eAppendix: Multiple-bias sensitivity analysis using bounds

A bound for outcome misclassification, selection bias, and unmeasured confounding

Result 1

Let A denote a binary exposure of interest, Y a binary outcome and Y^* the misclassified version, and C measured covariates. Additionally let S be a binary indicator of selection into a study, so that we can collect data only on the subset of the population for which $S = 1$. Finally, assume that there exist U_s and U_c such that $Y \amalg S \mid A, C, U_s$ and $Y_a \amalg A \mid C, U_c$, but that it is not necessarily true that $Y \amalg S \mid A, C$ or $Y_a \amalg A \mid C$.

We can estimate a confounded risk ratio observed in the selected population, subject to (potentially differential) outcome misclassification, $\mathrm{RR}_{AY}^{\mathrm{obs}}$, but our inferential goal is a causal risk ratio for the true outcome in the entire population, $\mathrm{RR}_{AY}^{\mathrm{true}}$:

$$\mathrm{RR}_{AY}^{\mathrm{obs}} = \frac{\Pr\left(Y^* = 1 \mid A = 1, S = 1, c\right)}{\Pr\left(Y^* = 1 \mid A = 0, S = 1, c\right)}$$
$$\mathrm{RR}_{AY}^{\mathrm{true}} = \frac{\Pr\left(Y_1 = 1 \mid c\right)}{\Pr\left(Y_0 = 1 \mid c\right)}$$

We have from VanderWeele & Li[1] that, for $\mathrm{RR}_{AY}^{\mathrm{true}} \geq 1$,

$$\mathrm{RR}_{AY}^{\mathrm{obs}} \leq \mathrm{BF}_m \times \frac{\Pr\left(Y = 1 \mid A = 1, S = 1, c\right)}{\Pr\left(Y = 1 \mid A = 0, S = 1, c\right)} \tag{1}$$

for

$$\mathrm{BF}_m = \mathrm{RR}_{AY^* \mid y, S=1} = \max_y \frac{\Pr\left(Y^* = 1 \mid Y = y, A = 1, S = 1, c\right)}{\Pr\left(Y^* = 1 \mid Y = y, A = 0, S = 1, c\right)} \,. \tag{2}$$

Then, since we are assuming that $Y \amalg S \mid A, C, U_s$, from Smith & VanderWeele[2] we have that

$$\frac{\Pr\left(Y = 1 \mid A = 1, S = 1, c\right)}{\Pr\left(Y = 1 \mid A = 0, S = 1, c\right)} \leq \mathrm{BF}_s \times \frac{\Pr\left(Y = 1 \mid A = 1, c\right)}{\Pr\left(Y = 1 \mid A = 0, c\right)} \tag{3}$$

for

$$\mathrm{BF}_s = \frac{\mathrm{RR}_{U_s Y \mid A=1} \times \mathrm{RR}_{SU_s \mid A=1}}{\mathrm{RR}_{U_s Y \mid A=1} + \mathrm{RR}_{SU_s \mid A=1} - 1} \times \frac{\mathrm{RR}_{U_s Y \mid A=0} \times \mathrm{RR}_{SU_s \mid A=0}}{\mathrm{RR}_{U_s Y \mid A=0} + \mathrm{RR}_{SU_s \mid A=0} - 1}$$

where

$$\begin{aligned}
\mathrm{RR}_{U_sY|A=a} &= \frac{\max_u \Pr\left(Y=1 \mid A=a, c, U_s=u\right)}{\min_u \Pr\left(Y=1 \mid A=a, c, U_s=u\right)} \text{ for } a=0,1 \\
\mathrm{RR}_{SU_s|A=1} &= \max_u \frac{\Pr\left(U_s=u \mid A=1, S=1, c\right)}{\Pr\left(U_s=u \mid A=1, S=0, c\right)} \\
\mathrm{RR}_{SU_s|A=0} &= \max_u \frac{\Pr\left(U_s=u \mid A=0, S=0, c\right)}{\Pr\left(U_s=u \mid A=0, S=1, c\right)} \,.
\end{aligned} \tag{4}$$

Finally, since we are assuming that $Y_a \amalg A \mid C, U_c$ from Ding & VanderWeele[3] we have

$$\frac{\Pr\left(Y=1 \mid A=1, c\right)}{\Pr\left(Y=1 \mid A=0, c\right)} \leq \mathrm{BF}_c \times \frac{\Pr\left(Y_1=1 \mid c\right)}{\Pr\left(Y_0=1 \mid c\right)} \tag{5}$$

for

$$\mathrm{BF}_c = \frac{\mathrm{RR}_{AU_c} \times \mathrm{RR}_{U_cY}}{\mathrm{RR}_{AU_c} + \mathrm{RR}_{U_cY} - 1} \tag{6}$$

where

$$\begin{aligned}
\mathrm{RR}_{AU_c} &= \max_u \frac{\Pr\left(U_c=u \mid A=1, c\right)}{\Pr\left(U_c=u \mid A=0, c\right)} \\
\mathrm{RR}_{U_cY} &= \max_a \frac{\max_u \Pr\left(Y=1 \mid A=a, c, U_c=u\right)}{\min_u \Pr\left(Y=1 \mid A=a, c, U_c=u\right)} \,.
\end{aligned}$$

Putting together expressions (1), (3), and (5), we have Result 1:

$$\begin{aligned}
\mathrm{RR}_{AY}^{\mathrm{obs}} &\leq \mathrm{BF}_m \times \frac{\Pr\left(Y=1 \mid A=1, S=1, c\right)}{\Pr\left(Y=1 \mid A=0, S=1, c\right)} \\
&\leq \mathrm{BF}_m \times \mathrm{BF}_s \times \frac{\Pr\left(Y=1 \mid A=1, c\right)}{\Pr\left(Y=1 \mid A=0, c\right)} \\
&\leq \mathrm{BF}_m \times \mathrm{BF}_s \times \mathrm{BF}_c \times \frac{\Pr\left(Y_1=1 \mid c\right)}{\Pr\left(Y_0=1 \mid c\right)} \\
&= \mathrm{BF}_m \times \mathrm{BF}_s \times \mathrm{BF}_c \times \mathrm{RR}_{AY}^{\mathrm{true}} \,.
\end{aligned} \tag{7}$$

An alternative decomposition

Now assume that there exist U_s and U_c such that $Y^* \amalg S \mid A, C, U_s$ and $Y_a \amalg A \mid C, U_c$. This may be the case if, for example, selection into the study is based on a factor related to the (mis)measured outcome, not the true outcome.

