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Causal Mediation Analysis for an Ordinal Outcome with Multiple Mediators

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ABSTRACT
Causal mediation analysis is a popular approach for investigating whether the effect of an exposure on an outcome is through a mediator to better understand the underlying causal mechanism. In recent literature, mediation analysis with multiple mediators has been proposed for continuous and dichotomous outcomes. In contrast, methods for mediation analysis for an ordinal outcome are still underdeveloped. In this paper, we first review mediation analysis methods with a continuous mediator for an ordinal outcome and then develop mediation analysis with a binary mediator for an ordinal outcome. We further consider multiple mediators for an ordinal outcome in the counterfactual framework and provide identification assumptions for identifying the mediation effects. Under the identification assumptions, we propose a regression-based method to estimate the mediation effects through multiple mediators while allowing the presence of exposure-mediator interactions. The closed-form expressions of mediation effects are also obtained for three scenarios: multiple continuous mediators, multiple binary mediators, and multiple mixed mediators. We conduct simulation studies to assess the finite sample performance of our new methods and present the biases, standard errors, and confidence intervals to demonstrate that our proposed estimators perform well in a wide range of practical settings. Finally, we apply our proposed methods to assess the mediation effects of candidate DNA methylation CpG sites in the causal pathway from socioeconomic index to body mass index.

KEYWORDS
Causal mediation analysis; multiple mediators; natural direct effect; natural indirect effect; ordinal outcome; total effect

1. Introduction

Causal mediation analysis is a popular approach that enables researchers to understand the causal mechanism of an observed exposure-outcome association in a scientific study. It has widespread applications in many disciplines including psychology, epidemiology, behavioral science, economics, and neuroscience. The aim of mediation analysis is to determine whether the effect of an exposure on an outcome is wholly or in part due to a mediator, so that it can reveal the underlying causal mechanism and provide a way of performing intervention on the mediator (Baron & Kenny, 1986; Preacher & Hayes, 2008; VanderWeele, 2015).

In mediation analysis, the effect of the exposure on the outcome not through the mediator is referred to as the direct effect, and the effect of the exposure on the outcome through the mediator is referred to as the indirect effect. In the counterfactual framework, Robins and Greenland (1992) and Pearl (2001) provided the model-free definitions of the direct and indirect effects. Following their framework, there is a rich body of evaluating the direct and indirect effects for both continuous and binary outcomes. For further developments, one may refer to, for example, Rubin (2004), Imai et al. (2010), VanderWeele (2010), Albert and Nelson (2011), Vansteelandt and VanderWeele (2012), Tchetgen and Shpitser (2014), and the references therein.

In real situations, the exposure's effects on the outcome can also be transmitted through multiple mediators. A major challenge of mediation analysis with multiple mediators is the structural dependence among the multiple mediators, including the multiple causally ordered mediators, the multiple interdependent mediators and the multiple parallel mediators. There is a growing body of literature on mediation analysis with multiple mediators. The multiple causally ordered mediator models in the counterfactual framework have been studied by Daniel et al. (2015), Huang and Yang (2017), and Steen et al. (2017). For a continuous or binary outcome, the regression-based approaches to estimate the multiple interdependent mediation effects have been studied by VanderWeele and Vansteelandt (2014) and Saunders and Blume (2018). In addition, analytical approaches to express the total effect in the multiple parallel mediator models have also been provided by Bellavia and Valeri (2018) and Taguri et al. (2018). For multiple mediation analysis with a survival outcome, Yu et al. (2018) and Yu et al. (2019) considered multiple correlated mediators to propose the nonparametric or semiparametric methods to estimate the mediation effects.

Note that most existing methods for mediation analysis with multiple mediators are developed for continuous or binary outcomes. In practice, however, an ordinal outcome can also arise in medical research and other disciplines. In obesity studies, study subjects can be categorized into several groups: healthy weight, overweight, obese, and severely obese, based on their body mass index (BMI), for example, see Devick et al. (2022).

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To our knowledge, there exists little literature on the research of mediation analysis for an ordinal outcome. In recent years, Liu et al. (2013) proposed an appropriate procedure for categorical data in mediation models when the outcome variable is ordinal. VanderWeele et al. (2016) studied the mediation effects for an ordinal outcome with a single mediator. In this paper, we focus on mediation analysis for an ordinal outcome with multiple mediators in the counterfactual framework. Specifically, we propose a regression-based method to estimate the natural direct and indirect effects with multiple mediators. The key advantages of our approach are that the estimated natural direct and indirect effects have closed-form expressions, and the flexible regression models are allowed to be specified for both continuous and discrete multiple mediators.

The remainder of this paper is organized as follows. In Section 2, we provide the definitions of the direct and indirect effects for an ordinal outcome with multiple mediators and specify their identification assumptions. In Section 3, we review the existing methods for identifying and estimating the direct and indirect effects for an ordinal outcome with a single continuous mediator, and then develop new methods for mediation analysis for an ordinal outcome with a binary mediator. In Section 4, we propose a regression-based method to express the mediation effects with multiple mediators for three different scenarios: multiple continuous mediators, multiple binary mediators and multiple mixed mediators. We then conduct simulation studies to assess the finite sample performance of our proposed methods in Section 5 and demonstrate the usefulness of our proposed methods through the socioeconomic index (SI)-body mass index (BMI) data in Section 6. Finally, we conclude the paper with discussions in Section 7 and provide the detailed derivations in the Appendices.

2. Definition and Identification Assumptions

Consider a causal mediation model that includes an exposure X, an ordinal outcome Y with ordered categories $1, 2, \ldots, J$, and a total of K mediators $\boldsymbol{M} = (M^{(1)}, \ldots, M^{(K)})^T$, where T represents the transpose of a vector. The exposure X may affect the outcome Y directly, or it may affect some of the mediators $\boldsymbol{M}$, which in turn affects the outcome Y. Let $\boldsymbol{C}$ be a p-dimensional vector of all relevant confounding variables. Then, the relationship among the exposure, mediators, outcome and confounders can be represented by a causal diagram in Figure 1.

In the counterfactual framework, let Y_x and $\boldsymbol{M}_x$ denote the values of the outcome and mediators, that would have been observed if the exposure X was set to level x. Let $Y_{x,\boldsymbol{m}}$ denote the value of the outcome that would have been observed if the exposure X was set to level x and the mediators $\boldsymbol{M}$ were set to $\boldsymbol{m} = (m^{(1)}, m^{(2)}, \ldots, m^{(K)})^T$. Let $Y_{x,\boldsymbol{M}_{x^*}}$ denote the value of the outcome that would have been observed if the exposure X was set to level x and the mediators $\boldsymbol{M}$ were set to $\boldsymbol{M}_{x^*}$ that it would have taken at some reference exposure level x^*. We also need two technical assumptions referred to as the consistency and composition assumptions. The consistency assumption states that the counterfactual outcome Y_x and the mediators $\boldsymbol{M}_x$ are equal to Y and $\boldsymbol{M}$ when $X = x$, respectively. Furthermore, when $X = x$ and $\boldsymbol{M} = \boldsymbol{m}$, the counterfactual outcome $Y_{x,\boldsymbol{m}}$ is equal to Y. The composition assumption is $Y_x = Y_{x,\boldsymbol{M}_x}$, that the outcome associated to the exposure $X = x$ is equal to the outcome associated to setting X to x and the mediators to $\boldsymbol{M}_x$, which is the value it would have naturally attained under $X = x$ (VanderWeele & Vansteelandt, 2009).

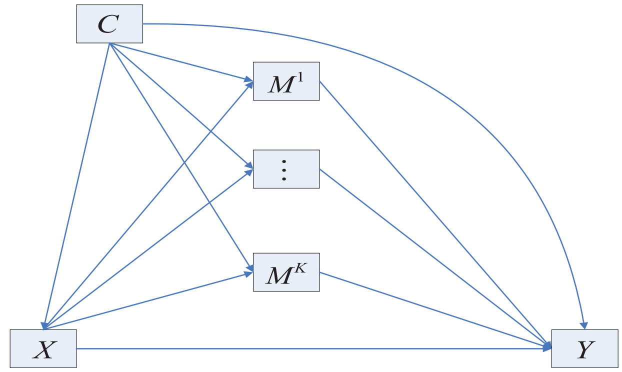

Figure 1. A causal diagram with the exposure X, the mediators $(M^{(1)}, \ldots, M^{(K)})$, the outcome Y and the confounding variable $\boldsymbol{C}$. The directions of arrows indicate the causal pathways.

Here, we adopt the odds ratio scale to define the direct and indirect effects for the multiple mediator setting. The total effect (TE) conditional on $\boldsymbol{C} = \boldsymbol{c}$ is defined by

$$\mathrm{TE}_{\mathrm{OR}} = \frac{P(Y_{x,\boldsymbol{M}_x} > j|\boldsymbol{c})/P(Y_{x,\boldsymbol{M}_x} \leq j|\boldsymbol{c})}{P(Y_{x^*,\boldsymbol{M}_{x^*}} > j|\boldsymbol{c})/P(Y_{x^*,\boldsymbol{M}_{x^*}} \leq j|\boldsymbol{c})}, \tag{1}$$

which measures the effect of the exposure X on the outcome Y when the exposure level set to x^* versus the exposure level set to x, where $1 \leq j \leq J - 1$.

The controlled direct effect (CDE) conditional on $\boldsymbol{C} = \boldsymbol{c}$ is defined by

$$\mathrm{CDE}_{\mathrm{OR}} = \frac{P(Y_{x,\boldsymbol{m}} > j|\boldsymbol{c})/P(Y_{x,\boldsymbol{m}} \leq j|\boldsymbol{c})}{P(Y_{x^*,\boldsymbol{m}} > j|\boldsymbol{c})/P(Y_{x^*,\boldsymbol{m}} \leq j|\boldsymbol{c})}, \tag{2}$$

which measures the effect of the exposure X on the outcome Y unmediated through the mediators $\boldsymbol{M}$ while fixing the mediators at $\boldsymbol{m}$. Alternatively, the natural effect sets the mediators at their natural levels that would be observed. Then, the natural direct effect (NDE) conditional on $\boldsymbol{C} = \boldsymbol{c}$ is defined by

$$\mathrm{NDE}_{\mathrm{OR}} = \frac{P(Y_{x,\boldsymbol{M}_{x^*}} > j|\boldsymbol{c})/P(Y_{x,\boldsymbol{M}_{x^*}} \leq j|\boldsymbol{c})}{P(Y_{x^*,\boldsymbol{M}_{x^*}} > j|\boldsymbol{c})/P(Y_{x^*,\boldsymbol{M}_{x^*}} \leq j|\boldsymbol{c})}, \tag{3}$$

which measures the effect on the outcome changing the exposure X from level x^* to level x, but blocking any effect on the mediators.

