Reviews and Opinions

A Systematic Review of Methodology: Time Series Regression Analysis for Environmental Factors and Infectious Diseases

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Abstract: Background: Time series analysis is suitable for investigations of relatively direct and short-term effects of exposures on outcomes. In environmental epidemiology studies, this method has been one of the standard approaches to assess impacts of environmental factors on acute non-infectious diseases (e.g. cardiovascular deaths), with conventionally generalized linear or additive models (GLM and GAM). However, the same analysis practices are often observed with infectious diseases despite of the substantial differences from non-infectious diseases that may result in analytical challenges. Methods: Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, systematic review was conducted to elucidate important issues in assessing the associations between environmental factors and infectious diseases using time series analysis with GLM and GAM. Published studies on the associations between weather factors and malaria, cholera, dengue, and influenza were targeted. Findings: Our review raised issues regarding the estimation of susceptible population and exposure lag times, the adequacy of seasonal adjustments, the presence of strong autocorrelations, and the lack of a smaller observation time unit of outcomes (i.e. daily data). These concerns may be attributable to features specific to infectious diseases, such as transmission among individuals and complicated causal mechanisms. Conclusion: The consequence of not taking adequate measures to address these issues is distortion of the appropriate risk quantifications of exposures factors. Future studies should pay careful attention to details and examine alternative models or methods that improve studies using time series regression analysis for environmental determinants of infectious diseases.

Key words: time series, seasonality, infectious disease, environmental factor, weather, review, GLM, GAM

INTRODUCTION

Time series regression analysis is one of the most common methods practiced in environmental epidemiology studies. Time series analysis usually follows one population or community throughout the study period and requires health outcome (dependent) and exposure (independent) variables measured repeatedly over time and at the fixed interval (e.g. on daily or weekly basis). In the analysis, impacts of exposures on outcomes are evaluated by comparing the changes over time in the rates of outcome occurrences and the corresponding level of exposures. Because within-one-community comparison does not require the denominator data unless the targeted population changes over time [1], the advantages of the analysis is that individual level confounders and uncertainty of the covered area for study are not considered as problems. Instead, time-varying covariates are considered important confounding factors.

Time series analysis is typically suitable for investigations on relatively direct and short-term effects of exposures. In environmental epidemiology studies, it has long been applied to assess the impacts of air pollution and meteorological variability on acute non-infectious diseases that are routinely collected in database, that is, deaths, hospital admissions or visits [2]. Conventionally, generalized linear models (GLMs) and generalized additive models (GAMs) are the standard models for the analyses [1–3]. Though time series analysis in environmental epidemiology studies has been widely used for non-infectious...
diseases, it is also being used for infectious diseases in the same manner. Infectious diseases are substantially different from acute non-infectious diseases (e.g. cardiovascular deaths, cardiac arrests, asthma attacks) in the nature of causal mechanisms and the population at risk. More precisely, the distinct difference from non-infectious diseases is that the incidence of infectious disease often dependent on transmissions among individuals, the presence of intermediators (e.g. vectors), and temporary or permanent immunity protection. These differences might consequently result in statistical challenges when applying infectious diseases to the conventional time series method, yet no study to date has summarized the potential considerations. The present article is a review of the literature for studies in which associations between infectious disease and environmental factors are evaluated with GLMs and GAMs, aiming to characterize the potential methodological challenges involved in the analyses. Other time-series methods developed from econometrics [4] and forecasting such as autoregressive integrated moving average (ARIMA) are not considered here because of the different modeling structure and required model components. The literature review was conducted following the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [5].

**Time series regression model**

Here we first introduce a brief overview of the time series regression model. An outcome of interest is usually a count of disease occurrence. The outcome counts and measured exposure factors of interest should be in order of time and at the fixed interval in dataset. The most common regression model is Poisson regression model, also known as GLM with Poisson distribution, which can be expressed as follows:

\[
Y \sim \text{Poisson} (\mu) \\
\log(\mu) = \zeta_0 + \zeta x + \sum_p \eta_p f(z_p) + f(t).
\]

where \(Y\) is the disease count at the time \(t\), \(\zeta_0\) is the intercept, \(f(t)\) denotes the smoothing function of time to remove the effects of seasonality and long term trend, \(x\) represents the exposure factors, and \(\sum_p f(z_p)\) denotes other time-varying covariates [6]. Adjustments of seasonal variation and long term trend in a model characterize the traditional time series method and are required to differentiate their effects from the short-term associations between exposures factors and outcome of interest. For the seasonal variation adjustments, alternatively, the time stratifications and trigonometric terms (Fourier) are widely used. Further details about time series regression models are described elsewhere [6].

