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Education Corner

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Assessing the impact of unmeasured confounding for binary outcomes using confounding functions

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Abstract

A critical assumption of causal inference is that of no unmeasured confounding: for estimated exposure effects to have valid causal interpretations, a sufficient set of predictors of exposure and outcome must be adequately measured and correctly included in the respective inference model(s). In an observational study setting, this assumption will often be unsatisfied, and the potential impact of unmeasured confounding on effect estimates should be investigated. The confounding function approach allows the impact of unmeasured confounding on estimates to be assessed, where unmeasured confounding may be due to unmeasured confounders and/or biases such as collider bias or information bias. Although this approach is easy to implement and pertains to the sum of all bias, its use has not been widespread, and discussion has typically been limited to continuous outcomes. In this paper, we consider confounding functions for use with binary outcomes and illustrate the approach with an example. We note that confounding function choice encodes assumptions about effect modification: some choices encode the belief that the true causal effect differs across exposure groups, whereas others imply that any difference between the true causal parameter and the estimate is entirely due to imbalanced risks between exposure groups. The confounding function approach is a useful method for assessing the impact of unmeasured confounding, in particular when alternative approaches, e.g. external adjustment or instrumental variable approaches, cannot be applied. We provide Stata and R code for the implementation of this approach when the causal estimand of interest is an odds or risk ratio.

Key words: causal inference, confounding function, sensitivity analysis, unmeasured confounding

Key Messages

- Unmeasured confounding is often a problem in the analysis of data from observational studies: confounding may be due to particular confounders being difficult to measure, and thus not being included in the dataset, or due to issues such as measurement error.
- The confounding function approach is a useful method for assessing the impact of unmeasured confounding, in particular when alternative approaches cannot be applied, or to assess the impact of the sum of all bias on estimates.
- Bias due to unmeasured confounding is composed of parts that are explained by different outcome risks in the exposure groups that are due to the effects of unmeasured factors on the outcome (rather than due to the effect of exposure) and parts that are explained by differential effect magnitudes in the exposure groups (i.e. interaction or effect modification by unmeasured factors).
- Confounding functions are sensitivity analysis parameters expressing beliefs about the presence, direction and magnitude of possible violations of the exchangeability assumption, and about unmeasured effect modification.

Introduction

The aim of causal inference is the estimation of causal quantities, in particular mean *potential outcomes*, where contrasts in these measures, under the validity of certain assumptions, can be interpreted as average causal effects.[1] Causal inference approaches are required in non-experimental settings such as epidemiological studies where randomized allocation of intervention or exposure conditions is unethical or impossible. In such settings, it is usual that exposure and outcome are at least partly determined by one or more common causes. Hence, the unconditional/unadjusted estimate of an exposure–outcome association will be biased for the true underlying causal quantity of interest. Random variables that mimic these common causes of exposures and outcomes are commonly called *confounding variables* or *confounders*. Methods that attempt to account for measured confounders in order to reduce bias in effect estimation can be classified as design or analysis strategies.[2] Design strategies include matching or stratification of subjects, whereas analysis strategies include adjustment for covariates using a multivariable regression analysis, or using propensity score-based approaches.[3]

The 'no unmeasured confounding' assumption to identify the average treatment effect (ATE) requires that a sufficient set of relevant confounders of the exposure–outcome relationship are adequately measured and correctly included in statistical models. However, it is possible that important confounders will remain unmeasured, perhaps due to technological limitations or because human understanding of the causal mechanisms is incorrect or incomplete.

There are many approaches available for assessing the sensitivity of estimated causal effects to unmeasured confounding,[4–13] and the appropriateness of a particular method for use in a given application largely depends upon subject-matter considerations. For example, if there exist variables with particular properties (e.g. instrumental variables), approaches that exploit these variables are available.[10,11] We will later discuss alternative approaches and compare them with the so-called *confounding function* approach,[14,15] which adjusts estimates using confounding functions that describe the degree of unmeasured confounding. Sensitivity analyses are conducted by varying the confounding functions. The approach appears to have gained most traction in situations where exposures are time-varying.[9,16,17] Although confounding functions for fixed-time-point exposures and outcomes have previously been addressed,[18–20] there is little guidance on their use for binary outcomes, where the causal quantity of interest is a ratio, with an exception being Chiba (2009).[21] In this article, we describe the confounding function approach in this situation, discuss the implications of the choices of values of the confounding functions and contrast this approach with alternative approaches. Unlike in Chiba (2009)[21], we provide results for odds ratios and discuss implicit assumptions regarding effect modification. We consider an example using publicly available data to illustrate the use of the confounding function, and provide Stata and R code as Supplementary Material, available as Supplementary Data at *IJE* online, for implementation.

