Session 8 - Survival Analysis III

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Welcome and outline - session 8

Learning Objectives:

- Check model assumptions and fit of the Cox model
  - residuals analysis
  - log-minus-log plot
- Fit and interpret multivariate Cox models
  - perform tests for trend
  - predict survival for specific covariate patterns
  - predict survival for adjusted coefficients
- Explain and perform stratified analysis and its use
- Explain time-dependent covariates and when to use them
- Vittinghoff sections 6.2-6.4

Cox proportional hazards model

- Cox proportional hazard regression assesses the relationship between a right-censored, time-to-event outcome and multiple predictors:
  - categorical variables (e.g., treatment groups)
  - continuous variables

$$log(HR(x_i)) = log\frac{h(t|x_i)}{h_0(t)} = \beta_0 + \beta_1 x_{1i} + \beta_2 x_{2i} + ... + \beta_p x_{pi}$$

- $HR(x_i)$ is the hazard of patient i relative to baseline
- $h(t|x_i)$ is the time-dependent hazard function $h(t)$ for patient i
- $h_0(t)$ is the *baseline hazard function*, and is the negative of the slope of the $S_0(t)$, the baseline *survival* function.
- Multiplicative model

Caveats and Assumptions

- Categories with no events
  - can occur when the group is small or its risk is low
  - HRs with respect to such a reference group are infinite
  - hypothesis tests and CIs are difficult / impossible to interpret
- Assumptions of Cox PH model
  - Constant hazard ratio over time (proportional hazards)
  - Linear association between log(HR) and predictors (log-linearity) / multiplicative relationship between hazard and predictors
  - Independence of survival times between individuals in the sample

Residuals analysis

- Residuals are used to investigate the lack of fit of a model to a given subject.
- For Cox regression, there's no easy analog to the usual "observed minus predicted" residual

```
library(pensim); set.seed(1)
mydat <- create.data(nvars=c(1, 1), nsamples=500,
    cors=c(0, 0), associations=c(0.5, 0.5),
    firstonly=c(TRUE, TRUE), censoring=c(0, 8.5))$data
```

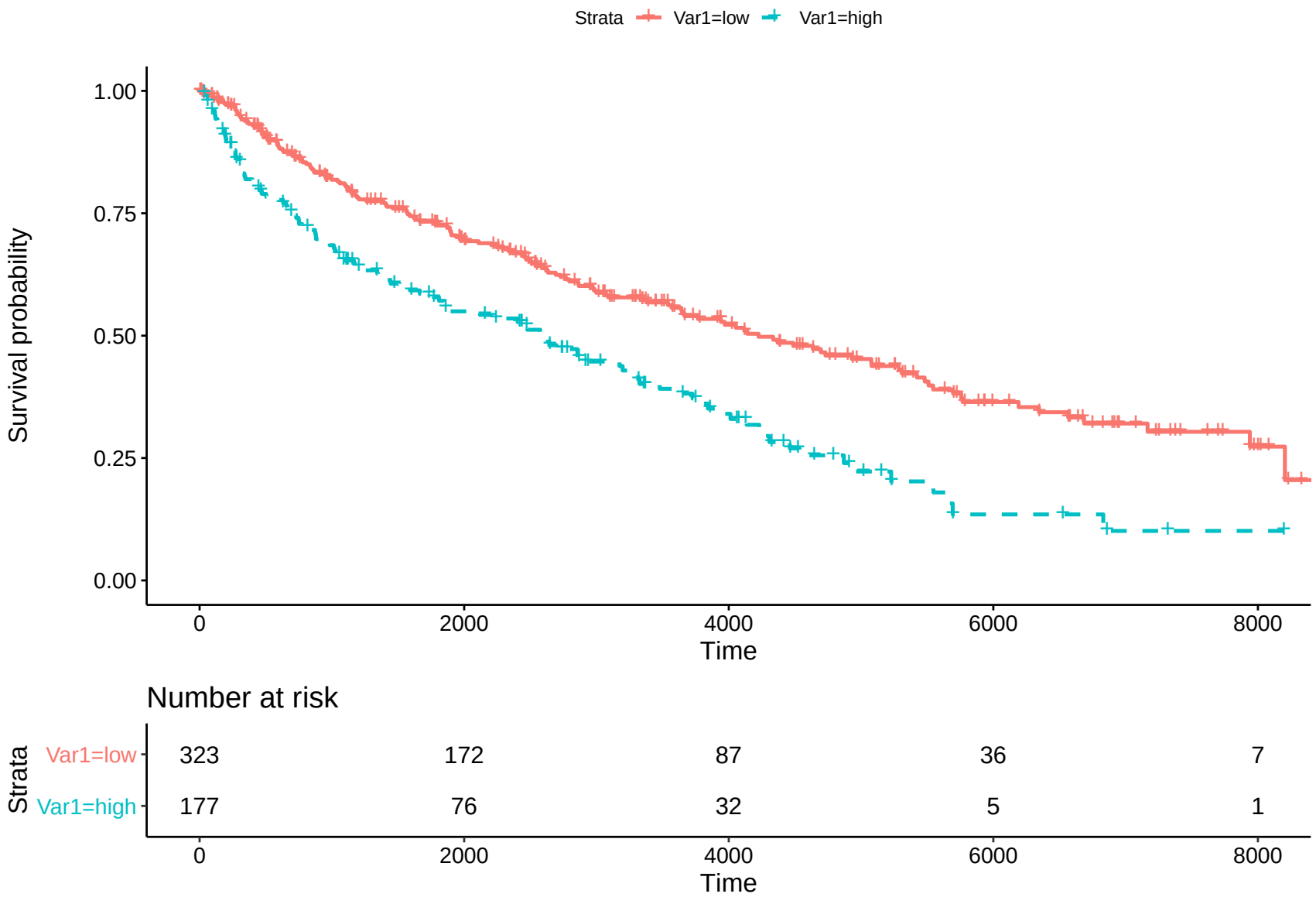
```
## Rename variables of simulated data, and make one variable categorica
colnames(mydat)[1:2] <- c("Var1", "Var2")
mydat$Var1 <- cut(mydat$Var1, breaks=2, labels=c("low", "high"))
mydat$time <- ceiling(mydat$time*1000)
```

