An evaluation of the product method for estimating natural indirect effect and mediation proportion in epidemiological studies

Chao Cheng
Email: c.cheng@yale.edu
Joint work with Fan Li and Donna Spiegelman

Center for Methods in Implementation and Prevention Science,
Yale School of Public Health

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0 Outline

1 Path diagram for the mediation model

(a) Path diagram without the mediator

(b) Path diagram with the mediator

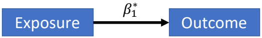
1 Quantities of Interest

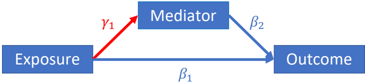
- Natural Indirect Effect (NIE), the effect through the pre-specified mediator (the red pathway).
- Natural Direct Effect (NDE), the effect solely from the exposure (the blue pathway).
- Total Effect (TE), the summation of NIE and NDE.
- Mediation Proportion (MP), defined as NIE/TE or NIE/(NIE+NDE).

In mediation analysis, NIE is usually of more interest as it tells us how much we could exploit the exposure-disease mechanism by designing interventions targeting the mediator in cases when it is challenging or impossible to manipulate the exposure (Barfield et al, 2017).

Sometimes, researchers also calculate the MP to capture the relative importance of the mediator in explaining the pathway through which the exposure has an effect on the outcome.

- Regression Models
- Model I:
  Outcome $= \beta_0^* + \beta_1^* \times$ Exposure $+$ Error$_1$
- Model II:
  Outcome $= \beta_0 + \beta_1 \times$ Exposure $+ \beta_2 \times$ Mediator $+$ Error$_2$
- Model III:
  Mediator $= \gamma_0 + \gamma_1 \times$ Exposure $+$ Error$_3$
- Difference Method (Models I and II)
  NIE $= \beta_1^* - \beta_1$; MP $= \frac{\beta_1^* - \beta_1}{\beta_1^*}$
- Product Method (Models II and III)
  NIE $= \beta_2\gamma_1$; MP $= \frac{\beta_2\gamma_1}{\beta_2\gamma_1 + \beta_1}$
- In this paper, We conducted simulation studies to examine the empirical performance of **product method** for calculating the point and interval estimates of NIE and MP.





1 Difference Method v.s. Product Method

References for difference method:

[1] Nevo, D., Liao, X., & Spiegelman, D. (2017). Estimation and inference for the mediation proportion. The international journal of biostatistics, 13(2).
[2] MacKinnon, D. P., Warsi, G., & Dwyer, J. H. (1995). A simulation study of mediated effect measures. Multivariate behavioral research, 30(1), 41-62.
[3] Baron, R. M., & Kenny, D. A. (1986). The moderator–mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. Journal of personality and social psychology, 51(6), 1173.

2 Outline

2 Four Data Types

We consider four cases of data type for the mediator and outcome variables.

- Case #1: Continuous Outcome and Continuous Mediator
- Case #2: Continuous Outcome and Binary Mediator
- Case #3: Binary Outcome and Continuous Mediator
- Case #4: Binary Outcome and Binary Mediator

- Notations: Outcome (Y), mediator (M), exposure (X), and a vector of confounders ($\boldsymbol{W}$).
- Model for the Outcome:
  $E(Y|X, M, \boldsymbol{W}) = \beta_0 + \beta_1 X + \beta_2 M + \boldsymbol{\beta}_3^T \boldsymbol{W}$
- Model for the Mediator:
  $E(M|X, \boldsymbol{W}) = \gamma_0 + \gamma_1 X + \boldsymbol{\gamma}_2^T \boldsymbol{W}$
- Valeri and VanderWeele (2013): Based on four identifiability assumptions, we can show
- Natural Indirect Effect (NIE) for X in change from x^* to x:
  $\beta_2\gamma_1(x - x^*)$
- Natural Direct Effect (NDE) for X in change from x^* to x: $\beta_1(x - x^*)$
- Mediation Proportion (MP): $\text{MP} = \frac{\text{NIE}}{\text{TE}} = \frac{\beta_2\gamma_1}{\beta_2\gamma_1 + \beta_1}$

- Identifiability assumptions include: (A.1) no unmeasured confounding of the exposure-outcome relationship, (A.2) no unmeasured confounding of mediator-outcome relationship, (A.3) no unmeasured confounding of the exposure-mediator relationship, and (A.4) no mediator-outcome confounder affected by the exposure.

- Point Estimates: The ordinary least squared method can be used to obtain the parameter estimates in the outcome model and mediator model. Then, the $\widehat{\text{NIE}}$ and $\widehat{\text{MP}}$ are obtained by replacing the parameters with their corresponding estimators.

- 95% Interval Estimates
  - Multivariate Delta Method
  - Percentile Bootstrap Method

Let $\boldsymbol{\theta} = [\gamma_0, \gamma_1, \boldsymbol{\gamma}_2^T, \beta_0, \beta_1, \beta_2, \boldsymbol{\beta}_3^T]^T$ and $\widehat{\boldsymbol{\Sigma}}_{\boldsymbol{\theta}} = \begin{bmatrix} \widehat{\boldsymbol{\Sigma}}_\gamma & \mathbf{0} \\ \mathbf{0} & \widehat{\boldsymbol{\Sigma}}_{\boldsymbol{\beta}} \end{bmatrix}$ the estimated variance-covariance matrix of $\hat{\boldsymbol{\theta}}$. Then the estimated variances of $\widehat{\text{NIE}}$ and $\widehat{\text{MP}}$ are

$$\widehat{\text{Var}}(\widehat{\text{NIE}}) = \left(\frac{\partial \mathscr{NIE}(\boldsymbol{\theta})}{\partial \boldsymbol{\theta}} \bigg|_{\boldsymbol{\theta}=\hat{\boldsymbol{\theta}}} \right)^T \widehat{\boldsymbol{\Sigma}}_{\boldsymbol{\theta}} \frac{\partial \mathscr{NIE}(\boldsymbol{\theta})}{\partial \boldsymbol{\theta}} \bigg|_{\boldsymbol{\theta}=\hat{\boldsymbol{\theta}}},$$
$$\widehat{\text{Var}}(\widehat{\text{MP}}) = \left(\frac{\partial \mathscr{MP}(\boldsymbol{\theta})}{\partial \boldsymbol{\theta}} \bigg|_{\boldsymbol{\theta}=\hat{\boldsymbol{\theta}}} \right)^T \widehat{\boldsymbol{\Sigma}}_{\boldsymbol{\theta}} \frac{\partial \mathscr{MP}(\boldsymbol{\theta})}{\partial \boldsymbol{\theta}} \bigg|_{\boldsymbol{\theta}=\hat{\boldsymbol{\theta}}},$$

where $\mathscr{NIE}(\boldsymbol{\theta})$ and $\mathscr{MP}(\boldsymbol{\theta})$ are the parametric expressions of NIE and MP (i.e., $\mathscr{NIE}(\boldsymbol{\theta}) = \beta_2\gamma_1(x - x^*)$ and $\mathscr{MP}(\boldsymbol{\theta}) = \frac{\beta_2\gamma_1}{\beta_2\gamma_1+\beta_1}$).
Given these variance estimators, 95% confidence intervals of NIE and MP can be computed by normal approximation as
$\left\{\widehat{\text{NIE}} - 1.96 \times \sqrt{\widehat{\text{Var}}(\widehat{\text{NIE}})}, \widehat{\text{NIE}} + 1.96 \times \sqrt{\widehat{\text{Var}}(\widehat{\text{NIE}})}\right\}$ and
$\left\{\widehat{\text{MP}} - 1.96 \times \sqrt{\widehat{\text{Var}}(\widehat{\text{MP}})}, \widehat{\text{MP}} + 1.96 \times \sqrt{\widehat{\text{Var}}(\widehat{\text{MP}})}\right\}$, respectively.

2 Percentile Bootstrap Method

The percentile bootstrap approach could approximate the empirical distributions of $\widehat{\text{NIE}}$ by resampling the dataset with replacement and re-estimating all model parameters.

- Step I: Resample the dataset with replacement
- Step II: calculate NIE
- Step III: Repeat Steps I and II for a large of times (generally 1000 or more), and generate the empirical distribution of $\widehat{\text{NIE}}$
- Step IV: The 2.5% and 97.5% percentiles of the bootstrap sample distribution are the lower and upper boundaries of the 95% confidence interval of NIE.

Similar procedure applies to the 95% CI of $\widehat{\text{MP}}$.

