Estimating marginal effects in competing risks using regression standardisation in large registry studies

Paul C Lambert[1,2], Mark J Rutherford[1], Michael J Crowther[1]

[1]Biostatistics Research Group, Department of Health Sciences, University of Leicester, UK
[2]Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

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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].

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

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

- 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.

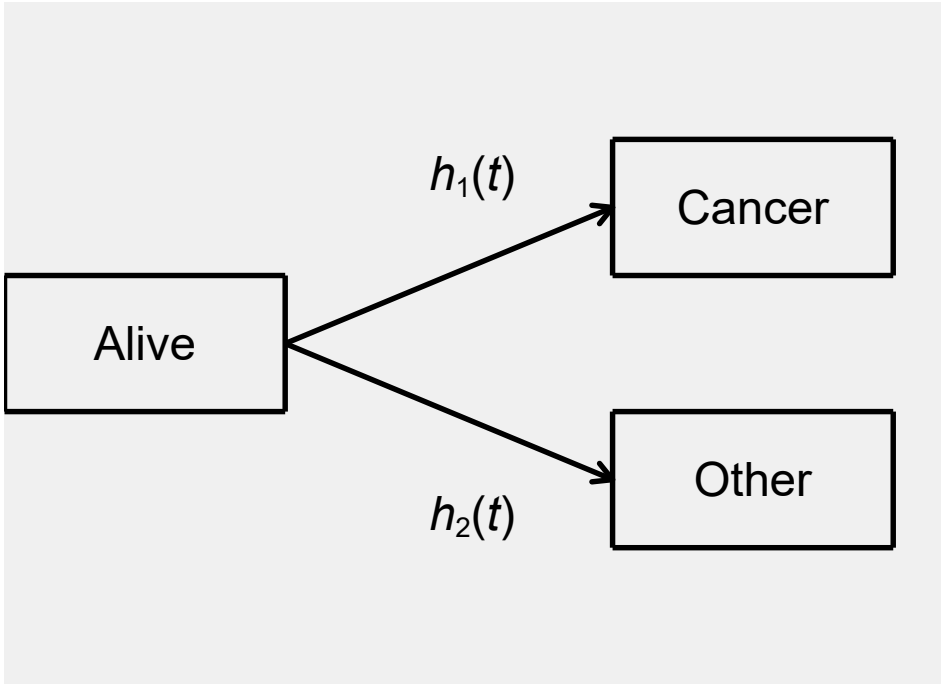
Estimation

- 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.

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

- Use their observed covariate pattern, $Z = z_i$.
- We can standardize to an external (reference) population (Mark Rutherford's talk on Wednesday).

Competing risks



Separate models for each cause, e.g.

$$h_1(t|Z) = h_{0,1}(t)\exp(\beta_1 Z)$$

$$h_2(t|Z) = h_{0,2}(t)\exp(\beta_2 Z)$$

Two types of probability

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

(1) *In the absence of other causes (net)*

$$F_k(t) = 1 - S_k(t) = P(T_k \leq t) = \int_0^t S_k(u)h_k(u)du$$

- We may be interested in cumulative incidence functions.