Simulated data to test residuals methods

```
summary(mydat)
```

```
##    Var1          Var2                time           cens
##  low :323   Min.   :-2.99695   Min.   :   5   Min.   :0.000
##  high:177   1st Qu.:-0.79008   1st Qu.: 691   1st Qu.:0.000
##             Median :-0.02126   Median :1970   Median :1.000
##             Mean   :-0.04594   Mean   :2529   Mean   :0.526
##             3rd Qu.: 0.68933   3rd Qu.:3874   3rd Qu.:1.000
##             Max.   : 3.05574   Max.   :8481   Max.   :1.000
```

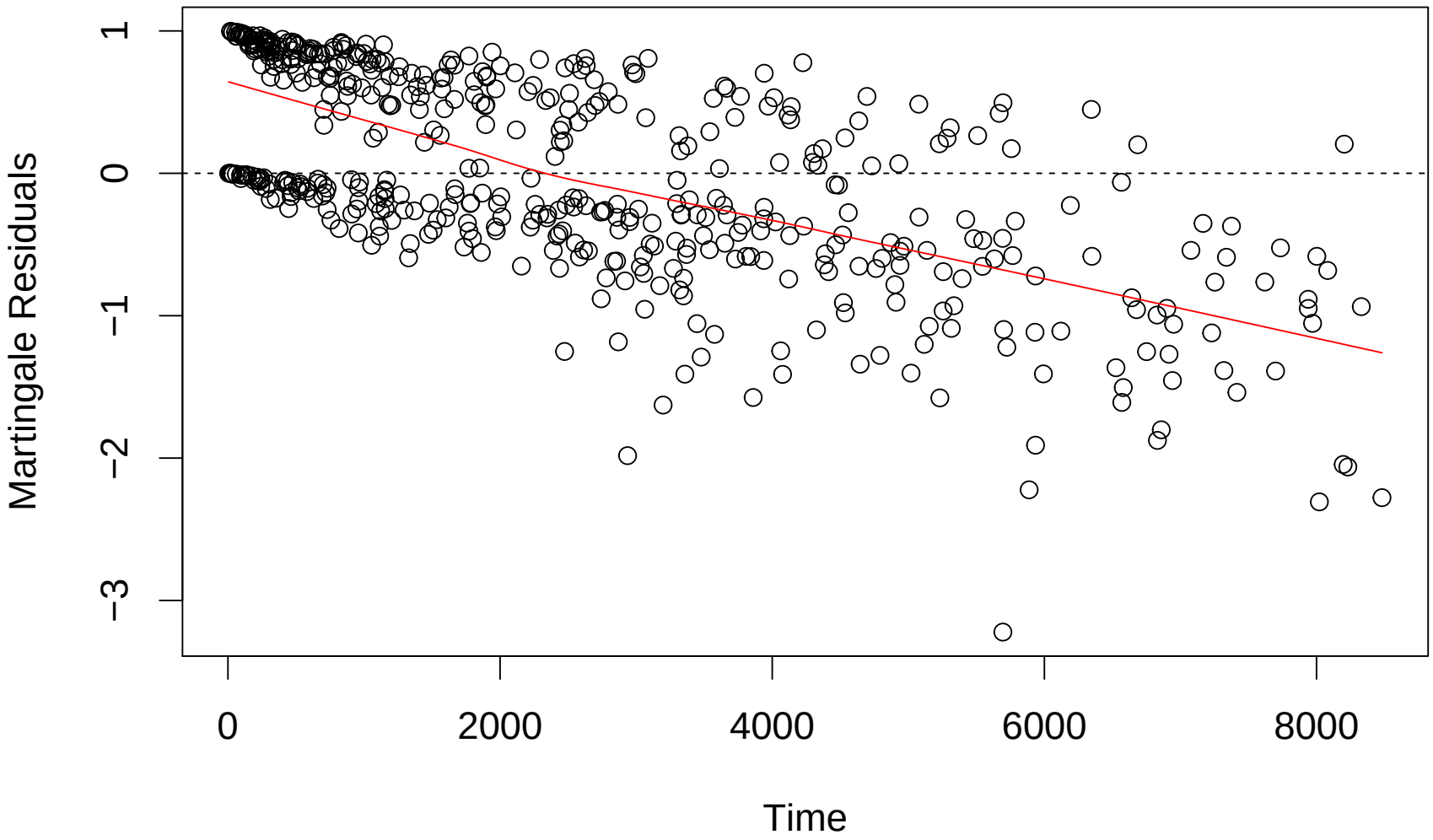
Kaplan-Meier plot of simulated data, stratified by Var1



