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

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## 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>.

### 1.1 -nearest-neighbors-based method

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

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

(3). For any two different cities, and , if is one of the nearest cities to or is one of the nearest cities to , then .

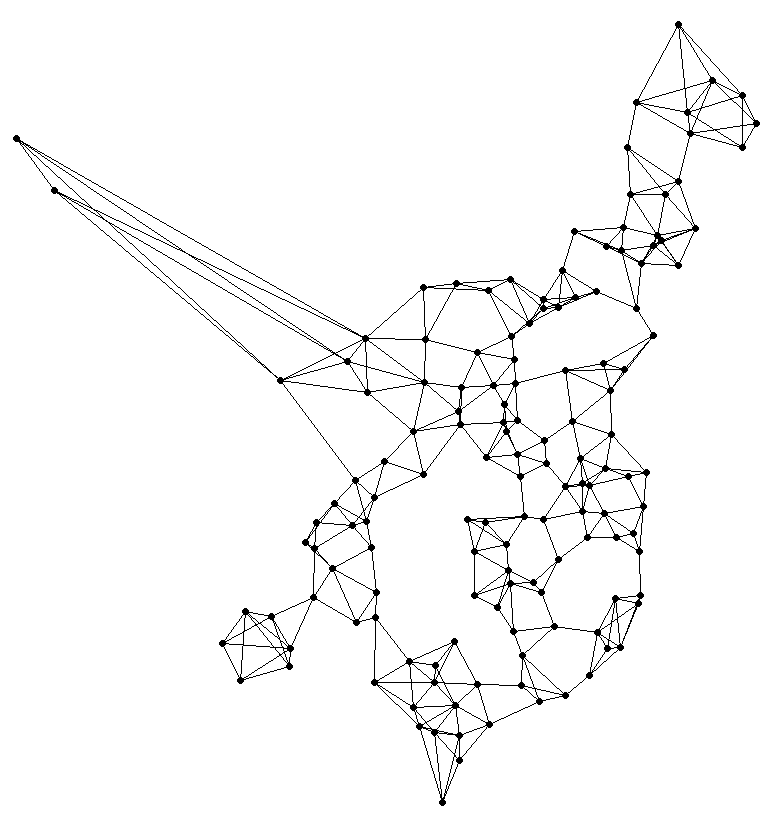
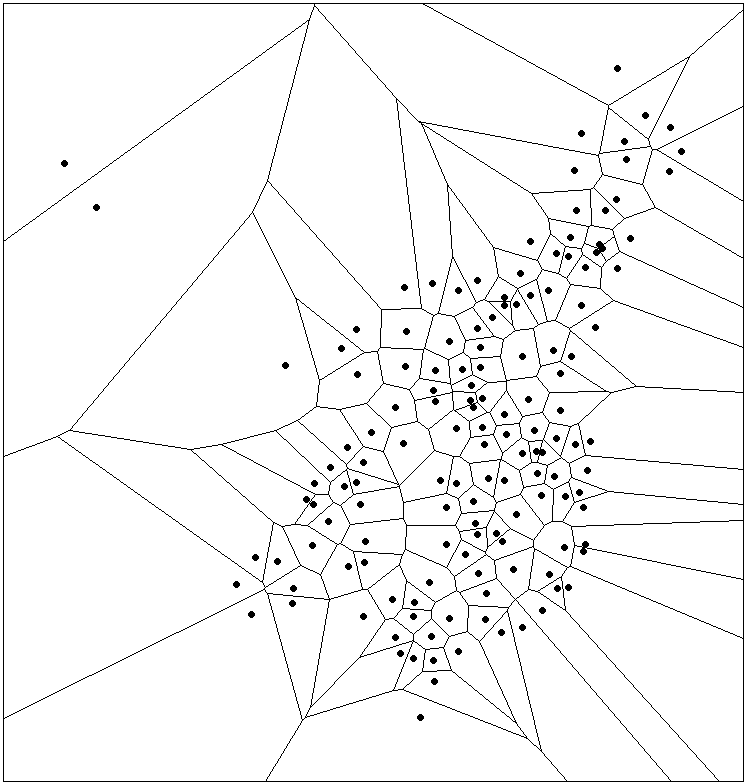
The example is shown in Figure S1A.