- Model for the Outcome:
  $E(Y|X, M, \boldsymbol{W}) = \beta_0 + \beta_1 X + \beta_2 M + \boldsymbol{\beta}_3^T \boldsymbol{W}$
- Model for the Mediator:
  $\text{logit}\{P(M = 1|X, \boldsymbol{W})\} = \gamma_0 + \gamma_1 X + \boldsymbol{\gamma}_2^T \boldsymbol{W}$
- Natural Indirect Effect (NIE) conditional on $\boldsymbol{W} = \boldsymbol{w}$ for X in change from x^* to x: $\text{NIE} = \beta_2 \left(\frac{e^{\gamma_0+\gamma_1 x+\boldsymbol{\gamma}_2^T \boldsymbol{w}}}{1+e^{\gamma_0+\gamma_1 x+\boldsymbol{\gamma}_2 \boldsymbol{w}}} - \frac{e^{\gamma_0+\gamma_1 x^*+\boldsymbol{\gamma}_2^T \boldsymbol{w}}}{1+e^{\gamma_0+\gamma_1 x^*+\boldsymbol{\gamma}_2^T \boldsymbol{w}}} \right)$
- Natural Direct Effect (NDE) conditional on $\boldsymbol{W} = \boldsymbol{w}$ for X in change from x^* to x: $\beta_1(x - x^*)$
- Mediation Proportion (MP):

$$\text{MP} = \frac{\text{NIE}}{\text{NDE} + \text{NIE}} = \frac{\beta_2 \left(\frac{e^{\gamma_0+\gamma_1 x+\boldsymbol{\gamma}_2^T \boldsymbol{w}}}{1+e^{\gamma_0+\gamma_1 x+\boldsymbol{\gamma}_2^T \boldsymbol{w}}} - \frac{e^{\gamma_0+\gamma_1 x^*+\boldsymbol{\gamma}_2^T \boldsymbol{w}}}{1+e^{\gamma_0+\gamma_1 x^*+\boldsymbol{\gamma}_2^T \boldsymbol{w}}} \right)}{\beta_1(x - x^*) + \beta_2 \left(\frac{e^{\gamma_0+\gamma_1 x+\boldsymbol{\gamma}_2^T \boldsymbol{w}}}{1+e^{\gamma_0+\gamma_1 x+\boldsymbol{\gamma}_2^T \boldsymbol{w}}} - \frac{e^{\gamma_0+\gamma_1 x^*+\boldsymbol{\gamma}_2^T \boldsymbol{w}}}{1+e^{\gamma_0+\gamma_1 x^*+\boldsymbol{\gamma}_2^T \boldsymbol{w}}} \right)}.$$

- Model for the Outcome:
  $\text{logit}\{P(Y=1|X,M,\boldsymbol{W})\} = \beta_0 + \beta_1 X + \beta_2 M + \boldsymbol{\beta}_3^T \boldsymbol{W}$
- Model for the Mediator:
  $E(M|X,\boldsymbol{W}) = \gamma_0 + \gamma_1 X + \boldsymbol{\gamma}_2^T \boldsymbol{W}$
- VanderWeele and Vansteelandt (2010) showed that under the assumption (1) the outcome is rare and (2) the error term in the mediator model follows a normal distribution:
- $\text{NIE} \approx \beta_2\gamma_1(x - x^*)$
- $\text{NDE} \approx \beta_1(x - x^*)$
- $\text{MP} = \frac{\text{NIE}}{\text{TE}} \approx \frac{\beta_2\gamma_1}{\beta_2\gamma_1 + \beta_1}$
- Note: Above three quantities are defined on a log odds ratio scale for the change of the exposure from x^* to x, conditional on $\boldsymbol{W} = \boldsymbol{w}$.

2 Case #3: Binary Outcome and Continuous Mediator

However, in many epidemiological studies, the disease outcome is not rare. In this paper, we propose the exact expressions of NIE and MP accounting for the common outcomes.

$$\mathrm{NIE} = \log\left(\frac{\int_m \frac{\exp\left(-\frac{m^2-2(\sigma^2\beta_2+\gamma_0+\gamma_1 x+\boldsymbol{\gamma}_2^T\mathbf{w})m}{2\sigma^2}\right)}{1+\exp(\beta_0+\beta_1 x+\beta_2 m+\boldsymbol{\beta}_3^T\mathbf{w})}\,\mathrm{d}m}{\int_m \frac{\exp\left(-\frac{m^2-2(\gamma_0+\gamma_1 x+\boldsymbol{\gamma}_2^T\mathbf{w})m}{2\sigma^2}\right)}{1+\exp(\beta_0+\beta_1 x+\beta_2 m+\boldsymbol{\beta}_3^T\mathbf{w})}\,\mathrm{d}m}\right) - \log\left(\frac{\int_m \frac{\exp\left(-\frac{m^2-2(\sigma^2\beta_2+\gamma_0+\gamma_1 x^*+\boldsymbol{\gamma}_2^T\mathbf{w})m}{2\sigma^2}\right)}{1+\exp(\beta_0+\beta_1 x+\beta_2 m+\boldsymbol{\beta}_3^T\mathbf{w})}\,\mathrm{d}m}{\int_m \frac{\exp\left(-\frac{m^2-2(\gamma_0+\gamma_1 x^*+\boldsymbol{\gamma}_2^T\mathbf{w})m}{2\sigma^2}\right)}{1+\exp(\beta_0+\beta_1 x+\beta_2 m+\boldsymbol{\beta}_3^T\mathbf{w})}\,\mathrm{d}m}\right),$$

$$\mathrm{TE} = \beta_1(x-x^*) + \log\left(\frac{\int_m \frac{\exp\left(-\frac{m^2-2(\sigma^2\beta_2+\gamma_0+\gamma_1 x+\boldsymbol{\gamma}_2^T\mathbf{w})m}{2\sigma^2}\right)}{1+\exp(\beta_0+\beta_1 x+\beta_2 m+\boldsymbol{\beta}_3^T\mathbf{w})}\,\mathrm{d}m}{\int_m \frac{\exp\left(-\frac{m^2-2(\gamma_0+\gamma_1 x+\boldsymbol{\gamma}_2^T\mathbf{w})m}{2\sigma^2}\right)}{1+\exp(\beta_0+\beta_1 x+\beta_2 m+\boldsymbol{\beta}_3^T w)}\,\mathrm{d}m}\right) - \log\left(\frac{\int_m \frac{\exp\left(-\frac{m^2-2(\sigma^2\beta_2+\gamma_0+\gamma_1 x^*+\boldsymbol{\gamma}_2^T\mathbf{w})m}{2\sigma^2}\right)}{1+\exp(\beta_0+\beta_1 x^*+\beta_2 m+\boldsymbol{\beta}_3^T\mathbf{w})}\,\mathrm{d}m}{\int_m \frac{\exp\left(-\frac{m^2-2(\gamma_0+\gamma_1 x^*+\boldsymbol{\gamma}_2^T\mathbf{w})m}{2\sigma^2}\right)}{1+\exp(\beta_0+\beta_1 x^*+\beta_2 m+\boldsymbol{\beta}_3^T\mathbf{w})}\,\mathrm{d}m}\right)$$

$$\mathrm{MP} = \frac{\mathrm{NIE}}{\mathrm{TE}}$$

Note: The normality assumption in the mediator model is still needed.

- Model for the Outcome:
  $\text{logit}\{P(Y=1|X,M,\boldsymbol{W})\} = \beta_0 + \beta_1 X + \beta_2 M + \boldsymbol{\beta}_3^T \boldsymbol{W}$
- Model for the Mediator:
  $\text{logit}\{P(M=1|X,\boldsymbol{W})\} = \gamma_0 + \gamma_1 X + \boldsymbol{\gamma}_2^T \boldsymbol{W}$
- VanderWeele (2015) showed that under the assumption that the outcome is rare:
- NIE $\approx \log\left(\frac{(1+e^{\gamma_0+\gamma_1 x^*+\boldsymbol{\gamma}_2^T \boldsymbol{w}})(1+e^{\beta_2+\gamma_0+\gamma_1 x+\boldsymbol{\gamma}_2^T \boldsymbol{w}})}{(1+e^{\gamma_0+\gamma_1 x+\boldsymbol{\gamma}_2^T \boldsymbol{w}})(1+e^{\beta_2+\gamma_0+\gamma_1 x^*+\boldsymbol{\gamma}_2^T \boldsymbol{w}})}\right)$
- NDE $\approx \beta_1(x-x^*)$
- MP $\approx \dfrac{\log\left(\frac{(1+e^{\gamma_0+\gamma_1 x^*+\boldsymbol{\gamma}_2^T \boldsymbol{w}})(1+e^{\beta_2+\gamma_0+\gamma_1 x+\boldsymbol{\gamma}_2^T \boldsymbol{w}})}{(1+e^{\gamma_0+\gamma_1 x+\boldsymbol{\gamma}_2^T \boldsymbol{w}})(1+e^{\beta_2+\gamma_0+\gamma_1 x^*+\boldsymbol{\gamma}_2^T \boldsymbol{w}})}\right)}{\beta_1(x-x^*)+\log\left(\frac{(1+e^{\gamma_0+\gamma_1 x^*+\boldsymbol{\gamma}_2^T \boldsymbol{w}})(1+e^{\beta_2+\gamma_0+\gamma_1 x+\boldsymbol{\gamma}_2^T \boldsymbol{w}})}{(1+e^{\gamma_0+\gamma_1 x+\boldsymbol{\gamma}_2^T \boldsymbol{w}})(1+e^{\beta_2+\gamma_0+\gamma_1 x^*+\boldsymbol{\gamma}_2^T \boldsymbol{w}})}\right)}$
- Note: Above three quantities are defined on a log odds ratio scale for the change of the exposure from x^* to x, conditional on $\boldsymbol{W}=\boldsymbol{w}$.

