

Practice of Epidemiology

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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Initially submitted May 4, 2020; accepted for publication March 2, 2021.

In the causal mediation framework, several parametric-regression-based approaches have been introduced in the last decade 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 (SAS Institute, Inc., Cary, North Carolina) we developed, our approach is illustrated to assess the separate effects of exposure to inhaled corticosteroids and placental abruption on low birth weight mediated by prematurity. Our exact natural-effects estimators are found to work properly in both simulations and the real data example.

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

Abbreviations: NDE, natural direct effect; NEM, natural effect model; NIE, natural indirect effect; OR, odds ratio; RD, risk difference; ROA, rare outcome assumption; RR, risk ratio; TE, total effect.

Mediation analysis approaches that rely on the specification of parametric models for the mediator and outcome variables are naturally appealing to practitioners because of their conceptual simplicity. However, notoriously, 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 the resources available for estimating direct and indirect effects with binary outcomes. However, a number of proposed approaches 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 the natural direct effect (NDE) and the natural indirect effect (NIE) on the odds ratio (OR) scale for continuous and binary mediators. For a normally distributed mediator, Gaynor et al. (4) used a probit approximation of 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 of Gaynor et al. (4), introduced an exact estimator for a nonrare 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 of Valeri and VanderWeele (3) is popular among applied researchers, arguably because of its accessible implementation in standard statistical software (e.g., the SAS procedure PROC

CAUSALMED (SAS Institute, Inc., Cary, North Carolina) and the Stata module PARAMED (StataCorp LLC, 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 is 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 et al. (12) and Gaynor et al. (4) independently introduced a logistic-regression-based estimator for cohort data that uses the parameterized 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 (i.e., 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 Valeri and VanderWeele (3) approximate estimator and found that the former was unbiased for the NDE and NIE ORs (OR^{NDE} and OR^{NIE} , respectively), unlike the latter. Commenting on Samoilenko et al. (12), VanderWeele et al. (13) acknowledged that the ROA needs to hold in strata formed by covariates, *including the 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. However, more work is required to fully develop inference. In the paper by Samoilenko et al. (12), the variance computation for the OR^{NDE} and OR^{NIE} estimators was done using bootstrapping only. In Gaynor et al. (4), the standard error formulas were not provided in the paper but were implemented in R code (R Foundation for Statistical Computing, Vienna, Austria) developed for scenarios based on specific data sets. In the paper by Doretti et al. (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 this article is 2-fold. Our 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 the paper by Samoilenko et al. (12). While the bootstrap is indicated for inference on the indirect effect (15), it is more computer-intensive and not assumption-free (16, 17). Therefore, providing both delta and percentile bootstrap confidence intervals allows

for greater flexibility and increased confidence in mediation results. Our 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 3 scales using the same logistic model for the outcome.

METHODS

Models and nested counterfactual outcome probabilities

As in the papers by 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:

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

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

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

Under identification assumptions (19) and the modeling assumptions in equations 1 and 2, the nested counterfactual outcome $Y(a, M(a^*))$ probability is expressed as

$$\begin{aligned} P(Y(a, M(a^*)) = 1|C = c) \\ = \text{expit}(\theta_0 + \theta_1 a + \theta_2 + \theta_3 a + \theta'_4 c) \\ \times \text{expit}(\beta_0 + \beta_1 a^* + \beta'_2 c) \\ + \text{expit}(\theta_0 + \theta_1 a + \theta'_4 c) \\ \times (1 - \text{expit}(\beta_0 + \beta_1 a^* + \beta'_2 c)), \end{aligned} \quad (3)$$

where

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

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

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

Natural direct and indirect effects on the OR, RR, and RD scales

Explicit expressions for the (conditional) NDE and NIE ORs, $OR^{NDE}_{a,a^*|c}$ and $OR^{NIE}_{a,a^*|c}$, corresponding to a change in the exposure level from $A = a^*$ to $A = a$ (also see Samoilenko et al. (12) and Gaynor et al. (4)), are derived using the nested

counterfactual outcome probabilities defined in equation 3 as follows:

$$\begin{aligned} \text{OR}_{a,a^*|c}^{\text{NDE}} &= \frac{\frac{P(Y(a, M(a^*))=1|C=c)}{1-P(Y(a, M(a^*))=1|C=c)}}{\frac{P(Y(a^*, M(a^*))=1|C=c)}{1-P(Y(a^*, M(a^*))=1|C=c)}}, \\ \text{OR}_{a,a^*|c}^{\text{NIE}} &= \frac{\frac{P(Y(a, M(a))=1|C=c)}{1-P(Y(a, M(a))=1|C=c)}}{\frac{P(Y(a, M(a^*))=1|C=c)}{1-P(Y(a, M(a^*))=1|C=c)}}. \end{aligned} \quad (4)$$

