eAppendix for "Sensitivity Analysis Without Assumptions"

The eAppendix contains the following ten sections.

eAppendix 1: Three useful lemmas which are used repeatedly in the proofs in later sections;

eAppendix 2: The new bounding factor introduced in the main text and its implied Cornfield conditions with proofs;

eAppendix 3: Another bounding factor with the exposure-confounder relationship on the odds ratio scale and its implied Cornfield conditions with proofs;

eAppendix 4: Relations between the new bounding factor and some existing results including Schlesselman's formula[1] and Flanders and Khoury's results[2];

eAppendix 5: Results for the risk difference using sensitivity parameters on the relative risk scale with proofs;

eAppendix 6: Results for the risk difference using sensitivity parameters on the risk difference scale with proofs;

eAppendix 7: A bounding factor for rare time-to-event outcome on the hazard ratio scale and its implied Cornfield conditions;

eAppendix 8: A bounding factor for general nonnegative outcomes;

eAppendix 9: SAS code for the risk ratio using sensitivity parameters on the relative risk scale;

eAppendix 10: SAS code for the risk difference using sensitivity parameters on the relative risk scale.

eAppendix 1 Useful Lemmas

Lemma A.1. *Define* $h(x) = (c_1x+1)/(c_2x+1)$. *When* $c_1 > c_2$, $h'(x) > 0$ *and* $h(x)$ *is increasing; when* $c_1 \leq c_2$, $h'(x) \leq 0$ *and* $h(x)$ *is non-increasing.*

Proof of Lemma A.1. The first derivative of $h(x)$ is

$$h'(x) = \frac{c_1(c_2x+1)-(c_1x+1)c_2}{(c_2x+1)^2} = \frac{c_1-c_2}{(c_2x+1)^2}.$$

When $c_1 > c_2$, $h'(x) > 0$ and $h(x)$ is increasing in x. When $c_1 \leq c_2$, we have opposite results.

□

Lemma A.2. *When* $x, y > 1$, $h(x,y) = (xy)/(x+y-1)$ *is increasing in both x and y.*

Proof of Lemma A.2. The first partial derivative of $h(x,y)$ with respect to x is

$$\frac{\partial h(x,y)}{\partial x} = \frac{y(x+y-1)-xy}{(x+y-1)^2} = \frac{y(y-1)}{(x+y-1)^2}.$$

When $x, y > 1$, $\partial h(x,y)/\partial x > 0$ and $h(x,y)$ is increasing in x. By symmetry, the conclusion holds also for y. □

Lemma A.3. *When* $x, y > 1$, $h(x,y) = (\sqrt{xy}+1)/(\sqrt{x}+\sqrt{y})$ *is increasing in both x and y.*

Proof of Lemma A.3. The first partial derivative of $h(x,y)$ with respect to x is

$$\frac{\partial h(x,y)}{\partial x} = \frac{\frac{1}{2}\sqrt{y/x}(\sqrt{x}+\sqrt{y}) - \frac{1}{2}(\sqrt{xy}+1)/\sqrt{x}}{(\sqrt{x}+\sqrt{y})^2} = \frac{y-1}{2\sqrt{x}(\sqrt{x}+\sqrt{y})^2}.$$

When $x, y > 1$, $\partial h(x,y)/\partial x > 0$ and $h(x,y)$ is increasing in x. By symmetry, the conclusion holds also for y. □

eAppendix 2 The New Bounding Factor and Implied Cornfield Conditions

eAppendix 2.1 Technical Measure-Theoretical Details

This subsection presents the technical framework for the proofs. A less technical reader can skip this subsection and move directly to the next subsection eAppendix 2.2 on the new bounding factor. Throughout the eAppendix, we allow the unmeasured confounder U to take arbitrary values, which is a measurable mapping from probability space $(\Omega, \mathscr{F}, \mathrm{P})$ to a measurable space $(\Upsilon, \mathscr{U})$. For $\mathbf{V} \in \mathscr{U}$, we define $F_1(\mathbf{V}) = \mathrm{P}(U \in \mathbf{V} \mid E = 1)$ as the distribution of U with exposure, $F_0(\mathbf{V}) = \mathrm{P}(U \in \mathbf{V} \mid E = 0)$ as the distribution of U without exposure, and $F(\mathbf{V}) = \mathrm{P}(U \in \mathbf{V})$ as the marginal distribution of U. The distributions $F_1(\cdot), F_0(\cdot)$ and $F(\cdot)$ are measurable mappings from Υ to $[0,1]$, which correspondingly induce three probability measures on the measurable space $(\Upsilon, \mathscr{U})$. When the confounder U is a scalar on the real line, these definitions reduce to $F_1(u) = \mathrm{P}(U \leq u \mid E = 1)$, the cumulative distribution function (CDF) of U with exposure, $F_0(u) = \mathrm{P}(U \leq u \mid E = 0)$, the CDF of U without exposure, and $F(u) = \mathrm{P}(U \leq u)$, its marginal CDF. Correspondingly, the CDFs, F_1, F_0, and F, also induce three measures on the real line. In the following, we assume that the measure F_1 is absolutely continuous with respect to the measure F_0, with the Radon–Nikodym derivative defined as $\mathrm{RR}_{EU}(u) = F_1(du)/F_0(du)$, which is the generalized relative risk of E on U at $U = u$. The absolute continuous assumption about F_1 and F_0 holds automatically for categorical and absolutely continuous unmeasured confounder U. For general confounder U, this is only

a mild regularity condition.

eAppendix 2.2 The New Bounding Factor

We assume for the next several sections that analysis is done conditional on, or within strata of the measured confounders C. We define the maximal relative risk of E on U as $\mathrm{RR}_{EU} = \max_u \mathrm{RR}_{EU}(u)$. Define $r(u) = \mathrm{P}(D = 1 \mid E = 0, U = u)$ and $r^*(u) = \mathrm{P}(D = 1 \mid E = 1, U = u)$ as the probabilities of the outcome within stratum $U = u$ without and with exposure. Define the maximal relative risk of U on D as $\mathrm{RR}_{UD|E=0} = \max_u r(u)/\min_u r(u)$ and $\mathrm{RR}_{UD|E=1} = \max_u r^*(u)/\min_u r^*(u)$ without and with exposure, and $\mathrm{RR}_{UD} = \max(\mathrm{RR}_{UD|E=0}, \mathrm{RR}_{UD|E=1})$ as the maximum of these two relative risks. The maxima and minima are taken over the space Υ, and hereinafter. When U is a categorical confounder with levels $0, 1, \ldots, K-1$, the definitions above reduce to the definitions in the main text. To allow for causal interpretations, we invoke the counterfactural or potential outcomes framework, with $D_i(1)$ and $D_i(0)$ being the potential outcomes for individual i with and without the exposure, respectively; we also need to make the ignorability assumption[3] $E \perp\!\!\!\perp \{D(1), D(0)\} \mid U$.

The observed relative risk of the exposure E on the outcome D is

$$\mathrm{RR}_{ED}^{\mathrm{obs}} = \frac{\int \mathrm{P}(D = 1 \mid E = 1, U = u) F_1(du)}{\int \mathrm{P}(D = 1 \mid E = 0, U = u) F_0(du)} = \frac{\int r^*(u) F_1(du)}{\int r(u) F_0(du)},$$

where the integrals are over Υ and hereinafter. The relative risks standardized by the exposed, the unexposed, and the whole population are as follows:

$$\mathrm{RR}_{ED+}^{\mathrm{true}} = \frac{\int r^*(u) F_1(du)}{\int r(u) F_1(du)}, \quad \mathrm{RR}_{ED-}^{\mathrm{true}} = \frac{\int r^*(u) F_0(du)}{\int r(u) F_0(du)}, \quad \mathrm{RR}_{ED}^{\mathrm{true}} = \frac{\int r^*(u) F(du)}{\int r(u) F(du)}.$$

When unmeasure confounder U is categorical, $\mathrm{RR}_{ED}^{\mathrm{true}}$ reduces to the form in the main text, and all other relative risk measures can be simplifies by replacing integrations by summations.

The corresponding confounding relative risks standardized by the exposed, the unexposed, and the whole population are

$$\mathrm{CRR}_{ED+} = \frac{\mathrm{RR}_{ED}^{\mathrm{obs}}}{\mathrm{RR}_{ED+}^{\mathrm{true}}} = \frac{\int r(u)F_1(du)}{\int r(u)F_0(du)}, \quad \mathrm{CRR}_{ED-} = \frac{\mathrm{RR}_{ED}^{\mathrm{obs}}}{\mathrm{RR}_{ED-}^{\mathrm{true}}} = \frac{\int r^*(u)F_1(du)}{\int r^*(u)F_0(du)},$$

and $\mathrm{CRR}_{ED} = \mathrm{RR}_{ED}^{\mathrm{obs}}/\mathrm{RR}_{ED}^{\mathrm{true}}$. Similar to Lee[4], we have that $\mathrm{RR}_{ED}^{\mathrm{true}}$ is a weighted average of $\mathrm{RR}_{ED+}^{\mathrm{true}}$ and $\mathrm{RR}_{ED-}^{\mathrm{true}}$, and CRR_{ED} is a harmonic average of CRR_{ED+} and CRR_{ED-}.

Proposition A.1. *We have*

$$\mathrm{RR}_{ED}^{true} = w\mathrm{RR}_{ED+}^{true} + (1-w)\mathrm{RR}_{ED-}^{true}, \quad 1/\mathrm{CRR}_{ED} = w/\mathrm{CRR}_{ED+} + (1-w)/\mathrm{CRR}_{ED-},$$

where $f = P(E=1)$ and w is a weight between zero and one:

$$w = \frac{f\int r(u)F_1(du)}{f\int r(u)F_1(du) + (1-f)\int r(u)F_0(du)} \in [0,1].$$

Proof of Proposition A.1. The conclusions follow from the following decomposition:

$$\begin{aligned}
\mathrm{RR}_{ED}^{\mathrm{true}} &= \frac{\int r^*(u)F(du)}{\int r(u)F(du)} = \frac{f\int r^*(u)F_1(du) + (1-f)\int r^*(u)F_0(du)}{f\int r(u)F_1(du) + (1-f)\int r(u)F_0(du)} \\
&= \frac{f\int r(u)F_1(du)}{f\int r(u)F_1(du) + (1-f)\int r(u)F_0(du)} \times \frac{\int r^*(u)F_1(du)}{\int r(u)F_0(du)} \\
&\quad + \frac{(1-f)\int r(u)F_0(du)}{f\int r(u)F_1(du) + (1-f)\int r(u)F_0(du)} \times \frac{\int r^*(u)F_0(du)}{\int r(u)F_0(du)}.
\end{aligned}$$

□

The confounding relative risks can be bounded from above by the bounding factor

$$\mathrm{BF}_U = \frac{\mathrm{RR}_{EU} \times \mathrm{RR}_{UD}}{\mathrm{RR}_{EU} + \mathrm{RR}_{UD} - 1},$$

as shown in the following proposition.

Proposition A.2. *The confounding relative risks can be bounded from above by*

$$\mathrm{CRR}_{ED+} = \frac{\mathrm{RR}_{ED}^{obs}}{\mathrm{RR}_{ED+}^{true}} \le \mathrm{BF}_U, \quad \mathrm{CRR}_{ED-} = \frac{\mathrm{RR}_{ED}^{obs}}{\mathrm{RR}_{ED-}^{true}} \le \mathrm{BF}_U, \quad \mathrm{CRR}_{ED} = \frac{\mathrm{RR}_{ED}^{obs}}{\mathrm{RR}_{ED}^{true}} \le \mathrm{BF}_U.$$

Proof of Proposition A.2. In the following proof, we first discuss CRR_{ED+}. The key observation is to write CRR_{ED+} in terms of a binary confounder with two levels corresponding to $\max_u r(u)$ and $\min_u r(u)$. To be more specific, we have that

$$\mathrm{CRR}_{ED+} = \frac{w_1 \max_u r(u) + (1-w_1)\min_u r(u)}{w_0 \max_u r(u) + (1-w_0)\min_u r(u)},$$

where

$$\begin{aligned} w_1 &= \frac{\int\{r(u)-\min_u r(u)\}F_1(du)}{\max_u r(u)-\min_u r(u)}, \qquad & 1-w_1 &= \frac{\int\{\max_u r(u)-r(u)\}F_1(du)}{\max_u r(u)-\min_u r(u)}, \\ w_0 &= \frac{\int\{r(u)-\min_u r(u)\}F_0(du)}{\max_u r(u)-\min_u r(u)}, \qquad & 1-w_0 &= \frac{\int\{\max_u r(u)-r(u)\}F_0(du)}{\max_u r(u)-\min_u r(u)}. \end{aligned}$$

Define $\Gamma = w_1/w_0$, and we have

$$\begin{aligned} \Gamma &= \frac{w_1}{w_0} = \frac{\int\{r(u)-\min_u r(u)\}F_1(du)}{\int\{r(u)-\min_u r(u)\}F_0(du)} = \frac{\int\{r(u)-\min_u r(u)\}\mathrm{RR}_{EU}(u)F_0(du)}{\int\{r(u)-\min_u r(u)\}F_0(du)} \\ &\leq \frac{\max_u \mathrm{RR}_{EU}(u) \times \int\{r(u)-\min_u r(u)\}F_0(du)}{\int\{r(u)-\min_u r(u)\}F_0(du)} = \mathrm{RR}_{EU}. \end{aligned}$$

We can write $w_0 = w_1/\Gamma$, and therefore we have

$$\mathrm{CRR}^{+}_{ED} = \frac{\{\max_u r(u)-\min_u r(u)\} \times w_1 + \min_u r(u)}{\{\max_u r(u)-\min_u r(u)\}/\Gamma \times w_1 + \min_u r(u)}.$$

In the following, we divide our discussion into two cases. If $\Gamma > 1$, then CRR^{+}_{ED} is increasing in w_1 according to Lemma A.1, and it attains the maximum at $w_1 = 1$. Thus we have

$$\mathrm{CRR}^{+}_{ED} \leq \frac{\Gamma \times \mathrm{RR}_{UD|E=0}}{\Gamma + \mathrm{RR}_{UD|E=0} - 1} \leq \frac{\mathrm{RR}_{EU} \times \mathrm{RR}_{UD|E=0}}{\mathrm{RR}_{EU} + \mathrm{RR}_{UD|E=0} - 1},$$

where the second inequality follows from Lemma A.2. If $\Gamma \leq 1$, then CRR^{+}_{ED} is non-increasing in w_1, and it attains the maximum at $w_1 = 0$. Thus we have

$$\mathrm{CRR}^{+}_{ED} \leq 1 \leq \frac{\mathrm{RR}_{EU} \times \mathrm{RR}_{UD|E=0}}{\mathrm{RR}_{EU} + \mathrm{RR}_{UD|E=0} - 1},$$

where the the second inequality again follows from Lemma A.2.

