Causal mediation analysis with multiple time-varying mediators

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Abstract

In longitudinal studies with time-varying exposures and mediators, the mediational g-formula is an important method for the assessment of direct and indirect effects. However, current methodologies based on the mediational g-formula can deal with only one mediator. This limitation makes these methodologies inapplicable to many scenarios. Hence, we develop a novel methodology by extending the mediational g-formula to cover cases with multiple time-varying mediators. We formulate two variants of our approach that are each suited to a distinct set of assumptions and effect definitions and present nonparametric identification results of each variant. We further show how complex causal mechanisms (whose complexity derives from the presence of multiple time-varying mediators) can be untangled. A parametric method along with a user-friendly algorithm was implemented in R software. We illustrate our method by investigating the complex causal mechanism underlying the progression of chronic obstructive pulmonary disease. We found that the effects of lung function impairment mediated by dyspnea symptoms and mediated by physical activity accounted for 13.7% and 10.8% of the total effect, respectively. Our analyses thus illustrate the power of this approach, providing evidence for the mediating role of dyspnea and physical activity on the causal pathway from lung function impairment to health status.

Introduction

Causal mediation analysis has been widely applied to assess how mediators of interest might explain some of the effect of an exposure on an outcome. Various well-formulated methodologies have been proposed for studies with point exposures in which the effects of interested are for an exposure at a certain given time point (Huang and Yang, 2017; Huang and Cai, 2015; Lin and VanderWeele, 2017; VanderWeele and Vansteelandt, 2014; VanderWeele and Vansteelandt, 2010; Vansteelandt and Daniel, 2017). However, attention on mediation analysis for longitudinal studies with time-varying exposures and mediators has been more limited. The mediational g-formula (Lin et al., 2017a; VanderWeele and Tchetgen Tchetgen, 2017) proposed by VanderWeele and Tchetgen Tchetgen successfully extends Robins' g-formula to causal mediation analysis in longitudinal studies. This method can also adjust for time-varying confounders. A user-friendly software package based on an SAS macro has been developed (Lin et al., 2017a) along with an extension to survival settings (Lin et al., 2017b).

However, the present form of the mediational g-formula can deal with only one mediator at a time. This limitation makes the formula inapplicable to many scenarios. We aim to remedy this limitation by providing new methodology to address this setting; and we use the potential mechanisms underlying chronic obstructive pulmonary disease (COPD) as an example.

For patients with COPD, airflow limitation is a crucial predictor of early mortality, exacerbations and poor health related quality of life (HRQL). However, the causal mechanism through which early poor lung function causes poor HRQL features a complex interrelationship among several factors. Specifically, airflow limitation leads to COPD exacerbations, lung hyperinflation, and reduced exercise capacity. Such a

reduction in exercise capacity further induces the vicious cycle of dyspnea, physical inactivity, and depression and anxiety among patients with COPD. These factors may serve as both mediators and confounders in the causal pathway from poor lung function to impaired life quality (Ramon et al., 2018). For example, patients with low physical activity may exhibit more depressive symptoms and depression that, in turn, may make them less physically active. Therefore, depression both mediates and confounds the association between low physical activity and poor HRQL. However, studies have yet to address how such complex relationships in longitudinal studies can be analyzed using modern methods in causal inference. Thus, to solve this problem, it is crucial to develop methods that allow for multiple time-varying mediators.

This study extends the mediational g-formula to settings with multiple time-varying mediators. We propose two variants of our approach. The first variant is a two-way decomposition approach based on the method of VanderWeele and Vansteelandt; this variant is applicable if the causal structures relating the multiple mediators to one another are unclear (VanderWeele and Vansteelandt, 2014). The second variant is a decomposition approach based on the method of Vansteelandt and Daniel (2017) and this variant can be used if the causal structures among mediators are known and if the contribution of each mediator to the causal effect is of interest to the analyst. We also state the assumptions required for identification for each variant, propose a parametric method along with a user-friendly algorithm implemented in R, and illustrate our method by investigating the complex causal mechanism underlying COPD disease progression.

Methods

Brief review of causal mediation analysis under fixed-time settings: Natural direct and indirect effects and their random-intervention analogues

First, consider a setting with an exposure, mediator, and outcome measured at a single time point. Let A, Y, and M denote the exposure, the outcome, and a mediator, respectively, and let V denote a set of baseline confounders. The relations between these variables are illustrated in Figure 1(A). Based on counterfactual models (Hernán, 2004; Rubin, 1990), $Y(a)$ and $M(a)$ denote the counterfactual values of the outcome and mediator, respectively, if the exposure A is set to a. $Y(a, m)$ is the counterfactual value of the outcome if the exposure A and mediator M are set to a and m, respectively. Additionally, $Y(a, M(a^*))$ is the counterfactual value of the outcome if the exposure A and mediator M are set to a and $M(a^*)$, respectively. We also require the consistency assumption (Pearl, 2009; VanderWeele and Vansteelandt, 2009; VanderWeele, 2009); under this assumption, $Y(a) = Y$ and $M(a) = M$ if $A = a$, and $Y(a, m) = Y$ if $A = a$ and $M = m$. We also require the composition assumption, according to which $Y(a, M(a^*)) = Y$ if $A = a$ and $M = M(a^*)$.

To investigate the magnitude of the overall effect of A on Y as mediated by M, we decompose the overall effect into two components: a direct effect (the component of the effect that does not pass through the mediator) and an indirect effect (the component that passes through the mediator). Based on counterfactual models, causal mediation analysis distinguishes effects into the total effect (TE), natural direct effect (NDE), and natural indirect effect (NIE) to represent the overall, direct, and indirect effects, respectively. Formally, let $A = a$ and $A = a^*$ denote the two hypothetical intervention statuses of exposure and nonexposure. The corresponding effect definitions are $\text{TE} \equiv E[Y(a) - Y(a^*)]$, $\text{NDE} \equiv E[Y(a, M(a^*)) - Y(a^*, M(a^*))]$, and $\text{NIE} \equiv E[Y(a, M(a)) - Y(a, M(a^*))]$ (Pearl, 2001; Robins and Greenland, 1992; VanderWeele and Vansteelandt, 2009). However, in the presence of time-varying

confounders, the NDE and NIE cannot be straightforwardly identified from the data even if these confounders are observed.(Avin, Shpitser and Pearl, 2005; VanderWeele, 2015) To address the problem of identification, an alternative definition uses the interventional analogues of TE, NDE, and NIE (abbreviated as iTE, IDE, and IIE, respectively) to represent the overall, direct, and indirect effects, respectively (Didelez, Dawid and Geneletti, 2012; Geneletti, 2007; VanderWeele, Vansteelandt and Robins, 2014). Let $G(a)$ denote a random draw from the mediator distribution with an exposure status of $A = a$. Then, iTE is defined as $E[Y(a, G(a))] - E[Y(a^*, G(a^*))]$. IDE is defined as $E[Y(a, G(a^*))] - E[Y(a^*, G(a^*))]$; this compares the effects of exposure to no exposure on the outcome with the mediator randomly drawn from a population without exposure. Finally, IIE is defined as $E[Y(a, G(a))] - E[Y(a, G(a^*))]$; this compares the effects of randomly drawing the mediator from populations with and without exposure. We have the decomposition

$$E[Y(a, G(a))] - E[Y(a^*, G(a^*))]$$
$$= \{E[Y(a, G(a))] - E[Y(a, G(a^*))]\} + \{E[Y(a, G(a^*))] - E[Y(a^*, G(a^*))]\},$$

where the overall effect is decomposed as a sum of the direct and indirect effects.