Then we can bound the bias with the same final expression, but some of the parameters within the bias factors are defined slightly differently.

The possible magnitude of selection bias can be defined in terms of the misclassified outcome, so that

$$\text{BF}_s = \frac{\text{RR}_{U_s Y^*|A=1} \times \text{RR}_{SU_s|A=1}}{\text{RR}_{U_s Y^*|A=1} + \text{RR}_{SU_s|A=1} - 1} \times \frac{\text{RR}_{U_s Y^*|A=0} \times \text{RR}_{SU_s|A=0}}{\text{RR}_{U_s Y^*|A=0} + \text{RR}_{SU_s|A=0} - 1}$$

where

$$\text{RR}_{U_s Y^*|A=a} = \frac{\max_u \Pr\left(Y^* = 1 \mid A = a, c, U_s = u\right)}{\min_u \Pr\left(Y^* = 1 \mid A = a, c, U_s = u\right)} \text{ for } a = 0, 1$$

and $\text{RR}_{SU_s|A=1}$ and $\text{RR}_{SU_s|A=0}$ are defined as in (4) above.

Then, the measurement error correction applies to the entire population, so that

$$\text{BF}_m = \text{RR}_{AY^*|y} = \max_y \frac{\Pr\left(Y^* = 1 \mid Y = y, A = 1, c\right)}{\Pr\left(Y^* = 1 \mid Y = y, A = 0, c\right)} .$$

Expression (7) now holds with the newly defined BF_s and BF_m.

A bound for exposure misclassification, selection bias, and unmeasured confounding

Unlike the bound for outcome misclassification, the bound for exposure misclassification from VanderWeele & Li[1] applies to the odds ratio, not the risk ratio, and the sensitivity parameters are also not risk ratios. That is,

$$\frac{\frac{\Pr(Y=1|A^*=1,c)}{\Pr(Y=0|A^*=1,c)}}{\frac{\Pr(Y=1|A^*=0,c)}{\Pr(Y=0|A^*=0,c)}} \leq \text{BF}'_m \times \frac{\frac{\Pr(Y=1|A=1,c)}{\Pr(Y=0|A=1,c)}}{\frac{\Pr(Y=1|A=0,c)}{\Pr(Y=0|A=0,c)}} \tag{8}$$

for

$$\text{BF}'_m = \text{OR}_{YA^*|a} = \max\left(\frac{\frac{s'_1}{1-s'_1}}{\frac{s'_0}{1-s'_0}}, \frac{\frac{f'_1}{1-f'_1}}{\frac{f'_0}{1-f'_0}}, \frac{\frac{f'_1}{f'_0}}{\frac{1-s'_1}{1-s'_0}}, \frac{\frac{s'_1}{s'_0}}{\frac{1-f'_1}{1-f'_0}}\right) \tag{9}$$

where $s'_y = \Pr\left(A^* = 1 \mid Y = y, A = 1, c\right)$ and $f'_y = \Pr\left(A^* = 1 \mid Y = y, A = 0, c\right)$.

Applying this bound after factoring out selection bias, we would find that we are left with

$$\mathrm{RR}_{AY}^{\mathrm{obs}} \leq \mathrm{BF}'_m \times \mathrm{BF}_s \times \mathrm{BF}_c \times \mathrm{RR}_{AY}^{\mathrm{true}} \times \frac{\Pr(Y=0 \mid A=0,c)}{\Pr(Y=0 \mid A=1,c)} \times \frac{\Pr(Y=0 \mid A^*=1,c)}{\Pr(Y=0 \mid A^*=0,c)}$$

for some BF'_m, BF_s, and BF_c, which is not as useful for sensitivity analysis. However, if the outcome is sufficiently rare that $\Pr(Y=0 \mid \cdot) \approx 1$ in all strata, a simpler bound holds approximately, as we show next.

Again we can define the parameters in the bound in two ways by considering two sets of assumptions.

Result 2

If there exist U_s and U_c such that $Y \amalg S \mid A, C, U_s$ and $Y_a \amalg A \mid C, U_c$, and if $\Pr(Y=0 \mid \cdot) \approx 1$, then we have Result 2:

$$\begin{aligned}\mathrm{RR}_{AY}^{\mathrm{obs}'} &= \frac{\Pr(Y=1 \mid A^*=1, S=1, c)}{\Pr(Y=1 \mid A^*=0, S=1, c)} \\ &\lesssim \mathrm{BF}'_m \times \mathrm{BF}_s \times \mathrm{BF}_c \times \mathrm{RR}_{AY}^{\mathrm{true}}\end{aligned}$$

for $\mathrm{BF}'_m = \mathrm{OR}_{YA^*|a,S=1}$ equivalent to the expression (9), but with $s'_y = \Pr(A^*=1 \mid Y=y, A=1, S=1, c)$ and $f'_y = \Pr(A^*=1 \mid Y=y, A=0, S=1, c)$; BF_s as defined in (4); and BF_c as defined in (6).

An alternative decomposition

Alternatively, if $Y \amalg S \mid A^*, C, U_s$ and $Y_a \amalg A \mid C, U_c$, then the bound holds approximately with

$$\mathrm{BF}_s = \frac{\mathrm{RR}_{U_sY|A^*=1} \times \mathrm{RR}_{SU_s|A^*=1}}{\mathrm{RR}_{U_sY|A^*=1} + \mathrm{RR}_{SU_s|A^*=1} - 1} \times \frac{\mathrm{RR}_{U_sY|A^*=0} \times \mathrm{RR}_{SU_s|A^*=0}}{\mathrm{RR}_{U_sY|A^*=0} + \mathrm{RR}_{SU_s|A^*=0} - 1}$$

where $\mathrm{RR}_{U_sY|A^*=a}$ and $\mathrm{RR}_{SU_s|A^*=0}$ are defined as above, with all A replaced with A^* and Y^* replaced with Y, and with BF'_m as originally defined in expression (9).

