# S6 Text: More Simulation Results

## Details of Simulation Setups

We used three parameters $(\beta_{YX}, \mu_\alpha, \sigma_\alpha)$ in each simulation setup. $\beta_{YX}$ controls the causal effect size, $\mu_\alpha$ controls the mean direct effect size, $\sigma_\alpha$ controls the variation of the (random) direct effect sizes. We tried 75 different combinations of $\beta_{YX} = -0.2, -0.1, 0, 0.1, 0.2, \mu_\alpha = 0, 0.2, 0.4, 0.6, 1, \sigma_\alpha = 0, 0.1, 0.2$. For each setup we first generated $\boldsymbol{\beta}_{Xg} = (\beta_{Xg_1}, \beta_{Xg_2}, ..., \beta_{Xg_{22}})^T$, the vector of the effect sizes of the 22 SNPs on $X$, with each element independently drawn from a truncated standard normal distribution (truncated at 0.5 to ensure $|\beta_{Xg_j}| \geq 0.5$). Then in each simulation, we generated the two traits from the true models:

$$X_i = \boldsymbol{Z}_i \boldsymbol{\beta}_{Xg} + U_i + \varepsilon_{Xi}, \qquad Y_i = \beta_{YX} \cdot X_i + \boldsymbol{Z}_i \boldsymbol{\alpha} + U_i + \varepsilon_{Yi},$$

where $\boldsymbol{Z}_i$ was the (row) vector of the genotype scores of the 22 SNPs for subject $i = 1, 2, ..., n$, $U_i \sim N(0,1)$ was a confounder; the direct effects of the SNPs on $Y$, $\boldsymbol{\alpha} = (\alpha_1, ..., \alpha_{22})^T$, were generated independently $\alpha_i \sim N(\mu_\alpha, \sigma_\alpha^2)$; and both error terms $\varepsilon_{Xi}, \varepsilon_{Yi}$ were independently from $N(0,4)$.

## Estimating $K_{YX}$

Table A shows simulation results for estimating $K_{YX}$ of CD-Ratio, CD-Egger, and CD-GLS, for the setup $\mu_\alpha = 0$, $\sigma_\alpha = 0$, and various $\beta_{YX}$ levels. In each row we list the value $\beta_{YX}$ in the first column, and corresponding true value $K_{YX}$ in the second column, and for each of three methods we show the estimation results similar to Table 5 in the main text. Table B to Table O show similar results for other setups. When $\beta_{YX} \neq 0$ the true causal direction is from $X$ to $Y$, we can calculate the true value of $K_{YX} = \beta_{YX} \cdot \frac{\sqrt{var(X)}}{\sqrt{var(Y)}}$, here

$$\begin{aligned} var(X) &= \boldsymbol{\beta}_{Xg}^T \boldsymbol{\Sigma} \boldsymbol{\beta}_{Xg} + var(U) + var(\varepsilon_X) \\ var(Y) &= (\mu_\alpha \cdot \mathbf{1} + \beta_{YX} \cdot \boldsymbol{\beta}_{Xg})^T \boldsymbol{\Sigma} (\mu_\alpha \cdot \mathbf{1} + \beta_{YX} \cdot \boldsymbol{\beta}_{Xg}) + (\beta_{YX}+1)^2 var(U) + \beta_{YX}^2 var(\varepsilon_X) + var(\varepsilon_Y) \end{aligned} \tag{1}$$

$\boldsymbol{\Sigma}$ is the covariance matrix of SNPs. When $\beta_{YX} = 0$, we have $K_{YX} = 0$.

Table A: Results of $\mu_\alpha = 0$, $\sigma_\alpha = 0$: $K_{YX}$

| | | CD-Ratio | | | CD-Egger | | | CD-GLS | | |
|---|---|---|---|---|---|---|---|---|---|---|
| $\beta_{YX}$ | $K_{YX}$ | Mean($\hat{K}$) | sd($\hat{K}$) | Mean($se(\hat{K})$) | Mean($\hat{K}$) | sd($\hat{K}$) | Mean($se(\hat{K})$) | Mean($\hat{K}$) | sd($\hat{K}$) | Mean($se(\hat{K})$) |
| -0.2 | -0.442 | -0.4415 | 0.0028 | 0.0036 | -0.4415 | 0.0028 | 0.0035 | -0.4415 | 0.0028 | 0.0036 |
| -0.1 | -0.2344 | -0.2341 | 0.0032 | 0.0036 | -0.2341 | 0.0032 | 0.0036 | -0.2341 | 0.0032 | 0.0036 |
| 0 | 0 | 0.0001 | 0.0034 | 0.0035 | 0.0001 | 0.0034 | 0.0036 | 0.0001 | 0.0034 | 0.0036 |
| 0.1 | 0.2257 | 0.2256 | 0.0033 | 0.0036 | 0.2256 | 0.0033 | 0.0036 | 0.2256 | 0.0033 | 0.0036 |
| 0.2 | 0.4139 | 0.4137 | 0.003 | 0.0036 | 0.4137 | 0.003 | 0.0035 | 0.4137 | 0.003 | 0.0036 |

Table B: Results of $\mu_\alpha = 0.2$, $\sigma_\alpha = 0$: $K_{YX}$

| | | CD-Ratio | | | CD-Egger | | | CD-GLS | | |
|---|---|---|---|---|---|---|---|---|---|---|
| $\beta_{YX}$ | $K_{YX}$ | Mean($\hat{K}$) | sd($\hat{K}$) | Mean($se(\hat{K})$) | Mean($\hat{K}$) | sd($\hat{K}$) | Mean($se(\hat{K})$) | Mean($\hat{K}$) | sd($\hat{K}$) | Mean($se(\hat{K})$) |
| -0.2 | -0.3995 | -0.4106 | 0.003 | 0.0038 | -0.3992 | 0.0026 | 0.0034 | -0.3992 | 0.0026 | 0.0035 |
| -0.1 | -0.2093 | -0.2191 | 0.0032 | 0.0039 | -0.2091 | 0.0029 | 0.0035 | -0.2091 | 0.0029 | 0.0035 |
| 0 | 0 | -0.0097 | 0.0034 | 0.0039 | 0 | 0.0031 | 0.0035 | 0 | 0.0031 | 0.0035 |
| 0.1 | 0.2027 | 0.1947 | 0.0034 | 0.0039 | 0.2026 | 0.003 | 0.0035 | 0.2026 | 0.003 | 0.0036 |
| 0.2 | 0.3773 | 0.3675 | 0.0031 | 0.0039 | 0.3771 | 0.0028 | 0.0035 | 0.3771 | 0.0028 | 0.0036 |

Table C: Results of $\mu_\alpha = 0.4$, $\sigma_\alpha = 0$: $K_{YX}$

| | | CD-Ratio | | | CD-Egger | | | CD-GLS | | |
|---|---|---|---|---|---|---|---|---|---|---|
| $\beta_{YX}$ | $K_{YX}$ | Mean($\hat{K}$) | sd($\hat{K}$) | Mean$(se(\hat{K}))$ | Mean($\hat{K}$) | sd($\hat{K}$) | Mean$(se(\hat{K}))$ | Mean($\hat{K}$) | sd($\hat{K}$) | Mean$(se(\hat{K}))$ |
| -0.2 | -0.3203 | -0.3298 | 0.0031 | 0.004 | -0.3202 | 0.0022 | 0.0032 | -0.3202 | 0.0022 | 0.0033 |
| -0.1 | -0.1649 | -0.1777 | 0.0032 | 0.0041 | -0.1648 | 0.0023 | 0.0033 | -0.1648 | 0.0023 | 0.0033 |
| 0 | 0 | -0.0158 | 0.0033 | 0.0041 | 0 | 0.0025 | 0.0033 | 0 | 0.0025 | 0.0034 |
| 0.1 | 0.1614 | 0.1464 | 0.0033 | 0.0041 | 0.1613 | 0.0025 | 0.0034 | 0.1613 | 0.0025 | 0.0034 |
| 0.2 | 0.3079 | 0.2956 | 0.0032 | 0.0041 | 0.3078 | 0.0024 | 0.0034 | 0.3078 | 0.0024 | 0.0035 |

Table D: Results of $\mu_\alpha = 0.6$, $\sigma_\alpha = 0$: $K_{YX}$

| | | CD-Ratio | | | CD-Egger | | | CD-GLS | | |
|---|---|---|---|---|---|---|---|---|---|---|
| $\beta_{YX}$ | $K_{YX}$ | Mean($\hat{K}$) | sd($\hat{K}$) | Mean$(se(\hat{K}))$ | Mean($\hat{K}$) | sd($\hat{K}$) | Mean$(se(\hat{K}))$ | Mean($\hat{K}$) | sd($\hat{K}$) | Mean$(se(\hat{K}))$ |
| -0.2 | -0.2535 | -0.2713 | 0.0033 | 0.0041 | -0.2535 | 0.0018 | 0.0031 | -0.2535 | 0.0018 | 0.0032 |
| -0.1 | -0.129 | -0.1538 | 0.0034 | 0.0042 | -0.129 | 0.0019 | 0.0031 | -0.129 | 0.0019 | 0.0032 |
| 0 | 0 | -0.0304 | 0.0034 | 0.0042 | 0 | 0.002 | 0.0032 | 0 | 0.002 | 0.0032 |
| 0.1 | 0.1272 | 0.0955 | 0.0034 | 0.0042 | 0.1272 | 0.002 | 0.0033 | 0.1272 | 0.002 | 0.0033 |
| 0.2 | 0.2469 | 0.2181 | 0.0033 | 0.0042 | 0.2468 | 0.002 | 0.0034 | 0.2468 | 0.002 | 0.0034 |

Table E: Results of $\mu_\alpha = 1$, $\sigma_\alpha = 0$: $K_{YX}$

| | | CD-Ratio | | | CD-Egger | | | CD-GLS | | |
|---|---|---|---|---|---|---|---|---|---|---|
| $\beta_{YX}$ | $K_{YX}$ | Mean($\hat{K}$) | sd($\hat{K}$) | Mean$(se(\hat{K}))$ | Mean($\hat{K}$) | sd($\hat{K}$) | Mean$(se(\hat{K}))$ | Mean($\hat{K}$) | sd($\hat{K}$) | Mean$(se(\hat{K}))$ |
| -0.2 | -0.171 | -0.2063 | 0.0036 | 0.0042 | -0.171 | 0.0013 | 0.003 | -0.171 | 0.0012 | 0.003 |
| -0.1 | -0.0862 | -0.1297 | 0.0036 | 0.0043 | -0.0862 | 0.0013 | 0.003 | -0.0862 | 0.0013 | 0.003 |
| 0 | 0 | -0.0503 | 0.0036 | 0.0043 | 0 | 0.0013 | 0.0031 | 0 | 0.0013 | 0.0031 |
| 0.1 | 0.0856 | 0.0315 | 0.0035 | 0.0043 | 0.0855 | 0.0014 | 0.0032 | 0.0856 | 0.0014 | 0.0032 |
| 0.2 | 0.1687 | 0.1144 | 0.0035 | 0.0043 | 0.1687 | 0.0014 | 0.0033 | 0.1687 | 0.0014 | 0.0033 |

