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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This work was funded by grants from the Fonds de recherche Québec-Santé (FRQ-S) and the Natural Sciences and Engineering Research Council of Canada. Geneviève Lefebvre is a FRQ-S Research Scholar.

Conflict of interest: none declared.

Running head: Exact Binary Regression-Based Natural Effects Estimator

ABSTRACT:

In the causal mediation framework, several parametric regression-based approaches have been introduced in past years for estimating natural direct and indirect effects. For a binary outcome, a number of proposed estimators use a logistic model and rely on specific assumptions or approximations that may be delicate or not easy to verify in practice. To circumvent the challenges prompted by the rare outcome assumption in this context, an exact closed-form natural effects estimator on the odds ratio scale was recently introduced for a binary mediator. In this work, we further push this exact approach and extend it for the estimation of natural effects on the risk ratio and risk difference scales. Explicit formulas for the delta method standard errors are provided. The performance of our proposed exact estimators is demonstrated in simulation scenarios featuring various levels of outcome rareness/commonness. The total effect decomposition property on the multiplicative scales is also examined. Using a SAS macro provided, we illustrate our approach to assess the separate effects of treatment to inhaled corticosteroids and placental abruption on low birthweight mediated by prematurity. Our exact natural effects estimators are found to work properly in both simulations and real data example.

KEYWORDS: binary mediator, binary outcome, causal mediation regression-based analysis, exact natural effects estimator, outcome rareness/commonness

WORD COUNT ABSTRACT: 195

WORD COUNT MANUSCRIPT: 3846

Mediation analysis approaches that rely on the specification of parametric models for the mediator and outcome variables are naturally appealing to practitioners due to their conceptual simplicity. However, it is notorious that the development of such approaches is more challenging when the outcome is binary, as opposed to continuous, due to the consideration of nonlinear models (1). In this line of research, contributions made over the years in the causal inference framework have helped to increase resources available to estimate direct and indirect effects with binary outcomes. However, a number of these invoke specific assumptions or approximations, some of which may be delicate or not easy to verify in practice. VanderWeele and Vansteelandt (2) and Valeri and Vanderweele (3) relied on the rare outcome assumption (ROA) to propose regression-based estimators of natural direct and indirect effects (NDE, NIE) on the odds ratio (OR) scale for continuous and binary mediators. For a normally distributed mediator, Gaynor, Schwartz and Lin (4) used a probit approximation to the logit function to provide an estimator of the NDE and NIE on the OR scale that can be used when the outcome is common. Previous work by Tchetgen Tchetgen (5), which motivated the work by Gaynor et al. (4), introduced an exact estimator for a non-rare outcome, but the approach assumed a bridge distribution for the continuous mediator.

For a binary outcome and a binary mediator, the logistic regression-based causal mediation approach by Valeri and Vanderweele (3) (V&V) is popular among applied researchers, arguably because of its accessible implementation in standard statistical software (e.g. SAS procedure PROC CAUSALMED and Stata module PARAMED (SAS Institute, Inc., Cary, North Carolina; StataCorp LP, College Station, Texas; (6-8)). First designed for cohort data, this approximate approach is based on the simplifying ROA, which is crucial in the development of the proposed closed-form natural effects OR estimator. In practical contexts, the ROA is commonly verified by checking that the marginal outcome prevalence $P(Y = 1)$ is reasonably small (9-11). However, as further expanded below, there is an increased awareness that this marginal definition is inadequate for the ROA in causal mediation settings.

For a binary mediator, both Samoilenko, Blais and Lefebvre (12) and Gaynor et al. (4) independently introduced a logistic regression-based estimator for cohort data that uses the parametrized outcome and mediator probabilities to express the NDE and NIE on the OR scale. This estimator is qualified as exact since it does not rely on approximations and can be used regardless of the rareness or commonness of the outcome.

Samoilenko et al. (12) presented a simulation scenario mimicking real perinatal data in which the outcome was rare marginally (that is, with $P(Y = 1) < 0.1$), but not in the strata formed by the exposure and mediator. They compared the proposed exact OR estimator with the V&V approximate estimator and found that the former was unbiased for the NDE and NIE ORs (OR^{NDE}, OR^{NIE}) unlike the latter. Commenting on Samoilenko et al. (12), VanderWeele, Valeri and Ananth (13) acknowledged that the ROA needs to hold in strata formed by covariates, *including mediator*, for their estimator to be valid. However, to require that the outcome be rare in strata of a mediator is questionable when the mediator is strongly associated with the outcome.

The recent parametric estimator proposed by Samoilenko et al. (12) and Gaynor et al. (4) for a binary mediator is attractive since it overcomes the marginal or conditional verification of the ROA. Yet, more work is required to fully develop inference. In Samoilenko et al. (12), the variance computation for the OR^{NDE} and OR^{NIE} estimators was done using bootstrap only. In Gaynor et al. (4), the standard error formulas were not provided in the paper but were implemented in a R code (R Foundation for Statistical Computing, Vienna, Austria) developed for scenarios based on specific datasets. In Doretti, Raggi and Stanghellini (14), the exact parametric formulas for the natural effects on the log OR scale were extended for all possible interactions in the outcome model (including exposure-mediator-confounding covariates' interactions); corresponding expressions for standard errors were derived using the delta method. However, the authors did not release computer code to provide easy implementation. The purpose of our article is two-fold. The first objective is to provide explicit and straightforward formulas for the delta method standard errors for the case of the mediator-exposure interaction and make this option available in the general SAS macro developed in Samoilenko et al. (12). While the bootstrap is indicated for inference on indirect effect (15), it is more computer-intensive and not assumption-free (16, 17). Therefore, providing both delta and percentile bootstrap confidence intervals (CIs) allows for greater flexibility and increased confidence in mediation results. The second objective is to go beyond the OR scale and provide analogous results for the NDE and NIE on the risk ratio (RR) and risk difference (RD) scales, with all three scales using the same logistic model for the outcome.

METHODS

Models and counterfactual nested outcome probabilities

As in Samoilenko et al. (12) and Gaynor et al. (4), we assume the following logistic regression models for the binary mediator M and binary outcome Y, respectively:

$$\text{logit}\left(P(M=1|A=a,\boldsymbol{C}=\boldsymbol{c})\right)=\beta_0+\beta_1 a+\boldsymbol{\beta}_2'\boldsymbol{c}, \quad (1)$$

$$\text{logit}\left(P(Y=1|A=a,M=m,\boldsymbol{C}=\boldsymbol{c})\right)=\theta_0+\theta_1 a+\theta_2 m+\theta_3 am+\boldsymbol{\theta}_4'\boldsymbol{c}, \quad (2)$$

where A is the exposure (binary or continuous) and $\boldsymbol{C}$ is the set of covariates sufficient to control for exposure-outcome, mediator-outcome, and exposure-mediator confounding (18).

