Web-based Supplementary Materials for: "Post-randomization Biomarker Effect Modification in an HIV Vaccine Clinical Trial"

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1 Web Appendix A: Derivation of Nonparametric Identifiability Results Stated in Section 3.2

We derive results achieving nonparametric identifiability of $CEP(s_1, s_0)$ for $(s_1, s_0) \in \{(0,0),(1,0),(1,1)$, highlighting how **A4**, **A4′**, **A4″**, **A5**, and Case CB reduce the number of non-identified terms.

A1–A3, **A5**, *Variable Biomarker (VB)* $S^\tau(0)$. We start with a slightly weaker assumption set than scenario **NEE-VB**. Our objective is to estimate the three $CEP(s_1, s_0)$ parameters [for $(s_1, s_0) \in \{(0,0),(1,0),(1,1)\}$], by estimating each of the three risk pairs $\{risk_1(0,0), risk_0(0,0)\}$, $\{risk_1(1,1), risk_0(1,1)\}$, and $\{risk_1(1,0), risk_0(1,0)\}$. Because $(Y^\tau(1), S^\tau(1))$ and $(Y^\tau(0), S^\tau(0))$ are never both observed, these risk pairs are not identified from **A1–A3**, **A5**. Following Shepherd et al. (2011), without additional assumptions 3 sensitivity parameters are needed to nonparametrically identify each of the three risk pairs, totaling 9 sensitivity parameters. For example, define

$$\pi(s_1, s_0) \equiv P(S^\tau(1) = s_1, S^\tau(0) = s_0, Y^\tau(1) = Y^\tau(0) = 0),$$

$$\pi_1(s_1, s_0) \equiv P(S^\tau(1) = s_1, Y^\tau(1) = 0 | S^\tau(0) = s_0, Y^\tau(0) = 0, Y(0) = 1),$$

$$\pi_0(s_1, s_0) \equiv P(S^\tau(0) = s_0, Y^\tau(0) = 0 | S^\tau(1) = s_1, Y^\tau(1) = 0, Y(1) = 1).$$

Then $\{risk_1(0,0), risk_0(0,0)\}$, $\{risk_1(1,1), risk_0(1,1)\}$, and $\{risk_1(1,0), risk_0(1,0)\}$ are identified by the three triplets of parameters $\{\pi(0,0), \pi_1(0,0), \pi_0(0,0)\}$, $\{\pi(1,1), \pi_1(1,1),$

$\pi_0(1,1)\}$, and $\{\pi(1,0), \pi_1(1,0), \pi_0(1,0)\}$, respectively. From equation (2), each $risk_z$ for $z = 0, 1$ is also identified by these 9 sensitivity parameters because $p(s_1, s_0) = \pi(s_1, s_0)/$ $\{\pi(0,0) + \pi(1,1) + \pi(1,0)\}$. Other sensitivity parameterizations can also achieve identifiability, but at least 9 sensitivity parameters will still be required.

Under **A1–A3***,* **A4′***,* **A5***, Variable Biomarker* $S^\tau(0)$. Adding **A4′** to **A1–A3** and **A5**, $\pi(1,1)$ and $risk_0(1,1)$ are nonparametrically identified as $P(S^\tau(0) = 1, Y^\tau(0) = 0)$ and $P(Y(0) = 1|S^\tau(0) = 1, Y^\tau(0) = 0)$. Therefore, identifying $risk_1(1,1)$ requires only one sensitivity parameter, $\pi_0(1,1)$. Identifying $risk_z(0,0)$ for $z = 0, 1$ requires specifying three parameters, $\{\pi(0,0), \pi_1(0,0), \pi_0(0,0)\}$. Once $\pi(0,0)$ is specified, $\pi(1,0)$ is identified as $\pi(1,0) = P(S^\tau(0) = 0, Y^\tau(0) = 0) - \pi(0,0)$; also everyone with $\{S^\tau(0) = 0, Y^\tau(0) = 0\}$ who does not have $\{S^\tau(1) = 0, Y^\tau(1) = 0\}$ has to have $\{S^\tau(1) = 1, Y^\tau(1) = 0\}$, and therefore specifying $\pi_1(0,0)$ also fixes $\pi_1(1,0) = 1 - \pi_1(0,0)$ and thus identifies $risk_0(1,0)$. Hence, only one additional sensitivity parameter, $\pi_0(1,0)$, is needed to identify $risk_1(1,0)$, bringing the total number of sensitivity parameters to 5.

Under **A1–A5***, Variable Biomarker* $S^\tau(0)$ *[Scenario* **NEE-VB***].* Strengthening **A4′** to **A4**, $\pi(1,1)$ and $risk_0(1,1)$ are still nonparametrically identified, and identification of $risk_1(1,1)$ still requires only one sensitivity parameter, $\pi_0(1,1)$. This same sensitivity parameter also identifies $risk_1(1,0)$ as $\pi_0(1,0) = 1 - \pi_0(1,1)$ because by **A4** everyone with $(S^\tau(1) = 1, Y^\tau(1) = 0)$ must have $Y^\tau(0) = 0$. Then $\pi(0,0)$ and $risk_1(0,0)$ are also nonparametrically identified. Therefore, to identify $risk_0(0,0)$ only the sensitivity parameter $\pi_1(0,0)$ needs to be specified. As before under **A4′**, specifying $\pi_1(0,0)$ also identifies $risk_0(1,0)$. Hence a total of two sensitivity parameters are needed in scenario **NEE-VB**.

Under **A1–A4***, Constant Biomarker [Scenario* **NEE-CB***].* Scenario **NEE-CB** is similar to scenario **NEE-VB** except that now the cell $(S^\tau(0) = 1, S^\tau(1) = 1, Y^\tau(0) = 0, Y^\tau(1) = 0)$ is empty. This implies that $risk_z(1,1)$ is undefined, for $z = 0, 1$. Also, in addition to $risk_1(0,0)$ being identified, $risk_1(1,0)$ is now also nonparametrically identified. Similar to scenario **NEE-VB**, $risk_0(0,0)$ is identified with a sensitivity parameter $\pi_1(0,0)$ which then

also identifies $risk_0(1,0)$. Therefore, only one sensitivity parameter is needed for scenario **NEE-CB**.

Under **A1–A3***,* **A4′***, Constant Biomarker [Scenario* **NEH-CB***].* Identifiability is more challenging when relaxing **A4** to **A4′**, as 3 sensitivity parameters (e.g., $\pi(0,0), \pi_0(0,0)$, and $\pi_1(0,0)$) are needed to identify $\{risk_1(0,0), risk_0(0,0)\}$. The sensitivity parameters $\pi(0,0)$ and $\pi_1(0,0)$ also identify $risk_0(1,0)$. Moreover, one additional sensitivity parameter, $\pi_0(1,0)$, is required to identify $risk_1(1,0)$. Hence a total of 4 sensitivity parameters are needed.

Under **A1–A3***,* **A4″***, Constant Biomarker [Scenario* **NEB-CB***].* When relaxing **A4** to **A4″**, $risk_1(0,0)$ and $risk_1(1,0)$ remain nonparametrically identified. To identify $risk_0(0,0)$, similar to scenario **NEE-CB**, we need to specify a sensitivity parameter $\pi_1(0,0)$. However, unlike scenario **NEE-CB**, this additional parameter does not also identify $risk_0(1,0)$; to identify it, we need an additional sensitivity parameter $\pi_1(1,0)$. Therefore, a total of 2 sensitivity parameters are needed for identification.

