R package *regmedint*: extension of regression-based causal mediation analysis with effect measure modification by covariates

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Funding:

The research was supported by the Shore/Brigham and Women's Hospital Department of Medicine Fellowship Award to KY. KY received additional support from the Rheumatology Research Foundation K Bridge Award and National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) K23 AR076453.

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Overview of this document

This is the supplementary document of the R package `regmedint` (<https://cran.r-project.org/web/packages/regmedint/index.html>), providing additional technical details for the causal mediation analysis method implemented in the package. The document covers the following topics:

1. Definition and identification of causal quantities of interest
2. Parametric models implemented in `regmedint`
3. Closed-form point estimate and standard deviation formulas

Section 1 reviews the basic concepts, notations and assumptions in the literature. Section 2 gives the model specifications of mediator and outcome models. These models extend the ones in the original regression-based causal mediation literature (Valeri & VanderWeele, 2013; T. VanderWeele, 2015), including effect measure modification by covariates in mediator and outcome models. Section 3 gives the extended mathematical formulas for point estimate and standard error.

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1 Brief description of causal mediation analysis

The literature on causal mediation analysis is vast (T. VanderWeele, 2015). Thus, only the pieces relevant for the current software are reviewed here. This section discusses the decompositions of total treatment effect, controlled effect, natural effect, and identification assumptions.

1.1 Decomposition of total effect

Let Y be the outcome variable of interest, A be the treatment variable of interest, M be the mediator variable of interest, and $\mathbf{C}$ be a vector of the covariates that need to be adjusted. The treatment contrast of interest is a vs a^* , where a^* is the baseline/reference level. The potential outcome $Y_{a,m}$ is the value of Y for an individual when, possibly contrary to the fact, if the treatment level is a and mediator level is m .

The total effect (TE), the causal effect of moving the treatment level from the reference level a^* to the level of interest a , is defined as follows at the covariate level $\mathbf{C} = \mathbf{c}$:

$$TE = E[Y_a | \mathbf{C} = \mathbf{c}] - E[Y_{a^*} | \mathbf{C} = \mathbf{c}]$$

The conditional direct effect ($CDE(m)$), the effect of moving the treatment level from the reference level a^* to the level of interest a while fixing the mediator at m is the following at the covariate level $\mathbf{C} = \mathbf{c}$:

$$CDE(m) = E[Y_{a,m} | \mathbf{C} = \mathbf{c}] - E[Y_{a^*,m} | \mathbf{C} = \mathbf{c}]$$

TE can be decomposed into direct effect and indirect effect in two different ways (Robins & Greenland, 1992), although the sum of pure natural direct effect (PNDE) and total natural indirect effect (TNIE) is the more usual way of decomposition (Pearl, 2001). Note that the treatment value indexing the mediator M is fixed at a^* in the PNDE, whereas the treatment value indexing the outcome Y is fixed at a in the TNIE. These are emphasized with $\sim$.

$$PNDE = E[Y_{a, \widetilde{M_{a^*}}} | \mathbf{C} = \mathbf{c}] - E[Y_{a^*, \widetilde{M_{a^*}}} | \mathbf{C} = \mathbf{c}]$$

$$TNIE = E[Y_{a, M_a} | \mathbf{C} = \mathbf{c}] - E[Y_{a, M_{a^*}} | \mathbf{C} = \mathbf{c}]$$

The other decomposition of TE is the sum of pure natural indirect effect (PNIE) and total natural direct effect (TNDE) (Robins & Greenland, 1992). Note that the treatment value indexing the mediator M is fixed at a in the TNDE, whereas the treatment value indexing the outcome Y is fixed at a^* in the PNIE. These are emphasized with $\sim$ throughout the document.

$$TNDE = E[Y_{a, \widetilde{M_a}} | \mathbf{C} = \mathbf{c}] - E[Y_{a^*, \widetilde{M_a}} | \mathbf{C} = \mathbf{c}]$$

$$PNIE = E[Y_{\widetilde{a^*}, M_a} | \mathbf{C} = \mathbf{c}] - E[Y_{\widetilde{a^*}, M_{a^*}} | \mathbf{C} = \mathbf{c}]$$

More intuitively, the subtle difference between two decompositions is in the cross-world counterfactual state (the subscripts in the definition of natural direct and indirect effects). In natural direct effects, the treatment levels moves from a^* to a , and the mediator level is fixed. In PNDE, the mediator level is fixed to the natural level that it would be if treatment level is the reference level (a^*), while in TNDE, the mediator level is fixed to the natural level that it would be if treatment level is the level of interest (a). In natural indirect effects, the treatment level is fixed, and the mediator level changes. In TNIE, the treatment level is fixed to the level of interest (a), while in PNIE, the treatment level is fixed to the reference level (a^*).

In either case, the effect that has the component of $Y_{a^*} = Y_{a^*, M_{a^*}}$ is the pure effect (PNDE and PNIE) and the effect that has the component of $Y_a = Y_{a, M_a}$ is the total natural effect (TNDE and TNIE). See (T. J. VanderWeele, 2013, 2014) for the meaning of these two decompositions in terms of causal interaction.

1.2 Identification of natural effects

Several conditional exchangeabilities must be assumed for identification of effects in the causal mediation framework. See (T. VanderWeele, 2015) (p463) for details.

- A1.** $Y_{a,m} \perp\!\!\!\perp A | \mathbf{C}$
- A2.** $Y_{a,m} \perp\!\!\!\perp M | \{A, \mathbf{C}\}$
- A3.** $M_a \perp\!\!\!\perp A | \mathbf{C}$
- A4.** $Y_{a,m} \perp\!\!\!\perp M_{a^*} | \mathbf{C}$

The controlled direct effect (CDE) can be identified with only A1 and A2. The identification of natural effects (PNDE, TNIE, TNDE, PNIE) require all four assumptions.

Given these four assumptions, the mean counterfactual with different treatment values indexing the outcome Y and the mediator M can be identified as follows. For simlicity, we assume M is categorical. For a continuous M , $\sum$ is replaced with $\int$, and $P(M = m)$ is replaced with $dF(M)$.

$$\begin{aligned}
E[Y_{a,M_{a^*}} | \mathbf{C} = \mathbf{c}] &= E[E(Y_{a,M_{a^*}} | M_{a^*}, \mathbf{C} = \mathbf{c}) | \mathbf{C} = \mathbf{c}] && \text{(Law of iterative expectation)} \\
&= \sum_m E[Y_{a,M_{a^*}} | M_{a^*} = m, \mathbf{C} = \mathbf{c}] P(M_{a^*} = m | \mathbf{C} = \mathbf{c}) \\
&= \sum_m E[Y_{a,m} | M_{a^*} = m, \mathbf{C} = \mathbf{c}] P(M_{a^*} = m | \mathbf{C} = \mathbf{c}) && (M_{a^*} = m) \\
&= \sum_m E[Y_{a,m} | \mathbf{C} = \mathbf{c}] P(M_{a^*} = m | \mathbf{C} = \mathbf{c}) && (\text{A4. } Y_{a,m} \perp\!\!\!\perp M_{a^*} | \mathbf{C}) \\
&= \sum_m E[Y_{a,m} | \mathbf{C} = \mathbf{c}] P(M_{a^*} = m | A, \mathbf{C} = \mathbf{c}) && (\text{A3. } M_a \perp\!\!\!\perp A | \mathbf{C}) \\
&= \sum_m E[Y_{a,m} | \mathbf{C} = \mathbf{c}] P(M_{a^*} = m | A = a^*, \mathbf{C} = \mathbf{c}) && (\text{Any given } A \text{ is equivalent, use stratum } a^*) \\
&= \sum_m E[Y_{a,m} | \mathbf{C} = \mathbf{c}] P(M = m | A = a^*, \mathbf{C} = \mathbf{c}) && (\text{Consistency for } M) \\
&= \sum_m E[Y_{a,m} | A, \mathbf{C} = \mathbf{c}] P(M = m | A = a^*, \mathbf{C} = \mathbf{c}) && (\text{A1. } Y_{a,m} \perp\!\!\!\perp A | \mathbf{C}) \\
&= \sum_m E[Y_{a,m} | A = a, \mathbf{C} = \mathbf{c}] P(M = m | A = a^*, \mathbf{C} = \mathbf{c}) && (\text{Any given } A \text{ is equivalent, use stratum } a) \\
&= \sum_m E[Y_{a,m} | A = a, M, \mathbf{C} = \mathbf{c}] P(M = m | A = a^*, \mathbf{C} = \mathbf{c}) && (\text{A3. } Y_{a,m} \perp\!\!\!\perp M | \{A, \mathbf{C}\}) \\
&= \sum_m E[Y_{a,m} | A = a, M = m, \mathbf{C} = \mathbf{c}] P(M = m | A = a^*, \mathbf{C} = \mathbf{c}) && (\text{Any given } M \text{ is equivalent, use stratum } m) \\
&= \sum_m E[Y | A = a, M = m, \mathbf{C} = \mathbf{c}] P(M = m | A = a^*, \mathbf{C} = \mathbf{c}) && (\text{Consistency for } Y) \\
&= E[E(Y | A = a, M, \mathbf{C} = \mathbf{c}) | A = a^*, \mathbf{C} = \mathbf{c}]
\end{aligned}$$

The resulting short-hand identification formula for the counterfactual expectation is the following:

$$E[Y_{a,M_{a^*}} | \mathbf{c}] = E[E(Y | a, M, \mathbf{c}) | a^*, \mathbf{c}]$$

Similarly, we obtain expressions for the other three potential outcomes:

$$E[Y_{a,M_a} | \mathbf{C} = \mathbf{c}] = E[E(Y | a, M, \mathbf{c}) | a, \mathbf{c}]$$

$$E[Y_{a^*,M_{a^*}} | \mathbf{C} = \mathbf{c}] = E[E(Y | a^*, M, \mathbf{c}) | a^*, \mathbf{c}]$$

$$E[Y_{a,M_{a^*}} | \mathbf{C} = \mathbf{c}] = E[E(Y | a, M, \mathbf{c}) | a^*, \mathbf{c}]$$

2 Implementation of the regression-based causal mediation analysis method

In this section, we describe the model specifications implemented in `regmedint`, which are the extensions of Valeri and VanderWeele’s original model specifications when there is effect measure modification (EMM) by covariates. We use the notation convention in (T. VanderWeele, 2015; Valeri & VanderWeele, 2013, 2015).

