Performance of Variance Estimators of The Cumulative Incidence Function for Left-Truncated Competing Risks Data

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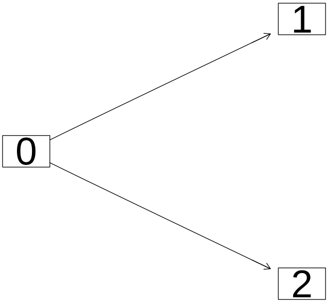
Competing Risks Multistate Model



- Competing risks process: $X_{t \geq 0} \in \{0, 1, 2\}$
- Failure time: $T = \inf(t \in [0, \infty\} \,|\, X_t \neq 0)$
- Time until the first event T, and type of this first event X_T

Competing Risks Multistate Model

- Cause-specific hazard (CSH)

$$\alpha_{0j}(t)dt = \mathrm{P}(T \in dt, X_T = j | T \geq t), \, j = 1, 2$$

- Cumulative incidence function (CIF)

$$\mathrm{P}(T \leq t, X_T = j) = \int_0^t \mathrm{P}(T \geq u-)\alpha_{0j}(u)du, \, j = 1, 2,$$

which is estimated by the Aalen-Johansen estimator in the presence of right-censoring and left-truncation

Variance Estimation

- Two major variance estimators
  - Greenwood
  - Aalen
- Derived using Martingale and counting processes techniques for the general Aalen-Johansen estimator of transition probabilities in time-inhomogeneous Markov multistate models (Andersen et al., 1993)

Previous Findings

- Klein (1991) compared the analogues of the Greenwood and Aalen variance estimators for the variance of the Kaplan-Meier estimator
  - Both estimators were found to be negatively biased
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  - Some estimators performed poorly

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- The preferred estimator in these simulation studies is in fact equal to the Greenwood variance estimator (Allignol et al., 2009b)
- Objectives:
  Extend these simulation studies to the left-truncated competing risks data situation
  - With left-truncation, risk sets are extremely small at the beginning of the time interval

Data Example (Meister and Schaefer, 2008)

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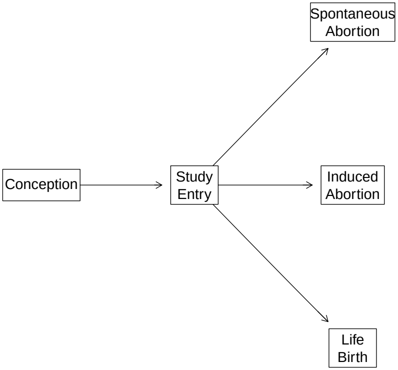

- Spontaneous abortion is the event of interest
- 2 competing events:
  - Induced Abortion
  - Life Birth
- Data subject to left-truncation as women usually enter the study several weeks after conception

Data Example

- Informations on 1186 pregnant women
  - 173 exposed to coumarin derivatives
  - 1013 controls

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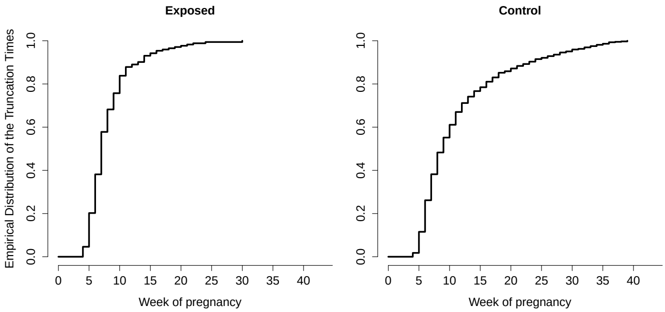

- Independence of left-truncation has been investigated (Allignol et al., 2009b)