2 Web Appendix B: Application of Chiba and VanderWeele's (2011) SACE Method for Evaluating a Binary Intermediate Response Endpoint as a Principal Stratification Effect Modifier Under Scenarios NEE-VB and NEE-CB

Under Scenario **NEE-VB**, we show how the simple SACE method of Chiba and VanderWeele (2011) can be applied to evaluate a binary intermediate response endpoint as a principal stratification effect modifier using an additive contrast $h(x,y) = x - y$. Define two sensitivity parameters α_k, $k = 0, 1$, by $\alpha_k \equiv P(Y(k) = 1|Z = 1, S_k = 1) - P(Y(k) = 1|Z = 0, S_k = 1)$ with $S_0 \equiv [1 - Y^\tau][1 - S^\tau]$ and $S_1 \equiv [1 - Y^\tau]S^\tau$. Then

$$\begin{aligned} CEP(k,k;\alpha_k) &= P(Y=1|Z=1,S_k=1) - P(Y=1|Z=0,S_k=1) - \alpha_k \quad (1) \\ &= \mu_{1k} - \mu_{0k} - \alpha_k \quad \text{for } k = 0,1. \end{aligned}$$

A simple approach to estimating each μ_{zk}, $(z,k) \in \{(0,0),(0,1),(1,0)\}$, solves $\sum_{i=1}^{n} R_i U_i^{0zk}(O_i;\mu_{zk})/\pi(O_i,\hat{\psi}) = 0$ with $U_i^{0zk}(O_i;\mu_{zk}) \equiv (1-Y_i^{\tau})I(Z_i = z)I(S_i^{\tau} = k)(Y_i - \mu_{zk})$. Then, $CEP(k,k;\alpha_k)$ is estimated by $\hat{\mu}_{1k} - \hat{\mu}_{0k} - \alpha_k$ where α_k is a known constant fixed by the user. Lastly, plugging the above estimates into equation (3) of the main article yields estimates of $risk_1(1,0;\alpha_1)$ and $risk_0(1,0;\alpha_0)$, and hence of $CEP(1,0;\alpha_0,\alpha_1)$.

By standard estimating equation theory, the above estimators are consistent and asymptotically normal for given fixed α_0 and α_1. To obtain Wald confidence intervals for each $CEP(s_1,s_0;\alpha_0,\alpha_1)$, consistent sandwich variance estimators may be used, e.g., the estimated variance of μ_{zk} for each $k = 0,1$ is given by $\sum_{i=1}^{n}\left(R_i/\pi(O_i,\hat{\psi})\right)\left[U_i^{0zk}(O_i;\hat{\mu}_{zk})\right]^2$. The estimated variance of $\hat{CEP}(1,0)$ may be obtained by the delta method.

To perform a sensitivity analysis, the user may specify a plausible range $[l_k,u_k]$ (or maximum possible) for each α_k, $k = 0,1$. An ignorance interval for $CEP(s_1,s_0)$ may be calculated as the minimum and maximum estimates (obtained with α_0 and α_1 set to the boundary values). Using the method of Imbens and Manski (2004) and Vansteelandt et al. (2006), a Wald asymptotic (1-α)% estimated uncertainty interval (EUI) for $CEP(s_1,s_0)$ may be calculated as in formulas (40) and (41) of Richardson et al. (2014), using the variance estimates of the minimum and maximum $CEP(s_1,s_0)$ estimates. This approach requires that $CEP(k,k;\alpha_k)$ is monotone in α_k, which holds by (1).

3 Web Appendix C: Adapting the SACE Methods for a Time-to-Event Outcome with Right-Censoring

The approach to estimation of $CEP(0,0)$, $CEP(1,0)$, and $CEP(1,1)$ using the published SACE methods described above is similar if the binary outcome Y is defined as $Y \equiv I(T \leq t)$ with T subject to right-censoring and t is a fixed time point of interest. The estimating equations used to estimate the needed terms are the same as those described above, except that new estimating functions $U(O_i;\cdot)$ are swapped into the equations that are designed to

handle the right-censoring. For example, consider the first estimating equation in Section 5.2 of the main article, $\sum_{i=1}^{n} U_i^{0z}(O_i; risk_z) = 0$. With $Y \equiv I(T \leq t)$, the same estimating equation can be used swapping in the estimating function of the Kaplan-Meier estimator (Reid, 1981) or of the targeted maximum likelihood estimator of a survival curve (Moore and van der Laan, 2009). The same type of swap is made for the other estimating equations. For implementing the IPW GBH SACE Method approach, as described in Shepherd et al. (2006, 2011), a modification to the weight functions $w_z(\cdot; \alpha_z, \beta_z)$ is needed, where now they are indexed by time t: $w_z(t; \alpha_z, \beta_z) = \{1 + \exp(-\alpha_z - \beta_z \min(t, \nu))\}^{-1}$, where ν is near the end of follow-up. In addition, the summation $\sum_{y=0}^{1} w_0(y; \alpha_0, \beta_0)\hat{P}(Y(0) = y|S(0) = 1)$ in equation (4) of the main article is changed to $\int_0^{\infty} w_0(t; \alpha_0, \beta_0)\hat{P}(T(0) \leq t|S(0) = 1)$ and the summation $\sum_{y=0}^{1} w_1(y; \alpha_1, \beta_1)\hat{P}(Y(1) = y|S(1) = 1)$ in equation (5) of the main article is changed to $\int_0^{\infty} w_1(t; \alpha_1, \beta_1)\hat{P}(T(1) \leq t|S(1) = 1)$.

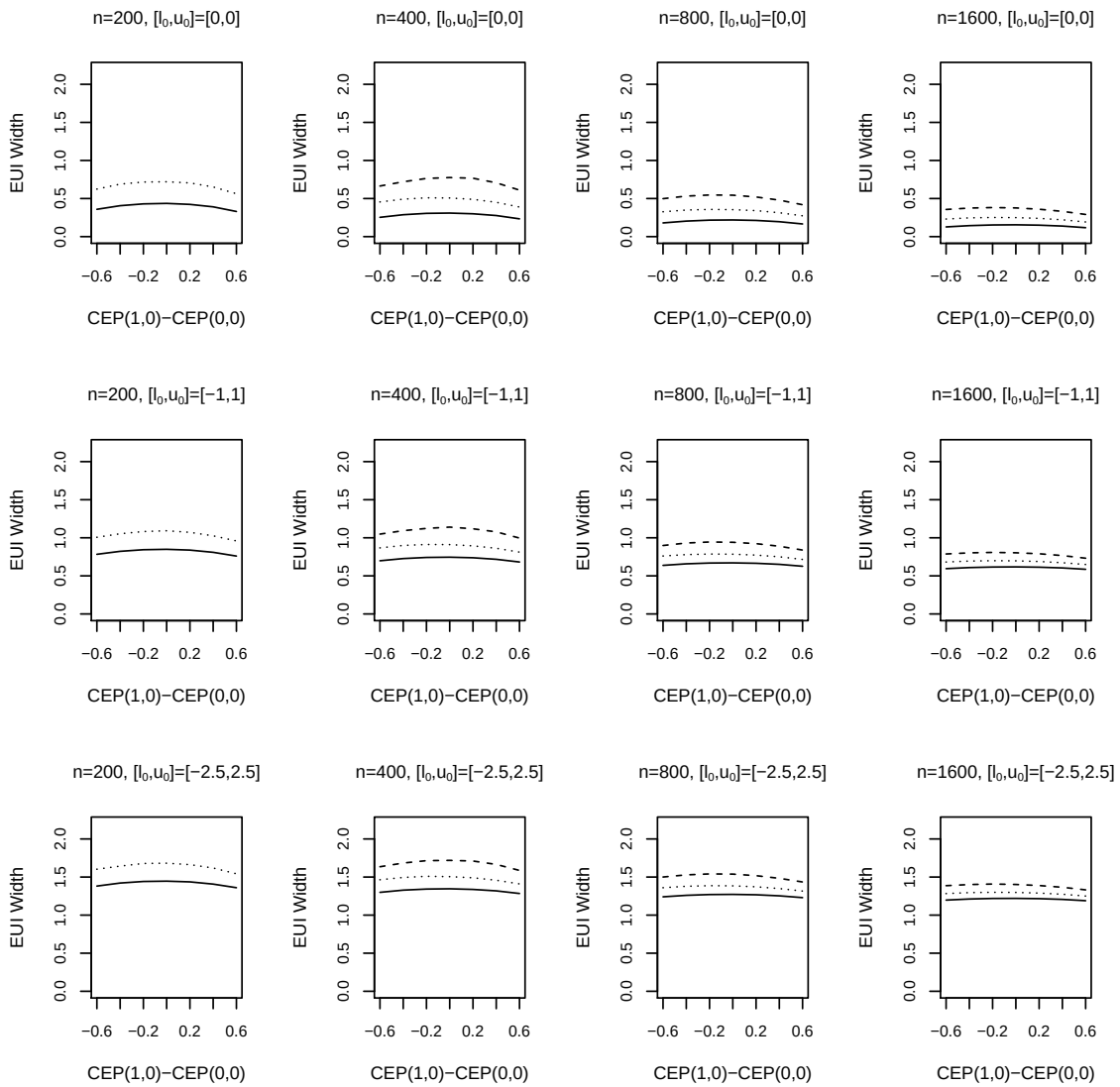
4 Web Appendix D: Additional Figures Showing Results of the First and Second Simulation Studies, and Details of the Second Simulation Study

