

# Supplemental Figures

Figure S1: BIC and scatter plot: Asthma

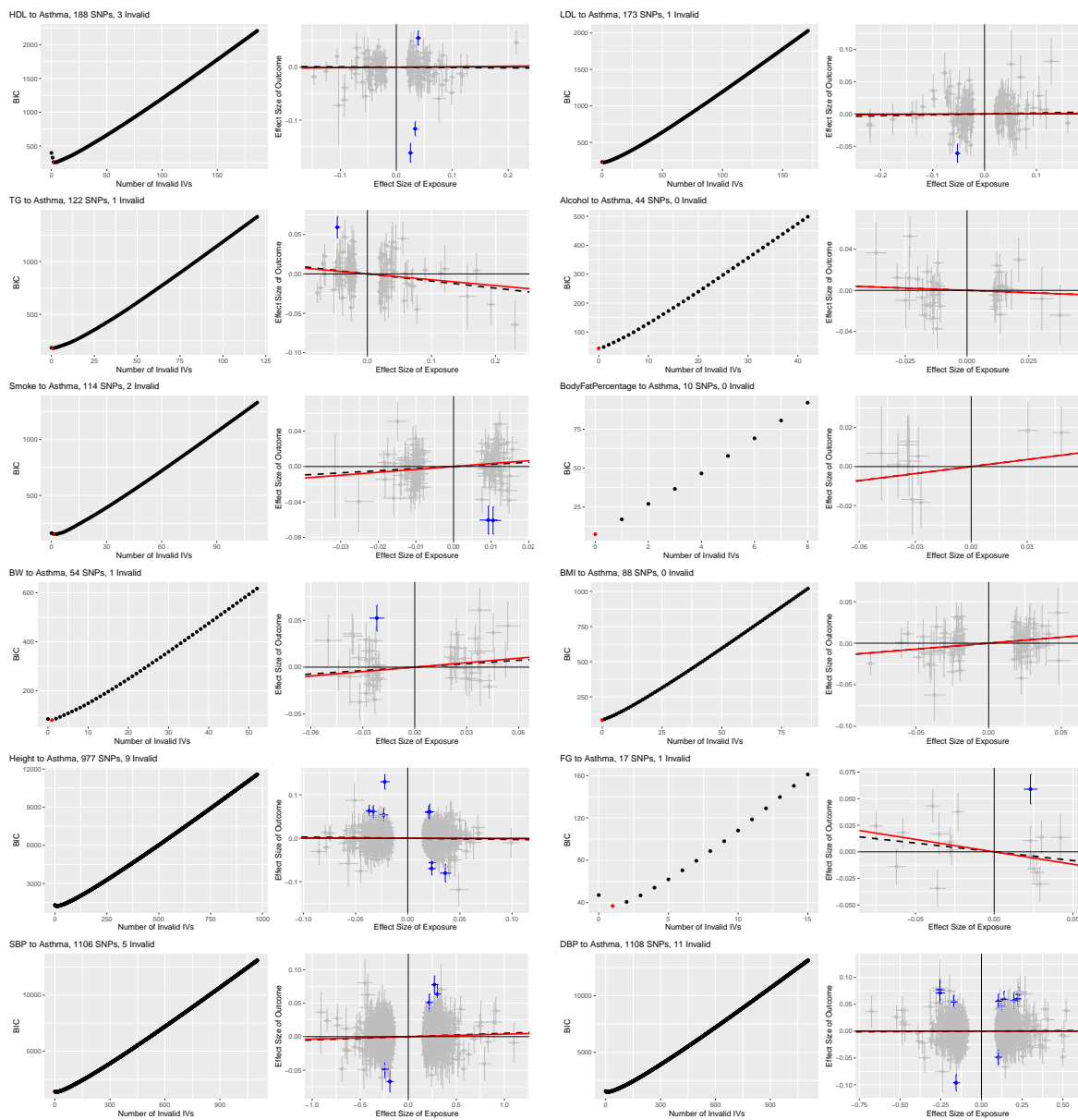


Figure S2: BIC and scatter plot: CAD

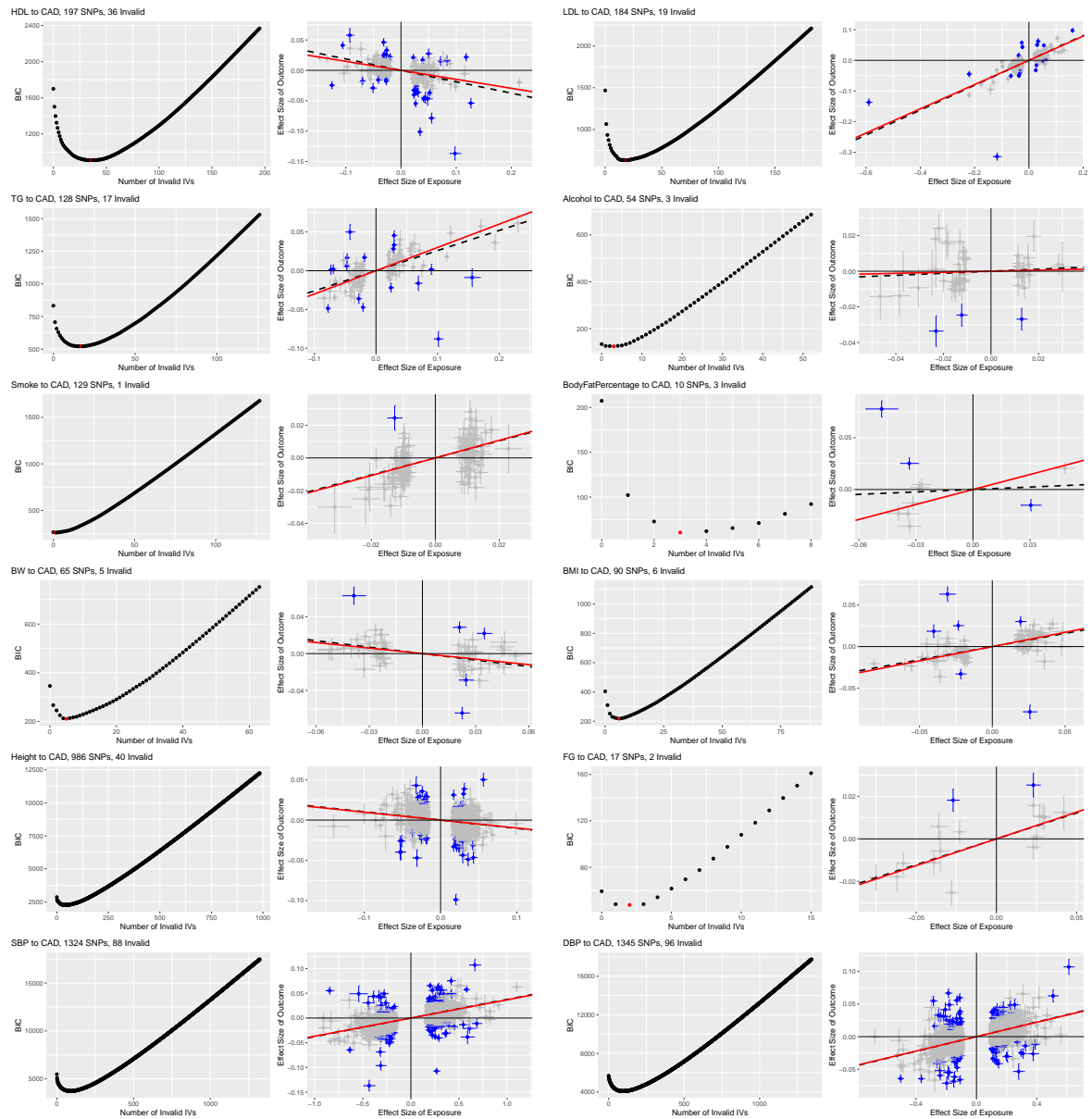


Figure S3: BIC and scatter plot: Stroke

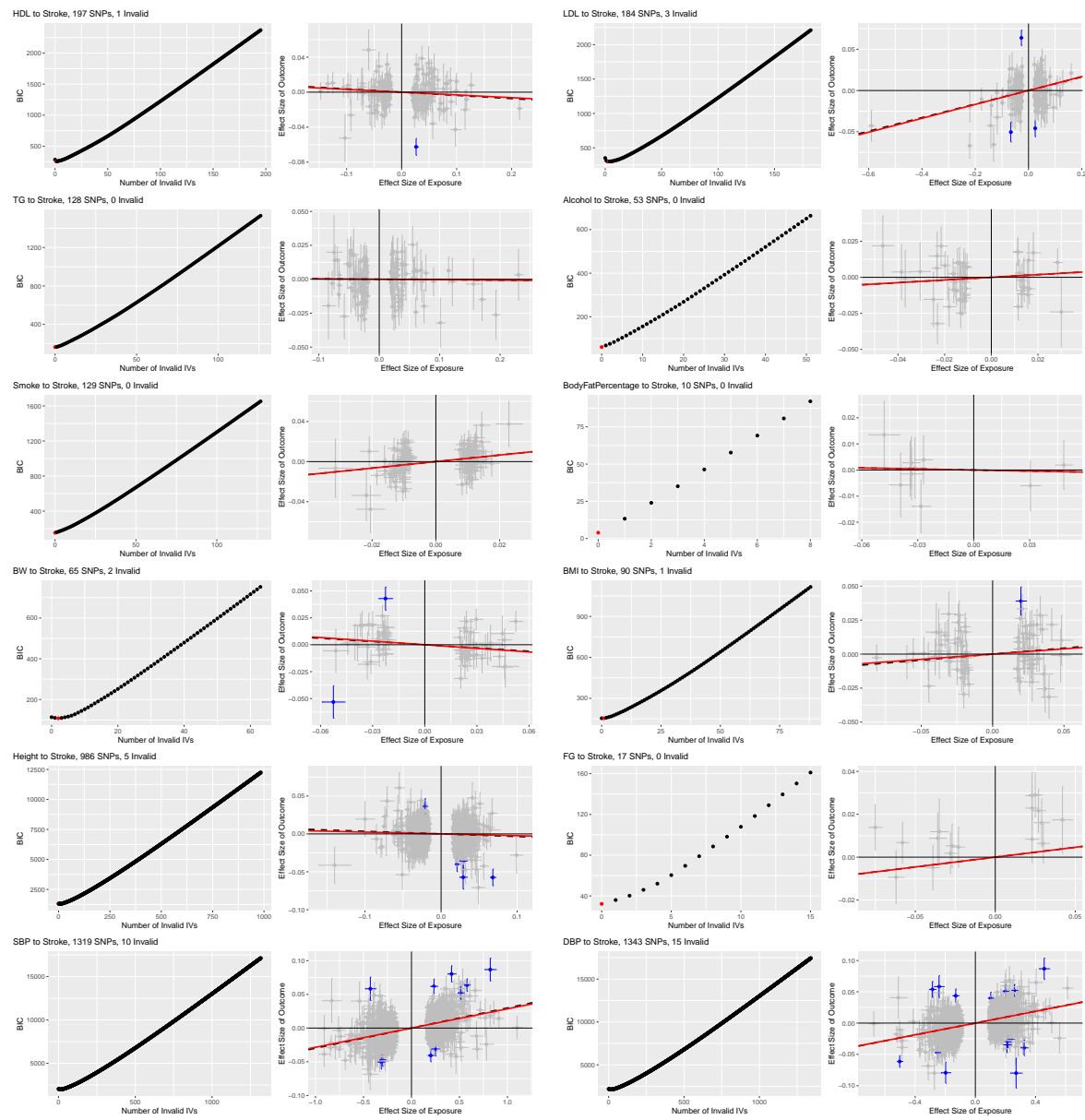


Figure S4: BIC and scatter plot: T2D

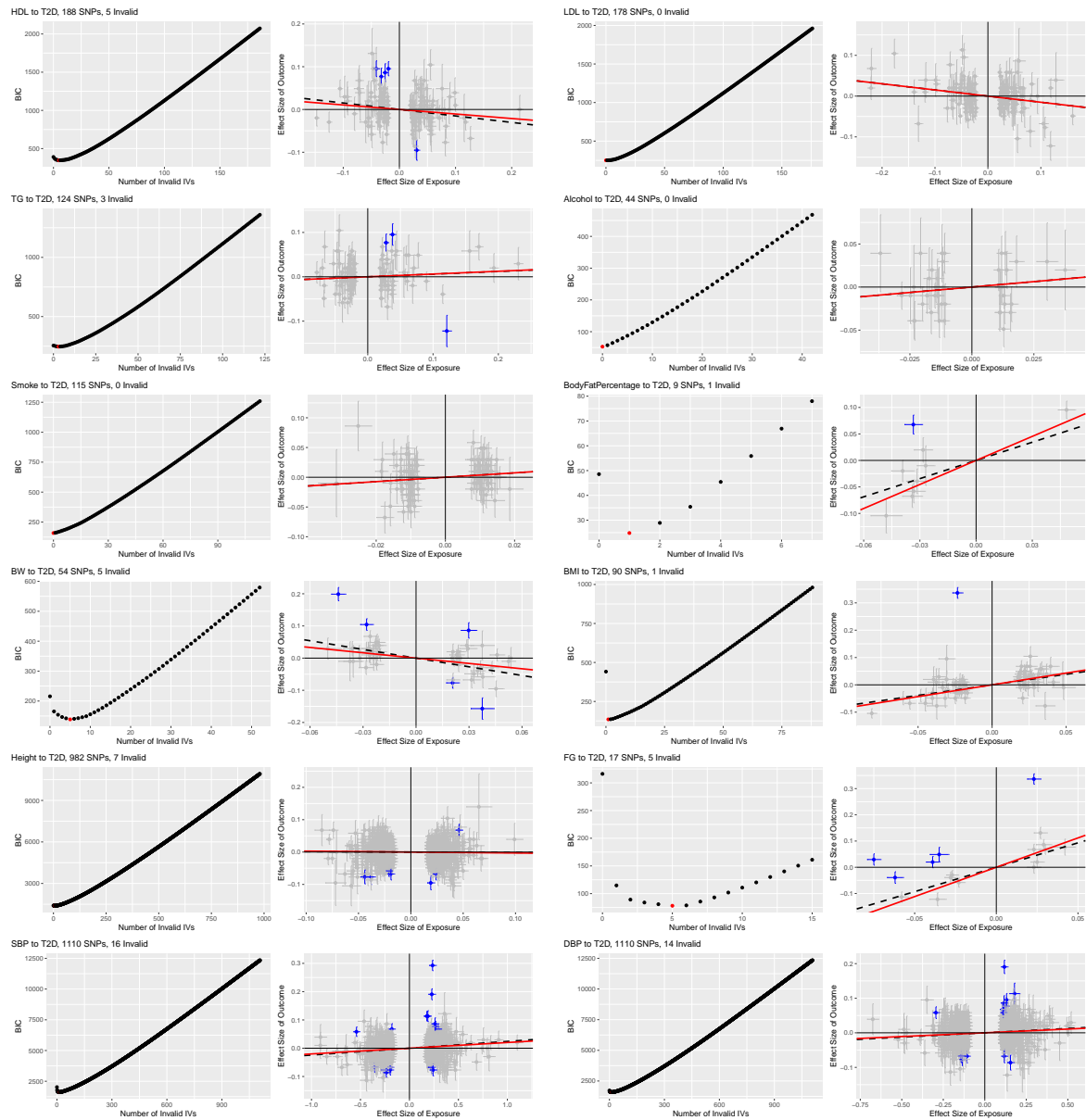


Figure S5: 53 trait pairs in secondary real data analysis: Q-Q plots for all 14 methods.

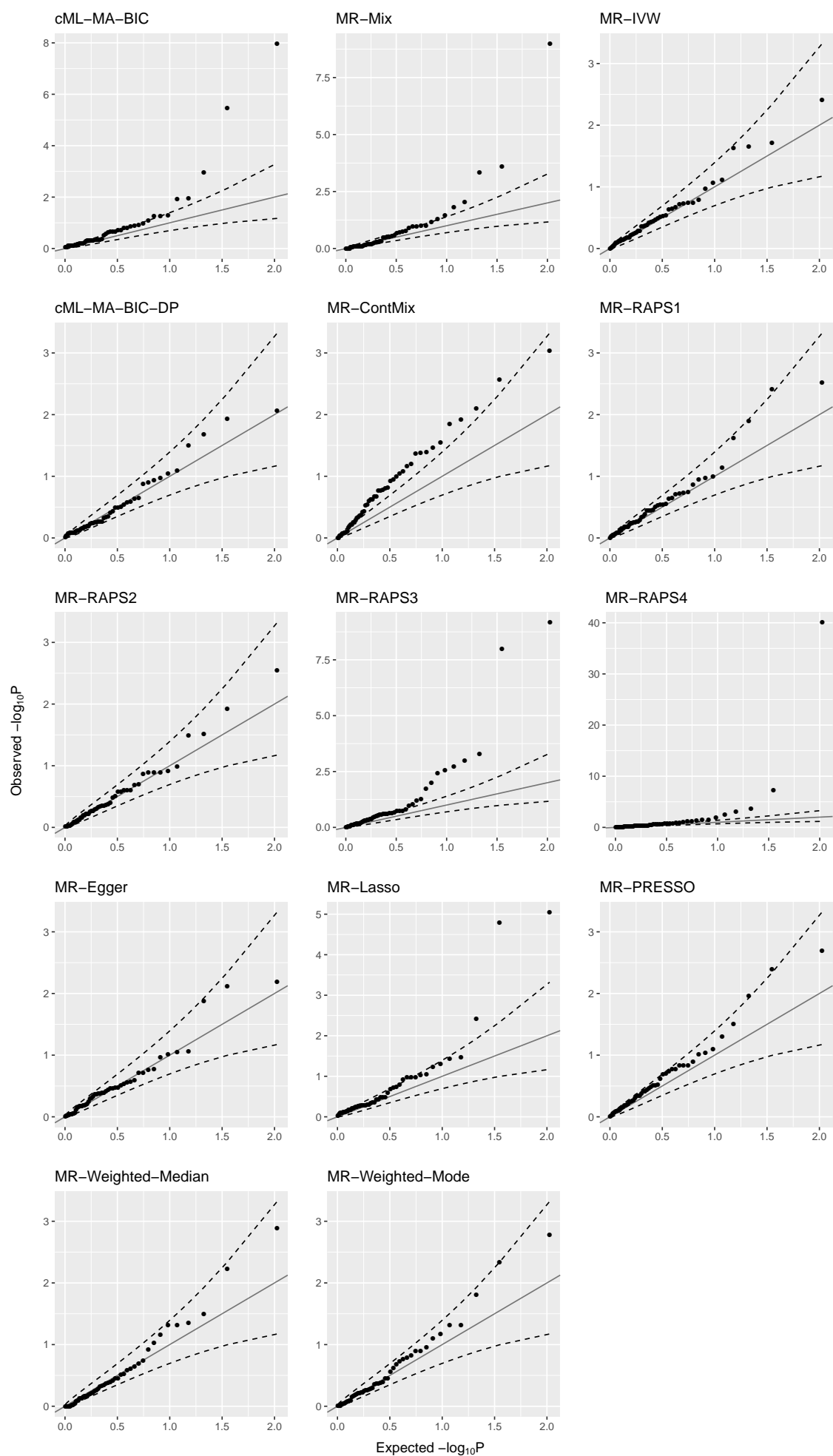


Figure S6: Main simulations: the empirical type-I error rates at the nominal level of 0.05 with sample size  $N = 50000$  and with  $m = 10$  or 100 SNPs, among which 0 to 60% were invalid IVs with the InSIDE assumption either holding or violated. The results were based on 10,000 simulations.

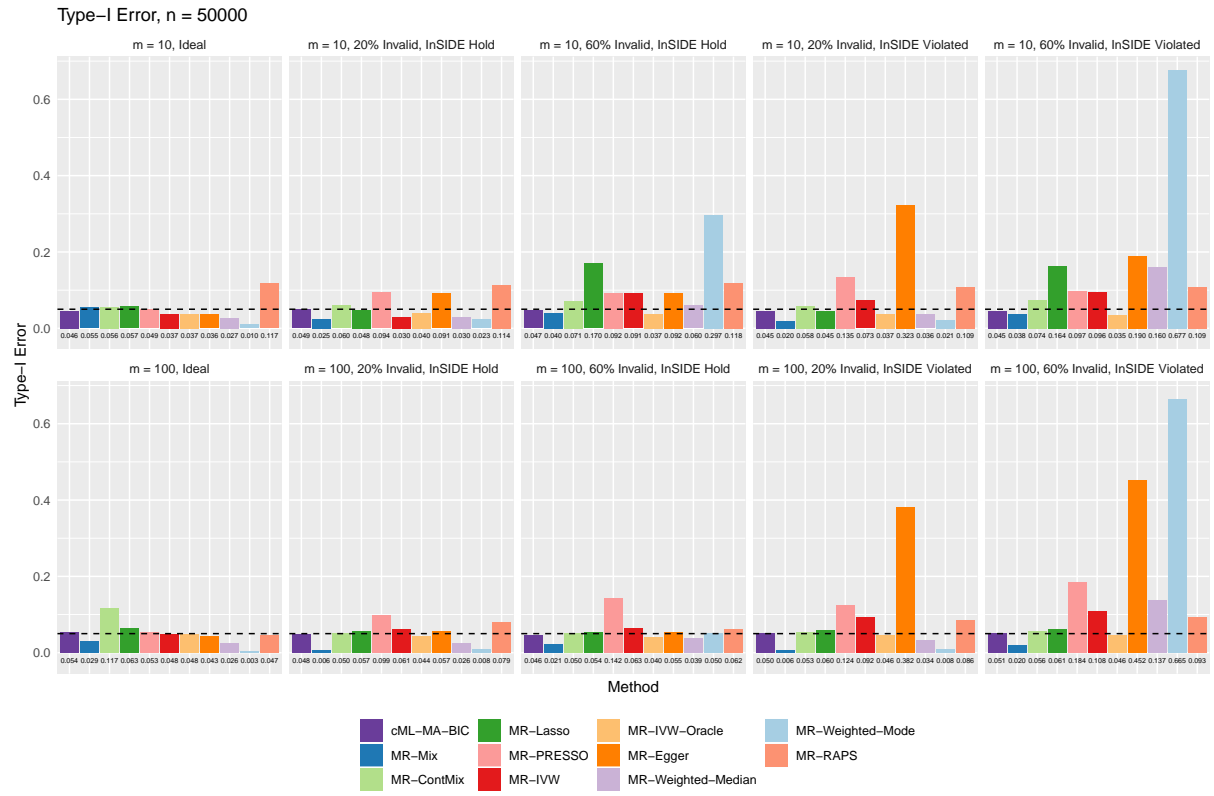


Figure S7: Secondary simulations: empirical type-I error rates (for  $\theta = 0$ ) and power (for  $\theta \neq 0$ ) with sample size  $N = 50000$  or  $100000$ , and with  $m = 10$  or  $100$  exposure-associated SNPs. The  $p$ -value cutoff  $0.001$  was used for CAUSE to select IVs.

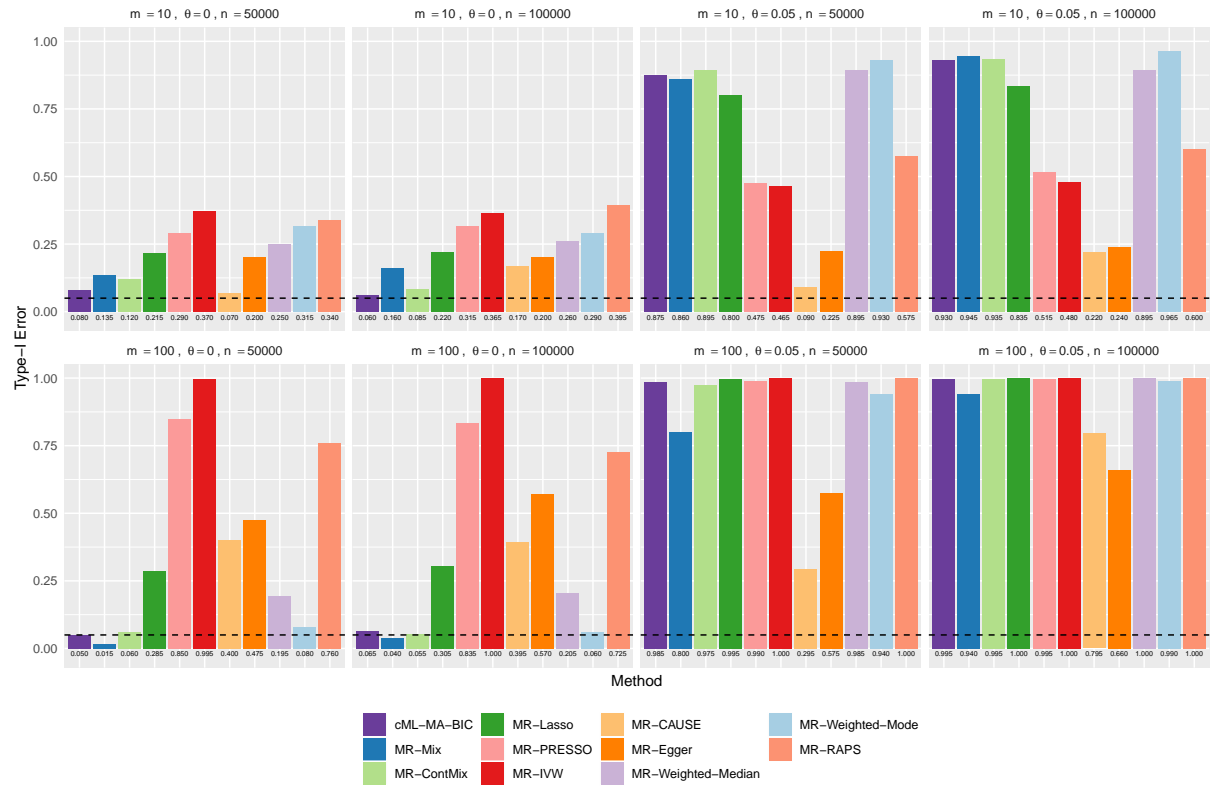
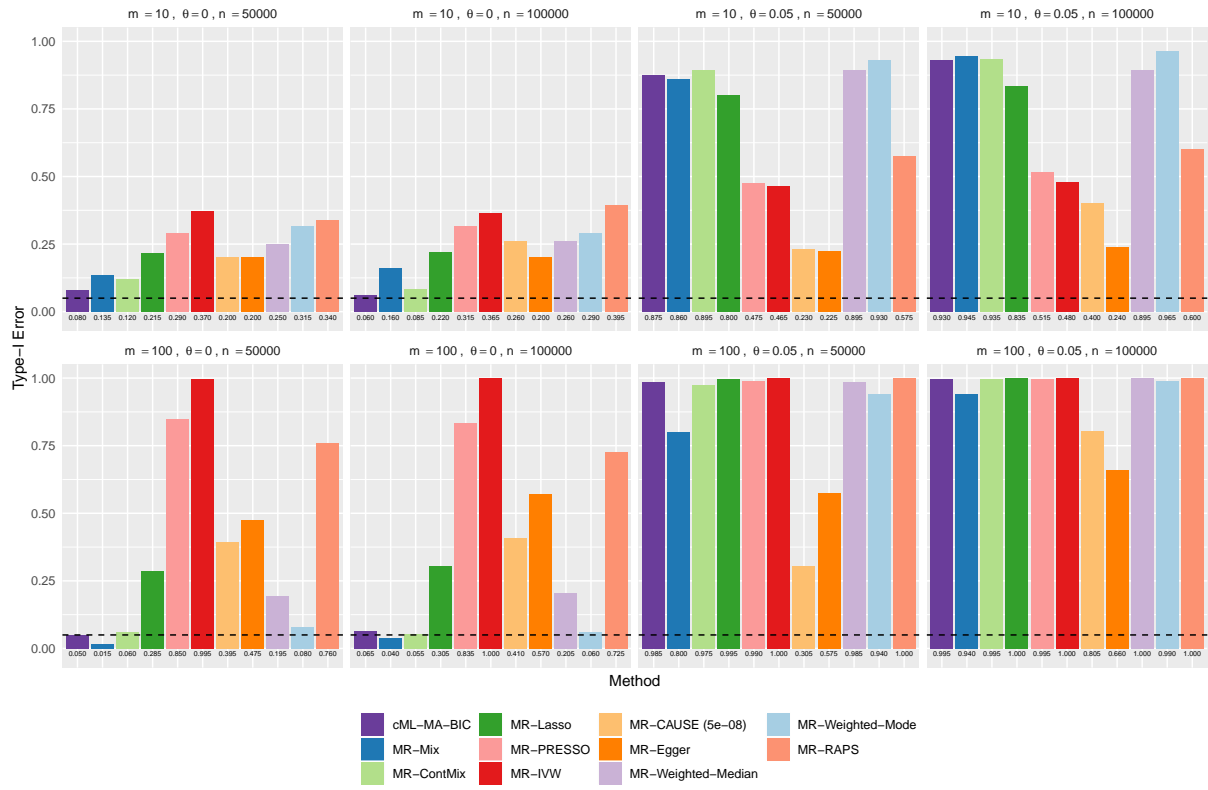


Figure S8: Secondary simulations: empirical type-I error rates (for  $\theta = 0$ ) and power (for  $\theta \neq 0$ ) with sample size  $N = 50000$  or  $100000$ , and with  $m = 10$  or  $100$  exposure-associated SNPs. The  $p$ -value cutoff  $5 \times 10^{-8}$  was used for CAUSE to select IVs.





# Supplemental Tables

Table S1: Inferring causal effects of 12 risk factors on Asthma, in each cell from top to bottom are  $p$ -value, estimated causal effect  $\hat{\theta}$  and its standard error  $SE(\hat{\theta})$ . Cells with  $p$ -value less than Bonferroni adjusted significant cutoff 0.001 are marked with red.

Method \ Exposure	HDL(188)	LDL(173)	TG(122)	Alcohol(44)	Smoke(114)	BF(10)	BW(54)	BMI(88)	Height(977)	FG(17)	SBP(1106)	DBP(1108)
cML-MA- AIC	1.2e-02, -9.2e-02, 3.6e-02	4.1e-01, 2.4e-02, 2.9e-02	3.9e-01, -3.8e-02, 4.5e-02	3.0e-01, -1.8e-01, 1.8e-01	1.3e-01, 2.4e-01, 1.6e-01	8.3e-01, 5.0e-02, 2.3e-01	1.1e-02, 2.6e-01, 1.0e-01	7.4e-03, 1.9e-01, 7.0e-02	2.9e-01, 2.2e-02, 2.1e-02	1.8e-02, -3.0e-01, 1.3e-01	1.7e-01, 2.9e-03, 2.1e-03	9.7e-02, -6.8e-03, 4.1e-03
cML- AIC	3.2e-03, -9.4e-02, 3.2e-02	5.7e-01, 1.6e-02, 2.8e-02	9.5e-01, 2.5e-03, 4.0e-02	2.9e-01, -1.7e-01, 1.6e-01	2.2e-01, 1.8e-01, 1.5e-01	3.8e-01, 1.2e-01, 1.4e-01	1.1e-02, 2.3e-01, 9.1e-02	1.4e-02, 1.5e-01, 6.2e-02	2.6e-01, 2.3e-02, 2.1e-02	6.2e-03, -3.2e-01, 1.2e-01	1.1e-01, 3.2e-03, 2.0e-03	4.8e-02, -7.0e-03, 3.6e-03
cML-MA-BIC-max	7.2e-01, 9.6e-03, 2.7e-02	9.1e-01, 2.8e-03, 2.5e-02	2.7e-02, -7.5e-02, 3.4e-02	5.7e-01, -8.6e-02, 1.5e-01	2.2e-02, 3.1e-01, 1.3e-01	3.8e-01, 1.2e-01, 1.4e-01	4.8e-02, 1.5e-01, 7.8e-02	1.5e-02, 1.4e-01, 5.9e-02	5.7e-01, -1.1e-02, 1.9e-02	1.7e-02, -2.4e-01, 9.9e-02	3.6e-02, 3.8e-03, 1.8e-03	9.8e-01, -8.9e-05, 3.1e-03
cML-BIC-max	7.2e-01, 9.7e-03, 2.7e-02	8.6e-01, 4.5e-03, 2.5e-02	2.7e-02, -7.4e-02, 3.4e-02	5.5e-01, -8.9e-02, 1.5e-01	1.4e-02, 3.3e-01, 1.3e-01	3.8e-01, 1.2e-01, 1.4e-01	3.9e-02, 1.6e-01, 7.7e-02	1.6e-02, 1.4e-01, 5.9e-02	5.9e-01, -1.0e-02, 1.9e-02	1.7e-02, -2.3e-01, 9.8e-02	3.2e-02, 3.9e-03, 1.8e-03	1.0e+00, 1.4e-05, 3.1e-03
cML-MA-BIC	7.3e-01, 9.4e-03, 2.7e-02	9.2e-01, 2.4e-03, 2.5e-02	2.7e-02, -7.5e-02, 3.4e-02	5.9e-01, -8.2e-02, 1.5e-01	2.1e-02, 3.1e-01, 1.3e-01	3.8e-01, 1.2e-01, 1.4e-01	4.8e-02, 1.5e-01, 7.8e-02	1.5e-02, 1.4e-01, 5.9e-02	5.8e-01, -1.1e-02, 1.9e-02	1.6e-02, -2.4e-01, 1.0e-01	5.0e-02, 3.6e-03, 1.8e-03	1.0e+00, 2.0e-06, 3.1e-03
cML-BIC	7.2e-01, 9.7e-03, 2.7e-02	8.6e-01, 4.5e-03, 2.5e-02	2.7e-02, -7.4e-02, 3.4e-02	5.5e-01, -8.9e-02, 1.5e-01	1.4e-02, 3.3e-01, 1.3e-01	3.8e-01, 1.2e-01, 1.4e-01	3.9e-02, 1.6e-01, 7.7e-02	1.6e-02, 1.4e-01, 5.9e-02	6.0e-01, -1.0e-02, 1.9e-02	1.7e-02, -2.3e-01, 9.8e-02	4.2e-02, 3.7e-03, 1.8e-03	9.8e-01, -7.0e-05, 3.1e-03
cML-MA-BIC-DP-Max	7.9e-01, 8.6e-03, 3.2e-02	8.7e-01, 4.7e-03, 2.9e-02	6.8e-02, -7.9e-02, 4.3e-02	6.1e-01, -8.3e-02, 1.7e-01	4.2e-02, 3.2e-01, 1.6e-01	4.4e-01, 1.1e-01, 1.5e-01	1.0e-01, 1.5e-01, 9.5e-02	2.3e-02, 1.5e-01, 6.6e-02	6.8e-01, -9.4e-03, 2.3e-02	7.3e-02, -2.3e-01, 1.3e-01	9.4e-02, 3.6e-03, 2.1e-03	9.0e-01, 4.5e-04, 3.6e-03
cML-BIC-DP-Max	8.2e-01, 7.5e-03, 3.3e-02	8.9e-01, 3.6e-03, 2.7e-02	7.4e-02, -8.1e-02, 4.6e-02	6.2e-01, -8.0e-02, 1.6e-01	3.8e-02, 3.3e-01, 1.6e-01	4.3e-01, 1.1e-01, 1.5e-01	7.6e-02, 1.5e-01, 8.6e-02	1.9e-02, 1.5e-01, 6.5e-02	6.8e-01, -8.9e-03, 2.2e-02	5.1e-02, -2.1e-01, 1.1e-01	8.9e-02, 3.6e-03, 2.1e-03	8.8e-01, 5.3e-04, 3.4e-03
cML-MA-BIC-DP	8.0e-01, 8.4e-03, 3.3e-02	8.8e-01, 4.5e-03, 2.9e-02	7.0e-02, -7.9e-02, 4.4e-02	6.2e-01, -8.5e-02, 1.7e-01	4.3e-02, 3.2e-01, 1.6e-01	4.4e-01, 1.1e-01, 1.5e-01	1.1e-01, 1.5e-01, 9.5e-02	2.4e-02, 1.5e-01, 6.7e-02	6.9e-01, -9.2e-03, 2.3e-02	7.9e-02, -2.4e-01, 1.4e-01	1.4e-01, 3.3e-03, 2.3e-03	9.2e-01, 3.8e-04, 3.9e-03
cML-BIC-DP	8.2e-01, 7.5e-03, 3.3e-02	8.9e-01, 3.6e-03, 2.7e-02	7.4e-02, -8.1e-02, 4.6e-02	6.0e-01, -8.9e-02, 1.7e-01	3.8e-02, 3.3e-01, 1.6e-01	4.3e-01, 1.1e-01, 1.5e-01	7.6e-02, 1.5e-01, 8.6e-02	1.9e-02, 1.5e-01, 6.5e-02	6.8e-01, -8.9e-03, 2.2e-02	8.7e-02, -2.5e-01, 1.5e-01	1.5e-01, 3.3e-03, 2.3e-03	9.1e-01, 4.5e-04, 4.0e-03
cML-MA-AIC-Profile	1.2e-02, -9.2e-02, 3.0e-02	4.1e-01, 2.4e-02, 3.0e-02	4.0e-01, -3.8e-02, 4.5e-02	3.1e-01, -1.8e-01, 1.8e-01	1.4e-01, 2.4e-01, 1.6e-01	8.3e-01, 5.0e-02, 2.4e-01	1.3e-02, 2.6e-01, 1.0e-01	8.2e-03, 1.9e-01, 7.0e-02	3.0e-01, 2.3e-02, 2.2e-02	1.9e-02, -3.0e-01, 1.3e-01	1.8e-01, 2.9e-03, 2.2e-03	1.0e-01, -6.8e-03, 4.2e-03
cML-AIC-Profile	3.5e-03, -9.4e-02, 3.2e-02	5.7e-01, 1.6e-02, 2.8e-02	9.5e-01, 2.5e-03, 4.1e-02	3.0e-01, -1.7e-01, 1.6e-01	2.4e-01, 1.8e-01, 1.5e-01	3.8e-01, 1.2e-01, 1.4e-01	1.3e-02, 2.3e-01, 9.3e-02	1.5e-02, 1.5e-01, 6.3e-02	2.7e-01, 2.3e-02, 2.1e-02	6.8e-03, -3.2e-01, 1.2e-01	1.2e-01, 3.2e-03, 2.1e-03	5.2e-02, -7.0e-03, 3.6e-03
cML-MA-BIC-max-Profile	7.2e-01, 9.6e-03, 2.7e-02	9.1e-01, 2.8e-03, 2.5e-02	2.7e-02, -7.5e-02, 3.4e-02	5.7e-01, -8.6e-02, 1.5e-01	2.4e-02, 3.1e-01, 1.4e-01	3.8e-01, 1.2e-01, 1.4e-01	4.8e-02, 1.5e-01, 7.8e-02	1.6e-02, 1.4e-01, 6.0e-02	5.7e-01, -1.1e-02, 1.9e-02	1.6e-02, -2.4e-01, 9.9e-02	3.7e-02, 3.8e-03, 1.8e-03	9.8e-01, -8.9e-05, 3.1e-03
cML-BIC-max-Profile	7.2e-01, 9.7e-03, 2.7e-02	8.6e-01, 4.5e-03, 2.5e-02	2.7e-02, -7.4e-02, 3.4e-02	5.6e-01, -8.9e-02, 1.5e-01	1.5e-02, 3.3e-01, 1.3e-01	3.8e-01, 1.2e-01, 1.4e-01	4.0e-02, 1.6e-01, 7.7e-02	1.7e-02, 1.4e-01, 6.0e-02	5.9e-01, -1.0e-02, 1.9e-02	1.6e-02, -2.3e-01, 9.8e-02	3.3e-02, 3.9e-03, 1.8e-03	1.0e+00, 1.4e-05, 3.1e-03
cML-MA-BIC-Profile	7.3e-01, 9.4e-03, 2.7e-02	9.2e-01, 2.4e-03, 2.5e-02	2.7e-02, -7.5e-02, 3.4e-02	5.9e-01, -8.2e-02, 1.5e-01	2.3e-02, 3.1e-01, 1.4e-01	3.8e-01, 1.2e-01, 1.4e-01	4.8e-02, 1.5e-01, 7.8e-02	1.6e-02, 1.4e-01, 6.0e-02	5.8e-01, -1.1e-02, 1.9e-02	1.6e-02, -2.4e-01, 1.0e-01	5.2e-02, 3.6e-03, 1.8e-03	1.0e+00, 2.0e-06, 3.1e-03
cML-BIC-Profile	7.2e-01, 9.7e-03, 2.7e-02	8.6e-01, 4.5e-03, 2.5e-02	2.7e-02, -7.4e-02, 3.4e-02	5.6e-01, -8.9e-02, 1.5e-01	1.5e-02, 3.3e-01, 1.3e-01	3.8e-01, 1.2e-01, 1.4e-01	4.0e-02, 1.6e-01, 7.7e-02	1.7e-02, 1.4e-01, 6.0e-02	6.0e-01, -1.0e-02, 1.9e-02	1.6e-02, -2.3e-01, 9.8e-02	4.3e-02, 3.7e-03, 1.8e-03	9.8e-01, -7.0e-05, 3.1e-03
CAUSE	1.0e+00, 9.5e-03, NA	8.7e-01, -1.8e-02, NA	1.7e-01, -9.2e-02, NA	8.1e-01, -7.1e-02, NA	5.0e-01, 1.3e-01, NA	5.7e-01, 9.6e-02, NA	7.3e-01, 5.7e-02, NA	1.6e-01, 1.3e-01, NA	1.0e+00, -2.7e-03, NA	3.5e-01, -2.0e-01, NA	7.6e-01, 2.5e-03, NA	5.9e-01, 3.9e-03, NA
MR-Mix	6.4e-01, 1.0e-02, 2.1e-02	4.7e-01, -1.0e-02, 1.4e-02	1.0e+00, 0.0e+00, 4.9e-02	9.5e-01, -3.0e-02, 4.6e-01	2.3e-01, 1.5e-01, 1.3e-01	3.4e-01, 4.0e-02, 4.2e-02	3.8e-01, 7.0e-02, 8.0e-02	1.4e-01, 4.5e-02, 3.0e-02	1.0e+00, 0.0e+00, 1.2e-02	7.3e-02, -5.0e-02, 2.8e-02	1.0e+00, 0.0e+00, 2.0e-02	1.0e+00, 0.0e+00, 2.1e-02
MR-ContMix	3.2e-01, -3.9e-02, NA	7.7e-01, -7.8e-03, NA	1.5e-01, -7.4e-02, NA	3.2e-01, -2.5e-01, NA	1.6e-01, 5.0e-01, NA	2.9e-01, 2.5e-01, NA	2.4e-02, 4.0e-01, NA	1.3e-02, 1.9e-01, NA	4.6e-01, 2.1e-02, NA	8.8e-02, -2.0e-01, NA	2.0e-01, 6.9e-03, NA	1.6e-01, -1.2e-02, NA
MR-Lasso	8.7e-01, -4.6e-03, 2.8e-02	9.3e-01, -2.2e-03, 2.5e-02	6.4e-03, -9.5e-02, 3.5e-02	5.6e-01, -8.7e-02, 1.5e-01	1.0e-02, 3.4e-01, 1.3e-01	3.8e-01, 1.2e-01, 1.3e-01	6.0e-03, 2.2e-01, 8.2e-02	1.6e-02, 1.4e-01, 5.9e-02	7.1e-01, -7.0e-03, 1.9e-02	7.1e-02, -2.3e-01, 1.3e-01	8.1e-02, 3.2e-03, 1.8e-03	8.0e-01, 8.2e-04, 3.2e-03
MR-PRESSO	7.4e-01, 9.6e-03, 2.9e-02	8.7e-01, 4.5e-03, 2.8e-02	6.2e-02, -7.4e-02, 3.9e-02	5.6e-01, -8.7e-02, 1.5e-01	2.5e-02, 3.2e-01, 1.4e-01	3.4e-01, 1.2e-01, 1.2e-01	7.6e-02, 1.5e-01, 8.7e-02	1.5e-02, 1.4e-01, 5.8e-02	7.0e-01, -7.9e-03, 2.0e-02	7.1e-02, -2.3e-01, 1.3e-01	5.2e-02, 3.8e-03, 2.0e-03	8.6e-01, 6.3e-04, 3.5e-03
MR-IVW	8.6e-01, -6.6e-03, 3.9e-02	6.2e-01, 1.4e-02, 2.9e-02	2.9e-02, -9.0e-02, 4.1e-02	5.6e-01, -8.7e-02, 1.5e-01	1.4e-01, 2.3e-01, 1.5e-01	3.8e-01, 1.2e-01, 1.3e-01	2.2e-01, 1.2e-01, 9.5e-02	1.6e-02, 1.4e-01, 5.9e-02	2.0e-01, -2.8e-02, 2.2e-02	3.3e-01, -1.6e-01, 1.6e-01	1.6e-02, 4.9e-03, 2.0e-03	6.5e-01, 1.6e-03, 3.6e-03
MR-Egger	9.9e-01, 7.5e-04, 7.3e-02	8.2e-01, -1.2e-02, 5.3e-02	5.1e-01, -4.8e-02, 7.3e-02	1.4e-01, -6.9e-01, 4.7e-01	4.9e-01, 5.1e-01, 7.4e-01	9.3e-01, 6.1e-02, 3.5e-01	8.5e-01, 6.7e-02, 3.5e-01	6.4e-02, 2.8e-01, 1.5e-01	5.6e-01, -3.9e-02, 6.7e-02	3.9e-01, -3.6e-01, 4.1e-01	8.5e-01, 1.2e-03, 6.0e-03	8.6e-02, -1.8e-02, 1.1e-02
MR-Weighted-Median	5.1e-01, 3.1e-02, 4.7e-02	2.6e-01, 4.7e-02, 4.1e-02	9.4e-01, -4.1e-03, 5.7e-02	5.9e-01, -1.2e-01, 2.0e-01	1.4e-01, 3.0e-01, 2.0e-01	9.0e-01, 2.3e-02, 1.8e-01	1.5e-01, 1.7e-01, 1.2e-01	1.0e-02, 2.5e-01, 9.5e-02	4.2e-01, -2.4e-02, 3.0e-02	2.0e-02, -3.2e-01, 1.4e-01	8.6e-01, 5.3e-04, 2.9e-03	1.8e-01, -6.9e-03, 5.2e-03
MR-Weighted-Mode	9.3e-01, 5.1e-03, 6.2e-02	6.2e-01, 2.3e-02, 4.6e-02	3.5e-01, -5.9e-02, 6.4e-02	4.3e-01, -2.8e-01, 3.5e-01	9.4e-01, 3.7e-02, 4.9e-01	5.3e-01, -1.7e-01, 2.8e-01	4.5e-01, 2.1e-01, 2.8e-01	4.9e-02, 2.4e-01, 1.2e-01	1.3e-01, -1.5e-01, 9.9e-02	8.8e-02, -2.7e-01, 1.6e-01	3.4e-01, -1.1e-02, 1.2e-02	1.5e-01, -2.9e-02, 2.0e-02
MR-RAPS1	9.9e-01, -4.9e-04, 3.8e-02	5.9e-01, 1.5e-02, 2.9e-02	2.0e-02, -9.4e-02, 4.1e-02	5.6e-01, -8.9e-02, 1.5e-01	1.6e-01, 2.3e-01, 1.6e-01	3.8e-01, 1.2e-01, 1.4e-01	1.8e-01, 1.3e-01, 9.6e-02	1.6e-02, 1.4e-01, 6.0e-02	2.4e-01, -2.6e-02, 2.2e-02	3.5e-01, -1.5e-01, 1.6e-01	2.2e-02, 4.7e-03, 2.1e-03	7.1e-01, 1.4e-03, 3.7e-03
MR-RAPS2	7.7e-01, 9.3e-03, 3.1e-02	8.0e-01, 7.3e-03, 2.9e-02	4.3e-02, -8.4e-02, 4.1e-02	6.2e-01, -7.7e-02, 1.5e-01	3.0e-02, 3.2e-01, 1.5e-01	4.1e-01, 1.2e-01, 1.4e-01	1.0e-01, 1.5e-01, 9.5e-02	1.4e-02, 1.5e-01, 6.2e-02	7.5e-01, -6.8e-03, 2.1e-02	2.3e-01, -1.9e-01, 1.6e-01	1.0e-01, 3.4e-03, 2.1e-03	9.8e-01, 8.7e-05, 3.6e-03
MR-RAPS3	8.0e-01, -6.7e-03, 2.7e-02	5.7e-01, 1.4e-02, 2.5e-02	7.0e-03, -9.1e-02, 3.4e-02	5.6e-01, -8.9e-02, 1.5e-01	1.4e-01, 2.4e-01, 1.4e-01	3.8e-01, 1.2e-01, 1.4e-01	1.2e-01, 1.2e-01, 7.8e-02	1.6e-02, 1.4e-01, 6.0e-02	1.3e-01, -2.9e-02, 1.9e-02	9.5e-02, -1.6e-01, 9.9e-02	6.6e-03, 5.0e-03, 1.8e-03	5.9e-01, 1.7e-03, 3.1e-03
MR-RAPS4	8.7e-01, 4.5e-03, 2.7e-02	8.7e-01, 4.2e-03, 2.6e-02	3.7e-02, -7.2e-02, 3.4e-02	6.2e-01, -7.7e-02, 1.5e-01	1.6e-02, 3.3e-01, 1.4e-01	4.0e-01, 1.2e-01, 1.4e-01	3.2e-02, 1.7e-01, 7.9e-02	1.4e-02, 1.5e-01, 6.1e-02	7.3e-01, -6.8e-03, 2.0e-02	1.1e-02, -2.5e-01, 1.0e-01	8.6e-02, 3.2e-03, 1.9e-03	1.0e+00, 2.0e-05, 3.2e-03

Table S2: Inferring causal effects of 12 risk factors on CAD, in each cell from top to bottom are  $p$ -value, estimated causal effect  $\hat{\theta}$  and its standard error  $SE(\hat{\theta})$ . Cells with  $p$ -value less than Bonferroni adjusted significant cutoff 0.001 are marked with red.

Exposure Method	HDL(197)	LDL(184)	TG(128)	Alcohol(54)	Smoke(129)	BF(10)	BW(65)	BMI(90)	Height(986)	FG(17)	SBP(1324)	DBP(1345)
cML-MA- AIC	3.4e-18, -1.4e-01, 1.6e-02	2.6e-132, 4.4e-01, 1.8e-02	6.0e-02, 1.2e-01, 6.4e-02	4.7e-04, 2.4e-01, 6.9e-02	6.1e-26, 7.5e-01, 7.1e-02	5.1e-07, 4.8e-01, 9.6e-02	4.6e-01, -3.1e-02, 4.2e-02	3.9e-28, 3.7e-01, 3.3e-02	4.7e-24, -9.8e-02, 9.6e-03	1.0e-07, 2.6e-01, 4.8e-02	3.9e-92, 3.0e-02, 1.5e-03	1.3e-153, 5.2e-02, 2.0e-03
cML- AIC	3.0e-23, -1.4e-01, 1.4e-02	1.1e-178, 4.4e-01, 1.5e-02	1.8e-14, 1.6e-01, 2.1e-02	8.0e-05, 2.6e-01, 6.6e-02	1.5e-33, 7.4e-01, 6.2e-02	7.2e-10, 5.1e-01, 8.2e-02	3.1e-01, -3.8e-02, 3.8e-02	8.2e-40, 3.8e-01, 2.9e-02	3.4e-25, -9.6e-02, 9.3e-03	3.6e-09, 2.6e-01, 4.3e-02	2.4e-247, 3.0e-02, 8.9e-04	1.7e-229, 5.1e-02, 1.6e-03
cML-MA-BIC-max	3.3e-30, -1.4e-01, 1.2e-02	1.3e-209, 4.0e-01, 1.3e-02	3.9e-55, 2.9e-01, 1.8e-02	3.4e-01, 6.0e-02, 6.3e-02	1.3e-23, 5.4e-01, 5.4e-02	2.4e-09, 4.7e-01, 7.8e-02	3.1e-11, -2.0e-01, 3.1e-02	9.8e-47, 3.4e-01, 2.4e-02	2.6e-36, 3.4e-01, 7.9e-03	3.1e-10, 2.7e-01, 4.2e-02	0.0e+00, 3.7e-02, 7.5e-04	0.0e+00, 5.6e-02, 1.4e-03
cML-BIC-max	2.9e-33, -1.3e-01, 1.1e-02	2.5e-306, 4.0e-01, 1.1e-02	1.6e-88, 2.8e-01, 1.4e-02	6.1e-01, 2.9e-02, 5.8e-02	1.9e-24, 5.4e-01, 5.3e-02	4.3e-12, 4.8e-01, 7.0e-02	1.6e-11, -2.0e-01, 3.0e-02	2.4e-48, 3.4e-01, 2.4e-02	2.7e-38, -1.0e-01, 7.7e-03	4.2e-12, 2.8e-01, 4.0e-02	0.0e+00, 3.7e-02, 7.3e-04	0.0e+00, 5.5e-02, 1.2e-03
cML-MA-BIC	4.7e-27, -1.5e-01, 1.4e-02	1.4e-206, 4.1e-01, 1.3e-02	3.3e-70, 3.0e-01, 1.7e-02	3.6e-01, 5.8e-02, 6.4e-02	1.1e-23, 5.5e-01, 5.4e-02	1.1e-07, 4.6e-01, 8.7e-02	1.1e-10, -2.0e-01, 3.1e-02	1.6e-46, 3.4e-01, 2.4e-02	4.6e-36, -9.8e-02, 7.8e-03	1.4e-08, 2.5e-01, 4.4e-02	0.0e+00, 3.7e-02, 7.5e-04	0.0e+00, 5.6e-02, 1.3e-03
cML-BIC	9.7e-40, -1.5e-01, 1.1e-02	2.9e-293, 4.0e-01, 1.1e-02	9.9e-96, 3.0e-01, 1.4e-02	6.1e-01, 2.9e-02, 5.8e-02	1.9e-24, 5.4e-01, 5.3e-02	4.3e-12, 4.8e-01, 7.0e-02	1.6e-11, -2.0e-01, 3.0e-02	2.4e-48, 3.4e-01, 2.4e-02	6.6e-37, -9.9e-02, 7.8e-03	3.2e-10, 2.5e-01, 4.0e-02	0.0e+00, 3.7e-02, 7.3e-04	0.0e+00, 5.5e-02, 1.3e-03
cML-MA-BIC-DP-Max	9.1e-08, -1.6e-01, 2.9e-02	9.9e-33, 4.0e-01, 3.4e-02	2.9e-10, 2.6e-01, 4.2e-02	1.9e-01, 1.1e-01, 8.8e-02	8.4e-14, 5.5e-01, 7.4e-02	3.7e-03, 4.5e-01, 1.6e-01	4.3e-05, -1.9e-01, 4.7e-02	2.7e-28, 3.4e-01, 3.1e-02	7.9e-18, -9.7e-02, 1.1e-02	5.3e-06, 2.5e-01, 5.6e-02	9.1e-134, 3.6e-02, 1.4e-03	2.6e-100, 5.5e-02, 2.6e-03
cML-BIC-DP-Max	8.4e-08, -1.6e-01, 2.9e-02	4.1e-28, 4.0e-01, 3.7e-02	2.6e-10, 2.6e-01, 4.2e-02	1.9e-01, 1.2e-01, 8.8e-02	4.0e-14, 5.6e-01, 7.4e-02	4.7e-03, 4.7e-01, 1.6e-01	3.3e-05, -2.0e-01, 4.7e-02	8.1e-29, 3.4e-01, 3.1e-02	8.1e-18, 2.5e-01, 1.1e-02	5.6e-06, 2.5e-01, 5.5e-02	2.4e-131, 3.6e-02, 1.5e-03	1.8e-101, 5.5e-02, 2.6e-03
cML-MA-BIC-DP	5.7e-07, -1.6e-01, 3.2e-02	3.3e-28, 4.0e-01, 3.7e-02	7.2e-10, 2.6e-01, 4.3e-02	1.8e-01, 1.2e-01, 8.8e-02	1.1e-13, 5.5e-01, 7.4e-02	1.1e-02, 4.5e-01, 1.8e-01	8.3e-05, -1.9e-01, 4.8e-02	1.0e-27, 3.4e-01, 3.2e-02	1.0e-17, -9.7e-02, 1.1e-02	5.7e-06, 2.5e-01, 5.5e-02	4.4e-133, 3.6e-02, 1.5e-03	1.4e-100, 5.5e-02, 2.6e-03
cML-BIC-DP	8.4e-08, -1.6e-01, 2.9e-02	4.1e-28, 4.0e-01, 3.7e-02	2.6e-10, 2.6e-01, 4.2e-02	1.9e-01, 1.2e-01, 8.8e-02	2.8e-13, 5.4e-01, 7.4e-02	4.7e-03, 4.7e-01, 1.6e-01	8.4e-05, -1.9e-01, 4.8e-02	8.1e-29, 3.4e-01, 3.1e-02	1.8e-17, -9.8e-02, 1.1e-02	5.6e-06, 2.5e-01, 5.5e-02	2.4e-131, 3.6e-02, 1.5e-03	1.8e-101, 5.5e-02, 2.6e-03
cML-MA-AIC-Profile	3.6e-15, -1.5e-01, 1.9e-02	6.7e-105, 4.2e-01, 1.9e-02	6.1e-02, 1.2e-01, 6.4e-02	6.1e-04, 2.4e-01, 7.0e-02	7.5e-25, 7.5e-01, 7.3e-02	7.2e-07, 4.8e-01, 9.8e-02	4.4e-01, -3.3e-02, 4.2e-02	1.7e-27, 3.7e-01, 3.4e-02	3.0e-23, -9.8e-02, 9.8e-03	1.3e-07, 2.6e-01, 4.8e-02	1.2e-168, 3.1e-02, 1.1e-03	1.9e-168, 5.2e-02, 1.9e-03
cML-AIC-Profile	6.5e-26, -1.6e-01, 1.5e-02	7.9e-161, 4.2e-01, 1.6e-02	3.4e-14, 1.6e-01, 2.1e-02	1.1e-04, 2.4e-01, 6.8e-02	1.2e-31, 7.4e-01, 6.3e-02	1.3e-09, 5.1e-01, 8.4e-02	3.2e-01, -3.8e-02, 3.9e-02	1.5e-38, 3.8e-01, 2.9e-02	1.8e-24, -9.6e-02, 9.4e-03	5.4e-09, 2.6e-01, 4.4e-02	8.2e-251, 3.1e-02, 9.2e-04	1.6e-224, 5.2e-02, 1.6e-03
cML-MA-BIC-max-Profile	1.0e-30, -1.4e-01, 1.2e-02	3.9e-274, 4.0e-01, 1.1e-02	4.1e-61, 2.9e-01, 1.7e-02	3.4e-01, 6.0e-02, 6.3e-02	3.1e-24, 5.4e-01, 5.3e-02	8.3e-10, 4.7e-01, 7.6e-02	1.2e-11, -2.0e-01, 3.0e-02	4.5e-47, 3.4e-01, 2.4e-02	4.2e-37, -1.0e-01, 7.8e-03	2.3e-10, 2.7e-01, 4.2e-02	0.0e+00, 3.7e-02, 7.3e-04	0.0e+00, 5.6e-02, 1.3e-03
cML-BIC-max-Profile	2.6e-34, -1.3e-01, 1.1e-02	0.0e+00, 4.0e-01, 1.1e-02	6.6e-91, 2.8e-01, 1.4e-02	6.1e-01, 2.9e-02, 5.8e-02	3.8e-25, 5.4e-01, 5.2e-02	6.7e-13, 4.8e-01, 6.7e-02	5.9e-12, -2.0e-01, 2.9e-02	1.1e-48, 3.4e-01, 2.3e-02	7.2e-39, -1.0e-01, 7.7e-03	2.5e-12, 2.8e-01, 3.9e-02	0.0e+00, 3.7e-02, 7.2e-04	0.0e+00, 5.6e-02, 1.2e-03
cML-MA-BIC-Profile	3.0e-25, -1.5e-01, 1.4e-02	2.2e-220, 4.0e-01, 1.3e-02	2.0e-76, 2.9e-01, 1.6e-02	3.6e-01, 5.8e-02, 6.4e-02	2.9e-24, 5.5e-01, 5.4e-02	6.0e-08, 4.6e-01, 8.5e-02	4.6e-11, -2.0e-01, 3.0e-02	7.6e-47, 3.4e-01, 2.4e-02	1.0e-36, -9.8e-02, 7.8e-03	1.3e-08, 2.5e-01, 4.4e-02	0.0e+00, 3.7e-02, 7.3e-04	0.0e+00, 5.6e-02, 1.3e-03
cML-BIC-Profile	8.5e-41, -1.5e-01, 1.1e-02	8.5e-298, 3.9e-01, 1.1e-02	6.4e-96, 2.9e-01, 1.4e-02	6.1e-01, 2.9e-02, 5.8e-02	3.8e-25, 5.4e-01, 5.2e-02	6.7e-13, 4.8e-01, 6.7e-02	5.9e-12, -2.0e-01, 2.9e-02	1.1e-48, 3.4e-01, 2.3e-02	2.3e-37, -9.9e-02, 7.7e-03	2.8e-10, 2.5e-01, 4.0e-02	0.0e+00, 3.7e-02, 7.2e-04	0.0e+00, 5.6e-02, 1.2e-03
CAUSE	4.4e-04, -2.0e-01, NA	6.3e-12, 3.6e-01, NA	8.5e-02, 2.8e-01, NA	8.2e-01, 3.7e-02, NA	9.2e-08, 4.8e-01, NA	3.3e-01, 1.3e-01, NA	1.4e-03, -1.4e-01, NA	1.2e-04, 2.5e-01, NA	1.8e-04, -6.5e-02, NA	2.5e-01, 1.1e-01, NA	6.6e-31, 2.5e-02, NA	1.3e-26, 3.7e-02, NA
MR-Mix	8.4e-04, -5.0e-02, 1.5e-02	2.4e-11, 1.8e-01, 2.7e-02	6.5e-30, 2.1e-01, 1.8e-02	1.1e-01, 9.0e-02, 5.7e-02	3.4e-06, 3.5e-01, 7.5e-02	7.3e-05, 2.0e-01, 5.0e-02	3.0e-01, -4.0e-02, 3.8e-02	8.0e-16, 1.6e-01, 2.0e-02	2.3e-06, -3.0e-02, 6.3e-03	1.5e-05, 5.0e-02, 1.2e-02	1.2e-59, 2.0e-01, 1.2e-02	2.8e-21, 1.9e-01, 2.0e-02
MR-ContMix	5.7e-08, -1.2e-01, NA	4.5e-43, 4.8e-01, NA	3.9e-06, 4.3e-01, NA	5.4e-04, 2.6e-01, NA	9.8e-13, 5.0e-01, NA	3.8e-03, 5.0e-01, NA	1.3e-01, -1.3e-01, NA	1.8e-17, 3.4e-01, NA	2.4e-11, -1.0e-01, NA	1.7e-05, 2.7e-01, NA	7.5e-116, 3.9e-02, NA	1.6e-85, 6.4e-02, NA
MR-Lasso	2.3e-25, -1.5e-01, 1.4e-02	1.4e-178, 4.0e-01, 1.4e-02	9.8e-47, 2.7e-01, 1.8e-02	1.1e-01, 1.1e-01, 6.8e-02	1.1e-27, 6.0e-01, 5.5e-02	3.0e-03, 3.7e-01, 1.2e-01	7.3e-06, -1.6e-01, 3.5e-02	1.5e-40, 3.2e-01, 2.4e-02	1.0e-26, -9.0e-02, 8.4e-03	6.3e-07, 2.2e-01, 4.5e-02	0.0e+00, 3.2e-02, 8.0e-04	7.7e-275, 5.1e-02, 1.4e-03
MR-PRESSO	5.2e-16, -1.5e-01, 1.9e-02	3.6e-112, 3.8e-01, 1.7e-02	1.7e-25, 2.6e-01, 2.5e-02	1.1e-01, 1.1e-01, 6.8e-02	1.0e-12, 4.8e-01, 6.8e-02	7.5e-01, 5.7e-02, 1.8e-01	4.3e-05, -1.9e-01, 4.6e-02	1.9e-28, 3.3e-01, 3.0e-02	9.0e-21, -9.8e-02, 1.0e-02	6.3e-07, 2.2e-01, 4.5e-02	2.0e-246, 3.5e-02, 1.0e-03	2.3e-177, 5.2e-02, 1.8e-03
MR-IVW	6.5e-10, -1.7e-01, 2.8e-02	4.6e-51, 3.7e-01, 2.5e-02	3.8e-14, 2.4e-01, 3.2e-02	5.4e-01, 5.5e-02, 8.9e-02	2.8e-11, 4.9e-01, 7.3e-02	8.9e-01, 3.5e-02, 2.5e-01	1.4e-03, -2.1e-01, 6.5e-02	7.1e-10, 3.0e-01, 4.8e-02	9.6e-15, -9.8e-02, 1.3e-02	1.6e-03, 2.3e-01, 7.4e-02	2.0e-138, 3.5e-02, 1.4e-03	2.7e-106, 5.2e-02, 2.4e-03
MR-Egger	5.5e-01, -3.0e-02, 5.1e-02	5.6e-19, 3.5e-01, 4.0e-02	2.3e-03, 1.7e-01, 5.7e-02	5.4e-01, 1.6e-01, 2.6e-01	1.4e-02, 8.5e-01, 2.6e-01	9.3e-01, -1.1e-01, 3.5e+00	9.4e-01, 1.6e-02, 2.3e-01	1.2e-01, 2.0e-01, 1.3e-01	1.4e-01, -5.5e-02, 3.7e-02	2.4e-01, 2.2e-01, 1.9e-01	7.0e-18, 3.5e-02, 4.1e-03	5.9e-21, 6.3e-02, 6.7e-03
MR-Weighted-Median	3.0e-11, -1.4e-01, 2.1e-02	2.8e-45, 2.7e-01, 1.9e-02	3.2e-13, 2.1e-01, 2.8e-02	6.0e-02, 1.7e-01, 9.2e-02	2.0e-09, 5.0e-01, 8.4e-02	6.8e-05, 4.1e-01, 1.0e-01	1.9e-02, -1.1e-01, 4.8e-02	9.3e-15, 3.0e-01, 3.8e-02	2.6e-11, -8.5e-02, 1.3e-02	2.8e-06, 2.5e-01, 5.3e-02	1.5e-124, 3.1e-02, 1.3e-03	3.3e-113, 5.1e-02, 2.3e-03
MR-Weighted-Mode	3.4e-06, -1.3e-01, 2.7e-02	1.9e-49, 2.6e-01, 1.7e-02	2.1e-07, 2.0e-01, 3.9e-02	3.6e-02, 2.7e-01, 1.3e-01	2.8e-04, 8.8e-01, 2.4e-01	9.2e-05, 4.1e-01, 1.1e-01	2.9e-01, -8.0e-02, 7.6e-02	2.4e-12, 3.3e-01, 4.8e-02	2.8e-04, -1.6e-01, 4.5e-02	8.4e-06, 2.6e-01, 5.8e-02	3.9e-08, 2.9e-02, 5.4e-03	3.6e-07, 5.9e-02, 1.2e-02
MR-RAPS1	3.0e-10, -1.8e-01, 2.8e-02	7.9e-51, 3.8e-01, 2.5e-02	2.8e-13, 2.2e-01, 3.0e-02	3.6e-01, 8.0e-02, 8.7e-02	6.1e-12, 5.2e-01, 7.5e-02	5.0e-01, 7.9e-02, 1.2e-01	1.6e-03, -2.1e-01, 6.5e-02	5.9e-07, 2.6e-02, 5.3e-02	4.9e-15, 2.4e-01, 1.3e-02	7.5e-04, 3.5e-02, 7.1e-02	1.9e-141, 3.5e-02, 1.4e-03	4.3e-110, 5.3e-02, 2.4e-03
MR-RAPS2	1.8e-09, -1.4e-01, 2.3e-02	0.0e+00, 4.1e-01, 9.1e-03	6.1e-94, 2.7e-01, 1.3e-02	2.0e-01, 1.1e-01, 8.2e-02	1.7e-13, 5.5e-01, 7.5e-02	2.7e-14, 4.9e-01, 6.5e-02	2.7e-03, -1.6e-01, 5.3e-02	0.0e+00, -2.9e+01, 4.4e-01	1.2e-17, -9.8e-02, 1.1e-02	5.8e-04, 2.4e-01, 7.1e-02	1.5e-204, 3.5e-02, 1.1e-03	3.0e-147, 5.3e-02, 2.1e-03
MR-RAPS3	6.1e-74, -1.9e-01, 1.0e-02	0.0e+00, 4.1e-01, 9.4e-03	2.6e-84, 2.6e-01, 1.3e-02	3.3e-01, 5.7e-02, 5.9e-02	1.0e-21, 5.2e-01, 5.4e-02	5.0e-01, 7.9e-02, 1.2e-01	1.1e-13, -2.3e-01, 3.1e-02	2.3e-39, 3.2e-01, 2.4e-02	9.2e-40, -1.0e-01, 7.8e-03	1.1e-09, 2.4e-01, 4.0e-02	0.0e+00, 3.8e-02, 7.4e-04	0.0e+00, 5.6e-02, 1.2e-03
MR-RAPS4	3.2e-53, -1.5e-01, 9.9e-03	0.0e+00, 4.1e-01, 9.1e-03	6.1e-94, 2.7e-01, 1.3e-02	1.1e-02, 5.9e-01, 5.9e-02	2.6e-27, 5.9e-01, 5.5e-02	2.7e-14, 4.9e-01, 6.5e-02	1.8e-09, -9.8e-01, 3.0e-02	1.5e-47, 3.4e-01, 2.4e-02	1.2e-33, -9.5e-02, 7.8e-03	4.4e-10, 2.5e-01, 4.0e-02	0.0e+00, 3.5e-02, 7.2e-04	0.0e+00, 5.5e-02, 1.2e-03

Table S3: Inferring causal effects of 12 risk factors on Stroke, in each cell from top to bottom are  $p$ -value, estimated causal effect  $\hat{\theta}$  and its standard error  $SE(\hat{\theta})$ . Cells with  $p$ -value less than Bonferroni adjusted significant cutoff 0.001 are marked with red.

Exposure Method	HDL(197)	LDL(184)	TG(128)	Alcohol(53)	Smoke(129)	BF(10)	BW(65)	BMI(90)	Height(986)	FG(17)	SBP(1319)	DBP(1343)
cML-MA- AIC	7.1e-05, -8.0e-02, 2.0e-02	1.3e-06, 8.1e-02, 1.7e-02	6.1e-01, 1.5e-02, 3.1e-02	3.3e-01, -1.4e-01, 1.4e-01	4.2e-04, 3.4e-01, 9.7e-02	8.1e-01, -2.4e-02, 1.0e-01	1.2e-04, -2.5e-01, 6.4e-02	6.8e-01, 2.1e-02, 5.0e-02	1.3e-01, -2.3e-02, 1.5e-02	4.6e-01, -6.7e-02, 9.0e-02	1.6e-86, 2.7e-02, 1.4e-03	4.4e-91, 4.7e-02, 2.3e-03
cML- AIC	5.4e-05, -7.6e-02, 1.9e-02	3.5e-07, 8.4e-02, 1.6e-02	4.3e-01, 2.0e-02, 2.5e-02	7.5e-02, -2.0e-01, 1.1e-01	1.3e-04, 3.6e-01, 9.3e-02	6.1e-01, -4.9e-02, 9.6e-02	4.9e-06, -2.5e-01, 5.5e-02	6.6e-01, 2.0e-02, 4.7e-02	4.8e-02, -2.9e-02, 1.5e-02	5.5e-01, -4.4e-02, 7.4e-02	1.9e-94, 2.7e-02, 1.3e-03	8.2e-97, 4.8e-02, 2.3e-03
cML-MA-BIC-max	5.8e-02, -3.2e-02, 1.7e-02	6.5e-08, 8.4e-02, 1.6e-02	8.6e-01, -4.0e-03, 2.2e-02	3.3e-01, 9.3e-02, 9.5e-02	1.2e-04, 3.2e-01, 8.4e-02	8.9e-01, -1.3e-02, 9.3e-02	2.0e-02, -1.1e-01, 4.9e-02	4.4e-02, 8.2e-02, 4.1e-02	5.3e-02, -2.5e-02, 1.3e-02	2.0e-01, 9.0e-02, 7.0e-02	8.8e-134, 2.9e-02, 1.2e-03	1.8e-124, 4.7e-02, 2.0e-03
cML-BIC-max	6.1e-02, -3.2e-02, 1.7e-02	1.0e-08, 8.4e-02, 1.5e-02	8.8e-01, -3.3e-03, 2.2e-02	3.2e-01, 9.3e-02, 9.4e-02	1.1e-04, 3.3e-01, 8.4e-02	8.9e-01, -1.3e-02, 9.3e-02	1.9e-02, -1.1e-01, 4.8e-02	2.8e-02, 8.8e-02, 4.0e-02	5.2e-02, -2.5e-02, 1.3e-02	1.8e-01, 9.2e-02, 6.9e-02	3.1e-135, 2.8e-02, 1.1e-03	4.2e-126, 4.7e-02, 2.0e-03
cML-MA-BIC	5.7e-02, -3.2e-02, 1.7e-02	3.9e-07, 8.1e-02, 1.6e-02	8.4e-01, -4.3e-03, 2.2e-02	3.3e-01, 9.2e-02, 9.5e-02	1.2e-04, 3.2e-01, 8.4e-02	8.8e-01, -1.4e-02, 9.3e-02	2.4e-02, -1.1e-01, 4.9e-02	4.6e-02, 8.1e-02, 4.1e-02	6.0e-02, -2.4e-02, 1.3e-02	2.2e-01, 8.7e-02, 7.0e-02	2.6e-134, 2.9e-02, 1.2e-03	9.3e-125, 4.7e-02, 2.0e-03
cML-BIC	6.1e-02, -3.2e-02, 1.7e-02	1.0e-08, 8.4e-02, 1.5e-02	8.8e-01, -3.3e-03, 2.2e-02	3.2e-01, 9.3e-02, 9.4e-02	1.1e-04, 3.3e-01, 8.4e-02	8.9e-01, -1.3e-02, 9.3e-02	1.9e-02, -1.1e-01, 4.8e-02	5.6e-02, 7.7e-02, 4.0e-02	6.5e-02, -2.4e-02, 1.3e-02	1.8e-01, 9.2e-02, 6.9e-02	3.7e-136, 2.9e-02, 1.1e-03	2.5e-126, 4.7e-02, 2.0e-03
cML-MA-BIC-DP-Max	4.6e-02, -3.6e-02, 1.8e-02	3.3e-05, 7.8e-02, 1.9e-02	8.7e-01, -3.6e-03, 2.3e-02	3.8e-01, 8.9e-02, 1.0e-01	5.9e-04, 3.3e-01, 9.5e-02	8.7e-01, -1.7e-02, 1.0e-01	4.8e-02, -1.3e-01, 6.5e-02	8.4e-02, 8.0e-02, 4.6e-02	1.4e-01, -2.3e-02, 1.5e-02	2.5e-01, 9.7e-02, 8.4e-02	7.0e-103, 2.9e-02, 1.3e-03	4.1e-88, 4.7e-02, 2.4e-03
cML-BIC-DP-Max	4.1e-02, -3.6e-02, 1.8e-02	6.7e-05, 7.8e-02, 1.9e-02	8.7e-01, -3.7e-03, 2.2e-02	3.1e-01, 9.3e-02, 9.2e-02	5.9e-04, 3.2e-01, 9.5e-02	8.7e-01, -1.7e-02, 1.0e-01	4.2e-02, -1.2e-01, 6.1e-02	4.0e-02, 8.3e-02, 4.1e-02	1.4e-01, -2.3e-02, 1.5e-02	2.1e-01, 9.7e-02, 7.8e-02	7.0e-105, 2.9e-02, 1.3e-03	2.3e-89, 4.7e-02, 2.4e-03
cML-MA-BIC-DP	4.6e-02, -3.7e-02, 1.8e-02	5.2e-05, 7.8e-02, 1.9e-02	8.8e-01, -3.6e-03, 2.3e-02	4.0e-01, 8.7e-02, 1.0e-01	7.8e-04, 3.3e-01, 9.7e-02	8.7e-01, -1.7e-02, 1.0e-01	5.1e-02, -1.3e-01, 6.8e-02	9.1e-02, 8.0e-02, 4.7e-02	1.4e-01, -2.3e-02, 1.5e-02	3.4e-01, 9.3e-02, 9.9e-02	4.5e-86, 2.9e-02, 1.5e-03	1.2e-79, 4.7e-02, 2.5e-03
cML-BIC-DP	4.1e-02, -3.6e-02, 1.8e-02	6.7e-05, 7.8e-02, 1.9e-02	8.7e-01, -3.7e-03, 2.2e-02	4.2e-01, 8.8e-02, 1.1e-01	5.9e-04, 3.2e-01, 9.5e-02	8.7e-01, -1.7e-02, 1.0e-01	4.7e-02, -1.3e-01, 6.5e-02	1.2e-01, 7.9e-02, 5.1e-02	1.4e-01, -2.3e-02, 1.5e-02	2.1e-01, 9.7e-02, 7.8e-02	5.7e-77, 2.9e-02, 1.5e-03	1.2e-79, 4.7e-02, 2.5e-03
cML-MA-AIC-Profile	8.4e-05, -8.0e-02, 2.0e-02	1.6e-06, 8.1e-02, 1.7e-02	6.2e-01, 1.5e-02, 3.1e-02	3.4e-01, -1.4e-01, 1.4e-01	6.3e-04, 3.4e-01, 1.0e-01	8.2e-01, -2.4e-02, 1.0e-01	1.5e-04, -2.5e-01, 6.5e-02	6.9e-01, 2.1e-02, 5.1e-02	1.3e-01, -2.3e-02, 1.6e-02	4.6e-01, -6.7e-02, 9.0e-02	1.0e-87, 2.7e-02, 1.4e-03	3.2e-88, 4.7e-02, 2.4e-03
cML-AIC-Profile	6.3e-05, -7.6e-02, 1.9e-02	4.2e-07, 8.4e-02, 1.7e-02	4.4e-01, 2.0e-02, 2.6e-02	8.1e-02, -2.0e-01, 1.1e-01	2.1e-04, 3.6e-01, 9.6e-02	6.2e-01, -4.9e-02, 9.9e-02	8.2e-06, -2.9e-01, 5.7e-02	6.7e-01, 2.0e-02, 4.7e-02	5.2e-02, -2.9e-02, 1.5e-02	5.6e-01, -4.4e-02, 7.5e-02	3.0e-91, 2.7e-02, 1.3e-03	3.8e-95, 4.8e-02, 2.3e-03
cML-MA-BIC-max-Profile	5.9e-02, -3.2e-02, 1.7e-02	6.6e-08, 8.4e-02, 1.6e-02	8.6e-01, -4.0e-03, 2.2e-02	3.3e-01, 9.3e-02, 9.5e-02	1.4e-04, 3.2e-01, 8.5e-02	8.9e-01, -1.3e-02, 9.5e-02	2.0e-02, -1.1e-01, 4.9e-02	4.4e-02, 8.2e-02, 4.1e-02	5.4e-02, -2.5e-02, 1.3e-02	1.9e-01, 9.0e-02, 6.9e-02	1.8e-133, 2.9e-02, 1.2e-03	2.2e-124, 4.7e-02, 2.0e-03
cML-BIC-max-Profile	6.1e-02, -3.2e-02, 1.7e-02	1.1e-08, 8.4e-02, 1.5e-02	8.8e-01, -3.3e-03, 2.2e-02	3.3e-01, 9.3e-02, 9.5e-02	1.3e-04, 3.3e-01, 8.5e-02	8.9e-01, -1.3e-02, 9.5e-02	1.9e-02, -1.1e-01, 4.8e-02	2.8e-02, 8.8e-02, 4.0e-02	5.3e-02, -2.5e-02, 1.3e-02	1.8e-01, 9.2e-02, 6.9e-02	6.4e-135, 2.8e-02, 1.1e-03	5.0e-126, 4.7e-02, 2.0e-03
cML-MA-BIC-Profile	5.8e-02, -3.2e-02, 1.7e-02	4.0e-07, 8.1e-02, 1.6e-02	8.4e-01, -4.3e-03, 2.2e-02	3.3e-01, 9.2e-02, 9.5e-02	1.5e-04, 3.2e-01, 8.5e-02	8.9e-01, -1.4e-02, 9.5e-02	2.4e-02, -1.1e-01, 5.0e-02	4.6e-02, 8.1e-02, 4.1e-02	6.1e-02, -2.4e-02, 1.3e-02	2.2e-01, 8.7e-02, 7.0e-02	5.9e-134, 2.9e-02, 1.2e-03	1.3e-124, 4.7e-02, 2.0e-03
cML-BIC-Profile	6.1e-02, -3.2e-02, 1.7e-02	1.1e-08, 8.4e-02, 1.5e-02	8.8e-01, -3.3e-03, 2.2e-02	3.3e-01, 9.3e-02, 9.5e-02	1.3e-04, 3.3e-01, 8.5e-02	8.9e-01, -1.3e-02, 9.5e-02	1.9e-02, -1.1e-01, 4.8e-02	5.5e-02, 7.7e-02, 4.0e-02	6.6e-02, -2.4e-02, 1.3e-02	1.8e-01, 9.2e-02, 6.9e-02	8.4e-136, 2.9e-02, 1.1e-03	3.5e-126, 4.7e-02, 2.0e-03
CAUSE	2.7e-01, -3.5e-02, NA	4.6e-02, 6.2e-02, NA	9.9e-01, 8.1e-03, NA	2.5e-01, 1.3e-01, NA	2.3e-02, 2.9e-01, NA	1.0e+00, 4.4e-03, NA	8.8e-02, -1.1e-01, NA	2.3e-01, 7.2e-03, NA	5.5e-01, -1.6e-02, NA	9.9e-01, 9.6e-03, NA	4.1e-09, 2.2e-02, NA	1.1e-03, 3.2e-02, NA
MR-Mix	1.0e+00, 0.0e+00, 2.1e-02	1.5e-01, 2.0e-02, 1.4e-02	2.1e-02, 8.0e-02, 3.5e-02	1.0e+00, 2.0e-17, 4.6e-02	1.0e+00, 2.0e-17, 4.3e-02	1.0e+00, 1.0e-17, 2.3e-02	2.9e-01, -4.0e-02, 3.8e-02	1.0e+00, 2.0e-17, 2.0e-02	8.6e-02, 1.0e-02, 5.8e-03	8.2e-01, -1.0e-02, 4.4e-02	7.0e-11, 1.0e-01, 1.5e-02	1.7e-07, 1.1e-01, 2.1e-02
MR-ContMix	3.8e-03, -6.5e-02, NA	6.8e-05, 7.2e-02, NA	8.5e-01, -4.6e-03, NA	3.3e-01, -1.4e-01, NA	1.9e-03, 5.0e-01, NA	6.1e-01, -4.9e-02, NA	6.2e-04, -2.8e-01, NA	7.1e-01, 1.7e-02, NA	7.5e-01, -6.6e-03, NA	5.5e-01, -4.4e-02, NA	2.6e-63, 3.9e-02, NA	5.4e-60, 7.0e-02, NA
MR-Lasso	4.6e-03, -4.8e-02, 1.7e-02	6.6e-06, 6.9e-02, 1.5e-02	6.8e-01, -9.4e-03, 2.3e-02	5.6e-01, 5.6e-02, 9.6e-02	3.5e-04, 3.0e-01, 8.4e-02	8.9e-01, -1.3e-02, 9.2e-02	2.3e-03, -1.5e-01, 4.9e-02	5.3e-02, 8.1e-02, 4.2e-02	1.6e-01, -1.8e-02, 1.3e-02	6.9e-01, 3.3e-02, 8.1e-02	1.6e-119, 2.8e-02, 1.2e-03	3.3e-108, 4.5e-02, 2.0e-03
MR-PRESSO	9.4e-02, -3.1e-02, 1.9e-02	2.9e-06, 8.2e-02, 1.7e-02	9.0e-01, -3.2e-03, 2.5e-02	3.7e-01, 9.1e-02, 1.0e-01	5.4e-04, 3.1e-01, 9.0e-02	8.3e-01, -1.3e-02, 6.1e-02	7.7e-02, -9.2e-02, 5.2e-02	1.4e-01, 7.5e-02, 5.0e-02	6.8e-02, -2.6e-02, 1.4e-02	3.6e-01, 9.0e-02, 9.7e-02	1.1e-93, 2.8e-02, 1.3e-03	6.0e-88, 4.6e-02, 2.3e-03
MR-IVW	7.2e-02, -3.6e-02, 2.0e-02	6.0e-05, 8.1e-02, 2.0e-02	9.0e-01, -3.2e-03, 2.5e-02	3.7e-01, 9.1e-02, 1.0e-01	5.4e-04, 3.1e-01, 9.0e-02	8.9e-01, -1.3e-02, 9.2e-02	1.2e-01, -9.6e-02, 6.1e-02	9.9e-02, 8.6e-02, 5.2e-02	2.1e-02, -3.4e-02, 1.5e-02	3.6e-01, 9.0e-02, 9.7e-02	3.3e-95, 2.9e-02, 1.4e-03	1.9e-79, 4.6e-02, 2.4e-03
MR-Egger	4.8e-01, 2.6e-02, 3.7e-02	3.2e-04, 1.1e-01, 3.2e-02	1.0e-01, -7.1e-02, 4.3e-02	3.9e-01, -2.5e-01, 3.0e-01	6.2e-03, 1.2e+00, 4.3e-01	7.0e-01, -1.8e-01, 4.6e-01	3.9e-02, 4.3e-01, 2.1e-01	7.3e-01, -4.8e-02, 1.4e-01	5.3e-01, -2.7e-02, 4.3e-02	3.1e-02, -4.4e-01, 2.0e-01	9.2e-25, 4.2e-02, 4.1e-03	1.1e-17, 5.9e-02, 6.9e-03
MR-Weighted-Median	7.2e-02, -5.1e-02, 2.8e-02	7.9e-03, 7.3e-02, 2.7e-02	8.0e-01, 9.0e-03, 3.5e-02	8.7e-01, 2.3e-02, 1.4e-01	2.9e-02, 2.7e-01, 1.2e-01	9.3e-01, -9.5e-03, 1.2e-01	1.2e-01, -1.2e-01, 7.3e-02	6.0e-01, 3.7e-02, 7.0e-02	2.3e-01, -2.4e-02, 1.9e-02	3.4e-01, -9.4e-02, 9.8e-02	5.6e-49, 2.9e-02, 1.9e-03	3.2e-53, 5.0e-02, 3.2e-03
MR-Weighted-Mode	1.0e-01, -4.6e-02, 2.8e-02	1.6e-03, 7.4e-02, 2.3e-02	9.5e-01, 2.5e-03, 3.8e-02	7.8e-01, -7.8e-02, 2.8e-01	2.0e-01, 3.8e-01, 3.0e-01	9.4e-01, 1.3e-02, 1.7e-01	2.3e-01, -2.2e-01, 1.9e-01	8.1e-01, 2.0e-02, 8.3e-02	9.1e-01, -9.1e-03, 7.8e-02	4.5e-01, 8.2e-02, 1.1e-01	1.5e-07, 3.0e-02, 5.8e-03	2.1e-07, 5.5e-02, 1.1e-02
MR-RAPS1	8.5e-02, -3.5e-02, 2.0e-02	7.4e-06, 8.6e-02, 1.9e-02	7.8e-01, -6.9e-03, 2.5e-02	3.9e-01, 8.8e-02, 1.0e-01	4.9e-04, 3.3e-01, 9.3e-02	8.9e-01, -1.3e-02, 9.3e-02	1.4e-01, -9.1e-02, 6.2e-02	1.5e-01, 7.6e-02, 5.3e-02	2.0e-02, -3.4e-02, 1.5e-02	3.3e-01, 9.3e-02, 9.6e-02	1.3e-97, 3.0e-02, 1.4e-03	1.5e-80, 4.6e-02, 2.4e-03
MR-RAPS2	3.0e-02, -4.0e-02, 1.9e-02	8.7e-06, 7.9e-02, 1.8e-02	7.9e-01, -7.0e-03, 2.6e-02	5.3e-01, 6.8e-02, 1.1e-01	6.5e-04, 3.3e-01, 9.6e-02	8.7e-01, -1.6e-02, 9.6e-02	2.9e-02, -1.3e-01, 5.9e-02	2.2e-01, 6.7e-02, 5.5e-02	1.3e-01, -2.2e-02, 1.5e-02	4.2e-01, 8.3e-02, 1.0e-01	8.6e-95, 2.9e-02, 1.4e-03	2.4e-83, 4.7e-02, 2.4e-03
MR-RAPS3	3.0e-02, -3.7e-02, 1.7e-02	2.7e-08, 8.2e-02, 1.5e-02	8.8e-01, -3.3e-03, 2.2e-02	3.3e-01, 9.3e-02, 9.6e-02	1.5e-04, 3.3e-01, 8.6e-02	8.9e-01, -1.3e-02, 9.3e-02	3.7e-02, -1.0e-01, 4.8e-02	3.0e-02, 8.8e-02, 4.1e-02	7.6e-03, -3.4e-02, 1.3e-02	1.9e-01, 9.2e-02, 7.0e-02	3.6e-147, 3.0e-02, 1.2e-03	2.2e-128, 4.7e-02, 2.0e-03
MR-RAPS4	1.3e-02, -4.3e-02, 1.7e-02	5.2e-07, 7.6e-02, 1.5e-02	8.8e-01, -3.3e-03, 2.3e-02	4.7e-01, 7.2e-02, 9.8e-02	1.8e-04, 3.3e-01, 8.8e-02	8.7e-01, -1.6e-02, 9.6e-02	2.4e-03, -1.5e-01, 4.9e-02	9.4e-02, 7.0e-02, 4.2e-02	1.1e-01, -2.1e-02, 1.3e-02	3.9e-01, 6.1e-02, 7.2e-02	5.1e-130, 2.9e-02, 1.2e-03	3.1e-123, 4.7e-02, 2.0e-03

Table S4: Inferring causal effects of 12 risk factors on T2D, in each cell from top to bottom are  $p$ -value, estimated causal effect  $\hat{\theta}$  and its standard error  $SE(\hat{\theta})$ . Cells with  $p$ -value less than Bonferroni adjusted significant cutoff 0.001 are marked with red.

Method \ Exposure	HDL(188)	LDL(178)	TG(124)	Alcohol(44)	Smoke(115)	BF(9)	BW(54)	BMI(90)	Height(982)	FG(17)	SBP(1110)	DBP(1110)
cML-MA- AIC	1.0e-01, -8.9e-02, 5.4e-02	1.1e-04, -1.6e-01, 4.1e-02	5.7e-01, 3.3e-02, 5.8e-02	1.9e-01, 3.3e-01, 2.5e-01	6.8e-01, 8.3e-02, 2.0e-01	5.0e-11, 1.9e+00, 2.8e-01	2.1e-03, -4.1e-01, 1.3e-01	2.9e-19, 9.5e-01, 1.1e-01	9.9e-01, -4.2e-04, 3.0e-02	3.8e-12, 2.1e+00, 3.0e-01	8.2e-17, 2.4e-02, 2.8e-03	9.7e-10, 3.1e-02, 5.1e-03
cML- AIC	6.2e-02, -8.2e-02, 4.4e-02	1.7e-05, -1.7e-01, 3.9e-02	5.7e-01, 3.2e-02, 5.7e-02	3.9e-01, 2.1e-01, 2.4e-01	9.2e-01, -1.9e-02, 1.9e-01	1.4e-12, 1.8e+00, 2.6e-01	1.9e-04, -4.7e-01, 1.3e-01	8.0e-21, 9.1e-01, 9.7e-02	8.9e-01, -4.1e-03, 2.9e-02	9.2e-20, 2.0e+00, 2.2e-01	2.3e-16, 2.3e-02, 2.8e-03	5.5e-11, 3.1e-02, 4.7e-03
cML-MA-BIC-max	2.7e-03, -1.1e-01, 3.7e-02	9.2e-06, -1.6e-01, 3.5e-02	2.6e-01, 5.4e-02, 4.8e-02	2.3e-01, 2.5e-01, 2.1e-01	3.5e-02, 3.6e-01, 1.7e-01	4.1e-11, 1.5e+00, 2.3e-01	6.5e-07, -5.7e-01, 1.1e-01	4.6e-27, 8.7e-01, 8.0e-02	3.6e-01, -2.3e-02, 2.6e-02	1.4e-16, 2.1e+00, 2.5e-01	1.2e-17, 2.1e-02, 2.5e-03	2.9e-08, 2.3e-02, 4.2e-03
cML-BIC-max	4.0e-03, -1.1e-01, 3.7e-02	1.2e-05, -1.5e-01, 3.4e-02	1.8e-01, 6.2e-02, 4.7e-02	2.3e-01, 2.5e-01, 2.1e-01	3.1e-02, 3.7e-01, 1.7e-01	2.3e-11, 1.5e+00, 2.3e-01	2.8e-07, -5.5e-01, 1.1e-01	4.0e-27, 8.6e-01, 8.0e-02	3.7e-01, -2.3e-02, 2.5e-02	2.1e-27, 2.2e+00, 2.1e-01	2.7e-18, 2.1e-02, 2.4e-03	8.0e-09, 2.4e-02, 4.2e-03
cML-MA-BIC	2.3e-03, -1.1e-01, 3.8e-02	6.9e-06, -1.6e-01, 3.6e-02	2.2e-01, 5.8e-02, 4.8e-02	2.2e-01, 2.6e-01, 2.1e-01	4.5e-02, 3.5e-01, 1.7e-01	4.6e-11, 1.5e+00, 2.3e-01	1.5e-06, -5.6e-01, 1.2e-01	5.0e-27, 8.7e-01, 8.1e-02	3.2e-01, -2.6e-02, 2.6e-02	8.3e-18, 2.1e+00, 2.5e-01	2.2e-16, 2.0e-02, 2.5e-03	3.2e-07, 2.2e-02, 4.2e-03
cML-BIC	4.0e-03, -1.1e-01, 3.7e-02	1.2e-05, -1.5e-01, 3.4e-02	1.8e-01, 6.2e-02, 4.7e-02	2.3e-01, 2.5e-01, 2.1e-01	3.1e-02, 3.7e-01, 1.7e-01	2.3e-11, 1.5e+00, 2.3e-01	2.8e-07, -5.5e-01, 1.1e-01	4.0e-27, 8.6e-01, 8.0e-02	2.5e-01, -2.9e-02, 2.5e-02	2.1e-27, 2.2e+00, 2.1e-01	1.5e-16, 2.0e-02, 2.4e-03	2.3e-07, 2.2e-02, 4.2e-03
cML-MA-BIC-DP-Max	2.1e-02, -1.2e-01, 5.1e-02	2.3e-04, -1.5e-01, 4.2e-02	3.0e-01, 6.8e-02, 6.6e-02	2.9e-01, 2.5e-01, 2.4e-01	8.9e-02, 3.4e-01, 2.0e-01	6.2e-07, 1.5e+00, 3.0e-01	1.7e-03, -5.5e-01, 1.8e-01	3.6e-19, 8.7e-01, 9.7e-02	5.6e-01, -1.7e-02, 3.0e-02	2.1e-04, 1.9e+00, 5.1e-01	4.7e-12, 2.1e-02, 3.1e-03	3.5e-06, 2.2e-02, 4.7e-03
cML-BIC-DP-Max	3.4e-02, -1.1e-01, 5.4e-02	8.0e-05, -1.5e-01, 3.9e-02	3.4e-01, 6.3e-02, 6.6e-02	2.2e-01, 3.4e-01, 2.2e-01	9.4e-02, 3.4e-01, 2.0e-01	1.2e-08, 1.5e+00, 2.6e-01	2.2e-03, -5.5e-01, 1.8e-01	1.4e-23, 8.6e-01, 8.6e-02	4.7e-01, -1.9e-02, 2.7e-02	3.9e-04, 1.9e+00, 5.3e-01	5.2e-12, 2.1e-02, 3.1e-03	2.6e-06, 2.2e-02, 4.7e-03
cML-MA-BIC-DP	3.4e-02, -1.1e-01, 5.4e-02	8.7e-04, -1.5e-01, 4.6e-02	3.1e-01, 7.0e-02, 6.8e-02	3.4e-01, 2.5e-01, 2.6e-01	1.2e-01, 3.3e-01, 2.1e-01	9.8e-07, 1.5e+00, 3.1e-01	2.3e-03, -5.4e-01, 1.8e-01	6.5e-15, 8.7e-01, 1.1e-01	7.2e-01, -1.3e-02, 3.5e-02	2.3e-04, 1.9e+00, 5.2e-01	4.6e-12, 2.1e-02, 3.1e-03	2.4e-05, 2.2e-02, 5.3e-03
cML-BIC-DP	3.4e-02, -1.1e-01, 5.4e-02	2.3e-03, -1.5e-01, 5.1e-02	3.2e-01, 7.2e-02, 7.1e-02	3.7e-01, 2.3e-01, 2.6e-01	9.4e-02, 3.4e-01, 2.0e-01	1.2e-08, 1.5e+00, 2.6e-01	2.2e-03, -5.5e-01, 1.8e-01	3.0e-14, 8.7e-01, 1.1e-01	7.3e-01, -1.2e-02, 3.5e-02	3.9e-04, 1.9e+00, 5.3e-01	1.6e-12, 2.1e-02, 3.0e-03	1.7e-05, 2.2e-02, 5.2e-03
cML-MA-AIC-Profile	9.3e-02, -9.1e-02, 5.4e-02	1.2e-04, -1.6e-01, 4.2e-02	5.7e-01, 3.3e-02, 5.9e-02	2.0e-01, 3.3e-01, 2.5e-01	6.9e-01, 8.3e-02, 2.1e-01	1.2e-10, 1.9e+00, 2.9e-01	4.1e-03, -3.9e-01, 1.4e-01	6.8e-19, 9.5e-01, 1.1e-01	9.9e-01, -4.2e-04, 3.1e-02	6.0e-12, 2.1e+00, 3.0e-01	2.2e-16, 2.4e-02, 2.9e-03	1.5e-09, 3.1e-02, 5.2e-03
cML-AIC-Profile	6.4e-02, -8.2e-02, 4.4e-02	2.0e-05, -1.7e-01, 3.9e-02	5.7e-01, 3.2e-02, 5.7e-02	4.0e-01, 2.1e-01, 2.5e-01	9.2e-01, -1.9e-02, 2.0e-01	4.9e-12, 1.8e+00, 2.7e-01	2.6e-04, -4.7e-01, 1.3e-01	4.0e-20, 9.1e-01, 9.9e-02	8.9e-01, -4.1e-03, 2.9e-02	2.4e-19, 2.0e+00, 2.2e-01	7.1e-16, 2.3e-02, 2.8e-03	1.1e-10, 3.1e-02, 4.8e-03
cML-MA-BIC-max-Profile	2.6e-03, -1.1e-01, 3.7e-02	9.4e-06, -1.6e-01, 3.5e-02	2.6e-01, 5.4e-02, 4.8e-02	2.3e-01, 2.5e-01, 2.1e-01	3.5e-02, 3.6e-01, 1.7e-01	4.1e-11, 1.5e+00, 2.3e-01	5.8e-07, -5.7e-01, 1.1e-01	4.6e-27, 8.7e-01, 8.0e-02	3.6e-01, -2.3e-02, 2.6e-02	1.3e-16, 2.1e+00, 2.5e-01	1.4e-17, 2.1e-02, 2.5e-03	3.0e-08, 2.3e-02, 4.2e-03
cML-BIC-max-Profile	4.0e-03, -1.1e-01, 3.7e-02	1.2e-05, -1.5e-01, 3.4e-02	1.8e-01, 6.2e-02, 4.6e-02	2.3e-01, 2.5e-01, 2.1e-01	3.2e-02, 3.7e-01, 1.7e-01	2.2e-11, 1.5e+00, 2.3e-01	2.4e-07, -5.5e-01, 1.1e-01	3.8e-27, 8.6e-01, 8.0e-02	3.7e-01, -2.3e-02, 2.5e-02	1.2e-27, 2.2e+00, 2.1e-01	3.1e-18, 2.1e-02, 2.4e-03	8.3e-09, 2.4e-02, 4.2e-03
cML-MA-BIC-Profile	2.3e-03, -1.1e-01, 3.8e-02	7.1e-06, -1.6e-01, 3.6e-02	2.2e-01, 5.8e-02, 4.8e-02	2.2e-01, 2.6e-01, 2.1e-01	4.5e-02, 3.5e-01, 1.7e-01	4.7e-11, 1.5e+00, 2.3e-01	1.4e-06, -5.6e-01, 1.2e-01	5.2e-27, 8.7e-01, 8.1e-02	3.2e-01, -2.6e-02, 2.6e-02	7.7e-18, 2.1e+00, 2.5e-01	2.6e-16, 2.0e-02, 2.5e-03	3.4e-07, 2.2e-02, 4.3e-03
cML-BIC-Profile	4.0e-03, -1.1e-01, 3.7e-02	1.2e-05, -1.5e-01, 3.4e-02	1.8e-01, 6.2e-02, 4.6e-02	2.3e-01, 2.5e-01, 2.1e-01	3.2e-02, 3.7e-01, 1.7e-01	2.2e-11, 1.5e+00, 2.3e-01	2.4e-07, -5.5e-01, 1.1e-01	3.8e-27, 8.6e-01, 8.0e-02	2.5e-01, -2.9e-02, 2.6e-02	1.2e-27, 2.2e+00, 2.1e-01	1.7e-16, 2.0e-02, 2.5e-03	2.5e-07, 2.2e-02, 4.2e-03
CAUSE	5.6e-02, -1.6e-01, NA	3.2e-01, -1.3e-01, NA	1.5e-01, 1.8e-01, NA	9.9e-01, 6.9e-02, NA	6.7e-01, 1.5e-01, NA	1.0e+00, 6.5e-02, NA	6.4e-02, -2.7e-01, NA	4.8e-03, 7.5e-01, NA	9.6e-01, 1.3e-02, NA	1.3e-02, 1.3e+00, NA	1.0e-02, 1.4e-02, NA	2.0e-02, 2.0e-02, NA
MR-Mix	1.6e-01, -3.0e-02, 2.2e-02	1.5e-01, -7.0e-02, 4.9e-02	5.4e-01, 6.0e-02, 9.8e-02	1.0e+00, 2.0e-17, 8.7e-02	4.9e-01, -2.1e-01, 3.1e-01	2.9e-05, 5.1e-01, 1.2e-01	1.0e-01, -1.1e-01, 6.7e-02	1.1e-03, 3.0e-01, 9.2e-02	6.9e-01, 4.0e-02, 1.0e-01	2.0e-04, 3.3e-01, 8.9e-02	2.1e-03, 9.0e-02, 2.9e-02	8.2e-02, 4.0e-02, 2.3e-02
MR-ContMix	4.1e-01, -4.1e-02, NA	1.5e-03, -1.5e-01, NA	1.9e-01, 1.2e-01, NA	1.8e-01, 4.7e-01, NA	7.9e-01, 5.0e-02, NA	2.7e-01, 4.4e-01, NA	2.5e-02, -4.1e-01, NA	3.4e-09, 5.0e-01, NA	7.6e-01, 1.2e-02, NA	2.1e-01, 5.0e-01, NA	3.2e-11, 2.6e-02, NA	4.5e-06, 3.4e-02, NA
MR-Lasso	1.5e-02, -9.6e-02, 3.9e-02	9.7e-06, -1.6e-01, 3.6e-02	9.5e-02, 8.5e-02, 5.1e-02	1.5e-01, 3.2e-01, 2.2e-01	1.9e-01, 2.3e-01, 1.8e-01	2.1e-06, 1.5e+00, 3.1e-01	4.3e-05, -4.9e-01, 1.2e-01	2.7e-21, 8.3e-01, 8.7e-02	8.5e-01, 4.9e-03, 2.6e-02	1.8e-05, 1.5e+00, 3.6e-01	3.7e-17, 2.1e-02, 2.5e-03	5.1e-06, 1.9e-02, 4.3e-03
MR-PRESSO	9.0e-03, -1.2e-01, 4.6e-02	2.5e-04, -1.5e-01, 4.1e-02	2.4e-01, 7.4e-02, 6.3e-02	2.8e-01, 2.5e-01, 2.3e-01	7.4e-02, 3.5e-01, 2.0e-01	1.5e-03, 1.2e+00, 3.7e-01	1.2e-05, -5.9e-01, 1.3e-01	2.1e-19, 8.4e-01, 9.3e-02	3.3e-01, -2.9e-02, 2.9e-02	2.9e-10, 1.7e+00, 2.7e-01	6.0e-13, 2.0e-02, 2.8e-03	5.1e-06, 2.2e-02, 4.8e-03
MR-IVW	4.5e-03, -1.5e-01, 5.2e-02	2.5e-04, -1.5e-01, 4.1e-02	3.7e-01, 5.9e-02, 6.5e-02	2.8e-01, 2.5e-01, 2.3e-01	7.4e-02, 3.5e-01, 2.0e-01	4.1e-02, 1.0e+00, 4.9e-01	4.4e-05, -8.3e-01, 2.0e-01	4.2e-05, 7.1e-01, 1.7e-01	6.2e-01, -1.5e-02, 3.0e-02	2.3e-02, 1.4e+00, 6.3e-01	5.8e-13, 2.3e-02, 3.2e-03	1.8e-06, 2.4e-02, 5.1e-03
MR-Egger	6.0e-01, 5.0e-02, 9.7e-02	6.8e-04, -2.7e-01, 7.8e-02	5.2e-01, 7.5e-02, 1.2e-01	1.5e-01, 1.0e+00, 7.2e-01	2.3e-01, -1.1e+00, 9.1e-01	2.6e-02, 5.1e+00, 2.3e+00	1.6e-01, -1.0e+00, 7.1e-01	8.9e-03, 1.2e+00, 4.5e-01	3.0e-01, 9.3e-02, 9.0e-02	2.9e-01, -1.5e+00, 1.4e+00	1.3e-01, 1.5e-02, 9.8e-03	2.5e-01, 1.7e-02, 1.5e-02
MR-Weighted-Median	1.0e+00, 0.0e+00, 6.7e-02	2.5e-02, -1.3e-01, 5.9e-02	2.3e-01, 9.5e-02, 7.8e-02	2.6e-01, 3.7e-01, 3.3e-01	1.0e+00, 0.0e+00, 2.6e-01	2.5e-07, 1.8e+00, 3.4e-01	4.6e-03, -4.7e-01, 1.7e-01	8.3e-11, 8.6e-01, 1.3e-01	1.0e+00, 0.0e+00, 4.2e-02	1.3e-02, 7.3e-01, 2.9e-01	1.3e-06, 2.0e-02, 4.0e-03	1.2e-03, 2.3e-02, 7.1e-03
MR-Weighted-Mode	8.2e-01, 1.5e-02, 6.6e-02	4.9e-03, -1.9e-01, 6.7e-02	2.4e-01, 1.0e-01, 8.8e-02	3.1e-01, 4.8e-01, 4.7e-01	8.6e-01, 8.7e-02, 5.1e-01	5.9e-08, -5.9e-01, 3.4e-01	2.4e-01, -2.7e-01, 2.2e-01	6.5e-09, 1.0e+00, 1.8e-01	9.0e-01, 1.9e-02, 1.5e-01	6.0e-01, 2.1e-01, 4.0e-01	4.7e-02, 1.8e-02, 8.9e-03	6.1e-03, 4.5e-02, 1.6e-02
MR-RAPS1	4.6e-03, -1.5e-01, 5.3e-02	8.5e-05, -1.6e-01, 4.1e-02	3.3e-01, 6.2e-02, 6.3e-02	2.9e-01, 2.5e-01, 2.4e-01	6.1e-02, 3.9e-01, 2.1e-01	1.9e-02, 1.1e+00, 4.7e-01	5.2e-05, -8.3e-01, 2.1e-01	6.1e-05, 7.1e-01, 1.8e-01	6.3e-01, -1.5e-02, 3.1e-02	2.7e-02, 1.3e+00, 6.0e-01	2.8e-12, 2.3e-02, 3.3e-03	2.2e-06, 2.5e-02, 5.3e-03
MR-RAPS2	1.1e-02, -1.3e-01, 5.1e-02	1.6e-04, -1.6e-01, 4.2e-02	2.0e-01, 8.2e-02, 6.4e-02	2.8e-01, 2.7e-01, 2.5e-01	1.0e-01, 3.5e-01, 2.1e-01	7.7e-03, 1.2e+00, 4.6e-01	2.9e-04, -6.0e-01, 1.7e-01	8.8e-27, 8.8e-01, 8.2e-02	7.1e-01, -1.2e-02, 3.1e-02	2.3e-38, 2.0e+00, 1.5e-01	1.8e-12, 2.1e-02, 3.0e-03	6.6e-06, 2.3e-02, 5.1e-03
MR-RAPS3	4.1e-05, -1.5e-01, 3.7e-02	1.3e-05, -1.5e-01, 3.5e-02	1.9e-01, 6.0e-02, 4.6e-02	2.4e-01, 2.5e-01, 2.1e-01	3.5e-02, 3.7e-01, 1.8e-01	6.1e-07, 1.1e+00, 2.3e-01	1.6e-16, -9.0e-01, 1.1e-01	6.4e-20, 7.7e-01, 8.5e-02	5.5e-01, -1.5e-02, 2.6e-02	6.6e-23, 1.9e+00, 1.9e-01	2.2e-22, 2.4e-02, 2.5e-03	2.7e-09, 2.5e-02, 4.2e-03
MR-RAPS4	3.9e-03, -1.1e-01, 3.8e-02	1.0e-05, -1.6e-01, 3.5e-02	1.3e-01, 7.1e-02, 4.7e-02	1.9e-01, 2.9e-01, 2.2e-01	9.0e-02, 3.0e-01, 1.8e-01	3.2e-13, 1.6e+00, 2.2e-01	1.9e-06, -5.0e-01, 1.0e-01	8.8e-27, 8.8e-01, 8.2e-02	6.4e-01, -1.2e-02, 2.6e-02	2.3e-38, 2.0e+00, 1.5e-01	2.2e-17, 2.1e-02, 2.5e-03	2.0e-07, 2.2e-02, 4.3e-03

Table S5: For each pair of exposure and outcome, from top to bottom are number of IVs used, number of invalid IVs detected by cML-BIC, and proportion of detected invalid IVs. Results are got with one starting point set at 0, and 100 randomly generated starting points.

Exposure Outcome	HDL	LDL	TG	Alcohol	Smoke	BF	BW	BMI	Height	FG	SBP	DBP
Asthma	188, 3, 1.60%	173, 1, 0.58%	122, 1, 0.82%	44, 0, 0.00%	114, 2, 1.75%	10, 0, 0.00%	54, 1, 1.85%	88, 0, 0.00%	977, 9, 0.92%	17, 1, 5.88%	1106, 5, 0.45%	1108, 11, 0.99%
CAD	197, 36, 18.27%	184, 19, 10.33%	128, 17, 13.28%	54, 3, 5.56%	129, 1, 0.78%	10, 3, 30.00%	65, 5, 7.69%	90, 6, 6.67%	986, 40, 4.06%	17, 2, 11.76%	1324, 88, 6.65%	1345, 96, 7.14%
Stroke	197, 1, 0.51%	184, 3, 1.63%	128, 0, 0.00%	53, 0, 0.00%	129, 0, 0.00%	10, 0, 0.00%	65, 2, 3.08%	90, 1, 1.11%	986, 5, 0.51%	17, 0, 0.00%	1319, 10, 0.76%	1343, 15, 1.12%
T2D	188, 5, 2.66%	178, 0, 0.00%	124, 3, 2.42%	44, 0, 0.00%	115, 0, 0.00%	9, 1, 11.11%	54, 5, 9.26%	90, 1, 1.11%	982, 7, 0.71%	17, 5, 29.41%	1110, 16, 1.44%	1110, 14, 1.26%

Table S6: For each pair of exposure and outcome, from top to bottom are number of IVs used, number of invalid IVs detected by cML-BIC, and proportion of detected invalid IVs. Results are got with one starting point set at 0.

Exposure Outcome	HDL	LDL	TG	Alcohol	Smoke	BF	BW	BMI	Height	FG	SBP	DBP
Asthma	188, 3, 1.60%	173, 1, 0.58%	122, 1, 0.82%	44, 0, 0.00%	114, 2, 1.75%	10, 0, 0.00%	54, 1, 1.85%	88, 0, 0.00%	977, 9, 0.92%	17, 1, 5.88%	1106, 5, 0.45%	1108, 11, 0.99%
CAD	197, 37, 18.78%	184, 19, 10.33%	128, 15, 11.72%	54, 3, 5.56%	129, 1, 0.78%	10, 4, 40.00%	65, 5, 7.69%	90, 6, 6.67%	986, 41, 4.16%	17, 2, 11.76%	1324, 89, 6.72%	1345, 96, 7.14%
Stroke	197, 1, 0.51%	184, 3, 1.63%	128, 0, 0.00%	53, 0, 0.00%	129, 0, 0.00%	10, 0, 0.00%	65, 2, 3.08%	90, 1, 1.11%	986, 5, 0.51%	17, 0, 0.00%	1319, 10, 0.76%	1343, 15, 1.12%
T2D	188, 5, 2.66%	178, 0, 0.00%	124, 3, 2.42%	44, 0, 0.00%	115, 0, 0.00%	9, 1, 11.11%	54, 5, 9.26%	90, 1, 1.11%	982, 8, 0.81%	17, 3, 17.65%	1110, 16, 1.44%	1110, 14, 1.26%

Table S7: Goodness-of-fit tests for Asthma: the cells with the p-values less than the Bonferroni adjusted significance cutoff 0.001 are marked with red.

Exposure Method	HDL	LDL	TG	Alcohol	Smoke	BF	BW	BMI	Height	FG	SBP	DBP
GOF1-Max	6.1e-01	7.8e-02	3.6e-02	2.4e-01	2.9e-02	3.7e-01	8.0e-02	2.4e-01	2.6e-01	7.8e-02	4.0e-01	3.9e-02
GOF2-Max	6.4e-01	1.0e-01	5.2e-02	2.5e-01	3.0e-02	3.6e-01	7.2e-02	2.9e-01	2.7e-01	8.0e-02	4.0e-01	3.5e-02
GOF1	6.1e-01	7.8e-02	3.6e-02	2.4e-01	2.9e-02	3.7e-01	8.0e-02	2.4e-01	2.5e-01	7.8e-02	4.8e-02	8.9e-03
GOF2	6.4e-01	1.0e-01	5.2e-02	2.5e-01	3.0e-02	3.6e-01	7.2e-02	2.9e-01	2.6e-01	8.0e-02	5.9e-02	8.7e-03

Table S8: Goodness-of-fit tests for CAD: the cells with the p-values less than the Bonferroni adjusted significance cutoff 0.001 are marked with red.

Exposure Method	HDL	LDL	TG	Alcohol	Smoke	BF	BW	BMI	Height	FG	SBP	DBP
GOF1-Max	2.6e-14	1.1e-16	8.7e-13	1.2e-07	5.2e-01	8.2e-06	8.5e-06	6.9e-04	1.9e-03	1.6e-08	5.2e-14	3.1e-11
GOF2-Max	2.5e-16	4.7e-14	3.6e-16	4.3e-08	5.6e-01	1.4e-09	2.5e-06	2.2e-03	1.0e-03	2.1e-06	1.8e-12	4.8e-10
GOF1	2.7e-14	1.6e-14	7.5e-18	1.2e-07	5.2e-01	8.2e-06	8.5e-06	6.9e-04	1.7e-07	4.5e-06	1.3e-12	9.8e-11
GOF2	8.3e-19	2.3e-17	3.7e-18	4.3e-08	5.6e-01	1.4e-09	2.5e-06	2.2e-03	4.0e-07	8.4e-06	9.0e-11	2.8e-11

Table S9: Goodness-of-fit tests for Stroke: the cells with the p-values less than the Bonferroni adjusted significance cutoff 0.001 are marked with red.

Exposure Method	HDL	LDL	TG	Alcohol	Smoke	BF	BW	BMI	Height	FG	SBP	DBP
GOF1-Max	7.3e-01	3.0e-02	5.1e-01	6.7e-01	1.4e-01	2.0e-01	3.6e-05	7.2e-01	8.8e-01	5.6e-02	7.4e-04	4.6e-02
GOF2-Max	7.2e-01	3.6e-02	5.4e-01	6.6e-01	1.7e-01	1.7e-01	1.8e-04	7.1e-01	8.7e-01	5.5e-02	1.4e-03	3.8e-02
GOF1	7.3e-01	3.0e-02	5.1e-01	6.7e-01	1.4e-01	2.0e-01	3.6e-05	8.4e-01	1.7e-01	5.6e-02	1.3e-02	6.9e-03
GOF2	7.2e-01	3.6e-02	5.4e-01	6.6e-01	1.7e-01	1.7e-01	1.8e-04	8.5e-01	2.0e-01	5.5e-02	1.1e-02	2.4e-03

Table S10: Goodness-of-fit tests for T2D: the cells with the p-values less than the Bonferroni adjusted significance cutoff 0.001 are marked with red.

Exposure Method	HDL	LDL	TG	Alcohol	Smoke	BF	BW	BMI	Height	FG	SBP	DBP
GOF1-Max	5.2e-02	7.4e-02	3.5e-02	5.1e-01	1.5e-01	2.5e-01	9.8e-07	1.6e-02	7.2e-02	4.0e-12	3.7e-02	1.2e-01
GOF2-Max	5.6e-02	1.1e-01	1.5e-02	5.2e-01	1.7e-01	8.8e-02	2.4e-08	3.3e-02	8.4e-02	2.2e-16	5.5e-02	9.4e-02
GOF1	5.2e-02	7.4e-02	3.5e-02	5.1e-01	1.5e-01	2.5e-01	9.8e-07	1.6e-02	2.3e-01	4.0e-12	2.6e-02	4.6e-03
GOF2	5.6e-02	1.1e-01	1.5e-02	5.2e-01	1.7e-01	8.8e-02	2.4e-08	3.3e-02	2.3e-01	2.2e-16	2.2e-02	1.0e-02

Table S11: GWAS data used for 13 traits in secondary real data analysis.

Trait Name	ID in TwoSampleMR	Sample Size	Ref.
FP	ebi-a-GCST001212	10,701	[9]
Height	ieu-a-89	253,288	[12]
HOMA	ebi-a-GCST005180	36,466	[3]
LDL	ebi-a-GCST002222	94,595	[11]
RA	ebi-a-GCST002318	58,284	[7]
SCZ	ieu-b-42	77,096	[8]
T2D	ieu-a-26	69,033	[5]
ASmk	ieu-a-964	47,961	[4]
ANRX	ieu-a-45	17,767	[2]
CIQ	ieu-a-16	12,441	[1]
ESmk	ieu-a-962	74,035	[4]
FSmk	ieu-a-963	41,969	[4]
IHC	ieu-a-28	10,768	[10]

Table S12: Secondary real data analysis, set 1.

Method \ Exp/Out	FP/ASmk (6)	FP/ANRX (6)	FP/CIQ (4)	FP/ESmk (6)	FP/FSmk (6)	FP/Height (6)	FP/HOMA (6)	FP/IHC (6)	FP/LDL (5)
cML-MA-BIC-Max	2.3e-01, -1.9e-02, 1.6e-02	6.1e-01, 9.0e-02, 1.8e-01	1.9e-01, -1.3e-01, 1.0e-01	6.7e-01, -3.5e-02, 8.3e-02	1.1e-01, -1.8e-01, 1.1e-01	4.3e-02, 4.8e-02, 2.4e-02	3.7e-08, -2.5e-01, 4.6e-02	4.5e-01, -7.3e-02, 9.6e-02	2.0e-01, 4.5e-02, 3.5e-02
cML-BIC-Max	2.3e-01, -1.9e-02, 1.6e-02	6.0e-01, 9.3e-02, 1.8e-01	1.9e-01, -1.3e-01, 1.0e-01	5.7e-01, -4.5e-02, 7.8e-02	1.1e-01, -1.8e-01, 1.1e-01	5.1e-02, 4.0e-02, 2.1e-02	5.4e-11, -2.8e-01, 4.2e-02	4.4e-01, -7.4e-02, 9.6e-02	3.5e-01, 2.6e-02, 2.7e-02
cML-MA-BIC	2.3e-01, -1.9e-02, 1.6e-02	6.2e-01, 8.9e-02, 1.8e-01	1.9e-01, -1.3e-01, 1.0e-01	7.9e-01, -2.3e-02, 8.8e-02	1.1e-01, -1.8e-01, 1.1e-01	5.2e-02, 4.2e-02, 2.2e-02	1.1e-08, -2.6e-01, 4.6e-02	4.5e-01, -7.3e-02, 9.6e-02	1.3e-01, 6.2e-02, 4.1e-02
cML-BIC	2.3e-01, -1.9e-02, 1.6e-02	6.0e-01, 9.3e-02, 1.8e-01	1.9e-01, -1.3e-01, 1.0e-01	5.7e-01, -4.5e-02, 7.8e-02	1.1e-01, -1.8e-01, 1.1e-01	5.1e-02, 4.0e-02, 2.1e-02	5.4e-11, -2.8e-01, 4.2e-02	4.4e-01, -7.4e-02, 9.6e-02	4.3e-02, 5.9e-02, 2.9e-02
cML-MA-BIC-DP-Max	2.5e-01, -2.0e-02, 1.7e-02	6.9e-01, 7.6e-02, 1.9e-01	2.2e-01, -1.3e-01, 1.0e-01	7.8e-01, -2.8e-02, 1.0e-01	1.2e-01, -1.8e-01, 1.2e-01	7.8e-02, 4.5e-02, 2.6e-02	4.5e-01, -1.3e-01, 1.7e-01	4.5e-01, -7.8e-02, 1.0e-01	2.9e-01, 4.9e-02, 4.7e-02
cML-BIC-DP-Max	2.4e-01, -2.0e-02, 1.7e-02	6.8e-01, 7.5e-02, 1.8e-01	2.2e-01, -1.3e-01, 1.0e-01	5.5e-01, -5.0e-02, 8.3e-02	1.1e-01, -1.8e-01, 1.2e-01	8.5e-02, 4.3e-02, 2.5e-02	3.7e-01, -1.4e-01, 1.5e-01	4.4e-01, -7.9e-02, 1.0e-01	2.4e-01, 5.0e-02, 4.2e-02
cML-MA-BIC-DP	2.6e-01, -2.0e-02, 1.8e-02	6.9e-01, 7.6e-02, 1.9e-01	2.2e-01, -1.3e-01, 1.0e-01	9.1e-01, -1.3e-02, 1.1e-01	1.3e-01, -1.8e-01, 1.2e-01	9.0e-02, 4.3e-02, 2.5e-02	4.8e-01, -1.2e-01, 1.7e-01	4.5e-01, -7.8e-02, 1.0e-01	2.8e-01, 6.0e-02, 5.6e-02
cML-BIC-DP	2.4e-01, -2.0e-02, 1.7e-02	6.8e-01, 7.5e-02, 1.8e-01	2.2e-01, -1.3e-01, 1.0e-01	9.2e-01, 1.2e-02, 1.2e-01	1.1e-01, -1.8e-01, 1.2e-01	8.5e-02, 4.3e-02, 2.5e-02	5.5e-01, -1.1e-01, 1.9e-01	4.4e-01, -7.9e-02, 1.0e-01	2.4e-01, 5.0e-02, 4.2e-02
MR-Mix	2.0e-01, -3.0e-02, 2.3e-02	8.0e-01, 1.0e-02, 3.8e-02	1.7e-01, -7.0e-02, 5.1e-02	7.8e-01, 1.0e-02, 3.7e-02	1.1e-01, -4.0e-02, 2.5e-02	6.8e-02, 2.0e-02, 1.1e-02	1.0e-09, -3.2e-01, 5.2e-02	4.7e-01, -3.5e-02, 4.9e-02	2.5e-04, 3.5e-02, 2.7e-02
MR-ContMix	2.5e-01, -1.7e-02, NA	6.1e-01, 9.5e-02, NA	2.4e-01, -1.3e-01, NA	5.6e-01, 5.0e-02, NA	1.7e-01, -2.1e-01, NA	1.1e-01, 3.8e-02, NA	1.4e-02, -2.7e-01, NA	4.8e-01, -7.7e-02, NA	2.3e-01, 1.4e-01, NA
MR-Lasso	3.7e-01, -1.5e-02, 1.7e-02	8.0e-01, -5.3e-02, 2.1e-01	1.9e-01, -1.3e-01, 9.9e-02	6.7e-01, -4.4e-02, 1.0e-01	1.1e-01, -1.8e-01, 1.1e-01	5.0e-02, 4.0e-02, 2.1e-02	5.8e-02, -1.5e-01, 8.1e-02	4.4e-01, -7.4e-02, 9.6e-02	6.8e-01, 2.4e-02, 5.9e-02
MR-PRESSO	1.3e-01, -1.9e-02, 1.1e-02	5.5e-01, 9.2e-02, 1.4e-01	1.5e-01, -1.3e-01, 6.7e-02	6.9e-01, -4.4e-02, 1.0e-01	9.7e-02, -1.8e-01, 8.7e-02	8.0e-02, 4.0e-02, 1.7e-02	5.0e-02, 5.6e-02, 4.4e-03	1.7e-01, -7.4e-02, 4.6e-02	3.1e-01, 5.8e-02, 4.7e-02
MR-IVW	2.3e-01, -1.9e-02, 1.6e-02	6.1e-01, 9.2e-02, 1.8e-01	1.9e-01, -1.3e-01, 9.9e-02	6.7e-01, -4.4e-02, 1.0e-01	1.1e-01, -1.8e-01, 1.1e-01	7.6e-02, 6.5e-02, 3.6e-02	7.1e-01, -3.1e-02, 8.2e-02	4.4e-01, -7.4e-02, 9.6e-02	6.8e-01, 2.4e-02, 5.9e-02
MR-Egger	4.6e-01, -2.8e-02, 3.8e-02	8.9e-01, 5.5e-02, 3.9e-01	9.1e-01, -2.8e-02, 2.4e-01	1.9e-01, -2.9e-01, 2.2e-01	9.0e-01, 3.2e-02, 2.5e-01	7.0e-01, -3.0e-02, 7.8e-02	1.7e-01, 2.1e-01, 1.6e-01	9.6e-01, 1.2e-02, 2.2e-01	9.5e-01, -1.1e-02, 1.7e-01
MR-Weighted-Median	6.2e-01, -9.5e-03, 1.9e-02	9.4e-01, 1.7e-02, 2.2e-01	3.5e-01, -1.1e-01, 1.2e-01	9.6e-01, 5.4e-03, 1.0e-01	3.0e-01, -1.4e-01, 1.3e-01	1.2e-01, 3.8e-02, 2.5e-02	6.9e-02, 6.8e-02, 3.8e-02	6.2e-01, -5.5e-02, 1.1e-01	4.1e-01, 2.8e-02, 3.4e-02
MR-Weighted-Mode	1.6e-01, -3.3e-02, 2.4e-02	6.0e-01, -1.7e-01, 3.2e-01	6.0e-01, -6.9e-02, 1.3e-01	8.9e-01, 1.7e-02, 1.2e-01	4.2e-01, -1.2e-01, 1.6e-01	1.9e-01, 3.6e-02, 2.7e-02	1.7e-03, 9.8e-02, 3.1e-02	6.7e-01, -5.6e-02, 1.3e-01	5.1e-01, 2.4e-02, 3.7e-02
MR-RAPS1	2.3e-01, -1.9e-02, 1.6e-02	6.1e-01, 9.3e-02, 1.8e-01	1.9e-01, -1.3e-01, 1.0e-01	5.7e-01, -4.5e-02, 8.0e-02	1.1e-01, -1.8e-01, 1.1e-01	1.0e-01, 5.1e-02, 3.1e-02	9.1e-01, 7.4e-03, 6.5e-02	4.4e-01, -7.4e-02, 9.6e-02	5.8e-01, 2.8e-02, 5.0e-02
MR-RAPS2	2.5e-01, -1.9e-02, 1.6e-02	6.4e-01, 8.7e-02, 1.8e-01	2.1e-01, -1.3e-01, 1.0e-01	9.5e-01, -4.9e-03, 8.1e-02	1.2e-01, -1.8e-01, 1.1e-01	1.3e-01, 4.6e-02, 3.0e-02	8.5e-01, 1.3e-02, 7.2e-02	4.7e-01, -7.1e-02, 9.9e-02	6.0e-01, 2.9e-02, 5.5e-02
MR-RAPS3	2.3e-01, -1.9e-02, 1.6e-02	6.1e-01, 9.3e-02, 1.8e-01	1.9e-01, -1.3e-01, 1.0e-01	5.7e-01, -4.5e-02, 8.0e-02	1.1e-01, -1.8e-01, 1.1e-01	1.0e-03, 6.7e-02, 2.1e-02	1.5e-01, -3.7e-02, 2.6e-02	4.4e-01, -7.4e-02, 9.6e-02	3.6e-01, 2.6e-02, 2.8e-02
MR-RAPS4	2.5e-01, -1.9e-02, 1.6e-02	6.4e-01, 8.7e-02, 1.8e-01	2.1e-01, -1.3e-01, 1.0e-01	9.5e-01, -4.9e-03, 8.1e-02	1.2e-01, -1.8e-01, 1.1e-01	3.8e-02, 4.2e-02, 2.0e-02	3.0e-03, -6.9e-02, 2.3e-02	4.7e-01, -7.1e-02, 9.9e-02	1.0e-01, 4.7e-02, 2.8e-02

Table S13: Secondary real data analysis, set 2.

