Mediation Analysis for Time-to-Event Data

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Outline

Classical Mediation Analysis

Semi-Competing Risks

Identification Strategies

Application

Interventionist Approach

Concluding Remarks

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Mediation Analysis at a Fixed Time Point

- We are interested in how the treatment exerts its effect on the outcome.
- Consider a randomized controlled trial (RCT), where $Z \in \{0, 1\}$ is the treatment, $M(z)$ is the potential mediator, and $Y(z, m)$ is the potential outcome of interest.
- Mediation analysis stands on a philosophical view that the mediator can be manipulated, so $Y(z, m)$ is a potential outcome of both the initial treatment and mediator.

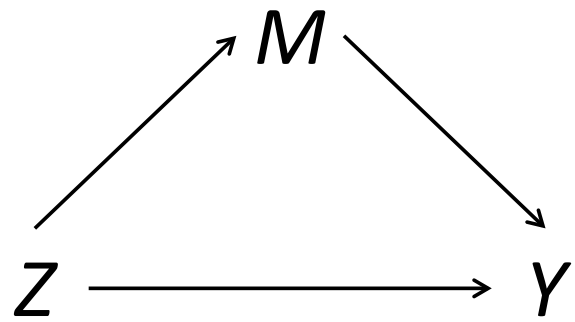
The Total Treatment Effect

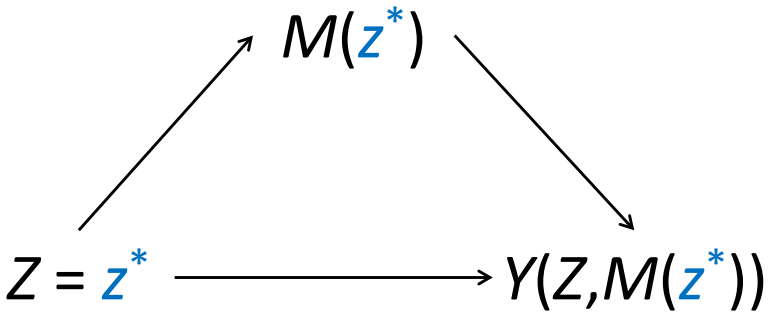
- Under the treated, the mediator is $M(1)$, and the outcome is $Y(1, M(1))$.
- Under the control, the mediator is $M(0)$, and the outcome is $Y(0, M(0))$.
- The total treatment effect

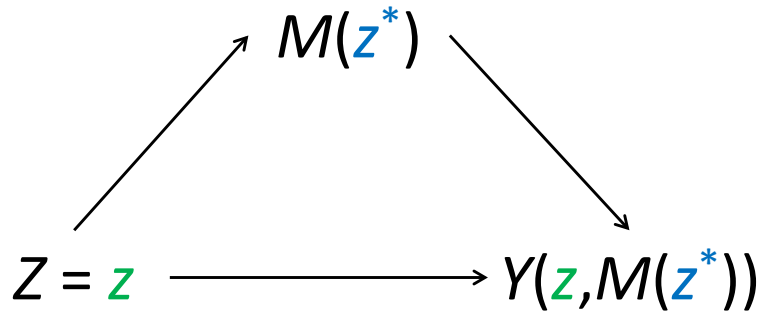
$$TE = E\{Y(1, M(1))\} - E\{Y(0, M(0))\}.$$

- It evaluates a joint effect of the initial treatment and the mediator.
- How to separate the direct treatment effect and the indirect treatment effect through the mediator?

Causal Graph







Natural Direct and Indirect Effects

- The natural direct effect

$$NDE(x) = E\{Y(1, M(x))\} - E\{Y(0, M(x))\}.$$

- The natural indirect effect

$$NIE(x) = E\{Y(x, M(1))\} - E\{Y(x, M(0))\}.$$

- Obviously,

$$TE = NDE(0) + NIE(1).$$

- How to identify them?

Assumptions for Identification

- Ignorability: the treatment is randomized,

$$\{M(z), Y(z^*, m)\} \perp\!\!\!\perp Z.$$

- Sequential ignorability: the mediator is randomized,

$$Y(z^*, m) \perp\!\!\!\perp M(z) \mid Z = z.$$

- Positivity:

$$0 < P(Z = z, M(z) = m) < 1.$$

- Causal consistency:

$$M = M(Z), \;\; Y = Y(Z, M(Z)).$$

Identification

$$
\begin{aligned}
& E\{Y(z, M(z^*))\} \\
= & \int E\{Y(z,m) \mid M(z^*) = m\} dF_{M(z^*)}(m) \\
= & \int E\{Y(z,m) \mid Z = z^*, M(z^*) = m\} dF_{M(z^*)}(m) && \text{(I)} \\
= & \int E\{Y(z,m) \mid Z = z^*\} dF_{M(z^*)}(m) && \text{(SI)} \\
= & \int E\{Y(z,m) \mid Z = z\} dF_{M(z^*)|Z=z^*}(m) && \text{(I)} \\
= & \int E\{Y(z,m) \mid Z = z, M(z) = m\} dF_{M(z^*)|Z=z^*}(m) && \text{(SI)} \\
= & \int E\{Y \mid Z = z, M = m\} dF_{M|Z=z^*}(m) && \text{(C)}
\end{aligned}
$$

Critiques to Mediation Analysis

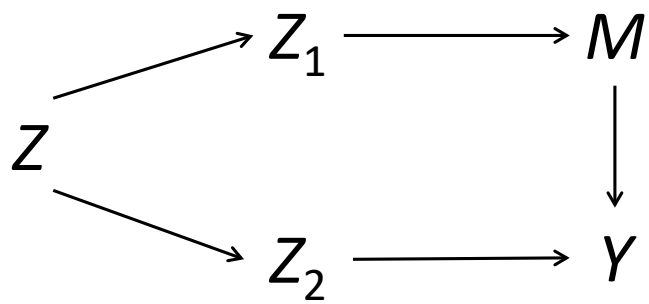
- Identification of natural direct/indirect effects requires untestable assumptions involving cross-world independence.
- Are there alternatives that use frameworks and assumptions that are verifiable in principle?

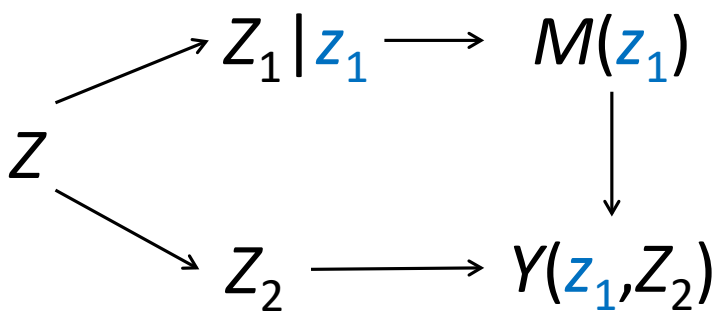
Critiques to Mediation Analysis

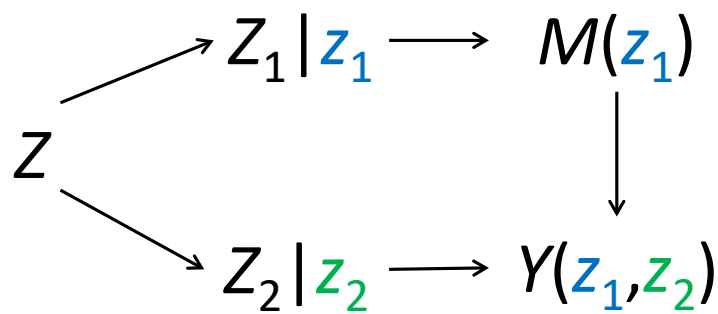
- Identification of natural direct/indirect effects requires untestable assumptions involving cross-world independence.
- Are there alternatives that use frameworks and assumptions that are verifiable in principle?
- Let's consider an example to study the direct and indirect effects of smoking (Z) on heart disease (Y).
- Nicotine increases heart disease (Y) by increasing hypertention (M).
- Non-nicotine components do not have direct effects on hypertention.

