Tang *et al. BMC Public Health* (2024) 24:2825
https://doi.org/10.1186/s12889-024-20342-x

BMC Public Health

RESEARCH

Open Access

Air pollution's numerical, spatial, and temporal heterogeneous impacts on childhood hand, foot and mouth disease: a multi-model county-level study from China

Zhangying Tang[1†], Qi Sun[1†], Jay Pan[2,3], Mingyu Xie[4], Zhoufeng Wang[1], Xiaojun Lin[2,3], Xiuli Wang[2,3], Yumeng Zhang[2,3], Qingping Xue[5], Yanchen Bo[6], Jinfeng Wang[7], Xin Liu[1,8,9*] and Chao Song[2,3*]

Abstract

Background While stationary links between childhood hand, foot and mouth disease (HFMD) and air pollution are known, a comprehensive study on their heterogeneous relationships (nonstationarity), jointly considering numerical, temporal and spatial dimensions, has not been reported.

Methods Monthly HFMD incidence and air pollution data were collected at the county level from Sichuan-Chongqing, China (2009–2011), alongside meteorological and social environmental covariates. Key influential factors were identified using random forest (RF) under the stationary assumption. Factors' numerically, temporally, and spatially heterogeneous relationships with HFMD were assessed using generalized additive model (GAM) and geographically and temporally weighted regression (GTWR).

Results Our findings highlighted the relatively higher stationary contributions of fine particulate matter ($PM_{2.5}$) and ozone (O_3) to HFMD incidence across Sichuan-Chongqing counties. We further uncovered heterogeneous impacts of $PM_{2.5}$ and O_3 from three nonstationary perspectives. Numerically, $PM_{2.5}$ showed an inverse 'V'-shaped relationship with HFMD incidence, while O_3 exhibited a complex pattern, with increased HFMD incidence at low $PM_{2.5}$ and moderate O_3 concentrations. Temporally, $PM_{2.5}$'s impact peaked in autumn and was weakest in spring, whereas O_3's effect was strongest in summer. Spatially, hotspot mapping revealed high-risk clusters for $PM_{2.5}$ impact across all seasons, with notable geographical variations, and for O_3 in spring, summer, and autumn, concentrated in specific regions of Sichuan-Chongqing.

Conclusions This study underscores the nuanced and three-perspective heterogeneous influences of air pollution on HFMD in small areas, emphasizing the need for differentiated, localized, and time-sensitive prevention and control

†Zhangying Tang and Qi Sun contributed equally to this work.

*Correspondence:
Xin Liu
liuxin_swpu@163.com
Chao Song
chaosong@scu.edu.cn

Full list of author information is available at the end of the article

strategies to enhance the precision of dynamic early warnings and predictive models for HFMD and other infectious diseases, particularly in the fields of environmental and spatial epidemiology.

Keywords HFMD, Heterogeneous impacts, Spatiotemporal nonstationarity, Numerical nonlinearity, Small area, China

Introduction

Hand, foot and mouth disease (HFMD) in children was initially reported in Canada in 1957 [1] and has since evolved into a global infectious disease [2]. HFMD is characterized by a diverse pathogen composition, enterovirus recombination, and co-infection [3], with a primary occurrence in children under 5 years old [4]. The transmission of HFMD mainly depends on close contact and airborne routes [5, 6]. While most symptoms are mild and self-limited [7], clinical manifestations such as fever and oral lesions can lead to misdiagnosis, potentially worsening the condition [8]. Moreover, a small percentage of patients may experience severe complications, including encephalitis or even death [9]. During 2004–2013, HFMD exhibited the highest incidence rate among children in China, ranking among the top five infectious diseases in terms of mortality and imposing a significant disease burden on the country [10]. Enhancing strategies for preventing and controlling HFMD can improve children's health and well-being, in line with the targets of Sustainable Development Goal (SDG) 3 [11].

The prevalence of HFMD is intricately linked to natural and social environmental conditions, making it of significant epidemiological research value and practical importance for prevention and control efforts [12]. Numerous studies have established the association between meteorological environmental factors and HFMD, including temperature [13], relative humidity [14], precipitation [15], wind speed [16], and atmospheric pressure [17]. Social environmental factors, such as population density [18] and regional economic development level [19] also influence HFMD occurrence to some extent. Recent research has expanded the discussion to include air pollution as a key risk factor for HFMD. Studies document that air pollution may elevate infection rates by damaging the respiratory system [20] and prolonging the survival time of HFMD viruses [21]. Especially, children contribute significantly to deaths caused by air pollution, likely due to their underdeveloped lungs and immune systems, coupled with increased outdoor activity and higher air intake per unit weight compared to adults [22]. Furthermore, research confirms that enterovirus adheres to particulate matter, facilitating long-distance spread [23], thereby amplifying the risk of virus exposure. Additionally, exposure to a polluted environment compromises the body's immune resistance, heightening susceptibility to infection [24]. Hence, it is crucial to comprehend the association between air pollutants and HFMD for effective disease surveillance.

Due to the advancements in air pollution-related ground monitoring systems and the availability of related remote sensing product datasets [25], research on the impact of air pollutants on HFMD has been extensively discussed, including $PM_{2.5}$ [21], PM_{10} [26], O_3 [27], NO_2 [27], and SO_2 [28]. However, there is inconsistency in the results regarding the relationships between air pollution factors and HFMD. For instance, a study conducted in Guilin suggested that extremely low levels of $PM_{2.5}$ had protective effects on HFMD, whereas high concentrations of $PM_{2.5}$ had the opposite effects [21]. Instead, another study conducted in Chengdu revealed that $PM_{2.5}$ was not associated with the development of HFMD [28]. This disparity in findings may arise from these studies not fully considering proven environmental factors such as meteorology and socio-economic conditions when examining the effects of air pollution on HFMD, resulting in misleading associations between these factors.

Furthermore, it is necessary to consider nonstationary bias when examining the associations between environmental factors and health outcomes [29]. Nonstationary bias implies that the influence of environmental factors on health outcomes changes with variations in space, time, and numerical values [29]. These variations are referred to as spatial nonstationarity, temporal nonstationarity, and numerical nonstationarity, respectively. For large- and fine-scale research on HFMD and environmental factors, the exposure-response relationship might be misidentified due to shifts in geographical space, time, and numerical size. Presently, many studies on air pollution and HFMD only focus on numerical nonstationarity, overlooking spatiotemporal nonstationarity [30]. Additionally, a study utilized GAM and time series analysis methods, considered both numerical and temporal nonstationarity, determining that NO_2 promoted HFMD among infants with the cumulative relative risk peaking at lag 9 day [31]. However, no study has yet focused on air pollution factors, jointly considering these three forms of nonstationarity, to explore the numerical, temporal, and spatial heterogeneity of their impacts on HFMD. This neglect can lead to uncertain, incomplete or even incorrect identification of key risk factors of HFMD [29].

Overall, there is still a research gap in understanding the connections between air pollution and HFMD, particularly when fully accounting for the three-perspective nonstationary bias in environmental health research and the impact of controlling meteorological and socio-economic factors in assessing the health risks linked to air pollution. To address these issues, we adopted air pollution factors as the main independent variables, with meteorological and social environmental factors serving as control variables, to explore the heterogeneous relationship between environmental factors and HFMD from the perspectives of numerical, temporal, and spatial nonstationarity. We selected the Sichuan-Chongqing area in China as our study area, driven by the increasing prevalence of HFMD, the severe air pollution problems [32], as well as the presence of a complex terrain and climate system that may manifest distinct epidemiological characteristics across time and space [6]. We collected county-level HFMD case data spanning 36 months from 2009 to 2011, along with relevant factors related to air pollution, meteorology, and the social environment.