In an analogous manner, equation 3 leads to exact NDE and NIE RR expressions, $\text{RR}_{a,a^*|c}^{\text{NDE}}$ and $\text{RR}_{a,a^*|c}^{\text{NIE}}$, respectively:

$$\begin{aligned} \text{RR}_{a,a^*|c}^{\text{NDE}} &= \frac{P(Y(a, M(a^*))=1|C=c)}{P(Y(a^*, M(a^*))=1|C=c)}, \\ \text{RR}_{a,a^*|c}^{\text{NIE}} &= \frac{P(Y(a, M(a))=1|C=c)}{P(Y(a, M(a^*))=1|C=c)}. \end{aligned} \quad (5)$$

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

$$\begin{aligned} \text{OR}_{a,a^*|c}^{\text{TE}} &= \text{OR}_{a,a^*|c}^{\text{NDE}} \times \text{OR}_{a,a^*|c}^{\text{NIE}}, \\ \text{RR}_{a,a^*|c}^{\text{TE}} &= \text{RR}_{a,a^*|c}^{\text{NDE}} \times \text{RR}_{a,a^*|c}^{\text{NIE}}. \end{aligned} \quad (6)$$

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

$$\begin{aligned} \text{RD}_{a,a^*|c}^{\text{NDE}} &= P(Y(a, M(a^*))=1|C=c) \\ &\quad - P(Y(a^*, M(a^*))=1|C=c), \\ \text{RD}_{a,a^*|c}^{\text{NIE}} &= P(Y(a, M(a))=1|C=c) \\ &\quad - P(Y(a, M(a^*))=1|C=c). \end{aligned} \quad (7)$$

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

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

For each effect scale, the NDE and NIE estimators are induced by replacing the coefficients in equations 1 and 2 with corresponding estimators. The formulas for calculating the natural-effects standard errors via the delta method are provided in Web Appendix 1 (available online at <https://doi.org/10.1093/aje/kwab055>).

Valeri and VanderWeele (3) approximate NDE and NIE approach

As detailed by Samoilenko et al. (12), the approximate expressions for the $\text{OR}_{a,a^*|c}^{\text{NDE}}$ and $\text{OR}_{a,a^*|c}^{\text{NIE}}$ provided in the paper by 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 with exponential functions; and second, approximate the OR by RR, that is, replace equation 4 with equation 5:

$$\begin{aligned} P_{\text{app}}(Y(a, M(a^*))=1|C=c) \\ &= \exp(\theta_0 + \theta_1 a + \theta_2 + \theta_3 a + \theta'_4 c) \\ &\quad \times \text{expit}(\beta_0 + \beta_1 a^* + \beta'_2 c) + \exp(\theta_0 + \theta_1 a + \theta'_4 c) \\ &\quad \times (1 - \text{expit}(\beta_0 + \beta_1 a^* + \beta'_2 c)); \end{aligned} \quad (8)$$

$$\begin{aligned} \text{app OR}_{a,a^*|c}^{\text{NDE}} &= \frac{P_{\text{app}}(Y(a, M(a^*))=1|C=c)}{P_{\text{app}}(Y(a^*, M(a^*))=1|C=c)}, \\ \text{app OR}_{a,a^*|c}^{\text{NIE}} &= \frac{P_{\text{app}}(Y(a, M(a))=1|C=c)}{P_{\text{app}}(Y(a, M(a^*))=1|C=c)}. \end{aligned} \quad (9)$$

The approximate expression for the TE is then given by

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

Simulation studies

We conducted 2 simulation studies to examine the behavior of proposed exact estimators. In the first simulation study, no covariates C were included for the sake of simplicity, while 2 covariates were included in the second study. Both studies considered 4 scenarios corresponding to different levels of outcome rareness/commonness:

Scenario 1. The outcome is rare in all of 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 1 stratum defined by the binary exposure and binary mediator.