In contract to NDE, the joint natural indirect effect (NIE) through the mediators $\boldsymbol{M}$ conditional on $\boldsymbol{C} = \boldsymbol{c}$ is defined by

$$\mathrm{NIE}_{\mathrm{OR}} = \frac{P(Y_{x,\boldsymbol{M}_x} > j|\boldsymbol{c})/P(Y_{x,\boldsymbol{M}_x} \leq j|\boldsymbol{c})}{P(Y_{x,\boldsymbol{M}_{x^*}} > j|\boldsymbol{c})/P(Y_{x,\boldsymbol{M}_{x^*}} \leq j|\boldsymbol{c})}, \tag{4}$$

which measures the effect on the outcome when the mediators are changed by the exposure X from level x^* to level x and the exposure is fixed at level x at the same time. Note that the total effect decomposes into the product of natural direct and indirect effects, namely, $\mathrm{TE}_{OR} = NDE_{OR} \times NIE_{OR}$.

In the multiple mediator models, we further consider the mediation effects through an individual mediator. From

Figure 1, the joint natural indirect effect can be decomposed into K mediation effects within the K-mediator model under the assumption of no interaction among the mediators. We now define the natural indirect effect through a single mediator. The natural indirect effect through the mediator $M^{(i)}$ alone is defined by

$$\mathrm{NIE}_{\mathrm{OR}}^{(i)} = \frac{P(Y_{x,M_x^{(1)},\ldots,M_x^{(i-1)},M_x^{(i)},\ldots,M_x^{(K)}} > j|\boldsymbol{c})/P(Y_{x,M_x^{(1)},\ldots,M_x^{(i-1)},M_x^{(i)},\ldots,M_x^{(K)}} \le j|\boldsymbol{c})}{P(Y_{x,M_x^{(1)},\ldots,M_x^{(i-1)},M_{x^*}^{(i)},\ldots,M_x^{(K)}} > j|\boldsymbol{c})/P(Y_{x,M_x^{(1)},\ldots,M_x^{(i-1)},M_{x^*}^{(i)},\ldots,M_x^{(K)}} \le j|\boldsymbol{c})}, \tag{5}$$

which measures the indirect effect of the exposure X on the outcome Y only through the ith mediator with i from 1 to K. Note that under the independent assumption of mediators, it provides a proper decomposition of a joint natural indirect effect among individual mediators as follows:

$$\mathrm{NIE}_{\mathrm{OR}} = \prod_{i=1}^{K} \mathrm{NIE}_{\mathrm{OR}}^{(i)}.$$

In some studies, the natural effects are probably preferred since we may not be able to set the mediator at a specific level. Thus, stronger assumptions are needed to identify the natural effects. Let $A \coprod B|\boldsymbol{C}$ denote that A is independent of B conditional on $\boldsymbol{C}$. To identify the total effect, it is generally assumed that, conditional on the covariates $\boldsymbol{C}$, the effect of exposure X on outcome Y is unconfounded. In the counterfactual notation, this is denoted as $Y_x \coprod X|\boldsymbol{C} = \boldsymbol{c}$ for all $\boldsymbol{c}$. In addition, in order to identify the CDE, NDE and NIE, we need the following assumptions.

(A1) No unmeasured exposure-outcome confounding:
$Y_{x,\boldsymbol{m}} \coprod X|\boldsymbol{C} = \boldsymbol{c}$ for all x, $\boldsymbol{m}$ and $\boldsymbol{c}$.

(A2) No unmeasured mediator-outcome confounding:
$Y_{x,\boldsymbol{m}} \coprod \boldsymbol{M}_x|\{X = x, \boldsymbol{C} = \boldsymbol{c}\}$ for all x, $\boldsymbol{m}$ and $\boldsymbol{c}$.

(A3) No unmeasured exposure-mediator confounding:
$M_x^{(i)} \coprod X|\boldsymbol{C} = \boldsymbol{c}$ for all x, i and $\boldsymbol{c}$.

(A4) The cross-world independence assumption:
(A4.1) $Y_{x,\boldsymbol{m}} \coprod \boldsymbol{M}_{x^*}|\boldsymbol{C} = \boldsymbol{c}$ for all x, x^*, $\boldsymbol{m}$ and $\boldsymbol{c}$,
(A4.2) $M_x^{(i)} \coprod M_{x^*}^{(j)}|\boldsymbol{C} = \boldsymbol{c}$ for all $\boldsymbol{c}, x, x^*$ and $i \neq j$.

Note that the CDE can be identified under assumptions (A1) and (A2), and the identification of NDE and NIE requires assumptions (A3) and (A4). With all the four assumptions, the CDE, NDE and NIE can be estimated by fitting the regression models for the outcome and multiple mediators.

3. Mediation Analysis for an Ordinal Outcome with a Single Mediator

For an ordinal outcome, we first review mediation analysis with a continuous mediator proposed by VanderWeele et al. (2016). We then develop mediation analysis with a binary mediator for an ordinal outcome and obtain closed-form expressions for the mediation effects. For a single mediator M proposed by VanderWeele et al. (2016), the NIE, NDE and CDE are defined as $\mathrm{NIE}_{\mathrm{OR}} = \frac{P(Y_{x,M_x}>j|\boldsymbol{c})/P(Y_{x,M_x}\le j|\boldsymbol{c})}{P(Y_{x,M_{x^*}}>j|\boldsymbol{c})/P(Y_{x,M_{x^*}}\le j|\boldsymbol{c})}$, $\mathrm{NDE}_{\mathrm{OR}} = \frac{P(Y_{x,M_{x^*}}>j|\boldsymbol{c})/P(Y_{x,M_{x^*}}\le j|\boldsymbol{c})}{P(Y_{x^*,M_{x^*}}>j|\boldsymbol{c})/P(Y_{x^*,M_{x^*}}\le j|\boldsymbol{c})}$, and $\mathrm{CDE}_{\mathrm{OR}} = \frac{P(Y_{x,m}>j|\boldsymbol{c})/P(Y_{x,m}\le j|\boldsymbol{c})}{P(Y_{x^*,m}>j|\boldsymbol{c})/P(Y_{x^*,m}\le j|\boldsymbol{c})}$, respectively.

For a single mediator, we need the following identification assumptions (B): $Y_{x,m} \coprod X|\boldsymbol{C} = \boldsymbol{c}$, $Y_{x,m} \coprod M_x|\{X = x, \boldsymbol{C} = \boldsymbol{c}\}$, $M_x \coprod X|\boldsymbol{C} = \boldsymbol{c}$ and $Y_{x,m} \coprod M_{x^*}|\boldsymbol{C} = \boldsymbol{c}$. For mediation analysis for an ordinal outcome with a binary mediator, we propose a logistic regression model for the mediator and a logistic proportional odds model for the outcome, respectively. Under these identification assumptions, the closed-form expressions for NIE, NDE and CDE are derived.

3.1. A Review of the Mediation Analysis with a Continuous Mediator

In this section, we briefly review mediation analysis for an ordinal outcome with a continuous mediator. VanderWeele et al. (2016) investigated the mediation effects for an ordinal outcome with a continuous mediator. To obtain the closed-form expressions for the mediation effects, it is needed to make a rare outcome assumption: the reference category $J = 1$ is sufficiently common, e.g. $P(Y = 1|x, \boldsymbol{m}, \boldsymbol{c}) > 0.9$.

The natural direct and indirect effects can be parameterized by the so-called mediation and outcome models as follows:

$$M|_{X=x,\boldsymbol{C}=\boldsymbol{c}} = \alpha_0 + \alpha_1 x + \alpha_2^T \boldsymbol{c} + \varepsilon, \tag{6}$$

$$\mathrm{logit}(P(Y > j|x, m, \boldsymbol{c})) = -\beta_0^j + \beta_1 x + \beta_2 m + \beta_3 xm + \beta_4^T \boldsymbol{c}, \tag{7}$$

where ε is normally distributed with zero mean and variance σ^2 and $1 \le j \le J - 1$. Under models (6) and (7), the NIE, NDE and CDE are given by

$$\begin{aligned}
\mathrm{NIE}_{\mathrm{OR}} &\approx \exp\{(\alpha_1\beta_2 + \alpha_1\beta_3 x)(x - x^*)\},\\
\mathrm{NDE}_{\mathrm{OR}} &\approx \exp\{[\beta_1 + \beta_3(\alpha_0 + \alpha_1 x^* + \alpha_2^T \boldsymbol{c} + \beta_2\sigma^2)](x - x^*)\\
&\quad + 0.5\beta_3\sigma^2(x^2 - x^{*2})\},\\
\mathrm{CDE}_{\mathrm{OR}} &= \exp\{(\beta_1 + \beta_3 m)(x - x^*)\}.
\end{aligned}$$

Note that the CDE and NDE are approximately equal if there is no interaction between the exposure and the mediator.

3.2. Mediation Analysis for an Ordinal Outcome with a Binary Mediator

In this section, we develop theory and methods for mediation analysis for an ordinal outcome with a binary mediator. To evaluate the mediation effects by a binary mediator, we fit a logistic regression as follows:

$$\text{logit}(P(M=1|x,\boldsymbol{c})) = \alpha_0 + \alpha_1 x + \alpha_2^T \boldsymbol{c}. \quad (8)$$

If a rare outcome assumption holds, then model (7) can be approximately represented as

$$\log\left(P(Y>j|x,m,\boldsymbol{c})\right) \approx \text{logit}(P(Y>j|x,m,\boldsymbol{c})) \\ = -\beta_0^j + \beta_1 x + \beta_2 m + \beta_3 xm + \beta_4^T \boldsymbol{c}.$$

Under the identification assumptions (B), the NIE, NDE and CDE can be derived as

$$\text{NIE}_{\text{OR}} \approx \frac{1+\exp\left(\alpha_0+\alpha_1 x^* + \alpha_2^T \boldsymbol{c}\right)}{1+\exp\left(\alpha_0+\alpha_1 x + \alpha_2^T \boldsymbol{c}\right)} \cdot \frac{1+\exp\left(\beta_2+\beta_3 x+\alpha_0+\alpha_1 x + \alpha_2^T \boldsymbol{c}\right)}{1+\exp\left(\beta_2+\beta_3 x+\alpha_0+\alpha_1 x^* + \alpha_2^T \boldsymbol{c}\right)},$$

$$\text{NDE}_{\text{OR}} \approx \exp\left(\beta_1(x-x^*)\right) \cdot \frac{1+\exp\left(\beta_2+\beta_3 x+\alpha_0+\alpha_1 x^* + \alpha_2^T \boldsymbol{c}\right)}{1+\exp\left(\beta_2+\beta_3 x^*+\alpha_0+\alpha_1 x^* + \alpha_2^T \boldsymbol{c}\right)},$$

$$\text{CDE}_{\text{OR}} = \exp\left\{(\beta_1+\beta_3 m)(x-x^*)\right\}.$$

The detailed derivation is given in Appendix A. If there is no exposure-mediator interaction in the outcome regression model (7), we have

$$\text{NIE}_{\text{OR}} \approx \frac{1+\exp\left(\alpha_0+\alpha_1 x^* + \alpha_2^T \boldsymbol{c}\right)}{1+\exp\left(\alpha_0+\alpha_1 x + \alpha_2^T \boldsymbol{c}\right)} \cdot \frac{1+\exp\left(\beta_2+\alpha_0+\alpha_1 x + \alpha_2^T \boldsymbol{c}\right)}{1+\exp\left(\beta_2+\alpha_0+\alpha_1 x^* + \alpha_2^T \boldsymbol{c}\right)},$$

$$\text{NDE}_{\text{OR}} \approx \exp\left(\beta_1(x-x^*)\right),$$

$$\text{CDE}_{\text{OR}} = \exp\left\{\beta_1(x-x^*)\right\}.$$

Note that the CDE and NDE are approximately equal when there is no exposure-mediator interaction.

