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Detecting the association between meteorological factors and hand, foot, and mouth disease using spatial panel data models

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SUMMARY

Objectives: The aim of this study was to quantify the relationship between meteorological factors and the occurrence of hand, foot, and mouth disease (HFMD) among children in Shandong Province, China, at a county level, using spatial panel data models.

Methods: Descriptive analysis was applied to describe the epidemic characteristics of HFMD from January 2008 to December 2012, and then a global autocorrelation statistic (Moran's I) was used to detect the spatial autocorrelation of HFMD in each year. Finally, spatial panel data models were performed to explore the association between the incidence of HFMD and meteorological factors.

Results: Moran's I at the county level were high, from 0.30 to 0.45 ($p < 0.001$), indicating the existence of a high spatial autocorrelation on HFMD. Spatial panel data models are more appropriate to describe the data. Results showed that the incidences of HFMD in Shandong Province, China were significantly associated with average temperature, relative humidity, vapor pressure, and wind speed.

Conclusions: Spatial panel data models are useful when longitudinal data with multiple units are available and spatial autocorrelation exists. The association found between HFMD and meteorological factors makes a contribution towards advancing knowledge with respect to the causality of HFMD and has policy implications for HFMD prevention and control.

1. Introduction

Hand, foot, and mouth disease (HFMD) is a common infectious disease, particularly in those under the age of 5 years.[1] It is mainly caused by the enteroviruses, especially coxsackievirus A16 (CA16) and enterovirus 71 (EV71).[2] Direct contact with respiratory droplets, feces, and blister fluid of an infective patient, or contact with a contaminated environment, e.g., water, food, or surfaces, can result in the spread of the disease.[3] In recent years, the HFMD outbreak trend has increased among children in China,[4–6] and this is regarded as an important public health problem by health officers.[1]

Many studies have been performed to analyze the association between meteorological factors and climate-sensitive infectious diseases due to their potential as early warning tools.[7–9] The relationship between meteorological factors and HFMD has been investigated in a number of studies.[10–14] For instance, Hu et al.[10] found that climate factors were potential determinants of the incidence of HFMD in most areas in China, using geographically weighted regression. A study by Huang et al.[12] provided evidence that the incidence of HFMD in children was associated with the high average temperature and high relative humidity in Guangzhou. However, to our knowledge, most previous studies have been conducted focusing only on a spatial dimension or on a time dimension approach. Spatial dimension analysis alone is performed on the basis of data at a certain temporal point, and time series analysis alone usually focuses on a certain region, which might result in a loss of information by ignoring the heterogeneity in both time and space. The space–time scan statistic provides a method for detecting possible spatial–temporal clusters of disease during a given study period, but it cannot be used to examine the risk factors of disease.[15]

Compared to traditional methods based on cross-sectional or time-series data alone, spatial panel data models are more informative,[16] and can enable researchers to control for both spatial dependency and unknown heterogeneity.[17] In this study,

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spatial panel data models were performed to analyze the relationship between meteorological variables and the incidence of HFMD among children in 140 counties in Shandong Province, China.

2. Materials and methods

2.1. Study site

Shandong Province, located between latitude 34°25′ and 38°23′ North, and longitude 114°36′ and 112°43′ East, is a coastal province in East China with a population of approximately 98 million (Figure 1). Shandong Province features a monsoon climate of medium latitudes.

2.2. HFMD surveillance data

County-level HFMD data for Shandong Province for the period January 2008 to January 2012 were obtained from the China Information System for Disease Control and Prevention (CISDCP, http://www.cdpc.chinacdc.cn). The clinical criteria for diagnosis of an HFMD case were provided in a guidebook published by the Chinese Ministry of Health in 2009.[18]

Meteorological county-level monthly climate factor data for Shandong Province for the period January 2008 to December 2012 were obtained from the China Meteorological Data Sharing Service System. Monthly meteorological variables assessed in this study included average atmospheric pressure (AAP), average temperature (AT), average vapor pressure (AVP), average relative humidity (ARH), monthly precipitation (MP), average wind speed (AWS), and monthly total sunshine hours (MSH).

