Research Article

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A note on a sensitivity analysis for unmeasured confounding, and the related E-value

<https://doi.org/10.1515/jci-2020-0012>

Received Sep 14, 2020; accepted May 18, 2020

Abstract: Unmeasured confounding is one of the most important threats to the validity of observational studies. In this paper we scrutinize a recently proposed sensitivity analysis for unmeasured confounding. The analysis requires specification of two parameters, loosely defined as the maximal strength of association that an unmeasured confounder may have with the exposure and with the outcome, respectively. The E-value is defined as the strength of association that the confounder must have with the exposure and the outcome, to fully explain away an observed exposure-outcome association. We derive the feasible region of the sensitivity analysis parameters, and we show that the bounds produced by the sensitivity analysis are not always sharp. We finally establish a region in which the bounds are guaranteed to be sharp, and we discuss the implications of this sharp region for the interpretation of the E-value. We illustrate the theory with a real data example and a simulation.

Keywords: Causal inference, confounding, counterfactuals, E-value, sensitivity analysis

2020 Mathematics Subject Classification: 62D20

1 Introduction

Unmeasured confounding is one of the most important threats to the validity of observational studies. In a recent publication, Ding and VanderWeele [3], hereafter DV, proposed a method to assess the sensitivity of observed associations to unmeasured confounding. Briefly, the method requires the analyst to provide guesses of certain sensitivity analysis parameters, defined as the maximal strength of association that an unmeasured confounder may have with the exposure and with the outcome. Given these parameters, the method gives bounds for the causal risk ratio, i.e. a range of values that is guaranteed to include the true exposure effect. In a subsequent publication, VanderWeele and Ding [16] proposed the ‘E-value’ as a measure of sensitivity to unmeasured confounding, defined as the maximal strength of association that an unmeasured confounder would need to have with the exposure and the outcome, to fully explain away an observed exposure-outcome association.

The method has already been highly influential; as of July 21, 2020, the two publications have 208 and 711 citations, respectively, according to Google Scholar. In a systematic literature search up to the end of 2018, Blum *et al.* [1] found 87 papers presenting 516 E-values. In this paper we complement DV’s work, by deriving and clarifying several important points regarding their sensitivity analysis and E-value. The paper is organized as follows. In Section 2 we review the key elements of DV’s sensitivity analysis. In Section 3 we derive the feasible region of DV’s sensitivity analysis parameters, which has not been derived previously by these authors. In Section 4 we compare DV’s bounds with alternative, assumption-free bounds. We conclude from this comparison that DV’s bounds are not always sharp, which contradicts a previous claim by these authors, and we give analytic arguments as to when and why DV’s bounds can be expected to be non-sharp. In Section

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5 we establish a region in which DV's bounds are guaranteed to be sharp, and we discuss the implications of this sharp region for the interpretation of the E-value. In line with Ding and VanderWeele [3] and VanderWeele and Ding [16] we focus on sensitivity analysis for the causal risk ratio, but we show in Section 6 that all our results carry over with no or little modification to the causal risk difference. Finally, in Sections 7 and 8 we provide a real data example and a simulation, respectively.

2 DV's sensitivity analysis

We adopt the notation of Ding and VanderWeele [3]. Let E and D denote the binary exposure and outcome, respectively. DV's method applies conditionally on measured covariates C ; for notational convenience we will make this conditioning implicit everywhere. Let $p(E = e)$ denote the marginal probability of $E = e$, let $p(D = d|E = e)$ denote the conditional probability of $D = d$, given $E = e$, and let $p(D = d, E = e)$ denote the joint probability of $(D = d, E = e)$, for $(d, e) \in \{0, 1\}$. The observed exposure-outcome risk ratio is defined as

$$RR_{ED}^{\text{obs}} = \frac{p(D = 1|E = 1)}{p(D = 1|E = 0)}.$$

To define the causal exposure effect, let $D(e)$ be the potential outcome [12, 14] for a given subject, had that subject been exposed to level $E = e$. The causal exposure-outcome risk ratio is defined as

$$RR_{ED}^{\text{true}} = \frac{p\{D(1) = 1\}}{p\{D(0) = 1\}}.$$

Let U denote a set of unmeasured confounders. To avoid technicalities we follow DV and assume that U can be coded as a categorical variable with levels $0, \dots, K - 1$, but we emphasize that all results and conclusions that we make hold for any type of U . We assume that U (together with the measured covariates C) is sufficient for confounding control.

The method proposed by DV uses certain sensitivity analysis parameters, informally defined as the maximal strength of association between E and U , and between U and D , respectively. Formally, the parameter RR_{UD} is defined as

$$RR_{UD} = \max_e \left\{ \frac{\max_k p(D = 1|E = e, U = k)}{\min_k p(D = 1|E = e, U = k)} \right\},$$

and the parameter RR_{EeU} is defined as

$$RR_{EeU} = \max_k \left\{ \frac{p(U = k|E = e)}{p(U = k|E = 1 - e)} \right\}.$$

In the latter we have deviated slightly from DV's notation; our parameters RR_{E1U} and RR_{E0U} correspond to their parameters RR_{EU} and $RR_{\bar{E}U}$, respectively, where RR_{EU} was defined in the main text of Ding and VanderWeele [3], and $RR_{\bar{E}U}$ was defined in proposition A.4 of that paper's eAppendix.

Define the bounding factor

$$BF_e = \frac{RR_{EeU} \times RR_{UD}}{RR_{EeU} + RR_{UD} - 1}.$$

Ding and VanderWeele [3] showed that, given RR_{EeU} and RR_{UD} , RR_{ED}^{true} is bounded by

$$RR_{ED}^{\text{obs}} / BF_1 \leq RR_{ED}^{\text{true}} \leq RR_{ED}^{\text{obs}} BF_0. \quad (1)$$

By providing guesses of $\{RR_{E0U}, RR_{E1U}, RR_{UD}\}$, the analyst may use DV's bounds to infer a plausible range for RR_{ED}^{true} .

In many situations, one may observe a positive association between the exposure and the outcome ($RR_{ED}^{\text{obs}} > 1$), and one may wonder how much confounding is required to fully 'explain away' this association.

VanderWeele and Ding [16] labeled this magnitude of confounding as the ‘E-value’. Formally, VanderWeele *et al.* [17] defined the E-value as

$$\text{E-value} = \min_{\{RR_{E1U}, RR_{UD}\}: BF_1 \geq RR_{ED}^{\text{obs}}} \max\{RR_{E1U}, RR_{UD}\}. \quad (2)$$

They showed that the E-value is equal to $RR_{ED}^{\text{obs}} + \sqrt{RR_{ED}^{\text{obs}}(RR_{ED}^{\text{obs}} - 1)}$.

3 Feasible region of DV’s sensitivity analysis parameters

In order for DV’s sensitivity analysis to give meaningful results, the guesses of $\{RR_{E0U}, RR_{E1U}, RR_{UD}\}$ must be confined to their feasible region, i.e. the region of parameter values that are logically possible. However, Ding and VanderWeele [3] did not derive this region.