4. Mediation Analysis for an Ordinal Outcome with Multiple Mediators

In many applications, we make attempts to separate the effect of an exposure on an outcome into its effects through a number of different pathways. Thus, exploring the relative strength of different pathways from an exposure to an outcome is an interesting topic in recent years. In this section, we mainly consider the mediation effects for an ordinal outcome with multiple mediators in three scenarios: multiple continuous mediators, multiple binary mediators and multiple mixed mediators.

4.1. Mediation Analysis with Multiple Continuous Mediators

For mediation analysis with multiple mediators, the question that arises is the complex structure among multiple mediators. For the setting of binary exposure, Nguyen et al. (2016) and Taguri et al. (2018) studied the mediation effects for multiple mediators with independent structure. Wang et al. (2013) and Daniel et al. (2015) considered the mediation effects for multiple mediators with dependent structure. We first consider the mediation effects when all mediators are continuous variables and explore the effect of an exposure on an ordinal outcome through all mediators. We can fit a linear regression for every mediator $M^{(i)}$ and a logistic regression for the outcome Y, and allow for the exposure-mediator interaction. For every mediator $M^{(i)}$, the regression model can be written as

$$M^{(i)}|_{X=x,\boldsymbol{C}=\boldsymbol{c}} = \alpha_{0i} + \alpha_{1i} x + \alpha_{2i}^T \boldsymbol{c} + \varepsilon_i, \quad i=1,\ldots,K, \quad (9)$$

where the error ε_i follows a normal distribution with zero mean and variance σ_i^2. Then in matrix notation, the whole model can be represented as

$$\boldsymbol{M}|_{X=x,\boldsymbol{C}=\boldsymbol{c}} = \alpha_0 + \alpha_1 x + \Lambda \boldsymbol{c} + \varepsilon, \quad (10)$$

where $\alpha_0 = (\alpha_{01},\ldots,\alpha_{0K})^T$ is a vector of intercepts, $\alpha_1 = (\alpha_{11},\ldots,\alpha_{1K})^T$ represents the effects of the exposure, $\Lambda = (\alpha_{21},\ldots,\alpha_{2K})^T$ represents the regression coefficients of the confounders, and the error vector $\varepsilon = (\varepsilon_1,\ldots,\varepsilon_K)^T$ follows a multivariate normal distribution with zero mean vector and covariance matrix Σ, where the diagonal elements of Σ are $\sigma_1^2,\ldots,\sigma_K^2$, and the off-diagonal elements of Σ may be nonzero. That is, in the continuous mediator setting, the mediators are allowed to be correlated with dependent structure.

For the ordinal outcome Y, the proportional odds logistic model can be written as

$$\text{logit}(P(Y>j|x,\boldsymbol{m},\boldsymbol{c})) = -\beta_0^j + \beta_1 x + \beta_2^T \boldsymbol{m} + \beta_3^T x\boldsymbol{m} + \beta_4^T \boldsymbol{c}, \quad (11)$$

where β_0^j is the intercept, β_1 represents the effect of the exposure on the outcome, $\beta_2 = (\beta_{21},\ldots,\beta_{2K})^T$ represents the effects of the mediators on the outcome, $\beta_3 = (\beta_{31},\ldots,\beta_{3K})^T$ represents the interaction effects of the exposure-mediator terms on the outcome, and $\beta_4 = (\beta_{41},\ldots,\beta_{4p})^T$ represents the regression coefficients of the confounders. Here, we consider the interaction between the exposure and the mediators.

Suppose that assumptions (A1)–(A3) and (A4.1) and a rare outcome assumption hold and the models are correctly specified, it can be shown that the NIE, NDE and CDE are given by

$$\text{NIE}_{\text{OR}} \approx \exp\left\{(\beta_2+\beta_3 x)^T \alpha_1 (x-x^*)\right\},$$
$$\text{NDE}_{\text{OR}} \approx \exp\left\{(\beta_1 + \beta_3^T \mu^* + \beta_2^T \Sigma \beta_3 + \frac{1}{2}\beta_3^T \Sigma \beta_3 (x+x^*))(x-x^*)\right\},$$
$$\text{CDE}_{\text{OR}} = \exp\left\{(\beta_1 + \beta_3^T \boldsymbol{m})(x-x^*)\right\},$$

where $\mu^* = \alpha_0 + \alpha_1 x^* + \Lambda \boldsymbol{c}$. The expressions of mediation effects are more complicated as it involves the correlation among multiple mediators. The detailed derivation is given in Appendix B.

In particular, when all mediators are independent of each other, that is, assumption (A4.2) holds, the covariance matrix is a diagonal matrix with $\Sigma = \text{diag}(\sigma_1^2,\ldots,\sigma_K^2)$. Thus, the corresponding NIE and NDE can be rewritten as

$$\text{NIE}_{\text{OR}} \approx \exp\left\{\sum_{i=1}^K \alpha_{1i}(\beta_{2i}+\beta_{3i}x)(x-x^*)\right\},$$

$$\text{NDE}_{\text{OR}} \approx \exp\left\{(\beta_1 + \sum_{i=1}^K \beta_{3i}(\mu_i^* + \beta_{2i}\sigma_i^2 + \frac{1}{2}\beta_{3i}\sigma_i^2(x+x^*)))(x-x^*)\right\}.$$

This result is an extension of mediation analysis for an ordinal outcome with a single continuous mediator. If we take $\beta_2 = (1, 0, \ldots, 0)^T$ and $\beta_3 = (1, 0, \ldots, 0)^T$, this result reduces to the setting for a single mediator as proposed in VanderWeele et al. (2016). In the absence of the interaction between the exposure and mediators, the NIE, NDE and CDE can be written as

$$\begin{aligned} \mathrm{NIE}_{\mathrm{OR}} &\approx \exp\{\beta_2^T \alpha_1 (x - x^*)\}, \\ \mathrm{NDE}_{\mathrm{OR}} &\approx \exp\{\beta_1 (x - x^*)\}, \\ \mathrm{CDE}_{\mathrm{OR}} &= \exp\{\beta_1 (x - x^*)\}. \end{aligned}$$

In what follows, we consider the natural indirect effect through each mediator $M^{(i)}$ and explore the effect of the exposure on the ordinal outcome through a mediator. Provided that the models are correctly specified and under the independence assumption among multiple mediators, we can derive its natural indirect effects as

$$\mathrm{NIE}_{\mathrm{OR}}^{(i)} \approx \exp\{\alpha_{1i}(\beta_{2i} + \beta_{3i} x)(x - x^*)\}, \quad i = 1, \ldots, K.$$

Note that the joint natural indirect effect through all mediators can be decomposed into the product of the natural indirect effect through each mediator under the independence assumption among multiple mediators, that is, $\mathrm{NIE}_{\mathrm{OR}} = \prod_{i=1}^{K} \mathrm{NIE}_{\mathrm{OR}}^{(i)}$.

4.2. Mediation Analysis with Multiple Binary Mediators

In this section, we consider the mediation effects when all mediators are binary variables. Hence, for every mediator $M^{(i)}$, we can fit the following logistic regression:

$$\operatorname{logit}(P(M^{(i)} = 1 | x, \boldsymbol{c})) = \gamma_{0i} + \gamma_{1i} x + \gamma_{2i}^T \boldsymbol{c}, \quad i = 1, \ldots, K, \tag{12}$$

where γ_{0i} is an intercept, γ_{1i} represents the effect of the exposure on the mediator $M^{(i)}$, and γ_{2i} represents the regression coefficients of the confounders. The logistic regression model for the outcome Y is kept the same as Equation (11).

For the case of binary mediators, it is still required to assume a rare outcome. Under this assumption, the logistic regression model is replaced by a log-linear model for the ordinal outcome. If assumptions (A1)-(A4) hold, we can derive the NIE, NDE and CDE as follows:

The detailed derivation is given in Appendix C.

In the absence of exposure-mediator interaction, we can eliminate the $\beta_3^T x \boldsymbol{m}$ term from model (11) and obtain the mediation effects as

$$\begin{aligned} \mathrm{NIE}_{\mathrm{OR}} &\approx \frac{\prod_{i=1}^{k} \{1 + \exp(\beta_{2i} + \gamma_{0i} + \gamma_{1i} x + \gamma_{2i}^T \boldsymbol{c})\}\{1 + \exp(\gamma_{0i} + \gamma_{1i} x + \gamma_{2i}^T \boldsymbol{c})\}^{-1}}{\prod_{i=1}^{k} \{1 + \exp(\beta_{2i} + \gamma_{0i} + \gamma_{1i} x^* + \gamma_{2i}^T \boldsymbol{c})\}\{1 + \exp(\gamma_{0i} + \gamma_{1i} x^* + \gamma_{2i}^T \boldsymbol{c})\}^{-1}} \\ \mathrm{NDE}_{\mathrm{OR}} &\approx \exp\{\beta_1 (x - x^*)\}, \\ \mathrm{CDE}_{\mathrm{OR}} &= \exp\{\beta_1 (x - x^*)\}. \end{aligned}$$

In this setting, the NDE and CDE are approximately equal to each other.

In what follows, we consider the effect of the exposure on the ordinal outcome through a binary mediator. We use the logistics regression to fit the outcome model and the mediator model. Under the independence assumption among multiple mediators, we can derive the natural indirect effect through the mediator $M^{(i)}$ for $i = 1, \ldots, K$ as

$$\mathrm{NIE}_{\mathrm{OR}}^{(\mathrm{i})} \approx \frac{\{1 + \exp(\beta_{2i} + \beta_{3i} x + \gamma_{i0} + \gamma_{i1} x + \gamma_{i2}' \boldsymbol{c})\}\{1 + \exp(\gamma_{i0} + \gamma_{i1} x + \gamma_{i2}^T \boldsymbol{c})\}^{-1}}{\{1 + \exp(\beta_{2i} + \beta_{3i} x + \gamma_{i0} + \gamma_{i1} x^* + \gamma_{i2}' \boldsymbol{c})\}\{1 + \exp(\gamma_{i0} + \gamma_{i1} x^* + \gamma_{i2}^T \boldsymbol{c})\}^{-1}}.$$

We also note that it holds $\mathrm{NIE}_{\mathrm{OR}} = \prod_{i=1}^{K} \mathrm{NIE}_{\mathrm{OR}}^{(i)}$ under the independence assumption among multiple binary mediators.

