On the conventional definition of path-specific effects

– fully mediated interaction with multiple ordered mediators

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Abstract

Path-specific effects (PSEs) are a critical measure for assessing mediation in the presence of multiple mediators. However, the conventional definition of PSEs has generated controversy because it often causes misinterpretation of the results of multiple mediator analysis. For in-depth analysis of this issue, we propose the concept of decomposing fully mediated interaction (FMI) from the average causal effect. We show that FMI misclassification is the main cause of PSE misinterpretation. Two strategies for specifying FMI are proposed: isolating FMI and reclassifying FMI. The choice of strategy depends on the objective. Isolating FMI is the superior strategy when the main objective is elucidating the mediation mechanism whereas reclassifying FMI is superior when the main objective is precisely interpreting the mediation analysis results. To compare performance, this study used the two proposed strategies and the conventional decomposition strategy to analyze the mediating roles of dyspnea and anxiety in the effect of impaired lung function on poor health status in a population of patients with chronic obstructive pulmonary disease. The estimation result showed that the conventional decomposition strategy underestimates the importance of dyspnea as a mechanism of this disease. Specifically, the strategy of reclassifying FMI revealed that 50% of the average causal effect is attributable to mediating effects, particularly the mediating effect of dyspnea.

Introduction

Causal mediation analysis with multiple mediators is an important technique for investigating biologic or mechanistic pathways that contribute to the average causal effect (ACE) of an exposure or treatment on an outcome. Typically, path-specific effects (PSEs) decomposed from ACE are derived to explain how exposure affects an outcome through different mediation paths [1]. However, most PSEs cannot be identified nonparametrically[1,2]. To this end, numerous researchers have considered different assumptions and conditions for identifying PSEs [2-9] in a counterfactual framework [10,11]. The most common conventional strategy is deriving the identifiable path effects through sequential effect decomposition[2,7,12-14] (also called partially forward decomposition strategy [15] or three-way decomposition strategy for two mediators [6]). For K ordered mediators, this approach decomposes ACE into K+1 components: one component is the direct effect, and the remaining K PSE components are indirect effects corresponding to K mediators. In this article, K+1 PSEs obtained by sequential effect decomposition are referred to as $\{\mathrm{PSE}_k^{(S0)}; k = 0,1,\dots,\mathrm{K}\}$. The $\{\mathrm{PSE}_k^{(S0)}; k = 0,1,\dots,\mathrm{K}\}$ can be viewed as the direct extension of natural direct and indirect effects (the standard decomposition of ACE in the case of one mediator [16]). The $S0$ represents the conventional sequential effect decomposition strategy. Moreover, Steen, et al. [6] noted that this strategy maximizes the precision of decomposition performed under multiple ordered mediators without introducing sensitivity parameters or parametric assumptions. Sequential effect decomposition strategy has also been successfully integrated in statistical models applied in various contexts, including analyses of survival [7,12,13], continuous outcomes[2], and dichotomous mediators and outcomes[14].

Although sequential effect decomposition is the conventional approach that has proven most effective in previous works, causal interpretations of $\{\mathrm{PSE}_k^{(S0)}; k = 0,1,\dots,\mathrm{K}\}$ have not been fully investigated. Therefore, this study specifically discussed the misinterpretation issue

in sequential effect decomposition. According to the intervention scheme for exposing a exposure on mediators, PSE with respect to the *k*th mediator (i.e., $\mathrm{PSE}_k^{(S0)}$) is used to assess how the effect of an exposure on an outcome is mediated through a specific set of paths, which starts at the *k*th mediator. This PSE type is also referred to as a mediator-leading indirect effect since the path of mediation is led by the corresponding mediator variable[15]. However, the conventional definition of $\mathrm{PSE}_k^{(S0)}$ does not reflect this "mediator-leading" property. Therefore, inferring mediation based on $\{\mathrm{PSE}_k^{(S0)}; k = 0,1, \dots, \mathrm{K}\}$ may obtain a misleading interpretation. The key cause of misinterpretation is that sequential effect decomposition does not consider interaction. To explain this phenomenon, we propose a novel component decomposed from ACE: fully mediated interaction (FMI). The derivation of FMI is inspired by the four-way decomposition developed by VanderWeele [17], which disentangles interaction and mediation from ACE. The FMI explains how the effect of the exposure changes when the outcome results from a complex interaction among full or partial mediator variables. In this study, we demonstrate why the sequential effect decomposition approach misclassifies FMI, which causes misinterpretation in multiple mediation analysis.

To remedy this problem, this study first clarifies the role of FMI by comprehensively extracting its underlying mechanism. We show that FMI can be reduced to a mediated interaction, as described in Taguri, et al. [18], under a parallel mediation structure. When mediators are causally ordered, FMI captures more interaction details compared to the Taguri mediated interaction. Next, we propose two alternative strategies for decomposing ACE to enhance interpretation of multiple mediation analysis results: the isolate FMI strategy and the reclassify FMI strategy. The choice of strategy depends on the specific objectives and requirements of the investigator and on the specific conditions of the analysis. The reclassify FMI strategy suggests an alternative definition of $\mathrm{PSE}_k^{(S0)}$, and PSEs obtained by this strategy can perfectly reflect the effects along with expected interpretations. We demonstrate the

application of the two strategies in analysis of chronic obstructive pulmonary disease (COPD). Specifically, we explore the mediating roles of dyspnea and anxiety in the effect of impaired lung function on poor health status.