Under four assumptions that there exist (1) $Y(a, m) \perp A|V$ (no unmeasured exposure–outcome confounder, where $\perp$ denotes independence), (2) $Y(a, m) \perp M|A, V$ (no unmeasured mediator–outcome confounder), (3) $M(a) \perp A|V$ (no unmeasured exposure–mediator confounder), and (4) $Y(a, m) \perp M(a^*)|V$ (no mediator–outcome confounder affected by the exposure) (Avin et al., 2005; VanderWeele and Vansteelandt, 2009), the NDE and NIE are identified as

$$\sum_v \sum_m \{E[Y|a, m, v] - E[Y|a^*, m, v]\}P(m|a^*, v)P(v) \text{ and}$$
$$\sum_v \sum_m E[Y|a, m, v]\{P(m|a, v) - P(m|a^*, v)\}P(v),$$

respectively. However, the fourth assumption is violated when an existing mediator–outcome confounder L is affected by the exposure (Figure 1(B)), even if this confounder is observed.

If the fourth assumption fails, but assumptions (1) to (3) hold and the mediator–outcome confounder is observed, then IDE and IIE are still identifiable from the data using the formulas

$\sum_{v,l,m}\{E[Y|a,l,m,v]P(l|a,v) - E[Y|a^*,l,m,v]P(l|a^*,v)\}P(m|a^*,v)P(v)$ and
$\sum_{v,l,m}E[Y|a,l,m,v]P(l|a,v)\{P(m|a,v) - P(m|a^*,v)\}P(v)$, respectively.

Obviously, the fourth assumption does not hold under time-varying settings. Therefore, the interventional direct and indirect effects, instead of natural direct and indirect effects, are adopted for the rest of this article.

Review of causal mediation analysis with one time-varying mediator: The mediational g-formula

Consider exposures, mediators, and confounders that vary over time in longitudinal settings and are measured at times $t = 0, 1, 2, \ldots, T-1$. Let $(A_{(0)}, A_{(1)}, \ldots, A_{(T-1)})$, $(M_{(0)}, M_{(1)}, \ldots, M_{(T-1)})$, and $(L_{(0)}, L_{(1)}, \ldots, L_{(T-1)})$ denote the values of the time-varying exposures, mediators, and confounders, respectively, at times $0, \ldots, T-1$ in relation to the final outcome of interest Y. The baseline confounders are denoted as V. Figure 1(C) depicts a possible data generating mechanism under which these assumptions would hold.

For any variable W, let $\widetilde{W}_{(t)} = (W_{(0)}, W_{(1)}, \ldots, W_{(t)})$ and $\widetilde{W} = \widetilde{W}_{(T-1)} = (W_{(0)}, W_{(1)}, \ldots, W_{(T-1)})$. Let $Y(\tilde{a}, \widetilde{m})$ be the counterfactual value of Y given $\tilde{A} = \tilde{a}$ and $\widetilde{M} = \widetilde{m}$. Let $M_{(t)}(\tilde{a})$ be the counterfactual value of $M_{(t)}$ given $\tilde{A}_{(t)} = \tilde{a}_{(t)}$. Let $G_{(t)}(\tilde{a})$ denote a random draw from the distribution of the mediator $M_{(t)}(\tilde{a})$. Let $\tilde{A} =$

$\tilde{a}$ and $\tilde{A} = \tilde{a}^*$ denote the two hypothetical intervention statuses of exposure and nonexposure, respectively. In this setting, we define TE as $E[Y(\tilde{a})] - E[Y(\tilde{a}^*)]$ (i.e., $E[Y(\tilde{a}, M(\tilde{a}))] - E[Y(\tilde{a}^*, M(\tilde{a}^*))]$), NDE as $E[Y(\tilde{a}, M(\tilde{a}^*))] - E[Y(\tilde{a}^*, M(\tilde{a}^*))]$, and NIE as $E[Y(\tilde{a}, M(\tilde{a}))] - E[Y(\tilde{a}, M(\tilde{a}^*))]$. We also define the iTE as $E[Y(\tilde{a}, G(\tilde{a}))] - E[Y(\tilde{a}^*, G(\tilde{a}^*))]$, IDE as $E[Y(\tilde{a}, G(\tilde{a}^*))] - E[Y(\tilde{a}^*, G(\tilde{a}^*))]$, and IIE as $E[Y(\tilde{a}, G(\tilde{a}))] - E[Y(\tilde{a}, G(\tilde{a}^*))]$. We also can decompose TE into NDE and NIE. Similarly, iTE is decomposed into IDE and IIE (i.e., $E[Y(\tilde{a}, G(\tilde{a}))] - E[Y(\tilde{a}^*, G(\tilde{a}^*))] = \{E[Y(\tilde{a}, G(\tilde{a}^*))] - E[Y(\tilde{a}^*, G(\tilde{a}^*))]\} + \{E[Y(\tilde{a}, G(\tilde{a}))] - E[Y(\tilde{a}, G(\tilde{a}^*))]\}$).

Three assumptions are required for identifying iTE, IDE, and IIE for all t: (1) $Y(\tilde{a}, \widetilde{m}) \perp A_{(t)} | \tilde{A}_{(t-1)}, \widetilde{M}_{(t-1)}, \tilde{L}_{(t)}, V$ (no exposure–outcome confounding conditional on past variables), (2) $Y(\tilde{a}, \widetilde{m}) \perp M_{(t)} | \tilde{A}_{(t)}, \widetilde{M}_{(t-1)}, \tilde{L}_{(t)}, V$ (no mediator–outcome confounding conditional on past variables), and (3) $M_{(t)}(\tilde{a}) \perp A_{(t)} | \tilde{A}_{(t-1)}, \widetilde{M}_{(t-1)}, \tilde{L}_{(t)}, V$ (no exposure–mediator confounding conditional on past variables), where $X \perp Y \,|\, Z$ indicates that X is independent of Y conditional on Z. Given these three assumptions, VanderWeele and Tchetgen Tchetgen (2017) show that the IDE and IIE are identified nonparametrically by $Q^{(m)}(\tilde{a}, \tilde{a}^*) - Q^{(m)}(\tilde{a}^*, \tilde{a}^*)$ and $Q^{(m)}(\tilde{a}, \tilde{a}) - Q^{(m)}(\tilde{a}, \tilde{a}^*)$, where

$$Q^{(m)}(\tilde{a}_1, \tilde{a}_2) = \sum_{\widetilde{m}} \sum_{v, \tilde{l}} E[Y | \tilde{a}_1, \widetilde{m}, \tilde{l}, v] \prod_{t=0}^{T-1} P(l_{(t)} | \tilde{a}_{1,(t-1)}, \widetilde{m}_{(t-1)}, \tilde{l}_{(t-1)}, v)$$
$$\times \sum_{\tilde{l}'} \prod_{t=0}^{T-1} P(m_{(t)} | \tilde{a}_{2,(t)}, \widetilde{m}_{(t-1)}, \tilde{l}'_{(t)}, v) P(l'_{(t)} | \tilde{a}_{2,(t-1)}, \widetilde{m}_{(t-1)}, \tilde{l}'_{(t-1)}, v) P(v).$$

This is referred to as the mediational g-formula. When mediators are absent (i.e., $\widetilde{M}$ is empty), $Q^{(m)}(\tilde{a}_1, \tilde{a}_2)$ reduces to

$$Q^{(g)}(\tilde{a}_1) = \sum_{v, \tilde{l}} E[Y | \tilde{a}_1, \tilde{l}, v] \prod_{t=0}^{T-1} P(l_{(t)} | \tilde{a}_{1,(t-1)}, \tilde{l}_{(t-1)}, v) P(v),$$

which is the standard g-formula.

Notation and causal structure for causal mediation analysis with multiple time-varying mediators

In this section, we consider cases with multiple time-varying mediators. Let $M_{k,(t)}$ denote the kth mediator measured for $t = 0, \dots, T-1$ and for $k = 1, \dots, K$. The causal relationship among all variables is illustrated in Figure 2(A). For simplicity, we explicitly give the exposition for two mediators, as in Figure 2(B), and it is straightforward to generalize to a case with an arbitrary number of mediators based on the framework provided below.