Treatment Components

- Decompose the initial treatment Z into two parts: Z_1 and Z_2.
- Z_1 has direct effect on M but not on Y.
- Z_2 has direct effect on Y but not on M.







Separable Effects

- The total effect
$$TE = E\{Y(1,1) - Y(0,0)\}.$$
- The separable direct effect
$$SDE(x) = E\{Y(x,1)\} - E\{Y(x,0)\}.$$
- The separable indirect effect
$$SIE(x) = E\{Y(1,x)\} - E\{Y(0,x)\}.$$
- Obviously,
$$TE = SDE(1) + SIE(0).$$
- How to identify them?

Assumptions for Identification

- Ignorability:
$$\{M(z_1, z_2), Y(z_1, z_2)\} \perp\!\!\!\perp Z.$$
- Dismissible component 1:
$$M(z_1, z_2) = M(z_1, z_1).$$
- Dismissible component 2:
$$E\{Y(z_1, z_2) \mid M(z_1, z_2)\} = E\{Y(z_2, z_2) \mid M(z_2, z_2)\}.$$
- Positivity:
$$0 < P(Z = z, M(z, z) = m) < 1.$$
- Causal consistency:
$$M = M(Z, Z), Y = Y(Z, Z).$$

Identification

- Dismissible component 1 says that the hazard of M is irrelevant to z_2.
- Dismissible component 2 says that the hazard of Y is irrelevant to z_1.

$$
\begin{aligned}
& E\{Y(z_1, z_2)\} \\
= & \int E\{Y(z_1, z_2) \mid M(z_1, z_2) = m\} dF_{M(z_1, z_2)}(m) \\
= & \int E\{Y(z_2, z_2) \mid M(z_2, z_2) = m\} dF_{M(z_1, z_1)}(m) \\
= & \int E\{Y(z_2, z_2) \mid M(z_2, z_2) = m, Z_1 = Z_2 = z_2\} dF_{M(z_1, z_1) \mid Z_1 = Z_2 = z_1}(m) \\
= & \int E\{Y \mid M = m, Z = z_2\} dF_{M \mid Z = z_1}(m)
\end{aligned}
$$

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Mediation Analysis at Varying Time Points

- For time-to-event data, the mediator and outcome become processes.
- The mediator process $M(t) \in \{0, 1\}$: whether the intermediate event happens or not at t.
- The outcome process of interest $Y(t)$: whether the terminal event happens or not at t.

$M(t^-)$	$Y(t)$	Description
0	0	No intermediate event, no terminal event
0	1	No intermediate event, a terminal event
1	0	An intermediate event, no terminal event
1	1	An intermediate event, a terminal event

Semi-Competing Risks

- Semi-competing risks refer to the phenomenon that the terminal event can truncate the non-terminal event but not vice versa (Fine et al, 2001).
- The terminal event and non-terminal events have a competing nature.
- Some individuals develop terminal events after intermediate events, while others without intermediate events.
- For example, in the study of stem cell transplantation, mortality is a terminal event, and relapse is an intermediate event.

Formal Definition

- Let $d\tilde{N}_1(t; z_1)$ be the jump of potential counting process for the intermediate event during $[t, t + dt)$ when the treatment is set at z_1.
- Let $d\tilde{N}_2(t; z_2, n_1)$ be the jump of potential counting process for the terminal event during $[t, t + dt)$ when the treatment is set at z_2 and the counting process for the intermediate event at t^- is set at n_1.
- Markovness:

$$\begin{aligned} &P(d\tilde{N}_2(t; z_2, n_1) = 1 \mid \tilde{N}_2(t^-; z_2, z_1) = 0, \tilde{N}_1(t^-; z_1) = n_1, \tilde{N}_1(s^-; z_1) = n_1^*) \\ &= P(d\tilde{N}_2(t; z_2, n_1) = 1 \mid \tilde{N}_2(t^-; z_2, z_1) = 0, \tilde{N}_1(t^-; z_1) = n_1), \ s \leq t. \end{aligned}$$

Formal Definition

- Denote

$$\tilde{N}_1(t; z_1) = \int_0^t d\tilde{N}_1(s; z_1), \ \tilde{N}_2(t; z_2, z_1) = \int_0^t d\tilde{N}_2(s; z_2, \tilde{N}_1(t^-; z_1)).$$

- The potential time to intermediate event $T_1(z_1)$ is the time that $\tilde{N}_1(t; z_1)$ jumps, and the potential time to terminal event $T_2(z_1, z_2)$ is the time that $\tilde{N}_2(t; z_2, z_1)$ jumps.
- Causal consistency:

$$\tilde{N}_1(t; Z) = \tilde{N}_1(t), \ \tilde{N}_2(t; Z, Z) = \tilde{N}_2(t).$$

- Under causal consistency, $T_1 = T_1(Z)$ and $T_2 = T_2(Z, Z)$.

Estimand

- The counterfactual cumulative incidence

$$F(t; z_1, z_2) = P(T(z_1, z_2) \leq t) = P(\tilde{N}_2(t; z_2, z_1) = 1)$$

  is of primary interest.
- It is equivalent to identify the hazard

$$d\Lambda(t; z_1, z_2) = d \log\{1 - F(t; z_1, z_2)\}.$$

- Total treatment effect: $F(t; 1, 1) - F(t; 0, 0)$.
- Natural direct effect: $F(t; 0, 1) - F(t; 0, 0)$.
- Natural indirect effect: $F(t; 1, 1) - F(t; 0, 1)$.

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Assumptions for Identification

- Ignorability: the treatment is randomized,

$$\{d\tilde{N}_1(t; z_1), d\tilde{N}_2(t; z_2, n_1) : 0 < t < t^*\} \perp\!\!\!\perp Z.$$

- Random censoring:

$$\{\tilde{N}_1(t; z), \tilde{N}_2(t; z, z) : 0 < t < t^*\} \perp\!\!\!\perp C \mid Z.$$

- Positivity:

$$P(Z = z, \tilde{N}_1(t^-; z) = n_1) > 0, \;\; P(C > t^* \mid Z) > 0.$$

Observed Processes

- The censoring indicators for the intermediate event and terminal event $\delta_1 = I\{T_1 \leq C\}$ and $\delta_2 = I\{T_2 \leq C\}$, respectively.
- The observed counting process for the intermediate event $N_*(t; z) = I\{T_1 \leq t, T_2 \geq T_1, \delta_1 = 1, Z = z\}$.
- The observed at-risk process for the intermediate event $Y_*(t; z) = I\{T_1 \geq t, T_2 \geq t, C \geq t, Z = z\}$.

Observed Processes

- The observed counting process for the terminal event without prior intermediate event $N_0(t;z) = I\{T_2 \leq t, T_1 \geq T_2, \delta_2 = 1, Z = z\}$.
- The observed counting process for the terminal event with prior intermediate event $N_1(t;z) = I\{T_2 \leq t, T_1 < t, \delta_2 = 1, Z = z\}$.
- The observed at-risk process for the terminal event without prior intermediate event $Y_0(t;z) = I\{T_2 \geq t, T_1 \geq t, C \geq t, Z = z\}$.
- The observed at-risk process for the terminal event with prior intermediate event $Y_1(t;z) = I\{T_2 \geq t, T_1 < t, C \geq t, Z = z\}$.
- $Y_*(t;z) = Y_0(t;z)$ becasue the intermediate event and the direct terminal event are a pair of competing events, sharing the same at-risk set.

