Interventional Effect Models for Multiple Mediators

Wen Wei Loh\textsuperscript{1,*}, Beatrijs Moerkerke\textsuperscript{1}, Tom Loeys\textsuperscript{1}, Stijn Vansteelandt\textsuperscript{2,3}

\textsuperscript{1} Department of Data Analysis, Ghent University, Gent, Belgium
\textsuperscript{2} Department of Applied Mathematics, Computer Science and Statistics, Ghent University, Ghent, Belgium
\textsuperscript{3} Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, United Kingdom

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Abstract

In settings that involve multiple mediators, approaches focusing on fine-grained decompositions of natural (in)direct effects are only valid under strong assumptions. In particular, the assumptions are known to be violated when – as often – the structural dependence between the multiple mediators is unknown. In contrast, interventional (in)direct effects, introduced by VanderWeele et al. (2014), can be identified under much weaker conditions than natural (in)direct effects, but have the drawback of not adding up to the total effect. Vansteelandt and Daniel (2017) adapted their proposal to achieve an exact decomposition of the total effect, and generalized the interventional effects to the multiple mediator setting. In this article, we introduce interventional effect models that allow for simultaneous and parsimonious modeling of the interventional effects when there are multiple mediators. The parameters in the effect models encode the effects of a treatment on an outcome that are mediated by distinct mediators, even when the directions of the causal effects between the

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mediators are unknown, or when the mediators share hidden common causes. The mediators and outcome can be continuous or noncontinuous. Estimation proceeds via Monte Carlo integration and only requires specifying a joint distribution of the mediators and an outcome model.

**Keywords:** Direct and indirect effects; Effect decomposition; Imputation; Mediation analysis; Path analysis; Potential outcomes

1 **Introduction**

Mediation analysis is used to assess the extent to which the effect of a treatment or exposure \( A \) on an outcome \( Y \) is transmitted via an intermediate variable that lies on a causal pathway from \( A \) to \( Y \). A formal framework for mediation analysis has been developed using counterfactual-based distribution-free definitions of *natural direct and indirect effects* (Robins and Greenland, 1992; Pearl, 2001). This development permits the decomposition of the total effect into a direct and an indirect effect using the mediation formula (Pearl, 2012), when ignorability assumptions needed to identify the natural (in)direct effects hold, regardless of the assumed statistical model. In practice, the natural (in)direct effects can be estimated using nonlinear models for the mediator and the outcome. Notwithstanding these advances, there are reservations about the usefulness of natural (in)direct effects. They may be uninformative of real-life interventions as it may be unfeasible to set multiple variables simultaneously to individual-specific counterfactual values (Petersen et al., 2006; Robins and Richardson, 2010; Naimi et al., 2014). It can be difficult to conceptualize interventions that capture the notion of natural direct effects (Didelez et al., 2006), or impossible to perform experiments in which the identification assumptions for natural (in)direct effects are guaranteed to be satisfied (Robins and Richardson, 2010; Imai et al., 2013).

The problem lies in that natural (in)direct effects are defined in terms of so-called cross-
world counterfactuals \cite{RobinsRichardson2010} involving composite, or nested, counterfactuals for the mediator and outcome. Identification thus demands either specifying Non-Parametric Structural Equations Model \cite{Pearl2009} structures for all observed variables, or assuming independence of mediator and outcome counterfactuals under different treatments. In particular, the latter assumption is known to be violated when confounders of the mediator-outcome association are affected by treatment \cite{Avinetal2005,VansteelandtVanderWeele2012,VanderWeeleetal2014}. This complicates extensions of mediation analysis using natural effects to settings that involve multiple mediators. Many mediation analyses involve multiple mediators, either because scientific interest is in multiple causal pathways, or because certain confounders affected by treatment are perceived as competing mediators at the same time. Under such settings, one mediator can play the role of a time-varying confounder of the mediator-outcome association for another mediator, so that it is difficult or impossible to identify the natural or path-specific effects \cite{ImaiYamamoto2013,VanderWeeleVansteelandt2014,Danieletal2015}. Approaches focusing on fine-grained decompositions of natural (in)direct effects are only valid under stringent assumptions, such as when the mediators are independent \cite{Langeetal2013} or can be causally ordered \cite{VanderWeeleetal2014,Steenetal2017}, and share no hidden, or unmeasured, common causes. \cite{Shpitser2013} describes how path-specific effects can be identified under certain criteria, where there is merely observed time-varying confounding and some degree of hidden confounding, using the counterfactual graphical model framework. However, in most realistic scenarios, the directions of the causal effects between the various mediators is unknown, thus either violating the assumptions needed to identify the path-specific effects, or requiring further assumptions about the (correct) specification of the causal structure.
In contrast, *interventional (in)direct effects*, introduced by VanderWeele et al. (2014), are not defined in terms of cross-world counterfactuals. Unlike natural effects that are defined in terms of individual-level (deterministic) interventions on the mediator, interventional effects consider population-level (stochastic) interventions that set the value of the mediator to a random draw from its counterfactual distribution. Moreno-Betancur and Carlin (2018) describe how to recreate such population-level interventions using hypothetical randomized controlled trials. Natural effects require an “in-between world” intervention where treatment is set to one condition but the mediator is simultaneously set to its potential value under a different condition, whereas interventional effects concern ideal (distinct) interventions on the treatment and the mediator distribution, without changing anything else in the causal structure (Quynh Nguyen et al., 2019). Interventional effects thus remain meaningful even when the exposure cannot be manipulated at the individual level. For example, VanderWeele and Robinson (2014) and Jackson and VanderWeele (2018) describe interventional (in)direct effects using race as the exposure and socioeconomic status as the mediator, without having to define nested potential outcomes with respect to race or the exposure effects of race. Interventional effects can be identified under much weaker conditions than natural effects, but have the drawback of not adding up to the total effect. Vansteelandt and Daniel (2017) adapted the interventional (in)direct effect estimands to achieve an exact decomposition of the total effect, and generalized the definition of interventional effects to the multiple mediator setting. In particular, the joint indirect effect of a treatment on an outcome can be decomposed into separate indirect effects via each distinct mediator, and an indirect effect via the mediators’ mutual dependence, regardless of the underlying causal structure of the mediators.

In this article, we introduce interventional effect models that facilitate simultaneous
and parsimonious modeling of the interventional effects when there are multiple correlated and/or repeatedly measured mediators. We adopt the functional form of natural effect models for multiple mediators (Lange et al., 2013; Steen et al., 2017) that express the mean of nested counterfactuals in terms of hypothetical treatment levels for each mediator. Natural effect models directly parametrize the path-specific effects via each mediator, and generalize marginal structural models (Robins, 2000) to allow for effect decomposition for mediation analysis with multiple mediators. Similarly, the parameters in our proposed (interventional) effect models encode the direct effect and indirect effects via each mediator, even when the directions of the causal effects between the mediators are unknown, or the mediators are manifestations of an underlying latent process, or the mediators share hidden common causes. The mediators and outcome can be continuous or noncontinuous. Estimation proceeds via a Monte Carlo-based regression approach and only requires specifying a joint distribution of the mediators and an outcome model.

The remainder of this article is as follows. In Section 2 notation is introduced, the interventional (in)direct effects are defined, and the exact decomposition of the total effect into the direct effect and indirect effects via each mediator is presented. The indirect effects defined in this article are identical to those in Vansteelandt and Daniel (2017) when there are two mediators, but differ when there are more than two mediators. In Section 3 (interventional) effect models are introduced, and the estimation procedure using Monte Carlo integration is described. In Section 4 path analysis estimators of the interventional effects under a certain class of linear models are proposed. It is shown that the estimators are robust to misspecification of the direction of the causal effects between the mediators. In Section 5 the proposed methods are assessed via simulation studies. In Section 6 the methods are utilized to assess the effect of gender on body mass index (BMI) that is possibly
mediated by seven distinct behavior variables in an observational study on children’s weight and behavior. A brief discussion is provided in Section [7].

2 Interventional effects

2.1 Definition of potential outcomes

Consider the setting with a treatment or exposure $A$, multiple mediators $M_1, \ldots, M_t$, and an outcome $Y$. Uppercase letters denote (observed) random variables and (possibly unobserved) potential outcomes, and lowercase letters denote specific values. Let $Y_{am_1\cdots m_t}$ denote the potential outcome for $Y$ if, possibly counter to fact, $A$ is set to $a$, and each mediator $M_s$ is set to the value $m_s, s = 1, \ldots, t$. Let $M_{sa(s)}$ denote the potential outcome for $M_s$ if, possibly counter to fact, $A$ is set to $a(s)$. Let $Y_{a(0)}\tilde{M}_{1a(1)}|C\cdots \tilde{M}_{ta(t)}|C$ denote the potential outcome for $Y$ under treatment $A = a(0)$, and the value of each mediator is set to a random draw from the marginal counterfactual distribution (given baseline covariates $C$), i.e., $\tilde{M}_{sa(s)}|C \sim F(M_{sa(s)}|C), s = 1, \ldots, t$, where $F(\cdot)$ denotes a cumulative distribution function. Let $a^{(t)} = (a^{(0)}, a^{(1)}, \ldots, a^{(t)})$ denote the set of hypothetical treatment levels; the potential outcome for $Y$ may then be written as $Y_{a^{(t)}} = Y_{a^{(0)}a^{(1)}\cdots a^{(t)}} = Y_{a^{(0)}\tilde{M}_{1a(1)}|C\cdots \tilde{M}_{ta(t)}|C}$, where the dependence on $C$ is omitted for notational simplicity.

Potential outcomes where the mediators are set to random draws from the joint counterfactual distribution (given $C$) are denoted by (curly) brackets in the subscripts. Let $Y_{a^{(0)}\{\tilde{M}_{1a(1)}\cdots \tilde{M}_{ta(t)}|C\}}$ denote the potential outcome under treatment $A = a^{(0)}$, and the values of the mediators are set to a random draw from the joint counterfactual distribution under treatment $A = a^{(1)}$, i.e., $\{\tilde{M}_{1a(1)}, \ldots, \tilde{M}_{ta(t)}\} \sim F(M_{1a(1)}, \ldots, M_{ta(t)}|C)$. In this paper, we only consider the joint counterfactual distribution for all the mediators, and
not subsets of the mediators, under the same treatment, e.g., \( A = a^{(1)} \). Further, write \( Y_{a^{(0)}\{a^{(1)}\}} = Y_{a^{(0)}\{\tilde{M}_{1a^{(1)}} \cdots \tilde{M}_{ta^{(1)}}|C\}} \), where the dependence on \( C \) is omitted for notational simplicity; when \( a^{(0)} = a^{(1)} \), let \( Y_{\{a^{(0)}\}} = Y_{a^{(0)}\{a^{(0)}\}} \) by composition.