Martingale residuals

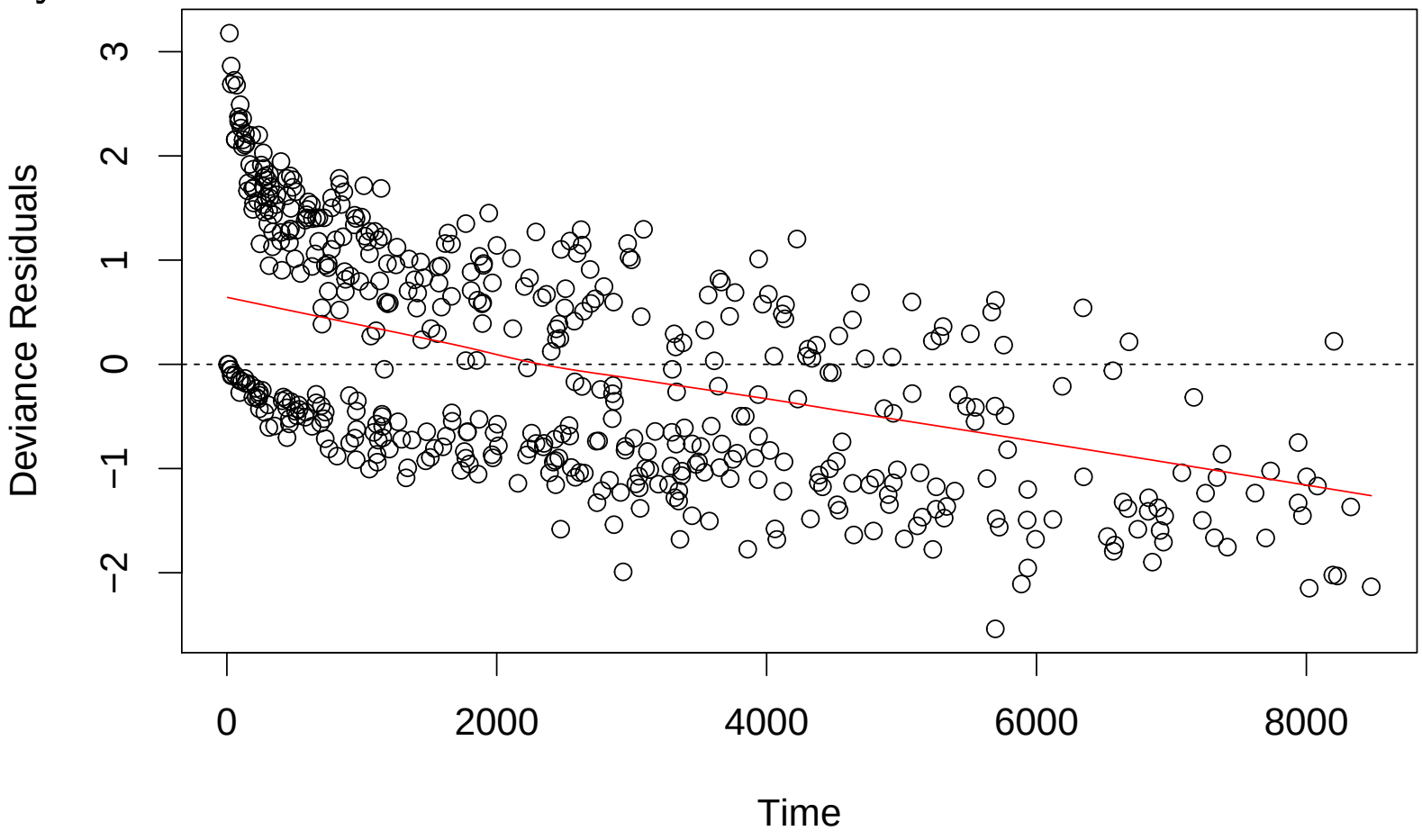
- censoring variable c_i (1 if event, 0 if censored) minus the estimated cumulative hazard function $H(t_i, X_i, \beta_i)$ (1 - survival function)
  - E.g., for a subject censored at 1 year ($c_i = 0$), whose predicted cumulative hazard at 1 year was 30%, Martingale = 0 - 0.30 = -0.30.
  - E.g. for a subject who had an event at 6 months, and whose predicted cumulative hazard at 6 months was 80%, Margingale = 1 - 0.8 = 0.2.
- Problem: not symmetrically distributed, even when model fits the data well

Martingale residuals in simulated data



Deviance residuals in simulated data

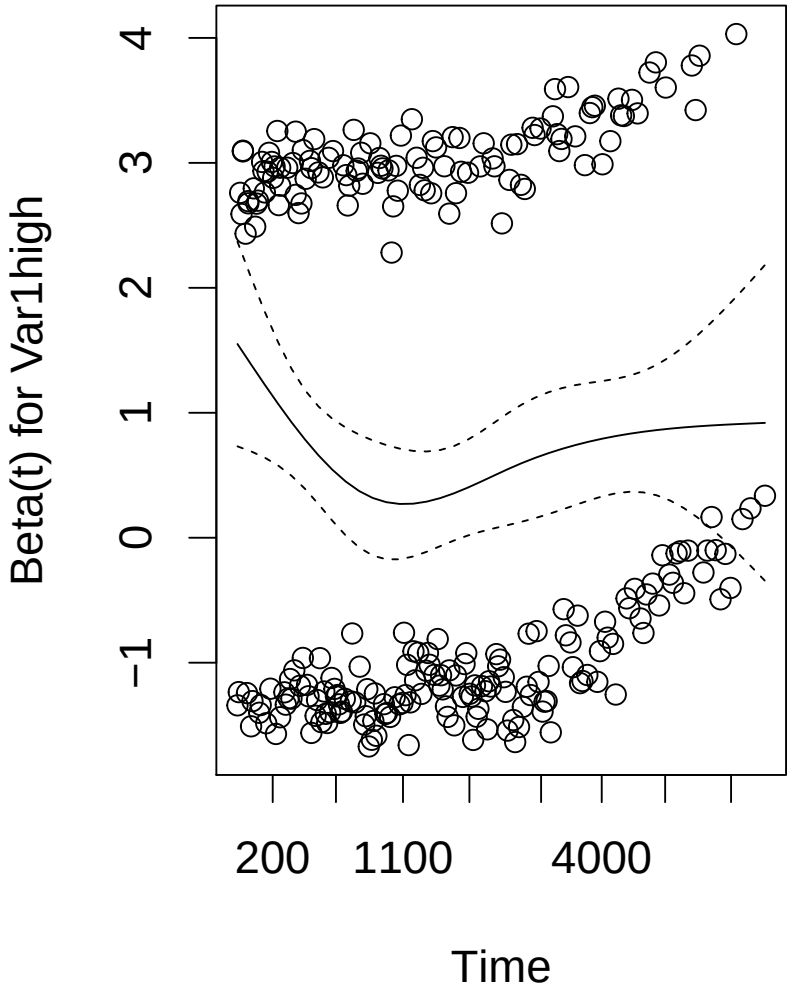
- Deviance residuals are scaled Martingale residuals
- Should be more symmetrically distributed about zero?
- Observations with large deviance residuals are poorly predicted by the model