Cause-Specific Hazards

- Define the cause-specific hazard of the terminal event

$$\begin{aligned} & d\Lambda_{n_1}(t; z_1, z_2) \\ = & P(d\tilde{N}_2(t; z_2, n_1) = 1 \mid \tilde{N}_1(t^-; z_1) = n_1, \tilde{N}_2(t^-; z_2, z_1) = 0). \end{aligned}$$

- It involves cross-world quantity. How to identify it?

Sequential Ignorability

- What is lost? — Sequential ignorability!

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$$P(\tilde{N}_2(t; z_2, n_1) = 1 \mid Z = z_2, \tilde{N}_1(t^-; z_1) = n_1, \tilde{N}_2(t^-; z_2, z_1) = 0))$$
$$= P(\tilde{N}_2(t; z_2, n_1) = 1 \mid Z = z_2, \tilde{N}_1(t^-) = n_1, \tilde{N}_2(t^-) = 0)).$$

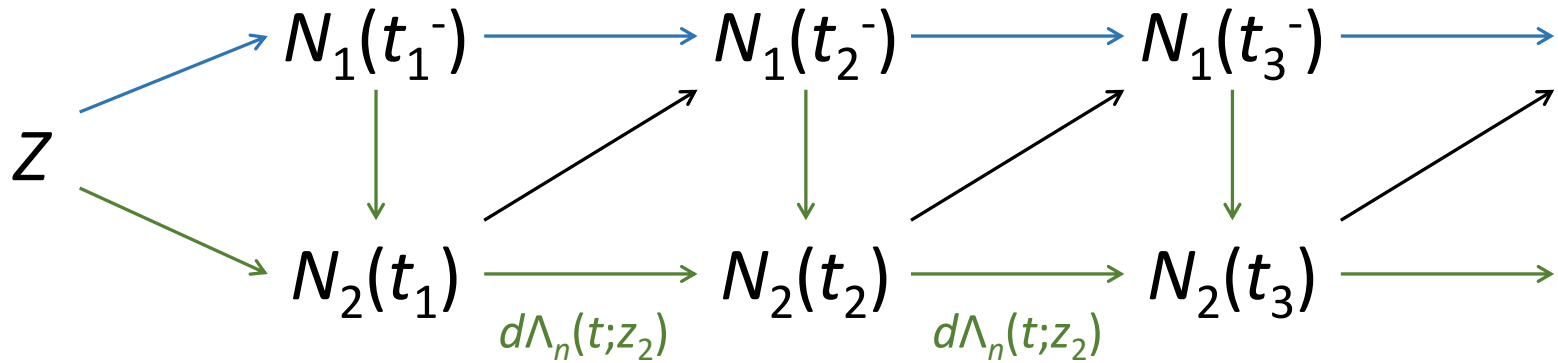
- The cause-specific hazard can be estimated by Nelson-Aalen estimators,

$$d\hat{\Lambda}_{n_1}(t; z_2) = \frac{I\{\bar{Y}_{n_1}(t; z_2) > 0\}}{\bar{Y}_{n_1}(t; z_2)} d\bar{N}_{n_1}(t; z_2).$$

- This sequential ignorability precludes cross-world reliance of $\tilde{N}_2(t; z_2, n_1)$ on z_1.

Sequential Ignorability on Processes

- How about the cross-world reliance of $\tilde{N}_1(t; z_1)$ on z_2?



Sequential Ignorability, Part 2

- Huang (2021) proposed the following version:

$$\begin{aligned} & P(\tilde{N}_1(t; z_1) = 1 \mid Z = z_1, \tilde{N}_1(t^-; z_1) = 0, \tilde{N}_2(t^-; z_2, z_1) = 0)) \\ = \; & P(\tilde{N}_1(t; z_1) = 1 \mid Z = z_1, \tilde{N}_1(t^-) = 0, \tilde{N}_2(t^-) = 0)). \end{aligned}$$

- The prevalence of intermediate events, $w_{n_1}(t; z_1, z_2) = w_{n_1}(t; z_1)$ defined above, is randomized concerning Z_2.

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- The prevalence of intermediate events, $w_{n_1}(t; z_1, z_2) = w_{n_1}(t; z_1)$ defined above, is randomized concerning Z_2.
- Estimator for the prevalence:

$$\hat{w}_{n_1}(t; z_1) = \frac{I\{\bar{Y}_0(t; z_1) + \bar{Y}_1(t; z_1) > 0\}}{\bar{Y}_0(t; z_1) + \bar{Y}_1(t; z_1)} \bar{Y}_{n_1}(t; z_1).$$

Controlling the Prevalence

- Under all the assumptions above,

$$\frac{d}{dt}\Lambda(t; z_1, z_2) = \sum_{n_1 \in \{0,1\}} \frac{d}{dt}\Lambda_{n_1}(t; z_2) \cdot w_{n_1}(t; z_1).$$

- The natural direct effect measures the treatment effect on the cumulative incidence of terminal event via changing the cause-specific hazards of terminal events while controlling the prevalence of intermediate events.
- The natural indirect effect mausures the treatment effect on the cumulative incidence of terminal event via changing the prevalence of intermediate events while controlling the cause-specific hazards of terminal events.

A Paradox

- In some scenarios, interpreting the natural direct effect as "controlling the prevalence of intermediate events" may not be meaningful.
- For example, if a novel therapy completely removes the terminal event, we may think that the direct effect should be large but the indirect effect is null.
- However, since the prevalence of intermediate events increases to one by removing terminal events, the indirect effect can also be large.

Sequential Ignorability, Part 2

- We modify the sequential ignorability:

$$\begin{aligned} & P(d\tilde{N}_1(t; z_1) = 1 \mid Z = z_1, \tilde{N}_1(t^-; z_1) = 0, \tilde{N}_2(t^-; z_2, z_1) = 0)) \\ = \; & P(d\tilde{N}_1(t; z_1) = 1 \mid Z = z_1, \tilde{N}_1(t^-) = 0, \tilde{N}_2(t^-) = 0)). \end{aligned}$$

- So $d\Lambda_*(t; z_1, z_2) = d\Lambda_*(t; z_1)$.

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- So $d\Lambda_*(t; z_1, z_2) = d\Lambda_*(t; z_1)$.
- It can be estimated by Nelson-Aalen estimators,

$$d\hat{\Lambda}_*(t; z_1) = \frac{I\{\bar{Y}_*(t; z_1) > 0\}}{\bar{Y}_*(t; z_1)} dN_*(t; z_1).$$

Sub-distribution

- We partition the terminal event into a direct outcome event which does not have a history of intermediate event and an indirect event which has a history of intermediate event.
- The cumulative incidence of the terminal event

$$F(t; z_1, z_2) = F_0(t; z_1, z_2) + F_1(t; z_1, z_2),$$

where

$$\begin{aligned} & F_0(t; z_1, z_2) \\ = & \int_0^t \exp\{-\Lambda_*(s^-; z_1) - \Lambda_0(s^-; z_2)\} d\Lambda_0(s; z_2), \\ & F_1(t; z_1, z_2) \\ = & \int_0^t \exp\{-\Lambda_*(s^-; z_1) - \Lambda_0(s^-; z_2)\}[1 - \exp\{-\Lambda_1(t; z_2) + \Lambda_1(s; z_2)\}] d\Lambda_*(s; z_1). \end{aligned}$$