(2) *In the presence of other causes (crude)*

$$CIF_k(t) = P\left(T \leq t, \text{event} = k\right) = \int_0^t S(u)h_k(u)du$$

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

Description of Example

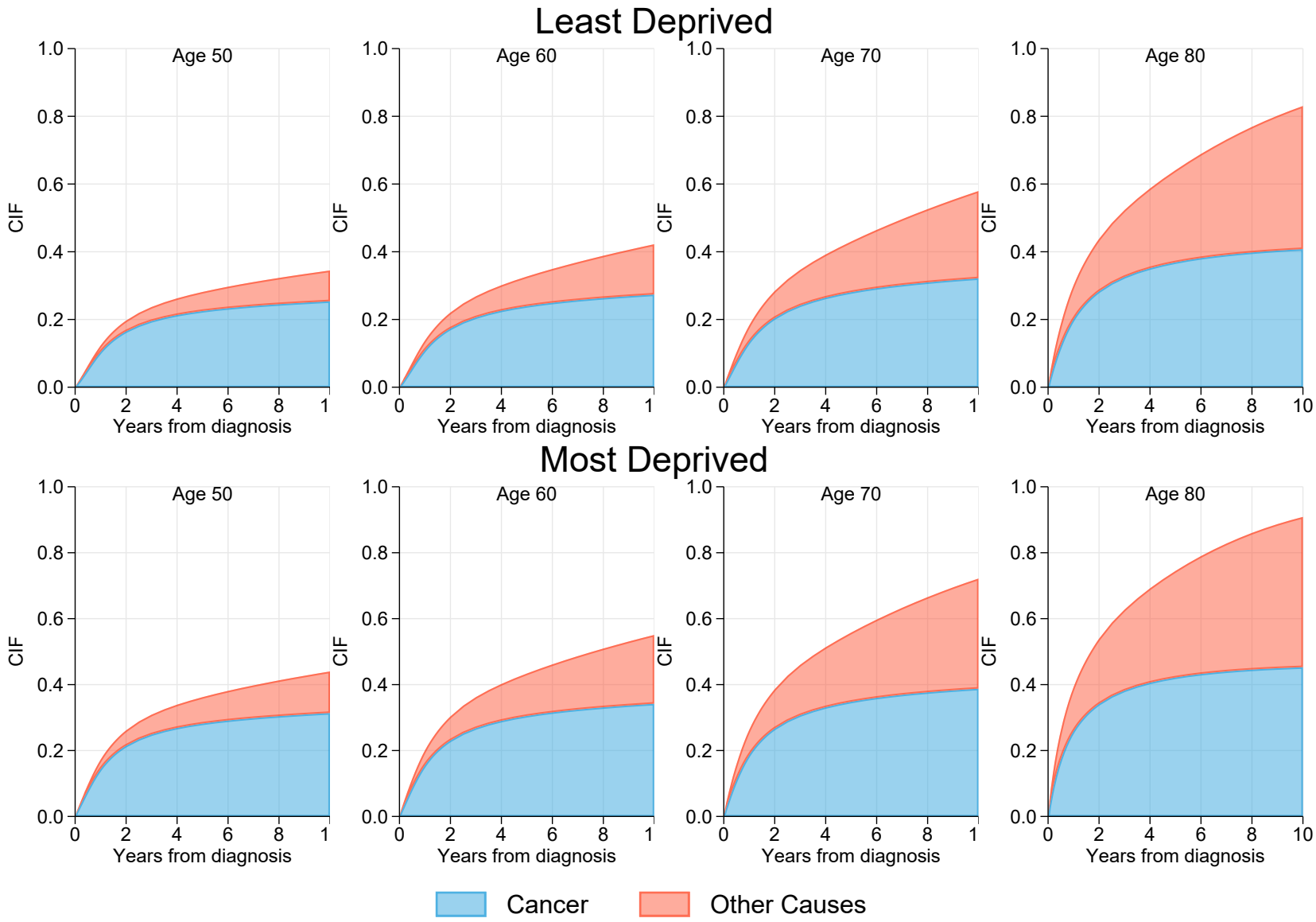
- 102,062 patients with bladder cancer in England (2002-2013).
- Death due to cancer and other causes.
- Covariates age, sex and deprivation in five groups.
- Restrict here to most and least deprived.

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.

- Predictions obtained using Stata `standsurv` command.

Conditional cause-specific CIFs (Females)



