General approach of causal mediation analysis with causally ordered multiple mediators and survival outcome

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Summary

Causal mediation analysis with multiple mediators (causal multi-mediation analysis) is critical in understanding why an intervention works, especially in medical research. Deriving the path-specific effects (PSEs) of exposure on the outcome through a certain set of mediators can detail the causal mechanism of interest. However, the existing models of causal multi-mediation analysis are usually restricted to partial decomposition, which can only evaluate the cumulative effect of several paths. Moreover, the general form of PSEs for an arbitrary number of mediators has not been proposed. In this study, we provide a generalized definition of PSE for partial decomposition (partPSE) and for complete decomposition, which are extended to the survival outcome. We apply the interventional analogues of PSE (iPSE) for complete decomposition to address the difficulty of non-identifiability. Based on Aalen's additive hazards model and Cox's proportional hazards model, we derive the generalized analytic forms and illustrate asymptotic property for both iPSEs and partPSEs for survival outcome. The simulation is conducted to evaluate the performance of estimation in several scenarios. We apply the new methodology to investigate the mechanism of methylation signals on mortality mediated through the expression of three nested genes among lung cancer patients.

1. Introduction

Causal mediation analysis in the presence of multiple mediators (termed as "causal multi-mediation analysis" throughout this article) is one of the most powerful methods to investigate the detailed mechanism of a confirmed causal effect. To explicitly describe the detailed compositions of this causal mechanism, Avin et al. proposed path-specific effects (PSEs) based on a counterfactual framework to quantify pathways comprised of mediators of interest (Avin*, et al.*, 2005). However, most PSEs cannot be nonparametrically identified (Daniel*, et al.*, 2015). Several methods have been proposed to address the difficulty of non-identifiability, which are summarized in Figure 1. In settings with K mediators, we categorize the existing approaches into three groups according to the number of paths to be decomposed: (1) Two-way decomposition; (2) Partial decomposition; and (3) Complete decomposition. Two-way decomposition treats all mediators as one unit and decomposes total effect (TE) into the natural direct and indirect effects rather than detailed PSEs (Fasanelli*, et al.*, 2019; VanderWeele and Vansteelandt, 2014). Partial decomposition decomposes natural indirect effects into K (or K+1) paths through each distinct mediator, and can be further categorized into three subgroups according to different assumptions of causal structure among mediators: (2.1) partial parallel decomposition, (2.2) partial sequential decomposition, and (2.3) partial unstructured decomposition. Specifically, partial parallel decomposition assumes that the multiple mediators are not affected by each other (Taguri*, et al.*, 2015; Wang*, et al.*, 2013). Partial sequential decomposition assumes that mediators are causally ordered (Steen*, et al.*, 2017; Vanderweele*, et al.*, 2014). Partial unstructured decomposition does not assume the structure among mediators and decomposes the joint indirect effect into K separate indirect effect through each mediator and one indirect effect through the dependence among mediators (Loh*, et al.*, 2019; Moreno-Betancur*, et al.*, 2019; Vansteelandt and Daniel, 2017). However, the character of an undefined structure causes that partial unstructured decomposition cannot explicitly identify the paths of interest in general, which leads to the difficulty of interpreting the causal mechanism. Complete decomposition (also termed full or finest decomposition) decomposes TE into all 2^K PSEs, most of which are unidentified. Two choices are available: (3.1) sensitivity analysis approach and (3.2) complete interventional approach. Sensitivity analysis approach evaluates the boundary of PSE (Albert*, et al.*, 2019; Daniel*, et al.*, 2015), while interventional approach proposed a randomized interventional analogues of PSE (iPSE) (Lin and VanderWeele, 2017). The typical interventional approach has been widely used for settings with one mediator (Didelez*, et al.*, 2012; Geneletti, 2007; Vanderweele*, et al.*, 2014), time-varying mediators (Lin*, et al.*, 2017; Lin*, et al.*, 2017; VanderWeele and Tchetgen

Tchetgen, 2017; Zheng and van der Laan, 2012), and multiple mediator with partial decomposition (Moreno-Betancur*, et al.*, 2019; Vansteelandt and Daniel, 2017).

In terms of the survival framework, the method involving one mediator was first proposed by Lange and Hansen based on additive hazard model (Lange and Hansen, 2011). VanderWeele extended Lange and Hansen's approach using both the Cox's proportional hazards model and the accelerated failure time model with a rare disease assumption (VanderWeele, 2011), while Tchetgen and Shpitser proposed a more general semiparametric approach (Tchetgen and Shpitser, 2012). Several methods have been proposed for scenarios with two or three causally ordered multiple mediators (Cho and Huang, 2019; Fasanelli*, et al.*, 2019; Huang and Yang, 2017; Huang and Cai, 2015; Yu*, et al.*, 2019). Although these studies specifically derived the analytic form of PSEs for survival outcome, two issues have not been fully addressed yet. First, due to the exponential increase in the number of PSEs along with the number of mediators, the existing methods only allow a small number of mediators (Figure1). A general form of PSE with an arbitrary number of mediators is necessary for a wide application in general cases. Second, the existing approaches for survival outcome mainly focus on partial decomposition which only estimates the cumulative effect of several paths. A complete decomposition of each path is necessary for the comprehensive understanding of the causal mechanism. Furthermore, the existing methods need to assume no time-varying confounders, which restricts the utility of these methods on longitudinal data.

To address the issues mentioned above, this study proposes a generalized framework for causal multi-mediation analysis via both partial sequential decomposition and complete interventional approach, especially for the survival outcome. For simplicity, we name partial sequential decomposition as partial decomposition approach and name complete interventional approach as interventional approach in the following paragraphs and sections. There are two contributions in this study. First, we propose comprehensive definitions of partial decomposition and interventional approaches, under which a generalized form of PSE with an arbitrary number of mediators has been provided. Second, we extend partial decomposition and interventional approaches into the context of survival analysis. We demonstrate the mediation parameters of interest perform a g-formula while mediators are weighted by a normally distributed variable when all mediators are continuous and normally distributed. The parameters can be viewed as a general form of a series of previous works in this topic (Cho and Huang, 2019; Huang and Yang, 2017; VanderWeele, 2011; Yu*, et al.*, 2019).

The remainder of this paper is organized as follows. In Section 2, we introduce notations and definition for causal multi-mediation analysis under partial decomposition and interventional approaches for the setting with an arbitrary number of mediators and any types of outcomes. In Section 3, we derive the estimators in terms of survival analysis by using Aalen's additive hazards model and Cox's proportional hazards model. In Section 4, we demonstrate the asymptotic properties. In Section 5, we provide the simulation results in different scenarios to demonstrate the performance of estimation. In Section 6, we illustrate an application to investigate the mechanism of methylation signals on mortality through the transcriptional activity of several genes which are nested to each other. We discuss the strength and limitations in Section 7.

2. Generalized framework of causal multi-mediation analysis

In this section, we first provide the generalized definition of PSEs for any types of outcome variables. Since PSEs cannot be nonparametrically identified, interventional approach for completely decomposing all PSEs and partial decomposition approach without changing the PSE definition are used to address this issue. The corresponding identification processes and the required assumptions will also be demonstrated.

2.1. Notation, parameter of interest in ordered multiple mediators, and difficulties

To simplify the notation, we denote $V_{(i_1,i_2)} = \left(V_{i_1}, V_{i_1+1}, \dots, V_{i_2}\right)$ as a subvector of a vector V where i_1 and i_2 are two nonnegative integers satisfied $i_1 < i_2$; we further define $V_{(i_1,i_2)} = v_i$ for $i_1 = i_2 = i$, and $V_{(i_1,i_2)} =$ a null vector for $i_1 > i_2$. Furthermore, we use $V_{(1:K;-i)}$ to denote $(V_1, , \dots, V_{i-1}, V_{i+1}, \dots, V_K)$. Let K denotes the number of mediators, A the exposure, $M = \left(M_{(1:K)}\right)$ the causally ordered mediators, Y the outcome, C_0 the baseline confounders, and $C = \left(C_{(1:K)}\right)$ the time-varying confounders. C_k represents the *k*-th confounders among the *k*-th mediator M_k and Y which occurs after and is potentially affected by M_{k-1} and the other previous variables for $k \in \{1,2, \dots, K\}$. The causal relationship among all variables is illustrated by a directed acyclic graph (DAG) in Figure 2.

In the counterfactual framework, $Y(a, m_{(1,K)})$ represents the counterfactual value of Y suppose $(A, M_{(1,K)})$ is set to $(a, m_{(1,K)})$. Let $M_k(a, m_{(1,k-1)})$ be the counterfactual value of M_k suppose $(A, M_{(1,k-1)})$ is set to $(a, m_{(1,k-1)})$ for $k \in \{1, 2, \dots, K\}$ (Robins, 1986). Furthermore, we assume consistency (Pearl, 2009; VanderWeele and Vansteelandt, 2009; VanderWeele, 2009), under which $Y\left(a, m_{(1,K)}\right)$ is equal to the observed Y if $(A, M_{(1,K)})$ is equal to $(a, m_{(1,K)})$ and $M_k(a, m_{(1,k-1)})$ is equal to the observed M_k if $(A, M_{(1,k-1)})$ is equal to $(a, m_{(1,k-1)})$ for $k \in \{1, 2, \dots, K\}$.

Since the number of PSEs increases exponentially ($= 2^K$) according to the involvement of $M_{(1,K)}$, a definition system is required for a generalized setting. We propose a comprehensive coding system for notation simplification and define PSEs. In the setting with K ordered mediators, a set of all paths is defined as

$$L = \{\, l_d = \big(I(M_1), \dots, I(M_K)\big) \mid$$
$$d = \sum_{k=1}^{K} I(M_k) \times 2^{k-1} + 1\,, I(M_k) \in \{0,1\} \text{ for } k = 1, \dots, K \,\},$$

where $I(M_k) = 1$ represents the path l_d passing through the k-th mediator, M_k. For simplicity, each path $l_d = \big(I(M_1), \dots, I(M_K)\big)$ in L is numbered as d, which is an integer converted by a one-to-one converted function (ξ), which is defined as $\xi\big(I(M_1), \dots, I(M_K)\big) = \sum_{k=1}^{K} I(M_k) \times 2^{k-1} + 1$. Each converted number (i.e. d) is specifically mapped to one path. On the basis of these converted numbers, PSE can be qualitatively defined as a function of the converted number as follows:

Definition 1 (Qualitative definition of Path-Specific Effect, $\mathrm{PSE}_K(d)$).
For K mediators, $\mathrm{PSE}_K(d)$ represents the path-specific effect with respect to the path $l_d = \big(I(M_1), \dots, I(M_K)\big)$, where $d \in \{1,2,3, \dots, 2^K\}$ and $I(M_k) = 1$ represents the path l_d passing through the k-th mediator, M_k.

In additional to the qualitative definition, the $\mathrm{PSE_K}(d)$ is needed to be quantitatively defined under counterfactual model. Before this, we must define "iterative counterfactual mediators" and "multi-mediation parameter" as *Definition 2* and *Definition 3*, respectively, for simplifying the notation.

Definition 2 (Iterative counterfactual mediators, $M_k^*(a_{(1,2^{k-1})})$).
For $k = 1$, $M_1^*(a_1) \equiv M_1(a_1)$, which is the counterfactual value of M_1 suppose $A = a_1$. For $k \in \{2, \dots, K\}$, let $M_k^*(a_{(1,2^{k-1})}) \equiv M_k(a_1, M_1^*(a_2), \dots, M_{k-1}^*(a_{(2^{k-2}+1,2^{k-1})}))$, which is the counterfactual value of M_k suppose $(A, M_{(1,k-1)})$ is set to $(a_1, M_1^*(a_2), \dots, M_{k-1}^*(a_{(2^{k-2}+1,2^{k-1})}))$. For any $k \in \{1, \dots, K\}$, M_k^* is a function of $a_{(1,2^{k-1})}$.

On the basis of *Definition 2*, we can further define multi-mediation parameter in a general form as *Definition 3*.

Definition 3. (Multi-mediation parameter $\vartheta_K\big(a_{(1,2^K)}|W_t\big)$)

$$\vartheta_K\left(a_{(1,2^K)}|W_t\right) \equiv E\left[W_t\left(Y\left(a_1, M_1^*(a_2), M_2^*(a_3,a_4), \dots, M_K^*\left(a_{(2^{K-1}+1,2^K)}\right)\right)\right)\right]$$

where $W_t(\cdot)$ is a transfer function.

Typically, we consider the identity function as the transfer function $(W_t(x) = x)$ in the case of studying time-independent outcome, and thus, the multi-mediation parameter in *Definition 3* is simplified as the expectation of the counterfactual outcome suppose that $\big(A, M_{(1,K)}\big)$ is set to $(a_1, M_1^*(a_2), M_2^*(a_3,a_4), \dots, M_K^*(a_{(2^{K-1}+1,2^K)}))$. Additionally, for survival outcome, the transfer function is specified as an indicator function with respect to the time variable t $\big(W_t(x) = I(x \geq t)\big)$, and subsequently, the

$\vartheta_K(a_{(1,2^K)}|W_t)$ can be rewritten as the survival function of the counterfactual outcome. Based on *Definitions 2* and *3*, we can use ϑ to quantitatively define PSE.

