Incorporating spatial autocorrelation into multivariate meta-regression to study the heterogeneous exposure-response relationships: a multivariate conditional meta autoregression

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Contents

1. Method of transforming spatial point data to spatially adjacent matrix

The R codes or constructing the following spatially adjacent matrices are available at https://github.com/winkey1230/MCMAR-article.

1.1 k-nearest-neighbors-based method

(1). Calculate the distance matrix among cities based on their geographical centers.

(2). For each city, obtain k cites which are nearest to it.

(3). For any two different cities, i and j, if i is one of the k nearest cities to j or j is one of the k nearest cities to i, then $i \sim j$.

The example is shown in Figure S1A.

1.2 Thiessen-polygons-based method

(1). Use the point data obtain Voronoi diagram

(2). Each polygon corresponds to a city. If polygon i and j share a border, then the corresponding city i and j are neighbors.

The example is shown in Figure S1B.

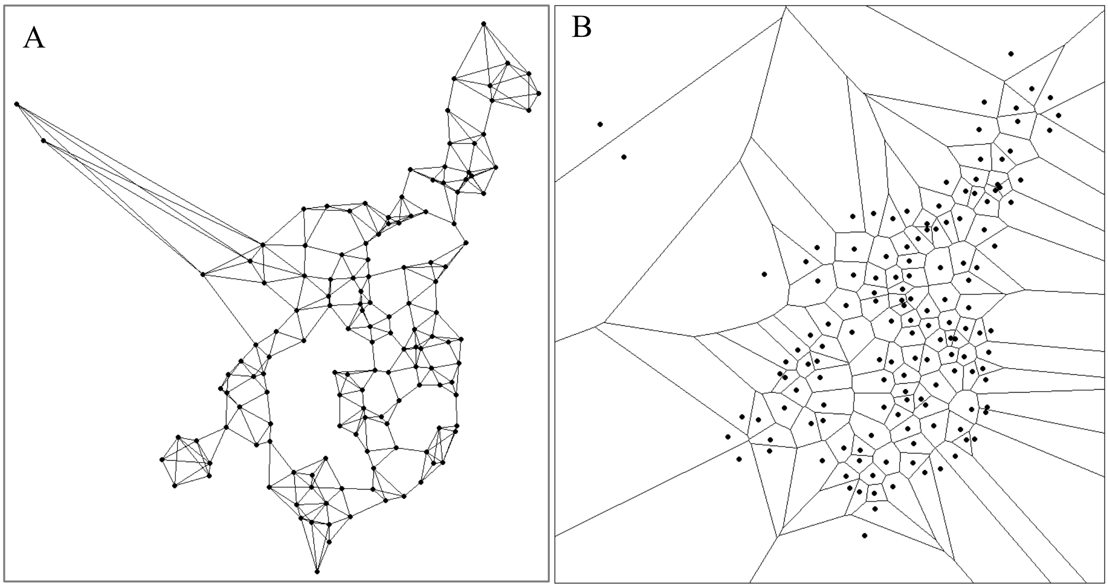

Figure S1 The spatially adjacent relationships among the 143 cities in the motivating example. In subfigure A coming from the 4-nearest-neighbors-based method, two cities linked by a straight line are neighbors and the number of neighbors for each city is at least 4. In subfigure B coming from the Thiessen-polygons-based method, each polygon corresponds to a city. If polygon i and j share a border, then the corresponding city i and j are neighbors.

2. Derivation for the estimation of ξ_i

We set $\widetilde{\boldsymbol{y}} = \widehat{\boldsymbol{\theta}}^* - \mathbf{X}^*\boldsymbol{\beta} = \boldsymbol{\xi}^* + \boldsymbol{\varepsilon}^*$, and $\mathbf{H} = \mathbf{U} \otimes \mathbf{V}$. Given $\widetilde{\boldsymbol{y}}$, $\mathbf{V}$ and $\mathbf{U}$ estimated by ML or REML, the likelihood function with respect to $\boldsymbol{\xi}^*$ can be written as

$$
\begin{aligned}
\widetilde{ll}(\boldsymbol{\xi}^*|\widetilde{\boldsymbol{y}}, \mathbf{H}, \mathbf{D}) &= \ln[\Pr(\boldsymbol{\xi}^*|\mathbf{H})\Pr(\widetilde{\boldsymbol{y}}|\boldsymbol{\xi}^*, \mathbf{D})] \\
&= -\frac{mk}{2}\ln(2\pi) - \frac{1}{2}\ln(|\mathbf{H}|) - \frac{1}{2}\boldsymbol{\xi}^{*\mathrm{T}}\mathbf{H}^{-1}\boldsymbol{\xi}^* - \frac{mk}{2}\ln(2\pi) - \frac{1}{2}\ln(|\mathbf{D}|) \\
&\quad -\frac{1}{2}[\widetilde{\boldsymbol{y}} - \boldsymbol{\xi}^*]^{\mathrm{T}}\mathbf{D}^{-1}[\widetilde{\boldsymbol{y}} - \boldsymbol{\xi}^*] \\
&= Constant - \frac{1}{2}\boldsymbol{\xi}^{*\mathrm{T}}\mathbf{H}^{-1}\boldsymbol{\xi}^* - \frac{1}{2}[\widetilde{\boldsymbol{y}} - \boldsymbol{\xi}^*]^{\mathrm{T}}\mathbf{D}^{-1}[\widetilde{\boldsymbol{y}} - \boldsymbol{\xi}^*] \\
&= Constant - \frac{1}{2}\boldsymbol{\xi}^{*\mathrm{T}}\mathbf{H}^{-1}\boldsymbol{\xi}^* + \frac{1}{2}\widetilde{\boldsymbol{y}}^T\mathbf{D}^{-1}\boldsymbol{\xi}^* - \frac{1}{2}\boldsymbol{\xi}^{*\mathrm{T}}\mathbf{D}^{-1}\boldsymbol{\xi}^* + \frac{1}{2}\boldsymbol{\xi}^{*T}\mathbf{D}^{-1}\widetilde{\boldsymbol{y}} \\
&= Constant - \left[\frac{1}{2}\boldsymbol{\xi}^{*\mathrm{T}}(\mathbf{H}^{-1} + \mathbf{D}^{-1})\boldsymbol{\xi}^* - \frac{1}{2}\widetilde{\boldsymbol{y}}^T\mathbf{D}^{-1}\boldsymbol{\xi}^* - \frac{1}{2}\boldsymbol{\xi}^{*T}\mathbf{D}^{-1}\widetilde{\boldsymbol{y}}\right].
\end{aligned}
$$

