Letter to the Editor

Ambient Temperature Increases the Hand, Foot, and Mouth Disease Incidence: A Time Series Analysis in Tokyo, Japan, 2000–2019

*Keita Wagatsuma [1,2]

1. *Division of International Health (Public Health), Graduate School of Medical and Dental Sciences, Niigata University, Niigata, Japan*
2. *Institute for Research Administration, Niigata University, Niigata, Japan*

*Correspondence: Email: waga@med.niigata-u.ac.jp

Dear Editor-in-Chief

Hand, foot, and mouth disease (HFMD) is an enteric infection caused by enteroviruses, primarily Enterovirus A71 and Coxsackievirus A16, that imposes a substantial health burden across the Asia-Pacific region, including China, Hong Kong, Singapore, and Japan (1). In temperate regions of Japan, HFMD demonstrates pronounced seasonality, with outbreaks peaking during summer months (from June to August) and minimal incidence during winter (from December to February) (2). The seasonality of HFMD, however, varies widely across countries and regions, with meteorological factors likely playing a critical role. Nevertheless, studies investigating these effects have produced inconsistent conclusions. In China, a time-series analysis conducted in Chongqing identified a positive association between HFMD incidence and mean temperature (3). We aimed to investigate the short-term association between ambient temperature and HFMD incidence in Tokyo, Japan, employing advanced statistical techniques to control for potential confounders.

We analyzed weekly time-series data on HFMD incidence and ambient temperature spanning two decades (2000–2019) in Tokyo, Japan. Tokyo, officially referred to as the Tokyo Metropolis and serving as Japan's capital, is situated in the western Pacific region at 35°N latitude and 139 °E longitude. Weekly HFMD case counts for Tokyo were sourced from the National Institute of Infectious Diseases under Japan's Ministry of Health, Labor, and Welfare (https://www.niid.go.jp/niid/en/). HFMD cases were identified based on clinical diagnoses, defined as the presence of vesicular lesions on the hands, feet, and mouth—often accompanied by ulcers—and frequently on the buttocks, with or without fever, following the guidelines of the Act on Prevention of Infectious Diseases and Medical Care for Patients Suffering from Infectious Diseases. Daily mean temperature (°C) and relative humidity (%) were retrieved from a single monitoring station in Tokyo operated by the Japan Meteorological Agency (https://www.jma.go.jp/jma/indexe.html). These daily measurements were aggregated into weekly averages for analysis. Other variables, including year, month, week, and the number of

national public holidays per week, were also incorporated into the dataset.

We utilized quasi-Poisson regression integrated with distributed lag non-linear models (DLNMs) to analyze the time-series data, accommodating overdispersion to capture the intricate relationship between mean temperature and HFMD incidence in Tokyo (4). Specifically, cross-basis functions were constructed using a natural cubic B-spline with three internal knots placed at the 25th, 50th, and 75th percentiles of the temperature distribution in Tokyo. Delayed lag effects, extending up to 4 weeks, were modeled with a natural cubic B-spline featuring three internal knots spaced equidistantly on the logarithmic scale. Seasonal and long-term trends were addressed by incorporating a natural cubic B-spline of time with 8 degrees of freedom (df) per year. To control for potential confounding factors, the analysis included relative humidity, modeled using a natural cubic B-spline with 3 df, and the weekly count of national public holidays. The median value of temperature was used as the reference value to calculate the relative risks (RRs) and 95% confidence intervals (CIs). Sensitivity analyses

tested the robustness of the modeling choices by adjusting the df for time trends (6 or 10 df per year). Two-tailed *P*-values below 0.05 were deemed statistically significant. All analyses were conducted using R version 4.1.0. Ethical approval was not required as the study utilized secondary data without personal identifiers.

