

Non-proportional hazards in survival analysis

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Objectives

Already known:

- ▶ Fit a Cox's proportional hazards regression in R, interpret results and explain the meaning of a hazard ratio

New:

- ▶ Describe methods to check the assumption of proportional hazards in the Cox's model
- ▶ Describe methods how to deal with non-proportional hazards in the Cox's model

Cox's proportional hazards regression

- ▶ Time to event data; Cox's model typically used for survival analysis in medicine.

- ▶ The Cox's model estimates the hazard λ_i for patient i for time t by multiplying the baseline hazard function by the subject's risk score as

$$\lambda_i(t, \beta, X_i) = \lambda_0(t) r_i(\beta, X_i) = \lambda_0(t) e^{\beta X_i}$$

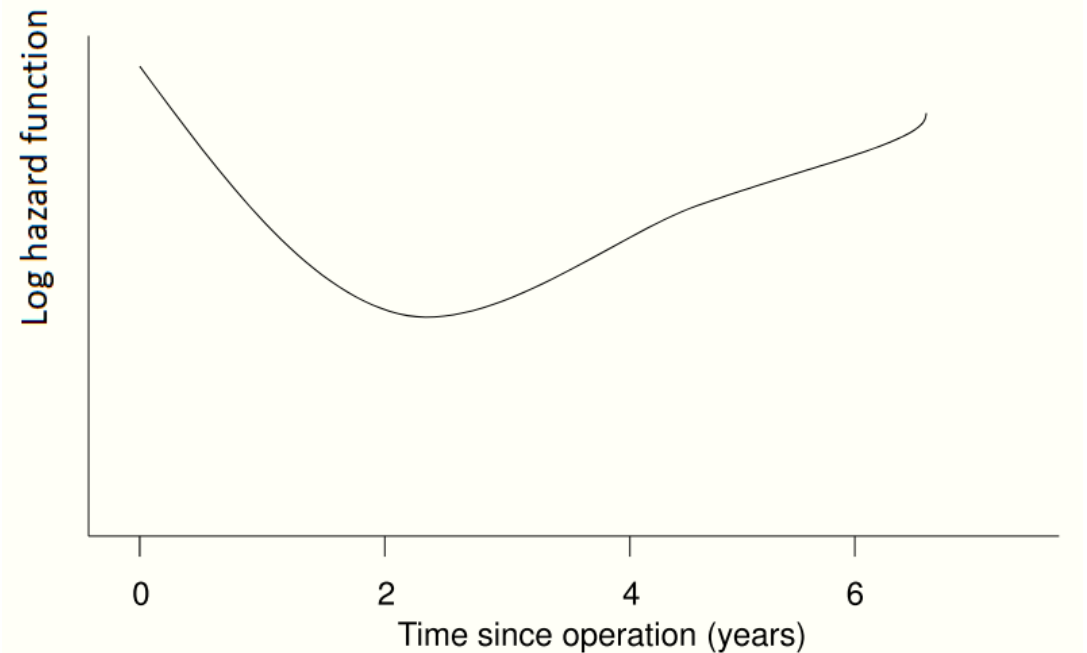
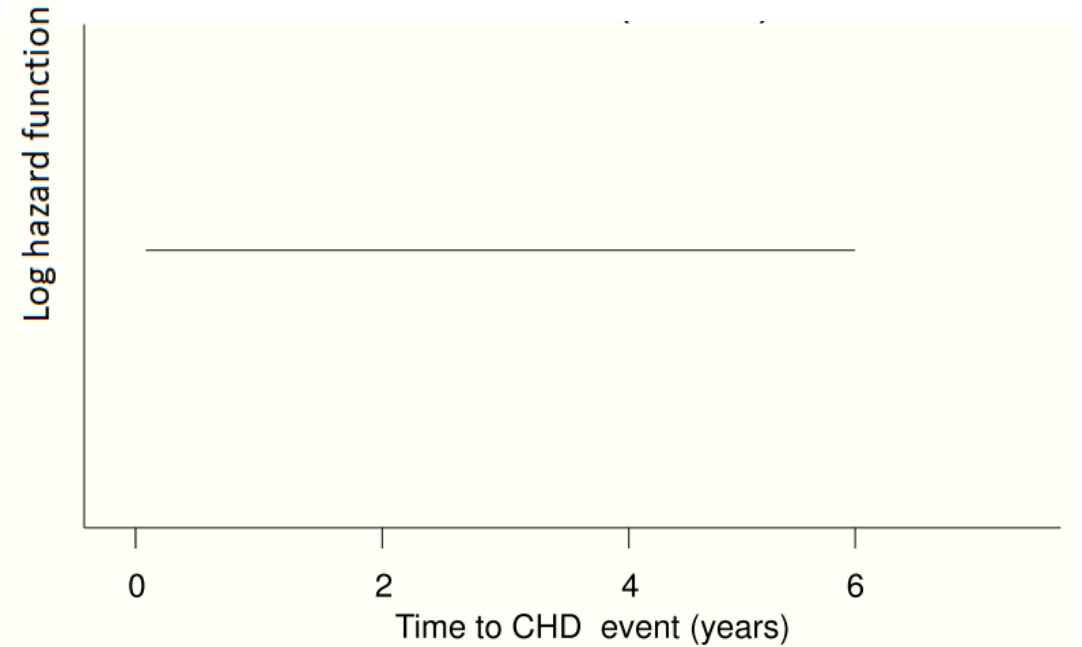
- ▶ Taking a ratio of the hazard functions for two subjects i and j who differ in one risk factor x and not in the other risk factors,