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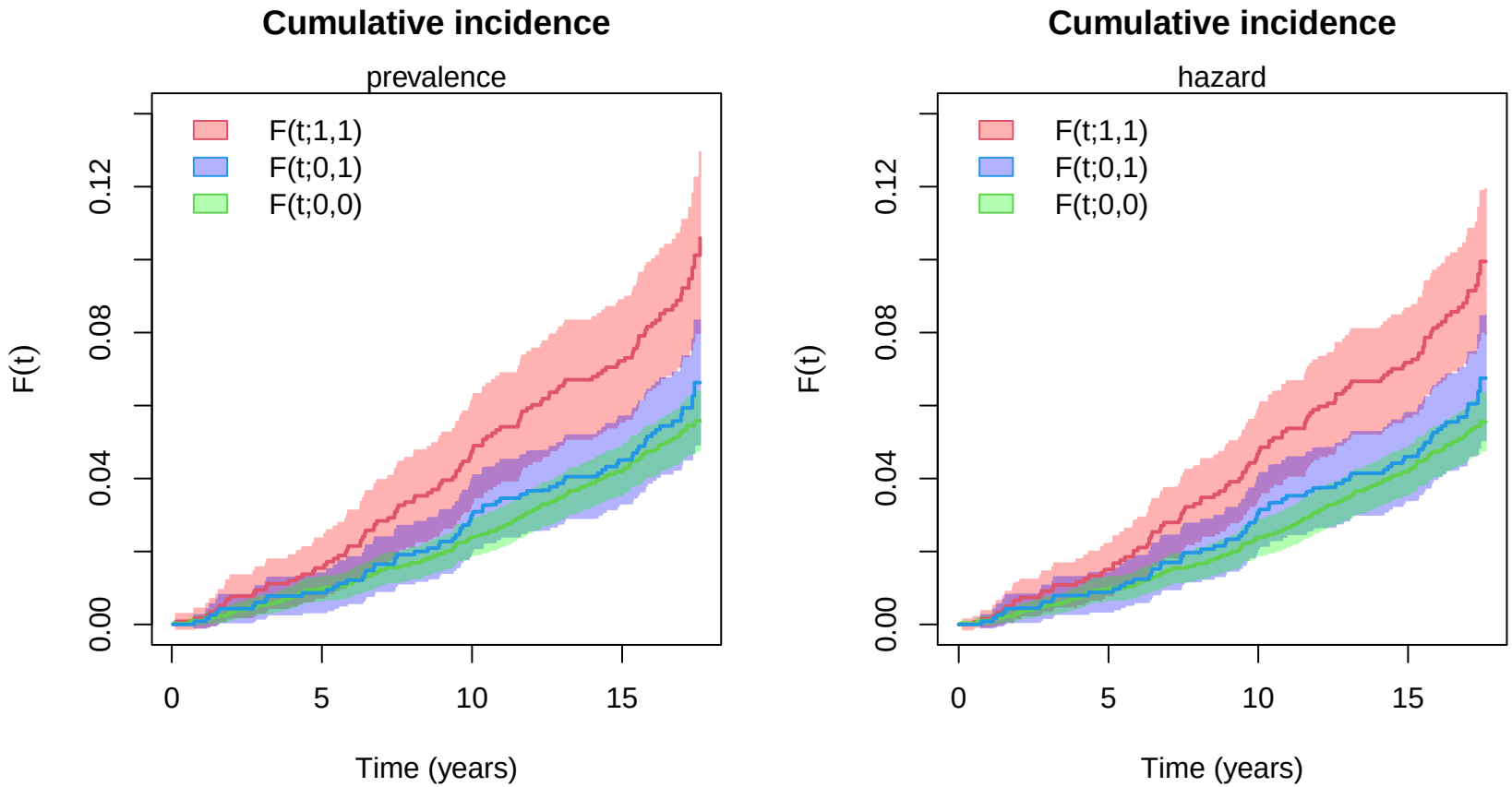
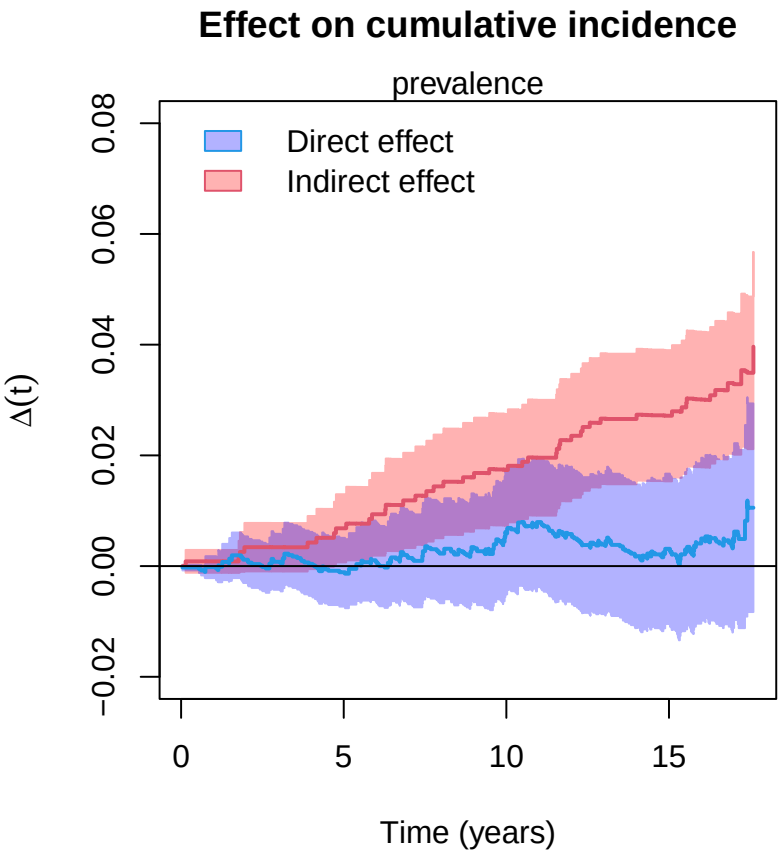
Hepatitis B Data

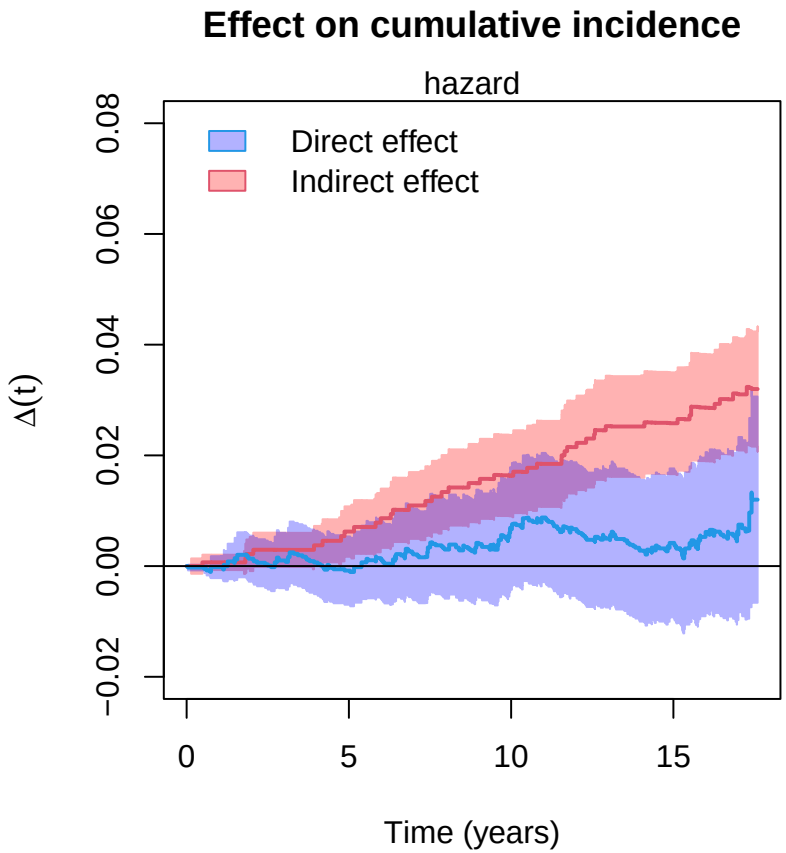
- Z: Hepatitis B; T_1: cancer; T_2: mortality.