The maximal likelihood estimation is $\widehat{\boldsymbol{\xi}}^* = \max_{\boldsymbol{\xi}^*}\widetilde{ll}(\boldsymbol{\xi}^*|\widetilde{\boldsymbol{y}}, \mathbf{H}, \mathbf{D})$ which is also the best linear unbiased estimation due to the multivariate normal distribution. The derivative of $\widetilde{ll}(\boldsymbol{\xi}^*|\widetilde{\boldsymbol{y}}, \mathbf{H}, \mathbf{D})$ is

$$\frac{\partial\widetilde{ll}(\boldsymbol{\xi}^*|\widetilde{\boldsymbol{y}}, \mathbf{H}, \mathbf{D})}{\partial\boldsymbol{\xi}^*} = \mathbf{D}^{-1}\widetilde{\boldsymbol{y}} - (\mathbf{H}^{-1} + \mathbf{D}^{-1})\boldsymbol{\xi}^*.$$

So

$$\mathbf{D}^{-1}\widetilde{\boldsymbol{y}} - (\mathbf{H}^{-1} + \mathbf{D}^{-1})\widehat{\boldsymbol{\xi}}^* = 0$$

$$
\begin{aligned}
\widehat{\boldsymbol{\xi}}^* &= (\mathbf{H}^{-1} + \mathbf{D}^{-1})^{-1}\mathbf{D}^{-1}\widetilde{\boldsymbol{y}} = \mathbf{H}(\mathbf{H} + \mathbf{D})^{-\mathbf{1}}\mathbf{D}\mathbf{D}^{-1}\widetilde{\boldsymbol{y}} = \mathbf{H}(\mathbf{H} + \mathbf{D})^{-\mathbf{1}}\widetilde{\boldsymbol{y}} \\
&= (\widehat{\mathbf{U}} \otimes \widehat{\mathbf{V}})(\widehat{\mathbf{U}} \otimes \widehat{\mathbf{V}} + \mathbf{D})^{-\mathbf{1}}\left(\widehat{\boldsymbol{\theta}}^* - \mathbf{X}^*\widehat{\boldsymbol{\beta}}\right).
\end{aligned}
$$

Then we use the fisher information to calculate the variance of $\widehat{\boldsymbol{\xi}}^*$, so

$$\frac{\partial\partial\widetilde{ll}(\boldsymbol{\xi}^*|\widetilde{\boldsymbol{y}}, \mathbf{H}, \mathbf{D})}{\partial\boldsymbol{\xi}^*\partial\boldsymbol{\xi}^*} = -(\mathbf{H}^{-1} + \mathbf{D}^{-1}).$$

$$
\begin{aligned}
\mathrm{cov}(\widehat{\boldsymbol{\xi}}^*) &= (\mathbf{H}^{-1} + \mathbf{D}^{-1})^{-1} = \mathbf{H}(\mathbf{H} + \mathbf{D})^{-\mathbf{1}}\mathbf{D} \\
&= (\widehat{\mathbf{U}} \otimes \widehat{\mathbf{V}}) - (\widehat{\mathbf{U}} \otimes \widehat{\mathbf{V}})(\widehat{\mathbf{U}} \otimes \widehat{\mathbf{V}} + \mathbf{D})^{-\mathbf{1}}(\widehat{\mathbf{U}} \otimes \widehat{\mathbf{V}}).
\end{aligned}
$$

3. Derivation of Cochran Q test in MCMAR

Let $\widetilde{\boldsymbol{y}} = \widehat{\boldsymbol{\theta}}^* - \mathbf{X}^*\widehat{\boldsymbol{\beta}}$, according to formula (4) and (8) in the main paper, then

$$\widetilde{\boldsymbol{y}} = \widehat{\boldsymbol{\theta}}^* - \mathbf{X}^*\widehat{\boldsymbol{\beta}} = \widehat{\boldsymbol{\theta}}^* - \mathbf{X}^*\left[\mathbf{X}^{*\mathrm{T}}\boldsymbol{\Sigma}^{-1}\mathbf{X}^*\right]^{-1}\mathbf{X}^{*\mathrm{T}}\boldsymbol{\Sigma}^{-1}\widehat{\boldsymbol{\theta}}^*$$