4.3. Mediation Analysis with Multiple Mixed Mediators

In practical applications, the mediators may be partially binary or partially continuous. We first consider the mediation effects for the simple case with one binary mediator and other continuous mediators. For the simple case, suppose that $M^{(l)}$ is a binary mediator and other mediators are continuous. Then, we can fit a logistic regression model for the binary mediator $M^{(l)}$ as follows:

$$\operatorname{logit}(P(M^{(l)} = 1 | x, m)) = \alpha_{0l} + \alpha_{1l} x + \alpha_{2l}^T \boldsymbol{c}. \tag{13}$$

For other continuous mediators, we still fit a linear regression model as

$$\begin{aligned} M^{(i)}|_{X=x, \boldsymbol{C}=\boldsymbol{c}} &= \alpha_{0i} + \alpha_{1i} x + \alpha_{2i}^T \boldsymbol{c} + \varepsilon_i, \quad i \\ &= 1, \ldots, K \quad \text{and} \quad i \neq l, \end{aligned}$$

$$\begin{aligned} \mathrm{NIE}_{\mathrm{OR}} &\approx \frac{\prod_{i=1}^{K} \{1 + \exp(\beta_{2i} + \beta_{3i} x + \gamma_{0i} + \gamma_{1i} x + \gamma_{2i}^T \boldsymbol{c})\}\{1 + \exp(\gamma_{0i} + \gamma_{1i} x + \gamma_{2i}^T \boldsymbol{c})\}^{-1}}{\prod_{i=1}^{K} \{1 + \exp(\beta_{2i} + \beta_{3i} x + \gamma_{0i} + \gamma_{1i} x^* + \gamma_{2i}^T \boldsymbol{c})\}\{1 + \exp(\gamma_{0i} + \gamma_{1i} x^* + \gamma_{2i}^T \boldsymbol{c})\}^{-1}}, \\ \mathrm{NDE}_{\mathrm{OR}} &\approx \exp\{\beta_1 (x - x^*)\} \frac{\prod_{i=1}^{K} \{1 + \exp(\beta_{2i} + \beta_{3i} x + \gamma_{0i} + \gamma_{1i} x^* + \gamma_{2i}^T \boldsymbol{c})\}}{\prod_{i=1}^{K} \{1 + \exp(\beta_{2i} + \beta_{3i} x^* + \gamma_{0i} + \gamma_{1i} x^* + \gamma_{2i}^T \boldsymbol{c})\}}, \\ \mathrm{CDE}_{\mathrm{OR}} &= \exp\{(\beta_1 + \beta_3^T \boldsymbol{m})(x - x^*)\}. \end{aligned}$$

where the error ε_i is normally distributed with zero mean and variance σ_i^2. The logistic regression model for the outcome Y is still represented by Equation (11).

Provided that the models are correctly specified, and assumptions (A1)–(A5) and a rare outcome assumption are satisfied, then the expression for the controlled direct effect remains the same as those in Section 4.1, and the NIE and NDE can be written as

$$\begin{aligned}\mathrm{NIE}_{\mathrm{OR}} \approx & \prod_{i=1,\, i\neq l}^{K} \exp\{\alpha_{1i}(\beta_{2i}+\beta_{3i}x)(x-x^*)\} \\ & \cdot \frac{1+\exp(\beta_{2l}+\beta_{3l}x+\alpha_{0l}+\alpha_{1l}x+\alpha_{2l}^T\boldsymbol{c})}{1+\exp(\beta_{2l}+\beta_{3l}x+\alpha_{0l}+\alpha_{1l}x^*+\alpha_{2l}^T\boldsymbol{c})} \\ & \times \frac{1+\exp(\alpha_{0l}+\alpha_{1l}x^*+\alpha_{2l}^T\boldsymbol{c})}{1+\exp(\alpha_{0l}+\alpha_{1l}x+\alpha_{2l}^T\boldsymbol{c})},\end{aligned}$$

$$\begin{aligned}\mathrm{NDE}_{\mathrm{OR}} \approx & \exp\{\beta_1(x-x^*)\} \prod_{i=1,\, i\neq l}^{K} \\ & \exp\{\beta_{3i}(\mu_i^*+\beta_{2i}\sigma_i^2+\frac{1}{2}\beta_{3i}\sigma_i^2(x+x^*))(x-x^*)\} \\ & \times \frac{1+\exp(\beta_{2l}+\beta_{3l}x+\alpha_{0l}+\alpha_{1l}x^*+\alpha_{2l}^T\boldsymbol{c})}{1+\exp(\beta_{2l}+\beta_{3l}x^*+\alpha_{0l}+\alpha_{1l}x^*+\alpha_{2l}^T\boldsymbol{c})}.\end{aligned}$$

The detailed derivation is given in Appendix D. Similarly, the expressions of NIE and NDE can be extended to the case with several binary mediators and other continuous mediators.

5. Simulation Studies

In this section, we conduct simulation studies to assess the finite sample performance of the proposed methods for mediation analysis for an ordinal outcome. To investigate the performance, we consider the two-mediator models with three different combinations of mediator types, including (i) mediation model with two continuous mediators, (ii) mediation model with two binary mediators, and (iii) mediation model with one continuous mediator and one binary mediator. For each two-mediator model, we investigate the bias, standard error (SE) and confidence interval (CI) of the mediation effects, where the SEs and CIs are estimated using the bootstrap method. And for each scenario, the order of the ordinal outcome is set as $J=3$.

5.1. Mediation Model with Two Continuous Mediators

In this section, we consider two continuous mediators. We first generate data for the two continuous mediators $M^{(1)}$ and $M^{(2)}$ from the models

$$\begin{aligned}M^{(1)}|_{X=x,\boldsymbol{C}=\boldsymbol{c}} &= \alpha_{01}+\alpha_{11}x+\alpha_{21}\boldsymbol{c}+\varepsilon_1, \\ M^{(2)}|_{X=x,\boldsymbol{C}=\boldsymbol{c}} &= \alpha_{02}+\alpha_{12}x+\alpha_{22}\boldsymbol{c}+\varepsilon_2.\end{aligned}$$

We then generate the outcome Y from a Bernoulli distribution with the success probability given by the following logistic regression model,

$$\begin{aligned}\mathrm{logit}(P(Y>j|x,\boldsymbol{m},\boldsymbol{c})) = & -\beta_0^j+\beta_1x+\beta_{21}m^{(1)}+\beta_{22}m^{(2)} \\ & +\beta_3xm^{(1)}+\beta_4\boldsymbol{c},\end{aligned}$$

where $\alpha_1=(\alpha_{01},\alpha_{11},\alpha_{21})^T=(0,-0.6,0.2)^T$, $\alpha_2=(\alpha_{02},\alpha_{12},\alpha_{22})^T=(-0.2,0.5,0.4)^T$, $\beta_0=(\beta_0^1,\beta_0^2,\beta_0^3)^T=(-0.5,0.4,0.7)^T$, $\beta_1=0.4$, $\beta_2=(\beta_{21},\beta_{22})^T=(-0.4,0.6)^T$, $\beta_3=0$, and $\beta_4=0.3$.

Assume that the exposure X is simulated from a normal distribution $N(0,0.5^2)$. The confounding variable $\boldsymbol{C}$ is generated from the normal distribution $N(0.2X,0.5^2)$, representing a confounder correlated with the exposure X. In addition, the random errors ε_1 and ε_2 are both independently generated from the normal distribution $N(0,0.75^2)$. With the above settings, the mediators $M^{(1)}$, $M^{(2)}$ and the outcome Y are then generated from the above models. We consider three different sample sizes: $n=100$, 200 and 500, corresponding to small, moderate and large samples, respectively.

The estimates of NIE and NDE are obtained using our proposed method described in Section 4.1. Their estimated values are then averaged across 500 simulations for each setting. In addition, their biases are reported to assess the performance of our proposed estimates. The SEs and the 95% CIs for both NIE and NDE are estimated using the bootstrap methods with 200 bootstrap samples. The estimated SEs are based on the standard deviations of bootstrap samples and the estimated 95% CIs are based on the percentile bootstrap CIs.

The simulation results are reported in Table 1. Compared with the true and estimated values for each mediation effect, we observe that the estimated values are very close to the true ones, particularly for the large sample sizes. In addition, we also see that for fixed sample sizes, the biases for the indirect effect estimators tend to be smaller than the direct effect estimators. We note that the SEs of the mediation effects are relatively small for each setting, it further validates that our proposed methods perform well. For the CI estimates of NIE and NDE, we observe that the CIs are more accurate with larger sample sizes.

5.2. Mediation Model with Two Binary Mediators

In this section, the binary mediator simulation proceeds similarly. The exposure X and the confounder variable $\boldsymbol{C}$ are once again simulated from $N(0,0.5^2)$ and $N(0.2X,0.5^2)$,

Table 1. Estimations of joint natural indirect effect (NIE), natural indirect effect through mediator $M^{(1)}$ (NIE1), natural indirect effect through mediator $M^{(2)}$ (NIE2), and natural direct effect (NDE) with two continuous mediators $M^{(1)}$ and $M^{(2)}$.

	n	True	Estimate	Bias	SE	95% CI
	100	1.434	1.498	0.064	0.364	(0.841, 2.192)
NIE	200	1.438	1.451	0.013	0.204	(1.167, 1.948)
	500	1.437	1.443	0.006	0.112	(1.067, 1.497)
	100	1.174	1.198	0.024	0.125	(0.897, 1.382)
NIE1	200	1.175	1.179	0.004	0.111	(1.012, 1.438)
	500	1.174	1.177	0.003	0.046	(1.004, 1.183)
	100	1.222	1.249	0.027	0.274	(0.826, 1.852)
NIE2	200	1.223	1.231	0.005	0.113	(1.070, 1.503)
	500	1.223	1.226	0.003	0.085	(1.010, 1.340)
	100	1.306	1.376	0.070	0.584	(0.736, 2.908)
NDE	200	1.308	1.365	0.068	0.236	(1.188, 2.092)
	500	1.308	1.331	0.023	0.188	(1.028, 1.748)

Note: The SEs and the 95% CIs of the mediation effects are estimated using the bootstrap methods with 200 bootstrap samples.

respectively. For the two binary mediators $M^{(1)}$ and $M^{(2)}$, the data are generated from the following logistic models as

$$\operatorname{logit}(P(M^{(1)} = 1|x, \boldsymbol{c})) = \alpha_{01} + \alpha_{11}x + \alpha_{21}\boldsymbol{c},$$
$$\operatorname{logit}(P(M^{(2)} = 1|x, \boldsymbol{c})) = \alpha_{02} + \alpha_{12}x + \alpha_{22}\boldsymbol{c}.$$

Each mediator $M^{(i)}$ for $i = 1, 2$ receives a mediator probability, $p_i^{\alpha}(x, \boldsymbol{c}) = P(M^{(i)} = 1|x, \boldsymbol{c}) = \exp(\alpha_{0i} + \alpha_{1i}x + \alpha_{2i}\boldsymbol{c})/(1 + \exp(\alpha_{0i} + \alpha_{1i}x + \alpha_{2i}\boldsymbol{c}))$, with which we generate the mediator value from Bernoulli$(p_i^{\alpha}(x, \boldsymbol{c}))$. The outcome variable is generated from the model

$$\operatorname{logit}(P(Y > j|x, \boldsymbol{m}, \boldsymbol{c})) = -\beta_0^j + \beta_1 x + \beta_{21}m^{(1)} + \beta_{22}m^{(2)} + \beta_3 x m^{(1)} + \beta_4\boldsymbol{c}.$$

Note that the parametric settings of the models are kept the same as those in Section 5.1.

