Supplementary material for "An alternative pseudolikelihood method for multivariate random-effects meta-analysis"

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In this supplemental document, we provide the regression extension of the Pseudo-REML method, additional simulation results for the comparison of the REML method, Riley method and Pseudo-REML method, and SPLUS/R program code to fit the Pseudo-REML method with a working example. We consider additional settings when sample size is small (i.e., $m = 5$), when the within-study/between-study variation ratio is set to be close to 0.5 (i.e., median of s_{ij}^2 is 0.25 and $\tau_1^2 = \tau_2^2 = 0.5$), and when the within-study correlation is generated from the uniform distribution.

Regression extension of the Pseudo-REML method

The pseudolikelihood involving covariances can be defined as

$$\log L_p(\boldsymbol{\eta}_1, \boldsymbol{\eta}_2) = \log L_1(\boldsymbol{\eta}_1) + \log L_2(\boldsymbol{\eta}_2) \tag{1}$$

where

$$\log L_j(\boldsymbol{\eta}_j) = -\frac{1}{2} \sum_{i=1}^{m} \left\{ \log(s_{ij}^2 + \tau_j^2) + \frac{(Y_{ij} - \boldsymbol{\beta}_j{}^T \boldsymbol{X})^2}{s_{ij}^2 + \tau_j^2} \right\} \quad \text{for} \quad j = 1, 2, \tag{2}$$

and $\boldsymbol{X}$ is the $p \times 1$ covariance vector.

The maximum pseudolikelihood estimator $(\tilde{\boldsymbol{\eta}}_1, \tilde{\boldsymbol{\eta}}_2)$ can be shown to be consistent and asymptotically normal with covariance matrix

$$\Sigma = \begin{pmatrix} \mathbf{I}_{11}^{-1} & \mathbf{I}_{11}^{-1} \mathbf{I}_{12} \mathbf{I}_{22}^{-1} \\ \left(\mathbf{I}_{11}^{-1} \mathbf{I}_{12} \mathbf{I}_{22}^{-1}\right)^T & \mathbf{I}_{22}^{-1} \end{pmatrix},$$

where

$$\mathbf{I}_{jj} = E\left\{ -\frac{\partial^2 \log L_j(\boldsymbol{\eta}_j)}{\partial \boldsymbol{\eta}_j^2} \right\} \quad \text{and} \quad \mathbf{I}_{12} = E\left[\left\{ \frac{\partial \log L_1(\boldsymbol{\eta}_1)}{\partial \boldsymbol{\eta}_1} \right\} \left\{ \frac{\partial \log L_2(\boldsymbol{\eta}_2)}{\partial \boldsymbol{\eta}_2} \right\}^T \right] \quad \text{for} \quad j = 1, 2.$$

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The information matrices $\mathbf{I}_{11}$, $\mathbf{I}_{22}$ and $\mathbf{I}_{12}$ can be empirically estimated as

$$\hat{\mathbf{I}}_{11} = \frac{1}{m}\sum_{i=1}^{m}\mathbf{U}_{1i}(\tilde{\boldsymbol{\eta}}_1)\mathbf{U}_{1i}(\tilde{\boldsymbol{\eta}}_1)^T, \quad \hat{\mathbf{I}}_{22} = \frac{1}{m}\sum_{i=1}^{m}\mathbf{U}_{2i}(\tilde{\boldsymbol{\eta}}_2)\mathbf{U}_{2i}(\tilde{\boldsymbol{\eta}}_2)^T$$

$$\hat{\mathbf{I}}_{12} = \frac{1}{m}\sum_{i=1}^{m}\mathbf{U}_{1i}(\tilde{\boldsymbol{\eta}}_1)\mathbf{U}_{2i}(\tilde{\boldsymbol{\eta}}_2)^T,$$

and

$$\mathbf{U}_{ji}(\tilde{\boldsymbol{\eta}}_j) = \left(\frac{Y_{ij} - \tilde{\boldsymbol{\beta}}_j^T\boldsymbol{X}}{s_{ij}^2 + \tilde{\tau}_j^2}, -\frac{1}{2(s_{ij}^2 + \tilde{\tau}_j^2)} + \frac{(Y_{ij} - \tilde{\boldsymbol{\beta}}_j^T\boldsymbol{X})^2}{2(s_{ij}^2 + \tilde{\tau}_j^2)^2}\right)^T, \quad \text{for} \quad j = 1, 2 \quad \text{and} \quad i = 1, \dots, m.$$

