Mapping the short-term exposure-response relationships between environmental factors and health outcomes and identifying the causes of heterogeneity: A multivariate-conditional-meta-autoregression-based two-stage strategy

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**Author contributions**

WW and YM conceptualized this study and wrote the main manuscript text. WW derived the methodology and carried out the simulation and case study. FL carried out the case study and edited the manuscript. FY reviewed and edited the manuscript. YM and FY obtained the funding.

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# Mapping the short-term exposure-response relationships between environmental factors and health outcomes and identifying the causes of heterogeneity: A multivariate-conditional-meta-autoregression-based two-stage strategy

## Abstract

Studying the spatial distribution of short-term exposure-response relationships (ERRs) between environmental factors and health-related outcomes and identifying the causes of spatial heterogeneity are of great importance on making region-specific environment-related public health policies. However, the widely used multivariate meta-regression (MMR)-based two-stage strategy does not consider the spatial dependence between regions, which may give unsatisfactory results, even a false policy implication. More importantly, possibly due to the limitation, the spatial distribution of short-term ERRs is less frequently focused on. In this work, we combined the conditional autoregression with MMR to construct an extended model called MCMAR. Then a MCMAR-based two-stage strategy is developed to map the ERRs and identify the causes of heterogeneity. A published motivating example and a simulation study were used to validate the efficiency of our strategy. Results show that the MCMAR-based strategy achieved considerably better fit performance in terms of the Akaike information criterion, obtained a more reasonable spatial distribution of ERRs, and identified more accurate causes of heterogeneity than the classic strategy. As numerous spatial ERR datasets have been and are being produced, we believed that MCMAR-based two-stagy strategy will have an important and wide application value.

**Keywords**: Spatial distribution, exposure-response association, multivariate meta-regression, two-stage strategy, conditional autoregression

## 1. Introduction

In the last few decades, with the improvement in environmental monitoring systems and disease surveillance systems, a large number of time-series studies have been carried out to characterize the exposure-response relationships (ERRs) between environmental risk factors and health-related outcomes [1-5]. Due to the distinctions in culture, natural conditions, economic levels and sanitary conditions, different regions often present heterogeneous ERRs. For example, Shah et al.’s [6] study shows a stronger association between air pollution and stroke in low-income countries. Tian et al.’s [7] study shows a stronger association between air pollution and cardiovascular disease-related hospital admission in central south, eastern, and northern Chinese cities, and temperature and humidity significantly modify the association. Studying such heterogeneity of ERRs among different regions, including but not limited to characterizing region-specific ERRs (i.e., characterizing the spatial distribution of ERRs), synthesizing heterogeneous ERRs, and identifying the causes of heterogeneity, assists in 1) making reasonable region-specific public health interventions, 2) constructing region-specific early warning systems, 3) assessing the environment-related attributable disease burden, and 4) identifying high-risk effect-modifying factors and high-sensitivity risk region. These items play important roles on making cost-effective environment-related policies, for example, decreasing the exposure to certain environment factor is more cost-effective in the regions with high-sensitivity risk.

Currently, the two-stage strategy has become the main tool for investigating (or dealing with) the heterogeneity of ERRs since Gasparrini et al.’s work [8]. In the first stage, common region-stratified time-series regression models with the same model forms, such as general linear models, generalized linear models, and generalized additive models (GAMs), are used to obtain rough region-specific ERR estimations. When the ERR presents nonlinear and even lag effects, which frequently occur in environmental risk factors due to complex pathogenic mechanisms, the ERR is defined by multiple parameters (i.e., a vector) commonly estimated by a GAM, such as a distributed lag nonlinear model (DLNM) [9, 10]. In the second stage, meta-analysis (or meta-regression), hereafter MR, is used to pool the estimations for more accurate average and region-specific estimations as well as to explore the causes of heterogeneity by incorporating the region-level predictors into the model. When the ERR is defined by multiple parameters, multivariate MR (MMR) is used as the replacement. As MR is a special case of MMR, to write with brevity, we use MMR to represent MR and MMR. With its flexibility in adjusting confounders and characterizing complex ERRs in the first stage, the MMR-based two-stage strategy has been widely used in epidemiological studies.

However, MMR in the second stage does not consider commonly existing spatial autocorrelation [11], i.e., two regions closer together are more related to each other. Previous studies [12, 13] have shown that ignoring spatial autocorrelation will lead to a loss of model performance, possibly increasing false positive error and decreasing predictive ability. Therefore, the MMR-based two-stage strategy is likely to falsely identify the causes of heterogeneity and obtain an inaccurate spatial distribution of heterogeneous ERRs, which may provide a false implication for public health intervention. Introducing spatial autocorrelation may have the potential to further elevate the performance of the classic two-stage strategy. More notably, due to not considering the spatial distribution, the MMR-based strategy is less frequently used to map the ERRs. The ideal Bayesian spatiotemporal model will cost unacceptably intensive computation sources due to the complex confounders and the long time series. With the lack of efficient tools, it is of great application value to develop a method to accurately map the short-term ERRs and identify the causes of heterogeneity.

Since Besag et al.’s work [14], the conditional autoregression (CAR) model has been the rule used to characterize the spatial distribution of risks in disease mapping, but the CAR model focused on the observed raw data without estimation error rather than the estimated data with standard error, such as the ERR estimations from the first stage, which are of interest in meta-regression. Some meta-regressions have been developed to consider the autocorrelations between observed values[15, 16], but they are neither available for multivariate response values, nor make full use of the common CAR-based spatial structure, especially the more flexible Leroux CAR prior. In this work, by combining the CAR with multivariate meta-regression, an extended model, called multivariate conditional meta autoregression (MCMAR), was constructed. Univariate conditional meta autoregression, as a special case of MCMAR, is not mentioned here for brevity. By using MCMAR to substitute MMR in the second stage, a novel MCMAR-based two-stage strategy can be used to improve the performance of the MMR-based two-stage strategy. In Section 2, the methodology regarding MCMAR is detailed. In Section 3, a published motivating example is used to illustrate the application of the MCMAR-based two-stage strategy in mapping the complex heterogeneous ERRs and exploring the causes of such heterogeneity. In Section 4, a simulation study is used to verify the advantage of MCMAR over MMR. Section 5 presents a general discussion.

## 2. Methods

In this section, based on the region-specific ERRs estimated by GAMs in the first stage, we detailed the methodology of MCMAR. The MCMAR-based two-stage strategy can be easily derived, seen in section 3.

