STAT6061/STAT5008 – Causal Inference

Part 9. Multiple mediation analysis

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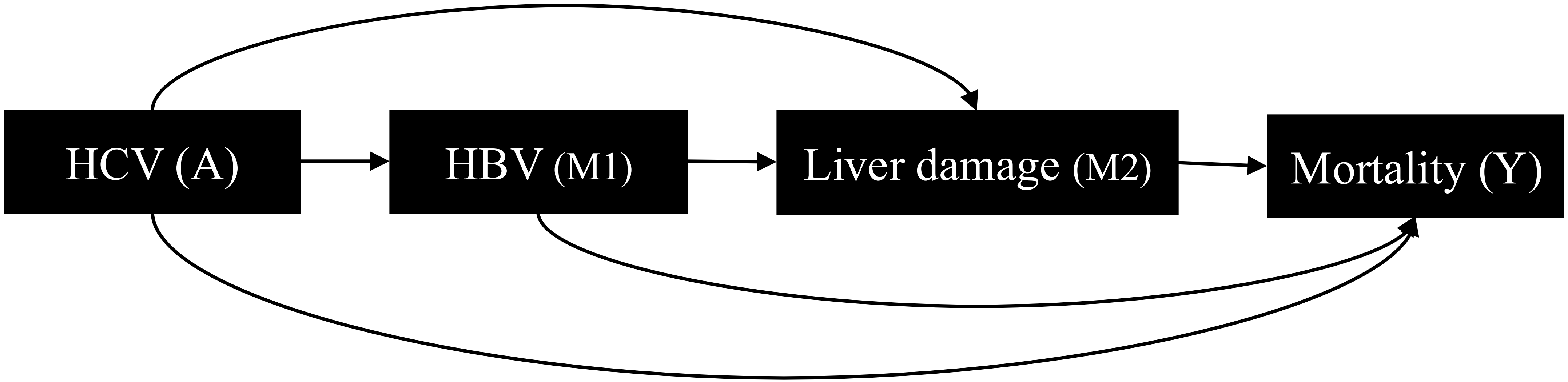
Two-mediator model

Path-specific effects (PSEs)



- Direct effect = PSE_0; Indirect effect = $\text{PSE}_{M_1} + \text{PSE}_{M_2} + \text{PSE}_{M_1M_2}$

PSE_0: $A \to Y$
PSE_{M_1}: $A \to M_1 \to Y$
PSE_{M_2}: $A \to M_2 \to Y$
$\text{PSE}_{M_1M_2}$: $A \to M_1 \to M_2 \to Y$

Two-mediator model

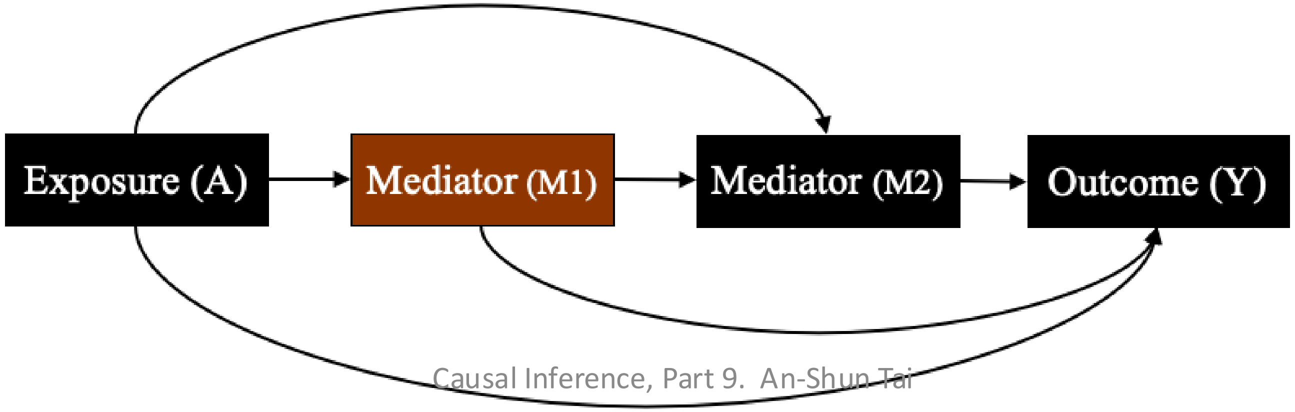
Cross-world assumption in the context of multiple mediators

Can all of four PSEs be identified from observational data?

- It is difficult without additional assumptions.

- In the case of two mediators, M1 is obvious to be a intermediated confounder in the relationship among A, M2, and Y.