Causal effects in the form of odds ratios and risk ratios

Marginal odds ratios and risk ratios

Here, the outcome of interest, Y, is binary, with $Y=1$ indicating that the outcome occurred and A denotes the binary exposure variable of interest: $A=0$ indicating 'unexposed' and $A=1$ indicating 'exposed'.

Using the potential outcomes framework,[22] where Y_i^a is the outcome that would have been observed for subject had

they experienced exposure $A=a$ (i.e. the counterfactual outcome for subjects with exposure $A=1-a$), in this paper, either the marginal odds ratio (OR) or marginal risk ratio (RR) is the causal effect parameter of interest:

$$OR = \frac{P(Y^1=1)}{1-P(Y^1=1)} \Big/ \frac{P(Y^0=1)}{1-P(Y^0=1)}, RR = \frac{P(Y^1=1).}{P(Y^0=1)}$$

If the exchangeability assumption $P(Y^a=1|A=0) = P(Y^a=1|A=1)$ and the consistency assumption $P(Y^a=1|A=a)=P(Y=1|A=a)$, $a \in \{0,1\}$ are valid, the OR and RR can be unbiasedly estimated by:

$$\widehat{OR} = \frac{P(Y=1\ |A=1)}{1-P(Y=1\ |A=1)} \Big/ \frac{P(Y=1\ |A=0)}{1-P(Y=1\ |A=0)},$$

$$\widehat{RR} = \frac{P(Y=1|A=1)}{P(Y=1|A=0)}.$$

Measured confounders

OR and RR as defined above do not include adjustment for adequately measured confounders of the exposure–outcome relationship. However, in most studies, there will exist measured confounders that should be adjusted for when comparing exposure groups. A difficulty in comparing conditional and marginal ORs is that of non-collapsibility: a marginal OR may be different to an OR conditional on a variable even if exposure groups are exchangeable (as is expected to occur for large randomized trials). In addition, equality of marginal and conditional ORs is no guarantee that the variable conditioned on is not a confounder of the exposure–outcome relationship.[23] We use inverse probability of treatment weighting (IPTW) to incorporate measured confounders in the estimation of marginal effect parameters, and all relevant probabilities defining the effect parameters are estimated within the weighted space.[24] Denoting the set of measured confounders for subject i by $\boldsymbol{X}_i$, the probability that subject i is exposed, $p_i = P(A=1|\boldsymbol{X}=\boldsymbol{x}_i)$, can be estimated by using a suitable prediction approach for a dichotomous variable, e.g. binary logistic regression. The observation for each subject is then weighted by the probability of their observed exposure when calculating any of the probabilities in the expression for $\widehat{OR}$ or $\widehat{RR}$.

The confounding function approach

For binary outcomes where interest is in the estimation of OR or RR, the confounding function, which allows for relaxation of the exchangeability assumption, is given by

$$c(a) = \frac{P(Y^a=1\ |A=1)}{P(Y^a=1\ |A=0)},\ a \in \{0,1\}.$$

Thus, for the purpose of sensitivity analysis, two quantities are of interest: $c(0)$ and $c(1)$. These quantities represent the marginal RRs between actually exposed subjects ($A=1$) and unexposed subjects ($A=0$) in two counterfactual scenarios: (i) all subjects unexposed ($c(0)$) and (ii) all subjects exposed ($c(1)$). Hence, the confounding function compares the risk profiles (potential outcomes) between actually exposed and unexposed individuals, and therefore expresses the presence, direction and magnitude of possible violations of the exchangeability assumption. In the absence of unmeasured confounding, $c(0)=c(1)=1$. A related approach and a variant for categorical exposures in the context of marginal structural models for hazard ratios have previously been described.[16,17,19] The confounding function approach is thus particularly useful when confounding by indication is thought to be present: e.g. those patients who received the exposure of interest tend to be more likely to experience the outcome of interest in both hypothetical populations.