**Method**

**Literature search strategy**

Our aim was to summarize the characteristics of analyses of studies using GLMs or GAMs to assess associations between infectious diseases and environmental factors. We conducted systematic reviews on published articles in the online electronic database of PubMed (http://www.ncbi.nlm.nih.gov/pubmed). Since the exposure factors of our interest were particularly climate or weather, we limited our review to the climate-sensitive infectious diseases for targeted diseases in this study, that is, malaria, cholera, dengue, and influenza. In the search on PubMed, the following key designated terms were included: “weather” OR “climate” OR “temperature” OR “rainfall” OR “precipitation” OR “humidity” AND the name of each disease (“malaria”, “dengue”, “cholera” and “influenza”). For further specific identifications, studies were restricted to journal articles written in English and targeting human health outcomes through the additional filter functions of “article types”, “language” and “species” on PubMed. Publications dated from January 1st, 1995 to November 5th, 2013, identified as of December 4th, 2013, were included in the search.

**Selection of articles**

A total of 2,598 reports was found through the designated search on the online database. Since a large number of articles was identified, precise measures were taken for screening and eligibility assessments (Fig. 1). After the duplicates were removed, two authors screened the titles of the studies to determine whether the studies looked at associations between infectious diseases and weather or climate factors. The articles selected by either one of two authors in the title screening process were then re-assembled, and the following procedure of eligibility selections was conducted in two steps by one author. First, the abstract and method sections were examined to determine whether the studies looked at associations between infectious diseases and weather or climate factors. The articles selected by either one of two authors in the title screening process were then re-assembled, and the following procedure of eligibility selections was conducted in two steps by one author. First, the abstract and method sections were examined to determine whether GLMs or GAMs were used as analysis methods, and studies apparently using irrelevant methods were discarded. In the second step, the full text of the rest of the studies was reviewed to confirm that the purpose and analysis method of each study were suitable for our literature review.

**Review schemes for study designs and analytical methods**

In order to pursue the strategic reviews of analytic methodology, we have set certain schemes to investigate. The 13 schemes are as follows; author and publication year; study period; study location; age and group of targe-
Results

Of the 2,598 reports initially identified by our designated electronic search on PubMed, 33 articles were selected for our review at the end of the eligibility evaluation. These 33 articles consist of 9 malaria [7–15], 13 dengue [16–28], 9 cholera [29–37], and 2 influenza [38, 39] studies (Table 1). Table 2 shows the locations in which the reviewed studies were conducted. The study locations are mostly low- and middle-income countries in tropics, as our targeted diseases, except for influenza, are most prevalent in the areas [40].

The counts for outcome diseases of interest used in the studies were mostly in the time unit of weeks and months (29 studies). Daily and yearly counts were not as common, being only 5 and 1 studies respectively (Table 3).

As specified in the review criteria, the regression models were GLM and GAM with different distribution models, i.e. Poisson, quasi-Poisson, and negative binomial (31 studies). The other two studies integrated mixed models. Among the studies, 18 used models allowing for overdispersion, if any, by inclusion of an overdispersion parameter or selection of different distribution models (e.g. quasi-Poisson or negative binomial).

As mentioned above, an adjustment of seasonal variation and long-term trend is part of the standard approach in the typical time-series regression. In our review, 25 of the 33 studies (76%) included terms in models that allow for seasonality and trends with natural spline functions on time, trigonometric functions, or month and year indicator variables. Other than adjustments for cyclic seasonality and long term trend effects, more than half of the reviewed studies commonly indicated considerations or attempts to control autocorrelation (21 studies). Autocorrelation adjustments may have been necessary because time series are generally subjected to high autocorrelation caused by serial correlations between observations close in time distance. In those 21 studies, the most popular method for autocorrelation controls was to incorporate autoregressive terms including lagged outcome values, the logarithm of lagged outcome values, and lagged model residuals (19 studies).