Additional simulation results

Table S1 summarizes the results from $1,000$ simulations under different within-study correlation and between-study correlation, when number of studies is small (i.e., $m = 5$). When the between-group heterogeneity is comparable, Riley method tends to underestimate the standard error, leading to confidence intervals with coverage probabilities that are less than the nominal level (range of CP: $84 \sim 89\%$). In contrast, the standard error of estimate for Δ using the Pseudo-REML method is well estimated, and the coverage probabilities of confidence intervals are close to the nominal level (range of CP: $91 \sim 95\%$). When the between-group heterogeneity is relatively small, the ranges of CPs are $84 \sim 89\%$ for Riley method and $94 \sim 97\%$ for the Pseudo-REML method, respectively. When the between-group heterogeneity is relatively large, the ranges of CPs are $85\% \sim 89\%$, $94\% \sim 96\%$ for the Riley and pseudo-REML methods, respectively. The performance of Riley method when the between-group heterogeneity is relatively large is slightly better than that when the between-group heterogeneity is comparable or relatively small. In contrast, the performance of the Pseudo-REML method is similar to that in settings when the between-group heterogeneity is comparable or relatively large. In summary, the Pseudop-REML method can produce confidence intervals with coverage probabilities close to the nominal level under all settings considered.

Table S2 summarizes the results from $1,000$ simulations under different within-study correlation and between-study correlation, when number of studies is large (i.e., $m = 25$), and the within-study correlations are generated from uniform distributions. The findings are similar to those under constant within-study correlations. When for meta-analysis with large number of studies, the three methods under comparison perform well in terms of bias, and coverage probability.

To compare the efficiency in estimation between the Riley method and Pseudo-REML methods when the number of studies is small, we plot the relative efficiency (RE) against the between-study correlation in Figure S1. When the between-group heterogeneity is comparable, the relative efficiency of Riley method is around 83% with range $60 \sim 101\%$ when $m = 5$, indicating a sizable efficiency loss. The results when the between-group heterogeneity is relatively small and large are similar. In summary, our simulation studies suggest that the Pseudo-REML method maintains good coverage probability of confidence intervals and high relative efficiency when number of studies is small.

To assess the singular covariance matrix problem, we display the percentage of the singular covariance matrix (SP) under different settings when $m = 10$ in Figure S2. We find that the REML method suffers greatly from the singular estimated covariance matrix problem (SP$> 25\%$ under all settings). Riley's method alleviates this problem to some extent, but still has a sizable proportion of singular estimated covariance matrix in some settings (range of SP: $0 \sim 20\%$). In contrast, there is no singular estimated covariance matrix problem for the Pseudo-REML method. In summary, for meta-analysis with small number of studies, REML method suffers greatly from the singular estimated covariance matrix problem, even when within-study correlations are known. Riley method alleviates such singular problem to some extend but still has a sizable proportion of singular estimated covariance matrix. The pseudop-REML method suffers very little from singular estimated covariance matrix .

We also compared the performance of estimates under three different methods when the estimated covariance matrix using REML method is singular. The results are summarized in Figure S3 when the number of studies

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Table S1: Estimates of bias, empirical standard error (ESE), model based standard error (MBSE), coverage probability (CP) of $\Delta = \beta_1 - \beta_2$ in $1,000$ simulations based on data generated from BRMA model, withnumber of studies $m = 5$, for different between-study correlation ρ_B and within-study correlations ρ_{Wi}. All entries in the table are multiplied by 100.

VR	ρ_{Wi}	ρ_B	REML		Riley method				Pseudo-REML			
			Bias	ESE	Bias	ESE	MBSE	CP	Bias	ESE	MBSE	CP
1	-0.5	-0.5	-2.4	53.4	-1.2	63.3	53.3	84.4	-0.5	52.9	63.6	92.8
		0.0	1.1	52.2	1.9	56.1	48.9	86.9	1.3	50.8	60.0	91.7
		0.5	0.4	44.6	-0.1	47.3	44.5	89.1	0.2	43.9	55.3	93.4
	0.0	-0.5	-1.8	50.6	0.1	56.7	49.7	84.1	-0.8	52.3	60.3	91.3
		0.0	1.0	48.7	-0.8	50.5	45.6	86.4	0.8	47.8	57.4	92.7
		0.5	-0.9	40.5	0.9	43.0	41.0	88.4	-2.5	41.9	54.3	93.7
	0.5	-0.5	-1.5	46.7	-1.6	55.4	46.8	86.6	-0.5	49.7	58.2	92.5
		0.0	0.9	43.2	0.9	43.6	40.9	87.1	0.8	44.5	54.0	92.0
		0.5	0.2	36.5	0.0	38.5	35.0	85.2	0.3	38.1	49.0	94.6
	U[-0.8, 0.8]	-0.5	-1.0	51.7	-1.2	56.1	50.7	87.7	-2.7	53.1	61.0	92.2
		0.0	-1.3	46.9	-2.3	51.3	45.0	87.0	-1.5	48.9	56.1	92.3
		0.5	0.9	40.4	1.9	46.3	41.3	86.1	0.1	42.5	54.6	94.0
	U[-0.8, 0.0]	-0.5	-3.0	55.0	-0.8	58.9	52.6	86.0	-3.6	54.9	63.0	91.6
		0.0	-3.2	51.6	-1.9	55.2	48.7	85.9	-1.6	51.6	60.9	92.4
		0.5	0.2	46.0	-1.2	49.9	45.0	88.5	0.7	45.5	56.4	94.4
	U[0.0, 0.8]	-0.5	-0.7	47.1	-1.6	52.7	47.5	88.0	-2.2	50.1	58.8	91.4
		0.0	-0.6	44.9	-1.7	47.3	42.1	86.8	-1.4	46.4	52.9	91.6
		0.5	0.2	38.5	1.4	41.0	36.3	87.0	-0.2	39.5	49.8	93.4