2 Case #4: Binary Outcome and Binary Mediator

We also propose the exact expressions of NIE and MP without the rare outcome assumption.

$$
\begin{aligned}
\text{NIE} =& \log\left(\frac{1+e^{\beta_0+\beta_1 x+\beta_2+\boldsymbol{\beta}_3^T w}+e^{\gamma_0+\gamma_1 x^*+\boldsymbol{\gamma}_2^T w}(1+e^{\beta_0+\beta_1 x+\boldsymbol{\beta}_3^T w})}{1+e^{\beta_0+\beta_1 x+\beta_2+\boldsymbol{\beta}_3^T w}+e^{\gamma_0+\gamma_1 x+\boldsymbol{\gamma}_2^T w}(1+e^{\beta_0+\beta_1 x+\boldsymbol{\beta}_3^T w})}\right) \\
&+\log\left(\frac{1+e^{\beta_0+\beta_1 x+\beta_2+\boldsymbol{\beta}_3^T \mathbf{w}}+e^{\beta_2+\gamma_0+\gamma_1 x+\boldsymbol{\gamma}_2^T \mathbf{w}}(1+e^{\beta_0+\beta_1 x+\boldsymbol{\beta}_3^T \mathbf{w}})}{1+e^{\beta_0+\beta_1 x+\beta_2+\boldsymbol{\beta}_3^T \mathbf{w}}+e^{\beta_2+\gamma_0+\gamma_1 x^*+\boldsymbol{\gamma}_2 \mathbf{w}}(1+e^{\beta_0+\beta_1 x+\boldsymbol{\beta}_3^T \mathbf{w}})}\right), \\
\text{TE} =& \beta_1(x-x^*)+\log\left(\frac{1+e^{\beta_0+\beta_1 x^*+\beta_2+\boldsymbol{\beta}_3^T w}+e^{\gamma_0+\gamma_1 x^*+\boldsymbol{\gamma}_2^T w}(1+e^{\beta_0+\beta_1 x^*+\boldsymbol{\beta}_3^T w})}{1+e^{\beta_0+\beta_1 x+\beta_2+\boldsymbol{\beta}_3^T w}+e^{\gamma_0+\gamma_1 x+\boldsymbol{\gamma}_2^T w}(1+e^{\beta_0+\beta_1 x+\boldsymbol{\beta}_3^T w})}\right) \\
&+\log\left(\frac{1+e^{\beta_0+\beta_1 x+\beta_2+\boldsymbol{\beta}_3^T \mathbf{w}}+e^{\beta_2+\gamma_0+\gamma_1 x+\boldsymbol{\gamma}_2^T \mathbf{w}}(1+e^{\beta_0+\beta_1 x+\boldsymbol{\beta}_3^T \mathbf{w}})}{1+e^{\beta_0+\beta_1 x^*+\beta_2+\boldsymbol{\beta}_3^T \mathbf{w}}+e^{\beta_2+\gamma_0+\gamma_1 x^*+\boldsymbol{\gamma}_2^T \mathbf{w}}(1+e^{\beta_0+\beta_1 x^*+\boldsymbol{\beta}_3^T \mathbf{w}})}\right), \\
\text{MP} =& \frac{\text{NIE}}{\text{TE}}
\end{aligned}
$$

3 Outline

3 Simulation Settings

- Cases of Continuous Outcome (Cases #1 and #2)
  - 4 levels of sample sizes: 150, 500, 1000, 5000
  - $\text{TE} \in \{0.25, 0.5, 1\}$
  - $\text{MP} \in \{0.05, 0.2, 0.5\}$
- Cases of Binary Outcome (Cases #3 and #4)
  - $P(Y = 1|X = M = 0) = 3\%$
  - 4 levels of sample sizes: 500, 1000, 5000, 20000
  - $\text{TE} \in \{\log(1.2), \log(1.5), \log(2)\}$
  - $\text{MP} \in \{0.05, 0.2, 0.5\}$
- No confounding variables
- Binary exposure with $P(X = 1) = 0.5$
- Exposure-mediator correlation $\text{Corr}(X, M) = 0.2$

3 Data Generation Procedure

- Simulate $X \sim \mathit{Bernoulli}(0.5)$
- Simulate M given X according to

$$\begin{cases} M = \gamma_0 + \gamma_1 X + N(0,1) & \text{if M is continuous,} \\ P(M=1|X) = \dfrac{\exp\{\gamma_0 + \gamma_1 X\}}{1+\exp\{\gamma_0 + \gamma_1 X\}} & \text{if M is binary,} \end{cases}$$

  where γ_0 and γ_1 are selected to ensure $\text{Corr}(X, M) = 0.2$.
- Simulate Y given M and X, according to

$$\begin{cases} Y = \beta_0 + \beta_1 X + \beta_2 M + N(0,1) & \text{if Y is continuous,} \\ P(Y=1|X,M) = \dfrac{\exp\{\beta_0 + \beta_1 X + \beta_2 M\}}{1+\exp\{\beta_0 + \beta_1 X + \beta_2 M\}} & \text{if Y is binary,} \end{cases}$$

  where β_0 and β_1 and β_2 are selected to satisfy the TE, MP and $P(Y = 1|X = M = 0) = 0.03$ for the cases of binary outcome.
- Obtain $\widehat{\text{NIE}}$ and $\widehat{\text{MP}}$, variance estimates by the multivariate delta method, and the corresponding 95% confidence intervals by the multivariate delta method and percentile bootstrap method.
- Repeat the previous steps for 5,000 times.

- Percent Bias (Bias(%)): Bias(%) $= median(\frac{\hat{p}-p}{p}) \times 100\%$, where p denotes the true value of the casual mediation measure (NIE and MP), and $\hat{p}$ is the point estimate of the simulated casual mediation measure.
- Variance Ratio (VR): defined as the ratio between the median of the estimated variance and the empirical variance, and is used to determined the accuracy of the variance estimator obtained by the multivariate delta method
- 95% Confidence Interval Coverage Rate (CR): the coverage rate of the 95% confidence interval across 5,000 replications

