

# Supplement to “Some Statistical Consideration in Transcriptome-Wide Association Studies”

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<sup>3</sup>Data used in preparation of this article were obtained from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database ([adni.loni.usc.edu](http://adni.loni.usc.edu)). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: [http://adni.loni.usc.edu/wp-content/uploads/how\\_to\\_apply/ADNI\\_Acknowledgement\\_List\\_Sep23.pdf](http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List_Sep23.pdf).

# 1 More About Real Data Results

As we mentioned in section 3.1, we perform  $F$ -tests in the first stage to ensure the first IV assumption is satisfied. For  $p$ -value cutoff 0.05, there are 9102 genes with  $p$ -value smaller than it, we show Q-Q plots of them in Figure S1; for  $p$ -value cutoff 0.1, there are 10564 genes with  $p$ -value smaller than it, we show Q-Q plots of them in Figure S2.

Figure S1: The ADNI data analysis: Q-Q plots of the obtained  $p$ -values of 9102 genes from each method versus the expected  $p$ -values under the null hypothesis of no association

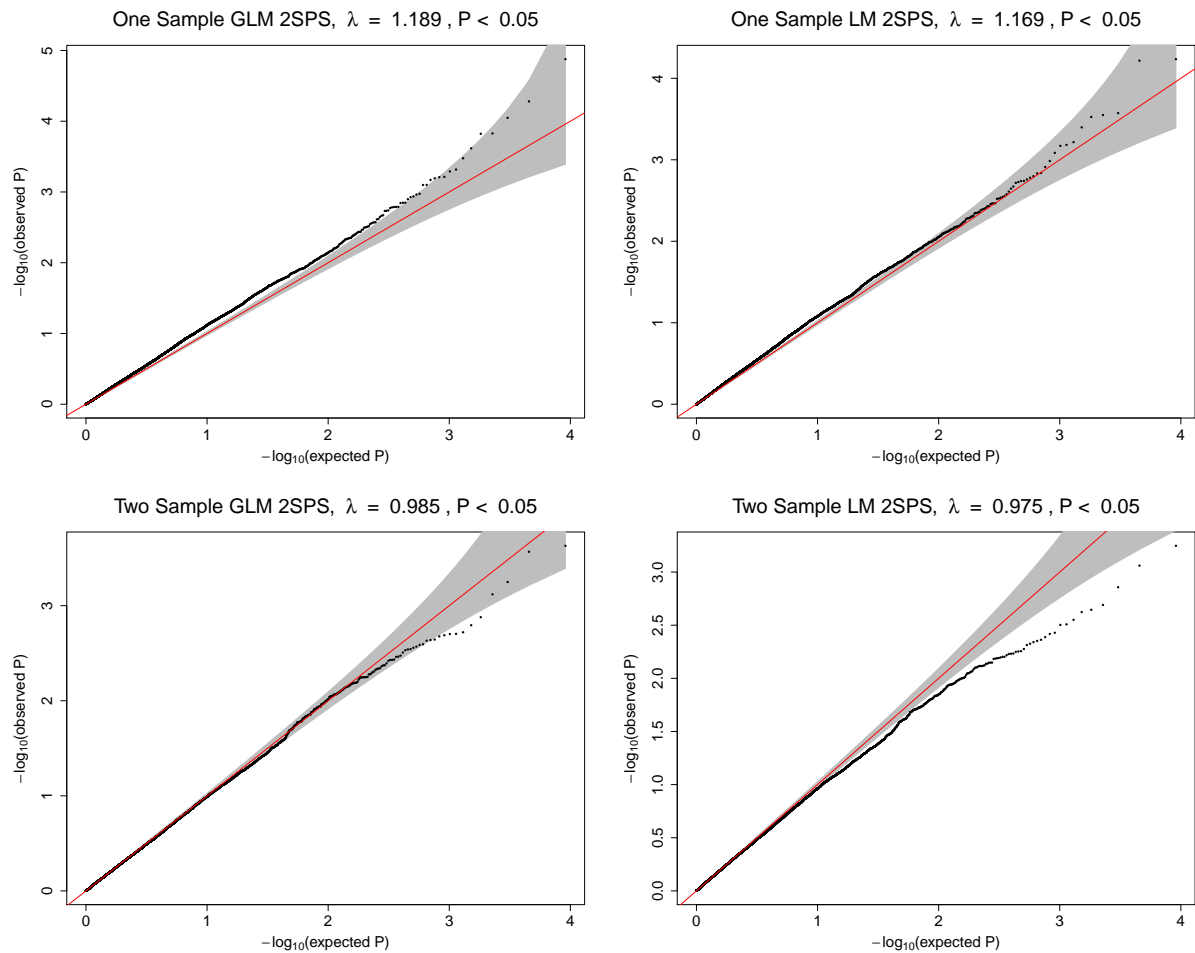


Figure S1 (Cont.): The ADNI data analysis: Q-Q plots of the obtained p-values of 9102 genes from each method versus the expected p-values under the null hypothesis of no association

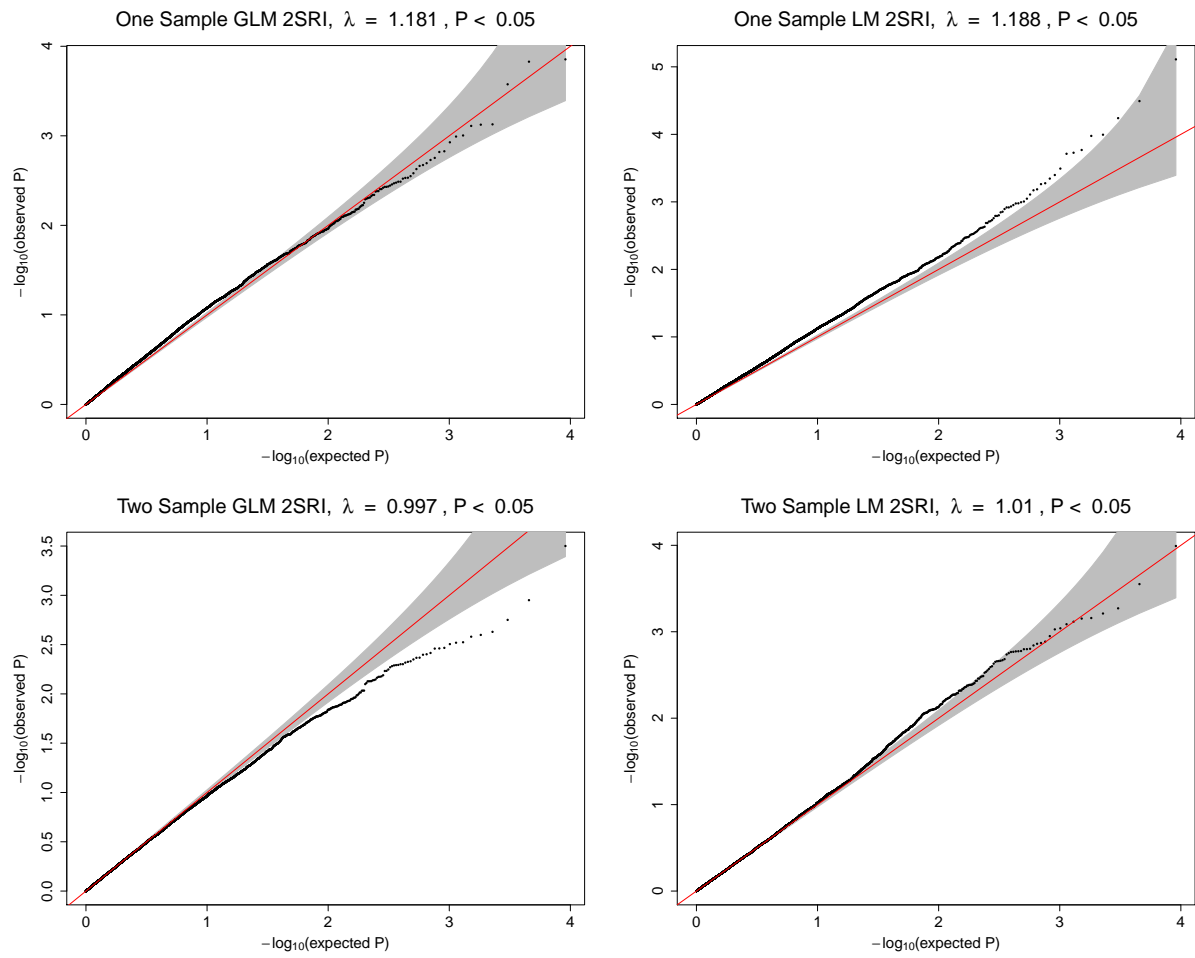


Figure S2: The ADNI data analysis: Q-Q plots of the obtained p-values of 10564 genes from each method versus the expected p-values under the null hypothesis of no association

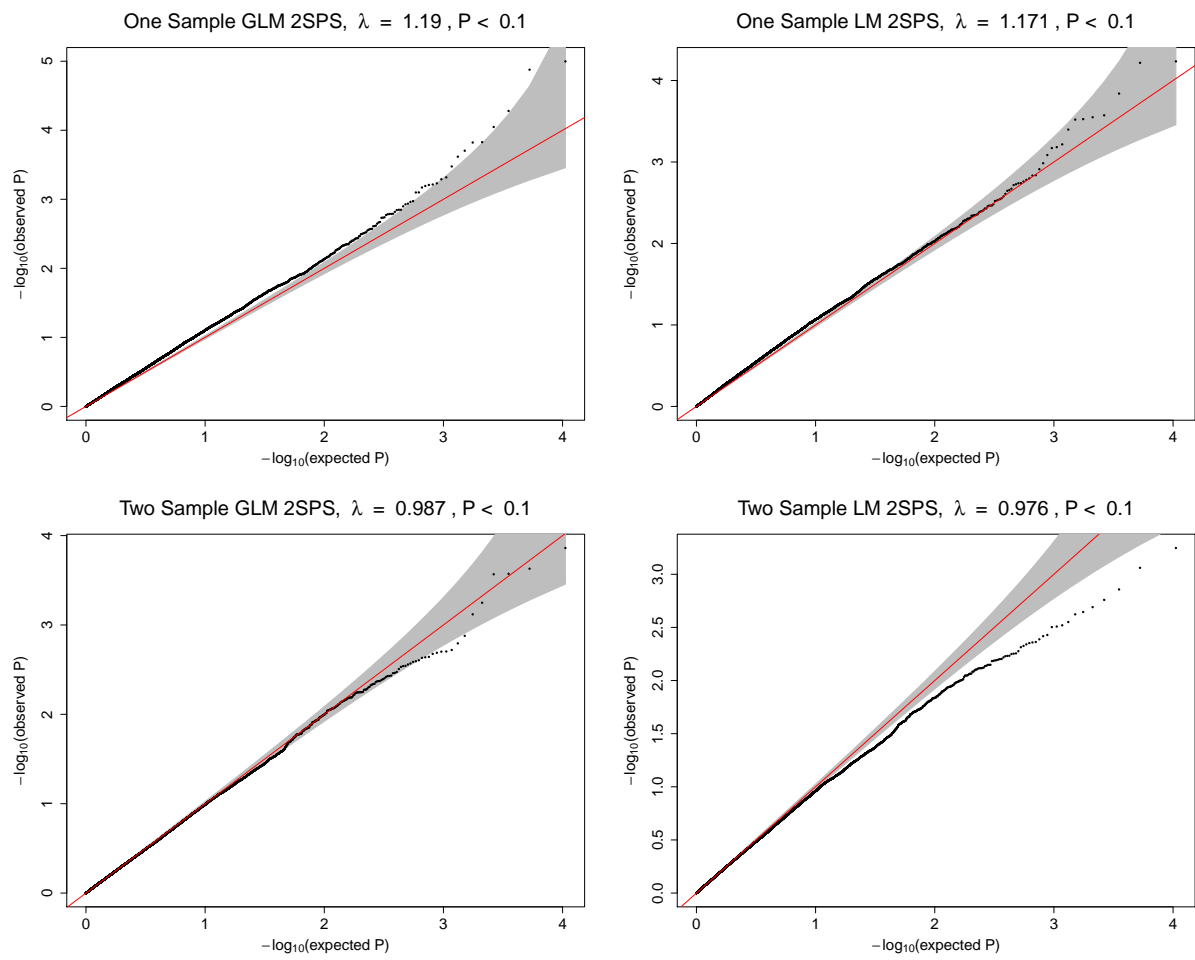
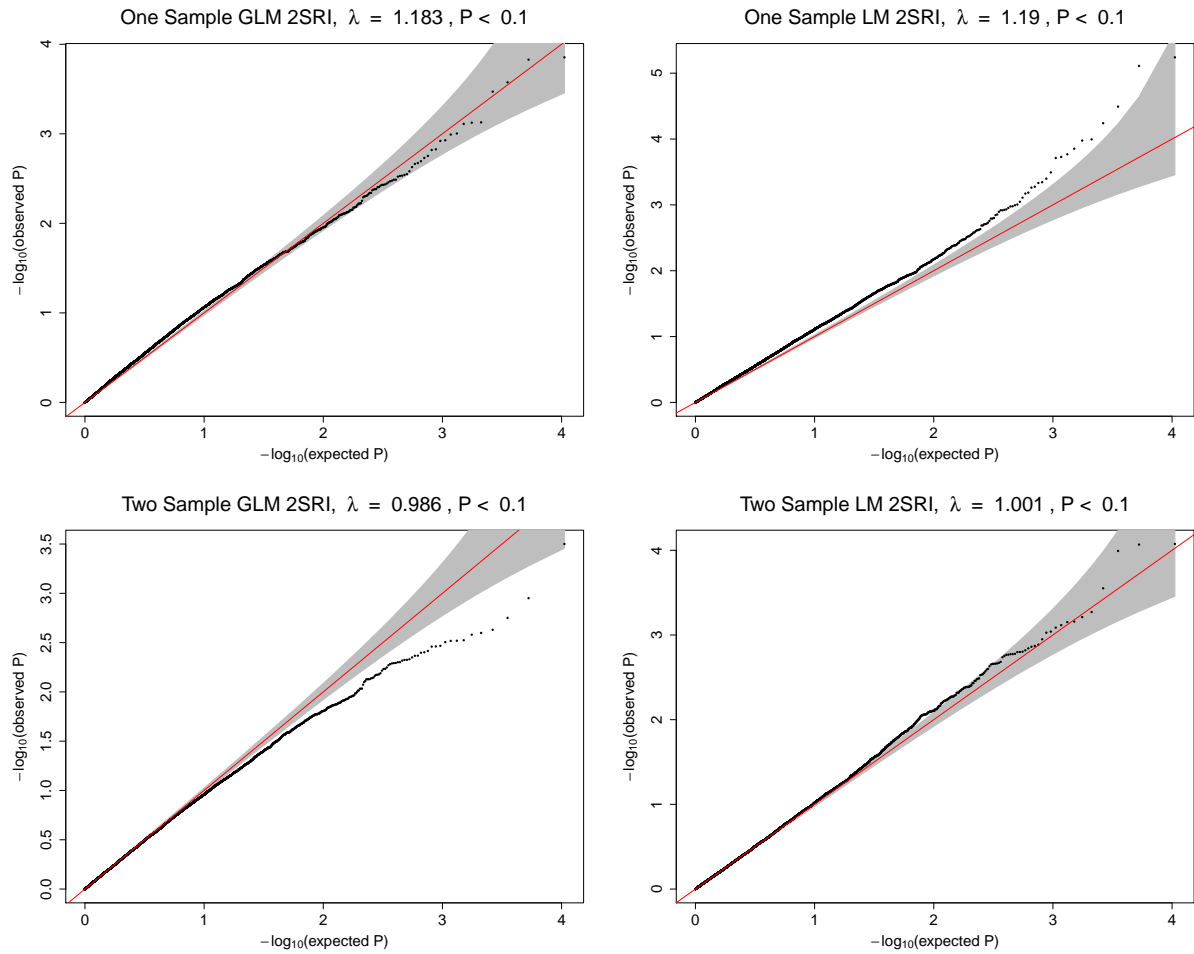




Figure S2 (Cont.): The ADNI data analysis: Q-Q plots of the obtained p-values of 10564 genes from each method versus the expected p-values under the null hypothesis of no association



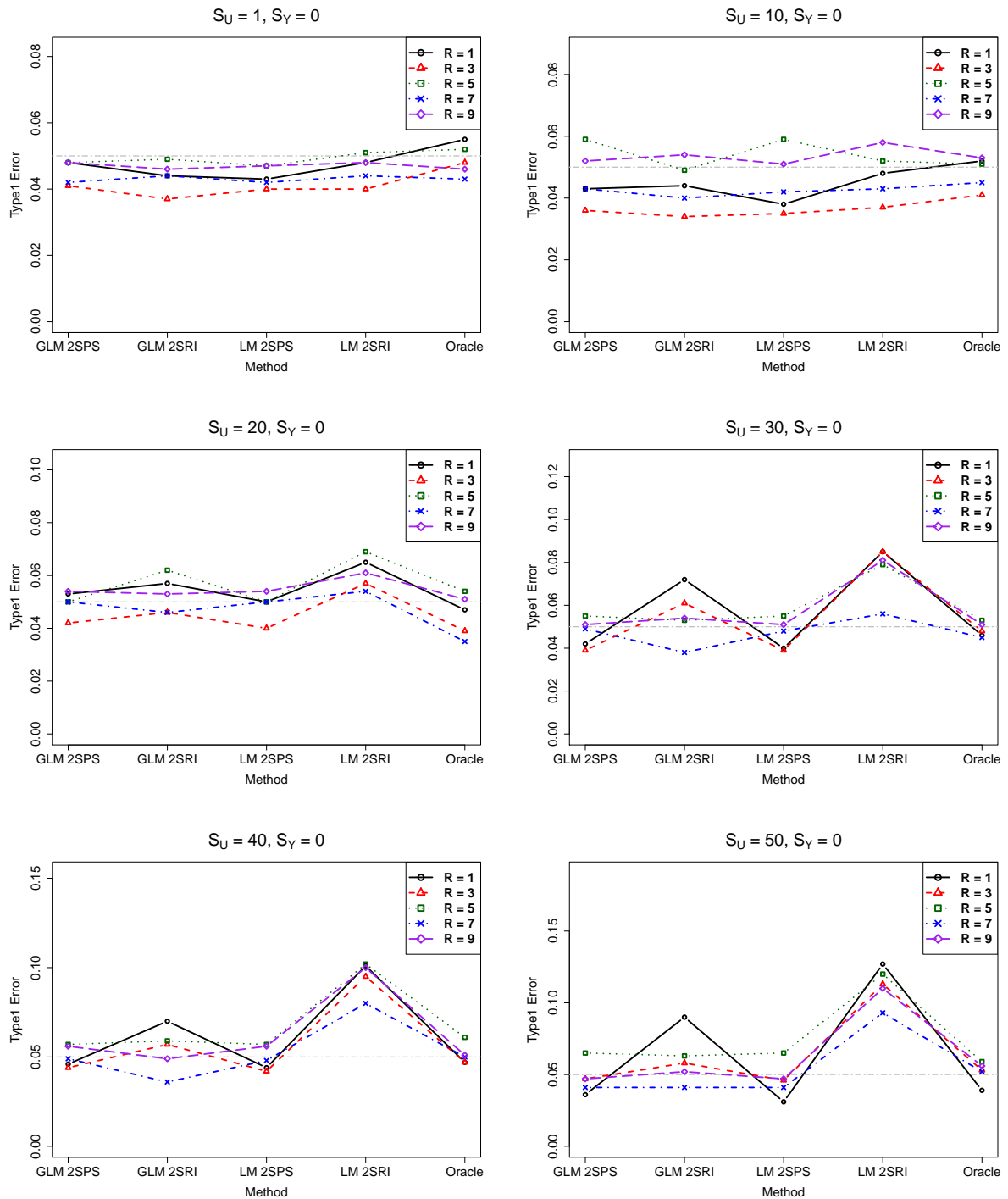
## 2 More About Simulation Results

In section 3.2, we showed part of our simulation results about comparing Type I Error, Power, Bias, and Standard Error for our methods. Here we show the full results for combinations  $\{(R, S_Y, S_U) | R = 1, 3, 5, 7, 9; S_Y = 0, 1, 2, 3, 4, 5; S_U = 1, 10, 20, 30, 40, 50\}$ .

## 2.1 Two-sample Approaches

### 2.1.1 Type I Error

Figure S3: Simulations with the two-sample approaches: empirical Type I error rates of various methods.



## 2.1.2 Power

Figure S4: Simulations with the two-sample approaches: empirical power of various methods,  $S_Y = 1$ .

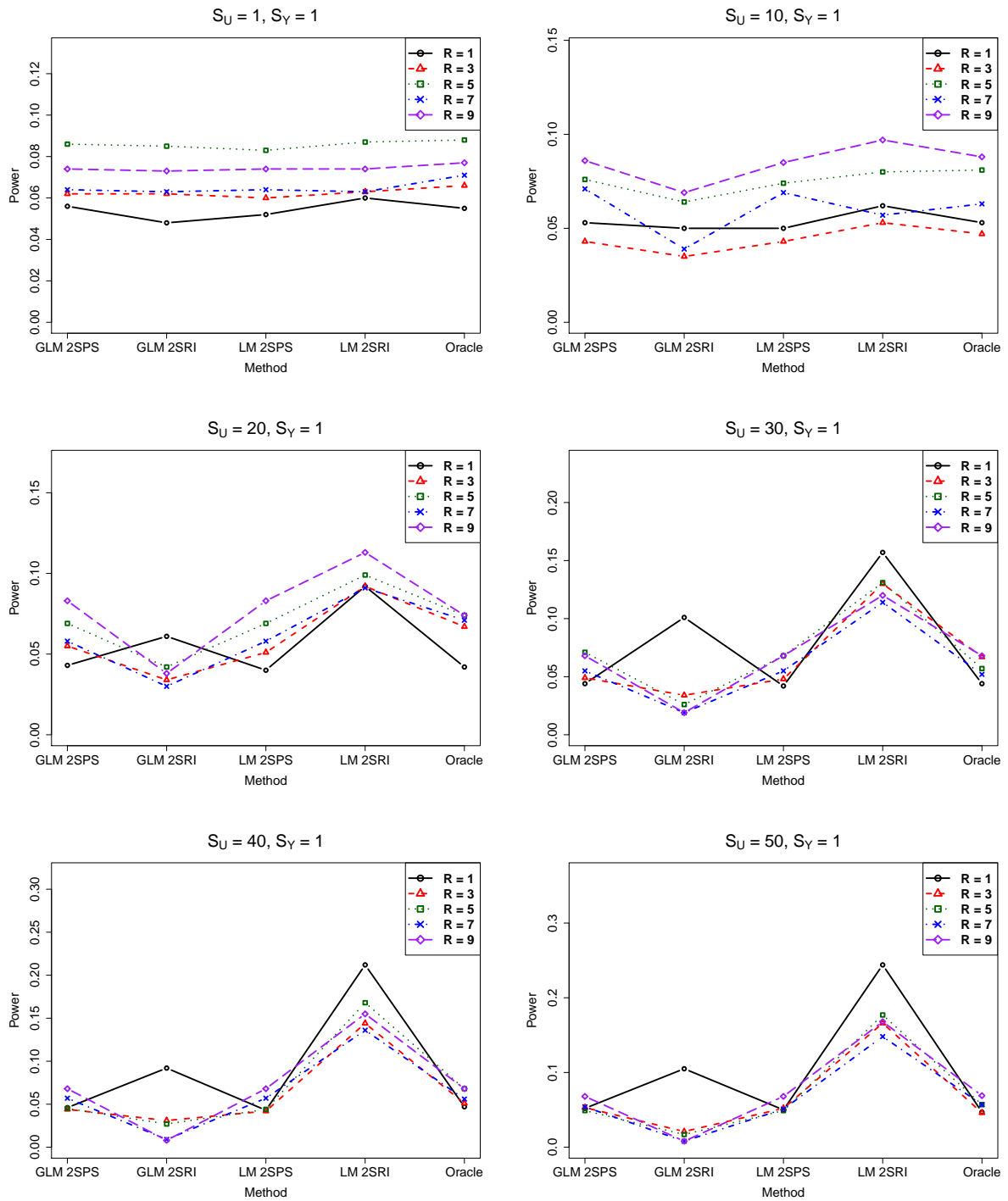


Figure S5: Simulations with the two-sample approaches: empirical power of various methods,  $S_Y = 2$ .

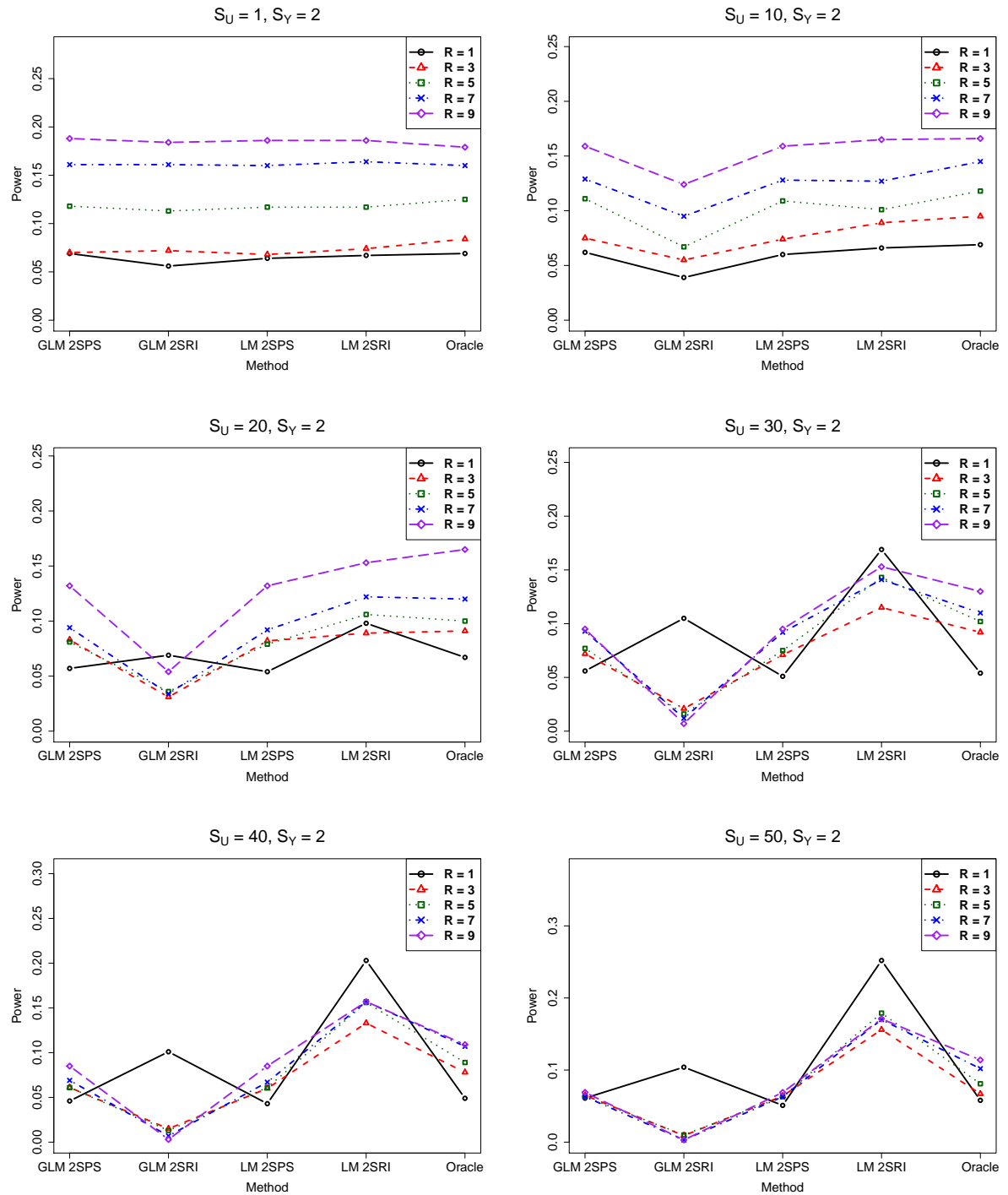


Figure S6: Simulations with the two-sample approaches: empirical power of various methods,  $S_Y = 3$ .

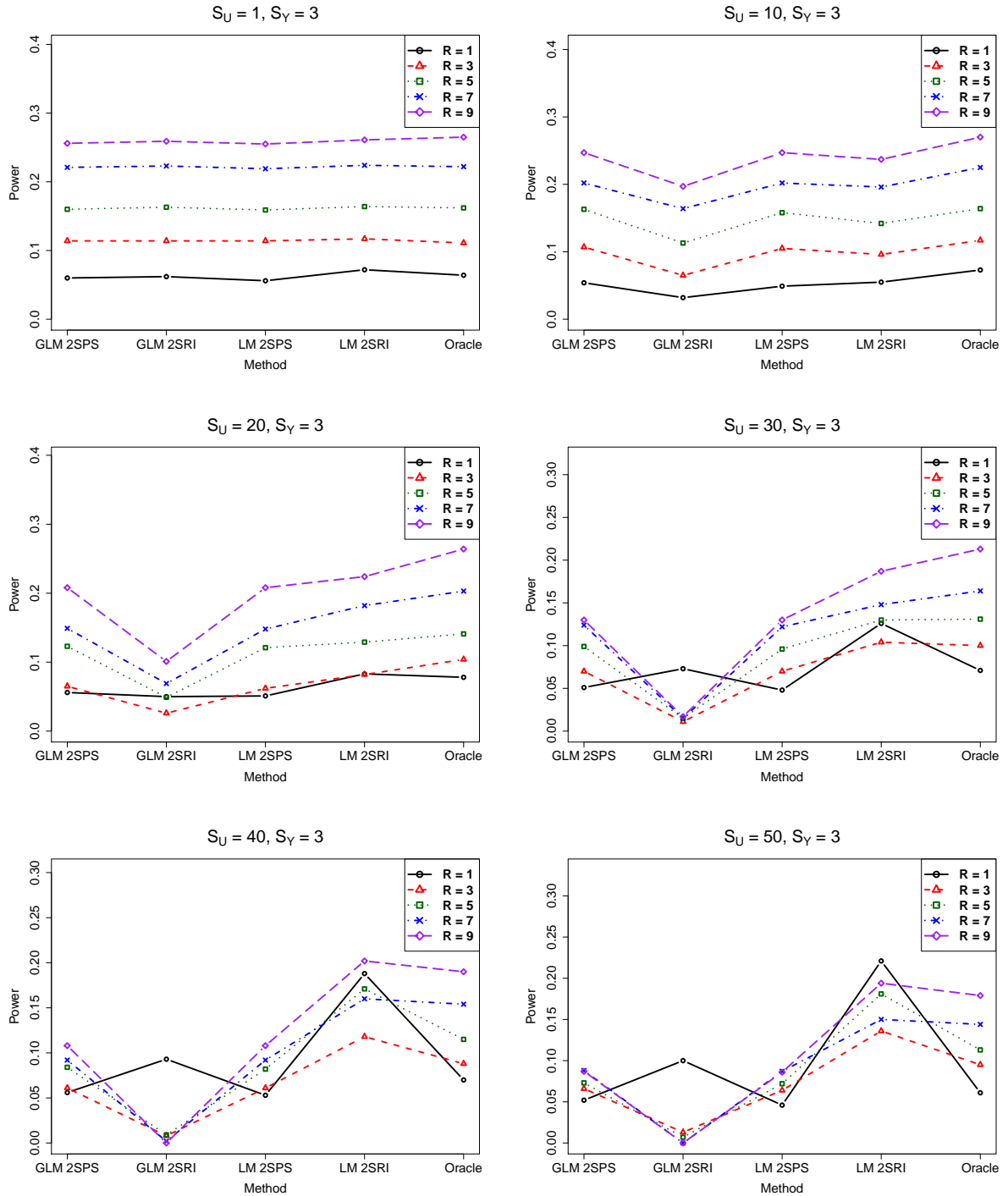


Figure S7: Simulations with the two-sample approaches: empirical power of various methods,  $S_Y = 4$ .

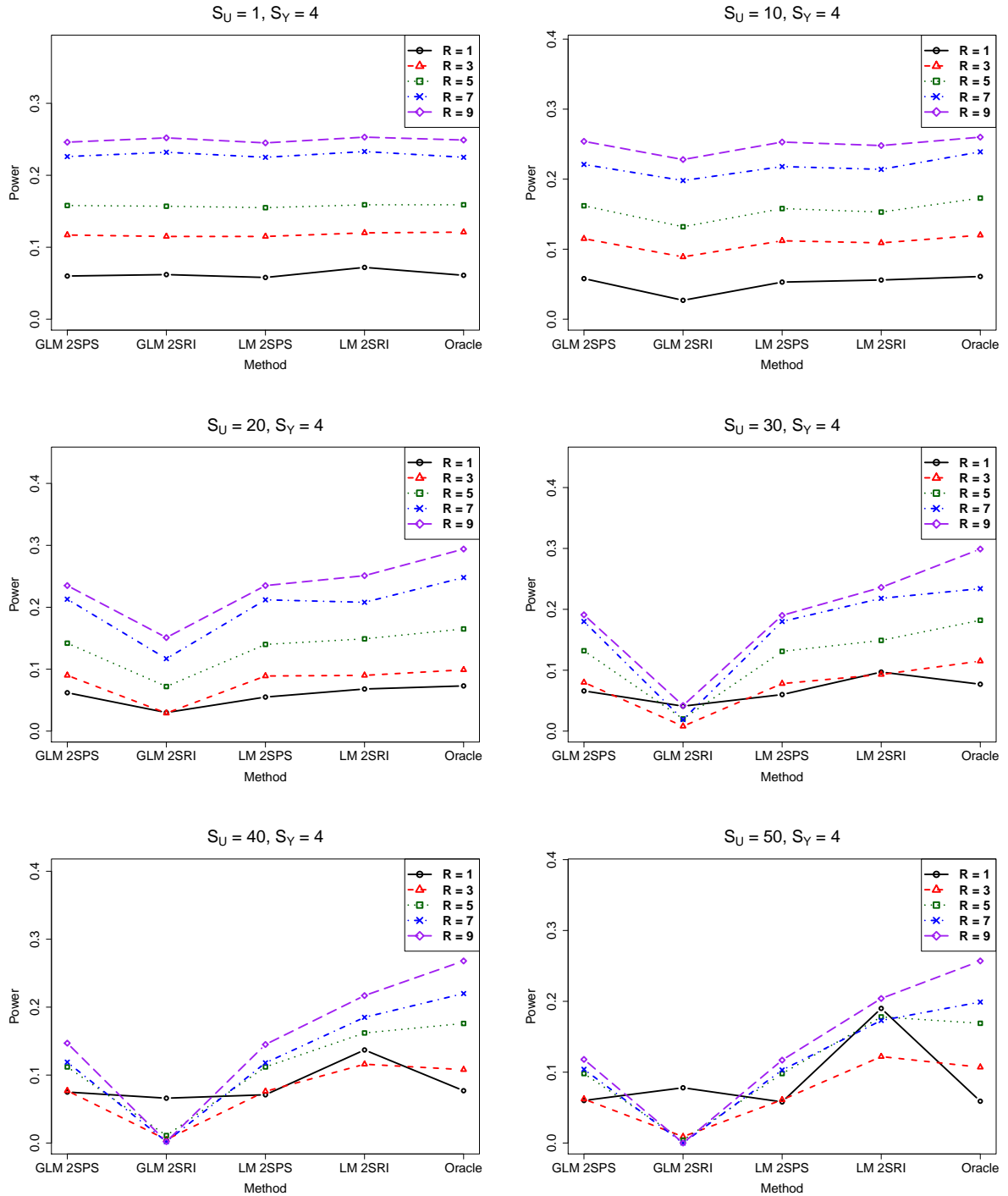
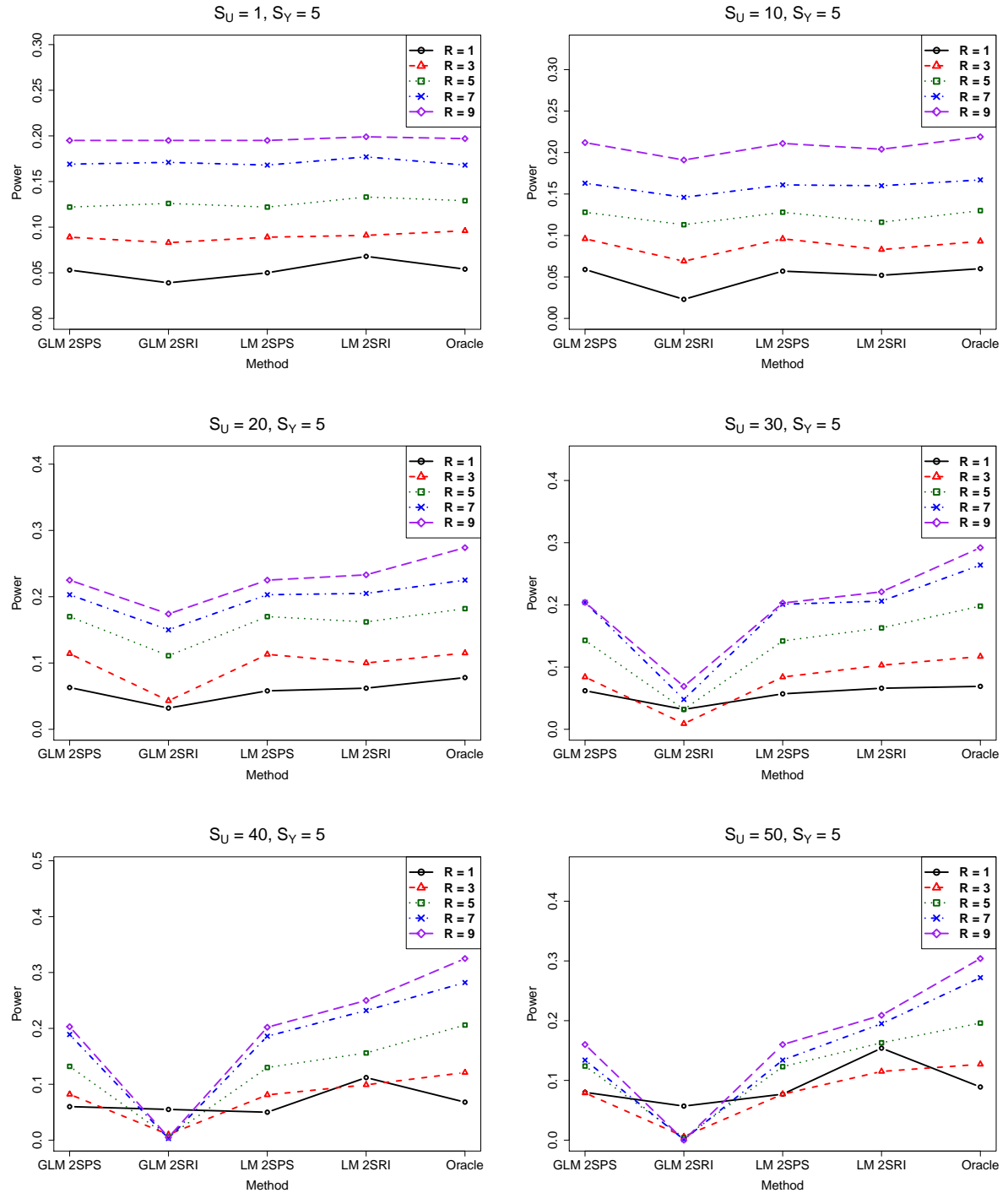


Figure S8: Simulations with the two-sample approaches: empirical power of various methods,  $S_Y = 5$ .