### 1.2 Thiessen-polygons-based method

(1). Use the point data obtain Voronoi diagram

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

The example is shown in Figure S1B.



A

B

Figure S1 The spatially adjacent relationships among the 143 cities in the motivating example. In subfigure A coming from the -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

We set , and . Given , and estimated by ML or REML, the likelihood function with respect to can be written as

The maximal likelihood estimation is which is also the best linear unbiased estimation due to the multivariate normal distribution. The derivative of is

So

Then we use the fisher information to calculate the variance of , so

## 3. Derivation of Cochran Q test in MCMAR

Let , according to formula (4) and (8) in the main paper, then

As let , then

Let , which is idempotent, i.e., , according to Ogasawara and Takahashi’s work[1, 2], the necessary and sufficient condition that has distribution is

(SE.1)

in which case the degrees of freedom is the rank of .

Let , then

So, which satisfies the condition (SE.1). Then follows distribution with degrees of freedom equal to the rank of . The rank is

Under the null hypothesis , i.e., , as is a block diagonal matrix with as the blocks, then

and the rank of is also . Therefore,

follows distribution with degrees of freedom equal to .

**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  single predictor | AIC | |  | Test predictor (*P*) | |  | in MCMAR1 | |  | Cochran Q test2 | |
| MMR | MCMAR |  | MMR | MCMAR |  | value | *P* |  |  |  |
| Intercept only3 | 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  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 |

### 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  single predictor | AIC | |  | Test predictor (*P*) | |  | in MCMAR1 | |  | Cochran Q test2 | |
| MMR | MCMAR |  | MMR | MCMAR |  | value | *P* |  |  |  |
| Intercept only3 | 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  single predictor | AIC | |  | Test predictor (*P*) | |  | in MCMAR1 | |  | Cochran Q test2 | |
| MMR | MCMAR |  | MMR | MCMAR |  | value | *P* |  |  |  |
| Intercept only3 | 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  single predictor | AIC | |  | Test predictor (*P*) | |  | in MCMAR1 | |  | Cochran Q test2 | |
| MMR | MCMAR |  | MMR | MCMAR |  | value | *P* |  |  |  |
| Intercept only3 | 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  single predictor | AIC | |  | Test predictor (*P*) | |  | in MCMAR1 | |  | Cochran Q test2 | |
| MMR | MCMAR |  | MMR | MCMAR |  | value | *P* |  |  |  |
| Intercept only3 | 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  single predictor | AIC | |  | Test predictor (*P*) | |  | in MCMAR1 | |  | Cochran Q test2 | |
| MMR | MCMAR |  | MMR | MCMAR |  | value | *P* |  |  |  |
| Intercept only3 | 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*) | |  | in MCMAR1 | |  | Cochran Q test2 | |
| MMR | MCMAR |  | MMR | MCMAR |  | value | *P* |  |  |  |
| Intercept only3 | 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  single predictor | AIC | |  | Test predictor (*P*) | |  | in MCMAR1 | |  | Cochran Q test2 | |
| MMR | MCMAR |  | MMR | MCMAR |  | value | *P* |  |  |  |
| Intercept only3 | 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  single predictor | AIC | |  | Test predictor (*P*) | |  | in MCMAR1 | |  | Cochran Q test2 | |
| MMR | MCMAR |  | MMR | MCMAR |  | value | *P* |  |  |  |
| Intercept only3 | 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 | OPT1 |  | MMR | MCMAR | OPT |
| **RMAE for** **; RMAE for** **in Scen1; MAE for**  **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 |