The effect estimates are averaged across 1,000 simulations for each setting. The estimators of NIE and NDE are obtained using our proposed method described in Section 4.2. The SEs and the 95% CIs for both NIE and NDE are estimated using the bootstrap methods with 200 bootstrap samples. The simulation results are reported in Table 2 for every estimated effect, from which we can draw the following conclusions. As the sample size increases, the absolute biases and SEs of both NIE and NDE become smaller and the CIs become more accurate. Furthermore, for fixed sample sizes, the SEs of NIE remain relatively smaller than those of NDE for most settings.

5.3. Mediation Model with One Continuous Mediator and One Binary Mediator

In this section, we focus on simulation studies for the mediation model with one continuous mediator and one binary mediator. We generate data from the linear model for the continuous mediator $M^{(1)}$ and from the logistic model for the binary $M^{(2)}$ as follows:

$$M^{(1)}|_{X=x, C=\boldsymbol{c}} = \alpha_{01} + \alpha_{11}x + \alpha_{21}\boldsymbol{c} + \varepsilon_1,$$
$$\operatorname{logit}(P(M^{(2)} = 1|x, \boldsymbol{c})) = \alpha_{02} + \alpha_{12}x + \alpha_{22}\boldsymbol{c},$$

where the error ε_1 is normally distributed with zero mean and variance 0.5^2. Note that the mediator $M^{(2)}$ receives a mediator probability, $p^{\alpha}(x, \boldsymbol{c}) = P(M^{(2)} = 1|x, \boldsymbol{c}) = \exp(\alpha_{02} + \alpha_{12}x + \alpha_{22}\boldsymbol{c})/(1 + \exp(\alpha_{02} + \alpha_{12}x + \alpha_{22}\boldsymbol{c}))$, with which we generate the mediator $M^{(2)}$ from Bernoulli$(p^{\alpha}(x, \boldsymbol{c}))$. The outcome variable is generated from the logistic model

$$\operatorname{logit}(P(Y > j|x, \boldsymbol{m}, \boldsymbol{c})) = -\beta_0^j + \beta_1 x + \beta_{21}m^{(1)} + \beta_{22}m^{(2)} + \beta_3 x m^{(1)} + \beta_4\boldsymbol{c}.$$

All other settings are kept the same as those in Section 5.1.

We repeat the simulation 1,000 times for each setting and report the simulation results in Table 3. Note that the estimated SEs and CIs are obtained using the bootstrap method with 200 bootstrap samples. From the results, we see that the biases are relatively small. We also note that, as the sample size increases, the SEs tend to become smaller and the 95% CIs tend to become more accurate. Overall, our proposed method performs well for the case with one continuous mediator and one binary mediator.

6. Real Data Analysis

In this section, we apply our proposed methods to a real data set to estimate the mediation effects of socioeconomic index (SI) on body mass index (BMI) that might be mediated by DNA methylation CpG sites on chromosome 17, where SI is quantified by a scalar index ranging from 0 to 100 and BMI is a reliable indicator of body fatness for most people. The data set contains the methylation values from the whole blood for 74 samples on the human chromosome 17 (Loucks et al., 2016). The methylation values were preprocessed and normalized using the R package *methylumi* (Davis et al., 2015). For illustrating our proposed methods, we choose five continuous mediators from DNA methylation CpG sites: cg05156120, cg05157340, cg05157970, cg05158219 and cg05158913, and categorize BMI into an ordinal outcome: healthy weight, overweight, obese, and severely obese, corresponding to the ordinal values 1 for $18.5 < \text{BMI} \leq 25$, 2 for $25 < \text{BMI} \leq 30$, 3 for $30 < \text{BMI} \leq 40$, and 4 for $\text{BMI} > 40$, respectively. By computing the correlation coefficients for five mediators, this shows that there are no correlations between them. Therefore, they can be regarded as the independence of each other and there are no interaction among them. In addition, the value 1 takes up a large enough proportion in the real data, with a proportion of nearly 50%. Thus, it approximatively satisfies the assumption of a rare outcome.

Table 2. Estimations of joint natural indirect effect (NIE), natural indirect effect through mediator $M^{(1)}$ (NIE1), natural indirect effect through mediator $M^{(2)}$ (NIE2), and natural direct effect (NDE) with two binary mediators $M^{(1)}$ and $M^{(2)}$.

	n	True	Estimate	Bias	SE	95% CI
	100	1.434	1.648	0.214	1.201	(0.645, 4.065)
NIE	200	1.436	1.501	0.065	0.347	(0.876, 2.178)
	500	1.438	1.448	0.010	0.157	(1.023, 1.624)
	100	1.174	1.249	0.075	0.409	(0.716, 2.140)
NIE1	200	1.174	1.194	0.020	0.167	(0.868, 1.508)
	500	1.175	1.179	0.004	0.083	(0.961, 1.284)
	100	1.221	1.312	0.091	0.780	(0.693, 2.952)
NIE2	200	1.222	1.256	0.034	0.237	(0.886, 1.777)
	500	1.223	1.227	0.004	0.107	(0.995, 1.404)
	100	1.306	1.408	0.102	0.518	(0.804, 2.754)
NDE	200	1.307	1.349	0.042	0.291	(0.930, 2.042)
	500	1.308	1.317	0.009	0.166	(1.046, 1.683)

Note: The SEs and the 95% CIs of the mediation effects are estimated using the bootstrap methods with 200 bootstrap samples.

Table 3. Estimations of joint natural indirect effect (NIE), natural indirect effect through mediator $M^{(1)}$ (NIE1), natural indirect effect through mediator $M^{(2)}$ (NIE2), and natural direct effect (NDE) with one continuous mediator $M^{(1)}$ and one binary mediator $M^{(2)}$.

	n	True	Estimate	Bias	SE	95% CI
	100	1.434	1.571	0.137	1.530	(0.722, 3.843)
NIE	200	1.435	1.490	0.055	0.298	(0.908, 2.021)
	500	1.437	1.445	0.008	0.141	(1.041, 1.582)
	100	1.173	1.186	0.013	0.158	(0.864, 1.476)
NIE1	200	1.174	1.188	0.014	0.096	(0.932, 1.303)
	500	1.175	1.179	0.004	0.056	(0.985, 1.202)
	100	1.221	1.318	0.097	1.623	(0.684, 3.548)
NIE2	200	1.222	1.254	0.032	0.255	(0.866, 1.819)
	500	1.223	1.225	0.002	0.116	(0.989, 1.434)
	100	1.306	1.407	0.101	0.583	(0.766, 2.925)
NDE	200	1.307	1.337	0.030	0.316	(0.891, 2.103)
	500	1.308	1.325	0.017	0.181	(1.031, 1.728)

Note: The SEs and the 95% CIs of the mediation effects are estimated using the bootstrap methods with 200 bootstrap samples.

For mediation analysis, we take SI as the exposure X, the five continuous DNA methylation as the mediators $\boldsymbol{M}$, and the ordinal BMI as the outcome Y. In addition, sex, age, race and cigarette smoking are included as the confounding variables $\boldsymbol{C}$. We propose the following mediator and outcome models, respectively,

$$\mathrm{E}(\boldsymbol{M}|X,\boldsymbol{C}) = \alpha_0 + \alpha_1 X + \Lambda\boldsymbol{C},$$
$$\mathrm{logit}(P(Y>j)|X,\boldsymbol{M},\boldsymbol{C}) = -\beta_0^j + \beta_1 X + \beta_2^T\boldsymbol{M} + \beta_3^T\boldsymbol{C},$$

where $\alpha_0 = (\alpha_{01},\alpha_{02},\alpha_{03},\alpha_{04},\alpha_{05})^T$, $\alpha_1 = (\alpha_{11},\alpha_{12},\alpha_{13},\alpha_{14},\alpha_{15})^T$, $\Lambda = (\Lambda_1,\Lambda_2,\Lambda_3,\Lambda_4,\Lambda_5)^T$ with $\Lambda_i = (\Lambda_{i1},\Lambda_{i2},\Lambda_{i3},\Lambda_{i4})^T$ for i from 1 to 5, β_0^j and β_1 are two constants, $\beta_2 = (\beta_{21},\beta_{22},\beta_{23},\beta_{24},\beta_{25})^T$, and $\beta_3 = (\beta_{31},\beta_{32},\beta_{33},\beta_{34})^T$.

The NIE and NDE are estimated using our proposed method in Section 4.1, and the SEs and the 95% CIs for both NIE and NDE are estimated using the bootstrap method with 200 bootstrap samples. To estimate the NDE and NIE, we consider the exposure changed from $x^* = x_{0.25} = 21.25$, set at the corresponding 25th percentile, to $x = x_{0.75} = 56.75$, set at its 75th percentile. We calculate the mediation effects for the exposure SI changing from x^* to x. Table 4 summarizes the TE, NDE, NIE and NIE through every mediator for a change in exposure from x^* to x.

Comparing the NIE with the corresponding NDE from Table 4, we see that the point estimates for the NIE are larger than the point estimate for the NDE, whether for the joint indirect effect or for the indirect effect through every mediator. In addition, the confidence intervals for the NIE tend to be narrower than the NDE confidence intervals and their confidence intervals don't contain zero. Therefore, it indicates that the mediation effects of socioeconomic index on body mass index through five chosen mediators distinctly exist. That is, socioeconomic index affects body mass index mediated by the five DNA methylation CpG sites. This helps us understand the causal mechanism between socioeconomic index and body mass index.

7. Discussion

In this paper, we have proposed new methods for assessing the mediation effects of an exposure on an ordinal outcome through multiple mediators allowing the presence of the exposure-mediator interactions. In the counterfactual framework, we first defined the total effect, natural direct effect and natural indirect effect on the odds ratio scale for the ordinal outcome with multiple mediators. To estimate the mediation effects, we have proposed a regression-based approach, where the outcome model is fitted by the proportional odds logistic regression and the mediator models are fitted by the linear regression for the continuous mediator or by the logistic regression for the binary mediator. Under the rare outcome assumptions, we have obtained the closed-form expressions of the mediation effects for three scenarios: multiple continuous mediators, multiple binary mediators, and multiple mixed mediators. Simulation studies have also shown that our proposed methods perform well in all three scenarios.