$$\lambda(t, \beta, X) = \frac{\lambda_i(t, \beta, X_i)}{\lambda_j(t, \beta, X_j)} = \frac{\lambda_0(t) e^{\beta x_1}}{\lambda_0(t) e^{\beta x_0}} = \frac{e^{\beta x_1}}{e^{\beta x_0}} = e^{\beta x (x_0 - x_1)}.$$

- ▶ This means that the baseline hazard $\lambda_0(t)$ does not have to be specified and the hazard ratio $e^{\beta x (x_0 - x_1)}$ is constant with respect to time t .

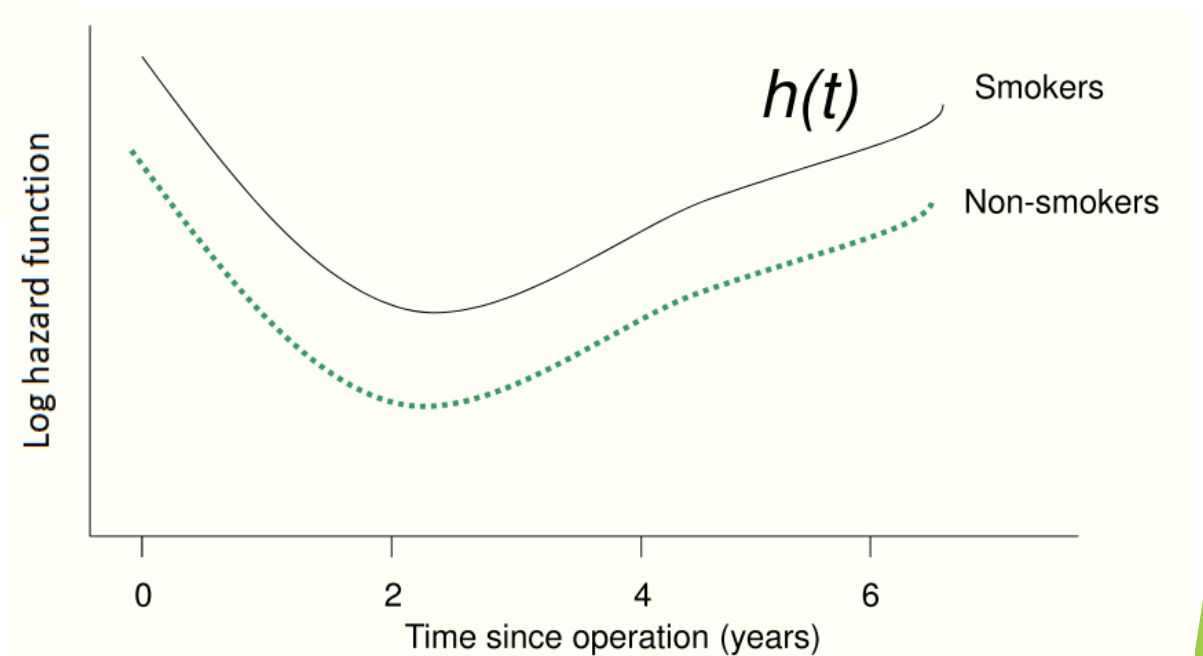
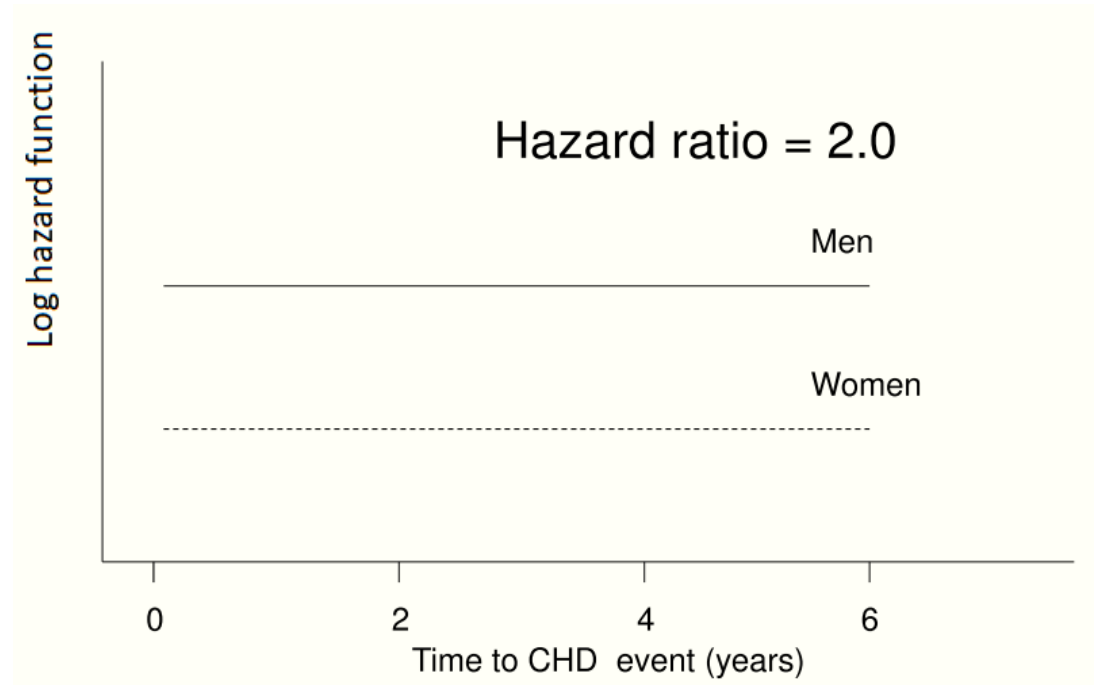
Hazard function

- ▶ Represents instantaneous failure rate at time t
 - ▶ Probability that an individual will experience the event at time t given that the event has not yet occurred.



Hazard ratio

- ▶ Comparison of two hazard functions
- ▶ Cox's model assumes constant hazard ratio over time



Proportional hazards assumption

- ▶ Graphical methods:
 - ▶ Comparison of Kaplan-Meier estimates by group
 - ▶ Plot (minus the log cumulative baseline hazard) for each group against (log survival time)
- ▶ Formal tests:
 - ▶ Grambsch and Therneau's test based on Schoenfeld residuals
 - ▶ Include interaction between covariate and a function of time
 - ▶ Log(time) often used but could be any function of time