Method \ Exp/Out	FP/RA (6)	FP/SCZ (6)	FP/T2D (6)	Height/ASmk (310)	Height/ESmk (310)	Height/FP (307)	Height/FSmk (310)	Height/HOMA (303)	Height/RA (306)
cML-MA-BIC-Max	5.6e-01, -6.8e-02, 1.2e-01	8.3e-02, -1.2e-01, 6.7e-02	2.2e-01, -4.9e-01, 4.0e-01	5.7e-01, 3.0e-03, 5.2e-03	1.4e-01, -4.0e-02, 2.7e-02	3.7e-01, 1.4e-02, 1.6e-02	7.4e-01, -1.2e-02, 3.6e-02	2.6e-01, -8.3e-03, 7.4e-03	1.3e-02, 8.1e-02, 3.3e-02
cML-BIC-Max	2.7e-01, -1.1e-01, 9.9e-02	8.6e-02, -1.1e-01, 6.6e-02	3.3e-05, -6.8e-01, 1.6e-01	6.5e-01, 2.3e-03, 5.0e-03	1.2e-01, -4.1e-02, 2.6e-02	3.4e-01, 1.5e-02, 1.6e-02	8.5e-01, -6.9e-03, 3.6e-02	2.4e-01, -8.6e-03, 7.3e-03	1.3e-02, 8.1e-02, 3.2e-02
cML-MA-BIC	7.7e-01, -3.7e-02, 1.2e-01	8.0e-02, -1.2e-01, 6.8e-02	6.9e-01, -2.8e-01, 7.0e-01	5.0e-01, 3.6e-03, 5.3e-03	1.2e-01, -4.1e-02, 2.7e-02	4.7e-01, 1.1e-02, 1.6e-02	6.4e-01, -1.7e-02, 3.6e-02	2.8e-01, -8.1e-03, 7.4e-03	1.1e-02, 8.6e-02, 3.4e-02
cML-BIC	2.7e-01, -1.1e-01, 9.9e-02	8.6e-02, -1.1e-01, 6.6e-02	3.3e-05, -6.8e-01, 1.6e-01	6.5e-01, 2.3e-03, 5.0e-03	1.2e-01, -4.1e-02, 2.6e-02	4.9e-01, 1.1e-02, 1.6e-02	5.9e-01, -1.9e-02, 3.6e-02	3.1e-01, -7.5e-03, 7.4e-03	8.6e-03, 8.5e-02, 3.2e-02
cML-MA-BIC-DP-Max	6.3e-01, -7.5e-02, 1.6e-01	9.1e-02, -1.2e-01, 7.3e-02	8.2e-01, -2.2e-01, 9.6e-01	6.0e-01, 3.0e-03, 5.8e-03	1.9e-01, -3.9e-02, 3.0e-02	4.0e-01, 1.4e-02, 1.6e-02	7.1e-01, -1.5e-02, 3.9e-02	4.6e-01, -6.6e-03, 9.0e-03	2.8e-02, 9.7e-02, 4.4e-02
cML-BIC-DP-Max	8.3e-01, -3.7e-02, 1.8e-01	7.7e-02, -1.2e-01, 6.8e-02	8.2e-01, 2.1e-01, 9.1e-01	6.8e-01, 2.3e-03, 5.5e-03	1.5e-01, -4.3e-02, 2.9e-02	3.8e-01, 1.4e-02, 1.5e-02	6.1e-01, -2.0e-02, 3.8e-02	5.6e-01, -5.2e-03, 9.0e-03	2.1e-02, 9.7e-02, 4.2e-02
cML-MA-BIC-DP	7.5e-01, -5.6e-02, 1.8e-01	1.1e-01, -1.3e-01, 7.9e-02	8.2e-01, 2.3e-01, 1.0e+00	5.6e-01, 3.5e-03, 6.0e-03	2.3e-01, -3.7e-02, 3.1e-02	5.4e-01, 1.2e-02, 1.9e-02	8.2e-01, -9.9e-03, 4.3e-02	5.4e-01, -5.5e-03, 9.1e-03	3.1e-02, 1.0e-01, 4.7e-02
cML-BIC-DP	8.3e-01, -3.7e-02, 1.8e-01	7.7e-02, -1.2e-01, 6.8e-02	8.2e-01, 2.1e-01, 9.1e-01	5.3e-01, 3.7e-03, 6.0e-03	2.1e-01, -3.8e-02, 3.0e-02	5.9e-01, 1.1e-02, 2.0e-02	8.3e-01, -9.7e-03, 4.5e-02	5.6e-01, -5.2e-03, 9.0e-03	4.8e-02, 9.8e-02, 5.0e-02
MR-Mix	3.3e-01, 4.0e-02, 4.1e-02	6.6e-01, -7.0e-02, 1.6e-01	3.4e-02, -1.3e-01, 6.1e-02	8.0e-01, 5.0e-02, 2.0e-01	1.1e-01, -4.0e-02, 2.5e-02	8.5e-01, -8.0e-02, 4.3e-01	3.1e-01, -3.0e-02, 3.0e-02	6.4e-01, 6.0e-02, 1.3e-01	2.6e-01, 3.0e-02, 2.7e-02
MR-ContMix	2.1e-01, 1.8e-01, NA	3.4e-02, -1.5e-01, NA	4.0e-02, -9.1e-01, NA	6.1e-01, 2.2e-03, NA	8.4e-01, 9.3e-03, NA	2.9e-01, 2.8e-02, NA	8.5e-01, 1.3e-02, NA	8.2e-01, -7.9e-03, NA	2.7e-03, 2.0e-01, NA
MR-Lasso	5.6e-01, -1.0e-01, 1.8e-01	1.8e-01, -1.1e-01, 8.4e-02	2.1e-01, 7.6e-01, 6.0e-01	3.3e-01, 5.0e-03, 5.1e-03	9.3e-02, -4.4e-02, 2.6e-02	4.9e-01, 1.1e-02, 1.6e-02	6.0e-01, -1.9e-02, 3.6e-02	4.7e-01, -5.4e-03, 7.5e-03	6.0e-05, 1.5e-01, 3.4e-02
MR-PRESSO	8.8e-01, 2.4e-02, 1.5e-01	2.4e-01, -1.1e-01, 8.4e-02	4.2e-01, 6.5e-01, 5.1e-01	6.6e-01, 2.2e-03, 5.0e-03	3.0e-01, -2.8e-02, 2.7e-02	3.6e-01, 1.5e-02, 1.6e-02	6.1e-01, -1.9e-02, 3.7e-02	3.1e-01, -8.4e-03, 8.3e-03	3.1e-02, 8.6e-02, 4.0e-02
MR-IVW	5.6e-01, -1.0e-01, 1.8e-01	1.8e-01, -1.1e-01, 8.4e-02	4.2e-01, 7.7e-01, 9.6e-01	6.6e-01, 2.2e-03, 5.0e-03	3.0e-01, -2.8e-02, 2.7e-02	3.6e-01, 1.5e-02, 1.6e-02	8.6e-01, -6.8e-03, 3.8e-02	3.1e-01, -8.4e-03, 8.3e-03	1.9e-02, 1.1e-01, 4.7e-02
MR-Egger	5.7e-01, 2.3e-01, 4.0e-01	4.0e-01, -1.7e-01, 2.0e-01	6.8e-01, -9.3e-01, 2.2e+00	6.5e-01, 6.1e-03, 1.3e-02	9.1e-01, -7.7e-03, 7.2e-02	9.3e-01, -3.7e-03, 4.3e-02	4.3e-01, -8.1e-02, 1.0e-01	2.8e-01, -2.4e-02, 2.3e-02	1.7e-01, 1.6e-01, 1.2e-01
MR-Weighted-Median	3.9e-01, 1.2e-01, 1.4e-01	3.2e-02, -1.8e-01, 8.3e-02	5.9e-03, -7.5e-01, 2.7e-01	1.0e+00, 0.0e+00, 8.1e-03	6.9e-01, -1.7e-02, 4.1e-02	4.3e-01, 1.9e-02, 2.4e-02	1.0e+00, 9.2e-05, 5.8e-02	5.7e-01, -6.6e-03, 1.2e-02	4.8e-01, 4.0e-02, 5.7e-02
MR-Weighted-Mode	4.1e-01, 1.2e-01, 1.5e-01	1.1e-01, -1.6e-01, 1.0e-01	1.6e-02, -4.3e-01, 1.8e-01	6.1e-01, -1.2e-02, 2.3e-02	9.7e-01, -3.1e-03, 7.8e-02	8.0e-01, 1.3e-02, 5.3e-02	6.9e-01, 4.8e-02, 1.2e-01	5.5e-01, 1.5e-02, 2.6e-02	6.7e-02, 1.8e-01, 9.6e-02
MR-RAPS1	8.1e-01, -3.6e-02, 1.5e-01	1.4e-01, -1.1e-01, 7.7e-02	5.6e-01, 4.1e-01, 7.0e-01	6.5e-01, 2.3e-03, 5.2e-03	3.0e-01, -2.9e-02, 2.8e-02	3.6e-01, 1.5e-02, 1.6e-02	8.6e-01, -6.8e-03, 3.8e-02	2.9e-01, -8.7e-03, 8.2e-03	1.3e-02, 1.2e-01, 4.8e-02
MR-RAPS2	9.4e-01, -1.2e-02, 1.6e-01	1.3e-01, -1.2e-01, 8.1e-02	6.9e-01, 2.9e-01, 7.1e-01	4.6e-01, 3.9e-03, 5.3e-03	2.0e-01, -3.6e-02, 2.8e-02	4.3e-01, 1.3e-02, 1.6e-02	8.1e-01, -9.1e-03, 3.8e-02	4.4e-01, -6.4e-03, 8.3e-03	3.1e-02, 9.4e-02, 4.4e-02
MR-RAPS3	2.7e-01, -1.1e-01, 1.0e-01	9.1e-02, -1.1e-01, 6.7e-02	6.8e-10, 2.1e+00, 3.4e-01	6.5e-01, 2.3e-03, 5.1e-03	2.8e-01, -2.8e-02, 2.6e-02	3.5e-01, 1.5e-02, 1.6e-02	8.5e-01, -6.9e-03, 3.6e-02	2.5e-01, -8.6e-03, 7.4e-03	5.1e-04, 1.1e-01, 3.2e-02
MR-RAPS4	9.6e-01, -5.1e-03, 1.0e-01	6.0e-02, -1.3e-01, 6.9e-02	3.8e-02, 2.6e-01, 1.3e-01	4.4e-01, 4.0e-03, 5.2e-03	1.9e-01, -3.6e-02, 2.7e-02	4.3e-01, 1.3e-02, 1.6e-02	7.9e-01, -9.6e-03, 3.7e-02	4.2e-01, -6.1e-03, 7.6e-03	9.2e-04, 1.1e-01, 3.3e-02



Table S14: Secondary real data analysis, set 3.

Method \ Exp/Out	Height/SCZ (288)	Height/T2D (307)	HOMA/ASmk (2)	HOMA/ESmk (2)	HOMA/FP (2)	HOMA/FSmk (2)	HOMA/Height (2)	HOMA/IHC (2)	HOMA/LDL (2)
cML-MA-BIC-Max	1.3e-01, -3.8e-02, 2.5e-02	7.8e-01, -1.1e-02, 4.0e-02	3.3e-01, -5.3e-02, 5.5e-02	6.8e-01, 1.2e-01, 2.8e-01	1.6e-01, 2.4e-01, 1.7e-01	2.3e-02, 8.8e-01, 3.9e-01	3.3e-02, -1.6e-01, 7.3e-02	1.8e-01, 4.6e-01, 3.4e-01	7.7e-01, -2.8e-02, 9.5e-02
cML-BIC-Max	1.1e-01, -3.9e-02, 2.5e-02	9.7e-01, -1.7e-03, 4.0e-02	3.3e-01, -5.3e-02, 5.5e-02	6.8e-01, 1.2e-01, 2.8e-01	1.6e-01, 2.4e-01, 1.7e-01	2.3e-02, 8.8e-01, 3.9e-01	3.3e-02, -1.6e-01, 7.3e-02	1.8e-01, 4.6e-01, 3.4e-01	7.7e-01, -2.8e-02, 9.5e-02
cML-MA-BIC	1.4e-01, -3.7e-02, 2.5e-02	7.4e-01, -1.4e-02, 4.1e-02	3.3e-01, -5.3e-02, 5.5e-02	6.8e-01, 1.2e-01, 2.8e-01	1.6e-01, 2.4e-01, 1.7e-01	2.3e-02, 8.8e-01, 3.9e-01	3.3e-02, -1.6e-01, 7.3e-02	1.8e-01, 4.6e-01, 3.4e-01	7.7e-01, -2.8e-02, 9.5e-02
cML-BIC	9.3e-02, -4.1e-02, 2.5e-02	5.8e-01, -2.2e-02, 4.0e-02	3.3e-01, -5.3e-02, 5.5e-02	6.8e-01, 1.2e-01, 2.8e-01	1.6e-01, 2.4e-01, 1.7e-01	2.3e-02, 8.8e-01, 3.9e-01	3.3e-02, -1.6e-01, 7.3e-02	1.8e-01, 4.6e-01, 3.4e-01	7.7e-01, -2.8e-02, 9.5e-02
cML-MA-BIC-DP-Max	3.9e-01, -3.3e-02, 3.8e-02	9.2e-01, 5.0e-03, 5.0e-02	4.3e-01, -5.0e-02, 6.4e-02	6.8e-01, 1.3e-01, 3.2e-01	2.1e-01, 2.5e-01, 2.0e-01	4.8e-02, 9.1e-01, 4.6e-01	7.1e-02, -1.5e-01, 8.5e-02	2.3e-01, 4.8e-01, 4.1e-01	8.3e-01, -2.5e-02, 1.1e-01
cML-BIC-DP-Max	4.3e-01, -3.1e-02, 3.9e-02	9.2e-01, 5.1e-03, 4.9e-02	4.3e-01, -5.0e-02, 6.4e-02	6.8e-01, 1.3e-01, 3.2e-01	2.1e-01, 2.5e-01, 2.0e-01	4.8e-02, 9.1e-01, 4.6e-01	7.1e-02, -1.5e-01, 8.5e-02	2.3e-01, 4.8e-01, 4.1e-01	8.3e-01, -2.5e-02, 1.1e-01
cML-MA-BIC-DP	3.7e-01, -3.7e-02, 4.1e-02	9.3e-01, 4.7e-03, 5.3e-02	4.3e-01, -5.0e-02, 6.4e-02	6.8e-01, 1.3e-01, 3.2e-01	2.1e-01, 2.5e-01, 2.0e-01	4.8e-02, 9.1e-01, 4.6e-01	7.1e-02, -1.5e-01, 8.5e-02	2.3e-01, 4.8e-01, 4.1e-01	8.3e-01, -2.5e-02, 1.1e-01
cML-BIC-DP	3.2e-01, -4.2e-02, 4.2e-02	9.2e-01, 5.1e-03, 4.9e-02	4.3e-01, -5.0e-02, 6.4e-02	6.8e-01, 1.3e-01, 3.2e-01	2.1e-01, 2.5e-01, 2.0e-01	4.8e-02, 9.1e-01, 4.6e-01	7.1e-02, -1.5e-01, 8.5e-02	2.3e-01, 4.8e-01, 4.1e-01	8.3e-01, -2.5e-02, 1.1e-01
MR-Mix	7.1e-01, -7.0e-02, 1.9e-01	7.0e-01, 4.0e-02, 1.1e-01	NA	NA	NA	NA	NA	NA	NA
MR-ContMix	2.8e-02, -1.0e-01, NA	6.7e-01, 3.4e-02, NA	NA	NA	NA	NA	NA	NA	NA
MR-Lasso	3.7e-02, -5.6e-02, 2.7e-02	9.3e-01, 4.0e-03, 4.3e-02	NA	NA	NA	NA	NA	NA	NA
MR-PRESSO	4.5e-01, -2.5e-02, 3.3e-02	7.6e-01, -1.5e-02, 4.9e-02	NA	NA	NA	NA	NA	NA	NA
MR-IVW	4.3e-01, -3.0e-02, 3.7e-02	1.0e+00, 8.5e-05, 5.1e-02	NA	NA	NA	NA	NA	NA	NA
MR-Egger	9.2e-01, 9.6e-03, 1.0e-01	3.1e-01, 1.4e-01, 1.4e-01	NA	NA	NA	NA	NA	NA	NA
MR-Weighted-Median	4.1e-01, -3.5e-02, 4.3e-02	1.0e+00, 0.0e+00, 6.5e-02	NA	NA	NA	NA	NA	NA	NA
MR-Weighted-Mode	9.8e-01, 2.6e-03, 1.0e-01	9.8e-01, 3.9e-03, 1.9e-01	NA	NA	NA	NA	NA	NA	NA
MR-RAPS1	3.5e-01, -3.5e-02, 3.7e-02	9.9e-01, -7.7e-04, 5.2e-02	NA	NA	NA	NA	NA	NA	NA
MR-RAPS2	3.3e-01, -3.6e-02, 3.7e-02	8.8e-01, 8.1e-03, 5.2e-02	NA	NA	NA	NA	NA	NA	NA
MR-RAPS3	2.1e-01, -3.0e-02, 2.4e-02	1.0e+00, 8.7e-05, 4.0e-02	NA	NA	NA	NA	NA	NA	NA
MR-RAPS4	1.5e-01, -3.6e-02, 2.5e-02	8.4e-01, 8.2e-03, 4.1e-02	NA	NA	NA	NA	NA	NA	NA

Table S15: Secondary real data analysis, set 4.

Method \ Exp/Out	HOMA/RA (2)	HOMA/SCZ (2)	HOMA/T2D (2)	LDL/ASmk (69)	LDL/ANRX (52)	LDL/ESmk (69)	LDL/FP (68)	LDL/FSmk (69)	LDL/HOMA (68)
cML-MA-BIC-Max	3.8e-01, 3.4e-01, 3.9e-01	2.9e-01, 2.7e-01, 2.6e-01	3.8e-01, 3.5e-01, 4.0e-01	1.9e-01, -8.4e-03, 6.5e-03	5.3e-02, 1.6e-01, 8.1e-02	4.1e-01, -2.8e-02, 3.4e-02	1.1e-02, -5.3e-02, 2.1e-02	1.6e-01, 6.5e-02, 4.6e-02	8.1e-01, 2.3e-03, 9.4e-03
cML-BIC-Max	3.8e-01, 3.4e-01, 3.9e-01	2.9e-01, 2.7e-01, 2.6e-01	3.8e-01, 3.5e-01, 4.0e-01	1.9e-01, -8.5e-03, 6.4e-03	5.2e-02, 1.6e-01, 8.1e-02	3.0e-01, -3.4e-02, 3.3e-02	1.1e-02, -5.3e-02, 2.1e-02	1.8e-01, 6.1e-02, 4.6e-02	8.2e-01, 2.0e-03, 9.2e-03
cML-MA-BIC	3.8e-01, 3.4e-01, 3.9e-01	2.9e-01, 2.7e-01, 2.6e-01	3.8e-01, 3.5e-01, 4.0e-01	1.9e-01, -8.4e-03, 6.5e-03	5.5e-02, 1.6e-01, 8.1e-02	4.2e-01, -2.7e-02, 3.4e-02	1.2e-02, -5.3e-02, 2.1e-02	1.5e-01, 6.6e-02, 4.6e-02	7.6e-01, 2.9e-03, 9.4e-03
cML-BIC	3.8e-01, 3.4e-01, 3.9e-01	2.9e-01, 2.7e-01, 2.6e-01	3.8e-01, 3.5e-01, 4.0e-01	1.9e-01, -8.5e-03, 6.4e-03	5.2e-02, 1.6e-01, 8.1e-02	4.8e-01, -2.4e-02, 3.3e-02	1.1e-02, -5.3e-02, 2.1e-02	1.8e-01, 6.1e-02, 4.6e-02	8.2e-01, 2.0e-03, 9.2e-03
cML-MA-BIC-DP-Max	4.3e-01, 3.6e-01, 4.6e-01	3.4e-01, 2.9e-01, 3.0e-01	4.2e-01, 3.8e-01, 4.7e-01	2.9e-01, -7.9e-03, 7.5e-03	8.8e-02, 1.6e-01, 9.3e-02	6.5e-01, -1.7e-02, 3.7e-02	1.9e-02, -5.4e-02, 2.3e-02	1.3e-01, 7.3e-02, 4.9e-02	8.2e-01, 2.9e-03, 1.1e-02
cML-BIC-DP-Max	4.3e-01, 3.6e-01, 4.6e-01	3.4e-01, 2.9e-01, 3.0e-01	4.2e-01, 3.8e-01, 4.7e-01	3.4e-01, -7.5e-03, 7.9e-03	6.9e-02, 1.6e-01, 8.9e-02	7.2e-01, -1.4e-02, 3.9e-02	1.8e-02, -5.4e-02, 2.3e-02	1.3e-01, 7.3e-02, 4.8e-02	9.3e-01, 9.8e-04, 1.1e-02
cML-MA-BIC-DP	4.3e-01, 3.6e-01, 4.6e-01	3.4e-01, 2.9e-01, 3.0e-01	4.2e-01, 3.8e-01, 4.7e-01	3.2e-01, -7.6e-03, 7.7e-03	1.2e-01, 1.6e-01, 9.9e-02	6.6e-01, -1.7e-02, 3.8e-02	2.1e-02, -5.5e-02, 2.4e-02	1.3e-01, 7.4e-02, 4.9e-02	7.5e-01, 3.4e-03, 1.1e-02
cML-BIC-DP	4.3e-01, 3.6e-01, 4.6e-01	3.4e-01, 2.9e-01, 3.0e-01	4.2e-01, 3.8e-01, 4.7e-01	3.4e-01, -7.5e-03, 7.9e-03	1.3e-01, 1.6e-01, 1.0e-01	7.2e-01, -1.4e-02, 3.9e-02	2.0e-02, -5.5e-02, 2.4e-02	1.3e-01, 7.3e-02, 4.8e-02	7.1e-01, 4.2e-03, 1.1e-02
MR-Mix	NA	NA	NA	3.1e-01, -1.5e-02, 1.5e-02	5.1e-02, 3.9e-01, 2.0e-01	5.2e-01, 1.0e-02, 1.6e-02	2.9e-01, -7.0e-02, 6.6e-02	3.4e-01, 2.0e-02, 2.1e-02	1.0e-01, 3.0e-02, 1.8e-02
MR-ContMix	NA	NA	NA	4.4e-01, -7.1e-03, NA	8.9e-02, 1.6e-01, NA	9.9e-01, -8.4e-05, NA	7.9e-03, -6.5e-02, NA	1.0e-01, 1.1e-01, NA	3.8e-01, 6.9e-03, NA
MR-Lasso	NA	NA	NA	2.5e-01, -7.4e-03, 6.4e-03	1.0e-01, 1.4e-01, 8.9e-02	5.2e-01, -2.3e-02, 3.6e-02	3.9e-03, -6.0e-02, 2.1e-02	9.1e-02, 7.7e-02, 4.6e-02	5.5e-01, 5.5e-03, 9.3e-03
MR-PRESSO	NA	NA	NA	1.4e-01, -8.5e-03, 5.7e-03	9.2e-02, 1.6e-01, 9.2e-02	3.8e-01, -3.4e-02, 3.8e-02	4.0e-03, -6.0e-02, 2.0e-02	1.8e-01, 6.1e-02, 4.5e-02	8.0e-01, -2.9e-03, 1.2e-02
MR-IVW	NA	NA	NA	1.9e-01, -8.5e-03, 6.4e-03	8.6e-02, 1.6e-01, 9.2e-02	3.8e-01, -3.4e-02, 3.8e-02	3.9e-03, -6.0e-02, 2.1e-02	1.8e-01, 6.1e-02, 4.5e-02	8.0e-01, -2.9e-03, 1.2e-02
MR-Egger	NA	NA	NA	3.7e-01, 9.8e-03, 1.1e-02	4.3e-01, 1.1e-01, 1.4e-01	6.5e-01, -2.9e-02, 6.4e-02	3.0e-01, -3.8e-02, 3.6e-02	3.4e-01, 7.4e-02, 7.7e-02	6.3e-01, -9.7e-03, 2.0e-02
MR-Weighted-Median	NA	NA	NA	6.9e-01, 4.3e-03, 1.1e-02	1.8e-01, 1.6e-01, 1.2e-01	2.0e-01, -6.6e-02, 5.2e-02	9.3e-02, -5.3e-02, 3.2e-02	3.1e-01, 6.9e-02, 6.7e-02	8.1e-01, 3.3e-03, 1.4e-02
MR-Weighted-Mode	NA	NA	NA	3.6e-01, 1.0e-02, 1.1e-02	1.5e-01, 1.5e-01, 1.0e-01	2.1e-01, -5.6e-02, 4.5e-02	1.3e-01, -4.8e-02, 3.1e-02	2.4e-01, 7.7e-02, 6.5e-02	8.3e-01, 2.7e-03, 1.3e-02
MR-RAPS1	NA	NA	NA	1.9e-01, -8.5e-03, 6.5e-03	7.2e-02, 1.6e-01, 8.8e-02	3.6e-01, -3.5e-02, 3.8e-02	3.9e-03, -6.0e-02, 2.1e-02	1.9e-01, 6.2e-02, 4.8e-02	6.7e-01, -4.9e-03, 1.1e-02
MR-RAPS2	NA	NA	NA	2.5e-01, -7.7e-03, 6.6e-03	1.0e-01, 1.5e-01, 9.4e-02	5.6e-01, -2.2e-02, 3.9e-02	1.2e-02, -5.4e-02, 2.1e-02	1.3e-01, 7.3e-02, 4.8e-02	9.5e-01, 7.2e-04, 1.1e-02
MR-RAPS3	NA	NA	NA	1.9e-01, -8.5e-03, 6.5e-03	5.3e-02, 1.6e-01, 8.2e-02	3.1e-01, -3.4e-02, 3.3e-02	3.9e-03, -6.0e-02, 2.1e-02	1.8e-01, 6.1e-02, 4.6e-02	7.5e-01, -3.0e-03, 9.2e-03
MR-RAPS4	NA	NA	NA	2.5e-01, -7.7e-03, 6.6e-03	6.3e-02, 1.6e-01, 8.4e-02	5.9e-01, -1.8e-02, 3.4e-02	1.2e-02, -5.4e-02, 2.1e-02	1.2e-01, 7.3e-02, 4.7e-02	6.4e-01, 4.4e-03, 9.4e-03

Table S16: Secondary real data analysis, set 5.

Method \ Exp/Out	LDL/IHC (67)	LDL/RA (71)	LDL/SCZ (69)	LDL/T2D (67)	RA/SCZ (47)	SCZ/ASmk (35)	SCZ/CIQ (20)	SCZ/FP (34)	SCZ/FSmk (35)
cML-MA-BIC-Max	4.7e-01, -2.8e-02, 3.9e-02	7.9e-01, -9.9e-03, 3.7e-02	7.6e-01, -8.7e-03, 2.8e-02	1.2e-03, -1.7e-01, 5.3e-02	1.6e-01, 1.8e-02, 1.3e-02	5.0e-01, -3.8e-03, 5.6e-03	4.6e-01, -3.1e-02, 4.3e-02	6.0e-01, -9.7e-03, 1.9e-02	6.9e-01, -1.6e-02, 4.2e-02
cML-BIC-Max	5.0e-01, -2.6e-02, 3.8e-02	8.2e-01, -8.6e-03, 3.7e-02	7.7e-01, -8.2e-03, 2.8e-02	1.9e-03, -1.6e-01, 5.0e-02	2.0e-01, 1.6e-02, 1.2e-02	5.1e-01, -3.7e-03, 5.6e-03	4.4e-01, -3.3e-02, 4.2e-02	5.1e-01, -1.2e-02, 1.8e-02	7.8e-01, -1.1e-02, 3.9e-02
cML-MA-BIC	4.8e-01, -2.7e-02, 3.8e-02	7.8e-01, -1.0e-02, 3.7e-02	7.6e-01, -8.5e-03, 2.8e-02	1.1e-03, -1.7e-01, 5.3e-02	1.6e-01, 1.8e-02, 1.3e-02	5.0e-01, -3.8e-03, 5.6e-03	5.0e-01, -2.9e-02, 4.3e-02	5.0e-01, -1.2e-02, 1.9e-02	6.7e-01, -1.8e-02, 4.2e-02
cML-BIC	5.0e-01, -2.6e-02, 3.8e-02	8.2e-01, -8.6e-03, 3.7e-02	7.7e-01, -8.2e-03, 2.8e-02	6.4e-04, -1.7e-01, 5.1e-02	2.0e-01, 1.6e-02, 1.2e-02	5.1e-01, -3.7e-03, 5.6e-03	4.4e-01, -3.3e-02, 4.2e-02	5.1e-01, -1.2e-02, 1.8e-02	7.8e-01, -1.1e-02, 3.9e-02
cML-MA-BIC-DP-Max	5.4e-01, -2.9e-02, 4.7e-02	7.6e-01, -1.2e-02, 4.1e-02	8.1e-01, -7.6e-03, 3.1e-02	1.1e-02, -1.7e-01, 7.0e-02	3.2e-01, 1.8e-02, 1.6e-02	5.4e-01, -4.0e-03, 6.5e-03	6.1e-01, -2.6e-02, 5.0e-02	7.6e-01, -7.1e-03, 2.3e-02	6.6e-01, -2.3e-02, 5.3e-02
cML-BIC-DP-Max	4.7e-01, -2.9e-02, 4.1e-02	7.9e-01, -1.0e-02, 3.8e-02	8.2e-01, -7.2e-03, 3.2e-02	8.2e-03, -1.8e-01, 6.8e-02	3.4e-01, 1.4e-02, 1.5e-02	5.5e-01, -3.5e-03, 5.8e-03	6.1e-01, -2.6e-02, 5.2e-02	7.7e-01, -6.2e-03, 2.2e-02	5.9e-01, -2.9e-02, 5.5e-02
cML-MA-BIC-DP	5.8e-01, -2.8e-02, 5.2e-02	7.6e-01, -1.3e-02, 4.2e-02	8.1e-01, -7.6e-03, 3.1e-02	1.2e-02, -1.8e-01, 7.1e-02	3.2e-01, 1.6e-02, 1.6e-02	5.4e-01, -4.0e-03, 6.6e-03	6.6e-01, -2.4e-02, 5.5e-02	7.7e-01, -7.1e-03, 2.4e-02	6.5e-01, -2.5e-02, 5.5e-02
cML-BIC-DP	5.8e-01, -2.7e-02, 4.9e-02	7.6e-01, -1.3e-02, 4.4e-02	8.2e-01, -7.2e-03, 3.2e-02	8.2e-03, -1.8e-01, 6.8e-02	3.4e-01, 1.4e-02, 1.5e-02	5.3e-01, -4.4e-03, 7.0e-03	6.1e-01, -2.6e-02, 5.2e-02	7.2e-01, -9.1e-03, 2.5e-02	5.9e-01, -2.9e-02, 5.5e-02
MR-Mix	1.0e+00, 0.0e+00, 3.6e-02	7.8e-01, 1.0e-02, 3.6e-02	5.2e-01, -1.0e-02, 1.6e-02	1.5e-02, -9.0e-02, 3.7e-02	9.7e-02, 2.0e-02, 1.8e-02	5.7e-01, -2.0e-02, 3.5e-02	1.0e+00, 2.0e-17, 9.9e-02	4.9e-01, 1.0e-01, 1.5e-01	1.3e-01, -1.0e-01, 6.6e-02
MR-ContMix	8.1e-01, -9.2e-03, NA	3.7e-01, -3.4e-02, NA	8.3e-01, -1.2e-02, NA	4.2e-02, -1.4e-01, NA	8.3e-02, 2.4e-02, NA	6.9e-02, -1.4e-02, NA	5.5e-01, -2.7e-02, NA	9.3e-01, 8.4e-04, NA	1.6e-01, -6.8e-02, NA
MR-Lasso	5.2e-01, -2.6e-02, 4.0e-02	5.2e-01, -2.5e-02, 3.9e-02	7.3e-01, -9.5e-03, 2.8e-02	8.8e-06, -2.3e-01, 5.1e-02	1.2e-01, 2.0e-02, 1.3e-02	5.1e-01, -3.6e-03, 5.5e-03	8.1e-01, -1.1e-02, 4.6e-02	5.5e-01, -1.1e-02, 1.8e-02	1.1e-01, -6.7e-02, 1.8e-02
MR-PRESSO	3.3e-01, -4.3e-02, 4.4e-02	8.3e-01, -8.6e-03, 3.9e-02	9.8e-01, -7.5e-04, 3.2e-02	1.1e-02, -1.7e-01, 6.5e-02	1.7e-01, 2.0e-02, 1.4e-02	4.5e-01, -3.6e-03, 4.7e-03	5.3e-01, -3.2e-02, 5.0e-02	5.7e-01, -1.1e-02, 2.0e-02	8.1e-01, -1.0e-02, 4.4e-02
MR-IVW	3.3e-01, -4.3e-02, 4.4e-02	7.3e-01, 2.6e-02, 7.5e-02	7.9e-01, -1.0e-02, 3.8e-02	2.2e-02, -1.5e-01, 6.7e-02	6.0e-01, 9.7e-03, 1.8e-02	5.1e-01, -3.6e-03, 5.5e-03	5.2e-01, -3.2e-02, 5.0e-02	9.5e-01, -1.3e-03, 2.2e-02	8.1e-01, -1.0e-02, 4.4e-02
MR-Egger	3.3e-01, 6.8e-02, 7.1e-02	6.8e-01, 5.0e-02, 1.2e-01	4.1e-01, 4.9e-02, 6.0e-02	7.6e-03, -3.2e-01, 1.2e-01	8.6e-02, 5.7e-02, 3.3e-02	4.2e-01, -1.9e-02, 2.4e-02	6.5e-03, 9.0e-01, 3.3e-01	2.7e-01, -9.7e-02, 8.8e-02	1.3e-02, 4.2e-01, 1.7e-01
MR-Weighted-Median	4.6e-01, -4.6e-02, 6.2e-02	1.0e+00, 0.0e+00, 5.4e-02	3.5e-01, 3.9e-02, 4.2e-02	4.4e-02, -1.7e-01, 8.4e-02	4.8e-02, 3.7e-02, 1.9e-02	2.5e-01, -8.7e-03, 7.6e-03	4.5e-01, -4.6e-02, 6.0e-02	5.4e-01, -1.7e-02, 2.7e-02	2.6e-01, -6.5e-02, 5.8e-02
MR-Weighted-Mode	8.9e-01, 8.3e-03, 5.8e-02	8.5e-01, -9.8e-03, 5.3e-02	5.1e-01, 2.5e-02, 3.8e-02	4.8e-02, -1.7e-01, 8.4e-02	8.0e-02, 3.3e-02, 1.9e-02	1.7e-01, -1.9e-02, 1.4e-02	6.3e-01, -4.7e-02, 9.8e-02	8.3e-01, -9.0e-03, 4.1e-02	4.3e-01, -1.1e-01, 1.5e-01
MR-RAPS1	3.6e-01, -3.9e-02, 4.3e-02	5.6e-01, 4.2e-02, 7.2e-02	8.2e-01, -8.1e-03, 3.6e-02	3.0e-03, -2.0e-01, 6.6e-02	4.6e-01, 1.3e-02, 1.7e-02	5.1e-01, -3.7e-03, 5.6e-03	5.4e-01, -3.1e-02, 5.0e-02	8.7e-01, -3.6e-03, 2.2e-02	8.2e-01, -9.9e-03, 4.4e-02
MR-RAPS2	4.4e-01, -3.1e-02, 4.0e-02	6.3e-01, -1.8e-02, 3.8e-02	9.0e-01, -3.7e-03, 3.1e-02	2.8e-03, -2.0e-01, 6.6e-02	3.1e-01, 1.7e-02, 1.7e-02	4.2e-01, -4.6e-03, 5.8e-03	6.1e-01, -2.7e-02, 5.2e-02	7.6e-01, -6.6e-03, 2.2e-02	5.1e-01, -2.9e-02, 4.4e-02
MR-RAPS3	2.6e-01, -4.3e-02, 3.8e-02	4.7e-01, 2.7e-02, 3.8e-02	7.0e-01, -1.0e-02, 2.8e-02	1.9e-03, -1.6e-01, 5.0e-02	4.2e-01, 9.9e-03, 1.2e-02	5.1e-01, -3.7e-03, 5.6e-03	4.5e-01, -3.3e-02, 4.3e-02	9.4e-01, -1.4e-03, 1.8e-02	7.9e-01, -1.1e-02, 4.0e-02
MR-RAPS4	4.4e-01, -3.0e-02, 3.9e-02	6.3e-01, -1.8e-02, 3.8e-02	8.7e-01, -4.7e-03, 2.8e-02	2.5e-04, -1.9e-01, 5.2e-02	1.7e-01, 1.7e-02, 1.3e-02	4.2e-01, -4.6e-03, 5.8e-03	5.5e-01, -2.7e-02, 4.4e-02	6.9e-01, -7.3e-03, 1.8e-02	4.3e-01, -3.2e-02, 4.1e-02

Table S17: Secondary real data analysis, set 6.

Method \ Exp/Out	SCZ/Height (35)	SCZ/HOMA (35)	SCZ/IHC (35)	SCZ/LDL (36)	SCZ/RA (69)	SCZ/T2D (35)	T2D/ASmk (10)	T2D/ANRX (6)	T2D/CIQ (7)
cML-MA-BIC-Max	3.6e-01, -8.1e-03, 8.9e-03	2.2e-01, 9.9e-03, 8.1e-03	8.0e-01, -9.2e-03, 3.6e-02	8.9e-01, -1.7e-03, 1.2e-02	3.0e-01, 2.7e-02, 2.6e-02	8.9e-01, 6.2e-03, 4.4e-02	7.6e-01, -1.8e-03, 5.8e-03	9.0e-01, 1.2e-02, 9.9e-02	6.6e-01, 1.7e-02, 3.8e-02
cML-BIC-Max	4.2e-01, -6.2e-03, 7.7e-03	2.2e-01, 9.9e-03, 8.1e-03	7.6e-01, -1.1e-02, 3.5e-02	9.5e-01, -7.9e-04, 1.2e-02	2.5e-01, 2.9e-02, 2.6e-02	9.1e-01, 5.0e-03, 4.4e-02	7.6e-01, -1.8e-03, 5.8e-03	8.9e-01, 1.3e-02, 9.9e-02	6.7e-01, 1.6e-02, 3.8e-02
cML-MA-BIC	2.2e-01, -1.1e-02, 8.6e-03	2.2e-01, 9.8e-03, 8.1e-03	7.5e-01, -1.2e-02, 3.6e-02	8.9e-01, -1.8e-03, 1.2e-02	3.0e-01, 2.7e-02, 2.6e-02	8.9e-01, 6.3e-03, 4.4e-02	7.6e-01, -1.8e-03, 5.8e-03	9.1e-01, 1.2e-02, 9.9e-02	6.5e-01, 1.8e-02, 3.8e-02
cML-BIC	6.5e-02, -1.4e-02, 7.9e-03	2.2e-01, 9.9e-03, 8.1e-03	7.6e-01, -1.1e-02, 3.5e-02	9.5e-01, -7.9e-04, 1.2e-02	2.5e-01, 2.9e-02, 2.6e-02	9.1e-01, 5.0e-03, 4.4e-02	7.6e-01, -1.8e-03, 5.8e-03	8.9e-01, 1.3e-02, 9.9e-02	6.7e-01, 1.6e-02, 3.8e-02
cML-MA-BIC-DP-Max	8.5e-01, -3.0e-03, 1.5e-02	2.5e-01, 1.0e-02, 8.8e-03	8.9e-01, -6.9e-03, 4.9e-02	9.7e-01, -6.3e-04, 1.8e-02	3.9e-01, 2.9e-02, 3.4e-02	8.5e-01, 1.0e-02, 5.5e-02	8.2e-01, -1.3e-03, 5.8e-03	8.3e-01, 2.5e-02, 1.2e-01	7.1e-01, 1.6e-02, 4.3e-02
cML-BIC-DP-Max	9.2e-01, -1.4e-03, 1.4e-02	2.2e-01, 1.0e-02, 8.5e-03	9.5e-01, -3.0e-03, 4.6e-02	9.8e-01, 5.3e-04, 1.8e-02	3.9e-01, 2.9e-02, 3.4e-02	8.4e-01, 1.1e-02, 5.4e-02	8.3e-01, -1.2e-03, 5.7e-03	8.2e-01, 2.7e-02, 1.2e-01	7.0e-01, 1.6e-02, 4.2e-02
cML-MA-BIC-DP	8.1e-01, -3.9e-03, 1.6e-02	2.6e-01, 9.9e-03, 8.9e-03	8.3e-01, -1.2e-02, 5.5e-02	9.7e-01, -6.4e-04, 1.8e-02	3.9e-01, 2.9e-02, 3.4e-02	8.5e-01, 1.0e-02, 5.5e-02	8.2e-01, -1.3e-03, 5.9e-03	8.4e-01, 2.4e-02, 1.2e-01	7.1e-01, 1.7e-02, 4.5e-02
cML-BIC-DP	8.6e-01, -3.3e-03, 1.9e-02	2.2e-01, 1.0e-02, 8.5e-03	8.1e-01, -1.5e-02, 6.0e-02	9.8e-01, 5.3e-04, 1.8e-02	3.9e-01, 2.9e-02, 3.4e-02	8.4e-01, 1.1e-02, 5.4e-02	8.3e-01, -1.2e-03, 5.7e-03	8.2e-01, 2.7e-02, 1.2e-01	7.0e-01, 1.6e-02, 4.2e-02
MR-Mix	1.9e-01, -4.0e-02, 3.0e-02	2.0e-01, 5.0e-02, 3.9e-02	8.1e-01, -1.2e-01, 5.1e-01	1.0e+00, 2.0e-17, 5.8e-02	8.9e-01, -2.0e-02, 1.5e-01	1.0e+00, 2.0e-17, 6.5e-02	7.9e-01, -1.5e-02, 5.5e-02	8.4e-01, 2.5e-02, 1.2e-01	1.0e+00, 2.0e-17, 2.0e-01
MR-ContMix	9.3e-01, 2.8e-04, NA	2.9e-01, 1.1e-02, NA	1.2e-02, -1.7e-01, NA	1.5e-01, 2.1e-02, NA	4.6e-01, 2.7e-02, NA	6.3e-02, 1.4e-01, NA	5.2e-01, -1.5e-02, NA	6.4e-01, -5.1e-02, NA	1.7e-01, 6.6e-02, NA
MR-Lasso	6.0e-01, -5.3e-03, 1.0e-02	3.3e-01, 7.8e-03, 8.1e-03	7.9e-01, -1.1e-02, 4.0e-02	5.7e-01, -7.7e-03, 1.4e-02	7.6e-01, 8.4e-03, 2.7e-02	6.3e-01, 2.5e-02, 5.2e-02	7.6e-01, -1.7e-03, 5.7e-03	8.9e-01, 1.3e-02, 9.8e-02	7.2e-01, 1.6e-02, 4.4e-02
MR-PRESSO	7.9e-01, 3.2e-03, 1.2e-02	1.5e-01, 9.8e-03, 6.6e-03	7.9e-01, -1.1e-02, 4.0e-02	9.6e-01, -7.5e-04, 1.6e-02	3.4e-01, 2.8e-02, 3.0e-02	9.3e-01, 4.8e-03, 5.3e-02	7.2e-01, -1.7e-03, 4.6e-03	8.7e-01, 1.3e-02, 7.5e-02	7.3e-01, 1.6e-02, 4.4e-02
MR-IVW	2.1e-01, 2.1e-02, 1.7e-02	2.2e-01, 9.8e-03, 8.0e-03	7.6e-01, 1.4e-02, 4.5e-02	9.6e-01, -7.5e-04, 1.6e-02	3.4e-01, 2.8e-02, 3.0e-02	9.3e-01, 4.8e-03, 5.3e-02	7.6e-01, -1.7e-03, 5.7e-03	8.9e-01, 1.3e-02, 9.8e-02	7.2e-01, 1.6e-02, 4.4e-02
MR-Egger	3.8e-01, -6.3e-02, 7.3e-02	7.7e-01, -1.1e-02, 3.7e-02	8.9e-01, -2.6e-02, 2.0e-01	6.6e-01, 3.1e-02, 7.1e-02	8.9e-02, 2.3e-01, 1.4e-01	8.7e-01, 4.0e-02, 2.4e-01	9.7e-02, 5.3e-02, 3.2e-02	6.6e-01, -3.3e-01, 7.6e-01	2.0e-01, 3.2e-01, 2.5e-01
MR-Weighted-Median	7.1e-01, -4.5e-03, 1.2e-02	6.6e-01, 4.9e-03, 1.1e-02	8.3e-01, -1.2e-02, 5.3e-02	6.9e-01, 7.5e-03, 1.9e-02	1.0e+00, 0.0e+00, 4.0e-02	1.0e+00, 0.0e+00, 6.9e-02	9.8e-01, -2.3e-04, 7.6e-03	8.9e-01, -1.7e-02, 1.2e-01	5.9e-01, 2.7e-02, 5.0e-02
MR-Weighted-Mode	6.4e-01, -7.4e-03, 1.6e-02	9.0e-01, 2.3e-03, 1.9e-02	4.9e-02, -2.0e-01, 1.0e-01	5.6e-01, 1.8e-02, 3.2e-02	5.4e-01, 5.2e-02, 8.4e-02	9.2e-01, -1.3e-02, 1.4e-01	4.2e-01, 9.6e-03, 1.2e-02	8.0e-01, -4.4e-02, 1.8e-01	5.5e-01, 4.7e-02, 7.8e-02
MR-RAPS1	2.8e-01, 1.8e-02, 1.7e-02	2.2e-01, 9.9e-03, 8.2e-03	7.2e-01, 1.6e-02, 4.5e-02	9.3e-01, -1.4e-03, 1.6e-02	2.8e-01, 3.3e-02, 3.1e-02	8.9e-01, 7.3e-03, 5.3e-02	7.6e-01, -1.8e-03, 5.8e-03	8.9e-01, 1.3e-02, 9.9e-02	6.6e-01, 1.7e-02, 4.0e-02
MR-RAPS2	6.9e-01, 5.9e-03, 1.5e-02	2.6e-01, 9.4e-03, 8.4e-03	9.7e-01, -1.9e-03, 4.5e-02	9.4e-01, -1.3e-03, 1.7e-02	3.9e-01, 2.6e-02, 3.1e-02	8.0e-01, 1.5e-02, 5.8e-02	7.5e-01, -1.9e-03, 6.0e-03	9.6e-01, 4.9e-03, 1.0e-01	6.1e-01, 2.2e-02, 4.4e-02
MR-RAPS3	2.7e-03, 2.4e-02, 8.1e-03	2.2e-01, 9.9e-03, 8.2e-03	6.9e-01, 1.4e-02, 3.5e-02	9.5e-01, -7.9e-04, 1.3e-02	2.6e-01, 2.9e-02, 2.6e-02	9.1e-01, 5.0e-03, 4.5e-02	7.6e-01, -1.8e-03, 5.8e-03	8.9e-01, 1.3e-02, 9.9e-02	6.7e-01, 1.6e-02, 3.8e-02
MR-RAPS4	3.4e-01, -7.1e-03, 7.5e-03	2.6e-01, 9.4e-03, 8.4e-03	6.7e-01, -1.6e-02, 3.6e-02	9.6e-01, -6.7e-04, 1.3e-02	3.3e-01, 2.6e-02, 2.7e-02	6.8e-01, 1.9e-02, 4.6e-02	7.5e-01, -1.9e-03, 6.0e-03	9.6e-01, 4.9e-03, 1.0e-01	6.1e-01, 2.0e-02, 3.9e-02

Table S18: Secondary real data analysis, set 7.

Exp/Out Method	T2D/ESmk (10)	T2D/FP (10)	T2D/FSmk (10)	T2D/Height (10)	T2D/HOMA (10)	T2D/IHC (10)	T2D/LDL (10)	T2D/RA (10)	T2D/SCZ (8)
cML-MA-BIC-Max	6.4e-01, 1.4e-02, 3.0e-02	3.8e-01, 1.8e-02, 2.1e-02	7.5e-01, 1.3e-02, 4.1e-02	3.7e-01, -7.8e-03, 8.7e-03	6.2e-06, -5.0e-02, 1.1e-02	4.4e-01, -2.9e-02, 3.7e-02	5.8e-01, 5.4e-03, 9.8e-03	2.2e-01, -4.1e-02, 3.4e-02	5.5e-02, -5.9e-02, 3.1e-02
cML-BIC-Max	6.6e-01, 1.3e-02, 3.0e-02	2.7e-01, 2.2e-02, 1.9e-02	7.5e-01, 1.3e-02, 4.1e-02	2.6e-01, -9.1e-03, 8.1e-03	2.7e-07, -4.9e-02, 9.5e-03	4.1e-01, -3.0e-02, 3.6e-02	5.4e-01, 5.9e-03, 9.6e-03	2.4e-01, -3.9e-02, 3.3e-02	5.6e-02, -5.8e-02, 3.0e-02
cML-MA-BIC	6.4e-01, 1.4e-02, 3.0e-02	4.7e-01, 1.6e-02, 2.2e-02	7.5e-01, 1.3e-02, 4.1e-02	4.6e-01, -6.7e-03, 9.1e-03	3.5e-06, -5.1e-02, 1.1e-02	4.8e-01, -2.7e-02, 3.8e-02	5.9e-01, 5.3e-03, 9.9e-03	2.2e-01, -4.1e-02, 3.4e-02	5.5e-02, -5.9e-02, 3.1e-02
cML-BIC	6.6e-01, 1.3e-02, 3.0e-02	2.7e-01, 2.2e-02, 1.9e-02	7.5e-01, 1.3e-02, 4.1e-02	2.6e-01, -9.1e-03, 8.1e-03	2.7e-07, -4.9e-02, 9.5e-03	4.1e-01, -3.0e-02, 3.6e-02	5.4e-01, 5.9e-03, 9.6e-03	2.4e-01, -3.9e-02, 3.3e-02	5.6e-02, -5.8e-02, 3.0e-02
cML-MA-BIC-DP-Max	5.8e-01, 1.7e-02, 3.1e-02	4.2e-01, 2.4e-02, 3.1e-02	6.9e-01, 1.7e-02, 4.1e-02	5.7e-01, -7.1e-03, 1.3e-02	8.7e-03, -4.8e-02, 1.8e-02	5.2e-01, -2.5e-02, 3.8e-02	5.8e-01, 5.8e-03, 1.1e-02	3.1e-01, -3.8e-02, 3.7e-02	8.0e-02, -5.8e-02, 3.3e-02
cML-BIC-DP-Max	5.9e-01, 1.6e-02, 3.0e-02	4.3e-01, 2.5e-02, 3.1e-02	6.8e-01, 1.7e-02, 4.0e-02	6.5e-01, -6.3e-03, 1.4e-02	9.9e-03, -4.8e-02, 1.9e-02	4.7e-01, -2.6e-02, 3.6e-02	4.8e-01, 6.9e-03, 9.7e-03	3.0e-01, -3.6e-02, 3.4e-02	6.0e-02, -5.8e-02, 3.1e-02
cML-MA-BIC-DP	5.8e-01, 1.7e-02, 3.2e-02	4.6e-01, 2.4e-02, 3.3e-02	6.9e-01, 1.6e-02, 4.1e-02	6.4e-01, -6.5e-03, 1.4e-02	8.5e-03, -4.8e-02, 1.8e-02	5.7e-01, -2.3e-02, 4.1e-02	6.0e-01, 5.7e-03, 1.1e-02	3.1e-01, -3.8e-02, 3.7e-02	8.1e-02, -5.8e-02, 3.3e-02
cML-BIC-DP	5.9e-01, 1.6e-02, 3.0e-02	4.3e-01, 2.5e-02, 3.1e-02	6.8e-01, 1.7e-02, 4.0e-02	6.5e-01, -6.3e-03, 1.4e-02	9.9e-03, -4.8e-02, 1.9e-02	4.7e-01, -2.6e-02, 3.6e-02	4.8e-01, 6.9e-03, 9.7e-03	3.0e-01, -3.6e-02, 3.4e-02	6.0e-02, -5.8e-02, 3.1e-02
MR-Mix	7.6e-01, 1.5e-02, 5.0e-02	8.7e-01, 6.0e-02, 3.6e-01	8.0e-01, 1.5e-02, 5.8e-02	6.0e-01, -3.0e-02, 5.7e-02	8.8e-03, -3.5e-01, 1.3e-01	6.3e-01, -1.0e-01, 2.1e-01	8.3e-01, 2.5e-02, 1.2e-01	6.4e-01, -1.8e-01, 3.9e-01	4.7e-04, -2.5e-01, 7.1e-02
MR-ContMix	1.5e-01, 5.8e-02, NA	2.1e-01, 3.8e-02, NA	9.0e-01, 1.5e-02, NA	1.2e-01, 2.2e-02, NA	9.1e-04, -5.2e-02, NA	1.0e+00, -4.9e-03, NA	7.8e-01, -2.5e-03, NA	4.3e-01, -9.7e-02, NA	4.3e-02, -1.3e-01, NA
MR-Lasso	6.6e-01, 1.3e-02, 3.0e-02	5.0e-01, 2.0e-02, 3.0e-02	7.5e-01, 1.3e-02, 4.1e-02	3.3e-01, 1.1e-02, 1.1e-02	3.4e-02, -3.6e-02, 1.1e-02	4.3e-01, -3.0e-02, 3.8e-02	7.8e-01, -2.9e-03, 1.0e-02	3.7e-01, -3.8e-02, 4.2e-02	1.6e-01, -5.6e-02, 4.0e-02
MR-PRESSO	6.6e-01, 1.3e-02, 2.9e-02	2.0e-01, 3.8e-02, 2.7e-02	6.3e-01, 1.3e-02, 2.6e-02	5.0e-01, 9.3e-03, 1.3e-02	2.0e-03, -5.6e-02, 1.1e-02	4.5e-01, -3.0e-02, 3.8e-02	5.6e-01, 5.7e-03, 9.5e-03	3.9e-01, -3.8e-02, 4.2e-02	2.1e-01, -5.6e-02, 4.0e-02
MR-IVW	6.6e-01, 1.3e-02, 3.0e-02	2.9e-01, 4.8e-02, 4.5e-02	7.5e-01, 1.3e-02, 4.1e-02	5.7e-01, 1.8e-02, 3.1e-02	2.4e-02, -5.0e-02, 2.2e-02	4.3e-01, -3.0e-02, 3.8e-02	5.5e-01, 5.7e-03, 9.5e-03	3.7e-01, -3.8e-02, 4.2e-02	1.6e-01, -5.6e-02, 4.0e-02
MR-Egger	4.1e-01, -1.3e-01, 1.6e-01	5.0e-01, 1.8e-01, 2.6e-01	6.2e-01, 1.1e-01, 2.2e-01	3.4e-01, -1.6e-01, 1.7e-01	9.9e-01, -1.5e-03, 1.3e-01	2.5e-01, -2.4e-01, 2.1e-01	1.1e-01, 8.3e-02, 5.1e-02	5.0e-01, 1.6e-01, 2.4e-01	3.5e-01, -2.3e-01, 2.5e-01
MR-Weighted-Median	8.2e-01, 9.5e-03, 4.2e-02	2.2e-01, 3.2e-02, 2.6e-02	7.5e-01, 1.7e-02, 5.3e-02	7.4e-01, -4.2e-03, 1.3e-02	1.3e-03, -4.1e-02, 1.3e-02	7.5e-01, -1.5e-02, 4.8e-02	5.2e-01, -8.3e-03, 1.3e-02	9.6e-01, -2.4e-03, 4.8e-02	4.8e-02, -8.5e-02, 4.3e-02
MR-Weighted-Mode	2.7e-01, 9.3e-02, 8.5e-02	3.5e-01, 3.1e-02, 3.4e-02	9.2e-01, 7.0e-03, 7.0e-02	6.1e-01, 1.0e-02, 2.0e-02	4.7e-03, -4.4e-02, 1.6e-02	7.0e-01, -3.0e-02, 7.6e-02	4.4e-01, -1.6e-02, 2.1e-02	9.7e-01, -2.5e-03, 7.7e-02	1.3e-01, -1.1e-01, 7.1e-02
MR-RAPS1	6.6e-01, 1.3e-02, 3.0e-02	1.8e-01, 6.5e-02, 4.9e-02	7.5e-01, 1.3e-02, 4.1e-02	7.0e-01, 1.1e-02, 2.8e-02	2.4e-02, -4.8e-02, 2.1e-02	4.1e-01, -3.0e-02, 3.7e-02	5.5e-01, 5.9e-03, 9.8e-03	3.1e-01, -3.7e-02, 3.6e-02	1.1e-01, -5.9e-02, 3.7e-02
MR-RAPS2	5.4e-01, 1.9e-02, 3.1e-02	2.5e-01, 2.3e-02, 2.0e-02	7.8e-01, 1.2e-02, 4.2e-02	4.9e-01, -5.5e-03, 8.0e-03	3.2e-02, -4.7e-02, 2.2e-02	5.5e-01, -2.3e-02, 3.8e-02	8.1e-01, 2.4e-03, 1.0e-02	2.6e-01, -4.3e-02, 3.8e-02	1.4e-01, -6.2e-02, 4.1e-02
MR-RAPS3	6.6e-01, 1.3e-02, 3.0e-02	9.8e-03, 5.3e-02, 2.1e-02	7.5e-01, 1.3e-02, 4.1e-02	1.8e-02, 2.5e-02, 1.0e-02	1.0e-08, -5.7e-02, 1.0e-02	4.1e-01, -3.0e-02, 3.7e-02	5.5e-01, 5.9e-03, 9.8e-03	2.5e-01, -3.9e-02, 3.4e-02	6.1e-02, -5.8e-02, 3.1e-02
MR-RAPS4	5.4e-01, 1.9e-02, 3.1e-02	2.5e-01, 2.3e-02, 2.0e-02	7.8e-01, 1.2e-02, 4.2e-02	9.2e-01, 1.7e-01, 1.2e-02	5.9e-08, -4.9e-02, 9.1e-03	5.5e-01, -2.3e-02, 3.8e-02	8.1e-01, 2.4e-03, 1.0e-02	2.0e-01, -4.5e-02, 3.5e-02	4.9e-02, -6.3e-02, 3.2e-02

Table S19: Goodness-of-fit tests for secondary real data analysis, set 1.

Exp/Out Method	FP/ASmk (6)	FP/ANRX (6)	FP/CIQ (4)	FP/ESmk (6)	FP/FSmk (6)	FP/Height (6)	FP/HOMA (6)	FP/IHC (6)	FP/LDL (5)
GOF1-Max	4.5e-01	7.5e-01	7.2e-01	4.6e-01	4.4e-01	3.4e-02	2.3e-130	4.1e-01	1.1e-01
GOF2-Max	4.3e-01	7.5e-01	7.2e-01	4.4e-01	4.4e-01	1.5e-02	1.0e-20	4.0e-01	9.7e-02
GOF1	4.5e-01	7.5e-01	7.2e-01	4.6e-01	4.4e-01	3.4e-02	2.3e-130	4.1e-01	1.0e-04
GOF2	4.3e-01	7.5e-01	7.2e-01	4.4e-01	4.4e-01	1.5e-02	1.0e-20	4.0e-01	1.0e-04

Table S20: Goodness-of-fit tests for secondary real data analysis, set 2.

Exp/Out Method	FP/RA (6)	FP/SCZ (6)	FP/T2D (6)	Height/ASmk (310)	Height/ESmk (310)	Height/FP (307)	Height/FSmk (310)	Height/HOMA (303)	Height/RA (306)
GOF1-Max	4.3e-01	7.2e-01	1.6e-28	2.5e-01	1.4e-01	2.0e-01	2.7e-01	3.6e-01	1.7e-03
GOF2-Max	4.4e-01	7.2e-01	9.4e-21	2.0e-01	1.8e-01	2.6e-01	2.2e-01	3.6e-01	1.8e-03
GOF1	4.3e-01	7.2e-01	1.6e-28	2.5e-01	1.4e-01	2.4e-01	6.6e-02	1.9e-01	1.5e-02
GOF2	4.4e-01	7.2e-01	9.4e-21	2.0e-01	1.8e-01	2.4e-01	3.9e-02	2.0e-01	1.2e-02

Table S21: Goodness-of-fit tests for secondary real data analysis, set 3.

Method \ Exp/Out	Height/SCZ (288)	Height/T2D (307)	HOMA/ASmk (2)	HOMA/ESmk (2)	HOMA/FP (2)	HOMA/FSmk (2)	HOMA/Height (2)	HOMA/IHC (2)	HOMA/LDL (2)
GOF1-Max	3.4e-05	3.7e-04	1.4e-01	1.5e-01	1.2e-01	1.0e-01	1.1e-01	8.7e-02	7.1e-02
GOF2-Max	5.2e-05	1.9e-03	1.4e-01	1.5e-01	1.2e-01	1.0e-01	1.1e-01	8.9e-02	7.4e-02
GOF1	1.4e-04	2.9e-04	1.4e-01	1.5e-01	1.2e-01	1.0e-01	1.1e-01	8.7e-02	7.1e-02
GOF2	1.0e-04	5.3e-05	1.4e-01	1.5e-01	1.2e-01	1.0e-01	1.1e-01	8.9e-02	7.4e-02

Table S22: Goodness-of-fit tests for secondary real data analysis, set 4.

Method \ Exp/Out	HOMA/RA (2)	HOMA/SCZ (2)	HOMA/T2D (2)	LDL/ASmk (69)	LDL/ANRX (52)	LDL/ESmk (69)	LDL/FP (68)	LDL/FSmk (69)	LDL/HOMA (68)
GOF1-Max	1.4e-01	1.2e-01	1.3e-01	5.5e-01	4.7e-01	5.6e-01	1.2e-01	5.8e-01	3.3e-02
GOF2-Max	1.4e-01	1.2e-01	1.2e-01	5.6e-01	4.7e-01	5.7e-01	1.2e-01	5.9e-01	3.7e-02
GOF1	1.4e-01	1.2e-01	1.3e-01	5.5e-01	4.7e-01	5.4e-01	1.2e-01	5.8e-01	3.3e-02
GOF2	1.4e-01	1.2e-01	1.2e-01	5.6e-01	4.7e-01	5.0e-01	1.2e-01	5.9e-01	3.7e-02

Table S23: Goodness-of-fit tests for secondary real data analysis, set 5.

Method \ Exp/Out	LDL/IHC (67)	LDL/RA (71)	LDL/SCZ (69)	LDL/T2D (67)	RA/SCZ (47)	SCZ/ASmk (35)	SCZ/CIQ (20)	SCZ/FP (34)	SCZ/FSmk (35)
GOF1-Max	1.7e-01	1.9e-01	3.1e-01	8.8e-01	2.9e-03	3.7e-01	9.4e-01	3.8e-03	1.9e-01
GOF2-Max	2.0e-01	1.7e-01	3.2e-01	8.9e-01	3.0e-03	3.8e-01	9.4e-01	3.7e-03	2.0e-01
GOF1	1.7e-01	1.9e-01	3.1e-01	6.8e-03	2.9e-03	3.7e-01	9.4e-01	3.8e-03	1.9e-01
GOF2	2.0e-01	1.7e-01	3.2e-01	1.4e-02	3.0e-03	3.8e-01	9.4e-01	3.7e-03	2.0e-01

Table S24: Goodness-of-fit tests for secondary real data analysis, set 6.

Method \ Exp/Out	SCZ/Height (35)	SCZ/HOMA (35)	SCZ/IHC (35)	SCZ/LDL (36)	SCZ/RA (69)	SCZ/T2D (35)	T2D/ASmk (10)	T2D/ANRX (6)	T2D/CIQ (7)
GOF1-Max	4.8e-08	4.4e-01	4.8e-05	3.5e-02	7.1e-01	2.2e-01	8.7e-01	3.4e-02	1.4e-01
GOF2-Max	3.1e-11	4.6e-01	4.9e-05	4.7e-02	7.5e-01	2.2e-01	8.6e-01	4.4e-02	1.7e-01
GOF1	1.6e-07	4.4e-01	4.8e-05	3.5e-02	7.1e-01	2.2e-01	8.7e-01	3.4e-02	1.4e-01
GOF2	1.1e-13	4.6e-01	4.9e-05	4.7e-02	7.5e-01	2.2e-01	8.6e-01	4.4e-02	1.7e-01

Table S25: Goodness-of-fit tests for secondary real data analysis, set 7.

Method \ Exp/Out	T2D/ESmk (10)	T2D/FP (10)	T2D/FSmk (10)	T2D/Height (10)	T2D/HOMA (10)	T2D/IHC (10)	T2D/LDL (10)	T2D/RA (10)	T2D/SCZ (8)
GOF1-Max	1.0e+00	1.8e-03	9.1e-01	5.2e-01	7.2e-11	9.6e-01	9.4e-01	8.1e-01	8.7e-01
GOF2-Max	1.0e+00	6.0e-04	9.0e-01	5.2e-01	2.0e-12	9.6e-01	9.4e-01	8.0e-01	8.6e-01
GOF1	1.0e+00	1.8e-03	9.1e-01	5.2e-01	7.2e-11	9.6e-01	9.4e-01	8.1e-01	8.7e-01
GOF2	1.0e+00	6.0e-04	9.0e-01	5.2e-01	2.0e-12	9.6e-01	9.4e-01	8.0e-01	8.6e-01

Table S26: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean(SE( $\hat{\theta}$ )) when  $m = 10$ , ideal case,  $q = 0$ ,  $N = 50000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	0.817, -0.0867, 0.0292, 0.03	0.261, -0.0394, 0.0262, 0.0298	0.086, -0.0227, 0.0243, 0.0295	0.023, -0.0078, 0.0228, 0.0294	0.014, -0.0007, 0.0228, 0.0295	0.023, 0.0067, 0.0231, 0.0297	0.084, 0.0215, 0.0253, 0.0304	0.233, 0.0382, 0.0279, 0.0312	0.728, 0.0847, 0.0319, 0.0331
cML-MA-AIC-Profile	0.810, -0.0869, 0.0292, 0.0302	0.254, -0.0395, 0.0262, 0.0299	0.083, -0.0228, 0.0244, 0.0297	0.023, -0.0078, 0.0228, 0.0296	0.014, -0.0007, 0.0228, 0.0297	0.023, 0.0067, 0.0232, 0.0299	0.084, 0.0215, 0.0253, 0.0306	0.231, 0.0382, 0.0280, 0.0314	0.728, 0.0849, 0.0319, 0.0333
cML-AIC	0.904, -0.0932, 0.0321, 0.0246	0.478, -0.0446, 0.0307, 0.025	0.239, -0.0263, 0.0297, 0.0253	0.085, -0.0094, 0.0288, 0.0255	0.081, -0.0009, 0.0290, 0.0257	0.084, 0.0079, 0.0292, 0.0258	0.208, 0.0251, 0.0310, 0.0261	0.413, 0.0436, 0.0323, 0.0264	0.872, 0.0922, 0.0343, 0.0271
cML-AIC-Profile	0.906, -0.0935, 0.0321, 0.0248	0.474, -0.0447, 0.0307, 0.0252	0.234, -0.0263, 0.0298, 0.0255	0.081, -0.0094, 0.0288, 0.0257	0.080, -0.0009, 0.0290, 0.0258	0.083, 0.0079, 0.0292, 0.026	0.203, 0.0251, 0.0310, 0.0263	0.407, 0.0436, 0.0324, 0.0265	0.871, 0.0923, 0.0343, 0.0273
cML-MA-BIC	0.991, -0.1004, 0.0229, 0.023	0.589, -0.0504, 0.0232, 0.0234	0.252, -0.0304, 0.0234, 0.0236	0.062, -0.0105, 0.0235, 0.0239	0.050, -0.0005, 0.0236, 0.024	0.068, 0.0095, 0.0238, 0.0241	0.222, 0.0294, 0.0240, 0.0244	0.531, 0.0493, 0.0243, 0.0246	0.976, 0.0993, 0.0251, 0.0254
cML-MA-BIC-Profile	0.991, -0.1004, 0.0229, 0.0231	0.583, -0.0504, 0.0232, 0.0235	0.248, -0.0304, 0.0234, 0.0237	0.061, -0.0105, 0.0235, 0.0239	0.049, -0.0005, 0.0236, 0.0241	0.068, 0.0095, 0.0238, 0.0242	0.219, 0.0294, 0.0241, 0.0244	0.525, 0.0493, 0.0243, 0.0247	0.976, 0.0993, 0.0251, 0.0255
cML-BIC	0.991, -0.1005, 0.0229, 0.0227	0.608, -0.0505, 0.0233, 0.0231	0.262, -0.0305, 0.0235, 0.0233	0.073, -0.0105, 0.0237, 0.0235	0.054, -0.0005, 0.0238, 0.0236	0.072, 0.0095, 0.0239, 0.0238	0.235, 0.0295, 0.0242, 0.024	0.546, 0.0495, 0.0245, 0.0243	0.979, 0.0995, 0.0251, 0.025
cML-BIC-Profile	0.991, -0.1005, 0.0229, 0.0228	0.607, -0.0505, 0.0233, 0.0232	0.260, -0.0305, 0.0235, 0.0234	0.069, -0.0105, 0.0237, 0.0236	0.053, -0.0005, 0.0238, 0.0237	0.072, 0.0095, 0.0239, 0.0238	0.234, 0.0295, 0.0242, 0.0241	0.543, 0.0495, 0.0245, 0.0244	0.979, 0.0995, 0.0251, 0.0251
MR-Mix	0.728, -0.1007, 0.0461, 0.1046	0.405, -0.0488, 0.0398, 0.0826	0.191, -0.0291, 0.0381, 0.0675	0.063, -0.0101, 0.0376, 0.0854	0.056, -0.0004, 0.0372, 0.0551	0.070, 0.0089, 0.0370, 0.0592	0.165, 0.0274, 0.0376, 0.0715	0.358, 0.0456, 0.0392, 0.0901	0.710, 0.0888, 0.0448, 0.083
MR-ContMix	0.938, -0.1216, 0.0323, NA	0.468, -0.0689, 0.0391, NA	0.210, -0.0434, 0.0419, NA	0.067, -0.0151, 0.0455, NA	0.045, -0.0016, 0.0460, NA	0.064, 0.0126, 0.0458, NA	0.181, 0.0419, 0.0432, NA	0.398, 0.0674, 0.0406, NA	0.900, 0.1221, 0.0349, NA
MR-Lasso	0.975, -0.0998, 0.0246, 0.0241	0.544, -0.0504, 0.0251, 0.0246	0.244, -0.0305, 0.0254, 0.0248	0.078, -0.0105, 0.0260, 0.0251	0.056, -0.0006, 0.0257, 0.0252	0.078, 0.0095, 0.0260, 0.0253	0.222, 0.0296, 0.0261, 0.0256	0.488, 0.0487, 0.0261, 0.0258	0.957, 0.0991, 0.0267, 0.0266
MR-PRESSO	0.969, -0.1001, 0.0230, 0.0217	0.511, -0.0503, 0.0234, 0.0221	0.225, -0.0304, 0.0236, 0.0223	0.075, -0.0105, 0.0237, 0.0225	0.052, -0.0005, 0.0239, 0.0226	0.067, 0.0094, 0.0240, 0.0227	0.200, 0.0292, 0.0243, 0.023	0.457, 0.0491, 0.0245, 0.0232	0.936, 0.0989, 0.0253, 0.0239
MR-IVW	0.983, -0.1001, 0.0226, 0.0244	0.531, -0.0503, 0.0229, 0.0249	0.225, -0.0304, 0.0231, 0.0251	0.047, -0.0105, 0.0233, 0.0253	0.039, -0.0005, 0.0234, 0.0255	0.056, 0.0094, 0.0235, 0.0256	0.195, 0.0293, 0.0238, 0.0258	0.488, 0.0492, 0.0240, 0.0261	0.966, 0.0990, 0.0247, 0.0269
MR-IVW-Oracle	0.983, -0.1001, 0.0226, 0.0244	0.531, -0.0503, 0.0229, 0.0249	0.225, -0.0304, 0.0231, 0.0251	0.047, -0.0105, 0.0233, 0.0253	0.039, -0.0005, 0.0234, 0.0255	0.056, 0.0094, 0.0235, 0.0256	0.195, 0.0293, 0.0238, 0.0258	0.488, 0.0492, 0.0240, 0.0261	0.966, 0.0990, 0.0247, 0.0269
MR-Egger	0.106, -0.0841, 0.1285, 0.1343	0.058, -0.0403, 0.1307, 0.1372	0.047, -0.0228, 0.1317, 0.1385	0.053, -0.0052, 0.1328, 0.1398	0.042, 0.0035, 0.1335, 0.1405	0.043, 0.0123, 0.1341, 0.1413	0.043, 0.0299, 0.1354, 0.1427	0.049, 0.0474, 0.1368, 0.1443	0.082, 0.0912, 0.1407, 0.1484
MR-Weighted-Median	0.924, -0.0992, 0.0265, 0.0304	0.374, -0.0502, 0.0270, 0.0309	0.127, -0.0307, 0.0273, 0.0312	0.029, -0.0110, 0.0275, 0.0315	0.025, -0.0012, 0.0276, 0.0316	0.027, 0.0086, 0.0277, 0.0318	0.114, 0.0282, 0.0280, 0.0321	0.298, 0.0478, 0.0284, 0.0324	0.851, 0.0969, 0.0293, 0.0334
MR-Weighted-Mode	0.640, -0.0992, 0.0355, 0.0448	0.142, -0.0505, 0.0365, 0.0457	0.050, -0.0312, 0.0369, 0.046	0.013, -0.0115, 0.0373, 0.0465	0.007, -0.0015, 0.0376, 0.0467	0.008, 0.0082, 0.0377, 0.0469	0.044, 0.0279, 0.0379, 0.0475	0.122, 0.0475, 0.0381, 0.048	0.519, 0.0964, 0.0392, 0.0494
MR-RAPS1	0.988, -0.1005, 0.0226, 0.024	0.557, -0.0505, 0.0230, 0.0244	0.233, -0.0305, 0.0232, 0.0247	0.053, -0.0105, 0.0234, 0.0249	0.042, -0.0005, 0.0235, 0.025	0.059, 0.0094, 0.0236, 0.0251	0.201, 0.0294, 0.0238, 0.0254	0.498, 0.0494, 0.0241, 0.0257	0.966, 0.0994, 0.0248, 0.0265
MR-RAPS2	0.982, 0.2085, 4.1153, 0.0831	0.603, 0.3626, 4.1546, 0.0897	0.306, -0.0550, 3.7213, 0.076	0.141, 0.3252, 3.3704, 0.0641	0.128, 0.3278, 3.3292, 0.0602	0.143, 0.1586, 2.9538, 0.0586	0.283, 0.2962, 4.1884, 0.0748	0.554, 0.0538, 4.9955, 0.0979	0.963, 0.2696, 4.5346, 0.1002
MR-RAPS3	0.991, -0.1006, 0.0227, 0.0227	0.607, -0.0506, 0.0230, 0.0232	0.261, -0.0306, 0.0232, 0.0234	0.070, -0.0105, 0.0234, 0.0236	0.050, -0.0005, 0.0235, 0.0237	0.068, 0.0095, 0.0236, 0.0238	0.232, 0.0295, 0.0239, 0.0241	0.545, 0.0495, 0.0241, 0.0243	0.981, 0.0995, 0.0248, 0.0251
MR-RAPS4	0.987, -0.1006, 0.0232, 0.0233	0.587, -0.0506, 0.0236, 0.0238	0.250, -0.0305, 0.0238, 0.024	0.058, -0.0105, 0.0240, 0.0242	0.048, -0.0005, 0.0241, 0.0243	0.067, 0.0095, 0.0242, 0.0244	0.217, 0.0295, 0.0245, 0.0247	0.513, 0.0495, 0.0247, 0.025	0.975, 0.0995, 0.0255, 0.0257

Table S27: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean( $SE(\hat{\theta})$ ) when  $m = 10$ , the ideal case of  $q = 0$ , and  $N = 100000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	0.963, -0.0897, 0.0207, 0.0213	0.491, -0.0404, 0.0200, 0.0213	0.173, -0.0225, 0.0182, 0.021	0.023, -0.0065, 0.0164, 0.0207	0.012, 0.0004, 0.0160, 0.0208	0.032, 0.0076, 0.0166, 0.0209	0.185, 0.0233, 0.0187, 0.0216	0.469, 0.0413, 0.0209, 0.0223	0.937, 0.0898, 0.0232, 0.0235
cML-MA-AIC-Profile	0.962, -0.0899, 0.0208, 0.0213	0.490, -0.0405, 0.0200, 0.0213	0.170, -0.0225, 0.0182, 0.021	0.023, -0.0065, 0.0164, 0.0208	0.012, 0.0004, 0.0161, 0.0208	0.032, 0.0076, 0.0166, 0.021	0.184, 0.0234, 0.0187, 0.0217	0.469, 0.0413, 0.0210, 0.0224	0.936, 0.0899, 0.0232, 0.0235
cML-AIC	0.986, -0.0947, 0.0221, 0.0173	0.688, -0.0446, 0.0224, 0.0177	0.349, -0.0255, 0.0215, 0.0179	0.103, -0.0071, 0.0208, 0.0181	0.079, 0.0007, 0.0206, 0.0182	0.120, 0.0089, 0.0210, 0.0183	0.356, 0.0263, 0.0222, 0.0185	0.664, 0.0455, 0.0237, 0.0187	0.976, 0.0950, 0.0252, 0.0192
cML-AIC-Profile	0.986, -0.0948, 0.0222, 0.0174	0.684, -0.0446, 0.0224, 0.0178	0.350, -0.0255, 0.0215, 0.0179	0.102, -0.0071, 0.0208, 0.0182	0.079, 0.0007, 0.0206, 0.0183	0.118, 0.0089, 0.0210, 0.0183	0.355, 0.0264, 0.0222, 0.0185	0.664, 0.0456, 0.0237, 0.0187	0.975, 0.0951, 0.0252, 0.0193
cML-MA-BIC	1.000, -0.0997, 0.0158, 0.0161	0.857, -0.0496, 0.0161, 0.0165	0.425, -0.0296, 0.0162, 0.0166	0.074, -0.0096, 0.0163, 0.0168	0.047, 0.0004, 0.0164, 0.0168	0.096, 0.0104, 0.0165, 0.0169	0.429, 0.0304, 0.0167, 0.0171	0.834, 0.0504, 0.0169, 0.0173	1.000, 1.0005, 0.0174, 0.0178
cML-MA-BIC-Profile	1.000, -0.0997, 0.0158, 0.0162	0.856, -0.0496, 0.0161, 0.0165	0.422, -0.0296, 0.0162, 0.0166	0.074, -0.0096, 0.0163, 0.0168	0.047, 0.0004, 0.0164, 0.0169	0.095, 0.0104, 0.0165, 0.017	0.427, 0.0304, 0.0167, 0.0171	0.834, 0.0504, 0.0169, 0.0173	1.000, 1.0005, 0.0174, 0.0179
cML-BIC	1.000, -0.0998, 0.0158, 0.016	0.863, -0.0497, 0.0161, 0.0163	0.436, -0.0297, 0.0162, 0.0164	0.077, -0.0097, 0.0164, 0.0166	0.052, 0.0004, 0.0165, 0.0167	0.098, 0.0104, 0.0166, 0.0167	0.444, 0.0304, 0.0168, 0.0169	0.843, 0.0504, 0.0169, 0.0171	1.000, 1.0005, 0.0175, 0.0176
cML-BIC-Profile	1.000, -0.0998, 0.0158, 0.016	0.863, -0.0497, 0.0161, 0.0163	0.436, -0.0297, 0.0162, 0.0165	0.077, -0.0097, 0.0164, 0.0166	0.052, 0.0004, 0.0165, 0.0167	0.096, 0.0104, 0.0166, 0.0168	0.444, 0.0304, 0.0168, 0.017	0.843, 0.0504, 0.0169, 0.0171	1.000, 1.0005, 0.0175, 0.0177
MR-Mix	0.784, -0.0965, 0.0400, 0.0397	0.562, -0.0466, 0.0298, 0.0788	0.268, -0.0271, 0.0277, 0.0689	0.071, -0.0086, 0.0267, 0.0939	0.062, 0.0007, 0.0266, 0.1207	0.096, 0.0101, 0.0268, 0.05	0.294, 0.0282, 0.0278, 0.0602	0.555, 0.0461, 0.0297, 0.1415	0.780, 0.0886, 0.0387, 0.0599
MR-ContMix	1.000, -0.1137, 0.0202, NA	0.703, -0.0644, 0.0248, NA	0.321, -0.0404, 0.0284, NA	0.070, -0.0138, 0.0314, NA	0.051, 0.0010, 0.0321, NA	0.093, 0.0152, 0.0319, NA	0.333, 0.0423, 0.0293, NA	0.680, 0.0658, 0.0261, NA	0.994, 1.163, 0.0217, NA
MR-Lasso	1.000, -0.0994, 0.0171, 0.017	0.795, -0.0493, 0.0171, 0.0174	0.394, -0.0296, 0.0175, 0.0176	0.080, -0.0093, 0.0179, 0.0178	0.050, 0.0005, 0.0176, 0.0178	0.092, 0.0103, 0.0178, 0.0179	0.403, 0.0303, 0.0179, 0.0181	0.783, 0.0505, 0.0183, 0.0183	1.000, 1.003, 0.0187, 0.0188
MR-PRESSO	1.000, -0.0996, 0.0160, 0.0154	0.781, -0.0496, 0.0162, 0.0157	0.374, -0.0296, 0.0164, 0.0159	0.077, -0.0096, 0.0165, 0.016	0.056, 0.0003, 0.0166, 0.0161	0.092, 0.0103, 0.0167, 0.0162	0.351, 0.0303, 0.0169, 0.0163	0.746, 0.0503, 0.0170, 0.0165	0.999, 1.0003, 0.0175, 0.017
MR-IVW	1.000, -0.0995, 0.0158, 0.0172	0.818, -0.0496, 0.0160, 0.0175	0.371, -0.0296, 0.0256, 0.0177	0.055, -0.0096, 0.0163, 0.0179	0.041, 0.0004, 0.0164, 0.0179	0.077, 0.0104, 0.0164, 0.018	0.382, 0.0304, 0.0166, 0.0182	0.795, 0.0504, 0.0168, 0.0184	1.000, 1.004, 0.0173, 0.019
MR-IVW-Oracle	1.000, -0.0995, 0.0158, 0.0172	0.818, -0.0496, 0.0160, 0.0175	0.371, -0.0296, 0.0256, 0.0177	0.055, -0.0096, 0.0163, 0.0179	0.041, 0.0004, 0.0164, 0.0179	0.077, 0.0104, 0.0164, 0.018	0.382, 0.0304, 0.0166, 0.0182	0.795, 0.0504, 0.0168, 0.0184	1.000, 1.004, 0.0173, 0.019
MR-Egger	0.161, -0.0938, 0.0886, 0.0965	0.079, -0.0469, 0.0900, 0.0986	0.050, -0.0282, 0.0907, 0.0995	0.035, -0.0094, 0.0914, 0.1005	0.032, 0.0000, 0.0918, 0.101	0.029, 0.0093, 0.0922, 0.1015	0.034, 0.0281, 0.0931, 0.1026	0.059, 0.0469, 0.0940, 0.1038	0.142, 0.0938, 0.0967, 0.1068
MR-Weighted-Median	0.999, -0.0991, 0.0187, 0.0214	0.627, -0.0495, 0.0191, 0.0218	0.246, -0.0297, 0.0192, 0.022	0.041, -0.0098, 0.0194, 0.0222	0.028, 0.0002, 0.0195, 0.0223	0.040, 0.0101, 0.0196, 0.0224	0.252, 0.0300, 0.0199, 0.0226	0.602, 0.0499, 0.0201, 0.0229	0.993, 0.0996, 0.0206, 0.0236
MR-Weighted-Mode	0.912, -0.0986, 0.0251, 0.0317	0.316, -0.0489, 0.0254, 0.0323	0.090, -0.0290, 0.0256, 0.0326	0.011, -0.0091, 0.0259, 0.0329	0.006, 0.0008, 0.0261, 0.0331	0.012, 0.0107, 0.0262, 0.0332	0.097, 0.0303, 0.0266, 0.0336	0.327, 0.0502, 0.0270, 0.034	0.854, 0.0997, 0.0280, 0.035
MR-RAPS1	1.000, -0.0998, 0.0158, 0.0169	0.834, -0.0497, 0.0161, 0.0172	0.392, -0.0297, 0.0162, 0.0173	0.061, -0.0096, 0.0163, 0.0175	0.041, 0.0004, 0.0164, 0.0176	0.082, 0.0104, 0.0165, 0.0177	0.403, 0.0304, 0.0166, 0.0178	0.816, 0.0505, 0.0168, 0.018	1.000, 1.006, 0.0173, 0.0186
MR-RAPS2	1.000, 0.1027, 1.0726, 0.0351	0.853, -0.0015, 2.4214, 0.0583	0.492, 0.1487, 2.5566, 0.0549	0.184, 0.1367, 2.4835, 0.049	0.131, 0.1945, 2.1665, 0.0422	0.176, 0.1989, 2.4643, 0.0461	0.470, 0.3043, 2.6780, 0.0576	0.829, 0.1506, 2.5923, 0.0593	0.999, 0.2744, 1.5985, 0.0441
MR-RAPS3	1.000, -0.0998, 0.0158, 0.016	0.864, -0.0497, 0.0161, 0.0163	0.435, -0.0296, 0.0162, 0.0164	0.075, -0.0096, 0.0163, 0.0166	0.050, 0.0004, 0.0164, 0.0167	0.096, 0.0104, 0.0165, 0.0168	0.445, 0.0305, 0.0166, 0.0169	0.844, 0.0505, 0.0168, 0.0171	1.000, 1.006, 0.0173, 0.0177
MR-RAPS4	1.000, -0.0997, 0.0161, 0.0164	0.845, -0.0496, 0.0164, 0.0167	0.425, -0.0296, 0.0165, 0.0169	0.070, -0.0095, 0.0166, 0.017	0.042, 0.0005, 0.0167, 0.0171	0.101, 0.0105, 0.0168, 0.0172	0.426, 0.0305, 0.0170, 0.0174	0.824, 0.0506, 0.0172, 0.0176	1.000, 0.1007, 0.0177, 0.0181



Table S28: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean(SE( $\hat{\theta}$ )) when  $m = 10$ , the ideal case of  $q = 0$ , and  $N = 200000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	0.999, -0.0942, 0.0147, 0.015	0.809, -0.0443, 0.0148, 0.0152	0.402, -0.0252, 0.0139, 0.015	0.053, -0.0082, 0.0120, 0.0146	0.020, -0.0008, 0.0116, 0.0147	0.045, 0.0065, 0.0119, 0.0148	0.338, 0.0232, 0.0138, 0.0154	0.739, 0.0420, 0.0152, 0.016	0.990, 0.0915, 0.0163, 0.0166
cML-MA-AIC-Profile	0.999, -0.0944, 0.0148, 0.0151	0.809, -0.0443, 0.0148, 0.0152	0.402, -0.0252, 0.0139, 0.015	0.053, -0.0082, 0.0120, 0.0147	0.020, -0.0008, 0.0116, 0.0147	0.045, 0.0065, 0.0119, 0.0148	0.337, 0.0232, 0.0138, 0.0155	0.739, 0.0420, 0.0152, 0.016	0.990, 0.0916, 0.0163, 0.0166
cML-AIC	1.000, -0.0978, 0.0156, 0.0123	0.925, -0.0478, 0.0159, 0.0125	0.600, -0.0282, 0.0156, 0.0126	0.146, -0.0095, 0.0146, 0.0127	0.071, -0.0009, 0.0145, 0.0128	0.127, 0.0076, 0.0147, 0.0129	0.536, 0.0260, 0.0156, 0.013	0.876, 0.0453, 0.0167, 0.0131	0.996, 0.0952, 0.0175, 0.0135
cML-AIC-Profile	1.000, -0.0980, 0.0156, 0.0123	0.925, -0.0478, 0.0159, 0.0125	0.601, -0.0282, 0.0156, 0.0126	0.147, -0.0096, 0.0146, 0.0128	0.071, -0.0009, 0.0145, 0.0128	0.126, 0.0076, 0.0147, 0.0129	0.535, 0.0260, 0.0156, 0.013	0.877, 0.0453, 0.0167, 0.0131	0.996, 0.0953, 0.0175, 0.0135
cML-MA-BIC	1.000, -0.1004, 0.0111, 0.0114	0.991, -0.0504, 0.0114, 0.0116	0.738, -0.0304, 0.0115, 0.0117	0.132, -0.0104, 0.0116, 0.0118	0.053, -0.0004, 0.0116, 0.0119	0.120, 0.0096, 0.0117, 0.0119	0.692, 0.0296, 0.0119, 0.0121	0.986, 0.0496, 0.0120, 0.0122	1.000, 0.0996, 0.0124, 0.0126
cML-MA-BIC-Profile	1.000, -0.1004, 0.0111, 0.0114	0.991, -0.0504, 0.0114, 0.0116	0.738, -0.0304, 0.0115, 0.0117	0.132, -0.0104, 0.0116, 0.0118	0.053, -0.0004, 0.0116, 0.0119	0.120, 0.0096, 0.0117, 0.0119	0.691, 0.0296, 0.0119, 0.0121	0.986, 0.0496, 0.0120, 0.0122	1.000, 0.0996, 0.0124, 0.0126
cML-BIC	1.000, -0.1004, 0.0112, 0.0113	0.991, -0.0504, 0.0114, 0.0115	0.747, -0.0304, 0.0115, 0.0116	0.138, -0.0104, 0.0116, 0.0117	0.056, -0.0004, 0.0117, 0.0118	0.127, 0.0096, 0.0118, 0.0118	0.700, 0.0296, 0.0119, 0.012	0.986, 0.0496, 0.0120, 0.0121	1.000, 0.0997, 0.0124, 0.0125
cML-BIC-Profile	1.000, -0.1004, 0.0112, 0.0113	0.991, -0.0504, 0.0114, 0.0115	0.746, -0.0304, 0.0115, 0.0116	0.138, -0.0104, 0.0116, 0.0117	0.056, -0.0004, 0.0117, 0.0118	0.126, 0.0096, 0.0118, 0.0118	0.699, 0.0296, 0.0119, 0.012	0.986, 0.0496, 0.0120, 0.0121	1.000, 0.0997, 0.0124, 0.0125
MR-Mix	0.843, -0.0985, 0.0333, 0.0504	0.734, -0.0484, 0.0222, 0.0459	0.528, -0.0293, 0.0188, 0.0576	0.103, -0.0102, 0.0168, 0.0535	0.050, -0.0008, 0.0167, 0.0485	0.094, 0.0085, 0.0167, 0.0696	0.464, 0.0267, 0.0187, 0.0701	0.712, 0.0447, 0.0217, 0.0583	0.836, 0.0889, 0.0303, 0.0313
MR-ContMix	1.000, -0.1081, 0.0137, NA	0.955, -0.0617, 0.0156, NA	0.606, -0.0410, 0.0179, NA	0.128, -0.0159, 0.0210, NA	0.051, -0.0010, 0.0219, NA	0.107, 0.0133, 0.0217, NA	0.527, 0.0392, 0.0192, NA	0.911, 0.0605, 0.0169, NA	1.000, 0.1080, 0.0150, NA
MR-Lasso	1.000, -0.1004, 0.0120, 0.012	0.982, -0.0506, 0.0122, 0.0123	0.690, -0.0306, 0.0124, 0.0124	0.136, -0.0105, 0.0125, 0.0125	0.049, -0.0006, 0.0124, 0.0126	0.115, 0.0094, 0.0126, 0.0126	0.642, 0.0294, 0.0129, 0.0128	0.964, 0.0494, 0.0128, 0.0129	1.000, 0.0994, 0.0133, 0.0132
MR-PRESSO	1.000, -0.1004, 0.0112, 0.0108	0.973, -0.0504, 0.0115, 0.011	0.679, -0.0304, 0.0116, 0.0111	0.132, -0.0105, 0.0117, 0.0112	0.048, -0.0005, 0.0118, 0.0112	0.113, 0.0095, 0.0118, 0.0113	0.616, 0.0295, 0.0120, 0.0114	0.951, 0.0495, 0.0121, 0.0116	1.000, 0.0995, 0.0125, 0.0119
MR-IVW	1.000, -0.1003, 0.0112, 0.0121	0.986, -0.0504, 0.0114, 0.0124	0.696, -0.0304, 0.0115, 0.0125	0.120, -0.0104, 0.0116, 0.0126	0.042, -0.0004, 0.0117, 0.0127	0.100, 0.0095, 0.0117, 0.0127	0.651, 0.0295, 0.0119, 0.0129	0.969, 0.0495, 0.0120, 0.013	1.000, 0.0995, 0.0124, 0.0134
MR-IVW-Oracle	1.000, -0.1003, 0.0112, 0.0121	0.986, -0.0504, 0.0114, 0.0124	0.696, -0.0304, 0.0115, 0.0125	0.120, -0.0104, 0.0116, 0.0126	0.042, -0.0004, 0.0117, 0.0127	0.100, 0.0095, 0.0117, 0.0127	0.651, 0.0295, 0.0119, 0.0129	0.969, 0.0495, 0.0120, 0.013	1.000, 0.0995, 0.0124, 0.0134
MR-Egger	0.283, -0.0936, 0.0641, 0.0691	0.091, -0.0455, 0.0653, 0.0705	0.061, -0.0263, 0.0658, 0.0711	0.039, -0.0070, 0.0664, 0.0718	0.039, 0.0026, 0.0668, 0.0721	0.041, 0.0122, 0.0671, 0.0725	0.058, 0.0314, 0.0678, 0.0732	0.085, 0.0507, 0.0686, 0.074	0.257, 0.0988, 0.0706, 0.0761
MR-Weighted-Median	1.000, -0.1004, 0.0134, 0.0151	0.918, -0.0506, 0.0137, 0.0154	0.516, -0.0307, 0.0138, 0.0155	0.065, -0.0108, 0.0139, 0.0157	0.029, -0.0008, 0.0140, 0.0157	0.058, 0.0091, 0.0140, 0.0158	0.442, 0.0290, 0.0142, 0.016	0.883, 0.0488, 0.0143, 0.0162	1.000, 0.0985, 0.0148, 0.0166
MR-Weighted-Mode	0.995, -0.1006, 0.0176, 0.0225	0.662, -0.0509, 0.0181, 0.0229	0.229, -0.0311, 0.0184, 0.0231	0.032, -0.0112, 0.0186, 0.0233	0.013, -0.0013, 0.0187, 0.0235	0.025, 0.0086, 0.0188, 0.0236	0.184, 0.0284, 0.0190, 0.0238	0.564, 0.0483, 0.0192, 0.0241	0.979, 0.0976, 0.0197, 0.0249
MR-RAPS1	1.000, -0.1005, 0.0112, 0.0119	0.988, -0.0504, 0.0114, 0.0121	0.706, -0.0304, 0.0115, 0.0122	0.124, -0.0104, 0.0116, 0.0124	0.048, -0.0004, 0.0117, 0.0124	0.106, 0.0096, 0.0117, 0.0125	0.670, 0.0296, 0.0119, 0.0126	0.974, 0.0496, 0.0120, 0.0127	1.000, 0.0996, 0.0124, 0.0131
MR-RAPS2	1.000, -0.0155, 0.3022, 0.0151	0.984, 0.0743, 1.0341, 0.0308	0.753, 0.0333, 1.4742, 0.0393	0.239, 0.1931, 2.2589, 0.0358	0.151, 0.0831, 1.8815, 0.0335	0.213, 0.1960, 2.0820, 0.0336	0.714, 0.1130, 1.8206, 0.0418	0.971, 0.1235, 1.1682, 0.0342	1.000, 0.1630, 0.4813, 0.0201
MR-RAPS3	1.000, -0.1005, 0.0112, 0.0113	0.992, -0.0505, 0.0114, 0.0115	0.746, -0.0305, 0.0115, 0.0116	0.140, -0.0105, 0.0116, 0.0117	0.055, -0.0004, 0.0117, 0.0118	0.124, 0.0096, 0.0117, 0.0118	0.699, 0.0296, 0.0119, 0.012	0.986, 0.0496, 0.0120, 0.0121	1.000, 0.0996, 0.0124, 0.0125
MR-RAPS4	1.000, -0.1006, 0.0113, 0.0116	0.992, -0.0505, 0.0115, 0.0118	0.726, -0.0280, 0.0582, 0.0119	0.132, -0.0103, 0.0130, 0.012	0.053, -0.0005, 0.0118, 0.0121	0.118, 0.0099, 0.0158, 0.0122	0.683, 0.0299, 0.0145, 0.0123	0.978, 0.0504, 0.0240, 0.0124	1.000, 0.0995, 0.0126, 0.0128

Table S29: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean( $SE(\hat{\theta})$ ) when  $m = 10$ , the InSIDE satisfied,  $q = 0.2$ , and  $N = 50000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	0.680, -0.0831, 0.0338, 0.0347	0.204, -0.0371, 0.0304, 0.0341	0.072, -0.0216, 0.0277, 0.0338	0.020, -0.0075, 0.0261, 0.0338	0.022, -0.0004, 0.0259, 0.0339	0.023, 0.0065, 0.0261, 0.034	0.065, 0.0207, 0.0278, 0.0348	0.164, 0.0368, 0.0303, 0.0356	0.607, 0.0818, 0.0357, 0.0379
cML-MA-AIC-Profile	0.670, -0.0833, 0.0338, 0.0349	0.199, -0.0372, 0.0305, 0.0343	0.070, -0.0216, 0.0278, 0.034	0.020, -0.0075, 0.0261, 0.034	0.021, -0.0004, 0.0259, 0.0341	0.023, 0.0065, 0.0261, 0.0342	0.063, 0.0207, 0.0278, 0.035	0.163, 0.0368, 0.0303, 0.0358	0.604, 0.0820, 0.0358, 0.0381
cML-AIC	0.828, -0.0908, 0.0381, 0.028	0.380, -0.0428, 0.0360, 0.0284	0.205, -0.0250, 0.0344, 0.0288	0.090, -0.0083, 0.0333, 0.029	0.073, -0.0004, 0.0332, 0.0292	0.098, 0.0082, 0.0334, 0.0293	0.175, 0.0245, 0.0349, 0.0296	0.355, 0.0426, 0.0366, 0.03	0.772, 0.0903, 0.0409, 0.0307
cML-AIC-Profile	0.827, -0.0911, 0.0381, 0.0282	0.375, -0.0428, 0.0360, 0.0286	0.201, -0.0251, 0.0345, 0.029	0.089, -0.0084, 0.0333, 0.0292	0.072, -0.0004, 0.0332, 0.0294	0.095, 0.0082, 0.0334, 0.0295	0.174, 0.0245, 0.0349, 0.0298	0.354, 0.0426, 0.0366, 0.0301	0.772, 0.0904, 0.0410, 0.0309
cML-MA-BIC	0.969, -0.1001, 0.0262, 0.0261	0.475, -0.0501, 0.0266, 0.0266	0.214, -0.0302, 0.0268, 0.0268	0.068, -0.0102, 0.0270, 0.0271	0.051, -0.0003, 0.0271, 0.0272	0.061, 0.0097, 0.0273, 0.0273	0.197, 0.0296, 0.0276, 0.0276	0.441, 0.0495, 0.0280, 0.0279	0.937, 0.0995, 0.0289, 0.0287
cML-MA-BIC-Profile	0.969, -0.1001, 0.0262, 0.0262	0.472, -0.0501, 0.0266, 0.0267	0.211, -0.0302, 0.0268, 0.0269	0.068, -0.0102, 0.0270, 0.0272	0.050, -0.0003, 0.0271, 0.0273	0.059, 0.0097, 0.0273, 0.0274	0.196, 0.0296, 0.0276, 0.0277	0.439, 0.0495, 0.0280, 0.028	0.933, 0.0995, 0.0289, 0.0289
cML-BIC	0.973, -0.1002, 0.0260, 0.0258	0.487, -0.0503, 0.0266, 0.0262	0.219, -0.0303, 0.0268, 0.0264	0.074, -0.0103, 0.0271, 0.0267	0.055, -0.0003, 0.0272, 0.0268	0.065, 0.0097, 0.0274, 0.027	0.203, 0.0298, 0.0276, 0.0272	0.447, 0.0498, 0.0280, 0.0275	0.942, 0.0997, 0.0289, 0.0284
cML-BIC-Profile	0.972, -0.1002, 0.0260, 0.0259	0.483, -0.0503, 0.0266, 0.0263	0.216, -0.0303, 0.0268, 0.0265	0.072, -0.0103, 0.0271, 0.0268	0.054, -0.0003, 0.0272, 0.0269	0.062, 0.0097, 0.0274, 0.0271	0.201, 0.0298, 0.0276, 0.0273	0.448, 0.0498, 0.0280, 0.0276	0.941, 0.0997, 0.0289, 0.0285
MR-Mix	0.870, -0.1053, 0.0296, 0.0358	0.280, -0.0515, 0.0296, 0.0357	0.110, -0.0308, 0.0294, 0.0356	0.035, -0.0104, 0.0294, 0.0356	0.023, -0.0002, 0.0294, 0.0356	0.032, 0.0098, 0.0295, 0.0357	0.099, 0.0295, 0.0294, 0.0357	0.265, 0.0488, 0.0295, 0.036	0.799, 0.0952, 0.0296, 0.036
MR-ContMix	0.954, -0.1002, 0.0282, NA	0.481, -0.0503, 0.0288, NA	0.227, -0.0304, 0.0290, NA	0.076, -0.0104, 0.0294, NA	0.060, -0.0005, 0.0296, NA	0.080, 0.0094, 0.0298, NA	0.210, 0.0294, 0.0301, NA	0.446, 0.0493, 0.0305, NA	0.904, 0.0991, 0.0314, NA
MR-Lasso	0.946, -0.0996, 0.0271, 0.0276	0.433, -0.0500, 0.0278, 0.0282	0.198, -0.0301, 0.0278, 0.0284	0.062, -0.0101, 0.0282, 0.0287	0.046, -0.0003, 0.0280, 0.0288	0.058, 0.0095, 0.0280, 0.029	0.171, 0.0293, 0.0285, 0.0292	0.400, 0.0495, 0.0291, 0.0295	0.899, 0.0993, 0.0298, 0.0304
MR-PRESSO	0.525, -0.0803, 0.2115, 0.0929	0.257, -0.0339, 0.2085, 0.0907	0.154, -0.0150, 0.2073, 0.0897	0.106, 0.0025, 0.2045, 0.0874	0.107, 0.0114, 0.2046, 0.0873	0.114, 0.0211, 0.2045, 0.087	0.159, 0.0380, 0.2024, 0.0851	0.261, 0.0554, 0.1995, 0.083	0.522, 0.1011, 0.1943, 0.079
MR-IVW	0.112, -0.0890, 0.2471, 0.2342	0.055, -0.0390, 0.2470, 0.2342	0.043, -0.0191, 0.2470, 0.2342	0.032, 0.0009, 0.2470, 0.2342	0.025, 0.0109, 0.2470, 0.2342	0.027, 0.0209, 0.2470, 0.2342	0.037, 0.0409, 0.2470, 0.2342	0.050, 0.0609, 0.2470, 0.2342	0.113, 0.1108, 0.2470, 0.2342
MR-IVW-Oracle	0.949, -0.0998, 0.0258, 0.0278	0.422, -0.0500, 0.0268, 0.0284	0.187, -0.0301, 0.0268, 0.0286	0.054, -0.0102, 0.0268, 0.0289	0.040, -0.0002, 0.0270, 0.029	0.051, 0.0097, 0.0271, 0.0292	0.164, 0.0296, 0.0274, 0.0295	0.393, 0.0495, 0.0277, 0.0298	0.900, 0.0993, 0.0285, 0.0306
MR-Egger	0.081, -0.1124, 1.3324, 1.2673	0.079, -0.0683, 1.3322, 1.2671	0.080, -0.0507, 1.3321, 1.267	0.081, -0.0330, 1.3320, 1.267	0.083, -0.0242, 1.3319, 1.267	0.083, -0.0154, 1.3319, 1.267	0.085, 0.0022, 1.3318, 1.2669	0.087, 0.0199, 1.3318, 1.2669	0.087, 0.0639, 1.3317, 1.2669
MR-Weighted-Median	0.829, -0.0979, 0.0319, 0.0337	0.309, -0.0492, 0.0325, 0.0343	0.124, -0.0296, 0.0328, 0.0346	0.037, -0.0101, 0.0331, 0.035	0.032, -0.0003, 0.0333, 0.0351	0.045, 0.0095, 0.0334, 0.0353	0.123, 0.0290, 0.0337, 0.0357	0.278, 0.0484, 0.0341, 0.0361	0.747, 0.0970, 0.0349, 0.0372
MR-Weighted-Mode	0.755, -0.0987, 0.0340, 0.0376	0.253, -0.0496, 0.0347, 0.0383	0.101, -0.0299, 0.0351, 0.0386	0.037, -0.0105, 0.0355, 0.039	0.021, -0.0007, 0.0356, 0.0392	0.031, 0.0091, 0.0358, 0.0394	0.090, 0.0287, 0.0362, 0.0398	0.236, 0.0485, 0.0367, 0.0402	0.674, 0.0976, 0.0377, 0.0414
MR-RAPS1	0.136, -0.0889, 0.2410, 0.2238	0.078, -0.0389, 0.2411, 0.2238	0.058, -0.0189, 0.2411, 0.2238	0.043, 0.0012, 0.2412, 0.2238	0.040, 0.0112, 0.2412, 0.2238	0.040, 0.0212, 0.2412, 0.2238	0.048, 0.0412, 0.2413, 0.2238	0.066, 0.0612, 0.2413, 0.2238	0.147, 0.1113, 0.2414, 0.2239
MR-RAPS2	0.901, -0.0764, 3.2138, 0.0776	0.757, 0.0771, 2.5930, 0.0648	0.672, 0.4224, 2.9590, 0.0665	0.629, 0.5567, 3.7350, 0.079	0.623, 0.5403, 3.8176, 0.074	0.624, 0.7386, 4.7511, 0.0832	0.690, 1.1735, 5.7913, 0.1106	0.749, 1.1140, 5.2713, 0.1117	0.896, 0.6427, 6.0397, 0.1136
MR-RAPS3	0.899, -0.1889, 0.5604, 0.0732	0.810, 0.0415, 3.8089, 14.8032	0.797, 0.0731, 3.2619, 2.8162	0.794, 0.0099, 0.4702, 0.0626	0.785, 0.0260, 0.4535, 0.0582	0.795, 0.0428, 0.4449, 0.0561	0.791, 0.0768, 0.4335, 0.0538	0.818, 0.1099, 0.4251, 0.0521	0.886, 0.1877, 0.4064, 0.0495
MR-RAPS4	0.995, -0.2234, 1.2807, 0.0503	0.907, 0.0267, 1.2697, 0.0486	0.858, 0.0880, 1.2736, 0.0484	0.810, 0.2014, 1.2339, 0.0475	0.798, 0.2672, 1.2305, 0.0477	0.795, 0.3081, 1.1909, 0.0462	0.824, 0.4070, 1.1715, 0.0467	0.873, 0.4891, 1.1353, 0.0465	0.991, 0.7079, 1.0264, 0.0464

Table S30: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean( $SE(\hat{\theta})$ ) when  $m = 10$ , the InSIDE satisfied,  $q = 0.2$ , and  $N = 100000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	0.926, -0.0863, 0.0232, 0.0246	0.341, -0.0378, 0.0217, 0.0245	0.117, -0.0205, 0.0200, 0.024	0.025, -0.0057, 0.0183, 0.0237	0.022, 0.0013, 0.0182, 0.0237	0.042, 0.0081, 0.0188, 0.024	0.134, 0.0233, 0.0212, 0.0247	0.387, 0.0407, 0.0235, 0.0255	0.872, 0.0885, 0.0264, 0.0269
cML-MA-AIC-Profile	0.926, -0.0864, 0.0233, 0.0247	0.338, -0.0378, 0.0217, 0.0245	0.117, -0.0205, 0.0200, 0.0241	0.024, -0.0058, 0.0183, 0.0238	0.022, 0.0013, 0.0182, 0.0238	0.042, 0.0081, 0.0188, 0.0241	0.133, 0.0233, 0.0212, 0.0247	0.385, 0.0407, 0.0235, 0.0256	0.873, 0.0887, 0.0264, 0.027
cML-AIC	0.965, -0.0921, 0.0256, 0.0197	0.572, -0.0428, 0.0251, 0.0201	0.280, -0.0239, 0.0232, 0.0202	0.098, -0.0069, 0.0232, 0.0204	0.080, 0.0015, 0.0229, 0.0205	0.109, 0.0097, 0.0235, 0.0206	0.309, 0.0269, 0.0251, 0.0208	0.603, 0.0455, 0.0269, 0.021	0.937, 0.0947, 0.0284, 0.0217
cML-AIC-Profile	0.964, -0.0922, 0.0257, 0.0198	0.569, -0.0428, 0.0251, 0.0201	0.281, -0.0239, 0.0245, 0.0203	0.097, -0.0069, 0.0232, 0.0205	0.079, 0.0015, 0.0229, 0.0205	0.109, 0.0097, 0.0235, 0.0207	0.308, 0.0269, 0.0251, 0.0209	0.602, 0.0455, 0.0269, 0.0211	0.938, 0.0950, 0.0284, 0.0217
cML-MA-BIC	0.999, -0.0988, 0.0189, 0.0183	0.733, -0.0488, 0.0192, 0.0187	0.342, -0.0288, 0.0193, 0.0188	0.084, -0.0089, 0.0195, 0.019	0.051, 0.0011, 0.0195, 0.0191	0.092, 0.0110, 0.0196, 0.0192	0.371, 0.0310, 0.0199, 0.0194	0.728, 0.0510, 0.0202, 0.0196	0.997, 0.1010, 0.0208, 0.0202
cML-MA-BIC-Profile	0.999, -0.0988, 0.0189, 0.0184	0.730, -0.0488, 0.0192, 0.0187	0.341, -0.0288, 0.0193, 0.0188	0.083, -0.0089, 0.0195, 0.019	0.051, 0.0011, 0.0195, 0.0191	0.092, 0.0110, 0.0196, 0.0192	0.369, 0.0310, 0.0199, 0.0194	0.727, 0.0510, 0.0202, 0.0196	0.997, 0.1010, 0.0208, 0.0202
cML-BIC	1.000, -0.0990, 0.0189, 0.0181	0.743, -0.0489, 0.0192, 0.0185	0.353, -0.0289, 0.0193, 0.0186	0.088, -0.0089, 0.0195, 0.0188	0.055, 0.0011, 0.0196, 0.0189	0.094, 0.0111, 0.0197, 0.019	0.376, 0.0310, 0.0200, 0.0192	0.740, 0.0511, 0.0202, 0.0194	0.997, 0.1011, 0.0207, 0.02
cML-BIC-Profile	1.000, -0.0990, 0.0189, 0.0182	0.740, -0.0490, 0.0192, 0.0185	0.353, -0.0289, 0.0193, 0.0186	0.087, -0.0089, 0.0195, 0.0188	0.055, 0.0011, 0.0196, 0.0189	0.094, 0.0111, 0.0197, 0.019	0.375, 0.0310, 0.0200, 0.0192	0.739, 0.0511, 0.0202, 0.0194	0.997, 0.1011, 0.0207, 0.02
MR-Mix	0.988, -0.1047, 0.0219, 0.0254	0.539, -0.0509, 0.0219, 0.0253	0.189, -0.0301, 0.0219, 0.0254	0.034, -0.0096, 0.0217, 0.0254	0.026, 0.0006, 0.0218, 0.0254	0.048, 0.0105, 0.0217, 0.0254	0.214, 0.0302, 0.0219, 0.0254	0.524, 0.0495, 0.0218, 0.0256	0.964, 0.0958, 0.0220, 0.0255
MR-ContMix	0.997, -0.0984, 0.0197, NA	0.731, -0.0483, 0.0201, NA	0.356, -0.0283, 0.0204, NA	0.103, -0.0084, 0.0205, NA	0.065, 0.0016, 0.0208, NA	0.105, 0.0116, 0.0209, NA	0.390, 0.0315, 0.0212, NA	0.740, 0.0515, 0.0215, NA	0.991, 0.1013, 0.0221, NA
MR-Lasso	0.996, -0.0985, 0.0193, 0.0194	0.673, -0.0486, 0.0196, 0.0199	0.307, -0.0286, 0.0197, 0.02	0.075, -0.0088, 0.0201, 0.0202	0.051, 0.0012, 0.0202, 0.0203	0.083, 0.0112, 0.0202, 0.0204	0.344, 0.0312, 0.0205, 0.0206	0.690, 0.0511, 0.0207, 0.0209	0.989, 0.1010, 0.0215, 0.0215
MR-PRESSO	0.517, -0.0953, 0.2290, 0.1123	0.318, -0.0459, 0.2287, 0.1116	0.176, -0.0263, 0.2285, 0.1113	0.072, -0.0061, 0.2281, 0.111	0.065, 0.0034, 0.2278, 0.1105	0.091, 0.0130, 0.2276, 0.1102	0.210, 0.0328, 0.2277, 0.1104	0.338, 0.0524, 0.2276, 0.1105	0.525, 0.1007, 0.2264, 0.1093
MR-IVW	0.106, -0.0966, 0.2365, 0.2336	0.038, -0.0465, 0.2365, 0.2336	0.029, -0.0264, 0.2365, 0.2336	0.020, -0.0064, 0.2365, 0.2336	0.019, 0.0036, 0.2364, 0.2336	0.024, 0.0136, 0.2364, 0.2336	0.034, 0.0337, 0.2364, 0.2336	0.048, 0.0537, 0.2364, 0.2336	0.107, 0.1037, 0.2364, 0.2336
MR-IVW-Oracle	0.998, -0.0988, 0.0187, 0.0196	0.673, -0.0488, 0.0191, 0.02	0.302, -0.0289, 0.0193, 0.0202	0.069, -0.0089, 0.0194, 0.0204	0.044, 0.0011, 0.0195, 0.0205	0.075, 0.0110, 0.0196, 0.0206	0.331, 0.0310, 0.0198, 0.0208	0.686, 0.0510, 0.0200, 0.021	0.993, 0.1009, 0.0206, 0.0216
MR-Egger	0.084, -0.0660, 1.4052, 1.3167	0.081, -0.0187, 1.4047, 1.3167	0.080, 0.0002, 1.4045, 1.3167	0.079, 0.0191, 1.4043, 1.3167	0.077, 0.0285, 1.4042, 1.3167	0.077, 0.0379, 1.4041, 1.3167	0.077, 0.0568, 1.4038, 1.3168	0.077, 0.0757, 1.4038, 1.3168	0.081, 0.1229, 1.4034, 1.3169
MR-Weighted-Median	0.990, -0.0975, 0.0222, 0.0237	0.513, -0.0481, 0.0226, 0.0242	0.203, -0.0283, 0.0228, 0.0244	0.046, -0.0086, 0.0230, 0.0246	0.031, 0.0012, 0.0232, 0.0247	0.062, 0.0111, 0.0233, 0.0248	0.225, 0.0308, 0.0236, 0.0251	0.534, 0.0505, 0.0239, 0.0254	0.970, 0.0997, 0.0246, 0.0261
MR-Weighted-Mode	0.959, -0.0977, 0.0243, 0.0266	0.422, -0.0482, 0.0247, 0.0271	0.171, -0.0284, 0.0247, 0.0273	0.033, -0.0085, 0.0247, 0.0276	0.023, 0.0014, 0.0249, 0.0277	0.045, 0.0112, 0.0251, 0.0279	0.176, 0.0310, 0.0254, 0.0281	0.458, 0.0507, 0.0256, 0.0285	0.925, 0.1003, 0.0262, 0.0293
MR-RAPS1	0.148, -0.0954, 0.2296, 0.2225	0.055, -0.0454, 0.2296, 0.2226	0.042, -0.0254, 0.2296, 0.2226	0.033, -0.0054, 0.2297, 0.2226	0.031, 0.0046, 0.2297, 0.2226	0.033, 0.0147, 0.2297, 0.2226	0.040, 0.0347, 0.2297, 0.2226	0.058, 0.0547, 0.2297, 0.2226	0.142, 0.1047, 0.2298, 0.2227
MR-RAPS2	0.926, -0.1293, 3.9699, 0.0665	0.756, 0.0720, 2.9083, 0.0457	0.420, 0.2497, 3.7601, 0.048	0.187, 0.2705, 3.6465, 0.0536	0.160, 0.5470, 3.1943, 0.0544	0.200, 0.6700, 8.0029, 0.0618	0.485, 0.8761, 3.9672, 0.0751	0.755, 1.0341, 4.2728, 0.0865	0.924, 0.6349, 3.9908, 0.084
MR-RAPS3	0.929, -0.2029, 0.4917, 0.0509	0.859, -0.0747, 0.5223, 0.0917	0.842, -0.0463, 0.4329, 0.0418	0.829, -0.0095, 0.4212, 0.0392	0.836, 0.0088, 0.4169, 0.0386	0.836, 0.0270, 0.4131, 0.038	0.846, 0.0626, 0.4058, 0.0371	0.851, 0.0971, 0.3990, 0.0363	0.918, 0.1775, 0.3834, 0.0347
MR-RAPS4	0.999, -0.0988, 0.0193, 0.0167	0.797, -0.0488, 0.0197, 0.0169	0.407, -0.0288, 0.0199, 0.0171	0.129, -0.0088, 0.0200, 0.0172	0.093, 0.0012, 0.0201, 0.0173	0.138, 0.0112, 0.0202, 0.0174	0.451, 0.0312, 0.0204, 0.0176	0.788, 0.0513, 0.0207, 0.0178	0.999, 0.1013, 0.0213, 0.0183

Table S31: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean(SE( $\hat{\theta}$ )) when  $m = 10$ , the InSIDE satisfied,  $q = 0.2$ , and  $N = 200000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	0.990, -0.0916, 0.0166, 0.0175	0.665, -0.0418, 0.0163, 0.0177	0.255, -0.0231, 0.0151, 0.0174	0.040, -0.0071, 0.0130, 0.017	0.024, -0.0003, 0.0129, 0.0169	0.033, 0.0066, 0.0135, 0.017	0.247, 0.0224, 0.0157, 0.0178	0.609, 0.0407, 0.0177, 0.0184	0.975, 0.0898, 0.0191, 0.0192
cML-MA-AIC-Profile	0.990, -0.0917, 0.0167, 0.0176	0.665, -0.0418, 0.0163, 0.0177	0.255, -0.0231, 0.0151, 0.0174	0.040, -0.0071, 0.0130, 0.017	0.024, -0.0003, 0.0129, 0.0169	0.033, 0.0066, 0.0135, 0.017	0.246, 0.0224, 0.0157, 0.0178	0.609, 0.0408, 0.0177, 0.0184	0.975, 0.0899, 0.0191, 0.0192
cML-AIC	0.993, -0.0959, 0.0182, 0.014	0.845, -0.0460, 0.0180, 0.0142	0.497, -0.0265, 0.0175, 0.0143	0.126, -0.0082, 0.0165, 0.0144	0.076, -0.0002, 0.0165, 0.0145	0.126, 0.0080, 0.0172, 0.0146	0.478, 0.0258, 0.0184, 0.0147	0.788, 0.0449, 0.0198, 0.0149	0.987, 0.0943, 0.0207, 0.0153
cML-AIC-Profile	0.993, -0.0960, 0.0183, 0.014	0.845, -0.0461, 0.0180, 0.0142	0.497, -0.0265, 0.0175, 0.0143	0.126, -0.0082, 0.0165, 0.0144	0.076, -0.0002, 0.0165, 0.0145	0.124, 0.0080, 0.0172, 0.0146	0.477, 0.0258, 0.0184, 0.0147	0.788, 0.0449, 0.0198, 0.0149	0.987, 0.0944, 0.0207, 0.0154
cML-MA-BIC	1.000, -0.1005, 0.0133, 0.0129	0.965, -0.0505, 0.0135, 0.0131	0.636, -0.0306, 0.0136, 0.0132	0.118, -0.0106, 0.0137, 0.0134	0.049, -0.0006, 0.0137, 0.0134	0.120, 0.0094, 0.0138, 0.0135	0.577, 0.0293, 0.0140, 0.0136	0.932, 0.0493, 0.0141, 0.0138	1.000, 0.0993, 0.0145, 0.0142
cML-MA-BIC-Profile	1.000, -0.1005, 0.0133, 0.0129	0.965, -0.0505, 0.0135, 0.0131	0.636, -0.0306, 0.0136, 0.0133	0.117, -0.0106, 0.0137, 0.0134	0.049, -0.0006, 0.0137, 0.0134	0.120, 0.0094, 0.0138, 0.0135	0.575, 0.0293, 0.0140, 0.0136	0.932, 0.0493, 0.0141, 0.0138	1.000, 0.0993, 0.0145, 0.0142
cML-BIC	1.000, -0.1006, 0.0133, 0.0128	0.966, -0.0506, 0.0135, 0.013	0.643, -0.0306, 0.0136, 0.0131	0.121, -0.0106, 0.0137, 0.0133	0.053, -0.0006, 0.0138, 0.0133	0.122, 0.0093, 0.0138, 0.0134	0.584, 0.0293, 0.0140, 0.0135	0.935, 0.0493, 0.0141, 0.0137	1.000, 0.0993, 0.0145, 0.0141
cML-BIC-Profile	1.000, -0.1006, 0.0133, 0.0128	0.966, -0.0506, 0.0135, 0.013	0.643, -0.0306, 0.0136, 0.0131	0.122, -0.0106, 0.0137, 0.0133	0.053, -0.0006, 0.0138, 0.0133	0.122, 0.0093, 0.0138, 0.0134	0.584, 0.0293, 0.0140, 0.0135	0.935, 0.0493, 0.0141, 0.0137	1.000, 0.0993, 0.0145, 0.0141
MR-Mix	0.999, -0.1061, 0.0159, 0.0183	0.846, -0.0526, 0.0158, 0.0182	0.416, -0.0315, 0.0157, 0.0182	0.062, -0.0111, 0.0157, 0.0182	0.025, -0.0010, 0.0157, 0.0182	0.056, 0.0090, 0.0157, 0.0182	0.354, 0.0287, 0.0156, 0.0182	0.769, 0.0479, 0.0158, 0.0182	0.994, 0.0945, 0.0157, 0.0183
MR-ContMix	1.000, -0.1002, 0.0138, NA	0.958, -0.0504, 0.0140, NA	0.660, -0.0304, 0.0141, NA	0.144, -0.0104, 0.0142, NA	0.078, -0.0005, 0.0143, NA	0.133, 0.0095, 0.0143, NA	0.607, 0.0294, 0.0145, NA	0.936, 0.0494, 0.0146, NA	1.000, 0.0993, 0.0151, NA
MR-Lasso	1.000, -0.1006, 0.0137, 0.0138	0.941, -0.0506, 0.0139, 0.0141	0.589, -0.0307, 0.0140, 0.0142	0.104, -0.0108, 0.0141, 0.0144	0.048, -0.0008, 0.0142, 0.0144	0.107, 0.0092, 0.0143, 0.0145	0.522, 0.0291, 0.0144, 0.0146	0.896, 0.0491, 0.0146, 0.0148	0.999, 0.0990, 0.0151, 0.0152
MR-PRESSO	0.493, -0.1154, 0.2375, 0.1207	0.387, -0.0654, 0.2371, 0.12	0.243, -0.0454, 0.2371, 0.1198	0.088, -0.0255, 0.2369, 0.1194	0.066, -0.0156, 0.2369, 0.1192	0.093, -0.0055, 0.2369, 0.1192	0.241, 0.0143, 0.2368, 0.119	0.370, 0.0342, 0.2367, 0.119	0.495, 0.0842, 0.2364, 0.1184
MR-IVW	0.128, -0.1158, 0.2418, 0.2338	0.056, -0.0657, 0.2417, 0.2338	0.035, -0.0456, 0.2416, 0.2338	0.022, -0.0256, 0.2416, 0.2337	0.022, -0.0156, 0.2415, 0.2337	0.023, -0.0056, 0.2415, 0.2337	0.029, 0.0145, 0.2415, 0.2337	0.039, 0.0345, 0.2414, 0.2337	0.100, 0.0845, 0.2413, 0.2337
MR-IVW-Oracle	1.000, -0.1004, 0.0132, 0.0139	0.942, -0.0505, 0.0134, 0.0142	0.581, -0.0306, 0.0135, 0.0143	0.093, -0.0106, 0.0136, 0.0145	0.036, -0.0006, 0.0137, 0.0145	0.102, 0.0094, 0.0137, 0.0146	0.522, 0.0293, 0.0139, 0.0147	0.903, 0.0493, 0.0140, 0.0149	0.999, 0.0992, 0.0144, 0.0153
MR-Egger	0.071, -0.1706, 1.3437, 1.3309	0.070, -0.1222, 1.3435, 1.3308	0.069, -0.1028, 1.3434, 1.3307	0.070, -0.0834, 1.3433, 1.3307	0.070, -0.0737, 1.3432, 1.3307	0.070, -0.0641, 1.3432, 1.3307	0.068, -0.0447, 1.3431, 1.3306	0.069, -0.0253, 1.3430, 1.3306	0.071, 0.0231, 1.3428, 1.3306
MR-Weighted-Median	1.000, -0.0999, 0.0157, 0.0168	0.855, -0.0503, 0.0160, 0.0171	0.423, -0.0305, 0.0162, 0.0173	0.079, -0.0106, 0.0164, 0.0174	0.040, -0.0007, 0.0165, 0.0175	0.057, 0.0092, 0.0166, 0.0176	0.392, 0.0290, 0.0168, 0.0178	0.781, 0.0489, 0.0171, 0.018	0.999, 0.0984, 0.0177, 0.0185
MR-Weighted-Mode	1.000, -0.0999, 0.0166, 0.0189	0.769, -0.0502, 0.0170, 0.0193	0.337, -0.0304, 0.0172, 0.0194	0.060, -0.0105, 0.0173, 0.0196	0.030, -0.0005, 0.0174, 0.0197	0.046, 0.0095, 0.0176, 0.0198	0.322, 0.0293, 0.0178, 0.02	0.707, 0.0492, 0.0182, 0.0202	0.993, 0.0990, 0.0188, 0.0208
MR-RAPS1	0.171, -0.1144, 0.2336, 0.2223	0.069, -0.0644, 0.2336, 0.2223	0.044, -0.0444, 0.2336, 0.2223	0.030, -0.0244, 0.2336, 0.2223	0.030, -0.0144, 0.2336, 0.2223	0.024, -0.0044, 0.2336, 0.2223	0.036, 0.0156, 0.2336, 0.2223	0.058, 0.0356, 0.2336, 0.2223	0.126, 0.0855, 0.2336, 0.2224
MR-RAPS2	0.939, 0.0667, 4.1364, 0.071	0.923, -0.0469, 3.3717, 0.0709	0.731, 0.1500, 4.0999, 0.0735	0.335, 0.1544, 3.5386, 0.0687	0.264, -0.0108, 3.5733, 0.0658	0.350, -0.0979, 4.4794, 0.0763	0.678, -0.3080, 5.0440, 0.0742	0.904, 0.0703, 3.7687, 0.0663	0.943, 0.2736, 3.4304, 0.0647
MR-RAPS3	0.939, -0.3156, 2.7672, 0.4842	0.910, -0.1309, 0.5608, 0.0832	0.906, -0.0820, 0.4483, 0.0292	0.893, -0.0450, 0.4358, 0.0277	0.897, -0.0266, 0.4311, 0.0273	0.881, -0.0083, 0.4268, 0.0272	0.879, 0.0283, 0.4190, 0.0267	0.890, 0.0628, 0.4128, 0.0256	0.940, 0.1434, 0.3973, 0.0244
MR-RAPS4	1.000, -0.1005, 0.0135, 0.0117	0.973, -0.0493, 0.0347, 0.0119	0.705, -0.0256, 0.0647, 0.0121	0.189, 0.0035, 0.1212, 0.0123	0.104, 0.0133, 0.1092, 0.0123	0.171, 0.0194, 0.0893, 0.0123	0.642, 0.0323, 0.0504, 0.0124	0.957, 0.0503, 0.0315, 0.0125	1.000, 0.0994, 0.0148, 0.0129