Scenario 3. This scenario is similar to scenario 2, but it features 2 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 1,000 independent samples of size $n = 5,000$ 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

$$\begin{aligned} \text{true OR}^{\text{NDE}} &= \frac{P_{10}/(1-P_{10})}{P_{00}/(1-P_{00})}, \text{ true OR}^{\text{NIE}} = \frac{P_{11}/(1-P_{11})}{P_{10}/(1-P_{10})}, \\ \text{true RR}^{\text{NDE}} &= P_{10}/P_{00}, \text{ true RR}^{\text{NIE}} = P_{11}/P_{10}, \\ \text{true RD}^{\text{NDE}} &= P_{10} - P_{00}, \text{ true RD}^{\text{NIE}} = P_{11} - P_{10}, \end{aligned} \quad (11)$$

Table 1. Data-Generating Mechanisms for a Simulation Study Without Covariates Conducted to Evaluate Proposed Exact Estimators

Simulation Parameters ^a	Simulation Scenario			
	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	0.05	0.08	0.15	0.40

^a A, binary exposure; M, binary mediator; P, probability; Y, binary outcome.

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

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

The true total causal effects were calculated correspondingly as

$$\begin{aligned} \text{true OR}^{\text{TE}} &= \text{true OR}^{\text{NDE}} \times \text{true OR}^{\text{NIE}}, \\ \text{true RR}^{\text{TE}} &= \text{true RR}^{\text{NDE}} \times \text{true RR}^{\text{NIE}}, \\ \text{true RD}^{\text{TE}} &= \text{true RD}^{\text{NDE}} + \text{true RD}^{\text{NIE}}. \end{aligned}$$

For each sample, exact estimates of natural direct and indirect effects were calculated on the OR, RR, and RD scales. The mean value, bias, relative bias, standard deviation, and root mean squared error of proposed exact estimators were then estimated over the 1,000 samples generated; the true ORs, RRs, and RDs defined in equation 11 were used as the 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 with 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 the reference. The calculations described above were performed using SAS, version 9.5.

For each scenario and sample, we also considered 2 other existing approaches for comparison with the exact method being introduced here. For all 3 scales (OR, RR, and 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 an 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.'s (27) 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; 1,000 Monte Carlo draws were used for each sample generated. Note that *mediation* version 4.5.0 returns NDE and NIE estimates on the RD scale only.

We computed the coverage probabilities of 95% confidence interval estimators by calculating the proportion of times confidence intervals enclosed corresponding true values of the NDE, NIE, and TE. For the exact and approximate approaches, 95% confidence intervals were constructed by percentile bootstrap based on 500 resamples with replacement (29) and using the first-order delta method. For the NEM approach, 95% confidence intervals were obtained using robust standard errors based on the sandwich estimator (30). For the quasi-Bayesian approach, 95% confidence intervals were based on 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:

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

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

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

and

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

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

$$\begin{aligned}P_{ij} = & \text{expit}(\theta_0 + \theta_1 i + \theta_2 + \theta_3 i + \theta_{41} \bar{c}_1 + \theta_{42} \bar{c}_2) \\ & \times \text{expit}(\beta_0 + \beta_1 j + \beta_{21} \bar{c}_1 + \beta_{22} \bar{c}_2) \\ & + \text{expit}(\theta_0 + \theta_1 i + \theta_{41} \bar{c}_1 + \theta_{42} \bar{c}_2) \\ & \times (1 - \text{expit}(\beta_0 + \beta_1 j + \beta_{21} \bar{c}_1 + \beta_{22} \bar{c}_2))\end{aligned}$$

and $\bar{c}_1 = 0.5$, $\bar{c}_2 = 0$.

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. However, for the RR scale in scenario 4, the NEM was fitted using a Poisson regression model instead of a log-binomial model 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 . Note 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 mean values 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 coverage probability 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 the 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 and 3 and Web Tables 2 and 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 the true RRs were used as reference values (between 0.13% and 5.24%). Corresponding coverage probabilities by the 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 coverage probability values. The same tendencies for relative biases and coverage probabilities 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 coverage probability values equal to 0% in some cases.

The TE estimates obtained from the exact approach by the multiplication of corresponding NDE and NIE estimates were closer to the nonmediated TE estimates as compared with the approximate approach (Web Tables 5 and 6).

