A comparison of estimation methods adjusting for selection bias in adaptive enrichment designs with time-to-event endpoints - Supplementary Material

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1 Additional simulation scenarios

In this supplementary material we present additional simulation scenarios cited in the main article. In Figure 1 we set the threshold to $b = 0$. In Figure 2 we set $\tilde{T}_1$ to 3 months after the interim analysis. We also compare 4 sub-populations while keeping the other parameters as in the main setting and in Figure 3 we present the results averaged in all sub-populations, while in Figure 4 we show the performance of the estimators in each sub-population in the case of linear effects on the sub-populations. In Tables 1, 2 and 3 we present also the empirical probabilities of selection for the different sub-populations in the different scenarios.

Log HR	$\boldsymbol{\delta_i} = 0$	$\boldsymbol{\delta_i} = -0.1$	$\boldsymbol{\delta_i} = -0.2$	$\boldsymbol{\delta_i} = -0.3$
Probability of selection	50%	70%	84%	93%

Table 1: Empirical probability of selection for the different sub-populations in the simulation study when $b = 0$, according to their log HR.

Log HR	$\boldsymbol{\delta_i} = 0$	$\boldsymbol{\delta_i} = -0.1$	$\boldsymbol{\delta_i} = -0.2$	$\boldsymbol{\delta_i} = -0.3$
Probability of selection	30%	50%	69%	83%

Table 2: Empirical probability of selection for the different sub-populations in the simulation study when $\tilde{T}_1 = T_1 + 90\ days$, according to their log HR.

Log HR	$\boldsymbol{\delta_i} = 0$	$\boldsymbol{\delta_i} = -0.1$	$\boldsymbol{\delta_i} = -0.2$	$\boldsymbol{\delta_i} = -0.3$
Probability of selection	33%	50%	65%	80%

Table 3: Empirical probability of selection for the different sub-populations in the simulation study when 4 sub-populations are included, according to their log HR.

