Competing risks analysis of the Finnish diabetes prevention study

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Survival analysis

- Clinical studies usually consider one primary event of interest (disease-related) in the presence of other non-disease related events.
  - When one event prevents another event from happening or being observed => ‘Competing risks’
    e.g. if a subject drops out (DO), later events are unobservable
  - If competing events are independent of each other, they are treated as independent censoring
Survival analysis

\[ X = \min(T, U) \]

\( T = \text{Time to event of interest} \)

\( U = \text{Censoring time} \)

\[ \lambda(t_i) = \frac{d_i \text{ (number of disease-related events at time } t_i)}{n_i \text{ (risk set: number of subjects known to survive just prior time } t_i)} \]

\[ S(t) = \prod_{i: t_i \leq t} \left(1 - \frac{d_i}{n_i}\right) \]

\[ S(t) = e^{-\int_0^t \lambda(x) \, dx} \]
Survival analysis (Key assumptions)

1) \( n_i \) is a random sample of the population at risk at time \( t_i \) for all \( t \), i.e. censoring is independent.

2) Outcome data \([X = \min(T, U)]\) is exact.

<table>
<thead>
<tr>
<th>( t_i )</th>
<th>( n_i )</th>
<th>( d_i )</th>
<th>( nd_i )</th>
<th>( \lambda(t_i) )</th>
<th>( S(t_i) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>50</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>1</td>
<td>0</td>
<td>1/50</td>
<td>([1-(1/50)] \times 1 = 0.98)</td>
</tr>
<tr>
<td>5</td>
<td>49</td>
<td>0</td>
<td>1</td>
<td>0/49</td>
<td>([1-(0/49)] \times 0.98 = 0.98)</td>
</tr>
<tr>
<td>6</td>
<td>48</td>
<td>1</td>
<td>0</td>
<td>1/48</td>
<td>([1-(1/48)] \times 0.98 = 0.96)</td>
</tr>
</tbody>
</table>

This implies that the risk of subjects with censored time do not differ from that of subjects still in \( n_i \).
Dependence between censoring and event of interest

if the risk of disease and drop-out are correlated

- Time of disease manifestation is unobservable in DO subjects
- $S()$ is inestimable from the data\textsuperscript{1}
- Biased estimates of the cumulative probabilities\textsuperscript{2}

\textsuperscript{1}Tsiatis A, Proc Natl Acad Sci. 1975; 72: 20-22; \textsuperscript{2}Verduijn M et al., Nephrol Dial Transplant. 2010; 26: 56-61
Clinical status is only observed at finite time points e.g. at medical visits

Multiple events are possible within this interval

Biased estimates of the disease incidence\(^1,2\)

Event-free visit

Event-free visit

Diseased?

DO visit

Competing risks with interval-censored data

• Multi-state model\textsuperscript{1,2}
  – Hypothesis testing
  – Account for competing risks
  – Account for interval-censoring, i.e. the probability of developing non-terminal events in the interval between the medical visits
  – Allow simultaneous estimation of covariate effects on the different competing risks

Finnish Diabetes Prevention Study (FDPS)

- Randomized controlled multicenter study carried out in Finland for 6 years with a follow-up of 10 years\(^1\)

Overweight, middle-aged subjects with impaired glucose tolerance

- Investigate the effects of lifestyle intervention

\(^1\)Tuomilehto J et al., N Engl J Med 2001; 344:1343–50
Finnish Diabetes Prevention Study (FDPS)

- Clinical status assessed at yearly medical visits using OGTT*
  - Subjects who developed diabetes mellitus (DM) were excluded from the study at the visit of diagnosis
  - Yearly OGTT => Insulin sensitivity ($S_I$) by 9 surrogate methods$^1$
    - QUICKI, HOMA, Avignon, Matsuda, etc

$^1$Patarrão RS et al., Rev Port Endocrinol Diabetes Metab 2014; 9(1): 65–73; *OGTT – Oral Glucose Tolerance Test
Finnish Diabetes Prevention Study (FDPS)
Finnish Diabetes Prevention Study (FDPS)

- Previously analyzed by Kaplan-Meier estimator to obtain the survival curve\(^1\)
  - Did not take interval-censoring into account
  - Regarded drop out as a non-informative (independent censoring)
  - Did not have access to follow-up data

\(^1\)Tuomilehto J et al., N Engl J Med 2001; 344:1343–50
Aims

- Develop a multi-state model for competing risks analysis of data from FDPS and its follow-up
- Use the model to investigate
  - covariate effects on the different competing risks
  - predictiveness of methods of $S_i$ assessment for the onset of diabetes
Model building & assumptions

- Multi-state model
  - Hypothesis testing:
    - $\lambda_{H-D} = \lambda_{DO(H)-D}$
      ($\lambda_{15} = \lambda_{35}$)
    - $\lambda_{DM-D} = \lambda_{DO(DM)-D}$
    - $\lambda_{H-DM} = \lambda_{DO(H)-DO(DM)}$
  - $\lambda = $ Constant, Weibull, etc
Model building & assumptions