REAL-DATA EXAMPLE

We used cohort data presented in the paper by Samoilenko et al. (12) to illustrate our exact mediation approach. Briefly, the data consisted of 6,197 singleton pregnancies in asthmatic women who gave birth in the province of Quebec, Canada, between 1998 and 2008. Low birth weight and prematurity (preterm birth) were selected as the outcome and mediator, respectively, and 2 exposure variables were examined separately: 1) treatment with inhaled corticosteroids during pregnancy and 2) placental abruption. These data correspond to a scenario in which the outcome (low birth weight) is rare marginally but not rare in some strata of the mediator (preterm birth) and exposure.

We used our SAS macro *mediation_estimates* (see Web Appendices 2 and 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 years, 18–34 years, or >34 years), baby's sex, diabetes mellitus, and gestational diabetes. We also applied the SAS CAUSALMED procedure 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.

Table 2. Exact and Approximate Natural-Effects Estimators on the Odds Ratio Scale in Scenarios With Increasing Levels of Outcome Commonness (Simulation Study Without Covariates^a)

Effect and Type of Estimator	True Value	Mean	Bias	Relative Bias, %	SD	RMSE	Coverage Probability, %	
							Delta Method	Bootstrap
Scenario 1								
NDE OR	2.171							
Exact ^b		2.197	0.026	1.20	0.297	0.299	95.7	94.9
Approximate ^c		2.184	0.013	0.59	0.297	0.297	95.6	95.1
NIE OR	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 OR	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 OR	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 OR	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 OR	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 OR	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 OR	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 OR	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 OR	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 OR	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
TE OR	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: NDE, natural direct effect; NIE, natural indirect effect; OR, odds ratio; RMSE, root mean squared error; SD, standard deviation; TE, total effect.

^a Simulation study based on 1,000 independent samples of size $n = 5,000$.

^b Exact estimator proposed.

^c Approximate estimator of Valeri and VanderWeele (3).

Table 3. Exact and Approximate Natural-Effects Estimators on the Risk Ratio Scale in Scenarios With Increasing Levels of Outcome Commonness (Simulation Study Without Covariates^a)

Effect and Type of Estimator	True Value	Mean	Bias	Relative Bias, %	SD	RMSE	Coverage Probability, %	
							Delta Method	Bootstrap
Scenario 1								
NDE RR	2.086							
Exact ^b		2.109	0.023	1.11	0.271	0.272	95.5	94.9
Approximate ^c		2.184	0.098	4.72	0.297	0.313	94.5	94.0
NIE RR	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 RR	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 RR	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 RR	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 RR	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 RR	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 RR	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 RR	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 RR	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 RR	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 RR	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: NDE, natural direct effect; NIE, natural indirect effect; RMSE, root mean squared error; RR, risk ratio; SD, standard deviation; TE, total effect.

^a Simulation study based on 1,000 independent samples of size $n = 5,000$.

^b Exact estimator proposed.

^c Approximate estimator of Valeri and VanderWeele (3).

Table 4. Natural-Effects Estimators on the Risk Difference Scale in Scenarios With Increasing Levels of Outcome Commonness (Simulation Study Without Covariates^a)

Effect and Type of Estimator	True Value	Mean	Bias	Relative Bias, %	SD	RMSE	Coverage Probability, %	
							Delta Method/ Robust SE ^b	Bootstrap
Scenario 1								
NDE RD	0.038							
Exact ^c		0.038	0.000	0.04	0.007	0.007	95.8	95.4
Mediation ^d		0.038	0.000	0.16	0.007	0.007	95.8	
NIE RD	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 RD	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 RD	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 RD	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 RD	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 RD	−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 RD	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 RD	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 RD	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 RD	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 RD	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: NDE, natural direct effect; NIE, natural indirect effect; RD, risk difference; RMSE, root mean squared error; SD, standard deviation; SE, standard error; TE, total effect.

^a Simulation study based on 1,000 independent samples of size $n = 5,000$.

^b Delta method for the exact estimator; for *mediation*, the 95% confidence intervals were based on White's heteroskedasticity-consistent estimator for the covariance matrix (28).

^c Exact estimator proposed.

^d Quasi-Bayesian approach of Imai et al. (27) implemented in the R package *mediation* (28).