Although the numerator of $c(1)$ and the denominator of $c(0)$ are estimable under the validity of the consistency assumption, both the denominator of $c(1)$ and the numerator of $c(0)$ are counterfactual quantities. For example, $P(Y^1=1|A=0)$ is the probability of the outcome among unexposed subjects, had those subjects instead been exposed. Although there may exist situations in which these counterfactual quantities could be estimated, such as when the consistency assumption does not hold, we do not consider such situations here, and consider the confounding functions $c(0)$ and $c(1)$ to be sensitivity analysis parameters.

Assuming only that the consistency assumption holds, we write OR and RR in terms of estimable quantities and the $c(a)$ functions: derivations are provided in Supplementary Appendix 1, in the Supplementary Material available as Supplementary Data at *IJE* online. Rearranging the $c(a)$ functions as $h(a) = P(A=0) + c(a)P(A=1)$ simplifies formulae, and the marginal ORs and RRs can be rewritten as:

$$OR = \frac{\frac{h(1)}{c(1)}P(Y=1|A=1)}{1-\frac{h(1)}{c(1)}P(Y=1|A=1)} \Big/ \frac{h(0)P(Y=1|A=0)}{1-h(0)P(Y=1|A=0)},$$

$$RR = \frac{\frac{h(1)}{c(1)}P(Y=1|A=1)}{h(0)P(Y=1|A=0)}.$$

Confidence intervals (CIs) for OR and RR can be obtained via bootstrapping.[25]

Table 1. Interpretation of assumed values of $c(0)$ and $c(1)$ for causal estimands on the ratio scale

Assumed value		Interpretation and implications of the assumptions
$c(0)$	$c(1)$	
1	1	The risks of the potential outcomes among the exposed and unexposed individuals are equal under either counterfactual exposure condition, implying the belief that there is neither an effect of unmeasured confounding nor of unmeasured effect modifiers
<1	<1	Exposed individuals are supposed to have a *lower* risk of both potential outcomes than unexposed individuals. For example, in the case of an outcome such as death, this can be interpreted as the belief that the exposed individuals are healthier than unexposed individuals in some unmeasured way • If $c(0) = c(1)$, the implication is that confounding towards a lower risk in the exposed occurs *without* effect modification: the effect of the exposure is assumed to be the same in both unexposed and exposed subgroups • If $c(0) < c(1)$, the implication is that the effect of the exposure in the unexposed individuals is less (but in the same direction) than the effect of exposure in the exposed: presence of unmeasured effect modifiers that are differentially distributed across exposure groups • If $c(0) > c(1)$, the implication is that the effect of the exposure in the unexposed individuals is greater (but in the same direction) than the effect of exposure in the exposed: presence of unmeasured effect modifiers that are differentially distributed across exposure groups
>1	>1	Exposed individuals are supposed to have, under either possible exposure condition, *higher* risk of both potential outcomes than unexposed individuals. In the case of an outcome such as death, this indicates that the exposed individuals are believed to be less healthy than unexposed individuals in some unmeasured way • If $c(0) = c(1)$, the implication is that confounding towards a lower risk in the exposed occurs *without* effect modification: the effect of the exposure is assumed to be the same in both unexposed and exposed subgroups • If $c(0) < c(1)$, the implication is that the effect of the exposure in the unexposed individuals is less (but in the same direction) than the effect of exposure in the exposed: presence of unmeasured effect modifiers that are differentially distributed across exposure groups • If $c(0) > c(1)$, the implication is that the effect of the exposure in the unexposed individuals is greater (but in the same direction) than the effect of exposure in the exposed: presence of unmeasured effect modifiers that are differentially distributed across exposure groups
≤ 1	≥ 1 $c(0) \neq c(1)$	Unexposed individuals are supposed to have a higher risk of the outcome compared with exposed individuals if, contrary to their actual exposure, exposed individuals were unexposed. At the same time, if unexposed individuals were exposed, they are supposed to have a lower risk of the outcome as the actually exposed individuals The implication of this assumption is that the effect of exposure in the exposed is supposed to be greater than the effect of the exposure in the unexposed: presence of unmeasured effect modifiers that are differentially distributed across exposure groups
≥ 1	≤ 1 $c(0) \neq c(1)$	Unexposed individuals are supposed to have a lower risk of the outcome compared with exposed individuals if, contrary to their actual exposure, exposed individuals were unexposed. At the same time, if unexposed individuals were exposed, they are supposed to have the higher risk of the outcome as the actually exposed individuals The implication of this assumption is that the effect of exposure in the exposed must be less than the effect of the exposure in the unexposed:presence of unmeasured effect modifiers that are differentially distributed across exposure groups