There are at least two ways that restrictions on a parameter region can arise. First, its definition may imply a restriction. For instance, $\{RR_{E0U}, RR_{E1U}, RR_{UD}\}$ are all risk ratios, and are thus by definition restricted to non-negative values. Second, a parameter may be restricted by the observed data distribution. As an instructive example, note that we may use the law of total probability to decompose $p\{D(e) = 1\}$ as

$$p\{D(e) = 1\} = p\{D(e) = 1|E = e\}p(E = e) + p\{D(e) = 1|E = 1 - e\}p(E = 1 - e).$$

By consistency of counterfactuals [12], the potential outcome $D(e)$ is equal to the factual outcome D whenever the factual exposure E is equal to e , which implies that $p\{D(e) = 1|E = e\} = p(D = 1|E = e)$. We thus have that

$$p\{D(1) = 1\} = p(D = 1|E = 1)p(E = 1) + p\{D(1) = 1|E = 0\}p(E = 0) \quad (3)$$

and

$$p\{D(0) = 1\} = p(D = 1|E = 0)p(E = 0) + p\{D(0) = 1|E = 1\}p(E = 1). \quad (4)$$

In these expressions, only $p\{D(1) = 1|E = 0\}$ and $p\{D(0) = 1|E = 1\}$ are unknown. Kasza *et al.* [9] proposed an alternative sensitivity analysis for unmeasured confounding, by using the ratios

$$\frac{p(D = 1|E = 1)}{p\{D(1) = 1|E = 0\}} \quad (5)$$

and

$$\frac{p(D = 1|E = 0)}{p\{D(0) = 1|E = 1\}} \quad (6)$$

as sensitivity analysis parameters. By varying these parameters over a grid of plausible values one obtains a grid of plausible values for $p\{D(1) = 1\}$ and $p\{D(0) = 1\}$, and hence also RR_{ED}^{true} , through the relations in (3) and (4). However, the ratio in (5) cannot be smaller than $p(D = 1|E = 1)$ and the ratio in (6) cannot be smaller than $p(D = 1|E = 0)$; these limits are attained when the counterfactual probabilities $p\{D(1) = 1|E = 0\}$ and $p\{D(0) = 1|E = 1\}$ in the denominators of (5) and (6), respectively, are equal to 1. Hence, the feasible region of these sensitivity analysis parameters is restricted by the observed data distribution.

When the feasible region of a parameter is *not* restricted by the observed data distribution, we say that the parameter is *variation independent* of the observed data distribution. This variation independence is a desirable feature of a sensitivity analysis parameter, since it means that the analyst is free, in any given scenario, to speculate about the plausible values of the parameter, as long as these values are within the *a priori* feasible region of the parameter. This is particularly convenient when the set of measured confounders C is high-dimensional, in which case it would be a daunting task to verify that the considered values for the sensitivity analysis parameter are logically compatible with the observed data distribution within each level of C .

In Appendix A we prove the following theorem, which establishes the feasible region of DV’s sensitivity analysis parameters.

Theorem 1. $\{RR_{E0U}, RR_{E1U}, RR_{UD}\}$ are restricted by their definitions to values equal to or above 1. $\{RR_{E0U}, RR_{E1U}, RR_{UD}\}$ are variation independent of each other, and of the observed data distribution $p(D, E, U)$.

The theorem implies that the analyst should not consider values of these parameters below 1 in the sensitivity analysis. It further implies that, in any given scenario (i.e. for any observed data distribution), the analyst should consider all values of the parameters above or equal to 1 as logically possible, albeit not necessarily plausible.

4 DV's bounds vs the assumption-free bounds

Ding and VanderWeele [3] claimed, but did not prove, that their bounds are sharp, in the sense that, for any observed distribution $p(D, E)$ and correctly specified values of $\{RR_{E1U}, RR_{UD}\}$ the causal risk ratio RR_{ED}^{true} can always be as small as the lower bound in (1), and for any observed distribution $p(D, E)$ and correctly specified values of $\{RR_{E0U}, RR_{UD}\}$ the causal risk ratio RR_{ED}^{true} can always be as large as the upper bound in (1). This claim is not always correct though.

To see why, note that the relations in (3) and (4) can be used to derive alternative bounds for RR_{ED}^{true} , by arguing as Robins [13]. From (3) we have that $p\{D(1) = 1\}$ can be no smaller than $p(D = 1|E = 1)p(E = 1)$ and no larger than $p(D = 1|E = 1)p(E = 1) + p(E = 0)$; these bounds are attained when $p\{D(1) = 1|E = 0\} = 0$ and $p\{D(1) = 1|E = 0\} = 1$, respectively. Similarly, $p\{D(0) = 1\}$ can be no smaller than $p(D = 1|E = 0)p(E = 0)$ and no larger than $p(D = 1|E = 0)p(E = 0) + p(E = 1)$; these bounds are attained when $p\{D(0) = 1|E = 1\} = 0$ and $p\{D(0) = 1|E = 1\} = 1$, respectively. After some algebra, this gives the following bounds for RR_{ED}^{true} :

$$RR_{ED}^{\text{obs}}/\widetilde{BF}_1 \leq RR_{ED}^{\text{true}} \leq RR_{ED}^{\text{obs}}\widetilde{BF}_0, \quad (7)$$

where $\widetilde{BF}_e$ is the bounding factor

$$\widetilde{BF}_e = \frac{p(D = 1|E = 1 - e)p(E = 1 - e) + p(E = e)}{p(D = 1|E = 1 - e)p(E = e)}.$$

In contrast to DV's bounds, which require the analyst to speculate about $\{RR_{E0U}, RR_{E1U}, RR_{UD}\}$, the bounds in (7) do not require any particular assumptions (apart from consistency of counterfactuals); we thus refer to these bounds as 'assumption-free'. For some observed data distributions $p(D, E)$ and values of $\{RR_{E0U}, RR_{E1U}, RR_{UD}\}$, the assumption-free bounds may be sharper than DV's bounds. For instance, suppose that $p(E = 1) = p(D = 1|E = 0) = 0.9$ and $p(D = 1|E = 1) = 0.99$. We then have that $RR_{ED}^{\text{obs}} = 1.1$ and the lower assumption-free bound is equal to 0.9. However, suppose that we consider values of RR_{E1U} and RR_{UD} as large as 10 as plausible. DV's lower bound is then equal to 0.21.

DV showed that their lower bound is decreasing in RR_{E1U} and RR_{UD} . By differentiating $\widetilde{BF}_e$ it is easy to show that, for a fixed observed risk ratio RR_{ED}^{obs} , the lower assumption-free bound is increasing in $p(E = 1)$ and $p(D = 1|E = 0)$. Hence, when $p(E = 1)$ and $p(D = 1|E = 0)$ are relatively large, RR_{E1U} and RR_{UD} must be relatively small, in order for DV's lower bound to be sharper than the assumption-free lower bound. Similarly, DV's upper bound is increasing in RR_{E0U} and RR_{UD} , and, for a fixed observed risk ratio RR_{ED}^{obs} , the assumption-free upper bound is decreasing in $p(E = 0)$ and $p(D = 1|E = 1)$. Hence, when $p(E = 0)$ and $p(D = 1|E = 1)$ are relatively large, RR_{E0U} and RR_{UD} must be relatively small, in order for DV's upper bound to be sharper than the assumption-free upper bound.

Figure 1 illustrates these relations. In this figure, each curve corresponds to particular values of $p(D = 1|E = 1 - e)$ and $p(E = e)$, as specified by the legend. The figure applies to the lower bounds when $e = 1$, and to the upper bounds when $e = 0$. For each pair of $p(D = 1|E = 1 - e)$ and $p(E = e)$, the region to the right of the corresponding curve are the values of RR_{EeU} and RR_{UD} for which the assumption-free bound is sharper than DV's bound. The dots at the curves indicate where $RR_{EeU} = RR_{UD}$. For instance, when $p(D = 1|E = 0) = 0.3$ and $p(E = 1) = 0.8$, the assumption-free lower bound is sharper than DV's lower bound when both RR_{E1U} and RR_{UD} are larger than 6.6. The assumption-free lower bound may be sharper than the DV's lower bound even if

Figure 1: Regions of $\{RR_{EeU}, RR_{UD}\}$ for which the assumption-free bounds are sharper than DV's bounds, for selected values of $p(D = 1|E = 1 - e)$ and $p(E = e)$. The figure applies to the lower bounds when $e = 1$, and to the upper bounds when $e = 0$. Both axes use logarithmic scale.

one of the parameters RR_{E1U} and RR_{UD} is smaller than 6.6, but then the other parameter has to be much larger, as indicated by the steep incline of the curve through the point 6.6. Similarly, when $p(D = 1|E = 1) = 0.3$ and $p(E = 0) = 0.8$, the assumption-free upper bound is sharper than DV's upper bound when both RR_{E0U} and RR_{UD} are larger than 6.6.

