Standardized survival curves and related measures using flexible parametric survival models

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Standardized/Marginal Effects

- With the introduction of the `margins` command in Stata 11, enabled estimation of standardized/marginal effects through regression adjustment.
- If the statistical model is sufficient for confounding control then certain contrasts of marginal/standardized effects can be interpreted as causal effects.
- `margins` is a very powerful command, but did not do what I want to do for survival data.

Marginal Effects and Causal Inference

X	-	is a binary exposure: 0 (unexposed) and 1 (exposed).
Y	-	is is an outcome (binary or continuous).
Y^0	-	is the potential outcome if X is set to 0.
Y^1	-	is the potential outcome if X is set to 1.

- Some outcomes are counterfactual.
- Average causal effects are contrasts between the expected value of the potential outcomes.
- For example, the average causal difference is

$$E[Y^1] - E[Y^0]$$

- Have to make assumptions as do not observe counterfactual outcomes

With survival data

- With survival data

X	-	is a binary exposure: 0 (unexposed) and 1 (exposed).
T	-	is 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.

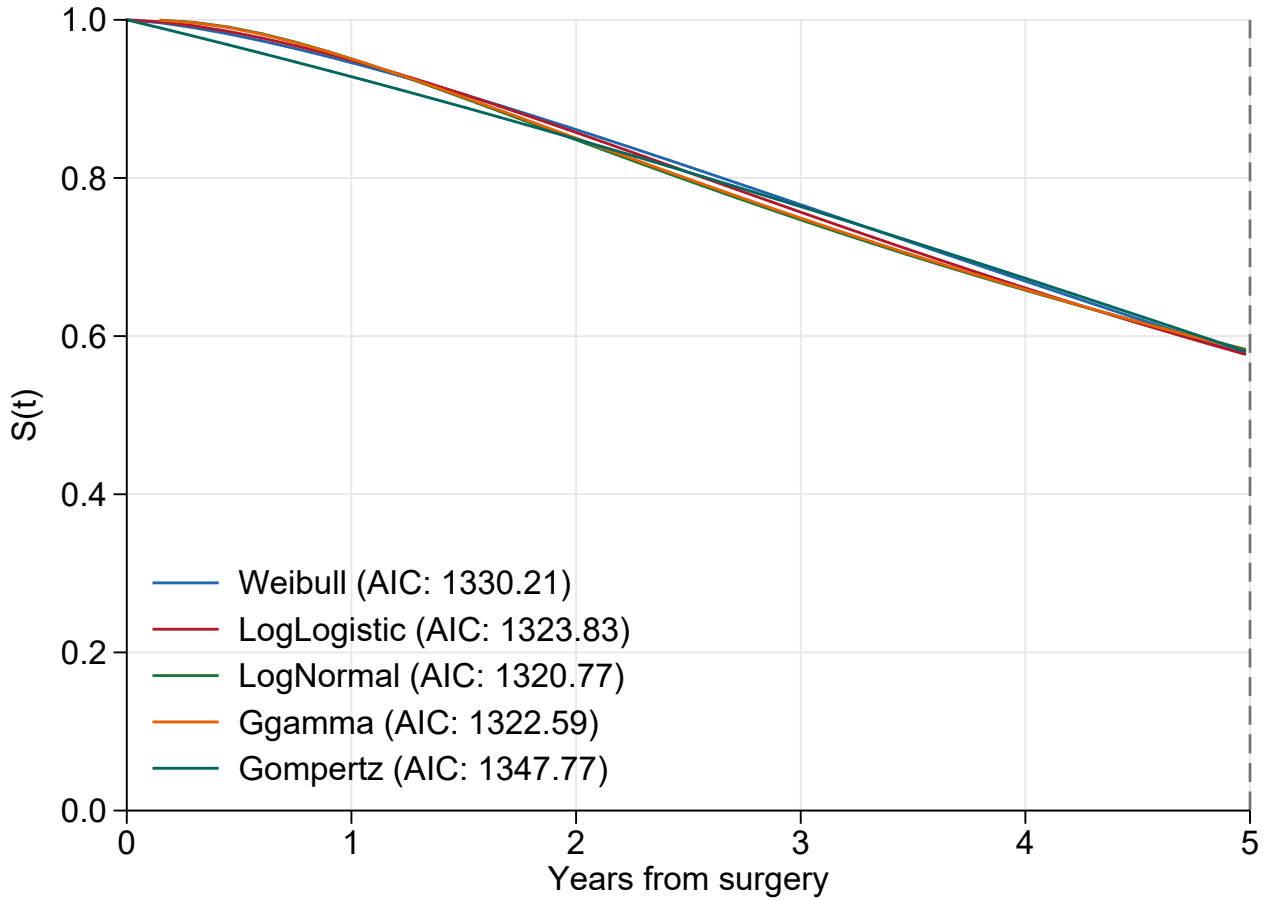
- The average causal difference is

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

- This is what `stteffects` can estimate.
- However, we often have limited follow-up and calculating the mean survival makes very strong distributional assumptions.

Limited follow-up

- Often limited follow-up in survival studies



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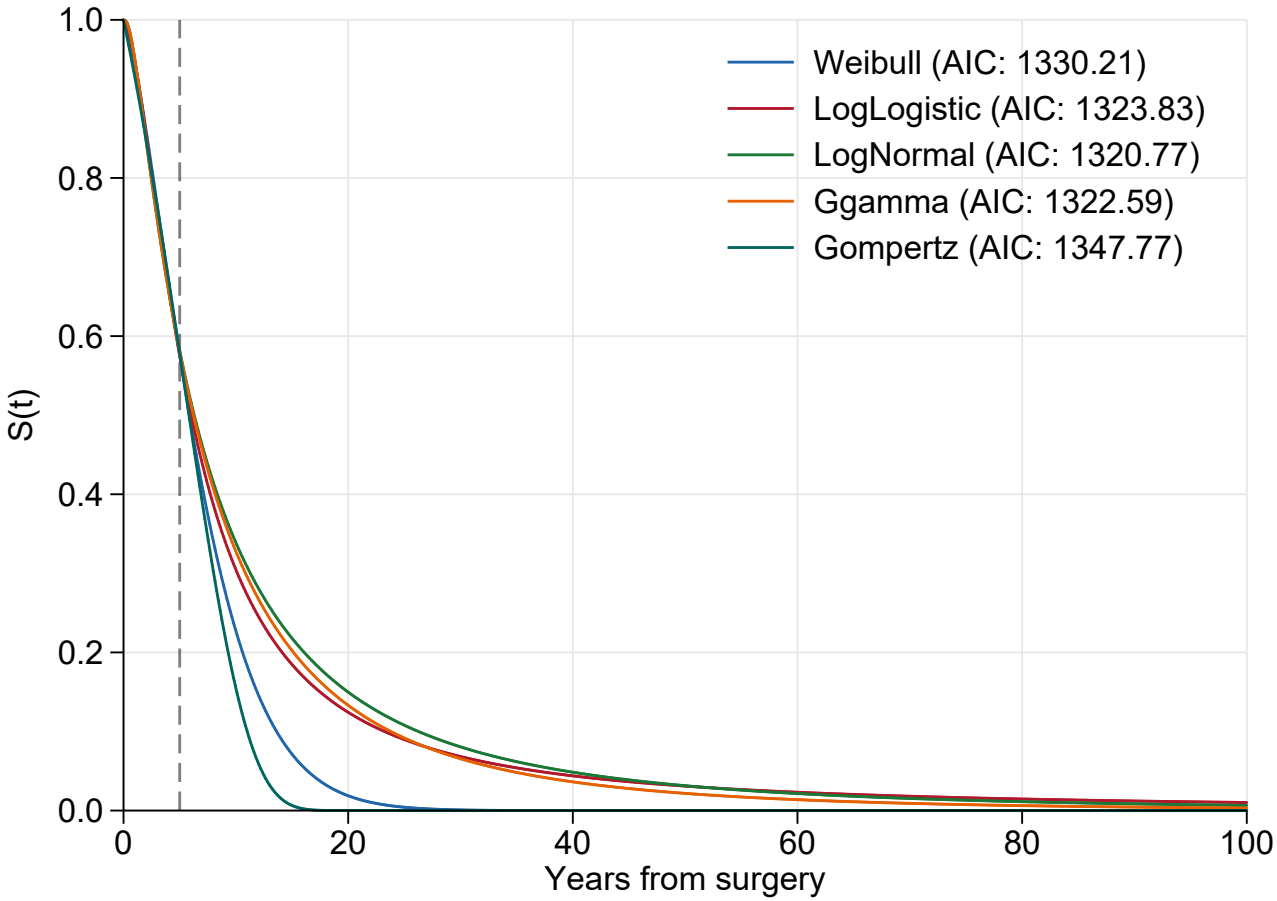


- Mean is area under curve - large variation after end of follow-up

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.
- Alternatively, we can write this as,

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

- Note that this is the expectation over the distribution of confounders Z.