2.1 Mediator and outcome model specifications

Two models are involved in the identification of natural effects: the outcome model $E[Y|A = a, M = m, \mathbf{C} = \mathbf{c}]$ and the mediator model $P(M|A = a, \mathbf{C} = \mathbf{c})$. The identification formulas do not specify any particular model structure (non-parametric). In the method described in (T. VanderWeele, 2015; Valeri & VanderWeele, 2013, 2015), a simple parametric model is proposed for each.

The mediator model with a link function g_M is parametrized as follows.

$$g_M(E[M|A = a, \mathbf{C} = \mathbf{c}]) = \beta_0 + \beta_1 a + \beta_2^T \mathbf{c} + \beta_3^T a \mathbf{c}.$$

The outcome model with a link function g_Y is parametrized as follows.

$$g_Y(E[Y|A = a, M = m, \mathbf{C} = \mathbf{c}]) = \theta_0 + \theta_1 a + \theta_2 m + \theta_3 a m + \theta_4^T \mathbf{c} + \theta_5^T a \mathbf{c} + \theta_6^T m \mathbf{c}.$$

Since $\mathbf{c}$ is a vector, β_2 , β_3 , θ_4 , θ_5 , θ_6 are vectors as well.

Under these parametric modeling assumptions, each effect of interest can be written as a function of the parameters (coefficients) of the the mediator model (β and sometimes σ^2) and the outcome model (θ).

Note: the non-linear g_Y can accommodate logistic, log-linear, Poisson, negative binomial, accelerated failure time (AFT), and Cox models. It is just that the scale of effect estimates varies by the link function. The following table shows the scale of the effect estimates under each type of outcome model (Valeri & VanderWeele, 2013, 2015).

Outcome model	Scale
Logistic	Odds ratio
Log-linear	Risk ratio
Poisson/negative binomial	Rate ratio
Accelerated failure time	Mean survival ratio
Cox’s proportional hazards	Hazard ratio

2.2 Proportion mediated

Proportion mediated (PM) is defined as follows.

For linear outcome model:

$$PM = \frac{TNIE}{PNDE + TNIE}$$

For non-linear outcome model:

$$PM = \frac{\exp(PNDE) \cdot [\exp(TNIE) - 1]}{\exp(PNDE) \cdot \exp(TNIE) - 1}$$

Please note that when PNDE and TNIE are in opposite directions, PM may be outside the range of $[0, 1]$ and is therefore not interpretable.

2.3 Standard errors via multivariate delta method

We can obtain the standard error of each effect estimate using the variance-covariance matrix for the coefficients and multivariate delta method (Ver Hoef, 2012).

Let the scalar quantity of interest be Q , a function of parameter vector $(\beta^T, \theta^T)^T$. Then, its gradient (vector of partial derivatives) with respect to the parameter vector $(\beta^T, \theta^T)^T$ is the following.

$$\nabla Q = \frac{\partial Q}{\partial(\beta^T, \theta^T)^T} = \begin{bmatrix} \frac{\partial Q}{\partial \beta_0} \\ \frac{\partial Q}{\partial \beta_1} \\ \frac{\partial Q}{\partial \beta_2} \\ \frac{\partial Q}{\partial \beta_3} \\ \frac{\partial Q}{\partial \theta_0} \\ \frac{\partial Q}{\partial \theta_1} \\ \frac{\partial Q}{\partial \theta_2} \\ \frac{\partial Q}{\partial \theta_3} \\ \frac{\partial Q}{\partial \theta_4} \\ \frac{\partial Q}{\partial \theta_5} \\ \frac{\partial Q}{\partial \theta_6} \end{bmatrix}$$

In the case of a linear mediator model and a non-linear outcome model, there is an additional element $\frac{\partial Q}{\partial \sigma^2}$ at the bottom of the gradient vector.

By the large sample approximation using the multivariate delta method, the variance of the quantity of interest evaluated at the MLEs $(\hat{\beta}^T, \hat{\theta}^T)^T$ is the following.

$$\underbrace{Var \left[Q \left\{ (\hat{\beta}^T, \hat{\theta}^T)^T \right\} \right]}_{\text{scalar}} \approx \underbrace{\left[\nabla Q \left((\hat{\beta}^T, \hat{\theta}^T)^T \right) \right]^T}_{\text{row vector}} \underbrace{Var((\hat{\beta}^T, \hat{\theta}^T)^T)}_{\text{matrix}} \underbrace{\left[\nabla Q \left((\hat{\beta}^T, \hat{\theta}^T)^T \right) \right]}_{\text{column vector}}$$

This expression is abbreviated as $\Gamma \Sigma \Gamma'$ in (T. VanderWeele, 2015; Valeri & VanderWeele, 2013, 2015). In these references, the treatment contrast $(a - a^*)$ is factored out from $\nabla Q \left((\hat{\beta}^T, \hat{\theta}^T)^T \right)$ when possible. In the following, we define Γ as a column vector to be consistent with the implementation of `regmedint`, thus, the corresponding expression appears as $\Gamma^T \Sigma \Gamma$.

$\Gamma_{PNDE}, \Gamma_{TNIE}, \Gamma_{TNDE}, \Gamma_{PNIE}$ can be calculated by straightforward partial derivatives with respect to $(\beta^T, \theta^T)^T$. Γ_{TE} and Γ_{PM} can be calculated by $\frac{\partial TE}{\partial(\beta^T, \theta^T)^T}$ and $\frac{\partial PM}{\partial(\beta^T, \theta^T)^T}$, where

$$\frac{\partial TE}{\partial(\beta^T, \theta^T)^T} = \frac{\partial(PNDE + TNIE)}{\partial(\beta^T, \theta^T)^T} = \frac{\partial PNDE}{\partial(\beta^T, \theta^T)^T} + \frac{\partial TNIE}{\partial(\beta^T, \theta^T)^T}$$

$$\frac{\partial PM}{\partial(\beta^T, \theta^T)^T} = \frac{\partial PM}{\partial PNDE} \frac{\partial PNDE}{\partial(\beta^T, \theta^T)^T} + \frac{\partial PM}{\partial TNIE} \frac{\partial TNIE}{\partial(\beta^T, \theta^T)^T}$$

$$\Sigma = \begin{bmatrix} \Sigma_{\beta} & 0 \\ 0 & \Sigma_{\theta} \end{bmatrix}$$

More calculation details are given in Section 3.

3 Estimation formulas for four model types

In this section, we give formulas for CDE(m), PNDE, TNIE, TNDE, PNIE, TE, PM. Proofs and derivations are included.

Please note that to be succinct in presenting the formulas, in this whole section, we only consider the case where there is only one covariate in the covariate vector $\mathbf{C}$. Therefore β_2^T , β_3^T , θ_4^T , θ_5^T and θ_6^T are all scalars, so we omit the transpose symbols. In `regmedint` implementation, a vector of covariates are supported, and in the source code of `regmedint` package, there are EMM terms, the vectors β_3 , θ_4 , θ_5 and θ_6 have the same length with the length of vector $\mathbf{C}$, where we pad non-effect modifiers with 0. We can assure that readers do not need to worry about these coding details.

3.1 Linear mediator model, linear outcome model

The function `calc_myreg_mreg_linear_yreg_linear_est()` implements the effect formulas.

3.1.1 Point estimate

$$\begin{aligned} E[M | a, c] &= \beta_0 + \beta_1 a + \beta_2 c + \beta_3 ac \\ E[Y | a, m, c] &= \theta_0 + \theta_1 a + \theta_2 m + \theta_3 am + \theta_4 c + \theta_5 ac + \theta_6 mc \end{aligned}$$

$$CDE(m) = (\theta_1 + \theta_3 m + \theta_5 c)(a - a^*) \quad (1)$$

$$\begin{aligned} PNDE &= E[Y_{a, M^{a^*}} - Y_{a^*, M^{a^*}} | c] \\ &= E[E(Y | a, M, c) - E(Y | a^*, M, c) | a^*, c] \\ &= E[E(Y | a, M, c) | a^*, c] - E[E(Y | a^*, M, c) | a^*, c] \\ &= E[(\theta_0 + \theta_1 a + \theta_2 M + \theta_3 aM + \theta_4 c + \theta_5 ac + \theta_6 Mc) | a^*, c] \\ &\quad - E[(\theta_0 + \theta_1 a^* + \theta_2 M + \theta_3 a^* M + \theta_4 c + \theta_5 a^* c + \theta_6 Mc) | a^*, c] \\ &= \theta_1(a - a^*) + \theta_3 \cdot E(M | a^*, c)(a - a^*) + \theta_5 c(a - a^*) \\ &= (a - a^*)[\theta_1 + \theta_3(\beta_0 + \beta_1 a^* + \beta_2 c + \beta_3 a^* c) + \theta_5 c] \end{aligned} \quad (2)$$

$$\begin{aligned} TNDE &= E[Y_{a, M^a} - Y_{a^*, M^a} | c] \\ &= E[E(Y | a, M, c) - E(Y | a^*, M, c) | a, c] \\ &= E[E(Y | a, M, c) | a, c] - E[E(Y | a^*, M, c) | a, c] \\ &= E[(\theta_0 + \theta_1 a + \theta_2 M + \theta_3 aM + \theta_4 c + \theta_5 ac + \theta_6 Mc) | a, c] \\ &\quad - E[(\theta_0 + \theta_1 a^* + \theta_2 M + \theta_3 a^* M + \theta_4 c + \theta_5 a^* c + \theta_6 Mc) | a, c] \\ &= \theta_1(a - a^*) + \theta_3 \cdot E(M | a, c)(a - a^*) + \theta_5 c(a - a^*) \\ &= (a - a^*)[\theta_1 + \theta_3(\beta_0 + \beta_1 a + \beta_2 c + \beta_3 ac) + \theta_5 c] \end{aligned} \quad (3)$$

