

# Online Appendix

## Multiplicative direct effects with error prone mediator

In this section, we consider effect decomposition of a multiplicative total effect:

$$\begin{aligned} TE_m(e, e^*, c) &= \mathbb{E}\{Y(e)|c\} / \mathbb{E}\{Y(e^*)|c\} \\ &= \frac{\mathbb{E}\{Y(e, M(e))|c\}}{\mathbb{E}\{Y(e, M(e^*))|c\}} \times \frac{\mathbb{E}\{Y(e, M(e^*))|c\}}{\mathbb{E}\{Y(e, M(e^*))|c\}} \\ &= NIE_m(e, e^*, c) \times NDE_m(e, e^*, c) \end{aligned}$$

in the context of a mismeasured mediator  $M_\epsilon$ . Under the NPSEM assumptions,  $NDE_m(e, e^*, c)$  is obtained by evaluating Pearl's mediation formula:

$$NDE_m(e, e^*, c) = \frac{\mathbb{E}(\mathbb{E}(Y|e, M, c)|e^*, c)}{\mathbb{E}(\mathbb{E}(Y|e^*, M, c)|e^*, c)}$$

For estimation, suppose that model (9) of the text holds, and that the residual  $\varepsilon_M = M - \mathbb{E}(M|E, C)$  is independent of  $(E, C)$ . Furthermore, assume the following log-linear outcome regression:

$$\log \mathbb{E}(Y|e, m, c_1) = \tilde{\alpha}_0 + \tilde{\alpha}_1 e + \tilde{\alpha}_2 m + \tilde{\alpha}_3^T c_1 \tag{OA.1}$$

where we make the simplifying assumption on no  $E$ - $M$  interaction.

Then, taking  $e^* = 0$ , one can show that<sup>20</sup>:

$$\log NDE_m(1, 0, c) = \tilde{\alpha}_1.$$

VanderWeele and Vansteelandt<sup>1</sup> derived the expression above in the case that  $Y$  is binary under the additional assumption that  $\varepsilon_M$  is normally distributed, but as shown by Tchetgen Tchetgen<sup>2</sup> the expression equally applies without the normality assumption, provided that as it is assumed above, the residual error  $\varepsilon_M = M - \mathbb{E}(M|E, C)$  is independent of  $(E, C)$ . Under models (9) and (OA.1), we propose to estimate  $\tilde{\alpha}_1$ , and thus  $NDE_m(1, 0, c)$  using the mismeasured mediator  $M_\epsilon$ , by implementing the following two-stage approach:

Stage 1: Using data  $(E_i, C_i, M_{\epsilon,i})$ ,  $i = 1, \dots, n$ , compute the OLS estimate of model (9) and compute the corresponding predicted values

$$\widehat{M}_i = \widehat{\eta}_0 + \widehat{\eta}_1 E_i + \widehat{\eta}_2^T C_i$$

$i = 1, \dots, n$ .

Stage 2: Compute  $\widehat{\alpha} = (\widehat{\alpha}_0, \widehat{\alpha}_1, \widehat{\alpha}_2, \widehat{\alpha}_3)$  the regression coefficients of  $Y_i$  regressed on  $(E_i, \widehat{M}_i, C_{1,i})$  using a log-link, under the working model for the mean of  $Y_i$ :

$$\exp(\widetilde{\alpha}_0 + \widetilde{\alpha}_1 E_i + \widetilde{\alpha}_2 \widehat{M}_i + \widetilde{\alpha}_3^T C_{1,i})$$

$\widehat{\alpha}_1$  is the two-stage estimator of  $NDE_m(1, 0, c)$

Below, we prove the following result:

*Result 3: Suppose the NPSEM (1) – (4) holds, and assume (9) and (OA.1) both hold. Then, we have that the two-stage estimator  $\widehat{\alpha}_1$  is consistent for  $NDE_m(1, 0, c)$ .*

The above result states that under the proposed NPSEM, with regression models (9) and (OA.1), it is possible to consistently estimate the multiplicative natural direct effect using the above two-stage approach, even if the mediator is measured with additive nondifferential error. It is

important to note that the result does not make any strong distributional assumption about either the distribution of the mediator, or that of the measurement error, and therefore, the approach applies quite generally. Thus, the above result effectively generalizes the previous results for additive natural direct effects with a mis-measured mediator to the multiplicative scale, however, in contrast with the additive setting, the result for the multiplicative scale does rely on the assumption that the mediator regression (9) is correct. If  $Y$  is binary and the outcome is rare, the second stage regression amounts to estimation of risk ratio parameters using as covariates  $(E_i, \widehat{M}_i, C_{1,i})$  which can be done by standard logistic regression. If the outcome is not rare, logistic regression fails to approximate risk ratio regression, but a number of methods have been proposed for risk ratio estimation in this context.<sup>3–11</sup> The recent estimator of risk ratio regression of Tchetgen Tchetgen<sup>12</sup> is of particular interest because of its computational stability, ease of implementation and asymptotic efficiency properties. For instance, the estimator of Tchetgen Tchetgen<sup>12</sup> delivers asymptotically efficient estimates of the regression coefficients  $(\tilde{\alpha}_1, \tilde{\alpha}_2, \tilde{\alpha}_3)$ , without requiring an estimate of the intercept  $\tilde{\alpha}_0$ . Therefore, by allowing the intercept to remain unrestricted, the approach avoids the convergence issues of other methods such as the log-binomial approach of Wacholder.<sup>3</sup> Upon obtaining an estimate of the direct effect, the indirect effect can be obtained by first estimating the total conditional effect of  $E$  under a multiplicative model such as:

$$\log \mathbb{E}(Y|e, c) = \omega_0 + \omega_1 e + \omega_3^T c$$

using one of the methods mentioned above; and by subsequently using the following expression of the indirect effect:<sup>2</sup>

$$NIE_m(1, 0, c) = \exp(\omega_1 - \tilde{\alpha}_1).$$

Finally, we should note that we have assumed above no  $E - M$  interaction in the outcome regression model (OA.1), and therefore the approach described in this section would not necessarily apply if this assumption were not to hold and an alternative approach would be needed to simultaneously account for measurement error and to incorporate the  $E - M$  interaction.

**Proof of Result 3:** Assuming that the first stage regression of  $M$  is correctly specified, we have that  $\widehat{M}_i$  is consistent for  $\mathbb{E}(M|E_i, C_i)$ , and therefore, the second stage regression estimate  $\widehat{\tilde{\alpha}}$  obtained say, using standard generalized linear models software, converges in probability to the solution  $\tilde{\alpha}^*$  of the population equation:

$$0 = \mathbb{E} \left\{ \begin{array}{l} (1, E, \mathbb{E}(M|E, C), C_1^T)^T \\ \times (Y - \exp(\tilde{\alpha}_0^* + \tilde{\alpha}_1^* E_i + \tilde{\alpha}_2^* \mathbb{E}(M|E, C) + \tilde{\alpha}_3^{*T} C_{1,i})) \end{array} \right\} \quad (\text{OA.2})$$

Note that provided  $\varepsilon_M$  admits a moment generating function such that

$$\mathbb{E}(\exp(tM) | E, C) = \exp(t\mathbb{E}(M|E, C))g(t),$$

where  $g(t)$  is the moment generating function of  $\varepsilon_M$  evaluated at  $t$ , we have that

$$\begin{aligned} & \mathbb{E}(\exp(\tilde{\alpha}_0 + \tilde{\alpha}_1 E_i + \tilde{\alpha}_2 M_i + \tilde{\alpha}_3^T C_{1,i}) | E_i, C_i) \\ &= \exp([\tilde{\alpha}_0 + \log(g(\tilde{\alpha}_2))] + \tilde{\alpha}_1 E_i + \tilde{\alpha}_2 \mathbb{E}(M|E_i, C_i) + \tilde{\alpha}_3^T C_{1,i}) \end{aligned}$$

which implies that  $\tilde{\alpha}_0^* = [\tilde{\alpha}_0 + \log(g(\tilde{\alpha}_2))]$ ,  $\tilde{\alpha}_1^* = \tilde{\alpha}_1$ ,  $\tilde{\alpha}_3^* = \tilde{\alpha}_3$  solves the population equation (OA.2). A sufficient condition for consistency of  $\widehat{\tilde{\alpha}}$  to  $\tilde{\alpha}^*$  is then that the matrix function  $\mathbb{E}[WW^T \exp(\tilde{\alpha}^T W)]$  is invertible which is ensured by the assumption that  $C_2$  is a valid instrumental variable.

Var( $\widehat{\alpha}$ ): The large sample behavior of  $\widehat{\alpha}$  is given by the following Taylor based approximation:

$$\begin{aligned}\widehat{\alpha} - \tilde{\alpha} &\approx n^{-1} \sum_i U_{6,i} \\ U_{6,i} &= \mathbb{E} \left( X_{3,i} X_{3,i}^T \exp(\tilde{\alpha}^T X_{3,i}) \right)^{-1} \\ &\quad \times \left\{ X_{3,i} (Y_i - \exp(\tilde{\alpha}^T X_{3,i})) \right. \\ &\quad \left. - \tilde{\alpha}_2 \mathbb{E} [X_{3,i} X_{1,i}^T \exp(\tilde{\alpha}^T X_{3,i})] U_{1,i} \right\}\end{aligned}$$

where  $U_{1,i}$  is defined in the Appendix of the paper. Thus, The variance-covariance matrix of  $\widehat{\alpha}$  is approximately given by  $n^{-1} \mathbb{E} (U_6 U_6^T)$ . An estimator of this matrix is obtained upon substituting all unknown parameters by the corresponding estimates, and by replacing population expectations with empirical expectations.

## References

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