Mediation Analysis for Censored Survival Data under an Accelerated Failure Time Model

Isabel Fulcher, Eric Tchetgen Tchetgen, and Paige Williams

Harvard University, Department of Biostatistics

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Mediation Analysis: An Overview

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$$\begin{tikzcd} A \arrow[r] \arrow[rr, bend left] & M \arrow[r] & Y \end{tikzcd}$$

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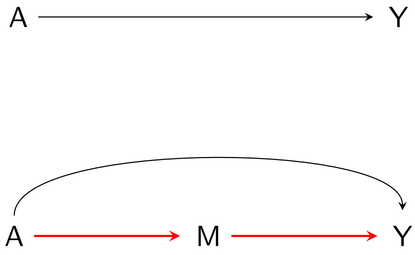

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Mediation Analysis: Linear Regression Setup

$$A \xrightarrow{\beta_1} Y$$

$$\begin{tikzcd}
A \arrow[r, "\alpha_1"'] \arrow[rr, bend left, "\theta_1"] & M \arrow[r, "\theta_2"'] & Y
\end{tikzcd}$$

$$Y = \theta_0 + \theta_1 A + \theta_2 M + \epsilon \tag{1}$$

$$Y = \beta_0 + \beta_1 A + \xi \tag{2}$$

$$M = \alpha_0 + \alpha_1 A + \zeta \tag{3}$$

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<u>Natural Direct Effect</u> $= \theta_1$

<u>Natural Indirect Effect</u> $= \theta_2\alpha_1 = \beta_1 - \theta_1$

The Breakdown of the Product-Difference Method Equality

$$\underbrace{\theta_2\alpha_1}_{\text{Product Method}} \neq \underbrace{\beta_1 - \theta_1}_{\text{Difference Method}}$$

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- Mediator is binary (logistic model is used)
- Difference in sample sizes across models (i.e. missing values for the Mediator)
- Survival outcomes fit using the Cox model

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- **Survival outcomes with censoring fit using an accelerated failure time model**

Motivating Example: HIV Infection and Sexual Maturity

- A dataset combining two long-term cohort studies (PHACS and PACTG 219C) was used
- HIV-exposed males and females were followed upon entry into study until they reached sexual maturity
- The outcome is age at sexual maturity for males
  - Normally distributed outcome
  - Outcome is right and interval censored

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$$\begin{tikzcd} \text{Perinatal HIV Infection} \arrow[r] \arrow[rr, bend left] & \text{Height} \arrow[r] & \text{Age at sexual maturity} \end{tikzcd}$$

Motivating Example: HIV Infection and Sexual Maturity

Table: Normal AFT mediation model effect estimates for age at sexual maturity by perinatal HIV status ($n = 1380$)

	Estimate	Standard Error	95% CI
Direct	4.14	3.55	(-2.82, 11.10)
Indirect (difference)	2.90	0.97	(1.00, 4.80)
Indirect (product)	2.99	0.65	(1.73, 4.26)
Total (difference)	7.04	3.63	(-0.07, 14.16)
Total (product)	7.13	3.28	(0.70, 13.56)

HIV-infected youth had a 7.1 month delay in age at sexual maturity compared to uninfected youth; height Z-score accounting for approximately 40% of the effect.

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Why is there is a 3% difference in the indirect effect estimates?

Measuring Indirect Effects in Accelerated Failure Time Models (no censoring)

$$
\begin{aligned}
A &: \text{binary exposure taking values } a{=}1 \text{ and } a{=}0\\
M &: \text{normally distributed mediator}\\
T &: \text{time to event outcome}\\
M(a) &: \text{counterfactual mediator and outcome had exposure}\\
&\quad\ \text{taken value } a\\
T(a, M(a)) &: \text{counterfactual outcome had exposure taken value } a\\
T(a, M(a^*)) &: \text{counterfactual outcome had exposure taken value } a\\
&\quad\ \text{and the mediator taken the value it would have under } a^*
\end{aligned}
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M : normally distributed mediator

T : time to event outcome

$M(a)$: counterfactual mediator and outcome had exposure taken value a

$T(a, M(a))$: counterfactual outcome had exposure taken value a

$T(a, M(a^*))$: counterfactual outcome had exposure taken value a and the mediator taken the value it would have under a^*

$$NDE\,(a, a^*) = \log E\,\{T(a, M(a^*))\} - \log E\,\{T(a^*, M(a^*))\}$$

$$NIE\,(a, a^*) = \log E\,\{T(a, M(a))\} - \log E\,\{T(a, M(a^*))\}$$

Derivation of Indirect Effect under AFT model

$$\log T = \beta_0 + \beta_a A + \beta_m M + \sigma\varepsilon \tag{4}$$

$$M = \alpha_0 + \alpha_a A + \xi \tag{5}$$

- ε is an independent residual not necessarily mean zero but of arbitrary distribution
- ξ is a normal random variable

Derivation of Indirect Effect under AFT model

Under binary exposure and the assumptions outlined above, it can be shown that the natural indirect effect is identified by:

$$\begin{aligned} NIE\left(a, a^*\right) &= \log E\left\{T(a, M(a))\right\} - \log E\left\{T(a, M(a^*))\right\} \\ &= \beta_m \alpha_a \left(a - a^*\right) \\ &= \beta_m \alpha_a \end{aligned}$$

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Is the product method, $\beta_m \alpha_a$, equivalent to the difference method?

