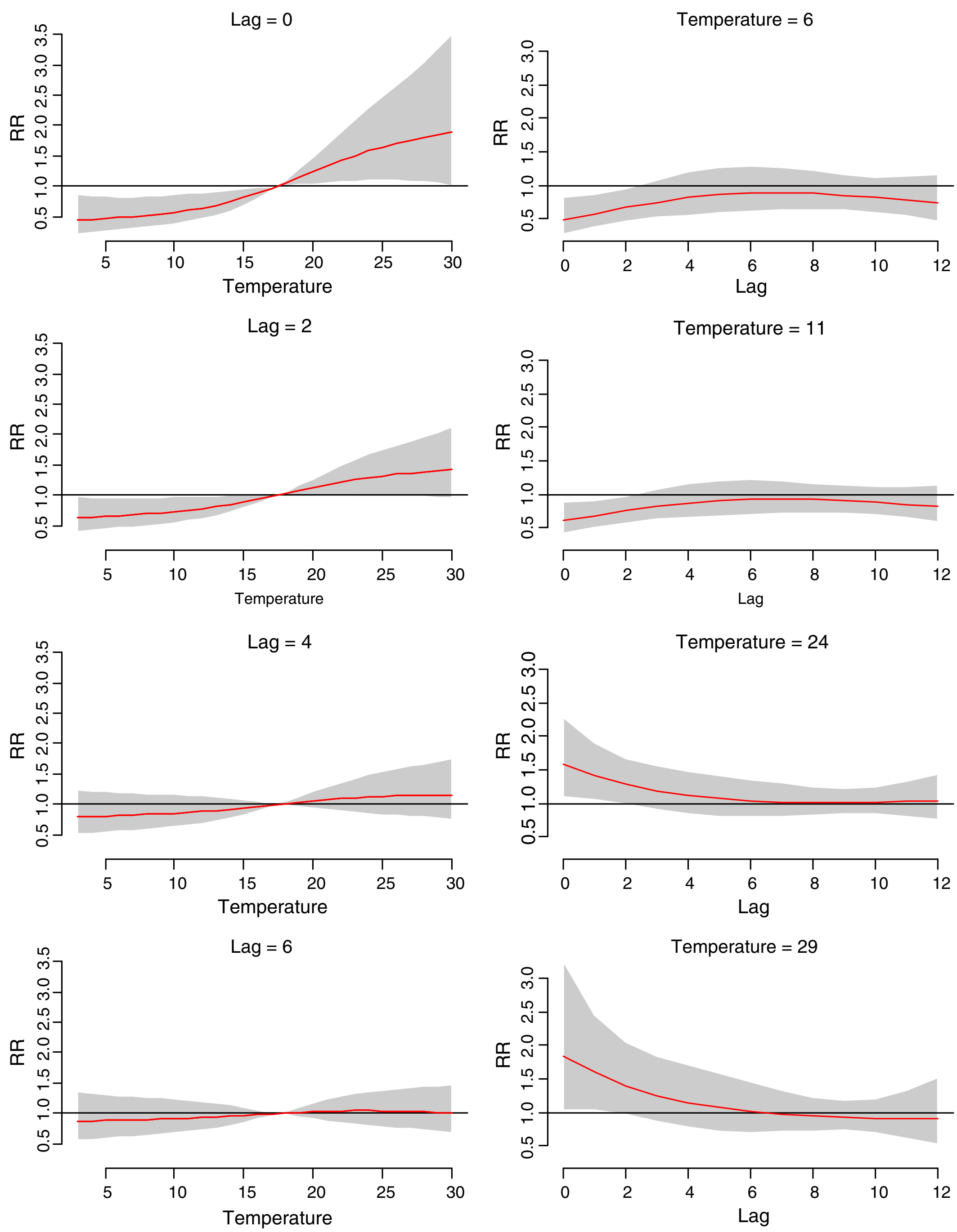

Fig. 4. Plot of relative risk (RR) by temperature for specific lag periods (left) and RR by lags for specific temperatures (right).