Estimation

- Fit a survival model for exposure X and confounders Z.
- Estimation of a marginal survival function is based on predicting a survival function for each individual and taking an average.

$$\frac{1}{N}\sum_{i=1}^{N}\widehat{S}\left(t|X_i=1,Z_i\right)-\frac{1}{N}\sum_{i=1}^{N}\widehat{S}\left(t|X_i=0,Z_i\right)$$

- Force everyone to be exposed and then unexposed.
- We use their observed covariate pattern, Z_i.
- Epidemiologists call this model based or regression standardization[1].
- Also know as marginal effect or G-computation.
- Can restrict to a subset of the population, e.g. the average causal effect in the exposed.

Flexible Parametric Models

- We do a lot of work with flexible parametric survival models.
- These are parametric survival models where we use splines to model the effect of the time scale.
- For example, on the log cumulative hazard scale is a follows,

$$\ln[H(t|\mathbf{x}_i)] = \eta_i(t) = s\left(\ln(t)|\boldsymbol{\gamma}, \mathbf{k}_0\right) + \mathbf{x}_i\boldsymbol{\beta}$$

- $s()$ is a restricted cubic spline function.
- We can transform to the survival and hazard scales

$$S(t|\mathbf{x}_i) = \exp(-\exp\left[\eta_i(t)\right])) \quad h(t|\mathbf{x}_i) = \frac{ds\left(\ln(t)|\boldsymbol{\gamma}, \mathbf{k}_0\right)}{dt}\exp\left[\eta_i(t)\right]$$

Why use flexible parametric models?

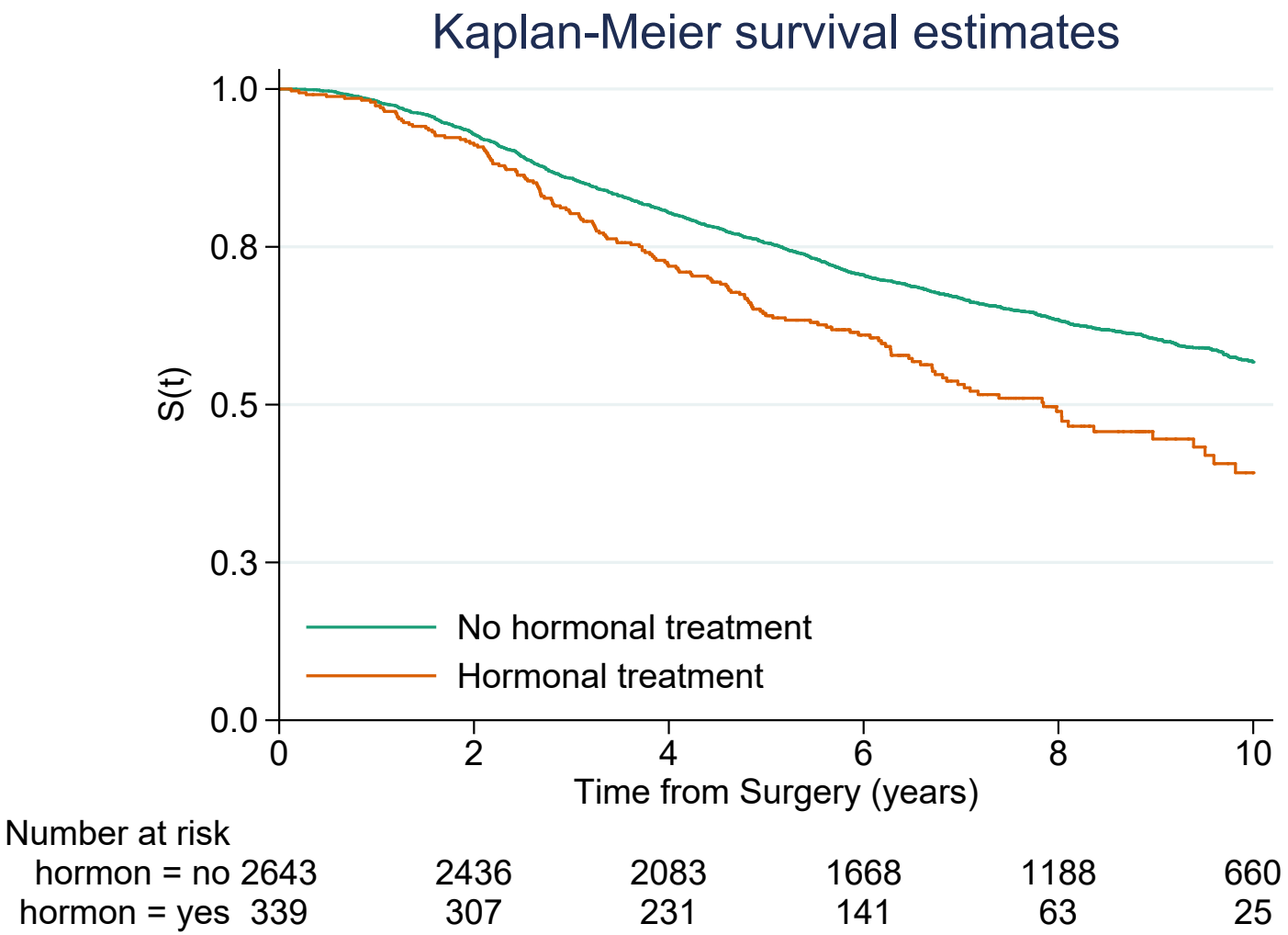
- Parametric model allows simple prediction of survival, hazard and related functions for any covariate pattern at any time point, t[2].
- Using splines gets around many of the limitations of standard parametric models.
- Extension to time-dependent effects (non-proportional hazards) is simple.
- Implemented in `stpm2` [3, 4]

Example

- I will use the Rotterdam breast cancer data: 2,982 women diagnosed with primary breast cancer.
- Observational study, but interest lies in comparing those taking and not taking hormonal therapy (`hormon`).
- Outcome is all-cause mortality.
- In a simplified analysis I will consider the following confounders.

`age`	Age at diagnosis
`enodes`	Number of positive lymph nodes (transformed).
`pr_1`	Progesterone receptors (fmol/l) (transformed)-

Kaplan-Meier Curves



- Just looking at unadjusted estimate, treatment appears worse.

Introducing confounders

- For simplicity I will just look at selected confounders.

```
. tabstat age nodes pr, by(hormon)

Summary statistics: mean
  by categories of: hormon (Hormonal therapy)
```

hormon	age	nodes	pr
no	54.09762	2.326523	168.706
yes	62.54867	5.719764	108.233
Total	55.05835	2.712274	161.8313

- Those taking treatment tend to be older and have more severe disease.