Table F: Results of $\mu_\alpha = 0$, $\sigma_\alpha = 0.1$: $K_{YX}$

| | | CD-Ratio | | | CD-Egger | | | CD-GLS | | |
|---|---|---|---|---|---|---|---|---|---|---|
| $\beta_{YX}$ | $K_{YX}$ | Mean($\hat{K}$) | sd($\hat{K}$) | Mean$(se(\hat{K}))$ | Mean($\hat{K}$) | sd($\hat{K}$) | Mean$(se(\hat{K}))$ | Mean($\hat{K}$) | sd($\hat{K}$) | Mean$(se(\hat{K}))$ |
| -0.2 | -0.442 | -0.4254 | 0.0477 | 0.0037 | -0.4335 | 0.0345 | 0.0386 | -0.4335 | 0.0347 | 0.0394 |
| -0.1 | -0.2344 | -0.2233 | 0.0545 | 0.0037 | -0.2296 | 0.0409 | 0.0408 | -0.2295 | 0.0414 | 0.0416 |
| 0 | 0 | 0.0013 | 0.0563 | 0.0037 | -0.0007 | 0.0431 | 0.041 | -0.0005 | 0.0436 | 0.0419 |
| 0.1 | 0.2257 | 0.2181 | 0.0531 | 0.0037 | 0.2201 | 0.0397 | 0.0393 | 0.2203 | 0.0402 | 0.0401 |
| 0.2 | 0.4139 | 0.4019 | 0.0459 | 0.0037 | 0.4056 | 0.0332 | 0.0362 | 0.4059 | 0.0334 | 0.0369 |

Table G: Results of $\mu_\alpha = 0.2$, $\sigma_\alpha = 0.1$: $K_{YX}$

| | | CD-Ratio | | | CD-Egger | | | CD-GLS | | |
|---|---|---|---|---|---|---|---|---|---|---|
| $\beta_{YX}$ | $K_{YX}$ | Mean($\hat{K}$) | sd($\hat{K}$) | Mean$(se(\hat{K}))$ | Mean($\hat{K}$) | sd($\hat{K}$) | Mean$(se(\hat{K}))$ | Mean($\hat{K}$) | sd($\hat{K}$) | Mean$(se(\hat{K}))$ |
| -0.2 | -0.3995 | -0.4048 | 0.0463 | 0.0038 | -0.3936 | 0.0328 | 0.035 | -0.3936 | 0.0326 | 0.0357 |
| -0.1 | -0.2093 | -0.2172 | 0.0517 | 0.0039 | -0.2061 | 0.037 | 0.0366 | -0.206 | 0.0373 | 0.0373 |
| 0 | 0 | -0.0112 | 0.0538 | 0.0039 | -0.0005 | 0.0386 | 0.0368 | -0.0004 | 0.0392 | 0.0375 |
| 0.1 | 0.2027 | 0.1898 | 0.0514 | 0.0039 | 0.1987 | 0.0369 | 0.0355 | 0.1989 | 0.0375 | 0.0362 |
| 0.2 | 0.3773 | 0.3612 | 0.0452 | 0.0039 | 0.3711 | 0.0326 | 0.0331 | 0.3714 | 0.0331 | 0.0338 |

Table H: Results of $\mu_\alpha = 0.4$, $\sigma_\alpha = 0.1$: $K_{YX}$

| | | CD-Ratio | | | CD-Egger | | | CD-GLS | | |
|---|---|---|---|---|---|---|---|---|---|---|
| $\beta_{YX}$ | $K_{YX}$ | Mean($\hat{K}$) | sd($\hat{K}$) | Mean($se(\hat{K})$) | Mean($\hat{K}$) | sd($\hat{K}$) | Mean($se(\hat{K})$) | Mean($\hat{K}$) | sd($\hat{K}$) | Mean($se(\hat{K})$) |
| -0.2 | -0.3203 | -0.3301 | 0.0412 | 0.004 | -0.3176 | 0.028 | 0.0282 | -0.3176 | 0.028 | 0.0288 |
| -0.1 | -0.1649 | -0.1796 | 0.0435 | 0.0041 | -0.1636 | 0.0298 | 0.029 | -0.1635 | 0.03 | 0.0296 |
| 0 | 0 | -0.0183 | 0.0448 | 0.0041 | -0.0004 | 0.0306 | 0.0291 | -0.0003 | 0.0311 | 0.0297 |
| 0.1 | 0.1614 | 0.1438 | 0.0448 | 0.0041 | 0.1593 | 0.0301 | 0.0285 | 0.1595 | 0.0307 | 0.029 |
| 0.2 | 0.3079 | 0.2925 | 0.0424 | 0.0041 | 0.3046 | 0.0284 | 0.0272 | 0.3049 | 0.029 | 0.0278 |

Table I: Results of $\mu_\alpha = 0.6$, $\sigma_\alpha = 0.1$: $K_{YX}$

| | | CD-Ratio | | | CD-Egger | | | CD-GLS | | |
|---|---|---|---|---|---|---|---|---|---|---|
| $\beta_{YX}$ | $K_{YX}$ | Mean($\hat{K}$) | sd($\hat{K}$) | Mean($se(\hat{K})$) | Mean($\hat{K}$) | sd($\hat{K}$) | Mean($se(\hat{K})$) | Mean($\hat{K}$) | sd($\hat{K}$) | Mean($se(\hat{K})$) |
| -0.2 | -0.2535 | -0.2721 | 0.0341 | 0.0041 | -0.2524 | 0.0228 | 0.0224 | -0.2524 | 0.0228 | 0.0229 |
| -0.1 | -0.129 | -0.1552 | 0.0351 | 0.0042 | -0.1285 | 0.0236 | 0.0228 | -0.1285 | 0.0238 | 0.0233 |
| 0 | 0 | -0.0317 | 0.0357 | 0.0042 | -0.0003 | 0.024 | 0.0228 | -0.0002 | 0.0244 | 0.0233 |
| 0.1 | 0.1272 | 0.0944 | 0.0362 | 0.0042 | 0.1261 | 0.024 | 0.0225 | 0.1263 | 0.0244 | 0.023 |
| 0.2 | 0.2469 | 0.217 | 0.0359 | 0.0042 | 0.2451 | 0.0234 | 0.0219 | 0.2454 | 0.0239 | 0.0224 |

Table J: Results of $\mu_\alpha = 1$, $\sigma_\alpha = 0.1$: $K_{YX}$

| | | CD-Ratio | | | CD-Egger | | | CD-GLS | | |
|---|---|---|---|---|---|---|---|---|---|---|
| $\beta_{YX}$ | $K_{YX}$ | Mean($\hat{K}$) | sd($\hat{K}$) | Mean($se(\hat{K})$) | Mean($\hat{K}$) | sd($\hat{K}$) | Mean($se(\hat{K})$) | Mean($\hat{K}$) | sd($\hat{K}$) | Mean($se(\hat{K})$) |
| -0.2 | -0.171 | -0.2066 | 0.0236 | 0.0042 | -0.1708 | 0.0157 | 0.0151 | -0.1708 | 0.0158 | 0.0154 |
| -0.1 | -0.0862 | -0.1301 | 0.0238 | 0.0043 | -0.0862 | 0.0159 | 0.0153 | -0.0862 | 0.0161 | 0.0156 |
| 0 | 0 | -0.0506 | 0.0241 | 0.0043 | -0.0002 | 0.0161 | 0.0153 | -0.0002 | 0.0164 | 0.0156 |
| 0.1 | 0.0856 | 0.0313 | 0.0244 | 0.0043 | 0.0851 | 0.0162 | 0.0152 | 0.0852 | 0.0165 | 0.0155 |
| 0.2 | 0.1687 | 0.1143 | 0.0247 | 0.0043 | 0.1681 | 0.0161 | 0.015 | 0.1682 | 0.0165 | 0.0153 |

Table K: Results of $\mu_\alpha = 0$, $\sigma_\alpha = 0.2$: $K_{YX}$

| | | CD-Ratio | | | CD-Egger | | | CD-GLS | | |
|---|---|---|---|---|---|---|---|---|---|---|
| $\beta_{YX}$ | $K_{YX}$ | Mean($\hat{K}$) | sd($\hat{K}$) | Mean($se(\hat{K})$) | Mean($\hat{K}$) | sd($\hat{K}$) | Mean($se(\hat{K})$) | Mean($\hat{K}$) | sd($\hat{K}$) | Mean($se(\hat{K})$) |
| -0.2 | -0.442 | -0.3933 | 0.0936 | 0.0038 | -0.4113 | 0.0669 | 0.0727 | -0.4111 | 0.0674 | 0.0742 |
| -0.1 | -0.2344 | -0.2037 | 0.1043 | 0.0039 | -0.2168 | 0.0771 | 0.0763 | -0.2166 | 0.0781 | 0.078 |
| 0 | 0 | 0.0031 | 0.107 | 0.0038 | -0.0017 | 0.0804 | 0.0768 | -0.0015 | 0.0815 | 0.0784 |
| 0.1 | 0.2257 | 0.2031 | 0.1021 | 0.0038 | 0.2066 | 0.0751 | 0.0738 | 0.2068 | 0.076 | 0.0754 |
| 0.2 | 0.4139 | 0.3767 | 0.0909 | 0.0038 | 0.385 | 0.0644 | 0.0685 | 0.3853 | 0.0648 | 0.07 |

Table L: Results of $\mu_\alpha = 0.2$, $\sigma_\alpha = 0.2$: $K_{YX}$

| | | CD-Ratio | | | CD-Egger | | | CD-GLS | | |
|---|---|---|---|---|---|---|---|---|---|---|
| $\beta_{YX}$ | $K_{YX}$ | Mean($\hat{K}$) | sd($\hat{K}$) | Mean($se(\hat{K})$) | Mean($\hat{K}$) | sd($\hat{K}$) | Mean($se(\hat{K})$) | Mean($\hat{K}$) | sd($\hat{K}$) | Mean($se(\hat{K})$) |
| -0.2 | -0.3995 | -0.3871 | 0.089 | 0.0039 | -0.3775 | 0.0632 | 0.0668 | -0.3773 | 0.0633 | 0.0682 |
| -0.1 | -0.2093 | -0.2079 | 0.099 | 0.0039 | -0.1971 | 0.0705 | 0.0695 | -0.1968 | 0.0712 | 0.071 |
| 0 | 0 | -0.0129 | 0.1023 | 0.0039 | -0.0012 | 0.0733 | 0.0698 | -0.0009 | 0.0744 | 0.0712 |
| 0.1 | 0.2027 | 0.1764 | 0.0977 | 0.0039 | 0.1889 | 0.0703 | 0.0675 | 0.1893 | 0.0715 | 0.0689 |
| 0.2 | 0.3773 | 0.3409 | 0.0874 | 0.0039 | 0.3555 | 0.0629 | 0.0633 | 0.3559 | 0.0639 | 0.0646 |

