**Parametric Regression-Based Causal Mediation Analysis of Binary Outcomes and Binary Mediators: Moving Beyond the Rareness or Commonness of the Outcome**

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**WEB APPENDIX 1**

**General formulas used in the delta method for the exact regression-based mediation effects**

The formulas for calculating the confidence intervals of the natural effects on the odd ratio, risk ratio, and risk difference scales depend upon the nested counterfactual outcome probability and its gradient with respect to the coefficients of the mediator and outcome models . The following equations will be used to derive the expression for the aforementioned gradient as well as those for the standard errors of estimates.

For any scalar function differentiable in where , the partial derivatives of and are:

|  |  |
| --- | --- |
|  | (A1) |

where .

For any scalar functions and , differentiable in and taking values in :

|  |  |
| --- | --- |
|  | (A2) |
|  | (A3) |

where , .

**Nested probability formulas based on the mediator and outcome logistic models**

Let denote the set of adjustment variables. Under identifying and modeling assumptions (1-2) from the main text, the nested probability for exposure levels and is expressed as follows:

Let denote this last expression:

|  |  |
| --- | --- |
|  | (A4) |

Then, using general formulas (A1), the partial derivatives of with respect to each of the coefficients are:

where is the cardinal number of.

Thus, the gradient of the scalar function with respect to the vector

is

|  |  |
| --- | --- |
|  | (A5) |

where

**Delta method for mediation exact regression-based odds ratios**

We define the following notation:

where is defined in (A5).

We can express the regression-based exact and in terms of defined in (A4) as follows:

To construct the 95% confidence intervals (CIs) for the exact natural effect OR by first-order multivariate delta method ([1](#_ENREF_1)), we have applied the same approach as in ([2](#_ENREF_2)), that is we have expressed standard errors (se) for and according to the following approximate formulas:

where is a block matrix, and are the covariance matrices for the vectorsand , respectively. The gradients of and are expressed using as follows:

Thus,

are the 95% CIs for and , respectively. Therefore, 95% CIs for and are given by

Finally, we have for the total effect odds ratio that

and

Thus, a 95% CI for is

and, consequently, approximate 95% CI for is given by

**Delta method for exact mediation regression-based risk ratios**

We have for the RR scale that

and, correspondingly,

The equation (A3) implies that

Thus,

and 95% CIs for and can be approximated by

Finally, we have for the total effect :

The 95% CI for can be approximated by

**Delta method for exact mediation regression-based risk differences**

We have for the RD scale:

Thus, 95% CIs for exact mediation effects , , and can be approximated by

**Mediation controlled direct effects**

Controlled direct effects reflect causal effect of the direct manipulation on the mediator and can be useful in policy evaluation ([3](#_ENREF_3), [4](#_ENREF_4)). We let be the potential outcome that would have been observed under the exposure and mediator levels and , respectively. Under outcome model (2) and independently of the mediator model, the corresponding counterfactual probability is expressed as

Thus, the logistic regression-based CDEs on the OR, RR and RD scales can be expressed as follows:

.

The derivatives of with respect to each of the coefficients of the outcome model are:

We define the following notation:

where is the gradient of with respect to .Then

and

is the approximate 95% CI for derived by the delta method.

Taking the derivative of with respect to the outcome model coefficients, we get

Let us define

Thus, by applying the delta method,

and

is the approximate 95% CI for . See ([3](#_ENREF_3)) for the delta method for .

**Decomposition property of the exact total effect estimator**

For binary outcomes, the total causal effect corresponding to a change in the binary exposure level from to , conditional on , is defined as a contrast between counterfactual probabilities and , and can be expressed, under the no unmeasured confounders, positivity and consistency assumptions, as a contrast between and ([2](#_ENREF_2), [3](#_ENREF_3)). In order to examine the decomposition property of the exact and approximate TE estimators on the OR and RR scales (Equations 6,10), we compared the estimate of the total effect calculated as the product of NIE and NDE estimates to the one obtained without consideration of the mediator. More precisely, for each sample generated, probabilities and were estimated from the outcome logistic regression model

as and converted to the so-called conventional (that is, non-mediated) TE estimates on the OR and RR scales:

The conventional TE estimates were then compared to TE estimates calculated as the product of the NIE and NDE based on proposed exact estimators using absolute and relative differences:

A similar approach was taken to examine the TE decomposition property of the approximate estimator . For both the exact and approximate estimators, the mean and standard deviation of these differences were computed over all 1000 samples generated.

The TE decomposition property results for the exact and approximate estimators are reported for the simulation study without covariates in Web Table 5. We can see, for all scenarios studied and both multiplicative scales, that the products of the exact NDE and NIE estimates over all samples generated were almost identical to the corresponding conventional TE estimates, with mean relative differences ranging between 0.0001% and 0.0029%. This is to be expected given that the logistic outcome model is saturated in this case and that corresponding estimated model-based probabilities for Y given A and M and for M given A match those that would be obtained from the corresponding two- and one-way frequency tables. For *Scenario 1*, the differences between the products of the approximate NDE and NIE estimates and conventional TE estimates were small: the mean relative differences were equal to -0.48% and 3.94% for the OR and RR scales, respectively. These differences were much larger for *Scenarios 2 – 4* (between 20.5% and 60.4%). In the approximate approach, the expit of the linear predictor associated to the outcome model is replaced by an exponential after the regression coefficients have been estimated (compare Equation 3 to Equation 8). Therefore, the corresponding model-based conditional probabilities do not match those from the frequency table anymore, hence producing a discrepancy between the two types of total effects. For the OR scale, this discrepancy is additionally explained by substitution of the OR by RR (see Equation 9).

The TE decomposition property results for the simulation study with covariates are presented in Web Table 6. When covariates are included in the outcome logistic model, it is expected to observe some difference between mediated and non mediated total effects ([5](#_ENREF_5)), but the magnitude of the disagreement is of interest. The mean relative differences between the products of the exact NDE and NIE estimates and the corresponding conventional TE estimates over all samples generated ranged between -1.59% and 0.50%. For *Scenario 1*, the differences between the products of the approximate NDE and NIE estimates and conventional TE estimates were equal to 0.06% and 3.83% for the OR and RR scales, respectively, while those were much larger for *Scenarios 2 – 4* (between 31.6% and 69.6%).

**Comments on estimation procedures**

***Simulation studies***

In order to reduce execution time when generating the exact and approximate results in the simulation study, we created a global macro (available upon request) based on our principal macro and the macro by [Valeri and VanderWeele (3)](#_ENREF_3) to compute results *simultaneously*. Consistency of results for the approximate estimates returned from this macro and V&V original macro was verified for a few randomly selected samples generated.

***Real data example***

Logistic regression was used to model the mediator in all the mediation analyses performed.

Logistic regression was used to model the outcome when estimating natural effects on the OR scale with the SAS CAUSALMED procedure ([6](#_ENREF_6)). For the RR scale, an outcome log-binomial regression model was specified in PROC CAUSALMED. An outcome Poisson regression model was used instead of a log-binomial model when the latter did not converge (notably with placental abruption as exposure). When using the delta method for the effect expressed on the OR and RR scales, our SAS macro *mediation\_estimates* returns a confidence interval as , as in the V&V SAS macro. Consequently, the symmetric confidence interval returned by PROC CAUSALMED is not perfectly comparable to the one obtained by our SAS macro when using the delta method for multiplicative scales.

A weighting-based approach to estimate conditional (or stratum-specific) natural effects was taken for all the mediation analyses performed using the R package *medflex* ([7](#_ENREF_7), [8](#_ENREF_8)); NEMs with *logit* and *log* link functions were used for OR and RR scales, respectively. The 95% CIs were constructed by percentile bootstrap based on 1000 resamples for the mediation effects when the exposure variable was treatment with ICS. Percentile bootstrap was also applied to obtain mediation effects on the OR scale with placental abruption as exposure; CIs based on the robust standard errors were calculated for the RR scale since *medflex* failed to provide bootstrap CIs for these specific exposure and scale.

The quasi-Bayesian approach was implemented using the R package *mediation* with a *logit* link for the outcome model. Corresponding results on the RD scale were based on 5000 Monte-Carlo draws. The 95% CIs were based on the White’s heteroskedasticity-consistent estimator for the covariance matrix ([9](#_ENREF_9)).

**WEB APPENDIX 2**

**Comments on the SAS macro *mediation\_estimates* execution**

Use of the SAS macro *mediation\_estimates* (see Web Appendix 3) requires the specification of macro variables. We provide three examples showing how to specify values for these variables.

The following statement returns crude (unadjusted) estimates for ORNDE, ORNDE and ORTE for a change in the exposure (binary or continuous) from level to level , assuming there is no exposure-mediator interaction, and using the delta method to construct 95% confidence intervals. Conventional logistic regressions without Firth penalization are also used.

%mediation\_estimates(mydata=*data*, A=*exposure*, M=*mediato*r, Y=*outcome,* interaction=0, adjusted=0, a1=, a0=, boot=0, scale="OR", Firth=0).

To perform an adjusted and penalized (with Firth) mediation analysis on the RR scale, allowing for an exposure-mediator interaction and using bootstrap based on 5000 samples with initial random seed = 1234 to construct 95% confidence intervals, our SAS macro *mediation\_estimates* should be executed as follows:

%mediation\_estimates(mydata=*data*, A=*exposure*, M=*mediato*r, Y=*outcome,* interaction=1, adjusted=1, cvar\_M=Mvar1 Mvar2 ... Mvarp, cvar\_Y=Yvar1 Yvar2 ... Yvars, a1=, a0=, boot=1, bootseed=1234, nboot=5000, scale="RR", Firth=1)

where Mvar1 Mvar2 ... Mvarp and Yvar1 Yvar2 ... Yvars are the set of adjustment covariates for the mediator and outcome models, correspondingly. Due to the non-collapsibility of the logistic regression model ([10](#_ENREF_10), [11](#_ENREF_11)), we advise against using different sets of adjustment covariates in the outcome and mediator models unless it is known that excluded covariates are independent of the response being modeled given the rest of covariates.