Definition 4. (Quantitative definition of PSE)

$$PSE_K(d, a_{(1:2^K;-d)}, a^*_{(1)}, a^*_{(0)}|Q, W_t)$$
$$\equiv Q(\vartheta_K([a_{(1:d-1)}, a^*_{(1)}, a_{(d+1:2^K)}]|W_t), \vartheta_K([a_{(1:d-1)}, a^*_{(0)}, a_{(d+1:2^K)}]|W_t)),$$

where $Q(\cdot)$ is a nonspecific comparative function.

In *Definition 4*, $PSE_K(d, a_{(1:2^K;-d)}, a^*_{(1)}, a^*_{(0)}|Q, W_t)$ is defined in terms of the change of ϑ_K by changing the value of a_d from $a^*_{(0)}$ to $a^*_{(1)}$ when all other variables are fixed as $a_{(1:2^K;-d)}$, and the definition of multi-mediation parameters guarantees that the influence of changing a_d reflects the effect of the exposure on the outcome through the *d*-th path. The interpretation of $PSE_K(d, a_{(1:2^K;-d)}, a^*_{(1)}, a^*_{(0)}|Q, W_t)$ is determined by $Q(x_1, x_2)$. For example, if *Y* is a binary variable and $W_t(x) = x$, three types of $Q(x_1, x_2)$ are commonly used in medical research:

(1) $Q(\mathrm{x}_1, \mathrm{x}_2) = (\mathrm{x}_1 - \mathrm{x}_2)$ for the risk difference scale,

(2) $Q(\mathrm{x}_1, \mathrm{x}_2) = \mathrm{x}_1/\mathrm{x}_2$ for the risk ratio scale, and

(3) $Q(\mathrm{x}_1, \mathrm{x}_2) = \frac{\mathrm{x}_1}{(1-\mathrm{x}_1)} / \frac{\mathrm{x}_2}{(1-\mathrm{x}_2)}$ for the odds ratio scale.

Furthermore, when *Y* is the survival time and $W_t(x) = I(x \geq t)$, the causal effect of interest is usually defined on the hazard function, and the corresponding comparative functions are formulated as

(4) $Q(\mathrm{x}_1(t), \mathrm{x}_2(t)) = \frac{-\frac{d\mathrm{x}_1(t)}{dt}}{\mathrm{x}_1(t)} / \frac{-\frac{d\mathrm{x}_2(t)}{dt}}{\mathrm{x}_2(t)} = \lambda_1(t)/\lambda_2(t)$ for the hazard ratio scale, and

(5) $Q(\mathrm{x}_1(t), \mathrm{x}_2(t)) = \frac{-\frac{d\mathrm{x}_1(t)}{dt}}{\mathrm{x}_1(t)} - \frac{-\frac{d\mathrm{x}_2(t)}{dt}}{\mathrm{x}_2(t)} = \lambda_1(t) - \lambda_2(t)$ for the hazard difference scale,

in which $\mathrm{x}_1(t)$ and $\mathrm{x}_2(t)$ are two survival functions, and $\lambda_1(t)$ and $\lambda_2(t)$ are the corresponding hazard functions. For simplicity, we use $Q(\mathrm{x}_1, \mathrm{x}_2) = (\mathrm{x}_1 - \mathrm{x}_2)$ throughout Section 2.

Although $a_{(1:2^K;-d)}$ can take any values in *Definition 4*, Denial et al. concluded that there are only $(2^K)!$ ways of decomposing the total effect into PSEs (Daniel*, et al.*, 2015). Following previous works (Lin and VanderWeele, 2017; Wang*, et al.*, 2013), we use one of the ways to specify PSE, and the expression is shown as follows:

Definition 5. (PSE for decomposition of TE).

$$PSE_K\left(d, a^*_{(1)}, a^*_{(0)}|W_t\right) \equiv \vartheta_K\left([\bar{a}^*_{(1)_d}, \bar{a}^*_{(0)_{2^K-d}}]|W_t\right) - \vartheta_K\left(\left[\bar{a}^*_{(1)_{d-1}}, \bar{a}^*_{(0)_{2^K-d+1}}\right]|W_t\right)$$

$$TE_K(a^*_{(1)}, a^*_{(0)}|W_t) \equiv \sum_{d=1}^{2^k} PSE_K\left(d, a^*_{(1)}, a^*_{(0)}|W_t\right)$$

where $\bar{a}^*_{(1)_i}$ and $\bar{a}^*_{(0)_i}$ represents a vector composed by $a^*_{(1)}$ and $a^*_{(0)}$ with length *i*, respectively. Here $TE_K(a^*_{(1)}, a^*_{(0)}|W_t)$ is equal to $E[W_t(Y(a^*_{(1)}))] - E[W_t(Y(a^*_{(0)}))]$ by consistency, which is the traditional counterfactual definition of the causal effect of *A* on *Y* with two levels $a^*_{(1)}$ and $a^*_{(0)}$.

Two issues merit to be noticed. First, if there is one mediator (i.e. K=1), $\mathrm{PSE}_2(1)$ and $\mathrm{PSE}_2(2)$ are exactly the same as natural direct effect and indirect effect, respectively, defined by Robins and Greenland (Robins and Greenland, 1992). Second, it is the same as the concept of PSE proposed by Avin (Avin*, et al.*, 2005), but we here propose a notation and framework which is suitable for the cases with any arbitrary number of ordered multiple mediators. However, as noted by Avin et al, $\vartheta_K\left(a_{(1,2^K)}|W_t\right)$ as well as most PSEs are not identifiable under conventional assumptions (Avin*, et al.*, 2005; Vanderweele*, et al.*, 2014). Two approaches are available to address this issue. First, we can use the interventional approach adopting an alternative definition instead of traditional PSE for effect decomposition. This definition has been widely used in natural direct and indirect effects with time-varying confounders (Lin*, et al.*, 2017; VanderWeele and Tchetgen Tchetgen, 2017; VanderWeele and Vansteelandt, 2014), and have been extended to the settings with ordered multiple mediators (Lin and VanderWeele, 2017). We will review this approach in Section 2.2. The second approach is to partially decompose the total effect into K+1 paths, instead completely decompose the total effect into 2^K PSE. This method is commonly adapted by researchers for two or three mediators. We will propose a general form for any arbitrary number of mediators in Section 2.3.

2.2. Approach 1: interventional approach based on randomized interventional analogue of path-specific effect (iPSE)

Before defining the iPSE, we must define "conditional iterative random draw of counterfactual mediators" and a "interventional multi-mediation parameter" in advance, as *Definition 2.a* and *Definition 3.a*.

Definition 2.a. (Conditional iterative random draw of counterfactual mediators, $G_k(a_{(1,2^{k-1})})$)
All definitions are conditional on baseline confounders C_0. $G_1(a_1)$ is a random draw of $M_1(a_1)$. $G_2(a_1,a_2)$ is a random draw of $M_2(a_1,G_1(a_2))$, which is the counterfactual value of M_2 suppose (A,M_1) is set to $(a_1,G_1(a_2))$. Consequently, for $k\in\{3,\dots,K\}$, let $G_k(a_{(1,2^{k-1})})$ be a random draw of $M_k(a_1,G_1(a_2),\dots,G_{k-1}(a_{(2^{k-2}+1,2^{k-1})}))$, which is the counterfactual value of M_k suppose $(A,M_{(1,k-1)})$ is set to $(a_1,G_1(a_2),\dots,G_{k-1}(a_{(2^{k-2}+1,2^{k-1})}))$. For any $k\in\{1,\dots,K\}$, G_k is a function of $a_{(1,2^{k-1})}$.

On the basis of *Definition 2.a*, we can further define multi-mediation parameters in an interventional form as *Definition 3.a.*

Definition 3.a. (Interventional multi-mediation parameter $\varphi_K\left(a_{(1,2^K)}|W_t\right)$)

$$\varphi_K\left(a_{(1,2^K)}|W_t\right)\equiv E\left[W_t(Y(a_1,G_1(a_2),G_2(a_3,a_4),\dots,G_K(a_{(2^{K-1}+1,2^K)})))\right].$$

Similar to *Definition 3*, the transfer function can be specified as the identity function for the time-independent outcome or the indicator function with respect to time t for survival outcome. As the result, the interventional multi-mediation parameter in *Definition 3.a* is the expectation of a transferred counterfactual outcome suppose that $\left(A, M_{(1,K)}\right)$ is set to $\left(a_1, G_1(a_2), G_2(a_3, a_4), \ldots, G_K(a_{(2^{K-1}+1,2^K)})\right)$. Next, we can use φ to define iPSE.

Definition 4.a. (Randomized interventional analogue of path-specific effect (iPSE))

$$iPSE(d, a_{(1:2^K;-d)}, a^*_{(1)}, a^*_{(0)}|Q, W_t)$$
$$\equiv Q(\varphi_K([a_{(1:d-1)}, a^*_{(1)}, a_{(d+1:2^K)}]|W_t), \varphi_K([a_{(1:d-1)}, a^*_{(0)}, a_{(d+1:2^K)}]|W_t)),$$

$iPSE(d, a_{(1:2^K;-d)}, a^*_{(1)}, a^*_{(0)}|Q, W_t)$ is defined in terms of the change of φ_K by changing the value of a_d from $a^*_{(0)}$ to $a^*_{(1)}$ when all other variables are fixed as $a_{(-d)}$. Similar to Definition 5, we specify iPSE using the following expression for convenience of decomposition and define the randomized interventional analogue of total effect (iTE):

Definition 5.a. (iPSE for decomposition of iTE).

$$iPSE_K\left(d, a^*_{(1)}, a^*_{(0)}|W_t\right) \equiv \varphi_K\left(\left[\bar{a}^*_{(1)_d}, \bar{a}^*_{(0)_{2^K-d}}\right]|W_t\right) - \varphi_K\left(\left[\bar{a}^*_{(1)_{d-1}}, \bar{a}^*_{(0)_{2^K-d+1}}\right]|W_t\right)$$
$$iTE_K(a^*_{(1)}, a^*_{(0)}|W_t) \equiv \sum_{d=1}^{2^K} iPSE_K\left(d, a^*_{(1)}, a^*_{(0)}|W_t\right)$$

2.3. Approach 2: Partial decomposition approach

Although the interventional approach can provide completely decomposition with 2^K paths, three limitations merit to be noticed. First, the definition of iPSE, although obtains the essence of PSE, still deviates from the traditional definition. Second, the sum of iPSE is also the analogue of total effect (iTE), instead a real one. Third, the interpretation of the definition based on iterative random draw is complicated. Therefore, some researchers prefer to keen the original definition of PSE. As a trade-off, the effect can only be partially decomposed into K+1 paths, instead of 2^K. The effects corresponding to these paths are termed partPSEs through this article and are exactly the sum of several non-identified PSEs. In previous literature, this partial decomposition has been applied to two or three mediators (Cho and Huang, 2019; Huang and Yang, 2017; Huang and Cai, 2015). An interventional analogue has been proposed (Moreno-Betancur and Carlin, 2018; Vansteelandt and Daniel, 2017). In this study, we propose a general definition for partial PSEs. We will identify the partial PSEs and discuss the assumption required for identification in Section 2.4. Similarly, we first define "Nested iterative counterfactual mediators" and a "partial multi-mediation parameter" as *Definition 2.b* and *Definition 3.b*, for simplifying the notation.

Definition 2.b. (Nested iterative counterfactual mediators, $M^\dagger_k\left(e_{(1,k)}\right)$).

$M_1^{\dagger}(e_1) \equiv M_1(e_1)$. For $k \in \{2, \dots, K\}$, let $M_k^{\dagger}(e_{(1,k)}) \equiv M_k(e_k, M_1^{\dagger}(e_1), \dots, M_{k-1}^{\dagger}(e_{(1,k-1)}))$, which is the counterfactual value of M_k suppose $(A, M_{(1,k-1)})$ is set to $\left(e_k, M_1^{\dagger}(e_1), \dots, M_{k-1}^{\dagger}(e_{(1,k-1)})\right)$. For any $k \in \{1, \dots, K\}$, $M_k^{\dagger}$ is a function of $e_{(1,k)}$.

On the basis of *Definition 2.b*, we can further define partial multi-mediation parameter in a general form as *Definition 3.b*.

Definition 3.b. (Partial multi-mediation parameter $\psi_K(a_1, e_{(1,K)}|W_t)$)

$$\psi_K(a_1, e_{(1,K)}|W_t) \equiv E\left[W_t\left(Y\left(a_1, M_1^{\dagger}(e_1), M_2^{\dagger}(e_{(1,2)}), M_3^{\dagger}(e_{(1,3)}), \dots, M_K^{\dagger}(e_{(1,K)})\right)\right)\right]$$

where W_t is a transfer function.

Definition 3.b implies that the partial multi-mediation parameter represents the cumulative effect of multiple paths, while the interventional multi-mediation parameter in *Definition 3.a* can be used to quantity each path. In Section 3, we provide a theorem to detail the relationship between partial PSE and interventional PSE in terms of survival analysis when analytical estimators are available. We next use the partial multi-mediation parameter in *Definition 3.b* to define the partPSE.