Table M: Results of $\mu_\alpha = 0.4$, $\sigma_\alpha = 0.2$: $K_{YX}$

| | | CD-Ratio | | | CD-Egger | | | CD-GLS | | |
|---|---|---|---|---|---|---|---|---|---|---|
| $\beta_{YX}$ | $K_{YX}$ | Mean($\hat{K}$) | sd($\hat{K}$) | Mean$(se(\hat{K}))$ | Mean($\hat{K}$) | sd($\hat{K}$) | Mean$(se(\hat{K}))$ | Mean($\hat{K}$) | sd($\hat{K}$) | Mean$(se(\hat{K}))$ |
| -0.2 | -0.3203 | -0.3305 | 0.0782 | 0.004 | -0.3097 | 0.0546 | 0.0548 | -0.3096 | 0.0546 | 0.0559 |
| -0.1 | -0.1649 | -0.1836 | 0.0837 | 0.004 | -0.1594 | 0.0578 | 0.0562 | -0.1592 | 0.0584 | 0.0574 |
| 0 | 0 | -0.0248 | 0.0871 | 0.004 | -0.0009 | 0.0593 | 0.0563 | -0.0006 | 0.0603 | 0.0575 |
| 0.1 | 0.1614 | 0.1345 | 0.0868 | 0.0041 | 0.1544 | 0.0584 | 0.0551 | 0.1547 | 0.0596 | 0.0562 |
| 0.2 | 0.3079 | 0.2805 | 0.082 | 0.0041 | 0.2962 | 0.0552 | 0.0527 | 0.2965 | 0.0564 | 0.0538 |

Table N: Results of $\mu_\alpha = 0.6$, $\sigma_\alpha = 0.2$: $K_{YX}$

| | | CD-Ratio | | | CD-Egger | | | CD-GLS | | |
|---|---|---|---|---|---|---|---|---|---|---|
| $\beta_{YX}$ | $K_{YX}$ | Mean($\hat{K}$) | sd($\hat{K}$) | Mean$(se(\hat{K}))$ | Mean($\hat{K}$) | sd($\hat{K}$) | Mean$(se(\hat{K}))$ | Mean($\hat{K}$) | sd($\hat{K}$) | Mean$(se(\hat{K}))$ |
| -0.2 | -0.2535 | -0.2754 | 0.0659 | 0.0041 | -0.2487 | 0.0448 | 0.044 | -0.2486 | 0.0449 | 0.0449 |
| -0.1 | -0.129 | -0.1595 | 0.0685 | 0.0041 | -0.1268 | 0.0463 | 0.0447 | -0.1266 | 0.0468 | 0.0456 |
| 0 | 0 | -0.0361 | 0.0706 | 0.0042 | -0.0007 | 0.0471 | 0.0447 | -0.0005 | 0.0479 | 0.0457 |
| 0.1 | 0.1272 | 0.0901 | 0.0716 | 0.0042 | 0.1236 | 0.047 | 0.0441 | 0.1239 | 0.048 | 0.045 |
| 0.2 | 0.2469 | 0.2122 | 0.0706 | 0.0042 | 0.2408 | 0.0459 | 0.0428 | 0.2411 | 0.0469 | 0.0437 |

Table O: Results of $\mu_\alpha = 1$, $\sigma_\alpha = 0.2$: $K_{YX}$

| | | CD-Ratio | | | CD-Egger | | | CD-GLS | | |
|---|---|---|---|---|---|---|---|---|---|---|
| $\beta_{YX}$ | $K_{YX}$ | Mean($\hat{K}$) | sd($\hat{K}$) | Mean$(se(\hat{K}))$ | Mean($\hat{K}$) | sd($\hat{K}$) | Mean$(se(\hat{K}))$ | Mean($\hat{K}$) | sd($\hat{K}$) | Mean$(se(\hat{K}))$ |
| -0.2 | -0.171 | -0.2087 | 0.0464 | 0.0042 | -0.1699 | 0.031 | 0.03 | -0.1699 | 0.0312 | 0.0306 |
| -0.1 | -0.0862 | -0.1321 | 0.0471 | 0.0042 | -0.0859 | 0.0315 | 0.0302 | -0.0858 | 0.0319 | 0.0309 |
| 0 | 0 | -0.0523 | 0.0479 | 0.0043 | -0.0005 | 0.0318 | 0.0302 | -0.0004 | 0.0324 | 0.0309 |
| 0.1 | 0.0856 | 0.0301 | 0.0486 | 0.0043 | 0.0842 | 0.032 | 0.03 | 0.0843 | 0.0326 | 0.0307 |
| 0.2 | 0.1687 | 0.1134 | 0.0492 | 0.0043 | 0.1665 | 0.0319 | 0.0296 | 0.1667 | 0.0326 | 0.0303 |

## Goodness-of-Fit Tests

We show the results of the Goodness-of-Fit tests for CD-Ratio, CD-Egger, and CD-GLS. Table P shows the results under setup $\mu_\alpha = 0, \sigma_\alpha = 0$, and various levels of $\beta_{YX}$. For each of the three methods, in each of 500 simulations we can calculate the test statistics $Q^{YX}$ and $Q^{XY}$, then perform the corresponding $\chi^2$-test to get $p$-value $p_{YX}$ for direction $X$ to $Y$, and $p$-value $p_{XY}$ for direction $Y$ to $X$, respectively. Then we show the proportion out of 500 simulated datasets $p_{YX}$'s less than 0.05, indicated by "$p_{YX} < 0.05$", and proportion of $p_{XY}$'s less than 0.05, indicated by "$p_{XY} < 0.05$". Table Q to A4 shows the results for other setups.

Table P: GOF Testing Results of $\mu_\alpha = 0$, $\sigma_\alpha = 0$

| | CD-Ratio | | CD-Egger | | CD-GLS | |
|---|---|---|---|---|---|---|
| $\beta_{YX}$ | $p_{YX} < 0.05$ | $p_{XY} < 0.05$ | $p_{YX} < 0.05$ | $p_{XY} < 0.05$ | $p_{YX} < 0.05$ | $p_{XY} < 0.05$ |
| -0.2 | 0.002 | 0.012 | 0 | 0.014 | 0 | 0 |
| -0.1 | 0.012 | 0.188 | 0 | 0 | 0 | 0 |
| 0 | 0.054 | 0.042 | 0.002 | 0 | 0.002 | 0.026 |
| 0.1 | 0.022 | 0.18 | 0.002 | 0 | 0 | 0 |
| 0.2 | 0 | 0.022 | 0 | 0.006 | 0 | 0 |

Table Q: GOF Results of $\mu_\alpha = 0.2$, $\sigma_\alpha = 0$

| | CD-Ratio | | CD-Egger | | CD-GLS | |
|---|---|---|---|---|---|---|
| $\beta_{YX}$ | $p_{YX} < 0.05$ | $p_{XY} < 0.05$ | $p_{YX} < 0.05$ | $p_{XY} < 0.05$ | $p_{YX} < 0.05$ | $p_{XY} < 0.05$ |
| -0.2 | 1 | 1 | 0 | 0.014 | 0 | 0 |
| -0.1 | 1 | 1 | 0 | 0 | 0 | 0 |
| 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| 0.1 | 1 | 1 | 0 | 0 | 0 | 0 |
| 0.2 | 1 | 1 | 0 | 0.006 | 0 | 0 |

Table R: GOF Results of $\mu_\alpha = 0.4$, $\sigma_\alpha = 0$

| | CD-Ratio | | CD-Egger | | CD-GLS | |
|---|---|---|---|---|---|---|
| $\beta_{YX}$ | $p_{YX} < 0.05$ | $p_{XY} < 0.05$ | $p_{YX} < 0.05$ | $p_{XY} < 0.05$ | $p_{YX} < 0.05$ | $p_{XY} < 0.05$ |
| -0.2 | 1 | 1 | 0 | 0.014 | 0 | 0 |
| -0.1 | 1 | 1 | 0 | 0 | 0 | 0 |
| 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| 0.1 | 1 | 1 | 0 | 0 | 0 | 0 |
| 0.2 | 1 | 1 | 0 | 0.006 | 0 | 0 |

Table S: GOF Results of $\mu_\alpha = 0.6$, $\sigma_\alpha = 0$

| | CD-Ratio | | CD-Egger | | CD-GLS | |
|---|---|---|---|---|---|---|
| $\beta_{YX}$ | $p_{YX} < 0.05$ | $p_{XY} < 0.05$ | $p_{YX} < 0.05$ | $p_{XY} < 0.05$ | $p_{YX} < 0.05$ | $p_{XY} < 0.05$ |
| -0.2 | 1 | 1 | 0 | 0.014 | 0 | 0 |
| -0.1 | 1 | 1 | 0 | 0 | 0 | 0 |
| 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| 0.1 | 1 | 1 | 0 | 0 | 0 | 0 |
| 0.2 | 1 | 1 | 0 | 0.006 | 0 | 0 |

Table T: GOF Results of $\mu_\alpha = 1$, $\sigma_\alpha = 0$

| | CD-Ratio | | CD-Egger | | CD-GLS | |
|---|---|---|---|---|---|---|
| $\beta_{YX}$ | $p_{YX} < 0.05$ | $p_{XY} < 0.05$ | $p_{YX} < 0.05$ | $p_{XY} < 0.05$ | $p_{YX} < 0.05$ | $p_{XY} < 0.05$ |
| -0.2 | 1 | 1 | 0 | 0.014 | 0 | 0 |
| -0.1 | 1 | 1 | 0 | 0 | 0 | 0 |
| 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| 0.1 | 1 | 1 | 0 | 0 | 0 | 0 |
| 0.2 | 1 | 1 | 0 | 0.006 | 0 | 0 |

Table U: GOF Results of $\mu_\alpha = 0$, $\sigma_\alpha = 0.1$

| | CD-Ratio | | CD-Egger | | CD-GLS | |
|---|---|---|---|---|---|---|
| $\beta_{YX}$ | $p_{YX} < 0.05$ | $p_{XY} < 0.05$ | $p_{YX} < 0.05$ | $p_{XY} < 0.05$ | $p_{YX} < 0.05$ | $p_{XY} < 0.05$ |
| -0.2 | 1 | 1 | 0 | 0 | 0 | 0 |
| -0.1 | 1 | 1 | 0 | 0 | 0 | 0 |
| 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| 0.1 | 1 | 1 | 0 | 0 | 0 | 0 |
| 0.2 | 1 | 1 | 0 | 0 | 0 | 0 |

Table V: GOF Results of $\mu_\alpha = 0.2$, $\sigma_\alpha = 0.1$

| | CD-Ratio | | CD-Egger | | CD-GLS | |
|---|---|---|---|---|---|---|
| $\beta_{YX}$ | $p_{YX} < 0.05$ | $p_{XY} < 0.05$ | $p_{YX} < 0.05$ | $p_{XY} < 0.05$ | $p_{YX} < 0.05$ | $p_{XY} < 0.05$ |
| -0.2 | 1 | 1 | 0 | 0 | 0 | 0 |
| -0.1 | 1 | 1 | 0 | 0 | 0 | 0 |
| 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| 0.1 | 1 | 1 | 0 | 0 | 0 | 0 |
| 0.2 | 1 | 1 | 0 | 0 | 0 | 0 |

Table W: GOF Results of $\mu_\alpha = 0.4$, $\sigma_\alpha = 0.1$

| | CD-Ratio | | CD-Egger | | CD-GLS | |
|---|---|---|---|---|---|---|
| $\beta_{YX}$ | $p_{YX} < 0.05$ | $p_{XY} < 0.05$ | $p_{YX} < 0.05$ | $p_{XY} < 0.05$ | $p_{YX} < 0.05$ | $p_{XY} < 0.05$ |
| -0.2 | 1 | 1 | 0 | 0 | 0 | 0 |
| -0.1 | 1 | 1 | 0 | 0 | 0 | 0 |
| 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| 0.1 | 1 | 1 | 0 | 0 | 0 | 0 |
| 0.2 | 1 | 1 | 0 | 0 | 0 | 0 |