Table S32: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean( $SE(\hat{\theta})$ ) when  $m = 10$ , the InSIDE satisfied,  $q = 0.4$ , and  $N = 50000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	0.559, -0.0821, 0.0343, 0.0398	0.120, -0.0364, 0.0303, 0.0392	0.034, -0.0208, 0.0282, 0.039	0.010, -0.0061, 0.0267, 0.0389	0.009, 0.0007, 0.0269, 0.0391	0.014, 0.0073, 0.0273, 0.0393	0.034, 0.0213, 0.0295, 0.0402	0.093, 0.0365, 0.0324, 0.0411	0.494, 0.0804, 0.0382, 0.0434
cML-MA-AIC-Profile	0.553, -0.0822, 0.0344, 0.04	0.117, -0.0364, 0.0303, 0.0395	0.034, -0.0208, 0.0282, 0.0392	0.008, -0.0061, 0.0268, 0.0392	0.009, 0.0007, 0.0269, 0.0393	0.014, 0.0073, 0.0274, 0.0396	0.034, 0.0213, 0.0295, 0.0404	0.093, 0.0365, 0.0324, 0.0414	0.493, 0.0806, 0.0383, 0.0437
cML-AIC	0.783, -0.0906, 0.0382, 0.0324	0.304, -0.0424, 0.0361, 0.033	0.144, -0.0249, 0.0350, 0.0332	0.056, -0.0072, 0.0344, 0.0336	0.045, 0.0008, 0.0349, 0.0337	0.060, 0.0086, 0.0353, 0.0339	0.134, 0.0251, 0.0373, 0.0343	0.273, 0.0420, 0.0395, 0.0347	0.707, 0.0889, 0.0441, 0.0358
cML-AIC-Profile	0.780, -0.0907, 0.0383, 0.0326	0.295, -0.0424, 0.0361, 0.0332	0.140, -0.0249, 0.0350, 0.0335	0.054, -0.0072, 0.0346, 0.0338	0.043, 0.0008, 0.0349, 0.0339	0.056, 0.0086, 0.0353, 0.0341	0.130, 0.0251, 0.0373, 0.0345	0.269, 0.0420, 0.0396, 0.035	0.706, 0.0891, 0.0442, 0.036
cML-MA-BIC	0.914, -0.1004, 0.0293, 0.0304	0.361, -0.0504, 0.0297, 0.031	0.152, -0.0305, 0.0299, 0.0313	0.052, -0.0106, 0.0301, 0.0315	0.042, -0.0007, 0.0302, 0.0317	0.045, 0.0093, 0.0304, 0.0318	0.135, 0.0291, 0.0307, 0.0322	0.315, 0.0491, 0.0311, 0.0325	0.855, 0.0990, 0.0321, 0.0334
cML-MA-BIC-Profile	0.913, -0.1004, 0.0293, 0.0305	0.356, -0.0504, 0.0297, 0.0311	0.151, -0.0305, 0.0299, 0.0314	0.051, -0.0106, 0.0301, 0.0317	0.041, -0.0007, 0.0302, 0.0318	0.044, 0.0093, 0.0304, 0.032	0.133, 0.0291, 0.0307, 0.0323	0.314, 0.0491, 0.0311, 0.0326	0.852, 0.0990, 0.0322, 0.0336
cML-BIC	0.924, -0.1008, 0.0294, 0.03	0.378, -0.0507, 0.0299, 0.0305	0.165, -0.0306, 0.0302, 0.0308	0.058, -0.0106, 0.0304, 0.0311	0.046, -0.0006, 0.0306, 0.0312	0.051, 0.0094, 0.0308, 0.0314	0.143, 0.0293, 0.0310, 0.0317	0.330, 0.0493, 0.0314, 0.032	0.860, 0.0994, 0.0323, 0.033
cML-BIC-Profile	0.923, -0.1008, 0.0294, 0.0301	0.371, -0.0507, 0.0299, 0.0307	0.162, -0.0306, 0.0302, 0.0309	0.055, -0.0106, 0.0304, 0.0312	0.046, -0.0006, 0.0306, 0.0314	0.049, 0.0094, 0.0308, 0.0315	0.140, 0.0293, 0.0310, 0.0318	0.327, 0.0493, 0.0314, 0.0322	0.859, 0.0994, 0.0323, 0.0331
MR-Mix	0.845, -0.1057, 0.0329, 0.0376	0.288, -0.0525, 0.0327, 0.0375	0.105, -0.0318, 0.0325, 0.0373	0.038, -0.0113, 0.0327, 0.0371	0.024, -0.0012, 0.0327, 0.0371	0.039, 0.0088, 0.0327, 0.037	0.095, 0.0283, 0.0328, 0.0372	0.235, 0.0476, 0.0328, 0.0372	0.743, 0.0935, 0.0329, 0.0375
MR-ContMix	0.912, -0.1000, 0.0308, NA	0.398, -0.0503, 0.0314, NA	0.178, -0.0304, 0.0317, NA	0.062, -0.0106, 0.0319, NA	0.048, -0.0006, 0.0320, NA	0.064, 0.0093, 0.0322, NA	0.153, 0.0291, 0.0325, NA	0.335, 0.0489, 0.0329, NA	0.861, 0.0987, 0.0339, NA
MR-Lasso	0.880, -0.0987, 0.0478, 0.0329	0.328, -0.0490, 0.0505, 0.0335	0.132, -0.0293, 0.0506, 0.0338	0.047, -0.0094, 0.0507, 0.0341	0.035, 0.0005, 0.0487, 0.0344	0.048, 0.0105, 0.0509, 0.0345	0.115, 0.0306, 0.0511, 0.0349	0.291, 0.0506, 0.0513, 0.0352	0.809, 0.1003, 0.0519, 0.0362
MR-PRESSO	0.396, -0.0857, 0.3268, 0.1621	0.212, -0.0373, 0.3259, 0.1603	0.154, -0.0177, 0.3262, 0.1606	0.128, 0.0011, 0.3253, 0.1586	0.125, 0.0108, 0.3251, 0.1581	0.127, 0.0207, 0.3251, 0.1581	0.161, 0.0399, 0.3244, 0.1559	0.234, 0.0587, 0.3231, 0.1532	0.391, 0.1063, 0.3219, 0.1516
MR-IVW	0.097, -0.0905, 0.3440, 0.3283	0.103, -0.0403, 0.3439, 0.3283	0.109, -0.0203, 0.3439, 0.3283	0.112, -0.0002, 0.3439, 0.3283	0.113, 0.0098, 0.3438, 0.3283	0.112, 0.0198, 0.3438, 0.3283	0.112, 0.0399, 0.3438, 0.3283	0.112, 0.0599, 0.3438, 0.3283	0.106, 0.1100, 0.3437, 0.3283
MR-IVW-Oracle	0.884, -0.1003, 0.0291, 0.0328	0.324, -0.0505, 0.0296, 0.0335	0.130, -0.0306, 0.0298, 0.0338	0.045, -0.0107, 0.0301, 0.0341	0.031, -0.0007, 0.0303, 0.0343	0.042, 0.0092, 0.0304, 0.0344	0.108, 0.0292, 0.0307, 0.0348	0.283, 0.0491, 0.0311, 0.0351	0.810, 0.0989, 0.0321, 0.0361
MR-Egger	0.079, -0.0580, 1.8427, 1.7924	0.079, -0.0142, 1.8425, 1.7922	0.080, 0.0033, 1.8424, 1.7921	0.082, 0.0208, 1.8424, 1.7921	0.082, 0.0296, 1.8423, 1.792	0.082, 0.0384, 1.8423, 1.792	0.081, 0.0559, 1.8422, 1.7919	0.080, 0.0734, 1.8422, 1.7919	0.080, 0.1171, 1.8421, 1.7918
MR-Weighted-Median	0.721, -0.0969, 0.0356, 0.0384	0.225, -0.0484, 0.0362, 0.0391	0.081, -0.0291, 0.0366, 0.0394	0.033, -0.0098, 0.0370, 0.0398	0.037, -0.0002, 0.0372, 0.04	0.044, 0.0095, 0.0375, 0.0402	0.085, 0.0288, 0.0380, 0.0406	0.199, 0.0480, 0.0386, 0.041	0.642, 0.0959, 0.0399, 0.0422
MR-Weighted-Mode	0.872, -0.0988, 0.0309, 0.0331	0.300, -0.0497, 0.0313, 0.0337	0.120, -0.0302, 0.0315, 0.034	0.047, -0.0103, 0.0318, 0.0343	0.044, -0.0005, 0.0321, 0.0345	0.052, 0.0093, 0.0322, 0.0346	0.104, 0.0289, 0.0325, 0.035	0.271, 0.0484, 0.0329, 0.0353	0.795, 0.0978, 0.0337, 0.0364
MR-RAPS1	0.105, -0.0930, 0.3354, 0.3142	0.116, -0.0429, 0.3355, 0.3142	0.120, -0.0229, 0.3355, 0.3142	0.119, -0.0029, 0.3355, 0.3142	0.118, 0.0072, 0.3355, 0.3142	0.115, 0.0172, 0.3355, 0.3142	0.117, 0.0372, 0.3355, 0.3142	0.114, 0.0572, 0.3355, 0.3142	0.111, 0.1073, 0.3356, 0.3143
MR-RAPS2	0.078, -0.0942, 0.3292, 0.327	0.076, -0.0450, 0.3300, 0.3276	0.084, -0.0233, 0.3317, 0.3279	0.086, -0.0028, 0.3293, 0.3286	0.092, 0.0066, 0.3299, 0.3291	0.092, 0.0167, 0.3302, 0.3295	0.087, 0.0354, 0.3275, 0.3285	0.087, 0.0570, 0.3269, 0.3275	0.079, 0.1062, 0.3302, 0.3301
MR-RAPS3	0.896, -0.3241, 13.0930, 12.7633	0.864, 0.1266, 20.7751, 38.25	0.857, 0.1445, 19.5143, 35.1805	0.856, 2.4271, 49.5897, 195.9921	0.862, 1.3950, 42.3294, 422.534	0.859, -0.3627, 10.3500, 10.6747	0.861, -0.0916, 7.1335, 57.192	0.877, 0.3121, 6.6967, 7.4227	0.896, 0.6502, 12.8237, 18.2533
MR-RAPS4	0.986, 0.3623, 1.5807, 0.1621	0.983, 0.3262, 1.6056, 0.1149	0.974, 0.3552, 1.5778, 0.1227	0.961, 0.3088, 1.6007, 0.8658	0.952, 0.3373, 1.6014, 0.1237	0.953, 0.2926, 1.5770, 0.1079	0.963, 0.2641, 1.6315, 0.1217	0.971, 0.2457, 1.6184, 0.1786	0.990, 0.1394, 1.6111, 0.1694

Table S33: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean( $SE(\hat{\theta})$ ) when  $m = 10$ , the InSIDE satisfied,  $q = 0.4$ , and  $N = 100000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	0.838, -0.0857, 0.0257, 0.0287	0.256, -0.0378, 0.0235, 0.0284	0.076, -0.0209, 0.0212, 0.0281	0.012, -0.0064, 0.0195, 0.0279	0.012, 0.0005, 0.0195, 0.0279	0.023, 0.0071, 0.0200, 0.0281	0.082, 0.0217, 0.0224, 0.0289	0.240, 0.0379, 0.0253, 0.0297	0.774, 0.0850, 0.0288, 0.0313
cML-MA-AIC-Profile	0.838, -0.0858, 0.0258, 0.0287	0.255, -0.0378, 0.0235, 0.0285	0.073, -0.0209, 0.0213, 0.0281	0.011, -0.0064, 0.0195, 0.0279	0.012, 0.0005, 0.0195, 0.028	0.021, 0.0071, 0.0200, 0.0282	0.082, 0.0217, 0.0225, 0.029	0.238, 0.0379, 0.0253, 0.0298	0.774, 0.0851, 0.0288, 0.0314
cML-AIC	0.920, -0.0921, 0.0286, 0.023	0.509, -0.0428, 0.0265, 0.0235	0.224, -0.0245, 0.0265, 0.0236	0.078, -0.0082, 0.0253, 0.0239	0.069, 0.0003, 0.0252, 0.024	0.085, 0.0084, 0.0259, 0.0241	0.214, 0.0249, 0.0280, 0.0243	0.470, 0.0427, 0.0297, 0.0246	0.890, 0.0916, 0.0317, 0.0252
cML-AIC-Profile	0.920, -0.0921, 0.0287, 0.0231	0.508, -0.0428, 0.0278, 0.0235	0.222, -0.0245, 0.0265, 0.0237	0.077, -0.0082, 0.0253, 0.0239	0.067, 0.0003, 0.0252, 0.0241	0.085, 0.0084, 0.0259, 0.0241	0.211, 0.0249, 0.0280, 0.0244	0.468, 0.0427, 0.0297, 0.0246	0.890, 0.0916, 0.0317, 0.0253
cML-MA-BIC	0.992, -0.0997, 0.0213, 0.0214	0.646, -0.0497, 0.0217, 0.0218	0.278, -0.0298, 0.0219, 0.022	0.076, -0.0099, 0.0221, 0.0222	0.045, 0.0001, 0.0222, 0.0223	0.070, 0.0100, 0.0223, 0.0224	0.260, 0.0300, 0.0226, 0.0226	0.581, 0.0499, 0.0229, 0.0229	0.984, 0.0999, 0.0236, 0.0235
cML-MA-BIC-Profile	0.992, -0.0997, 0.0213, 0.0215	0.644, -0.0497, 0.0217, 0.0218	0.275, -0.0298, 0.0219, 0.022	0.074, -0.0099, 0.0221, 0.0222	0.045, 0.0001, 0.0222, 0.0223	0.069, 0.0100, 0.0223, 0.0224	0.259, 0.0300, 0.0226, 0.0227	0.581, 0.0499, 0.0229, 0.0229	0.984, 0.0999, 0.0236, 0.0236
cML-BIC	0.992, -0.0999, 0.0213, 0.0212	0.654, -0.0499, 0.0218, 0.0215	0.286, -0.0299, 0.0220, 0.0217	0.081, -0.0099, 0.0222, 0.0219	0.050, 0.0001, 0.0223, 0.022	0.075, 0.0101, 0.0225, 0.0221	0.268, 0.0301, 0.0227, 0.0224	0.595, 0.0501, 0.0230, 0.0226	0.988, 0.1001, 0.0237, 0.0233
cML-BIC-Profile	0.992, -0.0999, 0.0213, 0.0212	0.654, -0.0499, 0.0218, 0.0216	0.284, -0.0299, 0.0220, 0.0218	0.080, -0.0099, 0.0222, 0.022	0.050, 0.0001, 0.0223, 0.0221	0.075, 0.0101, 0.0225, 0.0222	0.267, 0.0301, 0.0227, 0.0224	0.594, 0.0501, 0.0230, 0.0226	0.988, 0.1001, 0.0237, 0.0233
MR-Mix	0.971, -0.1040, 0.0241, 0.0273	0.502, -0.0511, 0.0240, 0.027	0.197, -0.0303, 0.0242, 0.027	0.053, -0.0100, 0.0242, 0.0276	0.035, -0.0001, 0.0243, 0.0276	0.052, 0.0098, 0.0243, 0.0277	0.173, 0.0293, 0.0243, 0.0276	0.441, 0.0485, 0.0243, 0.0278	0.943, 0.0945, 0.0243, 0.0273
MR-ContMix	0.992, -0.0998, 0.0225, NA	0.667, -0.0497, 0.0228, NA	0.312, -0.0297, 0.0230, NA	0.100, -0.0097, 0.0232, NA	0.071, 0.0003, 0.0233, NA	0.096, 0.0103, 0.0234, NA	0.295, 0.0303, 0.0236, NA	0.607, 0.0502, 0.0239, NA	0.985, 0.1001, 0.0246, NA
MR-Lasso	0.980, -0.0994, 0.0224, 0.0232	0.582, -0.0495, 0.0227, 0.0236	0.244, -0.0296, 0.0229, 0.0239	0.067, -0.0095, 0.0232, 0.0241	0.039, 0.0004, 0.0234, 0.0242	0.066, 0.0104, 0.0235, 0.0243	0.232, 0.0304, 0.0236, 0.0246	0.539, 0.0505, 0.0239, 0.0248	0.969, 0.1002, 0.0250, 0.0256
MR-PRESSO	0.394, -0.0834, 0.3375, 0.2048	0.256, -0.0338, 0.3374, 0.2043	0.173, -0.0142, 0.3373, 0.2034	0.132, 0.0057, 0.3373, 0.2034	0.120, 0.0159, 0.3373, 0.2031	0.122, 0.0260, 0.3373, 0.2031	0.170, 0.0456, 0.3368, 0.2008	0.244, 0.0657, 0.3363, 0.1987	0.402, 0.1150, 0.3353, 0.1947
MR-IVW	0.108, -0.0857, 0.3425, 0.3298	0.113, -0.0355, 0.3425, 0.3298	0.116, -0.0154, 0.3425, 0.3298	0.120, 0.0046, 0.3424, 0.3298	0.119, 0.0147, 0.3424, 0.3298	0.122, 0.0247, 0.3424, 0.3298	0.120, 0.0447, 0.3424, 0.3298	0.121, 0.0648, 0.3424, 0.3297	0.113, 0.1149, 0.3423, 0.3297
MR-IVW-Oracle	0.989, -0.0997, 0.0212, 0.0232	0.586, -0.0498, 0.0216, 0.0237	0.237, -0.0299, 0.0218, 0.0239	0.059, -0.0099, 0.0220, 0.0241	0.033, 0.0001, 0.0222, 0.0242	0.057, 0.0101, 0.0223, 0.0243	0.220, 0.0300, 0.0225, 0.0246	0.526, 0.0500, 0.0228, 0.0248	0.970, 0.0998, 0.0235, 0.0255
MR-Egger	0.094, -0.0602, 1.9334, 1.859	0.092, -0.0130, 1.9329, 1.859	0.092, 0.0058, 1.9327, 1.859	0.095, 0.0246, 1.9325, 1.859	0.095, 0.0341, 1.9324, 1.859	0.095, 0.0435, 1.9323, 1.859	0.095, 0.0623, 1.9320, 1.859	0.095, 0.0812, 1.9318, 1.859	0.095, 0.1282, 1.9314, 1.859
MR-Weighted-Median	0.948, -0.0974, 0.0259, 0.0271	0.436, -0.0483, 0.0264, 0.0276	0.161, -0.0287, 0.0266, 0.0278	0.044, -0.0090, 0.0268, 0.0281	0.043, 0.0008, 0.0269, 0.0282	0.052, 0.0107, 0.0270, 0.0284	0.181, 0.0303, 0.0273, 0.0287	0.411, 0.0499, 0.0277, 0.029	0.912, 0.0989, 0.0287, 0.0298
MR-Weighted-Mode	0.985, -0.0991, 0.0232, 0.0234	0.563, -0.0496, 0.0232, 0.0238	0.244, -0.0297, 0.0234, 0.024	0.066, -0.0100, 0.0235, 0.0242	0.042, 0.0000, 0.0235, 0.0243	0.054, 0.0100, 0.0236, 0.0245	0.219, 0.0298, 0.0239, 0.0247	0.527, 0.0496, 0.0245, 0.025	0.968, 0.0990, 0.0250, 0.0257
MR-RAPS1	0.112, -0.0893, 0.3355, 0.3135	0.119, -0.0393, 0.3356, 0.3135	0.123, -0.0193, 0.3356, 0.3136	0.125, 0.0007, 0.3356, 0.3136	0.126, 0.0107, 0.3356, 0.3136	0.129, 0.0207, 0.3356, 0.3136	0.127, 0.0407, 0.3356, 0.3136	0.126, 0.0607, 0.3356, 0.3136	0.115, 0.1106, 0.3357, 0.3136
MR-RAPS2	0.079, -0.0884, 0.3207, 0.3192	0.089, -0.0376, 0.3234, 0.3238	0.095, -0.0200, 0.3234, 0.3236	0.097, -0.0004, 0.3248, 0.324	0.098, 0.0090, 0.3245, 0.3247	0.091, 0.0212, 0.3291, 0.3251	0.090, 0.0389, 0.3249, 0.3255	0.088, 0.0607, 0.3264, 0.3275	0.082, 0.1090, 0.3269, 0.3279
MR-RAPS3	0.942, -15.7267, 585.1517, 13300	0.916, -0.3338, 10.4566, 26.03	0.908, 0.1956, 25.4131, 45.07	0.899, -1.2781, 45.5970, 116.2	0.887, -0.5316, 40.8729, 182	0.891, 0.1034, 28.1294, 39.4	0.898, -1.7426, 58.0315, 1103	0.907, 0.5672, 9.1414, 6.23	0.926, 0.2286, 5.0424, 2.527
MR-RAPS4	0.972, 0.8324, 1.6647, 0.2024	0.983, 0.7864, 1.6293, 0.1573	0.978, 0.7613, 1.6436, 0.1593	0.981, 0.7605, 1.6142, 0.3426	0.975, 0.7296, 1.6157, 0.1276	0.980, 0.7151, 1.6501, 0.1185	0.981, 0.6754, 1.6321, 0.1409	0.993, 0.5983, 1.6471, 0.0962	0.998, 0.4622, 1.6313, 0.0708

Table S34: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean( $SE(\hat{\theta})$ ) when  $m = 10$ , the InSIDE satisfied,  $q = 0.4$ , and  $N = 200000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	0.979, -0.0906, 0.0187, 0.0203	0.557, -0.0409, 0.0182, 0.0205	0.170, -0.0227, 0.0165, 0.0202	0.022, -0.0072, 0.0144, 0.0198	0.013, -0.0003, 0.0139, 0.0198	0.029, 0.0066, 0.0145, 0.0199	0.168, 0.0220, 0.0170, 0.0206	0.495, 0.0399, 0.0194, 0.0213	0.946, 0.0889, 0.0210, 0.0223
cML-MA-AIC-Profile	0.979, -0.0907, 0.0188, 0.0203	0.556, -0.0410, 0.0182, 0.0205	0.171, -0.0227, 0.0165, 0.0202	0.022, -0.0072, 0.0143, 0.0198	0.013, -0.0004, 0.0139, 0.0198	0.028, 0.0066, 0.0145, 0.0199	0.168, 0.0220, 0.0170, 0.0207	0.492, 0.0399, 0.0194, 0.0214	0.946, 0.0890, 0.0210, 0.0223
cML-AIC	0.986, -0.0950, 0.0210, 0.0163	0.739, -0.0450, 0.0209, 0.0166	0.412, -0.0261, 0.0200, 0.0167	0.103, -0.0086, 0.0186, 0.0169	0.068, -0.0005, 0.0183, 0.0169	0.107, 0.0075, 0.0187, 0.0171	0.368, 0.0250, 0.0204, 0.0173	0.698, 0.0439, 0.0222, 0.0174	0.977, 0.0937, 0.0231, 0.0179
cML-AIC-Profile	0.986, -0.0950, 0.0210, 0.0163	0.738, -0.0451, 0.0209, 0.0167	0.412, -0.0261, 0.0200, 0.0168	0.103, -0.0086, 0.0186, 0.0169	0.068, -0.0005, 0.0183, 0.017	0.106, 0.0075, 0.0187, 0.0171	0.368, 0.0250, 0.0204, 0.0173	0.698, 0.0439, 0.0222, 0.0175	0.977, 0.0937, 0.0231, 0.018
cML-MA-BIC	1.000, -0.1001, 0.0152, 0.0151	0.894, -0.0501, 0.0155, 0.0154	0.516, -0.0301, 0.0156, 0.0155	0.097, -0.0101, 0.0157, 0.0157	0.055, -0.0001, 0.0158, 0.0158	0.101, 0.0098, 0.0159, 0.0158	0.466, 0.0298, 0.0161, 0.016	0.861, 0.0498, 0.0163, 0.0162	1.000, 0.0998, 0.0168, 0.0166
cML-MA-BIC-Profile	1.000, -0.1001, 0.0152, 0.0152	0.894, -0.0501, 0.0155, 0.0154	0.515, -0.0301, 0.0156, 0.0156	0.097, -0.0101, 0.0157, 0.0157	0.055, -0.0001, 0.0158, 0.0158	0.100, 0.0098, 0.0159, 0.0159	0.466, 0.0298, 0.0161, 0.016	0.861, 0.0498, 0.0163, 0.0162	1.000, 0.0998, 0.0168, 0.0167
cML-BIC	1.000, -0.1002, 0.0152, 0.015	0.899, -0.0502, 0.0155, 0.0153	0.525, -0.0302, 0.0157, 0.0154	0.102, -0.0102, 0.0158, 0.0156	0.057, -0.0002, 0.0159, 0.0156	0.103, 0.0099, 0.0160, 0.0157	0.473, 0.0298, 0.0162, 0.0159	0.863, 0.0499, 0.0164, 0.0161	1.000, 0.0999, 0.0168, 0.0165
cML-BIC-Profile	1.000, -0.1002, 0.0152, 0.015	0.899, -0.0502, 0.0155, 0.0153	0.524, -0.0302, 0.0157, 0.0154	0.102, -0.0102, 0.0158, 0.0156	0.057, -0.0002, 0.0159, 0.0157	0.102, 0.0099, 0.0160, 0.0157	0.473, 0.0298, 0.0162, 0.0159	0.863, 0.0499, 0.0164, 0.0161	1.000, 0.0999, 0.0168, 0.0165
MR-Mix	0.995, -0.1042, 0.0170, 0.0196	0.785, -0.0512, 0.0168, 0.0196	0.348, -0.0305, 0.0168, 0.0196	0.061, -0.0102, 0.0169, 0.0194	0.033, -0.0002, 0.0169, 0.0193	0.061, 0.0098, 0.0169, 0.0193	0.337, 0.0294, 0.0169, 0.0192	0.725, 0.0486, 0.0170, 0.0192	0.998, 0.0948, 0.0171, 0.0193
MR-ContMix	1.000, -0.1001, 0.0157, NA	0.899, -0.0501, 0.0159, NA	0.547, -0.0301, 0.0161, NA	0.137, -0.0101, 0.0162, NA	0.081, -0.0001, 0.0163, NA	0.121, 0.0099, 0.0164, NA	0.515, 0.0299, 0.0165, NA	0.878, 0.0498, 0.0167, NA	1.000, 0.0998, 0.0173, NA
MR-Lasso	1.000, -0.1002, 0.0158, 0.0164	0.850, -0.0501, 0.0159, 0.0168	0.454, -0.0302, 0.0160, 0.0169	0.092, -0.0102, 0.0161, 0.0171	0.052, -0.0002, 0.0163, 0.0172	0.082, 0.0098, 0.0163, 0.0173	0.409, 0.0298, 0.0165, 0.0175	0.815, 0.0498, 0.0167, 0.0176	0.999, 0.0997, 0.0171, 0.0181
MR-PRESSO	0.356, -0.1064, 0.3365, 0.226	0.286, -0.0563, 0.3362, 0.2244	0.195, -0.0364, 0.3362, 0.2241	0.120, -0.0161, 0.3361, 0.2229	0.107, -0.0062, 0.3360, 0.2225	0.110, 0.0039, 0.3360, 0.2226	0.172, 0.0241, 0.3359, 0.222	0.254, 0.0442, 0.3359, 0.2217	0.350, 0.0944, 0.3356, 0.2197
MR-IVW	0.103, -0.1078, 0.3387, 0.3312	0.106, -0.0575, 0.3386, 0.3311	0.106, -0.0373, 0.3385, 0.3311	0.108, -0.0172, 0.3385, 0.3311	0.108, -0.0071, 0.3385, 0.3311	0.108, 0.0029, 0.3384, 0.3311	0.108, 0.0230, 0.3384, 0.3311	0.101, 0.0432, 0.3384, 0.3311	0.095, 0.0934, 0.3383, 0.331
MR-IVW-Oracle	1.000, -0.1000, 0.0151, 0.0165	0.851, -0.0501, 0.0154, 0.0168	0.447, -0.0301, 0.0156, 0.0169	0.084, -0.0101, 0.0157, 0.0171	0.048, -0.0001, 0.0158, 0.0172	0.078, 0.0099, 0.0158, 0.0172	0.411, 0.0299, 0.0160, 0.0174	0.820, 0.0499, 0.0162, 0.0176	1.000, 0.0999, 0.0166, 0.0181
MR-Egger	0.088, -0.1355, 1.9662, 1.8909	0.088, -0.0867, 1.9654, 1.8908	0.087, -0.0672, 1.9651, 1.8907	0.085, -0.0476, 1.9648, 1.8907	0.084, -0.0379, 1.9646, 1.8906	0.083, -0.0281, 1.9644, 1.8906	0.086, -0.0086, 1.9641, 1.8905	0.087, 0.0109, 1.9638, 1.8905	0.089, 0.0597, 1.9630, 1.8904
MR-Weighted-Median	0.999, -0.0996, 0.0187, 0.0192	0.759, -0.0501, 0.0190, 0.0195	0.337, -0.0303, 0.0192, 0.0197	0.070, -0.0105, 0.0194, 0.0199	0.045, -0.0007, 0.0195, 0.02	0.070, 0.0092, 0.0196, 0.0201	0.294, 0.0290, 0.0198, 0.0203	0.672, 0.0487, 0.0200, 0.0205	0.990, 0.0981, 0.0206, 0.0211
MR-Weighted-Mode	1.000, -0.0998, 0.0165, 0.0167	0.822, -0.0500, 0.0168, 0.017	0.423, -0.0300, 0.0171, 0.0171	0.084, -0.0101, 0.0171, 0.0173	0.058, -0.0001, 0.0172, 0.0174	0.090, 0.0098, 0.0173, 0.0175	0.388, 0.0297, 0.0174, 0.0176	0.799, 0.0496, 0.0176, 0.0178	1.000, 0.0995, 0.0182, 0.0183
MR-RAPS1	0.105, -0.1065, 0.3270, 0.3145	0.116, -0.0565, 0.3270, 0.3145	0.116, -0.0365, 0.3270, 0.3145	0.116, -0.0164, 0.3270, 0.3145	0.117, -0.0064, 0.3270, 0.3145	0.117, 0.0036, 0.3270, 0.3145	0.112, 0.0236, 0.3270, 0.3145	0.106, 0.0436, 0.3270, 0.3145	0.100, 0.0936, 0.3271, 0.3145
MR-RAPS2	0.069, -0.1094, 0.2086, 0.1913	0.038, -0.0573, 0.2082, 0.193	0.036, -0.0387, 0.2110, 0.1936	0.035, -0.0184, 0.2088, 0.1954	0.035, -0.0093, 0.2095, 0.1972	0.035, -0.0001, 0.2102, 0.1985	0.036, 0.0206, 0.2158, 0.202	0.039, 0.0407, 0.2213, 0.2035	0.060, 0.0914, 0.2214, 0.1992
MR-RAPS3	0.959, -2.1700, 46.0090, 67.0966	0.933, -0.2074, 39.5875, 69.0319	0.921, 0.1424, 7.9004, 4.7066	0.921, 1.3643, 48.5633, 443.2405	0.925, 0.6899, 30.4514, 80.3419	0.927, 0.4231, 10.0749, 6.9016	0.945, -0.0315, 10.7542, 7.7096	0.936, 0.1685, 5.9607, 2.5978	0.947, 0.3789, 3.6643, 0.6306
MR-RAPS4	1.000, -0.0757, 0.1110, 0.012	0.957, -0.0192, 0.1537, 0.0123	0.720, 0.0050, 0.1726, 0.0125	0.309, 0.0384, 0.2149, 0.0149	0.276, 0.0538, 0.2296, 0.0137	0.321, 0.0572, 0.2080, 0.0133	0.671, 0.0539, 0.1540, 0.0129	0.940, 0.0684, 0.1307, 0.0129	1.000, 0.1080, 0.0930, 0.0131

Table S35: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean( $SE(\hat{\theta})$ ) when  $m = 10$ , the InSIDE satisfied,  $q = 0.6$ , and  $N = 50000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	0.438, -0.0821, 0.0416, 0.0468	0.100, -0.0375, 0.0373, 0.0468	0.044, -0.0219, 0.0348, 0.0469	0.013, -0.0078, 0.0334, 0.0472	0.012, -0.0006, 0.0335, 0.0473	0.014, 0.0064, 0.0336, 0.0475	0.026, 0.0206, 0.0352, 0.0482	0.078, 0.0360, 0.0382, 0.0491	0.364, 0.0806, 0.0440, 0.0511
cML-MA-AIC-Profile	0.433, -0.0820, 0.0417, 0.0472	0.098, -0.0374, 0.0374, 0.0472	0.043, -0.0219, 0.0351, 0.0473	0.013, -0.0078, 0.0336, 0.0476	0.012, -0.0005, 0.0337, 0.0477	0.012, 0.0065, 0.0338, 0.048	0.025, 0.0207, 0.0354, 0.0487	0.077, 0.0361, 0.0385, 0.0495	0.361, 0.0809, 0.0446, 0.0517
cML-AIC	0.621, -0.0881, 0.0479, 0.0401	0.229, -0.0422, 0.0445, 0.0407	0.119, -0.0251, 0.0419, 0.0409	0.056, -0.0095, 0.0416, 0.0413	0.039, -0.0010, 0.0419, 0.0415	0.042, 0.0073, 0.0422, 0.0418	0.098, 0.0233, 0.0435, 0.0423	0.202, 0.0400, 0.0459, 0.0427	0.553, 0.0867, 0.0499, 0.0439
cML-AIC-Profile	0.617, -0.0881, 0.0479, 0.0403	0.227, -0.0422, 0.0445, 0.0409	0.116, -0.0252, 0.0428, 0.0412	0.056, -0.0095, 0.0416, 0.0416	0.038, -0.0010, 0.0419, 0.0418	0.042, 0.0073, 0.0422, 0.0421	0.096, 0.0233, 0.0435, 0.0426	0.200, 0.0400, 0.0459, 0.043	0.550, 0.0869, 0.0502, 0.0442
cML-MA-BIC	0.757, -0.0979, 0.0633, 0.0378	0.254, -0.0480, 0.0638, 0.0385	0.122, -0.0297, 0.0373, 0.0387	0.051, -0.0098, 0.0375, 0.0391	0.041, 0.0001, 0.0377, 0.0393	0.041, 0.0100, 0.0379, 0.0395	0.111, 0.0286, 0.0566, 0.0403	0.249, 0.0497, 0.0390, 0.0403	0.686, 0.0997, 0.0403, 0.0414
cML-MA-BIC-Profile	0.754, -0.0995, 0.1219, 0.0411	0.255, -0.0488, 0.1231, 0.0416	0.124, -0.0276, 0.1272, 0.0426	0.056, -0.0060, 0.1212, 0.0429	0.044, 0.0042, 0.1225, 0.043	0.046, 0.0143, 0.1232, 0.0432	0.111, 0.0346, 0.1246, 0.0435	0.248, 0.0549, 0.1260, 0.044	0.680, 0.1060, 0.1298, 0.0455
cML-BIC	0.774, -0.0985, 0.0642, 0.0372	0.258, -0.0484, 0.0646, 0.0379	0.126, -0.0300, 0.0377, 0.0382	0.058, -0.0099, 0.0381, 0.0385	0.044, 0.0001, 0.0382, 0.0387	0.049, 0.0101, 0.0385, 0.0389	0.120, 0.0286, 0.0644, 0.0393	0.262, 0.0500, 0.0395, 0.0397	0.696, 0.1002, 0.0406, 0.0409
cML-BIC-Profile	0.773, -0.0996, 0.1275, 0.0375	0.262, -0.0482, 0.1351, 0.0381	0.131, -0.0266, 0.1437, 0.0385	0.065, -0.0052, 0.1371, 0.0388	0.050, 0.0049, 0.1371, 0.039	0.056, 0.0149, 0.1372, 0.0392	0.123, 0.0349, 0.1372, 0.0396	0.265, 0.0548, 0.1374, 0.04	0.693, 0.1067, 0.1480, 0.0412
MR-Mix	0.707, -0.1028, 0.0389, 0.043	0.218, -0.0503, 0.0387, 0.044	0.099, -0.0300, 0.0384, 0.0424	0.043, -0.0099, 0.0385, 0.0423	0.035, -0.0001, 0.0385, 0.0423	0.039, 0.0097, 0.0385, 0.0422	0.087, 0.0289, 0.0384, 0.0422	0.218, 0.0479, 0.0387, 0.0424	0.625, 0.0936, 0.0391, 0.0429
MR-ContMix	0.786, -0.0998, 0.0382, NA	0.291, -0.0499, 0.0387, NA	0.152, -0.0298, 0.0389, NA	0.069, -0.0099, 0.0395, NA	0.060, 0.0001, 0.0397, NA	0.072, 0.0102, 0.0401, NA	0.148, 0.0299, 0.0403, NA	0.278, 0.0499, 0.0409, NA	0.713, 0.0996, 0.0423, NA
MR-Lasso	0.703, -0.0857, 0.4348, 0.0723	0.302, -0.0358, 0.4330, 0.0738	0.203, -0.0166, 0.4338, 0.0744	0.154, 0.0044, 0.4358, 0.0741	0.146, 0.0146, 0.4363, 0.0743	0.151, 0.0242, 0.4356, 0.0744	0.200, 0.0450, 0.4353, 0.0749	0.296, 0.0636, 0.4374, 0.0754	0.631, 0.1136, 0.4372, 0.0768
MR-PRESSO	0.226, -0.0997, 0.4016, 0.2312	0.136, -0.0508, 0.4012, 0.2291	0.115, -0.0310, 0.4008, 0.2277	0.101, -0.0114, 0.4007, 0.2275	0.092, -0.0018, 0.4005, 0.2262	0.091, 0.0082, 0.4003, 0.2254	0.105, 0.0276, 0.3999, 0.2245	0.131, 0.0473, 0.3995, 0.2228	0.220, 0.0967, 0.3991, 0.2216
MR-IVW	0.088, -0.1052, 0.4102, 0.4031	0.083, -0.0548, 0.4102, 0.4031	0.083, -0.0347, 0.4102, 0.4031	0.084, -0.0145, 0.4101, 0.4031	0.084, -0.0045, 0.4101, 0.4031	0.087, 0.0056, 0.4101, 0.4031	0.090, 0.0257, 0.4101, 0.4031	0.091, 0.0459, 0.4101, 0.4031	0.093, 0.0961, 0.4100, 0.4031
MR-IVW-Oracle	0.688, -0.0997, 0.0362, 0.0414	0.220, -0.0498, 0.0369, 0.0422	0.102, -0.0298, 0.0373, 0.0426	0.045, -0.0099, 0.0376, 0.043	0.032, 0.0001, 0.0378, 0.0432	0.036, 0.0101, 0.0380, 0.0434	0.091, 0.0300, 0.0384, 0.0438	0.205, 0.0500, 0.0389, 0.0443	0.607, 0.0998, 0.0401, 0.0455
MR-Egger	0.098, -0.0259, 2.2979, 2.164	0.098, 0.0183, 2.2978, 2.164	0.097, 0.0359, 2.2978, 2.164	0.096, 0.0536, 2.2977, 2.164	0.097, 0.0624, 2.2977, 2.164	0.098, 0.0712, 2.2977, 2.164	0.099, 0.0888, 2.2977, 2.164	0.099, 0.1065, 2.2977, 2.164	0.099, 0.1505, 2.2977, 2.164
MR-Weighted-Median	0.575, -0.0933, 0.0590, 0.0462	0.191, -0.0467, 0.0605, 0.047	0.093, -0.0281, 0.0619, 0.0474	0.055, -0.0094, 0.0635, 0.0478	0.049, -0.0001, 0.0645, 0.0481	0.051, 0.0094, 0.0655, 0.0483	0.089, 0.0278, 0.0681, 0.0489	0.168, 0.0461, 0.0709, 0.0494	0.493, 0.0919, 0.0792, 0.0511
MR-Weighted-Mode	0.542, -0.0841, 0.1044, 0.0469	0.351, -0.0419, 0.1062, 0.0477	0.306, -0.0254, 0.1078, 0.0482	0.291, -0.0083, 0.1087, 0.0487	0.282, 0.0001, 0.1099, 0.049	0.298, 0.0088, 0.1106, 0.0494	0.321, 0.0254, 0.1125, 0.0501	0.363, 0.0422, 0.1142, 0.0508	0.508, 0.0836, 0.1206, 0.053
MR-RAPS1	0.096, -0.1058, 0.4038, 0.3858	0.099, -0.0557, 0.4038, 0.3859	0.099, -0.0356, 0.4038, 0.3859	0.098, -0.0156, 0.4038, 0.3859	0.099, -0.0056, 0.4039, 0.3859	0.100, 0.0044, 0.4039, 0.3859	0.101, 0.0245, 0.4039, 0.3859	0.102, 0.0445, 0.4039, 0.386	0.112, 0.0946, 0.4040, 0.386
MR-RAPS2	0.105, -0.1042, 0.4391, 0.4183	0.103, -0.0558, 0.4367, 0.4189	0.111, -0.0349, 0.4374, 0.4177	0.112, -0.0165, 0.4373, 0.4186	0.110, -0.0048, 0.4382, 0.419	0.111, 0.0055, 0.4370, 0.419	0.111, 0.0259, 0.4399, 0.4189	0.111, 0.0454, 0.4368, 0.4191	0.123, 0.0965, 0.4469, 0.4183
MR-RAPS3	0.884, 63.3358, 2058.7795, 128300	0.875, -4.0102, 151.7719, 794.4	0.866, 4.2910, 146.2623, 1424	0.874, 1.5637, 43.2247, 75.2	0.882, 0.8245, 26.2799, 33.74	0.885, -2.7847, 109.0332, 475.1	0.886, -4.4656, 86.2928, 335.6	0.886, 0.4654, 12.9018, 7.783	0.896, 0.3751, 36.3773, 60.93
MR-RAPS4	0.988, 0.3407, 1.5671, 0.1651	0.988, 0.2469, 1.6003, 0.2481	0.980, 0.2280, 1.6874, 0.1746	0.983, 0.1159, 1.7280, 0.2294	0.976, 0.0777, 1.8078, 0.1743	0.978, 0.0733, 1.7938, 0.1889	0.982, -0.0743, 1.7813, 0.335	0.981, -0.1083, 1.7991, 0.1873	0.975, -0.4070, 1.8125, 0.2485



Table S36: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean( $SE(\hat{\theta})$ ) when  $m = 10$ , the InSIDE satisfied,  $q = 0.6$ , and  $N = 100000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	0.725, -0.0854, 0.0307, 0.0333	0.197, -0.0374, 0.0279, 0.0336	0.062, -0.0208, 0.0256, 0.0336	0.011, -0.0061, 0.0239, 0.0336	0.012, 0.0007, 0.0244, 0.0341	0.020, 0.0074, 0.0249, 0.0342	0.070, 0.0216, 0.0276, 0.0347	0.187, 0.0382, 0.0301, 0.0354	0.677, 0.0860, 0.0333, 0.0366
cML-MA-AIC-Profile	0.723, -0.0857, 0.0317, 0.034	0.197, -0.0376, 0.0287, 0.0343	0.062, -0.0209, 0.0263, 0.0344	0.010, -0.0062, 0.0246, 0.0343	0.011, 0.0009, 0.0247, 0.0344	0.020, 0.0075, 0.0252, 0.0345	0.070, 0.0217, 0.0280, 0.0351	0.187, 0.0384, 0.0306, 0.0358	0.676, 0.0863, 0.0340, 0.037
cML-AIC	0.825, -0.0896, 0.0345, 0.0283	0.372, -0.0409, 0.0326, 0.0289	0.165, -0.0230, 0.0313, 0.0292	0.060, -0.0071, 0.0302, 0.0294	0.046, 0.0012, 0.0303, 0.0295	0.072, 0.0090, 0.0307, 0.0296	0.168, 0.0244, 0.0330, 0.0298	0.338, 0.0425, 0.0348, 0.0302	0.811, 0.0912, 0.0372, 0.0311
cML-AIC-Profile	0.825, -0.0896, 0.0345, 0.0284	0.368, -0.0409, 0.0326, 0.029	0.165, -0.0231, 0.0314, 0.0293	0.060, -0.0071, 0.0302, 0.0295	0.046, 0.0012, 0.0303, 0.0296	0.072, 0.0090, 0.0307, 0.0297	0.166, 0.0244, 0.0330, 0.0299	0.336, 0.0425, 0.0349, 0.0303	0.810, 0.0912, 0.0372, 0.0312
cML-MA-BIC	0.959, -0.0994, 0.0263, 0.0266	0.468, -0.0495, 0.0268, 0.027	0.191, -0.0296, 0.0270, 0.0273	0.064, -0.0097, 0.0272, 0.0276	0.048, -0.0013, 0.0535, 0.0277	0.073, 0.0087, 0.0536, 0.0278	0.197, 0.0285, 0.0538, 0.0281	0.415, 0.0484, 0.0540, 0.0284	0.936, 0.0984, 0.0546, 0.0292
cML-MA-BIC-Profile	0.958, -0.1011, 0.1011, 0.0276	0.465, -0.0494, 0.0861, 0.0279	0.193, -0.0294, 0.0860, 0.0282	0.064, -0.0094, 0.0860, 0.0285	0.049, 0.0006, 0.0860, 0.0287	0.074, 0.0106, 0.0861, 0.0288	0.196, 0.0306, 0.0866, 0.0292	0.409, 0.0507, 0.0873, 0.0296	0.932, 0.1012, 0.0910, 0.0305
cML-BIC	0.960, -0.0997, 0.0263, 0.0263	0.477, -0.0498, 0.0269, 0.0268	0.199, -0.0298, 0.0271, 0.027	0.068, -0.0098, 0.0274, 0.0273	0.049, -0.0013, 0.0537, 0.0274	0.076, 0.0087, 0.0537, 0.0275	0.202, 0.0286, 0.0539, 0.0278	0.427, 0.0486, 0.0541, 0.0281	0.939, 0.0986, 0.0546, 0.0289
cML-BIC-Profile	0.961, -0.1008, 0.1006, 0.0264	0.475, -0.0492, 0.0846, 0.0269	0.200, -0.0292, 0.0848, 0.0271	0.070, -0.0092, 0.0849, 0.0274	0.050, 0.0008, 0.0850, 0.0275	0.077, 0.0108, 0.0850, 0.0276	0.203, 0.0308, 0.0852, 0.0279	0.425, 0.0507, 0.0853, 0.0282	0.938, 0.1025, 0.1028, 0.029
MR-Mix	0.930, -0.1028, 0.0279, 0.0299	0.419, -0.0502, 0.0279, 0.0297	0.160, -0.0298, 0.0279, 0.0298	0.053, -0.0097, 0.0279, 0.0298	0.046, 0.0002, 0.0280, 0.0298	0.061, 0.0099, 0.0280, 0.0299	0.162, 0.0291, 0.0280, 0.03	0.357, 0.0480, 0.0281, 0.0299	0.893, 0.0940, 0.0284, 0.0301
MR-ContMix	0.958, -0.0992, 0.0270, NA	0.525, -0.0494, 0.0274, NA	0.236, -0.0296, 0.0279, NA	0.094, -0.0097, 0.0284, NA	0.069, 0.0004, 0.0285, NA	0.094, 0.0103, 0.0286, NA	0.249, 0.0302, 0.0290, NA	0.467, 0.0502, 0.0294, NA	0.939, 0.1001, 0.0303, NA
MR-Lasso	0.901, -0.0983, 0.4216, 0.059	0.465, -0.0476, 0.4222, 0.0593	0.253, -0.0279, 0.4218, 0.0593	0.159, -0.0083, 0.4232, 0.0594	0.141, 0.0021, 0.4220, 0.0592	0.161, 0.0125, 0.4234, 0.0596	0.263, 0.0323, 0.4241, 0.0596	0.423, 0.0524, 0.4240, 0.06	0.880, 0.1026, 0.4253, 0.0605
MR-PRESSO	0.251, -0.0992, 0.3924, 0.2742	0.135, -0.0490, 0.3924, 0.2727	0.099, -0.0288, 0.3923, 0.2723	0.081, -0.0089, 0.3923, 0.2716	0.080, 0.0010, 0.3923, 0.2712	0.079, 0.0112, 0.3922, 0.2709	0.090, 0.0310, 0.3922, 0.2703	0.138, 0.0507, 0.3920, 0.2689	0.254, 0.0992, 0.3916, 0.2662
MR-IVW	0.087, -0.1006, 0.3958, 0.4046	0.080, -0.0501, 0.3958, 0.4046	0.079, -0.0299, 0.3958, 0.4046	0.077, -0.0098, 0.3958, 0.4046	0.077, 0.0003, 0.3958, 0.4046	0.077, 0.0104, 0.3958, 0.4046	0.075, 0.0305, 0.3958, 0.4046	0.080, 0.0507, 0.3957, 0.4045	0.089, 0.1010, 0.3957, 0.4045
MR-IVW-Oracle	0.919, -0.0995, 0.0262, 0.0292	0.406, -0.0496, 0.0268, 0.0298	0.162, -0.0297, 0.0270, 0.03	0.055, -0.0097, 0.0273, 0.0303	0.039, 0.0003, 0.0274, 0.0304	0.057, 0.0102, 0.0276, 0.0306	0.166, 0.0302, 0.0279, 0.0309	0.361, 0.0501, 0.0282, 0.0312	0.885, 0.1000, 0.0291, 0.032
MR-Egger	0.088, -0.0091, 2.3970, 2.2796	0.086, 0.0379, 2.3968, 2.2795	0.086, 0.0567, 2.3967, 2.2794	0.086, 0.0755, 2.3966, 2.2794	0.085, 0.0849, 2.3966, 2.2794	0.086, 0.0943, 2.3965, 2.2794	0.087, 0.1130, 2.3964, 2.2793	0.088, 0.1318, 2.3964, 2.2793	0.090, 0.1787, 2.3962, 2.2793
MR-Weighted-Median	0.822, -0.0956, 0.0335, 0.0327	0.339, -0.0476, 0.0343, 0.0332	0.151, -0.0283, 0.0347, 0.0335	0.057, -0.0091, 0.0352, 0.0338	0.045, 0.0003, 0.0355, 0.0339	0.065, 0.0100, 0.0359, 0.0341	0.162, 0.0291, 0.0367, 0.0345	0.312, 0.0483, 0.0377, 0.0349	0.777, 0.0956, 0.0425, 0.0361
MR-Weighted-Mode	0.670, -0.0826, 0.0899, 0.0335	0.459, -0.0392, 0.0909, 0.0341	0.417, -0.0225, 0.0921, 0.0344	0.392, -0.0053, 0.0935, 0.0348	0.392, 0.0033, 0.0944, 0.035	0.386, 0.0118, 0.0950, 0.0352	0.458, 0.0290, 0.0968, 0.0357	0.514, 0.0461, 0.0988, 0.0362	0.673, 0.0884, 0.1051, 0.0377
MR-RAPS1	0.091, -0.0999, 0.3860, 0.3857	0.080, -0.0499, 0.3860, 0.3857	0.078, -0.0299, 0.3860, 0.3858	0.076, -0.0099, 0.3861, 0.3858	0.077, 0.0001, 0.3861, 0.3858	0.078, 0.0101, 0.3861, 0.3858	0.083, 0.0301, 0.3861, 0.3858	0.093, 0.0501, 0.3862, 0.3858	0.097, 0.1002, 0.3862, 0.3858
MR-RAPS2	0.135, -0.1038, 0.5051, 0.4046	0.121, -0.0380, 0.4751, 0.408	0.116, -0.0207, 0.4889, 0.4078	0.131, -0.0120, 0.4854, 0.4057	0.128, 0.0058, 0.4772, 0.4081	0.127, 0.0138, 0.4746, 0.4076	0.131, 0.0278, 0.4822, 0.4094	0.128, 0.0490, 0.4713, 0.4106	0.135, 0.0976, 0.4618, 0.4109
MR-RAPS3	0.923, 0.8567, 30.6220, 30.4642	0.907, -6.2997, 193.5672, 1076.2517	0.908, 4.0412, 104.8374, 348.2075	0.905, 1.2127, 130.9044, 593.1527	0.902, -1.5129, 46.1664, 73.9518	0.903, 0.0637, 41.6720, 51.7658	0.910, -1.9248, 71.7011, 140.9863	0.906, -2.4762, 61.1978, 144.338	0.916, 0.6197, 56.7985, 162.8748
MR-RAPS4	0.997, 0.6986, 1.5290, 0.1044	0.994, 0.5614, 1.7044, 0.1188	0.992, 0.4942, 1.7518, 0.1268	0.986, 0.4093, 1.7620, 0.1576	0.989, 0.3672, 1.7635, 0.146	0.986, 0.3656, 1.7845, 0.1926	0.983, 0.1688, 1.8126, 0.228	0.983, 0.1251, 1.8405, 0.2136	0.987, -0.0863, 1.8639, 0.147

Table S37: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean(SE( $\hat{\theta}$ )) when  $m = 10$ , the InSIDE satisfied,  $q = 0.6$ , and  $N = 200000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	0.949, -0.0915, 0.0225, 0.0235	0.434, -0.0417, 0.0221, 0.0238	0.156, -0.0233, 0.0203, 0.0238	0.025, -0.0076, 0.0180, 0.0237	0.019, -0.0007, 0.0177, 0.0238	0.024, 0.0062, 0.0180, 0.0239	0.137, 0.0216, 0.0203, 0.0246	0.366, 0.0395, 0.0224, 0.0251	0.904, 0.0882, 0.0249, 0.0259
cML-MA-AIC-Profile	0.949, -0.0916, 0.0226, 0.0235	0.433, -0.0417, 0.0221, 0.0238	0.155, -0.0233, 0.0203, 0.0239	0.025, -0.0076, 0.0180, 0.0237	0.018, -0.0007, 0.0177, 0.0238	0.024, 0.0062, 0.0180, 0.0239	0.136, 0.0216, 0.0203, 0.0246	0.366, 0.0395, 0.0224, 0.0251	0.904, 0.0882, 0.0249, 0.0259
cML-AIC	0.960, -0.0942, 0.0254, 0.0201	0.617, -0.0446, 0.0251, 0.0204	0.306, -0.0256, 0.0239, 0.0206	0.083, -0.0085, 0.0222, 0.0206	0.057, -0.0008, 0.0220, 0.0208	0.076, 0.0067, 0.0224, 0.021	0.266, 0.0238, 0.0241, 0.0212	0.539, 0.0423, 0.0256, 0.0215	0.924, 0.0912, 0.0280, 0.0221
cML-AIC-Profile	0.960, -0.0943, 0.0255, 0.0201	0.617, -0.0446, 0.0251, 0.0204	0.305, -0.0256, 0.0239, 0.0206	0.082, -0.0085, 0.0222, 0.0207	0.057, -0.0008, 0.0220, 0.0209	0.076, 0.0067, 0.0224, 0.021	0.266, 0.0238, 0.0241, 0.0213	0.538, 0.0423, 0.0256, 0.0215	0.924, 0.0912, 0.0280, 0.0221
cML-MA-BIC	0.999, -0.1009, 0.0194, 0.0188	0.762, -0.0508, 0.0197, 0.0191	0.372, -0.0308, 0.0198, 0.0193	0.086, -0.0108, 0.0199, 0.0194	0.056, -0.0009, 0.0199, 0.0195	0.085, 0.0091, 0.0200, 0.0196	0.326, 0.0290, 0.0203, 0.0198	0.670, 0.0490, 0.0205, 0.02	0.992, 0.0991, 0.0210, 0.0206
cML-MA-BIC-Profile	0.999, -0.1009, 0.0194, 0.0188	0.762, -0.0508, 0.0197, 0.0191	0.369, -0.0308, 0.0198, 0.0193	0.085, -0.0108, 0.0199, 0.0195	0.056, -0.0009, 0.0199, 0.0195	0.085, 0.0091, 0.0200, 0.0196	0.326, 0.0290, 0.0203, 0.0198	0.669, 0.0490, 0.0205, 0.02	0.992, 0.0991, 0.0210, 0.0206
cML-BIC	1.000, -0.1010, 0.0194, 0.0187	0.767, -0.0509, 0.0196, 0.019	0.375, -0.0309, 0.0198, 0.0191	0.089, -0.0109, 0.0199, 0.0193	0.058, -0.0009, 0.0200, 0.0194	0.088, 0.0091, 0.0201, 0.0195	0.331, 0.0292, 0.0203, 0.0197	0.678, 0.0492, 0.0205, 0.0199	0.993, 0.0993, 0.0210, 0.0205
cML-BIC-Profile	1.000, -0.1010, 0.0194, 0.0187	0.767, -0.0509, 0.0196, 0.019	0.374, -0.0309, 0.0198, 0.0192	0.088, -0.0109, 0.0199, 0.0193	0.058, -0.0009, 0.0200, 0.0194	0.088, 0.0091, 0.0201, 0.0195	0.331, 0.0292, 0.0203, 0.0197	0.677, 0.0492, 0.0205, 0.0199	0.993, 0.0993, 0.0210, 0.0205
MR-Mix	0.997, -0.1042, 0.0205, 0.0214	0.705, -0.0516, 0.0206, 0.0212	0.318, -0.0310, 0.0207, 0.0212	0.069, -0.0108, 0.0207, 0.0212	0.048, -0.0009, 0.0207, 0.0212	0.069, 0.0089, 0.0208, 0.0212	0.282, 0.0283, 0.0206, 0.0212	0.601, 0.0472, 0.0205, 0.0213	0.985, 0.0930, 0.0207, 0.0214
MR-ContMix	0.999, -0.1009, 0.0197, NA	0.791, -0.0509, 0.0200, NA	0.423, -0.0309, 0.0201, NA	0.117, -0.0109, 0.0203, NA	0.085, -0.0009, 0.0204, NA	0.115, 0.0091, 0.0205, NA	0.388, 0.0291, 0.0206, NA	0.709, 0.0491, 0.0209, NA	0.992, 0.0991, 0.0214, NA
MR-Lasso	0.963, -0.0991, 0.4737, 0.0564	0.708, -0.0476, 0.4753, 0.0561	0.395, -0.0285, 0.4741, 0.0561	0.208, -0.0080, 0.4744, 0.056	0.181, 0.0024, 0.4747, 0.0563	0.201, 0.0131, 0.4752, 0.0564	0.367, 0.0337, 0.4750, 0.057	0.649, 0.0539, 0.4753, 0.0571	0.955, 1.056, 0.4766, 0.058
MR-PRESSO	0.227, -0.1135, 0.4187, 0.3124	0.129, -0.0627, 0.4185, 0.3112	0.097, -0.0425, 0.4185, 0.3109	0.067, -0.0226, 0.4184, 0.3106	0.068, -0.0125, 0.4184, 0.3106	0.069, -0.0025, 0.4184, 0.3103	0.085, 0.0176, 0.4183, 0.3103	0.131, 0.0377, 0.4183, 0.3103	0.222, 0.0881, 0.4181, 0.3076
MR-IVW	0.089, -0.1143, 0.4198, 0.4009	0.088, -0.0638, 0.4197, 0.4009	0.089, -0.0436, 0.4196, 0.4009	0.095, -0.0234, 0.4196, 0.4008	0.100, -0.0133, 0.4196, 0.4008	0.099, -0.0032, 0.4196, 0.4008	0.096, 0.0170, 0.4195, 0.4008	0.097, 0.0372, 0.4195, 0.4008	0.105, 0.0876, 0.4194, 0.4008
MR-IVW-Oracle	0.996, -0.1008, 0.0193, 0.0207	0.688, -0.0508, 0.0196, 0.0211	0.306, -0.0308, 0.0198, 0.0213	0.073, -0.0108, 0.0199, 0.0215	0.045, -0.0008, 0.0200, 0.0216	0.068, 0.0092, 0.0201, 0.0217	0.267, 0.0292, 0.0203, 0.0219	0.607, 0.0492, 0.0205, 0.0222	0.986, 0.0992, 0.0210, 0.0228
MR-Egger	0.079, -0.1149, 2.3920, 2.295	0.079, -0.0662, 2.3914, 2.295	0.079, -0.0468, 2.3912, 2.295	0.079, -0.0273, 2.3910, 2.295	0.079, -0.0176, 2.3908, 2.295	0.080, -0.0078, 2.3907, 2.295	0.080, 0.0116, 2.3905, 2.295	0.080, 0.0310, 2.3903, 2.295	0.081, 0.0796, 2.3898, 2.295
MR-Weighted-Median	0.969, -0.0985, 0.0258, 0.0233	0.591, -0.0499, 0.0265, 0.0236	0.285, -0.0305, 0.0270, 0.0238	0.076, -0.0112, 0.0278, 0.0241	0.065, -0.0015, 0.0282, 0.0242	0.086, 0.0082, 0.0287, 0.0243	0.239, 0.0275, 0.0298, 0.0247	0.523, 0.0469, 0.0312, 0.0251	0.937, 0.0948, 0.0352, 0.0263
MR-Weighted-Mode	0.786, -0.0894, 0.0842, 0.0241	0.599, -0.0465, 0.0856, 0.0246	0.550, -0.0287, 0.0865, 0.0248	0.535, -0.0119, 0.0878, 0.0251	0.527, -0.0030, 0.0882, 0.0252	0.519, 0.0057, 0.0891, 0.0254	0.550, 0.0229, 0.0908, 0.0258	0.586, 0.0404, 0.0926, 0.0261	0.722, 0.0817, 0.0985, 0.0272
MR-RAPS1	0.108, -0.1113, 0.4084, 0.3813	0.106, -0.0612, 0.4084, 0.3813	0.104, -0.0412, 0.4084, 0.3814	0.098, -0.0212, 0.4084, 0.3814	0.097, -0.0112, 0.4084, 0.3814	0.100, -0.0012, 0.4084, 0.3814	0.100, 0.0188, 0.4084, 0.3814	0.106, 0.0388, 0.4084, 0.3814	0.113, 0.0888, 0.4083, 0.3814
MR-RAPS2	0.275, -0.1105, 0.6861, 0.2873	0.245, -0.0540, 0.6572, 0.2963	0.237, -0.0308, 0.6357, 0.3002	0.244, -0.0168, 0.6418, 0.3003	0.224, 0.0039, 0.6283, 0.3083	0.236, 0.0008, 0.6400, 0.3106	0.228, 0.0170, 0.6296, 0.3108	0.224, 0.0563, 0.6160, 0.3171	0.228, 0.0987, 0.5859, 0.331
MR-RAPS3	0.943, -1.4311, 34.1674, 27.9	0.943, -0.0468, 32.6704, 22.82	0.941, 27.5745, 921.1527, 16430	0.929, -0.4064, 32.4517, 25.7	0.934, 3.4743, 138.5109, 321.6	0.937, -3.0060, 88.5082, 181.1	0.941, 3.5392, 70.1783, 119.4	0.948, 6.9374, 157.8841, 569.6	0.944, 4.2169, 73.4382, 161.5
MR-RAPS4	1.000, -0.1495, 0.4334, 0.015	0.993, 0.3332, 1.3073, 0.0453	0.976, 0.3997, 1.3479, 0.0858	0.960, 0.3748, 1.3709, 0.0988	0.985, 0.5552, 1.8731, 0.2677	0.947, 0.4655, 1.3436, 0.0952	0.974, 0.4762, 1.3067, 0.0649	0.985, 0.4427, 1.2900, 0.0777	1.000, 0.2559, 0.2574, 0.0147

Table S38: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean( $SE(\hat{\theta})$ ) when  $m = 10$ , the InSIDE violated,  $q = 0.2$ , and  $N = 50000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	0.712, -0.0846, 0.0303, 0.0339	0.189, -0.0379, 0.0273, 0.0334	0.055, -0.0214, 0.0254, 0.0331	0.012, -0.0065, 0.0238, 0.0331	0.009, 0.0005, 0.0236, 0.0332	0.018, 0.0076, 0.0240, 0.0334	0.058, 0.0220, 0.0256, 0.0342	0.150, 0.0380, 0.0281, 0.0352	0.644, 0.0839, 0.0325, 0.0374
cML-MA-AIC-Profile	0.711, -0.0848, 0.0304, 0.0341	0.188, -0.0380, 0.0274, 0.0336	0.053, -0.0214, 0.0254, 0.0333	0.012, -0.0065, 0.0238, 0.0333	0.009, 0.0005, 0.0236, 0.0334	0.018, 0.0076, 0.0240, 0.0336	0.057, 0.0220, 0.0256, 0.0344	0.149, 0.0380, 0.0281, 0.0354	0.640, 0.0840, 0.0326, 0.0376
cML-AIC	0.873, -0.0926, 0.0337, 0.0277	0.396, -0.0440, 0.0319, 0.0282	0.191, -0.0258, 0.0309, 0.0284	0.063, -0.0079, 0.0303, 0.0287	0.059, 0.0004, 0.0301, 0.0289	0.066, 0.0090, 0.0306, 0.029	0.163, 0.0256, 0.0315, 0.0293	0.349, 0.0436, 0.0331, 0.0296	0.830, 0.0917, 0.0363, 0.0305
cML-AIC-Profile	0.872, -0.0928, 0.0338, 0.0278	0.393, -0.0440, 0.0319, 0.0284	0.188, -0.0258, 0.0309, 0.0286	0.063, -0.0079, 0.0304, 0.0289	0.057, 0.0004, 0.0301, 0.0291	0.065, 0.0090, 0.0306, 0.0292	0.159, 0.0256, 0.0315, 0.0295	0.342, 0.0436, 0.0332, 0.0298	0.829, 0.0918, 0.0363, 0.0307
cML-MA-BIC	0.974, -0.0998, 0.0244, 0.026	0.499, -0.0497, 0.0249, 0.0264	0.185, -0.0297, 0.0250, 0.0267	0.046, -0.0098, 0.0252, 0.0269	0.036, 0.0002, 0.0253, 0.027	0.052, 0.0101, 0.0255, 0.0272	0.176, 0.0301, 0.0258, 0.0275	0.439, 0.0501, 0.0261, 0.0278	0.957, 0.1002, 0.0271, 0.0286
cML-MA-BIC-Profile	0.974, -0.0998, 0.0244, 0.0261	0.491, -0.0497, 0.0249, 0.0265	0.182, -0.0297, 0.0250, 0.0268	0.045, -0.0098, 0.0253, 0.027	0.034, 0.0002, 0.0253, 0.0271	0.050, 0.0101, 0.0255, 0.0273	0.175, 0.0301, 0.0258, 0.0276	0.432, 0.0501, 0.0261, 0.0279	0.956, 0.1002, 0.0271, 0.0287
cML-BIC	0.974, -0.1001, 0.0246, 0.0256	0.504, -0.0499, 0.0250, 0.0261	0.201, -0.0299, 0.0253, 0.0263	0.051, -0.0099, 0.0255, 0.0266	0.044, 0.0002, 0.0256, 0.0267	0.052, 0.0102, 0.0257, 0.0268	0.183, 0.0302, 0.0260, 0.0271	0.453, 0.0503, 0.0263, 0.0274	0.959, 0.1003, 0.0272, 0.0282
cML-BIC-Profile	0.973, -0.1001, 0.0246, 0.0257	0.501, -0.0499, 0.0250, 0.0262	0.195, -0.0299, 0.0253, 0.0264	0.051, -0.0099, 0.0255, 0.0267	0.043, 0.0002, 0.0256, 0.0268	0.052, 0.0102, 0.0257, 0.0269	0.179, 0.0302, 0.0260, 0.0272	0.447, 0.0503, 0.0263, 0.0275	0.958, 0.1003, 0.0272, 0.0283
MR-Mix	0.877, -0.1053, 0.0295, 0.0356	0.300, -0.0516, 0.0294, 0.0353	0.101, -0.0306, 0.0294, 0.0353	0.034, -0.0102, 0.0294, 0.0353	0.024, 0.0000, 0.0294, 0.0353	0.032, 0.0100, 0.0294, 0.0354	0.093, 0.0298, 0.0293, 0.0354	0.270, 0.0491, 0.0293, 0.0354	0.818, 0.0958, 0.0295, 0.0358
MR-ContMix	0.955, -0.0993, 0.0258, NA	0.485, -0.0496, 0.0259, NA	0.191, -0.0298, 0.0261, NA	0.051, -0.0100, 0.0262, NA	0.042, -0.0001, 0.0263, NA	0.061, 0.0099, 0.0265, NA	0.188, 0.0298, 0.0269, NA	0.436, 0.0497, 0.0272, NA	0.941, 0.0995, 0.0280, NA
MR-Lasso	0.951, -0.0994, 0.0251, 0.0274	0.447, -0.0497, 0.0254, 0.028	0.169, -0.0299, 0.0258, 0.0282	0.039, -0.0098, 0.0260, 0.0285	0.035, 0.0002, 0.0260, 0.0286	0.048, 0.0102, 0.0260, 0.0287	0.154, 0.0302, 0.0264, 0.029	0.409, 0.0501, 0.0268, 0.0293	0.934, 0.0995, 0.0278, 0.0302
MR-PRESSO	0.576, -0.0696, 0.2056, 0.0827	0.293, -0.0224, 0.2042, 0.0807	0.182, -0.0037, 0.2038, 0.0803	0.132, 0.0139, 0.2030, 0.0791	0.126, 0.0239, 0.2029, 0.0791	0.132, 0.0338, 0.2029, 0.0792	0.202, 0.0529, 0.2010, 0.0775	0.311, 0.0725, 0.1993, 0.0764	0.592, 0.1192, 0.1960, 0.0744
MR-IVW	0.098, -0.0820, 0.2459, 0.2323	0.090, -0.0320, 0.2459, 0.2323	0.083, -0.0120, 0.2459, 0.2323	0.086, 0.0080, 0.2459, 0.2323	0.082, 0.0180, 0.2459, 0.2323	0.083, 0.0280, 0.2458, 0.2323	0.089, 0.0480, 0.2458, 0.2323	0.099, 0.0680, 0.2458, 0.2323	0.132, 0.1179, 0.2458, 0.2323
MR-IVW-Oracle	0.954, -0.0995, 0.0243, 0.0276	0.439, -0.0497, 0.0247, 0.0282	0.165, -0.0297, 0.0250, 0.0284	0.035, -0.0098, 0.0252, 0.0287	0.032, 0.0002, 0.0253, 0.0288	0.042, 0.0101, 0.0255, 0.029	0.145, 0.0301, 0.0258, 0.0293	0.403, 0.0500, 0.0261, 0.0296	0.938, 0.0999, 0.0269, 0.0304
MR-Egger	0.319, 0.2228, 1.4474, 0.941	0.314, 0.2689, 1.4474, 0.9411	0.310, 0.2873, 1.4474, 0.9412	0.302, 0.3057, 1.4474, 0.9413	0.303, 0.3149, 1.4474, 0.9413	0.304, 0.3241, 1.4474, 0.9413	0.302, 0.3425, 1.4475, 0.9414	0.308, 0.3609, 1.4475, 0.9415	0.314, 0.4068, 1.4476, 0.9418
MR-Weighted-Median	0.842, -0.0991, 0.0304, 0.0336	0.304, -0.0504, 0.0307, 0.0342	0.110, -0.0309, 0.0309, 0.0345	0.039, -0.0115, 0.0312, 0.0348	0.027, -0.0019, 0.0314, 0.035	0.029, 0.0078, 0.0315, 0.0352	0.092, 0.0272, 0.0319, 0.0355	0.233, 0.0467, 0.0324, 0.036	0.754, 0.0952, 0.0336, 0.0371
MR-Weighted-Mode	0.770, -0.0976, 0.0317, 0.0377	0.223, -0.0486, 0.0324, 0.0384	0.079, -0.0290, 0.0327, 0.0388	0.023, -0.0094, 0.0331, 0.0391	0.013, 0.0005, 0.0333, 0.0393	0.023, 0.0110, 0.0363, 0.0395	0.073, 0.0303, 0.0365, 0.04	0.196, 0.0500, 0.0367, 0.0404	0.700, 0.0989, 0.0377, 0.0416
MR-RAPS1	0.122, -0.0833, 0.2428, 0.2224	0.098, -0.0332, 0.2428, 0.2225	0.095, -0.0132, 0.2428, 0.2225	0.095, 0.0069, 0.2428, 0.2225	0.102, 0.0169, 0.2428, 0.2225	0.101, 0.0269, 0.2428, 0.2226	0.105, 0.0469, 0.2429, 0.2226	0.126, 0.0670, 0.2429, 0.2226	0.159, 0.1170, 0.2429, 0.2227
MR-RAPS2	0.927, -0.0474, 5.9000, 0.2051	0.769, 0.0560, 7.7647, 0.2415	0.661, 0.3383, 6.2639, 0.1445	0.618, 0.0578, 3.0608, 0.0725	0.612, 0.3082, 4.9676, 0.0968	0.613, 0.2456, 4.0430, 0.0937	0.676, 0.1217, 5.2827, 0.0964	0.776, 0.3031, 4.8627, 0.1029	0.915, 0.1242, 4.7136, 0.484
MR-RAPS3	0.883, -0.1674, 2.0258, 0.825	0.866, -0.0560, 0.8177, 0.1021	0.865, -0.0563, 1.2277, 0.174	0.856, 0.0360, 1.2228, 0.1773	0.852, 0.0318, 0.7947, 0.0931	0.853, 0.0392, 0.6982, 0.079	0.848, 0.0592, 0.6803, 0.0787	0.835, 0.0688, 0.9214, 0.1387	0.878, 1.2930, 32.7496, 391.6584
MR-RAPS4	0.994, -0.2322, 5.2930, 0.1929	0.903, -0.0262, 5.7965, 0.224	0.827, 0.0720, 4.9655, 0.1233	0.795, 0.0055, 1.7865, 0.0654	0.773, -0.0142, 2.3852, 0.0823	0.768, 0.0085, 2.1923, 0.0693	0.809, 0.0703, 2.1411, 0.0688	0.896, 0.1224, 2.0957, 0.07	0.988, 0.3060, 2.9404, 0.4607

Table S39: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean( $SE(\hat{\theta})$ ) when  $m = 10$ , the InSIDE violated,  $q = 0.2$ , and  $N = 100000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	0.917, -0.0878, 0.0229, 0.0245	0.379, -0.0393, 0.0213, 0.0243	0.121, -0.0217, 0.0193, 0.024	0.021, -0.0065, 0.0177, 0.0237	0.017, 0.0006, 0.0176, 0.0237	0.032, 0.0076, 0.0178, 0.0239	0.121, 0.0223, 0.0202, 0.0247	0.351, 0.0395, 0.0228, 0.0255	0.877, 0.0872, 0.0253, 0.0269
cML-MA-AIC-Profile	0.917, -0.0879, 0.0230, 0.0245	0.374, -0.0393, 0.0213, 0.0244	0.120, -0.0217, 0.0193, 0.0241	0.020, -0.0065, 0.0177, 0.0238	0.017, 0.0006, 0.0176, 0.0238	0.032, 0.0076, 0.0178, 0.024	0.117, 0.0223, 0.0202, 0.0248	0.351, 0.0395, 0.0228, 0.0255	0.877, 0.0873, 0.0254, 0.027
cML-AIC	0.965, -0.0934, 0.0253, 0.0196	0.600, -0.0441, 0.0246, 0.02	0.297, -0.0252, 0.0237, 0.0202	0.087, -0.0077, 0.0225, 0.0203	0.075, 0.0007, 0.0226, 0.0204	0.099, 0.0088, 0.0228, 0.0205	0.284, 0.0256, 0.0248, 0.0207	0.589, 0.0444, 0.0262, 0.021	0.947, 0.0935, 0.0279, 0.0216
cML-AIC-Profile	0.964, -0.0936, 0.0253, 0.0197	0.602, -0.0442, 0.0247, 0.02	0.296, -0.0252, 0.0237, 0.0202	0.086, -0.0077, 0.0225, 0.0204	0.074, 0.0007, 0.0226, 0.0205	0.099, 0.0088, 0.0228, 0.0206	0.283, 0.0256, 0.0248, 0.0208	0.587, 0.0444, 0.0262, 0.021	0.947, 0.0935, 0.0279, 0.0217
cML-MA-BIC	0.999, -0.1000, 0.0181, 0.0182	0.776, -0.0500, 0.0185, 0.0186	0.369, -0.0301, 0.0186, 0.0187	0.085, -0.0101, 0.0188, 0.0189	0.045, -0.0002, 0.0189, 0.019	0.068, 0.0098, 0.0190, 0.0191	0.323, 0.0297, 0.0192, 0.0193	0.734, 0.0497, 0.0195, 0.0195	0.998, 0.0996, 0.0201, 0.0201
cML-MA-BIC-Profile	0.999, -0.1000, 0.0181, 0.0183	0.776, -0.0500, 0.0185, 0.0186	0.368, -0.0301, 0.0186, 0.0188	0.085, -0.0101, 0.0188, 0.019	0.045, -0.0002, 0.0189, 0.019	0.068, 0.0098, 0.0190, 0.0191	0.323, 0.0297, 0.0192, 0.0193	0.734, 0.0497, 0.0195, 0.0195	0.998, 0.0996, 0.0201, 0.0201
cML-BIC	0.999, -0.1001, 0.0181, 0.018	0.783, -0.0501, 0.0185, 0.0184	0.375, -0.0302, 0.0186, 0.0185	0.090, -0.0102, 0.0188, 0.0187	0.047, -0.0002, 0.0189, 0.0188	0.072, 0.0098, 0.0190, 0.0189	0.329, 0.0298, 0.0192, 0.0191	0.736, 0.0498, 0.0194, 0.0193	0.998, 0.0998, 0.0201, 0.0199
cML-BIC-Profile	0.999, -0.1001, 0.0181, 0.0181	0.783, -0.0501, 0.0185, 0.0184	0.375, -0.0302, 0.0186, 0.0186	0.090, -0.0102, 0.0188, 0.0187	0.047, -0.0002, 0.0189, 0.0188	0.072, 0.0098, 0.0190, 0.0189	0.329, 0.0298, 0.0192, 0.0191	0.736, 0.0498, 0.0194, 0.0193	0.998, 0.0998, 0.0201, 0.0199
MR-Mix	0.986, -0.1057, 0.0212, 0.0254	0.577, -0.0520, 0.0212, 0.0253	0.209, -0.0312, 0.0211, 0.0253	0.042, -0.0106, 0.0213, 0.0252	0.020, -0.0006, 0.0213, 0.0252	0.031, 0.0095, 0.0213, 0.0252	0.182, 0.0291, 0.0212, 0.0253	0.492, 0.0483, 0.0212, 0.0253	0.960, 0.0948, 0.0214, 0.0254
MR-ContMix	0.998, -0.0998, 0.0193, NA	0.781, -0.0500, 0.0196, NA	0.388, -0.0300, 0.0197, NA	0.100, -0.0100, 0.0199, NA	0.066, -0.0001, 0.0200, NA	0.090, 0.0099, 0.0201, NA	0.356, 0.0298, 0.0204, NA	0.729, 0.0497, 0.0206, NA	0.993, 0.0996, 0.0212, NA
MR-Lasso	0.997, -0.0999, 0.0186, 0.0194	0.727, -0.0500, 0.0191, 0.0198	0.324, -0.0302, 0.0191, 0.02	0.075, -0.0102, 0.0193, 0.0202	0.047, -0.0002, 0.0194, 0.0203	0.062, 0.0097, 0.0196, 0.0204	0.297, 0.0297, 0.0199, 0.0206	0.682, 0.0497, 0.0200, 0.0208	0.992, 0.0995, 0.0208, 0.0214
MR-PRESSO	0.476, -0.0771, 0.2305, 0.118	0.310, -0.0285, 0.2295, 0.1157	0.193, -0.0090, 0.2291, 0.1142	0.112, 0.0108, 0.2291, 0.1142	0.114, 0.0206, 0.2291, 0.1139	0.120, 0.0306, 0.2291, 0.1139	0.215, 0.0501, 0.2288, 0.1129	0.348, 0.0696, 0.2286, 0.1124	0.519, 0.1180, 0.2279, 0.1107
MR-IVW	0.098, -0.0766, 0.2444, 0.2346	0.074, -0.0266, 0.2445, 0.2346	0.066, -0.0066, 0.2445, 0.2346	0.066, 0.0134, 0.2445, 0.2346	0.061, 0.0234, 0.2445, 0.2346	0.060, 0.0334, 0.2445, 0.2346	0.066, 0.0534, 0.2445, 0.2346	0.085, 0.0734, 0.2445, 0.2346	0.123, 0.1233, 0.2446, 0.2346
MR-IVW-Oracle	0.997, -0.0999, 0.0179, 0.0196	0.728, -0.0501, 0.0183, 0.02	0.315, -0.0302, 0.0184, 0.0201	0.068, -0.0102, 0.0186, 0.0203	0.038, -0.0003, 0.0187, 0.0204	0.053, 0.0097, 0.0188, 0.0205	0.288, 0.0297, 0.0190, 0.0207	0.679, 0.0496, 0.0193, 0.0209	0.995, 0.0994, 0.0199, 0.0215
MR-Egger	0.330, 0.3324, 1.4737, 0.9709	0.337, 0.3804, 1.4737, 0.971	0.336, 0.3995, 1.4736, 0.971	0.336, 0.4187, 1.4736, 0.9711	0.336, 0.4283, 1.4736, 0.9711	0.336, 0.4379, 1.4735, 0.9711	0.337, 0.4570, 1.4735, 0.9712	0.338, 0.4762, 1.4735, 0.9712	0.336, 0.5241, 1.4734, 0.9714
MR-Weighted-Median	0.985, -0.0992, 0.0230, 0.0237	0.559, -0.0501, 0.0235, 0.0241	0.241, -0.0305, 0.0237, 0.0243	0.059, -0.0109, 0.0239, 0.0245	0.043, -0.0010, 0.0240, 0.0247	0.060, 0.0088, 0.0242, 0.0248	0.202, 0.0285, 0.0244, 0.025	0.496, 0.0481, 0.0247, 0.0253	0.960, 0.0971, 0.0257, 0.0261
MR-Weighted-Mode	0.963, -0.0991, 0.0247, 0.0272	0.459, -0.0498, 0.0247, 0.0276	0.172, -0.0301, 0.0249, 0.0278	0.033, -0.0103, 0.0251, 0.0281	0.027, -0.0004, 0.0253, 0.0282	0.037, 0.0096, 0.0253, 0.0283	0.155, 0.0296, 0.0257, 0.0286	0.418, 0.0493, 0.0260, 0.0289	0.920, 0.0986, 0.0270, 0.0298
MR-RAPS1	0.111, -0.0810, 0.2376, 0.2231	0.095, -0.0311, 0.2377, 0.2231	0.088, -0.0111, 0.2377, 0.2231	0.080, 0.0089, 0.2377, 0.2232	0.080, 0.0189, 0.2378, 0.2232	0.080, 0.0289, 0.2378, 0.2232	0.090, 0.0489, 0.2378, 0.2232	0.098, 0.0689, 0.2379, 0.2232	0.144, 0.1189, 0.2380, 0.2232
MR-RAPS2	0.933, 0.0234, 5.5185, 0.0626	0.774, 0.1909, 2.7853, 0.0453	0.438, 0.2053, 2.5708, 0.0425	0.179, 0.3617, 3.6355, 0.0503	0.140, 0.3763, 8.3796, 0.0575	0.173, 0.6863, 3.6344, 0.0574	0.431, 0.4991, 3.2395, 0.0608	0.746, 0.5010, 3.6159, 0.0629	0.937, 0.4110, 3.9224, 0.08
MR-RAPS3	0.900, -0.1626, 1.3875, 0.2522	0.907, 0.0097, 1.1390, 0.1243	0.905, 0.0080, 0.7449, 0.0664	0.907, 0.0090, 1.0339, 0.1888	0.907, 0.0602, 0.7714, 0.1315	0.903, 0.0591, 0.7535, 0.0976	0.911, 0.1050, 0.5903, 0.0552	0.902, 0.1287, 0.5444, 0.046	0.911, 0.2049, 0.4986, 0.0421
MR-RAPS4	0.999, -0.1000, 0.0186, 0.0165	0.823, -0.0501, 0.0189, 0.0168	0.449, -0.0313, 0.0294, 0.0169	0.130, -0.0141, 0.0484, 0.0171	0.084, -0.0034, 0.0474, 0.0171	0.127, 0.0068, 0.0429, 0.0172	0.418, 0.0257, 0.0511, 0.0174	0.787, 0.0493, 0.0271, 0.0176	1.000, 0.1702, 1.5046, 0.0375

Table S40: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean( $SE(\hat{\theta})$ ) when  $m = 10$ , the InSIDE violated,  $q = 0.2$ , and  $N = 200000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	0.999, -0.0919, 0.0163, 0.0174	0.675, -0.0421, 0.0163, 0.0176	0.282, -0.0233, 0.0150, 0.0172	0.037, -0.0073, 0.0129, 0.0168	0.013, -0.0004, 0.0124, 0.0167	0.036, 0.0066, 0.0129, 0.017	0.244, 0.0226, 0.0154, 0.0177	0.618, 0.0411, 0.0171, 0.0184	0.981, 0.0902, 0.0184, 0.0192
cML-MA-AIC-Profile	0.999, -0.0920, 0.0163, 0.0175	0.674, -0.0421, 0.0163, 0.0176	0.282, -0.0233, 0.0150, 0.0173	0.037, -0.0073, 0.0129, 0.0168	0.013, -0.0004, 0.0124, 0.0168	0.037, 0.0066, 0.0130, 0.017	0.242, 0.0226, 0.0154, 0.0177	0.617, 0.0411, 0.0171, 0.0184	0.981, 0.0903, 0.0184, 0.0192
cML-AIC	0.999, -0.0964, 0.0179, 0.0139	0.848, -0.0463, 0.0181, 0.0142	0.503, -0.0267, 0.0175, 0.0143	0.128, -0.0086, 0.0164, 0.0144	0.073, -0.0005, 0.0159, 0.0145	0.124, 0.0076, 0.0165, 0.0145	0.453, 0.0255, 0.0179, 0.0147	0.810, 0.0451, 0.0193, 0.0149	0.989, 0.0948, 0.0202, 0.0153
cML-AIC-Profile	0.999, -0.0965, 0.0180, 0.0139	0.847, -0.0464, 0.0181, 0.0142	0.503, -0.0267, 0.0175, 0.0143	0.127, -0.0086, 0.0164, 0.0144	0.073, -0.0005, 0.0159, 0.0145	0.124, 0.0076, 0.0165, 0.0146	0.453, 0.0255, 0.0179, 0.0147	0.806, 0.0451, 0.0193, 0.0149	0.989, 0.0949, 0.0202, 0.0154
cML-MA-BIC	1.000, -0.1002, 0.0130, 0.0129	0.956, -0.0502, 0.0132, 0.0131	0.637, -0.0302, 0.0133, 0.0132	0.122, -0.0102, 0.0134, 0.0134	0.053, -0.0002, 0.0135, 0.0134	0.119, 0.0097, 0.0136, 0.0135	0.593, 0.0297, 0.0138, 0.0136	0.945, 0.0497, 0.0139, 0.0138	1.000, 0.0997, 0.0144, 0.0142
cML-MA-BIC-Profile	1.000, -0.1002, 0.0130, 0.0129	0.956, -0.0502, 0.0132, 0.0131	0.638, -0.0302, 0.0133, 0.0133	0.121, -0.0102, 0.0134, 0.0134	0.053, -0.0002, 0.0135, 0.0135	0.119, 0.0097, 0.0136, 0.0135	0.590, 0.0297, 0.0138, 0.0137	0.944, 0.0497, 0.0139, 0.0138	1.000, 0.0997, 0.0144, 0.0142
cML-BIC	1.000, -0.1002, 0.0130, 0.0128	0.960, -0.0502, 0.0132, 0.013	0.644, -0.0302, 0.0133, 0.0132	0.123, -0.0102, 0.0135, 0.0133	0.057, -0.0002, 0.0135, 0.0133	0.122, 0.0098, 0.0136, 0.0134	0.600, 0.0298, 0.0138, 0.0135	0.946, 0.0498, 0.0139, 0.0137	1.000, 0.0998, 0.0144, 0.0141
cML-BIC-Profile	1.000, -0.1002, 0.0130, 0.0128	0.960, -0.0502, 0.0132, 0.0131	0.644, -0.0302, 0.0133, 0.0132	0.122, -0.0102, 0.0135, 0.0133	0.057, -0.0002, 0.0135, 0.0133	0.122, 0.0098, 0.0136, 0.0134	0.600, 0.0298, 0.0138, 0.0136	0.945, 0.0498, 0.0139, 0.0137	1.000, 0.0998, 0.0144, 0.0141
MR-Mix	0.997, -0.1052, 0.0152, 0.0183	0.848, -0.0516, 0.0151, 0.0183	0.389, -0.0307, 0.0151, 0.0183	0.060, -0.0102, 0.0151, 0.0182	0.025, -0.0001, 0.0151, 0.0182	0.071, 0.0099, 0.0151, 0.0183	0.379, 0.0297, 0.0152, 0.0183	0.791, 0.0490, 0.0152, 0.0183	0.998, 0.0955, 0.0154, 0.0183
MR-ContMix	1.000, -0.1001, 0.0133, NA	0.957, -0.0501, 0.0135, NA	0.665, -0.0302, 0.0136, NA	0.153, -0.0102, 0.0137, NA	0.071, -0.0002, 0.0138, NA	0.144, 0.0097, 0.0139, NA	0.615, 0.0297, 0.0140, NA	0.944, 0.0497, 0.0142, NA	1.000, 0.0996, 0.0147, NA
MR-Lasso	1.000, -0.1001, 0.0132, 0.0138	0.935, -0.0501, 0.0134, 0.0141	0.580, -0.0301, 0.0135, 0.0142	0.109, -0.0102, 0.0136, 0.0143	0.056, -0.0002, 0.0138, 0.0144	0.102, 0.0098, 0.0138, 0.0145	0.539, 0.0297, 0.0140, 0.0146	0.919, 0.0497, 0.0141, 0.0148	1.000, 0.0997, 0.0146, 0.0152
MR-PRESSO	0.402, -0.0816, 0.2386, 0.1461	0.309, -0.0320, 0.2384, 0.1447	0.209, -0.0122, 0.2384, 0.1448	0.100, 0.0078, 0.2383, 0.1448	0.089, 0.0178, 0.2382, 0.1442	0.097, 0.0278, 0.2382, 0.1442	0.207, 0.0478, 0.2376, 0.1439	0.328, 0.0679, 0.2376, 0.1416	0.436, 0.1175, 0.2371, 0.1396
MR-IVW	0.099, -0.0822, 0.2431, 0.2356	0.084, -0.0321, 0.2431, 0.2356	0.074, -0.0120, 0.2431, 0.2356	0.071, 0.0080, 0.2431, 0.2356	0.071, 0.0181, 0.2431, 0.2356	0.075, 0.0281, 0.2431, 0.2356	0.083, 0.0481, 0.2431, 0.2355	0.087, 0.0682, 0.2430, 0.2355	0.125, 0.1183, 0.2430, 0.2355
MR-IVW-Oracle	1.000, -0.1001, 0.0129, 0.0139	0.936, -0.0501, 0.0131, 0.0141	0.579, -0.0301, 0.0133, 0.0143	0.105, -0.0102, 0.0134, 0.0144	0.049, -0.0002, 0.0135, 0.0145	0.097, 0.0098, 0.0135, 0.0145	0.537, 0.0298, 0.0137, 0.0147	0.921, 0.0498, 0.0138, 0.0148	1.000, 0.0997, 0.0143, 0.0152
MR-Egger	0.341, 0.3442, 1.5425, 0.9761	0.347, 0.3933, 1.5424, 0.9761	0.347, 0.4129, 1.5424, 0.9761	0.345, 0.4326, 1.5423, 0.9761	0.345, 0.4424, 1.5423, 0.9761	0.347, 0.4522, 1.5423, 0.9761	0.348, 0.4718, 1.5422, 0.9761	0.348, 0.4914, 1.5422, 0.9761	0.353, 0.5405, 1.5422, 0.9762
MR-Weighted-Median	1.000, -0.1003, 0.0161, 0.0168	0.848, -0.0506, 0.0165, 0.0171	0.440, -0.0308, 0.0167, 0.0173	0.081, -0.0110, 0.0169, 0.0174	0.041, -0.0011, 0.0169, 0.0175	0.075, 0.0088, 0.0170, 0.0176	0.376, 0.0285, 0.0173, 0.0178	0.768, 0.0483, 0.0175, 0.018	1.000, 0.0977, 0.0180, 0.0185
MR-Weighted-Mode	0.997, -0.1003, 0.0194, 0.0194	0.747, -0.0503, 0.0197, 0.0198	0.341, -0.0302, 0.0200, 0.0199	0.049, -0.0103, 0.0201, 0.0201	0.026, -0.0004, 0.0203, 0.0202	0.052, 0.0096, 0.0205, 0.0203	0.312, 0.0295, 0.0207, 0.0205	0.687, 0.0498, 0.0191, 0.0207	0.995, 0.0988, 0.0300, 0.0213
MR-RAPS1	0.109, -0.0823, 0.2365, 0.2234	0.098, -0.0323, 0.2365, 0.2235	0.101, -0.0123, 0.2365, 0.2235	0.097, 0.0078, 0.2365, 0.2235	0.093, 0.0178, 0.2365, 0.2235	0.090, 0.0278, 0.2365, 0.2235	0.099, 0.0478, 0.2366, 0.2235	0.106, 0.0678, 0.2366, 0.2235	0.133, 0.1178, 0.2366, 0.2235
MR-RAPS2	0.945, 0.3227, 4.0103, 0.0599	0.906, -0.1949, 11.4382, 0.0628	0.691, 0.4203, 4.6843, 0.052	0.311, -0.1507, 15.9910, 0.0727	0.229, 0.4714, 4.1526, 0.0643	0.262, 0.2704, 3.1951, 0.0513	0.661, 0.0532, 4.0533, 0.0578	0.882, 0.2976, 3.0651, 0.0495	0.942, 0.5987, 5.4713, 0.0614
MR-RAPS3	0.936, -22.1268, 693.8632, 20170	0.945, -0.0436, 1.4025, 0.0965	0.932, -0.0903, 1.6370, 0.2188	0.917, 0.1199, 3.1922, 1.347	0.914, 0.0685, 0.8184, 0.0696	0.913, 0.0690, 0.7006, 0.0502	0.916, 0.0437, 1.8048, 0.4863	0.923, 0.1284, 0.5885, 0.0368	0.943, 0.1937, 0.5532, 0.0333
MR-RAPS4	1.000, -0.1009, 0.0183, 0.0117	0.970, -0.0514, 0.0699, 0.0119	0.708, -0.0292, 0.0875, 0.012	0.203, -0.0037, 0.1305, 0.0122	0.114, 0.0035, 0.1153, 0.0122	0.182, 0.0154, 0.1007, 0.0122	0.680, 0.0294, 0.0746, 0.0123	0.958, 0.0488, 0.0429, 0.0124	1.000, 0.1002, 0.0207, 0.0128

Table S41: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean( $SE(\hat{\theta})$ ) when  $m = 10$ , the InSIDE violated,  $q = 0.4$ , and  $N = 50000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	0.561, -0.0808, 0.0344, 0.0398	0.126, -0.0353, 0.0312, 0.0392	0.042, -0.0198, 0.0292, 0.0391	0.015, -0.0055, 0.0286, 0.039	0.016, 0.0015, 0.0282, 0.0393	0.013, 0.0080, 0.0285, 0.0395	0.050, 0.0218, 0.0306, 0.0402	0.116, 0.0375, 0.0330, 0.0412	0.491, 0.0817, 0.0385, 0.0436
cML-MA-AIC-Profile	0.557, -0.0808, 0.0345, 0.04	0.123, -0.0353, 0.0313, 0.0395	0.040, -0.0198, 0.0292, 0.0393	0.015, -0.0055, 0.0286, 0.0393	0.016, 0.0015, 0.0282, 0.0395	0.013, 0.0080, 0.0285, 0.0398	0.050, 0.0218, 0.0306, 0.0405	0.114, 0.0375, 0.0330, 0.0414	0.489, 0.0818, 0.0386, 0.0438
cML-AIC	0.755, -0.0882, 0.0387, 0.0324	0.283, -0.0402, 0.0376, 0.033	0.136, -0.0227, 0.0365, 0.0333	0.066, -0.0060, 0.0362, 0.0337	0.057, 0.0022, 0.0362, 0.0339	0.077, 0.0101, 0.0365, 0.034	0.146, 0.0261, 0.0377, 0.0344	0.302, 0.0436, 0.0398, 0.0348	0.708, 0.0908, 0.0438, 0.0357
cML-AIC-Profile	0.751, -0.0883, 0.0389, 0.0327	0.281, -0.0403, 0.0376, 0.0333	0.135, -0.0227, 0.0365, 0.0336	0.063, -0.0060, 0.0362, 0.0339	0.056, 0.0022, 0.0362, 0.0341	0.072, 0.0101, 0.0365, 0.0343	0.144, 0.0261, 0.0377, 0.0346	0.298, 0.0436, 0.0398, 0.035	0.706, 0.0908, 0.0438, 0.0359
cML-MA-BIC	0.898, -0.0990, 0.0299, 0.0304	0.363, -0.0490, 0.0304, 0.031	0.149, -0.0291, 0.0305, 0.0313	0.056, -0.0092, 0.0308, 0.0315	0.036, 0.0007, 0.0309, 0.0317	0.054, 0.0107, 0.0311, 0.0318	0.156, 0.0305, 0.0314, 0.0322	0.351, 0.0505, 0.0318, 0.0325	0.864, 0.1005, 0.0328, 0.0334
cML-MA-BIC-Profile	0.897, -0.0990, 0.0299, 0.0306	0.361, -0.0490, 0.0304, 0.0311	0.148, -0.0291, 0.0305, 0.0314	0.055, -0.0092, 0.0308, 0.0317	0.036, 0.0007, 0.0309, 0.0318	0.052, 0.0107, 0.0311, 0.032	0.152, 0.0305, 0.0314, 0.0323	0.347, 0.0505, 0.0318, 0.0326	0.862, 0.1005, 0.0328, 0.0336
cML-BIC	0.907, -0.0994, 0.0299, 0.03	0.375, -0.0493, 0.0305, 0.0306	0.157, -0.0293, 0.0307, 0.0308	0.060, -0.0093, 0.0309, 0.0311	0.042, 0.0008, 0.0312, 0.0313	0.062, 0.0108, 0.0314, 0.0314	0.162, 0.0308, 0.0317, 0.0317	0.361, 0.0508, 0.0321, 0.0321	0.874, 0.1007, 0.0329, 0.033
cML-BIC-Profile	0.906, -0.0994, 0.0299, 0.0302	0.372, -0.0493, 0.0305, 0.0307	0.156, -0.0293, 0.0307, 0.031	0.059, -0.0093, 0.0309, 0.0312	0.042, 0.0008, 0.0312, 0.0314	0.058, 0.0108, 0.0314, 0.0316	0.159, 0.0308, 0.0317, 0.0319	0.355, 0.0508, 0.0321, 0.0322	0.871, 0.1007, 0.0329, 0.0332
MR-Mix	0.814, -0.1038, 0.0327, 0.0377	0.268, -0.0505, 0.0325, 0.0388	0.097, -0.0301, 0.0325, 0.0375	0.037, -0.0097, 0.0326, 0.0374	0.030, 0.0004, 0.0325, 0.0373	0.036, 0.0103, 0.0326, 0.0372	0.099, 0.0297, 0.0325, 0.0372	0.257, 0.0488, 0.0327, 0.0373	0.759, 0.0949, 0.0325, 0.0374
MR-ContMix	0.903, -0.0988, 0.0313, NA	0.393, -0.0488, 0.0321, NA	0.179, -0.0289, 0.0323, NA	0.073, -0.0090, 0.0326, NA	0.056, 0.0009, 0.0328, NA	0.071, 0.0108, 0.0331, NA	0.179, 0.0306, 0.0335, NA	0.381, 0.0505, 0.0338, NA	0.862, 0.1007, 0.0351, NA
MR-Lasso	0.868, -0.0971, 0.0538, 0.033	0.327, -0.0471, 0.0540, 0.0337	0.139, -0.0270, 0.0542, 0.034	0.053, -0.0071, 0.0543, 0.0343	0.037, 0.0029, 0.0544, 0.0344	0.056, 0.0129, 0.0545, 0.0346	0.142, 0.0327, 0.0535, 0.0349	0.328, 0.0527, 0.0538, 0.0352	0.818, 0.1026, 0.0543, 0.0362
MR-PRESSO	0.366, -0.0568, 0.3305, 0.1626	0.200, -0.0085, 0.3300, 0.162	0.154, 0.0111, 0.3298, 0.1613	0.130, 0.0306, 0.3296, 0.1605	0.121, 0.0401, 0.3295, 0.1599	0.131, 0.0498, 0.3294, 0.1598	0.164, 0.0683, 0.3284, 0.1578	0.240, 0.0882, 0.3275, 0.1556	0.416, 0.1365, 0.3253, 0.1499
MR-IVW	0.119, -0.0575, 0.3493, 0.325	0.109, -0.0073, 0.3493, 0.325	0.111, 0.0127, 0.3493, 0.325	0.105, 0.0328, 0.3493, 0.325	0.106, 0.0428, 0.3493, 0.325	0.106, 0.0528, 0.3493, 0.325	0.106, 0.0729, 0.3493, 0.325	0.104, 0.0929, 0.3493, 0.325	0.108, 0.1430, 0.3493, 0.3251
MR-IVW-Oracle	0.875, -0.0991, 0.0295, 0.0327	0.320, -0.0493, 0.0300, 0.0333	0.132, -0.0293, 0.0303, 0.0336	0.043, -0.0094, 0.0305, 0.0339	0.027, 0.0005, 0.0307, 0.034	0.046, 0.0105, 0.0308, 0.0342	0.131, 0.0304, 0.0311, 0.0345	0.312, 0.0503, 0.0315, 0.0349	0.817, 0.1001, 0.0324, 0.0358
MR-Egger	0.198, 0.3768, 1.5720, 1.169	0.205, 0.4239, 1.5718, 1.17	0.208, 0.4428, 1.5717, 1.17	0.208, 0.4616, 1.5717, 1.17	0.209, 0.4710, 1.5717, 1.17	0.210, 0.4804, 1.5716, 1.17	0.211, 0.4992, 1.5716, 1.17	0.213, 0.5180, 1.5715, 1.17	0.216, 0.5649, 1.5714, 1.171
MR-Weighted-Median	0.743, -0.1006, 0.0437, 0.0391	0.287, -0.0532, 0.0457, 0.0399	0.138, -0.0343, 0.0466, 0.0402	0.069, -0.0153, 0.0476, 0.0406	0.058, -0.0058, 0.0482, 0.0408	0.060, 0.0037, 0.0489, 0.041	0.106, 0.0227, 0.0503, 0.0415	0.205, 0.0415, 0.0521, 0.042	0.591, 0.0884, 0.0569, 0.0433
MR-Weighted-Mode	0.831, -0.0975, 0.0649, 0.0382	0.281, -0.0489, 0.0679, 0.0389	0.113, -0.0291, 0.0684, 0.0394	0.043, -0.0102, 0.0731, 0.0397	0.039, -0.0004, 0.0732, 0.0398	0.048, 0.0093, 0.0733, 0.04	0.115, 0.0284, 0.0745, 0.0406	0.273, 0.0483, 0.0750, 0.0414	0.761, 0.0939, 0.0913, 0.043
MR-RAPS1	0.131, -0.0553, 0.3416, 0.3099	0.125, -0.0052, 0.3417, 0.31	0.122, 0.0148, 0.3417, 0.31	0.116, 0.0348, 0.3417, 0.31	0.116, 0.0449, 0.3417, 0.3101	0.114, 0.0549, 0.3417, 0.3101	0.111, 0.0749, 0.3418, 0.3101	0.115, 0.0950, 0.3418, 0.3101	0.110, 0.1450, 0.3419, 0.3102
MR-RAPS2	0.115, -0.0818, 0.5677, 0.3129	0.089, -0.0160, 0.3351, 0.3139	0.088, 0.0027, 0.3285, 0.3138	0.080, 0.0335, 0.4325, 0.3138	0.078, 0.0346, 0.3329, 0.3134	0.083, 0.0448, 0.3348, 0.3136	0.087, 0.0459, 0.8315, 0.316	0.086, 0.0865, 0.3255, 0.3141	0.093, 0.1109, 0.8306, 0.3169
MR-RAPS3	0.885, 1.3579, 44.4267, 165.6	0.884, 0.5522, 13.3942, 13.21	0.897, -0.0384, 16.5791, 17.56	0.905, 35.0963, 819.6598, 49490	0.909, 0.3326, 7.6864, 3.564	0.914, 0.4553, 18.7536, 38.44	0.916, 0.8766, 9.9464, 13.95	0.916, -0.5582, 21.6160, 51.22	0.914, 0.5238, 5.7278, 2.47
MR-RAPS4	0.983, -0.1091, 3.6669, 0.5702	0.953, -0.2614, 11.5315, 1.389	0.935, 0.0849, 3.9536, 0.8077	0.925, -0.0260, 7.6959, 1.438	0.919, -0.2501, 8.8183, 0.4624	0.911, -0.2434, 7.5444, 0.4677	0.924, -0.1388, 8.6924, 0.7604	0.944, -0.1657, 7.6694, 0.5314	0.980, 0.0310, 7.2304, 0.4874

Table S42: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean(SE( $\hat{\theta}$ )) when  $m = 10$ , the InSIDE violated,  $q = 0.4$ , and  $N = 100000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	0.851, -0.0861, 0.0267, 0.0284	0.258, -0.0379, 0.0247, 0.0283	0.092, -0.0215, 0.0221, 0.0279	0.015, -0.0063, 0.0205, 0.0277	0.013, 0.0002, 0.0200, 0.0278	0.019, 0.0070, 0.0205, 0.028	0.081, 0.0215, 0.0226, 0.0287	0.238, 0.0379, 0.0253, 0.0297	0.769, 0.0850, 0.0288, 0.0314
cML-MA-AIC-Profile	0.851, -0.0862, 0.0269, 0.0284	0.258, -0.0379, 0.0247, 0.0284	0.092, -0.0215, 0.0221, 0.028	0.015, -0.0063, 0.0205, 0.0278	0.012, 0.0002, 0.0200, 0.0279	0.018, 0.0070, 0.0205, 0.0281	0.080, 0.0215, 0.0226, 0.0288	0.236, 0.0380, 0.0253, 0.0298	0.766, 0.0851, 0.0288, 0.0315
cML-AIC	0.921, -0.0918, 0.0302, 0.0231	0.477, -0.0428, 0.0290, 0.0235	0.240, -0.0248, 0.0273, 0.0236	0.089, -0.0073, 0.0264, 0.0238	0.077, 0.0004, 0.0262, 0.0239	0.078, 0.0083, 0.0266, 0.0241	0.231, 0.0248, 0.0280, 0.0242	0.480, 0.0427, 0.0301, 0.0246	0.883, 0.0916, 0.0321, 0.0252
cML-AIC-Profile	0.921, -0.0920, 0.0304, 0.0231	0.476, -0.0428, 0.0290, 0.0235	0.240, -0.0248, 0.0273, 0.0237	0.088, -0.0073, 0.0264, 0.0239	0.076, 0.0004, 0.0262, 0.024	0.078, 0.0083, 0.0266, 0.0241	0.229, 0.0248, 0.0280, 0.0243	0.478, 0.0427, 0.0301, 0.0247	0.883, 0.0916, 0.0322, 0.0253
cML-MA-BIC	0.995, -0.0998, 0.0216, 0.0214	0.624, -0.0498, 0.0220, 0.0218	0.284, -0.0299, 0.0221, 0.022	0.067, -0.0100, 0.0224, 0.0222	0.047, -0.0001, 0.0225, 0.0223	0.072, 0.0099, 0.0226, 0.0225	0.276, 0.0298, 0.0229, 0.0227	0.600, 0.0498, 0.0232, 0.0229	0.983, 0.0998, 0.0239, 0.0236
cML-MA-BIC-Profile	0.995, -0.0998, 0.0216, 0.0215	0.622, -0.0498, 0.0220, 0.0219	0.282, -0.0299, 0.0221, 0.0221	0.067, -0.0100, 0.0224, 0.0223	0.048, -0.0001, 0.0225, 0.0224	0.072, 0.0099, 0.0226, 0.0225	0.275, 0.0298, 0.0229, 0.0227	0.597, 0.0498, 0.0232, 0.023	0.983, 0.0998, 0.0239, 0.0236
cML-BIC	0.995, -0.0999, 0.0216, 0.0212	0.636, -0.0499, 0.0220, 0.0216	0.292, -0.0299, 0.0222, 0.0217	0.070, -0.0100, 0.0226, 0.0219	0.051, 0.0001, 0.0227, 0.022	0.073, 0.0101, 0.0228, 0.0222	0.293, 0.0301, 0.0230, 0.0224	0.606, 0.0500, 0.0232, 0.0226	0.985, 0.1000, 0.0240, 0.0233
cML-BIC-Profile	0.995, -0.0999, 0.0216, 0.0212	0.635, -0.0499, 0.0220, 0.0216	0.292, -0.0299, 0.0222, 0.0218	0.070, -0.0100, 0.0226, 0.022	0.051, 0.0001, 0.0227, 0.0221	0.073, 0.0101, 0.0228, 0.0222	0.291, 0.0301, 0.0230, 0.0224	0.605, 0.0500, 0.0232, 0.0227	0.986, 0.1000, 0.0240, 0.0233
MR-Mix	0.973, -0.1043, 0.0241, 0.027	0.487, -0.0509, 0.0240, 0.0269	0.191, -0.0303, 0.0240, 0.0269	0.044, -0.0101, 0.0241, 0.027	0.029, 0.0000, 0.0240, 0.0272	0.050, 0.0099, 0.0241, 0.0297	0.188, 0.0294, 0.0241, 0.0275	0.468, 0.0487, 0.0241, 0.0275	0.937, 0.0946, 0.0240, 0.0273
MR-ContMix	0.992, -0.1001, 0.0224, NA	0.658, -0.0502, 0.0228, NA	0.330, -0.0303, 0.0229, NA	0.098, -0.0103, 0.0232, NA	0.069, -0.0003, 0.0233, NA	0.102, 0.0097, 0.0234, NA	0.316, 0.0296, 0.0237, NA	0.628, 0.0496, 0.0239, NA	0.980, 0.0996, 0.0247, NA
MR-Lasso	0.987, -0.0991, 0.0450, 0.0237	0.565, -0.0492, 0.0452, 0.0242	0.247, -0.0293, 0.0453, 0.0244	0.060, -0.0097, 0.0370, 0.0247	0.044, 0.0003, 0.0370, 0.0248	0.066, 0.0103, 0.0372, 0.0249	0.241, 0.0303, 0.0373, 0.0251	0.544, 0.0503, 0.0375, 0.0254	0.957, 0.1000, 0.0382, 0.026
MR-PRESSO	0.313, -0.0449, 0.3250, 0.2057	0.197, 0.0051, 0.3247, 0.2028	0.145, 0.0254, 0.3243, 0.2015	0.111, 0.0450, 0.3242, 0.2006	0.111, 0.0551, 0.3240, 0.2002	0.114, 0.0650, 0.3240, 0.1999	0.164, 0.0849, 0.3237, 0.198	0.228, 0.1044, 0.3237, 0.1971	0.357, 0.1534, 0.3231, 0.1931
MR-IVW	0.091, -0.0440, 0.3323, 0.3299	0.089, 0.0062, 0.3323, 0.3299	0.084, 0.0263, 0.3323, 0.3299	0.085, 0.0464, 0.3323, 0.3299	0.085, 0.0565, 0.3323, 0.3299	0.085, 0.0665, 0.3323, 0.3299	0.090, 0.0866, 0.3324, 0.3298	0.090, 0.1067, 0.3324, 0.3298	0.095, 0.1568, 0.3324, 0.3298
MR-IVW-Oracle	0.990, -0.0998, 0.0215, 0.0233	0.561, -0.0499, 0.0219, 0.0238	0.237, -0.0299, 0.0221, 0.024	0.053, -0.0099, 0.0223, 0.0242	0.037, 0.0000, 0.0224, 0.0244	0.058, 0.0100, 0.0225, 0.0245	0.229, 0.0300, 0.0227, 0.0247	0.540, 0.0499, 0.0230, 0.025	0.964, 0.0998, 0.0236, 0.0257
MR-Egger	0.235, 0.4847, 1.5839, 1.191	0.237, 0.5332, 1.5840, 1.191	0.240, 0.5526, 1.5840, 1.191	0.240, 0.5720, 1.5840, 1.191	0.240, 0.5816, 1.5840, 1.191	0.239, 0.5913, 1.5841, 1.191	0.239, 0.6107, 1.5841, 1.191	0.243, 0.6300, 1.5841, 1.191	0.238, 0.6784, 1.5842, 1.192
MR-Weighted-Median	0.941, -0.1013, 0.0325, 0.0276	0.461, -0.0528, 0.0341, 0.0281	0.214, -0.0335, 0.0350, 0.0284	0.093, -0.0141, 0.0359, 0.0286	0.072, -0.0045, 0.0364, 0.0288	0.080, 0.0051, 0.0369, 0.0289	0.171, 0.0244, 0.0380, 0.0293	0.388, 0.0437, 0.0394, 0.0296	0.851, 0.0916, 0.0427, 0.0306
MR-Weighted-Mode	0.981, -0.0995, 0.0328, 0.0284	0.530, -0.0501, 0.0329, 0.0289	0.218, -0.0304, 0.0328, 0.0291	0.059, -0.0106, 0.0330, 0.0293	0.040, -0.0008, 0.0330, 0.0295	0.056, 0.0091, 0.0331, 0.0297	0.212, 0.0291, 0.0333, 0.0299	0.522, 0.0488, 0.0336, 0.0301	0.943, 0.0976, 0.0400, 0.0311
MR-RAPS1	0.099, -0.0479, 0.3240, 0.3135	0.097, 0.0022, 0.3240, 0.3135	0.092, 0.0222, 0.3241, 0.3135	0.088, 0.0422, 0.3241, 0.3135	0.087, 0.0522, 0.3241, 0.3135	0.088, 0.0622, 0.3241, 0.3135	0.087, 0.0822, 0.3241, 0.3135	0.089, 0.1022, 0.3242, 0.3135	0.101, 0.1523, 0.3243, 0.3136
MR-RAPS2	0.106, -0.0890, 0.3025, 0.2722	0.088, -0.0380, 0.2975, 0.2783	0.086, -0.0171, 0.2906, 0.2816	0.079, 0.0049, 0.2950, 0.2842	0.078, 0.0542, 0.9588, 0.2888	0.077, 0.0408, 0.4487, 0.2898	0.074, 0.0507, 0.2983, 0.292	0.078, 0.0725, 0.3025, 0.2951	0.085, 0.1242, 0.3063, 0.3023
MR-RAPS3	0.922, -2.5105, 56.1160, 128.2	0.919, 0.4746, 27.9686, 42.39	0.922, 1.8887, 57.6319, 167.6	0.929, -1.3272, 50.4485, 126.7	0.937, 30.6530, 894.6462, 30780	0.936, 0.6059, 7.9225, 2.882	0.931, -2.4818, 58.5677, 539	0.938, 0.1966, 11.4127, 7.026	0.935, 0.2288, 9.1694, 4.466
MR-RAPS4	0.978, -0.1546, 10.1909, 0.471	0.970, 0.0731, 8.2261, 0.712	0.963, 0.1687, 7.9969, 2.363	0.950, -0.0474, 4.9448, 0.452	0.952, -0.0736, 5.1400, 0.5624	0.948, -0.0663, 5.1935, 2.667	0.960, -0.0506, 5.2175, 0.7871	0.965, -0.0820, 5.2784, 1.371	0.985, -0.2449, 8.5402, 0.3131

Table S43: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean( $SE(\hat{\theta})$ ) when  $m = 10$ , the InSIDE violated,  $q = 0.4$ , and  $N = 200000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	0.977, -0.0903, 0.0189, 0.0202	0.538, -0.0408, 0.0184, 0.0203	0.193, -0.0224, 0.0169, 0.02	0.025, -0.0068, 0.0147, 0.0197	0.011, 0.0001, 0.0143, 0.0196	0.028, 0.0070, 0.0147, 0.0199	0.183, 0.0222, 0.0173, 0.0207	0.479, 0.0402, 0.0194, 0.0213	0.957, 0.0893, 0.0210, 0.0222
cML-MA-AIC-Profile	0.977, -0.0905, 0.0189, 0.0202	0.536, -0.0408, 0.0184, 0.0203	0.192, -0.0224, 0.0169, 0.02	0.025, -0.0068, 0.0147, 0.0197	0.011, 0.0001, 0.0143, 0.0197	0.027, 0.0070, 0.0147, 0.0199	0.182, 0.0222, 0.0173, 0.0207	0.479, 0.0402, 0.0194, 0.0213	0.957, 0.0894, 0.0211, 0.0222
cML-AIC	0.989, -0.0949, 0.0208, 0.0162	0.749, -0.0452, 0.0206, 0.0165	0.413, -0.0258, 0.0199, 0.0166	0.101, -0.0083, 0.0186, 0.0168	0.062, 0.0002, 0.0182, 0.0169	0.094, 0.0083, 0.0185, 0.017	0.365, 0.0254, 0.0205, 0.0172	0.707, 0.0442, 0.0219, 0.0175	0.971, 0.0938, 0.0235, 0.0179
cML-AIC-Profile	0.989, -0.0952, 0.0206, 0.0162	0.749, -0.0452, 0.0206, 0.0165	0.413, -0.0258, 0.0199, 0.0167	0.101, -0.0083, 0.0186, 0.0168	0.062, 0.0002, 0.0182, 0.0169	0.093, 0.0083, 0.0185, 0.017	0.362, 0.0254, 0.0205, 0.0173	0.706, 0.0442, 0.0219, 0.0175	0.971, 0.0939, 0.0235, 0.0179
cML-MA-BIC	1.000, -0.0998, 0.0154, 0.0151	0.891, -0.0499, 0.0156, 0.0154	0.503, -0.0299, 0.0157, 0.0155	0.101, -0.0100, 0.0159, 0.0157	0.044, -0.0001, 0.0159, 0.0157	0.099, 0.0099, 0.0160, 0.0158	0.468, 0.0298, 0.0162, 0.016	0.870, 0.0498, 0.0163, 0.0161	1.000, 0.0998, 0.0168, 0.0166
cML-MA-BIC-Profile	1.000, -0.0999, 0.0154, 0.0151	0.891, -0.0499, 0.0156, 0.0154	0.501, -0.0299, 0.0157, 0.0155	0.101, -0.0100, 0.0159, 0.0157	0.044, -0.0001, 0.0159, 0.0157	0.099, 0.0099, 0.0160, 0.0158	0.467, 0.0298, 0.0162, 0.016	0.870, 0.0498, 0.0163, 0.0162	1.000, 0.0998, 0.0168, 0.0166
cML-BIC	1.000, -0.0999, 0.0153, 0.015	0.894, -0.0500, 0.0156, 0.0153	0.508, -0.0300, 0.0157, 0.0154	0.105, -0.0100, 0.0158, 0.0155	0.045, -0.0001, 0.0159, 0.0156	0.103, 0.0100, 0.0161, 0.0157	0.480, 0.0300, 0.0162, 0.0158	0.874, 0.0500, 0.0164, 0.016	1.000, 0.0999, 0.0170, 0.0165
cML-BIC-Profile	1.000, -0.0999, 0.0153, 0.015	0.893, -0.0500, 0.0156, 0.0153	0.508, -0.0300, 0.0157, 0.0154	0.105, -0.0100, 0.0158, 0.0155	0.045, -0.0001, 0.0159, 0.0156	0.102, 0.0100, 0.0161, 0.0157	0.479, 0.0300, 0.0162, 0.0158	0.874, 0.0500, 0.0164, 0.016	1.000, 0.0999, 0.0170, 0.0165
MR-Mix	0.999, -0.1042, 0.0176, 0.0191	0.782, -0.0513, 0.0174, 0.0191	0.361, -0.0305, 0.0174, 0.019	0.071, -0.0102, 0.0174, 0.0191	0.032, -0.0001, 0.0174, 0.0191	0.068, 0.0099, 0.0175, 0.0191	0.346, 0.0293, 0.0175, 0.0191	0.729, 0.0483, 0.0174, 0.0191	0.996, 0.0943, 0.0173, 0.0192
MR-ContMix	0.999, -0.0998, 0.0158, NA	0.900, -0.0499, 0.0161, NA	0.550, -0.0300, 0.0163, NA	0.126, -0.0100, 0.0164, NA	0.058, 0.0000, 0.0164, NA	0.135, 0.0100, 0.0165, NA	0.510, 0.0299, 0.0167, NA	0.880, 0.0498, 0.0169, NA	1.000, 0.0997, 0.0174, NA
MR-Lasso	0.997, -0.0998, 0.0480, 0.0173	0.843, -0.0496, 0.0470, 0.0175	0.450, -0.0297, 0.0470, 0.0177	0.095, -0.0097, 0.0471, 0.0178	0.046, 0.0003, 0.0471, 0.0179	0.085, 0.0103, 0.0471, 0.018	0.400, 0.0302, 0.0472, 0.0182	0.815, 0.0502, 0.0473, 0.0183	0.996, 1.002, 0.0475, 0.0188
MR-PRESSO	0.306, -0.0679, 0.3504, 0.239	0.234, -0.0180, 0.3504, 0.2378	0.169, 0.0022, 0.3504, 0.2378	0.112, 0.0219, 0.3503, 0.2368	0.103, 0.0319, 0.3503, 0.2368	0.112, 0.0419, 0.3503, 0.2368	0.175, 0.0621, 0.3502, 0.2353	0.239, 0.0823, 0.3501, 0.2351	0.322, 0.1322, 0.3500, 0.2328
MR-IVW	0.107, -0.0671, 0.3524, 0.3309	0.101, -0.0168, 0.3524, 0.3309	0.101, 0.0033, 0.3524, 0.3308	0.102, 0.0234, 0.3524, 0.3308	0.102, 0.0334, 0.3524, 0.3308	0.104, 0.0435, 0.3524, 0.3308	0.107, 0.0636, 0.3524, 0.3308	0.110, 0.0837, 0.3524, 0.3308	0.119, 0.1339, 0.3524, 0.3307
MR-IVW-Oracle	0.999, -0.0998, 0.0153, 0.0164	0.844, -0.0499, 0.0155, 0.0167	0.447, -0.0300, 0.0156, 0.0168	0.090, -0.0100, 0.0158, 0.017	0.039, 0.0000, 0.0158, 0.0171	0.079, 0.0099, 0.0159, 0.0172	0.403, 0.0299, 0.0161, 0.0173	0.819, 0.0499, 0.0162, 0.0175	0.999, 0.0998, 0.0167, 0.018
MR-Egger	0.240, 0.4842, 1.6226, 1.1645	0.244, 0.5335, 1.6226, 1.1645	0.248, 0.5533, 1.6224, 1.1645	0.248, 0.5730, 1.6224, 1.1646	0.249, 0.5828, 1.6224, 1.1646	0.248, 0.5927, 1.6223, 1.1646	0.249, 0.6124, 1.6223, 1.1646	0.251, 0.6321, 1.6222, 1.1646	0.254, 0.6813, 1.6221, 1.1646
MR-Weighted-Median	0.997, -0.1018, 0.0297, 0.0198	0.748, -0.0534, 0.0301, 0.0201	0.402, -0.0340, 0.0308, 0.0203	0.124, -0.0147, 0.0317, 0.0205	0.070, -0.0050, 0.0322, 0.0206	0.084, 0.0047, 0.0327, 0.0207	0.285, 0.0240, 0.0337, 0.021	0.610, 0.0434, 0.0350, 0.0212	0.965, 0.0916, 0.0389, 0.0219
MR-Weighted-Mode	0.996, -0.1005, 0.0240, 0.0181	0.817, -0.0504, 0.0240, 0.0185	0.420, -0.0307, 0.0240, 0.0186	0.075, -0.0109, 0.0241, 0.0188	0.039, -0.0009, 0.0243, 0.019	0.080, 0.0090, 0.0244, 0.019	0.378, 0.0286, 0.0248, 0.0195	0.788, 0.0492, 0.0252, 0.0195	0.991, 0.0961, 0.0497, 0.0201
MR-RAPS1	0.117, -0.0692, 0.3419, 0.314	0.115, -0.0192, 0.3420, 0.314	0.112, 0.0008, 0.3420, 0.314	0.108, 0.0208, 0.3420, 0.314	0.113, 0.0308, 0.3420, 0.314	0.111, 0.0408, 0.3421, 0.314	0.112, 0.0608, 0.3421, 0.314	0.115, 0.0808, 0.3421, 0.314	0.126, 0.1308, 0.3422, 0.314
MR-RAPS2	0.162, -0.1226, 0.2282, 0.1941	0.106, -0.0766, 0.2639, 0.1937	0.089, -0.0552, 0.2345, 0.1949	0.080, -0.0318, 0.2336, 0.1983	0.073, -0.0226, 0.2395, 0.1985	0.067, -0.0219, 0.3510, 0.2008	0.073, 0.0055, 0.2482, 0.2016	0.071, 0.0248, 0.2619, 0.2009	0.077, 0.0748, 0.2411, 0.2031
MR-RAPS3	0.940, -2.8247, 45.3076, 52.1233	0.948, 1.3487, 37.0838, 38.0906	0.953, 0.3711, 16.2788, 7.362	0.939, 2.7406, 82.6052, 127.3877	0.934, -1.7006, 55.5342, 167.3854	0.932, 0.0982, 11.3167, 6.5138	0.953, 0.1190, 17.1701, 9.3429	0.956, -5.8855, 174.8939, 804.4194	0.955, 0.9751, 17.4681, 7.0265
MR-RAPS4	1.000, -0.0657, 0.1245, 0.0117	0.965, -0.0174, 0.2065, 0.0122	0.735, 0.0086, 0.2540, 0.0127	0.399, 0.0330, 0.2728, 0.0129	0.344, 0.0416, 0.2802, 0.013	0.399, 0.0602, 0.2599, 0.0129	0.723, 0.0560, 0.2086, 0.0127	0.959, 0.0701, 0.1616, 0.0126	1.000, 0.1159, 0.1038, 0.0129