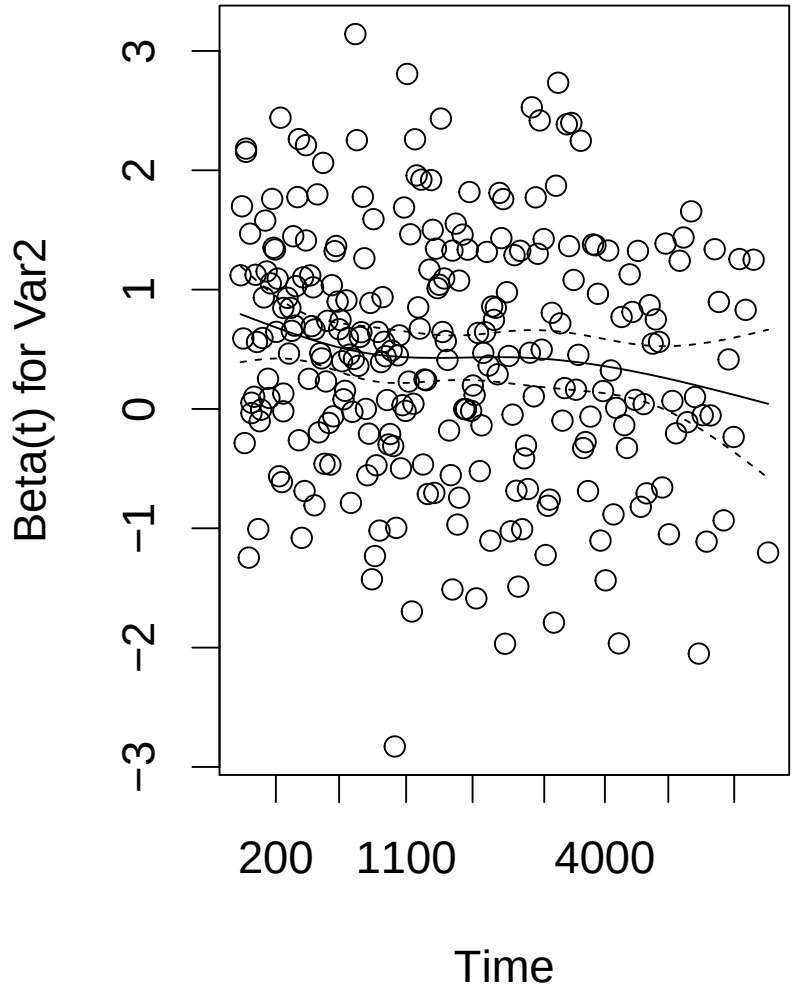


Schoenfeld residuals

- technical definition: contribution of a covariate at each event time to the partial derivative of the log-likelihood
- intuitive interpretation: the observed minus the expected values of the covariates at each event time.
- a random (unsystematic) pattern across event times gives evidence the covariate effect is not changing with respect to time
- If it is systematic, it suggests that as time passes, the covariate effect is changing.

