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Implications from assessing environmental effects on spatio-temporal pattern of schistosomiasis in the Yangtze Basin, China

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Abstract

Schistosomiasis remains a major public health problem in the South China, particularly in lake and marshland regions. Modelling the spatio-temporal pattern of schistosomiasis guides disease prevention and control programs and is a research area of growing interest. However, few attempts have been made to evaluate the changing (nonlinear) effects of environmental determinants on schistosomiasis. In this context, a hierarchical spatio-temporal model was applied to evaluate how environmental determinants affect the changing trend of schistosomiasis in Anhui Province, China, based on annual parasitological and environmental data for the period 1997-2010. Results showed that – compared to changing effect – environmental factors had a constant (linear) effect on schistosomiasis. The disease was also found to fluctuate over time, which was due to the two latest national schistosomiasis control programs. In addition to statistical benefits of this approach, our analysis implied that climate change might not contribute to variation of schistosomiasis; rather, prevention activities affect schistosomiasis when the disease prevalence remains at a low level. Finally, the analytical method proposed in our study provides a template for modelling the spatio-temporal pattern of a disease whose transmission is largely determined by environmental determinants.

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Introduction

Schistosoma japonicum is the main schistosome species in the People's Republic of China, causing intestinal schistosomiasis, a debilitating disease of public health importance (Collins *et al.*, 2012). After a multitude of national schistosomiasis control programs, the prevalence has been greatly reduced and currently remains at a low level (Li *et al.*, 2009). However, elimination of schistosomiasis is unlikely in the near to medium term future. The latest national schistosomiasis report concluded that there were 453 endemic counties (city or district) with 251 million residents at risk and estimated that approximately 116,000 persons were infected by the end of 2014 (Lei *et al.*, 2015). Based on geographical disease patterns and ecological characteristics of the vector snail, schistosomiasis endemic regions in China have been classified into three types: lake and marshland regions, plain regions with water-way networks, and hilly and mountainous regions (Chen and Feng, 1999). Compared to the other two regions, control of schistosomiasis in the lake and marshland regions is difficult due to the vast area of *Oncomelania hupensis* (the sole intermediate host) habits, and over 80% of nationwide schistosomiasis cases occur within these regions (Gray *et al.*, 2008). Hence, the lake and marshland regions are the focus of schistosomiasis control.

The transmission of schistosomiasis is closely related to the distribution of *O. hupensis*, which largely depends on physical conditions such as temperature of freshwater, rainfall, and quality and humidity of the soil. These physical conditions have therefore been considered when modelling the geographical or spatio-temporal distribution of schistosomiasis in numerous research studies (Yang *et al.*, 2005; Steinmann *et al.*, 2007; Clements *et al.*, 2009; Hu *et al.*, 2013; Soares Magalh Es *et al.*, 2014; Hu *et al.*, 2015; Hu *et al.*, 2016; Hu *et al.*, 2017). Almost all of these studies evaluated the linear effect of environmental conditions on the disease; nonlinear effects were seldom assessed. This linear assumption would be problematic particularly in modelling the spatio-temporal variation of schistosomiasis, in which changing effect, due to abnormal climate (*e.g.*, drought, flooding, tornado, *etc.*), of physical conditions on the disease would be expected. In this context, this paper aims to investigate the nonlinear effects of environmental factors on the spatio-temporal pattern of schistosomiasis in Anhui Province, East China, which is characterized by a typical lake and marshland environment (Hu *et al.*, 2014), using a spatio-temporal model.

Materials and Methods

Study area

In this study, a Hierarchical spatio-temporal model was developed to evaluate the nonlinear effects of environmental covariates on schistosomiasis prevalence. The analysis was conducted at the township-level schistosomiasis data from Anhui Province. Anhui Province, located across the lower reaches of the Yangtze River in East China, spans approximately 139,600 square kilometers with a population of 61.47 million (2015). Plains dominate the province, with a series of hills and ranges covering southwestern and southeastern Anhui. Major rivers include the Huaihe River in the north and the Yangtze River in the south (Figure 1).