Our study aimed to achieve two primary objectives. Firstly, we aimed to determine whether there is an evident global-scale stationary correlation between air pollution and HFMD. Specifically, we investigated whether air pollutants demonstrate relatively high contributions in all types of factors. The second objective was to reveal the three heterogeneous effects of air pollution factors on HFMD. We built GAM, a mainstream method for fitting numerical nonstationarity [33], and GTWR models, a common approach for exploring spatiotemporal nonstationarity [34]. Identifying these three types of nonstationarity is meaningful as it contributes to a deeper understanding of the pathogenesis and spatiotemporal patterns. Moreover, it provides crucial support for formulating specific prevention and control measures by taking these nonstationary into account to improve children's health to support the successful achievement of SDG 3.

Materials and methods

Study area and data

The Sichuan-Chongqing region (east longitude 97°36' ~ 110°19'; north latitude 26°05' ~ 34°32') is located in southwest China, featuring higher altitudes in the west and lower elevations in the east. It encompasses 178 county-level cities (Fig. 1). The region experiences a subtropical monsoon humid climate characterized by high temperatures and abundant rainfall in summer and mild winters with minimal rain. The topography of the eastern basin hinders the dispersion of air pollutants, causing relatively poor air quality in this area. Additionally, the dense population, approximately 116 million in

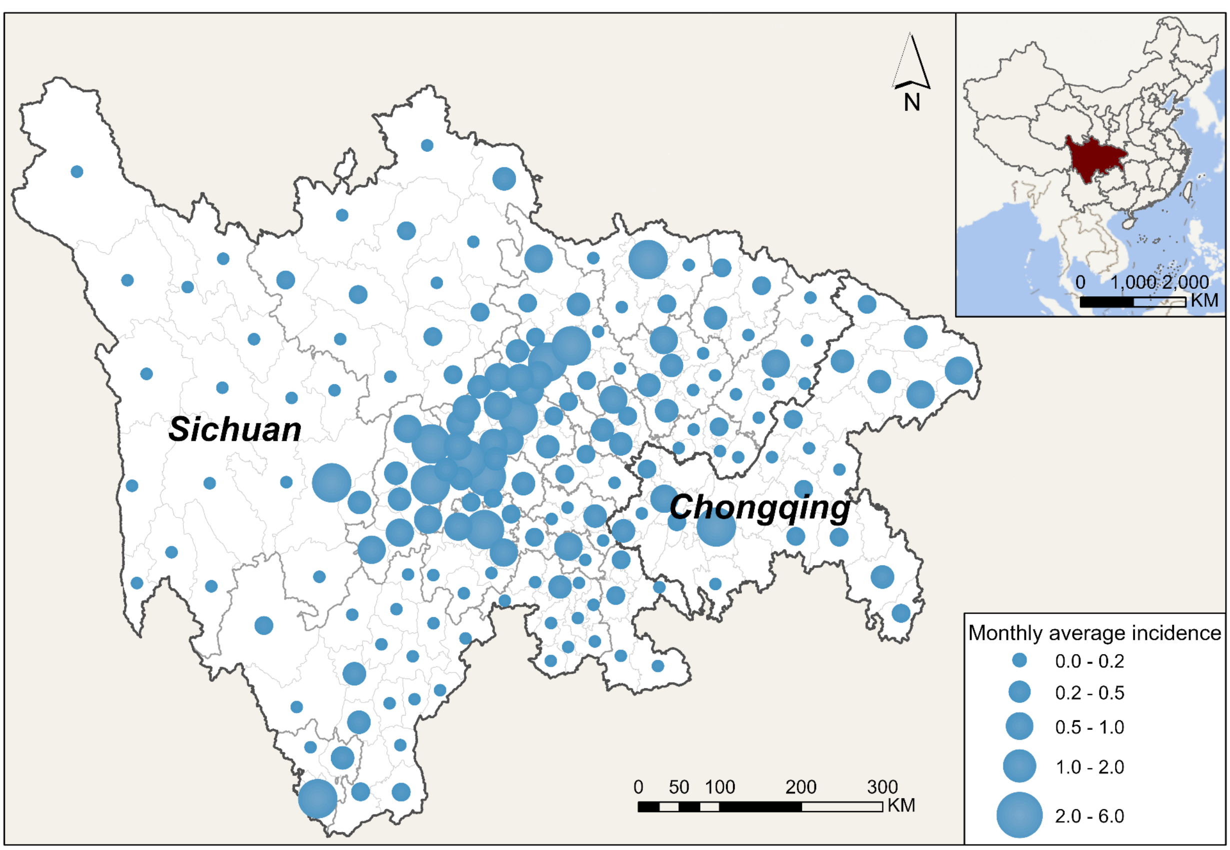

Fig. 1 The monthly average incidence of HFMD at the county level in Sichuan-Chongqing, China

this region, provides essential conditions for the HFMD epidemic.

Monthly data on HFMD incidence at the county level from 2009 to 2011 were obtained from the China Information System for Disease Control and Prevention (CISDCP). The Clinical diagnosis of HFMD aligns with the National Guideline on Diagnosis and Treatment of Hand Foot Mouth Disease issued by the Chinese Ministry of Health. To focus on the demographic most affected, namely children, we included cases in individuals aged between 0 and 9 years. Rigorous review by professionals guarantees the accuracy and reliability of all reported data. Figure 1 shows the distribution of monthly average incidence of HFMD at the county level in the Sichuan-Chongqing region.

Air pollution data were sourced from the China-HighAirPollutants dataset [25, 35–37], with a spatial resolution of 1 km. This dataset integrates ground-based measurements, satellite remote sensing products and atmospheric reanalysis data. The data results indicate that the estimated values of pollutants agree well with the ground-based measurements (CV-R^2>0.8). Previous research has identified O_3, PM_{10}, and $PM_{2.5}$ as the primary pollutants in Sichuan-Chongqing, especially in the eastern basin, where O_3 is the predominant pollutant, followed by $PM_{2.5}$ [38]. Therefore, our study focused on O_3, PM_{10} and $PM_{2.5}$ to investigate their impact on HFMD. All data were averaged to the county scale to align with HFMD incidence.

Based on previous studies [13–17], we collected meteorological and social environment factors that could potentially confound the association between air pollution and HFMD risk. In these factors, temperature, wind speed, air pressure, and relative humidity were obtained from the Goddard Earth Sciences Data and Information Services Center (GESD) (https://giovanni.gsfc.nasa.gov/giovanni) with a spatial resolution of 0.5×0.625°. Precipitation data were sourced from Precipitation Estimation from Remotely Sensed Information using Artificial Neural Networks (PERSIANN) (http://chrsdata.eng.uci.edu) with a spatial resolution of 0.25×0.25° [39]. Nighttime light data (approximately 1 km), representing the social and economic situation of a region [40], were retrieved from the global NPP-VIIRS nighttime light dataset (https://dataverse.harvard.edu/). Population density data were derived from the World Population Data Set (https://hub.worldpop.org) with a spatial resolution of 30 arc-seconds. All covariates were extracted based on county level to match the HFMD incidence.

Statistical analysis

Before conducting the statistical analysis, we used ArcGIS software to extract the average values of all variables for each grid based on the county-level map data. In this study, the variance inflation factor (VIF) test and the random forest method were employed to identify explanatory variables with a significant impact on HFMD incidence. Both of these methods were implemented in R, using the "car" [41] and "randomForest" [42] packages. The VIF assesses collinearity between variables, with higher VIF values indicating more severe collinearity. Variables with a VIF exceeding 5 were excluded [43, 44]. Additionally, the random forest, known for its fast training speed, simple implementation, good performance, and effective anti-overfitting capabilities [45], was utilized to measure the influence of these variables on HFMD by generating importance indices. We used %IncMSE value outputted by the RF model as the importance measure, with ntree set to 800 and mtry set to 3. A higher value for a variable means a greater effect in the model. To assure the stability of the importance measure, we repeated the RF model 30 times.

