Supplementary Material to "Monte Carlo Sensitivity Analysis for Unmeasured Confounding in Dynamic Treatment Regimes" by Eric J. Rose[1,2], Erica E. M. Moodie[1], and Susan M. Shortreed[3,4]

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A Derivation of Bias Formula

Proof that

$$\begin{aligned}
\text{bias}(\hat{\psi}_K) &= \text{E}(\hat{\psi}_K) - \psi_K \\
&= \Big[- \text{E}\left(\hat{w}_K A_K \boldsymbol{H}_{K,\psi} \boldsymbol{H}_{K,\beta}^T\right) \left\{\text{E}\left(\hat{w}_K \boldsymbol{H}_{K,\beta} \boldsymbol{H}_{K,\beta}^T\right)\right\}^{-1} \text{E}\left(\hat{w}_K A_K \boldsymbol{H}_{K,\beta} \boldsymbol{H}_{K,\psi}^T\right) \\
&\qquad + \text{E}\left(\hat{w}_K A_K \boldsymbol{H}_{K,\psi} \boldsymbol{H}_{K,\psi}^T\right) \Big]^{-1} \Big[\text{E}\left(\hat{w}_K A_K \boldsymbol{H}_{K,\psi} \beta_u U\right) \\
&\qquad - \text{E}\left(\hat{w}_K A_K \boldsymbol{H}_{K,\psi} \boldsymbol{H}_{K,\beta}^T\right) \left\{\text{E}\left(\hat{w}_K \boldsymbol{H}_{K,\beta} \boldsymbol{H}_{K,\beta}^T\right)\right\}^{-1} \text{E}\left(\hat{w}_K \boldsymbol{H}_{K,\beta} \beta_u U\right) \Big].
\end{aligned}$$

Recall that $\boldsymbol{B}_k = (\boldsymbol{H}_{k,\beta}^T, A_k \boldsymbol{H}_{k,\psi}^T)^T$. If the unmeasured confounder U is omitted from the analysis, then the expectation of the estimated coefficients are given by

$$\begin{pmatrix} \text{E}(\hat{\beta}_K) \\ \text{E}(\hat{\psi}_K) \end{pmatrix} = \left\{\text{E}\left(\hat{w}_K \boldsymbol{B}_K \boldsymbol{B}_K^T\right)\right\}^{-1} \text{E}\left(\hat{w}_K \boldsymbol{B}_K Y\right).$$

Note that

$$\left\{\mathrm{E}\left(\hat{w}_K \boldsymbol{B}_K \boldsymbol{B}_K^T\right)\right\}^{-1} = \begin{pmatrix} \mathrm{E}\left(\hat{w}_K \boldsymbol{H}_{K,\beta} \boldsymbol{H}_{K,\beta}^T\right) & \mathrm{E}\left(\hat{w}_K A_K \boldsymbol{H}_{K,\beta} \boldsymbol{H}_{K,\psi}^T\right) \\ \mathrm{E}\left(\hat{w}_K A_K \boldsymbol{H}_{K,\psi} \boldsymbol{H}_{K,\beta}^T\right) & \mathrm{E}\left(\hat{w}_K A_K \boldsymbol{H}_{K,\psi} \boldsymbol{H}_{K,\psi}^T\right) \end{pmatrix}^{-1}.$$

If we denote

$$\begin{pmatrix} \mathrm{E}\left(\hat{w}_K \boldsymbol{H}_{K,\beta} \boldsymbol{H}_{K,\beta}^T\right) & \mathrm{E}\left(\hat{w}_K A_K \boldsymbol{H}_{K,\beta} \boldsymbol{H}_{K,\psi}^T\right) \\ \mathrm{E}\left(\hat{w}_K A_K \boldsymbol{H}_{K,\psi} \boldsymbol{H}_{K,\beta}^T\right) & \mathrm{E}\left(\hat{w}_K A_K \boldsymbol{H}_{K,\psi} \boldsymbol{H}_{K,\psi}^T\right) \end{pmatrix} = \begin{pmatrix} A & B \\ C & D \end{pmatrix},$$

then

$$\begin{pmatrix} \mathrm{E}\left(\hat{w}_K \boldsymbol{H}_{K,\beta} \boldsymbol{H}_{K,\beta}^T\right) & \mathrm{E}\left(\hat{w}_K A_K \boldsymbol{H}_{K,\beta} \boldsymbol{H}_{K,\psi}^T\right) \\ \mathrm{E}\left(\hat{w}_K A_K \boldsymbol{H}_{K,\psi} \boldsymbol{H}_{K,\beta}^T\right) & \mathrm{E}\left(\hat{w}_K A_K \boldsymbol{H}_{K,\psi} \boldsymbol{H}_{K,\psi}^T\right) \end{pmatrix}^{-1}$$
$$= \begin{pmatrix} A^{-1} + A^{-1}B(D - CA^{-1}B)^{-1}CA^{-1} & -A^{-1}B(D - CA^{-1}B)^{-1} \\ -(D - CA^{-1}B)^{-1}CA^{-1} & (D - CA^{-1}B)^{-1} \end{pmatrix}.$$

Therefore

$$\begin{aligned}
\hat{\psi}_K =& \Big[\mathrm{E}\left(\hat{w}_K A_K \boldsymbol{H}_{K,\psi} \boldsymbol{H}_{K,\psi}^T\right) - \mathrm{E}\left(\hat{w}_K A_K \boldsymbol{H}_{K,\psi} \boldsymbol{H}_{K,\beta}^T\right) \left\{\mathrm{E}\left(\hat{w}_K \boldsymbol{H}_{K,\beta} \boldsymbol{H}_{K,\beta}^T\right)\right\}^{-1} \mathrm{E}\left(\hat{w}_K A_K \boldsymbol{H}_{K,\beta} \boldsymbol{H}_{K,\psi}^T\right)\Big]^{-1} \\
& \Big[\mathrm{E}\left(\hat{w}_K A_K \boldsymbol{H}_{K,\psi} Y\right) - \mathrm{E}\left(\hat{w}_K A_K \boldsymbol{H}_{K,\psi} \boldsymbol{H}_{K,\beta}^T\right) \left\{\mathrm{E}\left(\hat{w}_K \boldsymbol{H}_{K,\beta} \boldsymbol{H}_{K,\beta}^T\right)\right\}^{-1} \mathrm{E}\left(\hat{w}_K \boldsymbol{H}_{K,\beta} Y\right)\Big] \\
=& \Big[\mathrm{E}\left(\hat{w}_K A_K \boldsymbol{H}_{K,\psi} \boldsymbol{H}_{K,\psi}^T\right) - \mathrm{E}\left(\hat{w}_K A_K \boldsymbol{H}_{K,\psi} \boldsymbol{H}_{K,\beta}^T\right) \left\{\mathrm{E}\left(\hat{w}_K \boldsymbol{H}_{K,\beta} \boldsymbol{H}_{K,\beta}^T\right)\right\}^{-1} \mathrm{E}\left(\hat{w}_K A_K \boldsymbol{H}_{K,\beta} \boldsymbol{H}_{K,\psi}^T\right)\Big]^{-1} \\
& \Big[\mathrm{E}\left\{\hat{w}_K A_K \boldsymbol{H}_{K,\psi} \left(\beta_u U + \boldsymbol{H}_{K,\beta}^T \beta_K + A_K \boldsymbol{H}_{K,\psi}^T \psi_K + \epsilon\right)\right\} - \\
& \mathrm{E}\left(\hat{w}_K A_K \boldsymbol{H}_{K,\psi} \boldsymbol{H}_{K,\beta}^T\right) \left\{\mathrm{E}\left(\hat{w}_K \boldsymbol{H}_{K,\beta} \boldsymbol{H}_{K,\beta}^T\right)\right\}^{-1} \mathrm{E}\left\{\hat{w}_K \boldsymbol{H}_{K,\beta} \left(\beta_u U + \boldsymbol{H}_{K,\beta}^T \beta_K + A_K \boldsymbol{H}_{K,\psi}^T \psi_K + \epsilon\right)\right\}\Big] \\
=& \Big[\mathrm{E}\left(\hat{w}_K A_K \boldsymbol{H}_{K,\psi} \boldsymbol{H}_{K,\psi}^T\right) - \mathrm{E}\left(\hat{w}_K A_K \boldsymbol{H}_{K,\psi} \boldsymbol{H}_{K,\beta}^T\right) \left\{\mathrm{E}\left(\hat{w}_K \boldsymbol{H}_{K,\beta} \boldsymbol{H}_{K,\beta}^T\right)\right\}^{-1} \mathrm{E}\left(\hat{w}_K A_K \boldsymbol{H}_{K,\beta} \boldsymbol{H}_{K,\psi}^T\right)\Big]^{-1} \\
& \Big(\Big[\mathrm{E}\left(\hat{w}_K A_K \boldsymbol{H}_{K,\psi} \beta_u U\right) - \mathrm{E}\left(\hat{w}_K A_K \boldsymbol{H}_{K,\psi} \boldsymbol{H}_{K,\beta}^T\right) \left\{\mathrm{E}\left(\hat{w}_K \boldsymbol{H}_{K,\beta} \boldsymbol{H}_{K,\beta}^T\right)\right\}^{-1} \mathrm{E}\left(\hat{w}_K \boldsymbol{H}_{K,\beta} \beta_u U\right)\Big]
\end{aligned}$$