$$= \mathbf{X}^*\boldsymbol{\beta} + \boldsymbol{\xi}^* + \boldsymbol{\varepsilon}^* - \mathbf{X}^*\left[\mathbf{X}^{*\mathrm{T}}\boldsymbol{\Sigma}^{-1}\mathbf{X}^*\right]^{-1}\mathbf{X}^{*\mathrm{T}}\boldsymbol{\Sigma}^{-1}(\mathbf{X}^*\boldsymbol{\beta} + \boldsymbol{\xi}^* + \boldsymbol{\varepsilon}^*)$$

$$= \left\{\mathbf{I}_{mk} - \mathbf{X}^*\left[\mathbf{X}^{*\mathrm{T}}\boldsymbol{\Sigma}^{-1}\mathbf{X}^*\right]^{-1}\mathbf{X}^{*\mathrm{T}}\boldsymbol{\Sigma}^{-1}\right\}(\boldsymbol{\xi}^* + \boldsymbol{\varepsilon}^*).$$

As $\boldsymbol{\xi}^* + \boldsymbol{\varepsilon}^* \sim MN(0, \boldsymbol{\Sigma})$, let $\mathrm{Cov}(\widetilde{\boldsymbol{y}}) = \boldsymbol{\Sigma}_{\widetilde{\boldsymbol{y}}}$, then

$$\boldsymbol{\Sigma}_{\widetilde{\boldsymbol{y}}} = \left\{\mathbf{I}_{mk} - \mathbf{X}^*\left[\mathbf{X}^{*\mathrm{T}}\boldsymbol{\Sigma}^{-1}\mathbf{X}^*\right]^{-1}\mathbf{X}^{*\mathrm{T}}\boldsymbol{\Sigma}^{-1}\right\}\boldsymbol{\Sigma}\left\{\mathbf{I}_{mk} - \mathbf{X}^*\left[\mathbf{X}^{*\mathrm{T}}\boldsymbol{\Sigma}^{-1}\mathbf{X}^*\right]^{-1}\mathbf{X}^{*\mathrm{T}}\boldsymbol{\Sigma}^{-1}\right\}^{\mathrm{T}}$$

$$= \boldsymbol{\Sigma}\left\{\mathbf{I}_{mk} - \mathbf{X}^*\left[\mathbf{X}^{*\mathrm{T}}\boldsymbol{\Sigma}^{-1}\mathbf{X}^*\right]^{-1}\mathbf{X}^{*\mathrm{T}}\boldsymbol{\Sigma}^{-1}\right\}.$$

$$\widetilde{\boldsymbol{y}} \sim MN\left(\mathbf{0}, \boldsymbol{\Sigma}_{\widetilde{\boldsymbol{y}}}\right).$$

Let $\boldsymbol{Z} = \mathbf{I}_{mk} - \mathbf{X}^*\left[\mathbf{X}^{*\mathrm{T}}\boldsymbol{\Sigma}^{-1}\mathbf{X}^*\right]^{-1}\mathbf{X}^{*\mathrm{T}}\boldsymbol{\Sigma}^{-1}$, which is idempotent, i.e., $\boldsymbol{ZZ} = \boldsymbol{Z}$, according to Ogasawara and Takahashi's work[1, 2], the necessary and sufficient condition that $\widetilde{\boldsymbol{y}}^{\mathrm{T}}\mathbf{A}\widetilde{\boldsymbol{y}}$ has χ^2 distribution is

$$\boldsymbol{\Sigma}_{\widetilde{\boldsymbol{y}}}\mathbf{A}\boldsymbol{\Sigma}_{\widetilde{\boldsymbol{y}}}\mathbf{A}\boldsymbol{\Sigma}_{\widetilde{\boldsymbol{y}}} = \boldsymbol{\Sigma}_{\widetilde{\boldsymbol{y}}}\mathbf{A}\boldsymbol{\Sigma}_{\widetilde{\boldsymbol{y}}}, \tag{SE.1}$$

in which case the degrees of freedom is the rank of $\mathbf{A}\boldsymbol{\Sigma}_{\widetilde{\boldsymbol{y}}}$.

Let $\mathbf{A} = \boldsymbol{\Sigma}^{-1}$, then

$$\boldsymbol{\Sigma}_{\widetilde{\boldsymbol{y}}}\boldsymbol{\Sigma}^{-1}\boldsymbol{\Sigma}_{\widetilde{\boldsymbol{y}}}\boldsymbol{\Sigma}^{-1}\boldsymbol{\Sigma}_{\widetilde{\boldsymbol{y}}} = \boldsymbol{\Sigma}\mathbf{Z}\boldsymbol{\Sigma}^{-1}\boldsymbol{\Sigma}\mathbf{Z}\boldsymbol{\Sigma}^{-1}\boldsymbol{\Sigma}\mathbf{Z} = \boldsymbol{\Sigma}\mathbf{ZZZ} = \boldsymbol{\Sigma}\mathbf{Z},$$

$$\boldsymbol{\Sigma}_{\widetilde{\boldsymbol{y}}}\boldsymbol{\Sigma}^{-1}\boldsymbol{\Sigma}_{\widetilde{\boldsymbol{y}}} = \boldsymbol{\Sigma}\mathbf{Z}\boldsymbol{\Sigma}^{-1}\boldsymbol{\Sigma}\mathbf{Z} = \boldsymbol{\Sigma}\mathbf{ZZ} = \boldsymbol{\Sigma}\mathbf{Z}.$$