The same discussion applies to CRR_{ED}^{-}, and we can obtain that

$$\mathrm{CRR}_{ED}^{-} \leq \frac{\mathrm{RR}_{EU} \times \mathrm{RR}_{UD|E=1}}{\mathrm{RR}_{EU} + \mathrm{RR}_{UD|E=1} - 1}.$$

Using the fact $1/\mathrm{CRR}_{ED} = w/\mathrm{CRR}_{ED}^{+} + (1-w)/\mathrm{CRR}_{ED}^{-}$, we know that

$$\frac{1}{\mathrm{CRR}_{ED}} \geq \left(\frac{\mathrm{RR}_{EU} \times \mathrm{RR}_{UD}}{\mathrm{RR}_{EU} + \mathrm{RR}_{UD} - 1} \right)^{-1},$$

and the conclusion follows. □

eAppendix 2.3 The Implied Cornfield Conditions

Proposition A.2 says that the bounding factor is larger than or equal to all the confounding relative risks. It can be viewed as the Cornfield condition for the joint value of $(\mathrm{RR}_{EU}, \mathrm{RR}_{UD})$ in order to reduce the observed relative risk of $\mathrm{RR}_{ED}^{\mathrm{obs}}$ to the causal relative risk of $\mathrm{RR}_{ED}^{\mathrm{true}}$. If we specify one of the unmeasured confounding measure, for example RR_{EU}, then we can solve A.2 and obtain the lower bound of the other confounding measure:

$$\mathrm{RR}_{UD} \geq \frac{\mathrm{RR}_{EU} \times \mathrm{RR}_{ED}^{\mathrm{obs}} - \mathrm{RR}_{ED}^{\mathrm{obs}}}{\mathrm{RR}_{EU} \times \mathrm{RR}_{ED}^{\mathrm{true}} - \mathrm{RR}_{ED}^{\mathrm{obs}}}.$$

When $\mathrm{RR}_{ED}^{\mathrm{true}} = 1$, the above lower bound reduces to

$$\mathrm{RR}_{UD} \geq \frac{\mathrm{RR}_{EU} \times \mathrm{RR}_{ED}^{\mathrm{obs}} - \mathrm{RR}_{ED}^{\mathrm{obs}}}{\mathrm{RR}_{EU} - \mathrm{RR}_{ED}^{\mathrm{obs}}}.$$

Further, Proposition A.2 implies the following Cornfield-type conditions for RR_{EU} and RR_{UD}.

Proposition A.3. *We have the following Cornfield conditions:*

$$\min(\mathrm{RR}_{EU}, \mathrm{RR}_{UD}) \geq \mathrm{CRR}_{ED}, \quad \max(\mathrm{RR}_{EU}, \mathrm{RR}_{UD}) \geq \mathrm{CRR}_{ED} + \sqrt{\mathrm{CRR}_{ED}(\mathrm{CRR}_{ED} - 1)}.$$

Proof of Proposition A.3. According to Lemma A.2, the right-hand side of the last inequality in Proposition A.2 is increasing in both RR_{UD} and RR_{EU}. Therefore, the right-hand side of the above inequality in Proposition A.2 will increase if we let RR_{UD} or RR_{EU} go to large extremes. Let $\mathrm{RR}_{UD} \to \infty$, and we have $\mathrm{CRR}_{ED} \leq \mathrm{RR}_{EU}$. Let $\mathrm{RR}_{EU} \to \infty$, and we have $\mathrm{CRR}_{ED} \leq \mathrm{RR}_{UD}$. Therefore, we have the following low threshold: $\min(\mathrm{RR}_{UD}, \mathrm{RR}_{EU}) \geq \mathrm{CRR}_{ED}$. We can obtain the following inequality by replacing RR_{UD} and RR_{EU} in the bounding factor by their maximum value due to Lemma A.2:

$$\mathrm{CRR}_{ED} \leq \frac{\max^2(\mathrm{RR}_{UD}, \mathrm{RR}_{EU})}{2\max(\mathrm{RR}_{UD}, \mathrm{RR}_{EU}) - 1},$$

solving $\max(\mathrm{RR}_{UD}, \mathrm{RR}_{EU})$ from which we can obtain the following high threshold. □

eAppendix 2.4 Preventive Exposures

The bounding factor in Proposition A.2 is particularly useful for an apparently causative exposure with $\mathrm{RR}_{ED}^{\mathrm{obs}} > 1$, and the true causal relative risk is an attenuation of $\mathrm{RR}_{ED}^{\mathrm{obs}}$ by the bounding factor. However, for apparently preventive exposure with $\mathrm{RR}_{ED}^{\mathrm{obs}} < 1$, we can derive equally useful bias formula. For apparently preventive exposure, we modify the definition of the relative risk between E and U as $\mathrm{RR}_{EU} = \max_u \mathrm{RR}_{EU}^{-1}(u) = 1/\min_u \mathrm{RR}_{EU}(u)$, and obtain the following analogous result.

Proposition A.4. *For apparently preventive exposure, we have* $\mathrm{RR}_{ED}^{true}/\mathrm{RR}_{ED}^{obs} \leq \mathrm{BF}_U$. *Or, equivalently, the true causal relative risk is an inflation of* RR_{ED}^{obs} *by the bounding factor.*

Proof of Proposition A.4. Define $\bar{E} = 1 - E$, and the exposure $\bar{E}$ is apparently preventive for the outcome. Therefore, Proposition A.2 implies that

$$\frac{\mathrm{RR}_{\bar{E}D}}{\mathrm{RR}_{\bar{E}D}^{\mathrm{true}}} \leq \frac{\mathrm{RR}_{\bar{E}U} \times \mathrm{RR}_{UD}}{\mathrm{RR}_{\bar{E}U} + \mathrm{RR}_{UD} - 1}.$$

Since $\mathrm{RR}_{\bar{E}D} = 1/\mathrm{RR}^{\mathrm{obs}}_{ED}, \mathrm{RR}^{\mathrm{true}}_{\bar{E}D} = 1/\mathrm{RR}^{\mathrm{true}}_{ED}$, and $\mathrm{RR}_{\bar{E}U} = \max_u \mathrm{RR}^{-1}_{EU}(u) = \mathrm{RR}_{EU}$, the conclusion follows. □

eAppendix 2.5 Averaged Over Observed Covariates

All the results above are within strata of observed covariates C. The probabilities are conditional probabilities (e.g., $\mathrm{P}(D=1 \mid E=1, C=c), \mathrm{P}\{D(1)=1 \mid E=0, C=c\}, etc.$), the causal relative risks are conditional causal measures (e.g., $\mathrm{RD}^{\mathrm{true}}_{ED+} = \mathrm{P}\{D(1)=1 \mid E=1, C=c\}/\mathrm{P}\{D(0)=1 \mid E=0, C=c\}, etc.$), and the bounding factor is also conditional denoted as $\mathrm{BF}_{U|c} = \mathrm{RR}_{EU|c} \times \mathrm{RR}_{UD|c}/(\mathrm{RR}_{EU|c} + \mathrm{RR}_{UD|c} - 1)$.

We have the following decomposition:

$$\begin{aligned}
\mathrm{RR}^{\mathrm{true}}_{ED} &= \frac{\int \mathrm{P}(D=1 \mid E=1, C=c, U=u) F_{CU}(dcdu)}{\int \mathrm{P}(D=1 \mid E=0, C=c, U=u) F_{CU}(dcdu)} \\
&= \frac{\int\int \mathrm{P}(D=1 \mid E=1, C=c, U=u) F_{U|C}(du) F_C(dc)}{\int\int \mathrm{P}(D=1 \mid E=0, C=c, U=u) F_{U|C}(du) F_C(dc)} \\
&= \frac{\int \mathrm{P}\{D(1)=1 \mid C=c\} F_C(dc)}{\int \mathrm{P}\{D(0)=1 \mid C=c\} F_C(dc)} \\
&= \frac{\int \mathrm{RR}^{\mathrm{true}}_{ED|c} \mathrm{P}\{D(0)=1 \mid C=c\} F_C(dc)}{\int \mathrm{P}\{D(0)=1 \mid C=c\} F_C(dc)}.
\end{aligned}$$

Applying the result about conditional causal relative risk, we have

$$\mathrm{RR}^{\mathrm{true}}_{ED} \geq \frac{\int \frac{\mathrm{RR}^{\mathrm{obs}}_{ED|c}}{\mathrm{BF}_{U|c}} \mathrm{P}\{D(0)=1 \mid C=c\} F_C(dc)}{\int \mathrm{P}\{D(0)=1 \mid C=c\} F_C(dc)} \geq \min_c \frac{\mathrm{RR}^{\mathrm{obs}}_{ED|c}}{\mathrm{BF}_{U|c}}.$$

If we assume a common causal relative risk $\mathrm{RR}^{\mathrm{true}}_{ED|c} = \mathrm{RR}^{\mathrm{true}}_{ED}$, then we can sharpen the result as:

$$\mathrm{RR}^{\mathrm{true}}_{ED} \geq \max_c \frac{\mathrm{RR}^{\mathrm{obs}}_{ED|c}}{\mathrm{BF}_{U|c}}.$$

eAppendix 3 Another Bounding Factor and Implied Confield Conditions Using the Odds Ratio

eAppendix 3.1 Another Bounding Factor Using the Odds Ratio

Define $p(u) = \mathrm{P}(E = 1 \mid U = u)$ as the probability of the exposure, and $q(u) = p(u)/\{1 - p(u)\}$ as the odds of the exposure within level u of the confounder U. Let $\mathrm{OR}_{EU} = \max_u q(u)/\min_u q(u)$ be the ratio of the maximum and minimum of these odds. We use OR_{EU} to measure the association between the confounder U and the exposure E, which is defined as the maximal odds ratio between the exposure E and the confounder U. When the confounder U is binary, it reduces to the ordinary odds ratio. Using the odds ratio between the exposure E and U and the relative risk of the confounder U on the outcome D as the association measure as Bross and Lee[4–6], we have the following bounding factor that ties CRR_{ED} with OR_{EU} and RR_{UD}:

Proposition A.5. *We have*

$$\left(\frac{\sqrt{\mathrm{OR}_{EU}\mathrm{RR}_{UD}}+1}{\sqrt{\mathrm{OR}_{EU}}+\sqrt{\mathrm{RR}_{UD}}}\right)^2 \geq \frac{\mathrm{RR}_{ED}^{obs}}{\mathrm{RR}_{ED}^{true}} = \mathrm{CRR}_{ED}. \tag{A.1}$$

Proof of Proposition A.5. Lee[4] obtained the following results:

$$\mathrm{CRR}_{ED}^{+} \leq \left(\frac{\sqrt{\mathrm{OR}_{EU}\mathrm{RR}_{UD|E=0}}+1}{\sqrt{\mathrm{OR}_{EU}}+\sqrt{\mathrm{RR}_{UD|E=0}}}\right)^2, \quad \mathrm{CRR}_{ED}^{-} \leq \left(\frac{\sqrt{\mathrm{OR}_{EU}\mathrm{RR}_{UD|E=1}}+1}{\sqrt{\mathrm{OR}_{EU}}+\sqrt{\mathrm{RR}_{UD|E=1}}}\right)^2. \tag{A.2}$$