- Multi-state model
  - Covariates testing:
    - Base line covariates: No risk of selection/immortal bias.
    - Not the case for time-varying covariates
• Multi-state model

\[
\frac{dP_1}{dt} = -P_1 \cdot (\lambda_{12} + \lambda_{13} + \lambda_{15}) \\
\frac{dP_2}{dt} = -P_2 \cdot \lambda_{25} + P_1 \cdot \lambda_{12} \\
\frac{dP_3}{dt} = -P_3 \cdot \lambda_{34} - P_3 \cdot \lambda_{35} + P_1 \cdot \lambda_{13} \\
\frac{dP_4}{dt} = -P_4 \cdot \lambda_{45} + P_3 \cdot \lambda_{34} \\
\frac{dP_5}{dt} = P_1 \cdot \lambda_{15} + P_2 \cdot \lambda_{25} + P_3 \cdot \lambda_{35} + P_4 \cdot \lambda_{45}
\]
• Multi-state model
  – Stationary
    • $\lambda_{H-DO(H)}$ & $\lambda_{DO(H)-DO(DM)}$
    • $\text{COV}_{H-DO(H)} = f(\text{Intervention}, \text{BMI})$
  – Non-stationary
    • $\lambda_{H-DM}$ & $\lambda_{i-D}$
    • $\text{COV}_{H-DM} = f(\text{Intervention}, \text{BMI}, \text{HbA1C}, S_1)$
    • $\lambda_{i-D}$ followed Gompertz-Makeham formula
Multi-state model

- Hypothesis testing:
  - $\lambda_{i-D}$ were indeed independent of DO
  - No significant difference between
    - $\lambda_{H-D}$ & $\lambda_{DO(H)-D}$
    - $\lambda_{DM-D}$ & $\lambda_{DO(DM)-D}$
• Multi-state model
  – Hypothesis testing:
    • DO was an informative process
      – $\lambda_{H-DM} \neq \lambda_{DO(H)-DO(DM)}$
    • After DO, subjects were at $\sim 3.5$ times lower risk of developing DM
    • Subjects in the intervention group
      – 2 times higher risk of DO
      – 1.5 times lower risk of DM
• Multi-state model
  - Hazard of dying 20% higher among patients
    • $\lambda_{H-D} = \alpha + \beta \cdot e^{k \cdot (\theta_{15, \text{scale}} \cdot \text{age})}$
    • $\lambda_{DM-D} = \alpha + \beta \cdot e^{k \cdot (\theta_{25, \text{scale}} \cdot \text{age})}$
    • $\lambda_{H-D} = \lambda_{DO(H)-D}$
    • $\lambda_{DM-D} = \lambda_{DO(DM)-D}$
• Multi-state model
  – Measurements of $S_i$
    • QUICKI, HOMA, Avignon
  – Effects of significant covariates at different combinations can be assessed
    • HbA$_{1c}$=7% $\sim$ 2.5 times higher risk of DM than HbA$_{1c}$=6%
Results

<table>
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<tr>
<th>Control</th>
<th>Proportion of total subjects</th>
<th>Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy</td>
<td>Diabetes Mellitus</td>
<td>Drop out (Healthy)</td>
</tr>
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<td>0.8</td>
<td>0.6</td>
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• Thanks to follow up data, we knew that all DO subjects were healthy first:
  - allow DM manifestation in the interval between last healthy visit and the DO visit
• $\lambda_{14} = \lambda_{13} \cdot \lambda_{12}$
Conclusions

• Competing risks violates the standard survival analysis assumptions
• Interval censoring further complicates competing risks analysis
• Multi-state models:
  – Hypothesis testing & identifying influential assumptions
  – Describe the dependence of mechanisms leading to incomplete observations
  – Account for the occurrence probability of the non-terminal processes in the interval between visits
  – Allow simultaneous estimation of covariate effects on the different competing risks
  – extendable for PK/PD joint modeling and simulation of drugs, biomarkers and competing clinical outcomes
Acknowledgements

All members of the Pharmacometrics Group at Uppsala University, Sweden
Censoring is independent

- **Non-informative censoring** occurs if the distribution of censoring times $U$ provides no information about the distribution of survival times $T$, and vice versa.
  - $T$ with density $f()$ and survival $S()$;
  - $U$ with density $y()$ and survival $Z()$

\[
L \propto \prod_{i=1}^{n} [f(x_i)]^{\delta_i} \cdot [S(x_i)]^{1-\delta_i}
\]
• Cause-specific hazard for $k^{th}$ event:
  
  - The instantaneous risk of $k^{th}$ event given that the subject survived all other events until $t_i$
  
  $$\lambda_k(t_i) = \lim_{\Delta t \to 0} \frac{1}{\Delta t} P(t_i \leq T_k < t_i + \Delta t, K = k | T_k \geq t_i)$$
  
  $$S_k(t) = e^{(-\int_0^t \lambda_k(x) \, dx)}$$

Describes a hypothetical world where patients can have only $k^{th}$ event

Assumes independence

Little use for clinical decisions in the real world
Censoring is dependent

- The cumulative incidence function \( (C_k(t)) \):
  - The proportion of subjects who have \( k^{th} \) event, accounting for subjects failing from other events
  \[
  C_k(t) = \int_0^t S(x) \lambda_k(x) \, dx
  \]
  - Break down probabilities of failure
  - Calculate real world probabilities