Generalized Additive Model (GAM) [33] was used to reveal the exposure-response relationship between HFMD incidence and its influencing factors due to a lack of information about any underlying associations in the study area. What's more, we can identify variations in the response of these environmental factors to HFMD incidence at different values by GAM and thus capture numerical nonstationarity. GAM was implemented using the R software with the "mgcv" package [46]. In this study, we used a log link function for the HFMD incidence as the outcome variable. A smooth spline function with three or four degrees of freedom was applied to capture the nonlinear relationships [14].

Geographically and Temporally Weighted Regression (GTWR) is a local spatiotemporal model that considers both spatial and temporal nonstationarity, offering a more comprehensive explanation of the spatiotemporal heterogeneity in the relationships between independent and dependent variables [34]. For specific parameters, we used a Gaussian function to regulate the calculation of the spatiotemporal power function and spatiotemporal distance [34]. The neighborhood number and the bandwidth for the spatiotemporal distance ratio were set to 100 and 1, respectively. The GTWR analysis was conducted using ArcGIS 10.2, as developed by Huang [34]. Furthermore, by integrating the GTWR results with the Hot Spot Analysis (Getis-Ord Gi*) tool in ArcGIS, we uncovered spatial clusters of factors with positive and negative impacts on HFMD [47].

Results

Importance of environmental factors affecting HFMD under stationarity

We selected three air pollution factors ($PM_{2.5}$, O_3, and PM_{10}), five meteorological factors (mean temperature, wind speed, precipitation, relative humidity, and pressure), and two socio-economic factors (nighttime light and population density) as alternative explanatory factors. A VIF test and a correlation analysis were conducted to assess the multicollinearity and correlation between variables. The analysis revealed strong correlations between $PM_{2.5}$ and PM_{10}, as well as between temperature and humidity. Additionally, air pressure exhibited a notable correlation with both PM_{10} and $PM_{2.5}$ (Fig. S1). Following the VIF test results (Table S1), we removed PM_{10} (VIF: 42.71) since $PM_{2.5}$ played a more crucial role within the study area [48]. Subsequently, relative humidity (VIF: 16.93) and air pressure (VIF: 6.33) were also excluded. Ultimately, we retained $PM_{2.5}$, O_3, nighttime light, population density, mean temperature, precipitation, and wind speed as the seven independent factors influencing HFMD.

Random Forest results indicated a strong association between these factors and HFMD incidence (Fig. 2). Nighttime light emerged as the most significant factor, followed by precipitation and mean temperature, with $PM_{2.5}$ and O_3 also showing high importance. Building upon the stationary importance of variables, further

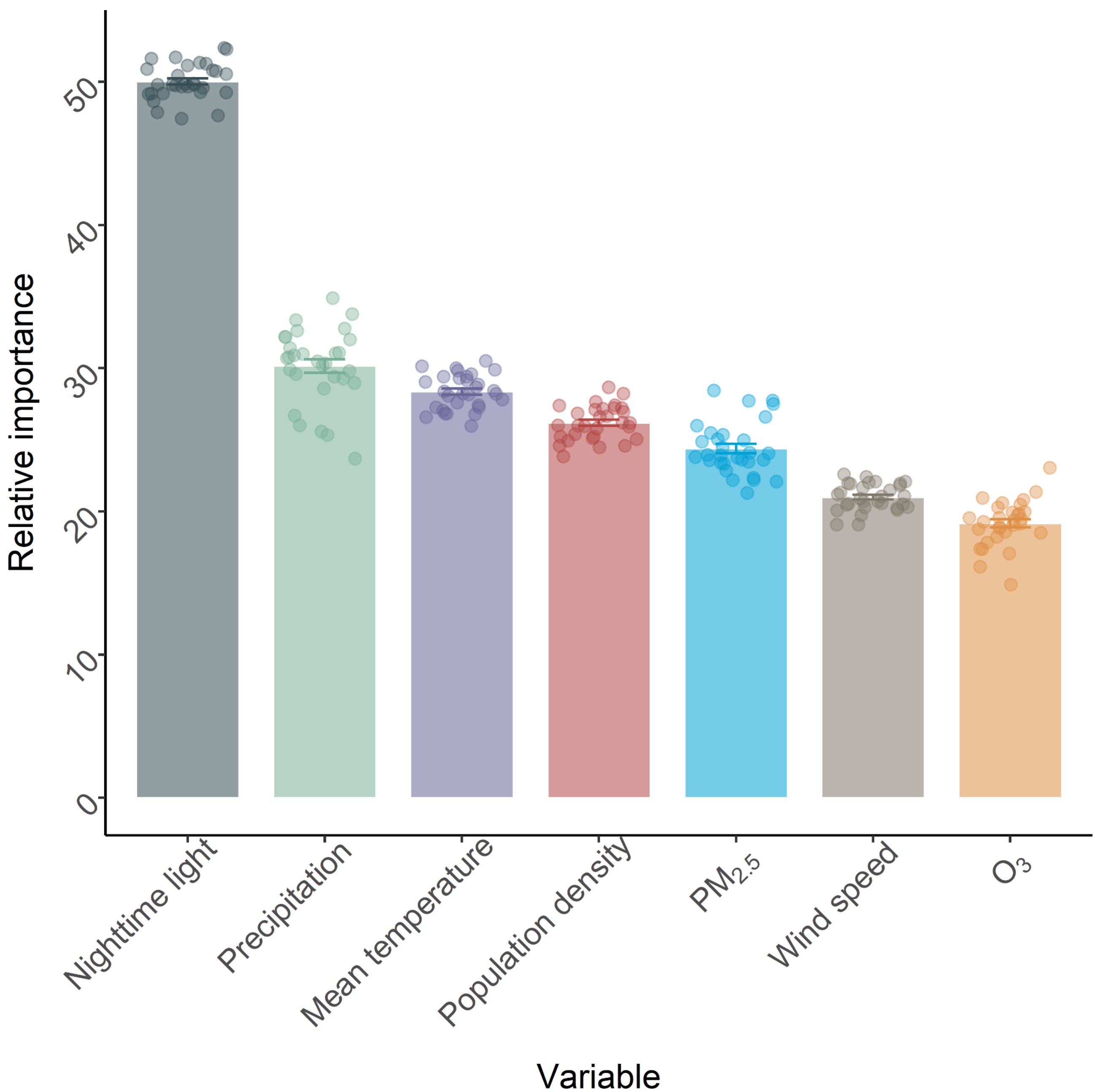

Fig. 2 Ranking of explanatory factors influencing HFMD incidence. This figure illustrates the global-scale stationary relative importance of seven key explanatory factors in the context of HFMD incidence, as determined by the importance index calculated using the random forest method

analysis can be conducted to explore the locally heterogeneous effects of these factors on HFMD incidence.

Numerical nonstationarity in HFMD-environment associations

Figure 3 illustrates the impact of environmental factors on HFMD incidence at the numerical nonstationary scale. All factors, except for wind speed, displayed clear nonlinear characteristics. $PM_{2.5}$, nighttime light, mean temperature, and precipitation exhibited inverted 'V'-shaped influence curves on HFMD incidence. Specifically, low concentrations of $PM_{2.5}$ and moderate concentrations of O_3 were positively associated with HFMD incidence. However, continuous increases in $PM_{2.5}$ concentrations and extreme concentrations of O_3 (either low or high) were linked to a reduction in HFMD incidence. Among the covariates, nighttime light showed a positive effect at low values but a negative effect at high values, while population density maintained an overall positive association with HFMD incidence. Mean temperature promoted HFMD incidence when below 10 °C, but became inhibitory beyond this threshold. Overall, changes in $PM_{2.5}$ and O_3 had a significant impact on HFMD incidence, indicating substantial numerical nonstationarity across the study area.