So, $\boldsymbol{\Sigma}_{\widetilde{\boldsymbol{y}}}\boldsymbol{\Sigma}^{-1}\boldsymbol{\Sigma}_{\widetilde{\boldsymbol{y}}}\boldsymbol{\Sigma}^{-1}\boldsymbol{\Sigma}_{\widetilde{\boldsymbol{y}}} = \boldsymbol{\Sigma}_{\widetilde{\boldsymbol{y}}}\boldsymbol{\Sigma}^{-1}\boldsymbol{\Sigma}_{\widetilde{\boldsymbol{y}}}$ which satisfies the condition (SE.1). Then $\widetilde{\boldsymbol{y}}^{\mathrm{T}}\boldsymbol{\Sigma}^{-1}\widetilde{\boldsymbol{y}} = \left(\widehat{\boldsymbol{\theta}}^* - \mathbf{X}^*\widehat{\boldsymbol{\beta}}\right)^{\mathrm{T}}\boldsymbol{\Sigma}^{-1}\left(\widehat{\boldsymbol{\theta}}^* - \mathbf{X}^*\widehat{\boldsymbol{\beta}}\right)$ follows χ^2 distribution with degrees of freedom equal to the rank of $\boldsymbol{\Sigma}^{-1}\boldsymbol{\Sigma}_{\widetilde{\boldsymbol{y}}}$. The rank is

$$\mathrm{Rank}\left(\boldsymbol{\Sigma}^{-1}\boldsymbol{\Sigma}_{\widetilde{\boldsymbol{y}}}\right) = \mathrm{Rank}\left\{\mathbf{I}_{mk} - \mathbf{X}^*\left[\mathbf{X}^{*\mathrm{T}}\boldsymbol{\Sigma}^{-1}\mathbf{X}^*\right]^{-1}\mathbf{X}^{*\mathrm{T}}\boldsymbol{\Sigma}^{-1}\right\} = (m-p)k.$$

Under the null hypothesis $\mathbf{U} \otimes \mathbf{V} = \mathbf{0}$, i.e., $\boldsymbol{\Sigma} = \mathbf{D}$, as $\mathbf{D}$ is a block diagonal matrix with $\{\mathbf{S}_i\}$ as the blocks, then

$$\left(\widehat{\boldsymbol{\theta}}^* - \mathbf{X}^*\widehat{\boldsymbol{\beta}}\right)^{\mathrm{T}}\boldsymbol{\Sigma}^{-1}\left(\widehat{\boldsymbol{\theta}}^* - \mathbf{X}^*\widehat{\boldsymbol{\beta}}\right) = \sum_{i=1}^{m}(\widehat{\boldsymbol{\theta}}_i - \mathbf{X}_i\widehat{\boldsymbol{\beta}})^{\mathrm{T}}\mathbf{S}_i^{-1}(\widehat{\boldsymbol{\theta}}_i - \mathbf{X}_i\widehat{\boldsymbol{\beta}}),$$

and the rank of $\boldsymbol{\Sigma}^{-1}\boldsymbol{\Sigma}_{\widetilde{\boldsymbol{y}}}$ is also $(m-p)k$. Therefore,

$Q = \sum_{i=1}^{m} (\widehat{\boldsymbol{\theta}}_i - \mathbf{X}_i\widehat{\boldsymbol{\beta}})^{\mathrm{T}} \mathbf{S}_i^{-1} (\widehat{\boldsymbol{\theta}}_i - \mathbf{X}_i\widehat{\boldsymbol{\beta}})$ follows χ^2 distribution with degrees of freedom equal to $(m-p)k$.

Reference

1. Ogasawara, T. and M. Takahashi, *Independence of quadratic quantities in a normal system.* Journal of Science of the Hiroshima University Ser A Mathematics Physics Chemistry, 1951. **15**: p. 1-9.
2. Rao, C.R., *Linear Statistical Inference and its Applications, 2nd Edition*. 1965: Linear Statistical Inference and its Applications, 2nd Edition. p.188.

4. Results for different spatially adjacent matrices in motivating example

We introduced different spatially adjacent matrices into MCMAR to carry out sensitivity analyses. Similar results were obtained, i.e., almost all the observed predictors did not significantly contribute to the city-level heterogeneity of ERRs and MCMAR outperformed MMR. Although, the two predictors, i.e., "rainfall" and "GDP increase", were tested as significantly contributing predictors in some spatially adjacent matrices, the *P* values were closed to 0.05. Based on AIC, the MCMAR with 6-nearest-neighbors-based spatially adjacent matrix were selected as the optimal model for both ML and REML methods. In the optimal models, all the predictors were identified to not significantly contribute to the city-level heterogeneity of ERRs. Notably, for models using ML and REML methods, the Cochran Q test results are identical due to no city-level random parameters needing to be estimated under null hypothesis.

4.1 Using ML method

4.1.1 3-nearest-neighbors -based method in ML

Table S1. Comparison between MMR and MCMAR in term of investigating the heterogeneity attributable to region-level predictors.