We propose two variants of our approach for conducting causal mediation analysis in the aforementioned setting. The first variant, called a two-way decomposition approach, treats all multiple time-varying mediators as a single multivariate mediator. The overall effect is decomposed into two components: one where a time-varying mediator is present (indirect effect) and the other where no mediator is present (direct effect). The second variant, called a path-specific approach, further decomposes the indirect effect according to the role of each specific mediator. The path-specific decomposition approach allows for the specific individual mediator mechanisms to be uncovered in greater detail, but at the cost of requiring more assumptions. We introduce these two variants in the following two subsections.

Variant 1: Two-way decomposition for multiple time-varying mediators

In this variant, we decompose iTE into IDE and IIE by treating multiple mediators as a single multivariate mediator (Figure 2(C)). IDE and IIE are defined as $E\big[Y(\tilde{a}, \tilde{G}(\tilde{a}^*))\big] - E\big[Y(\tilde{a}^*, \tilde{G}(\tilde{a}^*))\big]$ and $E\big[Y(\tilde{a}, \tilde{G}(\tilde{a}))\big] - E\big[Y(\tilde{a}, \tilde{G}(\tilde{a}^*))\big]$, respectively, where $\text{iTE} = \text{IDE} + \text{IIE}$. We also define a sensitivity parameter $\xi = \text{TE} - \text{iTE}$, which is the difference between the natural effect and intervention effect. As a result, we have $\text{TE} = \xi + \text{iTE} = \xi + \text{IDE} + \text{IIE}$. When time-varying confounders are absent and the three assumptions required for identification hold, $\xi = 0$ and iTE, IDE, and IIE are

reduced to TE, NDE, and NIE (Lin et al., 2017a; VanderWeele and Tchetgen Tchetgen, 2017). Although the three interventional effects (i.e., iTE, IDE, and IIE) have their own interpretation, we can use ζ to evaluate their suitability as analogues of natural effects.

To identify all causal effects, we make the following three assumptions:

(1) No unmeasured exposure–outcome confounding (i.e., $Y(\tilde{a}, \widetilde{m}_1, \widetilde{m}_2) \perp A_{(t)} | \tilde{A}_{(t-1)}, (\widetilde{M}_{1,(t-1)}, \widetilde{M}_{2,(t-1)}), \tilde{L}_{(t-1)}, V$ for $t = 0, 1, 2, \ldots, T-1$)

(2) No unmeasured mediator–outcome confounding (i.e., $Y(\tilde{a}, \widetilde{m}_1, \widetilde{m}_2) \perp (M_{1,(t)}, M_{2,(t)}) | \tilde{A}_{(t)}, (\widetilde{M}_{1,(t-1)}, \widetilde{M}_{2,(t-1)}), \tilde{L}_{(t)}, V$ for $t = 0, 1, 2, \ldots, T-1$)

(3) No unmeasured exposure–mediator confounding (i.e., $(M_{1,(t)}(\tilde{a}), M_{2,(t)}(\tilde{a})) \perp A_{(s)} | \tilde{A}_{(s-1)}, (\widetilde{M}_{1,(s-1)}, \widetilde{M}_{2,(s-1)}), \tilde{L}_{(s-1)}, V$ for $s = 0, \ldots, t$ and $t = 0, 1, 2, \ldots, T-1$)

Under the first assumption, TE can be identified as $Q^{(g)}(\tilde{a}) - Q^{(g)}(\tilde{a}^*)$, where

$$Q^{(g)}(\tilde{a}) =$$
$$\sum_{\widetilde{m}_1, \widetilde{m}_2} \sum_{v, \bar{l}} E[Y | \tilde{a}, \widetilde{m}_1, \widetilde{m}_2, \check{l}, v] \left[\prod_{t=0,\ldots,T-1} P\left(l_{(t)} | \tilde{a}_{(t)}, \widetilde{m}_{1,(t-1)}, \widetilde{m}_{2,(t-1)}, \check{l}_{(t-1)}, v\right) \right.$$
$$\left. \times \prod_{t=0,\ldots,T-1} P\left(m_{1,(t)}, m_{2,(t)} | \tilde{a}_{(t)}, \widetilde{m}_{1,(t-1)}, \widetilde{m}_{2,(t-1)}, \check{l}_{(t)}, v\right) \right] P(v).$$

Under all three assumptions, the four effects above ξ, iTE, IDE, and IIE can be identified as $\{Q^{(g)}(\tilde{a}) - Q^{(g)}(\tilde{a}^*)\} - \{Q^{(m)}(\tilde{a}, \tilde{a}) - Q^{(m)}(\tilde{a}^*, \tilde{a}^*)\}$, as $Q^{(m)}(\tilde{a}, \tilde{a}) - Q^{(m)}(\tilde{a}^*, \tilde{a}^*)$, as $Q^{(m)}(\tilde{a}, \tilde{a}^*) - Q^{(m)}(\tilde{a}^*, \tilde{a}^*)$, and as $Q^{(m)}(\tilde{a}, \tilde{a}) - Q^{(m)}(\tilde{a}, \tilde{a}^*)$, respectively, where

$$Q^{(m)}(\tilde{a}_1, \tilde{a}_2) =$$
$$\sum_{\widetilde{m}_1, \widetilde{m}_2} \sum_{v, \bar{l}} E[Y | \tilde{a}_1, \widetilde{m}_1, \widetilde{m}_2, \check{l}, v] \prod_{t=0,\ldots,T-1} P\left(l_{(t)} | \tilde{a}_{1,(t)}, \widetilde{m}_{1,(t-1)}, \widetilde{m}_{2,(t-1)}, \check{l}_{(t-1)}, v\right)$$
$$\times \sum_{\bar{l}'} \prod_{t=0,\ldots,T-1} P(m_{1,(t)}, m_{2,(t)} | \tilde{a}_{2,(t)}, \widetilde{m}_{1,(t-1)}, \widetilde{m}_{2,(t-1)}, \check{l}'_{(t)}, v)$$
$$\times P(l'_{(t)} | \tilde{a}_{2,(t)}, \widetilde{m}_{1,(t-1)}, \widetilde{m}_{2,(t-1)}, \check{l}'_{(t-1)}, v) P(v).$$

The derivation of $Q^{(m)}(\tilde{a}_1, \tilde{a}_2)$ straightforwardly follow by the mediational g-formula (VanderWeele and Tchetgen Tchetgen, 2017). This formula is identical to the mediational g-formula because the two time-varying mediators of interest are treated as a single multivariate variable. The interpretations for iTE, IDE, and IIE are the same. Because the two time-varying mediators are treated as a unified variable, we require no

knowledge on the causal structure between these two mediators; that is, it is not necessary to distinguish whether M_1 affects M_2 or M_2 affects M_1. Only the confounding between the exposure, mediator, and outcome must be adjusted for. Unmeasured confounding between mediators is allowed. However, we are sometimes interested in the importance of each mediator involved in the causal mechanism, which necessitates a further decomposition for the indirect effect. We therefore introduce our second variant in the following subsection.