Hazard ratios from a Cox model

- Unadjusted.

```
------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
      hormon |   1.540262    .132659     5.02   0.000     1.301016    1.823503
------------------------------------------------------------------------------
```

- Adjusted

```
------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
      hormon |   .7905871    .071509    -2.60   0.009     .6621526    .9439334
         age |   1.013249   .0024118     5.53   0.000     1.008533    1.017987
      enodes |   .1135842   .0110469   -22.37   0.000     .0938712     .137437
        pr_1 |   .9066648   .0119291    -7.45   0.000      .883583    .9303496
------------------------------------------------------------------------------
```

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- Effect of treatment changes direction after adjustment.

Same hazard ratios for stcox and stpm2

- stcox and stpm2 will give very similar hazard ratios[2].
- Advantage of stpm2 is that as a parametric model it is very simple to predict various measures for any covariate pattern at any point in time (both in and out of sample).

```
. estimate table stpm2 cox, keep(hormon age enodes pr_1) eform se eq(1:1)
```

Variable	stpm2	cox
hormon	.79064318	.79058708
	.07150772	.07150904
age	1.0132442	1.0132488
	.00241191	.00241185
enodes	.11325337	.11358424
	.01101349	.0110469
pr_1	.90648552	.90666481
	.01192822	.01192914

legend: b/se

This is our stpm2 model

```
. stpm2 hormon age enodes pr_1, scale(hazard) df(4) nolog eform
Log likelihood = -2668.4925                     Number of obs     =      2,982
```

	exp(b)	Std. Err.	z	P>|z|	[95% Conf.	Interval]
xb						
hormon	.7906432	.0715077	-2.60	0.009	.66221	.9439854
age	1.013244	.0024119	5.53	0.000	1.008528	1.017983
enodes	.1132534	.0110135	-22.40	0.000	.0935998	.1370337
pr_1	.9064855	.0119282	-7.46	0.000	.8834055	.9301685
_rcs1	2.632579	.073494	34.67	0.000	2.492403	2.780638
_rcs2	1.184191	.0329234	6.08	0.000	1.121389	1.25051
_rcs3	1.020234	.0150787	1.36	0.175	.9911046	1.05022
_rcs4	.996572	.0073038	-0.47	0.639	.9823591	1.010991
_cons	1.101826	.17688	0.60	0.546	.80439	1.509244

```
Note: Estimates are transformed only in the first equation.
```

Using stpm2_standsurv

- stpm2_standsurv is a post estimation command for stpm2.
- Can be used for standardized survival curves and contrasts, but also
  - Standardized restricted mean survival time.
  - Standardized hazard functions
  - Centiles of standardized survival functions.
  - User defined functions.
  - External standardization
  - Combined with IPW weights.
  - All options work for both standard and relative survival models.
- Faster and does more than the meansurv option in stpm2's predict command

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- Implemented in Mata. Uses analytical derivatives, so fast.

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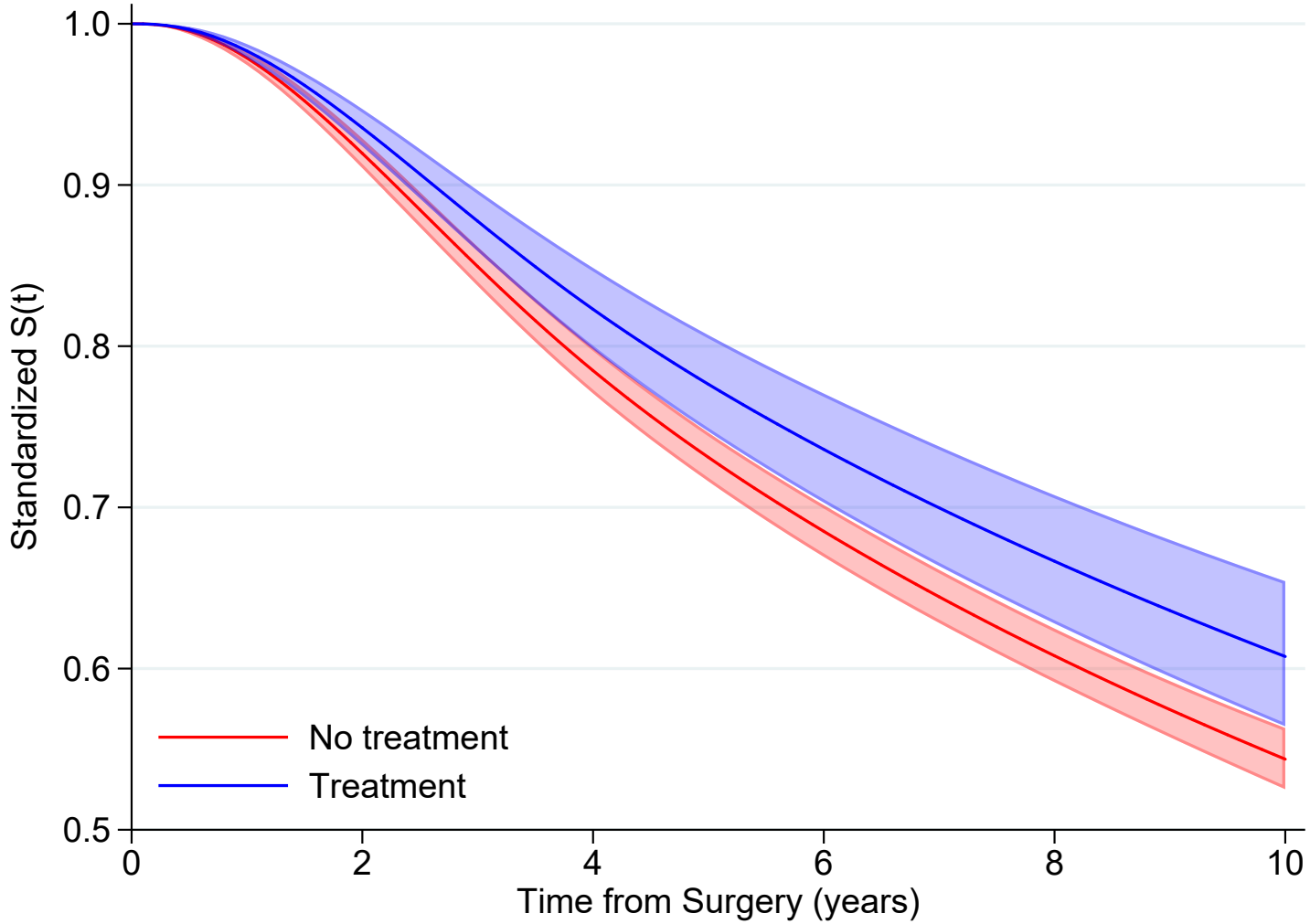
- Implemented in Mata. Uses analytical derivatives, so fast.
- Thanks to Michael Crowther for helping me understand pointers and structures!

