**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**

Wei Wang a, Fang Liao b, c, Fei Yin a, and Yue Ma a\*

a *West China School of Public Health and West China Fourth Hospital, Sichuan University.*

*b Sichuan Provincial Center for Mental Health, Sichuan Academy of Medical Sciences & Sichuan Provincial People’s Hospital, Chengdu, 610072, China.*

*c Key Laboratory of psychosomatic medicine, Chinese Academy of Medical Sciences, Chengdu 610072, China*

\* Corresponding author: [gordonrozen@scu.edu.cn](mailto:gordonrozen@scu.edu.cn).

**Contents**

[1. Method of transforming spatial point data to spatially adjacent matrix 3](#_Toc118725294)

[1.1 -nearest-neighbors-based method 3](#_Toc118725295)

[1.2 Thiessen-polygons-based method 3](#_Toc118725296)

[2. Parameter estimations and hypothesis tests 4](#_Toc118725297)

[2.1 Parameter estimation for and the 95% confidence interval 4](#_Toc118725298)

[2.2 The combination method of golden section search and successive parabolic interpolation and Broyden–Fletcher–Goldfarb–Shanno (BFGS) algorithm 5](#_Toc118725299)

[2.3 Derivation for the estimation of 5](#_Toc118725300)

[2.4 Derivation of Cochran Q test in MCMAR 6](#_Toc118725301)

[3. Results for different spatially adjacent matrices in motivating example 8](#_Toc118725302)

[3.1 Using ML method 8](#_Toc118725303)

[3.1.1 3-nearest-neighbors -based method in ML 8](#_Toc118725304)

[3.1.2 4-nearest-neighbors -based method in ML 9](#_Toc118725305)

[3.1.3 5-nearest-neighbors-based method in ML 10](#_Toc118725306)

[3.1.4 6-nearest-neighbors -based method in ML 11](#_Toc118725307)

[3.1.5 Thiessen-polygons-based method in ML 11](#_Toc118725308)

[3.2 Using REML method 12](#_Toc118725309)

[3.2.1 3-nearest-neighbors-based method in REML 12](#_Toc118725310)

[3.2.2 4-nearest-neighbors-based method in REML 13](#_Toc118725311)

[3.2.3 5-nearest-neighbors-based method in REML 14](#_Toc118725312)

[3.2.4 6-nearest-neighbors-based method in REML 15](#_Toc118725313)

[3.2.5 Thiessen-polygons-based method in REML 16](#_Toc118725314)

[4. Simulation results using ML method in the simulation study 17](#_Toc118725315)

## 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 .

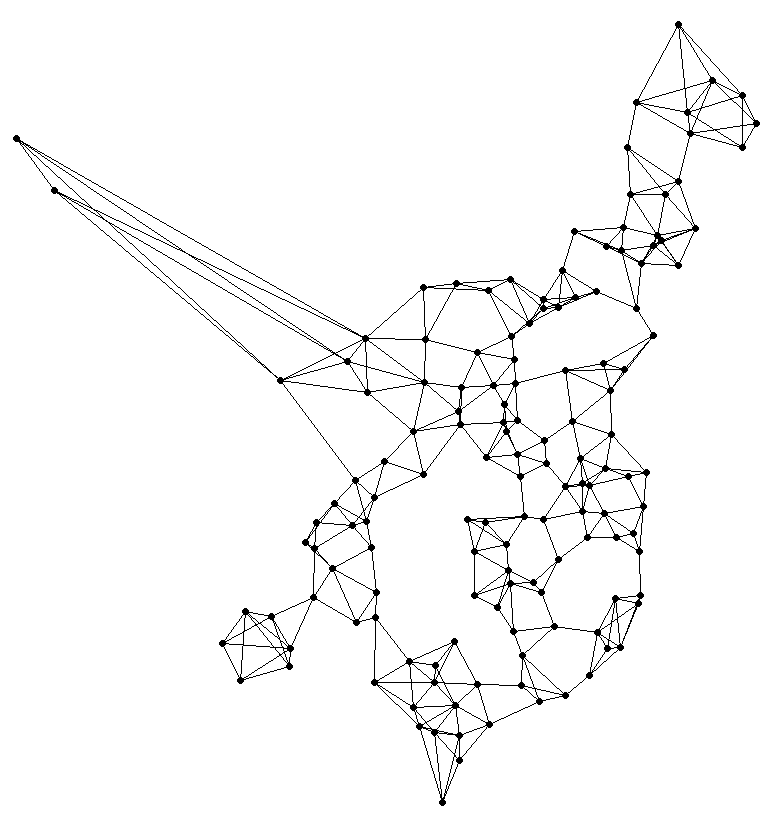
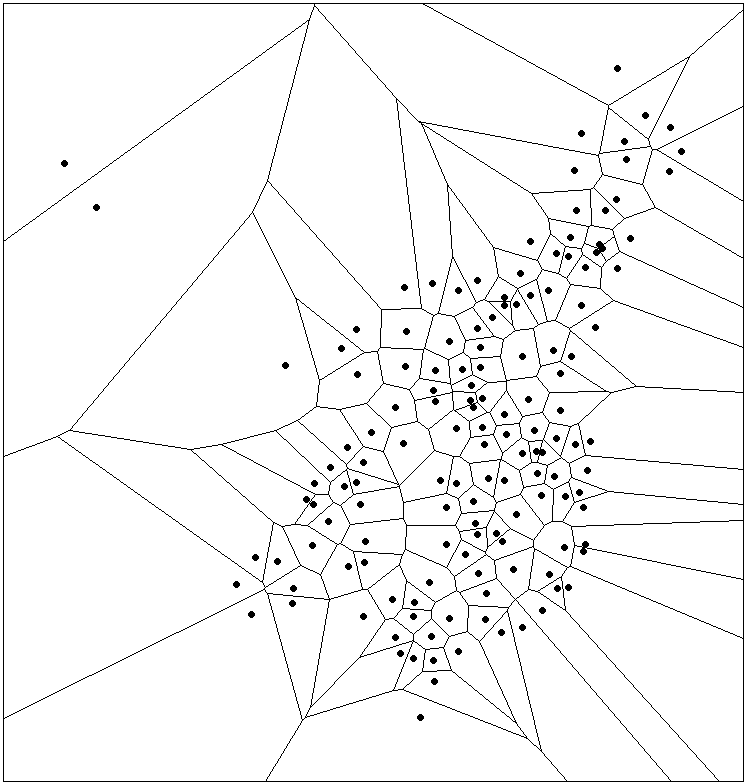
The example is shown in Figure S1A.

