Appendix A

Let X be a treatment variable, Z be an outcome variable, and r_z be a mapping variable from X to Z. To represent the four potential response types, we introduce a vector of potential response variables $r_z = (Z_{x_1}, Z_{x_0}) = (z_i, z_j)$ $(i, j = 1, 0)$. Then, 'doomed', 'causative', 'preventive' and 'immune' are represented by (z_1, z_1), (z_1, z_0), (z_0, z_1), (z_0, z_0), respectively. Similarly, let X be a treatment variable, Y be an outcome variable, and $r_{y|z_k}$ be a mapping variable from X to Y when Z is fixed to z_k $(k = 1, 0)$. We introduce another vector of potential response variables $r_{y|z_k} = (Y_{x_1,z_k}, Y_{x_0,z_k}) = (y_i, y_j)$ $(i, j = 1, 0)$. Then, 'doomed', 'causative', 'preventive' and 'immune' in this context are represented by (y_1, y_1), (y_1, y_0), (y_0, y_1), (y_0, y_0), respectively. Table 1 summarizes the 64 potential response types.

[Table 1 about here.]

Using the potential response types, we can rewrite equation (2) as

$$\begin{aligned} ACDE(z_0) &= \mathrm{pr}(Y_{x_1,z_0} = y_1) - \mathrm{pr}(Y_{x_0,z_0} = y_1) \\ &= \sum_{i=1}^{4}\sum_{k=1}^{4}\left(\sum_{j\in\{1,2\}} q_{ijk} - \sum_{j\in\{1,3\}} q_{ijk}\right) \end{aligned} \quad \text{(A.1)}$$

$$\begin{aligned} ACDE(z_1) &= \mathrm{pr}(Y_{x_1,z_1} = y_1) - \mathrm{pr}(Y_{x_0,z_1} = y_1) \\ &= \sum_{i=1}^{4}\sum_{j=1}^{4}\left(\sum_{k\in\{1,2\}} q_{ijk} - \sum_{k\in\{1,3\}} q_{ijk}\right) \end{aligned} \quad \text{(A.2)}$$

In addition, the observed joint probability distribution of Y and Z given X, i.e., $\mathrm{pr}(y, z|x)$, can also be represented by using potential response types on the basis of the consistent property (Pearl, 2000), i.e., $X = x \Rightarrow Y_x = Y$. These are shown as equations (A.3)-(A.12), which are consistent with Kaufman et al. (2005).

$$\mathrm{pr}(y_0, z_0|x_0) = \sum_{i\in\{2,4\}} \sum_{j\in\{2,4\}} \sum_{k=1}^{4} q_{ijk} \tag{A.3}$$

$$\mathrm{pr}(y_0, z_1|x_0) = \sum_{i\in\{1,3\}} \sum_{j=1}^{4} \sum_{k\in\{2,4\}} q_{ijk} \tag{A.4}$$

$$\mathrm{pr}(y_1, z_0|x_0) = \sum_{i\in\{2,4\}} \sum_{j\in\{1,3\}} \sum_{k=1}^{4} q_{ijk} \tag{A.5}$$

$$\mathrm{pr}(y_1, z_1|x_0) = \sum_{i\in\{1,3\}} \sum_{j=1}^{4} \sum_{k\in\{1,3\}} q_{ijk} \tag{A.6}$$

$$\mathrm{pr}(y_0, z_0|x_1) = \sum_{i\in\{3,4\}} \sum_{j\in\{3,4\}} \sum_{k=1}^{4} q_{ijk} \tag{A.7}$$

$$\mathrm{pr}(y_0, z_1|x_1) = \sum_{i\in\{1,2\}} \sum_{j=1}^{4} \sum_{k\in\{3,4\}} q_{ijk} \tag{A.8}$$

$$\mathrm{pr}(y_1, z_0|x_1) = \sum_{i\in\{3,4\}} \sum_{j\in\{1,2\}} \sum_{k=1}^{4} q_{ijk} \tag{A.9}$$

$$\mathrm{pr}(y_1, z_1|x_1) = \sum_{i\in\{1,2\}} \sum_{j=1}^{4} \sum_{k\in\{1,2\}} q_{ijk} \tag{A.10}$$

$$\sum_{i=1}^{4}\sum_{j=1}^{4}\sum_{k=1}^{4} q_{ijk} = 1 \tag{A.11}$$

$$q_{ijk} \geq 0, \text{ for } i, j, k = 1, \cdots, 4. \tag{A.12}$$

Then, optimizing the linear object functions as equations (A.1)-(A.2), subject to the set of linear constraints as equations (A.3)-(A.12), defines a linear programming problem that lends itself to closed-form solution.

Here, according to Balke (1995), we describe the process for deriving the bounds on the ACDE under the monotonic and no-interaction assumptions, which includes 12 potential response types. The process with 18 and 64 potential response types can be derived in the same way, except that it would involve larger numbers of allowable types.

First, by noting that $\{q_{i11}, q_{i22}, q_{i41}, q_{i44} : i = 1, 2, 4\}$ is used for evaluating the bound, the equality constraints in this specification allow us to eliminate seven of the variables $q_{122}, q_{211}, q_{111}, q_{441}, q_{144}, q_{411}$ and q_{241}, resulting in the following five non-trivial inequality constraints:

$$\max\{0, \text{pr}(y_0, z_1|x_1) - \text{pr}(y_0, z_1|x_0)\} \leq q_{244} \leq \text{pr}(y_0, z_1|x_1),$$

$$\max\{0, \text{pr}(y_1, z_0|x_1) - \text{pr}(y_1, z_0|x_0)\} \leq q_{422} \leq \text{pr}(y_1, z_0|x_1),$$

$$0 \leq q_{141} \leq \text{pr}(y_1, z_1|x_0),$$

$$0 \leq q_{444} \leq \text{pr}(y_0, z_0|x_1),$$

$$0 \leq q_{222} + q_{244} + q_{422} \leq \text{pr}(y_0, z_0|x_1) - \text{pr}(y_0, z_0|x_0).$$