### 2.2 Identification of average potential outcomes

Identification of the average potential outcomes defined above requires the following assumptions, respectively labelled (i’), (ii’) and (iii’) in Vansteelandt and Daniel (2017) under the setting with \( t = 2 \) mediators:

the effect of treatment \( A \) on outcome \( Y \) is unconfounded conditional on \( C \), i.e.,

\[
Y_{am_1 \cdots m_t} \perp A | C \quad \forall \, a, m_1, \ldots, m_t; \tag{1}
\]

the effect of all mediators \( M_1, \ldots M_t \) on outcome \( Y \) is unconfounded conditional on \( A \) and \( C \), i.e.,

\[
Y_{am_1 \cdots m_t} \perp (M_1, \ldots, M_t)|\{A = a, C\} \quad \forall \, a, m_1, \ldots, m_t; \tag{2}
\]

the effect of treatment \( A \) on all mediators is unconfounded conditional on \( C \), i.e.,

\[
(M_{1a}, \ldots, M_{ta}) \perp A | C \quad \forall \, a. \tag{3}
\]

Under assumptions (1)–(3), the average potential outcomes are identified by:

\[
\mathbb{E}(Y_{a^{(0)}\{a^{(1)}\}}) \\
= \mathbb{E} \left[ \sum_{m_1, \ldots, m_t} \mathbb{E}(Y_{a^{(0)}m_1 \cdots m_t}|C) \Pr(M_{1a^{(1)}} = m_1, \ldots, M_{ta^{(1)}} = m_t|C) \right] \\
= \mathbb{E} \left[ \sum_{m_1, \ldots, m_t} \mathbb{E}(Y|A = a^{(0)}, M_1 = m_1, \ldots, M_t = m_t, C) \Pr(M_1 = m_1, \ldots, M_t = m_t|A = a^{(1)}, C) \right];
\]
and
\[ E(Y_{a^{(t)}}) = E \left[ \sum_{m_1, \ldots, m_t} E(Y_{a^{(0)} m_1 \ldots m_t} | C) \prod_{s=1}^{t} \Pr(M_{sa^{(s)}} = m_s | C) \right] \]

\[ = E \left[ \sum_{m_1, \ldots, m_t} E(Y | A = a^{(0)}, M_1 = m_1, \ldots, M_t = m_t, C) \prod_{s=1}^{t} \Pr(M_s = m_s | A = a^{(s)}, C) \right]. \]

### 2.3 Definition of interventional effects and decomposition of indirect effects

In this section, we define the interventional effects and describe possible decompositions for a binary treatment \( A \). Denote the user-specified link function by \( g \). Define the total effect as \( g \{ E(Y_{a^{(1)}}) \} - g \{ E(Y_{a^{(0)}}) \} \). Define the direct effect as \( \text{DE}(a^{(1)}) = g \{ E(Y_{a^{(1)}}) \} - g \{ E(Y_{0a^{(1)}}) \} \); and the (joint) indirect effect as \( \text{IE}(a^{(0)}) = g \{ E(Y_{a^{(0)}a^{(1)}}) \} - g \{ E(Y_{a^{(0)}0}) \} \). The total effect can thus be decomposed into a direct effect and an indirect effect, respectively:

\[ \text{DE}(1 - a^*) = g \{ E(Y_{1\{1-a^*\}}) \} - g \{ E(Y_{0\{1-a^*\}}) \}, \quad (4) \]

\[ \text{IE}(a^*) = g \{ E(Y_{a^*\{1\}}) \} - g \{ E(Y_{a^*\{0\}}) \}; \quad a^* = 0, 1. \quad (5) \]

The (joint) indirect effect \([5]\) can be further decomposed into separate indirect effects via each mediator, and an indirect effect via the mutual dependence of the mediators, which are defined as follows. Let \( a^{(t)}_{-s} = (a^{(0)}, a^{(1)}, \ldots, a^{(s-1)}, a^{(s+1)}, \ldots, a^{(t)}) \) denote the set of \( t \) hypothetical treatments, excluding the treatment for the \( s \)-th mediator, \( a^{(s)} \). Define the indirect effect via \( M_s, s = 1, \ldots, t, \) as:

\[ \text{IE}_s(a^{(t)}_{-s}) = g \{ E(Y_{a^{(0)} a^{(1)} \ldots a^{(s-1)} 1 a^{(s+1)} \ldots a^{(t)}}) \} - g \{ E(Y_{a^{(0)} a^{(1)} \ldots a^{(s-1)} 0 a^{(s+1)} \ldots a^{(t)}}) \}. \quad (6) \]
Note that the total, direct and (joint) indirect effects are defined using potential outcomes where the mediators are drawn from a joint (counterfactual) distribution, whereas the separate indirect effects via each mediator are defined using potential outcomes where the mediators are drawn from their respective marginal (counterfactual) distributions.

Under certain values of $a^{(t)}, s = 1, \ldots, t$, the sum of the separate indirect effects equals:

$$
\sum_{s=1}^{t} \text{IE}_s(a^{(t)}_{-s}) = g\{E(Y_{a^{(0)}1})\} - g\{E(Y_{a^{(0)}0})\},
$$

where for notational simplicity, $Y_{a^{(0)}a^{(1)}} = Y_{a^{(0)}a^{(1)}\ldots a^{(1)}}$ denotes the potential outcome for $Y$ under the same treatment level for all mediator potential outcomes, i.e., $a^{(1)} = \cdots = a^{(t)}$.

The indirect effect via the mutual dependence of the mediators is thus defined as:

$$
\text{IE}_t(a^{(0)}) = \left[ g\{E(Y_{a^{(0)}1})\} - g\{E(Y_{a^{(0)}0})\} \right] - \left[ g\{E(Y_{a^{(0)}1})\} - g\{E(Y_{a^{(0)}0})\} \right] - \sum_{s=1}^{t} \text{IE}_s(a^{(t)}_{-s}).
$$

Hence the joint indirect effect via all mediators, $\text{IE}(a^{(0)})$, can be decomposed into separate indirect effects via each mediator, $\text{IE}_s(a^{(t)}_{-s})$, and an indirect effect resulting from the mutual dependence between the mediators, $\text{IE}_t(a^{(0)})$. The latter is an important component in the decomposition of the joint indirect effect: it describes the mediated effect of treatment on outcome when the relationships between the mediators, and their subsequent effects on the outcome, differ for different treatment levels, so that the indirect effect via the mediators cannot be considered separately only. In some cases, the latter may be of primary scientific interest (Vansteelandt and Daniel, 2017).

The decomposition in (8) only holds under certain values of $a^{(t)}_{-s}, s = 1, \ldots, t$ (the treatment levels held fixed in each indirect effect) for which (7) holds; i.e., that the sum of the separate indirect effects equals $g\{E(Y_{a^{(0)}1})\} - g\{E(Y_{a^{(0)}0})\}$. The number of possible
decompositions of the joint indirect effect can be determined as follows. Let $1_t(0_t)$ denote the (row) vector of $t$ ones (zeros). There are $t$ choices for setting $a_{-s}^{(t)} = 1_t$ so that $IE_s(1_t)$ includes the term $g\{E(Y_{a(0)})\}$, and $t - 1$ choices for setting $a_{-s'}^{(t')} = 0_t$, $s' \neq s$, so that $IE_{s'}(0_t)$ includes the term $g\{E(Y_{a(0)})\}$. There are then $(t - 2)!$ choices for cancelling the remaining terms out. Hence there are $t!$ possible decompositions of the joint indirect effect when there are $t$ mediators. For example, when there are three mediators ($t = 3$), the indirect effects via $M_1, M_2$ and $M_3$ are respectively defined as:

$$IE_1(a^{(0)}, a^{(2)}, a^{(3)}) = g\{E(Y_{a(0)}a^{(2)}a^{(3)})\} - g\{E(Y_{a(0)}a^{(2)}a^{(3)})\}.$$  

$$IE_2(a^{(0)}, a^{(1)}, a^{(3)}) = g\{E(Y_{a(0)}a^{(1)}a^{(3)})\} - g\{E(Y_{a(0)}a^{(1)}0_{a^{(3)})})\}.$$  

$$IE_3(a^{(0)}, a^{(1)}, a^{(2)}) = g\{E(Y_{a(0)}a^{(1)}a^{(2)})\} - g\{E(Y_{a(0)}a^{(1)}a^{(2)})\}.$$ 

The six different values of $a_{-s}^{(3)}$, $s = 1, 2, 3$, under which the (joint) indirect effect can be decomposed into the separate indirect effects via each mediator, and the indirect effect via the mutual dependence of the mediators, are shown in Table 1.