The model

- ▶ Data: parkison disease
 - ▶ Sample size of 520 patients
 - ▶ Study period of 17 years
- ▶ Outcome: time to death (266 events)
- ▶ Exposure: new vs standard treatment
- ▶ Covariates:
 - ▶ Sex (baseline male / female)
 - ▶ Age (baseline 25-59 / 60-69 / 70-92)

```
exp(coef) exp(-coef) lower .95 upper .95
treat      1.216      0.8221   0.9549   1.55
```

```
Concordance= 0.527 (se = 0.016 )
```

```
exp(coef) exp(-coef) lower .95 upper .95
treat      1.216      0.8224   0.9545   1.549
sex         1.031      0.9701   0.8099   1.312
```

```
Concordance= 0.522 (se = 0.018 )
```

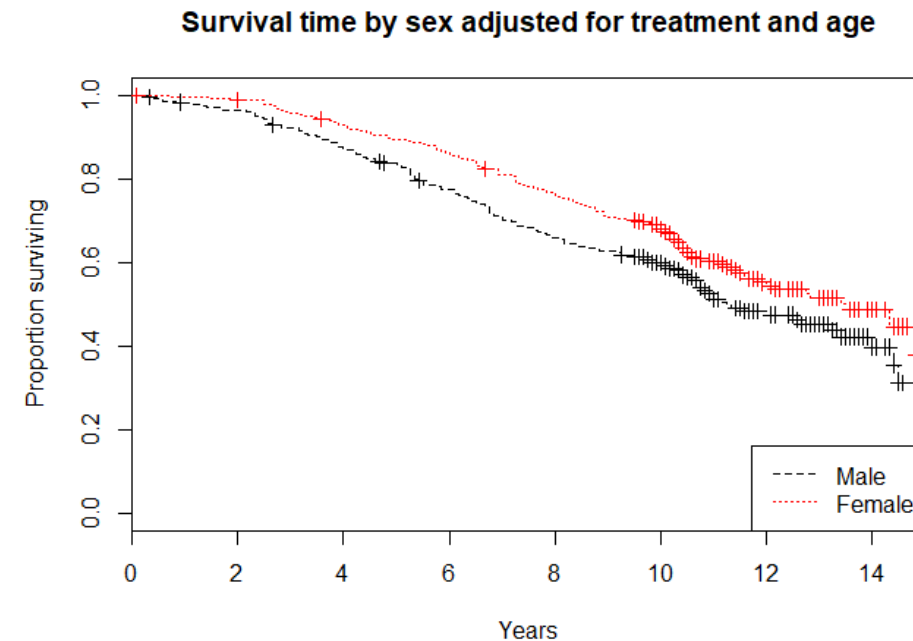
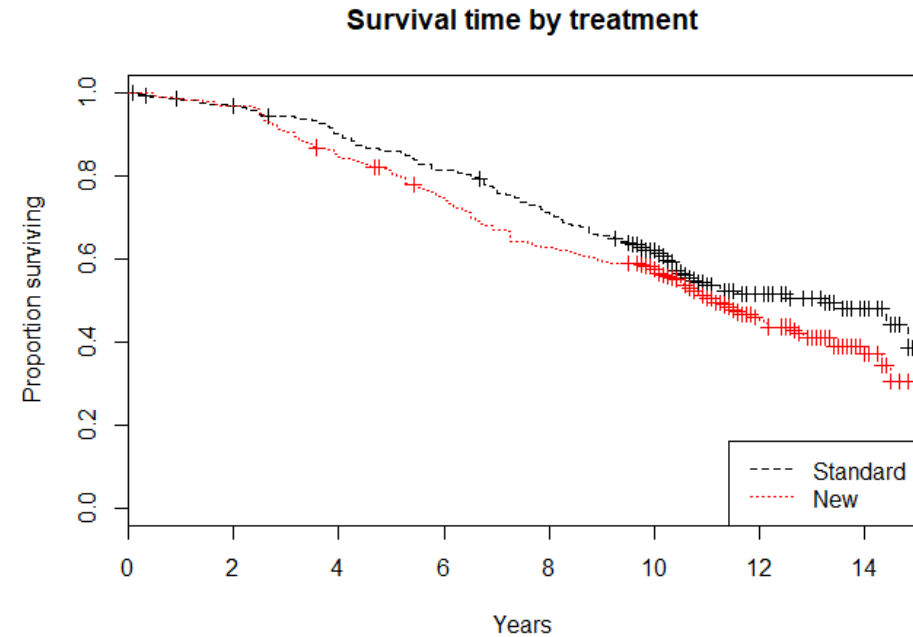
```
exp(coef) exp(-coef) lower .95 upper .95
treat      1.1615      0.8610   0.9101   1.4822
sex         0.7412      1.3491   0.5774   0.9516
agegrp2    3.4363      0.2910   2.3853   4.9504
agegrp3    7.7408      0.1292   5.3363  11.2286
```

```
Concordance= 0.706 (se = 0.019 )
```