Interpretation of the exposure misclassification parameters

While all of the sensitivity parameters we have considered thus far are risk ratios, we have seen that those making up the bound for exposure misclassification are not. If, however, the misclassified exposure is sufficiently rare that $\Pr(A^* = 0 \mid \cdot) \approx 1$, then we can interpret the sensitivity parameters as risk ratios:

$$\begin{aligned}
\mathrm{BF}'_m &= \mathrm{RR}_{YA^*|a} = \max_a \left(\frac{\Pr(A^* = 1 \mid Y = 1, A = a, c)}{\Pr(A^* = 1 \mid Y = 0, A = a, c)} \right) \quad \text{or} \\
\mathrm{BF}'_m &= \mathrm{RR}_{YA^*|a,S=1} = \max_a \left(\frac{\Pr(A^* = 1 \mid Y = 1, A = a, S = 1, c)}{\Pr(A^* = 1 \mid Y = 0, A = a, S = 1, c)} \right) .
\end{aligned}$$

Alternatively, if the exposure is not particularly rare, we can interpret the sensitivity parameters as squares of the RR equivalents, using the square-root approximation of the odds ratio.[4]

Inference in the selected population

Result 3 (Under outcome misclassification)

It may be that our target of inference is the selected population only, so that

$$\mathrm{RR}^{\text{true}}_{AY|S=1} = \frac{\Pr(Y_1 = 1 \mid S = 1, c)}{\Pr(Y_0 = 1 \mid S = 1, c)} .$$

In this case we need that assumption $Y_a \amalg A \mid S = 1, C, U_c, U_s$: we must simultaneously consider both the factor(s) creating selection bias and the factor(s) creating confounding (which may be one and the same). Let U_{sc} denote the vector (U_s, U_c). Then after factoring out the misclassification bias, we have Result 3:

$$\begin{aligned}
\mathrm{RR}^{\text{obs}}_{AY} &\leq \mathrm{BF}_m \times \frac{\Pr(Y = 1 \mid A = 1, S = 1, c)}{\Pr(Y = 1 \mid A = 0, S = 1, c)} \\
&\leq \mathrm{BF}_m \times \mathrm{BF}_{sc} \times \frac{\Pr(Y_1 = 1 \mid S = 1, c)}{\Pr(Y_0 = 1 \mid S = 1, c)} \\
&= \mathrm{BF}_m \times \mathrm{BF}_{sc} \times \mathrm{RR}^{\text{true}}_{AY|S=1} \qquad (10)
\end{aligned}$$

for

$$\mathrm{BF}_{sc} = \frac{\mathrm{RR}_{AU_{sc}} \times \mathrm{RR}_{U_{sc}Y}}{\mathrm{RR}_{AU_{sc}} + \mathrm{RR}_{U_{sc}Y} - 1}$$

where

$$\mathrm{RR}_{AU_{sc}} = \max_{u} \frac{\Pr\left(U_{sc} = u \mid A = 1, S = 1, c\right)}{\Pr\left(U_{sc} = u \mid A = 0, S = 1, c\right)}$$
$$\mathrm{RR}_{U_{sc}Y} = \max_{a} \frac{\max_u \Pr\left(Y = 1 \mid A = a, S = 1, c, U_{sc} = u\right)}{\min_u \Pr\left(Y = 1 \mid A = a, S = 1, c, U_{sc} = u\right)}$$

and BF_m is defined as in (2).

Under exposure misclassification

Again we consider the bias due to selection and unmeasured confounding jointly. The bound in expression (10) holds with BF'_m constructed with $s'_y = \Pr\left(A^* = 1 \mid Y = y, A = 1, S = 1, c\right)$ and $f'_y = \Pr\left(A^* = 1 \mid Y = y, A = 0, S = 1, c\right)$.

The multi-bias E-value

The bounds in Results 1, 2, and 3 allow researchers and consumers of research to choose values for bias parameters and investigate their possible effects on an observed risk ratio. Target-adjusted sensitivity analysis, on the other hand, quantifies the strength of bias necessary to shift an observation to another value, often the null value, though others can be used.[5] The E-value for unmeasured confounding is an example of this approach.[6] We can calculate an equivalent value for a combination of biases using the bounds in this article. The E-value for unmeasured confounding refers to a value that can be shown to be sufficient to explain away an observed estimate and that jointly minimizes the maximum of the two sensitivity parameters for unmeasured confounding.[6] Similarly, the multi-bias E-value describes the minimum value that all of the sensitivity parameters for each of the biases would have to take on for a given observed risk ratio to be compatible with a truly null risk ratio. Since the

overall bias is monotone increasing in the individual bias parameters, it follows that if any one of the bias parameters is less than the multi-bias E-value, then at least one other parameter would have to be greater than the multi-bias E-value in order to completely explain a result.

Recall that under non-differential misclassification of the exposure, the BF_m factor in the bound is not a risk ratio. If the misclassified exposure is rare, then that parameter can be interpreted as an approximate risk ratio; otherwise, an approximate square root transformation for the odds ratio can be applied so as to approximate the risk ratio.[1] In this way all the parameters that the multi-bias E-value pertains to are on the (approximate) risk ratio scale.

Figure 2 shows the size of the multiple-bias E-value for various combinations of biases and across a range of observed risk ratios. In general, this demonstrates that when there are multiple forms of bias, very little of each type could be sufficient to produce a risk ratio that is within the range we generally see in epidemiologic studies. For example, when the null is true, it is possible to observe a risk ratio of 4 if each of the outcome misclassification ($\text{RR}_{AY^*|y,S=1}$), selection bias ($\text{RR}_{U_sY|A=1}, \text{RR}_{U_sY|A=1}, \text{RR}_{SU_s|A=1}, \text{RR}_{SU_s|A=0}$), and unmeasured confounding ($\text{RR}_{U_cY}, \text{RR}_{AU_c}$) parameters is approximately 1.89.

