Marginal estimates through regression standardization in competing risks and relative survival models

Paul C Lambert\textsuperscript{1,2}

\textsuperscript{1}Biostatistics Research Group, Department of Health Sciences, University of Leicester, UK
\textsuperscript{2}Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

2019 Nordic and Baltic Stata Users Group meeting
Stockholm, 30 August 2019
Regression Standardization

1. Fit a statistical model that contains exposure, $X$, and potential confounders, $Z$.
2. Predict outcome for all individuals assuming they are all exposed (set $X = 1$).
3. Take mean to give marginal estimate of outcome.
4. Repeat by assuming all are unexposed (set $X = 0$).
5. Take the difference/ratio in means to form contrasts.

- Key point is the distribution of confounders, $Z$, is the same for the exposed and unexposed.
- If the model is sufficient for confounding control then such contrasts can be interpreted as causal effects.
- Also known as direct/model based standardization. G-formula (with no time-dependent confounders)[1].
Why not margins?

- **margins** does regression standardization, so why not use this?
- It is an excellent command, but does not do what I wanted for survival data.
- In particular, extensions to competing risks and relative survival.
Marginal survival time

- With survival data

\( X \) - is a binary exposure: 0 (unexposed) and 1 (exposed).
\( T \) - is a survival time.
\( T^0 \) - is the potential survival time if \( X \) is set to 0.
\( T^1 \) - is the potential survival time if \( X \) is set to 1.

- The average causal difference in mean survival time

\[ E[T^1] - E[T^0] \]

- This is what \texttt{stteffects} can estimate.

- We often have limited follow-up and calculating the mean survival requires extrapolation and makes very strong distributional assumptions.
Marginal Survival functions

Rather than use mean survival we can define our causal effect in terms of the marginal survival function.

\[ E[T^1 > t] - E[T^0 > t] \]

We can limit \( t \) within observed follow-up time.

For confounders, \( Z \), we can write this as,

\[ E[S(t|X = 1, Z)] - E[S(t|X = 0, Z)] \]

Note that this is the expectation over the distribution of \( Z \).
Fit a survival model for exposure $X$ and confounders $Z$.

Predict survival function for each individual setting $X = x$ and then average.

Force everyone to be exposed and then unexposed.

$$\frac{1}{N} \sum_{i=1}^{N} \hat{S}(t|X = 1, Z = z_i) - \frac{1}{N} \sum_{i=1}^{N} \hat{S}(t|X = 0, Z = z_i)$$

Use their observed covariate pattern, $Z = z_i$.

We can standardize to an external (reference) population.

$$\frac{1}{N} \sum_{i=1}^{N} w_i \hat{S}_i(t|X = x, Z = z_i)$$

`standsurg` will perform these calculation.
Competing risks

Separate models for each cause, e.g.

\[ h_1(t \mid Z) = h_{0,1}(t) \exp(\beta_1 Z) \]
\[ h_2(t \mid Z) = h_{0,2}(t) \exp(\beta_2 Z) \]
Two types of probability

- We may be interested in cause-specific survival/failure.

<table>
<thead>
<tr>
<th>(1) In the absence of other causes (net)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ F_k(t) = 1 - S_k(t) = P(T_k \leq t) = \int_0^t S_k(u)h_k(u) , du ]</td>
</tr>
</tbody>
</table>

- We may be interested in cumulative incidence functions.

<table>
<thead>
<tr>
<th>(2) In the presence of other causes (crude)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ CIF_k(t) = P(T \leq t, \text{event} = k) = \int_0^t S(u)h_k(u) , du ]</td>
</tr>
</tbody>
</table>

- Both are of interest - depends on research question.
- (1) Needs conditional independence assumption to interpret as net probability of death.
Description of Example

- Death due to cancer and other causes.
- Covariates age, sex and deprivation in five groups.
- Restrict here to most and least deprived.