$$
\begin{aligned}
&+\Big[-\mathrm{E}\left(\hat{w}_K A_K \boldsymbol{H}_{K,\psi}\boldsymbol{H}_{K,\beta}^T\right)\left\{\mathrm{E}\left(\hat{w}_K \boldsymbol{H}_{K,\beta}\boldsymbol{H}_{K,\beta}^T\right)\right\}^{-1}\mathrm{E}\left(\hat{w}_K \boldsymbol{H}_{K,\beta}\boldsymbol{H}_{K,\beta}^T\beta_K\right)\\
&\quad\mathrm{E}\left(\hat{w}_K A_K \boldsymbol{H}_{K,\psi}\boldsymbol{H}_{K,\beta}^T\beta_K\right)\Big]+\Big[\mathrm{E}\left(\hat{w}_K A_K \boldsymbol{H}_{K,\psi}\boldsymbol{H}_{K,\psi}^T\psi_K\right)\\
&-\mathrm{E}\left(\hat{w}_K A_K \boldsymbol{H}_{K,\psi}\boldsymbol{H}_{K,\beta}^T\right)\left\{\mathrm{E}\left(\hat{w}_K \boldsymbol{H}_{K,\beta}\boldsymbol{H}_{K,\beta}^T\right)\right\}^{-1}\mathrm{E}\left(\hat{w}_K A_K \boldsymbol{H}_{K,\beta}\boldsymbol{H}_{K,\psi}^T\psi_K\right)\Big\}\\
&+\Big[\mathrm{E}\left(\hat{w}_K A_K \boldsymbol{H}_{K,\psi}\epsilon\right)-\mathrm{E}\left(\hat{w}_K A_K \boldsymbol{H}_{K,\psi}\boldsymbol{H}_{K,\beta}^T\right)\left\{\mathrm{E}\left(\hat{w}_K \boldsymbol{H}_{K,\beta}\boldsymbol{H}_{K,\beta}^T\right)\right\}^{-1}\mathrm{E}\left(\hat{w}_K \boldsymbol{H}_{K,\beta}\epsilon\right)\Big]\Bigg)\\
=\psi_K+&\Big[-\mathrm{E}\left(\hat{w}_K A_K \boldsymbol{H}_{K,\psi}\boldsymbol{H}_{K,\beta}^T\right)\left\{\mathrm{E}\left(\hat{w}_K \boldsymbol{H}_{K,\beta}\boldsymbol{H}_{K,\beta}^T\right)\right\}^{-1}\mathrm{E}\left(\hat{w}_K A_K \boldsymbol{H}_{K,\beta}\boldsymbol{H}_{K,\psi}^T\right)\\
&\quad+\mathrm{E}\left(\hat{w}_K A_K \boldsymbol{H}_{K,\psi}\boldsymbol{H}_{K,\psi}^T\right)\Big]^{-1}\Big[\mathrm{E}\left(\hat{w}_K A_K \boldsymbol{H}_{K,\psi}\beta_u U\right)\\
&\quad-\mathrm{E}\left(\hat{w}_K A_K \boldsymbol{H}_{K,\psi}\boldsymbol{H}_{K,\beta}^T\right)\left\{\mathrm{E}\left(\hat{w}_K \boldsymbol{H}_{K,\beta}\boldsymbol{H}_{K,\beta}^T\right)\right\}^{-1}\mathrm{E}\left(\hat{w}_K \boldsymbol{H}_{K,\beta}\beta_u U\right)\Big].
\end{aligned}
$$

We then have that the bias is given by

$$
\begin{aligned}
\mathrm{bias}(\hat{\psi}_K) =&\mathrm{E}(\hat{\psi}_K)-\psi_K\\
=&\Big[-\mathrm{E}\left(\hat{w}_K A_K \boldsymbol{H}_{K,\psi}\boldsymbol{H}_{K,\beta}^T\right)\left\{\mathrm{E}\left(\hat{w}_K \boldsymbol{H}_{K,\beta}\boldsymbol{H}_{K,\beta}^T\right)\right\}^{-1}\mathrm{E}\left(\hat{w}_K A_K \boldsymbol{H}_{K,\beta}\boldsymbol{H}_{K,\psi}^T\right)\\
&\quad+\mathrm{E}\left(\hat{w}_K A_K \boldsymbol{H}_{K,\psi}\boldsymbol{H}_{K,\psi}^T\right)\Big]^{-1}\Big[\mathrm{E}\left(\hat{w}_K A_K \boldsymbol{H}_{K,\psi}\beta_u U\right)\\
&\quad-\mathrm{E}\left(\hat{w}_K A_K \boldsymbol{H}_{K,\psi}\boldsymbol{H}_{K,\beta}^T\right)\left\{\mathrm{E}\left(\hat{w}_K \boldsymbol{H}_{K,\beta}\boldsymbol{H}_{K,\beta}^T\right)\right\}^{-1}\mathrm{E}\left(\hat{w}_K \boldsymbol{H}_{K,\beta}\beta_u U\right)\Big].
\end{aligned}
$$

B Simulations with Binary U

We conducted a simulation study of the proposed Monte Carlo sensitivity analysis with a binary unmeasured confounder that closely resembles the study in the main paper. We will consider both a one-stage and a two-stage study. For the one-stage study, the data generating

models were given by:

$$
\begin{aligned}
&X_1 \sim N(0, \sigma^2_{x_1}),\\
&X_2 \sim N(0, \sigma^2_{x_2}),\\
&\mathrm{P}(U = 1|\boldsymbol{X} = \boldsymbol{x}) = \left[1 + \exp\left\{-(\zeta_0 + \zeta_1 x_1 + \zeta_2 x_2)\right\}\right]^{-1},\\
&\mathrm{P}(A = 1|\boldsymbol{X} = \boldsymbol{x}, U = u) = \left[1 + \exp\left\{-(\alpha_0 + \alpha_1 x_1 + \alpha_2 x_2 + \alpha_3 u)\right\}\right]^{-1},\\
&Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_u U + A(\psi_0 + \psi_1 X_1 + \psi_2 X_2) + \epsilon_y, \qquad \epsilon_y \sim N(0, \sigma^2_y).
\end{aligned}
$$

We again conducted 1000 repetitions for the simulation study with a sample size of $n = 1000$. For the sensitivity analysis, we conducted $B = 500$ Monte Carlo repetitions. The parameter values for the data generating models were given by:

$$
\begin{aligned}
&\psi = (\psi_0, \psi_1, \psi_2) = (-1, 0.5, 0.5), \quad \beta = (\beta_0, \beta_1, \beta_2, \beta_u) = (1, 1, 1, 2),\\
&\zeta = (0, 1, -1), \qquad\qquad\qquad\quad \alpha = (\alpha_0, \alpha_1, \alpha_2, \alpha_3) = (0, 1, 1, 2),\\
&\sigma^2_u = \sigma^2_{x_1} = \sigma^2_{x_2} = \sigma^2_y = 1.
\end{aligned}
$$

We posited four different sets of distributions for the parameters in the unmeasured confounder models given by: (i) narrow normal, correctly centered; (ii) wide normal, correctly centered; (iii) narrow normal, off-center; (iv) wide normal, off-center. As with the simulations for the continuous U in the main paper, for scenario (i), we posited models given by $\beta_u^{(b)} \sim N(\beta_u, 0.1)$ and $\zeta_j^{(b)} \sim N(\zeta_j, 0.1)$ for $j = 0, 1, 2$. For the wide distribution settings, the variance was increased to 0.5 and for the off-center scenarios the distribution was centered at the true mean plus 0.1.