2.3. Statistical analysis

2.3.1. Global spatial autocorrelation analysis

For the purpose of providing additional information about the presence of spatial dependence in the dependent variable, the HFMD incidences were annualized for 140 counties, and then the global Moran's *I* was calculated for each year. The global Moran's *I*, is a well-known measure to evaluate whether the spatial pattern is clustered, dispersed, or random.[19] Monte Carlo randomization was employed to assess the significance of Moran's *I*. A statistically significant estimate of Moran's *I* (*Z*-score $\geq$1.96) indicated that neighboring counties had similar incidences of HFMD.

2.3.2. Spatial panel data models

Spatial panel data models were used to quantify the association between the incidence of HFMD and meteorological variables, which could address data with spatial dependence and also enable researchers to consider both spatial and temporal heterogeneity. Spatial panel data typically refers to data containing continuous observations of a number of spatial units. According to Elhorst,[16] spatial panel data models are more informative and contain more variation and less collinearity among the variables compared to cross-sectional or time series models. The use of panel data results in a greater availability of degrees of freedom, and hence increases the efficiency of the estimation.

A simple linear model between a dependent variable *Y* and a set of *K* independent variables *X* is given as follows:

$$\mathrm{y_{it}} = \mathrm{X}\beta + \epsilon_{\mathrm{it}} \tag{1}$$

where *i* is an index for the cross-sectional dimension (spatial units), with *i* = 1, ..., *N*, and *t* is an index for the time dimension (time periods), with *t* = 1, ..., *T*. y_{it} is an observation on the dependent variable at *i* and *t*. X_{it} is a 1-by-*K* row vector of observations on the independent variables, and β is a matching *K*-by-1 vector of fixed but unknown parameters. ε_{it} is an independently and identically distributed error term for *i* and *t* with zero mean and variances.[2]

The main drawback of this model is its failure to account for spatial and temporal heterogeneity, because spatial units and time periods tend to have spatial or temporal heterogeneity, and space- and time-specific variables do influence the dependent variable. To incorporate a variable intercept m_i and/or g_t representing the effects of the omitted variables that are peculiar to each spatial unit and/or time period, the basic form of the simple panel data model with spatial and temporal specific effect is:

$$\mathrm{y_{it}} = \mu_{\mathrm{i}} + \gamma_t + \mathrm{X}\beta + \mu_{\mathrm{i}} + \epsilon_{\mathrm{it}} \tag{2}$$

where μ_i denotes a spatial specific effect and γ_t represents temporal specific effects. The spatial specific effects may be treated as fixed effects or as random effects. A random effect is an appropriate specification if a certain number of individuals are randomly drawn from a large population; the fixed effect model is favored[20] when the regression analysis is applied to a precise set of regions. For this reason, since our data contained all counties of the study region, we established fixed effects panel data models that included spatial error autocorrelation or a spatially lagged dependent variable. At the same time, we compared the random effects specification against fixed effects specification using Housman's specification test; it also suggested that fixed effects specification was more appropriate.

If spatial dependence exists, the simple panel data models with specific effects can be extended to include spatially lagged dependent variables or spatial error autocorrelation terms named as the spatial lag and the spatial error model, respectively.

The spatial lag model posits that the dependent variable depends on the dependent variable observed in neighboring units.[16] For example, the spatial and temporal fixed effects panel data model including a spatially lagged dependent variable can be specified as follows:[21]

$$y_{it} = \mu_i + \mu_t + \rho\sum_{j=1}^{N} W_{ij} y_{jt} + X'_{it}\beta + \epsilon_{it} \tag{3}$$

The fixed effects spatial error model can be written as:[21]

$$\begin{aligned} y_{it} &= \mu_i + \mu_t + X'_{it}\beta + \phi_{it} \\ \phi_{it} &= \lambda\sum_{j=1}^{N} W_{ij}\phi_{it} + \epsilon_{it} \end{aligned} \tag{4}$$

where *W* is an $N \times N$ positive non-stochastic spatial weight matrix; ρ is the spatial autoregressive coefficient and λ is usually called the spatial autocorrelation coefficient.