Of course, it is unlikely that each of these sensitivity analysis parameters would be equal to the others, and equal to 1.89. The bounds in this article can be used to assess the bias with a more realistic set of parameters. However, comparing multiple-bias E-values for various combinations of biases may be useful when planning studies to assess where resources should be invested to avoid certain biases, or to assess where a more in-depth bias analysis would be most useful.

Unfortunately, we know of no closed-form solution for this value when we are faced with all three types of bias, but it is easily solved numerically. The expressions to be solved are given in the final column of Table 1. To calculate the analogous multi-bias E-value needed to shift the observed $\text{RR}_{AY}^{\text{obs}}$ to some risk ratio, $\text{RR}_{AY}^{\text{true}}$, other than the null, one can simply

replace $\text{RR}_{AY}^{\text{obs}}$ in the each formula with $\text{RR}_{AY}^{\text{obs}}/\text{RR}_{AY}^{\text{true}}$. Also, each formula presupposes that $\text{RR}_{AY}^{\text{obs}} >= 1$; for apparently protective exposures, the inverse should be taken first.

We will demonstrate interpretation of the multiple bias E-value with respect to our examples, and then briefly describe an R package that can be used to implement the results.

Examples

Recall from the main text that the study of HIV infection in children found $\text{RR}_{AY}^{\text{obs}} = 6.75$,[7] which we determined was possibly affected by selection bias and unmeasured confounding. The multi-bias E-value for that study, given the assumptions about bias we have made, is 4.64. This tells us that $\text{RR}_{U_sY|A=1} = \text{RR}_{SU_s|A=1} = \text{RR}_{AU_c} = \text{RR}_{U_cY} =\geq 4.64$ could suffice to completely explain the observed result, but weaker combined bias would not. If, for example, selection bias were indeed weaker, the strength of the unmeasured confounding parameters would have to be stronger than 4.64 for the observation to be compatible with a truly null effect. Repeating the calculation with the lower limit of the confidence interval, we obtain a multi-bias E-value of 2.73. If all of the parameters were this large, it is possible that the confidence interval would include the null.

The estimate from the vitamins-leukemia study was $\text{RR}_{A^*Y}^{\text{obs}} = 0.51$.[8] After taking the inverse so that$\text{RR}_{A^*Y}^{\text{obs}} = 1/0.51 = 1.96$, we find that the multi-bias E-value for exposure misclassification and unmeasured confounding is 1.35. In order to interpret that number consistently across biases, the multi-bias E-value we have calculated pertains to RR_{AU_c}, RR_{U_cY}, and $\text{RR}_{YA^*|a}$, the latter being the square-root approximation of the $\text{OR}_{YA^*|a}$ term in the bound for exposure misclassification.[1] This allows us to interpret 1.35 as the minimum strength on the risk ratio scale that an unmeasured confounder, or set of confounders, would have to have on the outcome, that would have to relate vitamin use to the confounder, and that the false positive probability or sensitivity for vitamin use would have to be increase by, in order for these biases to explain the entire observed risk ratio. Again, this is simply a

heuristic, not something we would expect to be the case; for example, we might expect weaker misclassification but stronger confounding. For the limit of the confidence interval closest to the null, 0.89, if we take inverses, we obtain $1/0.89 = 1.12$ and the multi-bias E-value for this is only 1.06, indicating that whether the true risk ratio is smaller than or greater than 1 is indeed sensitive to relatively small amounts of bias.

Derivation

To form a multiple bias E-value,[6] we can set all of the parameters that make up the terms in the bounds equal to each other, then solve for that value to see what magnitude of bias would result in an $\mathrm{RR}_{AY}^{\mathrm{obs}}$ of at least the value observed, if $\mathrm{RR}_{AY}^{\mathrm{true}} = 1$.

For example, for the bound for outcome misclassification, general selection bias, and unmeasured confounding:

$$\begin{aligned}
\mathrm{RR}_{AY}^{\mathrm{obs}} &\leq \max \mathrm{RR}_{AY^*|y,S=1} \times \frac{\mathrm{RR}_{U_sY|A=1} \times \mathrm{RR}_{SU_s|A=1}}{\mathrm{RR}_{U_sY|A=1} + \mathrm{RR}_{SU_s|A=1} - 1} \times \\
&\quad \frac{\mathrm{RR}_{U_sY|A=0} \times \mathrm{RR}_{SU_s|A=0}}{\mathrm{RR}_{U_sY|A=0} + \mathrm{RR}_{SU_s|A=0} - 1} \times \frac{\mathrm{RR}_{AU_c} \times \mathrm{RR}_{U_cY}}{\mathrm{RR}_{AU_c} + \mathrm{RR}_{U_cY} - 1} \times 1 \\
&= x \times \frac{x^2}{2x-1} \times \frac{x^2}{2x-1} \times \frac{x^2}{2x-1} \\
&= \frac{x^7}{(2x-1)^3} \qquad (11)
\end{aligned}$$

for $x = \mathrm{RR}_{AY^*|y,S=1} = \mathrm{RR}_{U_sY|A=1} = \mathrm{RR}_{SU_s|A=1} = \mathrm{RR}_{U_sY|A=0} = \mathrm{RR}_{SU_s|A=0} = \mathrm{RR}_{AU_c} = \mathrm{RR}_{U_cY}$.

To our knowledge, this polynomial has no closed-form solution. However, we can easily solve it numerically.

For example, if $\mathrm{RR}_{AY}^{\mathrm{obs}} = 3$, then $x = 1.71$, meaning that if each of the parameters were at least 1.71, the observed risk ratio could be consistent with a truly null causal risk ratio. If any of the parameters were smaller than 1.71, others would have to be larger if the causal risk ratio were truly null.