By default, our SAS macro reports mediation effects evaluated at the sample-specific mean values of the covariates. In order to estimate mediation effects at specific values of some covariates (that is, stratum-specific effects), the user needs to provide SAS datasets DATA\_M and DATA\_Y containing those values **before** executing the SAS macro *mediation\_estimates*. For example, in order to estimate mediation effects corresponding to Mvar1=Cm1, Mvar2=Cm2, Mvar3=Cm3 (i.e., at user-defined values for the first three adjustment covariates in the mediator model), and Yvar3=Cy3, Yvar4=Cy4 (i.e., at user-defined values for the third and fourth covariates in the outcome model), datasets DATA\_M and DATA\_Y can be constructed using datalinesstatements as follows:

data DATA\_M; input Mvar1 Mvar2 Mvar3; datalines;

Cm1 Cm2 Cm3

;

data DATA\_Y; input Yvar3 Yvar4; datalines;

Cy3 Cy4

;

Common adjustment covariates in DATA\_M and DATA\_Y must have the same values; otherwise, the macro execution will be aborted, and a warning will be displayed in the SAS log. Moreover, the list of variables with unequal values will be shown in the SAS Results Viewer window.

For example, the user can estimate mediation effects on the RD scale that correspond to the covariate values specified in DATA\_M and DATA\_Y, assuming an exposure-mediator interaction and using the delta method to construct 95% confidence intervals, as follows:

%mediation\_estimates(mydata=*data*, A=*exposure*, M=*mediato*r, Y=*outcome,* interaction=1, adjusted=1, cvar\_M=Mvar1 Mvar2 ... Mvarp, cvar\_Y=Yvar1 Yvar2 ... Yvars, a1=, a0=, boot=0, scale="RD", Firth=0, stratum=1, cvar\_M\_data= DATA\_M, cvar\_Y\_data= DATA\_Y)

If the covariates specified in DATA\_M (DATA\_Y) constitute some proper subset of {Mvar1,Mvar2, ...,Mvarp} ({Yvar1,Yvar2, ...,Yvars}), then the other covariates will be set to their sample-specific mean levels.

**Categorical covariates**

If, for example, Mvar1 Mvar2 are two dummy variables coding some categorical covariate Vcat with three levels, we can estimate mediation effects at the reference level by constructing DATA\_M as follows:

data DATA\_M; input Mvar1 Mvar2; datalines;

**00**

;

In order to estimate mediation effects corresponding to the second level of Vcat, the user has to provide DATA\_M as

data DATA\_M; input Mvar1 Mvar2; datalines;

**10**

;

Finally, to estimate mediation effects corresponding to the third level of Vcat, DATA\_M should be provided as

data DATA\_M; input Mvar1 Mvar2; datalines;

**01**

;

The same strategy can be applied to the construction of DATA\_Y.

**Missing values**

Our SAS macro *mediation\_estimates* performs all computations on complete cases only. Users can apply multiple imputation techniques implemented in the R package *mice* ([12](#_ENREF_12))and the SAS MI procedure ([13](#_ENREF_13)) to handle missing data.

**WEB APPENDIX 3**

/\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*/

/\* The user needs to specify the values for the following macro variables in the macro %mediation\_estimates: \*/

/\* \*/

/\* mydata: input data that include the outcome, exposure and mediator variables as well as the covariates to be \*/

/\* adjusted for in the model; \*/

/\* A: the name of the exposure variable; \*/

/\* M: the name of the mediator variable; \*/

/\* Y: the name of the outcome variable; \*/

/\* interaction: the user needs to specify INTERACTION=0 or INTERACTION=1 for the outcome model without or with interaction \*/

/\* between the exposure and the mediator, respectively; \*/

/\* adjusted: the user needs to specify ADJUSTED=0 or ADJUSTED=1 to obtain unadjusted or adjusted NIE, NDE and TE, \*/

/\* respectively; \*/

/\* cvar\_M: the list of adjustment variables (covariates) in the mediator model; categorical variables need to be coded \*/

/\* as a series of dummy variables before being entered as covariates; use space to separate covariates’ names; \*/

/\* cvar\_Y: the list of adjustment variables (covariates) in the outcome model; categorical variables need to be coded \*/

/\* as a series of dummy variables before being entered as covariates; \*/

/\* a0: the exposure level corresponding to a\*; \*/

/\* a1: the exposure level corresponding to a; \*/

/\* boot: the user needs to specify BOOT=0 or BOOT=1 to obtain 95% confidence intervals by the delta method or \*/

/\* bootstrapping, respectively; \*/

/\* bootseed: if BOOT=1, that is bootstrap 95% confidence intervals are required, then the user needs to specify the \*/

/\* initial seed (positive integer) for random number generation; \*/

/\* nboot: if BOOT=1, that is bootstrap 95% confidence intervals are required, then the user needs to specify the \*/

/\* number of bootstrap samples; \*/

/\* scale: the user needs to specify SCALE="OR", SCALE="RR" or SCALE="RD" to obtain estimated mediation effects on \*/

/\* the odds ratio, risk ratio or risk difference scale, respectively; double quotation marks must be used, \*/

/\* e.g., "OR"; \*/

/\* Firth: the user needs to specify FIRTH=1 in order to use the Firth method in logistic regressions; if FIRTH=0, \*/

/\* conventional maximum likelihood estimates are returned by logistic regressions; \*/

/\* stratum: the user needs to specify STRATUM=1 to estimate mediation effects at specific values of some covariates \*/

/\* (that is, stratum-specific effects); \*/

/\* cvar\_M\_data: if STRATUM=1, the user needs to provide a SAS dataset with a single row that contains specific values for \*/

/\* some or all of the adjustment covariates cvar\_M in the mediator model; if the covariates specified in \*/

/\* cvar\_M\_data constitute some proper subset of cvar\_M, then the other covariates will be set to their \*/

/\* sample-specific mean levels; \*/

/\* cvar\_Y\_data: if STRATUM=1, the user needs to provide a SAS dataset with a single row that contains specific values for \*/

/\* some or all of the adjustment covariates cvar\_Y in the outcome model; if the covariates specified in \*/

/\* cvar\_Y\_data constitute some proper subset of cvar\_Y, then the other covariates will be set to their \*/

/\* sample-specific mean levels. \*/

/\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*/

%macro mediation\_estimates(mydata, A, M, Y, interaction, adjusted, cvar\_M, cvar\_Y, a1, a0, boot, bootseed, nboot, scale, Firth, stratum, cvar\_M\_data, cvar\_Y\_data);

 %if &adjusted=0 %then %do;

 %if &Firth=0 %then %do;

 proc logistic data=&mydata noprint outest=coeffs\_M (drop=\_:) desc; model &M = &A; run;

 %if &interaction=1 %then %do;

 proc logistic data=&mydata noprint outest=coeffs\_Y (drop=\_:) desc; model &Y = &A|&M; run;

 %end;

 %if &interaction=0 %then %do;

 proc logistic data=&mydata noprint outest=coeffs\_Y (drop=\_:) desc; model &Y = &A &M; run;

 %end;

 %end;

 %if &Firth=1 %then %do;

 proc logistic data=&mydata noprint outest=coeffs\_M (drop=\_:) desc;

 model &M = &A / Firth; run;

 %if &interaction=1 %then %do;

 proc logistic data=&mydata noprint outest=coeffs\_Y (drop=\_:) desc;

 model &Y = &A|&M / Firth; run;

 %end;

 %if &interaction=0 %then %do;

 proc logistic data=&mydata noprint outest=coeffs\_Y (drop=\_:) desc;

 model &Y = &A &M / Firth; run;

 %end;

 %end;

 %end;

 %if &adjusted=1 %then %do;

 %if &Firth=0 %then %do;

 proc logistic data=&mydata noprint outest=coeffs\_M (drop=\_:) desc; model &M = &A &cvar\_M; run;

 %if &interaction=1 %then %do;

 proc logistic data=&mydata noprint outest=coeffs\_Y (drop=\_:) desc; model &Y = &A|&M &cvar\_Y; run;

 %end;

 %if &interaction=0 %then %do;

 proc logistic data=&mydata noprint outest=coeffs\_Y (drop=\_:) desc; model &Y = &A &M &cvar\_Y; run;

 %end;

 %end;

 %if &Firth=1 %then %do;

 proc logistic data=&mydata noprint outest=coeffs\_M (drop=\_:) desc;

 model &M = &A &cvar\_M / Firth; run;

 %if &interaction=1 %then %do;

 proc logistic data=&mydata noprint outest=coeffs\_Y (drop=\_:) desc;

 model &Y = &A|&M &cvar\_Y / Firth; run;

 %end;

 %if &interaction=0 %then %do;

 proc logistic data=&mydata noprint outest=coeffs\_Y (drop=\_:) desc;

 model &Y = &A &M &cvar\_Y / Firth; run;

 %end;

 %end;

 proc means data=&mydata mean noprint; var &cvar\_M; output out=cvar\_values\_M (where=(\_STAT\_="MEAN")); run;

 proc means data=&mydata mean noprint; var &cvar\_Y; output out=cvar\_values\_Y (where=(\_STAT\_="MEAN")); run;

 %if &stratum=1 %then %do;

 proc datasets lib=work nolist; delete cvar\_names\_M cvar\_names\_Y; quit; run;

 %if %length(&cvar\_M\_data) = 0 %then %do;

