Causal inference of mediation mechanism

Part III: 從因果之間看肝炎三部曲

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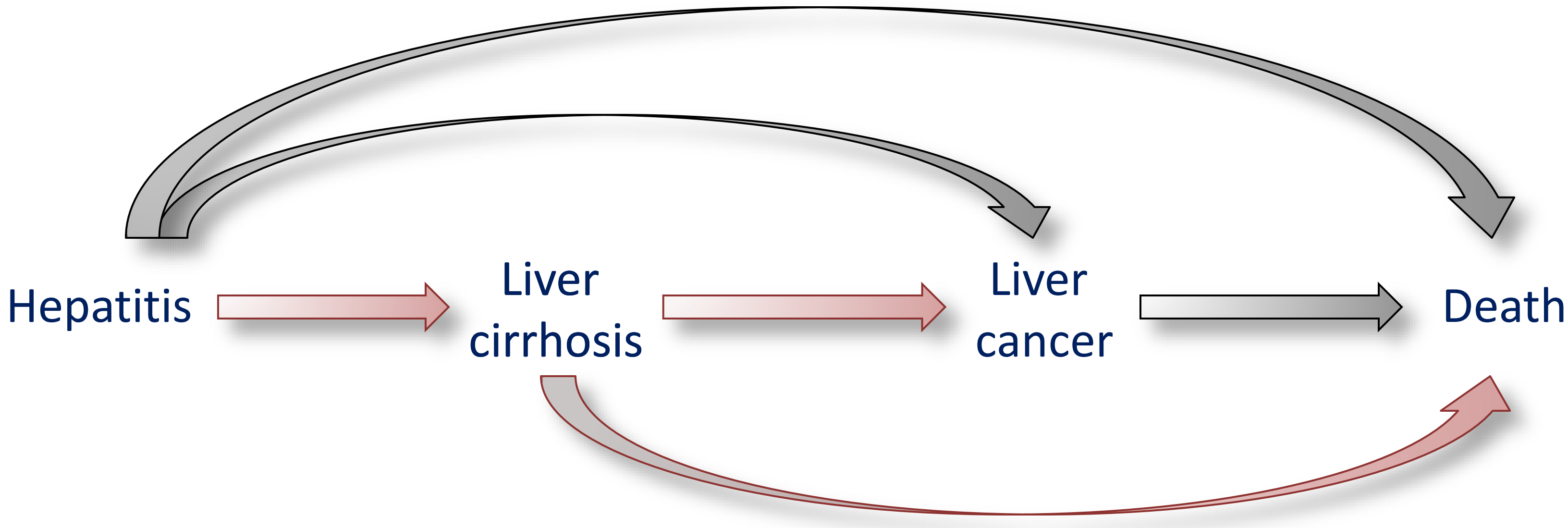
Outline

- Introduction
- Causal inference
- Statistical inference
- Summary

Time-varying post-treatment confounding



Biometrics. 2021;77:1143–1154. wileyonlinelibrary.com/journal/biom

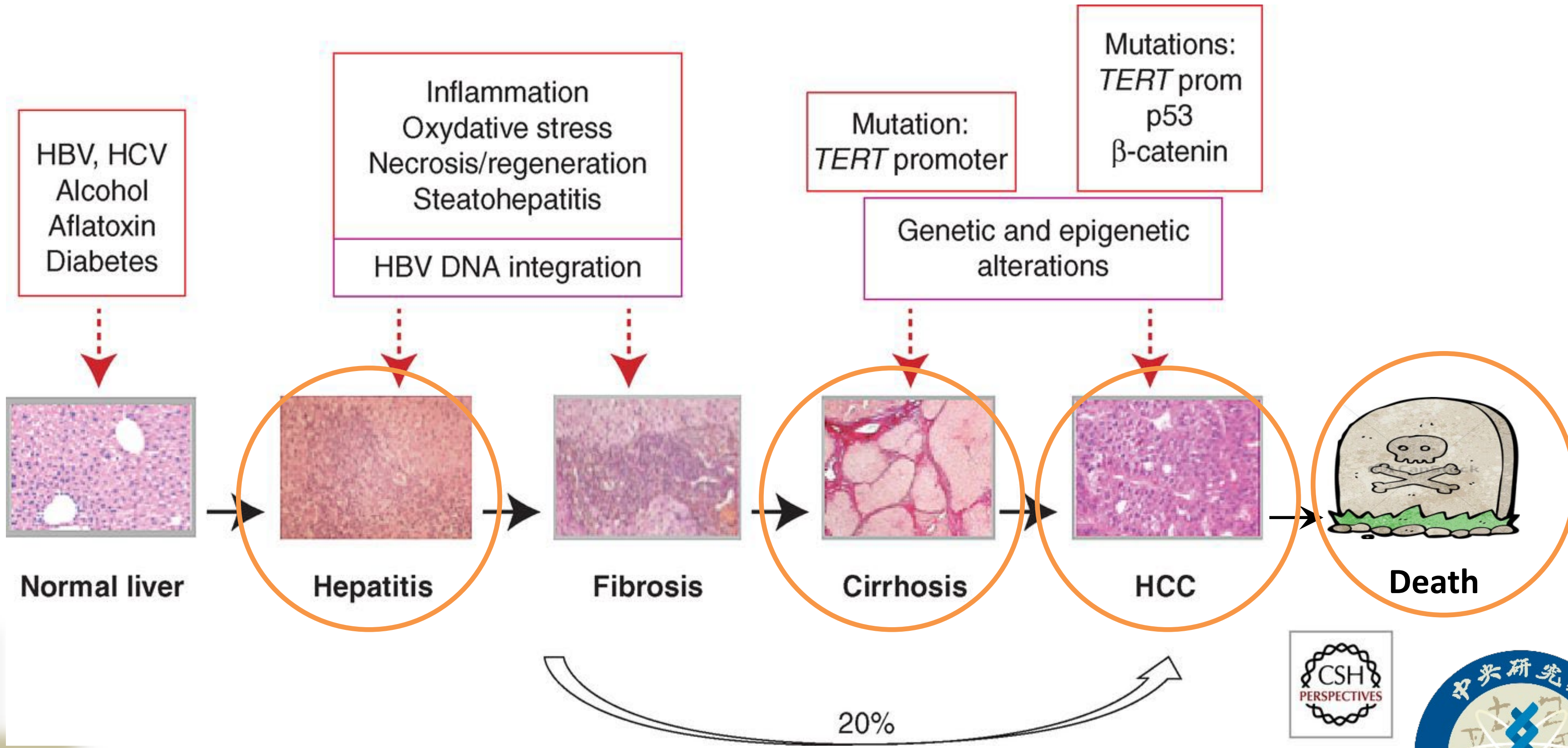
Biometrics
A JOURNAL OF THE INTERNATIONAL BIOMETRIC SOCIETY

BIOMETRIC METHODOLOGY

Causal mediation of semicompeting risks

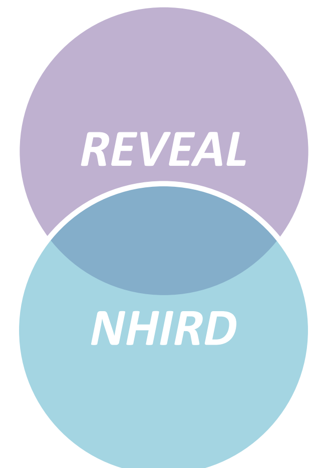
Yen-Tsung Huang

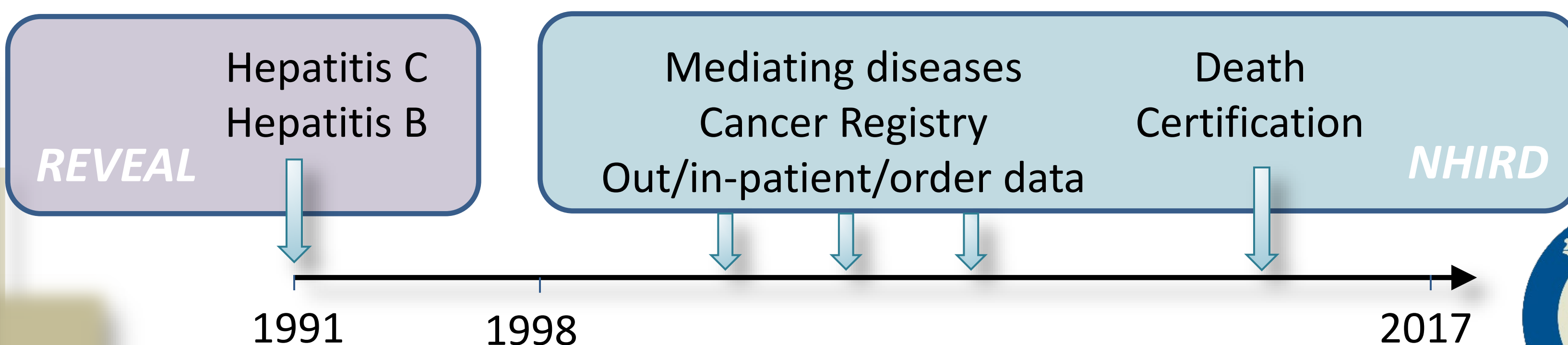
Natural history of hepatitis



REVEAL/NHIRD study

- REVEAL: a prospective cohort study starting during 1991-1992
  - Sample size: 23,820
- NHIRD（健保資料庫）: ascertainment of potential mediating diseases and death
  - NHIRD: covered 99.9% of the Taiwanese population; from 1998 to 2017





Outline

- Introduction
- Causal inference
  - Interventional approach
  - Counterfactual hazard
  - Interventional path-specific effects (iPSE)
- Statistical inference
- Summary

Interventional approach

Lin and VanderWeele. *Journal of Causal Inference* 2016.