Likelihood ratio (LR) tests can be used to determine the extension of the model with spatial and/or time-period fixed effects. Whether the spatial lag model and/or the spatial error model are more appropriate to describe the data than a simple panel data model can be tested using the Lagrange multiplier (LM) and robust Lagrange multiplier (robust LM) test. If the LM lag is more significant than LM error and the robust LM lag test is significant and robust LM error is not significant, then the spatial lag model is more appropriate, and vice versa. Model evaluation can be conducted based on the goodness of fit; R^2 and log-likelihood are the commonly used effective criteria.[22–24] The spatial panel data models and LR and LM tests used in this study were executed in Matlab R2009a (Mathworks Inc., Natick, MA, USA).

3. Results

3.1. Descriptive analysis

A total of 497 664 HFMD cases were reported in Shandong Province between 2008 and 2012. Table 1 shows that 93.99% of

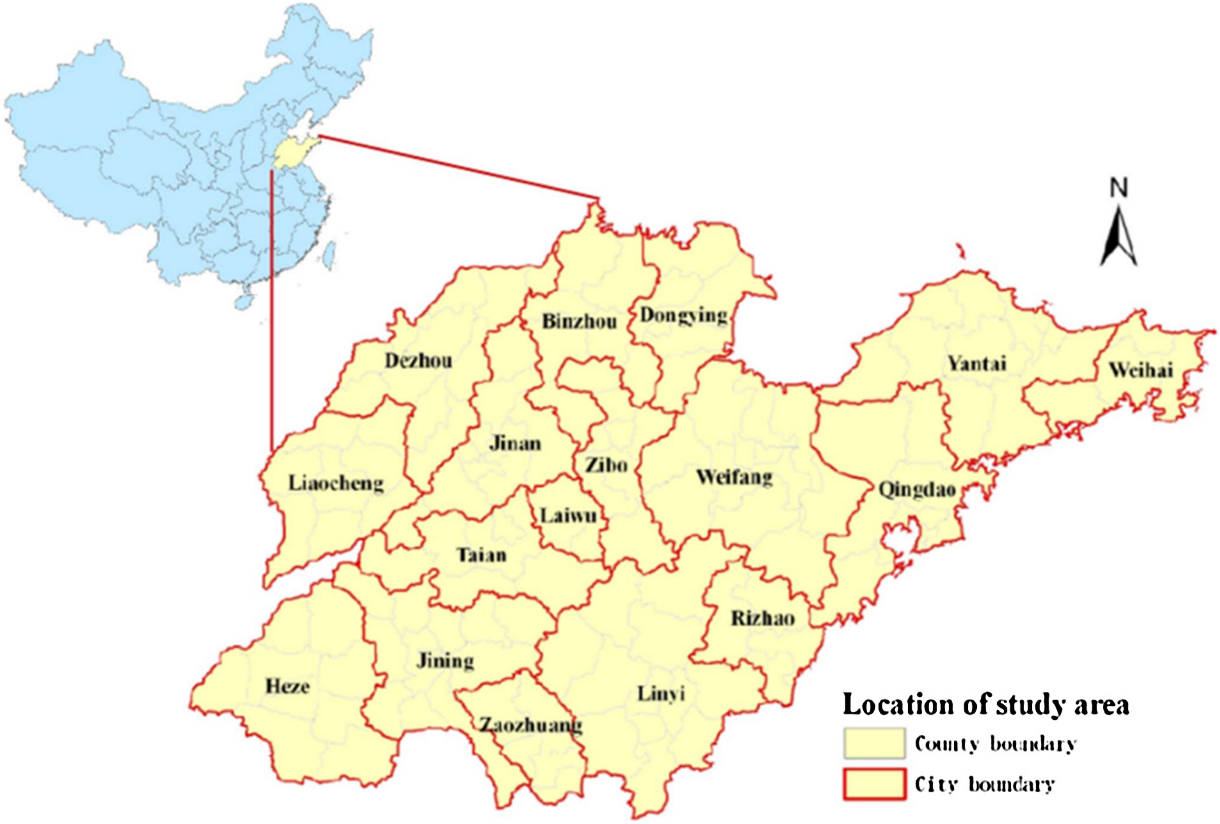

Figure 1. Location of the study area, Shandong Province in China.

cases in the outbreaks were under 5 years of age. Consequently, this study focused on the 0–5 years age group in the subsequent spatial analysis.

Figure 2 shows the epidemic trend in monthly incidence of HFMD among children aged 0–5 years; in the study areas, more cases occurred in April and July, indicating a potential seasonality in the incidence of HFMD. Table 2 shows the descriptive statistics for meteorological variables in Shandong Province in 2008–2012.

3.2. Spatial autocorrelation of HFMD incidence

