Survival Analysis of Worsening Hypertension

PSTAT 196: Research in Actuarial Science

Spring Quarter, 2017

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About the Dataset

- An extract from database THIN (The Health Improvement Network) based in England and Wales.
- Collected from mid-1990's through 2012
- Limitations:
  - 1 observation per person
  - Erroneous data entry - have to assume correctness aside from impossible values
- Everyone already has moderate hypertension (stage 2 of 3)
  - Transition from stage 2 to 3 is the event of interest for our study

Background

Hypertension (a.k.a. high blood pressure)

- About 75 million American adults (29%) have high blood pressure.[1]
- Total costs associated with high blood pressure in 2011 in the US were $46 billion.[1]
- Two stages of Hypertension
  - Primary → 90% of all cases, nonspecific lifestyle or genetic causes
  - Secondary → Attributed to specific diseases or disorders

[1] "High Blood Pressure Frequently Asked Questions (FAQs)," *Centers for Disease Control and Prevention*, accessed May 30, 2017.

Objectives and Methods

- Identify factors leading to severe hypertension
    - Using a Cox Proportional-Hazards Model
    - In the original dataset
- Further test our Cox P.H. model
    - Using Cross-Validation
- Investigate the medical factors leading to severe hypertension
    - In the 2nd dataset
- Extend the Cox model to time-dependent covariates
    - Through stratification and parametric models

Variables of Interest

Name	Description	Support
AGE_PRE	Age in years when subject entered the study	[-55, 101]
alcohol	Binary indicator for the use of alcohol (0: no, 1: yes)	{0,1}
BMInew	BMI at start of study in kg/m^2	[0.2, 66000]
Cigar	Binary indicator for the use of cigarettes (0: no, 1: yes)	{0, 1}
DURATION	Number of **days** between entering study and transitioning	[0, 41180]
Partial_code_ff	Transition code (2000: moderate hypertension, 3000: severe hypertension)	{2000, 3000} *{0,1}
Sex	Binary indicator for sex (1: male, 2: female)	{1, 2}
Socio-Economic	Categorical variable ranging from affluent (1) to deprived (5)	{1, 2, 3, 4, 5}

Data Cleaning and Vetting

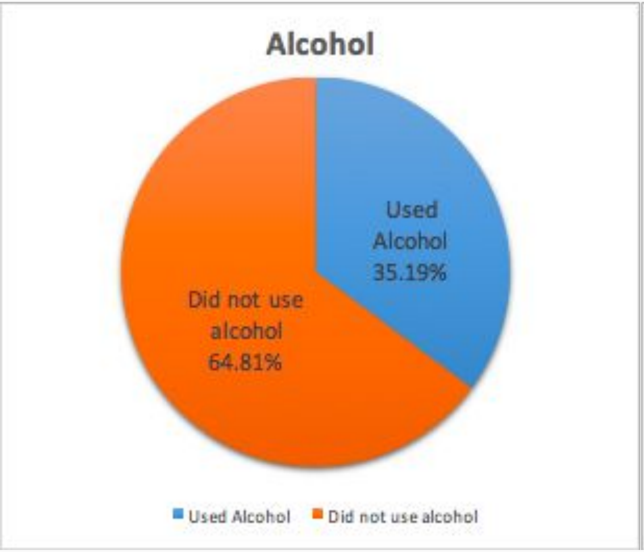
- Removed all subjects with:
  - BMI < 12 or BMI > 100
  - Starting age <= 0
  - Duration time equal to 0
  - Duplicate observations (no differences between the two)
- Define new categorical predictor: SC = sex * cigar
  - 4 factor variables: Male smoker, Male non-smoker, Female smoker, Female non-smoker
  - MS, MN, FS, FN