Methods

Notation and Causal diagram

Let A denote the exposure, Y denote the outcome of interest, M_1 and M_2 denote the two causally ordered mediators, and C denote the baseline confounders. Figure 1 depicts the causal structure as a directed acyclic graph. Next, we introduce the counterfactual outcome model [16]. Let $Y(a)$, $M_1(a)$ and $M_2(a)$ denote the counterfactual values of Y, M_1 and M_2, respectively, when A is set to a. Similarly, let $Y(a,m)$ denote the counterfactual value of Y when M is set to m and A is set to a. Moreover, the cross-world counterfactual is defined as follows: $M_2(a, M_1(a^*))$ is the counterfactual value of M_2 when A is set to a and M_1 is set to $M_1(a^*)$. Note that a and a^* are two arbitrary numbers. The following discussion focuses on a binary exposure where the values of a and a^* are in $\{0,1\}$.

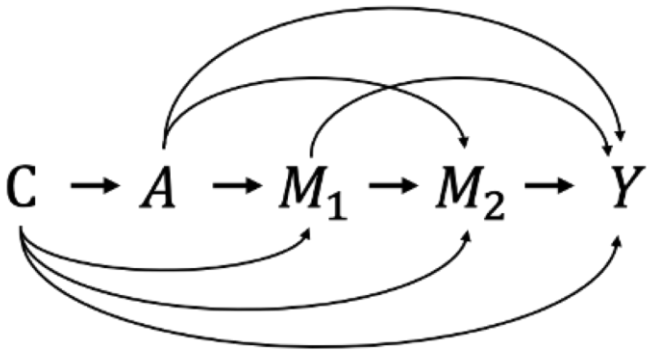

Figure 1 Causal diagram with exposure A, two causally ordered mediators M_1 and M_2, outcome Y, and baseline confounders C

PSE via the conventional sequential effect decomposition

Avin, et al. [1] extended the causal mediation analysis framework[16,19] by applying the PSE

concept in cases of multiple mediators. The authors decomposed ACE into several components corresponding to mediation paths. In cases with two causally ordered mediators, four PSE paths were defined: the path not through M_1 and not through M_2, the path through M_1 but not through M_2, the path through M_2 but not through M_1, and the path through M_1 and through M_2; the four paths were designated PSE_0, PSE_1, PSE_2, and PSE_{12}, respectively. However, a complete decomposition $\{PSE_0, PSE_1, PSE_2, PSE_{12}\}$ from ACE is not parametrically identifiable [1]. When additional sensitivity parameters are not needed to characterize relationships among mediators[2], sequential effect decomposition[6,15] is the strategy most commonly used to define identifiable PSEs in the literature[7,12-14]. This strategy decomposes ACE into three effects: the effect in the absence of mediators, the effect through M_1 (i.e., regardless of the effect through M_2, the effect first through M_1 then M_2 should be included in PSE_1), and the effect through M_2 only. As we denoted above, these effects are $PSE_0^{(S0)}$, $PSE_1^{(S0)}$ and $PSE_2^{(S0)}$. Figure 2 illustrates the paths accounted for by each effect under sequential effect decomposition. Based on the counterfactual model, these effects are defined as follows:

$$PSE_0^{(S0)} = \phi(1,0,0) - \phi(0,0,0)$$

$$PSE_1^{(S0)} = \phi(1,1,0) - \phi(1,0,0)$$

$$PSE_2^{(S0)} = \phi(1,1,1) - \phi(1,1,0)$$

where $\phi(a_1, a_2, a_3) \equiv E\left[Y\left(a_1, M_1(a_2), M_2\left(a_3, M_1(a_2)\right)\right)\right]$.

Although many statistical models have been proposed for estimating $PSE_0^{(S0)}$, $PSE_1^{(S0)}$ and $PSE_2^{(S0)}$[6,7,12], the sequential effect decomposition defined above has two limitations. First, definitions of PSE widely vary according to the reference exposure level. For example, $PSE_2^{(S0)}$ can be alternatively defined as $\phi(0,1,1) - \phi(0,1,0)$, $\phi(1,0,1) - \phi(1,0,0)$, or $\phi(0,0,1) - \phi(0,1,0)$. Other PSEs also apply alternative definitions. One solution proposed by Daniel et al is to calculate PSE according to all proposed definitions and then apply the average

value[2]. However, an ongoing controversy is what exposure level should be selected for the reference value. Second, the conventional definition of $PSE_2^{(S0)}$ is questionable because a further decomposition of $PSE_2^{(S0)}$ reveals that two components in $PSE_2^{(S0)}$ are irrelevant to the mediation effect of M_2. It implies that $PSE_2^{(S0)}$ is inappropriate for characterizing the mediation role of M_2. The next section formulates the second limitation, which is inspired by VanderWeele mediation-interaction analysis [17]. We then propose a plausible definition of PSEs in the presence of multiple ordered mediators.