Variant 2: Path-specific decomposition for multiple time-varying mediators

In this variant, we extend the framework of Vansteelandt and Daniel (2017) to the context of the present analysis (Figure 2(B)). We further decompose IIE into three parts: the part involving M_1 (path-specific effect 1, PSE$_1$), the part involving M_2 (path-specific effect 2, PSE$_2$), and the part involving the interdependence of M_1 and M_2 (mediator interdependence, MI). Namely, in this variant, we consider $TE = \xi + iTE = \xi + IDE + IIE = \xi + IDE + PSE_1 + PSE_2 + MI$. PSE_1, PSE_2, and MI are defined as follows:

$$PSE_1 = E\big[Y(\tilde{a}, \tilde{G}_1(\tilde{a}), \tilde{G}_2(\tilde{a}^*))\big] - E\big[Y(\tilde{a}, \tilde{G}_1(\tilde{a}^*), \tilde{G}_2(\tilde{a}^*))\big]$$

$$PSE_2 = E\big[Y(\tilde{a}, \tilde{G}_1(\tilde{a}), \tilde{G}_2(\tilde{a}))\big] - E\big[Y(\tilde{a}, \tilde{G}_1(\tilde{a}), \tilde{G}_2(\tilde{a}^*))\big]$$

$$MI = E\big[Y(\tilde{a}, \tilde{G}(\tilde{a}))\big] - E\big[Y(\tilde{a}^*, \tilde{G}(\tilde{a}^*))\big] - E\big[Y(\tilde{a}, \tilde{G}_1(\tilde{a}), \tilde{G}_2(\tilde{a}))\big]$$
$$+ E\big[Y(\tilde{a}^*, \tilde{G}_1(\tilde{a}^*), \tilde{G}_2(\tilde{a}^*))\big].$$

According to these definitions, the effect of A on Y mediated through both M_1 and M_2 is included into PSE_1 or PSE_2 depending on the causal structure of M_1 and M_2. Specifically, if M_1 is the cause of M_2, this effect is a part of PSE_2; if M_2 is the cause of M_1, then it is a part of PSE_1. Further discussions on PSE_1, PSE_2, and MI in the time-invariant exposure case can be found in previous works.(Tai and Lin, 2020; Vansteelandt and Daniel, 2017) In the following section, we use a structured equation

model (SEM) to explicitly illustrate the intuitive interpretation of the three components for the time-varying case.

To identify the aforementioned three effects, we must make four assumptions:
(1) No unmeasured exposure–outcome confounding (i.e., $Y(\tilde{a}, \tilde{m}_1, \tilde{m}_2) \perp A_{(t)} | \tilde{A}_{(t-1)}, \tilde{M}_{1,(t-1)}, \tilde{M}_{2,(t-1)}, \tilde{L}_{(t-1)}, V$ for $t = 0, 1, 2, \ldots, T-1$)
(2) No unmeasured mediator–outcome confounding (i.e., $Y(\tilde{a}, \tilde{m}_1, \tilde{m}_2) \perp (M_{1,(t)}, M_{2,(t)}) | \tilde{A}_{(t)}, \tilde{M}_{1,(t-1)}, \tilde{M}_{2,(t-1)}, \tilde{L}_{(t)}, V$ for $t = 0, 1, 2, \ldots, T-1$)
(3) No unmeasured exposure–first mediator confounding (i.e., $M_{1,(t)}(\tilde{a}) \perp A_{(s)} | \tilde{A}_{(s-1)}, \tilde{M}_{1,(s-1)}, \tilde{M}_{2,(s-1)}, \tilde{L}_{(s-1)}, V$ for $s = 0, \ldots, t$ and $t = 0, 1, 2, \ldots, T-1$)
(4) No unmeasured exposure–second mediator confounding (i.e., $M_{2,(t)}(\tilde{a}) \perp A_{(s)} | \tilde{A}_{(s-1)}, \tilde{M}_{1,(s-1)}, \tilde{M}_{2,(s-1)}, \tilde{L}_{(s-1)}, V$ for $s = 0, \ldots, t$ and $t = 0, 1, 2, \ldots, T-1$)

Under these four assumptions, PSE_1, PSE_2, and MI can be identified in terms of $Q^{(m)}$ and $Q^{(mt)}$ as follows (see Web Appendix A for details):

$$PSE_1 = Q^{(mt)}(\tilde{a}, \tilde{a}, \tilde{a}^*) - Q^{(mt)}(\tilde{a}, \tilde{a}^*, \tilde{a}^*)$$
$$PSE_2 = Q^{(mt)}(\tilde{a}, \tilde{a}, \tilde{a}) - Q^{(mt)}(\tilde{a}, \tilde{a}, \tilde{a}^*)$$
$$MI = Q^{(m)}(\tilde{a}, \tilde{a}) - Q^{(m)}(\tilde{a}^*, \tilde{a}^*) - Q^{(mt)}(\tilde{a}, \tilde{a}, \tilde{a}) + Q^{(mt)}(\tilde{a}^*, \tilde{a}^*, \tilde{a}^*)$$

where

$$
\begin{aligned}
Q^{(mt)}&(\tilde{a}, \tilde{e}_1, \tilde{e}_2) \\
&= \sum_{\tilde{l}, \tilde{m}_1, \tilde{m}_2, v} E[Y | \tilde{a}, \tilde{l}, \tilde{m}_1, \tilde{m}_2, v] \\
&\quad \times \prod_{u=0,\ldots,T-1} P(l_{(u)} | \tilde{a}_{(u)}, \tilde{l}_{(u-1)}, \tilde{m}_{1,(u-1)}, \tilde{m}_{2,(u-1)}, v) \\
&\quad \times \sum_{\tilde{m}_2^*} \sum_{\tilde{l}^*} \prod_{s=0,\ldots,T-1} \{ P(m_{1,(s)}, m_{2,(s)}^* | \tilde{e}_{1,(s)}, \tilde{l}_{(s)}^*, \tilde{m}_{1,(s-1)}, \tilde{m}_{2,(s-1)}^*, v) \\
&\qquad\qquad \times P(l_{(s)}^* | \tilde{e}_{1,(s)}, \tilde{l}_{(s-1)}^*, \tilde{m}_{1,(s-1)}, \tilde{m}_{2,(s-1)}^*, v) \} \\
&\quad \times \sum_{\tilde{m}_1^*} \sum_{\tilde{l}^{**}} \prod_{s=0,\ldots,T-1} \{ P(m_{1,(s)}^*, m_{2,(s)} | \tilde{e}_{2,(s)}, \tilde{l}_{(s)}^{**}, \tilde{m}_{1,(s-1)}^*, \tilde{m}_{2,(s-1)}, v) \\
&\qquad\qquad \times P(l_{(s)}^{**} | \tilde{e}_{2,(s)}, \tilde{l}_{(s-1)}^{**}, \tilde{m}_{1,(s-1)}^*, \tilde{m}_{2,(s-1)}, v) \} P(v).
\end{aligned}
$$

This decomposition strategy is similar to that described by Yamamuro et al. (2021).

Although the counterfactual definition is almost identical, the final identification result is different. The formula proposed by Yamamuro et al., in our notation, can be expressed as follows:

$$Q^{(mt)}(\tilde{a}, \tilde{e}_1, \tilde{e}_2)$$

$$= \sum_{\tilde{l}, \widetilde{m}_1, \widetilde{m}_2, v} E[Y \mid \tilde{a}, \tilde{l}, \widetilde{m}_1, \widetilde{m}_2, v]$$

$$\times \prod_{u=0,\dots,T-1} P(l_{(u)} \mid \tilde{a}_{(u)}, \tilde{l}_{(u-1)}, \widetilde{m}_{1,(u-1)}, \widetilde{m}_{2,(u-1)}, v)$$

$$\times \sum_{\tilde{l}^*} \prod_{s=0,\dots,T-1} \{ P(m_{1,(s)} \mid \tilde{e}_{1,(s)}, \tilde{l}^*_{(s)}, \widetilde{m}_{1,(s-1)}, \widetilde{m}_{2,(s-1)}, v)$$

$$\times P(l^*_{(s)} \mid \tilde{e}_{1,(s)}, \tilde{l}^*_{(s-1)}, \widetilde{m}_{1,(s-1)}, \widetilde{m}_{2,(s-1)}, v) \}$$

$$\times \sum_{\tilde{l}^{**}} \prod_{s=0,\dots,T-1} \{ P(m_{2,(s)} \mid \tilde{e}_{2,(s)}, \tilde{l}^{**}_{(s)}, \widetilde{m}_{1,(s-1)}, \widetilde{m}_{2,(s-1)}, v)$$

$$\times P(l^{**}_{(s)} \mid \tilde{e}_{2,(s)}, \tilde{l}^{**}_{(s-1)}, \widetilde{m}_{1,(s-1)}, \widetilde{m}_{2,(s-1)}, v) \} P(v).$$