Models

- Flexible parametric (Royston-Parmar) models[2]
- Separate model for cancer and other causes.
- Age modelled using splines (3 df)
- 2-way interactions
- Time-dependent effects for all covariates.
Two separate cause-specific models

**Cancer Model**

```
stset dod, failure(status==1) exit(time min(dx+365.24*10,mdy(12,31,2013))) ///
  origin(dx) id(patid) scale(365.24)

stpm2 dep5 male agercs* dep_agercs*, df(5) scale(hazard) ///
  tvc(agercs* male dep5) dftvc(3)
```

`estimates store cancer`

**Other cause Model**

```
stset dod, failure(status==2) exit(time min(dx+365.24*10,mdy(12,31,2013))) ///
  origin(dx) id(patid) scale(365.24)

stpm2 dep5 male agercs* dep_agercs*, df(5) scale(hazard) ///
  tvc(agercs* male dep5) dftvc(3)
```

`estimates store other`
Conditional cause-specific CIFs (Females)

Least Deprived

Most Deprived

Years from diagnosis

Years from diagnosis

CIF

CIF

Cancer

Other Causes
Standardized cause-specific survival/failure

- Probability of death in the absence of other causes.
- Consider a single cause: standardize and form contrasts.

**Cancer specific survival/failure**

\[
F_1(t) = 1 - S_1(t)
\]

\[
E[F_1(t)|X = 1, Z] - E[F_1(t)|X = 0, Z]
\]

\[
\frac{1}{N} \sum_{i=1}^{N} \hat{F}_1(t|X = 1, Z = z_i) - \frac{1}{N} \sum_{i=1}^{N} \hat{F}_1(t|X = 0, Z = z_i)
\]

- Not a ‘real world’ probability, but comparisons between exposures where differential other cause mortality is removed is of interest.
Using `standsurrv`

- Take mean of 102,062 survival functions where all individuals forced to be unexposed.
- Take mean of 102,062 survival functions where all individuals forced to be exposed.
Take mean of 102,062 survival functions where all individuals forced to be unexposed.

Take mean of 102,062 survival functions where all individuals forced to be exposed.

```
. estimates restore cancer
. range tt 0 10 101

. standsurv, timevar(tt) failure ci
   at1(dep5 0 dep_agercs1 0 dep_agercs2 0 dep_agercs3 0) ///
   at2(dep5 1 dep_agercs1=agercs1 dep_agercs2=agercs2 dep_agercs3=agercs3) ///
   contrast(difference) ///
   atvar(F_cancer_s_dep1 F_cancer_s_dep5) ///
   contrastvar(F_cancer_diff)
```
Using standsurv

- Take mean of 102,062 survival functions where all individuals forced to be unexposed.
- Take mean of 102,062 survival functions where all individuals forced to be exposed.

```stata
. estimates restore cancer
. range tt 0 10 101

. standsurv, timevar(tt) failure ci
   at1(dep5 0 dep_agercs1 0 dep_agercs2 0 dep_agercs3 0)
   at2(dep5 1 dep_agercs1=agercs1 dep_agercs2=agercs2 dep_agercs3=agercs3)
   contrast(difference)
   atvar(F_cancer_s_dep1 F_cancer_s_dep5)
   contrastvar(F_cancer_diff)
```
Using standsurv

- Take mean of 102,062 survival functions where all individuals forced to be unexposed.
- Take mean of 102,062 survival functions where all individuals forced to be exposed.

```
. estimates restore cancer
. range tt 0 10 101

. standsurv, timevar(tt) failure ci
   at1(dep5 0 dep_agercs1 0 dep_agercs2 0 dep_agercs3 0)
   at2(dep5 1 dep_agercs1=agercs1 dep_agercs2=agercs2 dep_agercs3=agercs3)
   contrast(difference)
   atvar(F_cancer_s_dep1 F_cancer_s_dep5)
   contrastvar(F_cancer_diff)
```
Using standsurv

- Take mean of 102,062 survival functions where all individuals forced to be unexposed.
- Take mean of 102,062 survival functions where all individuals forced to be exposed.

```
. estimates restore cancer
. range tt 0 10 101

. standsurv, timevar(tt) failure ci
   at1(dep5 0 dep_agercs1 0 dep_agercs2 0 dep_agercs3 0)  ///
   at2(dep5 1 dep_agercs1=agercs1 dep_agercs2=agercs2 dep_agercs3=agercs3)  ///
   contrast(difference)  ///
   atvar(F_cancer_s_dep1 F_cancer_s_dep5)  ///
   contrastvar(F_cancer_diff)
```
Using standsurv