### 2.1. Model structure of MCMAR

The ERR for each region is defined by a -dimensional vector along with its covariance, which usually comes from the first-stage model and the details can be found in section 3.3. We set a total of regions. is a -dimensional vector defining the estimated ERR in region from the first stage. is the covariance of . defines the unknown real ERR. Then,

(1)

where is the multivariate normal distribution. The incorporated region-level predictors in region are indicated by a -dimension vector with the first element of one as the intercept. We define

where is a identity matrix andis the Kronecker product. Then, can be formulized as

where is a -dimensional regression coefficient vector defining the association of predictors with ERR. is a -dimensional random effect vector defining the region-specific heterogeneous component that cannot be explained by region-level predictors. Thus, Model (1) can be written as follows:

|  |  |
| --- | --- |
|  | (2) |
|  |

where is a symbol indicating independence between two random variables. In MMR, and , with , are independent and identically distributed. In this work, we broke the independence condition and introduced spatial autocorrelation to construct the MCMAR model.

Letting be the th column vector of the matrix , we specify

(3)

where is the matrix normal distribution. is a matrix defining the correlation among rows, i.e., the correlation among the elements in . is a matrix defining the correlation among columns, i.e., the spatial autocorrelation. Furthermore, let and be the th column vector of matrix and , respectively, and let

where indicates vectorizing a matrix according to its column vectors. Combining Formulas (2) and (3), we constructed MCMAR as follows:

|  |  |
| --- | --- |
|  | (4) |
|  |

Then,

(5)

As Leroux prior-based conditional autoregression (LCAR) [17] has been commonly used to address the spatial autocorrelation issue due to its efficient computation and flexibility in considering both structured and unstructured random effects, according to the Leroux prior, we defined as follows:

where is the variance parameter. reflecting the structured random effect is a symmetric matrix with elements:

where indicates the number of neighbors around the th region, indicates that regions and are neighbors, and is the indicator function. Identity matrix reflects the unstructured random effect. balances the intensity between structured and unstructured random effects. When , MCMAR becomes MMR. When , an intuitive explanation can be presented as follows:

(6)

where is the random effect vector in region and is the random effect matrix in all the regions with the th region deleted. For , without any prior, an unstructured symmetric matrix is defined, i.e., with parameters to be estimated.

### 2.2. Parameter estimation

At present, various estimation methods have been well developed to estimate the parameters for MMR, such as likelihood-based methods, multivariate moment methods, estimating equations, Bayesian approaches, and iterative generalized least squares, in which likelihood-based methods have been frequently used since the release of the R package “mvmeta”. For the LCAR model, the Bayesian approach is the mainstream method. In this work, to enhance the comparison between MCMAR and MMR implemented by “mvmeta”, we used the maximum likelihood (ML) and restricted maximal likelihood (REML) methods to estimate the parameters in MCMAR.

According to Formula (5), the log-likelihood of MCMAR can be written as

(7)

where . When and areknown, i.e., is known, the ML estimators can be expressed using closed-form equations as follows:

(8)

(9)

which are also generalized least square estimators. When is unknown, an iterative method is needed to acquire the estimations of , and by maximizing the joint log-likelihood function in (7). As the ML estimator for covariance parameters does not consider the loss of degrees of freedom from the fixed parameter of , it will bias the estimations of and , thus biasing the estimations of and . The REML method is an alternative that can obtain unbiased estimations by maximizing an adjusted log-likelihood function when estimating and . The adjusted log-likelihood function is based on linearly independent error contrasts rather than the full data vector andis expressed as follows:

(10)

where is defined in Equation (8).

To guarantee that andare always positive definite in the iterative processes, we used Cholesky decomposition to define , i.e., ,where is an upper triangular matrix with parameters that need to be estimated. can be written as ,where . Then, and have the same eigenvectors. Let be an orthogonal matrix composed of the eigenvectors of , and be the diagonal matrix of the corresponding eigenvalues vector , i.e., the spectral decomposition of can be expressed as . Thus, the spectral decomposition of can be written as . We defined , and then and can be easily derived by limiting for every to make positive definite. To make the model identifiable, we set and . The iterative algorithm can be summarized as follows:

|  |
| --- |
| **The ML- or REML-based iterative algorithm for MCMAR** |
| 0. Use and to define and , respectively. Set and calculate the range of , i.e., . |
| 1. Use MMR to obtain the initial value of under . |
| 2. Given and from the last step, use Formula (8) to calculate . |
| 3. Given and from the last step, use the combination method of golden section search and successive parabolic interpolation[18] to obtain by maximizing Formula (7) or (10). |
| 4. Given and from the last step, use the Broyden–Fletcher–Goldfarb–Shanno (BFGS) algorithm[19] to obtain by maximizing Formula (7) or (10). |
| 5. Replicate steps 2-4 until convergency in terms of the maximum log-likelihood value in Formula (7) or (10). |
| 6. Obtain the final estimations of , and and calculate the covariance of based on Formula (9). |
| 7. Estimate  using the approach presented in Section 2.4. |

### 2.3. Hypothesis testing and model selection

The main parameters of interest in statistical inference may be the fixed effect parameter , the spatial autocorrelation parameter , and the random effect parameters .

For , we used the multivariate Wald test [20] to test the hypothesis with the null hypothesis (H0) of and the alternative hypothesis (H1) of . The test statistic is

which follows an asymptotical chi-square () distribution with degrees of freedom equal to the number of dimensions of . When a subset of elements in , for example, the coefficients of a specific covariate, are of interest, an extensive Wald test, with H0 of and H1 of , can be used. is a matrix that makes the parameter of interest. The extensive test statistic is

which follows an asymptotical distribution with degrees of freedom equal to the number of rows of . In addition, for from the ML method, the general likelihood ratio (LR) test is also appropriate. However, for from the REML method, a modified LR test is needed [21, 22].

For , we used the LR test to test the hypothesis with H0 of and H1 of . For the ML estimator, the test statistic is

which follows an asymptotical distribution with one degree of freedom. For the REML estimator, the LR test is also appropriate due to the identical fixed effects structures under H0 and H1, and the test statistic is

For , we may focus on whether region-level random effects exist, i.e., whether the heterogeneity among regions exists after adjusting for the covariates. In this case, the interesting hypothesis is that H0 of vs. H1 of .The multivariate extension of the Cochran Q test [23], as in Gasparrini et al.’s work [8], is also appropriate, and the detailed derivation can be seen in the supplementary material file via <https://github.com/winkey1230/MCMAR>. The test statistic is

where is the estimated fixed effect parameter from Equation (8) without random effects, i.e., with . follows an asymptotical distribution with degrees of freedom. In addition, the intensity of the region-level heterogeneity of the ERR can be calculated using the common and as follows:

where and measure the relative excess heterogeneity over that explained by sampling error and the proportion of region-level heterogeneity to total variation, respectively. Notably, the Cochran Q test in MCMAR is the same as that in MMR due to the identical models under the null hypothesis.