The objective function to be minimized/maximized $ACDE(z)$ may also be rewritten in terms of the remaining variables:

$$\mathrm{pr}(y_0, z_1|x_0) - \mathrm{pr}(y_0, z_1|x_1) + q_{222} + q_{244} + q_{422}.$$

Before this expression is minimized/maximized the constant terms $\mathrm{pr}(y_0, z_1|x_0) - \mathrm{pr}(y_0, z_1|x_1)$ will be dropped. After the minimization/maximization is completed these terms will be reattached. Therefore, the expression to be optimized by linear programming is given by:

$$q_{222} + q_{244} + q_{422}.$$

Balke (1995) describes a computer program that takes symbolic description of linear programming problems and returns symbolic expressions for the desired bounds. The program works by systematically enumerating the vertices of the constraint polygon of the dual problem. This program differs from other linear programming packages in that, its input is symbolic description and its output is symbolic solution, while others can only provide numerical solution for specific data, for example, the one used by Kaufman et al. (2005), which is available from the Mathematics and Computer Science Division of the Argonne National Laboratory (*http://www-fp.mcs.anl.gov/otc/Guide/SoftwareGuide/Categories/linearprog.html*). By applying Balke's method, the closed-form formulas for the bounds on the ACDE are derived. More details for Balke's method is available from *http://bayes.cs.ucla.edu/csl_papers.html*.

Appendix B

Let A_i, B_i, C_i and D_i represent the number of subjects in the treatment group $X = i$, and let n_i represent the total number in the corresponding group ($i = 1, 0$).

[Table 2 about here.]

In Table 2, assume that (A_1, B_1, C_1, D_1) is independent of (A_0, B_0, C_0, D_0), both of which follow the multinomial distribution. Then, since A_1 and A_0 follow the binomial distributions $BN\{n_1, \mathrm{pr}(y_1, z_1|x_1)\}$ and $BN\{n_0, \mathrm{pr}(y_1, z_1|x_0)\}$, respectively, the consistent estimators of $\mathrm{pr}(y_1, z_1|x_1)$ and $\mathrm{pr}(y_1, z_1|x_0)$ are given as

$$\hat{\mathrm{pr}}(y_1, z_1|x_1) = \frac{A_1}{n_1},\ \hat{\mathrm{pr}}(y_1, z_1|x_0) = \frac{A_0}{n_0},$$

respectively. In addition, the consistent estimators of $\mathrm{pr}(y_1|x_1)$ and $\mathrm{pr}(y_1|x_0)$ are given as

$$\hat{\mathrm{pr}}(y_1|x_1) = \frac{A_1 + B_1}{n_1},\ \hat{\mathrm{pr}}(y_1|x_0) = \frac{A_0 + B_0}{n_0},$$

respectively. Similar notations are used for other estimators. In the following, we provide the variances of the lower and upper bounds under no assumption (64 types), monotonic assumption (18 types), and both monotonic and no-interaction assumption (12 types).

1. Variance estimator under no assumption

In the binary case with 64 potential response types, for $z \in \{z_0, z_1\}$, the mean estimator and the variance estimator give

$$\hat{\mathrm{pr}}(y_0, z|x_0) + \hat{\mathrm{pr}}(y_1, z|x_1) - 1$$

and

$$\frac{\hat{\mathrm{pr}}(y_0, z|x_0)\{1 - \hat{\mathrm{pr}}(y_0, z|x_0)\}}{n_0} + \frac{\hat{\mathrm{pr}}(y_1, z|x_1)\{1 - \hat{\mathrm{pr}}(y_1, z|x_1)\}}{n_1}$$

for the lower bound, and

$$1 - \hat{\mathrm{pr}}(y_1, z|x_0) - \hat{\mathrm{pr}}(y_0, z|x_1)$$

and

$$\frac{\hat{\mathrm{pr}}(y_1, z|x_0)\{1 - \hat{\mathrm{pr}}(y_1, z|x_0)\}}{n_0} + \frac{\hat{\mathrm{pr}}(y_0, z|x_1)\{1 - \hat{\mathrm{pr}}(y_0, z|x_1)\}}{n_1}$$

for the upper bound.

2. Variance estimator under monotonic assumption

Regarding the upper bounds, the mean estimator and the variance estimator when $Z = z_1$ are given as

$$\hat{\mathrm{pr}}(y_0|x_0) - \hat{\mathrm{pr}}(y_0, z_1|x_1)$$

and

$$\frac{\hat{\mathrm{pr}}(y_0|x_0)\hat{\mathrm{pr}}(y_1|x_0)}{n_0} + \frac{\hat{\mathrm{pr}}(y_0, z_1|x_1)\{1 - \hat{\mathrm{pr}}(y_0, z_1|x_1)\}}{n_1}$$

respectively. In addition, the mean estimator and the variance estimator when $Z = z_0$ are given as

$$\hat{\mathrm{pr}}(y_1|x_1) - \hat{\mathrm{pr}}(y_1, z_0|x_0)$$

and

$$\frac{\hat{\mathrm{pr}}(y_0|x_1)\hat{\mathrm{pr}}(y_1|x_1)}{n_1} + \frac{\hat{\mathrm{pr}}(y_1, z_0|x_0)\{1 - \hat{\mathrm{pr}}(y_1, z_0|x_0)\}}{n_0}$$

respectively.