Model including a	AIC		Test predictor (*P*)		ρ in MCMAR[1]		Cochran Q test[2]	
single predictor	MMR	MCMAR	MMR	MCMAR	ρ value	*P*	I^2	*P*
Intercept only[3]	527.9	484.1	NA	NA	0.513	< 0.001	68.5	< 0.001
Latitude	514.8	485.4	< 0.001	0.124	0.421	< 0.001	67	< 0.001
Longitude	527	488.4	0.053	0.344	0.484	< 0.001	68.2	< 0.001
Altitude	522.4	485.1	0.008	0.112	0.473	< 0.001	67.7	< 0.001

Temperature	514.3	483.1	< 0.001	0.053	0.435	< 0.001	66.9	< 0.001
Relative humidity	515.1	488	< 0.001	0.302	0.416	< 0.001	67.1	< 0.001
Air pressure	521.6	484.8	0.006	0.098	0.471	< 0.001	67.6	< 0.001
Rainfall	501.3	482.2	< 0.001	**0.036**	0.335	< 0.001	66.5	< 0.001
Sunshine hours	523.2	486.3	0.011	0.171	0.474	< 0.001	67.6	< 0.001
Population increase	536.4	491.4	0.905	0.757	0.526	< 0.001	68.5	< 0.001
Population density	531.5	485.8	0.265	0.139	0.567	< 0.001	68.6	< 0.001
GDP per person	529	487.2	0.11	0.233	0.503	< 0.001	68.3	< 0.001
GDP increase	527.4	485.5	0.061	0.128	0.518	< 0.001	68.4	< 0.001
Licensed physicians	535.1	492.6	0.719	0.919	0.509	< 0.001	68.6	< 0.001
Hospital beds	535.5	490.4	0.785	0.603	0.528	< 0.001	68.6	< 0.001
Travel passengers	532.5	488.4	0.37	0.344	0.522	< 0.001	68.6	< 0.001
Number of students	535	490.5	0.718	0.613	0.524	< 0.001	68.2	< 0.001

4.1.2 4-nearest-neighbors -based method in ML

This result is also included in the main paper.

Table S2. Comparison between MMR and MCMAR in term of investigating the heterogeneity attributable to region-level predictors.

Model including a	AIC		Test predictor (P)		ρ in MCMAR[1]		Cochran Q test[2]	
single predictor	MMR	MCMAR	MMR	MCMAR	ρ value	P	I^2	P
Intercept only[3]	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

4.1.3 5-nearest-neighbors-based method in ML

Table S3. Comparison between MMR and MCMAR in term of investigating the heterogeneity attributable to region-level predictors.

Model including a	AIC		Test predictor (P)		ρ in MCMAR[1]		Cochran Q test[2]	
single predictor	MMR	MCMAR	MMR	MCMAR	ρ value	P	I^2	P
Intercept only[3]	527.9	474.8	NA	NA	0.491	< 0.001	68.5	< 0.001
Latitude	514.8	477.8	< 0.001	0.217	0.404	< 0.001	67	< 0.001
Longitude	527	481	0.053	0.577	0.46	< 0.001	68.2	< 0.001
Altitude	522.4	476.1	0.008	0.121	0.457	< 0.001	67.7	< 0.001
Temperature	514.3	475.3	< 0.001	0.09	0.418	< 0.001	66.9	< 0.001
Relative humidity	515.1	480	< 0.001	0.434	0.421	< 0.001	67.1	< 0.001
Air pressure	521.6	475.7	0.006	0.104	0.457	< 0.001	67.6	< 0.001
Rainfall	501.3	477.3	< 0.001	0.187	0.329	< 0.001	66.5	< 0.001
Sunshine hours	523.2	478.2	0.011	0.247	0.454	< 0.001	67.6	< 0.001
Population increase	536.4	482.7	0.905	0.824	0.501	< 0.001	68.5	< 0.001
Population density	531.5	474.8	0.265	0.075	0.545	< 0.001	68.6	< 0.001
GDP per person	529	476.3	0.11	0.13	0.49	< 0.001	68.3	< 0.001
GDP increase	527.4	475.9	0.061	0.111	0.502	< 0.001	68.4	< 0.001
Licensed physicians	535.1	483.1	0.719	0.885	0.49	< 0.001	68.6	< 0.001
Hospital beds	535.5	480.1	0.785	0.451	0.513	< 0.001	68.6	< 0.001

Travel passengers	532.5	478.2	0.37	0.247	0.504	< 0.001	68.6	< 0.001
Number of students	535	481.8	0.718	0.697	0.496	< 0.001	68.2	< 0.001

4.1.4 6-nearest-neighbors -based method in ML

Table S4. Comparison between MMR and MCMAR in term of investigating the heterogeneity attributable to region-level predictors.

Model including a	AIC		Test predictor (P)		ρ in MCMAR[1]		Cochran Q test[2]	
single predictor	MMR	MCMAR	MMR	MCMAR	ρ value	P	I^2	P
Intercept only[3]	527.9	466.8	NA	NA	0.515	< 0.001	68.5	< 0.001
Latitude	514.8	470.6	< 0.001	0.287	0.432	< 0.001	67	< 0.001
Longitude	527	473.9	0.053	0.707	0.49	< 0.001	68.2	< 0.001
Altitude	522.4	469	0.008	0.169	0.479	< 0.001	67.7	< 0.001
Temperature	514.3	468.1	< 0.001	0.119	0.449	< 0.001	66.9	< 0.001
Relative humidity	515.1	472.4	< 0.001	0.496	0.472	< 0.001	67.1	< 0.001
Air pressure	521.6	468.6	0.006	0.145	0.479	< 0.001	67.6	< 0.001
Rainfall	501.3	471.2	< 0.001	0.345	0.375	< 0.001	66.5	< 0.001
Sunshine hours	523.2	470.2	0.011	0.248	0.482	< 0.001	67.6	< 0.001
Population increase	536.4	474.7	0.905	0.837	0.523	< 0.001	68.5	< 0.001
Population density	531.5	467.1	0.265	0.083	0.56	< 0.001	68.6	< 0.001
GDP per person	529	468.8	0.11	0.155	0.512	< 0.001	68.3	< 0.001
GDP increase	527.4	467.6	0.061	0.099	0.53	< 0.001	68.4	< 0.001
Licensed physicians	535.1	475.1	0.719	0.882	0.515	< 0.001	68.6	< 0.001
Hospital beds	535.5	472.1	0.785	0.455	0.536	< 0.001	68.6	< 0.001
Travel passengers	532.5	469.9	0.37	0.226	0.527	< 0.001	68.6	< 0.001
Number of students	535	474.1	0.718	0.747	0.518	< 0.001	68.2	< 0.001

