

On Instrumental Variables Estimation of Causal Odds Ratios

Stijn Vansteelandt, Jack Bowden, Manoochehr Babanezhad and Els Goetghebeur

Abstract. Inference for causal effects can benefit from the availability of an instrumental variable (IV) which, by definition, is associated with the given exposure, but not with the outcome of interest other than through a causal exposure effect. Estimation methods for instrumental variables are now well established for continuous outcomes, but much less so for dichotomous outcomes. In this article we review IV estimation of so-called conditional causal odds ratios which express the effect of an arbitrary exposure on a dichotomous outcome conditional on the exposure level, instrumental variable and measured covariates. In addition, we propose IV estimators of so-called marginal causal odds ratios which express the effect of an arbitrary exposure on a dichotomous outcome at the population level, and are therefore of greater public health relevance. We explore interconnections between the different estimators and support the results with extensive simulation studies and three applications.

Key words and phrases: Causal effect, causal odds ratio, instrumental variable, marginal effect, Mendelian randomization, logistic structural mean model.

1. INTRODUCTION

Most causal analyses of observational data rely heavily on the untestable assumption of no unmeasured confounders. According to this assumption, one has available all prognostic factors of the exposure that are *also* associated with the outcome *other than via* a possible exposure effect on outcome. Concerns about the validity of this assumption plague observational data analyses and increase the uncertainty surrounding many study results (Greenland, 2005). This is espe-

cially true in settings where the data analysis is based on registry data or focuses on research questions different from those conceived at the time of data collection. Substantial progress can sometimes be made in settings where measurements are available on a so-called instrumental variable (IV). This is a prognostic factor of the exposure, which is *not* associated with the outcome, *except via* a possible exposure effect on outcome (Angrist, 1990; McClellan and Newhouse, 1994; Angrist, Imbens and Rubin, 1996; Hernán and Robins, 2006). An instrumental variable Z for the effect of exposure X on outcome Y thus satisfies the following properties: (a) Z is associated with X ; (b) Z affects the outcome Y only through X (i.e., often referred to as the exclusion restriction); (c) the association between Z and Y is unconfounded (i.e., often referred to as the randomization assumption) (Hernán and Robins, 2006). For instance, in the data analysis section, we will estimate the effect of Cox-2 treatment (versus nonselective NSAIDs) on gastrointestinal bleeding, thereby allowing for the possibility of unmeasured variables U confounding the association between X and Y , by choosing the physician's prescribing preference for Cox-2 (versus nonselective NSAIDs) as an instrumental

Stijn Vansteelandt is Associate Professor, Department of Applied Mathematics and Computer Science, Ghent University, B-9000 Gent, Belgium (e-mail: stijn.vansteelandt@UGent.be). Jack Bowden is Research Fellow, MRC Biostatistics Unit, Robinson Way, Cambridge, United Kingdom (e-mail: jack.bowden@mrc-bsu.cam.ac.uk). Manoochehr Babanezhad is Assistant Professor, Department of Statistics, Golestan University, Golestan, Gorgan, Iran (e-mail: m.babanezhad@gu.ac.ir). Els Goetghebeur is Professor, Department of Applied Mathematics and Computer Science, Ghent University, B-9000 Gent, Belgium (e-mail: els.goetghebeur@UGent.be).

variable (Brookhart and Schneeweiss, 2007). Because this is associated with Cox-2 treatment [i.e., (a)], it would qualify as an IV if it were reasonable that the physician's prescribing preference can only affect a patient's gastrointestinal bleeding through his/her prescription [i.e., (b)] and is not otherwise associated with that patient's gastrointestinal bleeding [i.e., (c)]. Assumption (b) could fail, however, if preferential prescription of Cox-2 were correlated with other treatment preferences that have their own impact on gastrointestinal bleeding; the latter assumption could fail if patients with high risk of bleeding are more often seen with physicians who prefer Cox-2 (Hernán and Robins, 2006). In this article, we will more generally assume that the instrumental variables assumptions (a), (b) and (c) hold conditional on a (possibly empty) set of measured covariates C .

IVs have a long tradition in econometrics and are becoming increasingly popular in biostatistics and epidemiology. This is partly because the plausibility of a measured variable as an IV can sometimes be partially justified on the basis of the study design or biological theory. For instance, in randomized encouragement designs whereby, say, pregnant women who smoke are randomly assigned to intensified encouragement to quit smoking or not, randomization could qualify as an IV for assessing the effects of smoking on low birth weight (Permutt and Hebel, 1989), since it guarantees the validity of IV assumption (c). The growing success of IV methods in biostatistics and epidemiology can, however, be mainly attributed to applications in genetic epidemiology (Smith and Ebrahim, 2004). Here, the random assortment of genes transferred from parents to offspring resembles the use of randomization in experiments and is therefore often referred to as "Mendelian randomization" (Katan, 1986). Building on this idea, genetic variants may sometimes qualify as an IV for estimating the relationship between a genetically affected exposure and a disease outcome, although violations of the necessary conditions may occur (see Didelez and Sheehan, 2007, and Lawlor et al., 2008, for rigorous discussions).

Estimation methods for IVs are now well established for continuous outcomes. The case of dichotomous outcomes has received more limited attention. It turns out to be much harder because of the need for additional modeling and because of difficulties to specify congenial model parameterizations (see Sections 2.2 and 3). This paper therefore combines different, scattered developments in the biostatistical, epidemiological and econometric literature and aims to improve

the clarity and comparability of these developments by casting them within a common causal language based on counterfactuals.

Traditional econometric approaches have their roots in structural equations theory and have thereby largely focused on the estimation of conditional causal effects, where rather than employing counterfactuals to define causal effects, conditioning is made on all common causes, U , of exposure X and outcome Y (see Blundell and Powell, 2003, for a review). By this conditioning, one can assign a causal interpretation to association measures such as

$$\frac{\text{odds}(Y = 1|X = x + 1, C, U)}{\text{odds}(Y = 1|X = x, C, U)}.$$

This can be seen by noting that this odds ratio measure can—under a consistency assumption that $Y = Y(x)$ if $X = x$ —equivalently be written as (Pearl, 1995)

$$(1) \quad \frac{\text{odds}\{Y(x + 1) = 1|C, U\}}{\text{odds}\{Y(x) = 1|C, U\}},$$

where $Y(x)$ denotes the (possibly) counterfactual outcome following an intervention setting X at the exposure level x and where for any V, W , $\text{odds}(W = 1|V) \equiv P(W = 1|V)/P(W = 0|V)$. Effect measure (1) thus compares the odds of "success" if the exposure X were uniformly set to $x + 1$ versus x within strata of C and U . Because U is unmeasured, these strata are not identified, which makes (1) less appealing as an effect measure and of limited use for policy making. Its interpretation is especially hindered in view of noncollapsibility of the odds ratio (Greenland, Robins and Pearl, 1999), following which the magnitude of conditional odds ratios changes with the conditioning sets, even in the absence of confounding or effect modification. Similar limitations are inherent to the so-called treatment effect on the treated at the IV level z of exposure x (Tan, 2010),

$$(2) \quad \frac{\text{odds}\{Y(x) = 1|X(z) = x\}}{\text{odds}\{Y(0) = 1|X(z) = x\}},$$

and to so-called local or principal stratification causal odds ratios (Hirano et al., 2000; Frangakis and Rubin 2002; Abadie, 2003; Clarke and Windmeyer, 2009; see Bowden et al., 2010, for a review). For a dichotomous instrumental variable Z and dichotomous exposure X taking values 0 and 1, the latter measure the association between instrumental variable and outcome within the nonidentifiable principal stratum of subjects for whom an increase in the instrumental variable induces an increase in the exposure; that is,

$$(3) \quad \frac{\text{odds}\{Y(1) = 1|X(1) > X(0), C\}}{\text{odds}\{Y(0) = 1|X(1) > X(0), C\}}.$$

Inference for principal stratification causal odds ratios is also more rigid in the sense of having no flexible extensions to more general settings involving continuous instruments and exposures. While dichotomization of the instrument and/or exposure is often employed in view of this, it not only implies a loss of information, but may also induce a violation of the exclusion restriction and may make the relevance of the principal stratum “ $X(1) > X(0)$ ” become dubious (see Pearl, 2011, for further discussion of these issues).

In view of the aforementioned limitations, our attention in this article will focus on causal effects which are defined within identifiable subsets of the population. Special attention will be given to the conditional causal odds ratio (Robins, 2000; Vansteelandt and Goetghebuer, 2003; Robins and Rotnitzky, 2004), which we define as

$$(4) \quad \frac{\text{odds}(Y = 1|X, Z, C)}{\text{odds}\{Y(0) = 1|X, Z, C\}}.$$

It expresses the effect of setting the exposure to zero within subgroups defined by the observed exposure level X , instrumental variables Z and covariates C . In the special case where X is a dichotomous treatment variable, taking the value 1 for treatment and 0 for no treatment, (4) evaluated at $X = 1$, that is,

$$\frac{\text{odds}\{Y(1) = 1|X = 1, Z, C\}}{\text{odds}\{Y(0) = 1|X = 1, Z, C\}}$$

is sometimes referred to as the treatment effect in the treated who are observed to have IV level Z (Hernán and Robins, 2006; Robins, VanderWeele and Richardson, 2006; Didelez, Meng and Sheehan, 2010; Tan, 2010). Conditional causal odds ratios would be of special interest if the goal of the study were to examine the impact of setting the exposure to zero for those with a given exposure level X , for example, to examine the impact of preventing nosocomial infection within those who acquired it (Vansteelandt et al., 2009).

While the comparison in (4) could alternatively be expressed as a risk difference or relative risk, our focus throughout will be limited to odds ratios because models for other association measures do not guarantee probabilities within the unit interval, and might not be applicable under case-control sampling (Bowden and Vansteelandt, 2011). We refer the interested reader to Robins (1994) and Mullahy (1997) for inference on the conditional relative risk

$$(5) \quad \frac{P(Y = 1|X, Z, C)}{P\{Y(0) = 1|X, Z, C\}},$$

and to van der Laan, Hubbard and Jewell (2007) for inference on the so-called switch relative risk, which is defined as (5) for subjects with values (X, Z, C) for which $P(Y = 1|X, Z, C) \leq P\{Y(0) = 1|X, Z, C\}$ and as

$$\frac{P(Y = 0|X, Z, C)}{P\{Y(0) = 0|X, Z, C\}},$$

for all remaining subjects. The latter causal effect parameter is more difficult to interpret, but has the advantage that models for the switch relative risk, unlike models for (5), guarantee probabilities within the unit interval.