We observe from Figure 1 that, unless $p(D = 1|E = 1 - e)$ and $p(E = e)$ are close to 1, it takes relatively large values of RR_{EeU} and RR_{UD} for the assumption-free bounds to be sharper than DV's bounds. Such large values may not be realistic if U only contains a few confounders. However, as noted by Ioannidis *et al.* [8], large values of RR_{EeU} and RR_{UD} may not be unrealistic if there are many unmeasured confounders with a large aggregated effect, which can often not be ruled out in practice.

5 A sharp region for DV's bounds

Even though DV's bounds are not always sharp, there is a region in which they are guaranteed to be sharp. This region is established by the following theorem, which we prove in Appendix B.

Theorem 2. *The lower bound in (1) is sharp if $BF_1 \leq 1/p(D = 1|E = 0)$, and the upper bound in (1) is sharp if $BF_0 \leq 1/p(D = 1|E = 1)$.*

The theorem implies that, if the analyst does not consider bounding factors outside the region given by the theorem as plausible, then any value of the causal risk ratio within DV's bounds should be considered as logically possible.

Theorem 2 has important implications for the E-value. To illustrate how to interpret the E-value, VanderWeele and Ding [16] considered a study of maternal breastfeeding and respiratory death by Victora *et al.* [18]. In this study, an exposure-outcome risk ratio equal to 3.9 was observed. Plugging this risk ratio into equation (2) gives an E-value equal to 7.26. DV concluded: ‘The observed risk ratio of 3.9 could be explained away by an unmeasured confounder that was associated with both the treatment and the outcome by a risk ratio of 7.2-fold each...’ Given that the E-value is derived from DV’s lower bound, and given that this bound is not always sharp, one may worry that the E-value is unnecessarily pessimistic. That is, can we be confident that a null causal effect is logically possible, given that $RR_{E1U} = RR_{UD} = 7.26$?

The reassuring answer is ‘yes we can’. Because $RR_{ED}^{obs} \leq 1/p(D = 1|E = 0)$, it follows from Theorem 2 that DV’s lower bound is guaranteed to be sharp when $BF_1 = RR_{ED}^{obs}$, that is, when the bound is equal to 1. Hence, an important corollary of Theorem 2 is that, whenever DV’s lower bound includes the null causal effect ($RR_{ED}^{true} = 1$), the null causal effect is also logically possible. In other words, the E-value is never unnecessarily pessimistic. In particular, the observed risk ratio of 3.9 in the study by Victora *et al.* [18] could indeed be explained away by an unmeasured confounder that was associated with both the treatment and the outcome by a risk ratio of 7.2-fold each.

6 Results for the causal risk difference

Ding and VanderWeele [3] and VanderWeele and Ding [16] focused on sensitivity analysis for the causal risk ratio. However, Ding and VanderWeele [3] did also provide bounds for the causal risk difference in propositions A.8 and A.10 of their eAppendix. After some algebraic rearrangement, these bounds can be expressed as

$$RD_{ED}^{obs} - BF_1^+ \leq RD_{ED}^{true} \leq RD_{ED}^{obs} + BF_0^+, \quad (8)$$

where

$$RD_{ED}^{obs} = p(D = 1|E = 1) - p(D = 1|E = 0),$$

$$RD_{ED}^{true} = p\{D(1) = 1\} - p\{D(0) = 1\}$$

and the bounding factor BF_e^+ is defined as

$$BF_e^+ = p(E = 1 - e)p(D = 1|E = e)(1 - 1/BF_e) \\ + p(E = e)p(D = 1|E = 1 - e)(BF_e - 1).$$

All results derived in Sections 3-5 for the causal risk ratio apply with little or no modification for the causal risk difference. First, Theorem 1 applies to the sensitivity analysis parameters $\{RR_{E0U}, RR_{E1U}, RR_{UD}\}$ regardless of how these are used, e.g. regardless of whether these are used to bound RD_{ED}^{true} instead of RR_{ED}^{true} . Second, just like the bounds for RR_{ED}^{true} in (1), the bounds for RD_{ED}^{true} in (8) are not sharp. This can be seen by noting that, when BF_1 and BF_0 go to infinity, the lower and upper bounds in (8) go to minus infinity and infinity, respectively. Since RD_{ED}^{true} is confined to the range $[-1, 1]$, the bounds thus include values that are not logically possible. Just like for the bounds in (1), we can sometimes improve the bounds in (8) by replacing them with assumption-free bounds, whenever these are sharper. Arguing as in Section 4, the assumption-free bounds for RR_{ED}^{true} are given by

$$RD_{ED}^{obs} - \widetilde{BF}_1^+ \leq RD_{ED}^{true} \leq RD_{ED}^{obs} + \widetilde{BF}_0^+,$$

where

$$\widetilde{BF}_e^+ = p(E = 1 - e)p(D = 1|E = e) + p(E = e)\{1 - p(D = 1|E = 1 - e)\}.$$

Finally, it can be shown (see Appendix C) that Theorem 2 carries over to the causal risk difference, i.e. that the lower bound in (8) is sharp if $BF_1 \leq 1/p(D = 1|E = 0)$, and the upper bound in (8) is sharp if $BF_0 \leq 1/p(D = 1|E = 1)$.

7 Real data example

In a series of papers, Hammond and Horn [4–6] studied the association between smoking and mortality. They found an extremely strong association between smoking and lung cancer mortality (incidence rate ratio above 10), which Ding and VanderWeele [3] used in an illustration of their sensitivity analysis. We focus here on the association with total mortality, which is more moderate and thus provides a more realistic and general illustration. We provide R code for the analysis in Appendix D.

Hammond and Horn stratified their analyses on age; we re-analyze the data from their oldest stratum, comprising 29105 subjects who were between 65 and 69 years old at baseline. Among these, 6287 reported that they had never smoked. We consider these 6287 subjects as unexposed ($E = 0$) and the remaining 22818 subjects as exposed ($E = 1$). During a follow-up period of 44 months, the number of subjects who died ($D = 1$) were 613 and 2837 among the unexposed and exposed, respectively. From these figures we obtain $p(E = 1) = 22818/29105 = 0.784$, $p(D = 1|E = 1) = 2837/22818 = 0.124$, $p(D = 1|E = 0) = 613/6287 = 0.098$ and $RR_{ED}^{obs} = 1.28$.

The contour plot in Figure 2 shows BF_1 and DV's lower bound for RR_{ED}^{true} , as functions of RR_{E1U} and RR_{UD} . In this plot, the curves represent constant values of BF_1 and the lower bound for RR_{ED}^{true} , as indicated by the figure legend. An analyst can use this plot to determine a lower bound RR_{ED}^{true} , given plausible values of RR_{E1U} and RR_{UD} . For instance, everywhere along the leftmost curve, which passes through the point $RR_{E1U} = RR_{UD} = 1.5$, BF_1 is equal to 1.11 and the lower bound for RR_{ED}^{true} is equal to 1.15. The rightmost curve, which passes through the point $RR_{E1U} = RR_{UD} = 20.6$, indicates where DV's lower bound is equal to the assumption-free lower bound; everywhere at this curve both bounds are equal to 0.12. Even though combinations of RR_{E1U} and RR_{UD} beyond this curve are logically possible by Theorem 1, it is not relevant to consider such values when

Figure 2: Contour plot for BF_1 and DV's lower bound for RR_{ED}^{true} , as functions of RR_{E1U} and RR_{UD} . Both axes use logarithmic scale.