Regarding the lower bound, the mean estimator and the variance estimator for the term $\mathrm{pr}(y_0, z_1|x_0) - \mathrm{pr}(y_0, z_1|x_1)$ are given as

$$\hat{\mu}_1 = \hat{\mathrm{pr}}(y_0, z_1|x_0) - \hat{\mathrm{pr}}(y_0, z_1|x_1),$$

and

$$\hat{\sigma}_1^2 = \frac{\hat{\mathrm{pr}}(y_0, z_1|x_0)\{1 - \hat{\mathrm{pr}}(y_0, z_1|x_0)\}}{n_0} + \frac{\hat{\mathrm{pr}}(y_0, z_1|x_1)\{1 - \hat{\mathrm{pr}}(y_0, z_1|x_1)\}}{n_1}$$

respectively. Similarly, the mean estimator and the variance estimator for the term $\mathrm{pr}(y_1, z_0|x_1) - \mathrm{pr}(y_1, z_0|x_0)$ are given as

$$\hat{\mu}_0 = \hat{\mathrm{pr}}(y_1, z_0|x_1) - \hat{\mathrm{pr}}(y_1, z_0|x_0)$$

and

$$\hat{\sigma}_0^2 = \frac{\hat{\mathrm{pr}}(y_1, z_0|x_1)\{1 - \hat{\mathrm{pr}}(y_1, z_0|x_1)\}}{n_1} + \frac{\hat{\mathrm{pr}}(y_1, z_0|x_0)\{1 - \hat{\mathrm{pr}}(y_1, z_0|x_0)\}}{n_0}$$

respectively. Since the binomial distribution can be approximated by the normal distribution when the sample size is large sufficiently (Anderson, 2003), the estimator of the lower bound follows the approximate truncated normal distribution. Then, letting $\phi(\cdot)$ and $\Phi(\cdot)$ be the standard normal density distribution and the standard normal cumulative distribution respectively, the approximate mean estimator of the lower bound is given as

$$\hat{\mu}_i + \hat{\sigma}_i \frac{\phi\left(-\frac{\hat{\mu}_i}{\hat{\sigma}_i}\right)}{1 - \Phi\left(-\frac{\hat{\mu}_i}{\hat{\sigma}_i}\right)},$$

and the approximate variance estimator of the lower bound is given as

$$\hat{\sigma}_i^2 \left[1 - \frac{\hat{\mu}_i \phi\left(-\frac{\hat{\mu}_i}{\hat{\sigma}_i}\right)}{\hat{\sigma}_i \left\{1 - \Phi\left(-\frac{\hat{\mu}_i}{\hat{\sigma}_i}\right)\right\}} - \left\{\frac{\phi\left(-\frac{\hat{\mu}_i}{\hat{\sigma}_i}\right)}{1 - \Phi\left(-\frac{\hat{\mu}_i}{\hat{\sigma}_i}\right)}\right\}^2\right]$$

for $i = 1, 0$.

3. Variance estimator under monotonic and no-interaction assumptions

It is easy to obtain the variance estimator of the upper bound:

$$\frac{\hat{\mathrm{pr}}(y_0|x_0)\hat{\mathrm{pr}}(y_1|x_0)}{n_0} + \frac{\hat{\mathrm{pr}}(y_0|x_1)\hat{\mathrm{pr}}(y_1|x_1)}{n_1}.$$

On the other hand, since the lower bound consists of four terms, the derivation of the variance estimator is complicated. Clark (1961) provided an algorithm to obtain the approximate variance of maximum value of the multivariate normal distribution, which is used in this paper. For the properties of the algorithm, refer to Clark (1961).

According to Clark (1961), we first derive the mean and variance estimators of $\max\{\mathrm{pr}(y_0, z_1|x_0) - \mathrm{pr}(y_0, z_1|x_1), \mathrm{pr}(y_1, z_0|x_1) - \mathrm{pr}(y_1, z_0|x_0)\}$. The mean and the variance estimators of $\xi = \hat{\mathrm{pr}}(y_0, z_1|x_0) - \hat{\mathrm{pr}}(y_0, z_1|x_1)$ are provided as

$$\begin{aligned}
\hat{\mu}_\xi &= \hat{\mathrm{pr}}(y_0, z_1|x_0) - \hat{\mathrm{pr}}(y_0, z_1|x_1), \\
\hat{\sigma}^2_\xi &= \frac{\hat{\mathrm{pr}}(y_0, z_1|x_0)\{1 - \hat{\mathrm{pr}}(y_0, z_1|x_0)\}}{n_0} + \frac{\hat{\mathrm{pr}}(y_0, z_1|x_1)\{1 - \hat{\mathrm{pr}}(y_0, z_1|x_1)\}}{n_1}.
\end{aligned}$$

In addition, the mean and the variance estimators of $\eta = \hat{\mathrm{pr}}(y_1, z_0|x_1) - \hat{\mathrm{pr}}(y_1, z_0|x_0)$ are provided as

$$\begin{aligned}
\hat{\mu}_\eta &= \hat{\mathrm{pr}}(y_1, z_0|x_1) - \hat{\mathrm{pr}}(y_1, z_0|x_0), \\
\hat{\sigma}^2_\eta &= \frac{\hat{\mathrm{pr}}(y_1, z_0|x_1)\{1 - \hat{\mathrm{pr}}(y_1, z_0|x_1)\}}{n_1} + \frac{\hat{\mathrm{pr}}(y_1, z_0|x_0)\{1 - \hat{\mathrm{pr}}(y_1, z_0|x_0)\}}{n_0}.
\end{aligned}$$

Furthermore, their covariance is

$$\hat{\sigma}_{\xi\eta} = \frac{\hat{\mathrm{pr}}(y_0, z_1|x_0)\hat{\mathrm{pr}}(y_1, z_0|x_0)}{n_0} + \frac{\hat{\mathrm{pr}}(y_0, z_1|x_1)\hat{\mathrm{pr}}(y_1, z_0|x_1)}{n_1}.$$