### 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.

## Parameter estimations and hypothesis tests

### 2.1 Parameter estimation for and the 95% confidence interval

The likelihood ratio (LR) test is used to test the hypothesis with H0 of vs H1 of . Referring to section 2.2 in the main text, the log likelihood function of MCMAR is

where and. Under H0 (), the maximum log likelihood is

Under H1 (), the maximum log likelihood is

The test statistic is

When the *P* value is smaller than a given significant level, e.g., 0.05, H0 is rejected.

Given the point estimation of  is , then, under H0 (), when the sample size is relatively large, a statistic can be constructed as

Then we get

So can be approximately estimated by letting

As such, the 95% confidence interval of  is .

### The combination method of golden section search and successive parabolic interpolation and Broyden–Fletcher–Goldfarb–Shanno (BFGS) algorithm

The combination method of golden section search and successive parabolic interpolation is designed for optimizing a continuous function with respect to a scalar variable, which can rapidly convergence, so we choose this method to estimate the scalar . This method has been well presented in Brent’s work (Brent, 1973) and can be easily implemented using the R function 'optimize’ in package ‘stats’.

BFGS is a quasi-Newton method (also known as a variable metric algorithm), which uses function values and gradients to build up a picture of the surface to be optimized, so we use BFGS to estimatewhich is composed of multiple parameters. The details of BFGS have been well presented in Fletcher et al.’s work (Fletcher et al., 1987) and can be easily implemented using the R function 'optim’ in package ‘stats’. In addition, BFGS is also the method of implementing multivariate meta-regression in R package ‘mvmeta’ (Gasparrini et al. 2012), which is frequently used in MMR-based two-stage strategy.

To help readers understand our method better, the R codes of implementing the parameter estimation of MCMAR are provided at <https://github.com/winkey1230/MCMAR>.

**Reference**

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

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

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.

### 2.3 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

### 2.4 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 Rao’s works (Ogasawara et al. 1951 and Rao 1965), 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**

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.

## 3. 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.

### 3.1 Using ML method

### 3.1.1 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 |

### 3.1.2 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 |

### 3.1.3 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 |

### 3.1.4 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 |

### 3.1.5 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 |

### 3.2 Using REML method

Under REML, the values of AIC are calculated based on the penalized likelihood, so it is not meaningful to compare the values of AIC between models with different fixed effects structures, i.e., different predictors. But it is available to compare the AICs between MMR and MCMAR with identical predictors or only with the intercept.

### 3.2.1 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 |

### 3.2.2 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 |

### 3.2.3 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 |

### 3.2.4 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 |

### 3.2.5 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 |

## 4. 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 | 0.253 | 0.251 | | 0.252 | |  | | 1.226 | | 1.242 | | 1.23 | |
| Scen1-rho1 | 0.241 | 0.225 | | 0.225 | |  | | 1.583 | | 1.388 | | 1.39 | |
| Scen1-rho2 | 0.482 | 0.436 | | 0.436 | |  | | 2.514 | | 2.413 | | 2.413 | |
| Scen1-rho3 | 0.36 | 0.327 | | 0.327 | |  | | 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 | |
| **Coverage rate of 95% CI for in model with only intercept and for in model with a predictor** | | | | | | | | | | | | | |
| Scen1-rho0 | 0.952 | | 0.965 | | 0.953 | |  | | 0.981 | | 0.973 | | 0.977 |
| Scen1-rho1 | 0.912 | | 0.993 | | 0.993 | |  | | 0.87 | | 0.959 | | 0.959 |
| Scen1-rho2 | 0.415 | | 0.961 | | 0.961 | |  | | 0.535 | | 0.794 | | 0.794 |
| Scen1-rho3 | 0.027 | | 0.667 | | 0.667 | |  | | 0.023 | | 0.424 | | 0.424 |
| Scen2-rho0 | 0.976 | | 0.966 | | 0.975 | |  | | 0.982 | | 0.974 | | 0.979 |
| Scen2-rho1 | 0.923 | | 0.988 | | 0.988 | |  | | 0.864 | | 0.951 | | 0.951 |
| Scen2-rho2 | 0.474 | | 0.907 | | 0.907 | |  | | 0.49 | | 0.789 | | 0.789 |
| Scen2-rho3 | 0.003 | | 0.32 | | 0.32 | |  | | 0.026 | | 0.435 | | 0.435 |
| **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 | |