→ We cannot separate (A → M1 → Y) and (A → M1 → M2 → Y)



Four effect decomposition strategies

A trade-off between assumption required and information obtained

- Two-way (TW) decomposition, Partially forward (PF) decomposition, Partially backward (PB) decomposition, and Complete decomposition.

$$PSE_{M_1}: A \to M_1 \to Y \;;\; PSE_{M_2}: A \to M_2 \to Y \;;\; PSE_{M_1 M_2}: A \to M_1 \to M_2 \to Y$$

TW decomposition

- Mediation structure-robust
- One indirect effect

  $PSE_{M_1} + PSE_{M_2} + PSE_{M_1 M_2}$
- Total effect

PF decomposition

- Sequential mediators
- Two indirect effects

  (***M*-leading indirect effect**)

  $PSE_{M_1} + PSE_{M_1 M_2}$

  PSE_{M_2}
- Total effect

PB decomposition

- Mediation structure-robust
- Two indirect effects

  (***M*-inducing indirect effect**)

  PSE_{M_1}

  $PSE_{M_2} + PSE_{M_1 M_2}$
- Interventional total effect

Complete decomposition

- Sequential mediators
- Three indirect effects

  PSE_{M_1}

  PSE_{M_2}

  $PSE_{M_1 M_2}$
- Interventional total effect

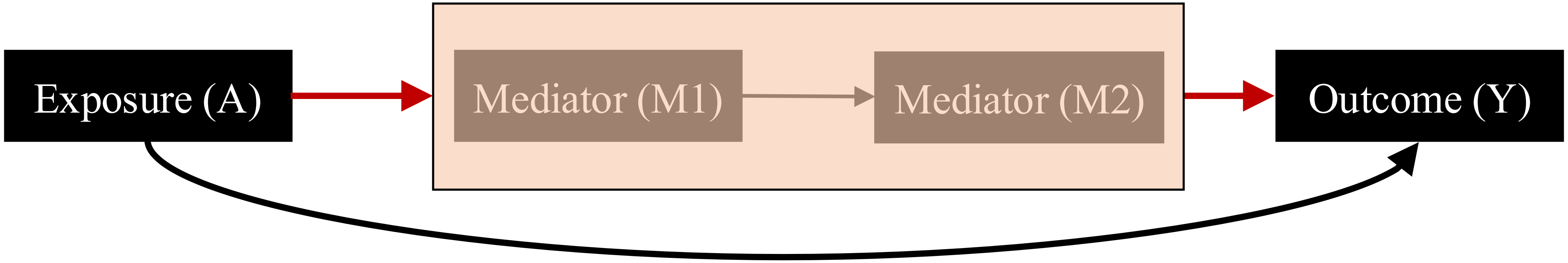
Two-way decomposition strategy

- Treating all mediators as a whole.

$\text{Direct effect} = \text{PSE}_0;\ \text{Indirect effect} = \text{PSE}_{\text{M}_1} + \text{PSE}_{\text{M}_2} + \text{PSE}_{\text{M}_1\text{M}_2}$