When there are two mediators ($t = 2$) and $g$ is the identity link, the interventional effects $DE(0)$, $IE_1(1,0)$, $IE_2(1,1)$ and $IE_2(1)$ are equivalent to the interventional effects defined in (5)–(8) of Vansteelandt and Daniel (2017) for $a = 1, a^* = 0$. In general, the definition of the indirect effect via each mediator $M_s$ in (6) differs from the definition in (1) of Vansteelandt and Daniel (2017 eAppendix B): under the latter definition, the mediators (excluding $M_s$) are drawn from a mixture of joint, and possibly marginal, distributions under different treatment levels. Under the definition in (6), each mediator is always drawn from its marginal distribution, thus making a clearer distinction between the joint (for all mediators) and separate (via each mediator) indirect effects, and providing a simpler expression and interpretation of the indirect effect via the mediators’ dependence in (8).
Table 1: Values of $a_{s}^{(3)}$, $s = 1, 2, 3$, so that (7) holds, when there are three mediators.

|        | IE$_1$ |        | IE$_2$ |        | IE$_3$ |
|--------|--------|--------|--------|--------|--------|
| $a^{(2)}$ | $a^{(3)}$ | $a^{(1)}$ | $a^{(3)}$ | $a^{(1)}$ | $a^{(2)}$ |
| 1      | 1      | 0      | 1      | 0      | 0      |
| 1      | 1      | 0      | 0      | 0      | 1      |
| 0      | 1      | 1      | 1      | 0      | 0      |
| 0      | 0      | 1      | 1      | 1      | 0      |
| 1      | 0      | 0      | 0      | 1      | 1      |
| 0      | 0      | 1      | 0      | 1      | 1      |

3 \hspace{1cm} \textit{Interventional effect models}

3.1 \hspace{1cm} \textit{Effect models}

We now posit the following set of effect models in which the parameters encode the causal effects defined in the previous section:

\begin{align*}
M^1 : & \quad g \{ E \{ Y_{a(0)}^{(-1)} \} \} = \mu_{01} + \gamma_{0}a^{(0)} + \gamma_{1}a^{(1)}, \\
M^2 : & \quad g \{ E \{ Y_{a(0)} \} \} = \mu_{02} + \sum_{s=0}^{t} \theta_{s}a^{(s)}. 
\end{align*}

Note that model $M^1$ describes average potential outcomes where the mediators are drawn from a joint (counterfactual) distribution, whereas model $M^2$ describes average potential outcomes where the mediators are drawn from their respective marginal (counterfactual) distributions. Hence model $M^2$ need not imply model $M^1$ if the treatments in the former
are set as $a^{(t)} = \cdots = a^{(1)}$. In fact, the parameters from both models jointly encode the indirect effect via the mutual dependence of the mediators. Linear combinations of the parameters in the posited models that encode the causal effects can thus be determined by comparing the (transformed) mean potential outcomes. In particular, the total effect is parameterized by $\gamma_0 + \gamma_1$ in model $\mathcal{M}^1$, which can be decomposed into the direct effect $\gamma_0$ and (joint) indirect effect $\gamma_1$. Similarly, the indirect effect via each mediator $M_s$ is encoded by $\theta_s$, $s = 1, \ldots, t$, in model $\mathcal{M}^2$. The indirect effect via the mediators’ dependence, as defined in (8), is thus encoded by $\gamma_1 - \sum_{s=1}^{t} \theta_s$.

Note that the parameter $\theta_0$ in model $\mathcal{M}^2$, that encodes the causal contrast $g\{E(Y_{1a^{(1)}})\} - g\{E(Y_{0a^{(1)}})\}$, is by definition equal to the direct effect (4), that is encoded by $\gamma_0$ in model $\mathcal{M}^1$, if either (i) the mediators $M_1, \ldots, M_t$ are independent, i.e.,

$$\Pr(M_{1a^{(1)}} = m_1, \ldots, M_{ta^{(1)}} = m_t | C) = \prod_{s=1}^{t} \Pr(M_{sa^{(1)}} = m_s | C);$$

or (ii) $g(\cdot)$ is the identity link, and the controlled direct effect is not modified by the mediators ("additive homogeneity"), e.g.,

$$E(Y_{1m_1 \ldots m_t} | C) - E(Y_{0m_1 \ldots m_t} | C) = E(Y_{1'm_1 \ldots m'_t} | C) - E(Y_{0'm_1 \ldots m'_t} | C), \quad \forall m_1, m_1', \ldots, m_t, m_t'.$$

Under the latter setting, suppose that the controlled direct effect is some function of $C$, e.g., $E(Y_{1m_1 \ldots m_t} | C) - E(Y_{0m_1 \ldots m_t} | C) = \delta(C)$, $\forall m_1, \ldots, m_t$. It is shown in Appendix A that the interventional direct effect is identified by $E[\delta(C)]$ in both effect models; hence under the posited models in (9) and (10), $\gamma_0 = \theta_0$.

### 3.2 Estimation via Monte Carlo integration

Estimators of the (in)direct effects can be obtained by fitting the effect models $\mathcal{M}^1$ and $\mathcal{M}^2$ using Monte Carlo integration. It follows from causal consistency that the potential out-
come \( Y_{a^{(0)}\{a^{(1)}\}} \) is only observable when the hypothetical treatments all equal the observed treatment \( A \), i.e., \( a^{(0)} = a^{(1)} = A \). Similarly, the mediator potential outcomes equal their observed values, i.e., \( \{\tilde{M}_{1a^{(1)}}, \ldots, \tilde{M}_{ta^{(1)}}\} = (M_1, \ldots, M_t) \), among individuals with \( a^{(1)} = A \). Hence when \( a^{(0)} \neq a^{(1)} \), the unobserved potential outcomes \( Y_{a^{(0)}\{a^{(1)}\}} \) for \( a^{(1)} = A \) can be predicted using an appropriate mean model for the outcome where treatment is set to \( a^{(0)} \), and the mediators are set to their observed values. This suggests an imputation procedure where duplicated data for each individual is constructed by complementing the observed outcome with imputed expected potential outcomes at different treatment levels for \( a^{(0)} \), but corresponding to the observed values of the mediators. For a posited effect model \( \mathcal{M}^1 \), e.g., (9), the proposed estimators of the direct and (joint) indirect effects, as encoded by the parameters \( \gamma_0 \) and \( \gamma_1 \) respectively, are obtained as follows:

A1. Fit an appropriate outcome model conditional on treatment, mediators and baseline covariates \( E(Y|A,M_1,\ldots,M_t,C) \) to the observed data set. The outcome model can be expressed as a function of its inputs, e.g., \( E(Y|A = a, M_1 = m_1, \ldots, M_t = m_t, C = c) = h(a, m_1, \ldots, m_t, c) \), where \( h(\cdot) \) is a user-specified function. Denote the estimated function by \( \hat{h}(a, m_1, \ldots, m_t, c) \).

A2. Construct the duplicated data for each individual as shown in Table 2 by considering both possible values of \( a^{(0)} \) for a binary treatment \( A \).

A3. Impute the expected potential outcome \( E(Y_{a^{(0)}\{a^{(1)}\}}|C) \) for the second row of Table 2 as a prediction \( \hat{h}(a = 1 - A, m_1 = M_1, \ldots, m_t = M_t, c = C) \) from the fitted outcome model.

A4. Fit the model \( \mathcal{M}^1 \) to the duplicated data.
Table 2: Duplicated data for each individual for estimating the parameters in $\mathcal{M}^1$.

| $a^{(0)}$ | $a^{(1)}$ | $\{\tilde{M}_{1a^{(1)}}, \ldots, \tilde{M}_{ta^{(1)}}\}$ | $E(Y_{a^{(0)}{\{a^{(1)}\}}}|C)$ |
|----------|----------|----------------------------------------------------------|---------------------------------|
| $A$      | $A$      | $(M_1, \ldots, M_t)$                                     | $Y$                             |
| $1 - A$  | $A$      | $(M_1, \ldots, M_t)$                                     | $\hat{h}(a = 1 - A, m_1 = M_1, \ldots, m_t = M_t, c = C)$ |

Standard errors can be estimated using a nonparametric percentile bootstrap procedure (Efron and Tibshirani, 1994) that randomly resamples observations with replacement and repeating steps A1 – A4 for each bootstrap sample. The imputation procedure for model $\mathcal{M}^1$ adopts the imputation estimation strategy of Vansteelandt et al. (2012) for a single mediator, by considering all the mediators as a single (multivariate) mediator.

We now consider the model $\mathcal{M}^2$. In general, the potential outcome $Y_{a(t)}$ is unobservable, even when the hypothetical treatments all equal the observed treatment $A$, i.e., $a^{(0)} = a^{(1)} = \ldots = a^{(t)} = A$. This is because each mediator potential outcome $\tilde{M}_{sa^{(s)}}|C$, even under the observed treatment $a^{(s)} = A$, is drawn from its marginal (counterfactual) distribution by definition, whereas the observed values $(M_1, \ldots, M_t)$ are drawn from a joint distribution. We propose the following imputation procedure where duplicated data for each individual requires randomly sampling mediator potential outcomes from their respective marginal distributions under different treatment levels for $a^{(1)}, \ldots, a^{(t)}$. The imputed expected potential outcomes $Y_{a(t)}$ can then be predicted using the fitted outcome model in step A1, where the treatment is set to $a^{(0)}$, and the mediator values are set to the stochastic draws. For a posited effect model $\mathcal{M}^2$, e.g., (10), the proposed estimators of the indirect effects via each mediator, and via their mutual dependence, are obtained as follows.
B1. Fit a (working) joint density of the mediators, e.g.,

\[ f(M_1, \ldots, M_t | A, C) = f(M_1 | A, C) \prod_{s=2}^{t} f(M_s | M_1, \ldots, M_{s-1}, A, C), \tag{11} \]

where \( f(\cdot) \) denotes a probability density function. Under assumption (3), the joint density of the mediator potential outcomes \( f(M_{1a} = m_1, \ldots, M_{ta} = m_t | C = c) \) is identified by \( f(M_1 = m_1, \ldots, M_t = m_t | A = a, C = c) \), which is henceforth denoted by \( f(m_1, \ldots, m_t | a, c) \). Let \( F(\cdot) \) denote the (cumulative) distribution function for \( f(\cdot) \). Fit the joint density of the mediators to the observed data, and denote the estimated density by \( \hat{f}(m_1, \ldots, m_t | a, c) \).

B2. Construct the duplicated data for each individual as shown in Table 8. In the first row, the hypothetical treatments are all set to the observed value \( A \), i.e., \( a^{(t)} = (A, \ldots, A) \); in row \( s + 1 \), where \( s = 0, \ldots, t \), set the \( s \)-th hypothetical treatment in \( a^{(t)} \) to \( 1 - A \), and the remaining hypothetical treatments to \( A \), i.e., \( a^{(s)} = 1 - A, a^{(s')} = A, s' = 0, \ldots, t, s' \neq s \).

