Article

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A Note on Formulae for Causal Mediation Analysis in an Odds Ratio Context

Abstract: In a recent article, VanderWeele and Vansteelandt (American Journal of Epidemiology, 2010, 172:1339–1348) (hereafter VWV) build on results due to Judea Pearl on causal mediation analysis and derive simple closed-form expressions for so-called natural direct and indirect effects in an odds ratio context for a binary outcome and a continuous mediator. The expressions obtained by VWV make two key simplifying assumptions:

- A. The mediator is normally distributed with constant variance.
- B. The binary outcome is rare.

Assumption A may not be appropriate in settings where, as can happen in routine epidemiologic applications, the distribution of the mediator variable is highly skew. However, in this commentary, the author establishes that under a key assumption of “no mediator–exposure interaction”, the simple formulae of VWV continue to hold even when assumption A is dropped. The author further shows that when the “no interaction” assumption is relaxed, the formula of VWV for the natural indirect effect continues to apply even if assumption A is also dropped. However, in this case, an alternative formula to that of VWV for the natural direct effect is derived without assumption A. When the binary outcome is not rare, simple closed-form formulae for odds ratio natural direct and indirect effects are obtained upon replacing assumptions A and B with a single alternative assumption C that the mediator follows a so-called “bridge distribution”. For a non-rare outcome, a more general approach entails estimating mediation effects on the risk ratio scale upon replacing the outcome logistic regression with a risk ratio regression model, in which case assumptions A–C are not needed.

Keywords: mediation analysis, causal inference, odds ratio, risk ratio, natural direct effect

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Recent advances in causal inference have provided a mathematical formalization of mediation analysis (Robins and Greenland 1992; Pearl 2001, 2011). Specifically, the counterfactual language of causal inference has allowed for new definitions of causal effects in the mediation context, accompanied by formal identification conditions, and corresponding nonparametric formulae for computing these new types of causal effects (Robins and Greenland 1992; Pearl 2001, 2011; van der Laan and Petersen 2005; Imai et al. 2010; VanderWeele and Vansteelandt 2010; Tchetgen Tchetgen and Shiptser 2012; Tchetgen Tchetgen 2011). In a recent manuscript, VanderWeele and Vansteelandt (2010) (hereafter VWV) build on results due to Judea Pearl (2001, 2011) on causal mediation analysis and derive simple closed-form expressions for so-called natural direct and indirect effects in an odds ratio context for a binary outcome and a continuous mediator.

As in VWV, we let A denote an exposure of interest, Y a dichotomous outcome, and M a potential mediator. We let C denote a set of baseline covariates not affected by the exposure. The relations among these variables are depicted in Figure 1.

Figure 1 Example of mediation with exposure A , mediator M , outcome Y , and confounder C

We assume that for each level $A = a$, $M = m$, there exist a potential outcome $Y_{a,m}$ corresponding to the outcome had possibly contrary to fact the exposure and mediator variables taken the value (a, m) and for $A = a$, there exist a counterfactual variable M_a corresponding to the mediator variable had possibly contrary to fact the exposure variable taken the value a . VWV then define the odds ratio natural direct and indirect

$$\text{OR}_{a,a^*|c}^{\text{NDE}}(a^*) = \frac{\Pr(Y_{aM_{a^*}} = 1|c) / \Pr(Y_{aM_{a^*}} = 0|c)}{\Pr(Y_{a^*M_{a^*}} = 1|c) / \Pr(Y_{a^*M_{a^*}} = 0|c)},$$

$$\text{OR}_{a,a^*|c}^{\text{NIE}}(a^*) = \frac{\Pr(Y_{a^*M_a} = 1|c) / \Pr(Y_{a^*M_a} = 0|c)}{\Pr(Y_{a^*M_{a^*}} = 1|c) / \Pr(Y_{a^*M_{a^*}} = 0|c)}.$$

As described by VWV, the conditional natural direct effect $\text{OR}_{a,a^*|c}^{\text{NDE}}(a^*)$ can be interpreted as comparing the odds, conditional on $C = c$, of the outcome Y if exposure had been a , but if the mediator had been fixed to M_{a^*} , to the odds, conditional on $C = c$, of the outcome Y if exposure had been a^* but if the mediator had been fixed at the same level M_{a^*} . The conditional natural indirect effect $\text{OR}_{a,a^*|c}^{\text{NIE}}(a^*)$ can be interpreted as comparing the odds, conditional on $C = c$, of the outcome Y if exposure had been a but if the mediator had been fixed to M_a , to the odds, conditional on $C = c$, of the outcome Y if exposure had been a but if the mediator had been fixed to M_{a^*} . Recall that the odds ratio total effect of A on Y conditional on $C = c$ is given by

$$\text{OR}_{a,a^*}^{\text{TE}} = \frac{\Pr(Y_a = 1|c) / \Pr(Y_a = 0|c)}{\Pr(Y_{a^*} = 1|c) / \Pr(Y_{a^*} = 0|c)}.$$

Then, it is straightforward to verify the odds ratio total effect decomposition

$$\text{OR}_{a,a^*}^{\text{TE}} = \text{OR}_{a,a^*|c}^{\text{NDE}}(a^*) \times \text{OR}_{a,a^*|c}^{\text{NIE}}(a^*).$$

Identification of natural direct and indirect effects requires additional assumptions. Throughout, we follow VWV and assume:

Consistency

if $A = a$, then $M_a = M$ w.p.1,
and if $A = a$ and $M = m$ then $Y_{a,m} = Y$ w.p.1.