Table S44: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean( $SE(\hat{\theta})$ ) when  $m = 10$ , the InSIDE violated,  $q = 0.6$ , and  $N = 50000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	0.448, -0.0825, 0.0411, 0.047	0.084, -0.0367, 0.0369, 0.0473	0.036, -0.0208, 0.0348, 0.0473	0.013, -0.0064, 0.0334, 0.0475	0.008, 0.0001, 0.0335, 0.0477	0.014, 0.0069, 0.0339, 0.048	0.033, 0.0214, 0.0358, 0.0487	0.076, 0.0363, 0.0392, 0.0495	0.363, 0.0801, 0.0455, 0.0515
cML-MA-AIC-Profile	0.445, -0.0826, 0.0412, 0.0473	0.084, -0.0367, 0.0369, 0.0476	0.035, -0.0208, 0.0348, 0.0477	0.013, -0.0064, 0.0334, 0.0478	0.008, 0.0001, 0.0335, 0.048	0.013, 0.0069, 0.0339, 0.0483	0.032, 0.0214, 0.0358, 0.049	0.076, 0.0363, 0.0394, 0.0498	0.363, 0.0801, 0.0455, 0.0518
cML-AIC	0.639, -0.0889, 0.0469, 0.04	0.210, -0.0416, 0.0441, 0.0407	0.112, -0.0241, 0.0429, 0.0411	0.057, -0.0076, 0.0422, 0.0416	0.050, 0.0002, 0.0425, 0.0418	0.051, 0.0080, 0.0430, 0.042	0.087, 0.0241, 0.0444, 0.0423	0.181, 0.0401, 0.0472, 0.0429	0.558, 0.0864, 0.0523, 0.0441
cML-AIC-Profile	0.638, -0.0890, 0.0470, 0.0403	0.205, -0.0416, 0.0441, 0.041	0.111, -0.0241, 0.0429, 0.0414	0.056, -0.0076, 0.0422, 0.0419	0.049, 0.0002, 0.0425, 0.0421	0.049, 0.0080, 0.0430, 0.0423	0.085, 0.0241, 0.0444, 0.0426	0.178, 0.0401, 0.0474, 0.0432	0.551, 0.0864, 0.0523, 0.0444
cML-MA-BIC	0.768, -0.1008, 0.0372, 0.0379	0.259, -0.0506, 0.0377, 0.0386	0.124, -0.0307, 0.0379, 0.0389	0.055, -0.0107, 0.0382, 0.0392	0.044, -0.0008, 0.0384, 0.0394	0.044, 0.0091, 0.0386, 0.0396	0.095, 0.0291, 0.0391, 0.04	0.219, 0.0488, 0.0395, 0.0404	0.673, 0.0989, 0.0410, 0.0415
cML-MA-BIC-Profile	0.766, -0.0993, 0.0591, 0.0388	0.256, -0.0490, 0.0634, 0.0393	0.125, -0.0290, 0.0648, 0.0395	0.056, -0.0090, 0.0661, 0.0398	0.044, 0.0009, 0.0667, 0.0399	0.045, 0.0109, 0.0672, 0.0401	0.096, 0.0309, 0.0683, 0.0405	0.217, 0.0507, 0.0693, 0.0408	0.667, 0.1008, 0.0713, 0.0419
cML-BIC	0.783, -0.1012, 0.0374, 0.0375	0.267, -0.0509, 0.0381, 0.0381	0.132, -0.0309, 0.0383, 0.0384	0.058, -0.0108, 0.0386, 0.0388	0.047, -0.0008, 0.0388, 0.0389	0.050, 0.0093, 0.0391, 0.0391	0.102, 0.0293, 0.0395, 0.0395	0.229, 0.0492, 0.0396, 0.0399	0.682, 0.0995, 0.0408, 0.0411
cML-BIC-Profile	0.781, -0.0992, 0.0717, 0.0377	0.264, -0.0490, 0.0721, 0.0383	0.132, -0.0290, 0.0722, 0.0386	0.059, -0.0089, 0.0724, 0.039	0.047, 0.0012, 0.0726, 0.0392	0.050, 0.0112, 0.0727, 0.0393	0.102, 0.0313, 0.0729, 0.0397	0.228, 0.0512, 0.0730, 0.0401	0.677, 0.1014, 0.0737, 0.0413
MR-Mix	0.726, -0.1045, 0.0395, 0.0423	0.219, -0.0516, 0.0396, 0.0419	0.100, -0.0313, 0.0395, 0.0419	0.051, -0.0111, 0.0397, 0.042	0.041, -0.0010, 0.0397, 0.0419	0.044, 0.0089, 0.0396, 0.0419	0.093, 0.0283, 0.0395, 0.0419	0.195, 0.0472, 0.0394, 0.0419	0.628, 0.0931, 0.0399, 0.0421
MR-ContMix	0.801, -0.1011, 0.0385, NA	0.305, -0.0510, 0.0394, NA	0.171, -0.0310, 0.0400, NA	0.086, -0.0111, 0.0403, NA	0.070, -0.0011, 0.0406, NA	0.076, 0.0090, 0.0408, NA	0.128, 0.0287, 0.0440, NA	0.266, 0.0487, 0.0444, NA	0.714, 0.0988, 0.0462, NA
MR-Lasso	0.736, -0.0499, 0.3745, 0.0678	0.321, -0.0003, 0.3767, 0.0682	0.229, 0.0195, 0.3775, 0.0688	0.174, 0.0390, 0.3741, 0.0691	0.168, 0.0497, 0.3746, 0.0697	0.163, 0.0597, 0.3753, 0.0699	0.194, 0.0799, 0.3755, 0.07	0.272, 0.1004, 0.3785, 0.0708	0.613, 0.1503, 0.3794, 0.0725
MR-PRESSO	0.246, -0.0304, 0.4048, 0.2281	0.140, 0.0183, 0.4046, 0.2254	0.122, 0.0382, 0.4042, 0.2248	0.110, 0.0584, 0.4039, 0.2243	0.110, 0.0678, 0.4038, 0.2234	0.107, 0.0776, 0.4037, 0.223	0.117, 0.0978, 0.4040, 0.2217	0.143, 0.1169, 0.4034, 0.2195	0.246, 0.1663, 0.4028, 0.2172
MR-IVW	0.105, -0.0306, 0.4136, 0.4028	0.100, 0.0198, 0.4136, 0.4027	0.103, 0.0400, 0.4136, 0.4027	0.101, 0.0601, 0.4136, 0.4027	0.099, 0.0702, 0.4136, 0.4027	0.103, 0.0803, 0.4136, 0.4027	0.102, 0.1004, 0.4136, 0.4026	0.104, 0.1205, 0.4136, 0.4026	0.111, 0.1708, 0.4135, 0.4026
MR-IVW-Oracle	0.713, -0.1010, 0.0366, 0.0413	0.212, -0.0510, 0.0373, 0.0422	0.105, -0.0310, 0.0376, 0.0425	0.044, -0.0110, 0.0380, 0.0429	0.036, -0.0010, 0.0382, 0.0431	0.038, 0.0090, 0.0384, 0.0433	0.081, 0.0290, 0.0388, 0.0437	0.181, 0.0490, 0.0392, 0.0442	0.609, 0.0991, 0.0404, 0.0454
MR-Egger	0.201, 0.6599, 1.5413, 1.2434	0.201, 0.7079, 1.5412, 1.2435	0.205, 0.7271, 1.5411, 1.2436	0.205, 0.7463, 1.5410, 1.2437	0.205, 0.7559, 1.5410, 1.2437	0.205, 0.7655, 1.5410, 1.2437	0.204, 0.7846, 1.5409, 1.2438	0.204, 0.8038, 1.5409, 1.2439	0.216, 0.8517, 1.5408, 1.2441
MR-Weighted-Median	0.638, -0.1093, 0.1281, 0.0502	0.314, -0.0676, 0.1306, 0.0509	0.226, -0.0507, 0.1323, 0.0513	0.187, -0.0342, 0.1346, 0.0517	0.174, -0.0256, 0.1360, 0.0519	0.178, -0.0175, 0.1366, 0.0522	0.199, -0.0013, 0.1388, 0.0527	0.255, 0.0155, 0.1421, 0.0532	0.484, 0.0572, 0.1501, 0.0547
MR-Weighted-Mode	0.749, -0.1287, 0.2185, 0.0473	0.718, -0.0924, 0.2217, 0.0476	0.704, -0.0779, 0.2227, 0.0479	0.691, -0.0635, 0.2247, 0.048	0.694, -0.0561, 0.2257, 0.0481	0.688, -0.0488, 0.2265, 0.0482	0.680, -0.0341, 0.2280, 0.0485	0.681, -0.0204, 0.2307, 0.049	0.690, 0.0166, 0.2373, 0.05
MR-RAPS1	0.107, -0.0264, 0.4036, 0.3842	0.106, 0.0237, 0.4037, 0.3842	0.108, 0.0437, 0.4037, 0.3842	0.109, 0.0638, 0.4037, 0.3842	0.105, 0.0738, 0.4037, 0.3842	0.106, 0.0838, 0.4037, 0.3842	0.106, 0.1039, 0.4037, 0.3842	0.114, 0.1239, 0.4037, 0.3842	0.117, 0.1740, 0.4037, 0.3843
MR-RAPS2	0.115, -0.0310, 0.4253, 0.4102	0.104, 0.0159, 0.4241, 0.41	0.107, 0.0380, 0.4250, 0.4108	0.114, 0.0582, 0.4379, 0.4104	0.109, 0.0663, 0.4368, 0.4102	0.107, 0.0794, 0.4374, 0.4118	0.109, 0.0988, 0.4382, 0.4115	0.112, 0.1225, 0.4263, 0.4126	0.120, 0.1701, 0.4255, 0.4117
MR-RAPS3	0.881, 2.0639, 93.7912, 252.4835	0.893, -1.6022, 54.9780, 106.569	0.902, -6.0948, 259.1498, 2527.0841	0.900, 7.5128, 202.9000, 2281.6167	0.905, 1.6741, 71.2527, 148.85	0.904, 3.6396, 88.6035, 721.006	0.889, -2.0102, 33.9409, 48.2306	0.893, 7.2212, 169.8092, 1117.9699	0.882, 4.9987, 77.2008, 953.607
MR-RAPS4	0.979, -0.7163, 7.9742, 0.8387	0.963, -0.7850, 9.7173, 1.2497	0.960, -0.5914, 8.6282, 1.3841	0.952, -0.3806, 7.5705, 2.7722	0.942, -0.3676, 9.3461, 2.5249	0.948, -0.2913, 9.6837, 1.4926	0.942, -0.4679, 8.5193, 2.3324	0.940, -0.2870, 8.0767, 1.4293	0.959, -0.2074, 9.8532, 1.1574

Table S45: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean(SE( $\hat{\theta}$ )) when  $m = 10$ , the InSIDE violated,  $q = 0.6$ , and  $N = 100000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	0.723, -0.0850, 3.100e- 02, 0.0335	0.196, -0.0374, 2.800e- 02, 0.0338	0.061, -0.0209, 2.580e- 02, 0.0337	0.012, -0.0062, 2.380e- 02, 0.0338	0.005, 0.0007, 2.360e- 02, 0.0339	0.014, 0.0073, 2.430e- 02, 0.0341	0.054, 0.0216, 2.620e- 02, 0.0348	0.184, 0.0380, 2.930e- 02, 0.0355	0.669, 0.0848, 3.360e- 02, 0.0368
cML-MA-AIC-Profile	0.722, -0.0851, 3.100e- 02, 0.0336	0.194, -0.0374, 2.800e- 02, 0.0339	0.060, -0.0209, 2.580e- 02, 0.0338	0.012, -0.0062, 2.380e- 02, 0.0339	0.005, 0.0007, 2.360e- 02, 0.034	0.013, 0.0072, 2.420e- 02, 0.0342	0.053, 0.0216, 2.620e- 02, 0.0349	0.184, 0.0380, 2.930e- 02, 0.0356	0.668, 0.0850, 3.370e- 02, 0.037
cML-AIC	0.816, -0.0888, 3.560e- 02, 0.0286	0.360, -0.0410, 3.280e- 02, 0.0291	0.163, -0.0235, 3.150e- 02, 0.0293	0.049, -0.0071, 3.010e- 02, 0.0295	0.036, 0.0010, 2.990e- 02, 0.0297	0.049, 0.0083, 3.050e- 02, 0.0299	0.163, 0.0242, 3.210e- 02, 0.0302	0.344, 0.0419, 3.380e- 02, 0.0305	0.788, 0.0892, 3.770e- 02, 0.0314
cML-AIC-Profile	0.817, -0.0889, 3.550e- 02, 0.0287	0.359, -0.0410, 3.280e- 02, 0.0292	0.161, -0.0235, 3.150e- 02, 0.0294	0.049, -0.0071, 3.010e- 02, 0.0297	0.035, 0.0010, 2.990e- 02, 0.0298	0.046, 0.0083, 3.050e- 02, 0.03	0.161, 0.0242, 3.210e- 02, 0.0303	0.340, 0.0419, 3.380e- 02, 0.0306	0.787, 0.0894, 3.790e- 02, 0.0315
cML-MA-BIC	0.955, -0.0988, 2.600e- 02, 0.0267	0.451, -0.0488, 2.650e- 02, 0.0272	0.188, -0.0288, 2.660e- 02, 0.0274	0.050, -0.0089, 2.680e- 02, 0.0276	0.036, 0.0010, 2.700e- 02, 0.0278	0.053, 0.0109, 2.710e- 02, 0.0279	0.202, 0.0308, 2.750e- 02, 0.0281	0.446, 0.0507, 2.790e- 02, 0.0284	0.935, 0.1007, 2.880e- 02, 0.0293
cML-MA-BIC-Profile	0.954, -0.0988, 2.600e- 02, 0.0268	0.448, -0.0488, 2.660e- 02, 0.0272	0.188, -0.0288, 2.660e- 02, 0.0275	0.050, -0.0089, 2.700e- 02, 0.0277	0.036, 0.0010, 2.700e- 02, 0.0278	0.053, 0.0109, 2.710e- 02, 0.0279	0.201, 0.0308, 2.750e- 02, 0.0282	0.445, 0.0507, 2.790e- 02, 0.0285	0.935, 0.1007, 2.880e- 02, 0.0293
cML-BIC	0.960, -0.0991, 2.600e- 02, 0.0264	0.466, -0.0491, 2.650e- 02, 0.0269	0.198, -0.0291, 2.670e- 02, 0.0271	0.055, -0.0091, 2.700e- 02, 0.0273	0.039, 0.0009, 2.710e- 02, 0.0275	0.056, 0.0109, 2.730e- 02, 0.0276	0.208, 0.0310, 2.760e- 02, 0.0279	0.457, 0.0510, 2.790e- 02, 0.0282	0.938, 0.1010, 2.880e- 02, 0.029
cML-BIC-Profile	0.960, -0.0991, 2.600e- 02, 0.0265	0.464, -0.0491, 2.650e- 02, 0.0269	0.197, -0.0291, 2.670e- 02, 0.0272	0.054, -0.0091, 2.700e- 02, 0.0274	0.039, 0.0009, 2.710e- 02, 0.0275	0.054, 0.0109, 2.730e- 02, 0.0277	0.207, 0.0310, 2.760e- 02, 0.0279	0.455, 0.0510, 2.790e- 02, 0.0282	0.937, 0.1010, 2.880e- 02, 0.0291
MR-Mix	0.929, -0.1019, 2.770e- 02, 0.031	0.395, -0.0491, 2.780e- 02, 0.0301	0.161, -0.0287, 2.780e- 02, 0.0301	0.047, -0.0086, 2.790e- 02, 0.0303	0.027, 0.0013, 2.800e- 02, 0.0304	0.046, 0.0111, 2.800e- 02, 0.0306	0.171, 0.0302, 2.810e- 02, 0.0304	0.388, 0.0494, 2.810e- 02, 0.0303	0.886, 0.0951, 2.830e- 02, 0.0303
MR-ContMix	0.955, -0.0989, 2.750e- 02, NA	0.507, -0.0489, 2.770e- 02, NA	0.244, -0.0290, 2.790e- 02, NA	0.091, -0.0090, 2.820e- 02, NA	0.071, 0.0010, 2.830e- 02, NA	0.081, 0.0110, 2.850e- 02, NA	0.252, 0.0310, 2.870e- 02, NA	0.494, 0.0510, 2.910e- 02, NA	0.937, 0.1010, 3.000e- 02, NA
MR-Lasso	0.888, -0.0570, 3.792e- 01, 0.0598	0.461, -0.0077, 3.800e- 01, 0.06	0.264, 0.0119, 3.795e- 01, 0.0604	0.169, 0.0320, 3.792e- 01, 0.0604	0.155, 0.0421, 3.791e- 01, 0.0606	0.164, 0.0521, 3.791e- 01, 0.0607	0.258, 0.0717, 3.789e- 01, 0.0609	0.435, 0.0917, 3.785e- 01, 0.0611	0.826, 0.1416, 3.787e- 01, 0.0617
MR-PRESSO	0.207, -0.0344, 4.203e- 01, 0.2848	0.121, 0.0164, 4.200e- 01, 0.2828	0.097, 0.0366, 4.199e- 01, 0.282	0.081, 0.0569, 4.197e- 01, 0.2805	0.085, 0.0671, 4.195e- 01, 0.2798	0.088, 0.0769, 4.195e- 01, 0.2792	0.105, 0.0968, 4.194e- 01, 0.278	0.135, 0.1170, 4.195e- 01, 0.2769	0.226, 0.1662, 4.195e- 01, 0.2743
MR-IVW	0.105, -0.0360, 4.230e- 01, 0.3961	0.099, 0.0145, 4.229e- 01, 0.3961	0.099, 0.0346, 4.229e- 01, 0.3961	0.102, 0.0548, 4.229e- 01, 0.396	0.105, 0.0649, 4.229e- 01, 0.396	0.106, 0.0750, 4.229e- 01, 0.396	0.108, 0.0951, 4.228e- 01, 0.396	0.111, 0.1152, 4.228e- 01, 0.396	0.116, 0.1655, 4.228e- 01, 0.3959
MR-IVW-Oracle	0.915, -0.0989, 2.580e- 02, 0.0297	0.381, -0.0489, 2.630e- 02, 0.0302	0.152, -0.0290, 2.660e- 02, 0.0305	0.043, -0.0090, 2.680e- 02, 0.0307	0.028, 0.0010, 2.700e- 02, 0.0309	0.040, 0.0110, 2.710e- 02, 0.031	0.162, 0.0310, 2.740e- 02, 0.0313	0.385, 0.0509, 2.770e- 02, 0.0316	0.886, 0.1009, 2.860e- 02, 0.0325
MR-Egger	0.164, 0.5210, 1.514e+00, 1.282	0.172, 0.5700, 1.514e+00, 1.282	0.172, 0.5896, 1.514e+00, 1.282	0.174, 0.6092, 1.514e+00, 1.282	0.175, 0.6190, 1.514e+00, 1.282	0.174, 0.6287, 1.514e+00, 1.282	0.175, 0.6483, 1.514e+00, 1.282	0.183, 0.6679, 1.514e+00, 1.282	0.189, 0.7167, 1.513e+00, 1.282
MR-Weighted-Median	0.842, -0.1081, 1.070e- 01, 0.0363	0.426, -0.0644, 1.095e- 01, 0.037	0.260, -0.0473, 1.104e- 01, 0.0372	0.167, -0.0301, 1.124e- 01, 0.0376	0.151, -0.0216, 1.134e- 01, 0.0377	0.153, -0.0131, 1.150e- 01, 0.0379	0.206, 0.0035, 1.183e- 01, 0.0382	0.328, 0.0200, 1.221e- 01, 0.0386	0.714, 0.0613, 1.327e- 01, 0.0397
MR-Weighted-Mode	0.807, -0.1414, 2.083e- 01, 0.0364	0.760, -0.1037, 2.086e- 01, 0.0368	0.750, -0.0886, 2.099e- 01, 0.0371	0.745, -0.0738, 2.106e- 01, 0.0375	0.739, -0.0660, 2.117e- 01, 0.0376	0.729, -0.0590, 2.130e- 01, 0.038	0.731, -0.0460, 2.107e- 01, 0.0383	0.733, -0.0311, 2.122e- 01, 0.039	0.724, 0.0032, 2.169e- 01, 0.0401
MR-RAPS1	0.105, -0.0345, 4.127e- 01, 0.3761	0.115, 0.0156, 4.128e- 01, 0.3761	0.116, 0.0356, 4.128e- 01, 0.3761	0.116, 0.0556, 4.128e- 01, 0.376	0.120, 0.0656, 4.128e- 01, 0.376	0.119, 0.0756, 4.128e- 01, 0.376	0.118, 0.0957, 4.129e- 01, 0.376	0.119, 0.1157, 4.129e- 01, 0.376	0.131, 0.1657, 4.129e- 01, 0.3761
MR-RAPS2	0.175, -0.0739, 4.584e- 01, 0.3739	0.165, -0.0255, 4.459e- 01, 0.3791	0.166, -0.0044, 4.529e- 01, 0.3781	0.162, 0.0230, 4.746e- 01, 0.3808	0.155, 0.0331, 4.536e- 01, 0.3814	0.151, 0.0370, 4.456e- 01, 0.3816	0.154, 0.0575, 4.658e- 01, 0.3823	0.138, 0.0872, 4.503e- 01, 0.3849	0.143, 0.1348, 4.528e- 01, 0.3878
MR-RAPS3	0.925, -1.4125, 5.300e+01, 120.8	0.930, -1.5231, 7.782e+01, 137.5	0.931, -19.4827, 7.148e+02, 11950	0.937, 1.1305, 1.432e+02, 535.1	0.934, 344.3808, 1.077e+04, 3045000	0.931, 0.2234, 2.287e+01, 14.1	0.931, -0.7363, 4.346e+01, 577	0.932, 0.4207, 2.871e+01, 29.4	0.931, 1.2562, 2.377e+01, 15.51
MR-RAPS4	0.977, -0.5602, 7.266e+00, 0.5505	0.969, -0.1700, 6.251e+00, 0.5518	0.967, -0.2526, 5.066e+00, 0.4514	0.973, 0.5137, 2.408e+01, 0.8991	0.973, -0.1766, 4.869e+00, 0.9432	0.967, -0.1216, 4.848e+00, 0.9423	0.980, -0.0620, 4.982e+00, 0.3102	0.977, -0.0546, 4.927e+00, 0.4632	0.976, -0.0612, 7.837e+00, 0.755

Table S46: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean( $SE(\hat{\theta})$ ) when  $m = 10$ , the InSIDE violated,  $q = 0.6$ , and  $N = 200000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	0.927, -0.0895, 0.0228, 0.0239	0.417, -0.0400, 0.0221, 0.0242	0.132, -0.0220, 0.0201, 0.0242	0.027, -0.0069, 0.0180, 0.0239	0.016, -0.0002, 0.0176, 0.0239	0.024, 0.0066, 0.0178, 0.024	0.121, 0.0220, 0.0201, 0.0246	0.369, 0.0400, 0.0224, 0.0251	0.903, 0.0890, 0.0241, 0.0259
cML-MA-AIC-Profile	0.926, -0.0896, 0.0228, 0.0239	0.412, -0.0399, 0.0221, 0.0243	0.132, -0.0220, 0.0203, 0.0242	0.026, -0.0069, 0.0180, 0.024	0.016, -0.0003, 0.0176, 0.0239	0.023, 0.0066, 0.0178, 0.0241	0.120, 0.0220, 0.0201, 0.0247	0.367, 0.0400, 0.0224, 0.0252	0.903, 0.0890, 0.0241, 0.026
cML-AIC	0.941, -0.0922, 0.0257, 0.0203	0.609, -0.0426, 0.0253, 0.0207	0.264, -0.0240, 0.0241, 0.0208	0.068, -0.0080, 0.0222, 0.0209	0.061, -0.0004, 0.0218, 0.021	0.083, 0.0075, 0.0219, 0.0211	0.240, 0.0241, 0.0237, 0.0213	0.558, 0.0428, 0.0254, 0.0215	0.925, 0.0921, 0.0268, 0.0221
cML-AIC-Profile	0.941, -0.0922, 0.0257, 0.0203	0.608, -0.0426, 0.0253, 0.0207	0.265, -0.0241, 0.0242, 0.0208	0.068, -0.0080, 0.0222, 0.021	0.060, -0.0004, 0.0218, 0.021	0.083, 0.0075, 0.0219, 0.0211	0.239, 0.0241, 0.0237, 0.0213	0.558, 0.0428, 0.0254, 0.0216	0.925, 0.0921, 0.0268, 0.0222
cML-MA-BIC	0.998, -0.0999, 0.0187, 0.0189	0.748, -0.0499, 0.0190, 0.0192	0.334, -0.0299, 0.0191, 0.0194	0.076, -0.0100, 0.0192, 0.0196	0.048, -0.0001, 0.0193, 0.0197	0.079, 0.0099, 0.0193, 0.0197	0.325, 0.0298, 0.0196, 0.0199	0.709, 0.0498, 0.0198, 0.0202	0.997, 0.0998, 0.0203, 0.0207
cML-MA-BIC-Profile	0.997, -0.0999, 0.0187, 0.0189	0.748, -0.0498, 0.0191, 0.0193	0.334, -0.0298, 0.0195, 0.0196	0.076, -0.0098, 0.0201, 0.0199	0.048, 0.0002, 0.0207, 0.0201	0.079, 0.0102, 0.0215, 0.0202	0.324, 0.0302, 0.0239, 0.0206	0.709, 0.0504, 0.0272, 0.0209	0.996, 0.1008, 0.0379, 0.0214
cML-BIC	0.998, -0.1001, 0.0187, 0.0187	0.756, -0.0501, 0.0189, 0.019	0.347, -0.0301, 0.0191, 0.0192	0.079, -0.0100, 0.0193, 0.0194	0.051, 0.0000, 0.0194, 0.0195	0.086, 0.0100, 0.0195, 0.0196	0.335, 0.0300, 0.0196, 0.0198	0.714, 0.0500, 0.0198, 0.02	0.998, 0.1000, 0.0204, 0.0205
cML-BIC-Profile	0.998, -0.1001, 0.0187, 0.0187	0.755, -0.0501, 0.0189, 0.0191	0.348, -0.0301, 0.0191, 0.0192	0.079, -0.0100, 0.0193, 0.0194	0.050, 0.0000, 0.0194, 0.0195	0.086, 0.0100, 0.0195, 0.0196	0.334, 0.0300, 0.0196, 0.0198	0.714, 0.0500, 0.0198, 0.02	0.998, 0.1016, 0.0527, 0.0206
MR-Mix	0.997, -0.1032, 0.0200, 0.0218	0.667, -0.0503, 0.0199, 0.0217	0.271, -0.0300, 0.0199, 0.0216	0.064, -0.0099, 0.0201, 0.0217	0.049, 0.0000, 0.0200, 0.0217	0.066, 0.0099, 0.0201, 0.0217	0.263, 0.0293, 0.0199, 0.0218	0.646, 0.0483, 0.0200, 0.0219	0.989, 0.0939, 0.0205, 0.0223
MR-ContMix	0.996, -0.1001, 0.0192, NA	0.789, -0.0502, 0.0195, NA	0.405, -0.0302, 0.0196, NA	0.118, -0.0102, 0.0198, NA	0.082, -0.0002, 0.0198, NA	0.125, 0.0098, 0.0199, NA	0.397, 0.0298, 0.0200, NA	0.744, 0.0498, 0.0202, NA	0.997, 0.0998, 0.0208, NA
MR-Lasso	0.967, -0.0560, 0.3638, 0.0485	0.695, -0.0055, 0.3633, 0.0487	0.355, 0.0154, 0.3634, 0.0493	0.179, 0.0358, 0.3634, 0.0493	0.153, 0.0457, 0.3630, 0.0494	0.171, 0.0560, 0.3633, 0.0498	0.328, 0.0756, 0.3635, 0.0498	0.639, 0.0955, 0.3635, 0.0501	0.927, 0.1466, 0.3633, 0.0506
MR-PRESSO	0.204, -0.0300, 0.4156, 0.3195	0.122, 0.0206, 0.4155, 0.3188	0.095, 0.0407, 0.4155, 0.3177	0.074, 0.0604, 0.4155, 0.3164	0.070, 0.0704, 0.4155, 0.3164	0.076, 0.0806, 0.4154, 0.3161	0.108, 0.1008, 0.4154, 0.3158	0.152, 0.1208, 0.4154, 0.3151	0.236, 0.1706, 0.4152, 0.3123
MR-IVW	0.091, -0.0309, 0.4167, 0.4016	0.093, 0.0196, 0.4167, 0.4016	0.091, 0.0397, 0.4166, 0.4016	0.091, 0.0599, 0.4166, 0.4016	0.092, 0.0700, 0.4166, 0.4015	0.094, 0.0801, 0.4166, 0.4015	0.095, 0.1002, 0.4166, 0.4015	0.100, 0.1204, 0.4166, 0.4015	0.116, 0.1707, 0.4165, 0.4015
MR-IVW-Oracle	0.992, -0.1000, 0.0191, 0.0211	0.668, -0.0500, 0.0189, 0.0215	0.274, -0.0300, 0.0191, 0.0217	0.060, -0.0100, 0.0192, 0.0219	0.042, -0.0001, 0.0193, 0.022	0.069, 0.0099, 0.0194, 0.0221	0.258, 0.0299, 0.0196, 0.0224	0.630, 0.0499, 0.0197, 0.0226	0.986, 0.0999, 0.0203, 0.0232
MR-Egger	0.209, 0.7085, 1.6364, 1.2704	0.215, 0.7579, 1.6364, 1.2704	0.217, 0.7777, 1.6365, 1.2704	0.218, 0.7974, 1.6365, 1.2704	0.220, 0.8073, 1.6365, 1.2704	0.220, 0.8171, 1.6365, 1.2704	0.219, 0.8369, 1.6366, 1.2704	0.221, 0.8566, 1.6366, 1.2704	0.229, 0.9059, 1.6366, 1.2704
MR-Weighted-Median	0.948, -0.1024, 0.1330, 0.0275	0.633, -0.0589, 0.1344, 0.0277	0.375, -0.0415, 0.1356, 0.0279	0.189, -0.0241, 0.1370, 0.0281	0.154, -0.0155, 0.1379, 0.0282	0.178, -0.0067, 0.1387, 0.0284	0.292, 0.0106, 0.1409, 0.0287	0.515, 0.0275, 0.1426, 0.0289	0.848, 0.0697, 0.1512, 0.0297
MR-Weighted-Mode	0.872, -0.1220, 0.2311, 0.0257	0.831, -0.0855, 0.2311, 0.0257	0.823, -0.0708, 0.2335, 0.0258	0.817, -0.0560, 0.2350, 0.0261	0.822, -0.0485, 0.2361, 0.0263	0.821, -0.0416, 0.2379, 0.0264	0.815, -0.0267, 0.2390, 0.0264	0.816, -0.0119, 0.2415, 0.0266	0.804, 0.0238, 0.2505, 0.027
MR-RAPS1	0.105, -0.2502, 8.2147, 1.3504	0.107, -1.5332, 44.5248, 22.2417	0.109, 0.1187, 3.3341, 0.4994	0.106, 0.0648, 2.2694, 0.4349	0.104, 0.0459, 2.4359, 0.4454	0.102, 0.0153, 3.1656, 0.4957	0.108, 0.1075, 1.2322, 0.3949	0.111, 0.1199, 1.3024, 0.4015	0.125, 0.1771, 0.7752, 0.3858
MR-RAPS2	0.281, -0.0856, 0.4947, 0.2646	0.240, -0.0360, 0.4766, 0.2679	0.233, -0.0273, 0.4684, 0.2643	0.198, -0.0010, 0.4759, 0.2757	0.188, 0.0019, 0.4607, 0.2742	0.187, 0.0129, 0.4854, 0.2731	0.180, 0.0209, 0.7618, 0.2786	0.171, 0.0543, 0.4452, 0.2824	0.174, 0.1114, 0.4689, 0.2928
MR-RAPS3	0.948, -3.9798, 133.1913, 265.2621	0.944, 27.6247, 703.6228, 8354.1716	0.946, -2.8912, 149.4389, 3683.3129	0.944, -5.1822, 141.8313, 587.2076	0.946, 1.0330, 56.3390, 57.5573	0.948, -0.5791, 57.5046, 67.6878	0.949, -15.4647, 752.9266, 8713.9481	0.950, 0.1444, 36.8795, 25.6024	0.947, -1.0000, 38.1072, 57.7633
MR-RAPS4	0.989, 0.0094, 3.2157, 0.2749	0.976, 0.0977, 3.3890, 0.3038	0.969, 0.1306, 3.4094, 0.4216	0.973, 0.1374, 4.1508, 0.3486	0.980, 0.1847, 4.3370, 0.2556	0.981, 0.1272, 4.2599, 0.3706	0.975, 0.3318, 8.0901, 0.3917	0.975, 0.1738, 4.1473, 0.5444	1.000, 0.2699, 0.2967, 0.0149

Table S47: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean( $SE(\hat{\theta})$ ) when  $m = 20$ , the ideal case of  $q = 0$ , and  $N = 50000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	0.969, -0.0915, 0.0221, 0.0201	0.559, -0.0424, 0.0217, 0.0203	0.239, -0.0240, 0.0206, 0.0202	0.054, -0.0070, 0.0192, 0.0201	0.046, 0.0010, 0.0190, 0.0202	0.071, 0.0089, 0.0194, 0.0204	0.244, 0.0256, 0.0210, 0.0208	0.518, 0.0436, 0.0228, 0.0213	0.957, 0.0921, 0.0248, 0.0223
cML-MA-AIC-Profile	0.969, -0.0918, 0.0223, 0.0203	0.554, -0.0425, 0.0217, 0.0204	0.238, -0.0240, 0.0206, 0.0203	0.053, -0.0070, 0.0192, 0.0202	0.045, 0.0010, 0.0190, 0.0203	0.070, 0.0089, 0.0194, 0.0205	0.241, 0.0256, 0.0210, 0.0209	0.517, 0.0436, 0.0228, 0.0215	0.957, 0.0924, 0.0249, 0.0224
cML-AIC	0.990, -0.0954, 0.0237, 0.0174	0.699, -0.0458, 0.0235, 0.0177	0.380, -0.0265, 0.0230, 0.0178	0.146, -0.0079, 0.0231, 0.018	0.117, 0.0011, 0.0231, 0.0181	0.152, 0.0101, 0.0233, 0.0182	0.389, 0.0284, 0.0238, 0.0184	0.672, 0.0474, 0.0248, 0.0186	0.987, 0.0968, 0.0258, 0.0191
cML-AIC-Profile	0.989, -0.0958, 0.0239, 0.0175	0.696, -0.0459, 0.0240, 0.0178	0.376, -0.0265, 0.0236, 0.018	0.141, -0.0079, 0.0230, 0.0181	0.114, 0.0011, 0.0231, 0.0182	0.149, 0.0101, 0.0233, 0.0183	0.386, 0.0284, 0.0238, 0.0185	0.666, 0.0475, 0.0248, 0.0187	0.987, 0.0969, 0.0259, 0.0192
cML-MA-BIC	1.000, -0.0995, 0.0162, 0.0161	0.855, -0.0496, 0.0165, 0.0164	0.430, -0.0296, 0.0167, 0.0166	0.090, -0.0097, 0.0168, 0.0167	0.052, 0.0003, 0.0169, 0.0168	0.097, 0.0102, 0.0170, 0.0169	0.417, 0.0301, 0.0172, 0.0171	0.831, 0.0501, 0.0174, 0.0173	1.000, 0.1000, 0.0180, 0.0178
cML-MA-BIC-Profile	1.000, -0.0996, 0.0162, 0.0162	0.854, -0.0496, 0.0165, 0.0165	0.426, -0.0296, 0.0167, 0.0166	0.088, -0.0097, 0.0168, 0.0168	0.049, 0.0003, 0.0169, 0.0169	0.094, 0.0102, 0.0170, 0.017	0.414, 0.0301, 0.0172, 0.0171	0.831, 0.0501, 0.0174, 0.0173	1.000, 0.1001, 0.0180, 0.0179
cML-BIC	1.000, -0.0996, 0.0162, 0.0159	0.862, -0.0497, 0.0165, 0.0162	0.443, -0.0297, 0.0166, 0.0164	0.097, -0.0097, 0.0168, 0.0165	0.057, 0.0002, 0.0169, 0.0166	0.101, 0.0102, 0.0170, 0.0167	0.433, 0.0302, 0.0172, 0.0169	0.840, 0.0502, 0.0174, 0.0171	1.000, 0.1001, 0.0180, 0.0176
cML-BIC-Profile	1.000, -0.0996, 0.0162, 0.016	0.861, -0.0497, 0.0165, 0.0163	0.442, -0.0297, 0.0166, 0.0164	0.095, -0.0097, 0.0168, 0.0166	0.054, 0.0002, 0.0169, 0.0167	0.099, 0.0102, 0.0170, 0.0167	0.432, 0.0302, 0.0172, 0.0169	0.838, 0.0502, 0.0174, 0.0171	1.000, 0.1001, 0.0180, 0.0176
MR-Mix	0.751, -0.0990, 0.0417, 0.1318	0.540, -0.0484, 0.0315, 0.2585	0.263, -0.0289, 0.0294, 0.1924	0.075, -0.0095, 0.0284, 0.1854	0.065, -0.0001, 0.0284, 0.0845	0.072, 0.0094, 0.0283, 0.1963	0.242, 0.0281, 0.0295, 0.0754	0.501, 0.0461, 0.0312, 0.2309	0.728, 0.0901, 0.0387, 0.0609
MR-ContMix	0.996, -0.1212, 0.0233, NA	0.714, -0.0681, 0.0296, NA	0.360, -0.0426, 0.0331, NA	0.104, -0.0138, 0.0363, NA	0.092, 0.0009, 0.0367, NA	0.114, 0.0155, 0.0360, NA	0.376, 0.0445, 0.0331, NA	0.673, 0.0697, 0.0304, NA	0.996, 0.1237, 0.0257, NA
MR-Lasso	1.000, -0.0991, 0.0171, 0.0165	0.824, -0.0495, 0.0178, 0.0169	0.412, -0.0295, 0.0179, 0.0171	0.098, -0.0098, 0.0180, 0.0172	0.062, 0.0002, 0.0180, 0.0173	0.103, 0.0103, 0.0182, 0.0174	0.401, 0.0297, 0.0183, 0.0175	0.790, 0.0500, 0.0185, 0.0177	1.000, 0.0996, 0.0194, 0.0183
MR-PRESSO	1.000, -0.0991, 0.0161, 0.0156	0.823, -0.0494, 0.0164, 0.0159	0.411, -0.0296, 0.0166, 0.016	0.095, -0.0097, 0.0168, 0.0162	0.062, 0.0002, 0.0168, 0.0163	0.089, 0.0101, 0.0169, 0.0163	0.395, 0.0300, 0.0171, 0.0165	0.794, 0.0499, 0.0173, 0.0167	1.000, 0.0995, 0.0179, 0.0172
MR-IVW	1.000, -0.0991, 0.0161, 0.0167	0.831, -0.0495, 0.0164, 0.0171	0.402, -0.0296, 0.0166, 0.0172	0.082, -0.0098, 0.0167, 0.0174	0.046, 0.0002, 0.0168, 0.0175	0.085, 0.0101, 0.0169, 0.0176	0.387, 0.0300, 0.0171, 0.0178	0.804, 0.0498, 0.0173, 0.018	1.000, 0.0995, 0.0179, 0.0185
MR-IVW-Oracle	1.000, -0.0991, 0.0161, 0.0167	0.831, -0.0495, 0.0164, 0.0171	0.402, -0.0296, 0.0166, 0.0172	0.082, -0.0098, 0.0167, 0.0174	0.046, 0.0002, 0.0168, 0.0175	0.085, 0.0101, 0.0169, 0.0176	0.387, 0.0300, 0.0171, 0.0178	0.804, 0.0498, 0.0173, 0.018	1.000, 0.0995, 0.0179, 0.0185
MR-Egger	0.183, -0.0863, 0.0826, 0.086	0.061, -0.0433, 0.0840, 0.0878	0.041, -0.0261, 0.0847, 0.0886	0.037, -0.0090, 0.0855, 0.0895	0.039, -0.0004, 0.0859, 0.0899	0.039, 0.0082, 0.0863, 0.0904	0.052, 0.0254, 0.0871, 0.0914	0.067, 0.0426, 0.0880, 0.0924	0.134, 0.0855, 0.0905, 0.095
MR-Weighted-Median	0.997, -0.0969, 0.0192, 0.0225	0.555, -0.0481, 0.0195, 0.0229	0.210, -0.0286, 0.0197, 0.0231	0.031, -0.0090, 0.0199, 0.0233	0.025, 0.0008, 0.0199, 0.0234	0.050, 0.0106, 0.0201, 0.0235	0.205, 0.0302, 0.0203, 0.0237	0.564, 0.0498, 0.0205, 0.024	0.994, 0.0985, 0.0210, 0.0247
MR-Weighted-Mode	0.794, -0.0960, 0.0293, 0.0371	0.209, -0.0469, 0.0293, 0.0377	0.051, -0.0272, 0.0295, 0.0381	0.007, -0.0075, 0.0298, 0.0384	0.006, 0.0020, 0.0301, 0.0386	0.010, 0.0118, 0.0302, 0.0388	0.056, 0.0310, 0.0304, 0.0392	0.203, 0.0506, 0.0306, 0.0397	0.720, 0.0991, 0.0315, 0.0408
MR-RAPS1	1.000, -0.0996, 0.0161, 0.0167	0.838, -0.0497, 0.0165, 0.017	0.415, -0.0298, 0.0166, 0.0171	0.084, -0.0098, 0.0168, 0.0173	0.051, 0.0002, 0.0169, 0.0174	0.087, 0.0102, 0.0170, 0.0175	0.392, 0.0301, 0.0172, 0.0177	0.808, 0.0501, 0.0174, 0.0179	1.000, 0.1000, 0.0180, 0.0184
MR-RAPS2	1.000, -0.1574, 4.1595, 0.0565	0.828, 0.0252, 4.4121, 0.0556	0.412, -0.0232, 4.4364, 0.0418	0.104, 0.0619, 1.9884, 0.0269	0.061, 0.0310, 2.0792, 0.0254	0.096, 0.0627, 2.2456, 0.0275	0.391, 0.0225, 4.1872, 0.0417	0.792, 0.1562, 4.7615, 0.0565	1.000, 0.2590, 4.6551, 0.0613
MR-RAPS3	1.000, -0.0997, 0.0162, 0.016	0.860, -0.0498, 0.0165, 0.0163	0.443, -0.0298, 0.0167, 0.0164	0.099, -0.0098, 0.0169, 0.0166	0.057, 0.0002, 0.0169, 0.0166	0.100, 0.0102, 0.0170, 0.0167	0.432, 0.0301, 0.0172, 0.0169	0.837, 0.0501, 0.0174, 0.0171	1.000, 0.1000, 0.0180, 0.0176
MR-RAPS4	1.000, -0.0996, 0.0165, 0.0164	0.848, -0.0497, 0.0169, 0.0167	0.418, -0.0297, 0.0170, 0.0168	0.096, -0.0097, 0.0172, 0.017	0.053, 0.0003, 0.0173, 0.0171	0.099, 0.0103, 0.0174, 0.0172	0.412, 0.0302, 0.0175, 0.0174	0.817, 0.0502, 0.0178, 0.0175	1.000, 0.1002, 0.0183, 0.0181

Table S48: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean( $SE(\hat{\theta})$ ) when  $m = 20$ , the ideal case of  $q = 0$ , and  $N = 100000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	0.998, -0.0942, 0.0155, 0.0145	0.823, -0.0445, 0.0156, 0.0147	0.419, -0.0252, 0.0149, 0.0146	0.074, -0.0080, 0.0133, 0.0144	0.039, -0.0001, 0.0129, 0.0144	0.080, 0.0076, 0.0135, 0.0145	0.386, 0.0250, 0.0154, 0.0149	0.795, 0.0441, 0.0165, 0.0153	0.996, 0.0936, 0.0173, 0.0158
cML-MA-AIC-Profile	0.998, -0.0945, 0.0155, 0.0145	0.822, -0.0445, 0.0156, 0.0147	0.420, -0.0253, 0.0149, 0.0146	0.075, -0.0080, 0.0133, 0.0144	0.039, -0.0001, 0.0129, 0.0144	0.080, 0.0077, 0.0135, 0.0145	0.385, 0.0250, 0.0155, 0.015	0.796, 0.0441, 0.0166, 0.0153	0.996, 0.0938, 0.0173, 0.0159
cML-AIC	1.000, -0.0972, 0.0167, 0.0123	0.901, -0.0474, 0.0171, 0.0126	0.580, -0.0277, 0.0166, 0.0127	0.162, -0.0090, 0.0158, 0.0128	0.104, 0.0000, 0.0157, 0.0129	0.163, 0.0086, 0.0159, 0.0129	0.535, 0.0270, 0.0172, 0.0131	0.874, 0.0468, 0.0178, 0.0132	1.000, 0.0967, 0.0183, 0.0136
cML-AIC-Profile	1.000, -0.0975, 0.0168, 0.0124	0.900, -0.0475, 0.0172, 0.0126	0.579, -0.0278, 0.0166, 0.0127	0.162, -0.0090, 0.0158, 0.0129	0.103, 0.0000, 0.0157, 0.0129	0.162, 0.0086, 0.0159, 0.013	0.533, 0.0270, 0.0172, 0.0131	0.874, 0.0468, 0.0178, 0.0132	1.000, 0.0968, 0.0183, 0.0137
cML-MA-BIC	1.000, -0.1001, 0.0110, 0.0114	0.993, -0.0501, 0.0112, 0.0116	0.739, -0.0301, 0.0113, 0.0117	0.129, -0.0102, 0.0114, 0.0118	0.039, -0.0002, 0.0114, 0.0119	0.114, 0.0098, 0.0115, 0.0119	0.686, 0.0298, 0.0116, 0.0121	0.983, 0.0498, 0.0118, 0.0122	1.000, 0.0997, 0.0121, 0.0126
cML-MA-BIC-Profile	1.000, -0.1001, 0.0110, 0.0114	0.993, -0.0501, 0.0112, 0.0116	0.738, -0.0301, 0.0113, 0.0117	0.129, -0.0102, 0.0114, 0.0118	0.038, -0.0002, 0.0114, 0.0119	0.113, 0.0098, 0.0115, 0.012	0.683, 0.0298, 0.0116, 0.0121	0.983, 0.0498, 0.0118, 0.0122	1.000, 0.0998, 0.0121, 0.0126
cML-BIC	1.000, -0.1002, 0.0110, 0.0113	0.992, -0.0502, 0.0112, 0.0115	0.748, -0.0302, 0.0113, 0.0116	0.134, -0.0102, 0.0114, 0.0117	0.039, -0.0002, 0.0115, 0.0118	0.116, 0.0098, 0.0115, 0.0118	0.696, 0.0298, 0.0117, 0.0119	0.983, 0.0498, 0.0118, 0.0121	1.000, 0.0998, 0.0122, 0.0124
cML-BIC-Profile	1.000, -0.1002, 0.0110, 0.0113	0.992, -0.0502, 0.0112, 0.0115	0.748, -0.0302, 0.0113, 0.0116	0.133, -0.0102, 0.0114, 0.0117	0.039, -0.0002, 0.0115, 0.0118	0.116, 0.0098, 0.0115, 0.0118	0.694, 0.0298, 0.0117, 0.012	0.983, 0.0498, 0.0118, 0.0121	1.000, 0.0998, 0.0122, 0.0125
MR-Mix	0.791, -0.0984, 0.0371, 0.0869	0.656, -0.0480, 0.0252, 0.0907	0.440, -0.0285, 0.0220, 0.1039	0.089, -0.0091, 0.0205, 0.058	0.050, 0.0004, 0.0202, 0.0482	0.090, 0.0096, 0.0205, 0.0588	0.428, 0.0282, 0.0222, 0.0654	0.647, 0.0463, 0.0248, 0.0866	0.763, 0.0901, 0.0342, 0.066
MR-ContMix	1.000, -0.1146, 0.0152, NA	0.923, -0.0663, 0.0186, NA	0.596, -0.0433, 0.0217, NA	0.145, -0.0158, 0.0249, NA	0.085, -0.0004, 0.0255, NA	0.131, 0.0147, 0.0252, NA	0.546, 0.0425, 0.0220, NA	0.905, 0.0668, 0.0191, NA	1.000, 0.1168, 0.0161, NA
MR-Lasso	1.000, -0.0998, 0.0120, 0.0118	0.985, -0.0501, 0.0121, 0.012	0.697, -0.0300, 0.0122, 0.0121	0.135, -0.0102, 0.0124, 0.0122	0.047, -0.0001, 0.0124, 0.0123	0.133, 0.0098, 0.0124, 0.0124	0.654, 0.0297, 0.0126, 0.0125	0.974, 0.0495, 0.0125, 0.0126	1.000, 0.0996, 0.0130, 0.013
MR-PRESSO	1.000, -0.0999, 0.0111, 0.0112	0.988, -0.0501, 0.0113, 0.0114	0.693, -0.0301, 0.0113, 0.0115	0.113, -0.0102, 0.0114, 0.0116	0.039, -0.0002, 0.0115, 0.0116	0.118, 0.0098, 0.0115, 0.0117	0.654, 0.0297, 0.0117, 0.0118	0.978, 0.0496, 0.0118, 0.0119	1.000, 0.0995, 0.0122, 0.0123
MR-IVW	1.000, -0.0999, 0.0110, 0.012	0.988, -0.0501, 0.0111, 0.0122	0.694, -0.0301, 0.0112, 0.0123	0.108, -0.0102, 0.0113, 0.0124	0.032, -0.0002, 0.0114, 0.0125	0.100, 0.0098, 0.0115, 0.0126	0.654, 0.0297, 0.0116, 0.0127	0.977, 0.0497, 0.0117, 0.0128	1.000, 0.0995, 0.0121, 0.0132
MR-IVW-Oracle	1.000, -0.0999, 0.0110, 0.012	0.988, -0.0501, 0.0111, 0.0122	0.694, -0.0301, 0.0112, 0.0123	0.108, -0.0102, 0.0113, 0.0124	0.032, -0.0002, 0.0114, 0.0125	0.100, 0.0098, 0.0115, 0.0126	0.654, 0.0297, 0.0116, 0.0127	0.977, 0.0497, 0.0117, 0.0128	1.000, 0.0995, 0.0121, 0.0132
MR-Egger	0.309, -0.0922, 0.0622, 0.0637	0.109, -0.0456, 0.0633, 0.065	0.067, -0.0270, 0.0639, 0.0656	0.045, -0.0084, 0.0645, 0.0662	0.045, 0.0009, 0.0648, 0.0665	0.049, 0.0102, 0.0651, 0.0669	0.064, 0.0288, 0.0658, 0.0675	0.113, 0.0475, 0.0665, 0.0683	0.284, 0.0940, 0.0685, 0.0702
MR-Weighted-Median	1.000, -0.0990, 0.0138, 0.016	0.895, -0.0495, 0.0140, 0.0162	0.435, -0.0297, 0.0141, 0.0164	0.050, -0.0100, 0.0142, 0.0165	0.018, -0.0001, 0.0143, 0.0166	0.067, 0.0098, 0.0144, 0.0167	0.405, 0.0296, 0.0146, 0.0169	0.848, 0.0494, 0.0148, 0.0171	1.000, 0.0989, 0.0153, 0.0176
MR-Weighted-Mode	0.973, -0.0990, 0.0207, 0.0267	0.456, -0.0494, 0.0209, 0.0272	0.131, -0.0298, 0.0210, 0.0274	0.015, -0.0099, 0.0212, 0.0277	0.005, 0.0000, 0.0213, 0.0278	0.012, 0.0099, 0.0214, 0.028	0.121, 0.0297, 0.0217, 0.0282	0.429, 0.0493, 0.0219, 0.0285	0.942, 0.0985, 0.0226, 0.0294
MR-RAPS1	1.000, -0.1002, 0.0110, 0.0119	0.989, -0.0502, 0.0112, 0.0121	0.709, -0.0302, 0.0113, 0.0122	0.114, -0.0102, 0.0114, 0.0123	0.033, -0.0002, 0.0114, 0.0124	0.101, 0.0098, 0.0115, 0.0124	0.661, 0.0298, 0.0116, 0.0126	0.978, 0.0498, 0.0118, 0.0127	1.000, 0.0997, 0.0121, 0.0131
MR-RAPS2	1.000, 0.1615, 1.2017, 0.0237	0.986, 0.0071, 2.4534, 0.0363	0.698, 0.0861, 2.9466, 0.0348	0.128, 0.0990, 1.5865, 0.0199	0.046, -0.0036, 1.0167, 0.016	0.131, 0.1293, 1.6882, 0.0217	0.653, 0.1774, 2.6544, 0.0358	0.974, 0.1085, 2.3809, 0.0362	1.000, 0.2511, 1.7903, 0.0319
MR-RAPS3	1.000, -0.1002, 0.0110, 0.0113	0.993, -0.0502, 0.0112, 0.0115	0.748, -0.0302, 0.0113, 0.0116	0.134, -0.0102, 0.0114, 0.0117	0.039, -0.0002, 0.0114, 0.0118	0.116, 0.0098, 0.0115, 0.0118	0.699, 0.0298, 0.0116, 0.012	0.983, 0.0498, 0.0118, 0.0121	1.000, 0.0998, 0.0121, 0.0125
MR-RAPS4	1.000, -0.1002, 0.0113, 0.0116	0.991, -0.0502, 0.0115, 0.0118	0.725, -0.0302, 0.0115, 0.0119	0.128, -0.0102, 0.0116, 0.012	0.040, -0.0002, 0.0117, 0.0121	0.118, 0.0098, 0.0118, 0.0121	0.667, 0.0298, 0.0119, 0.0123	0.983, 0.0498, 0.0120, 0.0124	1.000, 0.0998, 0.0124, 0.0128

Table S49: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean( $\text{SE}(\hat{\theta})$ ) when  $m = 20$ , the ideal case of  $q = 0$ , and  $N = 200000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	1.000, -0.0963, 0.0110, 0.0101	0.981, -0.0464, 0.0112, 0.0102	0.703, -0.0265, 0.0111, 0.0103	0.130, -0.0080, 0.0099, 0.0101	0.031, 0.0001, 0.0094, 0.0101	0.140, 0.0083, 0.0099, 0.0102	0.686, 0.0266, 0.0113, 0.0106	0.963, 0.0464, 0.0117, 0.0108	0.999, 0.0961, 0.0121, 0.0111
cML-MA-AIC-Profile	1.000, -0.0965, 0.0110, 0.0101	0.981, -0.0464, 0.0113, 0.0103	0.702, -0.0265, 0.0112, 0.0103	0.130, -0.0080, 0.0099, 0.0101	0.030, 0.0001, 0.0094, 0.0101	0.139, 0.0083, 0.0099, 0.0102	0.685, 0.0266, 0.0114, 0.0106	0.963, 0.0464, 0.0117, 0.0108	0.999, 0.0963, 0.0122, 0.0112
cML-AIC	1.000, -0.0983, 0.0116, 0.0087	0.989, -0.0482, 0.0119, 0.0088	0.808, -0.0282, 0.0121, 0.0089	0.242, -0.0089, 0.0116, 0.009	0.107, 0.0002, 0.0113, 0.009	0.259, 0.0093, 0.0117, 0.0091	0.793, 0.0285, 0.0125, 0.0092	0.984, 0.0484, 0.0127, 0.0093	1.000, 0.0983, 0.0129, 0.0096
cML-AIC-Profile	1.000, -0.0984, 0.0117, 0.0087	0.989, -0.0483, 0.0119, 0.0089	0.808, -0.0282, 0.0121, 0.0089	0.242, -0.0089, 0.0116, 0.009	0.106, 0.0002, 0.0113, 0.0091	0.259, 0.0093, 0.0117, 0.0091	0.793, 0.0285, 0.0125, 0.0092	0.984, 0.0484, 0.0126, 0.0093	1.000, 0.0984, 0.0130, 0.0096
cML-MA-BIC	1.000, -0.1001, 0.0078, 0.008	1.000, -0.0501, 0.0080, 0.0082	0.967, -0.0301, 0.0081, 0.0082	0.234, -0.0101, 0.0081, 0.0083	0.041, -0.0001, 0.0082, 0.0084	0.226, 0.0099, 0.0082, 0.0084	0.946, 0.0299, 0.0083, 0.0085	1.000, 0.0499, 0.0084, 0.0086	1.000, 0.0999, 0.0087, 0.0089
cML-MA-BIC-Profile	1.000, -0.1001, 0.0078, 0.008	1.000, -0.0501, 0.0080, 0.0082	0.967, -0.0301, 0.0081, 0.0083	0.233, -0.0101, 0.0081, 0.0083	0.041, -0.0001, 0.0082, 0.0084	0.226, 0.0099, 0.0082, 0.0084	0.946, 0.0299, 0.0083, 0.0085	1.000, 0.0499, 0.0084, 0.0086	1.000, 0.0999, 0.0087, 0.0089
cML-BIC	1.000, -0.1001, 0.0079, 0.008	1.000, -0.0501, 0.0080, 0.0081	0.968, -0.0301, 0.0081, 0.0082	0.238, -0.0101, 0.0081, 0.0083	0.046, -0.0001, 0.0082, 0.0083	0.231, 0.0099, 0.0082, 0.0083	0.948, 0.0299, 0.0083, 0.0084	1.000, 0.0499, 0.0084, 0.0085	1.000, 0.0999, 0.0087, 0.0088
cML-BIC-Profile	1.000, -0.1001, 0.0079, 0.008	1.000, -0.0501, 0.0080, 0.0081	0.968, -0.0301, 0.0081, 0.0082	0.238, -0.0101, 0.0081, 0.0083	0.046, -0.0001, 0.0082, 0.0083	0.231, 0.0099, 0.0082, 0.0083	0.948, 0.0299, 0.0083, 0.0084	1.000, 0.0499, 0.0084, 0.0085	1.000, 0.0999, 0.0087, 0.0088
MR-Mix	0.828, -0.0985, 0.0335, 0.0201, 0.0296	0.751, -0.0476, 0.0159, 0.01742	0.606, -0.0283, 0.0159, 0.379	0.140, -0.0094, 0.0138, 0.0608	0.061, 0.0002, 0.0135, 0.0518	0.157, 0.0095, 0.0137, 0.0487	0.627, 0.0281, 0.0161, 0.0422	0.736, 0.0462, 0.0198, 0.0668	0.829, 0.0894, 0.0319, 0.0301
MR-ContMix	1.000, -0.1073, 0.0094, NA	0.997, -0.0613, 0.0118, NA	0.836, -0.0407, 0.0139, NA	0.205, -0.0145, 0.0169, NA	0.071, 0.0003, 0.0175, NA	0.223, 0.0149, 0.0166, NA	0.817, 0.0402, 0.0138, NA	0.996, 0.0612, 0.0119, NA	1.000, 0.1086, 0.0102, NA
MR-Lasso	1.000, -0.1000, 0.0084, 0.0083	0.999, -0.0501, 0.0086, 0.0084	0.936, -0.0301, 0.0085, 0.0085	0.234, -0.0101, 0.0087, 0.0086	0.050, -0.0001, 0.0088, 0.0086	0.223, 0.0099, 0.0088, 0.0087	0.929, 0.0299, 0.0089, 0.0088	1.000, 0.0499, 0.0088, 0.0089	1.000, 0.0998, 0.0093, 0.0091
MR-PRESSO	1.000, -0.1000, 0.0079, 0.0078	1.000, -0.0501, 0.0080, 0.0079	0.945, -0.0301, 0.0081, 0.008	0.221, -0.0101, 0.0082, 0.0081	0.039, -0.0001, 0.0082, 0.0081	0.219, 0.0098, 0.0083, 0.0082	0.921, 0.0298, 0.0083, 0.0083	1.000, 0.0498, 0.0084, 0.0083	1.000, 0.0997, 0.0087, 0.0086
MR-IVW	1.000, -0.1000, 0.0078, 0.0084	1.000, -0.0500, 0.0080, 0.0086	0.949, -0.0301, 0.0081, 0.0086	0.211, -0.0101, 0.0081, 0.0087	0.033, -0.0001, 0.0082, 0.0088	0.210, 0.0099, 0.0082, 0.0088	0.929, 0.0299, 0.0083, 0.0089	1.000, 0.0498, 0.0084, 0.009	1.000, 0.0998, 0.0087, 0.0093
MR-IVW-Oracle	1.000, -0.1000, 0.0078, 0.0084	1.000, -0.0500, 0.0080, 0.0086	0.949, -0.0301, 0.0081, 0.0086	0.211, -0.0101, 0.0081, 0.0087	0.033, -0.0001, 0.0082, 0.0088	0.210, 0.0099, 0.0082, 0.0088	0.929, 0.0299, 0.0083, 0.0089	1.000, 0.0498, 0.0084, 0.009	1.000, 0.0998, 0.0087, 0.0093
MR-Egger	0.562, -0.0964, 0.0443, 0.0455	0.185, -0.0482, 0.0452, 0.0464	0.095, -0.0290, 0.0457, 0.0469	0.044, -0.0097, 0.0462, 0.0473	0.042, -0.0001, 0.0464, 0.0476	0.049, 0.0096, 0.0467, 0.0478	0.080, 0.0288, 0.0472, 0.0483	0.174, 0.0481, 0.0478, 0.0488	0.492, 0.0962, 0.0493, 0.0502
MR-Weighted-Median	1.000, -0.0997, 0.0099, 0.0112	0.996, -0.0499, 0.0101, 0.0114	0.756, -0.0300, 0.0102, 0.0115	0.114, -0.0101, 0.0103, 0.0116	0.019, -0.0002, 0.0103, 0.0117	0.117, 0.0098, 0.0104, 0.0117	0.724, 0.0297, 0.0105, 0.0119	0.994, 0.0496, 0.0106, 0.012	1.000, 0.0994, 0.0109, 0.0124
MR-Weighted-Mode	1.000, -0.0994, 0.0144, 0.0187	0.786, -0.0498, 0.0147, 0.019	0.345, -0.0299, 0.0148, 0.0192	0.020, -0.0102, 0.0150, 0.0194	0.007, -0.0004, 0.0151, 0.0195	0.026, 0.0095, 0.0152, 0.0196	0.305, 0.0295, 0.0153, 0.0198	0.740, 0.0494, 0.0155, 0.02	0.999, 0.0993, 0.0159, 0.0206
MR-RAPS1	1.000, -0.1001, 0.0079, 0.0083	1.000, -0.0501, 0.0080, 0.0085	0.952, -0.0301, 0.0081, 0.0086	0.219, -0.0101, 0.0082, 0.0086	0.035, -0.0001, 0.0082, 0.0087	0.215, 0.0099, 0.0082, 0.0087	0.930, 0.0299, 0.0083, 0.0088	1.000, 0.0499, 0.0084, 0.0089	1.000, 0.0999, 0.0087, 0.0092
MR-RAPS2	1.000, -0.0230, 0.2890, 0.0105	1.000, -0.0397, 1.0738, 0.0202	0.943, 0.0841, 3.4025, 0.025	0.235, 0.1322, 2.6761, 0.0189	0.052, 0.1164, 1.2820, 0.0128	0.238, 0.0919, 1.9255, 0.0197	0.925, 0.0723, 1.5577, 0.0239	1.000, 0.0851, 1.1493, 0.021	1.000, 0.1477, 0.4888, 0.0138
MR-RAPS3	1.000, -0.1001, 0.0078, 0.008	1.000, -0.0501, 0.0080, 0.0081	0.967, -0.0301, 0.0081, 0.0082	0.239, -0.0101, 0.0081, 0.0083	0.046, -0.0001, 0.0082, 0.0083	0.230, 0.0099, 0.0082, 0.0083	0.947, 0.0299, 0.0083, 0.0084	1.000, 0.0499, 0.0084, 0.0085	1.000, 0.0999, 0.0087, 0.0088
MR-RAPS4	1.000, -0.1001, 0.0080, 0.0082	1.000, -0.0501, 0.0082, 0.0083	0.956, -0.0301, 0.0082, 0.0084	0.224, -0.0101, 0.0083, 0.0085	0.039, -0.0001, 0.0083, 0.0085	0.221, 0.0099, 0.0084, 0.0086	0.943, 0.0299, 0.0085, 0.0086	1.000, 0.0499, 0.0086, 0.0087	1.000, 0.0999, 0.0089, 0.009

Table S50: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean( $SE(\hat{\theta})$ ) when  $m = 20$ , the InSIDE satisfied,  $q = 0.2$ , and  $N = 50000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	0.941, -0.0908, 0.0249, 0.0234	0.460, -0.0423, 0.0236, 0.0234	0.178, -0.0244, 0.0221, 0.0232	0.044, -0.0080, 0.0204, 0.0232	0.033, -0.0004, 0.0202, 0.0233	0.046, 0.0070, 0.0207, 0.0234	0.153, 0.0231, 0.0225, 0.0239	0.404, 0.0405, 0.0248, 0.0245	0.886, 0.0884, 0.0275, 0.0257
cML-MA-AIC-Profile	0.941, -0.0911, 0.0250, 0.0235	0.458, -0.0423, 0.0236, 0.0236	0.177, -0.0244, 0.0221, 0.0234	0.044, -0.0080, 0.0204, 0.0233	0.031, -0.0004, 0.0202, 0.0234	0.045, 0.0070, 0.0207, 0.0236	0.151, 0.0231, 0.0225, 0.024	0.399, 0.0406, 0.0248, 0.0246	0.884, 0.0886, 0.0276, 0.0259
cML-AIC	0.966, -0.0956, 0.0267, 0.0198	0.638, -0.0467, 0.0260, 0.0202	0.331, -0.0278, 0.0254, 0.0204	0.115, -0.0095, 0.0247, 0.0206	0.098, -0.0009, 0.0248, 0.0207	0.121, 0.0077, 0.0252, 0.0208	0.280, 0.0258, 0.0264, 0.021	0.549, 0.0444, 0.0277, 0.0212	0.952, 0.0934, 0.0290, 0.0218
cML-AIC-Profile	0.966, -0.0958, 0.0268, 0.02	0.636, -0.0468, 0.0261, 0.0203	0.328, -0.0279, 0.0254, 0.0205	0.115, -0.0095, 0.0247, 0.0207	0.098, -0.0009, 0.0248, 0.0208	0.122, 0.0078, 0.0253, 0.0209	0.277, 0.0258, 0.0264, 0.0211	0.548, 0.0444, 0.0277, 0.0213	0.951, 0.0936, 0.0291, 0.022
cML-MA-BIC	1.000, -0.1000, 0.0189, 0.0185	0.753, -0.0500, 0.0192, 0.0188	0.367, -0.0300, 0.0193, 0.0189	0.086, -0.0101, 0.0195, 0.0191	0.052, -0.0001, 0.0196, 0.0192	0.083, 0.0099, 0.0197, 0.0193	0.341, 0.0298, 0.0199, 0.0195	0.702, 0.0498, 0.0202, 0.0197	0.997, 0.0998, 0.0208, 0.0203
cML-MA-BIC-Profile	1.000, -0.1000, 0.0189, 0.0185	0.749, -0.0500, 0.0192, 0.0188	0.364, -0.0300, 0.0193, 0.019	0.083, -0.0101, 0.0195, 0.0192	0.052, -0.0001, 0.0196, 0.0193	0.083, 0.0099, 0.0197, 0.0193	0.339, 0.0298, 0.0199, 0.0195	0.701, 0.0498, 0.0202, 0.0198	0.997, 0.0998, 0.0208, 0.0203
cML-BIC	1.000, -0.1000, 0.0189, 0.0182	0.754, -0.0499, 0.0193, 0.0185	0.372, -0.0300, 0.0194, 0.0187	0.091, -0.0100, 0.0196, 0.0189	0.053, 0.0000, 0.0197, 0.019	0.092, 0.0100, 0.0198, 0.019	0.357, 0.0300, 0.0200, 0.0192	0.716, 0.0500, 0.0202, 0.0195	0.997, 0.1000, 0.0208, 0.02
cML-BIC-Profile	1.000, -0.1000, 0.0189, 0.0183	0.751, -0.0499, 0.0193, 0.0186	0.371, -0.0300, 0.0194, 0.0188	0.091, -0.0100, 0.0196, 0.0189	0.053, 0.0000, 0.0197, 0.019	0.092, 0.0100, 0.0198, 0.0191	0.355, 0.0300, 0.0200, 0.0193	0.715, 0.0500, 0.0202, 0.0195	0.997, 0.1000, 0.0208, 0.0201
MR-Mix	0.934, -0.1049, 0.0234, 0.0311	0.387, -0.0508, 0.0234, 0.0308	0.119, -0.0297, 0.0234, 0.0307	0.017, -0.0091, 0.0233, 0.0307	0.013, 0.0010, 0.0232, 0.0307	0.030, 0.0111, 0.0232, 0.0307	0.127, 0.0309, 0.0233, 0.0306	0.378, 0.0503, 0.0233, 0.0306	0.924, 0.0973, 0.0233, 0.0305
MR-ContMix	1.000, -0.0997, 0.0200, NA	0.725, -0.0502, 0.0204, NA	0.358, -0.0303, 0.0205, NA	0.098, -0.0104, 0.0206, NA	0.059, -0.0005, 0.0207, NA	0.089, 0.0095, 0.0209, NA	0.327, 0.0294, 0.0211, NA	0.677, 0.0492, 0.0214, NA	0.993, 0.0989, 0.0222, NA
MR-Lasso	1.000, -0.0997, 0.0192, 0.0191	0.730, -0.0499, 0.0197, 0.0194	0.334, -0.0300, 0.0197, 0.0196	0.085, -0.0101, 0.0199, 0.0198	0.050, -0.0002, 0.0199, 0.0199	0.080, 0.0098, 0.0201, 0.02	0.318, 0.0296, 0.0204, 0.0202	0.668, 0.0496, 0.0206, 0.0204	0.996, 0.0994, 0.0212, 0.021
MR-PRESSO	0.877, -0.1010, 0.0629, 0.0209	0.652, -0.0522, 0.0626, 0.021	0.461, -0.0324, 0.0610, 0.0208	0.303, -0.0130, 0.0617, 0.021	0.258, -0.0036, 0.0620, 0.0211	0.286, 0.0058, 0.0611, 0.0211	0.409, 0.0258, 0.0604, 0.0211	0.599, 0.0457, 0.0593, 0.0212	0.867, 0.0953, 0.0581, 0.0214
MR-IVW	0.107, -0.1078, 0.1697, 0.1654	0.089, -0.0579, 0.1696, 0.1654	0.083, -0.0379, 0.1696, 0.1654	0.088, -0.0179, 0.1696, 0.1654	0.085, -0.0079, 0.1696, 0.1654	0.086, 0.0020, 0.1696, 0.1654	0.083, 0.0220, 0.1696, 0.1654	0.082, 0.0420, 0.1696, 0.1654	0.097, 0.0919, 0.1696, 0.1654
MR-IVW-Oracle	1.000, -0.0994, 0.0186, 0.0193	0.722, -0.0497, 0.0190, 0.0197	0.318, -0.0298, 0.0191, 0.0198	0.073, -0.0099, 0.0193, 0.02	0.041, 0.0000, 0.0194, 0.0201	0.071, 0.0100, 0.0195, 0.0202	0.314, 0.0298, 0.0197, 0.0204	0.667, 0.0497, 0.0199, 0.0206	0.996, 0.0995, 0.0205, 0.0212
MR-Egger	0.071, -0.0209, 0.8701, 0.8466	0.074, 0.0223, 0.8701, 0.8466	0.075, 0.0396, 0.8702, 0.8466	0.075, 0.0568, 0.8702, 0.8466	0.075, 0.0655, 0.8702, 0.8466	0.076, 0.0741, 0.8703, 0.8467	0.076, 0.0914, 0.8703, 0.8467	0.076, 0.1086, 0.8704, 0.8467	0.072, 0.1518, 0.8705, 0.8468
MR-Weighted-Median	0.973, -0.0974, 0.0226, 0.0254	0.487, -0.0489, 0.0230, 0.0258	0.175, -0.0294, 0.0232, 0.026	0.041, -0.0100, 0.0235, 0.0263	0.025, -0.0003, 0.0236, 0.0264	0.043, 0.0094, 0.0237, 0.0265	0.158, 0.0289, 0.0239, 0.0268	0.432, 0.0484, 0.0242, 0.0271	0.949, 0.0971, 0.0252, 0.0279
MR-Weighted-Mode	0.916, -0.0980, 0.0263, 0.0308	0.344, -0.0490, 0.0268, 0.0314	0.123, -0.0297, 0.0272, 0.0316	0.023, -0.0100, 0.0274, 0.0319	0.023, -0.0001, 0.0277, 0.0321	0.032, 0.0097, 0.0277, 0.0322	0.117, 0.0292, 0.0283, 0.0326	0.298, 0.0488, 0.0285, 0.0329	0.862, 0.0977, 0.0296, 0.0339
MR-RAPS1	0.105, -0.1083, 0.1668, 0.1618	0.086, -0.0583, 0.1669, 0.1618	0.096, -0.0382, 0.1669, 0.1618	0.099, -0.0182, 0.1669, 0.1619	0.101, -0.0082, 0.1669, 0.1619	0.100, 0.0018, 0.1669, 0.1619	0.090, 0.0218, 0.1670, 0.1619	0.080, 0.0418, 0.1670, 0.1619	0.092, 0.0918, 0.1671, 0.162
MR-RAPS2	0.991, 0.2414, 3.4866, 0.0498	0.905, 0.2583, 3.3666, 0.035	0.778, 0.2497, 2.7536, 0.036	0.636, 0.3900, 3.9040, 0.0362	0.646, 0.5145, 5.0016, 0.0405	0.658, 0.3228, 3.0375, 0.0341	0.782, 0.5106, 3.2553, 0.0388	0.907, 0.3514, 3.7643, 0.0422	0.994, 0.2625, 3.8922, 0.0483
MR-RAPS3	0.901, -0.2260, 0.3464, 0.0404	0.848, -0.1187, 0.3423, 0.0393	0.829, -0.0770, 0.3387, 0.0387	0.828, -0.0363, 0.3341, 0.0382	0.831, -0.0164, 0.3315, 0.038	0.829, 0.0032, 0.3287, 0.0377	0.847, 0.0414, 0.3227, 0.0372	0.871, 0.0784, 0.3162, 0.0366	0.889, 0.1649, 0.2989, 0.0355
MR-RAPS4	1.000, -0.2182, 1.1830, 0.0353	0.968, -0.0554, 1.1372, 0.0333	0.901, 0.0073, 1.1520, 0.0335	0.849, 0.1234, 1.1165, 0.0323	0.837, 0.1738, 1.0960, 0.0319	0.847, 0.2090, 1.0959, 0.0321	0.898, 0.3159, 1.1012, 0.0327	0.956, 0.3864, 1.0980, 0.033	1.000, 0.5563, 1.0458, 0.0329

Table S51: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean( $SE(\hat{\theta})$ ) when  $m = 20$ , the InSIDE satisfied,  $q = 0.2$ , and  $N = 100000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	0.993, -0.0933, 0.0183, 0.0166	0.718, -0.0436, 0.0183, 0.0168	0.335, -0.0248, 0.0173, 0.0166	0.070, -0.0079, 0.0157, 0.0164	0.044, -0.0003, 0.0156, 0.0164	0.076, 0.0076, 0.0160, 0.0166	0.323, 0.0246, 0.0177, 0.0171	0.681, 0.0434, 0.0193, 0.0175	0.983, 0.0925, 0.0206, 0.0182
cML-MA-AIC-Profile	0.993, -0.0935, 0.0184, 0.0167	0.715, -0.0437, 0.0184, 0.0168	0.333, -0.0248, 0.0173, 0.0167	0.070, -0.0079, 0.0157, 0.0165	0.044, -0.0003, 0.0156, 0.0165	0.074, 0.0076, 0.0160, 0.0166	0.322, 0.0247, 0.0177, 0.0171	0.680, 0.0434, 0.0193, 0.0176	0.983, 0.0927, 0.0207, 0.0183
cML-AIC	0.996, -0.0968, 0.0195, 0.014	0.837, -0.0472, 0.0198, 0.0143	0.505, -0.0277, 0.0195, 0.0144	0.173, -0.0094, 0.0188, 0.0146	0.124, -0.0007, 0.0188, 0.0146	0.175, 0.0084, 0.0190, 0.0147	0.476, 0.0271, 0.0199, 0.0148	0.788, 0.0465, 0.0210, 0.015	0.995, 0.0962, 0.0219, 0.0154
cML-AIC-Profile	0.996, -0.0970, 0.0195, 0.0141	0.835, -0.0473, 0.0198, 0.0143	0.505, -0.0277, 0.0195, 0.0145	0.172, -0.0094, 0.0188, 0.0146	0.123, -0.0007, 0.0188, 0.0147	0.173, 0.0084, 0.0190, 0.0148	0.475, 0.0271, 0.0199, 0.0149	0.787, 0.0465, 0.0210, 0.0151	0.994, 0.0963, 0.0219, 0.0155
cML-MA-BIC	1.000, -0.1001, 0.0134, 0.013	0.960, -0.0501, 0.0137, 0.0133	0.612, -0.0301, 0.0138, 0.0134	0.123, -0.0102, 0.0139, 0.0135	0.050, -0.0002, 0.0140, 0.0136	0.120, 0.0098, 0.0141, 0.0136	0.586, 0.0297, 0.0143, 0.0138	0.939, 0.0497, 0.0144, 0.0139	1.000, 0.0997, 0.0149, 0.0143
cML-MA-BIC-Profile	1.000, -0.1001, 0.0137, 0.0131	0.960, -0.0501, 0.0137, 0.0133	0.610, -0.0301, 0.0138, 0.0134	0.122, -0.0102, 0.0139, 0.0135	0.050, -0.0002, 0.0140, 0.0136	0.120, 0.0098, 0.0141, 0.0137	0.585, 0.0297, 0.0143, 0.0138	0.938, 0.0497, 0.0144, 0.0139	1.000, 0.0997, 0.0149, 0.0144
cML-BIC	1.000, -0.1002, 0.0134, 0.0129	0.966, -0.0502, 0.0137, 0.0131	0.621, -0.0302, 0.0138, 0.0132	0.130, -0.0102, 0.0140, 0.0134	0.056, -0.0002, 0.0140, 0.0134	0.124, 0.0098, 0.0141, 0.0135	0.597, 0.0298, 0.0143, 0.0136	0.941, 0.0497, 0.0144, 0.0138	1.000, 0.0997, 0.0148, 0.0142
cML-BIC-Profile	1.000, -0.1002, 0.0134, 0.0129	0.965, -0.0502, 0.0137, 0.0132	0.621, -0.0302, 0.0138, 0.0133	0.130, -0.0102, 0.0140, 0.0134	0.053, -0.0002, 0.0140, 0.0134	0.124, 0.0098, 0.0141, 0.0135	0.597, 0.0298, 0.0143, 0.0137	0.941, 0.0497, 0.0144, 0.0138	1.000, 0.0997, 0.0148, 0.0142
MR-Mix	0.997, -0.1062, 0.0171, 0.0223	0.700, -0.0522, 0.0171, 0.0221	0.259, -0.0311, 0.0172, 0.0224	0.036, -0.0104, 0.0173, 0.0221	0.013, -0.0002, 0.0172, 0.0221	0.040, 0.0098, 0.0172, 0.022	0.246, 0.0296, 0.0171, 0.022	0.662, 0.0492, 0.0171, 0.022	0.990, 0.0958, 0.0172, 0.0221
MR-ContMix	1.000, -0.0997, 0.0141, NA	0.943, -0.0498, 0.0144, NA	0.604, -0.0299, 0.0145, NA	0.133, -0.0100, 0.0147, NA	0.068, 0.0000, 0.0148, NA	0.132, 0.0099, 0.0148, NA	0.586, 0.0299, 0.0150, NA	0.920, 0.0498, 0.0152, NA	1.000, 0.0997, 0.0158, NA
MR-Lasso	1.000, -0.0998, 0.0138, 0.0135	0.952, -0.0501, 0.0142, 0.0138	0.587, -0.0302, 0.0144, 0.0139	0.121, -0.0102, 0.0146, 0.0141	0.062, -0.0003, 0.0147, 0.0141	0.119, 0.0097, 0.0146, 0.0142	0.559, 0.0297, 0.0147, 0.0143	0.916, 0.0495, 0.0149, 0.0145	1.000, 0.0994, 0.0154, 0.0149
MR-PRESSO	0.849, -0.1053, 0.1180, 0.0314	0.714, -0.0573, 0.1173, 0.0312	0.540, -0.0375, 0.1166, 0.0308	0.363, -0.0177, 0.1167, 0.0306	0.336, -0.0080, 0.1154, 0.0305	0.357, 0.0018, 0.1153, 0.0306	0.540, 0.0219, 0.1146, 0.0303	0.689, 0.0419, 0.1136, 0.0299	0.825, 0.0898, 0.1090, 0.0285
MR-IVW	0.108, -0.1096, 0.1680, 0.1661	0.081, -0.0596, 0.1680, 0.166	0.079, -0.0396, 0.1680, 0.166	0.077, -0.0196, 0.1679, 0.166	0.078, -0.0096, 0.1679, 0.166	0.087, 0.0004, 0.1679, 0.166	0.079, 0.0204, 0.1679, 0.166	0.074, 0.0404, 0.1679, 0.166	0.081, 0.0904, 0.1679, 0.166
MR-IVW-Oracle	1.000, -0.0998, 0.0133, 0.0137	0.952, -0.0500, 0.0136, 0.0139	0.580, -0.0301, 0.0138, 0.0141	0.108, -0.0102, 0.0138, 0.0142	0.045, -0.0002, 0.0139, 0.0143	0.109, 0.0098, 0.0140, 0.0143	0.552, 0.0297, 0.0141, 0.0145	0.917, 0.0496, 0.0143, 0.0146	1.000, 0.0995, 0.0147, 0.0151
MR-Egger	0.053, -0.0970, 0.8833, 0.8867	0.050, -0.0504, 0.8830, 0.8866	0.052, -0.0318, 0.8828, 0.8866	0.049, -0.0132, 0.8827, 0.8865	0.049, -0.0039, 0.8826, 0.8865	0.047, 0.0054, 0.8826, 0.8865	0.046, 0.0240, 0.8824, 0.8865	0.047, 0.0426, 0.8823, 0.8865	0.051, 0.0891, 0.8820, 0.8865
MR-Weighted-Median	1.000, -0.0987, 0.0165, 0.018	0.787, -0.0493, 0.0168, 0.0183	0.357, -0.0296, 0.0169, 0.0185	0.060, -0.0098, 0.0171, 0.0186	0.026, 0.0000, 0.0172, 0.0187	0.058, 0.0099, 0.0173, 0.0188	0.343, 0.0295, 0.0175, 0.019	0.749, 0.0491, 0.0177, 0.0192	1.000, 0.0983, 0.0182, 0.0198
MR-Weighted-Mode	0.995, -0.0987, 0.0197, 0.0221	0.609, -0.0495, 0.0197, 0.0225	0.240, -0.0295, 0.0198, 0.0227	0.043, -0.0099, 0.0200, 0.0228	0.019, -0.0001, 0.0202, 0.023	0.039, 0.0099, 0.0203, 0.0231	0.228, 0.0295, 0.0205, 0.0233	0.577, 0.0493, 0.0208, 0.0236	0.985, 0.0987, 0.0214, 0.0243
MR-RAPS1	0.095, -0.1072, 0.1634, 0.1619	0.082, -0.0572, 0.1634, 0.1619	0.088, -0.0372, 0.1635, 0.1619	0.091, -0.0172, 0.1635, 0.1619	0.093, -0.0073, 0.1635, 0.1619	0.093, 0.0027, 0.1635, 0.1619	0.085, 0.0227, 0.1635, 0.162	0.070, 0.0427, 0.1635, 0.162	0.070, 0.0927, 0.1636, 0.162
MR-RAPS2	0.997, 0.6928, 3.3134, 0.0357	0.983, 0.2831, 2.9407, 0.0227	0.867, 0.4724, 4.6226, 0.0231	0.706, 0.3816, 2.2356, 0.0231	0.680, 0.2261, 3.4411, 0.0228	0.728, 0.2819, 2.4180, 0.0246	0.884, 0.8065, 8.6537, 0.0295	0.977, 0.3940, 4.7269, 0.0299	0.993, 0.7312, 8.8020, 0.0378
MR-RAPS3	0.925, -0.2304, 0.3421, 0.0293	0.918, -0.1214, 0.3384, 0.0282	0.887, -0.0792, 0.3384, 0.0278	0.873, -0.0381, 0.3384, 0.0274	0.868, -0.0180, 0.3312, 0.0272	0.884, 0.0018, 0.3284, 0.027	0.887, 0.0404, 0.3224, 0.0266	0.900, 0.0776, 0.3158, 0.0262	0.923, 0.1648, 0.2985, 0.0253
MR-RAPS4	1.000, 0.3571, 1.0738, 0.0253	0.999, 0.4107, 1.0289, 0.0235	0.999, 0.4326, 1.0006, 0.0227	0.932, 0.4616, 0.9527, 0.0217	0.931, 0.4855, 0.9528, 0.0219	0.928, 0.5026, 0.9786, 0.0226	0.974, 0.5353, 0.9597, 0.0221	0.994, 0.5806, 0.9693, 0.0225	1.000, 0.6787, 1.0068, 0.0237



Table S52: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean(SE( $\hat{\theta}$ )) when  $m = 20$ , the InSIDE satisfied,  $q = 0.2$ , and  $N = 200000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	0.999, -0.0951, 0.0124, 0.0119	0.929, -0.0452, 0.0125, 0.0121	0.560, -0.0255, 0.0122, 0.012	0.094, -0.0079, 0.0108, 0.0117	0.034, -0.0002, 0.0103, 0.0117	0.090, 0.0076, 0.0108, 0.0119	0.530, 0.0251, 0.0127, 0.0123	0.897, 0.0447, 0.0133, 0.0126	1.000, 0.0945, 0.0139, 0.013
cML-MA-AIC-Profile	0.999, -0.0953, 0.0124, 0.0119	0.929, -0.0452, 0.0126, 0.0121	0.558, -0.0255, 0.0122, 0.012	0.094, -0.0079, 0.0108, 0.0118	0.034, -0.0002, 0.0103, 0.0117	0.089, 0.0076, 0.0108, 0.0119	0.530, 0.0251, 0.0127, 0.0124	0.897, 0.0448, 0.0134, 0.0127	1.000, 0.0946, 0.0139, 0.013
cML-AIC	1.000, -0.0979, 0.0132, 0.0099	0.962, -0.0477, 0.0137, 0.0101	0.721, -0.0278, 0.0136, 0.0102	0.211, -0.0091, 0.0130, 0.0103	0.108, -0.0004, 0.0129, 0.0104	0.206, 0.0085, 0.0130, 0.0104	0.702, 0.0275, 0.0139, 0.0105	0.949, 0.0473, 0.0142, 0.0106	1.000, 0.0973, 0.0145, 0.0109
cML-AIC-Profile	1.000, -0.0979, 0.0132, 0.01	0.962, -0.0477, 0.0137, 0.0102	0.721, -0.0278, 0.0137, 0.0102	0.211, -0.0091, 0.0130, 0.0103	0.108, -0.0004, 0.0129, 0.0104	0.205, 0.0085, 0.0130, 0.0104	0.702, 0.0275, 0.0139, 0.0105	0.949, 0.0474, 0.0142, 0.0106	1.000, 0.0974, 0.0146, 0.0109
cML-MA-BIC	1.000, -0.1000, 0.0091, 0.0092	1.000, -0.0499, 0.0093, 0.0093	0.890, -0.0299, 0.0094, 0.0094	0.179, -0.0099, 0.0095, 0.0095	0.049, 0.0001, 0.0095, 0.0095	0.184, 0.0100, 0.0096, 0.0096	0.869, 0.0300, 0.0097, 0.0097	0.997, 0.0500, 0.0098, 0.0098	1.000, 0.1001, 0.0101, 0.0101
cML-MA-BIC-Profile	1.000, -0.1000, 0.0091, 0.0092	1.000, -0.0499, 0.0093, 0.0094	0.889, -0.0299, 0.0094, 0.0094	0.177, -0.0099, 0.0095, 0.0095	0.049, 0.0001, 0.0095, 0.0096	0.184, 0.0100, 0.0096, 0.0096	0.868, 0.0300, 0.0097, 0.0097	0.997, 0.0500, 0.0098, 0.0098	1.000, 0.1001, 0.0101, 0.0101
cML-BIC	1.000, -0.1000, 0.0091, 0.0091	1.000, -0.0500, 0.0093, 0.0093	0.897, -0.0299, 0.0094, 0.0093	0.181, -0.0099, 0.0095, 0.0094	0.050, 0.0001, 0.0095, 0.0095	0.191, 0.0101, 0.0096, 0.0095	0.874, 0.0301, 0.0097, 0.0096	0.997, 0.0501, 0.0098, 0.0097	1.000, 0.1001, 0.0101, 0.01
cML-BIC-Profile	1.000, -0.1000, 0.0091, 0.0091	1.000, -0.0500, 0.0093, 0.0093	0.897, -0.0299, 0.0094, 0.0094	0.181, -0.0099, 0.0095, 0.0094	0.050, 0.0001, 0.0095, 0.0095	0.190, 0.0101, 0.0096, 0.0095	0.874, 0.0301, 0.0097, 0.0096	0.997, 0.0501, 0.0098, 0.0097	1.000, 0.1001, 0.0101, 0.01
MR-Mix	1.000, -0.1062, 0.0126, 0.0162	0.933, -0.0517, 0.0126, 0.0161	0.479, -0.0307, 0.0124, 0.0161	0.052, -0.0101, 0.0125, 0.0161	0.009, 0.0000, 0.0124, 0.0161	0.051, 0.0101, 0.0124, 0.0161	0.497, 0.0300, 0.0124, 0.0161	0.888, 0.0496, 0.0123, 0.0161	0.998, 0.0966, 0.0124, 0.0163
MR-ContMix	1.000, -0.0998, 0.0095, NA	0.999, -0.0498, 0.0096, NA	0.892, -0.0299, 0.0097, NA	0.188, -0.0099, 0.0097, NA	0.065, 0.0001, 0.0098, NA	0.196, 0.0100, 0.0098, NA	0.861, 0.0300, 0.0100, NA	0.998, 0.0500, 0.0101, NA	1.000, 0.0999, 0.0104, NA
MR-Lasso	1.000, -0.0998, 0.0094, 0.0096	0.999, -0.0499, 0.0096, 0.0098	0.866, -0.0299, 0.0097, 0.0099	0.173, -0.0100, 0.0097, 0.01	0.048, 0.0000, 0.0098, 0.01	0.168, 0.0100, 0.0098, 0.0101	0.845, 0.0299, 0.0099, 0.0102	0.995, 0.0499, 0.0100, 0.0103	1.000, 0.0999, 0.0103, 0.0106
MR-PRESSO	0.671, -0.0931, 0.1512, 0.0583	0.599, -0.0440, 0.1501, 0.0566	0.528, -0.0243, 0.1496, 0.056	0.320, -0.0049, 0.1491, 0.0555	0.268, 0.0042, 0.1484, 0.0546	0.305, 0.0139, 0.1479, 0.054	0.507, 0.0335, 0.1473, 0.053	0.608, 0.0531, 0.1465, 0.0522	0.726, 0.1037, 0.1439, 0.0492
MR-IVW	0.087, -0.0969, 0.1706, 0.1654	0.077, -0.0468, 0.1706, 0.1654	0.084, -0.0267, 0.1706, 0.1653	0.086, -0.0067, 0.1706, 0.1653	0.087, 0.0034, 0.1706, 0.1653	0.087, 0.0134, 0.1706, 0.1653	0.087, 0.0334, 0.1705, 0.1653	0.090, 0.0535, 0.1705, 0.1653	0.110, 0.1036, 0.1705, 0.1653
MR-IVW-Oracle	1.000, -0.0998, 0.0091, 0.0097	0.999, -0.0499, 0.0093, 0.0099	0.867, -0.0299, 0.0094, 0.01	0.157, -0.0099, 0.0095, 0.0101	0.043, 0.0001, 0.0095, 0.0101	0.157, 0.0101, 0.0096, 0.0102	0.847, 0.0300, 0.0097, 0.0103	0.996, 0.0500, 0.0098, 0.0104	1.000, 0.1000, 0.0101, 0.0107
MR-Egger	0.077, -0.0769, 0.9564, 0.8961	0.078, -0.0286, 0.9563, 0.896	0.077, -0.0093, 0.9562, 0.896	0.077, 0.0100, 0.9562, 0.896	0.076, 0.0197, 0.9561, 0.8959	0.075, 0.0294, 0.9561, 0.8959	0.075, 0.0487, 0.9561, 0.8959	0.072, 0.0680, 0.9560, 0.8959	0.077, 0.1163, 0.9559, 0.8958
MR-Weighted-Median	1.000, -0.0992, 0.0114, 0.0127	0.981, -0.0495, 0.0117, 0.013	0.634, -0.0297, 0.0118, 0.0131	0.083, -0.0099, 0.0118, 0.0132	0.027, 0.0000, 0.0119, 0.0132	0.087, 0.0099, 0.0119, 0.0133	0.625, 0.0298, 0.0120, 0.0134	0.964, 0.0496, 0.0122, 0.0136	1.000, 0.0992, 0.0126, 0.014
MR-Weighted-Mode	1.000, -0.0994, 0.0134, 0.0157	0.895, -0.0495, 0.0137, 0.016	0.457, -0.0297, 0.0138, 0.0161	0.060, -0.0098, 0.0141, 0.0162	0.017, 0.0002, 0.0142, 0.0163	0.061, 0.0101, 0.0140, 0.0164	0.433, 0.0300, 0.0142, 0.0166	0.879, 0.0499, 0.0143, 0.0167	1.000, 0.0997, 0.0148, 0.0172
MR-RAPS1	0.080, -0.0973, 0.1657, 0.1607	0.076, -0.0473, 0.1658, 0.1607	0.086, -0.0273, 0.1658, 0.1607	0.097, -0.0073, 0.1658, 0.1607	0.100, 0.0027, 0.1658, 0.1607	0.097, 0.0127, 0.1658, 0.1607	0.088, 0.0327, 0.1658, 0.1607	0.081, 0.0527, 0.1658, 0.1607	0.102, 0.1027, 0.1659, 0.1607
MR-RAPS2	0.997, 0.4018, 2.9379, 0.0301	0.995, 0.4899, 2.6637, 0.0277	0.960, 0.5570, 3.2538, 0.0277	0.756, 0.4859, 3.1360, 0.0269	0.706, 0.4539, 2.3930, 0.0252	0.760, 0.5569, 5.9183, 0.0271	0.953, 0.4676, 2.5363, 0.0262	0.992, 0.5156, 2.6431, 0.025	0.995, 1.0016, 2.9849, 0.0319
MR-RAPS3	0.970, -0.2056, 0.3506, 0.0203	0.940, -0.0977, 0.3434, 0.0198	0.917, -0.0556, 0.3384, 0.0196	0.917, -0.0144, 0.3297, 0.0193	0.910, 0.0057, 0.3267, 0.0191	0.898, 0.0254, 0.3267, 0.0189	0.907, 0.0637, 0.3204, 0.0186	0.921, 0.1004, 0.3137, 0.0183	0.952, 0.1861, 0.2963, 0.0177
MR-RAPS4	1.000, 0.3556, 1.0514, 0.0168	1.000, 0.4648, 1.0059, 0.0162	0.995, 0.4820, 0.9893, 0.0169	0.965, 0.5276, 0.9934, 0.0168	0.953, 0.5601, 0.9828, 0.0163	0.962, 0.5651, 0.9825, 0.0156	0.993, 0.6407, 0.9894, 0.0163	1.000, 0.6812, 0.9645, 0.0161	1.000, 0.7718, 0.9746, 0.0166

Table S53: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean(SE( $\hat{\theta}$ )) when  $m = 20$ , the InSIDE satisfied,  $q = 0.4$ , and  $N = 50000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	0.834, -0.0882, 0.0294, 0.0286	0.317, -0.0410, 0.0270, 0.0283	0.132, -0.0241, 0.0254, 0.0279	0.033, -0.0090, 0.0237, 0.0278	0.023, -0.0017, 0.0234, 0.0279	0.029, 0.0058, 0.0235, 0.028	0.095, 0.0210, 0.0252, 0.0286	0.265, 0.0378, 0.0273, 0.0293	0.765, 0.0845, 0.0310, 0.0309
cML-MA-AIC-Profile	0.833, -0.0884, 0.0295, 0.0288	0.311, -0.0410, 0.0270, 0.0284	0.131, -0.0241, 0.0254, 0.0281	0.033, -0.0090, 0.0237, 0.028	0.021, -0.0017, 0.0234, 0.028	0.030, 0.0058, 0.0235, 0.0281	0.095, 0.0210, 0.0252, 0.0287	0.263, 0.0378, 0.0274, 0.0294	0.762, 0.0847, 0.0311, 0.0311
cML-AIC	0.929, -0.0945, 0.0316, 0.0236	0.501, -0.0460, 0.0308, 0.024	0.273, -0.0274, 0.0303, 0.0242	0.121, -0.0103, 0.0294, 0.0244	0.094, -0.0017, 0.0294, 0.0245	0.101, 0.0072, 0.0292, 0.0246	0.224, 0.0239, 0.0308, 0.0248	0.437, 0.0422, 0.0317, 0.0251	0.879, 0.0909, 0.0336, 0.0258
cML-AIC-Profile	0.925, -0.0947, 0.0318, 0.0237	0.499, -0.0460, 0.0309, 0.0241	0.269, -0.0275, 0.0303, 0.0243	0.119, -0.0103, 0.0294, 0.0245	0.093, -0.0017, 0.0294, 0.0246	0.099, 0.0072, 0.0292, 0.0247	0.223, 0.0240, 0.0309, 0.025	0.432, 0.0423, 0.0317, 0.0252	0.875, 0.0910, 0.0337, 0.0259
cML-MA-BIC	0.996, -0.1007, 0.0220, 0.0219	0.631, -0.0508, 0.0223, 0.0223	0.295, -0.0308, 0.0224, 0.0225	0.061, -0.0109, 0.0225, 0.0226	0.039, -0.0010, 0.0226, 0.0227	0.068, 0.0090, 0.0227, 0.0229	0.246, 0.0289, 0.0229, 0.0231	0.549, 0.0488, 0.0233, 0.0233	0.982, 0.0987, 0.0238, 0.024
cML-MA-BIC-Profile	0.996, -0.1007, 0.0220, 0.022	0.626, -0.0508, 0.0223, 0.0224	0.294, -0.0308, 0.0224, 0.0225	0.061, -0.0109, 0.0226, 0.0227	0.039, -0.0010, 0.0226, 0.0228	0.067, 0.0090, 0.0227, 0.0229	0.245, 0.0289, 0.0229, 0.0232	0.548, 0.0488, 0.0233, 0.0234	0.981, 0.0987, 0.0238, 0.0241
cML-BIC	0.996, -0.1009, 0.0219, 0.0216	0.640, -0.0509, 0.0222, 0.022	0.308, -0.0309, 0.0225, 0.0222	0.067, -0.0109, 0.0226, 0.0224	0.043, -0.0009, 0.0227, 0.0225	0.074, 0.0091, 0.0228, 0.0226	0.254, 0.0291, 0.0230, 0.0228	0.564, 0.0490, 0.0232, 0.023	0.985, 0.0990, 0.0238, 0.0237
cML-BIC-Profile	0.996, -0.1009, 0.0219, 0.0217	0.637, -0.0509, 0.0222, 0.0221	0.306, -0.0309, 0.0225, 0.0222	0.065, -0.0109, 0.0226, 0.0224	0.044, -0.0009, 0.0227, 0.0225	0.074, 0.0091, 0.0228, 0.0226	0.253, 0.0291, 0.0230, 0.0229	0.559, 0.0490, 0.0232, 0.0231	0.985, 0.0990, 0.0238, 0.0238
MR-Mix	0.939, -0.1039, 0.0246, 0.0978	0.389, -0.0510, 0.0246, 0.0314	0.128, -0.0304, 0.0245, 0.0313	0.020, -0.0102, 0.0245, 0.031	0.016, -0.0002, 0.0244, 0.031	0.027, 0.0096, 0.0244, 0.0309	0.120, 0.0291, 0.0244, 0.031	0.337, 0.0480, 0.0243, 0.0307	0.901, 0.0941, 0.0242, 0.0309
MR-ContMix	0.993, -0.1005, 0.0231, NA	0.633, -0.0509, 0.0234, NA	0.308, -0.0311, 0.0237, NA	0.079, -0.0113, 0.0240, NA	0.059, -0.0014, 0.0241, NA	0.083, 0.0085, 0.0242, NA	0.248, 0.0283, 0.0244, NA	0.550, 0.0483, 0.0247, NA	0.973, 0.0980, 0.0255, NA
MR-Lasso	0.983, -0.1004, 0.0229, 0.023	0.597, -0.0509, 0.0229, 0.0235	0.274, -0.0312, 0.0231, 0.0237	0.065, -0.0114, 0.0235, 0.0239	0.043, -0.0014, 0.0235, 0.024	0.064, 0.0085, 0.0236, 0.0241	0.227, 0.0284, 0.0237, 0.0243	0.508, 0.0482, 0.0241, 0.0245	0.961, 0.0982, 0.0251, 0.0251
MR-PRESSO	0.753, -0.0916, 0.1689, 0.0485	0.488, -0.0435, 0.1662, 0.0472	0.327, -0.0255, 0.1652, 0.047	0.249, -0.0068, 0.1635, 0.0462	0.235, 0.0032, 0.1626, 0.0459	0.254, 0.0127, 0.1632, 0.046	0.339, 0.0298, 0.1600, 0.045	0.478, 0.0479, 0.1584, 0.0445	0.762, 0.0967, 0.1530, 0.0431
MR-IVW	0.089, -0.0974, 0.2377, 0.2347	0.072, -0.0473, 0.2376, 0.2347	0.073, -0.0272, 0.2376, 0.2347	0.070, -0.0072, 0.2376, 0.2347	0.068, 0.0028, 0.2376, 0.2347	0.065, 0.0128, 0.2376, 0.2347	0.064, 0.0328, 0.2375, 0.2347	0.068, 0.0528, 0.2375, 0.2347	0.079, 0.1028, 0.2375, 0.2347
MR-IVW-Oracle	0.988, -0.1003, 0.0217, 0.0232	0.592, -0.0506, 0.0220, 0.0236	0.257, -0.0307, 0.0221, 0.0238	0.044, -0.0109, 0.0223, 0.024	0.029, -0.0009, 0.0224, 0.0242	0.055, 0.0090, 0.0225, 0.0243	0.224, 0.0289, 0.0226, 0.0245	0.502, 0.0488, 0.0228, 0.0247	0.974, 0.0985, 0.0234, 0.0254
MR-Egger	0.067, -0.0648, 1.2200, 1.2119	0.064, -0.0214, 1.2197, 1.2119	0.065, -0.0041, 1.2196, 1.2119	0.065, 0.0133, 1.2195, 1.2119	0.066, 0.0219, 1.2195, 1.2119	0.067, 0.0306, 1.2194, 1.2119	0.067, 0.0480, 1.2193, 1.2119	0.067, 0.0653, 1.2192, 1.2119	0.066, 0.1086, 1.2190, 1.212
MR-Weighted-Median	0.917, -0.0976, 0.0270, 0.0296	0.388, -0.0496, 0.0273, 0.0301	0.150, -0.0305, 0.0275, 0.0303	0.034, -0.0112, 0.0276, 0.0306	0.021, -0.0016, 0.0277, 0.0307	0.033, 0.0080, 0.0278, 0.0309	0.121, 0.0273, 0.0282, 0.0312	0.306, 0.0465, 0.0285, 0.0315	0.846, 0.0943, 0.0291, 0.0324
MR-Weighted-Mode	0.966, -0.0991, 0.0244, 0.0265	0.474, -0.0503, 0.0250, 0.027	0.191, -0.0307, 0.0252, 0.0272	0.042, -0.0113, 0.0253, 0.0275	0.030, -0.0014, 0.0254, 0.0276	0.040, 0.0082, 0.0256, 0.0277	0.142, 0.0276, 0.0258, 0.028	0.388, 0.0473, 0.0261, 0.0283	0.919, 0.0959, 0.0267, 0.029
MR-RAPS1	0.095, -0.0993, 0.2340, 0.2292	0.076, -0.0493, 0.2340, 0.2292	0.074, -0.0293, 0.2340, 0.2292	0.070, -0.0093, 0.2340, 0.2292	0.068, 0.0007, 0.2340, 0.2292	0.065, 0.0107, 0.2340, 0.2292	0.061, 0.0307, 0.2340, 0.2292	0.065, 0.0507, 0.2340, 0.2292	0.083, 0.1006, 0.2340, 0.2293
MR-RAPS2	0.085, -0.0999, 0.2354, 0.2385	0.063, -0.0492, 0.2340, 0.2376	0.053, -0.0285, 0.2317, 0.2369	0.053, -0.0088, 0.2337, 0.237	0.056, 0.0006, 0.2326, 0.2372	0.051, 0.0116, 0.2334, 0.2378	0.055, 0.0300, 0.2340, 0.2379	0.054, 0.0509, 0.2337, 0.2379	0.072, 0.1014, 0.2348, 0.2387
MR-RAPS3	0.888, -2.9695, 58.2053, 314.389	0.895, -0.7341, 19.9493, 42.8006	0.888, 1.5759, 57.7885, 294.0363	0.897, -0.5554, 17.9349, 24.6186	0.896, -0.4997, 12.1421, 14.5071	0.894, -0.4092, 17.3224, 23.2788	0.887, 0.1299, 9.1446, 10.8243	0.884, 0.3781, 11.4410, 10.2028	0.894, 1.5471, 20.6127, 47.8447
MR-RAPS4	0.992, 0.3520, 1.4681, 0.1099	0.993, 0.1808, 1.5481, 0.1598	0.987, 0.1103, 1.5868, 0.0659	0.982, 0.0891, 1.5686, 0.0626	0.970, 0.0791, 1.5665, 0.0632	0.977, 0.0371, 1.5944, 0.0764	0.978, -0.1037, 1.6249, 0.1249	0.991, -0.1298, 1.5901, 0.0654	1.000, -0.3085, 1.5074, 0.0619

Table S54: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean( $SE(\hat{\theta})$ ) when  $m = 20$ , the InSIDE satisfied,  $q = 0.4$ , and  $N = 100000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	0.978, -0.0906, 0.0201, 0.02	0.541, -0.0413, 0.0197, 0.02	0.208, -0.0229, 0.0183, 0.0197	0.042, -0.0069, 0.0166, 0.0195	0.028, 0.0004, 0.0165, 0.0195	0.045, 0.0079, 0.0171, 0.0197	0.228, 0.0238, 0.0192, 0.0202	0.541, 0.0420, 0.0212, 0.0209	0.950, 0.0905, 0.0230, 0.0219
cML-MA-AIC-Profile	0.977, -0.0908, 0.0202, 0.0201	0.538, -0.0413, 0.0197, 0.0201	0.208, -0.0229, 0.0183, 0.0198	0.041, -0.0069, 0.0166, 0.0195	0.028, 0.0004, 0.0165, 0.0196	0.045, 0.0079, 0.0171, 0.0197	0.227, 0.0239, 0.0192, 0.0203	0.540, 0.0420, 0.0212, 0.021	0.950, 0.0906, 0.0231, 0.0219
cML-AIC	0.993, -0.0954, 0.0219, 0.0164	0.730, -0.0456, 0.0213, 0.0167	0.377, -0.0262, 0.0213, 0.0169	0.113, -0.0079, 0.0204, 0.017	0.096, 0.0003, 0.0204, 0.0171	0.134, 0.0089, 0.0210, 0.0172	0.384, 0.0266, 0.0222, 0.0174	0.699, 0.0461, 0.0233, 0.0176	0.980, 0.0954, 0.0243, 0.0181
cML-AIC-Profile	0.993, -0.0955, 0.0217, 0.0165	0.729, -0.0457, 0.0220, 0.0168	0.377, -0.0262, 0.0213, 0.0169	0.110, -0.0079, 0.0204, 0.0171	0.096, 0.0003, 0.0204, 0.0172	0.133, 0.0089, 0.0210, 0.0173	0.384, 0.0266, 0.0222, 0.0174	0.699, 0.0462, 0.0233, 0.0176	0.980, 0.0955, 0.0244, 0.0181
cML-MA-BIC	1.000, -0.0996, 0.0149, 0.0153	0.887, -0.0495, 0.0152, 0.0156	0.480, -0.0295, 0.0153, 0.0157	0.083, -0.0095, 0.0154, 0.0159	0.050, 0.0005, 0.0155, 0.0159	0.092, 0.0104, 0.0156, 0.016	0.471, 0.0304, 0.0158, 0.0162	0.877, 0.0504, 0.0160, 0.0163	1.000, 0.1005, 0.0164, 0.0168
cML-MA-BIC-Profile	1.000, -0.0996, 0.0149, 0.0154	0.887, -0.0495, 0.0152, 0.0156	0.479, -0.0295, 0.0153, 0.0157	0.083, -0.0095, 0.0154, 0.0159	0.049, 0.0005, 0.0155, 0.016	0.091, 0.0104, 0.0156, 0.016	0.469, 0.0304, 0.0158, 0.0162	0.877, 0.0504, 0.0160, 0.0164	1.000, 0.1005, 0.0164, 0.0168
cML-BIC	1.000, -0.0997, 0.0149, 0.0152	0.895, -0.0496, 0.0152, 0.0154	0.487, -0.0296, 0.0153, 0.0155	0.092, -0.0096, 0.0154, 0.0157	0.055, 0.0004, 0.0155, 0.0157	0.094, 0.0104, 0.0156, 0.0158	0.482, 0.0304, 0.0157, 0.016	0.884, 0.0505, 0.0159, 0.0161	1.000, 0.1005, 0.0164, 0.0166
cML-BIC-Profile	1.000, -0.0997, 0.0149, 0.0152	0.895, -0.0496, 0.0152, 0.0154	0.487, -0.0296, 0.0153, 0.0156	0.091, -0.0096, 0.0154, 0.0157	0.055, 0.0004, 0.0155, 0.0158	0.093, 0.0104, 0.0156, 0.0159	0.481, 0.0304, 0.0157, 0.016	0.884, 0.0505, 0.0159, 0.0162	1.000, 0.1005, 0.0164, 0.0166
MR-Mix	0.993, -0.1033, 0.0174, 0.0225	0.676, -0.0506, 0.0174, 0.0223	0.244, -0.0300, 0.0174, 0.0223	0.035, -0.0097, 0.0174, 0.0223	0.017, 0.0003, 0.0175, 0.0223	0.034, 0.0102, 0.0175, 0.0223	0.244, 0.0297, 0.0175, 0.0223	0.644, 0.0488, 0.0175, 0.0222	0.988, 0.0952, 0.0176, 0.0223
MR-ContMix	1.000, -0.0993, 0.0157, NA	0.883, -0.0493, 0.0160, NA	0.480, -0.0294, 0.0162, NA	0.102, -0.0094, 0.0163, NA	0.065, 0.0006, 0.0164, NA	0.109, 0.0105, 0.0165, NA	0.480, 0.0305, 0.0166, NA	0.869, 0.0505, 0.0168, NA	1.000, 0.1005, 0.0171, NA
MR-Lasso	0.999, -0.0996, 0.0159, 0.0161	0.867, -0.0494, 0.0159, 0.0164	0.432, -0.0295, 0.0162, 0.0166	0.077, -0.0096, 0.0163, 0.0167	0.047, 0.0004, 0.0162, 0.0168	0.089, 0.0103, 0.0163, 0.0169	0.431, 0.0303, 0.0164, 0.0171	0.840, 0.0500, 0.0167, 0.0172	0.999, 0.1001, 0.0170, 0.0177
MR-PRESSO	0.669, -0.1132, 0.2158, 0.0802	0.508, -0.0636, 0.2152, 0.0796	0.369, -0.0445, 0.2143, 0.0784	0.244, -0.0249, 0.2137, 0.0774	0.225, -0.0154, 0.2138, 0.0774	0.251, -0.0056, 0.2135, 0.0771	0.366, 0.0145, 0.2132, 0.0768	0.512, 0.0331, 0.2119, 0.0755	0.671, 0.0827, 0.2105, 0.0738
MR-IVW	0.115, -0.1134, 0.2438, 0.2328	0.092, -0.0631, 0.2438, 0.2328	0.084, -0.0430, 0.2437, 0.2328	0.080, -0.0229, 0.2437, 0.2328	0.076, -0.0128, 0.2437, 0.2328	0.073, -0.0028, 0.2437, 0.2328	0.077, 0.0173, 0.2437, 0.2328	0.076, 0.0374, 0.2437, 0.2328	0.091, 0.0876, 0.2437, 0.2327
MR-IVW-Oracle	1.000, -0.0994, 0.0171, 0.0163	0.873, -0.0495, 0.0150, 0.0166	0.426, -0.0295, 0.0157, 0.0167	0.065, -0.0096, 0.0153, 0.0168	0.035, 0.0004, 0.0153, 0.0169	0.074, 0.0104, 0.0154, 0.017	0.429, 0.0304, 0.0156, 0.0172	0.840, 0.0503, 0.0157, 0.0173	1.000, 0.1003, 0.0162, 0.0178
MR-Egger	0.075, -0.1044, 1.2836, 1.2414	0.079, -0.0576, 1.2832, 1.2413	0.081, -0.0389, 1.2831, 1.2413	0.080, -0.0203, 1.2829, 1.2413	0.080, -0.0109, 1.2829, 1.2412	0.080, -0.0016, 1.2828, 1.2412	0.079, 0.0171, 1.2826, 1.2412	0.080, 0.0357, 1.2825, 1.2412	0.082, 0.0824, 1.2822, 1.2411
MR-Weighted-Median	0.999, -0.0976, 0.0189, 0.0208	0.668, -0.0488, 0.0193, 0.0211	0.260, -0.0292, 0.0194, 0.0213	0.057, -0.0097, 0.0197, 0.0215	0.030, 0.0000, 0.0199, 0.0216	0.059, 0.0098, 0.0200, 0.0217	0.253, 0.0293, 0.0202, 0.0219	0.614, 0.0488, 0.0205, 0.0221	0.989, 0.0977, 0.0212, 0.0227
MR-Weighted-Mode	1.000, -0.0984, 0.0171, 0.0188	0.740, -0.0487, 0.0176, 0.0191	0.315, -0.0288, 0.0175, 0.0192	0.052, -0.0091, 0.0176, 0.0194	0.037, 0.0008, 0.0177, 0.0195	0.063, 0.0105, 0.0178, 0.0195	0.339, 0.0303, 0.0179, 0.0198	0.728, 0.0503, 0.0181, 0.02	1.000, 0.0996, 0.0187, 0.0205
MR-RAPS1	0.119, -0.1123, 0.2371, 0.2272	0.086, -0.0623, 0.2371, 0.2272	0.078, -0.0423, 0.2371, 0.2272	0.075, -0.0223, 0.2371, 0.2272	0.074, -0.0123, 0.2371, 0.2272	0.073, -0.0023, 0.2371, 0.2272	0.071, 0.0177, 0.2371, 0.2272	0.074, 0.0377, 0.2371, 0.2272	0.093, 0.0878, 0.2372, 0.2273
MR-RAPS2	0.103, -0.1130, 0.2373, 0.2359	0.073, -0.0628, 0.2369, 0.2361	0.071, -0.0433, 0.2370, 0.2363	0.067, -0.0228, 0.2355, 0.2359	0.067, -0.0131, 0.2373, 0.2364	0.066, -0.0030, 0.2364, 0.2361	0.062, 0.0176, 0.2358, 0.2359	0.063, 0.0362, 0.2373, 0.2366	0.069, 0.0872, 0.2379, 0.2368
MR-RAPS3	0.925, -0.8929, 18.0217, 19.6811	0.932, 0.7958, 38.0980, 93.2854	0.922, 0.0503, 7.6305, 4.0117	0.920, 0.0199, 16.1430, 30.3805	0.917, 0.2883, 11.2263, 6.7844	0.914, 1.4861, 46.0627, 123.241	0.925, 0.1574, 11.9014, 21.7929	0.931, 0.7047, 11.9321, 9.4141	0.925, 0.8846, 16.3970, 13.1956
MR-RAPS4	0.979, 0.8757, 1.5868, 0.1991	0.985, 0.6696, 1.6607, 0.2606	0.983, 0.5895, 1.6646, 0.0987	0.980, 0.4293, 1.7081, 0.0749	0.981, 0.3695, 1.7272, 0.105	0.983, 0.2996, 1.7692, 0.0683	0.985, 0.1714, 1.6743, 0.0583	0.999, 0.0820, 1.7151, 0.055	0.998, -0.1306, 1.6148, 0.0519

Table S55: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean(SE( $\hat{\theta}$ )) when  $m = 20$ , the InSIDE satisfied,  $q = 0.4$ , and  $N = 200000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	1.000, -0.0936, 0.0142, 0.0143	0.842, -0.0437, 0.0142, 0.0145	0.412, -0.0245, 0.0134, 0.0143	0.054, -0.0074, 0.0117, 0.0139	0.022, 0.0002, 0.0115, 0.0139	0.057, 0.0077, 0.0121, 0.014	0.414, 0.0246, 0.0140, 0.0146	0.801, 0.0437, 0.0152, 0.0151	0.997, 0.0933, 0.0160, 0.0156
cML-MA-AIC-Profile	1.000, -0.0937, 0.0142, 0.0143	0.841, -0.0437, 0.0142, 0.0145	0.411, -0.0245, 0.0134, 0.0143	0.054, -0.0074, 0.0117, 0.0139	0.022, 0.0002, 0.0115, 0.0139	0.057, 0.0077, 0.0121, 0.014	0.412, 0.0246, 0.0140, 0.0146	0.801, 0.0437, 0.0152, 0.0151	0.997, 0.0934, 0.0160, 0.0156
cML-AIC	1.000, -0.0970, 0.0151, 0.0117	0.925, -0.0471, 0.0153, 0.0119	0.612, -0.0274, 0.0152, 0.012	0.152, -0.0088, 0.0145, 0.0121	0.092, 0.0000, 0.0143, 0.0122	0.163, 0.0087, 0.0147, 0.0122	0.595, 0.0272, 0.0159, 0.0124	0.911, 0.0470, 0.0163, 0.0125	0.999, 0.0968, 0.0168, 0.0128
cML-AIC-Profile	1.000, -0.0970, 0.0151, 0.0118	0.925, -0.0471, 0.0153, 0.0119	0.612, -0.0274, 0.0152, 0.012	0.151, -0.0088, 0.0145, 0.0122	0.092, 0.0000, 0.0143, 0.0122	0.161, 0.0087, 0.0147, 0.0123	0.596, 0.0272, 0.0159, 0.0124	0.911, 0.0470, 0.0163, 0.0125	0.999, 0.0969, 0.0169, 0.0129
cML-MA-BIC	1.000, -0.1001, 0.0109, 0.0109	0.991, -0.0501, 0.0111, 0.0111	0.768, -0.0301, 0.0111, 0.0112	0.139, -0.0101, 0.0112, 0.0113	0.051, -0.0001, 0.0112, 0.0113	0.142, 0.0099, 0.0113, 0.0114	0.741, 0.0298, 0.0114, 0.0115	0.986, 0.0498, 0.0115, 0.0116	1.000, 0.0998, 0.0118, 0.0119
cML-MA-BIC-Profile	1.000, -0.1001, 0.0109, 0.0109	0.991, -0.0501, 0.0111, 0.0111	0.767, -0.0301, 0.0111, 0.0112	0.139, -0.0101, 0.0112, 0.0113	0.051, -0.0001, 0.0112, 0.0113	0.142, 0.0099, 0.0113, 0.0114	0.741, 0.0298, 0.0114, 0.0115	0.986, 0.0498, 0.0115, 0.0116	1.000, 0.0998, 0.0118, 0.0119
cML-BIC	1.000, -0.1001, 0.0109, 0.0108	0.992, -0.0501, 0.0111, 0.011	0.771, -0.0301, 0.0111, 0.0111	0.146, -0.0101, 0.0112, 0.0111	0.055, -0.0001, 0.0113, 0.0112	0.150, 0.0099, 0.0113, 0.0113	0.748, 0.0299, 0.0114, 0.0114	0.989, 0.0499, 0.0115, 0.0115	1.000, 0.0998, 0.0118, 0.0118
cML-BIC-Profile	1.000, -0.1001, 0.0109, 0.0108	0.992, -0.0501, 0.0111, 0.011	0.769, -0.0301, 0.0111, 0.0111	0.145, -0.0101, 0.0112, 0.0112	0.055, -0.0001, 0.0113, 0.0112	0.150, 0.0099, 0.0113, 0.0113	0.746, 0.0299, 0.0114, 0.0114	0.989, 0.0499, 0.0115, 0.0115	1.000, 0.0998, 0.0118, 0.0118
MR-Mix	0.999, -0.1041, 0.0136, 0.0164	0.901, -0.0510, 0.0135, 0.0165	0.473, -0.0305, 0.0135, 0.0164	0.072, -0.0104, 0.0134, 0.0163	0.021, -0.0005, 0.0134, 0.0163	0.058, 0.0095, 0.0134, 0.0163	0.442, 0.0290, 0.0134, 0.0163	0.875, 0.0483, 0.0134, 0.0163	0.997, 0.0945, 0.0133, 0.0166
MR-ContMix	1.000, -0.0999, 0.0113, NA	0.990, -0.0500, 0.0114, NA	0.776, -0.0301, 0.0115, NA	0.160, -0.0101, 0.0116, NA	0.069, -0.0001, 0.0116, NA	0.166, 0.0099, 0.0117, NA	0.757, 0.0298, 0.0118, NA	0.985, 0.0498, 0.0119, NA	1.000, 0.0997, 0.0123, NA
MR-Lasso	1.000, -0.0999, 0.0112, 0.0114	0.986, -0.0500, 0.0114, 0.0117	0.732, -0.0300, 0.0115, 0.0117	0.127, -0.0101, 0.0115, 0.0119	0.050, -0.0001, 0.0115, 0.0119	0.127, 0.0099, 0.0115, 0.012	0.695, 0.0298, 0.0117, 0.0121	0.978, 0.0497, 0.0119, 0.0122	1.000, 0.0997, 0.0121, 0.0126
MR-PRESSO	0.530, -0.1029, 0.2321, 0.1158	0.449, -0.0532, 0.2317, 0.1145	0.364, -0.0330, 0.2312, 0.1129	0.214, -0.0131, 0.2309, 0.1122	0.187, -0.0031, 0.2309, 0.1118	0.206, 0.0064, 0.2306, 0.1109	0.373, 0.0260, 0.2305, 0.1108	0.476, 0.0462, 0.2299, 0.1094	0.560, 0.0944, 0.2287, 0.1068
MR-IVW	0.097, -0.1017, 0.2428, 0.2339	0.073, -0.0513, 0.2427, 0.2339	0.067, -0.0312, 0.2427, 0.2339	0.068, -0.0111, 0.2427, 0.2339	0.069, -0.0010, 0.2427, 0.2339	0.073, 0.0090, 0.2427, 0.2339	0.071, 0.0292, 0.2427, 0.2338	0.073, 0.0493, 0.2426, 0.2338	0.084, 0.0995, 0.2426, 0.2338
MR-IVW-Oracle	1.000, -0.1000, 0.0108, 0.0115	0.989, -0.0501, 0.0109, 0.0118	0.728, -0.0301, 0.0125, 0.0119	0.119, -0.0101, 0.0111, 0.012	0.043, -0.0001, 0.0111, 0.012	0.119, 0.0099, 0.0112, 0.0121	0.695, 0.0298, 0.0113, 0.0122	0.983, 0.0498, 0.0114, 0.0123	1.000, 0.0997, 0.0117, 0.0127
MR-Egger	0.072, -0.0795, 1.2764, 1.257	0.070, -0.0310, 1.2764, 1.2569	0.069, -0.0116, 1.2763, 1.2568	0.071, 0.0077, 1.2762, 1.2568	0.069, 0.0174, 1.2762, 1.2567	0.069, 0.0174, 1.2761, 1.2567	0.067, 0.0465, 1.2760, 1.2567	0.067, 0.0658, 1.2760, 1.2566	0.070, 0.1142, 1.2758, 1.2565
MR-Weighted-Median	1.000, -0.0989, 0.0135, 0.0148	0.924, -0.0496, 0.0138, 0.015	0.518, -0.0298, 0.0140, 0.0151	0.072, -0.0101, 0.0141, 0.0153	0.032, -0.0003, 0.0141, 0.0153	0.068, 0.0096, 0.0142, 0.0154	0.470, 0.0294, 0.0143, 0.0155	0.901, 0.0492, 0.0144, 0.0157	1.000, 0.0985, 0.0149, 0.0161
MR-Weighted-Mode	1.000, -0.0995, 0.0124, 0.0135	0.963, -0.0498, 0.0125, 0.0137	0.598, -0.0299, 0.0125, 0.0138	0.094, -0.0101, 0.0128, 0.0139	0.028, -0.0002, 0.0128, 0.014	0.090, 0.0098, 0.0129, 0.014	0.547, 0.0297, 0.0130, 0.0142	0.948, 0.0497, 0.0133, 0.0143	1.000, 0.0993, 0.0135, 0.0147
MR-RAPS1	0.111, -0.1027, 0.2379, 0.2278	0.077, -0.0527, 0.2379, 0.2278	0.072, -0.0327, 0.2379, 0.2279	0.068, -0.0127, 0.2380, 0.2279	0.068, -0.0027, 0.2380, 0.2279	0.066, 0.0073, 0.2380, 0.2279	0.063, 0.0273, 0.2380, 0.2279	0.067, 0.0473, 0.2380, 0.2279	0.098, 0.0973, 0.2380, 0.2279
MR-RAPS2	0.184, -0.1014, 0.1316, 0.1226	0.062, -0.0525, 0.1360, 0.1264	0.035, -0.0310, 0.1417, 0.1305	0.027, -0.0124, 0.1515, 0.134	0.029, -0.0025, 0.1554, 0.1346	0.034, 0.0080, 0.1578, 0.136	0.047, 0.0281, 0.1553, 0.1351	0.063, 0.0482, 0.1489, 0.1301	0.185, 0.0992, 0.1609, 0.141
MR-RAPS3	0.955, -0.4771, 12.4874, 5.8058	0.943, -3.2576, 82.3207, 686.8739	0.953, -0.2303, 8.2856, 3.4314	0.941, 0.1716, 11.3534, 6.0882	0.939, -9.5439, 229.1913, 1847.4207	0.947, -0.7703, 19.8328, 26.7187	0.951, -0.3191, 17.9694, 13.7273	0.951, 0.2955, 24.1995, 30.1402	0.950, 0.4838, 6.9566, 3.6628
MR-RAPS4	0.982, 1.1288, 1.6298, 0.1778	0.985, 0.9179, 1.7130, 0.1424	0.986, 0.8707, 1.7081, 0.106	0.978, 0.7828, 1.7112, 0.1156	0.984, 0.7917, 1.7037, 0.0817	0.987, 0.6884, 1.7087, 0.0722	0.996, 0.6199, 1.7184, 0.0566	0.998, 0.5362, 1.7694, 0.0456	1.000, 0.2991, 1.6853, 0.0349