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

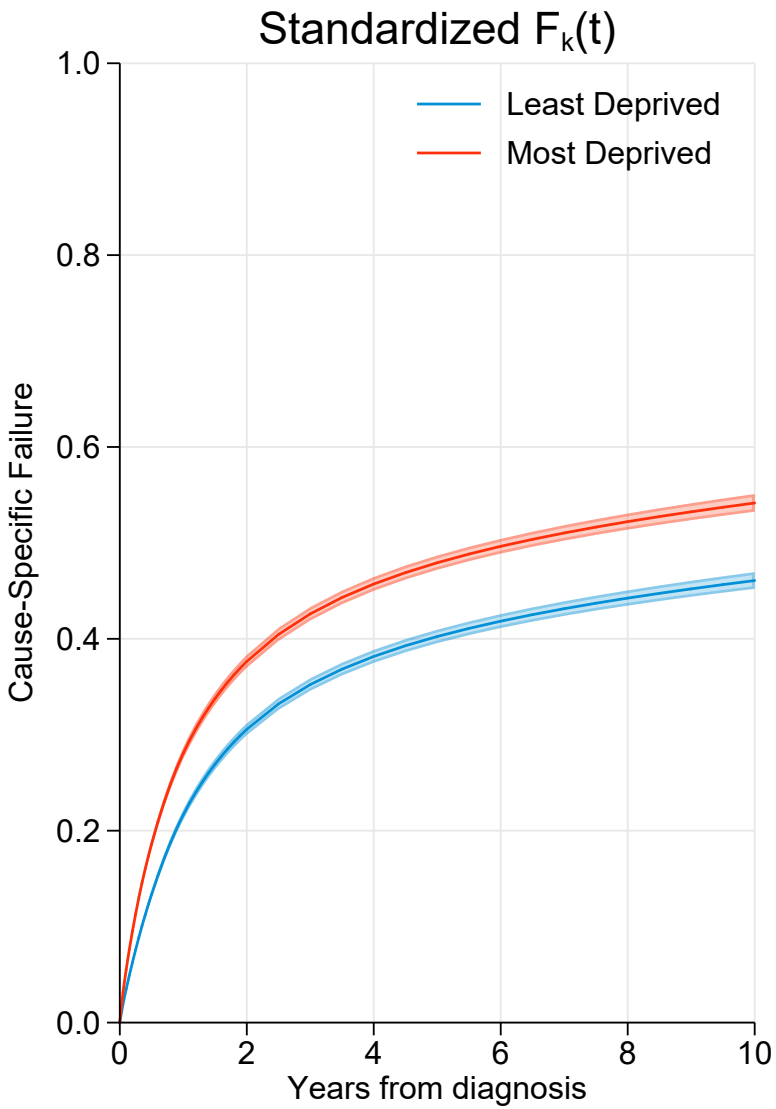
$$F_1(t) = 1 - S_1(t)$$

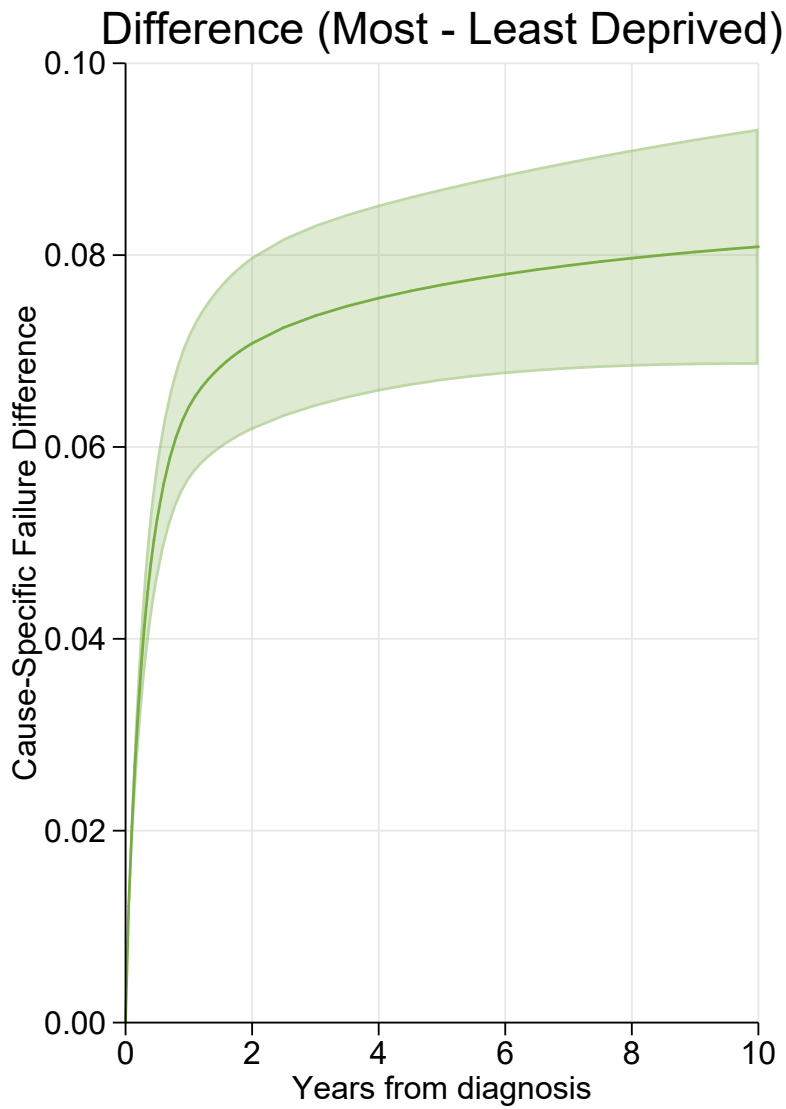
$$E\left[F_1(t)|X = 1, \boldsymbol{Z}\right] - E\left[F_1(t)|X = 0, \boldsymbol{Z}\right]$$