The second term $(\sum_{\tilde{l}^*} \prod_{s=0,\dots,T-1} \{ P(m_{1,(s)} \mid \tilde{e}_{1,(s)}, \tilde{l}^*_{(s)}, \widetilde{m}_{1,(s-1)}, \widetilde{m}_{2,(s-1)}, v)$

$\times P(l^*_{(s)} \mid \tilde{e}_{1,(s)}, \tilde{l}^*_{(s-1)}, \widetilde{m}_{1,(s-1)}, \widetilde{m}_{2,(s-1)}, v) \})$ is the function of both $\tilde{e}_1$ and $\widetilde{m}_2$,

while the second term in our formula is just a function of $\tilde{e}_1$

$(\sum_{\widetilde{m}_2^*} \sum_{\tilde{l}^*} \prod_{s=0,\dots,T-1} \{ P(m_{1,(s)}, m^*_{2,(s)} \mid \tilde{e}_{1,(s)}, \tilde{l}^*_{(s)}, \widetilde{m}_{1,(s-1)}, \widetilde{m}^*_{2,(s-1)}, v)$

$\times P(l^*_{(s)} \mid \tilde{e}_{1,(s)}, \tilde{l}^*_{(s-1)}, \widetilde{m}_{1,(s-1)}, \widetilde{m}^*_{2,(s-1)}, v) \}$). Since the second term is

corresponding to the $\tilde{G}_1(\tilde{e}_1)$, of which the value should only depend on $\tilde{e}_1$. Similar argument is applicable for the third term. Therefore, we believe that the proposed formula is the accurate extension of Vansteelandt's and Daniel's framework to the context of the present analysis.

Interpretation of path-specific effects and MI with structural equation modeling for simple cases

In this section, we discuss the interpretation of time-varying path-specific effects in the simplest case with only one fixed exposure (A), two time-varying mediators measured at two time points ($M_{1,(0)}$, $M_{2,(0)}$, $M_{1,(1)}$, $M_{2,(1)}$), and one outcome (Y).

Time-varying and baseline confounders are absent. The causal diagram is illustrated in Figure 3(A).

Recall that we obtain four components from the TE (i.e., IDE, PSE_1, PSE_2, and MI) in the case with two time-varying mediators. If we treat $(M_{1,(0)}, M_{2,(0)}, M_{1,(1)}, M_{2,(1)})$ as four distinct mediators, then the path from the exposure to the outcome can be decomposed into $2^4 = 16$ paths. IDE is identical to the direct effect, whereas the sum of PSE_1, PSE_2, and MI corresponds to the indirect effect. In addition, PSE_1 represents the indirect effect when the first mediator directly induces the outcome during the follow-up period. Specifically, the mediation paths corresponding to PSE_1 are the paths ending at $M_{1,(0)}$ and the paths ending at $M_{1,(1)}$. Similarly, PSE_2 is the indirect effect when the second mediator directly induces the outcome during the follow-up period. The mediation paths corresponding to PSE_2 are the paths ending at $M_{2,(0)}$ and the paths ending at $M_{2,(1)}$. The path mapping for PSE_1 and PSE_2 is detailed in Web Appendix B and depicted in Figure 3. As noted by Vansteelandt and Daniel (2017) MI captures the indirect effects relating to the effect of A on the dependence between $M_{1,(0)}$, $M_{2,(0)}$, $M_{1,(1)}$, and $M_{2,(1)}$, which does not belong to any path from the exposure to the outcome.

Moreover, to further illustrate the relationship between PSEs and the mediation paths, we construct a structural equation model (Web Appendix C) in which the estimators of PSE_1, PSE_2, and MI are derived under simple regression models with a mediator–mediator interaction term. Taking a product-method perspective, we show that the estimators of PSE_1 and PSE_2 correspond exactly to the paths present in Figures 3(B) and 3(C), respectively. The estimator of MI is shown to be related to the dependence between mediators.

Choosing between the two variants: Two-way or path-specific decomposition?

The two-way and path-specific decomposition variants proposed in this study have their unique uses and conditions under which they can be applied. Unlike path-specific decomposition, two-way decomposition does not require knowledge of the structures relating the mediators to each other. With regard to this assumption, correctly specifying the relationships between mediators can be challenging, especially in time-varying settings. Moreover, two-way decomposition into direct and indirect effects enables researchers to intuitively interpret the causal mechanism. However, if a more detailed investigation into the causal mechanism is required, path-specific decomposition is recommended. Indeed, the success of path-specific decomposition depends largely on the assumption that the analyst's mediation structure is correct. Consequently, the choice between the two-way decomposition and path-specific decomposition variants is a trade-off in which more information is obtained at the cost of making more assumptions and vice versa.

The decision flowchart in Figure 4 illustrates the process of selecting the appropriate variant. Briefly, the two-way decomposition variant, path-specific decomposition variant, or the mediational g-formula is recommended based on what results that the analyst wants to obtain and the assumptions that the analyst can make (VanderWeele and Tchetgen Tchetgen, 2017).

Parametric estimation method for time-varying PSE.

The estimation methods of the mediational g-formula (Lin et al., 2017a; VanderWeele and Tchetgen Tchetgen, 2017) can be directly applied to the statistical inference in the first, two-way variant, which treats all mediators as one multivariate mediator. Thus, in this section, we provide a G-computation-based method of

parametric estimation for the second, path-specific variant. Note that the second variant can be used to evaluate PSE_1, PSE_2, and MI, which are composed of $Q^{(mt)}(\tilde{a}, \tilde{e}_1, \tilde{e}_2)$ and $Q^{(m)}(\tilde{a}_1, \tilde{a}_2)$. The estimation of $Q^{(m)}(\tilde{a}_1, \tilde{a}_2)$ can be implemented by the method based on the mediational g-formula. The proposed algorithm is used to estimate $Q^{(mt)}(\tilde{a}, \tilde{e}_1, \tilde{e}_2)$. The algorithm for two time-varying mediators is detailed in Web Appendix D. Because the algorithm relies on a Monte Carlo simulation, a sufficiently large number of random samples is required. Following a heuristic approach, the sampling number (K) was set to 10,000 in the empirical application of our method, which is presented in the following section.

Illustration

We applied our analytical approaches to the dataset of the International Collaborative Effort on Chronic Obstructive Lung Disease: Exacerbation Risk Index Cohorts (ICE COLD ERIC) study. The ICE COLD ERIC study recruited 409 patients with COPD who were cared for by general practitioners in two European countries (the Netherlands and Switzerland) during 2008 to 2009, and their health was prospectively followed for up to 5 years. The study initially included patients who were diagnosed with COPD, who were aged 40 years or older, and who were free from exacerbations for more than 4 weeks before baseline assessment. The study design is detailed in protocol of the ICE COLD ERIC study (Siebeling et al., 2009). The study was approved by the ethics boards of the University of Zurich and University of Amsterdam.

At baseline, medical histories (e.g., date of birth, smoking status, and previous exacerbations) were obtained for all patients, and they underwent physical examinations (e.g., anthropometric measurements and lung function tests). At baseline and at each 6-month follow-up, the patients were assessed using several questionnaires on their health-related quality of life, physical activity, and mental health. The

researchers of the ICE COLD ERIC study used the measures of dyspnea symptoms from the modified Medical Research Council (mMRC) scale, ranging from *none* (Grade 0) to *almost complete incapacity* (Grade 4). General health was measured using a feeling thermometer from 0 (worse health status) to 100 (perfect health status). The researched used the measures of physical activity from the Longitudinal Aging Study Amsterdam Physical Activity Questionnaire (LAPAQ), where patients gave a score from 0 (lowest physical activity level) to 23 (highest physical activity level) (Yu et al., 2016). Mental health was measured using the Hospital Anxiety and Depression Scale (HADS), which ranges from 0 (lowest level of depression or anxiety symptoms) to 21 (highest level of depression or anxiety symptoms).