B3. Randomly sample the mediator potential outcomes in each row as follows. In all rows except the last, set the potential outcome \( \tilde{M}_{ta}^{a^{(s)}} | C \) to the observed value \( M_t \). In the last row, set the potential outcome \( \tilde{M}_{t-1,a^{(t-1)}} | C \) to the observed value \( M_{t-1} \). Let \( s^* \) denote the index of the mediator potential outcome set to its observed value in each row; i.e., \( s^* = t \) in all rows except the last, and \( s^* = t - 1 \) in the last row. In each row, for \( s = 1, \ldots, t, s \neq s^* \), randomly sample \( \tilde{M}_{sa}^{a^{(s)}} | C \) by making a random draw from the joint distribution \( \{ \tilde{M}_{1a}^{a^{(s)}}, \ldots, \tilde{M}_{ta}^{a^{(s)}} \} \sim F(m_1, \ldots, m_t | a = a^{(s)}, c) \), then setting \( \tilde{M}_{sa}^{a^{(s)}} | C = \tilde{M}_{sa}^{a^{(s)}} \). If \( a^{(s)} = A \), denote the random draw by \( M^*_s \), where the asterisk denotes a sampled value that may possibly differ from the observed value \( M_s \).
B4. Impute the expected potential outcomes \( E(Y_{a(t)}) \) for all rows of Table 8 as predicted values \( \hat{h}(a = a^{(0)}, m_1 = \tilde{M}_{1a^{(1)}|C}, \ldots, m_t = \tilde{M}_{ta^{(1)}|C}, c = C) \).

B5. Fit the model \( \mathcal{M}^2 \) to the duplicated data.

Table 3: Duplicated data for each individual, with \( t + 2 \) rows for a binary treatment \( A \), used to estimate the parameters in \( \mathcal{M}^2 \) when there are \( t \) mediators. The asterisk denotes a sampled mediator potential outcome used in place of an observed value.

| \( a^{(0)} \) | \( a^{(1)} \) | \( \ldots \) | \( a^{(t)} \) | \( \tilde{M}_{1a^{(1)}|C} \) | \( \ldots \) | \( \tilde{M}_{ta^{(1)}|C} \) | \( E(Y_{a(t)}) \) |
|---|---|---|---|---|---|---|---|
| \( A \) | \( A \) | \( \ldots \) | \( A \) | \( M^*_1 \) | \( \ldots \) | \( M_t \) | \( h(a = A, m_1 = M^*_1, \ldots, m_t = M_t, c = C) \) |
| \( 1 - A \) | \( A \) | \( \ldots \) | \( A \) | \( M^*_1 \) | \( \ldots \) | \( M_t \) | \( h(a = 1 - A, m_1 = M^*_1, \ldots, m_t = M_t, c = C) \) |
| \( A \) | \( 1 - A \) | \( A \) | \( A \) | \( M_{1,1-A} \) | \( \ldots \) | \( M_t \) | \( h(a = A, m_1 = M_{1,1-A}, \ldots, m_t = M_t, c = C) \) |
| \( \vdots \) | \( \vdots \) | \( \vdots \) | \( \vdots \) | \( \vdots \) | \( \vdots \) | \( \vdots \) | \( \vdots \) |
| \( A \) | \( A \) | \( A \) | \( 1 - A \) | \( M^*_1 \) | \( \ldots \) | \( M_{t,1-A} \) | \( h(a = A, m_1 = M^*_1, \ldots, m_t = M_{t,1-A}, c = C) \) |

We recommend specifying a joint mediator distribution, rather than separate marginal distributions for each mediator, in step B1 to avoid noncollapsibility [Greenland et al., 1999] of the conditional and marginal effects for nonlinear mediator models, e.g., when a mediator is binary. Assuming that the residuals from the mediator models fitted to the observed data in step B1 are independent of all variables, an alternative to random draws of the mediators from specified parametric distributions in step B3 is to resample (with replacement) the residuals, then attach them to the predicted mediator potential outcomes. Since our interest is only in the expected potential outcome \( E(Y_{a(t)}) \) in each row, steps B3 and B4 may be repeated e.g., 1000 times, and the average predicted value of \( E(Y_{a(t)}) \) over all random samples employed as the imputed average potential outcome. Standard errors
may then be obtained using a nonparametric percentile bootstrap procedure where steps B1 – B5 are repeated for each bootstrap sample.

The duplicated data in step B2 can be constructed using the score vector for the effect model parameters, with one row for each element of the score vector. For example, for model $M^2$ in (10), the score vector is $\partial E(Y_{a(t)}) / \partial \theta = (1, a(t)^{(0)}, \ldots, a(t)^{(t)})^T$, where $\theta = (\mu_0^2, \theta_0^2, \ldots, \theta_t^2)$; hence the duplicated data in Table 8 has $t+1$ rows. For a binary treatment $A$, set the treatments $a(t)$ in the $k$-th row of the duplicated data as follows: treatments that appear in the $k$-th element of the score vector are set to $1 - A$; all other treatments are set to the observed value $A$. Continuing the above example, in the first row of Table 8, $a(t) = (A, \ldots, A)$ since the first element of the score vector is 1; in the $(s+1)$-th row, set $a(s) = 1 - A$, since the $(s+1)$-th element in the score vector is $a(s)$, and set all other treatments in that row to $A$. The choice of setting $\tilde{M}_{s^*a^*(s^*)|C}$ to its observed value is motivated by the convention that the joint distribution of the mediators is typically decomposed into a product of conditional distributions, such as in (11), where mediators with larger indices are functions of mediators with smaller indices. Sampling from (marginal) distributions of mediators with larger indices would thus require first sampling from the (conditional) distributions of mediators with smaller indices. Hence the redundancy may be avoided by setting $\tilde{M}_{s^*a^*(s^*)|C}$ to to its observed value $M_s$.

The proposed imputation-based procedures are similar to the imputation-based strategies for G-computation (Snowden et al., 2011), and share their virtues and limitations (Vansteelandt and Keiding, 2011). It is simple to implement, and avoids using weights based on (ratios of) the mediator probability density or mass functions (Hong, 2010; Lange et al., 2012), which may be unstable and result in bias in certain situations. However, its simplicity may belie the same difficulty that multiple imputation estimators face for miss-
ing data analyses: specifying a model for the outcome that is “congenial” (Meng 1994) with both effect models of interest $\mathcal{M}^1$ and $\mathcal{M}^2$. An outcome model that is incoherent with the effect models may result in misspecification bias. In addition, it is assumed that $E(Y_{am_1\ldots m_t}|C = c)$ is identified by the outcome model $h(a, m_1, \ldots, m_t, c)$, and that the outcome model is well-defined for all possible values of $a, m_1, \ldots, m_t, c$ (“positivity”). When both $\mathcal{M}^1$ and $\mathcal{M}^2$ are linear, i.e., $g(\cdot)$ being the identity link, an outcome model that reflects the structure of the interventional effect model may be obtained by replacing $a^{(s)}$ in the given effect model with $M_s, s = 1, \ldots, t$. However, it may be difficult or impossible to specify an outcome model that is coherent with nonlinear effect model(s); see VanderWeele and Vansteelandt (2010); Tchetgen Tchetgen (2014) when using logistic regression to model binary outcomes. While uncongeniality can be avoided by using saturated outcome models, in practice, it may be unfeasible to fit such models to the observed data as (some of) the baseline covariates or the treatment variable, or both, are continuous. Vansteelandt et al. (2012) and Loeys et al. (2013) recommend using sufficiently rich outcome models that are more flexible than the effect models, e.g., by including higher-order or interaction terms.

4 Path analysis estimators of interventional effects

In this section we describe how to obtain estimators of the interventional effects defined above using path analysis methods (Wright 1934) under a certain class of linear models for the mediators and the outcome. Suppose that the outcome obeys the following linear and additive (i.e., without interactions) mean model:

$$E(Y|A, M_1, \ldots, M_t, C) = \beta_0 + \beta_A A + \sum_{s=1}^{t} \beta_s M_s + \beta_C C.$$  (12)
The average potential outcome $E(Y_{a(0)}^{a(1)})$, where the mediators are set to random draws from the joint counterfactual distribution, is identified upon plugging the assumed outcome model (12) and mediator distributions into the expressions in Section 2.2:

$$E(Y_{a(0)}^{a(1)}) = E\left[\{\beta_0 + \beta_A a(0) + \beta_C C\} + \sum_{s=1}^{t} \beta_s E(M_s|A = a^{(1)}, C)\right].$$

Similarly, the average potential outcome $E(Y_{a(t)})$, where the mediators are set to random draws from the respective marginal counterfactual distributions, is identified by:

$$E(Y_{a(t)}) = E\left[\{\beta_0 + \beta_A a(0) + \beta_C C\} + \sum_{s=1}^{t} \beta_s E(M_s|A = a^{(s)}, C)\right].$$

The detailed steps are stated in Appendix B. Suppose that the (marginal) mean model for each mediator $M_s$ is also linear and additive, e.g.,

$$E(M_s|A, C) = \delta_{0s} + \delta_s A + \delta_{Cs} C, \quad s = 1, \ldots, t. \quad (13)$$

It follows that the interventional direct and (joint) indirect effects are identified by (functions of) the parameters in the assumed models, $\beta_A$ and $\sum_{s=1}^{t} \beta_s \delta_s$ respectively. Similarly, the interventional indirect effect via mediator $M_s$ is identified by $\beta_s \delta_s$. It follows by hypothesis that the indirect effect via the mutual dependence of the mediators is zero; Vansteelandt and Daniel (2017) describe conditions for the assumed outcome and mediator mean models under which this indirect effect is nonzero.

Estimators of the interventional effects can thus be obtained by fitting the assumed linear and additive mean models in (12) and (13) to the observed data, then plugging in the regression coefficient estimates for the unknown quantities. No Monte Carlo integration as described in the imputation procedure in the previous section is needed. Unbiased estimation requires correctly specifying an outcome mean model (12) and mediator (marginal)
mean models under assumptions (1)–(3). In particular, since only the marginal mean model for each mediator, and not the conditional mean model that depends on other mediators, needs to be correctly specified, the resulting estimators, henceforth referred to as regression-based estimators, are consistent for the interventional effects regardless of the assumed causal structure of the mediators.