Web Figures 1–4 present results for the first simulation study.

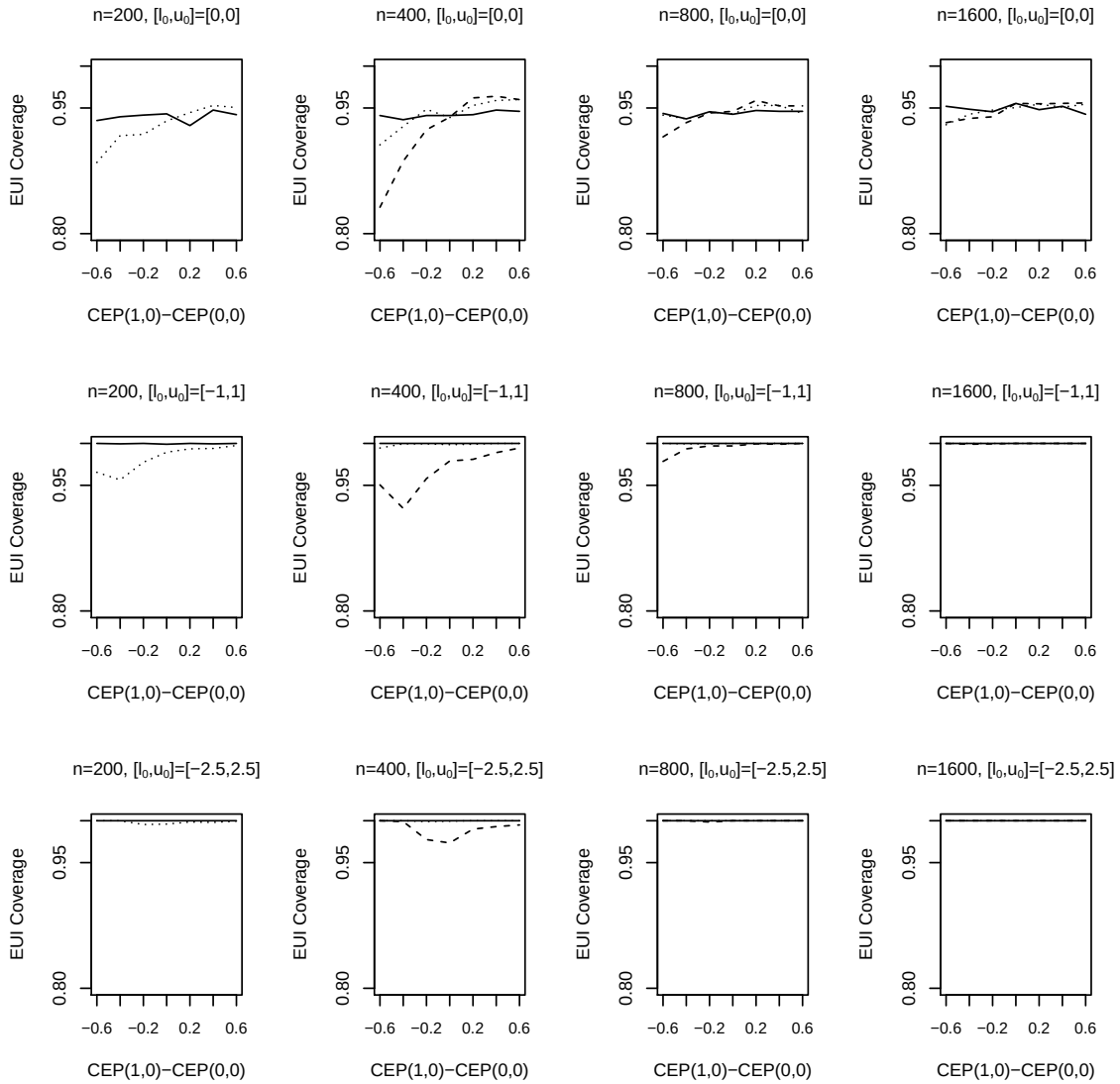
Web Figures 5–9 present results for the second simulation study. Here we provide details for the second simulation study. In this second study, data were simulated under scenario **NEH-CB** (**A1–A3**, **A4′**, Case CB) such that **A4** in scenario **NEE-CB** failed. First $(Y^{\tau}(1), Y^{\tau}(0))$ was set to (0,0), (0,1), or (1,1) with probabilities 0.7, 0.2, and 0.1, such that **A4′** (**NEH**) holds. If $Y^{\tau}(z) = 1$, then $Y(z)$ was set to 1, for $z = 0, 1$. Similar to the first simulation, if $(Y^{\tau}(1), Y^{\tau}(0)) = (0, 0)$, then $(S^{\tau}(1), S^{\tau}(0))$ was set to (0,0) or (1,0) with probabilities 0.4 and 0.6. If $(Y^{\tau}(1), Y^{\tau}(0)) = (0, 1)$, then $S^{\tau}(1)$ was set to 0 or 1 with probabilities 0.4 and 0.6. Data were otherwise simulated the same as for the first simulation (e.g., $Y(1)$, $Y(0)$, Z, other observed data). Analyses used $[l_j, u_j] \in \{[0, 0], [-0.5, 0.5], [-1, 1]\}$ for $j = 0, 2, 3, 4$. As for the **NEE-CB** simulations, all data sets were simulated under no

selection bias.