For policy making, the interest lies more usually in population-averaged or marginal effect measures (Greenland, 1987; Stock, 1988) such as

$$(6) \quad \frac{\text{odds}\{Y(x + 1) = 1\}}{\text{odds}\{Y(x) = 1\}},$$

where x is a user-specified reference level, or

$$(7) \quad \frac{\text{odds}\{Y(X + 1) = 1\}}{\text{odds}\{Y(X) = 1\}} \quad \text{or} \quad \frac{\text{odds}\{Y(1.1 \times X) = 1\}}{\text{odds}\{Y(X) = 1\}}.$$

Here, (6) evaluates the effect of changing the exposure from level x to $x + 1$ uniformly in the population. It thus reflects the effect that would have been estimated had an ideal randomized controlled trial (i.e., with 100% compliance) in fact been possible, randomizing subjects over exposure level x versus $x + 1$. In contrast, the effect measures in (7) allow for natural variation in the exposure between subjects by expressing the effect of an absolute or relative increase in the observed exposure. This may ultimately be of most interest in many observational studies, considering that many public health interventions would target a change in exposure level (e.g., diet, BMI, physical exercise, ...), starting from some natural, subject-specific exposure level X .

We review estimation of the conditional causal odds ratio (4) in Section 2. By casting different developments within the same causal framework based on counterfactuals, new insights into their interconnections will be developed. We propose novel estimators of the marginal causal odds ratios given in (6) and (7) in Section 3, as well as for the corresponding effect measures expressed as risk differences or relative risks. Extensive simulation studies are reported in Section 4 and an evaluation on 3 data sets is given in Section 5.

2. IV ESTIMATION OF THE CONDITIONAL CAUSAL ODDS RATIO

Identification of the conditional causal odds ratio (4) is studied in detail in Robins and Rotnitzky (2004) and Vansteelandt and Goetghebeur (2005), who find that—as for other IV estimators (Hernan and Robins, 2006)—parametric restrictions are required in addition to the standard instrumental variables assumptions. In particular, nonlinear exposure effects and modification of the exposure effect by the instrumental variable are not nonparametrically identified. We will therefore consider estimation of the conditional causal odds ratio under so-called logistic structural mean models (Robins, 2000; Vansteelandt and Goetghebeur, 2003; Robins and Rotnitzky, 2004), which impose parametric restrictions on the conditional causal odds ratio (4). In particular, these models postulate that the exposure effect is linear in the exposure on the conditional log odds ratio scale, and independent of the instrumental variable, in the sense that

$$(8) \quad \frac{\text{odds}(Y = 1|X, Z, C)}{\text{odds}\{Y(0) = 1|X, Z, C\}} = \exp\{m(C; \psi^*)X\},$$

where $m(C; \psi)$ is a known function (e.g., $\psi_0 + \psi_1 C$), smooth (i.e., with continuous first-order derivatives) in ψ , and ψ^* is an unknown finite dimensional parameter. In the absence of covariates, this gives rise to a relatively simple model of the form

$$(9) \quad \frac{\text{odds}(Y = 1|X, Z)}{\text{odds}\{Y(0) = 1|X, Z\}} = \exp(\psi^* X).$$

The assumption that the exposure effect is not modified by the IV substitutes the monotonicity assumption [that $X(z) \geq X(z')$ if $z \geq z'$] (Hernan and Robins, 2006) which is commonly adopted in the principal stratification approach. In spite of the randomization assumption [cf. IV assumption (c)], it may be violated because subjects with exposure level X are not exchangeable over levels of the IV, so that they might in particular experience different effects. The additional assumption of a linear exposure effect is only relevant for exposures that take on more than two levels. It must be cautiously interpreted because the conditional causal odds ratio (4) expresses effects for differently exposed subgroups which may not be exchangeable. Both these assumptions are critical because they are empirically unverifiable. Vansteelandt and Goetghebeur (2005) assess the sensitivity of the conditional causal odds ratio estimator to violation of the linearity assumption and note that, under violation of the linearity assumption, the estimator can still yield a meaningful first order approximation. In the remainder of this work, we will assume that model (8) is correctly specified.

2.1 Approximate Estimation

Approximate IV estimators of the conditional causal odds ratio can be obtained by averaging over the observed exposure values in model (8) using the following approximations:

$$(10) \quad \begin{aligned} & E\{\text{logit} E(Y|X, Z, C)|Z, C\} \\ & \approx \text{logit} E(Y|Z, C), \end{aligned}$$

$$(11) \quad \begin{aligned} & E[\text{logit} E\{Y(0)|X, Z, C\}|Z, C] \\ & \approx \text{logit} E\{Y(0)|Z, C\}. \end{aligned}$$

This together with the logistic structural mean model (8) implies

$$(12) \quad \begin{aligned} & \text{logit} E(Y|Z, C) \\ & \approx \text{logit} E\{Y(0)|Z, C\} + m(C; \psi^*)E(X|Z, C) \\ & = \text{logit} E\{Y(0)|C\} + m(C; \psi^*)E(X|Z, C), \end{aligned}$$

upon noting that the combined IV assumptions (b) and (c), conditional on C , imply $Y(x) \perp\!\!\!\perp Z|C$ for all x . It follows that approximate IV estimators of the conditional causal odds ratio can be obtained via the following two-stage approach:

1. Estimate the expected exposure in function of the IV and covariates by fitting an appropriate regression model. Let the predicted exposure be $\hat{X} \equiv \hat{E}(X|Z, C)$.
2. Regress the outcome on covariates C and on $m(C; \psi)\hat{X}$ through standard logistic regression to obtain an estimate of ψ^* . In the absence of covariates, this involves fitting a logistic regression model of the form

$$(13) \quad \text{logit} E(Y|Z) = \omega + \psi \hat{X}.$$

When, furthermore, the IV is dichotomous, it follows from (12) that

$$(14) \quad \begin{aligned} \text{OR}_{Y|Z} & \equiv \frac{\text{odds}(Y = 1|Z = 1)}{\text{odds}(Y = 1|Z = 0)} \\ & \approx \exp(\psi^*)^{\Delta_{X|Z}}, \end{aligned}$$

where $\Delta_{X|Z} \equiv E(X|Z = 1) - E(X|Z = 0)$, so that ψ^* can be estimated as $\log \hat{\text{OR}}_{Y|Z} / \hat{\Delta}_{X|Z}$.

The estimator obtained using the above two-stage approach is referred to as the standard IV estimator in Palmer et al. (2008), a Wald-type estimator in Didelez, Meng and Sheehan (2010) and the 2-stage logistic approach in Rassen et al. (2009). It is commonly employed in the analysis of Mendelian randomization

studies (Thompson et al., 2003; Palmer et al., 2008), where it is typically viewed as an approximate estimator of the conditional causal odds ratio (1). Our alternative development shows that it can also be viewed as an approximate estimator of the conditional causal odds ratio (4). To gain insight into the adequacy of the approximations (10) and (11), suppose for simplicity that there are no covariates, that the exposure has a normal distribution with constant variance σ_x^2 conditional on Z , that $\text{logit} E(Y|X, Z) = \beta_0 + \beta_x X + \beta_z Z$ and that $m(C; \psi) = \psi$. Then it is easily shown, using results in Zeger and Liang (1988), that

$$\text{logit} E(Y|Z) \approx \beta_0 \{\beta_x^2 \sigma_x^2\} + \beta_x \{\beta_x^2 \sigma_x^2\} E(X|Z) + \beta_z \{\beta_x^2 \sigma_x^2\} Z,$$

$$\begin{aligned} \text{logit} E\{Y(0)|Z\} &\approx \beta_0 \{(\beta_x - \psi^*)^2 \sigma_x^2\} \\ &+ (\beta_x - \psi^*) \{(\beta_x - \psi^*)^2 \sigma_x^2\} E(X|Z) \\ &+ \beta_z \{(\beta_x - \psi^*)^2 \sigma_x^2\} Z, \end{aligned}$$

where for any parameter β and variance component σ^2 , we define $\beta\{\sigma^2\} = \beta(c^2\sigma^2 + 1)^{-1/2}$ with $c = 16\sqrt{3}/15\pi$. It can relatively easily be deduced from these expressions and the fact that $E\{Y(0)|Z\} = E\{Y(0)\}$ that

$$\text{logit} E(Y|Z) \approx \beta'_0 + \frac{\psi^*}{\sqrt{c^2\beta_x^2\sigma_x^2 + 1}} E(X|Z),$$

for some β'_0 , suggesting increasing bias with increasing association between X and Y (given Z) and with increasing residual variance in X (given Z). This is true except at the null hypothesis of no causal effect because $Y \perp\!\!\!\perp Z$ at the null hypothesis so that the usual maximum likelihood estimator of ψ in model (13) will then converge to 0 in probability. Further, note that the standard IV estimator requires correct specification of the first stage regression model for the expected exposure (Didelez, Meng and Sheehan, 2010; Rassen et al., 2009; Henneman, van der Laan and Hubbard, 2002). In spite of its approximate nature, the standard IV estimator continues to be much used in Mendelian randomization studies because of its simplicity, because it can be used in meta-analyses of summary statistics, even when information on $\text{OR}_{Y|Z}$ and $\Delta_{X|Z}$ is obtained from different studies (Minelli et al., 2004; Smith et al., 2005; Bowden et al., 2006), and because the underlying principle extends to case-control studies when the first stage regression is evaluated on the controls and

the disease prevalence is low (Smith et al., 2005; Bowden and Vansteelandt, 2011). For relative risk estimators, the resulting bias due to basing the first stage regression on controls rather than a random population sample amounts to the difference between the log relative risk and the log odds ratio between Y and Z , inflated by the reciprocal of the exposure distortion $\Delta_{X|Z}$ (Bowden and Vansteelandt, 2011).

The bias of the standard IV estimator can sometimes be attenuated by including the first-stage residual $R \equiv X - \hat{X}$ as an additional regressor to \hat{X} in model (13). This is known as the control functions approach in econometrics (Smith and Blundell, 1986; Rivers and Vuong, 1988) and has also been considered in the biostatistical literature on noncompliance adjustment (Nagelkerke et al., 2000) and Mendelian randomization (Palmer et al., 2008). A control function refers to a random variable conditioning on which renders the exposure independent of the unmeasured variables that confound the association between exposure and outcome. Intuitively, the regression residual R may apply as a control function because it captures (part of) those confounders. In particular, let us summarize (without loss of generality) all confounders of the exposure effect into a scalar measurement U . Assume that the contributions of the instrument Z and confounder U are additive in the sense that $X = h(Z) + U$ for some function h . Suppose for simplicity that there are no covariates and that the conditional mean $E(X|Z)$ is known so that $\hat{X} = h(Z)$ (here we use that $U \perp\!\!\!\perp Z$, as implied by the IV assumptions). Then $R = U$ so that a (correctly specified) logistic regression of Y on X and R (or, equivalently, \hat{X} and R) will yield a consistent estimator of the conditional causal odds ratio (1), which is here identical to (4) because U is completely determined by X and Z . More generally, following the lines of Smith and Blundell (1986), assume that $X = h(Z) + V$, $U = \tilde{\beta}_1^* V + \varepsilon$, where ε follows a standard logistic distribution, and that $Y(x) = 1$ if and only if $\tilde{\beta}_0^* + \psi^* x + U > 0$ for some $\tilde{\beta}_0^*$, $\tilde{\beta}_1^*$. Then it also follows that $Y = 1$ if and only if $\varepsilon > -\tilde{\beta}_0^* - \psi^* X - \tilde{\beta}_1^* V$, from which

$$\text{logit} E(Y|X, V) = \tilde{\beta}_0^* + \psi^* X + \tilde{\beta}_1^* V.$$

Upon substituting V with the estimated regression residual R , one obtains an estimator $\exp(\hat{\psi})$ which consistently estimates the conditional causal odds ratio (1). In the Appendix we demonstrate that this is also a consistent estimator of the conditional causal odds ratio (4) when the exposure is normally distributed with constant variance, conditional on the instrument, but

not necessarily otherwise. Standard error calculation for the standard and adjusted IV estimators is also detailed in the [Appendix](#).