In practical studies, we may make a choice between MMR and MCMAR. The following two common recommendations may be available: 1) when the *P* value for the hypothesis test of is smaller than the prespecified test level, such as 0.05, MCMAR is selected; otherwise, MMR is used; 2) the model with a smaller Akaike information criterion (AIC) or Bayesian information criterion (BIC) is selected.

### 2.4. Spatially smoothed average ERR and region-specific ERRs

Given a set of region-level predictors labeled , let

The average ERR under is defined by as follows:

When the average ERR across all the studied regions is the focus, an MCMAR model including only the intercept is constructed, and the average ERR is defined by and .

The spatially smoothed region-specific ERRs are defined by as follows:

where is the estimated region-level random effect in region , i.e., the th column vector in matrix (the estimation of ). Let , and the best linear unbiased estimation (BLUE) of is (the detailed derivation can be seen in the supplementary materials):

and can be easily obtained by extracting the specific elements in and , respectively.

When we need to predict the ERR, defined by , in a new region, based on Expression (6), can be calculated as

(11)

where is the predictor matrix in the new region. As such, MCMAR is able to obtain a high-resolution spatial distribution in ERRs.

## 3. Motivating example

In this section, a published motivating example was used to compare MCMAR to MMR. This example derives from Xiong et al.’s work [24], in which the commonly used MMR-based two-stage strategy was employed to study the ERRs between temperature and hand, foot and mouth disease (HFMD) from 143 prefecture-level cities in China. In the first stage, a DLNM was independently constructed for each city to obtain a rough region-specific ERR. Then a multivariate meta-regression was used to obtain the average ERR and explore the causes of heterogeneity in ERRs. In this work, based on the region-specific ERRs estimated in the first stage by Xiong et al.’s work, we used the proposed MCMAR model to reanalyze the ERRs in the second stage. Then, the reanalyzed result was compared to that in Xiong et al.’s work. Notably, the spatial distribution of ERRs was not presented by Xiong et al., possibly due to the limitation of MMR.

### 3.1. ERR between temperature and HFMD

HFMD, caused by an enterovirus, has become a predominant childhood acute infectious disease in the Asia-Pacific region during the last two decades [25, 26]. Especially in mainland China, HFMD has caused a heavy disease burden, with the highest disability-adjusted life-years in children and more than one million cases reported annually [27, 28]. It is well known that temperature is one of the most important environmental factors related to HFMD, affecting the transmission of the disease by impacting virus reproduction, survival, and children’s behaviors [29-32]. Various studies [31-34] have shown that the relationship between temperature and HFMD may differ across regions due to the heterogeneity of the natural environment and economic development levels. Studying the spatial distribution of heterogeneous ERRs and the causes of heterogeneity will help to deepen the understanding of the temperature-HFMD ERR, to identify highly sensitive regions and to design region-specific public health interventions, which play important roles in HFMD control and prevention.

### 3.2. Data

In Xiong et al.’s well-presented work, the daily clinical cases of HFMD among children aged 0-12 years for each of 143 prefecture-level cities of mainland China between 2009 and 2014 were recorded. Data for a total of 3,060,450 cases were collected. The daily relative mean temperature was used as the studied environmental factor. In addition, the daily relative humidity, air pressure, rainfall and sunshine hours were also collected as potential confounders in the ERR between temperature and HFMD. The detailed descriptive analysis can be found in Xiong et al.’s work.

### 3.3. The first stage: Modeling city-specific ERRs

In the first stage, Xiong et al. used a DLNM to characterize the nonlinear exposure-response and lag-response relationship between daily mean temperature and daily HFMD cases for each city. To ensure DLNMs for all cities to yield non-missing estimates, the mean temperatures were scaled based on city-specific percentiles. A quasi-Poisson distribution with overdispersion was selected. For each city, the DLNM was expressed as

where is the observed number of HFMD cases at time in the specific city. are the autoregressive terms of HFMD daily counts on the logarithm scale at lag 1 and 2, which were selected based on the autocorrelation plot of residuals. is the cross-basis function regarding the relative mean temperatures, with a lag range of 4-14 days, 5-degrees of freedom () natural cubic splines for the exposure-response dimension and 4- natural cubic splines for the lag-response dimension, where is the parameter to be estimated and s are selected based on the quasi-AIC. More specifically, let and , then can be written as

where is the th row of  basis matrix obtained by the application of the natural-cubic-spline basis functions to the original . is the th column of basis matrix **c** obtained by the application of the natural-cubic-spline basis functions to . is an unknown 20-dimentional vector composed of . The maximum likelihood method is used to estimate the value of . Let where is a 11-dimentional vector of one, then, for city is , estimated as

The detailed methodology of defining ERR in DLNM can be found in Gasparrini et al.’s works[10, 35].

### 3.4. The second stage: Mapping the ERRs and identifying the causes of heterogeneity

In the second stage, Xiong et al. used MMR with only the intercept to obtain the average ERR across 143 cities and used MMR with a single region-level predictor to study the heterogeneity attributable to the predictor. In this work, we further used MCMAR to achieve the same objectives and compared the results to those from MMR. The spatially adjacent relationships among cities were constructed based on an empirical 4-nearest neighbors method. The other methods, such as 3, 5, 6-nearest neighbors methods and the Thiessen-polygons-based method, were also selected as sensitivity analyses. The details are shown in the supplementary material.

The comparison of heterogeneity is shown in Table 1. The Cochran Q test showed significant region-level heterogeneity in ERRs. Using the LR test, MMR identified eight of sixteen predictors that significantly contributed to the heterogeneity (*P* < 0.05), while MCMAR identified no predictor (*P* > 0.05). In all the models, MCMAR achieved considerably smaller AICs than MMR, which suggests that MCMAR may obtain more accurate results than MMR. Statistical tests for in MCMAR showed that the spatial autocorrelation of ERRs significantly existed in all the models (*P* < 0.001), suggesting the reasonableness of incorporating spatial autocorrelation into the second-stage model. In addition, we also constructed MMR or MCMAR with multiple predictors, which were selected using a forward method based on AIC. In MCMAR, no predictor was deserved to be incorporated. In MMR, four predictors, i.e., average rainfall, longitude, GDP increase, and average temperature, were incorporated, and the first three were identified as the significant causes contributing to the heterogeneity (*P* < 0.001) and the average temperature was not identified (*P* = 0.06). Furtherly, the AIC of MMR with the four predictors was still considerably larger than that of MCMAR with only intercept (497.6 vs 469.7).