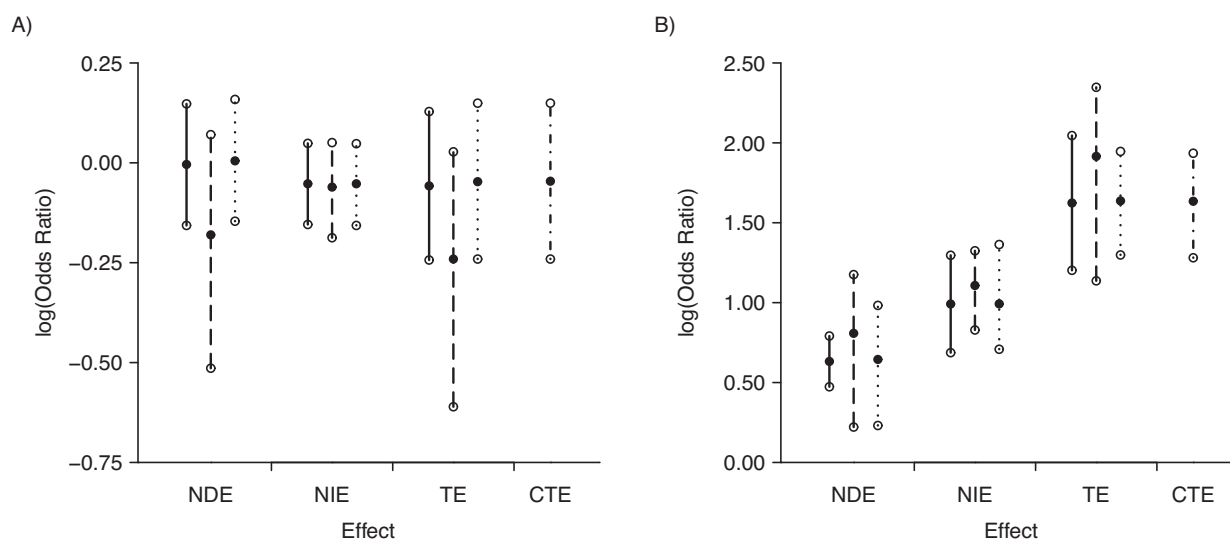


Figure 1. Comparison between natural direct effect (NDE), natural indirect effect (NIE), and total effect (TE) estimates on the odds ratio scale obtained from the exact estimator and existing estimators available in software (real-data example). A) Mediation analyses with use of inhaled corticosteroids as the exposure variable; B) mediation analyses with placental abruption as the exposure variable. The solid lines present 95% confidence intervals (CIs) obtained by the exact approach using the delta method. The dashed and dotted lines correspond to 95% CIs returned by the SAS (SAS Institute Inc., Cary, North Carolina) PROC CAUSALMED procedure (via the delta method) and the R package (R Foundation for Statistical Computing, Vienna, Austria) *medflex* (via percentile bootstrap), respectively. The dotted-dashed line presents 95% CIs for the conventional (nonmediated) TE (CTE) by percentile bootstrap. The black circles show effect point estimates, and the white circles show the CI endpoints.

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 the 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 generally did not agree, the only exception being the NIE in the mediation analysis with inhaled corticosteroids as the 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% confidence intervals for RR^{NDE} and RR^{TE} were returned by PROC CAUSALMED for inhaled corticosteroid 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 confidence intervals returned by *medflex* and exact delta confidence intervals for placental abruption. Exact estimates for the NDE and NIE on the RD scale were found to be close to corresponding effect estimates obtained using the quasi-Bayesian approach. Exact bootstrap confidence intervals were observed to be in better agreement with confidence intervals returned by the quasi-

Bayesian approach in comparison with exact delta confidence intervals.

The exact TE point estimates were found to be 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; for example, the approximate TE was $2.24 \times 3.03 = 6.79$ 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 2 different levels of fetal sex, maternal age, and diabetes status.

The data that support the findings for 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 3 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

Table 5. Comparison Between Natural Direct and Indirect Effect Estimates on the Odds Ratio, Risk Ratio, and Risk Difference Scales Obtained From the Exact Estimator and Existing Estimators Available in Various Software Packages (real-data example)