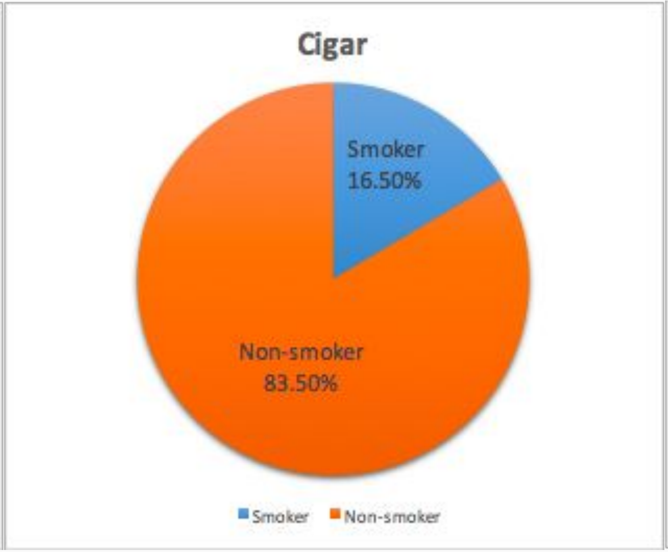
Dataset post-cleaning

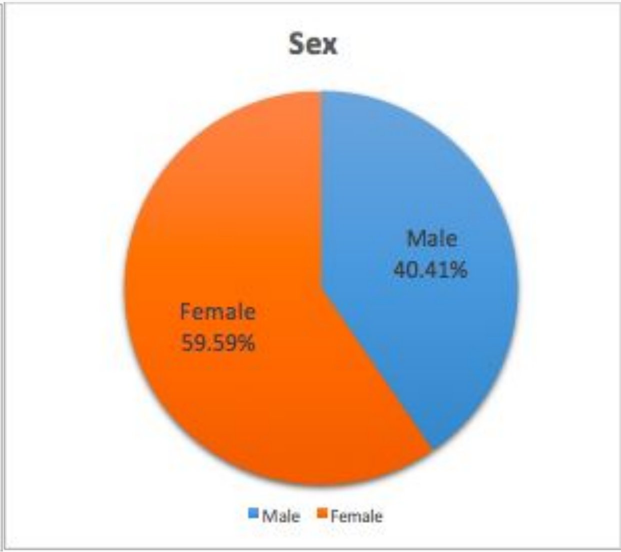
Variable	Before Cleaning	After Cleaning
AGE_PRE	[-55, 101]	[8, 101]
BMInew	[0.2, 66000]	[12.1, 98.5]
DURATION (days)	[0, 41180]	(0, 41180]