Schoenfeld residuals for simulated data



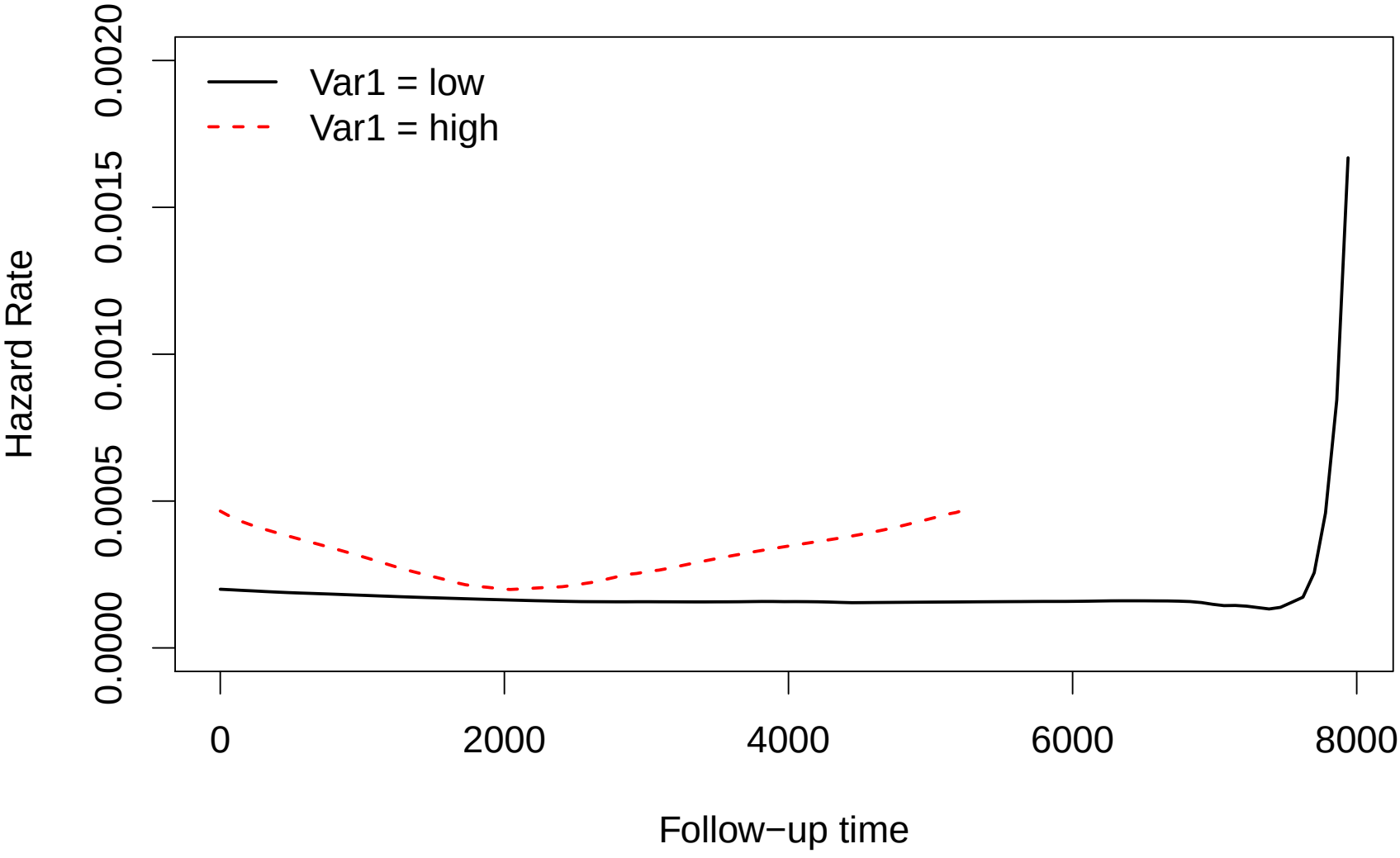


Schoenfeld test for proportional hazards

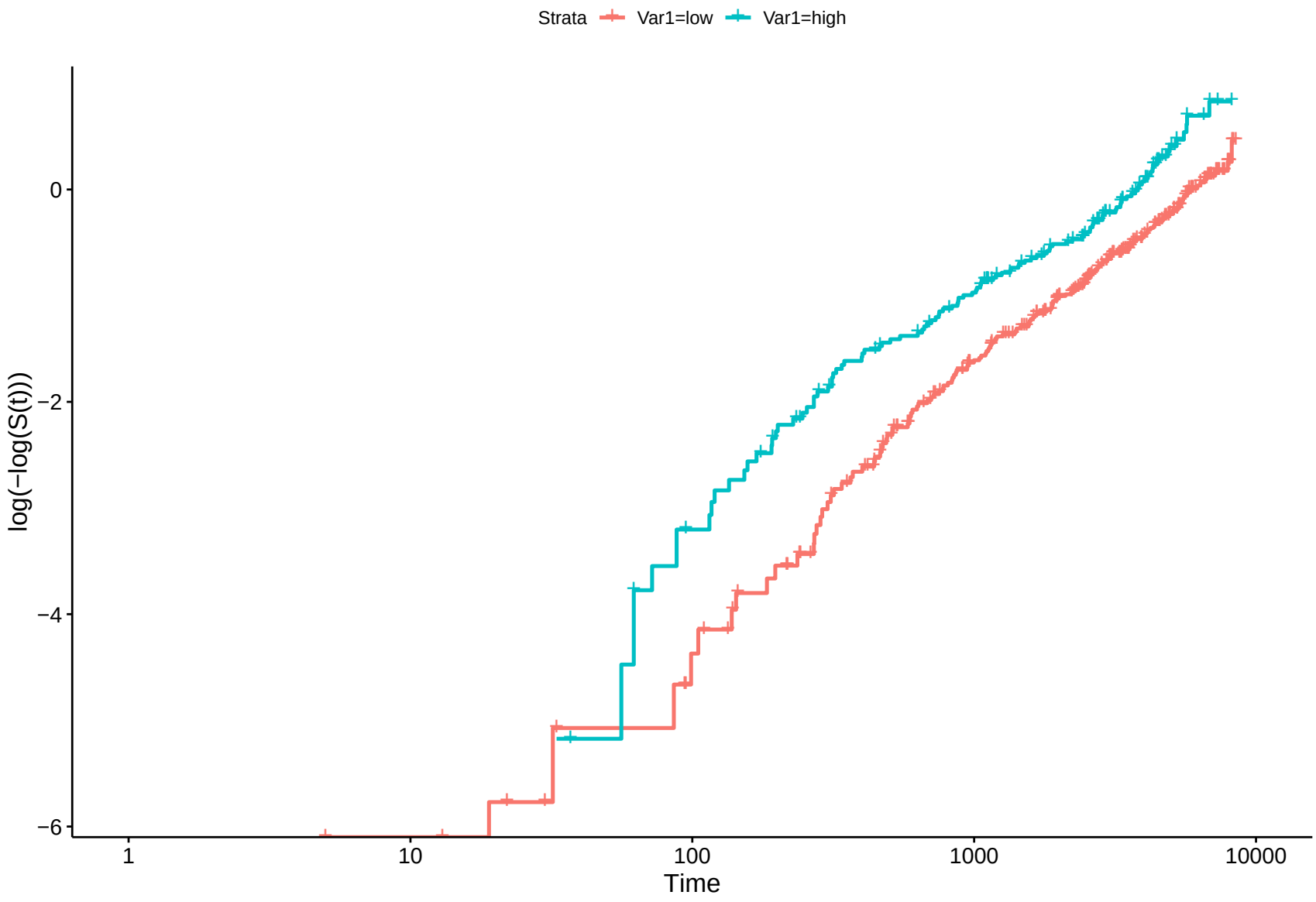
- Tests correlation between scaled Schoenfeld residuals and time
- Equivalent to fitting a simple linear regression model with time as the predictor and residuals as the outcome
- Parametric analog of smoothing the residuals against time using LOWESS
- If the hazard ratio is constant, correlation should be zero.
  - Positive values of the correlation suggest that the log-hazard ratio increases with time.

```
##                rho  chisq      p
## Var1high -0.0185 0.0903 0.7638
## Var2     -0.1315 4.6360 0.0313
## GLOBAL         NA 4.6438 0.0981
```