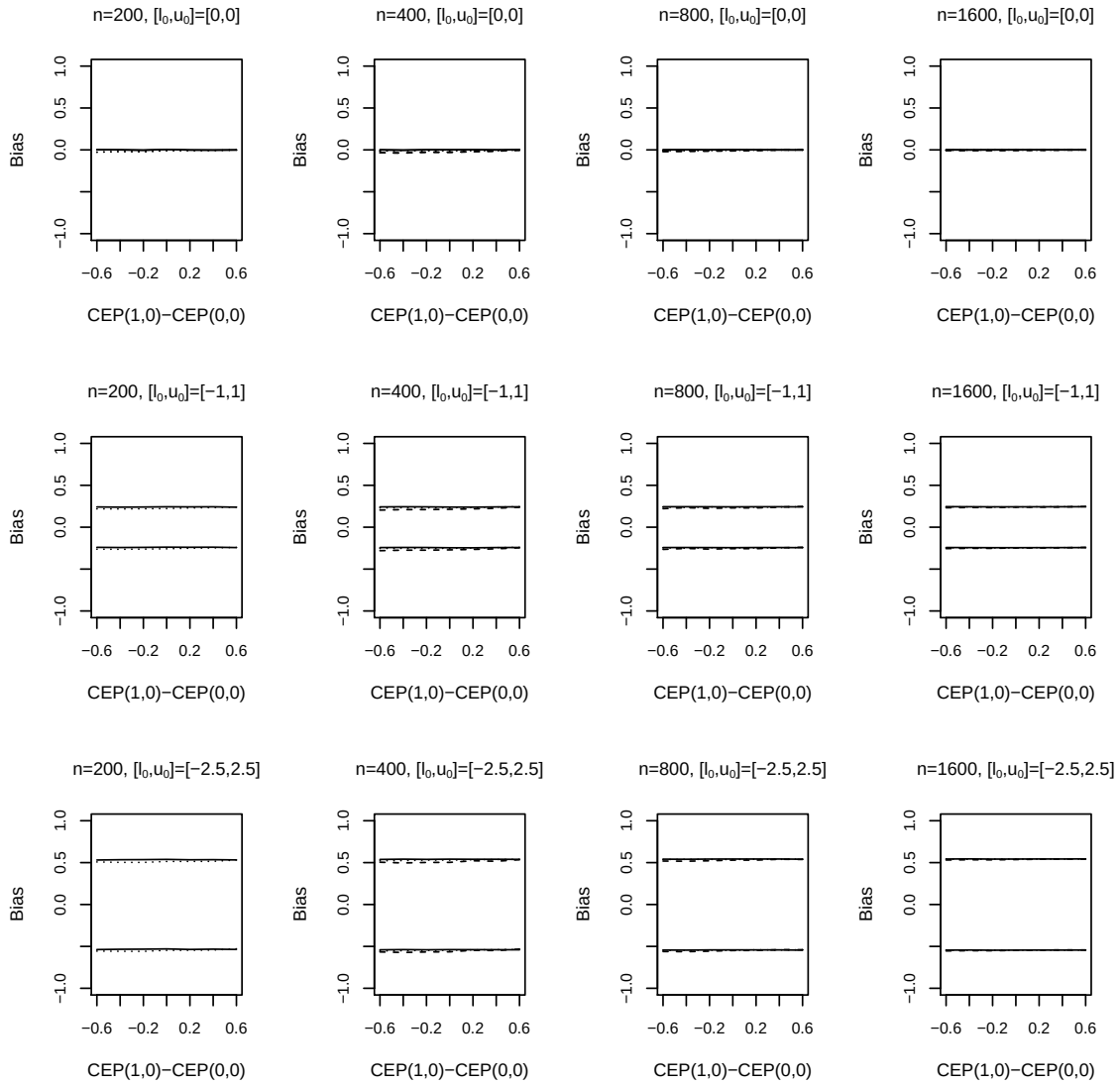
Results based on 2000 simulated data sets are shown in Web Figures 5–9. As for the methods under scenario **NEE-CB**, power and precision diminished as the interval $[l_0, u_0]$ became wider and the subcohort size decreased.



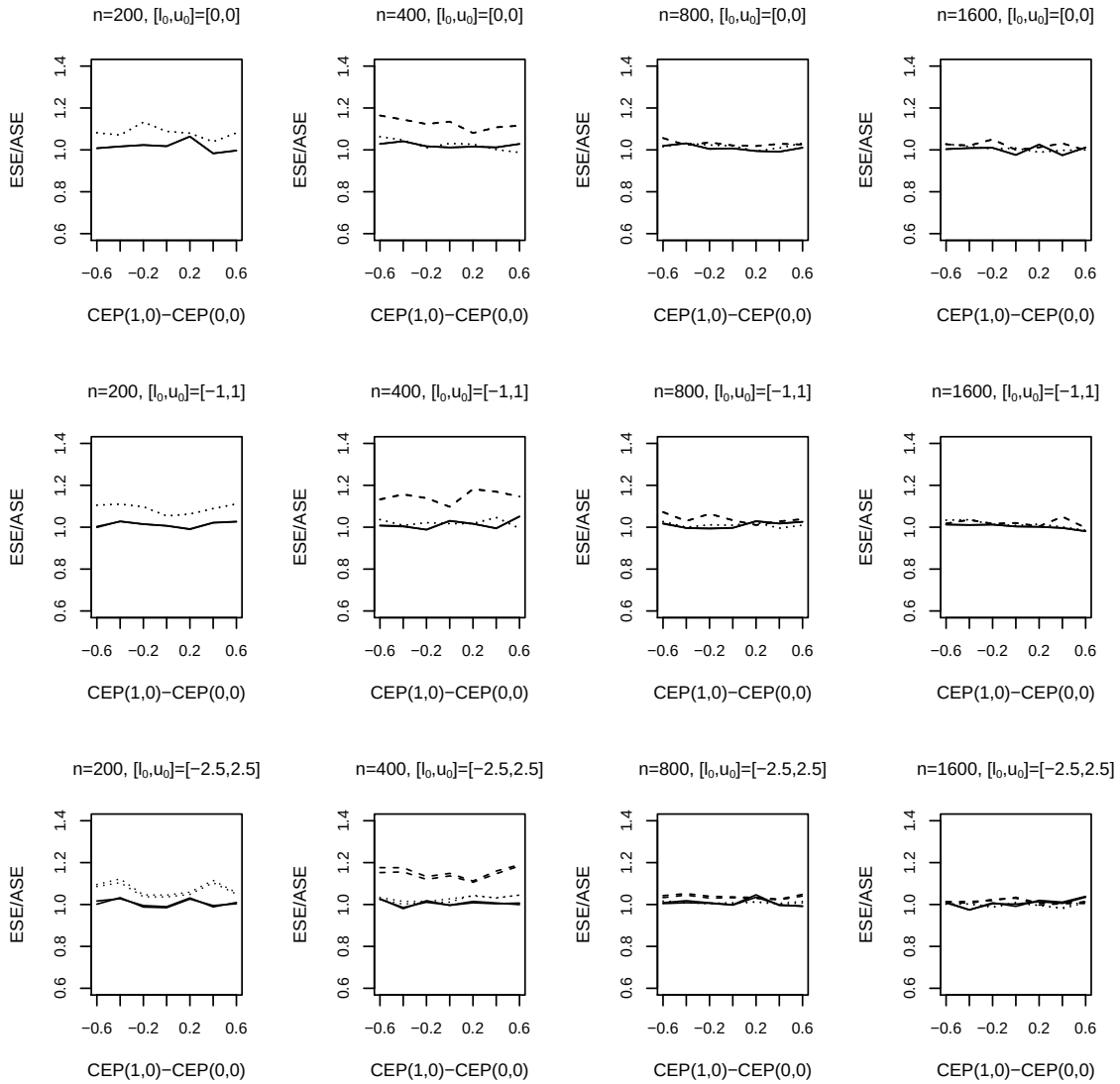
Web Figure 1. Average 95% EUI width for the first simulation study for methods with Scenario **NEE-CB** assumptions. Solid lines denote full cohort and dashed (dotted) lines denote case-cohort with 10% (25%) random subcohort.