In addition, we assume:

Ignorability

$$\begin{aligned} Y_{a,m} &\perp\!\!\!\perp A|C \\ Y_{a,m} &\perp\!\!\!\perp M|A, C \\ M_a &\perp\!\!\!\perp A|C \\ Y_{a,m} &\perp\!\!\!\perp M_{a^*}|C. \end{aligned}$$

The above ignorability assumption would generally hold under Pearl's nonparametric structural equations model (Pearl 2011), in which case, the assumption states that there is no unmeasured common cause of A and M , of A and Y , and of M and Y . In order to obtain closed-form expressions for natural direct and indirect effects, VWV also make two simplifying assumptions which are reproduced as follows:

A. The mediator is normally distributed with constant variance

B. The binary outcome is rare.

Assumption A may not always be appropriate in epidemiologic applications, for instance, if the distribution of the mediator is highly skew. In this note, the author shows that under an assumption of “no mediator–exposure odds-ratio interaction”, the simple formulae of VWV continue to hold even when the normality assumption of the mediator is dropped. The author further shows that when the “no interaction” assumption is relaxed, the formula of VWV for the natural indirect effect is still correct if assumption A is also dropped. However, an alternative formula to that of VWV for the natural direct effect is needed for this setting. When the outcome is not rare, the author presents some simple expressions for the odds ratio natural direct and indirect effects under an alternative assumption C to A and B, that the mediator follows a so-called bridge distribution (Wang and Louis 2003). Although the bridge distribution leads to simple expressions of direct and indirect effects even when the outcome is not rare, similar to the normality assumption A, the bridge distribution may not always be appropriate in epidemiologic applications. Thus, the author presents a more viable alternative, which entails using a recently proposed technique for direct risk ratio estimation for a binary outcome that may not be rare, for risk ratio mediation analysis free of assumptions A and B.

1 Relaxing the normality assumption

To proceed, consider the statistical models studied by VWV:

$$\text{logit Pr}(Y = 1|A = a, M = m, C = c) = \theta_0 + \theta_1 a + \theta_2 m + \theta'_4 c, \quad [1]$$

and

$$E[M|A = a, C = c] = \beta_0 + \beta_1 a + \beta'_2 c, \quad [2]$$

where, under eq. [2] the residual error $\Delta = (M - E[M|A, C])$ for the linear regression of M on (A, C) is normally distributed with constant variance. VWV show that under assumptions A and B, and models [1] and [2], the odds ratio natural direct and indirect effects are approximately:

$$\text{OR}_{a,a^*|c}^{\text{NDE}}(a^*) \approx \exp(\theta_1(a - a^*)), \quad [3]$$

$$\text{OR}_{a,a^*|c}^{\text{NIE}}(a^*) \approx \exp(\theta_2\beta_1(a - a^*)), \quad [4]$$

where the approximation holds to the extent the rare outcome assumption is valid. For a fixed value a^* , the total causal effect of A on Y within levels of C , comparing the odds of Y when $A = a$ versus when $A = a^*$

$$\text{OR}_{a,a^*}^{\text{TE}} = \frac{\text{Pr}(Y = 1|A = a, C = c) \text{Pr}(Y = 0|A = a^*, C = c)}{\text{Pr}(Y = 0|A = a, C = c) \text{Pr}(Y = 1|A = a^*, C = c)},$$

can be decomposed on the odds ratio scale into natural direct and indirect causal effects according to:

$$\begin{aligned} \text{OR}_{a,a^*}^{\text{TE}} &= \text{OR}_{a,a^*|c}^{\text{NDE}}(a^*) \times \text{OR}_{a,a^*|c}^{\text{NIE}}(a^*) \\ &\approx \exp((\theta_1 + \theta_2\beta_1)(a - a^*)). \end{aligned} \quad [5]$$

In the appendix, we show that formulae [3] and [4] and therefore, formula [5] continues to hold even if the normality assumption is replaced by the weaker assumption:

A'. The residual error Δ is independent of (A, C) , but its distribution is otherwise unrestricted.

Thus, by eliminating the requirement that the mediator is normally distributed, the result considerably broadens the range of settings where the formulae of VWV apply. In fact, the result states that eqs [3] and [4] continue to hold even when the mediator M is not normally distributed, provided that the regression model [2] completely captures the association between exposure and confounders, and the mediator, i.e. Δ does not further depend on (A, C) .