			$\widehat{\text{NIE}}$				$\widehat{\text{MP}}$			
N	MP	TE	Bias(%)	CR$^{(d)}$	CR$^{(b)}$	VR	Bias(%)	CR$^{(d)}$	CR$^{(b)}$	VR
150	0.05	0.25	-16.4	**99.2**	**96.4**	0.998	-27.5	**99.2**	**98.8**	0.000
	0.05	0.5	-15.1	**96.5**	**95.7**	0.992	-14.1	**96.9**	**96.5**	0.058
	0.05	1	-10.5	**92.2**	94.7	0.993	-9.8	**92.6**	95.1	0.949
	0.2	0.25	-10.5	**92.2**	94.7	0.993	-19.7	**90.6**	**97.3**	0.000
	0.2	0.5	-6.2	**92.5**	94.8	1.001	-2.8	**92.9**	**96.4**	0.092
	0.2	1	-2.1	94.8	94.9	1.012	-1.7	**95.7**	95.4	0.944
	0.5	0.25	-4.7	**93.2**	94.8	1.007	-14.1	**89.1**	**97.0**	0.000
	0.5	0.5	-1.6	95.1	95.0	1.012	-0.4	**96.0**	**97.0**	0.026
	0.5	1	-0.1	95.5	94.9	1.013	0.2	**97.5**	95.3	0.710
500	0.05	0.25	-4.4	**96.0**	94.4	0.997	-3.5	**97.8**	**96.6**	0.002
	0.05	0.5	-3.5	94.7	**94.2**	0.988	-3.4	95.3	94.5	0.855
	0.05	1	-2.6	**93.1**	**94.2**	0.983	-2.8	**93.4**	**94.4**	0.948
	0.2	0.25	-2.6	**93.1**	**94.2**	0.983	-1.5	**92.1**	**97.0**	0.001
	0.2	0.5	-1.5	**93.6**	94.5	0.982	-0.8	**94.4**	94.8	0.801
	0.2	1	-0.2	94.5	94.5	0.981	-0.1	94.7	94.6	0.945
	0.5	0.25	-0.9	**94.0**	94.5	0.980	-0.4	**92.3**	**97.5**	0.000
	0.5	0.5	-0.1	94.7	**94.3**	0.982	0.1	95.5	94.9	0.770
	0.5	1	0.6	94.5	94.5	0.983	0.0	95.6	94.7	0.915
1000	0.05	0.25	-4.0	95.4	94.7	0.969	-3.2	**97.0**	95.4	0.724
	0.05	0.5	-2.2	94.8	94.7	0.969	-2.8	95.2	95.1	0.924
	0.05	1	-2.1	**94.1**	94.8	0.971	-1.9	**94.0**	94.7	0.967
	0.2	0.25	-2.1	**94.1**	94.8	0.971	-1.1	**93.5**	**96.3**	0.580
	0.2	0.5	-1.1	**94.2**	94.6	0.981	-1.2	**94.2**	94.8	0.923
	0.2	1	-0.9	94.9	94.8	0.986	-0.8	94.6	94.4	0.981
	0.5	0.25	-1.1	94.4	94.6	0.983	-0.5	**92.8**	**96.6**	0.441
	0.5	0.5	-0.5	95.0	94.9	0.987	-0.5	94.9	94.6	0.916
	0.5	1	-0.3	94.8	94.7	0.988	-0.4	95.0	94.5	0.966
5000	0.05	0.25	-0.5	94.8	94.8	0.990	0.3	95.5	94.8	0.961
	0.05	0.5	-0.2	94.9	95.0	0.995	-0.3	95.4	95.0	0.990
	0.05	1	-0.2	95.0	95.1	1.007	-0.3	95.0	95.1	1.006
	0.2	0.25	-0.2	95.0	95.1	1.007	0.1	95.6	95.1	0.936
	0.2	0.5	-0.1	95.0	95.2	1.027	-0.1	95.1	95.3	1.004
	0.2	1	0.0	95.3	95.2	1.038	0.0	95.1	95.1	1.031
	0.5	0.25	0.0	95.3	95.5	1.032	0.1	95.0	94.7	0.920
	0.5	0.5	-0.1	95.3	95.2	1.040	0.0	95.2	95.0	0.995
	0.5	1	0.0	95.4	95.2	1.041	0.0	95.3	95.4	1.022

3 Simulation results for Case #2: continuous outcome and binary mediator.

			$\widehat{\text{NIE}}$				$\widehat{\text{MP}}$			
N	MP	TE	Bias(%)	CR$^{(d)}$	CR$^{(b)}$	VR	Bias(%)	CR$^{(d)}$	CR$^{(b)}$	VR
150	0.05	0.25	-25.2	**98.9**	**97.1**	1.039	-36.7	**99.1**	**98.9**	0.002
	0.05	0.5	-19.7	**96.0**	**96.2**	1.050	-18.5	**96.6**	**96.9**	0.069
	0.05	1	-12.8	**92.7**	95.2	1.042	-12.9	**92.5**	95.6	0.957
	0.2	0.25	-12.8	**92.7**	95.2	1.042	-21.6	**90.4**	**97.3**	0.000
	0.2	0.5	-7.6	**92.6**	95.3	1.043	-5.2	**92.7**	**96.8**	0.003
	0.2	1	-2.7	95.0	95.2	1.024	-2.5	**96.4**	**95.6**	0.941
	0.5	0.25	-5.9	**93.4**	95.4	1.038	-14.2	**89.6**	**97.5**	0.000
	0.5	0.5	-1.9	95.2	95.1	1.018	-1.9	**96.0**	**97.3**	0.036
	0.5	1	-0.3	94.9	94.8	1.007	-0.6	**98.1**	**95.7**	0.762
500	0.05	0.25	-3.3	**96.5**	95.1	1.013	-2.5	**98.2**	**96.9**	0.039
	0.05	0.5	-3.9	**95.7**	95.2	1.013	-3.2	**95.7**	95.3	0.937
	0.05	1	-2.6	**94.2**	95.0	1.012	-2.7	**94.1**	95.1	0.997
	0.2	0.25	-2.6	**94.2**	95.0	1.012	-0.5	**92.8**	**97.1**	0.035
	0.2	0.5	-1.6	**94.1**	95.1	1.018	-0.9	94.6	95.6	0.887
	0.2	1	-0.6	95.2	95.4	1.021	-0.5	95.3	95.2	1.004
	0.5	0.25	-1.2	94.4	95.3	1.018	0.0	**92.2**	**97.5**	0.002
	0.5	0.5	-0.4	95.5	95.4	1.024	0.0	**96.1**	95.5	0.814
	0.5	1	0.2	95.6	95.5	1.028	0.0	**96.0**	95.1	0.968
1000	0.05	0.25	-1.6	**95.6**	94.8	1.024	-2.7	**97.1**	95.2	0.733
	0.05	0.5	-2.7	95.2	95.0	1.028	-2.1	95.4	94.5	0.983
	0.05	1	-2.1	94.7	95.2	1.033	-1.6	94.4	94.8	1.019
	0.2	0.25	-2.1	94.7	95.2	1.033	0.5	**94.2**	**96.1**	0.539
	0.2	0.5	-0.8	94.5	95.0	1.031	-0.1	95.0	95.0	0.938
	0.2	1	-0.3	95.0	95.0	1.022	0.2	95.2	94.9	0.999
	0.5	0.25	-0.6	94.7	95.0	1.029	0.4	**93.8**	**97.1**	0.185
	0.5	0.5	-0.1	95.1	95.2	1.021	0.2	**95.7**	94.9	0.908
	0.5	1	0.0	94.8	94.9	1.014	0.2	95.3	95.0	0.973
5000	0.05	0.25	-0.7	95.0	95.0	0.981	-1.5	95.0	94.6	0.943
	0.05	0.5	-0.7	94.8	94.6	0.980	-0.9	94.5	**94.4**	0.972
	0.05	1	-0.3	94.8	94.8	0.978	-0.5	94.5	94.7	0.979
	0.2	0.25	-0.3	94.8	94.8	0.978	-0.6	94.6	94.9	0.909
	0.2	0.5	-0.1	95.1	94.9	0.981	-0.2	94.6	94.6	0.966
	0.2	1	-0.1	94.9	94.8	0.986	0.0	94.6	94.6	0.983
	0.5	0.25	-0.2	94.9	94.8	0.982	-0.3	95.3	95.0	0.885
	0.5	0.5	-0.1	94.9	95.0	0.988	-0.3	95.2	94.9	0.965
	0.5	1	0.0	94.9	94.9	0.991	0.0	95.1	95.0	0.982

3 Simulation results for Case #3: binary outcome and continuous mediator, based on the approximate NIE and MP expressions