### 2.1.3 Bias

Figure S9: Simulations with the two-sample approaches: biases of various methods,  $S_Y = 0$

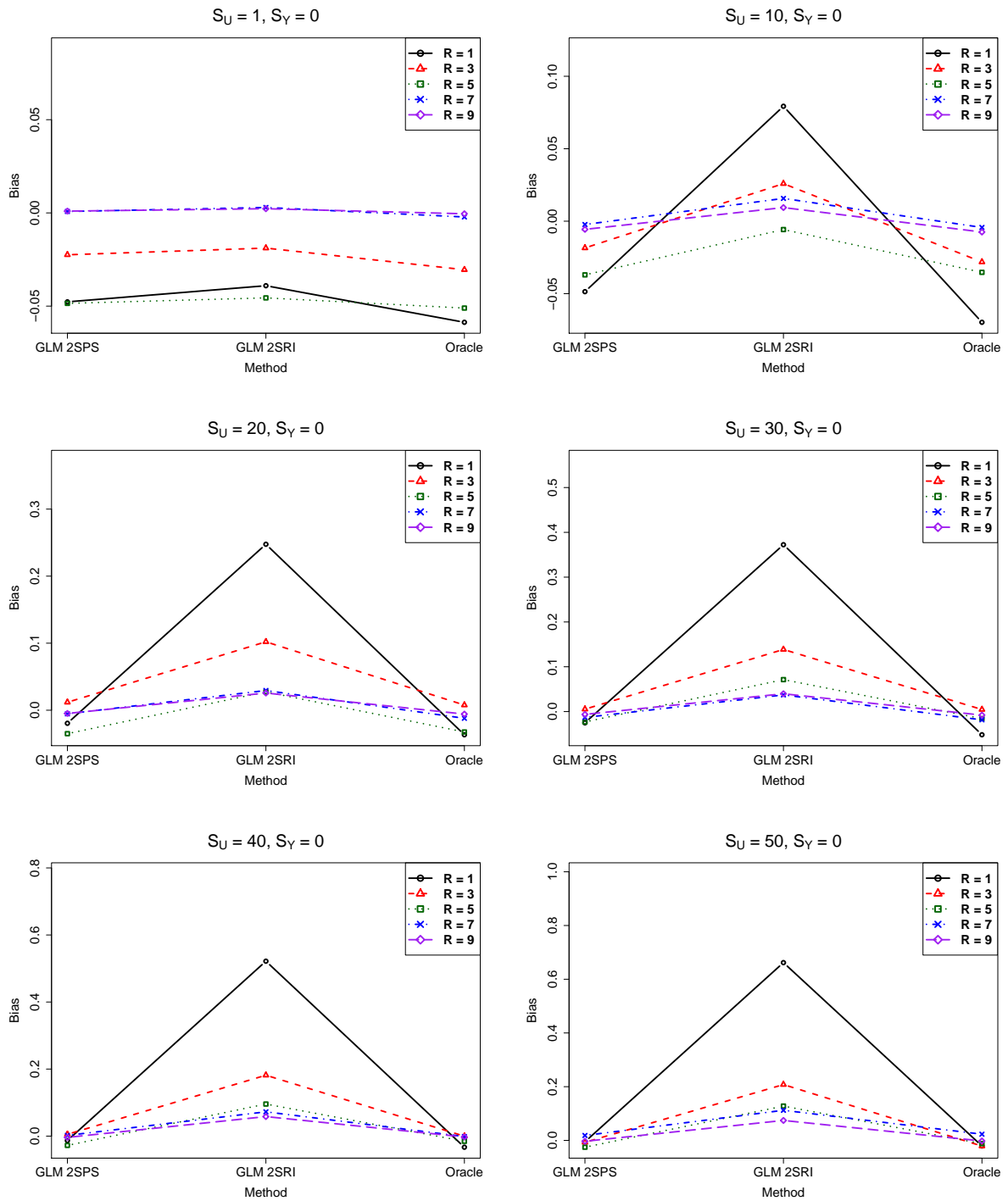




Figure S10: Simulations with the two-sample approaches: biases of various methods,  $S_Y = 1$

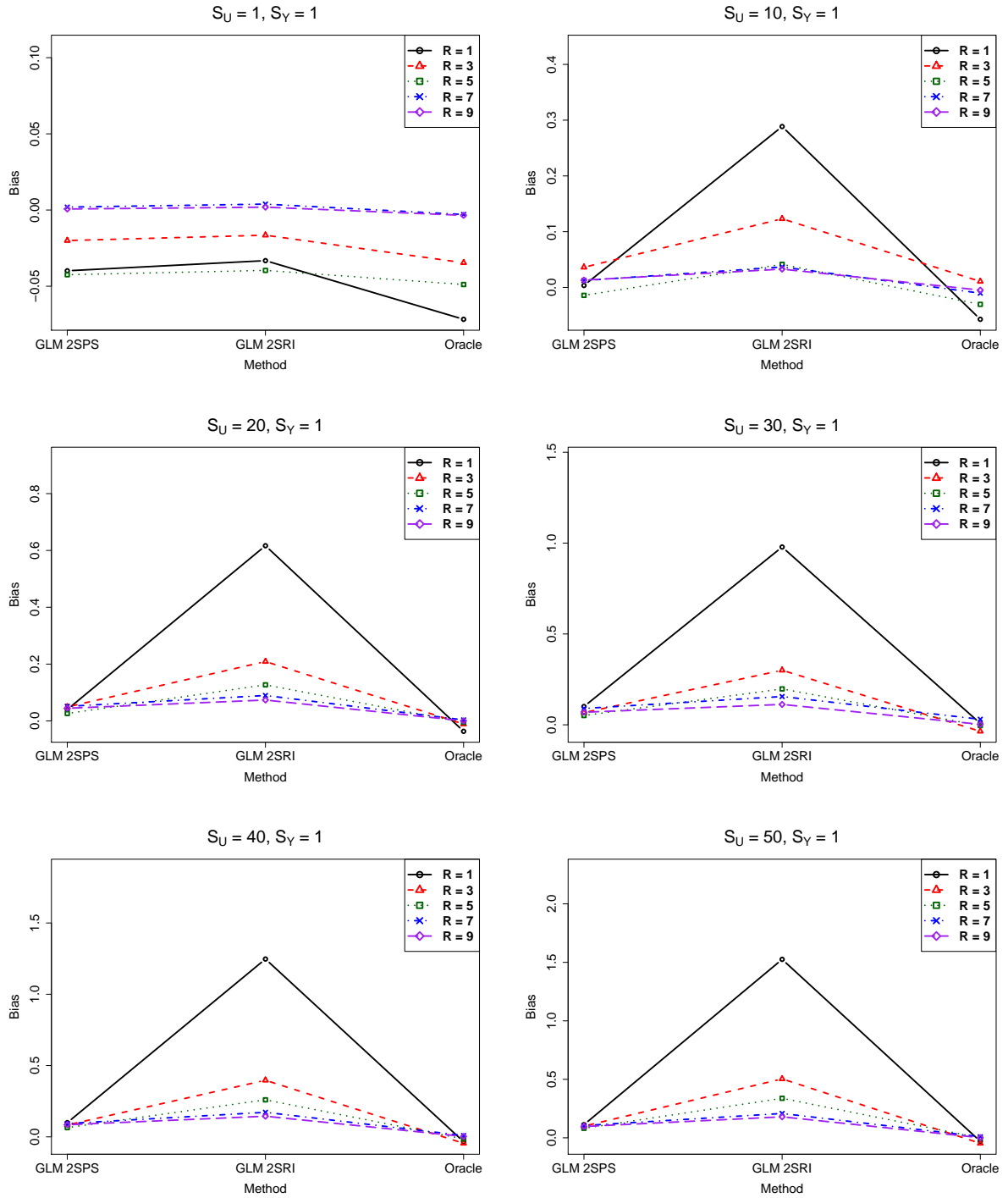


Figure S11: Simulations with the two-sample approaches: biases of various methods,  $S_Y = 2$

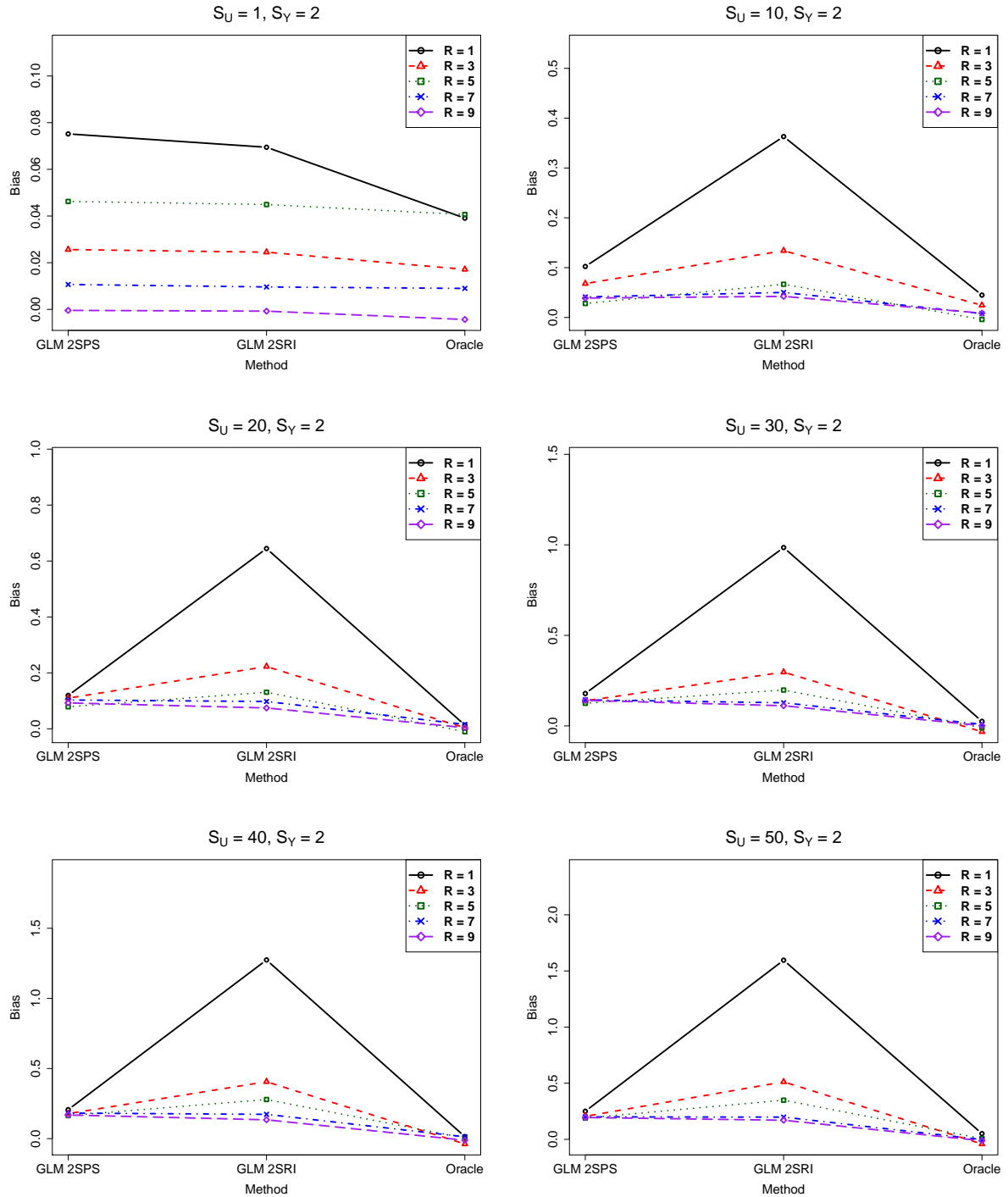


Figure S12: Simulations with the two-sample approaches: biases of various methods,  $S_Y = 3$

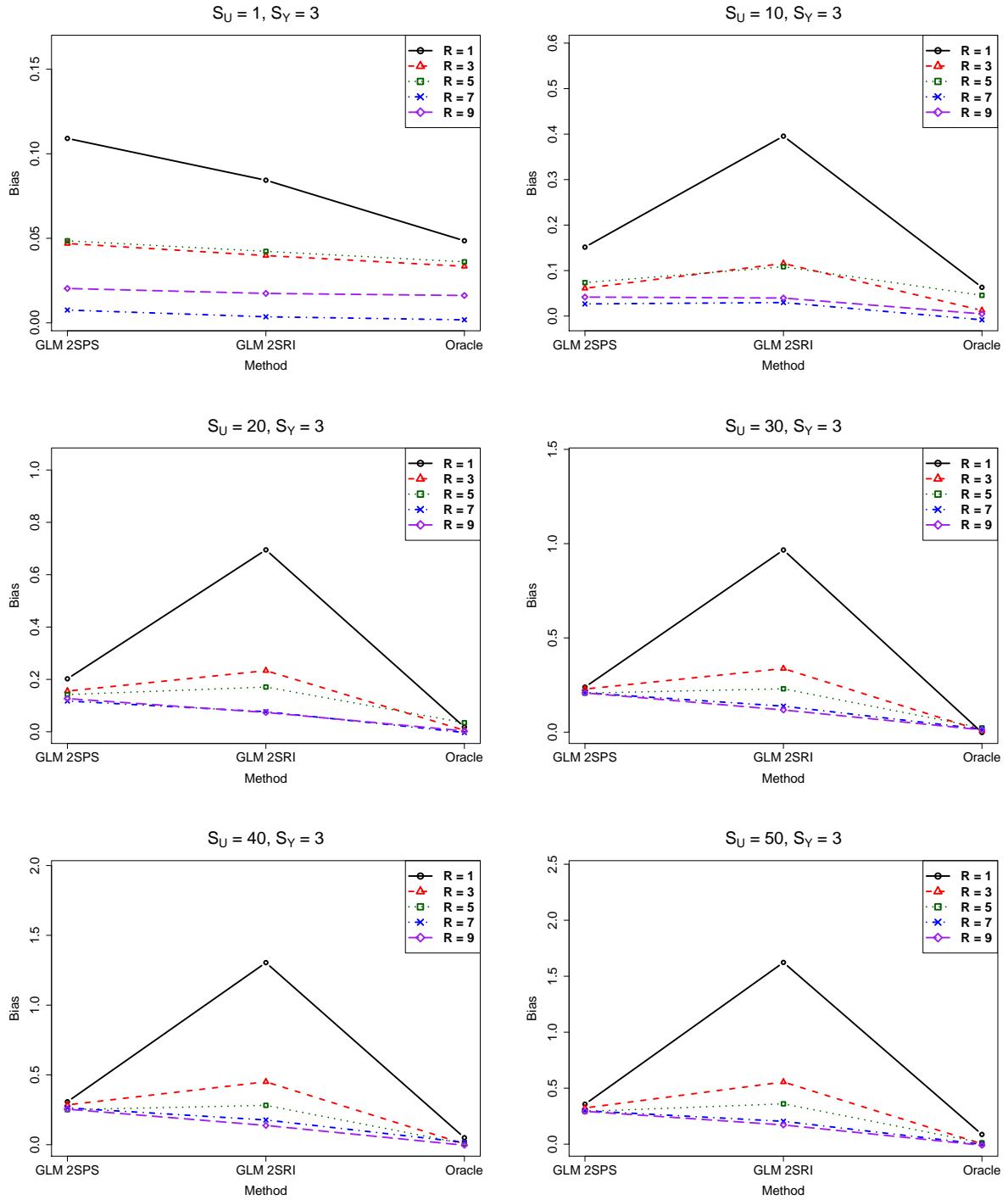


Figure S13: Simulations with the two-sample approaches: biases of various methods,  $S_Y = 4$

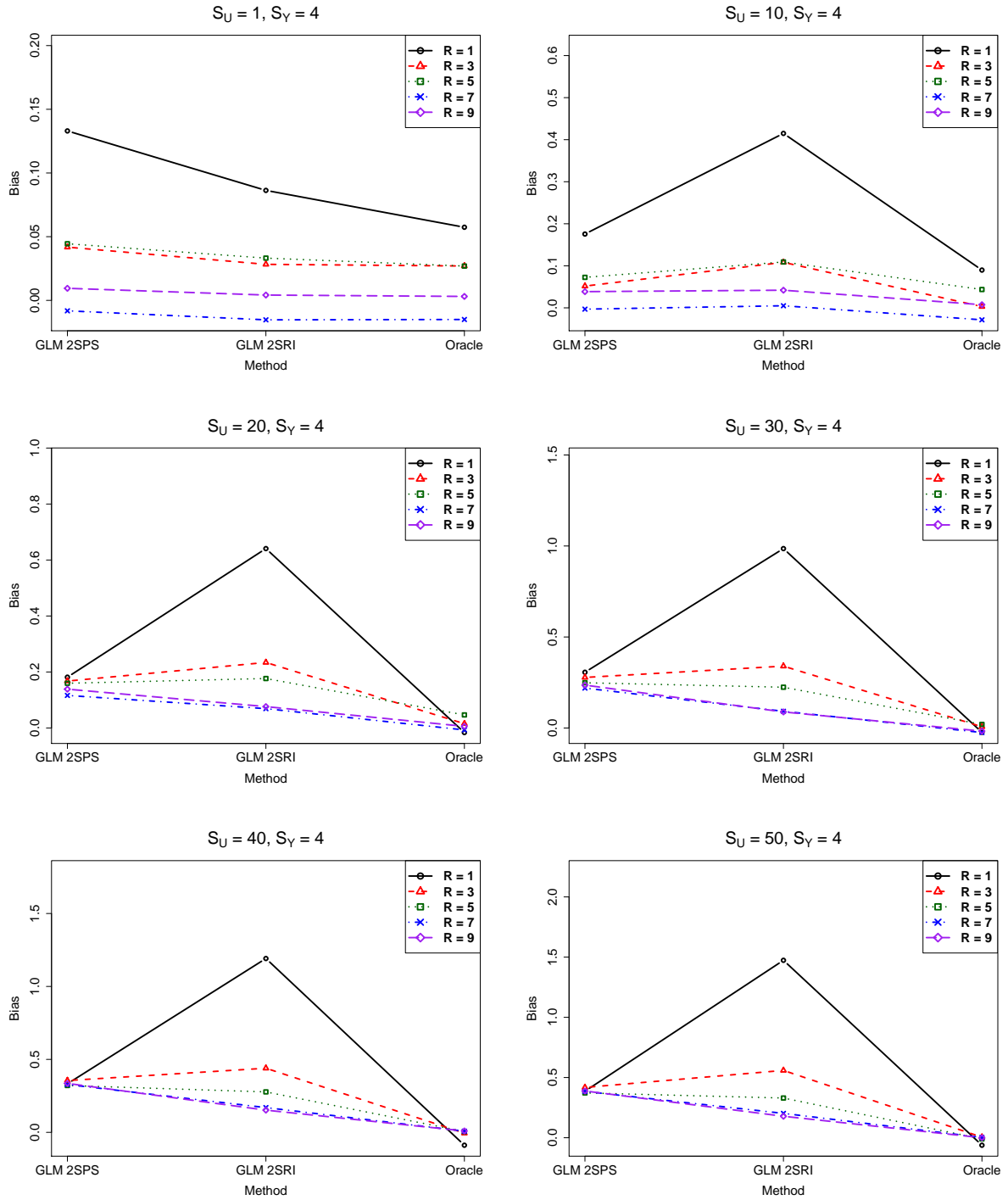
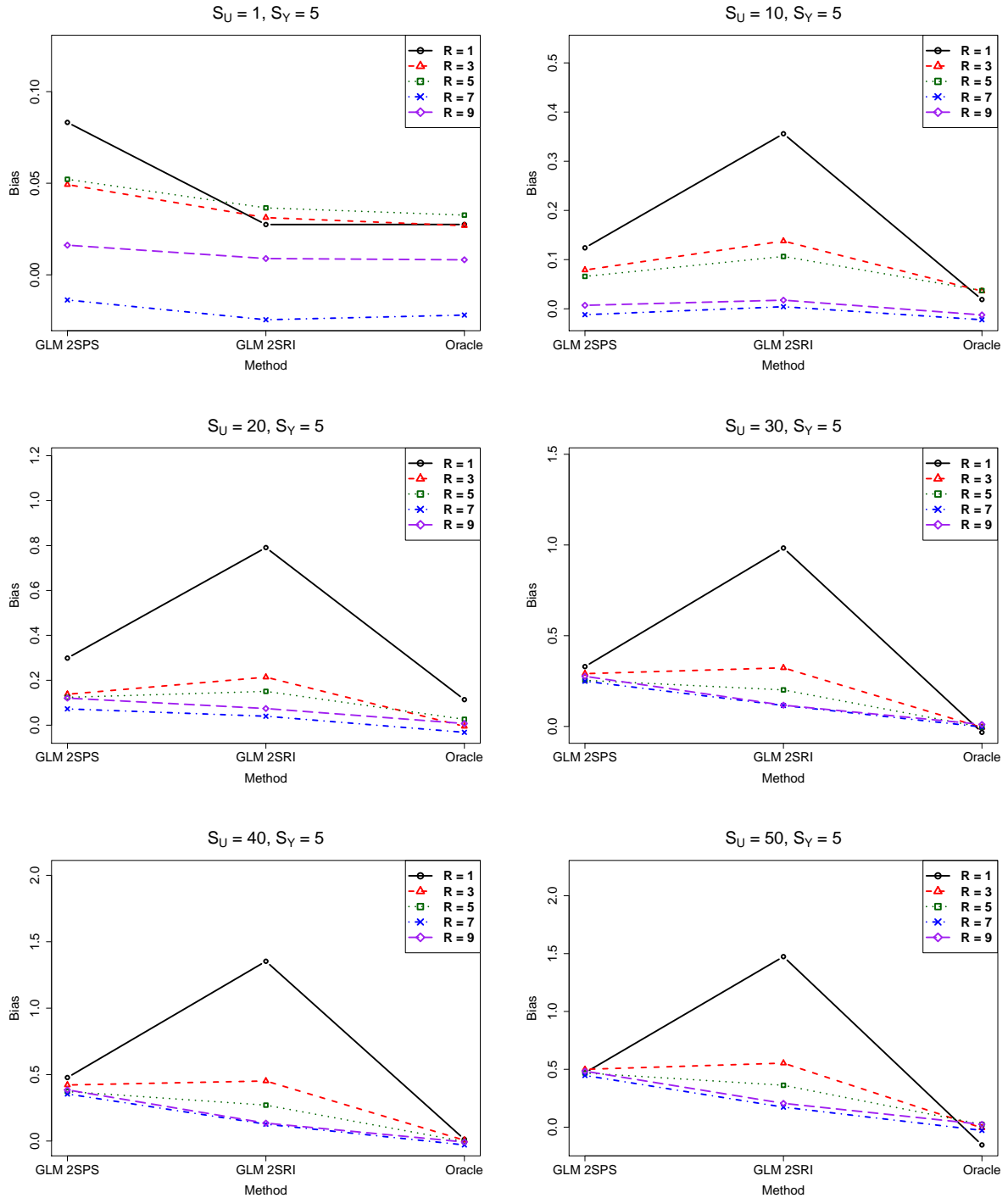


Figure S14: Simulations with the two-sample approaches: biases of various methods,  $S_Y = 5$



### 2.1.4 Comparison of the original and corrected standard error estimates

Figure S15: Simulations with the two-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 0, R = 1$ .

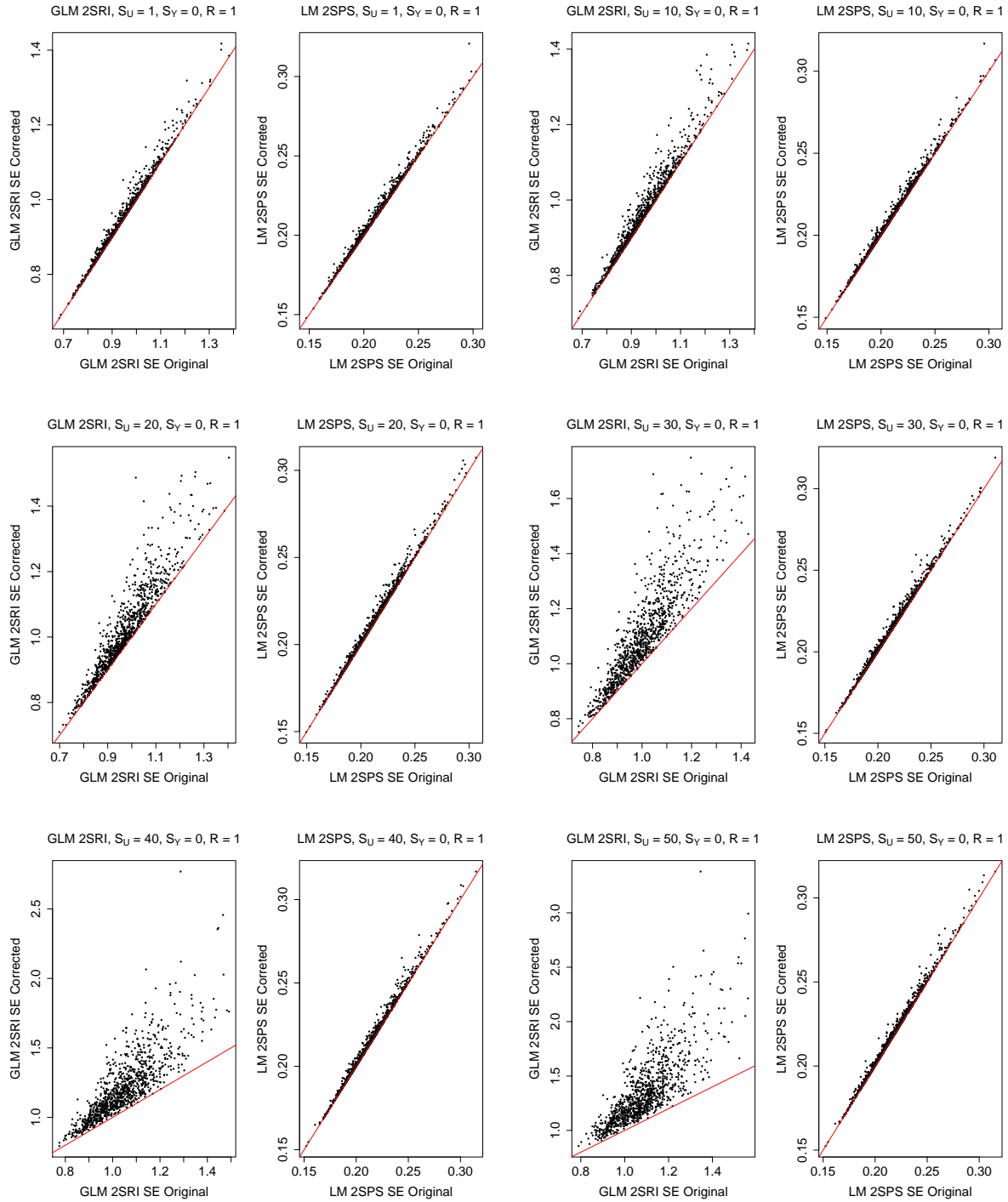


Figure S16: Simulations with the two-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 1, R = 1$ .

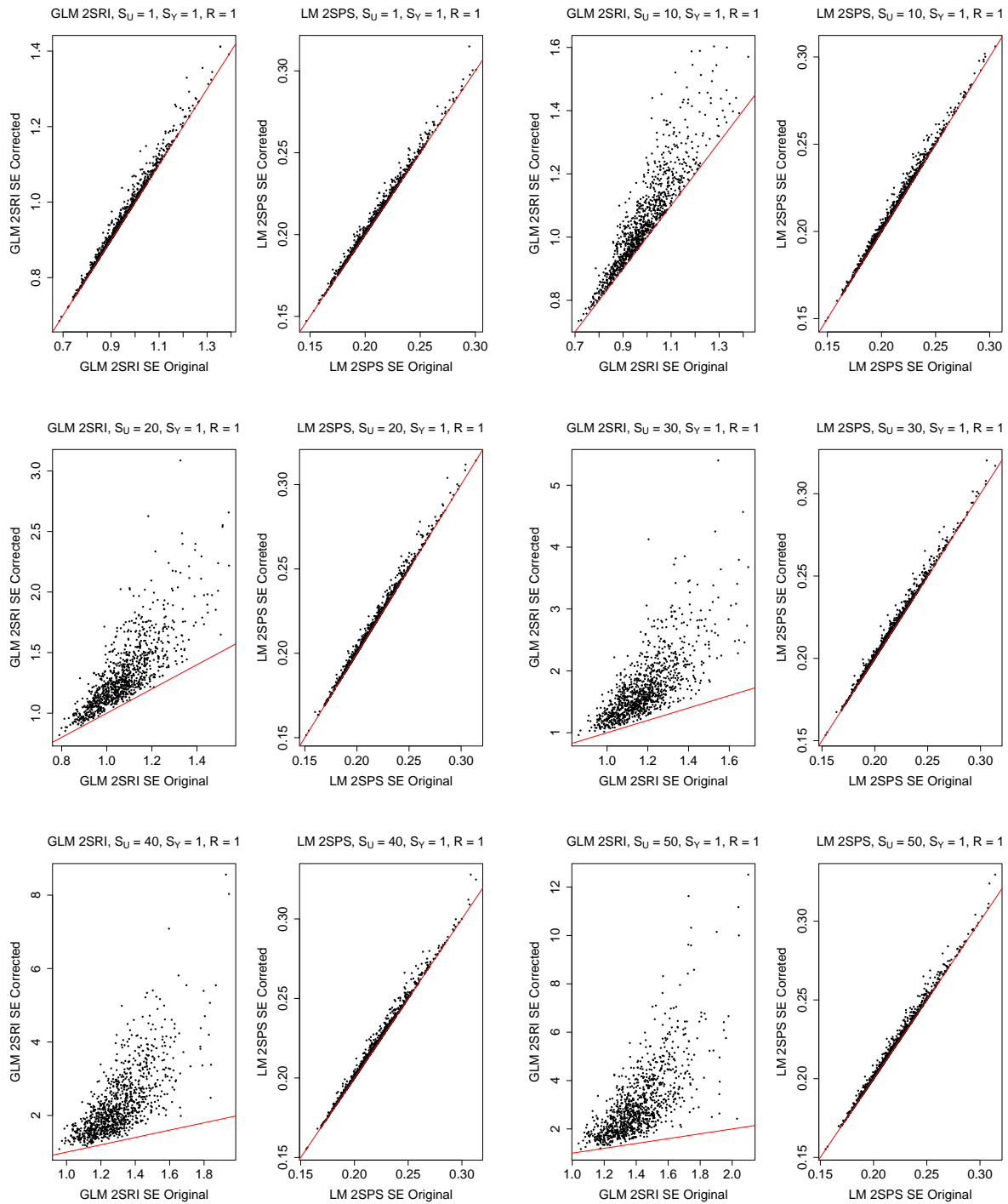


Figure S17: Simulations with the two-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 2, R = 1$ .

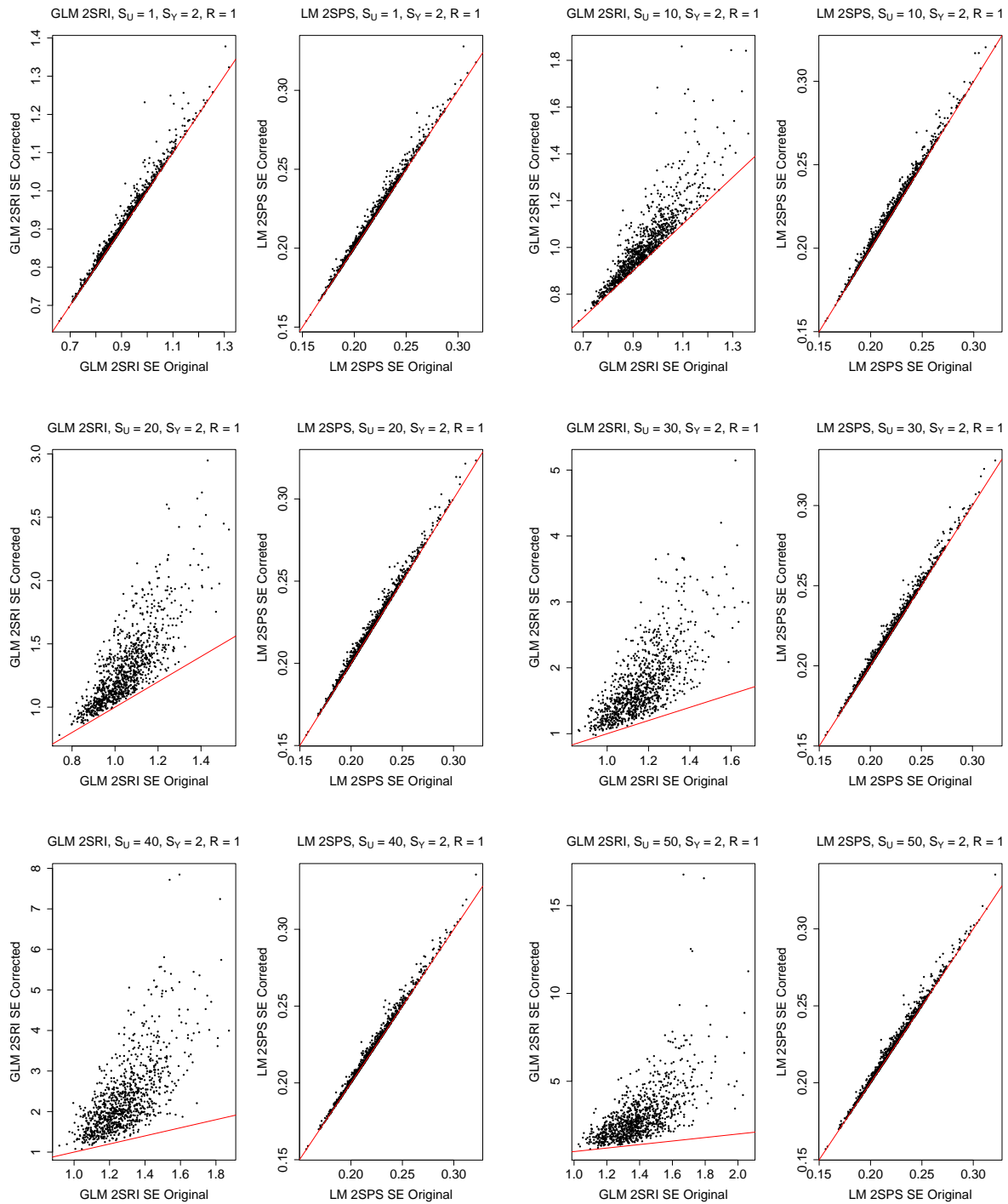




Figure S18: Simulations with the two-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 3, R = 1$ .

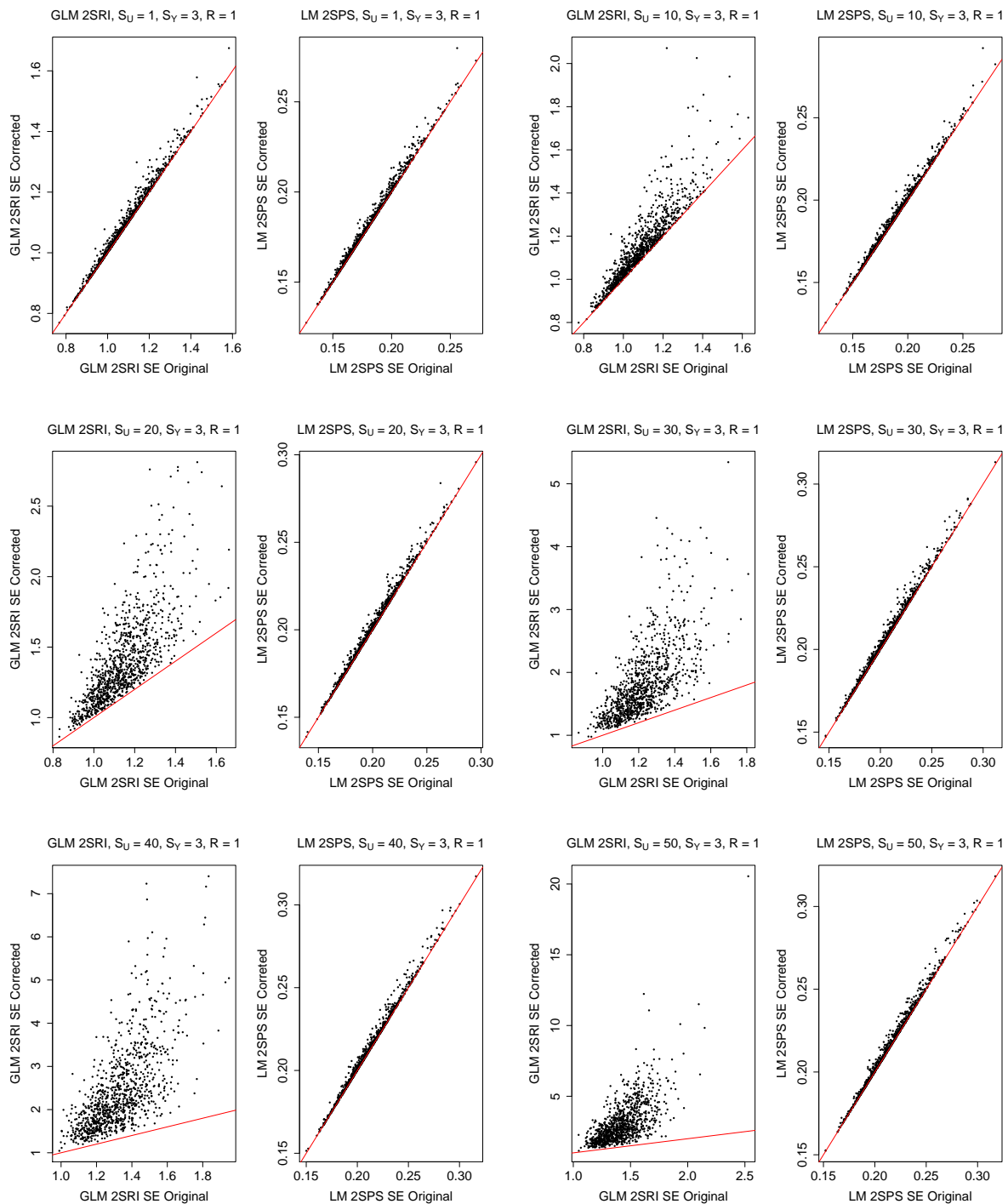


Figure S19: Simulations with the two-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 4, R = 1$ .

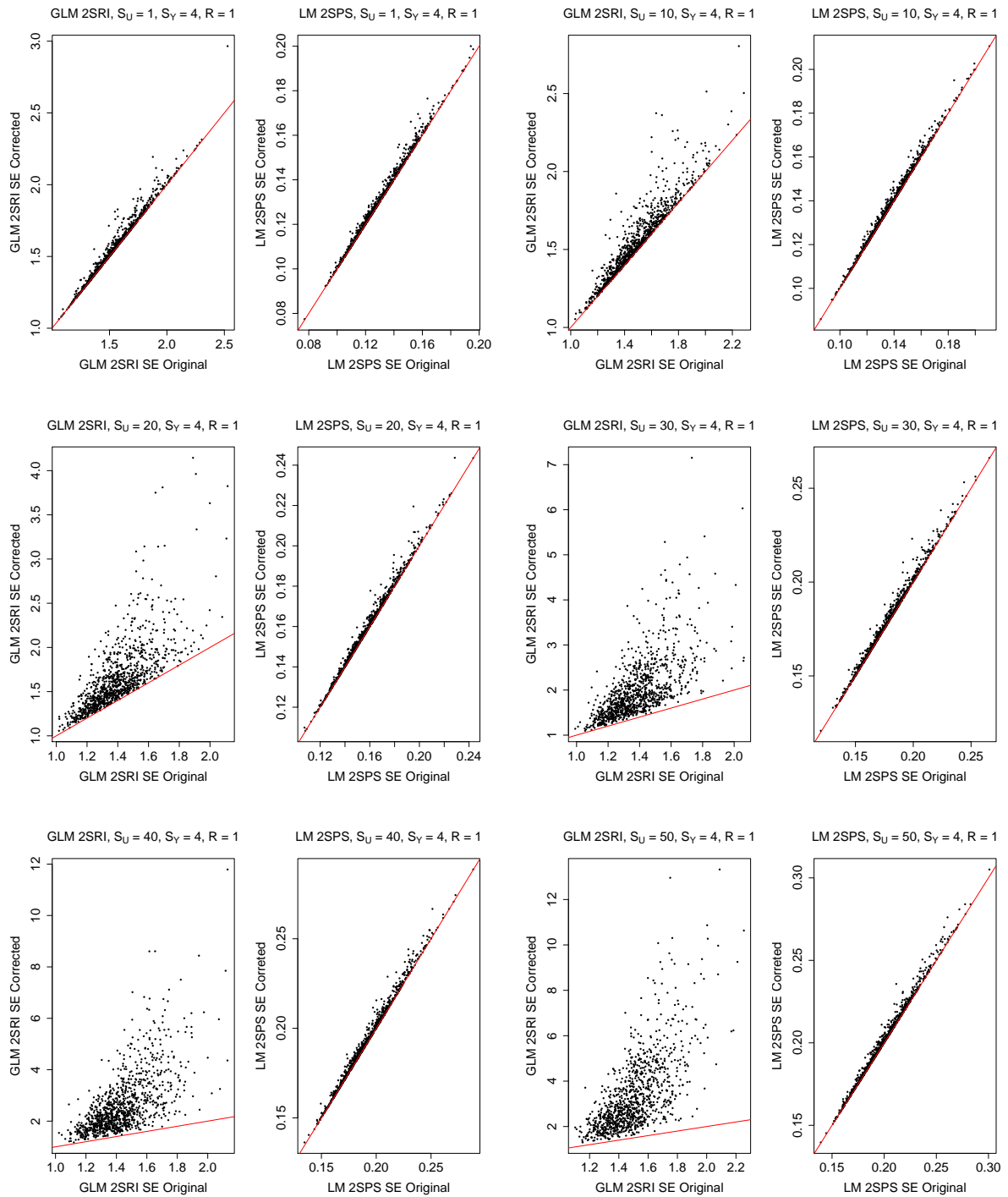


Figure S20: Simulations with the two-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 5, R = 1$ .