Over recent years, semiparametric analogs to the adjusted IV approach have been developed in the econometrics literature to alleviate concerns about model misspecification. Blundell and Powell (2004) and Rothe (2009), for instance, avoid parametric restrictions on the conditional expectations $E(X|Z, C)$ and $E(Y|X, Z, C)$ (and, in particular, on the distribution of ε) by using kernel regression estimators and semiparametric maximum likelihood estimation, respectively. Imbens and Newey (2009) allow for the contributions of the instrument Z and confounder U on the exposure to be nonadditive by extending the previous works to nonseparable exposure models of the form $X = h(Z, U, C)$ for some function h . They show that the association between exposure and outcome is unconfounded upon adjusting for $R = F_{X|Z, C}(X|Z, C)$ as a control function, where $F_{X|Z, C}$ is the conditional cumulative distribution function of X , given Z and C . To avoid parametric restrictions on the conditional expectations $F_{X|Z, C}(X|Z, C)$ and $E(Y|X, Z, C)$, they base inference on local linear regression estimators.

A limitation of all these semiparametric approaches is that, by avoiding assumptions on the distribution of ε , the causal parameter ψ^* becomes difficult to interpret so that it may be exclusively of interest for the calculation of marginal causal odds ratios (see Section 3). A further limitation is that all foregoing approaches require the exposure to be continuously distributed (Rothe, 2009); some additionally require the IV to be continuously distributed (Imbens and Newey, 2009). In the next section we review direct approaches to the estimation of the conditional causal odds ratio (4) which do not rely on assumptions about the exposure distribution.

2.2 Consistent Estimation

Remember that, although Y may well depend on Z (in the presence of an exposure effect), the IV assumptions imply that $Y(0) \perp\!\!\!\perp Z|C$. Vansteelandt and Goetghebeur (2003) make use of this to obtain a consistent estimator of ψ^* in model (8), which is chosen to make this independence happen. Because this is not possible without making additional parametric modeling assumptions (Robins and Rotnitzky, 2004), they model the expected observed outcome, conditional on the ex-

posure and IV, for example,

$$(15) \quad \begin{aligned} \text{logit P}(Y = 1|X, Z, C) \\ = \beta_0^* + \beta_1^* X + \beta_2^* Z + \beta_3^* XZ + \beta_4^* C, \end{aligned}$$

where $\beta_0^*, \beta_1^*, \beta_2^*, \beta_3^*$ and β_4^* are unknown scalar parameters. More generally, one may postulate that

$$(16) \quad \text{logit E}(Y|X, Z, C) = m(X, Z, C; \beta^*),$$

where $m(X, Z, C; \beta)$ is a known function, smooth in β , and β^* is an unknown finite-dimensional parameter. An estimator $\hat{\beta}$ of β^* can be obtained using standard methods (e.g., using maximum likelihood estimation). Combining the causal model (8) with the so-called association model (16) yields a prediction for the counterfactual outcome $Y(0)$ for each subject which, for given ψ , equals

$$H(\psi, \hat{\beta}) = \text{expit}\{m(X, Z, C; \hat{\beta}) - m(C; \psi)X\},$$

where $\text{expit}(a) \equiv \exp(a)/\{1 + \exp(a)\}$. Because $E\{Y(0)|Z, C\} = E\{Y(0)|C\}$ under the IV assumptions, the value of ψ^* can now be chosen as the value ψ which makes this mean independence happen, once $Y(0)$ is replaced by $H(\psi, \hat{\beta})$. When there are no covariates and the instrument Z is dichotomous, taking the values 0 and 1, one thus chooses ψ such that

$$(17) \quad \frac{\sum_i H_i(\psi, \hat{\beta}) Z_i}{\sum_i Z_i} = \frac{\sum_i H_i(\psi, \hat{\beta})(1 - Z_i)}{\sum_i (1 - Z_i)}.$$

When also the exposure is dichotomous, then model (15) is guaranteed to hold and a closed-form estimator is obtained, as given in the [Appendix](#). In most cases, the solution to (17) gives a unique estimator of the causal odds ratio, although multiple or no solutions are sometimes obtained when precision is limited due to small sample size or the outcome mean being close to 0 or 1. This is illustrated in Figure 1, which displays the left- and right-hand side of (17) in function of ψ for 3 settings. The top 2 panels are based on the same simulated data set. They show that 2 or no solutions can be obtained for the same data set, depending on whether the association model (16) includes an interaction between exposure and instrument (left panel) or not (right panel). The bottom panel corresponds to the data analysis of Section 5.1, where a single solution was obtained. Our experience indicates that, when 2 solutions are obtained, one of them corresponds to an effect size which is so large that it would be deemed unrealistic [and correspondingly yield unrealistically small or large values of $E\{Y(0)\}$]. When no solutions

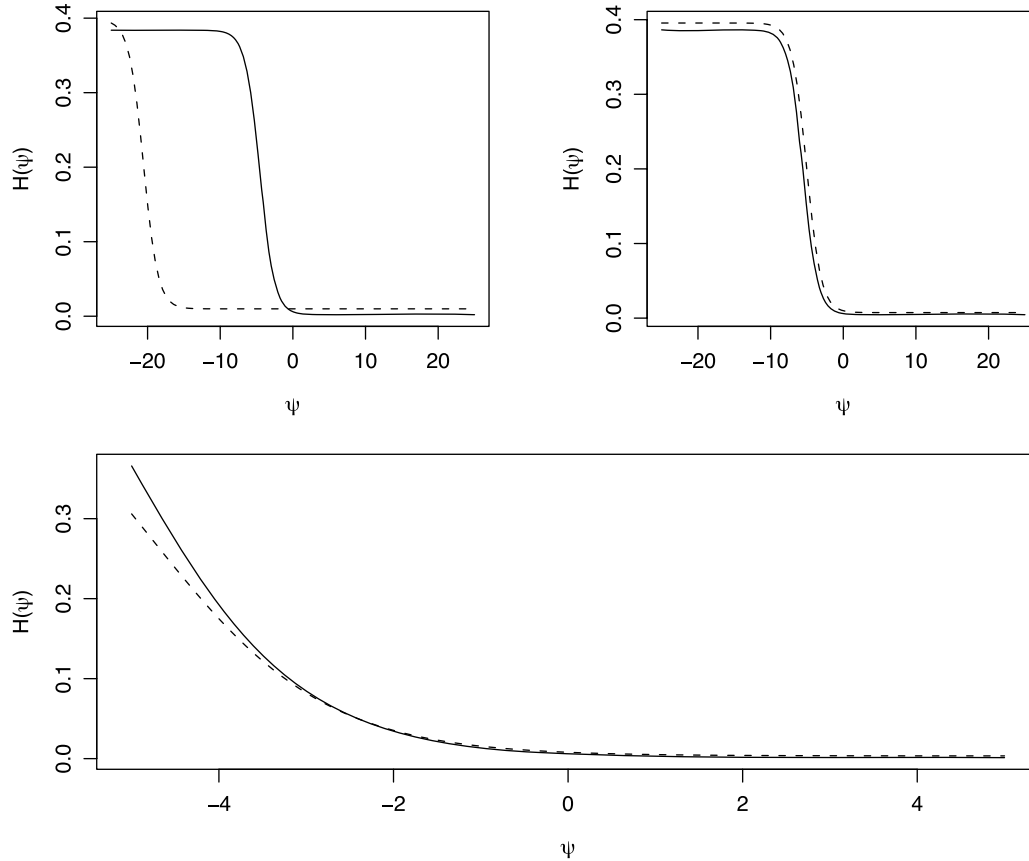


FIG. 1. Plot of the left- (solid) and right-hand side (dotted) of expression (17) as a function of ψ . Top: simulated data set [Right: with $\beta_4^* = 0$ in model (15)]; Bottom: data set analyzed in Section 5.1.

are obtained, this can sometimes be resolved by choosing a less parsimonious association model (as in Figure 1, top), but must be seen as an indication that information is very limited. In the simulation experiments of Section 4, a single solution was always obtained, but convergence of the root-finding algorithm (nlm in R) was sometimes very dependent on the choice of an adequate starting value.

For general instruments, a consistent point estimator of ψ^* can be found by solving unbiased estimating equation

$$(18) \quad 0 = \sum_{i=1}^n [d(Z_i, C_i) - E\{d(Z_i, C_i)|C_i\}] \cdot [H_i(\psi, \hat{\beta}) - E\{H_i(\psi, \hat{\beta})|C_i\}]$$

for ψ , where $d(Z_i, C_i)$ is an arbitrary function of Z_i and C_i , for example, $d(Z_i, C_i) = Z_i$ (see Bowden and Vansteelandt, 2011, for choices that yield a semiparametric efficient estimator of ψ^*). This thus leads to the following 2-stage approach:

1. First fit the association model (16), for instance, using maximum likelihood estimation, and obtain an estimator $\hat{\beta}$ of β^* ;
2. Next, solve equation (18) to obtain an estimator $\hat{\psi}$ of ψ^* .

Corresponding R-code is available from the first author's website (users.ugent.be/~svsteela). This approach is extended in Tan (2010) to enable estimation of the treatment effect on the treated at the IV level z of exposure x , as defined in (2), thus avoiding conditioning on C .

In the Appendix we show that when the association model includes an additive term in $d(Z_i, C_i) - E\{d(Z_i, C_i)|C_i\}$ and is fitted using maximum likelihood estimation as in standard generalized linear model software, then its solution is robust to misspecification of the association model (16) when $\psi^* = 0$. This means that a consistent estimator of $\psi^* = 0$ is obtained, even when all models are misspecified. In the absence of covariates and with $d(Z_i, C_i) = Z_i$ and $E\{d(Z_i, C_i)|C_i\} = \sum_{j=1}^n Z_j/n$, this is satisfied as soon

as the association model includes an intercept and main effect in Z_i [as in model (15)]. The proposed approach then yields a valid (Wald and score) test of the causal null hypothesis that $\psi^* = 0$, even when both models (8) and (16) are misspecified. This property, which we refer to as a “local” robustness property (Vansteelandt and Goetghebeur, 2003), also guarantees that estimators of the causal odds ratio will have small bias under model misspecification when the true exposure effect is close to, but not equal to, zero.