				$\widehat{\text{NIE}}^{(a)}$				$\widehat{\text{MP}}^{(a)}$			
N	Ncase (%)	MP	TE	Bias(%)	CR$^{(d)}$	CR$^{(b)}$	VR	Bias(%)	CR$^{(d)}$	CR$^{(b)}$	VR
	16 (3.2%)	0.05	log(1.2)	18.5	**97.3**	**93.5**	0.957	-82.2	**99.9**	**99.4**	0.000
	18 (3.7%)	0.05	log(1.5)	-2.8	**97.3**	**93.8**	0.965	-56.9	**99.8**	**99.1**	0.000
	22 (4.4%)	0.05	log(2)	-5.1	**97.2**	**94.1**	0.956	-22.2	**99.2**	**98.3**	0.000
	16 (3.2%)	0.2	log(1.2)	-3.2	**97.5**	**93.6**	0.958	-87.5	**92.1**	**97.6**	0.001
	18 (3.7%)	0.2	log(1.5)	-2.2	**96.4**	**93.7**	0.952	-51.2	**91.3**	**97.1**	0.000
500	23 (4.6%)	0.2	log(2)	-1.0	95.2	**94.3**	0.961	-11.8	**91.0**	**96.5**	0.000
	16 (3.3%)	0.5	log(1.2)	-1.7	**96.0**	**93.3**	0.932	-87.1	**70.8**	**93.8**	0.001
	20 (4.1%)	0.5	log(1.5)	-0.8	**94.3**	**93.7**	0.893	-40.4	**81.6**	**95.8**	0.000
	31 (6.1%)	0.5	log(2)	5.4	**94.3**	**94.1**	0.889	-3.1	**89.3**	**97.0**	0.000
	32 (3.2%)	0.05	log(1.2)	-2.5	**96.1**	**94.1**	0.942	-81.7	**99.7**	**99.6**	0.000
	37 (3.7%)	0.05	log(1.5)	-8.4	**95.7**	**94.1**	0.937	-33.3	**99.6**	**99.0**	0.000
	44 (4.4%)	0.05	log(2)	-5.4	95.5	**94.0**	0.957	-7.1	**98.6**	**97.1**	0.011
	32 (3.2%)	0.2	log(1.2)	-4.6	**96.1**	**93.8**	0.958	-78.8	**92.3**	**98.0**	0.000
	37 (3.7%)	0.2	log(1.5)	-1.7	**95.7**	94.6	0.974	-30.0	**91.3**	**97.4**	0.000
1000	46 (4.6%)	0.2	log(2)	-2.5	95.1	94.7	0.985	-5.2	**92.2**	**97.1**	0.006
	33 (3.3%)	0.5	log(1.2)	-2.1	**95.7**	**93.9**	0.973	-73.0	**73.6**	95.1	0.001
	41 (4.1%)	0.5	log(1.5)	-1.2	95.0	95.4	1.011	-19.7	**85.6**	**97.1**	0.006
	61 (6.1%)	0.5	log(2)	5.4	95.3	95.0	0.987	0.1	**91.6**	**97.6**	0.002
	164 (3.2%)	0.05	log(1.2)	3.5	94.9	94.5	0.970	-29.3	**99.6**	**99.2**	0.000
	186 (3.7%)	0.05	log(1.5)	-1.8	95.2	94.9	0.996	-4.3	**98.4**	**96.6**	0.035
	221 (4.4%)	0.05	log(2)	0.3	94.9	94.5	0.981	-0.4	**96.6**	95.0	0.864
	165 (3.2%)	0.2	log(1.2)	1.0	94.8	94.6	0.984	-27.7	**92.5**	**97.6**	0.000
	189 (3.7%)	0.2	log(1.5)	0.9	94.7	94.7	0.991	-0.6	**93.0**	**97.0**	0.003
5000	232 (4.6%)	0.2	log(2)	0.5	95.2	95.0	1.039	0.4	94.5	95.3	0.777
	168 (3.3%)	0.5	log(1.2)	0.2	94.8	94.8	0.979	-21.7	**84.3**	**96.6**	0.000
	207 (4.1%)	0.5	log(1.5)	1.0	95.1	95.3	1.015	0.0	**91.4**	**97.0**	0.001
	309 (6.1%)	0.5	log(2)	6.3	**92.5**	**91.0**	0.999	0.7	94.6	94.5	0.767
	657 (3.2%)	0.05	log(1.2)	2.5	95.3	\	1.024	0.0	**98.5**	\	0.002
	744 (3.7%)	0.05	log(1.5)	-0.3	95.5	\	1.017	0.2	**96.6**	\	0.903
	885 (4.4%)	0.05	log(2)	0.1	95.2	\	1.018	0.5	95.4	\	0.982
	660 (3.2%)	0.2	log(1.2)	0.6	95.2	\	1.010	-0.7	**92.9**	\	0.000
	756 (3.7%)	0.2	log(1.5)	0.0	95.3	\	1.004	0.3	94.6	\	0.783
20000	929 (4.6%)	0.2	log(2)	0.6	94.9	\	1.008	0.2	95.0	\	0.947
	672 (3.3%)	0.5	log(1.2)	0.4	95.4	\	1.007	-1.1	**90.8**	\	0.000
	831 (4.1%)	0.5	log(1.5)	1.1	95.1	\	1.013	0.4	**94.3**	\	0.781
	1237 (6.1%)	0.5	log(2)	6.1	**79.5**	\	0.980	0.9	95.0	\	0.945

3 Simulation results for Case #3: binary outcome and continuous mediator, based on the exact NIE and MP expressions

N	Ncase (%)	MP	TE	$\widehat{\text{NIE}}$ Bias(%)	$\widehat{\text{NIE}}$ $\text{CR}^{(d)}$	$\widehat{\text{NIE}}$ $\text{CR}^{(b)}$	$\widehat{\text{NIE}}$ VR	$\widehat{\text{MP}}$ Bias(%)	$\widehat{\text{MP}}$ $\text{CR}^{(d)}$	$\widehat{\text{MP}}$ $\text{CR}^{(b)}$	$\widehat{\text{MP}}$ VR
	16 (3.2%)	0.05	log(1.2)	18.5	**96.8**	**93.5**	0.962	-82.2	**99.9**	**99.4**	0.000
	18 (3.7%)	0.05	log(1.5)	-2.8	**96.9**	**93.8**	0.968	-56.9	**99.8**	**99.1**	0.000
	22 (4.4%)	0.05	log(2)	-5.1	**96.8**	**94.1**	0.957	-22.3	**99.2**	**98.3**	0.000
	16 (3.2%)	0.2	log(1.2)	-3.2	**97.0**	**93.6**	0.962	-87.5	**92.0**	**97.5**	0.001
500	18 (3.7%)	0.2	log(1.5)	-2.3	**96.0**	**93.7**	0.959	-51.4	**91.2**	**97.1**	0.000
	23 (4.6%)	0.2	log(2)	-1.8	94.9	**94.3**	0.970	-12.1	**90.9**	**96.5**	0.000
	16 (3.3%)	0.5	log(1.2)	-1.9	**95.7**	**93.3**	0.936	-87.1	**70.8**	**93.8**	0.001
	20 (4.1%)	0.5	log(1.5)	-2.2	**93.9**	**93.7**	0.906	-40.5	**81.5**	**95.8**	0.000
	31 (6.1%)	0.5	log(2)	-1.2	**93.1**	**94.0**	0.920	-3.8	**88.9**	**96.9**	0.000
	32 (3.2%)	0.05	log(1.2)	-2.5	**95.7**	**94.1**	0.941	-81.7	**99.7**	**99.6**	0.000
	37 (3.7%)	0.05	log(1.5)	-8.4	95.5	**94.1**	0.938	-33.3	**99.6**	**99.0**	0.000
	44 (4.4%)	0.05	log(2)	-5.4	95.3	**94.0**	0.957	-7.2	**98.6**	**97.1**	0.011
	32 (3.2%)	0.2	log(1.2)	-4.6	**95.8**	**93.8**	0.957	-78.9	**92.3**	**98.0**	0.000
1000	37 (3.7%)	0.2	log(1.5)	-1.9	95.6	94.6	0.974	-30.1	**91.3**	**97.4**	0.000
	46 (4.6%)	0.2	log(2)	-3.2	94.9	94.8	0.990	-5.4	**92.1**	**97.1**	0.006
	33 (3.3%)	0.5	log(1.2)	-2.2	95.6	**93.9**	0.973	-73.0	**73.6**	95.1	0.001
	41 (4.1%)	0.5	log(1.5)	-2.4	94.9	95.4	1.015	-19.8	**85.5**	**97.1**	0.006
	61 (6.1%)	0.5	log(2)	-1.0	94.5	95.2	1.003	-0.6	**91.3**	**97.5**	0.002
	164 (3.2%)	0.05	log(1.2)	3.5	94.8	94.5	0.970	-29.3	**99.6**	**99.2**	0.000
	186 (3.7%)	0.05	log(1.5)	-1.8	95.1	94.9	0.996	-4.3	**98.4**	**96.6**	0.035
	221 (4.4%)	0.05	log(2)	0.3	94.8	94.5	0.981	-0.4	**96.6**	95.0	0.864
	165 (3.2%)	0.2	log(1.2)	1.0	94.8	94.6	0.984	-27.7	**92.5**	**97.6**	0.000
5000	189 (3.7%)	0.2	log(1.5)	0.7	94.7	94.7	0.991	-0.6	**93.0**	**97.0**	0.003
	232 (4.6%)	0.2	log(2)	-0.1	95.1	95.0	1.039	0.3	94.4	95.3	0.776
	168 (3.3%)	0.5	log(1.2)	0.0	94.8	94.7	0.980	-21.7	**84.3**	**96.6**	0.000
	207 (4.1%)	0.5	log(1.5)	-0.2	95.1	95.3	1.015	-0.1	**91.3**	**97.0**	0.001
	309 (6.1%)	0.5	log(2)	0.0	95.2	95.3	1.005	0.0	**94.0**	**94.4**	0.766
	657 (3.2%)	0.05	log(1.2)	2.5	95.3	\	1.024	0.0	**98.5**	\	0.002
	744 (3.7%)	0.05	log(1.5)	-0.3	95.5	\	1.017	0.2	**96.6**	\	0.903
	885 (4.4%)	0.05	log(2)	0.1	95.2	\	1.018	0.5	95.4	\	0.982
	660 (3.2%)	0.2	log(1.2)	0.6	95.2	\	1.010	-0.7	**92.9**	\	0.000
20000	756 (3.7%)	0.2	log(1.5)	-0.2	95.2	\	1.004	0.3	94.6	\	0.783
	929 (4.6%)	0.2	log(2)	0.0	94.9	\	1.009	0.1	95.0	\	0.947
	672 (3.3%)	0.5	log(1.2)	0.3	95.3	\	1.007	-1.1	**90.8**	\	0.000
	831 (4.1%)	0.5	log(1.5)	-0.1	95.3	\	1.013	0.3	**94.2**	\	0.781
	1237 (6.1%)	0.5	log(2)	-0.1	94.7	\	0.980	0.2	94.7	\	0.944