- The number of observations shrinks from 126,665 to 124,393
    - 1.79% removed

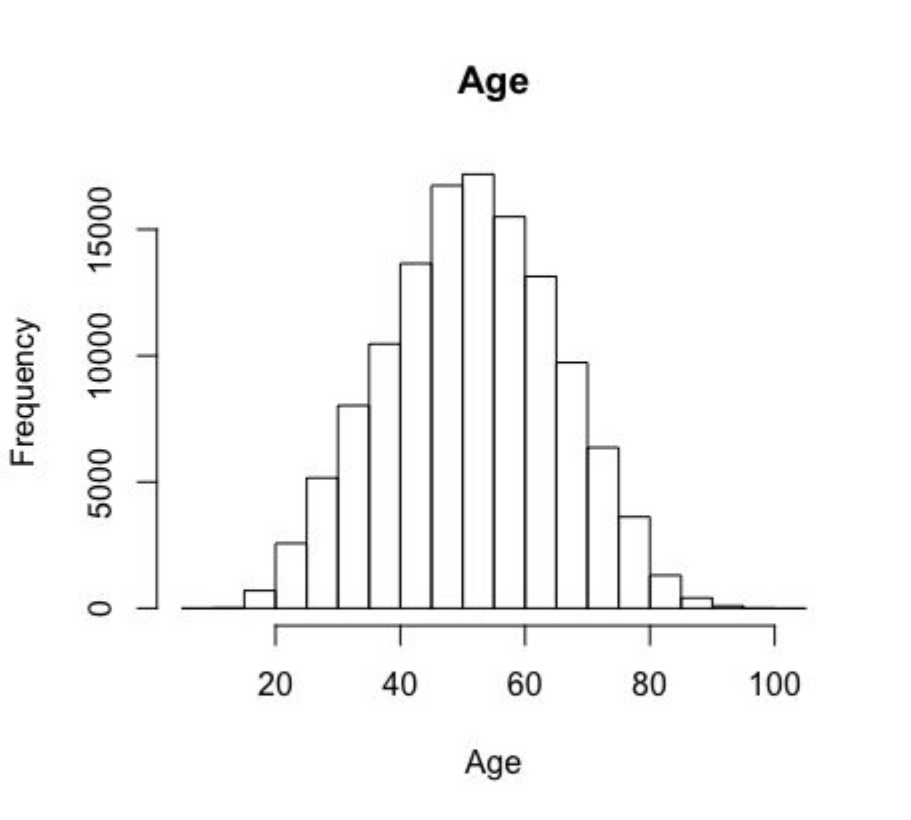
Exploratory Analysis



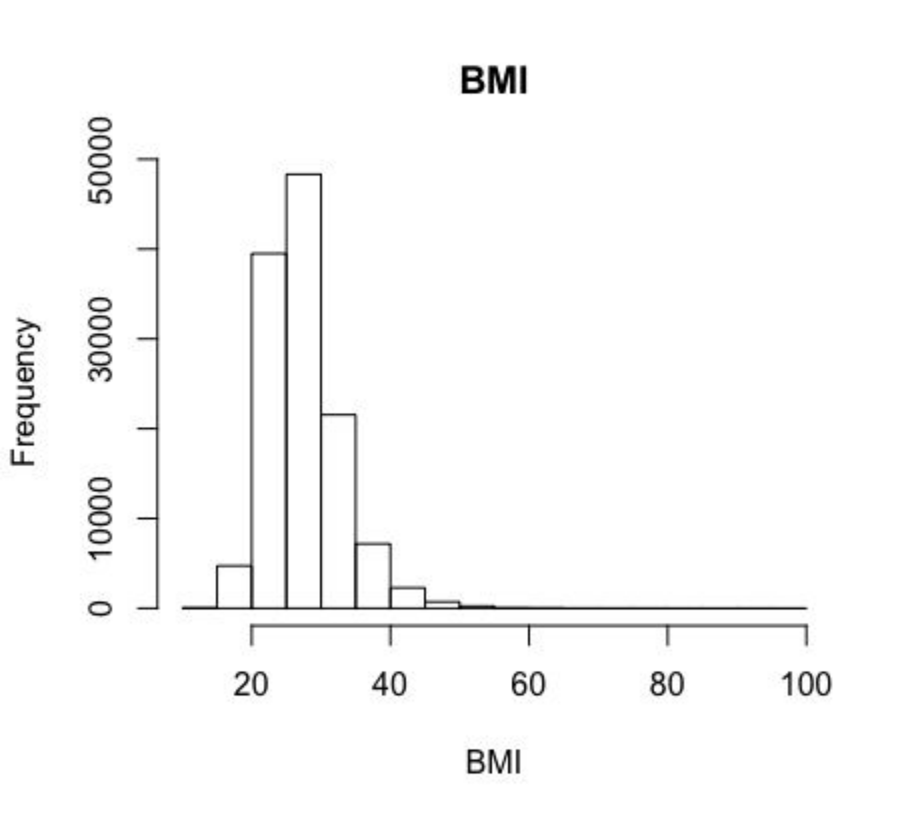




Exploratory Analysis