$$\begin{aligned} TNIE &= E[Y_{a, M^a} - Y_{a, M^{a^*}} | c] \\ &= E[E(Y | a, M, c) | a, c] - E[E(Y | a, M, c) | a^*, c] \\ &= E[(\theta_0 + \theta_1 a + \theta_2 M + \theta_3 aM + \theta_4 c + \theta_5 ac + \theta_6 Mc) | a, c] \\ &\quad - E[(\theta_0 + \theta_1 a + \theta_2 M + \theta_3 aM + \theta_4 c + \theta_5 ac + \theta_6 Mc) | a^*, c] \\ &= (\theta_0 + \theta_1 a + \theta_4 c + \theta_5 ac) + E[(\theta_2 M + \theta_3 aM + \theta_6 Mc) | a, c] \\ &\quad - (\theta_0 + \theta_1 a + \theta_4 c + \theta_5 ac) - E[(\theta_2 M + \theta_3 aM + \theta_6 Mc) | a^*, c] \\ &= (\theta_2 + \theta_3 a + \theta_6 c) \cdot [E(M | a, c) - E(M | a^*, c)] \end{aligned}$$

$$\begin{aligned}
&= (\theta_2 + \theta_3 a + \theta_6 c)[(\beta_0 + \beta_1 a + \beta_2 c + \beta_3 a c) - (\beta_0 + \beta_1 a^* + \beta_2 c + \beta_3 a^* c)] \\
&= (\theta_2 + \theta_3 a + \theta_6 c)(\beta_1 + \beta_3 c)(a - a^*)
\end{aligned} \tag{4}$$

$$\begin{aligned}
PNIE &= E[Y_{a^*, M^a} - Y_{a^*, M^{a^*}} \mid c] \\
&= E[E(Y \mid a^*, M, c) \mid a, c] - E[(Y \mid a^*, M, c) \mid a^*, c] \\
&= E[(\theta_0 + \theta_1 a^* + \theta_2 M + \theta_3 a^* M + \theta_4 c + \theta_5 a^* c + \theta_6 M c) \mid a, c] \\
&\quad - E[(\theta_0 + \theta_1 a^* + \theta_2 M + \theta_3 a^* M + \theta_4 c + \theta_5 a^* c + \theta_6 M c) \mid a^*, c] \\
&= (\theta_0 + \theta_1 a^* + \theta_4 c + \theta_5 a^* c) + E[(\theta_2 M + \theta_3 a^* M + \theta_6 M c) \mid a, c] \\
&\quad - (\theta_0 + \theta_1 a^* + \theta_4 c + \theta_5 a^* c) - E[(\theta_2 M + \theta_3 a^* M + \theta_6 M c) \mid a^*, c] \\
&= (\theta_2 + \theta_3 a^* + \theta_6 c) \cdot [E(M \mid a, c) - E(M \mid a^*, c)] \\
&= (\theta_2 + \theta_3 a^* + \theta_6 c)[(\beta_0 + \beta_1 a + \beta_2 c + \beta_3 a c) - (\beta_0 + \beta_1 a^* + \beta_2 c + \beta_3 a^* c)] \\
&= (\theta_2 + \theta_3 a^* + \theta_6 c)(\beta_1 + \beta_3 c)(a - a^*)
\end{aligned} \tag{5}$$

3.1.2 Standard error

The function `calc_myreg_mreg_linear_yreg_linear_se()` implements the standard error formulas.

$$(a - a^*)\Gamma_{CDE(m)} = \frac{\partial CDE(m)}{\partial(\beta^T, \theta^T)^T} = (a - a^*) \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 1 \\ 0 \\ m \\ 0 \\ c \\ 0 \end{bmatrix} \tag{6}$$

$$(a - a^*)\Gamma_{PNDE} = \frac{\partial PNDE}{\partial(\beta^T, \theta^T)^T} = (a - a^*) \begin{bmatrix} \theta_3 \\ \theta_3 a^* \\ \theta_3 c \\ \theta_3 a^* c \\ 0 \\ 1 \\ 0 \\ \beta_0 + \beta_1 a^* + \beta_2 c + \beta_3 a^* c \\ 0 \\ c \\ 0 \end{bmatrix} \tag{7}$$

$$(a - a^*)\Gamma_{TNDE} = \frac{\partial TNDE}{\partial(\beta^T, \theta^T)^T} = (a - a^*) \begin{bmatrix} \theta_3 \\ \theta_3 a \\ \theta_3 c \\ \theta_3 a c \\ 0 \\ 1 \\ 0 \\ \beta_0 + \beta_1 a + \beta_2 c + \beta_3 a c \\ 0 \\ c \\ 0 \end{bmatrix} \tag{8}$$

$$(a - a^*)\Gamma_{TNIE} = \frac{\partial TNIE}{\partial(\beta^T, \theta^T)^T} = (a - a^*) \begin{bmatrix} 0 \\ \theta_2 + \theta_3 a + \theta_6 c \\ 0 \\ c(\theta_2 + \theta_3 a + \theta_6 c) \\ 0 \\ 0 \\ \beta_1 + \beta_3 c \\ a(\beta_1 + \beta_3 c) \\ 0 \\ 0 \\ c(\beta_1 + \beta_3 c) \end{bmatrix} \quad (9)$$

$$(a - a^*)\Gamma_{PNIE} = \frac{\partial PNIE}{\partial(\beta^T, \theta^T)^T} = (a - a^*) \begin{bmatrix} 0 \\ \theta_2 + \theta_3 a^* + \theta_6 c \\ 0 \\ c(\theta_2 + \theta_3 a^* + \theta_6 c) \\ 0 \\ 0 \\ \beta_1 + \beta_3 c \\ a^*(\beta_1 + \beta_3 c) \\ 0 \\ 0 \\ c(\beta_1 + \beta_3 c) \end{bmatrix} \quad (10)$$

$$\begin{aligned} (a - a^*)\Gamma_{TE} &= \frac{\partial TE}{\partial(\beta^T, \theta^T, \sigma^2)^T} \\ &= \frac{\partial(PNDE + TNIE)}{\partial(\beta^T, \theta^T, \sigma^2)^T} \\ &= (a - a^*)(\Gamma_{PNDE} + \Gamma_{TNIE}) \end{aligned}$$

$$\begin{aligned} (a - a^*)\Gamma_{PM} &= \frac{\partial PM}{\partial(\beta^T, \theta^T, \sigma^2)^T} \\ &= \frac{\partial PM}{\partial PNDE} \frac{\partial PNDE}{\partial(\beta^T, \theta^T, \sigma^2)^T} + \frac{\partial PM}{\partial TNIE} \frac{\partial TNIE}{\partial(\beta^T, \theta^T, \sigma^2)^T} \\ &= \frac{\partial PM}{\partial PNDE} (a - a^*)\Gamma_{PNDE} + \frac{\partial PM}{\partial TNIE} (a - a^*)\Gamma_{TNIE} \\ &= -\frac{\exp(PNDE) \{\exp(TNIE) - 1\}}{\{\exp(PNDE) \exp(TNIE) - 1\}^2} (a - a^*)\Gamma_{PNDE} \\ &\quad + \frac{\exp(PNDE) \exp(TNIE) \{\exp(PNDE) - 1\}}{\{\exp(PNDE) \exp(TNIE) - 1\}^2} (a - a^*)\Gamma_{TNIE} \end{aligned}$$

$$\Sigma = \begin{bmatrix} \Sigma_\beta & 0 \\ 0 & \Sigma_\theta \end{bmatrix}$$

Hence,

$$\begin{aligned} SE(\widehat{CDE}(m)) &= \sqrt{\Gamma_{CDE(m)}^T \Sigma \Gamma_{CDE(m)}} |a - a^*| \\ SE(\widehat{PNDE}) &= \sqrt{\Gamma_{PNDE}^T \Sigma \Gamma_{PNDE}} |a - a^*| \\ SE(\widehat{TNIE}) &= \sqrt{\Gamma_{TNIE}^T \Sigma \Gamma_{TNIE}} |a - a^*| \end{aligned}$$

$$\begin{aligned}
SE(\widehat{TNDE}) &= \sqrt{\Gamma_{TNDE}^T \boldsymbol{\Sigma} \Gamma_{TNDE}} |a - a^*| \\
SE(\widehat{PNIE}) &= \sqrt{\Gamma_{PNIE}^T \boldsymbol{\Sigma} \Gamma_{PNIE}} |a - a^*| \\
SE(\widehat{TE}) &= \sqrt{\Gamma_{TE}^T \boldsymbol{\Sigma} \Gamma_{TE}} |a - a^*| \\
SE(\widehat{PM}) &= \sqrt{\Gamma_{PM}^T \boldsymbol{\Sigma} \Gamma_{PM}} |a - a^*|
\end{aligned}$$

3.2 Non-linear mediator model, linear outcome model

3.2.1 Point estimate

The function `calc_myreg_mreg_logistic_yreg_linear_est()` implements the effect formulas.