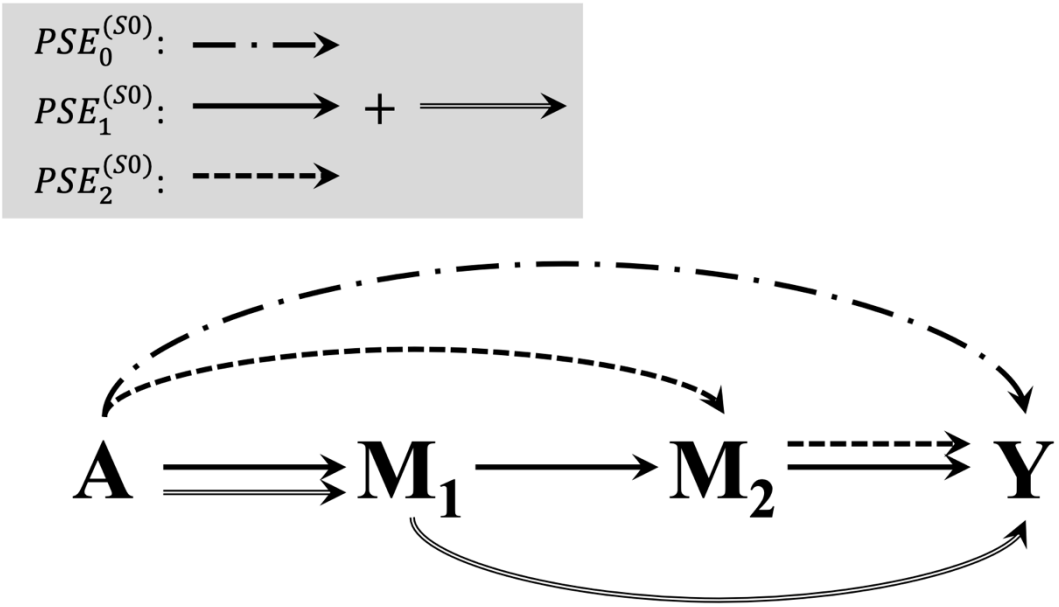

Figure. 2. Path illustration of path-specific effects (PSEs) under sequential effect decomposition with exposure A, two causally ordered mediators M_1 and M_2, and outcome Y.

Misclassified component in $PSE_2^{S0} - FMI$

To illustrate the issue that occurs in sequential effect decomposition, we further decompose $PSE_2^{(S0)}\,(=\phi(1,1,1)-\phi(1,1,0))$ into two components: $\phi(1,0,1)-\phi(1,0,0)$ and $[\phi(1,1,1)-\phi(1,1,0)]-[\phi(1,0,1)-\phi(1,0,0)]$. As mentioned above, the first component is an alternative definition of $PSE_2^{(S0)}$, where the reference level of exposure mediated by M_1 is set to 0 instead of 1. This component explicitly captures the mediating

effects of M_2. Only the reference level of exposure that intervenes in M_1 is set to zero, implying the path from A to M_1 has been cut off. The second component is fully mediated interaction (FMI), which mostly comprises full interacting effects in the path through M_1 and M_2. Classifying FMI into $PSE_2^{(S0)}$ can be problematic when interpreting causal mediation effects. Specifically, FMI captures effects corresponding to paths including $A \rightarrow M_1$. In the absence of a causal effect of A on M_1, $M_1(1) = M_1(0)$, and FMI is equal to zero. According to the interpretation of $PSE_2^{(S0)}$ (i.e., the effect through M_2 only), including FMI in $PSE_2^{(S0)}$ is inappropriate.

Additionally, we further investigate the details of all FMI components to determine whether FMI should belong to $PSE_1^{(S0)}$ or other. For simplicity of discussion, the analysis can be simplified as a decomposition of individual-level FMI (iFMI) as follows:

$$\text{iFMI} = Y\left(1, M_1(1), M_2\left(1, M_1(1)\right)\right) - Y\left(1, M_1(1), M_2\left(0, M_1(1)\right)\right) - Y\left(1, M_1(0), M_2\left(1, M_1(0)\right)\right) + Y\left(1, M_1(0), M_2\left(0, M_1(0)\right)\right).$$

The iFMI is decomposed into $\text{iFMI}_{\text{pure}}$ and $\text{iFMI}_{\text{endo}}$, where

$$\text{iFMI}_{\text{pure}} = [Y(1,1,1) - Y(1,1,0) - Y(1,0,1) + Y(1,0,0)]\,[M_1(1) - M_1(0)]\,[M_2(1,0) - M_2(0,0)] \quad \text{and}$$

$$\text{iFMI}_{\text{endo}} = [Y(1,1,1) - Y(1,1,0)]\,[M_1(1) - M_1(0)]\,[M_2(1,1) - M_2(1,0) - M_2(0,1) + M_2(0,0)].$$

The proof in Appendix A further disentangles the underlying mediation paths of $\text{iFMI}_{\text{pure}}$ and $\text{iFMI}_{\text{endo}}$. Figure 3 illustrates the mediation paths. $\text{iFMI}_{\text{pure}}$ and $\text{iFMI}_{\text{endo}}$ are the mediated interactive effects of A on Y, which is a measure of interaction [20], but $\text{iFMI}_{\text{pure}}$ and $\text{iFMI}_{\text{endo}}$ are induced by different mechanisms. The $\text{iFMI}_{\text{pure}}$ purely captures mediating effects of the interaction between M_1 and M_2 on Y. The first term $(Y(1,1,1) - Y(1,1,0) - Y(1,0,1) + Y(1,0,0))$ represents the mediating effects of the interaction between M_1 and M_2 on Y, and the second and third terms (i.e., $M_1(1) - M_1(0)$ and $M_2(1,0) - M_2(0,0)$, respectively) imply

that both M_1 and M_2 are induced by A. Taguri, et al. [18] introduced the concept of $\text{iFMI}_{\text{pure}}$ in the context of multiple parallel mediators. They decomposed the indirect effect into three paths: the path through M_1, the path through M_2, and the path through interaction between M_1 and M_2 on Y, which they termed the "mediated interaction (MI)". Notably, their use of the term MI differed from the use of the term MI in the VanderWeele four-way decomposition[17], which referred to the interaction among exposure and mediator. The Taguri's MI is the same as $\text{iFMI}_{\text{pure}}$ proposed in the current study, and the Taguri's MI can generally be decomposed from our iFMI.