Under identification assumptions ([19](#)) and modelling assumptions (1-2), the counterfactual nested outcome $Y(a, M(a^*))$ probability is expressed as:

$$P\big(Y\big(a, M(a^*)\big) = 1 \,\big|\, \boldsymbol{C} = \boldsymbol{c}\big)$$

$$= \operatorname{expit}\big(\theta_0 + \theta_1 a + \theta_2 + \theta_3 a + \boldsymbol{\theta}_4' \boldsymbol{c}\big) \cdot \operatorname{expit}\big(\beta_0 + \beta_1 a^* + \boldsymbol{\beta}_2' \boldsymbol{c}\big) \quad (3)$$

$$+ \operatorname{expit}\big(\theta_0 + \theta_1 a + \boldsymbol{\theta}_4' \boldsymbol{c}\big) \cdot \Big(1 - \operatorname{expit}\big(\beta_0 + \beta_1 a^* + \boldsymbol{\beta}_2' \boldsymbol{c}\big)\Big),$$

where

$$\operatorname{expit}(\alpha) = \frac{\exp(\alpha)}{1 + \exp(\alpha)}, \qquad 1 - \operatorname{expit}(\alpha) = \big(1 + \exp(\alpha)\big)^{-1}.$$

Generally, NDE compares $Y(a, M(a^*))$ to $Y(a^*, M(a^*))$, while NIE is defined as a contrast between $Y(a, M(a))$ and $Y(a, M(a^*))$. In the literature, NDE and NIE are also referred to as the pure (natural) direct effect and total (natural) indirect effect, respectively ([20-22](#)).

Equation 3 allows expressing the OR^{NDE}, OR^{NIE}, as well as the NDE and NIE RRs (RR^{NDE}, RR^{NIE}), and the NDE and NIE RDs (RD^{NDE}, RD^{NIE}) in an exact manner.

Natural direct and indirect effects on the odds ratio, risk ratio and risk difference scales

Explicit expressions for the (conditional) natural direct and indirect effects ORs, $OR^{NDE}_{a,a^*|\boldsymbol{c}}$ and $OR^{NIE}_{a,a^*|\boldsymbol{c}}$, corresponding to a change in the exposure level from $A = a^*$ to $A = a$ (also see [Samoilenko et al. (12)](#), [Gaynor et al. (4)](#)) are derived using counterfactual nested outcome probabilities defined in Equation 3 as follows:

$$OR^{NDE}_{a,a^*|\boldsymbol{c}} = \frac{\dfrac{P\big(Y\big(a, M(a^*)\big) = 1 \,\big|\boldsymbol{C} = \boldsymbol{c}\big)}{1 - P\big(Y\big(a, M(a^*)\big) = 1 \,\big|\boldsymbol{C} = \boldsymbol{c}\big)}}{\dfrac{P\big(Y\big(a^*, M(a^*)\big) = 1 \,\big|\boldsymbol{C} = \boldsymbol{c}\big)}{1 - P\big(Y\big(a^*, M(a^*)\big) = 1 \,\big|\boldsymbol{C} = \boldsymbol{c}\big)}},$$

(4)

$$OR^{NIE}_{a,a^*|\boldsymbol{c}} = \frac{\dfrac{P\big(Y\big(a, M(a)\big) = 1 \,\big|\boldsymbol{C} = \boldsymbol{c}\big)}{1 - P\big(Y\big(a, M(a)\big) = 1 \,\big|\boldsymbol{C} = \boldsymbol{c}\big)}}{\dfrac{P\big(Y\big(a, M(a^*)\big) = 1 \,\big|\boldsymbol{C} = \boldsymbol{c}\big)}{1 - P\big(Y\big(a, M(a^*)\big) = 1 \,\big|\boldsymbol{C} = \boldsymbol{c}\big)}}.$$

In an analogous manner, Equation 3 leads to exact natural direct and indirect effects RR expressions, $RR^{NDE}_{a,a^*|\boldsymbol{c}}$ and $RR^{NIE}_{a,a^*|\boldsymbol{c}}$, respectively:

$$RR^{NDE}_{a,a^*|\boldsymbol{c}} = \frac{P\big(Y\big(a, M(a^*)\big) = 1 \,\big|\boldsymbol{C} = \boldsymbol{c}\big)}{P\big(Y\big(a^*, M(a^*)\big) = 1 \,\big|\boldsymbol{C} = \boldsymbol{c}\big)}, \qquad RR^{NIE}_{a,a^*|\boldsymbol{c}} = \frac{P\big(Y\big(a, M(a)\big) = 1 \,\big|\boldsymbol{C} = \boldsymbol{c}\big)}{P\big(Y\big(a, M(a^*)\big) = 1 \,\big|\boldsymbol{C} = \boldsymbol{c}\big)}. \qquad (5)$$

The total effect (TE) odds and risk ratios, $OR^{TE}_{a,a^*|\boldsymbol{c}}$ and $RR^{TE}_{a,a^*|\boldsymbol{c}}$, are defined as the product of the NDE and NIE on their respective scale:

$$OR^{TE}_{a,a^*|\boldsymbol{c}} = OR^{NDE}_{a,a^*|\boldsymbol{c}} \cdot OR^{NIE}_{a,a^*|\boldsymbol{c}}, \qquad RR^{TE}_{a,a^*|\boldsymbol{c}} = RR^{NDE}_{a,a^*|\boldsymbol{c}} \cdot RR^{NIE}_{a,a^*|\boldsymbol{c}}. \qquad (6)$$

From Equation 3, the NDE and NIE exact expressions on the RD scale are:

$$RD^{NDE}_{a,a^*|\boldsymbol{c}} = P\big(Y\big(a, M(a^*)\big) = 1 \,\big|\boldsymbol{C} = \boldsymbol{c}\big) - P\big(Y\big(a^*, M(a^*)\big) = 1 \,\big|\boldsymbol{C} = \boldsymbol{c}\big),$$

(7)

$$RD^{NIE}_{a,a^*|\boldsymbol{c}} = P\big(Y\big(a, M(a)\big) = 1 \,\big|\boldsymbol{C} = \boldsymbol{c}\big) - P\big(Y\big(a, M(a^*)\big) = 1 \,\big|\boldsymbol{C} = \boldsymbol{c}\big).$$

On the RD scale, the TE, $RD^{TE}_{a,a^*|\boldsymbol{c}}$, is defined as the sum of the NDE and NIE:

$$RD^{TE}_{a,a^*|\boldsymbol{c}} = RD^{NDE}_{a,a^*|\boldsymbol{c}} + RD^{NIE}_{a,a^*|\boldsymbol{c}}.$$

For each effect scale, the NDE and NIE estimators are induced by replacing the coefficients in Equations 1-2 by corresponding estimators. The formulas for the natural effects standard errors by delta method are provided in Web Appendix 1.