Since $\mathrm{RR}_{UD} = \max(\mathrm{RR}_{UD|E=0}, \mathrm{RR}_{UD|E=1})$, Lemma A.3 implies that

$$\mathrm{CRR}_{ED}^{+} \leq \left(\frac{\sqrt{\mathrm{OR}_{EU}\mathrm{RR}_{UD}}+1}{\sqrt{\mathrm{OR}_{EU}}+\sqrt{\mathrm{RR}_{UD}}}\right)^2, \quad \mathrm{CRR}_{ED}^{-} \leq \left(\frac{\sqrt{\mathrm{OR}_{EU}\mathrm{RR}_{UD}}+1}{\sqrt{\mathrm{OR}_{EU}}+\sqrt{\mathrm{RR}_{UD}}}\right)^2,$$

which leads to

$$\frac{1}{\mathrm{CRR}_{ED}} = \frac{w}{\mathrm{CRR}_{ED}^{+}} + \frac{1-w}{\mathrm{CRR}_{ED}^{-}} \geq \left(\frac{\sqrt{\mathrm{OR}_{EU}}+\sqrt{\mathrm{RR}_{UD}}}{\sqrt{\mathrm{OR}_{EU}\mathrm{RR}_{UD}}+1}\right)^2,$$

and the conclusion follows. □

eAppendix 3.2 Implied Cornfield Conditions

The bounding factor in the last subsection implies the following Cornfield conditions:

Proposition A.6. *We have*

$$\min(\mathrm{OR}_{EU}, \mathrm{RR}_{UD}) \geq \mathrm{CRR}_{ED}, \quad \max(\mathrm{OR}_{EU}, \mathrm{RR}_{UD}) \geq \left(\sqrt{\mathrm{CRR}_{ED}} + \sqrt{\mathrm{CRR}_{ED} - 1}\right)^2.$$

Proof of Proposition A.6. According to Lemma A.3, we can let RR_{ED} goes to infinity, and obtain $\mathrm{OR}_{EU} \geq \mathrm{CRR}_{ED}$. Similarly, we can let OR_{EU} goes to infinity, and obtain $\mathrm{RR}_{UD} \geq \mathrm{CRR}_{ED}$. Combining them together, we have the following low threshold: $\min(\mathrm{OR}_{EU}, \mathrm{RR}_{UD}) \geq \mathrm{CRR}_{ED}$. According to Lemma A.3 again, we can replace OR_{EU} and RR_{UD} by $\max(\mathrm{OR}_{EU}, \mathrm{RR}_{UD})$ in the bounding factor in Section eAppendix 3.1 , and preserve the inequality as follows:

$$\left(\frac{\max(\mathrm{OR}_{EU}, \mathrm{RR}_{UD}) + 1}{2\sqrt{\max(\mathrm{OR}_{EU}, \mathrm{RR}_{UD})}}\right)^2 \geq \mathrm{CRR}_{ED}.$$

Solving the above inequality, we obtain $\sqrt{\max(\mathrm{OR}_{EU}, \mathrm{RR}_{UD})} \geq \sqrt{\mathrm{CRR}_{ED}} + \sqrt{\mathrm{CRR}_{ED} - 1}$, and the high threshold follows. □

Propositions A.5 and A.6 generalize the results of Bross[5,6] and Lee[4] from only being applicable under the null hypothesis of no effect (i.e., only being useful for assessing how much unmeasured confounding would suffice to completely explain away an effect estimate) to alternative hypotheses and sensitivity analysis.

eAppendix 3.3 Preventive Exposure

For apparently preventive exposure with $\mathrm{RR}_{ED}^{\mathrm{obs}} < 1$, we can derive bias formula similar to Proposition A.5, and we don't even need to modify the definition of OR_{EU}.

Proposition A.7. *For apparently preventive exposure, we have*

$$\frac{\mathrm{RR}_{ED}^{true}}{\mathrm{RR}_{ED}^{obs}} \leq \left(\frac{\sqrt{\mathrm{OR}_{EU}\mathrm{RR}_{UD}}+1}{\sqrt{\mathrm{OR}_{EU}}+\sqrt{\mathrm{RR}_{UD}}} \right)^2.$$

Proof of Proposition A.7. Define $\bar{E} = 1-E$. Applying Proposition A.5, we have

$$\frac{\mathrm{RR}_{\bar{E}D}}{\mathrm{RR}_{\bar{E}D}^{\text{true}}} \leq \left(\frac{\sqrt{\mathrm{OR}_{\bar{E}U}\mathrm{RR}_{UD}}+1}{\sqrt{\mathrm{OR}_{\bar{E}U}}+\sqrt{\mathrm{RR}_{UD}}} \right)^2.$$

Since $\mathrm{RR}_{\bar{E}D} = 1/\mathrm{RR}_{ED}^{\text{obs}}, \mathrm{RR}_{\bar{E}D}^{\text{true}} = 1/\mathrm{RR}_{ED}^{\text{true}}$, and

$$\mathrm{OR}_{\bar{E}U} = \frac{\max_u 1/q(u)}{\min_u 1/q(u)} = \frac{1/\min_u q(u)}{1/\max_u q(u)} = \frac{\max_u q(u)}{\min_u q(u)} = \mathrm{OR}_{EU},$$

the conclusion follows. □

eAppendix 4 Relations with Existing Results

eAppendix 4.1 Schlesselman's Formula

For a binary confounder U, Schlesselman[1] first obtained that

$$\frac{\mathrm{RR}_{ED}^{\text{obs}}}{\mathrm{RR}_{ED-}^{\text{true}}} = \frac{1+(\mathrm{RR}_{UD|E=1}-1)\mathrm{P}(U=1 \mid E=1)}{1+(\mathrm{RR}_{UD|E=0}-1)\mathrm{P}(U=1 \mid E=0)}.$$

He further assumed a common relative risk of the exposure E on the outcome D within both $U=0$ and $U=1$, and also a common relative risk of the confounder U on the outcome D within both $E=0$ and $E=1$, denoted by γ. Under the above no-interaction assumption, Schlesselman simplified the above identity to the following formula:

$$\frac{\mathrm{RR}_{ED}^{\text{obs}}}{\mathrm{RR}_{ED}^{\text{true}}} = \frac{1+(\gamma-1)\mathrm{P}(U=1 \mid E=1)}{1+(\gamma-1)\mathrm{P}(U=1 \mid E=0)}.$$

We can write $\mathrm{P}(U=1 \mid E=0) = \mathrm{P}(U=1 \mid E=1)/\mathrm{RR}_{EU}$ and then maximize the right-hand side of the above formula over $\mathrm{P}(U=1 \mid E=1)$, which gives us the following inequality:

$$\frac{\mathrm{RR}_{ED}^{\text{obs}}}{\mathrm{RR}_{ED}^{\text{true}}} \leq \frac{\mathrm{RR}_{EU} \times \gamma}{\mathrm{RR}_{EU}+\gamma-1}.$$

The inequality above is the same as our main result in the main text, but is derived under unnecessary assumptions. Our result is much more general than the previous result obtained by Schlesselman[1], and his assumptions are not necessary for deriving our new bounding factor.

eAppendix 4.2 Flanders and Khoury's results

Flanders and Khoury[2] used slightly different notation for categorical confounder U:

$$\begin{aligned} p_k &= \mathrm{P}(U=k \mid E=0), \\ \mathrm{OR}_k &= \frac{\mathrm{P}(U=k \mid E=1)/\mathrm{P}(U=0 \mid E=1)}{\mathrm{P}(U=k \mid E=0)/\mathrm{P}(U=0 \mid E=0)}, \\ \mathrm{RR}_k &= \frac{\mathrm{P}(D=1 \mid U=k, E=0)}{\mathrm{P}(D=1 \mid U=0, E=0)}. \end{aligned}$$

They expressed the confounding relative risk for the exposed population as

$$\mathrm{CRR}_{ED+} = \frac{\sum_k \mathrm{RR}_k \mathrm{OR}_k p_k}{(\sum_k \mathrm{OR}_k p_k)(\sum_k \mathrm{RR}_k p_k)}.$$

The above sensitivity analysis formula depends on a large number of sensitivity parameters, and requires specifying the prevalence of the unmeasured confounder among unexposed population. Flanders and Khoury simplified it for binary confounder. However, for general categorical confounder, they derived the following bounds on the confounding relative risk:

$$\mathrm{CRR}_{ED+} \leq \min\left\{ \frac{\max_k \mathrm{OR}_k}{\sum_k \mathrm{OR}_k p_k}, \frac{\max_k \mathrm{RR}_k}{\sum_k \mathrm{RR}_k p_k}, \max_k \mathrm{OR}_k, \max_k \mathrm{RR}_k, \frac{1}{p_{k^*}}, \frac{1}{p_{k^{**}}} \right\},$$

where k^* and k^{**} are the strata corresponding to the largest OR_k and RR_k, respectively. The upper bound depends on the prevalence of U. If we do not have any knowledge about the number of categories or the prevalence of U, the above bound reduces to

$$\mathrm{CRR}_{ED+} \leq \min\left\{ \max_k \mathrm{OR}_k, \max_k \mathrm{RR}_k \right\},$$

which is essentially the low threshold Cornfield condition.

eAppendix 5 Results for the Risk Difference Using Sensitivity Parameters on the Relative Risk Scale

eAppendix 5.1 Lower Bounds for the Causal Risk Differences

Define $p_1 = \mathrm{P}(D=1 \mid E=1)$ and $p_0 = \mathrm{P}(D=1 \mid E=0)$ as the probabilities of the outcome with and without exposure, and $f = \mathrm{P}(E=1)$ as the prevalence of the exposure. The causal risk differences for the exposed, unexposed and the whole population are defined as

$$\begin{aligned}
\mathrm{RD}^{\text{true}}_{ED+} &= \mathrm{P}\{D(1)=1 \mid E=1\} - \mathrm{P}\{D(0)=1 \mid E=1\} = p_1 - \mathrm{P}\{D(0)=1 \mid E=1\}, \\
\mathrm{RD}^{\text{true}}_{ED-} &= \mathrm{P}\{D(1)=1 \mid E=0\} - \mathrm{P}\{D(0)=1 \mid E=0\} = \mathrm{P}\{D(1)=1 \mid E=0\} - p_0, \\
\mathrm{RD}^{\text{true}}_{ED} &= \mathrm{P}\{D(1)=1\} - \mathrm{P}\{D(0)=1\}.
\end{aligned}$$

If U suffices to control the confounding between the exposure and the outcome, then the following standardized risk differences are the causal risk differences for the exposed, unexposed and the whole population:

$$\mathrm{RD}^{\text{true}}_{ED+} = p_1 - \int r(u)F_1(du), \quad \mathrm{RD}^{\text{true}}_{ED-} = \int r^*(u)F_0(du) - p_0, \quad \mathrm{RD}^{\text{true}}_{ED} = \int \{r^*(u) - r(u)\}F(du).$$

Proposition A.8. *The lower bounds for the causal risk differences are*

$$\mathrm{RD}^{true}_{ED+} \geq p_1 - p_0 \times \mathrm{BF}_U,$$

$$\mathrm{RD}^{true}_{ED-} \geq p_1/\mathrm{BF}_U - p_0,$$

$$\mathrm{RD}^{true}_{ED} \geq (p_1 - p_0 \times \mathrm{BF}_U) \times \{f + (1-f)/\mathrm{BF}_U\} = (p_1/\mathrm{BF}_U - p_0) \times \{f \times \mathrm{BF}_U + (1-f)\}.$$

Proof of Proposition A.8. From the data, we can identify:

$$\begin{aligned}
p_1 &= \int \mathrm{P}(D=1 \mid E=1, U=u)F_1(du) = \int r^*(u)F_1(du), \\
p_0 &= \int \mathrm{P}(D=1 \mid E=0, U=u)F_0(du) = \int r(u)F_0(du).
\end{aligned}$$

However, the following two counterfactual probabilities are not identifiable:

$$\begin{aligned} \mathrm{P}\{D(1)=1 \mid E=0\} &= \int \mathrm{P}(D=1 \mid E=1, U=u) F_0(du) = \int r^*(u) F_0(du), \\ \mathrm{P}\{D(0)=1 \mid E=1\} &= \int \mathrm{P}(D=1 \mid E=0, U=u) F_1(du) = \int r(u) F_1(du). \end{aligned}$$

First, we have

$$\frac{p_1}{\mathrm{P}\{D(1)=1 \mid E=0\}} = \frac{\int r^*(u) F_1(du)}{\int r^*(u) F_0(du)} = \mathrm{CRR}_{ED-} \leq \mathrm{BF}_U$$

according to Proposition A.2, and thus $\mathrm{P}\{D(1)=1 \mid E=0\} \geq p_1/\mathrm{BF}_U$. Second, we have

$$\frac{\mathrm{P}\{D(0)=1 \mid E=1\}}{p_0} = \frac{\int r(u) F_1(du)}{\int r(u) F_0(du)} = \mathrm{CRR}_{ED+} \leq \mathrm{BF}_U$$

according to Proposition A.2, and thus $\mathrm{P}\{D(0)=1 \mid E=1\} \leq p_0 \times \mathrm{BF}_U$. Therefore, the lower bound for $\mathrm{RD}^{\mathrm{true}}_{ED+}$ is $\mathrm{RD}^{\mathrm{true}}_{ED+} \geq p_1 - p_0 \times \mathrm{BF}_U$, and for $\mathrm{RD}^{\mathrm{true}}_{ED-}$ is $\mathrm{RD}^{\mathrm{true}}_{ED-} \geq p_1/\mathrm{BF}_U - p_0$. We can obtain the lower bound for $\mathrm{RD}^{\mathrm{true}}_{ED}$ using $\mathrm{RD}^{\mathrm{true}}_{ED} = f\mathrm{RD}^{\mathrm{true}}_{ED+} + (1-f)\mathrm{RD}^{\mathrm{true}}_{ED-}$. □

If the probability of $E=1$, f, is unknown, the above result about $\mathrm{RD}^{\mathrm{true}}_{ED}$ is not directly useful. In the following, we obtain a lower bound for $\mathrm{RD}^{\mathrm{true}}_{ED}$ based on $\mathrm{RD}^{\mathrm{true}}_{ED} = f\mathrm{RD}^{\mathrm{true}}_{ED+} + (1-f)\mathrm{RD}^{\mathrm{true}}_{ED-}$, which does not depend on f.