Definition 4.b. (Partial path-specific effect (partPSE))

$$partPSE_K(0, e_{(1,K)}, a_{(1)}^*, a_{(0)}^*|Q, W_t) \equiv Q\left(\psi_K(a_{(1)}^*, e_{(1,K)}|W_t) - \psi_K(a_{(0)}^*, e_{(1,K)}|W_t)\right)$$

$$partPSE_K(g, e_{(1:K;-g)}, a_{(1)}^*, a_{(0)}^*|Q, W_t)$$
$$\equiv Q\left(\psi_K(a_1, [e_{(1,g-1)}, a_{(1)}^*, e_{(g+1,K)}]|W_t) - \psi_K(a_1, [e_{(1,g-1)}, a_{(0)}^*, e_{(g+1,K)}]|W_t)\right)$$

for $g \in \{1, \dots, K\}$, where $Q(\cdot)$ a nonspecific comparative function.

In *Definition 4.b*, $partPSE(g, e_{(1:K;-g)}, a_{(1)}^*, a_{(0)}^*|Q, W_t)$ is defined in terms of the change of ψ_K by changing the value of e_g from $a_{(0)}^*$ to $a_{(1)}^*$ when all other variables are fixed as $e_{(1:K;-g)}$, and the definition of multi-mediation parameters guarantees that the influence of changing e_g reflects the effect of the exposure on the outcome through M_g, which includes all path passing or not the following mediators *($M_{(g+1,K)}$)*, but not through the previous mediators (i.e. $M_{(1,g-1)}$). Similarly, we further specify the value of $(a_1, e_{(1,K)})$ for all partPSEs in order to ensure that the sum is equal to TE as follows:

Definition 5.b. (partPSE for decomposition of TE).

$$partPSE_K(0, a_{(1)}^*, a_{(0)}^*|W_t) \equiv \psi_K\left(\left[a_{(1)}^*, \bar{a}_{(0)K}^*\right]|W_t\right) - \psi_K\left(\left[a_{(0)}^*, \bar{a}_{(0)K}^*\right]|W_t\right)$$

$$partPSE_K(g, a_{(1)}^*, a_{(0)}^*|W_t)$$
$$\equiv \psi_K\left(a_{(1)}^*, \left[\bar{a}_{(1)g}^*, \bar{a}_{(0)K-g}^*\right]|W_t\right) - \psi_K\left(a_{(1)}^*, \left[\bar{a}_{(1)g-1}^*, \bar{a}_{(0)K-g+1}^*\right]|W_t\right)$$

for $g > 0$, As a result, the sum of all partPSE will equal to total effect, i.e. $\sum_{g=0}^{K} partPSE_K(g, a_{(1)}^*, a_{(0)}^*|W_t) = \text{TE}$ by consistency.

2.4. Identification

In this section, we discuss the identification process and the required assumption for iPSE and partPSE. For PSE, four assumptions are required:

Assumption 1. Unconfoundedness among exposure and outcome.

$$Y\left(a, m_{(1,K)}\right) \perp\!\!\!\perp A|C_0$$

Assumption 2. Unconfoundedness among mediators and outcome.

$$Y\left(a, m_{(1,K)}\right) \perp\!\!\!\perp M_k\left|C_{(0,k)}, A, M_{(1,k-1)} \text{ for } k \in \{1,2,\dots,K\}\right.$$

Assumption 3. Unconfoundedness among exposure and mediators.

$$M_k\left(a, m_{(1,k-1)}\right) \perp\!\!\!\perp A|C_0 \text{ for } k \in \{1,2,\dots,K\}$$

Assumption 4. Unconfoundedness among mediators.

$$M_k\left(a, m_{(1,k-1)}\right) \perp\!\!\!\perp M_k\left|C_{(0,j)}, A, M_{(1,j-1)} \text{ for } j \in \{1,2,\dots,k-1\} \text{ and } k \in \{2,\dots,K\}\right.$$

Under consistency assumption and *Assumptions 1* to *4*, interventional multi-mediation parameter can be identified as

$$\varphi_K(a_{(1,2^K)}|W_t)$$
$$= \int_{c_0} \int_{m_{(1,K)}} E\left[W_t(Y(a_1, m_{(1,K)}))|c_0\right] \prod_{k=1}^{K} dF_{G_k(a_{(2^{k-1}+1,2^k)})|c_0}(m_k|c_0)\, dF_{C_0}(c_0)$$
$$= \int_{c_0} \int_{m_{(1,K)}} \Gamma(c_0, a_1, m_{(1,K)}|W_t) \prod_{k=1}^{K} H_k(m_k, a_{(2^{k-1}+1,2^k)}, c_0)\, dF_{C_0}(c_0). \qquad (1)$$

where $\Gamma\left(c_0, a_1, m_{(1,K)}|W_t\right) =$

$$\int_{c_{(1,K)}} E\left[W_t(Y)\middle|a_1, c_{(0,K)}, m_{(1,K)}\right] \prod_{k=1}^{K} dF_{C_k|C_{(0,k-1)},A,M_{(1,k-1)}}\left(c_k\middle|c_{(0,k-1)}, a_1, m_{(1,k-1)}\right)$$

and $H_k\left(m_k, a_{(2^{k-1}+1,2^k)}, c_0\right) =$

$$\int_{m_{(1,k-1)}} \int_{c_{(1,k)}} dF_{M_k|A,M_{(1,k-1)},C_{(0,k)}}\left(m_k\middle|a_{2^{k-1}+1}, m_{(1,k-1)}, c_{(0,k)}\right) \times$$
$$\prod_{j=1}^{k} dF_{C_j|A,M_{(1,j-1)},C_{(0,j-1)}}\left(c_j\middle|a_{2^{k-1}+1}, m_{(1,j-1)}, c_{(0,j-1)}\right) \times$$
$$\prod_{j=1}^{k-1} H_j\left(m_j, a_{(2^{k-1}+2^{j-1}+1,2^{k-1}+2^j)}, c_0\right)$$

The details about the identification process and *Assumptions 1* to *4* have been described in previous literature (Lin and VanderWeele, 2017).

Compared with iPSE, partPSE required two extra assumptions for identification:

Assumption 5. Confounders among mediators and outcome is not affected by previous covariates.

$$Y\left(a, m_{(1,K)}\right) \perp\!\!\!\perp (M_1(e_1), M_2(e_2, m_1), \dots, M_K\left(e_K, m_{(1,K-1)}\right))|C_0$$

Assumption 6. Confounders among mediators is not affected by previous covariates.

$$M_k\left(e_k, m_{(1,k-1)}\right) \perp\!\!\!\perp (M_1(e_1), M_2(e_2, m_1), \dots, M_{k-1}\left(e_{k-1}, m_{(1,k-2)}\right))|C_0 \text{ for } k \in \{2,\dots,K\}$$

Since the presence of time-varying confounders $C_{(1,k)}$ conflicts with *Assumptions 5* and *6*, an assumption of no time-varying confounders is further required for the identification of partPSE. Details about *Assumptions 5* and *6* will be illustrated in Appendix Sections 1.1 and 1.2.

Under consistency assumption and *Assumptions 1* to *6*, partial multi-mediation parameter $\psi_K\left(a_1, e_{(1,K)}|W_t\right)$ is identified as

$$\psi_K\left(a_1, e_{(1,K)}|W_t\right)$$
$$= \int_{c_0,m_{(1,K)}} E\left[W_t\left(Y\left(a_1, m_{(1,K)}\right)\right)|C_0 = c_0\right] \prod_{k=1}^{K} dF_{M_k(e_k,m_{(1,k-1)})|C_0}(m_k|c_0)\, dF_{C_0}(c_0)$$
$$= \int_{c_0,m_{(1,K)}} E\left[W_t(Y)\middle|a_1, c_0, m_{(1,K)}\right] \prod_{k=1}^{K} dF_{M_k|C_0,A,M_{(1,k-1)}}\left(m_k\middle|c_0, e_k, m_{(1,k-1)}\right) dF_{C_0}(c_0) \quad (2)$$

The identification of (2) is shown in Appendix Section 1.3. If we assume previous mediator will not affect the following mediator, the partial multi-mediation parameter can be rewritten as

$$\psi_K\left(a_1, e_{(1,K)}|W_t\right)$$
$$= \int_{c_0,m_{(1,K)}} E\left[W_t\left(Y\left(a_1, m_{(1,K)}\right)\right)|C_0 = c_0\right] \prod_{k=1}^{K} dF_{M_k(e_k)|C_0}(m_k|c_0)\, dF_{C_0}(c_0)$$
$$= \int_{c_0,m_{(1,K)}} E\left[W_t(Y)\middle|a_1, c_0, m_{(1,K)}\right] \prod_{k=1}^{K} dF_{M_k|C_0,A}(m_k|c_0, e_k)\, dF_{C_0}(c_0) \quad (3)$$

Formula (3) is exactly the multi-mediation parameter under paralleled mediators used by previous literatures (Taguri, *et al.*, 2015; Wang, *et al.*, 2013). Therefore, we conclude that the paralleled multi-mediation parameter is a special case of the partial multi-mediation parameter. Two multi-mediation parameters (2) and (3) are decomposing a total causal effect into K+1 pathways.

Assumptions 5 and *6* hinge the time-varying confounders even if all these confounders are collected. It is likely to be violated if the time period of all multiple mediators is long. In addition, as mentioned previously, partPSE cannot completely decompose the effect into 2^K paths. That is the trade-off to keep traditional definition. In cases of one mediator, the interventional analogue of natural direct and indirect effects will reduce to its standard definition when mediator-outcome confounders are not affected by exposure (Vanderweele, *et al.*, 2014), even under time-varying settings (VanderWeele and Tchetgen Tchetgen, 2017). By contrast, for multiple mediators without model assumptions, iPSE is not a general form of partPSE, even if time-varying confounders are absent. Given parametric models for outcome and mediators, the partPSE can be decomposed into several iPSEs, and the detail is shown in Section 3.

2.5. Definition of PSE for survival outcome

In Section 2.5 and what follows, we focus on the context when survival time is the outcome of interest (i.e $Y \equiv \mathrm{T}$). We applied *Approaches 1* and *2* to define PSE for survival outcome, separately. Before deriving PSE, the multi-mediation parameters in *Definition 3.a* and *Definition 3.b* are reformed as the survival functions of the counterfactual outcome. More specifically, given $W_t(x) = I(x \geq t)$, equations (1) and (2) can be rewritten as

$$\varphi_K^S\left(a_{(1,2^K)}; t\right) \equiv \varphi_K\left(a_{(1,2^K)}|W_t = I(x \geq t)\right)$$
$$= \int_{c_0} \int_{m_{(1,K)}} \Gamma^S(c_0, a_1, m_{(1,K)}; t) \prod_{k=1}^{K} H_k\left(m_k, a_{\left(2^{k-1}+1,2^k\right)}, c_0\right) dF_{C_0}(c_0), \quad (4)$$

where

$$\Gamma^S\left(c_0, a_1, m_{(1,K)}; t\right) \equiv \Gamma\left(c_0, a_1, m_{(1,K)}|W_t = I(x \geq t)\right)$$

$$= \int_{c_{(1,K)}} S_Y\left(t \middle| a_1, c_{(0,K)}, m_{(1,K)}\right) \prod_{k=1}^{K} dF_{C_k|C_{(0,k-1)},A,M_{(1,k-1)}}\left(c_k \middle| c_{(0,k-1)}, a_1, m_{(1,k-1)}\right)$$

and

$$\psi_K^S\left(a_1, e_{(1,K)}; t\right) \equiv \psi_K\left(a_1, e_{(1,K)} | W_t = I(x \geq t)\right)$$
$$= \int_{c_0, m_{(1,K)}} S_Y\left(t \middle| a_1, c_0, m_{(1,K)}\right) \prod_{k=1}^{K} dF_{M_k|C_0,A,M_{(1,k-1)}}\left(m_k \middle| c_0, e_k, m_{(1,k-1)}\right) dF_{C_0}(c_0)$$
$$(5)$$

$S_Y(t)$ is the survival function with respect to survival outcome *Y*, and $\psi_K^S\left(a_1, e_{(1,K)}; t\right)$ and $\varphi_K^S\left(a_{(1,2^K)}; t\right)$ are exactly the survival function of the counterfactual outcome by the definition. Let $\lambda_Y(t)$ is the hazard function of *Y*. We can define the corresponding hazard functions of the counterfactual outcome as

$$\tilde{\lambda}_\varphi\left(a_{(1,2^K)}; t\right) \equiv \lambda_{Y(a_1, G_1(a_2), G_2(a_3, a_4), \dots, G_K(a_{(2^{K-1}+1, 2^K)}))}(t) \equiv -\frac{d\varphi_K^S\left(a_{(1,2^K)}; t\right)/dt}{\varphi_K^S\left(a_{(1,2^K)}; t\right)}, \text{ and}$$

$$\tilde{\lambda}_\psi\left(a_1, e_{(1,K)}; t\right) \equiv \lambda_{Y(a_1, M_1^\dagger(e_1), M_2^\dagger(e_{(1,2)}), \dots, M_K^\dagger(e_{(1,K)}))}(t) \equiv -\frac{d\varphi_K^S\left(a_{(1,2^K)}; t\right)/dt}{\varphi_K^S\left(a_{(1,2^K)}; t\right)}.$$
$$(6)$$