Valeri and VanderWeele (2013) approximate natural direct and indirect effects approach

As detailed in Samoilenko et al. (12), the approximate expressions for the OR^{NDE} and OR^{NIE} provided in Valeri and Vanderweele (3) are obtained by invoking the ROA multiple times. First replace, in Equation 3, the expit functions stemming from the outcome model by exponential functions, and second, approximate the OR by RR, that is replace Equation 4 by Equation 5:

$$P_{app}\left(Y\left(a, M(a^*)\right) = 1 \,\middle|\, \boldsymbol{C} = \boldsymbol{c}\right)$$

$$= \exp\left(\theta_0 + \theta_1 a + \theta_2 + \theta_3 a + \boldsymbol{\theta}_4' \boldsymbol{c}\right) \cdot \operatorname{expit}\left(\beta_0 + \beta_1 a^* + \boldsymbol{\beta}_2' \boldsymbol{c}\right) \quad (8)$$

$$+ \exp\left(\theta_0 + \theta_1 a + \boldsymbol{\theta}_4' \boldsymbol{c}\right) \cdot \left(1 - \operatorname{expit}\left(\beta_0 + \beta_1 a^* + \boldsymbol{\beta}_2' \boldsymbol{c}\right)\right),$$

$$app\ OR^{NDE}_{a,a^*|\boldsymbol{c}} = \frac{P_{app}\left(Y\left(a, M(a^*)\right) = 1 \,\middle|\, \boldsymbol{C} = \boldsymbol{c}\right)}{P_{app}\left(Y\left(a^*, M(a^*)\right) = 1 \,\middle|\, \boldsymbol{C} = \boldsymbol{c}\right)},$$

$$app\ OR^{NIE}_{a,a^*|\boldsymbol{c}} = \frac{P_{app}\left(Y\left(a, M(a)\right) = 1 \,\middle|\, \boldsymbol{C} = \boldsymbol{c}\right)}{P_{app}\left(Y\left(a, M(a^*)\right) = 1 \,\middle|\, \boldsymbol{C} = \boldsymbol{c}\right)}. \quad (9)$$

The approximate expression for the TE is then given by

$$app\ OR^{TE}_{a,a^*|\boldsymbol{c}} = app\ OR^{NDE}_{a,a^*|\boldsymbol{c}} \cdot app\ OR^{NIE}_{a,a^*|\boldsymbol{c}}. \quad (10)$$

Simulation studies

Two simulation studies were conducted to examine the behavior of proposed exact estimators. In the first simulation study, no covariates $\boldsymbol{C}$ were included for the sake of simplicity, while two covariates were included in the second study. Both studies considered four scenarios corresponding to different levels of outcome rareness/commonness:

Scenario 1. The outcome is rare in all the strata defined by the binary exposure and binary mediator (conditional probabilities $P(Y=1|A=i, M=j) \leq 10\%,\ \ i,j=0,1$);

Scenario 2. The outcome is rare marginally ($P(Y=1) \leq 10\%$), but it is not rare in one stratum defined by the binary exposure and binary mediator;

Scenario 3. This scenario is similar to *Scenario 2*, but features two common strata and a slightly increased marginal outcome probability ($P(Y=1) \approx 15\%$);

Scenario 4. The outcome is not rare marginally (is common) with $P(Y=1) \approx 40\%$.

Simulation study without covariates

For each scenario, we generated 1000 independent samples of size $n = 5000$ nonparametrically using sequential Bernoulli sampling for A, M and Y. The probability values used to generate the exposure, mediator and outcome variables are presented in Table 1.

The true mediation OR, RR and RD effects were calculated as

$$true\ OR^{NDE} = \frac{P_{10}/(1-P_{10})}{P_{00}/(1-P_{00})}, \qquad true\ OR^{NIE} = \frac{P_{11}/(1-P_{11})}{P_{10}/(1-\ P_{10})},$$

$$true\ RR^{NDE} =\ P_{10}/\ P_{00}, \qquad true\ RR^{NIE} =\ P_{11}/\ P_{10}, \tag{11}$$

$$true\ RD^{NDE} = P_{10} -\ P_{00}, \qquad true\ RD^{NIE} = P_{11} -\ P_{10},$$

with P_{11}, P_{10}, P_{00} computed using values from Table 1:

$$P_{ij} = P(Y=1|A=i, M=1) \cdot P(M=1|A=j) + P(Y=1|A=i, M=0) \cdot \big(1 - P(M=1|A=j)\big).$$

The true total causal effects were calculated correspondingly as:

$$true\ OR^{TE} = true\ OR^{NDE} \cdot true\ OR^{NIE},$$

$$true\ RR^{TE} = true\ RR^{NDE} \cdot true\ RR^{NIE},$$

$$true\ RD^{TE} = true\ RD^{NDE} + true\ RD^{NIE}.$$

For each sample, exact estimates of natural direct and indirect effects were calculated on the OR, RR and RD scales. The mean, bias, relative bias, standard deviation (SD) and root mean square error (RMSE) of proposed exact estimators were then estimated over the 1000 samples generated; the true RRs, ORs and RDs defined in Equation 11 were used as gold standard. For each simulation scenario, the same statistics were also calculated for the approximate natural effects estimator based on Equations 8-10. The approximate natural effects OR estimator was evaluated in regard to both multiplicative scales (OR and RR). Indeed, because the approximate natural effects are generally reported as ORs (23), we first compared the approximate natural effect estimates to the true ORs. However, since the approximate ORs mimic RRs by construction (see correspondence between Equations 5 and 9) we also evaluated the performance of the approximate estimator using the true RRs as reference. The calculations described above were performed using SAS, Version 9.5.