 %put ERROR: if STRATUM=1, then cvar\_M\_data and cvar\_Y\_data must be specified;

 %abort; %end;

 %if %length(&cvar\_Y\_data) = 0 %then %do;

 %put ERROR: if STRATUM=1, then cvar\_M\_data and cvar\_Y\_data must be specified;

 %abort; %end;

 %if %sysfunc(exist(&cvar\_M\_data)) %then %do;

 proc contents data=&cvar\_M\_data noprint out=cvar\_names\_M (keep=name); run;

 %end;

 %else %do;

 %put ERROR: if STRATUM=1, then cvar\_M\_data must be provided;

 %abort; %end;

 %if %sysfunc(exist(&&cvar\_Y\_data)) %then %do;

 proc contents data=&cvar\_Y\_data noprint out=cvar\_names\_Y (keep=name); run;

 %end;

 %else %do;

 %put ERROR: if STRATUM=1, then cvar\_Y\_data must be provided;

 %abort; %end;

 proc sort data=cvar\_names\_M; by name; run;

 proc sort data=cvar\_names\_Y; by name; run;

 data common\_vars; merge cvar\_names\_M (in=a) cvar\_names\_Y (in=b); by name;

 if a and b then output; run;

 proc sql noprint; select count(\*) into :count1 from common\_vars; quit;

 %if &count1 ne 0 %then %do;

 ods exclude CompareDatasets CompareDifferences;

 proc compare base=&cvar\_M\_data compare=&cvar\_Y\_data nosummary out=check outnoequal; run;

 proc sql noprint; select count(\*) into :count2 from check; quit;

 %if &count2 ne 0 %then %do;

%put WARNING: Some common variables &cvar\_M\_data and &cvar\_Y\_data do not have the same values (are unequal);

 %put WARNING: See RESULTS for details;

 %abort;

 %end;

 %end;

 data cvar\_values\_M; merge cvar\_values\_M &cvar\_M\_data; run;

 data cvar\_values\_Y; merge cvar\_values\_Y &cvar\_Y\_data; run;

 %end;

 %end;

 %if &boot=0 %then %do;

 %if &adjusted=0 %then %do;

 %if &Firth=0 %then %do;

 proc logistic data=&mydata noprint outest=sigma\_M (drop=\_:) covout desc;

 model &M = &A ; run;

 %if &interaction=1 %then %do;

 proc logistic data=&mydata noprint outest=sigma\_Y (drop=\_:) covout desc;

 model &Y = &A|&M ; run;

 %end;

 %if &interaction=0 %then %do;

 proc logistic data=&mydata noprint outest=sigma\_Y (drop=\_:) covout desc;

 model &Y = &A &M; run;

 %end;

 %end;

 %if &Firth=1 %then %do;

 proc logistic data=&mydata noprint outest=sigma\_M (drop=\_:) covout desc;

 model &M = &A / Firth; run;

 %if &interaction=1 %then %do;

 proc logistic data=&mydata noprint outest=sigma\_Y (drop=\_:) covout desc;

 model &Y = &A|&M / Firth; run;

 %end;

 %if &interaction=0 %then %do;

 proc logistic data=&mydata noprint outest=sigma\_Y (drop=\_:) covout desc;

 model &Y = &A &M / Firth; run;

 %end;

 %end;

 %end;

 %if &adjusted=1 %then %do;

 %if &Firth=0 %then %do;

 proc logistic data=&mydata noprint outest=sigma\_M (drop=\_:) covout desc;

 model &M = &A &cvar\_M; run;

 %if &interaction=1 %then %do;

 proc logistic data=&mydata noprint outest=sigma\_Y (drop=\_:) covout desc;

 model &Y = &A|&M &cvar\_Y; run;

 %end;

 %if &interaction=0 %then %do;

 proc logistic data=&mydata noprint outest=sigma\_Y (drop=\_:) covout desc;

 model &Y = &A &M &cvar\_Y; run;

 %end;

 %end;

 %if &Firth=1 %then %do;

 proc logistic data=&mydata noprint outest=sigma\_M (drop=\_:) covout desc;

 model &M = &A &cvar\_M / Firth; run;

 %if &interaction=1 %then %do;

 proc logistic data=&mydata noprint outest=sigma\_Y (drop=\_:) covout desc;

 model &Y = &A|&M &cvar\_Y / Firth; run;

 %end;

 %if &interaction=0 %then %do;

 proc logistic data=&mydata noprint outest=sigma\_Y (drop=\_:) covout desc;

 model &Y = &A &M &cvar\_Y / Firth; run;

 %end;

 %end;

 %end;

 data sigma\_M; set sigma\_M; if \_n\_=1 then delete; run;

 data sigma\_Y; set sigma\_Y; if \_n\_=1 then delete; run;

 %end;

 proc iml;

 use coeffs\_M; read var {Intercept} into beta\_0;

 read var {&A} into beta\_1;

 %if &adjusted=1 %then %do; read var {&cvar\_M} into cov\_coeffs\_M; %end;

 %if &adjusted=0 %then %do; cov\_coeffs\_M=0; %end;

 use coeffs\_Y; read var {Intercept} into theta\_0;

 read var {&A} into theta\_1;

 read var {&M} into theta\_2;

 %if &interaction=1 %then %do; read var {&A.&M} into theta\_3; %end;

 %if &interaction=0 %then %do; theta\_3=0; %end;

 %if &adjusted=1 %then %do; read var {&cvar\_Y} into cov\_coeffs\_Y; %end;

 %if &adjusted=0 %then %do; cov\_coeffs\_Y=0; %end;

 %if &adjusted=1 %then %do;

 use cvar\_values\_M; read var {&cvar\_M} into cov\_values\_M;

 use cvar\_values\_Y; read var {&cvar\_Y} into cov\_values\_Y;

 product\_betas\_c = cov\_coeffs\_M\*t(cov\_values\_M);

 product\_thetas\_c = cov\_coeffs\_Y\*t(cov\_values\_Y);

 %end;

 %if &adjusted=0 %then %do;

 product\_betas\_c = 0; product\_thetas\_c = 0;

 %end;

 K\_1 = exp(beta\_0+beta\_1\*&a1+product\_betas\_c);

 K\_0 = exp(beta\_0+beta\_1\*&a0+product\_betas\_c);

 L\_1 = exp(theta\_0+theta\_1\*&a1+theta\_2+theta\_3\*&a1+product\_thetas\_c);

 L\_0 = exp(theta\_0+theta\_1\*&a0+theta\_2+theta\_3\*&a0+product\_thetas\_c);

 M\_1 = exp(theta\_0+theta\_1\*&a1+product\_thetas\_c);

 M\_0 = exp(theta\_0+theta\_1\*&a0+product\_thetas\_c);

 P11 = (L\_1/(1+L\_1))\*(K\_1/(1+K\_1))+(M\_1/(1+M\_1))\*(1/(1+K\_1));

 P10 = (L\_1/(1+L\_1))\*(K\_0/(1+K\_0))+(M\_1/(1+M\_1))\*(1/(1+K\_0));

 P00 = (L\_0/(1+L\_0))\*(K\_0/(1+K\_0))+(M\_0/(1+M\_0))\*(1/(1+K\_0));

 %if &scale = "OR" %then %do; NDE = (P10/(1-P10))/(P00/(1-P00)); NIE = (P11/(1-P11))/(P10/(1-P10)); TE = NDE\*NIE; %end;

 %if &scale = "RR" %then %do; NDE = P10/P00; NIE = P11/P10; TE = NDE\*NIE; %end;

 %if &scale = "RD" %then %do; NDE = P10-P00; NIE = P11-P10; TE = NDE+NIE; %end;

 %if &scale = "OR" %then %do; CDE\_0 = exp(theta\_1\*(&a1-&a0)); CDE\_1 = exp((theta\_1+theta\_3)\*(&a1-&a0)); %end;

 %if &scale = "RR" %then %do;

 CDE\_0 = exp(theta\_1\*(&a1-&a0))\*(1+M\_0)/(1+M\_1);

 CDE\_1 = exp((theta\_1+theta\_3)\*(&a1-&a0))\*(1+L\_0)/(1+L\_1);

 %end;

 %if &scale = "RD" %then %do; CDE\_0 = M\_1/(1+M\_1) - M\_0/(1+M\_0); CDE\_1 = L\_1/(1+L\_1) - L\_0/(1+L\_0); %end;

 point\_estimates = NDE // NIE // TE;

 create point\_estimates from point\_estimates[colname={"mediation\_effects"}]; append from point\_estimates;

close point\_estimates;

 point\_estimates\_CDE = CDE\_0 // CDE\_1;

 create point\_estimates\_CDE from point\_estimates\_CDE[colname={"CDE"}]; append from point\_estimates\_CDE;

close point\_estimates\_CDE;

 /\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* delta \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*/

 %if &boot=0 %then %do;

 q = quantile("NORMAL",.975);

 use sigma\_Y; read all into sigma\_Y;

 use sigma\_M; read all into sigma\_M;

 sigma = block(sigma\_Y,sigma\_M);

 sigma\_CDE = sigma\_Y;

 %if &interaction=0 %then %do;

 d=dimension(sigma); z = j(1,d[1],0); tmp = insert(sigma,z,4,0); z = j(1,d[1]+1,0); sigma=insert(tmp,t(z),0,4);

 d=dimension(sigma\_CDE);

 z = j(1,d[1],0); tmp = insert(sigma\_CDE,z,4,0); z = j(1,d[1]+1,0); sigma\_CDE=insert(tmp,t(z),0,4);

 %end;