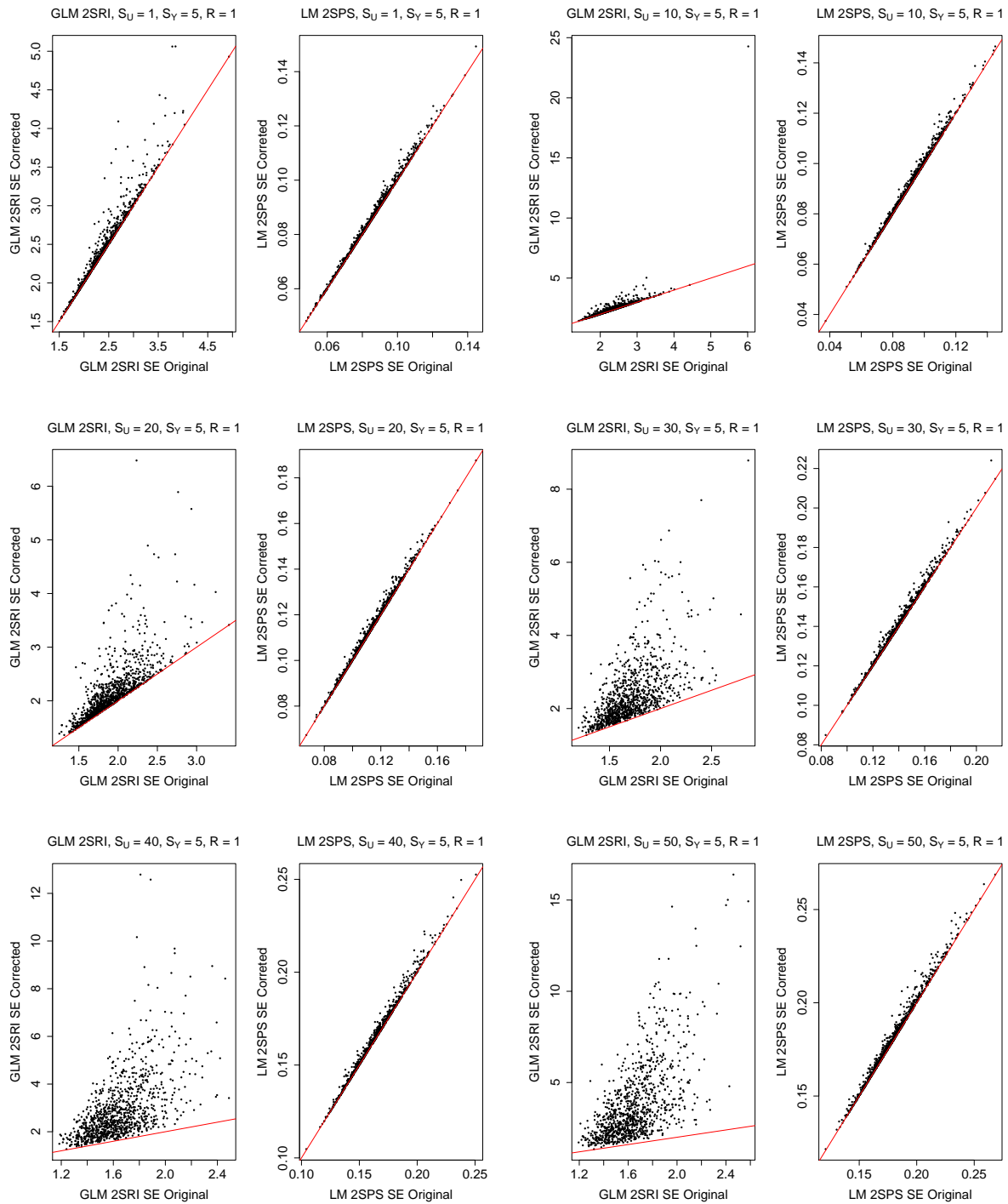


Figure S21: Simulations with the two-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 0, R = 3$ .

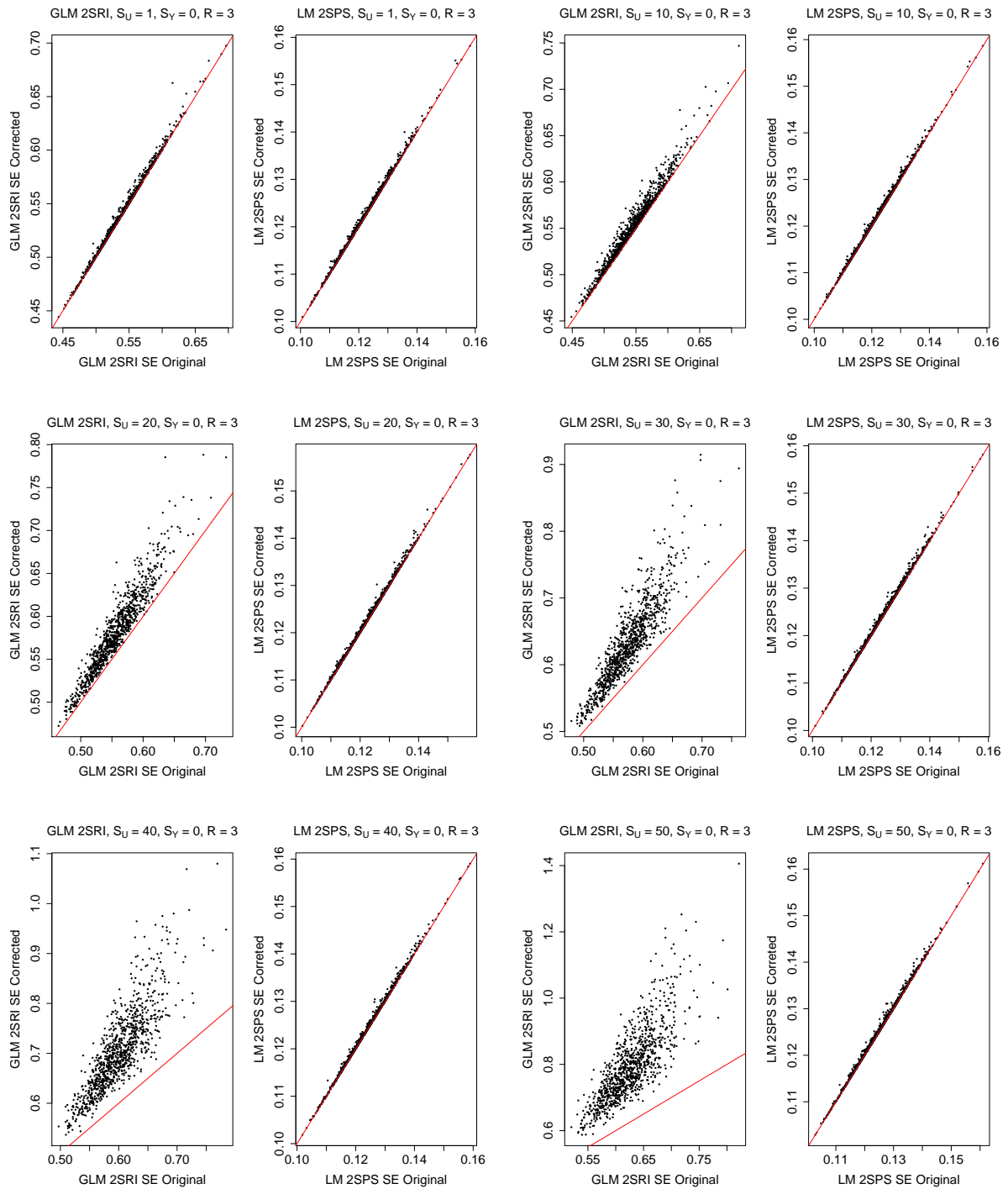


Figure S22: Simulations with the two-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 1, R = 3$ .

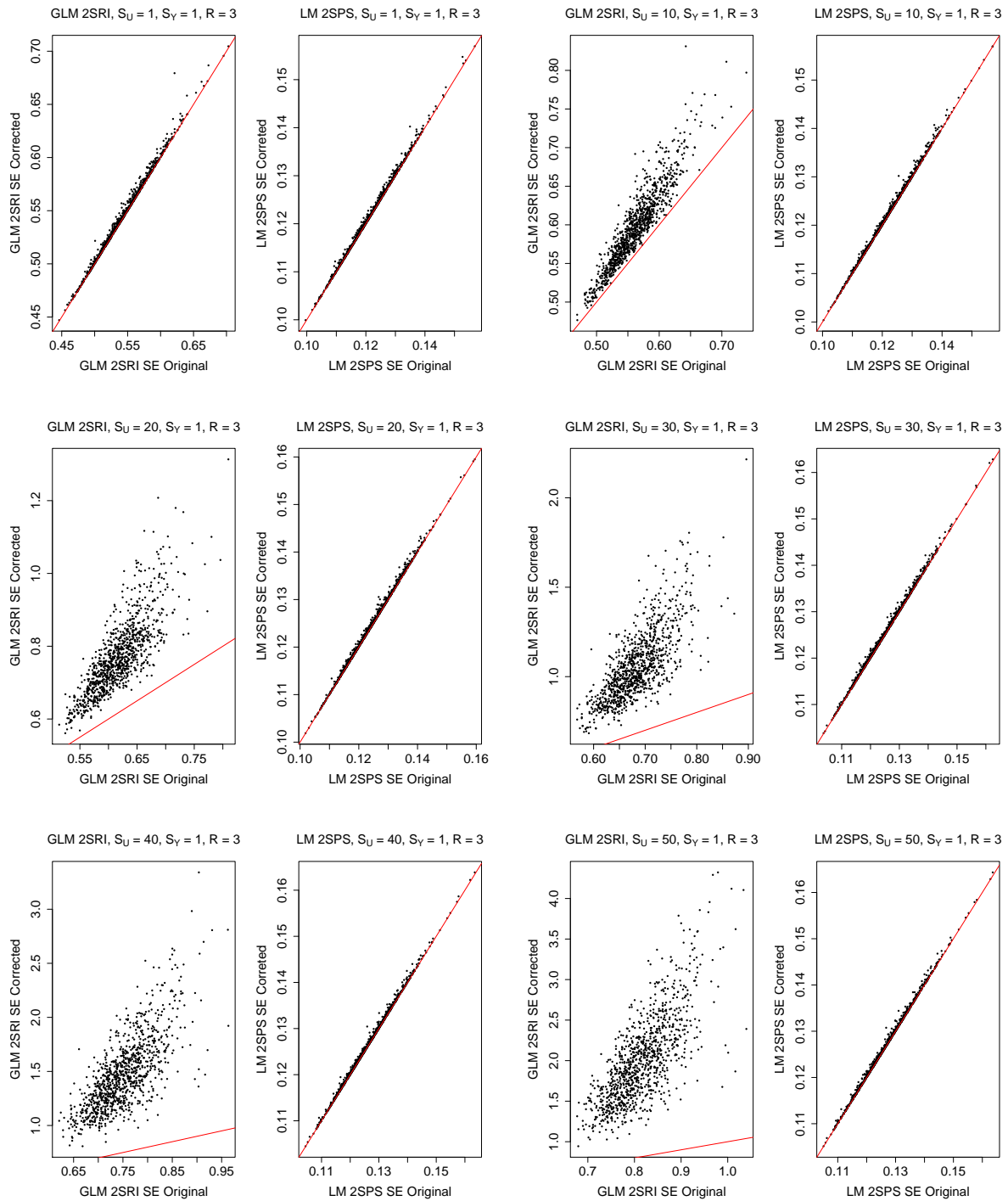


Figure S23: Simulations with the two-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 2, R = 3$ .

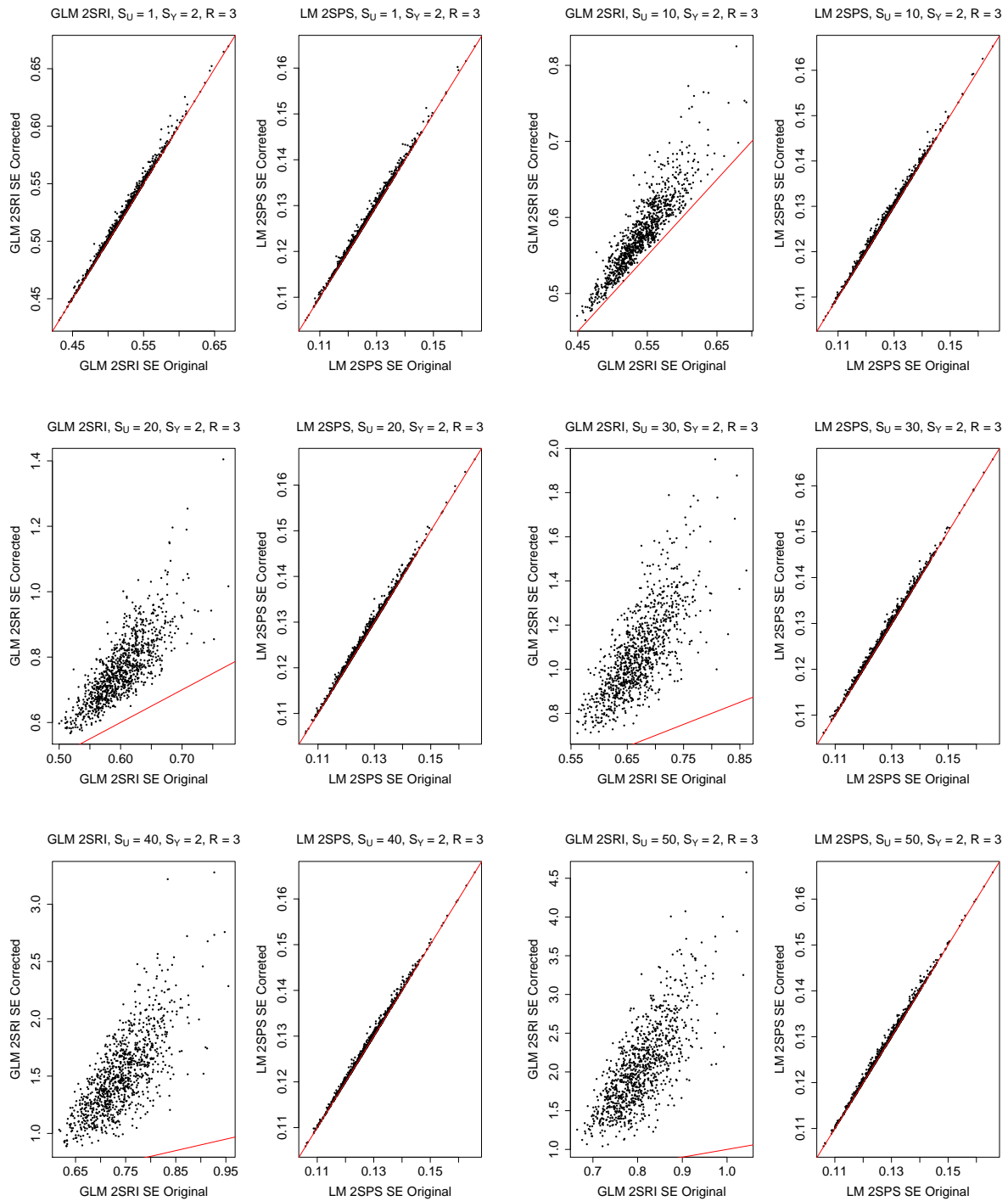


Figure S24: Simulations with the two-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 3, R = 3$ .

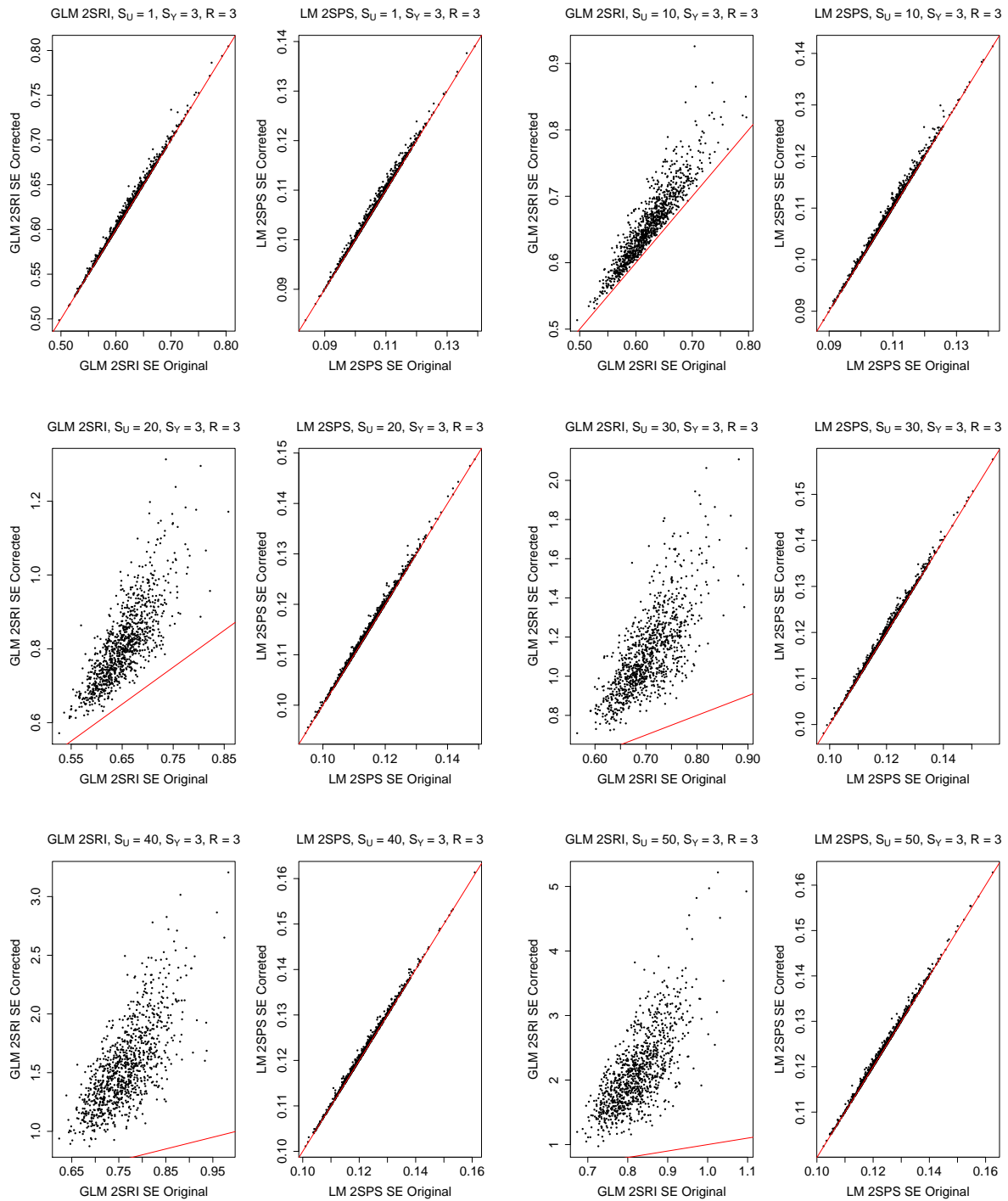


Figure S25: Simulations with the two-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 4, R = 3$ .

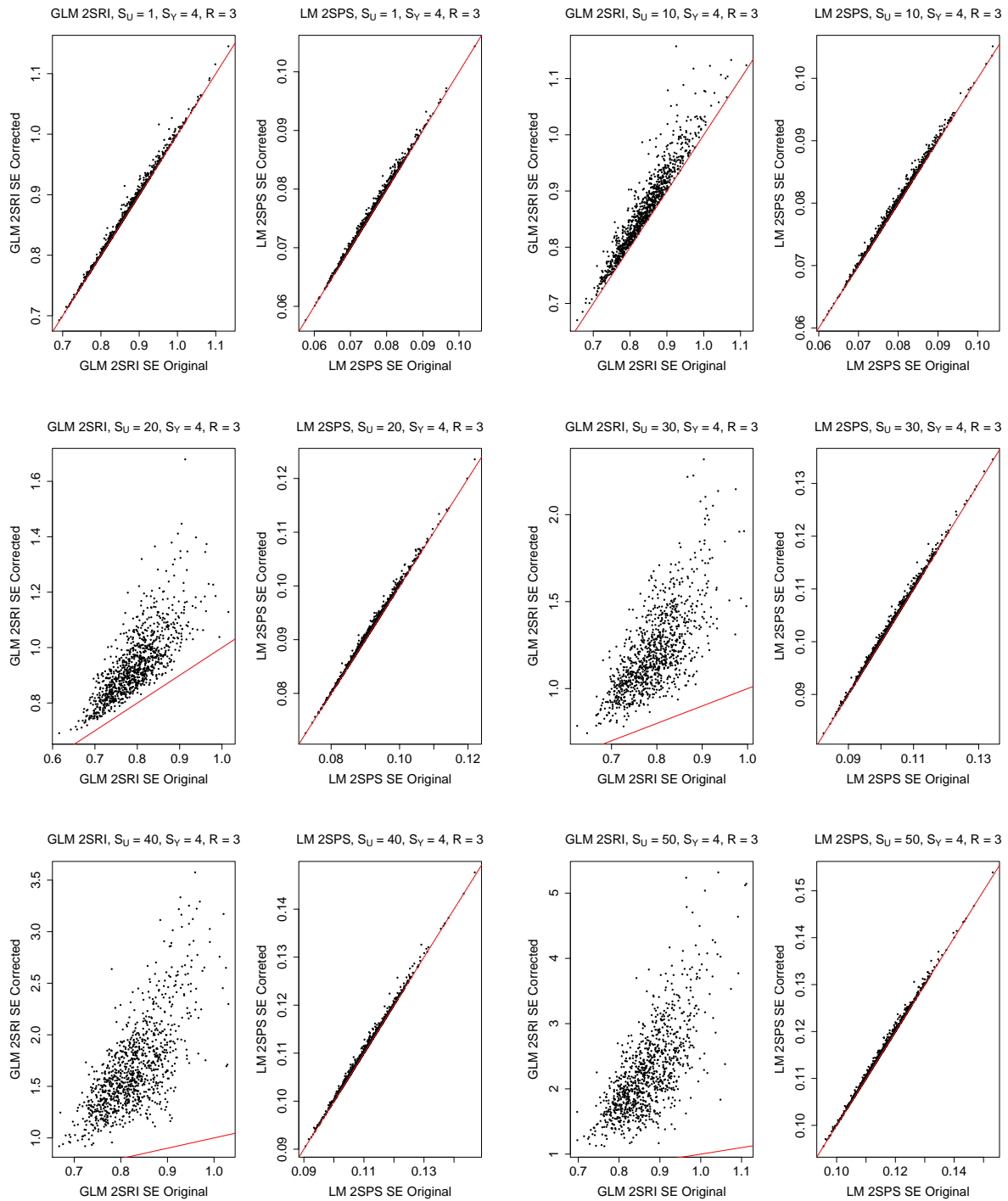




Figure S26: Simulations with the two-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 5, R = 3$ .

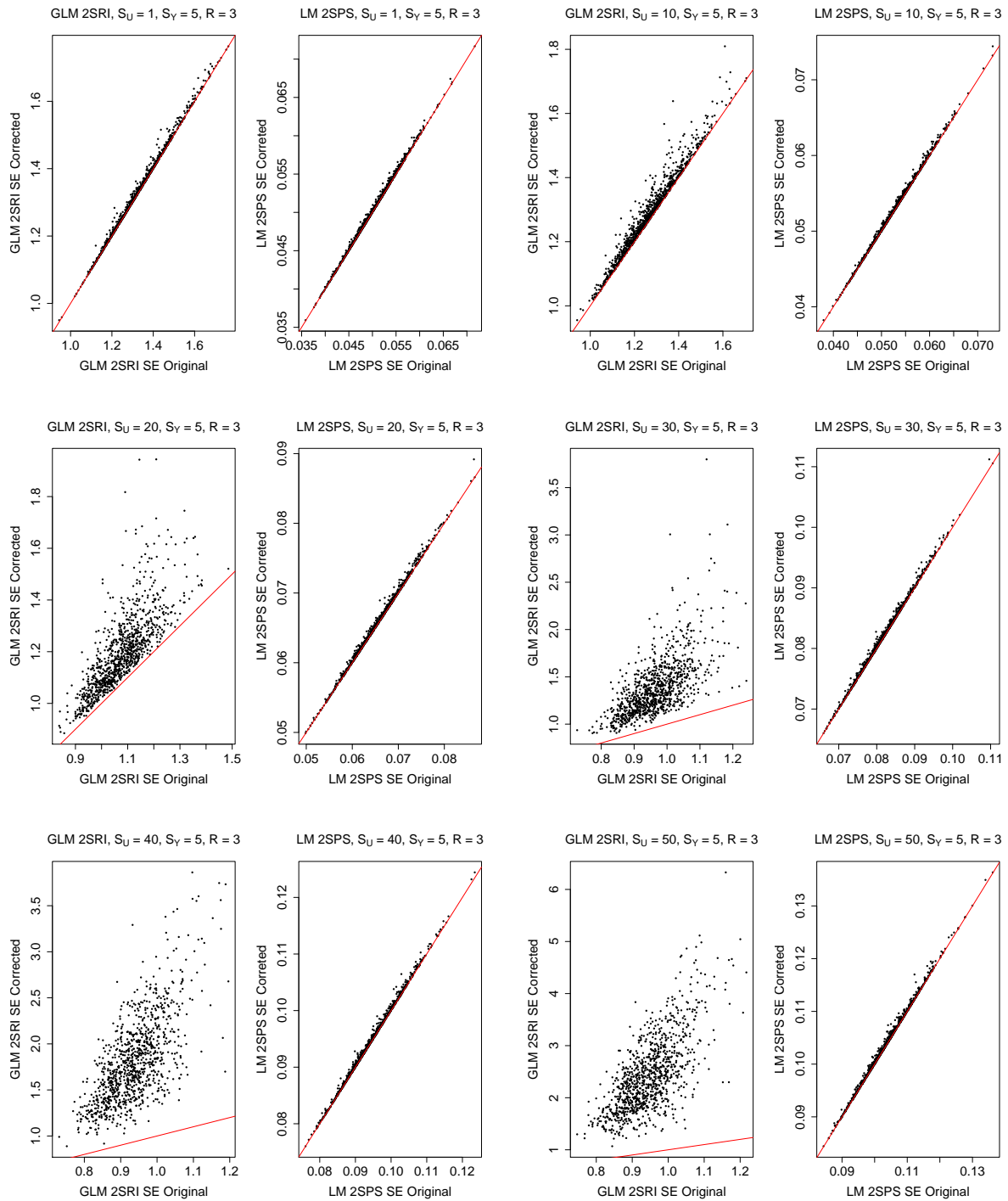


Figure S27: Simulations with the two-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 0, R = 5$ .

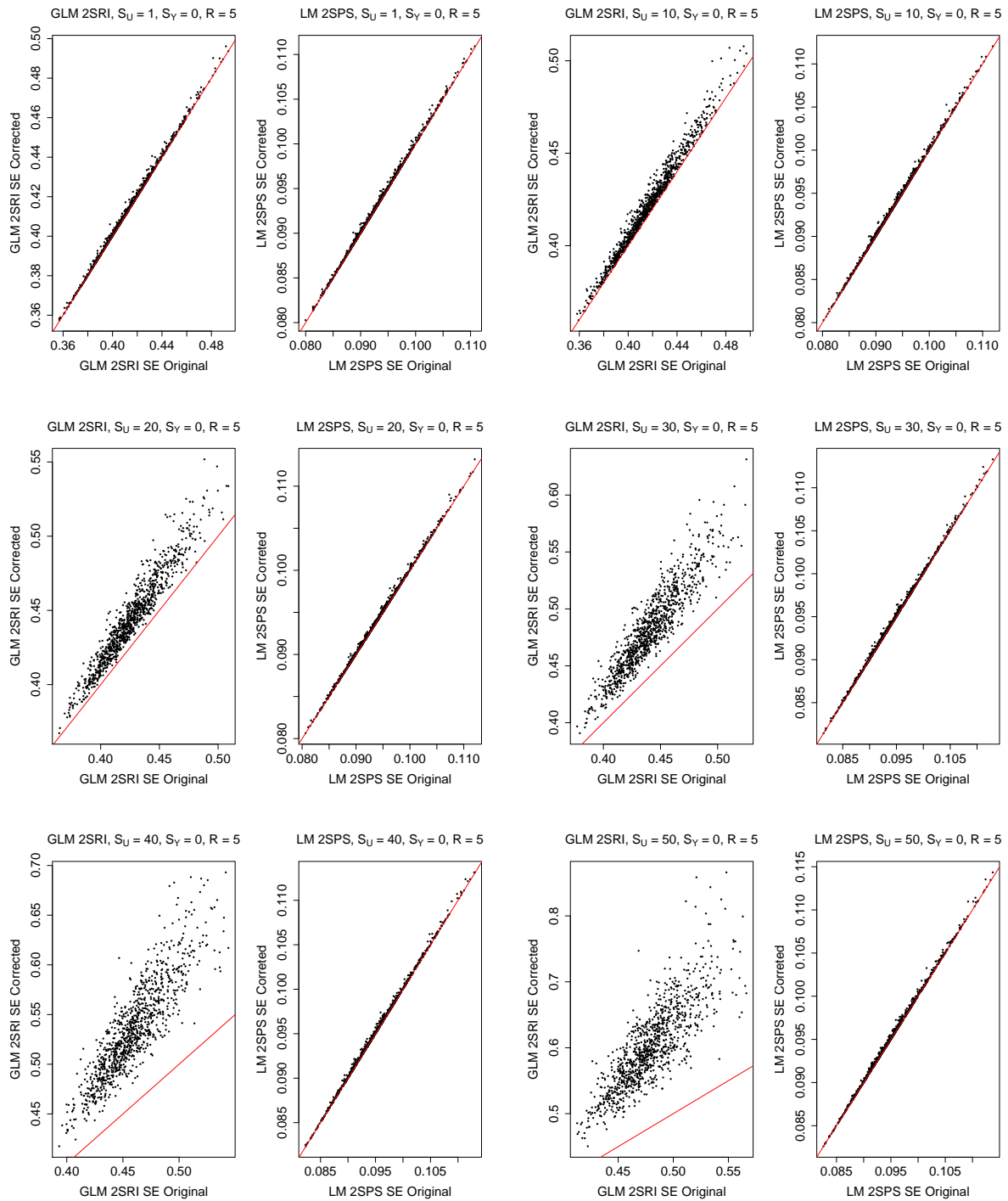


Figure S28: Simulations with the two-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 1, R = 5$ .

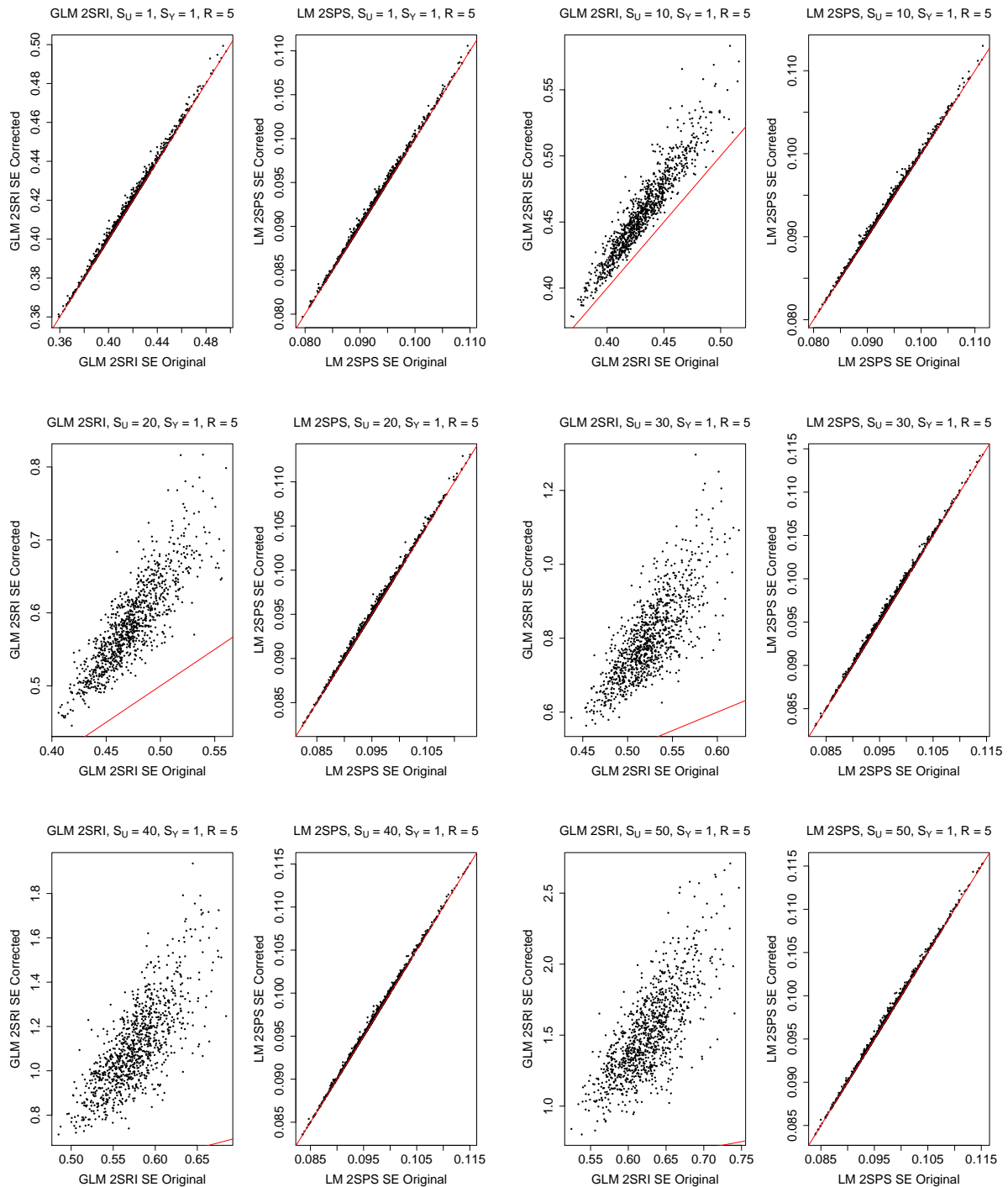


Figure S29: Simulations with the two-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 2, R = 5$ .

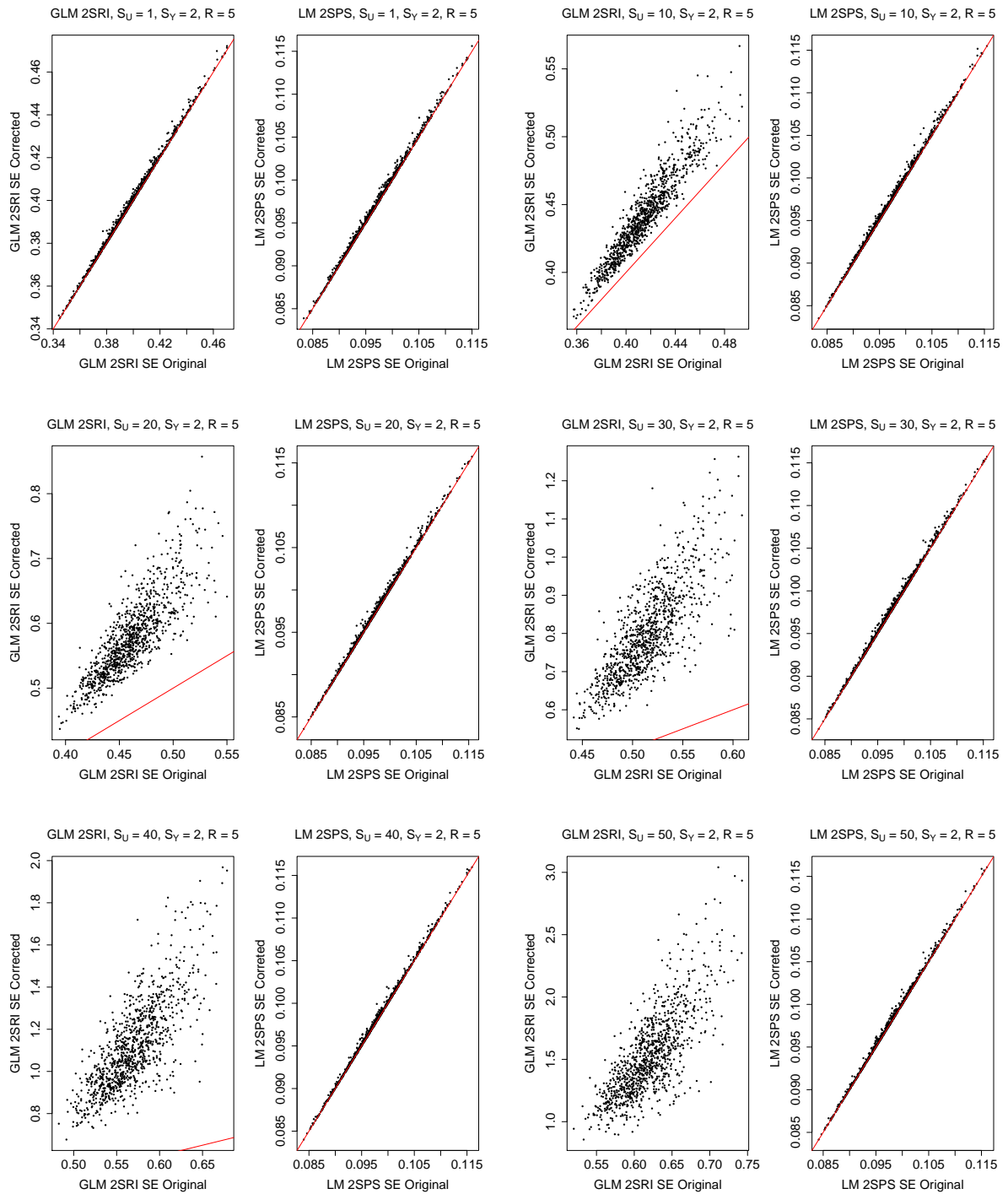


Figure S30: Simulations with the two-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 3, R = 5$ .

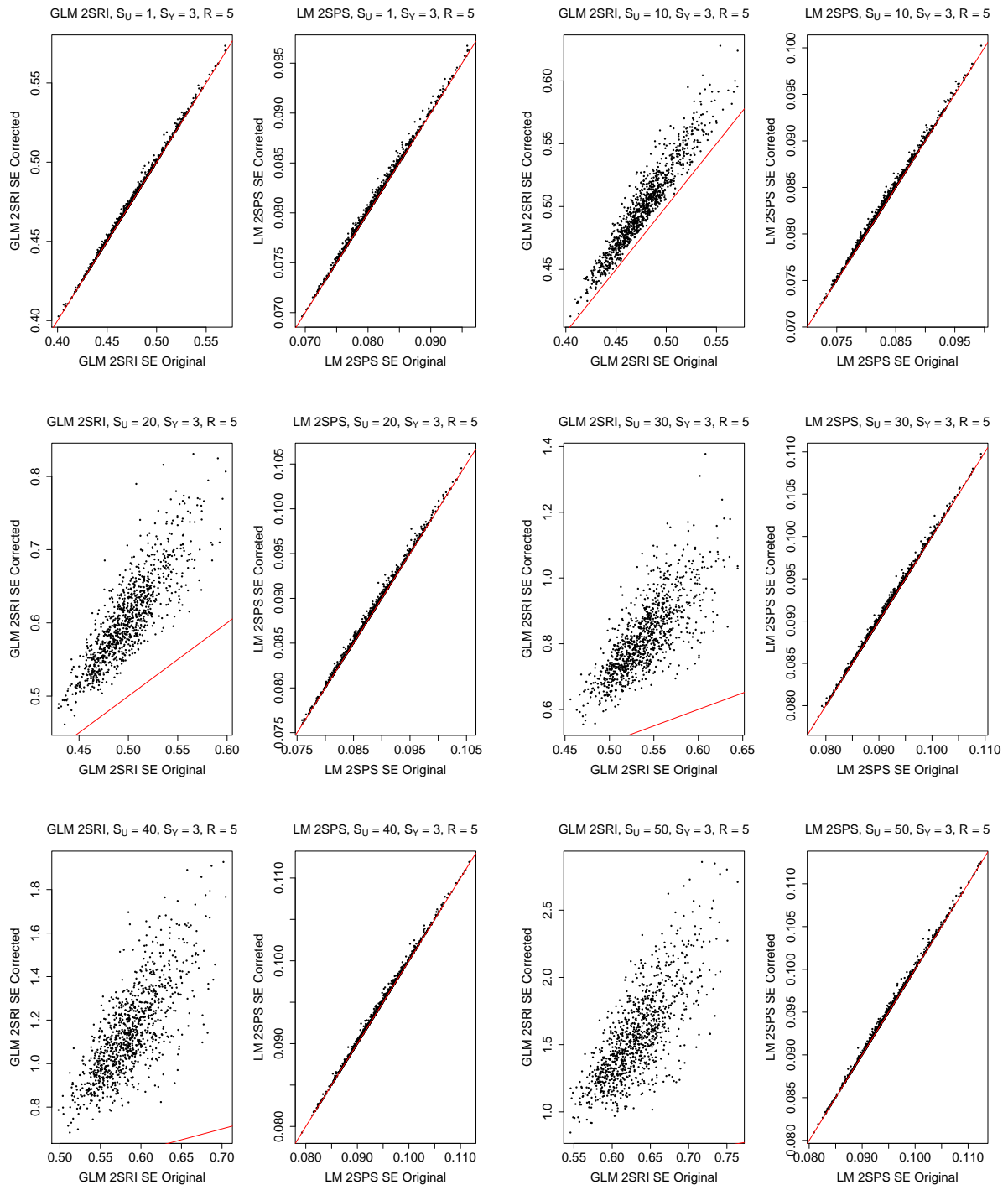


Figure S31: Simulations with the two-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 4, R = 5$ .