Using stpm2_standsurv

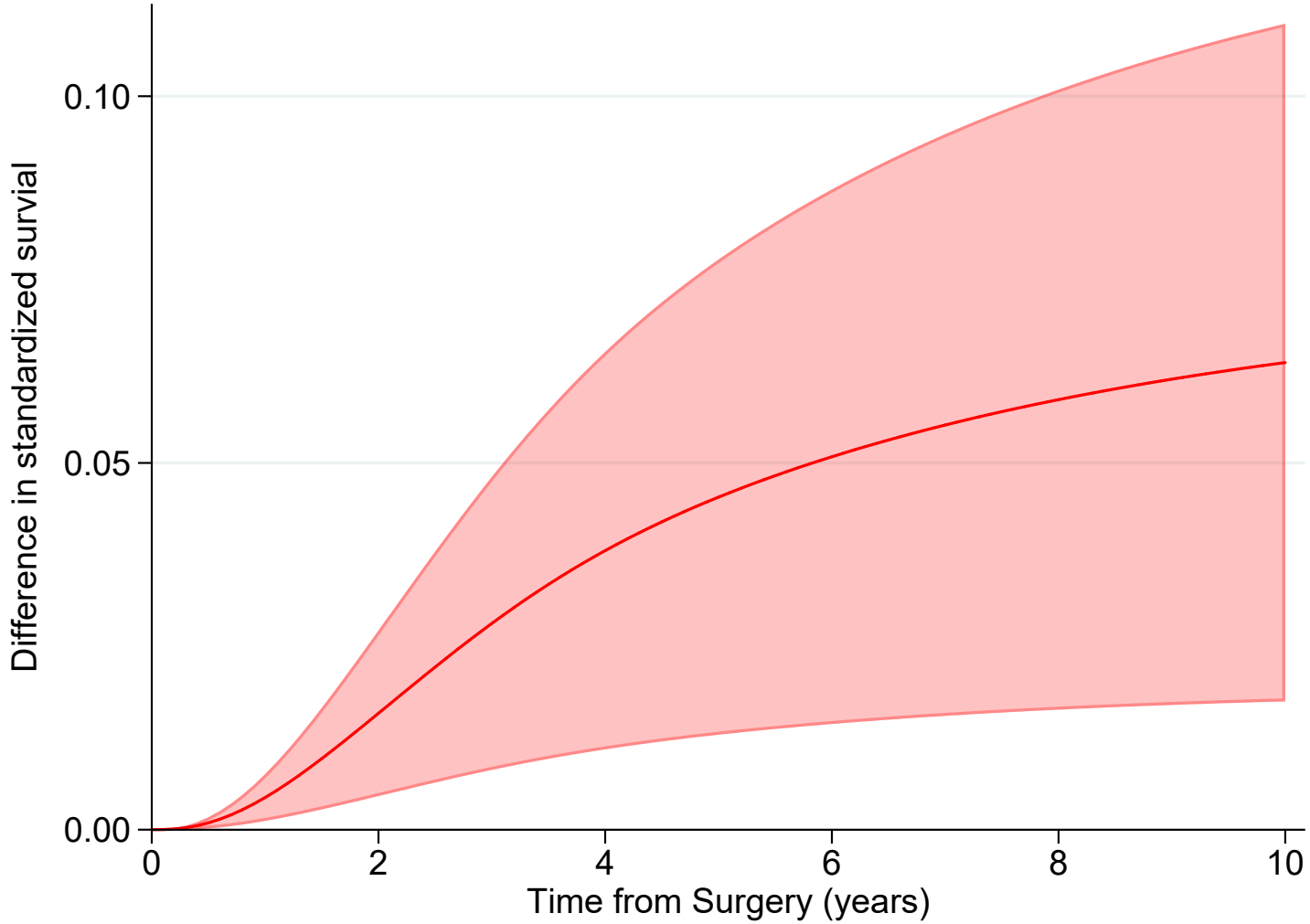
```
 . range tt 0 10 101
(2,881 missing values generated)
. stpm2_standsurv, at1(hormon 0) at2(hormon 1) timevar(tt) ci ///
>    contrast(difference) ///
>    atvars(S_hormon0 S_hormon1) contrastvar(Sdiff)
```

- Predict at 101 equally spaced observations between 0 and 10.
- Two standardized curves and their difference will be calculated.
- For each of the at() options 2,982 survival curves will be estimated and averaged.

Standardized survival curves

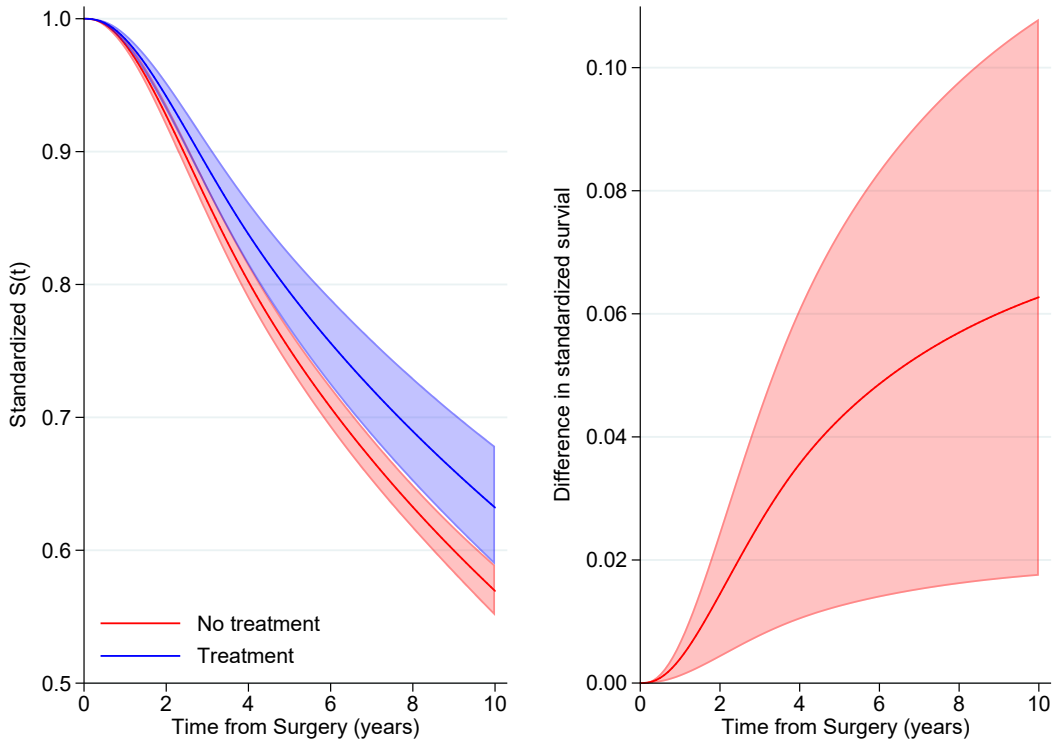


Difference in standardized survival curves



Standardize within a subgroup

```
. stpm2_standsurv if hormon==0, at1(hormon 0) at2(hormon 1) ci  ///
>    timevar(tt) contrast(difference) ///
>    atvars(S_hormon0b S_hormon1b) contrastvar(Sdiffb)
```



Other Standardized Measures

- We can derive other functions of the standardized curves

Restricted mean survival

$$RMST(t^*) = E\left[min(T, t^*)\right]$$

$$RMST_s(t^*|X = x, Z) = \int_0^{t^*} E\left[S(u|X = x, Z)\right] du$$

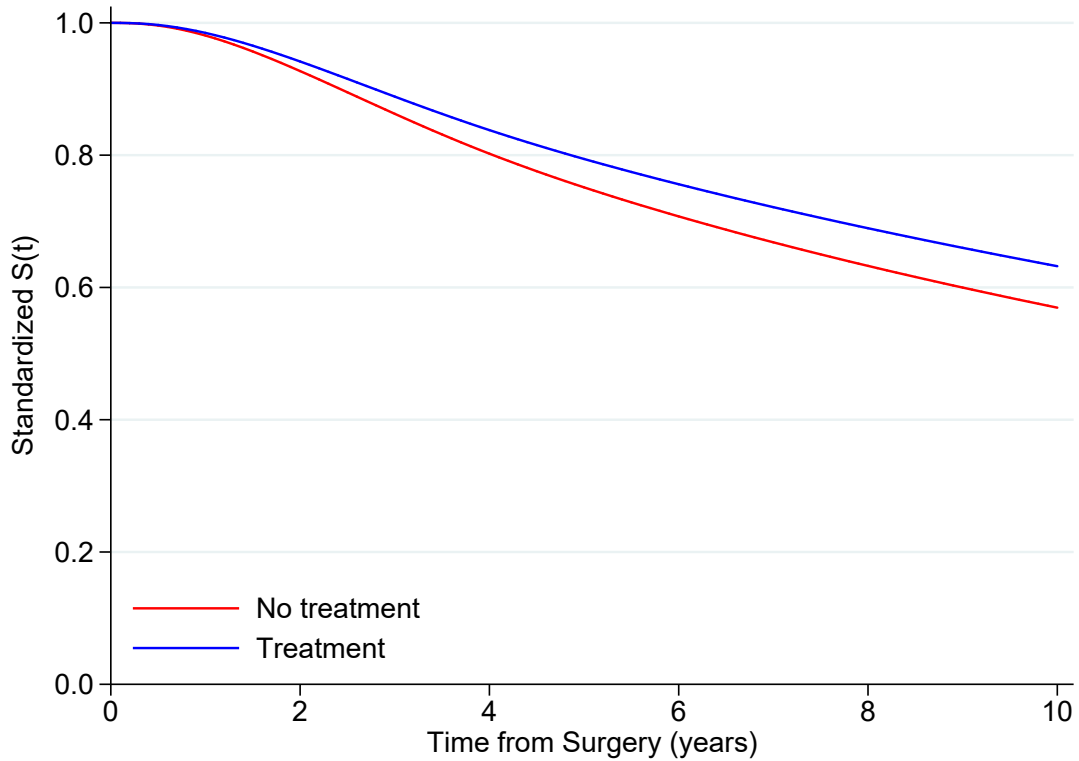
and is estimated by

$$\widehat{RMST}_s(t^*|X = x, Z) = \int_0^{t^*} \frac{1}{N} \sum_{i=1}^{N} S(u|X = x, Z = z_i) du$$

- We can then take contrasts (differences or ratios).