Temporal nonstationarity in HFMD-environment associations

Using the GTWR statistical model, we analyzed the temporally heterogeneous effects of seven environmental factors on HFMD risk, considering both seasonal and monthly scale variations (Fig. 4). First, an examination of monthly HFMD incidence trends from 2009 to 2011 (Fig. 4A), revealed a consistent seasonal pattern across all three years, with 2010 exhibiting the most pronounced peak in high-risk values. The incidence of HFMD peaked primarily in spring (April and May) and showed secondary peaks during the transitional months of autumn and winter (November and December).

O_3, mean temperature, and nighttime light displayed similar seasonal trends, with mean temperature having the most pronounced impact. Nighttime light exerted the strongest influence across all four seasons (Fig. 4B). $PM_{2.5}$ had a substantial impact in summer and autumn, while O_3 exhibited a strong influence in spring and summer.

On a monthly scale, the effects of $PM_{2.5}$, O_3, mean temperature, and nighttime light on HFMD risk varied (Fig. 4C). $PM_{2.5}$ had its greatest positive impact in October and the least in March. O_3 was most influential in July, while mean temperature had the strongest effect in March and the weakest in July. Nighttime light showed a higher influence in spring and summer, with its peak effect occurring in May. Additionally, precipitation had a stronger positive effect in January, while wind speed exerted its greatest influence in September.

Spatial nonstationarity in HFMD-environment associations

Using local-scale spatiotemporal regression coefficients estimated by the GTWR model, we generated a series of spatial heterogeneity maps illustrating the county-level

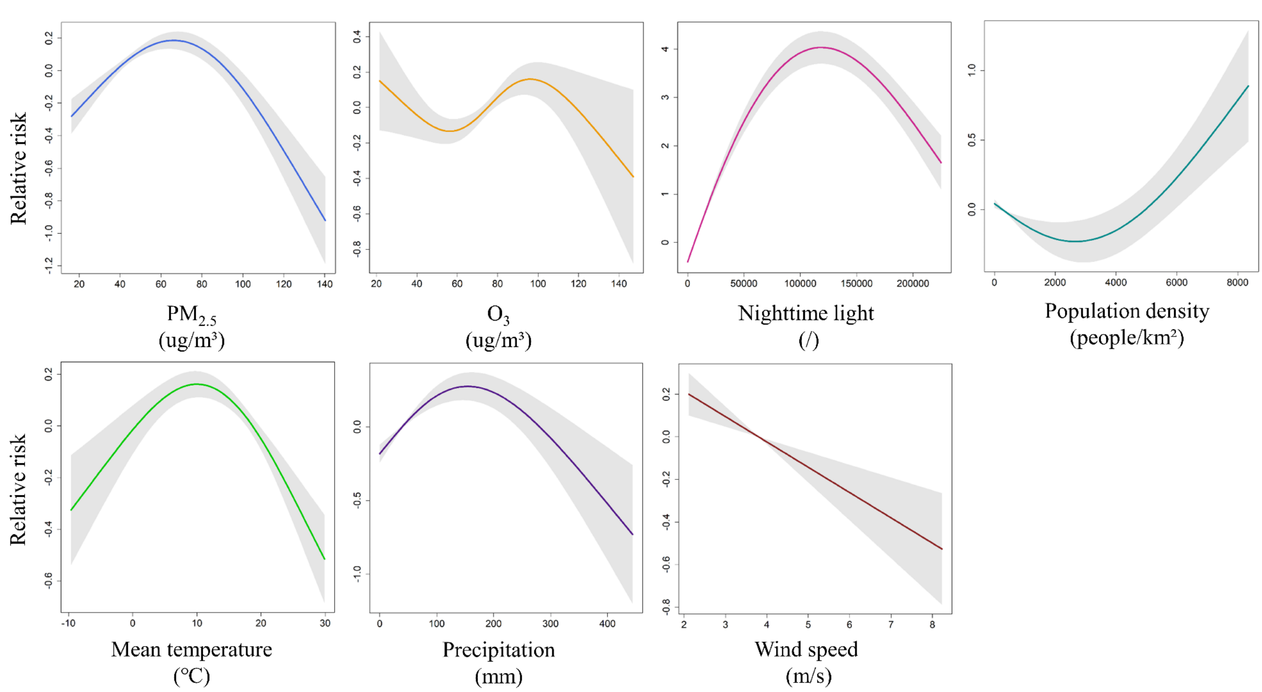

Fig. 3 Nonlinear exposure-response relationships (numerical nonstationarity) between HFMD incidence and seven environmental factors

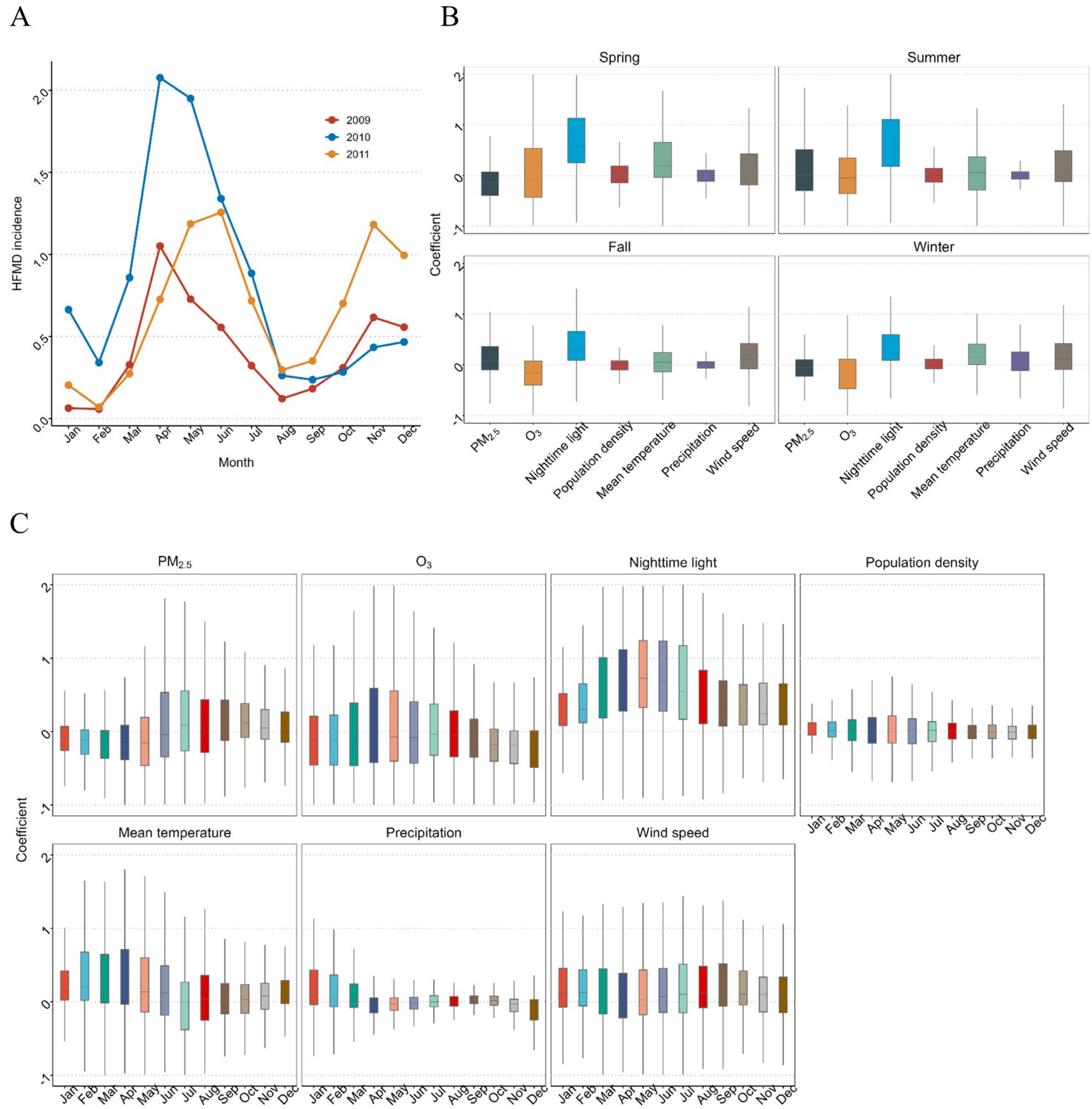

Fig. 4 Temporal heterogeneous associations of seven environmental factors with HFMD incidence. This figure is divided into three parts: (**A**) illustrates the monthly trend of HFMD incidence from 2009 to 2011; (**B**) depicts the seasonal magnitude of temporal nonstationary impacts of these factors; and (**C**) shows the monthly differences in their associations