Figure 1 shows boxplots of the point estimates of ψ across 1000 simulation repetitions before and after adjusting for the unmeasured confounder using Monte Carlo sensitivity analysis with different distributions for the bias parameters. When we did not adjust for bias due to the unmeasured confounder, the estimate of ψ_0 is biased with a root mean

squared error (rMSE) of 0.692. When we adjusted for the unmeasured confounder, the rMSE was reduced to 0.110 and 0.126 for the narrow and wide correctly centered bias parameter distributions, respectively. When the parameter distributions were not centered on the true value we saw a similar reduction in the rMSE to 0.115 and 0.104 for the narrow and wide distributions for the bias parameters. The unadjusted estimates of ψ_1 and ψ_2 were unbiased so the adjusted estimates using Monte Carlo sensitivity analysis were very similar to the unadjusted results.

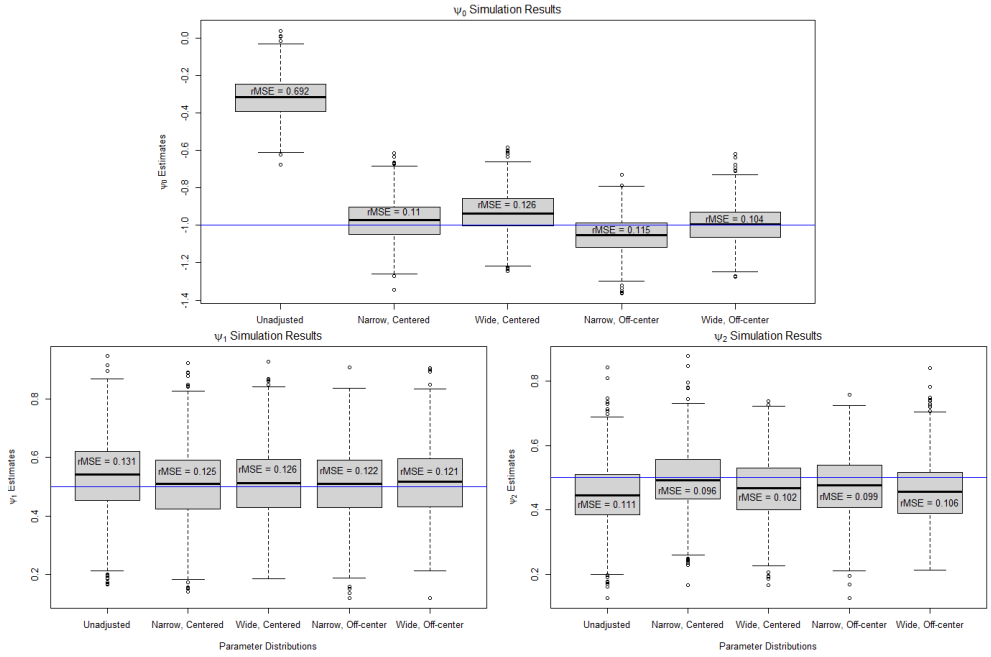

Figure 1: Boxplots of the point estimates for ψ under an unadjusted model and when using Monte Carlo sensitivity analysis to adjust for bias due to unmeasured confounding for the 1-stage data generating model with a binary unmeasured confounder.

Table 1 contains the proportion of new patients whose recommended treatment matched the true optimal treatment regime for each of the estimated unadjusted and adjusted treatment regimes. This was found by simulating 10000 additional patients for each simulation repetition and examining the treatment recommend by the estimated regimes. For this data generating model, the unadjusted regime matched the optimal 75.7% of the time. This in-

creased after adjusting for the bias to 95.9% for the narrow, correctly centered distributions and 96.1% for the wide, off-center distributions for the bias parameters. Table 2 contains the coverage and average width of 95% confidence intervals for the parameters in the blip model. When the unmeasured confounding was not taken into account, the coverage for each of the confidence intervals was below the nominal rate. After adjusting for the unmeasured confounding, the coverage was close to 95% for ψ_1 and ψ_2 while being conservative for ψ_0 under all of the parameter distributions. The wide parameter distributions produced wider confidence intervals as expected since there is more uncertainty in the distribution and effect of the unmeasured confounder.

Table 1: Proportion of patients whose recommended treatment when following each of the estimated regime matches the recommendation of the true optimal regime for the 1-stage data generating model with a binary unmeasured confounder.

Parameter Distr.	Proportion Optimal
Unadjusted	0.757
Narrow, Centered	0.959
Wide, Centered	0.957
Narrow, Off-center	0.963
Wide, Off-center	0.961

Table 2: Coverage (Cvr.) and average width (Wth.) of the 95% confidence intervals for ψ for the unadjusted analysis and sensitivity analysis under each of the posited parameter distributions for the 1-stage data generating model with a binary unmeasured confounder. * indicates coverages that are significantly different than 95%.

Parameter Distr.	Cvr. (Wth.) ψ_0	Cvr. (Wth.) ψ_1	Cvr. (Wth.) ψ_2
Unadjusted	0* (0.337)	0.878* (0.401)	0.871* (0.337)
Narrow, Centered	0.998* (0.735)	0.947 (0.497)	0.975* (0.43)
Wide, Centered	1* (1.351)	0.976* (0.578)	0.989* (0.56)
Narrow, Off-center	0.998* (0.764)	0.962 (0.507)	0.97* (0.44)
Wide, Off-center	1* (1.409)	0.987* (0.608)	0.994* (0.578)

We conducted a similar simulation study for a 2-stage study with a binary unmeasured

confounder. The data generating models were given by:

$$
\begin{aligned}
&X_{11} \sim N(0, \sigma^2_{x_{11}}), && X_{12} \sim N(0, \sigma^2_{x_{12}}),\\
&\mathrm{P}(U = 1|\boldsymbol{X}_1 = \boldsymbol{x}_1) = \left[1 + \exp\left\{-(\zeta_0 + \zeta_1 x_{11} + \zeta_2 x_{12})\right\}\right]^{-1},\\
&\mathrm{P}(A_1 = 1|\boldsymbol{X}_1 = \boldsymbol{x}_1, U = u) = \left[1 + \exp\left\{-(\alpha_{10} + \alpha_{11} x_{11} + \alpha_{12} x_{12} + \alpha_{13} u)\right\}\right]^{-1},\\
&X_2 = \varpi_0 + \varpi_1 X_{11} + \varpi_2 X_{12} + \epsilon_{x_2}, && \epsilon_{x_2} \sim N(0, \sigma^2_{x_2}),\\
&\mathrm{P}(A_2 = 1|\boldsymbol{H}_2 = \boldsymbol{h}_2, U = u) = \left[1 + \exp\left\{-(\alpha_{20} + \alpha_{21} x_{11} + \alpha_{22} x_{12} + \alpha_{23} a_1 + \alpha_{24} x_2 + \alpha_{25} u)\right\}\right]^{-1},\\
&Y = \beta_{20} + \beta_{21} X_{11} + \beta_{22} X_{12} + \beta_{23} A_1 + \beta_{24} A_1 X_{11} + \beta_{25} A_1 X_{12}\\
&\quad + \beta_{26} X_2 + \beta_u U + A_2(\psi_{20} + \psi_{21} X_{11} + \psi_{22} X_{12} + \psi_{23} X_2) + \epsilon_y, \quad \epsilon_y \sim N(0, \sigma^2_y).
\end{aligned}
$$

As with the one-stage study, we conducted 1000 repetitions for the simulation study, let the sample size equal $n = 1000$, and conducted the sensitivity analysis with $B = 500$ Monte Carlo repetitions. The parameter values used for the data generating process were:

$$
\begin{aligned}
&\psi_2 = (\psi_{20}, \psi_{21}, \psi_{22}, \psi_{23}) = (-1, 0.5, 0.5, 0.5),\\
&\beta_2 = (\beta_{20}, \beta_{21}, \beta_{22}, \beta_{23}, \beta_{24}, \beta_{25}, \beta_{26}, \beta_u) = (1, -1, 1, -1, 1, 1, 1, 2),\\
&\zeta = (0, 1, -1),\\
&\varpi = (\varpi_0, \varpi_1, \varpi_2) = (0, 1, 1),\\
&\alpha_1 = (\alpha_{10}, \alpha_{11}, \alpha_{12}, \alpha_{13}) = (0, 1, 1, 2),\\
&\alpha_2 = (\alpha_{20}, \alpha_{21}, \alpha_{22}, \alpha_{23}, \alpha_{24}, \alpha_{25}) = (0, 1, 1, 1, 1, 3),\\
&\sigma^2_u = \sigma^2_{x_{11}} = \sigma^2_{x_{12}} = \sigma^2_{x_2} = \sigma^2_y = 1.
\end{aligned}
$$

We again varied the posited distributions for the bias parameters using the same posited distributions as in the one-stage study.