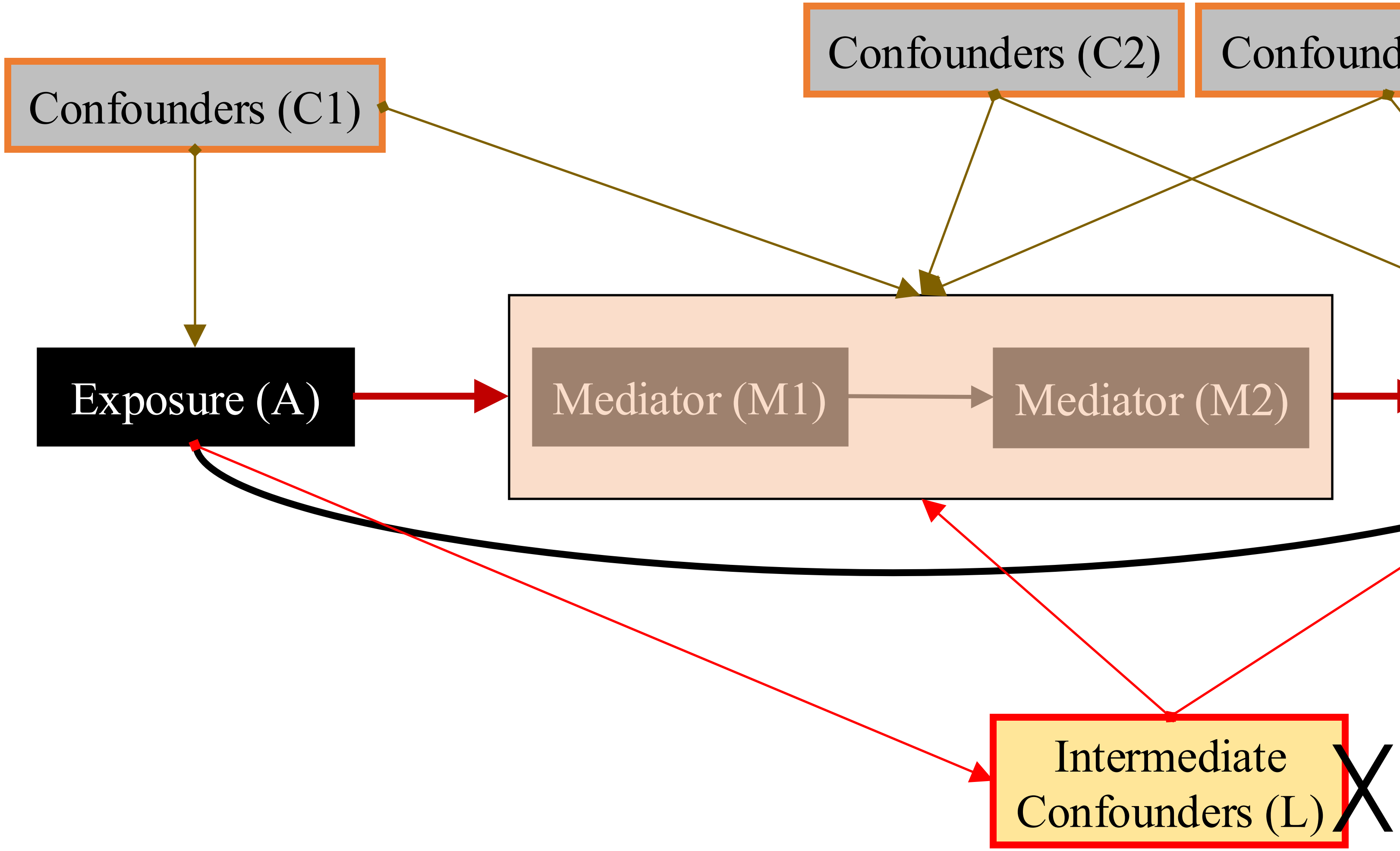
- Identification and estimation follow from the one-mediator model.

- It is simple but practically useful.



Two-way decomposition strategy

Assumptions

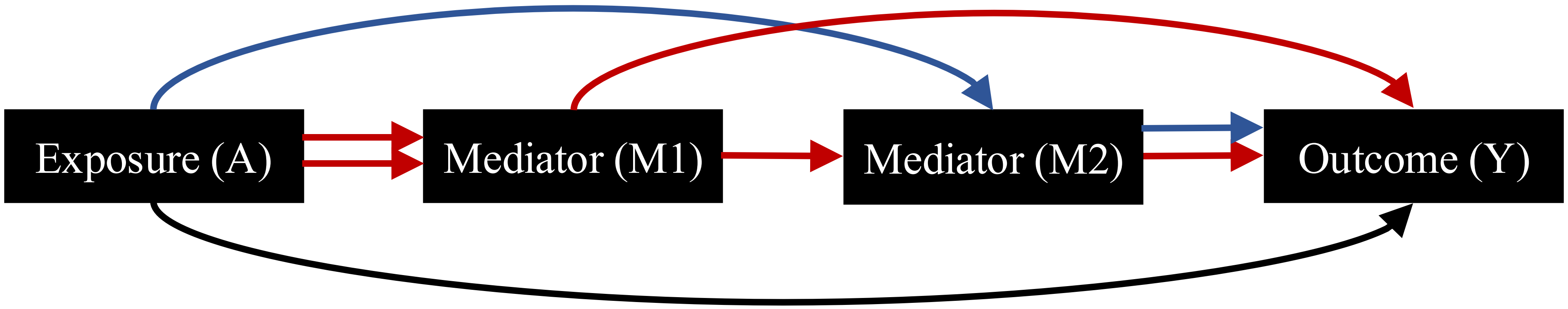


Partially forward decomposition strategy

- Three components are decomposed from the effect of A → Y.