Other covariates were also included in many studies, including spatial factors if studies involved different geographical areas, population number, risk related index, and holiday indicators. In risk assessments of exposure factors, time lag effects were considered in the majority of the reviewed studies (28 studies). However, we found that the analyzed lag forms (i.e. single lag, moving average lag, or distributed lag) and the time length of lag varied by study regardless of the same targeted disease. While evaluated lag lengths were, if predetermined, often supported by literature reviews and biological plausibility, many did not provide the rationales of assessed lag lengths. In some exploratory studies, on the other hand, long lag lengths were investigated to observe the thorough exposure effects over time. Another finding in our review was, even though infectious diseases generally confer temporary or permanent immunity, the susceptible or immune population was rare-
Table 1.

| Study period (year) | City (Country) | Exposure | Statistical model | Unit of data | Season | Trend | Others | Variation in susceptible population | Autocorrelation* | Assessed Log* | Overdispersion |
|---------------------|----------------|----------|-------------------|--------------|--------|-------|--------|-------------------------------------|-----------------|------------|---------------|
| 2001–2009 | the capital region (Korea) | temperature, RH, diurnal temperature range (DTR), duration of sunshine | GLM Poisson & monthly | | | | | | | | |
| 2000–2003 | Megarag (Niger) | rainfall | GAM negative binomial (NB) | daily | | | | | | |
| 1989–2008 | Rangamati district, (Bangladesh) | temperature, rainfall, humidity, normalized difference vegetation index (NDVI), SST of the Bay of Bengal, NINO1 | GLM NB | monthly | month | year | — | — | AR(1) included | all except NINO3 | 0 to 12 months (MA) | NBD distribution model |
| 1995–2006 | Hsinan (Chao) | temperature, rainfall, RH | Poisson regression | monthly | | | — | — | — | — | — |
| 1996–1999 | Brazilian Amazon region | temperature, rainfall | Poisson regression | monthly | | | — | — | — | — | — |
| 1982–2011 | western Kanyakumari highlands | rainfall, temperature | GLM Poisson | monthly | | | | | AR(1) included | 0 to 6 months (SL) | included overdispersion parameter |
| 1990–2000 | Ethiopia | temperature, rainfall | Poisson regression | weekly | week (of the year) | — | — | — | AR included (based on rainfall: 4 to 12 weeks on a moving average (MA) temperature: 4 to 6 weeks) |
| 1990–2000 | Ethiopia | temperature, rainfall | Poisson regression | weekly | time variable | — | distinct variation between time and distance | — | | |
| 1986–1993 | Ethiopia | temperature, rainfall | GLMM (mixed model) | monthly | | | — | log number of cases in the previous month was included as sector-specific random effects | — | | |
| 2000–2011 | Singapore | temperature, rainfall | Poisson regression | weekly | season parameter | trend | population (offset) | | — | — | |
| 2001–2009 | Rio de Janeiro (Brazil) | rainfall, temperature, proportions of days in the NB month mean temperature < 23°C, 23 ≤ mean temperature < 26, 26 ≤ mean temperature | GLM Poisson & monthly | | year | population the number of days in the month (offset) | — | | 1 and 2 months (SL) | NBD distribution model |
| 2001–2009 | Southeast Brazil | rainfall, temperature, Ozone GLMM NB | NINO3 index (ONI) | monthly | | — | expected number inclusion of unstructured log standardised temperature and rainfall: 3 NB distribution model (offset): the peer- random effects are non-overlap random month (MA); ONI: 4 lation = global gate for not only popula- 3 months was included | — | 0 to 12 months (MA) | |
| 2005–2009 | Dhaka (Bangladesh) | river levels, temperature, GLM Poison | rainfall | weekly | | | | | | |
| 2001–2008 | Singapore | rainfall, temperature, RH | Poisson regression | weekly | sinusoidal terms | — | — | — | AR(2) included | 0 to 12 weeks (SL) | included overdispersion parameter |
| 2004–2009 | Dak Lak province, Vietnam | temperature, duration of sunshine, larval rainfall, RH, larval index (threshold index, the container index, and the Bertioua index) | Poisson regression | monthly | | | | | | |
| 2000–2007 | Singapore | rainfall, temperature, RH | Poisson regression | weekly | | | | | | |