A drawback of the parameterization by Vansteelandt and Goetghebeur (2003) is that the association model may be uncongenial with the causal model. Specifically, given the observed data law $f(X, Z|C)$ and the limiting value β^* of $\hat{\beta}$, there may be no value of the causal parameter ψ for which $E\{H(\psi, \beta^*)|Z, C\} = E\{H(\psi, \beta^*)|C\}$ over the entire support of Z and C . In the Appendix, we show that this may happen when parametric restrictions are imposed on the main effect of the instrumental variable in the association model (16), along with its interaction with covariates C , but not when that main effect is left unrestricted. It follows that no congeniality problems arise in the common situation of a dichotomous instrument and no covariates, so long as a main effect of the IV is included in the association model. This continues to be true for categorical IVs with more than 2 levels when dummy regressors are used for the instrument in the association model and there are no covariates. For general IVs, one may consider generalized additive association models which leave the main effect of the IV unrestricted (apart from smoothness restrictions).

Robins and Rotnitzky (2004) developed an alternative approach for estimation of ψ^* in model (8), which guarantees a congenial parameterization by avoiding direct specification of an association model. They parameterize instead the selection-bias function

$$\begin{aligned} & \text{logit}E\{Y(0)|X, Z, C\} \\ (19) \quad & - \text{logit}E\{Y(0)|X = 0, Z, C\} \\ & = q(X, Z, C; \eta^*), \end{aligned}$$

where $q(X, Z, C; \eta)$ is a known function satisfying $q(0, Z, C; \eta) = 0$, smooth in η , and η^* is an unknown finite-dimensional parameter. That $q(X, Z, C; \eta^*)$ encodes the degree of selection bias can be seen because $q(X, Z, C; \eta^*) = 0$ for all X implies that $E\{Y(0)|X, Z, C\} = E\{Y(0)|Z, C\}$ and thus implies that the association between exposure and outcome [more precisely,

$Y(0)$] is unconfounded (conditional on Z and C). Relying on a parametric model for the conditional exposure distribution, $f(X|Z, C) = f(X|Z, C; \alpha^*)$ (fitted using maximum likelihood inference, for instance), their approach involves the following iterative procedure. First, for each fixed ψ (starting from an initial value ψ_0), maximum likelihood estimators $\hat{\eta}(\psi)$ and $\hat{\omega}(\psi)$ are computed for the parameters η^* and ω^* indexing the implied association model

$$\begin{aligned} & P(Y = 1|X, Z, C; \psi, \eta^*, \omega^*) \\ (20) \quad & = \text{expit}\{m(C; \psi)X + q(X, Z, C; \eta^*) \\ & \quad + v(Z, C; \eta^*, \omega^*)\}, \end{aligned}$$

where $v(Z, C; \eta^*, \omega^*) \equiv \text{logit}E\{Y(0)|X = 0, Z, C\}$ is the solution to the integral equation

$$\begin{aligned} & \text{logit}E\{Y(0)|C\} \\ & = t(C; \omega^*) \\ (21) \quad & = \int \text{expit}\{q(X = x, Z, C; \eta^*) \\ & \quad + v(Z, C; \eta^*, \omega^*)\} \\ & \quad \cdot f(X = x|Z, C; \alpha^*) dx, \end{aligned}$$

where $t(C; \omega)$ is a known function of C , smooth in ω , and where ω^* is an unknown finite-dimensional parameter. For the given estimators $\hat{\eta}(\psi)$ and $\hat{\omega}(\psi)$, an estimator of ψ is then obtained by solving a linear combination of the estimating equations (18) and estimating equations for the parameters indexing the association model (20). Both these steps are then iterated until convergence of the estimator. In the Appendix we suggest a somewhat simpler strategy which, nonetheless, also involves solving integral equations. Alternatively, one could focus on the switch relative risk of van der Laan, Hubbard and Jewell (2007), introduced in Section 1, to avoid the uncongeniality problems associated with the odds ratio.

An advantage of the approach of Robins and Rotnitzky (2004) is that it guarantees that $E\{Y(0)|Z, C\} = E\{Y(0)|C\}$ for all Z and C , although only under correct specification of the law $f(X|Z, C)$. Under the approach of Vansteelandt and Goetghebeur (2003), this is only guaranteed under congenial parameterizations as suggested previously, but regardless of whether a model for the law $f(X|Z, C)$ is (correctly) specified. A further advantage is that it might possibly give somewhat more efficient estimators by fully exploiting the a priori knowledge that $E\{Y(0)|Z, C\} = E\{Y(0)|C\}$ to estimate unknown parameters [i.e., $v(Z, C)$] and by

additionally relying on a model for the exposure distribution. A drawback is that the approach is computationally demanding, especially for continuous IVs and/or in the presence of covariates, as it involves solving integral equations for each (Z, C) and this within each iteration of the algorithm. In addition, standard error calculations are more complex. A further drawback is that consistent estimation (away from the null) requires correct specification of the conditional exposure distribution $f(X|Z, C)$.

The estimation procedure for logistic structural mean models simplifies when the logit link is replaced with the probit link and the exposure is assumed to be normally distributed conditional on the instrumental variable and covariates (with mean $\alpha_0^* + \alpha_1^*Z + \alpha_2^*C$ and constant standard deviation σ^* , where $\alpha_0^*, \alpha_1^*, \sigma^*$ are unknown). For instance, combining the probit structural mean model

$$(22) \quad \begin{aligned} & \Phi^{-1}\{E(Y|X, Z, C)\} - \Phi^{-1}\{E(Y(0)|X, Z, C)\} \\ & = \phi^* X, \end{aligned}$$

where Φ^{-1} is the probit link and ϕ^* is unknown, with the probit association model

$$(23) \quad \Phi^{-1}\{E(Y|X, Z, C)\} = \theta_0^* + \theta_1^* X + \theta_2^* Z + \theta_3^* C,$$

where $\theta_0^*, \theta_1^*, \theta_2^*$ are unknown, and averaging over the exposure, conditional on Z and C (see the [Appendix](#)), gives

$$(24) \quad \begin{aligned} & E\{Y(0)|Z, C\} \\ & = \Phi\{(\theta_0^* + \theta_2^* Z \\ & \quad + (\theta_1^* - \phi^*)(\alpha_0^* + \alpha_1^* Z + \alpha_2^* C) + \theta_3^* C) \\ & \quad \cdot (\sqrt{1 + (\theta_1^* - \phi^*)^2 \sigma^{2*}})^{-1}\}. \end{aligned}$$

Because this does not depend on Z under the IV assumptions, it follows that $\theta_2^* = (\phi^* - \theta_1^*)\alpha_1^*$. Averaging over the exposure in the association model (23) and using the previous identity, we obtain

$$E(Y|Z, C) = \Phi\left(\frac{\theta_0^* + \theta_1^* \alpha_0^* + \phi^* \alpha_1^* Z + \theta_3^* C}{\sqrt{1 + \theta_1^{*2} \sigma^{2*}}}\right).$$

This suggests regressing the outcome on the instrumental variable and covariate using the probit regression model

$$(25) \quad \Phi^{-1}\{E(Y|Z, C)\} = \lambda_0^* + \lambda_1^* Z + \lambda_2^* C$$

to obtain an estimate $\hat{\lambda}_1$ for the unknown regression slope λ_1^* , and then estimating ϕ^* as

$$(26) \quad \hat{\phi} = \frac{\hat{\lambda}_1 \sqrt{1 + \hat{\theta}_1^2 \hat{\sigma}^2}}{\hat{\alpha}_1}.$$

We will refer to this estimator as the ‘‘Probit-Normal SMM estimator’’ throughout. It is related to the instrumental variables probit (Lee, 1981) and the generalized two-stage simultaneous probit (Amemiya, 1978), both of which instead infer effect estimates conditional on the unmeasured confounder U . When the outcome mean lies between 10% and 90%, the above estimator yields an approximate estimate of the causal odds ratio through the identity $\exp(\psi^*) \approx \exp(\phi^*/0.6071)$ (McCullagh and Nelder, 1989). For dichotomous exposures, related estimators can be obtained via probit structural equation models that replace the linear regression model for X_i in assumption 1 above, with a probit regression model (see, e.g., Rassen et al., 2009).

3. IV ESTIMATION OF THE MARGINAL CAUSAL ODDS RATIO

We will now turn attention to the identification of marginal causal effects. Under linear structural models, these coincide with conditional causal effects under typical assumptions (Hernan and Robins, 2006). Consider, for instance, the extended linear structural mean model which imposes the restriction

$$E\{Y - Y(x)|X, C, Z\} = m(C, x; \psi^*)(X - x)$$

for each feasible exposure level x , where $m(C, x; \psi)$ is a known function (e.g., $\psi_0 + \psi_1 C + \psi_2 x$), smooth in ψ , and ψ^* an unknown finite dimensional parameter. Then it follows from the restriction

$$\begin{aligned} & E\{Y - m(C, x; \psi^*)(X - x)|C, Z\} \\ & = E\{Y - m(C, x; \psi^*)(X - x)|C\} \end{aligned}$$

for each x , that

$$\begin{aligned} & E\{Y - m(C, x; \psi^*)X|C, Z\} \\ & = E\{Y - m(C, x; \psi^*)X|C\} \end{aligned}$$

for each x , and thus that $m(C, x; \psi^*)$ does not depend on x . This then implies that the marginal causal effect equals

$$E\{Y(x^*) - Y(x)|C\} = m(C, 0; \psi^*)(x^* - x).$$

Unfortunately, this result does not extend to logistic structural mean models, so that the conditional causal odds ratio corresponding to a single reference exposure level (e.g., 0) does not uniquely map into the marginal causal odds ratio.