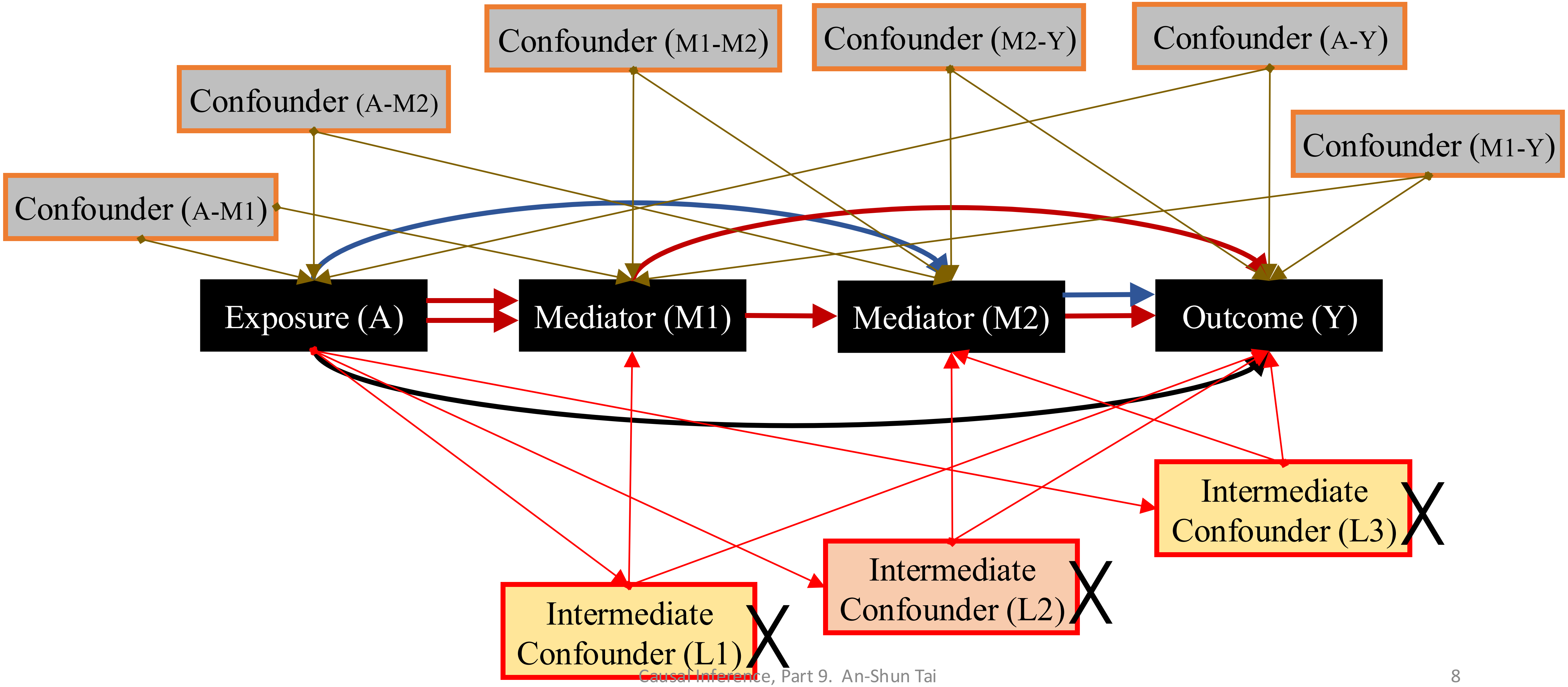
Direct effect $= \mathrm{PSE}_0$;
M1-leading indirect effect $= \mathrm{PSE}_{\mathrm{M}_1} + \mathrm{PSE}_{\mathrm{M}_1\mathrm{M}_2}$; M2-leading indirect effect $= \mathrm{PSE}_{\mathrm{M}_2}$

- Note that (A → M1 → Y) and (A → M1 → M2 → Y) cannot be separated naturally.



Partially forward decomposition strategy

Assumptions



Interventional approach

Geneletti, *JRSSB* 2007

From individual intervention to population intervention.

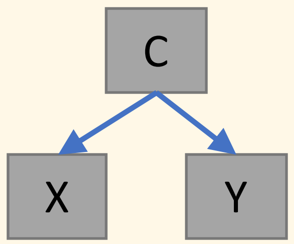
- The conventional approach for defining causal effects is

$$\mathrm{Y}(a,\mathrm{M}(a')) \to \mathrm{E}(\ \mathrm{Y}(a,\mathrm{M}(a'))\ )$$

- The interventional approach for defining causal effects is

$$\mathrm{E}(\ \mathrm{Y}(a,\mathrm{G}(a'))\ )$$

where $\mathrm{G}(a') \sim \mathrm{M}(a')|\mathrm{C}$



For ith individual, we have X_i and Y_i
$$Cor(X,Y) \neq 0$$

A and B are separate random draw, i.e.,
$A \sim f(X)$ and $\mathrm{B} \sim f(Y)$
$$Cor(A,B) = 0$$