Investigating the impact of unmeasured confounding for different values of $c(0)$ and $c(1)$ is necessary, and contextual knowledge from subject-matter experts can be used to provide a reasonable range of values. In situations in which there is little basis for assigning values to these parameters, a wide range of values should be considered. As has previously been discussed for continuous outcomes,[9] implicit in the selected values of $c(0)$ and $c(1)$ are assumptions regarding the effect of the exposure in the exposed and unexposed groups.

The different possible realizations of $c(0)$ and $c(1)$ in Table 1 reveal that bias due to unmeasured confounding is composed of parts that are due to the effects of unmeasured factors on the outcome (rather than due to the effect of exposure) and parts that are explained by differential effect magnitudes in the exposure groups. These differential

effect magnitudes could be due to an interaction between an unmeasured confounder and the exposure, leading to effect modification by the unmeasured confounder. For example, selecting $c(0) < 1$ and $c(1) > 1$ implies that the unexposed subjects would have had a greater risk of the outcome than the exposed subjects (had these subjects not been exposed, contrary to fact): some of the difference between the estimate and the causal parameter is due to unmeasured effect modification. A situation in which such choices may be plausible is when the exposure of interest is thought to have a pharmacological interaction with a medication thought to affect both the outcome and exposure status of subjects. On the other hand, selecting $c(0) = c(1)$ implies that the bias due to unmeasured confounding is assumed to be entirely explained by imbalanced risks, i.e. no effect modification by the unmeasured confounding variables.

For $c(1)$, the lower bound is given by $P(Y=1|A=1)$, whereas the upper bound is the counterfactual quantity $1/P(Y^1=1|A=0)$. Similarly, for $c(0)$, the upper bound is $1/P(Y=1|A=0)$, and the lower bound is a counterfactual quantity. Setting $c(0)$ or $c(1)$ equal to its upper or lower bound implies that one of the potential outcomes would have occurred with certainty for one of the exposure groups. For example, setting $c(1)$ to its upper bound implies that, if unexposed subjects had been exposed, they would certainly have experienced the outcome. Hence, in most settings, the range of possible values for $c(1)$ and $c(0)$ will always contain values <1 and > 1.

A value that may be of particular interest is $c(a)$ required to return a null value, or some other value that equates to a trivial or ignorable effect, for the causal OR or RR. For example, OR or RR will be equal to 1 if $c(0)$ and $c(1)$ take the following specific values:

$$c^1(1) = \frac{P(Y=1|A=1)P(A=0)}{h(0)P(Y=1|A=0) - P(Y=1, A=1)}$$

and

$$c^1(0) = \frac{\begin{array}{r} c(1)[P(Y=1,\ A=1) - P(Y=1, A=0)] \\ + P(Y=1|A=1)P(A=0) \end{array}}{c(1)P(Y=1|A=0)P(A=1)}.$$

Assuming $c(0) = c(1)$ (i.e. unmeasured confounding is explained solely by unmeasured differences in the risk profiles of the two exposure groups and is not due to differentially distributed unmeasured effect modifiers), OR or RR will be equal to 1 if $c^1(0) = c^1(1) = \frac{P(Y=1|A=1)}{P(Y=1|A=0)}$. Hence, the confounding functions must be at least as extreme as the observed RR to result in a changed conclusion about the direction of the observed effect. This is related to the classical Cornfield condition, which states that the hypothetical exposure-unmeasured confounder RR must be at least as large as the observed exposure–outcome RR to completely ameliorate the exposure–outcome RR.[26] However, the interpretation of the sensitivity analysis parameters $c(0)$ and $c(1)$ is in terms of counterfactual outcomes, rather than in terms of a specific unmeasured binary confounder.

Formulae for the required values of $c(a)$ to give unmeasured-confounding-adjusted ORs and RRs equal to non-null values are provided in Supplementary Appendix 2 in the Supplementary Material, available as Supplementary Data at *IJE* online.