Parasitological data

The *S. japonicum* infection prevalence data during 1997-2010 were obtained from cross-sectional surveys carried out by health professionals of the Anhui Institute of Parasitic Diseases (AIPD). The data were collected annually through village-based field surveys using a two pronged diagnostic approach: screening by a serological test of all residents 5 to 65 years old and confirmed by Kato-Katz stool examination (three thick-smear slides from one stool specimen) (Yu *et al.*, 2007). The results were then reported to AIPD via township offices. The database used in this study consisted of 97 sample townships located in the schistosome-endemic area, which were selected from the database of annual schistosomiasis surveys. For our analysis, townships that had no infected individuals during the study period were removed. Figure 1 shows the locations of the sample townships in the endemic area.

Environmental data

Environmental data included rainfall, temperature and distance to the Yangtze River. Monthly rainfall and temperature data during the study period were obtained from the China Meteorological Data Sharing Service System (http://cdc.cma.gov.cn/home.do). With climatic data at 756 meteorological stations nationwide, inverse distance weighting interpolation was used to derive estimates within the study area. ArcGIS software (version 10.0, ESRI

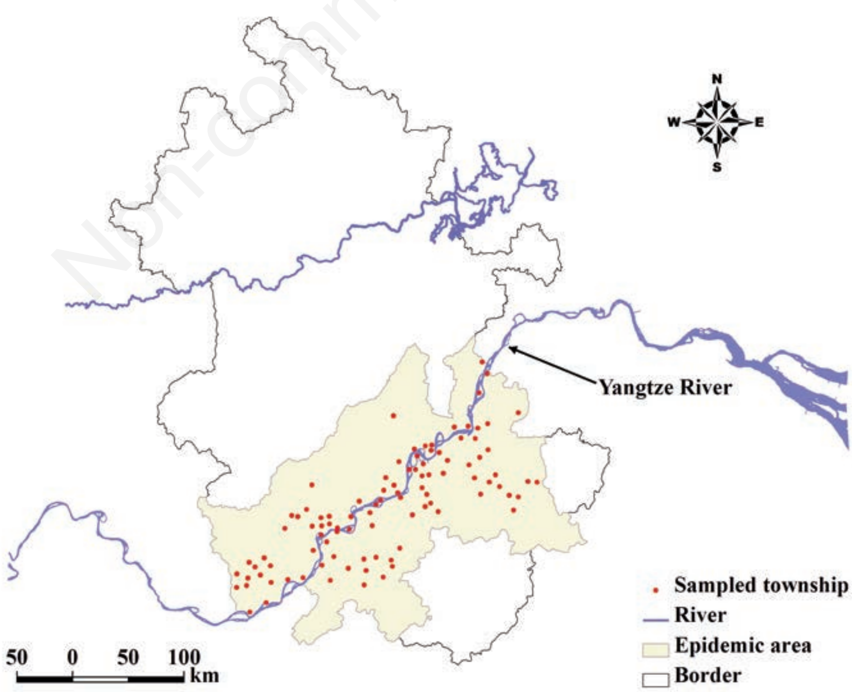

Figure 1. Location of sample townships in Anhui Province, China. The geographical layer of water bodies was overlaid. Yangtze River is shown in the south and Huaihe River in the north. The map was created using the AcrGIS software (version 10.0, ESRI Inc., Redlands, CA, USA).

Inc.; Redlands, CA, USA) was used to extract yearly-average rainfall and temperature for each county. Data on the Yangtze River were downloaded from Conservation Science Data Sets of World Wildlife Foundation at http://worldwildlife.org. For each township, the Euclidian distance to the Yangtze River was calculated using ArcGIS 10.0.

Statistical analysis

Hierarchical Bayesian model is used as the statistical method in this study. Assume that there is a true unobserved spatio-temporal process hidden behind the yearly counts of schistosomiasis cases, which is incorporated into the framework of a hierarchical Bayesian statistical model. The spatial domain is discrete and consists of the 97 townships in the study area. Consequently, the size of count data we model is fixed at 97. The basic representation of the hierarchical Bayesian model is typically composed of three levels, namely, data level (whose conditional probability distribution given processes and parameters is independent), process level (which determines change of data level given parameters), and parameter level (which exists in the previous levels).