Figures 2 and 3 show boxplots of the point estimates for ψ_2 and ψ_1, respectively, across 1000 simulation repetitions. These results were similar to the 2-stage results with a continuous unmeasured confounder that can be found in the main paper. For the second stage,

the estimate of ψ_{20} was biased in the unadjusted analysis with an rMSE of 0.808. Monte Carlo sensitivity analysis reduced the bias to 0.207 for the narrow and correctly centered bias parameter distributions. The results were similar for the other bias parameter distributions with the largest rMSE being 0.251 for the wide, correctly centered distributions. The unmeasured confounder did not bias the estimates of ψ_{21}, ψ_{22}, and ψ_{23} which caused the unadjusted and adjusted results to be similar. For the first stage models, the unmeasured confounder biased the estimate of ψ_{10} resulting in the unadjusted analysis having an rMSE of 0.536. The sensitivity analysis reduced the rMSE to 0.149 for the narrow, correctly centered bias parameter distributions and 0.153 for the wide, off-center distributions.

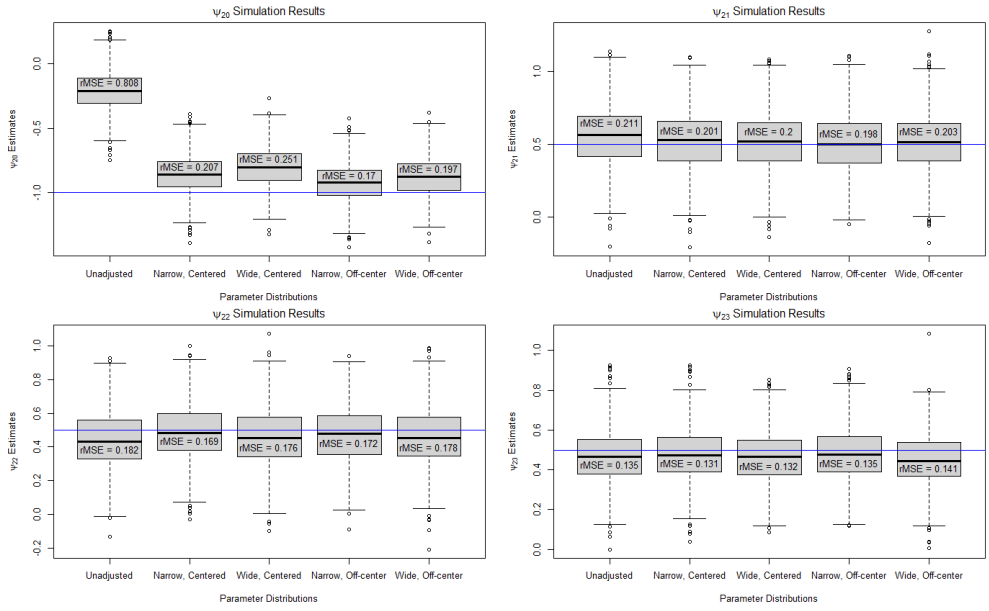

Figure 2: Boxplots of the point estimates for ψ_2 under an unadjusted model and when using Monte Carlo sensitivity analysis to adjust for bias due to unmeasured confounding for the 2-stage data generating model with a binary unmeasured confounder.

Table 3 displays the proportion of new patients whose recommended treatment matched the treatment recommended by the true optimal regime. The bias in the unadjusted regime led to patients being treated optimally 86.9% of the time during the first stage and 81.2% during the second stage. Adjusting for the bias increased the optimal proportion to 95.4%

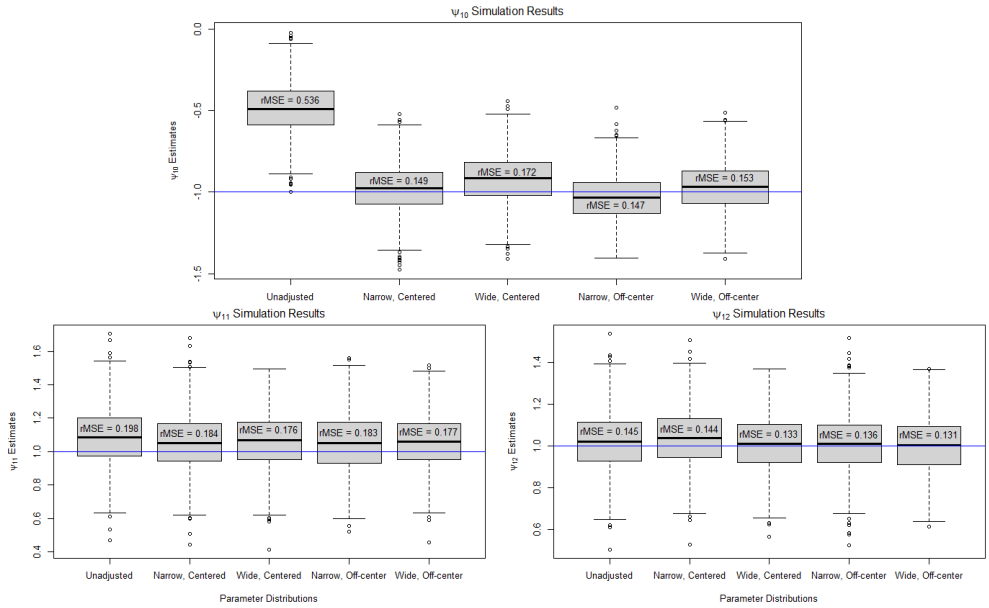

Figure 3: Boxplots of the point estimates for ψ_1 under an unadjusted model and when using Monte Carlo sensitivity analysis to adjust for bias due to unmeasured confounding for the 2-stage data generating model with a binary unmeasured confounder.

at the first stage and 94.4% at the second stage for the narrow, correctly centered bias parameter distributions. Tables 4 and 5 contain the coverage and average width of 95% confidence intervals for the parameters indexing the optimal treatment regime for the second stage and first stage, respectively. The unadjusted confidence intervals were far below the nominal rate for all the parameters at each stage. Monte Carlo sensitivity analysis produced wider confidence intervals that had a coverage of 94.9% or greater for all of the parameters when positing narrow, correctly centered bias parameter distributions. Wider distributions for the bias parameters produced more conservative confidence intervals as expected.

Table 3: Proportion of patients whose recommended treatment when following each of the estimated regime matches the recommendation of the true optimal regime at each stage for the 2-stage data generating model with a binary unmeasured confounder.

Parameter Distr.	Stage 1	Stage 2
Unadjusted	0.869	0.812
Narrow, Centered	0.954	0.944
Wide, Centered	0.950	0.939
Narrow, Off-center	0.955	0.946
Wide, Off-center	0.954	0.942

Table 4: Coverage (Cvr.) and average width (Wth.) of the 95% confidence intervals for ψ_2 for the unadjusted analysis and sensitivity analysis under each of the posited parameter distributions for the 2-stage data generating model with a binary unmeasured confounder. * indicates coverages that are significantly different than 95%.

Parameter Distr.	Cvr. (Wth.) ψ_{20}	Cvr. (Wth.) ψ_{21}	Cvr. (Wth.) ψ_{22}	Cvr. (Wth.) ψ_{23}
Unadjusted	0.000* (0.391)	0.765* (0.498)	0.773* (0.442)	0.794* (0.333)
Narrow, Centered	0.972* (0.832)	0.950 (0.788)	0.956 (0.699)	0.949 (0.513)
Wide, Centered	1.000* (1.360)	0.962 (0.847)	0.968* (0.777)	0.971* (0.567)
Narrow, Off-center	0.992* (0.858)	0.951 (0.798)	0.951 (0.701)	0.943 (0.513)
Wide, Off-center	1.000* (1.418)	0.962 (0.871)	0.967* (0.781)	0.952 (0.576)

Table 5: Coverage (Cvr.) and average width (Wth.) of the 95% confidence intervals for ψ_1 for the unadjusted analysis and sensitivity analysis under each of the posited parameter distributions for the 2-stage data generating model. * indicates coverages that are significantly different than 95%.