$m = 10$, ρ_{Wi} is sampled from a uniform distribution $U(0.8, 0.8)$, $\rho_B = 0.5$, and the within-study/between-study variation ratio (VR) is close to 0.5. Specifically, 33% of the 1000 simulations have singular estimated covariance matrix, which happened when the estimated correlation being -1 or 1. Overall speaking, when REML method has singular estimated covariance matrix, the point estimates from three methods were similar. But their standard error estimates were very different due to the singularity of estimated covariance matrix. This confirms that the singular estimated covariance matrix lead to biased inference on standard error estimation and inflated Type I errors.

Table S1: Estimates of bias, empirical standard error (ESE), model based standard error (MBSE), coverage probability (CP) of $\Delta = \beta_1 - \beta_2$ in $1,000$ simulations based on data generated from BRMA model, with number of studies $m = 5$, for different between-study correlation ρ_B and within-study correlations ρ_{Wi}. All entries in the table are multiplied by 100. **(continued)**

VR	ρ_{Wi}	ρ_B	REML		Riley method				Pseudo-REML			
			Bias	ESE	Bias	ESE	MBSE	CP	Bias	ESE	MBSE	CP
2.5	-0.5	-0.5	-2.9	40.1	-0.8	49.9	43.0	85.2	0.2	39.7	57.3	96.1
		0.0	0.7	42.2	1.7	45.6	42.3	86.6	1.1	39.5	55.7	95.5
		0.5	2.6	37.2	0.0	41.9	39.0	89.0	0.8	35.4	54.0	96.5
	0.0	-0.5	-2.2	40.6	-1.0	45.9	38.9	84.3	-0.4	39.4	54.1	94.5
		0.0	1.2	38.9	-1.9	40.6	38.3	88.6	-0.2	37.1	53.1	96.0
		0.5	-2.7	33.3	-0.6	37.1	35.2	87.9	-1.8	33.2	51.0	95.1
	0.5	-0.5	-1.3	34.9	0.2	41.3	35.2	85.4	0.2	36.8	50.7	94.3
		0.0	1.3	32.4	1.3	35.8	33.0	86.4	1.4	33.4	47.5	94.5
		0.5	-0.5	29.6	0.1	31.4	28.9	85.6	0.6	30.4	45.5	95.4
	U[-0.8, 0.8]	-0.5	-2.6	41.3	-2.2	43.2	39.7	86.5	-2.9	40.3	54.7	95.2
		0.0	-0.9	36.2	-1.0	42.3	35.8	85.3	-1.1	37.6	51.9	94.6
		0.5	1.6	34.9	3.1	37.1	34.9	86.9	-0.4	34.8	50.0	95.9
	U[-0.8, 0.0]	-0.5	-0.8	44.0	0.6	49.5	42.5	84.5	-2.8	42.3	57.1	95.2
		0.0	-1.8	39.9	-1.8	44.1	38.5	84.4	-1.5	40.0	55.8	94.6
		0.5	0.8	38.4	1.6	43.6	38.9	87.8	0.9	37.1	52.5	96.2
	U[0.0, 0.8]	-0.5	-1.5	36.6	-1.3	40.6	35.7	86.6	-1.9	37.2	50.8	94.1
		0.0	-0.5	35.0	-0.8	37.2	32.4	83.8	-1.4	35.4	47.9	93.6
		0.5	1.8	30.3	0.6	33.9	30.6	86.2	-0.5	31.7	46.8	95.9