 /\* DERIVATIVES for GRADIENTS \*/

 dP11\_dtheta0=(L\_1/((1+L\_1)\*\*2))\*(K\_1/(1+K\_1))+(M\_1/((1+M\_1)\*\*2))\*(1/(1+K\_1));

 dP11\_dtheta1=dP11\_dtheta0\*&a1;

 dP11\_dtheta2=(L\_1/((1+L\_1)\*\*2))\*(K\_1/(1+K\_1));

 dP11\_dtheta3=dP11\_dtheta2\*&a1\*&interaction;

 dP11\_dbeta0=(K\_1/((1+K\_1)\*\*2))\*(L\_1/(1+L\_1)-M\_1/(1+M\_1));

 dP11\_dbeta1=dP11\_dbeta0\*&a1;

 dP10\_dtheta0=(L\_1/((1+L\_1)\*\*2))\*(K\_0/(1+K\_0))+(M\_1/((1+M\_1)\*\*2))\*(1/(1+K\_0));

 dP10\_dtheta1=dP10\_dtheta0\*&a1;

 dP10\_dtheta2=(L\_1/((1+L\_1)\*\*2))\*(K\_0/(1+K\_0));

 dP10\_dtheta3=dP10\_dtheta2\*&a1\*&interaction;

 dP10\_dbeta0=(K\_0/((1+K\_0)\*\*2))\*(L\_1/(1+L\_1)-M\_1/(1+M\_1));

 dP10\_dbeta1=dP10\_dbeta0\*&a0;

 dP00\_dtheta0=(L\_0/((1+L\_0)\*\*2))\*(K\_0/(1+K\_0))+(M\_0/((1+M\_0)\*\*2))\*(1/(1+K\_0));

 dP00\_dtheta1=dP00\_dtheta0\*&a1;

 dP00\_dtheta2=(L\_0/((1+L\_0)\*\*2))\*(K\_0/(1+K\_0));

 dP00\_dtheta3=dP00\_dtheta2\*&a0\*&interaction;

 dP00\_dbeta0=(K\_0/((1+K\_0)\*\*2))\*(L\_0/(1+L\_0)-M\_0/(1+M\_0));

 dP00\_dbeta1=dP00\_dbeta0\*&a0;

 %if &adjusted=1 %then %do;

 dP11\_dtheta4=dP11\_dtheta0\*cov\_values\_Y;

 dP11\_dbeta2=dP11\_dbeta0\*cov\_values\_M;

 dP10\_dtheta4=dP10\_dtheta0\*cov\_values\_Y;

 dP10\_dbeta2=dP10\_dbeta0\*cov\_values\_M;

 dP00\_dtheta4=dP00\_dtheta0\*cov\_values\_Y;

 dP00\_dbeta2=dP00\_dbeta0\*cov\_values\_M;

 Gamma\_P11=dP11\_dtheta0||dP11\_dtheta1||dP11\_dtheta2||dP11\_dtheta3||dP11\_dtheta4||dP11\_dbeta0||dP11\_dbeta1||dP11\_dbeta2;

 Gamma\_P10=dP10\_dtheta0||dP10\_dtheta1||dP10\_dtheta2||dP10\_dtheta3||dP10\_dtheta4||dP10\_dbeta0||dP10\_dbeta1||dP10\_dbeta2;

 Gamma\_P00=dP00\_dtheta0||dP00\_dtheta1||dP00\_dtheta2||dP00\_dtheta3||dP00\_dtheta4||dP00\_dbeta0||dP00\_dbeta1||dP00\_dbeta2;

 %end;

 %if &adjusted=0 %then %do;

 Gamma\_P11=dP11\_dtheta0||dP11\_dtheta1||dP11\_dtheta2||dP11\_dtheta3||dP11\_dbeta0||dP11\_dbeta1;

 Gamma\_P10=dP10\_dtheta0||dP10\_dtheta1||dP10\_dtheta2||dP10\_dtheta3||dP10\_dbeta0||dP10\_dbeta1;

 Gamma\_P00=dP00\_dtheta0||dP00\_dtheta1||dP00\_dtheta2||dP00\_dtheta3||dP00\_dbeta0||dP00\_dbeta1;

 %end;

 %if &scale = "OR" %then %do;

 Gamma\_log\_NDE = Gamma\_P10/(P10\*(1-P10)) - Gamma\_P00/(P00\*(1-P00));

 Gamma\_log\_NIE = Gamma\_P11/(P11\*(1-P11)) - Gamma\_P10/(P10\*(1-P10));

 Gamma\_log\_TE = Gamma\_log\_NIE + Gamma\_log\_NDE;

 se\_log\_NDE = sqrt(Gamma\_log\_NDE\*sigma\*t(Gamma\_log\_NDE));

 se\_log\_NIE = sqrt(Gamma\_log\_NIE\*sigma\*t(Gamma\_log\_NIE));

 se\_log\_TE = sqrt(Gamma\_log\_TE\*sigma\*t(Gamma\_log\_TE));

 NDE\_low = NDE\*exp(-q\*se\_log\_NDE); NDE\_upp = NDE\*exp(q\*se\_log\_NDE);

 NIE\_low = NIE\*exp(-q\*se\_log\_NIE); NIE\_upp = NIE\*exp(q\*se\_log\_NIE);

 TE\_low = TE\*exp(-q\*se\_log\_TE); TE\_upp = TE\*exp(q\*se\_log\_TE);

 %end;

 %if &scale = "RR" %then %do;

 Gamma\_log\_NDE = Gamma\_P10/P10 - Gamma\_P00/P00;

 Gamma\_log\_NIE = Gamma\_P11/P11 - Gamma\_P10/P10;

 Gamma\_log\_TE = Gamma\_log\_NIE + Gamma\_log\_NDE;

 se\_log\_NDE = sqrt(Gamma\_log\_NDE\*sigma\*t(Gamma\_log\_NDE))\*abs(&a1-&a0);

 se\_log\_NIE = sqrt(Gamma\_log\_NIE\*sigma\*t(Gamma\_log\_NIE))\*abs(&a1-&a0);

 se\_log\_TE = sqrt(Gamma\_log\_TE\*sigma\*t(Gamma\_log\_TE))\*abs(&a1-&a0);

 NDE\_low = NDE\*exp(-q\*se\_log\_NDE); NDE\_upp = NDE\*exp(q\*se\_log\_NDE);

 NIE\_low = NIE\*exp(-q\*se\_log\_NIE); NIE\_upp = NIE\*exp(q\*se\_log\_NIE);

 TE\_low = TE\*exp(-q\*se\_log\_TE); TE\_upp = TE\*exp(q\*se\_log\_TE);

 %end;

 %if &scale = "RD" %then %do;

 Gamma\_NDE = Gamma\_P10 - Gamma\_P00;

 Gamma\_NIE = Gamma\_P11 - Gamma\_P10;

 Gamma\_TE = Gamma\_NDE + Gamma\_NDE;

 se\_NDE = sqrt(Gamma\_NDE\*sigma\*t(Gamma\_NDE));

 se\_NIE = sqrt(Gamma\_NIE\*sigma\*t(Gamma\_NIE));

 se\_TE = sqrt(Gamma\_TE\*sigma\*t(Gamma\_TE));

 NDE\_low = NDE-q\*se\_NDE; NDE\_upp = NDE+q\*se\_NDE;

 NIE\_low = NIE-q\*se\_NIE; NIE\_upp = NIE+q\*se\_NIE;

 TE\_low = TE -q\*se\_TE; TE\_upp = TE +q\*se\_TE;

 %end;

 NDE\_CI = NDE\_low || NDE\_upp;

 NIE\_CI = NIE\_low || NIE\_upp;

 TE\_CI = TE\_low || TE\_upp;

 delta\_CI = NDE\_CI // NIE\_CI // TE\_CI;

 create delta\_CI from delta\_CI[colname={"delta\_CI\_low" "delta\_CI\_upp"}]; append from delta\_CI; close delta\_CI;

 /\* CDE: DERIVATIVES for GRADIENTS \*/

 %if &scale = "OR" %then %do;

 dlog\_CDE\_0\_dtheta0=0;

 dlog\_CDE\_0\_dtheta1=(&a1-&a0);

 dlog\_CDE\_0\_dtheta2=0;

 dlog\_CDE\_0\_dtheta3=0;

 dlog\_CDE\_1\_dtheta0=0;

 dlog\_CDE\_1\_dtheta1=(&a1-&a0);

 dlog\_CDE\_1\_dtheta2=0;

 dlog\_CDE\_1\_dtheta3=(&a1-&a0)\*&interaction;

 %if &adjusted=1 %then %do;

 dlog\_CDE\_0\_dtheta4=0\*cov\_values\_Y;

 dlog\_CDE\_1\_dtheta4=0\*cov\_values\_Y;

 Gamma\_log\_CDE\_0=dlog\_CDE\_0\_dtheta0||dlog\_CDE\_0\_dtheta1||dlog\_CDE\_0\_dtheta2||dlog\_CDE\_0\_dtheta3||dlog\_CDE\_0\_dtheta4;

 Gamma\_log\_CDE\_1=dlog\_CDE\_1\_dtheta0||dlog\_CDE\_1\_dtheta1||dlog\_CDE\_1\_dtheta2||dlog\_CDE\_1\_dtheta3||dlog\_CDE\_1\_dtheta4;

 %end;

 %if &adjusted=0 %then %do;

 Gamma\_log\_CDE\_0=dlog\_CDE\_0\_dtheta0||dlog\_CDE\_0\_dtheta1||dlog\_CDE\_0\_dtheta2||dlog\_CDE\_0\_dtheta3;

 Gamma\_log\_CDE\_1=dlog\_CDE\_1\_dtheta0||dlog\_CDE\_1\_dtheta1||dlog\_CDE\_1\_dtheta2||dlog\_CDE\_1\_dtheta3;