Unlike $\text{iFMI}_{\text{pure}}$, which describes how a mediated interaction affects outcome, $\text{iFMI}_{\text{endo}}$ describes the effect of an endogenously mediated interaction, i.e., a mediated interactive effect on a subsequent mediator rather than on an outcome. In the case of two ordered mediators, $\text{iFMI}_{\text{endo}}$ captures all effects in which the mediated interaction between M_1 and A induces M_2 and then M_2 induces Y (i.e., $Y(1,1,1) - Y(1,1,0)$). This mediated interaction corresponds to the product of the second term $(M_1(1) - M_1(0))$ and third term $(M_2(1,1) - M_2(1,0) - M_2(0,1) + M_2(0,0))$, which precisely corresponds to the "mediated interaction" in the VanderWeele's four-way decomposition[17] when the mediator is replaced by M_1 and the outcome is replaced by M_2. In the illustrative example, $\text{iFMI}_{\text{endo}}$ specifically assesses how the interaction between lung function impairment (A) and dyspnea (M_1) affects anxiety (M_2) and then anxiety causes a change in health-related quality of life (Y). The function of this complex interaction requires that M_1 and M_2 have full roles in the mechanism. Therefore, classifying $\text{iFMI}_{\text{endo}}$ into $PSE_1^{(S0)}$ is appropriate according to the natural interpretation of PSE in relation toM_1[6,15]. If mediators are causally independent, no endogenously mediated interactions occur, and $\text{iFMI}_{\text{endo}} = 0$. Thus, the Taguri's MI and the proposed iFMI are identical when a parallel mediation structure is assumed. This property reveals that iFMI is a generalization of the Taguri's MI.

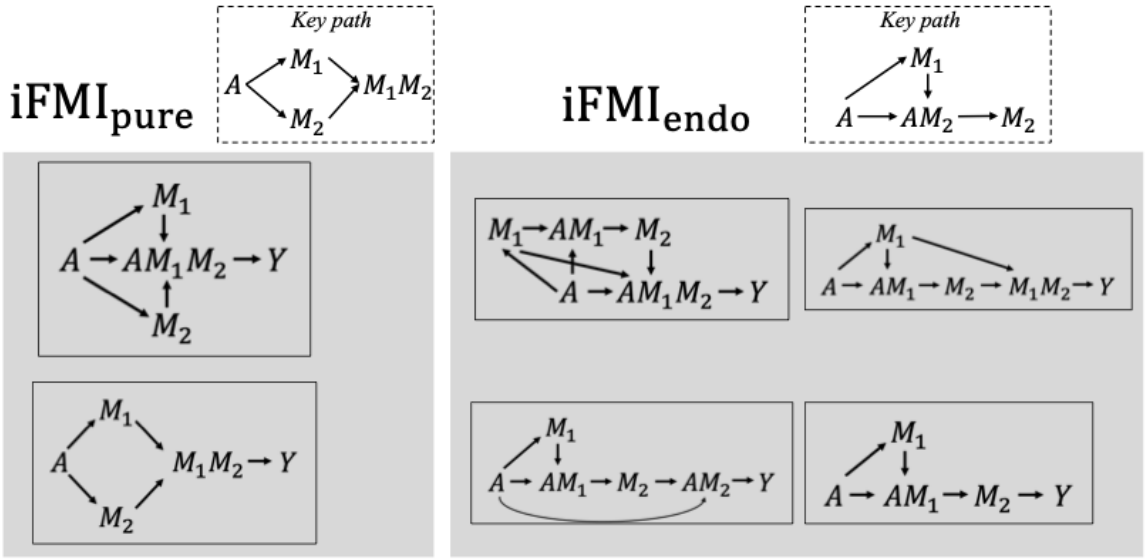

Figure. 3. Underlying mediation paths of $\mathrm{iFMI}_{\mathrm{pure}}$ and $\mathrm{iFMI}_{\mathrm{endo}}$ with exposure A, two causally ordered mediators M_1 and M_2, and outcome Y.

Two strategies for effect decomposition in two causally ordered mediators

We have shown the critical issue in the conventional sequential effect decomposition strategy by introducing $\mathrm{FMI}_{\mathrm{pure}}$ and $\mathrm{FMI}_{\mathrm{endo}}$, which are the population-level $\mathrm{iFMI}_{\mathrm{pure}}$ and $\mathrm{iFMI}_{\mathrm{endo}}$ (i.e., $E[\mathrm{iFMI}_{\mathrm{pure}}]$ and $E[\mathrm{iFMI}_{\mathrm{endo}}]$). Unfortunately, $\mathrm{FMI}_{\mathrm{pure}}$ and $\mathrm{FMI}_{\mathrm{endo}}$ are not generally separable and not identifiable without additional assumptions, and separating $\mathrm{FMI}_{\mathrm{pure}}$ and $\mathrm{FMI}_{\mathrm{endo}}$ is beyond the scope of this study. The aims of this study were to highlight misinterpretations of $PSE_1^{(S0)}$ and $PSE_2^{(S0)}$ resulting from sequential effect decomposition and to suggest the most appropriate approach to analyzing multiple mediators. Accordingly, we propose two strategies to remedy the problem of $PSE_1^{(S0)}$ and $PSE_2^{(S0)}$ and explicitly specify the role of FMI.

Isolate FMI strategy: FMI-specific effect decomposition

The FMI-specific effect decomposition strategy isolates FMI from PSEs. Note that, while $\mathrm{FMI}_{\mathrm{pure}}$ and $\mathrm{FMI}_{\mathrm{endo}}$ are not identifiable, FMI is identifiable without additional assumptions for defining PSE. Therefore, the proposed strategy decomposes ACE into four components. Based on the counterfactual model, FMI and three PSEs are defined below.

$PSE_0^{(S1)} = \phi(1,0,0) - \phi(0,0,0)$

$PSE_1^{(S1)} = \phi(1,1,0) - \phi(1,0,0)$

$PSE_2^{(S1)} = \phi(1,0,1) - \phi(1,0,0).$

$\mathrm{FMI} = [\phi(1,1,1) - \phi(1,1,0)] - [\phi(1,0,1) - \phi(1,0,0)].$

In the isolate FMI strategy, definitions of PSE_0^{S1} and PSE_1^{S1} are identical to the conventional definitions. The causal interpretations of these four effects are as follows: $PSE_0^{(S1)}$ is the effect for the paths irrelevant to either M_1 or M_2; PSE_1^{S1} is the effect for the paths starting at M_1 in any way, except the path of FMI with M_2; PSE_2^{S1} is the effect for the path through M_2 solely; FMI is the effect for fully mediated interaction paths through M_1 and M_2. As mentioned above, the effects obtained by the isolate FMI strategy correspond with the decomposed effects proposed by Taguri, et al. [18] under a parallel mediation structure. In such a case, $PSE_1^{(S1)}$ is simplified as the effect solely for the path through M_1, and FMI is the effect of purely mediated interaction. The $PSE_1^{(S1)}$ and FMI quantify different mechanisms. Thus, if mediators are causally independent, then $PSE_1^{(S1)}$ and FMI should be reported separately, and the – isolate FMI strategy is superior.