Proposition A.9. *We have* $\mathrm{RD}^{true}_{ED} \geq \min(p_1 - p_0 \times \mathrm{BF}_U, p_1/\mathrm{BF}_U - p_0)$. *When* $p_1 > p_0$ *and* $1 \leq \mathrm{BF}_U \leq \mathrm{RR}^{obs}_{ED}$, *the above lower bound reduces to* $\mathrm{RD}^{true}_{ED} \geq p_1 - p_0 \times \mathrm{BF}_U$.

The above results are particularly useful for an apparently causative exposure with $\mathrm{RD}^{\mathrm{obs}}_{ED} > 0$, which give (possibly positive) lower bounds for the causal risk differences. However, for an apparently preventive exposure with $\mathrm{RD}^{\mathrm{obs}}_{ED} < 0$, we need to modify the definition of RR_{EU} as $\mathrm{RR}_{EU} = \max_u \mathrm{RR}^{-1}_{EU}(u)$. And we have the following analogous results.

Proposition A.10. *For apparently preventive exposure with* $\mathrm{RD}_{ED}^{obs} < 0$*, we have*

$$\mathrm{RD}_{ED+}^{true} \leq p_1 \times \mathrm{BF}_U - p_0,$$

$$\mathrm{RD}_{ED-}^{true} \leq p_1 - p_0/\mathrm{BF}_U,$$

$$\mathrm{RD}_{ED}^{true} \leq (p_1 \times \mathrm{BF}_U - p_0) \times \{f + (1-f)/\mathrm{BF}_U\} = (p_1 - p_0/\mathrm{BF}_U) \times \{f \times \mathrm{BF}_U + (1-f)\}.$$

When f *is unknown and* $1 \leq \mathrm{BF}_U \leq 1/\mathrm{RR}_{ED}^{obs}$*, we have* $\mathrm{RR}_{ED}^{true} \leq p_1 - p_0/\mathrm{BF}_U$.

Proof of Proposition A.10. Define $\bar{E} = 1 - E$. Applying Proposition A.8, we have

$$\begin{aligned}
\mathrm{RD}_{\bar{E}D+}^{\mathrm{true}} &\geq \mathrm{P}(D=1 \mid \bar{E}=1) - \mathrm{P}(D=1 \mid \bar{E}=0) \times \mathrm{BF}_U, \\
\mathrm{RD}_{\bar{E}D-}^{\mathrm{true}} &\geq \mathrm{P}(D=1 \mid \bar{E}=1)/\mathrm{BF}_U - \mathrm{P}(D=1 \mid \bar{E}=0), \\
\mathrm{RD}_{\bar{E}D}^{\mathrm{true}} &\geq \{\mathrm{P}(D=1 \mid \bar{E}=1) - \mathrm{P}(D=1 \mid \bar{E}=0) \times \mathrm{BF}_U\} \times \{f + (1-f)/\mathrm{BF}_U\} \\
&= \{\mathrm{P}(D=1 \mid \bar{E}=1)/\mathrm{BF}_U - \mathrm{P}(D=1 \mid \bar{E}=0)\} \times \{f \times \mathrm{BF}_U + (1-f)\}.
\end{aligned}$$

Since $\mathrm{RD}_{\bar{E}D+}^{\mathrm{true}} = -\mathrm{RD}_{ED+}^{\mathrm{true}}, \mathrm{RD}_{\bar{E}D-}^{\mathrm{true}} = -\mathrm{RD}_{ED-}^{\mathrm{true}}$ and $\mathrm{RD}_{\bar{E}D}^{\mathrm{true}} = -\mathrm{RD}_{ED}^{\mathrm{true}}$, the first three conclusions follow. When f is unknown and $1 \leq \mathrm{BF}_U \leq 1/\mathrm{RR}_{ED}^{\mathrm{obs}}$, we have $\mathrm{RD}_{ED}^{\mathrm{true}} \leq \max(\mathrm{RD}_{ED+}^{\mathrm{true}}, \mathrm{RD}_{ED-}^{\mathrm{true}}) = p_1 - p_0/\mathrm{BF}_U$.

□

The above discussion is within strata of observed covariates C. All probabilities are essentially conditional probabilities, e.g., $\mathrm{P}(D=1 \mid E=1, C=c), \mathrm{P}(E=1 \mid C=c), etc.$ Consequently, the bounding factor and causal risk differences are also conditional, denoted as $\mathrm{BF}_{U|c}, \mathrm{RD}_{ED|c+}^{\mathrm{true}}, \mathrm{RD}_{ED|c-}^{\mathrm{true}}$ and $\mathrm{RD}_{ED|c}^{\mathrm{true}}$. Due to the linearity of the risk difference, i.e., $\mathrm{RD}_{ED+}^{\mathrm{true}} = \sum_c \mathrm{RD}_{ED|c+}^{\mathrm{true}} \mathrm{P}(C=c \mid E=1), \mathrm{RD}_{ED-}^{\mathrm{true}} = \sum_c \mathrm{RD}_{ED|c-}^{\mathrm{true}} \mathrm{P}(C=c \mid E=0)$ and $\mathrm{RD}_{ED}^{\mathrm{true}} =$

$\sum_c \mathrm{RD}^{\mathrm{true}}_{ED|c}\mathrm{P}(C=c)$, we have the following results about the marginal risk differences:

$$\begin{aligned}
\mathrm{RD}^{\mathrm{true}}_{ED+} &\geq \sum_c \left\{\mathrm{P}(D=1 \mid E=1, C=c) - \mathrm{P}(D=1 \mid E=0, C=c) \times \mathrm{BF}_{U|c}\right\} \mathrm{P}(C=c \mid E=1), \\
\mathrm{RD}^{\mathrm{true}}_{ED-} &\geq \sum_c \left\{\mathrm{P}(D=1 \mid E=1, C=c)/\mathrm{BF}_{U|c} - \mathrm{P}(D=1 \mid E=0, C=c)\right\} \mathrm{P}(C=c \mid E=0), \\
\mathrm{RD}^{\mathrm{true}}_{ED} &\geq f \sum_c \left\{\mathrm{P}(D=1 \mid E=1, C=c) - \mathrm{P}(D=1 \mid E=0, C=c) \times \mathrm{BF}_{U|c}\right\} \mathrm{P}(C=c \mid E=1) \\
&\quad + (1-f) \sum_c \left\{\mathrm{P}(D=1 \mid E=1, C=c)/\mathrm{BF}_{U|c} - \mathrm{P}(D=1 \mid E=0, C=c)\right\} \mathrm{P}(C=c \mid E=0).
\end{aligned}$$

eAppendix 5.2 Statistical Inference for the Causal Risk Differences

In previous subsections we discussed the population quantities assuming that we knew the distribution of (E, D, C). In this subsection, we will discuss the finite sample inference for the causal risk differences. We can straightforwardly estimate f, p_1 and p_0 by sample frequencies $\widehat{f}, \widehat{p}_1$ and $\widehat{p}_0$ with standard errors s, s_1 and s_0, respectively. Then we can estimate the lower bound for $\mathrm{RD}^{\mathrm{true}}_{ED+}$ by $\widehat{p}_1 - \widehat{p}_0 \times \mathrm{BF}_U$ with standard error $(s_1^2 + s_0^2 \times \mathrm{BF}_U^2)^{1/2}$, estimate the lower bound for $\mathrm{RD}^{\mathrm{true}}_{ED-}$ by $\widehat{p}_1/\mathrm{BF}_U - \widehat{p}_0$ with standard error $(s_1^2/\mathrm{BF}_U^2 + s_0^2)^{1/2}$, and estimate the lower bound for $\mathrm{RD}^{\mathrm{true}}_{ED}$ by $(\widehat{p}_1 - \widehat{p}_0 \times \mathrm{BF}_U) \times \{\widehat{f} + (1-\widehat{f})/\mathrm{BF}_U\}$ or $(\widehat{p}_1/\mathrm{BF}_U - \widehat{p}_0) \times \{\widehat{f} \times \mathrm{BF}_U + (1-\widehat{f})\}$ with standard error

$$\sqrt{(s_1^2 + s_0^2 \times \mathrm{BF}_U^2)\left(\widehat{f} + \frac{1-\widehat{f}}{\mathrm{BF}_U}\right)^2 + (\widehat{p}_1 - \widehat{p}_0 \times \mathrm{BF}_U)^2 (1 - \mathrm{BF}_U^{-1})^2 s^2},$$

using a standard argument of the delta-method. After obtaining the point estimates and their standard errors, we can construct confidence intervals for these causal risk differences.

Note that even without estimating the prevalence, f, of the exposure, if the exposure is apparently causative, we can use the lower bound of $\min(\mathrm{RD}^{\mathrm{true}}_{ED+}, \mathrm{RD}^{\mathrm{true}}_{ED-})$ as a lower bound for $\mathrm{RD}^{\mathrm{true}}_{ED}$. The point estimate of the causal risk difference averaged over the observed covariates can be obtained by the weighted average of the point estimates of the causal risk

differences within strata of C with the proportions of the strata as the weights, and the corresponding sampling variance is the weighted average of the sampling variances within strata with the squared proportions of the strata as the weights.

eAppendix 5.3 Implied Cornfield Conditions

The results in Proposition A.8 imply the following Cornfield conditions.

Proposition A.11. *For an unmeasured confounder to reduce the observed risk difference to be* $\mathrm{RD}^{true}_{ED+}, \mathrm{RD}^{true}_{ED-}$ *and* RD^{true}_{ED} *respectively, the joint Cornfield conditions are*

$$\mathrm{BF}_U \geq (p_1 - \mathrm{RD}^{true}_{ED+})/p_0,$$

$$\mathrm{BF}_U \geq p_1/(p_0 + \mathrm{RD}^{true}_{ED-}),$$

$$\mathrm{BF}_U \geq \frac{\sqrt{\{\mathrm{RD}^{true}_{ED} + p_0(1-f) - p_1 f\}^2 + 4p_1 p_0 f(1-f)} - \{\mathrm{RD}^{true}_{ED} + p_0(1-f) - p_1 f\}}{2p_0 f}.$$

Proof of Proposition A.11. It is straightforward to see that the first two conclusions of Proposition A.8 imply the first two inequalities. From the third conclusion of Proposition A.8, we have the following quadratic inequality about BF_U:

$$(p_0 f)\mathrm{BF}_U^2 + \{p_0(1-f) + \mathrm{RD}^{\mathrm{true}}_{ED} - p_1 f\}\mathrm{BF}_U - p_1(1-f) \geq 0.$$

The corresponding equation has one negative root and the following positive root:

$$\mathrm{BF}^*_U = \frac{\sqrt{\{\mathrm{RD}^{\mathrm{true}}_{ED} + p_0(1-f) - p_1 f\}^2 + 4p_1 p_0 f(1-f)} - \{\mathrm{RD}^{\mathrm{true}}_{ED} + p_0(1-f) - p_1 f\}}{2p_0 f}.$$

Since $\mathrm{BF}_U > 0$, the inequality has the solution $\mathrm{BF}_U \geq \mathrm{BF}^*_U$. □

Similar to the discussion in the last two sections, we can also derive the low and high threshold Cornfield conditions from the above joint Cornfield conditions for $(\mathrm{RR}_{EU}, \mathrm{RR}_{UD})$.

If $\mathrm{RD}^{\text{true}}_{ED+}, \mathrm{RD}^{\text{true}}_{ED-}$ and $\mathrm{RD}^{\text{true}}_{ED}$ are zero, all the conditions in Proposition A.11 reduce to $\mathrm{BF}_U \geq \mathrm{RR}^{\text{obs}}_{ED}$, the one derived from the result about the relative risk of the exposure on the outcome. Therefore, the formula from the risk difference is the same as that derived from the relative risk under the null hypothesis, but they are different under the alternative hypotheses.