RMST Example

```
. stpm2_standsurv, at1(hormon 0) at2(hormon 1) ci  ///
>    timevar(tt) contrast(difference) rmst ///
>    atvars(RMST_hormon0 RMST_hormon1) contrastvar(RMST_diff)
```



RMST Example

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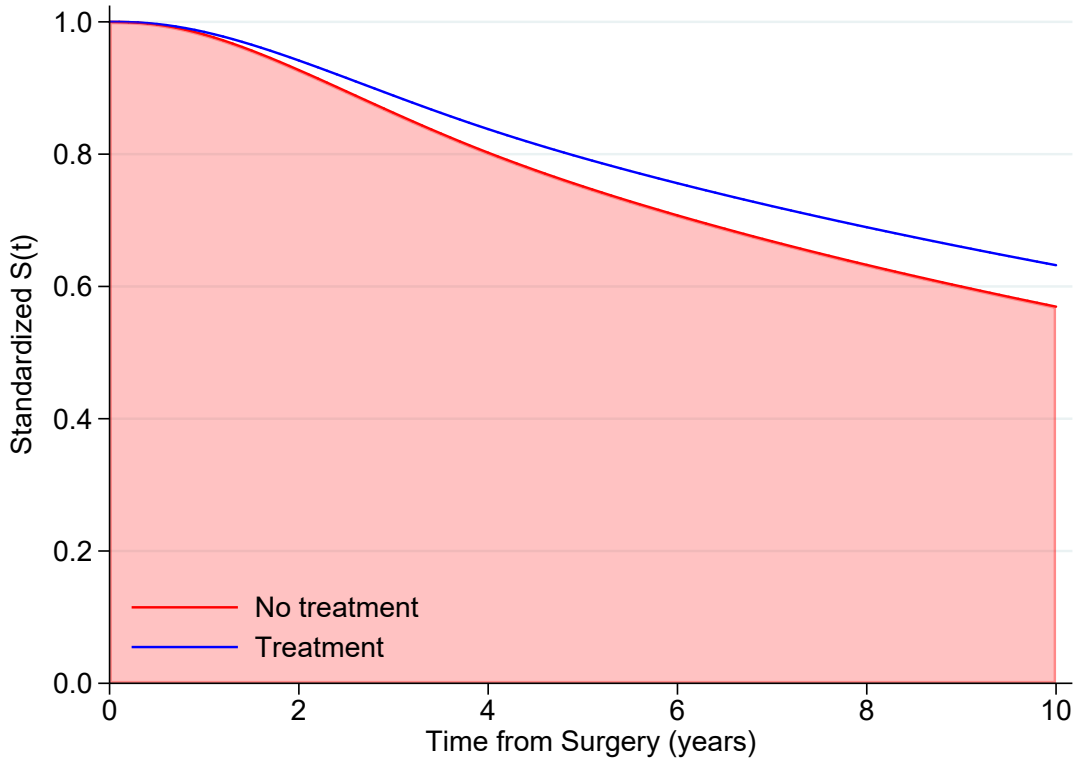
. stpm2_standsurv, at1(hormon 0) at2(hormon 1) ci  ///
>    timevar(tt) contrast(difference) rmst ///
>    atvars(RMST_hormon0 RMST_hormon1) contrastvar(RMST_diff)
```



RMST Example

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. stpm2_standsurv, at1(hormon 0) at2(hormon 1) ci  ///
>    timevar(tt) contrast(difference) rmst ///
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```

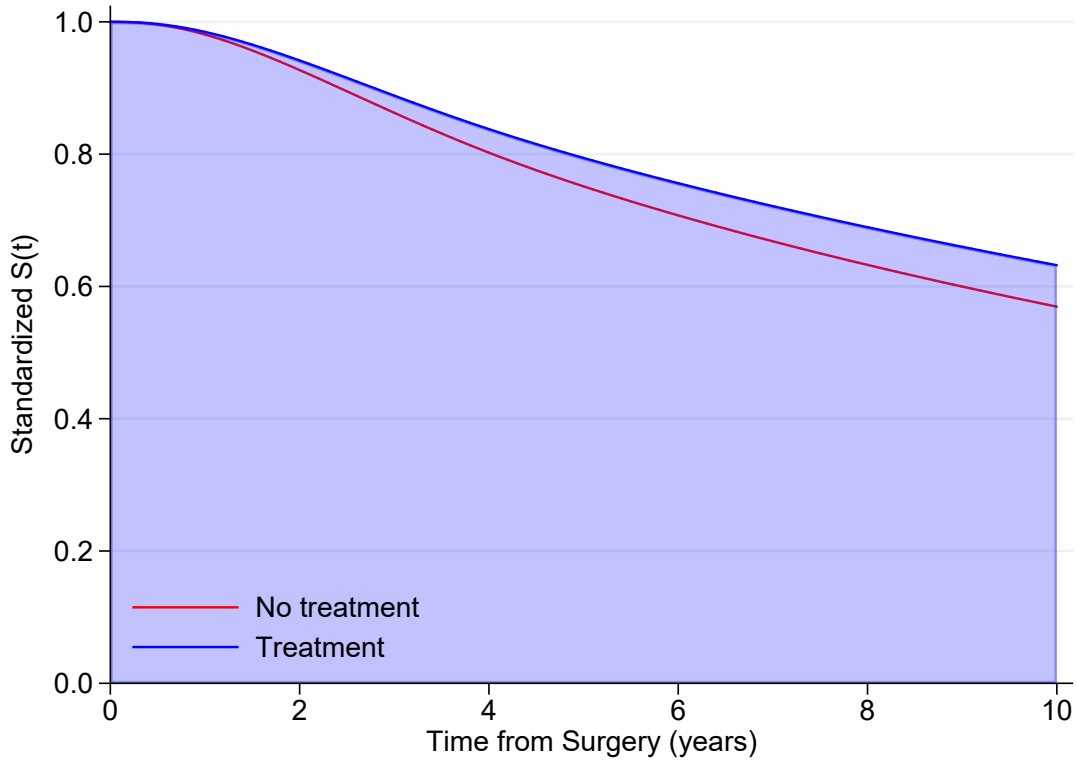

RMST Example

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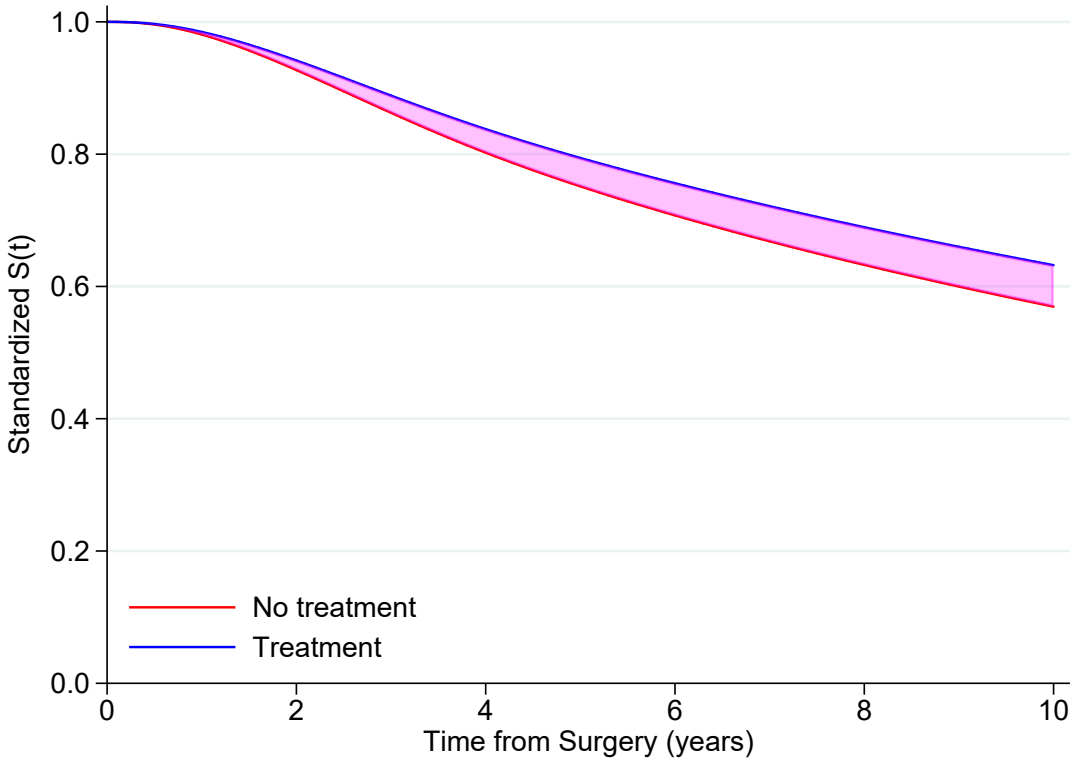
```