Kaplan-Meier plot

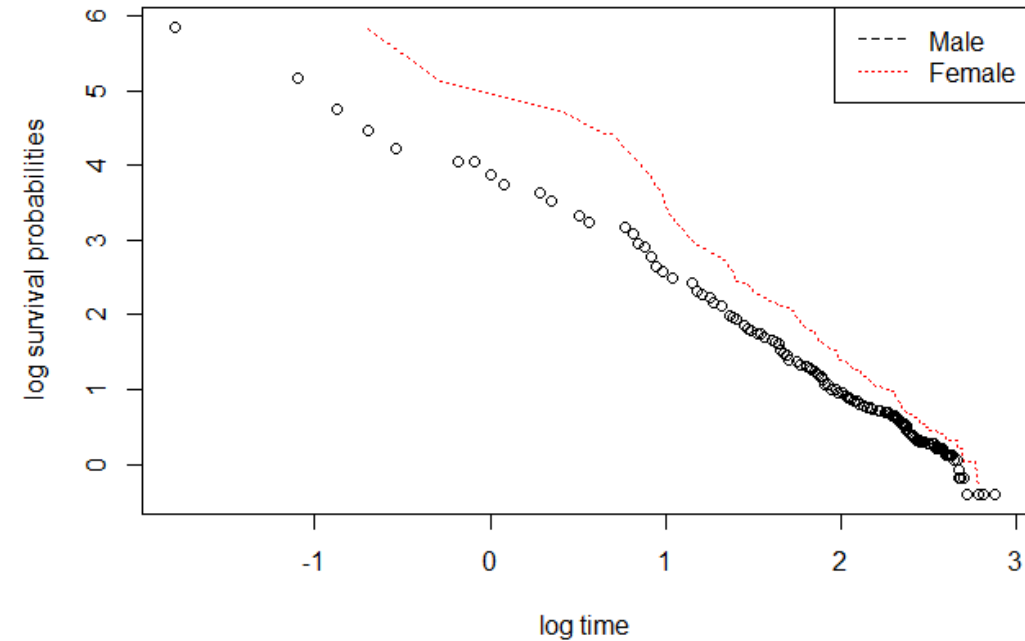
- ▶ Estimated survival function
- ▶ `plot(survfit(Surv(time, event) ~ covariate, data))`
 - ▶ Does not adjust for other covariates!
 - ▶ Crossing of hazard lines indicates non-proportional hazards
 - ▶ Otherwise, can be difficult to judge

Adjusted:
`fit_adj=coxph(Surv(time, event) ~ strata(variable_x) + covariates, data)`
`plot(survfit(fit_adj))`