Table 1. Comparison between MMR and MCMAR in terms of investigating the heterogeneity attributable to region-level predictors.

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Model including a  single predictor | AIC | |  | Test predictor (*P*) | |  | in MCMAR1 | |  | Cochran Q test2 | |
| MMR | MCMAR |  | MMR | MCMAR |  | value | *P* |  |  |  |
| Intercept only3 | 527.9 | 469.7 |  | NA | NA |  | 0.531 | < 0.001 |  | 68.5 | < 0.001 |
| Latitude | 514.8 | 472.8 |  | < 0.001 | 0.229 |  | 0.452 | < 0.001 |  | 67 | < 0.001 |
| Longitude | 527 | 475.9 |  | 0.053 | 0.576 |  | 0.501 | < 0.001 |  | 68.2 | < 0.001 |
| Altitude | 522.4 | 471.5 |  | 0.008 | 0.143 |  | 0.497 | < 0.001 |  | 67.7 | < 0.001 |
| Temperature | 514.3 | 470.5 |  | < 0.001 | 0.1 |  | 0.461 | < 0.001 |  | 66.9 | < 0.001 |
| Relative humidity | 515.1 | 474.8 |  | < 0.001 | 0.428 |  | 0.463 | < 0.001 |  | 67.1 | < 0.001 |
| Air pressure | 521.6 | 471.1 |  | 0.006 | 0.124 |  | 0.496 | < 0.001 |  | 67.6 | < 0.001 |
| Rainfall | 501.3 | 471.6 |  | < 0.001 | 0.152 |  | 0.385 | < 0.001 |  | 66.5 | < 0.001 |
| Sunshine hours | 523.2 | 472.8 |  | 0.011 | 0.231 |  | 0.501 | < 0.001 |  | 67.6 | < 0.001 |
| Population increase | 536.4 | 476.8 |  | 0.905 | 0.714 |  | 0.543 | < 0.001 |  | 68.5 | < 0.001 |
| Population density | 531.5 | 471.5 |  | 0.265 | 0.147 |  | 0.569 | < 0.001 |  | 68.6 | < 0.001 |
| GDP per person | 529 | 472.4 |  | 0.11 | 0.201 |  | 0.525 | < 0.001 |  | 68.3 | < 0.001 |
| GDP increase | 527.4 | 469.6 |  | 0.061 | 0.072 |  | 0.543 | < 0.001 |  | 68.4 | < 0.001 |
| Licensed physicians | 535.1 | 478.7 |  | 0.719 | 0.96 |  | 0.527 | < 0.001 |  | 68.6 | < 0.001 |
| Hospital beds | 535.5 | 476 |  | 0.785 | 0.601 |  | 0.544 | < 0.001 |  | 68.6 | < 0.001 |
| Travel passengers | 532.5 | 473.3 |  | 0.37 | 0.269 |  | 0.542 | < 0.001 |  | 68.6 | < 0.001 |
| Number of students | 535 | 476.5 |  | 0.718 | 0.666 |  | 0.536 | < 0.001 |  | 68.2 | < 0.001 |

Note: The parameters in MMR and MCMAR were estimated using the ML method, and the REML method gave a similar result, which can be found in the supplementary material. 1 The LR test was used to test the spatial autocorrelation in MCMAR. 2 The Cochran Q test presents the same results for MMR and MCMAR due to the identical model under the null hypothesis. 3 “Intercept only” indicates the MMR without any region-level predictor, so the test results for predictors are not available (NA).

The comparison of the pooled average ERRs across all cities obtained by MMR and MCMAR, both with only intercepts, is shown in Figure 1. As in Xiong et al.’s work, intuitive ERR curves with a 50% quantile of temperature as a reference were presented. The results showed that MMR and MCMAR obtained highly similar average ERRs, while the 95% confidence interval in MCMAR was wider than that in MMR, which conformed to our expectation because MMR would underestimate the variation due to ignoring the between-region correlation of ERRs.



Figure 1 The pooled average ERR curves obtained by MMR and MCMAR with only intercepts.

We also compared the spatial distributions of ERRs estimated by MMR and MCMAR. For a more intuitive exhibition, we used MMR and MCMAR with only intercepts to calculate the pooled relative risks (RRs) at 10%, 30%, 70% and 90% quantiles of temperature referring to 50% for each city. The comparison of spatial distributions is shown in Figure 2. MCMAR achieved a smoother spatial distribution than MMR, which was considerably found in RRs at the 90% quantile of temperature. The representative regions for comparison are marked by blue circles or ellipses, with that the RRs obtained by MMR show steeper distinction between adjacent cities than those obtained by MCMAR. The spatial distributions of ERRs show that high temperature increases the risk of HFMD mainly in the South and Northeast of China, but which does not in the Central.



Figure 2 The comparison of spatial distributions of ERRs estimated by MMR and MCMAR in terms of RR at the 10%, 30%, 70% and 90% quantiles of temperature referring to 50%.

## 4. Simulation study

The comparison between MMR and MCMAR in the motivating example may be somewhat subjective, especially for the comparison regarding spatial distributions, i.e., the city-specific predictions of ERRs. Therefore, we generated a batch of simulation datasets to further provide an objective comparison.

### 4.1 Simulation scenario setting and data generation process

Two situations were considered. One (Scen1) is that an observed predictor is able to explain part of the region-level heterogeneity, as shown in MMR, and the other (Scen2) is that there is no observed predictor able to explain the heterogeneity, as shown in MCMAR. For the former, rainfall was selected as the observed predictor as in Xiong et al.’s work, and the true parameters, i.e., the intercept () and regression coefficient () for the predictor, were set as the estimations from MMR with rainfall in the motivating example. For the latter, the intercept was set as the estimation from MCMAR with only the intercept, and was set as . For each situation, four different values were set to simulate different intensities of spatial autocorrelation in practical studies, i.e., . Other necessary parameters, including , and , also came from the motivating example. As such, a total of 8 simulation scenarios were set, which are shown in Table 2. For each scenario, the true ERR, , for city is

where is the predictor. is the th column of matrix , which is sampled from the matrix normal distribution with known and , as shown in Formula (3). Finally, we repeated the following random sampling 1000 times to simulate the estimated city-specific ERRs in the first stage.