1.1 Threshold equal to $b = 0$

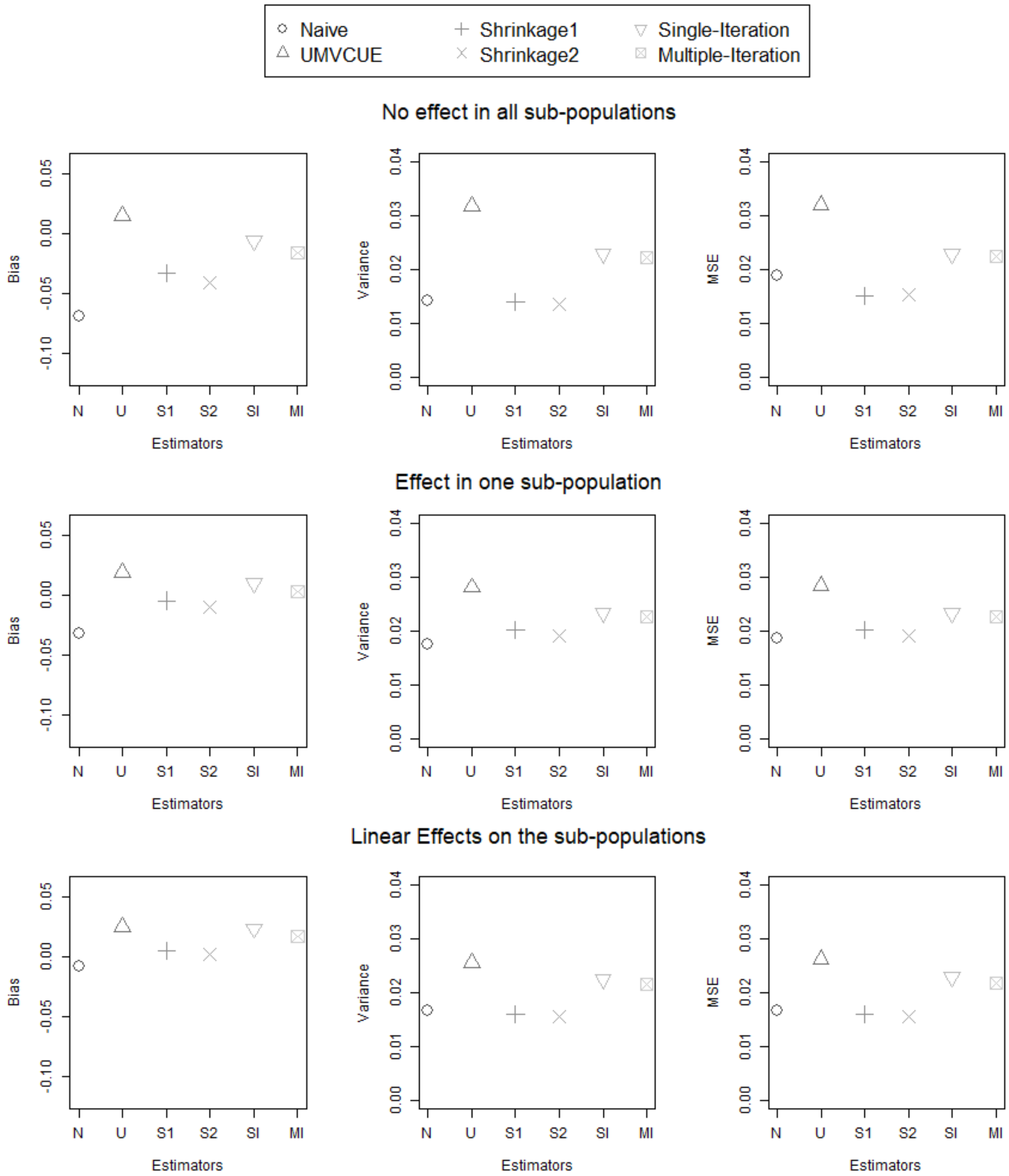

Figure 1: Estimators' performances in case of three sub-populations and $b = 0$. Top row: treatment ineffective in all sub-populations $\boldsymbol{\delta} = (0, 0, 0)$; Middle row: treatment effective only in one sub-population $\boldsymbol{\delta} = (0\ , 0\ , -0.3)$; Bottom row: linear effect on the sub-populations $\boldsymbol{\delta} = (-0.1, -0.2, -0.3)$. Left column: Bias; Centre column: Variance; Right column: Mean Squared Error.