Hepatitis B Data

- Hepatitis B increases mortality through increasing the risk of cancer.





Hepatitis B Data: Alternative Decomposition

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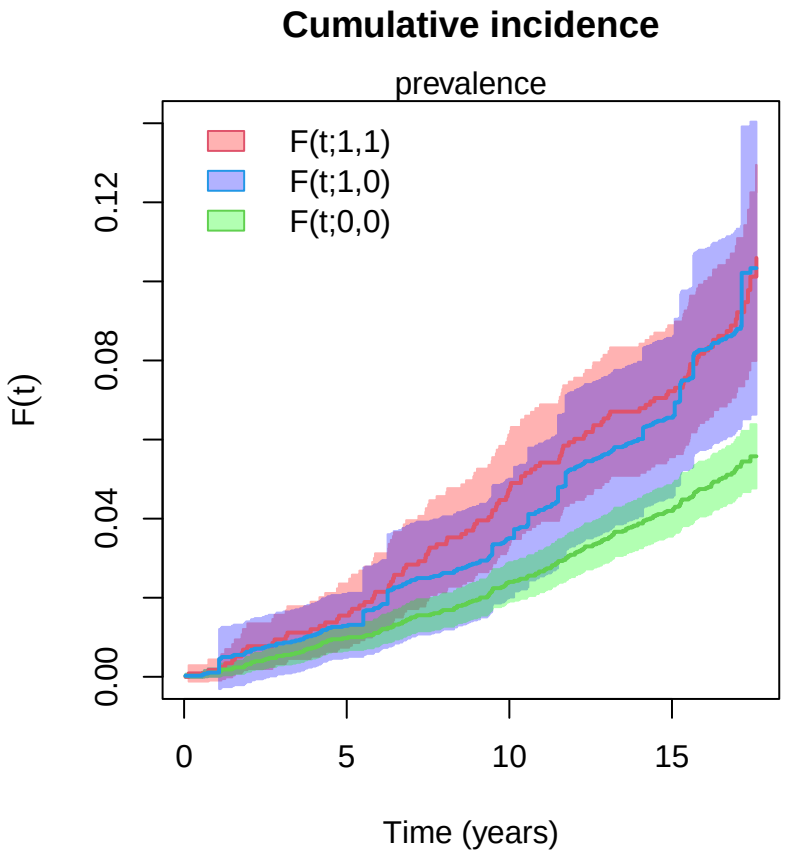