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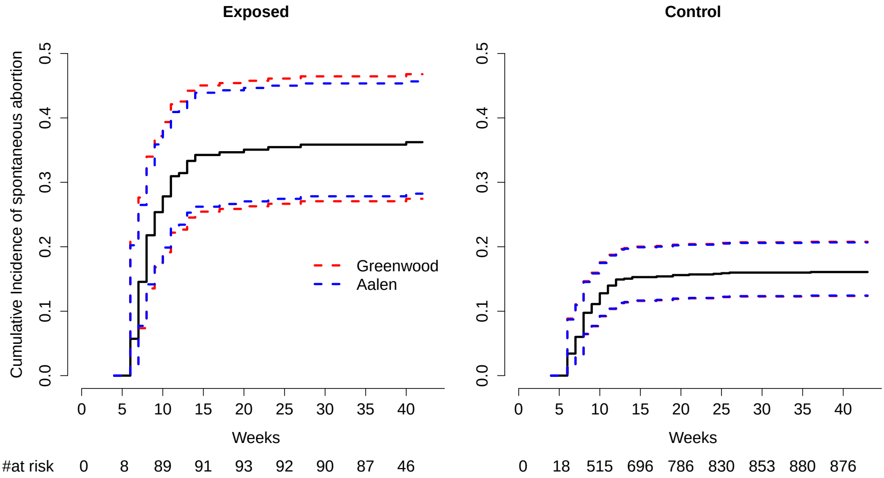

Simulation Study

- Simulation of competing risks data with 2 risks, event of type 1 being the one of interest
- Specification of the cause-specific hazards motivated by the data example
  - Constant hazard $\alpha_{01}(t) = 0.015$
  - Weibull-type hazard $\alpha_{02}(t) = 10.5/39.5 \cdot (t/39.5)^{9.5}$
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- Gamma distributed truncation times L independent of (T, X_T) with parameters chosen to give light, medium and heavy truncation
- We simulated $N \in \{100, 200, 300\}$ individuals. Only those with $L < T$ entered the sample
  - Light left-truncation: $0.85 \cdot N$ on average
  - Medium left-truncation $0.80 \cdot N$ on average
  - Heavy left-truncation $0.45 \cdot N$ on average
- 10 000 simulation studies for each scenario

Simulation Study

- Results are presented in terms of:
  - Relative bias
$$((\bar{\hat{V}} - V)/V)$$
  - Root mean squared error
$$\sqrt{(\bar{\hat{V}} - V)^2 + \mathrm{SE}(\hat{V})^2}$$

V is the empirical variance
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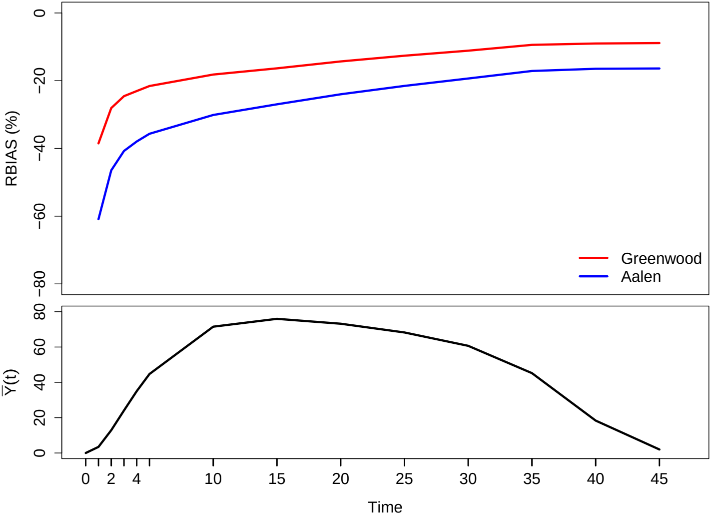
- Empty inner risk sets might occur with left-truncated data
  - Risk set $Y(t) = 0$ for some t after the first study entry time and before the last event time
  - Estimators rendered useless as they remain constant thereafter
  - Removed of the study, in line with Keiding and Gill (1990)