Table 3 lists the results of the spatial autocorrelation test, which demonstrated a high global spatial autocorrelation of HFMD at the county level in Shandong Province for each epidemic year during 2008–2012. The high Moran's *I*, from 0.30 to 0.45 ($p < 0.001$), indicated the existence of high spatial dependency on the occurrence of HFMD.

Therefore, spatial autocorrelation should be entered into the regression models, and the spatial panel data models are good options.

3.3. Spatial panel data models

Due to the dependent variable not showing a normal distribution, logarithmic transformation of the dependent variable was chosen; however because of some zeroes in the dependent variable, a very small value (0.01) was added before the logarithmic transformation.

Table 1
Descriptive characteristics of HFMD cases, Shandong Province, 2008–2012

Age	2008	2009	2010	2011	2012	Total
0–5 years	30 975	131 686	134 181	88 300	82 590	467 732
>5 years	2004	7640	7093	6942	6253	29 932
Total	32 979	139 326	141 274	95 242	88 843	497 664

HFMD, hand, foot, and mouth disease.

Table 4 shows the statistical test results to determine which specific fixed effect and which type of spatial dependency term should be included in the model. The LR tests justified the extension of the model with both spatial and time-period fixed effects. LM and robust LM test results demonstrated that the spatial lag model would be more appropriate than the spatial error model. Overall, the test results indicated that the spatial and time-period fixed effects models, including spatial lagged dependent variables, were more appropriate to describe the data.

Three models were then fitted; the results are shown in Table 5. By comparing their R^2 and log-likelihood values with that

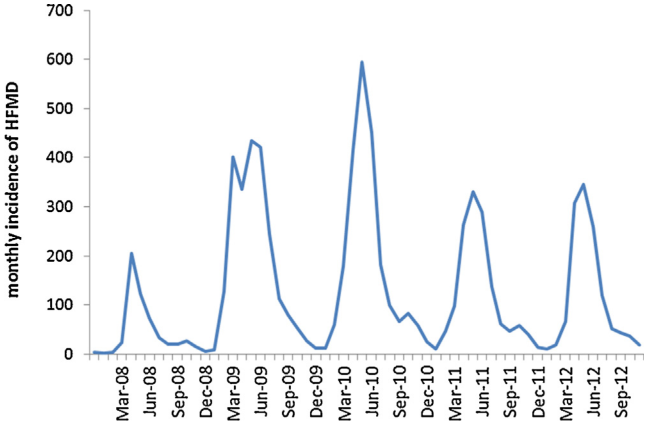

Figure 2. Monthly incidence (1/100 000) of HFMD (0–5 years) in Shandong Province from January 2008 to December 2012.