Table X: GOF Results of $\mu_\alpha = 0.6$, $\sigma_\alpha = 0.1$

| | CD-Ratio | | CD-Egger | | CD-GLS | |
|---|---|---|---|---|---|---|
| $\beta_{YX}$ | $p_{YX} < 0.05$ | $p_{XY} < 0.05$ | $p_{YX} < 0.05$ | $p_{XY} < 0.05$ | $p_{YX} < 0.05$ | $p_{XY} < 0.05$ |
| -0.2 | 1 | 1 | 0 | 0 | 0 | 0 |
| -0.1 | 1 | 1 | 0 | 0 | 0 | 0 |
| 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| 0.1 | 1 | 1 | 0 | 0 | 0 | 0 |
| 0.2 | 1 | 1 | 0 | 0 | 0 | 0 |

Table Y: GOF Results of $\mu_\alpha = 1$, $\sigma_\alpha = 0.1$

| | CD-Ratio | | CD-Egger | | CD-GLS | |
|---|---|---|---|---|---|---|
| $\beta_{YX}$ | $p_{YX} < 0.05$ | $p_{XY} < 0.05$ | $p_{YX} < 0.05$ | $p_{XY} < 0.05$ | $p_{YX} < 0.05$ | $p_{XY} < 0.05$ |
| -0.2 | 1 | 1 | 0 | 0 | 0 | 0 |
| -0.1 | 1 | 1 | 0 | 0 | 0 | 0 |
| 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| 0.1 | 1 | 1 | 0 | 0 | 0 | 0 |
| 0.2 | 1 | 1 | 0 | 0 | 0 | 0 |

Table Z: GOF Results of $\mu_\alpha = 0$, $\sigma_\alpha = 0.2$

| | CD-Ratio | | CD-Egger | | CD-GLS | |
|---|---|---|---|---|---|---|
| $\beta_{YX}$ | $p_{YX} < 0.05$ | $p_{XY} < 0.05$ | $p_{YX} < 0.05$ | $p_{XY} < 0.05$ | $p_{YX} < 0.05$ | $p_{XY} < 0.05$ |
| -0.2 | 1 | 1 | 0 | 0 | 0 | 0 |
| -0.1 | 1 | 1 | 0 | 0 | 0 | 0 |
| 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| 0.1 | 1 | 1 | 0 | 0 | 0 | 0 |
| 0.2 | 1 | 1 | 0 | 0 | 0 | 0 |

Table A1: GOF Results of $\mu_\alpha = 0.2$, $\sigma_\alpha = 0.2$

| | CD-Ratio | | CD-Egger | | CD-GLS | |
|---|---|---|---|---|---|---|
| $\beta_{YX}$ | $p_{YX} < 0.05$ | $p_{XY} < 0.05$ | $p_{YX} < 0.05$ | $p_{XY} < 0.05$ | $p_{YX} < 0.05$ | $p_{XY} < 0.05$ |
| -0.2 | 1 | 1 | 0 | 0 | 0 | 0 |
| -0.1 | 1 | 1 | 0 | 0 | 0 | 0 |
| 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| 0.1 | 1 | 1 | 0 | 0 | 0 | 0 |
| 0.2 | 1 | 1 | 0 | 0 | 0 | 0 |

Table A2: GOF Results of $\mu_\alpha = 0.4$, $\sigma_\alpha = 0.2$

| | CD-Ratio | | CD-Egger | | CD-GLS | |
|---|---|---|---|---|---|---|
| $\beta_{YX}$ | $p_{YX} < 0.05$ | $p_{XY} < 0.05$ | $p_{YX} < 0.05$ | $p_{XY} < 0.05$ | $p_{YX} < 0.05$ | $p_{XY} < 0.05$ |
| -0.2 | 1 | 1 | 0 | 0 | 0 | 0 |
| -0.1 | 1 | 1 | 0 | 0 | 0 | 0 |
| 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| 0.1 | 1 | 1 | 0 | 0 | 0 | 0 |
| 0.2 | 1 | 1 | 0 | 0 | 0 | 0 |

Table A3: GOF Results of $\mu_\alpha = 0.6$, $\sigma_\alpha = 0.2$

| $\beta_{YX}$ | CD-Ratio | | CD-Egger | | CD-GLS | |
|---|---|---|---|---|---|---|
| | $p_{YX} < 0.05$ | $p_{XY} < 0.05$ | $p_{YX} < 0.05$ | $p_{XY} < 0.05$ | $p_{YX} < 0.05$ | $p_{XY} < 0.05$ |
| -0.2 | 1 | 1 | 0 | 0 | 0 | 0 |
| -0.1 | 1 | 1 | 0 | 0 | 0 | 0 |
| 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| 0.1 | 1 | 1 | 0 | 0 | 0 | 0 |
| 0.2 | 1 | 1 | 0 | 0 | 0 | 0 |

Table A4: GOF Results of $\mu_\alpha = 1$, $\sigma_\alpha = 0.2$

| $\beta_{YX}$ | CD-Ratio | | CD-Egger | | CD-GLS | |
|---|---|---|---|---|---|---|
| | $p_{YX} < 0.05$ | $p_{XY} < 0.05$ | $p_{YX} < 0.05$ | $p_{XY} < 0.05$ | $p_{YX} < 0.05$ | $p_{XY} < 0.05$ |
| -0.2 | 1 | 1 | 0 | 0 | 0 | 0 |
| -0.1 | 1 | 1 | 0 | 0 | 0 | 0 |
| 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| 0.1 | 1 | 1 | 0 | 0 | 0 | 0 |
| 0.2 | 1 | 1 | 0 | 0 | 0 | 0 |

## Comparing the Decisions

We compare CD-Ratio, CD-Egger and CD-GLS with MR Steiger's and bi-directional MR in terms of their decisions made on the causal direction. Similar to Steiger's method, we also applied CD-Ratio to each of the 22 SNPs, then calculated the proportions of the three possible decisions, denoted by "CD-Ratio-Prop". We also pooled together the individual results from each of the 22 SNPs by majority voting to reach a final decision, denoted as "CD-Ratio-MV". For other methods, their notations are the same as in Fig. 9 in the main text. Figure A shows the comparison results for setup $\beta_{YX} = 0, \mu_\alpha = 0$, and $\sigma_\alpha = 0, 0.1, 0.2$. Figure B to Y show the comparison results for other simulation setups.

Figure A: Relative frequencies of decisions for causal direction of all methods: $\beta_{YX} = 0$, $\mu_\alpha = 0$

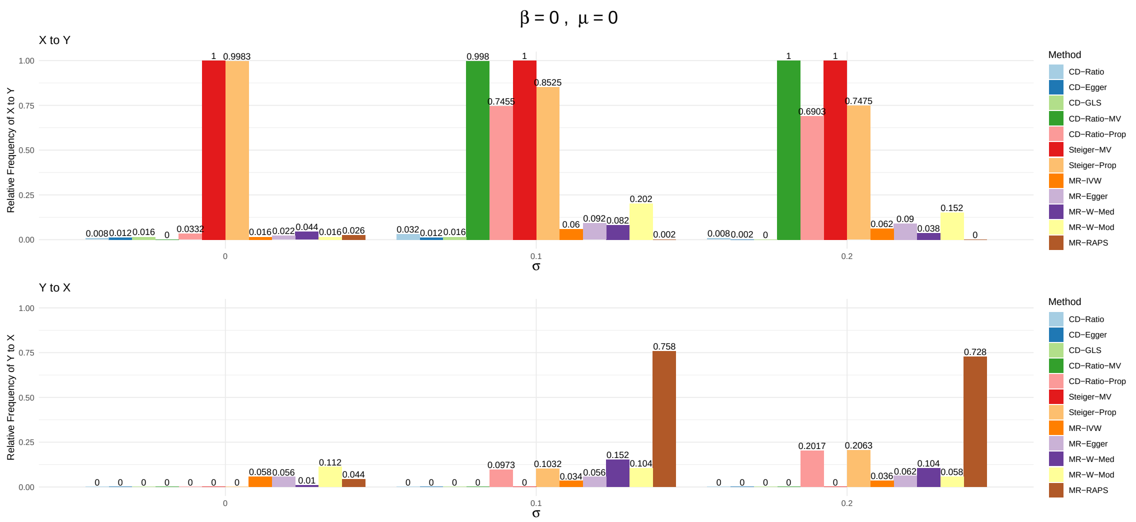

Figure B: Relative frequencies of decisions for causal direction of all methods: $\beta_{YX} = 0$, $\mu_\alpha = 0.2$

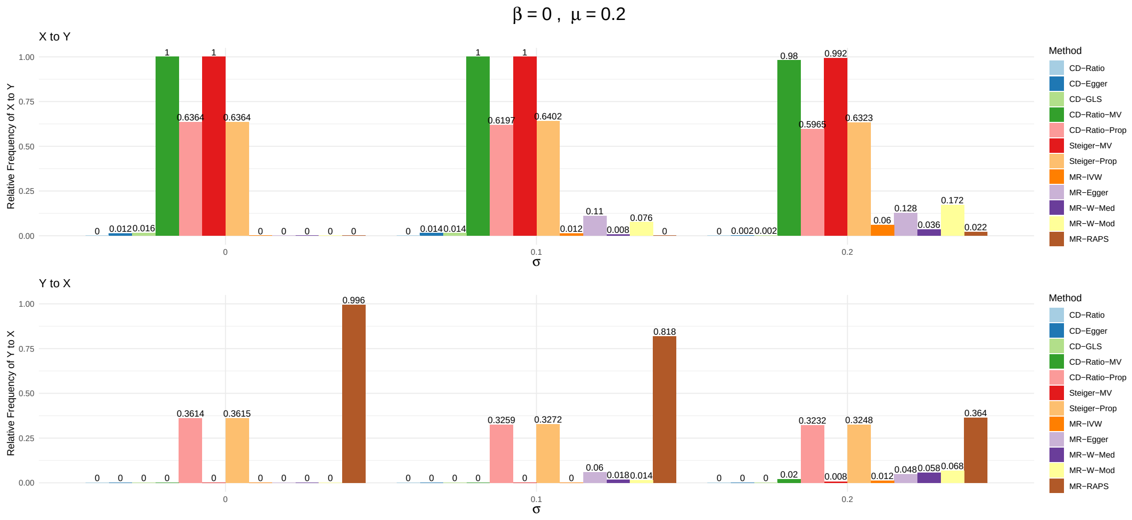


Figure C: Relative frequencies of decisions for causal direction of all methods: $\beta_{YX} = 0$, $\mu_\alpha = 0.4$