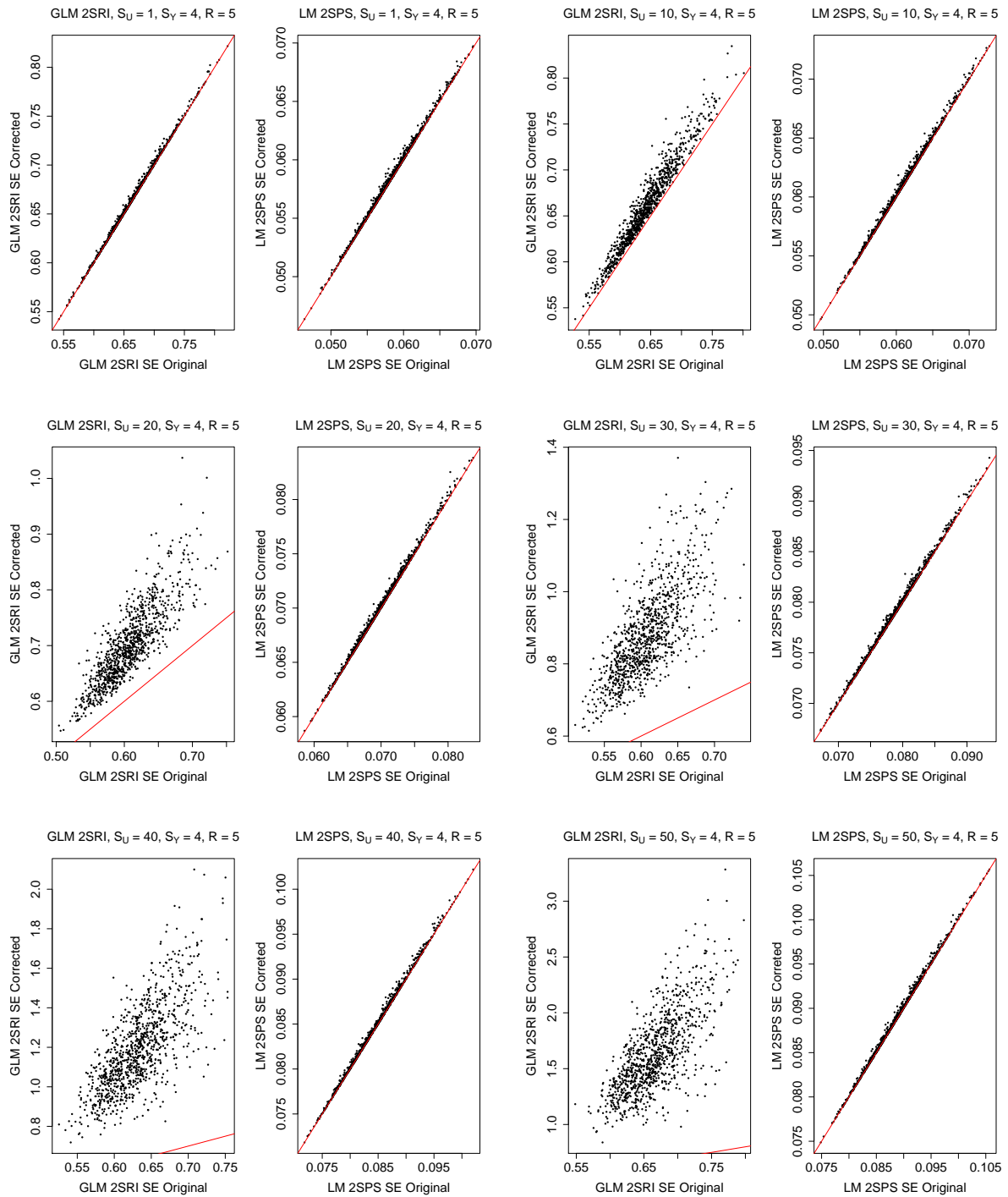


Figure S32: Simulations with the two-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 5, R = 5$ .

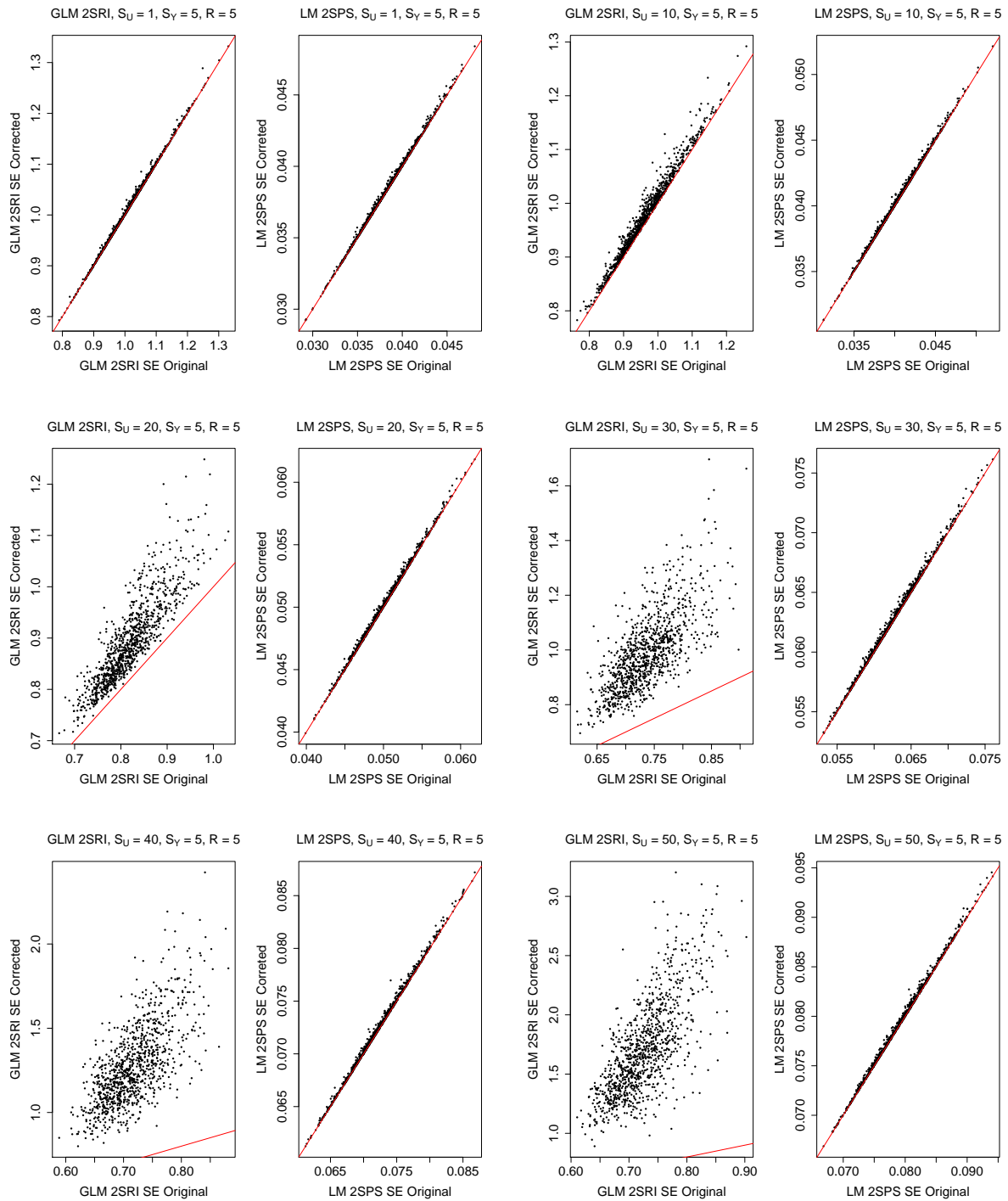


Figure S33: Simulations with the two-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 0, R = 7$ .

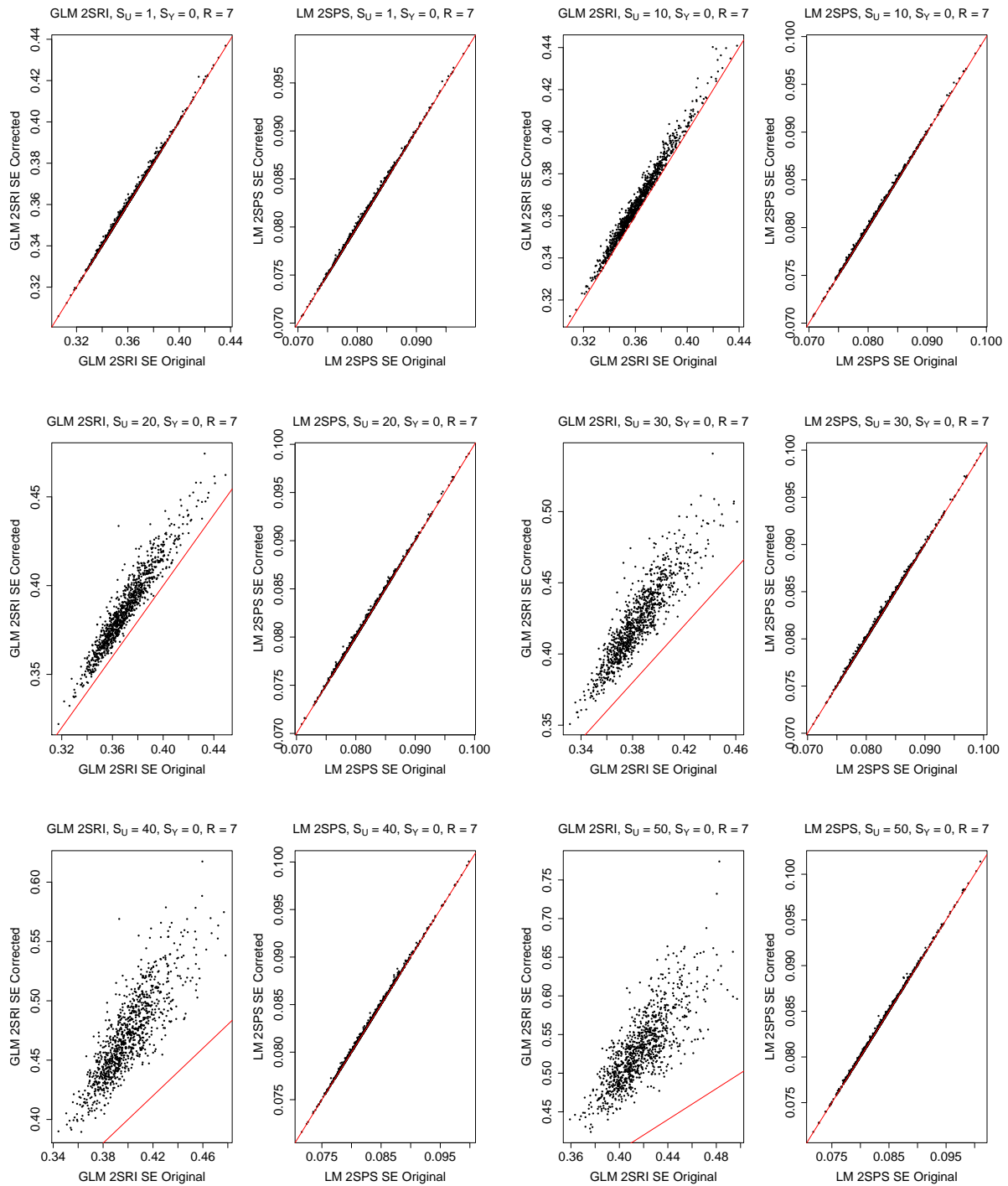




Figure S34: Simulations with the two-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 1, R = 7$ .

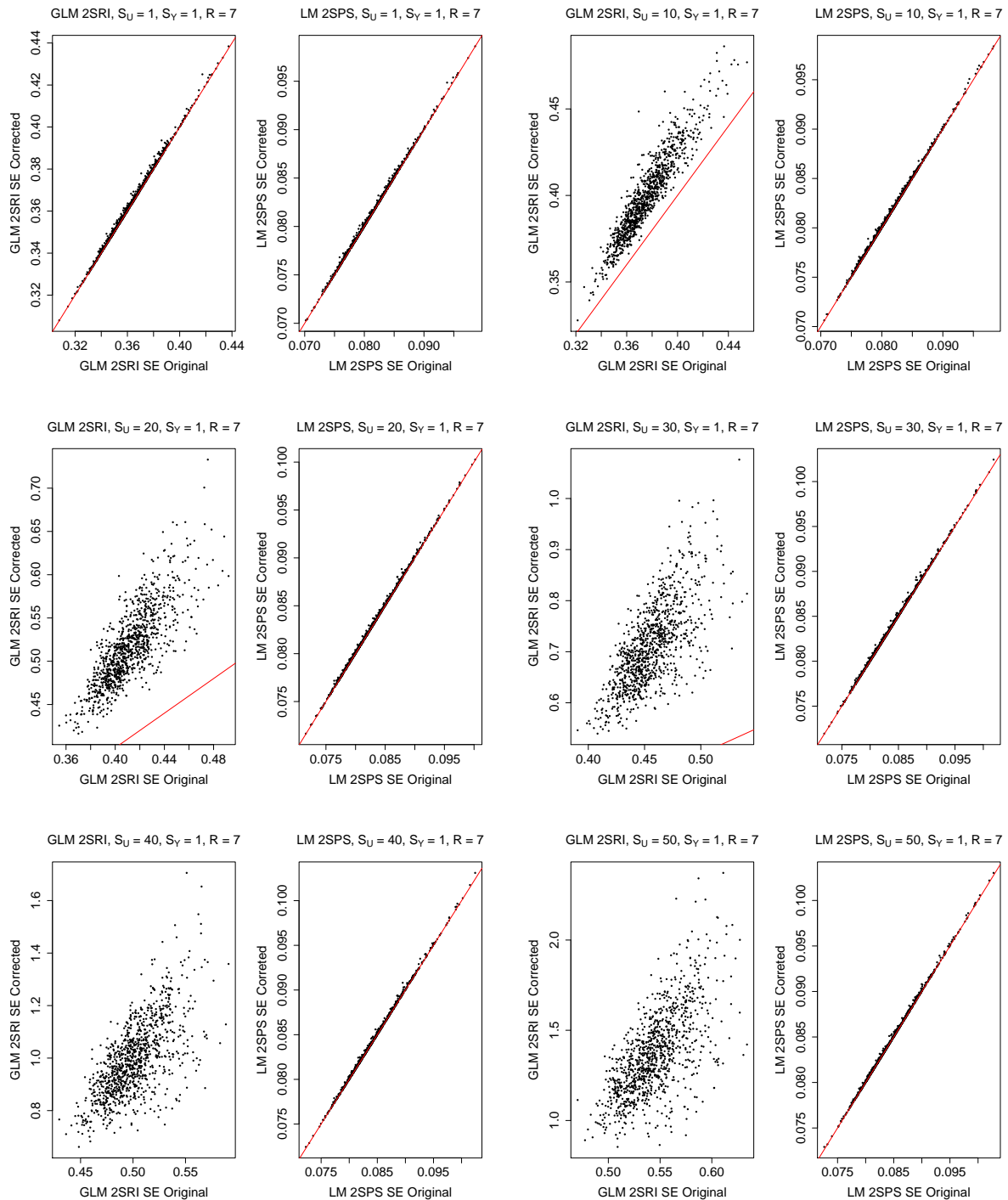


Figure S35: Simulations with the two-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 2, R = 7$ .

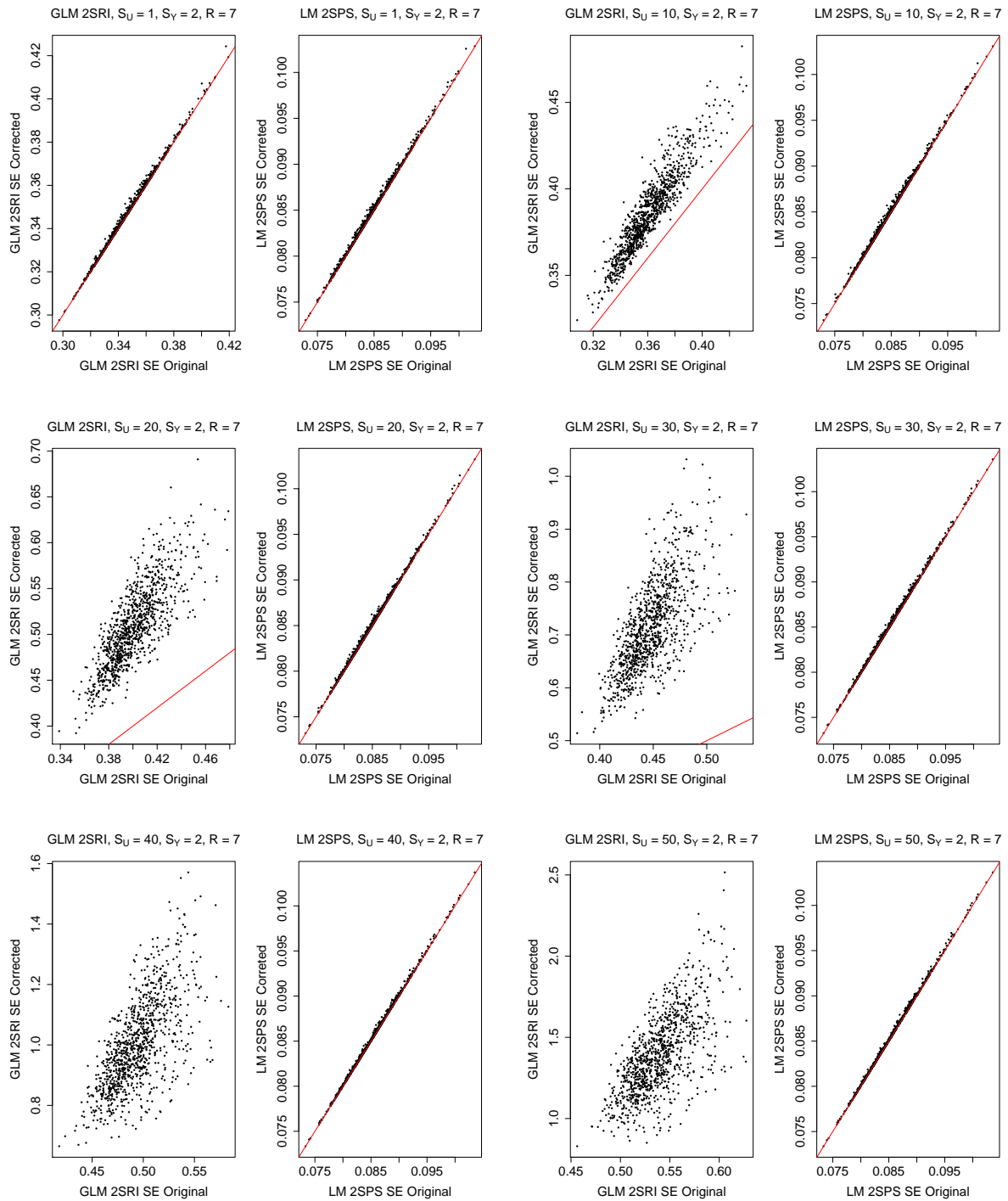


Figure S36: Simulations with the two-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 3, R = 7$ .

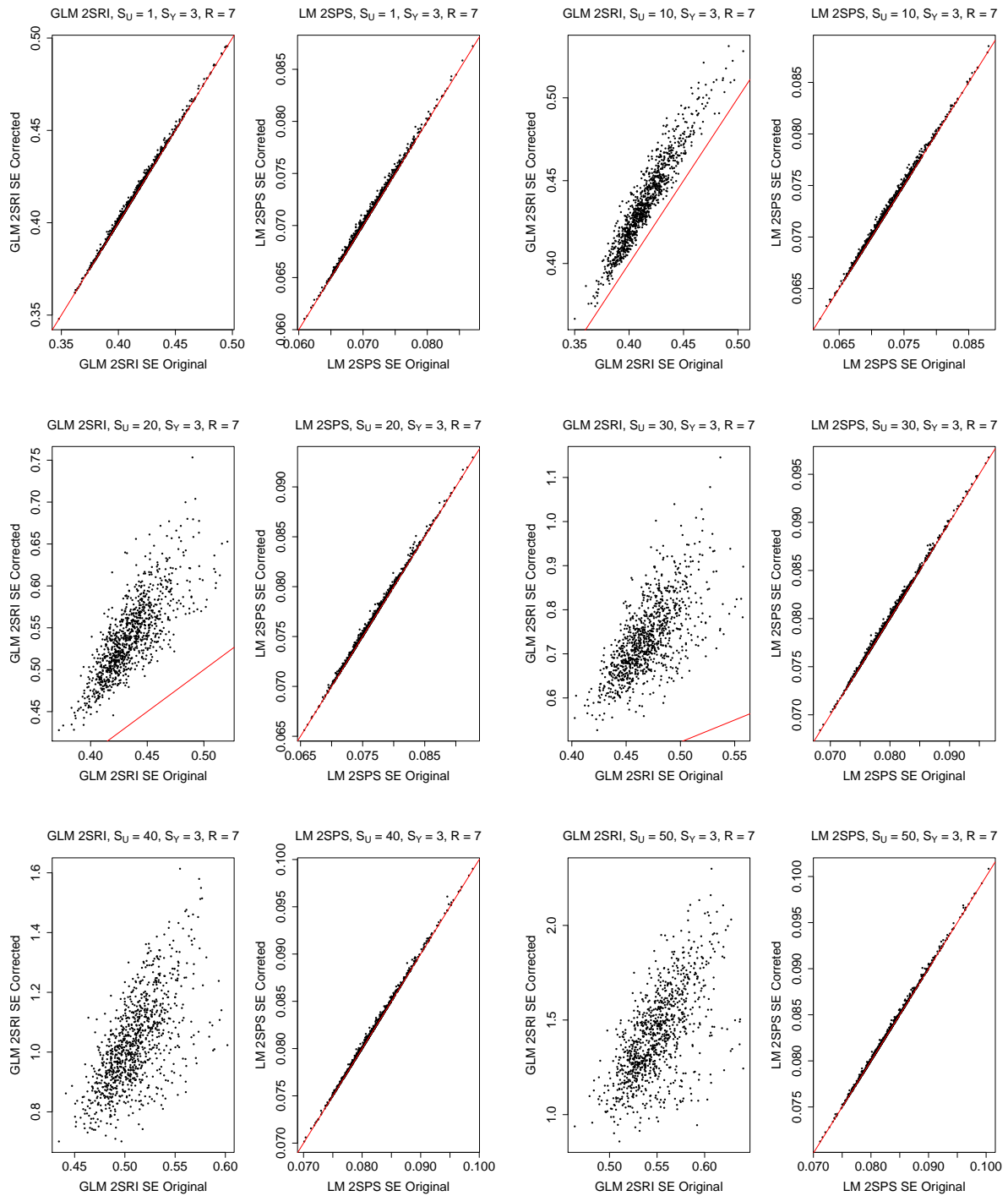


Figure S37: Simulations with the two-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 4, R = 7$ .

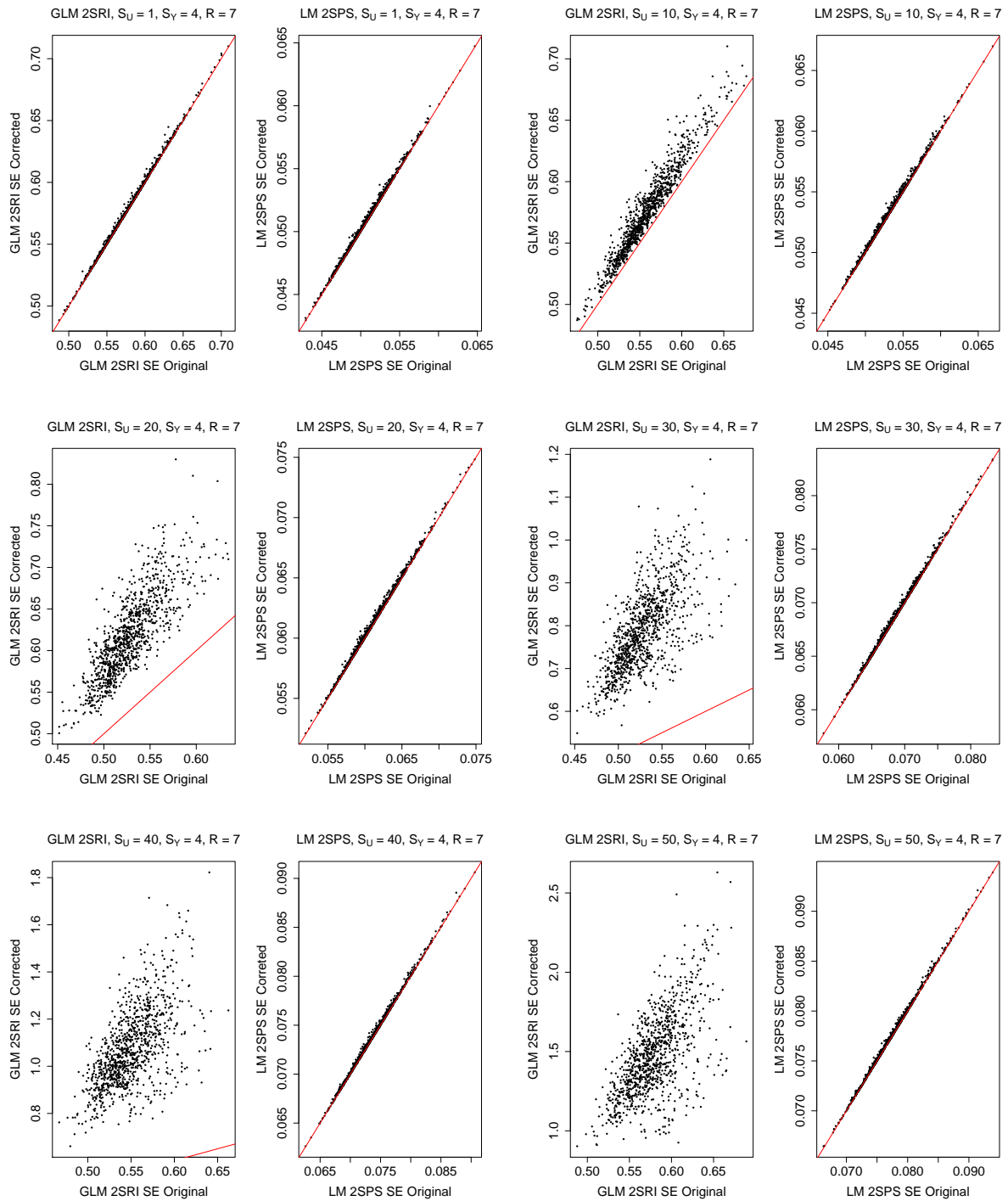


Figure S38: Simulations with the two-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 5, R = 7$ .

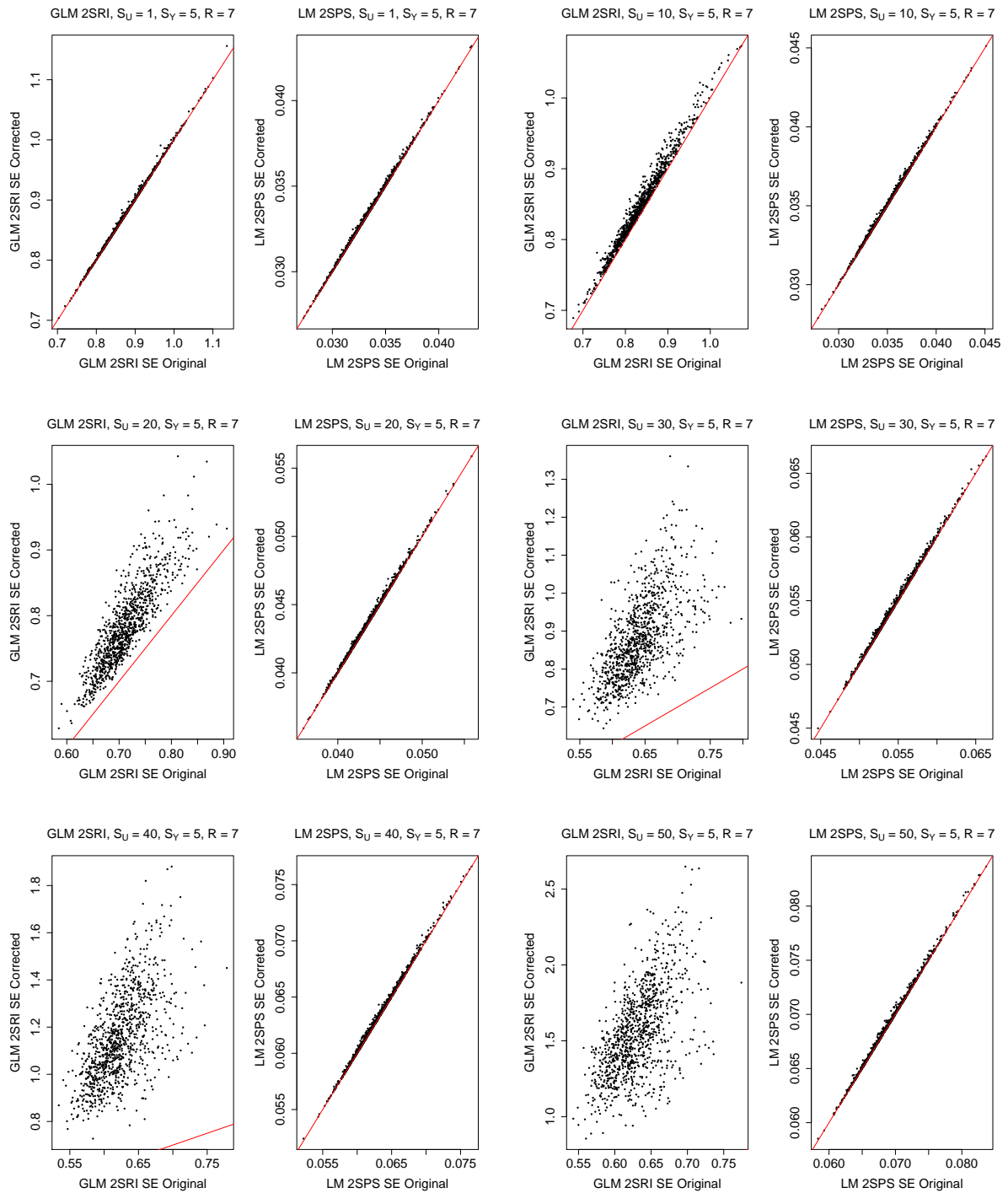


Figure S39: Simulations with the two-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 0, R = 9$ .

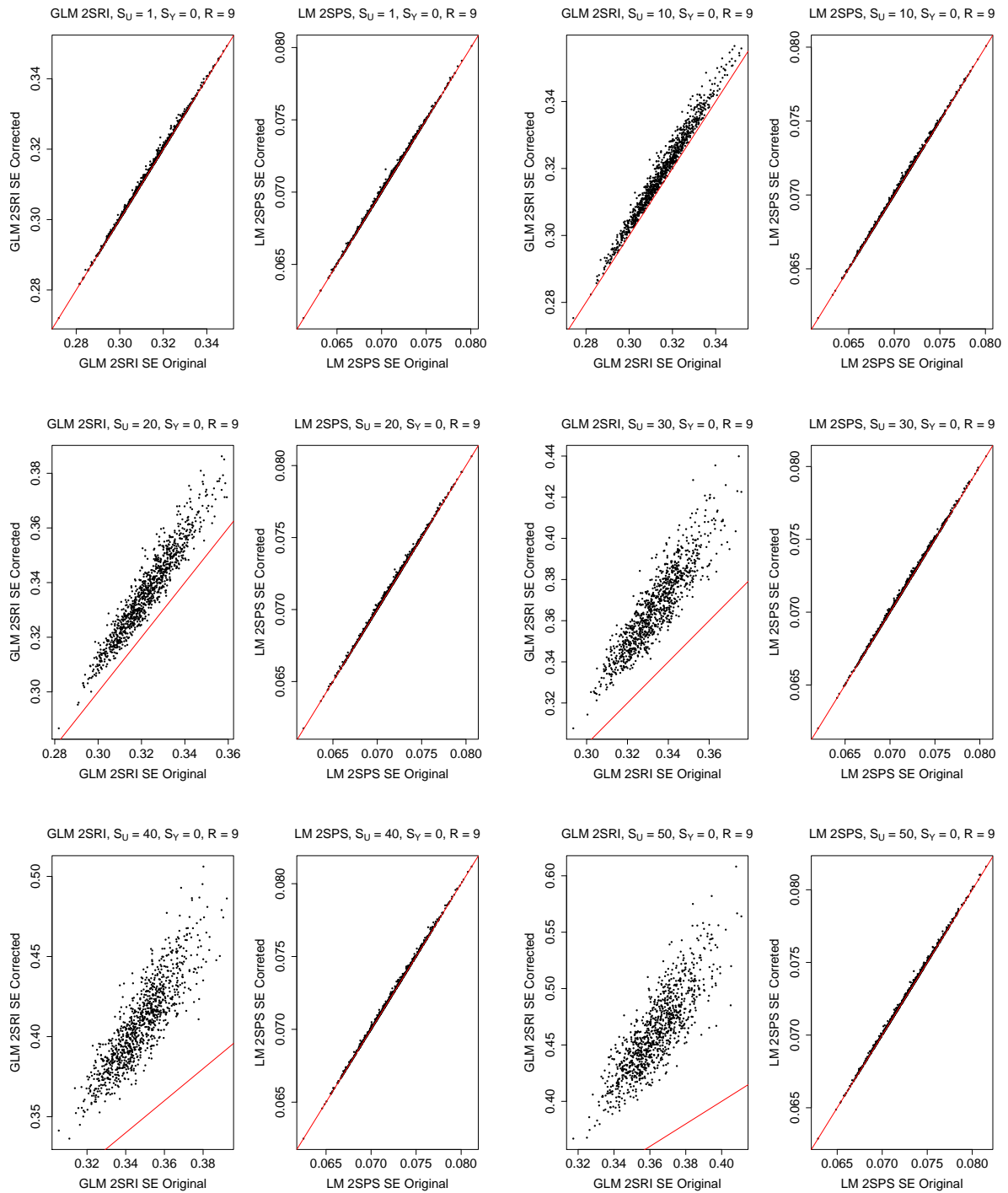


Figure S40: Simulations with the two-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 1, R = 9$ .

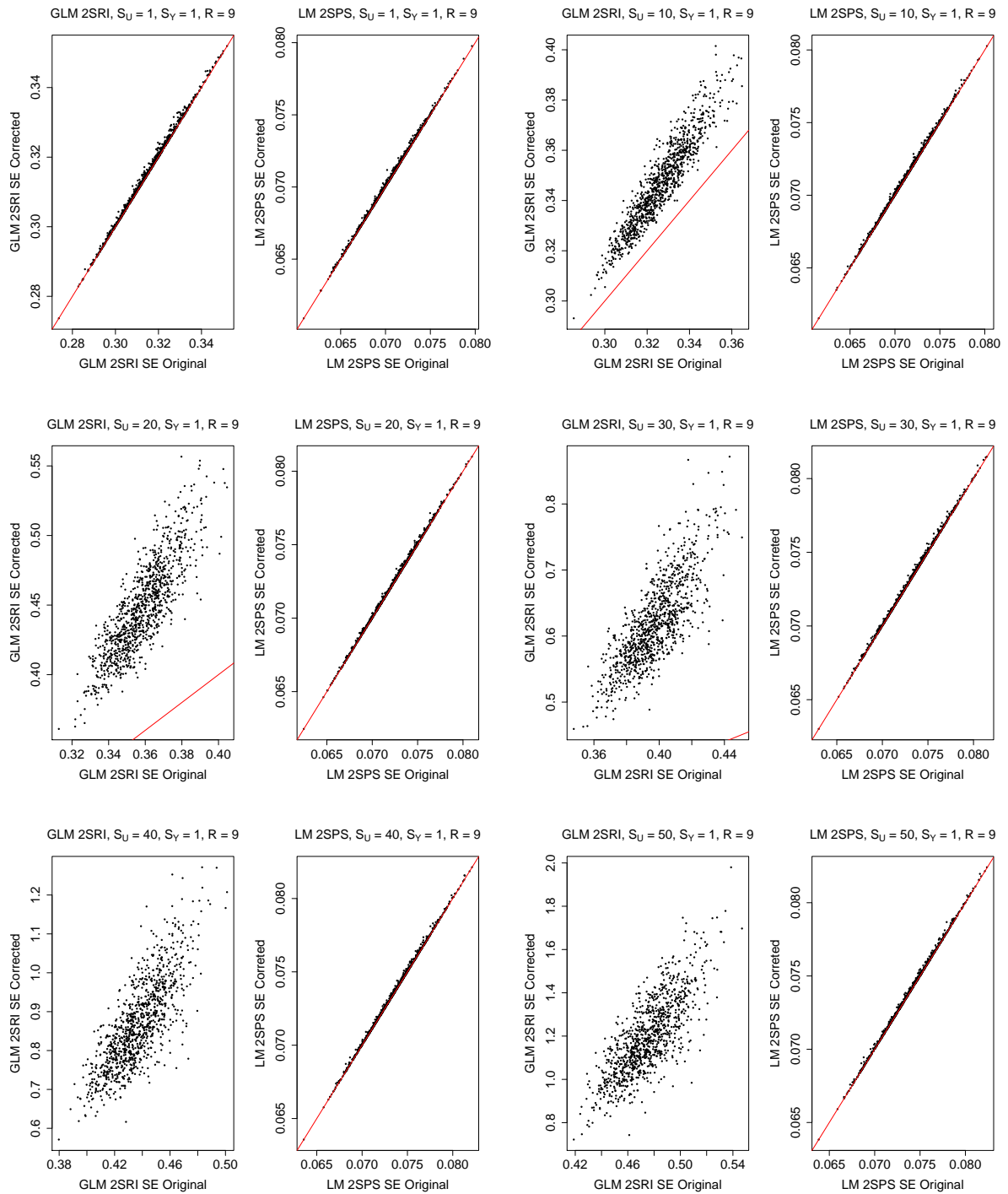


Figure S41: Simulations with the two-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 2, R = 9$ .

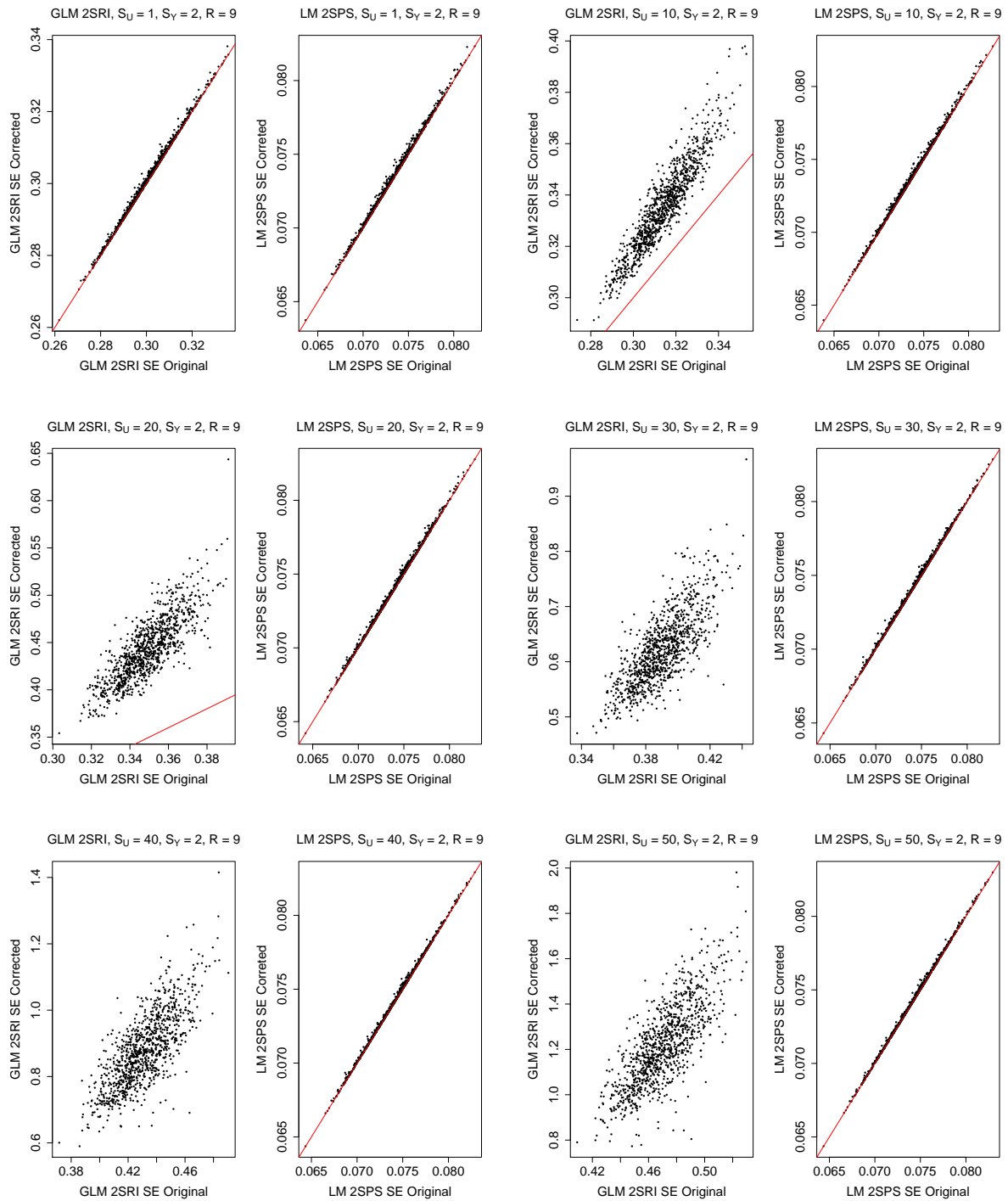




Figure S42: Simulations with the two-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 3, R = 9$ .