Alternative sensitivity analysis approaches

The most widely used method for assessing the impact of unmeasured confounding is external adjustment.[4–7] This method adjusts estimated exposure–outcome relationships assuming hypothesized characteristics of the unmeasured confounder(s). Different approaches exist and the precise nature of the hypothesized characteristics and adjustment depend on the particular approach selected. For example, one approach requires specification of the prevalence of a binary unmeasured confounder and the association between that unmeasured confounder and each of the exposure and the outcome.[6] This approach allows for interaction between the exposure and the unmeasured confounder, but assumes that the unmeasured confounder is independent of measured confounders and thus may overestimate the impact of the unmeasured confounder. A more general external adjustment approach allows for a vector of unmeasured confounders that are not restricted to being binary, and does not require independence between the measured and unmeasured confounders.[12] Although this approach provides bounds for causal estimands without assuming independence of measured and unmeasured confounders, this comes at a price: sensitivity parameters within each strata of measured confounders must be considered, which may be an unwieldy number of parameters.

An advantage of external adjustment approaches is that researchers may be more comfortable with external adjustment sensitivity parameters rather than confounding functions, which conceptualize outcomes in hypothetical populations in which all subjects were exposed or not exposed. However, a limitation of external adjustment approaches is that any related assumptions made may be as open to criticism as the assumption of no unmeasured confounding. This criticism may be partially overcome through investigating the impact of a broad range of sensitivity parameters, or assessing the characteristics required

of a particular unmeasured confounder to explain an effect entirely, as we also recommend for the confounding function approach. A more critical disadvantage of external adjustment is the restriction to considering the impact of unmeasured variables only. The confounding function approach allows consideration of the impact of the sum of all bias: bias due to unmeasured confounders and/or other biases such as information or collider biases.

Although confounding function values and external adjustment parameters can be selected to return the same adjusted effect measure, the major differences in the interpretation of the external adjustment parameters and the confounding function parameters makes direct comparison between the two methods difficult.

Instrumental variable and negative control outcome methods for addressing unmeasured confounding require the presence of variables satisfying strict assumptions.[10,11] An instrument is a variable that affects the outcome only through the exposure, and is not associated with unmeasured confounders, e.g. randomization group may be an instrument in randomized trials. Negative controls are outcome variables that are not directly influenced by the exposure, but are subject to unmeasured confounding in the same way as the outcome variable of interest. When the strict assumptions regarding instrumental variables or negative control outcomes are valid, these approaches are recommended.

An approach based on linear programming provides deterministic bounds for estimated causal effects when a risk difference is the causal estimand of interest and, like the confounding function approach, applies a potential outcomes framework and does not make any assumptions about particular unmeasured confounders.[13] However, the impact of varying the degree of unmeasured confounding is not the focus, and effect modification due to unmeasured confounding is not permitted. Strict deterministic bounds for estimated risk differences are provided, relying on observed data and a range of assumptions to decrease the width of the bounds. Although extensions of the linear programming approach are possible for risk or odds ratios, such extensions do not appear to have been implemented.

Example: abciximab and death

To illustrate the use of the confounding function for RRs, we consider data from 996 percutaneous coronary intervention (PCI) patients, from the 'twang' package in R,[27] a subset of the data analysed in Kereiakes et al. (2000).[28] One of the aims of the original study was to estimate the effect of abciximab (a platelet aggregation inhibitor, with abciximab receipt denoted by $A = 1$) on mortality at 6 months, where abciximab was not randomly administered. Of 996 patients, 698 received abciximab, of whom 11 died. Of the 298 patients who did not receive abciximab, 15 died. The crude RR for mortality is 0.31, 95% CI (0.15, 0.67). We include Stata and R code to obtain both the RR and OR, and to replicate Figures 1–2, as online Supplementary Material, available as Supplementary Data at *IJE* online.

We estimated IPTWs by fitting a logistic regression model for abciximab receipt including sex, height, diabetes (yes/no), an indicator for recent acute myocardial infarction, left ventricular ejection fraction, the number of vessels included in the PCI (0 to 5) and an indicator for the insertion of a coronary stent.