We can solve the inequality for any combination of parameters that make up a particular

bound in a given situation (e.g., for outcome misclassification and selection bias only, or for exposure misclassification with a rare outcome and unmeasured confounding). When considering exposure misclassification, to calculate a multiple bias E-value, we first must confirm that the outcome is rare. Then, if the misclassified exposure is rare, we can solve equation (11) and interpret it with respect to the appropriate parameters; if the exposure is not rare, we can solve

$$\begin{aligned}
\mathrm{RR}_{AY}^{\mathrm{obs}} \lesssim \mathrm{RR}^2_{YA^*|a,S=1} &\times \frac{\mathrm{RR}_{U_sY|A=1} \times \mathrm{RR}_{SU_s|A=1}}{\mathrm{RR}_{U_sY|A=1} + \mathrm{RR}_{SU_s|A=1} - 1} \times \\
&\frac{\mathrm{RR}_{U_sY|A=0} \times \mathrm{RR}_{SU_s|A=0}}{\mathrm{RR}_{U_sY|A=0} + \mathrm{RR}_{SU_s|A=0} - 1} \times \frac{\mathrm{RR}_{AU_c} \times \mathrm{RR}_{U_cY}}{\mathrm{RR}_{AU_c} + \mathrm{RR}_{U_cY} - 1} \times 1 \\
&= x^2 \times \frac{x^2}{2x-1} \times \frac{x^2}{2x-1} \times \frac{x^2}{2x-1} \\
&= \frac{x^8}{(2x-1)^3}
\end{aligned}$$

and interpret with respect to the same parameters.

Implementation in R

We can use new functions from the R package `EValue`[9] to either calculate the appropriate multiple bias E-value or to calculate a bound for the bias, given proposed parameters. The primary new functions in the package, `multi_bound()` and `multi_evalue()`, accept a set of biases (out of `confounding()`, `selection()`, and `misclassification()`, which take various arguments describing the bias in more detail). The function `multi_bias()` is used to declare those biases. The `multi_bound()` function requires values for the parameters making up the bound for the biases in question. The `multi_evalue()` function requires just a value for the observed risk ratio, and prints a message to the user about the sensitivity parameters it refers to.

We will demonstrate the new package functionality by working through the examples in the main text. We will then show how the new functions can be used to recreate examples

from earlier literature as well.

```
library(EValue)
```

Examples from the main text

The `multi_bias()` function takes as arguments one or more of the three bias functions, `confounding()`, `selection()`, and `misclassification()`. They should be listed in the order in which they occur in the data (i.e., does the measurement happen in the sample, or is the sample selected based on mismeasured exposure or outcome values?). Each of `selection()` and `misclassification()` take additional arguments depending on the assumptions and simplifications of a given scenario.

In the HIV example, we were interested in the composite bias due to confounding and selection. We were willing to make the assumption that the outcome is more likely in the selected portion of both exposure groups, so we include the argument `"increased risk"`. (The `"general"` argument is in contrast to `"selected"`, the latter meaning that we are only interested in inference in the selected population. Since `"general"` is the default, we could leave it out.)

```
HIV_biases <- multi_bias(confounding(),
                         selection("general", "increased risk"))
```

Printing the biases prints out the arguments that are required for the `multi_bound()` function for easy copying and pasting into that function.

```
HIV_biases
multi_bound(biases = HIV_biases,
            RRAUc = 2.3, RRUcY = 2.5, RRUsYA1 = 3, RRSUsA1 = 2)
```

```
[1] 2.269737
```

Because the labeling of the arguments is not necessarily intuitive, we might want to

confirm which refers to which parameter. We can use the `summary()` function on a object created with the `multi_bias()` function to print more information about the biases.

```
summary(HIV_biases)
```

```
         bias     output argument
1 confounding     RR_AUc    RRAUc
2 confounding     RR_UcY    RRUcY
3   selection RR_UsY|A=1  RRUsYA1
4   selection RR_SUs|A=1  RRSUsA1
```

For easy copying and pasting of the notation we used in this appendix and in the main text, the argument `latex = TRUE` can be used in the summary function to print out an additional column with the parameters in our notation.

To calculate a multi-bias E-value, we must provide the observed effect estimate along with the set of biases. There are two options for doing so. The first is to declare the effect estimate with one of `RR()`, `OR()`, or `HR()`, depending on whether it is a risk, odds, or hazard ratio.

```
multi_evalue(biases = HIV_biases,
             est = OR(6.75, rare = TRUE),
             lo = 2.79, hi = 16.31)
```

```
                      point    lower upper
RR                 6.750000 2.790000 16.31
Multi-bias E-values 4.635703 2.728474    NA
```

The lower and upper bound of the confidence interval are assumed to be on the same scale.

Next we will look at the vitamins-leukemia example from the text. The `misclassification()` bias requires one of either `"outcome"` or `"exposure"`; if exposure misclassification is of interest, the user is also required to specify whether the outcome and/or exposure are sufficiently rare to use a risk ratio approximation for an odds ratio (irrespective of whether

the effect estimate is actually on the odds ratio scale).

```
leuk_biases <- multi_bias(confounding(),
                          misclassification("exposure",
                                            rare_outcome = TRUE,
                                            rare_exposure = FALSE))
leuk_biases
```

Again we can calculate the bound and multi-bias E-value as in the text.

```
multi_bound(biases = leuk_biases, RRAUc = 2, RRUcY = 1.22, ORYAa = 1.59)
```

```
[1] 1.747568
```

```
multi_evalue(biases = leuk_biases,
             est = OR(0.51, rare = TRUE),
             lo = 0.3, hi = 0.89)
```

```
                      point lower    upper
RR                 0.510000   0.3 0.890000
Multi-bias E-values 1.351985    NA 1.058404
```

We can easily demonstrate that the E-value is the same whether or not the effect estimate is inverted if the exposure is apparently protective. Also, if we don't want the message about the parameters to print, we can use the argument `verbose = FALSE`.

```
multi_evalue(biases = leuk_biases,
             est = OR(1/0.51, rare = TRUE),
             hi = 1/0.3, lo = 1/0.89,
             verbose = FALSE)
```

```
                      point    lower    upper
RR                 1.960784 1.123596 3.333333
Multi-bias E-values 1.351985 1.058404       NA
```