During the study period, 213,059 HFMD cases were reported in Tokyo. Weekly mean temperatures ranged from 1.77 °C to 31.05 °C. While the seasonal peak in HFMD cases exhibited year-to-year variations, it predominantly aligned with Japan's hot summer months (Fig. 1). Fig. 2 illustrates the overall cumulative exposure–response relationship between weekly mean temperature and HFMD incidence across lags from 0 to 4 weeks in Tokyo. The association followed a non-linear trajectory. Using 17.05 °C (i.e., median) as the reference temperature, the RR reached its maximum at 23.8 °C (RR: 3.06, 95% CI: 2.01–4.65). Beyond this threshold, the RR gradually decreased, forming an inverted U-shaped curve. Sensitivity analyses confirmed that the estimates remained robust regardless of the model specifications (data not shown).
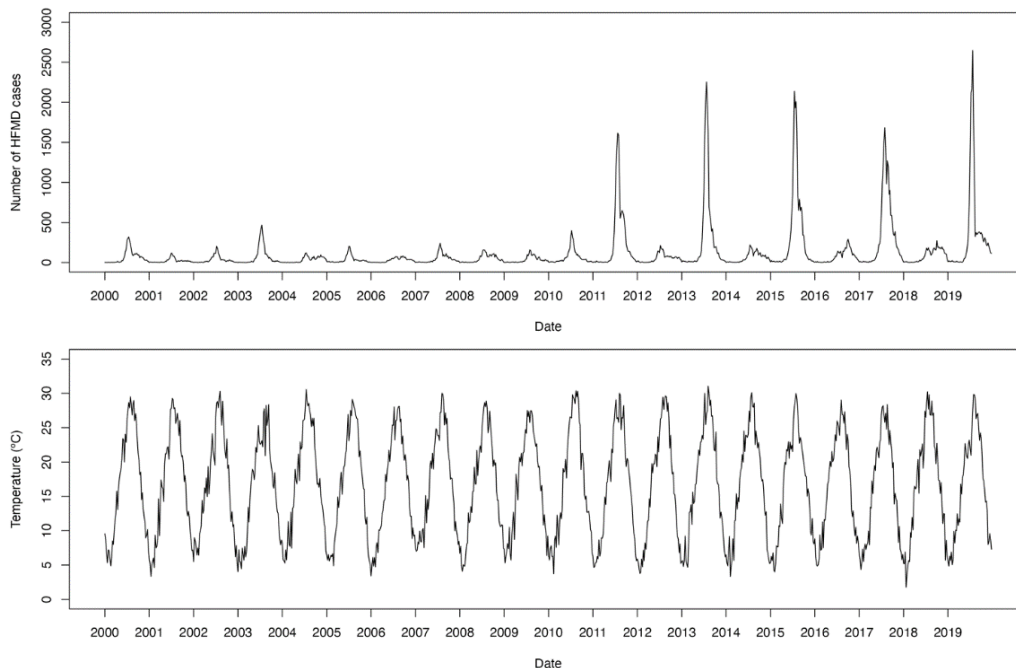

Fig. 1: Weekly counts of HFMD and mean temperature in Tokyo, Japan, 2000–2019. Abbreviations: HFMD, hand, foot, and mouse disease
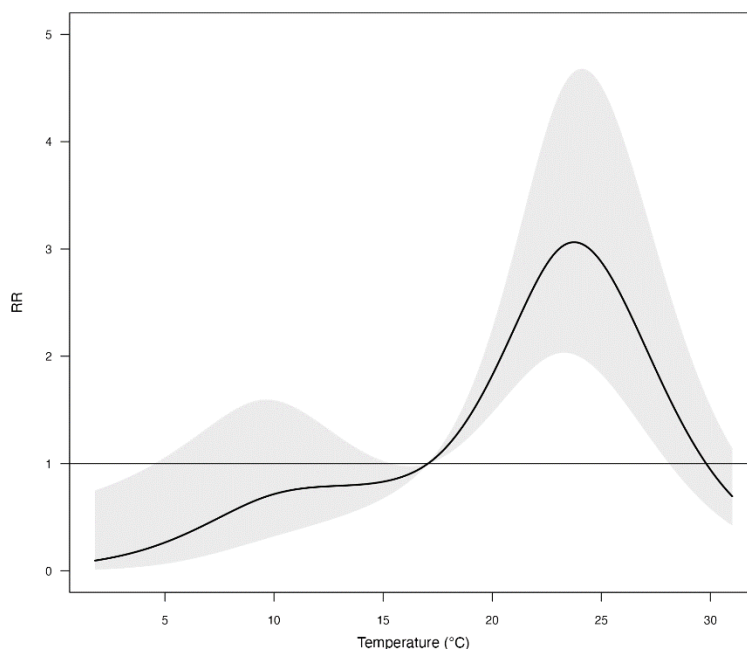
Fig. 2: Pooled estimates of the overall cumulative associations between weekly mean temperature and HFMD incidence across all lags in Tokyo, Japan. Notes: The relative risk curve with 95% confidence intervals (shaded region) for the association. Abbreviations: HFMD, hand, foot, and mouse disease; RR, relative risk

In conclusion, this study provides evidence of short-term associations between mean temperature and HFMD incidence in Tokyo based on time-series regression analysis. Higher temperatures may promote the replication, survival, and transmission of pathogens in the environment, increasing the likelihood of exposure to susceptible individuals (5). Warmer weather encourages outdoor activities, reducing time spent indoors and potentially amplifying the spread of enteroviruses through respiratory droplets, ruptured skin vesicles, or contaminated toys and surfaces (3). In light of global warming, conditions characterized by increased heat and humidity are expected to elevate HFMD activity. Public health authorities in Japan could strategically align prevention measures with forecasts of weather-driven increases in disease transmission.

Conflicts of interests

The author declares that there is no conflict of interests.

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