4.1.5 Thiessen-polygons-based method in ML

Table S5. Comparison between MMR and MCMAR in term of investigating the heterogeneity attributable to region-level predictors.

Model including a	AIC		Test predictor (P)		ρ in MCMAR[1]		Cochran Q test[2]	

single predictor	MMR	MCMAR	MMR	MCMAR	ρ value	P	I^2	P
Intercept only[3]	527.9	474.6	NA	NA	0.576	< 0.001	68.5	< 0.001
Latitude	514.8	478.3	< 0.001	0.277	0.462	< 0.001	67	< 0.001
Longitude	527	479.9	0.053	0.451	0.552	< 0.001	68.2	< 0.001
Altitude	522.4	478.8	0.008	0.323	0.525	< 0.001	67.7	< 0.001
Temperature	514.3	475.3	< 0.001	0.099	0.485	< 0.001	66.9	< 0.001
Relative humidity	515.1	481	< 0.001	0.608	0.499	< 0.001	67.1	< 0.001
Air pressure	521.6	478.3	0.006	0.277	0.523	< 0.001	67.6	< 0.001
Rainfall	501.3	477.3	< 0.001	0.201	0.384	< 0.001	66.5	< 0.001
Sunshine hours	523.2	478.6	0.011	0.309	0.531	< 0.001	67.6	< 0.001
Population increase	536.4	482.6	0.905	0.843	0.59	< 0.001	68.5	< 0.001
Population density	531.5	478.1	0.265	0.26	0.615	< 0.001	68.6	< 0.001
GDP per person	529	475.6	0.11	0.11	0.579	< 0.001	68.3	< 0.001
GDP increase	527.4	473.4	0.061	**0.048**	0.595	< 0.001	68.4	< 0.001
Licensed physicians	535.1	483	0.719	0.906	0.573	< 0.001	68.6	< 0.001
Hospital beds	535.5	480.6	0.785	0.557	0.597	< 0.001	68.6	< 0.001
Travel passengers	532.5	478.4	0.37	0.284	0.588	< 0.001	68.6	< 0.001
Number of students	535	481.4	0.718	0.671	0.584	< 0.001	68.2	< 0.001

4.2 Using REML method

4.2.1 3-nearest-neighbors-based method in REML

Table S6. Comparison between MMR and MCMAR in term of investigating the heterogeneity attributable to region-level predictors.

Model including a	AIC		Test predictor (P)		ρ in MCMAR[1]		Cochran Q test[2]	
single predictor	MMR	MCMAR	MMR	MCMAR	ρ value	P	I^2	P
Intercept only[3]	554.7	506.4	NA	NA	0.558	< 0.001	68.5	< 0.001
Latitude	588.1	551.4	< 0.001	0.138	0.509	< 0.001	67	< 0.001
Longitude	600.5	554.2	0.042	0.372	0.567	< 0.001	68.2	< 0.001
Altitude	661.3	617.9	0.006	0.117	0.533	< 0.001	67.7	< 0.001

Temperature	607.7	569.4	< 0.001	0.056	0.516	< 0.001	66.9	< 0.001
Relative humidity	590.5	557.2	< 0.001	0.324	0.493	< 0.001	67.1	< 0.001
Air pressure	638.4	595.4	0.004	0.103	0.531	< 0.001	67.6	< 0.001
Rainfall	581.4	556.8	< 0.001	**0.018**	0.41	< 0.001	66.5	< 0.001
Sunshine hours	603	559.1	0.008	0.177	0.546	< 0.001	67.6	< 0.001
Population increase	609.4	559.7	0.906	0.732	0.57	< 0.001	68.5	< 0.001
Population density	656.8	606.4	0.26	0.101	0.61	< 0.001	68.6	< 0.001
GDP per person	689.5	643.7	0.105	0.237	0.541	< 0.001	68.3	< 0.001
GDP increase	591.1	545.5	0.055	0.117	0.557	< 0.001	68.4	< 0.001
Licensed physicians	592.6	546.8	0.72	0.924	0.544	< 0.001	68.6	< 0.001
Hospital beds	597.5	548.6	0.786	0.584	0.566	< 0.001	68.6	< 0.001
Travel passengers	687.5	640.1	0.363	0.33	0.555	< 0.001	68.6	< 0.001
Number of students	621	571.3	0.715	0.601	0.569	< 0.001	68.2	< 0.001

4.2.2 4-nearest-neighbors-based method in REML

Table S7. Comparison between MMR and MCMAR in term of investigating the heterogeneity attributable to region-level predictors.