3 Simulation results for Case #4: binary outcome and binary mediator, based on the approximate NIE and MP expressions

N	Ncase (%)	MP	TE	$\widehat{\text{NIE}}^{(a)}$ Bias(%)	$\widehat{\text{NIE}}^{(a)}$ CR$^{(d)}$	$\widehat{\text{NIE}}^{(a)}$ CR$^{(b)}$	$\widehat{\text{NIE}}^{(a)}$ VR	$\widehat{\text{MP}}^{(a)}$ Bias(%)	$\widehat{\text{MP}}^{(a)}$ CR$^{(d)}$	$\widehat{\text{MP}}^{(a)}$ CR$^{(b)}$	$\widehat{\text{MP}}^{(a)}$ VR
500	16 (3.3%)	0.05	log(1.2)	-50.0	**93.1**	**93.7**	0.867	-92.1	**99.5**	**99.4**	0.000
	18 (3.7%)	0.05	log(1.5)	-17.7	**93.9**	**94.1**	0.892	-61.3	**99.2**	**99.3**	0.000
	22 (4.6%)	0.05	log(2)	-6.0	**94.3**	**94.1**	0.899	-22.9	**98.1**	**98.3**	0.000
	17 (3.4%)	0.2	log(1.2)	-10.0	**92.8**	**93.8**	0.868	-88.8	**89.9**	**97.5**	0.000
	20 (4.0%)	0.2	log(1.5)	-3.5	**93.2**	94.5	0.912	-50.5	**90.3**	**97.3**	0.000
	26 (5.2%)	0.2	log(2)	-2.8	**94.0**	94.9	0.940	-13.9	**90.1**	**96.8**	0.000
	18 (3.6%)	0.5	log(1.2)	-5.5	**92.6**	**94.3**	0.908	-84.8	**70.8**	**94.2**	0.000
	24 (4.8%)	0.5	log(1.5)	-1.7	**93.1**	94.9	0.949	-37.1	**81.9**	**95.7**	0.000
	37 (7.5%)	0.5	log(2)	-0.5	**93.9**	95.4	0.998	-6.1	**88.7**	**96.6**	0.000
1000	33 (3.3%)	0.05	log(1.2)	-7.5	**94.2**	94.9	0.922	-89.5	**99.4**	**99.4**	0.000
	37 (3.7%)	0.05	log(1.5)	-2.5	**94.3**	94.7	0.935	-32.6	**98.8**	**98.7**	0.000
	45 (4.6%)	0.05	log(2)	-4.4	**94.4**	94.7	0.959	-5.5	**97.3**	**97.0**	0.010
	34 (3.4%)	0.2	log(1.2)	0.8	**94.3**	94.6	0.936	-78.4	**91.4**	**97.9**	0.000
	40 (4.0%)	0.2	log(1.5)	-1.5	**94.0**	94.7	0.941	-25.8	**90.9**	**97.2**	0.000
	52 (5.2%)	0.2	log(2)	-0.7	**94.2**	94.8	0.957	-1.8	**91.6**	**96.6**	0.005
	36 (3.6%)	0.5	log(1.2)	-0.7	**94.4**	95.0	0.944	-70.8	**75.6**	95.5	0.000
	48 (4.8%)	0.5	log(1.5)	0.4	**94.2**	95.1	0.970	-14.0	**87.1**	**97.2**	0.000
	75 (7.5%)	0.5	log(2)	0.4	94.8	95.2	0.990	-2.8	**90.4**	**96.7**	0.004
5000	166 (3.3%)	0.05	log(1.2)	-14.5	95.1	95.2	0.995	-42.4	**99.3**	**98.2**	0.002
	190 (3.7%)	0.05	log(1.5)	-3.4	94.9	95.1	0.996	-4.7	**97.7**	**96.9**	0.011
	229 (4.6%)	0.05	log(2)	-2.2	94.9	95.0	0.998	-1.6	**96.3**	95.4	0.890
	171 (3.4%)	0.2	log(1.2)	-4.1	94.8	95.1	0.991	-31.3	**92.4**	**97.8**	0.001
	204 (4.0%)	0.2	log(1.5)	-0.9	95.1	95.2	0.999	-1.2	**93.5**	**97.5**	0.049
	261 (5.2%)	0.2	log(2)	0.5	95.0	95.1	0.991	0.4	95.2	95.3	0.832
	183 (3.6%)	0.5	log(1.2)	-1.4	94.8	95.1	0.980	-21.8	**85.5**	**97.4**	0.000
	242 (4.8%)	0.5	log(1.5)	0.2	94.9	95.0	0.981	0.5	**92.1**	**97.6**	0.000
	378 (7.5%)	0.5	log(2)	1.0	94.7	94.7	0.979	-1.9	**93.7**	95.1	0.851
20000	663 (3.3%)	0.05	log(1.2)	-5.1	95.1	\	1.022	-7.6	**98.4**	\	0.000
	759 (3.7%)	0.05	log(1.5)	-1.2	94.8	\	1.008	-1.5	**96.3**	\	0.886
	916 (4.6%)	0.05	log(2)	-0.1	95.3	\	1.016	-0.5	**95.8**	\	0.973
	684 (3.4%)	0.2	log(1.2)	-1.1	94.6	\	0.994	-2.0	**93.1**	\	0.002
	815 (4.0%)	0.2	log(1.5)	0.5	94.7	\	1.007	0.2	95.1	\	0.793
	1043 (5.2%)	0.2	log(2)	0.9	95.1	\	0.999	0.3	95.2	\	0.931
	731 (3.6%)	0.5	log(1.2)	0.3	94.7	\	0.996	-0.7	**91.0**	\	0.000
	969 (4.8%)	0.5	log(1.5)	1.0	94.8	\	0.994	0.1	**94.3**	\	0.796
	1514 (7.5%)	0.5	log(2)	1.1	94.7	\	0.995	-1.7	**92.7**	\	0.927

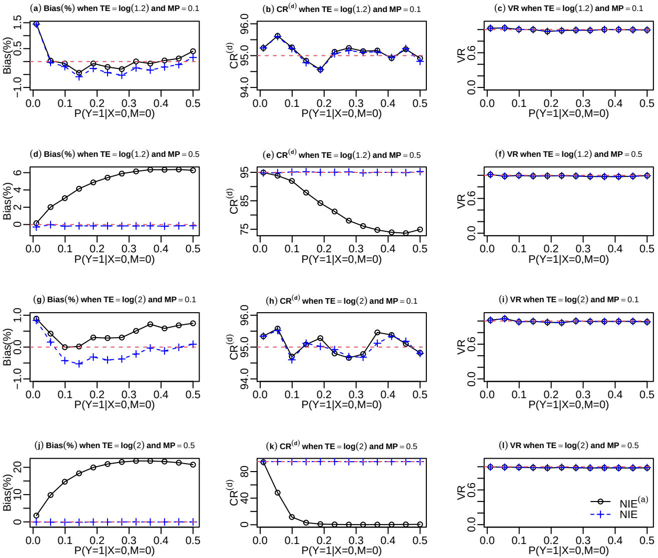
3 Simulation results for Case #4: binary outcome and binary mediator, based on the exact NIE and MP expressions