To see this, assume that the mediators are causally connected and ordered, without loss of generality, so that $M_1, \ldots, M_{s-1}$ causally precede $M_s$, $s = 2, \ldots, t$, and no mediators precede $M_1$. The path-specific effect for a particular path from $A$ to $B$, using the product-of-coefficients method, is the product of the edge coefficients along the sequence of edges on that path. The combined path-specific effect from $A$ to $B$ along multiple paths is the sum of the separate path-specific effects. It is shown in Appendix B that the interventional indirect effect via the mediator $M_s$, $s = 1, \ldots, t$, is equal to the combined path-specific effect along all paths from $A$ to $Y$ that intersect $M_s$ (and may intersect any of $M_1, \ldots, M_{s-1}$) and avoid all of $M_{s+1}, \ldots, M_t$. Note that this interpretation of the interventional indirect effects holds even if the directions of the causal effects between the mediators are incorrectly specified, or the mediators share hidden common causes, or both. The interventional indirect effect via a mediator $M_s$ by definition consists only of causal pathways from $A$ to $M_s$, then lead directly to $Y$; see Vansteelandt and Daniel (2017) for an example with two mediators.

Path analysis estimators of the interventional effects can thus be obtained by fitting a joint (path analysis) model to all variables, using e.g., structural equation modeling, then plugging in estimates of the edge coefficients in the combined path-specific effects. The resulting estimators are equivalent to the regression-based estimators defined above, and are similarly robust to misspecification of the directions of the causal effects between the mediators. In contrast, separate path-specific effects that depend on certain causal
orderings of the mediators may only be well-defined and identifiable, and the resulting estimates unbiased, when the causal structure of the mediators is correctly specified, and the mediators do not share any hidden common causes.

5 Simulation studies

In this section three different simulation studies are conducted to assess the empirical biases and standard errors of the proposed estimators. In studies 1 and 2, the setting with a randomly assigned treatment, two mediators and a continuous outcome is considered. In study 1, both mediators are continuous but there is unobserved confounding between them. The estimators of the interventional effects are shown to be empirically unbiased, whereas the estimators of the natural effects are empirically biased. In study 2, both mediators are noncontinuous, with no unobserved confounding between them. The estimators using different outcome models are compared. In study 3, the setting with a baseline covariate of treatment, mediators and (continuous) outcome is considered, with four correlated mediators that are jointly distributed as multivariate normal. The proposed path analysis estimators are shown to be empirically unbiased for the interventional effects, even when it is incorrectly assumed that the mediators are independent in the fitted mediator models.
5.1 Study 1

Each observed dataset was generated using the path model in Figure 1 with the following linear and additive equations:

\[
A \sim \text{Bernoulli}(0.5) \\
U \sim \mathcal{N}(1, 1) \\
M_1 = \alpha_{01} + \alpha_1 A + \alpha_U U + \epsilon_1, \epsilon_1 \sim \mathcal{N}(0, \sigma_1^2) \\
M_2 = \alpha_{02} + \alpha_2 A + \alpha_U U + \eta_{12} M_1 + \epsilon_2, \epsilon_2 \sim \mathcal{N}(0, \sigma_2^2) \\
Y = \beta_0 + \beta_A A + \beta_1 M_1 + \beta_2 M_2 + \epsilon_Y, \epsilon_Y \sim \mathcal{N}(0, \sigma_Y^2)
\]

It follows from Section 4 that the interventional indirect effects via \(M_1\) and \(M_2\) are respectively identified by \(\beta_1 \alpha_1\) and \(\beta_2 (\alpha_2 + \alpha_1 \eta_{12})\), and the joint indirect effect via the mutual dependence of \(M_1\) and \(M_2\) is zero. The natural indirect effects via \(M_1\) and \(M_2\) are respectively identified by \((\beta_1 + \beta_2 \eta_{12})\alpha_1\) and \(\beta_2 \alpha_2\). Note that the path-specific effect of the causal pathway \(A \rightarrow M_1 \rightarrow M_2 \rightarrow Y\), identified by \(\alpha_1 \eta_{12} \beta_2\), contributes to the interventional indirect effect via \(M_2\), but contributes to the natural indirect effect via \(M_1\). The direct effect
is identified by $\beta_A$. Estimates of the parameters in the (correctly-specified) interventional effect models (9) and (10) are obtained using Monte Carlo integration (“MC”) as presented in Section 3.2. For comparison, the natural effect estimates, using a natural effects (“NE”) model fitted with the imputation strategy of Steen et al. (2017), are calculated. The values of the coefficients were $\alpha_{01} = 3, \alpha_1 = 1.2, \alpha_{U1} = 2, \alpha_{02} = 2, \alpha_2 = 1.6, \alpha_{U2} = -2, \eta_{12} = 2, \beta_0 = 1.6, \beta_A = 0.4, \beta_1 = 0.6, \beta_2 = 1.2, \sigma_1 = \sigma_2 = \sigma_Y = 1$. Average biases and empirical standard errors over 100000 simulated datasets of size 400 are displayed below. The biases in the natural indirect effect estimates are due to the hidden common cause $U$ of the mediators.

Table 4: Average estimates (“mean”) and empirical standard errors (“ese”) of the estimators of each interventional effect in simulation study 1.

| Direct | Indirect via $M_1$ | Indirect via $M_2$ |
|--------|-------------------|-------------------|
|        | truth  | mean  | ese   |        | truth  | mean  | ese   |        | truth  | mean  | ese   |
| MC     | 0.4    | 0.4   | 0.14  | MC     | 0.72   | 0.72  | 0.15  | MC     | 4.8    | 4.80  | 0.39  |
| NE     | 0.4    | 0.4   | 0.14  | NE     | 3.6    | 2.43  | 0.47  | NE     | 1.92   | 3.09  | 0.22  |
5.2 Study 2

In a second simulation study, each observed dataset was generated using the following path model as shown in Figure 2:

\[
\begin{align*}
A & \sim \text{Bernoulli}(0.5) \\
M_1 & \sim \text{Poisson}(\alpha_{01}) \\
\tilde{M}_2 &= \alpha_{02} + \alpha_2 A + \eta_{12} M_1 + \epsilon_2, \epsilon_2 \sim \mathcal{N}(0, \sigma_2^2) \\
M_2 & \sim \text{Bernoulli}(\Phi(\tilde{M}_2)), \quad \Phi(z) = \Pr(Z \leq z), Z \sim \mathcal{N}(0, 1) \\
Y &= \beta_0 + \beta_A A + \beta_1 \sqrt{M_1} + \beta_2 M_1^3 + \epsilon_Y, \epsilon_Y \sim \mathcal{N}(0, \sigma_Y^2)
\end{align*}
\]

It follows from Section 2.2 that the direct effect is identified by $\beta_A$, and the indirect effects via $M_1$ and via $M_2$ are both zero. Estimates of the parameters in the (correctly-specified) effect models (9) and (10) are obtained using the procedure presented in Section 3.2. The models for the mediators and outcome used to generate the observed data are also fitted ("True"). In addition, three other outcome models are considered:

- A generalized additive model (Wood 2017) with tensor product smooths for $M_1$ and $\sqrt{M_1}$ ("GAM"),
  \[\text{gam}(Y \sim A + \text{te}(M_1, M_1\text{sqrt}) + M_2, \text{family} = \text{gaussian("identity")}).\]
The term $M_1\sqrt{\text{ }}$ was created separately as the square root of $M_1$; $M_2$ is binary and cannot be used in a smoother term.

- Random forests ([Breiman 2001]) using the `ranger` implementation ([Wright and Ziegler 2017]), with the predictors $M_1\sqrt{\text{ }}$ and a cubic term $M_1\text{pow}3$ created separately ("Random Forests"):
  
  ```r
  ranger(Y \sim A + M1 + M2 + M1\sqrt{\text{ }} + M1\text{pow}3).
  ```

- A misspecified linear and additive outcome model ("Additive"),
  
  ```r
  glm(Y \sim A + M1 + M2, family = gaussian("identity"))
  ```

The values of the coefficients were $\alpha_{01} = 1, \alpha_{02} = -2, \alpha_2 = 1, \eta_{12} = 1.5, \beta_0 = 1.6, \beta_A = 0.4, \beta_1 = 1.2, \beta_2 = 0.6, \sigma_2 = \sigma_Y = 1$. Average biases and empirical standard errors over 20000 simulated datasets of size 400 are displayed below.
Table 5: Average estimates ("mean") and empirical standard errors ("ese") of the estimators of each interventional effect in simulation study 2.

|                     | Direct                        | Joint indirect              |
|---------------------|-------------------------------|-----------------------------|
|                     | truth | mean | ese  | truth | mean | ese  |
| True                | 0.4   | 0.40 | 0.1  |        |      |     |
| GAM                 | 0.4   | 0.40 | 0.1  |        |      |     |
| Random Forests      | 0.4   | 0.29 | 0.1  |        |      |     |
| Additive            | 0.4   | 0.81 | 0.56 |        |      |     |
|                     |       |      |      | True  | 0    | 0.85|
|                     |       |      |      | GAM   | 0    | 0.85|
|                     |       |      |      | Random Forests | 0  | 0.11| 0.82|
|                     |       |      |      | Additive | 0  | -0.4 | 0.7 |

| Indirect via $M_1$ |                     | Indirect via $M_2$          |
|---------------------|----------------------------|-----------------------------|
|                     | truth | mean | ese  | truth | mean | ese  |
| True                | 0     | 0    | 0.69 | True  | 0    | 0    |
| GAM                 | 0     | 0    | 0.68 | GAM   | 0    | 0    |
| Random Forests      | 0     | 0    | 0.63 | Random Forests | 0  | 0.04 | 0.11|
| Additive            | 0     | 0.01 | 0.74 | Additive | 0  | -0.41| 0.23|

Indirect via mutual dependence of $M_1$ and $M_2$

|                     | truth | mean | ese  |
|---------------------|-------|------|------|
| True                | 0     | 0    | 0.52 |
| GAM                 | 0     | 0    | 0.52 |
| Random Forests      | 0     | 0.07 | 0.48 |
| Additive            | 0     | 0    | 0.02 |
5.3 Study 3

Figure 3: Data-generating model for simulation study 3 with four mediators. Bidirected (broken) edges between two nodes denote nonzero correlation between the variables.