We consider it unlikely that non-abciximab patients would have a greater risk of death than abciximab patients in the counterfactual population in which no one received the drug, whereas at the same time having a lower risk of death in the counterfactual population in which everyone received the drug: i.e. that $c(0) < 1 < c(1)$. Similarly, we consider $c(0) > 1 > c(1)$ unlikely. Additionally, it can be argued that, even after adjustment for the set of variables listed above, those patients who received abciximab were sicker than those who did not, and were thus more likely to die within 6 months of surgery. Hence we suppose that $c(0)$, $c(1) > 1$ is a more reasonable assumption than $c(0)$, $c(1) < 1$. Selecting $c(0) \neq c(1)$ encodes the belief that there exist effect modifiers that are differentially distributed between the two abciximab groups, whereas selecting $c(0) = c(1)$ encodes the assumption that any difference between the true causal effect of abciximab and the observed effect is due to imbalanced mortality risks only.

The RR obtained using IPTW is 0.19, with bootstrap-derived 95% CI (0.08, 0.50), indicating that the risk of death is much lower in those patients who received abciximab. Figure 1 displays a contour plot of the RR obtained using IPTW corrected for various values of $c(0)$ and $c(1)$. Particular choices of $c(0)$ and $c(1)$ are marked on the plot: $c(0) = 1$ with a dashed horizontal line; $c(1) = 1$ with a vertical dotted line; and $c(0) = c(1)$ with a solid line. Also displayed is $c_{RR}^{0.19}(1)$: the value of $c(1)$ required to return an unmeasured-confounding-adjusted RR of 0.19. If there is no effect modification, this value of $c_{RR}^{0.19}(1)$ is 1, but, in the presence of differentially distributed effect modifiers, a range of confounding function values would return the RR obtained using IPTW. Figure 2 displays the adjusted RR and its bootstrap-derived CI for $c(0) = c(1)$.

Figures 1 and 2 show that, as $c(0)$ and $c(1)$ increase, the adjusted RR decreases. Taking $c(0)$ and $c(1)$ to be greater than 1 encodes confounding by indication: those who received abciximab were sicker than those who did not receive it and, in the hypothetical populations in which no one or everyone received abciximab, would have been

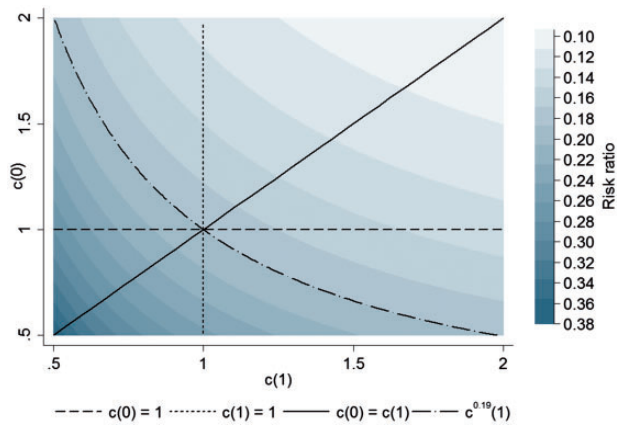

Figure 1. Contour plot of the sensitivity analysis for the marginal risk ratio for the abciximab data. Risk ratios for various combinations of $c(0)$ and $c(1)$ are calculated, using inverse probability of treatment weighting to adjust for measured confounders. When $c(0) = c(1) = 1$, the value of the risk ratio unadjusted for unmeasured confounding is returned (RR = 0.19). The line labelled $c^{0.19}(1)$ marks the values of $c(0)$ and $c(1)$ required to return an odds ratio of 0.19.

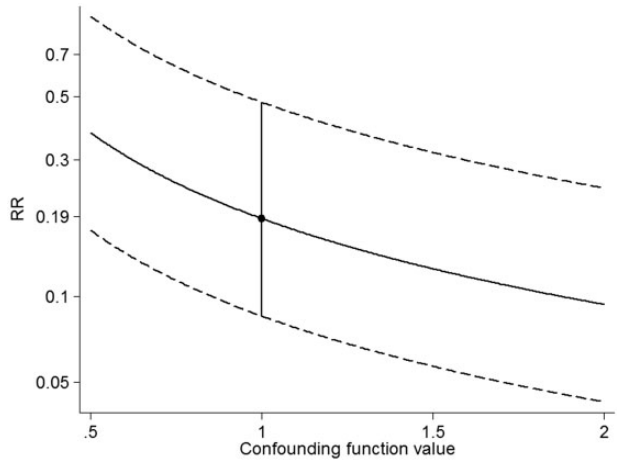

Figure 2. Sensitivity analysis for the risk ratio for the abciximab data. The solid line on this plot corresponds to the $c(0) = c(1)$ line on the contour plot in Figure 1. The dashed lines are 95% bootstrap bias corrected and accelerated confidence intervals. The risk ratio corresponding to $c(0) = c(1) = 1$ is marked with a solid circle.

