An Investigation of the Choice of Time Scale for Studies with Time-to-Dementia-related Outcomes

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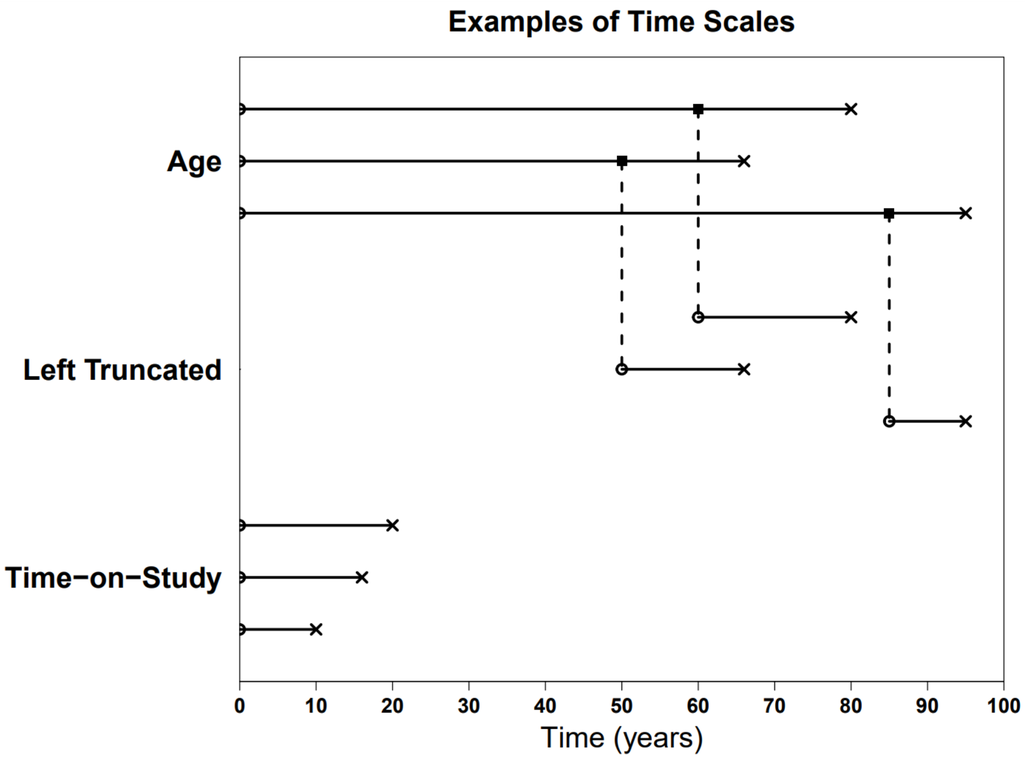
Background

- Time scales define how time is measured in time-to-event models.
- Common time scales are: 1) Age, 2) Left-truncated (LT) age, and 3) time-on-study (TOS).
  - Age measures time since birth.
  - LT-age, measures time from the age of first observation.
  - TOS measures time from the date of first observation.
- Experiments are generally consistent with TOS.
- Epidemiological studies, are less clear:
  - For some conditions, measuring time since birth makes sense.
  - For some conditions, time should be measured starting from some exposure date.
  - For some conditions, neither setting is quite natural.
- **<u>Which time scale is best for research questions with dementia-related outcomes?</u>**
  - TOS is unnatural.
  - Risk of dementia is effectively 0 until some age 40+.



- Time scale selection determines 1) the order of the events in the model, 2) whether risk sets are open or closed, and 3) if baseline age should be an adjustment covariate.

- Korn et al (1997) considered when the age and TOS time scales would result in equivalent results.
  - Argued for age time scale with stratification on birth cohort (largely based on heuristic arguments).
- Thiebaut and Benichou (2004) 1) assessed Korn's conditions and 2) considered the performance of the age and TOS time scales when age is the correct time scale.
  - Recommend using the age time scale for epidemiological studies with time-to-event outcomes.
- Chalise et al. (2009, 2012, 2013, 2016) considered 1) Korn's conditions mathematically and empirically, and 2) the bias and predictive ability of all three time scales when correctly and incorrectly specified.
  - They argue that the TOS time scale is more robust to time scale misspecification.
  - They also note better predictive ability of the TOS model.