Table S56: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean(SE( $\hat{\theta}$ )) when  $m = 20$ , the InSIDE satisfied,  $q = 0.6$ , and  $N = 50000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	0.660, -0.0828, 3.400e- 02, 0.0356	0.176, -0.0369, 3.040e- 02, 0.0351	0.056, -0.0213, 2.750e- 02, 0.0348	0.018, -0.0063, 2.610e- 02, 0.0348	0.014, 0.0007, 2.590e- 02, 0.0349	0.022, 0.0077, 2.600e- 02, 0.0351	0.062, 0.0221, 2.810e- 02, 0.0359	0.159, 0.0379, 3.050e- 02, 0.0368	0.607, 0.0832, 3.610e- 02, 0.0389
cML-MA-AIC-Profile	0.655, -0.0830, 3.420e- 02, 0.0358	0.172, -0.0370, 3.050e- 02, 0.0354	0.056, -0.0213, 2.760e- 02, 0.035	0.018, -0.0063, 2.610e- 02, 0.035	0.014, 0.0008, 2.590e- 02, 0.0351	0.020, 0.0077, 2.600e- 02, 0.0353	0.062, 0.0221, 2.810e- 02, 0.0361	0.156, 0.0380, 3.060e- 02, 0.037	0.606, 0.0833, 3.620e- 02, 0.0391
cML-AIC	0.825, -0.0902, 3.760e- 02, 0.0291	0.353, -0.0420, 3.600e- 02, 0.0296	0.169, -0.0248, 3.420e- 02, 0.0298	0.078, -0.0075, 3.360e- 02, 0.03	0.069, 0.0009, 3.330e- 02, 0.0302	0.094, 0.0090, 3.350e- 02, 0.0303	0.172, 0.0259, 3.520e- 02, 0.0307	0.327, 0.0433, 3.660e- 02, 0.031	0.790, 0.0911, 4.080e- 02, 0.0318
cML-AIC-Profile	0.825, -0.0905, 3.780e- 02, 0.0293	0.351, -0.0420, 3.600e- 02, 0.0298	0.169, -0.0248, 3.420e- 02, 0.03	0.075, -0.0075, 3.360e- 02, 0.0302	0.068, 0.0009, 3.330e- 02, 0.0304	0.091, 0.0090, 3.350e- 02, 0.0305	0.168, 0.0259, 3.520e- 02, 0.0309	0.317, 0.0433, 3.660e- 02, 0.0312	0.790, 0.0912, 4.080e- 02, 0.032
cML-MA-BIC	0.946, -0.0991, 2.790e- 02, 0.0273	0.429, -0.0490, 2.830e- 02, 0.0277	0.187, -0.0290, 2.850e- 02, 0.0279	0.065, -0.0090, 2.870e- 02, 0.0282	0.053, 0.0009, 2.880e- 02, 0.0283	0.076, 0.0109, 2.900e- 02, 0.0284	0.191, 0.0308, 2.930e- 02, 0.0287	0.412, 0.0508, 2.960e- 02, 0.029	0.920, 0.1009, 3.050e- 02, 0.0298
cML-MA-BIC-Profile	0.945, -0.0991, 2.790e- 02, 0.0274	0.425, -0.0490, 2.830e- 02, 0.0278	0.186, -0.0290, 2.850e- 02, 0.0281	0.065, -0.0090, 2.870e- 02, 0.0283	0.053, 0.0009, 2.880e- 02, 0.0284	0.076, 0.0109, 2.900e- 02, 0.0285	0.190, 0.0308, 2.930e- 02, 0.0288	0.406, 0.0508, 2.960e- 02, 0.0291	0.920, 0.1009, 3.050e- 02, 0.0299
cML-BIC	0.949, -0.0993, 2.790e- 02, 0.0269	0.444, -0.0492, 2.840e- 02, 0.0274	0.193, -0.0291, 2.870e- 02, 0.0276	0.069, -0.0090, 2.890e- 02, 0.0278	0.057, 0.0010, 2.910e- 02, 0.028	0.080, 0.0110, 2.920e- 02, 0.0281	0.199, 0.0310, 2.940e- 02, 0.0283	0.422, 0.0511, 2.980e- 02, 0.0286	0.927, 0.1012, 3.060e- 02, 0.0294
cML-BIC-Profile	0.948, -0.0993, 2.790e- 02, 0.0271	0.443, -0.0492, 2.840e- 02, 0.0275	0.192, -0.0291, 2.870e- 02, 0.0277	0.068, -0.0090, 2.890e- 02, 0.0279	0.056, 0.0010, 2.910e- 02, 0.0281	0.079, 0.0110, 2.920e- 02, 0.0282	0.198, 0.0310, 2.940e- 02, 0.0285	0.416, 0.0511, 2.980e- 02, 0.0288	0.927, 0.1012, 3.060e- 02, 0.0296
MR-Mix	0.879, -0.1008, 2.970e- 02, 0.0329	0.337, -0.0489, 2.960e- 02, 0.0325	0.141, -0.0289, 2.950e- 02, 0.0326	0.038, -0.0090, 2.950e- 02, 0.0325	0.036, 0.0009, 2.960e- 02, 0.0325	0.053, 0.0105, 2.960e- 02, 0.0327	0.146, 0.0297, 2.960e- 02, 0.0327	0.306, 0.0485, 2.960e- 02, 0.0325	0.854, 0.0937, 2.990e- 02, 0.0327
MR-ContMix	0.948, -0.0986, 2.860e- 02, NA	0.455, -0.0487, 2.900e- 02, NA	0.204, -0.0287, 2.930e- 02, NA	0.081, -0.0088, 2.940e- 02, NA	0.067, 0.0012, 2.960e- 02, NA	0.089, 0.0111, 2.970e- 02, NA	0.211, 0.0311, 3.010e- 02, NA	0.437, 0.0510, 3.040e- 02, NA	0.915, 0.1006, 3.130e- 02, NA
MR-Lasso	0.905, -0.1064, 2.198e- 01, 0.0363	0.416, -0.0559, 2.212e- 01, 0.0364	0.196, -0.0361, 2.213e- 01, 0.0366	0.100, -0.0160, 2.207e- 01, 0.0368	0.094, -0.0058, 2.213e- 01, 0.037	0.105, 0.0036, 2.217e- 01, 0.0373	0.198, 0.0239, 2.211e- 01, 0.0377	0.396, 0.0437, 2.208e- 01, 0.0379	0.879, 0.0939, 2.183e- 01, 0.0386
MR-PRESSO	0.574, -0.0951, 2.535e- 01, 0.0923	0.329, -0.0483, 2.509e- 01, 0.0897	0.208, -0.0290, 2.507e- 01, 0.0894	0.170, -0.0101, 2.510e- 01, 0.0894	0.169, -0.0005, 2.511e- 01, 0.0895	0.183, 0.0088, 2.505e- 01, 0.0888	0.239, 0.0274, 2.493e- 01, 0.0879	0.341, 0.0473, 2.486e- 01, 0.0871	0.591, 0.0952, 2.450e- 01, 0.0853
MR-IVW	0.091, -0.0984, 2.956e- 01, 0.2851	0.082, -0.0481, 2.956e- 01, 0.285	0.080, -0.0280, 2.955e- 01, 0.285	0.080, -0.0079, 2.955e- 01, 0.285	0.078, 0.0021, 2.955e- 01, 0.285	0.075, 0.0122, 2.955e- 01, 0.285	0.081, 0.0323, 2.955e- 01, 0.285	0.086, 0.0523, 2.955e- 01, 0.285	0.090, 0.1025, 2.955e- 01, 0.285
MR-IVW-Oracle	0.925, -0.0987, 2.760e- 02, 0.0289	0.394, -0.0489, 2.810e- 02, 0.0294	0.162, -0.0290, 2.830e- 02, 0.0296	0.058, -0.0091, 2.860e- 02, 0.0299	0.051, 0.0009, 2.870e- 02, 0.03	0.064, 0.0109, 2.880e- 02, 0.0301	0.165, 0.0308, 2.910e- 02, 0.0304	0.377, 0.0507, 2.940e- 02, 0.0307	0.897, 0.1006, 3.020e- 02, 0.0315
MR-Egger	0.077, -0.1458, 1.534e+00, 1.465	0.074, -0.1022, 1.534e+00, 1.465	0.071, -0.0847, 1.534e+00, 1.465	0.071, -0.0673, 1.534e+00, 1.465	0.071, -0.0586, 1.534e+00, 1.465	0.072, -0.0499, 1.533e+00, 1.465	0.072, -0.0324, 1.533e+00, 1.464	0.074, -0.0150, 1.533e+00, 1.464	0.076, 0.0285, 1.533e+00, 1.464
MR-Weighted-Median	0.754, -0.0940, 3.560e- 02, 0.0358	0.256, -0.0467, 3.600e- 02, 0.0363	0.103, -0.0278, 3.630e- 02, 0.0366	0.050, -0.0090, 3.650e- 02, 0.0368	0.049, 0.0005, 3.660e- 02, 0.037	0.058, 0.0099, 3.680e- 02, 0.0372	0.113, 0.0286, 3.730e- 02, 0.0375	0.240, 0.0473, 3.780e- 02, 0.0379	0.697, 0.0940, 3.910e- 02, 0.039
MR-Weighted-Mode	0.715, -0.0912, 5.670e- 02, 0.0331	0.381, -0.0462, 5.670e- 02, 0.0337	0.287, -0.0283, 5.700e- 02, 0.034	0.239, -0.0104, 5.750e- 02, 0.0344	0.225, -0.0013, 5.780e- 02, 0.0346	0.223, 0.0077, 5.830e- 02, 0.0348	0.275, 0.0258, 5.920e- 02, 0.0352	0.367, 0.0433, 5.990e- 02, 0.0357	0.616, 0.0874, 6.310e- 02, 0.0371
MR-RAPS1	0.092, -0.0942, 2.912e- 01, 0.2794	0.087, -0.0442, 2.912e- 01, 0.2794	0.082, -0.0242, 2.912e- 01, 0.2795	0.085, -0.0042, 2.912e- 01, 0.2795	0.081, 0.0058, 2.912e- 01, 0.2795	0.083, 0.0158, 2.912e- 01, 0.2795	0.080, 0.0358, 2.912e- 01, 0.2795	0.084, 0.0558, 2.912e- 01, 0.2795	0.093, 0.1058, 2.913e- 01, 0.2795
MR-RAPS2	0.101, -0.0929, 3.263e- 01, 0.3038	0.097, -0.0438, 3.234e- 01, 0.3041	0.092, -0.0226, 3.275e- 01, 0.3033	0.096, -0.0038, 3.234e- 01, 0.3041	0.091, 0.0062, 3.234e- 01, 0.3041	0.089, 0.0162, 3.234e- 01, 0.3041	0.092, 0.0365, 3.238e- 01, 0.3039	0.095, 0.0562, 3.296e- 01, 0.3037	0.105, 0.1066, 3.253e- 01, 0.3038
MR-RAPS3	0.889, -8.6896, 1.977e+02, 1147	0.901, -327.3507, 1.020e+04, 3105000	0.896, -2.5442, 1.350e+02, 564.2	0.897, -6.6228, 1.083e+02, 335.5	0.899, -2.0052, 1.216e+02, 774.8	0.893, 2.2011, 1.417e+02, 1037	0.887, 0.8221, 1.075e+02, 419.4	0.893, 2.3586, 4.626e+01, 97.77	0.889, 0.8809, 7.284e+01, 315.5
MR-RAPS4	0.998, 0.5745, 1.427e+00, 0.0731	0.997, 0.3660, 1.605e+00, 0.1091	0.994, 0.2539, 1.718e+00, 0.0968	0.994, 0.0906, 1.752e+00, 0.1012	0.993, 0.0353, 1.701e+00, 0.1042	0.990, 0.0109, 1.710e+00, 0.1225	0.989, -0.1278, 1.714e+00, 0.1149	0.990, -0.2992, 1.782e+00, 0.1431	0.990, -0.6071, 1.718e+00, 0.1665

Table S57: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean( $SE(\hat{\theta})$ ) when  $m = 20$ , the InSIDE satisfied,  $q = 0.6$ , and  $N = 100000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	0.888, -0.0874, 0.0242, 0.0262	0.330, -0.0390, 0.0227, 0.0259	0.102, -0.0221, 0.0204, 0.0253	0.030, -0.0076, 0.0188, 0.025	0.015, -0.0009, 0.0186, 0.025	0.022, 0.0062, 0.0191, 0.0252	0.108, 0.0211, 0.0214, 0.0259	0.295, 0.0381, 0.0238, 0.0267	0.853, 0.0858, 0.0269, 0.0281
cML-MA-AIC-Profile	0.888, -0.0875, 0.0243, 0.0263	0.328, -0.0390, 0.0227, 0.0259	0.101, -0.0221, 0.0204, 0.0254	0.030, -0.0076, 0.0188, 0.0251	0.015, -0.0009, 0.0186, 0.0251	0.022, 0.0062, 0.0191, 0.0253	0.108, 0.0211, 0.0214, 0.0259	0.293, 0.0381, 0.0238, 0.0268	0.853, 0.0859, 0.0269, 0.0282
cML-AIC	0.941, -0.0932, 0.0269, 0.0209	0.567, -0.0441, 0.0252, 0.0212	0.273, -0.0257, 0.0252, 0.0213	0.097, -0.0092, 0.0244, 0.0215	0.084, -0.0009, 0.0240, 0.0216	0.094, 0.0074, 0.0244, 0.0217	0.252, 0.0243, 0.0264, 0.0219	0.539, 0.0428, 0.0279, 0.0221	0.927, 0.0922, 0.0296, 0.0227
cML-AIC-Profile	0.943, -0.0935, 0.0272, 0.0209	0.567, -0.0441, 0.0269, 0.0213	0.270, -0.0257, 0.0252, 0.0214	0.096, -0.0092, 0.0244, 0.0216	0.083, -0.0009, 0.0240, 0.0217	0.094, 0.0074, 0.0245, 0.0217	0.249, 0.0242, 0.0264, 0.022	0.534, 0.0429, 0.0279, 0.0222	0.927, 0.0922, 0.0296, 0.0228
cML-MA-BIC	0.998, -0.1000, 0.0192, 0.0193	0.718, -0.0500, 0.0195, 0.0196	0.322, -0.0300, 0.0196, 0.0197	0.078, -0.0100, 0.0198, 0.0199	0.052, 0.0000, 0.0199, 0.02	0.071, 0.0099, 0.0200, 0.0201	0.320, 0.0299, 0.0203, 0.0203	0.699, 0.0499, 0.0205, 0.0205	0.993, 0.0999, 0.0211, 0.0211
cML-MA-BIC-Profile	0.998, -0.1000, 0.0192, 0.0193	0.717, -0.0500, 0.0195, 0.0196	0.322, -0.0300, 0.0196, 0.0198	0.078, -0.0100, 0.0198, 0.02	0.051, 0.0000, 0.0199, 0.02	0.071, 0.0099, 0.0200, 0.0201	0.319, 0.0299, 0.0203, 0.0203	0.697, 0.0499, 0.0205, 0.0205	0.993, 0.0999, 0.0211, 0.0211
cML-BIC	0.998, -0.1000, 0.0192, 0.0191	0.723, -0.0500, 0.0195, 0.0194	0.328, -0.0300, 0.0197, 0.0195	0.083, -0.0100, 0.0199, 0.0197	0.057, 0.0000, 0.0200, 0.0198	0.074, 0.0100, 0.0201, 0.0199	0.333, 0.0300, 0.0203, 0.02	0.711, 0.0500, 0.0205, 0.0203	0.993, 0.1001, 0.0212, 0.0208
cML-BIC-Profile	0.998, -0.1000, 0.0192, 0.0191	0.723, -0.0500, 0.0195, 0.0194	0.327, -0.0300, 0.0197, 0.0196	0.083, -0.0100, 0.0199, 0.0197	0.055, 0.0000, 0.0200, 0.0198	0.074, 0.0100, 0.0201, 0.0199	0.332, 0.0300, 0.0203, 0.0201	0.709, 0.0500, 0.0205, 0.0203	0.993, 0.1001, 0.0212, 0.0208
MR-Mix	0.976, -0.1017, 0.0210, 0.0245	0.562, -0.0499, 0.0209, 0.0243	0.224, -0.0298, 0.0209, 0.0242	0.051, -0.0099, 0.0208, 0.0243	0.030, -0.0001, 0.0209, 0.0243	0.040, 0.0097, 0.0209, 0.0244	0.212, 0.0288, 0.0208, 0.0243	0.554, 0.0476, 0.0208, 0.0243	0.970, 0.0932, 0.0209, 0.024
MR-ContMix	0.998, -0.1000, 0.0198, NA	0.740, -0.0501, 0.0201, NA	0.367, -0.0301, 0.0203, NA	0.098, -0.0102, 0.0205, NA	0.070, -0.0002, 0.0206, NA	0.091, 0.0098, 0.0206, NA	0.356, 0.0298, 0.0209, NA	0.726, 0.0498, 0.0212, NA	0.994, 0.0997, 0.0217, NA
MR-Lasso	0.984, -0.1014, 0.1710, 0.0261	0.662, -0.0515, 0.1705, 0.0264	0.295, -0.0314, 0.1705, 0.0266	0.098, -0.0114, 0.1705, 0.0268	0.073, -0.0012, 0.1716, 0.0269	0.089, 0.0086, 0.1724, 0.0271	0.302, 0.0284, 0.1735, 0.0272	0.638, 0.0485, 0.1731, 0.0273	0.974, 0.0990, 0.1679, 0.0278
MR-PRESSO	0.528, -0.1065, 0.2693, 0.1301	0.349, -0.0569, 0.2691, 0.129	0.229, -0.0375, 0.2690, 0.1288	0.159, -0.0179, 0.2685, 0.1277	0.143, -0.0078, 0.2685, 0.1277	0.152, 0.0019, 0.2684, 0.1272	0.229, 0.0209, 0.2674, 0.1263	0.350, 0.0406, 0.2674, 0.1248	0.524, 0.0907, 0.2659, 0.1215
MR-IVW	0.082, -0.1106, 0.2861, 0.2863	0.074, -0.0601, 0.2861, 0.2863	0.066, -0.0399, 0.2861, 0.2863	0.066, -0.0198, 0.2861, 0.2863	0.067, -0.0097, 0.2861, 0.2863	0.065, 0.0004, 0.2861, 0.2863	0.067, 0.0205, 0.2861, 0.2863	0.071, 0.0407, 0.2861, 0.2863	0.074, 0.0910, 0.2860, 0.2863
MR-IVW-Oracle	0.997, -0.0998, 0.0191, 0.0207	0.664, -0.0499, 0.0195, 0.0211	0.278, -0.0299, 0.0196, 0.0213	0.067, -0.0100, 0.0198, 0.0215	0.044, 0.0000, 0.0199, 0.0216	0.055, 0.0100, 0.0200, 0.0217	0.281, 0.0299, 0.0202, 0.0219	0.638, 0.0499, 0.0205, 0.0221	0.990, 0.0998, 0.0211, 0.0227
MR-Egger	0.095, -0.1206, 1.6542, 1.5192	0.097, -0.0738, 1.6538, 1.5191	0.099, -0.0550, 1.6537, 1.5191	0.099, -0.0363, 1.6536, 1.5191	0.099, -0.0270, 1.6535, 1.5191	0.100, -0.0176, 1.6534, 1.5191	0.099, 0.0011, 1.6533, 1.5191	0.098, 0.0198, 1.6532, 1.5191	0.095, 0.0665, 1.6529, 1.5191
MR-Weighted-Median	0.960, -0.0974, 0.0253, 0.0254	0.485, -0.0488, 0.0258, 0.0258	0.201, -0.0294, 0.0261, 0.026	0.075, -0.0101, 0.0266, 0.0262	0.054, -0.0006, 0.0268, 0.0263	0.067, 0.0091, 0.0270, 0.0264	0.193, 0.0284, 0.0275, 0.0266	0.442, 0.0476, 0.0281, 0.0269	0.919, 0.0955, 0.0295, 0.0276
MR-Weighted-Mode	0.840, -0.0914, 0.0476, 0.0236	0.521, -0.0462, 0.0482, 0.0241	0.395, -0.0282, 0.0488, 0.0243	0.300, -0.0100, 0.0494, 0.0245	0.313, -0.0009, 0.0496, 0.0247	0.317, 0.0082, 0.0498, 0.0248	0.392, 0.0264, 0.0508, 0.0251	0.516, 0.0446, 0.0518, 0.0254	0.796, 0.0896, 0.0542, 0.0264
MR-RAPS1	0.083, -0.1084, 0.2792, 0.2796	0.076, -0.0583, 0.2792, 0.2796	0.070, -0.0383, 0.2792, 0.2796	0.065, -0.0183, 0.2793, 0.2796	0.063, -0.0083, 0.2793, 0.2796	0.064, 0.0017, 0.2793, 0.2796	0.069, 0.0217, 0.2793, 0.2796	0.071, 0.0417, 0.2793, 0.2796	0.079, 0.0917, 0.2793, 0.2797
MR-RAPS2	0.098, -0.1111, 0.3274, 0.3027	0.080, -0.0585, 0.3159, 0.3038	0.080, -0.0395, 0.3162, 0.304	0.080, -0.0215, 0.3202, 0.3033	0.083, -0.0096, 0.3236, 0.3035	0.087, -0.0062, 0.3322, 0.3023	0.080, 0.0205, 0.3171, 0.304	0.084, 0.0349, 0.3305, 0.3024	0.094, 0.0917, 0.3196, 0.3036
MR-RAPS3	0.906, -2.7927, 89.2482, 172.8403	0.920, 8.5127, 256.4422, 1436.1815	0.915, 5.1277, 111.1046, 317.4877	0.911, -2.1372, 63.7077, 88.3011	0.917, 14.4961, 301.0921, 2142.2384	0.920, -8.176, 32.4694, 26.1085	0.928, -16.2561, 487.8015, 8034.2503	0.932, 1.2652, 18.5049, 9.8629	0.926, -3.7158, 103.9734, 262.3552
MR-RAPS4	0.992, 0.6529, 1.6028, 0.1007	0.996, 0.4470, 1.7693, 0.1051	0.995, 0.3015, 1.7968, 0.1154	0.992, 0.2050, 1.7899, 0.1383	0.992, 0.1195, 1.8489, 0.0914	0.993, 0.0096, 1.8731, 0.096	0.985, -0.2416, 1.9026, 0.3056	0.986, -0.3876, 1.9715, 0.1785	0.986, -0.7337, 1.7963, 0.143

Table S58: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean( $SE(\hat{\theta})$ ) when  $m = 20$ , the InSIDE satisfied,  $q = 0.6$ , and  $N = 200000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	0.987, -0.0908, 0.0174, 0.0183	0.631, -0.0411, 0.0170, 0.0183	0.241, -0.0227, 0.0156, 0.018	0.031, -0.0067, 0.0136, 0.0177	0.012, 0.0003, 0.0132, 0.0177	0.033, 0.0073, 0.0137, 0.0179	0.227, 0.0227, 0.0163, 0.0186	0.604, 0.0412, 0.0180, 0.0192	0.973, 0.0903, 0.0192, 0.0201
cML-MA-AIC-Profile	0.987, -0.0909, 0.0174, 0.0183	0.630, -0.0411, 0.0170, 0.0184	0.239, -0.0227, 0.0156, 0.018	0.030, -0.0067, 0.0135, 0.0177	0.012, 0.0003, 0.0132, 0.0177	0.033, 0.0073, 0.0137, 0.0179	0.226, 0.0227, 0.0163, 0.0186	0.603, 0.0412, 0.0180, 0.0193	0.973, 0.0904, 0.0192, 0.0201
cML-AIC	0.998, -0.0951, 0.0189, 0.0147	0.798, -0.0451, 0.0191, 0.015	0.445, -0.0257, 0.0185, 0.0151	0.123, -0.0079, 0.0173, 0.0152	0.079, 0.0002, 0.0170, 0.0152	0.114, 0.0085, 0.0175, 0.0153	0.444, 0.0260, 0.0191, 0.0154	0.774, 0.0455, 0.0200, 0.0156	0.985, 0.0950, 0.0209, 0.016
cML-AIC-Profile	0.998, -0.0952, 0.0189, 0.0147	0.796, -0.0451, 0.0191, 0.015	0.445, -0.0257, 0.0185, 0.0151	0.122, -0.0079, 0.0173, 0.0152	0.078, 0.0002, 0.0170, 0.0153	0.114, 0.0085, 0.0175, 0.0153	0.442, 0.0260, 0.0191, 0.0154	0.774, 0.0455, 0.0200, 0.0156	0.985, 0.0951, 0.0210, 0.016
cML-MA-BIC	1.000, -0.0999, 0.0134, 0.0136	0.949, -0.0499, 0.0137, 0.0138	0.575, -0.0299, 0.0138, 0.0139	0.112, -0.0100, 0.0139, 0.0141	0.043, 0.0000, 0.0139, 0.0141	0.103, 0.0100, 0.0140, 0.0142	0.560, 0.0299, 0.0142, 0.0143	0.926, 0.0499, 0.0144, 0.0145	1.000, 0.0999, 0.0148, 0.0149
cML-MA-BIC-Profile	1.000, -0.0999, 0.0134, 0.0136	0.948, -0.0499, 0.0137, 0.0138	0.575, -0.0299, 0.0138, 0.014	0.112, -0.0100, 0.0139, 0.0141	0.043, 0.0000, 0.0139, 0.0141	0.103, 0.0100, 0.0140, 0.0142	0.559, 0.0299, 0.0142, 0.0143	0.926, 0.0499, 0.0144, 0.0145	1.000, 0.0999, 0.0148, 0.0149
cML-BIC	1.000, -0.1000, 0.0134, 0.0135	0.950, -0.0500, 0.0136, 0.0137	0.584, -0.0300, 0.0137, 0.0138	0.118, -0.0100, 0.0139, 0.0139	0.044, 0.0000, 0.0140, 0.014	0.105, 0.0100, 0.0140, 0.0141	0.566, 0.0300, 0.0142, 0.0142	0.929, 0.0500, 0.0143, 0.0143	1.000, 0.1000, 0.0148, 0.0147
cML-BIC-Profile	1.000, -0.1000, 0.0134, 0.0135	0.949, -0.0500, 0.0136, 0.0137	0.584, -0.0300, 0.0137, 0.0138	0.117, -0.0100, 0.0139, 0.0139	0.044, 0.0000, 0.0140, 0.014	0.104, 0.0100, 0.0140, 0.0141	0.565, 0.0300, 0.0142, 0.0142	0.929, 0.0500, 0.0143, 0.0143	1.000, 0.1000, 0.0148, 0.0147
MR-Mix	0.993, -0.1019, 0.0151, 0.0177	0.826, -0.0500, 0.0149, 0.0178	0.410, -0.0300, 0.0148, 0.0178	0.063, -0.0100, 0.0149, 0.0178	0.024, -0.0001, 0.0149, 0.0178	0.058, 0.0096, 0.0149, 0.018	0.381, 0.0288, 0.0150, 0.0178	0.809, 0.0476, 0.0149, 0.0179	0.989, 0.0931, 0.0151, 0.0176
MR-ContMix	1.000, -0.0998, 0.0137, NA	0.949, -0.0499, 0.0140, NA	0.618, -0.0299, 0.0141, NA	0.147, -0.0099, 0.0143, NA	0.068, 0.0001, 0.0144, NA	0.130, 0.0101, 0.0145, NA	0.591, 0.0301, 0.0148, NA	0.930, 0.0500, 0.0149, NA	1.000, 0.0999, 0.0154, NA
MR-Lasso	0.998, -0.1096, 0.2275, 0.0205	0.920, -0.0598, 0.2284, 0.0207	0.537, -0.0399, 0.2284, 0.0208	0.136, -0.0199, 0.2296, 0.021	0.074, -0.0099, 0.2296, 0.021	0.124, 0.0001, 0.2296, 0.0211	0.497, 0.0202, 0.2294, 0.0212	0.886, 0.0402, 0.2294, 0.0213	0.996, 0.0905, 0.2315, 0.0215
MR-PRESSO	0.435, -0.1182, 0.2976, 0.1707	0.358, -0.0684, 0.2975, 0.1701	0.244, -0.0486, 0.2975, 0.1701	0.143, -0.0285, 0.2974, 0.1697	0.127, -0.0183, 0.2974, 0.1694	0.145, -0.0082, 0.2972, 0.169	0.235, 0.0119, 0.2972, 0.1686	0.355, 0.0322, 0.2970, 0.1678	0.451, 0.0831, 0.2967, 0.166
MR-IVW	0.101, -0.1186, 0.3029, 0.285	0.087, -0.0681, 0.3029, 0.285	0.087, -0.0479, 0.3029, 0.285	0.082, -0.0277, 0.3029, 0.2849	0.084, -0.0176, 0.3029, 0.2849	0.084, -0.0075, 0.3029, 0.2849	0.087, 0.0126, 0.3029, 0.2849	0.093, 0.0328, 0.3028, 0.2849	0.098, 0.0832, 0.3028, 0.2849
MR-IVW-Oracle	1.000, -0.0998, 0.0133, 0.0147	0.930, -0.0499, 0.0135, 0.0149	0.518, -0.0299, 0.0137, 0.015	0.098, -0.0099, 0.0138, 0.0152	0.033, 0.0000, 0.0139, 0.0152	0.084, 0.0100, 0.0139, 0.0153	0.499, 0.0300, 0.0141, 0.0154	0.896, 0.0500, 0.0143, 0.0156	1.000, 0.0999, 0.0147, 0.016
MR-Egger	0.074, -0.0935, 1.6365, 1.5486	0.073, -0.0448, 1.6361, 1.5485	0.074, -0.0254, 1.6359, 1.5485	0.073, -0.0059, 1.6358, 1.5485	0.073, 0.0038, 1.6357, 1.5484	0.074, 0.0135, 1.6356, 1.5484	0.071, 0.0329, 1.6355, 1.5484	0.068, 0.0524, 1.6353, 1.5483	0.068, 0.1009, 1.6349, 1.5482
MR-Weighted-Median	0.997, -0.0976, 0.0180, 0.018	0.776, -0.0488, 0.0182, 0.0182	0.351, -0.0292, 0.0183, 0.0184	0.075, -0.0097, 0.0185, 0.0185	0.047, 0.0000, 0.0186, 0.0186	0.077, 0.0098, 0.0187, 0.0187	0.349, 0.0292, 0.0189, 0.0188	0.733, 0.0487, 0.0192, 0.019	0.993, 0.0972, 0.0201, 0.0195
MR-Weighted-Mode	0.911, -0.0922, 0.0427, 0.0172	0.652, -0.0465, 0.0431, 0.0175	0.537, -0.0282, 0.0435, 0.0176	0.427, -0.0099, 0.0445, 0.0178	0.425, -0.0007, 0.0447, 0.0178	0.423, 0.0084, 0.0450, 0.018	0.495, 0.0266, 0.0457, 0.0182	0.645, 0.0451, 0.0468, 0.0184	0.893, 0.0905, 0.0490, 0.019
MR-RAPS1	0.099, -0.1177, 0.2950, 0.2782	0.092, -0.0676, 0.2950, 0.2782	0.091, -0.0476, 0.2950, 0.2782	0.089, -0.0276, 0.2950, 0.2782	0.083, -0.0176, 0.2950, 0.2782	0.085, -0.0076, 0.2950, 0.2782	0.083, 0.0124, 0.2950, 0.2782	0.085, 0.0324, 0.2950, 0.2782	0.091, 0.0824, 0.2951, 0.2782
MR-RAPS2	0.242, -0.1225, 0.4831, 0.222	0.184, -0.0638, 0.4537, 0.2304	0.175, -0.0462, 0.4579, 0.232	0.169, -0.0294, 0.4508, 0.2384	0.163, -0.0199, 0.4538, 0.2375	0.158, -0.0021, 0.4483, 0.2433	0.161, 0.0142, 0.4291, 0.2463	0.158, 0.0296, 0.4320, 0.2519	0.154, 0.0795, 0.4158, 0.2681
MR-RAPS3	0.944, -4.0115, 106.3931, 231.2409	0.934, 1.0247, 115.9425, 205.4114	0.943, -7.7396, 283.5044, 1403.6719	0.945, -9.6841, 302.9734, 1208.8483	0.937, 1.1517, 45.2390, 52.2286	0.934, -9.9359, 206.3759, 898.1968	0.939, 2.0667, 72.1215, 138.1285	0.940, -2.4343, 39.6826, 34.3873	0.952, -0.5707, 32.6778, 22.666
MR-RAPS4	0.998, 0.8086, 1.5711, 0.06	0.995, 0.6270, 1.7532, 0.0758	0.993, 0.5328, 1.8458, 0.1009	0.993, 0.3433, 1.9177, 0.0992	0.995, 0.1680, 1.9255, 0.0845	0.992, 0.1248, 1.9509, 0.1561	0.991, -0.0159, 2.0202, 0.1601	0.992, -0.2282, 1.9963, 0.1153	0.993, -0.5607, 1.9078, 1.2342

Table S59: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean( $SE(\hat{\theta})$ ) when  $m = 20$ , the InSIDE violated,  $q = 0.2$ , and  $N = 50000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	0.932, -0.0908, 0.0251, 0.0237	0.453, -0.0424, 0.0240, 0.0236	0.178, -0.0245, 0.0224, 0.0234	0.058, -0.0087, 0.0209, 0.0233	0.039, -0.0011, 0.0205, 0.0233	0.040, 0.0064, 0.0208, 0.0235	0.145, 0.0223, 0.0223, 0.0239	0.389, 0.0400, 0.0244, 0.0246	0.892, 0.0881, 0.0271, 0.0258
cML-MA-AIC-Profile	0.933, -0.0911, 0.0253, 0.0238	0.449, -0.0425, 0.0241, 0.0237	0.177, -0.0246, 0.0225, 0.0235	0.055, -0.0087, 0.0209, 0.0234	0.039, -0.0011, 0.0205, 0.0235	0.040, 0.0064, 0.0208, 0.0236	0.144, 0.0223, 0.0224, 0.0241	0.385, 0.0401, 0.0244, 0.0247	0.890, 0.0883, 0.0272, 0.0259
cML-AIC	0.965, -0.0956, 0.0268, 0.0199	0.611, -0.0464, 0.0269, 0.0203	0.344, -0.0275, 0.0260, 0.0205	0.133, -0.0099, 0.0254, 0.0207	0.098, -0.0009, 0.0253, 0.0207	0.115, 0.0078, 0.0254, 0.0208	0.278, 0.0252, 0.0262, 0.021	0.560, 0.0443, 0.0275, 0.0213	0.948, 0.0935, 0.0293, 0.0219
cML-AIC-Profile	0.965, -0.0959, 0.0270, 0.02	0.608, -0.0464, 0.0270, 0.0204	0.337, -0.0275, 0.0260, 0.0206	0.131, -0.0099, 0.0254, 0.0208	0.098, -0.0009, 0.0253, 0.0209	0.114, 0.0078, 0.0255, 0.021	0.274, 0.0252, 0.0263, 0.0212	0.558, 0.0443, 0.0275, 0.0214	0.947, 0.0936, 0.0293, 0.022
cML-MA-BIC	1.000, -0.1006, 0.0184, 0.0185	0.778, -0.0506, 0.0187, 0.0188	0.366, -0.0307, 0.0189, 0.019	0.083, -0.0107, 0.0190, 0.0192	0.042, -0.0008, 0.0191, 0.0192	0.078, 0.0092, 0.0192, 0.0193	0.315, 0.0291, 0.0194, 0.0195	0.677, 0.0490, 0.0197, 0.0197	0.996, 0.0990, 0.0203, 0.0203
cML-MA-BIC-Profile	1.000, -0.1006, 0.0185, 0.0186	0.773, -0.0506, 0.0187, 0.0189	0.365, -0.0307, 0.0189, 0.019	0.082, -0.0107, 0.0190, 0.0192	0.041, -0.0008, 0.0191, 0.0193	0.077, 0.0092, 0.0192, 0.0194	0.313, 0.0291, 0.0194, 0.0196	0.674, 0.0490, 0.0197, 0.0198	0.996, 0.0990, 0.0203, 0.0204
cML-BIC	1.000, -0.1007, 0.0184, 0.0183	0.787, -0.0508, 0.0187, 0.0186	0.384, -0.0308, 0.0189, 0.0188	0.089, -0.0108, 0.0190, 0.0189	0.045, -0.0008, 0.0191, 0.019	0.085, 0.0092, 0.0192, 0.0191	0.320, 0.0292, 0.0194, 0.0193	0.697, 0.0491, 0.0196, 0.0195	0.996, 0.0991, 0.0202, 0.0201
cML-BIC-Profile	1.000, -0.1007, 0.0184, 0.0183	0.783, -0.0508, 0.0187, 0.0187	0.382, -0.0308, 0.0189, 0.0188	0.088, -0.0108, 0.0190, 0.019	0.043, -0.0008, 0.0191, 0.0191	0.085, 0.0092, 0.0192, 0.0192	0.319, 0.0292, 0.0194, 0.0194	0.696, 0.0491, 0.0196, 0.0196	0.996, 0.0991, 0.0202, 0.0202
MR-Mix	0.952, -0.1064, 0.0233, 0.0305	0.399, -0.0524, 0.0231, 0.0305	0.135, -0.0314, 0.0231, 0.0304	0.024, -0.0107, 0.0229, 0.0304	0.016, -0.0005, 0.0229, 0.0304	0.025, 0.0096, 0.0228, 0.0305	0.116, 0.0294, 0.0228, 0.0305	0.355, 0.0488, 0.0230, 0.0305	0.906, 0.0953, 0.0229, 0.0307
MR-ContMix	1.000, -0.1002, 0.0194, NA	0.767, -0.0505, 0.0197, NA	0.375, -0.0307, 0.0199, NA	0.091, -0.0107, 0.0200, NA	0.054, -0.0008, 0.0201, NA	0.082, 0.0092, 0.0202, NA	0.316, 0.0290, 0.0204, NA	0.678, 0.0488, 0.0206, NA	0.992, 0.0984, 0.0213, NA
MR-Lasso	0.999, -0.1000, 0.0187, 0.0192	0.737, -0.0504, 0.0191, 0.0195	0.343, -0.0305, 0.0193, 0.0197	0.077, -0.0106, 0.0195, 0.0199	0.042, -0.0007, 0.0195, 0.02	0.071, 0.0092, 0.0196, 0.0201	0.290, 0.0290, 0.0198, 0.0203	0.659, 0.0488, 0.0200, 0.0205	0.995, 0.0983, 0.0206, 0.0211
MR-PRESSO	0.851, -0.0864, 0.0864, 0.0239	0.627, -0.0388, 0.0823, 0.0233	0.438, -0.0188, 0.0816, 0.0233	0.289, 0.0008, 0.0815, 0.0233	0.283, 0.0098, 0.0790, 0.0231	0.306, 0.0192, 0.0784, 0.0231	0.434, 0.0377, 0.0749, 0.0228	0.634, 0.0571, 0.0741, 0.0228	0.874, 0.1054, 0.0711, 0.0226
MR-IVW	0.125, -0.0745, 0.1795, 0.1673	0.107, -0.0246, 0.1795, 0.1673	0.102, -0.0047, 0.1794, 0.1673	0.088, 0.0153, 0.1794, 0.1673	0.085, 0.0253, 0.1794, 0.1673	0.085, 0.0352, 0.1794, 0.1673	0.084, 0.0552, 0.1794, 0.1635	0.095, 0.0751, 0.1793, 0.1673	0.136, 0.1250, 0.1793, 0.1673
MR-IVW-Oracle	1.000, -0.1002, 0.0183, 0.0194	0.738, -0.0505, 0.0186, 0.0197	0.336, -0.0306, 0.0187, 0.0199	0.066, -0.0108, 0.0189, 0.0201	0.035, -0.0008, 0.0190, 0.0202	0.064, 0.0091, 0.0190, 0.0203	0.281, 0.0290, 0.0192, 0.0205	0.647, 0.0488, 0.0194, 0.0207	0.995, 0.0985, 0.0200, 0.0212
MR-Egger	0.299, 0.3418, 1.0256, 0.6476	0.300, 0.3876, 1.0259, 0.6478	0.302, 0.4059, 1.0260, 0.6479	0.308, 0.4242, 1.0261, 0.648	0.308, 0.4334, 1.0262, 0.648	0.311, 0.4425, 1.0263, 0.6481	0.312, 0.4608, 1.0264, 0.6482	0.320, 0.4791, 1.0265, 0.6483	0.326, 0.5248, 1.0269, 0.6486
MR-Weighted-Median	0.976, -0.1001, 0.0234, 0.0255	0.529, -0.0518, 0.0239, 0.026	0.212, -0.0324, 0.0240, 0.0262	0.069, -0.0131, 0.0243, 0.0264	0.036, -0.0034, 0.0244, 0.0265	0.028, 0.0063, 0.0246, 0.0267	0.135, 0.0256, 0.0248, 0.0269	0.382, 0.0450, 0.0252, 0.0272	0.918, 0.0933, 0.0260, 0.028
MR-Weighted-Mode	0.917, -0.0988, 0.0286, 0.0324	0.327, -0.0500, 0.0291, 0.033	0.111, -0.0306, 0.0292, 0.0333	0.034, -0.0111, 0.0294, 0.0336	0.023, -0.0015, 0.0295, 0.0337	0.028, 0.0083, 0.0295, 0.0338	0.084, 0.0275, 0.0295, 0.0342	0.259, 0.0473, 0.0297, 0.0345	0.836, 0.0958, 0.0304, 0.0355
MR-RAPS1	0.129, -0.0762, 0.1737, 0.1633	0.100, -0.0262, 0.1736, 0.1634	0.096, -0.0062, 0.1736, 0.1634	0.088, 0.0138, 0.1736, 0.1634	0.088, 0.0238, 0.1736, 0.1634	0.082, 0.0338, 0.1736, 0.1634	0.083, 0.0537, 0.1736, 0.1635	0.095, 0.0737, 0.1736, 0.1635	0.146, 0.1237, 0.1736, 0.1635
MR-RAPS2	0.993, 0.0501, 3.2512, 0.0463	0.921, 0.0099, 2.4769, 0.0546	0.763, 0.1838, 3.5239, 0.0847	0.634, 0.3564, 5.7200, 0.3273	0.626, 0.0002, 3.0576, 0.0839	0.639, 0.1485, 3.4577, 0.0648	0.752, 0.1815, 2.6805, 0.0536	0.895, 0.0654, 3.0321, 0.0481	0.994, 0.5181, 3.9835, 0.043
MR-RAPS3	0.868, -0.3884, 5.7295, 12.3079	0.865, -0.0426, 0.5098, 0.062	0.866, -0.3797, 12.1020, 26.2886	0.863, 0.0463, 0.4602, 0.0553	0.855, 0.0616, 0.4663, 0.0599	0.866, 0.3869, 9.4974, 31.1292	0.857, 0.1258, 0.3945, 0.0452	0.881, 0.1597, 0.3779, 0.042	0.888, 0.2408, 0.3489, 0.0391
MR-RAPS4	1.000, -0.1754, 1.5628, 0.047	0.955, -0.0457, 1.5228, 0.0562	0.862, -0.0576, 1.5129, 0.0869	0.796, 0.0003, 1.5560, 0.3226	0.788, 0.0546, 1.4735, 0.0817	0.789, 0.0755, 1.5352, 0.0628	0.854, 0.1215, 1.6267, 0.0675	0.935, 0.1859, 1.5619, 0.0484	1.000, 0.3599, 1.3020, 0.0377



Table S60: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean( $SE(\hat{\theta})$ ) when  $m = 20$ , the InSIDE violated,  $q = 0.2$ , and  $N = 100000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	0.996, -0.0929, 0.0175, 0.0166	0.712, -0.0432, 0.0175, 0.0168	0.298, -0.0241, 0.0166, 0.0166	0.068, -0.0072, 0.0150, 0.0165	0.033, 0.0005, 0.0149, 0.0165	0.077, 0.0082, 0.0152, 0.0166	0.310, 0.0251, 0.0170, 0.0171	0.685, 0.0436, 0.0185, 0.0176	0.983, 0.0928, 0.0197, 0.0184
cML-MA-AIC-Profile	0.996, -0.0931, 0.0176, 0.0166	0.711, -0.0432, 0.0175, 0.0168	0.298, -0.0241, 0.0166, 0.0167	0.067, -0.0072, 0.0150, 0.0165	0.033, 0.0005, 0.0149, 0.0165	0.076, 0.0082, 0.0152, 0.0167	0.310, 0.0251, 0.0170, 0.0172	0.683, 0.0437, 0.0185, 0.0177	0.983, 0.0930, 0.0198, 0.0184
cML-AIC	0.998, -0.0963, 0.0189, 0.014	0.831, -0.0466, 0.0189, 0.0143	0.483, -0.0271, 0.0187, 0.0144	0.149, -0.0084, 0.0180, 0.0145	0.111, 0.0005, 0.0180, 0.0146	0.168, 0.0094, 0.0181, 0.0147	0.489, 0.0279, 0.0190, 0.0148	0.805, 0.0473, 0.0199, 0.015	0.991, 0.0967, 0.0209, 0.0154
cML-AIC-Profile	0.998, -0.0964, 0.0189, 0.0141	0.831, -0.0467, 0.0189, 0.0143	0.482, -0.0271, 0.0187, 0.0145	0.148, -0.0084, 0.0180, 0.0146	0.107, 0.0005, 0.0180, 0.0147	0.168, 0.0094, 0.0181, 0.0147	0.486, 0.0279, 0.0190, 0.0149	0.804, 0.0473, 0.0200, 0.015	0.991, 0.0968, 0.0210, 0.0155
cML-MA-BIC	1.000, -0.0994, 0.0130, 0.013	0.959, -0.0494, 0.0132, 0.0132	0.599, -0.0293, 0.0133, 0.0133	0.096, -0.0093, 0.0134, 0.0135	0.053, 0.0006, 0.0134, 0.0135	0.122, 0.0106, 0.0135, 0.0136	0.611, 0.0306, 0.0137, 0.0137	0.952, 0.0506, 0.0138, 0.0139	1.000, 0.1006, 0.0142, 0.0143
cML-MA-BIC-Profile	1.000, -0.0994, 0.0130, 0.013	0.959, -0.0494, 0.0132, 0.0133	0.597, -0.0293, 0.0133, 0.0134	0.095, -0.0093, 0.0134, 0.0135	0.052, 0.0006, 0.0134, 0.0136	0.119, 0.0106, 0.0135, 0.0136	0.609, 0.0306, 0.0137, 0.0138	0.952, 0.0506, 0.0138, 0.0139	1.000, 0.1006, 0.0142, 0.0143
cML-BIC	1.000, -0.0995, 0.0130, 0.0129	0.963, -0.0495, 0.0132, 0.0131	0.610, -0.0294, 0.0133, 0.0132	0.106, -0.0094, 0.0134, 0.0133	0.053, 0.0006, 0.0135, 0.0134	0.127, 0.0106, 0.0136, 0.0135	0.617, 0.0306, 0.0137, 0.0136	0.952, 0.0507, 0.0138, 0.0138	1.000, 0.1007, 0.0142, 0.0142
cML-BIC-Profile	1.000, -0.0995, 0.0130, 0.0129	0.962, -0.0495, 0.0132, 0.0131	0.606, -0.0294, 0.0133, 0.0132	0.105, -0.0094, 0.0134, 0.0134	0.053, 0.0006, 0.0135, 0.0134	0.126, 0.0106, 0.0136, 0.0135	0.617, 0.0306, 0.0137, 0.0136	0.952, 0.0507, 0.0138, 0.0138	1.000, 0.1007, 0.0142, 0.0142
MR-Mix	0.996, -0.1054, 0.0167, 0.0222	0.690, -0.0513, 0.0168, 0.0221	0.235, -0.0302, 0.0167, 0.022	0.027, -0.0096, 0.0166, 0.022	0.015, 0.0006, 0.0166, 0.022	0.035, 0.0106, 0.0167, 0.0219	0.256, 0.0305, 0.0166, 0.0219	0.672, 0.0501, 0.0168, 0.0219	0.994, 0.0968, 0.0167, 0.022
MR-ContMix	1.000, -0.0991, 0.0135, NA	0.950, -0.0492, 0.0138, NA	0.590, -0.0292, 0.0139, NA	0.113, -0.0093, 0.0140, NA	0.068, 0.0007, 0.0141, NA	0.140, 0.0107, 0.0141, NA	0.617, 0.0306, 0.0143, NA	0.937, 0.0506, 0.0145, NA	1.000, 0.1006, 0.0149, NA
MR-Lasso	1.000, -0.0992, 0.0133, 0.0136	0.942, -0.0492, 0.0133, 0.0139	0.560, -0.0292, 0.0134, 0.014	0.089, -0.0093, 0.0136, 0.0141	0.045, 0.0007, 0.0136, 0.0142	0.117, 0.0107, 0.0137, 0.0142	0.571, 0.0307, 0.0139, 0.0144	0.934, 0.0506, 0.0141, 0.0145	1.000, 0.1006, 0.0146, 0.0149
MR-PRESSO	0.797, -0.0817, 0.1256, 0.0349	0.681, -0.0332, 0.1245, 0.0342	0.503, -0.0138, 0.1241, 0.0337	0.325, 0.0049, 0.1228, 0.0331	0.309, 0.0146, 0.1219, 0.0326	0.341, 0.0244, 0.1209, 0.0321	0.542, 0.0444, 0.1198, 0.0317	0.709, 0.0627, 0.1174, 0.0308	0.846, 0.1112, 0.1142, 0.0295
MR-IVW	0.122, -0.0825, 0.1737, 0.1665	0.082, -0.0324, 0.1736, 0.1665	0.076, -0.0124, 0.1736, 0.1665	0.065, 0.0077, 0.1736, 0.1665	0.067, 0.0177, 0.1736, 0.1665	0.068, 0.0277, 0.1736, 0.1665	0.074, 0.0477, 0.1736, 0.1665	0.090, 0.0677, 0.1736, 0.1665	0.133, 0.1177, 0.1736, 0.1665
MR-IVW-Oracle	1.000, -0.0992, 0.0129, 0.0137	0.947, -0.0493, 0.0131, 0.0139	0.556, -0.0293, 0.0132, 0.0141	0.084, -0.0094, 0.0133, 0.0142	0.040, 0.0006, 0.0133, 0.0143	0.107, 0.0106, 0.0134, 0.0143	0.560, 0.0306, 0.0135, 0.0145	0.938, 0.0505, 0.0137, 0.0146	1.000, 0.1004, 0.0140, 0.0151
MR-Egger	0.296, 0.3378, 1.0560, 0.6644	0.297, 0.3856, 1.0560, 0.6645	0.294, 0.4047, 1.0560, 0.6645	0.296, 0.4238, 1.0560, 0.6645	0.295, 0.4334, 1.0560, 0.6645	0.298, 0.4430, 1.0560, 0.6645	0.303, 0.4621, 1.0559, 0.6646	0.308, 0.4812, 1.0559, 0.6646	0.317, 0.5289, 1.0559, 0.6647
MR-Weighted-Median	1.000, -0.0991, 0.0166, 0.018	0.794, -0.0501, 0.0169, 0.0183	0.362, -0.0304, 0.0170, 0.0185	0.071, -0.0108, 0.0172, 0.0186	0.034, -0.0010, 0.0173, 0.0187	0.057, 0.0089, 0.0174, 0.0188	0.332, 0.0285, 0.0176, 0.019	0.715, 0.0482, 0.0178, 0.0192	0.997, 0.0972, 0.0184, 0.0198
MR-Weighted-Mode	0.988, -0.0982, 0.0200, 0.0247	0.583, -0.0487, 0.0197, 0.0251	0.221, -0.0289, 0.0197, 0.0253	0.035, -0.0094, 0.0198, 0.0255	0.011, 0.0006, 0.0200, 0.0256	0.035, 0.0107, 0.0202, 0.0257	0.228, 0.0303, 0.0203, 0.0259	0.575, 0.0499, 0.0204, 0.0262	0.978, 0.0999, 0.0212, 0.0269
MR-RAPS1	0.128, -0.0825, 0.1704, 0.1621	0.086, -0.0325, 0.1704, 0.1621	0.075, -0.0124, 0.1705, 0.1621	0.074, 0.0076, 0.1705, 0.1621	0.075, 0.0176, 0.1705, 0.1621	0.075, 0.0276, 0.1705, 0.1621	0.072, 0.0476, 0.1705, 0.1622	0.085, 0.0676, 0.1705, 0.1622	0.130, 0.1176, 0.1705, 0.1622
MR-RAPS2	0.994, 0.0931, 3.3651, 0.0343	0.984, 0.1847, 4.0240, 0.0349	0.885, -0.0938, 4.1144, 0.0378	0.709, 0.1946, 5.7829, 0.0463	0.682, 0.1062, 2.4081, 0.0797	0.739, 0.1451, 3.0307, 0.0632	0.891, 0.1144, 2.1872, 0.0382	0.985, 0.3700, 2.9876, 0.036	0.997, 0.3341, 3.2080, 0.1277
MR-RAPS3	0.916, -0.1917, 0.4577, 0.0382	0.896, -0.0748, 0.4362, 0.0356	0.885, 0.0073, 1.2245, 0.036	0.892, 0.0149, 0.3966, 0.033	0.896, 0.0345, 0.3894, 0.0309	0.910, 0.0539, 0.3838, 0.0302	0.914, 0.0918, 0.3736, 0.0293	0.892, 0.1284, 0.3631, 0.0287	0.907, 0.2169, 0.3328, 0.0293
MR-RAPS4	1.000, -0.0389, 1.7384, 0.0325	0.992, 0.0334, 1.7535, 0.0376	0.959, 0.0483, 1.7108, 0.0339	0.884, 0.2189, 3.5802, 0.0813	0.871, 0.1198, 1.6998, 0.0805	0.886, 0.1617, 1.6979, 0.0614	0.963, 0.1920, 1.7682, 0.0387	0.996, 0.2335, 1.6196, 0.033	0.999, 0.3337, 1.5870, 0.1237

Table S61: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean( $SE(\hat{\theta})$ ) when  $m = 20$ , the InSIDE violated,  $q = 0.2$ , and  $N = 200000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	1.000, -0.0947, 0.0124, 0.0118	0.927, -0.0447, 0.0125, 0.012	0.546, -0.0251, 0.0121, 0.0119	0.086, -0.0073, 0.0108, 0.0117	0.039, 0.0006, 0.0106, 0.0117	0.104, 0.0084, 0.0113, 0.0118	0.576, 0.0262, 0.0131, 0.0122	0.911, 0.0458, 0.0138, 0.0125	1.000, 0.0955, 0.0141, 0.0129
cML-MA-AIC-Profile	1.000, -0.0948, 0.0124, 0.0118	0.927, -0.0448, 0.0125, 0.012	0.546, -0.0251, 0.0121, 0.012	0.086, -0.0073, 0.0108, 0.0117	0.039, 0.0005, 0.0106, 0.0117	0.103, 0.0084, 0.0113, 0.0118	0.576, 0.0262, 0.0131, 0.0122	0.911, 0.0458, 0.0138, 0.0125	1.000, 0.0956, 0.0141, 0.0129
cML-AIC	1.000, -0.0971, 0.0130, 0.0099	0.964, -0.0473, 0.0130, 0.0101	0.725, -0.0273, 0.0132, 0.0102	0.188, -0.0085, 0.0127, 0.0103	0.104, 0.0005, 0.0127, 0.0104	0.204, 0.0095, 0.0131, 0.0104	0.725, 0.0284, 0.0142, 0.0105	0.957, 0.0481, 0.0147, 0.0106	1.000, 0.0981, 0.0149, 0.0109
cML-AIC-Profile	1.000, -0.0972, 0.0130, 0.01	0.964, -0.0473, 0.0132, 0.0101	0.725, -0.0273, 0.0132, 0.0102	0.188, -0.0085, 0.0127, 0.0103	0.102, 0.0005, 0.0127, 0.0104	0.204, 0.0095, 0.0131, 0.0104	0.724, 0.0284, 0.0142, 0.0105	0.957, 0.0482, 0.0146, 0.0107	1.000, 0.0982, 0.0149, 0.011
cML-MA-BIC	1.000, -0.0998, 0.0095, 0.0092	0.999, -0.0498, 0.0096, 0.0094	0.881, -0.0298, 0.0097, 0.0095	0.188, -0.0098, 0.0097, 0.0095	0.050, 0.0001, 0.0098, 0.0096	0.183, 0.0101, 0.0098, 0.0096	0.870, 0.0301, 0.0099, 0.0097	1.000, 0.0501, 0.0100, 0.0098	1.000, 0.1001, 0.0102, 0.0101
cML-MA-BIC-Profile	1.000, -0.0998, 0.0095, 0.0092	0.999, -0.0498, 0.0096, 0.0094	0.881, -0.0298, 0.0097, 0.0095	0.188, -0.0098, 0.0097, 0.0096	0.050, 0.0001, 0.0098, 0.0096	0.183, 0.0101, 0.0098, 0.0096	0.869, 0.0301, 0.0099, 0.0097	1.000, 0.0501, 0.0100, 0.0098	1.000, 0.1001, 0.0102, 0.0101
cML-BIC	1.000, -0.0999, 0.0095, 0.0091	0.999, -0.0499, 0.0096, 0.0093	0.886, -0.0299, 0.0097, 0.0094	0.192, -0.0099, 0.0098, 0.0095	0.053, 0.0001, 0.0098, 0.0095	0.189, 0.0101, 0.0098, 0.0096	0.872, 0.0301, 0.0099, 0.0097	1.000, 0.0501, 0.0100, 0.0098	1.000, 0.1001, 0.0103, 0.01
cML-BIC-Profile	1.000, -0.0999, 0.0095, 0.0091	0.999, -0.0499, 0.0096, 0.0093	0.886, -0.0299, 0.0097, 0.0094	0.192, -0.0099, 0.0098, 0.0095	0.053, 0.0001, 0.0098, 0.0095	0.188, 0.0101, 0.0098, 0.0096	0.871, 0.0301, 0.0099, 0.0097	1.000, 0.0501, 0.0100, 0.0098	1.000, 0.1001, 0.0103, 0.0101
MR-Mix	1.000, -0.1060, 0.0128, 0.0161	0.919, -0.0522, 0.0129, 0.0159	0.522, -0.0311, 0.0128, 0.016	0.062, -0.0104, 0.0128, 0.0159	0.016, -0.0003, 0.0128, 0.0159	0.065, 0.0098, 0.0128, 0.0159	0.476, 0.0297, 0.0128, 0.0159	0.890, 0.0491, 0.0129, 0.0159	1.000, 0.0960, 0.0128, 0.016
MR-ContMix	1.000, -0.0996, 0.0098, NA	0.999, -0.0497, 0.0099, NA	0.876, -0.0298, 0.0099, NA	0.204, -0.0098, 0.0100, NA	0.069, 0.0002, 0.0100, NA	0.195, 0.0102, 0.0100, NA	0.873, 0.0302, 0.0101, NA	1.000, 0.0502, 0.0102, NA	1.000, 0.1001, 0.0104, NA
MR-Lasso	1.000, -0.0997, 0.0097, 0.0096	0.998, -0.0498, 0.0098, 0.0098	0.857, -0.0298, 0.0099, 0.0099	0.170, -0.0099, 0.0100, 0.01	0.049, 0.0001, 0.0100, 0.0101	0.159, 0.0101, 0.0100, 0.0101	0.836, 0.0301, 0.0100, 0.0102	1.000, 0.0501, 0.0101, 0.0103	1.000, 0.1000, 0.0105, 0.0106
MR-PRESSO	0.703, -0.0815, 0.1538, 0.0583	0.614, -0.0330, 0.1534, 0.0573	0.515, -0.0130, 0.1533, 0.0572	0.314, 0.0071, 0.1530, 0.0568	0.261, 0.0168, 0.1528, 0.0566	0.314, 0.0269, 0.1527, 0.0565	0.511, 0.0465, 0.1512, 0.0557	0.625, 0.0656, 0.1512, 0.0544	0.756, 0.1136, 0.1497, 0.0522
MR-IVW	0.109, -0.0832, 0.1742, 0.1672	0.080, -0.0331, 0.1742, 0.1671	0.076, -0.0130, 0.1742, 0.1671	0.077, 0.0070, 0.1742, 0.1671	0.081, 0.0170, 0.1742, 0.1671	0.081, 0.0271, 0.1742, 0.1671	0.083, 0.0471, 0.1742, 0.1671	0.089, 0.0671, 0.1742, 0.1671	0.119, 0.1172, 0.1742, 0.1671
MR-IVW-Oracle	1.000, -0.0997, 0.0094, 0.0097	0.999, -0.0498, 0.0095, 0.0099	0.862, -0.0298, 0.0096, 0.01	0.161, -0.0099, 0.0096, 0.0101	0.042, 0.0001, 0.0097, 0.0101	0.153, 0.0101, 0.0097, 0.0102	0.837, 0.0301, 0.0098, 0.0103	1.000, 0.0500, 0.0099, 0.0104	1.000, 0.1000, 0.0101, 0.0107
MR-Egger	0.311, 0.2987, 1.0869, 0.663	0.311, 0.3476, 1.0867, 0.663	0.311, 0.3671, 1.0866, 0.663	0.308, 0.3866, 1.0865, 0.663	0.310, 0.3964, 1.0865, 0.663	0.314, 0.4062, 1.0864, 0.663	0.318, 0.4257, 1.0864, 0.663	0.320, 0.4452, 1.0863, 0.663	0.334, 0.4940, 1.0861, 0.663
MR-Weighted-Median	1.000, -0.0995, 0.0118, 0.0128	0.976, -0.0502, 0.0121, 0.013	0.652, -0.0304, 0.0122, 0.0131	0.113, -0.0106, 0.0123, 0.0132	0.035, -0.0007, 0.0124, 0.0133	0.087, 0.0092, 0.0125, 0.0133	0.590, 0.0290, 0.0126, 0.0135	0.949, 0.0489, 0.0127, 0.0136	1.000, 0.0983, 0.0132, 0.014
MR-Weighted-Mode	0.997, -0.0992, 0.0148, 0.0165	0.890, -0.0493, 0.0147, 0.0167	0.446, -0.0292, 0.0147, 0.0169	0.063, -0.0093, 0.0149, 0.017	0.014, 0.0007, 0.0149, 0.0171	0.059, 0.0106, 0.0149, 0.0172	0.459, 0.0305, 0.0151, 0.0173	0.860, 0.0503, 0.0150, 0.0175	0.994, 0.0999, 0.0156, 0.018
MR-RAPS1	0.109, -0.0841, 0.1685, 0.1628	0.082, -0.0341, 0.1685, 0.1628	0.082, -0.0141, 0.1685, 0.1628	0.077, 0.0059, 0.1685, 0.1628	0.073, 0.0159, 0.1685, 0.1628	0.076, 0.0259, 0.1685, 0.1628	0.082, 0.0459, 0.1685, 0.1629	0.088, 0.0659, 0.1686, 0.1629	0.126, 0.1160, 0.1686, 0.1629
MR-RAPS2	0.997, 0.4776, 4.6454, 0.0282	0.997, 0.2965, 3.0003, 0.0224	0.967, 0.3959, 3.3803, 0.0243	0.773, 0.8531, 9.3107, 0.0277	0.719, 0.4960, 5.4037, 0.0258	0.769, 0.2048, 3.4138, 0.0246	0.958, 0.4515, 2.6366, 0.0234	0.996, 0.6053, 3.2164, 0.0272	0.995, 0.8674, 4.8518, 0.0311
MR-RAPS3	0.947, -0.1950, 0.8378, 0.1869	0.931, -0.0634, 0.4513, 0.0268	0.923, -0.0266, 0.4709, 0.0366	0.939, 0.0233, 0.4192, 0.0267	0.939, 0.0436, 0.4097, 0.0269	0.935, 0.0649, 0.4030, 0.0475	0.915, 0.1013, 0.3925, 0.0231	0.920, 0.1335, 0.4270, 0.0352	0.935, 0.2275, 0.3409, 0.0199
MR-RAPS4	1.000, 0.1360, 1.3740, 0.0222	1.000, 0.2449, 1.3457, 0.0199	0.992, 0.2399, 1.2422, 0.0189	0.956, 0.2792, 1.2027, 0.0177	0.948, 0.2848, 1.2068, 0.0177	0.941, 0.2876, 1.2341, 0.0198	0.990, 0.3457, 1.2200, 0.0182	1.000, 0.3862, 1.2230, 0.0184	1.000, 0.5011, 1.2763, 0.0185

Table S62: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean( $SE(\hat{\theta})$ ) when  $m = 20$ , the InSIDE violated,  $q = 0.4$ , and  $N = 50000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	0.855, -0.0875, 0.0272, 0.0283	0.295, -0.0394, 0.0254, 0.028	0.109, -0.0221, 0.0235, 0.0277	0.027, -0.0067, 0.0223, 0.0276	0.019, 0.0005, 0.0225, 0.0277	0.031, 0.0080, 0.0229, 0.0279	0.105, 0.0232, 0.0250, 0.0285	0.287, 0.0404, 0.0274, 0.0292	0.785, 0.0873, 0.0311, 0.0308
cML-MA-AIC-Profile	0.853, -0.0878, 0.0274, 0.0284	0.293, -0.0395, 0.0254, 0.0282	0.102, -0.0221, 0.0236, 0.0279	0.027, -0.0067, 0.0223, 0.0278	0.019, 0.0005, 0.0225, 0.0279	0.029, 0.0080, 0.0229, 0.0281	0.101, 0.0233, 0.0251, 0.0287	0.287, 0.0404, 0.0274, 0.0294	0.783, 0.0874, 0.0312, 0.031
cML-AIC	0.939, -0.0941, 0.0296, 0.0234	0.498, -0.0449, 0.0291, 0.0238	0.242, -0.0260, 0.0280, 0.024	0.098, -0.0082, 0.0278, 0.0243	0.076, 0.0006, 0.0278, 0.0244	0.100, 0.0092, 0.0281, 0.0245	0.248, 0.0268, 0.0295, 0.0247	0.477, 0.0454, 0.0309, 0.025	0.893, 0.0940, 0.0333, 0.0257
cML-AIC-Profile	0.938, -0.0943, 0.0297, 0.0235	0.490, -0.0449, 0.0291, 0.024	0.240, -0.0260, 0.0280, 0.0242	0.096, -0.0082, 0.0278, 0.0244	0.075, 0.0006, 0.0278, 0.0245	0.097, 0.0092, 0.0281, 0.0247	0.242, 0.0268, 0.0295, 0.0249	0.471, 0.0455, 0.0310, 0.0252	0.893, 0.0940, 0.0334, 0.0259
cML-MA-BIC	0.992, -0.0995, 0.0217, 0.0218	0.624, -0.0495, 0.0220, 0.0222	0.249, -0.0295, 0.0222, 0.0224	0.066, -0.0096, 0.0223, 0.0226	0.045, 0.0003, 0.0224, 0.0227	0.067, 0.0103, 0.0226, 0.0228	0.242, 0.0302, 0.0228, 0.023	0.593, 0.0502, 0.0231, 0.0233	0.987, 0.1001, 0.0239, 0.0239
cML-MA-BIC-Profile	0.992, -0.0995, 0.0217, 0.0219	0.622, -0.0495, 0.0220, 0.0223	0.248, -0.0295, 0.0222, 0.0225	0.066, -0.0096, 0.0223, 0.0227	0.045, 0.0003, 0.0224, 0.0228	0.067, 0.0103, 0.0226, 0.0229	0.242, 0.0302, 0.0228, 0.0231	0.590, 0.0502, 0.0231, 0.0233	0.987, 0.1001, 0.0239, 0.024
cML-BIC	0.992, -0.0996, 0.0216, 0.0215	0.638, -0.0497, 0.0220, 0.0219	0.257, -0.0297, 0.0221, 0.0221	0.072, -0.0096, 0.0223, 0.0223	0.048, 0.0003, 0.0224, 0.0224	0.071, 0.0103, 0.0225, 0.0225	0.246, 0.0303, 0.0228, 0.0227	0.605, 0.0503, 0.0231, 0.023	0.990, 0.1003, 0.0239, 0.0236
cML-BIC-Profile	0.992, -0.0996, 0.0216, 0.0216	0.633, -0.0497, 0.0220, 0.022	0.257, -0.0297, 0.0221, 0.0222	0.071, -0.0096, 0.0223, 0.0224	0.046, 0.0003, 0.0224, 0.0225	0.071, 0.0103, 0.0225, 0.0226	0.244, 0.0303, 0.0228, 0.0228	0.597, 0.0503, 0.0231, 0.023	0.990, 0.1003, 0.0239, 0.0237
MR-Mix	0.943, -0.1034, 0.0248, 0.0307	0.396, -0.0505, 0.0248, 0.0303	0.136, -0.0299, 0.0248, 0.0301	0.025, -0.0097, 0.0247, 0.0301	0.022, 0.0002, 0.0247, 0.0301	0.036, 0.0101, 0.0247, 0.0301	0.131, 0.0295, 0.0248, 0.0301	0.334, 0.0484, 0.0248, 0.0304	0.910, 0.0944, 0.0248, 0.0302
MR-ContMix	0.993, -0.0992, 0.0227, NA	0.632, -0.0494, 0.0229, NA	0.276, -0.0296, 0.0231, NA	0.079, -0.0096, 0.0233, NA	0.056, 0.0003, 0.0234, NA	0.083, 0.0102, 0.0235, NA	0.270, 0.0301, 0.0238, NA	0.603, 0.0499, 0.0241, NA	0.984, 0.0996, 0.0250, NA
MR-Lasso	0.989, -0.0992, 0.0222, 0.0228	0.600, -0.0495, 0.0226, 0.0232	0.237, -0.0297, 0.0229, 0.0234	0.061, -0.0098, 0.0230, 0.0236	0.042, 0.0001, 0.0231, 0.0237	0.069, 0.0101, 0.0233, 0.0239	0.231, 0.0300, 0.0236, 0.0241	0.548, 0.0499, 0.0238, 0.0243	0.971, 0.0994, 0.0247, 0.025
MR-PRESSO	0.727, -0.0733, 0.1770, 0.0515	0.477, -0.0278, 0.1748, 0.0496	0.333, -0.0082, 0.1748, 0.0494	0.249, 0.0109, 0.1728, 0.0486	0.240, 0.0200, 0.1721, 0.0483	0.255, 0.0290, 0.1713, 0.0482	0.355, 0.0480, 0.1703, 0.0478	0.511, 0.0670, 0.1686, 0.0473	0.777, 0.1140, 0.1629, 0.0455
MR-IVW	0.086, -0.0690, 0.2407, 0.2341	0.069, -0.0188, 0.2407, 0.234	0.068, 0.0012, 0.2407, 0.234	0.066, 0.0213, 0.2408, 0.234	0.067, 0.0313, 0.2408, 0.234	0.067, 0.0413, 0.2408, 0.234	0.076, 0.0614, 0.2408, 0.234	0.080, 0.0814, 0.2408, 0.234	0.108, 0.1315, 0.2408, 0.234
MR-IVW-Oracle	0.989, -0.0991, 0.0215, 0.0229	0.593, -0.0494, 0.0218, 0.0233	0.225, -0.0295, 0.0220, 0.0235	0.057, -0.0096, 0.0222, 0.0237	0.038, 0.0003, 0.0223, 0.0238	0.060, 0.0103, 0.0224, 0.024	0.226, 0.0302, 0.0226, 0.0242	0.541, 0.0500, 0.0229, 0.0244	0.977, 0.0998, 0.0236, 0.0251
MR-Egger	0.206, 0.5169, 1.0543, 0.7834	0.212, 0.5640, 1.0541, 0.7835	0.213, 0.5828, 1.0541, 0.7835	0.221, 0.6016, 1.0541, 0.7836	0.222, 0.6110, 1.0540, 0.7836	0.222, 0.6204, 1.0540, 0.7837	0.224, 0.6392, 1.0539, 0.7837	0.229, 0.6580, 1.0539, 0.7838	0.250, 0.7050, 1.0539, 0.784
MR-Weighted-Median	0.922, -0.1010, 0.0297, 0.0297	0.444, -0.0534, 0.0307, 0.0302	0.203, -0.0343, 0.0311, 0.0305	0.079, -0.0154, 0.0317, 0.0307	0.060, -0.0059, 0.0320, 0.0309	0.053, 0.0036, 0.0323, 0.031	0.129, 0.0227, 0.0328, 0.0313	0.272, 0.0418, 0.0333, 0.0317	0.786, 0.0894, 0.0349, 0.0326
MR-Weighted-Mode	0.932, -0.1023, 0.1260, 0.0497	0.410, -0.0534, 0.1259, 0.0502	0.149, -0.0323, 0.1286, 0.0505	0.037, -0.0130, 0.1285, 0.0507	0.025, -0.0033, 0.1284, 0.0507	0.042, 0.0065, 0.1283, 0.0509	0.152, 0.0258, 0.1282, 0.0512	0.383, 0.0454, 0.1280, 0.0515	0.901, 0.0945, 0.1276, 0.0526
MR-RAPS1	0.083, -0.0692, 0.2329, 0.2292	0.067, -0.0191, 0.2330, 0.2292	0.068, 0.0009, 0.2330, 0.2292	0.068, 0.0209, 0.2330, 0.2292	0.065, 0.0309, 0.2330, 0.2292	0.064, 0.0409, 0.2330, 0.2292	0.072, 0.0610, 0.2331, 0.2292	0.081, 0.0810, 0.2331, 0.2292	0.106, 0.1310, 0.2332, 0.2293
MR-RAPS2	0.082, -0.0864, 0.2243, 0.2299	0.058, -0.0379, 0.2284, 0.2308	0.060, -0.0177, 0.2281, 0.2305	0.060, 0.0042, 0.2283, 0.2306	0.059, 0.0124, 0.2288, 0.2309	0.060, 0.0234, 0.2300, 0.2314	0.066, 0.0412, 0.2357, 0.2305	0.073, 0.0626, 0.2298, 0.231	0.088, 0.1148, 0.2285, 0.2312
MR-RAPS3	0.896, -0.5866, 21.0060, 62.3479	0.895, -1.1754, 34.1200, 83.9749	0.890, 0.1021, 11.9450, 8.2491	0.897, -2.1821, 65.0454, 156.102	0.895, 2.4716, 58.1470, 216.8516	0.890, -3.1800, 102.3099, 716.7582	0.899, 0.3914, 9.2434, 6.128	0.896, -0.0317, 50.8193, 85.8968	0.895, 0.8791, 12.6109, 12.2244
MR-RAPS4	0.989, -0.0482, 6.6462, 0.387	0.974, -0.2519, 11.6099, 0.3825	0.974, -0.1746, 9.5661, 0.2742	0.911, -0.0919, 9.2975, 0.2694	0.906, -0.1390, 9.0784, 0.2925	0.907, -0.0308, 9.6594, 0.4394	0.929, -0.2430, 10.4690, 0.5783	0.969, -1.2295, 47.9748, 201.0763	0.998, -0.0585, 5.2586, 0.3555

Table S63: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean( $SE(\hat{\theta})$ ) when  $m = 20$ , the InSIDE violated,  $q = 0.4$ , and  $N = 100000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	0.979, -0.0914, 0.0203, 0.0198	0.569, -0.0419, 0.0200, 0.0199	0.209, -0.0235, 0.0185, 0.0197	0.050, -0.0071, 0.0169, 0.0195	0.036, 0.0002, 0.0165, 0.0195	0.044, 0.0077, 0.0169, 0.0197	0.217, 0.0238, 0.0191, 0.0203	0.525, 0.0421, 0.0208, 0.0209	0.948, 0.0908, 0.0228, 0.0219
cML-MA-AIC-Profile	0.979, -0.0915, 0.0204, 0.0199	0.568, -0.0419, 0.0200, 0.0199	0.208, -0.0235, 0.0185, 0.0197	0.048, -0.0071, 0.0169, 0.0196	0.035, 0.0002, 0.0165, 0.0196	0.044, 0.0077, 0.0169, 0.0197	0.216, 0.0239, 0.0191, 0.0204	0.523, 0.0422, 0.0209, 0.021	0.948, 0.0910, 0.0229, 0.022
cML-AIC	0.992, -0.0958, 0.0219, 0.0165	0.733, -0.0458, 0.0213, 0.0168	0.391, -0.0265, 0.0213, 0.017	0.140, -0.0082, 0.0209, 0.0172	0.101, 0.0001, 0.0207, 0.0172	0.139, 0.0089, 0.0207, 0.0173	0.399, 0.0269, 0.0222, 0.0175	0.708, 0.0463, 0.0232, 0.0177	0.975, 0.0954, 0.0247, 0.0181
cML-AIC-Profile	0.992, -0.0959, 0.0217, 0.0166	0.732, -0.0458, 0.0219, 0.0169	0.389, -0.0265, 0.0213, 0.017	0.140, -0.0082, 0.0209, 0.0172	0.100, 0.0002, 0.0208, 0.0173	0.137, 0.0089, 0.0207, 0.0173	0.396, 0.0269, 0.0223, 0.0175	0.707, 0.0463, 0.0232, 0.0177	0.975, 0.0956, 0.0248, 0.0182
cML-MA-BIC	1.000, -0.0998, 0.0156, 0.0154	0.884, -0.0498, 0.0159, 0.0156	0.476, -0.0298, 0.0160, 0.0158	0.098, -0.0098, 0.0161, 0.0159	0.058, 0.0002, 0.0162, 0.016	0.099, 0.0101, 0.0163, 0.016	0.467, 0.0301, 0.0165, 0.0162	0.857, 0.0501, 0.0167, 0.0164	1.000, 0.1001, 0.0173, 0.0168
cML-MA-BIC-Profile	1.000, -0.0998, 0.0156, 0.0154	0.882, -0.0498, 0.0159, 0.0157	0.470, -0.0298, 0.0160, 0.0158	0.098, -0.0098, 0.0161, 0.0159	0.058, 0.0002, 0.0162, 0.016	0.096, 0.0101, 0.0163, 0.0161	0.463, 0.0301, 0.0165, 0.0162	0.857, 0.0501, 0.0167, 0.0164	1.000, 0.1002, 0.0173, 0.0169
cML-BIC	1.000, -0.0999, 0.0156, 0.0152	0.889, -0.0499, 0.0159, 0.0155	0.485, -0.0299, 0.0160, 0.0156	0.105, -0.0098, 0.0162, 0.0157	0.062, 0.0002, 0.0163, 0.0158	0.101, 0.0102, 0.0164, 0.0159	0.475, 0.0302, 0.0165, 0.016	0.865, 0.0502, 0.0167, 0.0162	1.000, 0.1002, 0.0174, 0.0167
cML-BIC-Profile	1.000, -0.0999, 0.0156, 0.0152	0.887, -0.0499, 0.0159, 0.0155	0.485, -0.0299, 0.0160, 0.0156	0.105, -0.0098, 0.0162, 0.0158	0.061, 0.0002, 0.0163, 0.0158	0.099, 0.0102, 0.0164, 0.0159	0.473, 0.0302, 0.0165, 0.0161	0.863, 0.0502, 0.0167, 0.0162	1.000, 0.1002, 0.0174, 0.0167
MR-Mix	0.994, -0.1039, 0.0188, 0.0225	0.662, -0.0508, 0.0188, 0.0224	0.243, -0.0302, 0.0188, 0.0224	0.055, -0.0100, 0.0188, 0.0224	0.028, -0.0001, 0.0189, 0.0224	0.039, 0.0098, 0.0189, 0.0224	0.233, 0.0292, 0.0188, 0.0223	0.611, 0.0483, 0.0186, 0.0223	0.980, 0.0943, 0.0187, 0.0225
MR-ContMix	1.000, -0.0995, 0.0159, NA	0.889, -0.0497, 0.0163, NA	0.506, -0.0297, 0.0164, NA	0.124, -0.0097, 0.0166, NA	0.071, 0.0003, 0.0167, NA	0.120, 0.0103, 0.0168, NA	0.490, 0.0302, 0.0170, NA	0.874, 0.0502, 0.0171, NA	1.000, 0.1000, 0.0177, NA
MR-Lasso	1.000, -0.0997, 0.0157, 0.0162	0.853, -0.0497, 0.0161, 0.0165	0.448, -0.0299, 0.0163, 0.0166	0.091, -0.0099, 0.0165, 0.0167	0.060, 0.0001, 0.0166, 0.0168	0.090, 0.0101, 0.0167, 0.0169	0.427, 0.0301, 0.0168, 0.0171	0.836, 0.0501, 0.0170, 0.0172	1.000, 0.0999, 0.0176, 0.0177
MR-PRESSO	0.639, -0.0397, 0.2136, 0.0829	0.488, 0.0083, 0.2132, 0.0812	0.338, 0.0265, 0.2127, 0.0795	0.224, 0.0457, 0.2119, 0.0778	0.216, 0.0556, 0.2117, 0.0776	0.260, 0.0656, 0.2118, 0.0776	0.410, 0.0855, 0.2107, 0.0764	0.565, 0.1050, 0.2102, 0.0756	0.738, 0.1534, 0.2091, 0.0741
MR-IVW	0.082, -0.0323, 0.2371, 0.2328	0.088, 0.0180, 0.2371, 0.2328	0.085, 0.0381, 0.2371, 0.2328	0.091, 0.0582, 0.2371, 0.2328	0.090, 0.0682, 0.2371, 0.2328	0.089, 0.0783, 0.2371, 0.2328	0.098, 0.0983, 0.2371, 0.2328	0.106, 0.1184, 0.2371, 0.2328	0.130, 0.1686, 0.2371, 0.2327
MR-IVW-Oracle	1.000, -0.0996, 0.0155, 0.0163	0.849, -0.0498, 0.0158, 0.0166	0.438, -0.0298, 0.0160, 0.0167	0.085, -0.0098, 0.0161, 0.0169	0.053, 0.0001, 0.0162, 0.0169	0.084, 0.0101, 0.0163, 0.017	0.423, 0.0301, 0.0165, 0.0172	0.834, 0.0500, 0.0167, 0.0173	1.000, 0.0999, 0.0172, 0.0178
MR-Egger	0.227, 0.5207, 1.1342, 0.8026	0.234, 0.5694, 1.1340, 0.8027	0.240, 0.5889, 1.1339, 0.8027	0.245, 0.6084, 1.1339, 0.8028	0.247, 0.6181, 1.1339, 0.8028	0.249, 0.6278, 1.1338, 0.8028	0.252, 0.6473, 1.1338, 0.8028	0.258, 0.6667, 1.1337, 0.8029	0.265, 0.7153, 1.1336, 0.8029
MR-Weighted-Median	0.997, -0.1000, 0.0214, 0.021	0.678, -0.0514, 0.0219, 0.0213	0.326, -0.0318, 0.0222, 0.0215	0.091, -0.0123, 0.0226, 0.0217	0.061, -0.0026, 0.0228, 0.0218	0.075, 0.0072, 0.0229, 0.0219	0.248, 0.0266, 0.0233, 0.0221	0.548, 0.0460, 0.0237, 0.0224	0.973, 0.0945, 0.0248, 0.023
MR-Weighted-Mode	0.989, -0.0966, 0.0364, 0.0346	0.702, -0.0473, 0.0364, 0.035	0.283, -0.0271, 0.0361, 0.0351	0.058, -0.0073, 0.0359, 0.0354	0.035, 0.0023, 0.0359, 0.0354	0.059, 0.0120, 0.0359, 0.0355	0.304, 0.0312, 0.0406, 0.0357	0.679, 0.0511, 0.0405, 0.0359	0.983, 0.0999, 0.0408, 0.0366
MR-RAPS1	0.084, -0.0360, 0.2307, 0.2271	0.083, 0.0141, 0.2307, 0.2271	0.089, 0.0341, 0.2307, 0.2271	0.089, 0.0541, 0.2307, 0.2271	0.087, 0.0641, 0.2308, 0.2271	0.086, 0.0741, 0.2308, 0.2271	0.092, 0.0941, 0.2308, 0.2271	0.097, 0.1141, 0.2308, 0.2271	0.132, 0.1642, 0.2308, 0.2272
MR-RAPS2	0.142, -0.0780, 0.2208, 0.2112	0.108, -0.0258, 0.2251, 0.216	0.094, -0.0058, 0.2236, 0.2167	0.089, 0.0172, 0.2229, 0.2177	0.086, 0.0273, 0.2267, 0.2188	0.092, 0.0381, 0.2275, 0.2199	0.090, 0.0613, 0.2304, 0.2213	0.088, 0.0833, 0.2283, 0.2233	0.110, 0.1333, 0.2289, 0.2225
MR-RAPS3	0.933, -2.3384, 70.7258, 191.3771	0.924, 0.3391, 10.2598, 5.3413	0.921, 1.6787, 27.3294, 32.6694	0.913, 0.6886, 41.4050, 104.7941	0.910, 1.1393, 22.0445, 29.3033	0.906, 1.7040, 18.2553, 17.7291	0.915, -0.0513, 9.0579, 3.8172	0.920, 0.4360, 11.9486, 11.6837	0.929, 0.3862, 7.3367, 3.6125
MR-RAPS4	0.984, 0.2999, 9.8559, 0.517	0.986, 0.4626, 7.5855, 0.1915	0.970, 0.7042, 9.4893, 0.1727	0.940, 0.6981, 10.1499, 0.1708	0.929, 0.4933, 7.5349, 0.1882	0.938, 0.6048, 8.7619, 0.3101	0.954, 0.3249, 2.5576, 0.1281	0.991, 0.3620, 2.5130, 0.1438	0.993, 0.3066, 2.0239, 0.0938

Table S64: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean( $SE(\hat{\theta})$ ) when  $m = 20$ , the InSIDE violated,  $q = 0.4$ , and  $N = 200000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	0.997, -0.0936, 0.0145, 0.0142	0.836, -0.0438, 0.0145, 0.0143	0.418, -0.0245, 0.0138, 0.0141	0.069, -0.0073, 0.0121, 0.0138	0.024, 0.0002, 0.0117, 0.0138	0.068, 0.0078, 0.0121, 0.014	0.410, 0.0248, 0.0141, 0.0145	0.815, 0.0440, 0.0152, 0.015	0.997, 0.0934, 0.0161, 0.0155
cML-MA-AIC-Profile	0.998, -0.0937, 0.0145, 0.0142	0.836, -0.0438, 0.0146, 0.0143	0.417, -0.0245, 0.0138, 0.0142	0.066, -0.0073, 0.0120, 0.0138	0.024, 0.0002, 0.0117, 0.0138	0.067, 0.0078, 0.0121, 0.014	0.409, 0.0248, 0.0141, 0.0146	0.815, 0.0440, 0.0152, 0.015	0.997, 0.0936, 0.0162, 0.0155
cML-AIC	1.000, -0.0970, 0.0151, 0.0117	0.922, -0.0468, 0.0155, 0.0119	0.610, -0.0271, 0.0154, 0.012	0.164, -0.0083, 0.0146, 0.0121	0.102, 0.0004, 0.0146, 0.0122	0.161, 0.0090, 0.0147, 0.0122	0.605, 0.0275, 0.0159, 0.0123	0.908, 0.0472, 0.0164, 0.0125	0.999, 0.0968, 0.0172, 0.0128
cML-AIC-Profile	1.000, -0.0970, 0.0151, 0.0117	0.922, -0.0469, 0.0155, 0.0119	0.610, -0.0271, 0.0154, 0.012	0.163, -0.0083, 0.0146, 0.0121	0.101, 0.0004, 0.0146, 0.0122	0.160, 0.0090, 0.0147, 0.0122	0.605, 0.0275, 0.0159, 0.0124	0.907, 0.0472, 0.0164, 0.0125	0.999, 0.0968, 0.0173, 0.0129
cML-MA-BIC	1.000, -0.1000, 0.0108, 0.0108	0.996, -0.0500, 0.0110, 0.011	0.775, -0.0300, 0.0111, 0.0111	0.144, -0.0100, 0.0111, 0.0112	0.051, 0.0000, 0.0112, 0.0113	0.140, 0.0099, 0.0112, 0.0113	0.751, 0.0299, 0.0114, 0.0114	0.989, 0.0499, 0.0115, 0.0116	1.000, 0.0999, 0.0118, 0.0119
cML-MA-BIC-Profile	1.000, -0.1000, 0.0108, 0.0108	0.996, -0.0500, 0.0110, 0.011	0.775, -0.0300, 0.0111, 0.0112	0.144, -0.0100, 0.0111, 0.0112	0.051, 0.0000, 0.0112, 0.0113	0.138, 0.0099, 0.0112, 0.0113	0.751, 0.0299, 0.0114, 0.0114	0.989, 0.0499, 0.0115, 0.0116	1.000, 0.0999, 0.0118, 0.0119
cML-BIC	1.000, -0.1000, 0.0108, 0.0107	0.997, -0.0500, 0.0110, 0.0109	0.780, -0.0300, 0.0110, 0.011	0.148, -0.0101, 0.0111, 0.0112	0.052, -0.0001, 0.0112, 0.0112	0.146, 0.0099, 0.0112, 0.0112	0.758, 0.0299, 0.0113, 0.0113	0.990, 0.0499, 0.0115, 0.0115	1.000, 0.0999, 0.0118, 0.0118
cML-BIC-Profile	1.000, -0.1000, 0.0108, 0.0108	0.997, -0.0500, 0.0110, 0.0109	0.779, -0.0300, 0.0110, 0.011	0.147, -0.0101, 0.0111, 0.0112	0.052, -0.0001, 0.0112, 0.0112	0.145, 0.0099, 0.0112, 0.0112	0.758, 0.0299, 0.0113, 0.0113	0.990, 0.0499, 0.0115, 0.0115	1.000, 0.0999, 0.0118, 0.0118
MR-Mix	0.999, -0.1041, 0.0132, 0.0164	0.914, -0.0509, 0.0131, 0.0163	0.476, -0.0303, 0.0129, 0.0164	0.064, -0.0102, 0.0129, 0.0163	0.016, -0.0002, 0.0128, 0.0163	0.057, 0.0098, 0.0128, 0.0163	0.455, 0.0292, 0.0129, 0.0163	0.878, 0.0483, 0.0130, 0.0163	0.996, 0.0944, 0.0130, 0.0167
MR-ContMix	1.000, -0.0999, 0.0110, NA	0.995, -0.0500, 0.0113, NA	0.793, -0.0300, 0.0114, NA	0.164, -0.0101, 0.0114, NA	0.072, -0.0001, 0.0115, NA	0.168, 0.0099, 0.0116, NA	0.770, 0.0299, 0.0117, NA	0.987, 0.0498, 0.0118, NA	1.000, 0.0997, 0.0121, NA
MR-Lasso	1.000, -0.0998, 0.0112, 0.0115	0.986, -0.0499, 0.0114, 0.0117	0.733, -0.0299, 0.0115, 0.0118	0.130, -0.0100, 0.0115, 0.0119	0.047, 0.0000, 0.0115, 0.0119	0.126, 0.0099, 0.0116, 0.012	0.704, 0.0299, 0.0116, 0.0121	0.978, 0.0499, 0.0118, 0.0122	0.999, 0.0997, 0.0121, 0.0126
MR-PRESSO	0.537, -0.0499, 0.2351, 0.1138	0.459, -0.0003, 0.2349, 0.113	0.354, 0.0192, 0.2348, 0.1122	0.219, 0.0394, 0.2347, 0.112	0.200, 0.0490, 0.2347, 0.1117	0.233, 0.0589, 0.2346, 0.1115	0.402, 0.0786, 0.2341, 0.1101	0.498, 0.0984, 0.2337, 0.1089	0.608, 0.1473, 0.2329, 0.1056
MR-IVW	0.091, -0.0465, 0.2446, 0.234	0.086, 0.0038, 0.2445, 0.234	0.087, 0.0239, 0.2445, 0.234	0.085, 0.0440, 0.2444, 0.234	0.082, 0.0541, 0.2444, 0.234	0.079, 0.0642, 0.2444, 0.2339	0.090, 0.0843, 0.2444, 0.2339	0.095, 0.1043, 0.2443, 0.2339	0.116, 0.1546, 0.2443, 0.2339
MR-IVW-Oracle	1.000, -0.0999, 0.0107, 0.0115	0.990, -0.0499, 0.0109, 0.0117	0.732, -0.0300, 0.0109, 0.0118	0.122, -0.0100, 0.0111, 0.0119	0.042, 0.0000, 0.0111, 0.012	0.120, 0.0100, 0.0112, 0.012	0.703, 0.0299, 0.0113, 0.0122	0.982, 0.0499, 0.0114, 0.0123	1.000, 0.0998, 0.0117, 0.0126
MR-Egger	0.254, 0.5503, 1.1351, 0.7866	0.258, 0.5997, 1.1350, 0.7865	0.258, 0.6194, 1.1350, 0.7865	0.265, 0.6391, 1.1350, 0.7865	0.267, 0.6490, 1.1350, 0.7865	0.272, 0.6588, 1.1350, 0.7865	0.272, 0.6785, 1.1350, 0.7865	0.278, 0.6982, 1.1350, 0.7865	0.289, 0.7474, 1.1350, 0.7865
MR-Weighted-Median	1.000, -0.1005, 0.0153, 0.0148	0.927, -0.0514, 0.0157, 0.0151	0.543, -0.0318, 0.0159, 0.0152	0.133, -0.0121, 0.0163, 0.0153	0.062, -0.0023, 0.0165, 0.0154	0.079, 0.0074, 0.0167, 0.0155	0.434, 0.0270, 0.0171, 0.0156	0.832, 0.0466, 0.0177, 0.0158	0.996, 0.0954, 0.0191, 0.0163
MR-Weighted-Mode	0.990, -0.0992, 0.0158, 0.0157	0.919, -0.0493, 0.0157, 0.0159	0.530, -0.0296, 0.0159, 0.016	0.094, -0.0096, 0.0160, 0.0161	0.037, 0.0004, 0.0160, 0.0161	0.085, 0.0102, 0.0159, 0.0162	0.515, 0.0301, 0.0159, 0.0163	0.901, 0.0497, 0.0160, 0.0165	0.992, 0.0996, 0.0162, 0.0168
MR-RAPS1	0.094, -0.0472, 0.2392, 0.228	0.092, 0.0028, 0.2391, 0.228	0.086, 0.0228, 0.2391, 0.228	0.084, 0.0428, 0.2391, 0.228	0.077, 0.0528, 0.2391, 0.228	0.084, 0.0628, 0.2391, 0.228	0.092, 0.0828, 0.2391, 0.228	0.100, 0.1028, 0.2391, 0.228	0.125, 0.1528, 0.2390, 0.228
MR-RAPS2	0.284, -0.1275, 0.1607, 0.136	0.177, -0.0790, 0.1635, 0.137	0.136, -0.0575, 0.1710, 0.1386	0.095, -0.0431, 0.1589, 0.1374	0.082, -0.0327, 0.1597, 0.1378	0.078, -0.0206, 0.1602, 0.1373	0.065, -0.0012, 0.1626, 0.137	0.063, 0.0160, 0.1605, 0.1354	0.103, 0.0688, 0.1729, 0.1418
MR-RAPS3	0.932, -4.5043, 133.2929, 459.1634	0.930, -2.8573, 108.8086, 278.2873	0.926, 0.2790, 20.2050, 12.2365	0.944, 0.2108, 44.2770, 83.1364	0.951, -0.6234, 19.5964, 11.7936	0.955, -11.2173, 378.1344, 6799.6057	0.954, 1.1095, 15.8975, 8.7751	0.950, 0.2982, 9.1370, 4.4133	0.947, 0.3811, 11.3200, 4.5942
MR-RAPS4	0.990, 0.0360, 2.5810, 0.1226	0.993, 0.0936, 2.5583, 0.1412	0.986, 0.1421, 2.6249, 0.159	0.960, 0.1405, 2.6864, 0.1629	0.946, 0.1670, 2.6504, 0.114	0.955, 0.1783, 2.6050, 0.4293	0.993, 0.2380, 2.5032, 0.1101	0.999, 0.2547, 2.5032, 0.0807	0.998, 0.3534, 2.3370, 0.0701

Table S65: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean( $SE(\hat{\theta})$ ) when  $m = 20$ , the InSIDE violated,  $q = 0.6$ , and  $N = 50000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	0.621, -0.0822, 0.0340, 0.0363	0.170, -0.0372, 0.0302, 0.0357	0.060, -0.0215, 0.0282, 0.0355	0.023, -0.0072, 0.0265, 0.0354	0.016, -0.0005, 0.0259, 0.0354	0.010, 0.0064, 0.0263, 0.0356	0.049, 0.0203, 0.0279, 0.0364	0.138, 0.0360, 0.0304, 0.0373	0.557, 0.0799, 0.0359, 0.0396
cML-MA-AIC-Profile	0.618, -0.0823, 0.0342, 0.0365	0.170, -0.0372, 0.0302, 0.0359	0.059, -0.0215, 0.0282, 0.0357	0.022, -0.0072, 0.0265, 0.0356	0.016, -0.0005, 0.0259, 0.0356	0.010, 0.0064, 0.0263, 0.0358	0.047, 0.0203, 0.0279, 0.0367	0.136, 0.0360, 0.0304, 0.0375	0.554, 0.0801, 0.0360, 0.0399
cML-AIC	0.811, -0.0907, 0.0375, 0.0293	0.361, -0.0429, 0.0358, 0.03	0.178, -0.0258, 0.0346, 0.0302	0.080, -0.0084, 0.0343, 0.0305	0.073, -0.0008, 0.0337, 0.0305	0.076, 0.0078, 0.0339, 0.0307	0.157, 0.0237, 0.0360, 0.0311	0.331, 0.0410, 0.0379, 0.0315	0.750, 0.0875, 0.0412, 0.0323
cML-AIC-Profile	0.806, -0.0909, 0.0377, 0.0295	0.356, -0.0429, 0.0359, 0.0302	0.173, -0.0258, 0.0346, 0.0304	0.080, -0.0084, 0.0343, 0.0307	0.071, -0.0007, 0.0338, 0.0307	0.075, 0.0078, 0.0339, 0.0309	0.156, 0.0237, 0.0360, 0.0313	0.326, 0.0410, 0.0379, 0.0317	0.745, 0.0876, 0.0413, 0.0325
cML-MA-BIC	0.957, -0.1000, 0.0265, 0.0274	0.435, -0.0500, 0.0270, 0.0279	0.194, -0.0301, 0.0271, 0.0281	0.063, -0.0102, 0.0273, 0.0284	0.037, -0.0002, 0.0274, 0.0285	0.053, 0.0097, 0.0275, 0.0286	0.165, 0.0296, 0.0279, 0.0289	0.401, 0.0496, 0.0282, 0.0292	0.917, 0.0996, 0.0291, 0.03
cML-MA-BIC-Profile	0.955, -0.1000, 0.0265, 0.0276	0.433, -0.0500, 0.0270, 0.028	0.193, -0.0301, 0.0271, 0.0283	0.063, -0.0102, 0.0273, 0.0285	0.036, -0.0002, 0.0274, 0.0286	0.052, 0.0097, 0.0275, 0.0288	0.164, 0.0296, 0.0279, 0.029	0.399, 0.0496, 0.0282, 0.0293	0.916, 0.0996, 0.0291, 0.0301
cML-BIC	0.957, -0.1002, 0.0266, 0.0271	0.446, -0.0502, 0.0272, 0.0275	0.200, -0.0302, 0.0274, 0.0277	0.065, -0.0102, 0.0277, 0.028	0.042, -0.0002, 0.0277, 0.0281	0.060, 0.0098, 0.0279, 0.0282	0.180, 0.0298, 0.0281, 0.0285	0.423, 0.0498, 0.0284, 0.0288	0.922, 0.0998, 0.0292, 0.0296
cML-BIC-Profile	0.953, -0.1002, 0.0266, 0.0272	0.442, -0.0502, 0.0272, 0.0276	0.199, -0.0302, 0.0274, 0.0278	0.065, -0.0102, 0.0277, 0.0281	0.039, -0.0002, 0.0277, 0.0282	0.059, 0.0098, 0.0279, 0.0283	0.178, 0.0298, 0.0281, 0.0286	0.419, 0.0498, 0.0284, 0.0289	0.921, 0.0998, 0.0292, 0.0297
MR-Mix	0.869, -0.1021, 0.0287, 0.0339	0.335, -0.0503, 0.0286, 0.0338	0.140, -0.0301, 0.0285, 0.034	0.038, -0.0102, 0.0284, 0.0337	0.023, -0.0004, 0.0284, 0.0335	0.040, 0.0094, 0.0285, 0.0335	0.110, 0.0286, 0.0284, 0.0334	0.292, 0.0472, 0.0286, 0.0334	0.816, 0.0925, 0.0286, 0.0336
MR-ContMix	0.957, -0.0996, 0.0275, NA	0.477, -0.0499, 0.0279, NA	0.229, -0.0300, 0.0281, NA	0.079, -0.0102, 0.0283, NA	0.061, -0.0002, 0.0284, NA	0.077, 0.0097, 0.0286, NA	0.209, 0.0296, 0.0288, NA	0.440, 0.0495, 0.0291, NA	0.920, 0.0994, 0.0302, NA
MR-Lasso	0.908, -0.0774, 0.2046, 0.035	0.417, -0.0273, 0.2045, 0.0356	0.218, -0.0074, 0.2045, 0.0359	0.099, 0.0127, 0.2046, 0.0361	0.081, 0.0226, 0.2046, 0.0363	0.086, 0.0327, 0.2049, 0.0364	0.176, 0.0521, 0.2036, 0.037	0.357, 0.0722, 0.2052, 0.0375	0.854, 0.1223, 0.2062, 0.0382
MR-PRESSO	0.545, -0.0251, 0.2518, 0.0918	0.302, 0.0216, 0.2505, 0.0896	0.209, 0.0397, 0.2501, 0.0888	0.173, 0.0577, 0.2490, 0.0871	0.170, 0.0659, 0.2482, 0.086	0.185, 0.0743, 0.2473, 0.0848	0.259, 0.0936, 0.2469, 0.0842	0.349, 0.1131, 0.2465, 0.0834	0.627, 0.1596, 0.2440, 0.0816
MR-IVW	0.072, -0.0121, 0.2894, 0.2801	0.074, 0.0382, 0.2895, 0.2801	0.075, 0.0583, 0.2895, 0.2801	0.080, 0.0784, 0.2895, 0.2801	0.083, 0.0885, 0.2895, 0.2801	0.082, 0.0985, 0.2895, 0.2801	0.093, 0.1186, 0.2895, 0.2801	0.098, 0.1387, 0.2895, 0.2801	0.117, 0.1889, 0.2896, 0.2801
MR-IVW-Oracle	0.922, -0.0996, 0.0261, 0.0296	0.386, -0.0499, 0.0265, 0.0301	0.171, -0.0300, 0.0268, 0.0304	0.048, -0.0101, 0.0270, 0.0306	0.033, -0.0001, 0.0271, 0.0308	0.043, 0.0098, 0.0273, 0.0309	0.134, 0.0297, 0.0276, 0.0312	0.346, 0.0496, 0.0279, 0.0315	0.881, 0.0994, 0.0287, 0.0323
MR-Egger	0.185, 0.5815, 1.0311, 0.8485	0.187, 0.6295, 1.0311, 0.8486	0.192, 0.6487, 1.0311, 0.8486	0.194, 0.6678, 1.0311, 0.8487	0.196, 0.6774, 1.0311, 0.8487	0.199, 0.6870, 1.0311, 0.8487	0.200, 0.7062, 1.0311, 0.8488	0.203, 0.7253, 1.0311, 0.8488	0.219, 0.7731, 1.0311, 0.849
MR-Weighted-Median	0.791, -0.1045, 0.0564, 0.0375	0.385, -0.0593, 0.0572, 0.0383	0.219, -0.0415, 0.0582, 0.0386	0.139, -0.0237, 0.0600, 0.039	0.117, -0.0148, 0.0608, 0.0392	0.098, -0.0059, 0.0617, 0.0394	0.133, 0.0117, 0.0642, 0.0399	0.203, 0.0292, 0.0668, 0.0404	0.530, 0.0727, 0.0748, 0.0417
MR-Weighted-Mode	0.784, -0.1529, 0.1378, 0.0419	0.718, -0.1164, 0.1377, 0.0421	0.690, -0.1020, 0.1391, 0.0422	0.678, -0.0869, 0.1402, 0.0423	0.676, -0.0799, 0.1411, 0.0423	0.665, -0.0724, 0.1419, 0.0424	0.657, -0.0583, 0.1440, 0.0426	0.645, -0.0441, 0.1448, 0.0429	0.625, -0.0085, 0.1488, 0.0436
MR-RAPS1	0.084, -0.0149, 0.2856, 0.2745	0.081, 0.0352, 0.2857, 0.2746	0.081, 0.0552, 0.2857, 0.2746	0.085, 0.0752, 0.2857, 0.2746	0.084, 0.0852, 0.2857, 0.2746	0.086, 0.0952, 0.2857, 0.2746	0.092, 0.1153, 0.2857, 0.2746	0.095, 0.1353, 0.2858, 0.2746	0.113, 0.1853, 0.2858, 0.2747
MR-RAPS2	0.096, -0.0232, 0.3100, 0.2948	0.086, 0.0260, 0.3104, 0.2943	0.080, 0.0469, 0.3095, 0.2949	0.080, 0.0658, 0.3109, 0.2946	0.085, 0.0778, 0.3104, 0.2947	0.086, 0.0875, 0.3115, 0.2947	0.090, 0.1071, 0.3123, 0.2949	0.094, 0.1234, 0.3102, 0.2936	0.110, 0.1778, 0.3106, 0.2951
MR-RAPS3	0.895, -0.3470, 49.8288, 77.0998	0.887, 0.9905, 66.5783, 112.6095	0.887, -3.5865, 163.6478, 892.9504	0.896, -0.4220, 35.3251, 53.739	0.889, 10.5151, 220.5876, 1339.5784	0.899, 0.5375, 97.1229, 306.5017	0.894, -0.1168, 67.8534, 199.5718	0.898, -6.1403, 197.4045, 2342.1774	0.897, -2.8103, 115.7327, 743.884
MR-RAPS4	0.980, 0.1889, 7.6805, 0.4358	0.989, 0.4083, 6.9236, 0.4146	0.976, 0.7528, 12.1329, 3.9274	0.976, 0.4197, 6.4050, 1.3158	0.971, 0.4936, 6.7366, 0.8431	0.978, 0.4496, 6.6832, 1.5008	0.980, 0.5948, 6.5416, 0.3948	0.979, 1.0834, 14.7072, 155.2634	0.986, 0.5394, 4.3552, 0.3186

Table S66: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean( $SE(\hat{\theta})$ ) when  $m = 20$ , the InSIDE violated,  $q = 0.6$ , and  $N = 100000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	0.885, -0.0874, 0.0250, 0.0258	0.351, -0.0391, 0.0231, 0.0254	0.118, -0.0217, 0.0212, 0.025	0.033, -0.0066, 0.0192, 0.0248	0.020, 0.0006, 0.0188, 0.0248	0.025, 0.0075, 0.0191, 0.025	0.114, 0.0227, 0.0212, 0.0257	0.327, 0.0396, 0.0237, 0.0266	0.865, 0.0876, 0.0263, 0.028
cML-MA-AIC-Profile	0.884, -0.0875, 0.0251, 0.0258	0.352, -0.0391, 0.0232, 0.0255	0.116, -0.0217, 0.0212, 0.0251	0.032, -0.0066, 0.0191, 0.0249	0.020, 0.0006, 0.0188, 0.0249	0.024, 0.0075, 0.0191, 0.0251	0.113, 0.0227, 0.0212, 0.0258	0.327, 0.0396, 0.0237, 0.0267	0.863, 0.0877, 0.0264, 0.0281
cML-AIC	0.949, -0.0932, 0.0273, 0.0207	0.564, -0.0437, 0.0263, 0.0211	0.275, -0.0255, 0.0251, 0.0212	0.097, -0.0076, 0.0242, 0.0214	0.080, 0.0009, 0.0241, 0.0215	0.093, 0.0093, 0.0239, 0.0215	0.280, 0.0262, 0.0256, 0.0217	0.562, 0.0450, 0.0271, 0.022	0.938, 0.0940, 0.0289, 0.0226
cML-AIC-Profile	0.949, -0.0934, 0.0273, 0.0208	0.562, -0.0437, 0.0263, 0.0211	0.273, -0.0255, 0.0251, 0.0213	0.095, -0.0076, 0.0241, 0.0215	0.078, 0.0009, 0.0241, 0.0215	0.091, 0.0093, 0.0239, 0.0216	0.279, 0.0262, 0.0256, 0.0218	0.557, 0.0450, 0.0271, 0.022	0.938, 0.0941, 0.0290, 0.0227
cML-MA-BIC	0.999, -0.0996, 0.0195, 0.0193	0.700, -0.0495, 0.0198, 0.0196	0.330, -0.0295, 0.0199, 0.0198	0.078, -0.0095, 0.0201, 0.0199	0.051, 0.0004, 0.0201, 0.02	0.086, 0.0104, 0.0202, 0.0201	0.332, 0.0304, 0.0204, 0.0203	0.695, 0.0504, 0.0207, 0.0205	0.997, 0.1005, 0.0212, 0.0211
cML-MA-BIC-Profile	0.999, -0.0996, 0.0195, 0.0193	0.700, -0.0495, 0.0198, 0.0197	0.329, -0.0295, 0.0199, 0.0198	0.075, -0.0095, 0.0201, 0.02	0.050, 0.0004, 0.0201, 0.0201	0.086, 0.0104, 0.0202, 0.0202	0.331, 0.0304, 0.0204, 0.0203	0.692, 0.0504, 0.0207, 0.0206	0.997, 0.1005, 0.0212, 0.0211
cML-BIC	0.999, -0.0996, 0.0195, 0.0191	0.711, -0.0496, 0.0198, 0.0194	0.338, -0.0296, 0.0199, 0.0196	0.080, -0.0096, 0.0201, 0.0197	0.055, 0.0004, 0.0202, 0.0198	0.091, 0.0105, 0.0203, 0.0199	0.342, 0.0305, 0.0205, 0.0201	0.703, 0.0505, 0.0207, 0.0203	0.997, 0.1005, 0.0212, 0.0209
cML-BIC-Profile	0.999, -0.0996, 0.0195, 0.0191	0.710, -0.0496, 0.0198, 0.0194	0.335, -0.0296, 0.0199, 0.0196	0.080, -0.0096, 0.0201, 0.0198	0.055, 0.0004, 0.0202, 0.0198	0.091, 0.0105, 0.0203, 0.0199	0.341, 0.0305, 0.0205, 0.0201	0.700, 0.0505, 0.0207, 0.0203	0.997, 0.1005, 0.0212, 0.0209
MR-Mix	0.982, -0.1016, 0.0212, 0.0242	0.564, -0.0495, 0.0212, 0.0242	0.232, -0.0292, 0.0210, 0.0243	0.042, -0.0093, 0.0209, 0.0245	0.022, 0.0004, 0.0209, 0.0244	0.048, 0.0100, 0.0210, 0.0245	0.211, 0.0292, 0.0210, 0.0248	0.544, 0.0482, 0.0211, 0.0246	0.955, 0.0933, 0.0213, 0.0246
MR-ContMix	0.998, -0.0994, 0.0198, NA	0.731, -0.0495, 0.0201, NA	0.367, -0.0296, 0.0202, NA	0.098, -0.0096, 0.0205, NA	0.072, 0.0004, 0.0205, NA	0.106, 0.0104, 0.0206, NA	0.373, 0.0304, 0.0207, NA	0.716, 0.0504, 0.0210, NA	0.997, 0.1003, 0.0216, NA
MR-Lasso	0.984, -0.0953, 0.1476, 0.0237	0.653, -0.0455, 0.1465, 0.0243	0.302, -0.0252, 0.1469, 0.0245	0.095, -0.0042, 0.1502, 0.025	0.079, 0.0058, 0.1506, 0.0251	0.101, 0.0158, 0.1506, 0.0252	0.315, 0.0357, 0.1505, 0.0251	0.646, 0.0558, 0.1503, 0.0254	0.976, 0.1059, 0.1509, 0.026
MR-PRESSO	0.471, -0.0309, 0.2713, 0.1347	0.319, 0.0183, 0.2705, 0.1324	0.210, 0.0378, 0.2702, 0.1312	0.157, 0.0579, 0.2704, 0.1312	0.154, 0.0680, 0.2702, 0.1311	0.173, 0.0779, 0.2702, 0.1309	0.250, 0.0971, 0.2692, 0.1293	0.378, 0.1166, 0.2692, 0.1277	0.572, 0.1649, 0.2676, 0.1228
MR-IVW	0.062, -0.0259, 0.2859, 0.2806	0.072, 0.0246, 0.2858, 0.2806	0.079, 0.0447, 0.2858, 0.2806	0.080, 0.0649, 0.2858, 0.2806	0.082, 0.0750, 0.2858, 0.2806	0.087, 0.0850, 0.2858, 0.2806	0.091, 0.1052, 0.2858, 0.2806	0.096, 0.1253, 0.2858, 0.2806	0.120, 0.1756, 0.2857, 0.2806
MR-IVW-Oracle	0.998, -0.0995, 0.0193, 0.0207	0.650, -0.0495, 0.0196, 0.021	0.286, -0.0296, 0.0199, 0.0212	0.066, -0.0096, 0.0199, 0.0214	0.040, 0.0004, 0.0200, 0.0215	0.064, 0.0104, 0.0201, 0.0216	0.284, 0.0304, 0.0203, 0.0218	0.640, 0.0503, 0.0204, 0.022	0.992, 0.1002, 0.0210, 0.0226
MR-Egger	0.178, 0.5209, 1.0486, 0.849	0.192, 0.5700, 1.0486, 0.8491	0.199, 0.5896, 1.0487, 0.8491	0.201, 0.6092, 1.0487, 0.8492	0.204, 0.6190, 1.0487, 0.8492	0.204, 0.6288, 1.0487, 0.8492	0.206, 0.6484, 1.0488, 0.8492	0.210, 0.6679, 1.0488, 0.8492	0.224, 0.7168, 1.0489, 0.8493
MR-Weighted-Median	0.957, -0.1052, 0.0392, 0.0263	0.564, -0.0587, 0.0432, 0.0268	0.314, -0.0404, 0.0460, 0.0271	0.153, -0.0220, 0.0485, 0.0274	0.115, -0.0129, 0.0499, 0.0275	0.104, -0.0037, 0.0510, 0.0277	0.181, 0.0142, 0.0544, 0.028	0.382, 0.0323, 0.0569, 0.0284	0.812, 0.0764, 0.0674, 0.0293
MR-Weighted-Mode	0.866, -0.1558, 0.1479, 0.0513	0.813, -0.1189, 0.1488, 0.0514	0.784, -0.1033, 0.1501, 0.0514	0.767, -0.0890, 0.1505, 0.0515	0.766, -0.0819, 0.1512, 0.0516	0.756, -0.0740, 0.1516, 0.0517	0.743, -0.0610, 0.1525, 0.0519	0.726, -0.0461, 0.1536, 0.0521	0.729, -0.0105, 0.1590, 0.0523
MR-RAPS1	0.072, -0.0241, 0.2779, 0.2739	0.072, 0.0259, 0.2779, 0.2739	0.075, 0.0459, 0.2779, 0.2739	0.078, 0.0660, 0.2779, 0.2739	0.077, 0.0760, 0.2779, 0.2739	0.079, 0.0860, 0.2779, 0.2739	0.085, 0.1060, 0.2779, 0.274	0.099, 0.1260, 0.2779, 0.274	0.118, 0.1760, 0.2779, 0.274
MR-RAPS2	0.098, -0.0333, 0.3180, 0.2903	0.088, 0.0105, 0.3091, 0.2915	0.094, 0.0282, 0.3075, 0.2909	0.096, 0.0470, 0.3073, 0.2911	0.091, 0.0566, 0.3081, 0.2917	0.099, 0.0701, 0.3136, 0.2901	0.098, 0.0894, 0.3120, 0.2906	0.101, 0.1141, 0.3116, 0.2919	0.119, 0.1613, 0.3073, 0.2915
MR-RAPS3	0.926, 5.3303, 130.5940, 445.4344	0.922, 3.7135, 168.1767, 566.857	0.922, -1.4269, 141.4856, 401.2783	0.909, 5.3399, 85.1299, 189.6383	0.909, 1.3724, 40.2535, 41.5834	0.916, 1.3301, 74.8899, 191.5282	0.928, 1.9973, 73.1478, 181.7078	0.931, 2.0407, 29.8844, 30.6823	0.939, 0.3029, 31.9163, 39.36
MR-RAPS4	0.984, 0.1080, 12.4816, 0.5062	0.988, 0.6937, 10.4543, 115.5682	0.984, 0.7010, 11.1183, 0.4821	0.984, 0.7561, 11.5701, 0.5914	0.980, 0.9548, 15.3063, 0.7112	0.978, 0.7176, 9.5789, 0.4609	0.979, 0.4522, 8.1870, 0.3812	0.986, 0.4824, 8.1668, 0.3852	0.982, 0.4537, 2.7776, 0.2838

Table S67: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean( $SE(\hat{\theta})$ ) when  $m = 20$ , the InSIDE violated,  $q = 0.6$ , and  $N = 200000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	0.979, -0.0905, 0.0185, 0.0186	0.605, -0.0409, 0.0180, 0.0186	0.235, -0.0227, 0.0165, 0.0182	0.039, -0.0071, 0.0141, 0.0178	0.022, -0.0004, 0.0136, 0.0177	0.031, 0.0066, 0.0141, 0.0179	0.217, 0.0226, 0.0165, 0.0186	0.590, 0.0410, 0.0181, 0.0192	0.982, 0.0901, 0.0194, 0.02
cML-MA-AIC-Profile	0.979, -0.0906, 0.0184, 0.0186	0.605, -0.0409, 0.0180, 0.0186	0.234, -0.0227, 0.0165, 0.0183	0.039, -0.0071, 0.0141, 0.0178	0.021, -0.0004, 0.0136, 0.0178	0.030, 0.0066, 0.0141, 0.0179	0.217, 0.0226, 0.0165, 0.0186	0.588, 0.0410, 0.0181, 0.0192	0.982, 0.0902, 0.0194, 0.0201
cML-AIC	0.990, -0.0950, 0.0199, 0.0147	0.807, -0.0452, 0.0198, 0.015	0.467, -0.0259, 0.0151	0.124, -0.0085, 0.0174, 0.0152	0.079, -0.0003, 0.0171, 0.0152	0.129, 0.0078, 0.0174, 0.0153	0.424, 0.0258, 0.0191, 0.0155	0.785, 0.0453, 0.0198, 0.0156	0.995, 0.0950, 0.0208, 0.0161
cML-AIC-Profile	0.990, -0.0952, 0.0199, 0.0148	0.808, -0.0452, 0.0199, 0.015	0.464, -0.0259, 0.0193, 0.0151	0.121, -0.0085, 0.0174, 0.0152	0.079, -0.0003, 0.0171, 0.0153	0.127, 0.0078, 0.0174, 0.0153	0.423, 0.0258, 0.0191, 0.0155	0.783, 0.0454, 0.0199, 0.0156	0.995, 0.0950, 0.0208, 0.0161
cML-MA-BIC	1.000, -0.0998, 0.0143, 0.0136	0.944, -0.0498, 0.0145, 0.0139	0.567, -0.0298, 0.0146, 0.014	0.122, -0.0098, 0.0147, 0.0141	0.052, 0.0001, 0.0147, 0.0142	0.110, 0.0101, 0.0148, 0.0142	0.564, 0.0301, 0.0149, 0.0144	0.916, 0.0501, 0.0151, 0.0145	1.000, 0.1001, 0.0154, 0.0149
cML-MA-BIC-Profile	1.000, -0.0998, 0.0143, 0.0137	0.944, -0.0498, 0.0145, 0.0139	0.567, -0.0298, 0.0146, 0.014	0.121, -0.0098, 0.0147, 0.0141	0.052, 0.0001, 0.0147, 0.0142	0.110, 0.0101, 0.0148, 0.0142	0.564, 0.0301, 0.0149, 0.0144	0.916, 0.0501, 0.0151, 0.0145	1.000, 0.1001, 0.0154, 0.0149
cML-BIC	1.000, -0.0999, 0.0143, 0.0135	0.946, -0.0499, 0.0145, 0.0138	0.573, -0.0299, 0.0146, 0.0139	0.125, -0.0098, 0.0147, 0.014	0.054, 0.0001, 0.0147, 0.014	0.115, 0.0101, 0.0148, 0.0141	0.572, 0.0301, 0.0149, 0.0142	0.919, 0.0502, 0.0150, 0.0144	1.000, 0.1002, 0.0154, 0.0148
cML-BIC-Profile	1.000, -0.0999, 0.0143, 0.0135	0.946, -0.0499, 0.0145, 0.0138	0.573, -0.0299, 0.0146, 0.0139	0.125, -0.0098, 0.0147, 0.014	0.053, 0.0001, 0.0147, 0.014	0.113, 0.0101, 0.0148, 0.0141	0.570, 0.0301, 0.0149, 0.0143	0.919, 0.0502, 0.0150, 0.0144	1.000, 0.1002, 0.0154, 0.0148
MR-Mix	0.993, -0.1015, 0.0160, 0.0186	0.829, -0.0496, 0.0157, 0.0185	0.398, -0.0293, 0.0156, 0.0187	0.057, -0.0095, 0.0156, 0.0184	0.030, 0.0003, 0.0155, 0.0185	0.077, 0.0100, 0.0157, 0.0184	0.389, 0.0290, 0.0157, 0.0184	0.793, 0.0478, 0.0155, 0.0181	0.992, 0.0932, 0.0159, 0.0185
MR-ContMix	1.000, -0.0998, 0.0147, NA	0.953, -0.0499, 0.0148, NA	0.614, -0.0299, 0.0148, NA	0.158, -0.0099, 0.0149, NA	0.072, 0.0001, 0.0150, NA	0.151, 0.0101, 0.0151, NA	0.602, 0.0300, 0.0152, NA	0.927, 0.0499, 0.0154, NA	1.000, 0.0999, 0.0158, NA
MR-Lasso	0.996, -0.0901, 0.1634, 0.0195	0.908, -0.0401, 0.1635, 0.0197	0.516, -0.0204, 0.1631, 0.0199	0.130, -0.0001, 0.1644, 0.0199	0.072, 0.0099, 0.1644, 0.02	0.122, 0.0199, 0.1649, 0.0199	0.507, 0.0398, 0.1647, 0.02	0.869, 0.0598, 0.1647, 0.0202	0.988, 0.1099, 0.1647, 0.0206
MR-PRESSO	0.414, -0.0315, 0.2885, 0.1714	0.332, 0.0179, 0.2885, 0.1698	0.230, 0.0379, 0.2884, 0.1693	0.134, 0.0578, 0.2884, 0.1691	0.122, 0.0679, 0.2884, 0.1691	0.140, 0.0778, 0.2884, 0.1685	0.241, 0.0977, 0.2881, 0.1678	0.343, 0.1175, 0.2881, 0.1668	0.472, 0.1668, 0.2876, 0.1632
MR-IVW	0.084, -0.0302, 0.2936, 0.2806	0.083, 0.0203, 0.2936, 0.2805	0.079, 0.0405, 0.2936, 0.2805	0.079, 0.0607, 0.2935, 0.2805	0.078, 0.0708, 0.2935, 0.2805	0.079, 0.0808, 0.2935, 0.2805	0.088, 0.1010, 0.2935, 0.2805	0.096, 0.1212, 0.2935, 0.2805	0.124, 0.1715, 0.2935, 0.2804
MR-IVW-Oracle	1.000, -0.0998, 0.0142, 0.0147	0.915, -0.0498, 0.0144, 0.015	0.505, -0.0298, 0.0145, 0.0151	0.097, -0.0099, 0.0146, 0.0152	0.039, 0.0001, 0.0147, 0.0153	0.092, 0.0101, 0.0147, 0.0154	0.507, 0.0301, 0.0148, 0.0155	0.892, 0.0501, 0.0150, 0.0157	1.000, 0.1000, 0.0154, 0.0161
MR-Egger	0.178, 0.6026, 1.0480, 0.861	0.190, 0.6523, 1.0479, 0.861	0.195, 0.6722, 1.0479, 0.861	0.198, 0.6920, 1.0478, 0.861	0.201, 0.7019, 1.0478, 0.861	0.204, 0.7118, 1.0478, 0.861	0.211, 0.7316, 1.0477, 0.861	0.217, 0.7515, 1.0477, 0.861	0.224, 0.8009, 1.0476, 0.861
MR-Weighted-Median	0.996, -0.1057, 0.0355, 0.0188	0.825, -0.0585, 0.0423, 0.0191	0.489, -0.0398, 0.0456, 0.0193	0.162, -0.0212, 0.0491, 0.0195	0.118, -0.0119, 0.0508, 0.0196	0.112, -0.0026, 0.0526, 0.0197	0.302, 0.0158, 0.0562, 0.0199	0.600, 0.0342, 0.0596, 0.0201	0.941, 0.0800, 0.0668, 0.0209
MR-Weighted-Mode	0.903, -0.1554, 0.1328, 0.02	0.853, -0.1182, 0.1342, 0.0201	0.827, -0.1033, 0.1355, 0.0201	0.821, -0.0881, 0.1365, 0.0202	0.818, -0.0805, 0.1369, 0.0202	0.824, -0.0731, 0.1374, 0.0202	0.811, -0.0587, 0.1392, 0.0203	0.807, -0.0439, 0.1404, 0.0204	0.792, -0.0087, 0.1460, 0.0207
MR-RAPS1	0.082, -0.0314, 0.2870, 0.2733	0.077, 0.0186, 0.2870, 0.2733	0.084, 0.0387, 0.2870, 0.2733	0.085, 0.0587, 0.2870, 0.2733	0.091, 0.0687, 0.2870, 0.2733	0.091, 0.0787, 0.2870, 0.2733	0.093, 0.0987, 0.2870, 0.2733	0.105, 0.1187, 0.2870, 0.2733	0.128, 0.1687, 0.2870, 0.2733
MR-RAPS2	0.336, -0.1246, 0.4235, 0.192	0.263, -0.0631, 0.3437, 0.1986	0.233, -0.0415, 0.3206, 0.2012	0.208, -0.0216, 0.3156, 0.2038	0.197, -0.0147, 0.3100, 0.2053	0.188, 0.0027, 0.3270, 0.2067	0.172, 0.0271, 0.3306, 0.2081	0.151, 0.0403, 0.3146, 0.2138	0.149, 0.0989, 0.3201, 0.2239
MR-RAPS3	0.951, -37.8104, 941.3561, 10820	0.948, -4.2250, 101.5375, 205.8	0.940, -1.7704, 34.4377, 26.5	0.948, -5.5316, 130.4426, 241.9	0.952, 4.7789, 55.2695, 38.82	0.956, 0.0180, 18.2874, 6.667	0.951, 0.6276, 97.0454, 205.2	0.947, -4.7526, 147.4679, 499.1	0.949, -16.3133, 508.2776, 6162
MR-RAPS4	0.990, -0.1036, 3.4325, 0.229	0.984, -0.1812, 6.9522, 0.2887	0.980, -0.1244, 7.6520, 0.4416	0.977, -0.1260, 7.5668, 0.2581	0.981, -0.1665, 7.7123, 0.2555	0.985, -0.1443, 7.6815, 0.617	0.984, -0.1504, 7.7571, 0.3567	0.987, -0.0510, 7.2657, 0.2856	0.990, -0.0178, 7.4870, 0.2188