Then, since the binomial distribution can be approximated by the normal distribution when the sample size is large sufficiently (Anderson, 2003), the mean and the variance estimators of $\max(\xi, \eta)$ are provided as

$$
\begin{aligned}
\hat{\mu}_{\max(\xi,\eta)} &= \hat{\mu}_{\xi}\Phi\left(\frac{\hat{\mu}_{\xi}-\hat{\mu}_{\eta}}{\hat{\theta}_{\xi\eta}}\right)+\hat{\mu}_{\eta}\Phi\left(\frac{\hat{\mu}_{\eta}-\hat{\mu}_{\xi}}{\hat{\theta}_{\xi\eta}}\right)+\hat{\theta}_{\xi\eta}\phi\left(\frac{\hat{\mu}_{\eta}-\hat{\mu}_{\xi}}{\hat{\theta}_{\xi\eta}}\right), \\
\hat{\sigma}^2_{\max(\xi,\eta)} &= (\hat{\sigma}^2_{\xi}+\hat{\mu}^2_{\xi})\Phi\left(\frac{\hat{\mu}_{\xi}-\hat{\mu}_{\eta}}{\hat{\theta}_{\xi\eta}}\right)+(\hat{\sigma}^2_{\eta}+\hat{\mu}^2_{\eta})\Phi\left(\frac{\hat{\mu}_{\eta}-\hat{\mu}_{\xi}}{\hat{\theta}_{\xi\eta}}\right) \\
&\quad +(\hat{\mu}_{\xi}+\hat{\mu}_{\eta})\hat{\theta}_{\xi\eta}\phi\left(\frac{\hat{\mu}_{\eta}-\hat{\mu}_{\xi}}{\hat{\theta}_{\xi\eta}}\right)-\hat{\mu}^2_{\max(\xi,\eta)}
\end{aligned}
$$

where $\hat{\theta}_{\xi\eta} = \sqrt{\hat{\sigma}^2_{\xi}-2\hat{\rho}_{\xi\eta}\hat{\sigma}_{\xi}\hat{\sigma}_{\eta}+\hat{\sigma}^2_{\eta}}$ and $\hat{\rho}_{\xi\eta}$ is the correlation coefficient between ξ and η.

Second, we add the third term $\mathrm{pr}(y_0, z_1|x_0)-\mathrm{pr}(y_1, z_0|x_0)-\mathrm{pr}(y_0, z_1|x_1)+\mathrm{pr}(y_1, z_0|x_1)$. The mean and the variance estimators of $\zeta = \hat{\mathrm{pr}}(y_0, z_1|x_0) - \hat{\mathrm{pr}}(y_1, z_0|x_0) - \hat{\mathrm{pr}}(y_0, z_1|x_1) + \hat{\mathrm{pr}}(y_1, z_0|x_1)$ are provided as

$$
\begin{aligned}
\hat{\mu}_{\zeta} &= \hat{\mathrm{pr}}(y_0, z_1|x_0) - \hat{\mathrm{pr}}(y_1, z_0|x_0) - \hat{\mathrm{pr}}(y_0, z_1|x_1) + \hat{\mathrm{pr}}(y_1, z_0|x_1), \\
\hat{\sigma}^2_{\zeta} &= \frac{\hat{\mathrm{pr}}(y_0, z_1|x_0)\{1-\hat{\mathrm{pr}}(y_0, z_1|x_0)\}}{n_0}+\frac{\hat{\mathrm{pr}}(y_0, z_1|x_1)\{1-\hat{\mathrm{pr}}(y_0, z_1|x_1)\}}{n_1} \\
&\quad +\frac{\hat{\mathrm{pr}}(y_1, z_0|x_0)\{1-\hat{\mathrm{pr}}(y_1, z_0|x_0)\}}{n_0}+\frac{\hat{\mathrm{pr}}(y_1, z_0|x_1)\{1-\hat{\mathrm{pr}}(y_1, z_0|x_1)\}}{n_1} \\
&\quad +2\frac{\hat{\mathrm{pr}}(y_0, z_1|x_0)\hat{\mathrm{pr}}(y_1, z_0|x_0)}{n_0}+2\frac{\hat{\mathrm{pr}}(y_0, z_1|x_1)\hat{\mathrm{pr}}(y_1, z_0|x_1)}{n_1}.
\end{aligned}
$$

The covariances between ξ and ζ and between η and ζ are

$$
\begin{aligned}
\hat{\sigma}_{\xi\zeta} &= \frac{\hat{\mathrm{pr}}(y_0, z_1|x_0)\{1-\hat{\mathrm{pr}}(y_0, z_1|x_0)\}}{n_0}+\frac{\hat{\mathrm{pr}}(y_0, z_1|x_0)\hat{\mathrm{pr}}(y_1, z_0|x_0)}{n_0} \\
&\quad +\frac{\hat{\mathrm{pr}}(y_0, z_1|x_1)\{1-\hat{\mathrm{pr}}(y_0, z_1|x_1)\}}{n_1}+\frac{\hat{\mathrm{pr}}(y_0, z_1|x_1)\hat{\mathrm{pr}}(y_1, z_0|x_1)}{n_1} \\
\hat{\sigma}_{\eta\zeta} &= \frac{\hat{\mathrm{pr}}(y_1, z_0|x_1)\{1-\hat{\mathrm{pr}}(y_1, z_0|x_1)\}}{n_1}+\frac{\hat{\mathrm{pr}}(y_1, z_0|x_1)\hat{\mathrm{pr}}(y_0, z_1|x_1)}{n_1} \\
&\quad +\frac{\hat{\mathrm{pr}}(y_1, z_0|x_0)\{1-\hat{\mathrm{pr}}(y_1, z_0|x_0)\}}{n_0}+\frac{\hat{\mathrm{pr}}(y_1, z_0|x_0)\hat{\mathrm{pr}}(y_0, z_1|x_0)}{n_0}.
\end{aligned}
$$