Effect Scale	Exact Estimate ^a	Delta Method 95% CI	Bootstrap 95% CI ^b	Estimate by SAS PROC CAUSALMED ^c	Delta Method 95% CI	Bootstrap 95% CI ^b	Estimate by <i>medflex</i> ^d / <i>mediation</i> ^e R Package	95% CI ^f	Conventional TE	Bootstrap 95% CI ^b
<i>Exposure: Treatment With Inhaled Corticosteroids</i>										
NDE OR	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		
NIE OR	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		
TE OR	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
NDE RR	1.00	0.87, 1.15	0.86, 1.16	0.98	0.84, 1.11	0.49, 2.17	1.00	0.87, 1.16		
NIE RR	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		
TE RR	0.95	0.80, 1.13	0.79, 1.13	0.93	0.77, 1.09	0.45, 2.07	0.96	0.80, 1.15	0.96	0.80, 1.15
NDE RD	−0.00	−0.01, 0.01	−0.01, 0.01	NA	NA	NA	−0.00	−0.01, 0.01		
NIE RD	−0.00	−0.01, 0.00	−0.01, 0.00	NA	NA	NA	−0.00	−0.01, 0.00		
TE RD	−0.00	−0.03, 0.02	−0.02, 0.01	NA	NA	NA	−0.00	−0.02, 0.01		
<i>Exposure: Placental Abruption</i>										
NDE OR	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		
NIE OR	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		
TE OR	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
NDE RR	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		
NIE RR	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		
TE RR	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
NDE RD	0.05	0.04, 0.07	0.01, 0.09	NA	NA	NA	0.05	0.02, 0.10		
NIE RD	0.15	0.10, 0.20	0.10, 0.20	NA	NA	NA	0.15	0.10, 0.20		
TE RD	0.20	0.17, 0.23	0.14, 0.26	NA	NA	NA	0.20	0.14, 0.26		

Abbreviations: CI, confidence interval; NA, not available; NDE, natural direct effect; NIE, natural indirect effect; OR, odds ratio; RD, risk difference; RR, risk ratio; TE, total effect.

^a Estimate returned by the SAS macro (SAS Institute Inc., Cary, North Carolina) *mediation_estimates* (see Web Appendix 3).^b Percentile bootstrap based on 1,000 resamples with replacement.^c SAS procedure based on the approximate estimator by Valeri and VanderWeele (3).^d Natural effect model approach (24) using the weighting method implemented in the R package (R Foundation for Statistical Computing, Vienna, Austria) *medflex* (26).^e Quasi-Bayesian approach by Imai et al. (27) implemented in the R package *mediation* (28).^f See Web Appendix 1 for details.

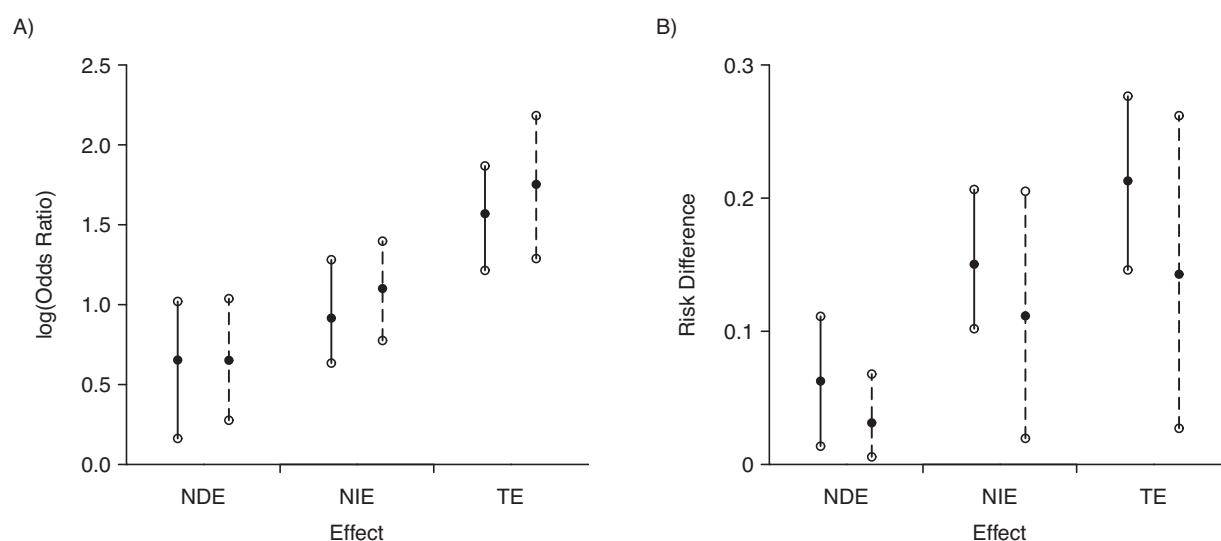


Figure 2. Exact natural direct effect (NDE), natural indirect effect (NIE), and total effect (TE) on the odds ratio (A) and risk difference (B) scales evaluated at particular levels of the adjustment covariates (real-data example with placental abruption as the exposure variable). Solid lines correspond to 95% confidence intervals (CIs) given the following set of covariate values: baby's sex = female, maternal age = 18–34 years, diabetes mellitus = no, and gestational diabetes = no. Dashed lines correspond to 95% CIs when the covariate values are specified as follows: baby's sex = male, maternal age <18 years, diabetes mellitus = no, and gestational diabetes = yes. The 95% CIs were constructed by percentile bootstrapping based on 1,000 resamples with replacement. The black circles show effect point estimates, and the white circles show the CI endpoints.