The true parameters and the simulated random datasets are available at [the](https://github.com/winkey1230/MCMAR-article) appendices.

Table 2. The parameter settings for the eight simulation scenarios

|  |  |  |  |
| --- | --- | --- | --- |
| Scenarios | Parameter for intercept () | Parameter for predictor () |  |
| Scen1-rho0 |  |  | 0 |
| Scen1-rho1 |  |  | 0.3 |
| Scen1-rho2 |  |  | 0.5 |
| Scen1-rho3 |  |  | 0.8 |
| Scen2-rho0 |  |  | 0 |
| Scen2-rho1 |  |  | 0.3 |
| Scen2-rho2 |  |  | 0.5 |
| Scen2-rho3 |  |  | 0.8 |

Note: For the first four scenarios, and are the estimated fixed effects in MMR with rainfall as a predictor in the motivating example. For the last scenarios, is the estimated intercept in MCMAR with only the intercept.

### 4.2 Parameter estimations and performance measures

For each simulation dataset, MMR and MCMAR with only intercepts were used to obtain the average ERR, i.e., to estimate . MMR and MCMAR with a predictor were used to investigate whether the incorporated predictor contributed to the region-level heterogeneity, i.e., to estimate and test the hypothesis of . For all the models, the pooled city-specific ERRs, i.e., , were estimated to reflect the spatial distribution, and the AIC values were calculated to evaluate the fit performance. In addition, for both model strategies, i.e., with only intercept and with a predictor, the optimal model (OPT) was selected from MMR and MCMAR based on the hypothesis test of . Specifically, when *P* < 0.05, MCMARwas chosen, and MMR was used otherwise. As such, a total of six model results were obtained for each dataset.

For each model in a dataset, the relative vector distance from the estimated parameter to the true parameter was used to measure the estimated error if the true parameter vector included no element of zero; otherwise, the absolute vector distance was used. Specifically, for , the relative distance was used. For , the relative and absolute distances were used in Scen1 and Scen2, respectively. For , the absolute distance was used due to zero-closed elements existing. Then, we averaged the absolute or relative vector distances over replicas to obtain the mean absolute error (MAE) or relative mean absolute error (RMAE) for each model in each scenario. The MAE and RMAE can be calculated as

The average AIC, the power of identifying in Scen1, and the false positive error (FPE) of identifying in Scen2 were calculated as

In addition, the coverage rates of 95% confidence intervals for and are also calculated to compare the uncertainty between MMR and MCMAR. Because and are vectors and the 95% confidence intervals are high-dimensional and not intuitive, we use the multivariate Wald test to judge whether the 95% confidence interval covers the true parameter. Taking as an example, the test statistic can be constructed as

which follows an asymptotical distribution with degrees of freedom equal to the number of dimensions of . When the *P* value of the test statistic is larger than 0.05, the 95% confidence interval covers the true parameter , otherwise it does not cover. The coverage rate is more closed to 0.95, and the performance for uncertainty is better.

### 4.3 Results

The comparison of the simulation results between MMR and MCMAR is shown in Table 3. As expected, MMR performed best in scenarios with no spatial autocorrelation, i.e., Scen1-rho0 and Scen2-rho0, whereas MCMAR performed very similarly to MMR and even obtained a smaller RMAE for , as seen in Scen1-rho0. In scenarios with , MCMAR outperformed MMR considerably in estimating the average and city-specific ERRs, estimating the effect of predictors, identifying the causes of heterogeneity, and evaluating the model fit based on the AIC. Overall, the advantage increased as increased. In Scen2 without any observed predictor contributing to the region-level heterogeneity of ERRs, MMR with a predictor had a high rate of falsely identifying the predictor as being able to explain the heterogeneity, and the false positive rate increased as was larger, even up to 0.971 when , which is unacceptable in practical studies. However, MCMAR with the predictor considerably reduced the false positive rate. In Scen1 with a predictor contributing to the region-level heterogeneity, both MMR and MCMAR achieved a power of 1 in correctly identifying the predictor. The OPT model achieved performance closer to the ideal MMR in scenarios with than MCMAR and did not reduce the advantage of MCMAR over MMR in scenarios with . For the coverage rates of 95% confidence intervals, in Scenario with no spatial dependence, both MMR and MCMAR obtained coverage rates closed to 0.95, while in scenarios with spatial dependence, the coverage rates obtained by MMR is much smaller than 0.95, especially in those with = 0.3 or 0.8, by contrast, MCMAR obtained much better coverage rates.