 %end;

 se\_log\_CDE\_0 = sqrt(Gamma\_log\_CDE\_0\*sigma\_CDE\*t(Gamma\_log\_CDE\_0));

 se\_log\_CDE\_1 = sqrt(Gamma\_log\_CDE\_1\*sigma\_CDE\*t(Gamma\_log\_CDE\_1));

 CDE\_0\_low = CDE\_0\*exp(-q\*se\_log\_CDE\_0); CDE\_0\_upp = CDE\_0\*exp(q\*se\_log\_CDE\_0);

 CDE\_1\_low = CDE\_1\*exp(-q\*se\_log\_CDE\_1); CDE\_1\_upp = CDE\_1\*exp(q\*se\_log\_CDE\_1);

 %end;

 %if &scale = "RR" %then %do;

 dlog\_CDE\_0\_dtheta0=M\_0/(1+M\_0)-M\_1/(1+M\_1);

 dlog\_CDE\_0\_dtheta1=&a1/(1+M\_1)-&a0/(1+M\_0);

 dlog\_CDE\_0\_dtheta2=0;

 dlog\_CDE\_0\_dtheta3=0;

 dlog\_CDE\_1\_dtheta0=L\_0/(1+L\_0)-L\_1/(1+L\_1);

 dlog\_CDE\_1\_dtheta1=&a1/(1+L\_1)-&a0/(1+L\_0);

 dlog\_CDE\_1\_dtheta2=dlog\_CDE\_1\_dtheta0;

 dlog\_CDE\_1\_dtheta3=dlog\_CDE\_1\_dtheta1\*&interaction;

 %if &adjusted=1 %then %do;

 dlog\_CDE\_0\_dtheta4=dlog\_CDE\_0\_dtheta0\*cov\_values\_Y;

 dlog\_CDE\_1\_dtheta4=dlog\_CDE\_1\_dtheta0\*cov\_values\_Y;

 Gamma\_log\_CDE\_0=dlog\_CDE\_0\_dtheta0||dlog\_CDE\_0\_dtheta1||dlog\_CDE\_0\_dtheta2||dlog\_CDE\_0\_dtheta3||dlog\_CDE\_0\_dtheta4;

 Gamma\_log\_CDE\_1=dlog\_CDE\_1\_dtheta0||dlog\_CDE\_1\_dtheta1||dlog\_CDE\_1\_dtheta2||dlog\_CDE\_1\_dtheta3||dlog\_CDE\_1\_dtheta4;

 %end;

 %if &adjusted=0 %then %do;

 Gamma\_log\_CDE\_0=dlog\_CDE\_0\_dtheta0||dlog\_CDE\_0\_dtheta1||dlog\_CDE\_0\_dtheta2||dlog\_CDE\_0\_dtheta3;

 Gamma\_log\_CDE\_1=dlog\_CDE\_1\_dtheta0||dlog\_CDE\_1\_dtheta1||dlog\_CDE\_1\_dtheta2||dlog\_CDE\_1\_dtheta3;

 %end;

 se\_log\_CDE\_0 = sqrt(Gamma\_log\_CDE\_0\*sigma\_CDE\*t(Gamma\_log\_CDE\_0));

 se\_log\_CDE\_1 = sqrt(Gamma\_log\_CDE\_1\*sigma\_CDE\*t(Gamma\_log\_CDE\_1));

 CDE\_0\_low = CDE\_0\*exp(-q\*se\_log\_CDE\_0); CDE\_0\_upp = CDE\_0\*exp(q\*se\_log\_CDE\_0);

 CDE\_1\_low = CDE\_1\*exp(-q\*se\_log\_CDE\_1); CDE\_1\_upp = CDE\_1\*exp(q\*se\_log\_CDE\_1);

 %end;

 %if &scale = "RD" %then %do;

 dCDE\_0\_dtheta0=M\_1/((1+M\_1)\*\*2) - M\_0/((1+M\_0)\*\*2);

 dCDE\_0\_dtheta1=&a1\*M\_1/((1+M\_1)\*\*2) - &a0\*M\_0/((1+M\_0)\*\*2);

 dCDE\_0\_dtheta2=0;

 dCDE\_0\_dtheta3=0;

 dCDE\_1\_dtheta0=L\_1/((1+L\_1)\*\*2) - L\_0/((1+L\_0)\*\*2);

 dCDE\_1\_dtheta1=&a1\*L\_1/((1+L\_1)\*\*2) - &a0\*L\_0/((1+L\_0)\*\*2);

 dCDE\_1\_dtheta2=dCDE\_1\_dtheta0;

 dCDE\_1\_dtheta3=dCDE\_1\_dtheta1\*&interaction;

 %if &adjusted=1 %then %do;

 dCDE\_0\_dtheta4=dCDE\_0\_dtheta0\*cov\_values\_Y;

 dCDE\_1\_dtheta4=dCDE\_1\_dtheta0\*cov\_values\_Y;

 Gamma\_CDE\_0=dCDE\_0\_dtheta0||dCDE\_0\_dtheta1||dCDE\_0\_dtheta2||dCDE\_0\_dtheta3||dCDE\_0\_dtheta4;

 Gamma\_CDE\_1=dCDE\_1\_dtheta0||dCDE\_1\_dtheta1||dCDE\_1\_dtheta2||dCDE\_1\_dtheta3||dCDE\_1\_dtheta4;

 %end;

 %if &adjusted=0 %then %do;

 Gamma\_CDE\_0=dCDE\_0\_dtheta0||dCDE\_0\_dtheta1||dCDE\_0\_dtheta2||dCDE\_0\_dtheta3;

 Gamma\_CDE\_1=dCDE\_1\_dtheta0||dCDE\_1\_dtheta1||dCDE\_1\_dtheta2||dCDE\_1\_dtheta3;

 %end;

 se\_CDE\_0 = sqrt(Gamma\_CDE\_0\*sigma\_CDE\*t(Gamma\_CDE\_0));

 se\_CDE\_1 = sqrt(Gamma\_CDE\_1\*sigma\_CDE\*t(Gamma\_CDE\_1));

 CDE\_0\_low = CDE\_0-q\*se\_CDE\_0; CDE\_0\_upp = CDE\_0+q\*se\_CDE\_0;

 CDE\_1\_low = CDE\_1-q\*se\_CDE\_1; CDE\_1\_upp = CDE\_1+q\*se\_CDE\_1;

 %end;

 CDE\_0\_CI = CDE\_0\_low || CDE\_0\_upp;

 CDE\_1\_CI = CDE\_1\_low || CDE\_1\_upp;

 delta\_CDE\_CI = CDE\_0\_CI // CDE\_1\_CI;

 create delta\_CDE\_CI from delta\_CDE\_CI[colname={"delta\_CI\_low" "delta\_CI\_upp"}];

 append from delta\_CDE\_CI; close delta\_CDE\_CI;

 %end; /\* end boot=0 (i.e. delta=1) \*/

 quit;

 /\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* boot \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*/

 %if &boot=1 %then %do;

 proc delete data=WORK.bootdata (gennum=all); run;

 %if %length(&nboot) = 0 %then %do;

 %put ERROR: if BOOT=1, then NBOOT and BOOTSEED must be specified;

 %abort; %end;

 %if %length(&bootseed) = 0 %then %do;

 %put ERROR: if BOOT=1, then NBOOT and BOOTSEED must be specified;

 %abort; %end;

 options nonotes nosource nosource2 errors=0;

 %if &adjusted=0 %then %do; data for\_boot; set &mydata; keep &A &M &Y; run; %end;

 %if &adjusted=1 %then %do; data for\_boot; set &mydata; keep &A &M &Y &cvar\_M &cvar\_Y; run; %end;

 proc surveyselect data= for\_boot noprint

 out=bootdata seed=&bootseed method=urs samprate=1 outhits rep=&nboot;

 run;

 %if &adjusted=0 %then %do;

 %if &Firth=0 %then %do;

 proc logistic data=bootdata noprint outest=coeffs\_M (drop=\_:) desc;

 model &M = &A; by Replicate; run;

 %if &interaction=1 %then %do;

 proc logistic data=bootdata noprint outest=coeffs\_Y (drop=\_:) desc;

 model &Y = &A|&M; by Replicate; run;

 %end;

 %if &interaction=0 %then %do;

 proc logistic data=bootdata noprint outest=coeffs\_Y (drop=\_:) desc;

 model &Y = &A &M; by Replicate; run;

 %end;

 %end;

 %if &Firth=1 %then %do;

 proc logistic data=bootdata noprint outest=coeffs\_M (drop=\_:) desc;

 model &M = &A / Firth; by Replicate; run;

 %if &interaction=1 %then %do;

 proc logistic data=bootdata noprint outest=coeffs\_Y (drop=\_:) desc;

 model &Y = &A|&M / Firth; by Replicate; run;

 %end;

 %if &interaction=0 %then %do;

 proc logistic data=bootdata noprint outest=coeffs\_Y (drop=\_:) desc;

 model &Y = &A &M / Firth; by Replicate; run;

 %end;

 %end;

 %end;

 %if &adjusted=1 %then %do;

 %if &Firth=0 %then %do;

 proc logistic data=bootdata noprint outest=coeffs\_M (drop=\_:) desc;

 model &M = &A &cvar\_M; by Replicate; run;

 %if &interaction=1 %then %do;

 proc logistic data=bootdata noprint outest=coeffs\_Y (drop=\_:) desc;

 model &Y = &A|&M &cvar\_Y; by Replicate; run;

 %end;

 %if &interaction=0 %then %do;

 proc logistic data=bootdata noprint outest=coeffs\_Y (drop=\_:) desc;

 model &Y = &A &M &cvar\_Y; by Replicate; run;

 %end;

 %end;