Vansteelandt and Daniel. *Epidemiology* 2017.

Zheng and van der Laan. *Journal of Causal Inference* 2017.

$$\begin{tikzcd}[column sep=large] Z \arrow[r] \arrow[rr, bend left] \arrow[rrr, bend left=50] & N_1 \arrow[r] \arrow[rr, bend right] & N_2 \arrow[r] & N_3 \end{tikzcd}$$

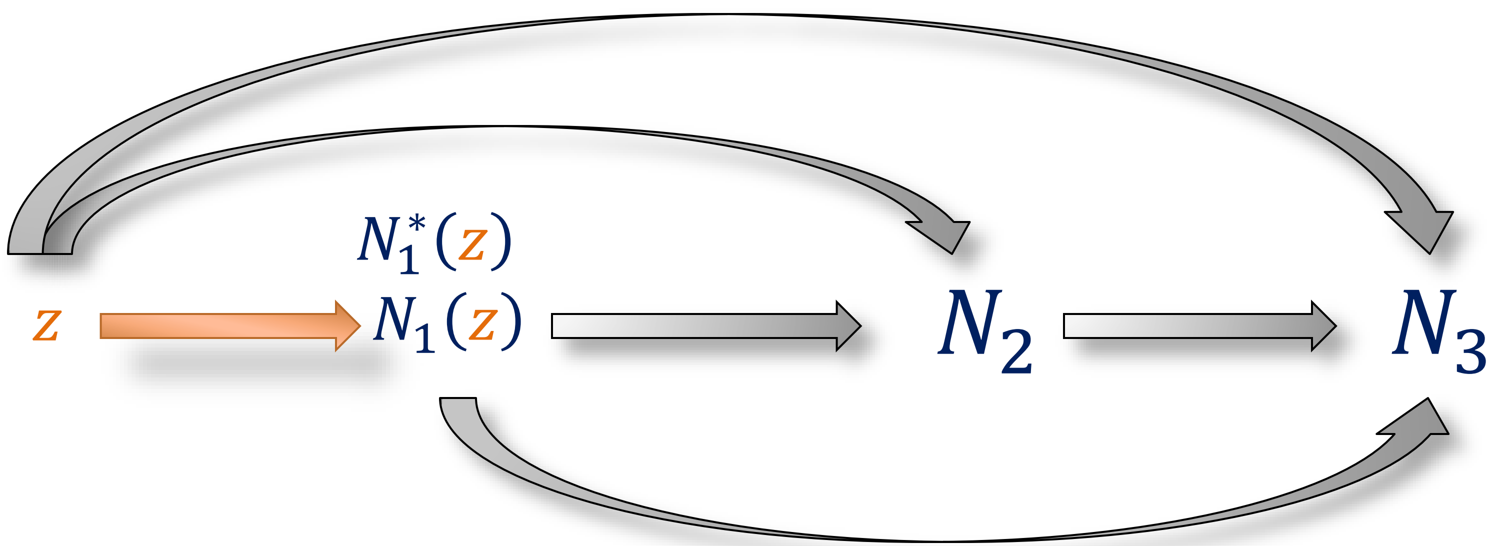
$\boldsymbol{N_1^*}(z)$

$$\begin{tikzcd}
Z \arrow[r] \arrow[rr, bend left] \arrow[rrr, bend left] & N_1 \arrow[r] \arrow[rr, bend right] & N_2 \arrow[r] & N_3
\end{tikzcd}$$

$N_1^*(z)$

$$\begin{tikzcd} z \arrow[r] \arrow[rr, bend left] \arrow[rrr, bend left] & N_1(z) \arrow[r] \arrow[rr, bend right] & N_2 \arrow[r] & N_3 \end{tikzcd}$$

$N_1(z)$ and $N_1^*(z)$ have the same distribution



$$\boldsymbol{N_2^*}\left(z_b, N_1^*(z_c)\right)$$

$$\begin{tikzcd}
Z \arrow[r] \arrow[rr, bend left] \arrow[rrr, bend left] & N_1 \arrow[r] \arrow[rr, bend right] & N_2 \arrow[r] & N_3
\end{tikzcd}$$

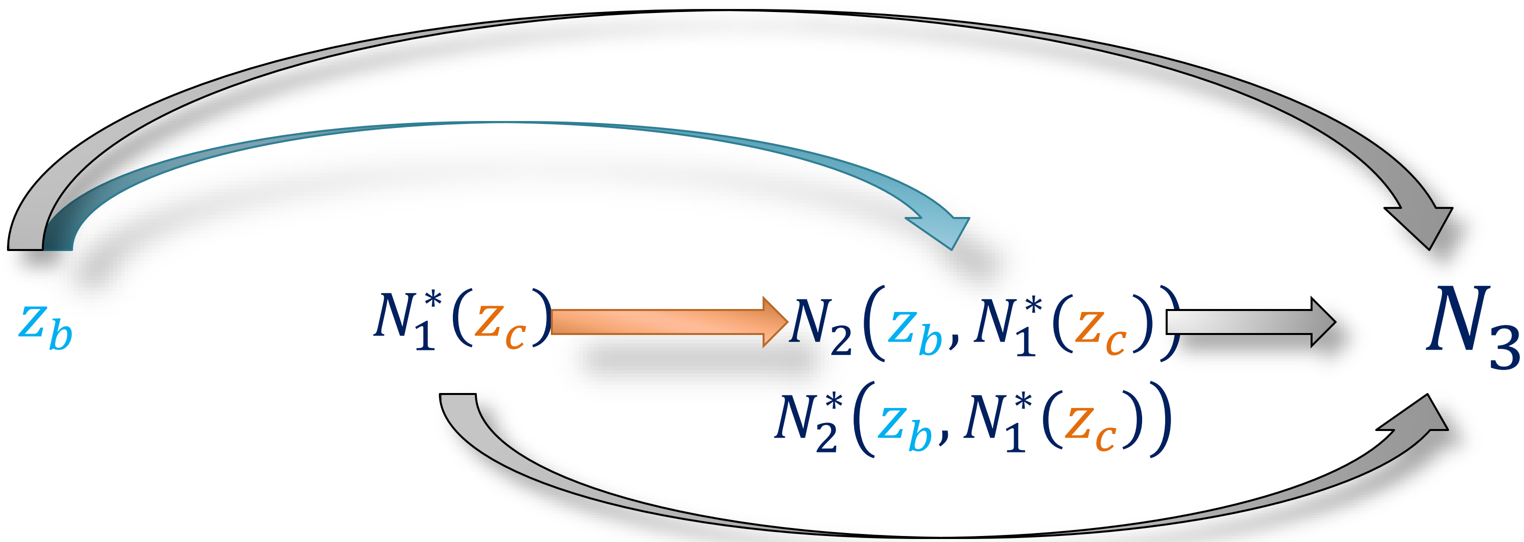
$$\boldsymbol{N_2^*}\left(z_b, N_1^*(z_c)\right)$$

$$\begin{tikzcd}
z_b \arrow[rr, bend left] \arrow[rrr, bend left=50] & N_1^*(z_c) \arrow[r] \arrow[rr, bend right] & N_2 \arrow[r] & N_3
\end{tikzcd}$$

$$N_2^*\left(z_b, N_1^*(z_c)\right)$$

$$
\begin{tikzcd}
z_b \arrow[rr, bend left] \arrow[rrr, bend left] & N_1^*(z_c) \arrow[r] \arrow[rr, bend right] & N_2\left(z_b, N_1^*(z_c)\right) \arrow[r] & N_3
\end{tikzcd}
$$