$$\frac{1}{N}\sum_{i=1}^{N} \widehat{F}_1(t|X = 1, \boldsymbol{Z} = z_i) - \frac{1}{N}\sum_{i=1}^{N} \widehat{F}_1(t|X = 0, \boldsymbol{Z} = z_i)$$

- Not a 'real world' probability, but comparisons between exposures where differential other cause mortality is removed is of interest.

Standardized cause-specific Failure $(1 - S_k(t))$





Standardized cause-specific CIF

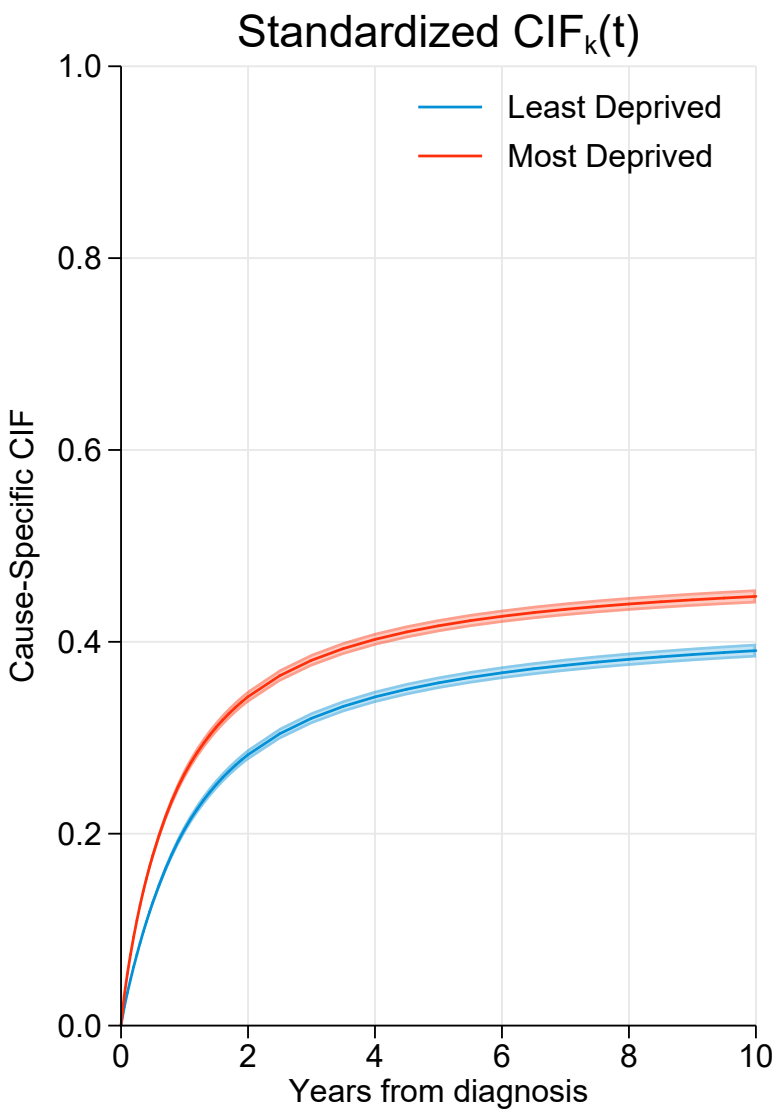
- Probability of death in the presence of other causes.
- We can standardize the cause-specific CIF in the same way.
- These requires combining K different models

