How to estimate beta-interferon treatment effectiveness in MS using some fancy modelling

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1. Why modelling
2. Why fancy modelling
3. A rough sketch
4. Take home message
Why modelling > Objective

- **Outcome**: Reaching a milestone in disability progression (time to sustained EDSS 6)
- **Treatment**: Use of $\beta$-interferons (3 kinds)
- **Objective**: Treatments have any long-term beneficial effect?

Randomized controlled trial or observational study?
Why modelling > Treatment Effect

Treated patient

Untreated patient

Study entry

Follow-up in years

Treatment Effect from ideal situation
Why modelling > Treatment Effect

Treatment Effect from ideal situation: KM / Cox PH model?
Why modelling > Less than ideal situation

Baseline covariates: Gender, Age, Disease duration
Time-varying covariates: Relapse, EDSS scores
Why modelling > Observational data

Patients are selected with similar eligibility criteria.
Why modelling > Standard analysis tool

Time-dependent (treatment) Cox Model:

$$\lambda_{Ta}(t|V) = \lambda_0 \times \exp(\beta_1a(t) + \beta_2V + \beta_3L)$$

Hazard at baseline  Hazard at time t  Treatment 
Baseline covariates  more covariates?

(1) Gender,  (4) Relapse, 
(2) Age,      (5) EDSS score
(3) Disease duration
Why modelling > Why time dependent covariate
Why modelling > Why time dependent covariate

[Coles, 2009]
Why modelling > Why time dependent covariate

Impact of a relapse on the hazard of reaching EDSS 6 at different time points

<table>
<thead>
<tr>
<th>Follow-up (i.e., disease duration from onset of MS)</th>
<th>Risk if relapse occurred</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5 years</td>
<td>Within 5 years from MS onset</td>
</tr>
<tr>
<td>&gt;5-10 years</td>
<td>&gt;5-10 years from MS onset</td>
</tr>
<tr>
<td>&gt;10 years</td>
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</tbody>
</table>

% Change in the hazard of reaching EDSS 6 (95% CI)

[Tremlett et al., 2009]
**Time-dependent Cox Proportional Hazards Model:**

$\lambda_{T_a}(t|V) = \lambda_0 \times \exp(\beta_1 a(t) + \beta_2 V + \beta_3 L(t))$

- Hazard at baseline
- Treatment at time t
- Baseline covariates
- Time-dependent covariates

(1) Gender, (2) Age, (3) Disease duration
(1) Relapse, (2) EDSS score
Why fancy modelling > Causal Graphs

Common Cause

\[ \mathcal{E} \rightarrow C \rightarrow \mathcal{D} \]

Mediator

\[ \mathcal{E} \rightarrow C \rightarrow \mathcal{D} \]

Cases itself

\[ \mathcal{E} \rightarrow C \rightarrow \mathcal{D} \]

Collider

\[ \mathcal{E} \rightarrow C \rightarrow \mathcal{D} \]
Relapse is both \textbf{confounder} and \textbf{mediator} variable.

Need to adjust for confounder, but adjusting for a mediator variable will \textbf{over-adjust/block causal path} [Hernán et al., 2004].
A rough sketch

Treatment Selection Model: \[ A(j) \sim \bar{A}(j - 1), V, \bar{L}(j) \]

Weight Model:

\[
SW(t) = \prod_{j=1}^{t} \frac{Pr(A(j) | \bar{A}(j - 1), V)}{Pr(A(j) | \bar{A}(j - 1), V, \bar{L}(j))}
\]
MSM Cox:
\[ \lambda_{T_a}(t|V) = \lambda_0 \times \exp(\beta_1 a(t) + \beta_2 V) \]

<table>
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<tr>
<th>Hazard at baseline</th>
<th>Hazard at time t</th>
<th>Treatment Baseline covariates</th>
</tr>
</thead>
</table>

(1) Gender, (2) Age, (3) Disease duration

with weights \( SW(t) \) (adjusting for time-dependent covariates) [Robins, 1999; Hernán et al., 2000; Robins et al., 2000].

Still need to check the assumptions behind this model.
Need to be very cautious while
• analyzing and
• interpreting results
from **observational** data,
especially while dealing with **time-dependent** variables.


Thank You!

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