With finite sample, we can also find the smallest bounding factor that can reduce the lower confidence limit of the lower bound of the causal risk differences to a certain magnitude. We will discuss $(1-\alpha)\%$ confidence intervals based on asymptotic normality, and let $z_\alpha = \Phi^{-1}(1-\alpha/2)$ denote the upper $\alpha/2$ quantile of the standard normal distribution (e.g., when $\alpha = 0.05$, $z_{0.05} = 1.96$). In order to reduce the confidence interval of the risk difference on the exposed to cover a true causal risk difference $\mathrm{RD}^{\text{true}}_{ED+}$, the bounding factor must satisfy

$$\widehat{p}_1 - \widehat{p}_0 \times \mathrm{BF}_U - z_\alpha \sqrt{s_1^2 + s_0^2 \times \mathrm{BF}_U^2} \leq \mathrm{RD}^{\text{true}}_{ED+},$$

which has the following solution:

$$\mathrm{BF}_U \geq \frac{\widehat{p}_0(\widehat{p}_1 - \mathrm{RD}^{\text{true}}_{ED+}) - \sqrt{\widehat{p}_0^2(\widehat{p}_1 - \mathrm{RD}^{\text{true}}_{ED+})^2 - (\widehat{p}_0^2 - z_\alpha^2 s_0^2)\{(\widehat{p}_1 + \mathrm{RD}^{\text{true}}_{ED+})^2 - z_\alpha^2 s_1^2\}}}{\widehat{p}_0^2 - z_\alpha^2 s_0^2}. \tag{A.3}$$

In order to reduce the confidence interval of the risk difference on the unexposed to cover a true causal risk difference $\mathrm{RD}^{\text{true}}_{ED-}$, the bounding factor must satisfy

$$\widehat{p}_1/\mathrm{BF}_U - \widehat{p}_0 - z_\alpha \sqrt{s_1^2/\mathrm{BF}_U^2 + s_0^2} \leq \mathrm{RD}^{\text{true}}_{ED-},$$

which has the following solution:

$$\mathrm{BF}_U \geq \frac{\widehat{p}_1(\widehat{p}_0 + \mathrm{RD}^{\text{true}}_{ED-}) - \sqrt{\widehat{p}_1^2(\widehat{p}_0 + \mathrm{RD}^{\text{true}}_{ED-})^2 - \{(\widehat{p}_0 + \mathrm{RD}^{\text{true}}_{ED-})^2 - z_\alpha^2 s_0^2\}(\widehat{p}_1^2 - z_\alpha^2 s_1^2)}}{(\widehat{p}_0 + \mathrm{RD}^{\text{true}}_{ED-})^2 - z_\alpha^2 s_0^2}. \tag{A.4}$$

Note that if we assume $\mathrm{RD}^{\text{true}}_{ED+} = \mathrm{RD}^{\text{true}}_{ED-} = 0$, the above solutions in (A.3) and (A.4) reduce to the same form:

$$\mathrm{BF}_U \geq \frac{\widehat{p}_1\widehat{p}_0 - \sqrt{\widehat{p}_1^2\widehat{p}_0^2 - (\widehat{p}_0^2 - z_\alpha^2 s_0^2)(\widehat{p}_1^2 - z_\alpha^2 s_1^2)}}{\widehat{p}_0^2 - z_\alpha^2 s_0^2}.$$

In order to reduce the confidence interval of the risk difference to cover a true causal risk difference $\mathrm{RD}_{ED}^{\text{true}}$, the bounding factor must satisfy

$$(\widehat{p}_1 - \widehat{p}_0 \times \mathrm{BF}_U)\left(\widehat{f} + \frac{1-\widehat{f}}{\mathrm{BF}_U}\right)$$
$$-z_\alpha \sqrt{(s_1^2 + s_0^2 \times \mathrm{BF}_U^2)\left(\widehat{f} + \frac{1-\widehat{f}}{\mathrm{BF}_U}\right)^2 + (\widehat{p}_1 - \widehat{p}_0 \times \mathrm{BF}_U)^2 (1 - \mathrm{BF}_U^{-1})^2 s^2} \leq \mathrm{RD}_{ED}^{\text{true}}, \tag{A.5}$$

which can be solved numerically. For example, we can apply a grid search for the solution of (A.5) over the following bounded range:

$$\mathrm{BF}_U \in \left(1, \frac{\sqrt{\{\mathrm{RD}_{ED}^{\text{true}} + \widehat{p}_0(1-\widehat{f}) - \widehat{p}_1\widehat{f}\}^2 + 4\widehat{p}_1\widehat{p}_0 f(1-\widehat{f})} - \{\mathrm{RD}_{ED}^{\text{true}} + \widehat{p}_0(1-\widehat{f}) - \widehat{p}_1\widehat{f}\}}{2\widehat{p}_0\widehat{f}}\right),$$

since the point estimate has already been reduced to $\mathrm{RD}_{ED}^{\text{true}}$ when BF_U attains the above upper bound of range.

eAppendix 6 Results for the Risk Difference Using Sensitivity Parameters on the Risk Difference Scale

eAppendix 6.1 A Useful Proposition

We first recall some definitions in the main text, and assume a categorical unmeasured confounder U. Let $\mathrm{RD}_{ED}^{\text{obs}} = \mathrm{P}(D=1 \mid E=1) - \mathrm{P}(D=1 \mid E=0)$ denote the observed risk difference,

$$\mathrm{RD}_{ED}^{\text{true}} = \sum_{k=0}^{K-1} \{\mathrm{P}(D=1 \mid E=1, U=k) - \mathrm{P}(D=1 \mid E=0, U=k)\}\mathrm{P}(U=k)$$

denote the true causal risk difference, and $\mathrm{CRD}_{ED} = \mathrm{RD}_{ED}^{\text{obs}} - \mathrm{RD}_{ED}^{\text{true}}$ denote the confounding risk difference of the exposure E on the outcome D. Define $\alpha_k = \mathrm{P}(U=k \mid E=1) - \mathrm{P}(U=k \mid E=0)$ and $\mathrm{RD}_{EU} = \max_{k \geq 1} |\alpha_k|$. Define $\beta_k^* = \mathrm{P}(D=1 \mid E=1, U=k) - \mathrm{P}(D=1 \mid E=$

$1, U = 0)$ and $\beta_k = \mathrm{P}(D = 1 \mid E = 0, U = k) - \mathrm{P}(D = 1 \mid E = 0, U = 0)$. Define $\mathrm{RD}_{UD|E=1} = \max_{k \geq 1} |\beta_k^*|, \mathrm{RD}_{UD|E=0} = \max_{k \geq 1} |\beta_k|$ and $\mathrm{RD}_{UD} = \max(\mathrm{RD}_{UD|E=1}, \mathrm{RD}_{UD|E=0})$. The confounding risk difference can be decomposed as follows.

Proposition A.12. *The confounding risk difference of E on D,* CRD_{ED}*, can be expressed as*

$$\mathrm{CRD}_{ED} = \mathrm{RD}_{ED}^{obs} - \mathrm{RD}_{ED}^{true} = \sum_{k=1}^{K-1} \alpha_k \{\beta_k^* P(E = 0) + \beta_k P(E = 1)\}.$$

Proof of Proposition A.12. The true and observed risk differences of E on D can be expressed as

$$\begin{aligned}
\mathrm{RD}_{ED}^{\text{true}} &= \sum_{k=0}^{K-1} \mathrm{P}(D = 1 \mid E = 1, U = k)\mathrm{P}(U = k) - \sum_{k=0}^{K-1} \mathrm{P}(D = 1 \mid E = 0, U = k)\mathrm{P}(U = k), \\
\mathrm{RD}_{ED}^{\text{obs}} &= \sum_{k=0}^{K-1} \mathrm{P}(D = 1 \mid E = 1, U = k)\mathrm{P}(U = k \mid E = 1) - \sum_{k=0}^{K-1} \mathrm{P}(D = 1 \mid E = 0, U = k)\mathrm{P}(U = k \mid E = 0).
\end{aligned}$$

Therefore, the confounding risk difference of E on D, CRD_{ED}, can be expressed as

$$\begin{aligned}
\mathrm{CRD}_{ED} &= \sum_{k=0}^{K-1} \mathrm{P}(D = 1 \mid E = 1, U = k)\{\mathrm{P}(U = k \mid E = 1) - \mathrm{P}(U = k)\} \\
&\quad - \sum_{k=0}^{K-1} \mathrm{P}(D = 1 \mid E = 0, U = k)\{\mathrm{P}(U = k \mid E = 0) - \mathrm{P}(U = k)\}.
\end{aligned}$$

Applying the law of total probability, we have the following results:

$$\mathrm{P}(U = k \mid E = 1) - \mathrm{P}(U = k) = \alpha_k \mathrm{P}(E = 0), \quad \mathrm{P}(U = k \mid E = 0) - \mathrm{P}(U = k) = -\alpha_k \mathrm{P}(E = 1).$$

Therefore, the confounding risk difference can be rewritten as

$$\begin{aligned}
\mathrm{CRD}_{ED} &= \sum_{k=0}^{K-1} \alpha_k \mathrm{P}(D = 1 \mid E = 1, U = k)\mathrm{P}(E = 0) + \sum_{k=0}^{K-1} \alpha_k \mathrm{P}(D = 1 \mid E = 0, U = k)\mathrm{P}(E = 1) \\
&= \sum_{k=0}^{K-1} \alpha_k \{\mathrm{P}(D = 1 \mid E = 1, U = k)\mathrm{P}(E = 0) + \mathrm{P}(D = 1 \mid E = 0, U = k)\mathrm{P}(E = 1)\}.
\end{aligned}$$

Using the fact that $\alpha_0 = -\sum_{k=1}^{K-1} \alpha_k$, we can obtain that

$$\begin{aligned}
\mathrm{CRD}_{ED} &= \sum_{k=1}^{K-1} \alpha_k \{\mathrm{P}(D=1 \mid E=1, U=k)\mathrm{P}(E=0) + \mathrm{P}(D=1 \mid E=0, U=k)\mathrm{P}(E=1)\} \\
&\quad - \sum_{k=1}^{K-1} \alpha_k \{\mathrm{P}(D=1 \mid E=1, U=0)\mathrm{P}(E=0) + \mathrm{P}(D=1 \mid E=0, U=0)\mathrm{P}(E=1)\} \\
&= \sum_{k=1}^{K-1} \alpha_k \{\beta_k^* \mathrm{P}(E=0) + \beta_k \mathrm{P}(E=1)\}. \square
\end{aligned}$$

eAppendix 6.2 Binary Confounder

For a binary confounder U with $K = 2$, we have the following proposition.

Proposition A.13. *When U is binary, we have $\mathrm{RD}_{EU} \times \mathrm{RD}_{UD} \geq \mathrm{RD}_{ED}^{obs} - \mathrm{RD}_{ED}^{true}$, implying*

$$\min(\mathrm{RD}_{EU}, \mathrm{RD}_{UD}) \geq \mathrm{RD}_{ED}^{obs} - \mathrm{RD}_{ED}^{true}, \quad \max(\mathrm{RD}_{EU}, \mathrm{RD}_{UD}) \geq \sqrt{\mathrm{RD}_{ED}^{obs} - \mathrm{RD}_{ED}^{true}}.$$

Proof of Proposition A.13. We have

$$\mathrm{CRD}_{ED} = \alpha_1 \{\beta_{11}\mathrm{P}(E=0) + \beta_{01}\mathrm{P}(E=1)\} = \mathrm{RD}_{EU}\{\mathrm{RD}_{UD|E=1}\mathrm{P}(E=0) + \mathrm{RD}_{UD|E=0}\mathrm{P}(E=1)\}.$$

Since $\mathrm{CRD}_{ED} \geq 0$ and $\mathrm{RD}_{EU} \geq 0$, we have $\mathrm{RD}_{UD|E=1}\mathrm{P}(E=0) + \mathrm{RD}_{UD|E=0}\mathrm{P}(E=1) \geq 0$.

Therefore, $\mathrm{RD}_{UD|E=1}$ and $\mathrm{RD}_{UD|E=0}$ cannot both be negative, and thus we have

$$\mathrm{RD}_{UD|E=1}\mathrm{P}(E=0) + \mathrm{RD}_{UD|E=0}\mathrm{P}(E=1) < \max(\mathrm{RD}_{UD|E=1}, \mathrm{RD}_{UD|E=0}) = \mathrm{RD}_{UD}.$$

Therefore, $\mathrm{CRD}_{ED} \leq \mathrm{RD}_{EU} \times \mathrm{RD}_{UD}$, which implies that $\min(\mathrm{RD}_{EU}, \mathrm{RD}_{UD}) \geq \mathrm{CRD}_{ED} = \mathrm{RD}_{ED}^{\mathrm{obs}} - \mathrm{RD}_{ED}^{\mathrm{true}}$, and $\max(\mathrm{RD}_{EU}, \mathrm{RD}_{UD}) \geq \sqrt{\mathrm{CRD}_{ED}} = \sqrt{\mathrm{RD}_{ED}^{\mathrm{obs}} - \mathrm{RD}_{ED}^{\mathrm{true}}}$. $\square$

eAppendix 6.3 General Categorical Confounder

For categorical confounder U, no simple form of the bounding factor is available, but we can still show that RD_{EU} and RD_{UD} must satisfy the following conditions:

Proposition A.14. *For a categorical confounder U, we have*

$$\mathrm{RD}_{EU} \geq (\mathrm{RD}_{ED}^{obs} - \mathrm{RD}_{ED}^{true})/(K-1),$$

$$\mathrm{RD}_{UD} \geq (\mathrm{RD}_{ED}^{obs} - \mathrm{RD}_{ED}^{true})/2,$$

$$\max(\mathrm{RD}_{EU}, \mathrm{RD}_{UD}) \geq \max\left\{\sqrt{(\mathrm{RD}_{ED}^{obs} - \mathrm{RD}_{ED}^{true})/(K-1)}, (\mathrm{RD}_{ED}^{obs} - \mathrm{RD}_{ED}^{true})/2\right\}.$$

When $K = 3$ such as a three-level genetic confounder, these conditions reduce to

$$\min(\mathrm{RD}_{EU}, \mathrm{RD}_{UD}) \geq (\mathrm{RD}_{ED}^{\mathrm{obs}} - \mathrm{RD}_{ED}^{\mathrm{true}})/2, \quad \max(\mathrm{RD}_{EU}, \mathrm{RD}_{UD}) \geq \sqrt{(\mathrm{RD}_{ED}^{\mathrm{obs}} - \mathrm{RD}_{ED}^{\mathrm{true}})/2}.$$

Proof of Proposition A.14. Since

$$\begin{aligned}
\mathrm{CRD}_{ED} &= \Big| \sum_{k=1}^{K-1} \alpha_k \{\beta_k^* \mathrm{P}(E=0) + \beta_k \mathrm{P}(E=1)\} \Big| \leq \mathrm{RD}_{EU} \sum_{k=1}^{K-1} |\beta_k^* \mathrm{P}(E=0) + \beta_k \mathrm{P}(E=1)| \\
&\leq \mathrm{RD}_{EU} \sum_{k=1}^{K-1} \max(|\beta_k^*|, |\beta_k|) \leq \mathrm{RD}_{EU}(K-1),
\end{aligned}$$

we have $\mathrm{RD}_{EU} \geq \mathrm{CRD}_{ED}/(K-1)$. The equality is attainable if and only if (c1) $\alpha_k = \mathrm{CRD}_{ED}/(K-1)$, and $\beta_k^* = \beta_k = 1$ for $k = 1, \ldots, (K-1)$; or (c2) $\alpha_k = -1$, and $\beta_k^* = \beta_k = -1$ for $k = 1, \ldots, K$. The condition (c1) requires that the risk difference of the exposure E on each category of U to be the same as $\mathrm{CRD}_{ED}/(K-1)$, and the confounder U is a perfect predictor of the disease D. Similar interpretation applies to condition (c2).