Since the counterfactual survival function are identified above, we can subsequently obtain the identified hazard functions in (6) by plugging the formulas of (4) and (5). Based on hazard functions, iPSE and partPSE in the hazard difference (HD) scale, termed $\mathrm{iPSE}_{\mathrm{K}}^{\mathrm{HD}}$ and $\mathrm{partPSE}_{\mathrm{K}}^{\mathrm{HD}}$, are defined as follows:

$$iPSE_K^{HD}\left(d, a_{(1)}^*, a_{(0)}^*\right)$$
$$= \tilde{\lambda}_\varphi\left(a_{(1,2^K)} = \left(\bar{a}_{(1)}^*{}_d, \bar{a}_{(0)}^*{}_{2^K-d}\right); t\right) - \tilde{\lambda}_\varphi\left(a_{(1,2^K)} = \left(\bar{a}_{(1)}^*{}_{d-1}, \bar{a}_{(0)}^*{}_{2^K-d+1}\right); t\right)$$

for $d \in \{1, \dots, 2^{\mathrm{K}}\}$, and

$$partPSE_K^{HD}\left(g, a_{(1)}^*, a_{(0)}^*\right)$$
$$= I_{(g=0)}\left[\tilde{\lambda}_\psi\left(a_1 = a_{(1)}^*, e_{(1,K)}; t\right) - \tilde{\lambda}_\psi\left(a_1 = a_{(0)}^*, e_{(1,K)}; t\right)\right] +$$
$$I_{(g>0)}\left[\tilde{\lambda}_\psi\left(a_1, e_{(1,K)} = (\bar{a}_{(1)}^*{}_g, \bar{a}_{(0)}^*{}_{K-g}); t\right) - \tilde{\lambda}_\psi\left(a_1, e_{(1,K)} = (\bar{a}_{(1)}^*{}_{g-1}, \bar{a}_{(0)}^*{}_{K-g+1}); t\right)\right]$$

for $g \in \{0, \dots, K\}$

$$(7)$$

where $I_{(g=0)}$ and $I_{(g>0)}$ are indicator functions for $g = 0$ and $g > 0$, respectively. Similarly, for the log transformed hazard ratio (HR) scale, iPSE and partPSE can be defined as follows:

$$iPSE_K^{HR}\left(d, a_{(1)}^*, a_{(0)}^*\right)$$
$$= log\left(\tilde{\lambda}_\varphi\left(a_{(1,2^K)} = \left(\bar{a}_{(1)}^*{}_d, \bar{a}_{(0)}^*{}_{2^K-d}\right)\right); t\right) - log\left(\tilde{\lambda}_\varphi\left(a_{(1,2^K)} = \left(\bar{a}_{(1)}^*{}_{d-1}, \bar{a}_{(0)}^*{}_{2^K-d+1}\right)\right); t\right)$$

for $d \in \{1, \dots, 2^K\}$ and,

$$partPSE_K^{HR}\left(g, a_{(1)}^*, a_{(0)}^*\right)$$
$$= I_{(g=0)}\left[log\left(\tilde{\lambda}_\psi\left(a_1 = a_{(1)}^*, e_{(1,K)}\right); t\right) - log\left(\tilde{\lambda}_\psi\left(a_1 = a_{(0)}^*, e_{(1,K)}\right); t\right)\right] +$$
$$I_{(g>0)}\left[log\left(\tilde{\lambda}_\psi(a_1, e_{(1,K)} = (\bar{a}_{(1)}^*{}_g, \bar{a}_{(0)}^*{}_{K-g})); t\right)\right.$$
$$\left. - log\left(\tilde{\lambda}_\psi(a_1, e_{(1,K)} = (\bar{a}_{(1)}^*{}_{g-1}, \bar{a}_{(0)}^*{}_{K-g+1})); t\right)\right]$$

for $g \in \{0, \dots, K\}$.

$$(8)$$

3. Estimation for PSE with survival outcome

In this section, we applied Aalen's additive hazards model to derive PSE in HD scale and Cox's proportional hazards model in log HR scale. We propose a parametric approach in which the statistical models of survival outcome, mediators and confounders are specified. We mainly focus on the case of assuming mediators' distribution are Gaussian in order to derive the analytic form.

3.1 Model specification for mediators and confounders

For the k-th mediators and confounders, the regression models are described as follows:

$$M_k = \alpha_k^M C_0 + \beta_k^M A + \sum_{h=1}^{k} \gamma_{kh}^M C_h + I_{(k>1)}\left[\sum_{h=1}^{k-1} \delta_{kh}^M M_h\right] + \varepsilon_{M,k}$$
$$C_k = \alpha_k^C C_0 + \beta_k^C A + I_{(k>1)}\left[\sum_{h=1}^{k-1} \gamma_{kh}^C C_h + \sum_{h=1}^{k-1} \delta_{kh}^C M_h\right] + \varepsilon_{C,k} \tag{9}$$

The error terms $\{\varepsilon_{M,k}\}$ and $\{\varepsilon_{C,k}\}$ are independent and normally distributed with mean zero and respective variances, $\{\sigma_{M,k}^2\}$ and $\{\sigma_{C,k}^2\}$. The parameters above

$$\boldsymbol{\theta} \equiv \{\boldsymbol{\alpha} = \{\alpha_k^M, \alpha_k^C | k = 1, \dots, K\}, \boldsymbol{\beta} = \{\beta_k^M, \beta_k^C | k = 1, \dots, K\}, \boldsymbol{\sigma^2} = \{\sigma_{M,k}^2, \sigma_{C,k}^2 | k = 1, \dots, K\},$$
$$\boldsymbol{\gamma} = \left\{\gamma_{11}^M, \{\gamma_{kh}^M, \gamma_{kk}^M, \gamma_{kh}^C | k = 2, \dots, K; h = 1, \dots, (k-1)\}\right\},$$
$$\boldsymbol{\delta} = \{\delta_{kh}^M, \delta_{kh}^C | k = 2, \dots, K; h = 1, \dots, (k-1)\}\}$$

can be estimated using the maximum likelihood approach, and the maximum likelihood estimator (MLE) of $\boldsymbol{\theta}$ is denoted as $\widehat{\boldsymbol{\theta}}$. Since the partial decomposition approach requires the assumption of no-confounders affected by previous covariates, the regression models of mediators are modified to drop out the time-varying confounders ($C_{(1:K)}$) from mean when we study partial decomposition. The models of mediators are modified as follows:

$$M_k = \alpha_k^M C_0 + \beta_k^M A + I_{(k>1)}\left[\sum_{h=1}^{k-1} \delta_{kh}^M M_h\right] + \varepsilon_{M,k} \text{ for } k = 2, \dots, K \tag{10}$$

To obtain the analytic forms of (4)-(8), we applied moment generating function uniqueness theorem to characterize $H_k\left(m_k, a_{(2^{k-1}+1,2^k)}, c_0\right)$ by *Theorem 1.*

Theorem 1. Let $H_k\left(m_k, a_{(2^{k-1}+1,2^k)}, c_0\right) = h_k\left(m_k, a_{(2^{k-1}+1,2^k)}, c_0\right) dm_k$. If mediators and confounders follow the regression models as above, then $h_k\left(m_k, a_{(2^{k-1}+1,2^k)}, c_0\right)$ is a Gaussian probability density function with mean $\mu_k^M(\boldsymbol{\theta}, a_{(2^{k-1}+1,2^k)}, c_0)$ and variance ${\tau^2}_k^M(\boldsymbol{\theta})$. Moreover, $\mu_k^M(\boldsymbol{\theta}, a_{(2^{k-1}+1,2^k)}, c_0)$ and ${\tau^2}_k^M(\boldsymbol{\theta})$ have recursive forms as follows:

$$\mu_k^M\left(\boldsymbol{\theta}, a_{(2^{k-1}+1,2^k)}, c_0\right) = \alpha_k^M c_0 + \beta_k^M a_{2^{k-1}+1} + \sum_{h=1}^{k} \gamma_{kh}^M \times$$
$$\mu_h^C\left(\boldsymbol{\theta}, a_{(2^{k-1}+1,2^{k-1}+2^{h-1})}, c_0\right) + I_{(k>1)}\left[\sum_{h=1}^{k-1} \delta_{kh}^M \times \mu_h^M\left(\boldsymbol{\theta}, a_{(2^{k-1}+2^{h-1}+1,2^{k-1}+2^h)}, c_0\right)\right]$$

for $k = 1, \dots, K$, where

$\mu_h^C\left(\boldsymbol{\theta}, a_{(2^{k-1}+1, 2^{k-1}+2^{h-1})}, c_0\right) = \alpha_h^C c_0 + \beta_h^C a_{2^{k-1}+1} + I_{(k>1)}[\sum_{h'=1}^{h-1} \gamma_{hh'}^C$
$\times \mu_{h'}^C(\boldsymbol{\theta}, a_{\left(2^{k-1}+1, 2^{k-1}+2^{h'-1}\right)}, c_0) + \sum_{h'=1}^{h-1} \delta_{hh'}^C \times \mu_{h'}^M(\boldsymbol{\theta}, a_{\left(2^{k-1}+2^{h'-1}+1, 2^{k-1}+2^{h'}\right)}, c_0)]$
and $\tau^{2}{}_k^M(\boldsymbol{\theta}) = \sigma_{M,k}^2 + \sum_{h=1}^{k}\left(\sum_{s=h}^{k} \gamma_{ks}^M \times (E_{ksh})\right)^2 \sigma_{C,h}^2 +$
$I_{(k>1)}\left[\sum_{h=1}^{k-1}\left(\delta_{kh}^M + \sum_{s=h+1}^{k} \gamma_{ks}^M \times (F_{ksh})\right)^2 \tau^{2}{}_h^M(\boldsymbol{\theta})\right]$, in which
$E_{ksh} = I_{(s>h)}\left[\sum_{l=1}^{s-1} E_{klh} \times \gamma_{sl}^C\right] + 1_{(s=h)}$ and $F_{ksh} = I_{(s>h)}\left[\delta_{s1}^C + \sum_{l=1}^{s-1} F_{klh} \times \gamma_{sl}^C\right]$.

The proof detail is presented in Appendix Section 2.1. Based on *Theorem 1*, we next derive the closed forms of estimators for iPSE and partPSE under HD scale using Aalen's additive hazards model in Section 3.2 and under log HR scales using Cox's proportional hazards model in Section 3.3.

3.2 Aalen's additive hazards model

Following the regression setting of mediators and confounders, we apply Aalen's additive hazards model for the outcome Y as follows:

$$\lambda_Y\left(t|A, C_{(0,K)}, M_{(1,K)}\right) = \lambda_0(t) + \alpha^Y C_0 + \beta^Y A + \sum_{h=1}^{K} \gamma_h^Y C_h + \sum_{h=1}^{K} \delta_h^Y M_h, \quad (11)$$

where $\lambda_0(t)$ is the baseline hazard and $\boldsymbol{\theta}_{\boldsymbol{y}}^{\mathbf{Aalen}} = \left(\alpha^Y, \beta^Y, \boldsymbol{\gamma}_{\boldsymbol{h}}^{\boldsymbol{Y}} = \{\gamma_h^Y | h = 1, \dots, K\}, \boldsymbol{\delta}_{\boldsymbol{h}}^{\boldsymbol{Y}} = \{\delta_h^Y | h = 1, \dots, K\}\right)$ is the regression coefficient. Typically, the estimator of $\boldsymbol{\theta}_{\boldsymbol{y}}^{\mathbf{Aalen}}$ can be derived by the semiparametric estimating equation (Lin and Ying, 1994), and we denote the estimator as $\widehat{\boldsymbol{\theta}}_{\boldsymbol{y}}^{\mathbf{Aalen}}$. Here, we separately introduce the estimators for $\mathrm{iPSE}_{\mathrm{K}}^{\mathrm{HD}}$ and $\mathrm{partPSE}_{\mathrm{K}}^{\mathrm{HD}}$.