For each scenario and sample, we also considered two other existing approaches for comparison with the exact method being introduced here. For all three scales (OR, RR, RD), we applied the natural effect model (NEM) approach (24, 25) using the R package *medflex* (26). This approach is not based on the ROA and directly parameterizes the natural effects. Two procedures, weighting and imputation, are implemented in *medflex*; we used the weighting one which requires specifying a regression model for the mediator and a NEM for the counterfactual outcome. A logistic model was specified for the mediator for all scales. NEMs $g(E\{Y(a,M(a^*))\}) = \gamma_0 + \gamma_1 a + \gamma_2 a^* + \gamma_3 aa^*$, where $g(\cdot)$ is a link function, were fitted using logistic, log-binomial and linear regressions for the OR, RR and RD scales, respectively. For the RD scale, we also applied Imai et al. (27)'s *Parametric Inference Algorithm* implemented in the R package *mediation* (28). This causal approach, which also does not rely on the ROA, is based on quasi-Bayesian Monte Carlo approximations and is provided as the default option in *mediation*. A logistic model was specified for the mediator as well as for the outcome, where the latter included a treatment-mediator interaction term as in the exact and approximate approaches; 1000 Monte Carlo draws were used for each sample generated. It should be noted that *mediation* version 4.5.0 returns NDE and NIE estimates on the RD scale only.

We computed the coverage probabilities (CPs) of 95% CIs estimators by calculating the proportion of times CIs enclosed corresponding true values of NDE, NIE and TE. For the exact and approximate approaches, 95% CIs were constructed by percentile bootstrap based on 500 resamples with replacement (29) and using first order delta method. For the NEM approach, 95% CIs were obtained using robust standard errors based on the sandwich estimator (30). For the quasi-Bayesian approach, 95% CIs were based on the White's heteroskedasticity-consistent estimator for the covariance matrix (28).

Simulation study with covariates

In all scenarios, covariates C_1 and C_2 were generated independently as $Bernoulli(0.5)$ and $N(0,1)$, respectively. The binary exposure A was generated according to the following model:

$$\text{logit}\big(P(A = 1 | C_1 = c_1, C_2 = c_2)\big) = -0.5 + 0.1\, c_1 - 0.15\, c_2.$$

Then, the binary mediator M and outcome Y were respectively generated under models

$$\text{logit}\big(P(M=1|A=a, C_1=c_1, C_2=c_2\,)\big) = \beta_0 + \beta_1 a + \beta_{21} c_1 + \beta_{22} c_2$$

and

$$\text{logit}\big(P(Y=1|A=a, M=m, C_1=c_1, C_2=c_2\,)\big) = \theta_0 + \theta_1 a + \theta_2 m + \theta_3 am + \theta_{41} c_1 + \theta_{42} c_2,$$

where $\beta_0 = -2.3,\ \beta_1 = 0.8,\ \beta_{21} = 0.2,\ \beta_{22} = 0.25$. The outcome simulation parameters are presented in Web Table 1 for each simulation scenario. Under these parameter values, the stratum-specific outcome prevalences were similar to those from the simulations without covariates.

The true mediation OR, RR and RD effects (gold standard) were calculated using simulation parameters according to Equation 11, where

$$P_{ij} = \text{expit}(\theta_0 + \theta_1 i + \theta_2 + \theta_3 i + \theta_{41}\overline{c_1} + \theta_{42}\overline{c_2})\,\text{expit}(\beta_0 + \beta_1 j + \beta_{21}\overline{c_1} + \beta_{22}\overline{c_2})$$

$$+\text{expit}(\theta_0 + \theta_1 i + \theta_{41}\overline{c_1} + \theta_{42}\overline{c_2})\big(1 - \text{expit}(\beta_0 + \beta_1 j + \beta_{21}\overline{c_1} + \beta_{22}\overline{c_2})\big),$$

and $\overline{c_1} = 0.5$, $\overline{c_2} = 0$.

The simulation study with covariates was conducted the same way as the one without covariates regarding number of samples generated, sample size and estimators investigated. For the RR scale in Scenario 4, the NEM was however fitted using a Poisson regression model instead of log-binomial because of failed convergence of the latter model for 77.6% of samples generated. For all approaches, models included covariates as main effect terms only and mediation effects were estimated at the sample-specific mean values for C_1 and C_2. It should be noted that in absence of exposure-covariate interactions, the conditional mediation effects returned by *medflex* are the same for any level of adjustment covariates (31).

The decomposition property of the exact and approximate TE estimators was examined in both simulation studies (see Web Appendix 1). Further details on the estimation procedures are provided in Web Appendix 1.

RESULTS

The performance of the proposed exact natural effects estimators on the OR, RR and RD scales is summarized in Tables 2–4 and Web Tables 2-4 for the simulation studies without covariates and with covariates, respectively (type of estimator = exact).

For the multiplicative scales, the means of exact NDE, NIE and TE estimates were very close to corresponding true values for each scenario and each type of simulation, with relative bias values ranging between -0.34% and 1.35%. All exact interval estimators (bootstrap and delta method) yielded CP values close to 95%. For the simulations without covariates, the exact results were almost identical to those returned by the NEM approach (results omitted from tables), while they were very close in the simulations with covariates. The exact results were also very close to those obtained using the quasi-Bayesian approach (for RD scale; see Table 4 and Web Table 4).

The results for the approximate natural effects estimator in the simulation studies without and with covariates under increasing degrees of the ROA violation are presented in Tables 2-3 and Web Tables 2-3, respectively (type of estimator = *Approximate*). In *Scenario 1* (rare outcome in all strata defined by A and M), the approximate OR estimator demonstrated small relative bias values when either the true ORs or RRs was used as reference values (between 0.13% and 5.24%). Corresponding CPs by delta method and bootstrap were close to the 95% nominal level. For *Scenario 2*, where the outcome Y is rare marginally, but not rare in the stratum defined by $A = 1$ and $M = 1$, we observed relative bias values ranging between 5.93% and 62.6%, and a significant decrease in CP values. The same tendencies for relative biases and CPs were seen for

Scenario 3. For *Scenario 4*, which violated the ROA in all strata defined by A and M, we obtained relative bias values up to 69.62% and CP values equal to 0% in some cases.

The total effect estimates obtained from the exact approach by the multiplication of corresponding NDE and NIE estimates were closer to the non-mediated total effect estimates as compared to the approximate approach (Web Tables 5-6).

REAL DATA EXAMPLE

We used cohort data presented in Samoilenko et al. (12) to illustrate our exact mediation approach. Briefly, the data consisted of 6197 singleton pregnancies from asthmatic women who gave birth in Quebec (Canada) between 1998 and 2008. Low birthweight (LBW) and prematurity (PTB) were selected as the outcome and mediator, respectively, and two exposure variables were examined separately: 1) treatment with inhaled corticosteroids (ICS) during pregnancy and 2) placental abruption. These data correspond to a scenario in which the outcome (LBW) is rare marginally, but not rare in some strata of mediator (PTB) and exposure.