SPLUS/R program to fit the Pseudo-REML method and a working example

```
library(MASS)
library(mvmeta)
# 1.  functions


## Function that can be directly used to analyze meta-analysis data
## Input:
##         mydat: data of n rows and 4 columns, where n is the number of studies and 4 columns are
##         Yi1 (effect size of outcome 1), Si1^2(variance of Yi1), Yi2(effect size of outcome 2), Si2^2(variance of Yi2)
##
## Output:
##         estim: point estimates of (beta1, tau1^2, beta2, tau2^2)
##         cov.estim: covariance matrix of the point estimates
pseudolik.est = function(mydat){
        mydat1 = subset(mydat, select=c("Yi1", "Si1.2"))
        mydat2 = subset(mydat, select=c("Yi2", "Si2.2"))
        m=dim(mydat)[1]
        estim.pseudo = rep(NA, length=4)

        ## 1.1. optimize the likelihood function to obtain the point estimates
        my.pseudo1= mvmeta(mydat1$Yi1,mydat$Si1.2,method="reml")
        my.pseudo2= mvmeta(mydat2$Yi2,mydat$Si2.2,method="reml")
        ## save the result for parameters: beta1, tau1^2
        estim.pseudo[c(1:2)]=c(coef(my.pseudo1), my.pseudo1$Psi)
        ## save the result for parameters: beta2, tau2^2
        estim.pseudo[c(3:4)]=c(coef(my.pseudo2), my.pseudo2$Psi)
```

Table S1: Estimates bias, empirical standard error (ESE), model based standard error (MBSE), coverage probability (CP) of $\Delta = \beta_1 - \beta_2$ in $1,000$ simulations based on data generated from BRMA model, with number of studies $m = 5$, for different between-study correlation ρ_{B} and within-study correlations $\rho_{\mathrm{W}i}$. All entries in the table are multiplied by 100. **(continued)**

VR	$\rho_{\mathrm{W}i}$	ρ_{B}	REML		Riley method				Pseudo-REML			
			Bias	ESE	Bias	ESE	MBSE	CP	Bias	ESE	MBSE	CP
0.5	-0.5	-0.5	-2.9	67.5	-1.7	73.2	66.6	87.4	-0.4	66.3	89.1	96.2
		0.0	1.1	64.6	1.6	66.3	58.2	85.8	2.8	62.1	80.1	94.5
		0.5	-1.0	52.3	-0.8	54.9	51.2	87.5	0.0	51.9	71.8	95.5
	0.0	-0.5	-2.6	65.8	-3.5	73.1	63.2	85.8	-0.8	66.6	83.8	93.2
		0.0	0.1	60.6	-1.1	61.0	55.3	87.8	1.5	59.9	77.8	93.9
		0.5	-1.7	48.7	-1.9	51.5	47.0	87.4	-1.8	49.1	70.8	95.4
	0.5	-0.5	-2.2	61.6	-1.6	65.7	60.5	87.0	-0.3	62.8	83.1	95.5
		0.0	2.4	53.9	1.3	56.9	51.5	87.7	1.2	54.6	73.5	94.4
		0.5	0.2	43.6	-1.8	46.3	41.9	86.3	0.3	43.9	65.3	95.9
	U[-0.8, 0.8]	-0.5	-0.8	65.5	-2.1	68.6	62.5	87.5	-2.5	65.5	84.6	94.5
		0.0	-0.8	59.5	-1.7	61.6	56.2	87.3	-1.8	59.8	77.3	94.7
		0.5	1.0	48.4	2.4	52.6	48.5	87.2	0.6	49.6	70.8	94.9
	U[-0.8, 0.0]	-0.5	-3.0	69.1	-1.2	71.6	64.6	87.6	-2.8	67.9	87.7	94.9
		0.0	-2.2	63.3	-1.4	66.0	58.8	85.4	-1.9	62.7	81.7	94.2
		0.5	1.6	53.2	1.6	55.3	51.9	89.3	1.2	54.0	75.0	95.8
	U[0.0, 0.8]	-0.5	-1.3	62.4	-1.2	69.7	60.9	88.4	-1.7	63.4	82.6	95.1
		0.0	-1.4	56.5	-2.4	59.1	52.6	85.7	-1.2	57.3	74.6	93.8
		0.5	-0.1	45.9	0.7	46.5	43.2	86.2	-0.2	46.3	66.4	94.5

```
    estim.pseudo = matrix(estim.pseudo, nrow=1)
    colnames(estim.pseudo)=c("beta1", "tau1^2", "beta2", "tau2^2")

    ## 1.2. Information matrix calculation
    ## calculate I11.hat and I22.hat
      Score1.beta = (mydat1$Yi1-coef(my.pseudo1))/(mydat1$Si1.2+my.pseudo1$Psi)
 Score2.beta = (mydat2$Yi2-coef(my.pseudo2))/(mydat2$Si2.2+my.pseudo2$Psi)
 Score1.tau2 = -1/(2*(mydat1$Si1.2+my.pseudo1$Psi)) + (mydat1$Yi1-coef(my.pseudo1))^2/(mydat1$Si1.2+my.pseudo1$Psi)^2/2
 Score2.tau2 = -1/(2*(mydat2$Si2.2+my.pseudo2$Psi)) + (mydat2$Yi2-coef(my.pseudo2))^2/(mydat2$Si2.2+my.pseudo2$Psi)^2/2

    Score1 = rbind(Score1.beta, Score1.tau2); Score2 = rbind(Score2.beta, Score2.tau2)
    I11.hat = Score1%*%t(Score1)/m; I22.hat = Score2%*%t(Score2)/m
    ## calculation of I12.hat
    I12.hat = Score1%*%t(Score2)/m

    ## 1.3. calculation of covariance matrix of estimates
    myoff.diag = solve(I11.hat,tol=1e-100)%*%I12.hat%*%solve(I22.hat,tol=1e-100)/m
    myupper = cbind(solve(m*I11.hat,tol=1e-100), (myoff.diag))
    mylower = cbind(t(myoff.diag), solve(m*I22.hat,tol=1e-100))
    myV=rbind(myupper,mylower)
    colnames=rownames(myV)=c("beta1", "tau1^2", "beta2", "tau2^2")
    mySandwich= myV

    ## 1.4. print the results
    myresults = list(estim = estim.pseudo, cov.estim = mySandwich)
    return(myresults)
}

# 2. Working Example
```