 %if &Firth=1 %then %do;

 proc logistic data=bootdata noprint outest=coeffs\_M (drop=\_:) desc;

 model &M = &A &cvar\_M / Firth; by Replicate; run;

 %if &interaction=1 %then %do;

 proc logistic data=bootdata noprint outest=coeffs\_Y (drop=\_:) desc;

 model &Y = &A|&M &cvar\_Y / Firth; by Replicate; run;

 %end;

 %if &interaction=0 %then %do;

 proc logistic data=bootdata noprint outest=coeffs\_Y (drop=\_:) desc;

 model &Y = &A &M &cvar\_Y / Firth; by Replicate; run;

 %end;

 %end;

 %end;

 proc iml;

 use coeffs\_M; read all var {Intercept} into beta\_0;

 read all var {&A} into beta\_1;

 %if &adjusted=1 %then %do; read all var {&cvar\_M} into cov\_coeffs\_M; %end;

 use coeffs\_Y; read all var {Intercept} into theta\_0;

 read all var {&A} into theta\_1;

 read all var {&M} into theta\_2;

 %if &interaction=1 %then %do; read all var {&A.&M} into theta\_3; %end;

 %if &interaction=0 %then %do; theta\_3=0; %end;

 %if &adjusted=1 %then %do; read all var {&cvar\_Y} into cov\_coeffs\_Y; %end;

 %if &adjusted=1 %then %do;

 use cvar\_values\_M; read all var {&cvar\_M} into cov\_values\_M;

 use cvar\_values\_Y; read all var {&cvar\_Y} into cov\_values\_Y;

 product\_betas\_c = cov\_coeffs\_M\*t(cov\_values\_M);

 product\_thetas\_c = cov\_coeffs\_Y\*t(cov\_values\_Y);

 %end;

 %if &adjusted=0 %then %do; product\_betas\_c = 0; product\_thetas\_c = 0; %end;

 K\_1 = exp(beta\_0+beta\_1\*&a1+product\_betas\_c);

 K\_0 = exp(beta\_0+beta\_1\*&a0+product\_betas\_c);

 L\_1 = exp(theta\_0+theta\_1\*&a1+theta\_2+theta\_3\*&a1 + product\_thetas\_c);

 L\_0 = exp(theta\_0+theta\_1\*&a0+theta\_2+theta\_3\*&a0 + product\_thetas\_c);

 M\_1 = exp(theta\_0+theta\_1\*&a1 + product\_thetas\_c);

 M\_0 = exp(theta\_0+theta\_1\*&a0 + product\_thetas\_c);

 P11 = (L\_1/(1+L\_1))#(K\_1/(1+K\_1))+(M\_1/(1+M\_1))#(1/(1+K\_1));

 P10 = (L\_1/(1+L\_1))#(K\_0/(1+K\_0))+(M\_1/(1+M\_1))#(1/(1+K\_0));

 P00 = (L\_0/(1+L\_0))#(K\_0/(1+K\_0))+(M\_0/(1+M\_0))#(1/(1+K\_0));

 %if &scale = "OR" %then %do; CDE\_0 = exp(theta\_1\*(&a1-&a0)); CDE\_1 = exp((theta\_1+theta\_3)\*(&a1-&a0)); %end;

 %if &scale = "RR" %then %do;

 CDE\_0 = exp(theta\_1\*(&a1-&a0))#((1+M\_0)/(1+M\_1));

 CDE\_1 = exp((theta\_1+theta\_3)\*(&a1-&a0))#((1+L\_0)/(1+L\_1));

 %end;

 %if &scale = "RD" %then %do;

 CDE\_0 = M\_1/(1+M\_1) - M\_0/(1+M\_0);

 CDE\_1 = L\_1/(1+L\_1) - L\_0/(1+L\_0);

 %end;

 probs = P11||P10||P00;

 create probabilities from probs[colname={'P11' 'P10' 'P00'}]; append from probs; close probabilities;

 CDE = CDE\_0 || CDE\_1;

 create CDE from CDE[colname={'CDE\_0' 'CDE\_1'}]; append from CDE; close CDE;

 quit;

 %if &scale="OR" %then %do;

 data boot\_effects; set probabilities;

 NDE = (P10/(1-P10))/(P00/(1-P00));

 NIE = (P11/(1-P11))/(P10/(1-P10));

 TE = NDE\*NIE;

 run;

 %end;

 %if &scale="RR" %then %do;

 data boot\_effects; set probabilities;

 NDE = P10/P00;

 NIE = P11/P10;

 TE = NDE\*NIE;

 run;

 %end;

 %if &scale="RD" %then %do;

 data boot\_effects; set probabilities;

 NDE = P10-P00;

 NIE = P11-P10;

 TE = NDE+NIE;

 run;

 %end;

 proc univariate data=boot\_effects noprint;

 var NIE NDE TE;

 output out=boot\_quantiles pctlpre= NIE NDE TE pctlpts=2.5 97.5 pctlname= pct\_low pct\_upp ;

 run;

 proc iml; use boot\_quantiles;

 read var {NDEpct\_low} into NDE\_low; read var {NDEpct\_upp} into NDE\_upp; NDE\_CI = NDE\_low || NDE\_upp;

 read var {NIEpct\_low} into NIE\_low; read var {NIEpct\_upp} into NIE\_upp; NIE\_CI = NIE\_low || NIE\_upp;

 read var {TEpct\_low} into TE\_low; read var {TEpct\_upp} into TE\_upp; TE\_CI = TE\_low || TE\_upp;

 boot\_CI = NDE\_CI // NIE\_CI // TE\_CI;

 create boot\_CI from boot\_CI[colname={"boot\_CI\_low" "boot\_CI\_upp"}]; append from boot\_CI; close boot\_CI; quit;

 proc univariate data=CDE noprint;

 var CDE\_0 CDE\_1;

 output out=CDE\_quantiles pctlpre= CDE\_0 CDE\_1 pctlpts=2.5 97.5 pctlname= pct\_low pct\_upp ;

 run;

 proc iml; use CDE\_quantiles;

 read var {CDE\_0pct\_low} into CDE\_0\_low; read var {CDE\_0pct\_upp} into CDE\_0\_upp;

 CDE\_0\_CI = CDE\_0\_low || CDE\_0\_upp;

 read var {CDE\_1pct\_low} into CDE\_1\_low; read var {CDE\_1pct\_upp} into CDE\_1\_upp;

 CDE\_1\_CI = CDE\_1\_low || CDE\_1\_upp;

 boot\_CDE\_CI = CDE\_0\_CI // CDE\_1\_CI;

 create boot\_CDE\_CI from boot\_CDE\_CI[colname={"boot\_CI\_low" "boot\_CI\_upp"}];

 append from boot\_CDE\_CI; close boot\_CDE\_CI; quit;

 options notes source source2 errors=20;

 %end; /\* end boot=1\*/

 /\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\* Mediation point estimates with CI \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*/

 %if &boot=0 %then %do;

 data all\_estimates; retain effect;

 if \_n\_=1 then effect="NDE"; if \_n\_=2 then effect="NIE"; if \_n\_=3 then effect="TE";

 merge point\_estimates delta\_CI; run;

 title color=blue "Scale=%qsysfunc(compress(&scale ,%str(%'))), adjusted=&adjusted, A-M interaction=&interaction, Firth=&Firth,";

 title2 color=blue "95% CI: delta method";

 proc print data=all\_estimates; run; title;

 data CDE\_estimates; retain effect;

 if \_n\_=1 then effect="CDE: M=0"; if \_n\_=2 then effect="CDE: M=1";

 merge point\_estimates\_CDE delta\_CDE\_CI; run;

 title color=blue "Scale=%qsysfunc(compress(&scale ,%str(%'))), adjusted=&adjusted, A-M interaction=&interaction, Firth=&Firth,";

 title2 color=blue "CDE 95% CI: delta method";

 proc print data=CDE\_estimates; run; title;

 %end;

 %if &boot=1 %then %do;

 data all\_estimates; retain effect;

 if \_n\_=1 then effect="NDE"; if \_n\_=2 then effect="NIE"; if \_n\_=3 then effect="TE";

 merge point\_estimates boot\_CI; run;

 title color=blue "Scale=%qsysfunc(compress(&scale ,%str(%'))), adjusted=&adjusted, A-M interaction=&interaction, Firth=&Firth,";

 title2 color=blue "95% CI: percentile bootstrap based on &nboot samples";

 proc print data=all\_estimates; run; title;

 data CDE\_estimates; retain effect;

 if \_n\_=1 then effect="CDE: M=0"; if \_n\_=2 then effect="CDE: M=1";

 merge point\_estimates\_CDE boot\_CDE\_CI; run;

 title color=blue "Scale=%qsysfunc(compress(&scale ,%str(%'))), adjusted=&adjusted, A-M interaction=&interaction, Firth=&Firth,";

 title2 color=blue "CDE 95% CI: percentile bootstrap based on &nboot samples";

 proc print data=CDE\_estimates; run; title;

 %end;

%mend mediation\_estimates;

**WEB TABLE 1**

**Web Table 1.** Data Generating Mechanisms for the Simulation Study With Covariates: Outcome Simulation Parameters

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Outcome simulation parameters | Scenario 1 | Scenario 2 | Scenario 3 | Scenario 4 |
|  | -3.60 | -3.60 | -1.85 | -0.90 |
|  | 0.80 | 0.80 | -0.85 | 0.40 |
|  | 1.00 | 1.00 | -0.50 | 1.50 |
|  | -0.60 | 1.50 | 3.00 | 0.40 |
|  | 0.25 | 0.25 | 0.25 | 0.25 |
|  | 0.20 | 0.20 | 0.20 | 0.20 |
| Marginal outcome probability | 0.049 | 0.077 | 0.148 | 0.405 |