Parameter Distr.	Cvr. (Wth.) ψ_{10}	Cvr. (Wth.) ψ_{11}	Cvr. (Wth.) ψ_{12}
Unadjusted	0.027* (0.446)	0.826* (0.531)	0.873* (0.447)
Narrow, Centered	0.958 (2.706)	0.995* (2.612)	0.994* (2.525)
Wide, Centered	0.988* (3.039)	0.999* (2.594)	0.997* (2.511)
Narrow, Off-center	0.984* (2.754)	0.999* (2.656)	0.996* (2.564)
Wide, Off-center	0.994* (3.120)	0.999* (2.658)	0.998* (2.557)

C Simulations with Limited Bias

We conducted additional simulations using the same data generating model as the main paper with different parameter values. These simulations demonstrate situations where the bias in ψ due to unmeasured confounding does not significantly effect the performance of the unadjusted treatment regime. For the single stage simulations, the parameter values were given by:

$$\begin{aligned}
&\psi = (\psi_0, \psi_1, \psi_2) = (1, 0.5, 0.5), && \alpha = (\alpha_0, \alpha_1, \alpha_2, \alpha_3) = (0, 1, 1, 2), \\
&\phi_1 = (\phi_{10}, \phi_{11}) = (0, 1), && \beta = (\beta_0, \beta_1, \beta_2, \beta_u) = (1, 1, 1, 1), \\
&\phi_2 = (\phi_{20}, \phi_{21}) = (0, -1), && \sigma_u^2 = \sigma_{x_1}^2 = \sigma_{x_2}^2 = \sigma_y^2 = 1.
\end{aligned}$$

We again varied the posited distributions for the parameters of the unmeasured confounder model and the effect of the unmeasured confounder using the same posited distributions as in the main paper.

Figure 4 show boxplots of the estimate of ψ across the 1000 repetitions of the simulation study. As before the unadjusted estimate of ψ_0 was biased with an rMSE of 0.552. Table 6 displays the proportion of patients that were recommended the same treatment as the true optimal regime for the different estimated treatment regimes. The unadjusted regime still matched the true optimal regime 93.9% of the time despite the bias in ψ_0. Since the true value of ψ_0 equaled 1 and the mean of X_1 and X_2 were 0, we have that treatment $A = 1$ was the better treatment on average. Therefore, since the bias in ψ_0 was positive, the bias tended to push patients towards the generally better treatment and only a small subset of patients were negatively impacted by the bias due to the unmeasured confounder. The coverage and width of the confidence intervals for ψ are displayed in Table 7.

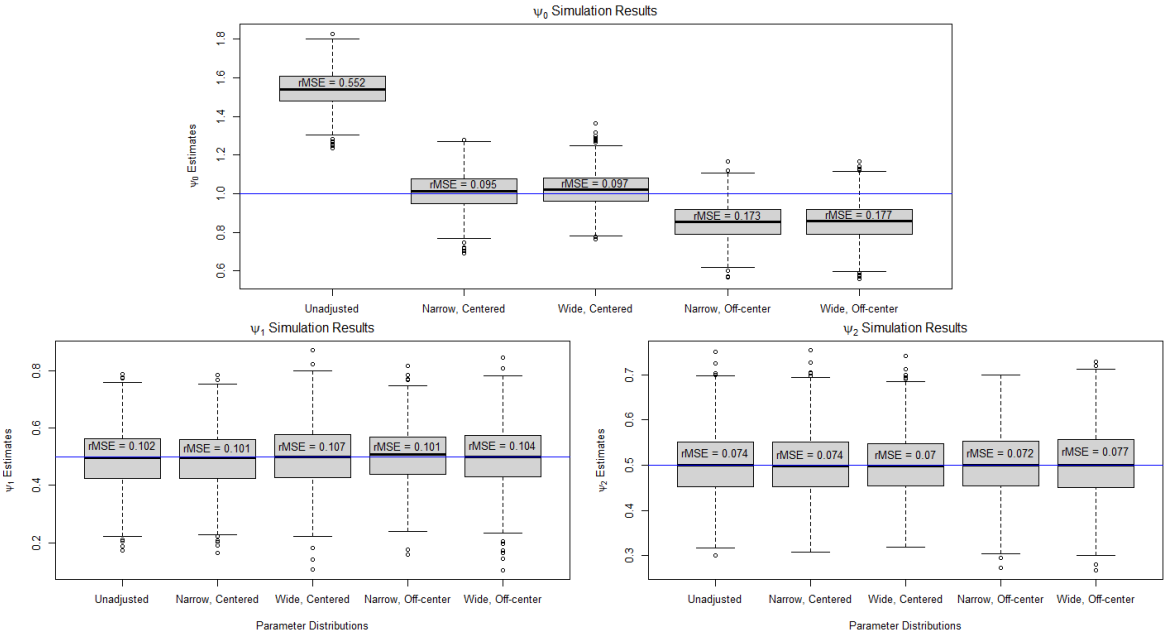

Figure 4: Boxplots of the point estimates for ψ under an unadjusted model and when using Monte Carlo sensitivity analysis to adjust for bias due to unmeasured confounding for the 1-stage data generating model.

Table 6: Proportion of patients whose recommended treatment when following each of the estimated regime matches the recommendation of the true optimal regime for the 1-stage data generating model.

Parameter Distr.	Proportion Optimal
Unadjusted	0.939
Narrow, Centered	0.967
Wide, Centered	0.968
Narrow, Off-center	0.949
Wide, Off-center	0.948

For the 2-stage study, the parameter values were given by:

$$\beta_2 = (\beta_{20}, \beta_{21}, \beta_{22}, \beta_{23}, \beta_{24}, \beta_{25}, \beta_{26}, \beta_u) = (1, -1, 1, -1, 1, 1, 1, 1), \quad \varpi = (\varpi_0, \varpi_1, \varpi_2) = (0, 1, 1)$$

$$\psi_2 = (\psi_{20}, \psi_{21}, \psi_{22}, \psi_{23}) = (1, 0.5, 0.5, 0.5), \qquad \phi_1 = (\phi_{10}, \phi_{11}) = (0, 1),$$

$$\alpha_1 = (\alpha_{10}, \alpha_{11}, \alpha_{12}, \alpha_{13}) = (0, 1, 1, 2), \qquad \phi_2 = (\phi_{10}, \phi_{11}) = (0, -1),$$

$$\alpha_2 = (\alpha_{20}, \alpha_{21}, \alpha_{22}, \alpha_{23}, \alpha_{24}, \alpha_{25}) = (0, 1, 1, 1, 1, 3), \qquad \sigma_u^2 = \sigma_{x_{11}}^2 = \sigma_{x_{12}}^2 = \sigma_{x_2}^2 = \sigma_y^2 = 1$$

Table 7: Coverage (Cvr.) and average width (Wth.) of the 95% confidence intervals for ψ for the unadjusted analysis and sensitivity analysis under each of the posited parameter distributions for the 1-stage data generating model. * indicates coverages that are significantly different than 95%.

Parameter Distr.	Cvr. (Wth.) ψ_0	Cvr. (Wth.) ψ_1	Cvr. (Wth.) ψ_2
Unadjusted	0.000* (0.280)	0.899* (0.332)	0.874* (0.234)
Narrow, Centered	1.000* (1.485)	0.954 (0.404)	0.932* (0.286)
Wide, Centered	1.000* (3.836)	0.942 (0.404)	0.950 (0.285)
Narrow, Off-center	1.000* (1.633)	0.944 (0.404)	0.951 (0.286)
Wide, Off-center	1.000* (4.103)	0.943 (0.404)	0.932* (0.287)

Figures 5 and 6 show boxplots of the estimate of ψ_2 and ψ_1 across the 1000 repetitions, respectively. As before the unmeasured confounder caused the estimate of ψ_{20} and ψ_{10} to be biased with an rMSE of 0.614 for ψ_{20} and 0.392 for ψ_{10}. Table 8 displays the proportion of patients that received the same treatment as the true optimal regime under each of the estimation methods. Note the unadjusted regime still recommended the same treatment as the optimal regime 90.5% of the time at the first stage and 89.0% of the time during the second stage. As with the single stage case above, this is due to the direction of the bias. The coverage and width of the confidence intervals for ψ_2 and ψ_1 are displayed in Tables 9 and 10, respectively.

Table 8: Proportion of patients whose recommended treatment when following each of the estimated regime matches the recommendation of the true optimal regime at each stage for the 2-stage data generating model.