*Overdispersion explained by the log standardised temperature and rainfall: 3 months was included in the model as a random effect for the overdispersion.
Table 1. Continued

| Reference | Year | Location(s) | Data Collection Period | Relevant Variables | Analysis Method(s) | Time Scale | Model Parameters | Notes |
|-----------|------|-------------|------------------------|--------------------|---------------------|------------|------------------|-------|
| Shang et al., 2010 | 1998–2007 | 3 areas in Southern Taiwan (Tainan, Kaohsiung, and Pingtung) | | Temperature, RH, wind speed | Poisson regression, GLM | Bi-weekly | Fourier terms, area density | Assessed 1 to 12 bi-weekly periods (SL) |
| Cho and et al., 2009 | 2000–2008 | Taipei and Kaohsiung (Taiwan) | | Temperature, RH, wind speed | Poisson regression | Monthly | Fourier terms, population density | The cases of the previous month (SL) |
| Quan and et al., 2006 | 1998–2005 | All provinces in Thailand | | Temperature, RH, wind speed | Poisson regression, GLM, NB distribution model | Monthly | Fourier terms, population density | Assessed 1 to 12 months (SL), used quasi-Poisson or NB model |
| Liu et al., 2009 | 2001–2007 | Guangzhou (China) | | Temperature, rainfall, wind velocity | Poisson regression, GLM | Monthly | Fourier terms, population density, GEE | AR(1) included, 0 to 3 months (SL) |
| Johansson and et al., 2009 | 1998–2006 | All municipalities in Puerto Rico | | Temperature, rainfall, wind velocity | Poisson regression | Monthly | Natural cubic spline on observational time, population density | Temperature: 0 to 2 month (DL), rain: 1 to 5 weeks (SL) |
| Taneeprathammalai, 2008 | 1997–1998 | 77 provinces in Thailand | | Temperature, RH, rainfall | GLM, SARIMA, quasi-Poisson regression | Daily | Exponential smoothing function | High rain: 0–8 (MA), included overdispersion parameter |
| Hashim, et al., 2011 | 1995–2007 | Dhaka (Bangladesh) | | DDSL, NINO3, SST, Chl-a, NINO3, SST, wind | Poisson regression, GLM, NB distribution model | Monthly | Fourier terms, month | Not considered, lagged model/residuals 0–3, 4–7, 8–11 months NIH distribution model, included (Breslow (MA) method) |
| Rajaprabha and et al., 2011 | 1996–2009 | Kolkata (India) | | Temperature, RH, rainfall, GLM, SARIMA | Poisson regression | Daily | Exponential smoothing function | High rain: 0–8 (MA), included overdispersion parameter, temperature: 0–4 (MA) |
| Hashim and et al., 2010 | 1983–2008 | Dhaka (Bangladesh) | | Temperature, rainfall, GLM | Poisson regression | Weekly | Sampling proportion | High rain: 0–8 (MA), included overdispersion parameter, temperature: 0–4 (MA) |
| Paz, 2009 | 1971–2010 | 8 African countries (Uganda, Kenya, Rwanda, Burundi, Tanzania, Malawi, Zambia, Mozambique) | | Air temperature, sea surface temperature (the western Indian Ocean, anomaly air temperature) | Poisson regression | Yearly | | AR(1) = cor(Y(t), Y(t-1)) and 1 year (SL) |
| Constantin de Magy, et al., 2009 | 1997–2006 | MetLife and Kullkata (India) | | SST, rain, chlorophyll a, GLM quasi-Poisson | Poisson regression | Monthly | Quarters of a year | Log (number of cases 0 and 1 month) (SL) |
| Murciano and et al., 2008 | 1994–2005 | Peru | | SST, sea height anomaly, GMN, NDVI, time lag | Poisson regression | Weekly | Thin plate regression splines | Observational time: 1 to 5 weeks (SL) |
| Luque Fornies, 2006 | 2003–2006 | Lasaka (Zambia) | | Temperature, rainfall, GLM | Poisson regression | Weekly | Fourier terms | The cases for the previous week. |
| Hardin and et al., 2008 | 1996–2002 | Dhaka (Bangladesh) | | Rainfall, river level, temperature, GLM | Poisson regression | Weekly | Fourier terms, year | Public holidays, AR(1) included | Rainfall: 0 to 16 weeks (MA), river level: 0 to 4 weeks (MA) |
| Hu and et al., 2008 | 1997–2009 | 5 different cities in Bangladesh (Bangladesh) | | Water temperature, air temperature, water depth, pH, soil visibility | Poisson regression | Bimonthly | | 0.2, 4, 8 months (SL) |
| Hu and et al., 2012 | 2009 | Brisbane (Australia) | | Temperature, rainfall, inter-annual action | Poisson regression, spatial-temporal analysis (CAR) | Weekly | Fourier terms, year | | AR(1) included, 1 week single lag (SL) |
| Joshi, et al., 2011 | 2009–2010 | Niger (Niger) | | Temperature, relative humidity, wind speed, visibility, GLM | Poisson regression, GLM | Daily | Seasonal components, trend components, day of the week, holidays, religious festivals, and pilgrimages | |