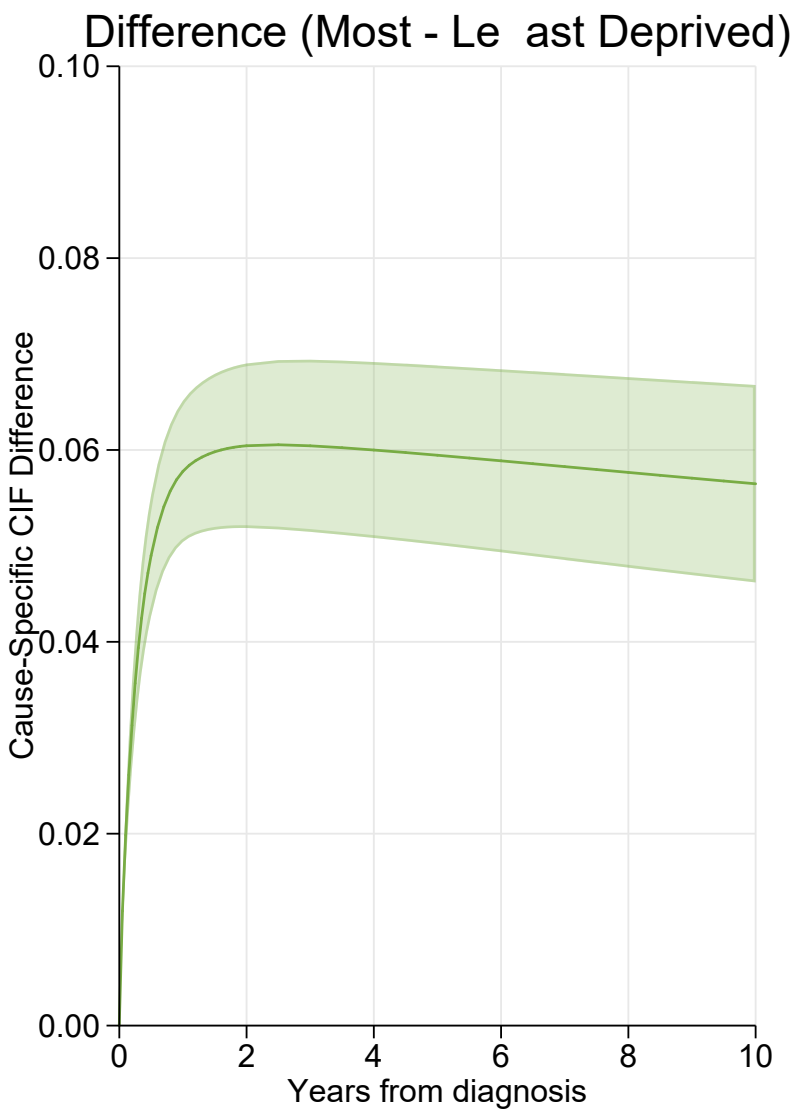
$$E\left[CIF_k(t)|X=x,Z\right]$$

$$\frac{1}{N}\sum_{i=1}^{N}\int_0^t \widehat{S}(u|X=x,\boldsymbol{Z}=z_i)\widehat{h}_k(u|X=x,\boldsymbol{Z}=\underset{\sim}{,}z_i)du$$