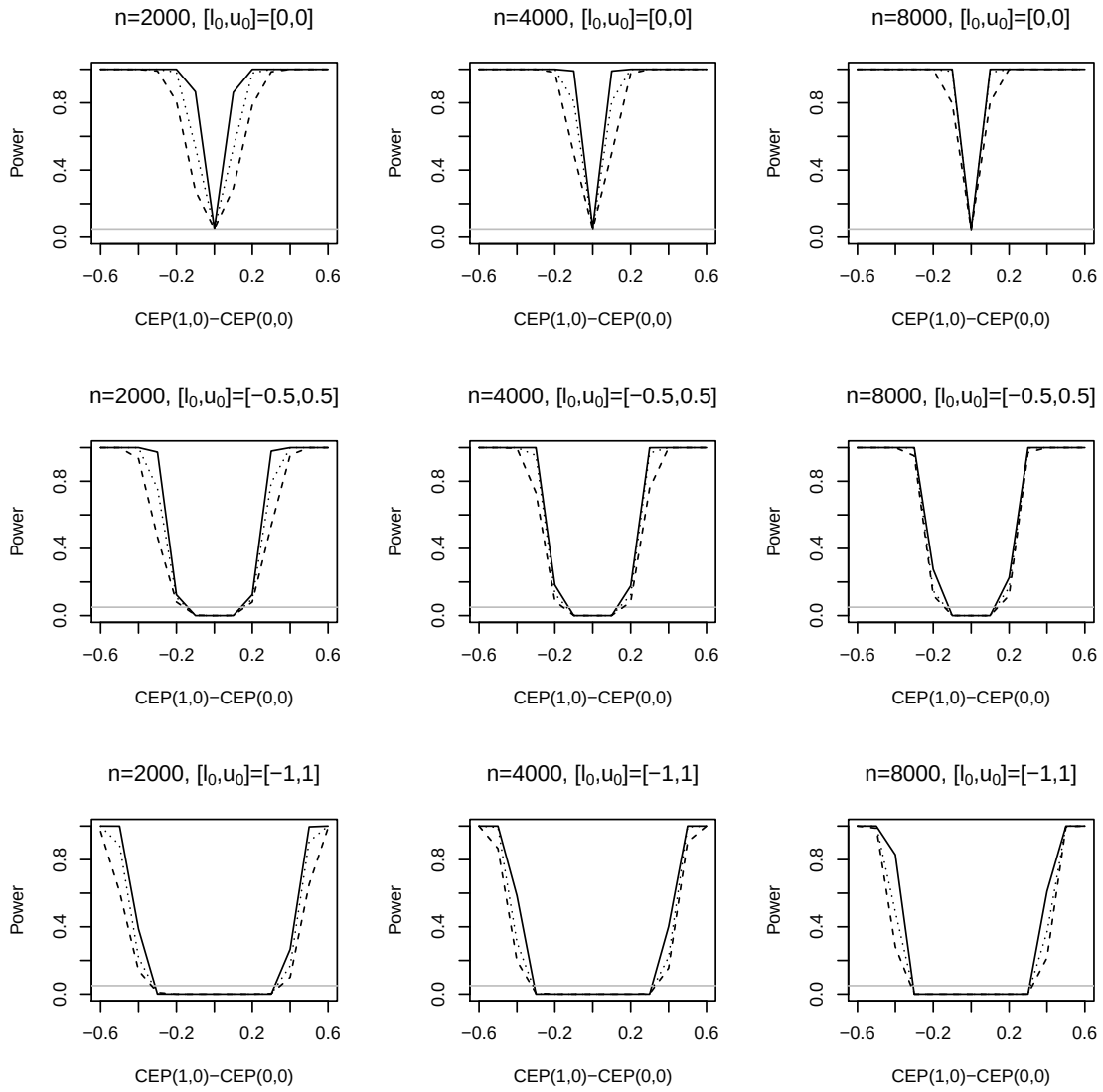
Web Figure 2. 95% EUI coverage for the first simulation study for methods with Scenario **NEE-CB** assumptions. Solid line denotes full cohort, dashed (dotted) line denotes case-cohort with 10% (25%) random subcohort.



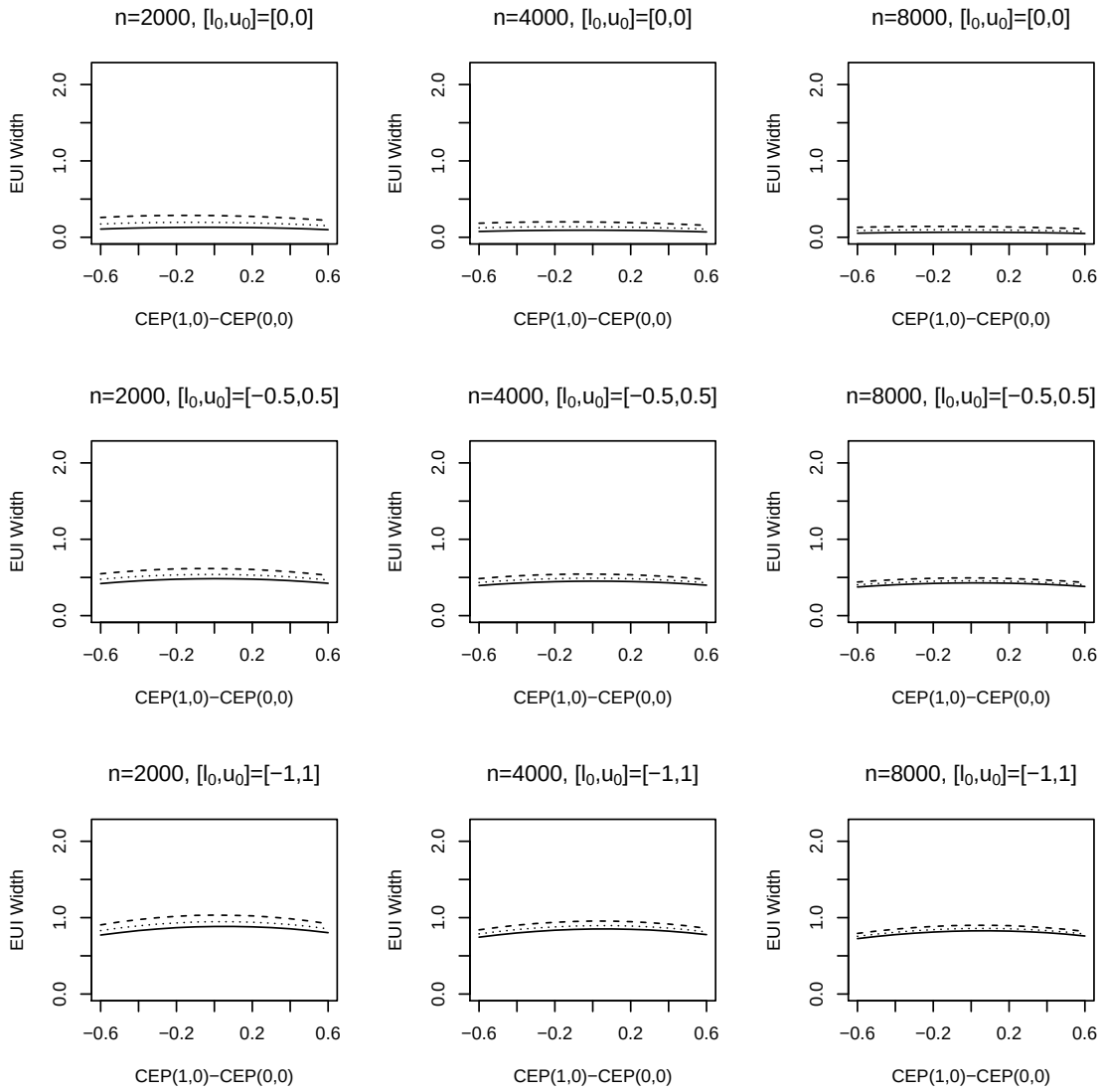
Web Figure 3. Bias for the first simulation study for methods under Scenario **NEE-CB** assumptions. The middle and lower panels show bias of the minimum and maximum estimates of $CEP(1,0) - CEP(0,0)$ over the plausible region $\Gamma = [l_0, u_0]$ of the sensitivity parameter β_0. Solid line denotes full cohort, dashed (dotted) line denotes case-cohort with 10% (25%) random subcohort.