**WEB TABLE 2**

**Web Table 2.** Simulation Study With Covariates (1000 independent samples of size n=5000): Natural Effects Estimators on the OR Scale by Scenarios With Increasing Outcome Commonness

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Effect | True value | Type of estimator a | Mean | Bias | Relative bias (%) | SD | RMSE | CP (%)b |
| *Scenario 1* |
| NDE | 2.004 | exact | 2.024 | 0.020 | 1.00 | 0.278 | 0.279 | 95.0 |
| approximate | 2.013 | 0.009 | 0.45 | 0.277 | 0.278 | 95.2 |
| medflex | 2.012 | 0.008 | 0.42 | 0.275 | 0.276 | 95.3 |
| NIE | 1.045 | exact | 1.045 | 0.000 | 0.01 | 0.027 | 0.027 | 93.6 |
| approximate | 1.046 | 0.001 | 0.13 | 0.028 | 0.028 | 93.6 |
| medflex | 1.046 | 0.001 | 0.13 | 0.028 | 0.028 | 93.8 |
| TE | 2.094 | exact | 2.114 | 0.020 | 0.95 | 0.286 | 0.287 | 95.8 |
| approximate | 2.105 | 0.011 | 0.52 | 0.286 | 0.287 | 95.6 |
| medflex | 2.104 | 0.010 | 0.49 | 0.284 | 0.285 | 95.7 |
| *Scenario 2* |
| NDE | 3.206 | exact | 3.239 | 0.033 | 1.02 | 0.398 | 0.399 | 95.4 |
| approximate | 4.065 | 0.859 | 26.79 | 0.526 | 1.007 | 54.8 |
| medflex | 3.265 | 0.060 | 1.86 | 0.401 | 0.405 | 95.3 |
| NIE | 1.433 | exact | 1.432 | -0.000 | -0.02 | 0.066 | 0.066 | 94.8 |
| approximate | 1.517 | 0.085 | 5.93 | 0.078 | 0.115 | 80.5 |
| medflex | 1.434 | 0.001 | 0.09 | 0.066 | 0.066 | 95.0 |
| TE | 4.593 | exact | 4.633 | 0.040 | 0.87 | 0.560 | 0.562 | 95.1 |
| approximate | 6.166 | 1.573 | 34.25 | 0.84 | 1.783 | 41.9 |
| medflex | 4.676 | 0.084 | 1.82 | 0.566 | 0.572 | 94.9 |
| *Scenario 3* |
| NDE | 0.736 | exact | 0.735 | -0.001 | -0.16 | 0.064 | 0.064 | 94.6 |
| approximate | 0.941 | 0.205 | 27.81 | 0.089 | 0.223 | 27.6 |
| medflex | 0.746 | 0.010 | 1.34 | 0.065 | 0.066 | 94.5 |
| NIE | 1.425 | exact | 1.424 | -0.001 | -0.04 | 0.063 | 0.063 | 94.7 |
| approximate | 1.517 | 0.092 | 6.48 | 0.077 | 0.120 | 78.0 |
| medflex | 1.424 | -0.001 | -0.04 | 0.063 | 0.063 | 94.8 |
| TE | 1.049 | exact | 1.046 | -0.004 | -0.34 | 0.086 | 0.086 | 94.2 |
| approximate | 1.427 | 0.378 | 36.02 | 0.146 | 0.405 | 16.1 |
| medflex | 1.062 | 0.012 | 1.17 | 0.088 | 0.089 | 94.0 |
| *Scenario 4* |
| NDE | 1.504 | exact | 1.500 | -0.003 | -0.23 | 0.090 | 0.090 | 95.0 |
| approximate | 1.740 | 0.237 | 15.74 | 0.147 | 0.279 | 59.5 |
| medflex | 1.503 | -0.000 | -0.03 | 0.091 | 0.091 | 95.4 |
| NIE | 1.177 | exact | 1.177 | -0.001 | -0.05 | 0.024 | 0.024 | 94.9 |
| approximate | 1.356 | 0.179 | 15.23 | 0.058 | 0.188 | 4.9 |
| medflex | 1.176 | -0.001 | -0.08 | 0.024 | 0.024 | 94.7 |
| TE | 1.770 | exact | 1.765 | -0.005 | -0.30 | 0.107 | 0.107 | 94.7 |
| approximate | 2.363 | 0.593 | 33.52 | 0.25 | 0.644 | 20.9 |
| medflex | 1.768 | -0.002 | -0.13 | 0.107 | 0.107 | 94.7 |
| *Abbreviations*: CP, coverage probability; NDE, natural direct effect; NIE, natural indirect effect; OR, odds ratio; RMSE, root mean square error; SD, standard deviation; TE, total effect.a: *exact*: exact estimator proposed; *approximate*: approximate estimator by [Valeri and VanderWeele (3)](#_ENREF_3); *medflex*: natural effect model approach ([7](#_ENREF_7)) using weighting method implemented in the R package *medflex* ([8](#_ENREF_8));b: Delta method for exact and approximate estimators, robust standard error for *medflex*. |

**WEB TABLE 3**

**Web Table 3.** Simulation Study With Covariates (1000 independent samples of size n=5000): Natural Effects Estimators on the RR Scale by Scenarios With Increasing Outcome Commonness

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Effect | True value | Type of estimatora | Mean | Bias | Relative bias (%) | SD | RMSE | CP (%)b |
| *Scenario 1* |
| NDE | 1.936 | exact | 1.954 | 0.018 | 0.92 | 0.255 | 0.256 | 95.4 |
| approximate | 2.013 | 0.077 | 3.96 | 0.277 | 0.288 | 94.2 |
| medflex | 1.935 | -0.001 | -0.06 | 0.250 | 0.250 | 95.1 |
| NIE | 1.042 | exact | 1.042 | 0.000 | 0.01 | 0.025 | 0.025 | 93.5 |
| approximate | 1.046 | 0.004 | 0.43 | 0.028 | 0.029 | 94.0 |
| medflex | 1.043 | 0.001 | 0.10 | 0.026 | 0.026 | 93.8 |
| TE | 2.017 | exact | 2.035 | 0.018 | 0.88 | 0.262 | 0.262 | 96.0 |
| approximate | 2.105 | 0.088 | 4.34 | 0.286 | 0.300 | 94.0 |
| medflex | 2.017 | -0.000 | -0.01 | 0.258 | 0.258 | 95.4 |
| *Scenario 2* |
| NDE | 2.977 | exact | 3.006 | 0.029 | 0.96 | 0.349 | 0.350 | 95.4 |
| approximate | 4.065 | 1.087 | 36.52 | 0.526 | 1.208 | 31.7 |
| medflex | 2.999 | 0.022 | 0.74 | 0.344 | 0.345 | 95.0 |
| NIE | 1.371 | exact | 1.371 | -0.000 | -0.01 | 0.056 | 0.056 | 94.9 |
| approximate | 1.517 | 0.146 | 10.68 | 0.078 | 0.166 | 48.6 |
| medflex | 1.367 | -0.004 | -0.32 | 0.055 | 0.055 | 94.3 |
| TE | 4.082 | exact | 4.117 | 0.034 | 0.84 | 0.466 | 0.467 | 94.7 |
| approximate | 6.166 | 2.083 | 51.03 | 0.84 | 2.246 | 14.3 |
| medflex | 4.095 | 0.013 | 0.31 | 0.459 | 0.459 | 94.8 |
| *Scenario 3* |
| NDE | 0.766 | exact | 0.764 | -0.001 | -0.19 | 0.058 | 0.058 | 94.8 |
| approximate | 0.941 | 0.175 | 22.90 | 0.089 | 0.197 | 41.7 |
| medflex | 0.778 | 0.012 | 1.60 | 0.059 | 0.060 | 94.1 |
| NIE | 1.360 | exact | 1.360 | -0.000 | -0.03 | 0.053 | 0.053 | 94.7 |
| approximate | 1.517 | 0.157 | 11.53 | 0.077 | 0.175 | 42.2 |
| medflex | 1.357 | -0.003 | -0.25 | 0.052 | 0.052 | 94.3 |
| TE | 1.042 | exact | 1.038 | -0.004 | -0.34 | 0.073 | 0.073 | 94.4 |
| approximate | 1.427 | 0.385 | 37.00 | 0.146 | 0.412 | 14.2 |
| medflex | 1.054 | 0.013 | 1.23 | 0.073 | 0.075 | 93.6 |
| *Scenario 4* |
| NDE | 1.278 | exact | 1.275 | -0.002 | -0.17 | 0.046 | 0.046 | 95.1 |
| approximate | 1.740 | 0.463 | 36.21 | 0.147 | 0.485 | 3.1 |
| medflex | 1.269 | -0.009 | -0.68 | 0.044 | 0.045 | 93.9 |
| NIE | 1.090 | exact | 1.090 | -0.000 | -0.01 | 0.012 | 0.012 | 95.0 |
| approximate | 1.356 | 0.266 | 24.39 | 0.058 | 0.272 | 0.0 |
| medflex | 1.086 | -0.004 | -0.39 | 0.011 | 0.012 | 92.0 |
| TE | 1.393 | exact | 1.391 | -0.003 | -0.20 | 0.049 | 0.049 | 94.8 |
| approximate | 2.363 | 0.97 | 69.62 | 0.25 | 1.002 | 0.0 |
| medflex | 1.378 | -0.015 | -1.08 | 0.047 | 0.049 | 92.2 |
| *Abbreviations*: CP, coverage probability; NDE, natural direct effect; NIE, natural indirect effect; RMSE, root mean square error; RR, risk ratio; SD, standard deviation; TE, total effect.a: *exact*: exact estimator proposed; *approximate*: approximate estimator by [Valeri and VanderWeele (3)](#_ENREF_3); *medflex*: natural effect model approach ([7](#_ENREF_7)) using weighting method implemented in the R package *medflex* ([8](#_ENREF_8));b: Delta method for exact and approximate estimators, robust standard error for *medflex*. |