Since

$$\begin{aligned}
\mathrm{CRD}_{ED} &= \Big| \sum_{k=1}^{K-1} \alpha_k \{\beta_k^* \mathrm{P}(E=0) + \beta_k \mathrm{P}(E=1)\} \Big| \leq \sum_{k=1}^{K-1} |\alpha_k| \max(|\beta_k^*|, |\beta_k|) \leq \mathrm{RD}_{UD} \sum_{k=1}^{K-1} |\alpha_k| \\
&\leq \mathrm{RD}_{UD} \sum_{k=1}^{K-1} \mathrm{P}(U=k \mid E=1) + \mathrm{RD}_{UD} \sum_{k=1}^{K-1} \mathrm{P}(U=k \mid E=0) \leq 2\mathrm{RD}_{UD},
\end{aligned}$$

the lower bound for RD_{UD} is $\mathrm{RD}_{UD} \geq \mathrm{CRD}_{ED}/2$. The equality is attainable if and only if $\mathrm{P}(U=0 \mid E=0) = \mathrm{P}(U=0 \mid E=1) = 0, \mathrm{P}(U=k \mid E=1)\mathrm{P}(U=k \mid E=0) = 0$ for $k = 1, ..., (K-1)$, and $\beta_k^* = \beta_k = \pm \mathrm{CRD}_{ED}/2$ with the sign the same as the sign of α_k.

Since $\mathrm{CRD}_{ED} \leq (K-1)\mathrm{RD}_{EU}\mathrm{RD}_{UD} \leq (K-1)\max^2(\mathrm{RD}_{EU}, \mathrm{RD}_{UD})$, we have $\max(\mathrm{RD}_{EU}, \mathrm{RD}_{UD}) \geq \sqrt{\mathrm{CRD}_{ED}/(K-1)}$, with the equality attainable if and only if $\alpha_k = \beta_k^* = \beta_k = \pm\sqrt{\mathrm{CRD}_{ED}/(K-1)}$ for $k = 1, \ldots, K-1$. Due to the constraint $\sum_{k=1}^{K-1} |\alpha_k| \leq 2$ discussed above, the equality is attainable if and only if $(K-1)\sqrt{\mathrm{CRD}_{ED}/(K-1)} \leq 2$ or $(K-1)\mathrm{CRD}_{ED} \leq 4$. When $(K-1)\mathrm{CRD}_{ED} > 4$, RD_{UD} can attain its lower bound CRD_{ED} with $\sum_{k=1}^{K-1} |\alpha_k| = 2$. Therefore, RD_{EU} can attain its lower bound $2/(K-1)$, which, in this case, is smaller than $\mathrm{CRD}_{ED}/2$. In summary, the lower bound for $\max(\mathrm{RD}_{EU}, \mathrm{RD}_{UD})$ is $\max(\mathrm{RD}_{EU}, \mathrm{RD}_{UD}) \geq \sqrt{\mathrm{CRD}_{ED}/(K-1)}$, if $(K-1)\mathrm{CRD}_{ED} \leq 4$, and $\max(\mathrm{RD}_{EU}, \mathrm{RD}_{UD}) \geq \mathrm{CRD}_{ED}/2$, if $(K-1)\mathrm{CRD}_{ED} > 4$. Equivalently, we have $\max(\mathrm{RD}_{EU}, \mathrm{RD}_{UD}) \geq \max\left\{\sqrt{\mathrm{CRD}_{ED}/(K-1)}, \mathrm{CRD}_{ED}/2\right\}$. □

For the Cornfield conditions for the risk difference, sharper conditions can be obtain by imposing the monotonicity assumption that $\alpha_k \geq 0$ for $k = 1, \cdots, (K-1)$. It requires that each non-zero category of U is more prevalent under exposure, which is naturally satisfied for binary confounder. Under the monotonicity assumption, the conditions for the risk difference can be strengthened.

Proposition A.15. *For a categorical confounder under monotonicity, we have that*

$$\mathrm{RD}_{EU} \geq (\mathrm{RD}_{ED}^{obs} - \mathrm{RD}_{ED}^{true})/(K-1),$$

$$\mathrm{RD}_{UD} \geq \mathrm{RD}_{ED}^{obs} - \mathrm{RD}_{ED}^{true},$$

$$\max(\mathrm{RD}_{EU}, \mathrm{RD}_{UD}) \geq \max\left\{\sqrt{(\mathrm{RD}_{ED}^{obs} - \mathrm{RD}_{ED}^{true})/(K-1)}, \mathrm{RD}_{ED}^{obs} - \mathrm{RD}_{ED}^{true}\right\}.$$

Proof. Proof of Proposition A.15. The bound for RD_{EU} remains the same. Since

$$\mathrm{CRD}_{ED} = \left|\sum_{k=1}^{K-1} \alpha_k\{\beta_k^* \mathrm{P}(E=0) + \beta_k(E=1)\}\right| \leq \mathrm{RD}_{UD}\sum_{k=1}^{K-1}|\alpha_k| \leq \mathrm{RD}_{UD}(-\alpha_0) \leq \mathrm{RD}_{UD},$$

the lower bound for RD_{UD} is $\mathrm{RD}_{UD} \geq \mathrm{CRD}_{ED}$ The equality is attainable if and only if $\alpha_0 = -1$ and $\beta_k^* = \beta_k = \mathrm{CRD}_{ED}$ for $k = 1, \ldots, K-1$. The condition requires that the presence or absence of the confounder U is perfectly predictive to the exposure E, and each category of U is equally predictive to the disease D.

Since $\mathrm{CRD}_{ED} \leq (K-1)\mathrm{RD}_{EU}\mathrm{RD}_{UD} \leq (K-1)\max^2(\mathrm{RD}_{EU}, \mathrm{RD}_{UD})$, we have $\max(\mathrm{RD}_{EU}, \mathrm{RD}_{UD}) \geq \sqrt{\mathrm{CRD}_{ED}/(K-1)}$, with the equality attainable if and only if $\alpha_k = \beta_k^* = \beta_k = \pm\sqrt{\mathrm{CRD}_{ED}/(K-1)}$ for $k = 1, \ldots, K-1$. Due to the constraint $\sum_{k=1}^{K-1} \alpha_k = -\alpha_0 \leq 1$ discussed above, the equality is attainable if and only if $(K-1)\sqrt{\mathrm{CRD}_{ED}/(K-1)} \leq 1$ or $(K-1)\mathrm{CRD}_{ED} \leq 1$. When $(K-1)\mathrm{CRD}_{ED} > 1$, RD_{UD} can attain its lower bound CRD_{ED} with $\sum_{k=1}^{K-1} \alpha_k = 1$. Therefore, RD_{EU} can attain its lower bound $1/(K-1)$, which, in this case, is smaller than CRD_{ED}. In summary, the lower bound for $\max(\mathrm{RD}_{EU}, \mathrm{RD}_{UD})$ is $\max(\mathrm{RD}_{EU}, \mathrm{RD}_{UD}) \geq \sqrt{\mathrm{CRD}_{ED}/(K-1)}$, if $(K-1)\mathrm{CRD}_{ED} \leq 1$, and $\max(\mathrm{RD}_{EU}, \mathrm{RD}_{UD}) \geq \mathrm{CRD}_{ED}$, if $(K-1)\mathrm{CRD}_{ED} > 1$. Equivalently, we have $\max(\mathrm{RD}_{EU}, \mathrm{RD}_{UD}) \geq \max\left\{\sqrt{\mathrm{CRD}_{ED}/(K-1)}, \mathrm{CRD}_{ED}\right\}$. □

The results in Propositions A.12 to A.15 generalize previous results[7] from the null hypothesis of no effect ($\mathrm{RD}_{ED}^{\mathrm{true}} = 0$) to alternative hypotheses ($\mathrm{RD}_{ED}^{\mathrm{true}}$ arbitrary).

eAppendix 7 A Bounding Factor for Rare Time-to-Event Outcome on the Hazard Ratio Scale

Let f, S, λ be the probability density, survival function and hazard function of a positive continuous outcome T. The outcome is rare in the sense that $\mathrm{P}(T \leq \mathscr{T})$ is not much greater than 0, where $\mathscr{T}$ is the time point of the end our research of interest. In the following, we will always make the rare outcome assumption. Although f, S, λ are defined on the whole positive real line, our interest only within interval $[0, \mathscr{T}]$. Let U be another random variable,

and $f(t \mid u), S(t \mid u), \lambda(t \mid u)$ are the conditional probability density, survival function, and hazard function of T given U. The following lemma is useful throughout our discussion.

Lemma A.4. *If T is a rare time-to-event outcome, we have the following approximation:*

$$\lambda(t) \approx \int \lambda(t \mid u) F(du).$$

Proof of Lemma A.4. Similar to the case with discrete U [8], we have $S(t \mid u) \approx 1$ for rare outcome, and therefore

$$\lambda(t) = \frac{f(t)}{S(t)} = \frac{\int \lambda(t \mid u) S(t \mid u) F(du)}{\int S(t \mid u) F(du)} \approx \frac{\int \lambda(t \mid u) F(du)}{\int F(du)} = \int \lambda(t \mid u) F(du).$$

□

Lemma A.4 essentially allows "Law of Total Probability" type of calculation for the hazard function with rare outcome.

In order to introduce the new bounding factor for hazard ratio, we need more formal notation. Define the potential outcomes for T as $T(1)$ and $T(0)$ with hazard functions $\lambda^{(1)}(t)$ and $\lambda^{(0)}(t)$ and conditional hazard functions can be defined intuitively as $\lambda^{(1)}(t \mid \cdot)$ and $\lambda^{(0)}(t \mid \cdot)$. We define $\lambda_t^*(u) = \lambda(t \mid E = 1, U = u)$ and $\lambda_t(u) = \lambda(t \mid E = 0, U = u)$ as the conditional hazard functions of T for the exposed and unexposed units within strata $U = u$, respectively. We define $\mathrm{HR}_{UT|E=1}(t) = \max_u \lambda_t^*(u) / \min_u \lambda_t^*(u)$ as the maximal hazard ratio function of the confounder U on the outcome T for exposed units, $\mathrm{HR}_{UT|E=0}(t) = \max_u \lambda_t(u) / \min_u \lambda_t(u)$ for unexposed, and their maximum, denoted by $\mathrm{HR}_{UT}(t) = \max\{\mathrm{HR}_{UT|E=1}(t), \mathrm{HR}_{UT|E=0}(t)\}$, as the maximal hazard ratio function of the confounder U on the outcome T. Note that the hazard ratios are time-dependent.