$\boldsymbol{N_2^*}(z_b, N_1^*(z_c))$ and $N_2(z_b, N_1^*(z_c))$ have the same distribution



$$\boldsymbol{N}_{3}\left(z_a, N_1^{*}(z_d), N_2^{*}\left(z_b, N_1^{**}(z_c)\right)\right)$$

$$\begin{tikzcd}
Z \arrow[r] \arrow[rr, bend left] \arrow[rrr, bend left=50] & N_1 \arrow[r] \arrow[rr, bend right] & N_2 \arrow[r] & N_3
\end{tikzcd}$$

$$\boldsymbol{N_3}\left(z_a, N_1^{*}(z_d), N_2^{*}\left(z_b, N_1^{**}(z_c)\right)\right)$$

$$\begin{tikzcd}
z_a \arrow[rrr, bend left] & N_1^{*}(z_d) \arrow[rr, bend right] & N_2^{*}\left(z_b, N_1^{**}(z_c)\right) \arrow[r] & N_3
\end{tikzcd}$$

$$N_3\left(z_a, N_1^*(z_d), N_2^*\left(z_b, N_1^{**}(z_c)\right)\right)$$

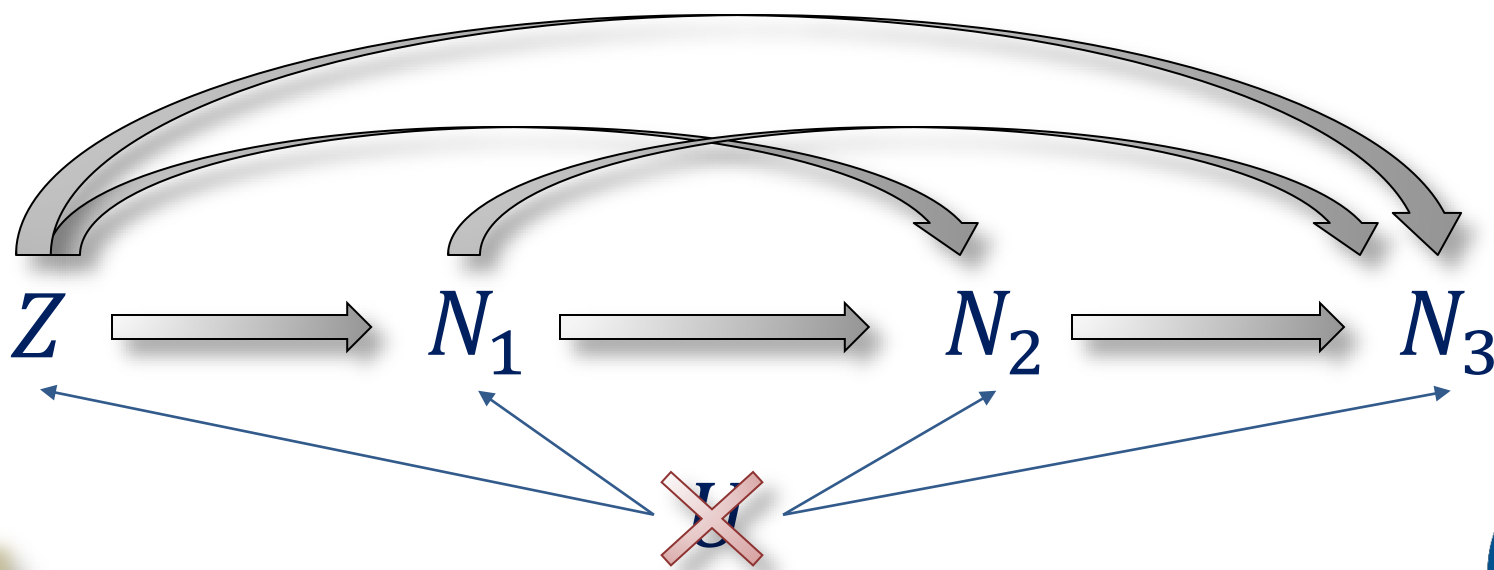
z_a $\quad$ $N_1^*(z_d)$ $\quad$ $N_2^*\left(z_b, N_1^{**}(z_c)\right)$ $\quad$ $N_3\left(z_a, N_1^*(z_d), N_2^*\left(z_b, N_1^{**}(z_c)\right)\right)$

Causal assumptions: sequential ignorability

B1) $\widetilde{N}_3(t; z, n_1, n_2) \perp \left(Z, \widetilde{N}_1(t), \widetilde{N}_2(t)\right)$

B2) $\widetilde{N}_2(t; z, n_1) \perp \left(Z, \widetilde{N}_1(t)\right) \mid \widetilde{N}_3(t) = 0$

B3) $\widetilde{N}_1(t; z) \perp Z \mid \widetilde{N}_3(t) = 0$



Interventional path-specific effects (iPSE)

$$N_3\left(z_a, N_1^*(z_d), N_2^*\left(z_{b1}, N_1^{**}(z_c)\right)\right) - N_3\left(z_a, N_1^*(z_d), N_2^*\left(z_{b0}, N_1^{**}(z_c)\right)\right)$$

$$\begin{tikzcd}
z_a \arrow[r] \arrow[rr, bend left] \arrow[rrr, bend left] & N_1^*(z_d) \arrow[r] \arrow[rr, bend right] & N_2^*\left(z_{b1}, N_1^{**}(z_c)\right) \arrow[r, shift left] \arrow[r, shift right] & N_3\left(z_a, N_1^*(z_d), N_2^*\left(z_{b1}, N_1^{**}(z_c)\right)\right)
\end{tikzcd}$$

$$\begin{tikzcd}
z_a \arrow[r] \arrow[rr, bend left] \arrow[rrr, bend left] & N_1^*(z_d) \arrow[r] \arrow[rr, bend right] & N_2^*\left(z_{b0}, N_1^{**}(z_c)\right) \arrow[r, shift left] \arrow[r, shift right] & N_3\left(z_a, N_1^*(z_d), N_2^*\left(z_{b0}, N_1^{**}(z_c)\right)\right)
\end{tikzcd}$$

$$\boldsymbol{N_3\left(z_a, N_1^*(z_d), N_2^*\left(z_{b1}, N_1^{**}(z_c)\right)\right) - N_3\left(z_a, N_1^*(z_d), N_2^*\left(z_{b0}, N_1^{**}(z_c)\right)\right)}$$

$$z_a \Rightarrow N_1^*(z_d) \Rightarrow N_2^*\left(z_{b1}, N_1^{**}(z_c)\right) \Rightarrow N_3\left(z_a, N_1^*(z_d), N_2^*\left(z_{b1}, N_1^{**}(z_c)\right)\right)$$

$$z_a \Rightarrow N_1^*(z_d) \Rightarrow N_2^*\left(z_{b0}, N_1^{**}(z_c)\right) \Rightarrow N_3\left(z_a, N_1^*(z_d), N_2^*\left(z_{b0}, N_1^{**}(z_c)\right)\right)$$

$$N_3\left(z_a, N_1^*(z_d), N_2^*\left(z_{b1}, N_1^{**}(z_c)\right)\right) - N_3\left(z_a, N_1^*(z_d), N_2^*\left(z_{b0}, N_1^{**}(z_c)\right)\right)$$

$$z_{b1} \Rightarrow N_1^*(z_d) \Rightarrow N_2^*\left(z_{b1}, N_1^{**}(z_c)\right) \Rightarrow N_3\left(z_a, N_1^*(z_d), N_2^*\left(z_{b1}, N_1^{**}(z_c)\right)\right)$$

$$z_{b0} \Rightarrow N_1^*(z_d) \Rightarrow N_2^*\left(z_{b0}, N_1^{**}(z_c)\right) \Rightarrow N_3\left(z_a, N_1^*(z_d), N_2^*\left(z_{b0}, N_1^{**}(z_c)\right)\right)$$

$$N_3\left(z_a, N_1^*(z_{d1}), N_2^*\left(z_b, N_1^{**}(z_c)\right)\right) - N_3\left(z_a, N_1^*(z_{d0}), N_2^*\left(z_b, N_1^{**}(z_c)\right)\right)$$

$$\begin{tikzcd}
z_{d1} \arrow[r] \arrow[rr, bend left] \arrow[rrr, bend left] & N_1^*(z_{d1}) \arrow[r] \arrow[rr, bend right] & N_2^*\left(z_b, N_1^{**}(z_c)\right) \arrow[r, Rightarrow] & N_3\left(z_a, N_1^*(z_{d1}), N_2^*\left(z_b, N_1^{**}(z_c)\right)\right)
\end{tikzcd}$$