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Table S2: Estimates of bias, empirical standard error (ESE), model based standard error (MBSE), coverage probability (CP) of $\Delta = \beta_1 - \beta_2$ in $1,000$ simulations based on data generated from REML model, with number of studies $m = 25$ and different between-study correlation ρ_B and within-study correlations ρ_{Wi}. All entries in the table are multiplied by 100.

VR	ρ_{Wi}	ρ_B	REML Bias	REML ESE	Riley method Bias	Riley method ESE	Riley method MBSE	Riley method CP	Pseudo-REML Bias	Pseudo-REML ESE	Pseudo-REML MBSE	Pseudo-REML CP
1	U[-0.8, 0.8]	-0.5	-0.1	21.9	0.1	22.7	21.1	92.2	0.1	22.6	22.2	92.9
		0.0	0.1	20.2	0.1	20.5	19.4	93.7	0.2	20.4	20.1	93.9
		0.5	0.8	17.2	0.6	17.3	17.2	93.8	0.8	17.5	17.9	93.5
	U[-0.8, 0.0]	-0.5	0.3	23.3	0.3	23.5	22.2	92.2	0.4	23.6	23.1	92.6
		0.0	0.3	21.7	0.2	21.6	20.8	93.8	0.4	21.5	21.1	93.2
		0.5	0.8	18.6	0.6	18.8	18.8	93.4	0.7	18.7	19.0	93.0
	U[0.0, 0.8]	-0.5	-0.5	20.8	-0.3	21.6	20.0	92.0	-0.2	21.6	21.3	92.9
		0.0	-0.1	19.0	-0.1	19.2	17.9	92.7	-0.1	19.2	19.0	94.2
		0.5	0.7	16.1	0.7	16.1	15.4	92.9	0.9	16.5	16.6	93.2
2.5	U[-0.8, 0.8]	-0.5	-0.5	16.0	0.2	16.6	15.2	90.9	0.0	16.7	16.0	91.8
		0.0	-0.3	15.2	0.1	15.6	14.4	92.0	0.1	15.6	14.9	91.9