The above result relies on the absence of an exposure–mediator interaction in the logistic regression [1]. VWV also considered mediation analyses under a slightly more general regression:

$$\text{logit Pr}(Y = 1|A = a, M = m, C = c) = \theta_0 + \theta_1 a + \theta_2 m + \theta_3 ma + \theta'_4 c, \quad [6]$$

where θ_3 now encodes a possible interaction between the exposure and the mediator. Under assumptions A and B, and models [2] and [6], VWV show that

$$\text{OR}_{a,a^*|c}^{\text{NIE}}(a^*) \approx \exp\{(\theta_2 + \theta_3 a)\beta_1(a - a^*)\}.$$

In the appendix, we show that the formula in the above display continues to hold if assumption A is replaced by the weaker assumption A'. However, the formula for $\text{OR}_{a,a^*|c}^{\text{NDE}}(a^*)$ given in VWV under model [6] no longer applies if assumption A does not hold, even if assumption A' holds. The correct expression for $\text{OR}_{a,a^*|c}^{\text{NDE}}(a^*)$ is given under Assumption A' in the appendix. For inference, the standard error of estimators of $\text{OR}_{a,a^*|c}^{\text{NIE}}(a^*)$ and $\text{OR}_{a,a^*|c}^{\text{NDE}}(a^*)$ under the various modeling assumptions considered above can be obtained as in VWV by a straightforward application of the delta method, details are relegated to the appendix.

2 Relaxing the rare disease assumption

2.1 Odds ratio mediation analysis

In this section, simple expressions are obtained for the natural direct and indirect odds ratios $\text{OR}_{a,a^*|c}^{\text{NIE}}(a^*)$ and $\text{OR}_{a,a^*|c}^{\text{NDE}}(a^*)$, without assumption B of a rare outcome. The formulae are obtained upon replacing both assumptions A (or equivalently assumptions A') and B with a single alternative distributional assumption for the mediator density:

C. The conditional density of $[\Delta|A, C]$ follows a bridge distribution (more specifically the bridge distribution for the logit link) introduced by Wang and Louis (2003). The bridge distribution has the following density function:

$$f_{\Delta}[d|A = a, C = c] = \frac{\sin(\pi\phi)}{\cos(\pi\phi) + \cosh(\phi d)}; -\infty < d < \infty, 0 < \phi < 1,$$

$$\text{with } \cosh(x) = \frac{1}{\exp(x) + \exp(-x)}.$$

The bridge density is denoted $B_l(0, \phi)$, with the first argument indicating that it has mean zero, ϕ is a scaling parameter and the subscript l stands for logistic. The variance of $B_l(0, \phi)$ can be expressed in terms of ϕ :

$$\frac{\pi^2}{3}(\phi^{-2} - 1),$$

so that the variance of $B_l(0, \phi)$ approaches zero as ϕ approaches one. $B_l(0, \phi)$ is symmetric and unimodal similar to the Gaussian density (Wang and Louis 2003). However, when standardized to have unit variance, the bridge density can be shown to have slightly heavier tails than the standard normal and lighter tails than the standard logistic. Wang and Louis (2003) provide a detailed study of $B_l(0, \phi)$ and we refer the reader to their manuscript for additional information about this density. For the purposes of this note, the bridge distribution $B_l(0, \phi)$ is mainly of interest, because it produces simple formulae of natural direct and indirect effects on the odds ratios scale even if the outcome is not rare. As shown in the appendix, this follows from the bridge distribution being the unique covariate distribution for which logistic regression is collapsible. Specifically, marginalization of logistic regression with respect to a single covariate with a bridge distribution is again a logistic regression. For instance, consider the standard logistic regression model [1] of Y given (A, M, C) then under model [2] paired with assumption C, marginalizing over M gives a regression model of Y given (A, C) which is again a standard logistic regression:

$$\text{logit Pr}(Y = 1|A = a, C = c) = \gamma_0 + \gamma_1 a + \gamma'_4 c,$$

where

$$\gamma_1 = k(\theta_1 + \theta_2 \beta_1),$$

and

$$k = \{\theta_2^2(\phi^{-2} - 1) + 1\}^{-1/2},$$

Similar expressions relating γ_0 and γ_4 to $\theta_1, \theta_2, \theta_4$, and ϕ are provided in the appendix. A more general formulation of the above result is used in the appendix to establish that under models [1] and [2], and assumption C:

$$\text{OR}_{a, a^*|c}^{\text{NDE}}(a^*) = \exp(k\theta_1(a - a^*)), \quad [7]$$

$$\text{OR}_{a, a^*|c}^{\text{NIE}}(a^*) = \exp(k\theta_2\beta_1(a - a^*)), \quad [8]$$

Note the similarity between formulae [3] and [4], and formulae [7] and [8] where the factor k in the latter two expressions accounts for the outcome not being rare. Note however that, whereas eqs [3] and [4] are only approximate, formulae [7] and [8] are exact. Analogous expressions are derived in the appendix for model [6] which allows for a possible interaction between the mediator and the exposure, and details for obtaining inference are also provided in the appendix.