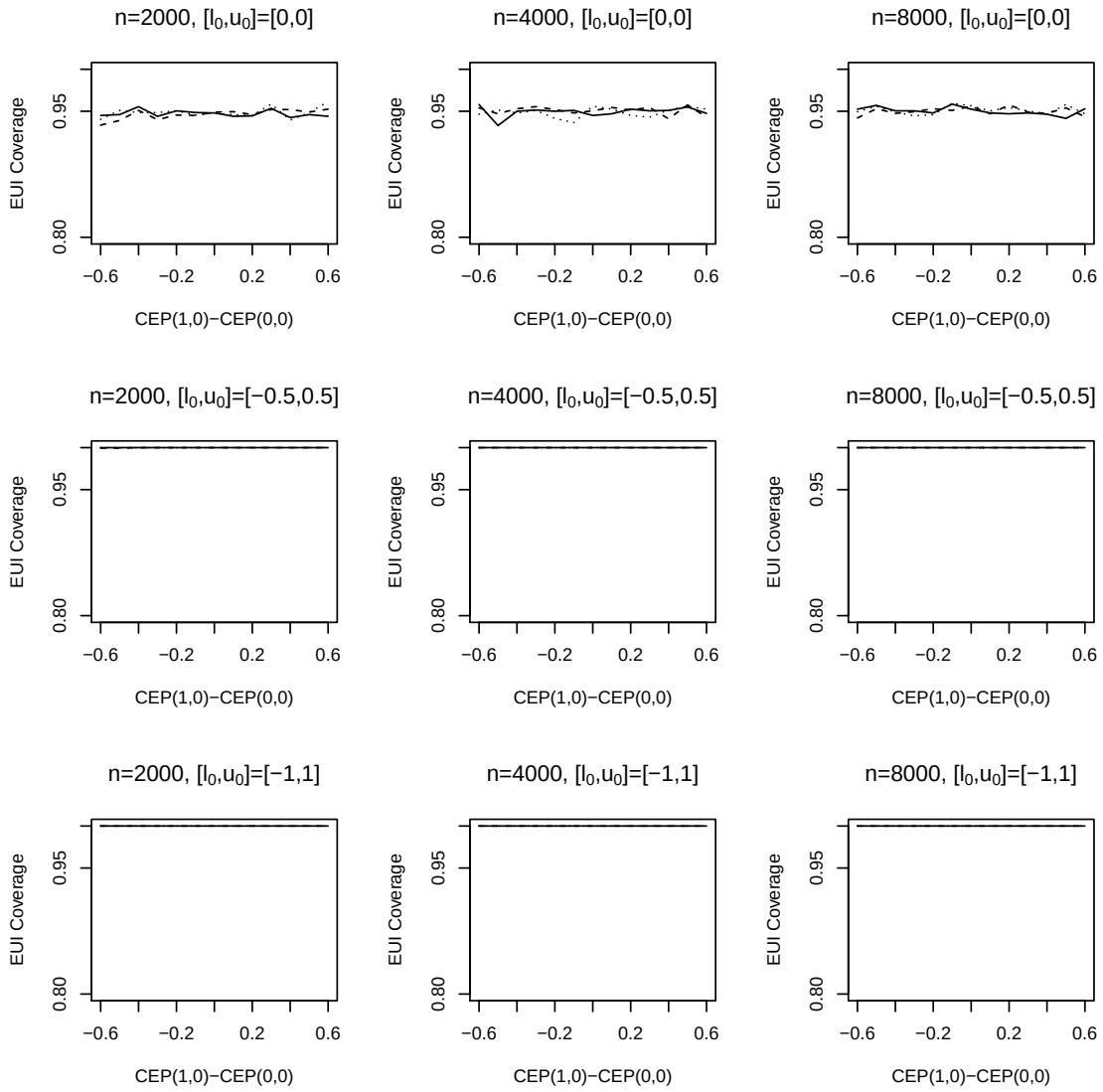
Web Figure 4. Ratio of empirical standard error (ESE) to average estimated standard error (ASE) for the first simulation study for methods under Scenario **NEE-CB** assumptions. Solid line denotes full cohort, dashed (dotted) line denotes case-cohort with 10% (25%) random subcohort.



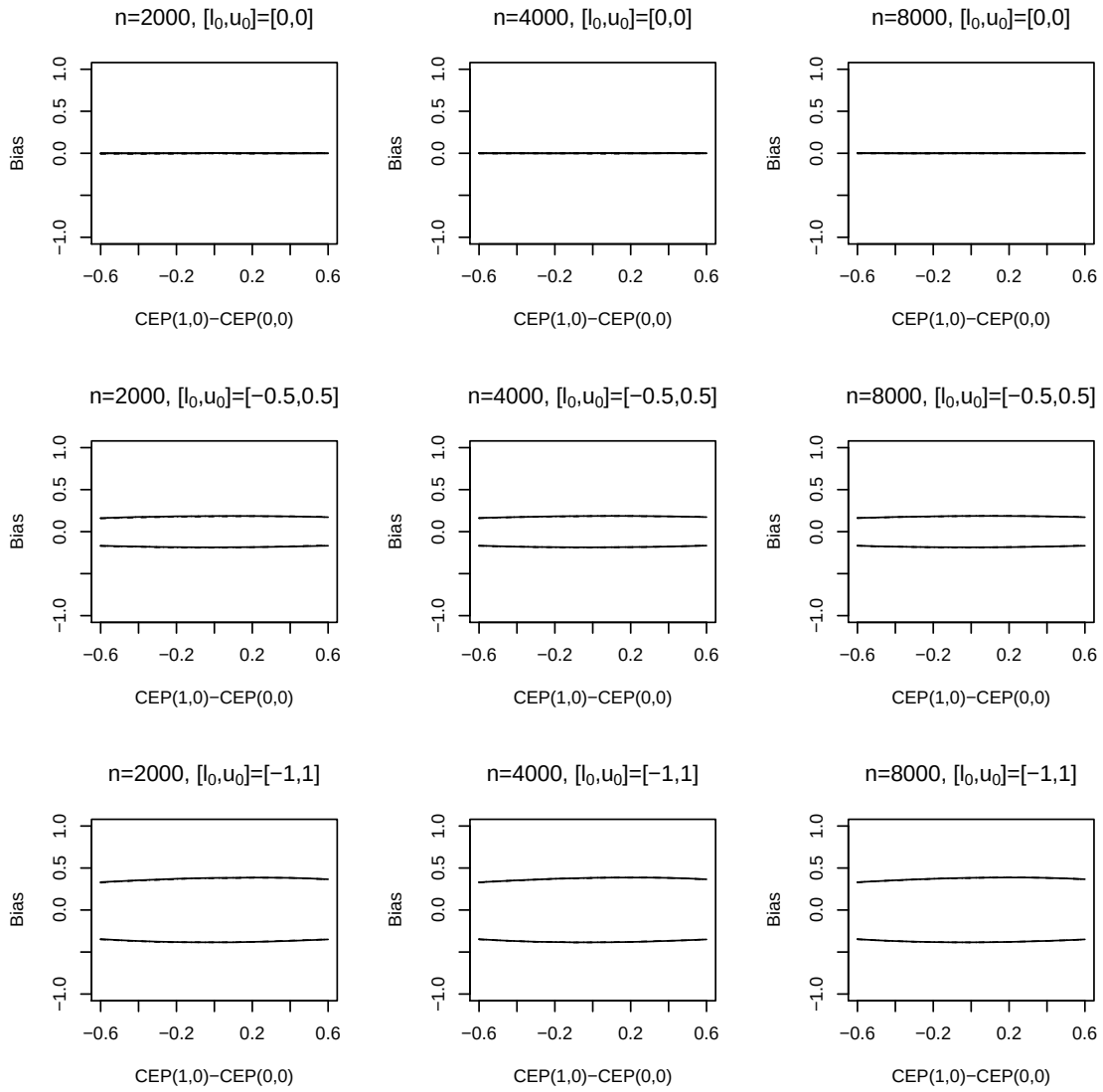
Web Figure 5. Power to reject $H_0 : \mu = CEP(1,0) = CEP(0,0)$ for the second simulation study for methods under Scenario **NEH-CB** assumptions. Solid black lines denote full cohort and dashed (dotted) lines denote case-cohort with 10% (25%) random subcohort. Horizontal gray lines denote significance level 0.05.