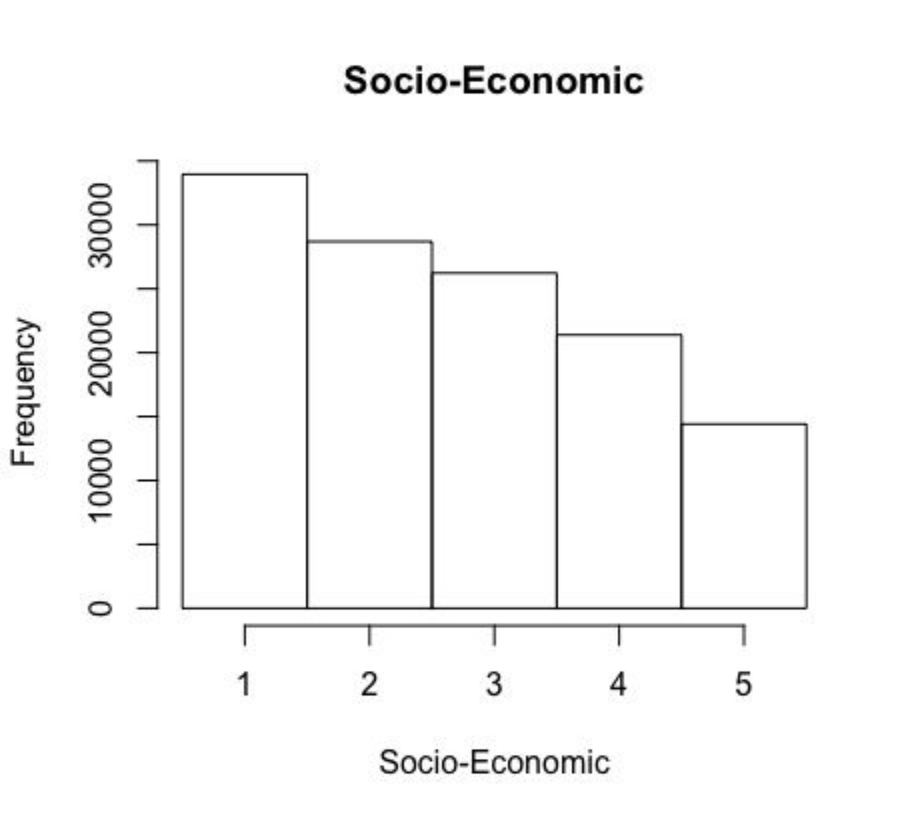


Mean = 51.90



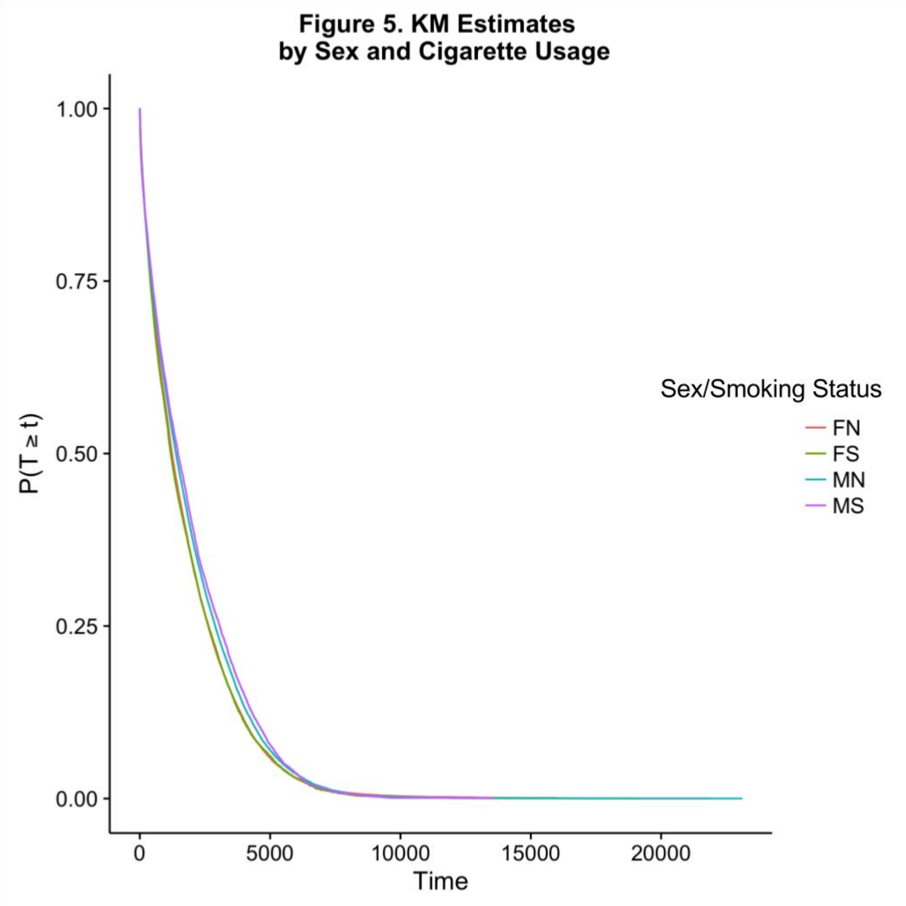
Mean = 27.50

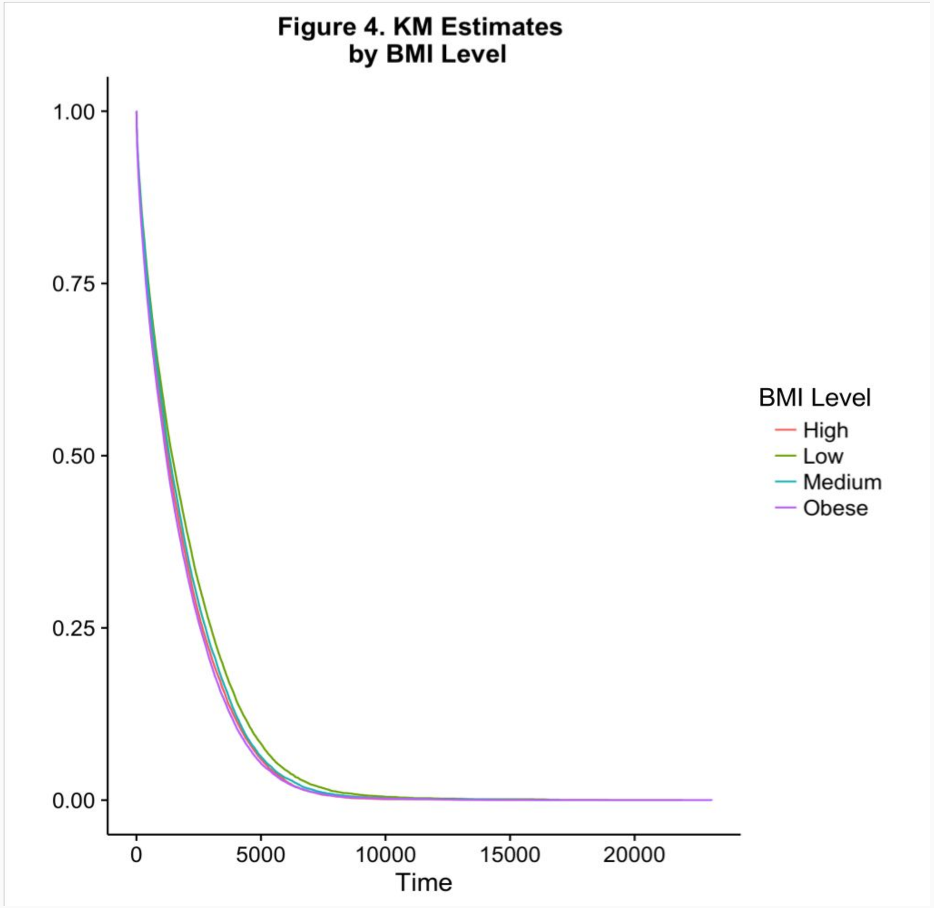
Exploratory Analysis



Socio-Economic	Counts	% of population
1 (affluent)	33959	27.23%