1.2 Stage 1 patients followed for 90 days after interim analysis

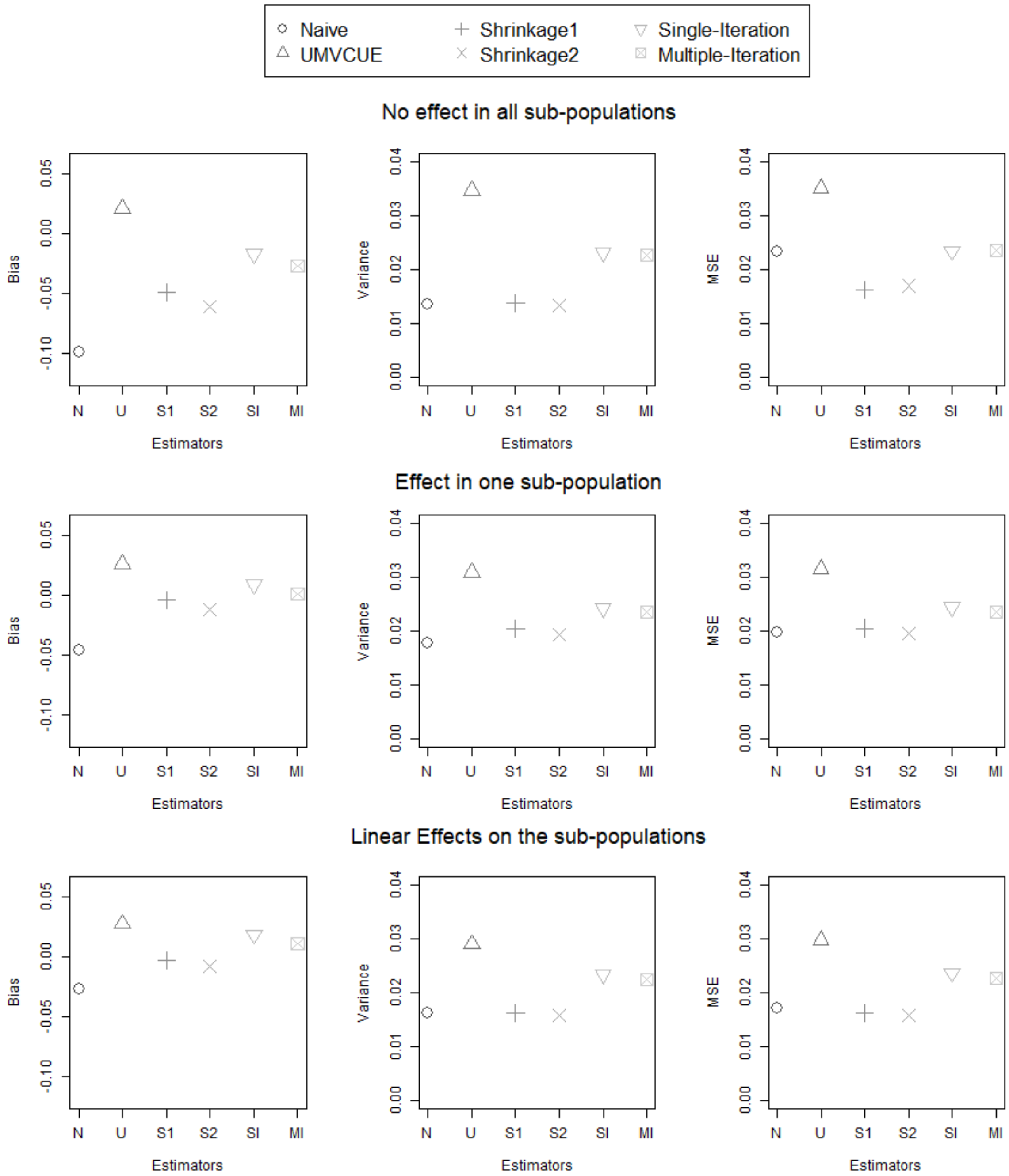

Figure 2: Estimators' performances in case of three sub-populations and $\tilde{T}_1 = T_1 + 90\ days$. Top row: treatment ineffective in all sub-populations $\boldsymbol{\delta} = (0, 0, 0)$; Middle row: treatment effective only in one sub-population $\boldsymbol{\delta} = (0\ , 0\ , -0.3)$; Bottom row: linear effect on the sub-populations $\boldsymbol{\delta} = (-0.1, -0.2, -0.3)$. Left column: Bias; Centre column: Variance; Right column: Mean Squared Error.