Finally, we presented a multi-bias E-value for all three biases. We can use the `summary()` function to just print the single value, instead of the matrix of the estimates and confidence

limits and E-values for both.

```
summary(multi_evalue(biases = multi_bias(confounding(),
                                         selection("general"),
                                         misclassification("outcome")),
                     est = RR(4)))
```

```
[1] 1.888478
```

Extensions not appearing in the main text

We may want to vary the magnitude of the parameters used to calculate the bounds. We'll use the biases from the HIV example to demonstrate.

```
# original bound
multi_bound(biases = HIV_biases, RRAUc = 2, RRUcY = 2.5,
            RRUsYA1 = 3, RRSUsA1 = 2)
```

```
[1] 2.142857
```

```
# vary RRAUc from 1.25 to 3
sapply(seq(1.25, 3, by = .25), function(RRAUc) {
  multi_bound(biases = HIV_biases, RRAUc = RRAUc,
              RRUcY = 2.5, RRUsYA1 = 3, RRSUsA1 = 2)
  })
```

```
[1] 1.704545 1.875000 2.019231 2.142857 2.250000 2.343750 2.426471 2.500000
```

```
# vary RRAUc and RRUcY
param_vals <- seq(1.25, 3, by = .25)

params <- expand.grid(RRAUc = param_vals,
                      RRUcY = param_vals)

vals <- mapply(multi_bound,
               RRAUc = params$RRAUc,
```

```
               RRUcY = params$RRUcY,
               MoreArgs = list(biases = HIV_biases,
                               RRUsYA1 = 3, RRSUsA1 = 2))
matrix(vals,
  ncol = length(param_vals),
  dimnames = list(param_vals, param_vals)
)
```

```
         1.25      1.5     1.75        2     2.25      2.5     2.75        3
1.25 1.562500 1.607143 1.640625 1.666667 1.687500 1.704545 1.718750 1.730769
1.5  1.607143 1.687500 1.750000 1.800000 1.840909 1.875000 1.903846 1.928571
1.75 1.640625 1.750000 1.837500 1.909091 1.968750 2.019231 2.062500 2.100000
2    1.666667 1.800000 1.909091 2.000000 2.076923 2.142857 2.200000 2.250000
2.25 1.687500 1.840909 1.968750 2.076923 2.169643 2.250000 2.320312 2.382353
2.5  1.704545 1.875000 2.019231 2.142857 2.250000 2.343750 2.426471 2.500000
2.75 1.718750 1.903846 2.062500 2.200000 2.320312 2.426471 2.520833 2.605263
3    1.730769 1.928571 2.100000 2.250000 2.382353 2.500000 2.605263 2.700000
```

Of course, all of the parameters in the bound could be varied, but summarizing the resulting bounds in a simple table or figure becomes more difficult with more than two dimensions.

When calculating a multi-bias E-value, we may also think that the null is unlikely but wish to consider how much bias could have shifted a different true value to the observed value. For example, in the HIV example, we could calculate a multi-bias E-value for a true risk ratio of 2 rather than the null value of 1:

```
multi_evalue(biases = HIV_biases,
             est = OR(6.75, rare = TRUE),
             lo = 2.79, hi = 16.31,
             true = 2)
```

```
                      point    lower upper
RR                 6.750000 2.790000 16.31
Multi-bias E-values 3.077243 1.643623    NA
```

The multi-bias E-value for the point estimate, 3.08 is of course smaller than the "null" E-value of 4.64, as less bias could have resulted in an OR of 6.75 if the true OR were 2 than would have been necessary to shift it from 1.

The interpretation of the parameters differs depending on the ordering of the selection bias and misclassification. We can see that the parameters expected in the `multi_bound()` function and printed by the `multi_evalue()` function reflect the ordering in which the biases are added to `multi_bias()` (see `output` column).

```
# misclassification occurs in the selected group
summary(
  multi_bias(selection("general"),
             misclassification("exposure", rare_outcome = TRUE))
  )
```

```
                      bias     output argument
1                selection RR_UsY|A=1  RRUsYA1
2                selection RR_SUs|A=1  RRSUsA1
3                selection RR_UsY|A=0  RRUsYA0
4                selection RR_SUs|A=0  RRSUsA0
5 exposure misclassification OR_YA*|a,S   ORYAaS
```

```
# selection is of misclassified individuals
summary(
  multi_bias(misclassification("exposure", rare_outcome = TRUE),
             selection("general"))
  )
```

```
                      bias      output argument
1                selection RR_UsY|A*=0  RRUsYA0
2                selection RR_SUs|A*=1  RRSUsA1
3                selection RR_UsY|A*=1  RRUsYA1
4                selection RR_SUs|A*=1  RRSUsA1
5 exposure misclassification    OR_YA*|a    ORYAa
```

When selection bias and confounding are both of interest, but restricting inference to the

selected population only is desired, the parameters are shared by the two biases:

```
summary(
  multi_bias(confounding(),
             selection("selected"),
             misclassification("exposure", rare_outcome = TRUE))
  )
```

```
                        bias     output argument
1  confounding and selection  RR_AUsc|S  RRAUscS
2  confounding and selection  RR_UscY|S  RRUscYS
3 exposure misclassification OR_YA*|a,S   ORYAaS
```

Finally, we can see the expected relationship between the multi-bias bound and the multi-bias E-value.

```
biases <- multi_bias(confounding(),
                     selection("general", "decreased risk"),
                     misclassification("outcome"))

# calculate bound with those parameters all equal to 2
multi_bound(biases, RRAUc = 2, RRUcY = 2, RRUsYA0 = 2, RRSUsA0 = 2, RRAYyS = 2)
```

```
[1] 3.555556
```

```
# get multi-bias e-value for that value; should be ~2
summary(multi_evalue(biases, est = RR(3.555556)))
```

```
[1] 1.999997
```

Examples from earlier literature

The multi-bias bound and E-value are generalizations of previously published results. To demonstrate, we recreate here some examples from three articles introducing the bound and E-value concept for confounding, selection bias, and differential misclassification.