$$\begin{aligned}
 \text{logit } P[M = 1 \mid a, c] &= \beta_0 + \beta_1 a + \beta_2 c + \beta_3 ac \\
 \Rightarrow P[M = 1 \mid a, c] &= \frac{\exp(\beta_0 + \beta_1 a + \beta_2 c + \beta_3 ac)}{1 + \exp(\beta_0 + \beta_1 a + \beta_2 c + \beta_3 ac)} \\
 E[Y \mid a, m, c] &= \theta_0 + \theta_1 a + \theta_2 m + \theta_4 c + \theta_3 am + \theta_5 ac + \theta_6 mc \\
 CDE(m) &= (\theta_1 + \theta_3 m + \theta_5 c)(a - a^*)
 \end{aligned} \tag{11}$$

$$\begin{aligned}
 PNDE &= E[Y_{a, M^{a^*}} - Y_{a^*, M^{a^*}} \mid c] \\
 &= E[E(Y \mid a, M, c) - E(Y \mid a^*, M, c) \mid a^*, c] \\
 &= E[\theta_1(a - a^*) + \theta_3 M(a - a^*) + \theta_5 c(a - a^*) \mid a^*, c] \\
 &= \theta_1(a - a^*) + \theta_3 \cdot E(M \mid a^*, c)(a - a^*) + \theta_5 c(a - a^*) \\
 &= (a - a^*) \left[\theta_1 + \theta_3 \frac{\exp(\beta_0 + \beta_1 a^* + \beta_2 c + \beta_3 a^* c)}{1 + \exp(\beta_0 + \beta_1 a^* + \beta_2 c + \beta_3 a^* c)} + \theta_5 c \right] \\
 &= (a - a^*) [\theta_1 + \theta_3 \cdot \text{expit}(\beta_0 + \beta_1 a^* + \beta_2 c + \beta_3 a^* c) + \theta_5 c]
 \end{aligned} \tag{12}$$

$$\begin{aligned}
 TNDE &= E[Y_{a, M^a} - Y_{a^*, M^a} \mid c] \\
 &= E[E(Y \mid a, M, c) - E(Y \mid a^*, M, c) \mid a, c] \\
 &= E[\theta_1(a - a^*) + \theta_3 M(a - a^*) + \theta_5 c(a - a^*) \mid a, c] \\
 &= \theta_1(a - a^*) + \theta_3 \cdot E(M \mid a, c)(a - a^*) + \theta_5 c(a - a^*) \\
 &= (a - a^*) \left[\theta_1 + \theta_3 \frac{\exp(\beta_0 + \beta_1 a + \beta_2 c + \beta_3 ac)}{1 + \exp(\beta_0 + \beta_1 a + \beta_2 c + \beta_3 ac)} + \theta_5 c \right] \\
 &= (a - a^*) [\theta_1 + \theta_3 \cdot \text{expit}(\beta_0 + \beta_1 a + \beta_2 c + \beta_3 ac) + \theta_5 c]
 \end{aligned} \tag{13}$$

$$\begin{aligned}
 TNIE &= E[Y_{a, M^a} - Y_{a^*, M^{a^*}} \mid c] \\
 &= E[E(Y \mid a, M, c) \mid a, c] - E[E(Y \mid a, M, c) \mid a^*, c] \\
 &= E[(\theta_0 + \theta_1 a + \theta_2 M + \theta_3 a M + \theta_4 c + \theta_5 ac + \theta_6 M c) \mid a, c] \\
 &\quad - E[(\theta_0 + \theta_1 a + \theta_2 M + \theta_3 a M + \theta_4 c + \theta_5 ac + \theta_6 M c) \mid a^*, c] \\
 &= (\theta_2 + \theta_3 a + \theta_6 c) \cdot E(M \mid a, c) - E(M \mid a^*, c) \\
 &= (\theta_2 + \theta_3 a + \theta_6 c) \left[\frac{\exp(\beta_0 + \beta_1 a + \beta_2 c + \beta_3 ac)}{1 + \exp(\beta_0 + \beta_1 a + \beta_2 c + \beta_3 ac)} - \frac{\exp(\beta_0 + \beta_1 a^* + \beta_2 c + \beta_3 a^* c)}{1 + \exp(\beta_0 + \beta_1 a^* + \beta_2 c + \beta_3 a^* c)} \right] \\
 &= (\theta_2 + \theta_3 a + \theta_6 c) [\text{expit}(\beta_0 + \beta_1 a + \beta_2 c + \beta_3 ac) - \text{expit}(\beta_0 + \beta_1 a^* + \beta_2 c + \beta_3 a^* c)]
 \end{aligned} \tag{14}$$

$$\begin{aligned}
 PNIE &= E[Y_{a^*, M^a} - Y_{a^*, M^{a^*}} \mid c] \\
 &= E[E(Y \mid a^*, M, c) \mid a, c] - E[E(Y \mid a^*, M, c) \mid a^*, c] \\
 &= E[(\theta_0 + \theta_1 a^* + \theta_2 M + \theta_3 a^* M + \theta_4 c + \theta_5 a^* c + \theta_6 M c) \mid a, c] \\
 &\quad - E[(\theta_0 + \theta_1 a^* + \theta_2 M + \theta_3 a^* M + \theta_4 c + \theta_5 a^* c + \theta_6 M c) \mid a^*, c] \\
 &= (\theta_2 + \theta_3 a^* + \theta_6 c) \cdot [E(M \mid a, c) - E(M \mid a^*, c)] \\
 &= (\theta_2 + \theta_3 a^* + \theta_6 c) \left[\frac{\exp(\beta_0 + \beta_1 a + \beta_2 c + \beta_3 ac)}{1 + \exp(\beta_0 + \beta_1 a + \beta_2 c + \beta_3 ac)} - \frac{\exp(\beta_0 + \beta_1 a^* + \beta_2 c + \beta_3 a^* c)}{1 + \exp(\beta_0 + \beta_1 a^* + \beta_2 c + \beta_3 a^* c)} \right] \\
 &= (\theta_2 + \theta_3 a^* + \theta_6 c) [\text{expit}(\beta_0 + \beta_1 a + \beta_2 c + \beta_3 ac) - \text{expit}(\beta_0 + \beta_1 a^* + \beta_2 c + \beta_3 a^* c)]
 \end{aligned} \tag{15}$$

3.2.2 Standard error

The function `calc_myreg_mreg_logistic_yreg_linear_se()` implements the standard error formulas.

$$(a - a^*)\Gamma_{CDE(m)} = \frac{\partial CDE(m)}{\partial(\beta^T, \theta^T)^T} = (a - a^*) \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 1 \\ 0 \\ m \\ 0 \\ c \\ 0 \end{bmatrix} \quad (16)$$

$$(a - a^*)\Gamma_{PNDE} = \frac{\partial PNDE}{\partial(\beta^T, \theta^T)^T} = (a - a^*) \begin{bmatrix} \theta_3 \cdot \text{expit}[a^*(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c] \cdot \{1 - \text{expit}[a^*(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c]\} \\ a^* \cdot \theta_3 \cdot \text{expit}[a^*(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c] \cdot \{1 - \text{expit}[a^*(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c]\} \\ c \cdot \theta_3 \cdot \text{expit}[a^*(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c] \cdot \{1 - \text{expit}[a^*(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c]\} \\ a^* \cdot c \cdot \theta_3 \cdot \text{expit}[a^*(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c] \cdot \{1 - \text{expit}[a^*(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c]\} \\ 0 \\ 1 \\ 0 \\ \text{expit}[a^*(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c] \\ 0 \\ c \\ 0 \end{bmatrix} \quad (17)$$

$$(a - a^*)\Gamma_{TNDE} = \frac{\partial TNDE}{\partial(\beta^T, \theta^T)^T} = (a - a^*) \begin{bmatrix} \theta_3 \cdot \text{expit}[a(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c] \cdot \{1 - \text{expit}[a(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c]\} \\ a \cdot \theta_3 \cdot \text{expit}[a(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c] \cdot \{1 - \text{expit}[a(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c]\} \\ c \cdot \theta_3 \cdot \text{expit}[a(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c] \cdot \{1 - \text{expit}[a(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c]\} \\ a \cdot c \cdot \theta_3 \cdot \text{expit}[a(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c] \cdot \{1 - \text{expit}[a(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c]\} \\ 0 \\ 1 \\ 0 \\ \text{expit}[a(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c] \\ 0 \\ c \\ 0 \end{bmatrix} \quad (18)$$

$$\begin{aligned}
\Gamma_{TNIE} &= \frac{\partial TNIE}{\partial(\beta^T, \theta^T)^T} \\
&= \begin{bmatrix}
(\theta_2 + \theta_3 a + \theta_6 c) \cdot \left(\text{expit}[a(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c] \cdot \{1 - \text{expit}[a(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c]\} \right. \\
\quad \left. - \text{expit}[a^*(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c] \cdot \{1 - \text{expit}[a^*(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c]\} \right) \\
(\theta_2 + \theta_3 a + \theta_6 c) \cdot \left(a \cdot \{ \text{expit}[a(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c] \} \cdot \{1 - \text{expit}[a(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c]\} \right. \\
\quad \left. - a^* \cdot \{ \text{expit}[a^*(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c] \} \cdot \{1 - \text{expit}[a^*(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c]\} \right) \\
c \cdot (\theta_2 + \theta_3 a + \theta_6 c) \cdot \left(\text{expit}[a(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c] \cdot \{1 - \text{expit}[a(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c]\} \right. \\
\quad \left. - \text{expit}[a^*(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c] \cdot \{1 - \text{expit}[a^*(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c]\} \right) \\
c \cdot (\theta_2 + \theta_3 a + \theta_6 c) \cdot \left(a \cdot \{ \text{expit}[a(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c] \} \cdot \{1 - \text{expit}[a(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c]\} \right. \\
\quad \left. - a^* \cdot \{ \text{expit}[a^*(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c] \} \cdot \{1 - \text{expit}[a^*(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c]\} \right) \\
0 \\
0 \\
\text{expit}[a(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c] - \text{expit}[a^*(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c] \\
a \cdot \left(\text{expit}[a(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c] - \text{expit}[a^*(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c] \right) \\
0 \\
0 \\
c \cdot \left(\text{expit}[a(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c] - \text{expit}[a^*(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c] \right)
\end{bmatrix} \quad (19)
\end{aligned}$$