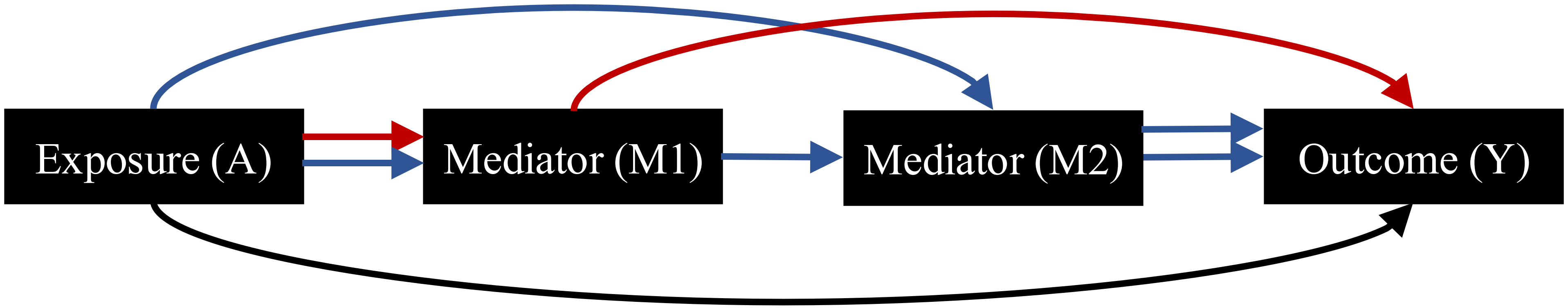
Partially backward decomposition strategy

- Three components are decomposed from the effect of A → Y.

Direct effect $= \mathrm{PSE}_0$;
M1-inducing indirect effect $= \mathrm{PSE}_{M_1}$; M2-inducing indirect effect $= \mathrm{PSE}_{M_2} + \mathrm{PSE}_{M_1 M_2}$

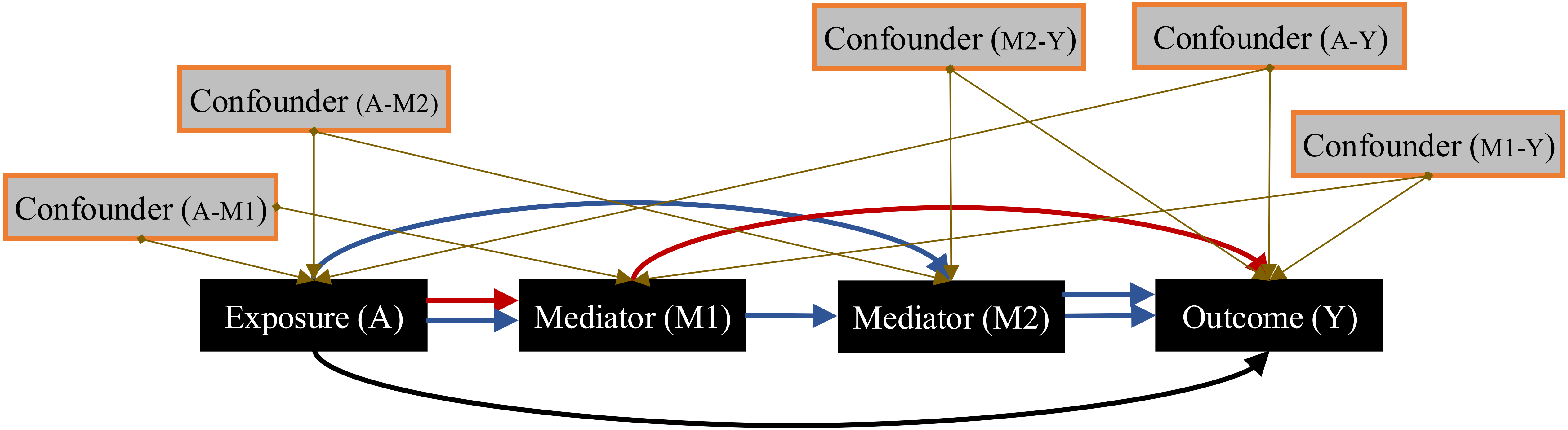
- Define causal effects by an **interventional approach**.

- Structure-free



Partially backward decomposition strategy

Assumptions

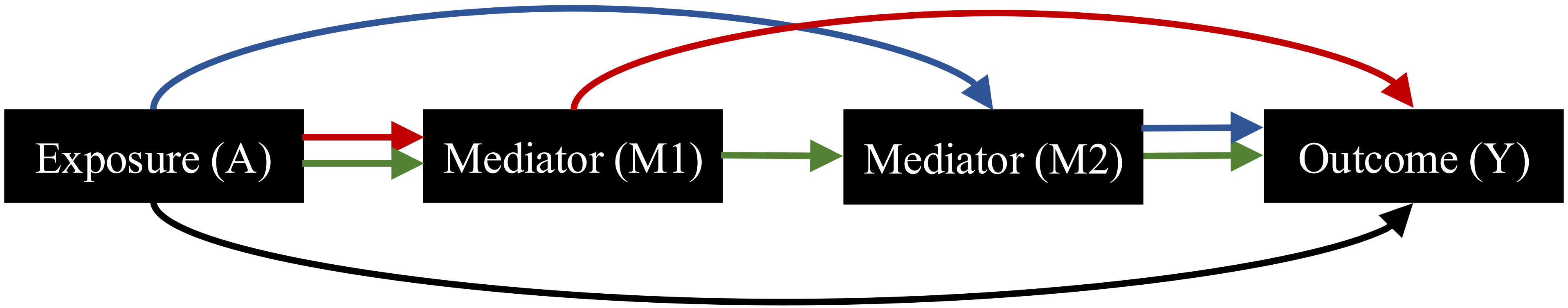


Complete decomposition strategy

➢ Four components are decomposed from the effect of A → Y.