- Take mean of 102,062 survival functions where all individuals forced to be unexposed.
- Take mean of 102,062 survival functions where all individuals forced to be exposed.

```
. estimates restore cancer
. range tt 0 10 101

. standsurv, timevar(tt) failure ci
   ///
   at1(dep5 0 dep_agercs1 0 dep_agercs2 0 dep_agercs3 0) ///
   at2(dep5 1 dep_agercs1=agercs1 dep_agercs2=agercs2 dep_agercs3=agercs3) ///
   contrast(difference) ///
   atvar(F_cancer_s_dep1 F_cancer_s_dep5) ///
   contrastvar(F_cancer_diff)
```
Using `standsurrv`

- Take mean of 102,062 survival functions where all individuals forced to be unexposed.
- Take mean of 102,062 survival functions where all individuals forced to be exposed.

```
. estimates restore cancer
. range tt 0 10 101

. standsurrv, timevar(tt) failure ci
   at1(dep5 0 dep_agercs1 0 dep_agercs2 0 dep_agercs3 0)
   at2(dep5 1 dep_agercs1=agercs1 dep_agercs2=agercs2 dep_agercs3=agercs3)
   contrast(difference)
   atvar(F_cancer_s_dep1 F_cancer_s_dep5)
   contrastvar(F_cancer_diff)
```
Standardized cause-specific Failure $(1 - S_k(t))$

**Standardized $F_k(t)$**
- Least Deprived
- Most Deprived

**Difference (Most - Least Deprived)**
- Cause-Specific Failure Difference
- Years from diagnosis

Paul C Lambert  
Standardization in competing risks  
30 August 2019
Standardized cause-specific CIF

- Probability of death in the presence of other causes.
- We can standardize the cause-specific CIF in the same way.
- These requires combining \( K \) different models

\[
E \left[ CIF_k(t) \mid X = x, Z \right]
\]

\[
\frac{1}{N} \sum_{i=1}^{N} \int_{0}^{t} \hat{S}(u \mid X = x, Z = z_i) \hat{h}_k(u \mid X = x, Z = z_i) \, du
\]

- Calculate for \( X=1 \) and \( X=0 \) and then obtain contrast.
- Can be interpreted as causal effects under assumptions[3].
Using standsurv

- Take mean of 102,062 CIFs where all individuals forced to be unexposed.
- Take mean of 102,062 CIFs where all individuals forced to be exposed.
Using standsurv

- Take mean of 102,062 CIFs where all individuals forced to be unexposed.
- Take mean of 102,062 CIFs where all individuals forced to be exposed.

```
. standsurv, crmodels(cancer other) timevar(tt) cif ci
    ///
    at1(dep5 0 dep_agercs1 0 dep_agercs2 0 dep_agercs3 0) ///
    at2(dep5 1 dep_agercs1=agercs1 dep_agercs2=agercs2 dep_agercs3=agercs3) ///
    contrast(difference) ///
    atvar(CIF_s_dep1 CIF_s_dep5)) ///
    contrastvar(CIF_diff)
```
Using \texttt{standsurv}

- Take mean of 102,062 CIFs where all individuals forced to be unexposed.
- Take mean of 102,062 CIFs where all individuals forced to be exposed.

\begin{verbatim}
. standsurv, crmodels(cancer other) timevar(tt) cif ci ///
at1(dep5 0 dep_agercs1 0 dep_agercs2 0 dep_agercs3 0) ///
at2(dep5 1 dep_agercs1=agercs1 dep_agercs2=agercs2 dep_agercs3=agercs3) ///
contrast(difference) ///
atvar(CIF_s_dep1 CIF_s_dep5)) ///
contrastvar(CIF_diff)
\end{verbatim}
Using standsurv

- Take mean of 102,062 CIFs where all individuals forced to be unexposed.
- Take mean of 102,062 CIFs where all individuals forced to be exposed.

```bash
. standsurv, crmodels(cancer other) timevar(tt) cif ci
   at1(dep5 0 dep_agercs1 0 dep_agercs2 0 dep_agercs3 0) ///
   at2(dep5 1 dep_agercs1=agercs1 dep_agercs2=agercs2 dep_agercs3=agercs3) ///
   contrast(difference) ///
   atvar(CIF_s_dep1 CIF_s_dep5)) ///
   contrastvar(CIF_diff)
```
Using `standsurv`