2.2 Risk ratio mediation analysis

Although assumption C of a bridge distribution for the mediator leads to the simple expressions of direct and indirect effects of the previous section, similar to the normality assumption, the bridge distribution may not always be appropriate in epidemiologic applications. As an alternative, one may wish to conduct mediation analyses on a risk ratio scale even when the outcome is not rare. It is straightforward to establish that the formulae previously obtained under assumption B that the disease is rare, essentially continue to hold when the disease is not rare, upon replacing the logit link function of eqs [1] and [6], with the log-link function. For estimation, a variety of methods exist to compute the risk ratio parameters of the log-linear regression of Y on (A, M, C) (Breslow 1974; Wacholder 1986; Lee 1994; Skov et al. 1998; Greenland 2004; Zou 2004; Spiegelman and Hertzmark 2005; Chu and Cole 2010; Tchetgen Tchetgen 2012). The recent two-stage estimator of risk ratio regression of Tchetgen Tchetgen (2012) is of particular interest because of its computational stability, ease of implementation, and asymptotic efficiency properties. For instance, the estimator of Tchetgen Tchetgen (2012) delivers asymptotically efficient estimates of the regression

coefficients $(\theta_1, \theta_2, \theta_3, \theta_4)$ in eq. [6] with the logit link replaced by the log link, without requiring an estimate of the intercept θ_0 , and therefore, it avoids the convergence issues of some other methods such as the log-binomial approach of Wacholder (1986). Estimation details may be found in Tchetgen Tchetgen (2012), and after obtaining these risk ratio estimates, one can subsequently compute the risk ratio natural direct and indirect effects using the formulae previously derived for $OR_{a, a^*|c}^{NDE}$ and $OR_{a, a^*|c}^{NIE}$, respectively, for the rare outcome case. However, we note that the expressions derived for the direct and indirect effects under a rare outcome approximation are now exact, irrespective of the prevalence of the outcome. An important advantage of conducting mediation analyses on the risk ratio scale as we have described is that when model mis-specification is absent, the resulting inferences are generally valid provided assumption A' holds, even if assumptions A–C do not hold.

3 Concluding remarks

In this note, the author has extended the results of VWV in a number of interesting directions, by providing weaker conditions under which their proposed estimators of natural direct and indirect effects remain valid, and by providing alternative distributional assumptions under which the assumption of a rare outcome can be dropped and yet simple formulae are still available for easy use in epidemiologic practice. However, it is important to note that as in VWV, the methods described herein rely on fairly strong modeling assumptions and can deliver possibly biased inferences in the presence of modeling error of either model [2] or model [6]. As a possible remedy, alternative so-called multiply robust estimators have recently been proposed, that deliver valid inferences about natural direct and indirect effects even when, a model for the joint conditional density of (Y, M, A) given C is partially mis-specified (Tchetgen Tchetgen and Shpitser 2011, 2012; Zheng and van der Laan 2012).

Appendix

Closed-form expressions for $OR_{a, a^*|c}^{NDE}(a^*)$ and $OR_{a, a^*|c}^{NIE}(a^*)$

Under the identifying consistency and ignorability assumptions, assumptions A' and B given in this article, and the parametric modeling assumptions [2] and [7], we have that

$$\begin{aligned} g(a, a^*, c) &= \int \Pr\{Y = 1|A = a, C = c, M = m\} f(m|A = a^*, C) dm \\ &\approx \int \exp(\theta_0 + \theta_1 a + \theta_2 m + \theta_3 m a + \theta'_4 c) f(m|A = a^*, C) dm \\ &= \exp(\theta_0 + \theta_1 a + \theta'_4 c) \int \exp(\theta_2 m + \theta_3 m a) f(m|A = a^*, C) dm \\ &= \exp(\theta_0 + \theta_1 a + \theta'_4 c) \int \exp((\theta_2 + \theta_3 a)m) f(m|A = a^*, C) dm \\ &= \exp(\theta_0 + \theta_1 a + \theta'_4 c) \mathcal{M}_{M|A=a^*, C=c}(\theta_2 + \theta_3 a) \end{aligned} \quad [9]$$

where $\mathcal{M}_{M|A=a^*, C=c}(\cdot)$ is the moment generating function of $[M|A = a^*, C = c]$ evaluated at $(\cdot)$. Note that under our assumptions,

$$\mathcal{M}_{M|A=a^*, C=c}(\theta_2 + \theta_3 a) = \exp\{(\theta_2 + \theta_3 a)(\beta_0 + \beta_1 a^* + \beta'_2 c)\} \mathcal{M}_\Delta(\theta_2 + \theta_3 a) \quad [10]$$

where $\mathcal{M}_\Delta(\cdot)$ is the moment generating function of $[\Delta|A = a^*, C = c]$ evaluated at $(\cdot)$. We conclude that by a result due to Pearl (2001, 2011) (also see VWV)