From *Sensitivity Analysis without Assumptions*, Ding & VanderWeele 2016[3]

```
# example from page 370
biases_ex1 <- confounding()
# specifying parameters in bound
multi_bound(biases = biases_ex1, RRAUc = 2, RRUcY = 2)
```

```
[1] 1.333333
```

```
# Table 1, page 371
# consider all possible combinations for bound
param_vals <- c(1.3, 1.5, 1.8, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10)
params <- expand.grid(RRAUc = param_vals,
                      RRUcY = param_vals)
table1_vals <- mapply(multi_bound, RRAUc = params$RRAUc, RRUcY = params$RRUcY,
                      MoreArgs = list(biases = biases_ex1))
table1 <- matrix(table1_vals,
  ncol = length(param_vals),
  dimnames = list(param_vals, param_vals)
)
round(table1, 2)
```

```
     1.3  1.5  1.8    2  2.5    3  3.5    4    5    6    8   10
1.3 1.06 1.08 1.11 1.13 1.16 1.18 1.20 1.21 1.23 1.24 1.25 1.26
1.5 1.08 1.12 1.17 1.20 1.25 1.29 1.31 1.33 1.36 1.38 1.41 1.43
1.8 1.11 1.17 1.25 1.29 1.36 1.42 1.47 1.50 1.55 1.59 1.64 1.67
2   1.13 1.20 1.29 1.33 1.43 1.50 1.56 1.60 1.67 1.71 1.78 1.82
2.5 1.16 1.25 1.36 1.43 1.56 1.67 1.75 1.82 1.92 2.00 2.11 2.17
3   1.18 1.29 1.42 1.50 1.67 1.80 1.91 2.00 2.14 2.25 2.40 2.50
3.5 1.20 1.31 1.47 1.56 1.75 1.91 2.04 2.15 2.33 2.47 2.67 2.80
4   1.21 1.33 1.50 1.60 1.82 2.00 2.15 2.29 2.50 2.67 2.91 3.08
5   1.23 1.36 1.55 1.67 1.92 2.14 2.33 2.50 2.78 3.00 3.33 3.57
6   1.24 1.38 1.59 1.71 2.00 2.25 2.47 2.67 3.00 3.27 3.69 4.00
8   1.25 1.41 1.64 1.78 2.11 2.40 2.67 2.91 3.33 3.69 4.27 4.71
10  1.26 1.43 1.67 1.82 2.17 2.50 2.80 3.08 3.57 4.00 4.71 5.26
```

```r
# reduce an observed RR of 2.5 to true value of 1.5, page 371
summary(multi_evalue(biases = confounding(), est = RR(2.5), true = 1.5))
```

```
[1] 2.720763
```

```r
# smoking and lung cancer e-value, page 373
summary(multi_evalue(biases = confounding(), est = RR(10.73)))
```

```
[1] 20.94777
```

From *Bounding bias due to selection*, Smith & VanderWeele, 2019[2]

```r
biases_ex2 <- selection("general")

# result 1A example
multi_bound(biases = biases_ex2,
            RRUsYA1 = 2, RRSUsA1 = 1.7, RRUsYA0 = 2, RRSUsA0 = 1.5)
```

```
[1] 1.511111
```

```r
# result 1B example
multi_evalue(biases = biases_ex2, est = OR(73.1, rare = TRUE), lo = 13.0)
```

```
                       point     lower upper
RR                  73.10000 13.000000    NA
Multi-bias E-values 16.58415  6.670587    NA
```

```r
# result 4B example
summary(multi_evalue(biases = selection("general", "S = U", "increased risk"),
             est = OR(5.2, rare = TRUE)))
```

```
[1] 5.2
```

```r
# result 5B example
multi_evalue(biases = selection("selected"),
             est = OR(1.5, rare = TRUE), lo = 1.22)
```

```
                       point    lower upper
RR                  1.500000 1.220000    NA
Multi-bias E-values 2.366025 1.738081    NA
```

From *Simple Sensitivity Analysis for Differential Measurement Error*, VanderWeele & Li 2019[1]

```r
biases_ex3 <- misclassification("exposure",
                                rare_outcome = TRUE, rare_exposure = TRUE)
multi_evalue(biases = biases_ex3, est = OR(1.51, rare = TRUE), lo = 1.03)
```

```
                    point lower upper
RR                   1.51  1.03    NA
Multi-bias E-values  1.51  1.03    NA
```