For the ordered mediators in Figure. 1, decomposing FMI from ACE can still elucidate the mechanism. In practice, however, quantifying FMI is rarely a primary research objective. Moreover, the underlying mediation paths captured by $\mathrm{FMI}_{\mathrm{endo}}$ certainly pass through M_1 and M_2 sequentially (see Figure. 3), which indicates that the boundary between FMI and $PSE_1^{(S1)}$ is extremely vague from a mechanistic perspective. Therefore, FMI and $PSE_1^{(S1)}$ should be merged in the case of ordered mediators. Therefore, we suggest using an effect

decomposition method in the reclassify FMI strategy.

Reclassify FMI strategy: conversely sequential effect decomposition

To implement the reclassify FMI strategy, ACE is decomposed into the three following components.

$PSE_0^{(S2)} = \phi(1,0,0) - \phi(0,0,0)$

$PSE_1^{(S2)} = \phi(1,1,1) - \phi(1,0,1)$

$PSE_2^{(S2)} = \phi(1,0,1) - \phi(1,0,0).$

Comparing effects between the isolate FMI strategy and the reclassify FMI strategy reveals $PSE_1^{(S2)} = PSE_1^{(S1)} + \text{FMI}$ and $PSE_2^{(S2)} = PSE_2^{(S1)}$. The effects obtained by the reclassify FMI strategy are appealing for two reasons. First, $\{PSE_0^{(S2)}, PSE_1^{(S2)}, PSE_2^{(S2)}\}$ in the reclassify FMI strategy is an alternative to the conventional formulation of PSEs $\{PSE_0^{(S0)}, PSE_1^{(S0)}, PSE_2^{(S0)}\}$. Thus, the identification assumptions of the reclassify FMI strategy is identical to that of the conventional sequential effect decomposition strategy. Moreover, the scheme for performing an exposure intervention in PSEs when using the reclassify FMI strategy is converse to that in conventional PSEs when using sequential effect decomposition. Thus, the reclassify FMI strategy is considered a conversely sequential effect decomposition. Second, the reclassify FMI strategy enables a more precise interpretation of the expected mechanism compared to conventional sequential effect decomposition. Similar to $PSE_2^{(S1)}$ in the isolate FMI strategy, $PSE_2^{(S2)}$ precisely captures the effect mediated through M_2. The $PSE_1^{(S2)}$ fully reflects the mediation mechanism, in which M_1 is always activated. Meanwhile, if M_2 is activated, it should be induced by M_1 regardless of whether the mechanism is mediation or interaction. The general formulations of K mediators for the isolate FMI strategy and for the reclassify FMI strategy are presented in Appendix B. Additionally, Table 1 compares sequential effect decomposition between the isolate FMI strategy and the reclassify FMI strategy.

Table 1. Comparison of isolate FMI strategy and reclassify FMI strategy.

Strategy	Definition	Interpretation	Recommendation for use
Sequential effect decomposition			
$PSE_0^{(S0)}$	$\phi(1,0,0) - \phi(0,0,0)$	Effect corresponding to the paths irrelevant to either M_1 or M_2	There is no any interaction among variables.
$PSE_1^{(S0)}$	$\phi(1,1,0) - \phi(1,0,0)$	Effect corresponding to the paths starting at M_1 in any way, except the way of FMI with M_2	
$PSE_2^{(S0)}$	$\phi(1,1,1) - \phi(1,1,0)$	Effect corresponding to the paths through M_2 solely and the paths present in FMI	
Proposed Isolate FMI strategy			
$PSE_0^{(S1)}$	$\phi(1,0,0) - \phi(0,0,0)$	The same as $PSE_0^{(S0)}$	Interaction exists, mediators are causally independent, and further interested in assessing FMI.
$PSE_1^{(S1)}$	$\phi(1,1,0) - \phi(1,0,0)$	The same as $PSE_1^{(S0)}$	
$PSE_2^{(S1)}$	$\phi(1,0,1) - \phi(1,0,0)$	Effect corresponding to the paths through M_2 solely	
FMI	$[\phi(1,1,1) - \phi(1,1,0)] - [\phi(1,0,1) - \phi(1,0,0)]$	Effect corresponding to the paths of mediated interaction fully through M_1 and M_2	
Proposed Reclassify FMI strategy			
$PSE_0^{(S2)}$	$\phi(1,0,0) - \phi(0,0,0)$	The same as $PSE_0^{(S0)}$	Interaction exists, mediators are causally dependent, and interested in assessing mediation only.
$PSE_1^{(S2)}$	$\phi(1,1,1) - \phi(1,0,1)$	Effect corresponding to the paths starting at M_1	
$PSE_2^{(S2)}$	$\phi(1,0,1) - \phi(1,0,0)$	The same as $PSE_2^{(S1)}$	

Note: $\phi(a_1, a_2, a_3) \equiv E\left[Y\left(a_1, M_1(a_2), M_2\left(a_3, M_1(a_2)\right)\right)\right]$; PSE: path-specific effect

Identification and assumptions

Since both strategies are defined by the counterfactual model, an identification process is needed to link counterfactual values with observations. Based on previous studies,[6,15] five assumptions of the identification process are as follows: (1) exchangeability between outcome and exposure, (2) exchangeability between outcome and mediators, (3) exchangeability between mediators and exposure, (4) cross-world exchangeability between outcome and mediators, and (5) cross-world exchangeability among mediators. Consequently, the estimators of PSEs in the two strategies are shown below.