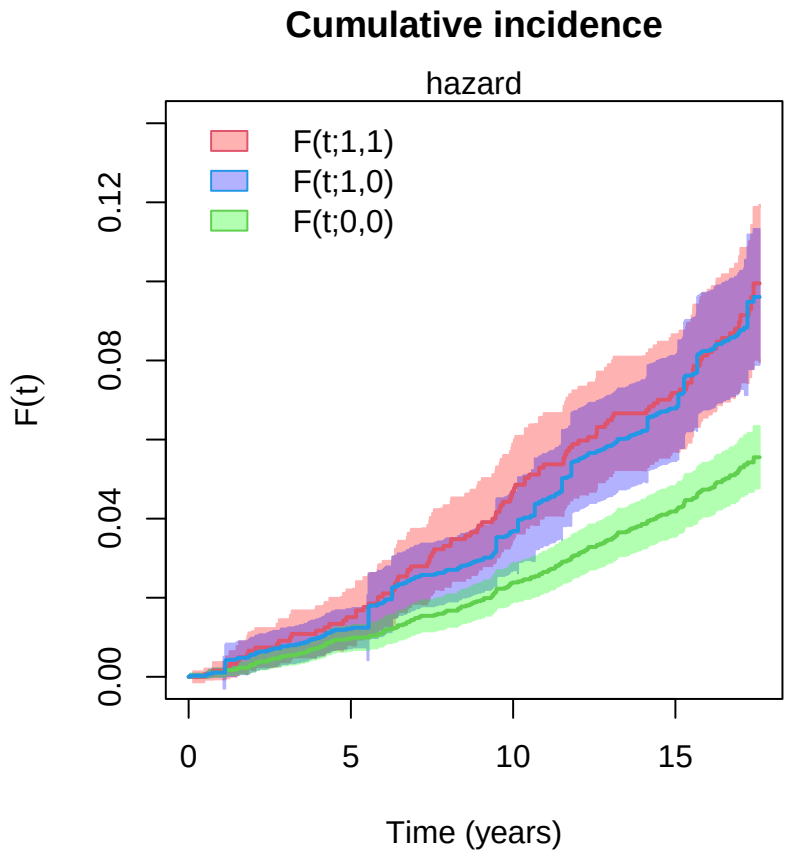

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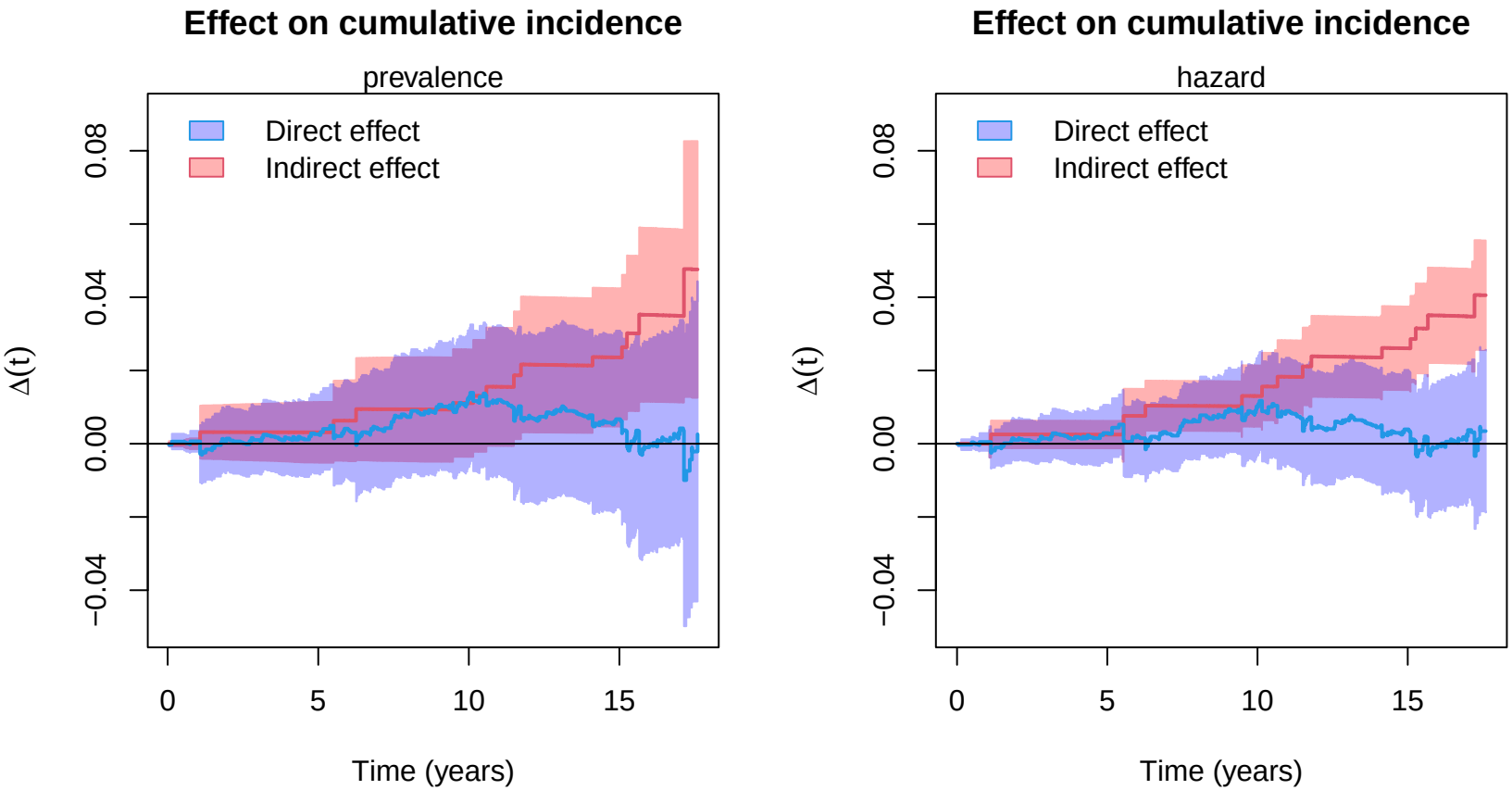
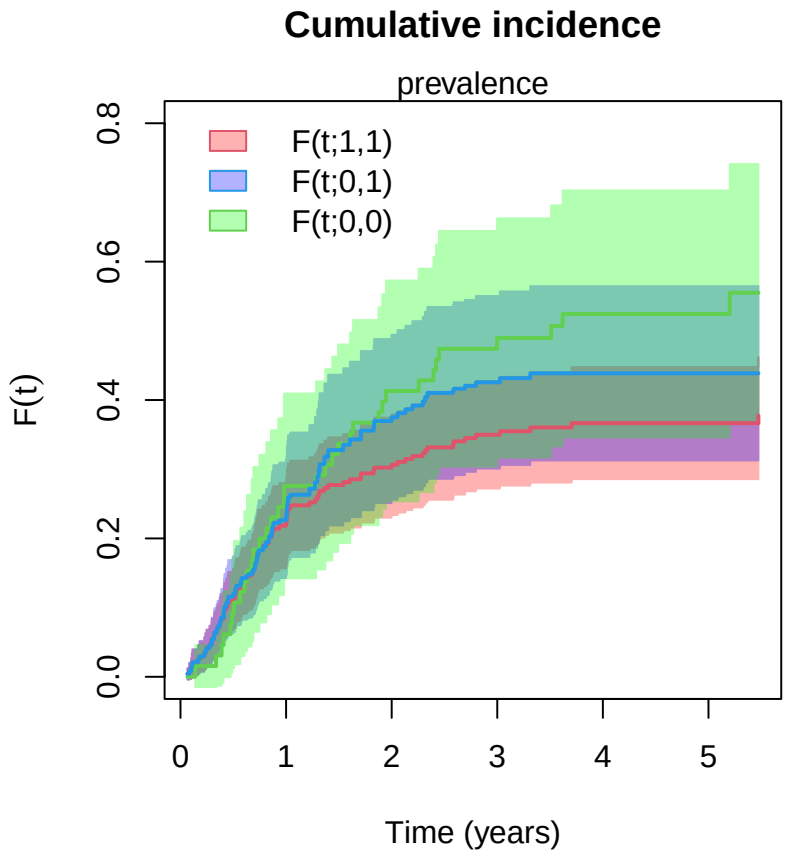
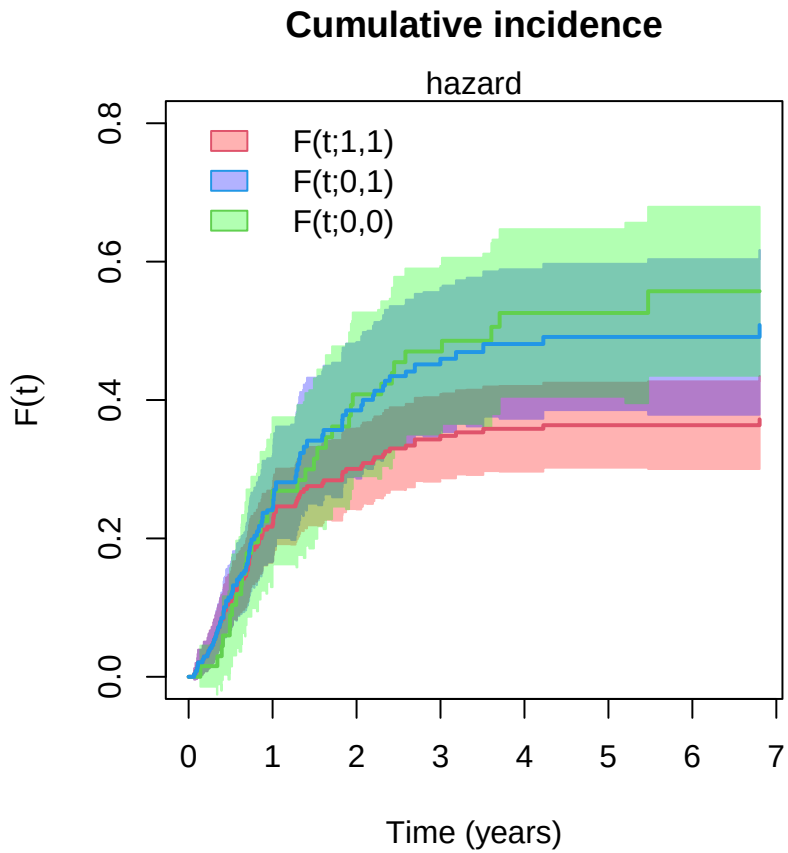


Leukemia Data

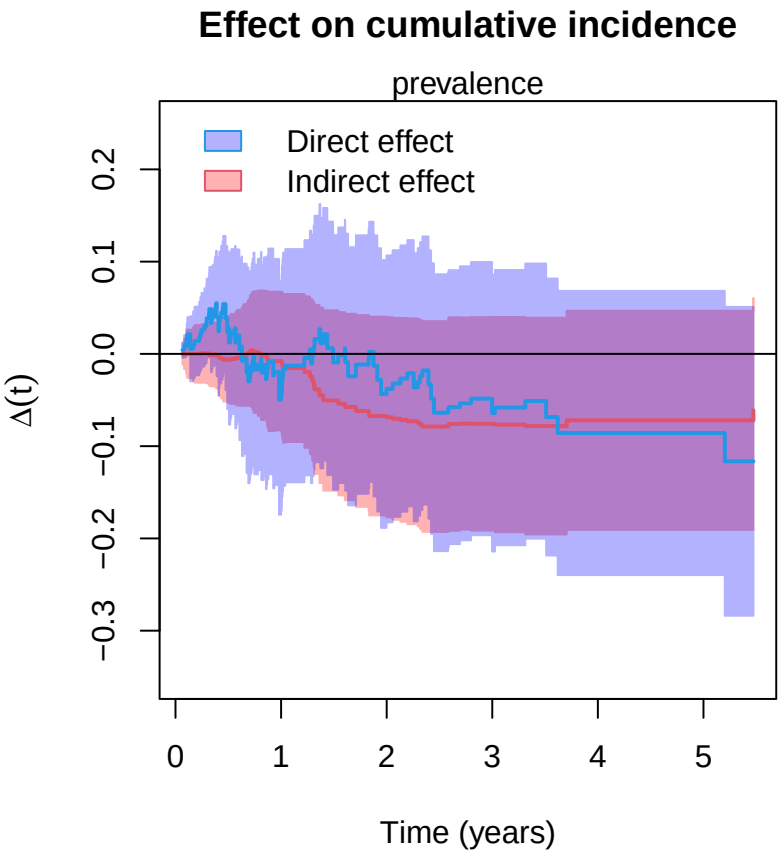
- Z: Haplo-SCT; T_1: relapse; T_2: mortality.

