Session 8: Survival analysis part 3

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Learning objectives and outline

Learning objectives

1. Check model assumptions and fit of the Cox model
   - residuals analysis
   - log-minus-log plot
2. Fit and interpret multivariate Cox models
   - perform tests for trend
   - predict survival for specific covariate patterns
   - predict survival for adjusted coefficients
3. Explain stratified analysis
4. Identify situations of competing risks
5. Describe the application of Propensity Score analysis

- Vittinghoff sections 6.2-6.4

Outline

Review

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.

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

Checking assumptions of Cox model

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 cate
colnames(mydat)[1:2] <- c("Var1", "Var2")
mydat$Var1 <- cut(mydat$Var1, breaks=2, labels=c("low", "high"))
mydat$time <- ceiling(mydat$time*1000)
```

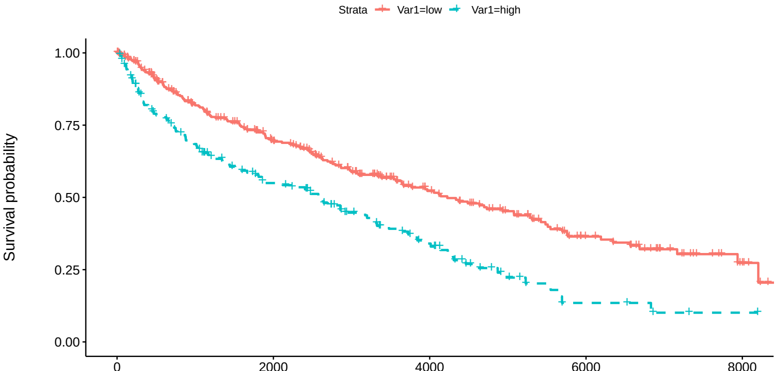
Simulated data to test residuals methods

```r
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

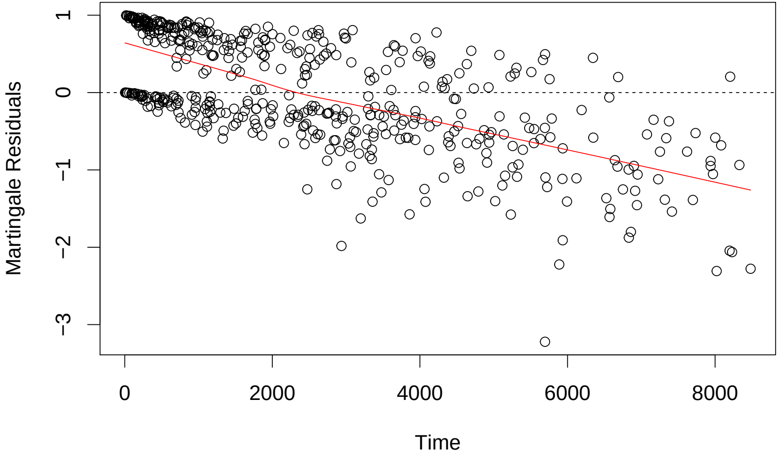
```
## Loading required package: ggplot2

## Loading required package: ggpubr

## Warning: Vectorized input to ‘element_text()‘ is n
## Results may be unexpected or may change in future
```



Martingale residuals

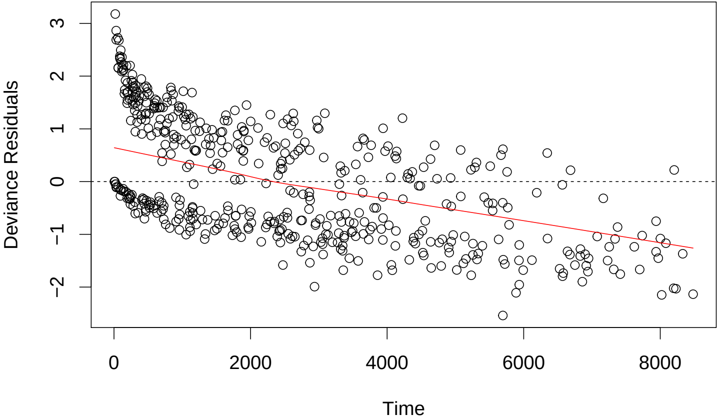
- censoring variable c_i (1 if event, 0 if censored) minus the estimated cumulative hazard function $H(t_i, X_i, \beta_i)$ (1 - survival function)
  - E.g., for a subject censored at 1 year ($c_i = 0$), whose predicted cumulative hazard at 1 year was 30%, Martingale $= 0 - 0.30 = -0.30$.
  - E.g. for 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