1.3 4 sub-populations

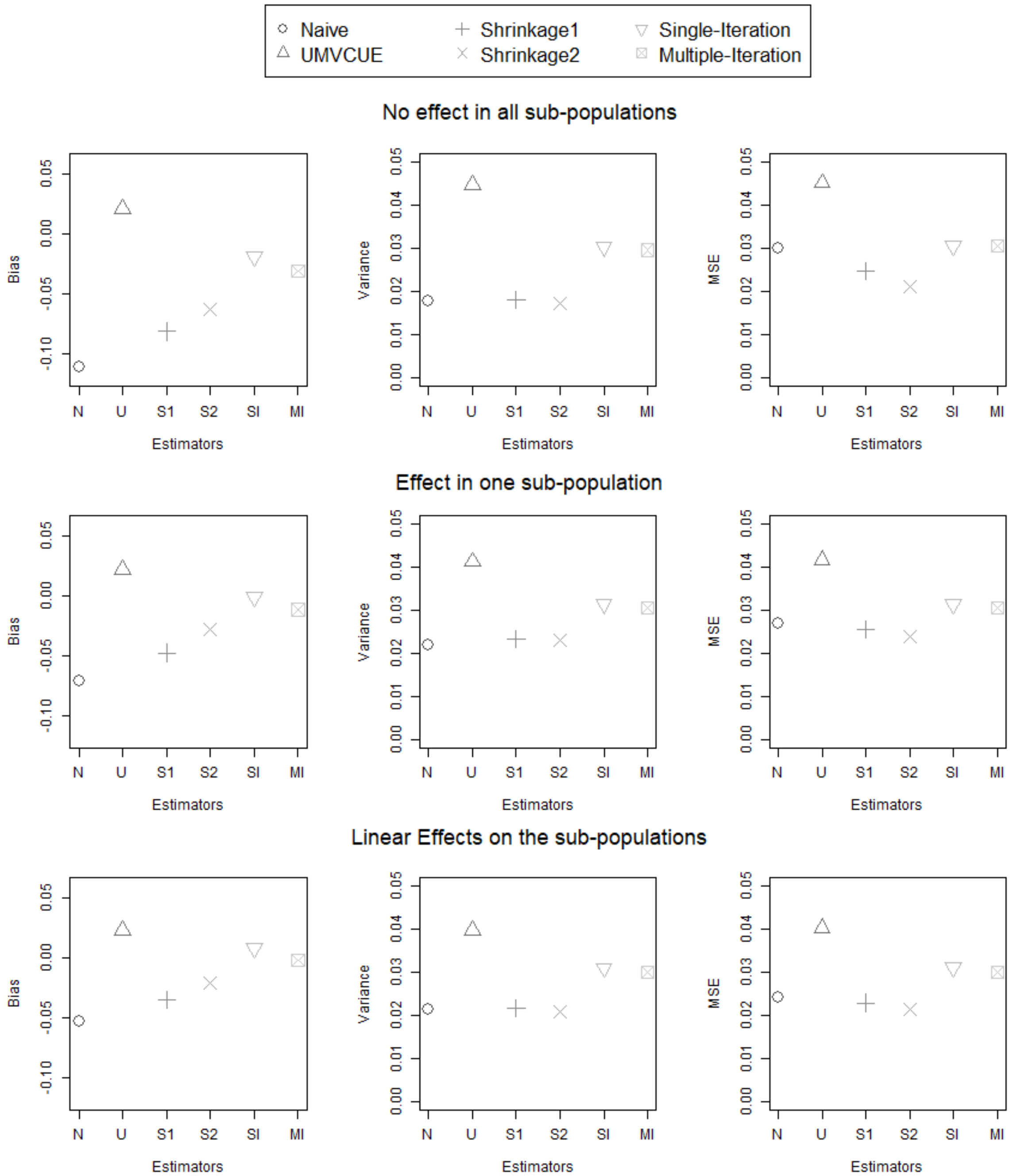

Figure 3: Estimators' performances in case of four sub-populations. Top row: treatment ineffective in all sub-populations $\boldsymbol{\delta} = (0, 0, 0, 0)$; Middle row: treatment effective only in one sub-population $\boldsymbol{\delta} = (0\ , 0\ , 0\ , -0.3)$; Bottom row: linear effect on the sub-populations $\boldsymbol{\delta} = (0\ , -0.1, -0.2, -0.3)$. Left column: Bias; Centre column: Variance; Right column: Mean Squared Error.