Each observed dataset was generated using the path model in Figure 3 with the following linear and additive equations:

\[ C \sim \mathcal{N}(0, 1) \]
\[ A \sim \text{Bernoulli}(\Phi(C)) \]
\[ M_s = \alpha_{0s} + \alpha_s A + \alpha_{Cs} C + \epsilon_s, \quad s = 1, \ldots, 4, \]
\[ (\epsilon_1, \epsilon_2, \epsilon_3, \epsilon_4)^T \sim \mathcal{N}_4(0_4, \Sigma) \]
\[ Y = \beta_0 + \beta_A A + \sum_{s=1}^4 \beta_s M_s + \beta_{C} C + \epsilon_Y, \quad \epsilon_Y \sim \mathcal{N}(0, \sigma_Y^2) \]

Hence the marginal distribution of each mediator is 
\[ M_s \sim \mathcal{N}(\alpha_{0s} + \alpha_s A + \alpha_{Cs} C, \Sigma_{ss}), \quad s = 1, \ldots, 4, \]
where \( \Sigma_{ss} \) is the s-th entry along the diagonal of \( \Sigma \). It follows from Section 4 that the path analysis estimator of the indirect effect via each mediator \( M_s \) is identified by \( \beta_s \alpha_s \). The values of the coefficients were \( \alpha_{01} = 3, \alpha_{02} = 2, \alpha_{03} = 1, \alpha_{04} = 0, \alpha_1 = 1.2, \alpha_2 = 27 \)
1.6, \alpha_3 = 2, \alpha_4 = 2.4, \alpha_{C1} = \ldots = \alpha_{C4} = 1, \beta_0 = 1.6, \beta_A = 0.4, \beta_1 = 0.6, \beta_2 = 1.2, \beta_3 = 0.6, \beta_4 = 0, \sigma_Y = 1, \text{ and } \Sigma_{ss'} = 1 \text{ if } s = s' \text{ and } 0.85 \text{ otherwise, } s, s' = 1, \ldots, 4. \text{ Average biases and empirical standard errors over 20000 simulated datasets of size 400 are displayed below.}

Table 6: Average estimates ("mean") and empirical standard errors ("ese") of the path analysis estimators of each interventional effect in simulation study 3.

| truth | mean | ese  |
|-------|------|------|
| \theta_0 | 0.40 | 0.40 | 0.19 |
| \theta_1 | 0.72 | 0.72 | 0.15 |
| \theta_2 | 1.92 | 1.92 | 0.23 |
| \theta_3 | 1.20 | 1.20 | 0.24 |
| \theta_4 | 0.00 | 0.00 | 0.27 |

6 Application

The proposed estimation procedure is illustrated using a publicly-available data set from an observational study exploring the relationship between children’s weight and behavior. The data set “weight_behavior” is distributed as part of the mma package [Yu and Li, 2017] via the Comprehensive R Archive Network [https://CRAN.R-project.org/package=mma].

The data was collected by Dr. Richard Scribner from the Louisiana State University Health Sciences Center through a survey of children, teachers and parents in Grenada in 2014, with 691 observations and 15 variables. However, we only consider an amended version of this
data set with 539 observations after removing all missing and erroneous values; in practice, we recommend adjusting for missing data using multiple imputation or inverse probability weighting (Carpenter et al., 2006; Vansteelandt et al., 2010; Seaman et al., 2012).

Following Yu and Li (2017), we will assess the effect of gender \( (A) \) on BMI \( (Y) \), possibly mediated by seven behavior variables: number of hours watching TV each week \( (M_1) \), number of hours using a computer each week \( (M_2) \), number of hours playing with a cell phone each week \( (M_3) \), number of hours of exercises each week \( (M_4) \), number of hours doing sweat-producing activities each week \( (M_5) \), whether or not the child participated in a sports team \( (M_6) \), and whether or not the child had a daily snack \( (M_7) \). With the exception of the binary mediators \( M_6 \) and \( M_7 \), we will assume the remaining mediators to be continuous for the purposes of illustrating the proposed estimation procedure. Scatterplots of the mediators \( M_1, \ldots, M_5 \), and the outcome \( Y \), and the pairwise correlations, are shown in Figure 4.

The remaining family background variables in the data set (age, number of cars in the family, the mode of transportation for going to school, the number of people in the family, and race) are assumed to be baseline covariates \( C \) that are unaffected by treatment, mediators or outcome. We will assume that the observed covariates in \( C \) are sufficient for the identification assumptions 1–3 to hold. The direct effect of gender not through the mediating behaviors is interpreted as the average difference in BMI between female and male children if the mediating behaviors of the females are set equal to that of the males (e.g., by setting the behavior for each female to a random draw from the joint counterfactual distribution for males). Similarly, the (joint) indirect effect is interpreted as how BMI for females would change on average if the counterfactual distribution of the mediating behavior(s) is(are) shifted from that of the females to that of the males. The
effect models (9) and (10) are used to assess the interventional direct and indirect effects. The following (generalized) linear models for the (conditional) means of the mediators and the outcome are assumed:

\[
E(M_1 | A, C) = \alpha_{01} + \alpha_1 A + \alpha_C C;
\]

\[
E(M_s | M_1, \ldots, M_{s-1}, A, C) = \alpha_{0s} + \alpha_s A + \sum_{r=1}^{s-1} (\eta_{rs} + \eta_{rSA} A) M_r
+ \sum_{r,r' = 1 \atop r < r'} (\eta_{rr's} + \eta_{rr'sA} A) M_r M_{r'} + \alpha_C s C, \ s = 2, \ldots, 5;
\]

\[
E(M_s | M_1, \ldots, M_{s-1}, A, C) = \text{expit} \left( \alpha_{0s} + \alpha_s A + \sum_{r=1}^{s-1} (\eta_{rs} + \eta_{rSA} A) M_r
+ \sum_{r,r' = 1 \atop r < r'} (\eta_{rr's} + \eta_{rr'sA} A) M_r M_{r'} + \alpha_C s C \right), \ s = 6, 7;
\]

\[
E(Y | A, M_1, \ldots, M_7, C) = \beta_0 + \beta A + \sum_{s=1}^{7} (\beta_s + \beta_s A) M_s
+ \sum_{s,s' = 1 \atop s < s'} (\beta_{ss'} + \beta_{ss'A} A) M_s M_{s'} + \beta_C C
\]

The link function in (16) is defined as \(\text{expit}(z) = \exp(z) / 1 + \exp(z)\). The (second-order) interaction terms between the mediators, and the (second and third-order) interaction terms between the treatment and the mediators, are included in the fitted models to allow for an indirect effect via the joint dependence of the mediators (Vansteelandt and Daniel, 2017). The marginal mean model \(E(M_s | A, C) = \alpha'_{0s} + \alpha'_s A + \alpha'_{Cs} C, s = 2, \ldots, 5\), can be obtained by averaging over the other mediators in the linear conditional mean model (15). The potential outcomes for \(M_1, \ldots, M_5\) are then sampled from a normal distribution...
with the aforementioned marginal mean, while the potential outcomes for \( M_6 \) and \( M_7 \) are sampled from a Bernoulli distribution with conditional mean (16). 10000 Monte Carlo samples are used to estimate the parameters in the effect models; standard errors were calculated using 1000 bootstrap samples. The estimated effects are shown in Table 7. The estimated interventional indirect effect via sport participation (\( M_6 \)) can be interpreted as the estimated average increase in BMI for females being \( 0.165 (95\% \text{ CI} = (0.02, 0.34)) \) if the counterfactual distribution of sport participation is shifted from that of the females to that of the males. Similarly the interventional direct effect is interpreted as female children having a higher BMI than male children by \( 1.163 (95\% \text{ CI} = (0.30, 1.94)) \) if the mediating behaviors of the females are set equal to that of the males.

7 Discussion

In behavioral, medical, social sciences and other settings, mediation analysis involves multiple mediators when interest is in decomposing the total effect of a treatment on an outcome into a direct effect and separate indirect effects on causal pathways via different mediators. Even when interest is in a single mediator, confounders of the mediator-outcome association that are affected by treatment may concurrently be perceived as competing mediators, thus requiring methods for multiple mediators to disentangle the effects via the mediator and via the confounders. Decomposing the total effect into multiple separate path-specific effects requires strong untestable assumptions about the causal structure of the mediators, and about the absence of hidden common causes of all mediators. Furthermore, when there are many mediators, scientific interest is often in the effects that are mediated through each distinct mediator, and seldom in each separate path-specific effect.
| Interventional effect                     | Parameter | Estimate | Bootstrap SE | 95% CI      |
|-----------------------------------------|-----------|----------|--------------|-------------|
| Direct effect                           | $\gamma_0$ | 1.163    | 0.46         | (0.30, 1.94) |
| Joint indirect effect                   | $\gamma_1$ | 0.152    | 0.35         | (-0.36, 0.73) |
| Indirect effect via $M_1$ (TV)          | $\theta_1$ | 0.009    | 0.04         | (-0.07, 0.09) |
| Indirect effect via $M_2$ (computer)    | $\theta_2$ | 0.014    | 0.04         | (-0.07, 0.09) |
| Indirect effect via $M_3$ (cell phone)  | $\theta_3$ | 0.023    | 0.04         | (-0.05, 0.10) |
| Indirect effect via $M_4$ (exercise)    | $\theta_4$ | -0.034   | 0.06         | (-0.17, 0.07) |
| Indirect effect via $M_5$ (sweat)       | $\theta_5$ | 0.032    | 0.05         | (-0.07, 0.14) |
| Indirect effect via $M_6$ (sport)       | $\theta_6$ | 0.165    | 0.08         | (0.02, 0.34)  |
| Indirect effect via $M_7$ (snack)       | $\theta_7$ | -0.027   | 0.34         | (-0.35, 0.51) |
| Indirect effect via mutual dependence   | $\gamma_1 - \sum_{s=1}^{7} \theta_s$ | -0.030   | 0.19         | (-0.39, 0.30) |

In this paper we adapted the definition of interventional effects by [Vansteelandt and Daniel (2017)](Vansteelandt2017) that exactly decompose the total effect, and presented indirect effects that are identical to those in [Vansteelandt and Daniel (2017)](Vansteelandt2017) when there are two mediators, but have a simpler interpretation when there are more than two mediators. We proposed interventional effect models that directly parameterize the direct and indirect effects through each distinct mediator, even when the directions of the causal effects between the mediators are unknown, or the mediators are manifestations of an underlying latent process, or the mediators share hidden common causes. The mediators and outcome can be continuous
or noncontinuous. Estimation proceeds via a Monte Carlo-based regression approach and only requires specifying a joint distribution of the mediators and an outcome model. Under a certain class of linear models, we proposed path analysis estimators of the interventional effects that are robust to misspecification of the causal structure of the mediators in the assumed path analysis model.