impacts of seven factors on HFMD incidence across different seasons in the Sichuan-Chongqing region of China (Fig. 5). The distinct variation in coefficients across counties supports the "single county, single policy" approach for disease prevention and control. Additionally, we performed a geographical hotspot analysis using the Getis-Ord Gi* statistic to identify significant clusters (Fig. 5), where hot spots represent significant positive associations between environmental factors and HFMD incidence, and cold spots represent significant negative associations [47]. The analysis revealed clear spatial clustering patterns in the county-level impacts of $PM_{2.5}$ and O_3 on HFMD risk across all four seasons.

Specifically, $PM_{2.5}$ formed significant hot clusters in western Sichuan during spring, northern Sichuan in summer, and around Chengdu in autumn and winter. Conversely, $PM_{2.5}$ exhibited significant cold clusters around Chengdu in spring and in eastern Chongqing during summer and autumn. For O_3, noticeable hot clusters emerged in western Sichuan during summer,

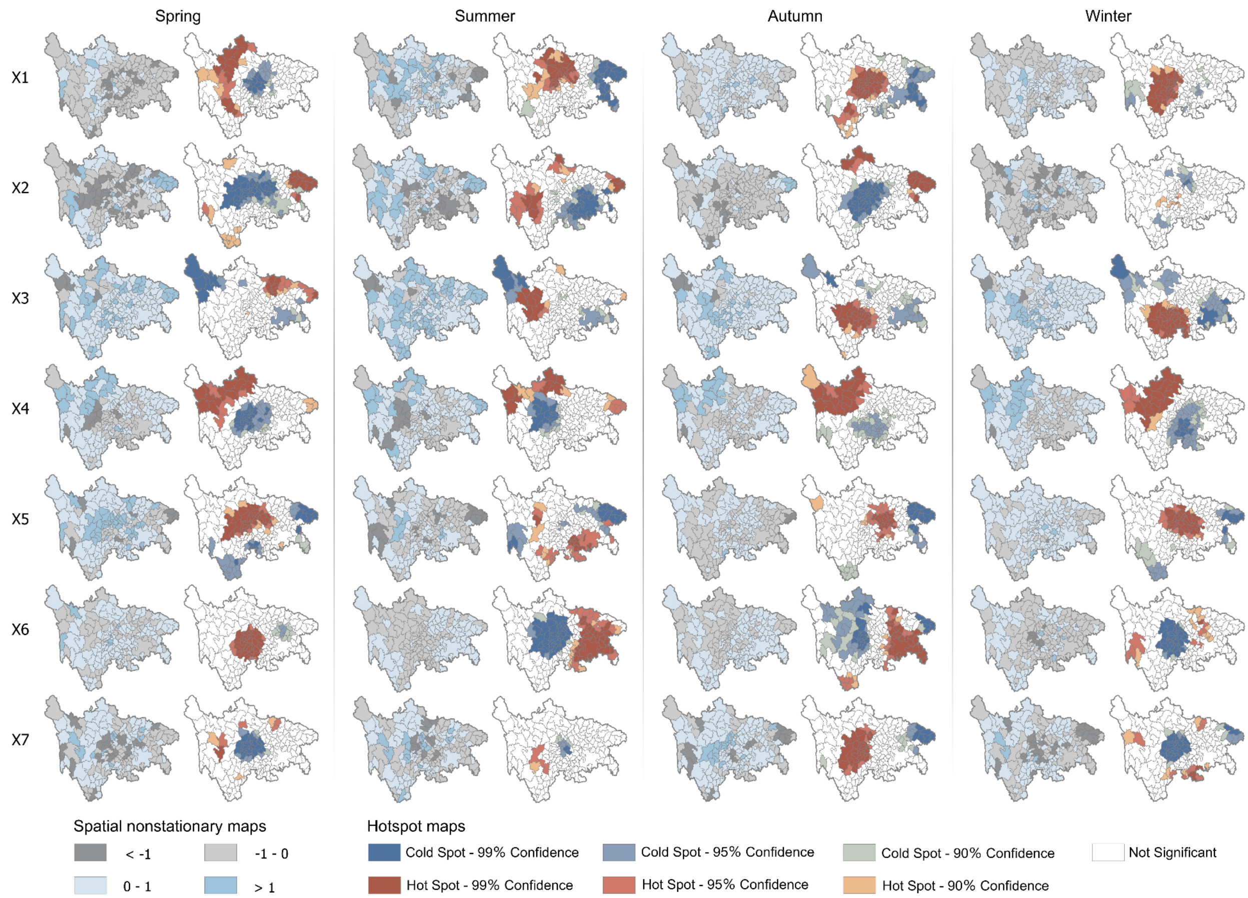

Fig. 5 Spatial heterogeneous associations between HFMD incidence and environmental factors at the county level in Sichuan-Chongqing, China. This figure presents spatial nonstationary maps that reveal county-level variations in the impact of seven environmental factors on HFMD incidence. These variations are quantified using local coefficients derived from the Geographically and Temporally Weighted Regression (GTWR) model. Additionally, hotspot maps, based on an in-depth analysis of these local coefficients, highlight regions experiencing significant, clustered impacts from the specified environmental factors. The factors examined here are X1: $PM_{2.5}$; X2: O_3; X3: Nighttime light; X4: Population density; X5: Mean temperature; X6: Precipitation; and X7: Wind speed

while cold clusters were found in the central region during spring and autumn, and in the eastern part during summer. Other covariates also displayed distinct spatial aggregation. For example, nighttime light formed significant high-risk clusters in western Sichuan during summer and in central areas during autumn and winter, while temperature showed notable high-risk clusters mainly in Chengdu and its surrounding areas. Overall, by examining the spatial nonstationarity and hotspot maps, we identified the spatially heterogeneous impacts of air pollution on HFMD at both the county level and in broader regions through hotspot clustering.

Discussion

Air pollution is a critical global public health concern, with significant implications for well-being, making the investigation of its impact on childhood HFMD essential to support SDG 3 [26]. More importantly, recognizing the three-dimensional nonstationarity of air pollution factors in relation to HFMD enhances the precision and reliability of identifying key risk determinants [49]. This approach avoids oversimplified, global-scale interpretations and fosters a more nuanced understanding of the issue [29]. In this study, we took the Sichuan-Chongqing region in China as an example and, for the first time, addressed the three aspects of numerical, temporal, and spatial nonstationarity to comprehensively elucidate the heterogeneous effects of air pollution factors on small-area HFMD incidence. After controlling for meteorological and social environmental factors, we identified the nonlinear numerical effects of $PM_{2.5}$ and O_3 on HFMD and revealed their spatially and temporally heterogeneous impacts at county and monthly scales. In the following discussion, we will explore these findings from the three distinct perspectives of nonstationarity in environmental health research.

Initially, the findings from the nonlinear relationships shed light on threshold effects between air pollution and HFMD incidence in the Sichuan-Chongqing region, uncovering the numerical nonstationarity of air pollution factors. We observed that low concentrations of $PM_{2.5}$ increased the risk of HFMD as levels rose, a pattern consistent with previous studies [50]. We speculate that $PM_{2.5}$ may elicit adverse reactions in alveolar phagocytes [51], heightening the risk of HFMD. Moreover, $PM_{2.5}$'s potential damage to the central nervous system could heighten susceptibility to the EV-71 virus, which is linked to HFMD [52]. Furthermore, low $PM_{2.5}$ levels may promote outdoor activities, potentially contributing to higher HFMD incidence [53]. Conversely, at high $PM_{2.5}$ concentrations, reduced outdoor activities might naturally lower the risk of infection.