- Take mean of 102,062 CIFs where all individuals forced to be unexposed.
- Take mean of 102,062 CIFs where all individuals forced to be exposed.

```plaintext
. standsurv, crmodels(cancer other) timevar(tt) cif ci
   at1(dep5 0 dep_agercs1 0 dep_agercs2 0 dep_agercs3 0) //
   at2(dep5 1 dep_agercs1=agercs1 dep_agercs2=agercs2 dep_agercs3=agercs3) //
   contrast(difference) //
   atvar(CIF_s_dep1 CIF_s_dep5)) //
   contrastvar(CIF_diff)
```

Paul C Lambert

Standardization in competing risks

30 August 2019
Standardized cause-specific CIF

Standardized $\text{CIF}_k(t)$

- Least Deprived
- Most Deprived

Difference (Most - Least Deprived)
Standardized cause-specific CIF

![Graph showing Standardized CIF and Difference (Most - Least Deprived) over Years from diagnosis.](image-url)
Timings for standardized survival/failure functions

- $N$ individuals, 1 event, exposure $X$, 10 confounders $Z$.
- Fit model: Standardized $S(t|X = x, Z)$ for $X = 0$ & $X = 1$ and contrasts with CIs.
- Calculate time for Weibull models and FPMs.

<table>
<thead>
<tr>
<th>N</th>
<th>Weibull</th>
<th>FPM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Point Estimate</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>1,000</td>
<td>0.02</td>
<td>0.03</td>
</tr>
<tr>
<td>10,000</td>
<td>0.04</td>
<td>0.1</td>
</tr>
<tr>
<td>100,000</td>
<td>0.4</td>
<td>0.7</td>
</tr>
<tr>
<td>250,000</td>
<td>1.0</td>
<td>1.8</td>
</tr>
<tr>
<td>500,000</td>
<td>2.0</td>
<td>3.5</td>
</tr>
<tr>
<td>1,000,000</td>
<td>3.9</td>
<td>4.6</td>
</tr>
</tbody>
</table>

Times in seconds on standard issue University of Leicester laptop.
Timings for standardized cause-specific CIF

- $N$ individuals, 2 events, exposure $X$, 10 confounders $Z$.
- Fit 2 models: standardized CIF for $X = 0$ & $X = 1$ and contrast with CIs.
- Calculate time for Weibull models and FPMs.

<table>
<thead>
<tr>
<th>N</th>
<th>Weibull</th>
<th></th>
<th>FPM</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Point Estimate</td>
<td>Confidence Interval</td>
<td>Point Estimate</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>1,000</td>
<td>0.1</td>
<td>0.3</td>
<td>0.3</td>
<td>1.4</td>
</tr>
<tr>
<td>10,000</td>
<td>0.2</td>
<td>2.1</td>
<td>2.1</td>
<td>8.6</td>
</tr>
<tr>
<td>100,000</td>
<td>13.2</td>
<td>16.8</td>
<td>20.6</td>
<td>93.9</td>
</tr>
<tr>
<td>250,000</td>
<td>5.8</td>
<td>48.1</td>
<td>56.1</td>
<td>246.4</td>
</tr>
<tr>
<td>500,000</td>
<td>10.1</td>
<td>97.7</td>
<td>117.2</td>
<td>521.2</td>
</tr>
<tr>
<td>1,000,000</td>
<td>24.2</td>
<td>159.0</td>
<td>225.6</td>
<td>1018.9</td>
</tr>
</tbody>
</table>

Times in seconds on standard issue University of Leicester laptop.
Relative Survival

- Relative survival models used with large population cancer registry data when cause of death not available or not reliable.

\[ h(t|X, Z) = h^*(t|X, Z) + \lambda(t|X, Z) \]

- \( h(t|X, Z) \) - All-cause mortality rate
- \( h^*(t|X, Z) \) - Expected mortality rate
- \( \lambda(t|X, Z) \) - Excess mortality rate

- Expected mortality rates obtained from national lifetables.
- On survival scale.