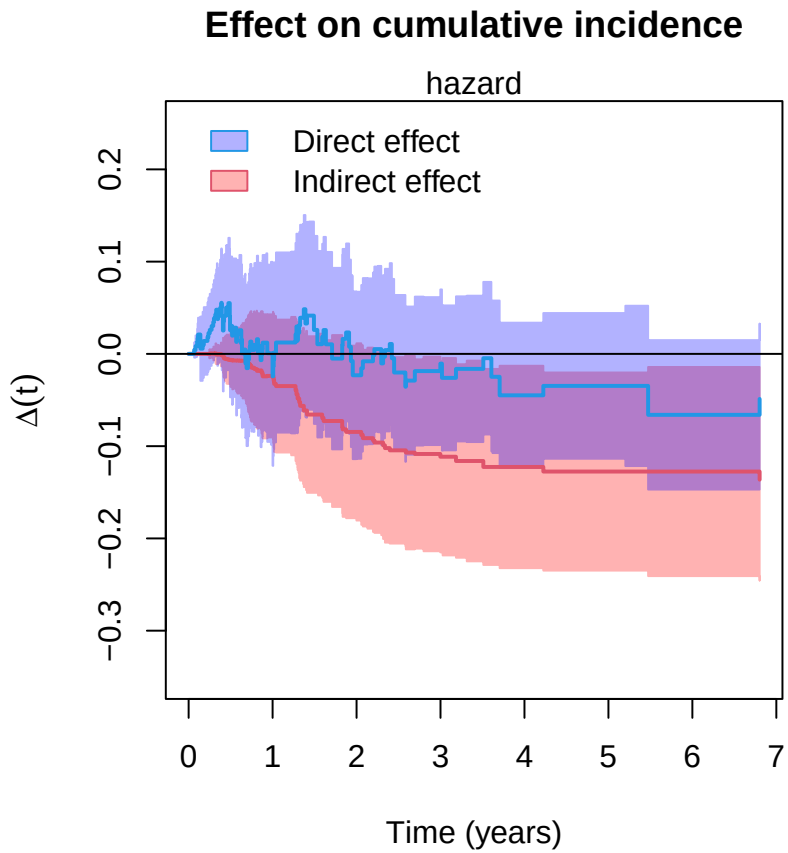




Leukemia Data

- Haplo-SCT reduces mortality through reducing the risk of relapse.





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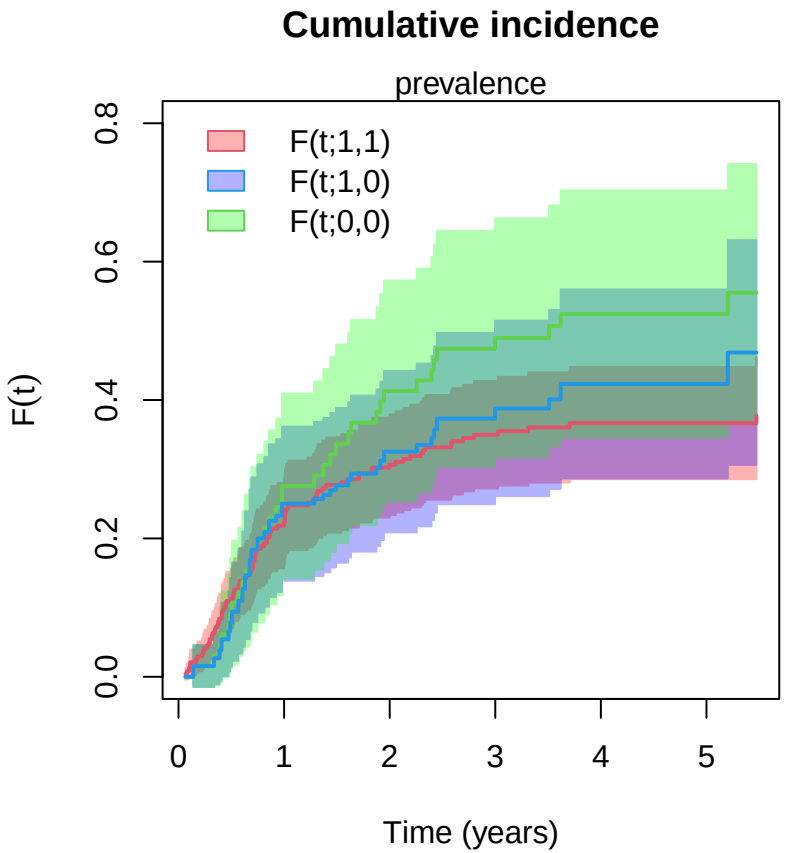
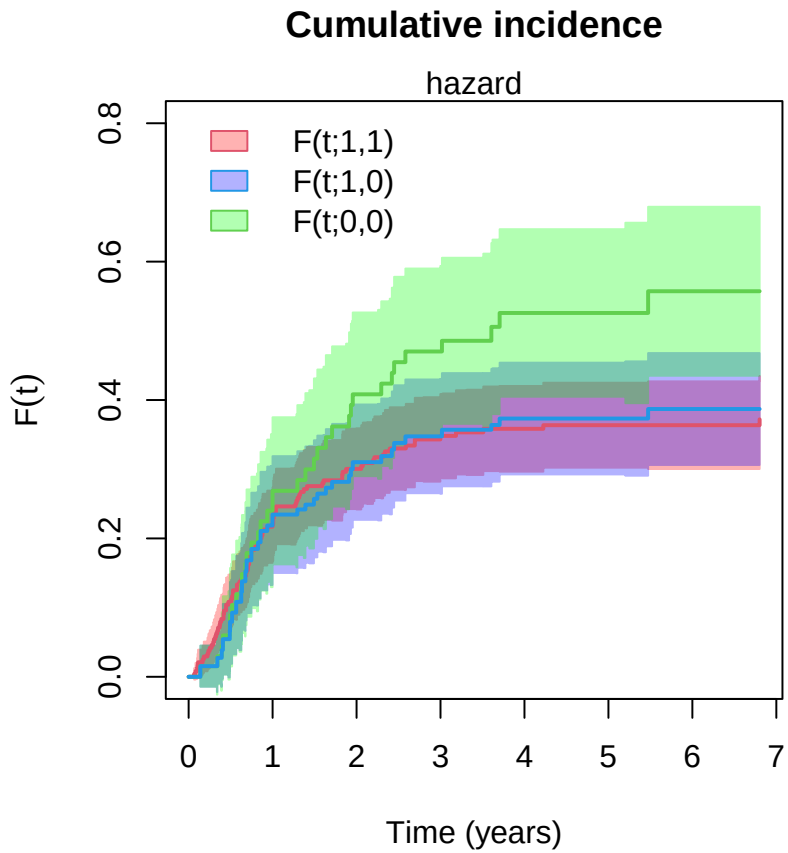
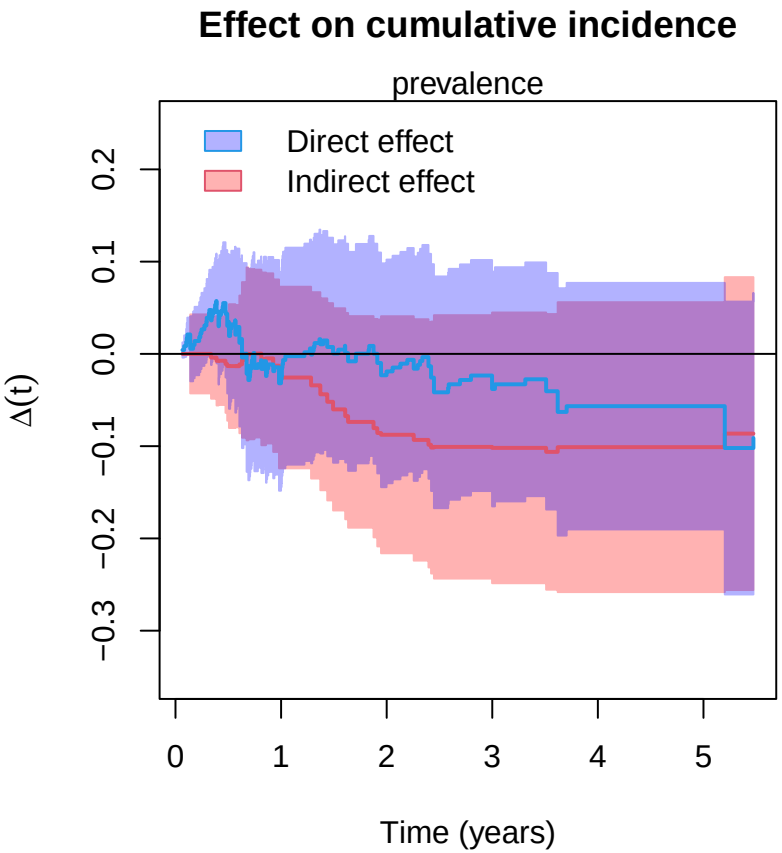
- Z: Haplo-SCT; T_1: relapse; T_2: mortality.