Survival plot

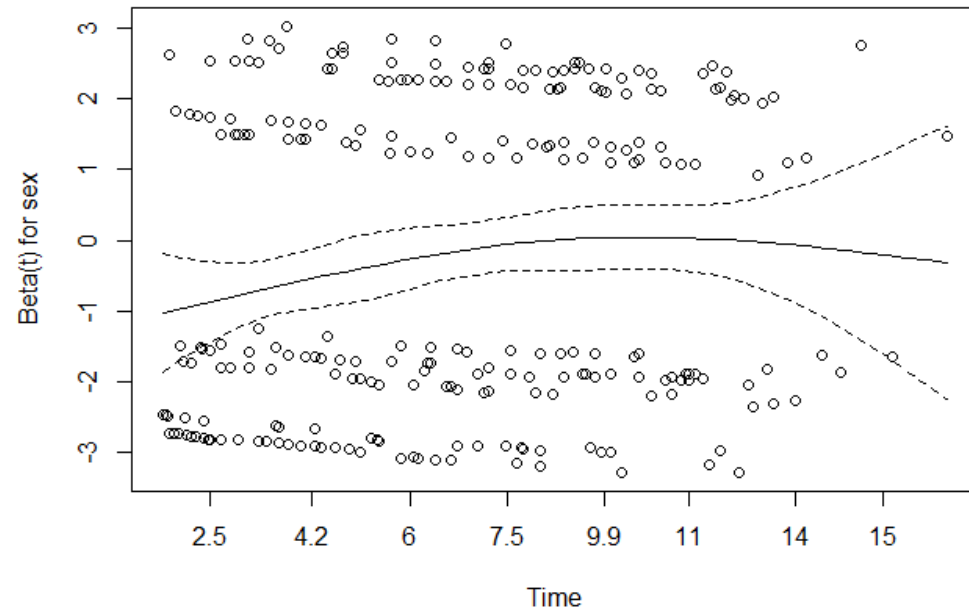
- ▶ `plot(log(basehaz(fit)$time),
-log(basehaz(fit)$hazard))`
 - ▶ Can be unadjusted and adjusted (here adjusted for treatment and age group)
 - ▶ Proportional hazards assumption violated if curves are not parallel to each other



Grambsch and Therneau's test

- ▶ Testing correlation between Schoenfeld residuals and survival time
- ▶ Significant correlation indicates non-proportional hazards
- ▶ `cox.zph(coxph(Surv(time, event) ~ exposure + confounders, data))`
- ▶ `plot(cox.zph(coxph(Surv(time, event) ~ exposure + confounders, data)))`

	rho	chisq	p
treat	-0.06626	1.156192	0.2823
sex	0.13732	5.459043	0.0195
agegrp2	0.00114	0.000344	0.9852
agegrp3	-0.07785	1.658215	0.1978
GLOBAL	NA	8.123383	0.0872



Interaction with log(time)

- ▶ Testing interaction of covariate with time
- ▶ Significant correlation indicates non-proportional hazards
- ▶ `summary(coxph(Surv(time, event) ~ exposure + confounders + exposure*log(time) + confounder*log(time), data))`
- ▶ NB: very sensitive

n= 520, number of events= 266

	coef	exp(coef)	se(coef)	z	Pr(> z)	
treat	4.078e+00	5.905e+01	5.989e-01	6.810	9.76e-12	***
sex	3.109e+00	2.239e+01	4.942e-01	6.290	3.17e-10	***
agegrp2	1.814e+01	7.566e+07	2.184e+00	8.307	< 2e-16	***
agegrp3	1.903e+01	1.843e+08	2.149e+00	8.857	< 2e-16	***
treat:log(time)	-2.054e+00	1.283e-01	2.900e-01	-7.081	1.43e-12	***
sex:log(time)	-1.590e+00	2.040e-01	2.493e-01	-6.377	1.81e-10	***
agegrp2:log(time)	-7.222e+00	7.300e-04	8.989e-01	-8.035	8.88e-16	***
agegrp3:log(time)	-7.597e+00	5.019e-04	8.938e-01	-8.500	< 2e-16	***

Signif. codes:	0	'***'	0.001	'**'	0.01	'*' 0.05 '.' 0.1 ' ' 1

What if the proportional hazards assumption is not met?