Parameter Distr.	Stage 1	Stage 2
Unadjusted	0.905	0.890
Narrow, Centered	0.955	0.958
Wide, Centered	0.954	0.957
Narrow, Off-center	0.957	0.960
Wide, Off-center	0.956	0.958

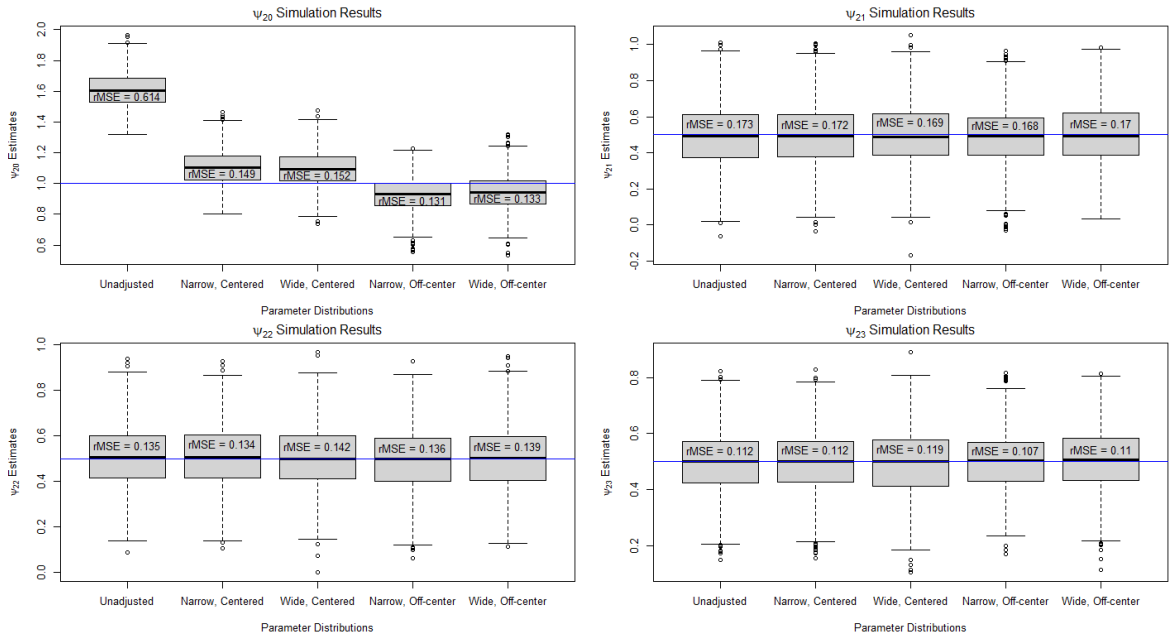

Figure 5: Boxplots of the point estimates for ψ_2 under an unadjusted model and when using Monte Carlo sensitivity analysis to adjust for bias due to unmeasured confounding for the 2-stage data generating model.

Table 9: Coverage (Cvr.) and average width (Wth.) of the 95% confidence intervals for ψ_2 for the unadjusted analysis and sensitivity analysis under each of the posited parameter distributions for the 2-stage data generating model. * indicates coverages that are significantly different than 95%.

Parameter Distr.	Cvr. (Wth.) ψ_{20}	Cvr. (Wth.) ψ_{21}	Cvr. (Wth.) ψ_{22}	Cvr. (Wth.) ψ_{23}
Unadjusted	0.000* (0.276)	0.779* (0.430)	0.810* (0.354)	0.797* (0.292)
Narrow, Centered	1.000* (1.494)	0.947 (0.660)	0.960 (0.541)	0.947 (0.443)
Wide, Centered	1.000* (3.823)	0.943 (0.656)	0.945 (0.538)	0.942 (0.439)
Narrow, Off-center	1.000* (1.644)	0.939 (0.655)	0.947 (0.539)	0.954 (0.439)
Wide, Off-center	1.000* (4.088)	0.949 (0.656)	0.953 (0.538)	0.941 (0.439)

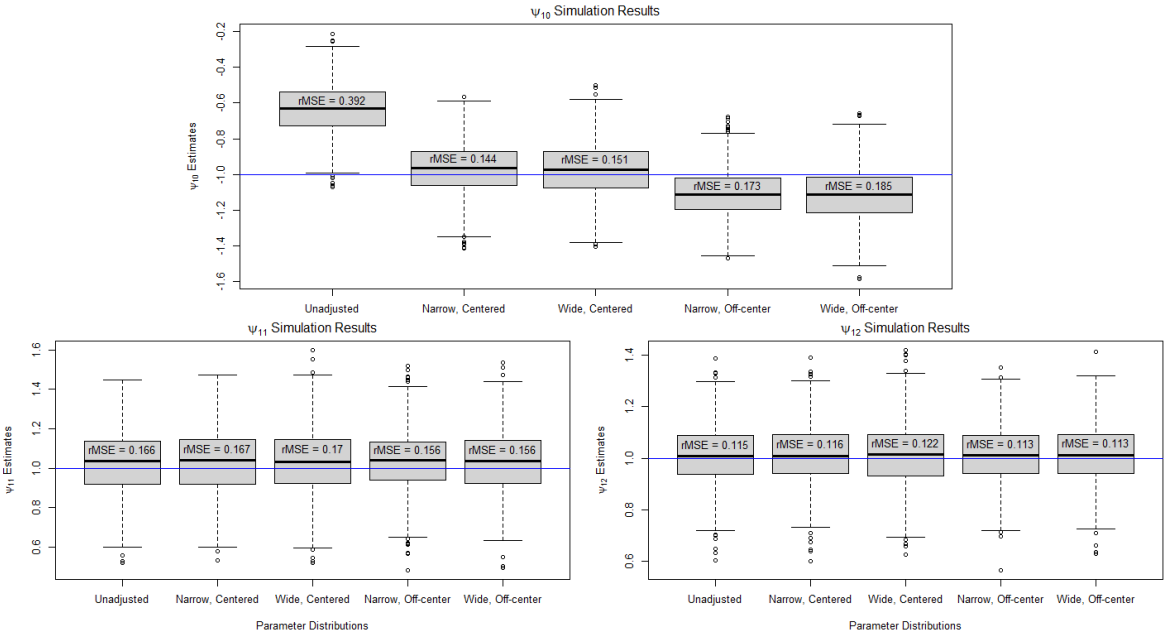

Figure 6: Boxplots of the point estimates for ψ_1 under an unadjusted model and when using Monte Carlo sensitivity analysis to adjust for bias due to unmeasured confounding for the 2-stage data generating model.

Table 10: Coverage (Cvr.) and average width (Wth.) of the 95% confidence intervals for ψ_1 for the unadjusted analysis and sensitivity analysis under each of the posited parameter distributions for the 2-stage data generating model. * indicates coverages that are significantly different than 95%.

Parameter Distr.	Cvr. (Wth.) ψ_{10}	Cvr. (Wth.) ψ_{11}	Cvr. (Wth.) ψ_{12}
Unadjusted	0.140* (0.441)	0.880* (0.524)	0.887* (0.370)
Narrow, Centered	1.000* (3.311)	0.997* (2.559)	0.978* (2.401)
Wide, Centered	1.000* (5.166)	1.000* (2.650)	0.998* (2.470)
Narrow, Off-center	1.000* (3.582)	0.998* (2.675)	0.985* (2.525)
Wide, Off-center	1.000* (5.592)	1.000* (2.789)	0.996* (2.608)

D Sensitivity Analysis with G-estimation

G-estimation is an alternative approach to estimating DTRs that focuses on estimating the blip functions (Robins, 2004). We will restrict attention to only one-stage treatment regimes in this section. Recall that for a one-stage study the blip function is defined as

$$\gamma_1(\boldsymbol{h}_1, a_1) = \mathrm{E}\{Y^*(a_1) - Y^*(0)|\boldsymbol{H}_1 = \boldsymbol{h}_1\}.$$

As before, we assume that the blip function is linear so we have that a model for the blip is given by $\gamma_1(\boldsymbol{h}_1, a_1; \psi) = a_1 \boldsymbol{h}_{1,\psi}^T \psi$ such that ψ^* denotes the true value of ψ. Under the stable unit treatment value assumption (SUTVA) we have that

$$Y^*(0) = Y - \gamma_1(\boldsymbol{H}_1, A_1; \psi^*).$$

Define

$$H(\psi) = Y - \gamma_1(\boldsymbol{H}_1, A_1; \psi)$$

and let

$$\text{logit}\left[\mathrm{P}\{A_1 = 1|H(\psi), \boldsymbol{H}_1 = \boldsymbol{h}_1\}\right] = \xi_0 + H(\psi)(\boldsymbol{h}_{1,\psi}^T \xi_1) + \boldsymbol{h}_1^T \xi_2.$$

G-estimation assumes that sequential ignorability holds which implies that $\xi_1 = \mathbf{0}$. Therefore, to estimate the true value of ψ, we can find the value of ψ for $H(\psi)$ that leads to $\hat{\xi}_1 = \mathbf{0}$ when fitting the logistic regression model. If there is an unmeasured confounder, we have that $\xi_1 \neq \mathbf{0}$. Therefore, we can conduct sensitivity analysis by setting ξ_1 to a range of different fixed values and estimating ψ to see how sensitive the estimated treatment regime is to unmeasured confounding. Refer to Robins et al. (1999) and Hernan and Robins (2020) for additional details on G-estimation and this approach to conducting sensitivity analysis for unmeasured confounding.