$$\begin{aligned}
\Gamma_{PNIE} &= \frac{\partial PNIE}{\partial(\beta^T, \theta^T)^T} \\
&= \begin{bmatrix}
(\theta_2 + \theta_3 a^* + \theta_6 c) \cdot \left(\text{expit}[a(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c] \cdot \{1 - \text{expit}[a(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c]\} \right. \\
\quad \left. - \text{expit}[a^*(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c] \cdot \{1 - \text{expit}[a^*(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c]\} \right) \\
(\theta_2 + \theta_3 a^* + \theta_6 c) \cdot \left(a \cdot \{ \text{expit}[a(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c] \} \cdot \{1 - \text{expit}[a(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c]\} \right. \\
\quad \left. - a^* \cdot \{ \text{expit}[a^*(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c] \} \cdot \{1 - \text{expit}[a^*(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c]\} \right) \\
c \cdot (\theta_2 + \theta_3 a^* + \theta_6 c) \cdot \left(\text{expit}[a(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c] \cdot \{1 - \text{expit}[a(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c]\} \right. \\
\quad \left. - \text{expit}[a^*(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c] \cdot \{1 - \text{expit}[a^*(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c]\} \right) \\
c \cdot (\theta_2 + \theta_3 a^* + \theta_6 c) \cdot \left(a \cdot \{ \text{expit}[a(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c] \} \cdot \{1 - \text{expit}[a(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c]\} \right. \\
\quad \left. - a^* \cdot \{ \text{expit}[a^*(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c] \} \cdot \{1 - \text{expit}[a^*(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c]\} \right) \\
0 \\
0 \\
\text{expit}[a(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c] - \text{expit}[a^*(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c] \\
a^* \cdot \left(\text{expit}[a(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c] - \text{expit}[a^*(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c] \right) \\
0 \\
0 \\
c \cdot \left(\text{expit}[a(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c] - \text{expit}[a^*(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c] \right)
\end{bmatrix} \quad (20)
\end{aligned}$$

$$\Gamma_{TE} = \frac{\partial TE}{\partial(\beta^T, \theta^T)^T}$$

$$\begin{aligned}
&= \frac{\partial(PNDE + TNIE)}{\partial(\boldsymbol{\beta}^T, \boldsymbol{\theta}^T)^T} \\
&= (a - a^*)\Gamma_{PNDE} + \Gamma_{TNIE}
\end{aligned}$$

$$\begin{aligned}
\Gamma_{PM} &= \frac{\partial PM}{\partial(\boldsymbol{\beta}^T, \boldsymbol{\theta}^T)^T} \\
&= \frac{\partial PM}{\partial PNDE} \frac{\partial PNDE}{\partial(\boldsymbol{\beta}^T, \boldsymbol{\theta}^T)^T} + \frac{\partial PM}{\partial TNIE} \frac{\partial TNIE}{\partial(\boldsymbol{\beta}^T, \boldsymbol{\theta}^T)^T} \\
&= \frac{\partial PM}{\partial PNDE} (a - a^*)\Gamma_{PNDE} + \frac{\partial PM}{\partial TNIE} \Gamma_{TNIE} \\
&= \frac{-TNIE}{(PNDE + TNIE)^2} (a - a^*)\Gamma_{PNDE} + \frac{PNDE}{(PNDE + TNIE)^2} \Gamma_{TNIE} \\
&= \frac{-TNIE (a - a^*)\Gamma_{PNDE} + PNDE \Gamma_{TNIE}}{(PNDE + TNIE)^2}
\end{aligned}$$

$$\boldsymbol{\Sigma} = \begin{bmatrix} \boldsymbol{\Sigma}_\beta & 0 \\ 0 & \boldsymbol{\Sigma}_\theta \end{bmatrix}$$

Hence,

$$\begin{aligned}
SE(\widehat{CDE(m)}) &= \sqrt{\Gamma_{CDE(m)}^T \boldsymbol{\Sigma} \Gamma_{CDE(m)}} |a - a^*| \\
SE(\widehat{PNDE}) &= \sqrt{\Gamma_{PNDE}^T \boldsymbol{\Sigma} \Gamma_{PNDE}} |a - a^*| \\
SE(\widehat{TNIE}) &= \sqrt{\Gamma_{TNIE}^T \boldsymbol{\Sigma} \Gamma_{TNIE}} \\
SE(\widehat{TNDE}) &= \sqrt{\Gamma_{TNDE}^T \boldsymbol{\Sigma} \Gamma_{TNDE}} |a - a^*| \\
SE(\widehat{PNIE}) &= \sqrt{\Gamma_{PNIE}^T \boldsymbol{\Sigma} \Gamma_{PNIE}} \\
SE(\widehat{TE}) &= \sqrt{\Gamma_{TE}^T \boldsymbol{\Sigma} \Gamma_{TE}} \\
SE(\widehat{PM}) &= \sqrt{\Gamma_{PM}^T \boldsymbol{\Sigma} \Gamma_{PM}}
\end{aligned}$$

3.3 Linear mediator model, non-linear outcome model

3.3.1 Point estimate

The function `calc_myreg_mreg_linear_yreg_logistic_est()` implements the effect formulas.

$$\begin{aligned} E[M | a, c] &= \beta_0 + \beta_1 a + \beta_2 c + \beta_3 ac \\ \text{logit } P[Y = 1 | a, m, c] &= \theta_0 + \theta_1 a + \theta_2 m + \theta_4 c + \theta_3 am + \theta_5 ac + \theta_6 mc \end{aligned}$$

$$OR^{CDE}(m) = (\theta_1 + \theta_3 m + \theta_5 c)(a - a^*) \quad (21)$$

$$\begin{aligned} OR^{PNDE} &= \exp \left\{ \log \frac{P(Y_{a, M^{a^*}} = 1 | c) / [1 - P(Y_{a, M^{a^*}} = 1 | c)]}{P(Y_{a^*, M^{a^*}} = 1 | c) / [1 - P(Y_{a^*, M^{a^*}} = 1 | c)]} \right\} \\ &= \exp \left\{ \text{logit } P(Y_{a, M^{a^*}} = 1 | c) - \text{logit } P(Y_{a^*, M^{a^*}} = 1 | c) \right\} \\ \text{If } Y \text{ is rare, } &\approx \exp \left\{ \log P(Y_{a, M^{a^*}} = 1 | c) - \log P(Y_{a^*, M^{a^*}} = 1 | c) \right\} \\ &= \exp \left\{ \log \frac{P(Y_{a, M^{a^*}} = 1 | c)}{P(Y_{a^*, M^{a^*}} = 1 | c)} \right\} \end{aligned}$$

$$\begin{aligned} E(Y_{a, M^{a^*}} | c) &= E[E(Y | a, M, c) | a^*, c] \\ &\approx E[\exp(\theta_0 + \theta_1 a + \theta_2 M + \theta_4 c + \theta_3 a M + \theta_5 ac + \theta_6 M c) | a^*] \\ &\approx \exp(\theta_0 + \theta_1 a + \theta_4 c + \theta_5 ac) \cdot E\{\exp[(\theta_2 + \theta_3 a + \theta_6 c)M] | a^*, c\} \end{aligned}$$

$E\{\exp[(\theta_2 + \theta_3 a + \theta_6 c)M] | a^*, c\}$ can be calculated using moment generating function (MGF). Since

$$\begin{aligned} M &\sim N(\mu, \sigma^2), \\ E(e^{tM}) &= MGF_M(t) = e^{t\mu + \frac{1}{2}\sigma^2 t^2} \end{aligned}$$

where

$$\begin{aligned} \sigma^2 &\text{ is the variance of error in the linear mediator model,} \\ \mu &= E(M | a^*, c) = \beta_0 + \beta_1 a^* + \beta_2 c + \beta_3 a^* c, \\ t &= \theta_2 + \theta_3 a + \theta_6 c \end{aligned}$$

Plugging in and we have

$$E\{\exp[(\theta_2 + \theta_3 a + \theta_6 c)M] | a^*, c\} = \exp \left[(\theta_2 + \theta_3 a + \theta_6 c)(\beta_0 + \beta_1 a^* + \beta_2 c + \beta_3 a^* c) + \frac{1}{2}\sigma^2(\theta_2 + \theta_3 a + \theta_6 c)^2 \right]$$

Hence,

$$\begin{aligned} E(Y_{a, M^{a^*}} | c) &= \exp \left[(\theta_0 + \theta_1 a + \theta_4 c + \theta_5 ac) + (\theta_2 + \theta_3 a + \theta_6 c)(\beta_0 + \beta_1 a^* + \beta_2 c + \beta_3 a^* c) + \frac{1}{2}\sigma^2(\theta_2 + \theta_3 a + \theta_6 c)^2 \right] \\ \therefore \log E(Y_{a, M^{a^*}} | c) &= \theta_0 + \theta_1 a + \theta_4 c + \theta_5 ac + (\theta_2 + \theta_3 a + \theta_6 c)(\beta_0 + \beta_1 a^* + \beta_2 c + \beta_3 a^* c) + \frac{1}{2}\sigma^2(\theta_2 + \theta_3 a + \theta_6 c)^2 \end{aligned}$$

Similarly,

$$\begin{aligned} E(Y_{a^*, M^{a^*}} | c) &= \exp \left[(\theta_0 + \theta_1 a^* + \theta_4 c + \theta_5 a^* c) + (\theta_2 + \theta_3 a^* + \theta_6 c)(\beta_0 + \beta_1 a^* + \beta_2 c + \beta_3 a^* c) + \frac{1}{2}\sigma^2(\theta_2 + \theta_3 a^* + \theta_6 c)^2 \right] \\ \therefore \log E(Y_{a^*, M^{a^*}} | c) &= \theta_0 + \theta_1 a^* + \theta_4 c + \theta_5 a^* c + (\theta_2 + \theta_3 a^* + \theta_6 c)(\beta_0 + \beta_1 a^* + \beta_2 c + \beta_3 a^* c) + \frac{1}{2}\sigma^2(\theta_2 + \theta_3 a^* + \theta_6 c)^2 \end{aligned}$$