Isolate FMI strategy: $\widehat{PSE}_0^{(S1)} = Q(1,0,0) - Q(0,0,0)$; $\widehat{PSE}_1^{(S1)} = Q(1,1,0) - Q(1,0,0)$

$\widehat{PSE}_2^{(S1)} = Q(1,0,1) - Q(1,0,0)$; $\widehat{\text{FMI}} = [Q(1,1,1) - Q(1,1,0)] - [Q(1,0,1) - Q(1,0,0)]$.

Reclassify FMI strategy: $\widehat{PSE}_0^{(S1)} = Q(1,0,0) - Q(0,0,0)$; $\widehat{PSE}_1^{(S2)} = Q(1,1,1) - Q(1,0,1)$; $\widehat{PSE}_2^{(S2)} = Q(1,0,1) - Q(1,0,0)$.

In the above formulations of these estimators, $Q(a_1, a_2, a_3)$ represents the identified expression of $\phi(a_1, a_2, a_3)$ in the form of

$$Q(a_1, a_2, a_3) = \int_{c,m_1,m_2} E[Y|c, A = a_1, m_1, m_2] f(m_2|c, A = a_3, m_1) f(m_1|c, A = a_2) f(c) dm_2 dm_1 dc.$$

The detailed identification is given in Appendix C.

Estimation

In previous works, $Q(a_1, a_2, a_3)$ was estimated by using an imputation procedure[6] and by using inverse-probability-weighting[15]. Here, we illustrate the use of a standard regression-based approach. For example, suppose that the outcome is consistent with the model

$$E[Y|C, A, M_1, M_2] = \theta_0 + \theta_c C + \theta_a A + \theta_1 M_1 + \theta_2 M_2 + \theta_{a1} A M_1 + \theta_{a2} A M_2 + \theta_{a12} A M_1 M_2 + \theta_{12} M_1 M_2$$

with variance σ_y^2 and with mediators that have the conditional mean

$$E[M_1|C, A] = \alpha_0 + \alpha_c C + \alpha_a A$$

$$E[M_2|C, A, M_1] = \beta_0 + \beta_c C + \beta_a A + \beta_1 M_1 + \beta_{a1} A M_1$$

with variances σ_1^2 and σ_2^2. Specifying the interaction effects when modeling Y and M_2 is a critical step for our methodology because misinterpretation of conventional sequential effect decomposition always arises in the presence of interaction. The estimator of $Q(a, e_1, e_2)$ is given by

$$Q(a, e_1, e_2) = \theta_0 + \theta_a a + \theta_c E[C] + [\theta_2 + \theta_{a2} a][\beta_0 + \beta_c E[C] + \beta_a e_2] + \{\theta_1 + \theta_{a1} a + [\theta_{a12} a + \theta_{12}][\beta_0 + \beta_c E[C] + \beta_a e_2] + [\theta_2 + \theta_{a2} a][\beta_1 + \beta_{a1} e_2]\}[\alpha_0 + \alpha_c E[C] + \alpha_a e_1] + [\theta_{a12} a + \theta_{12}][\beta_1 + \beta_{a1} e_2]\{[\alpha_0 + \alpha_c E[C] + \alpha_a e_1]^2 + \sigma_1\}.$$

The estimators of PSEs in the isolate FMI strategy is derived as follows.

$$\widehat{PSE}_0^{(S1)} = \theta_a + \theta_{a2}[\beta_0 + \beta_c E[C]] + \{\theta_{a1} + \theta_{a12}[\beta_0 + \beta_c E[C]] + \theta_{a2}\beta_1\}[\alpha_0 + \alpha_c E[C]] + \theta_{a12}\beta_1\{[\alpha_0 + \alpha_c E[C]]^2 + \sigma_1^2\},$$

$$\widehat{PSE}_1^{(S1)} = \{\theta_1 + \theta_{a1} + [\theta_{a12} + \theta_{12}][\beta_0 + \beta_c E[C]] + [\theta_2 + \theta_{a2}]\beta_1\}\alpha_a + [\theta_{a12} + \theta_{12}]\beta_1\{2[\alpha_0 + \alpha_c E[C]]\alpha_a + \alpha_a^2\},$$

$$\widehat{PSE}_2^{(S1)} = [\theta_2 + \theta_{a2}]\beta_a + \{[\theta_{a12} + \theta_{12}]\beta_a + [\theta_2 + \theta_{a2}]\beta_{a1}\}[\alpha_0 + \alpha_c E[C]] + [\theta_{a12} + \theta_{12}]\beta_{a1}\{[\alpha_0 + \alpha_c E[C]]^2 + \sigma_1^2\}, \text{and}$$

$$\widehat{\text{FMI}} = \{[\theta_{a12} + \theta_{12}]\beta_a + [\theta_2 + \theta_{a2}]\beta_{a1}\}\alpha_a + [\theta_{a12} + \theta_{12}]\beta_{a1}\{2[\alpha_0 + \alpha_c E[C]]\alpha_a + \alpha_a^2\}.$$

If A has no causal effect on M_1, $\alpha_a = 0$, which results in $\widehat{\text{FMI}} = 0$. This confirms the above conclusion that FMI captures the effects through paths from A to M_1 and should be separated from $PSE_2^{(S0)}$.