We used our SAS macro *mediation_estimates* (see Web Appendices 2-3) to obtain exact NDE and NIE estimates on the OR, RR and RD scales for each exposure variable. Mediation analyses adjusted for *maternal age at the beginning of pregnancy* (< 18, > 18-34, > 34 years), *baby's sex*, *diabetes mellitus*, and *gestational diabetes*. The SAS CAUSALMED procedure was also applied to obtain natural effects on the multiplicative scales, implementing the approximate approach defined in Equations 8-10 for the OR scale. Mediation effects on the OR and RR scales were also estimated using the NEM approach, as described in the simulation studies, and on the RD scale using the quasi-Bayesian approach. For all approaches, exposure-mediator interaction was considered, and mediation effects were estimated at the sample-specific mean values of the covariates. However, since our SAS macro *mediation_estimates* allows for the estimation of conditional natural effects at user-specified values of the adjustment covariates (by default at the mean values of the covariates), we also obtained natural effects for placental abruption at more meaningful levels of the categorical covariates for purpose of illustration. More details on the real data analyses are presented in Web Appendix 1.

The main results are presented in Table 5 and Figure 1. The exact and approximate OR estimates did not generally agree, with the only exception of the NIE in the mediation analysis with ICS as exposure variable. For placental abruption, the observed discrepancies were quite remarkable. The RR point estimates computed by our SAS macro were close to those computed by PROC CAUSALMED with a log-binomial or Poisson outcome regression model. However, abnormally wide bootstrap 95% CIs for RR^{NDE} and RR^{TE} were returned by PROC CAUSALMED for ICS exposure.

For both exposures, the natural effects OR and RR point estimates obtained by our exact approach were similar to those obtained by the NEM approach. Some discrepancy was observed between CIs returned by *medflex* and exact delta CIs for placental abruption. Exact estimates for the NDE and NIE on the RD scale were found close to corresponding effect estimates obtained using the quasi-Bayesian approach. Exact bootstrap CIs were observed in better agreement with CIs returned by the quasi-Bayesian approach in comparison with exact delta CIs.

The exact TE point estimates were found close to the conventional TE estimates for both exposures and scales. However, the TE decomposition property was markedly not satisfied for the approximate OR estimates returned by PROC CAUSALMED, e.g. the approximate TE was 2.24*3.03=6.79 for placental abruption while the conventional TE was 5.13.

Finally, Figure 2 showcases our SAS macro by presenting natural effects on the OR and RD scales for placental abruption evaluated at two different sets of levels of fetal sex, maternal age and diabetes statuses.

The data that support the findings of this section are not publicly available because of privacy and ethical restrictions.

DISCUSSION

In this article, we introduced exact binary-binary regression-based estimators of the natural direct and indirect effects for the three most commonly used scales in epidemiology, namely the OR, RR and RD scales. Our work, which is based on the specification of a logistic outcome model, thus extends previous works that have proposed an exact binary-binary natural effects estimator on the OR scale. Our exact estimators were observed to be virtually unbiased, regardless of the effect scale and the rareness or commonness of the outcome. Corresponding standard error formulas were derived for each scale using first order delta method, thereby providing an alternative approach for computing confidence intervals (in addition to bootstrap). In our simulations, for which the sample size was relatively large, both the delta method and the bootstrap yielded coverage probabilities close to the nominal value. Unlike other mediation approaches implemented in the simulations and real data analyses, our exact approach was observed to be numerically stable no matter the effect scale on which results were obtained.

Our investigations have brought additional evidence regarding the performance of the approximate natural effects OR estimator proposed by Valeri and Vanderweele (3) for binary mediators and outcomes. As expected, this estimator was found to behave adequately in the scenario where the outcome was rare in all strata defined by mediator and exposure (*Scenario* 1), while the exact estimator performed comparably or better. In other scenarios investigated (*Scenarios* 2-4), in which the outcome was either rare or common marginally but not rare conditionally, the bias and variance of the approximate estimator were found systematically larger than those of proposed exact estimator under both multiplicative scales, with large biases and poor coverage probabilities sometimes exhibited.

Implementation of our proposed exact approach can be done using the SAS macro appended to this article (Web Appendix 3). By default, the exact NDE and NIE are estimated at the sample-specific mean values of the adjustment covariates, but our macro also handles user-specified levels for the entire set of covariates or for some proper subset (in the latter case, our macro sets the other covariates to the sample mean values). Another functionality of our macro is that it allows for Firth penalization by calling the *Firth* option in PROC LOGISTIC. Firth penalization is a general method designed to reduce bias of the maximum likelihood parameter estimator (32). This penalization has been shown to be effective in dealing with separation problems in logistic regression models in presence of small or sparse data (33-35).

Although the NDE and NIE are popular estimands in the applied literature, the controlled direct effect (CDE) can also be of interest to practitioners (36, 37). Valeri and VanderWeele (3) provided an expression for the CDE on the OR scale derived from logistic regression models for the mediator and outcome. This expression is not obtained by invoking the ROA and is thus exact by construction. For completeness, our macro also returns the CDE on all scales considered (see Web Appendix 1 for our extension to the RR and RD scales).

To conclude, our exact estimator is indicated for those wanting to perform a conventional binary-binary regression-based mediation analysis in the effect scale of their choice without worrying about the rareness or commonness of the outcome. By using the same two fitted logistic models for all effect scales (OR, RR and RD), our exact approach also simplifies applications and increases compatibility of mediation analyses results with binary mediators and outcomes. One limitation of our exact estimator is that it is currently only applicable to data from cohort studies; more developments will thus be required to extend proposed approach to accommodate data from case-control study designs in which cases are overrepresented compared to controls. Moreover, since our work has thus far focused on the case of a single mediator, it will also be worthwhile to study the multiple mediators case and expand our SAS macro further.

ACKNOWLEDGMENTS

Author affiliations: Department of Mathematics, Université du Québec à Montréal, Montréal, Canada (Mariia Samoilenko and Geneviève Lefebvre); Faculty of Pharmacy, Université de Montréal, Montréal, Canada (Geneviève Lefebvre); and Research Center, Centre hospitalier de l'Université de Montréal, Montréal, Canada (Geneviève Lefebvre).

This work was funded by grants from the Fonds de recherche Québec-Santé (FRQ-S) and the Natural Sciences and Engineering Research Council of Canada. Geneviève Lefebvre is a FRQ-S Research Scholar.

Conflict of interest: none declared.