derived for each scale using the first-order delta method, thereby providing an alternative approach for computing confidence intervals (in addition to the 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 produced 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 the mediator and the 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 to be systematically larger than those of the proposed exact estimator under both multiplicative scales, with large biases and poor coverage probabilities sometimes exhibited.

Our proposed exact approach can be implemented using the SAS macro accompanying 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 the presence of scarce or sparse data (33–35).

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

In conclusion, our exact estimator is indicated for those wanting to perform a conventional binary-binary regression-based mediation analysis on the effect scale of their choice without worrying about the rareness or commonness of the outcome. By using the same 2 fitted logistic models for all effect scales (OR, RR, and RD), our exact approach also simplifies applications and increases compatibility of mediation analysis results with binary mediators and outcomes. One limitation of our exact estimator is that it is currently only applicable to data from cohort studies; thus, more developments will be required to extend the proposed approach to accommodate data from case-control study designs in

which cases are overrepresented compared with controls. Moreover, since our work has thus far focused on the case of a single mediator, it will also be worthwhile to study the case of multiple mediators and expand our SAS macro further.

ACKNOWLEDGMENTS

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This work was funded by grants from the Fonds de recherche du Québec—Santé (FRQ-S) and the Natural Sciences and Engineering Research Council of Canada. G.L. is an FRQ-S Research Scholar.

Conflict of interest: none declared.