If the exposure and the outcome are unconfounded given U and the observed covariates C (which is omitted in conditional probablities for simplicity), Lemma A.4 allows us to write the true causal hazard ratios for the exposed, unexposed, and the whole population as

$$\begin{aligned}
\mathrm{HR}^{\mathrm{true}}_{ET+}(t) &= \frac{\lambda^{(1)}(t \mid E=1)}{\lambda^{(0)}(t \mid E=1)} \approx \frac{\int \lambda_t^*(u) F_1(du)}{\int \lambda_t(u) F_1(du)}, \\
\mathrm{HR}^{\mathrm{true}}_{ET-}(t) &= \frac{\lambda^{(1)}(t \mid E=0)}{\lambda^{(0)}(t \mid E=0)} \approx \frac{\int \lambda_t^*(u) F_0(du)}{\int \lambda_t(u) F_0(du)}, \\
\mathrm{HR}^{\mathrm{true}}_{ET}(t) &= \frac{\lambda^{(1)}(t)}{\lambda^{(0)}(t)} \approx \frac{\int \lambda_t^*(u) F(du)}{\int \lambda_t(u) F(du)},
\end{aligned}$$

and the observed harzard ratio as

$$\mathrm{HR}_{ET}(t) = \frac{\lambda(t \mid E=1)}{\lambda(t \mid E=0)} \approx \frac{\int \lambda_t^*(u) F_1(du)}{\int \lambda_t(u) F_0(du)}.$$

With categorical U taking values $0, 1, \ldots, K-1$, the true causal hazard ratios can be approximated by the following standardized hazard ratios:

$$\begin{aligned}
\mathrm{HR}^{\mathrm{true}}_{ET+}(t) &\approx \frac{\sum_{k=0}^{K-1} \lambda_t^*(k) \mathrm{P}(U=k \mid E=1)}{\sum_{k=0}^{K-1} \lambda_t(k) \mathrm{P}(U=k \mid E=1)}, \\
\mathrm{HR}^{\mathrm{true}}_{ET-}(t) &\approx \frac{\sum_{k=0}^{K-1} \lambda_t^*(k) \mathrm{P}(U=k \mid E=0)}{\sum_{k=0}^{K-1} \lambda_t(k) \mathrm{P}(U=k \mid E=0)}, \\
\mathrm{HR}^{\mathrm{true}}_{ET}(t) &\approx \frac{\sum_{k=0}^{K-1} \lambda_t^*(k) \mathrm{P}(U=k)}{\sum_{k=0}^{K-1} \lambda_t(k) \mathrm{P}(U=k)}
\end{aligned}$$

The confounding hazard ratios are defined as

$$\mathrm{CHR}_{ET+}(t) = \frac{\mathrm{HR}_{ET}(t)}{\mathrm{HR}^{\mathrm{true}}_{ET+}(t)}, \quad \mathrm{CHR}_{ET-}(t) = \frac{\mathrm{HR}_{ET}(t)}{\mathrm{HR}^{\mathrm{true}}_{ET-}(t)}, \quad \mathrm{CHR}_{ET}(t) = \frac{\mathrm{HR}_{ET}(t)}{\mathrm{HR}^{\mathrm{true}}_{ET}(t)}.$$

Analogous to the results for the relative risk, we have the following propositions for the hazard ratio. The proofs are straightforward if we replace $\{r(\cdot), r^*(\cdot)\}$ in the proofs for the relative risk by $\{\lambda_t(\cdot), \lambda_t^*(u)\}$.

Proposition A.16. *For rare time-to-event outcome, we approximately have*

$$\begin{aligned} \mathrm{HR}_{ET}^{true}(t) &= w_t \mathrm{HR}_{ET+}^{true}(t) + (1-w_t)\mathrm{HR}_{ET-}^{true}, \\ 1/\mathrm{CHR}_{ET}(t) &= w_t/\mathrm{CHR}_{ET+}(t) + (1-w_t)/\mathrm{CHR}_{ET-}(t), \end{aligned}$$

where w_t is a weight between zero and one:

$$w_t = \frac{f\int \lambda_t(u)F_1(du)}{f\int \lambda_t(u)F_1(du) + (1-f)\int \lambda_t(u)F_0(du)} \in [0,1].$$

Define the time-varying bounding factor as

$$\mathrm{BF}_U(t) = \frac{\mathrm{RR}_{EU} \times \mathrm{HR}_{UT}(t)}{\mathrm{RR}_{EU} + \mathrm{HR}_{UT}(t) - 1},$$

which is also time-dependent. The confounding hazard ratios can be bounded by the bounding factor, as shown in the following proposition.

Proposition A.17. *For rare time-to-event outcome, we approximately have*

$$\mathrm{CHR}_{ET+}(t) \le \mathrm{BF}_U(t), \quad \mathrm{CHR}_{ET-}(t) \le \mathrm{BF}_U(t), \quad \mathrm{CHR}_{ET}(t) \le \mathrm{BF}_U(t).$$

Proposition A.18. *The implied Cornfield conditions for the hazard ratio from Proposition A.17 are*

$$\begin{aligned} \mathrm{RR}_{EU} &\ge \max_t \mathrm{CHR}_{ET}(t), \\ \mathrm{HR}_{UT}(t) &\ge \mathrm{CHR}_{ET}(t), \\ \max\{\mathrm{RR}_{EU}, \mathrm{HR}_{UT}(t)\} &\ge \mathrm{CHR}_{ET}(t) + \sqrt{\mathrm{CHR}_{ET}(t)\{\mathrm{CHR}_{ET}(t)-1\}}. \end{aligned}$$

If a proportional hazards model[9] for the outcome is used as is often the case in practice, all the above exposure-outcome hazard ratio reduce to a constant $\mathrm{HR}_{ET}(t) = \mathrm{HR}_{ET}$. The above discussion works well for an exposure that is apparently causative at time t on the

harzard ratio scale. If at some time point t, the exposure is apparently preventive, then the above discussion needs to be modified. To be more specific, we need to modify the definition of RR_{EU} as in Section eAppendix 3.3, and the confounding hazard ratios above are replaced by their reciprocals. Likewise similar results on the hazard difference scale hold as those on the risk difference scale in eAppendix A.eAppendix 5 provided that the outcome is relatively rare.

eAppendix 8 A Bounding Factor for General Nonnegative Outcomes

The discussion above assumes a binary outcome D, and in fact all the proofs only use the property that $r(u)$ and $r^*(u)$ are nonnegative. Therefore, the bounding factor also applies to any nonnegative outcomes (counts, continuous positive outcome, etc), if we modify the definitions of $r(u), r^*(u)$, and RR_{UD} in the following way. For general nonnegative outcomes, we define $r^*(u) = \mathbb{E}(D \mid E = 1, U = u)$ and $r(u) = \mathbb{E}(D \mid E = 0, U = u)$ as the expectations of the outcome within stratum $U = u$ with and without exposure. Define $\mathrm{MR}_{UD|E=1} = \max_u r^*(u) / \min_u r^*(u)$ and $\mathrm{MR}_{UD|E=0} = \max_u r(u) / \min_u r(u)$ as the mean ratios of U on D with and without exposure, and $\mathrm{MR}_{UD} = \max(\mathrm{MR}_{UD|E=1}, \mathrm{MR}_{UD=0})$ as the maximum of these two mean ratios. Note that when D is binary, $r(u)$ and $r^*(u)$ reduce to probabilities, and the mean ratios reduce to the relative risks.

The observed mean ratio of the exposure on the outcome is

$$\mathrm{MR}_{ED} = \frac{\int \mathbb{E}(D \mid E = 1, U = u) F_1(du)}{\int \mathbb{E}(D \mid E = 0, U = u) F_0(du)} = \frac{\int r^*(u) F_1(du)}{\int r(u) F_0(du)}.$$

The true causal mean ratio of the exposure on the outcome for exposed is

$$\mathrm{MR}_{ED+}^{\text{true}} = \frac{\int \mathbb{E}(D \mid E=1, U=u) F_1(du)}{\int \mathbb{E}(D \mid E=0, U=u) F_1(du)} = \frac{\int r^*(u) F_1(du)}{\int r(u) F_1(du)},$$

the true causal mean ratio of the exposure on the outcome for unexposed is

$$\mathrm{MR}_{ED+}^{\text{true}} = \frac{\int \mathbb{E}(D \mid E=1, U=u) F_0(du)}{\int \mathbb{E}(D \mid E=0, U=u) F_0(du)} = \frac{\int r^*(u) F_0(du)}{\int r(u) F_0(du)},$$

and the true causal mean ratio of the exposure on the outcome for the whole population is

$$\mathrm{MR}_{ED+}^{\text{true}} = \frac{\int \mathbb{E}(D \mid E=1, U=u) F(du)}{\int \mathbb{E}(D \mid E=0, U=u) F(du)} = \frac{\int r^*(u) F(du)}{\int r(u) F(du)}.$$

Define the bounding factor as

$$\mathrm{BF}_U = \frac{\mathrm{RR}_{EU} \times \mathrm{MR}_{UD}}{\mathrm{RR}_{EU} + \mathrm{MR}_{UD} - 1}.$$

Since the discussion in Section eAppendix 2 still holds, the proofs for the following propositions are the same as those in Appendices A.2 and A.4. First, we have the following bounding factor for nonnegative outcomes:

Proposition A.19.

$$\mathrm{CMR}_{ED+} = \frac{\mathrm{MR}_{ED}}{\mathrm{MR}_{ED+}^{true}} \leq \mathrm{BF}_U, \quad \mathrm{CMR}_{ED-} = \frac{\mathrm{MR}_{ED}}{\mathrm{MR}_{ED-}^{true}} \leq \mathrm{BF}_U, \quad \mathrm{CMR}_{ED} = \frac{\mathrm{MR}_{ED}}{\mathrm{MR}_{ED}^{true}} \leq \mathrm{BF}_U.$$

In practice, we might also be interested in the average causal effect of the exposure on the outcome on the difference scale. The observed mean difference of the exposure on the outcome is

$$\mathbb{E}(D \mid E=1) - \mathbb{E}(D \mid E=0) \equiv m_1 - m_0.$$

The average causal effect of the exposure on the outcome for exposed is

$$\mathrm{ACE}_{ED+}^{\text{true}} = \int \mathbb{E}(D \mid E=1, U=u) F_1(du) - \int \mathbb{E}(D \mid E=0, U=u) F_1(du) = m_1 - \int r(u) F_1(du),$$

the average causal effect of the exposure on the outcome for unexposed is

$$\mathrm{ACE}^{\mathrm{true}}_{ED+} = \int \mathbb{E}(D \mid E=1, U=u) F_0(du) - \int \mathbb{E}(D \mid E=0, U=u) F_0(du) = \int r^*(u) F_0(du) - m_0,$$

and the average causal effect of the exposure on the outcome for the whole population is

$$\begin{aligned} \mathrm{ACE}^{\mathrm{true}}_{ED} &= \int \mathbb{E}(D \mid E=1, U=u) F(du) - \int \mathbb{E}(D \mid E=0, U=u) F(du) \\ &= f \mathrm{ACE}^{\mathrm{true}}_{ED+} + (1-f) \mathrm{ACE}^{\mathrm{true}}_{ED-}. \end{aligned}$$

Similar to the discussion in Section eAppendix 5 for the risk difference with sensitivity parameters expressed on the risk ratio scale, we have the following proposition about the average causal effect.

Proposition A.20. *For nonnegative outcomes, the lower bounds for the average causal effects are*

$$\mathrm{ACE}^{true}_{ED+} \geq m_1 - m_0 \times \mathrm{BF}_U,$$

$$\mathrm{ACE}^{true}_{ED-} \geq m_1 / \mathrm{BF}_U - m_0,$$

$$\mathrm{ACE}^{true}_{ED} \geq (m_1 - m_0 \times \mathrm{BF}_U) \times \{f + (1-f)/\mathrm{BF}_U\} = (m_1/\mathrm{BF}_U - m_0) \times \{f \times \mathrm{BF}_U + (1-f)\}.$$

We can also obtain similar forms of the conclusion for apparently preventive exposure, for average causal effects averaged over observed covariates, and for corresponding Cornfield conditions. The only difference is that (p_1, p_0) is replaced by (m_1, m_0).

eAppendix 9 SAS Code for the Risk Ratio

The SAS code for the cigarette smoking and lung cancer example in Table **??** is given below. A researcher could modify the code for use in other examples by just changing the first

few lines of code with the estimated observed relative controlling for only the measured covarates (RR=), and the lower and upper confidence interval for this estimate(RR_Lower=, RR_Upper=). The minimum and maximum strength of the unmeasured confounder can also be modified by adjusting the lines with "RR_EU=" and "RR_UD=" but we recommend always including at least some relatively large values, e.g., with RR_{EU} and RR_{UD} at least as high as 5 so as to get a sense as to how an estimate would change under fairly severe confounding.

```
proc iml;
/*the point estimator and confidence interval of RR*/
RR = 10.73;
RR_Lower = 8.02;
RR_Upper = 14.36;
/*strenghth of confounding resulting from U*/
RR_EU = {1.2 1.3 1.5 1.8 2 2.5 3 4 5 6 8 10};
RR_UD = {1.2 1.3 1.5 1.8 2 2.5 3 4 5 6 8 10};
highthreshold = ROUND(RR + SQRT(RR*(RR-1)), 0.01);
rownames_EU = CHAR(RR_EU, NCOL(RR_EU), 1);
colnames_UD = CHAR(RR_UD, NCOL(RR_UD), 1);
BiasFactor  = J(NCOL(RR_EU), NCOL(RR_UD), 1);
SPACE       = J(NCOL(RR_EU), NCOL(RR_UD), " ");
LeftP        = J(NCOL(RR_EU), NCOL(RR_UD), "(");
Mid         = J(NCOL(RR_EU), NCOL(RR_UD), ",");
RightP       = J(NCOL(RR_EU), NCOL(RR_UD), ")");
RR_true = BiasFactor;
RR_true_Lower = BiasFactor;
RR_true_Upper = BiasFactor;
RR_true_CI = BiasFactor;
DO i=1 TO NCOL(RR_EU);
      Do j=1 to NCOL(RR_UD);
      BiasFactor[i, j] = RR_EU[i]*RR_UD[j]/(RR_EU[i] + RR_UD[j] - 1);
  RR_true[i, j] = ROUND(RR/BiasFactor[i, j], 0.01);
          RR_true_Lower[i, j] = ROUND(RR_Lower/BiasFactor[i, j], 0.01);
          RR_true_Upper[i, j] = ROUND(RR_Upper/BiasFactor[i, j], 0.01);
  END;
END;
RR_true_CI = CATX(" ", CHAR(RR_true), LeftP, CHAR(RR_true_Lower), Mid, CHAR(RR_true_Upper), RightP);
print RR_true_CI[colname = colnames_UD
                 rowname = rownames_EU
                 label = "Bounds on corrected estimates and confidence intervals for unmeasured confounding
                 (columns correspond to increasing strength of the risk ratio of U on the outcome;
                 rows correspond to increasing strength of risk ratio relating the exposure and U)"];
run;
```

eAppendix 10 SAS Code for the Risk Difference Using Sensitivity Parameters on the Relative Risk Scale

In this section, we provide SAS code for sensitivity analysis on the risk difference scale. The SAS code here illustrates analysis using logistic regression for a binary outcome as this is an

approach that is commonly employed.