$$\begin{tikzcd}
z_{d0} \arrow[r] \arrow[rr, bend left] \arrow[rrr, bend left] & N_1^*(z_{d0}) \arrow[r] \arrow[rr, bend right] & N_2^*\left(z_b, N_1^{**}(z_c)\right) \arrow[r, Rightarrow] & N_3\left(z_a, N_1^*(z_{d0}), N_2^*\left(z_b, N_1^{**}(z_c)\right)\right)
\end{tikzcd}$$

$$N_3\left(z_a, N_1^*(z_d), N_2^*\left(z_b, N_1^{**}(z_{c1})\right)\right) - N_3\left(z_a, N_1^*(z_d), N_2^*\left(z_b, N_1^{**}(z_{c0})\right)\right)$$

$$z_{c1} \rightarrow N_1^{**}(z_{c1}) \rightarrow N_2^*\left(z_b, N_1^{**}(z_{c1})\right) \rightarrow N_3\left(z_a, N_1^*(z_d), N_2^*\left(z_b, N_1^{**}(z_{c1})\right)\right)$$

$$z_{c0} \rightarrow N_1^{**}(z_{c0}) \rightarrow N_2^*\left(z_b, N_1^{**}(z_{c0})\right) \rightarrow N_3\left(z_a, N_1^*(z_d), N_2^*\left(z_b, N_1^{**}(z_{c0})\right)\right)$$

$$N_3\left(z_{a1}, N_1^*(z_d), N_2^*\left(z_b, N_1^{**}(z_c)\right)\right) - N_3\left(z_{a0}, N_1^*(z_d), N_2^*\left(z_b, N_1^{**}(z_c)\right)\right)$$

$$z_{a1} \Rightarrow N_1^*(z_d) \Rightarrow N_2^*\left(z_b, N_1^{**}(z_c)\right) \Rightarrow N_3\left(z_{a1}, N_1^*(z_d), N_2^*\left(z_b, N_1^{**}(z_c)\right)\right)$$

$$z_{a0} \Rightarrow N_1^*(z_d) \Rightarrow N_2^*\left(z_b, N_1^{**}(z_c)\right) \Rightarrow N_3\left(z_{a0}, N_1^*(z_d), N_2^*\left(z_b, N_1^{**}(z_c)\right)\right)$$

Notations

- Random variables:
  - T_3: time to death
  - T_2: time to liver cancer
  - T_1: time to liver cirrhosis
  - Z: hepatitis status
  - C: censoring time

Notations: processes

- $\widetilde{N}_3(t) = I(T_3 \le t)$
- $\widetilde{N}_2(t) = I(T_2 \le t)$
- $\widetilde{N}_1(t) = I(T_1 \le t)$

- $N_3(t) = I(T_3 \le t, T_3 \le C)$
- $N_2(t) = I(T_2 \le t, T_2 \le \min(T_3, C))$
- $N_1(t) = I(T_1 \le t, T_1 \le \min(T_2, T_3, C))$

- $Y(t) = I(T_3 \ge t, C \ge t)$

Notations: counterfactual processes

- $\tilde{N}_3(t; z, n_1, n_2)$
  - Counterfactual process of death if the status of the trilogy [hepatitis, cirrhosis, cancer] at t^- had been set to (z, n_1, n_2)
- $\tilde{N}_2(t; z, n_1)$ and $\tilde{N}_2^*(t; z, n_1)$
  - Counterfactual process of liver cancer if the status of [hepatitis, cirrhosis] at t^- had been set to (z, n_1)
- $\tilde{N}_1(t; z)$ and $\tilde{N}_1^*(t; z)$
  - Counterfactual process of liver cirrhosis if the status of [hepatitis] at t^- had been set to z

Hazard
風險

- Definition:

$$d\Lambda(t) \coloneqq P\{\tilde{N}_3(t) = 1 \mid \tilde{N}_3(t^-) = 0\}$$

Counterfactual hazard
反事實風險

- Definition:

$$d\Lambda(t; z_a, z_b, z_c, z_d) \coloneqq$$
$$P\left\{\tilde{N}_3\left(t; z_a, \tilde{N}_1^*(t^-; z_c), \tilde{N}_2^*\left(t^-; z_b, \tilde{N}_1^{**}(t^-; z_d)\right)\right) = 1\right.$$
$$\left.\mid \tilde{N}_3\left(t^-; z_a, \tilde{N}_1^*(t^-; z_c), \tilde{N}_2^*\left(t^-; z_b, \tilde{N}_1^{**}(t^-; z_d)\right)\right) = 0\right\}$$

$$\tilde{\boldsymbol{N}}_{\boldsymbol{3}}\left(\boldsymbol{t}; \boldsymbol{z_a}, \tilde{\boldsymbol{N}}_{\boldsymbol{1}}^{*}(\boldsymbol{t}; \boldsymbol{z_c}), \tilde{\boldsymbol{N}}_{\boldsymbol{2}}^{*}\left(t; z_b, \tilde{N}_1^{**}(t; z_d)\right)\right) = \tilde{N}_3(t; z_a, n_1, n_2)$$

$$n_1 \leftarrow \tilde{N}_1^*(t; z_c) \qquad n_2 \leftarrow \tilde{N}_2^*(t; z_b, n_1)$$

$$n_1 \leftarrow \tilde{N}_1^{**}(t; z_d)$$

Counterfactual hazard
反事實風險

- By causal assumptions:

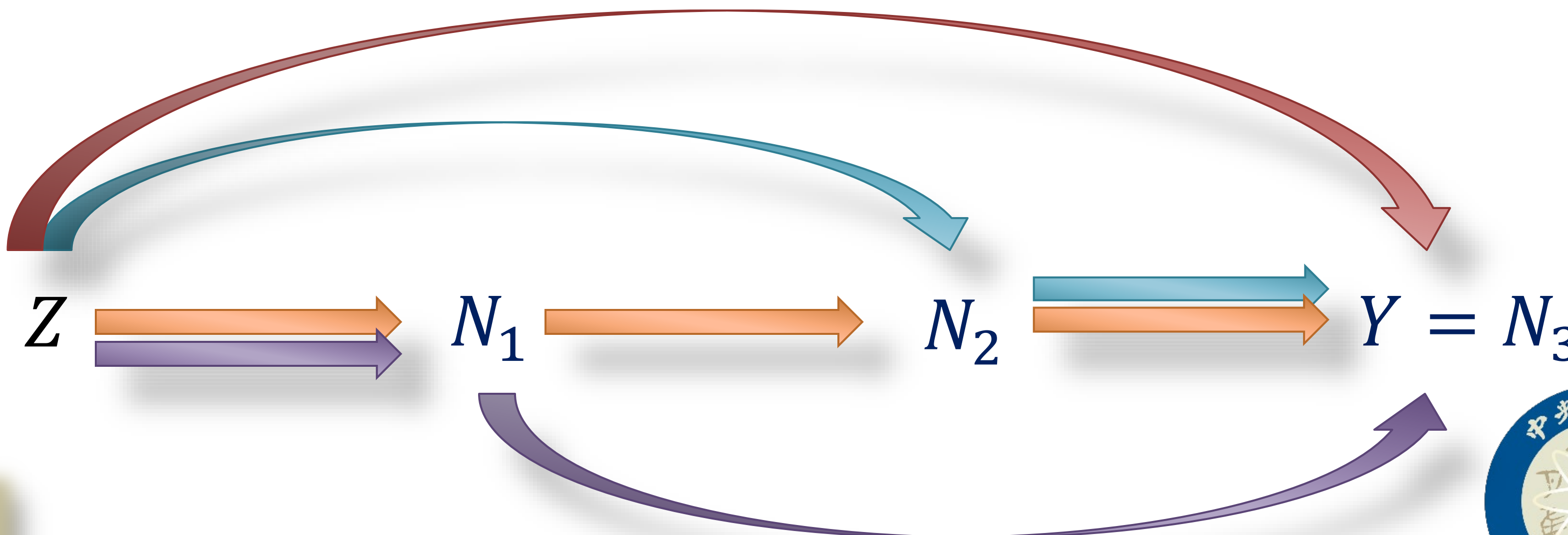
$$d\Lambda(t; z_a, z_b, z_c, z_d)$$

$$= \sum_{n_1}\sum_{n_2} \omega^a_{n_1 n_2}(t|z_a, z_b, z_c, z_d)\omega^b_{n_1 n_2}(t|z_b, z_c, z_d) d\Lambda_{n_1 n_2}(t|z_a)$$