Hence,

$$OR^{PNDE} \approx \exp\left([a - a^*] \cdot [\theta_1 + \theta_5 c + \theta_3 (\beta_0 + \beta_1 a^* + \beta_2 c + \beta_3 a^* c) + \frac{1}{2} \sigma^2 \theta_3 (2\theta_2 + \theta_3 a + \theta_3 a^* + 2\theta_6 c)]\right) \quad (22)$$

$$\begin{aligned} OR^{TNIE} &= \exp \left\{ \log \frac{P(Y_{a,M^a} = 1 | c) / [1 - P(Y_{a,M^a} = 1 | c)]}{P(Y_{a,M^{a^*}} = 1 | c) / [1 - P(Y_{a,M^{a^*}} = 1 | c)]} \right\} \\ &= \exp \{ \text{logit } P(Y_{a,M^a} = 1 | c) - \text{logit } P(Y_{a,M^{a^*}} = 1 | c) \} \\ \text{If } Y \text{ is rare, } &\approx \exp \left\{ \log \frac{P(Y_{a,M^a} = 1 | c)}{P(Y_{a,M^{a^*}} = 1 | c)} \right\} \end{aligned} \quad (23)$$

Using the same approach (MGF),

$$OR^{TNIE} \approx \exp \{ (\theta_2 + \theta_3 a + \theta_6 c) (\beta_1 + \beta_3 c) (a - a^*) \}$$

For OR^{TNDE} and OR^{PNIE} , notice that the first exponential term in OR^{PNDE} and OR^{TNIE} are just the exponentiated PNDE and TNIE in 2.1, we can easily write OR^{TNDE} and OR^{PNIE} .

$$OR^{TNDE} \approx \exp\left([a - a^*] \cdot [\theta_1 + \theta_5 c + \theta_3 (\beta_0 + \beta_1 a + \beta_2 c + \beta_3 a c) + \frac{1}{2} \sigma^2 \theta_3 (2\theta_2 + \theta_3 a + \theta_3 a^* + 2\theta_6 c)]\right) \quad (24)$$

$$OR^{PNIE} = \exp \{ (\theta_2 + \theta_3 a^* + \theta_6 c) (\beta_1 + \beta_3 c) (a - a^*) \} \quad (25)$$

3.3.2 Standard error

Reminder: The formulas are on log odds scale.

The function `calc_myreg_mreg_linear_yreg_logistic_se()` implements the standard error formulas.

For the convenience of programming, the parameter vector in the following variance formulas is $(\beta^T, \theta^T, \sigma^2)$, although NIE does not have σ^2 .

$$(a - a^*) \Gamma_{CDE(m)} = \frac{\partial \log(OR^{CDE(m)})}{\partial (\beta^T, \theta^T, \sigma^2)^T} = (a - a^*) \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 1 \\ 0 \\ m \\ 0 \\ c \\ 0 \\ 0 \end{bmatrix} \quad (26)$$

$$(a - a^*) \Gamma_{PNDE} = \frac{\partial \log(OR^{PNDE})}{\partial (\beta^T, \theta^T, \sigma^2)^T}$$

$$= (a - a^*) \begin{bmatrix} \theta_3 \\ \theta_3 a^* \\ \theta_3 c \\ \theta_3 a^* c \\ 0 \\ 1 \\ \theta_3 \sigma^2 \\ a^*(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c + \sigma^2[(\theta_2 + \theta_6 c) + \theta_3(a^* + a)] \\ 0 \\ c \\ \theta_3 c \sigma^2 \\ \frac{1}{2} \theta_3 \cdot [2(\theta_2 + \theta_6 c) + \theta_3(a^* + a)] \end{bmatrix} \quad (27)$$

$$(a - a^*) \Gamma_{TNDE} = \frac{\partial \log(OR^{TNDE})}{\partial(\beta^T, \theta^T, \sigma^2)^T} = (a - a^*) \begin{bmatrix} \theta_3 \\ \theta_3 a \\ \theta_3 c \\ \theta_3 a c \\ 0 \\ 1 \\ \theta_3 \sigma^2 \\ a(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c + \sigma^2[(\theta_2 + \theta_6 c) + \theta_3(a^* + a)] \\ 0 \\ c \\ \theta_3 c \sigma^2 \\ \frac{1}{2} \theta_3 \cdot [2(\theta_2 + \theta_6 c) + \theta_3(a^* + a)] \end{bmatrix} \quad (28)$$

$$(a - a^*) \Gamma_{TNIE} = \frac{\partial \log(OR^{TNIE})}{\partial(\beta^T, \theta^T, \sigma^2)^T} = (a - a^*) \begin{bmatrix} 0 \\ \theta_2 + \theta_3 a + \theta_6 c \\ 0 \\ c(\theta_2 + \theta_3 a + \theta_6 c) \\ 0 \\ 0 \\ \beta_1 + \beta_3 c \\ a(\beta_1 + \beta_3 c) \\ 0 \\ 0 \\ c(\beta_1 + \beta_3 c) \\ 0 \end{bmatrix} \quad (29)$$

$$(a - a^*) \Gamma_{PNIE} = \frac{\partial \log(OR^{PNIE})}{\partial(\beta^T, \theta^T, \sigma^2)^T} = (a - a^*) \begin{bmatrix} 0 \\ \theta_2 + \theta_3 a^* + \theta_6 c \\ 0 \\ c(\theta_2 + \theta_3 a^* + \theta_6 c) \\ 0 \\ 0 \\ \beta_1 + \beta_3 c \\ a^*(\beta_1 + \beta_3 c) \\ 0 \\ 0 \\ c(\beta_1 + \beta_3 c) \\ 0 \end{bmatrix} \quad (30)$$

$$\begin{aligned}
(a - a^*)\Gamma_{TE} &= \frac{\partial TE}{\partial(\beta^T, \boldsymbol{\theta}^T, \sigma^2)^T} \\
&= \frac{\partial(PNDE + TNIE)}{\partial(\beta^T, \boldsymbol{\theta}^T, \sigma^2)^T} \\
&= (a - a^*)(\Gamma_{PNDE} + \Gamma_{TNIE})
\end{aligned}$$

$$\begin{aligned}
(a - a^*)\Gamma_{PM} &= \frac{\partial PM}{\partial(\beta^T, \boldsymbol{\theta}^T, \sigma^2)^T} \\
&= \frac{\partial PM}{\partial PNDE} \frac{\partial PNDE}{\partial(\beta^T, \boldsymbol{\theta}^T, \sigma^2)^T} + \frac{\partial PM}{\partial TNIE} \frac{\partial TNIE}{\partial(\beta^T, \boldsymbol{\theta}^T, \sigma^2)^T} \\
&= \frac{\partial PM}{\partial PNDE} (a - a^*)\Gamma_{PNDE} + \frac{\partial PM}{\partial TNIE} (a - a^*)\Gamma_{TNIE} \\
&= - \frac{\exp(PNDE) \{\exp(TNIE) - 1\}}{\{\exp(PNDE) \exp(TNIE) - 1\}^2} (a - a^*)\Gamma_{PNDE} \\
&\quad + \frac{\exp(PNDE) \exp(TNIE) \{\exp(PNDE) - 1\}}{\{\exp(PNDE) \exp(TNIE) - 1\}^2} (a - a^*)\Gamma_{TNIE}
\end{aligned}$$

$$\begin{aligned}
\boldsymbol{\Sigma} &= \begin{bmatrix} \boldsymbol{\Sigma}_\beta & 0 & 0 \\ 0 & \boldsymbol{\Sigma}_\theta & 0 \\ 0 & 0 & \Sigma_{\sigma^2} \end{bmatrix} \\
\Sigma_{\sigma^2} &= \frac{2(\sigma^2)^2}{n - p}, \text{ where } p = \text{length}(\beta)
\end{aligned}$$

Hence,

$$\begin{aligned}
SE(\widehat{CDE}(m)) &= \sqrt{\Gamma_{CDE(m)}^T \boldsymbol{\Sigma} \Gamma_{CDE(m)}} |a - a^*| \\
SE(\widehat{PNDE}) &= \sqrt{\Gamma_{PNDE}^T \boldsymbol{\Sigma} \Gamma_{PNDE}} |a - a^*| \\
SE(\widehat{TNIE}) &= \sqrt{\Gamma_{TNIE}^T \boldsymbol{\Sigma} \Gamma_{TNIE}} |a - a^*| \\
SE(\widehat{TNDE}) &= \sqrt{\Gamma_{TNDE}^T \boldsymbol{\Sigma} \Gamma_{TNDE}} |a - a^*| \\
SE(\widehat{PNIE}) &= \sqrt{\Gamma_{PNIE}^T \boldsymbol{\Sigma} \Gamma_{PNIE}} |a - a^*| \\
SE(\widehat{TE}) &= \sqrt{\Gamma_{TE}^T \boldsymbol{\Sigma} \Gamma_{TE}} |a - a^*| \\
SE(\widehat{PM}) &= \sqrt{\Gamma_{PM}^T \boldsymbol{\Sigma} \Gamma_{PM}} |a - a^*|
\end{aligned}$$

3.4 Non-linear mediator model, non-linear outcome model

3.4.1 Point estimate

The function `calc_myreg_mreg_logistic_yreg_logistic_est()` implements the effect formulas.

$$\begin{aligned}\text{logit } E[M \mid a, c] &= \beta_0 + \beta_1 a + \beta_2 c + \beta_3 ac \\ \Rightarrow P[M = 1 \mid a, c] &= \frac{\exp(\beta_0 + \beta_1 a + \beta_2 c + \beta_3 ac)}{1 + \exp(\beta_0 + \beta_1 a + \beta_2 c + \beta_3 ac)} \\ \text{logit } P[Y = 1 \mid a, m, c] &= \theta_0 + \theta_1 a + \theta_2 m + \theta_4 c + \theta_3 am + \theta_5 ac + \theta_6 mc\end{aligned}$$

$$OR^{CDE}(m) = (\theta_1 + \theta_3 m + \theta_5 c)(a - a^*) \quad (31)$$

$$\text{If } Y \text{ is rare, } OR^{PNDE} \approx \exp \left\{ \log \frac{P(Y_{a, M^{a^*}} = 1 \mid c)}{P(Y_{a^*, M^{a^*}} = 1 \mid c)} \right\}$$

$$\begin{aligned}E(Y_{a, M^{a^*}} \mid c) &= E[E(Y \mid a, M, c) \mid a^*, c] \\ &\approx E[\exp(\theta_0 + \theta_1 a + \theta_2 M + \theta_4 c + \theta_3 a M + \theta_5 ac + \theta_6 M c) \mid a^*, c] \\ &= \exp(\theta_0 + \theta_1 a + \theta_4 c + \theta_5 ac) \cdot E\{\exp[(\theta_2 + \theta_3 a + \theta_6 c)M] \mid a^*, c\}\end{aligned}$$

$E\{\exp[(\theta_2 + \theta_3 a + \theta_6 c)M] \mid a^*, c\}$ can be calculated using MGF.