By using data from the ICE COLD ERIC study, this application aims to estimate the causal effect of lung function impairment at baseline on poor health status (feeling thermometer score) at the 4-year follow-up visit. Normalized forced expiratory volume in 1 s (FEV1) is the standard measure of lung function impairment, and the patients in the ICE COLD ERIC study were segmented into stages I to IV according to their FEV1 level (stages I to IV are defined by FEV1 values of $\geq 80\%$, 50–79%, 30–49%, and <30%, respectively). In this illustration, we conducted two analyses: one in which stages II to IV were compared with stage I and another in which stages III and IV were compared with stages I and II. After excluding patients with missing data, we obtained a final sample size of 257. The aim was to determine the indirect effects through dyspnea and physical activity for the effect of lung function impairment and poor health status. We treated country, gender, age, BMI, and smoking status as baseline confounders and we treated depression and anxiety as time-varying confounders (Figure 5). The descriptive statistics of the demographic variables are presented in Table 2.

The estimated mediation effects are shown in Table 2. In the results of our first analysis (stages II to IV vs. stage I), the effect of lung function impairment at baseline on health status at the 4-year follow-up visit was −14.28 (95% confidence interval (CI): −22.52 to −7.77). Thus, after baseline and time-varying confounders were adjusted for, the feeling thermometer scores at the 4-year follow-up visit of patients with lung function impairment at baseline were, on average, 14.28 points lower than those of patients without lung function impairment at baseline. The mediation model indicated that dyspnea symptoms and physical activity accounted for 14.1% and 12.2% of the TE of lung function impairment, respectively. These results elucidate the mediating roles of dyspnea and physical activity on the causal pathway from lung function impairment to health status, which can aid the design of COPD intervention programs. The second analysis (stages III and IV vs. stages I and II) yielded similar results. This consistency suggests that the relative importance of the mediators may be robust to changes in the FEV1 threshold used to define lung function impairment.

Discussion

In this study, we formulated a method for mediation analysis with multiple time-varying mediators. To the best of our knowledge, this is the first method for evaluating causal effects mediated through multiple mediators for longitudinal studies. The primary challenge of multiple time-varying mediators is the complex relationships between mediators, which causes mediator-specific indirect effects. These effects cannot be obtained through existing single-mediator methods (notably the mediational g-formula (Lin et al., 2017a; VanderWeele and Tchetgen Tchetgen, 2017)), which have overlapping mediation paths. Thus, when multiple time-varying mediators are present,

existing methods based on the mediational g-formula yield an ambiguous interpretation of the causal effects when applied one mediator at a time. To remedy this problem, we developed two variants of our methodology. In the first variant, we directly adopted the mediational g-formula by treating multiple mediators as a single multivariate mediator; the second variant can be used to assess the path-specific effects. As illustrated in Figure 5, the choice between the two approaches entails a trade-off between obtaining more information and the cost of making more assumptions. For the second, path-specific variant, we showed how analysts can interpret our time-varying PSEs using structural equation modeling. We also provided a parametric estimation method for time-varying PSEs based on Monte Carlo simulation. The proposed method can facilitate the identification of causal mechanisms in longitudinal studies with multiple time-varying mediators.

Future studies on this topic could develop sensitivity analyses and also alternative approaches that can deal with survival outcomes. Specifically, sensitivity analysis could be used to assess biases that arise from the assumptions of unmeasured confounding being violated. Several bias formulas of sensitivity analysis (VanderWeele, 2010; VanderWeele and Arah, 2011) have been proposed in the context of time-invariant mediators, but a bias formula for multiple time-varying mediators is lacking. In the present study, we assume that all mediators are fully observed. However, this assumption is not satisfied in some medical or biological studies, especially for survival outcomes. In such cases, the mediators of some participants may be truncated by death or be censored due to loss to follow-up. Future work could likewise extend the present methodology to address these issues as well.

Acknowledgments

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Table 1. Descriptive statistics of demographics variables in the ICE COLD ERIC study.

	FEV1 at Baseline			
	Stages II-IV: FEV1 < 80% (N = 247)	**Stage I: FEV1 ≥ 80% (N = 10)**	**Stages III-IV: FEV1 < 50% (N = 85)**	**Stages I-II: FEV1 ≥ 50% (N = 172)**
Confounders				
Country *0: Netherlands* *1: Switzerland*	N = 114 (46.2%)	N = 7 (70%)	N = 43 (50.6%)	N = 78 (45.3%)
Gender *0: Male* *1: Female*	N = 100 (40.5%)	N = 7 (70%)	N = 36 (42.6%)	N = 71 (41.3%)
Age	Mean = 65.6 (SD = 9.5)	Mean =68.3 (SD = 10.8)	Mean = 65.8 (SD = 9.0)	Mean =65.7 (SD = 9.8)
BMI	Mean =26.5 (SD = 5.1)	Mean =24.9 (SD = 3.5)	Mean = 25.8 (SD = 4.5)	Mean =26.8 (SD = 5.2)
Smoking (pack-years)	Mean =44.1 (SD = 26.7)	Mean =42.3 (SD = 27.7)	Mean = 45.2 (SD = 27.0)	Mean =43.7 (SD = 26.6)
Depression				
Baseline	Mean =4.3 (SD = 3.7)	Mean =2.5 (SD = 1.7)	Mean = 4.9 (SD = 3.8)	Mean =3.9 (SD = 3.5)
2-year follow-up	Mean =5.0 (SD = 4.0)	Mean =3.2 (SD = 1.5)	Mean = 5.6 (SD = 4.3)	Mean =4.6 (SD = 3.6)
4-year follow-up	Mean =5.4 (SD = 4.1)	Mean =3.3 (SD = 2.5)	Mean = 6.4 (SD = 4.5)	Mean =4.8 (SD = 3.9)
Anxiety				
Baseline	Mean =4.8 (SD = 4.3)	Mean =4.1 (SD = 2.5)	Mean = 4.5 (SD = 4.1)	Mean =4.9 (SD = 4.3)
2-year follow-up	Mean =4.8 (SD =4.2)	Mean =4.0 (SD =2.5)	Mean = 4.9 (SD = 4.5)	Mean =4.6 (SD = 4.0)
4-year follow-up	Mean =5.0 (SD = 4.2)	Mean =3.8 (SD = 1.9)	Mean = 5.4 (SD = 4.5)	Mean =4.7 (SD =3.8)
Dyspnea				
Baseline	Mean =1.6 (SD = 1.4)	Mean =0.8 (SD = 0.8)	Mean = 2.23 (SD = 1.3)	Mean =1.3 (SD = 1.3)
2-year follow-up	Mean =1.6 (SD = 1.2)	Mean =0.8 (SD = 0.6)	Mean = 2.15 (SD = 1.1)	Mean =1.3 (SD = 1.2)
4-year follow-up	Mean =1.9 (SD = 1.2)	Mean =0.8 (SD = 0.8)	Mean = 2.47 (SD = 1.1)	Mean =1.5 (SD = 1.1)
Physical activity score				
Baseline	Mean =11.2 (SD = 4.8)	Mean =13.6 (SD = 5.4)	Mean = 10.4 (SD = 5.2)	Mean =11.8 (SD = 4.5)
2-year follow-up	Mean =10.6 (SD = 5.2)	Mean =12.9 (SD = 6.3)	Mean = 9.4 (SD = 5.3)	Mean =11.3 (SD = 5.1)
4-year follow-up	Mean =10.0 (SD = 5.3)	Mean =12.5 (SD = 6.0)	Mean = 8.8 (SD =5.7)	Mean =10.7 (SD = 5.2)
Feeling thermometer score				
Baseline	Mean = 69.2 (SD = 15.5)	Mean =85 (SD = 10.3)	Mean = 62.5 (SD = 15.9)	Mean =73.3 (SD = 14.3)
2-year follow-up	Mean = 68.0 (SD = 14.5)	Mean = 80.4 (SD = 13.0)	Mean = 61.5 (SD = 15.7)	Mean =71.9 (SD = 12.7)
4-year follow-up	Mean = 65.6 (SD = 16.9)	Mean = 78 (SD = 17.8)	Mean = 58.1 (SD = 17.2)	Mean =69.7 (SD =15.5)

Abbreviations: N: sample size; FEV1: forced expiratory volume in 1 s; SD: standard deviation

Table 2. Results of ICE COLD ERIC study.