				$\widehat{NIE}$				$\widehat{MP}$			
N	Ncase (%)	MP	TE	Bias(%)	$CR^{(d)}$	$CR^{(b)}$	VR	Bias(%)	$CR^{(d)}$	$CR^{(b)}$	VR
500	16 (3.3%)	0.05	log(1.2)	-50.0	**93.4**	**93.7**	0.866	-91.6	**99.5**	**99.4**	0.000
	18 (3.7%)	0.05	log(1.5)	-17.8	**94.4**	**94.1**	0.893	-61.2	**99.3**	**99.3**	0.000
	22 (4.6%)	0.05	log(2)	-6.4	94.7	**94.1**	0.903	-23.3	**98.3**	**98.3**	0.000
	17 (3.4%)	0.2	log(1.2)	-10.3	**93.3**	**93.8**	0.868	-88.7	**90.1**	**97.5**	0.000
	20 (4.0%)	0.2	log(1.5)	-4.2	**93.5**	94.5	0.908	-50.8	**90.2**	**97.3**	0.000
	26 (5.2%)	0.2	log(2)	-4.0	**94.1**	94.9	0.935	-14.5	**90.0**	**96.8**	0.000
	18 (3.6%)	0.5	log(1.2)	-6.0	**92.9**	**94.3**	0.908	-84.7	**70.9**	**94.3**	0.000
	24 (4.8%)	0.5	log(1.5)	-3.0	**93.1**	94.9	0.942	-37.0	**81.9**	**95.7**	0.000
	37 (7.5%)	0.5	log(2)	-1.5	**93.5**	95.1	0.991	-3.4	**89.7**	**97.0**	0.000
1000	33 (3.3%)	0.05	log(1.2)	-7.5	94.4	94.9	0.922	-89.3	**99.5**	**99.4**	0.000
	37 (3.7%)	0.05	log(1.5)	-2.7	94.5	94.7	0.933	-32.7	**98.8**	**98.6**	0.000
	23 (4.6%)	0.05	log(2)	-4.9	94.7	94.6	0.961	-6.0	**97.6**	**97.0**	0.010
	34 (3.4%)	0.2	log(1.2)	0.5	94.4	94.6	0.933	-78.4	**91.5**	**97.8**	0.000
	40 (4.0%)	0.2	log(1.5)	-2.2	**94.2**	94.6	0.937	-26.2	**90.8**	**97.2**	0.000
	52 (5.2%)	0.2	log(2)	-2.1	**94.2**	94.9	0.956	-2.4	**91.5**	**96.5**	0.005
	36 (3.6%)	0.5	log(1.2)	-1.3	94.5	95.0	0.942	-70.9	**75.6**	95.5	0.000
	48 (4.8%)	0.5	log(1.5)	-0.8	**94.3**	95.2	0.968	-14.0	**87.0**	**97.2**	0.000
	75 (7.5%)	0.5	log(2)	-1.0	94.5	95.1	0.984	-0.7	**91.3**	**97.0**	0.007
5000	166 (3.3%)	0.05	log(1.2)	-24.5	95.2	95.2	0.995	-42.5	**99.4**	**99.2**	0.001
	190 (3.7%)	0.05	log(1.5)	-3.6	95.0	95.1	0.995	-4.8	**97.7**	**96.9**	0.015
	229 (4.6%)	0.05	log(2)	-2.6	95.0	95.1	0.999	-2.0	**96.3**	95.4	0.891
	171 (3.4%)	0.2	log(1.2)	-4.4	94.9	95.1	0.990	-31.4	**92.3**	**98.0**	0.000
	204 (4.0%)	0.2	log(1.5)	-1.6	95.0	95.3	1.000	-1.7	**93.3**	**97.4**	0.053
	261 (5.2%)	0.2	log(2)	-0.9	95.0	95.2	0.990	-0.3	94.9	95.0	0.829
	183 (3.6%)	0.5	log(1.2)	-2.0	94.7	95.0	0.980	-22.1	**85.4**	**97.4**	0.000
	242 (4.8%)	0.5	log(1.5)	-1.0	94.7	94.9	0.980	0.4	**92.0**	**97.6**	0.000
	378 (7.5%)	0.5	log(2)	-0.3	94.6	94.6	0.979	-0.1	94.9	95.3	0.861
20000	663 (3.3%)	0.05	log(1.2)	-5.2	95.1	\	1.022	-7.7	**98.4**	\	0.000
	759 (3.7%)	0.05	log(1.5)	-1.4	94.8	\	1.008	-1.7	**96.3**	\	0.888
	916 (4.6%)	0.05	log(2)	-0.5	95.2	\	1.015	-0.9	**95.7**	\	0.973
	684 (3.4%)	0.2	log(1.2)	-1.4	94.6	\	0.993	-2.2	**93.1**	\	0.002
	815 (4.0%)	0.2	log(1.5)	-0.1	94.6	\	1.007	-0.2	94.8	\	0.792
	1043 (5.2%)	0.2	log(2)	-0.5	95.1	\	0.999	-0.4	95.0	\	0.931
	731 (3.6%)	0.5	log(1.2)	-0.3	94.7	\	0.995	-1.0	**90.9**	\	0.000
	969 (4.8%)	0.5	log(1.5)	-0.2	94.8	\	0.994	0.0	**94.3**	\	0.797
	1514 (7.5%)	0.5	log(2)	-0.1	94.9	\	0.995	0.0	94.5	\	0.930

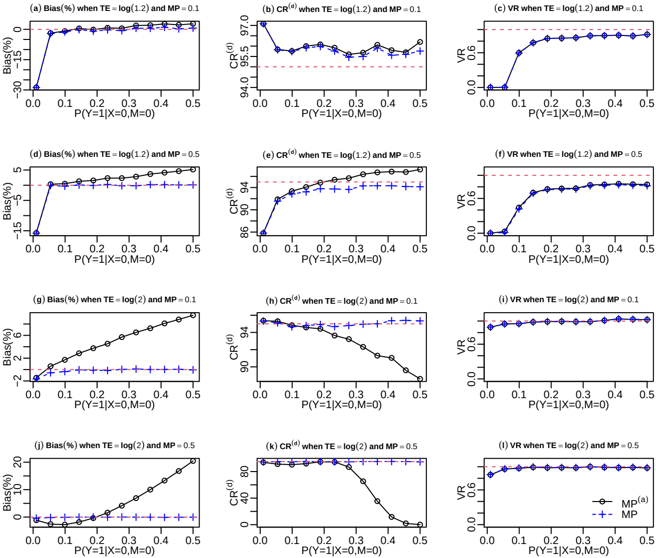
3 Outcome Prevalence

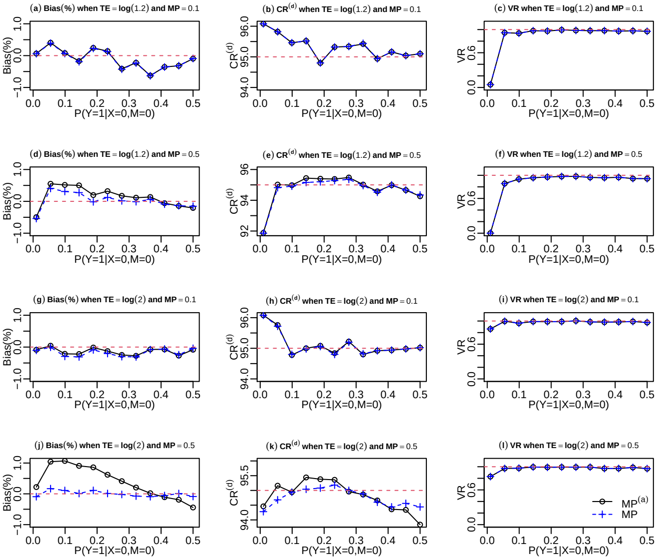
We conducted additional simulations to compare the mediation analyses based on the approximate expressions and exact expressions ($\widehat{\text{NIE}}^{(a)}$ v.s. $\widehat{\text{NIE}}$ and $\widehat{\text{MP}}^{(a)}$ v.s. $\widehat{\text{MP}}$) when the baseline outcome prevalence is varied from 1% to 50%. We considered TE$\in (\log(1.2), \log(2))$, MP$\in (0.1, 0.5)$ and a large sample size of 20,000.