We conducted a simulation study to examine the performance of this method using the same generative model as the one-stage study in the main paper. Therefore, the generative modes were given by:

$$
\begin{aligned}
&U \sim N(0, \sigma_u^2), \\
&X_1 = \phi_{10} + \phi_{11} U + \epsilon_{x_1}, && \epsilon_{x_1} \sim N(0, \sigma_{x_1}^2), \\
&X_2 = \phi_{20} + \phi_{21} U + \epsilon_{x_2}, && \epsilon_{x_2} \sim N(0, \sigma_{x_2}^2), \\
&\mathrm{P}(A = 1 | \boldsymbol{X} = \boldsymbol{x}, U = u) = \left[1 + \exp\left\{-(\alpha_0 + \alpha_1 x_1 + \alpha_2 x_2 + \alpha_3 u)\right\}\right]^{-1}, \\
&Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_u U + A(\psi_0 + \psi_1 X_1 + \psi_2 X_2) + \epsilon_y, && \epsilon_y \sim N(0, \sigma_y^2),
\end{aligned}
$$

and the parameter values used were again given by:

$$
\begin{aligned}
&\psi = (\psi_0, \psi_1, \psi_2) = (-1, 0.5, 0.5), && \alpha = (\alpha_0, \alpha_1, \alpha_2, \alpha_3) = (0, 1, 1, 2), \\
&\phi_1 = (\phi_{10}, \phi_{11}) = (0, 1), && \beta = (\beta_0, \beta_1, \beta_2, \beta_u) = (1, 1, 1, 2), \\
&\phi_2 = (\phi_{20}, \phi_{21}) = (0, -1), && \sigma_u^2 = \sigma_{x_1}^2 = \sigma_{x_2}^2 = \sigma_y^2 = 1.
\end{aligned}
$$

To compare this procedure to our proposed sensitivity analysis we will again use a Monte Carlo approach and posit distributions for the bias parameter ξ_1. For each Monte Carlo repetition, we take a bootstrap sample and sample ξ_1 from the posited distributions. We then calculate a bias adjusted estimate of ψ using G-estimation. A point estimate for ψ is then given by the mean across the Monte Carlo repetition and we construct a confidence interval by taking percentiles across the repetitions.

As before, we will use four different simulation settings given by (i) narrow normal, centered properly; (ii) wide normal, centered properly; (iii) narrow normal, off-center; (iv) wide normal, off-center. For scenario (i), we posited distributions for ξ_{1j} given by $\xi_{1j}^{(b)} \sim N(\xi_{1j}, 0.1)$ for $j = 0, 1, 2$. For the wide distributions settings we increased the variance to 0.5 and for the off-center simulations we centered the distribution at the true value of ξ_{1j}

plus 0.1. For this data generating model, $\xi_1 = (\xi_{10}, \xi_{11}, \xi_{12})$ is given by $(0.52, 0, 0)$. We will conduct two different simulation studies. The first will assume we know ξ_{11} and ξ_{12} and only sample ξ_{10} from the posited distribution. The bias parameters used at each Monte Carlo repetition is then given by $\xi_1^{(b)} = (\xi_{10}^{(b)}, 0, 0)$. The second will sample all three bias parameters, $(\xi_{10}^{(b)}, \xi_{11}^{(b)}, \xi_{12}^{(b)})$, to calculate a bias adjusted estimate for each Monte Carlo repetition.

Figure 7 displays boxplots for the estimate of ψ under each of the simulation settings when we assume we know ξ_{11} and ξ_{12}. For ψ_0, adjusting for the unmeasured confounder using a narrow, correctly centered distribution for ξ_{10} reduces the rMSE from 1.104 to 0.188. The estimate of ψ_0 is sensitive to misspecification of the parameter distribution with the incorrectly centered distribution resulting in an rMSE of 0.383 and 0.488 for the narrow and wide distributions, respectively. The bias adjusted estimates of ψ_1 and ψ_2 were worse than the unadjusted estimate with the rMSE increasing from 0.204 to 0.316 for ψ_1 and 0.125 to 0.184 for ψ_2 with the narrow, correctly centered bias parameter distribution. Table 11 shows the coverage and width of confidence intervals for the G-estimation sensitivity analysis. The confidence intervals were overly conservative with coverage above the nominal rate of 95% and far wider than those produced by our proposed Monte Carlo sensitivity analysis for all parameters and bias parameter distributions. Table 12 contains the proportion of new patients whose treatment recommendation under each of the estimated treatment regimes matches that of the true optimal regime. The adjusted treatment regime significantly improves upon the unadjusted regime with 93% of patients receiving the optimal treatment for the narrow, centered bias distribution. The performace was worse than our proposed Monte Carlo sensitivity analysis in which 95.6% of new patients were recommended the same treatment as the true optimal regime.

Figure 8 shows boxplots for the estimates of ψ when we do not assume we know the true value of any of the bias parameters and therefore posit distributions and sample from them for ξ_{10}, ξ_{11}, and ξ_{12}. The results for this method were poor with the bias adjusted

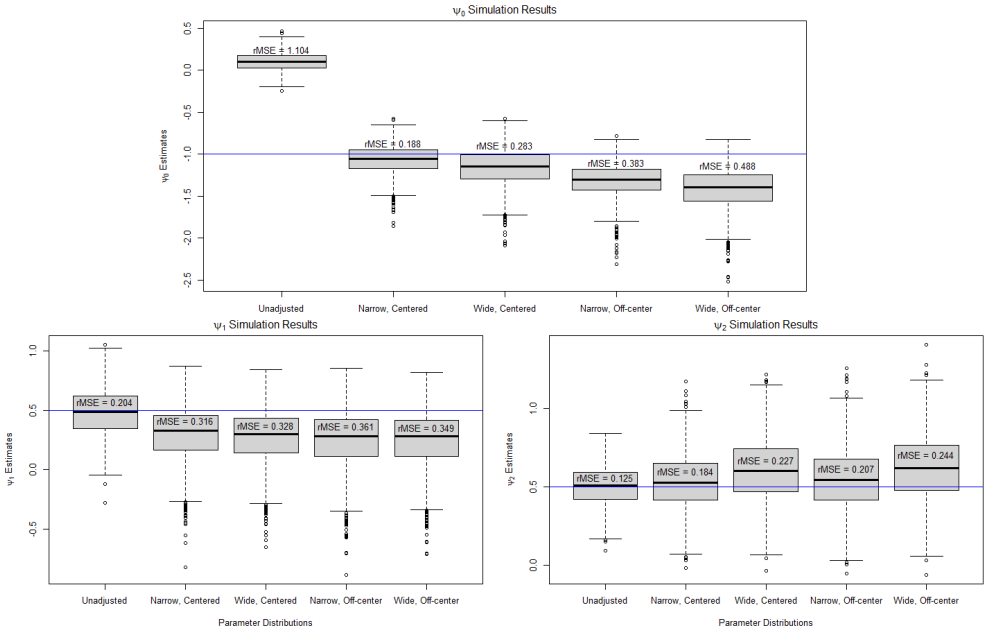

Figure 7: Boxplots of the point estimates for ψ under an unadjusted model and when using G-estimation sensitivity analysis to adjust for bias due to unmeasured confounding for the 1-stage data generating model when we assume we know ξ_{11} and ξ_{12}.

Table 11: Coverage (Cvr.) and average width (Wth.) of the 95% confidence intervals for ψ for the G-estimation sensitivity analysis under each of the posited parameter distributions for the 1-stage data generating model when we assume we know ξ_{11} and ξ_{12}. * indicates coverages that are significantly different than 95%.