$$\begin{aligned}\text{OR}_{a,a^*|c}^{\text{NDE}}(a^*) &\approx \frac{g(a, a^*, c)}{g(a^*, a^*, c)} \\ &= \frac{\exp(\theta_0 + \theta_1 a + \theta'_4 c) \exp\{(\theta_2 + \theta_3 a)(\beta_0 + \beta_1 a^* + \beta'_2 c)\} \mathcal{M}_\Delta(\theta_2 + \theta_3 a)}{\exp(\theta_0 + \theta_1 a^* + \theta'_4 c) \exp\{(\theta_2 + \theta_3 a^*)(\beta_0 + \beta_1 a^* + \beta'_2 c)\} \mathcal{M}_\Delta(\theta_2 + \theta_3 a^*)} \\ &= \exp\left[\left\{\theta_1 + (\theta_3(\beta_0 + \beta_1 a^* + \beta'_2 c))\right\}(a - a^*)\right] \frac{\mathcal{M}_\Delta(\theta_2 + \theta_3 a)}{\mathcal{M}_\Delta(\theta_2 + \theta_3 a^*)}\end{aligned}$$

and

$$\begin{aligned}\text{OR}_{a,a^*|c}^{\text{NIE}}(a^*) &= \frac{g(a, a, c)}{g(a, a^*, c)} \\ &= \frac{\exp(\theta_0 + \theta_1 a + \theta'_4 c) \exp\{(\theta_2 + \theta_3 a)(\beta_0 + \beta_1 a + \beta'_2 c)\} \mathcal{M}_\Delta(\theta_2 + \theta_3 a)}{\exp(\theta_0 + \theta_1 a + \theta'_4 c) \exp\{(\theta_2 + \theta_3 a)(\beta_0 + \beta_1 a^* + \beta'_2 c)\} \mathcal{M}_\Delta(\theta_2 + \theta_3 a)} \\ &= \exp\{\beta_1(\theta_2 + \theta_3 a)(a - a^*)\}\end{aligned}$$

which reduces to the formulae provided in the text for the special case where $\theta_3 = 0$. For inference when $\theta_3 \neq 0$, estimation of $\text{OR}_{a,a^*|c}^{\text{NDE}}(a^*)$ requires an estimator of $\mathcal{M}_\Delta(\theta_2 + \theta_3 a)$ and $\mathcal{M}_\Delta(\theta_2 + \theta_3 a^*)$. To motivate a simple estimator of the latter quantity, note that under model [2] and assumption C:

$$\mathcal{M}_\Delta(\theta_2 + \theta_3 a) = \frac{E[\exp\{(\theta_2 + \theta_3 a)M\}]}{E[\exp\{(\theta_2 + \theta_3 a)(\beta_0 + \beta_1 A + \beta'_2 C)\}]}$$

since the numerator is equal to

$$E[\exp\{(\theta_2 + \theta_3 a)M\}] = E[\exp\{(\theta_2 + \theta_3 a)(\beta_0 + \beta_1 A + \beta'_2 C)\}] \mathcal{M}_\Delta((\theta_2 + \theta_3 a))$$

and thus, we similarly have that

$$\mathcal{M}_\Delta((\theta_2 + \theta_3 a^*)) = \frac{E[\exp\{(\theta_2 + \theta_3 a^*)M\}]}{E[\exp\{(\theta_2 + \theta_3 a^*)(\beta_0 + \beta_1 A + \beta'_2 C)\}]}$$

which gives

$$\begin{aligned}\text{OR}_{a,a^*|c}^{\text{NDE}}(a^*) &\approx \exp\left[\left\{\theta_1 + (\theta_3(\beta_0 + \beta_1 a^* + \beta'_2 c))\right\}(a - a^*)\right] \frac{E[\exp\{(\theta_2 + \theta_3 a)M\}]E[\exp\{(\theta_2 + \theta_3 a^*)(\beta_0 + \beta_1 A + \beta'_2 C)\}]}{E[\exp\{(\theta_2 + \theta_3 a)(\beta_0 + \beta_1 A + \beta'_2 C)\}]E[\exp\{(\theta_2 + \theta_3 a^*)M\}]}\end{aligned}$$

We conclude that $\mathcal{M}_\Delta((\theta_2 + \theta_3 a))$ and $\mathcal{M}_\Delta((\theta_2 + \theta_3 a^*))$, and therefore, $\text{OR}_{a,a^*|c}^{\text{NDE}}(a^*)$ is consistently estimated upon substituting empirical averages for unknown marginal expectations and consistent estimates for unknown parameters in the equation in the above display. Note that consistent estimation of $\theta = (\theta_0, \theta_1, \theta_2, \theta_3, \theta'_4)'$ and $\beta = (\beta_0, \beta_1, \beta'_2)'$ are readily obtained by standard logistic regression maximum likelihood which gives $\hat{\theta}$ and ordinary least-squares which gives $\hat{\beta}$ respectively.