Let us therefore assume that in addition to the association model (16), the extended logistic structural mean model holds, which we define by the restriction

$$(27) \quad \frac{\text{odds}(Y = 1|X, Z, C)}{\text{odds}\{Y(x) = 1|X, Z, C\}} \\ = \exp\{m(C; \psi_x^*)(X - x)\},$$

for each feasible exposure level x , where $m(C; \psi_x)$ is a known function (e.g., $\psi_{x0} + \psi_{x1}C$), smooth in ψ_x , and ψ_x^* an unknown finite-dimensional parameter. The marginal causal odds ratio (6) can now be identified upon noting that

$$\begin{aligned} P\{Y(x) = 1\} \\ = E[\text{expit}\{m(X, Z, C; \beta^*) - m(C; \psi_x^*)(X - x)\}] \end{aligned}$$

and the marginal causal odds ratio [(7), left] upon noting that

$$\begin{aligned} P\{Y(X + 1) = 1\} \\ = E[\text{expit}\{m(X, Z, C; \beta^*) + m(C; \psi_{X+1}^*)\}]. \end{aligned}$$

A consistent estimator of (6) is thus obtained by first obtaining consistent estimators of β^* , ψ_x^* and ψ_{x+1}^* , using the strategy of the previous section, and then calculating $\hat{p}_{x+1}(1 - \hat{p}_x)/\{\hat{p}_x(1 - \hat{p}_{x+1})\}$, where for given x

$$\begin{aligned} \hat{p}_x = n^{-1} \sum_{i=1}^n \text{expit}\{m(X_i, Z_i, C_i; \hat{\beta}) \\ - m(C_i; \hat{\psi}_x)(X_i - x)\}. \end{aligned}$$

A consistent estimator of [(7), left] is obtained by first obtaining consistent estimators of β^* and ψ_{x+1}^* for each observed value X_i for x using the strategy of the previous section, and then calculating $\hat{p}_{X+1}(1 - \hat{p}_X)/\{\hat{p}_X(1 - \hat{p}_{X+1})\}$, where

$$\begin{aligned} \hat{p}_X = n^{-1} \sum_{i=1}^n Y_i, \\ \hat{p}_{X+1} = n^{-1} \sum_{i=1}^n \text{expit}\{m(X_i, Z_i, C_i; \hat{\beta}) \\ + m(C_i; \hat{\psi}_{X+1})\}. \end{aligned}$$

Standard error calculations are reported in the [Appendix](#). Using the above expressions, also estimators of the marginal risk difference $P\{Y(x + 1) = 1\} - P\{Y(x) = 1\}$ or relative risk $P\{Y(x + 1) = 1\}/P\{Y(x) = 1\}$ can straightforwardly be obtained.

A drawback of this strategy, which we discuss in the [Appendix](#), is that even when model (27) is congenial

with the association model (16) for $x = 0$ (or some other reference level), it need not be a well-specified model for all x . We conjecture that when this would happen, this may be partially detectable in the sense of yielding estimating equations with no solution, as the uncongeniality is then due to the nonexistence of a value of ψ_x^* for some x so that $E\{Y(x)|Z, C\} = E\{Y(x)|C\}$ for all (Z, C) . As with other causal models that are not guaranteed to be congenial (e.g., Petersen et al., 2007; Tan, 2010) and as confirmed in simulation studies in the next section, we believe this is unlikely to induce an important bias. The concern for bias is further alleviated by the aforementioned local robustness property, which continues to hold for extended logistic structural mean models.

The idea of using conditional causal effect estimates as plug-in estimates in inference for marginal effects has been advocated in the biostatistical and epidemiological literature (see, e.g., Greenland, 1987; Ten Have et al., 2003) and is commonly employed in the econometrics literature (see, e.g., Blundell and Powell, 2004; Imbens and Newey, 2009), where related proposals have been made starting from a semiparametric control functions approach. Alternative approaches involve assuming that all confounders of the exposure effect can be captured into a scalar variate U , which has an additive effect on the outcome (Amemiya, 1974; Foster, 1997; Johnston et al., 2008; Rassen et al., 2009) in the sense that

$$(28) \quad E(Y|X, C, U) = \text{expit}(\beta_0^* + \tilde{\psi}^*X + \beta_1^*C) + U,$$

where β_0^* , β_1^* , $\tilde{\psi}^*$ are unknown and where $E(U|C) = 0$; note that $E(U|X, C) \neq 0$ when there is confounding. Because, for each x , $Y(x) \perp\!\!\!\perp X|U, C$, model (28) implies the marginal structural model

$$\begin{aligned} E\{Y(x)|C\} = E[E\{Y(x)|X = x, C, U\}|C] \\ = \text{expit}(\beta_0^* + \tilde{\psi}^*x + \beta_1^*C) \end{aligned}$$

considered by Henneman, van der Laan and Hubbard (2002). This clarifies that $\exp(\tilde{\psi}^*)$ in model (28) can be interpreted as the marginal (i.e., population averaged) causal odds ratio

$$\exp(\tilde{\psi}^*) = \frac{\text{odds}\{Y(1) = 1|C\}}{\text{odds}\{Y(0) = 1|C\}}.$$

Using that $Z \perp\!\!\!\perp U|C$ under the IV assumptions, an estimator $\hat{\psi}$ for ψ^* can be obtained by solving the following unbiased estimating equations:

$$(29) \quad 0 = \sum_{i=1}^n \begin{pmatrix} 1 \\ Z_i \\ C_i \end{pmatrix} \{Y_i - \text{expit}(\beta_0 + \psi X_i + \beta_1 C_i)\}.$$

The marginal causal odds ratio (6) can be identified upon noting that

$$P\{Y(x) = 1\} = E[\text{expit}(\beta_0^* + \tilde{\psi}^*x + \beta_1^*C)];$$

it equals $\exp(\tilde{\psi}^*)$ when C is empty. The marginal causal odds ratio [(7), left] can be identified upon noting that

$$\begin{aligned} P\{Y(X + 1) = 1\} \\ = E[\text{expit}\{\beta_0^* + \tilde{\psi}^*(X + 1) + \beta_1^*C\}]. \end{aligned}$$

In the absence of covariates, it follows from the unbiasedness of the estimating functions at $\tilde{\psi}^* = 0$ that the resulting estimator is (locally) robust against model misspecification at the null hypothesis of no causal effect. However, it is not guaranteed to exist and may be inconsistent for $\psi^* \neq 0$ because the dichotomous nature of the outcome imposes strong restrictions on the distribution of U , which may be impossible to reconcile with the basic assumption that $Z \perp\!\!\!\perp U|C$ (Henneman, van der Laan and Hubbard, 2002).

4. SIMULATION STUDY

We conducted 5 simulation experiments, each with a sample size of 1,000 and with 1,000 simulation runs. As in Palmer et al. (2008), the instrumental variable Z was generated in such a manner as to represent the number of copies (0, 1 or 2) of a single bi-allelic SNP in the Hardy–Weinberg equilibrium. The underlying allele frequency in the population was assumed to be $p = 0.3$, and so Z was generated from a multinomial distribution with cell probabilities (0.09, 0.42, 0.49). The exposure X was generated to be $N(Z, 2)$ in simulation experiments a, b and e, $Z + t_2$ in simulation experiment c and $\Gamma(Z, 1)$ in simulation experiment d [with $\Gamma(\cdot, \cdot)$ referring to the Gamma distribution]. Finally, the outcome was generated to satisfy

$$P(Y = 1|X, Z) = \text{expit}(\beta_0 + \beta_x X + \beta_z Z),$$

where β_0 was fixed at different values to result in outcome means of 0.05, 0.1, 0.25 and 0.5 and β_x was chosen to yield $Y(0) \perp\!\!\!\perp Z$ under the logistic structural mean model (9) with ψ equaling 0 or 1. Finally, β_z was set to 1 in simulation experiments a and e, to 2 in simulation experiments b and c and to -2 in simulation experiment d to correspond to different degrees of unmeasured confounding. Indeed, note that the conditional association β_z between $Y(0)$ and Z , conditional on X , is largely explained by the extent of unmeasured confounding.

Table 1 compares the Wald estimator, the Adjusted IV estimator and the logistic structural mean model estimator of the conditional causal log odds ratio. We do not report results for the semiparametric control function approaches since these require the IV to be continuously distributed (Imbens and Newey, 2009). Table 1 demonstrates that the Wald estimator can have substantial bias when there is unmeasured confounding of the exposure–outcome association (cf. experiment b). As predicted by the theory, the adjusted IV estimator gives unbiased estimators when the exposure has a symmetric distribution with constant variance (cf. experiments a–c), conditional on the IV, but not when the exposure distribution is skewed (cf. experiment d) or when an exposure–IV interaction is ignored (cf. experiment e). Note, in particular, that the adjusted IV estimator is not locally robust to model misspecification at the causal null hypothesis $\psi^* = 0$, despite the existence of an asymptotically distribution-free test. The logistic SMM estimator is unbiased in all cases. It has slightly increased variance relative to the Adjusted IV estimator when the exposure is normally distributed, but reduced variance when the exposure is t -distributed because of outlying exposure residuals (i.e., control functions) affecting the Adjusted IV estimator.

Table 2 compares the proposed estimators of the marginal log odds ratio (6) (labeled “MLOR 1”) and (7) (labeled “MLOR 2”), as well as the same estimators where, for computational convenience, $\hat{\psi}_x$ is substituted with $\hat{\psi}_0$ for all x (labeled “Approx. MLOR 1” and “Approx. MLOR 2”). We do not report results on the estimators obtained by solving (29) since they were doing very poorly, often resulting in nonconvergence in over 80% of the simulation runs. Table 2 demonstrates that the approximate estimators perform adequately and much like the proposed estimators, although the nominal coverage level is slightly better attained for the proposed estimators. Given the good agreement, the results in Table 3 are based on the computationally more attractive approximate estimators. Interestingly, it reveals that the estimators of the marginal causal log odds ratio have a much reduced variance relative to the three considered estimators of the conditional causal log odds ratio. In particular, highly efficient estimates are obtained for the marginal causal log odds ratio (6) which we regard to be of most interest in many practical applications, since it essentially expresses the result that would be obtained in a randomized experiment.

TABLE 1

Bias ($\times 100$), empirical standard deviation ($\times 100$) (ESE), average sandwich standard error ($\times 100$) (SSE) and coverage of 95% confidence intervals (Cov.) for the standard IV estimator, the adjusted IV estimator and the logistic structural mean model estimator of the log conditional causal odds ratio