  - $\omega^a_{n_1 n_2}(t|z_a, z_b, z_c, z_d) = \dfrac{\exp[-\Lambda_{n_1 n_2}(t^-|z_a)]}{\sum_{n_1'}\sum_{n_2'} \omega^b_{n_1' n_2'}(t|z_b, z_c, z_d) \exp\left[-\Lambda_{n_1' n_2'}(t^-|z_a)\right]}$
  - $\omega^b_{n_1 n_2}(t|z_b, z_c, z_d) = \left[\sum_{n_1^*} w_{n_2|n_1^*}(t|z_b) w_{n_1^*\cdot}(t|z_d)\right] w_{n_1\cdot}(t|z_c)$
  - $d\Lambda_{n_1 n_2}(t|z) = P\{d\tilde{N}_3(t) = 1|z, \tilde{N}_1(t^-) = n_1, \tilde{N}_2(t^-) = n_2, \tilde{N}_3(t^-) = 0\}$
  - $w_{n_2|n_1}(t|z) = P\{\tilde{N}_2(t^-) = n_2|z, \tilde{N}_1(t^-) = n_1, \tilde{N}_3(t^-) = 0\}$
  - $w_{n_1\cdot}(t|z) = P\{\tilde{N}_1(t^-) = n_1|z, \tilde{N}_3(t^-) = 0\}$

iPSE

- $\Delta_{Z\to Y}(t) = \Lambda(t;1,0,0,0) - \Lambda(t;0,0,0,0)$
- $\Delta_{Z\to N_2\to Y}(t) = \Lambda(t;1,1,0,0) - \Lambda(t;1,0,0,0)$
- $\Delta_{Z\to N_1\to N_2\to Y}(t) = \Lambda(t;1,1,1,0) - \Lambda(t;1,1,0,0)$
- $\Delta_{Z\to N_1\to Y}(t) = \Lambda(t;1,1,1,1) - \Lambda(t;1,1,1,0)$



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- Introduction
- Causal inference
- Statistical inference – a nonparametric approach
- Summary

Three functions to be estimated

- $d\Lambda_{n_1 n_2}(t|z)$
  $= P\{d\widetilde{N}_3(t) = 1|z, \widetilde{N}_1(t^-) = n_1, \widetilde{N}_2(t^-) = n_2, \widetilde{N}_3(t^-) = 0\}$

- $w_{n_2|n_1}(t|z)$
  $= P\{\widetilde{N}_2(t^-) = n_2|z, \widetilde{N}_1(t^-) = n_1, \widetilde{N}_3(t^-) = 0\}$

- $w_{n_1\cdot}(t|z)$
  $= P\{\widetilde{N}_1(t^-) = n_1|z, \widetilde{N}_3(t^-) = 0\}$

Three nonparametric estimators

- $d\widehat{\Lambda}_{n_1 n_2}(t|z)$
$$= \frac{d\bar{N}_{3n_1n_2}(t|z)}{\bar{Y}_{n_1n_2}(t|z)}$$
- $\widehat{w}$ $(t|z)$

$$N_{3n_1n_2}(t) = N_3(t) \times I\big(\tilde{N}_1(t^-) = n_1, \tilde{N}_2(t^-) = n_2\big)$$
$$Y_{n_1n_2}(t) = Y(t) \times I\big(\tilde{N}_1(t^-) = n_1, \tilde{N}_2(t^-) = n_2\big)$$

- $\widehat{w}_{n_1\cdot}(t|z)$
$$= \frac{\bar{Y}_{n_10}(t|z) + \bar{Y}_{n_11}(t|z)}{\bar{Y}(t|z)}$$

The estimator for the counterfactual hazard

- Estimator

$$\hat{\Lambda}(t; z_a, z_b, z_c, z_d) = \sum_{n_1}\sum_{n_2}\int_0^t \hat{W}(t|z_a, z_b, z_c, z_d)\, d\hat{\Lambda}_{n_1 n_2}(t|z_a)$$

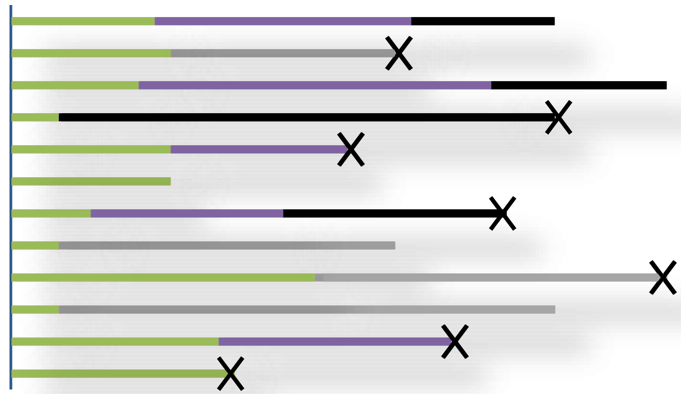
- where $\hat{W}(t|z_a, z_b, z_c, z_d) = \hat{\omega}^a_{n_1 n_2}(t|z_a, z_b, z_c, z_d)\hat{\omega}^b_{n_1 n_2}(t|z_b, z_c, z_d)$
  - $\hat{\omega}^a_{n_1 n_2}(s|z_a, z_b, z_c, z_d)$ is a functional of $d\hat{\Lambda}_{n_1 n_2}(t|z)$, $\hat{w}_{n_2|n_1}(t|z)$ and $\hat{w}_{n_1 \cdot}(t|z)$.
  - $\hat{\omega}^b_{n_1 n_2}(s|z_b, z_c, z_d)$ is a functional of $\hat{w}_{n_2|n_1}(t|z)$ and $\hat{w}_{n_1 \cdot}(t|z)$.

Illustration of the proposed estimator

$$d\hat{\Lambda}_{00}(t) = \frac{d\bar{N}_{300}(t)}{\bar{Y}_{00}(t)}$$

$$d\hat{\Lambda}_{01}(t) = \frac{d\bar{N}_{301}(t)}{\bar{Y}_{01}(t)}$$

$N_1(t)$	0	1	0	1
$N_2(t)$	0	0	1	1



$$d\hat{\Lambda}_{10}(t) = \frac{d\bar{N}_{310}(t)}{\bar{Y}_{10}(t)}$$

$$d\hat{\Lambda}_{11}(t) = \frac{d\bar{N}_{311}(t)}{\bar{Y}_{11}(t)}$$

$$d\hat{\Lambda}(t;\boldsymbol{z}) = \sum_{n_1}\sum_{n_2}\widehat{W}_{n_1n_2}(t|\boldsymbol{z})\,d\hat{\Lambda}_{n_1n_2}(t|z)$$