Mediator		Estimate (Proportion)	95% CI	P value
(A) Outcome: feeling thermometer score at 4-year follow-up (FEV1 < 80%)				
Total Effect		-14.28	(-22.52, -7.77)	P < 0.001
Direct effect		-10.52 (73.7%)	(-18.98, -4.02)	P = 0.001
Indirect effect		-3.76 (26.3%)	(-5.47, -2.30)	P < 0.001
	Dyspnea	-2.03 (14.1%)	(-3.21, -0.96)	P < 0.001
	Physical activity	-1.74 (12.2%)	(-2.88, -0.84)	P < 0.001
MI		0.18	(0.10, 0.26)	P < 0.001
ξ		0.03	(-0.05, 0.11)	P = 0.216
(B) Outcome: feeling thermometer score at 4-year follow-up (FEV1 < 50%)				
Total Effect		-13.20	(-15.78, -10.67)	P < 0.001
Direct effect		-10.55 (79.9%)	(-13.19, -8.05)	P < 0.001
Indirect effect		-2.65 (20.1%)	(-3.88, -1.45)	P < 0.001
	Dyspnea	-1.65 (12.5%)	(-2.77, -0.55)	P = 0.002
	Physical activity	-1.00 (7.6%)	(-1.61, -0.48)	P < 0.001
MI		0.15	(0.07, 0.23)	P = 0.001
ξ		0.06	(-0.02, 0.14)	P = 0.067

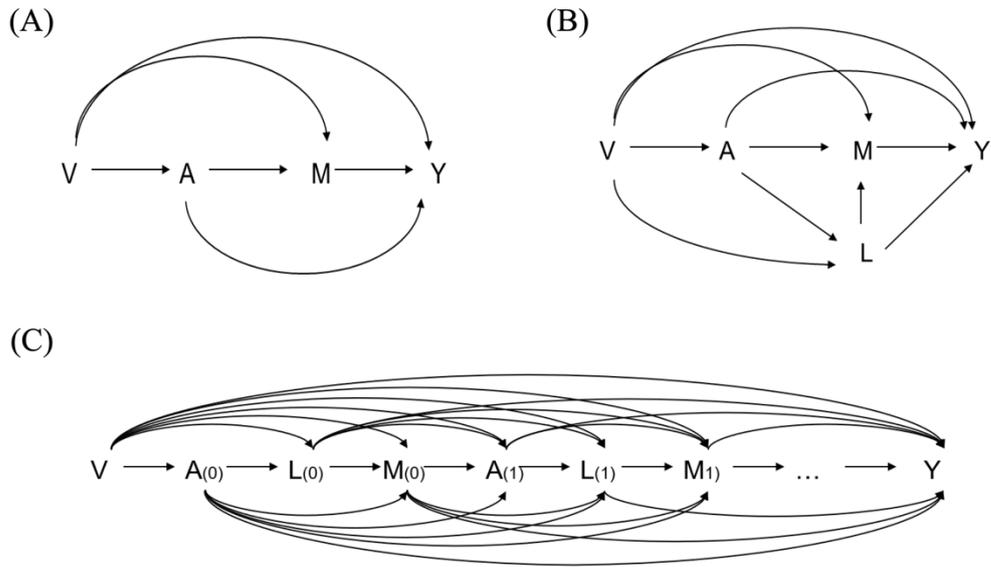Abbreviations: MI, mediator interdependence; FEV1, forced expiratory volume in 1 second.

Figure 1. (A) Simple model of mediation with baseline confounders (V), exposure (A), mediator (M), and the outcome (Y). (B) Mediation with a mediator–outcome confounder L that is affected by the exposure. (C) Time-varying mediation with ordering of variables of $A_{(t)}$, $L_{(t)}$, $M_{(t)}$, and Y. V denotes the baseline confounders.
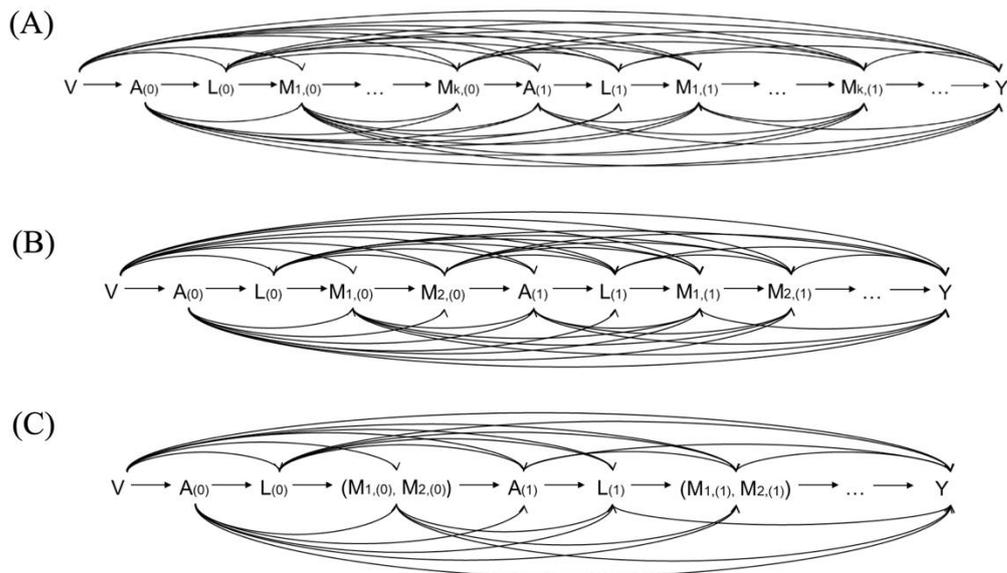

Figure 2. (A) Causal relationships between one time-varying exposure ($A_{(t)}$), K time-varying ordered mediators ($M_{1,(t)}$, $M_{2,(t)}$, …, $M_{K,(t)}$), a set of baseline confounders (V), set of time-varying confounders ($L_{(t)}$), and the outcome (Y). (B) Time-varying multiple