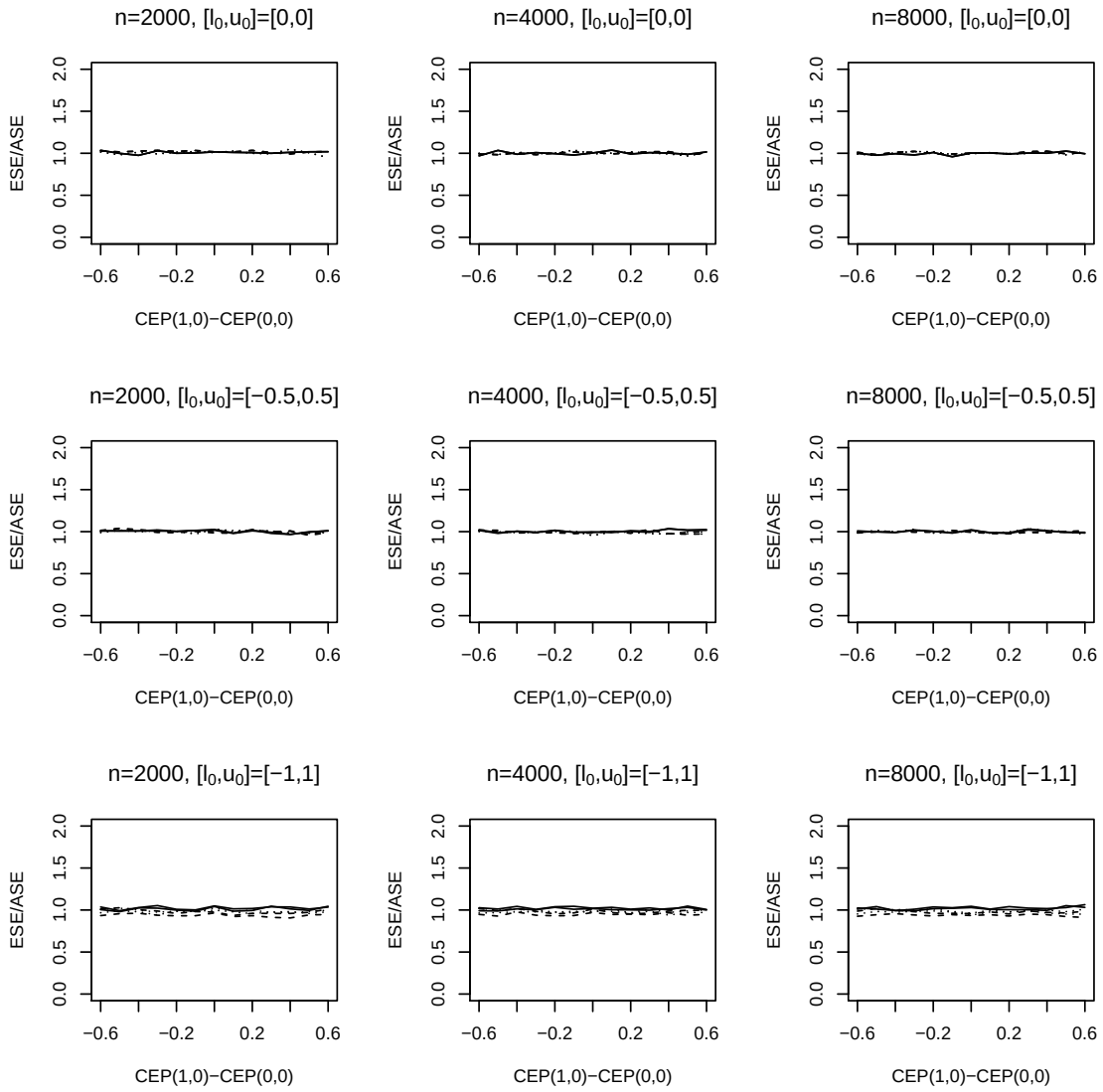
Web Figure 6. Average 95% EUI width for the second simulation study for methods under Scenario **NEH-CB** assumptions. Solid lines denote full cohort and dashed (dotted) lines denote case-cohort with 10% (25%) random subcohort.



Web Figure 7. 95% EUI coverage for the second simulation study for methods under Scenario **NEH-CB** assumptions. Solid line denotes full cohort, dashed (dotted) line denotes case-cohort with 10% (25%) random subcohort.



Web Figure 8. Bias for the second simulation study for methods under Scenario **NEH-CB** assumptions. The middle and lower panels show bias of the minimum and maximum estimates of $CEP(1,0) - CEP(0,0)$ over the plausible region $\Gamma = [l_0, u_0]$ of the sensitivity parameter β_0. Solid line denotes full cohort, dashed (dotted) line denotes case-cohort with 10% (25%) random subcohort.



Web Figure 9. Ratio of empirical standard error (ESE) to average estimated standard error (ASE) for the second simulation study for methods under Scenario **NEH-CB** assumptions. Solid line denotes full cohort, dashed (dotted) line denotes case-cohort with 10% (25%) random subcohort.

5 Web Appendix E: Additional Analyses for the HVTN 505 Application

5.1 Explanation of How the Results of the HVTN 505 Application are Very Similar for the Scenario NEE-CB and NEB-CB Methods

In this web appendix we show that under the condition $P(Y(0) = 1|Y^{\tau}(1) = 1, Y^{\tau}(0) = 0) = P(Y(0) = 1|Y^{\tau}(1) = 0, Y^{\tau}(0) = 0)$, then the scenario **NEE-CB** and scenario **NEB-CB** methods are equivalent. The typical estimand of interest in the article, $CEP(1,0) - CEP(0,0)$, is a function of $risk_1(1,0), risk_1(0,0), risk_0(1,0),$ and $risk_0(0,0)$. Under the set-up for scenario **NEB-CB** in the application section, we switch the direction of the monotonicity assumption which, when combined with Case CB, identifies $risk_1(1,0)$ and $risk_1(0,0)$. Thus, $risk_1(1,0)$ and $risk_1(0,0)$ are estimated in exactly the same way for the two scenarios:

$$\begin{aligned}\hat{risk}_1(j,0) &= \hat{P}(Y(1) = 1|S^{\tau}(1) = j, S^{\tau}(0) = 0, Y^{\tau}(1) = 0, Y^{\tau}(0) = 0) \\ &= \hat{P}(Y(1) = 1|S^{\tau}(1) = j, Y^{\tau}(1) = 0) \\ &= \hat{P}(Y = 1|S^{\tau} = j, Y^{\tau} = 0, Z = 1), \quad j = 0, 1.\end{aligned}$$

Therefore the results under each scenario will only differ in estimation of $risk_0(1,0)$ and $risk_0(0,0)$.

Scenario **NEE-CB**. Under scenario **NEE-CB**, $risk_0(1,0)$ and $risk_0(0,0)$ are estimated with a SACE method equivalent to solving the following mixing equations:

$$exp(\beta_0) = \frac{risk_0(0,0)/(1 - risk_0(0,0))}{risk_0(1,0)/(1 - risk_0(1,0))}$$

and

$$risk_0 = p(0,0)risk_0(0,0) + (1 - p(0,0))risk_0(1,0),$$

where $risk_0$ and $p(0,0)$ are identifiable under the assumptions of scenario **NEE-CB**. By

NEE, we estimate:

$$\begin{aligned}\hat{risk}_0 &= \hat{P}(Y(0)=1|Y^\tau(1)=0, Y^\tau(0)=0)\\ &= \hat{P}(Y(0)=1|Y^\tau(0)=0) = \hat{P}(Y=1|Y^\tau=0, Z=0),\end{aligned}$$

which is solved by the estimating equation

$$\sum_i (1-Z_i)(1-Y_i^\tau)(Y - risk_0) = 0.$$

In addition, by **NEE** and Case CB,

$$\begin{aligned}\hat{p}(0,0) &= \hat{P}(S^\tau(1)=0, S^\tau(0)=0|Y^\tau(1)=0, Y^\tau(0)=0)\\ &= \hat{P}(S^\tau(1)=0|Y^\tau(1)=0) = \hat{P}(S^\tau=0|Y^\tau=0, Z=1),\end{aligned}$$

which is solved by the estimating equation

$$\sum_i Z_i(1-Y_i^\tau)(1-S^\tau - p(0,0)) = 0.$$

Then $risk_0(1,0)$, and $risk_0(0,0)$ are estimated by solving the mixing equations once β_0 is specified.