In the reclassify FMI strategy, PSE estimators are derived as follows.

$$\widehat{PSE}_0^{(S2)} = \theta_a + \theta_{a2}[\beta_0 + \beta_c E[C]] + \{\theta_{a1} + \theta_{a12}[\beta_0 + \beta_c E[C]] + \theta_{a2}\beta_1\}[\alpha_0 + \alpha_c E[C]] + \theta_{a12}\beta_1\{[\alpha_0 + \alpha_c E[C]]^2 + \sigma_1^2\},$$

$$\widehat{PSE}_1^{(S2)} = \{\theta_1 + \theta_{a1} + [\theta_{a12} + \theta_{12}][\beta_0 + \beta_c E[C] + \beta_a] + [\theta_2 + \theta_{a2}][\beta_1 + \beta_{a1}]\}\alpha_a + [\theta_{a12} + \theta_{12}][\beta_1 + \beta_{a1}]\{2[\alpha_0 + \alpha_c E[C]]\alpha_a + \alpha_a^2\}, \text{and}$$

$$\widehat{PSE}_2^{(S2)} = [\theta_2 + \theta_{a2}]\beta_a + \{[\theta_{a12} + \theta_{12}]\beta_a + [\theta_2 + \theta_{a2}]\beta_{a1}\}[\alpha_0 + \alpha_c E[C]] + [\theta_{a12} + \theta_{12}]\beta_{a1}\{[\alpha_0 + \alpha_c E[C]]^2 + \sigma_1^2\}.$$

According to the above estimators, the absence of any interaction (i.e., θ_{a1}, θ_{a2}, θ_{a12}, and β_{a1} are zero) would ensure that the conventional strategy, the isolate FMI strategy, and the reclassify FMI strategy are identical. This standard regression-based approach is simple and efficient, but its drawback is the need for a new derivation each whenever the outcome or

mediator models change. A simple remedy for this issue is using G-computation for Monte Carlo sampling of counterfactual values of outcomes and mediators.

Illustration

The dataset used to illustrate the two strategies is the International Collaborative Effort on Chronic Obstructive Lung Disease: Exacerbation Risk Index Cohorts (ICE COLD ERIC). The ICE COLD ERIC study recruited 409 patients treated for COPD by general practitioners in two European countries (the Netherlands and Switzerland) between 2008 and 2009. Five-year follow-up data for these patients are available to researchers. The initial inclusion criteria for the study were a COPD diagnosis, age 40 years or older, and exacerbation-free status longer than 4 weeks. More details of the study design are given in the study protocol [21].

Our aim was to investigate possible explanations for the effects of impaired lung function at baseline on poor health status (feeling thermometer score) at the 4-year follow-up visit. The mediators of interest were dyspnea score at the 6-month follow up and anxiety score at the 3-year follow up. Figure 4 is the causal diagram. In accordance with the modified Medical Research Council Scale, dyspnea symptoms were graded from 0 (no symptoms) to 4 (almost complete incapacity). General health was measured using a feeling thermometer with a visual analogue scale ranging from 0 (worse health status) to 100 (perfect health status). Mental health was measured using the Hospital Anxiety and Depression Scale, which has a score range of 0 (lowest level of anxiety symptoms) to 21 (highest level of anxiety symptoms). Medical history was assessed at baseline in all patients. Demographic characteristics and medical history, including nationality, gender, age, BMI and smoking, were treated as baseline confounders. Table 2 presents the descriptive statistics for variables in this study.

Since forced expiratory volume in 1 second (FEV1) is the standard measure of lung function impairment, patients were categorized into FEV1 stages I-IV (FEV1 $\geq$ 80%; 50-79%;

30-49%; < 30%, respectively). For illustrative purposes, lung function impairment was defined as FEV1 < 50% (i.e., stages III-IV versus stages I-II). After excluding patients with missing data, the final sample size was 220. Conventional PSEs were derived for the isolate FMI strategy and for the reclassify FMI strategy. Table 3 presents the estimated PSEs, standard deviations, 95% confidence intervals, and p-values. Bootstrapping was performed for inference in this analysis. The critical finding in this analysis was the confirmation that FMI has a role in the contribution of impaired lung function to poor health status. The results for the isolate FMI strategy in Table 3 indicate that the effect of FMI was 2.013 (95% CI=(0.161, 3.864)), which accounted for 16.8% of ACE. Additionally, the estimated $PSE_2^{(S1)}$ approached zero. Overall, the present findings show that anxiety symptoms are not the sole mediator in the path from lung function impairment to poor health status. The FMI has a major role in the effect of anxiety symptoms on health status: specifically, synergistic interaction between anxiety and dyspnea can affect health status, and anxiety can lead to poor health status when interaction between lung function impairment and dyspnea contributes to anxiety symptoms.

Table 3 further reveals that the conventional approach underestimates the effect of lung function impairment through the mediation path of dyspnea. Note that, in this example, the mediation paths of dyspnea include the path through dyspnea alone and the path through dyspnea and anxiety sequentially. The conventional PSE, which is led by dyspnea (i.e., $PSE_1^{(S0)}$), accounts for 35.6% of ACE. In the reclassify FMI strategy, 52.4% of ACE is attributable to the mediation path of dyspnea (i.e., $PSE_1^{(S2)}$). These results demonstrate the essential role of dyspnea severity in the relationship between lung function and poor health status.