**WEB TABLE 4**

**Web Table 4.** Simulation Study With Covariates (1000 independent samples of size n=5000): Natural Effects Estimators on the RD Scale by Scenarios With Increasing Outcome Commonness

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Effect | True value | Type of estimatora | Mean | Bias | Relative bias (%) | SD | RMSE | CP (%)b |
| *Scenario 1* |
| NDE | 0.033 | exact | 0.032 | -0.000 | -0.46 | 0.007 | 0.007 | 95.8 |
| medflex | 0.033 | 0.000 | 1.20 | 0.007 | 0.007 | 95.2 |
| mediation | 0.032 | -0.000 | -0.24 | 0.007 | 0.007 | 95.4 |
| NIE | 0.003 | exact | 0.003 | -0.000 | -1.84 | 0.002 | 0.002 | 93.6 |
| medflex | 0.003 | 0.000 | 1.70 | 0.002 | 0.002 | 94.3 |
| mediation | 0.003 | 0.000 | 0.72 | 0.002 | 0.002 | 95.3 |
| TE | 0.035 | exact | 0.035 | -0.000 | -0.57 | 0.007 | 0.007 | 94.8 |
| medflex | 0.036 | 0.000 | 1.24 | 0.007 | 0.007 | 94.9 |
| mediation | 0.035 | -0.000 | -0.16 | 0.007 | 0.007 | 95.2 |
| *Scenario 2* |
| NDE | 0.069 | exact | 0.069 | -0.000 | -0.33 | 0.007 | 0.007 | 94.6 |
| medflex | 0.071 | 0.002 | 2.84 | 0.007 | 0.008 | 94.0 |
| mediation | 0.069 | -0.000 | -0.29 | 0.007 | 0.007 | 95.0 |
| NIE | 0.038 | exact | 0.038 | -0.000 | -0.81 | 0.005 | 0.005 | 94.2 |
| medflex | 0.038 | -0.000 | -0.19 | 0.005 | 0.005 | 94.2 |
| mediation | 0.038 | -0.000 | -0.84 | 0.005 | 0.005 | 97.1 |
| TE | 0.107 | exact | 0.107 | -0.001 | -0.50 | 0.009 | 0.009 | 94.4 |
| medflex | 0.109 | 0.002 | 1.76 | 0.009 | 0.009 | 94.7 |
| mediation | 0.107 | -0.001 | -0.48 | 0.009 | 0.009 | 95.2 |
| *Scenario 3* |
| NDE | -0.034 | exact | -0.035 | -0.000 | 1.42 | 0.009 | 0.009 | 94.9 |
| medflex | -0.033 | 0.001 | -3.22 | 0.010 | 0.010 | 94.2 |
| mediation | -0.035 | -0.000 | 1.19 | 0.009 | 0.009 | 95.4 |
| NIE | 0.040 | exact | 0.040 | -0.000 | -0.78 | 0.005 | 0.005 | 94.3 |
| medflex | 0.040 | -0.000 | -0.37 | 0.005 | 0.005 | 94.6 |
| mediation | 0.040 | -0.000 | -0.82 | 0.005 | 0.005 | 97.3 |
| TE | 0.006 | exact | 0.005 | -0.001 | -13.10 | 0.011 | 0.011 | 94.2 |
| medflex | 0.007 | 0.001 | 15.59 | 0.011 | 0.011 | 94.0 |
| mediation | 0.005 | -0.001 | -12.09 | 0.011 | 0.011 | 94.8 |
| *Scenario 4* |
| NDE | 0.097 | exact | 0.096 | -0.001 | -1.06 | 0.014 | 0.014 | 95.1 |
| medflex | 0.095 | -0.002 | -2.15 | 0.014 | 0.014 | 94.9 |
| mediation | 0.096 | -0.001 | -1.08 | 0.014 | 0.014 | 94.9 |
| NIE | 0.041 | exact | 0.04 | 0.000 | -0.51 | 0.005 | 0.005 | 94.8 |
| medflex | 0.040 | -0.001 | -2.56 | 0.005 | 0.005 | 93.6 |
| mediation | 0.040 | -0.000 | -0.71 | 0.005 | 0.005 | 97.0 |
| TE | 0.138 | exact | 0.137 | -0.001 | -0.90 | 0.015 | 0.015 | 94.7 |
| medflex | 0.135 | -0.003 | -2.27 | 0.014 | 0.015 | 94.0 |
|  | mediation | 0.137 | -0.001 | -0.98 | 0.015 | 0.015 | 94.7 |
| *Abbreviations*: CP, coverage probability; NDE, natural direct effect; NIE, natural indirect effect; RD, risk difference; RMSE, root mean square error; SD, standard deviation; TE, total effect.a: *exact*: exact estimator proposed; *medflex*: natural effect model approach ([7](#_ENREF_7)) using weighting method implemented in the R package *medflex* ([8](#_ENREF_8)); *mediation*:quasi-Bayesian approachby [Imai, Keele and Tingley (14)](#_ENREF_14) implemented in the R package *mediation* ([9](#_ENREF_9));b: Delta method for exact estimators, robust standard error for *medflex*; for *mediation*, the 95% CIs were based on the White’s heteroskedasticity-consistent estimator for the covariance matrix ([9](#_ENREF_9)). |

**WEB TABLE 5**

**Web Table 5.** Simulation Study Without Covariates: Total Effect Multiplicative Decomposition Property of Exact and Approximate Natural Effects Estimators by Scenarios With Increasing Outcome Commonness

|  |  |  |
| --- | --- | --- |
|  | Exact TE estimatea vsTE estimate by conventional approach | Approximate TE estimatea vsTE estimate by conventional approach |
| Differenceb | Relative Differencec, (%) | Differenceb | Relative Differencec, (%) |
| Scale | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| *Scenario 1* |
| OR | 0.0000 | 0.0001 | 0.0002 | 0.0042 | -0.0108 | 0.0127 | -0.48 | 0.56 |
| RR | 0.0000 | 0.0001 | 0.0001 | 0.0040 | 0.0887 | 0.0315 | 3.94 | 0.99 |
| *Scenario 2* |
| OR | 0.0001 | 0.0004 | 0.0029 | 0.0084 | 2.0826 | 0.4383 | 40.20 | 6.13 |
| RR | 0.0001 | 0.0003 | 0.0028 | 0.0083 | 2.7350 | 0.5293 | 60.37 | 7.70 |
| *Scenario 3* |
| OR | 0.0000 | 0.0001 | 0.0003 | 0.0060 | 0.4493 | 0.0851 | 40.98 | 6.14 |
| RR | 0.0000 | 0.0001 | 0.0003 | 0.0051 | 0.4643 | 0.0950 | 42.85 | 6.91 |
| *Scenario 4* |
| OR | 0.0000 | 0.0000 | 0.0003 | 0.0020 | 0.3678 | 0.1622 | 20.50 | 8.83 |
| RR | 0.0000 | 0.0000 | 0.0002 | 0.0012 | 0.7484 | 0.1826 | 52.90 | 12.10 |
| Abbreviations: OR, odds ratio; RR, risk ratio; SD, standard deviation; TE, total effect.a: TE estimate defined as a product of NDE and NIE estimates;b: TE estimate – TE estimate by conventional approach;c: (TE estimate – TE estimate by conventional approach) ∕ TE estimate by conventional approach. |

**WEB TABLE 6**

**Web Table 6.** Simulation Study With Covariates: Total Effect Multiplicative Decomposition Property of Exact and Approximate Natural Effects Estimators by Scenarios With Increasing Outcome Commonness

|  |  |  |
| --- | --- | --- |
|  | Exact TE estimatea vsTE estimate by conventional approach | Approximate TE estimatea vsTE estimate by conventional approach |
| Differenceb | Relative Differencec, (%) | Differenceb | Relative Differencec, (%) |
| Scale | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| *Scenario 1* |
| OR | 0.0104 | 0.0098 | 0.4955 | 0.4589 | 0.0014 | 0.0076 | 0.0576 | 0.3555 |
| RR | 0.0097 | 0.0090 | 0.4788 | 0.4380 | 0.0795 | 0.0274 | 3.8282 | 0.8760 |
| *Scenario 2* |
| OR | -0.0485 | 0.0403 | -1.0288 | 0.8297 | 1.4846 | 0.3400 | 31.572 | 5.2809 |
| RR | -0.0410 | 0.0336 | -0.9784 | 0.7802 | 2.0079 | 0.4178 | 48.026 | 6.6082 |
| *Scenario 3* |
| OR | -0.0170 | 0.0070 | -1.5937 | 0.6371 | 0.3645 | 0.0747 | 34.170 | 5.7028 |
| RR | -0.0143 | 0.0059 | -1.3601 | 0.5445 | 0.3746 | 0.0839 | 35.361 | 6.4171 |
| *Scenario 4* |
| OR | -0.0024 | 0.0014 | -0.1357 | 0.0757 | 0.5961 | 0.1957 | 33.656 | 10.571 |
| RR | -0.0008 | 0.0005 | -0.0543 | 0.0373 | 0.9719 | 0.2210 | 69.645 | 14.657 |
| Abbreviations: OR, odds ratio; RR, risk ratio; SD, standard deviation; TE, total effect.a: TE estimate defined as a product of NDE and NIE estimates;b: TE estimate – TE estimate by conventional approach;c: (TE estimate – TE estimate by conventional approach) ∕ TE estimate by conventional approach. |

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