Table 2
Descriptive statistics for meteorological variables, 2008–2012

	AAP (hPa)	AT (°C)	AVP (Pa)	ARH (%)	MP (mm)	AWS (km/h)	MSH (hours)
Minimum	968.9	−6.20	1.40	29.00	0	0.80	50.40
Mean	1009.1	13.44	12.29	64.19	57.97	2.37	186.00
Maximum	1032.2	29.20	31.90	94.00	519.10	7.20	332.10
SD	10.61	10.07	8.35	11.90	76.83	0.78	45.90

AAP, atmospheric pressure; AT, average temperature; AVP, average vapor pressure; ARH, average relative humidity; MP, monthly precipitation; AWS, average wind speed; MSH, monthly total sunshine hours; SD, standard deviation.

Table 3
Results of the spatial autocorrelation test on HFMD cases in Shandong Province, 2008–2012

Year	Moran's *I*	*Z*-score	*p*-Value
2008	0.3011	5.7715	<0.001
2009	0.3748	7.0003	<0.001
2010	0.2975	5.5843	<0.001
2011	0.4555	8.4924	<0.001
2012	0.3496	6.5377	<0.001

HFMD, hand, foot, and mouth disease.

of the classic fixed effects model, we found that the two spatial panel data models were better than the classic fixed effects model, and that the spatial lag model was more appropriate than the spatial error model. The spatial coefficients in both spatial panel models were positive and statistically significant, indicating that the HFMD incidence of a spatial unit correlates positively with the incidence of surrounding spatial units. Average temperature and relative humidity had a significant positive correlation with the incidence of HFMD; average vapor pressure and wind speed had a significant negative association with the incidence of HFMD. The R^2 was 0.6177, indicating that the meteorological factors and the spatial neighborhood effects could jointly explain 61.77% variation of the HFMD incidence.

4. Discussion

This study has, for the first time, quantified the relationship between HFMD and meteorological factors using spatial panel data models on the basis of longitudinal data from 140 counties for the period 2008 to 2012. The findings showed that the monthly incidences of HFMD in Shandong Province, China were significantly associated with average temperature, relative humidity, vapor pressure and wind speed. This research makes a contribution towards advancing knowledge with respect to the causality of HFMD and has policy implications for HFMD prevention and control.

In this study, children under 5 years of age accounted for most of the HFMD cases during the study period. The seasonality of HFMD in Shandong Province showed that there were larger seasonal peaks between April and July, which is similar to the results of other studies.[6,25]

In Shandong Province, the distribution patterns of HFMD at the county level were clustered, with high Moran's *I* from 0.30 to 0.46 ($p < 0.001$) during the study period. This is similar to the reported spatial autocorrelation patterns in the whole of mainland China at the province level.[26]

A positive relationship between temperature and HFMD incidence was observed, as well as between relative humidity and HFMD incidence, which is consistent with the findings of other recent studies.[27–29] The vapor pressure and wind speed were negatively correlated with HFMD. 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 and humidity.[30]

In the present study, vapor pressure was also found to be negatively associated with the occurrence of HFMD. However, no studies have yet been published revealing the underlying mechanism, thus further studies should be done to explore this finding. Comparing the results of three models (Table 5), the coefficients of spatial panel models were found to be smaller than

Table 4
Results of tests to determine which specific fixed effect and which type of spatial dependency term should be included in the model

Type of test	Tests to determine the inclusion of the model with spatial or temporal fixed effects		Tests to determine the inclusion of the model with spatial lagged or spatial error autocorrelated term			
	LR test for spatial fixed effects	LR test for time-period fixed effects	LM lag test	LM error test	Robust LM lag test	Robust LM error test
Statistics value	2264.74	2486.76	3370.98	3339.88	31.97	0.87
p-Value	<0.001	<0.001	<0.001	<0.001	<0.001	0.352

LR, likelihood ratio; LM, Lagrange multiplier.