Model including a	AIC		Test predictor (P)		ρ in MCMAR[1]		Cochran Q test[2]	
single predictor	MMR	MCMAR	MMR	MCMAR	ρ value	P	I^2	P
Intercept only[3]	554.7	490.7	NA	NA	0.587	< 0.001	68.5	< 0.001
Latitude	588.1	536.2	< 0.001	0.31	0.567	< 0.001	67	< 0.001
Longitude	600.5	539.4	0.042	0.649	0.604	< 0.001	68.2	< 0.001
Altitude	661.3	602.6	0.006	0.155	0.569	< 0.001	67.7	< 0.001
Temperature	607.7	554.5	< 0.001	0.123	0.559	< 0.001	66.9	< 0.001
Relative humidity	590.5	541.9	< 0.001	0.504	0.556	< 0.001	67.1	< 0.001
Air pressure	638.4	580	0.004	0.133	0.569	< 0.001	67.6	< 0.001
Rainfall	581.4	544.1	< 0.001	0.154	0.479	< 0.001	66.5	< 0.001
Sunshine hours	603	543.5	0.008	0.246	0.588	< 0.001	67.6	< 0.001
Population increase	609.4	543.8	0.906	0.685	0.598	< 0.001	68.5	< 0.001

Population density	656.8	590.7	0.26	0.115	0.625	< 0.001	68.6	< 0.001
GDP per person	689.5	627.6	0.105	0.202	0.575	< 0.001	68.3	< 0.001
GDP increase	591.1	528.3	0.055	0.062	0.595	< 0.001	68.4	< 0.001
Licensed physicians	592.6	531.4	0.72	0.964	0.576	< 0.001	68.6	< 0.001
Hospital beds	597.5	532.9	0.786	0.578	0.594	< 0.001	68.6	< 0.001
Travel passengers	687.5	623.3	0.363	0.252	0.59	< 0.001	68.6	< 0.001
Number of students	621	555.9	0.715	0.663	0.592	< 0.001	68.2	< 0.001

4.2.3 5-nearest-neighbors-based method in REML

Table S8. Comparison between MMR and MCMAR in term of investigating the heterogeneity attributable to region-level predictors.

Model including a single predictor	AIC		Test predictor (P)		ρ in MCMAR[1]		Cochran Q test[2]	
	MMR	MCMAR	MMR	MCMAR	ρ value	P	I^2	P
Intercept only[3]	554.7	495.4	NA	NA	0.563	< 0.001	68.5	< 0.001
Latitude	588.1	540.6	< 0.001	0.33	0.548	< 0.001	67	< 0.001
Longitude	600.5	543.9	0.042	0.662	0.591	< 0.001	68.2	< 0.001
Altitude	661.3	606.8	0.006	0.132	0.546	< 0.001	67.7	< 0.001
Temperature	607.7	558.8	< 0.001	0.121	0.538	< 0.001	66.9	< 0.001
Relative humidity	590.5	546.5	< 0.001	0.533	0.539	< 0.001	67.1	< 0.001
Air pressure	638.4	584.2	0.004	0.113	0.546	< 0.001	67.6	< 0.001
Rainfall	581.4	549.6	< 0.001	0.226	0.446	< 0.001	66.5	< 0.001
Sunshine hours	603	548.5	0.008	0.274	0.557	< 0.001	67.6	< 0.001
Population increase	609.4	549.2	0.906	0.803	0.572	< 0.001	68.5	< 0.001
Population density	656.8	593.4	0.26	0.051	0.619	< 0.001	68.6	< 0.001
GDP per person	689.5	631.2	0.105	0.128	0.554	< 0.001	68.3	< 0.001
GDP increase	591.1	534.1	0.055	0.097	0.57	< 0.001	68.4	< 0.001
Licensed physicians	592.6	535.4	0.72	0.889	0.553	< 0.001	68.6	< 0.001
Hospital beds	597.5	536.5	0.786	0.414	0.579	< 0.001	68.6	< 0.001
Travel passengers	687.5	627.7	0.363	0.228	0.567	< 0.001	68.6	< 0.001

Number of students	621	560.6	0.715	0.694	0.57	< 0.001	68.2	< 0.001

4.2.4 6-nearest-neighbors-based method in REML

Table S9. Comparison between MMR and MCMAR in term of investigating the heterogeneity attributable to region-level predictors.

Model including a	AIC		Test predictor (P)		ρ in MCMAR[1]		Cochran Q test[2]	
single predictor	MMR	MCMAR	MMR	MCMAR	ρ value	P	I^2	P
Intercept only[3]	554.7	486.3	NA	NA	0.606	< 0.001	68.5	< 0.001
Latitude	588.1	531.3	< 0.001	0.473	0.617	< 0.001	67	< 0.001
Longitude	600.5	534.9	0.042	0.782	0.655	< 0.001	68.2	< 0.001
Altitude	661.3	598.5	0.006	0.191	0.588	< 0.001	67.7	< 0.001
Temperature	607.7	549.7	< 0.001	0.169	0.602	< 0.001	66.9	< 0.001
Relative humidity	590.5	537	< 0.001	0.556	0.625	< 0.001	67.1	< 0.001
Air pressure	638.4	575.9	0.004	0.162	0.588	< 0.001	67.6	< 0.001
Rainfall	581.4	541.6	< 0.001	0.517	0.53	< 0.001	66.5	< 0.001
Sunshine hours	603	539.2	0.008	0.277	0.604	< 0.001	67.6	< 0.001
Population increase	609.4	540.2	0.906	0.818	0.614	< 0.001	68.5	< 0.001
Population density	656.8	584.9	0.26	0.06	0.653	< 0.001	68.6	< 0.001
GDP per person	689.5	622.7	0.105	0.156	0.595	< 0.001	68.3	< 0.001
GDP increase	591.1	524.6	0.055	0.083	0.618	< 0.001	68.4	< 0.001
Licensed physicians	592.6	526.2	0.72	0.885	0.598	< 0.001	68.6	< 0.001
Hospital beds	597.5	527.5	0.786	0.415	0.623	< 0.001	68.6	< 0.001
Travel passengers	687.5	618.5	0.363	0.207	0.61	< 0.001	68.6	< 0.001
Number of students	621	551.9	0.715	0.749	0.61	< 0.001	68.2	< 0.001

4.2.5 Thiessen-polygons-based method in REML

Table S10. Comparison between MMR and MCMAR in term of investigating the heterogeneity attributable to region-level predictors.