Since

$$\begin{aligned}M &\sim Ber(p), \\ E(e^{tM}) &= MGF_M(t) = 1 - p + pe^t\end{aligned}$$

where

$$\begin{aligned}p &= E(M \mid a^*, c) = \frac{\exp(\beta_0 + \beta_1 a^* + \beta_2 c + \beta_3 a^* c)}{1 + \exp(\beta_0 + \beta_1 a^* + \beta_2 c + \beta_3 a^* c)}, \\ t &= \theta_2 + \theta_3 a + \theta_6 c\end{aligned}$$

Plugging in and we have

$$E\{\exp[(\theta_2 + \theta_3 a + \theta_6 c)M] \mid a^*, c\} = \frac{1 + \exp(\beta_0 + \beta_1 a^* + \beta_2 c + \beta_3 a^* c + \theta_2 + \theta_3 a + \theta_6 c)}{1 + \exp(\beta_0 + \beta_1 a^* + \beta_2 c + \beta_3 a^* c)}$$

Hence,

$$\begin{aligned}E(Y_{a, M^{a^*}} \mid c) &= E[E(Y \mid a, M, c) \mid a^*, c] \\ &= \exp(\theta_0 + \theta_1 a + \theta_4 c + \theta_5 ac) \cdot \frac{1 + \exp(\beta_0 + \beta_1 a^* + \beta_2 c + \beta_3 a^* c + \theta_2 + \theta_3 a + \theta_6 c)}{1 + \exp(\beta_0 + \beta_1 a^* + \beta_2 c + \beta_3 a^* c)}\end{aligned}$$

Similarly,

$$\begin{aligned}E(Y_{a^*, M^{a^*}} \mid c) &= E[E(Y \mid a^*, M, c) \mid a^*, c] \\ &= \exp(\theta_0 + \theta_1 a^* + \theta_4 c + \theta_5 a^* c) \cdot \frac{1 + \exp(\beta_0 + \beta_1 a^* + \beta_2 c + \beta_3 a^* c + \theta_2 + \theta_3 a^* + \theta_6 c)}{1 + \exp(\beta_0 + \beta_1 a^* + \beta_2 c + \beta_3 a^* c)}\end{aligned}$$

Hence,

$$OR^{PNDE} \approx \exp[(\theta_1 + \theta_5 c)(a - a^*)] \frac{1 + \exp(\beta_0 + \beta_1 a^* + \beta_2 c + \beta_3 a^* c + \theta_2 + \theta_3 a + \theta_6 c)}{1 + \exp(\beta_0 + \beta_1 a^* + \beta_2 c + \beta_3 a^* c + \theta_2 + \theta_3 a^* + \theta_6 c)} \quad (32)$$

For OR^{TNIE} ,

$$\text{If } Y \text{ is rare, } OR^{TNIE} \approx \exp \left\{ \log \frac{P(Y_{a, M^a} = 1 \mid c)}{P(Y_{a, M^{a^*}} = 1 \mid c)} \right\}$$

$$OR^{TNIE} \approx \frac{1 + \exp(\beta_0 + \beta_1 a + \beta_2 c + \beta_3 ac + \theta_2 + \theta_3 a + \theta_6 c)}{1 + \exp(\beta_0 + \beta_1 a^* + \beta_2 c + \beta_3 a^* c + \theta_2 + \theta_3 a + \theta_6 c)} \cdot \frac{1 + \exp(\beta_0 + \beta_1 a^* + \beta_2 c + \beta_3 a^* c)}{1 + \exp(\beta_0 + \beta_1 a + \beta_2 c + \beta_3 ac)} \quad (33)$$

For OR^{TNDE} ,

$$\text{If } Y \text{ is rare, } OR^{TNDE} \approx \exp \left\{ \log \frac{P(Y_{a,M^a} = 1 | c)}{P(Y_{a^*,M^a} = 1 | c)} \right\}$$

$$\begin{aligned} E(Y_{a,M^a} | c) &= E[E(Y | a, M, c) | a, c] \\ &= \exp(\theta_0 + \theta_1 a + \theta_4 c + \theta_5 ac) \cdot E\{\exp[(\theta_2 + \theta_3 a + \theta_6 c)M] | a, c\} \\ &= \exp(\theta_0 + \theta_1 a + \theta_4 c + \theta_5 ac) \cdot \frac{1 + \exp(\beta_0 + \beta_1 a + \beta_2 c + \beta_3 ac + \theta_2 + \theta_3 a + \theta_6 c)}{1 + \exp(\beta_0 + \beta_1 a + \beta_2 c + \beta_3 ac)} \end{aligned}$$

Similarly,

$$\begin{aligned} E(Y_{a^*,M^a} | c) &= E[E(Y | a^*, M, c) | a, c] \\ &= \exp(\theta_0 + \theta_1 a^* + \theta_4 c + \theta_5 a^* c) \cdot \frac{1 + \exp(\beta_0 + \beta_1 a + \beta_2 c + \beta_3 ac + \theta_2 + \theta_3 a^* + \theta_6 c)}{1 + \exp(\beta_0 + \beta_1 a + \beta_2 c + \beta_3 ac)} \end{aligned}$$

Hence,

$$OR^{TNDE} \approx \exp[(\theta_1 + \theta_5 c)(a - a^*)] \cdot \frac{1 + \exp(\beta_0 + \beta_1 a + \beta_2 c + \beta_3 ac + \theta_2 + \theta_3 a + \theta_6 c)}{1 + \exp(\beta_0 + \beta_1 a + \beta_2 c + \beta_3 ac + \theta_2 + \theta_3 a^* + \theta_6 c)} \quad (34)$$

For OR^{PNIE} ,

$$\text{If } Y \text{ is rare, } OR^{PNIE} \approx \exp \left\{ \log \frac{P(Y_{a^*,M^a} = 1 | c)}{P(Y_{a^*,M^{a^*}} = 1 | c)} \right\}$$

$$\begin{aligned} E(Y_{a^*,M^{a^*}} | c) &= E[E(Y | a^*, M, c) | a^*, c] \\ &= \exp(\theta_0 + \theta_1 a^* + \theta_4 c + \theta_5 a^* c) \cdot E\{\exp[(\theta_2 + \theta_3 a^* + \theta_6 c)M] | a^*, c\} \\ &= \exp(\theta_0 + \theta_1 a^* + \theta_4 c + \theta_5 a^* c) \cdot \frac{1 + \exp(\beta_0 + \beta_1 a^* + \beta_2 c + \beta_3 a^* c + \theta_2 + \theta_3 a^* + \theta_6 c)}{1 + \exp(\beta_0 + \beta_1 a^* + \beta_2 c + \beta_3 a^* c)} \end{aligned}$$

$$\begin{aligned} E(Y_{a^*,M^a} | c) &= E[E(Y | a^*, M, c) | a, c] \\ &= \exp(\theta_0 + \theta_1 a^* + \theta_4 c + \theta_5 a^* c) \cdot E\{\exp[(\theta_2 + \theta_3 a^* + \theta_6 c)M] | a, c\} \\ &= \exp(\theta_0 + \theta_1 a^* + \theta_4 c + \theta_5 a^* c) \cdot \frac{1 + \exp(\beta_0 + \beta_1 a + \beta_2 c + \beta_3 ac + \theta_2 + \theta_3 a^* + \theta_6 c)}{1 + \exp(\beta_0 + \beta_1 a + \beta_2 c + \beta_3 ac)} \end{aligned}$$

Therefore,

$$OR^{PNIE} \approx \frac{1 + \exp(\beta_0 + \beta_1 a + \beta_2 c + \beta_3 ac + \theta_2 + \theta_3 a^* + \theta_6 c)}{1 + \exp(\beta_0 + \beta_1 a^* + \beta_2 c + \beta_3 a^* c + \theta_2 + \theta_3 a^* + \theta_6 c)} \cdot \frac{1 + \exp(\beta_0 + \beta_1 a^* + \beta_2 c + \beta_3 a^* c)}{1 + \exp(\beta_0 + \beta_1 a + \beta_2 c + \beta_3 ac)} \quad (35)$$

3.4.2 Standard error

Reminder: The formulas are on log odds scale.