mediation with ordering of variables of $A_{(t)}$, $L_{(t)}$, $M_{1,(t)}$, and $M_{2,(t)}$. With only two time-varying mediators (i.e., $K = 2$), this is a simplification of the causal structure in (A). (C) Time-varying multiple mediation with ordering of variables V, $A_{(t)}$, $L_{(t)}$, and $(M_{1,(t)}, M_{2,(t)})$.
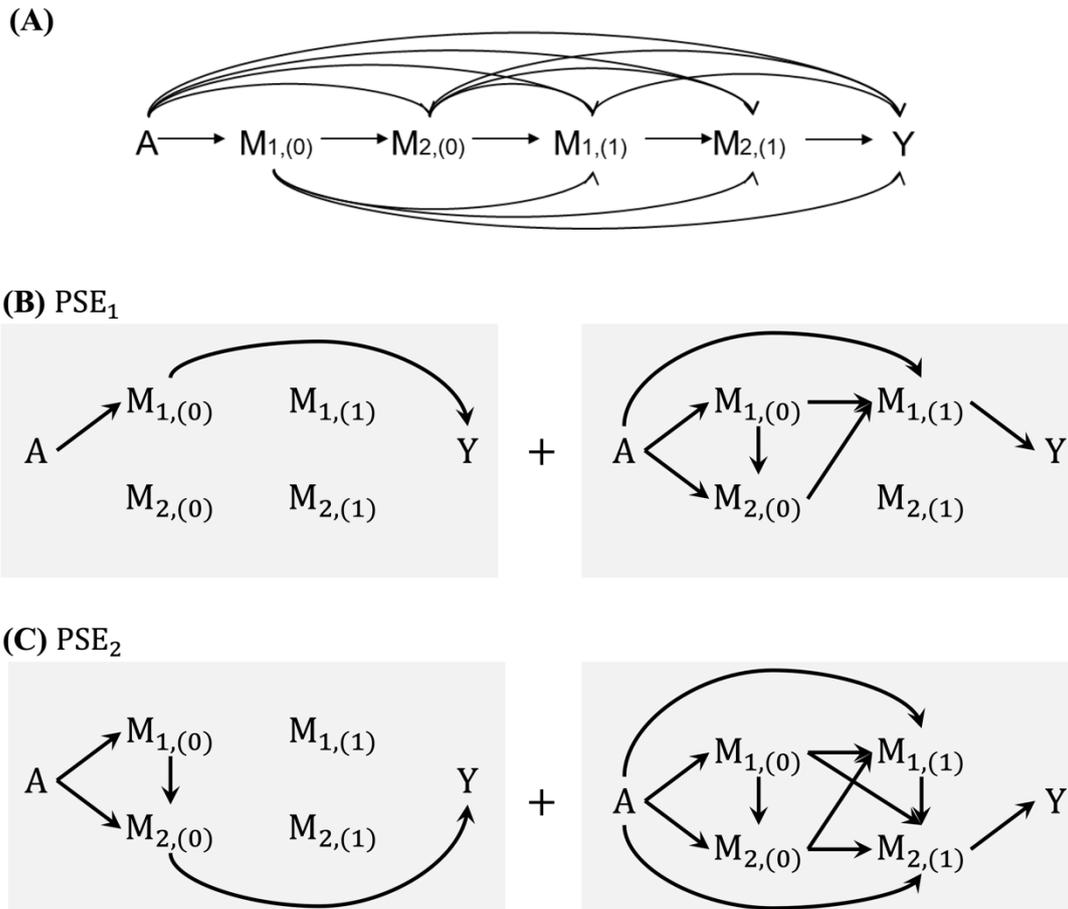
(A)

(B) PSE_1

(C) PSE_2

Figure 3. (A) Causal structure with one exposure, two causal mediators measured at two time points, and an outcome of interest. Path visualization of (B) PSE_1 and (C) PSE_2 with two mediators measured at times $t = 1$ and 2.
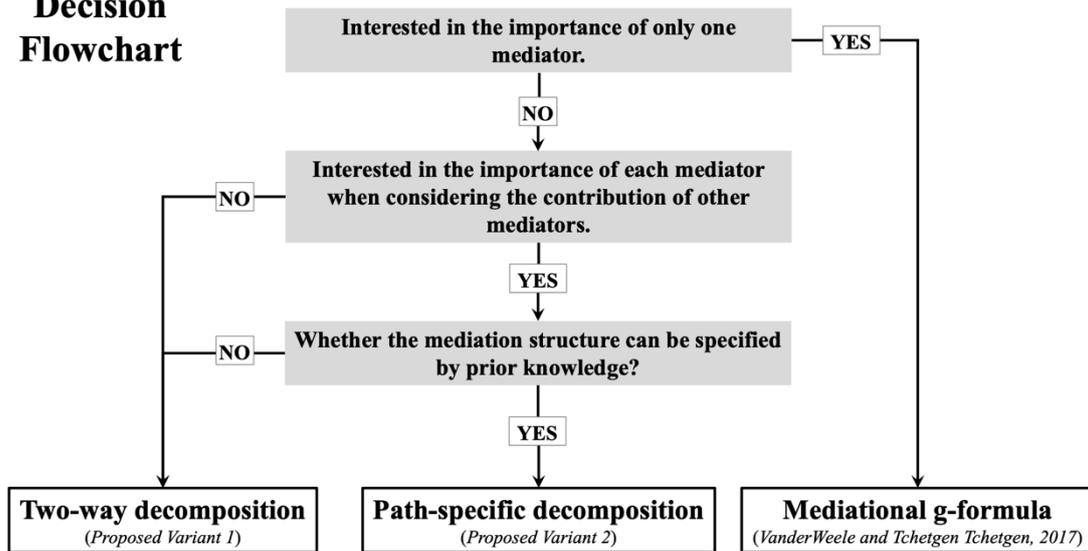
Figure 4. Decision flowchart for selecting the appropriate methodology for time-varying mediation analysis.
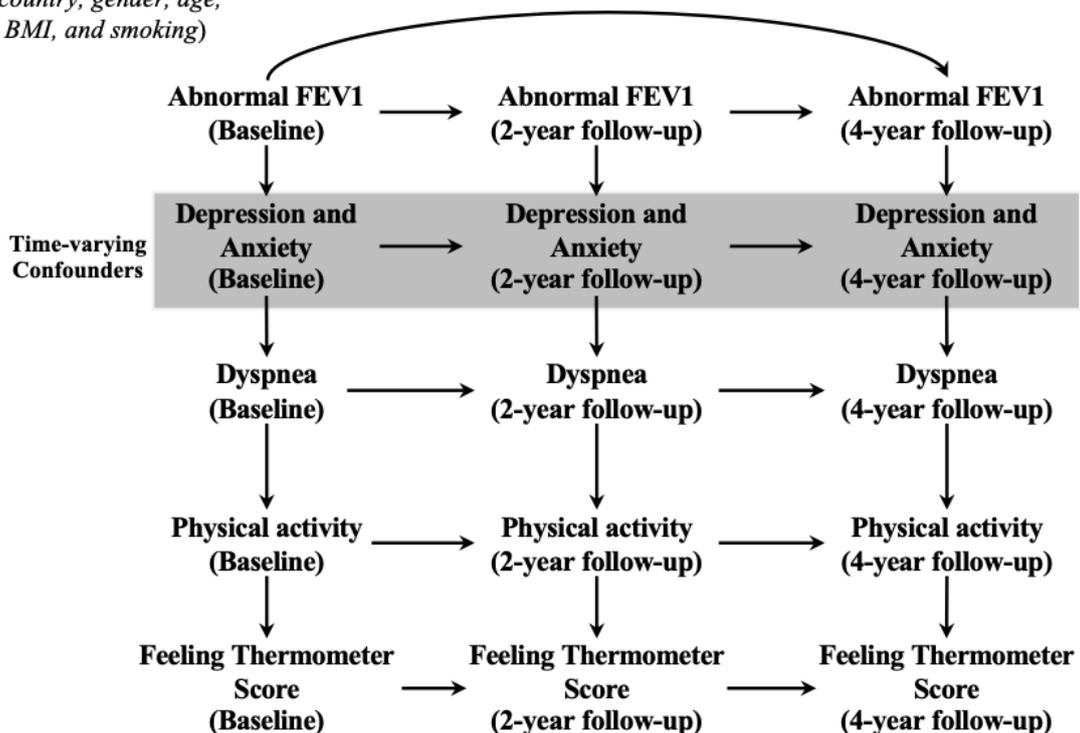

Figure 5. Causal relationship in the ICE COLD ERIC study. Abbreviation: FEV1, forced expiratory volume in 1 s.