Specifically, let Z_{it} denotes the number of infected individuals (data level) in township i (I = 1,2,..,97) at time t (t = 1997, 1998,…, 2010). The following distribution is assumed for the observed infected individuals (Eq. 1):

$$Z_{it} \backsim Binomial\,(p_{it}, N_{it}) \quad \text{Eq. 1}$$

where p_{it} and N_{it} are the probability that a randomly selected person will test positive for schistosomiasis and number of people tested in township i at time t, respectively. Considering low level of infection (*i.e.*, many townships had no observed infection, see the results section), we therefore assume Z_{it} follows a zero-inflated binomial distribution which is characterized by adding a zero-inflated parameter α into Eq. 1. p_{it} is regarded as the hidden process of interest (process level) in which the spatio-temporal dependence can be modelled. The logit transformation of p_{it} was used to model the linear and nonlinear environmental effects and spatio-temporal disease dependence as follows (Eq. 2):

$$\log\frac{p_{it}}{1-p_{it}} = b_0 + \sum f_k(x_{it}) + g(t) + \omega_{it} \quad \text{Eq. 2}$$

where x_{it} are covariates that are specified as the environmental factors; $f_k()$ and $g()$ are functions for the kth covariate and time, respectively, which could be linear or nonlinear; and the term ω_{it} refers to the latent spatio-temporal process, which changes in time with first-order autoregressive dynamics and spatially correlated residuals (Hu *et al.*, 2017). All the parameters included in hierarchical Bayesian model are assumed to be in the parameter level. More details about this spatio-temporal model can be found in our latest study (Hu *et al.*, 2017). This paper focuses more on the nonlinear effects of environmental factors and time on schistosomiasis and therefore assume all the $f_k()$ have a following form (Eq. 3):

$$f_k(x) = \beta_t x \quad \text{Eq. 3}$$

where the coefficient β_t follows a random walk pattern, namely,

$$\beta_t = \beta_{t-1} + \varepsilon_t \quad \text{Eq. 4}$$

where ε_t is a temporally uncorrelated noise, following a normal distribution with mean 0 and covariance τ^{-1}, *i.e.*, $\varepsilon \backsim N(0, \tau^{-1})$. Of note, if β_t does not change with time and remains constant, Eq. 3 returns to the ordinary linear function, namely,

$$f_k(x) = \beta x \quad \text{Eq. 5}$$

Similarly, $g()$ is assumed to have the same form.

In order to compare with the above full nonlinear spatio-temporal model (*i.e.*, $f_k()$ and $g()$ are both nonlinear and this is denoted as m_1), two mixed models (m_2, in which $f_k()$ is assumed to be linear while $g()$ is nonlinear, and m_3, in which $f_k()$ is assume to be nonlinear while $g()$ is linear) and a full linear model (m_4, in which both $f_k()$ and $g()$ are assumed to be linear; Table 1) are also specified. The deviance information criterion (DIC) (Spiegelhalter *et al.*, 2002) was also used to compare the fitness of these models to the data: smaller values denote a better fitting model. All the statistical analysis was implemented using R software (R Development Core Team 2013), particularly the R-INLA package.

Table 1. Deviance information criterion (DIC) values for all models fit to schistosomiasis prevalence data in Anhui Province, China, 1997 to 2010.

Model	f_k ()	g ()	DIC
m_1	nonlinear	nonlinear	7604.38
m_2	linear	nonlinear	7003.51
m_3	nonlinear	linear	7781.23
m_4	linear	linear	7773.22

f_k () and g () are functions for the kth covariate and time, respectively.

Results

As shown in Figure 2, the mean prevalence of schistosomiasis within the study area decreased during the study period from

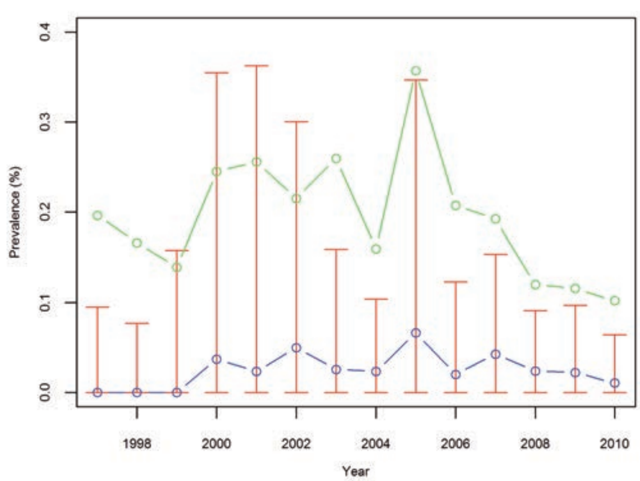

Figure 2. Prevalence of S. *japonicum* infection for sample townships in Anhui Province, China, from 1997 to 2010. The green circles denote the mean prevalence, and the blue circles the median prevalence. The red vertical lines represent interquartile ranges of annual prevalence estimates.