- ▶ Stratify the analysis
 - ▶ Fit one model: allow baseline hazards to vary by group but assume covariate effects are the same across strata
 - ▶ There should be no significant interactions between covariate and stratum variable
 - ▶ Fit separate models: allow both baseline hazards and hazard ratios to vary by group
- ▶ Include time-dependent effect
 - ▶ Continuous (could be of any function)
 - ▶ Split follow-up time such that the hazards are proportional within these time bands

Stratified analysis

- ▶ Check for interactions
- ▶ Fit one model
(n=520, events=266)
- ▶ Fit separate models
 - ▶ Male (n=283, events=141)
 - ▶ Female (n=237, events=125)
- ▶ Easy procedure but comes at the cost of no estimate for the effect of the violated variable associated with the outcome

	exp(coef)	exp(-coef)	lower .95	upper .95
treat	1.0395	0.9620	0.4877	2.216
sex	0.7895	1.2666	0.2964	2.103
agegrp2	2.1979	0.4550	0.7261	6.653
agegrp3	23.7526	0.0421	7.8517	71.855
treat:sex	1.0938	0.9142	0.6695	1.787
sex:agegrp2	1.3487	0.7415	0.6348	2.865
sex:agegrp3	0.4752	2.1045	0.2243	1.007

	exp(coef)	exp(-coef)	lower .95	upper .95
treat	1.162	0.8605	0.9099	1.484
agegrp2	3.392	0.2948	2.3549	4.887
agegrp3	7.389	0.1353	5.0865	10.735

	exp(coef)	exp(-coef)	lower .95	upper .95
treat	1.126	0.88817	0.8067	1.571
agegrp2	2.918	0.34272	1.8230	4.670
agegrp3	10.540	0.09488	6.5101	17.063

	exp(coef)	exp(-coef)	lower .95	upper .95
treat	1.258	0.7950	0.8737	1.811
agegrp2	4.005	0.2497	2.2151	7.242
agegrp3	5.335	0.1875	2.9578	9.622

Time-dependent effect

- ▶ Split follow-up time in intervals in which the proportional hazards assumption is no longer violated
- ▶ `data_survsplit=survSplit(data, cut=c(point), end="time", start="time0", event="event")`
- ▶ Create time dependent effect
 - ▶ Here: 0 = male's hazard (baseline), 1=female's hazard 0-9 years, 2=female's hazard 9+ years
- ▶ `summary(coxph(Surv(time0,time, event) ~ treat + t_sex + agegrp,data=data_survsplit))`
- ▶ More time consuming procedure due to creating the most effective time intervals

	exp(coef)	exp(-coef)	lower .95	upper .95
treat	1.1636	0.8594	0.9117	1.4852
t_sex1	0.6887	1.4520	0.5162	0.9188
t_sex2	0.9118	1.0968	0.5678	1.4641
agegrp2	3.4215	0.2923	2.3750	4.9291
agegrp3	7.5985	0.1316	5.2343	11.0305

	rho	chisq	p
treat	-0.06453	1.101428	0.2940
t_sex1	0.09955	2.762015	0.0965
t_sex2	0.02402	0.158846	0.6902
agegrp2	0.00158	0.000657	0.9795
agegrp3	-0.07938	1.708571	0.1912
GLOBAL	NA	6.446771	0.2651