Figure 3: Estimated maximal value of DV's lower bound and the assumption free bound (solid curve), together with nonparametric 95% bootstrap confidence intervals (dashed curves). Both axes use logarithmic scale.

computing DV's lower bound, since this bound would then include values of RR_{ED}^{true} that are ruled out by the assumption-free lower bound. In other words; to the right of the rightmost curve DV's bound is not sharp. The dashed curve indicates where $BF_1 = 1/p(D = 1|E = 0)$; everywhere to the left of this curve DV's lower bound is guaranteed to be sharp by Theorem 2.

Even though the sample size in this example is quite large, the quantities $p(E = 1)$, $p(D = 1|E = 1)$, $p(D = 1|E = 0)$ and RR_{ED}^{obs} are still estimated, and a proper sensitivity analysis needs to account for the sampling variability in the estimates. This is complicated by the fact that the desired lower bound is the maximal value of the DV's lower bound and the assumption-free lower bound. Cai *et al.* [2] derived analytic variance estimates for bounds that are on such a 'min/max' form, in the context of mediation analysis. Estimators on a 'min/max' form also occur in the optimization of dynamic treatment regimes [e.g. 10, 11, 15]; see also Hirano and Porter [7] for a more general discussion of this problem. Since our focus is on large-sample properties of the bounds, we here illustrate a simpler solution based on nonparametric bootstrap resampling. The solid curve in Figure 3 shows the estimated maximal value of DV's lower bound and the assumption free bound, as a function of RR_{E1U} and RR_{UD} when these are assumed equal, i.e. along a diagonal line with slope 1 through the origo in Figure 2. Beyond $RR_{E1U} = RR_{UD} = 20.6$ the curve is flat, since the estimated maximal value is equal to the assumption-free lower bound, which does not depend on RR_{E1U} and RR_{UD} . The dashed lower and upper curves indicate point-wise 95% lower and upper confidence limits, respectively. These were obtained by drawing 1000 bootstrap replicates from the sample, estimating the maximal bound for each sample, and using the 0.025 and 0.975 quantiles as confidence limits, at each value of $RR_{E1U} = RR_{UD}$. We observe that the confidence intervals are fairly narrow, as expected.

8 Simulation

We argued in Section 4 that DV's bounds may often, but not always, be sharper than the assumption-free bounds when there are only a few confounders. In this section we explore this issue further with a simulation study. We provide R code for the simulation in Appendix E.

In the simulation we assumed a single binary confounder U , and generated distributions $p(D, E, U)$ from the model

$$\begin{aligned} p(E = 1) &= \text{expit}(\phi) \\ p(U = 1|E) &= \text{expit}(\alpha + \beta E) \\ p(D = 1|E, U) &= \text{expit}(\gamma + \delta E + \psi U) \end{aligned}$$

where $\text{expit}(x) = 1/(1 + e^{-x})$ is inverse logit function. The parameters $\{\beta, \delta, \psi\}$ were assumed to be independent random variables, distributed as $N(0, \sigma^2)$. The standard deviation σ determines the probability of extreme causal effects and confounding effects. For instance, with $\sigma = 1$ and $\sigma = 3$, the magnitude of these effects would be larger than 3, on the log odds ratio scale, with 0.27% and 31.7% probability, respectively. For each value of $\{\beta, \delta, \psi\}$, the parameters $\{\phi, \alpha, \gamma\}$ were set to obtain certain marginal probabilities $\{p(U = 1), p(E = 1), p(D = 1)\}$, as specified below.

For each of the $2^4 = 16$ combinations of $\{p(U = 1), p(E = 1), p(D = 1)\} \in \{0.05, 0.2\}$ and $\sigma \in \{1, 3\}$ we generated 1000 distributions $p(D, E, U)$ from the model above. For each distribution we computed the true causal risk ratio RR_{ED}^{true} , the assumption-free bounds and DV's bounds; in the latter we used the correct values of $\{RR_{E0U}, RR_{E1U}, RR_{UD}\}$ as implied by the generated distribution $p(D, E, U)$. For the lower and upper bounds separately, we computed the proportion p of times that the assumption-free bound was sharper than DV's bound. We also computed the mean (over the 1000 distributions) absolute distance between the log of the bound and the log of the true causal risk ratio, which we denote with Δ for DV's bounds and $\tilde{\Delta}$ for the assumption-free bounds.

Tables 1 and 2 display the results, for $\sigma = 1$ and $\sigma = 3$, respectively. For $\sigma = 1$, the assumption-free bounds were never sharper than DV's bounds; $p = 0.00$ for all scenarios. The assumption-free bounds were on average much more conservative than DV's bounds; $\tilde{\Delta}$ and Δ were within the ranges (2.22, 3.68) and (0.12, 0.15) for the lower bounds, respectively, and within the ranges (1.71, 3.10) and (0.13, 0.17) for the upper bounds, respectively. For $\sigma = 3$ we observe a similar pattern, however not as extreme. DV's bounds were usually sharper than the assumption-free bounds, but not always; p was within the range (0, 0.05) for the lower bounds and within the range (0.05, 0.25) for the upper bounds. $\tilde{\Delta}$ and Δ were within the ranges (2.35, 3.93) and (0.49, 0.59) for the lower bounds, respectively, and within the ranges (2.13, 3.57) and (0.70, 0.82) for the upper bounds, respectively.

Table 1: Simulation results with $\sigma = 1$. p is the proportion of times that the assumption-free bound was sharper than DV's bound; Δ and $\tilde{\Delta}$ are the mean absolute distance between the log of the bound and the log of the true causal risk ratio, for DV's bounds and the assumption-free bounds, respectively.

$p(U = 1)$	$p(E = 1)$	$p(D = 1)$	lower bound			upper bound		
			p	$\tilde{\Delta}$	Δ	p	$\tilde{\Delta}$	Δ
0.05	0.05	0.05	0.00	3.67	0.15	0.00	3.04	0.17
0.05	0.05	0.20	0.00	3.18	0.13	0.00	1.71	0.15
0.05	0.20	0.05	0.00	3.23	0.13	0.00	3.10	0.17
0.05	0.20	0.20	0.00	2.22	0.13	0.00	1.76	0.13
0.20	0.05	0.05	0.00	3.68	0.14	0.00	3.05	0.17
0.20	0.05	0.20	0.00	3.18	0.12	0.00	1.71	0.16
0.20	0.20	0.05	0.00	3.26	0.14	0.00	3.07	0.17
0.20	0.20	0.20	0.00	2.23	0.13	0.00	1.71	0.14

Table 2: Simulation results with $\sigma = 3$. p is the proportion of times that the assumption-free bound was sharper than DV's bound; Δ and $\tilde{\Delta}$ are the mean absolute distance between the log of the bound and the log of the true causal risk ratio, for DV's bounds and the assumption-free bounds, respectively.