The inhibitory effect of O_3 on HFMD at both low and high concentrations, coupled with its promotive impact at medium concentrations, aligns with findings from previous studies [27, 31]. The promotive effect of O_3 may be attributed to its role as a lung irritant [54], which can adversely affect children's lung function and respiratory system, especially with prolonged exposure. This increased respiratory damage could elevate the risk of HFMD [20]. O_3 pollution tends to rise to relatively high levels on sunny days [53, 54], leading to greater O_3 exposure for children engaging in outdoor activities. The observation that high concentrations of O_3 had an inhibitory effect on HFMD risk is supported by previous studies [21], potentially due to O_3's ability to suppress the production of cytokines associated with EV-71 infection [55].

In line with prior research, our study affirmed the nonlinear impacts of socioeconomic and meteorological factors on HFMD. Increased population density facilitates easier virus transmission [56]. However, with ongoing economic development, improvements in healthcare, education, and hygiene practices help reduce the risk of HFMD. Mean temperature showed an inverted 'V'-shaped association with HFMD, aligning with previous studies [50]. Within an optimal temperature range, rising temperatures promote enterovirus secretion [57], and children are more likely to engage in outdoor activities during comfortable weather conditions. Conversely, extremely high temperatures shorten the survival time of enterovirus, diminishing the likelihood of transmission back to the host [58].

Beyond identifying nonlinear nonstationarity, our study highlights temporal nonstationarity by uncovering distinct seasonal trends in the influence of environmental factors on HFMD prevalence at the county level within the Sichuan-Chongqing region. Consistent seasonal patterns were observed between HFMD incidence and the effects of O_3, mean temperature, and nighttime light, suggesting a synergistic impact on HFMD risk. $PM_{2.5}$ notably increased HFMD risk during summer and autumn, underscoring the need for targeted air pollution control and self-protection measures in these seasons. In winter, while $PM_{2.5}$ concentrations were visibly high [38], preventive measures such as mask-wearing and reduced outdoor activities helped mitigate $PM_{2.5}$-associated risks. Despite lower $PM_{2.5}$ levels in summer, potential health risks remained a concern [59]. O_3 had a significant influence during spring and summer, which coincided with HFMD peaks. Given the increased O_3 exposure in late spring and summer [38], protective measures such as limiting outdoor activities during sunny afternoons become critical. These findings enable more accurate predictions of how future changes in meteorological conditions, air pollution, and socio-economic factors will influence HFMD risk. They also provide valuable insights for policymakers to develop timely, region-specific strategies for HFMD control and prevention.

We also validated the spatial nonstationarity of seven environmental factors influencing HFMD incidence across the four seasons using geographic hotspot detection techniques. Among these factors, $PM_{2.5}$ and O_3 demonstrated distinct seasonal and regional impacts, with O_3 emerging as the primary influencing factor in the western plateau and $PM_{2.5}$ in the basin area. Air pollutants were concentrated in high-high clusters in the basin, while low-low clusters predominated in the plateau region [38]. Tailoring prevention and control strategies to address specific pollutants like $PM_{2.5}$ and O_3 in these diverse regions could lead to more effective mitigation efforts. The use of hotspot maps to analyze the combined impacts of air pollution, meteorological factors, and socio-environmental covariates allows for the development of more comprehensive intervention strategies. For instance, in autumn, authorities in Chengdu could focus on simultaneously reducing $PM_{2.5}$ levels and wind speed to lower HFMD incidence. Prioritizing the combined effects of these factors in high-risk areas could significantly enhance the effectiveness of HFMD prevention and control measures.

Our study provides policy-relevant insights into the diverse effects of air pollution on HFMD across varying pollutant concentrations, regions, and timeframes, through a comprehensive three-perspective nonstationarity analysis. The findings reveal that even $PM_{2.5}$ and O_3 levels deemed 'safe' can pose significant health risks to children, emphasizing the need for stricter air quality monitoring. Temporal analysis pinpoints high-risk periods, highlighting the importance of time-specific interventions to preempt HFMD outbreaks. Seasonally adjusted strategies, such as focusing on $PM_{2.5}$ reduce in autumn and O_3 control in summer, could significantly lower HFMD risks. Spatial risk mapping further underscores the necessity of localized policies that target specific pollutants in high-risk areas. For instance, reducing

$PM_{2.5}$ in Chengdu during autumn and winter, and managing O_3 levels in western Sichuan during summer, exemplifies this targeted, region-specific approach. Such differentiated strategies, driven by three-perspective heterogeneous analysis, are crucial for improving early warning systems and predictive models. By adopting tailored interventions, policymakers can enhance public health measures, protect children's health, and mitigate HFMD risks more effectively. Identifying county-level temporal and spatial disparities, alongside pollutant concentrations, enables the customization of prevention strategies. Authorities can adjust environmental health policies to better protect vulnerable groups, particularly children. This data-driven approach is key to improving public health initiatives and reducing the community disease burden.

Conclusions

This study, from numerical, temporal, and spatial nonstationary perspectives, successfully unveiled the heterogeneous relationships between air pollution and HFMD in the Sichuan-Chongqing region, China, at both county and monthly scales. We highlighted the significant influences of $PM_{2.5}$ and O_3 on HFMD incidence, revealing that low concentrations of $PM_{2.5}$ and moderate concentrations of O_3 were associated with elevated risks. The sensitive periods for these pollutants were autumn for $PM_{2.5}$ and summer for O_3. Furthermore, the spatial clustering of $PM_{2.5}$ and O_3 impacts on HFMD emphasized the need for localized approaches. Our findings show that a one-size-fits-all approach to HFMD mitigation is ineffective. Instead, region-specific and time-sensitive interventions, tailored to local conditions and pollutant levels, are essential. By concurrently accounting for the three-perspective nonstationarity, our study supports the development of targeted prevention measures to improve children's health, contributing to the achievement of SDG 3. Incorporating the three dimensions of nonstationarity also enhances the precision of identifying environmental health determinants, offering a valuable modeling framework for future research.

Our study has certain limitations. First, the macro-geospatial ecological analysis may not fully capture individual-level exposure-response relationships. Second, limited access to up-to-date disease data, the absence of certain air pollution indicators, and the exclusion of factors like hygiene practices and vaccination rates constrained our analysis. Despite these challenges, we successfully identified HFMD's complex heterogeneous risk patterns, offering valuable insights for public health and policy development. Future research should explore biological mechanisms and risk factor interactions, using comprehensive data across various scales [60], such as grid and city levels, to provide more tailored public health recommendations.

Abbreviations

GAM	Generalized Additive Model
GTWR	Geographically and Temporally Weighted Regression
HFMD	Hand, Foot and Mouth Disease
RF	Random Forest
SDG	Sustainable Development Goal
VIF	Variance Inflation Factor

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12889-024-20342-x.

Additional file 1:Figure S1. Results of variables' correlation. **Table S1**. The VIF test results of factors.

Acknowledgements

We would like to express our gratitude to all study participants for their cooperation and three anonymous reviewers for their constructive suggestions regarding the manuscript.

Author contributions

CS, ZT and XL contributed to the concept and design of the manuscript. ZT, QS, and XL wrote the main manuscript text. YB and JW contributed to the acquisition, analysis, and interpretation of data. QS and XL completed statistical modelling. QS, XL, and MX contributed to the visualization. CS, JP, MX, YB, JW, XL, XW, YZ, QX, and ZW played role in the review and editing. All authors reviewed the manuscript and approved the final version.