Thus, the correlation coefficient between $\max(\xi,\eta)$ and ζ is

$$\hat{\rho}_{\zeta,\max(\xi,\eta)} = \left\{ \hat{\sigma}_\xi \hat{\rho}_{\xi\zeta} \Phi\left(\frac{\hat{\mu}_\xi - \hat{\mu}_\eta}{\hat{\theta}_{\xi\eta}} \right) + \hat{\sigma}_\eta \hat{\rho}_{\eta\zeta} \Phi\left(\frac{\hat{\mu}_\eta - \hat{\mu}_\xi}{\hat{\theta}_{\xi\eta}} \right) \right\} \Big/ \hat{\sigma}_{\max(\xi,\eta)}.$$

Then, according to Clark (1961), if $\max(\xi,\eta)$ is normally distributed asymptotically, the mean and variance estimators of $\max\{\max(\xi,\eta),\zeta\} = \max(\xi,\eta,\zeta)$ are

$$\begin{aligned} &\hat{\mu}_{\max(\xi,\eta,\zeta)} \\ &= \hat{\mu}_{\max(\xi,\eta)} \Phi\left(\frac{\hat{\mu}_{\max(\xi,\eta)} - \hat{\mu}_\zeta}{\hat{\theta}_{\max(\xi,\eta),\zeta}} \right) + \hat{\mu}_\zeta \Phi\left(\frac{\hat{\mu}_\zeta - \hat{\mu}_{\max(\xi,\eta)}}{\hat{\theta}_{\max(\xi,\eta),\zeta}} \right) \\ &\quad + \hat{\theta}_{\max(\xi,\eta),\zeta} \phi\left(\frac{\hat{\mu}_\zeta - \hat{\mu}_{\max(\xi,\eta)}}{\hat{\theta}_{\max(\xi,\eta),\zeta}} \right), \end{aligned}$$

$$\begin{aligned} &\hat{\sigma}^2_{\max(\xi,\eta,\zeta)} \\ &= (\hat{\sigma}^2_{\max(\xi,\eta)} + \hat{\mu}^2_{\max(\xi,\eta)}) \Phi\left(\frac{\hat{\mu}_{\max(\xi,\eta)} - \hat{\mu}_\zeta}{\hat{\theta}_{\max(\xi,\eta),\zeta}} \right) + (\hat{\sigma}^2_\zeta + \hat{\mu}^2_\zeta) \Phi\left(\frac{\hat{\mu}_\zeta - \hat{\mu}_{\max(\xi,\eta)}}{\hat{\theta}_{\max(\xi,\eta),\zeta}} \right) \\ &\quad + (\hat{\mu}_{\max(\xi,\eta)} + \hat{\mu}_\zeta) \hat{\theta}_{\max(\xi,\eta),\zeta} \phi\left(\frac{\hat{\mu}_\zeta - \hat{\mu}_{\max(\xi,\eta)}}{\hat{\theta}_{\max(\xi,\eta),\zeta}} \right) - \hat{\mu}^2_{\max(\xi,\eta,\zeta)}, \end{aligned}$$

where $\hat{\theta}_{\max(\xi,\eta),\zeta} = \sqrt{\hat{\sigma}^2_{\max(\xi,\eta)} - 2\hat{\rho}_{\max(\xi,\eta),\zeta} \hat{\sigma}_{\max(\xi,\eta)} \hat{\sigma}_\zeta + \hat{\sigma}^2_\zeta}$.

If $\max(\xi,\eta,\zeta)$ is normally distributed asymptotically, the estimator of the lower bound follows the approximate truncated normal distribution. Hence, the mean estimator of the lower bound is given as

$$\hat{\mu}_{\max(\xi,\eta,\zeta)} + \hat{\sigma}_{\max(\xi,\eta,\zeta)} \frac{\phi\left(-\frac{\hat{\mu}_{\max(\xi,\eta,\zeta)}}{\hat{\sigma}_{\max(\xi,\eta,\zeta)}} \right)}{1 - \Phi\left(-\frac{\hat{\mu}_{\max(\xi,\eta,\zeta)}}{\hat{\sigma}_{\max(\xi,\eta,\zeta)}} \right)},$$

and the variance estimator of the lower bound is given as

$$\hat{\sigma}^2_{\max(\xi,\eta,\zeta)}\left[1-\frac{\hat{\mu}_{\max(\xi,\eta,\zeta)}\phi\left(-\frac{\hat{\mu}_{\max(\xi,\eta,\zeta)}}{\hat{\sigma}_{\max(\xi,\eta,\zeta)}}\right)}{\hat{\sigma}_{\max(\xi,\eta,\zeta)}\left\{1-\Phi\left(-\frac{\hat{\mu}_{\max(\xi,\eta,\zeta)}}{\hat{\sigma}_{\max(\xi,\eta,\zeta)}}\right)\right\}}-\left\{\frac{\phi\left(-\frac{\hat{\mu}_{\max(\xi,\eta,\zeta)}}{\hat{\sigma}_{\max(\xi,\eta,\zeta)}}\right)}{1-\Phi\left(-\frac{\hat{\mu}_{\max(\xi,\eta,\zeta)}}{\hat{\sigma}_{\max(\xi,\eta,\zeta)}}\right)}\right\}^2\right].$$

4. Simulation study

In order to investigate the performance of the variance estimators discussed above, we did simulation experiments. The exact variances of the upper bounds can be obtained under the three cases, but only the approximate variances of the lower bounds can be obtained under 18 and 12 potential response types. Therefore, it is expected that whether the lower bound is zero or not would influence the variance, since the truncated normal distribution is used to approximate the variance. Based on this consideration, we consider three possible scenarios. In case 1, the probabilistic terms of the lower bounds in 18 types and 12 types take negative values, which lead to zero lower bounds. In case 2, the probabilistic terms of the lower bounds in 18 types and 12 types take positive values, which lead to positive lower bounds. In case 3, the probabilistic terms of the lower bounds in 18 types and 12 types equal zero, which also lead to zero lower bounds. The conditional probabilities $\mathrm{pr}(y, z|x)$ of these three cases are shown in Table 3.