Table 5
Results of the fixed effects model and spatial lag and spatial error fixed effects panel models

Variables	Fixed effects model			Spatial lag panel model			Spatial error panel model		
	Coefficient	*p*-Value	95% CI	Coefficient	*p*-Value	95% CI	Coefficient	*p*-Value	95% CI
AAP	0.0266	0.0811	−0.0033 to 0.0564	0.0189	0.1795	−0.0087 to 0.0465	0.0175	0.2716	−0.0137 to 0.0487
AT	0.1749	<0.0001	0.145 to 0.2047	0.1124	<0.0001	0.0846 to 0.1402	0.1323	<0.0001	0.0943 to 0.1703
AVP	−0.1451	<0.0001	−0.1809 to −0.1092	−0.0957	<0.0001	−0.129 to −0.0624	−0.1097	<0.0001	−0.1509 to −0.0684
ARH	0.3535	<0.0001	0.2789 to 0.4282	0.2298	<0.0001	0.1604 to 0.2992	0.2611	<0.0001	0.1722 to 0.35
MP	−0.0003	0.1705	−0.0008 to 0.0001	−0.0002	0.3362	−0.0007 to 0.0002	−0.0002	0.4647	−0.0008 to 0.0004
AWS	−0.1180	<0.0001	−0.1869 to −0.0491	−0.0709	0.0292	−0.1347 to −0.0072	−0.0504	0.1713	−0.1227 to 0.0218
MSH	−0.0084	0.1354	−0.0195 to 0.0026	−0.0051	0.3306	−0.0153 to 0.0051	−0.0061	0.3201	−0.0181 to 0.0059
Rho (ρ)				0.3780	<0.0001	0.3518 to 0.4042			
Lambda (λ)							0.3700	<0.0001	0.3436 to 0.3964
R^2	0.3163			0.6177			0.5637		
Log-likelihood	−11 347.15			−9683.54			−9693.67		

CI, confidence interval; AAP, atmospheric pressure; AT, average temperature; AVP, average vapor pressure; ARH, average relative humidity; MP, monthly precipitation; AWS, average wind speed; MSH, monthly total sunshine hours.

those of the classic panel model. This finding indicates that if the spatial autocorrelation were neglected, the effects of meteorological factors may be overestimated.

This study highlights the use of spatial panel data models to determine the relationship between HFMD and meteorological factors. Spatial dependence might exist between the observations at each unit, especially in infectious disease monitoring data.[31] The spatial panel model is typically used to analyze data containing time-series observations of a number of spatial units (counties, regions, states, countries, etc.).[32] As noted by Elhorst,[16] spatial panel data models are more informative and contain more variation and less collinearity among variables than purely cross-sectional models or time-series models. The model tests justify the inclusion of the spatial and temporal fixed effects, which indicate that spatial and temporal heterogeneity do affect the robustness of statistical models. Furthermore, taking into account the panel structure and spatial autocorrelation terms in the model simultaneously results in the better goodness-of-fit of data.

Some limitations of this study should be acknowledged. One is that the effects of many factors, such as social and economic status, health services, and environmental hygiene, were not quantified precisely. Moreover, it was assumed that the effect of meteorological variables on HFMD was consistent in all regions. However it would be difficult to uphold the spatial stationary assumption in a large area. Thus, a random coefficients model or geographical weighted regression model (GWR) will be used to explore the local effect of factors of interest in the future.

In this study a new method was adopted to explore the association between the incidence of HFMD and several meteorological factors. The results showed that it was more appropriate to use spatial panel data models when longitudinal data of multiple units were available and spatial autocorrelation existed, and would lead to better goodness of model fit and a more precise estimate of the effect size. It was found that meteorological factors affected the incidence of HFMD. HFMD prevention and control strategies would benefit from giving more consideration to climate variations.

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