Model including a	AIC		Test predictor (P)		ρ in MCMAR[1]		Cochran Q test[2]	
single predictor	MMR	MCMAR	MMR	MCMAR	ρ value	P	I^2	P

Intercept only[3]	554.7	494	NA	NA	0.699	< 0.001	68.5	< 0.001
Latitude	588.1	539.9	< 0.001	0.535	0.68	< 0.001	67	< 0.001
Longitude	600.5	541.4	0.042	0.504	0.744	< 0.001	68.2	< 0.001
Altitude	661.3	609.3	0.006	0.391	0.655	< 0.001	67.7	< 0.001
Temperature	607.7	557.7	< 0.001	0.163	0.671	< 0.001	66.9	< 0.001
Relative humidity	590.5	546.4	< 0.001	0.758	0.69	< 0.001	67.1	< 0.001
Air pressure	638.4	586.6	0.004	0.339	0.653	< 0.001	67.6	< 0.001
Rainfall	581.4	548.9	< 0.001	0.328	0.57	< 0.001	66.5	< 0.001
Sunshine hours	603	548.5	0.008	0.364	0.682	< 0.001	67.6	< 0.001
Population increase	609.4	547.6	0.906	0.805	0.716	< 0.001	68.5	< 0.001
Population density	656.8	595.1	0.26	0.198	0.746	< 0.001	68.6	< 0.001
GDP per person	689.5	629.3	0.105	0.105	0.692	< 0.001	68.3	< 0.001
GDP increase	591.1	530.2	0.055	**0.039**	0.714	< 0.001	68.4	< 0.001
Licensed physicians	592.6	534.2	0.72	0.91	0.685	< 0.001	68.6	< 0.001
Hospital beds	597.5	535.8	0.786	0.508	0.715	< 0.001	68.6	< 0.001
Travel passengers	687.5	626.9	0.363	0.261	0.7	< 0.001	68.6	< 0.001
Number of students	621	559.1	0.715	0.658	0.708	< 0.001	68.2	< 0.001

5. Simulation results using ML method in the simulation study

Table S1. The comparison between MMR and MCMAR in the simulation study using ML method

Scenarios	Model with only intercept			Model with a predictor		
	MMR	MCMAR	OPT[1]	MMR	MCMAR	OPT
RMAE for β_0; RMAE for β_1 in Scen1; MAE for β_1 in Scen2						
Scen1-rho0	5.978	5.961	5.974	1.226	1.242	1.23
Scen1-rho1	6.036	5.891	5.891	1.583	1.388	1.39
Scen1-rho2	6.408	6.228	6.228	2.514	2.413	2.413
Scen1-rho3	6.595	6.417	6.417	3.455	2.954	2.954
Scen2-rho0	0.379	0.378	0.379	0.006	0.006	0.006
Scen2-rho1	0.358	0.348	0.348	0.006	0.006	0.006
Scen2-rho2	0.691	0.665	0.665	0.008	0.008	0.008
Scen2-rho3	0.65	0.619	0.619	0.014	0.011	0.011
MAE for city-specific ERRs						

Scen1-rho0	0.468	0.469	0.469	0.467	0.467	0.467
Scen1-rho1	0.397	0.384	0.384	0.394	0.383	0.383
Scen1-rho2	0.386	0.366	0.366	0.381	0.364	0.364
Scen1-rho3	0.371	0.334	0.334	0.344	0.329	0.329
Scen2-rho0	0.464	0.464	0.464	0.467	0.467	0.467
Scen2-rho1	0.389	0.38	0.38	0.395	0.385	0.385
Scen2-rho2	0.379	0.361	0.361	0.381	0.364	0.364
Scen2-rho3	0.348	0.326	0.326	0.343	0.328	0.328
Average AIC over the replicas						
Scen1-rho0	396.745	397.608	396.536	371.215	371.655	370.899
Scen1-rho1	217.282	177.609	177.609	172.043	158.992	158.997
Scen1-rho2	153.288	107.188	107.188	103.717	81.073	81.073
Scen1-rho3	166.866	69.978	69.978	80.123	43.722	43.722
Scen2-rho0	367.533	368.453	367.354	372.936	373.544	372.675
Scen2-rho1	167.022	152.453	152.467	170.311	157.475	157.486
Scen2-rho2	103.625	76.593	76.593	102.443	79.558	79.558
Scen2-rho3	92.21	43.046	43.046	79.75	43.139	43.139
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	-	-	-	0.018	0.026	0.021
Scen2-rho1	-	-	-	0.136	0.049	0.049
Scen2-rho2	-	-	-	0.510	0.211	0.211
Scen2-rho3	-	-	-	0.974	0.565	0.565