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Table 1. Data Generating Mechanisms for the Simulation Study Without Covariates

Simulation parameters	Scenario 1	Scenario 2	Scenario 3	Scenario 4
$P(A = 1)$	0.40	0.40	0.40	0.40
$P(M = 1 \| A = 0)$	0.10	0.10	0.10	0.10
$P(M = 1 \| A = 1)$	0.20	0.20	0.20	0.20
$P(Y = 1 \| A = 0, M = 0)$	0.03	0.03	0.15	0.30
$P(Y = 1 \| A = 0, M = 1)$	0.08	0.08	0.10	0.70
$P(Y = 1 \| A = 1, M = 0)$	0.07	0.07	0.07	0.40
$P(Y = 1 \| A = 1, M = 1)$	0.10	0.50	0.50	0.80
Marginal outcome probability	0.051	0.083	0.149	0.396

A, binary exposure; M, binary mediator; Y, binary outcome

Table 2. Simulation Study Without Covariates[a]: Exact and Approximate Natural Effects Estimators on the OR Scale by Scenarios With Increasing Outcome Commonness

Effect and Type of Estimator[b]	True Value	Mean	Bias	Relative Bias, %	SD	RMSE	CP, %	
							Delta	Boot
Scenario 1								
NDE	2.171							
Exact		2.197	0.026	1.20	0.297	0.299	95.7	94.9
Approximate		2.184	0.013	0.59	0.297	0.297	95.6	95.1
NIE	1.044							
Exact		1.046	0.001	0.12	0.027	0.027	93.5	93.7
Approximate		1.047	0.003	0.24	0.028	0.028	93.4	93.7
TE	2.268							
Exact		2.296	0.028	1.25	0.304	0.305	95.3	95.2
Approximate		2.285	0.018	0.77	0.305	0.305	95.4	95.2
Scenario 2								
NDE	3.512							
Exact		3.556	0.044	1.25	0.436	0.438	94.6	94.7
Approximate		4.663	1.151	32.77	0.600	1.298	40.6	38.1
NIE	1.451							
Exact		1.454	0.004	0.24	0.066	0.066	93.8	93.5
Approximate		1.555	0.104	7.18	0.080	0.131	74.2	72.7
TE	5.096							
Exact		5.165	0.069	1.35	0.616	0.620	95.5	95.1
Approximate		7.248	2.151	42.22	0.971	2.361	26.0	24.3
Scenario 3								
NDE	0.751							
Exact		0.753	0.001	0.17	0.064	0.064	95.8	95.8
Approximate		0.992	0.241	32.11	0.094	0.259	17.7	18.3
NIE	1.451							
Exact		1.454	0.004	0.24	0.066	0.066	93.8	93.5
Approximate		1.555	0.104	7.18	0.080	0.131	74.2	72.7
TE	1.090							
Exact		1.093	0.003	0.27	0.087	0.087	96.3	95.9
Approximate		1.542	0.452	41.49	0.156	0.478	7.1	7.1

Scenario 4								
NDE	1.525							
Exact		1.525	-0.001	-0.04	0.090	0.090	95.3	95.3
Approximate		1.616	0.091	5.97	0.129	0.158	90.8	90.1
NIE	1.175							
Exact		1.175	0.000	0.02	0.023	0.023	94.7	95.1
Approximate		1.335	0.160	13.61	0.052	0.168	6.3	5.2
NDE	1.792							
Exact		1.791	-0.001	-0.04	0.105	0.105	95.4	95.5
Approximate		2.159	0.367	20.49	0.210	0.423	56.1	53.1

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]: Simulation study based on 1000 independent samples of size n=5000;
[b]: *exact*: exact estimator proposed; *approximate*: approximate estimator by Valeri and Vanderweele (3).

Table 3. Simulation Study Without Covariates[a]: Exact and Approximate Natural Effects Estimators on the RR Scale by Scenarios With Increasing Outcome Commonness

Effect and Type of Estimator[b]	True Value	Mean	Bias	Relative Bias, %	SD	RMSE	CP, %	
							Delta	Boot
Scenario 1								
NDE	2.086							
Exact		2.109	0.023	1.11	0.271	0.272	95.5	94.9
Approximate		2.184	0.098	4.72	0.297	0.313	94.5	94.0
NIE	1.041							
Exact		1.042	0.001	0.11	0.025	0.025	93.5	93.8
Approximate		1.047	0.006	0.57	0.028	0.028	94.6	93.9
TE	2.171							
Exact		2.197	0.025	1.16	0.276	0.277	95.2	95.0
Approximate		2.285	0.114	5.24	0.305	0.325	94.9	94.2
Scenario 2								
NDE	3.229							
Exact		3.266	0.037	1.16	0.377	0.379	94.9	94.5
Approximate		4.663	1.435	44.44	0.600	1.555	17.1	15.3
NIE	1.381							
Exact		1.383	0.003	0.20	0.055	0.055	94.0	93.7
Approximate		1.555	0.175	12.64	0.080	0.192	36.1	35.1
TE	4.457							
Exact		4.513	0.055	1.24	0.504	0.507	95.3	95.0
Approximate		7.248	2.790	62.60	0.971	2.955	3.6	3.0
Scenario 3								
NDE	0.779							
Exact		0.780	0.001	0.10	0.058	0.058	95.8	95.7
Approximate		0.992	0.213	27.34	0.094	0.233	29.1	28.7
NIE	1.381							
Exact		1.383	0.003	0.20	0.055	0.055	94.0	93.7
Approximate		1.555	0.175	12.64	0.080	0.192	36.1	35.1
TE	1.076							
Exact		1.078	0.002	0.18	0.072	0.072	96.3	95.9
Approximate		1.542	0.466	43.33	0.156	0.491	5.6	5.6

				Scenario 4				
NDE	1.294							
Exact		1.293	-0.001	-0.08	0.046	0.046	95.2	95.2
Approximate		1.616	0.322	24.89	0.129	0.347	20.9	22.1
NIE	1.091							
Exact		1.091	0.000	0.01	0.012	0.012	94.6	95.1
Approximate		1.335	0.244	22.35	0.052	0.249	0.0	0.0
TE	1.412							
Exact		1.411	-0.001	-0.08	0.048	0.048	95.5	95.4
Approximate		2.159	0.747	52.93	0.210	0.776	0.7	0.7

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]: Simulation study based on 1000 independent samples of size n=5000;

[b]: *exact*: exact estimator proposed; *approximate*: approximate estimator by Valeri and Vanderweele (3).