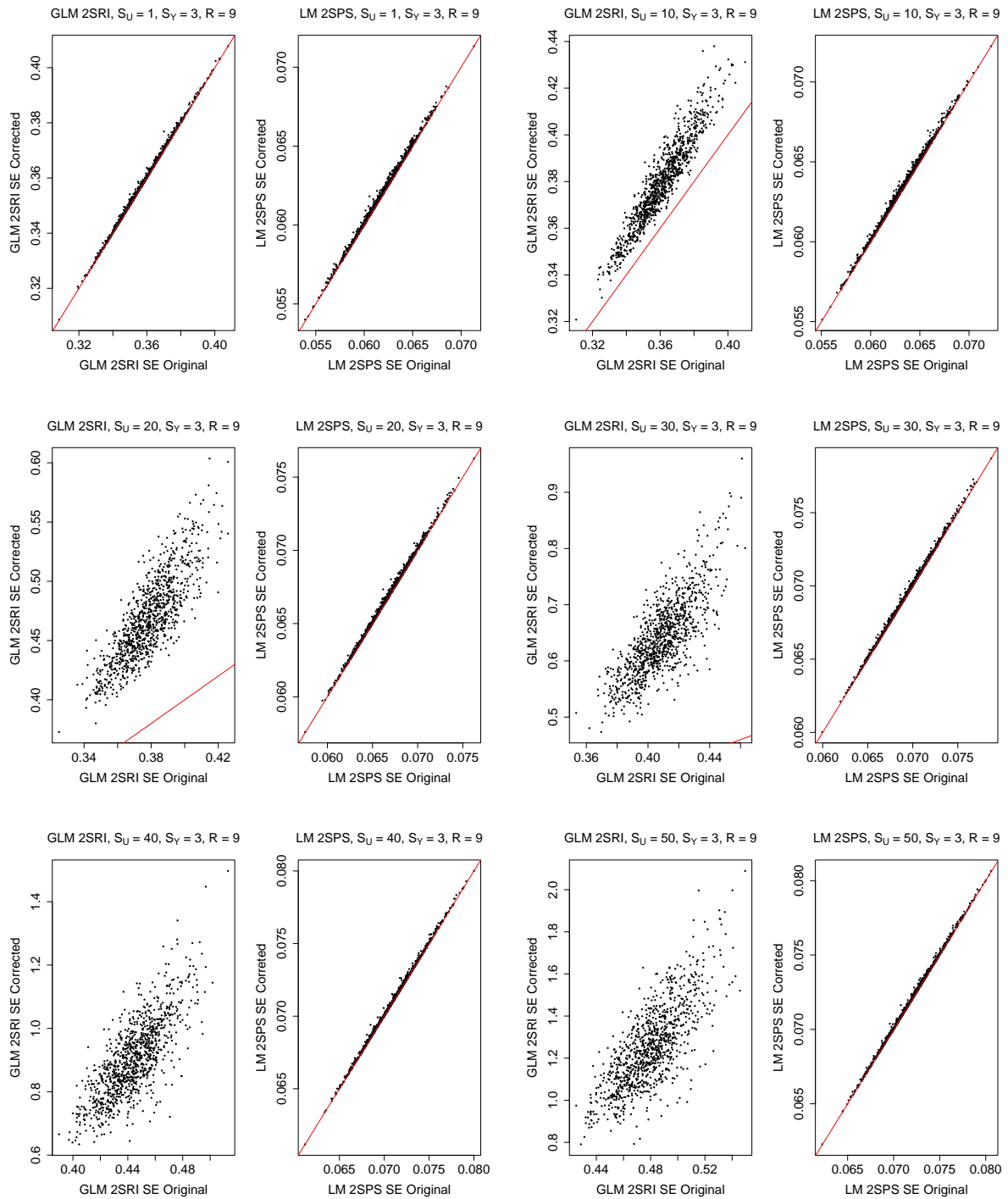


Figure S43: Simulations with the two-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 4, R = 9$ .

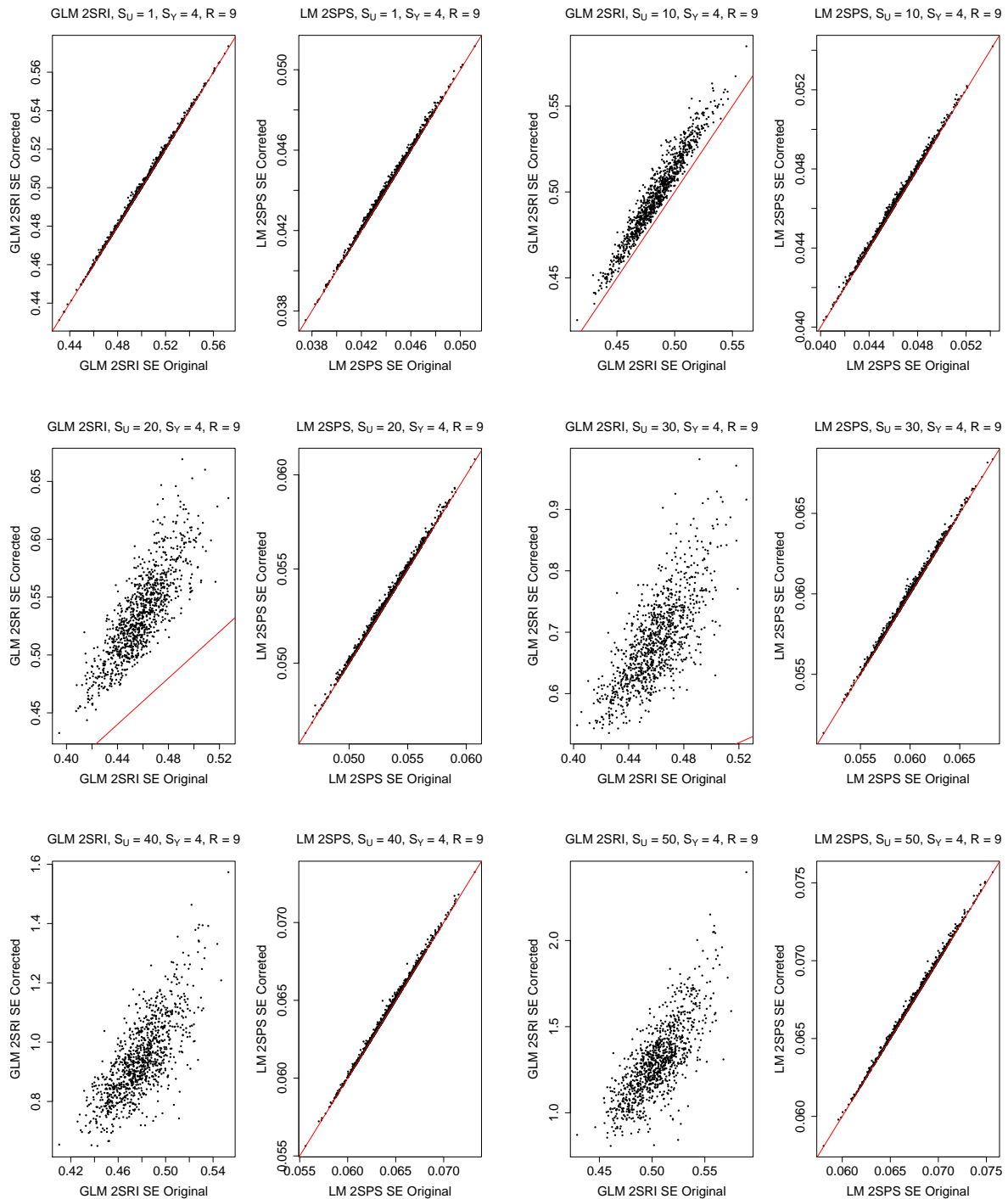
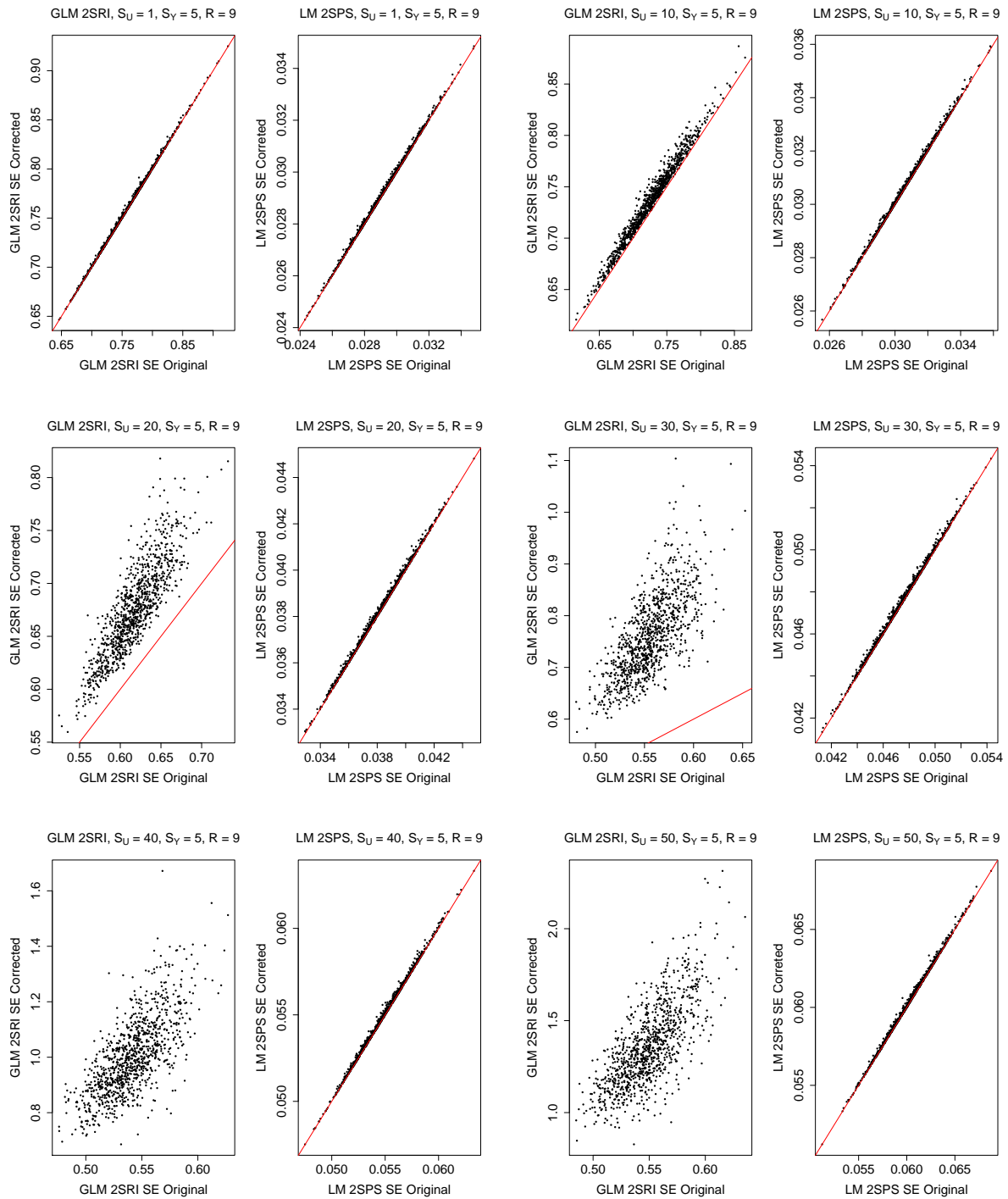


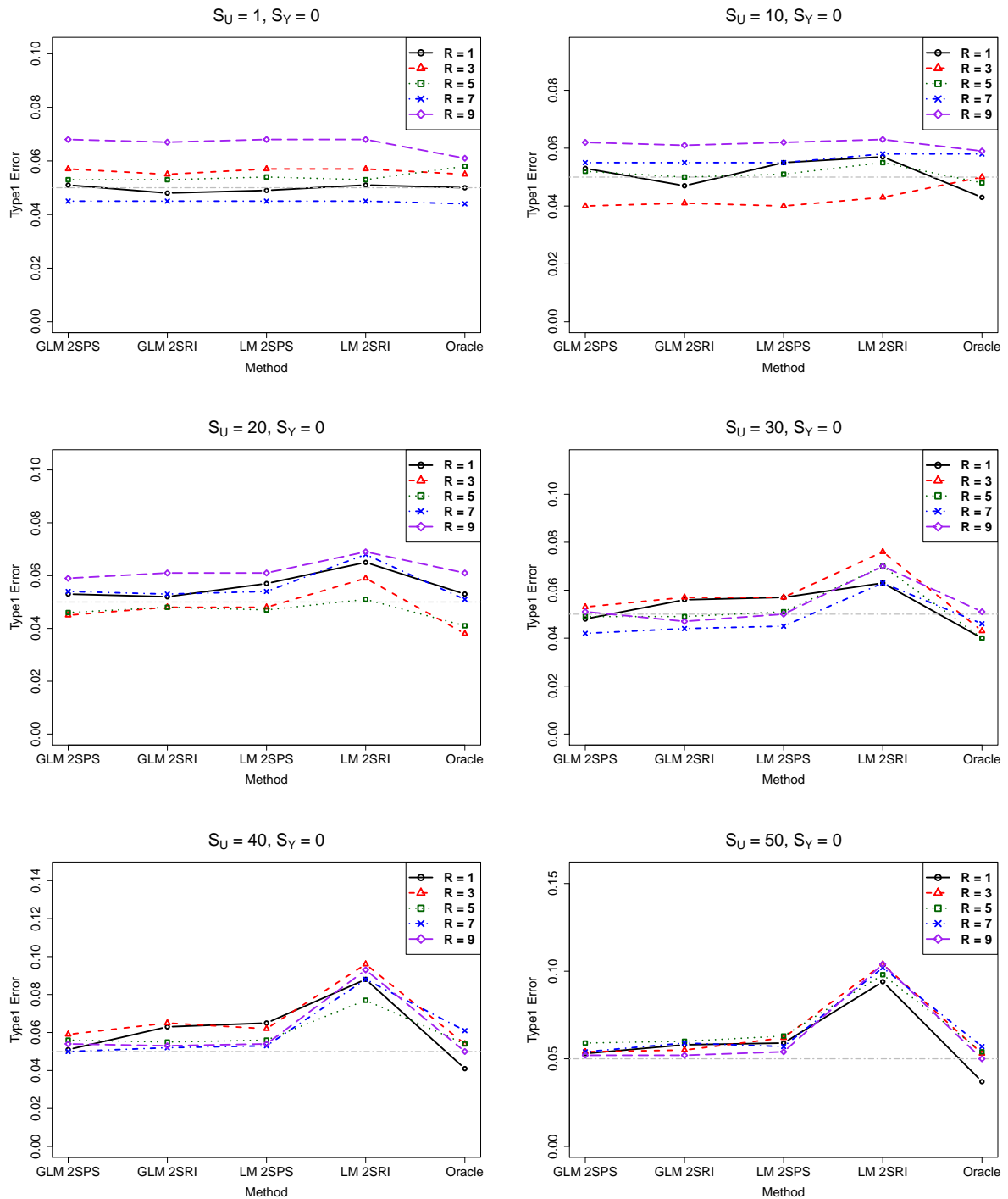
Figure S44: Simulations with the two-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 5, R = 9$ .



## 2.2 One-sample Approaches

### 2.2.1 Type I Error

Figure S45: Simulations with the one-sample approaches: empirical Type I error rates of various methods.



## 2.2.2 Power

Figure S46: Simulations with the one-sample approaches: empirical power of various methods,  $S_Y = 1$ .

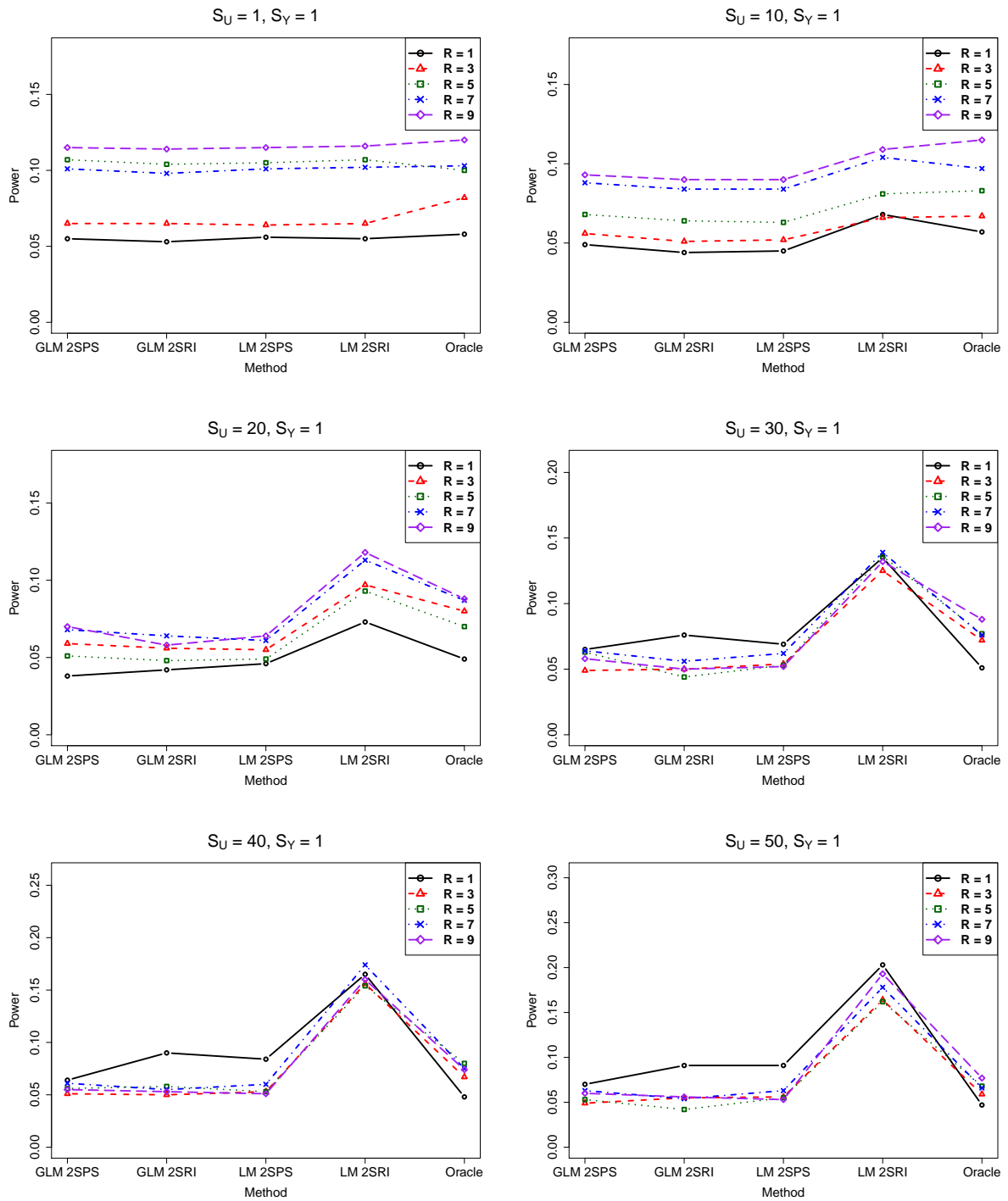


Figure S47: Simulations with the one-sample approaches: empirical power of various methods,  $S_Y = 2$ .

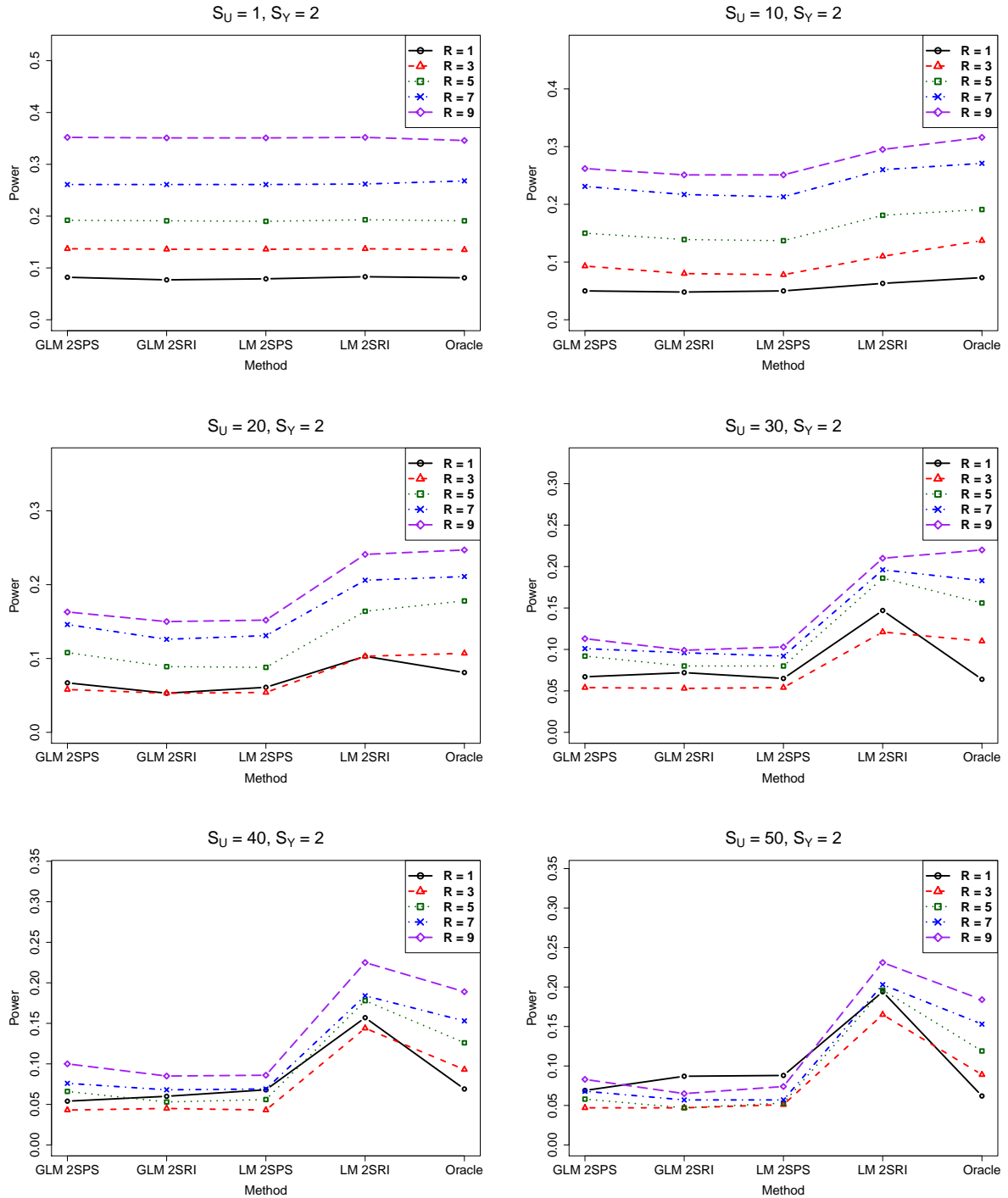


Figure S48: Simulations with the one-sample approaches: empirical power of various methods,  $S_Y = 3$ .

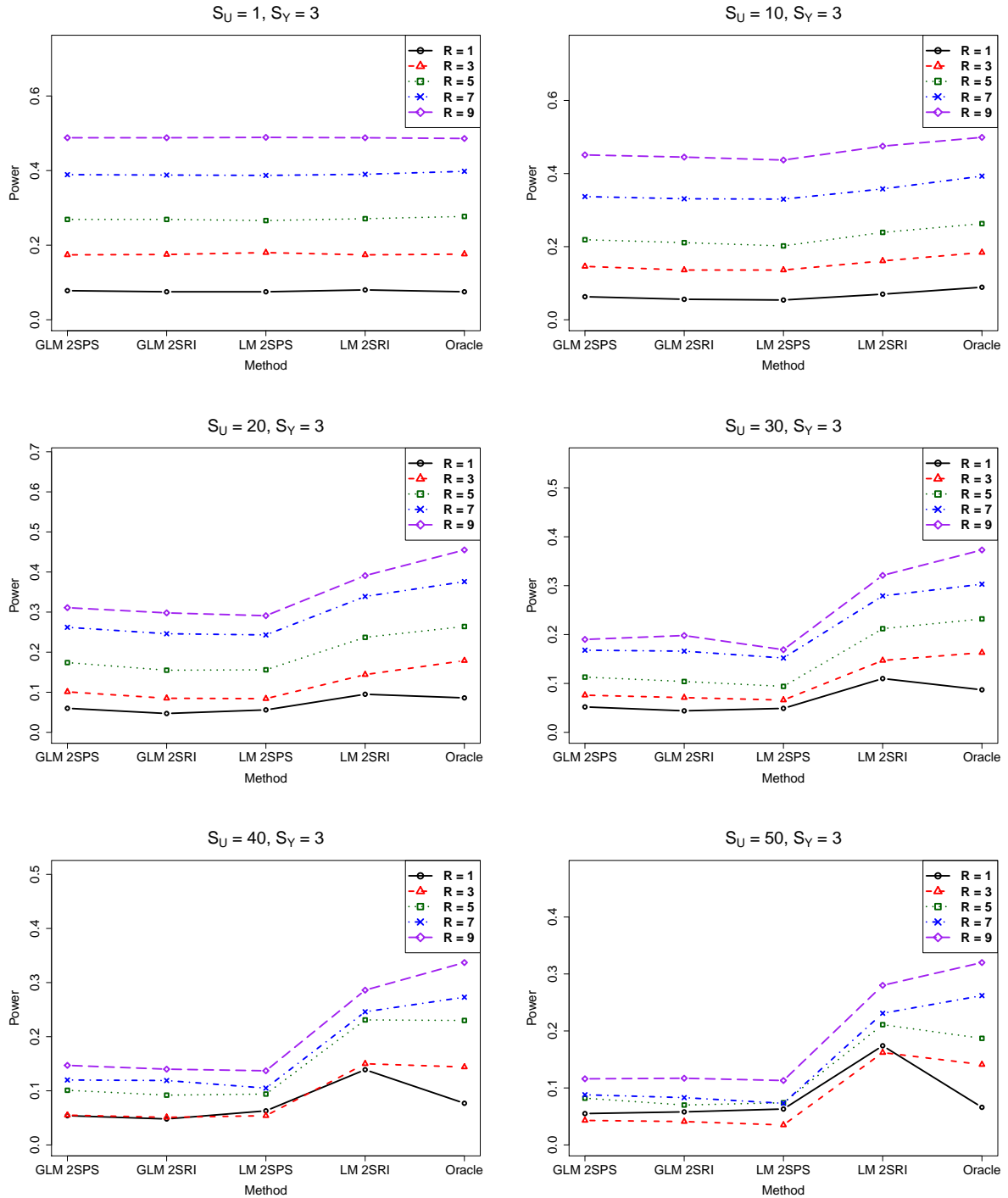


Figure S49: Simulations with the one-sample approaches: empirical power of various methods,  $S_Y = 4$ .

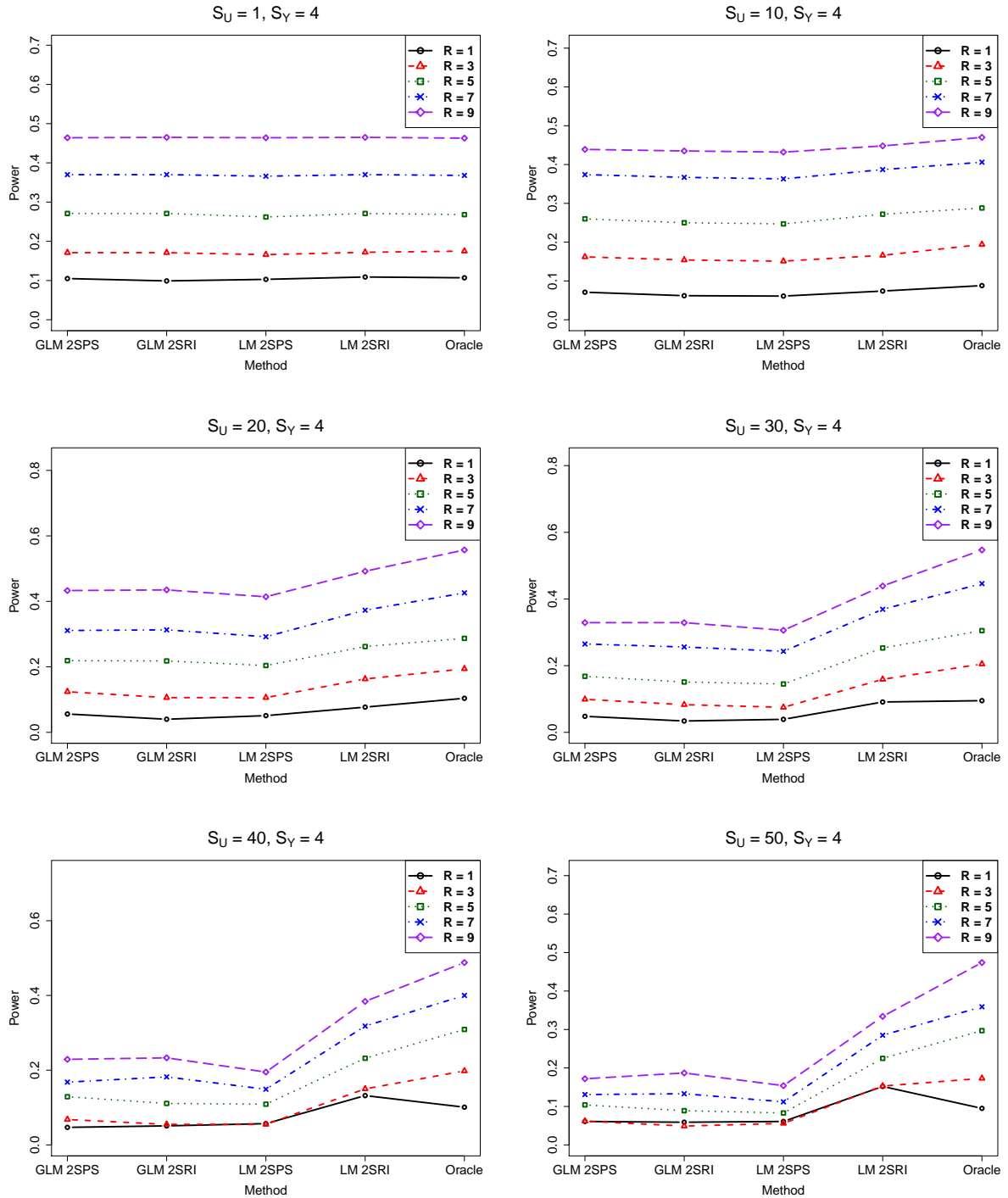
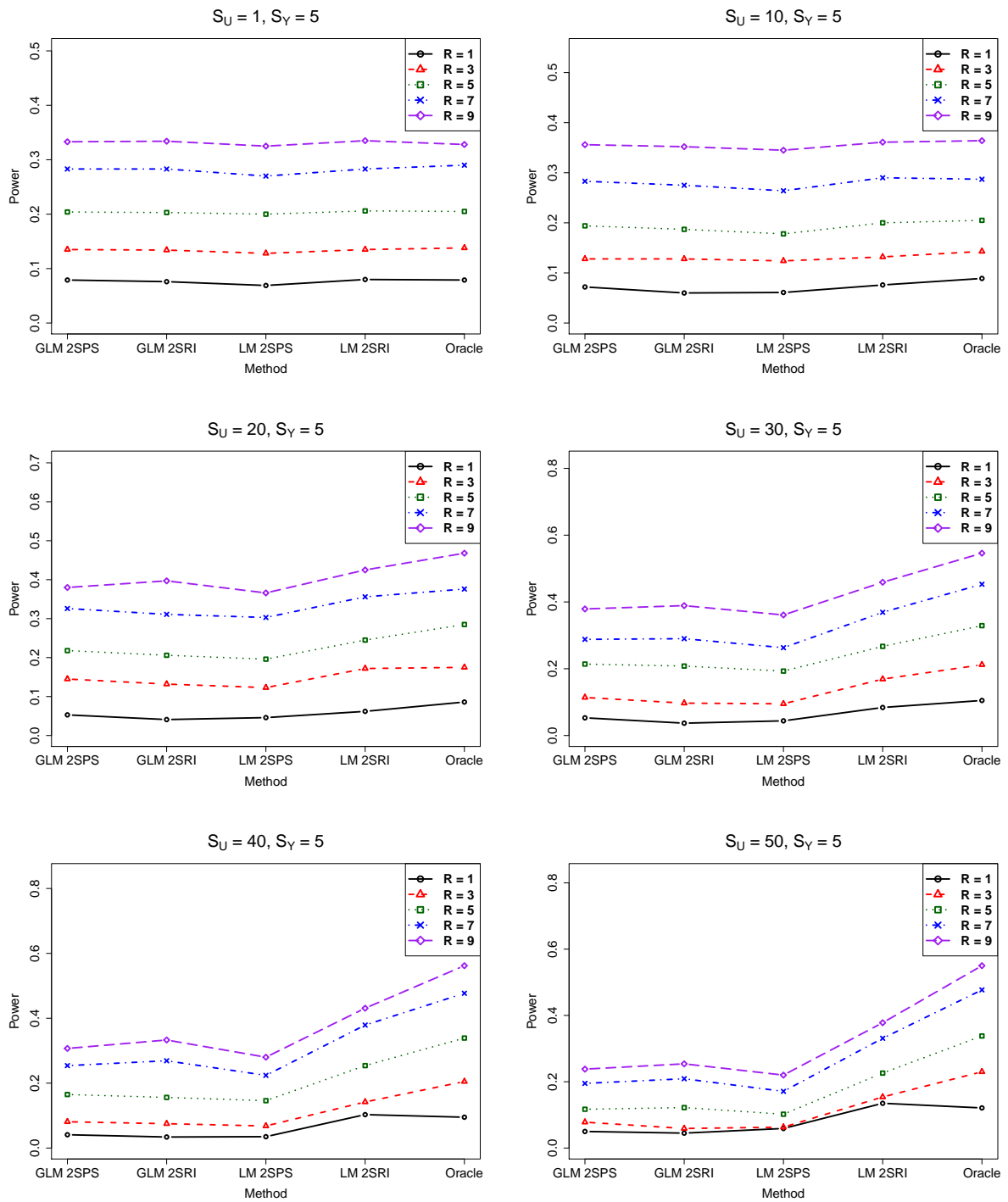




Figure S50: Simulations with the one-sample approaches: empirical power of various methods,  $S_Y = 5$ .



### 2.2.3 Bias

Figure S51: Simulations with the one-sample approaches: biases of various methods,  $S_Y = 0$

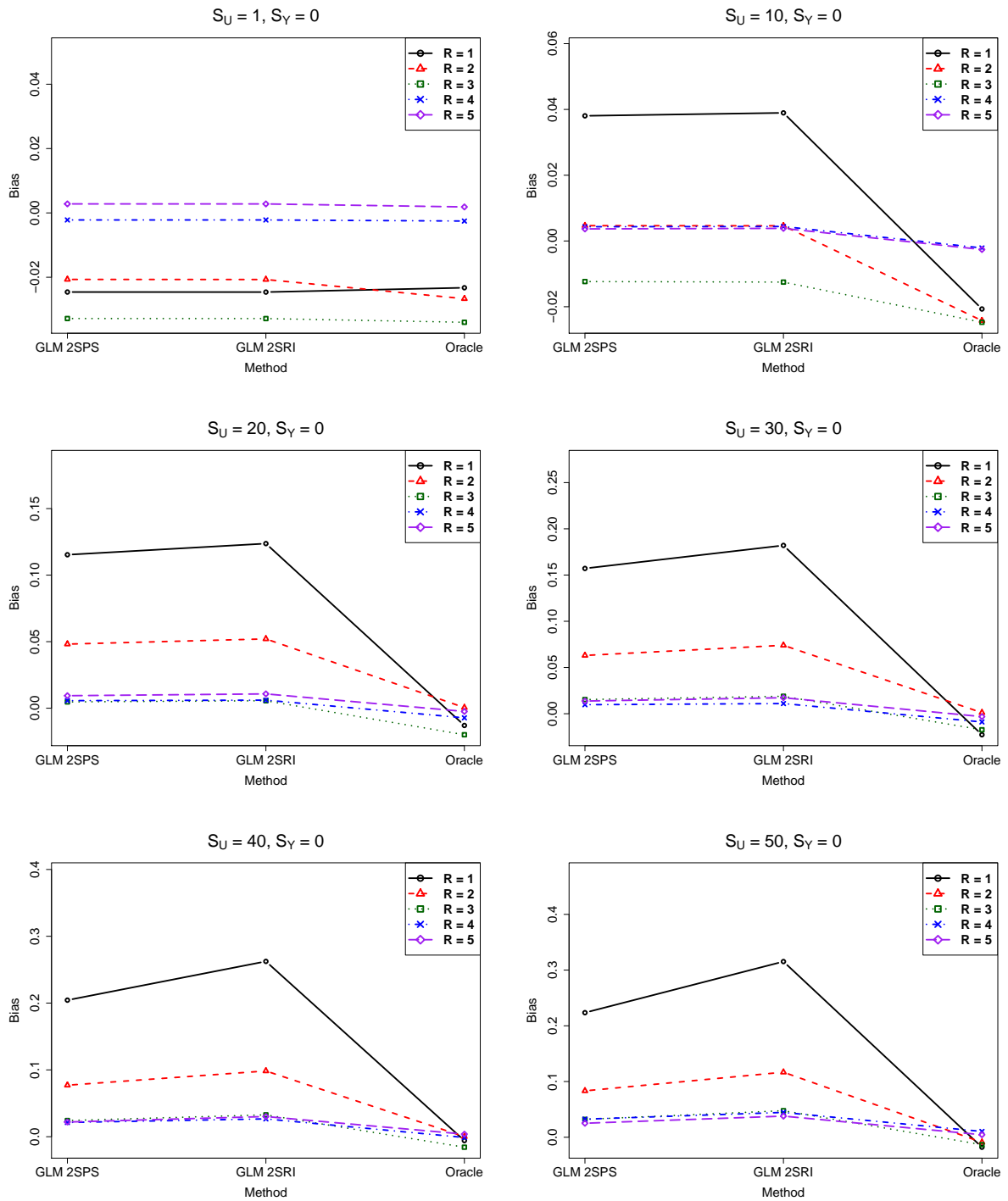


Figure S52: Simulations with the one-sample approaches: biases of various methods,  $S_Y = 1$

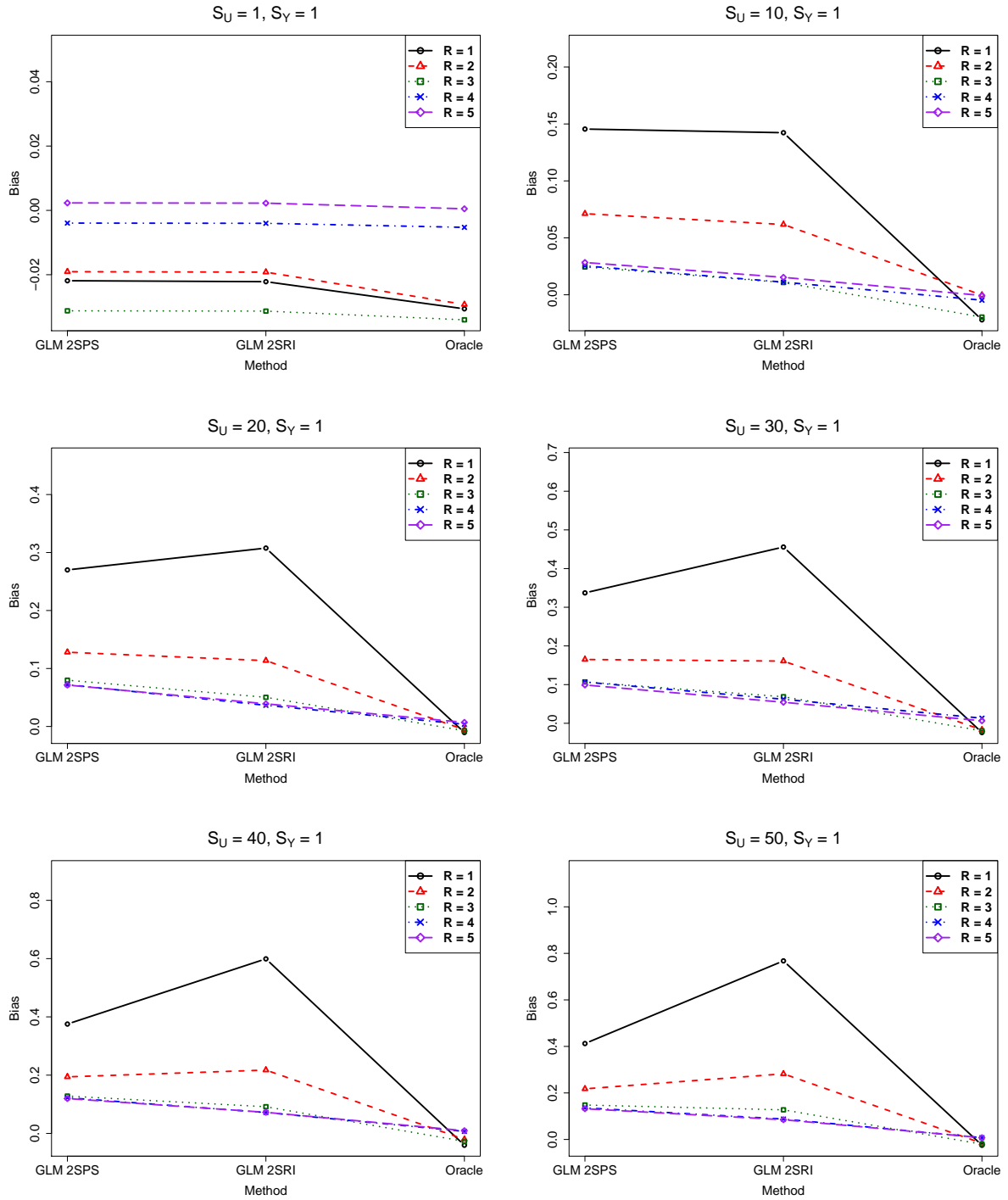


Figure S53: Simulations with the one-sample approaches: biases of various methods,  $S_Y = 2$