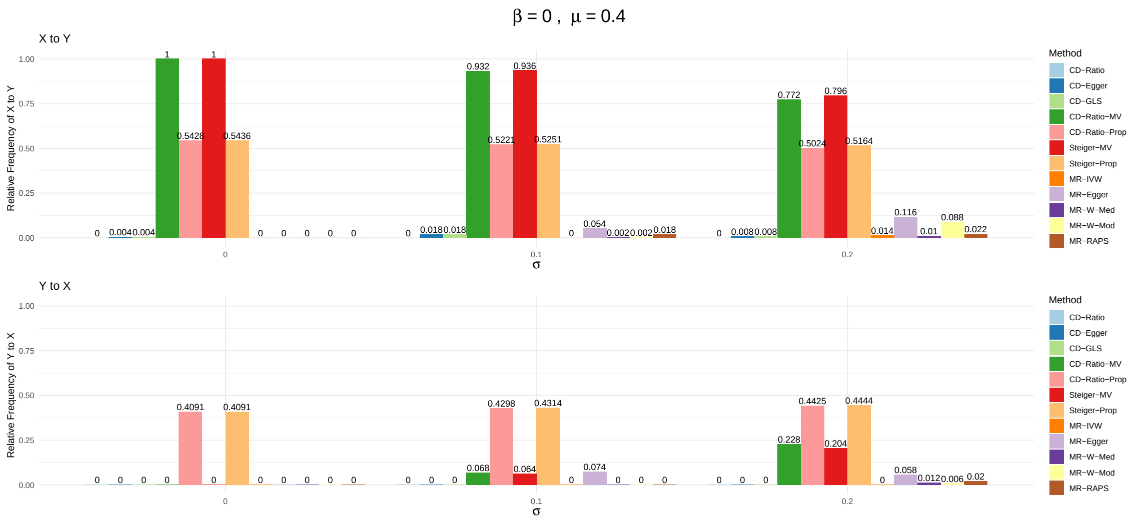

Figure D: Relative frequencies of decisions for causal direction of all methods: $\beta_{YX} = 0$, $\mu_\alpha = 0.6$

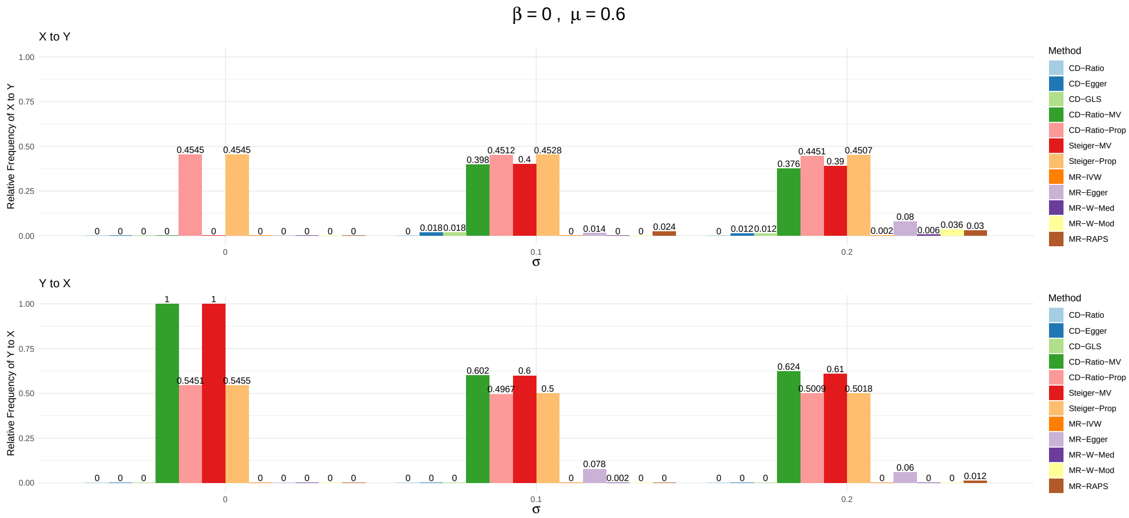


Figure E: Relative frequencies of decisions for causal direction of all methods: $\beta_{YX} = 0$, $\mu_\alpha = 1$

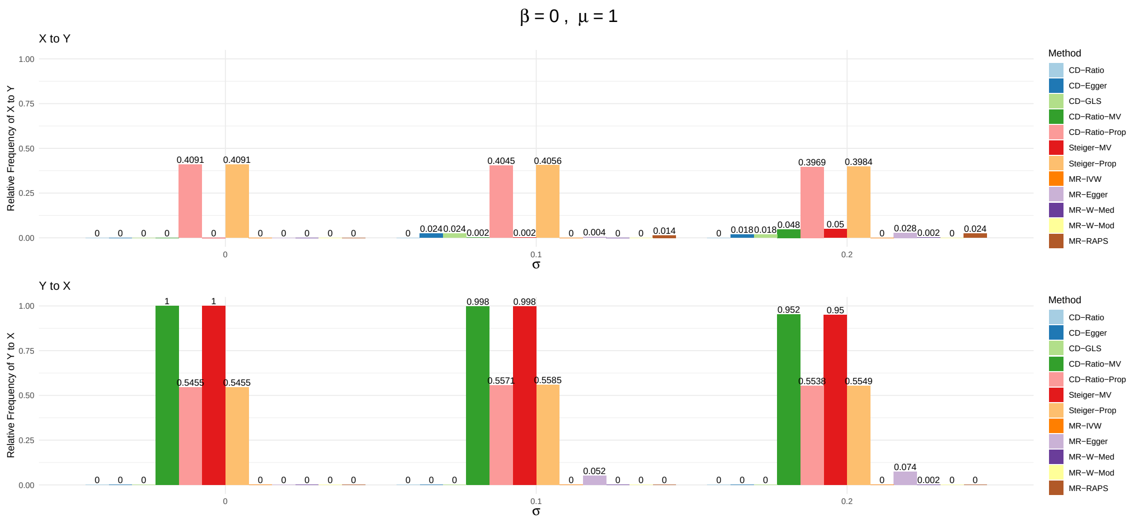

Figure F: Relative frequencies of decisions for causal direction of all methods: $\beta_{YX} = 0.1$, $\mu_\alpha = 0$

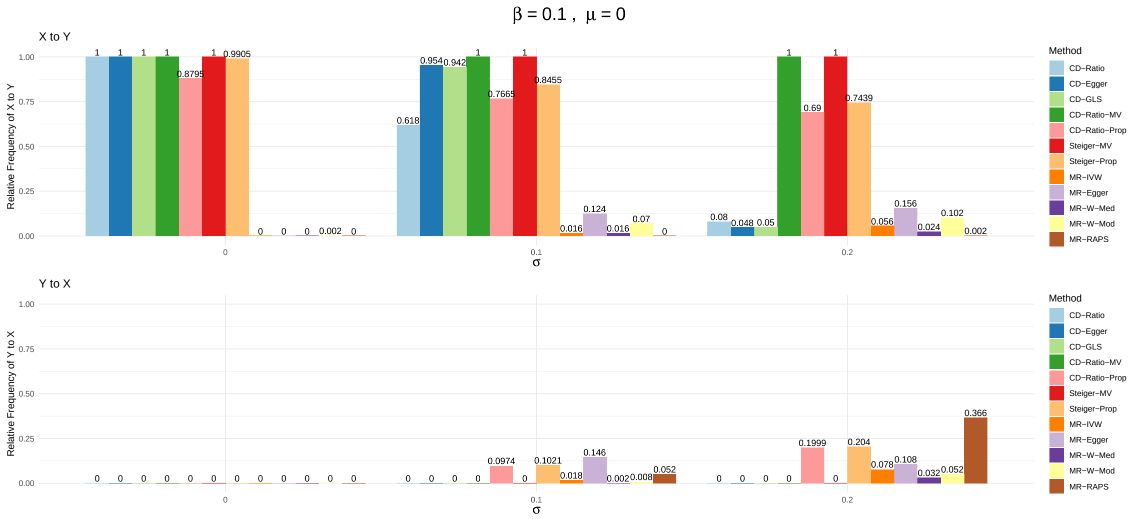


Figure G: Relative frequencies of decisions for causal direction of all methods: $\beta_{YX} = 0.1$, $\mu_\alpha = 0.2$

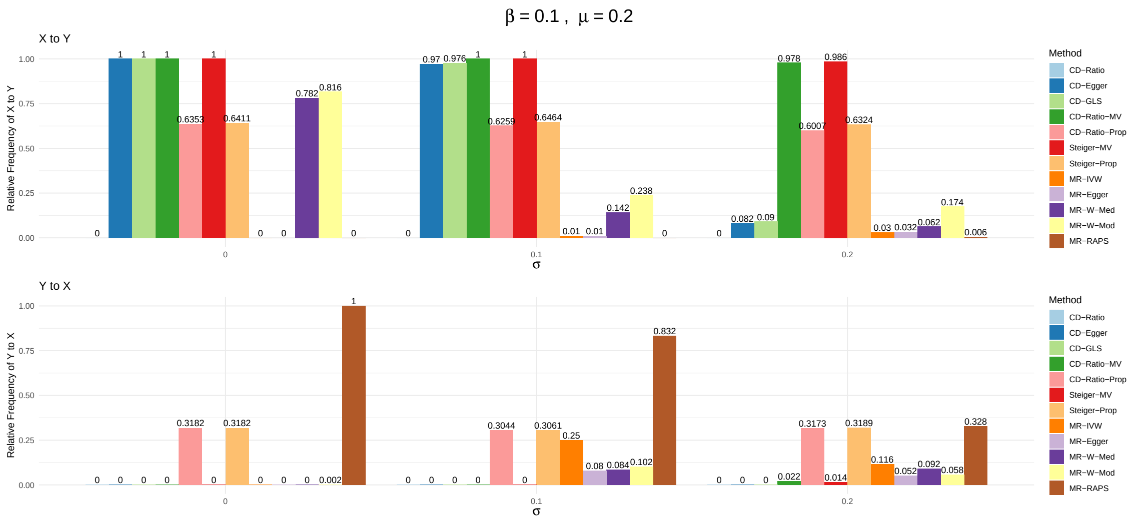

Figure H: Relative frequencies of decisions for causal direction of all methods: $\beta_{YX} = 0.1$, $\mu_\alpha = 0.4$

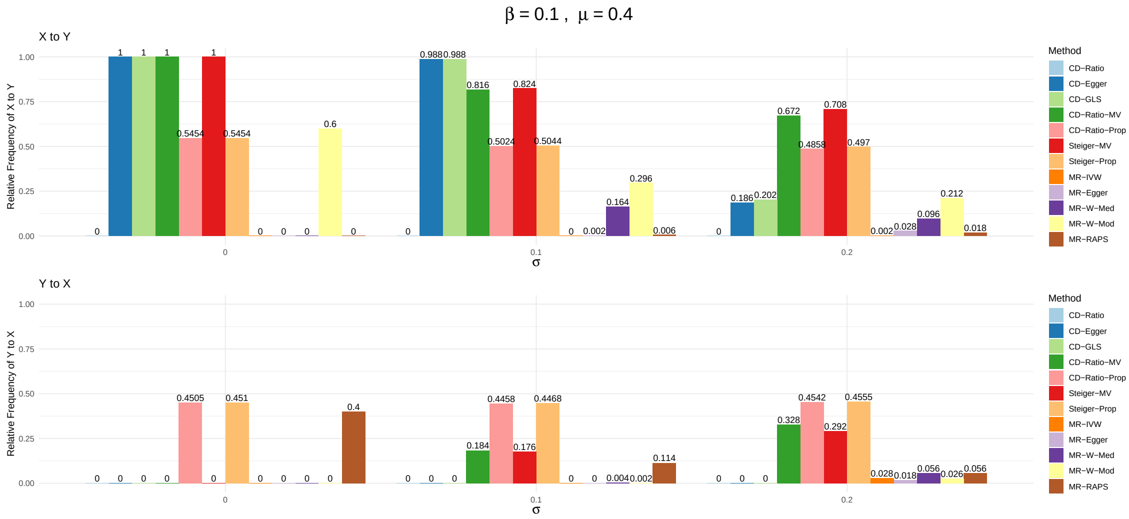


Figure I: Relative frequencies of decisions for causal direction of all methods: $\beta_{YX} = 0.1$, $\mu_\alpha = 0.6$