The variance–covariance matrix of the resulting estimator $\log(\widehat{\text{OR}}_{a,a^*|c}^{\text{NIE}}(a^*))$ of $\log(\text{OR}_{a,a^*|c}^{\text{NIE}}(a^*))$ is obtained using a straightforward application of the delta method and details can be found in VWV. The variance–covariance matrix of $\log(\widehat{\text{OR}}_{a,a^*|c}^{\text{NDE}}(a^*))$ is similarly obtained under the “no interaction” assumption. However, more generally when $\theta_3 \neq 0$, requires derivations not included in VWV. To proceed, let $\text{IF}_{\theta,\beta}$ denote the influence function of $(\widehat{\theta}, \widehat{\beta})$. Let

$$\begin{aligned}\Phi_1(\beta, \theta) &= \{\theta_1 + (\theta_3(\beta_0 + \beta_1 a^* + \beta'_2 C))\}(a - a^*), \\ \Phi_2(\beta, \theta) &= \log E[\exp\{(\theta_2 + \theta_3 a)M\}] \\ \Phi_3(\beta, \theta) &= \log E[\exp\{(\theta_2 + \theta_3 a)(\beta_0 + \beta_1 A + \beta'_2 C)\}] \\ \Phi_4(\beta, \theta) &= \log E[\exp\{(\theta_2 + \theta_3 a^*)M\}] \\ \Phi_5(\beta, \theta) &= \log E[\exp\{(\theta_2 + \theta_3 a^*)(\beta_0 + \beta_1 A + \beta'_2 C)\}]\end{aligned}$$

Then one can show that the influence function of $[\Phi_1(\beta, \theta), \Phi_2(\beta, \theta), \Phi_3(\beta, \theta), \Phi_4(\beta, \theta), \Phi_5(\beta, \theta)]'$ is given by

$$\text{IF}_{\Phi} = [\text{IF}_{\Phi_1}, \text{IF}_{\Phi_2}, \text{IF}_{\Phi_3}, \text{IF}_{\Phi_4}, \text{IF}_{\Phi_5}]'$$

where:

$$\text{IF}_{\Phi_k} = G_1 \text{IF}_{\theta, \beta}$$

with

$$\begin{aligned}G_1 &= [0, (a - a^*), 0, (\beta_0 + \beta_1 a^* + \beta'_2 C)(a - a^*), 0', \\ &\quad \theta_3(a - a^*), \theta_3 a^*(a - a^*), \theta_3 C'(a - a^*)], \\ \text{IF}_{\Phi_2} &= E[\exp\{(\theta_2 + \theta_3 a)M\}]^{-1} U_{\Phi_2}\end{aligned}$$

with

$$\begin{aligned}U_{\Phi_2} &= \exp\{(\theta_2 + \theta_3 a)M\} - E \exp\{(\theta_2 + \theta_3 a)M\} \\ &\quad + [0, 0, E[M \exp\{(\theta_2 + \theta_3 a)M\}], aE[M \exp\{(\theta_2 + \theta_3 a)M\}], 0, 0, 0, 0] \text{IF}_{\theta, \beta}\end{aligned}$$

and

$$\text{IF}_{\Phi_3} = E[\exp\{(\theta_2 + \theta_3 a)(\beta_0 + \beta_1 A + \beta'_2 C)\}]^{-1} U_{\Phi_3}$$

with

$$\begin{aligned}U_{\Phi_3} &= \exp\{(\theta_2 + \theta_3 a)(\beta_0 + \beta_1 A + \beta'_2 C)\} - E[\exp\{(\theta_2 + \theta_3 a)(\beta_0 + \beta_1 A + \beta'_2 C)\}] \\ &\quad + [0, 0, E[(\beta_0 + \beta_1 A + \beta'_2 C) \exp\{(\theta_2 + \theta_3 a)(\beta_0 + \beta_1 A + \beta'_2 C)\}], 0, \\ &\quad E[a(\beta_0 + \beta_1 A + \beta'_2 C) \exp\{(\theta_2 + \theta_3 a)(\beta_0 + \beta_1 A + \beta'_2 C)\}], 0, \\ &\quad E[(\theta_2 + \theta_3 a) \exp\{(\theta_2 + \theta_3 a)(\beta_0 + \beta_1 A + \beta'_2 C)\}], \\ &\quad E[A(\theta_2 + \theta_3 a) \exp\{(\theta_2 + \theta_3 a)(\beta_0 + \beta_1 A + \beta'_2 C)\}], \\ &\quad E[(\theta_2 + \theta_3 a)C' \exp\{(\theta_2 + \theta_3 a)(\beta_0 + \beta_1 A + \beta'_2 C)\}]] \times \text{IF}_{\theta, \beta}\end{aligned}$$

and

$$\begin{aligned}U_{\Phi_4} &= \exp\{(\theta_2 + \theta_3 a^*)M\} - E \exp\{(\theta_2 + \theta_3 a^*)M\} \\ &\quad + [0, 0, E[M \exp\{(\theta_2 + \theta_3 a^*)M\}], a^*E[M \exp\{(\theta_2 + \theta_3 a^*)M\}], 0, 0, 0, 0] \text{IF}_{\theta, \beta}\end{aligned}$$