$\boldsymbol{iPSE_K^{HD}}$

According to models (6), (9), and (11), we have the hazard function of counterfactual outcome incorporated with Aalen's additive hazards model as follows:

$$\begin{aligned}
&\tilde{\lambda}_{\varphi}\left(a_{(1,2^K)}; t\right) \\
&= \lambda_0(t) + \left(\beta^Y + \left(\sum_{j=1}^{K} R_j\left(\boldsymbol{\theta}, \boldsymbol{\theta}_{\boldsymbol{y}}^{\mathbf{Aalen}}\right)\beta_j^C\right)\right) a_1 + \left(\alpha^Y + \sum_{j=1}^{K} R_j\left(\boldsymbol{\theta}, \boldsymbol{\theta}_{\boldsymbol{y}}^{\mathbf{Aalen}}\right)\alpha_j^C\right) E(C_0) + \\
&\quad \sum_{j=1}^{K} Z_j\left(\boldsymbol{\theta}, \boldsymbol{\theta}_{\boldsymbol{y}}^{\mathbf{Aalen}}\right)\mu_j^M\left(\boldsymbol{\theta}, a_{(2^{j-1}+1, 2^j)}, c_0 = E(C_0)\right) - \sum_{j=1}^{K} R_j^2\left(\boldsymbol{\theta}, \boldsymbol{\theta}_{\boldsymbol{y}}^{\mathbf{Aalen}}\right)\sigma_{C,j}^2\, t - \\
&\quad \sum_{j=1}^{K} Z_j^2(\boldsymbol{\theta}, \boldsymbol{\theta}_{\boldsymbol{y}}^{\mathbf{Aalen}})\tau^{2}{}_j^M(\boldsymbol{\theta})\, t
\end{aligned}$$

where

$R_K(\boldsymbol{\theta}, \boldsymbol{\theta}_{\boldsymbol{y}}^{\mathbf{Aalen}}) = \gamma_K^Y$, $R_j(\boldsymbol{\theta}, \boldsymbol{\theta}_{\boldsymbol{y}}^{\mathbf{Aalen}}) = \gamma_j^Y + \sum_{d=j+1}^{K} R_d(\boldsymbol{\theta}, \boldsymbol{\theta}_{\boldsymbol{y}}^{\mathbf{Aalen}})\gamma_{d,j}^C$, and

$Z_{K-j}(\boldsymbol{\theta}, \boldsymbol{\theta}_{\boldsymbol{y}}^{\mathbf{Aalen}}) = \delta_{K-j}^Y + I_{(k>1)}[\sum_{j^\circ=0}^{j-1}(\gamma_{(K-j^\circ)}^Y\, (\sum_{s=1}^{2^{(j-1)-j^\circ}} \prod_{L \in P_s(K-j^\circ, K-j)} \gamma_L^C)\, \delta_{(K-j^\circ)(K-j)}^C)]$.

$P_s(K-j^\circ, K-j)$ is the s^th subset of P, and $P = \{(a,b) | a, b \in \{K-j^\circ, K-j^\circ+1, \dots, K-j+1\} \text{ and } a > b\} \cup \Phi$, where Φ is a null set. The detailed derivation is shown in Appendix Section 3. Consequently, $iPSE_K^{HD}$ in (7) can be derived as

for $d = 1$, $iPSE_K^{HD}\left(1, a_{(1)}^*, a_{(0)}^*\right) = \left(\beta^Y + \sum_{j=1}^{K} R_j(\boldsymbol{\theta}, \boldsymbol{\theta}_{\boldsymbol{y}}^{\boldsymbol{Aalen}})\beta_j^C\right)(a_{(1)}^* - a_{(0)}^*)$, and for $d > 1$, $iPSE_K^{HD}\left(d, a_{(1)}^*, a_{(0)}^*\right) = \mathcal{H}\left(\boldsymbol{\theta}, \boldsymbol{\theta}_{\boldsymbol{y}}^{\boldsymbol{Aalen}}, a_{(1,2^K)} = \left(\bar{a}_{(1)_d}^*, \bar{a}_{(0)_{2^K-d}}^*\right)\right) -$

$$\mathcal{H}\left(\boldsymbol{\theta}, \boldsymbol{\theta}_{\boldsymbol{y}}^{\boldsymbol{Aalen}}, a_{(1,2^K)} = \left(\bar{a}_{(1)_{d-1}}^*, \bar{a}_{(0)_{2^K-d+1}}^*\right)\right)$$

where $\mathcal{H}\left(\boldsymbol{\theta}, \boldsymbol{\theta}_{\boldsymbol{y}}^{\mathbf{Aalen}}, a_{(1,2^K)}\right) = \sum_{j=1}^{K} Z_j\left(\boldsymbol{\theta}, \boldsymbol{\theta}_{\boldsymbol{y}}^{\mathbf{Aalen}}\right)\mu_j^M\left(\boldsymbol{\theta}, a_{(2^{j-1}+1, 2^j)}, c_0 = E(C_0)\right)$

(12)

In particular, when time-varying confounders (i.e. $C_{(1,K)}$) are absence, equation (12) is identical to the structural equation modeling (SEM) estimator. We termed the PSE without time-varying confounders as $iPSE_K^{HD}\left(d, a_{(1)}^*, a_{(0)}^* | C_{(1,K)} = \emptyset\right)$. The analytic form is detailed in Appendix Section 2. For example, under two mediators, we have $iPSE_2^{HD}\left(4, a_{(1)}^*, a_{(0)}^* | C_{(1,K)} = \emptyset\right) = \delta_2^Y \delta_{21}^M \beta_1^M$ which is corresponding to the result of product method by the path $A \underset{\beta_1^M}{\rightarrow} M_1 \underset{\delta_{21}^M}{\rightarrow} M_2 \underset{\delta_2^Y}{\rightarrow} Y$. More examples of $iPSE_K^{HD}$ with and without time-varying confounder are illustrated in Appendix Section 3.

$\boldsymbol{partPSE_K^{HD}}$

Because the existence of time-varying confounders violates the assumptions of partial decomposition approach, additive hazard model in (11) should be modified as

$$\lambda_Y\left(t | A, C_0, M_{(1,K)}\right) = \lambda_0(t) + \alpha^Y C_0 + \beta^Y A + \sum_{h=1}^{K} \delta_h^Y M_h, \tag{13}$$

Based on equations (6), (10) and (13), we derived the hazard function of counterfactual outcome as below:

$$\begin{aligned}
&\tilde{\lambda}_\psi\left(a_1, e_{(1,K)}; t\right) \\
&\quad = \lambda_0(t) + \beta^Y a_1 + \sum_{j=1}^{K} Z_j^0\left(\boldsymbol{\theta}, \boldsymbol{\theta}_{\boldsymbol{y}}^{\mathbf{Aalen}}\right)\beta_j^M e_j + \left(\alpha^Y + \sum_{j=1}^{K} Z_j^0\left(\boldsymbol{\theta}, \boldsymbol{\theta}_{\boldsymbol{y}}^{\mathbf{Aalen}}\right)\alpha_j^M\right)E(C_0) - \\
&\quad \sum_{j=1}^{K}\left(Z_j^0\left(\boldsymbol{\theta}, \boldsymbol{\theta}_{\boldsymbol{y}}^{\mathbf{Aalen}}\right)\right)^2 \sigma_{M,j}^2\, t,
\end{aligned}$$

where $Z_K^0(\boldsymbol{\theta}, \boldsymbol{\theta}_{\boldsymbol{y}}^{\mathbf{Aalen}}) = \delta_K^Y$, $Z_j^0(\boldsymbol{\theta}, \boldsymbol{\theta}_{\boldsymbol{y}}^{\mathbf{Aalen}}) = \delta_j^Y + \sum_{d=j+1}^{K} Z_d^0(\boldsymbol{\theta}, \boldsymbol{\theta}_{\boldsymbol{y}}^{\mathbf{Aalen}})\delta_{d,j}^M$. The detail is provided in Appendix Section 3. Based on the result above, partPSE incorporating with Aalen's additive hazards model in HD scale (7) is

$$\begin{aligned}
&partPSE_K^{HD}\left(g, a_{(1)}^*, a_{(0)}^*\right) \\
&= I_{(g=0)}\beta^Y\left(a_{(1)}^* - a_{(0)}^*\right) + I_{(g>0)} Z_g^0\left(\boldsymbol{\theta}, \boldsymbol{\theta}_{\boldsymbol{y}}^{\mathbf{Aalen}}\right)\beta_g^M\left(a_{(1)}^* - a_{(0)}^*\right) \text{ for } g \in \{0, 1, 2, \dots, K\}.
\end{aligned} \tag{14}$$

In 2017, Huang and Yang proposed a multi-mediator model of survival come for partPSE (Huang and Yang, 2017), and they provide the corresponding estimators for the case of two ordered mediators. Formula (14) is essentially an extension of Huang's work to the general form of partPSE. More examples of $partPSE_K^{HD}$ are illustrated in Appendix Section 3. Additionally, the partPSE in formula (14) is the sum of a certain set of iPSEs under no time-varying confounder assumption. We subsequently proposed *Theorem 2* to verify the relation between them.

Theorem 2. In the setting with K mediators and Aalen's additive hazards model, we have

$$partPSE_K^{HD}\left(g, a_{(1)}^*, a_{(0)}^*\right) = \sum_{d \in D_g} iPSE_K^{HD}\left(d, a_{(1)}^*, a_{(0)}^* \middle| C_{(1,K)} = \emptyset\right),$$

where $g \in \{1,2,\ldots,K\}$ and $D_g = \left\{2^{g-1} + 1 + \sum_{\{b_s\}} 2^{b_s-1} \,\middle|\, \{b_s\} \subseteq \{g+1, g+2, \ldots, K\}\right\}$.

The proof of *Theorem 2* is presented in Appendix Section 2.2. In *Theorem 2*, D_g is a set of codes, and these codes are exactly corresponding to the paths starting from the g_{th} mediator. In another words, $partPSE_K^{HD}$ can be further decomposed into several specific $iPSE_K^{HD}$ which are all first mediated by the g_{th} mediator, implying that $iPSE_K^{HD}$ contains more detailed information about mechanism than $partPSE_K^{HD}$ for causal effect decomposition.

<u>*3.3 Cox's proportional hazards model*</u>

In this section, we further characterize $iPSE_K^{HR}$ and $partPSE_K^{HR}$ via Cox's proportional hazards model. Different from Aalen's additive hazards model, Cox's proportional hazards model assume that the hazard is determined by the covariates exponentially, that is

$$log\left(\lambda_Y\left(t \middle| A, C_{(0,K)}, M_{(1,K)}\right)\right) = log\left(\lambda_0(t)\right) + \alpha^Y C_0 + \beta^Y A + \sum_{h=1}^K \gamma_h^Y C_h + \sum_{h=1}^K \delta_h^Y M_h, \tag{15}$$

where $\lambda_0(t)$ is the baseline hazard and $\boldsymbol{\theta}_{\boldsymbol{y}}^{\mathbf{Cox}} = \left(\alpha^Y, \beta^Y, \boldsymbol{\gamma}_{\boldsymbol{h}}^{\boldsymbol{Y}} = \{\gamma_h^Y | h = 1, \ldots, K\}, \boldsymbol{\delta}_{\boldsymbol{h}}^{\boldsymbol{Y}} = \{\delta_h^Y | h = 1, \ldots, K\}\right)$ is the corresponding parameter. Similar to Section 3.2, we derived the corresponding estimators for $iPSE_K^{HR}$ and $partPSE_K^{HR}$ as follows.

$\boldsymbol{iPSE_K^{HR}}$

By formulas (6), (9), and (15), and the rare outcome assumption (Huang and Yang, 2017) which implies $e^{-\lambda_Y(t|A, C_{(0,K)}, M_{(1,K)})} \approx 1$, one approximation of the counterfactual log hazard is

$$\begin{aligned} log\left(\tilde{\lambda}_\varphi\left(a_{(1,2^K)}; t\right)\right) \approx\ & log\lambda_0(t) + \left(\beta^Y + \sum_{j=1}^K R_j\left(\boldsymbol{\theta}, \boldsymbol{\theta}_{\boldsymbol{y}}^{\mathbf{Cox}}\right)\beta_j^C\right)a_1 + \\ & \left(\alpha^Y + \sum_{j=1}^K R_j\left(\boldsymbol{\theta}, \boldsymbol{\theta}_{\boldsymbol{y}}^{\mathbf{Cox}}\right)\alpha_j^C\right)E(C_0) + \\ & \sum_{j=1}^K Z_j\left(\boldsymbol{\theta}, \boldsymbol{\theta}_{\boldsymbol{y}}^{\mathbf{Cox}}\right)\mu_j^M\left(\boldsymbol{\theta}, a_{(2^{j-1}+1, 2^j)}, c_0 = E(C_0)\right) + \sum_{j=1}^K Z_j\left(\boldsymbol{\theta}, \boldsymbol{\theta}_{\boldsymbol{y}}^{\mathbf{Cox}}\right)\tau^2{}_j^M(\boldsymbol{\theta}). \end{aligned}$$

where $R_j(\boldsymbol{\theta}, \boldsymbol{\theta}_y)$ and $Z_K(\boldsymbol{\theta}, \boldsymbol{\theta}_y)$ have been defined in Section 3.2. Derivation of the above expression is in Appendix Section 4. We then derived the analytic forms of (8) as follows:

for $d = 1$, $iPSE_K^{HR}\left(1, a_{(1)}^*, a_{(0)}^*\right) \approx \left(\beta^Y + \left(\sum_{j=1}^K R_j\left(\boldsymbol{\theta}, \boldsymbol{\theta}_{\boldsymbol{y}}^{\boldsymbol{Cox}}\right)\beta_j^C\right)\right)\left(a_{(1)}^* - a_{(0)}^*\right)$, and

for $d > 1$, $iPSE_K^{HR}\left(d, a_{(1)}^*, a_{(0)}^*\right) \approx \mathcal{H}\left(\boldsymbol{\theta}, \boldsymbol{\theta}_{\boldsymbol{y}}^{\boldsymbol{Cox}}, a_{(1,2^K)} = \left(\bar{a}_{(1)}^*{}_d, \bar{a}_{(0)}^*{}_{2^K-d}\right)\right) - \mathcal{H}\left(\boldsymbol{\theta}, \boldsymbol{\theta}_{\boldsymbol{y}}^{\boldsymbol{Cox}}, a_{(1,2^K)} = \left(\bar{a}_{(1)}^*{}_{d-1}, \bar{a}_{(0)}^*{}_{2^K-d+1}\right)\right)$

$$\text{where } \mathcal{H}\left(\boldsymbol{\theta}, \boldsymbol{\theta}_{\boldsymbol{y}}^{\mathbf{Cox}}, a_{(1,2^K)}\right) = \sum_{j=1}^K Z_j\left(\boldsymbol{\theta}, \boldsymbol{\theta}_{\boldsymbol{y}}^{\mathbf{Cox}}\right)\mu_j^M\left(\boldsymbol{\theta}, a_{(2^{j-1}+1, 2^j)}, c_0 = E(C_0)\right) \tag{16}$$