Suppose we have a dataset named "leadlogit" with variables lead, smoking, age, male. Suppose we are interested in the risk difference of smoking on the high blood lead level at the covariate level, age = 50 and male = 1.

To implement sensitivity analysis for risk difference we need to obtain point estimate and standard error for $f = \mathrm{P}(E = 1)$, which can be done via the following SAS code.

```
proc means data=lib.leadlogit ; /*f and se(f)*/
var smoking;
    output out=sumstat mean=mean var=var N=N;
run;

data sumstat (KEEP=MEAN SE);
set sumstat;
se=(var/N)**0.5;
run;
```

The following code obtains the predicted probabilities $p_{1|c} = \mathrm{P}\{Y(1) = 1 \mid C = c\}$ and $p_{0|c} = \mathrm{P}\{Y(0) = 1 \mid C = c\}$ with standard errors.

```
proc logistic data = lib.leadlogit;/*predict probs*/
model lead = smoking age male;
score data = lib.leadlogit_new out=logit_pred clm;
run;

proc contents data =logit_pred ;
run;

data logit_pred (keep=P_TRUE se_p);/*p1 p0 se(p1) se(p0)*/
set logit_pred;

logit_LCL_TRUE =log(LCL_TRUE/(1-LCL_TRUE));
logit_P_TRUE =log(P_TRUE/(1-P_TRUE));
logit_UCL_TRUE  =log(UCL_TRUE /(1-UCL_TRUE ));

se_eta  =(logit_UCL_TRUE-logit_LCL_TRUE)/2/1.96;
se_p =P_TRUE**2/EXP(logit_P_TRUE)*se_eta;
run;
```

In the following SAS code, we need to input from line 2 to line 7 the point estimates and standard errors of the prevalence f, and the two predicted outcome probabilities $p_{1|c}$ and $p_{0|c}$. The output contains lower bounds for the point estimates and confidence intervals of the causal risk differences for the exposed, unexposed and the whole population. Figure A.1

is the SAS output for the causal risk difference estimates for the whole population. For other problems, we need to change the numbers from line 2 to line 7 accordingly. We can also change the measures of the strength of confounding in lines 8 and 9. The output from SAS will be similar to the one shown in Figure A.1.

```
proc iml;/*Sensitivity analysis without assumptions for RD*/
f             = 0.2032934132;/*point and interval estimate of prevalence and response rates*/
p1            = 0.101645862;
p0            = 0.0398930775;
s2_f          = 0.0069647038;
s2_p1         = 0.0147497019;
s2_p0         = 0.0058931321;
RR_EU = {1.2 1.3 1.5 1.8 2 2.5 3 5};/*strenghth of confounding*/
RR_UD = {1.2 1.3 1.5 1.8 2 2.5 3 5};
rownames_EU = CHAR(RR_EU, NCOL(RR_EU), 1);
colnames_UD = CHAR(RR_UD, NCOL(RR_UD), 1);
BiasFactor  = J(NCOL(RR_EU), NCOL(RR_UD), 1);
SPACE       = J(NCOL(RR_EU), NCOL(RR_UD), " ");
LeftP       = J(NCOL(RR_EU), NCOL(RR_UD), "(");
Mid         = J(NCOL(RR_EU), NCOL(RR_UD), ",");
RightP      = J(NCOL(RR_EU), NCOL(RR_UD), ")");
/*initial values*/
RD_exposed   = BiasFactor;
RD_exposed_L = BiasFactor;
RD_exposed_U = BiasFactor;
RD_unexposed   = BiasFactor;
RD_unexposed_L = BiasFactor;
RD_unexposed_U = BiasFactor;
RD_whole   = BiasFactor;
RD_whole_L = BiasFactor;
RD_whole_U = BiasFactor;
W_whole = BiasFactor;
Var_exposed = BiasFactor;
Var_unexposed = BiasFactor;
Var_whole = BiasFactor;
/*Sensitivity analysis*/
DO i=1 TO NCOL(RR_EU);
      Do j=1 to NCOL(RR_UD);
      BiasFactor[i, j] = RR_EU[i]*RR_UD[j]/(RR_EU[i] + RR_UD[j] - 1);
  /*exposed*/
          RD_exposed[i, j]     = p1 - p0*BiasFactor[i, j];
          Var_exposed[i, j]    = s2_p1 + s2_p0*(BiasFactor[i, j])**2;
          RD_exposed_L[i, j]   = RD_exposed[i, j] - 1.96*sqrt(Var_exposed[i, j]);
  RD_exposed_U[i, j]   = RD_exposed[i, j] + 1.96*sqrt(Var_exposed[i, j]);
          /*exposed*/
          RD_unexposed[i, j]   = p1/BiasFactor[i, j] - p0;
  Var_unexposed[i, j]  = s2_p1/(BiasFactor[i, j])**2 + s2_p0;
          RD_unexposed_L[i, j] = RD_unexposed[i, j] - 1.96*sqrt(Var_unexposed[i, j]);
  RD_unexposed_U[i, j] = RD_unexposed[i, j] + 1.96*sqrt(Var_unexposed[i, j]);
          /*whole*/
  W_whole[i, j]        = f + (1-f)/BiasFactor[i, j];
          RD_whole[i, j]       = RD_exposed[i, j]*W_whole[i, j];
          Var_whole[i, j]      = Var_exposed[i, j]*(W_whole[i, j])**2
                                        + (RD_exposed[i, j])**2*(1-1/BiasFactor[i, j])**2*s2_f;
          RD_whole_L[i, j]     = RD_whole[i, j] - 1.96*sqrt(Var_whole[i, j]);
          RD_whole_U[i, j]     = RD_whole[i, j] + 1.96*sqrt(Var_whole[i, j]);
       END;
END;
/*print;*/
RD_exposed = CATX(" ", CHAR(round(RD_exposed, 0.0001)), LeftP, CHAR(round(RD_exposed_L, 0.0001)), Mid,
                       CHAR(round(RD_exposed_U, 0.0001)), RightP);
print RD_exposed[colname = colnames_UD
```

```
                rowname = rownames_EU
                label = "Bounds on corrected estimates and confidence intervals for risk difference
                among exposed (columns correspond to increasing strength of the risk ratio of U
                on the outcome; rows correspond to increasing strength of risk ratio
                relating the exposure and U)"];
RD_unexposed = CATX(" ", CHAR(round(RD_unexposed, 0.0001)), LeftP, CHAR(round(RD_unexposed_L, 0.0001)), Mid,
                          CHAR(round(RD_unexposed_U, 0.0001)), RightP);
print RD_unexposed[colname = colnames_UD
                   rowname = rownames_EU
                   label = "Bounds on corrected estimates and confidence intervals for risk difference
                   among unexposed (columns correspond to increasing strength of the risk ratio of U
                   on the outcome; rows correspond to increasing strength of risk ratio
                   relating the exposure and U)"];
RD_whole = CATX(" ", CHAR(round(RD_whole, 0.0001)), LeftP, CHAR(round(RD_whole_L, 0.0001)), Mid,
                           CHAR(round(RD_whole_U, 0.0001)), RightP);
print RD_whole[colname = colnames_UD
               rowname = rownames_EU
               label = "Bounds on corrected estimates and confidence intervals for risk difference
               among the whole population (columns correspond to increasing strength of the risk ratio of U
               on the outcome; rows correspond to increasing strength of risk ratio
               relating the exposure and U)"];
run;
```

References

[1] Schlesselman JJ. Assessing effects of confounding variables. *Am J Epidemiol.*, 108:3–8, 1978.

[2] Flanders WD and Khoury MJ. Indirect assessment of confounding: graphic description and limits on effect of adjusting for covariates. *Epidemiology*, 1:239–246, 1990.

[3] Rosenbaum PR and Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika*, 70:41–55, 1983.

[4] Lee WC. Bounding the bias of unmeasured factors with confounding and effect-modifying potentials. *Stat Med.*, 30:1007–1017, 2011.

[5] Bross IDJ. Spurious effects from an extraneous variable. *J Chronic Dis.*, 19:637–647, 1966.

[6] Bross IDJ. Pertinency of an extraneous variable. *J Chronic Dis.*, 20:487–495, 1967.

[7] Ding P and VanderWeele TJ. Generalized Cornfield conditions for the risk difference. *Biometrika*, 101:971–977, 2014.

[8] VanderWeele TJ. Unmeasured confounding and hazard scales: sensitivity analysis for total, direct, and indirect effects. *Eur J of Epidemiol*, 28:113–117, 2013.

[9] Cox DR. Regression models and life tables (with discussion). *J R Stat Soc Series B*, 34:187–220, 1972.

Bounds on corrected estimates and confidence intervals for risk difference among the whole population (columns correspond to increasing strength of the risk ratio of U on the outcome; rows correspond to increasing strength of risk ratio relating the exposure and U)				
	1.2	**1.3**	**1.5**	**1.8**
1.2	0.0593 (-0.2184 , 0.3369)	0.0583 (-0.2178 , 0.3345)	0.0568 (-0.217 , 0.3305)	0.0551 (-0.2161 , 0.3263)
1.3	0.0583 (-0.2178 , 0.3345)	0.057 (-0.2171 , 0.3311)	0.0548 (-0.216 , 0.3257)	0.0525 (-0.2148 , 0.3199)
1.5	0.0568 (-0.217 , 0.3305)	0.0548 (-0.216 , 0.3257)	0.0517 (-0.2145 , 0.318)	0.0483 (-0.2131 , 0.3098)
1.8	0.0551 (-0.2161 , 0.3263)	0.0525 (-0.2148 , 0.3199)	0.0483 (-0.2131 , 0.3098)	0.0438 (-0.2116 , 0.2991)
2.0	0.0543 (-0.2157 , 0.3242)	0.0514 (-0.2143 , 0.317)	0.0466 (-0.2125 , 0.3057)	0.0414 (-0.211 , 0.2939)
2.5	0.0528 (-0.215 , 0.3205)	0.0492 (-0.2134 , 0.3119)	0.0435 (-0.2115 , 0.2986)	0.0372 (-0.2103 , 0.2847)
3.0	0.0517 (-0.2145 , 0.318)	0.0478 (-0.2129 , 0.3085)	0.0414 (-0.211 , 0.2939)	0.0343 (-0.2101 , 0.2788)
5.0	0.0497 (-0.2136 , 0.313)	0.045 (-0.2119 , 0.3019)	0.0372 (-0.2103 , 0.2847)	0.0285 (-0.2105 , 0.2675)

Bounds on corrected estimates and confidence intervals for risk difference among the whole population (columns correspond to increasing strength of the risk ratio of U on the outcome; rows correspond to increasing strength of risk ratio relating the exposure and U)				
	2.0	**2.5**	**3.0**	**5.0**
1.2	0.0543 (-0.2157 , 0.3242)	0.0528 (-0.215 , 0.3205)	0.0517 (-0.2145 , 0.318)	0.0497 (-0.2136 , 0.313)
1.3	0.0514 (-0.2143 , 0.317)	0.0492 (-0.2134 , 0.3119)	0.0478 (-0.2129 , 0.3085)	0.045 (-0.2119 , 0.3019)
1.5	0.0466 (-0.2125 , 0.3057)	0.0435 (-0.2115 , 0.2986)	0.0414 (-0.211 , 0.2939)	0.0372 (-0.2103 , 0.2847)
1.8	0.0414 (-0.211 , 0.2939)	0.0372 (-0.2103 , 0.2847)	0.0343 (-0.2101 , 0.2788)	0.0285 (-0.2105 , 0.2675)
2.0	0.0388 (-0.2105 , 0.2881)	0.034 (-0.2101 , 0.2781)	0.0307 (-0.2102 , 0.2716)	0.024 (-0.2116 , 0.2595)
2.5	0.034 (-0.2101 , 0.2781)	0.028 (-0.2106 , 0.2667)	0.024 (-0.2116 , 0.2595)	0.0154 (-0.216 , 0.2468)
3.0	0.0307 (-0.2102 , 0.2716)	0.024 (-0.2116 , 0.2595)	0.0193 (-0.2136 , 0.2522)	0.0093 (-0.2212 , 0.2398)
5.0	0.024 (-0.2116 , 0.2595)	0.0154 (-0.216 , 0.2468)	0.0093 (-0.2212 , 0.2398)	-0.0045 (-0.2402 , 0.2312)

Figure A.1: SAS Output of Sensitivity Analysis on the Risk Difference Scale for the Whole Population