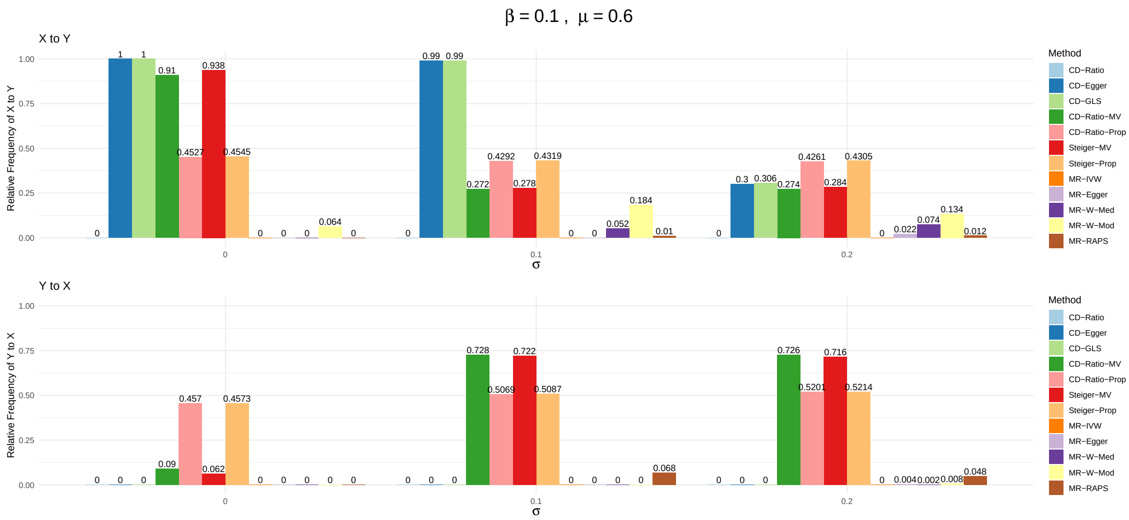

Figure J: Relative frequencies of decisions for causal direction of all methods: $\beta_{YX} = 0.1$, $\mu_\alpha = 1$

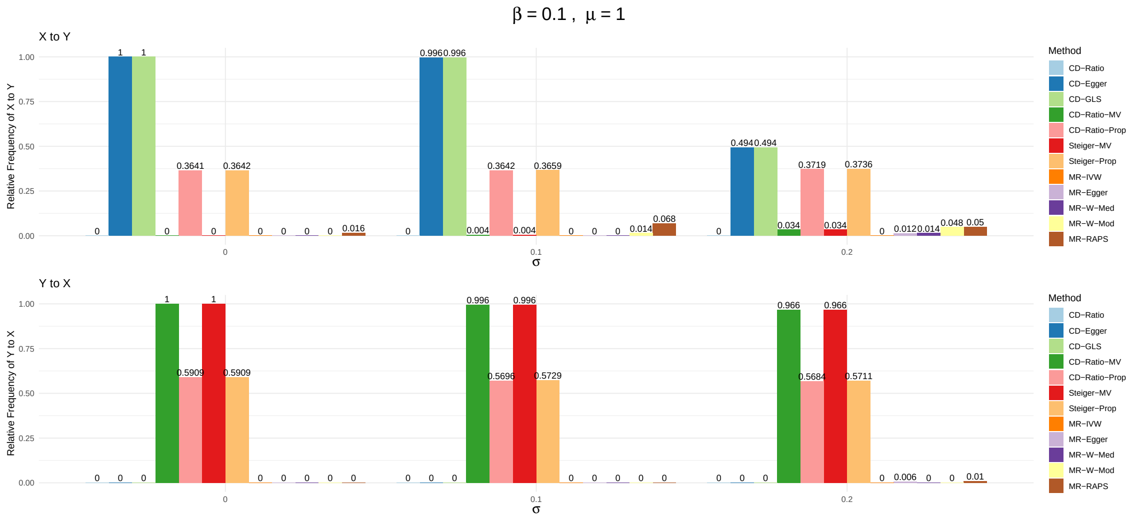


Figure K: Relative frequencies of decisions for causal direction of all methods: $\beta_{YX} = -0.1$, $\mu_\alpha = 0$

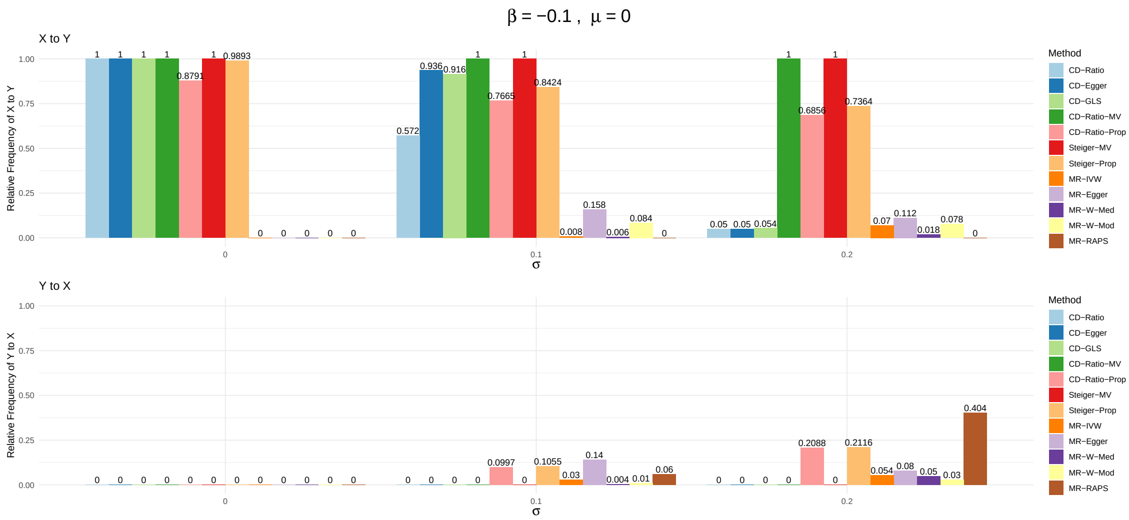

Figure L: Relative frequencies of decisions for causal direction of all methods: $\beta_{YX} = -0.1$, $\mu_\alpha = 0.2$

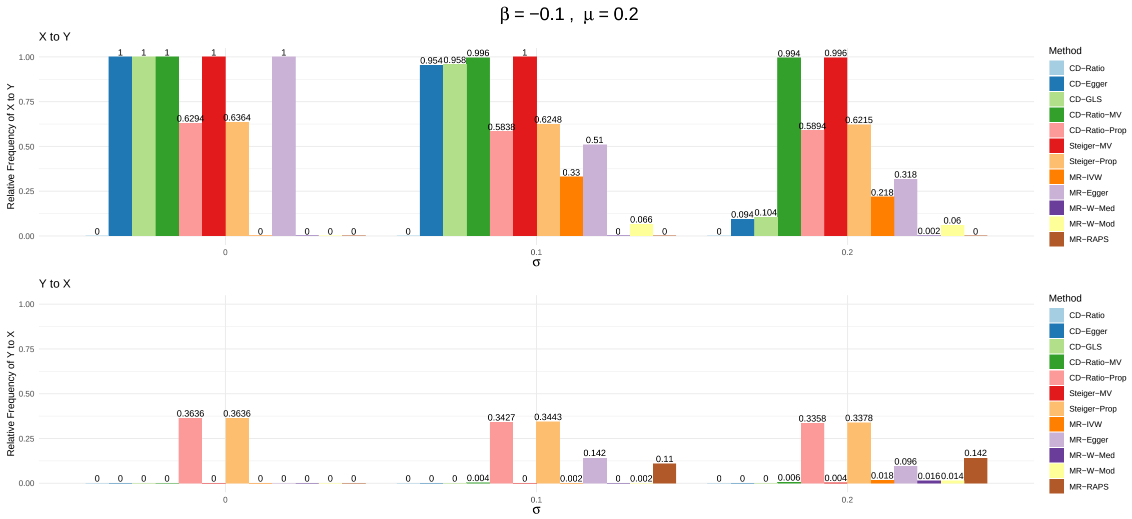


Figure M: Relative frequencies of decisions for causal direction of all methods: $\beta_{YX} = -0.1$, $\mu_\alpha = 0.4$

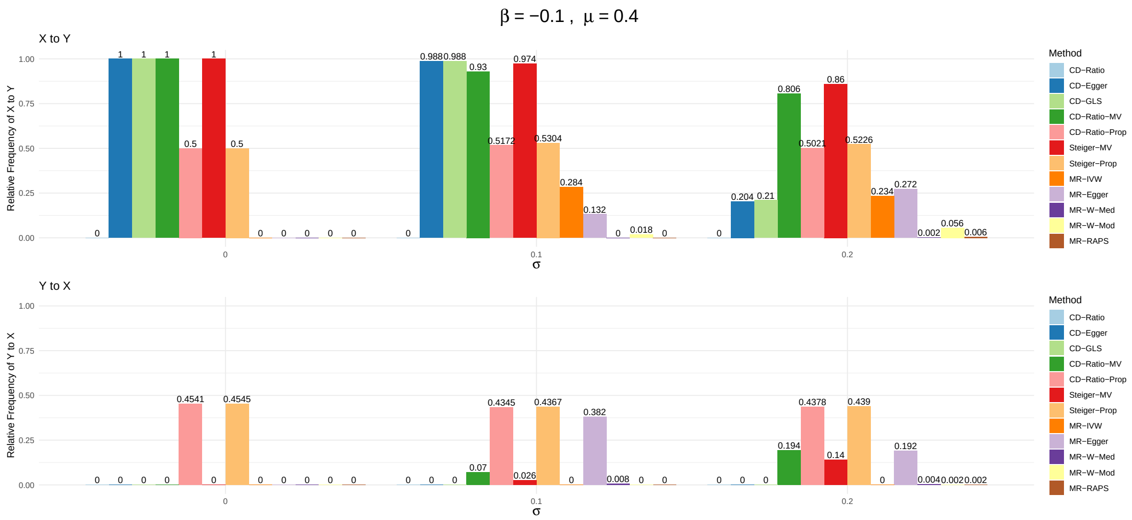

Figure N: Relative frequencies of decisions for causal direction of all methods: $\beta_{YX} = -0.1$, $\mu_\alpha = 0.6$