1.4 Sub-population specific bias, variance and MSE with 4 sub-populations

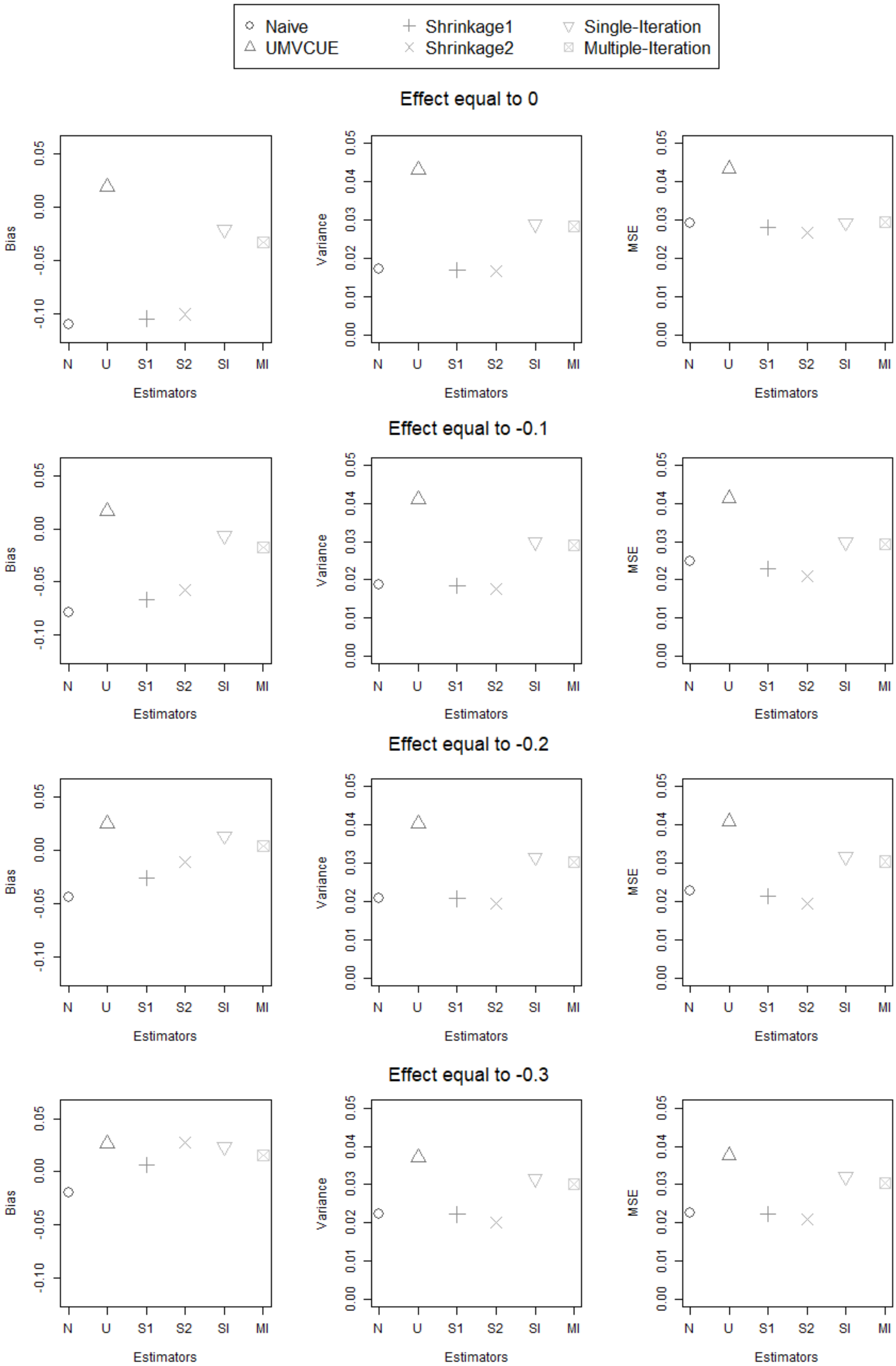

Figure 4: Estimators' performances in each sub-population in case of four sub-populations and linear effects on the sub-populations. From top row to bottom row effect equal to: $0, -0.1, -0.2, -0.3$. Left column: Bias; Centre column: Variance; Right column: Mean Squared Error.

2 Boxplots of the estimators

For completeness, we present also boxplots for the estimators.

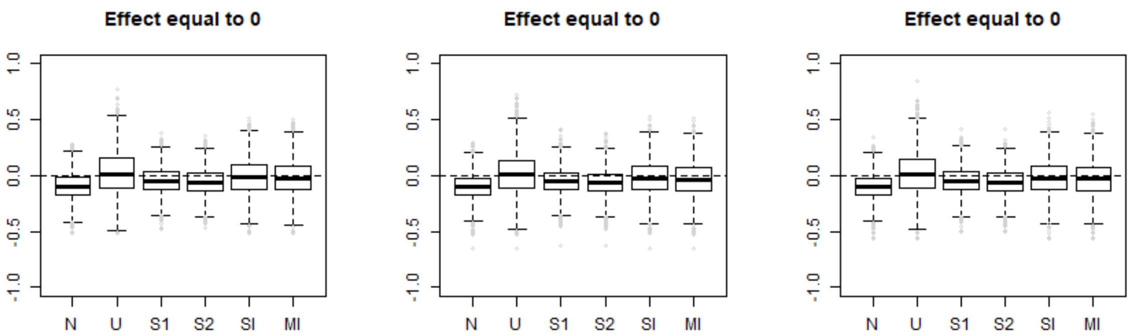

Figure 5: Estimators' boxplots for the different sub-populations in case of three sub-populations and effect equal to: $\boldsymbol{\delta} = (0, 0, 0)$.

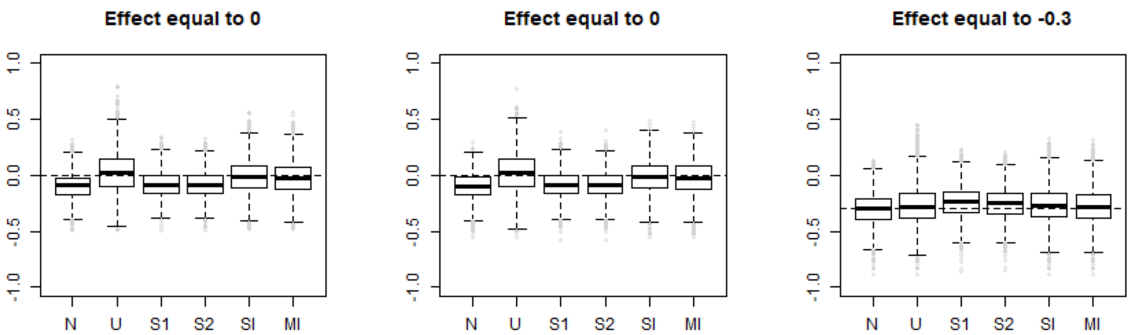

Figure 6: Estimators' boxplots for the different sub-populations in case of three sub-populations and effect equal to: $\boldsymbol{\delta} = (0, 0, -0.3)$.