Exp.	E(Y)	ψ	Standard IV				Adjusted IV				Logistic SMM			
			Bias	ESE	SSE	Cov.	Bias	ESE	SSE	Cov.	Bias	ESE	SSE	Cov.
a	0.1	0	1.15	16.2	15.9	95.5	1.11	19.2	18.9	95.1	1.62	20.1	19.6	95.6
	0.05	1	3.82	30.8	30.4	96.1	3.92	30.8	30.5	96.0	5.31	33.0	32.2	96.2
	0.1	1	1.71	22.0	21.9	95.3	1.80	22.0	21.9	95.5	2.71	23.6	23.0	95.6
	0.25	1	0.68	15.0	15.0	95.5	0.77	15.0	15.1	95.6	1.24	15.8	15.7	95.3
	0.5	1	1.18	12.3	12.7	95.1	1.28	12.3	12.7	95.3	1.46	12.6	13.0	95.6
b	0.1	0	1.28	15.7	15.9	95.1	1.31	24.8	25.1	95.5	2.86	28.3	28.3	95.9
	0.05	1	-7.12	31.1	27.9	88.9	4.38	34.4	33.4	95.3	6.63	38.7	37.3	95.1
	0.1	1	-13.5	22.1	18.9	80.1	2.69	25.4	25.7	95.3	4.37	29.0	28.9	95.2
	0.25	1	-21.9	15.3	11.6	49.2	1.84	19.8	20.1	95.1	2.76	22.1	22.2	95.8
	0.5	1	-26.0	13.2	8.89	26.5	1.28	18.0	18.3	95.4	1.65	19.3	19.4	95.4
c	0.1	0	1.77	17.0	17.1	95.0	7.06	73.5	61.3	94.4	5.31	39.8	39.5	95.2
	0.05	1	-34.8	36.1	30.4	55.4	10.8	79.8	69.4	94.4	12.2	58.0	56.2	93.1
	0.1	1	-29.1	34.9	26.6	50.5	9.82	83.0	63.5	94.8	8.15	41.1	39.7	95.9
	0.25	1	-25.6	30.3	21.2	41.9	7.45	68.3	54.2	93.1	3.50	26.9	25.2	95.1
	0.5	1	-24.7	26.8	18.9	39.2	7.23	66.9	53.1	93.8	1.8	19.7	19.0	95.3
d	0.1	0	0.08	15.6	15.8	95.3	-56.2	25.6	26.2	40.8	-1.03	28.6	28.5	94.0
	0.05	1	-48.0	24.1	26.2	51.7	-91.8	47.0	43.5	42.4	-1.09	40.0	34.1	87.7
	0.1	1	-55.8	15.8	19.0	14.3	-83.4	32.3	31.9	22.3	1.16	33.5	31.6	88.2
	0.25	1	-65.2	9.87	13.1	0.00	-61.8	23.3	23.1	21.2	1.59	26.8	27.0	94.0
	0.5	1	-72.8	8.53	10.8	0.00	-27.0	19.9	20.3	76.3	-0.07	27.3	28.5	95.2
e	0.1	0	2.55	15.5	15.4	94.8	2.83	18.6	19.2	95.9	3.25	26.8	26.4	97.2
	0.05	1	-37.7	25.8	25.2	62.2	-37.4	26.0	25.8	64.0	13.4	56.3	52.4	91.0
	0.1	1	-36.6	18.4	18.3	45.0	-36.4	18.6	18.9	48.1	8.38	39.8	38.0	93.9
	0.25	1	-31.0	12.7	13.0	34.3	-30.9	12.7	13.2	35.6	4.83	24.4	24.3	95.7
	0.5	1	-19.1	10.7	11.9	61.8	-18.7	10.8	11.4	60.4	4.18	17.1	17.4	96.0

5. APPLICATIONS

5.1 Analysis of a Health Register

Brookhart et al. (2006) and Brookhart and Schneeweiss (2007) assess short-term effects of Cox-2 treatment (as compared to nonsteroidal anti-inflammatory treatment) on the risk of gastrointestinal (GI) bleeding within 60 days. As Table 4 shows, of the 37,842 new nonselective NSAID users drawn from a large population based cohort of medicare beneficiaries who were eligible for a state-run pharmaceutical benefit plan, 26,407 patients were placed on Cox-2 treatment. Let the received treatment X equal 1 for subjects placed on Cox-2 and 0 for those on nonselective NSAIDs. Let the outcome Y indicate 1 for upper gastrointestinal (GI) bleeding within 60 days of initiating an NSAID and 0 otherwise. As in Brookhart and Schneeweiss (2007), we use the physician's prescribing preference for Cox-2 (versus nonselective NSAIDs) Z as an instrumen-

tal variable for the effect of Cox-2 treatment on gastrointestinal bleeding. The Wald and adjusted IV estimator of the conditional causal odds ratio were found to be identical: 0.26 (95% confidence interval 0.084–0.79, P 0.018). In contrast, the logistic structural mean model estimator [both using the approach of Vansteelandt and Goetghebeur (2003) and using the approach of Robins and Rotnitzky (2004)] was found to be 0.081 (95% confidence interval 0.0095–0.82, P 0.018), which might be more reliable, considering the nonnormality of the exposure distribution. The marginal causal odds ratio was estimated to be almost identical: 0.083 (95% confidence interval 0.0096–0.82). We thus estimate roughly that the use of nonselective NSAIDs instead of Cox-2 increases the odds (or risk) of gastrointestinal bleeding by at least 18% ($= 1 - 0.82$).

Besides the IV assumptions, all results rely on the assumption that the effect of Cox-2 versus nonselective NSAIDs is the same in Cox-2 users whose physician prefers Cox-2 treatment as in Cox-2 users whose

TABLE 2

Bias ($\times 100$), empirical standard deviation ($\times 100$) (ESE), average sandwich standard error ($\times 100$) (SSE) and coverage of 95% confidence intervals (Cov.) for the approximate and exact estimators of the logarithm of (6) (MLOR1) and the logarithm of (7) (leftmost) (MLOR2)

Exp.	E(Y)	ψ	Approx. MLOR 1				MLOR 1			
			Bias	ESE	SSE	Cov.	Bias	ESE	SSE	Cov.
a	0.1	0	-0.10	15.9	15.6	93.7	-0.30	15.7	15.6	94.9
	0.05	1	-0.31	9.82	9.79	93.6	-0.65	9.54	10.1	96.0
	0.1	1	-1.01	14.2	14.3	92.6	-1.52	14.0	15.0	95.2
	0.25	1	0.04	6.50	6.51	94.7	-0.16	6.31	6.52	95.6
	0.5	1	0.32	5.44	5.56	95.9	0.24	5.46	5.50	94.1
b	0.1	0	-0.49	15.5	15.9	94.1	-1.30	16.1	16.1	95.5
	0.05	1	-0.04	11.0	10.8	94.0	-0.58	10.7	12.0	96.4
	0.1	1	0.23	8.29	8.35	94.2	-0.24	7.89	8.90	96.3
	0.25	1	0.18	6.42	6.49	95.1	-0.06	6.12	6.52	96.1
	0.5	1	0.07	5.80	5.87	95.8	-0.04	5.70	5.80	95.5
			Approx. MLOR 2				MLOR 2			
			Bias	ESE	SSE	Cov.	Bias	ESE	SSE	Cov.
a	0.1	0	1.2	16.4	16.1	95.5	1.14	16.3	16.0	94.9
	0.05	1	1.57	20.6	20.2	95.6	1.04	19.4	23.9	94.8
	0.1	1	4.00	30.1	29.5	95.6	3.06	28.4	28.1	95.0
	0.25	1	0.24	12.7	12.7	95.1	0.00	12.0	14.0	95.7
	0.5	1	0.29	9.93	10.3	95.9	0.25	9.8	10.1	95.9
b	0.1	0	1.46	15.9	16.1	95.8	1.28	15.7	15.9	95.2
	0.05	1	3.74	28.4	28.7	96.4	2.97	26.3	26.7	95.3
	0.1	1	2.41	20.1	21.0	96.6	1.72	18.4	19.2	95.5
	0.25	1	1.24	14.2	15.1	96.5	0.80	12.8	13.9	96.0
	0.5	1	0.58	12.4	13.3	97.1	0.52	12.0	13.1	96.7

physician prefers nonselective NSAIDs (and likewise for the effect of nonselective NSAIDs). They are in stark contrast with the estimate obtained from an unadjusted logistic regression analysis: 1.12 (95% confidence interval 0.85–1.5).

5.2 Analysis of Randomized Cholesterol Reduction Trial with Noncompliance

We reanalyze the cholesterol reduction trial reported in Ten Have et al. (2003). Let Y be an indicator of treatment success (defined as a beneficial change in cholesterol), X be an indicator of using educational dietary home-based audio tapes (which equals 0 on the control arm) and Z be the experimental assignment to the use of educational dietary home-based audio tapes. The Wald estimator of the conditional causal odds ratio was found to be 1.37 (95% confidence interval 0.68–2.74, P 0.38), and analogous to the logistic structural mean model estimator, 1.31 (95% confidence interval 0.72–2.40, P 0.37). This expresses that in patients who used the audio tapes on the intervention arm, the odds of a beneficial reduction in cholesterol would have

been 1.31 times lower had they not received the intervention. The adjusted IV estimator was uninformative: 0.020 (95% confidence interval 0–10¹⁷¹, P 0.99). The marginal causal odds ratio (6) was estimated to be 1.28 (95% confidence interval 0.74–2.19, P 0.38). It expresses that, had all patients complied perfectly with their assigned treatment, the intention-to-treat analysis would have resulted in an odds ratio of 1.28. Since the exposure is dichotomous, the marginal causal odds ratio (7) is not of interest. Since subjects on the control arm have no access to the audio tapes, model (9) is only relevant for those who were assigned to the intervention arm (i.e., $Z = 1$); hence, this analysis does not rely on untestable assumptions regarding the absence of exposure effect modification by the instrumental variable.

5.3 Analysis of Randomized Blood Pressure Trial With Noncompliance

We reanalyze the blood pressure study reported in Vansteelandt and Goetghebeur (2003). Let Y be an indicator of successful blood pressure reduction, X mea-

TABLE 3

Bias ($\times 100$), empirical standard deviation ($\times 100$) (ESE), average sandwich standard error ($\times 100$) (ESE) and coverage of 95% confidence intervals (Cov.) for the logistic structural mean model estimator of the log conditional causal odds ratio (4), the approximate estimator of the logarithm of (6) (MLOR1) and the logarithm of (7) (leftmost) (MLOR2)

Exp.	E(Y)	ψ	Logistic SMM				MLOR 1				MLOR2			
			Bias	ESE	SSE	Cov.	Bias	ESE	SSE	Cov.	Bias	ESE	SSE	Cov.
a	0.1	0	1.62	20.1	19.6	95.6	-0.10	15.9	15.6	93.7	1.23	16.4	16.1	95.5
	0.05	1	5.31	33.0	32.2	96.2	-0.31	9.82	9.79	93.6	1.57	20.6	20.2	95.6
	0.1	1	2.71	23.6	23.0	95.6	-1.01	14.2	14.3	92.6	4.00	30.1	29.5	95.6
	0.25	1	1.24	15.8	15.7	95.3	0.04	6.50	6.51	94.7	0.24	12.7	12.7	95.1
	0.5	1	1.46	12.6	13.0	95.6	0.32	5.44	5.56	95.9	0.29	9.93	10.3	95.9
b	0.1	0	2.86	28.3	28.3	95.9	-0.49	15.5	15.9	94.1	1.46	15.9	16.1	95.8
	0.05	1	6.63	38.7	37.3	95.1	-0.04	11.0	10.8	94.0	3.74	28.4	28.7	96.4
	0.1	1	4.37	29.0	28.9	95.2	0.23	8.29	8.35	94.2	2.41	20.1	21.0	96.6
	0.25	1	2.76	22.1	22.2	95.8	0.18	6.42	6.49	95.1	1.24	14.2	15.1	96.5
	0.5	1	1.65	19.3	19.4	95.4	0.07	5.80	5.87	95.8	0.58	12.4	13.3	97.1
c	0.1	0	5.31	39.8	39.5	95.2	0.85	15.7	15.7	94.8	2.47	16.5	16.5	95.3
	0.05	1	12.2	58.0	56.2	93.1	1.30	17.4	17.0	91.0	7.10	36.4	36.4	93.2
	0.1	0	8.15	41.1	39.7	95.9	1.19	13.1	12.8	92.9	4.72	26.7	26.7	95.5
	0.25	1	3.50	26.9	25.2	95.1	0.35	9.24	8.69	93.9	1.62	17.2	16.8	95.6
	0.5	1	1.8	19.7	19.0	95.3	0.04	6.80	6.63	95.2	0.46	12.1	12.4	96.1
d	0.1	0	-1.03	28.6	28.5	94.0	0.31	21.3	20.6	92.9	2.31	21.6	21.4	97.0
	0.05	1	-1.09	40.0	34.1	87.7	-1.52	22.0	20.0	84.3	11.3	52.4	48.9	90.0
	0.1	0	1.16	33.5	31.6	88.2	0.17	14.9	14.8	90.9	6.78	36.2	35.0	93.5
	0.25	1	1.59	26.8	27.0	94.0	1.00	9.56	9.79	93.0	3.45	21.3	21.4	95.7
	0.5	1	-0.07	27.3	28.5	95.2	1.42	7.36	7.4	92.9	2.39	13.8	14.1	95.6
e	0.1	0	3.25	26.8	26.4	97.2	1.66	15.2	15.2	93.4	-0.73	15.1	15.1	93.9
	0.05	1	13.4	56.3	52.4	91.0	6.54	41.8	36.7	82.5	-1.93	13.3	11.5	85.2
	0.1	0	8.38	39.8	38.0	93.9	6.50	33.5	31.8	87.2	-0.38	11.1	10.7	83.6
	0.25	1	4.83	24.4	24.3	95.7	2.88	22.1	22.4	93.3	0.46	9.51	9.64	91.9
	0.5	1	4.18	17.1	17.4	96.0	-3.39	19.3	19.9	94.4	0.08	11.3	11.9	95.1