Table S68: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean(SE( $\hat{\theta}$ )) when  $m = 100$ , the ideal case of  $q = 0$ , and  $N = 50000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	1.000, -0.0973, 0.0105, 0.0084	0.996, -0.0478, 0.0107, 0.0085	0.841, -0.0279, 0.0108, 0.0086	0.206, -0.0085, 0.0102, 0.0086	0.099, 0.0006, 0.0100, 0.0086	0.241, 0.0097, 0.0104, 0.0087	0.846, 0.0290, 0.0112, 0.0089	0.991, 0.0489, 0.0114, 0.009	1.000, 0.0983, 0.0117, 0.0093
cML-MA-AIC-Profile	1.000, -0.0980, 0.0106, 0.0085	0.996, -0.0479, 0.0108, 0.0086	0.840, -0.0279, 0.0108, 0.0087	0.204, -0.0085, 0.0102, 0.0087	0.097, 0.0006, 0.0100, 0.0087	0.238, 0.0097, 0.0105, 0.0088	0.846, 0.0291, 0.0113, 0.0089	0.991, 0.0490, 0.0115, 0.0091	1.000, 0.0989, 0.0118, 0.0094
cML-AIC	1.000, -0.0985, 0.0109, 0.0077	0.998, -0.0487, 0.0111, 0.0079	0.882, -0.0287, 0.0111, 0.0079	0.280, -0.0089, 0.0111, 0.008	0.156, 0.0007, 0.0110, 0.0081	0.325, 0.0103, 0.0113, 0.0081	0.887, 0.0300, 0.0116, 0.0082	0.997, 0.0499, 0.0117, 0.0083	1.000, 0.0995, 0.0121, 0.0085
cML-AIC-Profile	1.000, -0.0989, 0.0111, 0.0078	0.998, -0.0487, 0.0111, 0.0079	0.880, -0.0287, 0.0112, 0.008	0.274, -0.0089, 0.0111, 0.0081	0.154, 0.0007, 0.0110, 0.0081	0.316, 0.0103, 0.0113, 0.0082	0.886, 0.0300, 0.0116, 0.0082	0.997, 0.0500, 0.0118, 0.0083	1.000, 0.0998, 0.0122, 0.0086
cML-MA-BIC	1.000, -0.0997, 0.0073, 0.0072	1.000, -0.0497, 0.0074, 0.0073	0.985, -0.0297, 0.0074, 0.0074	0.258, -0.0097, 0.0075, 0.0074	0.050, 0.0003, 0.0075, 0.0075	0.277, 0.0103, 0.0075, 0.0075	0.978, 0.0303, 0.0076, 0.0076	1.000, 0.0503, 0.0077, 0.0077	1.000, 0.1003, 0.0079, 0.0079
cML-MA-BIC-Profile	1.000, -0.0997, 0.0073, 0.0072	1.000, -0.0497, 0.0074, 0.0073	0.985, -0.0297, 0.0074, 0.0074	0.255, -0.0097, 0.0075, 0.0075	0.048, 0.0003, 0.0075, 0.0075	0.272, 0.0103, 0.0075, 0.0075	0.976, 0.0303, 0.0076, 0.0076	1.000, 0.0503, 0.0077, 0.0077	1.000, 0.1003, 0.0079, 0.008
cML-BIC	1.000, -0.0997, 0.0073, 0.0071	1.000, -0.0497, 0.0074, 0.0072	0.985, -0.0297, 0.0074, 0.0073	0.263, -0.0097, 0.0075, 0.0074	0.051, 0.0003, 0.0075, 0.0074	0.287, 0.0103, 0.0076, 0.0074	0.979, 0.0303, 0.0076, 0.0075	1.000, 0.0503, 0.0077, 0.0076	1.000, 0.1003, 0.0079, 0.0079
cML-BIC-Profile	1.000, -0.0997, 0.0073, 0.0072	1.000, -0.0497, 0.0074, 0.0073	0.985, -0.0297, 0.0074, 0.0073	0.258, -0.0097, 0.0075, 0.0074	0.050, 0.0003, 0.0075, 0.0074	0.285, 0.0103, 0.0076, 0.0075	0.979, 0.0303, 0.0076, 0.0076	1.000, 0.0503, 0.0077, 0.0076	1.000, 0.1003, 0.0079, 0.0079
MR-Mix	0.818, -0.1121, 0.0361, 0.0597	0.703, -0.0548, 0.0211, 0.0494	0.564, -0.0331, 0.0169, 0.27381	0.117, -0.0110, 0.0145, 0.2125	0.023, -0.0003, 0.0141, 0.0529	0.134, 0.0105, 0.0145, 0.2533	0.568, 0.0322, 0.0163, 0.0943	0.692, 0.0528, 0.0198, 0.0715	0.790, 0.1027, 0.0316, 0.1241
MR-ContMix	1.000, -0.1212, 0.0102, NA	0.998, -0.0687, 0.0132, NA	0.876, -0.0436, 0.0156, NA	0.234, -0.0149, 0.0176, NA	0.125, 0.0009, 0.0181, NA	0.275, 0.0162, 0.0177, NA	0.878, 0.0449, 0.0162, NA	0.997, 0.0701, 0.0142, NA	1.000, 0.1240, 0.0116, NA
MR-Lasso	1.000, -0.0990, 0.0075, 0.0071	1.000, -0.0494, 0.0077, 0.0073	0.980, -0.0296, 0.0076, 0.0073	0.266, -0.0097, 0.0077, 0.0074	0.058, 0.0002, 0.0077, 0.0074	0.288, 0.0101, 0.0078, 0.0075	0.972, 0.0301, 0.0078, 0.0076	1.000, 0.0498, 0.0078, 0.0076	1.000, 0.0994, 0.0082, 0.0079
MR-PRESSO	1.000, -0.0989, 0.0072, 0.0071	1.000, -0.0493, 0.0073, 0.0072	0.986, -0.0295, 0.0073, 0.0072	0.259, -0.0096, 0.0074, 0.0073	0.043, 0.0003, 0.0074, 0.0073	0.282, 0.0102, 0.0075, 0.0074	0.980, 0.0301, 0.0076, 0.0074	1.000, 0.0499, 0.0076, 0.0075	1.000, 0.0996, 0.0078, 0.0078
MR-IVW	1.000, -0.0990, 0.0072, 0.0073	1.000, -0.0493, 0.0073, 0.0074	0.984, -0.0295, 0.0073, 0.0075	0.244, -0.0096, 0.0074, 0.0075	0.043, 0.0003, 0.0074, 0.0076	0.267, 0.0102, 0.0074, 0.0076	0.980, 0.0301, 0.0075, 0.0077	1.000, 0.0499, 0.0076, 0.0078	1.000, 0.0996, 0.0078, 0.008
MR-IVW-Oracle	1.000, -0.0990, 0.0072, 0.0073	1.000, -0.0493, 0.0073, 0.0074	0.984, -0.0295, 0.0073, 0.0075	0.244, -0.0096, 0.0074, 0.0075	0.043, 0.0003, 0.0074, 0.0076	0.267, 0.0102, 0.0074, 0.0076	0.980, 0.0301, 0.0075, 0.0077	1.000, 0.0499, 0.0076, 0.0078	1.000, 0.0996, 0.0078, 0.008
MR-Egger	0.637, -0.0824, 0.0345, 0.0355	0.208, -0.0410, 0.0352, 0.0361	0.093, -0.0245, 0.0355, 0.0365	0.047, -0.0079, 0.0359, 0.0368	0.042, 0.0004, 0.0361, 0.037	0.050, 0.0087, 0.0363, 0.0372	0.100, 0.0252, 0.0367, 0.0376	0.194, 0.0418, 0.0372, 0.038	0.566, 0.0831, 0.0384, 0.0391
MR-Weighted-Median	1.000, -0.0971, 0.0091, 0.0104	0.998, -0.0485, 0.0093, 0.0106	0.811, -0.0291, 0.0095, 0.0106	0.121, -0.0096, 0.0096, 0.0107	0.029, 0.0002, 0.0096, 0.0108	0.125, 0.0099, 0.0096, 0.0108	0.801, 0.0294, 0.0098, 0.011	0.995, 0.0488, 0.0099, 0.0111	1.000, 0.0976, 0.0103, 0.0114
MR-Weighted-Mode	0.994, -0.0963, 0.0184, 0.0247	0.499, -0.0480, 0.0190, 0.0251	0.130, -0.0287, 0.0191, 0.0253	0.016, -0.0094, 0.0194, 0.0255	0.008, 0.0002, 0.0195, 0.0257	0.013, 0.0098, 0.0197, 0.0258	0.147, 0.0290, 0.0198, 0.0261	0.450, 0.0485, 0.0199, 0.0264	0.982, 0.0969, 0.0204, 0.0272
MR-RAPS1	1.000, -0.0996, 0.0073, 0.0073	1.000, -0.0497, 0.0073, 0.0073	0.984, -0.0297, 0.0074, 0.0075	0.247, -0.0097, 0.0074, 0.0076	0.041, 0.0003, 0.0075, 0.0076	0.266, 0.0103, 0.0075, 0.0076	0.980, 0.0303, 0.0076, 0.0077	1.000, 0.0503, 0.0076, 0.0078	1.000, 0.1003, 0.0079, 0.0081
MR-RAPS2	1.000, -0.1032, 1.1696, 0.0085	1.000, -0.0266, 0.7274, 0.0079	0.974, -0.0860, 2.2136, 0.0085	0.237, -0.0016, 0.2561, 0.0079	0.048, 0.0003, 0.0076, 0.0078	0.255, 0.0103, 0.0077, 0.0079	0.967, 0.0303, 0.0078, 0.0079	1.000, 0.0354, 0.4716, 0.0084	1.000, 0.1237, 1.0524, 0.009
MR-RAPS3	1.000, -0.0997, 0.0073, 0.0072	1.000, -0.0497, 0.0073, 0.0073	0.986, -0.0297, 0.0074, 0.0073	0.259, -0.0097, 0.0075, 0.0074	0.047, 0.0003, 0.0075, 0.0074	0.283, 0.0103, 0.0075, 0.0075	0.981, 0.0303, 0.0076, 0.0075	1.000, 0.0503, 0.0076, 0.0076	1.000, 0.1003, 0.0079, 0.0079
MR-RAPS4	1.000, -0.0997, 0.0075, 0.0073	1.000, -0.0497, 0.0075, 0.0075	0.979, -0.0297, 0.0076, 0.0075	0.249, -0.0097, 0.0076, 0.0076	0.054, 0.0003, 0.0077, 0.0076	0.279, 0.0103, 0.0077, 0.0077	0.970, 0.0303, 0.0078, 0.0077	1.000, 0.0503, 0.0079, 0.0078	1.000, 0.1003, 0.0081, 0.0081

Table S69: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean( $SE(\hat{\theta})$ ) when  $m = 100$ , the ideal case of  $q = 0$ , and  $N = 100000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	1.000, -0.0988, 0.0075, 0.0059	1.000, -0.0491, 0.0076, 0.0061	0.986, -0.0292, 0.0077, 0.0061	0.358, -0.0094, 0.0074, 0.0061	0.087, -0.0002, 0.0070, 0.0061	0.344, 0.0090, 0.0074, 0.0062	0.980, 0.0287, 0.0079, 0.0063	1.000, 0.0486, 0.0080, 0.0064	1.000, 0.0984, 0.0082, 0.0066
cML-MA-AIC-Profile	1.000, -0.0992, 0.0075, 0.006	1.000, -0.0492, 0.0076, 0.0061	0.986, -0.0292, 0.0077, 0.0061	0.357, -0.0094, 0.0074, 0.0061	0.086, -0.0002, 0.0070, 0.0061	0.343, 0.0090, 0.0074, 0.0062	0.980, 0.0287, 0.0079, 0.0063	1.000, 0.0487, 0.0080, 0.0064	1.000, 0.0987, 0.0083, 0.0066
cML-AIC	1.000, -0.0995, 0.0077, 0.0055	1.000, -0.0497, 0.0078, 0.0056	0.992, -0.0298, 0.0079, 0.0056	0.430, -0.0098, 0.0079, 0.0057	0.159, -0.0002, 0.0078, 0.0057	0.413, 0.0094, 0.0080, 0.0057	0.988, 0.0294, 0.0082, 0.0058	1.000, 0.0494, 0.0084, 0.0059	1.000, 0.0992, 0.0085, 0.006
cML-AIC-Profile	1.000, -0.0998, 0.0078, 0.0055	1.000, -0.0498, 0.0078, 0.0056	0.992, -0.0298, 0.0079, 0.0056	0.429, -0.0098, 0.0079, 0.0057	0.156, -0.0002, 0.0078, 0.0057	0.410, 0.0094, 0.0080, 0.0057	0.986, 0.0294, 0.0082, 0.0058	1.000, 0.0494, 0.0084, 0.0059	1.000, 0.0995, 0.0085, 0.0061
cML-MA-BIC	1.000, -0.1001, 0.0051, 0.0051	1.000, -0.0501, 0.0052, 0.0052	1.000, -0.0301, 0.0052, 0.0052	0.489, -0.0101, 0.0052, 0.0052	0.044, -0.0001, 0.0053, 0.0053	0.451, 0.0099, 0.0053, 0.0053	1.000, 0.0299, 0.0054, 0.0054	1.000, 0.0498, 0.0054, 0.0054	1.000, 0.0998, 0.0056, 0.0056
cML-MA-BIC-Profile	1.000, -0.1001, 0.0051, 0.0051	1.000, -0.0501, 0.0052, 0.0052	1.000, -0.0301, 0.0052, 0.0052	0.489, -0.0101, 0.0052, 0.0053	0.043, -0.0001, 0.0053, 0.0053	0.450, 0.0099, 0.0053, 0.0053	1.000, 0.0299, 0.0054, 0.0054	1.000, 0.0498, 0.0054, 0.0054	1.000, 0.0998, 0.0056, 0.0056
cML-BIC	1.000, -0.1001, 0.0051, 0.005	1.000, -0.0501, 0.0052, 0.0051	1.000, -0.0301, 0.0052, 0.0052	0.500, -0.0101, 0.0052, 0.0052	0.048, -0.0001, 0.0053, 0.0052	0.457, 0.0099, 0.0053, 0.0053	1.000, 0.0299, 0.0054, 0.0053	1.000, 0.0499, 0.0054, 0.0054	1.000, 0.0998, 0.0056, 0.0056
cML-BIC-Profile	1.000, -0.1001, 0.0051, 0.0051	1.000, -0.0501, 0.0052, 0.0051	1.000, -0.0301, 0.0052, 0.0052	0.499, -0.0101, 0.0052, 0.0052	0.048, -0.0001, 0.0053, 0.0052	0.457, 0.0099, 0.0053, 0.0053	1.000, 0.0299, 0.0054, 0.0053	1.000, 0.0499, 0.0054, 0.0054	1.000, 0.0998, 0.0056, 0.0056
MR-Mix	0.834, -0.1131, 0.0343, 0.0346	0.746, -0.0556, 0.0195, 0.2241	0.641, -0.0335, 0.0148, 0.0725	0.229, -0.0110, 0.0123, 0.3048	0.043, -0.0001, 0.0119, 0.0887	0.212, 0.0106, 0.0123, 0.224	0.643, 0.0315, 0.0150, 0.1184	0.727, 0.0522, 0.0191, 0.0797	0.834, 0.1019, 0.0312, 0.1323
MR-ContMix	1.000, -0.1142, 0.0064, NA	1.000, -0.0663, 0.0080, NA	0.991, -0.0435, 0.0097, NA	0.391, -0.0159, 0.0121, NA	0.114, -0.0002, 0.0128, NA	0.393, 0.0153, 0.0124, NA	0.989, 0.0429, 0.0104, NA	1.000, 0.0660, 0.0090, NA	1.000, 0.1159, 0.0072, NA
MR-Lasso	1.000, -0.0997, 0.0053, 0.0051	1.000, -0.0499, 0.0054, 0.0052	1.000, -0.0300, 0.0054, 0.0052	0.488, -0.0100, 0.0055, 0.0053	0.057, -0.0001, 0.0055, 0.0053	0.461, 0.0099, 0.0055, 0.0053	1.000, 0.0298, 0.0056, 0.0054	1.000, 0.0497, 0.0057, 0.0054	1.000, 0.0994, 0.0059, 0.0056
MR-PRESSO	1.000, -0.0997, 0.0051, 0.005	1.000, -0.0499, 0.0052, 0.0051	1.000, -0.0300, 0.0052, 0.0051	0.487, -0.0101, 0.0053, 0.0052	0.050, -0.0001, 0.0053, 0.0052	0.463, 0.0099, 0.0053, 0.0052	1.000, 0.0298, 0.0054, 0.0053	1.000, 0.0497, 0.0054, 0.0054	1.000, 0.0995, 0.0056, 0.0055
MR-IVW	1.000, -0.0997, 0.0051, 0.0052	1.000, -0.0499, 0.0052, 0.0052	1.000, -0.0300, 0.0052, 0.0053	0.481, -0.0101, 0.0053, 0.0053	0.044, -0.0001, 0.0053, 0.0054	0.446, 0.0099, 0.0053, 0.0054	1.000, 0.0298, 0.0054, 0.0055	1.000, 0.0497, 0.0054, 0.0055	1.000, 0.0995, 0.0056, 0.0057
MR-IVW-Oracle	1.000, -0.0997, 0.0051, 0.0052	1.000, -0.0499, 0.0052, 0.0052	1.000, -0.0300, 0.0052, 0.0053	0.481, -0.0101, 0.0053, 0.0053	0.044, -0.0001, 0.0053, 0.0054	0.446, 0.0099, 0.0053, 0.0054	1.000, 0.0298, 0.0054, 0.0055	1.000, 0.0497, 0.0054, 0.0055	1.000, 0.0995, 0.0056, 0.0057
MR-Egger	0.934, -0.0919, 0.0261, 0.0263	0.406, -0.0466, 0.0265, 0.0268	0.185, -0.0286, 0.0267, 0.027	0.062, -0.0105, 0.0270, 0.0272	0.045, -0.0014, 0.0271, 0.0274	0.059, 0.0076, 0.0272, 0.0275	0.162, 0.0257, 0.0272, 0.0278	0.350, 0.0438, 0.0279, 0.0281	0.876, 0.0890, 0.0288, 0.029
MR-Weighted-Median	1.000, -0.0989, 0.0064, 0.0073	1.000, -0.0496, 0.0065, 0.0075	0.991, -0.0299, 0.0065, 0.0075	0.246, -0.0102, 0.0065, 0.0076	0.023, -0.0003, 0.0066, 0.0076	0.205, 0.0096, 0.0066, 0.0077	0.982, 0.0293, 0.0066, 0.0078	1.000, 0.0491, 0.0067, 0.0079	1.000, 0.0983, 0.0069, 0.0081
MR-Weighted-Mode	1.000, -0.0992, 0.0130, 0.0177	0.856, -0.0499, 0.0132, 0.018	0.356, -0.0303, 0.0133, 0.0181	0.024, -0.0105, 0.0134, 0.0183	0.004, -0.0005, 0.0135, 0.0184	0.022, 0.0093, 0.0135, 0.0185	0.303, 0.0290, 0.0136, 0.0187	0.810, 0.0487, 0.0137, 0.0189	1.000, 0.0977, 0.0141, 0.0195
MR-RAPS1	1.000, -0.1001, 0.0051, 0.0052	1.000, -0.0501, 0.0052, 0.0053	1.000, -0.0301, 0.0052, 0.0053	0.483, -0.0101, 0.0053, 0.0053	0.045, -0.0001, 0.0053, 0.0054	0.446, 0.0099, 0.0053, 0.0054	1.000, 0.0299, 0.0054, 0.0055	1.000, 0.0499, 0.0054, 0.0055	1.000, 0.0998, 0.0056, 0.0057
MR-RAPS2	1.000, -0.0354, 1.0272, 0.0064	1.000, 0.0342, 1.1871, 0.0068	1.000, -0.0082, 1.1961, 0.0066	0.448, -0.0101, 0.0053, 0.0055	0.040, -0.0001, 0.0054, 0.0055	0.438, 0.0099, 0.0054, 0.0056	1.000, 0.0318, 0.5447, 0.0061	1.000, 0.1437, 2.2004, 0.007	1.000, 0.0740, 0.7759, 0.0065
MR-RAPS3	1.000, -0.1001, 0.0051, 0.005	1.000, -0.0501, 0.0052, 0.0051	1.000, -0.0301, 0.0052, 0.0052	0.500, -0.0101, 0.0052, 0.0052	0.051, -0.0001, 0.0053, 0.0052	0.461, 0.0099, 0.0053, 0.0053	1.000, 0.0299, 0.0054, 0.0053	1.000, 0.0499, 0.0055, 0.0054	1.000, 0.0999, 0.0056, 0.0056
MR-RAPS4	1.000, -0.1001, 0.0052, 0.0052	1.000, -0.0501, 0.0053, 0.0053	1.000, -0.0301, 0.0053, 0.0053	0.468, -0.0101, 0.0054, 0.0054	0.047, -0.0001, 0.0054, 0.0054	0.455, 0.0099, 0.0054, 0.0054	1.000, 0.0299, 0.0055, 0.0055	1.000, 0.0499, 0.0056, 0.0055	1.000, 0.0998, 0.0058, 0.0057

Table S70: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean( $SE(\hat{\theta})$ ) when  $m = 100$ , the ideal case of  $q = 0$ , and  $N = 200000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	1.000, -0.0989, 0.0053, 0.0042	1.000, -0.0491, 0.0054, 0.0043	1.000, -0.0291, 0.0055, 0.0043	0.536, -0.0092, 0.0054, 0.0044	0.081, 0.0000, 0.0050, 0.0043	0.551, 0.0094, 0.0054, 0.0044	0.999, 0.0292, 0.0055, 0.0045	1.000, 0.0492, 0.0056, 0.0045	1.000, 0.0990, 0.0057, 0.0046
cML-MA-AIC-Profile	1.000, -0.0992, 0.0053, 0.0043	1.000, -0.0492, 0.0054, 0.0043	1.000, -0.0292, 0.0055, 0.0043	0.536, -0.0092, 0.0054, 0.0044	0.081, 0.0000, 0.0050, 0.0043	0.551, 0.0094, 0.0054, 0.0044	0.999, 0.0293, 0.0055, 0.0045	1.000, 0.0492, 0.0056, 0.0045	1.000, 0.0992, 0.0058, 0.0047
cML-AIC	1.000, -0.0995, 0.0054, 0.0039	1.000, -0.0496, 0.0056, 0.0039	1.000, -0.0296, 0.0057, 0.004	0.618, -0.0096, 0.0057, 0.004	0.152, 0.0001, 0.0055, 0.004	0.623, 0.0098, 0.0057, 0.0041	0.999, 0.0297, 0.0058, 0.0041	1.000, 0.0497, 0.0058, 0.0041	1.000, 0.0995, 0.0060, 0.0043
cML-AIC-Profile	1.000, -0.0996, 0.0055, 0.0039	1.000, -0.0496, 0.0057, 0.0039	1.000, -0.0296, 0.0057, 0.004	0.618, -0.0096, 0.0057, 0.004	0.152, 0.0001, 0.0055, 0.004	0.622, 0.0098, 0.0057, 0.0041	0.999, 0.0297, 0.0058, 0.0041	1.000, 0.0498, 0.0058, 0.0041	1.000, 0.0997, 0.0060, 0.0043
cML-MA-BIC	1.000, -0.1000, 0.0036, 0.0036	1.000, -0.0500, 0.0037, 0.0036	1.000, -0.0300, 0.0037, 0.0037	0.788, -0.0100, 0.0037, 0.0037	0.048, 0.0000, 0.0037, 0.0037	0.760, 0.0099, 0.0037, 0.0037	1.000, 0.0299, 0.0037, 0.0038	1.000, 0.0499, 0.0038, 0.0038	1.000, 0.0999, 0.0039, 0.0039
cML-MA-BIC-Profile	1.000, -0.1000, 0.0036, 0.0036	1.000, -0.0500, 0.0037, 0.0036	1.000, -0.0300, 0.0037, 0.0037	0.788, -0.0100, 0.0037, 0.0037	0.047, 0.0000, 0.0037, 0.0037	0.759, 0.0099, 0.0037, 0.0037	1.000, 0.0299, 0.0037, 0.0038	1.000, 0.0499, 0.0038, 0.0038	1.000, 0.0999, 0.0039, 0.004
cML-BIC	1.000, -0.1001, 0.0036, 0.0036	1.000, -0.0501, 0.0037, 0.0036	1.000, -0.0301, 0.0037, 0.0036	0.791, -0.0101, 0.0037, 0.0037	0.049, -0.0001, 0.0037, 0.0037	0.764, 0.0100, 0.0037, 0.0037	1.000, 0.0300, 0.0037, 0.0038	1.000, 0.0500, 0.0038, 0.0038	1.000, 0.0999, 0.0039, 0.0039
cML-BIC-Profile	1.000, -0.1001, 0.0036, 0.0036	1.000, -0.0501, 0.0037, 0.0036	1.000, -0.0301, 0.0037, 0.0037	0.791, -0.0101, 0.0037, 0.0037	0.048, -0.0001, 0.0037, 0.0037	0.764, 0.0100, 0.0037, 0.0037	1.000, 0.0300, 0.0037, 0.0038	1.000, 0.0500, 0.0038, 0.0038	1.000, 0.0999, 0.0039, 0.0039
MR-Mix	0.859, -0.1121, 0.0340, 0.1045	0.809, -0.0549, 0.0175, 0.0315	0.731, -0.0326, 0.0120, 0.0487	0.404, -0.0105, 0.0083, 0.0341	0.072, 0.0004, 0.0075, 0.1511	0.361, 0.0110, 0.0081, 0.0297	0.725, 0.0321, 0.0120, 0.0291	0.806, 0.0527, 0.0171, 0.0874	0.844, 0.1021, 0.0307, 0.123
MR-ContMix	1.000, -0.1074, 0.0042, NA	1.000, -0.0616, 0.0050, NA	1.000, -0.0411, 0.0062, NA	0.597, -0.0156, 0.0084, NA	0.106, 0.0001, 0.0092, NA	0.613, 0.0156, 0.0086, NA	1.000, 0.0414, 0.0064, NA	1.000, 0.0623, 0.0053, NA	1.000, 0.1091, 0.0046, NA
MR-Lasso	1.000, -0.0998, 0.0038, 0.0036	1.000, -0.0499, 0.0038, 0.0036	1.000, -0.0300, 0.0038, 0.0037	0.766, -0.0100, 0.0038, 0.0037	0.061, 0.0000, 0.0039, 0.0037	0.745, 0.0099, 0.0039, 0.0038	1.000, 0.0299, 0.0039, 0.0038	1.000, 0.0499, 0.0039, 0.0038	1.000, 0.0998, 0.0040, 0.0039
MR-PRESSO	1.000, -0.0999, 0.0036, 0.0036	1.000, -0.0499, 0.0036, 0.0036	1.000, -0.0300, 0.0037, 0.0036	0.759, -0.0100, 0.0037, 0.0037	0.048, 0.0000, 0.0037, 0.0037	0.758, 0.0099, 0.0037, 0.0037	1.000, 0.0299, 0.0037, 0.0037	1.000, 0.0499, 0.0037, 0.0038	1.000, 0.0998, 0.0038, 0.0039
MR-IVW	1.000, -0.0999, 0.0036, 0.0036	1.000, -0.0500, 0.0036, 0.0037	1.000, -0.0300, 0.0037, 0.0037	0.761, -0.0100, 0.0037, 0.0038	0.043, -0.0001, 0.0037, 0.0038	0.750, 0.0099, 0.0037, 0.0038	1.000, 0.0299, 0.0037, 0.0039	1.000, 0.0499, 0.0037, 0.0039	1.000, 0.0998, 0.0038, 0.004
MR-IVW-Oracle	1.000, -0.0999, 0.0036, 0.0036	1.000, -0.0500, 0.0036, 0.0037	1.000, -0.0300, 0.0037, 0.0037	0.761, -0.0100, 0.0037, 0.0038	0.043, -0.0001, 0.0037, 0.0038	0.750, 0.0099, 0.0037, 0.0038	1.000, 0.0299, 0.0037, 0.0039	1.000, 0.0499, 0.0037, 0.0039	1.000, 0.0998, 0.0038, 0.004
MR-Egger	1.000, -0.0958, 0.0190, 0.019	0.702, -0.0481, 0.0193, 0.0194	0.320, -0.0291, 0.0195, 0.0195	0.086, -0.0100, 0.0197, 0.0197	0.050, -0.0005, 0.0197, 0.0198	0.073, 0.0091, 0.0198, 0.0199	0.285, 0.0281, 0.0201, 0.0201	0.644, 0.0472, 0.0203, 0.0204	0.997, 0.0948, 0.0209, 0.021
MR-Weighted-Median	1.000, -0.0993, 0.0046, 0.0052	1.000, -0.0496, 0.0047, 0.0053	1.000, -0.0297, 0.0047, 0.0053	0.435, -0.0099, 0.0048, 0.0054	0.028, 0.0000, 0.0048, 0.0054	0.466, 0.0100, 0.0049, 0.0054	1.000, 0.0298, 0.0049, 0.0055	1.000, 0.0497, 0.0049, 0.0056	1.000, 0.0993, 0.0050, 0.0057
MR-Weighted-Mode	1.000, -0.0987, 0.0096, 0.0126	0.988, -0.0492, 0.0098, 0.0128	0.661, -0.0295, 0.0100, 0.013	0.053, -0.0097, 0.0101, 0.0131	0.003, 0.0003, 0.0100, 0.0131	0.049, 0.0102, 0.0101, 0.0132	0.651, 0.0299, 0.0101, 0.0134	0.981, 0.0496, 0.0101, 0.0135	1.000, 0.0991, 0.0102, 0.014
MR-RAPS1	1.000, -0.1000, 0.0036, 0.0037	1.000, -0.0500, 0.0036, 0.0037	1.000, -0.0300, 0.0037, 0.0037	0.769, -0.0100, 0.0037, 0.0038	0.045, 0.0000, 0.0037, 0.0038	0.752, 0.0100, 0.0037, 0.0038	1.000, 0.0300, 0.0037, 0.0039	1.000, 0.0499, 0.0038, 0.0039	1.000, 0.0999, 0.0038, 0.004
MR-RAPS2	1.000, -0.0878, 0.1467, 0.0039	1.000, -0.0640, 0.4223, 0.0044	1.000, -0.0505, 0.9665, 0.0052	0.742, -0.0100, 0.0038, 0.0039	0.049, 0.0000, 0.0038, 0.0039	0.725, 0.0100, 0.0038, 0.0039	1.000, 0.0179, 0.7288, 0.0048	1.000, 0.0693, 0.5024, 0.0046	1.000, 0.0963, 0.2849, 0.0045
MR-RAPS3	1.000, -0.1001, 0.0036, 0.0036	1.000, -0.0501, 0.0036, 0.0036	1.000, -0.0301, 0.0036, 0.0036	0.791, -0.0101, 0.0037, 0.0037	0.049, -0.0001, 0.0037, 0.0037	0.763, 0.0099, 0.0037, 0.0037	1.000, 0.0300, 0.0037, 0.0038	1.000, 0.0500, 0.0038, 0.0038	1.000, 0.1000, 0.0039, 0.0039
MR-RAPS4	1.000, -0.1000, 0.0037, 0.0037	1.000, -0.0500, 0.0037, 0.0037	1.000, -0.0300, 0.0037, 0.0037	0.761, -0.0100, 0.0038, 0.0038	0.055, 0.0000, 0.0038, 0.0038	0.740, 0.0100, 0.0038, 0.0038	1.000, 0.0300, 0.0038, 0.0039	1.000, 0.0500, 0.0038, 0.0039	1.000, 0.1000, 0.0039, 0.004

Table S71: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean( $SE(\hat{\theta})$ ) when  $m = 100$ , the InSIDE satisfied,  $q = 0.2$ , and  $N = 50000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	1.000, -0.0970, 0.0128, 0.0104	0.975, -0.0473, 0.0129, 0.0105	0.695, -0.0274, 0.0128, 0.0106	0.157, -0.0083, 0.0120, 0.0106	0.077, 0.0008, 0.0118, 0.0106	0.182, 0.0097, 0.0123, 0.0107	0.704, 0.0288, 0.0133, 0.0109	0.974, 0.0487, 0.0134, 0.011	1.000, 0.0985, 0.0136, 0.0113
cML-MA-AIC-Profile	1.000, -0.0975, 0.0130, 0.0105	0.975, -0.0474, 0.0130, 0.0106	0.693, -0.0274, 0.0128, 0.0107	0.155, -0.0083, 0.0120, 0.0107	0.075, 0.0008, 0.0118, 0.0107	0.179, 0.0097, 0.0123, 0.0108	0.699, 0.0289, 0.0133, 0.011	0.974, 0.0488, 0.0135, 0.0111	1.000, 0.0990, 0.0138, 0.0114
cML-AIC	1.000, -0.0983, 0.0134, 0.0095	0.985, -0.0486, 0.0135, 0.0097	0.750, -0.0285, 0.0136, 0.0097	0.243, -0.0090, 0.0133, 0.0098	0.142, 0.0006, 0.0132, 0.0098	0.261, 0.0101, 0.0135, 0.0099	0.773, 0.0299, 0.0140, 0.01	0.981, 0.0500, 0.0141, 0.0101	1.000, 0.0999, 0.0143, 0.0104
cML-AIC-Profile	1.000, -0.0986, 0.0135, 0.0096	0.984, -0.0486, 0.0135, 0.0097	0.747, -0.0286, 0.0137, 0.0098	0.240, -0.0090, 0.0133, 0.0099	0.139, 0.0006, 0.0132, 0.0099	0.259, 0.0101, 0.0135, 0.01	0.767, 0.0299, 0.0140, 0.0101	0.981, 0.0501, 0.0141, 0.0102	1.000, 0.1003, 0.0144, 0.0104
cML-MA-BIC	1.000, -0.0997, 0.0087, 0.0088	0.999, -0.0497, 0.0088, 0.009	0.915, -0.0297, 0.0088, 0.009	0.182, -0.0097, 0.0089, 0.0091	0.053, 0.0003, 0.0089, 0.0091	0.192, 0.0103, 0.0090, 0.0092	0.910, 0.0303, 0.0091, 0.0093	1.000, 0.0503, 0.0091, 0.0093	1.000, 0.1003, 0.0094, 0.0096
cML-MA-BIC-Profile	1.000, -0.0997, 0.0087, 0.0089	0.999, -0.0497, 0.0088, 0.009	0.913, -0.0297, 0.0088, 0.0091	0.182, -0.0097, 0.0089, 0.0091	0.052, 0.0003, 0.0089, 0.0092	0.189, 0.0103, 0.0090, 0.0092	0.910, 0.0303, 0.0091, 0.0093	1.000, 0.0503, 0.0091, 0.0094	1.000, 0.1003, 0.0094, 0.0096
cML-BIC	1.000, -0.0997, 0.0087, 0.0088	0.999, -0.0497, 0.0088, 0.0089	0.924, -0.0297, 0.0089, 0.009	0.189, -0.0097, 0.0089, 0.009	0.053, 0.0003, 0.0090, 0.0091	0.197, 0.0103, 0.0090, 0.0091	0.912, 0.0303, 0.0091, 0.0092	1.000, 0.0503, 0.0092, 0.0093	1.000, 0.1003, 0.0094, 0.0095
cML-BIC-Profile	1.000, -0.0997, 0.0087, 0.0088	0.999, -0.0497, 0.0088, 0.0089	0.922, -0.0297, 0.0089, 0.009	0.188, -0.0097, 0.0089, 0.0091	0.052, 0.0003, 0.0090, 0.0091	0.196, 0.0103, 0.0090, 0.0091	0.912, 0.0303, 0.0091, 0.0092	1.000, 0.0503, 0.0092, 0.0093	1.000, 0.1003, 0.0094, 0.0096
MR-Mix	1.000, -0.1108, 0.0129, 0.0193	0.899, -0.0545, 0.0128, 0.0191	0.384, -0.0327, 0.0128, 0.019	0.031, -0.0113, 0.0128, 0.0189	0.011, -0.0007, 0.0129, 0.0189	0.024, 0.0099, 0.0129, 0.0189	0.340, 0.0308, 0.0131, 0.0188	0.858, 0.0513, 0.0131, 0.0187	1.000, 0.1009, 0.0130, 0.0186
MR-ContMix	1.000, -0.0987, 0.0093, NA	0.999, -0.0491, 0.0093, NA	0.874, -0.0292, 0.0094, NA	0.154, -0.0094, 0.0095, NA	0.045, 0.0006, 0.0095, NA	0.182, 0.0105, 0.0095, NA	0.881, 0.0303, 0.0097, NA	1.000, 0.0502, 0.0098, NA	1.000, 0.0999, 0.0100, NA
MR-Lasso	1.000, -0.0989, 0.0089, 0.0088	0.999, -0.0492, 0.0091, 0.009	0.908, -0.0293, 0.0090, 0.009	0.183, -0.0095, 0.0091, 0.0091	0.060, 0.0004, 0.0091, 0.0091	0.194, 0.0103, 0.0092, 0.0092	0.904, 0.0302, 0.0094, 0.0093	1.000, 0.0501, 0.0094, 0.0093	1.000, 0.0997, 0.0096, 0.0096
MR-PRESSO	1.000, -0.0988, 0.0105, 0.0085	0.995, -0.0492, 0.0106, 0.0086	0.878, -0.0294, 0.0105, 0.0087	0.236, -0.0095, 0.0106, 0.0088	0.094, 0.0004, 0.0106, 0.0088	0.239, 0.0103, 0.0106, 0.0088	0.885, 0.0301, 0.0106, 0.0089	0.997, 0.0499, 0.0106, 0.009	1.000, 0.0995, 0.0107, 0.0093
MR-IVW	0.269, -0.0992, 0.0755, 0.074	0.116, -0.0494, 0.0755, 0.074	0.074, -0.0294, 0.0755, 0.074	0.054, -0.0095, 0.0755, 0.074	0.057, 0.0005, 0.0755, 0.074	0.056, 0.0104, 0.0755, 0.074	0.069, 0.0304, 0.0755, 0.074	0.114, 0.0503, 0.0755, 0.074	0.274, 0.1001, 0.0755, 0.0741
MR-IVW-Oracle	1.000, -0.0991, 0.0086, 0.009	0.999, -0.0494, 0.0087, 0.0091	0.905, -0.0296, 0.0087, 0.0092	0.179, -0.0097, 0.0088, 0.0092	0.051, 0.0002, 0.0088, 0.0093	0.182, 0.0102, 0.0089, 0.0093	0.900, 0.0300, 0.0089, 0.0094	1.000, 0.0499, 0.0090, 0.0095	1.000, 0.0995, 0.0093, 0.0097
MR-Egger	0.074, -0.0853, 0.3835, 0.3612	0.071, -0.0437, 0.3834, 0.3612	0.072, -0.0270, 0.3834, 0.3612	0.069, -0.0103, 0.3834, 0.3612	0.049, -0.0020, 0.3834, 0.3612	0.046, 0.0063, 0.3834, 0.3612	0.067, 0.0230, 0.3834, 0.3612	0.069, 0.0396, 0.3834, 0.3613	0.071, 0.0812, 0.3834, 0.3613
MR-Weighted-Median	1.000, -0.0963, 0.0110, 0.0128	0.978, -0.0480, 0.0109, 0.0129	0.610, -0.0287, 0.0110, 0.013	0.076, -0.0094, 0.0110, 0.0131	0.019, 0.0004, 0.0111, 0.0132	0.073, 0.0101, 0.0112, 0.0132	0.606, 0.0294, 0.0114, 0.0134	0.968, 0.0488, 0.0116, 0.0135	1.000, 0.0971, 0.0119, 0.0139
MR-Weighted-Mode	0.998, -0.0963, 0.0173, 0.0221	0.588, -0.0480, 0.0173, 0.0224	0.201, -0.0288, 0.0176, 0.0226	0.024, -0.0095, 0.0177, 0.0227	0.009, 0.0004, 0.0179, 0.0228	0.023, 0.0100, 0.0178, 0.0229	0.211, 0.0295, 0.0181, 0.0231	0.574, 0.0489, 0.0183, 0.0233	0.990, 0.0974, 0.0188, 0.024
MR-RAPS1	0.265, -0.0994, 0.0735, 0.074	0.105, -0.0494, 0.0735, 0.074	0.072, -0.0294, 0.0735, 0.074	0.049, -0.0094, 0.0735, 0.074	0.046, 0.0006, 0.0735, 0.074	0.047, 0.0106, 0.0735, 0.074	0.063, 0.0306, 0.0736, 0.074	0.108, 0.0506, 0.0736, 0.074	0.265, 0.1006, 0.0736, 0.074
MR-RAPS2	1.000, 0.0598, 1.5440, 0.0137	1.000, 0.1228, 2.1237, 0.0138	0.972, 0.1311, 1.8903, 0.0134	0.704, 0.0071, 0.7392, 0.0123	0.620, 0.0196, 0.8700, 0.0125	0.699, 0.0482, 1.5487, 0.0132	0.970, -0.0728, 2.4757, 0.0137	1.000, -0.0804, 2.9620, 0.0139	1.000, -0.0340, 1.5029, 0.0144
MR-RAPS3	0.924, -0.2649, 0.1863, 0.0226	0.885, -0.1287, 0.1926, 0.0222	0.847, -0.0753, 0.1915, 0.0219	0.837, -0.0235, 0.1886, 0.0215	0.837, 0.0016, 0.1866, 0.0213	0.833, 0.0261, 0.1843, 0.0211	0.843, 0.0733, 0.1728, 0.0207	0.876, 0.1178, 0.1728, 0.0203	0.926, 0.2178, 0.1564, 0.0192
MR-RAPS4	1.000, 0.1534, 0.9997, 0.0161	1.000, 0.0905, 0.9088, 0.0144	0.988, 0.0856, 0.9108, 0.0143	0.848, 0.0637, 0.8849, 0.014	0.807, 0.0443, 0.8960, 0.0141	0.831, 0.0755, 0.8876, 0.014	0.985, 0.0051, 0.9049, 0.0142	1.000, -0.0316, 0.9254, 0.0144	1.000, -0.0231, 0.9971, 0.0152

Table S72: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean( $SE(\hat{\theta})$ ) when  $m = 100$ , the InSIDE satisfied,  $q = 0.2$ , and  $N = 100000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	1.000, -0.0982, 0.0090, 0.0074	1.000, -0.0484, 0.0091, 0.0075	0.919, -0.0285, 0.0092, 0.0075	0.254, -0.0090, 0.0087, 0.0075	0.081, 0.0000, 0.0084, 0.0075	0.258, 0.0091, 0.0088, 0.0076	0.915, 0.0286, 0.0095, 0.0077	0.999, 0.0485, 0.0096, 0.0078	1.000, 0.0982, 0.0098, 0.008
cML-MA-AIC-Profile	1.000, -0.0985, 0.0091, 0.0074	1.000, -0.0485, 0.0092, 0.0075	0.918, -0.0285, 0.0092, 0.0075	0.251, -0.0090, 0.0087, 0.0075	0.080, 0.0000, 0.0084, 0.0075	0.257, 0.0091, 0.0088, 0.0076	0.914, 0.0286, 0.0095, 0.0077	0.999, 0.0486, 0.0096, 0.0078	1.000, 0.0986, 0.0099, 0.008
cML-AIC	1.000, -0.0992, 0.0095, 0.0068	1.000, -0.0493, 0.0095, 0.0068	0.949, -0.0294, 0.0096, 0.0069	0.337, -0.0096, 0.0094, 0.0069	0.132, 0.0000, 0.0093, 0.007	0.346, 0.0096, 0.0095, 0.007	0.939, 0.0294, 0.0099, 0.0071	0.999, 0.0494, 0.0100, 0.0071	1.000, 0.0992, 0.0104, 0.0073
cML-AIC-Profile	1.000, -0.0995, 0.0095, 0.0068	1.000, -0.0493, 0.0095, 0.0069	0.948, -0.0294, 0.0096, 0.0069	0.336, -0.0096, 0.0094, 0.007	0.128, 0.0000, 0.0093, 0.007	0.343, 0.0096, 0.0095, 0.007	0.938, 0.0294, 0.0099, 0.0071	0.999, 0.0494, 0.0100, 0.0072	1.000, 0.0994, 0.0104, 0.0074
cML-MA-BIC	1.000, -0.0999, 0.0063, 0.0062	1.000, -0.0500, 0.0063, 0.0063	0.999, -0.0300, 0.0064, 0.0064	0.365, -0.0100, 0.0064, 0.0064	0.048, 0.0000, 0.0064, 0.0064	0.343, 0.0100, 0.0065, 0.0065	0.998, 0.0299, 0.0065, 0.0065	1.000, 0.0499, 0.0066, 0.0066	1.000, 0.0999, 0.0068, 0.0068
cML-MA-BIC-Profile	1.000, -0.0999, 0.0063, 0.0063	1.000, -0.0500, 0.0063, 0.0063	0.998, -0.0300, 0.0064, 0.0064	0.364, -0.0100, 0.0064, 0.0064	0.048, 0.0000, 0.0064, 0.0065	0.340, 0.0100, 0.0065, 0.0065	0.998, 0.0299, 0.0065, 0.0065	1.000, 0.0499, 0.0066, 0.0066	1.000, 0.0999, 0.0068, 0.0068
cML-BIC	1.000, -0.1000, 0.0062, 0.0062	1.000, -0.0500, 0.0063, 0.0063	0.999, -0.0300, 0.0063, 0.0063	0.374, -0.0100, 0.0064, 0.0064	0.051, 0.0000, 0.0064, 0.0064	0.345, 0.0100, 0.0064, 0.0064	0.998, 0.0300, 0.0065, 0.0065	1.000, 0.0499, 0.0066, 0.0066	1.000, 0.0999, 0.0068, 0.0067
cML-BIC-Profile	1.000, -0.1000, 0.0062, 0.0062	1.000, -0.0500, 0.0063, 0.0063	0.999, -0.0300, 0.0063, 0.0063	0.373, -0.0100, 0.0064, 0.0064	0.051, 0.0000, 0.0064, 0.0064	0.343, 0.0100, 0.0064, 0.0064	0.998, 0.0300, 0.0065, 0.0065	1.000, 0.0499, 0.0066, 0.0066	1.000, 0.0999, 0.0068, 0.0067
MR-Mix	1.000, -0.1107, 0.0095, 0.0152	0.983, -0.0545, 0.0096, 0.015	0.629, -0.0326, 0.0096, 0.015	0.041, -0.0110, 0.0094, 0.015	0.004, -0.0003, 0.0094, 0.0149	0.036, 0.0104, 0.0095, 0.0149	0.603, 0.0313, 0.0095, 0.0149	0.973, 0.0518, 0.0096, 0.0149	1.000, 0.1014, 0.0099, 0.0148
MR-ContMix	1.000, -0.0498, 0.0066, NA	1.000, -0.0498, 0.0067, NA	0.997, -0.0299, 0.0068, NA	0.332, -0.0100, 0.0068, NA	0.056, 0.0000, 0.0068, NA	0.327, 0.0100, 0.0069, NA	0.991, 0.0299, 0.0069, NA	1.000, 0.0498, 0.0070, NA	1.000, 0.0996, 0.0072, NA
MR-Lasso	1.000, -0.0996, 0.0066, 0.0062	1.000, -0.0498, 0.0066, 0.0063	0.996, -0.0299, 0.0066, 0.0064	0.368, -0.0100, 0.0067, 0.0064	0.067, 0.0000, 0.0068, 0.0065	0.341, 0.0099, 0.0068, 0.0065	0.998, 0.0298, 0.0068, 0.0066	1.000, 0.0498, 0.0069, 0.0066	1.000, 0.0996, 0.0070, 0.0068
MR-PRESSO	1.000, -0.0993, 0.0117, 0.006	0.991, -0.0496, 0.0116, 0.0061	0.953, -0.0298, 0.0115, 0.0061	0.453, -0.0099, 0.0114, 0.0062	0.198, 0.0000, 0.0114, 0.0062	0.429, 0.0100, 0.0114, 0.0062	0.957, 0.0299, 0.0113, 0.0063	0.993, 0.0497, 0.0113, 0.0063	1.000, 0.0994, 0.0112, 0.0065
MR-IVW	0.277, -0.0987, 0.0778, 0.0737	0.127, -0.0487, 0.0777, 0.0737	0.078, -0.0287, 0.0777, 0.0737	0.060, -0.0087, 0.0777, 0.0737	0.062, 0.0013, 0.0777, 0.0737	0.073, 0.0112, 0.0777, 0.0737	0.094, 0.0312, 0.0777, 0.0737	0.121, 0.0512, 0.0777, 0.0737	0.296, 0.1012, 0.0776, 0.0737
MR-IVW-Oracle	1.000, -0.0996, 0.0062, 0.0063	1.000, -0.0498, 0.0062, 0.0064	0.999, -0.0299, 0.0063, 0.0065	0.345, -0.0100, 0.0063, 0.0065	0.044, 0.0000, 0.0064, 0.0066	0.327, 0.0100, 0.0064, 0.0066	0.997, 0.0299, 0.0064, 0.0067	1.000, 0.0498, 0.0065, 0.0067	1.000, 0.0996, 0.0067, 0.0069
MR-Egger	0.067, -0.1045, 0.3841, 0.3757	0.063, -0.0589, 0.3840, 0.3757	0.058, -0.0406, 0.3840, 0.3757	0.053, -0.0224, 0.3839, 0.3757	0.052, -0.0133, 0.3839, 0.3757	0.049, -0.0041, 0.3839, 0.3757	0.047, 0.0141, 0.3839, 0.3757	0.045, 0.0323, 0.3839, 0.3757	0.055, 0.0779, 0.3838, 0.3757
MR-Weighted-Median	1.000, -0.0982, 0.0080, 0.009	1.000, -0.0491, 0.0082, 0.0092	0.922, -0.0295, 0.0082, 0.0092	0.153, -0.0099, 0.0083, 0.0093	0.033, -0.0001, 0.0083, 0.0093	0.142, 0.0098, 0.0083, 0.0094	0.898, 0.0294, 0.0084, 0.0094	1.000, 0.0491, 0.0086, 0.0095	1.000, 0.0981, 0.0088, 0.0098
MR-Weighted-Mode	1.000, -0.0987, 0.0122, 0.0158	0.918, -0.0493, 0.0122, 0.016	0.439, -0.0297, 0.0125, 0.0161	0.036, -0.0101, 0.0124, 0.0163	0.005, -0.0002, 0.0125, 0.0163	0.034, 0.0098, 0.0127, 0.0164	0.433, 0.0295, 0.0129, 0.0165	0.874, 0.0492, 0.0130, 0.0167	1.000, 0.0984, 0.0136, 0.0172
MR-RAPS1	0.280, -0.0983, 0.0751, 0.0735	0.112, -0.0483, 0.0751, 0.0735	0.075, -0.0283, 0.0751, 0.0735	0.060, -0.0083, 0.0751, 0.0735	0.058, 0.0017, 0.0751, 0.0735	0.063, 0.0117, 0.0751, 0.0735	0.077, 0.0317, 0.0751, 0.0735	0.118, 0.0517, 0.0751, 0.0735	0.290, 0.1017, 0.0751, 0.0736
MR-RAPS2	0.999, 0.4861, 2.3093, 0.0294	1.000, 0.1562, 1.9727, 0.0089	0.999, 0.0588, 1.2278, 0.0089	0.810, 0.0250, 0.7413, 0.0088	0.702, 0.0143, 0.7838, 0.0092	0.808, 0.0186, 0.7571, 0.0089	1.000, -0.0578, 1.3944, 0.0092	1.000, -0.0977, 1.3736, 0.0092	1.000, -0.2143, 1.8828, 0.0103
MR-RAPS3	0.953, -0.2591, 0.1907, 0.0158	0.908, -0.1249, 0.1963, 0.0155	0.907, -0.0723, 0.1951, 0.0153	0.897, -0.0214, 0.1920, 0.015	0.904, 0.0034, 0.1900, 0.0149	0.900, 0.0276, 0.1876, 0.0147	0.883, 0.0741, 0.1821, 0.0145	0.906, 0.1182, 0.1760, 0.0142	0.943, 0.2172, 0.1595, 0.0135
MR-RAPS4	1.000, 0.4068, 0.7992, 0.0107	1.000, 0.2108, 0.8180, 0.0096	0.999, 0.1523, 0.8198, 0.0094	0.934, 0.0743, 0.8509, 0.0097	0.885, 0.0572, 0.8755, 0.0098	0.920, 0.0582, 0.8647, 0.0096	1.000, -0.0247, 0.8465, 0.0095	1.000, -0.0852, 0.8816, 0.0098	1.000, -0.2750, 0.8467, 0.01

Table S73: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean( $SE(\hat{\theta})$ ) when  $m = 100$ , the InSIDE satisfied,  $q = 0.2$ , and  $N = 200000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	1.000, -0.0988, 0.0064, 0.0052	1.000, -0.0491, 0.0065, 0.0053	0.995, -0.0291, 0.0066, 0.0053	0.438, -0.0094, 0.0063, 0.0053	0.075, -0.0002, 0.0059, 0.0053	0.413, 0.0090, 0.0063, 0.0054	0.991, 0.0288, 0.0067, 0.0055	1.000, 0.0487, 0.0067, 0.0055	1.000, 0.0985, 0.0069, 0.0057
cML-MA-AIC-Profile	1.000, -0.0991, 0.0065, 0.0052	1.000, -0.0491, 0.0066, 0.0053	0.995, -0.0292, 0.0066, 0.0053	0.438, -0.0094, 0.0063, 0.0053	0.075, -0.0002, 0.0059, 0.0053	0.413, 0.0090, 0.0063, 0.0054	0.991, 0.0288, 0.0067, 0.0055	1.000, 0.0488, 0.0068, 0.0055	1.000, 0.0987, 0.0069, 0.0057
cML-AIC	1.000, -0.0995, 0.0067, 0.0048	1.000, -0.0497, 0.0067, 0.0048	0.996, -0.0297, 0.0069, 0.0049	0.507, -0.0098, 0.0068, 0.0049	0.151, -0.0002, 0.0066, 0.0049	0.495, 0.0094, 0.0068, 0.005	0.995, 0.0293, 0.0070, 0.005	1.000, 0.0492, 0.0071, 0.0051	1.000, 0.0991, 0.0072, 0.0052
cML-AIC-Profile	1.000, -0.0997, 0.0068, 0.0048	1.000, -0.0497, 0.0067, 0.0049	0.996, -0.0297, 0.0069, 0.0049	0.505, -0.0098, 0.0068, 0.0049	0.151, -0.0002, 0.0066, 0.0049	0.495, 0.0094, 0.0068, 0.005	0.995, 0.0293, 0.0070, 0.005	1.000, 0.0493, 0.0071, 0.0051	1.000, 0.0993, 0.0072, 0.0052
cML-MA-BIC	1.000, -0.1000, 0.0044, 0.0044	1.000, -0.0500, 0.0044, 0.0045	1.000, -0.0301, 0.0045, 0.0045	0.608, -0.0101, 0.0045, 0.0045	0.046, -0.0001, 0.0045, 0.0046	0.581, 0.0099, 0.0046, 0.0046	1.000, 0.0299, 0.0046, 0.0046	1.000, 0.0499, 0.0047, 0.0047	1.000, 0.0999, 0.0048, 0.0048
cML-MA-BIC-Profile	1.000, -0.1000, 0.0044, 0.0044	1.000, -0.0500, 0.0044, 0.0045	1.000, -0.0301, 0.0045, 0.0045	0.608, -0.0101, 0.0045, 0.0045	0.046, -0.0001, 0.0045, 0.0046	0.579, 0.0099, 0.0046, 0.0046	1.000, 0.0299, 0.0046, 0.0046	1.000, 0.0499, 0.0047, 0.0047	1.000, 0.0999, 0.0048, 0.0048
cML-BIC	1.000, -0.1000, 0.0044, 0.0044	1.000, -0.0501, 0.0045, 0.0044	1.000, -0.0301, 0.0045, 0.0045	0.615, -0.0101, 0.0045, 0.0045	0.048, -0.0001, 0.0045, 0.0045	0.581, 0.0099, 0.0046, 0.0045	1.000, 0.0299, 0.0046, 0.0046	1.000, 0.0499, 0.0047, 0.0046	1.000, 0.0999, 0.0048, 0.0048
cML-BIC-Profile	1.000, -0.1000, 0.0044, 0.0044	1.000, -0.0501, 0.0045, 0.0045	1.000, -0.0301, 0.0045, 0.0045	0.613, -0.0101, 0.0045, 0.0045	0.048, -0.0001, 0.0045, 0.0045	0.581, 0.0099, 0.0046, 0.0046	1.000, 0.0299, 0.0046, 0.0046	1.000, 0.0499, 0.0047, 0.0046	1.000, 0.0999, 0.0048, 0.0048
MR-Mix	0.998, -0.1105, 0.0079, 0.0119	0.993, -0.0543, 0.0079, 0.0118	0.866, -0.0324, 0.0079, 0.0118	0.083, -0.0108, 0.0079, 0.0117	0.005, 0.0000, 0.0079, 0.0117	0.091, 0.0107, 0.0080, 0.0116	0.842, 0.0318, 0.0081, 0.0116	0.994, 0.0523, 0.0081, 0.0116	1.000, 0.1018, 0.0081, 0.0115
MR-ContMix	1.000, -0.0999, 0.0045, NA	1.000, -0.0500, 0.0045, NA	1.000, -0.0300, 0.0046, NA	0.589, -0.0101, 0.0046, NA	0.051, -0.0001, 0.0046, NA	0.559, 0.0099, 0.0047, NA	1.000, 0.0299, 0.0047, NA	1.000, 0.0498, 0.0048, NA	1.000, 0.0998, 0.0050, NA
MR-Lasso	1.000, -0.0998, 0.0046, 0.0044	1.000, -0.0499, 0.0046, 0.0045	1.000, -0.0299, 0.0046, 0.0045	0.597, -0.0100, 0.0047, 0.0046	0.059, 0.0000, 0.0047, 0.0046	0.587, 0.0100, 0.0047, 0.0046	1.000, 0.0299, 0.0047, 0.0046	1.000, 0.0499, 0.0048, 0.0047	1.000, 0.0997, 0.0050, 0.0048
MR-PRESSO	0.998, -0.0996, 0.0149, 0.0045	0.982, -0.0498, 0.0145, 0.0045	0.941, -0.0299, 0.0144, 0.0046	0.646, -0.0100, 0.0144, 0.0046	0.341, 0.0000, 0.0143, 0.0046	0.638, 0.0100, 0.0142, 0.0046	0.939, 0.0299, 0.0142, 0.0046	0.988, 0.0498, 0.0140, 0.0047	1.000, 0.0996, 0.0136, 0.0048
MR-IVW	0.304, -0.1005, 0.0758, 0.0739	0.116, -0.0504, 0.0758, 0.0739	0.084, -0.0304, 0.0758, 0.0739	0.055, -0.0104, 0.0758, 0.0739	0.054, -0.0003, 0.0758, 0.0739	0.063, 0.0097, 0.0758, 0.0739	0.075, 0.0297, 0.0758, 0.0739	0.113, 0.0497, 0.0758, 0.0739	0.272, 0.0998, 0.0758, 0.0739
MR-IVW-Oracle	1.000, -0.0999, 0.0044, 0.0045	1.000, -0.0500, 0.0044, 0.0046	1.000, -0.0300, 0.0045, 0.0046	0.594, -0.0100, 0.0045, 0.0046	0.042, -0.0001, 0.0045, 0.0047	0.563, 0.0099, 0.0045, 0.0047	1.000, 0.0299, 0.0046, 0.0047	1.000, 0.0498, 0.0046, 0.0048	1.000, 0.0997, 0.0048, 0.0049
MR-Egger	0.069, -0.1074, 0.3914, 0.3839	0.074, -0.0596, 0.3913, 0.3838	0.068, -0.0405, 0.3913, 0.3838	0.070, -0.0214, 0.3912, 0.3838	0.069, -0.0119, 0.3912, 0.3838	0.071, -0.0023, 0.3912, 0.3838	0.068, 0.0168, 0.3912, 0.3838	0.065, 0.0358, 0.3911, 0.3838	0.062, 0.0836, 0.3911, 0.3837
MR-Weighted-Median	1.000, -0.0991, 0.0056, 0.0064	1.000, -0.0496, 0.0057, 0.0065	0.998, -0.0298, 0.0057, 0.0065	0.310, -0.0100, 0.0057, 0.0066	0.017, 0.0000, 0.0058, 0.0066	0.297, 0.0099, 0.0058, 0.0066	0.998, 0.0297, 0.0058, 0.0067	1.000, 0.0495, 0.0059, 0.0067	1.000, 0.0990, 0.0061, 0.0069
MR-Weighted-Mode	1.000, -0.0992, 0.0089, 0.0113	0.999, -0.0497, 0.0089, 0.0114	0.779, -0.0297, 0.0089, 0.0115	0.090, -0.0100, 0.0090, 0.0116	0.008, 0.0000, 0.0090, 0.0116	0.080, 0.0100, 0.0092, 0.0117	0.765, 0.0297, 0.0093, 0.0118	0.996, 0.0495, 0.0094, 0.0119	1.000, 0.0991, 0.0093, 0.0122
MR-RAPS1	0.299, -0.1011, 0.0740, 0.0735	0.113, -0.0511, 0.0741, 0.0735	0.075, -0.0311, 0.0741, 0.0735	0.053, -0.0111, 0.0741, 0.0735	0.053, -0.0011, 0.0741, 0.0735	0.055, 0.0089, 0.0741, 0.0735	0.080, 0.0289, 0.0741, 0.0735	0.105, 0.0489, 0.0741, 0.0735	0.255, 0.0989, 0.0741, 0.0735
MR-RAPS2	1.000, 0.4682, 2.3725, 0.0083	1.000, 0.1663, 0.6543, 0.0056	1.000, 0.1104, 0.9236, 0.0057	0.890, 0.1789, 0.7864, 0.0057	0.673, 0.2385, 1.1421, 0.0062	0.872, 0.1537, 0.9202, 0.0061	1.000, 0.2206, 1.0497, 0.0063	1.000, 0.2140, 1.1501, 0.0069	1.000, 0.1425, 1.4071, 0.0069
MR-RAPS3	0.962, -0.2666, 0.1861, 0.0113	0.929, -0.1304, 0.1924, 0.0111	0.911, -0.0771, 0.1914, 0.0109	0.924, -0.0253, 0.1886, 0.0107	0.927, -0.0002, 0.1866, 0.0106	0.920, 0.0243, 0.1843, 0.0105	0.937, 0.0715, 0.1728, 0.0103	0.924, 0.1161, 0.1728, 0.0101	0.960, 0.2162, 0.1563, 0.0096
MR-RAPS4	1.000, 0.5604, 0.5218, 0.0068	1.000, 0.4130, 0.6567, 0.0064	1.000, 0.3588, 0.6698, 0.0064	0.975, 0.3056, 0.6875, 0.0063	0.927, 0.2747, 0.6698, 0.006	0.970, 0.2826, 0.7208, 0.0062	1.000, 0.2625, 0.7754, 0.0066	1.000, 0.2126, 0.7782, 0.0064	1.000, 0.0270, 0.8856, 0.0069

Table S74: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean( $SE(\hat{\theta})$ ) when  $m = 100$ , the InSIDE satisfied,  $q = 0.4$ , and  $N = 50000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	1.000, -0.0964, 0.0164, 0.0132	0.886, -0.0467, 0.0166, 0.0134	0.516, -0.0270, 0.0163, 0.0134	0.136, -0.0083, 0.0153, 0.0134	0.079, 0.0005, 0.0151, 0.0134	0.155, 0.0094, 0.0155, 0.0135	0.533, 0.0280, 0.0167, 0.0137	0.870, 0.0475, 0.0173, 0.0139	1.000, 0.0971, 0.0176, 0.0142
cML-MA-AIC-Profile	1.000, -0.0969, 0.0165, 0.0134	0.884, -0.0468, 0.0167, 0.0135	0.509, -0.0271, 0.0163, 0.0135	0.133, -0.0083, 0.0153, 0.0134	0.076, 0.0005, 0.0151, 0.0135	0.151, 0.0094, 0.0155, 0.0136	0.525, 0.0280, 0.0168, 0.0138	0.868, 0.0476, 0.0174, 0.014	1.000, 0.0975, 0.0177, 0.0144
cML-AIC	1.000, -0.0983, 0.0169, 0.012	0.924, -0.0485, 0.0175, 0.0121	0.609, -0.0285, 0.0172, 0.0122	0.227, -0.0090, 0.0172, 0.0123	0.154, 0.0006, 0.0172, 0.0123	0.234, 0.0101, 0.0174, 0.0124	0.611, 0.0296, 0.0180, 0.0125	0.917, 0.0495, 0.0181, 0.0126	1.000, 0.0990, 0.0184, 0.0129
cML-AIC-Profile	1.000, -0.0986, 0.0172, 0.0121	0.924, -0.0486, 0.0176, 0.0122	0.607, -0.0286, 0.0175, 0.0123	0.223, -0.0090, 0.0172, 0.0124	0.150, 0.0006, 0.0172, 0.0124	0.229, 0.0101, 0.0174, 0.0125	0.606, 0.0296, 0.0180, 0.0126	0.915, 0.0496, 0.0182, 0.0127	1.000, 0.0993, 0.0185, 0.013
cML-MA-BIC	1.000, -0.1000, 0.0113, 0.0111	0.995, -0.0499, 0.0114, 0.0112	0.739, -0.0299, 0.0115, 0.0113	0.147, -0.0099, 0.0116, 0.0114	0.053, 0.0001, 0.0116, 0.0114	0.151, 0.0101, 0.0116, 0.0115	0.733, 0.0301, 0.0118, 0.0115	0.989, 0.0501, 0.0119, 0.0116	1.000, 0.1002, 0.0121, 0.0119
cML-MA-BIC-Profile	1.000, -0.1000, 0.0113, 0.0112	0.995, -0.0499, 0.0114, 0.0113	0.738, -0.0299, 0.0115, 0.0113	0.145, -0.0099, 0.0116, 0.0114	0.051, 0.0001, 0.0116, 0.0115	0.148, 0.0101, 0.0116, 0.0115	0.732, 0.0301, 0.0118, 0.0116	0.989, 0.0501, 0.0119, 0.0117	1.000, 0.1002, 0.0121, 0.012
cML-BIC	1.000, -0.1000, 0.0113, 0.011	0.994, -0.0500, 0.0114, 0.011	0.752, -0.0299, 0.0115, 0.0112	0.161, -0.0099, 0.0116, 0.0113	0.053, 0.0001, 0.0116, 0.0113	0.155, 0.0101, 0.0116, 0.0114	0.744, 0.0301, 0.0117, 0.0114	0.989, 0.0501, 0.0118, 0.0115	1.000, 0.1002, 0.0121, 0.0118
cML-BIC-Profile	1.000, -0.1000, 0.0113, 0.0111	0.994, -0.0500, 0.0114, 0.0112	0.749, -0.0299, 0.0115, 0.0112	0.158, -0.0099, 0.0116, 0.0113	0.052, 0.0001, 0.0116, 0.0114	0.153, 0.0101, 0.0116, 0.0114	0.744, 0.0301, 0.0117, 0.0115	0.989, 0.0501, 0.0118, 0.0116	1.000, 0.1002, 0.0121, 0.0119
MR-Mix	1.000, -0.1019, 0.0128, 0.0168	0.886, -0.0503, 0.0129, 0.0167	0.403, -0.0300, 0.0128, 0.0166	0.042, -0.0102, 0.0128, 0.0166	0.012, -0.0002, 0.0128, 0.0166	0.034, 0.0096, 0.0128, 0.0165	0.391, 0.0291, 0.0128, 0.0165	0.873, 0.0483, 0.0128, 0.0165	1.000, 0.0999, 0.0945, 0.0129, 0.0164
MR-ContMix	1.000, -0.0991, 0.0120, NA	0.985, -0.0494, 0.0121, NA	0.704, -0.0295, 0.0122, NA	0.146, -0.0097, 0.0123, NA	0.052, 0.0003, 0.0124, NA	0.161, 0.0102, 0.0124, NA	0.696, 0.0301, 0.0126, NA	0.983, 0.0500, 0.0128, NA	1.000, 0.0996, 0.0131, NA
MR-Lasso	1.000, -0.0992, 0.0120, 0.0111	0.988, -0.0496, 0.0121, 0.0113	0.730, -0.0297, 0.0122, 0.0113	0.152, -0.0098, 0.0122, 0.0114	0.066, 0.0001, 0.0122, 0.0115	0.162, 0.0101, 0.0122, 0.0115	0.725, 0.0299, 0.0123, 0.0116	0.981, 0.0498, 0.0123, 0.0117	1.000, 0.0995, 0.0128, 0.0119
MR-PRESSO	1.000, -0.0987, 0.0160, 0.0107	0.962, -0.0491, 0.0158, 0.0108	0.713, -0.0293, 0.0158, 0.0109	0.215, -0.0095, 0.0157, 0.011	0.141, 0.0004, 0.0157, 0.011	0.223, 0.0103, 0.0157, 0.0111	0.707, 0.0301, 0.0156, 0.0112	0.965, 0.0499, 0.0155, 0.0112	1.000, 0.0995, 0.0155, 0.0115
MR-IVW	0.152, -0.0955, 0.1052, 0.1044	0.079, -0.0454, 0.1051, 0.1044	0.062, -0.0255, 0.1051, 0.1044	0.057, -0.0055, 0.1051, 0.1044	0.055, 0.0045, 0.1051, 0.1044	0.054, 0.0145, 0.1051, 0.1044	0.067, 0.0345, 0.1051, 0.1044	0.081, 0.0545, 0.1051, 0.1044	0.169, 0.1044, 0.1051, 0.1044
MR-IVW-Oracle	1.000, -0.0994, 0.0111, 0.0113	0.995, -0.0497, 0.0112, 0.0115	0.728, -0.0298, 0.0113, 0.0115	0.133, -0.0099, 0.0114, 0.0116	0.045, 0.0001, 0.0114, 0.0117	0.134, 0.0100, 0.0115, 0.0117	0.710, 0.0299, 0.0116, 0.0118	0.990, 0.0498, 0.0117, 0.0119	1.000, 0.0995, 0.0120, 0.0121
MR-Egger	0.054, -0.0669, 0.5198, 0.5085	0.055, -0.0252, 0.5199, 0.5085	0.056, -0.0086, 0.5199, 0.5085	0.054, 0.0081, 0.5200, 0.5085	0.055, 0.0164, 0.5200, 0.5085	0.054, 0.0248, 0.5200, 0.5085	0.058, 0.0414, 0.5201, 0.5086	0.060, 0.0581, 0.5201, 0.5086	0.062, 0.0997, 0.5202, 0.5086
MR-Weighted-Median	1.000, -0.0950, 0.0144, 0.016	0.847, -0.0470, 0.0147, 0.0162	0.386, -0.0278, 0.0148, 0.0163	0.060, -0.0086, 0.0149, 0.0164	0.031, 0.0009, 0.0149, 0.0164	0.073, 0.0105, 0.0150, 0.0165	0.435, 0.0295, 0.0151, 0.0166	0.839, 0.0486, 0.0153, 0.0167	1.000, 0.0965, 0.0157, 0.0171
MR-Weighted-Mode	0.999, -0.0963, 0.0152, 0.0175	0.799, -0.0481, 0.0154, 0.0177	0.337, -0.0285, 0.0153, 0.0178	0.054, -0.0092, 0.0156, 0.0179	0.022, 0.0008, 0.0158, 0.018	0.064, 0.0107, 0.0159, 0.0181	0.381, 0.0299, 0.0160, 0.0182	0.788, 0.0493, 0.0158, 0.0183	1.000, 0.0981, 0.0162, 0.0188
MR-RAPS1	0.150, -0.0960, 0.1040, 0.1045	0.077, -0.0459, 0.1040, 0.1045	0.061, -0.0259, 0.1040, 0.1045	0.056, -0.0059, 0.1041, 0.1045	0.055, 0.0041, 0.1041, 0.1045	0.057, 0.0142, 0.1041, 0.1045	0.055, 0.0342, 0.1041, 0.1045	0.071, 0.0542, 0.1041, 0.1045	0.167, 0.1042, 0.1041, 0.1045
MR-RAPS2	0.137, -0.0954, 0.1067, 0.1088	0.065, -0.0454, 0.1067, 0.1088	0.057, -0.0253, 0.1067, 0.1088	0.053, -0.0053, 0.1067, 0.1088	0.049, 0.0047, 0.1067, 0.1088	0.051, 0.0147, 0.1068, 0.1088	0.051, 0.0347, 0.1068, 0.1089	0.070, 0.0547, 0.1068, 0.1089	0.157, 0.1048, 0.1068, 0.1089
MR-RAPS3	0.903, -1.6334, 20.9243, 26.1	0.877, -2.7050, 94.0318, 1013	0.871, 0.1730, 21.7599, 39.08	0.883, 0.2818, 10.2006, 10.77	0.886, 265.5101, 8383.5654, 29550000	0.895, -0.8724, 24.3864, 209.2	0.877, 1.3031, 27.4717, 70.51	0.878, -0.2543, 42.4199, 183.8	0.926, 0.7809, 3.4360, 3.107
MR-RAPS4	1.000, 0.6516, 0.7891, 0.0192	1.000, 0.4592, 1.1766, 0.0226	0.987, 0.3194, 1.3089, 0.024	0.931, 0.1129, 1.3928, 0.025	0.929, 0.0299, 1.4239, 0.0259	0.953, -0.0816, 1.4285, 0.026	0.988, -0.2905, 1.4087, 0.0264	0.999, -0.4865, 1.3267, 0.0263	1.000, -0.9263, 0.9757, 0.0265

Table S75: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean(SE( $\hat{\theta}$ )) when  $m = 100$ , the InSIDE satisfied,  $q = 0.4$ , and  $N = 100000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	1.000, -0.0975, 0.0108, 0.0094	0.991, -0.0478, 0.0109, 0.0095	0.798, -0.0280, 0.0109, 0.0095	0.171, -0.0088, 0.0102, 0.0095	0.061, 0.0000, 0.0098, 0.0095	0.163, 0.0089, 0.0102, 0.0096	0.785, 0.0279, 0.0112, 0.0097	0.994, 0.0478, 0.0114, 0.0098	1.000, 0.0974, 0.0117, 0.0101
cML-MA-AIC-Profile	1.000, -0.0978, 0.0109, 0.0094	0.991, -0.0479, 0.0110, 0.0095	0.795, -0.0280, 0.0109, 0.0096	0.169, -0.0088, 0.0102, 0.0095	0.061, 0.0000, 0.0098, 0.0095	0.161, 0.0089, 0.0102, 0.0096	0.783, 0.0280, 0.0113, 0.0098	0.994, 0.0479, 0.0115, 0.0099	1.000, 0.0977, 0.0118, 0.0101
cML-AIC	1.000, -0.0988, 0.0114, 0.0085	0.994, -0.0490, 0.0115, 0.0086	0.864, -0.0291, 0.0115, 0.0086	0.248, -0.0094, 0.0114, 0.0087	0.123, 0.0001, 0.0112, 0.0087	0.261, 0.0095, 0.0114, 0.0087	0.841, 0.0291, 0.0119, 0.0088	0.996, 0.0490, 0.0120, 0.0089	1.000, 0.0987, 0.0123, 0.0091
cML-AIC-Profile	1.000, -0.0990, 0.0115, 0.0085	0.994, -0.0490, 0.0115, 0.0086	0.864, -0.0291, 0.0116, 0.0087	0.247, -0.0094, 0.0114, 0.0087	0.122, 0.0001, 0.0112, 0.0087	0.257, 0.0095, 0.0114, 0.0088	0.840, 0.0291, 0.0120, 0.0088	0.996, 0.0491, 0.0120, 0.0089	1.000, 0.0989, 0.0124, 0.0091
cML-MA-BIC	1.000, -0.0999, 0.0078, 0.0078	1.000, -0.0499, 0.0079, 0.0079	0.961, -0.0299, 0.0080, 0.008	0.216, -0.0099, 0.0080, 0.008	0.059, 0.0001, 0.0081, 0.0081	0.231, 0.0101, 0.0081, 0.0081	0.956, 0.0300, 0.0082, 0.0082	1.000, 0.0500, 0.0083, 0.0082	1.000, 0.1000, 0.0085, 0.0084
cML-MA-BIC-Profile	1.000, -0.0999, 0.0078, 0.0079	1.000, -0.0499, 0.0079, 0.0079	0.961, -0.0299, 0.0080, 0.008	0.215, -0.0099, 0.0080, 0.008	0.058, 0.0001, 0.0081, 0.0081	0.230, 0.0101, 0.0081, 0.0081	0.956, 0.0300, 0.0082, 0.0082	1.000, 0.0500, 0.0083, 0.0082	1.000, 0.1000, 0.0085, 0.0084
cML-BIC	1.000, -0.0999, 0.0078, 0.0078	1.000, -0.0499, 0.0079, 0.0079	0.965, -0.0299, 0.0080, 0.0079	0.226, -0.0099, 0.0080, 0.008	0.061, 0.0001, 0.0081, 0.008	0.237, 0.0101, 0.0081, 0.008	0.961, 0.0301, 0.0082, 0.0081	1.000, 0.0501, 0.0083, 0.0082	1.000, 0.1001, 0.0085, 0.0084
cML-BIC-Profile	1.000, -0.0999, 0.0078, 0.0078	1.000, -0.0499, 0.0079, 0.0079	0.965, -0.0299, 0.0080, 0.0079	0.225, -0.0099, 0.0080, 0.008	0.061, 0.0001, 0.0081, 0.008	0.236, 0.0101, 0.0081, 0.008	0.961, 0.0301, 0.0082, 0.0081	1.000, 0.0501, 0.0083, 0.0082	1.000, 0.1001, 0.0085, 0.0084
MR-Mix	1.000, -0.1014, 0.0102, 0.0131	0.984, -0.0497, 0.0101, 0.013	0.638, -0.0294, 0.0101, 0.013	0.054, -0.0095, 0.0101, 0.013	0.013, 0.0004, 0.0101, 0.013	0.052, 0.0103, 0.0101, 0.013	0.653, 0.0295, 0.0101, 0.013	0.981, 0.0486, 0.0101, 0.013	1.000, 0.0948, 0.0101, 0.0129
MR-ContMix	1.000, -0.0996, 0.0081, NA	1.000, -0.0499, 0.0082, NA	0.951, -0.0299, 0.0082, NA	0.225, -0.0100, 0.0083, NA	0.056, 0.0000, 0.0083, NA	0.218, 0.0099, 0.0083, NA	0.941, 0.0298, 0.0084, NA	1.000, 0.0497, 0.0085, NA	1.000, 0.0996, 0.0087, NA
MR-Lasso	1.000, -0.0996, 0.0081, 0.0079	1.000, -0.0497, 0.0083, 0.008	0.953, -0.0298, 0.0082, 0.008	0.219, -0.0099, 0.0083, 0.0081	0.062, 0.0001, 0.0083, 0.0081	0.236, 0.0100, 0.0083, 0.0082	0.945, 0.0300, 0.0084, 0.0082	1.000, 0.0498, 0.0085, 0.0083	1.000, 0.0996, 0.0087, 0.0085
MR-PRESSO	0.994, -0.0993, 0.0193, 0.0078	0.964, -0.0497, 0.0191, 0.0078	0.865, -0.0299, 0.0190, 0.0079	0.378, -0.0100, 0.0189, 0.0079	0.255, -0.0001, 0.0189, 0.0079	0.381, 0.0099, 0.0188, 0.008	0.872, 0.0297, 0.0188, 0.008	0.962, 0.0495, 0.0187, 0.0081	0.996, 0.0992, 0.0183, 0.0083
MR-IVW	0.173, -0.0974, 0.1075, 0.1046	0.089, -0.0473, 0.1075, 0.1046	0.065, -0.0272, 0.1075, 0.1046	0.054, -0.0072, 0.1075, 0.1046	0.051, 0.0028, 0.1075, 0.1046	0.054, 0.0129, 0.1075, 0.1046	0.065, 0.0329, 0.1075, 0.1046	0.081, 0.0529, 0.1075, 0.1046	0.182, 0.1030, 0.1075, 0.1046
MR-IVW-Oracle	1.000, -0.0995, 0.0078, 0.008	1.000, -0.0497, 0.0079, 0.0081	0.957, -0.0298, 0.0079, 0.0082	0.205, -0.0099, 0.0080, 0.0082	0.054, 0.0001, 0.0080, 0.0082	0.212, 0.0100, 0.0080, 0.0083	0.952, 0.0299, 0.0081, 0.0083	1.000, 0.0499, 0.0082, 0.0084	1.000, 0.0997, 0.0084, 0.0086
MR-Egger	0.058, -0.0666, 0.5538, 0.5323	0.056, -0.0210, 0.5536, 0.5323	0.059, -0.0028, 0.5536, 0.5323	0.060, 0.0154, 0.5535, 0.5323	0.061, 0.0245, 0.5535, 0.5323	0.062, 0.0337, 0.5535, 0.5323	0.062, 0.0519, 0.5534, 0.5323	0.062, 0.0701, 0.5534, 0.5323	0.070, 0.1157, 0.5532, 0.5323
MR-Weighted-Median	1.000, -0.0972, 0.0097, 0.0113	0.996, -0.0485, 0.0098, 0.0114	0.755, -0.0290, 0.0099, 0.0115	0.101, -0.0096, 0.0100, 0.0116	0.022, 0.0001, 0.0100, 0.0116	0.101, 0.0099, 0.0101, 0.0117	0.745, 0.0294, 0.0102, 0.0118	0.991, 0.0489, 0.0103, 0.0119	1.000, 0.0974, 0.0107, 0.0121
MR-Weighted-Mode	1.000, -0.0985, 0.0105, 0.0127	0.985, -0.0492, 0.0105, 0.0128	0.659, -0.0296, 0.0106, 0.0129	0.073, -0.0100, 0.0107, 0.013	0.016, 0.0000, 0.0107, 0.0131	0.063, 0.0098, 0.0108, 0.0131	0.631, 0.0295, 0.0108, 0.0132	0.980, 0.0491, 0.0109, 0.0133	1.000, 0.0982, 0.0113, 0.0136
MR-RAPS1	0.160, -0.0971, 0.1043, 0.1042	0.083, -0.0471, 0.1043, 0.1042	0.063, -0.0271, 0.1043, 0.1042	0.050, -0.0071, 0.1043, 0.1042	0.050, 0.0029, 0.1044, 0.1042	0.048, 0.0129, 0.1044, 0.1042	0.056, 0.0329, 0.1044, 0.1042	0.073, 0.0529, 0.1044, 0.1042	0.168, 0.1029, 0.1044, 0.1042
MR-RAPS2	0.141, -0.0971, 0.1066, 0.1086	0.077, -0.0471, 0.1066, 0.1086	0.059, -0.0271, 0.1067, 0.1086	0.051, -0.0071, 0.1067, 0.1086	0.045, 0.0029, 0.1067, 0.1086	0.045, 0.0129, 0.1067, 0.1086	0.048, 0.0329, 0.1067, 0.1086	0.071, 0.0529, 0.1067, 0.1086	0.158, 0.1029, 0.1067, 0.1086
MR-RAPS3	0.935, 1.0078, 54.5723, 112.8361	0.917, -1.0769, 18.1137, 20.2496	0.904, 0.0886, 16.8509, 35.9937	0.920, -9.5900, 257.8822, 4776.09	0.922, -0.2141, 18.4052, 23.2109	0.908, 1.7566, 98.5441, 434.4651	0.905, -1.6525, 58.2242, 227.5009	0.925, 0.3291, 10.2074, 10.9309	0.950, 0.5993, 7.0298, 4.1958
MR-RAPS4	1.000, 0.7188, 0.7983, 0.0152	1.000, 0.4751, 1.2327, 0.0177	1.000, 0.2858, 1.3645, 0.0185	0.954, 0.0889, 1.4189, 0.0188	0.940, -0.0493, 1.4598, 0.0194	0.957, -0.1988, 1.4411, 0.0193	0.997, -0.3921, 1.3655, 0.0189	1.000, -0.6596, 1.2877, 0.0199	1.000, -0.9944, 0.8920, 0.0188



Table S76: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean( $\text{SE}(\hat{\theta})$ ) when  $m = 100$ , the InSIDE satisfied,  $q = 0.4$ , and  $N = 200000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	1.000, -0.0988, 0.0078, 0.0066	1.000, -0.0489, 0.0079, 0.0067	0.970, -0.0290, 0.0079, 0.0067	0.301, -0.0093, 0.0075, 0.0067	0.068, -0.0003, 0.0071, 0.0067	0.279, 0.0087, 0.0075, 0.0067	0.955, 0.0282, 0.0081, 0.0069	1.000, 0.0482, 0.0081, 0.0069	1.000, 0.0979, 0.0084, 0.0071
cML-MA-AIC-Profile	1.000, -0.0990, 0.0079, 0.0066	1.000, -0.0490, 0.0079, 0.0067	0.970, -0.0290, 0.0079, 0.0067	0.300, -0.0093, 0.0075, 0.0067	0.068, -0.0003, 0.0071, 0.0067	0.278, 0.0087, 0.0075, 0.0068	0.955, 0.0283, 0.0081, 0.0069	1.000, 0.0482, 0.0082, 0.0069	1.000, 0.0981, 0.0084, 0.0071
cML-AIC	1.000, -0.0996, 0.0082, 0.006	1.000, -0.0498, 0.0083, 0.0061	0.982, -0.0298, 0.0085, 0.0061	0.409, -0.0100, 0.0083, 0.0061	0.146, -0.0004, 0.0081, 0.0062	0.379, 0.0092, 0.0083, 0.0062	0.969, 0.0290, 0.0085, 0.0062	1.000, 0.0490, 0.0086, 0.0063	1.000, 0.0988, 0.0088, 0.0064
cML-AIC-Profile	1.000, -0.0997, 0.0082, 0.006	1.000, -0.0498, 0.0083, 0.0061	0.982, -0.0298, 0.0085, 0.0061	0.407, -0.0100, 0.0083, 0.0061	0.146, -0.0004, 0.0081, 0.0062	0.379, 0.0092, 0.0083, 0.0062	0.969, 0.0290, 0.0085, 0.0062	1.000, 0.0490, 0.0086, 0.0063	1.000, 0.0990, 0.0088, 0.0064
cML-MA-BIC	1.000, -0.1000, 0.0054, 0.0055	1.000, -0.0500, 0.0055, 0.0056	1.000, -0.0300, 0.0056, 0.0056	0.406, -0.0100, 0.0056, 0.0057	0.047, 0.0000, 0.0056, 0.0057	0.426, 0.0100, 0.0057, 0.0057	0.999, 0.0300, 0.0057, 0.0058	1.000, 0.0500, 0.0058, 0.0058	1.000, 0.1000, 0.0060, 0.0059
cML-MA-BIC-Profile	1.000, -0.1000, 0.0054, 0.0055	1.000, -0.0500, 0.0056, 0.0056	1.000, -0.0300, 0.0056, 0.0056	0.405, -0.0100, 0.0056, 0.0057	0.047, 0.0000, 0.0056, 0.0057	0.426, 0.0100, 0.0057, 0.0057	0.999, 0.0300, 0.0057, 0.0058	1.000, 0.0500, 0.0058, 0.0058	1.000, 0.1000, 0.0060, 0.0059
cML-BIC	1.000, -0.1000, 0.0054, 0.0055	1.000, -0.0500, 0.0055, 0.0056	0.999, -0.0300, 0.0056, 0.0056	0.413, -0.0100, 0.0056, 0.0056	0.047, 0.0000, 0.0056, 0.0057	0.438, 0.0100, 0.0057, 0.0057	0.999, 0.0300, 0.0057, 0.0057	1.000, 0.0500, 0.0058, 0.0058	1.000, 0.1000, 0.0060, 0.0059
cML-BIC-Profile	1.000, -0.1000, 0.0054, 0.0055	1.000, -0.0500, 0.0055, 0.0056	0.999, -0.0300, 0.0056, 0.0056	0.412, -0.0100, 0.0056, 0.0056	0.047, 0.0000, 0.0056, 0.0057	0.438, 0.0100, 0.0057, 0.0057	0.999, 0.0300, 0.0057, 0.0057	1.000, 0.0500, 0.0058, 0.0058	1.000, 0.1000, 0.0060, 0.0059
MR-Mix	1.000, -0.1016, 0.0076, 0.0103	0.999, -0.0499, 0.0075, 0.0102	0.896, -0.0297, 0.0075, 0.0102	0.147, -0.0097, 0.0075, 0.0102	0.024, 0.0002, 0.0076, 0.0102	0.171, 0.0100, 0.0075, 0.0102	0.870, 0.0294, 0.0075, 0.0101	0.998, 0.0487, 0.0075, 0.0101	1.000, 0.0950, 0.0077, 0.01
MR-ContMix	1.000, -0.0998, 0.0056, NA	1.000, -0.0499, 0.0057, NA	1.000, -0.0299, 0.0057, NA	0.403, -0.0100, 0.0058, NA	0.051, 0.0000, 0.0058, NA	0.427, 0.0100, 0.0058, NA	0.999, 0.0300, 0.0059, NA	1.000, 0.0500, 0.0060, NA	1.000, 0.0999, 0.0061, NA
MR-Lasso	1.000, -0.0997, 0.0057, 0.0056	1.000, -0.0499, 0.0058, 0.0056	0.998, -0.0299, 0.0058, 0.0057	0.402, -0.0100, 0.0059, 0.0057	0.053, 0.0000, 0.0059, 0.0057	0.423, 0.0100, 0.0059, 0.0058	0.996, 0.0299, 0.0060, 0.0058	1.000, 0.0499, 0.0061, 0.0059	1.000, 0.0998, 0.0063, 0.006
MR-PRESSO	0.986, -0.1011, 0.0268, 0.0062	0.946, -0.0514, 0.0268, 0.0063	0.901, -0.0316, 0.0267, 0.0063	0.581, -0.0117, 0.0265, 0.0063	0.417, -0.0017, 0.0265, 0.0064	0.551, 0.0083, 0.0265, 0.0064	0.880, 0.0282, 0.0263, 0.0064	0.940, 0.0481, 0.0261, 0.0064	0.986, 0.0977, 0.0240, 0.0064
MR-IVW	0.178, -0.1085, 0.1047, 0.1045	0.088, -0.0583, 0.1046, 0.1045	0.072, -0.0382, 0.1046, 0.1045	0.062, -0.0181, 0.1046, 0.1045	0.056, -0.0081, 0.1046, 0.1045	0.058, 0.0020, 0.1046, 0.1045	0.060, 0.0220, 0.1046, 0.1045	0.067, 0.0421, 0.1046, 0.1045	0.139, 0.0923, 0.1046, 0.1045
MR-IVW-Oracle	1.000, -0.0998, 0.0054, 0.0057	1.000, -0.0499, 0.0055, 0.0057	0.999, -0.0299, 0.0055, 0.0058	0.392, -0.0100, 0.0056, 0.0058	0.046, 0.0000, 0.0056, 0.0058	0.407, 0.0100, 0.0056, 0.0058	0.998, 0.0300, 0.0057, 0.0059	1.000, 0.0499, 0.0058, 0.0059	1.000, 0.0999, 0.0059, 0.0061
MR-Egger	0.052, -0.1017, 0.5651, 0.5433	0.052, -0.0538, 0.5650, 0.5433	0.049, -0.0346, 0.5650, 0.5432	0.048, -0.0155, 0.5650, 0.5432	0.051, -0.0059, 0.5650, 0.5432	0.051, 0.0036, 0.5650, 0.5432	0.056, 0.0228, 0.5649, 0.5432	0.057, 0.0419, 0.5649, 0.5432	0.060, 0.0897, 0.5649, 0.5432
MR-Weighted-Median	1.000, -0.0988, 0.0069, 0.008	1.000, -0.0495, 0.0070, 0.0081	0.973, -0.0297, 0.0071, 0.0081	0.212, -0.0101, 0.0071, 0.0082	0.020, -0.0002, 0.0072, 0.0082	0.194, 0.0096, 0.0072, 0.0082	0.964, 0.0293, 0.0073, 0.0083	1.000, 0.0490, 0.0073, 0.0084	1.000, 0.0981, 0.0075, 0.0086
MR-Weighted-Mode	1.000, -0.0994, 0.0078, 0.0092	1.000, -0.0499, 0.0078, 0.0093	0.939, -0.0301, 0.0079, 0.0094	0.169, -0.0102, 0.0081, 0.0094	0.018, -0.0003, 0.0081, 0.0095	0.129, 0.0096, 0.0083, 0.0095	0.892, 0.0293, 0.0082, 0.0096	1.000, 0.0494, 0.0083, 0.0096	1.000, 0.0990, 0.0084, 0.0099
MR-RAPS1	0.174, -0.1081, 0.1021, 0.1039	0.090, -0.0580, 0.1021, 0.1039	0.067, -0.0380, 0.1021, 0.1039	0.055, -0.0180, 0.1021, 0.1039	0.054, -0.0080, 0.1021, 0.1039	0.052, 0.0020, 0.1021, 0.1039	0.052, 0.0220, 0.1021, 0.1039	0.059, 0.0420, 0.1021, 0.1039	0.141, 0.0920, 0.1021, 0.104
MR-RAPS2	0.235, -0.1037, 0.0920, 0.0941	0.099, -0.0579, 0.0978, 0.1013	0.068, -0.0379, 0.0994, 0.1031	0.050, -0.0183, 0.0999, 0.1041	0.049, -0.0071, 0.0999, 0.104	0.049, 0.0036, 0.1008, 0.1042	0.054, 0.0226, 0.1020, 0.1036	0.069, 0.0430, 0.1019, 0.1033	0.145, 0.0928, 0.1029, 0.1046
MR-RAPS3	0.959, -11.1622, 305.9594, 4762.2712	0.933, 0.0348, 82.3958, 192.1699	0.943, -1.2186, 27.7718, 38.7595	0.939, 3.9690, 108.9560, 642.0259	0.929, 6.1388, 132.5582, 687.2719	0.924, 0.4160, 18.3534, 16.9941	0.945, -0.0042, 6.3809, 4.2503	0.944, 0.5246, 15.5979, 41.5097	0.956, 0.7122, 3.7180, 1.7861
MR-RAPS4	0.999, 0.9192, 1.2784, 0.033	1.000, 0.6188, 1.4998, 0.021	1.000, 0.3922, 1.6113, 0.019	0.974, 0.0502, 1.6427, 0.017	0.959, -0.0907, 1.6392, 0.0168	0.976, -0.2073, 1.6216, 0.0166	1.000, -0.5334, 1.5125, 0.016	1.000, -0.7904, 1.3714, 0.0158	1.000, -1.0600, 0.8739, 0.0138

Table S77: Main simulations: in each cell, from top to bottom are empirical type-I error/power,  $\text{mean}(\hat{\theta})$ ,  $\text{SD}(\hat{\theta})$ ,  $\text{mean}(\text{SE}(\hat{\theta}))$  when  $m = 100$ , the InSIDE satisfied,  $q = 0.6$ , and  $N = 50000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	0.995, -0.0953, 0.0211, 0.0176	0.698, -0.0458, 0.0212, 0.0177	0.331, -0.0266, 0.0205, 0.0176	0.114, -0.0088, 0.0192, 0.0176	0.068, -0.0004, 0.0190, 0.0176	0.093, 0.0083, 0.0193, 0.0178	0.352, 0.0261, 0.0207, 0.018	0.672, 0.0450, 0.0220, 0.0183	0.983, 0.0941, 0.0229, 0.0188
cML-MA-AIC-Profile	0.994, -0.0956, 0.0213, 0.0177	0.698, -0.0459, 0.0213, 0.0178	0.331, -0.0267, 0.0205, 0.0178	0.113, -0.0088, 0.0193, 0.0177	0.067, -0.0004, 0.0190, 0.0178	0.092, 0.0083, 0.0193, 0.0179	0.345, 0.0262, 0.0207, 0.0181	0.667, 0.0451, 0.0220, 0.0184	0.983, 0.0945, 0.0230, 0.0189
cML-AIC	0.999, -0.0979, 0.0225, 0.0157	0.786, -0.0481, 0.0223, 0.0159	0.431, -0.0286, 0.0223, 0.016	0.197, -0.0095, 0.0218, 0.016	0.139, -0.0003, 0.0218, 0.0161	0.163, 0.0092, 0.0220, 0.0162	0.460, 0.0282, 0.0228, 0.0163	0.740, 0.0478, 0.0234, 0.0164	0.994, 0.0972, 0.0236, 0.0167
cML-AIC-Profile	0.999, -0.0980, 0.0226, 0.0159	0.783, -0.0482, 0.0226, 0.016	0.427, -0.0286, 0.0223, 0.0161	0.194, -0.0095, 0.0218, 0.0162	0.137, -0.0003, 0.0218, 0.0162	0.163, 0.0092, 0.0220, 0.0163	0.453, 0.0282, 0.0228, 0.0164	0.739, 0.0478, 0.0235, 0.0165	0.994, 0.0974, 0.0238, 0.0168
cML-MA-BIC	1.000, -0.1003, 0.0151, 0.0146	0.924, -0.0504, 0.0153, 0.0148	0.524, -0.0304, 0.0154, 0.0148	0.112, -0.0104, 0.0154, 0.0149	0.059, -0.0005, 0.0155, 0.015	0.112, 0.0095, 0.0155, 0.015	0.506, 0.0294, 0.0157, 0.0151	0.892, 0.0494, 0.0158, 0.0152	1.000, 0.0993, 0.0162, 0.0155
cML-MA-BIC-Profile	1.000, -0.1003, 0.0151, 0.0147	0.923, -0.0504, 0.0153, 0.0148	0.521, -0.0304, 0.0154, 0.0149	0.111, -0.0104, 0.0154, 0.015	0.059, -0.0005, 0.0155, 0.015	0.109, 0.0095, 0.0155, 0.0151	0.504, 0.0294, 0.0157, 0.0152	0.891, 0.0494, 0.0158, 0.0153	1.000, 0.0994, 0.0162, 0.0156
cML-BIC	1.000, -0.1004, 0.0151, 0.0145	0.928, -0.0504, 0.0153, 0.0146	0.533, -0.0304, 0.0154, 0.0147	0.119, -0.0105, 0.0155, 0.0148	0.063, -0.0005, 0.0156, 0.0148	0.118, 0.0095, 0.0156, 0.0148	0.518, 0.0295, 0.0157, 0.015	0.895, 0.0495, 0.0158, 0.0151	1.000, 0.0994, 0.0162, 0.0154
cML-BIC-Profile	1.000, -0.1004, 0.0151, 0.0145	0.928, -0.0504, 0.0153, 0.0147	0.529, -0.0304, 0.0154, 0.0147	0.117, -0.0105, 0.0155, 0.0148	0.063, -0.0005, 0.0156, 0.0149	0.118, 0.0095, 0.0156, 0.0149	0.516, 0.0295, 0.0157, 0.015	0.895, 0.0495, 0.0158, 0.0151	1.000, 0.0994, 0.0162, 0.0154
MR-Mix	1.000, -0.0950, 0.0151, 0.0171	0.803, -0.0473, 0.0149, 0.017	0.334, -0.0284, 0.0149, 0.017	0.054, -0.0095, 0.0148, 0.017	0.033, -0.0003, 0.0149, 0.017	0.050, 0.0087, 0.0148, 0.017	0.312, 0.0268, 0.0149, 0.017	0.758, 0.0445, 0.0151, 0.017	0.997, 0.0883, 0.0151, 0.017
MR-ContMix	1.000, -0.0996, 0.0157, NA	0.917, -0.0501, 0.0158, NA	0.508, -0.0304, 0.0158, NA	0.108, -0.0105, 0.0159, NA	0.058, -0.0006, 0.0160, NA	0.105, 0.0094, 0.0160, NA	0.484, 0.0292, 0.0162, NA	0.881, 0.0491, 0.0163, NA	0.999, 0.0987, 0.0167, NA
MR-Lasso	1.000, -0.0995, 0.0155, 0.0148	0.915, -0.0502, 0.0161, 0.0149	0.521, -0.0302, 0.0161, 0.015	0.118, -0.0103, 0.0162, 0.0151	0.067, -0.0004, 0.0163, 0.0151	0.122, 0.0095, 0.0164, 0.0152	0.506, 0.0293, 0.0164, 0.0153	0.876, 0.0491, 0.0165, 0.0154	0.999, 0.0989, 0.0172, 0.0157
MR-PRESSO	0.991, -0.1010, 0.0241, 0.0141	0.879, -0.0517, 0.0241, 0.0143	0.556, -0.0319, 0.0241, 0.0143	0.243, -0.0121, 0.0241, 0.0144	0.166, -0.0022, 0.0242, 0.0145	0.207, 0.0077, 0.0241, 0.0145	0.511, 0.0274, 0.0239, 0.0146	0.819, 0.0472, 0.0239, 0.0147	0.980, 0.0967, 0.0236, 0.015
MR-IVW	0.160, -0.1092, 0.1371, 0.1276	0.102, -0.0591, 0.1371, 0.1276	0.091, -0.0391, 0.1371, 0.1276	0.079, -0.0191, 0.1371, 0.1276	0.077, -0.0091, 0.1371, 0.1276	0.071, 0.0009, 0.1371, 0.1276	0.073, 0.0209, 0.1371, 0.1276	0.076, 0.0409, 0.1371, 0.1276	0.123, 0.0909, 0.1370, 0.1276
MR-IVW-Oracle	1.000, -0.0996, 0.0150, 0.015	0.914, -0.0500, 0.0151, 0.0151	0.500, -0.0301, 0.0152, 0.0152	0.103, -0.0103, 0.0153, 0.0153	0.053, -0.0004, 0.0154, 0.0154	0.105, 0.0095, 0.0154, 0.0154	0.485, 0.0294, 0.0155, 0.0155	0.881, 0.0492, 0.0156, 0.0156	0.999, 0.0988, 0.0160, 0.0159
MR-Egger	0.056, -0.0827, 0.6337, 0.6235	0.047, -0.0409, 0.6338, 0.6235	0.049, -0.0242, 0.6338, 0.6235	0.050, -0.0074, 0.6338, 0.6235	0.049, 0.0009, 0.6338, 0.6235	0.050, 0.0093, 0.6339, 0.6235	0.051, 0.0260, 0.6339, 0.6235	0.051, 0.0427, 0.6339, 0.6235	0.056, 0.0845, 0.6340, 0.6236
MR-Weighted-Median	0.994, -0.0936, 0.0203, 0.0208	0.624, -0.0471, 0.0205, 0.021	0.260, -0.0285, 0.0205, 0.0211	0.064, -0.0100, 0.0207, 0.0212	0.052, -0.0008, 0.0208, 0.0213	0.071, 0.0084, 0.0209, 0.0213	0.247, 0.0270, 0.0211, 0.0215	0.558, 0.0455, 0.0214, 0.0216	0.982, 0.0917, 0.0223, 0.0221
MR-Weighted-Mode	1.000, -0.0966, 0.0179, 0.0176	0.787, -0.0488, 0.0180, 0.0178	0.383, -0.0295, 0.0177, 0.0179	0.097, -0.0106, 0.0181, 0.018	0.058, -0.0011, 0.0183, 0.018	0.086, 0.0084, 0.0184, 0.0181	0.345, 0.0278, 0.0188, 0.0182	0.732, 0.0469, 0.0189, 0.0183	0.999, 0.0948, 0.0195, 0.0188
MR-RAPS1	0.158, -0.1095, 0.1323, 0.1278	0.095, -0.0595, 0.1323, 0.1278	0.079, -0.0395, 0.1323, 0.1278	0.068, -0.0195, 0.1323, 0.1278	0.064, -0.0095, 0.1323, 0.1278	0.060, 0.0005, 0.1323, 0.1278	0.063, 0.0205, 0.1323, 0.1278	0.064, 0.0405, 0.1323, 0.1278	0.106, 0.0905, 0.1323, 0.1278
MR-RAPS2	0.154, -0.1105, 0.1474, 0.1398	0.099, -0.0608, 0.1484, 0.1397	0.085, -0.0405, 0.1474, 0.1398	0.072, -0.0205, 0.1474, 0.1398	0.071, -0.0105, 0.1474, 0.1398	0.067, -0.0005, 0.1474, 0.1398	0.071, 0.0195, 0.1474, 0.1398	0.067, 0.0395, 0.1474, 0.1398	0.100, 0.0894, 0.1474, 0.1398
MR-RAPS3	0.910, -2.1143, 57.5230, 66.8294	0.886, -0.7317, 115.9904, 275.8253	0.863, -3.6738, 90.3998, 184.4749	0.854, -2.4649, 190.1472, 847.3009	0.865, -2.1861, 60.2495, 85.8505	0.867, -2.4260, 127.6301, 441.303	0.890, 0.9557, 55.5136, 75.8285	0.885, 7.6228, 250.1111, 1644.7824	0.923, -0.8295, 70.4745, 140.3801
MR-RAPS4	1.000, 0.6525, 1.2628, 0.0287	1.000, 0.4226, 1.4593, 0.0302	1.000, 0.3563, 2.0883, 0.0538	1.000, 0.1760, 1.5444, 0.0312	0.997, 0.1625, 1.5643, 0.0316	0.998, 0.1393, 1.5965, 0.0326	0.999, 0.0387, 1.5797, 0.0309	1.000, -0.0182, 1.4614, 0.028	1.000, -0.2419, 1.3946, 0.0285

Table S78: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean(SE( $\hat{\theta}$ )) when  $m = 100$ , the InSIDE satisfied,  $q = 0.6$ , and  $N = 100000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	1.000, -0.0966, 1.460e- 02, 0.0124	0.923, -0.0467, 1.470e- 02, 0.0126	0.562, -0.0270, 1.430e- 02, 0.0126	0.109, -0.0084, 1.330e- 02, 0.0125	0.072, 0.0003, 1.310e- 02, 0.0125	0.135, 0.0089, 1.360e- 02, 0.0126	0.550, 0.0274, 1.490e- 02, 0.0128	0.910, 0.0471, 1.550e- 02, 0.013	1.000, 0.0969, 1.600e- 02, 0.0133
cML-MA-AIC-Profile	1.000, -0.0968, 1.470e- 02, 0.0125	0.922, -0.0467, 1.470e- 02, 0.0126	0.560, -0.0270, 1.440e- 02, 0.0126	0.107, -0.0084, 1.330e- 02, 0.0125	0.071, 0.0003, 1.310e- 02, 0.0125	0.131, 0.0089, 1.360e- 02, 0.0126	0.548, 0.0274, 1.490e- 02, 0.0128	0.909, 0.0471, 1.560e- 02, 0.013	1.000, 0.0971, 1.610e- 02, 0.0133
cML-AIC	1.000, -0.0985, 1.520e- 02, 0.0111	0.958, -0.0484, 1.510e- 02, 0.0112	0.655, -0.0285, 1.510e- 02, 0.0113	0.203, -0.0088, 1.490e- 02, 0.0114	0.135, 0.0005, 1.480e- 02, 0.0114	0.219, 0.0098, 1.500e- 02, 0.0114	0.656, 0.0292, 1.580e- 02, 0.0115	0.945, 0.0491, 1.610e- 02, 0.0116	1.000, 0.0989, 1.680e- 02, 0.0119
cML-AIC-Profile	1.000, -0.0986, 1.520e- 02, 0.0112	0.958, -0.0485, 1.510e- 02, 0.0113	0.653, -0.0285, 1.510e- 02, 0.0113	0.200, -0.0088, 1.490e- 02, 0.0114	0.131, 0.0005, 1.480e- 02, 0.0114	0.216, 0.0098, 1.500e- 02, 0.0115	0.655, 0.0292, 1.580e- 02, 0.0116	0.945, 0.0492, 1.620e- 02, 0.0116	1.000, 0.0991, 1.680e- 02, 0.0119
cML-MA-BIC	1.000, -0.1000, 1.030e- 02, 0.0103	0.999, -0.0500, 1.050e- 02, 0.0104	0.803, -0.0300, 1.050e- 02, 0.0105	0.162, -0.0100, 1.060e- 02, 0.0105	0.042, -0.0001, 1.060e- 02, 0.0106	0.167, 0.0099, 1.070e- 02, 0.0106	0.798, 0.0299, 1.080e- 02, 0.0107	0.996, 0.0499, 1.090e- 02, 0.0107	1.000, 0.0999, 1.120e- 02, 0.011
cML-MA-BIC-Profile	1.000, -0.1000, 1.030e- 02, 0.0103	0.999, -0.0500, 1.050e- 02, 0.0104	0.801, -0.0300, 1.050e- 02, 0.0105	0.161, -0.0100, 1.060e- 02, 0.0105	0.042, -0.0001, 1.060e- 02, 0.0106	0.165, 0.0099, 1.070e- 02, 0.0106	0.797, 0.0299, 1.080e- 02, 0.0107	0.996, 0.0499, 1.090e- 02, 0.0108	1.000, 0.0999, 1.120e- 02, 0.011
cML-BIC	1.000, -0.1001, 1.030e- 02, 0.0102	0.999, -0.0500, 1.040e- 02, 0.0103	0.806, -0.0300, 1.050e- 02, 0.0104	0.167, -0.0101, 1.060e- 02, 0.0104	0.043, -0.0001, 1.060e- 02, 0.0105	0.176, 0.0100, 1.070e- 02, 0.0105	0.806, 0.0299, 1.080e- 02, 0.0106	0.996, 0.0499, 1.090e- 02, 0.0107	1.000, 0.0999, 1.120e- 02, 0.0109
cML-BIC-Profile	1.000, -0.1001, 1.030e- 02, 0.0102	0.999, -0.0500, 1.040e- 02, 0.0103	0.804, -0.0300, 1.050e- 02, 0.0104	0.167, -0.0101, 1.060e- 02, 0.0105	0.043, -0.0001, 1.060e- 02, 0.0105	0.176, 0.0100, 1.070e- 02, 0.0105	0.804, 0.0299, 1.080e- 02, 0.0106	0.996, 0.0499, 1.090e- 02, 0.0107	1.000, 0.0999, 1.120e- 02, 0.0109
MR-Mix	1.000, -0.0950, 1.060e- 02, 0.0131	0.970, -0.0468, 1.070e- 02, 0.013	0.580, -0.0281, 1.080e- 02, 0.0129	0.066, -0.0095, 1.090e- 02, 0.0129	0.008, -0.0001, 1.090e- 02, 0.0129	0.053, 0.0090, 1.080e- 02, 0.0129	0.544, 0.0271, 1.070e- 02, 0.0129	0.968, 0.0451, 1.070e- 02, 0.0129	1.000, 0.0890, 1.100e- 02, 0.0129
MR-ContMix	1.000, -0.0995, 1.070e- 02, NA	0.997, -0.0498, 1.090e- 02, NA	0.803, -0.0299, 1.090e- 02, NA	0.160, -0.0100, 1.090e- 02, NA	0.054, 0.0000, 1.100e- 02, NA	0.172, 0.0099, 1.100e- 02, NA	0.782, 0.0298, 1.120e- 02, NA	0.994, 0.0497, 1.130e- 02, NA	1.000, 0.0995, 1.160e- 02, NA
MR-Lasso	1.000, -0.0996, 1.080e- 02, 0.0105	0.996, -0.0499, 1.100e- 02, 0.0106	0.791, -0.0299, 1.090e- 02, 0.0106	0.167, -0.0100, 1.110e- 02, 0.0107	0.048, 0.0000, 1.120e- 02, 0.0107	0.170, 0.0099, 1.130e- 02, 0.0108	0.791, 0.0298, 1.140e- 02, 0.0108	0.992, 0.0498, 1.150e- 02, 0.0109	1.000, 0.0996, 1.160e- 02, 0.0111
MR-PRESSO	0.977, -0.0997, 3.090e- 02, 0.0107	0.917, -0.0500, 3.060e- 02, 0.0107	0.711, -0.0301, 3.040e- 02, 0.0108	0.347, -0.0103, 3.030e- 02, 0.0108	0.294, -0.0003, 3.030e- 02, 0.0108	0.355, 0.0096, 3.020e- 02, 0.0109	0.734, 0.0295, 3.010e- 02, 0.0109	0.908, 0.0497, 2.700e- 02, 0.0109	0.980, 0.0992, 2.650e- 02, 0.0111
MR-IVW	0.139, -0.1001, 1.356e- 01, 0.1277	0.083, -0.0499, 1.356e- 01, 0.1277	0.071, -0.0298, 1.356e- 01, 0.1277	0.069, -0.0097, 1.356e- 01, 0.1277	0.067, 0.0003, 1.356e- 01, 0.1277	0.068, 0.0104, 1.356e- 01, 0.1277	0.069, 0.0305, 1.356e- 01, 0.1277	0.084, 0.0505, 1.356e- 01, 0.1277	0.135, 0.1007, 1.355e- 01, 0.1277
MR-IVW-Oracle	1.000, -0.0997, 1.020e- 02, 0.0106	0.999, -0.0499, 1.030e- 02, 0.0107	0.786, -0.0299, 1.040e- 02, 0.0108	0.150, -0.0100, 1.050e- 02, 0.0108	0.033, -0.0001, 1.050e- 02, 0.0109	0.147, 0.0099, 1.060e- 02, 0.0109	0.783, 0.0298, 1.070e- 02, 0.011	0.995, 0.0497, 1.080e- 02, 0.0111	1.000, 0.0995, 1.100e- 02, 0.0113
MR-Egger	0.058, -0.0848, 6.559e- 01, 0.6496	0.057, -0.0391, 6.559e- 01, 0.6496	0.059, -0.0208, 6.560e- 01, 0.6496	0.060, -0.0025, 6.560e- 01, 0.6496	0.063, 0.0066, 6.561e- 01, 0.6496	0.062, 0.0158, 6.561e- 01, 0.6496	0.062, 0.0340, 6.561e- 01, 0.6496	0.063, 0.0523, 6.561e- 01, 0.6496	0.066, 0.0979, 6.562e- 01, 0.6496
MR-Weighted-Median	1.000, -0.0955, 1.440e- 02, 0.0147	0.898, -0.0476, 1.460e- 02, 0.0148	0.471, -0.0285, 1.470e- 02, 0.0149	0.088, -0.0093, 1.470e- 02, 0.015	0.038, 0.0003, 1.480e- 02, 0.015	0.097, 0.0098, 1.490e- 02, 0.0151	0.466, 0.0288, 1.510e- 02, 0.0152	0.872, 0.0479, 1.520e- 02, 0.0153	1.000, 0.0955, 1.590e- 02, 0.0156
MR-Weighted-Mode	1.000, -0.0974, 1.320e- 02, 0.0127	0.950, -0.0487, 1.350e- 02, 0.0128	0.641, -0.0294, 1.370e- 02, 0.0129	0.125, -0.0098, 1.370e- 02, 0.013	0.062, -0.0001, 1.380e- 02, 0.013	0.131, 0.0096, 1.380e- 02, 0.013	0.570, 0.0290, 1.380e- 02, 0.0131	0.944, 0.0484, 1.410e- 02, 0.0132	1.000, 0.0965, 1.440e- 02, 0.0135
MR-RAPS1	0.130, -0.1009, 1.324e- 01, 0.1274	0.086, -0.0509, 1.324e- 01, 0.1274	0.069, -0.0309, 1.324e- 01, 0.1274	0.063, -0.0109, 1.324e- 01, 0.1274	0.060, -0.0009, 1.324e- 01, 0.1274	0.059, 0.0091, 1.324e- 01, 0.1274	0.064, 0.0291, 1.324e- 01, 0.1274	0.081, 0.0491, 1.324e- 01, 0.1274	0.135, 0.0991, 1.324e- 01, 0.1274
MR-RAPS2	0.122, -0.1012, 1.477e- 01, 0.1394	0.088, -0.0512, 1.476e- 01, 0.1394	0.072, -0.0312, 1.476e- 01, 0.1394	0.070, -0.0112, 1.476e- 01, 0.1394	0.062, -0.0012, 1.476e- 01, 0.1394	0.062, 0.0088, 1.476e- 01, 0.1394	0.067, 0.0288, 1.476e- 01, 0.1394	0.085, 0.0488, 1.476e- 01, 0.1394	0.125, 0.0988, 1.476e- 01, 0.1394
MR-RAPS3	0.941, 503.2040, 1.594e+04, 3919000	0.920, 6.3746, 1.885e+02, 570.8	0.894, -11.3066, 2.174e+02, 725.9	0.923, -2.3240, 5.227e+01, 46.58	0.920, 2.8694, 8.390e+01, 134.1	0.911, -22.8691, 5.550e+02, 5556	0.921, 2.4172, 9.464e+01, 154.3	0.919, 1.5489, 6.579e+01, 74.78	0.932, 7.4360, 1.186e+02, 254.6
MR-RAPS4	1.000, 0.8504, 1.058e+00, 0.0197	1.000, 0.6833, 1.392e+00, 0.0228	1.000, 0.5158, 1.604e+00, 0.0256	0.997, 0.2713, 1.657e+00, 0.0255	0.997, 0.1822, 1.785e+00, 0.0285	0.999, 0.0994, 1.724e+00, 0.0274	1.000, -0.1098, 1.712e+00, 0.0282	1.000, -0.2692, 1.694e+00, 0.0317	1.000, -0.5520, 1.520e+00, 0.027

Table S79: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean( $\text{SE}(\hat{\theta})$ ) when  $m = 100$ , the InSIDE satisfied,  $q = 0.6$ , and  $N = 200000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	1.000, -0.0968, 0.0105, 0.0088	0.986, -0.0470, 0.0107, 0.0089	0.813, -0.0270, 0.0105, 0.009	0.175, -0.0080, 0.0097, 0.0089	0.061, 0.0007, 0.0094, 0.0088	0.201, 0.0093, 0.0099, 0.0089	0.848, 0.0284, 0.0108, 0.0091	0.995, 0.0482, 0.0110, 0.0092	1.000, 0.0980, 0.0113, 0.0094
cML-MA-AIC-Profile	1.000, -0.0970, 0.0106, 0.0089	0.986, -0.0470, 0.0107, 0.009	0.812, -0.0270, 0.0105, 0.009	0.173, -0.0080, 0.0097, 0.0089	0.060, 0.0007, 0.0094, 0.0089	0.197, 0.0093, 0.0099, 0.0089	0.847, 0.0284, 0.0108, 0.0091	0.993, 0.0483, 0.0111, 0.0092	1.000, 0.0982, 0.0113, 0.0094
cML-AIC	1.000, -0.0981, 0.0112, 0.0079	0.994, -0.0483, 0.0115, 0.008	0.881, -0.0283, 0.0114, 0.008	0.266, -0.0087, 0.0109, 0.008	0.135, 0.0007, 0.0108, 0.0081	0.285, 0.0101, 0.0110, 0.0081	0.895, 0.0297, 0.0114, 0.0081	0.995, 0.0495, 0.0115, 0.0082	1.000, 0.0994, 0.0117, 0.0084
cML-AIC-Profile	1.000, -0.0982, 0.0112, 0.0079	0.994, -0.0483, 0.0115, 0.008	0.880, -0.0283, 0.0114, 0.008	0.266, -0.0087, 0.0109, 0.0081	0.133, 0.0007, 0.0108, 0.0081	0.285, 0.0101, 0.0110, 0.0081	0.893, 0.0297, 0.0114, 0.0082	0.995, 0.0496, 0.0115, 0.0082	1.000, 0.0995, 0.0118, 0.0084
cML-MA-BIC	1.000, -0.0997, 0.0072, 0.0073	1.000, -0.0496, 0.0073, 0.0073	0.983, -0.0296, 0.0073, 0.0074	0.260, -0.0096, 0.0074, 0.0074	0.044, 0.0003, 0.0074, 0.0074	0.300, 0.0103, 0.0074, 0.0075	0.987, 0.0303, 0.0075, 0.0075	1.000, 0.0503, 0.0075, 0.0076	1.000, 0.1003, 0.0077, 0.0077
cML-MA-BIC-Profile	1.000, -0.0997, 0.0072, 0.0073	1.000, -0.0496, 0.0073, 0.0074	0.983, -0.0296, 0.0073, 0.0074	0.260, -0.0096, 0.0074, 0.0074	0.044, 0.0003, 0.0074, 0.0075	0.296, 0.0103, 0.0074, 0.0075	0.986, 0.0303, 0.0075, 0.0075	1.000, 0.0503, 0.0075, 0.0076	1.000, 0.1003, 0.0077, 0.0078
cML-BIC	1.000, -0.0997, 0.0072, 0.0072	1.000, -0.0497, 0.0073, 0.0073	0.985, -0.0297, 0.0073, 0.0073	0.270, -0.0097, 0.0074, 0.0074	0.045, 0.0003, 0.0074, 0.0074	0.297, 0.0103, 0.0074, 0.0074	0.985, 0.0303, 0.0075, 0.0075	1.000, 0.0503, 0.0075, 0.0075	1.000, 0.1003, 0.0077, 0.0077
cML-BIC-Profile	1.000, -0.0997, 0.0072, 0.0072	1.000, -0.0497, 0.0073, 0.0073	0.985, -0.0297, 0.0073, 0.0073	0.270, -0.0097, 0.0074, 0.0074	0.044, 0.0003, 0.0074, 0.0074	0.294, 0.0103, 0.0074, 0.0074	0.985, 0.0303, 0.0075, 0.0075	1.000, 0.0503, 0.0075, 0.0075	1.000, 0.1003, 0.0077, 0.0077
MR-Mix	1.000, -0.0946, 0.0081, 0.0099	0.999, -0.0466, 0.0079, 0.0099	0.883, -0.0276, 0.0078, 0.0099	0.170, -0.0089, 0.0080, 0.0098	0.035, 0.0002, 0.0081, 0.0098	0.183, 0.0094, 0.0081, 0.0098	0.886, 0.0277, 0.0078, 0.0098	0.999, 0.0456, 0.0079, 0.0098	1.000, 0.0895, 0.0080, 0.0098
MR-ContMix	1.000, -0.0994, 0.0074, NA	1.000, -0.0495, 0.0074, NA	0.981, -0.0296, 0.0075, NA	0.260, -0.0096, 0.0075, NA	0.053, 0.0004, 0.0075, NA	0.294, 0.0103, 0.0075, NA	0.985, 0.0303, 0.0076, NA	1.000, 0.0503, 0.0077, NA	1.000, 0.1002, 0.0079, NA
MR-Lasso	1.000, -0.0995, 0.0077, 0.0074	1.000, -0.0496, 0.0077, 0.0075	0.973, -0.0295, 0.0078, 0.0075	0.258, -0.0095, 0.0078, 0.0076	0.055, 0.0005, 0.0078, 0.0076	0.290, 0.0105, 0.0078, 0.0076	0.973, 0.0304, 0.0079, 0.0077	1.000, 0.0503, 0.0080, 0.0077	1.000, 0.1003, 0.0082, 0.0079
MR-PRESSO	0.964, -0.0976, 0.0587, 0.0107	0.902, -0.0485, 0.0568, 0.0105	0.822, -0.0286, 0.0568, 0.0106	0.490, -0.0088, 0.0578, 0.0106	0.391, 0.0008, 0.0578, 0.0107	0.518, 0.0108, 0.0578, 0.0107	0.839, 0.0310, 0.0567, 0.0106	0.894, 0.0508, 0.0557, 0.0105	0.971, 0.1007, 0.0554, 0.0106
MR-IVW	0.129, -0.0973, 0.1332, 0.1278	0.084, -0.0470, 0.1332, 0.1278	0.074, -0.0269, 0.1332, 0.1278	0.065, -0.0068, 0.1332, 0.1278	0.065, 0.0033, 0.1332, 0.1278	0.060, 0.0133, 0.1332, 0.1278	0.065, 0.0335, 0.1332, 0.1278	0.071, 0.0536, 0.1332, 0.1278	0.138, 0.1038, 0.1332, 0.1278
MR-IVW-Oracle	1.000, -0.0995, 0.0072, 0.0075	1.000, -0.0496, 0.0072, 0.0076	0.982, -0.0296, 0.0073, 0.0076	0.242, -0.0097, 0.0073, 0.0077	0.039, 0.0003, 0.0073, 0.0077	0.275, 0.0103, 0.0074, 0.0077	0.980, 0.0303, 0.0074, 0.0078	1.000, 0.0502, 0.0075, 0.0078	1.000, 0.1002, 0.0076, 0.008
MR-Egger	0.060, -0.1015, 0.6714, 0.6652	0.053, -0.0536, 0.6713, 0.6652	0.053, -0.0344, 0.6713, 0.6652	0.051, -0.0152, 0.6712, 0.6652	0.052, -0.0057, 0.6712, 0.6652	0.052, 0.0039, 0.6712, 0.6652	0.052, 0.0231, 0.6712, 0.6652	0.056, 0.0422, 0.6712, 0.6652	0.054, 0.0901, 0.6711, 0.6652
MR-Weighted-Median	1.000, -0.0966, 0.0103, 0.0104	0.992, -0.0480, 0.0104, 0.0105	0.774, -0.0285, 0.0105, 0.0106	0.144, -0.0091, 0.0106, 0.0106	0.050, 0.0006, 0.0106, 0.0106	0.155, 0.0103, 0.0107, 0.0107	0.796, 0.0296, 0.0108, 0.0107	0.991, 0.0490, 0.0109, 0.0108	1.000, 0.0974, 0.0112, 0.0111
MR-Weighted-Mode	1.000, -0.0979, 0.0104, 0.0097	0.997, -0.0489, 0.0102, 0.0097	0.838, -0.0290, 0.0104, 0.0098	0.175, -0.0093, 0.0104, 0.0098	0.063, 0.0004, 0.0107, 0.0099	0.204, 0.0104, 0.0107, 0.0099	0.839, 0.0298, 0.0108, 0.0099	0.996, 0.0491, 0.0107, 0.01	1.000, 0.0984, 0.0108, 0.0101
MR-RAPS1	0.130, -0.0970, 0.1289, 0.1272	0.072, -0.0470, 0.1289, 0.1272	0.062, -0.0270, 0.1289, 0.1272	0.054, -0.0070, 0.1289, 0.1272	0.051, 0.0030, 0.1289, 0.1272	0.051, 0.0130, 0.1289, 0.1272	0.062, 0.0330, 0.1289, 0.1272	0.072, 0.0530, 0.1289, 0.1272	0.132, 0.1030, 0.1289, 0.1273
MR-RAPS2	0.135, -0.0858, 0.1858, 0.1382	0.081, -0.0419, 0.1756, 0.1387	0.073, -0.0247, 0.1617, 0.1389	0.060, -0.0068, 0.1438, 0.1392	0.057, 0.0033, 0.1438, 0.1391	0.059, 0.0126, 0.1457, 0.1389	0.069, 0.0332, 0.1439, 0.1393	0.078, 0.0525, 0.1518, 0.1388	0.122, 0.1032, 0.1439, 0.1393
MR-RAPS3	0.954, 12.3642, 306.2539, 912.4	0.946, 6.7734, 240.0308, 678.1	0.929, -0.4972, 82.9198, 80.98	0.934, -10.9033, 354.2821, 1499	0.942, -2.8934, 155.7400, 268.9	0.944, -5.2507, 189.0625, 494.7	0.933, 0.3578, 133.3709, 224.1	0.931, 316.9602, 9703.3823, 1083000	0.963, 2.2182, 52.7535, 43.62
MR-RAPS4	1.000, 0.8989, 1.1818, 0.0167	1.000, 0.6943, 1.4533, 0.0177	1.000, 0.4703, 1.6982, 0.0205	1.000, 0.3016, 1.8434, 0.0239	0.999, 0.0379, 1.9194, 0.026	0.999, -0.0888, 1.9151, 0.0256	1.000, -0.3865, 1.9576, 0.0297	1.000, -0.6355, 1.9502, 0.0329	1.000, -1.0642, 1.6312, 0.0331