There are several avenues of possible future research related to mediation analyses with multiple mediators using interventional effects developed in this paper. While only main effects for the treatments are included in the effect models (9) and (10), the effect models can in general include interactions between the treatments when the (in)direct effects differ for different subpopulations. The duplicated data required for estimation can then be constructed using the strategy described in Section 3.2. For example, the saturated effect models for a binary treatment and three mediators are stated in Appendix C and the corresponding duplicated data displayed in Table 8. In principle, for a binary treatment, the duplicated data can always include all possible combinations of the hypothetical treatments, regardless of the posited effect models. However, the imputed potential outcomes may require extrapolations from the fitted mediator and outcome models, yielding biased and/or inefficient estimators. Future work could be in determining the minimal number of rows, and the hypothetical treatment levels, in the duplicated data that are sufficient to ensure identifiability of the parameters in the given effect models, using e.g., the D-optimality criterion in regression designs (John and Draper, 1975). Building on the empirical results in this paper, future research may be in examining theoretical properties of different flexible outcome models used for imputing the potential outcomes. Since unbiased estimation is contingent on the choice of outcome model, possible extensions include formalizing sufficient and/or necessary conditions for congeniality of an assumed outcome
model with a posited effect model. The proposed Monte Carlo-based regression methods may be extended to nonlinear and/or nonadditive effect models, but may require separate outcome models for each effect model to avoid uncongeniality. Assessing whether the parameters in the effect models are variation-independent, e.g., whether all possible values of the parameters in $M^1$ are compatible with all possible values of the parameters in $M^2$, and when such a property is possible or desirable, might also be considered. Another possible extension is to derive double-robust estimators of the parameters in the effects models that are consistent for the interventional effects when the effect models hold and, in addition, either the outcome mean model (given the treatment, mediators and confounders) is correctly specified; or both the joint distribution of the mediators (given the treatment and confounders) and the propensity score model for the exposure (given the confounders), are correctly specified. This double robustness is theoretically appealing because it implies that any misspecification bias arising from an outcome model that is uncongenial with the effect model may be eliminated when the joint mediator distribution and propensity score model for the exposure are both correctly specified.
Figure 4: Scatterplot (upper panels) and correlations (lower panels) between the mediators $M_1, \ldots, M_5$ and the outcome $Y$ for female (top) and male (bottom) observations. Random uniform jitter has been added to the points in the scatterplots.
A Identification of the direct effect in the interventional effect models

Suppose that the controlled direct effect is some function of $C$, e.g., $E(Y_{1m_1\cdots m_t}|C) - E(Y_{0m_1\cdots m_t}|C) = \delta(C), \forall m_1, \ldots, m_t$. Then the interventional direct effect is identified by $E[\delta(C)]$ in both effect models, since:

$$E(\{Y_{\{a(1)\}}\}) - E(\{Y_{\{0a(1)\}}\})$$

$$= E \left[ \sum_{m_1,\ldots,m_t} \{E(Y|A = 1, M_1 = m_1, \ldots, M_t = m_t, C) - E(Y|A = 0, M_1 = m_1, \ldots, M_t = m_t, C)\} \right]$$

$$\times \Pr(M_1 = m_1, \ldots, M_t = m_t|A = a^{(1)}, C)$$

$$= E \left[ \delta(C) \sum_{m_1,\ldots,m_t} \Pr(M_1 = m_1, \ldots, M_t = m_t|A = a^{(1)}, C) \right]$$

$$= E[\delta(C)];$$
similarly,

\[ E\left( Y_{1a(t)} \cdots a(t) \right) - E\left( Y_{0a(t)} \cdots a(t) \right) \]

\[ = E \left[ \sum_{m_1, \ldots, m_t} \{ E(Y|A = 1, M_1 = m_1, \ldots, M_t = m_t, C) - E(Y|A = 0, M_1 = m_1, \ldots, M_t = m_t, C) \} \right] \]

\[ \times \prod_{s=1}^{t} \Pr(M_s = m_s|A = a^{(1)}, C) \]

\[ = E \left[ \delta(C) \prod_{s=1}^{t} \sum_{m_s} \Pr(M_s = m_s|A = a^{(1)}, C) \right] \]

\[ = E[\delta(C)]. \]

B Identification results assuming linear mean models with no interactions

Suppose that the outcome obeys the mean model (12), which is restated here as:

\[ E(Y|A, M_1, \ldots, M_t, C) = \beta_0 + \beta_A A + \sum_{s=1}^{t} \beta_s M_s + \beta_C C. \]

The average potential outcome \( E(Y_{a(0)}|a^{(1)}) \), where the mediators are set to random draws from the joint counterfactual distribution, is identified upon plugging the assumed outcome model (12) and mediator distributions into the expressions in Section 2.2.
\[
E(Y_{a^{(0)}}|a^{(1)})
= E \left[ \sum_{m_1, \ldots, m_t} E(Y|A = a^{(0)}, M_1 = m_1, \ldots, M_t = m_t, C) \Pr(M_1 = m_1, \ldots, M_t = m_t|A = a^{(1)}, C) \right]
\]

\[
= E \left[ \sum_{m_1, \ldots, m_t} \left\{ \beta_0 + \beta_A a^{(0)} + \sum_{s=1}^{t} \beta_s m_s + \beta_C C \right\} \Pr(M_1 = m_1, \ldots, M_t = m_t|A = a^{(1)}, C) \right]
\]

\[
= E \left[ \left\{ \beta_0 + \beta_A a^{(0)} + \beta_C C \right\} \sum_{m_1, \ldots, m_t} \Pr(M_1 = m_1, \ldots, M_t = m_t|A = a^{(1)}, C) \right] + \sum_{m_1, \ldots, m_t} \sum_{s=1}^{t} \beta_s m_s \Pr(M_1 = m_1, \ldots, M_t = m_t|A = a^{(1)}, C)
\]

\[
= E \left[ \left\{ \beta_0 + \beta_A a^{(0)} + \beta_C C \right\} + \sum_{s=1}^{t} \beta_s \sum_{m_s} \sum_{j=1, j\neq s}^{t} \sum_{m_j} \Pr(M_1 = m_1, \ldots, M_t = m_t|A = a^{(1)}, C) \right] \Pr(M_s = m_s|A = a^{(s)}, C)
\]

\[
= E \left[ \left\{ \beta_0 + \beta_A a^{(0)} + \beta_C C \right\} \sum_{s=1}^{t} \beta_s E(M_s|A = a^{(1)}, C) \right].
\]

Similarly, the average potential outcome where the mediators are set to random draws
from the respective marginal counterfactual distributions is identified by:

\[
E(Y_{a^{(i)}}) = E \left( \sum_{m_1, \ldots, m_t} \Pr(M_j = m_j | A = a^{(j)}, C) \prod_{j=1}^t \Pr(M_j = m_j | A = a^{(j)}, C) \right)
\]

Suppose that the mediators are causally connected and ordered, without loss of generality, so that \( M_1, \ldots, M_{s-1} \) causally precede \( M_s, s = 2, \ldots, t \), and no mediators precede \( M_1 \). Assume that each mediator obeys the linear and additive (conditional) mean model:

\[
E(M_s | M_1, \ldots, M_{s-1}, A, C) = \alpha_0s + \alpha_s A + \sum_{r=1}^{s-1} \eta_{rs} M_r + \alpha_{Cs} C, \quad s = 1, \ldots, t, \quad (18)
\]

where \( \eta_{rs} = 0 \) if \( r \geq s \). The parameters \( \alpha_0s \) and \( \alpha_{Cs} \) encode the intercept and coefficient(s) for the baseline covariate(s) respectively; the direct effect of \( A \) on \( M_s \) is encoded by \( \alpha_s \).

To show that certain combined path-specific effects are equivalent to the interventional indirect effects, we first express the interventional effects in terms of the parameters in
the (conditional) mean models (18), then demonstrate that the resulting expression is equivalent to the combined path-specific effects using the product-of-coefficients method.

For \( s = 1 \), the parameters in the (marginal) mean model (13) are equivalent to the parameters in the (conditional) mean model (18), i.e., \( \delta_{01} = \alpha_{01}, \delta_{C1} = \alpha_{C1}, \delta_1 = \alpha_1 \). For \( s = 2, \ldots, t \), the parameters in (13) can be expressed in terms of the parameters in (18) by averaging over the distributions for \( M_1, \ldots, M_{s-1} \); i.e.,

\[
E(M_s|A, C) = \alpha_{0s} + \alpha_s A + \sum_{r=1}^{s-1} \eta_{rs} E(M_r|A, C) + \alpha_{Cs} C.
\]

In particular, by grouping the coefficients of \( A \), the (marginal) effect of treatment on the mediator \( M_s \) is \( \delta_s = \alpha_s + \sum_{r=1}^{s-1} \delta_r \eta_{rs} \), which can be further expressed only in terms of the coefficients in (18), \( \alpha_r, r = 1, \ldots, s \), and \( \eta_{rs'}, r, s' = 1, \ldots, s, r < s' \). For example,

\[
\begin{align*}
\delta_1 &= \alpha_1, \\
\delta_2 &= \alpha_2 + \delta_1 \eta_{12} = \alpha_2 + \alpha_1 \eta_{12}, \\
\delta_3 &= \alpha_3 + \delta_1 \eta_{13} + \delta_2 \eta_{23} = \alpha_3 + \alpha_2 \eta_{23} + \alpha_1 (\eta_{13} + \eta_{12} \eta_{23}).
\end{align*}
\]