sure the percentage of assigned active dose which was actually taken (which equals 0 on the control arm) and Z be the experimental assignment to active treatment or placebo. The Wald and adjusted IV estimator of the conditional causal odds ratio were found to be identical, 4.29 (95% confidence interval 1.6–11.3, $P 0.0032$), and analogous to the logistic structural mean model estimator, 4.44 (95% confidence interval 1.6–12.6, $P 0.0049$). This expresses that in patients on the intervention arm with unit exposure per day, the odds of a beneficial reduction in diastolic blood pressure would have been 4.44 times lower had they not received the experimental treatment. The marginal causal odds ratio (6) was estimated to be 4.12 (95% confidence interval 1.6–10.3, $P 0.0025$). It expresses that, had all patients complied perfectly with their assigned treatment, the intention-to-treat analysis would have resulted in an odds ratio of 4.12.

TABLE 4

Observed data with X_i indicating received treatment [Cox-2 (1) versus nonselective NSAIDs (0)], Z_i indicating the physician's prescribing preference [Cox-2 (1) versus nonselective NSAIDs (0)], and Y_i indicating gastrointestinal (GI) bleeding (1) within 60 days of initiating an NSAID for subject i

	$Z_i = 0$		$Z_i = 1$	
	$Y_i = 0$	$Y_i = 1$	$Y_i = 0$	$Y_i = 1$
$X_i = 0$	5640	39	5722	34
$X_i = 1$	6740	60	19493	114

APPENDIX

A.1 Closed-Form Estimator

When X and Z are both dichotomous, taking values 0 and 1, the logistic structural mean model estimator is

obtainable in closed form as

$$\hat{\psi} = \log \left[\frac{-Q_1 \pm \sqrt{Q_1^2 - 4Q_2(Q_2 - \hat{X}_{11} + \hat{X}_{10})Q_3}}{2Q_2} \right], \quad (30)$$

where \hat{X}_{xz} is the percentage of subjects with $X = x$ among those with $Z = z$, and

$$\begin{aligned} Q_1 &= (Q_2 + \hat{X}_{10}) \exp(\hat{\beta}_0 + \hat{\beta}_1) \\ &\quad + (Q_2 - \hat{X}_{11}) \exp(\hat{\beta}_0 + \hat{\beta}_1 + \hat{\beta}_2 + \hat{\beta}_3), \\ Q_2 &= \text{expit}(\hat{\beta}_0) \hat{X}_{00} - \text{expit}(\hat{\beta}_0 + \hat{\beta}_2) \hat{X}_{01}, \\ Q_3 &= \exp(\hat{\beta}_0 + \hat{\beta}_1 + \hat{\beta}_2 + \hat{\beta}_3) \times \exp(\hat{\beta}_0 + \hat{\beta}_1). \end{aligned}$$

A.2 Standard Errors for Conditional Causal Log Odds Ratio Estimators

Suppose that X satisfies the conditional mean model

$$E(X|Z, C) = g(Z, C; \theta^*),$$

where $g(Z, C; \theta)$ is a known function, smooth in θ , and θ^* is an unknown finite-dimensional parameter; for example, $g(Z, C; \theta) = \theta_0 + \theta_1 Z + \theta_2 C$. With $R(\theta^*) \equiv X - g(Z, C; \theta^*)$, assume further that

$$\begin{aligned} \text{logit } E(Y|Z, C, R(\theta^*)) \\ = m_0(C, R(\theta^*); \omega^*) + m(C; \psi^*)g(Z, C; \theta^*), \end{aligned}$$

where $m_0(C, R(\theta^*); \omega)$ is a known function, smooth in ω , and ω^* is an unknown finite-dimensional parameter; for example, $m_0(C, R(\theta^*); \omega) = \omega_0 + \omega_1 C + \omega_2 R(\theta^*)$. Then the adjusted IV estimator is equivalently obtained by solving the multivariate score equation $\sum_{i=1}^n S_i(\xi) = 0$ for $\xi \equiv (\theta', \omega', \psi')'$ and taking the solution for ψ , where $S_i(\theta, \omega, \psi)$ equals

$$(31) \quad \begin{pmatrix} \frac{\partial g}{\partial \theta}(Z_i, C_i; \theta) \text{Var}^{-1}(X_i|Z_i, C_i) R_i(\theta) \\ \left(\begin{array}{c} \frac{\partial m_0}{\partial \omega}(C_i, R_i(\theta); \omega) \\ \frac{\partial m}{\partial \psi}(C_i; \psi)g(Z_i, C_i; \theta) \end{array} \right) \\ \cdot [Y_i - \text{expit}\{m_0(C_i, R_i(\theta); \omega) \\ \quad + m(C_i; \psi) \\ \quad \cdot g(Z_i, C_i; \theta)\}] \end{pmatrix}.$$

The asymptotic variance of the adjusted IV estimator can now be obtained from the “sandwich” expression

$$\frac{1}{n} E^{-1} \left(\frac{\partial S_i(\xi)}{\partial \xi} \right) \text{Var}\{S_i(\xi)\} E^{-1} \left(\frac{\partial S_i(\xi)}{\partial \xi} \right)^T.$$

The asymptotic variance of the standard IV estimator is similarly obtained upon redefining $m_0(C, R(\theta^*); \omega)$ to be a function of only C and ω . The asymptotic variance of the logistic SMM-estimator is obtained as in Vansteelandt and Goetghebeur (2003).

A.3 Theoretical Comparison of the Adjusted IV Estimator and the Logistic Structural Mean Model Estimator

To simplify the exposition, suppose that there are no covariates. Assume that X is normally distributed, conditional on Z . Let the adjusted IV estimator be based on the model

$$\text{logit } P(Y = 1|R, Z) = \omega_0 + \omega_1 R + \omega_2 E(X|Z),$$

and assume, for the purpose of comparability, that this is also the association model underlying the logistic structural mean model estimator [e.g., when $E(X|Z)$ is linear in Z , then this is equivalent with a standard logistic regression model with main effects in X and Z]. Under model (9), it then follows that

$$\begin{aligned} \text{logit } P(Y(0) = 1|X, Z) \\ = \omega_0 + (\omega_1 - \psi)R + (\omega_2 - \psi)E(X|Z). \end{aligned}$$

We will now demonstrate that the adjusted IV estimator $\hat{\omega}_2$ is a consistent estimator of the causal parameter ψ^* indexing the logistic structural mean model. We will do so by demonstrating that the estimating equations for the logistic structural mean model estimator $\hat{\psi}$ have mean zero at $\psi = \omega_2$.

Note that, at $\omega_2 = \psi$, $\text{logit } P(Y(0) = 1|X, Z) = \omega_0 + (\omega_1 - \psi)R$. A Taylor series expansion of the estimating function for ψ , that is,

$$[d(Z) - E\{d(Z)\}] \text{expit}[\omega_0 + (\omega_1 - \psi)\{X - E(X|Z)\}],$$

around $X = E(X|Z)$ then gives

$$\begin{aligned} \sum_{k=0}^{\infty} [d(Z) - E\{d(Z)\}]\{X - E(X|Z)\}^k \\ \cdot \text{expit}^{(k)}(\omega_0) \frac{(\omega_1 - \psi)^k}{k!}, \end{aligned}$$

where $\text{expit}^{(k)}(\omega_0)$ refers to the k th order derivative of $\text{expit}(\omega_0)$ w.r.t. ω_0 . When X is normally distributed, conditional on Z , with constant variance, then this is a mean zero equation because then $E[\{X - E(X|Z)\}^k | Z] = E[\{X - E(X|Z)\}^k]$ for all k . It thus follows that $\hat{\omega}_2$ is a consistent estimator of the causal parameter ψ^* . This result continues to hold for other distributions than the normal, which satisfy that for each k , either $E[\{X - E(X|Z)\}^k | Z] = E[\{X - E(X|Z)\}^k]$ or $\text{expit}^{(k)}(\omega_0) = 0$. For instance, when X is normally distributed, conditional on Z , with variance depending on Z and when, in addition, $\text{expit}(\omega_0) = 1/2$, then $\hat{\omega}_2$ stays a consistent estimator of the causal parameter ψ^* because $E[\{X - E(X|Z)\}^k | Z] = E[\{X - E(X|Z)\}^k]$ for all $k \neq 2$ and $\text{expit}^{(2)}(\omega_0) = \text{expit}(\omega_0)\{1 - \text{expit}(\omega_0)\}\{1 - 2 \text{expit}(\omega_0)\} = 0$.

A.4 Local Robustness

Suppose first that C_i is empty, $d(Z_i, C_i) = Z_i$ and $E\{d(Z_i, C_i)|C_i\} = \sum_{j=1}^n Z_j/n$. When $\psi^* = 0$, then equation (18) becomes $\sum_{i=1}^n (Z_i - \frac{\sum_{j=1}^n Z_j}{n}) \cdot \expit\{m(X_i, Z_i; \hat{\beta})\}$. Suppose now that the association model includes an intercept and main effect in Z_i , and that $\hat{\beta}$ is the standard maximum likelihood estimator of β^* . We then show that equation (18) equals $\sum_{i=1}^n (Z_i - \frac{\sum_{j=1}^n Z_j}{n}) Y_i$, which has mean zero at $\psi^* = 0$, even under model misspecification. That this equality is true follows because $\hat{\beta}$ satisfies the following score equations:

$$0 = \sum_{i=1}^n \begin{pmatrix} 1 \\ Z_i \end{pmatrix} [Y_i - \expit\{m(X_i, Z_i; \hat{\beta})\}]$$

from which $\sum_{i=1}^n Z_i Y_i = \sum_{i=1}^n Z_i \expit\{m(X_i, Z_i; \hat{\beta})\}$ and

$$\sum_{i=1}^n \frac{\sum_{j=1}^n Z_j}{n} Y_i = \sum_{i=1}^n \frac{\sum_{j=1}^n Z_j}{n} \expit\{m(X_i, Z_i; \hat{\beta})\}.$$

Extending this argument, it is seen that local robustness is attained whenever the association model includes an additive term in $d(Z_i, C_i) - E\{d(Z_i, C_i)|C_i\}$.