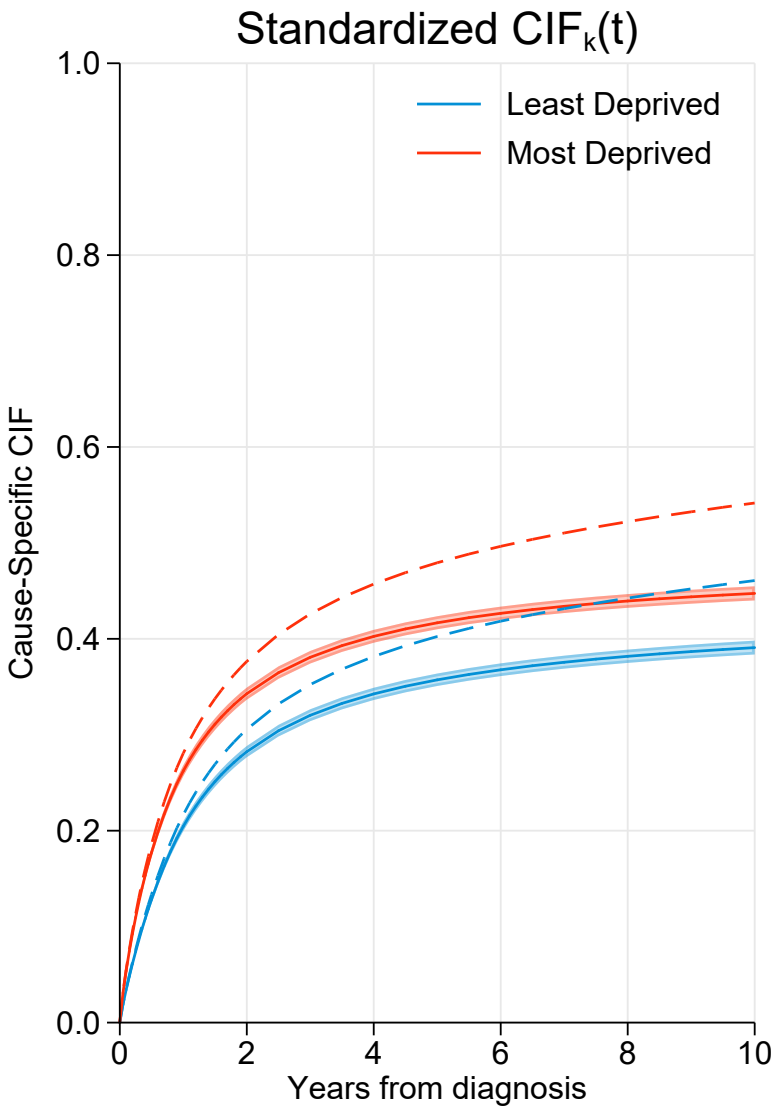
- Calculate for X=1 and X=0 and then obtain contrast.
- Can be interpreted as causal effects under assumptions[3].