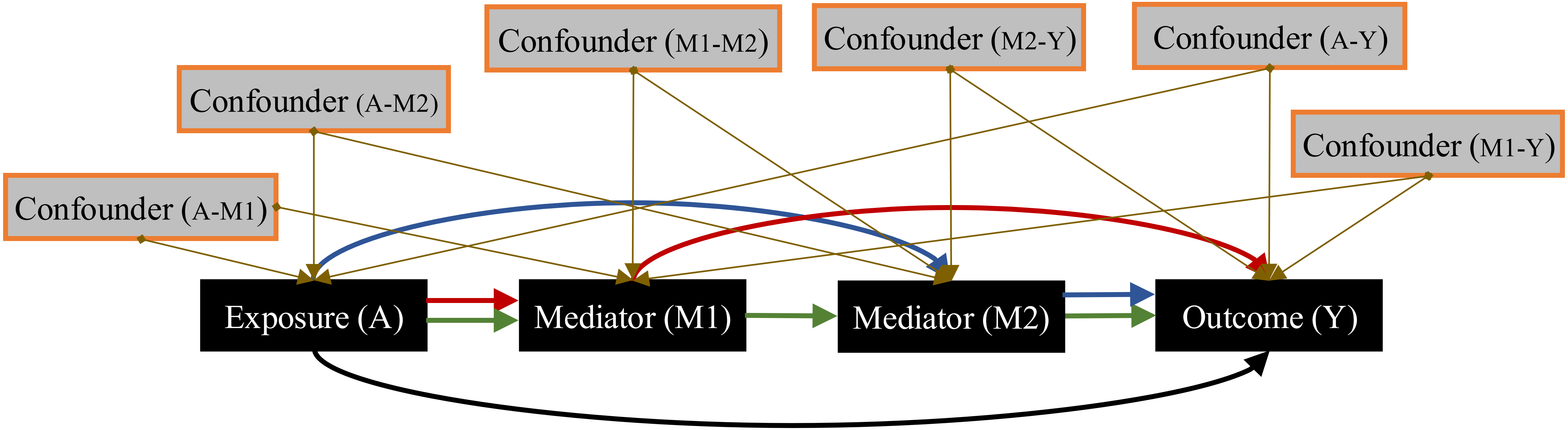
Direct effect $= \mathrm{PSE}_0$;
$\mathrm{PSE}_{\mathrm{M}_1}$; $\mathrm{PSE}_{\mathrm{M}_2}$; $\mathrm{PSE}_{\mathrm{M}_1\mathrm{M}_2}$

➢ Define causal effects by a **interventional approach**



Complete decomposition strategy

Assumptions



Four effect decomposition strategies

A trade-off between assumption required and information obtained

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TW decomposition

- Mediation structure-robust
- One indirect effect

  $PSE_{M_1} + PSE_{M_2} + PSE_{M_1M_2}$
- Total effect

PF decomposition

- Sequential mediators
- Two indirect effects (***M*-leading indirect effect**)

  $PSE_{M_1} + PSE_{M_1M_2}$

  PSE_{M_2}
- Total effect

PB decomposition

- Mediation structure-robust
- Two indirect effects (***M*-inducing indirect effect**)