and

$$\text{IF}_{\Phi_5} = E[\exp\{(\theta_2 + \theta_3 a^*)(\beta_0 + \beta_1 A + \beta'_2 C)\}]^{-1} U_{\Phi_5}$$

with

$$\begin{aligned} U_{\Phi_5} = & \exp\{(\theta_2 + \theta_3 a^*)(\beta_0 + \beta_1 A + \beta'_2 C)\} - E[\exp\{(\theta_2 + \theta_3 a^*)(\beta_0 + \beta_1 A + \beta'_2 C)\}] \\ & + [0, 0, E[(\beta_0 + \beta_1 A + \beta'_2 C) \exp\{(\theta_2 + \theta_3 a^*)(\beta_0 + \beta_1 A + \beta'_2 C)\}], \\ & E[a^*(\beta_0 + \beta_1 A + \beta'_2 C) \exp\{(\theta_2 + \theta_3 a^*)(\beta_0 + \beta_1 A + \beta'_2 C)\}], 0, \\ & E[(\theta_2 + \theta_3 a^*) \exp\{(\theta_2 + \theta_3 a^*)(\beta_0 + \beta_1 A + \beta'_2 C)\}], \\ & E[A(\theta_2 + \theta_3 a^*) \exp\{(\theta_2 + \theta_3 a^*)(\beta_0 + \beta_1 A + \beta'_2 C)\}], \\ & E[(\theta_2 + \theta_3 a^*)C' \exp\{(\theta_2 + \theta_3 a^*)(\beta_0 + \beta_1 A + \beta'_2 C)\}]] \times \text{IF}_{\theta, \beta} \end{aligned}$$

Thus, the large sample variance of $\log(\widehat{\text{OR}}_{a, a^*|c}^{\text{NDE}}(a^*))$ is approximately given by

$$n^{-1}[1, 1, -1, -1, 1]E(\text{IF}_{\Phi}\text{IF}_{\Phi}^T)[1, 1, -1, -1, 1]'$$

A consistent estimator of the above quantity is obtained by substituting empirical expectations for all unknown expectations and consistent estimators of unknown parameters. The above construction requires the influence function $\text{IF}_{\theta, \beta}$ for standard logistic regression and ordinary least squares estimation, which is

$$\begin{pmatrix} E(X_1 X_1^T)^{-1} X_1 \varepsilon \\ E(X_2 X_2^T)^{-1} X_2 \Delta \end{pmatrix}$$

with $X_1 = [1, A, M, AM, C']'$, $X_2 = [1, A, C']'$, and $\varepsilon = Y - \Pr(Y = 1|A, M, C)$.

Closed-form expressions for $\text{OR}_{a, a^*|c}^{\text{NDE}}(a^*)$ and $\text{OR}_{a, a^*|c}^{\text{NIE}}(a^*)$ under a Bridge distribution

Consider the logistic regression model

$$\text{logit } \Pr(Y = 1|A = a, M = m, C = c) = \theta_0 + \theta_1 a + \theta_2 m + \theta_3 ma + \theta'_4 c$$

where

$$M = \beta_0 + \beta_1 A + \beta'_2 C + \Delta$$

and

$$\Delta|A, C] \sim B_l(0, \phi)$$

Note that

$$\begin{aligned} g(a, a^*, c) &= \int \Pr(Y = 1|A = a, M = m, C = c) f(m|a^*, c) \\ &= \int \expit\{\theta_0 + \theta_1 a + (\theta_2 + \theta_3 a)(\beta_0 + \beta_1 a^* + \beta'_2 c) + (\theta_2 + \theta_3 a)\Delta + \theta'_4 c\} f(\Delta) d\Delta \\ &= \int \expit\{\theta_0 + \theta_1 a + (\theta_2 + \theta_3 a)(\beta_0 + \beta_1 a^* + \beta'_2 c) + \tilde{\Delta} + \theta'_4 c\} f(\tilde{\Delta}) d\tilde{\Delta} \end{aligned}$$

where $\expit(\logit(x)) = 1, f(\tilde{\Delta})$ is a bridge density with rescaling parameter

$$\tilde{\phi}(a) = \tilde{\phi}(a; \theta_2, \theta_3, \phi) = \left\{ (\theta_2 + \theta_3 a)^2 (\phi^{-2} - 1) + 1 \right\}^{-1/2}.$$