0.20% in 1997 to 0.14% in 1999, then increased and fluctuated during the period 2000-2005 before gradually decreasing to 0.10% by 2010. Of note, there was a resurgence with mean prevalence of 0.36% in 2005. A higher prevalence was accompanied by a wider interquartile range. In addition, the excess zero observed prevalence (denoted by the first quartile) indicated the need to considering a zero-inflated distribution in Eq. 1.

Figure 3 shows the annual change in estimated temperature and rainfall in the study area during the period 1997-2010. The annual average temperature (Figure 3A) fluctuated during the study period and showed an overall decreasing trend whereas annual rainfall fluctuated prior to 2005 and then remained relatively constant afterwards; overall, rainfall showed an increasing trend during the study period. Notably, both annual average temperature and annual rainfall showed an abnormality in 2003.

The DIC results of all models are presented in Table 1. As indicated by these DICs, model m_2 outperform the other models, with the smallest DIC (7003.51). Hence, model m_2 was selected as the best fitting model for evaluating effects of environmental covariates on schistosomiasis.

Table 2 shows the posterior estimates produced by model m_2 using data for the period 1997-2010. Temperature was significantly negatively associated with schistosomiasis whereas rainfall and distance of townships to the Yangtze River were significantly positively correlated with the disease. The posterior mean of the precision parameter for random walk (τ) was 9.74e-02 and the 95% credible interval (CI) was 9.73e-02 to 9.76e-02. The posterior mean of the zero-inflated parameter (α) was significantly different from zero (posterior mean 79.10e-02, 95% CI: 79.07e-02 to 79.14e-02).

Discussion

With the improvement of national and local epidemic surveillance systems, more space-time epidemiological data are becoming available; together with advances in space-time statistics, modelling the spatio-temporal pattern of schistosomiasis has become a growing area of research interest. As a disease strongly associated with the physical environment, schistosomiasis has been found to be sensitive to changes in determinants such as temperature, moisture, and rainfall (Engels *et al.*, 2002). Hence, evaluating the changing effect of these determinants is critical when modelling the spatio-temporal pattern of schistosomiasis. However, previously few studies have incorporated such nonlinearities into the analysis of schistosomiasis data. In this context, the purpose of the current study was to investigate changing (nonlinear) effects of environmental factors on the spatio-temporal pattern of schistosomiasis.

The smallest value of DIC (7003.51) for model m_2 indicated that compared to changing effect (m_1 and m_3), constant (linear) effects of environmental factors fitted the observed data better. A geographical study has shown rainfall and air temperature in Anhui Province to have increased annually during the last six decades (Zeng *et al.*, 2014) and extreme weather in the form of heavy precipitation occurred in 2003 (Wang, 2014) (Figure 3B). The linear part, *i.e.*, $f_k()$ in model m_2 suggests that changing effects of climatic factors could be neglected but the nonlinear function $g()$ indicates that schistosomiasis changes over time; this latter nonlinear part can be well explained by the two national schistosomiasis control strategies implemented during the study period. In 1992 the Chinese government launched a 10-year World Bank Loan Project (WBLP) on schistosomiasis control, mainly based on large-scale chemotherapy with some auxiliary interventions such as health