Parameter Distr.	Cvr. (Wth.) ψ_0	Cvr. (Wth.) ψ_1	Cvr. (Wth.) ψ_2
Narrow, Centered	1.000* (3.382)	0.969* (1.708)	0.969* (1.064)
Wide, Centered	1.000* (8.076)	0.984* (2.122)	0.993* (1.899)
Narrow, Off-center	1.000* (3.889)	0.968* (1.990)	0.971* (1.295)
Wide, Off-center	1.000* (8.316)	0.986* (2.277)	0.994* (2.057)

estimates having a larger rMSE than the undjusted estimates for each of the parameters. Table 14 displays the coverage and width of 95% confidence intervals for ψ for each of the simulation settings. The coverage for all confidence intervals was 100% with intervals that were significantly wider than those generated by our proposed sensitivity analysis procedure. This indicates that the estimated regime is far more sensitive to differences in the bias

Table 12: Proportion of patients whose recommended treatment when following each of the estimated regimes resulting from G-estimation sensitivity analysis matches the recommendation of the true optimal regime for the 1-stage data generating model when we assume we know ξ_{11} and ξ_{12}.

Parameter Distr.	Proportion Optimal
Unadjusted	0.521
Narrow, Centered	0.930
Wide, Centered	0.923
Narrow, Off-center	0.929
Wide, Off-center	0.927

parameters for the G-estimation analysis. Table 13 displays the proportion of new patients who receive the same treatment as the true optimal regime under each of the estimated regimes. Even though the rMSE is greater for the estimate of ψ the estimated regime increases the optimal proportion from 0.524 to 0.903 for the narrow, correctly centered bias distribution. This is due to the direction of the bias in the estimate of ψ_0. The optimal proportion for the adjusted G-estimation analysis is still below the proposed Monte Carlo sensitivity analysis which resulted in 95.6% matching the optimal when using the same bias parameter distributions.

Table 13: Proportion of patients whose recommended treatment when following each of the estimated regimes resulting from G-estimation sensitivity analysis matches the recommendation of the true optimal regime for the 1-stage data generating model.

Parameter Distr.	Proportion Optimal
Unadjusted	0.524
Narrow, Centered	0.903
Wide, Centered	0.924
Narrow, Off-center	0.916
Wide, Off-center	0.921

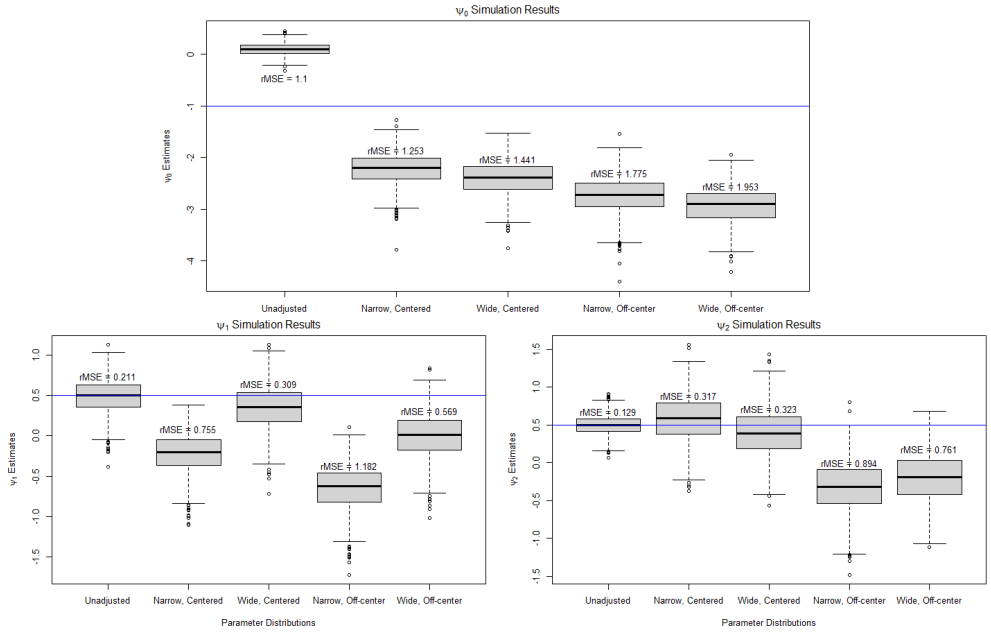

Figure 8: Boxplots of the point estimates for ψ under an unadjusted model and when using G-estimation sensitivity analysis to adjust for bias due to unmeasured confounding for the 1-stage data generating model.

Table 14: Coverage (Cvr.) and average width (Wth.) of the 95% confidence intervals for ψ for the G-estimation sensitivity analysis under each of the posited parameter distributions for the 1-stage data generating model. * indicates coverages that are significantly different than 95%.

Parameter Distr.	Cvr. (Wth.) ψ_0	Cvr. (Wth.) ψ_1	Cvr. (Wth.) ψ_2
Narrow, Centered	1.000* (10.430)	1.000* (9.785)	1.000* (16.789)
Wide, Centered	1.000* (18.999)	1.000* (18.419)	1.000* (19.947)
Narrow, Off-center	1.000* (10.081)	1.000* (9.552)	1.000* (16.241)
Wide, Off-center	1.000* (18.083)	1.000* (17.853)	1.000* (19.887)

E Alternative MCSA using KPWA Data

In the main paper, we evaluated assessing the bias in the estimated regime to reduce depression symptoms when obesity is unmeasured using EHR data from KPWA. For this analysis, we replicated using a secondary data set to posit models for the bias parameters by taking a random sample of 250 patients. We also conducted sensitivity analysis using the same outcome and unmeasured confounder models, but with different distributions posited for the bias parameters. We first estimated β_u and ζ using the full data. We then considered obesity to be unmeasured and posited normal distributions for β_u and ζ that are centered at the estimated values of the parameters with standard deviations equal to 0.05 for β_u, 0.05 for ζ_0, and 0.1 for ζ_j for $j = 1, \ldots, 6$. The smaller standard deviation for ζ_0 reflects that we have less uncertainty in the prevalence of obesity in our population of interest.

Table 15 contains estimates and confidence intervals for ψ after adjusting for the bias using the proposed MCSA as well as from the full model and the model with obesity unmeasured. The estimates of ψ after adjusting for the unmeasured obesity were close to the estimates from the full model with obesity included.

Table 15: Estimates and 95% confidence intervals for treatment decision rule parameters ψ from models with and without obesity and adjusted estimates from the sensitivity analysis for unmeasured confounding of obesity.

Covariate	Full Model	Obesity Unmeasured	Adjusted Est.
A	-1.56 (-3.11, 0.00)	-1.46 (-3.02, 0.10)	-1.57 (-3.33, 0.10)
$A \times$ SEX	0.72 (-0.34, 1.79)	0.69 (-0.38, 1.76)	0.73 (-0.59, 2.06)
$A \times$ AGE	0.00 (-0.03, 0.03)	0.00 (-0.03, 0.03)	0.00 (-0.04, 0.04)
$A \times$ PHQ	0.12 (0.02, 0.22)	0.12 (0.02, 0.22)	0.12 (0.01, 0.24)

F KPWA Data

Table 16: Estimated value of β and standard errors from the KPWA data used to generate the data for the plasmode simulation study.

Covariate	Estimate	Std. Error
Intercept	-0.85	0.58
SEX	-0.88	0.38
AGE	0.02	0.01
PHQ	-0.43	0.04
OBESE	-0.99	0.27

Table 17: Estimated value of ψ and standard errors from the KPWA data used to generate the data for the plasmode simulation study.

Covariate	Estimate	Std. Error
A	-1.56	0.79
A $\times$ SEX	0.72	0.54
A $\times$ AGE	0.00	0.01
A $\times$ PHQ	0.12	0.05

Table 18: Estimated value of ζ and standard errors from the KPWA data used to generate the data for the plasmode simulation study.

Covariate	Estimate	Std. Error
Intercept	-1.26	0.33
AGE	0.01	0.00
PHQ	0.04	0.01
Black	0.86	0.40
Hispanic	0.55	0.36
Hawaiian/Pacific Islander	1.35	0.68
Indigenous	0.32	0.49
White	0.58	0.27
Other Race	1.45	0.83
Unknown Race	0.81	0.43
EDU	0.46	0.11
ANX	-0.21	0.12
A	-0.49	0.13

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