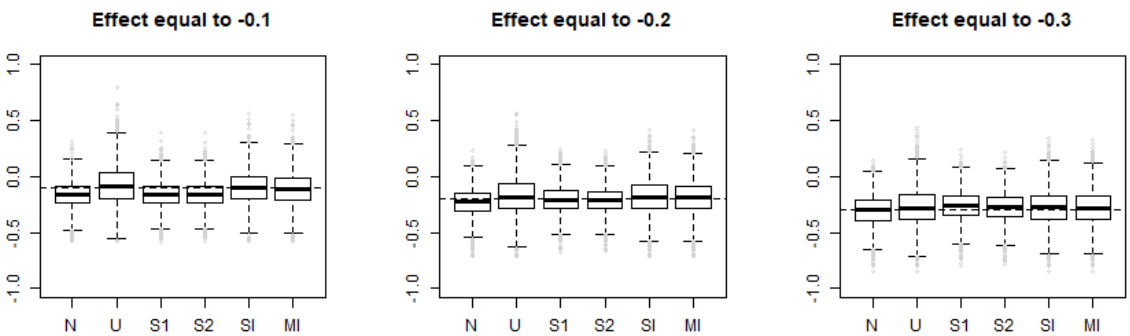

Figure 7: Estimators' boxplots for the different sub-populations in case of three sub-populations and effect equal to: $\boldsymbol{\delta} = (-0.1, -0.2, -0.3)$.