Table S80: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean( $SE(\hat{\theta})$ ) when  $m = 100$ , the InSIDE violated,  $q = 0.2$ , and  $N = 50000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	1.000, -0.0969, 0.0132, 0.0105	0.972, -0.0472, 0.0133, 0.0107	0.673, -0.0274, 0.0133, 0.0107	0.168, -0.0083, 0.0125, 0.0107	0.091, 0.0006, 0.0123, 0.0107	0.189, 0.0096, 0.0126, 0.0108	0.691, 0.0287, 0.0136, 0.011	0.969, 0.0485, 0.0139, 0.0111	1.000, 0.0982, 0.0141, 0.0114
cML-MA-AIC-Profile	1.000, -0.0974, 0.0133, 0.0106	0.971, -0.0474, 0.0134, 0.0107	0.672, -0.0274, 0.0133, 0.0108	0.165, -0.0083, 0.0125, 0.0107	0.090, 0.0006, 0.0123, 0.0108	0.183, 0.0096, 0.0126, 0.0108	0.689, 0.0287, 0.0137, 0.011	0.969, 0.0487, 0.0139, 0.0112	1.000, 0.0987, 0.0143, 0.0115
cML-AIC	1.000, -0.0982, 0.0139, 0.0096	0.984, -0.0485, 0.0139, 0.0097	0.744, -0.0285, 0.0138, 0.0098	0.247, -0.0087, 0.0138, 0.0099	0.156, 0.0008, 0.0138, 0.0099	0.268, 0.0102, 0.0140, 0.01	0.763, 0.0299, 0.0145, 0.0101	0.980, 0.0499, 0.0145, 0.0101	1.000, 0.0998, 0.0147, 0.0104
cML-AIC-Profile	1.000, -0.0985, 0.0139, 0.0097	0.984, -0.0486, 0.0140, 0.0098	0.743, -0.0285, 0.0140, 0.0099	0.243, -0.0087, 0.0138, 0.0099	0.152, 0.0008, 0.0138, 0.01	0.264, 0.0102, 0.0140, 0.01	0.759, 0.0299, 0.0144, 0.0101	0.980, 0.0499, 0.0145, 0.0102	1.000, 0.1001, 0.0149, 0.0105
cML-MA-BIC	1.000, -0.0998, 0.0090, 0.0089	1.000, -0.0498, 0.0091, 0.009	0.901, -0.0298, 0.0092, 0.0091	0.191, -0.0098, 0.0093, 0.0091	0.055, 0.0002, 0.0093, 0.0092	0.200, 0.0102, 0.0093, 0.0092	0.893, 0.0302, 0.0094, 0.0093	1.000, 0.0502, 0.0095, 0.0094	1.000, 0.1003, 0.0098, 0.0097
cML-MA-BIC-Profile	1.000, -0.0998, 0.0091, 0.0089	1.000, -0.0498, 0.0091, 0.0091	0.901, -0.0298, 0.0092, 0.0091	0.191, -0.0098, 0.0093, 0.0092	0.055, 0.0002, 0.0093, 0.0092	0.199, 0.0102, 0.0093, 0.0093	0.890, 0.0302, 0.0094, 0.0093	1.000, 0.0502, 0.0095, 0.0094	1.000, 0.1003, 0.0098, 0.0097
cML-BIC	1.000, -0.0999, 0.0091, 0.0088	1.000, -0.0499, 0.0092, 0.0089	0.906, -0.0298, 0.0092, 0.009	0.196, -0.0098, 0.0093, 0.0091	0.061, 0.0002, 0.0093, 0.0091	0.203, 0.0102, 0.0094, 0.0092	0.897, 0.0302, 0.0094, 0.0092	1.000, 0.0503, 0.0095, 0.0093	1.000, 0.1003, 0.0098, 0.0096
cML-BIC-Profile	1.000, -0.0999, 0.0091, 0.0089	1.000, -0.0499, 0.0092, 0.009	0.903, -0.0298, 0.0092, 0.009	0.193, -0.0098, 0.0093, 0.0091	0.059, 0.0002, 0.0093, 0.0091	0.203, 0.0102, 0.0094, 0.0092	0.897, 0.0302, 0.0094, 0.0093	1.000, 0.0503, 0.0095, 0.0094	1.000, 0.1003, 0.0098, 0.0096
MR-Mix	0.999, -0.1108, 0.0132, 0.0196	0.884, -0.0548, 0.0130, 0.0194	0.392, -0.0327, 0.0131, 0.0194	0.030, -0.0111, 0.0130, 0.0193	0.004, -0.0004, 0.0130, 0.0193	0.023, 0.0103, 0.0131, 0.0193	0.330, 0.0311, 0.0131, 0.0192	0.853, 0.0517, 0.0132, 0.0192	1.000, 0.1012, 0.0133, 0.0191
MR-ContMix	1.000, -0.0990, 0.0094, NA	1.000, -0.0494, 0.0095, NA	0.882, -0.0296, 0.0096, NA	0.197, -0.0097, 0.0096, NA	0.055, 0.0003, 0.0097, NA	0.188, 0.0102, 0.0097, NA	0.864, 0.0301, 0.0098, NA	0.999, 0.0499, 0.0099, NA	1.000, 0.0996, 0.0103, NA
MR-Lasso	1.000, -0.0990, 0.0094, 0.0089	1.000, -0.0493, 0.0095, 0.009	0.883, -0.0295, 0.0096, 0.0091	0.195, -0.0096, 0.0097, 0.0092	0.068, 0.0004, 0.0097, 0.0092	0.221, 0.0103, 0.0098, 0.0092	0.888, 0.0302, 0.0098, 0.0093	1.000, 0.0500, 0.0099, 0.0094	1.000, 0.0998, 0.0103, 0.0096
MR-PRESSO	1.000, -0.0966, 0.0121, 0.0086	0.982, -0.0471, 0.0120, 0.0087	0.834, -0.0273, 0.0120, 0.0087	0.214, -0.0075, 0.0120, 0.0088	0.138, 0.0024, 0.0119, 0.0088	0.310, 0.0124, 0.0119, 0.0089	0.895, 0.0322, 0.0119, 0.009	0.999, 0.0520, 0.0118, 0.009	1.000, 0.1014, 0.0118, 0.0093
MR-IVW	0.168, -0.0692, 0.0809, 0.0749	0.084, -0.0193, 0.0809, 0.0749	0.078, 0.0006, 0.0809, 0.0749	0.091, 0.0205, 0.0809, 0.0749	0.100, 0.0305, 0.0809, 0.0749	0.101, 0.0405, 0.0809, 0.0749	0.143, 0.0604, 0.0809, 0.0749	0.208, 0.0804, 0.0809, 0.0749	0.420, 0.1302, 0.0809, 0.0749
MR-IVW-Oracle	1.000, -0.0992, 0.0089, 0.009	1.000, -0.0495, 0.0090, 0.0092	0.901, -0.0296, 0.0091, 0.0092	0.184, -0.0098, 0.0091, 0.0093	0.053, 0.0002, 0.0092, 0.0093	0.192, 0.0101, 0.0092, 0.0094	0.886, 0.0300, 0.0093, 0.0095	1.000, 0.0499, 0.0094, 0.0095	1.000, 0.0995, 0.0097, 0.0098
MR-Egger	0.349, 0.3253, 0.4658, 0.2819	0.366, 0.3702, 0.4660, 0.282	0.380, 0.3882, 0.4660, 0.282	0.382, 0.4061, 0.4661, 0.2821	0.385, 0.4151, 0.4661, 0.2821	0.392, 0.4241, 0.4661, 0.2821	0.409, 0.4420, 0.4662, 0.2822	0.422, 0.4599, 0.4663, 0.2822	0.456, 0.5047, 0.4664, 0.2823
MR-Weighted-Median	1.000, -0.0980, 0.0118, 0.0129	0.980, -0.0496, 0.0119, 0.013	0.636, -0.0303, 0.0120, 0.0131	0.120, -0.0111, 0.0121, 0.0132	0.031, -0.0014, 0.0122, 0.0133	0.076, 0.0082, 0.0123, 0.0133	0.539, 0.0275, 0.0124, 0.0134	0.937, 0.0468, 0.0126, 0.0136	1.000, 0.0950, 0.0130, 0.0139
MR-Weighted-Mode	0.939, -0.0972, 0.0308, 0.048	0.506, -0.0486, 0.0301, 0.0483	0.183, -0.0296, 0.0296, 0.0484	0.021, -0.0097, 0.0296, 0.0487	0.006, -0.0004, 0.0287, 0.0488	0.019, 0.0096, 0.0288, 0.0489	0.174, 0.0290, 0.0295, 0.0491	0.512, 0.0492, 0.0289, 0.0493	0.923, 0.0966, 0.0298, 0.0501
MR-RAPS1	0.171, -0.0698, 0.0789, 0.0747	0.086, -0.0198, 0.0789, 0.0747	0.069, 0.0003, 0.0789, 0.0747	0.074, 0.0203, 0.0789, 0.0747	0.085, 0.0303, 0.0789, 0.0747	0.097, 0.0403, 0.0789, 0.0747	0.142, 0.0603, 0.0789, 0.0747	0.205, 0.0803, 0.0789, 0.0748	0.419, 0.1304, 0.0790, 0.0748
MR-RAPS2	1.000, 0.0184, 0.7491, 0.0125	1.000, 0.0428, 0.7641, 0.0125	0.962, 0.0682, 0.7370, 0.0122	0.653, 0.1387, 1.1355, 0.0133	0.559, 0.1015, 1.3704, 0.0126	0.640, 0.1526, 0.7543, 0.0125	0.967, 0.1430, 0.8293, 0.0134	1.000, 0.2281, 0.7863, 0.0131	1.000, 0.2073, 1.9485, 0.0145
MR-RAPS3	0.887, -0.1942, 0.2254, 0.0248	0.853, -0.0490, 0.2245, 0.0238	0.846, 0.0058, 0.2200, 0.0232	0.847, 0.0577, 0.2139, 0.0227	0.857, 0.0825, 0.2104, 0.0224	0.869, 0.1066, 0.2067, 0.0221	0.875, 0.1522, 0.1989, 0.0215	0.911, 0.1947, 0.1908, 0.0209	0.959, 0.2884, 0.1712, 0.0196
MR-RAPS4	1.000, 0.0747, 0.9888, 0.0155	1.000, 0.0707, 0.9559, 0.0147	0.975, 0.1220, 0.8988, 0.0141	0.753, 0.1447, 0.9533, 0.015	0.675, 0.1786, 0.8948, 0.0141	0.737, 0.1954, 0.9082, 0.0143	0.985, 0.2146, 0.9771, 0.0159	1.000, 0.2529, 0.9886, 0.0155	1.000, 0.3087, 1.0549, 0.0161

Table S81: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean( $SE(\hat{\theta})$ ) when  $m = 100$ , the InSIDE violated,  $q = 0.2$ , and  $N = 100000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	1.000, -0.0980, 0.0090, 0.0074	1.000, -0.0483, 0.0092, 0.0075	0.925, -0.0284, 0.0093, 0.0076	0.252, -0.0089, 0.0088, 0.0076	0.083, 0.0001, 0.0085, 0.0076	0.248, 0.0092, 0.0089, 0.0076	0.916, 0.0287, 0.0095, 0.0078	0.998, 0.0485, 0.0097, 0.0079	1.000, 0.0982, 0.0099, 0.0081
cML-MA-AIC-Profile	1.000, -0.0984, 0.0091, 0.0075	1.000, -0.0484, 0.0092, 0.0076	0.925, -0.0284, 0.0093, 0.0076	0.248, -0.0089, 0.0088, 0.0076	0.081, 0.0001, 0.0085, 0.0076	0.248, 0.0092, 0.0089, 0.0077	0.916, 0.0287, 0.0096, 0.0078	0.998, 0.0486, 0.0097, 0.0079	1.000, 0.0985, 0.0100, 0.0081
cML-AIC	1.000, -0.0990, 0.0095, 0.0068	1.000, -0.0492, 0.0096, 0.0069	0.940, -0.0293, 0.0097, 0.0069	0.333, -0.0094, 0.0096, 0.007	0.144, 0.0002, 0.0095, 0.007	0.332, 0.0098, 0.0097, 0.007	0.932, 0.0295, 0.0100, 0.0071	0.999, 0.0495, 0.0101, 0.0072	1.000, 0.0992, 0.0103, 0.0074
cML-AIC-Profile	1.000, -0.0992, 0.0095, 0.0068	1.000, -0.0492, 0.0096, 0.0069	0.940, -0.0293, 0.0097, 0.007	0.330, -0.0094, 0.0096, 0.007	0.142, 0.0002, 0.0095, 0.007	0.331, 0.0098, 0.0097, 0.0071	0.932, 0.0296, 0.0101, 0.0071	0.999, 0.0495, 0.0101, 0.0072	1.000, 0.0994, 0.0104, 0.0074
cML-MA-BIC	1.000, -0.0998, 0.0063, 0.0063	1.000, -0.0498, 0.0064, 0.0064	0.995, -0.0298, 0.0064, 0.0064	0.335, -0.0098, 0.0065, 0.0065	0.048, 0.0002, 0.0065, 0.0065	0.335, 0.0102, 0.0065, 0.0065	0.992, 0.0302, 0.0066, 0.0066	1.000, 0.0501, 0.0067, 0.0066	1.000, 0.1001, 0.0069, 0.0068
cML-MA-BIC-Profile	1.000, -0.0998, 0.0064, 0.0063	1.000, -0.0498, 0.0064, 0.0064	0.995, -0.0298, 0.0064, 0.0064	0.333, -0.0098, 0.0065, 0.0065	0.048, 0.0002, 0.0065, 0.0065	0.334, 0.0102, 0.0065, 0.0065	0.992, 0.0302, 0.0066, 0.0066	1.000, 0.0501, 0.0067, 0.0067	1.000, 0.1001, 0.0069, 0.0068
cML-BIC	1.000, -0.0998, 0.0063, 0.0062	1.000, -0.0498, 0.0064, 0.0063	0.995, -0.0298, 0.0064, 0.0064	0.347, -0.0098, 0.0065, 0.0064	0.053, 0.0002, 0.0065, 0.0064	0.340, 0.0102, 0.0065, 0.0065	0.993, 0.0302, 0.0066, 0.0065	1.000, 0.0502, 0.0067, 0.0066	1.000, 0.1002, 0.0069, 0.0068
cML-BIC-Profile	1.000, -0.0998, 0.0063, 0.0062	1.000, -0.0498, 0.0064, 0.0063	0.995, -0.0298, 0.0064, 0.0064	0.344, -0.0098, 0.0065, 0.0064	0.052, 0.0002, 0.0065, 0.0065	0.338, 0.0102, 0.0065, 0.0065	0.993, 0.0302, 0.0066, 0.0065	1.000, 0.0502, 0.0067, 0.0066	1.000, 0.1002, 0.0069, 0.0068
MR-Mix	0.999, -0.1102, 0.0102, 0.0155	0.981, -0.0539, 0.0099, 0.0153	0.578, -0.0320, 0.0098, 0.0153	0.037, -0.0102, 0.0099, 0.0152	0.006, 0.0004, 0.0100, 0.0152	0.048, 0.0111, 0.0100, 0.0152	0.614, 0.0320, 0.0100, 0.0152	0.967, 0.0527, 0.0100, 0.0151	1.000, 0.1021, 0.0102, 0.015
MR-ContMix	1.000, -0.0995, 0.0065, NA	1.000, -0.0497, 0.0066, NA	0.992, -0.0297, 0.0066, NA	0.336, -0.0098, 0.0066, NA	0.054, 0.0002, 0.0067, NA	0.324, 0.0101, 0.0067, NA	0.993, 0.0300, 0.0067, NA	1.000, 0.0500, 0.0068, NA	1.000, 0.0998, 0.0070, NA
MR-Lasso	1.000, -0.0994, 0.0065, 0.0063	1.000, -0.0496, 0.0066, 0.0064	0.992, -0.0296, 0.0066, 0.0064	0.337, -0.0097, 0.0067, 0.0065	0.057, 0.0003, 0.0068, 0.0065	0.341, 0.0102, 0.0068, 0.0065	0.991, 0.0301, 0.0069, 0.0066	1.000, 0.0500, 0.0069, 0.0067	1.000, 0.0998, 0.0071, 0.0068
MR-PRESSO	0.997, -0.0952, 0.0142, 0.0062	0.964, -0.0456, 0.0139, 0.0062	0.891, -0.0258, 0.0137, 0.0063	0.385, -0.0060, 0.0136, 0.0063	0.249, 0.0039, 0.0135, 0.0063	0.507, 0.0138, 0.0134, 0.0064	0.964, 0.0336, 0.0133, 0.0064	0.998, 0.0534, 0.0132, 0.0065	1.000, 0.1030, 0.0129, 0.0066
MR-IVW	0.171, -0.0677, 0.0826, 0.075	0.096, -0.0177, 0.0826, 0.0749	0.081, 0.0023, 0.0826, 0.0749	0.086, 0.0223, 0.0826, 0.0749	0.093, 0.0323, 0.0827, 0.0749	0.103, 0.0423, 0.0827, 0.0749	0.157, 0.0623, 0.0827, 0.0749	0.217, 0.0823, 0.0827, 0.0749	0.437, 0.1322, 0.0827, 0.0749
MR-IVW-Oracle	1.000, -0.0994, 0.0062, 0.0064	1.000, -0.0496, 0.0063, 0.0065	0.995, -0.0297, 0.0064, 0.0065	0.317, -0.0098, 0.0064, 0.0066	0.046, 0.0002, 0.0065, 0.0066	0.317, 0.0101, 0.0065, 0.0066	0.993, 0.0300, 0.0066, 0.0067	1.000, 0.0500, 0.0066, 0.0068	1.000, 0.0998, 0.0068, 0.0069
MR-Egger	0.340, 0.3448, 0.4780, 0.29	0.374, 0.3922, 0.4780, 0.29	0.387, 0.4112, 0.4780, 0.29	0.406, 0.4301, 0.4780, 0.2901	0.411, 0.4396, 0.4780, 0.2901	0.412, 0.4491, 0.4780, 0.2901	0.432, 0.4680, 0.4780, 0.2901	0.445, 0.4869, 0.4780, 0.2901	0.479, 0.5342, 0.4780, 0.2902
MR-Weighted-Median	1.000, -0.0991, 0.0080, 0.0091	1.000, -0.0501, 0.0081, 0.0092	0.930, -0.0305, 0.0082, 0.0093	0.198, -0.0110, 0.0083, 0.0094	0.034, -0.0012, 0.0084, 0.0094	0.119, 0.0086, 0.0085, 0.0094	0.866, 0.0282, 0.0086, 0.0095	1.000, 0.0478, 0.0087, 0.0096	1.000, 0.0965, 0.0091, 0.0099
MR-Weighted-Mode	0.961, -0.0958, 0.0654, 0.0386	0.794, -0.0462, 0.0656, 0.0388	0.360, -0.0267, 0.0656, 0.039	0.026, -0.0074, 0.0657, 0.0391	0.010, 0.0020, 0.0655, 0.0392	0.042, 0.0119, 0.0655, 0.0393	0.370, 0.0316, 0.0656, 0.0394	0.783, 0.0516, 0.0655, 0.0396	0.958, 0.1010, 0.0657, 0.0401
MR-RAPS1	0.169, -0.0680, 0.0797, 0.0745	0.084, -0.0180, 0.0797, 0.0745	0.072, 0.0020, 0.0798, 0.0745	0.079, 0.0220, 0.0798, 0.0745	0.088, 0.0320, 0.0798, 0.0745	0.107, 0.0420, 0.0798, 0.0745	0.153, 0.0620, 0.0798, 0.0745	0.217, 0.0820, 0.0798, 0.0745	0.435, 0.1320, 0.0798, 0.0745
MR-RAPS2	1.000, 0.0870, 1.7760, 0.01	1.000, 0.0671, 1.1320, 0.0085	0.999, 0.0293, 0.7147, 0.0084	0.735, -0.0223, 2.7815, 0.009	0.590, 0.1094, 1.3610, 0.0086	0.746, 0.0895, 0.7111, 0.0084	0.999, 0.1275, 0.7095, 0.0087	1.000, 0.1287, 0.7081, 0.0086	1.000, 0.3490, 3.3538, 0.0108
MR-RAPS3	0.929, -0.1908, 0.2315, 0.0177	0.905, -0.0452, 0.2294, 0.017	0.902, 0.0097, 0.2241, 0.0166	0.908, 0.0619, 0.2173, 0.0162	0.899, 0.0868, 0.2134, 0.016	0.894, 0.1110, 0.2094, 0.0157	0.910, 0.1568, 0.2011, 0.0153	0.947, 0.1994, 0.1928, 0.0149	0.969, 0.2930, 0.1732, 0.0139
MR-RAPS4	1.000, 0.0490, 0.9184, 0.0102	1.000, 0.0622, 0.8915, 0.0099	0.999, 0.0779, 0.8715, 0.0097	0.858, 0.0940, 0.8595, 0.0096	0.786, 0.0861, 0.8717, 0.0097	0.870, 0.1029, 0.8807, 0.0097	0.999, 0.1307, 0.8970, 0.0098	1.000, 0.1300, 0.9079, 0.0099	1.000, 0.0845, 0.9769, 0.0106

Table S82: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean( $SE(\hat{\theta})$ ) when  $m = 100$ , the InSIDE violated,  $q = 0.2$ , and  $N = 200000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	1.000, -0.0988, 0.0063, 0.0053	1.000, -0.0489, 0.0065, 0.0053	0.996, -0.0289, 0.0066, 0.0054	0.398, -0.0091, 0.0064, 0.0054	0.084, 0.0000, 0.0060, 0.0053	0.417, 0.0092, 0.0065, 0.0054	0.991, 0.0290, 0.0068, 0.0055	1.000, 0.0490, 0.0069, 0.0056	1.000, 0.0987, 0.0070, 0.0057
cML-MA-AIC-Profile	1.000, -0.0990, 0.0064, 0.0053	1.000, -0.0490, 0.0065, 0.0053	0.996, -0.0289, 0.0066, 0.0054	0.398, -0.0091, 0.0064, 0.0054	0.084, 0.0000, 0.0060, 0.0053	0.417, 0.0092, 0.0065, 0.0054	0.991, 0.0290, 0.0068, 0.0055	1.000, 0.0490, 0.0069, 0.0056	1.000, 0.0990, 0.0071, 0.0057
cML-AIC	1.000, -0.0995, 0.0066, 0.0048	1.000, -0.0495, 0.0067, 0.0049	0.997, -0.0295, 0.0069, 0.0049	0.480, -0.0095, 0.0068, 0.0049	0.147, 0.0001, 0.0067, 0.005	0.506, 0.0097, 0.0069, 0.005	0.992, 0.0296, 0.0071, 0.005	1.000, 0.0496, 0.0071, 0.0051	1.000, 0.0995, 0.0074, 0.0052
cML-AIC-Profile	1.000, -0.0996, 0.0066, 0.0048	1.000, -0.0495, 0.0068, 0.0049	0.997, -0.0295, 0.0069, 0.0049	0.479, -0.0096, 0.0068, 0.0049	0.146, 0.0001, 0.0066, 0.005	0.506, 0.0097, 0.0069, 0.005	0.992, 0.0296, 0.0071, 0.005	1.000, 0.0496, 0.0071, 0.0051	1.000, 0.0996, 0.0074, 0.0052
cML-MA-BIC	1.000, -0.0999, 0.0043, 0.0044	1.000, -0.0499, 0.0044, 0.0045	1.000, -0.0299, 0.0044, 0.0045	0.579, -0.0099, 0.0045, 0.0046	0.049, 0.0001, 0.0045, 0.0046	0.595, 0.0101, 0.0045, 0.0046	1.000, 0.0301, 0.0046, 0.0046	1.000, 0.0501, 0.0046, 0.0047	1.000, 0.1001, 0.0048, 0.0048
cML-MA-BIC-Profile	1.000, -0.0999, 0.0043, 0.0044	1.000, -0.0499, 0.0044, 0.0045	1.000, -0.0299, 0.0045, 0.0046	0.578, -0.0099, 0.0045, 0.0046	0.049, 0.0001, 0.0045, 0.0046	0.590, 0.0101, 0.0045, 0.0046	1.000, 0.0301, 0.0046, 0.0046	1.000, 0.0501, 0.0046, 0.0047	1.000, 0.1001, 0.0048, 0.0048
cML-BIC	1.000, -0.0999, 0.0043, 0.0044	1.000, -0.0499, 0.0044, 0.0045	1.000, -0.0299, 0.0045, 0.0045	0.582, -0.0099, 0.0045, 0.0045	0.055, 0.0001, 0.0045, 0.0045	0.597, 0.0101, 0.0046, 0.0046	1.000, 0.0301, 0.0046, 0.0046	1.000, 0.0501, 0.0047, 0.0047	1.000, 0.1001, 0.0048, 0.0048
cML-BIC-Profile	1.000, -0.0999, 0.0043, 0.0044	1.000, -0.0499, 0.0044, 0.0045	1.000, -0.0299, 0.0045, 0.0045	0.582, -0.0099, 0.0045, 0.0045	0.055, 0.0001, 0.0045, 0.0046	0.597, 0.0101, 0.0046, 0.0046	1.000, 0.0301, 0.0046, 0.0046	1.000, 0.0501, 0.0047, 0.0047	1.000, 0.1001, 0.0048, 0.0048
MR-Mix	0.999, -0.1104, 0.0080, 0.012	0.994, -0.0543, 0.0080, 0.0119	0.847, -0.0322, 0.0079, 0.0118	0.064, -0.0105, 0.0080, 0.0118	0.011, 0.0002, 0.0080, 0.0119	0.087, 0.0107, 0.0080, 0.0119	0.819, 0.0315, 0.0080, 0.0119	0.991, 0.0520, 0.0080, 0.0118	0.999, 0.1017, 0.0081, 0.0118
MR-ContMix	1.000, -0.0997, 0.0044, NA	1.000, -0.0498, 0.0045, NA	1.000, -0.0299, 0.0045, NA	0.564, -0.0099, 0.0046, NA	0.057, 0.0001, 0.0046, NA	0.596, 0.0101, 0.0046, NA	1.000, 0.0300, 0.0047, NA	1.000, 0.0500, 0.0047, NA	1.000, 0.0999, 0.0049, NA
MR-Lasso	1.000, -0.0997, 0.0045, 0.0044	1.000, -0.0497, 0.0046, 0.0045	1.000, -0.0298, 0.0046, 0.0046	0.565, -0.0099, 0.0046, 0.0046	0.055, 0.0001, 0.0046, 0.0046	0.593, 0.0101, 0.0047, 0.0046	1.000, 0.0301, 0.0047, 0.0047	1.000, 0.0500, 0.0048, 0.0047	1.000, 0.0999, 0.0049, 0.0048
MR-PRESSO	0.994, -0.0950, 0.0178, 0.0047	0.956, -0.0455, 0.0158, 0.0047	0.889, -0.0256, 0.0158, 0.0047	0.601, -0.0057, 0.0157, 0.0047	0.354, 0.0042, 0.0155, 0.0047	0.691, 0.0142, 0.0155, 0.0047	0.969, 0.0340, 0.0154, 0.0047	0.991, 0.0539, 0.0152, 0.0048	1.000, 0.1036, 0.0148, 0.0049
MR-IVW	0.208, -0.0778, 0.0783, 0.0748	0.082, -0.0277, 0.0783, 0.0748	0.062, -0.0076, 0.0783, 0.0748	0.062, 0.0124, 0.0783, 0.0748	0.074, 0.0224, 0.0783, 0.0748	0.088, 0.0324, 0.0783, 0.0748	0.117, 0.0525, 0.0783, 0.0748	0.183, 0.0725, 0.0784, 0.0748	0.368, 0.1226, 0.0784, 0.0748
MR-IVW-Oracle	1.000, -0.0997, 0.0043, 0.0045	1.000, -0.0498, 0.0044, 0.0046	1.000, -0.0298, 0.0045, 0.0046	0.563, -0.0099, 0.0045, 0.0047	0.045, 0.0001, 0.0045, 0.0047	0.584, 0.0101, 0.0045, 0.0047	1.000, 0.0301, 0.0046, 0.0047	1.000, 0.0500, 0.0046, 0.0048	1.000, 0.0999, 0.0048, 0.0049
MR-Egger	0.344, 0.3366, 0.4740, 0.2926	0.383, 0.3854, 0.4739, 0.2926	0.398, 0.4049, 0.4739, 0.2927	0.406, 0.4244, 0.4739, 0.2927	0.406, 0.4341, 0.4739, 0.2927	0.417, 0.4438, 0.4739, 0.2927	0.424, 0.4633, 0.4738, 0.2927	0.437, 0.4828, 0.4738, 0.2927	0.476, 0.5314, 0.4738, 0.2927
MR-Weighted-Median	1.000, -0.0999, 0.0058, 0.0064	1.000, -0.0504, 0.0058, 0.0065	0.999, -0.0306, 0.0058, 0.0066	0.353, -0.0108, 0.0058, 0.0066	0.031, -0.0010, 0.0058, 0.0066	0.244, 0.0089, 0.0059, 0.0067	0.994, 0.0287, 0.0059, 0.0067	1.000, 0.0484, 0.0060, 0.0068	1.000, 0.0977, 0.0062, 0.007
MR-Weighted-Mode	0.967, -0.1036, 0.1158, 0.0315	0.906, -0.0536, 0.1161, 0.0316	0.625, -0.0338, 0.1162, 0.0316	0.061, -0.0140, 0.1163, 0.0317	0.002, -0.0042, 0.1163, 0.0317	0.064, 0.0062, 0.1165, 0.0317	0.632, 0.0262, 0.1169, 0.0317	0.913, 0.0458, 0.1169, 0.0317	0.971, 0.0962, 0.1173, 0.032
MR-RAPS1	0.195, -0.0781, 0.0762, 0.0742	0.085, -0.0280, 0.0762, 0.0742	0.058, -0.0080, 0.0762, 0.0742	0.063, 0.0120, 0.0762, 0.0742	0.066, 0.0220, 0.0762, 0.0742	0.079, 0.0320, 0.0763, 0.0742	0.119, 0.0520, 0.0763, 0.0742	0.173, 0.0720, 0.0763, 0.0742	0.378, 0.1220, 0.0763, 0.0742
MR-RAPS2	1.000, -0.0155, 0.0781, 0.0054	1.000, -0.0329, 2.2290, 0.0061	1.000, -0.0271, 0.5893, 0.0054	0.853, 0.0669, 0.9552, 0.0056	0.609, 0.0317, 0.5726, 0.0053	0.857, 0.0631, 0.9608, 0.0061	1.000, 0.0686, 0.5920, 0.0055	1.000, 0.0717, 1.4411, 0.0062	1.000, 0.1832, 2.2115, 0.0063
MR-RAPS3	0.957, -0.2170, 0.2136, 0.0123	0.925, -0.0715, 0.2171, 0.0118	0.933, -0.0162, 0.2136, 0.0116	0.922, 0.0366, 0.2084, 0.0113	0.921, 0.0619, 0.2052, 0.0112	0.934, 0.0864, 0.2018, 0.011	0.923, 0.1331, 0.1943, 0.0107	0.943, 0.1767, 0.1865, 0.0105	0.974, 0.2728, 0.1672, 0.0098
MR-RAPS4	1.000, -0.0865, 0.8985, 0.0071	1.000, -0.0529, 0.8316, 0.0065	1.000, -0.0219, 0.7790, 0.0063	0.946, 0.0228, 0.7810, 0.0063	0.837, 0.0387, 0.7647, 0.0062	0.941, 0.0464, 0.7928, 0.0063	1.000, 0.0730, 0.8056, 0.0064	1.000, 0.1114, 0.8503, 0.0066	1.000, 0.0825, 0.9615, 0.0083

Table S83: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean( $SE(\hat{\theta})$ ) when  $m = 100$ , the InSIDE violated,  $q = 0.4$ , and  $N = 50000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	1.000, -0.0970, 0.0166, 0.0133	0.879, -0.0474, 0.0167, 0.0135	0.531, -0.0278, 0.0164, 0.0135	0.142, -0.0092, 0.0155, 0.0135	0.085, -0.0003, 0.0152, 0.0135	0.132, 0.0085, 0.0155, 0.0136	0.493, 0.0271, 0.0167, 0.0138	0.848, 0.0466, 0.0172, 0.0141	0.998, 0.0961, 0.0179, 0.0144
cML-MA-AIC-Profile	1.000, -0.0975, 0.0167, 0.0136	0.879, -0.0475, 0.0168, 0.0136	0.527, -0.0279, 0.0165, 0.0136	0.141, -0.0092, 0.0155, 0.0136	0.083, -0.0003, 0.0152, 0.0136	0.130, 0.0085, 0.0155, 0.0137	0.486, 0.0271, 0.0167, 0.0139	0.847, 0.0467, 0.0173, 0.0142	0.998, 0.0965, 0.0180, 0.0145
cML-AIC	1.000, -0.0988, 0.0172, 0.0121	0.923, -0.0492, 0.0175, 0.0122	0.612, -0.0293, 0.0172, 0.0123	0.222, -0.0099, 0.0172, 0.0124	0.156, -0.0004, 0.0172, 0.0124	0.212, 0.0090, 0.0173, 0.0125	0.591, 0.0284, 0.0178, 0.0126	0.908, 0.0483, 0.0181, 0.0127	0.999, 0.0980, 0.0186, 0.013
cML-AIC-Profile	1.000, -0.0991, 0.0174, 0.0122	0.921, -0.0492, 0.0175, 0.0123	0.609, -0.0294, 0.0176, 0.0124	0.221, -0.0099, 0.0172, 0.0125	0.155, -0.0004, 0.0172, 0.0125	0.208, 0.0090, 0.0173, 0.0126	0.590, 0.0284, 0.0178, 0.0127	0.907, 0.0484, 0.0182, 0.0128	0.999, 0.0981, 0.0187, 0.0131
cML-MA-BIC	1.000, -0.1005, 0.0113, 0.0112	0.992, -0.0504, 0.0114, 0.0113	0.772, -0.0304, 0.0114, 0.0114	0.150, -0.0104, 0.0115, 0.0115	0.049, -0.0004, 0.0115, 0.0115	0.125, 0.0096, 0.0115, 0.0115	0.732, 0.0296, 0.0116, 0.0116	0.989, 0.0496, 0.0117, 0.0117	1.000, 0.0996, 0.0120, 0.012
cML-MA-BIC-Profile	1.000, -0.1005, 0.0113, 0.0112	0.991, -0.0504, 0.0114, 0.0114	0.771, -0.0304, 0.0114, 0.0114	0.148, -0.0104, 0.0115, 0.0115	0.048, -0.0004, 0.0115, 0.0115	0.122, 0.0096, 0.0115, 0.0116	0.731, 0.0296, 0.0116, 0.0117	0.989, 0.0496, 0.0117, 0.0118	1.000, 0.0996, 0.0120, 0.0121
cML-BIC	1.000, -0.1005, 0.0113, 0.0111	0.990, -0.0505, 0.0114, 0.0112	0.777, -0.0304, 0.0114, 0.0113	0.156, -0.0104, 0.0115, 0.0114	0.053, -0.0004, 0.0115, 0.0114	0.135, 0.0096, 0.0115, 0.0114	0.735, 0.0296, 0.0116, 0.0115	0.990, 0.0496, 0.0117, 0.0116	1.000, 0.0997, 0.0120, 0.0119
cML-BIC-Profile	1.000, -0.1005, 0.0113, 0.0111	0.990, -0.0505, 0.0114, 0.0113	0.776, -0.0304, 0.0114, 0.0113	0.156, -0.0104, 0.0115, 0.0114	0.049, -0.0004, 0.0115, 0.0114	0.132, 0.0096, 0.0115, 0.0115	0.731, 0.0296, 0.0116, 0.0116	0.989, 0.0496, 0.0117, 0.0117	1.000, 0.0997, 0.0120, 0.012
MR-Mix	1.000, -0.1025, 0.0132, 0.017	0.894, -0.0509, 0.0131, 0.0169	0.393, -0.0306, 0.0131, 0.0168	0.041, -0.0106, 0.0131, 0.0168	0.019, -0.0006, 0.0132, 0.0168	0.040, 0.0092, 0.0132, 0.0167	0.352, 0.0286, 0.0131, 0.0167	0.830, 0.0476, 0.0132, 0.0167	1.000, 0.0940, 0.0130, 0.0166
MR-ContMix	1.000, -0.0997, 0.0116, NA	0.993, -0.0501, 0.0117, NA	0.755, -0.0302, 0.0117, NA	0.151, -0.0104, 0.0118, NA	0.054, -0.0004, 0.0118, NA	0.133, 0.0095, 0.0118, NA	0.717, 0.0294, 0.0119, NA	0.986, 0.0492, 0.0120, NA	1.000, 0.0989, 0.0123, NA
MR-Lasso	1.000, -0.0997, 0.0118, 0.0112	0.990, -0.0500, 0.0119, 0.0114	0.752, -0.0302, 0.0119, 0.0114	0.161, -0.0104, 0.0119, 0.0115	0.060, -0.0005, 0.0120, 0.0116	0.137, 0.0095, 0.0121, 0.0116	0.722, 0.0293, 0.0120, 0.0117	0.986, 0.0492, 0.0120, 0.0118	1.000, 0.0989, 0.0125, 0.012
MR-PRESSO	0.997, -0.0942, 0.0168, 0.0108	0.922, -0.0448, 0.0165, 0.011	0.625, -0.0251, 0.0163, 0.011	0.178, -0.0054, 0.0161, 0.0111	0.143, 0.0045, 0.0160, 0.0111	0.283, 0.0144, 0.0160, 0.0112	0.785, 0.0341, 0.0158, 0.0113	0.981, 0.0539, 0.0157, 0.0114	1.000, 0.1032, 0.0155, 0.0116
MR-IVW	0.073, -0.0461, 0.1046, 0.104	0.047, 0.0039, 0.1046, 0.104	0.055, 0.0239, 0.1046, 0.104	0.074, 0.0439, 0.1046, 0.104	0.090, 0.0539, 0.1046, 0.104	0.102, 0.0639, 0.1046, 0.104	0.142, 0.0839, 0.1046, 0.104	0.178, 0.1039, 0.1046, 0.104	0.318, 0.1538, 0.1046, 0.104
MR-IVW-Oracle	1.000, -0.0998, 0.0112, 0.0114	0.991, -0.0501, 0.0113, 0.0115	0.760, -0.0302, 0.0113, 0.0116	0.139, -0.0104, 0.0114, 0.0117	0.042, -0.0004, 0.0114, 0.0117	0.117, 0.0095, 0.0114, 0.0118	0.706, 0.0293, 0.0115, 0.0119	0.984, 0.0492, 0.0116, 0.012	1.000, 0.0989, 0.0118, 0.0123
MR-Egger	0.341, 0.4698, 0.4515, 0.3364	0.376, 0.5165, 0.4516, 0.3364	0.390, 0.5352, 0.4516, 0.3364	0.404, 0.5539, 0.4517, 0.3365	0.413, 0.5632, 0.4517, 0.3365	0.420, 0.5725, 0.4517, 0.3365	0.440, 0.5912, 0.4518, 0.3365	0.456, 0.6098, 0.4518, 0.3366	0.498, 0.6564, 0.4519, 0.3367
MR-Weighted-Median	1.000, -0.1008, 0.0158, 0.0161	0.913, -0.0535, 0.0164, 0.0163	0.549, -0.0346, 0.0165, 0.0164	0.159, -0.0157, 0.0167, 0.0165	0.071, -0.0063, 0.0168, 0.0166	0.048, 0.0032, 0.0169, 0.0166	0.267, 0.0221, 0.0170, 0.0168	0.694, 0.0410, 0.0171, 0.0169	0.995, 0.0878, 0.0177, 0.0174
MR-Weighted-Mode	0.848, -0.0868, 0.3201, 0.185	0.540, -0.0388, 0.3211, 0.1865	0.230, -0.0186, 0.3215, 0.1867	0.033, 0.0019, 0.3219, 0.1868	0.017, 0.0118, 0.3222, 0.1868	0.036, 0.0206, 0.3223, 0.1868	0.192, 0.0393, 0.3228, 0.1868	0.489, 0.0577, 0.3231, 0.1869	0.839, 0.1079, 0.3239, 0.1871
MR-RAPS1	0.078, -0.0472, 0.1023, 0.1039	0.044, 0.0028, 0.1023, 0.1039	0.051, 0.0228, 0.1023, 0.1039	0.067, 0.0429, 0.1023, 0.1039	0.080, 0.0529, 0.1023, 0.1039	0.100, 0.0629, 0.1023, 0.1039	0.133, 0.0829, 0.1024, 0.1039	0.168, 0.1029, 0.1024, 0.1039	0.310, 0.1529, 0.1024, 0.104
MR-RAPS2	0.110, -0.0715, 0.1041, 0.1051	0.055, -0.0215, 0.1041, 0.1051	0.049, -0.0014, 0.1041, 0.1051	0.051, 0.0186, 0.1041, 0.1051	0.054, 0.0286, 0.1041, 0.1051	0.058, 0.0386, 0.1041, 0.1051	0.087, 0.0586, 0.1042, 0.1051	0.125, 0.0786, 0.1042, 0.1051	0.223, 0.1287, 0.1042, 0.1051
MR-RAPS3	0.864, -1.2666, 68.7670, 1087.3079	0.893, 0.3820, 10.4769, 7.9368	0.884, -8.9530, 227.2274, 4070.7404	0.887, 0.0867, 13.0961, 11.3686	0.889, 2.9726, 68.4385, 1234.79	0.885, 1.4535, 29.6133, 158.5749	0.911, 0.4151, 13.2447, 23.6993	0.915, 1.2800, 7.4228, 6.3155	0.952, 0.8816, 2.3314, 1.291
MR-RAPS4	0.999, 0.5523, 1.7444, 0.0571	0.999, 0.7790, 1.2723, 0.0271	0.980, 0.9208, 4.1125, 0.091	0.853, 0.8560, 1.2464, 0.0273	0.836, 0.8779, 1.2527, 0.0279	0.861, 0.9026, 1.1729, 0.0264	0.972, 0.9476, 1.2062, 0.028	1.000, 0.9871, 1.0706, 0.0252	1.000, 1.0574, 0.9596, 0.0232



Table S84: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean( $SE(\hat{\theta})$ ) when  $m = 100$ , the InSIDE violated,  $q = 0.4$ , and  $N = 100000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	1.000, -0.0974, 0.0113, 0.0094	0.988, -0.0476, 0.0113, 0.0095	0.786, -0.0277, 0.0113, 0.0096	0.172, -0.0087, 0.0104, 0.0095	0.071, 0.0002, 0.0102, 0.0095	0.180, 0.0090, 0.0106, 0.0096	0.777, 0.0281, 0.0115, 0.0098	0.987, 0.0480, 0.0117, 0.0099	1.000, 0.0977, 0.0119, 0.0102
cML-MA-AIC-Profile	1.000, -0.0977, 0.0113, 0.0094	0.988, -0.0477, 0.0114, 0.0095	0.782, -0.0277, 0.0113, 0.0096	0.171, -0.0087, 0.0104, 0.0096	0.070, 0.0002, 0.0102, 0.0095	0.178, 0.0090, 0.0106, 0.0096	0.776, 0.0281, 0.0115, 0.0098	0.987, 0.0480, 0.0117, 0.01	1.000, 0.0980, 0.0120, 0.0102
cML-AIC	1.000, -0.0985, 0.0117, 0.0085	0.997, -0.0488, 0.0117, 0.0086	0.844, -0.0289, 0.0118, 0.0087	0.259, -0.0093, 0.0115, 0.0087	0.135, 0.0002, 0.0115, 0.0088	0.266, 0.0096, 0.0117, 0.0088	0.837, 0.0294, 0.0121, 0.0089	0.998, 0.0492, 0.0121, 0.0089	1.000, 0.0991, 0.0123, 0.0092
cML-AIC-Profile	1.000, -0.0987, 0.0117, 0.0086	0.997, -0.0488, 0.0117, 0.0087	0.844, -0.0289, 0.0118, 0.0087	0.258, -0.0093, 0.0115, 0.0088	0.133, 0.0002, 0.0115, 0.0088	0.264, 0.0096, 0.0117, 0.0088	0.835, 0.0294, 0.0121, 0.0089	0.997, 0.0493, 0.0121, 0.009	1.000, 0.0993, 0.0125, 0.0092
cML-MA-BIC	1.000, -0.0998, 0.0082, 0.0079	1.000, -0.0498, 0.0082, 0.008	0.946, -0.0298, 0.0083, 0.008	0.239, -0.0098, 0.0083, 0.0081	0.058, 0.0002, 0.0083, 0.0081	0.245, 0.0102, 0.0084, 0.0081	0.951, 0.0301, 0.0084, 0.0082	1.000, 0.0502, 0.0085, 0.0083	1.000, 0.1002, 0.0087, 0.0085
cML-MA-BIC-Profile	1.000, -0.0998, 0.0082, 0.0079	1.000, -0.0498, 0.0082, 0.008	0.946, -0.0298, 0.0083, 0.008	0.236, -0.0098, 0.0083, 0.0081	0.058, 0.0002, 0.0083, 0.0081	0.241, 0.0102, 0.0084, 0.0082	0.951, 0.0301, 0.0084, 0.0082	1.000, 0.0502, 0.0085, 0.0083	1.000, 0.1002, 0.0087, 0.0085
cML-BIC	1.000, -0.0999, 0.0082, 0.0078	1.000, -0.0498, 0.0082, 0.0079	0.949, -0.0298, 0.0083, 0.008	0.245, -0.0098, 0.0083, 0.008	0.060, 0.0002, 0.0083, 0.008	0.247, 0.0102, 0.0084, 0.0081	0.958, 0.0302, 0.0084, 0.0081	1.000, 0.0502, 0.0085, 0.0082	1.000, 0.1002, 0.0087, 0.0084
cML-BIC-Profile	1.000, -0.0999, 0.0082, 0.0078	1.000, -0.0498, 0.0082, 0.0079	0.949, -0.0298, 0.0083, 0.008	0.242, -0.0098, 0.0083, 0.008	0.060, 0.0002, 0.0083, 0.0081	0.247, 0.0102, 0.0084, 0.0081	0.958, 0.0302, 0.0084, 0.0082	1.000, 0.0502, 0.0085, 0.0082	1.000, 0.1002, 0.0087, 0.0084
MR-Mix	1.000, -0.1017, 0.0101, 0.0134	0.985, -0.0501, 0.0099, 0.0133	0.652, -0.0299, 0.0099, 0.0133	0.055, -0.0099, 0.0099, 0.0132	0.004, -0.0001, 0.0099, 0.0132	0.0097, 0.0099, 0.0099, 0.0132	0.637, 0.0292, 0.0099, 0.0132	0.986, 0.0484, 0.0099, 0.0132	1.000, 0.0948, 0.0096, 0.0131
MR-ContMix	1.000, -0.0995, 0.0083, NA	1.000, -0.0496, 0.0084, NA	0.942, -0.0297, 0.0084, NA	0.245, -0.0098, 0.0085, NA	0.067, 0.0002, 0.0085, NA	0.246, 0.0102, 0.0085, NA	0.951, 0.0301, 0.0086, NA	1.000, 0.0500, 0.0086, NA	1.000, 0.0998, 0.0088, NA
MR-Lasso	1.000, -0.0994, 0.0087, 0.0079	1.000, -0.0496, 0.0087, 0.0081	0.934, -0.0297, 0.0087, 0.0081	0.248, -0.0097, 0.0087, 0.0082	0.072, 0.0003, 0.0088, 0.0082	0.254, 0.0102, 0.0088, 0.0082	0.944, 0.0301, 0.0090, 0.0083	1.000, 0.0501, 0.0090, 0.0083	1.000, 0.0998, 0.0092, 0.0085
MR-PRESSO	0.973, -0.0904, 0.0242, 0.0082	0.877, -0.0409, 0.0234, 0.0082	0.775, -0.0211, 0.0232, 0.0082	0.409, -0.0013, 0.0231, 0.0082	0.337, 0.0085, 0.0229, 0.0083	0.477, 0.0184, 0.0228, 0.0083	0.918, 0.0382, 0.0225, 0.0083	0.987, 0.0580, 0.0223, 0.0084	0.999, 0.1074, 0.0217, 0.0085
MR-IVW	0.101, -0.0481, 0.1118, 0.1042	0.067, 0.0020, 0.1118, 0.1042	0.077, 0.0221, 0.1118, 0.1042	0.095, 0.0421, 0.1118, 0.1042	0.102, 0.0522, 0.1118, 0.1042	0.126, 0.0622, 0.1118, 0.1042	0.148, 0.0822, 0.1118, 0.1042	0.181, 0.1023, 0.1118, 0.1042	0.299, 0.1524, 0.1118, 0.1042
MR-IVW-Oracle	1.000, -0.0995, 0.0081, 0.0081	1.000, -0.0496, 0.0082, 0.0082	0.942, -0.0297, 0.0082, 0.0082	0.224, -0.0098, 0.0082, 0.0083	0.055, 0.0002, 0.0083, 0.0083	0.228, 0.0102, 0.0083, 0.0084	0.947, 0.0301, 0.0083, 0.0084	1.000, 0.0500, 0.0084, 0.0085	1.000, 0.0998, 0.0086, 0.0087
MR-Egger	0.351, 0.5000, 0.4731, 0.3425	0.388, 0.5484, 0.4731, 0.3425	0.404, 0.5677, 0.4731, 0.3425	0.419, 0.5870, 0.4731, 0.3426	0.426, 0.5967, 0.4731, 0.3426	0.430, 0.6063, 0.4731, 0.3426	0.445, 0.6257, 0.4731, 0.3426	0.464, 0.6450, 0.4731, 0.3426	0.503, 0.6932, 0.4732, 0.3426
MR-Weighted-Median	1.000, -0.1007, 0.0114, 0.0114	0.991, -0.0524, 0.0115, 0.0115	0.814, -0.0330, 0.0116, 0.0116	0.219, -0.0136, 0.0118, 0.0117	0.072, -0.0039, 0.0118, 0.0117	0.081, 0.0058, 0.0119, 0.0118	0.548, 0.0251, 0.0121, 0.0119	0.954, 0.0443, 0.0123, 0.012	1.000, 0.0924, 0.0128, 0.0123
MR-Weighted-Mode	0.924, -0.0893, 0.3770, 0.1024	0.734, -0.0402, 0.3749, 0.1027	0.396, -0.0215, 0.3746, 0.103	0.048, -0.0025, 0.3738, 0.1031	0.018, 0.0079, 0.3734, 0.1032	0.052, 0.0182, 0.3730, 0.1032	0.374, 0.0369, 0.3722, 0.1034	0.749, 0.0566, 0.3713, 0.1037	0.916, 0.1059, 0.3692, 0.1041
MR-RAPS1	0.097, -0.0497, 0.1092, 0.1037	0.065, 0.0003, 0.1092, 0.1037	0.069, 0.0203, 0.1092, 0.1037	0.089, 0.0404, 0.1092, 0.1037	0.098, 0.0504, 0.1092, 0.1037	0.109, 0.0604, 0.1092, 0.1037	0.138, 0.0804, 0.1092, 0.1037	0.174, 0.1004, 0.1092, 0.1038	0.293, 0.1504, 0.1092, 0.1038
MR-RAPS2	0.127, -0.0731, 0.1112, 0.1047	0.076, -0.0231, 0.1113, 0.1048	0.063, -0.0035, 0.1111, 0.1048	0.072, 0.0169, 0.1113, 0.1048	0.080, 0.0266, 0.1108, 0.1047	0.085, 0.0366, 0.1111, 0.1048	0.104, 0.0566, 0.1111, 0.1048	0.132, 0.0753, 0.1096, 0.1045	0.226, 0.1257, 0.1104, 0.1046
MR-RAPS3	0.920, -4.2014, 136.2241, 961.1	0.916, 0.4917, 14.6667, 14.1	0.908, 4.5525, 116.2892, 264	0.910, -14.1242, 501.7183, 10180	0.909, 1.2589, 38.5047, 125.4	0.914, -5.5832, 202.6511, 2083	0.920, 1.5148, 24.0154, 19.03	0.953, 0.8808, 2.1430, 0.5891	0.970, 0.8017, 2.5321, 0.4719
MR-RAPS4	0.999, 0.7460, 3.2510, 0.0875	1.000, 0.7666, 1.4070, 0.0228	0.999, 0.8381, 1.3410, 0.0215	0.941, 0.8566, 1.3580, 0.0259	0.893, 0.8719, 1.3516, 0.0223	0.927, 1.0403, 4.6978, 0.5823	0.998, 0.9122, 1.3008, 0.0207	1.000, 0.9391, 1.2918, 0.0205	1.000, 1.0060, 1.2068, 0.0211

Table S85: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean(SE( $\hat{\theta}$ )) when  $m = 100$ , the InSIDE violated,  $q = 0.4$ , and  $N = 200000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	1.000, -0.0984, 0.0081, 0.0066	1.000, -0.0485, 0.0082, 0.0067	0.959, -0.0285, 0.0083, 0.0067	0.278, -0.0089, 0.0078, 0.0067	0.086, 0.0001, 0.0074, 0.0067	0.286, 0.0090, 0.0078, 0.0068	0.953, 0.0286, 0.0084, 0.0069	1.000, 0.0485, 0.0085, 0.007	1.000, 0.0983, 0.0087, 0.0072
cML-MA-AIC-Profile	1.000, -0.0986, 0.0081, 0.0067	1.000, -0.0485, 0.0082, 0.0067	0.957, -0.0286, 0.0083, 0.0068	0.277, -0.0089, 0.0078, 0.0068	0.085, 0.0001, 0.0074, 0.0067	0.285, 0.0090, 0.0078, 0.0068	0.953, 0.0286, 0.0084, 0.0069	1.000, 0.0485, 0.0085, 0.007	1.000, 0.0985, 0.0087, 0.0072
cML-AIC	1.000, -0.0993, 0.0085, 0.006	1.000, -0.0494, 0.0086, 0.0061	0.968, -0.0294, 0.0086, 0.0061	0.387, -0.0095, 0.0086, 0.0062	0.145, 0.0001, 0.0084, 0.0062	0.370, 0.0096, 0.0085, 0.0062	0.973, 0.0295, 0.0087, 0.0063	1.000, 0.0494, 0.0088, 0.0063	1.000, 0.0993, 0.0091, 0.0065
cML-AIC-Profile	1.000, -0.0994, 0.0086, 0.006	1.000, -0.0494, 0.0086, 0.0061	0.968, -0.0294, 0.0086, 0.0061	0.381, -0.0095, 0.0086, 0.0062	0.144, 0.0001, 0.0084, 0.0062	0.369, 0.0096, 0.0085, 0.0062	0.973, 0.0295, 0.0087, 0.0063	1.000, 0.0494, 0.0089, 0.0063	1.000, 0.0994, 0.0091, 0.0065
cML-MA-BIC	1.000, -0.1000, 0.0056, 0.0056	1.000, -0.0500, 0.0056, 0.0056	0.999, -0.0300, 0.0056, 0.0057	0.427, -0.0100, 0.0057, 0.0057	0.045, 0.0000, 0.0057, 0.0057	0.412, 0.0100, 0.0057, 0.0057	1.000, 0.0300, 0.0057, 0.0058	1.000, 0.0500, 0.0058, 0.0058	1.000, 0.1000, 0.0059, 0.006
cML-MA-BIC-Profile	1.000, -0.1001, 0.0056, 0.0056	1.000, -0.0500, 0.0056, 0.0056	0.999, -0.0300, 0.0056, 0.0057	0.426, -0.0100, 0.0057, 0.0057	0.045, 0.0000, 0.0057, 0.0057	0.411, 0.0100, 0.0057, 0.0057	1.000, 0.0300, 0.0057, 0.0058	1.000, 0.0500, 0.0058, 0.0058	1.000, 0.1000, 0.0059, 0.006
cML-BIC	1.000, -0.1001, 0.0056, 0.0055	1.000, -0.0501, 0.0056, 0.0056	0.998, -0.0301, 0.0057, 0.0056	0.431, -0.0101, 0.0057, 0.0057	0.045, -0.0001, 0.0057, 0.0057	0.418, 0.0099, 0.0057, 0.0057	1.000, 0.0299, 0.0058, 0.0058	1.000, 0.0500, 0.0058, 0.0058	1.000, 0.1000, 0.0059, 0.0059
cML-BIC-Profile	1.000, -0.1001, 0.0056, 0.0055	1.000, -0.0501, 0.0056, 0.0056	0.998, -0.0301, 0.0057, 0.0056	0.431, -0.0101, 0.0057, 0.0057	0.045, -0.0001, 0.0057, 0.0057	0.417, 0.0099, 0.0057, 0.0057	1.000, 0.0299, 0.0058, 0.0058	1.000, 0.0500, 0.0058, 0.0058	1.000, 0.1000, 0.0059, 0.006
MR-Mix	1.000, -0.1024, 0.0078, 0.0103	0.997, -0.0505, 0.0076, 0.0102	0.879, -0.0301, 0.0076, 0.0102	0.150, -0.0101, 0.0076, 0.0102	0.018, -0.0002, 0.0076, 0.0102	0.134, 0.0097, 0.0076, 0.0101	0.871, 0.0291, 0.0077, 0.0101	0.999, 0.0482, 0.0075, 0.0101	0.999, 0.0945, 0.0075, 0.0102
MR-ContMix	1.000, -0.0998, 0.0056, NA	1.000, -0.0499, 0.0057, NA	0.997, -0.0300, 0.0057, NA	0.437, -0.0100, 0.0057, NA	0.051, 0.0000, 0.0057, NA	0.418, 0.0100, 0.0058, NA	1.000, 0.0300, 0.0058, NA	1.000, 0.0499, 0.0059, NA	1.000, 0.0998, 0.0060, NA
MR-Lasso	1.000, -0.0999, 0.0058, 0.0056	1.000, -0.0500, 0.0058, 0.0057	0.998, -0.0300, 0.0058, 0.0057	0.418, -0.0100, 0.0058, 0.0058	0.050, 0.0000, 0.0059, 0.0058	0.406, 0.0100, 0.0059, 0.0058	1.000, 0.0299, 0.0059, 0.0059	1.000, 0.0499, 0.0060, 0.0059	1.000, 0.0998, 0.0061, 0.006
MR-PRESSO	0.944, -0.0840, 0.0417, 0.0079	0.826, -0.0349, 0.0397, 0.0077	0.792, -0.0153, 0.0387, 0.0076	0.529, 0.0043, 0.0377, 0.0076	0.461, 0.0142, 0.0377, 0.0076	0.667, 0.0241, 0.0377, 0.0076	0.959, 0.0437, 0.0367, 0.0074	0.978, 0.0633, 0.0377, 0.0075	0.993, 0.1118, 0.0321, 0.0071
MR-IVW	0.076, -0.0409, 0.1104, 0.1038	0.069, 0.0094, 0.1104, 0.1038	0.092, 0.0295, 0.1104, 0.1038	0.105, 0.0495, 0.1104, 0.1038	0.127, 0.0596, 0.1104, 0.1038	0.138, 0.0696, 0.1104, 0.1038	0.169, 0.0897, 0.1104, 0.1038	0.202, 0.1098, 0.1104, 0.1038	0.353, 0.1600, 0.1104, 0.1038
MR-IVW-Oracle	1.000, -0.0999, 0.0056, 0.0057	1.000, -0.0500, 0.0056, 0.0058	0.998, -0.0300, 0.0056, 0.0058	0.404, -0.0100, 0.0057, 0.0058	0.040, -0.0001, 0.0057, 0.0059	0.394, 0.0099, 0.0057, 0.0059	0.999, 0.0299, 0.0057, 0.0059	1.000, 0.0499, 0.0058, 0.006	1.000, 0.0998, 0.0059, 0.0061
MR-Egger	0.370, 0.5112, 0.4918, 0.3434	0.405, 0.5606, 0.4917, 0.3435	0.425, 0.5803, 0.4917, 0.3435	0.444, 0.6000, 0.4917, 0.3435	0.452, 0.6098, 0.4917, 0.3435	0.463, 0.6197, 0.4917, 0.3435	0.476, 0.6393, 0.4917, 0.3435	0.494, 0.6590, 0.4917, 0.3435	0.539, 0.7081, 0.4916, 0.3435
MR-Weighted-Median	1.000, -0.1010, 0.0080, 0.008	1.000, -0.0520, 0.0082, 0.0081	0.978, -0.0324, 0.0082, 0.0082	0.339, -0.0128, 0.0083, 0.0082	0.068, -0.0030, 0.0083, 0.0083	0.129, 0.0068, 0.0084, 0.0083	0.882, 0.0263, 0.0085, 0.0084	0.997, 0.0459, 0.0086, 0.0084	1.000, 0.0947, 0.0090, 0.0087
MR-Weighted-Mode	0.955, -0.0956, 0.1314, 0.0516	0.862, -0.0457, 0.1313, 0.0517	0.572, -0.0253, 0.1312, 0.0518	0.091, -0.0048, 0.1315, 0.0518	0.016, 0.0053, 0.1314, 0.052	0.084, 0.0151, 0.1313, 0.052	0.588, 0.0349, 0.1312, 0.0521	0.856, 0.0546, 0.1309, 0.0521	0.957, 0.1041, 0.1307, 0.0523
MR-RAPS1	0.078, -0.0416, 0.1086, 0.1033	0.065, 0.0084, 0.1086, 0.1033	0.079, 0.0284, 0.1086, 0.1033	0.107, 0.0484, 0.1086, 0.1033	0.122, 0.0584, 0.1086, 0.1033	0.130, 0.0684, 0.1086, 0.1033	0.154, 0.0884, 0.1086, 0.1033	0.195, 0.1084, 0.1086, 0.1033	0.335, 0.1585, 0.1086, 0.1033
MR-RAPS2	0.789, -0.1567, 0.0695, 0.0538	0.516, -0.1006, 0.0753, 0.0587	0.422, -0.0770, 0.0795, 0.0607	0.327, -0.0523, 0.0835, 0.064	0.281, -0.0398, 0.0850, 0.0659	0.236, -0.0292, 0.0852, 0.067	0.165, -0.0049, 0.0866, 0.0707	0.130, 0.0202, 0.0896, 0.0739	0.195, 0.0859, 0.0974, 0.0828
MR-RAPS3	0.943, 0.3306, 27.5148, 21.53	0.944, 1.0042, 26.5163, 53.14	0.941, -0.7208, 26.6908, 23.05	0.945, 0.4942, 14.3938, 6.016	0.934, 0.9393, 10.2557, 7.132	0.948, 26.8984, 826.3173, 20840	0.949, 1.1222, 16.4003, 10.52	0.952, -2.1333, 68.5526, 269.6	0.974, 0.0435, 27.4894, 56.52
MR-RAPS4	1.000, 0.7092, 1.6767, 0.022	1.000, 0.7537, 2.7266, 0.0545	1.000, 0.9134, 1.4843, 0.0175	0.966, 0.9259, 1.4549, 0.0172	0.937, 0.9613, 1.4161, 0.0167	0.965, 0.9620, 1.3361, 0.0155	1.000, 0.9878, 1.3782, 0.016	1.000, 1.0207, 1.3258, 0.0158	1.000, 1.0632, 1.2758, 0.0161

Table S86: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean( $SE(\hat{\theta})$ ) when  $m = 100$ , the InSIDE violated,  $q = 0.6$ , and  $N = 50000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	0.998, -0.0949, 0.0203, 0.0176	0.700, -0.0452, 0.0203, 0.0178	0.322, -0.0262, 0.0193, 0.0177	0.087, -0.0082, 0.0181, 0.0177	0.063, 0.0004, 0.0180, 0.0177	0.092, 0.0089, 0.0183, 0.0178	0.343, 0.0268, 0.0199, 0.0181	0.678, 0.0459, 0.0209, 0.0184	0.990, 0.0955, 0.0219, 0.0188
cML-MA-AIC-Profile	0.998, -0.0952, 0.0204, 0.0178	0.697, -0.0453, 0.0204, 0.0179	0.321, -0.0262, 0.0194, 0.0179	0.084, -0.0082, 0.0182, 0.0178	0.063, 0.0004, 0.0180, 0.0178	0.089, 0.0089, 0.0184, 0.0179	0.343, 0.0268, 0.0199, 0.0182	0.673, 0.0460, 0.0210, 0.0185	0.989, 0.0958, 0.0221, 0.019
cML-AIC	0.998, -0.0978, 0.0210, 0.0158	0.795, -0.0480, 0.0212, 0.016	0.442, -0.0283, 0.0209, 0.0161	0.158, -0.0091, 0.0203, 0.0162	0.125, 0.0003, 0.0204, 0.0162	0.155, 0.0096, 0.0205, 0.0163	0.433, 0.0287, 0.0215, 0.0164	0.774, 0.0484, 0.0220, 0.0165	0.994, 0.0982, 0.0229, 0.0169
cML-AIC-Profile	0.998, -0.0979, 0.0211, 0.0159	0.793, -0.0481, 0.0212, 0.0161	0.436, -0.0283, 0.0209, 0.0162	0.153, -0.0091, 0.0203, 0.0163	0.126, 0.0003, 0.0204, 0.0163	0.152, 0.0096, 0.0205, 0.0164	0.431, 0.0288, 0.0215, 0.0165	0.769, 0.0484, 0.0221, 0.0166	0.994, 0.0985, 0.0231, 0.017
cML-MA-BIC	1.000, -0.0996, 0.0150, 0.0147	0.916, -0.0496, 0.0151, 0.0149	0.481, -0.0296, 0.0152, 0.0149	0.116, -0.0096, 0.0153, 0.015	0.050, 0.0003, 0.0153, 0.0151	0.103, 0.0103, 0.0154, 0.0151	0.534, 0.0303, 0.0155, 0.0152	0.885, 0.0503, 0.0156, 0.0154	1.000, 0.1003, 0.0160, 0.0157
cML-MA-BIC-Profile	1.000, -0.0996, 0.0150, 0.0148	0.916, -0.0496, 0.0151, 0.0149	0.479, -0.0296, 0.0152, 0.015	0.115, -0.0096, 0.0153, 0.0151	0.049, 0.0003, 0.0153, 0.0151	0.100, 0.0103, 0.0154, 0.0152	0.534, 0.0303, 0.0155, 0.0153	0.882, 0.0503, 0.0156, 0.0154	1.000, 0.1003, 0.0160, 0.0158
cML-BIC	1.000, -0.0996, 0.0150, 0.0146	0.923, -0.0496, 0.0151, 0.0147	0.495, -0.0296, 0.0152, 0.0148	0.123, -0.0096, 0.0153, 0.0149	0.054, 0.0004, 0.0154, 0.0149	0.110, 0.0104, 0.0154, 0.015	0.543, 0.0303, 0.0155, 0.0151	0.888, 0.0503, 0.0156, 0.0152	1.000, 0.1003, 0.0160, 0.0155
cML-BIC-Profile	1.000, -0.0996, 0.0150, 0.0146	0.921, -0.0496, 0.0151, 0.0148	0.492, -0.0296, 0.0152, 0.0149	0.120, -0.0096, 0.0153, 0.015	0.054, 0.0004, 0.0154, 0.015	0.106, 0.0104, 0.0154, 0.015	0.541, 0.0303, 0.0155, 0.0152	0.887, 0.0503, 0.0156, 0.0153	1.000, 0.1003, 0.0160, 0.0156
MR-Mix	1.000, -0.0946, 0.0151, 0.0172	0.780, -0.0467, 0.0151, 0.0171	0.324, -0.0278, 0.0151, 0.0171	0.057, -0.0093, 0.0151, 0.0171	0.020, -0.0002, 0.0149, 0.0171	0.047, 0.0091, 0.0149, 0.017	0.317, 0.0273, 0.0150, 0.017	0.750, 0.0453, 0.0152, 0.017	0.999, 0.0887, 0.0151, 0.017
MR-ContMix	1.000, -0.0989, 0.0152, NA	0.910, -0.0493, 0.0154, NA	0.496, -0.0295, 0.0155, NA	0.123, -0.0097, 0.0156, NA	0.057, 0.0002, 0.0156, NA	0.110, 0.0101, 0.0157, NA	0.531, 0.0300, 0.0158, NA	0.879, 0.0499, 0.0159, NA	1.000, 0.0995, 0.0164, NA
MR-Lasso	1.000, -0.0990, 0.0156, 0.0148	0.899, -0.0493, 0.0157, 0.015	0.474, -0.0296, 0.0158, 0.0151	0.115, -0.0097, 0.0158, 0.0152	0.059, 0.0002, 0.0160, 0.0153	0.117, 0.0103, 0.0162, 0.0153	0.519, 0.0301, 0.0164, 0.0154	0.871, 0.0501, 0.0163, 0.0155	0.999, 0.0996, 0.0172, 0.0158
MR-PRESSO	0.968, -0.0907, 0.0249, 0.0143	0.760, -0.0413, 0.0243, 0.0144	0.423, -0.0217, 0.0240, 0.0145	0.184, -0.0020, 0.0241, 0.0146	0.182, 0.0079, 0.0239, 0.0146	0.261, 0.0177, 0.0239, 0.0146	0.642, 0.0374, 0.0237, 0.0147	0.916, 0.0571, 0.0237, 0.0148	0.997, 0.1064, 0.0234, 0.0152
MR-IVW	0.060, -0.0262, 0.1298, 0.1256	0.057, 0.0239, 0.1298, 0.1256	0.071, 0.0439, 0.1298, 0.1256	0.086, 0.0640, 0.1298, 0.1256	0.107, 0.0740, 0.1298, 0.1256	0.125, 0.0840, 0.1298, 0.1256	0.152, 0.1040, 0.1298, 0.1256	0.185, 0.1240, 0.1298, 0.1256	0.293, 0.1741, 0.1298, 0.1256
MR-IVW-Oracle	1.000, -0.0989, 0.0148, 0.015	0.904, -0.0493, 0.0149, 0.0152	0.460, -0.0294, 0.0150, 0.0153	0.105, -0.0096, 0.0151, 0.0154	0.047, 0.0004, 0.0151, 0.0154	0.094, 0.0103, 0.0152, 0.0155	0.508, 0.0301, 0.0153, 0.0156	0.879, 0.0500, 0.0154, 0.0157	1.000, 0.0996, 0.0158, 0.016
MR-Egger	0.379, 0.5690, 0.4384, 0.3636	0.422, 0.6165, 0.4385, 0.3636	0.433, 0.6355, 0.4385, 0.3636	0.453, 0.6545, 0.4385, 0.3637	0.459, 0.6640, 0.4386, 0.3637	0.464, 0.6735, 0.4386, 0.3637	0.484, 0.6924, 0.4386, 0.3637	0.509, 0.7114, 0.4386, 0.3638	0.546, 0.7588, 0.4387, 0.3638
MR-Weighted-Median	0.995, -0.1045, 0.0234, 0.0211	0.774, -0.0593, 0.0237, 0.0214	0.497, -0.0413, 0.0240, 0.0215	0.201, -0.0232, 0.0244, 0.0216	0.123, -0.0142, 0.0246, 0.0217	0.094, -0.0052, 0.0249, 0.0218	0.130, 0.0127, 0.0253, 0.022	0.314, 0.0306, 0.0257, 0.0222	0.868, 0.0750, 0.0268, 0.0228
MR-Weighted-Mode	0.841, -0.1783, 0.1960, 0.2919	0.788, -0.1372, 0.1972, 0.2913	0.748, -0.1250, 0.2041, 0.2915	0.694, -0.1086, 0.2036, 0.2919	0.664, -0.0994, 0.2034, 0.2925	0.622, -0.0908, 0.2032, 0.2926	0.550, -0.0752, 0.2025, 0.293	0.448, -0.0576, 0.2021, 0.2933	0.253, -0.0176, 0.2026, 0.2941
MR-RAPS1	0.053, -0.0268, 0.1255, 0.1257	0.047, 0.0233, 0.1255, 0.1257	0.065, 0.0433, 0.1255, 0.1257	0.080, 0.0633, 0.1255, 0.1257	0.093, 0.0733, 0.1255, 0.1257	0.103, 0.0833, 0.1255, 0.1257	0.142, 0.1033, 0.1255, 0.1257	0.173, 0.1234, 0.1255, 0.1257	0.299, 0.1734, 0.1256, 0.1258
MR-RAPS2	0.066, -0.0402, 0.1394, 0.1356	0.053, 0.0098, 0.1394, 0.1356	0.062, 0.0298, 0.1394, 0.1356	0.074, 0.0498, 0.1394, 0.1356	0.084, 0.0598, 0.1394, 0.1356	0.095, 0.0698, 0.1394, 0.1356	0.110, 0.0898, 0.1394, 0.1356	0.140, 0.1094, 0.1390, 0.1356	0.218, 0.1593, 0.1391, 0.1356
MR-RAPS3	0.892, 1.2454, 171.6271, 697.2	0.866, 209.9883, 6699.4141, 1249000	0.876, 21.2117, 534.7323, 6772	0.891, -26.3794, 810.1790, 24370	0.900, 3.3468, 59.4460, 78.77	0.912, -4.3093, 154.9911, 725.9	0.908, 0.0604, 40.8081, 40.55	0.911, 4.9292, 309.3501, 2518	0.945, 1.4952, 23.8250, 20.02
MR-RAPS4	0.997, 0.3198, 17.8347, 9.695	0.995, 0.0360, 11.6924, 1.787	0.995, 1.4661, 15.7388, 1.647	0.986, 0.7936, 5.1224, 0.3005	0.981, 0.7884, 4.2352, 0.3116	0.984, 0.9206, 1.8818, 0.0714	0.999, 0.9950, 2.2961, 0.0696	0.998, 1.0811, 1.9398, 0.0668	0.999, 1.2547, 1.4721, 0.0698

Table S87: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean( $SE(\hat{\theta})$ ) when  $m = 100$ , the InSIDE violated,  $q = 0.6$ , and  $N = 100000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	1.000, -0.0958, 0.0151, 0.0127	0.892, -0.0459, 0.0152, 0.0128	0.547, -0.0263, 0.0147, 0.0128	0.115, -0.0081, 0.0134, 0.0126	0.055, 0.0004, 0.0131, 0.0126	0.122, 0.0090, 0.0135, 0.0127	0.548, 0.0273, 0.0151, 0.013	0.890, 0.0470, 0.0157, 0.0132	1.000, 0.0966, 0.0159, 0.0135
cML-MA-AIC-Profile	1.000, -0.0961, 0.0153, 0.0127	0.892, -0.0460, 0.0153, 0.0128	0.544, -0.0263, 0.0147, 0.0128	0.115, -0.0080, 0.0134, 0.0127	0.054, 0.0004, 0.0131, 0.0127	0.121, 0.0090, 0.0135, 0.0128	0.545, 0.0273, 0.0151, 0.013	0.890, 0.0470, 0.0157, 0.0132	1.000, 0.0969, 0.0160, 0.0135
cML-AIC	1.000, -0.0978, 0.0157, 0.0112	0.939, -0.0479, 0.0158, 0.0113	0.661, -0.0282, 0.0156, 0.0114	0.207, -0.0089, 0.0152, 0.0115	0.117, 0.0005, 0.0151, 0.0115	0.213, 0.0098, 0.0153, 0.0116	0.659, 0.0290, 0.0161, 0.0116	0.931, 0.0490, 0.0165, 0.0117	1.000, 0.0988, 0.0167, 0.012
cML-AIC-Profile	1.000, -0.0980, 0.0158, 0.0113	0.939, -0.0480, 0.0159, 0.0114	0.660, -0.0282, 0.0157, 0.0115	0.206, -0.0089, 0.0152, 0.0115	0.114, 0.0004, 0.0151, 0.0116	0.212, 0.0098, 0.0153, 0.0116	0.657, 0.0290, 0.0161, 0.0117	0.930, 0.0490, 0.0165, 0.0118	1.000, 0.0990, 0.0168, 0.012
cML-MA-BIC	1.000, -0.0998, 0.0108, 0.0104	0.994, -0.0497, 0.0109, 0.0105	0.797, -0.0297, 0.0110, 0.0106	0.165, -0.0097, 0.0110, 0.0106	0.057, 0.0003, 0.0111, 0.0107	0.168, 0.0103, 0.0111, 0.0107	0.783, 0.0303, 0.0112, 0.0108	0.994, 0.0503, 0.0113, 0.0109	1.000, 0.1003, 0.0116, 0.0111
cML-MA-BIC-Profile	1.000, -0.0998, 0.0108, 0.0104	0.994, -0.0497, 0.0109, 0.0105	0.797, -0.0297, 0.0110, 0.0106	0.164, -0.0097, 0.0110, 0.0107	0.057, 0.0003, 0.0111, 0.0107	0.168, 0.0103, 0.0111, 0.0107	0.781, 0.0303, 0.0112, 0.0108	0.994, 0.0503, 0.0113, 0.0109	1.000, 0.1003, 0.0116, 0.0111
cML-BIC	1.000, -0.0998, 0.0108, 0.0103	0.994, -0.0498, 0.0109, 0.0104	0.799, -0.0298, 0.0110, 0.0105	0.175, -0.0098, 0.0110, 0.0106	0.058, 0.0002, 0.0111, 0.0106	0.174, 0.0102, 0.0111, 0.0106	0.785, 0.0303, 0.0112, 0.0107	0.994, 0.0503, 0.0113, 0.0108	1.000, 0.1003, 0.0116, 0.011
cML-BIC-Profile	1.000, -0.0998, 0.0108, 0.0103	0.994, -0.0498, 0.0109, 0.0105	0.799, -0.0298, 0.0110, 0.0105	0.174, -0.0098, 0.0110, 0.0106	0.058, 0.0002, 0.0111, 0.0106	0.173, 0.0102, 0.0111, 0.0106	0.784, 0.0303, 0.0112, 0.0107	0.994, 0.0503, 0.0113, 0.0108	1.000, 0.1003, 0.0116, 0.011
MR-Mix	1.000, -0.0951, 0.0111, 0.0132	0.960, -0.0470, 0.0111, 0.0131	0.583, -0.0281, 0.0112, 0.0131	0.060, -0.0093, 0.0112, 0.013	0.024, 0.0000, 0.0113, 0.013	0.071, 0.0092, 0.0112, 0.013	0.554, 0.0274, 0.0109, 0.013	0.959, 0.0453, 0.0112, 0.013	1.000, 0.0892, 0.0112, 0.013
MR-ContMix	1.000, -0.0994, 0.0110, NA	0.994, -0.0496, 0.0110, NA	0.806, -0.0296, 0.0111, NA	0.173, -0.0097, 0.0111, NA	0.066, 0.0003, 0.0112, NA	0.184, 0.0103, 0.0112, NA	0.790, 0.0302, 0.0113, NA	0.992, 0.0502, 0.0114, NA	1.000, 0.1000, 0.0117, NA
MR-Lasso	1.000, -0.0994, 0.0112, 0.0106	0.988, -0.0495, 0.0113, 0.0107	0.781, -0.0295, 0.0114, 0.0108	0.163, -0.0097, 0.0114, 0.0108	0.060, 0.0003, 0.0114, 0.0109	0.163, 0.0102, 0.0114, 0.0109	0.763, 0.0301, 0.0115, 0.011	0.990, 0.0501, 0.0116, 0.011	1.000, 0.1000, 0.0120, 0.0113
MR-PRESSO	0.933, -0.0854, 0.0336, 0.0112	0.792, -0.0364, 0.0310, 0.0112	0.632, -0.0166, 0.0307, 0.0112	0.314, 0.0031, 0.0303, 0.0112	0.323, 0.0129, 0.0300, 0.0112	0.441, 0.0228, 0.0298, 0.0113	0.845, 0.0425, 0.0294, 0.0113	0.966, 0.0623, 0.0293, 0.0113	0.996, 0.1119, 0.0289, 0.0115
MR-IVW	0.073, -0.0242, 0.1347, 0.1257	0.076, 0.0260, 0.1347, 0.1257	0.087, 0.0461, 0.1347, 0.1257	0.106, 0.0662, 0.1347, 0.1257	0.121, 0.0762, 0.1347, 0.1257	0.131, 0.0863, 0.1347, 0.1257	0.163, 0.1064, 0.1347, 0.1257	0.188, 0.1264, 0.1347, 0.1257	0.289, 0.1766, 0.1347, 0.1257
MR-IVW-Oracle	1.000, -0.0994, 0.0107, 0.0107	0.994, -0.0496, 0.0108, 0.0108	0.775, -0.0296, 0.0109, 0.0109	0.152, -0.0097, 0.0110, 0.0109	0.047, 0.0003, 0.0110, 0.011	0.154, 0.0102, 0.0110, 0.011	0.767, 0.0302, 0.0111, 0.0111	0.991, 0.0501, 0.0112, 0.0112	1.000, 0.1000, 0.0115, 0.0114
MR-Egger	0.389, 0.5783, 0.4525, 0.3677	0.426, 0.6271, 0.4525, 0.3678	0.438, 0.6467, 0.4524, 0.3678	0.463, 0.6662, 0.4524, 0.3678	0.470, 0.6759, 0.4524, 0.3678	0.488, 0.6857, 0.4524, 0.3678	0.501, 0.7052, 0.4524, 0.3678	0.516, 0.7247, 0.4524, 0.3678	0.559, 0.7734, 0.4523, 0.3679
MR-Weighted-Median	1.000, -0.1042, 0.0182, 0.015	0.930, -0.0574, 0.0186, 0.0152	0.699, -0.0386, 0.0188, 0.0153	0.302, -0.0199, 0.0191, 0.0154	0.167, -0.0105, 0.0192, 0.0154	0.125, -0.0011, 0.0194, 0.0155	0.248, 0.0175, 0.0197, 0.0156	0.621, 0.0361, 0.0200, 0.0158	0.993, 0.0827, 0.0207, 0.0162
MR-Weighted-Mode	0.914, -0.1861, 0.2148, 0.1606	0.868, -0.1449, 0.2143, 0.1607	0.840, -0.1278, 0.2145, 0.1602	0.804, -0.1111, 0.2145, 0.1606	0.776, -0.1027, 0.2143, 0.1607	0.733, -0.0937, 0.2144, 0.1609	0.660, -0.0775, 0.2148, 0.1609	0.572, -0.0615, 0.2148, 0.1611	0.385, -0.0194, 0.2149, 0.1617
MR-RAPS1	0.066, -0.0237, 0.1311, 0.1253	0.068, 0.0263, 0.1311, 0.1253	0.086, 0.0463, 0.1311, 0.1253	0.098, 0.0663, 0.1311, 0.1253	0.108, 0.0763, 0.1311, 0.1253	0.120, 0.0863, 0.1311, 0.1253	0.153, 0.1063, 0.1311, 0.1253	0.184, 0.1263, 0.1311, 0.1253	0.300, 0.1763, 0.1311, 0.1253
MR-RAPS2	0.079, -0.0369, 0.1455, 0.1352	0.071, 0.0126, 0.1446, 0.1351	0.078, 0.0332, 0.1455, 0.1352	0.091, 0.0532, 0.1455, 0.1352	0.096, 0.0632, 0.1455, 0.1352	0.113, 0.0732, 0.1455, 0.1352	0.128, 0.0932, 0.1455, 0.1352	0.157, 0.1132, 0.1455, 0.1352	0.240, 0.1632, 0.1455, 0.1352
MR-RAPS3	0.917, 25.1174, 805.4906, 8805.7142	0.919, 2.3288, 179.6817, 550.0199	0.918, 23.8104, 546.1389, 5379.2702	0.924, 0.9100, 40.5061, 29.0598	0.922, 3.1148, 37.4361, 25.0112	0.921, 0.6864, 41.8040, 34.2991	0.930, -0.1778, 53.2802, 71.1757	0.939, 5.7914, 65.8989, 80.7173	0.956, -5.6541, 236.2347, 1300.2416
MR-RAPS4	0.998, -0.2801, 16.3670, 1.0631	0.997, 0.5836, 8.2056, 0.7236	0.996, 0.7451, 13.5943, 2.2242	0.996, 0.7734, 2.1873, 0.0414	0.989, 0.8248, 2.1544, 0.0475	0.995, 0.8971, 2.0181, 0.0423	0.999, 0.9619, 2.2797, 0.0698	1.000, 1.0511, 1.7062, 0.031	1.000, 1.1992, 1.5983, 0.0298

Table S88: Main simulations: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean( $SE(\hat{\theta})$ ) when  $m = 100$ , the InSIDE violated,  $q = 0.6$ , and  $N = 200000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-AIC	1.000, -0.0977, 0.0104, 0.0089	0.996, -0.0479, 0.0106, 0.009	0.827, -0.0281, 0.0105, 0.0091	0.205, -0.0090, 0.0097, 0.0089	0.056, -0.0004, 0.0093, 0.0089	0.178, 0.0083, 0.0097, 0.009	0.797, 0.0272, 0.0107, 0.0092	0.990, 0.0471, 0.0109, 0.0093	1.000, 0.0969, 0.0110, 0.0095
cML-MA-AIC-Profile	1.000, -0.0979, 0.0105, 0.009	0.996, -0.0480, 0.0106, 0.009	0.826, -0.0281, 0.0105, 0.0091	0.201, -0.0090, 0.0097, 0.009	0.056, -0.0003, 0.0093, 0.0089	0.177, 0.0083, 0.0097, 0.009	0.796, 0.0272, 0.0107, 0.0092	0.990, 0.0471, 0.0109, 0.0093	1.000, 0.0970, 0.0111, 0.0095
cML-AIC	1.000, -0.0990, 0.0110, 0.0079	0.996, -0.0492, 0.0112, 0.008	0.883, -0.0292, 0.0112, 0.0081	0.286, -0.0096, 0.0108, 0.0081	0.116, -0.0003, 0.0107, 0.0081	0.275, 0.0089, 0.0111, 0.0082	0.859, 0.0284, 0.0114, 0.0082	0.993, 0.0484, 0.0115, 0.0083	1.000, 0.0982, 0.0117, 0.0085
cML-AIC-Profile	1.000, -0.0991, 0.0110, 0.008	0.996, -0.0492, 0.0112, 0.008	0.882, -0.0293, 0.0112, 0.0081	0.286, -0.0096, 0.0108, 0.0081	0.116, -0.0003, 0.0107, 0.0082	0.274, 0.0089, 0.0111, 0.0082	0.858, 0.0284, 0.0114, 0.0082	0.993, 0.0484, 0.0115, 0.0083	1.000, 0.0983, 0.0117, 0.0085
cML-MA-BIC	1.000, -0.1004, 0.0072, 0.0073	1.000, -0.0504, 0.0073, 0.0074	0.982, -0.0304, 0.0073, 0.0075	0.292, -0.0104, 0.0074, 0.0075	0.043, -0.0005, 0.0074, 0.0075	0.234, 0.0095, 0.0074, 0.0076	0.978, 0.0295, 0.0075, 0.0076	1.000, 0.0495, 0.0075, 0.0077	1.000, 0.0995, 0.0077, 0.0078
cML-MA-BIC-Profile	1.000, -0.1004, 0.0073, 0.0073	1.000, -0.0504, 0.0073, 0.0074	0.982, -0.0304, 0.0073, 0.0075	0.290, -0.0104, 0.0074, 0.0075	0.043, -0.0005, 0.0074, 0.0075	0.233, 0.0095, 0.0074, 0.0076	0.978, 0.0295, 0.0075, 0.0076	1.000, 0.0495, 0.0075, 0.0077	1.000, 0.0995, 0.0077, 0.0078
cML-BIC	1.000, -0.1004, 0.0072, 0.0073	1.000, -0.0504, 0.0073, 0.0074	0.981, -0.0304, 0.0073, 0.0074	0.301, -0.0105, 0.0074, 0.0074	0.046, -0.0005, 0.0074, 0.0075	0.239, 0.0095, 0.0074, 0.0075	0.977, 0.0295, 0.0075, 0.0076	1.000, 0.0495, 0.0075, 0.0076	1.000, 0.0995, 0.0077, 0.0078
cML-BIC-Profile	1.000, -0.1004, 0.0072, 0.0073	1.000, -0.0504, 0.0073, 0.0074	0.981, -0.0304, 0.0073, 0.0074	0.300, -0.0105, 0.0074, 0.0075	0.046, -0.0005, 0.0074, 0.0075	0.238, 0.0095, 0.0074, 0.0075	0.976, 0.0295, 0.0075, 0.0076	1.000, 0.0495, 0.0075, 0.0076	1.000, 0.0995, 0.0077, 0.0078
MR-Mix	1.000, -0.0957, 0.0084, 0.0102	0.995, -0.0474, 0.0081, 0.0102	0.880, -0.0285, 0.0081, 0.0102	0.188, -0.0098, 0.0081, 0.0101	0.038, -0.0007, 0.0081, 0.0101	0.148, 0.0085, 0.0081, 0.0101	0.838, 0.0269, 0.0081, 0.01	0.994, 0.0451, 0.0083, 0.01	1.000, 0.0885, 0.0083, 0.01
MR-ContMix	1.000, -0.1002, 0.0073, NA	1.000, -0.0504, 0.0074, NA	0.981, -0.0304, 0.0075, NA	0.325, -0.0105, 0.0075, NA	0.049, -0.0005, 0.0075, NA	0.245, 0.0095, 0.0075, NA	0.979, 0.0294, 0.0076, NA	1.000, 0.0494, 0.0077, NA	1.000, 0.0992, 0.0078, NA
MR-Lasso	1.000, -0.1002, 0.0075, 0.0075	1.000, -0.0503, 0.0075, 0.0076	0.973, -0.0304, 0.0076, 0.0076	0.280, -0.0104, 0.0076, 0.0077	0.043, -0.0004, 0.0077, 0.0077	0.228, 0.0095, 0.0077, 0.0077	0.966, 0.0295, 0.0077, 0.0078	1.000, 0.0494, 0.0078, 0.0078	1.000, 0.0994, 0.0080, 0.008
MR-PRESSO	0.897, -0.0709, 0.0746, 0.0138	0.763, -0.0225, 0.0719, 0.0131	0.683, -0.0027, 0.0718, 0.0131	0.444, 0.0166, 0.0704, 0.013	0.436, 0.0265, 0.0704, 0.013	0.587, 0.0365, 0.0705, 0.013	0.929, 0.0556, 0.0685, 0.0127	0.958, 0.0750, 0.0677, 0.0125	0.981, 0.1225, 0.0611, 0.0119
MR-IVW	0.070, -0.0162, 0.1297, 0.1257	0.069, 0.0341, 0.1297, 0.1257	0.083, 0.0542, 0.1297, 0.1257	0.102, 0.0743, 0.1297, 0.1257	0.112, 0.0844, 0.1297, 0.1257	0.124, 0.0944, 0.1297, 0.1257	0.168, 0.1145, 0.1297, 0.1257	0.202, 0.1346, 0.1297, 0.1257	0.319, 0.1848, 0.1297, 0.1256
MR-IVW-Oracle	1.000, -0.1002, 0.0073, 0.0076	1.000, -0.0503, 0.0073, 0.0077	0.976, -0.0304, 0.0073, 0.0077	0.265, -0.0104, 0.0073, 0.0078	0.035, -0.0004, 0.0074, 0.0078	0.218, 0.0095, 0.0074, 0.0078	0.969, 0.0295, 0.0074, 0.0079	1.000, 0.0494, 0.0075, 0.0079	1.000, 0.0993, 0.0077, 0.0081
MR-Egger	0.408, 0.6105, 0.4612, 0.37	0.443, 0.6600, 0.4612, 0.37	0.460, 0.6798, 0.4612, 0.37	0.471, 0.6996, 0.4612, 0.37	0.481, 0.7095, 0.4612, 0.37	0.493, 0.7194, 0.4612, 0.37	0.499, 0.7392, 0.4612, 0.3701	0.525, 0.7589, 0.4612, 0.3701	0.565, 0.8083, 0.4611, 0.3701
MR-Weighted-Median	1.000, -0.1032, 0.0117, 0.0106	0.996, -0.0553, 0.0119, 0.0107	0.903, -0.0361, 0.0121, 0.0108	0.350, -0.0170, 0.0123, 0.0108	0.136, -0.0075, 0.0124, 0.0109	0.088, 0.0021, 0.0124, 0.0109	0.504, 0.0211, 0.0126, 0.011	0.916, 0.0402, 0.0128, 0.0111	0.999, 0.0878, 0.0135, 0.0114
MR-Weighted-Mode	0.945, -0.1606, 0.3591, 0.1746	0.913, -0.1179, 0.3586, 0.1865	0.887, -0.0995, 0.3583, 0.1764	0.858, -0.0838, 0.3581, 0.1804	0.829, -0.0766, 0.3580, 0.1781	0.802, -0.0686, 0.3579, 0.1702	0.708, -0.0535, 0.3565, 0.1689	0.625, -0.0362, 0.3564, 0.1731	0.436, 0.0047, 0.3562, 0.1647
MR-RAPS1	0.060, -0.0170, 0.1265, 0.125	0.057, 0.0330, 0.1264, 0.125	0.073, 0.0530, 0.1264, 0.125	0.094, 0.0730, 0.1264, 0.125	0.103, 0.0830, 0.1264, 0.125	0.118, 0.0930, 0.1264, 0.125	0.162, 0.1130, 0.1264, 0.125	0.202, 0.1329, 0.1264, 0.125	0.310, 0.1829, 0.1264, 0.125
MR-RAPS2	0.106, -0.0399, 0.1520, 0.1311	0.085, 0.0155, 0.1582, 0.1325	0.085, 0.0356, 0.1477, 0.1332	0.100, 0.0556, 0.1495, 0.1332	0.106, 0.0693, 0.1541, 0.1336	0.110, 0.0776, 0.1418, 0.1342	0.136, 0.0996, 0.1484, 0.1342	0.173, 0.1186, 0.1481, 0.134	0.261, 0.1703, 0.1479, 0.1345
MR-RAPS3	0.931, -4.3662, 120.3558, 148.8028	0.943, -0.8313, 72.0796, 59.7488	0.937, -0.3019, 214.2086, 491.0617	0.945, 2.1165, 47.2097, 27.6602	0.948, -0.6127, 103.8212, 126.1302	0.950, 10.8055, 349.7168, 1383.0164	0.956, 3.4670, 134.0669, 228.6325	0.958, 1.4311, 35.1436, 15.5759	0.984, 3.0832, 17.7638, 5.1696
MR-RAPS4	1.000, 0.3480, 2.6821, 0.0441	0.999, 0.7353, 2.1236, 0.0389	0.999, 0.6685, 2.4392, 0.068	0.999, 0.8426, 3.0054, 0.0636	0.990, 0.9712, 2.6826, 0.0492	0.997, 0.9250, 2.1687, 0.0401	0.999, 0.9291, 2.2197, 0.0372	0.999, 1.0774, 1.7498, 0.0362	1.000, 1.1822, 2.6545, 0.0505

Table S89: Main simulations: the relative frequencies of cML-BIC selecting  $\hat{K} = K_0$  for  $m = 10$  and the InSIDE satisfied.

$\theta$	$q = 0$			$q = 0.2$			$q = 0.4$			$q = 0.6$		
	N = 50k	N = 100k	N = 200k	N = 50k	N = 100k	N = 200k	N = 50k	N = 100k	N = 200k	N = 50k	N = 100k	N = 200k
-0.1	0.992	0.998	0.996	0.994	0.996	0.998	0.996	0.997	0.998	0.997	1.000	0.999
-0.05	0.989	0.997	0.996	0.994	0.997	0.998	0.994	0.996	0.997	0.997	0.998	0.998
-0.03	0.988	0.997	0.996	0.994	0.997	0.998	0.994	0.996	0.997	0.998	0.998	0.998
-0.01	0.989	0.995	0.996	0.994	0.997	0.998	0.994	0.996	0.997	0.998	0.998	0.998
0	0.989	0.995	0.996	0.994	0.996	0.998	0.994	0.996	0.997	0.998	0.997	0.998
0.01	0.989	0.995	0.996	0.994	0.996	0.998	0.994	0.996	0.997	0.998	0.997	0.998
0.03	0.987	0.994	0.996	0.994	0.995	0.998	0.994	0.996	0.996	0.997	0.998	0.998
0.05	0.987	0.994	0.996	0.994	0.995	0.997	0.994	0.996	0.996	0.996	0.998	0.998
0.1	0.988	0.993	0.995	0.993	0.995	0.997	0.994	0.996	0.996	0.997	0.998	0.998

Table S90: Main simulations: the relative frequencies of cML-BIC selecting  $\hat{K} = K_0$  for  $m = 10$  and the InSIDE violated.

$\theta$	$q = 0$			$q = 0.2$			$q = 0.4$			$q = 0.6$		
	N = 50k	N = 100k	N = 200k	N = 50k	N = 100k	N = 200k	N = 50k	N = 100k	N = 200k	N = 50k	N = 100k	N = 200k
-0.1	0.992	0.998	0.996	0.991	0.994	0.996	0.997	0.998	0.998	0.995	0.998	0.999
-0.05	0.989	0.997	0.996	0.994	0.994	0.996	0.996	0.997	0.998	0.995	0.999	0.999
-0.03	0.988	0.997	0.996	0.993	0.995	0.996	0.995	0.996	0.999	0.996	0.999	0.998
-0.01	0.989	0.995	0.996	0.992	0.994	0.996	0.997	0.996	0.999	0.996	0.999	0.999
0	0.989	0.995	0.996	0.992	0.994	0.996	0.996	0.995	0.999	0.996	0.999	0.999
0.01	0.989	0.995	0.996	0.992	0.994	0.996	0.996	0.995	0.998	0.996	0.999	0.999
0.03	0.987	0.994	0.996	0.992	0.995	0.996	0.996	0.995	0.999	0.996	0.999	0.999
0.05	0.987	0.994	0.996	0.992	0.995	0.996	0.996	0.996	0.999	0.998	0.999	0.999
0.1	0.988	0.993	0.995	0.993	0.994	0.996	0.998	0.995	0.997	0.998	0.999	0.999

Table S91: Main simulations: the relative frequencies of cML-BIC selecting  $\hat{K} = K_0$  for  $m = 20$  and the InSIDE satisfied.

$\theta$	$q = 0$			$q = 0.2$			$q = 0.4$			$q = 0.6$		
	N = 50k	N = 100k	N = 200k	N = 50k	N = 100k	N = 200k	N = 50k	N = 100k	N = 200k	N = 50k	N = 100k	N = 200k
-0.1	0.980	0.985	0.993	0.979	0.990	0.992	0.989	0.994	0.994	0.991	0.995	0.997
-0.05	0.983	0.987	0.994	0.981	0.988	0.995	0.989	0.992	0.995	0.992	0.994	0.998
-0.03	0.986	0.989	0.994	0.979	0.988	0.995	0.987	0.993	0.995	0.992	0.994	0.998
-0.01	0.987	0.988	0.994	0.982	0.988	0.995	0.987	0.993	0.995	0.993	0.995	0.997
0	0.987	0.989	0.994	0.983	0.988	0.995	0.987	0.993	0.995	0.993	0.995	0.997
0.01	0.987	0.990	0.994	0.983	0.987	0.995	0.987	0.994	0.995	0.992	0.995	0.997
0.03	0.987	0.990	0.993	0.982	0.987	0.996	0.986	0.995	0.993	0.993	0.995	0.997
0.05	0.988	0.989	0.993	0.983	0.987	0.996	0.987	0.995	0.993	0.992	0.995	0.998
0.1	0.987	0.990	0.992	0.982	0.989	0.996	0.986	0.996	0.992	0.992	0.996	0.996

Table S92: Main simulations: the relative frequencies of cML-BIC selecting  $\hat{K} = K_0$  for  $m = 20$  and the InSIDE violated.

$\theta$	$q = 0$			$q = 0.2$			$q = 0.4$			$q = 0.6$		
	N = 50k	N = 100k	N = 200k	N = 50k	N = 100k	N = 200k	N = 50k	N = 100k	N = 200k	N = 50k	N = 100k	N = 200k
-0.1	0.980	0.985	0.993	0.990	0.993	0.989	0.995	0.998	0.996	0.988	0.995	0.997
-0.05	0.983	0.987	0.994	0.988	0.993	0.989	0.993	0.995	0.994	0.984	0.995	0.997
-0.03	0.986	0.989	0.994	0.988	0.991	0.989	0.993	0.994	0.995	0.984	0.994	0.997
-0.01	0.987	0.988	0.994	0.987	0.991	0.989	0.993	0.994	0.994	0.984	0.995	0.997
0	0.987	0.989	0.994	0.986	0.990	0.989	0.992	0.993	0.994	0.985	0.995	0.998
0.01	0.987	0.990	0.994	0.986	0.990	0.989	0.991	0.993	0.994	0.985	0.995	0.998
0.03	0.987	0.990	0.993	0.987	0.990	0.989	0.992	0.993	0.994	0.986	0.995	0.998
0.05	0.988	0.989	0.993	0.986	0.990	0.989	0.994	0.992	0.994	0.985	0.995	0.998
0.1	0.987	0.990	0.992	0.986	0.990	0.990	0.992	0.988	0.993	0.986	0.996	0.998

Table S93: Main simulations: the relative frequencies of cML-BIC selecting  $\hat{K} = K_0$  for  $m = 100$  and the InSIDE satisfied.

$\theta$	$q = 0$			$q = 0.2$			$q = 0.4$			$q = 0.6$		
	N = 50k	N = 100k	N = 200k	N = 50k	N = 100k	N = 200k	N = 50k	N = 100k	N = 200k	N = 50k	N = 100k	N = 200k
-0.1	0.897	0.928	0.958	0.931	0.945	0.957	0.945	0.957	0.974	0.963	0.965	0.988
-0.05	0.906	0.937	0.957	0.936	0.944	0.955	0.942	0.964	0.975	0.963	0.973	0.989
-0.03	0.906	0.936	0.956	0.936	0.945	0.958	0.939	0.967	0.974	0.964	0.973	0.988
-0.01	0.903	0.935	0.950	0.940	0.945	0.957	0.938	0.964	0.976	0.963	0.971	0.988
0	0.903	0.937	0.949	0.942	0.947	0.957	0.940	0.964	0.976	0.964	0.970	0.986
0.01	0.908	0.939	0.950	0.940	0.945	0.957	0.940	0.964	0.976	0.964	0.971	0.986
0.03	0.909	0.937	0.952	0.942	0.945	0.956	0.942	0.965	0.977	0.963	0.971	0.986
0.05	0.913	0.932	0.952	0.941	0.950	0.956	0.940	0.963	0.978	0.961	0.970	0.986
0.1	0.912	0.928	0.955	0.943	0.947	0.961	0.941	0.969	0.975	0.963	0.970	0.984

Table S94: Main simulations: the relative frequencies of cML-BIC selecting  $\hat{K} = K_0$  for  $m = 100$  and the InSIDE violated.

$\theta$	$q = 0$			$q = 0.2$			$q = 0.4$			$q = 0.6$		
	N = 50k	N = 100k	N = 200k	N = 50k	N = 100k	N = 200k	N = 50k	N = 100k	N = 200k	N = 50k	N = 100k	N = 200k
-0.1	0.897	0.928	0.958	0.930	0.946	0.961	0.943	0.948	0.965	0.971	0.975	0.987
-0.05	0.906	0.937	0.957	0.916	0.947	0.967	0.946	0.952	0.971	0.968	0.975	0.988
-0.03	0.906	0.936	0.956	0.915	0.951	0.966	0.948	0.951	0.973	0.965	0.976	0.986
-0.01	0.903	0.935	0.950	0.913	0.951	0.966	0.947	0.952	0.971	0.965	0.976	0.985
0	0.903	0.937	0.949	0.914	0.951	0.967	0.949	0.953	0.972	0.965	0.977	0.985
0.01	0.908	0.939	0.950	0.913	0.951	0.966	0.952	0.952	0.972	0.966	0.978	0.985
0.03	0.909	0.937	0.952	0.915	0.954	0.966	0.949	0.952	0.973	0.964	0.978	0.985
0.05	0.913	0.932	0.952	0.917	0.955	0.963	0.949	0.955	0.972	0.962	0.978	0.985
0.1	0.912	0.928	0.955	0.912	0.951	0.962	0.947	0.956	0.974	0.958	0.978	0.984

Table S95: Comparison of cML-MA-BIC and cML-BIC with cML-MA-BIC-DP and cML-BIC-DP: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean(SE( $\hat{\theta}$ )) when  $m = 10$ , the InSIDE violated,  $q = 0.6$ ,  $N = 50000$ .

$\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
Methods									
cML-MA-BIC	0.768, -0.1008, 0.0372, 0.0379	0.259, -0.0506, 0.0377, 0.0386	0.124, -0.0307, 0.0379, 0.0389	0.055, -0.0107, 0.0382, 0.0392	0.044, -0.0008, 0.0384, 0.0394	0.044, 0.0091, 0.0386, 0.0396	0.095, 0.0291, 0.0391, 0.0400	0.219, 0.0488, 0.0395, 0.0404	0.673, 0.0989, 0.0410, 0.0415
cML-BIC	0.783, -0.1012, 0.0374, 0.0375	0.267, -0.0509, 0.0381, 0.0381	0.132, -0.0309, 0.0383, 0.0384	0.058, -0.0108, 0.0386, 0.0388	0.047, -0.0008, 0.0388, 0.0389	0.050, 0.0093, 0.0391, 0.0391	0.102, 0.0293, 0.0395, 0.0395	0.229, 0.0492, 0.0396, 0.0399	0.682, 0.0995, 0.0408, 0.0411
cML-MA-BIC-DP, T = 100	0.774, -0.1004, 0.0371, 0.0375	0.259, -0.0505, 0.0374, 0.0382	0.127, -0.0307, 0.0375, 0.0385	0.060, -0.0110, 0.0377, 0.0389	0.043, -0.0012, 0.0379, 0.0391	0.043, 0.0086, 0.0381, 0.0394	0.091, 0.0283, 0.0386, 0.0399	0.205, 0.0480, 0.0392, 0.0405	0.647, 0.0976, 0.0408, 0.0421
cML-BIC-DP, T = 100	0.803, -0.1016, 0.0373, 0.0366	0.281, -0.0514, 0.0379, 0.0375	0.145, -0.0314, 0.0382, 0.0379	0.068, -0.0113, 0.0385, 0.0383	0.051, -0.0013, 0.0387, 0.0385	0.052, 0.0087, 0.0389, 0.0388	0.104, 0.0288, 0.0393, 0.0393	0.226, 0.0487, 0.0398, 0.0398	0.682, 0.0988, 0.0411, 0.0411
cML-MA-BIC-DP, T = 200	0.756, -0.1002, 0.0372, 0.0378	0.258, -0.0503, 0.0375, 0.0385	0.119, -0.0305, 0.0376, 0.0388	0.058, -0.0108, 0.0378, 0.0392	0.041, -0.0010, 0.0380, 0.0394	0.045, 0.0089, 0.0382, 0.0396	0.091, 0.0285, 0.0387, 0.0401	0.202, 0.0483, 0.0393, 0.0406	0.654, 0.0979, 0.0409, 0.0422
cML-BIC-DP, T = 200	0.785, -0.1014, 0.0374, 0.0369	0.278, -0.0512, 0.0380, 0.0377	0.138, -0.0311, 0.0383, 0.0381	0.064, -0.0111, 0.0386, 0.0385	0.052, -0.0010, 0.0388, 0.0387	0.050, 0.0090, 0.0389, 0.0390	0.104, 0.0290, 0.0394, 0.0394	0.227, 0.0490, 0.0398, 0.0399	0.684, 0.0992, 0.0410, 0.0412
cML-MA-BIC-DP, T = 500	0.761, -0.1002, 0.0371, 0.0377	0.254, -0.0503, 0.0374, 0.0384	0.120, -0.0306, 0.0375, 0.0387	0.056, -0.0108, 0.0377, 0.0390	0.040, -0.0010, 0.0378, 0.0392	0.043, 0.0088, 0.0380, 0.0394	0.092, 0.0285, 0.0385, 0.0399	0.214, 0.0483, 0.0391, 0.0405	0.655, 0.0979, 0.0408, 0.0420
cML-BIC-DP, T = 500	0.789, -0.1014, 0.0373, 0.0369	0.277, -0.0512, 0.0379, 0.0376	0.135, -0.0312, 0.0382, 0.0380	0.063, -0.0111, 0.0385, 0.0384	0.049, -0.0011, 0.0386, 0.0386	0.053, 0.0089, 0.0388, 0.0388	0.107, 0.0289, 0.0392, 0.0393	0.232, 0.0490, 0.0397, 0.0398	0.683, 0.0991, 0.0410, 0.0410

Table S96: Comparison of cML-MA-BIC and cML-BIC with cML-MA-BIC-DP and cML-BIC-DP: in each cell, from top to bottom are empirical type-I error/power,  $\text{mean}(\hat{\theta})$ ,  $\text{SD}(\hat{\theta})$ ,  $\text{mean}(\text{SE}(\hat{\theta}))$  when  $m = 10$ , the InSIDE violated,  $q = 0.6$ ,  $N = 100000$ .

Methods $\backslash \theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-BIC	0.955, -0.0988, 0.0260, 0.0267	0.451, -0.0488, 0.0265, 0.0272	0.188, -0.0288, 0.0266, 0.0274	0.050, -0.0089, 0.0268, 0.0276	0.036, 0.0010, 0.0270, 0.0278	0.053, 0.0109, 0.0271, 0.0279	0.202, 0.0308, 0.0275, 0.0281	0.446, 0.0507, 0.0279, 0.0284	0.935, 0.1007, 0.0288, 0.0293
cML-BIC	0.960, -0.0991, 0.0260, 0.0264	0.466, -0.0491, 0.0265, 0.0269	0.198, -0.0291, 0.0267, 0.0271	0.055, -0.0091, 0.0270, 0.0273	0.039, 0.0009, 0.0271, 0.0275	0.056, 0.0109, 0.0273, 0.0276	0.208, 0.0310, 0.0276, 0.0279	0.457, 0.0510, 0.0279, 0.0282	0.938, 0.1010, 0.0288, 0.0290
cML-MA-BIC-DP, T = 100	0.954, -0.0984, 0.0261, 0.0263	0.457, -0.0485, 0.0264, 0.0268	0.183, -0.0287, 0.0264, 0.0270	0.055, -0.0090, 0.0266, 0.0273	0.039, 0.0008, 0.0267, 0.0274	0.057, 0.0107, 0.0269, 0.0276	0.195, 0.0303, 0.0273, 0.0280	0.433, 0.0501, 0.0278, 0.0284	0.919, 0.1000, 0.0289, 0.0294
cML-BIC-DP, T = 100	0.961, -0.0992, 0.0260, 0.0257	0.487, -0.0492, 0.0265, 0.0263	0.203, -0.0291, 0.0268, 0.0266	0.061, -0.0091, 0.0270, 0.0269	0.044, 0.0009, 0.0272, 0.0270	0.065, 0.0108, 0.0273, 0.0272	0.213, 0.0309, 0.0276, 0.0275	0.464, 0.0509, 0.0280, 0.0278	0.933, 0.1009, 0.0289, 0.0288
cML-MA-BIC-DP, T = 200	0.957, -0.0984, 0.0260, 0.0265	0.449, -0.0485, 0.0263, 0.0270	0.184, -0.0287, 0.0264, 0.0272	0.051, -0.0090, 0.0265, 0.0274	0.038, 0.0008, 0.0266, 0.0275	0.056, 0.0107, 0.0268, 0.0277	0.195, 0.0304, 0.0273, 0.0281	0.444, 0.0502, 0.0278, 0.0284	0.928, 0.1000, 0.0289, 0.0295
cML-BIC-DP, T = 200	0.964, -0.0992, 0.0261, 0.0259	0.472, -0.0491, 0.0265, 0.0264	0.206, -0.0291, 0.0267, 0.0267	0.058, -0.0091, 0.0270, 0.0270	0.044, 0.0009, 0.0271, 0.0271	0.061, 0.0109, 0.0272, 0.0273	0.213, 0.0309, 0.0276, 0.0276	0.468, 0.0509, 0.0279, 0.0279	0.938, 0.1010, 0.0288, 0.0288
cML-MA-BIC-DP, T = 500	0.956, -0.0984, 0.0261, 0.0265	0.461, -0.0485, 0.0264, 0.0269	0.187, -0.0286, 0.0265, 0.0271	0.052, -0.0089, 0.0266, 0.0273	0.039, 0.0009, 0.0268, 0.0275	0.056, 0.0107, 0.0269, 0.0276	0.200, 0.0304, 0.0274, 0.0280	0.443, 0.0502, 0.0279, 0.0284	0.929, 0.1001, 0.0290, 0.0294
cML-BIC-DP, T = 500	0.962, -0.0991, 0.0262, 0.0258	0.486, -0.0491, 0.0266, 0.0264	0.205, -0.0291, 0.0268, 0.0266	0.062, -0.0091, 0.0271, 0.0269	0.048, 0.0009, 0.0272, 0.0271	0.067, 0.0109, 0.0274, 0.0272	0.215, 0.0309, 0.0277, 0.0275	0.465, 0.0509, 0.0280, 0.0278	0.939, 0.1010, 0.0289, 0.0287

Table S97: Comparison of cML-MA-BIC and cML-BIC with cML-MA-BIC-DP and cML-BIC-DP: in each cell, from top to bottom are empirical type-I error/power,  $\text{mean}(\hat{\theta})$ ,  $\text{SD}(\hat{\theta})$ ,  $\text{mean}(\text{SE}(\hat{\theta}))$  when  $m = 10$ , the InSIDE violated,  $q = 0.6$ ,  $N = 200000$ .

Methods $\backslash \theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-BIC	0.998, -0.0999, 0.0187, 0.0189	0.748, -0.0499, 0.0190, 0.0192	0.334, -0.0299, 0.0190, 0.0194	0.076, -0.0100, 0.0192, 0.0196	0.048, -0.0001, 0.0193, 0.0197	0.079, 0.0099, 0.0193, 0.0197	0.325, 0.0298, 0.0196, 0.0199	0.709, 0.0498, 0.0198, 0.0202	0.997, 0.0998, 0.0203, 0.0207
cML-BIC	0.998, -0.1001, 0.0187, 0.0187	0.756, -0.0501, 0.0189, 0.0190	0.347, -0.0301, 0.0191, 0.0192	0.079, -0.0100, 0.0193, 0.0194	0.051, 0.0000, 0.0194, 0.0195	0.086, 0.0100, 0.0195, 0.0196	0.335, 0.0300, 0.0196, 0.0198	0.714, 0.0500, 0.0198, 0.0200	0.998, 0.1000, 0.0204, 0.0205
cML-MA-BIC-DP, T = 100	0.996, -0.0997, 0.0188, 0.0186	0.752, -0.0497, 0.0190, 0.0190	0.343, -0.0298, 0.0190, 0.0191	0.077, -0.0100, 0.0190, 0.0193	0.054, -0.0001, 0.0191, 0.0194	0.082, 0.0097, 0.0192, 0.0195	0.324, 0.0295, 0.0195, 0.0198	0.703, 0.0494, 0.0198, 0.0201	0.995, 0.0994, 0.0204, 0.0208
cML-BIC-DP, T = 100	0.997, -0.1002, 0.0187, 0.0182	0.771, -0.0502, 0.0190, 0.0186	0.373, -0.0302, 0.0191, 0.0188	0.085, -0.0102, 0.0193, 0.0190	0.061, -0.0002, 0.0193, 0.0192	0.088, 0.0098, 0.0195, 0.0193	0.341, 0.0298, 0.0197, 0.0195	0.720, 0.0498, 0.0198, 0.0197	0.997, 0.0999, 0.0204, 0.0204
cML-MA-BIC-DP, T = 200	0.997, -0.0998, 0.0187, 0.0187	0.755, -0.0497, 0.0190, 0.0191	0.342, -0.0298, 0.0190, 0.0192	0.076, -0.0100, 0.0190, 0.0194	0.047, -0.0002, 0.0191, 0.0195	0.080, 0.0097, 0.0192, 0.0196	0.329, 0.0295, 0.0195, 0.0199	0.701, 0.0494, 0.0198, 0.0201	0.996, 0.0994, 0.0203, 0.0208
cML-BIC-DP, T = 200	0.997, -0.1002, 0.0187, 0.0183	0.773, -0.0502, 0.0190, 0.0187	0.365, -0.0302, 0.0191, 0.0189	0.085, -0.0102, 0.0192, 0.0191	0.052, -0.0002, 0.0193, 0.0192	0.083, 0.0098, 0.0194, 0.0194	0.345, 0.0298, 0.0196, 0.0196	0.714, 0.0498, 0.0197, 0.0198	0.997, 0.0999, 0.0203, 0.0204
cML-MA-BIC-DP, T = 500	0.998, -0.0997, 0.0187, 0.0186	0.758, -0.0497, 0.0189, 0.0190	0.341, -0.0298, 0.0190, 0.0191	0.076, -0.0100, 0.0190, 0.0193	0.046, -0.0001, 0.0191, 0.0194	0.078, 0.0097, 0.0192, 0.0195	0.321, 0.0295, 0.0195, 0.0198	0.709, 0.0494, 0.0198, 0.0200	0.997, 0.0994, 0.0203, 0.0207
cML-BIC-DP, T = 500	0.998, -0.1002, 0.0187, 0.0183	0.773, -0.0501, 0.0190, 0.0187	0.362, -0.0301, 0.0191, 0.0188	0.080, -0.0101, 0.0192, 0.0190	0.048, -0.0001, 0.0193, 0.0192	0.090, 0.0099, 0.0194, 0.0193	0.341, 0.0298, 0.0196, 0.0195	0.723, 0.0498, 0.0198, 0.0197	0.998, 0.0999, 0.0203, 0.0203



Table S98: Comparison of cML-MA-BIC and cML-BIC with cML-MA-BIC-DP and cML-BIC-DP: in each cell, from top to bottom are empirical type-I error/power,  $\text{mean}(\hat{\theta})$ ,  $\text{SD}(\hat{\theta})$ ,  $\text{mean}(\text{SE}(\hat{\theta}))$  when  $m = 20$ , the InSIDE violated,  $q = 0.6$ ,  $N = 50000$ .

Methods $\backslash \theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-BIC	0.957, -0.1000, 0.0265, 0.0274	0.435, -0.0500, 0.0270, 0.0279	0.194, -0.0301, 0.0271, 0.0281	0.063, -0.0102, 0.0273, 0.0284	0.037, -0.0002, 0.0274, 0.0285	0.053, 0.0097, 0.0275, 0.0286	0.165, 0.0296, 0.0279, 0.0289	0.401, 0.0496, 0.0282, 0.0292	0.917, 0.0996, 0.0291, 0.0300
cML-BIC	0.957, -0.1002, 0.0266, 0.0271	0.446, -0.0502, 0.0272, 0.0275	0.200, -0.0302, 0.0274, 0.0277	0.065, -0.0102, 0.0277, 0.0280	0.042, -0.0002, 0.0277, 0.0281	0.060, 0.0098, 0.0279, 0.0282	0.180, 0.0298, 0.0281, 0.0285	0.423, 0.0498, 0.0284, 0.0288	0.922, 0.0998, 0.0292, 0.0296
cML-MA-BIC-DP, T = 100	0.929, -0.0986, 0.0266, 0.0291	0.385, -0.0488, 0.0267, 0.0293	0.162, -0.0292, 0.0267, 0.0294	0.052, -0.0098, 0.0267, 0.0295	0.031, -0.0001, 0.0268, 0.0296	0.041, 0.0096, 0.0270, 0.0297	0.138, 0.0290, 0.0274, 0.0301	0.353, 0.0486, 0.0279, 0.0306	0.880, 0.0981, 0.0292, 0.0317
cML-BIC-DP, T = 100	0.950, -0.0998, 0.0267, 0.0278	0.425, -0.0497, 0.0271, 0.0282	0.189, -0.0298, 0.0272, 0.0284	0.065, -0.0099, 0.0275, 0.0286	0.037, 0.0000, 0.0276, 0.0287	0.060, 0.0099, 0.0277, 0.0289	0.165, 0.0297, 0.0281, 0.0291	0.406, 0.0497, 0.0284, 0.0294	0.899, 0.0995, 0.0295, 0.0304
cML-MA-BIC-DP, T = 200	0.935, -0.0989, 0.0266, 0.0286	0.392, -0.0492, 0.0267, 0.0289	0.169, -0.0296, 0.0267, 0.0290	0.053, -0.0101, 0.0267, 0.0292	0.033, -0.0005, 0.0268, 0.0293	0.043, 0.0092, 0.0269, 0.0294	0.138, 0.0286, 0.0274, 0.0299	0.345, 0.0482, 0.0279, 0.0303	0.880, 0.0977, 0.0291, 0.0316
cML-BIC-DP, T = 200	0.955, -0.1002, 0.0266, 0.0273	0.438, -0.0502, 0.0271, 0.0278	0.191, -0.0302, 0.0272, 0.0281	0.067, -0.0103, 0.0275, 0.0283	0.041, -0.0004, 0.0276, 0.0284	0.056, 0.0095, 0.0277, 0.0286	0.174, 0.0294, 0.0281, 0.0289	0.414, 0.0492, 0.0285, 0.0292	0.898, 0.0991, 0.0294, 0.0302
cML-MA-BIC-DP, T = 500	0.936, -0.0986, 0.0265, 0.0290	0.373, -0.0489, 0.0266, 0.0293	0.160, -0.0293, 0.0265, 0.0293	0.050, -0.0099, 0.0265, 0.0295	0.027, -0.0003, 0.0266, 0.0296	0.038, 0.0094, 0.0268, 0.0297	0.127, 0.0288, 0.0272, 0.0302	0.341, 0.0483, 0.0278, 0.0306	0.877, 0.0978, 0.0290, 0.0319
cML-BIC-DP, T = 500	0.945, -0.0999, 0.0266, 0.0278	0.429, -0.0499, 0.0269, 0.0282	0.183, -0.0300, 0.0271, 0.0284	0.061, -0.0101, 0.0273, 0.0287	0.036, -0.0002, 0.0274, 0.0288	0.056, 0.0097, 0.0276, 0.0289	0.165, 0.0295, 0.0279, 0.0292	0.394, 0.0494, 0.0283, 0.0295	0.906, 0.0993, 0.0293, 0.0305

Table S99: Comparison of cML-MA-BIC and cML-BIC with cML-MA-BIC-DP and cML-BIC-DP: in each cell, from top to bottom are empirical type-I error/power,  $\text{mean}(\hat{\theta})$ ,  $\text{SD}(\hat{\theta})$ ,  $\text{mean}(\text{SE}(\hat{\theta}))$  when  $m = 20$ , the InSIDE violated,  $q = 0.6$ ,  $N = 100000$ .

Methods $\backslash \theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-BIC	0.999, -0.0996, 0.0195, 0.0193	0.700, -0.0495, 0.0198, 0.0196	0.330, -0.0295, 0.0198, 0.0198	0.078, -0.0095, 0.0201, 0.0199	0.051, 0.0004, 0.0201, 0.0200	0.086, 0.0104, 0.0202, 0.0201	0.332, 0.0304, 0.0204, 0.0203	0.695, 0.0504, 0.0207, 0.0205	0.997, 0.1005, 0.0212, 0.0211
cML-BIC	0.999, -0.0996, 0.0195, 0.0191	0.711, -0.0496, 0.0198, 0.0194	0.338, -0.0296, 0.0199, 0.0196	0.080, -0.0096, 0.0201, 0.0197	0.055, 0.0004, 0.0202, 0.0198	0.091, 0.0105, 0.0203, 0.0199	0.342, 0.0305, 0.0205, 0.0201	0.703, 0.0505, 0.0207, 0.0203	0.997, 0.1005, 0.0212, 0.0209
cML-MA-BIC-DP, T = 100	0.998, -0.0989, 0.0196, 0.0201	0.663, -0.0488, 0.0198, 0.0203	0.296, -0.0290, 0.0198, 0.0204	0.066, -0.0093, 0.0197, 0.0205	0.040, 0.0005, 0.0198, 0.0205	0.070, 0.0103, 0.0199, 0.0207	0.299, 0.0299, 0.0202, 0.0209	0.659, 0.0498, 0.0206, 0.0212	0.994, 0.0997, 0.0212, 0.0219
cML-BIC-DP, T = 100	0.999, -0.0996, 0.0196, 0.0193	0.698, -0.0495, 0.0199, 0.0196	0.337, -0.0295, 0.0200, 0.0198	0.081, -0.0095, 0.0201, 0.0199	0.054, 0.0005, 0.0202, 0.0200	0.089, 0.0105, 0.0203, 0.0201	0.333, 0.0305, 0.0205, 0.0203	0.706, 0.0505, 0.0207, 0.0205	0.994, 0.1005, 0.0213, 0.0211
cML-MA-BIC-DP, T = 200	0.999, -0.0991, 0.0196, 0.0197	0.672, -0.0490, 0.0198, 0.0200	0.308, -0.0292, 0.0197, 0.0201	0.068, -0.0095, 0.0197, 0.0202	0.043, 0.0003, 0.0198, 0.0203	0.075, 0.0101, 0.0198, 0.0204	0.308, 0.0298, 0.0202, 0.0207	0.659, 0.0496, 0.0205, 0.0211	0.993, 0.0995, 0.0212, 0.0218
cML-BIC-DP, T = 200	0.999, -0.0997, 0.0196, 0.0190	0.707, -0.0496, 0.0199, 0.0193	0.351, -0.0296, 0.0200, 0.0195	0.077, -0.0096, 0.0201, 0.0197	0.056, 0.0004, 0.0201, 0.0198	0.092, 0.0103, 0.0202, 0.0199	0.344, 0.0303, 0.0204, 0.0201	0.699, 0.0503, 0.0207, 0.0204	0.995, 0.1003, 0.0213, 0.0210
cML-MA-BIC-DP, T = 500	0.998, -0.0989, 0.0195, 0.0200	0.662, -0.0489, 0.0197, 0.0203	0.297, -0.0290, 0.0197, 0.0204	0.061, -0.0094, 0.0196, 0.0205	0.039, 0.0004, 0.0197, 0.0205	0.065, 0.0102, 0.0198, 0.0207	0.299, 0.0298, 0.0201, 0.0210	0.649, 0.0496, 0.0205, 0.0213	0.993, 0.0996, 0.0211, 0.0220
cML-BIC-DP, T = 500	0.999, -0.0996, 0.0195, 0.0193	0.709, -0.0495, 0.0198, 0.0196	0.338, -0.0295, 0.0199, 0.0198	0.075, -0.0095, 0.0200, 0.0199	0.050, 0.0004, 0.0201, 0.0200	0.084, 0.0104, 0.0202, 0.0201	0.330, 0.0304, 0.0204, 0.0204	0.693, 0.0504, 0.0206, 0.0206	0.997, 0.1005, 0.0212, 0.0212

Table S100: Comparison of cML-MA-BIC and cML-BIC with cML-MA-BIC-DP and cML-BIC-DP: in each cell, from top to bottom are empirical type-I error/power,  $\text{mean}(\hat{\theta})$ ,  $\text{SD}(\hat{\theta})$ ,  $\text{mean}(\text{SE}(\hat{\theta}))$  when  $m = 20$ , the InSIDE violated,  $q = 0.6$ ,  $N = 200000$ .