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>    timevar(tt) contrast(difference) rmst ///
>    atvars(RMST_hormon0 RMST_hormon1) contrastvar(RMST_diff)
```
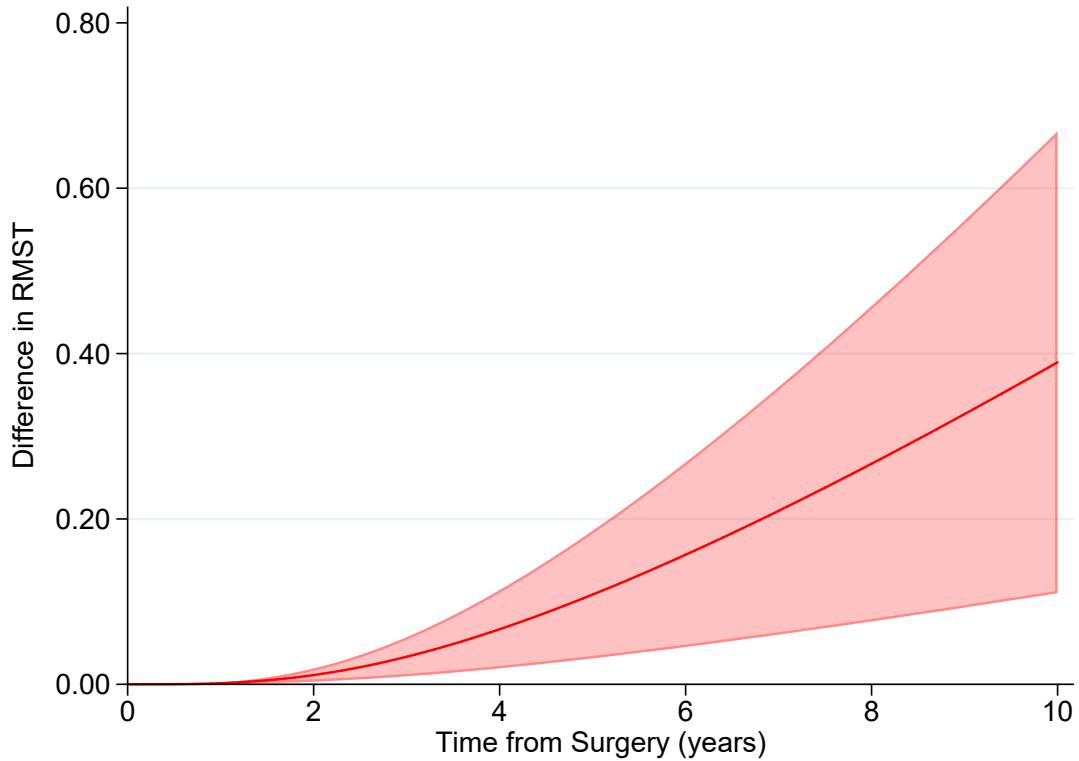



Hazard of the marginal survival function

- Apply standard transformation from survival to hazard of marginal survival function.

Marginal hazard

$$h(t) = -\frac{d}{dt} \ln \left(E \left[S(t|X = x, Z) \right] \right)$$

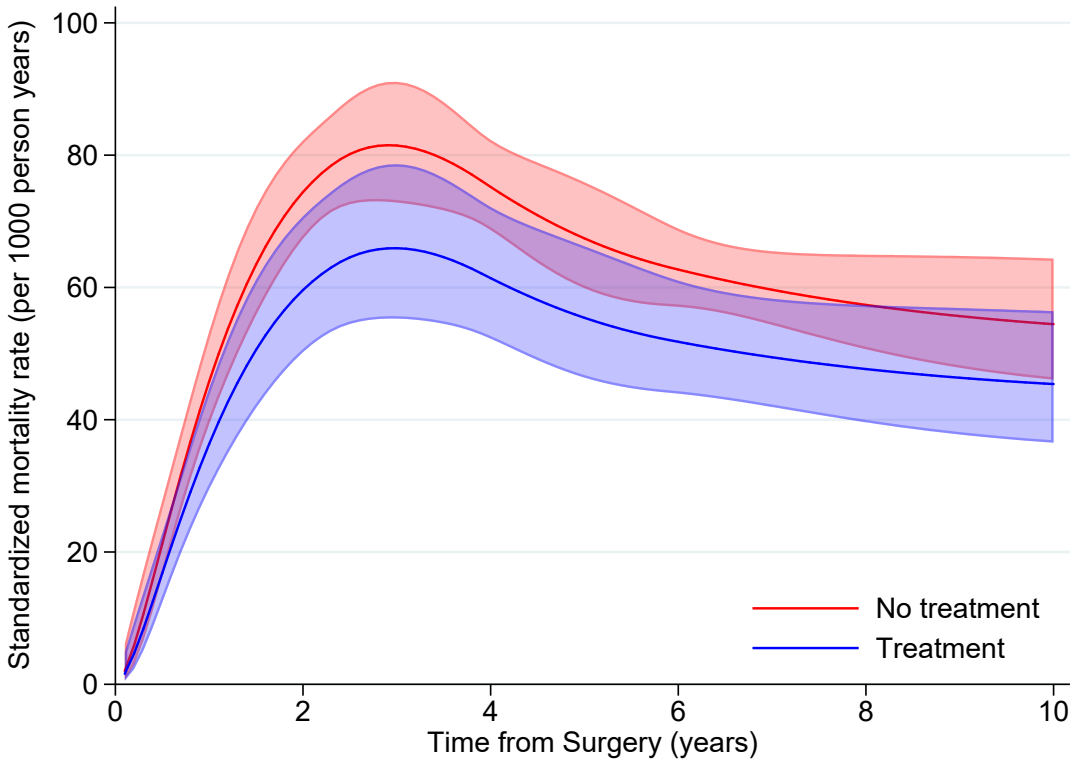
and is estimated by

$$\widehat{h}_s(t) = \frac{\sum_{i=1}^{N} \widehat{S}(t|X = x, Z = z_i) \widehat{h}(t|X = x, Z = z_i)}{\sum_{i=1}^{N} \widehat{S}(t|X = x, Z = z_i)}$$

- Note this is very different from the mean of the hazard functions.
- Can perform contrasts to get marginal hazard ratios (or differences).

Hazard Example