The function `calc_myreg_mreg_logistic_yreg_logistic_se()` implements the standard error formulas.

$$(a - a^*)\Gamma_{CDE(m)} = \frac{\partial \log(OR^{CDE(m)})}{\partial(\beta^T, \theta^T)^T} = (a - a^*) \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 1 \\ 0 \\ 0 \\ m \\ 0 \\ c \\ 0 \end{bmatrix} \quad (36)$$

$$\Gamma_{PNDE} = \frac{\partial \log(OR^{PNDE})}{\partial(\beta^T, \theta^T)^T} = \begin{bmatrix} \text{expit}[a^*(\beta_1 + \beta_3 c) + a\theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2] \\ -\text{expit}[a^*(\beta_1 + \beta_3 c) + a^*\theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2] \\ a^* \cdot \left(\text{expit}[a^*(\beta_1 + \beta_3 c) + a\theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2] \right. \\ \left. - \text{expit}[a^*(\beta_1 + \beta_3 c) + a^*\theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2] \right) \\ c \cdot \left(\text{expit}[a^*(\beta_1 + \beta_3 c) + a\theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2] \right. \\ \left. - \text{expit}[a^*(\beta_1 + \beta_3 c) + a^*\theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2] \right) \\ a^* c \cdot \left(\text{expit}[a^*(\beta_1 + \beta_3 c) + a\theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2] \right. \\ \left. - \text{expit}[a^*(\beta_1 + \beta_3 c) + a^*\theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2] \right) \\ 0 \\ a - a^* \\ \text{expit}[a^*(\beta_1 + \beta_3 c) + a\theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2] \\ -\text{expit}[a^*(\beta_1 + \beta_3 c) + a^*\theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2] \\ a \cdot \text{expit}[a^*(\beta_1 + \beta_3 c) + a\theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2] \\ -a^* \cdot \text{expit}[a^*(\beta_1 + \beta_3 c) + a^*\theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2] \\ 0 \\ c(a - a^*) \\ c \cdot \left(\text{expit}[a^*(\beta_1 + \beta_3 c) + a\theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2] \right. \\ \left. - \text{expit}[a^*(\beta_1 + \beta_3 c) + a^*\theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2] \right) \end{bmatrix} \quad (37)$$

$$\Gamma_{TNDE} = \frac{\partial \log(OR^{TNDE})}{\partial(\beta^T, \theta^T)^T} = \begin{bmatrix} \text{expit}[a(\beta_1 + \beta_3 c) + a\theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2] \\ -\text{expit}[a(\beta_1 + \beta_3 c) + a^*\theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2] \\ \\ a \cdot \left(\text{expit}[a(\beta_1 + \beta_3 c) + a\theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2] \right. \\ \left. - \text{expit}[a(\beta_1 + \beta_3 c) + a^*\theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2] \right) \\ \\ c \cdot \left(\text{expit}[a(\beta_1 + \beta_3 c) + a\theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2] \right. \\ \left. - \text{expit}[a(\beta_1 + \beta_3 c) + a^*\theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2] \right) \\ \\ ac \cdot \left(\text{expit}[a(\beta_1 + \beta_3 c) + a\theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2] \right. \\ \left. - \text{expit}[a(\beta_1 + \beta_3 c) + a^*\theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2] \right) \\ \\ 0 \\ a - a^* \\ \\ \text{expit}[a(\beta_1 + \beta_3 c) + a\theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2] \\ -\text{expit}[a(\beta_1 + \beta_3 c) + a^*\theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2] \\ \\ a \cdot \text{expit}[a(\beta_1 + \beta_3 c) + a\theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2] \\ -a^* \cdot \text{expit}[a(\beta_1 + \beta_3 c) + a^*\theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2] \\ \\ 0 \\ c(a - a^*) \\ \\ c \cdot \left(\text{expit}[a(\beta_1 + \beta_3 c) + a\theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2] \right. \\ \left. - \text{expit}[a(\beta_1 + \beta_3 c) + a^*\theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2] \right) \end{bmatrix} \quad (38)$$

$$\begin{aligned}
\Gamma_{TNIE} &= \frac{\partial \log(OR^{TNIE})}{\partial(\beta^T, \theta^T)^T} \\
&= \begin{bmatrix}
\begin{aligned}
&\text{expit}[a^*(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c] - \text{expit}[a^*(\beta_1 + \beta_3 c) + a\theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2] \\
&- \text{expit}[a(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c] + \text{expit}[a(\beta_1 + \beta_3 c) + a\theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2]
\end{aligned} \\
a^* \cdot \left(\text{expit}[a^*(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c] - \text{expit}[a^*(\beta_1 + \beta_3 c) + a\theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2] \right) \\
+ a \cdot \left(- \text{expit}[a(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c] + \text{expit}[a(\beta_1 + \beta_3 c) + a\theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2] \right) \\
c \cdot \left(\text{expit}[a^*(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c] - \text{expit}[a^*(\beta_1 + \beta_3 c) + a\theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2] \right. \\
\left. - \text{expit}[a(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c] + \text{expit}[a(\beta_1 + \beta_3 c) + a\theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2] \right) \\
c \cdot \left(a^* \cdot \left(\text{expit}[a^*(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c] - \text{expit}[a^*(\beta_1 + \beta_3 c) + a\theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2] \right) \right. \\
\left. + a \cdot \left(- \text{expit}[a(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c] + \text{expit}[a(\beta_1 + \beta_3 c) + a\theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2] \right) \right) \\
0 \\
0 \\
\begin{aligned}
&\text{expit}[a(\beta_1 + \beta_3 c) + a\theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2] \\
&- \text{expit}[a^*(\beta_1 + \beta_3 c) + a\theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2]
\end{aligned} \\
a \cdot \left(\text{expit}[a(\beta_1 + \beta_3 c) + a\theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2] \right. \\
\left. - \text{expit}[a^*(\beta_1 + \beta_3 c) + a\theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2] \right) \\
0 \\
0 \\
\begin{aligned}
&c \left(\text{expit}[a(\beta_1 + \beta_3 c) + a\theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2] \right. \\
&\left. - \text{expit}[a^*(\beta_1 + \beta_3 c) + a\theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2] \right)
\end{aligned}
\end{bmatrix} \quad (39)
\end{aligned}$$

$$\begin{aligned}
\Gamma_{PNIE} &= \frac{\partial \log(OR^{PNIE})}{\partial(\beta^T, \theta^T)^T} \\
&= \begin{bmatrix}
\begin{aligned}
&\text{expit}[a^*(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c] - \text{expit}[a^*(\beta_1 + \beta_3 c) + a^* \theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2] \\
&- \text{expit}[a(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c] + \text{expit}[a(\beta_1 + \beta_3 c) + a^* \theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2]
\end{aligned} \\
a^* \cdot \left(\text{expit}[a^*(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c] - \text{expit}[a^*(\beta_1 + \beta_3 c) + a^* \theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2] \right) \\
+ a \cdot \left(- \text{expit}[a(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c] + \text{expit}[a(\beta_1 + \beta_3 c) + a^* \theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2] \right) \\
c \cdot \left(\text{expit}[a^*(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c] - \text{expit}[a^*(\beta_1 + \beta_3 c) + a^* \theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2] \right. \\
\left. - \text{expit}[a(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c] + \text{expit}[a(\beta_1 + \beta_3 c) + a^* \theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2] \right) \\
c \cdot \left(a^* \cdot \left(\text{expit}[a^*(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c] - \text{expit}[a^*(\beta_1 + \beta_3 c) + a^* \theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2] \right) \right. \\
\left. + a \cdot \left(- \text{expit}[a(\beta_1 + \beta_3 c) + \beta_0 + \beta_2 c] + \text{expit}[a(\beta_1 + \beta_3 c) + a^* \theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2] \right) \right) \\
0 \\
0 \\
\begin{aligned}
&\text{expit}[a(\beta_1 + \beta_3 c) + a^* \theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2] \\
&- \text{expit}[a^*(\beta_1 + \beta_3 c) + a^* \theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2]
\end{aligned} \\
a^* \cdot \left(\text{expit}[a(\beta_1 + \beta_3 c) + a^* \theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2] \right. \\
\left. - \text{expit}[a^*(\beta_1 + \beta_3 c) + a^* \theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2] \right) \\
0 \\
0 \\
c \cdot \left(\text{expit}[a(\beta_1 + \beta_3 c) + a^* \theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2] \right. \\
\left. - \text{expit}[a^*(\beta_1 + \beta_3 c) + a^* \theta_3 + \beta_0 + c(\beta_2 + \theta_6) + \theta_2] \right)
\end{bmatrix} \quad (40)
\end{aligned}$$

$$\begin{aligned}
\Gamma_{TE} &= \frac{\partial TE}{\partial(\beta^T, \theta^T)^T} \\
&= \frac{\partial(PNDE + TNIE)}{\partial(\beta^T, \theta^T)^T} \\
&= \Gamma_{PNDE} + \Gamma_{TNIE}
\end{aligned}$$

$$\begin{aligned}
\Gamma_{PM} &= \frac{\partial PM}{\partial(\beta^T, \theta^T)^T} \\
&= \frac{\partial PM}{\partial PNDE} \frac{\partial PNDE}{\partial(\beta^T, \theta^T)^T} + \frac{\partial PM}{\partial TNIE} \frac{\partial TNIE}{\partial(\beta^T, \theta^T)^T} \\
&= \frac{\partial PM}{\partial PNDE} \Gamma_{PNDE} + \frac{\partial PM}{\partial TNIE} \Gamma_{TNIE} \\
&= - \frac{\exp(PNDE) \{ \exp(TNIE) - 1 \}}{\{ \exp(PNDE) \exp(TNIE) - 1 \}^2} \Gamma_{PNDE} \\
&\quad + \frac{\exp(PNDE) \exp(TNIE) \{ \exp(PNDE) - 1 \}}{\{ \exp(PNDE) \exp(TNIE) - 1 \}^2} \Gamma_{TNIE}
\end{aligned}$$

$$\mathbf{\Sigma} = \begin{bmatrix} \mathbf{\Sigma}_{\beta} & 0 \\ 0 & \mathbf{\Sigma}_{\theta} \end{bmatrix}$$

Hence,

$$SE(\widehat{CDE}(m)) = \sqrt{\Gamma_{CDE(m)}^T \mathbf{\Sigma} \Gamma_{CDE(m)}}$$

$$SE(\widehat{PNDE}) = \sqrt{\Gamma_{PNDE}^T \mathbf{\Sigma} \Gamma_{PNDE}}$$

$$SE(\widehat{TNIE}) = \sqrt{\Gamma_{TNIE}^T \mathbf{\Sigma} \Gamma_{TNIE}}$$

$$SE(\widehat{TNDE}) = \sqrt{\Gamma_{TNDE}^T \mathbf{\Sigma} \Gamma_{TNDE}}$$

$$SE(\widehat{PNIE}) = \sqrt{\Gamma_{PNIE}^T \mathbf{\Sigma} \Gamma_{PNIE}}$$

$$SE(\widehat{TE}) = \sqrt{\Gamma_{TE}^T \mathbf{\Sigma} \Gamma_{TE}}$$

$$SE(\widehat{PM}) = \sqrt{\Gamma_{PM}^T \mathbf{\Sigma} \Gamma_{PM}}$$

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