2	28697	23.01%
3	26231	21.04%
4	21391	17.16%
5 (deprived)	14414	11.56%

Exploratory Modeling





Cox Proportional Hazards Model Review

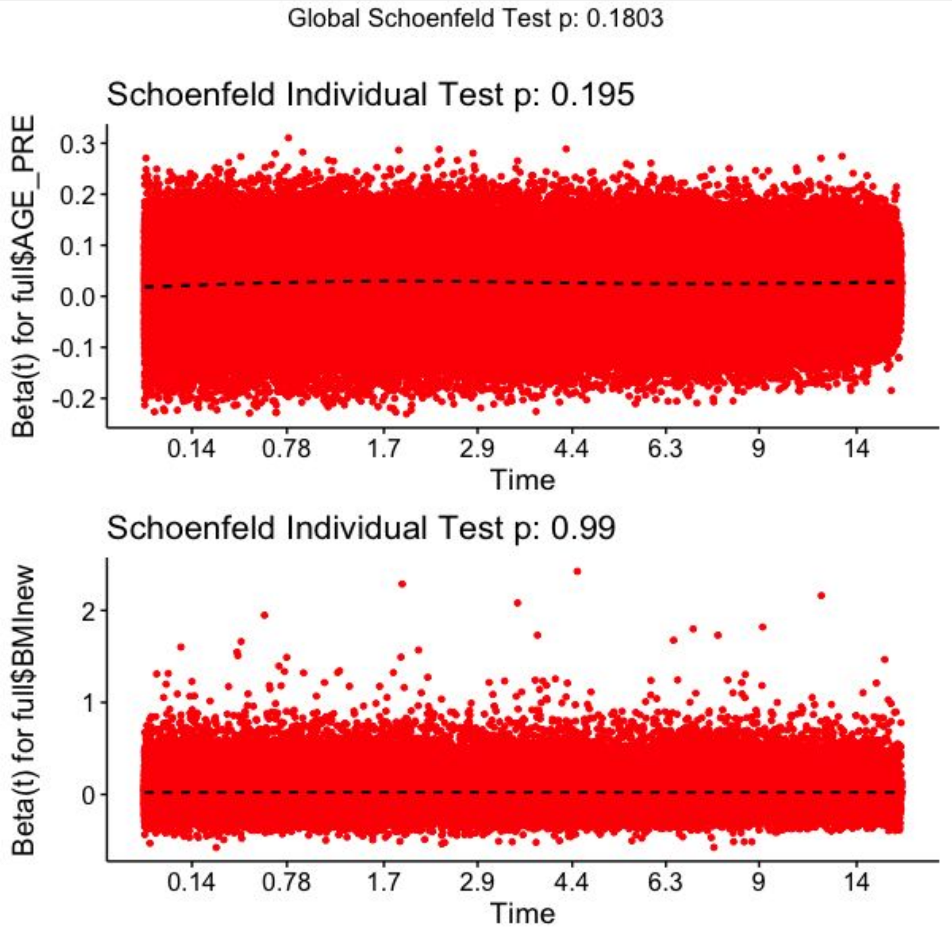
$$h(t) = h_0(t)\exp(\beta_1 X_1 + \cdots + \beta_n X_n)$$