Blanks represent unknown for the case no statements are made in articles regarding each category. Otherwise whether it was considered or how it was considered are stated in this table.

* SL: single lag, MA: moving average, DL: distribute lag, AR: auto-regressive term
ly addressed in study models. No studies computed or integrated the estimated susceptible population, and a few studies instead included proxies (e.g. vaccination rate) to account for the target population’s susceptible risk.

**DISCUSSION**

While time series analysis with GLMs or GAMs is the established method in environmental epidemiology research, our review brings attention to several potential issues when the same application of the traditional approach for non-infectious diseases extends to infectious diseases.

First, immune protection, which is one of the unique features of infectious diseases, can lead to rapid changes in the underlying population at risk over the course of the study period, but few studies have addressed the susceptible or immune population in their models. The information on immune population can be critical as host immune competence (intrinsic factor) and environmental (extrinsic) factors are both important contributors to seasonal disease activity [41]. In particular, the importance of the interplay of intrinsic and extrinsic factors is illustrated in one cholera study in which the developments of outbreaks is unsuccessful, even with the disease’s favorable environmental conditions when the susceptible population is small [42]. The consequence of not taking into account the susceptible population in a model is the misquantification of the effects of environmental exposures. However, since estimates of immune or susceptible individuals within a population seldom exist in data, it is often necessary to create alternative measures to increase the precision of the analysis. The alternative approaches may include, but are not limited to, reconstructing estimation of susceptible population by deterministic models (e.g. susceptible-infected-recovered models) and proxy indicators such as vaccination rates.

**Table 2. Study locations.**

| Region               | Countries                                                                 | Number of studies (n = 33) |
|----------------------|---------------------------------------------------------------------------|-----------------------------|
| Africa               | Burundi, Ethiopia, Kenya, Niger, Malawi, Rwanda, Tanzania, Uganda, Zambia | 8                           |
| East Asia            | China, Taiwan, Korea                                                     | 5                           |
| Southeast Asia       | Thailand, Vietnam, Singapore                                             | 6                           |
| South Asia           | India, Bangladesh                                                        | 8                           |
| Central/South America| Peru, Puerto Rico, Brazil                                                | 5                           |
| Oceania              | Australia                                                                | 1                           |

**Table 3. Summary of modelling characteristics**

| Unit of outcome data          | Number of studies (n = 33) |
|-------------------------------|-----------------------------|
| Daily                         | 3                           |
| Weekly (including bi-weekly)  | 13                          |
| Monthly (including bi-monthly)| 16                          |
| Yearly                        | 1                           |
| Regression models             |                             |
| GLM (Poisson, quasi-Poisson, negative binomial) | 28 |
| GAM (Poisson, negative binomial) | 3                           |
| Mixed models                  | 2                           |
| Control of seasonality and long term trend |                 |
| Some adjustments were included in the model | 25 |
| No adjustments / not described | 8                           |
| Autocorrelation               |                             |
| Examined / included parameters to control autocorrelation | 21 |
| No specific measures / not described | 12  |
| Lag effects of exposure       |                             |
| Lag effects of whether variables were assessed | 28 |
| No lag effect assessments     | 5                           |
Secondly, while adjustments for seasonal variations and long term trends were common, one third of the reviewed articles did not include the adjustment measures in their models. The reason is unknown, yet one possible reason might be less apparent seasonal variations of disease activity. For instance, while in temperate climate regions have epidemics of influenza on a regular basis in winter time, malaria often presents a less obvious periodic pattern of seasonality. In general, adjustments for seasonality variation in the traditional time series analysis involve two important meanings, i.e. elimination of the effects of unknown time-varying covariates and realization of the regression assumption of independence. Realization of the independence assumption is a particularly important underlying regression hypothesis for time series analysis, because observations of a variable that are close in time tend to be similar and are generally correlated (i.e. autocorrelation) [1]. When seasonality is absent in the outcome data at a glance, the question may naturally arise whether there is any necessity to implement seasonal adjustments in a model. However, given the possibility of serial correlations that may naturally exist in time series data, the question of whether to include seasonal adjustments should be carefully examined using statistical validations (e.g. model fitness and residuals).