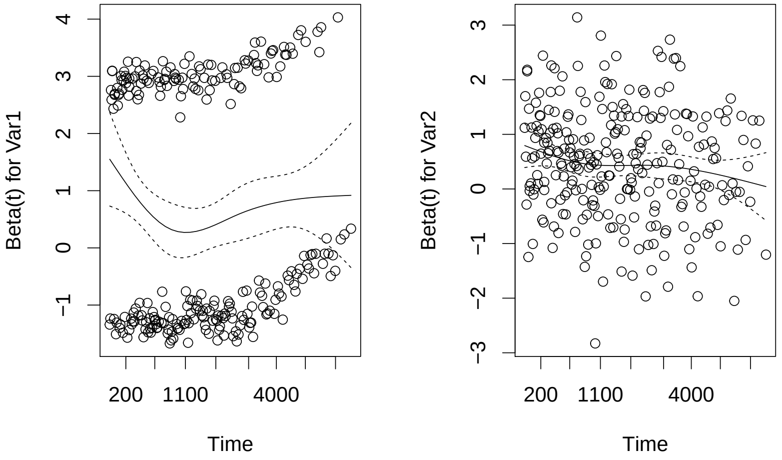
- Deviance residuals are scaled Martingale residuals
- Should be more symmetrically distributed about zero?
- Observations with large deviance residuals are poorly predicted by the model



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

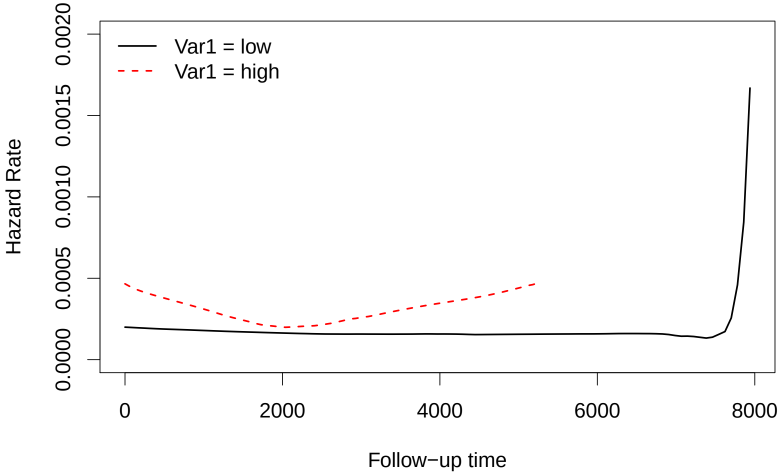


Schoenfeld test for proportional hazards

- 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.

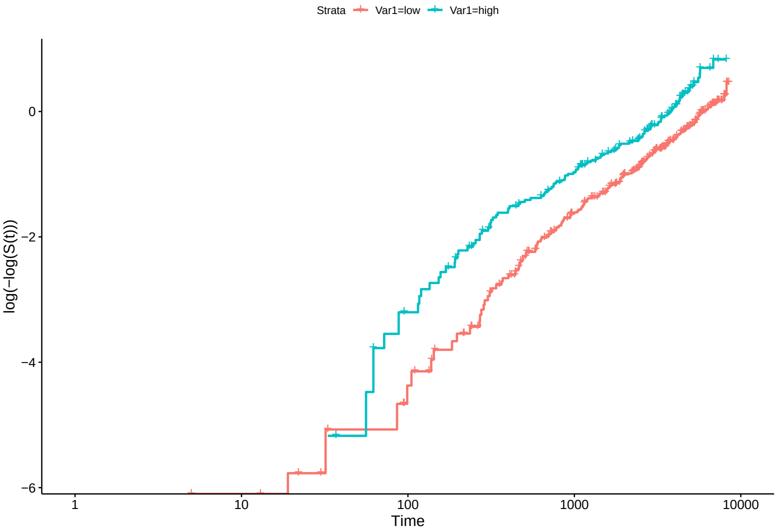
```
##          chisq df     p
## Var1   0.00887  1 0.925
## Var2   4.92734  1 0.026
## GLOBAL 5.07415  2 0.079
```