3 Case #3, binary outcome and continuous mediator

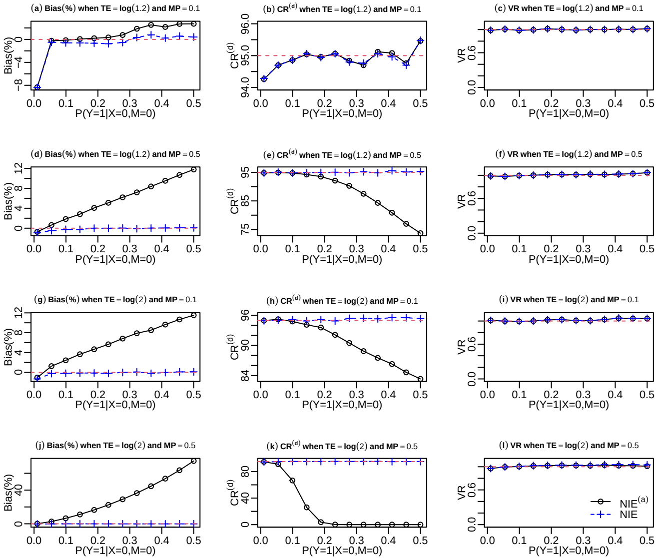


3 Case #3, binary outcome and continuous mediator




(a) Bias(%) when TE = log(1.2) and MP = 0.1
(b) CR(d) when TE = log(1.2) and MP = 0.1
(c) VR when TE = log(1.2) and MP = 0.1
(d) Bias(%) when TE = log(1.2) and MP = 0.5
(e) CR(d) when TE = log(1.2) and MP = 0.5
(f) VR when TE = log(1.2) and MP = 0.5
(g) Bias(%) when TE = log(2) and MP = 0.1
(h) CR(d) when TE = log(2) and MP = 0.1
(i) VR when TE = log(2) and MP = 0.1
(j) Bias(%) when TE = log(2) and MP = 0.5
(k) CR(d) when TE = log(2) and MP = 0.5
(l) VR when TE = log(2) and MP = 0.5
Bias(%)
CR(d)
VR
P(Y=1|X=0,M=0)
MP(a)
MP

3 Case #4, binary outcome and binary mediator



- $\widehat{\text{NIE}}$ generally has minimal bias, and both the delta and the bootstrap method introduce accurate NIE interval estimates.
- Larger sample size is needed to obtain appropriate MP point and interval estimates.
  - When the outcome is continuous, a sample size of 500 is required for good point and interval estimates of MP.
  - In the scenario with binary outcome and a rare disease condition is employed, sample size of 5000 and number of cases at 200 is required to obtain a satisfactory MP point estimate and bootstrap interval estimates.
  - The delta method does not perform well in the scenarios of binary outcome except $N = 20000$.
- Bootstrap method provides better interval estimates comparing to the delta method.
- When baseline outcome prevalence is less than 5%, the rare outcome assumption works well and $\widehat{\text{NIE}}^{(a)}$ and $\widehat{\text{MP}}^{(a)}$ are likely appropriate.

MaxART is a stepped-wedge randomized trial among HIV-positive participants in Eswatini, whose primary objective is to understand the impact of early access to antiretroviral therapy (EAAA) versus standard of care (SOC) among HIV-positive participants. From September 2014 to August 2017, the MaxART Consortium randomly assigned 14 participating clinics in pairs to shift from SoC to EAAA at pre-specified dates.

Previous analysis of MaxART study observed that EAAA improves retention in HIV care (Khan et al., 2020), but the mechanisms underlying the intervention-retention relationship is unknown. In this illustrative example, we investigated the extent to which the effect of intervention (SoC v.s. EAAA) on 12-month retention in HIV care is through 6-month visit adherence.

- **Outcome:** 12-month retention in HIV care (non-retention=1, retention=0)
  - Definition: Participant is classified as retained in HIV care for 12 months if, at the end of the 12th month past enrollment, the participant is alive and has not stopped treatment, whereby either the last clinic visit is less than 90 days or next scheduled visit date is within 30 days.
  - We excluded the participants whoes enrollment date is less than 12 months to the end of the study.
- **Exposure:** intervention (EAAA=1, SoC=0)
  - We excluded the participants who initially received SoC treatment and the transition date to EAAA is less than 12 months from enrollment.
- **Mediator:** 6-month visit adherence (success=1, failure=0)
  - The participants are expected to have a follow-up visit in every 30 days. It follows that at the end of the 6th month the participants are expected to complete 6 or more clinical visits. Here, the operating definition of the 6-month visit adherence is given as whether the participant has completed 5 or more clinical visits at end of the 6th month after enrollment.

4 Illustrative Example: MaxART study

Finally, 1,731 participants were used in our illustrative analysis.

Intervention	EAAA	SoC
	717 (41%)	1014 (59%)
12-month Retention	**Non-retention**	**Retention**
	396 (23%)	1335 (77%)
6-month Visit Adherence	**Success**	**Failure**
	831 (48%)	900 (52%)

We consider two scenarios for the confounding adjustment (i.e., $\boldsymbol{W}$) in the outcome and mediator models.

- **Scenario I:** only adjusted for the steptime.
- **Scenario II:** adjusted for all the factors that may confound intervention-retention relationship, visit adherence-retention relationship, and intervention-visit adherence relationship.
  - The confounders include steptime, age at study enrollment (<20 yrs, $[20, 30)$ yrs, $[30, 40)$ yrs, $[40, 50)$ yrs, $[50, 60)$ yrs, ≥ 60 yrs), sex, marital status, education, CD4 counts (<350 cells/ul, $[350, 500]$ cells/ul, >500 cells/ul), WHO stage, BMI (<18.5, $[18.5, 25)$, $[25, 30)$, ≥ 30), screened for TB symptoms (yes, no), viral load (<5000 copies/ml, $[5000, 30000]$ copies/ml, >30000 copies/ml), treatment support (yes, no), level of clinic, time from HIV tested positive to enrollment (<1 yr, 1-3 yrs, >3 yrs), clinic volume (Low: $<$ median, High $\geq$ median).
- The missing indicator method (Groenwold et al., 2012) was used to account for missing confounders, where missing data was treated as a separate group for each of the confounding variables in the models.

Table: Results of NIE, TE and MP estimates based on the approximate expression under a rare outcome assumption (upper panel) and exact expression (lower panel).

Expression	Scenario	Parameter	Point	S.E.	Delta 95% CI	Bootstrap 95% CI
Approximate	Steptime adjusted	NIE[a]	-0.601	0.091	(-0.779,-0.424)	(-0.782,-0.445)
		TE[a]	-1.472	0.226	(-1.915,-1.030)	(-1.973,-1.031)
		MP[a]	0.408	0.069	(0.273,0.544)	(0.305,0.559)
	Multivariate adjusted	NIE[a]	-0.972	0.121	(-1.208,-0.735)	(-1.287,-0.775)
		TE[a]	-2.520	0.287	(-3.082,-1.958)	(-3.282,-1.975)
		MP[a]	0.386	0.050	(0.288,0.483)	(0.292,0.494)
Exact	Steptime adjusted	NIE	-0.630	0.093	(-0.813,-0.448)	(-0.816,-0.474)
		TE	-1.444	0.213	(-1.862,-1.027)	(-1.922,-1.023)
		MP	0.437	0.073	(0.293,0.580)	(0.327,0.597)
	Multivariate adjusted	NIE	-0.970	0.120	(-1.205,-0.735)	(-1.282,-0.772)
		TE	-2.316	0.267	(-2.841,-1.792)	(-3.033,-1.819)
		MP	0.419	0.054	(0.313,0.525)	(0.322,0.539)

Note: All the mediation measures are defined on a log odds ratio scale for the intervention in change from SoC to EAAA, conditional on the most frequent level of the confounding variables. S.E. denotes the standard error of the point estimates, which is calculated by the multivariate delta method.

5 Outline

5 Software

The R package "mediateP" for implementing the mediation models in this paper is presented in https://github.com/chaochengstat/mediateP.

We can use the following statements to install the "mediateP" package

```
> devtools::install_github("chaochengstat/mediateP")
> library("mediateP")
```

The main function of the "mediateP" package is `mediate()`, which presents the mediation analysis results. It can be called with

```
> mediate(data, outcome, mediator, exposure, binary.outcome,
               binary.mediator, covariate.outcome, covariate.mediator,
               x0, x1, c.outcome, c.mediator, boot, R)
```

Use the `help(mediate)` command to find the meaning of the parameters.

- Computational issues for the bootstrap method.
- The effect size of the TE and the performance of MP estimates.
  - A larger TE benefits the performance of the MP estimate ($\text{MP} = \frac{\text{NIE}}{\text{TE}}$).
  - For binary outcome, if there is prior information that the TE is not small, the delta method can provide satisfactory MP interval estimates when $N \geq 5000$ and number of cases ≥ 150.
- Limitations and future work.
  - For simplicity, our simulation study do not include confounders.
  - We consider the scenarios that the outcome and mediator can be binary or continuous. As a future topic, we will consider the scenarios of ordinal and right-censoring survival outcomes.
  - The relative efficiency between the product and difference methods were not fully investigated among current literatures, which could be another interesting future topic.

5 References

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Thank you