```
. stpm2_standsurv, at1(hormon 0) at2(hormon 1) ci  ///
>    timevar(tt) contrast(ratio) hazard ///
>    atvars(h_hormon0 h_hormon1) contrastvar(hratio) per(1000)
```



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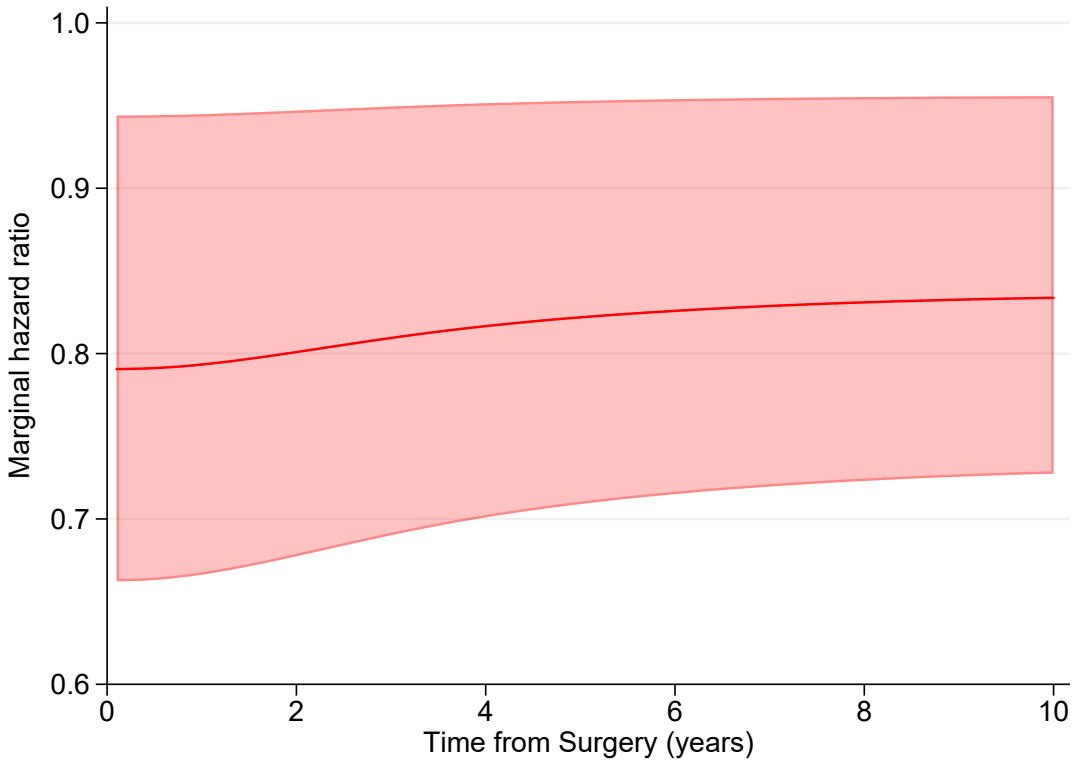
```



Centiles of the marginal survival function

$$E\left[S(t_p|X = x, Z)\right] = \alpha$$

- Estimated through root finding (using Brent's root finder) by solving for t_p,

$$\frac{1}{N}\sum_{i=1}^{N} S(t_p|X = x, Z) - \alpha = 0$$

- Can perform contrasts, e.g. difference in median of marginal survival functions.

Centiles Example

- We can estimate the time at which different proportions have died within the two groups.
- And then take contrasts.

```
. stpm2_standsurv, at1(hormon 0) at2(hormon 1) ci  ///
>    timevar(tt) contrast(difference) centile(5(5)25) ///
>     atvars(c_hormon0 c_hormon1) contrastvar(c_diff)
. list _centvals c_hormon? c_diff* in 1/5, abbrev(14) noobs
```

_centvals	c_hormon0	c_hormon1	c_diff	c_diff_lci	c_diff_uci
5	1.5346497	1.7325535	.1979038	.03711724	.35869036
10	2.2820533	2.6152135	.33316013	.05809522	.60822504
15	2.9915436	3.4869162	.4953726	.07588789	.91485732
20	3.7497893	4.4720429	.72225362	.09968314	1.3448241
25	4.6268882	5.6394187	1.0125305	.13849862	1.8865623

User defined functions

- We may need other transformations of standardized functions.
- Use `userfunction()` option for this.
- For example, in survival studies the attributable fraction is defined as,

$$AF(t) = \frac{E[F(t|X,Z)] - E[F(t|X=0,Z)]}{E[F(t|X,Z)]}$$

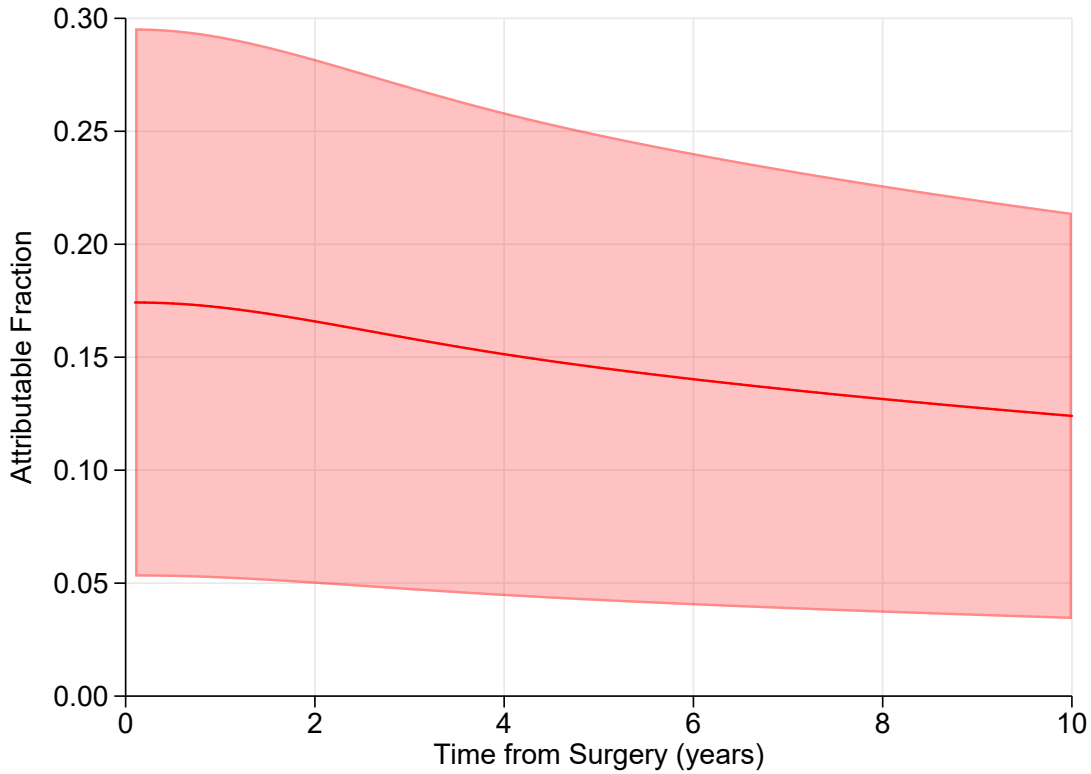
User function

```
mata:
function calcAF(at)
{
    // at2 is F(t|unexposed,Z)
    // at1 is F(t|X,Z)
    return((at[1] - at[2])/at[1])
}
```

- Idea for `userfunction()` option taken from Arvid Sjölanders `stdReg` R-package[6, 7].