\[ S(t|X, Z) = S^*(t|X, Z)R(t|X, Z) \]

- The equivalent of a CIF is know as a crude probability in the relative survival framework.
Melanoma Example

**Relative Survival Model**

\[
R(t|X = x, Z) = \frac{1}{N} \sum_{i=1}^{N} R_i(t|X = x, Z = z_i)
\]

**Standardized Relative Survival**

\[
\text{standsurv, timevar(tt) ci}
\]

```plaintext
///
at1(dep5 0 agercs1_dep5 0 agercs2_dep5 0 agercs3_dep5 0)
///
at2(dep5 1 agercs1_dep5=agercs1 agercs2_dep5=agercs2 agercs3_dep5=agercs3)
///
contrast(difference)
///
atvar(R_dep5 R_dep1)
///
contrastvar(R_diff)
```
All-cause Survival

\[ \overline{S}(t | X = x, Z) = \frac{1}{N} \sum_{i=1}^{N} S^* (t | X = x, Z = z_i) \]

```bash
standsurv, timevar(tt) ci
    at1(dep5 0 agercs1_depl5 0 agercs2_depl5 0 agercs3_depl5 0) ///
    at2(dep5 1 agercs1_depl5=agercs1 agercs2_depl5=agercs2 agercs3_depl5=agercs3) ///
    expsurv(using(popmort.uk.regions.2017.dta) ///
        datediag(dx) ///
        agediag(agediag) ///
        pmrate(rate) ///
        pmage(age) ///
        pmyear(year) ///
        pmother(sex dep region) ///
        pmmaxyear(2016) ///
        at1(dep 1) ///
        at2(dep 5)) ///
contrast(difference) ///
atvar(S.depl5 S.depl1) ///
contrastvar(S.diff)
```
Standardized All-cause Survival

[Graph showing two line charts. The left chart plots All-Cause Probability of Death against Years from diagnosis for Least Deprived and Most Deprived categories. The right chart plots Difference in All-cause Survival against Years from diagnosis.]
Standardized Crude Probabilities

\[
\bar{F}_c(t|X = x, Z) = \frac{1}{N} \sum_{i=1}^{N} \int_0^t S^*(u|X = x, Z = z_i) R(u|X = x, Z = z_i) \lambda(u|X = x, Z = z_i),
\]

standsurv, crudeprob timevar(tt) ci
  at1(dep5 0 agercs1_dep5 0 agercs2_dep5 0 agercs3_dep5 0) ///
  at2(dep5 1 agercs1_dep5=agercs1 agercs2_dep5=agercs2 agercs3_dep5=agercs3) ///
  expsurv(using(popmort.uk.regions.2017.dta) ///
  datediag(dx)
  agediag(agediag)
  pmrate(rate)
  pmage(age)
  pmyear(year)
  pmother(sex dep region)
  pmmaxyear(2016)
  at1(dep 1)
  at2(dep 5)) ///
  contrast(difference)
  atvar(CP_dep5 CP_dep1) ///
  contrastvar(CP_diff)
Standardized Crude Probabilities of Death

[Graph showing the Crude Probability of Death for Least Deprived and Most Deprived groups over 10 years from diagnosis, with a shaded area indicating the difference in probabilities.]
standsurv

- **standsurv** works for a many parametric models
  - `streg`: Exponential, Weibull, Gompertz, LogNormal, LogLogistic
  - Flexible parametric (Splines: `stcrs` (log hazard) or `stpm2` (log cumulative hazard))

- Standard, relative survival and competing risks models
  - Can use different models for different causes. E.g. Weibull for one cause and flexible parametric model for another

- Various Standardizations
  - Survival, restricted means, centiles, hazards... and more

- Standard errors calculated using delta-method or M-estimation with all analytical derivatives, so fast

More information on **standsurv** available at

https://pclambert.net/software/standsurv/
Regression standardisation is a simple and underused tool
Can also estimate causal effects using IPW.
Advantages of regression adjustment
- Not a big leap from what people doing at the moment - model may be the same, just report in a different way.
- We often do not want to just report marginal effects - predictions for specific covariate patterns are still of interest.
As long as we can predict survival function, models can be as complex as we like (non-linear effects, non-proportional hazards, interactions with exposure etc.)
References