		0.5	0.7	13.6	0.4	13.5	13.4	92.9	0.5	13.7	13.8	93.8
	U[-0.8, 0.0]	-0.5	0.2	17.1	0.3	17.3	16.1	92.0	0.2	17.5	16.8	92.7
		0.0	0.3	16.5	0.1	16.6	15.6	93.0	0.2	16.6	15.7	92.1
		0.5	0.5	14.8	0.5	15.0	14.9	93.5	0.6	14.7	14.8	93.9
	U[0.0, 0.8]	-0.5	-0.4	27.6	-0.4	28.2	26.7	92.6	-0.2	15.7	15.2	92.0
		0.0	-0.2	24.3	-0.2	24.6	23.4	93.8	-0.2	14.4	14.0	93.1
		0.5	1.0	19.8	0.9	19.9	19.3	93.4	0.6	13.1	12.7	92.7
0.5	U[-0.8, 0.8]	-0.5	-0.2	28.8	0.0	29.3	27.9	93.5	0.1	29.3	30.6	94.8
		0.0	0.0	25.5	0.0	25.8	24.9	93.6	0.1	25.7	27.0	95.0
		0.5	1.0	20.9	0.8	21.2	21.1	93.8	1.0	21.3	23.1	94.5
	U[-0.8, 0.0]	-0.5	0.7	29.8	0.6	29.9	29.4	94.4	0.9	29.8	31.9	95.8
		0.0	0.0	27.0	-0.1	27.0	26.7	93.4	0.0	26.8	28.5	95.2
		0.5	-0.3	21.8	-0.3	22.1	22.9	95.0	-0.3	22.1	24.6	96.5
	U[0.0, 0.8]	-0.5	-0.4	27.6	-0.4	28.2	26.7	92.6	-0.3	28.1	29.5	94.9
		0.0	-0.2	24.3	-0.2	24.6	23.4	93.8	-0.2	24.5	25.8	95.6
		0.5	1.0	19.8	0.9	19.9	19.3	93.4	1.1	20.2	21.7	95.1

```
# Data from Section 5.1 Sasee et al. (2012)
# Comparison between overall survival and disease-free survival for prostate cancer
# Log-hazard ratio estimates comparing combined therapy using Goserelin acetate with radiotherapy
# with respect to the overall survival (Yi1) and that with respect to disease-free survival (Yi2)

mydat=data.frame(cbind(c(1:5),