The hazard function h(t), stratified by Var1



Log-minus-log plot

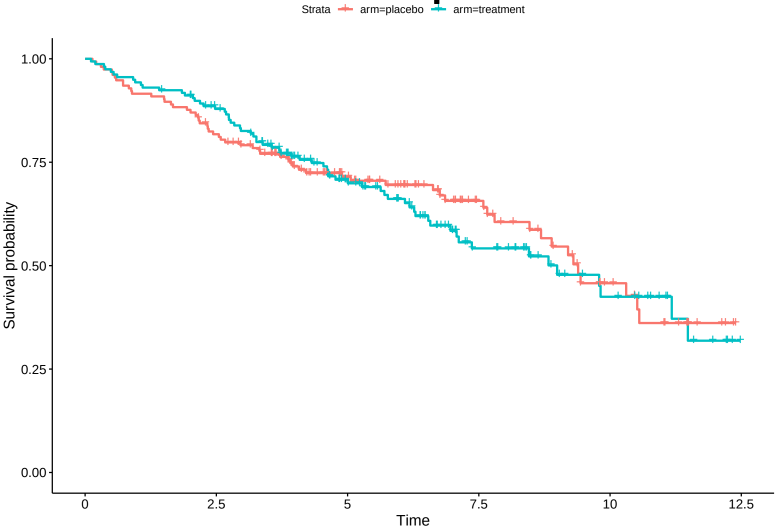
- Used to check proportional hazards assumption



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



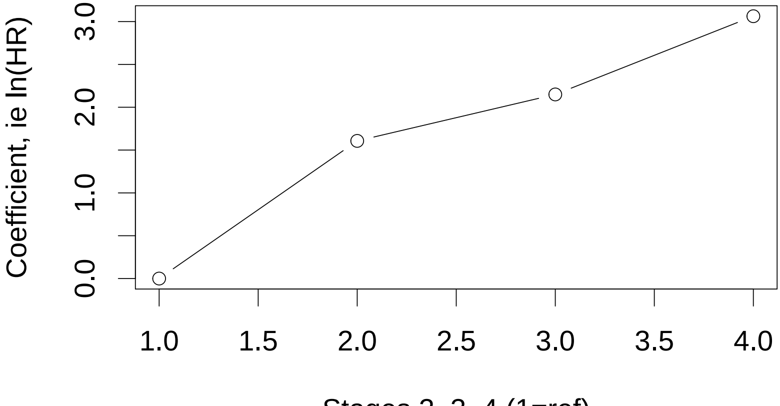

```
## Warning: Vectorized input to `element_text()` is n
```

Tests for trend

What are tests for trend?

What are tests for trend?

- For any kind of multivariate model including an ordinal variable
- Such as cancer stage (1, 2, 3, 4), age category, ...
  - Is there a linear / quadratic / cubic relationship between coefficients and their order?
  - Test by LRT or Wald Test

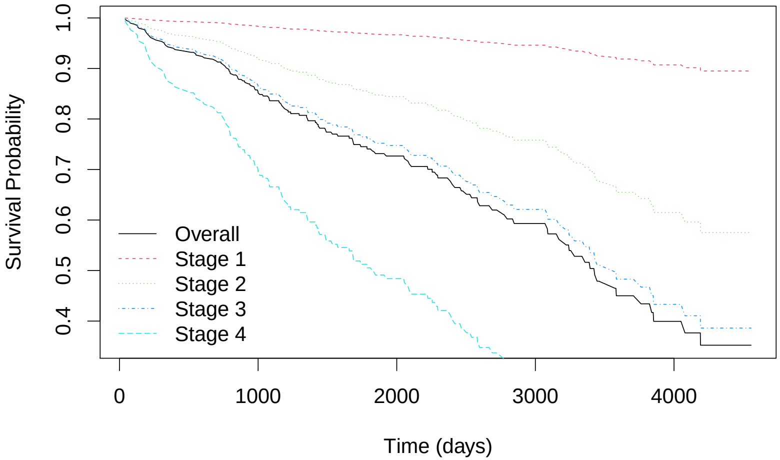


Predictions for specific covariate patterns

How to predict survival from a Cox model?

- 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

```
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 **
## sexf        -0.317540  0.727938  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
##
##              exp(coef) exp(-coef) lower .95 upper .95
## age             1.0280    0.97276    1.0093     1.047
## sexf            0.7279    1.37374    0.4470     1.186
## edema0.5        1.7138    0.58350    0.9992     2.940
## edema1          8.0078    0.12488    4.6534    13.780
## stage2          4.6425    0.21540    0.6108    35.288
## stage3          7.3759    0.13558    1.0067    54.040
## stage4         14.3861    0.06951    1.9630   105.430
## armtreatment    1.0597    0.94370    0.7313     1.535
##
## Concordance= 0.77  (se = 0.022 )
## Likelihood ratio test= 107.6  on 8 df,   p=<2e-16
## Wald test            = 120.8  on 8 df,   p=<2e-16
## Score (logrank) test = 177.1  on 8 df,   p=<2e-16
```

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 (cont'd)

- and in an adjusted model:

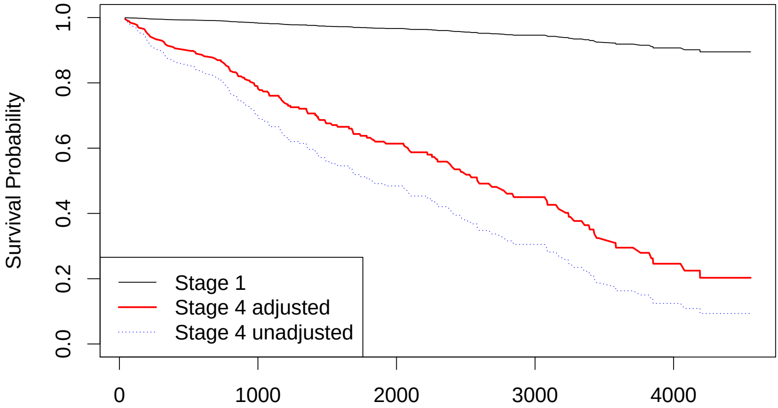
```
adjfit <- coxph(Surv(time, os) ~ age + sex + edema
                + stage + arm, data = pbc.os)
coef(adjfit)
```

```
##       age       sexf    edema0.5     edema1      stag
##   0.0276179  -0.3175396   0.5387152   2.0804217    1.5352
##      stage4 armtreatment
##   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

What is stratification?

- relevant to all kinds of regression, not just survival analysis
- when analysis is separated into groups or 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.
- Vittinghoff 6.3.2

How to stratify

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 = p
##
##   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 )
## 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
```

Competing Risks Data

What are competing risks?

- Example from Vittinghoff 6.5: The MrOS study (Orwoll et al. 2005) followed men over 65 to examine predictors of bone fracture and low BMD (subclinical bone loss)
- At end of study participants had:
  - developed fracture (outcome of interest),
  - remained alive without fracture (incomplete follow-up), or
  - died prior to fracture (incomplete follow-up)

Orwoll, E. *et al.* (2005). Design and baseline characteristics of the osteoporotic fractures in men (MrOS) study–a large observational study of the determinants of fracture in older men. Contemporary Clinical Trials, 26(5), 569–585.

Why not treat died prior to fracture and alive without fracture as censored?

- Recall the independent censoring assumption (Vittinghoff 6.6.4):
  - censored people are similar to those who remain at risk in terms of developing the event of interest;
  - censoring is independent of the event of interest.
  - For patients who died this assumption is highly suspect

Reasons for right censored data

- Cut-off date of analysis (administrative censoring):
  - Censoring usually independent
- Loss to follow-up
  - Independence may be problematic if sicker individuals discontinue participant in study (lack of energy, too ill, return to home country)
  - or if healthier individuals discontinue participation (don't feel the need to continue, start new life in other country)
- Competing risks:
  - Often informative.
  - In competing risks analysis, independence between competing risks is not required

Very brief summary of competing risk methods

- 1-to-1 mapping between hazard and cumulative incidence function is lost in competing risks
- Standard Kaplan-Meier estimator is biased for competing risks data
  - Aalen-Johansen estimator is better choice
- *Gary's test* is analogous to log-rank test
- cause-specific standard Cox PH model might be useful for prognostic (causal) testing, but not estimating a population Hazard Ratio

Resources for competing risk methods

- Z. Zhang, Survival analysis in the presence of competing risks, Ann Transl Med. 2017 Feb; 5(3): 47. PMID: 28251126
- cmprsk package
- riskRegression package

Propensity score analysis

What is propensity score analysis?

- an alternative to multivariate regression to control for hypothesized confounders in observational studies:

```
outcome ~ exposure + counfounder1 + confounder2
```

- a stratification approach that is more practical than stratifying on multiple hypothesized confounders
- an approach to summarizing many covariates into a single score
- a convenient approach to controlling for many hypothesized confounders

Propensity score approach to correction for confounders

- *Step 1*: fit the propensity score model (no outcome) that predicts propensity for exposure based on confounders:

```
exposure ~ counfounder1 + confounder2
```

- *Step 2*: use propensity predictions to match or stratify participants with similar propensity (for example, stratifying on quintiles of propensity)
- *Step 3*: check adequacy of matching or stratification, ie by comparing attributes of matched participants
- *Step 4*: test hypothesis *among matched participants*:

```
outcome ~ exposure
```

Propensity score references

- P.C. Austin (2011), An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivariate Behavioral Research, 46:3, 399-424, DOI: 10.1080/00273171.2011.568786
- R. d'Agostino (1998), Tutorial in Biostatistics: propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Stat. Med. 17, 2265-2281. http://www.stat.ubc.ca/~john/papers/DAgostinoSIM1998.pdf
- You don't need any special package to do basic propensity score matching (e.g. stratifying by quintiles), but the MatchIt package provides multiple matching approaches, diagnostics, good documentation