Our proposed methods have several advantages. The proposed mediation framework provides an opportunity for analyzing the effect of the mediators on an ordinal outcome. Our proposed methods provide closed-form expressions of mediation effects and an additional insight for multiple mediators on the mediation mechanism for an ordinal outcome. Consequently, this may help to make a decision for a better intervention when an effect on an outcome is mediated by multiple intermediate variables. Mediation analysis also provides a way for analyzing the data under a hypothesized pathway structure. Obviously, our proposed methods can be widely applied to the ordinal data analysis to assess mediation effects, which allow for the distributions of the mediators to be flexible for both continuous and binary mediators.

One limitation of our methods is that it is needed to assume a rare outcome. Certainly, we can relax this assumption and follow the approach on a binary outcome proposed by Gaynor et al. (2019), while allowing for multiple mediators and proceeding without making a rare assumption on an ordinal outcome. This extension will be considered in future research. In addition, our methods are specified as parametric models and thus required a correct model specification. An advantage of parametric models is that the estimation is efficient when all the models are correctly specified (Tchetgen & Shpitser, 2012). However, as pointed out by Robins and Wasserman (1997), the parametric models can often be mis-specified and the resulting estimators for the mediation effects are hence biased. For this reason, semiparametric estimation methods have also been proposed for a continuous or binary outcome with a single mediator. For more details, one may refer to, for example, VanderWeele (2009), Tchetgen and Shpitser (2012), Vansteelandt et al. (2012), Yu et al. (2014), Yu et al. (2018), Yu et al. (2019) and Yu and Li (2022). Further research is needed for mediation analysis to apply the semiparametric estimation methods for the setting of an ordinal outcome with multiple mediators.

Table 4. The estimated mediation effects in the SI-BMI data.

	Estimate	SE	95% CI
NIE	0.4903	0.1859	(0.1625, 0.8823)
NIE1	0.8767	0.1641	(0.5736, 1.1937)
NIE2	0.9985	0.0771	(0.8513, 1.1824)
NIE3	0.5697	0.1727	(0.1781, 0.8586)
NIE4	0.9805	0.1495	(0.7659, 1.3844)
NIE5	1.0025	0.1010	(0.8177, 1.2848)
NDE	0.3501	0.3406	(0.0495, 1.0557)
CDE	0.3501	0.3406	(0.0495, 1.0557)
TE	0.1717	0.1299	(0.0325, 0.5055)

Notes: All effects are estimated for a change of exposure SI from its 25th percentile $x^* = 21.25$ to its 75th percentile $x = 56.75$. The SEs and 95% CIs are estimated using the bootstrap method with 200 bootstrap samples. NIE is denoted as the joint natural indirect effect through five mediators: cg05156120, cg05157340, cg05157970, cg05158219, and cg05158913, and NIE1, NIE2, NIE3, NIE4, and NIE5 are denoted as the natural indirect effects through each mediator, respectively.

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Appendix A: Mediation Analysis for an Ordinal Outcome with a Binary Mediator

In this section, we consider mediation analysis for an ordinal outcome with a binary mediator. Under a rare outcome assumption, we have

$$\log\{\frac{P(Y>j|x,m,\boldsymbol{c})}{P(Y\le j|x,m,\boldsymbol{c})}\} \approx \log\left(P(Y>j|x,m,\boldsymbol{c})\right) \approx -\beta_0^j+\beta_1 x+\beta_2 m+\beta_3 xm+\beta_4^T\boldsymbol{c}.$$

Then, we have

$$P(Y>j|x,m,\boldsymbol{c}) \approx \exp\left(-\beta_0^j+\beta_1 x+\beta_2 m+\beta_3 xm+\beta_4^T\boldsymbol{c}\right).$$

In addition, we also know that

$$\begin{aligned}
&\log\{\frac{P(Y_{x,M_x}>j|\boldsymbol{c})}{P(Y_{x,M_x}\le j|\boldsymbol{c})}\}\\
&\approx \log(P(Y_{x,M_x}>j|\boldsymbol{c}))\\
&=\log\{\int P(Y_{x,m}>j|M_x=m,\boldsymbol{c})P(M_x=m|\boldsymbol{c})dm\}\\
&=\log\{\int P(Y>j|x,m,\boldsymbol{c})P(M=m|x,\boldsymbol{c})dm\}\\
&\approx \log\{\int \exp(-\beta_0^j+\beta_1x+\beta_2m+\beta_3xm+\beta_4^T\boldsymbol{c})P(M=m|x,\boldsymbol{c})dm\}\\
&=\log\{\exp(-\beta_0^j+\beta_1x+\beta_4^T\boldsymbol{c})\int\exp(\beta_2m+\beta_3xm)P(M=m|x,\boldsymbol{c})dm\}\\
&=\log\{\exp(-\beta_0^j+\beta_1x+\beta_4^T\boldsymbol{c})E\{\exp((\beta_2+\beta_3x)M)|x,\boldsymbol{c}\}\}.
\end{aligned}$$

In what follows, we calculate $E\{\exp((\beta_2+\beta_3x)M)|x,\boldsymbol{c}\}$. For a binary M, we have

$$E\{\exp((\beta_2+\beta_3x)M)|x,\boldsymbol{c}\}=\exp(\beta_2+\beta_3x)P(M=1|x,\boldsymbol{c})+P(M=0|x,\boldsymbol{c}).$$

By $P(M=1|x,\boldsymbol{c})=\exp(\alpha_0+\alpha_1x+\alpha_2^T\boldsymbol{c})/\{1+\exp(\alpha_0+\alpha_1x+\alpha_2^T\boldsymbol{c})\}$, then we have

$$\begin{aligned}
&E\{\exp((\beta_2+\beta_3x)M)|x,\boldsymbol{c}\}\\
&=\exp(\beta_2+\beta_3x)\frac{\exp(\alpha_0+\alpha_1x+\alpha_2^T\boldsymbol{c})}{1+\exp(\alpha_0+\alpha_1x+\alpha_2^T\boldsymbol{c})}+\frac{1}{1+\exp(\alpha_0+\alpha_1x+\alpha_2^T\boldsymbol{c})}\\
&=\frac{1+\exp(\beta_2+\beta_3x+\alpha_0+\alpha_1x+\alpha_2^T\boldsymbol{c})}{1+\exp(\alpha_0+\alpha_1x+\alpha_2^T\boldsymbol{c})}.
\end{aligned}$$

Therefore, we obtain

$$\frac{P(Y_{x,M_x}>j|\boldsymbol{c})}{P(Y_{x,M_x}\le j|\boldsymbol{c})}\approx\exp(-\beta_0^j+\beta_1x+\beta_4^T\boldsymbol{c})\frac{1+\exp(\beta_2+\beta_3x+\alpha_0+\alpha_1x+\alpha_2^T\boldsymbol{c})}{1+\exp(\alpha_0+\alpha_1x+\alpha_2^T\boldsymbol{c})}.$$

Similarly, we can get

$$\frac{P(Y_{x,M_{x^*}}>j|\boldsymbol{c})}{P(Y_{x,M_{x^*}}\le j|\boldsymbol{c})}\approx\exp(-\beta_0^j+\beta_1x+\beta_4^T\boldsymbol{c})\frac{1+\exp(\beta_2+\beta_3x+\alpha_0+\alpha_1x^*+\alpha_2^T\boldsymbol{c})}{1+\exp(\alpha_0+\alpha_1x^*+\alpha_2^T\boldsymbol{c})}.$$

By the definition of NIE, we get the NIE for a binary mediator as follows:

$$\mathrm{NIE}_{\mathrm{OR}}\approx\frac{1+\exp(\beta_2+\beta_3x+\alpha_0+\alpha_1x+\alpha_2^T\boldsymbol{c})}{1+\exp(\alpha_0+\alpha_1x+\alpha_2^T\boldsymbol{c})}\Big/\frac{1+\exp(\beta_2+\beta_3x+\alpha_0+\alpha_1x^*+\alpha_2^T\boldsymbol{c})}{1+\exp(\alpha_0+\alpha_1x^*+\alpha_2^T\boldsymbol{c})}.$$

In addition, we can derive that

$$\frac{P(Y_{x^*,M_{x^*}}>j|\boldsymbol{c})}{P(Y_{x^*,M_{x^*}}\le j|\boldsymbol{c})}\approx\exp(-\beta_0^j+\beta_1x^*+\beta_4^T\boldsymbol{c})\frac{1+\exp(\beta_2+\beta_3x^*+\alpha_0+\alpha_1x^*+\alpha_2^T\boldsymbol{c})}{1+\exp(\alpha_0+\alpha_1x^*+\alpha_2^T\boldsymbol{c})}.$$

This leads to

$$\mathrm{NDE}_{\mathrm{OR}}\approx\exp(\beta_1(x-x^*))\frac{1+\exp(\beta_2+\beta_3x+\alpha_0+\alpha_1x^*+\alpha_2^T\boldsymbol{c})}{1+\exp(\beta_2+\beta_3x^*+\alpha_0+\alpha_1x^*+\alpha_2^T\boldsymbol{c})}.$$

In what follows, we further obtain the CDE for the fixing mediator. Specifically, the CDE can be derived as

$$\begin{aligned}
\mathrm{CDE}_{\mathrm{OR}}&=\frac{P(Y_{x,m}>j|\boldsymbol{c})/P(Y_{x,m}\le j|\boldsymbol{c})}{P(Y_{x^*,m}>j|\boldsymbol{c})/P(Y_{x^*,m}\le j|\boldsymbol{c})}\\
&=\frac{P(Y>j|x,m,\boldsymbol{c})/P(Y\le j|x,m,\boldsymbol{c})}{P(Y>j|x^*,m,\boldsymbol{c})/P(Y\le j|x^*,m,\boldsymbol{c})}\\
&=\exp\{(\beta_1+\beta_3m)(x-x^*)\}.
\end{aligned}$$

Appendix B: Mediation Analysis with Multiple Continuous Mediators

If a rare outcome assumption holds, then it is easy to derive that

$$\begin{aligned}
\log\{\frac{P(Y>j|x,\boldsymbol{m},\boldsymbol{c})}{P(Y\le j|x,\boldsymbol{m},\boldsymbol{c})}\}&\approx\log(P(Y>j|x,\boldsymbol{m},\boldsymbol{c}))\\
&\approx-\beta_0^j+\beta_1x+\beta_2^T\boldsymbol{m}+\beta_3^Tx\boldsymbol{m}+\beta_4^T\boldsymbol{c},
\end{aligned}$$

where $\boldsymbol{m}=(m^{(1)},\ldots,m^{(k)})^T$. Or equivalently, we have

$$P(Y>j|x,\boldsymbol{m},\boldsymbol{c})\approx\exp\{-\beta_0^j+\beta_1x+\beta_2^T\boldsymbol{m}+\beta_3^Tx\boldsymbol{m}+\beta_4^T\boldsymbol{c}\}.$$