$p(U = 1)$	$p(E = 1)$	$p(D = 1)$	lower bound			upper bound		
			p	$\tilde{\Delta}$	Δ	p	$\tilde{\Delta}$	Δ
0.05	0.05	0.05	0.00	3.78	0.59	0.13	3.39	0.82
0.05	0.05	0.20	0.01	3.18	0.50	0.21	2.16	0.70
0.05	0.20	0.05	0.01	3.60	0.50	0.05	3.61	0.77
0.05	0.20	0.20	0.05	2.35	0.56	0.12	2.24	0.58
0.20	0.05	0.05	0.00	3.93	0.59	0.12	3.44	0.78
0.20	0.05	0.20	0.00	3.25	0.49	0.25	2.19	0.78
0.20	0.20	0.05	0.00	3.81	0.59	0.05	3.57	0.76
0.20	0.20	0.20	0.03	2.42	0.56	0.19	2.13	0.72

It is not surprising that the advantage of DV's bounds become less pronounced with increasing σ . When extreme confounding effects become more likely, the sensitivity analysis parameters RR_{E0U} and RR_{UD} tend to become more extreme as well, and it thus happens more often that DV's bounds include values of the causal risk ratio that are logically ruled out by the observed data distribution.

In practice, the true values of $\{RR_{E0U}, RR_{E1U}, RR_{UD}\}$ would rarely be known by the analyst. Hence, by using the true values of these parameters in the computation of DV's bounds, the simulation may give an unrealistic advantage of DV's bounds over the assumption-free bounds. To enable a more realistic comparison we repeated the simulation, using values of $\{RR_{E0U}, RR_{E1U}, RR_{UD}\}$ that were 15% larger than the true values. We present the results of these simulations in Appendix F. In summary, we observed that DV's bounds were slightly more conservative than before, but with no dramatic deterioration. This indicates that DV's bounds are not overly sensitive to a conservative guess of the sensitivity analysis parameters.

9 Conclusion

In this paper we have derived and clarified several important points related to the sensitivity analysis proposed by DV. We have shown that DV's sensitivity analysis parameters are confined to values equal to or above 1, and we have shown that the parameters are variation independent of each other and of the observed data distribution (Theorem 1). We have further shown that DV's bounds for the causal risk ratio are not always sharp, and we have established a region when they are guaranteed to be sharp (Theorem 2). We have finally shown that this region includes the E-value, which implies that the E-value is not overly pessimistic.

A simple way to improve DV's bounds is to replace them with the assumption-free bounds whenever the latter are narrower. We have argued, and indicated by simulations, that this may rarely happen when there are only a few unmeasured confounders. In practice though, there may often be many unmeasured confounders with a large aggregated confounding effect, which may force DV's bounds to extremes. In such scenarios, the assumption-free bounds may provide a useful alternative.

We end with a technical remark. Theorem 2 shows that DV's bounds are sharp whenever the bounding factors $\{BF_0, BF_1\}$ are within a certain region. However, the theorem does not show the converse, i.e. that the bounding factors are within this region whenever DV's bounds are sharp. In fact, we conjecture that DV's bounds may be sharp for some bounding factors outside this region as well. We recognize the proof (or disproof) of this conjecture as an important topic for future research.

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A Proof of Theorem 1

Define $f(e) = \max_k p(D = 1|E = e, U = k) / \min_k p(D = 1|E = e, U = k)$, so that $RR_{UD} = \max_e \{f(e)\}$. To see that $RR_{UD} \geq 1$, note that $f(e) \geq 1$ by definition, which implies that $\max_e \{f(e)\} \geq 1$. Define $g(k) = p(U = k|E = e) / p(U = k|E = 1 - e)$, so that $RR_{EeU} = \max_k \{g(k)\}$. To see that $RR_{EeU} \geq 1$, note that $E\{g(U)|E = 1 - e\} = \sum_k g(k)p(U = k|E = 1 - e) = \sum_k p(U = k|E = e) = 1$, which implies that $g(k) \geq 1$ for at least one k , which in turn implies that $\max_k \{g(k)\} \geq 1$.

To show that $\{RR_{E0U}, RR_{E1U}, RR_{UD}, p(D, E)\}$ are variation independent, we show that it is possible to construct a distribution $p(D, E, U)$ that marginalizes to any given set $\{RR_{E0U}^*, RR_{E1U}^*, RR_{UD}^*, p^*(D, E)\}$. To avoid technicalities we assume that $\{RR_{E0U}^*, RR_{E1U}^*, RR_{UD}^*\} > 1$ and $0 < p^*(D = d, E = e) < 1$ for $(d, e) \in \{0, 1\}$. We construct the distribution $p(D, E, U)$ in the following steps.

1. Let $p(E) = p^*(E)$.
2. Let U be ternary, with

$$\begin{aligned} p(U = 0|E = 0) &= \frac{(1 - \epsilon)RR_{E0U}^*(RR_{E1U}^* - 1)}{RR_{E0U}^*RR_{E1U}^* - 1} \\ p(U = 1|E = 0) &= \frac{(1 - \epsilon)(RR_{E0U}^* - 1)}{RR_{E0U}^*RR_{E1U}^* - 1} \\ p(U = 2|E = 0) &= \epsilon \\ p(U = 0|E = 1) &= \frac{(1 - \epsilon)(RR_{E1U}^* - 1)}{RR_{E0U}^*RR_{E1U}^* - 1} \\ p(U = 1|E = 1) &= \frac{(1 - \epsilon)RR_{E1U}^*(RR_{E0U}^* - 1)}{RR_{E0U}^*RR_{E1U}^* - 1} \\ p(U = 2|E = 1) &= \epsilon, \end{aligned}$$

where $0 < \epsilon < 1$ is defined in the next step. We have that $\sum_k p(U = k|E = e) = 1$ for $e \in \{0, 1\}$ and $0 < p(U = k|E = e) < 1$ for $k \in \{0, 1, 2\}$ and $e \in \{0, 1\}$. We further have that $p(U = 0|E = 1)/p(U = 0|E = 0) = 1/RR_{E0U}^*$, $p(U = 1|E = 1)/p(U = 1|E = 0) = RR_{E1U}^*$ and $p(U = 2|E = 1)/p(U = 2|E = 0) = 1$, so that $RR_{E0U} = p(U = 0|E = 0)/p(U = 1|E = 1) = RR_{E0U}^*$ and $RR_{E1U} = p(U = 1|E = 1)/p(U = 1|E = 0) = RR_{E1U}^*$.

3. Let

$$\begin{aligned} p(D = 1|E = 0, U = k) &= p^*(D = 1|E = 0) \text{ for } k \in \{0, 1, 2\} \\ p(D = 1|E = 1, U = 0) &= p^*(D = 1|E = 1) \\ p(D = 1|E = 1, U = 1) &= p^*(D = 1|E = 1) \frac{RR_{UD}^* \{p(U = 1|E = 1) + \epsilon\}}{RR_{UD}^* p(U = 1|E = 1) + \epsilon} \\ p(D = 1|E = 1, U = 2) &= p^*(D = 1|E = 1) \frac{p(U = 1|E = 1) + \epsilon}{RR_{UD}^* p(U = 1|E = 1) + \epsilon} \end{aligned}$$

We have that

$$\frac{\partial p(D = 1|E = 1, U = 1)}{\partial \epsilon} = p^*(D = 1|E = 1)RR_{UD}^* \frac{p(U = 1|E = 1)(RR_{UD}^* - 1)}{\{RR_{UD}^* p(U = 1|E = 1) + \epsilon\}^2} > 0,$$

which implies that $p(D = 1|E = 1, U = 1)$ is increasing in ϵ , with $\lim_{\epsilon \rightarrow 0} p(D = 1|E = 1, U = 1) = p^*(D = 1|E = 1)$. Hence, we let ϵ be an arbitrary number between 0 and 1, sufficiently close to 0 to ensure that $p(D = 1|E = 1, U = 1) < 1$. We thus have that $0 < p(D = 1|E = e, U = k) < 1$ for $e \in \{0, 1\}$ and $k \in \{0, 1, 2\}$. We also have that $p(D = 1|E = e) = \sum_k p(D = 1|E = e, U = k)p(U = k|E = e) = p^*(D = 1|E = e)$ for $e \in \{0, 1\}$. We further have that $p(D = 1|E = 0, U = 0) = p(D = 1|E = 0, U = 1) = p(D = 1|E = 0, U = 2)$ and $p(D = 1|E = 1, U = 1) > p(D = 1|E = 1, U = 0) > p(D = 1|E = 1, U = 2)$, so that $RR_{UD} = p(D = 1|E = 1, U = 1)/p(D = 1|E = 1, U = 2) = RR_{UD}^*$.