A.5 Uncongenial Models

It follows from the parameterization of Robins and Rotnitzky (2004) that, for each law $f(X|Z, C)$, the logistic structural mean model (8) is congenial with association models of the form

$$\begin{aligned} P(Y = 1|X, Z, C) \\ = \expit\{m(C; \psi^*)X + q(X, Z, C) + v(Z, C)\} \end{aligned}$$

for each function $q(X, Z, C)$ of (X, Z, C) satisfying $q(0, Z, C) = 0$ for all Z, C , each function $t(C)$ of C , and $v(Z, C)$ solving

$$\begin{aligned} t(C) = \int \expit\{q(X = x, Z, C) + v(Z, C)\} \\ \cdot f(X = x|Z, C) dx. \end{aligned}$$

It thus follows that, for each law $f(X|Z, C)$, the logistic structural mean model (8) is also congenial with association models of the form

$$\begin{aligned} (32) \quad P(Y = 1|X, Z, C) \\ = \expit\{m(C; \psi^*)X + q(X, Z, C) \\ + t^*(C) + v^*(Z, C)\} \end{aligned}$$

for each such function, each function $t^*(C)$ of C , and $v^*(Z, C)$ satisfying $v^*(0, C) = 0$ for all C and

$$\begin{aligned} (33) \quad & \int \expit\{q(X = x, 0, C) + t^*(C)\} \\ & \cdot f(X = x|Z = 0, C) dx \\ & = \int \expit\{q(X = x, Z, C) \\ & \quad + t^*(C) + v^*(Z, C)\} \\ & \cdot f(X = x|Z, C) dx \end{aligned}$$

for each Z . Indeed, this follows upon defining $t^*(C)$ as the solution to

$$\begin{aligned} t(C) = \int \expit\{q(X = x, 0, C) + t^*(C)\} \\ \cdot f(X = x|Z = 0, C) dx. \end{aligned}$$

It follows that a given association model is congenial with the logistic structural mean model (8) when no restrictions are imposed on the function $v^*(Z, C)$, which encodes the main effect of Z , along with interactions with C . The above derivation also suggests an easier strategy for fitting the model of Robins and Rotnitzky (2004), whereby the association model is of the form (32) and integral equations of the form (33) are solved.

Consider now the extended logistic SMM (27). Suppose that model (27) is congenial with the association model (16) for $x = 0$ in the sense that for the given β^* , there exists a value ψ_0^* such that

$$\int \expit\{m(X, Z, C; \beta^*) - m(C; \psi_0^*)X\} f(X|Z, C) dX$$

does not depend on Z . Then it does not necessarily follow that there exists a value ψ_x^* for given x such that

$$\begin{aligned} \int \expit\{m(X, Z, C; \beta^*) \\ - m(C; \psi_x^*)(X - x)\} f(X|Z, C) dX \end{aligned}$$

does not depend on Z . Model (27) being congenial with the association model (16) for $x = 0$ hence does not imply congeniality for all x .

A.6 Probit-Normal SMM Estimator

We explain how to derive $E(Y(0)|Z, C)$ under models (22) and (23). Note that

$$\begin{aligned} E\{Y(0)|Z, X, C\} \\ = P(U \leq \theta_0^* + \theta_1^* X + \theta_2^* Z + \theta_3^* C - \phi^* X), \end{aligned}$$

where U is a standard normally distributed variate, independent of (Z, X) . Averaging over the exposure, conditional on Z and C , then yields

$$\begin{aligned} E\{Y(0)|Z, C\} &= \int_{-\infty}^{\infty} P(U + (\phi^* - \theta_1^*)X \\ &\leq \theta_0^* + \theta_2^*Z + \theta_3^*C) dF(X|Z, C), \end{aligned}$$

where $F(X|Z, C)$ refers to the conditional distribution of X , given Z and C . Define $U^* = U + (\phi^* - \theta_1^*)X$. Then, for normally distributed X with mean $\alpha_0^* + \alpha_1^*Z + \alpha_2^*C$ and constant variance σ^{2*} , conditional on Z and C , U^* has a normal distribution with mean $(\phi^* - \theta_1^*)(\alpha_0 + \alpha_1 Z + \alpha_2^*C)$ and variance $1 + (\phi^* - \theta_1^*)^2\sigma^2$. Then

$$E\{Y(0)|Z, C\} = \int_{-\infty}^{\infty} \int_{-\infty}^{\theta_0^* + \theta_2^*Z + \theta_3^*C} dF(U^*, X|Z, C),$$

which is as given in (24). The conditional mean $E(Y|Z, C)$ can be derived using similar arguments.

A.7 Standard Errors for Marginal Causal Log Odds Ratio Estimators

Consider the marginal log odds ratio defined by

$$(34) \quad \eta = \log \frac{\mu_1(1 - \mu_0)}{\mu_0(1 - \mu_1)},$$

where $\mu_x = E[\text{expit}\{m(X, Z, C; \beta^*) + m(C; \psi_x^*)(x - X)\}]$ for $x = 0, 1$, and let the corresponding estimators be $\hat{\eta}$ and $\hat{\mu}_x$, $x = 0, 1$, respectively. Then a Taylor series expansion shows that

$$\begin{aligned} 0 &= \frac{1}{\sqrt{n}} \sum_{i=1}^n \text{expit}\{m(X_i, Z_i, C_i; \hat{\beta}) \\ &\quad + m(C_i; \hat{\psi}_x)(x - X_i)\} - \hat{\mu}_x \\ &= \frac{1}{\sqrt{n}} \sum_{i=1}^n \text{expit}\{m(X_i, Z_i, C_i; \beta) \\ &\quad + m(C_i; \psi_x)(x - X_i)\} - \mu_x \\ &\quad + \frac{1}{\sqrt{n}} \sum_{i=1}^n E \left[\frac{\partial}{\partial \theta_x} \text{expit}\{m(X_i, Z_i, C_i; \beta) \right. \\ &\quad \left. + m(C_i; \psi_x)(x - X_i)\} \right] \\ &\quad \cdot E^{-1} \left(\frac{\partial U_{ix}(\theta_x)}{\partial \theta_x} \right) U_{ix}(\theta_x) \\ &\quad - \sqrt{n}(\hat{\mu}_x - \mu_x), \end{aligned}$$

where $\theta_x \equiv (\beta^T, \psi_x^T)^T$ and $U_{ix}(\theta_x)$ is the vector of estimating functions for θ_x , from which the influence function for $\hat{\mu}_x$ is

$$\begin{aligned} &\text{expit}\{m(X_i, Z_i, C_i; \beta) + m(C_i; \psi_x)(x - X_i)\} - \mu_x \\ &\quad + \frac{1}{\sqrt{n}} \sum_{i=1}^n E \left[\frac{\partial}{\partial \theta_x} \text{expit}\{m(X_i, Z_i, C_i; \beta) \right. \\ &\quad \left. + m(C_i; \psi_x)(x - X_i)\} \right] \\ &\quad \cdot E^{-1} \left(\frac{\partial U_{ix}(\theta_x)}{\partial \theta_x} \right) U_{ix}(\theta_x). \end{aligned}$$

From the Delta method, it then follows that the influence function for $\hat{\eta}$ is

$$\begin{aligned} &\frac{1}{\mu_1(1 - \mu_1)} \\ &\quad \cdot \left[\text{expit}\{m(X_i, Z_i, C_i; \beta) \right. \\ &\quad \left. + m(C_i; \psi_1)(1 - X_i)\} - \mu_1 \right. \\ &\quad \left. + \frac{1}{\sqrt{n}} \sum_{i=1}^n E \left[\frac{\partial}{\partial \theta_1} \text{expit}\{m(X_i, Z_i, C_i; \beta) \right. \right. \\ &\quad \left. \left. + m(C_i; \psi_1)(1 - X_i)\} \right] \right. \\ &\quad \left. \cdot E^{-1} \left(\frac{\partial U_{i1}(\theta_1)}{\partial \theta_1} \right) U_{i1}(\theta_1) \right] \\ &\quad - \frac{1}{\mu_0(1 - \mu_0)} \\ &\quad \cdot \left[\text{expit}\{m(X_i, Z_i, C_i; \beta) \right. \\ &\quad \left. + m(C_i; \psi_0)(0 - X_i)\} - \mu_0 \right. \\ &\quad \left. + \frac{1}{\sqrt{n}} \sum_{i=1}^n E \left[\frac{\partial}{\partial \theta_0} \text{expit}\{m(X_i, Z_i, C_i; \beta) \right. \right. \\ &\quad \left. \left. + m(C_i; \psi_0)(0 - X_i)\} \right] \right. \\ &\quad \left. \cdot E^{-1} \left(\frac{\partial U_{i0}(\theta_0)}{\partial \theta_0} \right) U_{i0}(\theta_0) \right]. \end{aligned}$$

The asymptotic variance of $\hat{\eta}$ thus equals 1 over n times the variance of this influence function (where averages and variances can be replaced with sample analogs, and population values with consistent estimators).

Consider the marginal log odds ratio defined by (34) with the redefinitions

$$\mu_1 = E[\text{expit}\{m(X, Z, C; \beta^*) + m(C; \psi_{X+1}^*)\}]$$

and $\mu_0 = E(Y)$. Then using similar arguments as before, we obtain that the influence function for $\hat{\eta}$ is

$$\begin{aligned} & \frac{1}{\mu_1(1 - \mu_1)} \\ & \cdot \left[\text{expit}\{m(X_i, Z_i, C_i; \beta) \right. \\ & \quad \left. + m(C_i; \psi_{X_{i+1}})\} - \mu_1 \right. \\ & \quad \left. + \frac{1}{\sqrt{n}} \sum_{i=1}^n E \left[\frac{\partial}{\partial \theta_{X_{i+1}}} \text{expit}\{m(X_i, Z_i, C_i; \beta) \right. \right. \\ & \quad \quad \left. \left. + m(C_i; \psi_{X_{i+1}})\} \right] \right. \\ & \quad \left. \cdot E^{-1} \left(\frac{\partial U_{i, X_{i+1}}(\theta_{X_{i+1}})}{\partial \theta_{X_{i+1}}} \right) U_{i, X_{i+1}}(\theta_{X_{i+1}}) \right] \\ & - \frac{1}{\mu_0(1 - \mu_0)} [Y_i - \mu_0]. \end{aligned}$$

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