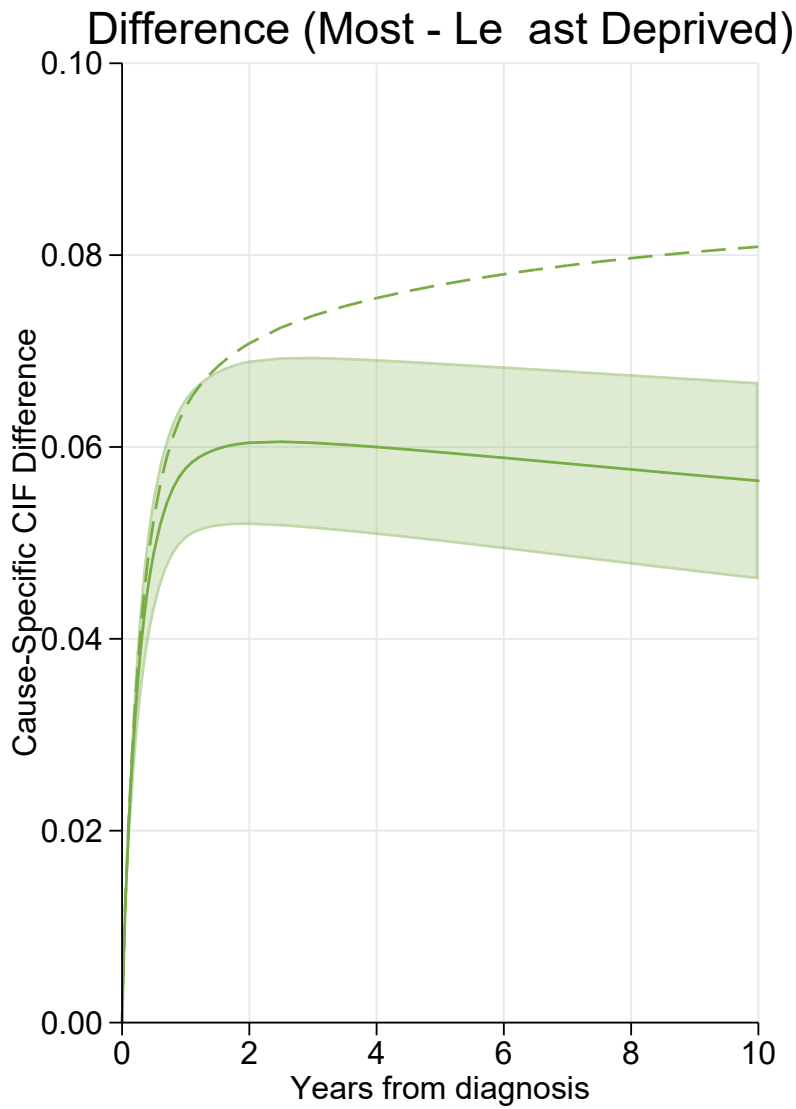
Standardized cause-specific CIF



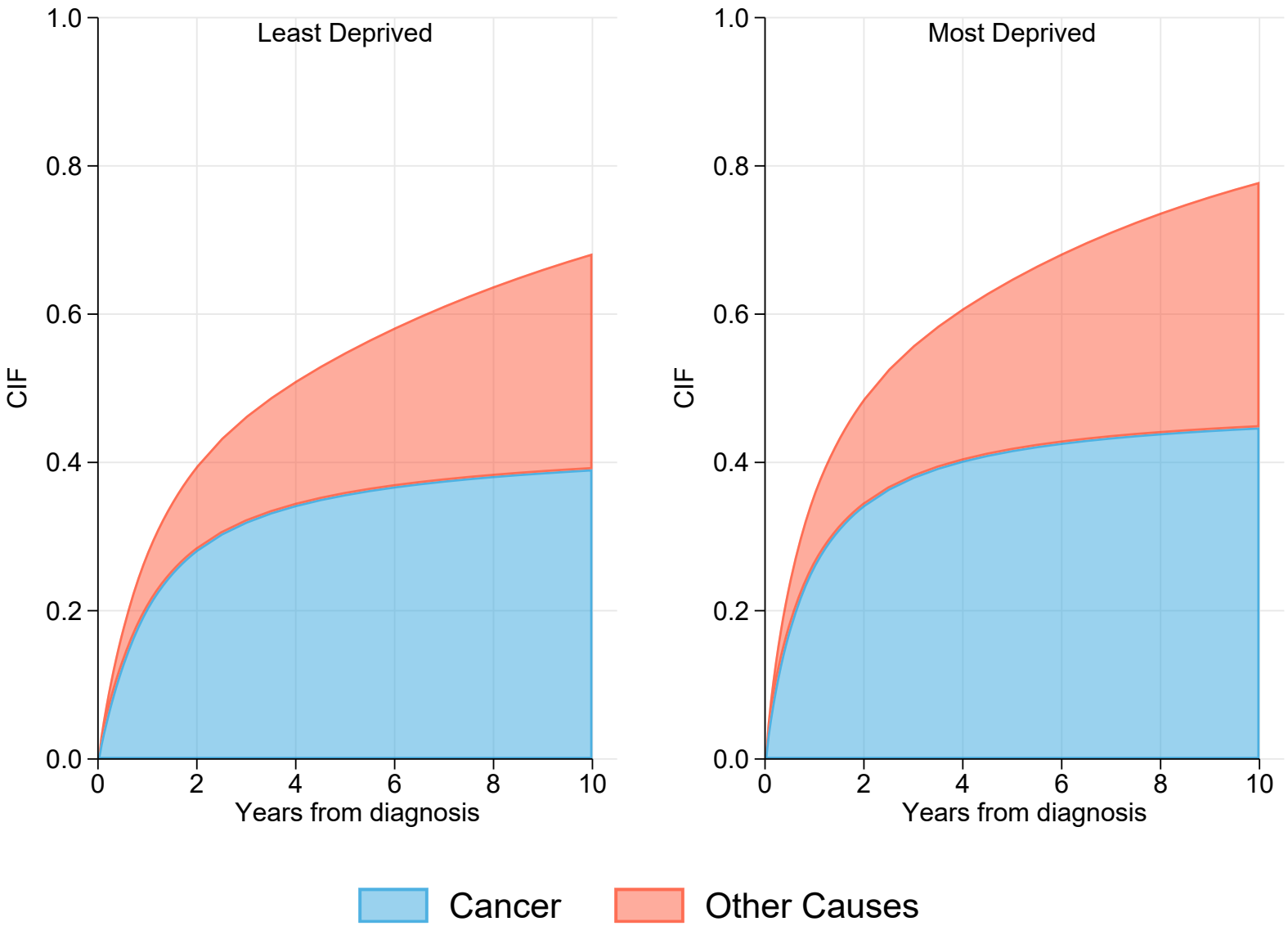


Standardized cause-specific CIF





Stacked standardized cause-specific CIF



Software

- All analysis in Stata.
- `standsurv` works for a many parametric models
  - Exponential, Weibull, Gompertz, LogNormal, LogLogistic
  - Flexible parametric (Splines:log-hazard or log cumulative scales)
- Standard, relative survival and competing risks models
  - Can use different models for different causes.
- 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/

Timings for standardized survival/failure functions

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

N	Weibull		FPM	
	Point Estimate	Confidence Interval	Point Estimate	Confidence Interval
1,000	0.02	0.03	0.03	0.05
10,000	0.04	0.1	0.09	0.1
100,000	0.4	0.7	0.6	0.9
250,000	1.0	1.8	1.6	2.6
500,000	2.0	3.5	2.5	4.5
1,000,000	3.9	4.6	5.5	11.1

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.

N	Weibull		FPM	
	Point Estimate	Confidence Interval	Point Estimate	Confidence Interval
1,000	0.1	0.3	0.3	1.4
10,000	0.2	2.1	2.1	9.5
100,000	13.2	16.8	20.6	104.5
250,000	5.8	48.1	56.1	330.8
500,000	10.1	97.7	117.2	546.2
1,000,000	24.2	159.0	225.6	1128.9

Times in seconds on standard issue University of Leicester laptop.

Further Extensions

- Other competing risk measures.
  - e.g. Expected life years lost (Sarwar Islam Mozumder - Wednesday)
- Various extension in relative survival framework
  - Relative Survival & Mediation Analysis (Betty Syriopoulou- Wednesday)

Summary

- 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.)
- In R use `stdReg`[4] (Cox based) or `Rstpm2` (standardized survival). Some nice recent work in R for competing risks models[5].

References

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

[2] Royston P, Lambert PC. *Flexible parametric survival analysis in Stata: Beyond the Cox model*. Stata Press, 2011.

[3] Young JG, Tchetgen Tchetgen EJ, Hernan MA. The choice to define competing risk events as censoring events and implications for causal inference. *arXiv preprint* 2018;.

[4] Sjölander A. Regression standardization with the R package stdReg. *European Journal of Epidemiology* 2016;**31**:563–574.

[5] Kipourou DK, Charvat H, Rachet B, Belot A. Estimation of the adjusted cause-specific cumulative probability using flexible regression models for the cause-specific hazards. *Statistics in medicine* 2019;.