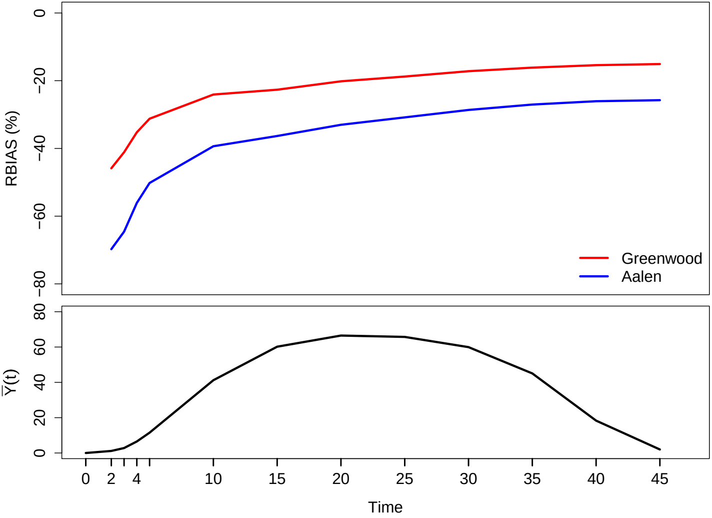
Light Left-Truncation

100 Individuals



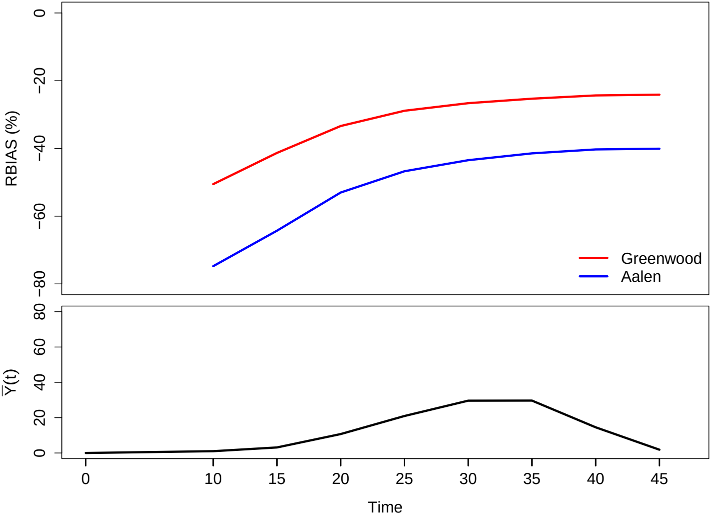
Medium Left-Truncation

100 Individuals



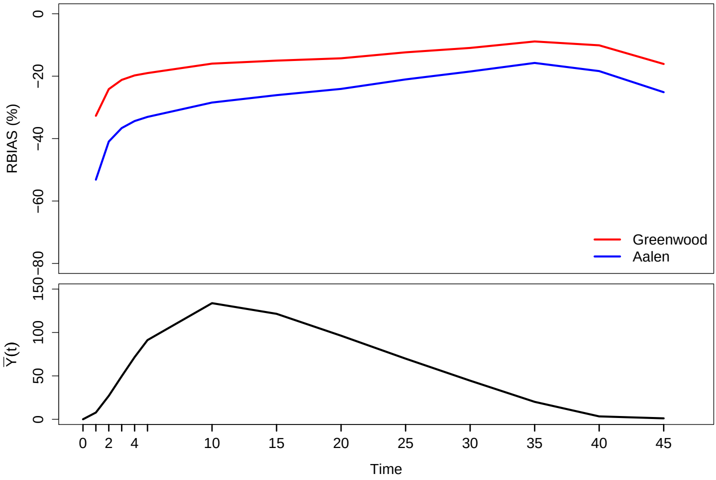
Heavy Left-Truncation

100 Individuals



Light Left-Truncation, Heavy Right-Censoring

200 Individuals



Summary

- The Greenwood estimator was found to perform well with left-truncated data
- It is algebraically identical to the one that performed the best in right-censored competing risks data
- The Greenwood estimator also available for more complex multistate models
- Implemented in the R-package **etm** (Allignol et al., 2009a)

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  - Potential ways to repair the small sample bias
  - Contribution of truncation and censoring in the 'overall' bias

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$\Rightarrow$ We recommend the use of the Greenwood estimator both for right-censored and left-truncated competing risks data

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