Table 3. Comparison between MMR and MCMAR in the simulation study

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Scenarios | Model with only intercept | | |  | Model with a predictor | | |
| MMR | MCMAR | OPT1 |  | MMR | MCMAR | OPT |
| **RMAE for** 2**; RMAE for** **in Scen1; MAE for**  **in Scen2** | | | | | | | |
| Scen1-rho0 | 0.253 | 0.25 | 0.252 |  | 1.228 | 1.235 | 1.23 |
| Scen1-rho1 | 0.241 | 0.225 | 0.225 |  | 1.577 | 1.363 | 1.364 |
| Scen1-rho2 | 0.481 | 0.432 | 0.432 |  | 2.503 | 2.4 | 2.4 |
| Scen1-rho3 | 0.359 | 0.326 | 0.326 |  | 3.45 | 2.823 | 2.823 |
| Scen2-rho0 | 0.379 | 0.379 | 0.379 |  | 0.006 | 0.006 | 0.006 |
| Scen2-rho1 | 0.358 | 0.348 | 0.348 |  | 0.006 | 0.006 | 0.006 |
| Scen2-rho2 | 0.69 | 0.661 | 0.661 |  | 0.008 | 0.008 | 0.008 |
| Scen2-rho3 | 0.649 | 0.615 | 0.615 |  | 0.014 | 0.01 | 0.01 |
| **Coverage rates of 95% confidence intervals for in model with only intercept and for in model with a predictor** | | | | | | | |
| Scen1-rho0 | 0.954 | 0.971 | 0.957 |  | 0.981 | 0.976 | 0.981 |
| Scen1-rho1 | 0.914 | 0.995 | 0.995 |  | 0.883 | 0.972 | 0.972 |
| Scen1-rho2 | 0.422 | 0.977 | 0.977 |  | 0.547 | 0.853 | 0.853 |
| Scen1-rho3 | 0.027 | 0.751 | 0.751 |  | 0.027 | 0.571 | 0.571 |
| Scen2-rho0 | 0.977 | 0.971 | 0.976 |  | 0.984 | 0.98 | 0.982 |
| Scen2-rho1 | 0.926 | 0.992 | 0.992 |  | 0.868 | 0.962 | 0.962 |
| Scen2-rho2 | 0.486 | 0.95 | 0.95 |  | 0.501 | 0.843 | 0.843 |
| Scen2-rho3 | 0.003 | 0.437 | 0.437 |  | 0.029 | 0.569 | 0.569 |
| **MAE for city-specific ERRs** | | | |  |  |  |  |
| Scen1-rho0 | 0.468 | 0.469 | 0.468 |  | 0.466 | 0.467 | 0.466 |
| Scen1-rho1 | 0.397 | 0.384 | 0.384 |  | 0.394 | 0.382 | 0.382 |
| Scen1-rho2 | 0.386 | 0.366 | 0.366 |  | 0.381 | 0.363 | 0.363 |
| Scen1-rho3 | 0.371 | 0.334 | 0.334 |  | 0.344 | 0.329 | 0.329 |
| Scen2-rho0 | 0.463 | 0.464 | 0.464 |  | 0.466 | 0.467 | 0.466 |
| Scen2-rho1 | 0.389 | 0.38 | 0.38 |  | 0.395 | 0.384 | 0.384 |
| Scen2-rho2 | 0.379 | 0.361 | 0.361 |  | 0.381 | 0.363 | 0.363 |
| Scen2-rho3 | 0.349 | 0.326 | 0.326 |  | 0.343 | 0.328 | 0.328 |
| **Average AIC values over the replicas 3** | | | |  |  |  |  |
| Scen1-rho0 | 424.236 | 424.59 | 423.815 |  | 452.762 | 453.894 | 452.676 |
| Scen1-rho1 | 246.129 | 202.118 | 202.118 |  | 256.6 | 238.924 | 238.925 |
| Scen1-rho2 | 182.777 | 131.715 | 131.715 |  | 189.74 | 160.916 | 160.916 |
| Scen1-rho3 | 196.18 | 92.058 | 92.058 |  | 166.178 | 122.547 | 122.547 |
| Scen2-rho0 | 395.242 | 396.455 | 395.15 |  | 454.459 | 455.701 | 454.38 |
| Scen2-rho1 | 196.251 | 179.056 | 179.06 |  | 254.89 | 237.473 | 237.477 |
| Scen2-rho2 | 133.552 | 102.601 | 102.601 |  | 188.474 | 159.374 | 159.374 |
| Scen2-rho3 | 122.048 | 67.868 | 67.868 |  | 165.806 | 121.962 | 121.962 |
| **Power or false positive error of identifying the predictor contributing to heterogeneity** | | | | | | | |
| Scen1-rho0 | - | - | - |  | 1 | 1 | 1 |
| Scen1-rho1 | - | - | - |  | 1 | 1 | 1 |
| Scen1-rho2 | - | - | - |  | 1 | 1 | 1 |
| Scen1-rho3 | - | - | - |  | 1 | 1 | 1 |
| Scen2-rho0 | - | - | - |  | 0.016 | 0.020 | 0.018 |
| Scen2-rho1 | - | - | - |  | 0.132 | 0.038 | 0.038 |
| Scen2-rho2 | - | - | - |  | 0.499 | 0.157 | 0.157 |
| Scen2-rho3 | - | - | - |  | 0.971 | 0.431 | 0.431 |

Note: The parameters were estimated using the REML method. The comparison results based on the ML method can be found in the supplementary materials. 1 OPT is the model selected from MMR and MCMAR based on the hypothesis test of . 2  defines the true average association across all regions. 3 The values of AIC are calculated based on the penalized likelihood, so the comparison of AICs is only available between MMR and MCMAR with identical fixed effects structures.

## 5. Discussion

In this work, we combined LCAR with MMR to construct an extended model called MCMAR which can sufficiently utilize the spatial autocorrelation information between regions. Then, a novel MCMAR-based two-stage strategy was developed to map the ERRs between environment risk factors and health-related outcomes and identify the causes of heterogeneity. A motivating example and a simulation study demonstrated that, the MCMAR-based strategy exhibited considerably better performance than the classic MMR-based strategy. More accurate spatial distribution of ERRs and causes of heterogeneity are essential to make region-specific environment-related invention policies for promoting health, for example, decreasing the exposure to certain environment factor is more cost-effective in the regions with high-sensitivity risk. More notably, possibly due to the MMR-based strategy not considering the spatial distribution, the spatial distribution of short-term ERRs is less frequently focused on.

In the motivating example, the spatial distribution of temperature-HFMD ERRs shows that high temperature increases the risk of HFMD mainly in the South of China, but which does not in the Central, which suggests that high-temperature-related interventions for controlling HFMD should be carried out in the South rather than the Central. Compared to the MMR-based strategy, MCMAR achieved a considerably smaller AIC (469.7 vs. 527.9). The LR test regarding spatial autocorrelation, i.e., , also supported that a significant spatial autocorrelation existed in ERRs (*P* < 0.001). These results suggest that MCMAR may obtain more accurate results than the classic MMR. Regarding the identification of predictors contributing to city-level heterogeneity, MCMAR identified no observed predictor as significant, while MMR identified half of the observed predictors as significant. We further analyzed the spatial autocorrelation in the identified predictors. Moran’s *I* test showed that significant spatial autocorrelations existed in these predictors, which suggests that the effect of predictors in MMR may be severely confounded by spatial autocorrelation. More specifically, if an observed false predictor (“false” denotes that the predictor does not contribute to the heterogeneity, and “true” denotes the opposite) and a batch of unobserved true predictors exhibited similar spatial autocorrelation patterns, MMR would attribute the effect of unobserved true predictors to the incorporated false predictor and thus lead to a false identification, while MCMAR would considerably relieve the confounding by adjusting spatial autocorrelation, which was also supported by the simulation study. Therefore, the identified predictors, e.g., rainfall, by MMR in Xiong et al.’s work may make a false positive error, at least, there is no enough evidence showing that these predictors contributed to the heterogeneity in the study. A false cause may mislead the policy and the understanding about the mechanism underlying the environment factors and health outcomes.

