Supplementary Methods File

Christian A. Maino Vieytes, May A. Baydoun

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1 Four-Way Decomposition Models

1.1 *Background*

Let Y denote the response, A the exposure (in this case hospital-treated infections (binary–none/non-hospital treated infection or hospital treated infection), a its realized value (in the binary exposure case it is "1" or "0"), M the mediator (individual plasma proteomic marker levels or principal component scores), m its realized value, and $\boldsymbol{c}$ the vector of confounders. Under the assumption of no confounding, namely:

$$\text{i. } Y_{am} \coprod A|C$$

$$\text{ii. } Y_{am} \coprod M|(A,C)$$

$$\text{iii. } M_a \coprod A|C$$

$$\text{iv. } Y_{am} \coprod A*|C$$

that the effect of A on Y is unconfounded conditional on C (i), that the effect of M on Y is unconfounded conditional on (A,C), (ii), the effect of A on M is unconfounded conditional on C (iii), and that any mediator outcome confounders are not affected by the exposure (iv), we can partition the sources of total effect of the model into four components (Equation 1).[1]

$$TE = CDE + INT_{ref} + INT_{med} + PIE \tag{1}$$

and using notation (in the case of both binary exposure and meditator variables):

$$Y_1 - Y_0 = (Y_{10} - Y_{00}) + (Y_{11} - Y_{10} - Y_{01} + Y_{00})(M_0)$$
$$+(Y_{11} - Y_{10} - Y_{01} + Y_{00})(M_1 - M_0) + (Y_{01} - Y_{00})(M_1 - M_0)$$

We interpret this model to reflect that the total effect of the exposure, A, on the outcome, Y, is a sum of the *controlled direct effect* (CDE–i.e., the effect of A on Y not due to any interaction or mediation $[Y_{10} - Y_{00}]$), *the reference interaction* (INT_{ref}–i.e., the effect of interaction only $[(Y_{11} - Y_{10} - Y_{01} + Y_{00})(M_0)]$), *the mediated interaction* (INT_{med}–i.e., the effect of interaction and mediation $[Y_{00})(M_0) + (Y_{11} - Y_{10} - Y_{01} + Y_{00})(M_1 - M_0)]$), and *the purely indirect effect* (PIE–i.e., the indirect effect only $[(Y_{01} - Y_{00})(M_1 - M_0)]$). In lay terms, we conceptialize these components in the following manner[1]:

- *controlled direct effect*: the effect of the exposure on the outcome without the presence of the mediator.
- *the reference interaction*: the exposure affects the outcome in the presence of the mediator and the presence of the exposure is not required for the presence of the mediator.
- *the mediated interaction*: the exposure affects the outcome in the presence of the mediator and the presence of the exposure is required for the presence of the mediator.
- *the purely indirect effect*: also called the "mediated main effect" and reflects that the mediator causes the outcome in the absence of the exposure but the exposure is required for the mediator to become present.

Additional details on the four-way decomposition model are provided in an original publication that we refer the readers to.[1]

1.2 *Two-Way Decomposition*

Similarly, notation for a two-way decomposition can be formulated, which decomposes the total effect into a *pure direct effect (PDE)* and *total indirect effect (TIE)*. This is simply done by summing the *controlled direct effect* and the *reference interaction* to yield the *PDE* and summing the *mediated interaction* and *PIE* to yield the *TIE*:

$$TE = (CDE + INT_{ref}) + (INT_{med} + PIE) \tag{1.01}$$

$$TE = PDE + TIE \tag{1.02}$$

and using notation we have:

$$Y_1 - Y_0 = (Y_{1M_0} - Y_{0M_0}) + (Y_{1M_1} - Y_{1M_0}) \tag{1.03}$$

In this case, the interaction is picked up by the TIE whereas PDE does not, and the notation can be interpreted as the average difference in the outcome when the exposure is present (subscript "1") and the mediator is set to the level it would have been had the exposure been present (M_1) versus had it been set to the level when the exposure was not present (M_0)[2].

1.3 *Four-Way Decomposition: Implementation*

The process of estimating the components of the partitioned model in Equation 1 requires the fitting of two regression models and then using the parameter estimates for the final computation of the components. A robust summary of the *med4way* command in Stata is described elsewhere and we refer the reviewers to that commentary though we provide a succinct summary of the implementation and estimation of the effects.[3] Under the assumption of no unmeasured confounding (as detailed above in **1.1**) we can estimate, on average, the four components of the model on a population but not the individual-level effects. The two regression models required are provided and include a model for the expectation Y conditioned on the exposure, mediator, and confounders (Equation 2) and a model for the expectation of M conditioned on the exposure and confounders (Equation 3):

$$\mathrm{E}[Y|(a, m, \boldsymbol{c})] = \theta_0 + \theta_1 a + \theta_2 m + \theta_3 a * m + \boldsymbol{\theta}_c c \tag{2}$$

$$\mathrm{E}[M|(a, \boldsymbol{c})] = \beta_0 + \beta_1 a + \boldsymbol{\beta}_c^T \boldsymbol{c} \tag{3}$$

Estimates of these parameters therefore facilitate the direct computation of estimates of the four component sources of variation for the total effect (TE):

$$\mathrm{E}[CDE|c] = \theta_1(a - a')$$

$$\mathrm{E}[INT_{ref}|c] = \theta_3(\beta_0 + \beta_1 a' + \boldsymbol{\beta}_c^T \boldsymbol{c})(a - a')$$

$$\mathrm{E}[INT_{med}|c] = \theta_3\beta_1(a - a')(a - a')$$

$$\mathrm{E}[PIE|c] = (\theta_2\beta_1 + \theta_3\beta_1 a')(a - a')$$

where $a = 1$ and $a' = 0$ if the exposure is binary (as it is in this case).[4] The models we describe are generalizable and *Med4way* can handle outcome variables from several distributions (e.g., binomial, log-binomial, Poisson, negative binomial, Weibull, Cox, etc.).[3] In our analysis, $\mathrm{E}[Y|(a, m, c)]$ and $\mathrm{E}[M|(a, c)]$ are specified as follows:

$$\lambda(t|x, v, \boldsymbol{z}) = \lambda_0(t) + \theta_1 x + \theta_2 v + \theta_3 x * v + \boldsymbol{\theta}_z^T \boldsymbol{z} \tag{4}$$

$$\mathrm{E}[V|(x, \boldsymbol{z})] = \beta_0 + \beta_1 x + \boldsymbol{\beta}_z^T \boldsymbol{z} \tag{5}$$

where, in Equation 4, we model the log hazard at time t as a function of x, hospital-treated infection, v, an individual proteomic biomarker or a principal component score, and $\boldsymbol{z}$, the vector of confounders/covariates discussed in the manuscript. In Equation 5, we model the expectation of the mediator, V, as a function of hospital-treated infection and the other covariates using ordinary least squares.

References

1. VanderWeele, T. J. A unification of mediation and interaction: a four-way decomposition. *Epidemiology (Cambridge, Mass.)* **25,** 749 (2014).
2. VanderWeele, T. J. A three-way decomposition of a total effect into direct, indirect, and interactive effects. *Epidemiology (Cambridge, Mass.)* **24,** 224 (2013).
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4. VanderWeele, T. J. & Tchetgen Tchetgen, E. J. Mediation analysis with time varying exposures and mediators. *Journal of the Royal Statistical Society Series B: Statistical Methodology* **79,** 917–938 (2017).