The hazard function h(t), stratified by Var1



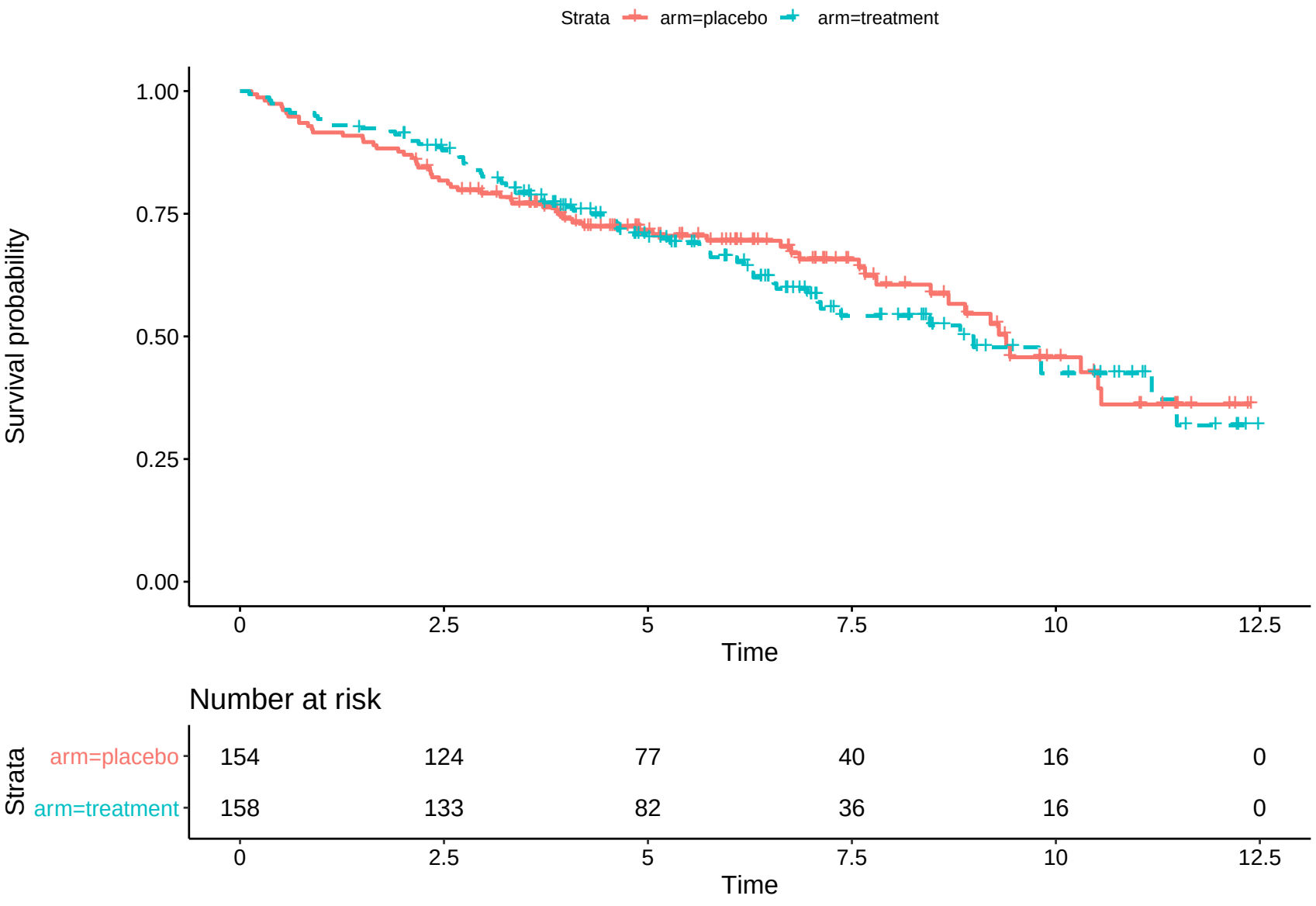
Log-minus-log plot



Example: Primary Biliary Cirrhosis (PBC)

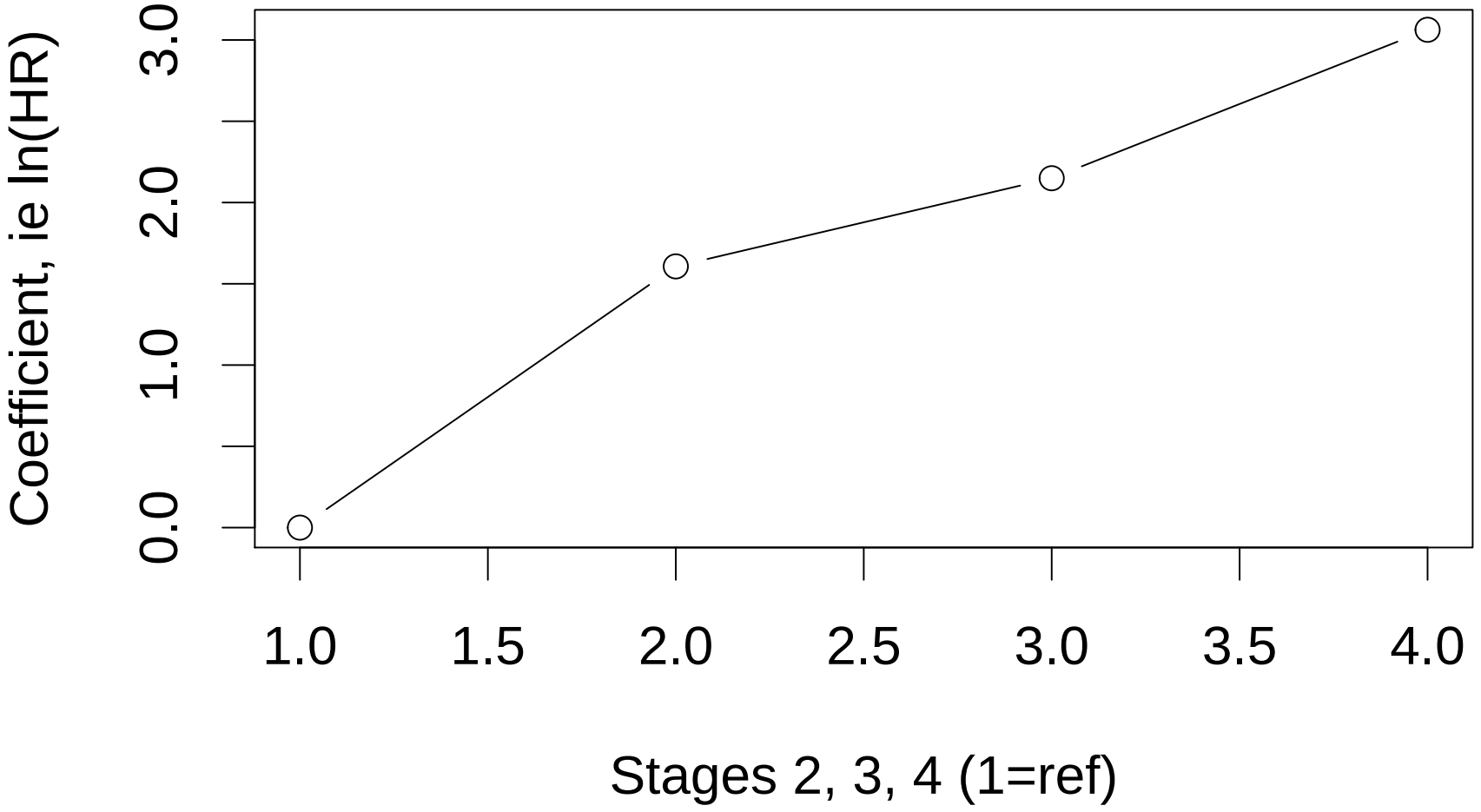
- Mayo Clinic trial in primary biliary cirrhosis (PBC) of the liver conducted between 1974 and 1984, n=424 patients.
- randomized placebo controlled trial of the drug D-penicillamine.
  - 312 cases from RCT, plus additional 112 not from RCT.
- Primary outcome is (censored) time to death