Good practice: questions to ask when specifying a covariate

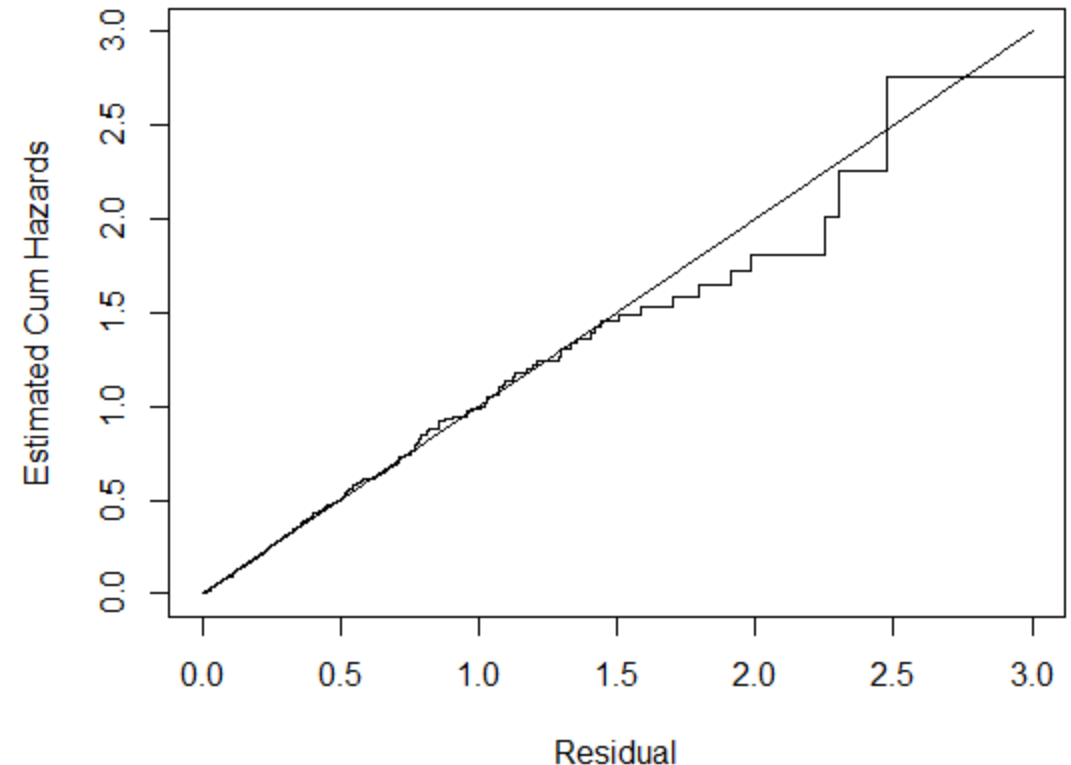
- ▶ What is the reference group?
- ▶ What is clinically relevant? How have other researchers specified a covariate?
- ▶ What is the size of each subgroup and how many events were observed in each subgroup?
- ▶ Are there missing entries? What are the possible reasons for that?
- ▶ Are there time-dependent effects? If yes, what is clinically relevant to know?
 - ▶ E.g. Does the effect need to be known or simply adjusted for? If former: time-dependent effects. If latter: stratification.
- ▶ Are the results biologically plausible? Are they clinically relevant? How are they compared to previous studies?

Extra: residual plots

- ▶ Overall goodness-of-fit: Cox-Snell residuals against cumulative baseline hazard
 - ▶ Good fit: if residuals follow 45-degree line. Deviations could be due to uncertainty in estimated parameters and cumulative baseline hazard, such as with small sample sizes and in the right-hand tail of the distribution, where the baseline hazard is more variable because of the reduced effective sample caused by prior failures and censoring.
- ▶ Influential observations: $dfbeta$'s against sample
 - ▶ Good fit: symmetric pattern around 0. Positive values correspond to individuals that “died too soon” compared to expected survival times. Negative values correspond to individual that “lived too long”. Very large or small values are outliers, which are poorly predicted by the model.
- ▶ Non-linearity for continuous covariates: martingale residuals against continuous covariate
 - ▶ Good fit: linear line. Martingale residuals may present any value in the range $(-\infty, +1)$, where a value near 1 correspond to individuals that “died too soon”, and large negative values correspond to individuals that “lived too long”.

Cox-Snell residuals

- ▶ Overall goodness-of-fit
 - ▶ First survival model with treatment, sex, and age group. Graph indicates good fit.
- ▶ Cox-Snell residuals against cumulative baseline hazard
 - ▶ `mres = resid(fit, type="martingale")`
 - ▶ `csres = event - mres`
 - ▶ `r.surv = survfit(Surv(csres,event)~1, type="fleming-harrington")`
 - ▶ `plot(r.surv$time, -log(r.surv$surv), type='s', lty=1, xlim = c(0,3), ylim = c(0,3), xlab="Residual", ylab="Estimated Cum Hazards")`
`lines(c(0,3),c(0,3))`



Dfbetas

- ▶ Influential observations
 - ▶ First survival model with treatment, sex, and age group. Graph indicates no influential observations.
- ▶ Plot dfbetas against sample
 - ▶ `fit_dfbeta=residuals(fit,type='dfbeta')`
 - ▶ `for (j in 1:ncol(fit1_dfbeta)) {plot (fit1_dfbeta[,j],ylab=names(coef(fit1))[j])abline (h=0,lty=2)}`