B Proof of Theorem 2

To show that the lower bound in (1) is sharp when $BF_1 \leq 1/p(D = 1|E = 0)$, we show that it is possible to construct a distribution $p(D, E, U)$ that marginalizes to any given set $\{RR_{E1U}^*, RR_{UD}^*, p^*(D, E)\}$ for which $BF_1^* \leq 1/p^*(D = 1|E = 0)$ and $RR_{ED}^{\text{true}} = RR_{ED}^{\text{obs}}/BF_1$. We construct the distribution $p(D, E, U)$ in the following steps.

1. Let $p(E) = p^*(E)$.
2. Let U be binary, with

$$\begin{aligned} p(U = 1|E = 1) &= 1 \\ p(U = 1|E = 0) &= 1/RR_{E1U}^* \end{aligned}$$

We have that $0 < p(U = 1|E = e) \leq 1$ for $e \in \{0, 1\}$. We also have that $p(U = 1|E = 1)/p(U = 1|E = 0) = RR_{E1U}^*$ and $p(U = 0|E = 1)/p(U = 0|E = 0) = 0$, so that $RR_{E1U} = p(U = 1|E = 1)/p(U = 1|E = 0) = RR_{E1U}^*$.

3. Let

$$\begin{aligned} p(D = 1|E = 0, U = 0) &= p^*(D = 1|E = 0)BF_1^*/RR_{UD}^* \\ p(D = 1|E = 0, U = 1) &= p^*(D = 1|E = 0)BF_1^* \\ p(D = 1|E = 1, U = 0) &= p^*(D = 1|E = 1)/RR_{UD}^* \\ p(D = 1|E = 1, U = 1) &= p^*(D = 1|E = 1) \end{aligned}$$

We have that $0 < p(D = 1|E = e, U = k) < 1$ for $(e, k) \in \{0, 1\}$, provided that $BF_1^* \leq 1/p^*(D = 1|E = 0)$. We also have that $p(D = 1|E = 1, U = 1)/p(D = 1|E = 1, U = 0) = p(D = 1|E = 0, U = 1)/p(D = 1|E = 0, U = 0) = RR_{UD}^*$, so that $RR_{UD} = RR_{UD}^*$. We further have that $RR_{ED}^{\text{true}} = \sum_k p(D = 1|E = 1, U = k)p(U = k)/\sum_k p(D = 1|E = 0, U = k)p(U = k) = RR_{ED}^{\text{obs}}/BF_1^* = RR_{ED}^{\text{obs}}/BF_1$, and $p(D = 1|E = 1) = \sum_k p(D = 1|E = 1, U = k)p(U = k|E = 1) = p^*(D = 1|E = 1)$. We finally have that

$$\begin{aligned} p(D = 1|E = 0) &= p(D = 1|E = 0, U = 1)p(U = 1|E = 0) \\ &\quad + p(D = 1|E = 0, U = 0)p(U = 0|E = 0) \\ &= p^*(D = 1|E = 0)\{BF_1^*/RR_{E1U}^* + BF_1^*/RR_{UD}^*(1 - 1/RR_{E1U}^*)\} \\ &= p^*(D = 1|E = 0). \end{aligned}$$

To show that the upper bound in (1) is sharp when $BF_0 \leq 1/p(D = 1|E = 1)$, we show that it is possible to construct a distribution $p(D, E, U)$ that marginalizes to any given set $\{RR_{E0U}^*, RR_{UD}^*, p^*(D, E)\}$ for which $BF_0^* \leq 1/p^*(D = 1|E = 1)$ and $RR_{ED}^{\text{true}} = RR_{ED}^{\text{obs}}BF_0$. We construct the distribution $p(D, E, U)$ in the following steps.

1. Let $p(E) = p^*(E)$.
2. Let U be binary, with

$$\begin{aligned} p(U = 1|E = 0) &= 1 \\ p(U = 1|E = 1) &= 1/RR_{E0U}^* \end{aligned}$$

We have that $0 < p(U = 1|E = e) \leq 1$ for $e \in \{0, 1\}$. We also have that $p(U = 1|E = 0)/p(U = 1|E = 1) = RR_{E0U}^*$ and $p(U = 0|E = 0)/p(U = 0|E = 1) = 0$, so that $RR_{E0U} = p(U = 1|E = 0)/p(U = 1|E = 1) = RR_{E0U}^*$.

3. Let

$$\begin{aligned} p(D = 1|E = 0, U = 0) &= p^*(D = 1|E = 0)/RR_{UD}^* \\ p(D = 1|E = 0, U = 1) &= p^*(D = 1|E = 0) \end{aligned}$$

$$p(D = 1|E = 1, U = 0) = p^*(D = 1|E = 1)BF_0^*/RR_{UD}^*$$

$$p(D = 1|E = 1, U = 1) = p^*(D = 1|E = 1)BF_0^*$$

We have that $0 < p(D = 1|E = e, U = k) < 1$ for $(e, k) \in \{0, 1\}$, provided that $BF_0^* \leq 1/p^*(D = 1|E = 1)$. We also have that $p(D = 1|E = 1, U = 1)/p(D = 1|E = 1, U = 0) = p(D = 1|E = 0, U = 1)/p(D = 1|E = 0, U = 0) = RR_{UD}^*$, so that $RR_{UD} = RR_{UD}^*$. We further have that $RR_{ED}^{\text{true}} = \sum_k p(D = 1|E = 1, U = k)p(U = k)/\sum_k p(D = 1|E = 0, U = k)p(U = k) = RR_{ED}^{\text{obs}}BF_0^* = RR_{ED}^{\text{obs}}BF_0$, and $p(D = 1|E = 0) = \sum_k p(D = 1|E = 0, U = k)p(U = k|E = 0) = p^*(D = 1|E = 0)$. We finally have that

$$\begin{aligned} p(D = 1|E = 1) &= p(D = 1|E = 1, U = 1)p(U = 1|E = 1) \\ &\quad + p(D = 1|E = 1, U = 0)p(U = 0|E = 1) \\ &= p^*(D = 1|E = 1)\{BF_0^*/RR_{E0U}^* + BF_0^*/RR_{UD}^*(1 - 1/RR_{E0U}^*)\} \\ &= p^*(D = 1|E = 0). \end{aligned}$$