        c(-0.21, -0.17, -0.67, -0.17, -0.46),
        c(-0.85, -0.62, -0.87, -0.33, -0.56),
        c(0.0576, 0.0121, 0.0324, 0.0169, 0.0196),
        c(0.0064, 0.0121, 0.0441, 0.0144, 0.0121)))
colnames(mydat)=c("ID", "Yi1", "Yi2", "Si1.2", "Si2.2")

## Point estimates and covariance estimate
myresults = pseudolik.est(mydat)
```

```
## The model based standard errors of beta1, beta2 and (beta1-beta2)
beta1.mbse = sqrt(diag(myresults$cov.estim)[1])
beta2.mbse = sqrt(diag(myresults$cov.estim)[3])
beta.df.mbse =sqrt(diag(myresults$cov.estim)[1]+diag(myresults$cov.estim)[3]-2*myresults$cov.estim[1,3])
mbse.pseudo =c(beta1.mbse, beta2.mbse, beta.df.mbse)
```
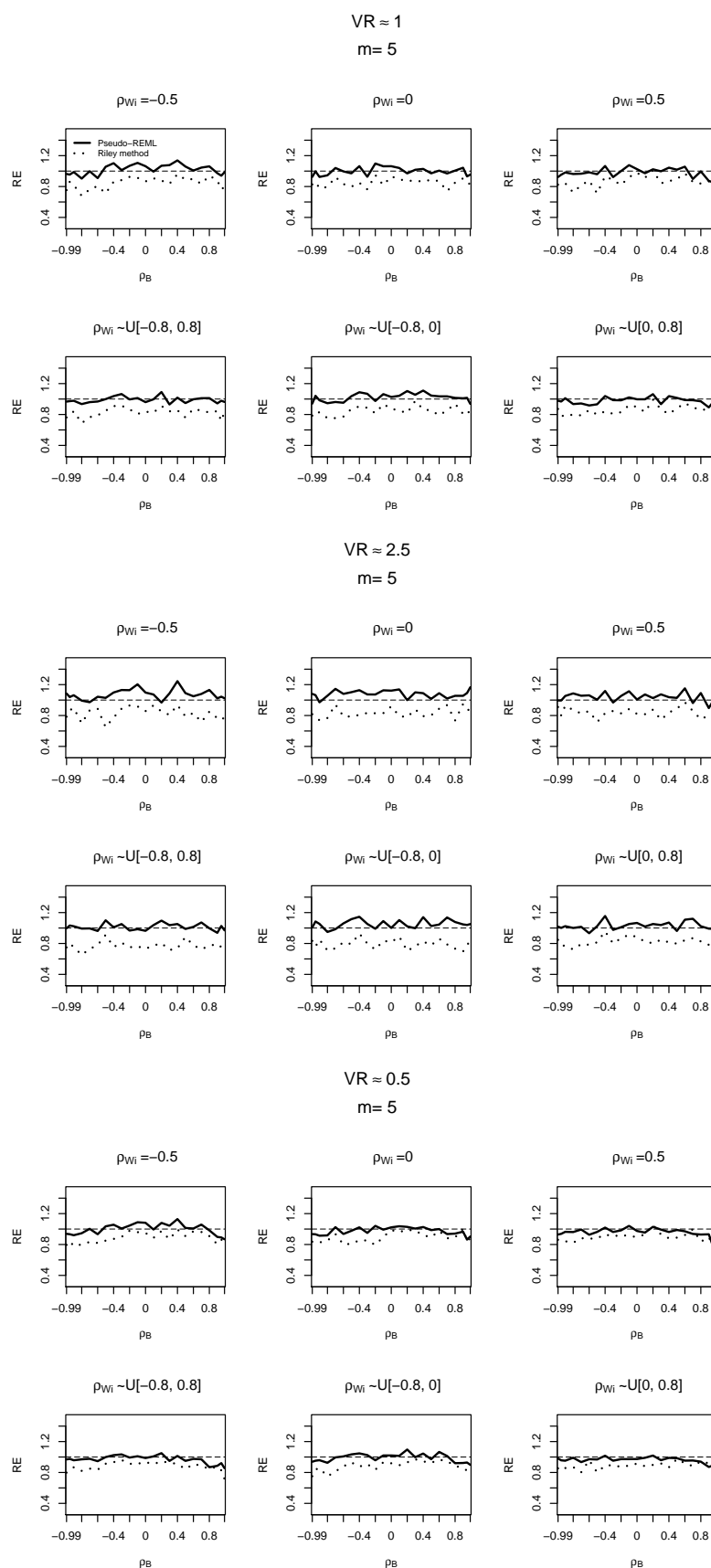
Figure S1: Relative efficiency (RE) of estimator of $\Delta = \beta_1 - \beta_2$ based on Riley method and Pseudo-REML method comparing to the estimator based on REML model, with number of studies $m = 5$ and different between-study correlation ρ_B and within-study correlations ρ_{Wi}. Number of simulations is $1,000$.
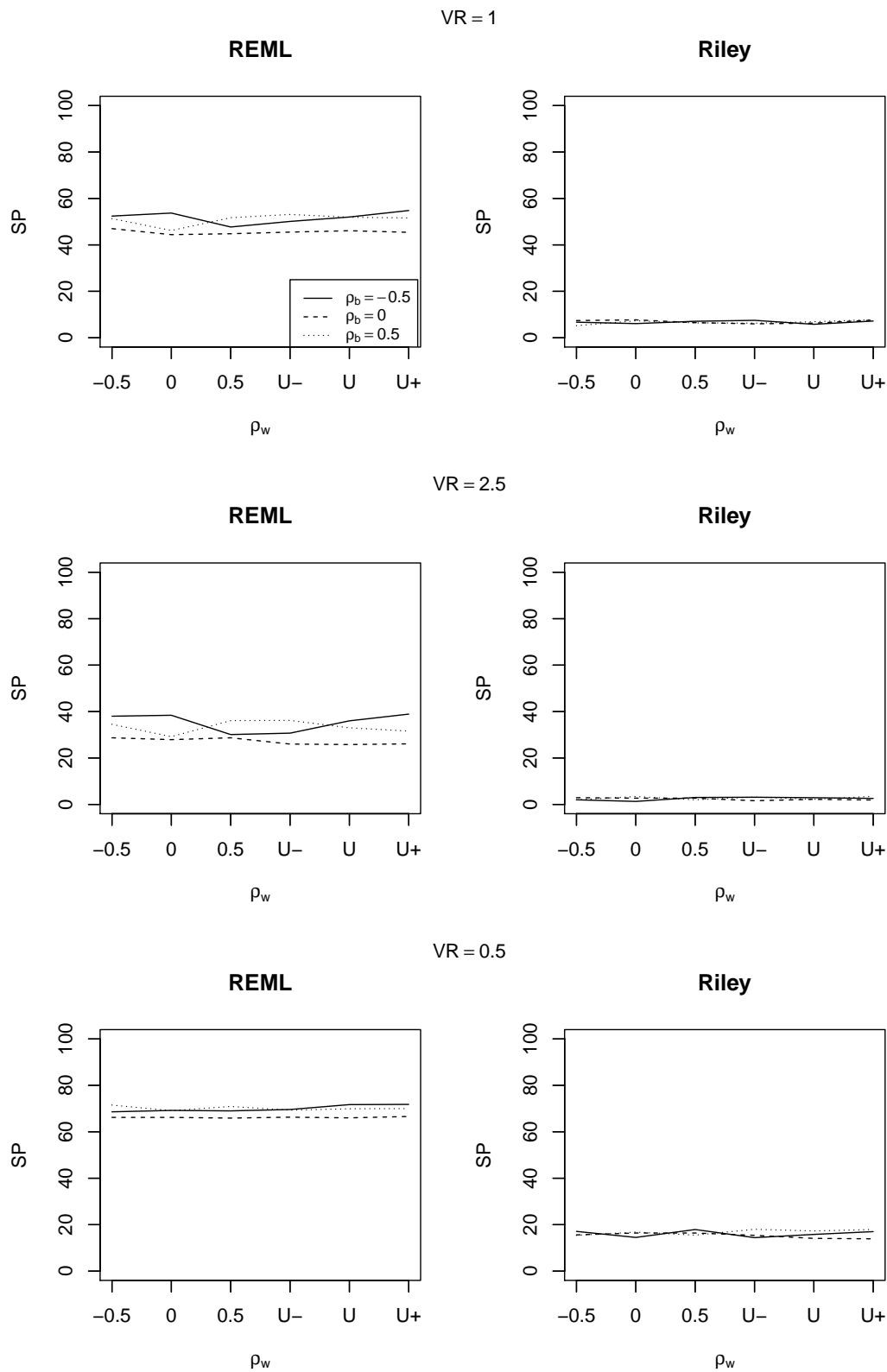
Figure S2: Percentage of singular estimated covariance matrix (SP) with number of studies $m = 10$. U+, U-, and U denote the uniform distributions U[-0.8, 0], U[-0.8, 0.8], and U[0, 0.8], respectively.