If assumptions (A1)-(A4) hold, then we have

$$\begin{aligned}
&\log\{\frac{P(Y_{x,\boldsymbol{M}_x}>j|\boldsymbol{c})}{P(Y_{x,\boldsymbol{M}_x}\le j|\boldsymbol{c})}\}\approx\log(P(Y_{x,\boldsymbol{M}_x}>j|\boldsymbol{c}))\\
&=\log\{\int P(Y_{x\boldsymbol{m}}>j|\boldsymbol{M}_x=\boldsymbol{m},\boldsymbol{c})P(\boldsymbol{M}_x=\boldsymbol{m}|\boldsymbol{c})d\boldsymbol{m}\}\\
&=\log\{\int P(Y>j|x,\boldsymbol{m},\boldsymbol{c})P(\boldsymbol{M}=\boldsymbol{m}|x,\boldsymbol{c})d\boldsymbol{m}\}\\
&\approx\log\{\int\exp(-\beta_0^j+\beta_1x+\beta_2^T\boldsymbol{m}+\beta_3^Tx\boldsymbol{m}+\beta_4^T\boldsymbol{c})P(\boldsymbol{M}=\boldsymbol{m}|x,\boldsymbol{c})d\boldsymbol{m}\}\\
&=\log\{\exp(-\beta_0^j+\beta_1x+\beta_4^T\boldsymbol{c})\int\exp(\beta_2^T\boldsymbol{m}+\beta_3^Tx\boldsymbol{m})P(\boldsymbol{M}=\boldsymbol{m}|x,\boldsymbol{c})d\boldsymbol{m}\}\\
&=\log\{\exp(-\beta_0^j+\beta_1x+\beta_4^T\boldsymbol{c})E\{\exp((\beta_2+\beta_3x)^T\boldsymbol{M})|x,\boldsymbol{c}\}.
\end{aligned}$$

Note that $\boldsymbol{M}$ follows a multivariate normal distribution with mean vector $\mu=\alpha_0+\alpha_1x+\Lambda\boldsymbol{c}$ and covariance matrix Σ. Therefore, we have

$$\begin{aligned}
&E\{\exp((\beta_2+\beta_3x)^T\boldsymbol{M})|x,\boldsymbol{c}\}\\
&=A\int\exp\{(\beta_2+\beta_3x)^T\boldsymbol{m}\}\exp\{-\frac{1}{2}(\boldsymbol{m}-\mu)^T\Sigma^{-1}(\boldsymbol{m}-\mu)\}d\boldsymbol{m}\\
&=A\int\exp\{-\frac{1}{2}\Big[\boldsymbol{m}^T\Sigma^{-1}\boldsymbol{m}-2(\mu+\Sigma(\beta_2+\beta_3x))^T\Sigma^{-1}\boldsymbol{m}+\mu^T\Sigma^{-1}\mu\Big]\}d\boldsymbol{m}\\
&=A\int\exp\{-\frac{1}{2}[\boldsymbol{m}-(\mu+\Sigma(\beta_2+\beta_3x))]^T\Sigma^{-1}[\boldsymbol{m}-(\mu+\Sigma(\beta_2+\beta_3x))]\\
&\quad+\frac{1}{2}(\mu+\Sigma(\beta_2+\beta_3x))^T\Sigma^{-1}(\mu+\Sigma(\beta_2+\beta_3x))-\frac{1}{2}\mu^T\Sigma^{-1}\mu\}d\boldsymbol{m}\\
&=\exp\{(\beta_2+\beta_3x)^T\mu+\frac{1}{2}(\beta_2+\beta_3x)^T\Sigma(\beta_2+\beta_3x)\},
\end{aligned}$$

where $A=\{(2\pi)^{K/2}|\Sigma|^{-1/2}\}^{-1}$. Then, we obtain that

$$\frac{P(Y_{x,\boldsymbol{M}_x}>j|\boldsymbol{c})}{P(Y_{x,\boldsymbol{M}_x}\le j|\boldsymbol{c})}\approx\exp\{-\beta_0^j+\beta_1x+\beta_4^T\boldsymbol{c}+(\beta_2+\beta_3x)^T\mu+\frac{1}{2}(\beta_2+\beta_3x)^T\Sigma(\beta_2+\beta_3x)\}.$$

Similarly, we have

$$\frac{P(Y_{x,\boldsymbol{M}_{x^*}}>j|\boldsymbol{c})}{P(Y_{x,\boldsymbol{M}_{x^*}}\le j|\boldsymbol{c})}\approx\exp\{-\beta_0^j+\beta_1x+\beta_4^T\boldsymbol{c}+(\beta_2+\beta_3x)^T\mu^*+\frac{1}{2}(\beta_2+\beta_3x)^T\Sigma(\beta_2+\beta_3x)\},$$

and

$$\frac{P(Y_{x^*,\boldsymbol{M}_{x^*}}>j|\boldsymbol{c})}{P(Y_{x^*,\boldsymbol{M}_{x^*}}\le j|\boldsymbol{c})}\approx\exp\{-\beta_0^j+\beta_1x^*+\beta_4^T\boldsymbol{c}+(\beta_2+\beta_3x^*)^T\mu^*+\frac{1}{2}(\beta_2+\beta_3x^*)^T\Sigma(\beta_2+\beta_3x^*)\},$$

where $\mu^*=\alpha_0+\alpha_1x^*+\Lambda\boldsymbol{c}$.

Therefore, we can get

$$\mathrm{NIE}_{\mathrm{OR}}\approx\exp\{(\beta_2+\beta_3x)^T\alpha_1(x-x^*)\},$$

$$\mathrm{NDE}_{\mathrm{OR}}\approx\exp\{(\beta_1+\beta_3^T\mu^*+\beta_2^T\Sigma\beta_3+\frac{1}{2}\beta_3^T\Sigma\beta_3(x+x^*))(x-x^*)\}.$$

Finally, we obtain the CDE as

$$\begin{aligned}\mathrm{CDE}_{\mathrm{OR}} &= \frac{P(Y_{x,\boldsymbol{m}} > j|\boldsymbol{c})/P(Y_{x,\boldsymbol{m}} \le j|c)}{P(Y_{x^*,\boldsymbol{m}} > j|\boldsymbol{c})/P(Y_{x^*,\boldsymbol{m}} \le j|\boldsymbol{c})}\\ &= \frac{P(Y > j|x,\boldsymbol{m},\boldsymbol{c})/P(Y \le j|x,\boldsymbol{m},\boldsymbol{c})}{P(Y > j|x^*,\boldsymbol{m},\boldsymbol{c})/P(Y \le j|x^*,\boldsymbol{m},\boldsymbol{c})}\\ &= \exp\{(\beta_1 + \beta_3^T\boldsymbol{m})(x - x^*)\}.\end{aligned}$$

Now we consider the NIE through the mediator $M^{(1)}$ only. By the definition of NIE through $M^{(1)}$ and noting that $(M^{(1)}, \ldots, M^{(K)})$ are independent of each other, we can readily derive that

$$\begin{aligned}&\log\left\{\frac{P(Y_{x,M_{x^*}^{(1)},M_x^{(2)},\ldots,M_x^{(K)}} > j|\boldsymbol{c})}{P(Y_{x,M_{x^*}^{(1)},M_x^{(2)},\ldots,M_x^{(K)}} \le j|\boldsymbol{c})}\right\} \approx \log\{P(Y_{x,M_{x^*}^{(1)},M_x^{(2)},\ldots,M_x^{(K)}} > j|\boldsymbol{c})\}\\ &= \log\{\exp(-\beta_0^j + \beta_1 x + \beta_4^T c)E\{\exp((\beta_{21} + \beta_{31}x)M^{(1)})|x^*,\boldsymbol{c}\}\\ &\times\prod_{i=2}^{K}E\{\exp((\beta_{2i} + \beta_{3i}x)M^{(i)})|x,\boldsymbol{c}\}\}.\end{aligned}$$

Therefore, we get

$$\begin{aligned}\mathrm{NIE}_{OR}^{(1)} &= \frac{P(Y_{x,M_x^{(1)},M_x^{(2)},\ldots,M_x^{(K)}} > j|\boldsymbol{c})/P(Y_{x,M_x^{(1)},M_x^{(2)},\ldots,M_x^{(K)}} \le j|\boldsymbol{c})}{P(Y_{x,M_{x^*}^{(1)},M_x^{(2)},\ldots,M_x^{(K)}} > j|\boldsymbol{c})/P(Y_{x,M_{x^*}^{(1)},M_x^{(2)},\ldots,M_x^{(K)}} \le j|\boldsymbol{c})}\\ &\approx \frac{E\{\exp((\beta_{21} + \beta_{31}x)M^{(1)})|x,\boldsymbol{c}\}}{E\{\exp((\beta_{21} + \beta_{31}x)M^{(1)})|x*,\boldsymbol{c}\}}\\ &= \exp\{a_{11}(\beta_{21} + \beta_{31}x)(x - x^*)\}.\end{aligned}$$

Similarly, we obtain the NIE through the mediator $M^{(i)}$ represented as

$$\mathrm{NIE}_{\mathrm{OR}}^{(i)} \approx \exp\{a_{1i}(\beta_{2i} + \beta_{3i}x)(x - x^*)\}, \qquad i = 2, \ldots, K.$$

Appendix C: Mediation Analysis with Multiple Binary Mediators

Under a rare outcome assumption, it is similar to obtain

$$P(Y > j|x,\boldsymbol{m},\boldsymbol{c}) \approx \exp\{-\beta_0^j + \beta_1 x + \beta_2^T\boldsymbol{m} + \beta_3^T x\boldsymbol{m} + \beta_4^T\boldsymbol{c}\}.$$

In addition, under assumptions (A1)-(A4), we can derive the same conclusions as those in Web Appendix B,

$$\log\{\frac{P(Y_{x,\boldsymbol{M}_x} > j|\boldsymbol{c})}{P(Y_{x,\boldsymbol{M}_x} \le j|\boldsymbol{c})}\} \approx \log\{\exp(-\beta_0^j + \beta_1 x + \beta_4^T\boldsymbol{c})E\{\exp((\beta_2 + \beta_3 x)^T\boldsymbol{M})|x,\boldsymbol{c}\}\}.$$

Under the independent assumption of mediator, we have

$$\begin{aligned}E\{\exp((\beta_2 + \beta_3 x)^T\boldsymbol{M})|x,\boldsymbol{c}\} &= E\{\exp(\sum_{i=1}^{K}(\beta_{2i} + \beta_{3i}x)M^{(i)})|x,\boldsymbol{c}\}\\ &= \prod_{i=1}^{K}E\{\exp((\beta_{2i} + \beta_{3i}x)M^{(i)})|x,\boldsymbol{c}\}.\end{aligned}$$

Further, we calculate that

$$E\{\exp((\beta_{2i} + \beta_{3i}x)M^{(i)})|x,\boldsymbol{c}\} = \exp(\beta_{2i} + \beta_{3i}x)P(M^{(i)} = 1|x,\boldsymbol{c}) + P(M^{(i)} = 0|x,\boldsymbol{c}).$$