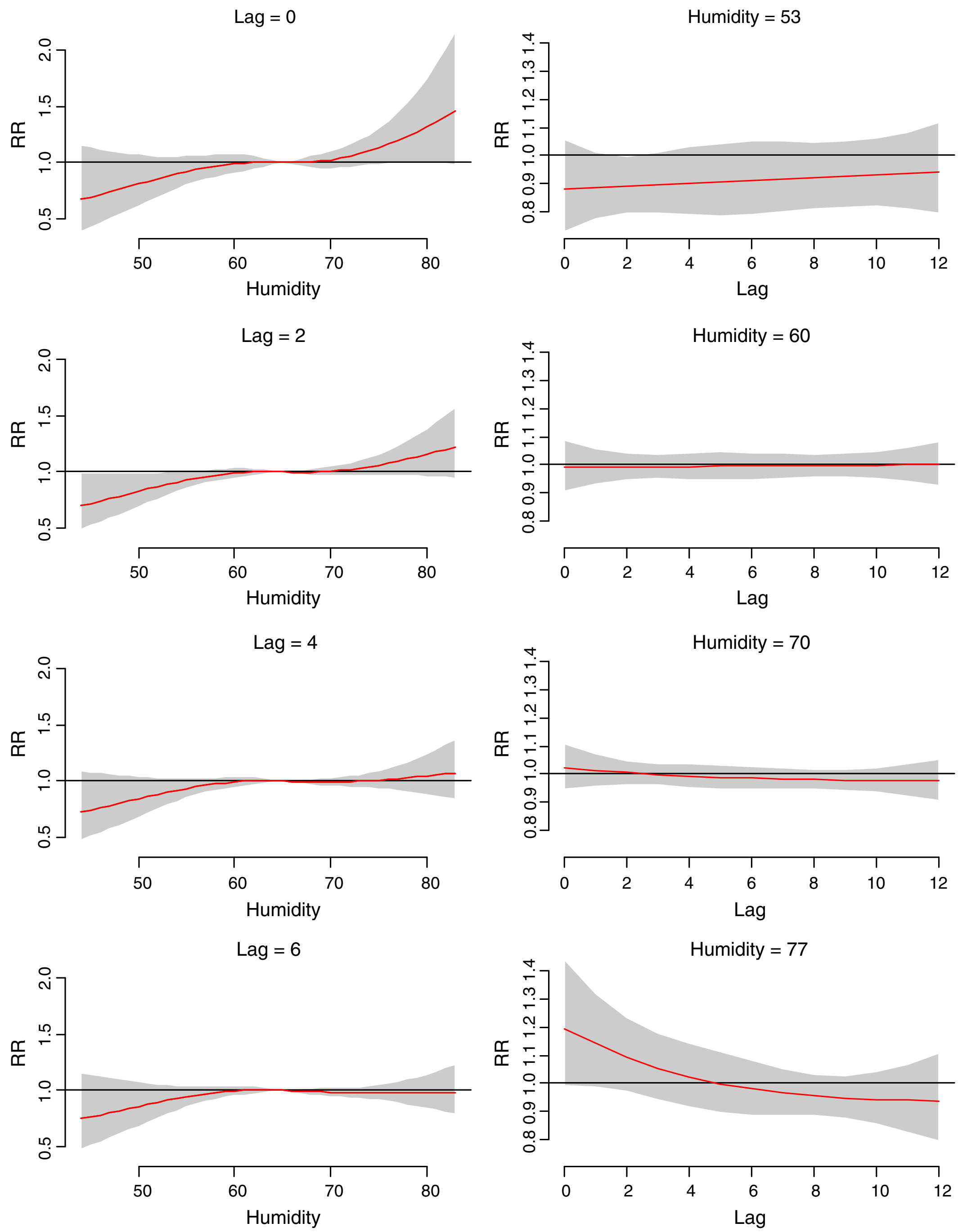

Fig. 5. Plot of relative risk (RR) by humidity for specific lag periods (left) and RR by lags for specific humidity (right).

4. Discussion

Our analysis of the effects of temperature and humidity on the incidence of HFMD in Fukuoka, Japan has yielded several notable findings. After adjustment for potential confounding by seasonal patterns and inter-year variations, we detected that the number of HFMD cases increased with increasing temperature and relative humidity. Notably, this increase was most remarkable in children aged less than 10 years. Our results demonstrate that weather factors have a significant influence on the incidence of HFMD infections.

Our results are consistent with a previous study in Tokyo, Japan, which suggested that higher temperature and humidity may have influenced the increase of HFMD incidence observed between 1999 and 2002 (Urashima et al., 2003), and with the findings of a more recent study in Hong Kong indicating that HFMD consultation rates were positively associated with temperature and humidity (Ma et al., 2010b). However, a recent study in Singapore showed that in addition to a maximum daily temperature above 32 °C, rainfall of up to 75 mm was associated with an increased incidence of HFMD (Hii et al., 2011). Although we initially examined the effects of rainfall on HFMD incidence, no evidence of an association with the number of HFMD cases was detected. This discrepancy might be due to the effects of relative humidity, which were controlled for in the present study in Fukuoka, Japan, but not in the study conducted in Singapore. Our present findings suggest that weather factors might explain short-term associations and peaks in the incidence of HFMD infections among children.