All estimtes

Subset 1: estimates with nonsingular estimated covariance matrix

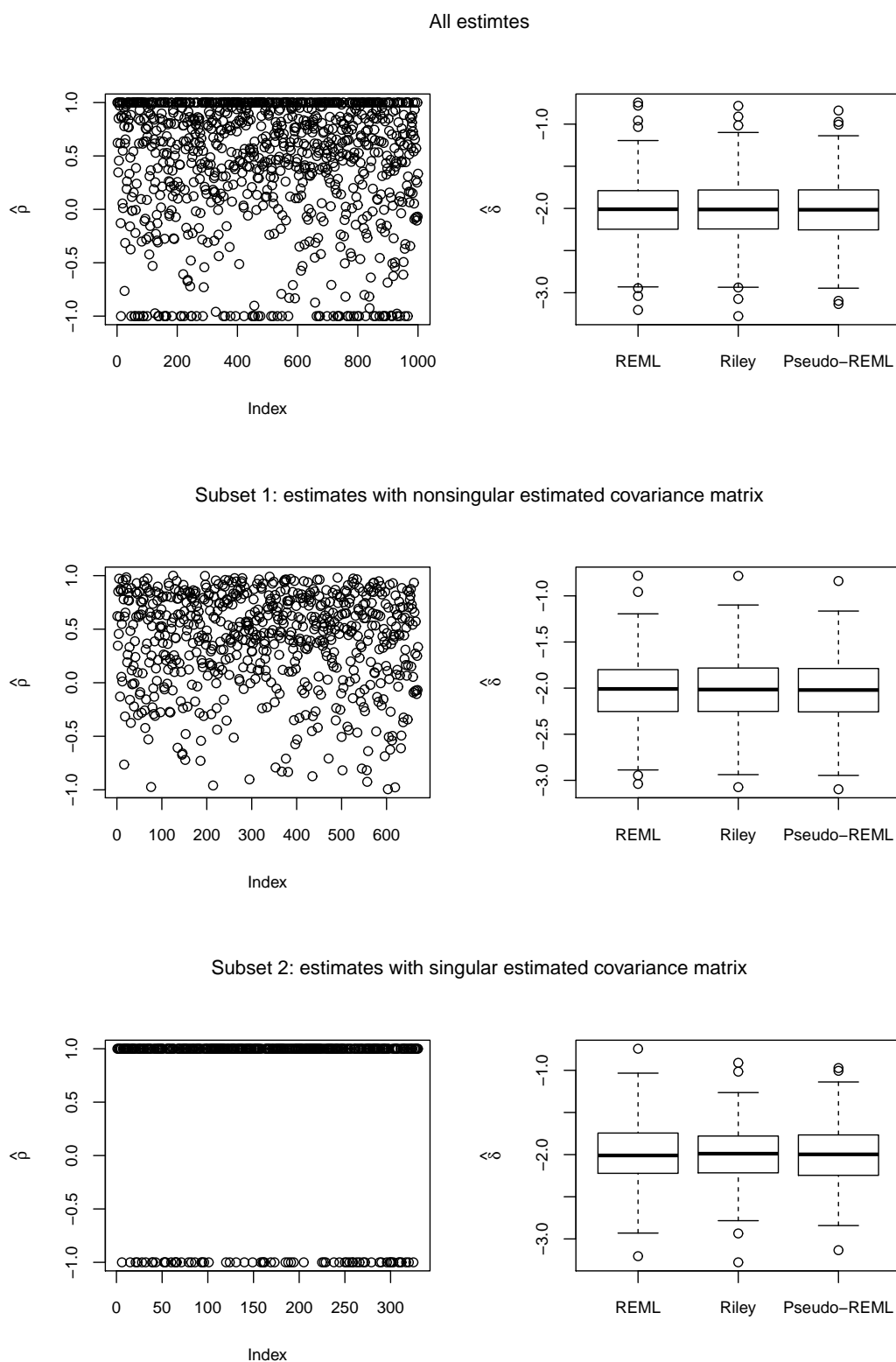Subset 2: estimates with singular estimated covariance matrix

Figure S3: Impact of the singular estimated covariance matrix in simulations based on data generated from REML model, with number of studies $m = 10$, $\rho_{\mathrm{W}i} = 0.5$ and $\rho_{\mathrm{B}} = 0.5$, and the within-study/between-study variation ratio (VR) close to 0.5.