[Table 3 about here.]

We did simulation experiments based on the conditional probabilities in Table 3 with sample size $n = 500, 1000$ and 2000 ($n = n_0 = n_1$). Table 4 reports the variance estimates from 3000 replications in various sample sizes. The first line shows the value of the upper and lower bounds calculated from the conditional probabilities in Table 3. The even-numbered line shows the value of the approximate standard error (SE) based on the proposed variance estimators in each sample size, and the odd-numbered line shows the value of the sample SE obtained from simulation experiments.

Comparing the approximate SEs with SEs in Table 4, the ratios are close to 1 in all cases, except for the lower bounds of 18 types and 12 types in case 1. In case 1, the sample SEs of the lower bounds in 18 types and 12 types are equal to 0.000. This is because the negative probabilistic term leads to zero lower bound in each replication. Therefore, the proposed variance estimators provide good approximation of the variance in the case where the probabilistic terms of the lower bounds are nonnegative.

In spite that the sample SEs of the lower bounds of 18 types and 12 types in case 1 equal 0.000, the corresponding approximate SEs are not so close to 0.000. These may result from the normal approximation and the negative value μ/σ in the truncated normal distribution $\phi(\cdot)/\{1-\Phi(\cdot)\}$. Moreover, in 12 types, this may also result from the normal approximation of the distribution of the order statistics, which are assumed to follow the normal distribution although they are not the normal distribution (Clark,1961).

[Table 4 about here.]

[Table 5 about here.]

References in Appendix B

Anderson, T. W. (2003). *An Introduction to Multivariate Statistical Analysis, 3rd ed.*, Wiley &Sons.

Clark, C. E. (1961). The greatest of a finite set of random variables. *Operations Research* **9**,145-162.

Appendix C

We only consider the case of $ACDE(z_0)$. The case of $ACDE(z_1)$ can be derived in a similar process. From equation (A.1), we can obtain

$$\begin{aligned} ACDE(z_0) &= \sum_{i=1}^{4}\sum_{k=1}^{4}\left\{\sum_{j\in\{1,2\}} q_{ijk} - \sum_{j\in\{1,3\}} q_{ijk}\right\} \\ &= \sum_{s}\left[\sum_{i=1}^{4}\sum_{k=1}^{4}\left\{\sum_{j\in\{1,2\}} q_{ijk\cdot s} - \sum_{j\in\{1,3\}} q_{ijk\cdot s}\right\}\right]\mathrm{pr}(s) \\ &= \sum_{s} ACDE(z_0|s)\mathrm{pr}(s) \end{aligned}$$

by introducing a covariate S. Here, $q_{ijk\cdot s} = \mathrm{pr}(r_z = i, r_{y|z_0} = j, r_{y|z_1} = k|s)$. By replacing q_{ijk} and $\mathrm{pr}(y_i, z_j|x_k)$ in equations (A.3)-(A.12) with $q_{ijk\cdot s}$ and $\mathrm{pr}(y_i, z_j|x_k, s)$ respectively and using the similar procedure in Appendix A, we can obtain the bounds on the $ACDE(z_0|s)$, which are provided in section 3. Letting $LB_s(z)$ and $UB_s(z)$ be the lower and upper bounds in stratum s, by noting that X is independent of S, we can obtain

$$\begin{aligned} LB(z) &\leq \sum_{s} LB_s(z)\mathrm{pr}(s) \leq \sum_{s} ACDE(z|s)\mathrm{pr}(s) = ACDE(z) \\ &\leq \sum_{s} UB_s(z)\mathrm{pr}(s) \leq UB(z). \end{aligned}$$

Thus, the bounds obtained in Section 3 should not be wider than those in Section 2.

Appendix D

According to Balke and Pearl (1997), $\mathrm{ACDE}(y,z,x,x')$ in Fig. 1 is defined as

$$\begin{aligned}\mathrm{ACDE}(y,z,x,x') &= \mathrm{pr}\{y|\mathrm{do}(x'),\mathrm{do}(z)\} - \mathrm{pr}(y|\mathrm{do}(x),\mathrm{do}(z)\} \\ &= \sum_u \{\mathrm{pr}(y|u,x',z) - \mathrm{pr}(y|u,x,z)\}\mathrm{pr}(u).\end{aligned}$$

Since X is an exogenous variable, which indicates that $X \perp\!\!\!\perp U$ holds true, then $\mathrm{pr}(u) = \mathrm{pr}(u|x) = \mathrm{pr}(u|x')$ can be obtained. Thus,

$$\begin{aligned}&\mathrm{ACDE}(y,z,x,x') \\ &= \sum_u \sum_{z'} \{\mathrm{pr}(y|u,x',z)\mathrm{pr}(u|z',x')\mathrm{pr}(z'|x') - \mathrm{pr}(y|u,x,z)\mathrm{pr}(u|x,z')\mathrm{pr}(z'|x)\} \\ &= \mathrm{pr}(y,z|x') - \mathrm{pr}(y,z|x) \\ &\quad + \sum_u \sum_{z'\neq z} \{\mathrm{pr}(y|u,x',z)\mathrm{pr}(u|z',x')\mathrm{pr}(z'|x') - \mathrm{pr}(y|u,x,z)\mathrm{pr}(u|x,z')\mathrm{pr}(z'|x)\}.\end{aligned}$$