Proposed estimators for iPSE

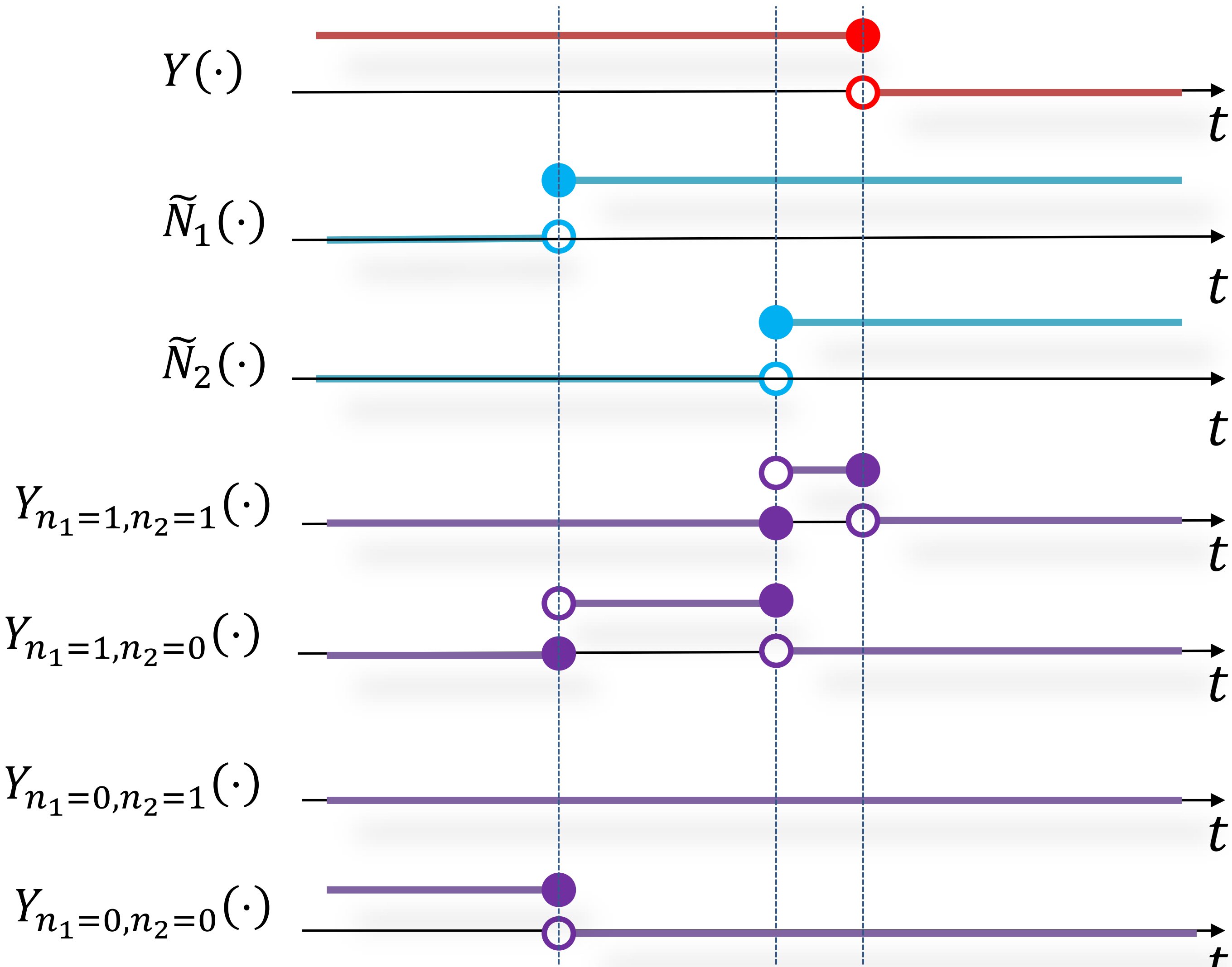
- $\widehat{\Delta}_{Z\to Y}(t)=\widehat{\Lambda}(t;1,0,0,0)-\widehat{\Lambda}(t;0,0,0,0)$
- $\widehat{\Delta}_{Z\to N_2\to Y}(t)=\widehat{\Lambda}(t;1,1,0,0)-\widehat{\Lambda}(t;1,0,0,0)$
- $\widehat{\Delta}_{Z\to N_1\to N_2\to Y}(t)=\widehat{\Lambda}(t;1,1,1,0)-\widehat{\Lambda}(t;1,1,0,0)$
- $\widehat{\Delta}_{Z\to N_1\to Y}(t)=\widehat{\Lambda}(t;1,1,1,1)-\widehat{\Lambda}(t;1,1,1,0)$

  - where

$$\widehat{\Lambda}(t;z_a,z_b,z_c,z_d)=\sum_{n_1}\sum_{n_2}\widehat{\Lambda}_{n_1n_2}(t;z_a,z_b,z_c,z_d)$$

$$=\sum_{n_1}\sum_{n_2}\int_0^t \widehat{W}_{n_1n_2}(s|\boldsymbol{z})\frac{I\left(\bar{Y}_{n_1n_2}(s|z_a)>0\right)}{\bar{Y}_{n_1n_2}(s|z_a)}d\bar{N}_{3n_1n_2}(s|z_a)$$

$Y_{n_1 n_2}(\cdot)$


$Y(\cdot)$
$\tilde{N}_1(\cdot)$
$\tilde{N}_2(\cdot)$
$Y_{n_1=1,n_2=1}(\cdot)$
$Y_{n_1=1,n_2=0}(\cdot)$
$Y_{n_1=0,n_2=1}(\cdot)$
$Y_{n_1=0,n_2=0}(\cdot)$
t
t
t
t
t
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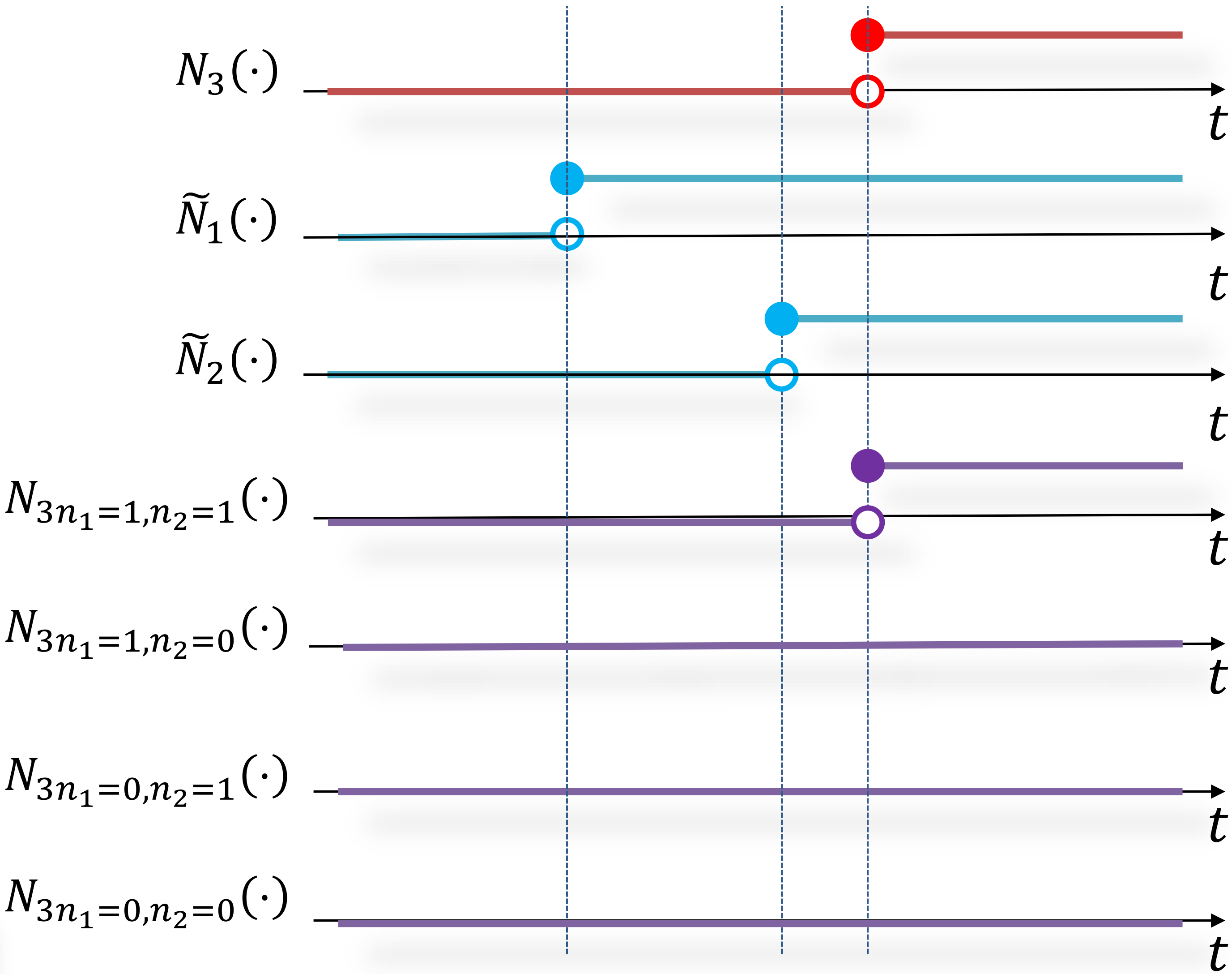
t

$N_{3n_1n_2}(\cdot)$


$N_3(\cdot)$
t
$\widetilde{N}_1(\cdot)$
t
$\widetilde{N}_2(\cdot)$
t
$N_{3n_1=1,n_2=1}(\cdot)$
t
$N_{3n_1=1,n_2=0}(\cdot)$
t
$N_{3n_1=0,n_2=1}(\cdot)$
t
$N_{3n_1=0,n_2=0}(\cdot)$
t

$N_{3n_1n_2}(t|Z) - A_{n_1n_2}(t|Z)$

- Filtration
  - $\mathcal{F}_t = \sigma\{N_{3n_1n_2i}(u), Y_{n_1n_2i}(u^+), \widetilde{N}_{1i}(u), \widetilde{N}_{2i}(u), Z_i;$
    $i = 1, \dots, m, n_1, n_2 \in \{0,1\}, 0 \le u \le t\}$
- Compensator
  - $A_{n_1n_2}(t|Z) = \int_0^t Y_{n_1n_2}(s|Z) d\Lambda_{n_1n_2}(s|Z)$

$M_{n_1n_2}(t|Z) \coloneqq N_{3n_1n_2}(t|Z) - A_{n_1n_2}(t|Z)$ is a zero mean martingale with respect to the filtration $\mathcal{F}_t$.