C Proof that Theorem 2 carries over to the causal risk difference

To show that the lower bound in (8) is sharp when $BF_1 \leq 1/p(D = 1|E = 0)$, we show that it is possible to construct a distribution $p(D, E, U)$ that marginalizes to any given set $\{RR_{E1U}^*, RR_{UD}^*, p^*(D, E)\}$ for which $BF_1^* \leq 1/p^*(D = 1|E = 0)$ and $RD_{ED}^{\text{true}} = RD_{ED}^{\text{obs}} - BF_1^+$. We use the same distribution as in the proof of Theorem 2 for the lower bound in (1), in Appendix B. It thus remains to show that, for this distribution, $RD_{ED}^{\text{true}} = RD_{ED}^{\text{obs}} - BF_1^+$. We have that

$$\begin{aligned} RD_{ED}^{\text{true}} &= \sum_k [p\{D(1)|U = k\} - p\{D(0) = 1|U = k\}]p(U = k) \\ &= \sum_k [p\{D = 1|E = 1, U = k\} - p\{D = 1|E = 0, U = k\}] \sum_e p(U = k|E = e)p(E = e) \\ &= \{p^*(D = 1|E = 1) - p^*(D = 1|E = 0)BF_1^*\} \{p^*(E = 1) + p^*(E = 0)/RR_{E1U}^*\} \\ &\quad + \{p^*(D = 1|E = 1)/RR_{UD}^* - p^*(D = 1|E = 0)BF_1^*/RR_{UD}^*\} p^*(E = 0)(1 - 1/RR_{E1U}^*) \\ &= \{p^*(D = 1|E = 1)/BF_1^* - p^*(D = 1|E = 0)\} \\ &\quad \times BF_1^* [p^*(E = 1) + p^*(E = 0)\{1/RR_{E1U}^* + (1 - 1/RR_{E1U}^*)/RR_{UD}^*\}] \\ &= \{p^*(D = 1|E = 1)/BF_1^* - p^*(D = 1|E = 0)\} \{p^*(E = 1)BF_1^* + p^*(E = 0)\} \\ &= \{p(D = 1|E = 1)/BF_1 - p(D = 1|E = 0)\} \{p(E = 1)BF_1 + p(E = 0)\}. \end{aligned}$$

The last expression is identical to the lower bound for RD_{ED}^{true} given in proposition A.8 in the eAppendix of [3], which is algebraically equivalent with $RD_{ED}^{\text{obs}} - BF_1^+$.

To show that the upper bound in (8) is sharp when $BF_0 \leq 1/p(D = 1|E = 1)$, we show that it is possible to construct a distribution $p(D, E, U)$ that marginalizes to any given set $\{RR_{E0U}^*, RR_{UD}^*, p^*(D, E)\}$ for which $BF_0^* \leq 1/p^*(D = 1|E = 1)$ and $RD_{ED}^{\text{true}} = RD_{ED}^{\text{obs}} + BF_0^+$. We use the same distribution as in the proof of Theorem 2 for the upper bound in (1), Appendix B. It thus remains to show that, for this distribution, $RD_{ED}^{\text{true}} = RD_{ED}^{\text{obs}} + BF_0^+$. We have that

$$\begin{aligned} RD_{ED}^{\text{true}} &= \sum_k [p\{D(1)|U = k\} - p\{D(0) = 1|U = k\}]p(U = k) \\ &= \sum_k [p\{D = 1|E = 1, U = k\} - p\{D = 1|E = 0, U = k\}] \sum_e p(U = k|E = e)p(E = e) \\ &= \{p^*(D = 1|E = 1)BF_0^* - p^*(D = 1|E = 0)\} \{p^*(E = 1)/RR_{E0U}^* + p^*(E = 0)\} \\ &\quad + \{p^*(D = 1|E = 1)BF_0^*/RR_{UD}^* - p^*(D = 1|E = 0)/RR_{UD}^*\} p^*(E = 1)(1 - 1/RR_{E0U}^*) \\ &= \{p^*(D = 1|E = 1) - p^*(D = 1|E = 0)/BF_0^*\} \\ &\quad \times BF_0^* [p^*(E = 0) + p^*(E = 1)\{1/RR_{E0U}^* + (1 - 1/RR_{E0U}^*)/RR_{UD}^*\}] \\ &= \{p^*(D = 1|E = 1) - p^*(D = 1|E = 0)/BF_0^*\} \{p^*(E = 0)BF_0^* + p^*(E = 1)\} \\ &= \{p(D = 1|E = 1) - p(D = 1|E = 0)/BF_0\} \{p(E = 0)BF_0 + p(E = 1)\}. \end{aligned}$$

The last expression is identical to the upper bound for RD_{ED}^{true} given in proposition A.10 in the eAppendix of [3], which is algebraically equivalent with $RD_{ED}^{\text{obs}} + BF_0^+$.

D R code for the real data example

```
#Data from Hammond and Horn, 1954 and 1958
#Only age-group 65-69

n <- 29105      #From Hammond and Horn 1954, Table 3
nE0 <- 6287     #From Hammond and Horn 1954, Table 3
nE1 <- n-nE0
pE0 <- nE0/n
pE1 <- 1-pE0
nD1 <- 3450     #From From Hammond and Horn 1958, Table 2
nD1.E0 <- 613  #From From Hammond and Horn 1958, Table 2
nD1.E1 <- nD1-nD1.E0
pD1.E0 <- nD1.E0/nE0
pD1.E1 <- nD1.E1/nE1
RRobs <- pD1.E1/pD1.E0

#assumption-free lower bound
BF1.tilde <- (pD1.E0*pE0+pE1)/(pD1.E0*pE1)
lower.tilde <- RRobs/BF1.tilde

print("RRobs")
print(RRobs)
print("BF1.tilde")
print(BF1.tilde)
print("lower.tilde")
print(lower.tilde)

#r = common value of RRE1U and RRUD at which BF1 = BF1.tilde,
#such that DV's lower bound = assumption-free lower bound
BF1 <- BF1.tilde
r <- BF1+sqrt(BF1*(BF1-1))
print("Common value of RRE1U and RRUD at which BF1 = BF1.tilde")
print(r)

min <- 1
max <- 90
plot(c(min, max), c(min, max), type="n", xlab=expression(RR[E1U]),
     ylab=expression(RR[UD]), xlim=c(min, max), ylim=c(min, max),
     log="xy")
tt <- NULL
RRtrue <- c(1.15, 1, 0.5, lower.tilde)
for(i in 1:length(RRtrue)){
  BF1 <- RRobs/RRtrue[i]
  r <- BF1+sqrt(BF1*(BF1-1))
  RRE1U <- seq(BF1, max, 0.001)
  RRUD <- (BF1*RRE1U-BF1)/(RRE1U-BF1)
  lines(RRE1U, RRUD)
  points(r, r, pch=i)
  text(x=r, y=r, labels=round(r,1), pos=4)
```

```

tt <- c(tt, bquote(BF[1]*"="*
  .(round(BF1,2))*", "~RR[ED]^"true">=.(round(RRtrue[i],2))))
}
BF1 <- 1/pD1.E0
r <- BF1+sqrt(BF1*(BF1-1))
RRE1U <- seq(BF1, max, 0.01)
RRUD <- (BF1*RRE1U-BF1)/(RRE1U-BF1)
lines(RRE1U, RRUD, lty="dashed")
legend(x="topright", pch=c(1,2,3,4), lty=1, legend=as.expression(tt),
  bty="n")

boundfun <- function(RRobs, RRE1U, RRUD, pD1.E0, pE1){
  BF1 <- RRE1U*RRUD/(RRE1U+RRUD-1)
  pE0 <- 1-pE1
  BF1.tilde <- (pD1.E0*(1-pE1)+pE1)/(pD1.E0*pE1)
  RRobs/pmin(BF1, BF1.tilde)
}
r <- seq(1, 25, 0.1)
bound <- matrix(nrow=length(r), ncol=3)
B <- 1000
pE1.boot <- rbinom(n=B,size=n, prob=pE1)/n
pD1.E0.boot <- rbinom(n=B,size=nE0, prob=pD1.E0)/nE0
pD1.E1.boot <- rbinom(n=B,size=nE1, prob=pD1.E1)/nE1
RRobs.boot <- pD1.E1.boot/pD1.E0.boot
for(i in 1:length(r)){
  bound[i, 1] <- boundfun(RRobs, r[i], r[i], pD1.E0, pE1)
  bound.boot <- boundfun(RRobs.boot, r[i], r[i], pD1.E0.boot,
    pE1.boot)
  qq <- quantile(x=bound.boot, probs=c(0.025, 0.975))
  bound[i, 2] <- qq[1]
  bound[i, 3] <- qq[2]
}
windows()
plot(0, xlim=c(min(r), max(r)), ylim=c(min(bound), max(bound)),
  type="n", log="xy", xlab=bquote(RR[E1U]*"="*RR[UD]),
  ylab="lower bound")
matlines(r, bound, lty=c("solid", "dashed", "dashed"), col="black")