By substituting 0 and 1 to $\mathrm{pr}(y|u,x',z)$ and $\mathrm{pr}(y|u,x,z)$ $(z' \neq z)$ respectively, we can obtain the lower bound

$$\mathrm{ACDE}(y,z,x,x') \geq -1 + \mathrm{pr}(z|x) + \mathrm{pr}(y,z|x') - \mathrm{pr}(y,z|x),$$

and by substituting 1 and 0 to $\mathrm{pr}(y|u,x',z)$ and $\mathrm{pr}(y|u,x,z)$ $(z' \neq z)$ respectively, we can obtain the upper bound

$$\mathrm{ACDE}(y,z,x,x') \leq 1 - \mathrm{pr}(z|x') + \mathrm{pr}(y,z|x') - \mathrm{pr}(y,z|x).$$

Table 1. 64 potential response types

	r_z		$r_{y\|z_0}$		$r_{y\|z_1}$	
	Z_{x_1}	Z_{x_0}	Y_{x_1,z_0}	Y_{x_0,z_0}	Y_{x_1,z_1}	Y_{x_0,z_1}
q_{111}	z_1	z_1	y_1	y_1	y_1	y_1
q_{112}	z_1	z_1	y_1	y_1	y_1	y_0
q_{113}	z_1	z_1	y_1	y_1	y_0	y_1
q_{114}	z_1	z_1	y_1	y_1	y_0	y_0
q_{121}	z_1	z_1	y_1	y_0	y_1	y_1
q_{122}	z_1	z_1	y_1	y_0	y_1	y_0
q_{123}	z_1	z_1	y_1	y_0	y_0	y_1
q_{124}	z_1	z_1	y_1	y_0	y_0	y_0
q_{131}	z_1	z_1	y_0	y_1	y_1	y_1
q_{132}	z_1	z_1	y_0	y_1	y_1	y_0
q_{133}	z_1	z_1	y_0	y_1	y_0	y_1
q_{134}	z_1	z_1	y_0	y_1	y_0	y_0
q_{141}	z_1	z_1	y_0	y_0	y_1	y_1
q_{142}	z_1	z_1	y_0	y_0	y_1	y_0
q_{143}	z_1	z_1	y_0	y_0	y_0	y_1
q_{144}	z_1	z_1	y_0	y_0	y_0	y_0
q_{211}	z_1	z_0	y_1	y_1	y_1	y_1
q_{212}	z_1	z_0	y_1	y_1	y_1	y_0
q_{213}	z_1	z_0	y_1	y_1	y_0	y_1
q_{214}	z_1	z_0	y_1	y_1	y_0	y_0
q_{221}	z_1	z_0	y_1	y_0	y_1	y_1
q_{222}	z_1	z_0	y_1	y_0	y_1	y_0
q_{223}	z_1	z_0	y_1	y_0	y_0	y_1
q_{224}	z_1	z_0	y_1	y_0	y_0	y_0
q_{231}	z_1	z_0	y_0	y_1	y_1	y_1
q_{232}	z_1	z_0	y_0	y_1	y_1	y_0
q_{233}	z_1	z_0	y_0	y_1	y_0	y_1
q_{234}	z_1	z_0	y_0	y_1	y_0	y_0
q_{241}	z_1	z_0	y_0	y_0	y_1	y_1
q_{242}	z_1	z_0	y_0	y_0	y_1	y_0
q_{243}	z_1	z_0	y_0	y_0	y_0	y_1
q_{244}	z_1	z_0	y_0	y_0	y_0	y_0

	r_z		$r_{y\|z_0}$		$r_{y\|z_1}$	
	Z_{x_1}	Z_{x_0}	Y_{x_1,z_0}	Y_{x_0,z_0}	Y_{x_1,z_1}	Y_{x_0,z_1}
q_{311}	z_0	z_1	y_1	y_1	y_1	y_1
q_{312}	z_0	z_1	y_1	y_1	y_1	y_0
q_{313}	z_0	z_1	y_1	y_1	y_0	y_1
q_{314}	z_0	z_1	y_1	y_1	y_0	y_0
q_{321}	z_0	z_1	y_1	y_0	y_1	y_1
q_{322}	z_0	z_1	y_1	y_0	y_1	y_0
q_{323}	z_0	z_1	y_1	y_0	y_0	y_1
q_{324}	z_0	z_1	y_1	y_0	y_0	y_0
q_{331}	z_0	z_1	y_0	y_1	y_1	y_1
q_{332}	z_0	z_1	y_0	y_1	y_1	y_0
q_{333}	z_0	z_1	y_0	y_1	y_0	y_1
q_{334}	z_0	z_1	y_0	y_1	y_0	y_0
q_{341}	z_0	z_1	y_0	y_0	y_1	y_1
q_{342}	z_0	z_1	y_0	y_0	y_1	y_0
q_{343}	z_0	z_1	y_0	y_0	y_0	y_1
q_{343}	z_0	z_1	y_0	y_0	y_0	y_0
q_{411}	z_0	z_0	y_1	y_1	y_1	y_1
q_{412}	z_0	z_0	y_1	y_1	y_1	y_0
q_{413}	z_0	z_0	y_1	y_1	y_0	y_1
q_{414}	z_0	z_0	y_1	y_1	y_0	y_0
q_{421}	z_0	z_0	y_1	y_0	y_1	y_1
q_{422}	z_0	z_0	y_1	y_0	y_1	y_0
q_{423}	z_0	z_0	y_1	y_0	y_0	y_1
q_{424}	z_0	z_0	y_1	y_0	y_0	y_0
q_{431}	z_0	z_0	y_0	y_1	y_1	y_1
q_{432}	z_0	z_0	y_0	y_1	y_1	y_0
q_{433}	z_0	z_0	y_0	y_1	y_0	y_1
q_{434}	z_0	z_0	y_0	y_1	y_0	y_0
q_{441}	z_0	z_0	y_0	y_0	y_1	y_1
q_{442}	z_0	z_0	y_0	y_0	y_1	y_0
q_{443}	z_0	z_0	y_0	y_0	y_0	y_1
q_{444}	z_0	z_0	y_0	y_0	y_0	y_0