$\boldsymbol{partPSE_K^{HR}}$

To derive partPSE via Cox's proportional hazards model, a log hazard model without time-varying confounders is required, and we modified model (15) as

$$log\left(\lambda_Y\left(t|A, C_{(0,K)}, M_{(1,K)}\right)\right) = log(\lambda_0(t)) + \alpha^Y C_0 + \beta^Y A + \sum_{h=1}^{K} \delta_h^Y M_h. \quad (17)$$

By equations (6), (9) and (17), the approximated log hazard function of counterfactual outcome is given by

$$log\left(\tilde{\lambda}_\psi\left(a_1, e_{(1,K)}; t\right)\right) \approx log\left(\lambda_0(t)\right) + \beta^Y a_1 + \sum_{j=1}^{K} Z_j^0\left(\boldsymbol{\theta}, \boldsymbol{\theta}_{\boldsymbol{y}}^{\mathbf{Cox}}\right)\beta_j^M e_j$$
$$+\left(\alpha^Y + \sum_{j=1}^{K} Z_j^0(\boldsymbol{\theta}, \boldsymbol{\theta}_{\boldsymbol{y}}^{\mathbf{Cox}})\alpha_j^M\right)E(C_0) + \frac{1}{2}\sum_{j=1}^{K} Z_j^0(\boldsymbol{\theta}, \boldsymbol{\theta}_{\boldsymbol{y}}^{\mathbf{Cox}})\sigma_{M,j}^2$$

where $Z_K^0(\boldsymbol{\theta}, \boldsymbol{\theta}_{\boldsymbol{y}}^{\mathbf{Cox}}) = \delta_K^Y,\ Z_j^0(\boldsymbol{\theta}, \boldsymbol{\theta}_{\boldsymbol{y}}^{\mathbf{Cox}}) = \delta_j^Y + \sum_{d=j+1}^{K} Z_d^0(\boldsymbol{\theta}, \boldsymbol{\theta}_{\boldsymbol{y}}^{\mathbf{Cox}})\delta_{d,j}^M$. Derivation of the above expression is in Appendix Section 4. Based on the result above, partPSE incorporating with Cox's proportional hazards model in log HR scale (8) is

$$partPSE_K^{HR}\left(g, a_{(1)}^*, a_{(0)}^*\right)$$
$$= I_{(g=0)}\beta^Y\left(a_{(1)}^* - a_{(0)}^*\right) + I_{(g>0)}Z_g^0\left(\boldsymbol{\theta}, \boldsymbol{\theta}_{\boldsymbol{y}}^{\mathbf{Cox}}\right)\beta_g^M\left(a_{(1)}^* - a_{(0)}^*\right) \text{ for } g \in \{0,1,2,\dots,K\}. \quad (18)$$

The examples of $iPSE_K^{HR}\left(d, a_{(1)}^*, a_{(0)}^*\right)$ and $partPSE_K^{HR}\left(g, a_{(1)}^*, a_{(0)}^*\right)$ are shown in Appendix Section 4.

Obviously, the estimator of $iPSE_K^{HR}$ is the same as that of $iPSE_K^{HD}$ by replacing $\boldsymbol{\theta}_{\boldsymbol{y}}^{\mathbf{Aalen}}$ by $\boldsymbol{\theta}_{\boldsymbol{y}}^{\mathbf{Cox}}$. As a result, all properties, including the comparison with SEM estimator and the relation between $iPSE_K^{HD}$ and $partPSE_K^{HD}$ which are discussed in Section 3.2, are still applicable for $iPSE_K^{HR}$ and $partPSE_K^{HR}$.

4. Asymptotic theorems

For simplification, we set $a_{(1)}^*$ and $a_{(0)}^*$ as one and zero in Sections 4 and 5, respectively. Based on the proposed estimators for PSEs in the previous section, the following result shows the asymptotic properties about $iPSE_K^{HD}(d)$, $partPSE_K^{HD}(d)$, $iPSE_K^{HR}(g)$, and $partPSE_K^{HR}(g)$ for each d and g. Since these estimators are the functions of $\boldsymbol{\theta}$ and $\boldsymbol{\theta}_y^{\mathbf{Aalen}}$ (or $\boldsymbol{\theta}_{\boldsymbol{y}}^{\mathbf{Cox}}$), these PSEs can be represented as

$iPSE_K^{HD}\left(\boldsymbol{\theta}, \boldsymbol{\theta}_y^{\mathbf{Aalen}}\right) = \{\, iPSE_K^{HD}(d) \big| d = 1, \dots, 2^K\}$,
$partPSE_K^{HD}\left(\boldsymbol{\theta}, \boldsymbol{\theta}_y^{\mathbf{Aalen}}\right) = \{\, partPSE_K^{HD}(g) \big| g = 0, 1, \dots, K\}$,
$iPSE_K^{HR}\left(\boldsymbol{\theta}, \boldsymbol{\theta}_{\boldsymbol{y}}^{\mathbf{Cox}}\right) = \{\, iPSE_K^{HR}(d) \big| d = 1, \dots, 2^K\}$, and
$partPSE_K^{HR}\left(\boldsymbol{\theta}, \boldsymbol{\theta}_{\boldsymbol{y}}^{\mathbf{Cox}}\right) = \{\, partPSE_K^{HR}(g) \big| g = 0, 1, \dots, K\}$.

We first provided a theorem to show the asymptotic distributions of PSE estimators on Aalen's additive hazards model. As mentioned above, $\widehat{\boldsymbol{\theta}}$ is the MLE and for $\boldsymbol{\theta}$,

$\widehat{\boldsymbol{\theta}}_y^{\mathbf{Aalen}}$ the estimator via semiparametric estimating equation for $\boldsymbol{\theta}_y^{\mathbf{Aalen}}$, and $\widehat{\boldsymbol{\theta}}_y^{\mathbf{Cox}}$ the partial likelihood estimator for $\boldsymbol{\theta}_y^{\mathbf{Cox}}$. We denote the true value of $(\boldsymbol{\theta}, \boldsymbol{\theta}_y^{\mathbf{Aalen}}, \boldsymbol{\theta}_y^{\mathbf{Cox}})$ by $(\boldsymbol{\theta}_\mathbf{0}, \boldsymbol{\theta}_{y0}^{\mathbf{Aalen}}, \boldsymbol{\theta}_{y0}^{\mathbf{Cox}})$. Under causal assumptions in Section 2, we have *Theorems 3* and *4* for the asymptotic distributions.

Theorem 3.

(1) Under *Assumptions 1* to *4*, we have

$$\sqrt{n}\left(iPSE_K^{HD}\left(\widehat{\boldsymbol{\theta}}, \widehat{\boldsymbol{\theta}}_y^{\mathbf{Aalen}}\right) - iPSE_K^{HD}\left(\boldsymbol{\theta}_0, \boldsymbol{\theta}_{y0}^{\mathbf{Aalen}}\right)\right) \xrightarrow{D} N(0, \boldsymbol{\Sigma}_{\boldsymbol{int}}^{\boldsymbol{HD}}),$$

where $\boldsymbol{\Sigma}_{\boldsymbol{int}}^{\boldsymbol{HD}} = \frac{\partial iPSE_K^{HD}(\boldsymbol{\theta}_0, \boldsymbol{\theta}_{y0}^{\mathbf{Aalen}})}{\partial(\boldsymbol{\theta}, \boldsymbol{\theta}_y^{\mathbf{Aalen}})^T} \mathrm{Cov}\left(\boldsymbol{\theta}_0, \boldsymbol{\theta}_{y0}^{\mathbf{Aalen}}\right) \frac{\partial iPSE_K^{HD}(\boldsymbol{\theta}_0, \boldsymbol{\theta}_{y0}^{\mathbf{Aalen}})}{\partial(\boldsymbol{\theta}, \boldsymbol{\theta}_y^{\mathbf{Aalen}})}$, and

(2) Under *Assumptions 1* to *6*, we have

$$\sqrt{n}\left(partPSE_K^{HD}\left(\widehat{\boldsymbol{\theta}}, \widehat{\boldsymbol{\theta}}_y^{\mathbf{Aalen}}\right) - partPSE_K^{HD}\left(\boldsymbol{\theta}_0, \boldsymbol{\theta}_{y0}^{\mathbf{Aalen}}\right)\right) \xrightarrow{\mathrm{D}} N(0, \boldsymbol{\Sigma}_{\boldsymbol{part}}^{\boldsymbol{HD}})$$

where $\boldsymbol{\Sigma}_{\boldsymbol{part}}^{\boldsymbol{HD}} = \frac{\partial partPSE_K^{HD}(\boldsymbol{\theta}_0, \boldsymbol{\theta}_{y0}^{\mathbf{Aalen}})}{\partial(\boldsymbol{\theta}, \boldsymbol{\theta}_y^{\mathbf{Aalen}})^T} \mathrm{Cov}\left(\boldsymbol{\theta}_0, \boldsymbol{\theta}_{y0}^{\mathbf{Aalen}}\right) \frac{\partial partPSE_K^{HD}(\boldsymbol{\theta}_0, \boldsymbol{\theta}_{y0}^{\mathbf{Aalen}})}{\partial(\boldsymbol{\theta}, \boldsymbol{\theta}_y^{\mathbf{Aalen}})}$.

Here, $\frac{\partial iPSE_K^{HD}(\boldsymbol{\theta}_0, \boldsymbol{\theta}_{y0}^{\mathbf{Aalen}})}{\partial(\boldsymbol{\theta}, \boldsymbol{\theta}_y^{\mathbf{Aalen}})^T}$, $\frac{\partial partPSE_K^{HD}(\boldsymbol{\theta}_0, \boldsymbol{\theta}_{y0}^{\mathbf{Aalen}})}{\partial(\boldsymbol{\theta}, \boldsymbol{\theta}_y^{\mathbf{Aalen}})^T}$, and $\mathrm{Cov}\left(\boldsymbol{\theta}_0, \boldsymbol{\theta}_{y0}^{\mathbf{Aalen}}\right)$ are estimated by $\frac{\partial iPSE_K^{HD}\left(\widehat{\boldsymbol{\theta}}, \widehat{\boldsymbol{\theta}}_y^{\mathbf{Aalen}}\right)}{\partial\left(\boldsymbol{\theta}, \boldsymbol{\theta}_y^{\mathbf{Aalen}}\right)^T}$, $\frac{\partial partPSE_K^{HD}\left(\widehat{\boldsymbol{\theta}}, \widehat{\boldsymbol{\theta}}_y^{\mathbf{Aalen}}\right)}{\partial\left(\boldsymbol{\theta}, \boldsymbol{\theta}_y^{\mathbf{Aalen}}\right)^T}$ and $\widehat{\mathrm{Cov}}\left(\widehat{\boldsymbol{\theta}}, \widehat{\boldsymbol{\theta}}_y^{\mathbf{Aalen}}\right)$. Similarly, the asymptotic distributions of $iPSE_K^{HR}(\boldsymbol{\theta}, \boldsymbol{\theta}_{\boldsymbol{y}}^{\mathbf{Cox}})$ and $partPSE_K^{HR}(\boldsymbol{\theta}, \boldsymbol{\theta}_{\boldsymbol{y}}^{\mathbf{Cox}})$ are derived in the following theorem.

Theorem 4.