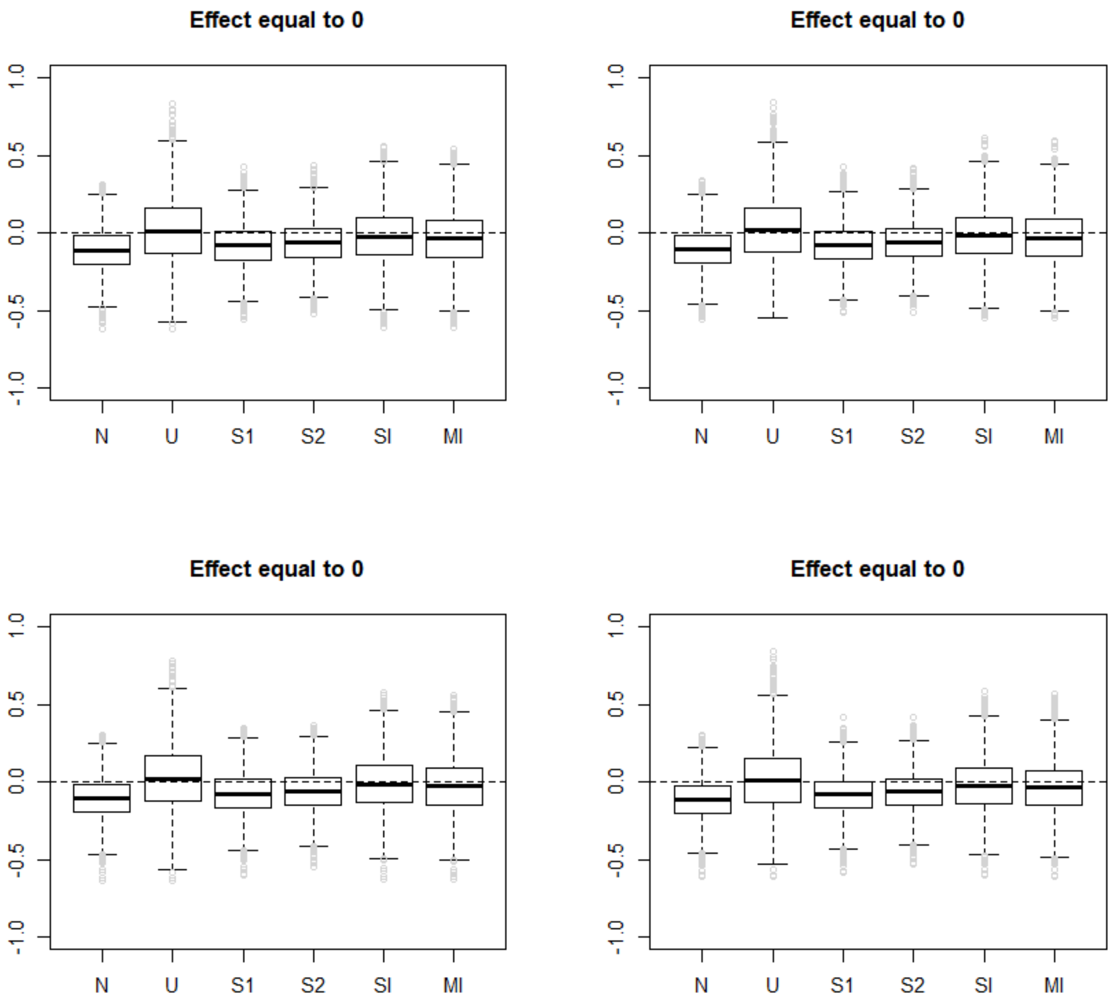

Figure 8: Estimators' boxplots for the different sub-populations in case of four sub-populations and effect equal to: $\boldsymbol{\delta} = (0, 0, 0, 0)$.

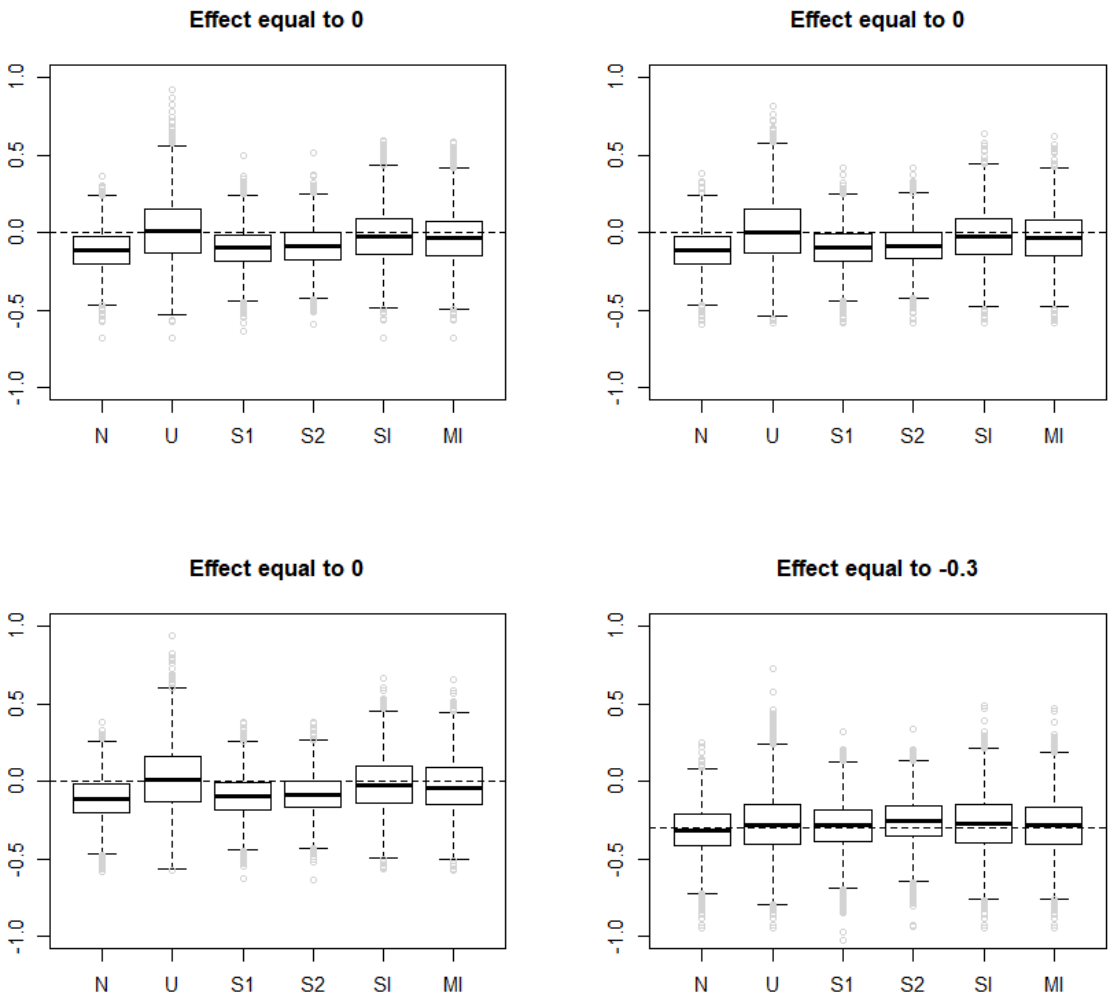

Figure 9: Estimators' boxplots for the different sub-populations in case of four sub-populations and effect equal to: $\boldsymbol{\delta} = (0, 0, 0, -0.3)$.