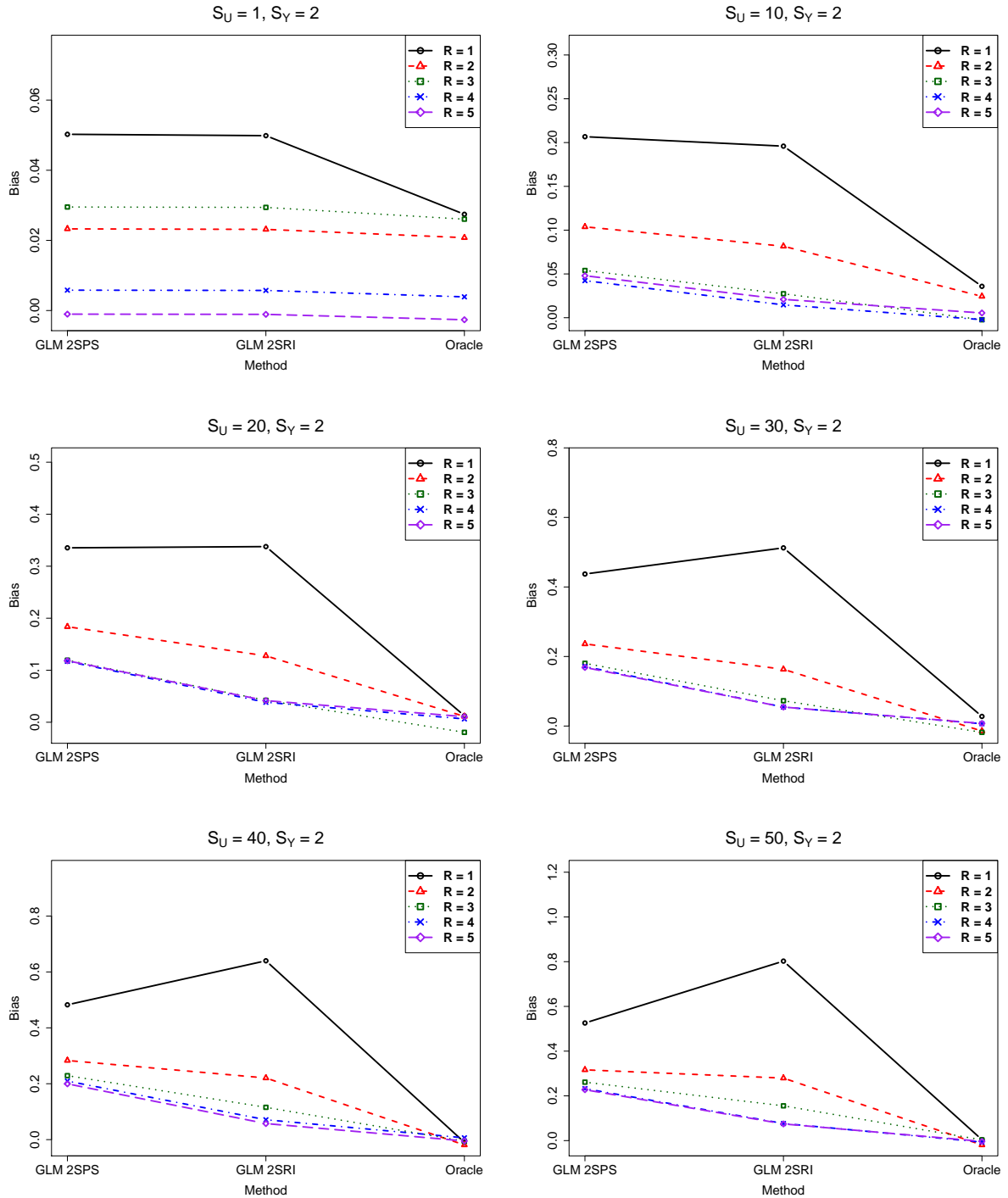


Figure S54: Simulations with the one-sample approaches: biases of various methods,  $S_Y = 3$

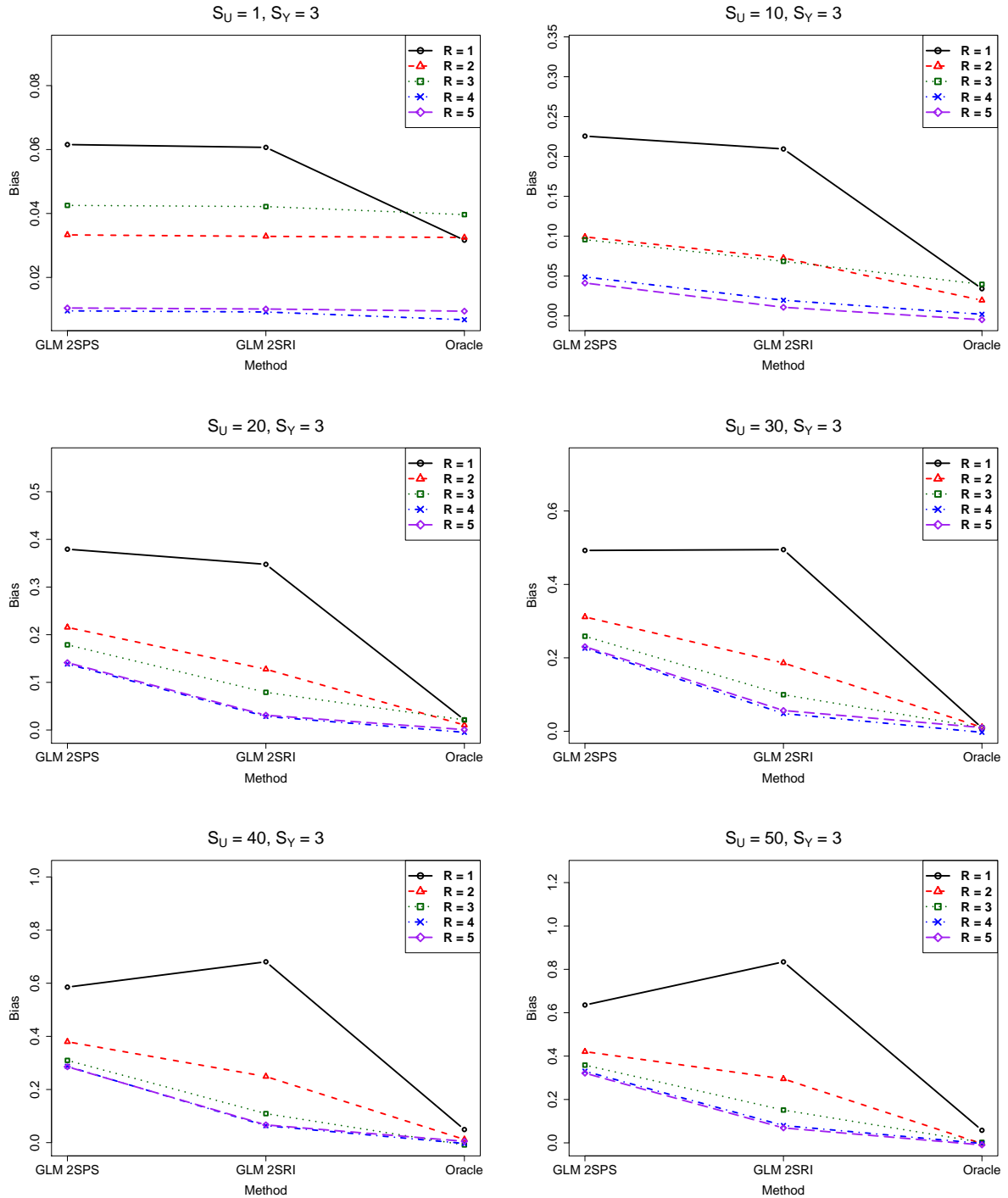


Figure S55: Simulations with the one-sample approaches: biases of various methods,  $S_Y = 4$

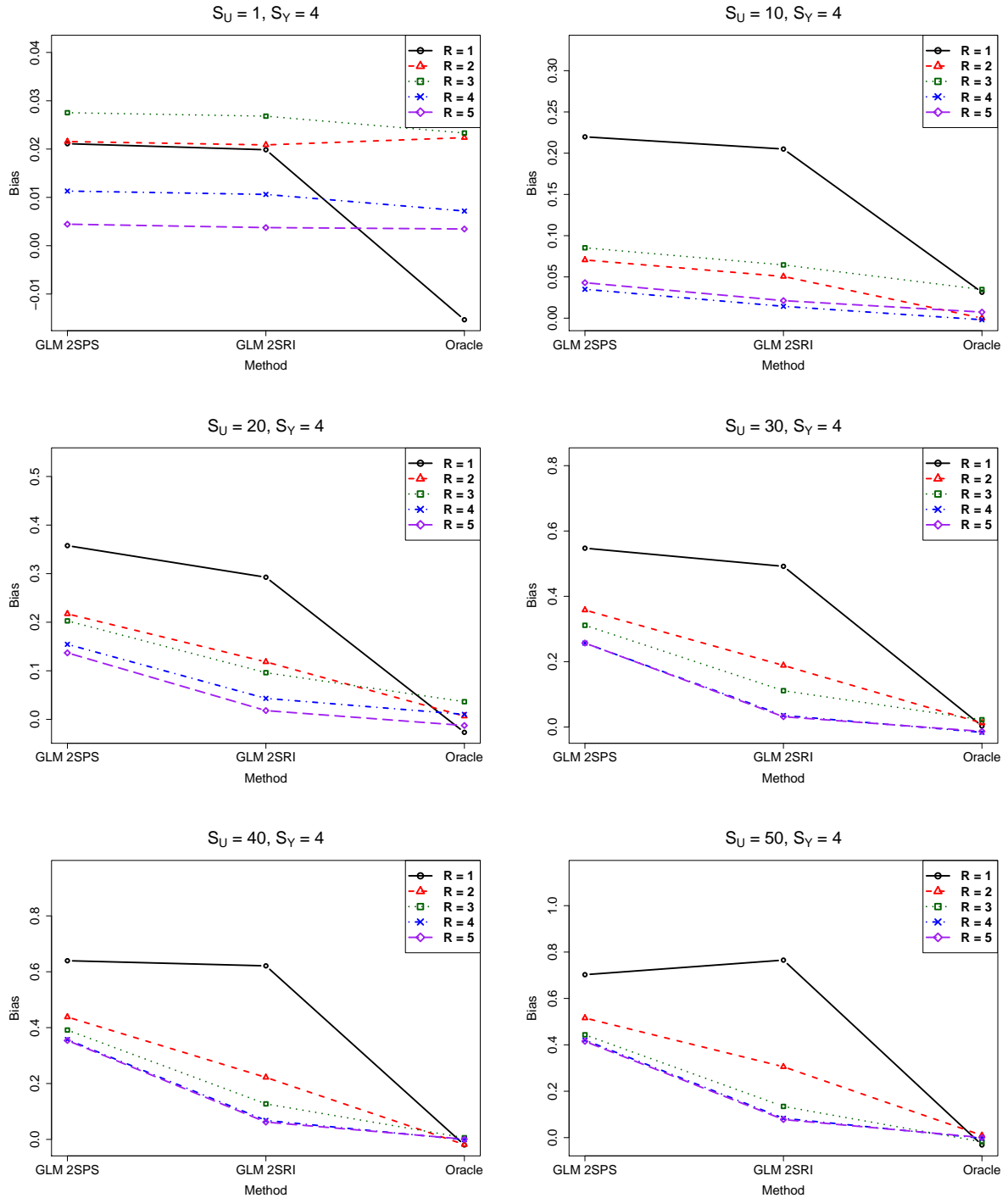
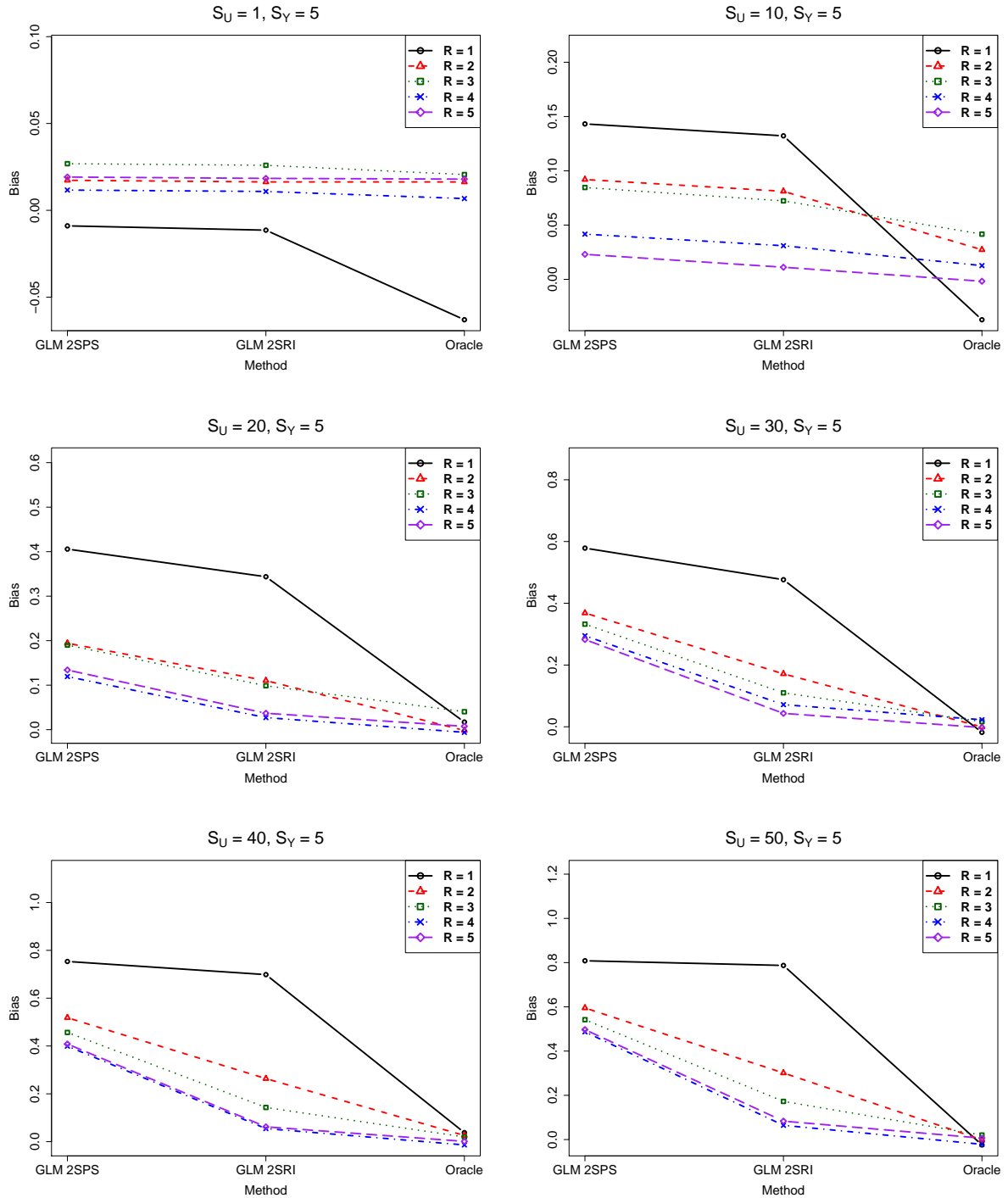


Figure S56: Simulations with the one-sample approaches: biases of various methods,  $S_Y = 5$



## 2.2.4 Comparison of the original and corrected standard error estimates

Figure S57: Simulations with the one-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 0, R = 1$ .

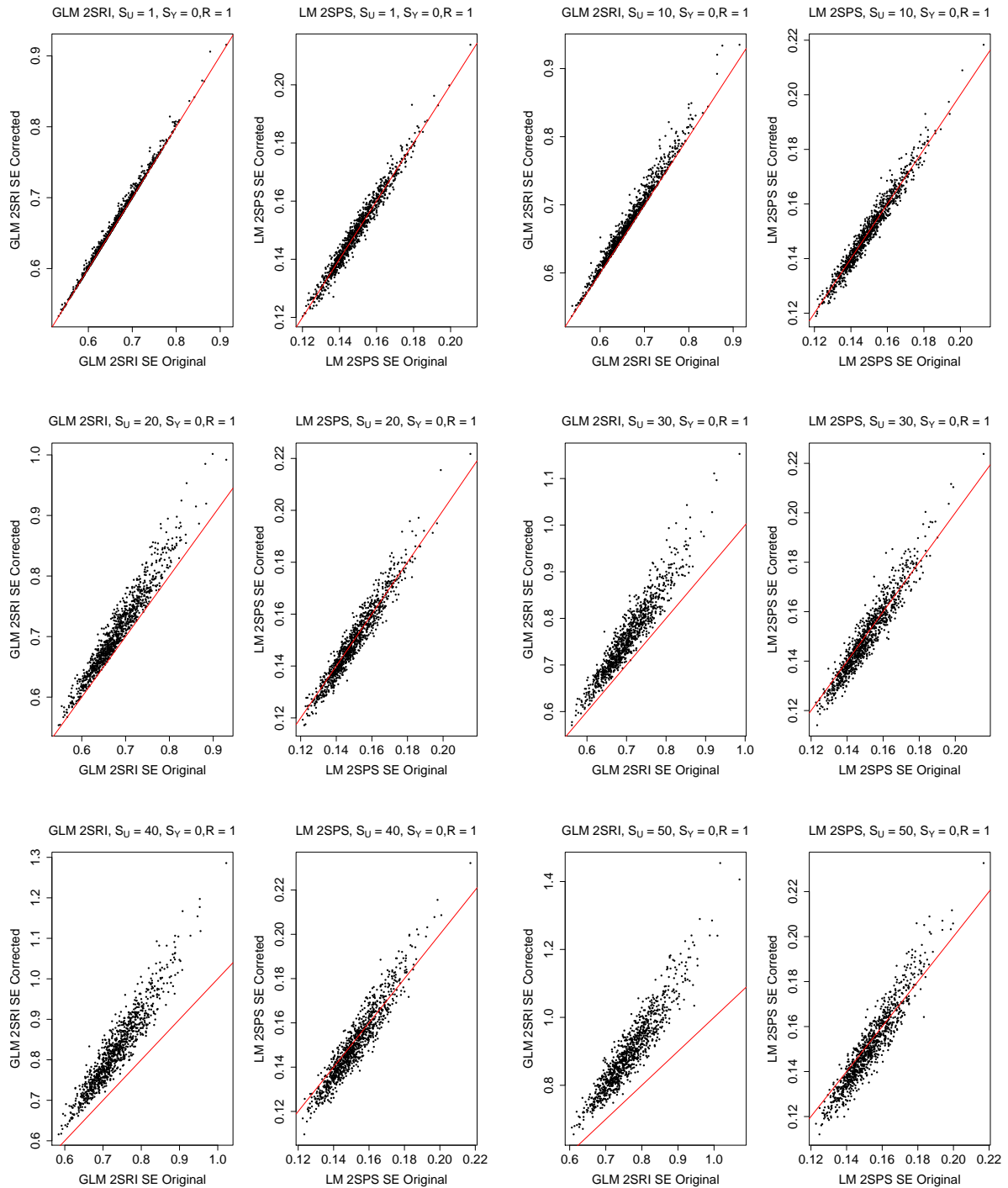




Figure S58: Simulations with the one-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 1, R = 1$ .

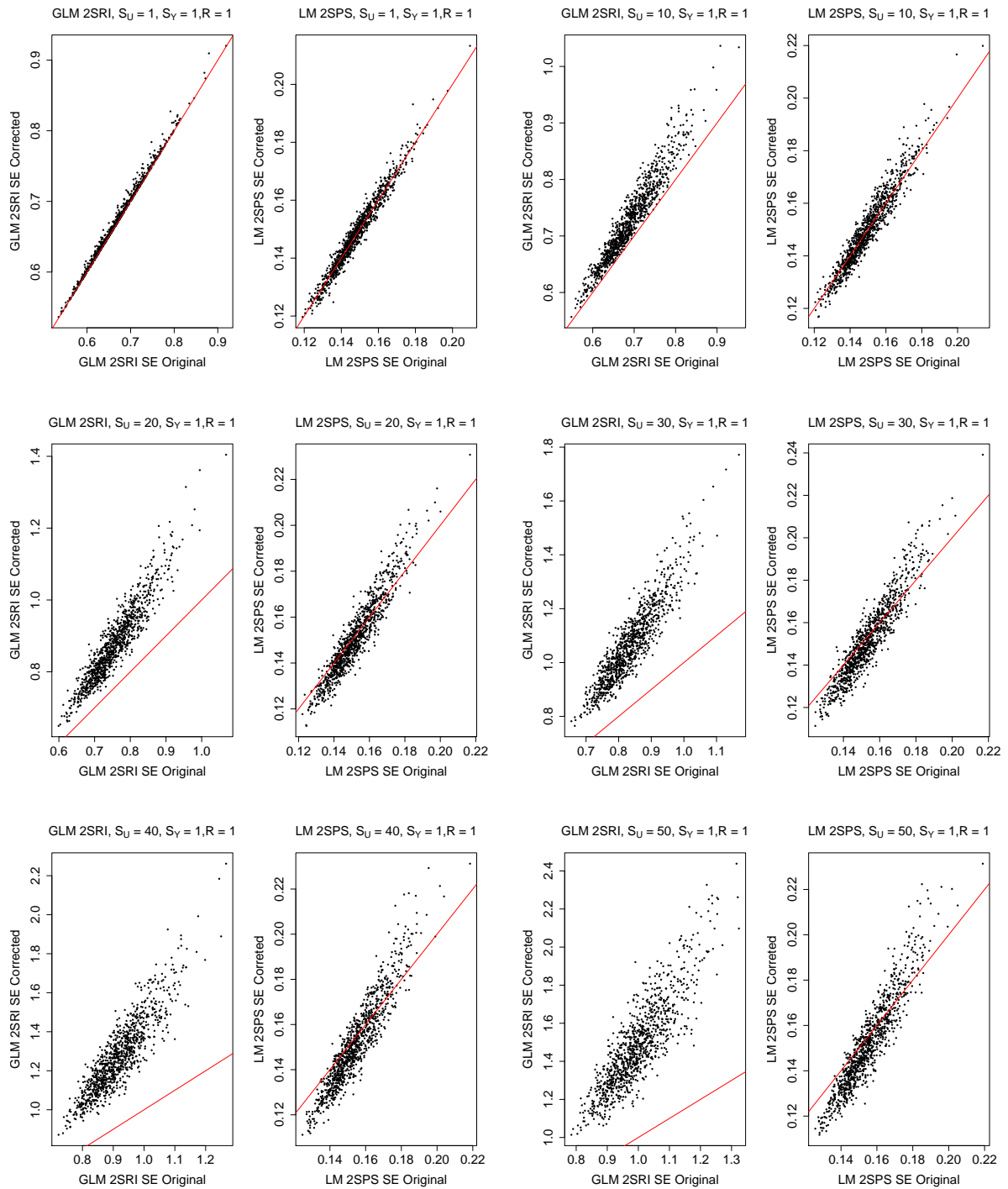


Figure S59: Simulations with the one-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 2, R = 1$ .

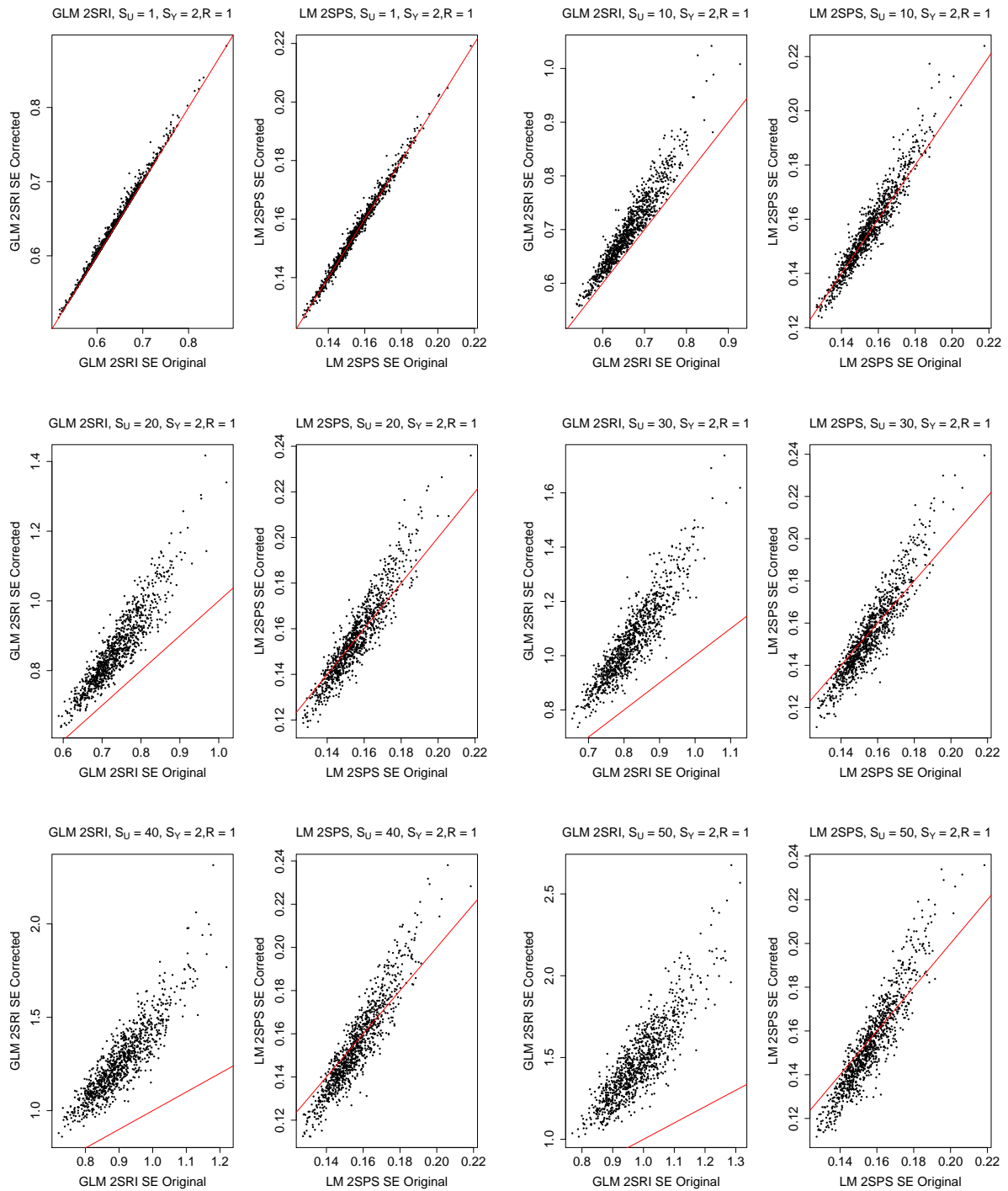


Figure S60: Simulations with the one-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 3, R = 1$ .

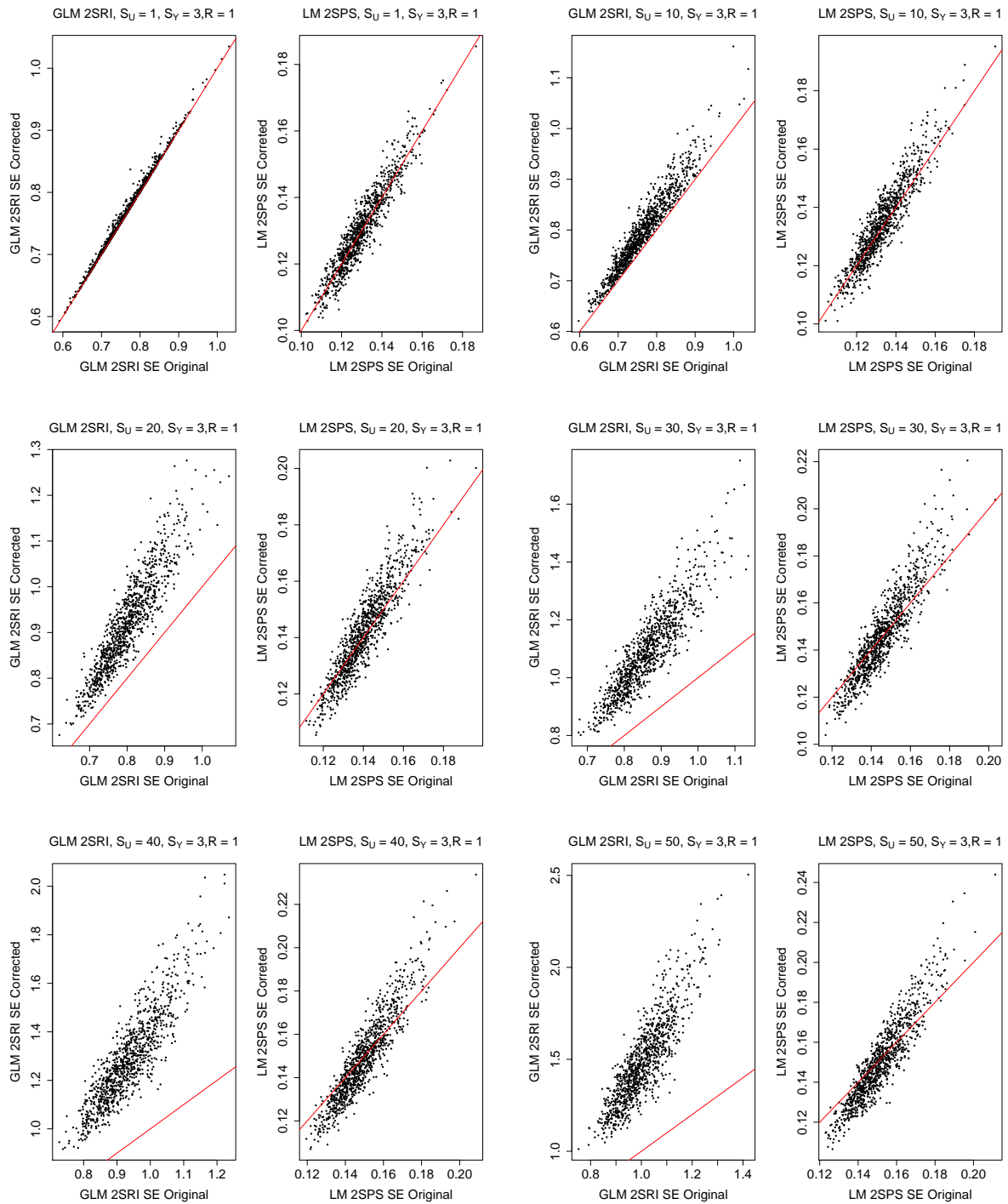


Figure S61: Simulations with the one-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 4, R = 1$ .

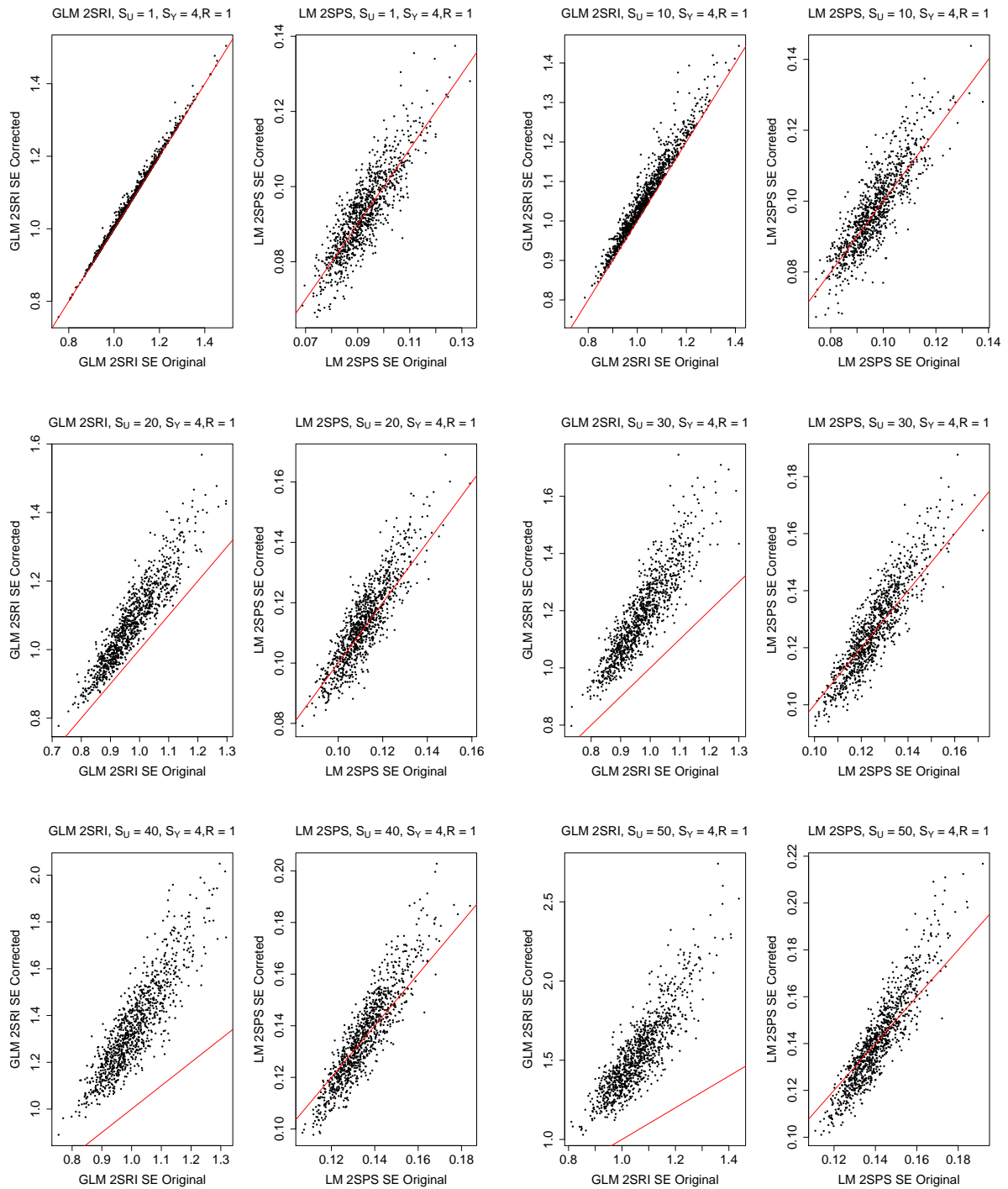


Figure S62: Simulations with the one-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 5, R = 1$ .

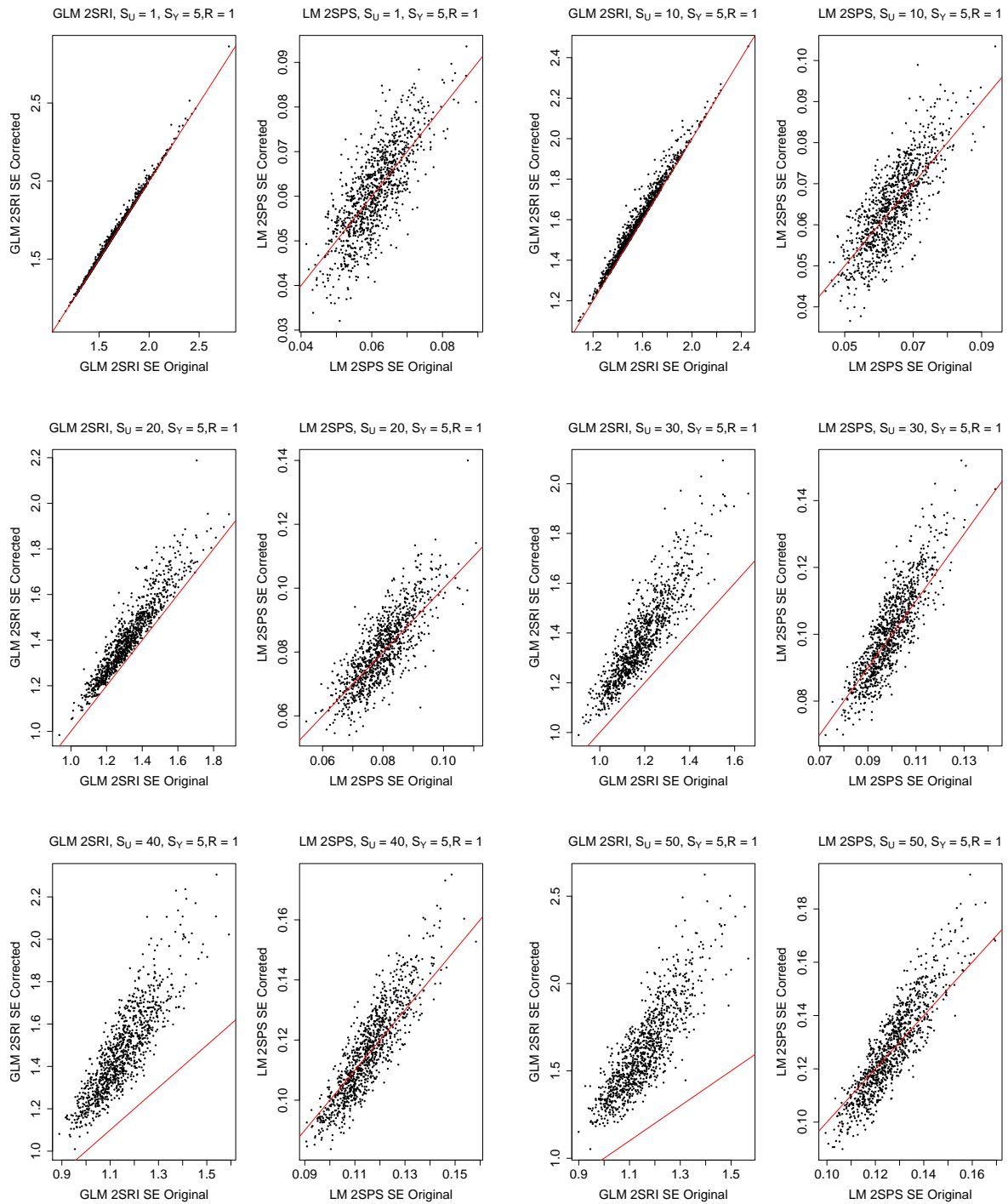


Figure S63: Simulations with the one-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 0, R = 3$ .

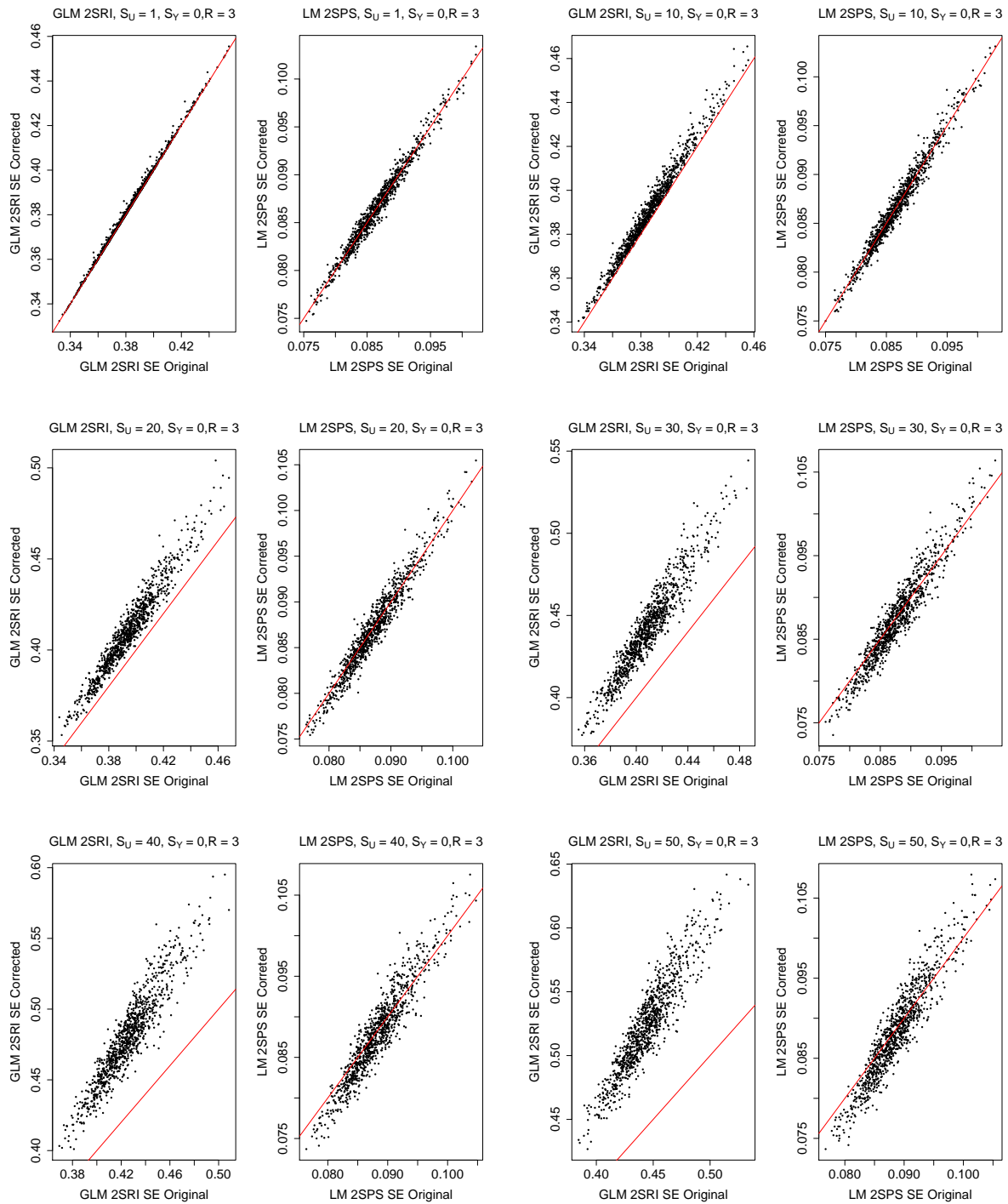


Figure S64: Simulations with the one-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 1, R = 3$ .