(1) Under *Assumptions 1* to *4* and rare outcome assumption, we have

$$\sqrt{n}\left(iPSE_K^{HR}\left(\widehat{\boldsymbol{\theta}}, \widehat{\boldsymbol{\theta}}_y^{\mathbf{cox}}\right) - iPSE_K^{HR}\left(\boldsymbol{\theta}_0, \boldsymbol{\theta}_{\boldsymbol{y0}}^{\mathbf{Cox}}\right)\right) \xrightarrow{\mathrm{D}} N(0, \boldsymbol{\Sigma}_{\boldsymbol{int}}^{\boldsymbol{HR}}),$$

where $\boldsymbol{\Sigma}_{\boldsymbol{int}}^{\boldsymbol{HR}} = \frac{\partial \mathrm{iPSE}_K^{\mathrm{HR}}(\boldsymbol{\theta}_0, \boldsymbol{\theta}_{\boldsymbol{y0}}^{\mathbf{Cox}})}{\partial(\boldsymbol{\theta}, \boldsymbol{\theta}_y^{\mathbf{Cox}})^{\mathrm{T}}} \mathrm{Cov}\left(\boldsymbol{\theta}_0, \boldsymbol{\theta}_{\boldsymbol{y0}}^{\mathbf{Cox}}\right) \frac{\partial \mathrm{iPSE}_K^{\mathrm{HR}}(\boldsymbol{\theta}_0, \boldsymbol{\theta}_{\boldsymbol{y0}}^{\mathbf{Cox}})}{\partial(\boldsymbol{\theta}, \boldsymbol{\theta}_y^{\mathbf{Cox}})}$, and

(2) Under *Assumptions 1* to *6* and rare outcome assumption, we have

$$\sqrt{n}\left(partPSE_K^{HR}\left(\widehat{\boldsymbol{\theta}}, \widehat{\boldsymbol{\theta}}_y^{\mathbf{cox}}\right) - partPSE_K^{HR}\left(\boldsymbol{\theta}_0, \boldsymbol{\theta}_{\boldsymbol{y0}}^{\mathbf{Cox}}\right)\right) \xrightarrow{\mathrm{D}} N(0, \boldsymbol{\Sigma}_{\boldsymbol{part}}^{\boldsymbol{HR}})$$

where $\boldsymbol{\Sigma}_{\boldsymbol{part}}^{\boldsymbol{HR}} = \frac{\partial \mathrm{partPSE}_K^{HR}(\boldsymbol{\theta}_0, \boldsymbol{\theta}_{\boldsymbol{y0}}^{\mathbf{Cox}})}{\partial(\boldsymbol{\theta}, \boldsymbol{\theta}_y^{\mathbf{Cox}})^{\mathrm{T}}} \mathrm{Cov}\left(\boldsymbol{\theta}_0, \boldsymbol{\theta}_{\boldsymbol{y0}}^{\mathbf{Cox}}\right) \frac{\partial \mathrm{partPSE}_K^{HR}(\boldsymbol{\theta}_0, \boldsymbol{\theta}_{\boldsymbol{y0}}^{\mathbf{Cox}})}{\partial(\boldsymbol{\theta}, \boldsymbol{\theta}_y^{\mathbf{Cox}})}$.

Similarly, $\frac{\partial iPSE_K^{HR}(\boldsymbol{\theta}_0, \boldsymbol{\theta}_{y0}^{\mathbf{Cox}})}{\partial(\boldsymbol{\theta}, \boldsymbol{\theta}_y^{\mathbf{Cox}})^T}$, $\frac{\partial partPSE_K^{HR}(\boldsymbol{\theta}_0, \boldsymbol{\theta}_{y0}^{\mathbf{Cox}})}{\partial(\boldsymbol{\theta}, \boldsymbol{\theta}_y^{\mathbf{Cox}})^T}$, and $\mathrm{Cov}\left(\boldsymbol{\theta}_0, \boldsymbol{\theta}_{y0}^{\mathbf{Cox}}\right)$ can be estimated by $\frac{\partial iPSE_K^{HR}\left(\widehat{\boldsymbol{\theta}}, \widehat{\boldsymbol{\theta}}_y^{\mathbf{Cox}}\right)}{\partial\left(\boldsymbol{\theta}, \boldsymbol{\theta}_y^{\mathbf{Cox}}\right)^T}$, $\frac{\partial partPSE_K^{HR}\left(\widehat{\boldsymbol{\theta}}, \widehat{\boldsymbol{\theta}}_y^{\mathbf{Cox}}\right)}{\partial\left(\boldsymbol{\theta}, \boldsymbol{\theta}_y^{\mathbf{Cox}}\right)^T}$ and $\widehat{\mathrm{Cov}}\left(\widehat{\boldsymbol{\theta}}, \widehat{\boldsymbol{\theta}}_y^{\mathbf{Cox}}\right)$, respectively. The details of *Theorems 3* and *4* can be found in Appendix Section 2.3.

5. Simulation

In this section, we conduct a simulation study to evaluate the performance of our proposed models with particular sample sizes based on Cox's proportional hazards model. The Aalen's additive hazards model can smoothly substitute Cox's proportional hazards model in this simulation. Since iPSE and partPSE are the approaches based on two different assumptions, we consider two scenarios, with and without time-varying confounders, for evaluation.

In scenario A, we simulated the exposure variable (A), two baseline confounders (C_{01}, C_{02}), three mediators (M_1, M_2, M_3), and three corresponding time-varying confounders (C_1, C_2, C_3) under the models

$$A \sim Bernoulli(0.2),\ C_{01}, C_{02} \sim Bernoulli(0.2),$$
$$C_1 = 0.5 + 0.5(A + C_{01} + C_{02}) + \varepsilon_{C1},$$
$$M_1 = 0.5 + 0.5^2(A + C_{01} + C_{02}) + 0.25C_1 + \varepsilon_{M1},$$
$$C_2 = 0.5 + 0.5^3(A + C_{01} + C_{02} + C_1 + M_1) + 0.25M_1 + \varepsilon_{C2},$$
$$M_2 = 0.5 + 0.5^4(A + C_{01} + C_{02} + C_1 + M_1 + C_2) + 0.25C_2 + \varepsilon_{M2},$$
$$C_3 = 0.5 + 0.5^5(A + C_{01} + C_{02} + C_1 + M_1 + C_2 + M_2) + 0.25M_2 + \varepsilon_{C3},\ \text{and}$$
$$M_3 = 0.5 + 0.5^6(A + C_{01} + C_{02} + C_1 + M_1 + C_2 + M_2 + C_3) + 0.25C_3 + \varepsilon_{M3},$$

where ε_{C1}, ε_{M1}, ε_{C2}, ε_{M2}, ε_{C3}, and ε_{M3} follow a normal distribution with zero mean and standard deviation is 0.5. To simulate the survival times (*Y*) from Cox's proportional hazards model, we applied the inverse probability method into data generation (Bender, *et al.*, 2005), and the simulation procedure is shown as follows. The event times (*T*) are generated according to a Weibull distribution as

$$T = -\,log(u)\ /\ (0.01\ \times\ e^{\mu_T}),\ u \sim \text{Uniform}(0,1)\ \text{ where}$$

$$\mu_T = 0.5 + 0.5(A + C_{01} + C_{02} + 0.2C_1 + 0.2M_1 + 0.4C_2 + 0.4M_2 + 0.8C_3 + 0.8M_3),$$

The censoring times (C_T) are randomly drawn from an exponential distribution with a rate of 0.001. As a result, the observed survival times is defined as the minimum of T and C_T. Different from scenario A including time-varying confounders, scenario B aims to investigate the properties of partPSE, which assumes no time-varying confounders. Thus, we generated data without time-varying confounders in scenario B, and, the generative models are modified as follows:

$$A \sim Bernoulli(0.2),\ C_{01}, C_{02} \sim Bernoulli(0.2),$$
$$M_1 = 0.5 + 0.5^2(A + C_{01} + C_{02}) + \varepsilon_{M1},$$
$$M_2 = 0.5 + 0.5^4(A + C_{01} + C_{02} + M_1) + \varepsilon_{M2},\ \text{and}$$
$$M_3 = 0.5 + 0.5^6(A + C_{01} + C_{02} + M_1 + M_2) + \varepsilon_{M3}.$$

Similarly, the event times in scenario B are also generated by

$$T = -\,log(u)\ /\ (0.01\ \times\ e^{\mu_T}), u \sim \text{Uniform}(0,1), \text{and}$$
$$\mu_T = 0.5 + 0.5(A + C_{01} + C_{02} + 0.2M_1 + 0.4M_2 + 0.8M_3).$$

For both scenarios, with sample sizes *n* = 1000, we report the simulation results from 1000 replicates in the next section.

The results of eight ($=2^3$) $iPSE_3^{HR}$ under scenario A are presented in Table 1, and we used bias, standard deviation (SD), root mean square error (RMSE), and coverage rate (CR) to measure the performance of point and interval estimates. We adopted the bootstrap approach for SD estimation instead of applying the asymptotic variance for simplicity. This simulation includes three ordered mediators, and the effects of eight different paths are estimated. As a result, the absolute value of the bias for each effect less than 0.003, and the CRs are around 95%. While the CRs for the paths of **A→M$_2$→M$_3$→Y** and **A→M$_1$→M$_2$→M$_3$→Y** are slightly away from 95%, the small bias and RMSE of these effects reveal that the estimators are efficient. Additionally, the true effect values of the two paths above are relatively small than the others, implying that more samples are required for the paths with small effect sizes to increase accuracy. Under scenario B, Table 2 shows the simulation result of four (=3+1) $\mathrm{partPSE}_3^{\mathrm{HR}}$. The biases are close to zero, and the CRs are around 95%. The CR of **A→M$_3$→Y** in Table 2 also less than 95% due to the small effect.

To explore the asymptotic properties of the proposed estimators, we varied the sample sizes for both scenarios in this section. The simulated data sets are generated from the same models of scenarios A and B, and fifty different sample sizes uniformly selected from the interval of (200, 10000) are considered in this simulation. Figures 3(a) and 3(c) show the quantity of bias under different sample sizes for $iPSE_3^{HR}$ and $partPSE_3^{HR}$, respectively. Figures 3(b) and 3(d) illustrate the patterns of SD when sample sizes increase. Consequently, when the sample size increases, the bias and SD in both approaches massively decreases. The result provides clear evidence that the proposed estimators converge to the correct parameters in large sample size.

6. Data application

Epigenetics is a molecular process that influences the flow of information between the underlying DNA sequence and variable gene expression patterns without altering DNA sequences. DNA methylation is one of the critical epigenetic factors to regulate gene expression during development and cell proliferation (Jaenisch and Bird, 2003). Recently, the DNA-methylated regions have been studied extensively in cancer studies (Hansen*, et al.*, 2011). While the correlation between DNA methylation and gene expression in cancer has been reported (Spainhour*, et al.*, 2019), the causal mechanism across genes remains to be studied. In this section, we used the proposed causal multi-mediation analysis to explore the underlying causal mechanism in TCGA (The Cancer Genome Atlas) database.

We chose 453 patients with lung cancer, 226 with adenocarcinoma and 227 with squamous cell carcinoma, and all of the genomics data and patients' information were downloaded from TCGA website. DNA methylation and gene expression were measured in these patients using Illumina Human-Methylation 450K and Agilent gene expression arrays, respectively. All genomic markers were measured on primary tumor samples collected during surgery. From the pre-analysis of the association between the methylation-expression pairs and the survival outcome, we identified that the methylation change in the gene CD109 can significantly affect the survival outcome. In the literature, DNA methylation of CD109 has a role in gastrointestinal cancer and colorectal cancer for poor survival (Shigaki, *et al.*, 2015; Yi, *et al.*, 2011). In this study, we illustrate our method by investigating the detailed mechanisms of CD109 methylation influencing the survival outcome through gene expression in lung cancer patients.

Let DNA methylation of CD109 at cg06340118 as the exposure (A), survival as the outcome (Y), gene expression of CD109 as the third mediator (M_3). We further included another two gene expressions (SLC16A3, CLIC6) as (M_1, M_2) based on the pre-selected methylation-expression pairs that affected survival. SLC16A3 and CLIC6 have a function concerning ion channels and transporters that are a new class of membrane proteins aberrantly expressed in cancer (Lastraioli, *et al.*, 2015). To investigate the causal mechanism, we consider the causal structures as shown in Figure 4. We applied our method to decompose the total effects into eight iPSEs and four partPSEs, separately. Since the genomic experiment usually does not include the time-varying confounders, we adopted the reduced version of iPSE without time-varying confounders as discussed in Section 2. We employed Aalen's additive hazards model and Cox's proportional hazards model for survival analyses. Patients' age, gender, ethnicity, radiation therapy, cancer type, cancer stage, and smoking pack-years were adjusted as baseline confounders (C_0).

The result of PSE estimation is shown in Table 3. At 0.05 α-level, partial PSEs estimated by $partPSE_3^{HD}$ are all significant. In addition, the detailed decomposition estimated by $iPSE_3^{HD}$ reveals that the effect sizes of methylation through some pathways are relatively small. For example, $partPSE_3^{HD}(1)$, which is the effect first mediated by M_1 (that is $\mathbf{A \rightarrow M_1 Y}$), is significant. $\mathbf{A \rightarrow M_1 Y}$ can be decomposed into four paths, $\mathbf{A \rightarrow M_1 \rightarrow Y}$, $\mathbf{A \rightarrow M_1 \rightarrow M_2 \rightarrow Y}$, $\mathbf{A \rightarrow M_1 \rightarrow M_3 \rightarrow Y}$, and $\mathbf{A \rightarrow M_1 \rightarrow M_2 \rightarrow M_3 \rightarrow Y}$, and the result of $iPSE_3^{HD}$ shows that the significant effect of $\mathbf{A \rightarrow M_1 Y}$ is mostly contributed by pathways $\mathbf{A \rightarrow M_1 \rightarrow Y}$ and $\mathbf{A \rightarrow M_1 \rightarrow M_3 \rightarrow Y}$. The result above reflects the utility of iPSE for comprehensively exploring the causal mechanism. Additionally, in agreement with the literature, the estimated direct effects of DNA methylation at cg06340118 in survival ($\mathbf{A \rightarrow Y}$) significantly away from zero (Shigaki, *et al.*, 2015; Yi, *et al.*, 2011). Moreover, the effect of CD109 methylation at locus cg06340118 on survival time mediated through CD109 gene expression ($\mathbf{A \rightarrow M_3 \rightarrow Y}$) are negative. The negative correlation between DNA methylation and gene expression among the promoter region has been a pattern commonly found by a pan-cancer analyses (Anastasiadi, *et al.*, 2018; Spainhour, *et al.*, 2019).