Comparing the average ERRs across all cities, MMR and MCMAR obtained similar point estimations, but MMR obtained a narrower confidence interval than MCMAR, which is explained by a statistical knowledge that ignoring the correlation among sample data will underestimate the variance, thus leading to an over-narrow confidence interval. Underestimated variance will reduce the accuracy of estimation in MMR. The simulation study also confirmed that MMR achieved worse performance than MCMAR in estimating the average and city-specific ERRs.

When predicting the ERR in a new location, which is necessary for characterizing high-resolution spatial distribution in the whole studied area, MMR is only able to utilize the fixed effect, e.g., , as in Wu and Zhao et al.’s works [36, 37]. Especially when no predictor is included, the predictions for all new locations are identical, i.e., regardless of their spatial positions, which may lead to an unsatisfactory spatial distribution in ERRs. MCMAR is able to use both the spatial random effects and fixed effects to obtain the prediction as in Equation (11), which provides a smoother and more rational spatial distribution. Therefore, in Wu and Zhao et al.’s works, if MCMAR were used, a more accurate ERR spatial distribution might be obtained, and then the related attributable disease burdens would be evaluated more accurately, which are essential to make cost-effective region-specific policies for decreasing exposure and allocating medical sources. In addition, the MMR-based two-stage strategy has also been used to investigate the associations between meteorological factors and air pollutants, as in Yang et al.’s study [38], which is important for air pollutant control and forecast, so our strategy may provide a more accurate alternative tool in this field.

In the motivating example, the spatially adjacent relationships among cities were constructed based on the -nearest neighbors method, which may be somewhat arbitrary. We also used the 3-, 5- and -nearest neighbors methods and Thiessen polygon-based method to construct the spatially adjacent relationships as sensitivity analyses. MCMAR still outperformed MMR and the details can be found in the supplementary materials. Currently, many related studies have been carried out across the globe; in these cases, spatially adjacent relationships may be independently constructed for each continent due to their isolated spatial positions. In practical studies, model fit statistics, such as the AIC and BIC, can be used to select an appropriate method of constructing spatially adjacent relationships. In addition, the spatial locations of the studied regions may be sparsely distributed in practical studies, and the spatial autocorrelation of the ERR may be slight or may not even exist. In these cases, we can use the LR test to test whether the spatial autocorrelation, i.e.,, actually exists and is significant; if significantly exists, MCMAR should be selected, and MMR should be selected otherwise. This selection may limit the overfitting risk derived from introducing false spatial autocorrelation, which is also supported by the simulation study regarding the performance of the OPT model. As model selection indicators, the AIC and BIC may also be appropriate for selecting either MCMAR or MMR.

In this study, an unstructured matrix was selected for to maintain flexibility. However, in some cases, the dimension of the ERR-defining vector may be relatively large, and selecting an unstructured will lead to many parameters to be estimated, which will result in unstable estimations and intensive use of computing resources. In these cases, selecting a structured may be more appropriate, as in MMR. Without any prior, since both and reflect the correlations between elements in the ERR-defining vector, a structured may be set by limiting the correlation reflected by being same with the average correlation reflected by all the s.

Similar to MMR, MCMAR does not depend on raw data and only depends on result data from the first stage. Therefore, MCMAR can also be applied to published (or second-hand) datasets with spatial positions, including but not limited to ERR datasets, longitudinal profiles [39], receiver operating characteristic (ROC) curves [40] and survival curves [41, 42]. With the improvement in geographic information systems and disease surveillance systems, a large number of such spatial datasets have been and are being produced, which will provide MCMAR with a wide range of applications. Another issue worth noting is that if the ERR-defining vectors, estimated by a GAM, come from different studies, they cannot usually be used directly in MCMAR due to dimensional differences among vectors; even with an identical number of dimensions, the vectors also have different mathematical meanings due to different choices of spline functions. In such cases, the estimated relative risks with covariance can alternatively be used in MCMAR. Taking the ERR between temperature and HFMD as an example, first, a series of representative objective temperatures are selected. Then, for each region, the estimated ERR-defining vector from a GAM in the first stage is used to obtain the logarithmic relative risks vector with covariance over the reference temperature. Finally, the region-specific logarithmic relative risks vector with covariance can be used in MCMAR due to the similar epidemiological meanings. In this case, a structured **V** needs to be selected due to the large dimensions.

## Appendices

The supplementary materials include information on the methods of constructing spatially adjacent matrices, the sensitivity analysis results with different spatially adjacent matrices, and some formula derivations mentioned in the main text. The supplementary materials and the data and R codes for replicating our results are available from <https://github.com/winkey1230/MCMAR>.

## Competing interesting

The authors declare that they have no competing interests

## 7. References

1. Shah ASV, Langrish JP, Nair H, et al. Global association of air pollution and heart failure: a systematic review and meta-analysis. Lancet. 2013;382(9897):1039-48.

2. Katsouyanni K, Touloumi G, Spix C, et al. Short term effects of ambient sulphur dioxide and particulate matter on mortality in 12 European cities: Results from time series data from the APHEA project. Bmj-British Medical Journal. 1997;314(7095):1658-63.

3. Shang Y, Sun ZW, Cao JJ, et al. Systematic review of Chinese studies of short-term exposure to air pollution and daily mortality. Environment International. 2013;54:100-11.

4. Newell K, Kartsonaki C, Lam KBH, Kurmi OP. Cardiorespiratory health effects of particulate ambient air pollution exposure in low-income and middle-income countries: a systematic review and meta-analysis. Lancet Planetary Health. 2017;1(9):E368-E80.

5. Requia WJ, Adams MD, Arain A, Papatheodorou S, Koutrakis P, Mahmoud M. Global Association of Air Pollution and Cardiorespiratory Diseases: A Systematic Review, Meta-Analysis, and Investigation of Modifier Variables. American Journal of Public Health. 2018;108:S123-S30.

6. Shah ASV, Lee KK, McAllister DA, et al. Short term exposure to air pollution and stroke: systematic review and meta-analysis. BMJ. 2015;350:h1295.

7. Tian Y, Liu H, Wu Y, et al. Association between ambient fine particulate pollution and hospital admissions for cause specific cardiovascular disease: time series study in 184 major Chinese cities. Bmj-British Medical Journal. 2019;367.

8. Gasparrini A, Armstrong B, Kenward MG. Multivariate meta-analysis for non-linear and other multi-parameter associations. Statistics in Medicine. 2012;31(29):3821-39.

9. Gasparrini A, Armstrong B, Kenward MG. Distributed lag non-linear models. Statistics in Medicine. 2010;29(21):2224-34.

10. Gasparrini A. Modeling exposure-lag-response associations with distributed lag non-linear models. Statistics in Medicine. 2014;33(5):881-99.