Another concern regarding autocorrelations arises when the magnitude of strength and the potential underlying cause are considered. In our literature review, inclusion of autoregressive terms in addition to seasonal adjustments to control autocorrelation was commonly observed (19 studies), which, for one reason, may imply that the adjustment of seasonality variation alone is not sufficient. In general, an imperfect control of autocorrelation suggests omissions of other significant time-varying covariates from a model [43]. However, given the characteristics of infectious diseases, a stronger autocorrelation than controlled seasonality may be induced by the actual correlation in outcome observations due to disease transmissions among individuals. In other words, the true dependence among neighboring observations can be present with infectious disease data because the number of newly infected individuals depends on the number of previously infected individuals in the population. In fact, some studies [15, 16] included autoregressive terms (e.g. a lagged outcome or logarithm of lagged outcome) to account for the dependency of infectious diseases data. This correlation is also known as “true contagion” [44], and the resulting violation of the assumption of independence will cause biases not in the regression coefficients but in the estimates of standard errors [43]. Thus, the discussion again returns to the importance of implementing adequate seasonality adjustments with statistical validations and the need for additional measures if autocorrelation in model residuals remains. In order to competently address the autocorrelation resulting from true contagion or transmissibility of infectious diseases, it might be worthwhile in the future to explore what approaches are not only statistically effective but also biologically compelling from the aspect of disease mechanisms.

Thirdly, in the process of estimating lag effects of exposure factors, the lag timings evaluated varied by studies in spite of the same targeted disease. This may be because the quantitative evidences needed to establish the optimal lag timings remains elusive with most diseases, although there might be qualitatively convincing ideas. The difficulty of estimating the optimal lag times may be especially severe in vector-borne diseases. In these diseases, the transmission mechanisms become highly complicated due to the intermediating effects of vectors which influence the strong disease seasonality [45], but they can also be highly content-dependent. For instance, the association patterns and lags of rainfall effects in malaria vary widely by region and climate conditions (e.g. whether the region is generally dry or has abundant rain) [46]. More importantly, however, time lags and association patterns can be more complicated in infectious diseases than non-infectious diseases because the mechanism of disease manifestation (e.g. incubation period) and the transmission dynamics of pathogenic microorganisms (e.g. bacteria, viruses, parasites, or fungi) play a critical role in the causal pathway. Therefore, an understanding of biological mechanisms can be of great help in estimating lags and association patterns. If no certain prior knowledge exists or complicated transmission pathways are expected, then strategic exploration approaches are required to find the optimal estimates.

Lastly, most of our reviewed studies conducted an analysis using weekly or monthly data (including bi-weekly and bi-monthly). Unlike non-infectious diseases, daily count outcomes were much less common. This relates to only certain infectious diseases, but it is worth noting that using the longer time unit of data may sometimes lead to an underestimation of risk factors when the optimal time lags of exposure effects and disease incubation periods are short (e.g. monthly data is used for analysis when the optimal exposure effects are expected in one week lag). Wherever possible, selection of the most statistically robust and biologically plausible time unit of data is desirable for analysis.

Our study has some limitations. The first is that, among all the diseases potentially linked to weather variability, only four diseases were selected for the review. As a result, we may have eliminated studies that could have de-
livered some insightful analytical approaches. In review of our aim to characterize the methodological trends, however, our selected diseases were probably sufficient because they consist of different types of infectious diseases including water-borne, vector-borne, and air-borne diseases. Another limitation is that GLMs and GAMs were the only targeted models, even though other methods such as autoregressive integrated moving average can also fall into the category of time series regression models. Those other time-series methods might have provided solutions for the concerns raised here, but we believe that we have looked at important issues in common with the above that deserve careful attention and awareness. In conclusion, the careful implementation of time series regression analysis is required in the study of environmental determinants of infectious diseases. Further studies are required to explore alternative models and to address methods that will improve the time series analysis.

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CONFLICT OF INTEREST

None to declare.

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