Figures

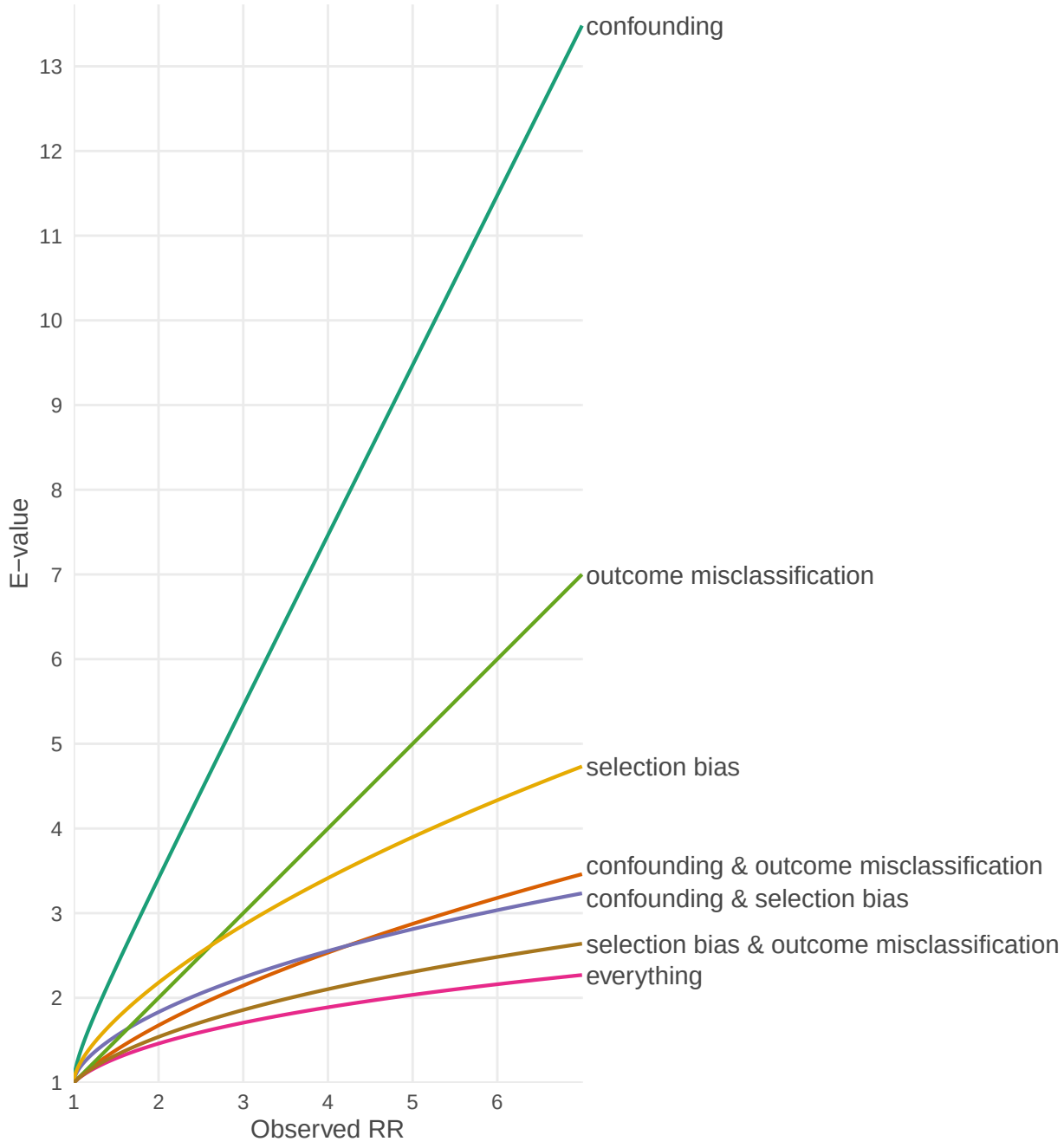
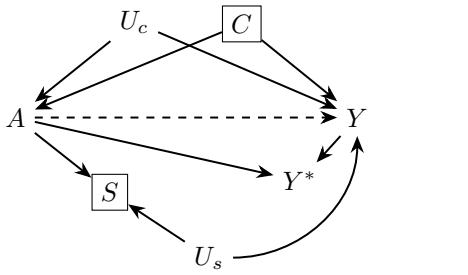
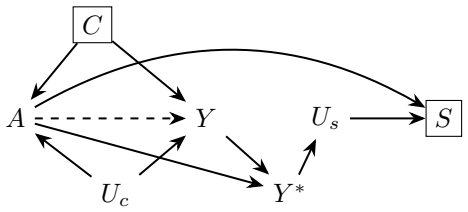


Figure 1: *Multi-bias E-values for various combinations of biases and for observed risk ratios ranging from 1 to 7.*

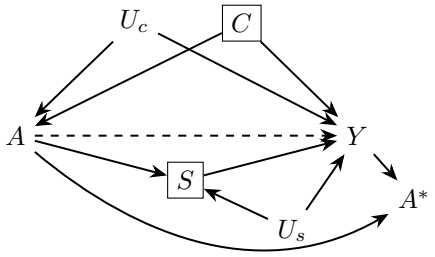
These examples show how various combinations of biases can be represented by directed acyclic graphs, and the independence assumptions that are implied.



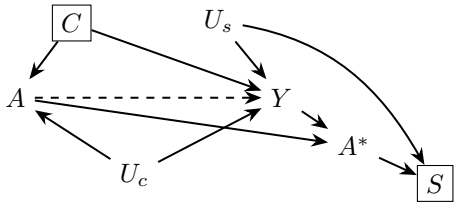
A. This DAG depicts unmeasured confounding (through U_c), selection bias (through U_s), and differential misclassification of the outcome (due to the $A \rightarrow Y^*$ edge). The assumptions $Y \amalg S \mid A, C, U_s$ and $Y_a \amalg A \mid C, U_c$ are met. This implies that we can apply the outcome misclassification bound, then the selection bias bound, then the unmeasured confounding bound for inference in the total population.



B. This DAG depicts unmeasured confounding (through U_c), selection bias (through U_s), and differential misclassification of the outcome (due to the $A \rightarrow Y^*$ edge). The assumptions $Y^* \amalg S \mid A, C, U_s$ and $Y_a \amalg A \mid C, U_c$ are met. This implies that we can apply the selection bias bound, then the outcome misclassification bound, then the unmeasured confounding bound for inference in the total population.



C. This DAG depicts unmeasured confounding (through U_c), selection bias (through U_s), and differential misclassification of the exposure (due to the $Y \rightarrow A^*$ edge). The assumption $Y_a \amalg A \mid S = 1, C, U_s, U_c$ is met. This implies that we can apply the the exposure misclassification bound, then the joint bound for selection bias and unmeasured confounding for inference in the selected population.



D. This DAG depicts unmeasured confounding (through U_c), selection bias (through U_s), and differential misclassification of the exposure (due to the $Y \rightarrow A^*$ edge). The assumptions $Y \amalg S \mid A^*, C, U_s$ and $Y_a \amalg A \mid C, U_c$ are met. This implies that we can apply the selection bias bound, then the exposure misclassification bound, then the unmeasured confounding bound for inference in the total population.

Figure 2: *Directed acyclic graphs depicting multiple biases.*

References

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5. Phillips CV, LaPole LM. Quantifying errors without random sampling. *BMC Medical Research Methodology*. 2003;3:1–10.

6. VanderWeele TJ, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-Value. *Annals of Internal Medicine*. 2017;167:268–275.

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9. Mathur MB, Ding P, Riddell CA, et al. Website and R Package for Computing E-values. *Epidemiology*. 2018;29:e45–e47.