Asymptotic properties

Asymptotic unbiasedness: as $m \rightarrow \infty$,

$$\mathrm{E}\left[\widehat{\Lambda}(t; z_a, z_b, z_c, z_d) - \Lambda(t; z_a, z_b, z_c, z_d)\right] \rightarrow 0.$$

Uniform convergence

$$\sup_{0 \le t \le \tau} \left|\widehat{\Lambda}(t; z_a, z_b, z_c, z_d) - \Lambda(t; z_a, z_b, z_c, z_d)\right| \xrightarrow{p} 0$$

Uniform convergence in probability

$$\sup_{0\le t\le\tau}\left|\hat{\Delta}_{Z\to Y}(t)-\Delta_{Z\to Y}(t)\right|\xrightarrow{p}0$$

$$\sup_{0\le t\le\tau}\left|\hat{\Delta}_{Z\to N_1\to Y}(t)-\Delta_{Z\to N_1\to Y}(t)\right|\xrightarrow{p}0$$

$$\sup_{0\le t\le\tau}\left|\hat{\Delta}_{Z\to N_2\to Y}(t)-\Delta_{Z\to N_2\to Y}(t)\right|\xrightarrow{p}0$$

$$\sup_{0\le t\le\tau}\left|\hat{\Delta}_{Z\to N_1\to N_2\to Y}(t)-\Delta_{Z\to N_1\to N_2\to Y}(t)\right|\xrightarrow{p}0$$

Weak convergence

$$\sqrt{m}\left[\hat{\Delta}_{Z\to Y}(\cdot) - \Delta_{Z\to Y}(\cdot)\right] \xrightarrow{w} \mathcal{g}_{Z\to Y}(\cdot)$$

$\mathcal{g}_{Z\to Y}(\cdot)$: zero-mean Gaussian process

$$\sqrt{m}\left[\hat{\Delta}_{Z\to N_1\to Y}(\cdot) - \Delta_{Z\to N_1\to Y}(\cdot)\right] \xrightarrow{w} \mathcal{g}_{Z\to N_1\to Y}(\cdot)$$

$\mathcal{g}_{Z\to N_1\to Y}(\cdot)$: zero-mean Gaussian process

$$\sqrt{m}\left[\hat{\Delta}_{Z\to N_2\to Y}(\cdot) - \Delta_{Z\to N_2\to Y}(\cdot)\right] \xrightarrow{w} \mathcal{g}_{Z\to N_2\to Y}(\cdot)$$

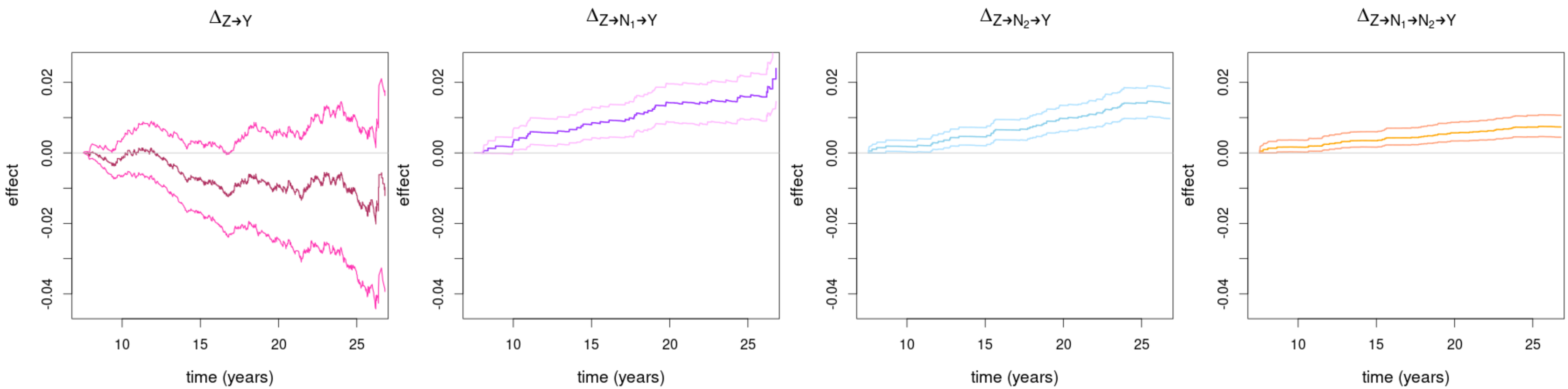
$\mathcal{g}_{Z\to N_2\to Y}(\cdot)$: zero-mean Gaussian process

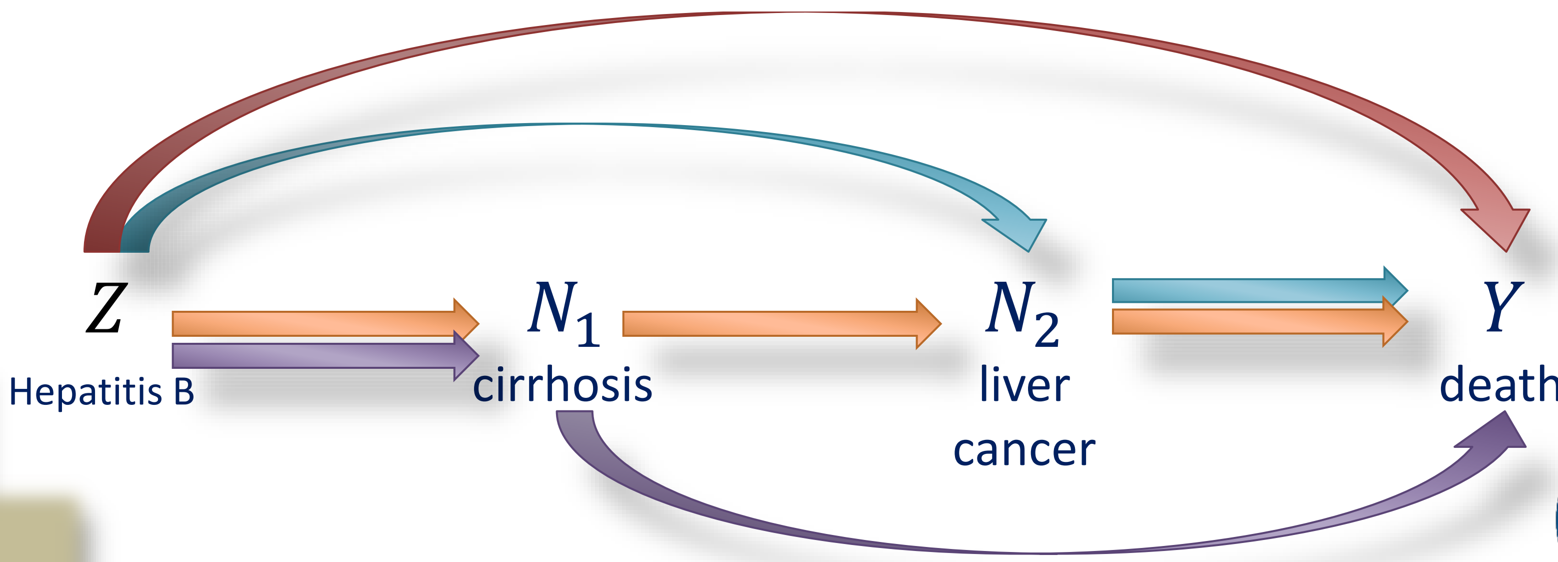
$$\sqrt{m}\left[\hat{\Delta}_{Z\to N_1\to N_2\to Y}(\cdot) - \Delta_{Z\to N_1\to N_2\to Y}(\cdot)\right] \xrightarrow{w} \mathcal{g}_{Z\to N_1\to N_2\to Y}(\cdot)$$