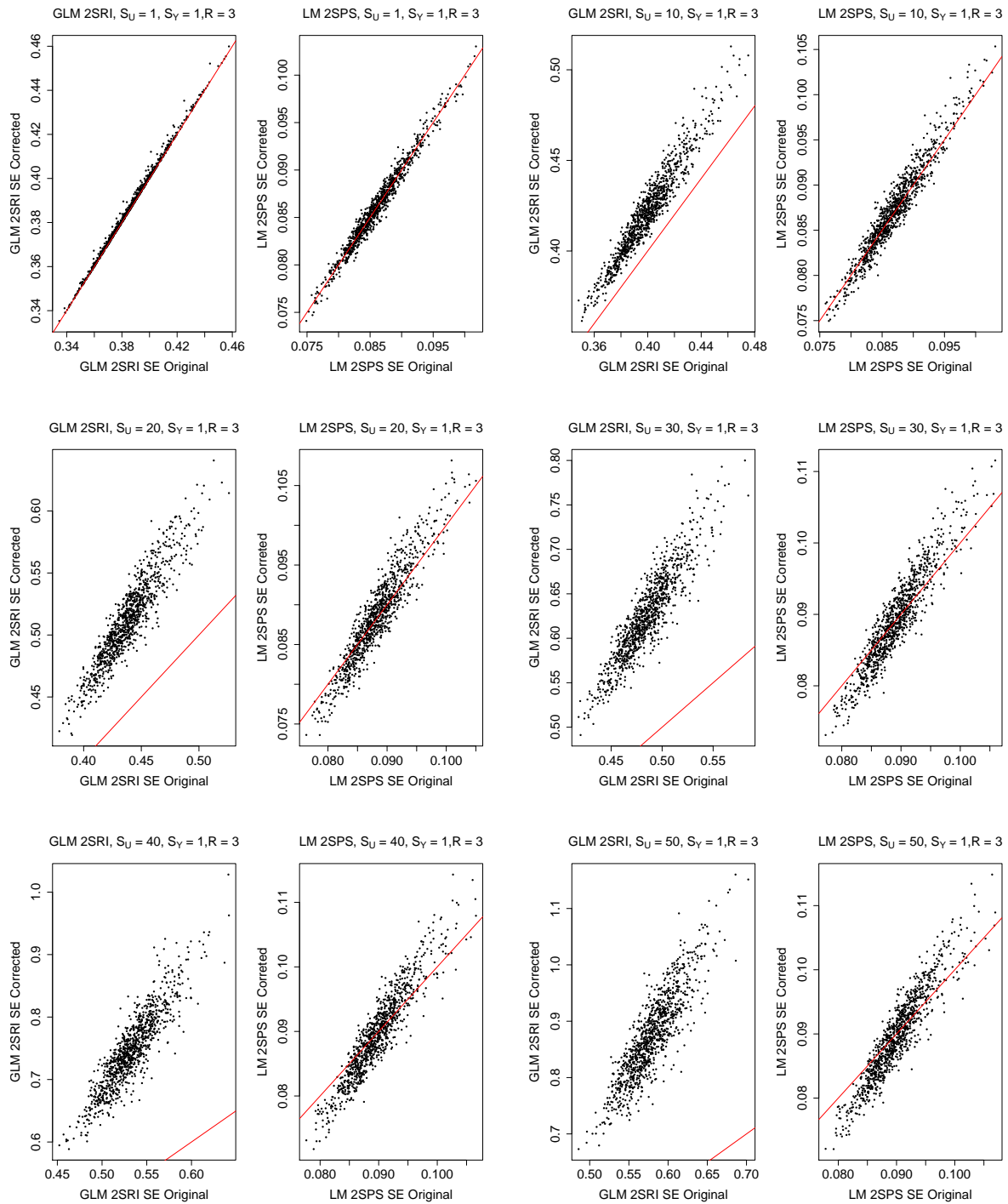


Figure S65: Simulations with the one-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 2, R = 3$ .

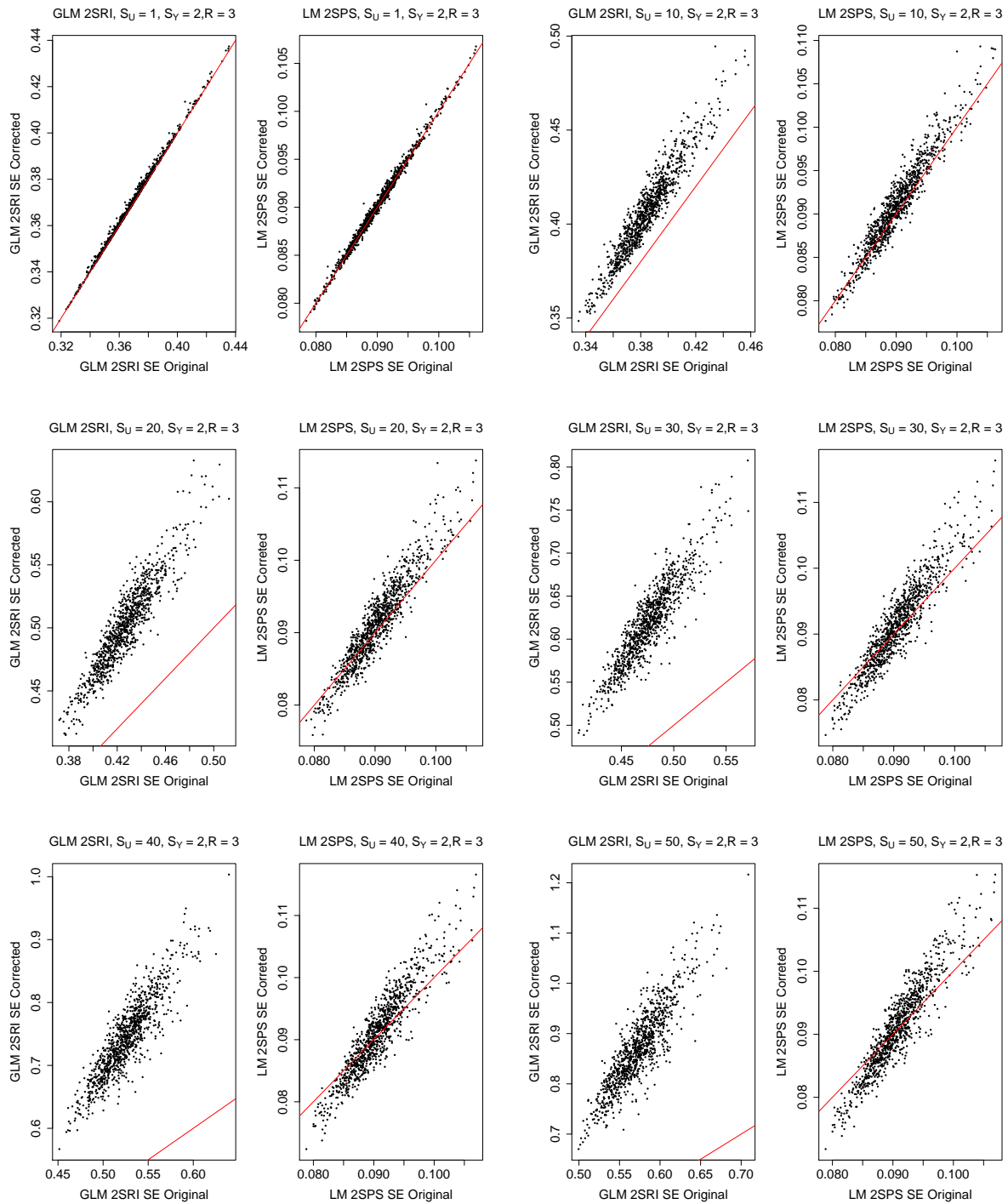




Figure S66: Simulations with the one-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 3, R = 3$ .

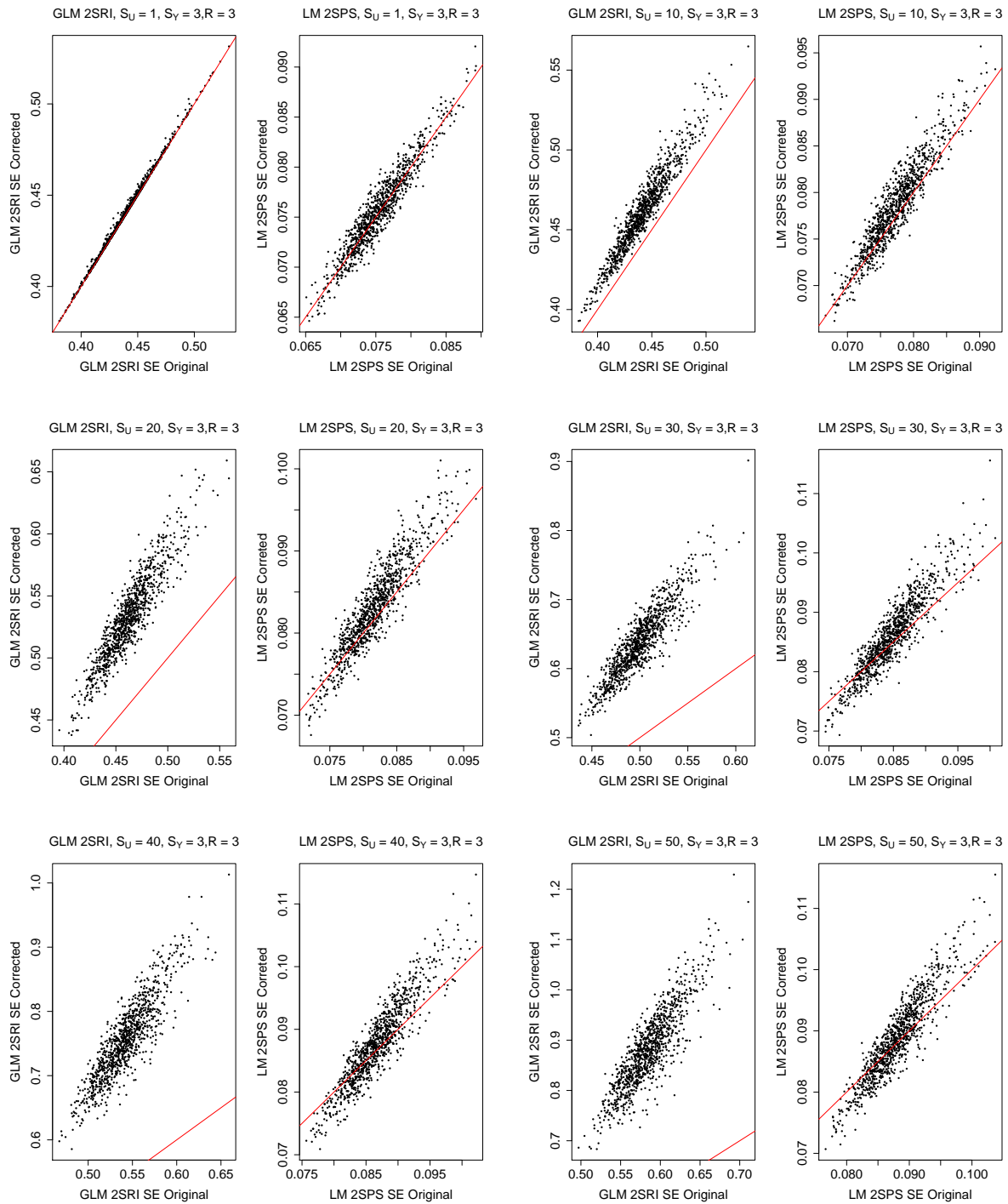


Figure S67: Simulations with the one-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 4, R = 3$ .

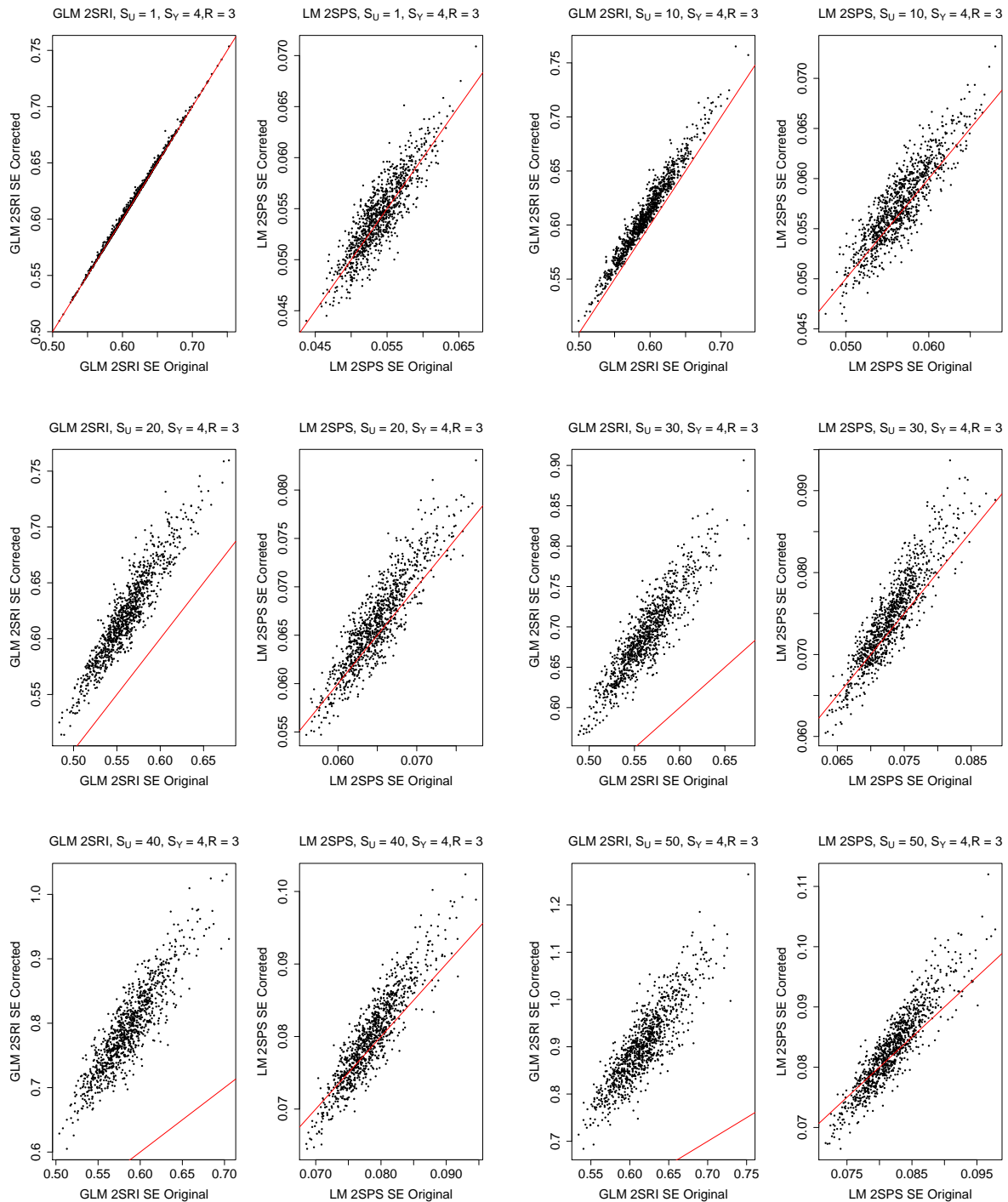


Figure S68: Simulations with the one-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 5, R = 3$ .

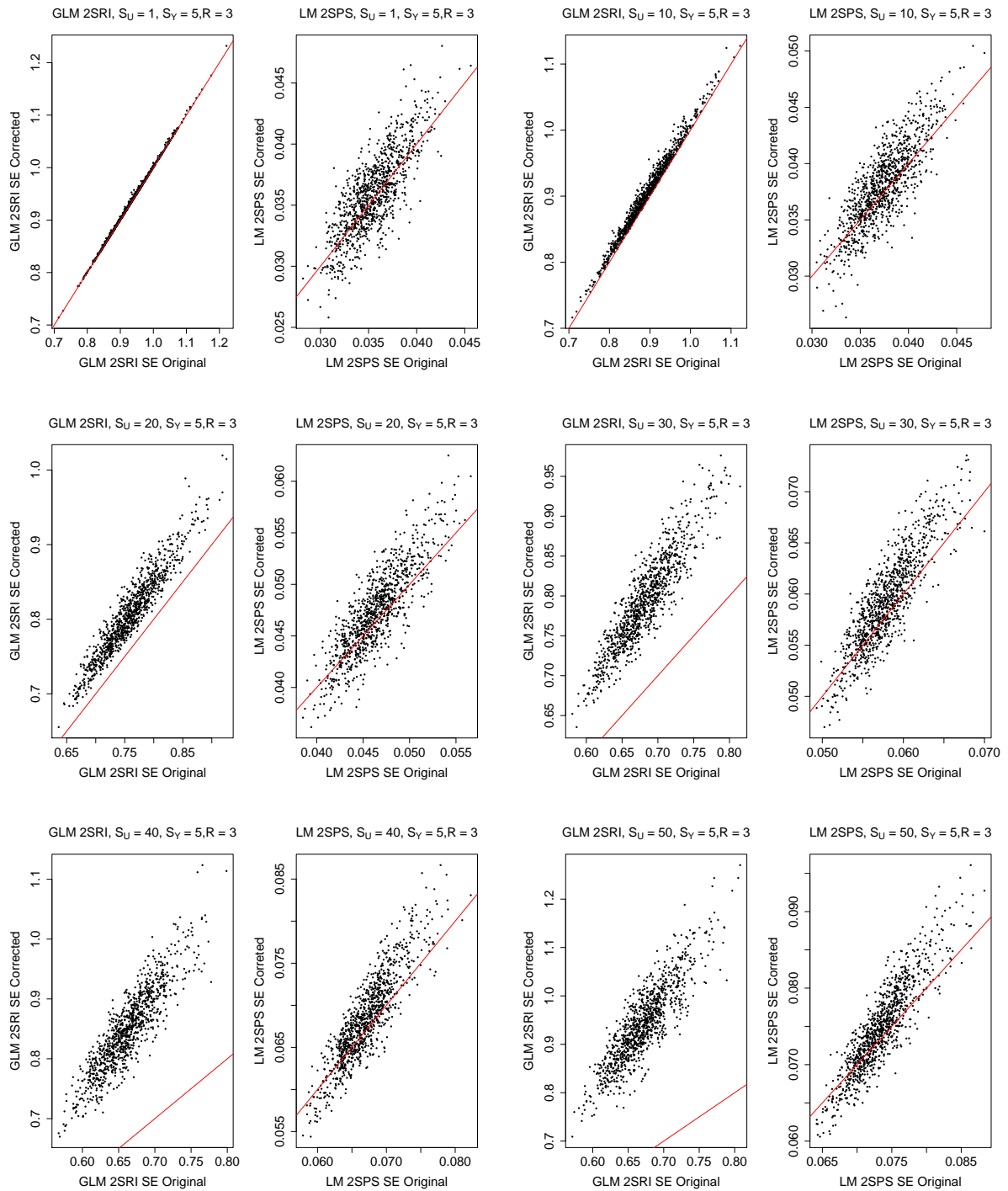


Figure S69: Simulations with the one-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 0, R = 5$ .

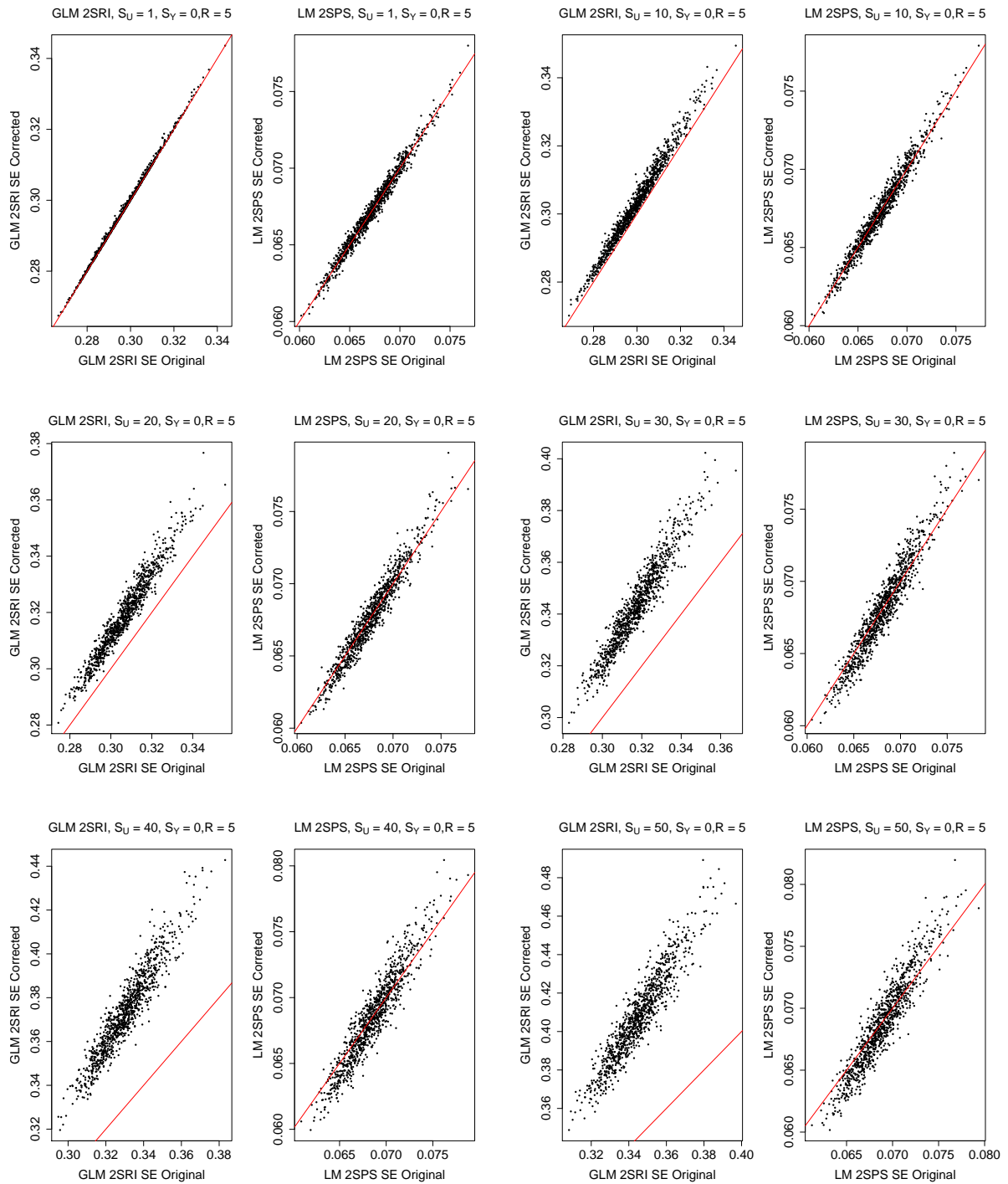


Figure S70: Simulations with the one-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 1, R = 5$ .

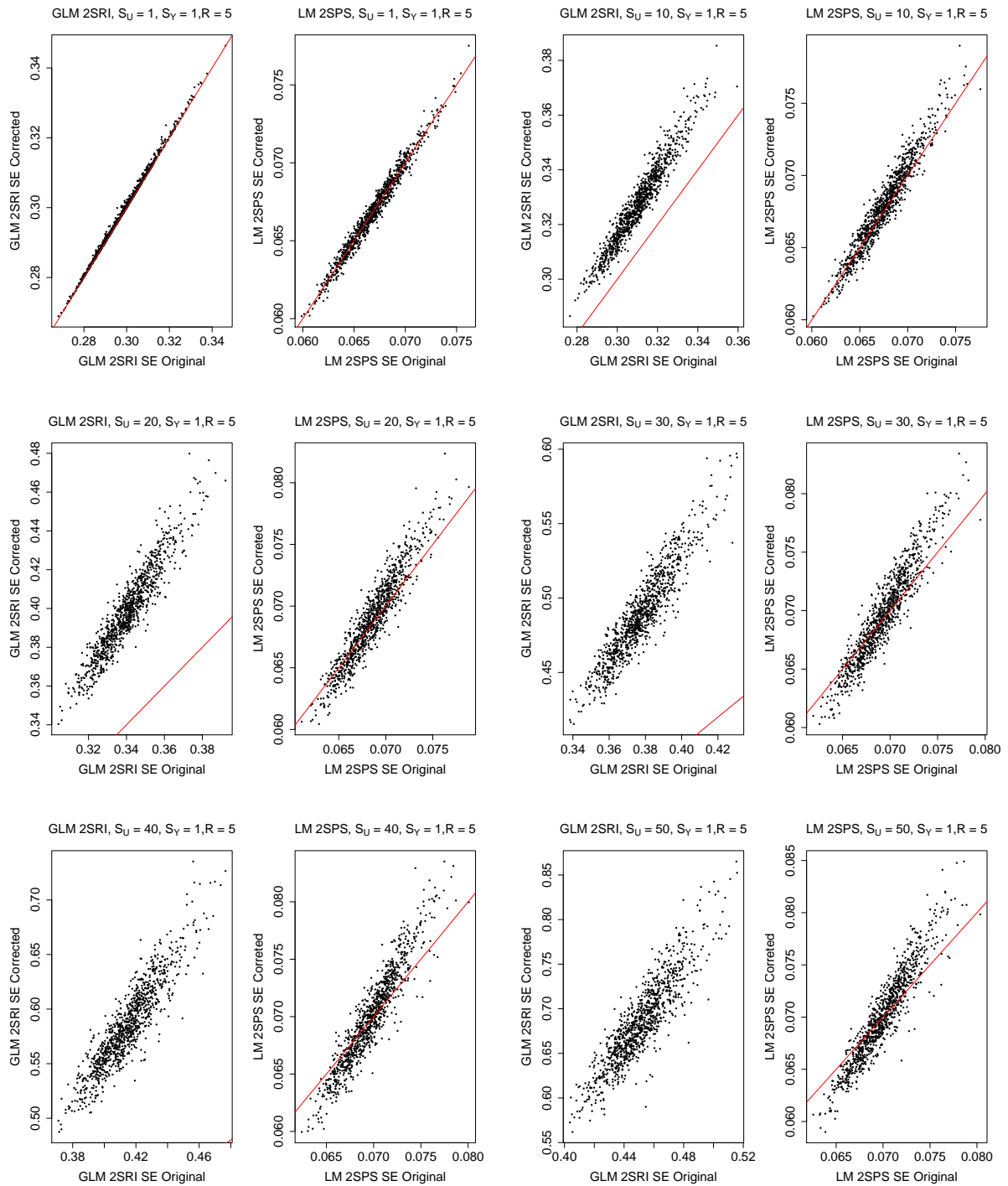


Figure S71: Simulations with the one-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 2, R = 5$ .

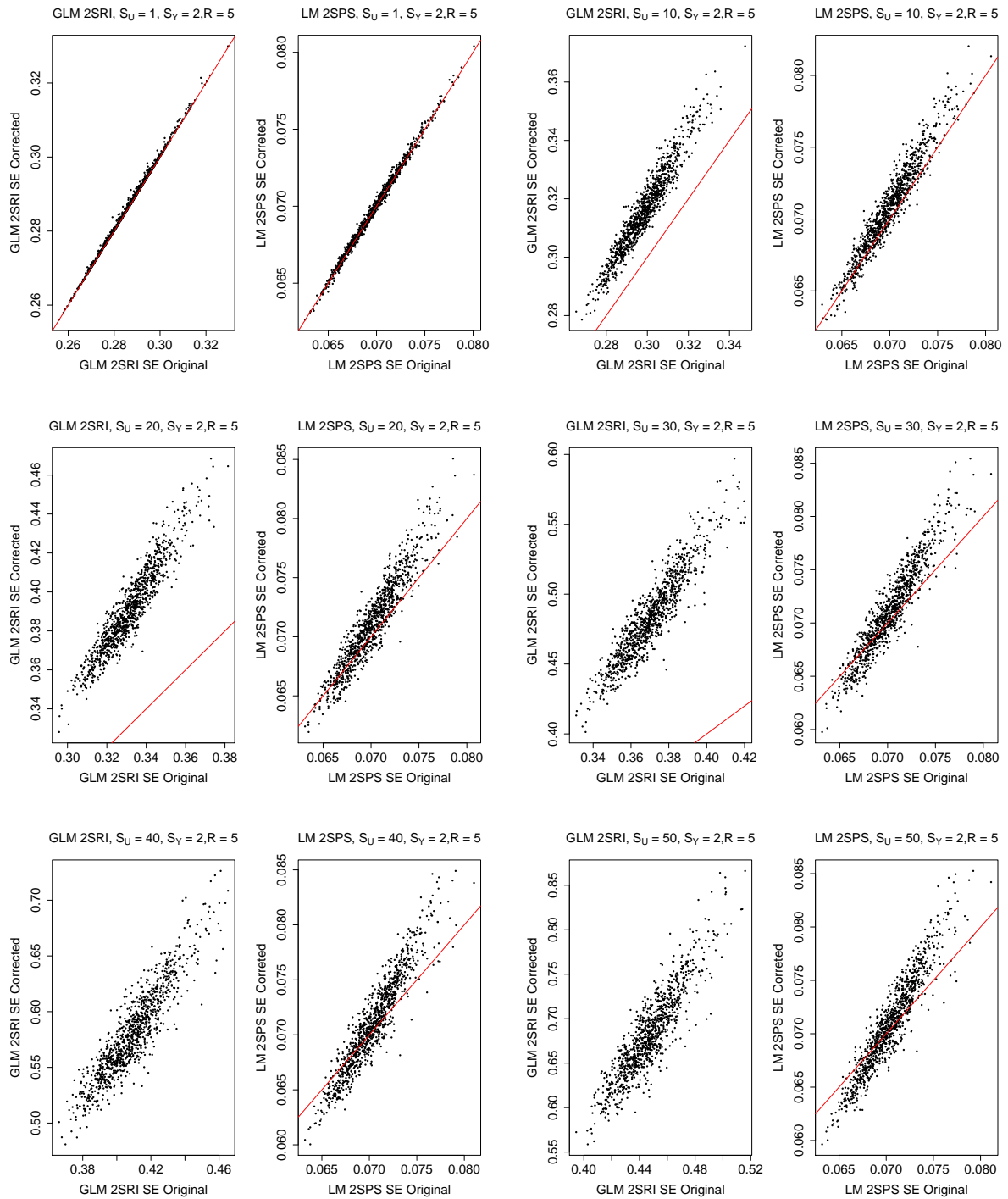


Figure S72: Simulations with the one-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 3, R = 5$ .

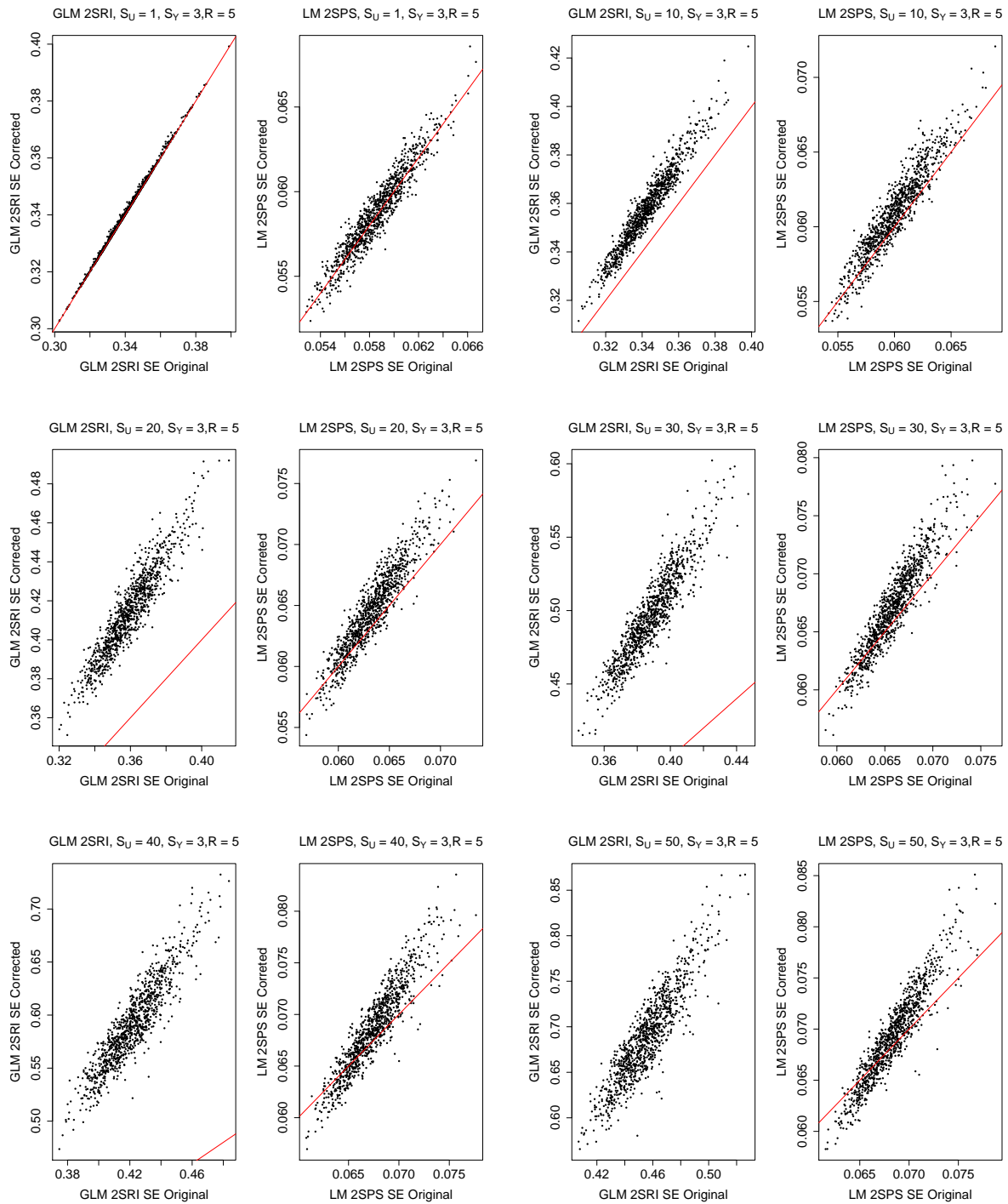


Figure S73: Simulations with the one-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 4, R = 5$ .

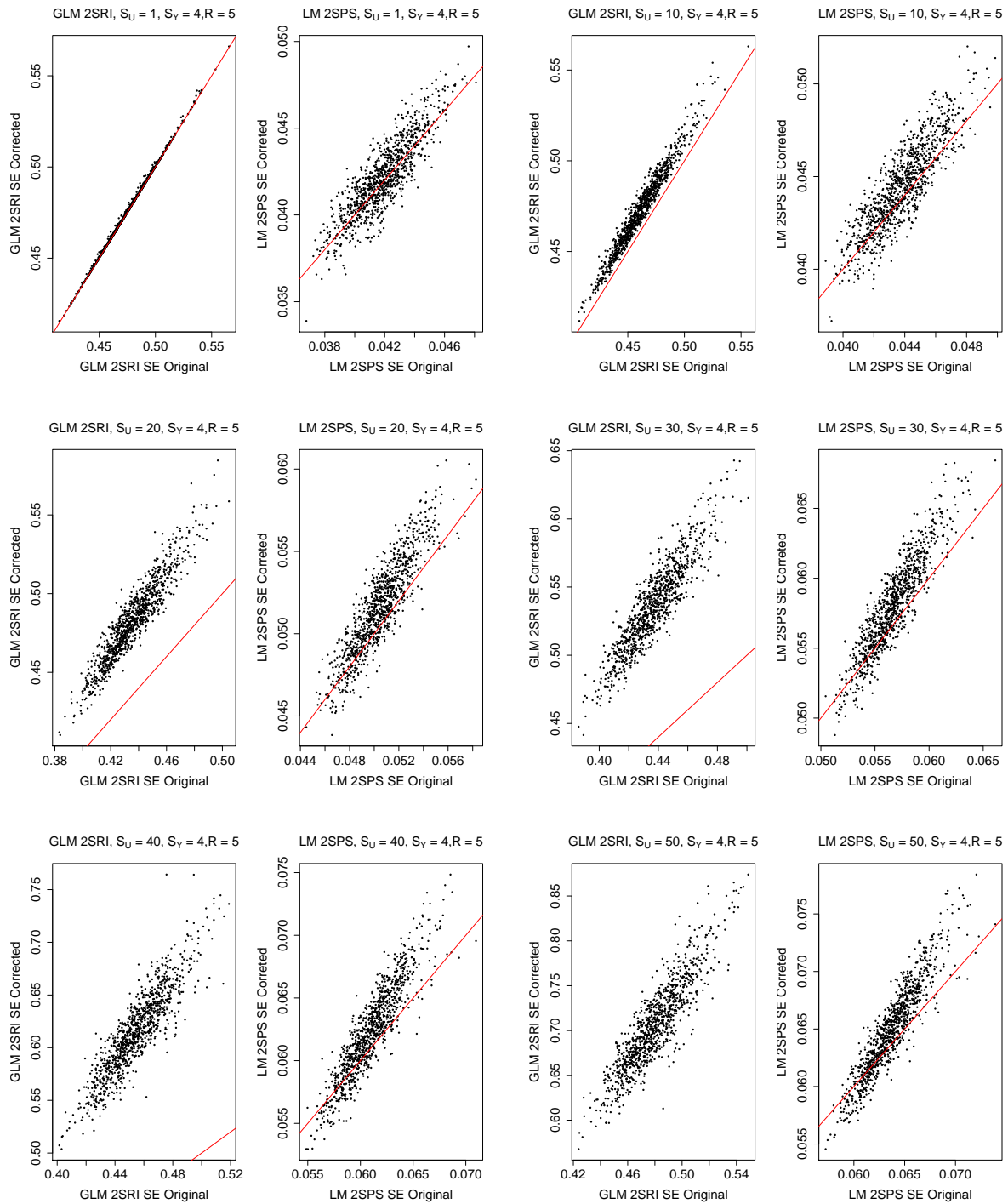




Figure S74: Simulations with the one-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 5, R = 5$ .

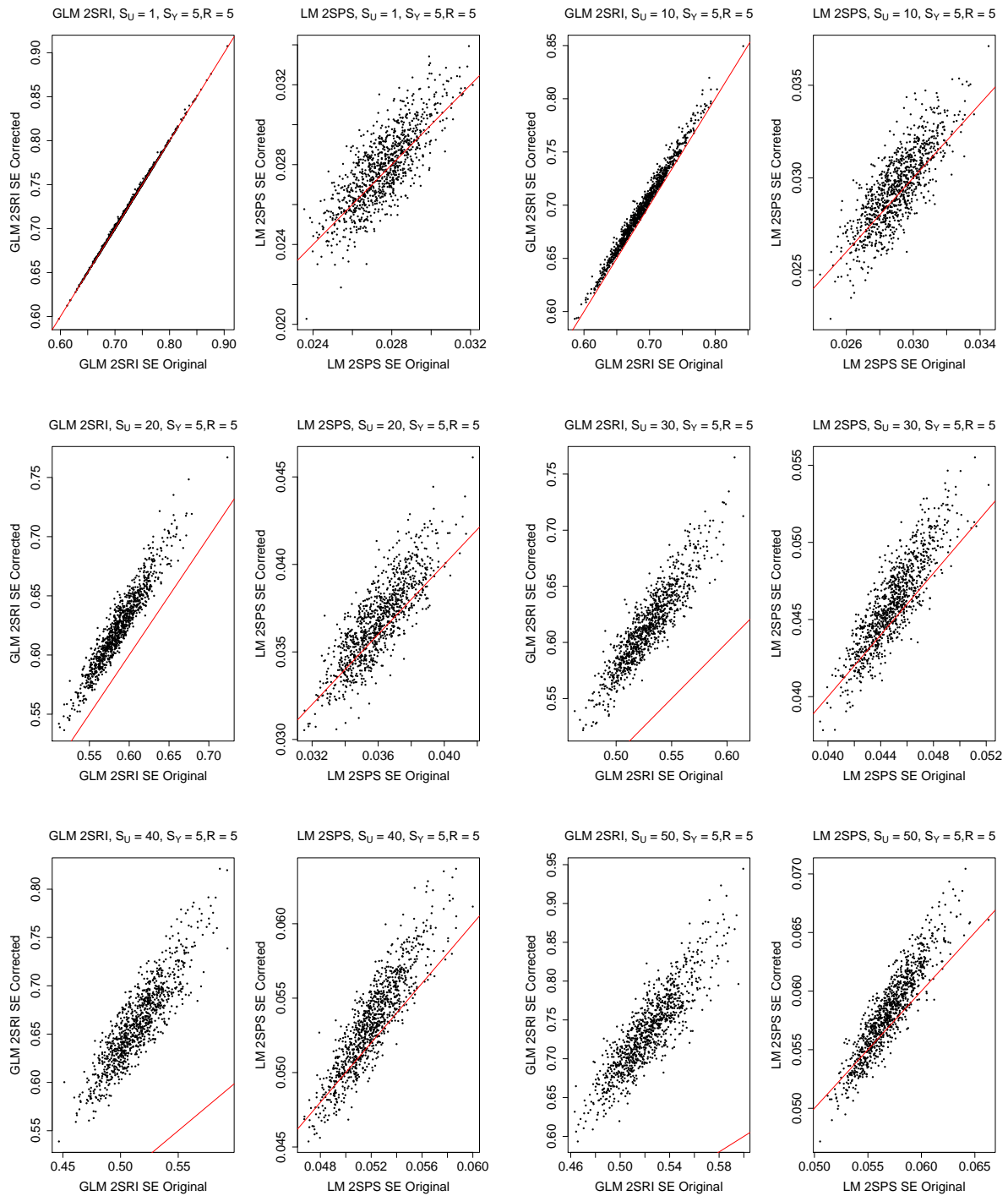


Figure S75: Simulations with the one-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 0, R = 7$ .