Methodology

Let $\lambda(\cdot)$ represent the hazard function where $\lambda_0(\cdot)$ is the baseline hazard function, A represent age model where a is an age and a_0 is the baseline age. Similarly, let T be the time-on-study model where t is a time. Suppose z is a covariate value, and β and γ are unknown parameters.

M1) $\lambda_A(a \mid z) = \lambda_{0A}(a)e^{\beta z}$

M2) $\lambda_A(a \mid z, a_0) = \lambda_{0A}(a \mid a_0)e^{\beta z}$

M3) $\lambda_T(t \mid z, a_0) = \lambda_{0T}(t)e^{\beta z + \gamma a_0}$

The partial likelihood for M1 can be derived to be:

$$PL_A(\beta) = \prod_{j=1}^{n} \left(\frac{e^{\beta_A z_j}}{\sum_{i \in R_{jA}} e^{\beta_A z_i}} \right)^{\delta_j}$$

The partial likelihood for M3 can be derived to be:

$$PL_T(\beta) = \prod_{j=1}^{n} \left(\frac{e^{\beta_T z_j + \gamma a_{0j}}}{\sum_{i \in R_{jT}} e^{\beta_T z_i + \gamma a_{0i}}} \right)^{\delta_j}$$

- Mathematically, these two quantities will be maximized for the same value of β when the γa_{0k} term cancels out of the partial likelihood for M3.
  - This will occur when the baseline is the same for all participants in the study.
- These are different than the conditions that Korn et al (1997) argued would result in equivalent estimates between the two models.

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Simulation Results

Correlation a_0 and Z	Correct TS	
	Age	TOS
	$\rho(a_0, Z) \neq 0$	$\rho(a_0, Z) \neq 0$
	Age	TOS
	$\rho(a_0, Z) = 0$	$\rho(a_0, Z) = 0$

Table 1: We considered 4 simulation settings.

- Table 1 depicts the 4 settings we simulated to assess the robustness of M1, M2, and M3 under misspecification of the time scale.
- We set $T_0 = 50$ to be the age at which dementia risk begins.
  - In age time scale, the risk of dementia was very small prior to age 50.
  - In the TOS time scale, the risk of dementia was 0 until age 50.
- Dementia time was simulated from a Weibull distribution to allow risk to grow with age.
- We used a binary covariate of interest, Z, which was consider in settings where it was either correlated or uncorrelated with age-at-entry to study, a_0.

Table 2: Results for uncorrelated simulations. Z uncorrelated with a_0

	Truth	M1 Est (% Bias)	M2 Est (%)	M3 Est (%)
Age	0.406	0.405 (0.1%)	0.405 (0.2%)	0.405 (0.1%)*
TOS	0.406	0.383 (5.4%)	0.383 (5.4%)	0.413 (1.9%)

Table 3: Results for correlated simulations. Z correlated with a_0

	Truth	M1 Est (% Bias)	M2 Est (%)	M3 Est (%)
Age	0.406	0.389 (4.1%)	0.405 (0.2%)	0.405 (0.02%)*
TOS	0.406	0.476 (17.3%)	0.476 (17.3%)	0.413 (1.7%)

- Table 2 shows the results for the simulations where baseline age and the covariate of interest are uncorrelated. Note that all three models perform well, regardless of which time scale is more correct.
  - Top row shows unbiased estimates for all 3 models when age is the closer time scale.
  - M1 and M2 show a little bias when TOS is the more correct time scale.
  - M3 shows negligible bias when time-on-study is the more correct time scale.
- Table 3 shows the results when baseline age and the covariate of interest are correlated. These depend on model choice and the more correct time scale.
  - M1 shows bias for both time scales.
  - M2 shows no bias when age is the correct time scale.
  - M2 shows bias when TOS is the correct time scale.
  - M3 shows no little-to-no bias in both settings.

Conclusions

- Our simulations suggest that the TOS model (with covariate adjustment for baseline age) is more robust to misspecification of the true time scale.
  - These results hold regardless of the correlation between the covariate of interest of interest and the age-at-entry to the study.
- These results are consistent with the work of Chalise et al (2009, 2012, 2013, 2016).
- Between our work and the work discussed in the background, we recommend using the TOS model in any setting where the true time scale may not necessarily be age.

Future Work

- Consider the performance with a time-varying covariate of interest.
- Quantify how these results may impact conclusions in subpopulations with effect modification.

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