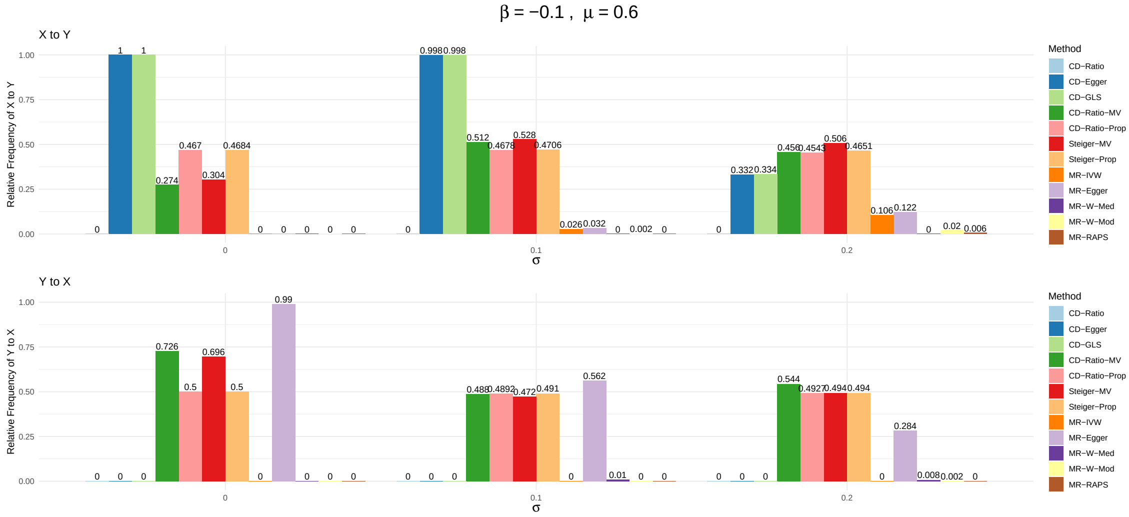


Figure O: Relative frequencies of decisions for causal direction of all methods: $\beta_{YX} = -0.1$, $\mu_\alpha = 1$

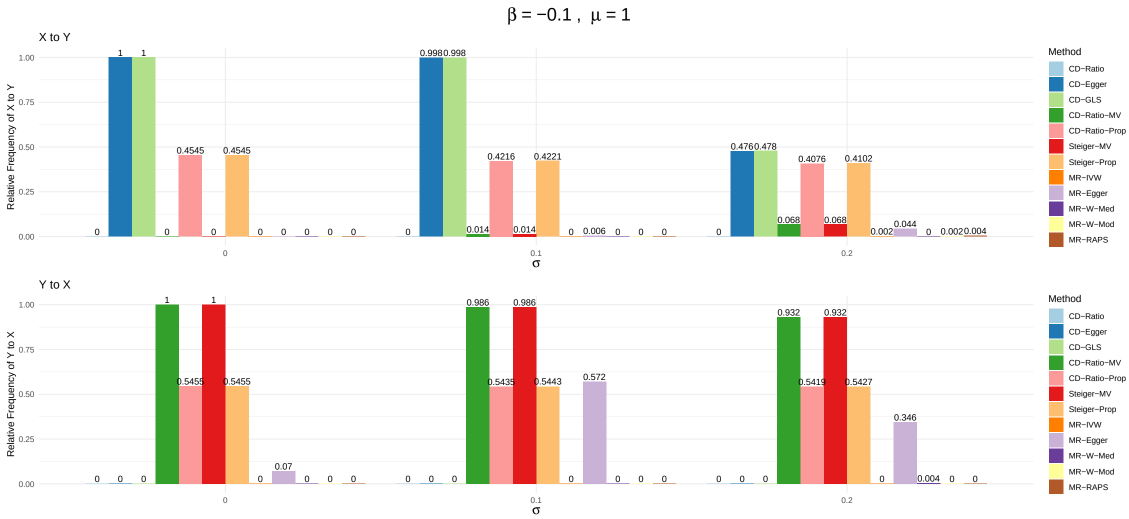

Figure P: Relative frequencies of decisions for causal direction of all methods: $\beta_{YX} = 0.2$, $\mu_\alpha = 0$

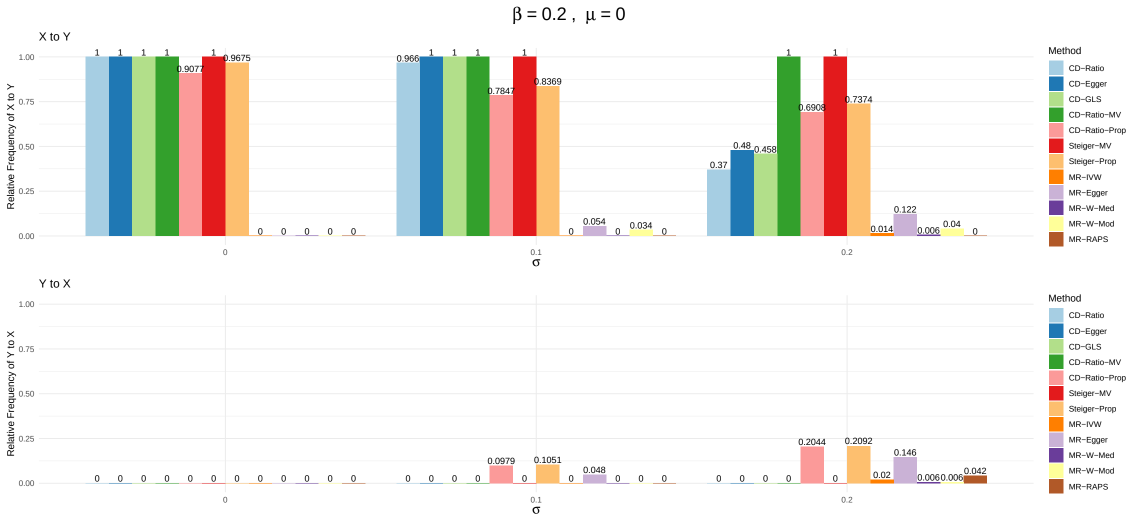


Figure Q: Relative frequencies of decisions for causal direction of all methods: $\beta_{YX} = 0.2$, $\mu_\alpha = 0.2$

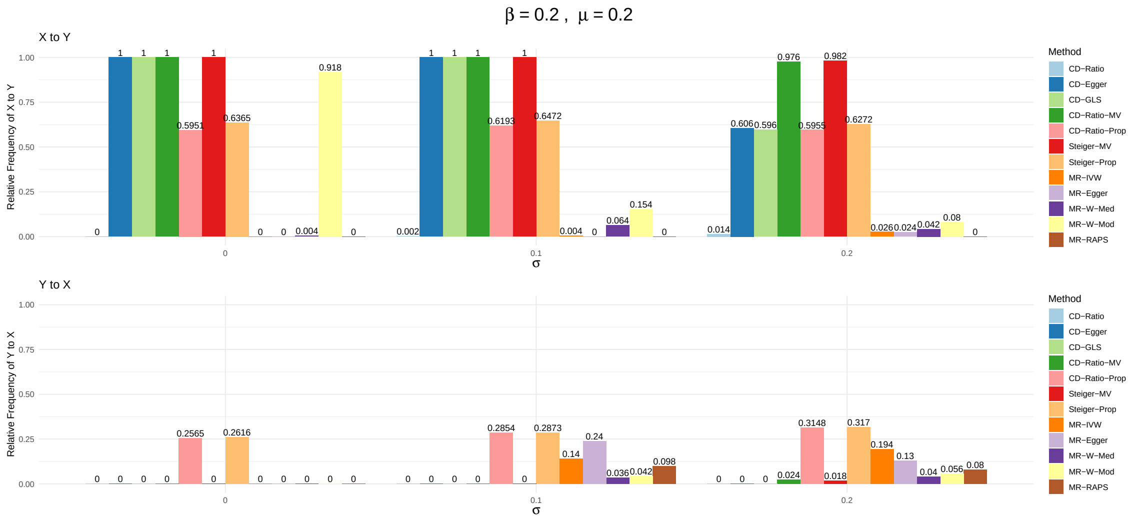

Figure R: Relative frequencies of decisions for causal direction of all methods: $\beta_{YX} = 0.2$, $\mu_\alpha = 0.4$

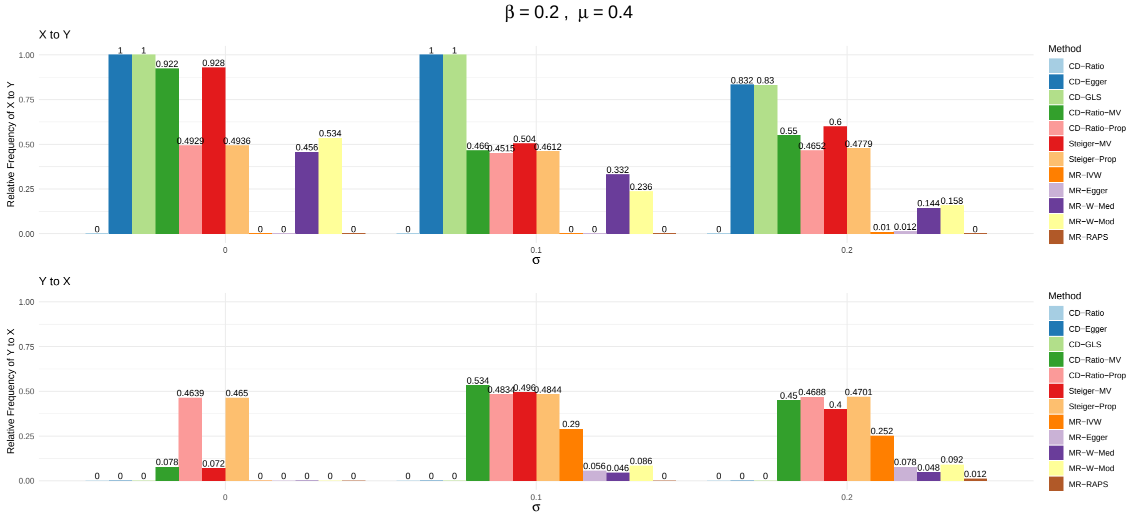


Figure S: Relative frequencies of decisions for causal direction of all methods: $\beta_{YX} = 0.2$, $\mu_\alpha = 0.6$

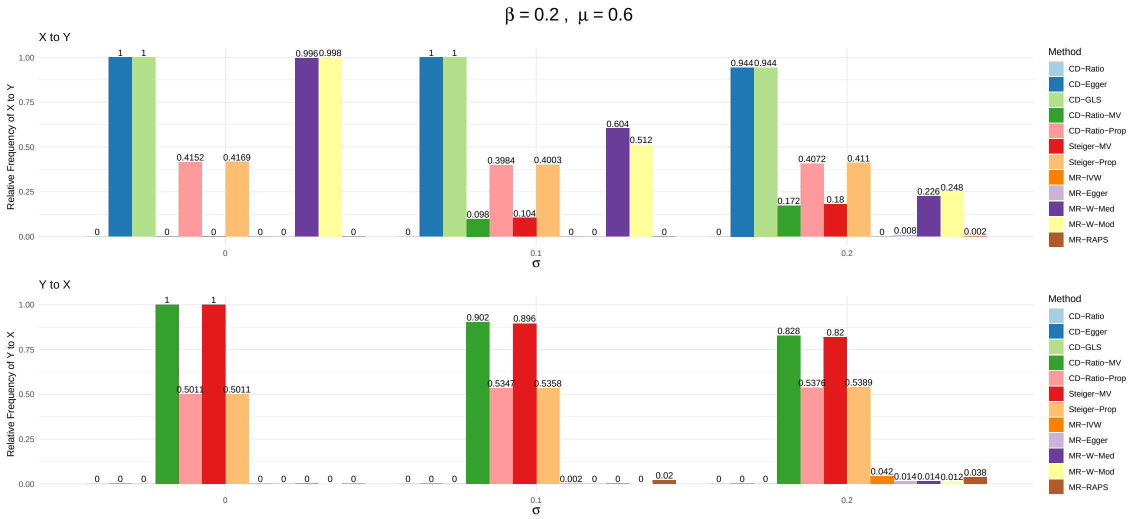

Figure T: Relative frequencies of decisions for causal direction of all methods: $\beta_{YX} = 0.2$, $\mu_\alpha = 1$