Table 4. Simulation Study Without Covariates[a]: Natural Effects Estimators on the RD Scale by Scenarios With Increasing Outcome Commonness

Effect and Type of Estimator[b]	True Value	Mean	Bias	Relative Bias, %	SD	RMSE	CP, %	
							Delta/ Robust SE[c]	Boot
Scenario 1								
NDE	0.038							
Exact		0.038	0.000	0.04	0.007	0.007	95.8	95.4
Mediation		0.038	0.000	0.16	0.007	0.007	95.8	
NIE	0.003							
Exact		0.003	0.000	1.26	0.002	0.002	93.7	93.3
Mediation		0.003	0.000	3.81	0.002	0.002	94.4	
TE	0.041							
Exact		0.041	0.000	0.13	0.007	0.007	96.1	95.8
Mediation		0.041	0.000	0.42	0.007	0.007	95.8	
Scenario 2								
NDE	0.078							
Exact		0.078	0.000	0.07	0.007	0.007	95.4	95.1
Mediation		0.078	0.000	0.06	0.007	0.007	95.4	
NIE	0.043							
Exact		0.043	0.000	0.27	0.005	0.005	94.3	94.2
Mediation		0.043	0.000	0.25	0.005	0.005	97.4	
TE	0.121							
Exact		0.121	0.000	0.14	0.009	0.009	95.9	95.8
Mediation		0.121	0.000	0.13	0.009	0.009	96.8	
Scenario 3								
NDE	-0.032							
Exact		-0.032	-0.000	0.39	0.009	0.009	95.8	95.4
Mediation		-0.032	-0.000	0.22	0.009	0.009	96.0	
NIE	0.043							
Exact		0.043	0.000	0.27	0.005	0.005	94.3	94.2
Mediation		0.043	0.000	0.25	0.005	0.005	97.5	
TE	0.011							
Exact		0.011	-0.000	-0.10	0.010	0.010	96.4	96.0
Mediation		0.011	0.000	0.33	0.010	0.010	96.8	

				Scenario 4				
NDE	0.10							
Exact		0.099	-0.001	-0.50	0.014	0.014	95.0	95.4
Mediation		0.099	-0.000	-0.52	0.014	0.014	95.0	
NIE	0.04							
Exact		0.040	-0.000	-0.06	0.005	0.005	94.6	95.2
Mediation		0.040	-0.000	-0.21	0.005	0.005	97.5	
TE	0.14							
Exact		0.139	-0.001	-0.38	0.014	0.014	95.4	95.2
Mediation		0.139	-0.001	-0.43	0.014	0.014	96.0	

Abbreviations: CP, coverage probability; NDE, natural direct effect; NIE, natural indirect effect; RD, risk difference; RMSE, root mean square error; SD, standard deviation; SE, standard error; TE, total effect.

[a]: Simulation study based on 1000 independent samples of size n=5000;

[b]: *exact*: exact estimator proposed; *mediation*: quasi-Bayesian approach by Imai et al. (27) implemented in the R package *mediation* (28).

[c]: Delta method for exact estimator; for *mediation*, the 95% CIs were based on the White's heteroskedasticity-consistent estimator for the covariance matrix (28).

Table 5. Real Data Example: Comparison Between Natural Direct and Indirect Effect Estimates on the OR, RR and RD Scales Obtained From Exact Estimator and Existing Estimators Available in Software

Effect Scale	Exact Estimates[a]	Delta 95% CI	Boot 95% CI[b]	Estimates by SAS PROC CAUSALMED[c]	Delta 95% CI	Boot 95% CI[b]	Estimates by Medflex/ Mediation R Packages[d]	95% CI[e]	Convent. TE	Boot 95% CI[b]
Exposure: treatment by inhaled corticosteroids										
OR NDE	1.00	0.86, 1.16	0.85, 1.17	0.84	0.60, 1.07	0.63, 1.14	1.00	0.86, 1.17		
OR NIE	0.95	0.86, 1.05	0.87, 1.05	0.94	0.83, 1.05	0.83, 1.07	0.95	0.86, 1.05		
OR TE	0.94	0.78, 1.14	0.77, 1.15	0.79	0.54, 1.03	0.58, 1.07	0.95	0.79, 1.16	0.95	0.79, 1.16
RR NDE	1.00	0.87, 1.15	0.86, 1.16	0.98	0.84, 1.11	0.49, 217	1.00	0.87, 1.16		
RR NIE	0.95	0.87, 1.05	0.87, 1.04	0.95	0.87, 1.04	0.84, 1.05	0.95	0.87, 1.05		
RR TE	0.95	0.80, 1.13	0.79, 1.13	0.93	0.77, 1.09	0.45, 207	0.96	0.80, 1.15	0.96	0.80, 1.15
RD NDE	-0.00	-0.01, 0.01	-0.01, 0.01	NA	NA	NA	-0.00	-0.01, 0.01		
RD NIE	-0.00	-0.01, 0.00	-0.01, 0.00	NA	NA	NA	-0.00	-0.01, 0.00		
RD TE	-0.00	-0.03, 0.02	-0.02, 0.01	NA	NA	NA	-0.00	-0.02, 0.01		
Exposure: Placental abruption										
OR NDE	1.88	1.61, 2.21	1.23, 2.63	2.24	1.25, 3.24	1.44, 3.70	1.90	1.26, 2.67		
OR NIE	2.70	1.99, 3.66	2.02, 3.86	3.03	2.29, 3.76	2.37, 3.81	2.70	2.03 3.91		
OR TE	5.07	3.33, 7.73	3.51, 6.90	6.79	3.12, 10.46	4.09, 12.04	5.14	3.66 7.00	5.13	3.60, 6.92
RR NDE	1.78	1.52, 2.08	1.21, 2.38	1.76	1.12, 2.40	1.18, 2.32	1.78	1.29, 2.46		
RR NIE	2.24	1.73, 2.91	1.76, 3.01	2.20	1.59 2.81	1.73, 2.97	2.21	1.71, 2.85		
RR TE	3.99	2.71, 5.86	2.99, 5.02	3.86	2.66, 5.06	3.02, 4.80	3.94	3.12, 4.98	4.02	3.06, 5.03
RD NDE	0.05	0.04, 0.07	0.01, 0.09	NA	NA	NA	0.05	0.02, 0.10		
RD NIE	0.15	0.10, 0.20	0.10, 0.20	NA	NA	NA	0.15	0.10, 0.20		
RD TE	0.20	0.17, 0.23	0.14, 0.26	NA	NA	NA	0.20	0.14, 0.26		

Abbreviations: CI, confidence interval; NDE, natural direct effect; NIE, natural indirect effect; OR, odds ratio; RD, risk difference; RR, risk ratio; TE, total effect.