  PSE_{M_1}

  $PSE_{M_2} + PSE_{M_1M_2}$
- Interventional total effect

Complete decomposition

- Sequential mediators
- Three indirect effects

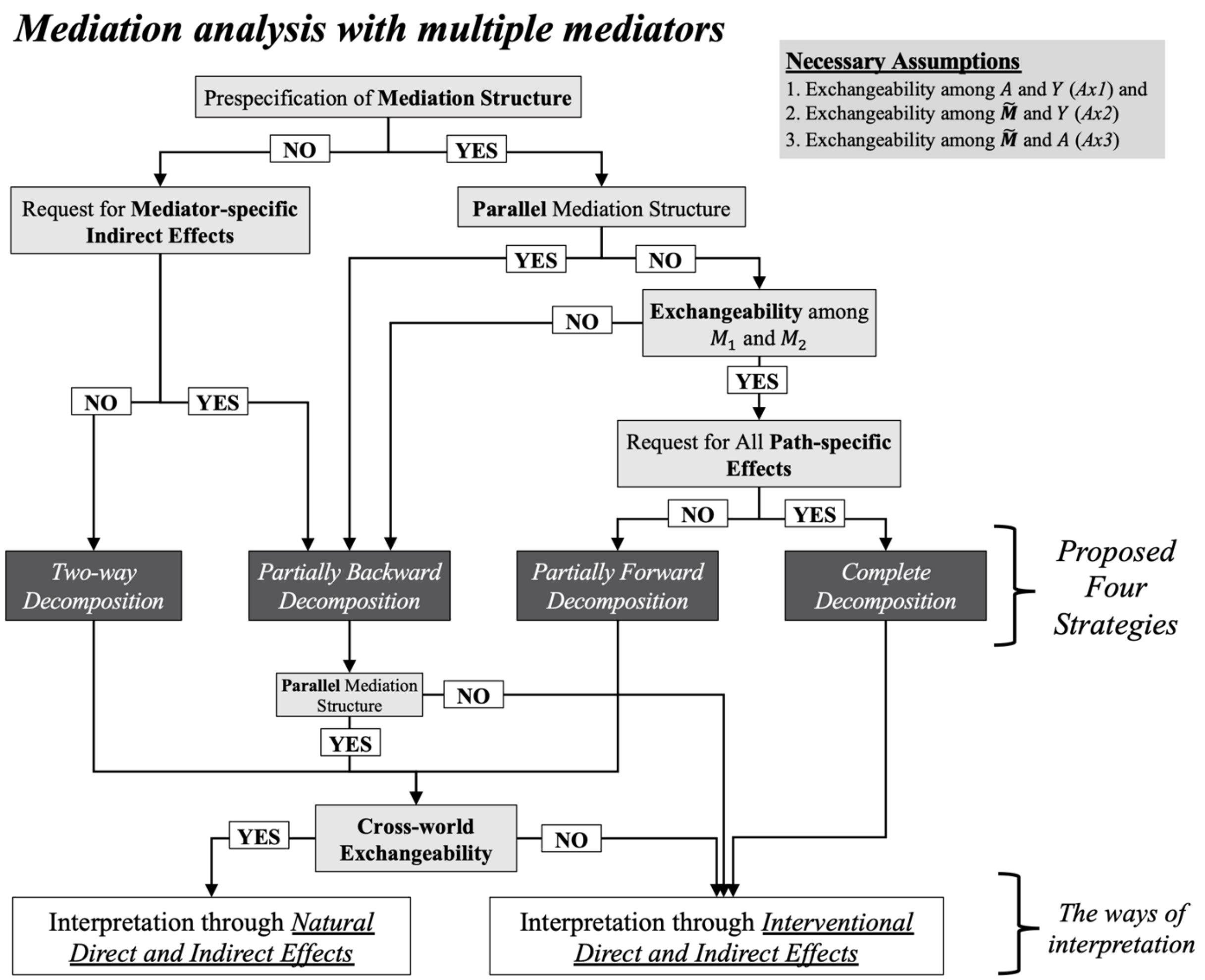
  PSE_{M_1}

  PSE_{M_2}

  $PSE_{M_1M_2}$
- Interventional total effect

Integrated multiple mediation analysis

Flowchart



Identification

- Two-way decomposition

$$Q_{TW}(a,e) \equiv \int \mathrm{E}[Y|a,\tilde{\boldsymbol{m}}]\, f(\tilde{\boldsymbol{m}}|e)\, d\tilde{\boldsymbol{m}}$$

Direct effect $Q_{TW}(1,0) - Q_{TW}(0,0)$; Indirect effect $Q_{TW}(1,1) - Q_{TW}(1,0)$

- PF decomposition

$$Q_F(a,e_1,e_2) \equiv \int E[Y|a,\tilde{\boldsymbol{m}}] f(m_1|e_1) f(m_2|e_2,m_1) d\tilde{\boldsymbol{m}}$$

Direct effect $Q_F(1,0,0) - Q_F(0,0,0)$; M1-Indirect effect $Q_F(1,1,0) - Q_F(1,0,0)$; M2-Indirect effect $Q_F(1,1,1) - Q_F(1,1,0)$

- PB decomposition

$$Q_B(a,e_1,e_2) \equiv \int E[Y|a,\tilde{\boldsymbol{m}}] f(m_1|e_1) f(m_2|e_2) d\tilde{\boldsymbol{m}}$$

Direct effect $Q_B(1,0,0) - Q_B(0,0,0)$; M1-Indirect effect $Q_B(1,1,0) - Q_B(1,0,0)$; M2-Indirect effect $Q_B(1,1,1) - Q_B(1,1,0)$

- Complete decomposition

$$Q_C(a,e_1,e_2,e_3) \equiv \int E[Y|a,\tilde{\boldsymbol{m}}]\, f(m_1|e_1) \left\{ \int f(m_2|e_2,m_1^*)\, f(m_1^*|e_3)\, dm_1^* \right\} d\tilde{\boldsymbol{m}}.$$