Funding

The study received collaborative support from various sources, including grants from the National Natural Science Foundation of China (42071379, 41701448, 72374149, 72104159, 72104158, 72204175, 72204031), the Sichuan Science and Technology Program (2023YFS0406, 2022NSFSC0642), and the Institute of New Productive Forces in Health (HN240301A) at West China School of Public Health/West China Fourth Hospital, Sichuan University.

Data availability

Please contact the corresponding authors for data requests.

Declarations

Ethics approval and consent to participate

According to the "Ethical Review Measures for Biomedical Research Involving Humans" publicly available on the website of the Central People's Government of the People's Republic of China (https://www.gov.cn/zhengce/2016-10/12/content_5713806.htm), our study focused on spatial epidemiological studies at the macro-population level, employing a geographical perspective. Since all of the patients' records were anonymized and no individual information were used, an ethical review was deemed unnecessary.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]State Key Laboratory of Oil and Gas Reservoir Geology and Exploitation, School of Geoscience and Technology, Southwest Petroleum University, Chengdu, Sichuan, China
[2]West China Health & Medical Geography Group within HEOA Think Tank, West China School of Public Health and West China Fourth Hospital, Sichuan University, Chengdu, Sichuan, China

[3]Institute for Healthy Cities and West China Research Centre for Rural Health Development, West China-PUMC C.C. Chen Institute of Health, Sichuan University, Chengdu, Sichuan, China
[4]School of Public Health, Xi'an Jiaotong University, Xi'an, Shaanxi, China
[5]Department of Epidemiology and Biostatistics, School of Public Health, Chengdu Medical College, Chengdu, Sichuan, China
[6]State Key Laboratory of Remote Sensing Science, Faculty of Geographical Science, Beijing Normal University, Beijing, China
[7]State Key Laboratory of Resources and Environmental Information System (LREIS), Institute of Geographic Sciences and Natural Resources Research, Chinese Academy of Sciences, Beijing, China
[8]School of Spatial Planning and Design, Hangzhou City University, Hangzhou, Zhejiang, China
[9] School of Public Health and Emergency Management, Southern University of Science and Technology, Nanshan, Shenzhen, China

Received: 1 April 2024 / Accepted: 9 October 2024
Published online: 15 October 2024

References

1. Robinson CR, Doane FW, Rhodes AJ. Report of an outbreak of febrile illness with pharyngeal lesions and exanthem: Toronto, summer 1957; isolation of group a Coxsackie virus. Can Med Assoc J. 1958;79:615–21.
2. Bian L, Wang Y, Yao X, Mao Q, Xu M, Liang Z. Coxsackievirus A6: a new emerging pathogen causing hand, foot and mouth disease outbreaks worldwide. Expert Rev Anti Infect Ther. 2015;13:1061–71.
3. Yang F, Zhang T, Hu Y, Wang X, Du J, Li Y, et al. Survey of enterovirus infections from hand, foot and mouth disease outbreak in China, 2009. Virol J. 2011;8:508.
4. Zhang X, Zhang Y, Li H, Liu L. Hand-Foot-and-Mouth Disease-Associated Enterovirus and the development of multivalent HFMD vaccines. Int J Mol Sci. 2023;24:169.
5. Xing W, Liao Q, Viboud C, Zhang J, Sun J, Wu JT, et al. Hand, foot, and mouth disease in China, 2008-12: an epidemiological study. Lancet Infect Dis. 2014;14:308–18.
6. Peng D, Ma Y, Liu Y, Lv Q, Yin F. Epidemiological and aetiological characteristics of hand, foot, and mouth disease in Sichuan Province, China, 2011–2017. Sci Rep. 2020;10:6117.
7. Li M, Ma Y, Luo C, Lv Q, Liu Y, Zhang T, et al. Modification effects of socioeconomic factors on associations between air pollutants and hand, foot, and mouth disease: a multicity time-series study based on heavily polluted areas in the basin area of Sichuan Province, China. PLoS Negl Trop Dis. 2022;16:e0010896.
8. Aggarwal M, Bansal N, Naresh A, Tikute S, Dubey S, Rajmohan KS, et al. Clinical profile and molecular typing of viral etiological agents associated with Hand, Foot and Mouth Disease (HFMD): a study from Udhampur, Northern India. Indian J Med Microbiol. 2023;41:97–100.
9. Koh WM, Bogich T, Siegel K, Jin J, Chong EY, Tan CY, et al. The epidemiology of Hand, Foot and Mouth Disease in Asia: a systematic review and analysis. Pediatr Infect Dis J. 2016;35:e285–300.
10. Yang S, Wu J, Ding C, Cui Y, Zhou Y, Li Y, et al. Epidemiological features of and changes in incidence of infectious diseases in China in the first decade after the SARS outbreak: an observational trend study. Lancet Infect Dis. 2017;17:716–25.
11. Coll-Seck A, Clark H, Bahl R, Peterson S, Costello A, Lucas T. Framing an agenda for children thriving in the SDG era: a WHO–UNICEF–Lancet Commission on Child Health and Wellbeing. Lancet. 2019;393:109–12.
12. Cao C, Li G, Zheng S, Cheng J, Lei G, Tian K et al. Research on the environmental impact factors of Hand-Foot-Mouth Disease in Shenzhen, China using RS and GIS technologies. Int Geosci Remote Sens Symp. 2012;:7240–3.
13. Leong PF, Labadin J, Rahman SBA, Juan SFS. Quantifying the relationship between the climate and Hand-Foot-Mouth Disease (HFMD) incidences. 2011 4th Int Conf Model Simul Appl Optim ICMSAO 2011. 2011;:1–5.
14. Kim BI, Ki H, Park S, Cho E, Chun BC. Effect of climatic factors on hand, foot, and mouth disease in South Korea, 2010–2013. PLoS ONE. 2016;11:e0157500.
15. Huang J, Wang J, Bo Y, Xu C, Hu M, Huang D. Identification of health risks of hand, foot and mouth disease in China using the geographical detector technique. Int J Environ Res Public Health. 2014;11:3407–23.
16. Bo YC, Song C, Wang JF, Li XW. Using an autologistic regression model to identify spatial risk factors and spatial risk patterns of hand, foot and mouth disease (HFMD) in Mainland China. BMC Public Health. 2014;14:358.
17. Li T, Yang Z, Di B, Wang M. Hand-foot-and-mouth disease and weather factors in Guangzhou, southern China. Epidemiol Infect. 2014;142:1741–50.
18. Phung D, Nguyen HX, Nguyen HLT, Do CM, Tran QD, Chu C. Spatiotemporal variation of hand-foot-mouth disease in relation to socioecological factors: a multiple-province analysis in Vietnam. Sci Total Environ. 2018;610–611:983–91.
19. Song C, Shi X, Bo Y, Wang J, Wang Y, Huang D. Exploring spatiotemporal nonstationary effects of climate factors on hand, foot, and mouth disease using bayesian spatiotemporally varying coefficients (STVC) model in Sichuan, China. Sci Total Environ. 2019;648:550–60.
20. Huang R, Bian G, He T, Chen L, Xu G. Effects of meteorological parameters and PM10 on the incidence of hand, foot, and mouth disease in children in China. Int J Environ Res Public Health. 2016;13:481.
21. Yu G, Li Y, Cai J, Yu D, Tang J, Zhai W, et al. Short-term effects of meteorological factors and air pollution on childhood hand-foot-mouth disease in Guilin, China. Sci Total Environ. 2019;646:460–70.
22. Selgrade MK, Plopper CG, Gilmour MI, Conolly RB, Foos BSP. Assessing the Health effects and risks Associated with Children's inhalation exposures—Asthma and Allergy. J Toxicol Environ Health. 2008;71:196–207.
23. Chen G, Zhang W, Li S, Williams G, Liu C, Morgan GG, et al. Is short-term exposure to ambient fine particles associated with measles incidence in China? A multi-city study. Environ Res. 2017;156:306–11.
24. Cheng Y, Kan H. Effect of the interaction between outdoor air pollution and extreme temperature on daily mortality in Shanghai, China. J Epidemiol. 2012;22:28–36.
25. Wei J, Li Z, Lyapustin A, Sun L, Peng Y, Xue W, et al. Reconstructing 1-km-resolution high-quality PM2.5 data records from 2000 to 2018 in China: spatiotemporal variations and policy implications. Remote Sens Environ. 2021;252:112136.
26. Yin F, Ma Y, Zhao X, Lv Q, Liu Y, Li X, et al. Analysis of the effect of PM10 on hand, foot and mouth disease in a basin terrain city. Sci Rep. 2019;9:3233.
27. Gu S, Li D, Lu B, Huang R, Xu G. Associations between ambient air pollution and daily incidence of pediatric hand, foot and mouth disease in Ningbo, 2014–2016: a distributed lag nonlinear model. Epidemiol Infect. 2020;148:e46.
28. Peng H, Chen Z, Cai L, Liao J, Zheng K, Li S, et al. Relationship between meteorological factors, air pollutants and hand, foot and mouth disease from 2014 to 2020. BMC Public Health. 2022;22:998.
29. Kwan MP. The stationarity bias in research on the environmental determinants of health. Heal Place. 2021;70:102609.
30. Tao J, Ma Y, Zhuang X, Lv Q, Liu Y, Zhang T, et al. How to improve infectiousdisease prediction by integratingenvironmental data: an application of a novel ensemble analysis strategyto predict HFMD. Epidemiol Infect. 2021;149:e34.
31. Yan S, Wei L, Duan Y, Li H, Liao Y, Lv Q, et al. Short-term effects of meteorological factors and air pollutants on hand, foot and mouth disease among children in Shenzhen, China, 2009–2017. Int J Environ Res Public Health. 2019;16:3639.
32. Qian J, Luo C, Lv Q, Liu Y, Zhang T, Yin F, et al. Associations between ambient air pollutants and childhood hand, foot, and mouth disease in Sichuan, China: a spatiotemporal study. Sci Rep. 2023;13:3993.
33. Hastie T, Tibshirani R. Generalized additive models for medical research. Stat Methods Med Res. 1995;4:187–96.
34. Huang B, Wu B, Barry M. Geographically and temporally weighted regression for modeling spatio-temporal variation in house prices. Int J Geogr Inf Sci. 2010;24:383–401.
35. Wei J, Li Z, Li K, Dickerson RR, Pinker RT, Wang J, et al. Full-coverage mapping and spatiotemporal variations of ground-level ozone (O3) pollution from 2013 to 2020 across China. Remote Sens Environ. 2022;270:112775.
36. Wei J, Li Z, Xue W, Sun L, Fan T, Liu L, et al. The ChinaHighPM10 dataset: generation, validation, and spatiotemporal variations from 2015 to 2019 across China. Environ Int. 2021;146:106290.
37. Wei J, Li Z, Chen X, Li C, Sun Y, Wang J, et al. Separating Daily 1 km PM2.5 Inorganic Chemical composition in China since 2000 via Deep Learning Integrating Ground, Satellite, and Model Data. Environ Sci Technol. 2023;57:18282–95.
38. Jin Z, Gao X, Li B, Zhai D, Xu J, Li F. Spatio-temporal distribution pattern and influencing factors of air quality in Sichuan-Chongqing region. ACTA Ecol Sin. 2022;42:4379–88.