more likely to die than those patients who did not actually receive it. Hence, given that the RR estimated using IPTW is in favour of abciximab, adjusting for the fact that those patients who received the drug were more likely to die than those who did not (had they in fact received it) serves to further strengthen the evidence in favour of abciximab. In fact, the value of $c(0) = c(1)$ required to return an unmeasured-confounding-adjusted RR of 1 is 0.19 (in accordance with the Cornfield condition). This indicates that, for the true RR (corrected for the impact of unmeasured confounding) to have been 1, the patients who did not receive abciximab would have had to have been about five times more likely to die than those who did receive abciximab, had all patients actually received the same treatment, adjusting for all measured confounders [if $c(0) = c(1) = P(Y^1 = 1|A = 1)/P(Y^1 = 1|A = 0) = 0.19$, then $P(Y^1 = 1|A = 0) \approx 5 \times P(Y^1 = 1|A = 1)$]. A confounding function in this direction and of this magnitude seems implausible, particularly given the set of covariates already adjusted for using IPTW. In fact, to reduce the crude RR from 0.31 to 0.19, $c(0) = c(1) = 1.92$. Hence, adjusting for all measured confounders is equivalent to supposing that patients who actually received abciximab were almost twice as likely to die as patients who did not, had all patients received the same treatment. Given this, a confounding function equal to 0.19 seems implausible, and abciximab appears to be protective against death within 6 months of PCI.

Application of the external adjustment approach of Ding and VanderWeele[12] to this example is described in the online Supplementary Material, available as Supplementary Data at *IJE* online. This approach requires specifying values for the ratio of the confounder prevalence between abciximab exposure levels, and the RR of the unmeasured confounder on mortality: details are provided in Supplementary Appendix 3 in the Supplementary Material, available as Supplementary Data at *IJE* online. To explain the entirety of the abciximab-mortality RR, there would need to exist an unmeasured confounder that was half as prevalent among those who did receive abciximab compared with those who did not, and was at the same time associated with a 50% reduced risk of death. This scenario seems implausible, unless the outcome or unmeasured confounder prevalence is very low,[29] and hence this approach reaches a similar conclusion to the confounding function approach.

Discussion

The confounding function approach discussed here is useful in settings where interest is in understanding the entire impact of all unmeasured confounding, not just that due to a hypothesized set of unmeasured confounders, and instruments/negative controls are unavailable. Although simple to implement, confounding functions are infrequently used to assess the impact of unmeasured confounding. Stata and R code is provided to facilitate further use in Supplementary Appendices 4 and 5 in the Supplementary Material, available as Supplementary Data at *IJE* online.

The confounding function approach requires comparing the expectation of potential outcomes in exposed and unexposed groups on the balance of all unmeasured confounding. The sensitivity analysis parameters that must be specified quantify the differences in potential outcomes that are due to unaccounted-for differences between the

exposure groups, rather than due to the effect of exposure on outcome. In some situations, subject-matter experts will have an understanding of the relative probabilities that exposed and unexposed individuals will experience each of the potential outcomes. In an example comparing kidney-dialysis modalities,[30] the prevailing opinion of nephrologists was that one exposure group was sicker than another in ways that were not captured by the available data. Clinical insight may thus make the choice of the direction of confounding functions clear, although a range of values should still be considered.

In some situations, there may be little internal or external basis for the selection of values for the confounding functions: it may be difficult for investigators to precisely elucidate how exposure groups differ with respect to potential outcomes. For example, the exposed group may be believed to be healthier than the unexposed group in some (unmeasured) ways, but less healthy in other ways. The confounding function approach requires taking a holistic view of the differences between groups, but, in situations like this, it may not be clear which direction is most appropriate. Interpretation of the value of $c(a)$ required to give $OR = 1$ or $RR = 1$, or required to return some other value θ, may provide insights. Although confounding functions will not always be more appropriate than alternative approaches, this approach provides a useful alternative in situations where the set of available variables is limited, the interest is in understanding the entire impact of unmeasured confounding or when interest is in investigating unmeasured effect modification.

Supplementary Data

Supplementary data are available at *IJE* online.

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