From the logistic regression model (12) in the main text, we know that

$$\begin{aligned}P(M^{(i)} = 1|x,\boldsymbol{c}) &= \frac{\exp(\gamma_{i0} + \gamma_{i1}x + \gamma_{i2}^T\boldsymbol{c})}{1 + \exp(\gamma_{i0} + \gamma_{i1}x + \gamma_{i2}^T\boldsymbol{c})}, P(M^{(i)} = 0|x,\boldsymbol{c})\\ &= \frac{1}{1 + \exp(\gamma_{i0} + \gamma_{i1}x + \gamma_{i2}^T\boldsymbol{c})}.\end{aligned}$$

Therefore, we have

$$E\{\exp((\beta_2 + \beta_3 x)^T\boldsymbol{M})|x,\boldsymbol{c}\} = \prod_{i=1}^{K}\frac{1 + \exp(\beta_{2i} + \beta_{3i}x + \gamma_{i0} + \gamma_{i1}x + \gamma_{i2}^T\boldsymbol{c})}{1 + \exp(\gamma_{i0} + \gamma_{i1}x + \gamma_{i2}^T\boldsymbol{c})}.$$

Then, we can get

$$\frac{P(Y_{x,\boldsymbol{M}_x} > j|\boldsymbol{c})}{P(Y_{x,\boldsymbol{M}_x} \le j|\boldsymbol{c})} \approx \exp(-\beta_0^j + \beta_1 x + \beta_4^T\boldsymbol{c})\prod_{i=1}^{K}\frac{1 + \exp(\beta_{2i} + \beta_{3i}x + \gamma_{i0} + \gamma_{i1}x + \gamma_{i2}^T\boldsymbol{c})}{1 + \exp(\gamma_{i0} + \gamma_{i1}x + \gamma_{i2}^T\boldsymbol{c})}.$$

It is similar to obtain that

$$\frac{P(Y_{x,\boldsymbol{M}_{x^*}} > j|\boldsymbol{c})}{P(Y_{x,\boldsymbol{M}_{x^*}} \le j|\boldsymbol{c})} \approx \exp(-\beta_0^j + \beta_1 x + \beta_4^T\boldsymbol{c})\prod_{i=1}^{K}\frac{1 + \exp(\beta_{2i} + \beta_{3i}x + \gamma_{i0} + \gamma_{i1}x^* + \gamma_{i2}^T\boldsymbol{c})}{1 + \exp(\gamma_{i0} + \gamma_{i1}x^* + \gamma_{i2}^T\boldsymbol{c})},$$

and

$$\frac{P(Y_{x^*,\boldsymbol{M}_{x^*}} > j|\boldsymbol{c})}{P(Y_{x^*,\boldsymbol{M}_{x^*}} \le j|\boldsymbol{c})} \approx \exp(-\beta_0^j + \beta_1 x^* + \beta_4^T\boldsymbol{c})\prod_{i=1}^{K}\frac{1 + \exp(\beta_{2i} + \beta_{3i}x^* + \gamma_{i0} + \gamma_{i1}x^* + \gamma_{i2}^T\boldsymbol{c})}{1 + \exp(\gamma_{i0} + \gamma_{i1}x^* + \gamma_{i2}^T\boldsymbol{c})}.$$

Hence, the NIE, NDE and CDE are derived as

$$\begin{aligned}\mathrm{NIE}_{\mathrm{OR}} &\approx \frac{\prod_{i=1}^{K}\{1 + \exp(\beta_{2i} + \beta_{3i}x + \gamma_{i0} + \gamma_{i1}x + \gamma_{i2}^T\boldsymbol{c})\}\{1 + \exp(\gamma_{i0} + \gamma_{i1}x + \gamma_{i2}^T\boldsymbol{c})\}^{-1}}{\prod_{i=1}^{K}\{1 + \exp(\beta_{2i} + \beta_{3i}x + \gamma_{i0} + \gamma_{i1}x^* + \gamma_{i2}^T\boldsymbol{c})\}\{1 + \exp(\gamma_{i0} + \gamma_{i1}x^* + \gamma_{i2}^T\boldsymbol{c})\}^{-1}}\\ \mathrm{NDE}_{\mathrm{OR}} &\approx \exp\{\beta_1(x - x^*)\}\frac{\prod_{i=1}^{K}\{1 + \exp(\beta_{2i} + \beta_{3i}x + \gamma_{i0} + \gamma_{i1}x^* + \gamma_{i2}^T\boldsymbol{c})\}}{\prod_{i=1}^{K}\{1 + \exp(\beta_{2i} + \beta_{3i}x^* + \gamma_{i0} + \gamma_{i1}x^* + \gamma_{i2}^T\boldsymbol{c})\}},\\ \mathrm{CDE}_{\mathrm{OR}} &= \exp\{(\beta_1 + \beta_3^T m)(x - x^*)\}.\end{aligned}$$

From the above derivation, it is easy to obtain the NIE through $M^{(i)}$ as

$$\mathrm{NIE}_{\mathrm{OR}}^{(i)} \approx \frac{\{1 + \exp(\beta_{2i} + \beta_{3i}x + \gamma_{i0} + \gamma_{i1}x + \gamma_{i2}^T\boldsymbol{c})\}\{1 + \exp(\gamma_{i0} + \gamma_{i1}x + \gamma_{i2}^T\boldsymbol{c})\}^{-1}}{\{1 + \exp(\beta_{2i} + \beta_{3i}x + \gamma_{i0} + \gamma_{i1}x^* + \gamma_{i2}^T\boldsymbol{c})\}\{1 + \exp(\gamma_{i0} + \gamma_{i1}x^* + \gamma_{i2}^T\boldsymbol{c})\}^{-1}}$$

Appendix D: Mediation Analysis with Multiple Mixed Mediators

Noting that $M^{(1)}, \ldots, M^{(K)}$ are independent of each other, we have

$$\begin{aligned}E(\exp(\beta_2^T + \beta_3^T x)\boldsymbol{M}|x,\boldsymbol{c}) &= E\{\exp(\sum_{i=1}^{K}(\beta_{2i} + \beta_{3i}x)M^{(i)})|x,\boldsymbol{c}\}\\ &= \prod_{i=1}^{K}E\{\exp((\beta_{2i} + \beta_{3i}x)M^{(i)})|x,\boldsymbol{c}\}.\end{aligned}$$

When $M^{(i)}$ is continuous ($i \neq 1$), we can get

$$\begin{aligned}&E\{\exp((\beta_{2i} + \beta_{3i}x)M^{(i)})|x,\boldsymbol{c}\}\\ &= \frac{1}{\sqrt{2\pi}\sigma}\int\exp\{(\beta_{2i} + \beta_{3i}x)m\}\exp\{-(m - \mu_i)^2/(2\sigma_i^2)\}dm\\ &= \exp\{(\beta_{2i} + \beta_{3i}x)\mu_i + \frac{\sigma_i^2}{2}(\beta_{2i} + \beta_{3i}x)^2\},\end{aligned}$$

where $\mu_i = \alpha_{i0} + \alpha_{i1}x + \alpha_{i2}^T\boldsymbol{c}$. When $M^{(l)}$ is binary, we have

$$E\{\exp(\beta_{2l}+\beta_{3l}x)M^{(l)})|x,\boldsymbol{c}\} = \exp(\beta_{2l}+\beta_{3l}x)P(M^{(l)}=1|x,\boldsymbol{c}) + P(M^{(l)}=0|x,\boldsymbol{c})$$
$$= \exp(\beta_{2l}+\beta_{3l}x)\frac{\exp(\alpha_{0l}+\alpha_{1l}x+\alpha_{2l}^T\boldsymbol{c})}{1+\exp(\alpha_{0l}+\alpha_{1l}x+\alpha_{2l}^T\boldsymbol{c})} + \frac{1}{1+\exp(\alpha_{0l}+\alpha_{1l}x+\alpha_{2l}^T\boldsymbol{c})}$$
$$= \frac{1+\exp\{\beta_{2l}+\beta_{3l}x+\alpha_{0l}+\alpha_{1l}x+\alpha_{2l}^T\boldsymbol{c}\}}{1+\exp(\alpha_{0l}+\alpha_{1l}x+\alpha_{2l}^T\boldsymbol{c})}.$$

Therefore, we obtain

$$\frac{P(Y_{x,\boldsymbol{M}_x}>j|\boldsymbol{c})}{P(Y_{x,\boldsymbol{M}_x}\le j|\boldsymbol{c})} \approx \exp\left\{-\beta_0^j+\beta_1 x+\beta_4^T c+\sum_{i\ne l}^{K}(\beta_{2i}+\beta_{3i}x)\mu_i + \frac{1}{2}\sum_{i\ne l}^{K}\sigma_i^2(\beta_{2i}+\beta_{3i}x)^2\right\} \times \frac{1+\exp\{\beta_{2l}+\beta_{3l}x+\alpha_{0l}+\alpha_{1l}x+\alpha_{2l}^T\boldsymbol{c}\}}{1+\exp(\alpha_{0l}+\alpha_{1l}x+\alpha_{2l}^T\boldsymbol{c})}.$$

Similarly, we have

$$\frac{P(Y_{x,\boldsymbol{M}_{x^*}}>j|\boldsymbol{c})}{P(Y_{x,\boldsymbol{M}_{x^*}}\le j|\boldsymbol{c})} \approx \exp\left\{-\beta_0^j+\beta_1 x+\beta_4^T c+\sum_{i\ne l}^{K}(\beta_{2i}+\beta_{3i}x)\mu_i^* + \frac{1}{2}\sum_{i\ne l}^{K}\sigma_i^2(\beta_{2i}+\beta_{3i}x)^2\right\} \times \frac{1+\exp\{\beta_{2l}+\beta_{3l}x+\alpha_{0l}+\alpha_{1l}x^*+\alpha_{2l}^T\boldsymbol{c}\}}{1+\exp(\alpha_{0l}+\alpha_{1l}x^*+\alpha_{2l}^T\boldsymbol{c})},$$

and

$$\frac{P(Y_{x^*,\boldsymbol{M}_{x^*}}>j|\boldsymbol{c})}{P(Y_{x^*,\boldsymbol{M}_{x^*}}\le j|\boldsymbol{c})} \approx \exp\left\{-\beta_0^j+\beta_1 x^*+\beta_4^T \boldsymbol{c}+\sum_{i\ne l}^{K}(\beta_{2i}+\beta_{3i}x^*)\mu_i^* + \frac{1}{2}\sum_{i\ne l}^{K}\sigma_i^2(\beta_{2i}+\beta_{3i}x^*)^2\right\} \times \frac{1+\exp\{\beta_{2l}+\beta_{3l}x^*+\alpha_{0l}+\alpha_{1l}x^*+\alpha_{2l}^T\boldsymbol{c}\}}{1+\exp(\alpha_{0l}+\alpha_{1l}x^*+\alpha_{2l}^T\boldsymbol{c})},$$

where $\mu_i^* = \alpha_{i0}+\alpha_{i1}x^*+\alpha_{i2}^T\boldsymbol{c}$. This yields the NIE, NDE and CDE as