Table 2. A contingency table with a treatment X, an intermediate Z and an outcome Y

	x_1		x_0	
	z_1	z_0	z_1	z_0
y_1	A_1	B_1	A_0	B_0
y_0	C_1	D_1	C_0	D_0
total	n_1		n_0	

Table 3. Simulation settings

case 1

	x_1		x_0	
	z_1	z_0	z_1	z_0
y_1	0.2000	0.0100	0.1000	0.0500
y_0	0.7400	0.0500	0.5500	0.3000

case 2

	x_1		x_0	
	z_1	z_0	z_1	z_0
y_1	0.3000	0.0500	0.1000	0.0100
y_0	0.4500	0.2000	0.5900	0.3000

case 3

	x_1		x_0	
	z_1	z_0	z_1	z_0
y_1	0.2000	0.0500	0.0700	0.0500
y_0	0.4800	0.2700	0.4800	0.4000

Table 4. Simulation results

case 1

			64 types		18 types		12 types	
			lower	upper	lower	upper	lower	upper
z_0	n	bound	-0.6900	0.9000	0.0000	0.1600	0.0000	0.0600
	500	approximate SE	0.0210	0.0138	0.0024	0.0207	0.0107	0.0242
		sample SE	0.0205	0.0137	0.0000	0.0214	0.0000	0.0249
	1000	approximate SE	0.0148	0.0097	0.0013	0.0146	0.0076	0.0171
		sample SE	0.0149	0.0097	0.0000	0.0149	0.0000	0.0172
	2000	approximate SE	0.0105	0.0069	0.0012	0.0103	0.0054	0.0121
		sample SE	0.0104	0.0069	0.0000	0.0104	0.0000	0.0123
z_1	n	bound	-0.2500	0.1600	0.0000	0.1100	0.0000	0.0600
	500	approximate SE	0.0285	0.0219	0.0297	0.0253	0.0107	0.0242
		sample SE	0.0292	0.0238	0.0000	0.0260	0.0000	0.0249
	1000	approximate SE	0.0202	0.0168	0.0210	0.0179	0.0076	0.0171
		sample SE	0.0202	0.0168	0.0000	0.0179	0.0000	0.0172
	2000	approximate SE	0.0143	0.0119	0.0148	0.0126	0.0054	0.0121
		sample SE	0.0143	0.0121	0.0000	0.0128	0.0000	0.0123

case 2

			64 types		18 types		12 types	
			lower	upper	lower	upper	lower	upper
z_0	n	bound	-0.6500	0.7900	0.0400	0.3400	0.1800	0.2400
	500	approximate SE	0.0227	0.0184	0.0107	0.0218	0.0306	0.0255
		sample SE	0.0227	0.0186	0.0108	0.0221	0.0345	0.0257
	1000	approximate SE	0.0160	0.0130	0.0076	0.0154	0.0227	0.0180
		sample SE	0.0162	0.0130	0.0078	0.0154	0.0250	0.0181
	2000	approximate SE	0.0113	0.0092	0.0054	0.0109	0.0168	0.0128
		sample SE	0.0114	0.0090	0.0054	0.0107	0.0173	0.0127
z_1	n	bound	-0.1100	0.4500	0.1400	0.4400	0.1800	0.2400
	500	approximate SE	0.0301	0.0260	0.0313	0.0263	0.0306	0.0255
		sample SE	0.0301	0.0258	0.0309	0.0262	0.0345	0.0257
	1000	approximate SE	0.0213	0.0184	0.0221	0.0186	0.0227	0.0180
		sample SE	0.0217	0.0182	0.0224	0.0185	0.0250	0.0181
	2000	approximate SE	0.0150	0.0130	0.0156	0.0131	0.0168	0.0128
		sample SE	0.0151	0.0129	0.0157	0.0131	0.0173	0.0127

Table 4. Simulation results (cont.)

case 3

			64 types		18 types		12 types	
			lower	upper	lower	upper	lower	upper
z_0	n	bound	-0.5500	0.6800	0.0000	0.2000	0.0000	0.1300
	500	approximate SE	0.0240	0.0221	0.0083	0.0217	0.0188	0.0242
		sample SE	0.0240	0.0223	0.0080	0.0219	0.0214	0.0243
	1000	approximate SE	0.0170	0.0156	0.0059	0.0153	0.0133	0.0171
		sample SE	0.0170	0.0160	0.0056	0.0157	0.0145	0.0173
	2000	approximate SE	0.0120	0.0111	0.0042	0.0108	0.0094	0.0121
		sample SE	0.0120	0.0110	0.0039	0.0108	0.0106	0.0119
z_1	n	bound	-0.3200	0.4500	0.0000	0.4000	0.0000	0.1300
	500	approximate SE	0.0286	0.0251	0.0190	0.0267	0.0188	0.0242
		sample SE	0.0285	0.0253	0.0185	0.0267	0.0214	0.0243
	1000	approximate SE	0.0202	0.0177	0.0135	0.0188	0.0133	0.0171
		sample SE	0.0205	0.0180	0.0126	0.0191	0.0145	0.0173
	2000	approximate SE	0.0143	0.0125	0.0095	0.0133	0.0094	0.0121
		sample SE	0.0143	0.0125	0.0092	0.0132	0.0106	0.0119