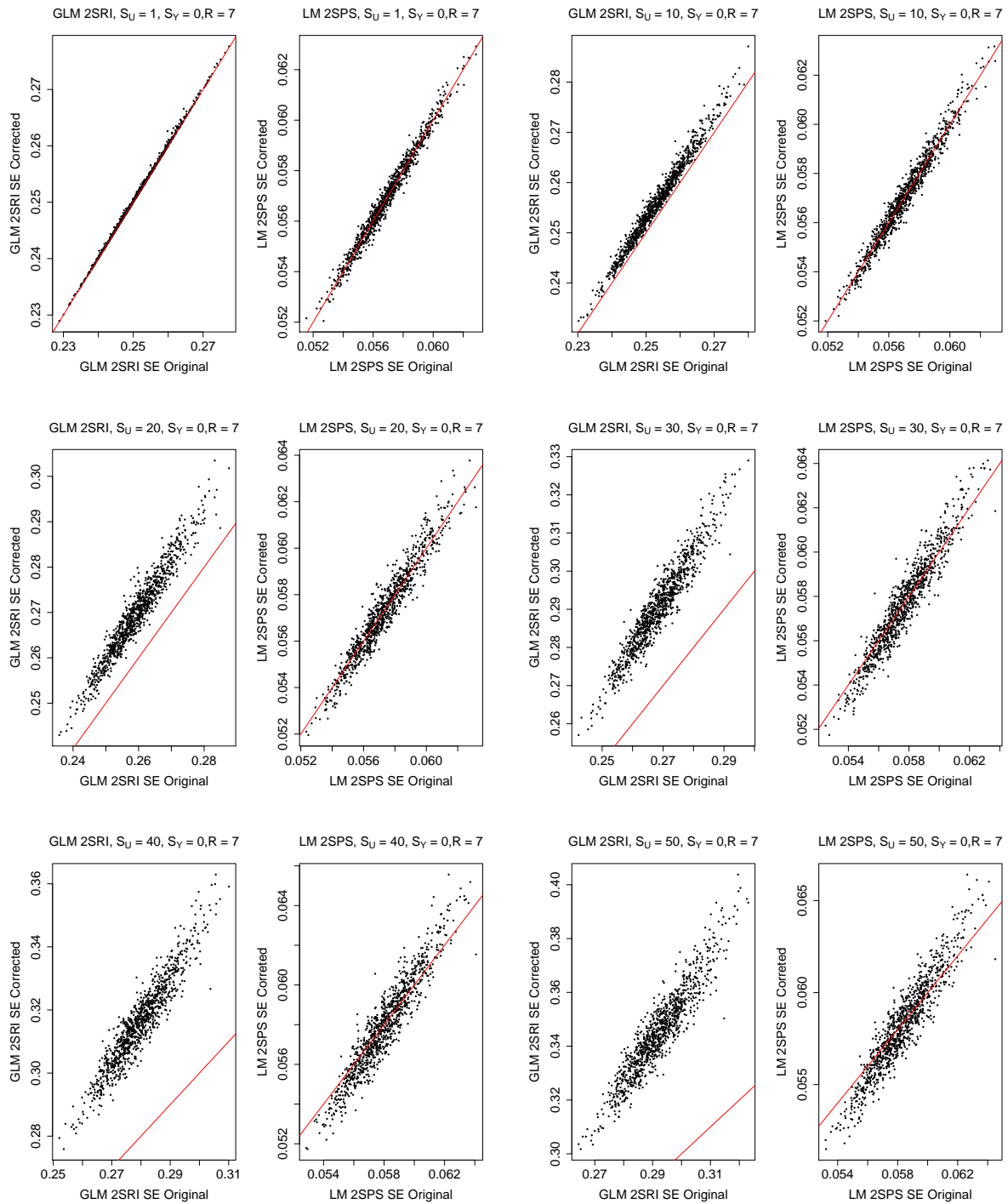


Figure S76: Simulations with the one-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 1, R = 7$ .

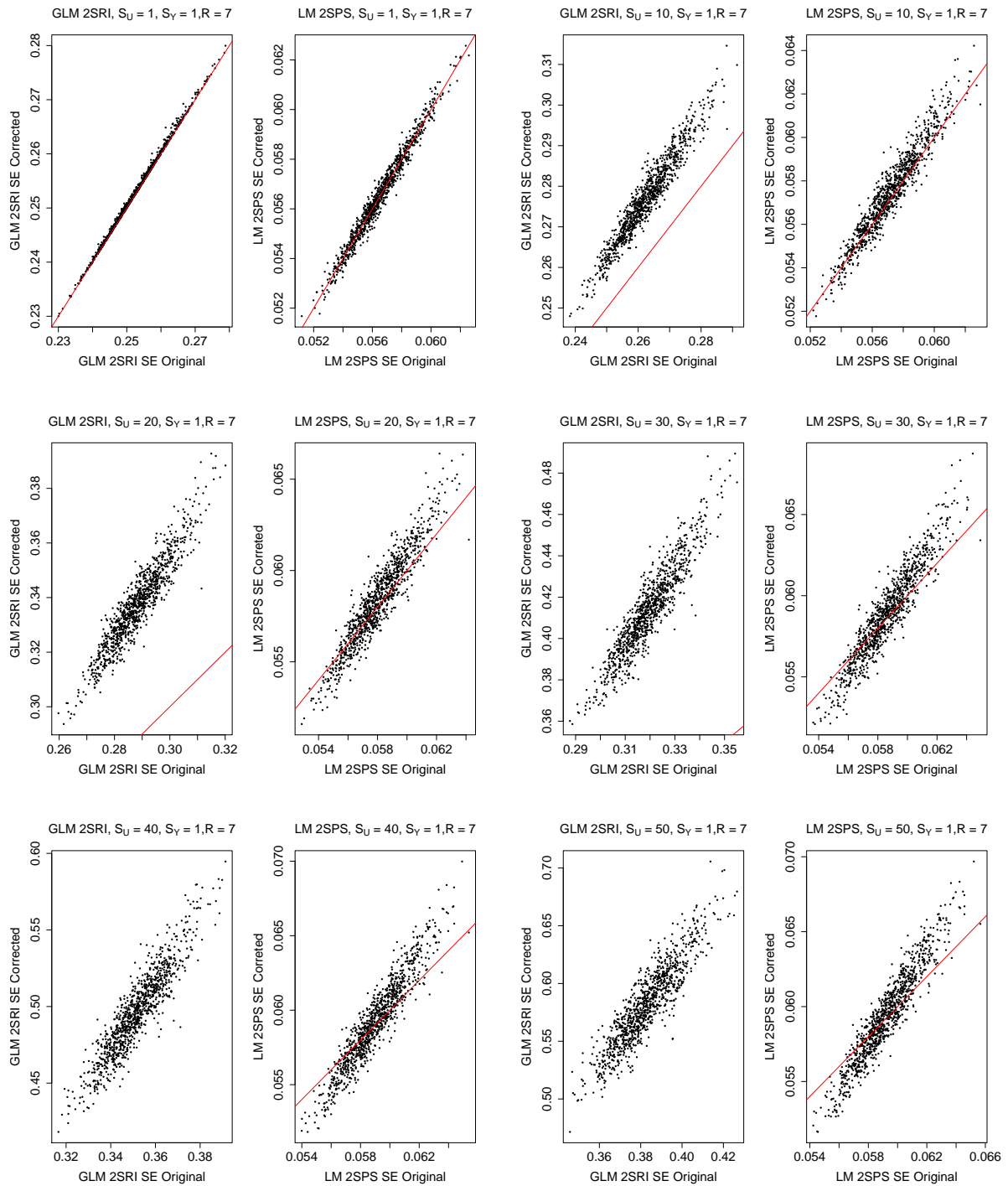


Figure S77: Simulations with the one-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 2, R = 7$ .

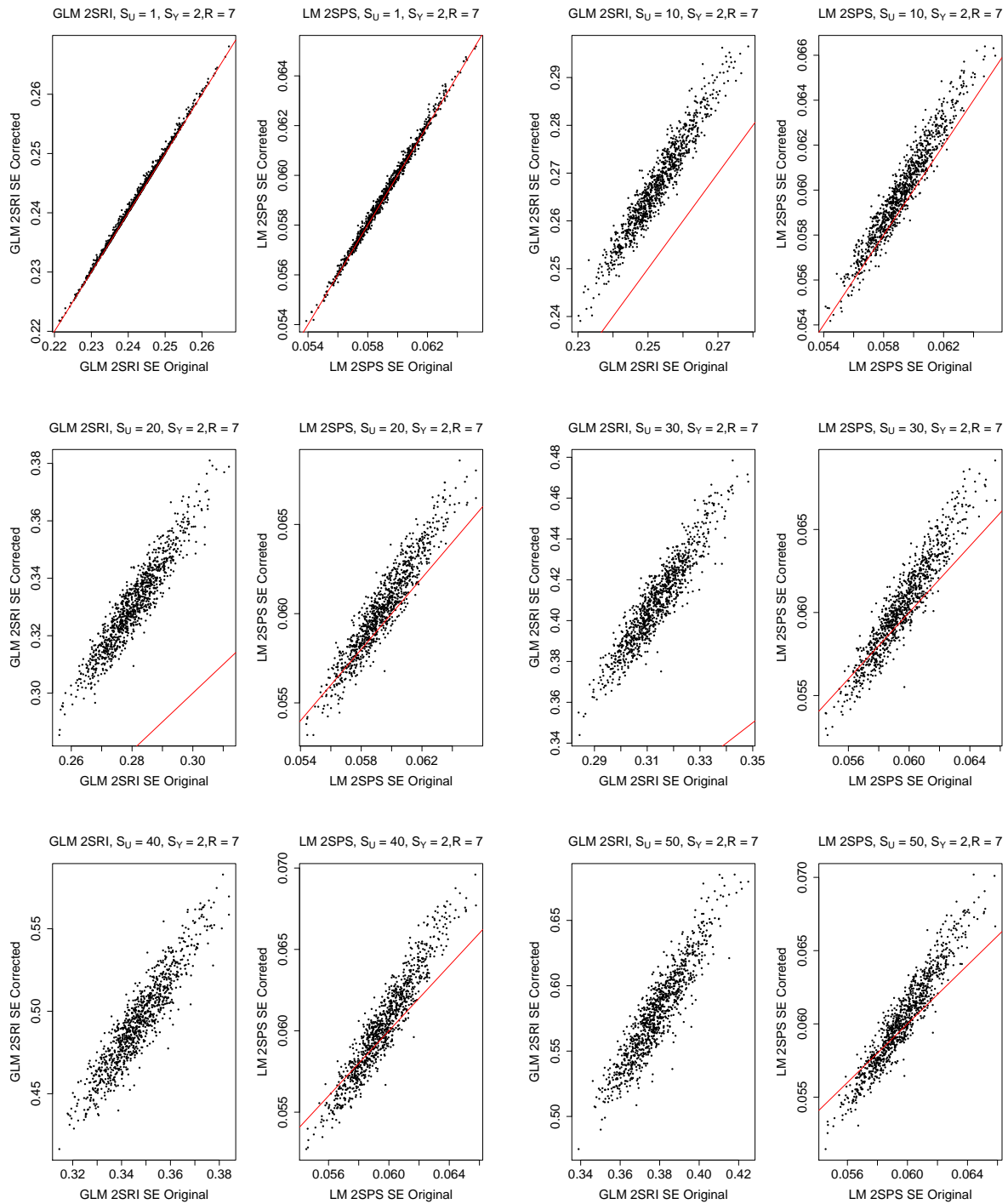


Figure S78: Simulations with the one-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 3, R = 7$ .

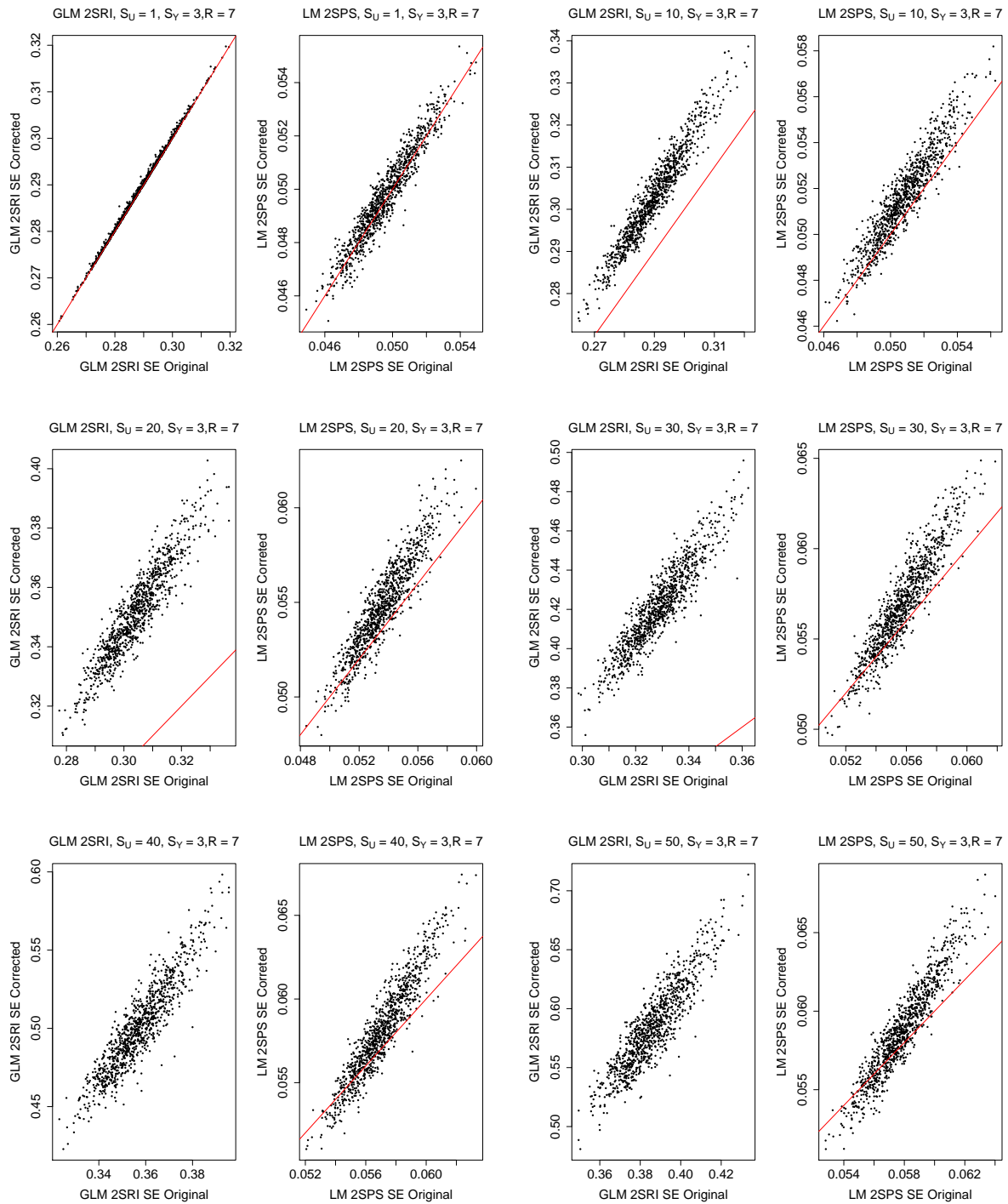


Figure S79: Simulations with the one-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 4, R = 7$ .

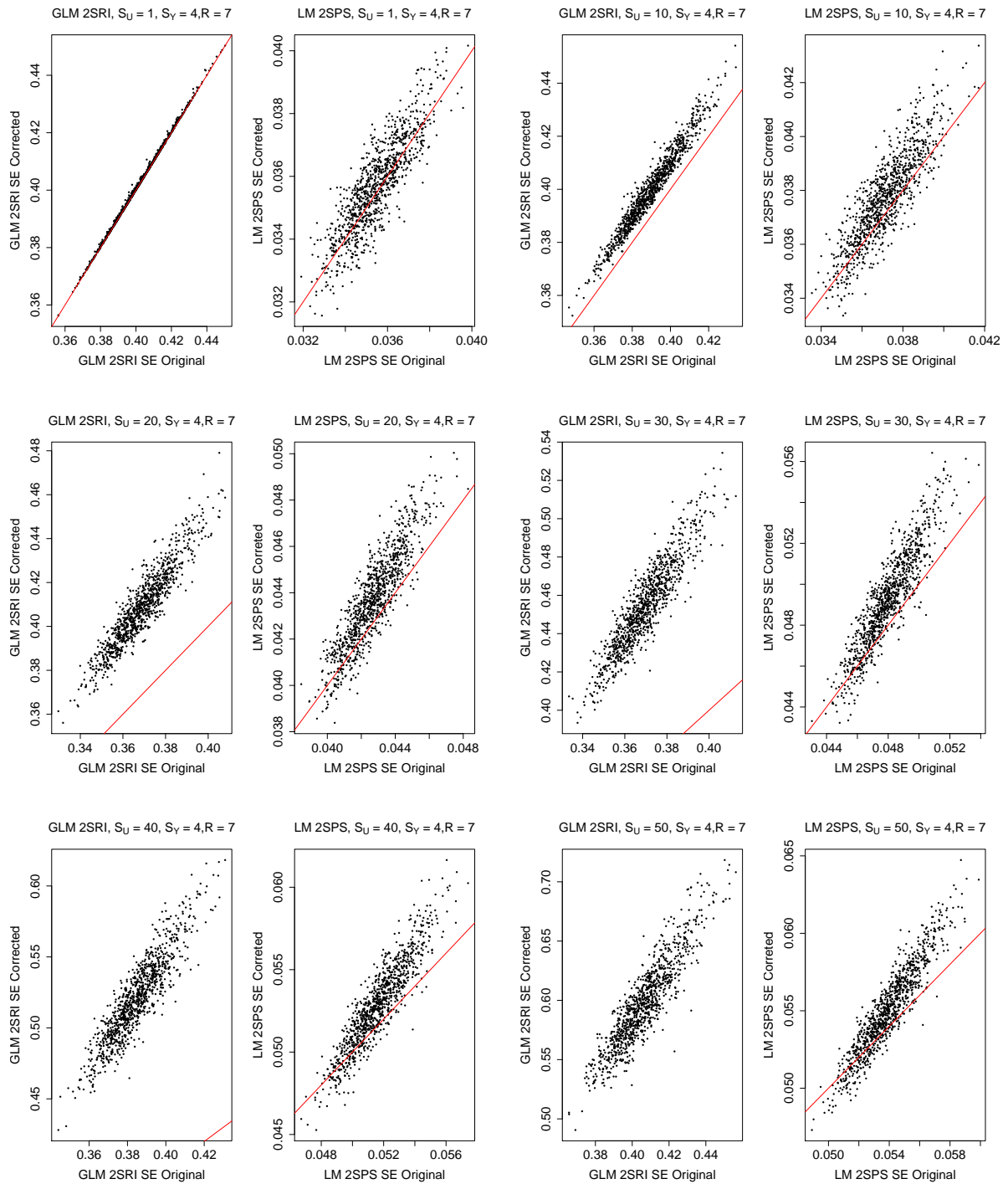


Figure S80: Simulations with the one-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 5, R = 7$ .

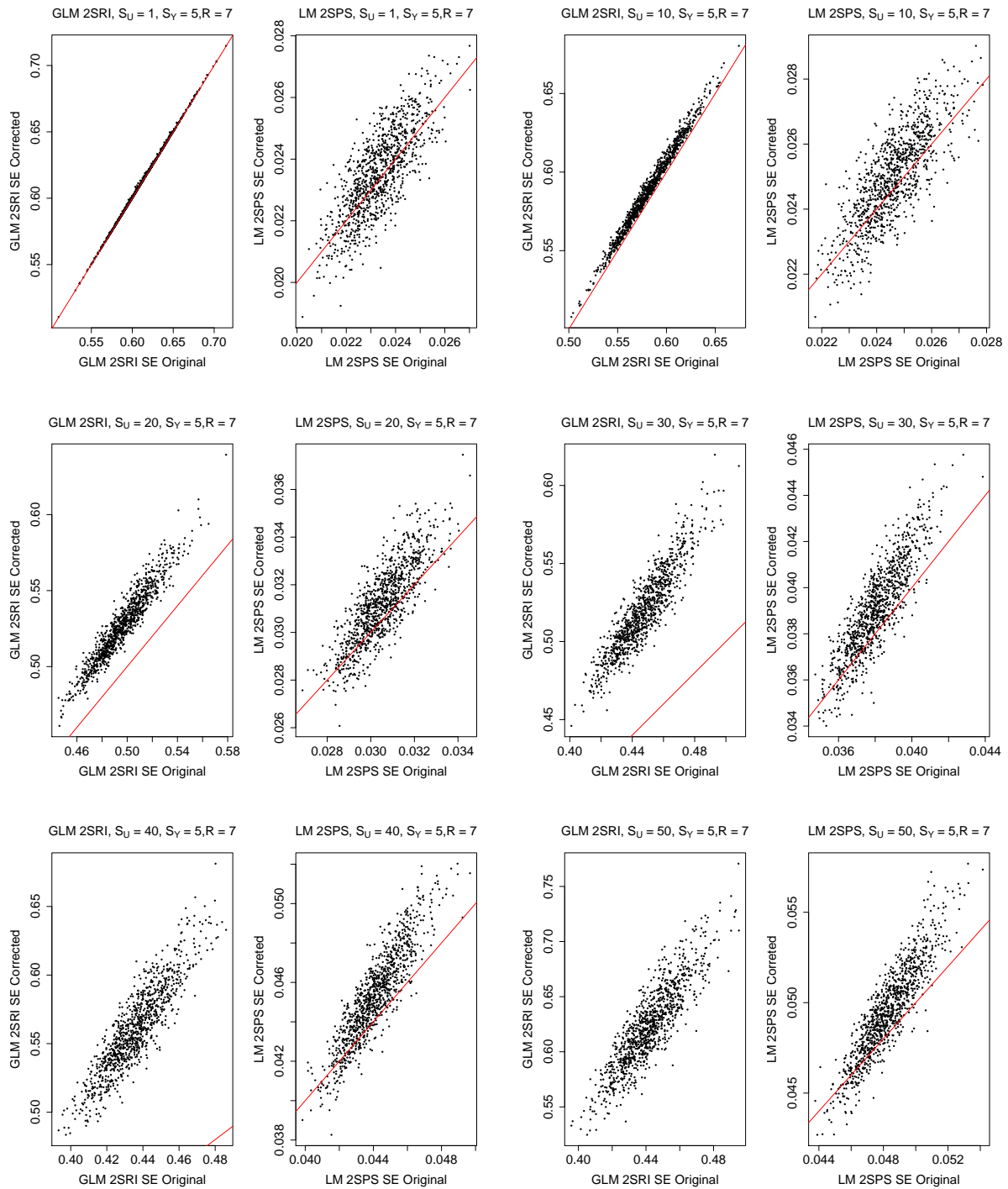


Figure S81: Simulations with the one-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 0, R = 9$ .

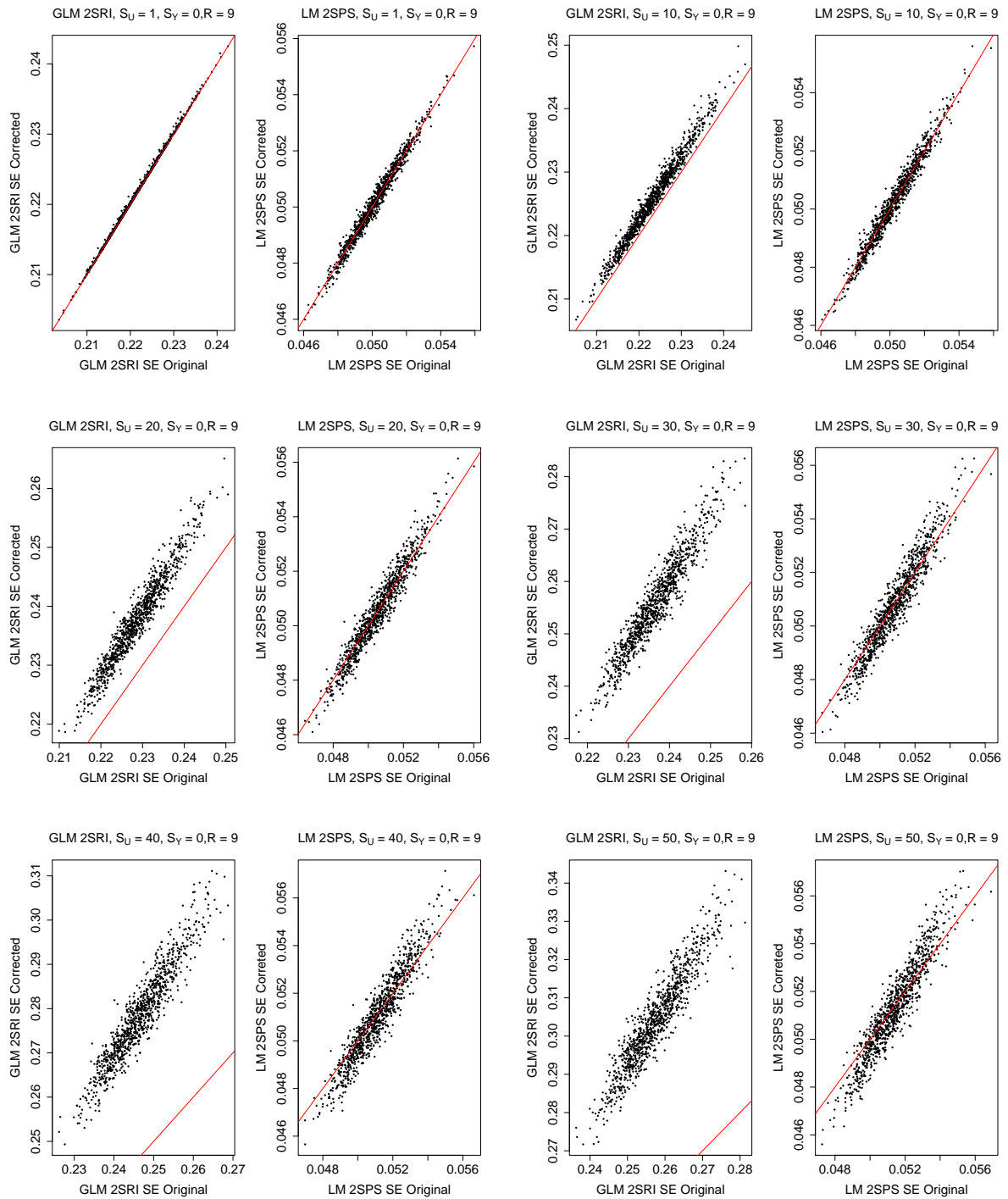




Figure S82: Simulations with the one-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 1, R = 9$ .

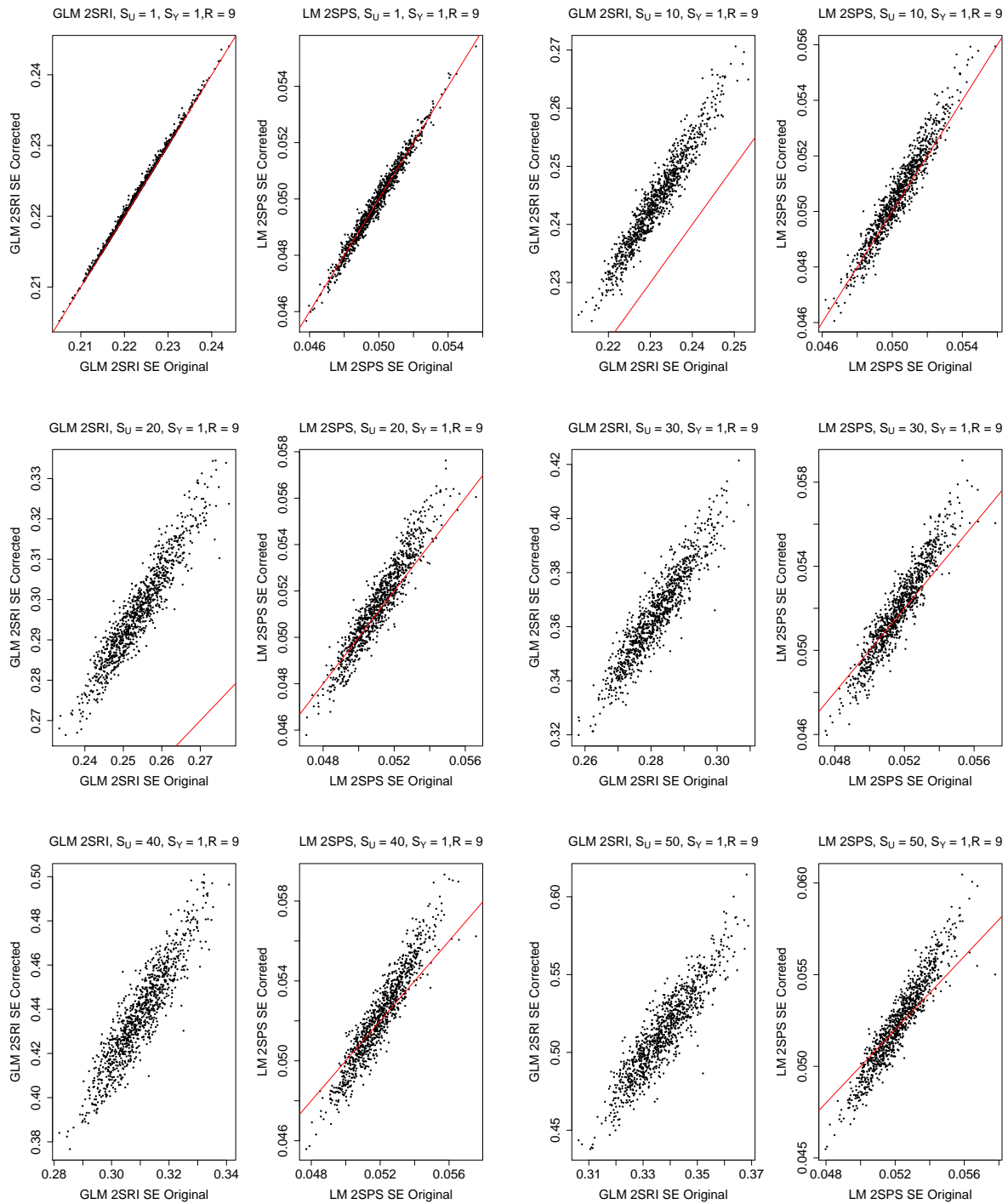


Figure S83: Simulations with the one-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 2, R = 9$ .

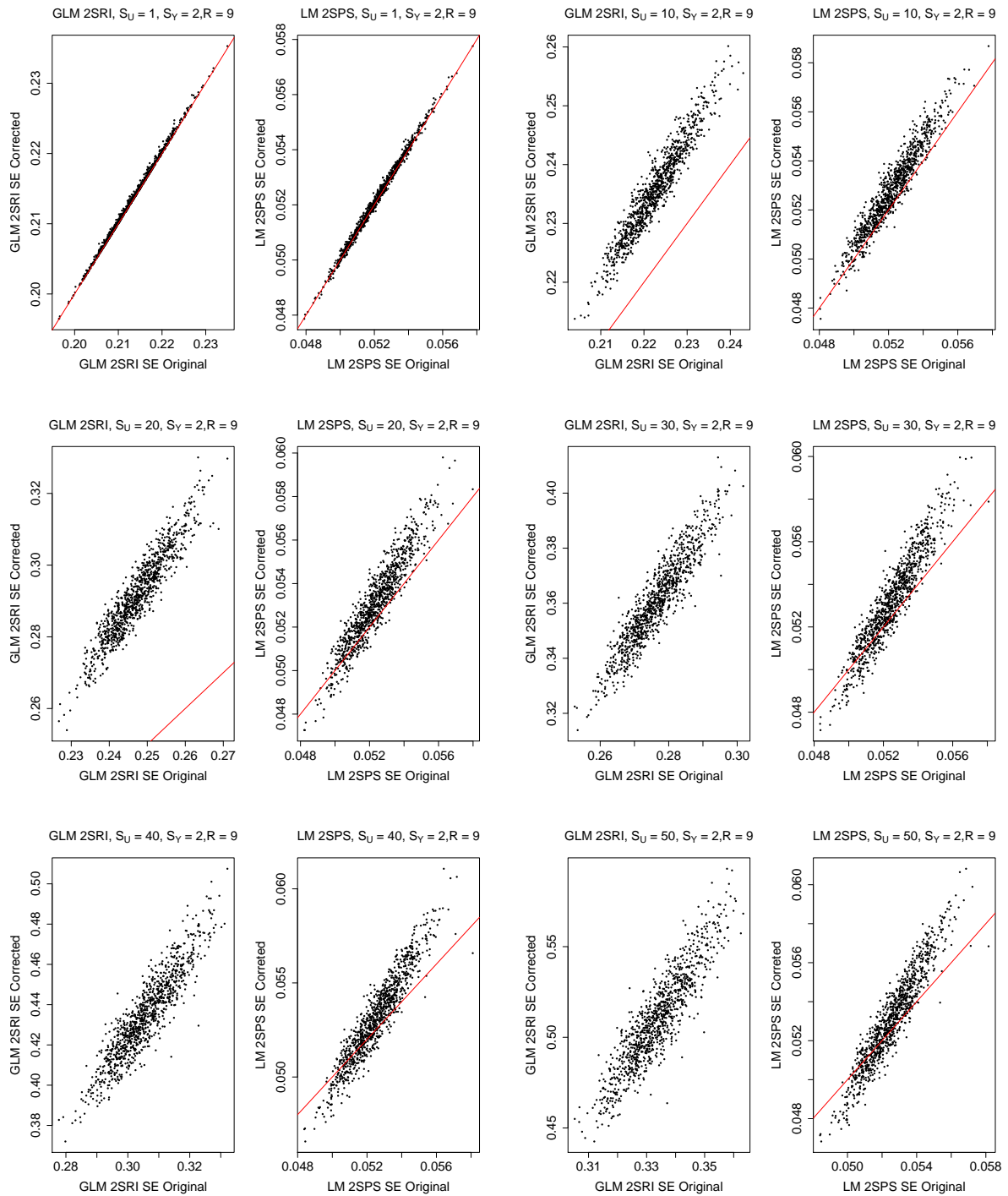


Figure S84: Simulations with the one-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 3, R = 9$ .

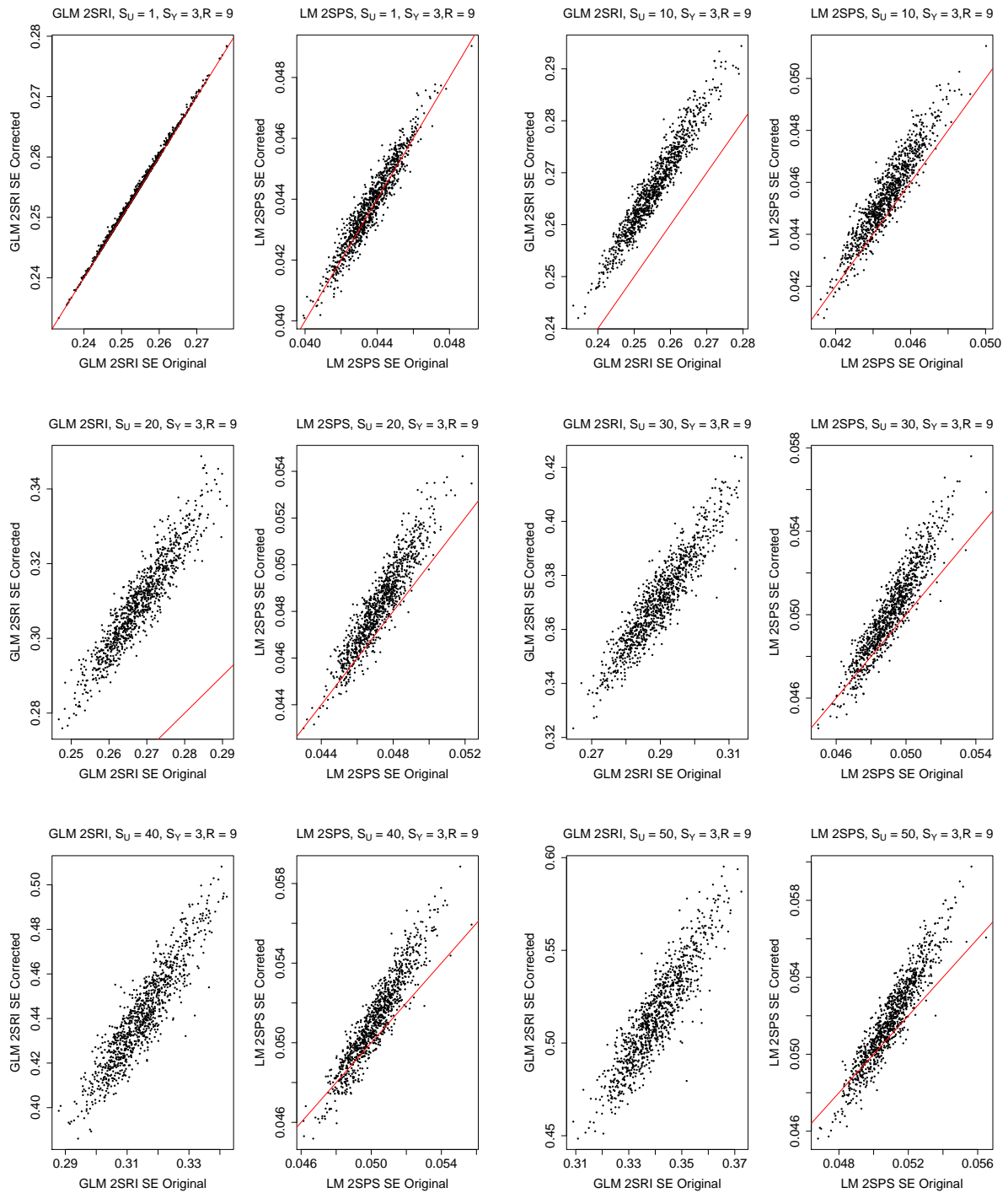


Figure S85: Simulations with the one-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 4, R = 9$ .

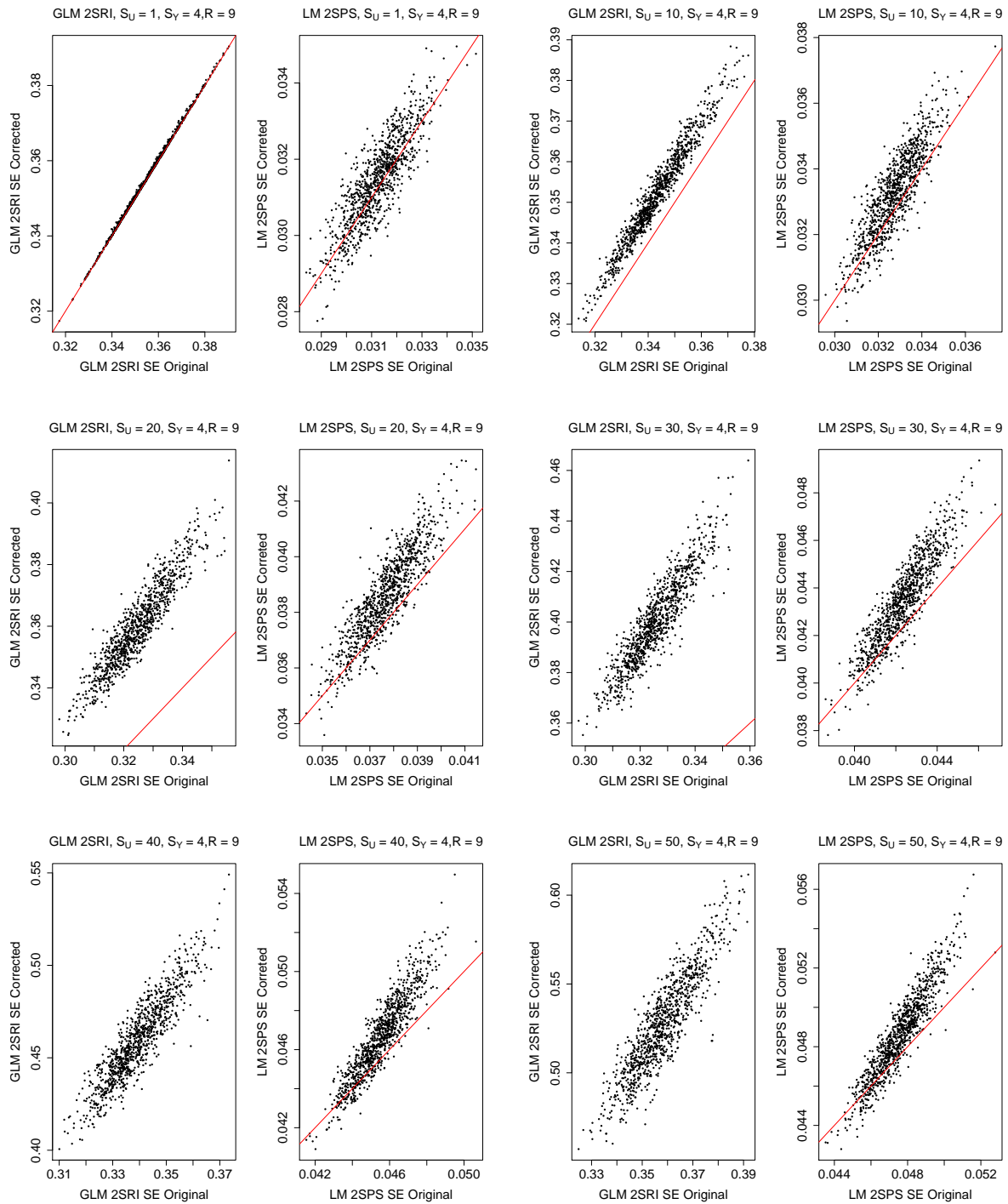


Figure S86: Simulations with the one-sample approaches: comparison of the original and corrected standard error estimates,  $S_Y = 5, R = 9$ .