REFERENCES

- Loeys T, Moerkerke B, de Smet O, et al. Flexible mediation analysis in the presence of nonlinear relations: beyond the mediation formula. *Multivariate Behav Res*. 2013;48(6): 871–894.
- VanderWeele TJ, Vansteelandt S. Odds ratios for mediation analysis for a dichotomous outcome. *Am J Epidemiol*. 2010; 172(12):1339–1348.
- Valeri L, VanderWeele TJ. Mediation analysis allowing for exposure-mediator interactions and causal interpretation: theoretical assumptions and implementation with SAS and SPSS macros. *Psychol Methods*. 2013;18(2):137–150.
- Gaynor SM, Schwartz J, Lin X. Mediation analysis for common binary outcomes. *Stat Med*. 2019;38(4):512–529.
- Tchetgen Tchetgen EJ. A note on formulae for causal mediation analysis in an odds ratio context. *Epidemiol Methods*. 2014;2(1):21–31.
- Yung Y-F, Lamm M, Zhang W. Causal mediation analysis with the CAUSALMED procedure. In: *Proceedings of the SAS Global Forum 2018 Conference*. Cary, NC: SAS Institute Inc.; 2018. (Paper SAS1991-2018). <https://www.sas.com/content/dam/SAS/support/en/sas-global-forum-proceedings/2018/1991-2018.pdf>. Accessed November 2, 2020.
- SAS Institute Inc. *SAS/STAT® 14.3 User's Guide*. Cary, NC: SAS Institute, Inc.; 2017.
- Emsley R, Liu H. PARAMED: Stata module to perform causal mediation analysis using parametric regression models. Boston, MA: Department of Economics, Boston College; 2013.
- TJ VW. *Explanation in Causal Inference: Methods for Mediation and Interaction*. New York, NY: Oxford University Press; 2015.
- Feingold A, MacKinnon DP, Capaldi DM. Mediation analysis with binary outcomes: direct and indirect effects of pro-alcohol influences on alcohol use disorders. *Addict Behav*. 2019;94:26–35.
- Rijnhart JJM, Twisk JWR, Eekhout I, et al. Comparison of logistic-regression based methods for simple mediation analysis with a dichotomous outcome variable. *BMC Med Res Methodol*. 2019;19(1):Article 19.
- Samoilenko M, Blais L, Lefebvre G. Comparing logistic and log-binomial models for causal mediation analyses of binary mediators and rare binary outcomes: evidence to support cross-checking of mediation results in practice. *Obs Stud*. 2018;4:193–216.
- VanderWeele TJ, Valeri L, Ananth CV. Counterpoint: mediation formulas with binary mediators and outcomes and the “rare outcome assumption”. *Am J Epidemiol*. 2019; 188(7):1204–1205.
- Doretti M, Raggi M, Stanghellini E. Exact parametric causal mediation analysis for a binary outcome with a binary mediator [preprint]. *arXiv*. 2020. (doi: [arXiv:1811.00439v3](https://arxiv.org/abs/1811.00439v3)). Accessed November 2, 2020.
- Hayes AF, Little TD. *Introduction to Mediation, Moderation, and Conditional Process Analysis: A Regression-Based Approach*. 2nd ed. New York, NY: The Guilford Press; 2018.
- Davison AC, Hinkley DV, eds. *The basic bootstraps*. In: *Bootstrap Methods and Their Application*. (Cambridge Series in Statistical and Probabilistic Mathematics). Cambridge, United Kingdom: Cambridge University Press; 1997: 11–69.
- Efron B, Tibshirani RJ, Tibshirani R. *An Introduction to the Bootstrap*. London, United Kingdom: Chapman & Hall Ltd.; 1993.
- VanderWeele TJ. Mediation analysis: a practitioner's guide. *Annu Rev Public Health*. 2016;37(1):17–32.
- VanderWeele TJ, Vansteelandt S. Conceptual issues concerning mediation, interventions and composition. *Stat Interface*. 2009;2(4):457–468.
- Robins JM, Greenland S. Identifiability and exchangeability for direct and indirect effects. *Epidemiology*. 1992;3(2): 143–155.
- de Stavola BL, Daniel RM, Ploubidis GB, et al. Mediation analysis with intermediate confounding: structural equation modeling viewed through the causal inference lens. *Am J Epidemiol*. 2015;181(1):64–80.
- Wang A, Arah OA. G-computation demonstration in causal mediation analysis. *Eur J Epidemiol*. 2015;30(10): 1119–1127.
- Oberg AS, VanderWeele TJ, Almqvist C, et al. Pregnancy complications following fertility treatment—disentangling the role of multiple gestation. *Int J Epidemiol*. 2018;47(4): 1333–1342.
- Lange T, Vansteelandt S, Bekaert M. A simple unified approach for estimating natural direct and indirect effects. *Am J Epidemiol*. 2012;176(3):190–195.
- Lange T, Hansen KW, Sørensen R, et al. Applied mediation analyses: a review and tutorial. *Epidemiol Health*. 2017; 39:e2017035.
- Steen J, Loeys T, Moerkerke B, et al. medflex: An R package for flexible mediation analysis using natural effect models. *J Stat Softw*. 2017;76(11):1–46.
- Imai K, Keele L, Tingley D. A general approach to causal mediation analysis. *Psychol Methods*. 2010;15(4): 309–334.
- Tingley D, Yamamoto T, Hirose K, et al. Mediation: R package for causal mediation analysis. *J Stat Softw*. 2014; 59(5):1–38.
- Chernick MR. *Bootstrap Methods: A Guide for Practitioners and Researchers*. 2nd ed. Hoboken, NJ: John Wiley & Sons, Inc.; 2011.

30. Liang K-Y, Zeger SL. Longitudinal data analysis using generalized linear models. *Biometrika*. 1986;73(1):13–22.
31. Starkopf L, Andersen M, Gerds T, et al. *Comparison of Five Software Solutions to Mediation Analysis*. Copenhagen, Denmark: University of Copenhagen; 2017.
32. Firth D. Bias reduction of maximum likelihood estimates. *Biometrika*. 1993;80(1):27–38.
33. Heinze G, Schemper M. A solution to the problem of separation in logistic regression. *Stat Med*. 2002;21(16):2409–2419.
34. Mansournia MA, Geroldinger A, Greenland S, et al. Separation in logistic regression: causes, consequences, and control. *Am J Epidemiol*. 2018;187(4):864–870.
35. Allison PD. *Logistic Regression Using SAS: Theory and Application*. 2nd ed. Cary, NC: SAS Institute Inc.; 2012.
36. VanderWeele TJ. Controlled direct and mediated effects: definition, identification and bounds. *Scand Stat Theory Appl*. 2011;38(3):551–563.
37. Imai K, Tingley D, Yamamoto T. Experimental designs for identifying causal mechanisms. *J R Stat Soc A Stat Soc*. 2013;176(1):5–51.