Methods $\backslash \theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-BIC	1.000, -0.0998, 0.0143, 0.0136	0.944, -0.0498, 0.0145, 0.0139	0.567, -0.0298, 0.0146, 0.0140	0.122, -0.0098, 0.0147, 0.0141	0.052, 0.0001, 0.0147, 0.0142	0.110, 0.0101, 0.0148, 0.0142	0.564, 0.0301, 0.0149, 0.0144	0.916, 0.0501, 0.0151, 0.0145	1.000, 0.1001, 0.0154, 0.0149
cML-BIC	1.000, -0.0999, 0.0143, 0.0135	0.946, -0.0499, 0.0145, 0.0138	0.573, -0.0299, 0.0146, 0.0139	0.125, -0.0098, 0.0147, 0.0140	0.054, 0.0001, 0.0147, 0.0140	0.115, 0.0101, 0.0148, 0.0141	0.572, 0.0301, 0.0149, 0.0142	0.919, 0.0502, 0.0150, 0.0144	1.000, 0.1002, 0.0154, 0.0148
cML-MA-BIC-DP, T = 100	1.000, -0.0995, 0.0144, 0.0140	0.932, -0.0495, 0.0145, 0.0143	0.531, -0.0296, 0.0146, 0.0143	0.116, -0.0098, 0.0145, 0.0144	0.048, 0.0000, 0.0146, 0.0144	0.099, 0.0099, 0.0146, 0.0145	0.528, 0.0297, 0.0149, 0.0147	0.899, 0.0496, 0.0151, 0.0149	1.000, 0.0996, 0.0155, 0.0153
cML-BIC-DP, T = 100	1.000, -0.0999, 0.0144, 0.0136	0.939, -0.0499, 0.0146, 0.0138	0.563, -0.0299, 0.0147, 0.0139	0.129, -0.0099, 0.0147, 0.0141	0.053, 0.0001, 0.0148, 0.0141	0.116, 0.0101, 0.0148, 0.0142	0.567, 0.0300, 0.0149, 0.0143	0.912, 0.0501, 0.0151, 0.0145	1.000, 0.1001, 0.0154, 0.0148
cML-MA-BIC-DP, T = 200	1.000, -0.0996, 0.0144, 0.0138	0.936, -0.0495, 0.0146, 0.0141	0.546, -0.0296, 0.0146, 0.0142	0.111, -0.0098, 0.0146, 0.0142	0.048, 0.0000, 0.0146, 0.0143	0.100, 0.0099, 0.0147, 0.0144	0.541, 0.0297, 0.0149, 0.0146	0.900, 0.0496, 0.0151, 0.0148	1.000, 0.0996, 0.0155, 0.0153
cML-BIC-DP, T = 200	1.000, -0.0999, 0.0144, 0.0134	0.944, -0.0499, 0.0146, 0.0137	0.578, -0.0299, 0.0147, 0.0138	0.132, -0.0099, 0.0148, 0.0139	0.055, 0.0001, 0.0148, 0.0140	0.115, 0.0100, 0.0148, 0.0141	0.573, 0.0300, 0.0150, 0.0142	0.914, 0.0500, 0.0151, 0.0144	1.000, 0.1000, 0.0155, 0.0148
cML-MA-BIC-DP, T = 500	1.000, -0.0995, 0.0143, 0.0140	0.931, -0.0494, 0.0145, 0.0143	0.535, -0.0295, 0.0145, 0.0143	0.107, -0.0097, 0.0145, 0.0144	0.047, 0.0001, 0.0145, 0.0144	0.097, 0.0099, 0.0146, 0.0145	0.530, 0.0297, 0.0149, 0.0148	0.899, 0.0496, 0.0151, 0.0150	1.000, 0.0996, 0.0154, 0.0154
cML-BIC-DP, T = 500	1.000, -0.0999, 0.0143, 0.0136	0.943, -0.0499, 0.0145, 0.0138	0.564, -0.0298, 0.0146, 0.0140	0.121, -0.0099, 0.0147, 0.0141	0.052, 0.0001, 0.0147, 0.0142	0.106, 0.0101, 0.0148, 0.0142	0.565, 0.0301, 0.0149, 0.0144	0.916, 0.0501, 0.0150, 0.0145	1.000, 0.1001, 0.0154, 0.0149

Table S101: Comparison of cML-MA-BIC and cML-BIC with cML-MA-BIC-DP and cML-BIC-DP: in each cell, from top to bottom are empirical type-I error/power,  $\text{mean}(\hat{\theta})$ ,  $\text{SD}(\hat{\theta})$ ,  $\text{mean}(\text{SE}(\hat{\theta}))$  when  $m = 100$ , the InSIDE violated,  $q = 0.6$ ,  $N = 50000$ .

Methods $\backslash \theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-BIC	1.000, -0.0996, 0.0151, 0.0147	0.916, -0.0496, 0.0151, 0.0149	0.481, -0.0296, 0.0152, 0.0149	0.116, -0.0096, 0.0153, 0.0150	0.050, 0.0003, 0.0153, 0.0151	0.103, 0.0103, 0.0154, 0.0151	0.534, 0.0303, 0.0155, 0.0152	0.885, 0.0503, 0.0156, 0.0154	1.000, 0.1003, 0.0160, 0.0157
cML-BIC	1.000, -0.0996, 0.0150, 0.0146	0.923, -0.0496, 0.0151, 0.0147	0.495, -0.0296, 0.0152, 0.0148	0.123, -0.0096, 0.0153, 0.0149	0.054, 0.0004, 0.0154, 0.0149	0.110, 0.0104, 0.0154, 0.0150	0.543, 0.0303, 0.0155, 0.0151	0.888, 0.0503, 0.0156, 0.0152	1.000, 0.1003, 0.0160, 0.0155
cML-MA-BIC-DP, T = 100	1.000, -0.0988, 0.0151, 0.0163	0.861, -0.0489, 0.0152, 0.0165	0.391, -0.0290, 0.0151, 0.0165	0.074, -0.0094, 0.0150, 0.0163	0.031, 0.0003, 0.0150, 0.0164	0.063, 0.0100, 0.0151, 0.0165	0.419, 0.0295, 0.0154, 0.0168	0.822, 0.0493, 0.0157, 0.0171	1.000, 0.0992, 0.0161, 0.0175
cML-BIC-DP, T = 100	1.000, -0.0989, 0.0152, 0.0160	0.861, -0.0489, 0.0152, 0.0162	0.407, -0.0291, 0.0152, 0.0162	0.088, -0.0094, 0.0151, 0.0161	0.037, 0.0003, 0.0151, 0.0161	0.072, 0.0100, 0.0152, 0.0162	0.444, 0.0297, 0.0155, 0.0165	0.845, 0.0495, 0.0157, 0.0168	1.000, 0.0994, 0.0161, 0.0172
cML-MA-BIC-DP, T = 200	1.000, -0.0987, 0.0150, 0.0163	0.865, -0.0488, 0.0152, 0.0164	0.400, -0.0290, 0.0151, 0.0164	0.073, -0.0094, 0.0150, 0.0163	0.034, 0.0003, 0.0150, 0.0163	0.060, 0.0100, 0.0151, 0.0164	0.429, 0.0295, 0.0154, 0.0167	0.831, 0.0493, 0.0157, 0.0170	1.000, 0.0992, 0.0161, 0.0174
cML-BIC-DP, T = 200	1.000, -0.0988, 0.0151, 0.0159	0.872, -0.0489, 0.0153, 0.0160	0.417, -0.0290, 0.0152, 0.0160	0.088, -0.0094, 0.0151, 0.0160	0.035, 0.0004, 0.0151, 0.0160	0.078, 0.0101, 0.0152, 0.0161	0.453, 0.0297, 0.0155, 0.0164	0.843, 0.0496, 0.0158, 0.0166	1.000, 0.0994, 0.0161, 0.0170
cML-MA-BIC-DP, T = 500	1.000, -0.0987, 0.0150, 0.0163	0.860, -0.0488, 0.0152, 0.0165	0.401, -0.0290, 0.0151, 0.0164	0.065, -0.0094, 0.0150, 0.0163	0.033, 0.0003, 0.0150, 0.0163	0.062, 0.0100, 0.0150, 0.0164	0.425, 0.0295, 0.0154, 0.0168	0.828, 0.0493, 0.0157, 0.0171	1.000, 0.0992, 0.0160, 0.0175
cML-BIC-DP, T = 500	1.000, -0.0989, 0.0151, 0.0159	0.868, -0.0490, 0.0152, 0.0161	0.418, -0.0291, 0.0152, 0.0160	0.090, -0.0094, 0.0151, 0.0160	0.040, 0.0003, 0.0151, 0.0160	0.078, 0.0101, 0.0152, 0.0161	0.454, 0.0298, 0.0155, 0.0164	0.838, 0.0496, 0.0157, 0.0166	1.000, 0.0995, 0.0161, 0.0170

Table S102: Comparison of cML-MA-BIC and cML-BIC with cML-MA-BIC-DP and cML-BIC-DP: in each cell, from top to bottom are empirical type-I error/power,  $\text{mean}(\hat{\theta})$ ,  $\text{SD}(\hat{\theta})$ ,  $\text{mean}(\text{SE}(\hat{\theta}))$  when  $m = 100$ , the InSIDE violated,  $q = 0.6$ ,  $N = 100000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-BIC	1.000, -0.0998, 0.0108, 0.0104	0.994, -0.0497, 0.0109, 0.0105	0.797, -0.0297, 0.0110, 0.0106	0.165, -0.0097, 0.0110, 0.0106	0.057, 0.0003, 0.0111, 0.0107	0.168, 0.0103, 0.0111, 0.0107	0.783, 0.0303, 0.0112, 0.0108	0.994, 0.0503, 0.0113, 0.0109	1.000, 0.1003, 0.0116, 0.0111
cML-BIC	1.000, -0.0998, 0.0108, 0.0103	0.994, -0.0498, 0.0109, 0.0104	0.799, -0.0298, 0.0110, 0.0105	0.175, -0.0098, 0.0110, 0.0106	0.058, 0.0002, 0.0111, 0.0106	0.174, 0.0102, 0.0111, 0.0106	0.785, 0.0303, 0.0112, 0.0107	0.994, 0.0503, 0.0113, 0.0108	1.000, 0.1003, 0.0116, 0.0110
cML-MA-BIC-DP, T = 100	1.000, -0.0992, 0.0109, 0.0113	0.989, -0.0492, 0.0110, 0.0115	0.732, -0.0293, 0.0110, 0.0115	0.121, -0.0095, 0.0109, 0.0114	0.034, 0.0002, 0.0109, 0.0114	0.125, 0.0100, 0.0110, 0.0115	0.720, 0.0298, 0.0113, 0.0117	0.988, 0.0497, 0.0114, 0.0118	1.000, 0.0997, 0.0116, 0.0121
cML-BIC-DP, T = 100	1.000, -0.0993, 0.0110, 0.0111	0.988, -0.0493, 0.0111, 0.0112	0.731, -0.0293, 0.0111, 0.0112	0.130, -0.0095, 0.0110, 0.0112	0.048, 0.0003, 0.0110, 0.0112	0.136, 0.0101, 0.0111, 0.0113	0.732, 0.0299, 0.0113, 0.0114	0.988, 0.0499, 0.0114, 0.0116	1.000, 0.0998, 0.0117, 0.0118
cML-MA-BIC-DP, T = 200	1.000, -0.0992, 0.0108, 0.0113	0.989, -0.0492, 0.0110, 0.0114	0.724, -0.0292, 0.0110, 0.0114	0.121, -0.0095, 0.0109, 0.0113	0.034, 0.0003, 0.0108, 0.0113	0.128, 0.0100, 0.0109, 0.0114	0.718, 0.0298, 0.0112, 0.0117	0.988, 0.0498, 0.0113, 0.0118	1.000, 0.0997, 0.0116, 0.0120
cML-BIC-DP, T = 200	1.000, -0.0993, 0.0109, 0.0110	0.988, -0.0494, 0.0110, 0.0111	0.739, -0.0294, 0.0111, 0.0111	0.142, -0.0096, 0.0110, 0.0111	0.047, 0.0002, 0.0110, 0.0111	0.135, 0.0101, 0.0111, 0.0112	0.736, 0.0299, 0.0113, 0.0114	0.991, 0.0499, 0.0114, 0.0115	1.000, 0.0999, 0.0117, 0.0117
cML-MA-BIC-DP, T = 500	1.000, -0.0992, 0.0108, 0.0113	0.991, -0.0493, 0.0110, 0.0114	0.732, -0.0293, 0.0110, 0.0114	0.123, -0.0095, 0.0108, 0.0113	0.037, 0.0002, 0.0108, 0.0113	0.120, 0.0100, 0.0109, 0.0114	0.726, 0.0298, 0.0112, 0.0117	0.987, 0.0498, 0.0113, 0.0118	1.000, 0.0997, 0.0116, 0.0120
cML-BIC-DP, T = 500	1.000, -0.0994, 0.0109, 0.0109	0.991, -0.0494, 0.0110, 0.0110	0.758, -0.0294, 0.0110, 0.0111	0.140, -0.0096, 0.0109, 0.0110	0.048, 0.0003, 0.0109, 0.0111	0.136, 0.0101, 0.0110, 0.0111	0.753, 0.0300, 0.0112, 0.0113	0.989, 0.0500, 0.0113, 0.0114	1.000, 0.0999, 0.0116, 0.0116

Table S103: Comparison of cML-MA-BIC and cML-BIC with cML-MA-BIC-DP and cML-BIC-DP: in each cell, from top to bottom are empirical type-I error/power,  $\text{mean}(\hat{\theta})$ ,  $\text{SD}(\hat{\theta})$ ,  $\text{mean}(\text{SE}(\hat{\theta}))$  when  $m = 100$ , the InSIDE violated,  $q = 0.6$ ,  $N = 200000$ .

Methods \ $\theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
cML-MA-BIC	1.000, -0.1004, 0.0072, 0.0073	1.000, -0.0504, 0.0073, 0.0074	0.982, -0.0304, 0.0073, 0.0075	0.292, -0.0104, 0.0073, 0.0075	0.043, -0.0005, 0.0074, 0.0075	0.234, 0.0095, 0.0074, 0.0076	0.978, 0.0295, 0.0075, 0.0076	1.000, 0.0495, 0.0075, 0.0077	1.000, 0.0995, 0.0077, 0.0078
cML-BIC	1.000, -0.1004, 0.0072, 0.0073	1.000, -0.0504, 0.0073, 0.0074	0.981, -0.0304, 0.0073, 0.0074	0.301, -0.0105, 0.0074, 0.0074	0.046, -0.0005, 0.0074, 0.0075	0.239, 0.0095, 0.0074, 0.0075	0.977, 0.0295, 0.0075, 0.0076	1.000, 0.0495, 0.0075, 0.0076	1.000, 0.0995, 0.0077, 0.0078
cML-MA-BIC-DP, T = 100	1.000, -0.1001, 0.0072, 0.0078	1.000, -0.0502, 0.0073, 0.0079	0.969, -0.0302, 0.0073, 0.0080	0.234, -0.0103, 0.0073, 0.0079	0.027, -0.0005, 0.0073, 0.0079	0.192, 0.0093, 0.0073, 0.0080	0.960, 0.0292, 0.0075, 0.0081	1.000, 0.0492, 0.0076, 0.0082	1.000, 0.0991, 0.0077, 0.0084
cML-BIC-DP, T = 100	1.000, -0.1002, 0.0073, 0.0076	1.000, -0.0502, 0.0073, 0.0077	0.973, -0.0302, 0.0074, 0.0077	0.267, -0.0103, 0.0073, 0.0077	0.038, -0.0004, 0.0073, 0.0077	0.220, 0.0094, 0.0074, 0.0078	0.963, 0.0293, 0.0075, 0.0079	1.000, 0.0493, 0.0076, 0.0080	1.000, 0.0992, 0.0077, 0.0082
cML-MA-BIC-DP, T = 200	1.000, -0.1001, 0.0072, 0.0078	1.000, -0.0501, 0.0073, 0.0079	0.970, -0.0302, 0.0073, 0.0079	0.230, -0.0103, 0.0073, 0.0079	0.026, -0.0005, 0.0073, 0.0079	0.195, 0.0093, 0.0073, 0.0079	0.958, 0.0292, 0.0075, 0.0081	1.000, 0.0492, 0.0076, 0.0082	1.000, 0.0991, 0.0077, 0.0083
cML-BIC-DP, T = 200	1.000, -0.1002, 0.0072, 0.0076	1.000, -0.0502, 0.0073, 0.0077	0.970, -0.0303, 0.0073, 0.0077	0.263, -0.0103, 0.0073, 0.0077	0.040, -0.0005, 0.0073, 0.0077	0.225, 0.0094, 0.0074, 0.0077	0.964, 0.0293, 0.0075, 0.0079	1.000, 0.0493, 0.0076, 0.0079	1.000, 0.0992, 0.0078, 0.0081
cML-MA-BIC-DP, T = 500	1.000, -0.1001, 0.0072, 0.0078	1.000, -0.0501, 0.0073, 0.0079	0.971, -0.0302, 0.0073, 0.0080	0.227, -0.0103, 0.0073, 0.0079	0.028, -0.0005, 0.0073, 0.0079	0.191, 0.0093, 0.0073, 0.0080	0.961, 0.0292, 0.0075, 0.0081	1.000, 0.0492, 0.0075, 0.0082	1.000, 0.0991, 0.0077, 0.0084
cML-BIC-DP, T = 500	1.000, -0.1003, 0.0073, 0.0076	1.000, -0.0503, 0.0073, 0.0077	0.971, -0.0303, 0.0074, 0.0077	0.265, -0.0104, 0.0073, 0.0077	0.038, -0.0005, 0.0073, 0.0077	0.214, 0.0094, 0.0074, 0.0077	0.968, 0.0293, 0.0075, 0.0079	1.000, 0.0493, 0.0076, 0.0079	1.000, 0.0993, 0.0078, 0.0081

Table S104: Relative frequencies of goodness-of-fit tests' rejecting the null at the  $p$ -value cutoff 0.05 when  $m = 10$ , the InSIDE violated,  $q = 0.6$ .

Methods $\backslash \theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
GOF1, N = 50k, T = 100	0.009	0.007	0.006	0.004	0.004	0.004	0.005	0.001	0.003
GOF2, N = 50k, T = 100	0.012	0.009	0.008	0.005	0.006	0.005	0.006	0.001	0.004
GOF1, N = 50k, T = 200	0.002	0.002	0.002	0.003	0.003	0.003	0.003	0.001	0.003
GOF2, N = 50k, T = 200	0.002	0.002	0.003	0.003	0.003	0.004	0.003	0.001	0.004
GOF1, N = 50k, T = 500	0.002	0.003	0.003	0.003	0.004	0.004	0.003	0.001	0.005
GOF2, N = 50k, T = 500	0.002	0.003	0.003	0.003	0.004	0.004	0.003	0.001	0.005
GOF1, N = 100k, T = 100	0.014	0.007	0.006	0.004	0.004	0.003	0.001	0.000	0.000
GOF2, N = 100k, T = 100	0.019	0.012	0.010	0.008	0.006	0.004	0.002	0.002	0.000
GOF1, N = 100k, T = 200	0.002	0.001	0.001	0.001	0.001	0.001	0.000	0.000	0.000
GOF2, N = 100k, T = 200	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.000	0.000
GOF1, N = 100k, T = 500	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.000	0.001
GOF2, N = 100k, T = 500	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.000	0.001
GOF1, N = 200k, T = 100	0.029	0.022	0.019	0.015	0.014	0.012	0.010	0.009	0.003
GOF2, N = 200k, T = 100	0.032	0.024	0.020	0.016	0.015	0.014	0.012	0.009	0.006
GOF1, N = 200k, T = 200	0.015	0.004	0.003	0.002	0.002	0.001	0.001	0.001	0.001
GOF2, N = 200k, T = 200	0.013	0.004	0.002	0.001	0.001	0.001	0.001	0.001	0.001
GOF1, N = 200k, T = 500	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
GOF2, N = 200k, T = 500	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001

Table S105: Relative frequencies of goodness-of-fit tests' rejecting the null at  $p$ -value cutoff 0.05 when  $m = 20$ , the InSIDE violated,  $q = 0.6$ .

Methods $\backslash \theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
GOF1, N = 50k, T = 100	0.047	0.056	0.055	0.052	0.051	0.051	0.056	0.055	0.057
GOF2, N = 50k, T = 100	0.035	0.039	0.039	0.041	0.039	0.039	0.039	0.042	0.054
GOF1, N = 50k, T = 200	0.046	0.053	0.053	0.052	0.052	0.053	0.050	0.049	0.051
GOF2, N = 50k, T = 200	0.045	0.051	0.052	0.050	0.047	0.049	0.045	0.045	0.053
GOF1, N = 50k, T = 500	0.050	0.053	0.052	0.053	0.050	0.049	0.048	0.046	0.048
GOF2, N = 50k, T = 500	0.048	0.049	0.050	0.048	0.047	0.046	0.043	0.042	0.051
GOF1, N = 100k, T = 100	0.062	0.068	0.076	0.078	0.082	0.084	0.085	0.087	0.092
GOF2, N = 100k, T = 100	0.045	0.052	0.059	0.062	0.064	0.067	0.069	0.075	0.079
GOF1, N = 100k, T = 200	0.068	0.064	0.064	0.064	0.065	0.064	0.064	0.065	0.064
GOF2, N = 100k, T = 200	0.065	0.063	0.065	0.063	0.063	0.063	0.062	0.062	0.067
GOF1, N = 100k, T = 500	0.043	0.040	0.037	0.031	0.030	0.030	0.031	0.028	0.025
GOF2, N = 100k, T = 500	0.036	0.033	0.032	0.030	0.028	0.028	0.028	0.025	0.025
GOF1, N = 200k, T = 100	0.066	0.071	0.075	0.079	0.080	0.083	0.086	0.088	0.101
GOF2, N = 200k, T = 100	0.052	0.061	0.064	0.064	0.065	0.066	0.070	0.074	0.087
GOF1, N = 200k, T = 200	0.072	0.074	0.072	0.073	0.072	0.072	0.071	0.072	0.074
GOF2, N = 200k, T = 200	0.067	0.068	0.065	0.066	0.065	0.066	0.066	0.065	0.066
GOF1, N = 200k, T = 500	0.049	0.047	0.048	0.048	0.049	0.050	0.050	0.047	0.045
GOF2, N = 200k, T = 500	0.042	0.043	0.044	0.044	0.043	0.043	0.042	0.042	0.044

Table S106: Relative frequencies of goodness-of-fit tests' rejecting the null at  $p$ -value cutoff 0.05 when  $m = 100$ , the InSIDE violated,  $q = 0.6$ .

Methods $\backslash \theta$	-0.1	-0.05	-0.03	-0.01	0	0.01	0.03	0.05	0.1
GOF1, N = 50k, T = 100	0.083	0.085	0.080	0.079	0.077	0.075	0.078	0.082	0.084
GOF2, N = 50k, T = 100	0.063	0.068	0.063	0.059	0.060	0.062	0.059	0.065	0.075
GOF1, N = 50k, T = 200	0.057	0.057	0.057	0.054	0.051	0.051	0.057	0.059	0.074
GOF2, N = 50k, T = 200	0.048	0.050	0.050	0.048	0.046	0.045	0.052	0.058	0.077
GOF1, N = 50k, T = 500	0.057	0.057	0.056	0.054	0.051	0.048	0.059	0.081	0.105
GOF2, N = 50k, T = 500	0.057	0.057	0.058	0.056	0.053	0.050	0.065	0.079	0.110
GOF1, N = 100k, T = 100	0.082	0.074	0.075	0.073	0.071	0.074	0.067	0.068	0.066
GOF2, N = 100k, T = 100	0.065	0.060	0.061	0.058	0.056	0.056	0.055	0.054	0.053
GOF1, N = 100k, T = 200	0.059	0.065	0.062	0.058	0.057	0.056	0.059	0.060	0.059
GOF2, N = 100k, T = 200	0.054	0.051	0.051	0.053	0.049	0.048	0.050	0.050	0.050
GOF1, N = 100k, T = 500	0.061	0.062	0.061	0.063	0.059	0.058	0.059	0.061	0.060
GOF2, N = 100k, T = 500	0.059	0.059	0.060	0.058	0.056	0.055	0.057	0.059	0.060
GOF1, N = 200k, T = 100	0.082	0.081	0.083	0.081	0.074	0.076	0.077	0.073	0.075
GOF2, N = 200k, T = 100	0.072	0.073	0.071	0.067	0.063	0.063	0.066	0.069	0.066
GOF1, N = 200k, T = 200	0.082	0.084	0.084	0.086	0.084	0.084	0.087	0.086	0.094
GOF2, N = 200k, T = 200	0.080	0.080	0.080	0.081	0.077	0.078	0.079	0.080	0.081
GOF1, N = 200k, T = 500	0.066	0.064	0.066	0.066	0.063	0.063	0.064	0.064	0.067
GOF2, N = 200k, T = 500	0.062	0.063	0.063	0.064	0.065	0.065	0.066	0.067	0.066

Table S107: Simulations with weak invalid IVs: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean( $SE(\hat{\theta})$ ) when  $h_y = 0.1$  and  $h_u = 0$ .

Methods \ $\theta$	-0.2	-0.1	-0.05	0	0.05	0.1	0.2
cML-MA-BIC	0.997, -0.1943, 0.0330, 0.0145	0.974, -0.0955, 0.0296, 0.0143	0.766, -0.0468, 0.0273, 0.0142	0.228, -0.0002, 0.0245, 0.0142	0.777, 0.0470, 0.0263, 0.0143	0.978, 0.0963, 0.0283, 0.0143	0.999, 0.1953, 0.0311, 0.0145
cML-BIC	0.998, -0.1956, 0.0333, 0.0131	0.982, -0.0966, 0.0302, 0.0130	0.811, -0.0474, 0.0284, 0.0129	0.299, -0.0001, 0.0263, 0.0129	0.814, 0.0482, 0.0273, 0.0129	0.984, 0.0975, 0.0290, 0.0130	1.000, 0.1966, 0.0317, 0.0131
cML-MA-BIC-DP, T = 100	0.952, -0.1804, 0.0359, 0.0311	0.830, -0.0872, 0.0275, 0.0266	0.454, -0.0421, 0.0232, 0.0233	0.047, 0.0000, 0.0204, 0.0208	0.447, 0.0424, 0.0231, 0.0232	0.846, 0.0879, 0.0271, 0.0264	0.958, 0.1814, 0.0342, 0.0313
cML-BIC-DP, T = 100	0.953, -0.1809, 0.0362, 0.0303	0.833, -0.0876, 0.0277, 0.0263	0.477, -0.0423, 0.0234, 0.0230	0.050, 0.0000, 0.0208, 0.0206	0.455, 0.0427, 0.0233, 0.0230	0.851, 0.0885, 0.0272, 0.0259	0.960, 0.1824, 0.0339, 0.0305
cML-MA-BIC-DP, T = 200	0.951, -0.1800, 0.0361, 0.0314	0.833, -0.0870, 0.0276, 0.0267	0.462, -0.0421, 0.0232, 0.0234	0.046, -0.0001, 0.0204, 0.0209	0.440, 0.0423, 0.0231, 0.0233	0.845, 0.0877, 0.0271, 0.0265	0.956, 0.1810, 0.0345, 0.0316
cML-BIC-DP, T = 200	0.953, -0.1807, 0.0360, 0.0307	0.835, -0.0874, 0.0277, 0.0263	0.466, -0.0423, 0.0235, 0.0231	0.052, 0.0000, 0.0208, 0.0207	0.450, 0.0426, 0.0233, 0.0230	0.850, 0.0882, 0.0273, 0.0262	0.960, 0.1820, 0.0343, 0.0309
cML-MA-BIC-DP, T = 500	0.948, -0.1797, 0.0363, 0.0317	0.829, -0.0869, 0.0275, 0.0269	0.454, -0.0420, 0.0231, 0.0235	0.042, -0.0001, 0.0203, 0.0209	0.442, 0.0422, 0.0230, 0.0234	0.844, 0.0875, 0.0270, 0.0267	0.953, 0.1807, 0.0347, 0.0319
cML-BIC-DP, T = 500	0.951, -0.1804, 0.0361, 0.0311	0.836, -0.0873, 0.0276, 0.0264	0.467, -0.0422, 0.0233, 0.0232	0.048, -0.0001, 0.0205, 0.0207	0.456, 0.0424, 0.0231, 0.0231	0.849, 0.0879, 0.0271, 0.0263	0.958, 0.1814, 0.0344, 0.0313
MR-Mix	0.984, -0.2001, 0.0337, 0.0270	0.904, -0.0995, 0.0346, 0.0262	0.574, -0.0495, 0.0346, 0.0290	0.121, 0.0008, 0.0350, 0.0266	0.565, 0.0510, 0.0349, 0.0281	0.904, 0.1011, 0.0351, 0.0271	0.985, 0.2009, 0.0357, 0.0289
MR-ContMix	0.999, -0.1990, 0.0298, NA	0.985, -0.0993, 0.0297, NA	0.829, -0.0492, 0.0293, NA	0.313, 0.0006, 0.0293, NA	0.831, 0.0506, 0.0291, NA	0.989, 0.1004, 0.0295, NA	1.000, 0.1995, 0.0289, NA
MR-Lasso	1.000, -0.1987, 0.0261, 0.0153	0.989, -0.0992, 0.0254, 0.0153	0.806, -0.0497, 0.0254, 0.0153	0.215, 0.0000, 0.0254, 0.0153	0.799, 0.0496, 0.0256, 0.0153	0.986, 0.0993, 0.0253, 0.0153	1.000, 0.1990, 0.0260, 0.0154
MR-PRESSO	1.000, -0.1994, 0.0312, 0.0182	0.967, -0.0998, 0.0309, 0.0179	0.702, -0.0498, 0.0306, 0.0178	0.201, 0.0000, 0.0305, 0.0178	0.688, 0.0497, 0.0305, 0.0179	0.968, 0.0995, 0.0306, 0.0179	1.000, 0.1990, 0.0306, 0.0182
MR-IVW	0.963, -0.1998, 0.0499, 0.0502	0.533, -0.1003, 0.0498, 0.0502	0.179, -0.0506, 0.0498, 0.0501	0.054, -0.0008, 0.0498, 0.0501	0.171, 0.0489, 0.0499, 0.0502	0.509, 0.0986, 0.0499, 0.0502	0.962, 0.1981, 0.0499, 0.0502
MR-IVW-Oracle	1.000, -0.1983, 0.0173, 0.0176	1.000, -0.0988, 0.0171, 0.0175	0.804, -0.0491, 0.0170, 0.0174	0.041, 0.0006, 0.0170, 0.0174	0.815, 0.0504, 0.0170, 0.0174	0.999, 0.1001, 0.0170, 0.0175	1.000, 0.1995, 0.0173, 0.0176
MR-Egger	0.658, -0.2008, 0.0841, 0.0844	0.234, -0.1014, 0.0841, 0.0844	0.100, -0.0517, 0.0842, 0.0844	0.053, -0.0020, 0.0842, 0.0844	0.099, 0.0477, 0.0842, 0.0844	0.237, 0.0974, 0.0843, 0.0844	0.632, 0.1969, 0.0844, 0.0845
MR-Weighted-Median	0.999, -0.1928, 0.0309, 0.0204	0.959, -0.0972, 0.0297, 0.0201	0.685, -0.0494, 0.0294, 0.0200	0.140, -0.0012, 0.0293, 0.0200	0.643, 0.0468, 0.0294, 0.0201	0.955, 0.0948, 0.0297, 0.0201	0.998, 0.1910, 0.0310, 0.0204
MR-Weighted-Mode	0.718, -0.1953, 0.1579, 1.0123	0.551, -0.1038, 0.1629, 1.0020	0.323, -0.0491, 0.1451, 1.0032	0.096, -0.0066, 0.1448, 0.9972	0.325, 0.0438, 0.1440, 0.9936	0.561, 0.0911, 0.1528, 0.9987	0.720, 0.1857, 0.1560, 0.9929
MR-RAPS1	0.965, -0.2008, 0.0501, 0.0499	0.539, -0.1008, 0.0501, 0.0499	0.186, -0.0508, 0.0501, 0.0499	0.057, -0.0009, 0.0501, 0.0499	0.177, 0.0491, 0.0501, 0.0499	0.517, 0.0991, 0.0501, 0.0499	0.964, 0.1991, 0.0502, 0.0500
MR-RAPS2	0.985, -0.2011, 0.0428, 0.0411	0.681, -0.1007, 0.0430, 0.0410	0.299, -0.0506, 0.0430, 0.0410	0.087, -0.0006, 0.0431, 0.0410	0.289, 0.0494, 0.0429, 0.0411	0.655, 0.0994, 0.0429, 0.0412	0.985, 0.1996, 0.0432, 0.0413
MR-RAPS3	1.000, -0.2275, 0.0578, 0.0118	0.951, -0.1148, 0.0579, 0.0117	0.821, -0.0580, 0.0579, 0.0117	0.687, -0.0010, 0.0578, 0.0117	0.806, 0.0560, 0.0578, 0.0117	0.948, 0.1128, 0.0577, 0.0117	1.000, 0.2256, 0.0575, 0.0118
MR-RAPS4	0.999, -0.2027, 0.0494, 0.0107	0.992, -0.1008, 0.0371, 0.0105	0.898, -0.0509, 0.0315, 0.0105	0.393, 0.0006, 0.0347, 0.0104	0.900, 0.0516, 0.0295, 0.0105	0.999, 0.1001, 0.0440, 0.0105	1.000, 0.2038, 0.0546, 0.0107

Table S108: Simulations with weak invalid IVs: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean( $SE(\hat{\theta})$ ) when  $h_y = 0.2$  and  $h_u = 0$ .

Methods \ $\theta$	-0.2	-0.1	-0.05	0	0.05	0.1	0.2
cML-MA-BIC	0.996, -0.1952, 0.0320, 0.0151	0.980, -0.0966, 0.0281, 0.0149	0.784, -0.0477, 0.0260, 0.0149	0.196, 0.0000, 0.0243, 0.0148	0.784, 0.0480, 0.0257, 0.0149	0.978, 0.0975, 0.0273, 0.0150	0.997, 0.1963, 0.0301, 0.0151
cML-BIC	0.999, -0.1963, 0.0325, 0.0139	0.986, -0.0974, 0.0290, 0.0137	0.816, -0.0482, 0.0269, 0.0137	0.269, -0.0001, 0.0259, 0.0136	0.823, 0.0488, 0.0267, 0.0137	0.983, 0.0984, 0.0281, 0.0137	0.997, 0.1973, 0.0309, 0.0139
cML-MA-BIC-DP, T = 100	0.945, -0.1810, 0.0355, 0.0315	0.840, -0.0882, 0.0270, 0.0263	0.485, -0.0430, 0.0228, 0.0230	0.042, 0.0000, 0.0203, 0.0206	0.484, 0.0432, 0.0226, 0.0229	0.849, 0.0891, 0.0260, 0.0261	0.941, 0.1816, 0.0349, 0.0320
cML-BIC-DP, T = 100	0.947, -0.1818, 0.0355, 0.0308	0.851, -0.0886, 0.0272, 0.0259	0.497, -0.0432, 0.0231, 0.0227	0.050, 0.0000, 0.0208, 0.0203	0.494, 0.0435, 0.0228, 0.0225	0.859, 0.0895, 0.0261, 0.0256	0.947, 0.1825, 0.0349, 0.0310
cML-MA-BIC-DP, T = 200	0.943, -0.1805, 0.0359, 0.0320	0.829, -0.0879, 0.0271, 0.0266	0.472, -0.0428, 0.0227, 0.0231	0.045, 0.0000, 0.0203, 0.0207	0.471, 0.0431, 0.0225, 0.0231	0.846, 0.0889, 0.0260, 0.0263	0.940, 0.1811, 0.0351, 0.0325
cML-BIC-DP, T = 200	0.948, -0.1813, 0.0358, 0.0312	0.832, -0.0884, 0.0270, 0.0262	0.494, -0.0431, 0.0229, 0.0228	0.054, 0.0000, 0.0205, 0.0205	0.490, 0.0433, 0.0226, 0.0228	0.850, 0.0894, 0.0261, 0.0259	0.944, 0.1820, 0.0347, 0.0316
cML-MA-BIC-DP, T = 500	0.940, -0.1803, 0.0360, 0.0322	0.827, -0.0878, 0.0270, 0.0266	0.471, -0.0428, 0.0227, 0.0231	0.039, 0.0000, 0.0202, 0.0207	0.474, 0.0430, 0.0224, 0.0231	0.848, 0.0888, 0.0259, 0.0264	0.940, 0.1810, 0.0351, 0.0326
cML-BIC-DP, T = 500	0.947, -0.1810, 0.0359, 0.0315	0.839, -0.0882, 0.0271, 0.0262	0.490, -0.0431, 0.0229, 0.0228	0.046, 0.0000, 0.0204, 0.0205	0.484, 0.0432, 0.0226, 0.0228	0.850, 0.0892, 0.0259, 0.0260	0.943, 0.1817, 0.0348, 0.0319
MR-Mix	0.986, -0.1997, 0.0314, 0.0250	0.911, -0.0997, 0.0301, 0.0258	0.598, -0.0496, 0.0299, 0.0261	0.111, 0.0004, 0.0299, 0.0258	0.594, 0.0503, 0.0300, 0.1315	0.907, 0.1003, 0.0300, 0.0272	0.983, 0.2005, 0.0297, 0.0266
MR-ContMix	1.000, -0.1990, 0.0284, NA	0.991, -0.0993, 0.0276, NA	0.840, -0.0495, 0.0276, NA	0.279, 0.0003, 0.0274, NA	0.834, 0.0498, 0.0274, NA	0.990, 0.0997, 0.0273, NA	1.000, 0.1993, 0.0275, NA
MR-Lasso	1.000, -0.1986, 0.0268, 0.0161	0.986, -0.0992, 0.0265, 0.0161	0.803, -0.0498, 0.0262, 0.0160	0.198, -0.0001, 0.0265, 0.0160	0.796, 0.0499, 0.0261, 0.0160	0.979, 0.0995, 0.0264, 0.0161	1.000, 0.1991, 0.0273, 0.0162
MR-PRESSO	0.994, -0.1986, 0.0391, 0.0192	0.943, -0.0992, 0.0388, 0.0189	0.686, -0.0499, 0.0388, 0.0189	0.242, -0.0003, 0.0389, 0.0189	0.671, 0.0494, 0.0387, 0.0189	0.933, 0.0991, 0.0387, 0.0190	0.998, 0.1986, 0.0390, 0.0193
MR-IVW	0.814, -0.2000, 0.0695, 0.0702	0.301, -0.1006, 0.0695, 0.0702	0.113, -0.0508, 0.0695, 0.0702	0.048, -0.0011, 0.0695, 0.0702	0.118, 0.0486, 0.0695, 0.0702	0.312, 0.0984, 0.0695, 0.0702	0.798, 0.1979, 0.0695, 0.0702
MR-IVW-Oracle	1.000, -0.1983, 0.0173, 0.0176	1.000, -0.0988, 0.0171, 0.0175	0.804, -0.0491, 0.0170, 0.0174	0.041, 0.0006, 0.0170, 0.0174	0.815, 0.0504, 0.0170, 0.0174	0.999, 0.1001, 0.0170, 0.0175	1.000, 0.1995, 0.0173, 0.0176
MR-Egger	0.420, -0.2013, 0.1176, 0.1181	0.149, -0.1018, 0.1176, 0.1181	0.068, -0.0521, 0.1177, 0.1181	0.051, -0.0024, 0.1177, 0.1181	0.079, 0.0473, 0.1177, 0.1181	0.144, 0.0970, 0.1178, 0.1181	0.396, 0.1964, 0.1179, 0.1182
MR-Weighted-Median	0.997, -0.1906, 0.0342, 0.0213	0.942, -0.0963, 0.0325, 0.0210	0.655, -0.0489, 0.0325, 0.0209	0.135, -0.0013, 0.0327, 0.0209	0.625, 0.0463, 0.0331, 0.0209	0.946, 0.0939, 0.0336, 0.0210	0.993, 0.1892, 0.0344, 0.0213
MR-Weighted-Mode	0.672, -0.1951, 0.1847, 1.3382	0.503, -0.1026, 0.1823, 1.3283	0.278, -0.0545, 0.1760, 1.3229	0.109, -0.0033, 0.1779, 1.3167	0.285, 0.0438, 0.1903, 1.3139	0.511, 0.0892, 0.2169, 1.3198	0.676, 0.1770, 0.1952, 1.3048
MR-RAPS1	0.820, -0.2011, 0.0699, 0.0698	0.313, -0.1011, 0.0699, 0.0698	0.117, -0.0511, 0.0699, 0.0698	0.052, -0.0011, 0.0699, 0.0698	0.121, 0.0489, 0.0699, 0.0698	0.314, 0.0989, 0.0699, 0.0698	0.805, 0.1989, 0.0699, 0.0699
MR-RAPS2	0.902, -0.2015, 0.0580, 0.0552	0.469, -0.1014, 0.0582, 0.0550	0.248, -0.0512, 0.0582, 0.0550	0.095, -0.0013, 0.0582, 0.0552	0.237, 0.0466, 0.0898, 0.0551	0.459, 0.0988, 0.0584, 0.0550	0.886, 0.1995, 0.0585, 0.0555
MR-RAPS3	0.994, -0.2629, 0.0957, 0.0138	0.925, -0.1339, 0.0964, 0.0138	0.838, -0.0680, 0.0965, 0.0137	0.778, -0.0017, 0.0963, 0.0137	0.808, 0.0647, 0.0959, 0.0138	0.920, 0.1307, 0.0954, 0.0138	1.000, 0.2600, 0.0943, 0.0138
MR-RAPS4	1.000, -0.2039, 0.0807, 0.0107	0.998, -0.1016, 0.0322, 0.0105	0.907, -0.0517, 0.0464, 0.0105	0.379, -0.0004, 0.0454, 0.0104	0.903, 0.0508, 0.0392, 0.0105	0.999, 0.1016, 0.0437, 0.0105	1.000, 0.2049, 0.0944, 0.0108

Table S109: Simulations with weak invalid IVs: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean( $SE(\hat{\theta})$ ) when  $h_y = 0.4$  and  $h_u = 0$ .

Methods \ $\theta$	-0.2	-0.1	-0.05	0	0.05	0.1	0.2
cML-MA-BIC	0.996, -0.1960, 0.0311, 0.0157	0.983, -0.0978, 0.0254, 0.0155	0.787, -0.0485, 0.0240, 0.0155	0.153, 0.0000, 0.0227, 0.0154	0.795, 0.0486, 0.0238, 0.0154	0.985, 0.0982, 0.0248, 0.0155	0.998, 0.1978, 0.0268, 0.0156
cML-BIC	0.998, -0.1971, 0.0315, 0.0146	0.986, -0.0987, 0.0261, 0.0144	0.810, -0.0492, 0.0251, 0.0143	0.207, 0.0001, 0.0241, 0.0143	0.831, 0.0494, 0.0246, 0.0143	0.988, 0.0991, 0.0255, 0.0144	0.998, 0.1989, 0.0274, 0.0146
cML-MA-BIC-DP, T = 100	0.950, -0.1831, 0.0346, 0.0305	0.887, -0.0902, 0.0249, 0.0250	0.512, -0.0438, 0.0216, 0.0222	0.037, 0.0002, 0.0196, 0.0200	0.537, 0.0444, 0.0216, 0.0221	0.891, 0.0910, 0.0244, 0.0249	0.967, 0.1850, 0.0312, 0.0302
cML-BIC-DP, T = 100	0.951, -0.1839, 0.0342, 0.0296	0.890, -0.0906, 0.0248, 0.0244	0.539, -0.0440, 0.0217, 0.0218	0.045, 0.0002, 0.0197, 0.0196	0.550, 0.0447, 0.0218, 0.0216	0.898, 0.0915, 0.0244, 0.0243	0.969, 0.1858, 0.0311, 0.0293
cML-MA-BIC-DP, T = 200	0.951, -0.1826, 0.0351, 0.0310	0.882, -0.0899, 0.0249, 0.0253	0.502, -0.0437, 0.0215, 0.0225	0.032, 0.0002, 0.0195, 0.0202	0.528, 0.0442, 0.0216, 0.0223	0.891, 0.0908, 0.0244, 0.0251	0.963, 0.1845, 0.0313, 0.0308
cML-BIC-DP, T = 200	0.950, -0.1834, 0.0348, 0.0301	0.890, -0.0903, 0.0250, 0.0249	0.524, -0.0439, 0.0217, 0.0221	0.041, 0.0001, 0.0197, 0.0199	0.538, 0.0445, 0.0218, 0.0219	0.895, 0.0913, 0.0244, 0.0246	0.966, 0.1854, 0.0312, 0.0300
cML-MA-BIC-DP, T = 500	0.950, -0.1824, 0.0352, 0.0311	0.878, -0.0899, 0.0249, 0.0253	0.507, -0.0438, 0.0215, 0.0224	0.034, 0.0001, 0.0195, 0.0202	0.530, 0.0442, 0.0216, 0.0223	0.890, 0.0907, 0.0244, 0.0251	0.961, 0.1842, 0.0315, 0.0310
cML-BIC-DP, T = 500	0.951, -0.1832, 0.0351, 0.0304	0.888, -0.0904, 0.0249, 0.0249	0.527, -0.0441, 0.0215, 0.0221	0.036, 0.0001, 0.0196, 0.0199	0.540, 0.0443, 0.0217, 0.0219	0.892, 0.0910, 0.0244, 0.0247	0.965, 0.1850, 0.0313, 0.0303
MR-Mix	0.992, -0.2004, 0.0269, 0.0257	0.930, -0.1004, 0.0266, 0.0259	0.597, -0.0503, 0.0266, 0.0260	0.094, 0.0000, 0.0263, 0.0813	0.602, 0.0500, 0.0266, 0.0274	0.929, 0.1001, 0.0265, 0.0263	0.989, 0.2005, 0.0272, 0.0255
MR-ContMix	1.000, -0.1991, 0.0257, NA	0.993, -0.0995, 0.0254, NA	0.833, -0.0494, 0.0256, NA	0.255, 0.0002, 0.0258, NA	0.850, 0.0500, 0.0258, NA	0.992, 0.0998, 0.0258, NA	1.000, 0.1994, 0.0261, NA
MR-Lasso	1.000, -0.1989, 0.0271, 0.0168	0.985, -0.0999, 0.0269, 0.0167	0.795, -0.0502, 0.0267, 0.0166	0.168, -0.0003, 0.0264, 0.0167	0.778, 0.0489, 0.0268, 0.0166	0.980, 0.0989, 0.0266, 0.0166	1.000, 0.1989, 0.0277, 0.0167
MR-PRESSO	0.977, -0.1985, 0.0550, 0.0207	0.901, -0.0995, 0.0550, 0.0205	0.691, -0.0499, 0.0550, 0.0205	0.285, -0.0004, 0.0547, 0.0205	0.687, 0.0489, 0.0548, 0.0205	0.890, 0.0984, 0.0549, 0.0206	0.973, 0.1978, 0.0549, 0.0208
MR-IVW	0.548, -0.2004, 0.0975, 0.0987	0.168, -0.1009, 0.0975, 0.0987	0.085, -0.0512, 0.0975, 0.0987	0.047, -0.0014, 0.0975, 0.0987	0.081, 0.0483, 0.0975, 0.0987	0.179, 0.0980, 0.0975, 0.0987	0.523, 0.1975, 0.0975, 0.0987
MR-IVW-Oracle	1.000, -0.1983, 0.0173, 0.0176	1.000, -0.0988, 0.0171, 0.0175	0.804, -0.0491, 0.0170, 0.0174	0.041, 0.0006, 0.0170, 0.0174	0.815, 0.0504, 0.0170, 0.0174	0.999, 0.1001, 0.0170, 0.0175	1.000, 0.1995, 0.0173, 0.0176
MR-Egger	0.238, -0.2019, 0.1653, 0.1661	0.098, -0.1025, 0.1654, 0.1661	0.053, -0.0528, 0.1654, 0.1661	0.048, -0.0031, 0.1655, 0.1661	0.067, 0.0466, 0.1655, 0.1661	0.102, 0.0964, 0.1655, 0.1661	0.242, 0.1958, 0.1656, 0.1661
MR-Weighted-Median	0.991, -0.1893, 0.0366, 0.0221	0.937, -0.0955, 0.0342, 0.0218	0.630, -0.0483, 0.0339, 0.0217	0.138, -0.0011, 0.0339, 0.0216	0.606, 0.0460, 0.0349, 0.0216	0.935, 0.0932, 0.0358, 0.0217	0.990, 0.1876, 0.0380, 0.0221
MR-Weighted-Mode	0.611, -0.1957, 0.2474, 1.7626	0.433, -0.1032, 0.2596, 1.7570	0.238, -0.0531, 0.2733, 1.7426	0.116, -0.0174, 0.2997, 1.7348	0.242, 0.0212, 0.2746, 1.7399	0.437, 0.0724, 0.2637, 1.7390	0.626, 0.1641, 0.2735, 1.7241
MR-RAPS1	0.555, -0.2014, 0.0980, 0.0982	0.181, -0.1014, 0.0980, 0.0982	0.088, -0.0514, 0.0980, 0.0982	0.053, -0.0014, 0.0980, 0.0982	0.085, 0.0486, 0.0980, 0.0982	0.180, 0.0986, 0.0980, 0.0982	0.534, 0.1985, 0.0980, 0.0982
MR-RAPS2	0.709, -0.2033, 0.0945, 0.0757	0.348, -0.1019, 0.0806, 0.0760	0.211, -0.0529, 0.0834, 0.0756	0.094, -0.0013, 0.0823, 0.0758	0.214, 0.0487, 0.0813, 0.0756	0.348, 0.1000, 0.0898, 0.0760	0.687, 0.1993, 0.0815, 0.0760
MR-RAPS3	0.978, -0.3806, 0.2224, 0.0220	0.916, -0.2052, 0.2554, 0.0233	0.862, -0.1165, 0.3253, 0.0334	0.842, -0.0112, 0.3403, 0.0265	0.830, -0.4931, 15.5916, 12.8425	0.911, 0.2063, 0.3738, 0.0321	0.975, 0.3540, 0.7622, 0.0580
MR-RAPS4	1.000, -0.2024, 0.1177, 0.0108	0.999, -0.1026, 0.0472, 0.0105	0.917, -0.0498, 0.0774, 0.0105	0.377, 0.0033, 0.1136, 0.0105	0.922, 0.0545, 0.0637, 0.0105	0.997, 0.1012, 0.0549, 0.0105	0.999, 0.2060, 0.1311, 0.0109

Table S110: Simulations with weak invalid IVs: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean( $SE(\hat{\theta})$ ) when  $h_y = 0.6$  and  $h_u = 0$ .

Methods \ $\theta$	-0.2	-0.1	-0.05	0	0.05	0.1	0.2
cML-MA-BIC	0.996, -0.1968, 0.0294, 0.0161	0.987, -0.0982, 0.0242, 0.0157	0.792, -0.0485, 0.0233, 0.0157	0.152, 0.0002, 0.0223, 0.0156	0.799, 0.0489, 0.0233, 0.0156	0.985, 0.0986, 0.0241, 0.0157	0.999, 0.1980, 0.0266, 0.0158
cML-BIC	0.999, -0.1977, 0.0295, 0.0149	0.992, -0.0990, 0.0246, 0.0147	0.820, -0.0491, 0.0238, 0.0146	0.185, 0.0001, 0.0233, 0.0146	0.827, 0.0495, 0.0238, 0.0146	0.992, 0.0993, 0.0245, 0.0147	0.999, 0.1986, 0.0272, 0.0149
cML-MA-BIC-DP, T = 100	0.953, -0.1853, 0.0324, 0.0291	0.900, -0.0914, 0.0239, 0.0242	0.544, -0.0444, 0.0211, 0.0217	0.029, 0.0002, 0.0192, 0.0197	0.575, 0.0450, 0.0212, 0.0215	0.913, 0.0922, 0.0236, 0.0239	0.965, 0.1871, 0.0297, 0.0285
cML-BIC-DP, T = 100	0.959, -0.1860, 0.0321, 0.0284	0.906, -0.0918, 0.0240, 0.0237	0.559, -0.0447, 0.0214, 0.0214	0.036, 0.0002, 0.0195, 0.0194	0.582, 0.0453, 0.0212, 0.0211	0.916, 0.0927, 0.0238, 0.0234	0.967, 0.1877, 0.0295, 0.0278
cML-MA-BIC-DP, T = 200	0.953, -0.1848, 0.0326, 0.0296	0.897, -0.0911, 0.0238, 0.0245	0.530, -0.0443, 0.0210, 0.0220	0.025, 0.0002, 0.0191, 0.0199	0.557, 0.0449, 0.0211, 0.0218	0.912, 0.0919, 0.0236, 0.0243	0.964, 0.1866, 0.0300, 0.0291
cML-BIC-DP, T = 200	0.952, -0.1855, 0.0326, 0.0289	0.900, -0.0915, 0.0238, 0.0240	0.542, -0.0445, 0.0212, 0.0216	0.032, 0.0002, 0.0193, 0.0196	0.565, 0.0451, 0.0213, 0.0214	0.912, 0.0923, 0.0237, 0.0238	0.966, 0.1871, 0.0301, 0.0283
cML-MA-BIC-DP, T = 500	0.950, -0.1847, 0.0327, 0.0297	0.900, -0.0911, 0.0238, 0.0245	0.536, -0.0443, 0.0210, 0.0219	0.025, 0.0002, 0.0191, 0.0198	0.560, 0.0448, 0.0211, 0.0218	0.913, 0.0919, 0.0237, 0.0242	0.965, 0.1864, 0.0301, 0.0293
cML-BIC-DP, T = 500	0.952, -0.1855, 0.0325, 0.0290	0.902, -0.0914, 0.0238, 0.0240	0.548, -0.0444, 0.0211, 0.0215	0.032, 0.0003, 0.0194, 0.0195	0.572, 0.0452, 0.0212, 0.0214	0.914, 0.0923, 0.0237, 0.0238	0.967, 0.1871, 0.0298, 0.0286
MR-Mix	0.990, -0.2003, 0.0259, 0.0254	0.926, -0.1001, 0.0260, 0.0244	0.619, -0.0502, 0.0259, 0.0246	0.095, 0.0000, 0.0259, 0.0252	0.616, 0.0499, 0.0260, 0.0241	0.929, 0.0998, 0.0264, 0.0247	0.987, 0.1996, 0.0270, 0.0280
MR-ContMix	1.000, -0.1988, 0.0252, NA	0.998, -0.0995, 0.0248, NA	0.827, -0.0497, 0.0251, NA	0.225, 0.0002, 0.0251, NA	0.844, 0.0499, 0.0252, NA	0.992, 0.0997, 0.0250, NA	1.000, 0.1991, 0.0252, NA
MR-Lasso	0.999, -0.1989, 0.0275, 0.0170	0.985, -0.0994, 0.0268, 0.0170	0.781, -0.0497, 0.0269, 0.0169	0.161, -0.0001, 0.0270, 0.0169	0.777, 0.0496, 0.0272, 0.0169	0.982, 0.0993, 0.0268, 0.0170	1.000, 0.1984, 0.0273, 0.0171
MR-PRESSO	0.965, -0.1988, 0.0676, 0.0222	0.886, -0.0997, 0.0677, 0.0220	0.694, -0.0499, 0.0682, 0.0219	0.314, -0.0004, 0.0685, 0.0219	0.682, 0.0491, 0.0688, 0.0220	0.878, 0.0986, 0.0689, 0.0221	0.958, 0.1980, 0.0697, 0.0224
MR-IVW	0.396, -0.2006, 0.1190, 0.1206	0.135, -0.1012, 0.1190, 0.1206	0.075, -0.0514, 0.1190, 0.1206	0.048, -0.0017, 0.1190, 0.1206	0.066, 0.0480, 0.1190, 0.1206	0.134, 0.0978, 0.1190, 0.1206	0.383, 0.1973, 0.1191, 0.1207
MR-IVW-Oracle	1.000, -0.1983, 0.0173, 0.0176	1.000, -0.0988, 0.0171, 0.0175	0.804, -0.0491, 0.0170, 0.0174	0.041, 0.0006, 0.0170, 0.0174	0.815, 0.0504, 0.0170, 0.0174	0.999, 0.1001, 0.0170, 0.0175	1.000, 0.1995, 0.0173, 0.0176
MR-Egger	0.174, -0.2024, 0.2021, 0.2030	0.076, -0.1030, 0.2021, 0.2030	0.050, -0.0533, 0.2022, 0.2030	0.046, -0.0036, 0.2022, 0.2030	0.065, 0.0462, 0.2023, 0.2030	0.088, 0.0959, 0.2023, 0.2030	0.180, 0.1953, 0.2024, 0.2031
MR-Weighted-Median	0.991, -0.1889, 0.0377, 0.0225	0.939, -0.0951, 0.0348, 0.0221	0.622, -0.0480, 0.0345, 0.0220	0.136, -0.0008, 0.0345, 0.0220	0.599, 0.0463, 0.0354, 0.0220	0.934, 0.0930, 0.0376, 0.0221	0.989, 0.1870, 0.0408, 0.0224
MR-Weighted-Mode	0.579, -0.1987, 0.3192, 2.0935	0.401, -0.1091, 0.3490, 2.0830	0.218, -0.0514, 0.3560, 2.0716	0.123, -0.0277, 0.3437, 2.0523	0.208, 0.0177, 0.3348, 2.0355	0.390, 0.0654, 0.3432, 2.0462	0.584, 0.1556, 0.3505, 2.0312
MR-RAPS1	0.400, -0.2017, 0.1196, 0.1201	0.139, -0.1017, 0.1196, 0.1201	0.079, -0.0517, 0.1196, 0.1201	0.051, -0.0017, 0.1197, 0.1201	0.069, 0.0483, 0.1197, 0.1201	0.137, 0.0983, 0.1197, 0.1201	0.390, 0.1983, 0.1197, 0.1201
MR-RAPS2	0.576, -0.2012, 0.1014, 0.0923	0.300, -0.1017, 0.1009, 0.0921	0.179, -0.0503, 0.1007, 0.0926	0.096, -0.0021, 0.1060, 0.0922	0.191, 0.0499, 0.0996, 0.0928	0.282, 0.1002, 0.1182, 0.0927	0.558, 0.2006, 0.1152, 0.0918
MR-RAPS3	0.966, -0.7063, 1.9905, 0.2124	0.916, -0.3195, 7.6792, 3.5350	0.871, -1.1323, 19.2401, 20.4664	0.866, -0.1304, 5.9349, 2.4806	0.860, 0.2791, 9.7956, 6.5607	0.914, 3.7189, 114.1616, 912.8000	0.963, 0.4145, 5.1670, 0.8545
MR-RAPS4	1.000, -0.2078, 0.1447, 0.0110	0.999, -0.0994, 0.1253, 0.0107	0.917, -0.0432, 0.1208, 0.0106	0.370, 0.0033, 0.1853, 0.0109	0.930, 0.0593, 0.1198, 0.0106	0.997, 0.1127, 0.1408, 0.0108	0.999, 0.2148, 0.1713, 0.0112



Table S111: Simulations with weak invalid IVs: in each cell, from top to bottom are empirical type-I error/power,  $\text{mean}(\hat{\theta})$ ,  $\text{SD}(\hat{\theta})$ ,  $\text{mean}(\text{SE}(\hat{\theta}))$  when  $h_y = 0.1$  and  $h_u = 0.1$ .

Methods \ $\theta$	-0.2	-0.1	-0.05	0	0.05	0.1	0.2
cML-MA-BIC	0.980, -0.1857, 0.0415, 0.0150	0.961, -0.0919, 0.0288, 0.0149	0.720, -0.0440, 0.0259, 0.0147	0.230, 0.0028, 0.0240, 0.0147	0.799, 0.0507, 0.0256, 0.0148	0.988, 0.1001, 0.0270, 0.0148	0.998, 0.1998, 0.0283, 0.0150
cML-MA-BIC-DP, T = 200	0.826, -0.1615, 0.0467, 0.0404	0.746, -0.0806, 0.0284, 0.0280	0.387, -0.0384, 0.0227, 0.0231	0.043, 0.0032, 0.0202, 0.0206	0.532, 0.0467, 0.0229, 0.0228	0.895, 0.0935, 0.0259, 0.0253	0.980, 0.1898, 0.0302, 0.0282
MR-Mix	0.979, -0.2005, 0.0286, 0.0269	0.914, -0.1005, 0.0276, 0.0293	0.594, -0.0502, 0.0275, 0.0267	0.117, -0.0001, 0.0276, 0.0268	0.575, 0.0499, 0.0277, 0.0270	0.907, 0.0999, 0.0277, 0.0264	0.984, 0.2004, 0.0293, 0.0265
MR-ContMix	0.999, -0.1959, 0.0284, NA	0.989, -0.0960, 0.0283, NA	0.803, -0.0466, 0.0280, NA	0.321, 0.0031, 0.0279, NA	0.848, 0.0528, 0.0279, NA	0.992, 0.1026, 0.0279, NA	1.000, 0.2021, 0.0285, NA
MR-Lasso	0.986, -0.1734, 0.0396, 0.0170	0.884, -0.0743, 0.0390, 0.0169	0.560, -0.0245, 0.0394, 0.0169	0.375, 0.0252, 0.0394, 0.0168	0.927, 0.0750, 0.0390, 0.0168	0.998, 0.1255, 0.0403, 0.0168	1.000, 0.2251, 0.0401, 0.0169
MR-PRESSO	0.884, -0.1360, 0.0597, 0.0220	0.613, -0.0370, 0.0595, 0.0218	0.423, 0.0125, 0.0597, 0.0217	0.585, 0.0619, 0.0598, 0.0217	0.940, 0.1114, 0.0598, 0.0218	0.996, 0.1608, 0.0592, 0.0219	1.000, 0.2602, 0.0589, 0.0220
MR-IVW	0.312, -0.0930, 0.0690, 0.0649	0.079, 0.0066, 0.0690, 0.0648	0.160, 0.0564, 0.0690, 0.0649	0.378, 0.1062, 0.0690, 0.0649	0.676, 0.1560, 0.0690, 0.0649	0.863, 0.2057, 0.0690, 0.0649	0.994, 0.3053, 0.0690, 0.0649
MR-IVW-Oracle	1.000, -0.1985, 0.0172, 0.0176	0.998, -0.0989, 0.0169, 0.0175	0.818, -0.0492, 0.0168, 0.0174	0.038, 0.0006, 0.0168, 0.0174	0.819, 0.0503, 0.0167, 0.0174	0.999, 0.1001, 0.0168, 0.0175	1.000, 0.1996, 0.0170, 0.0176
MR-Egger	0.145, -0.0862, 0.1164, 0.1091	0.076, 0.0135, 0.1163, 0.1091	0.115, 0.0633, 0.1163, 0.1091	0.206, 0.1131, 0.1163, 0.1091	0.350, 0.1629, 0.1163, 0.1091	0.502, 0.2127, 0.1162, 0.1091	0.790, 0.3124, 0.1162, 0.1092
MR-Weighted-Median	0.918, -0.1440, 0.0631, 0.0224	0.751, -0.0535, 0.0569, 0.0221	0.409, -0.0081, 0.0534, 0.0219	0.367, 0.0378, 0.0508, 0.0218	0.861, 0.0841, 0.0486, 0.0217	0.992, 0.1308, 0.0473, 0.0217	1.000, 0.2247, 0.0446, 0.0218
MR-Weighted-Mode	0.635, -0.1477, 0.2699, 0.8810	0.386, -0.0612, 0.2838, 0.9130	0.229, -0.0095, 0.2803, 0.9292	0.191, 0.0272, 0.2852, 0.9340	0.422, 0.0719, 0.2822, 0.9462	0.598, 0.1180, 0.2650, 0.9544	0.726, 0.2192, 0.2635, 0.9867
MR-RAPS1	0.322, -0.0934, 0.0693, 0.0645	0.081, 0.0066, 0.0693, 0.0645	0.169, 0.0566, 0.0693, 0.0645	0.383, 0.1067, 0.0693, 0.0645	0.684, 0.1567, 0.0693, 0.0645	0.867, 0.2067, 0.0693, 0.0645	0.994, 0.3068, 0.0693, 0.0646
MR-RAPS2	0.563, -0.1214, 0.0670, 0.0522	0.203, -0.0201, 0.0719, 0.0522	0.226, 0.0285, 0.0792, 0.0522	0.354, 0.0798, 0.0705, 0.0522	0.690, 0.1302, 0.0712, 0.0522	0.901, 0.1785, 0.0778, 0.0521	0.995, 0.2807, 0.0703, 0.0525
MR-RAPS3	0.919, -0.1172, 0.0880, 0.0123	0.777, 0.0091, 0.0892, 0.0123	0.863, 0.0723, 0.0895, 0.0123	0.923, 0.1351, 0.0897, 0.0124	0.979, 0.1972, 0.0898, 0.0124	0.999, 0.2585, 0.0897, 0.0125	1.000, 0.3779, 0.0891, 0.0126
MR-RAPS4	0.998, -0.1898, 0.0823, 0.0101	0.996, -0.0936, 0.0682, 0.0099	0.892, -0.0243, 0.1124, 0.0099	0.444, 0.0153, 0.0904, 0.0099	0.926, 0.0577, 0.0458, 0.0099	0.998, 0.1061, 0.1458, 0.0120	1.000, 0.2433, 0.1837, 0.0104

Table S112: Simulations with weak invalid IVs: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean( $SE(\hat{\theta})$ ) when  $h_y = 0.2$  and  $h_u = 0.1$ .

Methods \ $\theta$	-0.2	-0.1	-0.05	0	0.05	0.1	0.2
cML-MA-BIC	0.990, -0.1900, 0.0370, 0.0155	0.972, -0.0944, 0.0276, 0.0153	0.746, -0.0456, 0.0253, 0.0152	0.205, 0.0018, 0.0240, 0.0151	0.791, 0.0493, 0.0258, 0.0151	0.983, 0.0992, 0.0267, 0.0152	0.996, 0.1979, 0.0304, 0.0153
cML-MA-BIC-DP, T = 200	0.878, -0.1698, 0.0417, 0.0374	0.799, -0.0839, 0.0276, 0.0273	0.427, -0.0403, 0.0225, 0.0230	0.038, 0.0017, 0.0199, 0.0205	0.518, 0.0452, 0.0225, 0.0227	0.884, 0.0918, 0.0254, 0.0253	0.963, 0.1861, 0.0324, 0.0299
MR-Mix	0.987, -0.2004, 0.0284, 0.0282	0.905, -0.1002, 0.0281, 0.0280	0.578, -0.0502, 0.0278, 0.0265	0.118, -0.0002, 0.0278, 0.0267	0.589, 0.0500, 0.0281, 0.0264	0.913, 0.1003, 0.0284, 0.0258	0.988, 0.2003, 0.0288, 0.0265
MR-ContMix	1.000, -0.1969, 0.0278, NA	0.987, -0.0974, 0.0277, NA	0.811, -0.0476, 0.0274, NA	0.280, 0.0022, 0.0275, NA	0.850, 0.0517, 0.0274, NA	0.990, 0.1013, 0.0276, NA	0.999, 0.2005, 0.0277, NA
MR-Lasso	0.984, -0.1780, 0.0395, 0.0173	0.891, -0.0792, 0.0391, 0.0171	0.591, -0.0291, 0.0385, 0.0171	0.327, 0.0210, 0.0396, 0.0171	0.895, 0.0710, 0.0397, 0.0171	0.995, 0.1206, 0.0401, 0.0171	1.000, 0.2202, 0.0404, 0.0172
MR-PRESSO	0.861, -0.1369, 0.0681, 0.0229	0.652, -0.0382, 0.0671, 0.0228	0.436, 0.0113, 0.0672, 0.0227	0.551, 0.0606, 0.0668, 0.0227	0.918, 0.1104, 0.0668, 0.0228	0.993, 0.1601, 0.0666, 0.0228	0.999, 0.2588, 0.0661, 0.0230
MR-IVW	0.237, -0.0931, 0.0846, 0.0798	0.070, 0.0065, 0.0845, 0.0798	0.130, 0.0563, 0.0845, 0.0798	0.284, 0.1061, 0.0845, 0.0798	0.506, 0.1559, 0.0845, 0.0798	0.729, 0.2057, 0.0845, 0.0798	0.953, 0.3053, 0.0846, 0.0798
MR-IVW-Oracle	1.000, -0.1985, 0.0172, 0.0176	0.998, -0.0989, 0.0169, 0.0175	0.818, -0.0492, 0.0168, 0.0174	0.038, 0.0006, 0.0168, 0.0174	0.819, 0.0503, 0.0167, 0.0174	0.999, 0.1001, 0.0168, 0.0175	1.000, 0.1996, 0.0170, 0.0176
MR-Egger	0.120, -0.0864, 0.1440, 0.1341	0.081, 0.0132, 0.1439, 0.1341	0.098, 0.0631, 0.1439, 0.1341	0.163, 0.1129, 0.1438, 0.1341	0.260, 0.1627, 0.1438, 0.1342	0.383, 0.2125, 0.1438, 0.1342	0.639, 0.3122, 0.1438, 0.1342
MR-Weighted-Median	0.926, -0.1508, 0.0647, 0.0228	0.774, -0.0603, 0.0583, 0.0224	0.447, -0.0145, 0.0550, 0.0222	0.342, 0.0315, 0.0527, 0.0221	0.822, 0.0776, 0.0514, 0.0220	0.981, 0.1239, 0.0498, 0.0219	0.999, 0.2173, 0.0469, 0.0220
MR-Weighted-Mode	0.618, -0.1636, 0.3395, 1.0469	0.367, -0.0720, 0.3339, 1.0773	0.199, -0.0274, 0.3384, 1.0939	0.173, 0.0231, 0.3240, 1.0998	0.355, 0.0761, 0.3268, 1.0959	0.549, 0.1206, 0.3301, 1.1169	0.693, 0.2167, 0.2906, 1.1571
MR-RAPS1	0.244, -0.0935, 0.0850, 0.0793	0.073, 0.0065, 0.0849, 0.0793	0.131, 0.0566, 0.0849, 0.0793	0.289, 0.1066, 0.0849, 0.0794	0.516, 0.1566, 0.0849, 0.0794	0.737, 0.2066, 0.0849, 0.0794	0.956, 0.3067, 0.0850, 0.0794
MR-RAPS2	0.485, -0.1517, 0.9320, 0.0629	0.213, -0.0195, 0.0903, 0.0624	0.225, 0.0292, 0.0905, 0.0625	0.287, 0.0783, 0.0801, 0.0622	0.564, 0.1286, 0.0807, 0.0623	0.784, 0.1772, 0.0866, 0.0622	0.976, 0.2808, 0.0934, 0.0626
MR-RAPS3	0.905, -0.1358, 0.1288, 0.0146	0.804, 0.0111, 0.1307, 0.0146	0.865, 0.0848, 0.1309, 0.0146	0.917, 0.1575, 0.1308, 0.0146	0.972, 0.2287, 0.1304, 0.0146	0.988, 0.2977, 0.1296, 0.0146	0.998, 0.4291, 0.1271, 0.0146
MR-RAPS4	0.998, -0.1966, 0.0621, 0.0101	0.996, -0.0931, 0.0782, 0.0100	0.910, -0.0358, 0.1117, 0.0099	0.425, 0.0149, 0.1100, 0.0099	0.931, 0.0570, 0.0712, 0.0099	0.998, 0.1048, 0.0512, 0.0099	1.000, 0.2364, 0.1993, 0.0104

Table S113: Simulations with weak invalid IVs: in each cell, from top to bottom are empirical type-I error/power,  $\text{mean}(\hat{\theta})$ ,  $\text{SD}(\hat{\theta})$ ,  $\text{mean}(\text{SE}(\hat{\theta}))$  when  $h_y = 0.4$  and  $h_u = 0.1$ .

Methods \ $\theta$	-0.2	-0.1	-0.05	0	0.05	0.1	0.2
cML-MA-BIC	0.995, -0.1937, 0.0289, 0.0156	0.979, -0.0953, 0.0258, 0.0155	0.767, -0.0466, 0.0235, 0.0155	0.173, 0.0018, 0.0225, 0.0155	0.799, 0.0499, 0.0238, 0.0155	0.982, 0.0995, 0.0251, 0.0156	0.999, 0.1986, 0.0289, 0.0157
cML-MA-BIC-DP, T = 200	0.920, -0.1772, 0.0361, 0.0337	0.850, -0.0870, 0.0257, 0.0259	0.473, -0.0420, 0.0214, 0.0222	0.035, 0.0014, 0.0191, 0.0200	0.527, 0.0454, 0.0213, 0.0221	0.904, 0.0921, 0.0245, 0.0246	0.968, 0.1865, 0.0313, 0.0292
MR-Mix	0.990, -0.1990, 0.0263, 0.0256	0.922, -0.0988, 0.0257, 0.0254	0.573, -0.0485, 0.0259, 0.0269	0.102, 0.0016, 0.0259, 0.0251	0.615, 0.0516, 0.0265, 0.0248	0.929, 0.1016, 0.0264, 0.0258	0.991, 0.2017, 0.0268, 0.0259
MR-ContMix	1.000, -0.1978, 0.0249, NA	0.993, -0.0984, 0.0248, NA	0.818, -0.0487, 0.0250, NA	0.260, 0.0012, 0.0251, NA	0.855, 0.0510, 0.0252, NA	0.990, 0.1008, 0.0254, NA	1.000, 0.2002, 0.0258, NA
MR-Lasso	0.988, -0.1827, 0.0390, 0.0175	0.916, -0.0838, 0.0383, 0.0174	0.636, -0.0341, 0.0386, 0.0174	0.260, 0.0154, 0.0382, 0.0174	0.865, 0.0651, 0.0379, 0.0174	0.993, 0.1147, 0.0381, 0.0175	1.000, 0.2145, 0.0394, 0.0175
MR-PRESSO	0.856, -0.1394, 0.0800, 0.0242	0.670, -0.0409, 0.0791, 0.0242	0.484, 0.0088, 0.0793, 0.0242	0.520, 0.0585, 0.0789, 0.0242	0.879, 0.1080, 0.0786, 0.0242	0.980, 0.1574, 0.0783, 0.0242	0.996, 0.2567, 0.0784, 0.0244
MR-IVW	0.171, -0.0932, 0.1091, 0.1033	0.066, 0.0064, 0.1091, 0.1033	0.106, 0.0562, 0.1091, 0.1033	0.200, 0.1060, 0.1091, 0.1033	0.349, 0.1558, 0.1091, 0.1033	0.521, 0.2056, 0.1091, 0.1034	0.822, 0.3051, 0.1091, 0.1034
MR-IVW-Oracle	1.000, -0.1985, 0.0172, 0.0176	0.998, -0.0989, 0.0169, 0.0175	0.818, -0.0492, 0.0168, 0.0174	0.038, 0.0006, 0.0168, 0.0174	0.819, 0.0503, 0.0167, 0.0174	0.999, 0.1001, 0.0168, 0.0175	1.000, 0.1996, 0.0170, 0.0176
MR-Egger	0.101, -0.0867, 0.1873, 0.1737	0.083, 0.0129, 0.1872, 0.1737	0.087, 0.0628, 0.1872, 0.1737	0.124, 0.1126, 0.1872, 0.1737	0.195, 0.1624, 0.1872, 0.1737	0.267, 0.2122, 0.1871, 0.1738	0.454, 0.3119, 0.1871, 0.1738
MR-Weighted-Median	0.941, -0.1571, 0.0675, 0.0233	0.828, -0.0680, 0.0580, 0.0227	0.448, -0.0227, 0.0541, 0.0225	0.271, 0.0232, 0.0519, 0.0223	0.773, 0.0690, 0.0491, 0.0222	0.964, 0.1153, 0.0483, 0.0222	0.997, 0.2085, 0.0472, 0.0224
MR-Weighted-Mode	0.575, -0.1704, 0.3591, 1.3495	0.366, -0.0765, 0.3536, 1.3530	0.212, -0.0339, 0.3342, 1.3557	0.166, 0.0095, 0.3400, 1.3582	0.299, 0.0551, 0.3489, 1.3552	0.473, 0.0983, 0.3429, 1.3698	0.645, 0.1921, 0.3487, 1.4165
MR-RAPS1	0.173, -0.0936, 0.1096, 0.1028	0.070, 0.0064, 0.1096, 0.1028	0.110, 0.0564, 0.1096, 0.1028	0.205, 0.1065, 0.1096, 0.1028	0.356, 0.1565, 0.1096, 0.1028	0.528, 0.2065, 0.1096, 0.1028	0.826, 0.3066, 0.1096, 0.1028
MR-RAPS2	0.377, -0.1229, 0.1006, 0.0803	0.210, -0.0263, 0.1735, 0.0803	0.198, 0.0274, 0.1032, 0.0803	0.224, 0.0791, 0.0998, 0.0802	0.422, 0.1310, 0.1038, 0.0806	0.618, 0.1811, 0.1115, 0.0799	0.879, 0.2850, 0.1348, 0.0805
MR-RAPS3	0.909, -0.1952, 0.4104, 0.0433	0.834, -0.0018, 0.5471, 0.0522	0.886, 0.1124, 0.6015, 0.0421	0.922, 0.2390, 1.0189, 0.5774	0.949, 0.3844, 1.3282, 0.1987	0.978, 0.4322, 0.2918, 0.0241	0.997, 0.5802, 0.2460, 0.0211
MR-RAPS4	1.000, -0.1990, 0.1049, 0.0103	0.998, -0.0883, 0.1092, 0.0100	0.918, -0.0338, 0.1397, 0.0100	0.415, 0.0277, 0.1423, 0.0100	0.952, 0.0657, 0.1178, 0.0100	0.998, 0.1060, 0.0979, 0.0100	1.000, 0.2256, 0.1793, 0.0104

Table S114: Simulations with weak invalid IVs: in each cell, from top to bottom are empirical type-I error/power, mean( $\hat{\theta}$ ), SD( $\hat{\theta}$ ), mean( $SE(\hat{\theta})$ ) when  $h_y = 0.6$  and  $h_u = 0.1$ .

Methods $\theta$	-0.2	-0.1	-0.05	0	0.05	0.1	0.2
cML-MA-BIC	0.996, -0.1956, 0.0284, 0.0159	0.988, -0.0970, 0.0238, 0.0156	0.784, -0.0474, 0.0226, 0.0156	0.165, 0.0012, 0.0217, 0.0156	0.794, 0.0497, 0.0227, 0.0156	0.994, 0.0993, 0.0233, 0.0157	0.997, 0.1986, 0.0264, 0.0158
cML-MA-BIC-DP, T = 200	0.942, -0.1814, 0.0346, 0.0314	0.886, -0.0894, 0.0244, 0.0249	0.509, -0.0433, 0.0210, 0.0218	0.037, 0.0007, 0.0188, 0.0196	0.533, 0.0451, 0.0209, 0.0217	0.904, 0.0920, 0.0237, 0.0242	0.959, 0.1864, 0.0309, 0.0286
MR-Mix	0.991, -0.1991, 0.0253, 0.0255	0.930, -0.0988, 0.0247, 0.0245	0.583, -0.0486, 0.0249, 0.0243	0.087, 0.0016, 0.0247, 0.0366	0.620, 0.0515, 0.0246, 0.0239	0.933, 0.1015, 0.0248, 0.0243	0.991, 0.2017, 0.0252, 0.0250
MR-ContMix	0.999, -0.1977, 0.0243, NA	0.998, -0.0981, 0.0238, NA	0.829, -0.0482, 0.0236, NA	0.252, 0.0015, 0.0235, NA	0.835, 0.0513, 0.0234, NA	1.000, 0.1010, 0.0236, NA	1.000, 0.2005, 0.0238, NA
MR-Lasso	0.987, -0.1863, 0.0384, 0.0177	0.929, -0.0871, 0.0377, 0.0176	0.676, -0.0372, 0.0373, 0.0176	0.221, 0.0126, 0.0380, 0.0176	0.835, 0.0626, 0.0378, 0.0177	0.993, 0.1126, 0.0378, 0.0177	1.000, 0.2118, 0.0377, 0.0178
MR-PRESSO	0.830, -0.1379, 0.0932, 0.0259	0.696, -0.0393, 0.0925, 0.0256	0.528, 0.0105, 0.0928, 0.0256	0.511, 0.0597, 0.0923, 0.0257	0.844, 0.1087, 0.0918, 0.0257	0.969, 0.1577, 0.0906, 0.0256	0.991, 0.2561, 0.0894, 0.0258
MR-IVW	0.140, -0.0933, 0.1289, 0.1224	0.067, 0.0063, 0.1289, 0.1224	0.088, 0.0561, 0.1289, 0.1224	0.159, 0.1059, 0.1289, 0.1225	0.271, 0.1557, 0.1289, 0.1225	0.415, 0.2055, 0.1289, 0.1225	0.705, 0.3051, 0.1290, 0.1225
MR-IVW-Oracle	1.000, -0.1985, 0.0172, 0.0176	0.998, -0.0989, 0.0169, 0.0175	0.818, -0.0492, 0.0168, 0.0174	0.038, 0.0006, 0.0168, 0.0174	0.819, 0.0503, 0.0167, 0.0174	0.999, 0.1001, 0.0168, 0.0175	1.000, 0.1996, 0.0170, 0.0176
MR-Egger	0.095, -0.0869, 0.2223, 0.2058	0.076, 0.0127, 0.2223, 0.2058	0.081, 0.0625, 0.2223, 0.2058	0.110, 0.1124, 0.2222, 0.2058	0.155, 0.1622, 0.2222, 0.2059	0.220, 0.2120, 0.2222, 0.2059	0.348, 0.3116, 0.2222, 0.2059
MR-Weighted-Median	0.945, -0.1619, 0.0686, 0.0236	0.844, -0.0728, 0.0583, 0.0229	0.485, -0.0273, 0.0555, 0.0227	0.245, 0.0183, 0.0534, 0.0225	0.739, 0.0645, 0.0519, 0.0224	0.954, 0.1105, 0.0493, 0.0224	0.993, 0.2036, 0.0484, 0.0226
MR-Weighted-Mode	0.550, -0.1718, 0.4068, 1.5883	0.339, -0.0669, 0.4114, 1.6090	0.200, -0.0152, 0.4135, 1.6105	0.160, 0.0234, 0.4037, 1.6022	0.290, 0.0710, 0.3903, 1.5991	0.440, 0.1162, 0.3854, 1.6165	0.627, 0.2027, 0.3928, 1.6543
MR-RAPS1	0.147, -0.0937, 0.1296, 0.1218	0.069, 0.0063, 0.1296, 0.1218	0.091, 0.0564, 0.1296, 0.1218	0.163, 0.1064, 0.1296, 0.1218	0.279, 0.1564, 0.1296, 0.1218	0.423, 0.2064, 0.1296, 0.1218	0.707, 0.3065, 0.1296, 0.1218
MR-RAPS2	0.332, -0.1226, 0.1175, 0.0949	0.204, -0.0244, 0.1195, 0.0945	0.176, 0.0264, 0.1152, 0.0947	0.190, 0.0782, 0.1199, 0.0947	0.348, 0.1285, 0.1298, 0.0944	0.503, 0.1791, 0.1255, 0.0950	0.783, 0.2809, 0.1351, 0.0948
MR-RAPS3	0.906, -0.4046, 4.5092, 2.0607	0.857, 2.3722, 74.5197, 769.0805	0.898, 0.3082, 4.0494, 0.8431	0.918, 1.6598, 39.1988, 36.9932	0.947, 0.4372, 4.3331, 0.9291	0.958, 0.5583, 5.8561, 1.4798	0.992, 0.8442, 0.5724, 0.0473
MR-RAPS4	1.000, -0.2004, 0.1303, 0.0105	0.998, -0.0789, 0.1614, 0.0102	0.926, -0.0140, 0.1828, 0.0102	0.480, 0.0309, 0.2152, 0.0103	0.944, 0.0873, 0.2288, 0.0104	1.000, 0.1306, 0.2075, 0.0104	0.999, 0.2198, 0.1919, 0.0106

Table S115: Relative frequencies of goodness-of-fit tests' rejecting the null at  $p$ -value cutoff 0.05 when  $h_y = 0.1$  and  $h_u = 0$ .

Methods $\theta$	-0.2	-0.1	-0.05	0	0.05	0.1	0.2
GOF1, T = 100	0.941	0.950	0.946	0.898	0.942	0.952	0.949
GOF2, T = 100	0.965	0.958	0.954	0.906	0.948	0.958	0.966
GOF1, T = 200	0.976	0.987	0.986	0.967	0.981	0.984	0.981
GOF2, T = 200	0.987	0.988	0.989	0.969	0.983	0.989	0.990
GOF1, T = 500	0.998	0.998	0.999	0.996	1.000	1.000	0.999
GOF2, T = 500	0.999	0.999	0.999	0.997	1.000	1.000	0.999

Table S116: Relative frequencies of goodness-of-fit tests' rejecting the null at  $p$ -value cutoff 0.05 when  $h_y = 0.2$  and  $h_u = 0$ .

Methods \ $\theta$	-0.2	-0.1	-0.05	0	0.05	0.1	0.2
GOF1, T = 100	0.915	0.926	0.915	0.819	0.906	0.919	0.901
GOF2, T = 100	0.935	0.936	0.921	0.833	0.909	0.934	0.941
GOF1, T = 200	0.971	0.982	0.980	0.947	0.973	0.977	0.965
GOF2, T = 200	0.981	0.985	0.982	0.953	0.971	0.978	0.984
GOF1, T = 500	0.995	0.996	0.994	0.977	0.987	0.992	0.992
GOF2, T = 500	0.996	0.997	0.994	0.979	0.987	0.992	0.995

Table S117: Relative frequencies of goodness-of-fit tests' rejecting the null at  $p$ -value cutoff 0.05 when  $h_y = 0.4$  and  $h_u = 0$ .

Methods \ $\theta$	-0.2	-0.1	-0.05	0	0.05	0.1	0.2
GOF1, T = 100	0.817	0.829	0.804	0.669	0.810	0.840	0.819
GOF2, T = 100	0.867	0.847	0.813	0.697	0.821	0.864	0.876
GOF1, T = 200	0.912	0.929	0.916	0.846	0.917	0.929	0.930
GOF2, T = 200	0.929	0.930	0.917	0.867	0.928	0.942	0.954
GOF1, T = 500	0.976	0.975	0.969	0.940	0.975	0.977	0.979
GOF2, T = 500	0.979	0.976	0.972	0.946	0.976	0.982	0.983

Table S118: Relative frequencies of goodness-of-fit tests' rejecting the null at  $p$ -value cutoff 0.05 when  $h_y = 0.6$  and  $h_u = 0$ .

Methods \ $\theta$	-0.2	-0.1	-0.05	0	0.05	0.1	0.2
GOF1, T = 100	0.746	0.766	0.731	0.579	0.737	0.764	0.756
GOF2, T = 100	0.809	0.795	0.735	0.595	0.754	0.786	0.808
GOF1, T = 200	0.872	0.885	0.867	0.764	0.874	0.889	0.878
GOF2, T = 200	0.900	0.904	0.878	0.787	0.881	0.901	0.909
GOF1, T = 500	0.944	0.948	0.942	0.900	0.942	0.960	0.952
GOF2, T = 500	0.955	0.952	0.945	0.902	0.947	0.963	0.964

Table S119: Relative frequencies of goodness-of-fit tests' rejecting the null at  $p$ -value cutoff 0.05 with  $T = 200$  when  $h_u = 0.1$ .

Methods \ $\theta$	-0.2	-0.1	-0.05	0	0.05	0.1	0.2
GOF1, $h_y = 0.1$	0.983	0.989	0.982	0.939	0.976	0.978	0.973
GOF2, $h_y = 0.1$	0.995	0.991	0.981	0.947	0.978	0.979	0.980
GOF1, $h_y = 0.2$	0.955	0.969	0.958	0.887	0.941	0.943	0.938
GOF2, $h_y = 0.2$	0.980	0.976	0.965	0.898	0.947	0.953	0.956
GOF1, $h_y = 0.4$	0.915	0.923	0.902	0.815	0.887	0.901	0.893
GOF2, $h_y = 0.4$	0.949	0.940	0.911	0.828	0.899	0.922	0.922
GOF1, $h_y = 0.6$	0.887	0.886	0.854	0.758	0.840	0.869	0.851
GOF2, $h_y = 0.6$	0.906	0.898	0.862	0.771	0.852	0.891	0.885

Table S120: Simulation results with valid and weaker IVs and  $h_y = 0.2$ ,  $h_u = 0$ .

Methods $\backslash$ $\theta$	-0.2	-0.1	-0.05	0	0.05	0.1	0.2
cML-MA-BIC	1.000, -0.1991, 0.0176, 0.0171	1.000, -0.0992, 0.0173, 0.0169	0.823, -0.0492, 0.0173, 0.0168	0.054, 0.0007, 0.0171, 0.0168	0.828, 0.0504, 0.0173, 0.0168	0.998, 0.1004, 0.0174, 0.0169	1.000, 0.2004, 0.0176, 0.0171
cML-BIC	1.000, -0.1993, 0.0177, 0.0169	0.999, -0.0993, 0.0175, 0.0166	0.835, -0.0493, 0.0174, 0.0165	0.057, 0.0006, 0.0173, 0.0165	0.835, 0.0506, 0.0174, 0.0165	0.999, 0.1005, 0.0174, 0.0166	1.000, 0.2005, 0.0177, 0.0168
cML-MA-BIC-DP, T = 200	1.000, -0.1965, 0.0176, 0.0195	0.996, -0.0969, 0.0175, 0.0192	0.698, -0.0472, 0.0172, 0.0190	0.027, 0.0007, 0.0163, 0.0182	0.733, 0.0487, 0.0172, 0.0189	0.996, 0.0984, 0.0174, 0.0191	1.000, 0.1980, 0.0176, 0.0193
cML-BIC-DP, T = 200	1.000, -0.1968, 0.0179, 0.0190	0.997, -0.0972, 0.0176, 0.0189	0.712, -0.0474, 0.0174, 0.0187	0.034, 0.0007, 0.0165, 0.0180	0.750, 0.0489, 0.0174, 0.0185	0.994, 0.0987, 0.0176, 0.0187	1.000, 0.1983, 0.0177, 0.0188
GOF1, T = 200	0.063	0.066	0.065	0.054	0.062	0.065	0.057
GOF2, T = 200	0.059	0.06	0.061	0.053	0.056	0.056	0.051

Table S121: Comparison of computational times (in seconds) of different MR methods as averaged over 10 simulations for  $m$  IVs.

Methods $\backslash$ $m$	10	20	50	70	100
cML-MA-BIC, 0 Random Start	0.0151	0.0272	0.0964	0.1548	0.2282
cML-MA-BIC, 5 Random Start	0.2237	0.6305	1.7965	2.7234	4.0821
cML-MA-BIC-DP, 0 Random Start	1.5327	3.0729	10.9926	15.803	24.9949
cML-MA-BIC-DP, 5 Random Start	18.5582	53.7983	170.9803	267.4588	408.589
MR-Mix	3.6973	4.667	6.1285	6.7372	7.6673
MR-ContMix	0.1198	0.1327	0.1695	0.2237	0.2388
MR-Lasso	0.0386	0.041	0.0536	0.0582	0.0673
MR-PRESSO	3.4478	5.5814	11.6707	15.9898	22.4874
MR-IVW	0.0012	0.001	0.0011	0.0011	0.001
MR-Egger	0.0012	0.0016	0.0014	0.0017	0.0013
MR-Weighted-Median	0.0489	0.0531	0.0582	0.0632	0.0697
MR-Weighted-Mode	2.3047	2.2967	2.3596	2.3546	2.3933
MR-RAPS	0.0809	0.1237	0.1035	0.2068	0.1276

## Supplemental Methods and Results

### S1 Proof of Theorem 1

**Theorem 1.** With Assumptions 1 and 2 satisfied, if  $K_0 \in \mathcal{K}$ , we have  $P(\hat{K} = K_0) \rightarrow 1$  and  $P(\hat{B}_{\hat{K}} = B_0) \rightarrow 1$  as  $N_1, N_2 \rightarrow \infty$ .

*Proof.* First, we show  $P(\hat{B}_{K_0} = B_0) \rightarrow 1$ , which is equivalent to show for any  $B_1 \subseteq \{1, \dots, m\}$  such that  $|B_1| = K_0$  and  $B_1 \neq B_0$ ,  $P(\hat{B}_{K_0} = B_1) \rightarrow 0$  as  $N_1, N_2 \rightarrow \infty$ . We have

$$\begin{aligned} P(\hat{B}_{K_0} = B_1) &\leq P\left(\min_{\tilde{\theta}, \tilde{b}_{Xi}} \sum_{i \in B_1^c} \left( \frac{(\hat{\beta}_{Xi} - \tilde{b}_{Xi})^2}{\hat{\sigma}_{Xi}^2} + \frac{(\hat{\beta}_{Yi} - \tilde{\theta} \tilde{b}_{Xi})^2}{\hat{\sigma}_{Yi}^2} \right) \leq \min_{\tilde{\theta}, \tilde{b}_{Xi}} \sum_{i \in B_0^c} \left( \frac{(\hat{\beta}_{Xi} - \tilde{b}_{Xi})^2}{\hat{\sigma}_{Xi}^2} + \frac{(\hat{\beta}_{Yi} - \tilde{\theta} \tilde{b}_{Xi})^2}{\hat{\sigma}_{Yi}^2} \right)\right) \\ &\leq P\left(\min_{\tilde{\theta}, \tilde{b}_{Xi}} \sum_{i \in B_1^c} \left( \frac{(\hat{\beta}_{Xi} - \tilde{b}_{Xi})^2}{\hat{\sigma}_{Xi}^2} + \frac{(\hat{\beta}_{Yi} - \tilde{\theta} \tilde{b}_{Xi})^2}{\hat{\sigma}_{Yi}^2} \right) \leq \sum_{i \in B_0^c} \left( \frac{(\hat{\beta}_{Xi} - \beta_{Xi})^2}{\hat{\sigma}_{Xi}^2} + \frac{(\hat{\beta}_{Yi} - \theta \beta_{Xi})^2}{\hat{\sigma}_{Yi}^2} \right)\right). \end{aligned}$$

Note that, for  $i \in B_0^c$ ,  $\frac{\hat{\beta}_{Xi} - \beta_{Xi}}{\hat{\sigma}_{Xi}} \sim N(0, 1)$  and  $\frac{\hat{\beta}_{Yi} - \theta \beta_{Xi}}{\hat{\sigma}_{Yi}} \sim N(0, 1)$ . So for any  $\varepsilon > 0$ , there exists  $C > 0$  such that

$$P\left(\sum_{i \in B_0^c} \left( \frac{(\hat{\beta}_{Xi} - \beta_{Xi})^2}{\hat{\sigma}_{Xi}^2} + \frac{(\hat{\beta}_{Yi} - \theta \beta_{Xi})^2}{\hat{\sigma}_{Yi}^2} \right) > C\right) < \frac{\varepsilon}{2}. \quad (1)$$

And we have

$$\begin{aligned} P\left(\min_{\tilde{\theta}, \tilde{b}_{Xi}} \sum_{i \in B_1^c} \left( \frac{(\hat{\beta}_{Xi} - \tilde{b}_{Xi})^2}{\hat{\sigma}_{Xi}^2} + \frac{(\hat{\beta}_{Yi} - \tilde{\theta} \tilde{b}_{Xi})^2}{\hat{\sigma}_{Yi}^2} \right) \leq \sum_{i \in B_0^c} \left( \frac{(\hat{\beta}_{Xi} - \beta_{Xi})^2}{\hat{\sigma}_{Xi}^2} + \frac{(\hat{\beta}_{Yi} - \theta \beta_{Xi})^2}{\hat{\sigma}_{Yi}^2} \right)\right) \\ \leq P\left(\min_{\tilde{\theta}, \tilde{b}_{Xi}} \sum_{i \in B_1^c} \left( \frac{(\hat{\beta}_{Xi} - \tilde{b}_{Xi})^2}{\hat{\sigma}_{Xi}^2} + \frac{(\hat{\beta}_{Yi} - \tilde{\theta} \tilde{b}_{Xi})^2}{\hat{\sigma}_{Yi}^2} \right) \leq C\right) + P\left(\sum_{i \in B_0^c} \left( \frac{(\hat{\beta}_{Xi} - \beta_{Xi})^2}{\hat{\sigma}_{Xi}^2} + \frac{(\hat{\beta}_{Yi} - \theta \beta_{Xi})^2}{\hat{\sigma}_{Yi}^2} \right) > C\right). \end{aligned}$$

After profiling out  $\tilde{b}_{Xi}$ 's, we get

$$\min_{\tilde{\theta}, \tilde{b}_{Xi}} \sum_{i \in B_1^c} \left( \frac{(\hat{\beta}_{Xi} - \tilde{b}_{Xi})^2}{\hat{\sigma}_{Xi}^2} + \frac{(\hat{\beta}_{Yi} - \tilde{\theta} \tilde{b}_{Xi})^2}{\hat{\sigma}_{Yi}^2} \right) = \min_{\tilde{\theta}} \sum_{i \in B_1^c} \frac{(\hat{\beta}_{Yi} - \tilde{\theta} \cdot \hat{\beta}_{Xi})^2}{\hat{\sigma}_{Yi}^2 + \tilde{\theta}^2 \hat{\sigma}_{Xi}^2},$$

so

$$\begin{aligned} P\left(\min_{\tilde{\theta}, \tilde{b}_{Xi}} \sum_{i \in B_1^c} \left( \frac{(\hat{\beta}_{Xi} - \tilde{b}_{Xi})^2}{\hat{\sigma}_{Xi}^2} + \frac{(\hat{\beta}_{Yi} - \tilde{\theta} \tilde{b}_{Xi})^2}{\hat{\sigma}_{Yi}^2} \right) \leq C\right) \\ = P\left(\min_{\tilde{\theta}} \sum_{i \in B_1^c} \frac{(\hat{\beta}_{Yi} - \tilde{\theta} \cdot \hat{\beta}_{Xi})^2}{\hat{\sigma}_{Yi}^2 + \tilde{\theta}^2 \hat{\sigma}_{Xi}^2} \leq C\right). \end{aligned}$$

We have  $\frac{\hat{\beta}_{Yi} - \tilde{\theta} \cdot \hat{\beta}_{Xi}}{\sqrt{\hat{\sigma}_{Yi}^2 + \tilde{\theta}^2 \hat{\sigma}_{Xi}^2}} \sim N\left(\frac{\theta \cdot \beta_{Xi} + r_i - \tilde{\theta} \cdot \beta_{Xi}}{\sqrt{\hat{\sigma}_{Yi}^2 + \tilde{\theta}^2 \hat{\sigma}_{Xi}^2}}, 1\right)$ , so  $\sum_{i \in B_1^c} \frac{(\hat{\beta}_{Yi} - \tilde{\theta} \cdot \hat{\beta}_{Xi})^2}{\hat{\sigma}_{Yi}^2 + \tilde{\theta}^2 \hat{\sigma}_{Xi}^2}$  follows non-central  $\chi^2$  distribution with degrees of freedom  $(m - K_0)$  and non-centrality parameter  $\lambda_{\tilde{\theta}}$  depending on  $\tilde{\theta}$

$$\lambda_{\tilde{\theta}} = \sum_{i \in B_1^c} \frac{(\theta \cdot \beta_{Xi} + r_i - \tilde{\theta} \cdot \beta_{Xi})^2}{\hat{\sigma}_{Yi}^2 + \tilde{\theta}^2 \hat{\sigma}_{Xi}^2}.$$

With Assumption 2, we get

$$\lambda_{\tilde{\theta}} \geq \sum_{i \in B_1^c} \frac{(\theta \cdot \beta_{Xi} + r_i - \tilde{\theta} \cdot \beta_{Xi})^2}{\frac{u_Y}{N_2} + \tilde{\theta}^2 \cdot \frac{u_X}{l_N \cdot N_2}} = N_2 \cdot \sum_{i \in B_1^c} \frac{(\theta \cdot \beta_{Xi} + r_i - \tilde{\theta} \cdot \beta_{Xi})^2}{u_Y + \tilde{\theta}^2 \cdot \frac{u_X}{l_N}}.$$

With Assumption 1, we know

$$\min_{\tilde{\theta}} \sum_{i \in B_1^c} \frac{(\theta \cdot \beta_{Xi} + r_i - \tilde{\theta} \cdot \beta_{Xi})^2}{u_Y + \tilde{\theta}^2 \cdot \frac{u_X}{l_N}} = v > 0,$$

here  $v$  is a constant. This is because, with Assumption 1, there is no  $\tilde{\theta}$  making  $\theta \cdot \beta_{Xi} + r_i - \tilde{\theta} \cdot \beta_{Xi} = 0$  for all  $i \in B_1^c$  simultaneously. So we have  $\min_{\tilde{\theta}} \lambda_{\tilde{\theta}} \geq N_2 \cdot v$ . Then as  $N_2$  large enough, we have

$$P(\min_{\tilde{\theta}} \sum_{i \in B_1^c} \frac{(\hat{\beta}_{Yi} - \tilde{\theta} \cdot \hat{\beta}_{Xi})^2}{\hat{\sigma}_{Yi}^2 + \tilde{\theta}^2 \hat{\sigma}_{Xi}^2} \leq C) \leq \frac{\varepsilon}{2}. \quad (2)$$

Combining (1) and (2), we get  $P(\hat{B}_{K_0} = B_0) \rightarrow 1$  as  $N_1, N_2 \rightarrow \infty$ .

Next, we show  $P(\hat{K} = K_0) \rightarrow 1$ . For any  $K_1 < K_0$ , we have

$$\begin{aligned} P(\hat{K} = K_1) &\leq P(\text{BIC}(K_1) \leq \text{BIC}(K_0)) \\ &= P(-2 \cdot L(\hat{\theta}(K_1), \hat{b}_{Xi}(K_1), \hat{r}_i(K_1)) + \log(N) \cdot K_1 \leq -2 \cdot L(\hat{\theta}(K_0), \hat{b}_{Xi}(K_0), \hat{r}_i(K_0)) + \log(N) \cdot K_0) \\ &= P(2 \cdot L(\hat{\theta}(K_0), \hat{b}_{Xi}(K_0), \hat{r}_i(K_0)) - 2 \cdot L(\hat{\theta}(K_1), \hat{b}_{Xi}(K_1), \hat{r}_i(K_1)) \leq \log(N)(K_0 - K_1)). \end{aligned}$$

As we have shown  $P(\hat{B}_{K_0} = B_0) \rightarrow 1$ , with probability goes to 1 we have

$$\begin{aligned} &2 \cdot L(\hat{\theta}(K_0), \hat{b}_{Xi}(K_0), \hat{r}_i(K_0)) - 2 \cdot L(\hat{\theta}(K_1), \hat{b}_{Xi}(K_1), \hat{r}_i(K_1)) \\ &= \min_{\tilde{\theta}, \tilde{b}_{Xi}} \sum_{i \in \hat{B}_{K_1}^c} \left( \frac{(\hat{\beta}_{Xi} - \tilde{b}_{Xi})^2}{\hat{\sigma}_{Xi}^2} + \frac{(\hat{\beta}_{Yi} - \tilde{\theta} \tilde{b}_{Xi})^2}{\hat{\sigma}_{Yi}^2} \right) - \min_{\tilde{\theta}, \tilde{b}_{Xi}} \sum_{i \in B_0^c} \left( \frac{(\hat{\beta}_{Xi} - \tilde{b}_{Xi})^2}{\hat{\sigma}_{Xi}^2} + \frac{(\hat{\beta}_{Yi} - \tilde{\theta} \tilde{b}_{Xi})^2}{\hat{\sigma}_{Yi}^2} \right) \\ &\geq \min_{\tilde{\theta}, \tilde{b}_{Xi}} \sum_{i \in \hat{B}_{K_1}^c} \left( \frac{(\hat{\beta}_{Xi} - \tilde{b}_{Xi})^2}{\hat{\sigma}_{Xi}^2} + \frac{(\hat{\beta}_{Yi} - \tilde{\theta} \tilde{b}_{Xi})^2}{\hat{\sigma}_{Yi}^2} \right) - \sum_{i \in B_0^c} \left( \frac{(\hat{\beta}_{Xi} - \beta_{Xi})^2}{\hat{\sigma}_{Xi}^2} + \frac{(\hat{\beta}_{Yi} - \theta \beta_{Xi})^2}{\hat{\sigma}_{Yi}^2} \right). \end{aligned}$$

Then we get

$$\begin{aligned} &P(\hat{K} = K_1) \\ &\leq P\left(\min_{\tilde{\theta}, \tilde{b}_{Xi}} \sum_{i \in \hat{B}_{K_1}^c} \left( \frac{(\hat{\beta}_{Xi} - \tilde{b}_{Xi})^2}{\hat{\sigma}_{Xi}^2} + \frac{(\hat{\beta}_{Yi} - \tilde{\theta} \tilde{b}_{Xi})^2}{\hat{\sigma}_{Yi}^2} \right) \leq \sum_{i \in B_0^c} \left( \frac{(\hat{\beta}_{Xi} - \beta_{Xi})^2}{\hat{\sigma}_{Xi}^2} + \frac{(\hat{\beta}_{Yi} - \theta \beta_{Xi})^2}{\hat{\sigma}_{Yi}^2} \right) + \log(N)(K_0 - K_1)\right) \\ &\leq \sum_{|B|=K_1} P\left(\min_{\tilde{\theta}, \tilde{b}_{Xi}} \sum_{i \in B^c} \left( \frac{(\hat{\beta}_{Xi} - \tilde{b}_{Xi})^2}{\hat{\sigma}_{Xi}^2} + \frac{(\hat{\beta}_{Yi} - \tilde{\theta} \tilde{b}_{Xi})^2}{\hat{\sigma}_{Yi}^2} \right) \leq \sum_{i \in B_0^c} \left( \frac{(\hat{\beta}_{Xi} - \beta_{Xi})^2}{\hat{\sigma}_{Xi}^2} + \frac{(\hat{\beta}_{Yi} - \theta \beta_{Xi})^2}{\hat{\sigma}_{Yi}^2} \right) + \log(N)(K_0 - K_1)\right) \end{aligned}$$

Similar as above, we get

$$\min_{\tilde{\theta}, \tilde{b}_{Xi}} \sum_{i \in B^c} \left( \frac{(\hat{\beta}_{Xi} - \tilde{b}_{Xi})^2}{\hat{\sigma}_{Xi}^2} + \frac{(\hat{\beta}_{Yi} - \tilde{\theta} \tilde{b}_{Xi})^2}{\hat{\sigma}_{Yi}^2} \right) = \min_{\tilde{\theta}} \sum_{i \in B^c} \frac{(\hat{\beta}_{Yi} - \tilde{\theta} \cdot \hat{\beta}_{Xi})^2}{\hat{\sigma}_{Yi}^2 + \tilde{\theta}^2 \hat{\sigma}_{Xi}^2},$$

and  $\sum_{i \in B^c} \frac{(\hat{\beta}_{Yi} - \tilde{\theta} \cdot \hat{\beta}_{Xi})^2}{\hat{\sigma}_{Yi}^2 + \tilde{\theta}^2 \hat{\sigma}_{Xi}^2}$  follows non-central  $\chi^2$  distribution with degrees of freedom  $(m - K_1)$  and non-centrality parameter  $\lambda_{\tilde{\theta}}$  depending on  $\tilde{\theta}$

$$\lambda_{\tilde{\theta}} = \sum_{i \in B^c} \frac{(\theta \cdot \beta_{Xi} + r_i - \tilde{\theta} \cdot \beta_{Xi})^2}{\hat{\sigma}_{Yi}^2 + \tilde{\theta}^2 \hat{\sigma}_{Xi}^2}.$$



Similarly, since  $K_1 < K_0$ , with Assumption 2 we have  $\lambda_{\hat{\theta}} \geq N_2 \cdot v$  for some constant  $v$ , so for any  $|B| = K_1$ , we get

$$P\left(\min_{\hat{\theta}, \hat{b}_{Xi}} \sum_{i \in B^c} \left( \frac{(\hat{\beta}_{Xi} - \tilde{b}_{Xi})^2}{\hat{\sigma}_{Xi}^2} + \frac{(\hat{\beta}_{Yi} - \tilde{\theta} \tilde{b}_{Xi})^2}{\hat{\sigma}_{Yi}^2} \right) \leq \sum_{i \in B_0^c} \left( \frac{(\hat{\beta}_{Xi} - \beta_{Xi})^2}{\hat{\sigma}_{Xi}^2} + \frac{(\hat{\beta}_{Yi} - \theta \beta_{Xi})^2}{\hat{\sigma}_{Yi}^2} \right) + \log(N)(K_0 - K_1) \right) \rightarrow 0.$$

This gives us  $P(\hat{K} = K_1) \rightarrow 0$  for any  $K_1 < K_0$ . For any  $K_1 > K_0$ , we have

$$\begin{aligned} & P(\hat{K} = K_1) \\ & \leq P\left(\log(N)(K_1 - K_0) \leq \sum_{i \in B_0^c} \left( \frac{(\hat{\beta}_{Xi} - \beta_{Xi})^2}{\hat{\sigma}_{Xi}^2} + \frac{(\hat{\beta}_{Yi} - \theta \beta_{Xi})^2}{\hat{\sigma}_{Yi}^2} \right) - \min_{\hat{\theta}, \hat{b}_{Xi}} \sum_{i \in \hat{B}_{K_1}^c} \left( \frac{(\hat{\beta}_{Xi} - \tilde{b}_{Xi})^2}{\hat{\sigma}_{Xi}^2} + \frac{(\hat{\beta}_{Yi} - \tilde{\theta} \tilde{b}_{Xi})^2}{\hat{\sigma}_{Yi}^2} \right) \right) \\ & \leq P\left(\log(N)(K_1 - K_0) \leq \sum_{i \in B_0^c} \left( \frac{(\hat{\beta}_{Xi} - \beta_{Xi})^2}{\hat{\sigma}_{Xi}^2} + \frac{(\hat{\beta}_{Yi} - \theta \beta_{Xi})^2}{\hat{\sigma}_{Yi}^2} \right) \right) \end{aligned}$$

Since  $\sum_{i \in B_0^c} \left( \frac{(\hat{\beta}_{Xi} - \beta_{Xi})^2}{\hat{\sigma}_{Xi}^2} + \frac{(\hat{\beta}_{Yi} - \theta \beta_{Xi})^2}{\hat{\sigma}_{Yi}^2} \right)$  is a central  $\chi^2$  distribution with degrees of freedom  $2(m - K_0)$ , we get  $P(\hat{K} = K_1) \rightarrow 0$  for any  $K_1 > K_0$ . So we have  $P(\hat{K} = K_0) \rightarrow 1$  as  $N_1, N_2 \rightarrow \infty$ .  $\square$

## S2 Standard Error of $\hat{\theta}$

For any given  $K$ , denote the index set of  $K$  non-zero  $\hat{r}_i$ 's as  $\hat{B}_K$ . The  $(m - K + 1)$  by  $(m - K + 1)$  Fisher information matrix is

$$\mathcal{J} = \begin{pmatrix} \frac{\partial^2(-l)}{\partial \theta^2} & \frac{\partial^2(-l)}{\partial \theta \partial \beta'_{XB}} \\ \frac{\partial^2(-l)}{\partial \theta \partial \beta_{XB}} & \frac{\partial^2(-l)}{\partial \beta_{XB} \partial \beta'_{XB}} \end{pmatrix}, \quad (3)$$

where  $\beta_{XB}$  is a vector of elements  $\beta_{Xi}$  with  $i \in \hat{B}_K^c$ . Plug  $\hat{\theta}$ ,  $\hat{b}_{Xi}$ 's into  $\mathcal{J}$ , we obtain the standard error of  $\hat{\theta}$  as  $\text{SE}(\hat{\theta}) = \sqrt{(\mathcal{J}^{-1})_{11}}$ .

We have

$$\begin{aligned} \left. \frac{\partial^2(-l)}{\partial \theta^2} \right|_{\hat{\theta}, \hat{b}_{Xi}} &= \sum_{i \in \hat{B}_K^c} \frac{\hat{b}_{Xi}^2}{\hat{\sigma}_{Yi}^2}, \\ \left. \frac{\partial^2(-l)}{\partial \beta_{Xi}^2} \right|_{\hat{\theta}, \hat{b}_{Xi}} &= \frac{1}{\hat{\sigma}_{Xi}^2} + \frac{\hat{\theta}^2}{\hat{\sigma}_{Yi}^2} \\ \left. \frac{\partial^2(-l)}{\partial \theta \partial \beta_{Xi}} \right|_{\hat{\theta}, \hat{b}_{Xi}} &= \frac{2\hat{b}_{Xi}\hat{\theta} - \hat{\beta}_{Yi}}{\hat{\sigma}_{Yi}^2}. \end{aligned} \quad (4)$$

And

$$\begin{aligned} \text{SE}(\hat{\theta}) &= \sqrt{(\mathcal{J}^{-1})_{11}} = \frac{1}{V}, \\ V &= \sum_{i \in \hat{B}_K^c} \frac{\hat{b}_{Xi}^2}{\hat{\sigma}_{Yi}^2} - \sum_{i \in \hat{B}_K^c} \left( \frac{2\hat{b}_{Xi}\hat{\theta} - \hat{\beta}_{Yi}}{\hat{\sigma}_{Yi}^2} \right)^2 \cdot \frac{1}{\frac{1}{\hat{\sigma}_{Xi}^2} + \frac{\hat{\theta}^2}{\hat{\sigma}_{Yi}^2}}. \end{aligned} \quad (5)$$

From our Assumption 2, we get  $N_1, N_2$  are  $O(N)$  for some  $N$ , and  $\hat{\sigma}_{Xi}^2, \hat{\sigma}_{Yi}^2$  are both  $O(1/N)$ . And as  $N \rightarrow \infty$ ,  $\hat{\beta}_{Xi} \rightarrow \beta_{Xi}$  with probability 1, and from the IV Assumption A1 we have  $\beta_{Xi} \neq 0$ . So in Theorem 3.3 of [13], as  $N_1, N_2 \rightarrow \infty$ , i.e.  $N \rightarrow \infty$ ,  $\hat{\sigma}_{Xi}$  and  $\hat{\sigma}_{Yi}$  are both  $o_p(\hat{\beta}_{Xi})$ , we have asymptotic variance of  $\hat{\theta}$  as  $1/V^*$  and

$$V^* = \sum_{i \in \hat{B}_K^c} \frac{\hat{\beta}_{Xi}^2 \hat{\sigma}_{Yi}^2 + \hat{\beta}_{Yi}^2 \hat{\sigma}_{Xi}^2}{(\hat{\theta}^2 \hat{\sigma}_{Xi}^2 + \hat{\sigma}_{Yi}^2)^2}. \quad (6)$$

Since we have

$$\hat{b}_{Xi} = \frac{\frac{\hat{\beta}_{Xi}}{\hat{\sigma}_{Xi}^2} + \frac{\hat{\theta}\hat{\beta}_{Yi}}{\hat{\sigma}_{Yi}^2}}{\frac{1}{\hat{\sigma}_{Xi}^2} + \frac{\hat{\theta}^2}{\hat{\sigma}_{Yi}^2}}. \quad (7)$$

Plug (7) in (5), we get

$$V - V^* = \sum_{i \in \hat{B}_K^c} -\frac{4\hat{\sigma}_{Xi}^2\hat{\sigma}_{Yi}^2(\hat{\beta}_{Yi} - \hat{\theta}\hat{\beta}_{Xi})^2}{(\hat{\theta}^2\hat{\sigma}_{Xi}^2 + \hat{\sigma}_{Yi}^2)^3} + \frac{2\hat{\sigma}_{Xi}^2\hat{\beta}_{Yi}(\hat{\beta}_{Yi} - \hat{\theta}\hat{\beta}_{Xi})}{(\hat{\theta}^2\hat{\sigma}_{Xi}^2 + \hat{\sigma}_{Yi}^2)^2}. \quad (8)$$

With our Theorem 1 we have  $P(\hat{K} = K_0) \rightarrow 1$  and  $P(\hat{B}_{\hat{K}} = B_0) \rightarrow 1$ , and when  $\hat{B}_{\hat{K}} = B_0$ , we have  $\hat{\beta}_{Yi} - \hat{\theta}\hat{\beta}_{Xi} \rightarrow 0$  for  $i \in \hat{B}_{\hat{K}}^c$ . For the first part in (8), divided by the corresponding part in (6), because  $\hat{\sigma}_{Xi}^2, \hat{\sigma}_{Yi}^2, \hat{\theta}^2\hat{\sigma}_{Xi}^2 + \hat{\sigma}_{Yi}^2, \hat{\beta}_{Xi}^2\hat{\sigma}_{Yi}^2 + \hat{\beta}_{Yi}^2\hat{\sigma}_{Xi}^2$  are all  $O_p(1/N)$  and  $\hat{\beta}_{Yi} - \hat{\theta}\hat{\beta}_{Xi} \rightarrow 0$ , we get

$$-\frac{4\hat{\sigma}_{Xi}^2\hat{\sigma}_{Yi}^2(\hat{\beta}_{Yi} - \hat{\theta}\hat{\beta}_{Xi})^2}{(\hat{\theta}^2\hat{\sigma}_{Xi}^2 + \hat{\sigma}_{Yi}^2)^3} \Big/ \frac{\hat{\beta}_{Xi}^2\hat{\sigma}_{Yi}^2 + \hat{\beta}_{Yi}^2\hat{\sigma}_{Xi}^2}{(\hat{\theta}^2\hat{\sigma}_{Xi}^2 + \hat{\sigma}_{Yi}^2)^2} = -\frac{4\hat{\sigma}_{Xi}^2\hat{\sigma}_{Yi}^2(\hat{\beta}_{Yi} - \hat{\theta}\hat{\beta}_{Xi})^2}{(\hat{\theta}^2\hat{\sigma}_{Xi}^2 + \hat{\sigma}_{Yi}^2)(\hat{\beta}_{Xi}^2\hat{\sigma}_{Yi}^2 + \hat{\beta}_{Yi}^2\hat{\sigma}_{Xi}^2)} \rightarrow 0.$$

Similarly, for the second part in (8), divided by the corresponding part in (6), because  $\hat{\sigma}_{Xi}^2, \hat{\sigma}_{Yi}^2$  are both  $O_p(1/N)$  and  $\hat{\beta}_{Yi} - \hat{\theta}\hat{\beta}_{Xi} \rightarrow 0$ , we get

$$\frac{2\hat{\sigma}_{Xi}^2\hat{\beta}_{Yi}(\hat{\beta}_{Yi} - \hat{\theta}\hat{\beta}_{Xi})}{(\hat{\theta}^2\hat{\sigma}_{Xi}^2 + \hat{\sigma}_{Yi}^2)^2} \Big/ \frac{\hat{\beta}_{Xi}^2\hat{\sigma}_{Yi}^2 + \hat{\beta}_{Yi}^2\hat{\sigma}_{Xi}^2}{(\hat{\theta}^2\hat{\sigma}_{Xi}^2 + \hat{\sigma}_{Yi}^2)^2} = \frac{2\hat{\sigma}_{Xi}^2\hat{\beta}_{Yi}(\hat{\beta}_{Yi} - \hat{\theta}\hat{\beta}_{Xi})}{\hat{\beta}_{Xi}^2\hat{\sigma}_{Yi}^2 + \hat{\beta}_{Yi}^2\hat{\sigma}_{Xi}^2} \rightarrow 0.$$

Hence we have  $V - V^* = o_p(V^*)$ , implying that  $V$  and  $V^*$  are asymptotically equivalent. This shows that our cMLE and the MPLE asymptotically share the same variance; this was also confirmed in our simulations and real data examples.

### S3 Full Real Data Results

#### S3.1 Inference and Estimation Results of All Methods

Here we show the full real data results estimating and inferring causal effects of 12 risk factors on 4 common diseases from Table S1 to S4. We implemented cML methods, CAUSE, MR-Mix, MR-ContMix, MR-Lasso, MR-PRESSO, MR-IVW, MR-Egger, MR-Weighted-Median, MR-Weighted-Mode, and MR-RAPS. For cML method with BIC, we could use the smaller one of sample sizes of exposure and outcome (denoted by cML-BIC, cML-MA-BIC, cML-BIC-DP, cML-MA-BIC-DP), or we could use the larger one of them (denoted by cML-BIC-max, cML-MA-BIC-max, cML-BIC-DP-Max, cML-MA-BIC-DP-Max). These two choices give essentially the same results. We can also get  $\hat{\theta}$  and  $SE(\hat{\theta})$  with profile likelihood as described in [13] (denoted by cML-MA-AIC-Profile, cML-AIC-Profile, cML-MA-BIC-max-Profile, cML-BIC-max-Profile, cML-MA-BIC-Profile, and cML-BIC-Profile). These two estimation approaches give almost the same results. For CAUSE, we extract its original results from Supplementary Table 3 of [6].

CAUSE and MR-ContMix do not provide the standard error of estimate, so we show their standard errors as NA.

#### S3.2 BIC and Scatter Plots

Table S5 shows the number of IVs used, number of invalid IVs detected by cML-BIC, and the proportion of detected invalid IVs for each exposure-outcome pair, with one default starting point set at 0 and

another 100 randomly generated starting points. Table S6 shows the results for only using the default starting point set at 0. There are 7 pairs giving different numbers of invalid IVs for the two runs with different starting points.

Figure S1 to S4 show BIC and scatter plots for each exposure-outcome pair in primary real data examples.

### S3.3 Goodness-of-Fit Test Results

Tables S7 to S10 show the goodness-of-fit (GOF) test results for the 48 trait pairs. Each cell in each table shows the  $p$ -value of the corresponding GOF test. To calculate the BIC, we could use either the smaller one of the sample sizes for the exposure and the outcome (denoted by GOF1 and GOF2), or we could use the larger one of them (denoted by GOF1-Max and GOF2-Max). These two choices gave essentially the same results.

## S4 Full Secondary Real Data Results

### S4.1 GWAS Data and IV Selection

Table S11 shows the details of GWAS summary data used for the 13 traits in secondary real data examples. For each exposure-outcome pair, we used R package TwoSampleMR to select IVs and extract summary statistics following the standard procedure in the package. Here we show the example code for fasting proinsulin as the exposure and age at smoking as the outcome.

```
library(TwoSampleMR)
# ID of Fasting Proinsulin as exposure, ID of Age at Smoking as outcome
exp_id = "ebi-a-GCST001212"
out_id = "ieu-a-964"
# Extract IVs for exposure
exposure_dat <- extract_instruments(exp_id)
# LD-clumping of extracted IVs
exposure_dat <- clump_data(exposure_dat)
# Extract summary statistics of outcome, do not use proxy
outcome_dat <- extract_outcome_data(exposure_dat$SNP, out_id, proxies = 0)
# Harmonize data: correct strand for non-palindromic SNPs, drop all palindromic SNPs
dat <- harmonise_data(exposure_dat, outcome_dat, action = 3)
final_dat = dat[dat$mr_keep,]
# Get final estimates and standard errors for exposure and outcome
b_exp = final_dat$beta.exposure
b_out = final_dat$beta.outcome
se_exp = final_dat$se.exposure
se_out = final_dat$se.outcome
```

### S4.2 Inference and Estimation Results of All Methods

See Table S12 to S18 and Figure S5.

### S4.3 Goodness-of-fit Tests Results

See Table S19 to S25.

## **S5 Full Main Simulation Results**

In our main simulations, we implemented our proposed cML method, MR-Mix, MR-ContMix, MR-Lasso, MR-PRESSO, MR-IVW, MR-IVW-Oracle, MR-Egger, MR-Weighted-Median, MR-Weighted-Mode and MR-RAPS. For cML methods, we could use AIC or BIC to select the best  $K$  (denoted by cML-AIC and cML-BIC), or generate AIC- or BIC-based weights for model averaging (denoted by cML-MA-AIC and cML-MA-BIC). We could use our iterative algorithm to get the constrained maximum likelihood estimate  $\hat{\theta}$ , and its standard error  $SE(\hat{\theta})$  with Fisher's information matrix as described in Section 4.4 (denoted by cML-MA-AIC, cML-AIC, cML-MA-BIC, and cML-BIC); or get  $\hat{\theta}$  and  $SE(\hat{\theta})$  with the profile likelihood as described in [13] (denoted by cML-MA-AIC-Profile, cML-AIC-Profile, cML-MA-BIC-Profile, and cML-BIC-Profile). The two likelihood approaches gave almost the same results.

### **S5.1 Inference and Estimation Results**

Table S26 to S88 show the inference and estimation results for the main simulations for  $m = 10, 20, 100$ , the ideal case with  $q = 0$ , and  $q = 0.2, 0.4, 0.6$  with the InSIDE assumption holding or violated, and  $N = 50000, 100000, 200000$ .

MR-ContMix does not provide the standard error of an estimate, so we show its mean standard error as NA.

### **S5.2 Selection Results**

Tables S89 to S94 show the relative frequencies of cML-BIC's selecting  $\hat{K} = K_0$ . We can see that, for each set-up, as  $N$  increased from 50000 to 200000, the relative frequencies of the correct selection also increased.

### **S5.3 Type-I Errors Based on 10,000 Simulations**

In Figure 2 of the main text, we showed type-I errors of different methods for 10 setups based on 1000 simulations. We increased the number of simulations for each of these 10 setups to 10,000 and calculated the empirical type-I errors of different methods as shown in Figure S6.

### **S5.4 Data Perturbation Results**

#### **S5.4.1 Inference and Estimation Results**

See Table S95 to S103.

#### **S5.4.2 Goodness-of-Fit Test Results**

See Table S104 to S106.

## **S6 Full Secondary Simulation Results**

See Figure S7 and S8.

## S7 Full Simulation Results with Weak Invalid IVs

### S7.1 Inference and Estimation Results

See Table S107 to S114.

### S7.2 Goodness-of-Fit Test Results

See Table S115 to S119.

### S7.3 cML-MA-BIC and cML-MA-BIC-DP with Valid IVs

In the simulation setup 30 of 50 SNPs were invalid IVs while the other 20 were valid IVs. For valid IVs, their effects  $\gamma_i$ 's on  $X$  were generated from  $N(0, h_x/m)$ , where  $h_x = 0.5$ ,  $m = 50$ , and pleiotropic effects  $\alpha_i$ 's and  $\phi_i$ 's were 0. We can see that the IV effects  $\gamma_i$ 's were weaker than in those in the Main simulations.

We applied cML-MA-BIC, cML-BIC, cML-MA-BIC-DP and cML-BIC-DP (with  $T = 200$ ) to the simulated data with only 20 valid IVs. Note that, since  $h_y$  only affected  $\alpha_i$ 's of invalid IVs, the results were the same for  $h_y = 0.1, 0.2, 0.4, 0.6$  as we only used 20 valid IVs. Table S120 shows the results. For cML-MA-BIC, cML-BIC, cML-MA-BIC-DP and cML-BIC-DP, in each cell from top to bottom are power/type-I error,  $\text{Mean}(\hat{\theta})$ ,  $\text{SD}(\hat{\theta})$ , and  $\text{Mean}(\text{SE}(\hat{\theta}))$ . For GOF1 and GOF2, the cells show the relative frequencies of their rejecting the null. The methods appeared to perform well.

## S8 Computational Time

We compared the computational time taken by different methods. For cML-MA-BIC we tried with 0 or 5 random starting points (in addition to the single default starting point). For cML-MA-BIC-DP we set the number of data perturbations  $T = 200$  and tried with 0 or 5 random starting points (in addition to the single default starting point) for each perturbed dataset. For MR-ContMix we set  $\text{CIMin} = -0.5$ ,  $\text{CIMax} = 0.5$ ,  $\text{CISStep} = 0.0001$ . For MR-RAPS we set  $\text{over.dispersion} = \text{TRUE}$ ,  $\text{loss.function} = \text{"tukey"}$ . All other methods were implemented with their default parameters. Since CAUSE took a much longer running time, we did not include it for comparison.

We generated the simulated data following Section 2.9.3 in the Main text. We tried different numbers of IVs  $m = 10, 20, 50, 70$  and  $100$ , and set  $h_y = 0.2$ ,  $\theta = 0$ , and 60% IVs as invalid IVs. For each  $m$  we did 10 simulations and applied different methods, counted each one's average running time over the 10 simulations. Table S121 shows the results. All methods were run on a 2016 MacBook Pro with a 2.7 GHz Intel Core i5 processor and 8 GB memory.

## Supplemental References

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