39. Sorooshian S, Hsu KL, Gao X, Gupta HV, Imam B, Braithwaite D. Evaluation of PERSIANN system satellite-based estimates of tropical rainfall. Bull Am Meteorol Soc. 2000;81:2035–46.
40. Li X, Xu H, Chen X, Li C. Potential of NPP-VIIRS Nighttime Light Imagery for modeling the Regional Economy of China. Remote Sens. 2013;5:3057–81.
41. Fox J, Weisberg S. An {R} companion to Applied Regression. Third. Sage; 2019.
42. Liaw A, Wiener M. Classification and regression by randomForest. R News. 2002;2:18–22.
43. O'Brien RM. A caution regarding rules of thumb for variance inflation factors. Qual Quant. 2007;41:673–90.
44. Song C, Fang L, Xie M, Tang Z, Zhang Y, Tian F, et al. Revealing spatiotemporal inequalities, hotspots, and determinants in healthcare resource distribution: insights from hospital beds panel data in 2308 Chinese counties. BMC Public Health. 2024;24:423.
45. Breiman L. Random forests. Mach Learn. 2001;45:5–32.
46. Wood SN. Fast stable restricted maximum likelihood and marginal likelihood estimation of semiparametric generalized linear models. J R Stat Soc. 2011;73:3–36.
47. Wan Q, Tang Z, Pan J, Xie M, Wang S, Yin H, et al. Spatiotemporal heterogeneity in associations of national population ageing with socioeconomic and environmental factors at the global scale. J Clean Prod. 2022;373:133781.
48. Luo J, Zhang J, Huang X, Liu Q, Luo B, Zhang W, et al. Characteristics, evolution, and regional differences of biomass burning particles in the Sichuan Basin, China. J Environ Sci. 2020;89:35–46.
49. Chen VYJ, Wu PC, Yang TC, Su HJ. Examining non-stationary effects of social determinants on cardiovascular mortality after cold surges in Taiwan. Sci Total Environ. 2010;408:2042–9.
50. Du Z, Lawrence WR, Zhang W, Zhang D, Yu S, Hao Y. Interactions between climate factors and air pollution on daily HFMD cases: a time series study in Guangdong, China. Sci Total Environ. 2019;656:1358–64.
51. You S, Yao Z, Dai Y, Wang CH. A comparison of PM exposure related to emission hotspots in a hot and humid urban environment: concentrations, compositions, respiratory deposition, and potential health risks. Sci Total Environ. 2017;599–600:464–73.
52. Yang Z, Hao J, Huang S, Yang W, Zhu Z, Tian L, et al. Acute effects of air pollution on the incidence of hand, foot, and mouth disease in Wuhan, China. Atmos Environ. 2020;225:117358.
53. United States EPA. Air quality and outdoor activity guidance for schools. 2014.
54. Wang T, Xue L, Brimblecombe P, Lam YF, Li L, Zhang L. Ozone pollution in China: a review of concentrations, meteorological influences, chemical precursors, and effects. Sci Total Environ. 2017;575:1582–96.
55. Lin YC, Juan HC, Cheng YC. Ozone exposure in the culture medium inhibits enterovirus 71 virus replication and modulates cytokine production in rhabdomyosarcoma cells. Antiviral Res. 2007;76:241–51.
56. Li L, Qiu W, Xu C, Wang J. A spatiotemporal mixed model to assess the influence of environmental and socioeconomic factors on the incidence of hand, foot and mouth disease. BMC Public Health. 2018;18:274.
57. Bélanger M, Gray-Donald K, O'loughlin J, Paradis G, Hanley J. Influence of Weather conditions and season on physical activity in adolescents. Ann Epidemiol. 2009;19:180–6.
58. Zhu L, Wang X, Guo Y, Xu J, Xue F, Liu Y. Assessment of temperature effect on childhood hand, foot and mouth disease incidence (0-5years) and associated effect modifiers: a 17 cities study in Shandong Province, China, 2007–2012. Sci Total Environ. 2016;551–552:452–9.
59. Liu C, Chen R, Sera F, Vicedo-Cabrera AM, Guo Y, Tong S, et al. Ambient Particulate Air Pollution and Daily Mortality in 652 cities. N Engl J Med. 2019;381:705–15.
60. Song C, Yin H, Shi X, Xie M, Yang S, Zhou J, et al. Spatiotemporal disparities in regional public risk perception of COVID-19 using bayesian spatiotemporally varying coefficients (STVC) series models across Chinese cities. Int J Disaster Risk Reduct. 2022;77:103078.

Publisher's note