Estimation

Inverse-probability-weighting for PF decomposition

$$\mathrm{Q}_F(a, e_1, e_2) = \int E[Y|a, \tilde{\boldsymbol{m}}, C] f_{M_1|A,C}(m_1|e_1, C) f_{M_2|A,M_1,C}(m_2|e_2, m_1, C) d\tilde{\boldsymbol{m}}$$

$$= \mathrm{E}(W_F(a, e_1, e_2; M_1, M_2) \times Y)$$

where $W_F(a, e_1, e_2; M_1, M_2) = [f_{M_1|A,C}(M_1|e_1, C) f_{M_2|A,M_1,C}(M_2|e_2, M_1, C)\mathrm{I}(A = a)]/$

$[f_{A|C}(A|C) f_{M_1|A,C}(M_1|A, C) f_{M_2|A,M_1,C}(M_2|A, M_1, C)]$.

The IPW estimator for $\mathrm{Q}_F(a, e_1, e_2)$ is

$$\widehat{\Delta}_F^{IPW}(a, e_1, e_2) = \mathbb{P}_n(\widehat{W}_F(a, e_1, e_2; M_1, M_2) \times Y),$$

where $\widehat{W}_F(a, e_1, e_2; M_1, M_2)$ is the weight estimated by substituting $\hat{f}_{A|C}$, $\hat{f}_{M_1|A,C}$, and $\hat{f}_{M_2|A,M_1,C}$.

Application

Causal mechanism of hepatitis C virus (HCV) infection on mortality

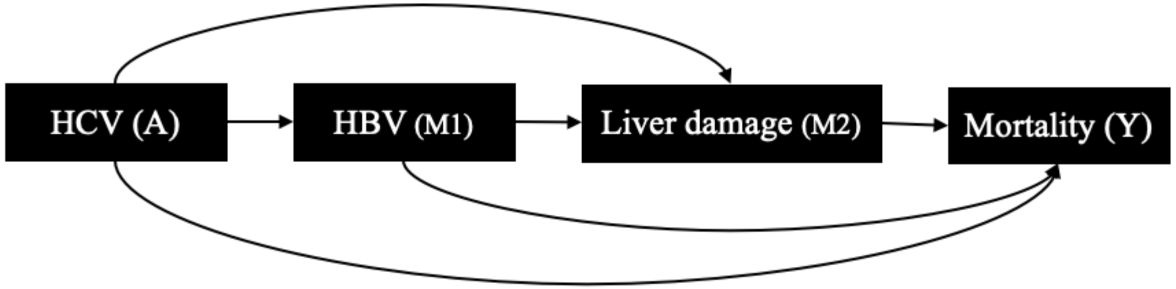


Table 7. Effect decomposition of HCV (A) on mortality (Y) through HBV (M1) and abnormal ALT (M2) under the four decomposition strategies.

<table>
<tr><th rowspan="3">Path</th><th colspan="8">Strategy</th></tr>
<tr><th colspan="2">Complete decomposition</th><th colspan="2">PF decomposition</th><th colspan="2">PB decomposition</th><th colspan="2">Two-way decomposition</th></tr>
<tr><th>effect (SD)</th><th>P value</th><th>effect (SD)</th><th>P value</th><th>effect (SD)</th><th>P value</th><th>effect (SD)</th><th>P value</th></tr>
<tr><td>A→Y</td><td>0.109 (0.053)</td><td>0.034*</td><td>0.098 (0.049)</td><td>0.038*</td><td>0.109 (0.053)</td><td>0.034*</td><td>0.098 (0.049)</td><td>0.038*</td></tr>
<tr><td>A→M₁→Y</td><td>-0.083 (0.035)</td><td>0.013*</td><td rowspan="2">-0.081 (0.032)</td><td rowspan="2">0.010*</td><td>-0.083 (0.034)</td><td>0.013*</td><td rowspan="3">-0.028 (0.039)</td><td rowspan="3">0.409</td></tr>
<tr><td>A→M₁→M₂→Y</td><td>-0.009 (0.003)</td><td>0.003*</td><td rowspan="2">0.045 (0.017)</td><td rowspan="2">0.010*</td></tr>
<tr><td>A→M₂→Y</td><td>0.054 (0.017)</td><td>0.002*</td><td>0.052 (0.017)</td><td>0.002*</td></tr>
<tr><td>Total effect</td><td>0.071 (0.030)</td><td>0.018*</td><td>0.070 (0.029)</td><td>0.019*</td><td>0.071 (0.030)</td><td>0.018*</td><td>0.070 (0.029)</td><td>0.019*</td></tr>
</table>

Abbreviations: HCV: hepatitis C virus; HBV: hepatitis B virus; ALT: alanine aminotransferase; PF: partially forward; PB: partially backward; SD: standard deviation