Scenario **NEB-CB**. Under scenario **NEB-CB**, we relax the **NEE** assumption $[P(Y^\tau(1) = Y^\tau(0)) = 1]$ to **NEB** $[P(Y^\tau(1) \geq Y^\tau(0)) = 1]$. Now, $risk_0 = P(Y(0) = 1|Y^\tau(1) = Y^\tau(0) = 0)$ is no longer identifiable. So first, an intermediate SACE method must be performed to estimate $risk_0$, and then the same SACE method as above is performed to estimate $risk_0(1,0)$ and $risk_0(0,0)$. We can write mixing equations in a similar form to those in the previous section, with new sensitivity parameter β_5 defined in assumption **B.5** of the main text:

$$exp(\beta_5) = \frac{risk_0/(1-risk_0)}{P(Y(0)=1|Y^\tau(1)=1, Y^\tau(0)=0)/(1-P(Y(0)=1|Y^\tau(1)=1, Y^\tau(0)=0))}$$

and

$$\begin{aligned}P(Y(0)=1|Y^\tau(0)=0) &= P(Y^\tau(1)=0|Y^\tau(0)=0)risk_0\\ &\quad + P(Y^\tau(1)=1|Y^\tau(0)=0)P(Y(0)=1|Y^\tau(1)=1, Y^\tau(0)=0)\end{aligned}$$

where $P(Y^\tau(1) = 1|Y^\tau(0) = 0) = 1 - P(Y^\tau(1) = 0|Y^\tau(0) = 0)$. Note that $\beta_5 = 0$ expresses the equality $P(Y(0) = 1|Y^\tau(1) = 1, Y^\tau(0) = 0) = P(Y(0) = 1|Y^\tau(1) = 0, Y^\tau(0) = 0)$. Now, when $\beta_5 = 0$, we estimate

$$\begin{aligned}\hat{risk}_0 &= \hat{P}(Y(0) = 1|Y^\tau(1) = 1, Y^\tau(0) = 0) \\ &= \hat{P}(Y(0) = 1|Y^\tau(0) = 0) = \hat{P}(Y = 1|Y^\tau = 0, Z = 0),\end{aligned}$$

which is found by solving the same estimating equation as in scenario **NEE-CB**:

$$\sum_i (1 - Z_i)(1 - Y_i^\tau)(Y - risk_0) = 0.$$

Therefore the estimate for $risk_0$ in scenario **NEB-CB** will be the same as that in scenario **NEE-CB** when $\beta_5 = 0$. In addition, the estimate for $p(0, 0)$ under scenario **NEB-CB** will be the same as that under scenario **NEE-CB** by monotonicity and Case CB:

$$\begin{aligned}\hat{p}(0, 0) &= \hat{P}(S^\tau(1) = 0, S^\tau(0) = 0|Y^\tau(1) = 0, Y^\tau(0) = 0) \\ &= \hat{P}(S^\tau(1) = 0|Y^\tau(1) = 0) = \hat{P}(S^\tau = 0|Y^\tau = 0, Z = 1),\end{aligned}$$

which is solved by the same estimating equation:

$$\sum_i Z_i(1 - Y_i^\tau)(1 - S^\tau - p(0, 0)) = 0.$$

After estimating these terms, $risk_0(1, 0)$ and $risk_0(0, 0)$ are estimated via the same SACE method described for scenario **NEE-CB**. We have shown that when $\beta_5 = 0$, the estimated $risk_0$ and $p(0, 0)$ used in the mixing equations will be the same as those estimated in scenario **NEE-CB**. Thus, the estimated $risk_0(1, 0)$ and $risk_0(0, 0)$ (as well as the estimate of $CEP(1, 0) - CEP(0, 0)$) will be the same under each scenario when $\beta_5 = 0$.

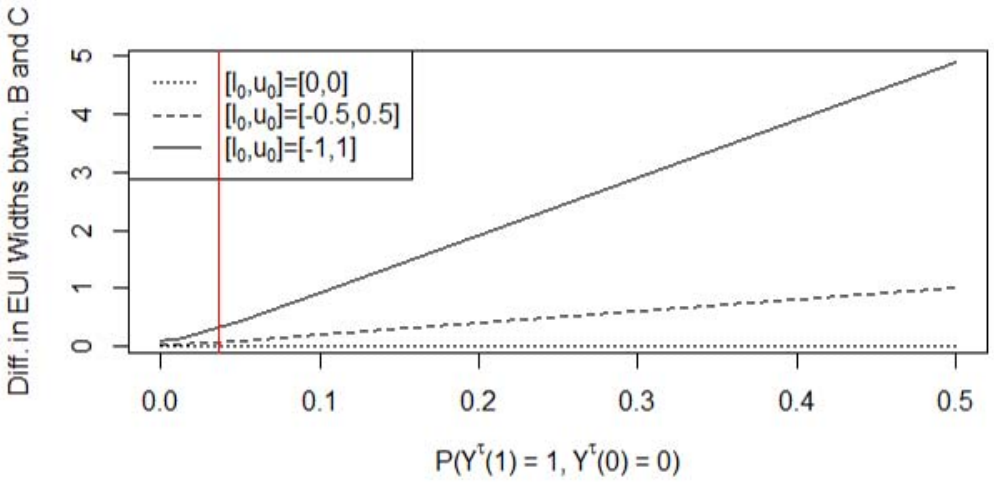
As β_5 moves further away from 0, the estimates for $risk_0$ will become more different between the two methods, as will the subsequent results. Note that this is different from what was described in the main article about the scenario **NEH-CB** method, which is more complex due to the monotonicity assumption being in the usual direction.

As described in the application section of the main text, there may be situations where it is not clear whether the assumptions of scenario **NEE-CB** or **NEB-CB** hold for the data being used. We study this issue by simulating the difference in EUI widths for the two scenarios under various supposed values of $P(Y^{\tau}(1) = 1, Y^{\tau}(0) = 0)$, which is implicitly assumed to be 0 under Scenario **NEE-CB**, but not under scenario **NEB-CB**. Each point on the plot in Web Figure 9 is the average of the differences in EUI widths calculated across 100 simulations. The red line represents the estimated value of $P(Y^{\tau}(1) = 1, Y^{\tau}(0) = 0)$ for the HVTN 505 data set analyzed in the application section.

For data sets with a small estimated value of $P(Y^{\tau}(1) = 0, Y^{\tau}(0) = 1)$, we would expect the two methods to give very similar results, with the intervals from scenario **NEB-CB** being only slightly wider than those from scenario **NEE-CB**. For such data sets it may be unclear whether to analyze under scenario **NEE-CB** or scenario **NEB-CB**. In general, justification for use of the scenario **NEE-CB** method would need to come from knowledge that the **NEE** assumption is plausibly true. In addition, use of the **NEB-CB** method would require knowledge that A7′ is plausible.

5.2 Comparison of results in the Application for scenarios NEE-CB or NEB-CB under different early infection data distributions

Web Figure 10 shows the identical results as Figure 2 in the main article, except conducting the analysis under scenario **NEE-CB** instead of under scenario **NEB-CB**



Web Figure 10. Difference in 95% EUI width for the HVTN 505 application in the main article for analysis under scenario **NEE-CB** (labeled B on the y-axis) versus under scenario **NEB-CB** (labeled C on the y-axis).

6 Web Appendix F: R Computer code

R code is provided on the first author's website that implements the simulation studies and the data analysis of the HVTN 505 study:

`http://faculty.washington.edu/peterg/programs.html?`

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