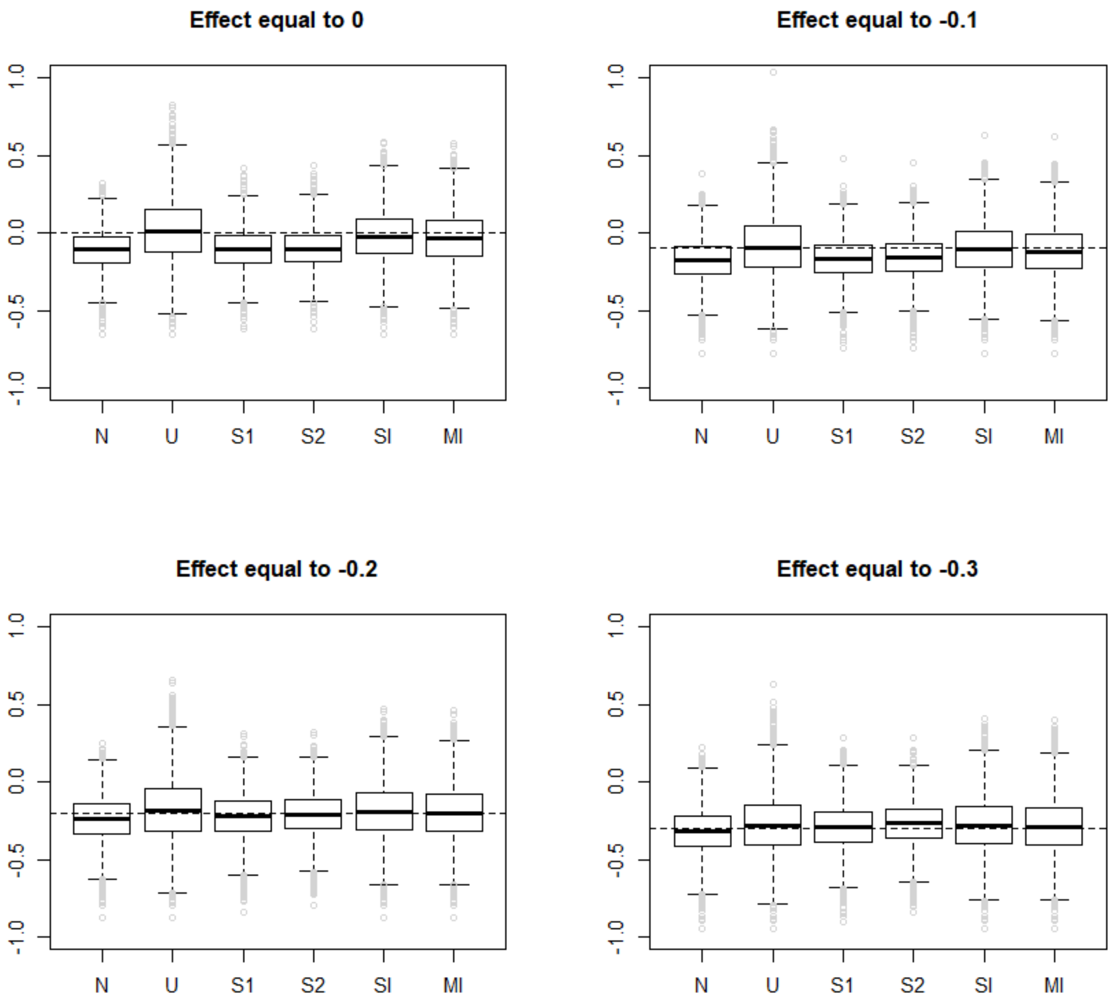

Figure 10: Estimators' boxplots for the different sub-populations in case of four sub-populations and effect equal to: $\boldsymbol{\delta} = (0, -0.1, -0.2, -0.3)$.