7. Discussion

Two significant contributions have been made by this study. First, we provide a framework of causal multi-mediation analysis for an arbitrary number of ordered mediators, including a general definition and two approaches for addressing the difficulty of non-identifiability of traditional PSE. Second, we extend partPSE and iPSE into the context of the survival analysis. Based on Aalen's additive hazards model and Cox's proportional hazards model as well as normally distributed mediators, the analytic forms of partPSE and iPSE can be obtained in both HD and HR scales. In particular, when time-varying confounders are absence, the proposed iPSE is identical to the SEM estimator.

Several limitations merit notice, and some should be improved in further studies. First, the unmeasured confounding assumption is difficult to verified, and it is challenging to collect all possible covariates comprehensively. Sensitivity analysis technique is required in the future when a set of confounders are known in previous literature but not collected in a study. Second, this framework may not be applicable to settings with mediators truncated or semi-competed by the survival outcome, that could cause biased or even undefined PSE estimation. In the future, it is worthy to extend iPSE and partPSE into the analysis of truncated mediators. Third, although the causal multi-mediation analysis can detail the mechanism of causal effects, the causal structure including the order of mediators should be assumed based on domain knowledge. Finally, a criterion for path selection or mediator selection is necessary to increase the power of this method when the number of mediators is large.

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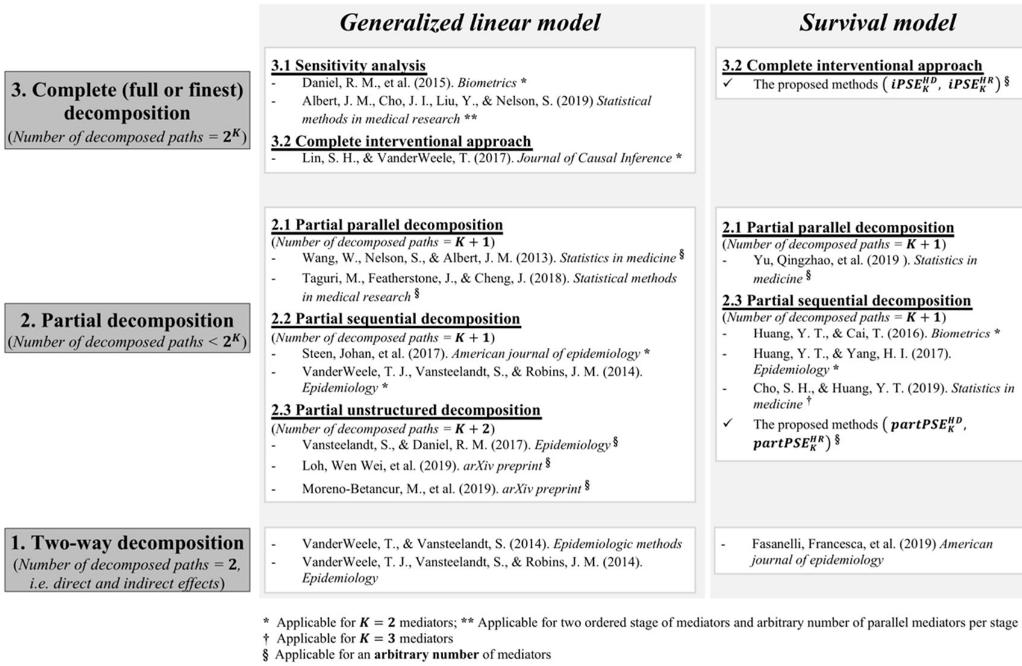

Figure 1. Literature review of causal multi-mediation analysis with *K* mediators.

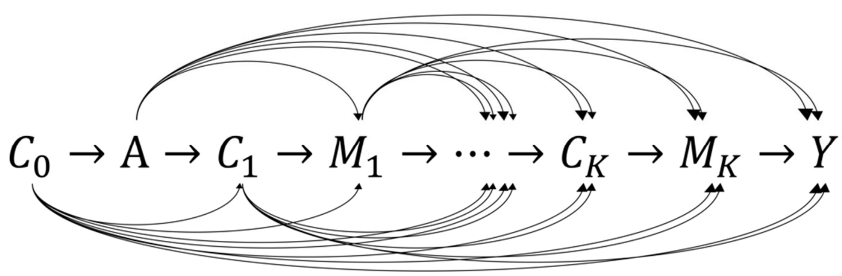

Figure 2. The causal relationship among all variables is demonstrated by a direct acyclic graph (DAG). A, $M_{(1,K)}$, Y, C_0, and $C_{(1,K)}$, denote the exposure, the mediators, the outcome, the baseline confounders, and the time-varying confounders, respectively.

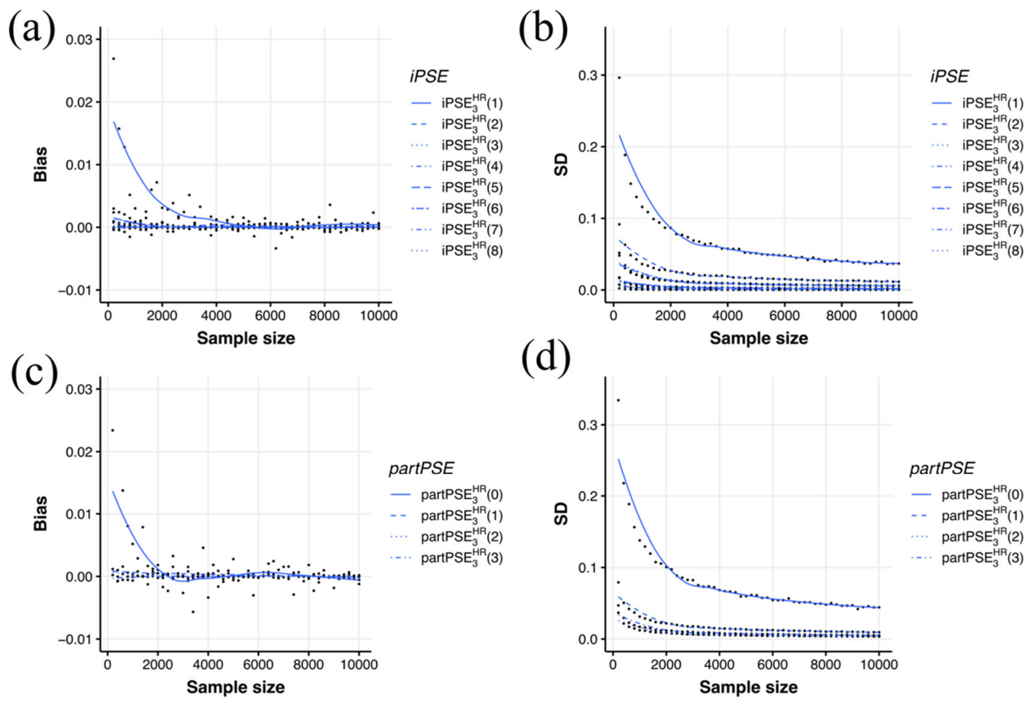

Figure 3. The scatter plots of bias and standard deviation across fifty different sample sizes uniformly selected from the interval of (200, 10000). (a) and (b) are the plots of bias and standard deviation (SD) for $iPSE_3^{HR}$ based on scenarios A, respectively. (c) and (d) are the plots of bias and SD for $partPSE_3^{HR}$ based on scenarios B, respectively. The smoothing curves are done by locally weighted regression, controlling the degree of smoothing at 0.6.

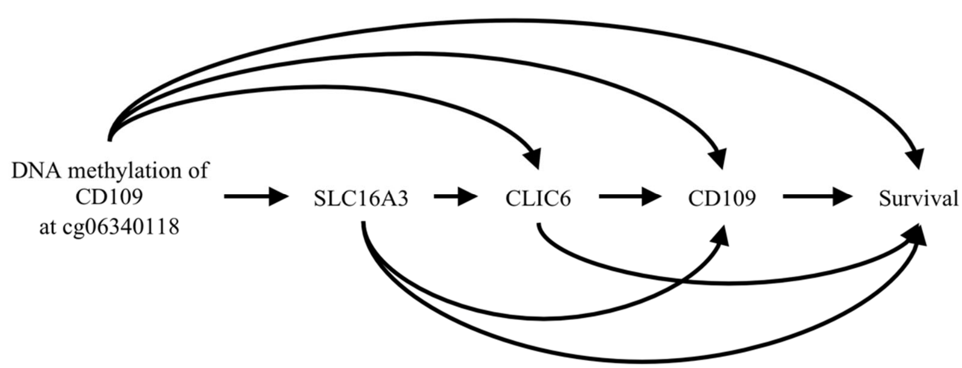

Figure 4. The causal diagram of DNA methylation of CD109, gene expression on different genes (including SLC16A3, CLIC6, and CD109), and lung cancer.

Table 1. Simulation result under the scenario A for $iPSE_3^{HR}$

Path*	True value	Bias	SD	RMSE	CR
A→Y	0.609	0.00300	0.11594	0.11598	95.3
A→M_1→Y	0.062	0.00082	0.03613	0.03614	94.8
A→M_2→Y	0.042	0.00088	0.01985	0.01987	95.1
A→M_1→M_2→Y	0.009	-0.0001	0.00566	0.00566	95.0
A→M_3→Y	0.016	0.00002	0.01768	0.01768	95.0
A→M_1→M_3→Y	0.003	0.00013	0.00664	0.00665	95.6
A→M_2→M_3→Y	0.001	0.00001	0.00273	0.00273	93.9
A→M_1→M_2→M_3→Y	0.0002	0.00001	0.00064	0.00064	94.4

*Both baseline confounders and time-varying confounders are present in each path.
Abbreviation: SD, standard deviation; RMSE, root mean square error; CR, coverage rate.

Table 2. Simulation result under the scenario B for $partPSE_3^{HR}$

Path*	True value	Bias	SD	RMSE	CR
A→Y	0.50000	0.00519	0.13789	0.13799	95.2
A→M_1Y**	0.02979	-0.00066	0.03134	0.03135	95.1
A→M_2Y**	0.01289	-0.00009	0.01217	0.01217	94.8
A→M_3→Y	0.00625	0.00033	0.01707	0.01707	93.8

*Only baseline confounders are present in each path.
**(A→M_2Y) = (A→M_2→Y) + (A→M_2→M_3→Y); (A→M_1Y) follows the same definition.
Abbreviation: SD, standard deviation; RMSE, root mean square error; CR, coverage rate.

Table 3. Effect decomposition of CD109 methylation (**A**) on lung cancer (**Y**) through the gene expression of SLC16A3 (**M_1**), CLIC6 (**M_2**), and CD109 (**M_3**).

Path	Aalen's additive hazards model (in HD scale)				Cox's proportional hazards model (in log HR scale)			
	$iPSE_3^{HD}$		$partPSE_3^{HD}$		$iPSE_3^{HR}$		$partPSE_3^{HR}$	
	PSE (SD)	P value	PSE (SD)	P value	PSE (SD)	P value	PSE (SD)	P value
A→Y	0.061 (0.002)	0.002*	0.061 (0.020)	0.002*	0.397 (0.128)	0.002*	0.397 (0.128)	0.002*
A→M_1→Y	-0.015 (0.006)	0.016*	-0.018 (0.007)	0.008*	-0.095 (0.037)	0.011*	-0.113 (0.040)	0.005*
A→M_1→M_3→Y	-0.002 (0.006)	0.057			-0.018 (0.028)	0.039*		
A→M_1→M_2→Y	-0.0001 (0.001)	0.927			-5×10^{-4} (0.005)	0.922		
A→M_1→M_2→M_3→Y	-8×10^{-6} (0.013)	0.933			-1×10^{-4} (0.077)	0.929		
A→M_2→Y	-0.013 (0.001)	0.018*	-0.015 (0.006)	0.013*	-0.075 (0.009)	0.009*	-0.085 (0.031)	0.006*
A→M_2→M_3→Y	-0.001 (0.001)	0.108			-0.01 (0.006)	0.082		
A→M_3→Y	-0.029 (0.0001)	0.024*	-0.029 (0.013)	0.024*	-0.197 (0.001)	0.009*	-0.199 (0.077)	0.009*

* P value < 0.05
Abbreviation: PSE, path-specific effect; HD, hazard difference; HR, hazard ratio; SD, standard deviation.