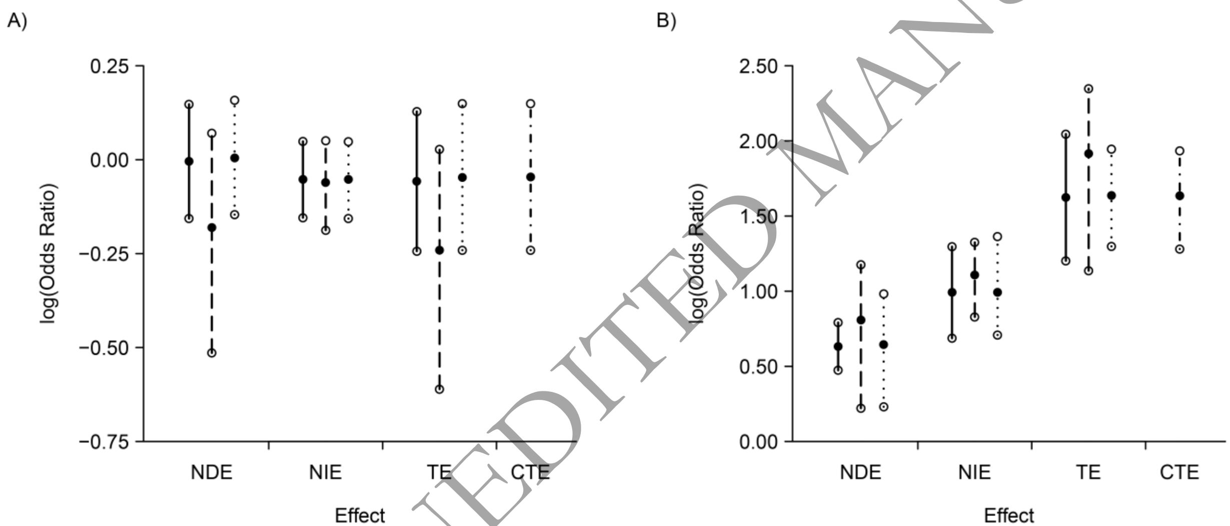
[a]: Estimates returned by SAS macro *mediation_estimates* (see Web Appendix 3);

[b]: Percentile bootstrap based on 1000 resamples with replacement;

[c]: SAS procedure based on the approximate estimator by Valeri and Vanderweele (3);
[d]: *medflex*: natural effect models approach (24) using weighting method implemented in the R package *medflex* (26); *mediation*: quasi-Bayesian approach by Imai et al. (27) implemented in the R package *mediation* (28);
[e]: See Appendix for details.

Figure 1. Real data example: comparison between natural direct effect, natural indirect effect and total effect estimates on the odds ratio scale obtained from exact estimator and existing estimators available in software. Left panel A): mediation analyses with inhaled corticosteroids as exposure variable. Right panel B): mediation analyses with placental abruption as exposure variable. The solid lines present 95% confidence intervals (CIs) obtained by the exact approach using delta method. The dashed and dotted lines correspond to 95% CIs returned by the PROC CAUSALMED SAS procedure (by delta method) and the R package *medflex* (by percentile bootstrap), respectively. The dot-dash line presents 95% CI for the conventional (non-mediated) total effect (by percentile bootstrap). The bullets provide the effect point estimates; the empty circles correspond to the CI endpoints. NDE, natural direct effect; NIE, natural indirect effect; TE, total effect; CTE, conventional total effect.

Figure 2. Real data example with placental abruption as exposure variable: exact natural direct effect, natural indirect effect and total effect on the odds ratio (left panel A)) and risk difference (right panel B)) scales evaluated at particular levels of the adjustment covariates. Solid lines correspond to 95% confidence intervals (CIs) given the following set of covariate values: *baby's sex* = *girl*, *maternal age* between 18 and 34 years, *diabetes mellitus = no*, *gestational diabetes* = *no*. Dashed lines correspond to 95% CIs when the covariate values are specified as follows: *baby's sex* = *boy*, *maternal age* under 18 years, *diabetes mellitus = no*, *gestational diabetes* = *yes*. 95% CIs are constructed by percentile bootstrap based on 1000 resamples with replacement. The bullets provide the effect point estimates; the empty circles correspond to the CI endpoints. NDE, natural direct effect; NIE, natural indirect effect; TE, total effect.


A)
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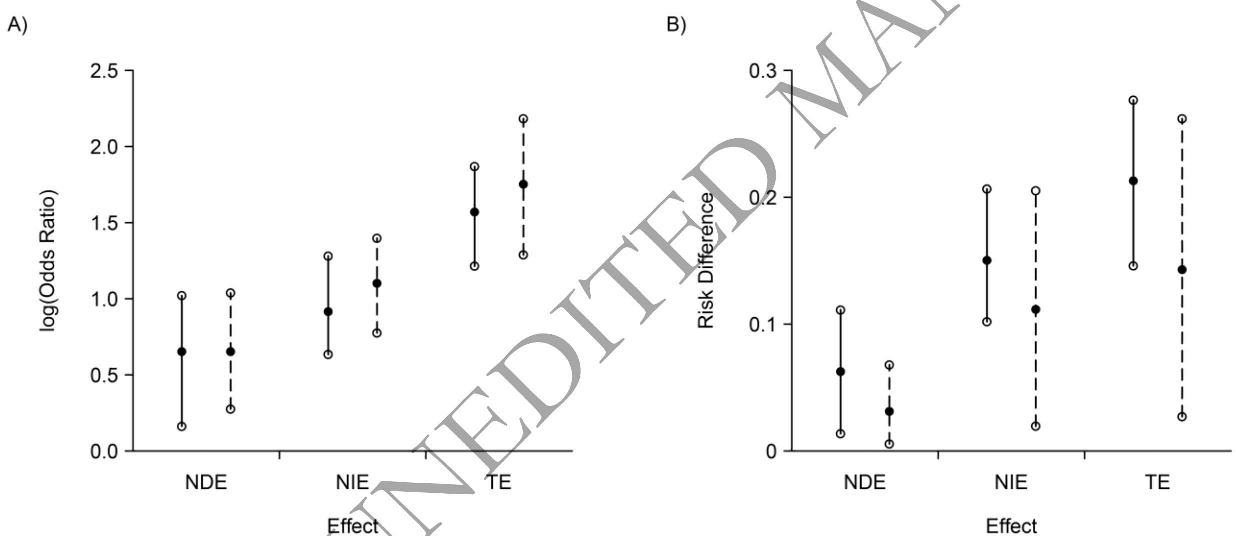
A)
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NIE
TE
Effect
B)
0.3
0.2
0.1
0
Risk Difference
NDE
NIE
TE
Effect