Then, by Wang and Louis (2003):

$$g(a, a^*, c) = \text{expit} \left(\tilde{\phi}(a) \{ \theta_0 + \theta_1 a + (\theta_2 + \theta_3 a) (\beta_0 + \beta_1 a^* + \beta'_2 c) + \theta'_4 c \} \right)$$

is a standard logistic regression, and therefore,

$$\begin{aligned} \text{OR}_{a, a^* | c}^{\text{NDE}}(a^*) &= \frac{\exp \left(\tilde{\phi}(a) \{ \theta_0 + \theta_1 a + (\theta_2 + \theta_3 a) (\beta_0 + \beta_1 a^* + \beta'_2 c) + \theta'_4 c \} \right)}{\exp \left(\tilde{\phi}(a^*) \{ \theta_0 + \theta_1 a^* + (\theta_2 + \theta_3 a^*) (\beta_0 + \beta_1 a^* + \beta'_2 c) + \theta'_4 c \} \right)} \\ \text{OR}_{a, a^* | c}^{\text{NIE}}(a^*) &= \frac{\exp \left(\tilde{\phi}(a) \{ \theta_0 + \theta_1 a + (\theta_2 + \theta_3 a) (\beta_0 + \beta_1 a + \beta'_2 c) + \theta'_4 c \} \right)}{\exp \left(\tilde{\phi}(a) \{ \theta_0 + \theta_1 a + (\theta_2 + \theta_3 a) (\beta_0 + \beta_1 a^* + \beta'_2 c) + \theta'_4 c \} \right)} \\ &= \exp \left(\beta_1 (\theta_2 + \theta_3 a) \tilde{\phi}(a) (a - a^*) \right) \end{aligned}$$

under “no interaction”, i.e. $\theta_3 = 0$, we have

$$\begin{aligned} \text{OR}_{a, a^* | c}^{\text{NDE}}(a^*) &= \exp \left(\{ \theta_2^2 (\phi^{-2} - 1) + 1 \} \theta_1 (a - a^*) \right) \\ &= \exp(k \theta_1 (a - a^*)) \\ \text{OR}_{a, a^* | c}^{\text{NIE}}(a^*) &= \exp(k \beta_1 \theta_2 (a - a^*)) \end{aligned}$$

A consistent estimator $\hat{\phi}$ of ϕ is obtained by the method of moment upon noting that $\phi = \phi(\alpha) = \text{expit}(\alpha)$ solves the population equation:

$$E\{U_\alpha(\alpha; \beta)\} = 0$$

where $U_\alpha(\alpha; \beta) = \Delta(\beta)^2 - \frac{\pi^2}{3} ([\text{expit}(\alpha)]^{-2} - 1)$. It can then be shown that the influence function of $(\hat{\theta}, \hat{\beta}, \hat{\alpha})$ is given by $\text{IF}_{\theta, \beta, \alpha}$

$$\text{IF}_{\theta, \beta, \alpha} = \begin{pmatrix} E(X_1 X_1^T)^{-1} X_1 \varepsilon \\ E(X_2 X_2^T)^{-1} X_2 \Delta \\ E\left(\frac{\partial U_\alpha(\phi; \beta)}{\partial \phi}\right)^{-1} U_\alpha(\alpha; \beta) \end{pmatrix}$$

Let $\widehat{\text{OR}}_{a, a^* | c}^{\text{NDE}}(a^*)$ and $\widehat{\text{OR}}_{a, a^* | c}^{\text{NIE}}(a^*)$ denote the estimators of $\text{OR}_{a, a^* | c}^{\text{NDE}}(a^*)$ and $\text{OR}_{a, a^* | c}^{\text{NIE}}(a^*)$, respectively, obtained upon substituting $(\hat{\theta}, \hat{\beta}, \hat{\phi})$ for (θ, β, ϕ) . The large sample variances of $\widehat{\text{OR}}_{a, a^* | c}^{\text{NDE}}(a^*)$ and $\widehat{\text{OR}}_{a, a^* | c}^{\text{NIE}}(a^*)$ are then obtained by a straightforward application of the delta method, mainly:

$$\text{var} \left(\widehat{\text{OR}}_{a, a^* | c}^{\text{NDE}}(a^*) \right) \approx n^{-1} H_1' E \left(\text{IF}_{\theta, \beta, \alpha} \text{IF}_{\theta, \beta, \alpha}' \right) H_1$$

where

$$H_1 = \frac{\partial}{\partial(\theta', \beta', \alpha)'} \left\{ \begin{aligned} &\tilde{\phi}(a; \theta_2, \theta_3, \phi(\alpha)) \{ \theta_0 + \theta_1 a + (\theta_2 + \theta_3 a) (\beta_0 + \beta_1 a^* + \beta'_2 c) + \theta'_4 c \} \\ &- \tilde{\phi}(a^*; \theta_2, \theta_3, \phi(\alpha)) \{ \theta_0 + \theta_1 a^* + (\theta_2 + \theta_3 a^*) (\beta_0 + \beta_1 a^* + \beta'_2 c) + \theta'_4 c \} \end{aligned} \right\}$$

and

$$\text{var}\left(\widehat{\text{OR}}_{a,a^*|c}^{\text{NIE}}(a^*)\right) \approx n^{-1}H_2'E\left(\text{IF}_{\theta,\beta,\alpha}\text{IF}'_{\theta,\beta,\alpha}\right)H_2$$

where

$$H_2 = \frac{\partial}{\partial(\theta', \beta', \alpha')} \left\{ \beta_1(\theta_2 + \theta_3 a) \tilde{\phi}(a; \theta_2, \theta_3, \phi(a))(a - a^*) \right\}$$

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