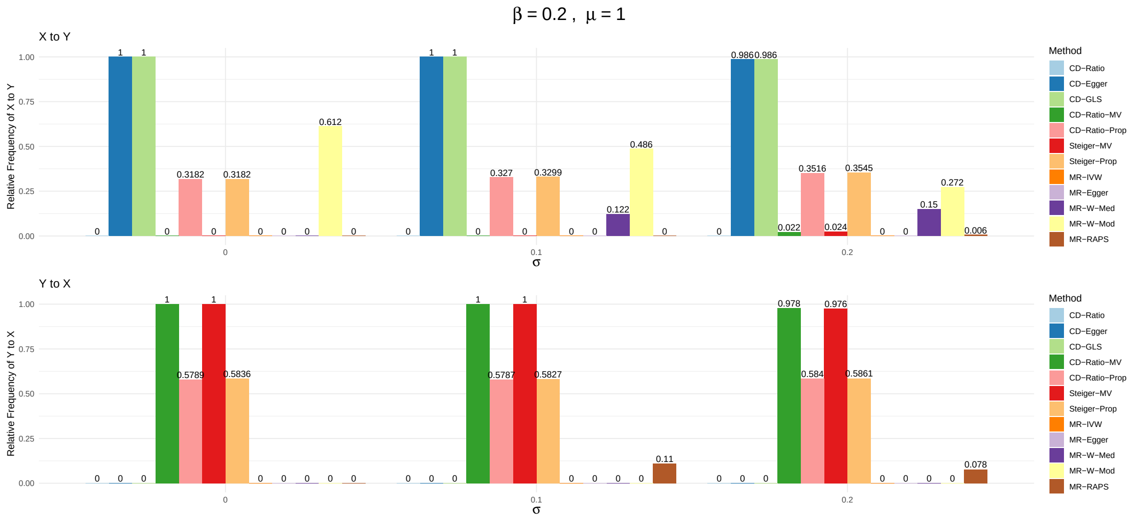


Figure U: Relative frequencies of decisions for causal direction of all methods: $\beta_{YX} = -0.2$, $\mu_\alpha = 0$

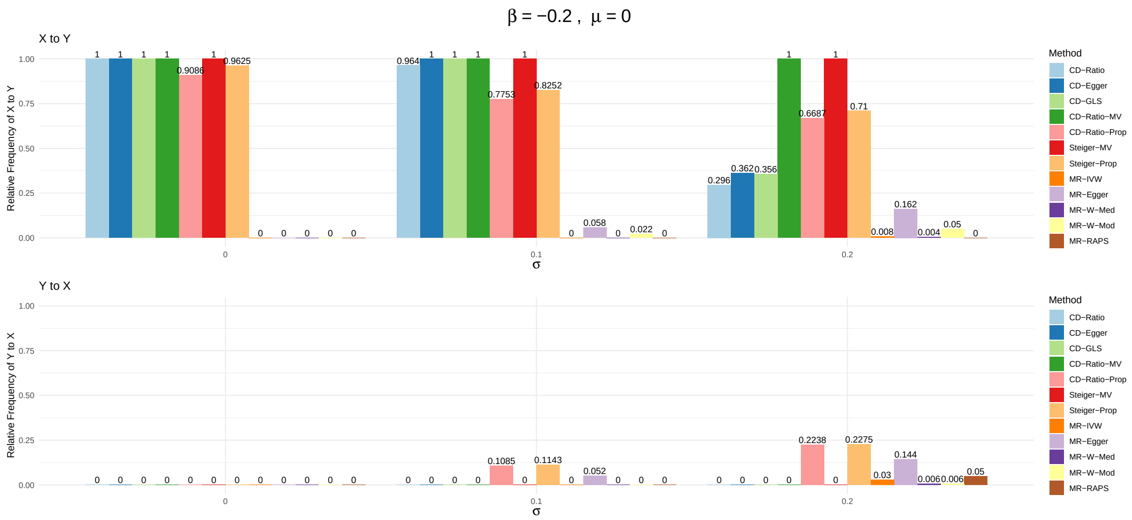

Figure V: Relative frequencies of decisions for causal direction of all methods: $\beta_{YX} = -0.2$, $\mu_\alpha = 0.2$

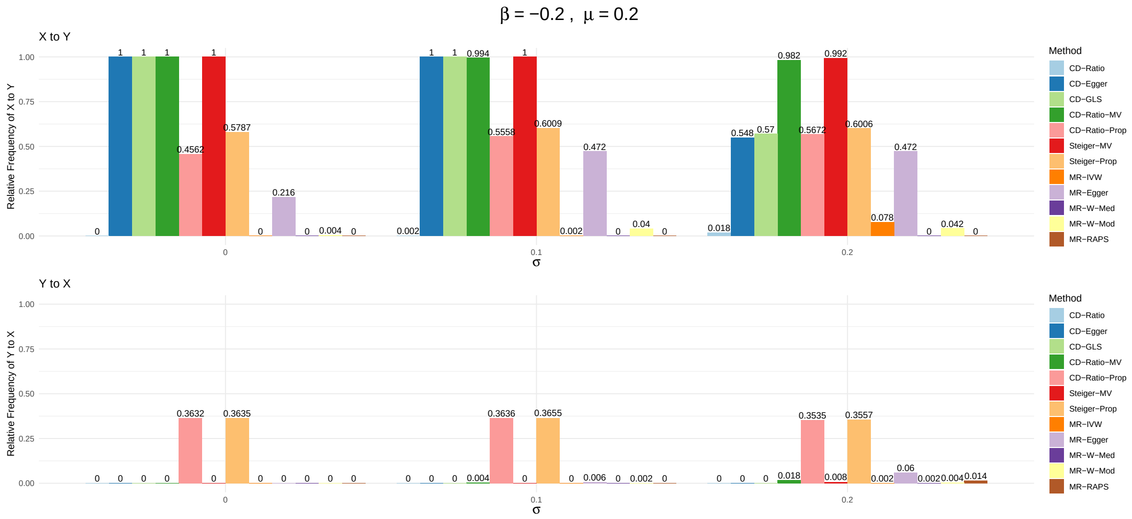


Figure W: Relative frequencies of decisions for causal direction of all methods: $\beta_{YX} = -0.2$, $\mu_\alpha = 0.4$

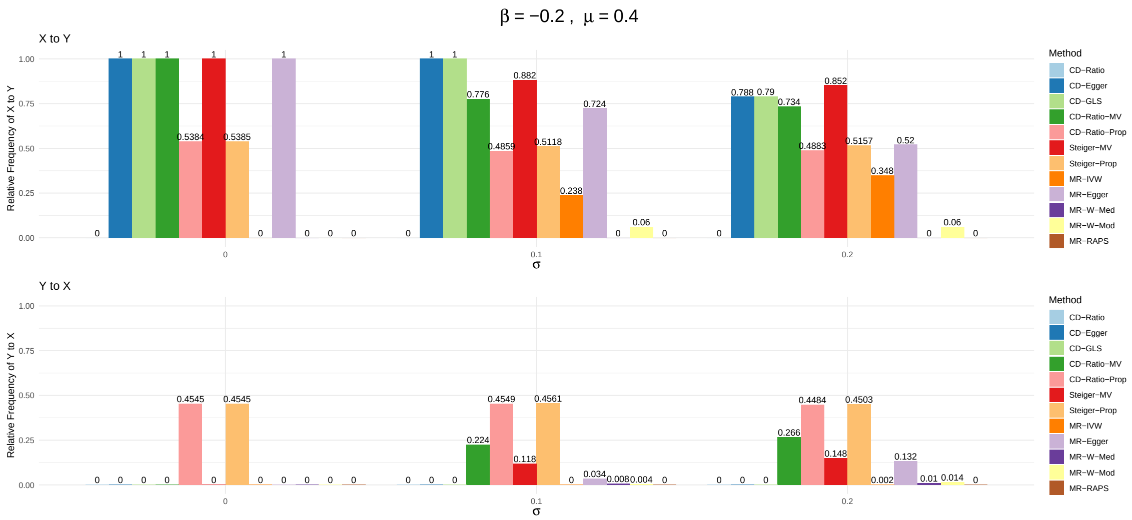

Figure X: Relative frequencies of decisions for causal direction of all methods: $\beta_{YX} = -0.2$, $\mu_\alpha = 0.6$

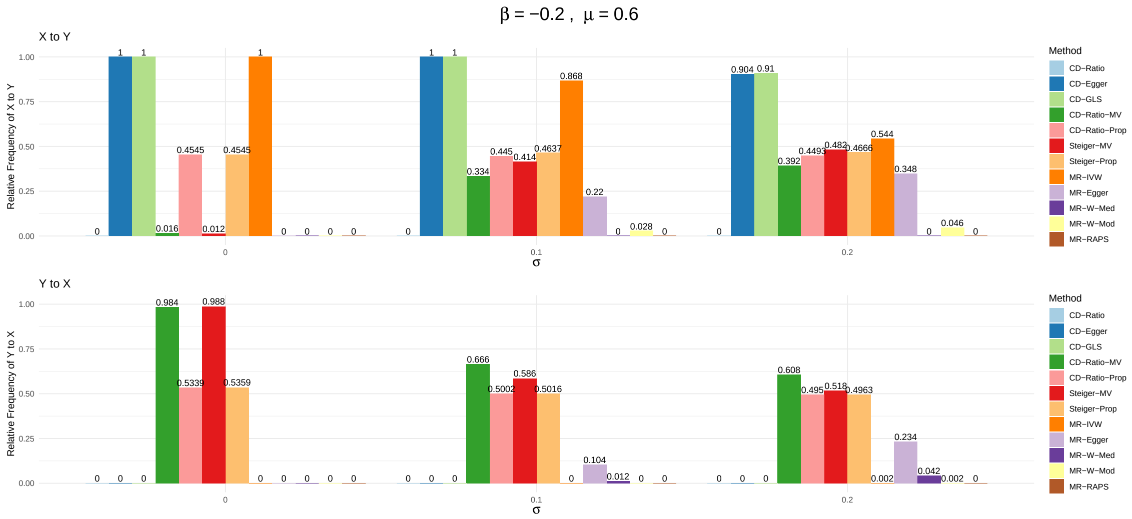


Figure Y: Relative frequencies of decisions for causal direction of all methods: $\beta_{YX} = -0.2$, $\mu_\alpha = 1$