Kaplan-Meier plot of treatment and placebo arms



Tests for trend

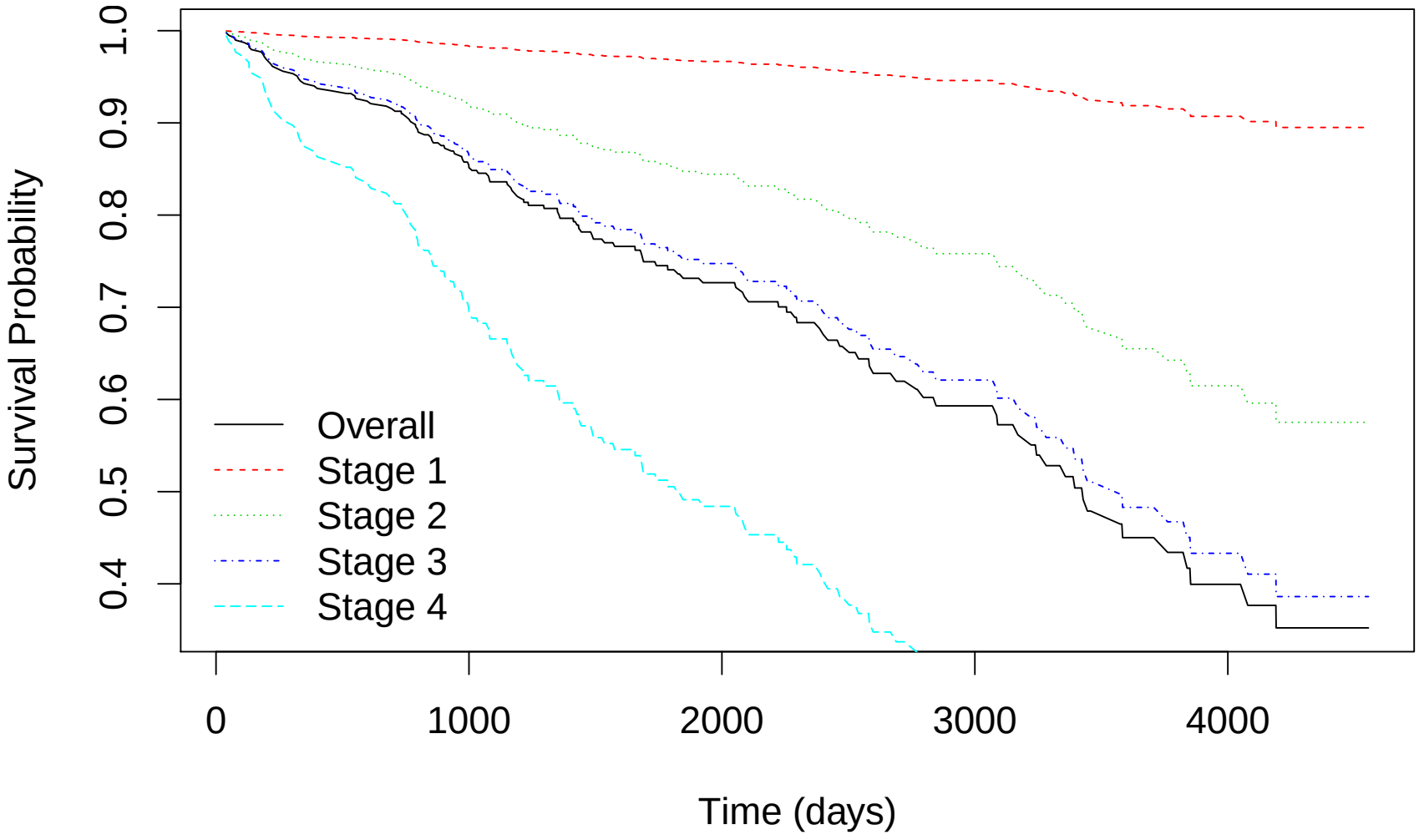
- For ordinal variables like stage (1, 2, 3, 4)
  - This is a test for linear / quadratic / cubic relationship between coefficients and their index
  - Model selection by LRT or Wald Test



Predicted survival for specific covariate patterns

- The Cox model is a *relative* risk model
  - only predicts relative risks between pairs of subjects
- Key is to calculate the overall $S(t)$, then multiply it by the relative hazard for the specific covariate pattern.
- In this example we plot the baseline survival for all stages together, then for stages 1-4 separately.

Predicted survival for specific covariate patterns



Multivariate regression

- Same coding and objectives as for `lm()` and `glm()`
  - controlling for confounding
  - testing for mediation
  - testing for interaction

Multivariate regression

```
fit <- coxph(Surv(time, os) ~ age + sex + edema
                + stage + arm, data=pbc.os)
summary(fit)
```

```
## Call:
## coxph(formula = Surv(time, os) ~ age + sex + edema + stage +
##     arm, data = pbc.os)
##
##   n= 312, number of events= 125
##
##                    coef exp(coef)  se(coef)     z Pr(>|z|)
## age            0.027618  1.028003  0.009362 2.950  0.00318 **
## sexm           0.317540  1.373744  0.248839 1.276  0.20193
## edema0.5       0.538715  1.713804  0.275287 1.957  0.05036 .
## edema1         2.080422  8.007845  0.276959 7.512 5.84e-14 ***
## stage2         1.535263  4.642546  1.034854 1.484  0.13793
## stage3         1.998217  7.375893  1.016097 1.967  0.04923 *
## stage4         2.666263 14.386101  1.016234 2.624  0.00870 **
## armtreatment   0.057946  1.059658  0.189200 0.306  0.75940
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
```

Predicted survival for adjusted coefficients

- Can create Kaplan-Meier curves for crude or unadjusted coefficients
  - Section 6.3.2.3 in Vittinghoff
- Idea is to estimate hazard ratio in an unadjusted model:

```
unadjfit <- coxph(Surv(time, os) ~ stage, data=pbc.os)
coef(unadjfit)
```

```
##   stage2   stage3   stage4
## 1.607014 2.149500 3.062775
```

Predicted survival for adjusted coefficients

- and in an adjusted model:

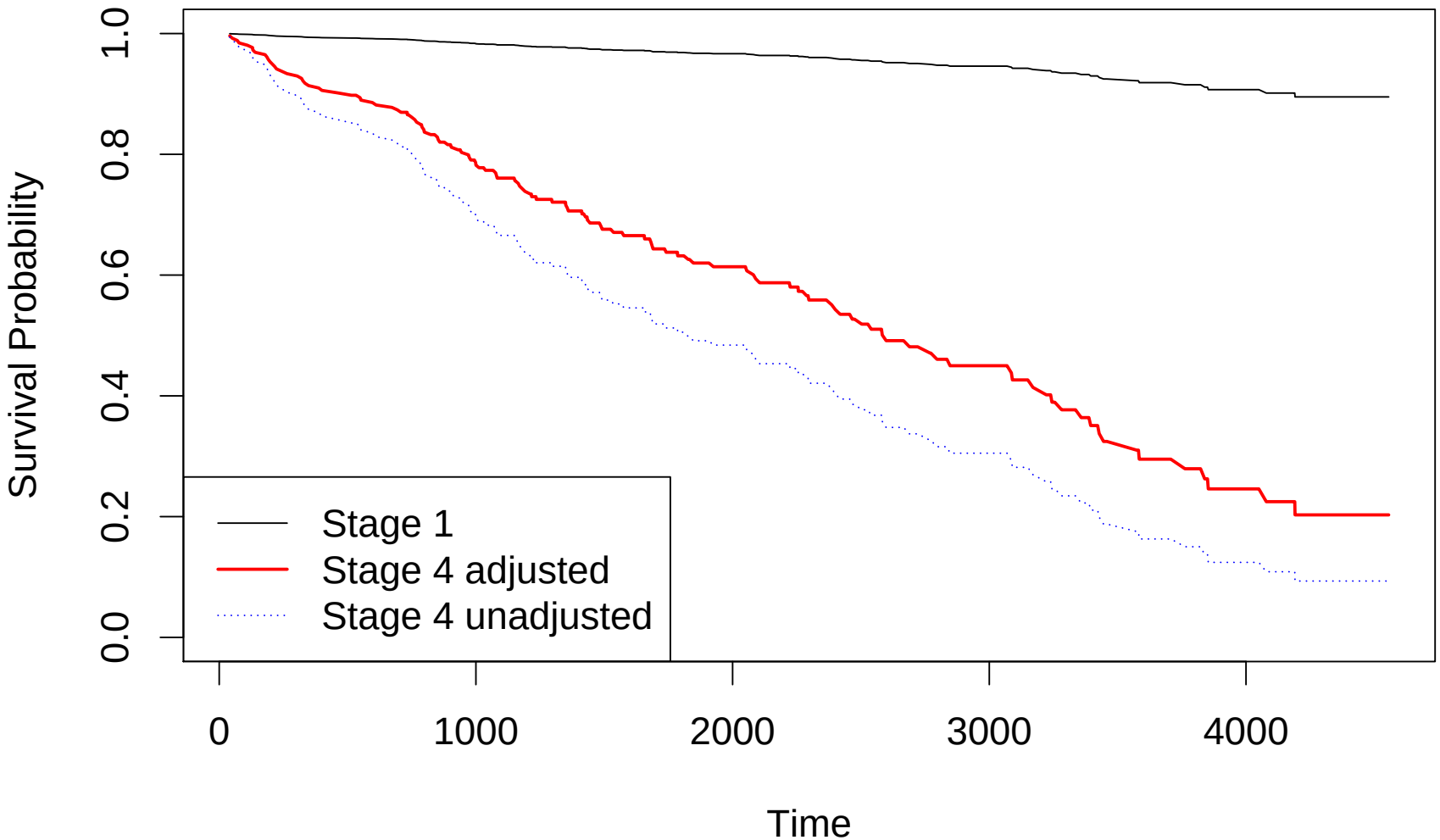
```
adjfit <- coxph(Surv(time, os) ~ age + sex + edema
                + stage + arm, data=pbc.os)
coef(adjfit)
```

```
##          age         sexm     edema0.5       edema1       stage2
##    0.0276179    0.3175396    0.5387152    2.0804217    1.5352629
##       stage3       stage4 armtreatment
##    1.9982170    2.6662626    0.0579460
```

Predicted survival for adjusted coefficients (cont'd)

- The survival function will be calculated for a "baseline" group, say stage 1, then exponentiated with the adjusted coefficient, e.g.:

$$[S_{stage=1}(t)]^{exp(\beta_{stage=4})}$$



Stratification

- Vittinghoff 6.3.2
- Separates the analysis into strata
  - must have an adequate number of events in each stratum (at least 5 to 7)
  - can be used to adjust for variables with strong impact on survival
  - can help solve proportional hazards violations
- Strata have different baseline hazards
- Coefficients / Hazard Ratios are calculated within stratum then combined.

Stratification

Example - in R, strata() can be added to any model formula

```
mycox <- coxph(Surv(time, os) ~ trt + strata(stage), data=pbc.os)
summary(mycox)
```

```
## Call:
## coxph(formula = Surv(time, os) ~ trt + strata(stage), data = pbc.os)
##
##   n= 312, number of events= 125
##
##        coef exp(coef) se(coef)      z Pr(>|z|)
## trt -0.1063    0.8992   0.1814 -0.586    0.558
##
##     exp(coef) exp(-coef) lower .95 upper .95
## trt    0.8992      1.112    0.6302     1.283
##
## Concordance= 0.494  (se = 0.025 )
## Rsquare= 0.001   (max possible= 0.958 )
## Likelihood ratio test= 0.34  on 1 df,   p=0.6
## Wald test            = 0.34  on 1 df,   p=0.6
## Score (logrank) test = 0.34  on 1 df,   p=0.6
```

Immortal Time Bias in observational studies

- For example, Yee *et al.* reported that new statin users reported a 26% reduction in the risk of diabetes progression with one year or more of treatment relative to never-users (adjusted HR 0.74, 95% CI: 0.56 to 0.97).
  - New users excludes those who had received a lipid lowering drug from three years before to six months after cohort entry
- This is a surprising finding because of confounding: people whose diabetes progresses are more likely to develop cardiovascular disease, an indication for statins.
  - would result in HR > 1
- Why?

- Yee *et al.* Statin use in type 2 diabetes mellitus is associated with a delay in starting insulin (http://onlinelibrary.wiley.com/doi/10.1111/j.1464-5491.2004.01263.x/full)

Immortal Time Bias in observational studies

- Why?
  - all person days between cohort entry and end of follow-up were **classified as treated** for those who met the statin user definition, regardless of the date on which they met this definition and as untreated for non-users
  - thus all persons in the *treated* group are "immortal" from time 0 until the initiation of statin treatment
  - this period of immortality makes treatment look more effective

A solution: Time-dependent covariates (TDC)

Definition: A time-dependent covariate in a Cox model is a predictor whose values may vary with time.

- A solution is treating statin prescription as a Time Dependent Covariate (TDC) (Levesque *et al.*)
- Levesque *et al.* Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes (https://doi.org/10.1136/bmj.b5087)

Lab exercises

Use the **PBC** dataset for these exercises.

1. Does the dataset actually contain `n=424` patients as stated above?
2. For how many patients is there complete data for `time`, `status`, and `trt`?
3. Which variables are categorical, and which are continuous?
4. Make a Kaplan-Meier plot for overall survival, stratified by the `trt` variable.
5. Fit univariate Cox models for each available covariate, using a loop. Which have significant p-values (you can ignore multiple testing for now)?
6. Fit a multivariate Cox model with `trt` and `spiders` as covariates.
   - 6.1 Interpret the coefficients and p-values from this multivariate model.
   - 6.2 Create a log-minus-log plots for `treatment+spiders` model. At what times, if any, does it look like there might be any violation of the proportional hazards assumption?