```

E R code for the simulation

```

set.seed(1)

pU1fun <- function(alpha, beta, pE1){
  pU1.E0 <- plogis(alpha)
  pU1.E1 <- plogis(alpha+beta)
  pU1 <- pU1.E1*pE1+pU1.E0*(1-pE1)
  pU1
}

pD1fun <- function(gamma, delta, psi, pU1.E0, pU1.E1, pE1){
  pD1.E0U0 <- plogis(gamma)
  pD1.E0U1 <- plogis(gamma+psi)
  pD1.E1U0 <- plogis(gamma+delta)
  pD1.E1U1 <- plogis(gamma+delta+psi)
  pD1.E0 <- pD1.E0U1*pU1.E0+pD1.E0U0*(1-pU1.E0)
  pD1.E1 <- pD1.E1U1*pU1.E1+pD1.E1U0*(1-pU1.E1)
  pD1 <- pD1.E0*(1-pE1)+pD1.E1*pE1
  pD1
}

PU1 <- c(0.05, 0.2)
PE1 <- c(0.05, 0.2)
PD1 <- c(0.05, 0.2)
s <- 1
m <- 1
lU <- length(PU1)
lE <- length(PE1)
lD <- length(PD1)
out <- matrix(nrow=lU*lE*lD, ncol=9)
r <- 0
n <- 1000
for(i in 1:lU){
  pU1 <- PU1[i]
  for(j in 1:lE){
    pE1 <- PE1[j]
    for(k in 1:lD){
      pD1 <- PD1[k]
      r <- r+1
      results <- matrix(nrow=n, ncol=6)
      for(l in 1:n){
        beta <- rnorm(1, sd=s)
        delta <- rnorm(1, sd=s)
        psi <- rnorm(1, sd=s)
        alpha <- uniroot(f=function(alpha, beta, pE1)
          pU1fun(alpha, beta, pE1)-pU1, lower=-100, upper=100,
          beta=beta, pE1=pE1)$root
        pU1.E0 <- plogis(alpha)
        pU1.E1 <- plogis(alpha+beta)
        gamma <-

```

```

uniroot(f=function(gamma, delta, psi, pU1.E0, pU1.E1, pE1)
  pD1fun(gamma, delta, psi, pU1.E0, pU1.E1, pE1)-pD1,
  lower=-100, upper=100, delta=delta, psi=psi,
  pU1.E0=pU1.E0, pU1.E1=pU1.E1, pE1=pE1)$root
pD1.E0U0 <- plogis(gamma)
pD1.E0U1 <- plogis(gamma+psi)
pD1.E1U0 <- plogis(gamma+delta)
pD1.E1U1 <- plogis(gamma+delta+psi)
pD1.E0 <- pD1.E0U1*pU1.E0+pD1.E0U0*(1-pU1.E0)
pD1.E1 <- pD1.E1U1*pU1.E1+pD1.E1U0*(1-pU1.E1)
RRobs <- pD1.E1/pD1.E0
RRtrue <- (pD1.E1U1*pU1+pD1.E1U0*(1-pU1))/
  (pD1.E0U1*pU1+pD1.E0U0*(1-pU1))
RRE1U <- max(pU1.E1/pU1.E0, (1-pU1.E1)/(1-pU1.E0))
RREOU <- max(pU1.E0/pU1.E1, (1-pU1.E0)/(1-pU1.E1))
RRUD <- max(max(pD1.E1U1,pD1.E1U0)/min(pD1.E1U1,pD1.E1U0),
  max(pD1.E0U1,pD1.E0U0)/min(pD1.E0U1,pD1.E0U0))
BF1 <- m*RRE1U*m*RRUD/(m*RRE1U+m*RRUD-1)
BF0 <- m*RREOU*m*RRUD/(m*RREOU+m*RRUD-1)
lower <- RRobs/BF1
upper <- RRobs*BF0
BF1.tilde <- (pD1.E0*(1-pE1)+pE1)/(pD1.E0*pE1)
BF0.tilde <- (pD1.E1*pE1+(1-pE1))/(pD1.E1*(1-pE1))
lower.tilde <- RRobs/BF1.tilde
upper.tilde <- RRobs*BF0.tilde
results[l, ] <- c(lower.tilde>lower,
  log(RRtrue)-log(lower.tilde), log(RRtrue)-log(lower),
  upper.tilde<upper, log(upper.tilde)-log(RRtrue),
  log(upper)-log(RRtrue))
}
out[r, ] <- c(pU1, pE1, pD1, round(colMeans(results), 2))
}
}
}
print(out)

```

F Additional simulation results

The setup for these simulations is identical to the simulation setup in the main text, with the exception that DV's bounds were computed here using values of $\{RR_{E0U}, RR_{E1U}, RR_{UD}\}$ that were 15% larger than the true values. The results are displayed in Tables F3 and F4.

Table F3: Simulation results with $\sigma = 1$. p is the proportion of times that the assumption-free bound was sharper than DV's bound; Δ and $\tilde{\Delta}$ are the mean absolute distance between the log of the bound and the log of the true causal risk ratio, for DV's bounds and the assumption-free bounds, respectively.

$p(U = 1)$	$p(E = 1)$	$p(D = 1)$	lower bound			upper bound		
			p	$\tilde{\Delta}$	Δ	p	$\tilde{\Delta}$	Δ
0.05	0.05	0.05	0.00	3.67	0.23	0.00	3.04	0.26
0.05	0.05	0.20	0.00	3.18	0.21	0.01	1.71	0.23
0.05	0.20	0.05	0.00	3.23	0.21	0.00	3.10	0.26
0.05	0.20	0.20	0.00	2.22	0.21	0.00	1.76	0.21
0.20	0.05	0.05	0.00	3.68	0.22	0.00	3.05	0.26
0.20	0.05	0.20	0.00	3.18	0.20	0.01	1.71	0.24
0.20	0.20	0.05	0.00	3.26	0.22	0.00	3.07	0.25
0.20	0.20	0.20	0.00	2.23	0.21	0.00	1.71	0.23

Table F4: Simulation results with $\sigma = 3$. p is the proportion of times that the assumption-free bound was sharper than DV's bound; Δ and $\tilde{\Delta}$ are the mean absolute distance between the log of the bound and the log of the true causal risk ratio, for DV's bounds and the assumption-free bounds, respectively.

$p(U = 1)$	$p(E = 1)$	$p(D = 1)$	lower bound			upper bound		
			p	$\tilde{\Delta}$	Δ	p	$\tilde{\Delta}$	Δ
0.05	0.05	0.05	0.01	3.78	0.71	0.14	3.39	0.94
0.05	0.05	0.20	0.01	3.18	0.61	0.27	2.16	0.82
0.05	0.20	0.05	0.01	3.60	0.62	0.06	3.61	0.89
0.05	0.20	0.20	0.06	2.35	0.67	0.14	2.24	0.69
0.20	0.05	0.05	0.00	3.93	0.70	0.14	3.44	0.90
0.20	0.05	0.20	0.00	3.25	0.61	0.29	2.19	0.90
0.20	0.20	0.05	0.01	3.81	0.70	0.06	3.57	0.88
0.20	0.20	0.20	0.04	2.42	0.68	0.21	2.13	0.84