11. Tobler WR. A Computer Movie Simulating Urban Growth in the Detroit Region. Economic Geography. 1970;46(2).

12. Anselin L. Spatial Econometrics: Methods and Models1988.

13. Zadnik V, Reich BJ. Analysis of the relationship between socioeconomic factors and stomach cancer incidence in Slovenia. Neoplasma. 2006;53(2):103-10.

14. Besag J, York J, Mollié A. Bayesian image restoration, with two applications in spatial statistics. Annals of the Institute of Statistical Mathematics. 1991;43(1):1-20.

15. Hedges LV, Olkin I. Statistical methods for meta-analysis. New Directions for Program Evaluation. 1985;1984(24):25-42.

16. Viechtbauer W. Conducting Meta-Analyses in R with the metafor Package. Journal of Statistical Software. 2010;36(3):1 - 48.

17. Leroux B, Lei X, Breslow N, Leroux BG. Estimation of Disease Rates in Small Areas: A new Mixed Model for Spatial Dependence: Statistical Models in Epidemiology, the Environment, and Clinical Trials; 2000.

18. Brent RP. Algorithms for Minimization Without Derivatives. Mathematics of Computation. 1973;19(5).

19. Fletcher R. Practical Methods of Optimization, Second Edition: Practical Methods of Optimization, Second Edition; 1987.

20. Harrell FE. Regression Modeling Strategies: With Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis: Regression Modeling Strategies: With Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis; 2015.

21. Roger KJH. Small sample inference for fixed effects from restricted maximum likelihood. Biometrics. 1997;53(3):983-97.

22. A MGK, B JHR. An improved approximation to the precision of fixed effects from restricted maximum likelihood. Computational Statistics & Data Analysis. 2009;53(7):2583-95.

23. Ritz J, Demidenko E, Spiegelman D. Multivariate meta-analysis for data consortia, individual patient meta-analysis, and pooling projects. Journal of Statistical Planning & Inference. 2008;138(7):1919-33.

24. Xiao X, Gasparrini A, Huang J, et al. The exposure-response relationship between temperature and childhood hand, foot and mouth disease: A multicity study from mainland China. Environment International. 2017;100:102-9.

25. Huang J, Liao QH, Ooi MH, et al. Epidemiology of Recurrent Hand, Foot and Mouth Disease, China, 2008-2015. Emerging Infectious Diseases. 2018;24(3):432-42.

26. Zhuang ZC, Kou ZQ, Bai YJ, et al. Epidemiological Research on Hand, Foot, and Mouth Disease in Mainland China. Viruses-Basel. 2015;7(12):6400-11.

27. Koh WM, Badaruddin H, La H, Chen MIC, Cook AR. Severity and burden of hand, foot and mouth disease in Asia: a modelling study. Bmj Global Health. 2018;3(1).

28. Xing WJ, Liao QH, Viboud C, et al. Hand, foot, and mouth disease in China, 2008-12: an epidemiological study. Lancet Infectious Diseases. 2014;14(4):308-18.

29. Belanger M, Gray-Donald K, O'Loughlin J, Paradis G, Hanley J. Influence of Weather Conditions and Season on Physical Activity in Adolescents. Annals of Epidemiology. 2009;19(3):180-6.

30. Bertrand I, Schijven JF, Sanchez G, et al. The impact of temperature on the inactivation of enteric viruses in food and water: a review. Journal of Applied Microbiology. 2012;112(6):1059-74.

31. Yi LP, Xu X, Ge WX, et al. The impact of climate variability on infectious disease transmission in China: Current knowledge and further directions. Environmental Research. 2019;173:255-61.

32. Cheng Q, Bai LJ, Zhang YW, et al. Ambient temperature, humidity and hand, foot, and mouth disease: A systematic review and meta-analysis. Science of the Total Environment. 2018;625:828-36.

33. Zhu L, Wang XJ, Guo YM, Xu J, Xue FZ, Liu YX. Assessment of temperature effect on childhood hand, foot and mouth disease incidence (0-5 years) and associated effect modifiers: A 17 cities study in Shandong Province, China, 2007-2012. Science of the Total Environment. 2016;551:452-9.

34. Nguyen HX, Chu C, Nguyen HLT, et al. Temporal and spatial analysis of hand, foot, and mouth disease in relation to climate factors: A study in the Mekong Delta region, Vietnam. Science of the Total Environment. 2017;581:766-72.

35. Gasparrini A, Armstrong B. Reducing and meta-analysing estimates from distributed lag non-linear models. BMC medical research methodology. 2013;13(1):1-10.

36. Wu Y, Li S, Zhao Q, et al. Global, regional, and national burden of mortality associated with short-term temperature variability from 2000-19: a three-stage modelling study. The Lancet Planetary health. 2022;6(5):e410-e21.

37. Zhao Q, Guo Y, Ye T, Gasparrini A, Li S. Global, regional, and national burden of mortality associated with non-optimal ambient temperatures from 2000 to 2019: a three-stage modelling study. The Lancet Planetary Health. 2021;5(7):E415-E25.

38. Yang Z, Yang J, Li M, Chen J, Ou C-Q. Nonlinear and lagged meteorological effects on daily levels of ambient PM2.5 and O3: Evidence from 284 Chinese cities. Journal of Cleaner Production. 2021;278:123931.

39. Ishak KJ, Platt RW, Joseph L, Hanley JA, Caro JJ. Meta-analysis of longitudinal studies. Clinical Trials. 2007;4(5):525.

40. Arends LR, Hamza TH, Houwelingen J, Heijenbrok-Kal MH, Stijnen T. Bivariate Random Effects Meta-Analysis of ROC Curves. Medical Decision Making. 2008;28(5):621-38.

41. Dear K. Iterative generalized least squares for meta-analysis of survival data at multiple times. Biometrics. 1994;50(4):989-1002.

42. Lidia, R., Arends, et al. Meta-analysis of summary survival curve data. Statistics in Medicine. 2008;27(22):4381-96.

Table 1. Comparison between MMR and MCMAR in terms of investigating the heterogeneity attributable to region-level predictors.

Table 2. The parameter settings for the eight simulation scenarios.

Table 3. Comparison between MMR and MCMAR in the simulation study.

Figure 1. The pooled average ERR curves obtained by MMR and MCMAR with only intercepts.

Figure 2. The comparison of spatial distributions of ERRs estimated by MMR and MCMAR in terms of RR at the 10%, 30%, 70% and 90% quantiles of temperature referring to 50%