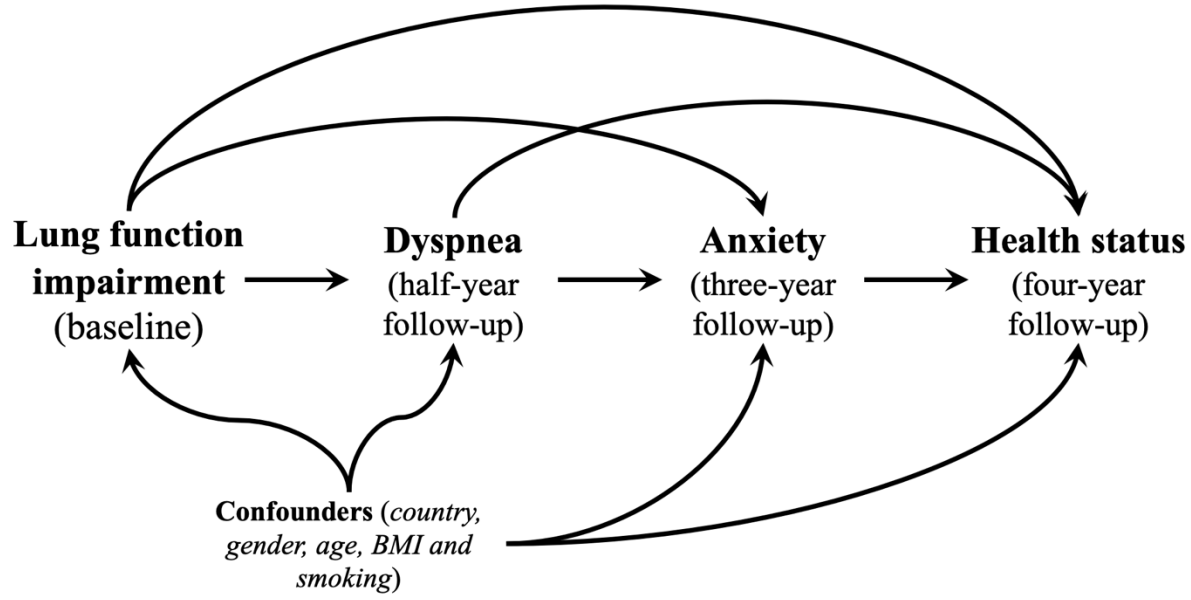

Figure. 4. Causal diagram of the illustrated example

Table 2. Descriptive statistics of variables in the application.

	Case ($FEV_1 < 50\%$) (N = 74)	Control ($FEV_1 > 50\%$) (N = 146)
Confounder		
Country {0: Netherlands; 1: Switzerland}	N = 35 (47.3%) N = 39 (52.7%)	N = 78 (53.42%) N = 68 (46.58%)
Gender {0: male; 1: female}	N = 41 (55.41%) N = 33 (44.59%)	N = 88 (60.27%) N = 58 (39.73%)
Age	Mean = 66.1 (SD = 8.98)	Mean = 66.5 (SD = 9.12)
BMI	Mean = 25.92 (SD = 4.59)	Mean = 26.83 (SD = 5.42)
Smoking (pack-year)	Mean = 44.26 (SD = 26.77)	Mean = 44.48 (SD = 27.6)
M_1		
Dyspnea score (the higher, the better)	Mean = 4.136 (SD = 1.515)	Mean = 5.296 (SD = 1.443)
M_2		
Anxiety score (the higher, the more anxious)	Mean = 5.027 (SD = 4.629)	Mean = 4.541 (SD = 4.141)
Outcome		
Feeling thermometer score (the higher, the better)	Mean = 57.7 (SD = 17.91)	Mean = 69.73 (SD = 15.8)

Abbreviation: FEV: forced expiratory volume in one second; SD: standard deviation

Table 3. Estimated PSEs via conventional approach and Strategies 1 and 2 in the application.

Method	Estimate	SD	95% CI	P-value
Sequential effect decomposition				
$PSE_0^{(S0)}$	6.57	2.486	(1,697, 11.443)	0.0082
$PSE_1^{(S0)}$	4.281	1.404	(1.529, 7.034)	0.0023
$PSE_2^{(S0)}$	1.161	1.170	(-1.132, 3.455)	0.3210
Isolate FMI strategy				
$PSE_0^{(S1)}$	6.57	2.486	(1,697, 11.443)	0.0082
$PSE_1^{(S1)}$	4.281	1.404	(1.529, 7.034)	0.0023
$PSE_2^{(S1)}$	-0.852	1.253	(-3.308, 1.605)	0.4969
FMI	2.013	0.945	(0.161, 3.864)	0.0331
Reclassify FMI strategy				
$PSE_0^{(S2)}$	6.57	2.486	(1.697, 11.443)	0.0082
$PSE_1^{(S2)}$	6.294	1.472	(3.409, 9.180)	< 0.0001
$PSE_2^{(S2)}$	-0.852	1.253	(-3.308, 1.605)	0.4969
Average casual effect	12.012	2.428	(7.254, 16.772)	< 0.0001

Abbreviation: CI: confidence interval; SD, standard deviation; PSE: path-specific effect

Discussion

We first discussed why causal misinterpretation is problematic in conventional sequential effect decomposition. To address this misinterpretation problem, we proposed two strategies, isolate FMI and reclassify FMI. The isolate FMI strategy provides relatively more details about the interpretation mechanism, and the reclassify FMI strategy has the advantage of higher accuracy in interpreting the results of causal mediation analysis with multiple mediators. Generally, we recommend the isolate FMI strategy for analysis of a parallel mediator relationship since the presence of FMI_{pure} purely represents the effects of the mediated interaction between M_1 and M_2 on Y. In contrast, for a causally ordered mediation structure, the choice between the isolate FMI strategy and the reclassify FMI strategy depends on how detailed an analysis the researchers require. For example, in the COPD study, if the assessment of the mediated interactive effect between dyspnea and anxiety is not the primary goal, use of the reclassify FMI strategy is suggested for evaluating effects mediated through the paths led by dyspnea and

anxiety.

Notably, FMI does not capture all mediated interactions present in the system. The FMI only includes mediated interactions involving both M_1 and M_2. Other mediated interactions are dispersed in PSEs. This research did not decompose the effects of mediated interactions in PSEs because these effects are classified correctly. Finally, we note that this illustrative example is likely to be overly simplistic since the assumptions for identification may well be violated. For example, personal behavior may affect the severity of anxiety and health status. That is, personal behavior is a potential confounder between M_2 and Y, which was not controlled in this study. Fortunately, our analysis controlled for a surrogate of personal behavior, i.e., smoking behavior. This substitution may not be perfect, but it is reasonable.

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