Our age-specific analyses showed that the marked temperature and humidity effects on the incidence of HFMD predominantly occurred in children aged 0–4 and 5–9 years. With regard to HFMD infections, a previous seroepidemiological study reported that 44.0% of expecting mothers had antibodies to EV71; however, the levels of circulating antibodies had waned so rapidly that only 1 month after birth, none of the infants tested had maternal antibodies to EV71 (Ooi et al., 2002). Moreover, it was also found that most EV71 infections occurred in preschool-aged children (Ooi et al., 2002). A recent seroepidemiological study has also shown that > 50% of children aged < 5 years lack neutralizing antibodies against EV71 and CA16 (Zhu et al., 2010). Thus, our finding that temperature and humidity predominantly affect HFMD infections in younger children likely reflects the pattern of spread of HFMD among immunologically unprotected children and the acquisition of serum antibodies to HFMD by children as they age.

Using the distributed lag non-linear models, the number of HFMD cases was found to increase with increasing temperature and relative humidity, and was generally positive at all examined lag period lengths. We speculate that this finding is related to the fact that HFMD has a long contagious period and that clinical presentations might be detected late. Although the incubation period of HFMD typically ranges from 1 to 7 days, and infected persons are most contagious during the first week following signs of illness (Goh et al., 1982), the causative viruses that cause HFMD can remain in the body for weeks after symptoms have disappeared (CDC, 2011). This is of significance as asymptomatic carriers are capable of spreading the causative viruses, and that more cases of HFMD are reported clinically than are confirmed by laboratories. These characteristics of HFMD infections also highlight the need for more precise modeling of lag effects of weather on disease risk.

Nearly all previous studies extrapolating weather-HFMD relationships from seasonal patterns of HFMD were subject to the influence of other factors that cause departures from the typical seasonal patterns, such as interannual and seasonal patterns. In contrast, our results were not subject to confounding bias by such factors. Although we did not have access to data concerning the specific causative pathogens of HFMD, a previous study has suggested that the sharing of toys and other items in child-care centers or kindergartens might contribute to EV71 infections (Ooi et al., 2002). Recent studies have indicated that meteorological conditions are related to physical activity in open-air settings (Suminski et al., 2008), and that physical activity during adolescence is lower during winter and increases during warmer months (Belanger et al., 2009). We therefore speculate that weather conditions may be associated with behavioral patterns that lead to increased contact among children, thereby facilitating the spread of HFMD infection. In addition, a laboratory-based study suggested that enteroviruses are resilient to the environmental conditions of the gastrointestinal tract, and that their stability in external environmental conditions is dependent on temperature, humidity, and UV radiation (Rajtar et al., 2008). For these reasons, an increased number of enteroviral infections might be expected to occur during the summer and early autumn seasons in temperate areas; meanwhile, enteroviral infections might maintain a constant level throughout the year in tropical and subtropical areas (Fong and Lipp, 2005). Although the exact mechanism is not clear, our combined temperature and humidity results indicate that weather factors affect the incidence of HFMD infections.

A few limitations of this study warrant mention. First, surveillance data for HFMD do not capture all cases in the community. This under-reporting of infections can occur anywhere in the reporting chain, from the initial decision of a patient to not seek health care to the failure to record cases in the disease registry, due to the mildness or lack of symptoms. The degree of under-reporting may also vary between epidemic and non-epidemic periods. Second, the participating sentinel medical institutions were recruited on a voluntary basis; however, this is not expected to significantly influence the validity of the comparisons over time, which is the subject of this study.

Global climatic change has profound impacts on infectious disease. Infectious pathogens, such as viruses, parasites and bacteria, are devoid of thermostatic mechanisms, and reproduction and survival rates are strongly affected by fluctuations in temperature (Meerburg and Kijlstra, 2009; Patz et al., 2005). Thus, elucidation of the effects of weather variability on the epidemiology of infectious diseases is important for disease control by public health officials. The results of this study may aid in the prediction of epidemics and in preparation for the effects of climatic changes on the epidemiology of HFMD through implementation of preventive public health interventions, such as promoting good hygiene practices, temporary closure of educational institutions, and campaigns that include press releases and media events to encourage preventive activities. It is expected that such activities might be practically useful for preventing or limiting the spread of HFMD infections.

In conclusion, our study provides quantitative evidence that the number of HFMD cases in Fukuoka, Japan increased significantly with increased average temperature and relative humidity, and suggests that preventive measures for limiting the spread of HFMD, particularly in younger children, should be considered during extended periods of high temperature and humidity.

Supplementary materials related to this article can be found online at doi:10.1016/j.scitotenv.2011.09.055.

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Conflict of interest

None declared.

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