Deriving the closed-form expression for \( \delta_s \) in general requires first introducing some notation. For \( r = 1, \ldots, s - 1 \), let \( \langle r, s \rangle \) denote the set of all \( 2^{s-r-1} \) (ordered) unique subsets of the integers \( (r, r+1, \ldots, s-1, s) \) that include \( r \) as the smallest integer and \( s \) as the largest integer. Let \( \mathcal{I}^{r,s} = (i_{0}^{r,s}, i_{1}^{r,s}, \ldots, i_{l}^{r,s}, i_{l+1}^{r,s}) \) be a subset of \( \langle r, s \rangle \) where \( r = i_{0}^{r,s} < i_{1}^{r,s} < \ldots < i_{l}^{r,s} < i_{l+1}^{r,s} = s \). For example, \( \langle 1,3 \rangle \) comprises both \( (1,2,3) \) and \( (1,3) \), whereas \( \langle 2,3 \rangle \) contains only \( (2,3) \). By iteratively substituting \( \delta_r, r = 1, \ldots, s - 1 \) into \( \delta_s = \alpha_s + \sum_{r=1}^{s-1} \delta_r \eta_{rs} \), and grouping the terms for \( \alpha_r, r = 1, \ldots, s - 1 \), the coefficient of \( A \) in the marginal mean model for \( M_s \) in (13) is:

\[
\delta_s = \alpha_s + \sum_{r=1}^{s-1} \alpha_r \sum_{\mathcal{I}^{r,s} \subseteq \langle r, s \rangle} \prod_{k=0}^{l} \eta_{k+1}^{r,s} \eta_{k+1}^{r,s}.
\]
The interventional indirect effect via mediator $M_s$ is thus identified by $\beta_s \delta_s$, where $\delta_s$ takes the form of (19).

Now consider a path analysis model with the linear and additive mean models for the outcome and mediators in (12) and (18) respectively. The coefficient for the edge from $A$ to $M_s$ is parametrized by $\alpha_s$, the coefficient for the edge from $M_r$ to $M_s$ is parametrized by $\eta_{rs}, r = 1, \ldots, s - 1$, and the edge from $M_s$ to $Y$ is parametrized by $\beta_s$. For $i^{r,s} = (i_0^{r,s}, i_1^{r,s}, \ldots, i_{l+1}^{r,s})$ as defined above, where $i_0^{r,s} = r, i_{l+1}^{r,s} = s$, consider the path $A \rightarrow M_r \rightarrow M_{i_1^{r,s}} \rightarrow \ldots \rightarrow M_{i_{l+1}^{r,s}} \rightarrow M_s$. Using the product-of-coefficients method, the path-specific effect of $A$ on $M_s$ for this particular path is $\alpha_r \prod_{k=0}^{l} \eta^{r,s}_{k+1}$. The sum of all path-specific effects for the paths that contribute to the effect of $A$ on $M_s$ is thus:

$$\delta_s = \alpha_s + \sum_{r=1}^{s-1} \alpha_r \sum_{i^{r,s} \in \langle r, s \rangle} \prod_{k=0}^{l} \eta^{r,s}_{k+1},$$

which is equivalent to the expression in (19). There are $2^{s-r-1}$ unique subsets in $\langle r, s \rangle$, so that the number of paths from $A$ to $M_s$, excluding the edge directly from $A$ to $M_s$, is $\sum_{r=1}^{s-1} 2^{s-r-1} = 2^{s-2} - 1$. There are thus $2^{s-1}$ paths that contribute to the combined effect of $A$ on $M_s$, and a single path from $M_s$ to $Y$. It follows that the combined path-specific effect is $\beta_s \delta_s$, which is equivalent to the interventional indirect effect. The interventional indirect effect via the mediator $M_s, s = 1, \ldots, t$, thus captures the combined effect along all $2^{s-1}$ paths from $A$ to $Y$ that intersect $M_s$ (and may intersect any of its causal ancestors $M_1, \ldots, M_{s-1}$) then lead directly to $Y$, while avoiding all of $M_{s+1}, \ldots, M_t$.  


C  Saturated effect models for three mediators

\[ M^1 : \quad g \{ E \{ Y_{a(0)}(t) \} \} = \mu_{01} + \gamma_0 a^{(0)} + \gamma_1 a^{(1)} + \gamma_{01} a^{(0)} a^{(1)}, \quad (20) \]

\[ M^2 : \quad g \{ E \{ Y_{a(t)} \} \} = \mu_{02} + \theta_0 a^{(0)} + \theta_1 a^{(1)} + \theta_2 a^{(2)} + \theta_3 a^{(3)} \\
\quad + \theta_{01} a^{(0)} a^{(1)} + \theta_{02} a^{(0)} a^{(2)} + \theta_{03} a^{(0)} a^{(3)} + \theta_{12} a^{(1)} a^{(2)} + \theta_{13} a^{(1)} a^{(3)} + \theta_{23} a^{(2)} a^{(3)} \\
\quad + \theta_{012} a^{(0)} a^{(1)} a^{(2)} + \theta_{013} a^{(0)} a^{(1)} a^{(3)} + \theta_{023} a^{(0)} a^{(2)} a^{(3)} + \theta_{123} a^{(1)} a^{(2)} a^{(3)} + \theta_{0123} a^{(0)} a^{(1)} a^{(2)} a^{(3)}. \quad (21) \]

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Table 8: Duplicated data for each individual, with 16 rows for a binary treatment $A$, for estimating the parameters in the saturated effect model \((21)\) when there are three mediators. The asterisk denotes a sampled potential outcome used in place of an observed potential outcome.

| Score vector | $a^{(0)}$ | $a^{(1)}$ | $a^{(2)}$ | $a^{(3)}$ | $\tilde{M}_{1a^{(1)}|C}$ | $\tilde{M}_{2a^{(2)}|C}$ | $\tilde{M}_{3a^{(3)}|C}$ | $E(Y_{a^{(0)}})$ |
|--------------|-----------|-----------|-----------|-----------|----------------|----------------|----------------|----------------|
| 1            | A         | A         | A         | A         | $M_1^*$        | $M_2^*$        | $M_3$          | $h(a = A, m_1 = M_1^*, m_2 = M_2^*, m_3 = M_3, c = C)$ |
| $a^{(0)}$    | 1 - A     | A         | A         | A         | $M_1^*$        | $M_2^*$        | $M_3$          | $h(a = 1 - A, m_1 = M_1^*, m_2 = M_2^*, m_3 = M_3, c = C)$ |
| $a^{(1)}$    | A         | 1 - A     | A         | A         | $M_{1,1-A}$    | $M_2^*$        | $M_3$          | $h(a = A, m_1 = M_{1,1-A}, m_2 = M_2^*, m_3 = M_3, c = C)$ |
| $a^{(2)}$    | A         | A         | 1 - A     | A         | $M_1^*$        | $M_{2,1-A}$    | $M_3$          | $h(a = A, m_1 = M_1^*, m_2 = M_{2,1-A}, m_3 = M_3, c = C)$ |
| $a^{(3)}$    | A         | A         | A         | 1 - A     | $M_1^*$        | $M_2$          | $M_{3,1-A}$    | $h(a = A, m_1 = M_1^*, m_2 = M_2, m_3 = M_{3,1-A}, c = C)$ |
| $a^{(0)}a^{(1)}$ | 1 - A     | 1 - A     | A         | A         | $M_{1,1-A}$    | $M_2^*$        | $M_3$          | $h(a = 1 - A, m_1 = M_{1,1-A}, m_2 = M_2^*, m_3 = M_3, c = C)$ |
| $a^{(0)}a^{(2)}$ | 1 - A     | A         | 1 - A     | A         | $M_1^*$        | $M_{2,1-A}$    | $M_3$          | $h(a = 1 - A, m_1 = M_1^*, m_2 = M_{2,1-A}, m_3 = M_3, c = C)$ |
| $a^{(0)}a^{(3)}$ | 1 - A     | A         | A         | 1 - A     | $M_1^*$        | $M_2$          | $M_{3,1-A}$    | $h(a = 1 - A, m_1 = M_1^*, m_2 = M_2, m_3 = M_{3,1-A}, c = C)$ |
| $a^{(1)}a^{(2)}$ | A         | 1 - A     | 1 - A     | A         | $M_{1,1-A}$    | $M_{2,1-A}$    | $M_3$          | $h(a = A, m_1 = M_{1,1-A}, m_2 = M_{2,1-A}, m_3 = M_3, c = C)$ |
| $a^{(1)}a^{(3)}$ | A         | 1 - A     | A         | 1 - A     | $M_{1,1-A}$    | $M_2$          | $M_{3,1-A}$    | $h(a = A, m_1 = M_{1,1-A}, m_2 = M_2, m_3 = M_{3,1-A}, c = C)$ |
| $a^{(2)}a^{(3)}$ | A         | A         | 1 - A     | 1 - A     | $M_{1,1-A}$    | $M_{2,1-A}$    | $M_{3,1-A}$    | $h(a = A, m_1 = M_{1,1-A}, m_2 = M_{2,1-A}, m_3 = M_{3,1-A}, c = C)$ |
| $a^{(0)}a^{(1)}a^{(2)}$ | 1 - A     | 1 - A     | 1 - A     | A         | $M_{1,1-A}$    | $M_{2,1-A}$    | $M_3$          | $h(a = 1 - A, m_1 = M_{1,1-A}, m_2 = M_{2,1-A}, m_3 = M_3, c = C)$ |
| $a^{(0)}a^{(1)}a^{(3)}$ | 1 - A     | 1 - A     | A         | 1 - A     | $M_{1,1-A}$    | $M_2$          | $M_{3,1-A}$    | $h(a = 1 - A, m_1 = M_{1,1-A}, m_2 = M_2, m_3 = M_{3,1-A}, c = C)$ |
| $a^{(1)}a^{(2)}a^{(3)}$ | A         | 1 - A     | A         | 1 - A     | $M_{1,1-A}$    | $M_{2,1-A}$    | $M_{3,1-A}$    | $h(a = A, m_1 = M_{1,1-A}, m_2 = M_{2,1-A}, m_3 = M_{3,1-A}, c = C)$ |