Attributable Fraction Example

```
. stpm2_standsurv, at1(.) at2(hormon 1) ci failure  ///
>    timevar(tt) userfunction(calcAF) userfunctionvar(AF)
```



Competing Risks

- Sarwar described how when restructuring data using `stcrprep` you can use standard survival analysis commands to estimate/model cause-specific cumulative incidence functions.
- You can use `stpm2` to directly model cause-specific cumulative incidence functions (see Lambert *et al.* [8, 9]).

```
. stcrprep , events(cause2) every(0.1) wtstpm2 trans(1) ///
     keep(hormon enodes age pr_1 size2 size3)
```

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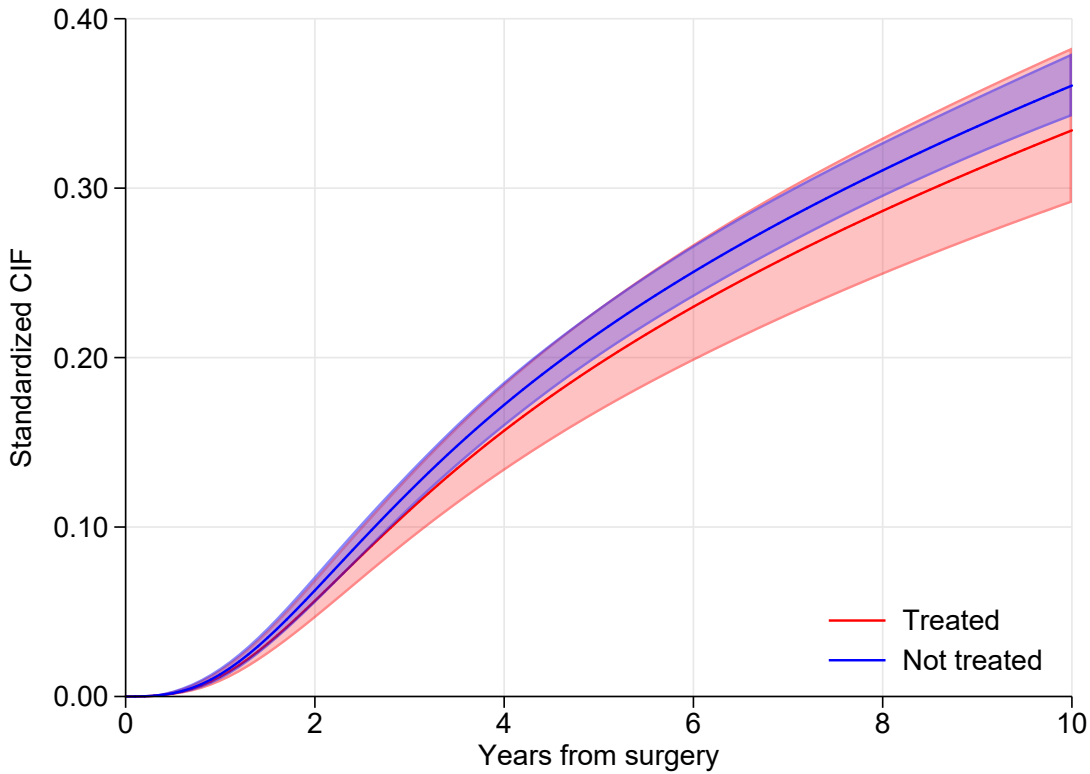
```
. stcrprep , events(cause2) every(0.1) wtstpm2 trans(1) ///
     keep(hormon enodes age pr_1 size2 size3)

. gen event = failcode == cause2
. stset tstop [iw=weight_c], failure(event==1) enter(tstart)
// fit proportional subhazards model
. stpm2 hormon age enodes pr_1, scale(hazard) df(4)
```

- Flexible parametric version of the Fine and Gray model.
- Now `stpm2_standsurv` will estimate standardized cause-specific cumulative incidence functions and contrasts.
- Multiple rows by id: restrict standardization to first row.

Standardized CIFs

```
. bysort pid (_t): gen first = _n==1
. range tt 0 10 101
(16,241 missing values generated)
. stpm2_standsurv if first, at1(hormon 1) at2(hormon 0) timevar(tt) ///
>     ci  failure contrast(difference)
```



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```

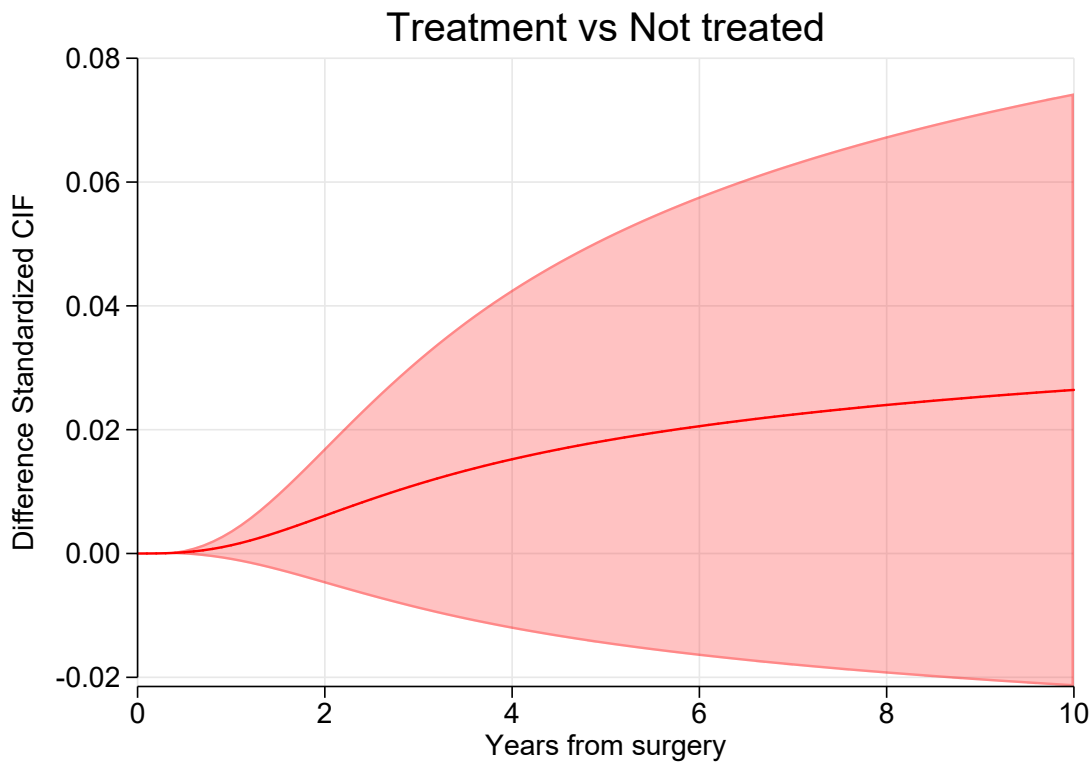

Things I have not had time to mention...

- Standardized relative survival and related measures
  - Standardizing to an external population (`indweights` option).
  - Avoidable deaths
- Fit model with IPW weights and then standardize.
- Mediation analysis (simple).
- Code exactly the same with time-dependent effects.
- Survival model can be as complex as you want, interactions with exposure, confounders and time. As long as we can predict a survival function.

For epidemiologists already fitting survival models (probably Cox) and reporting adjusted hazard ratios, it is not a huge leap to obtain alternative (and potentially more useful) estimates by reporting standardized estimates and contrasts.

References

[1] Vansteelandt S, Keiding N. Invited commentary: G-computation–lost in translation? *Am J Epidemiol* 2011;**173**:739–742.

[2] Rutherford MJ, Crowther MJ, Lambert PC. The use of restricted cubic splines to approximate complex hazard functions in the analysis of time-to-event data: a simulation study. *Journal of Statistical Computation and Simulation* 2015;**85**:777–793.

[3] Lambert PC, Royston P. Further development of flexible parametric models for survival analysis. *The Stata Journal* 2009;**9**:265–290.

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