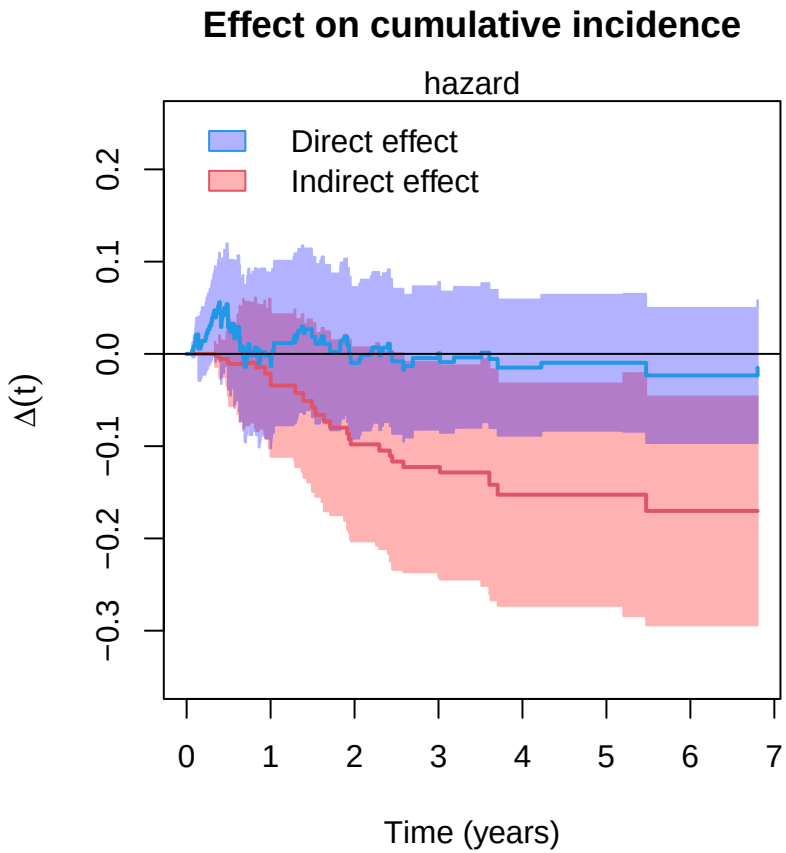




Leukemia Data: Alternative Decomposition

- Haplo-SCT reduces mortality through reducing the risk of relapse.





Outline

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Semi-Competing Risks

Identification Strategies

Application

Interventionist Approach

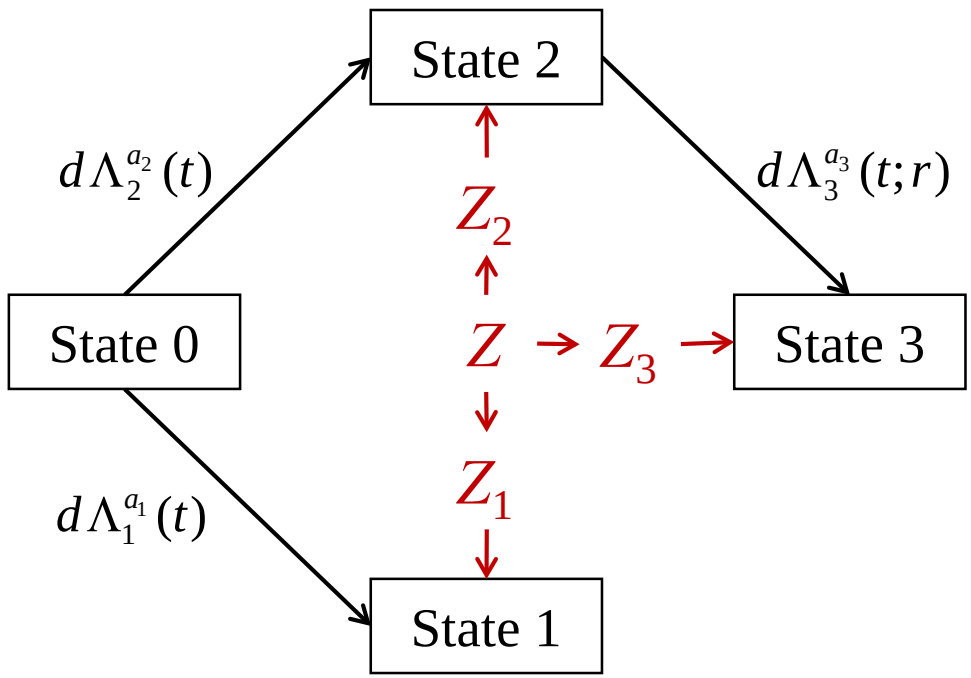
Concluding Remarks

Separable Effects

- The treatment is decomposed to $Z = (Z_1, Z_2, Z_3)$.
- Z_1 influences the direct terminal event.
- Z_2 influences the intermediate event.
- Z_3 influences the indirect terminal after intermediate event.
- In the realized trial, $Z = Z_1 = Z_2 = Z_3$. But in future experiments, Z_1, Z_2 and Z_3 can be unequal.

A Multi-State Model

- State 0: original status
- State 1: direct outcome (terminal) event
- State 2: intermediate event
- State 3: indirect outcome (terminal) event following intermediate event



New Estimand and Assumption

- Potential time to terminal event T^z.
- Potential time to intermediate event R^z.
- The quantity of interest is the counterfactual cumulative incidence of the terminal event

$$F^{z=(z_1,z_2,z_3)}(t) = P(T^{z=(z_1,z_2,z_3)} \leq t).$$

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$$F^{z=(z_1,z_2,z_3)}(t) = P(T^{z=(z_1,z_2,z_3)} \leq t).$$

- Dismissible treatment components:

$$d\Lambda_j^{z=(z_1,z_2,z_3)}(t) = d\Lambda_j^{z_j}(t).$$

- It has a similar meaning with sequential ignorability.

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Discussion: Challenges

- Interaction effect.

$\rightarrow$ To distinguish the heterogeneous effect of cause-specific hazards on terminal venets. Solved by separable effects approach.

- Baseline confounders.

$\rightarrow$ Generalized Nelson-Aalen estimator.

- Time-varying confounders.

$\rightarrow$ G-formula.

Acknowledgements

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- Preprints:
  Deng Y, Wang Y, Zhou X-H. Direct and indirect treatment effects in the presence of semi-competing risks. 2023.
  Deng Y, Wang Y, Zhan X, Zhou X-H. Separable pathway effects of semi-competing risks via multi-state models. 2023.