AFT Model with a Normal Outcome
No censoring

Consider the full AFT model and mediator model where ε and ξ are normally distributed.

$$\begin{aligned}\log T &= \beta_0 + \beta_a A + \beta_m M + \sigma\varepsilon \\ &= \beta_0 + \beta_a A + \beta_m(\alpha_0 + \alpha_a A + \xi) + \sigma\varepsilon \\ &= \beta_0 + \beta_m\alpha_0 + (\beta_a + \beta_m\alpha_a)A + (\sigma\varepsilon + \beta_m\xi) \\ &= \beta_0^* + \tau_a A + \quad \widetilde{\sigma}\widetilde{\varepsilon}\end{aligned}$$

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$$\tau_a = \alpha_a\beta_m + \beta_a \implies \alpha_a\beta_m = \tau_a - \beta_a \implies \text{product} = \text{difference}$$

AFT Model with a Weibull Outcome
No censoring

Similarly as above, except ε follows an extreme value density

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- The $\widetilde{\sigma}\widetilde{\varepsilon}$ will NOT follow an extreme value density
- The reduced-form density of $\log T$ given A is NOT of correct form
- We cannot simply fit the model without the mediator and equate product and difference methods

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product $\neq$ difference

Consistency of maximum likelihood estimator for τ_a under model misspecification

What happens if we naively move forward?

If one incorrectly assumes that the reduced form density of T given A is Weibull distributed...

- The product and difference method will not produce mathematically equivalent estimates
- Fortunately, it can be shown that in the absence of censoring, the difference method estimate is consistent for the indirect effect

Recap: Indirect Effect estimation in AFT Models

We have shown the following:

- Under a Normal AFT model with no censoring, the difference method is a valid estimate of the indirect effect (i.e. equivalence of product and difference method)
- Under a Weibull AFT model with no censoring, the difference method is not mathematically equivalent to the product method (indirect effect estimate), but it is a consistent estimator

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What happens in the presence of censoring?

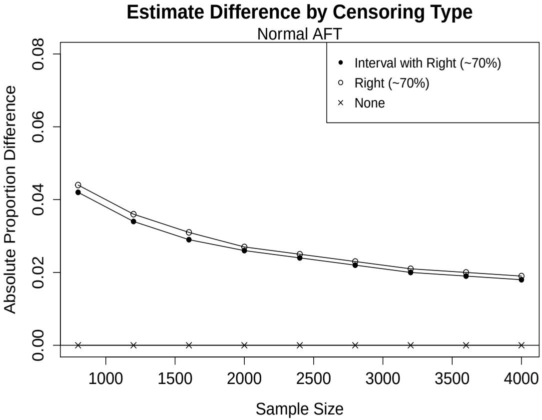
Simulations for Normal and Weibull AFT Models

Key question: In the presence of censoring, what is the behavior of the indirect effect estimates under the difference method?

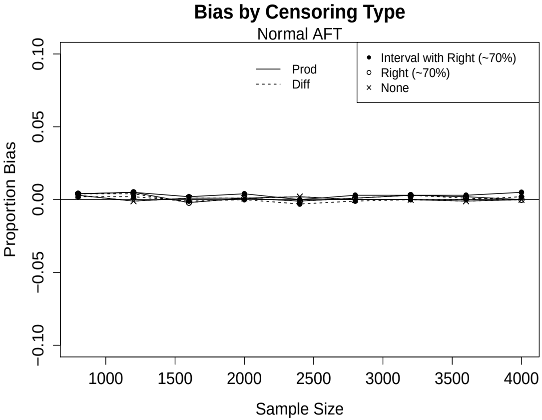
- AFT Outcomes:
  1. Normal
  2. Weibull
- Censoring Types:
  1. None
  2. Right
  3. Interval
- Reported Characteristics (by sample size)
  1. Absolute Proportion Difference* between the estimators
  2. Proportion Bias** of the estimator

* Absolute difference in product and difference estimate divided by the product estimate
** Difference between truth and estimate divided by the truth

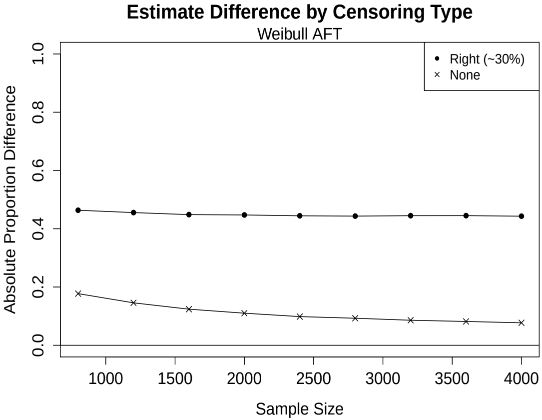
Simulation, Normal AFT Model, Absolute Proportion Difference



Simulation, Normal AFT Model, Bias



Simulation, Weibull AFT Model, Absolute Proportion Difference



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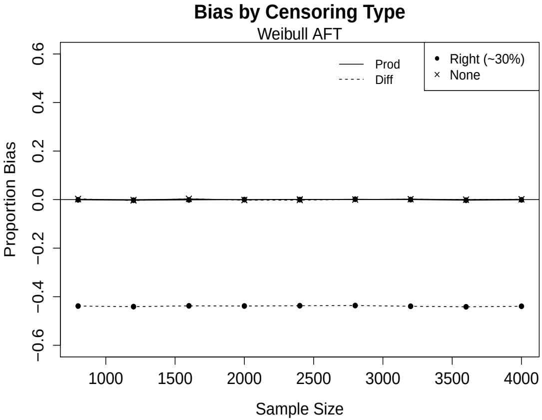

Conclusions

- In the presence of censoring, this misspecification can cause bias of the difference estimator of indirect effect
- In the absence of censoring, the difference method yields a consistent estimator of the indirect effect
- The normal mediator-normal outcome model is an exception to the above phenomenon because the reduced form accelerated failure time model is correctly specified
- Consistency relies on both the mediator and the outcome following a normal distribution
- Use the product method!

Selected References

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Questions?