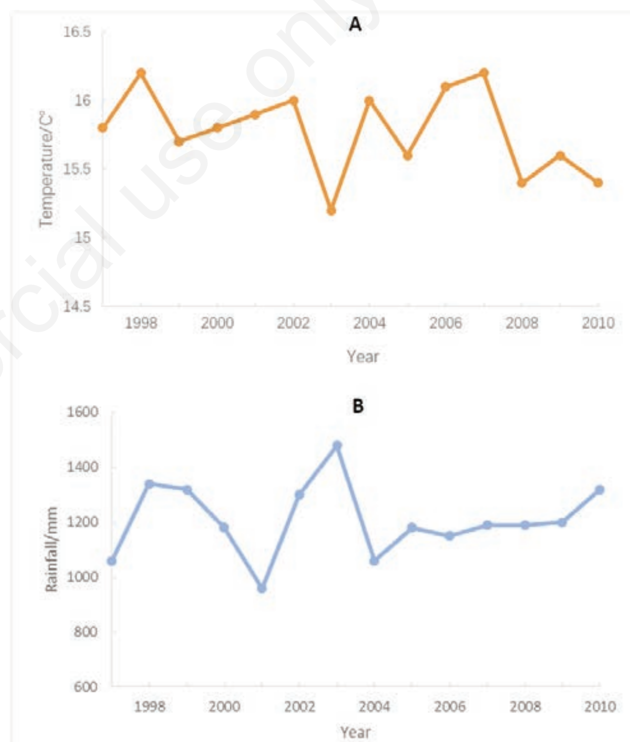

Figure 3. Changing trend in climatic factors in Anhui Province, China, from 1997 to 2010. (A) Annual average temperature; (B) annual average rainfall.

Table 2. Posterior estimates (mean, standard deviation [SD], and quantiles [Q]) for model 2 (Table 1) of schistosomiasis prevalence in Anhui Province, China, 1997 to 2010.

Parameter	Mean	SD	$Q_{0.025}$	$Q_{0.500}$	$Q_{0.975}$
Temperature	-0.13	0.06	-0.25	-0.13	-0.01
Rainfall	0.17e-02	0.06e-02	0.05e-02	0.17e-02	0.28e-02
River	0.81e-02	0.23e-02	0.37e-02	0.81e-02	1.25e-02
τ	9.74e-02	8.13e-05	9.73 e-02	9.74 e-02	9.76e-02
α	79.10e-02	0.02e-02	79.07e-02	79.10e-02	79.14e-02

τ, precision parameter for random walk; α, zero-inflated parameter.

education, chemical control of snails, and other environmental exposure modifications (Yuan *et al.*, 2005). However, the disease rebounded shortly after the conclusion of the WBLP in 2001 (Utzinger *et al.*, 2003). In response, a revised program has been implemented from 2005 until present, aiming to reduce the role of bovines and humans as sources of infection (Li *et al.*, 2009). In addition to chemotherapy and health education, water buffaloes have been replaced by tractors. This integrated program also includes such strategies as treatment of night-soil and provision of piped, safe water, keeping domestic animals in barns, and reduction of snail habitats through the construction of water conservation projects (Zhang *et al.*, 2005).

Model m_2 provided modeling benefits as well as important epidemiological insights. From a statistical aspect, linear effects of environmental factors on infection risk were confirmed by our model, hence simplifying the spatio-temporal modeling of schistosomiasis. The epidemiological interpretation of model m_2 is also useful in the design and implementation of disease control programs; it reinforces the concept that changes in environmental factors do not contribute to variation of schistosomiasis; rather, changes in schistosomiasis over time are likely due to disease prevention activities. This indicates that – compared to environmental factors – there should be more focus on prevention activities. However, this overall conclusion needs to be interpreted with caution because schistosomiasis prevalence has remained at a very low level during the study period (Figure 2) and the same conclusions might not be applied in endemic areas with high disease risk. Another limitation of our study is that the specificity of serological assays and the sensitivity of stool examination tests are not perfect (Wang *et al.*, 2008) and this uncertainty has not been considered in our modeling (although any diagnosed error is assumed to be non-differential over time and place). Modeling that incorporates diagnostic errors might be considered in further studies.

Conclusions

This study investigated the effect of changing environmental factors on the spatio-temporal pattern of schistosomiasis in Anhui Province – a typical endemic area of the lake and marshland region in China – using a dynamic spatio-temporal model. Our model showed that environmental factors had a constant effect on schistosomiasis but that the infection risk changed over time. The proposed analytical method in our study provides a case study of modelling spatio-temporal disease patterns when such disease risk is environmentally determined.

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