$\mathcal{g}_{Z\to N_1\to N_2\to Y}(\cdot)$: zero-mean Gaussian process

REVEAL-NHIRD Hepatitis B

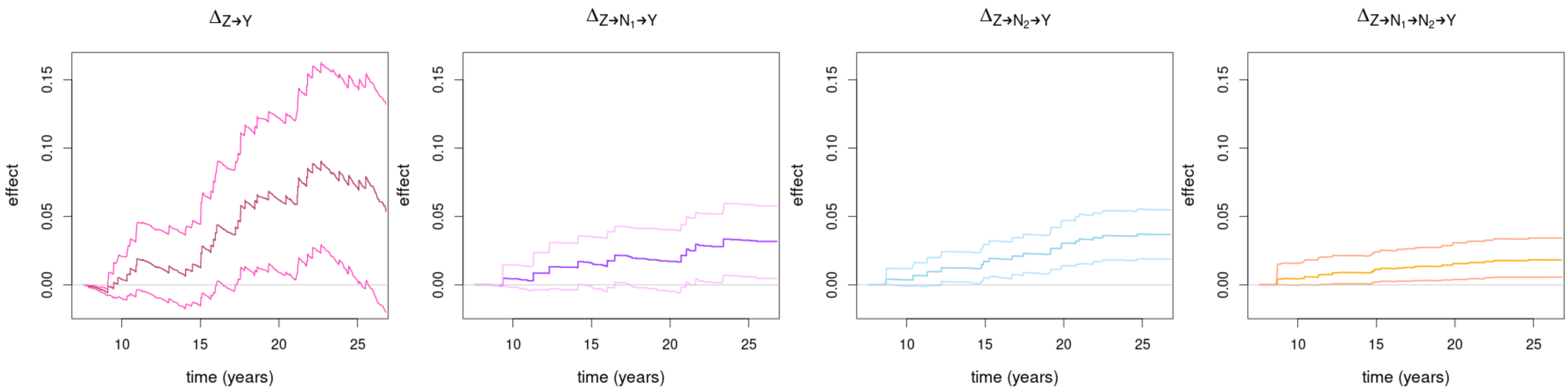
Men with age < 55 (n=7782)

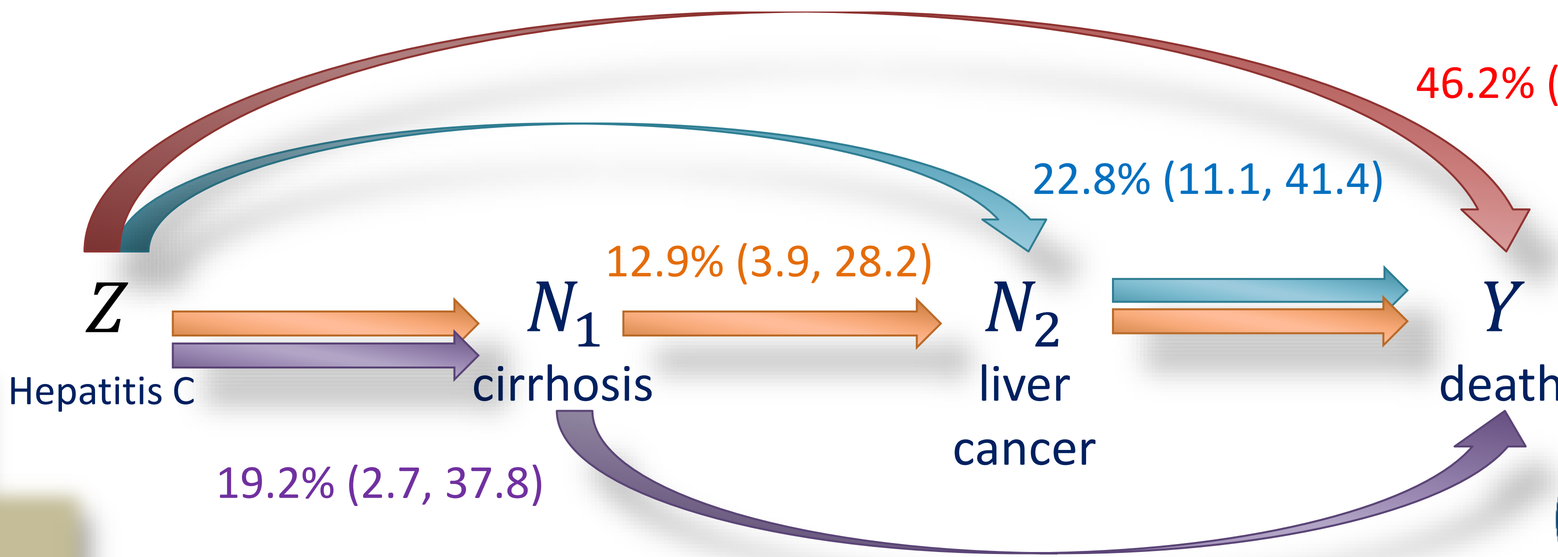




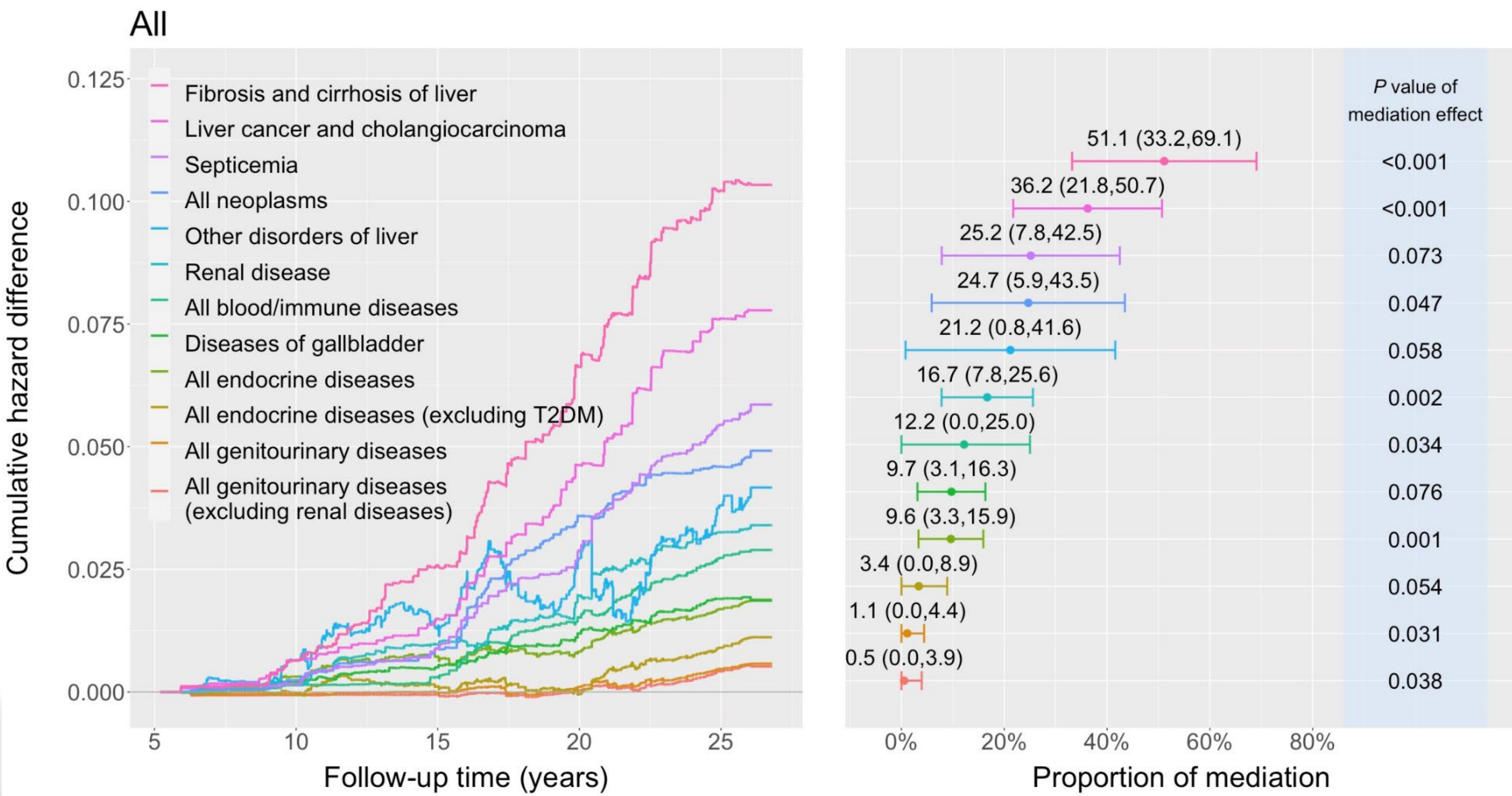
REVEAL-NHIRD Hepatitis C

Men with age < 55 (n=6305)





REVEAL-NHIRD Hepatitis C



Summary

- Disease natural history can be conceptualized as a causal mediation model.
- We propose nonparametric estimators for iPSEs and establish their asymptotics.
- Both liver cirrhosis and liver cancer mediate hepatitis B/C-related mortality.
- Extrahepatic diseases also mediated hepatitis C-related mortality.
- Time-varying post-treatment confounding: modeling rather than adjusting

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