- The Cox approach models the hazard rate, $h(t)$, over time
- Increase in a covariate → multiplicative effect on $h(t)$
- The baseline hazard, $h_0(t)$, is **not** estimated
- So the Cox model assumes that the covariates' effects are multiplicatively (or proportionally) related to $h(t)$

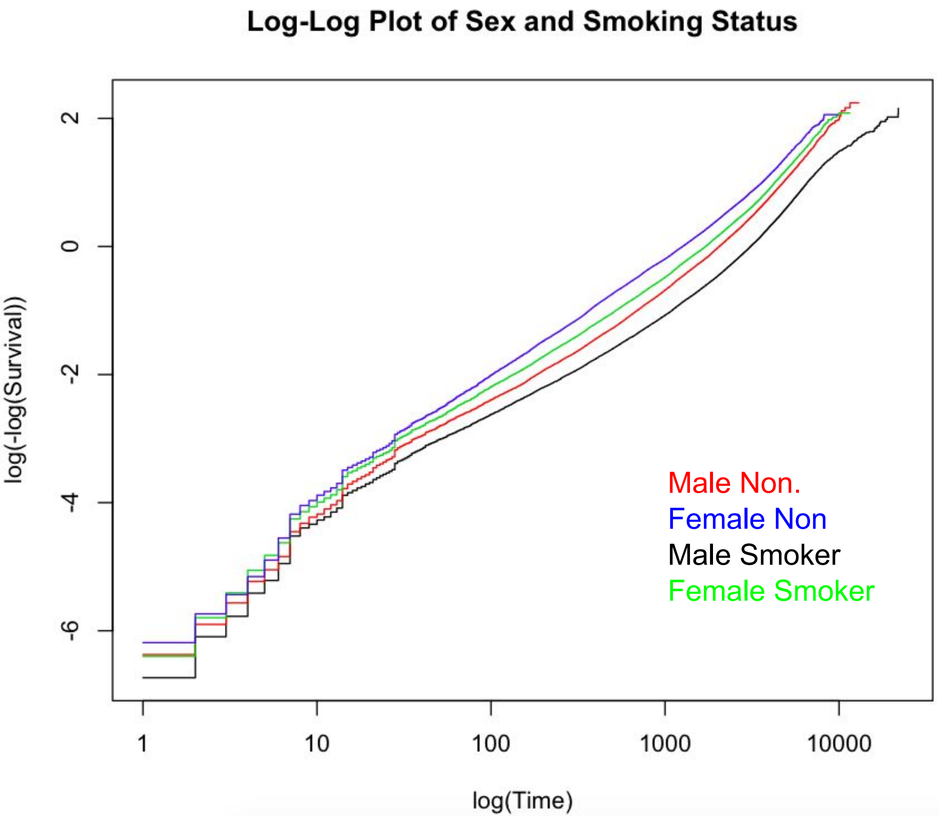
Checking the Model Assumptions

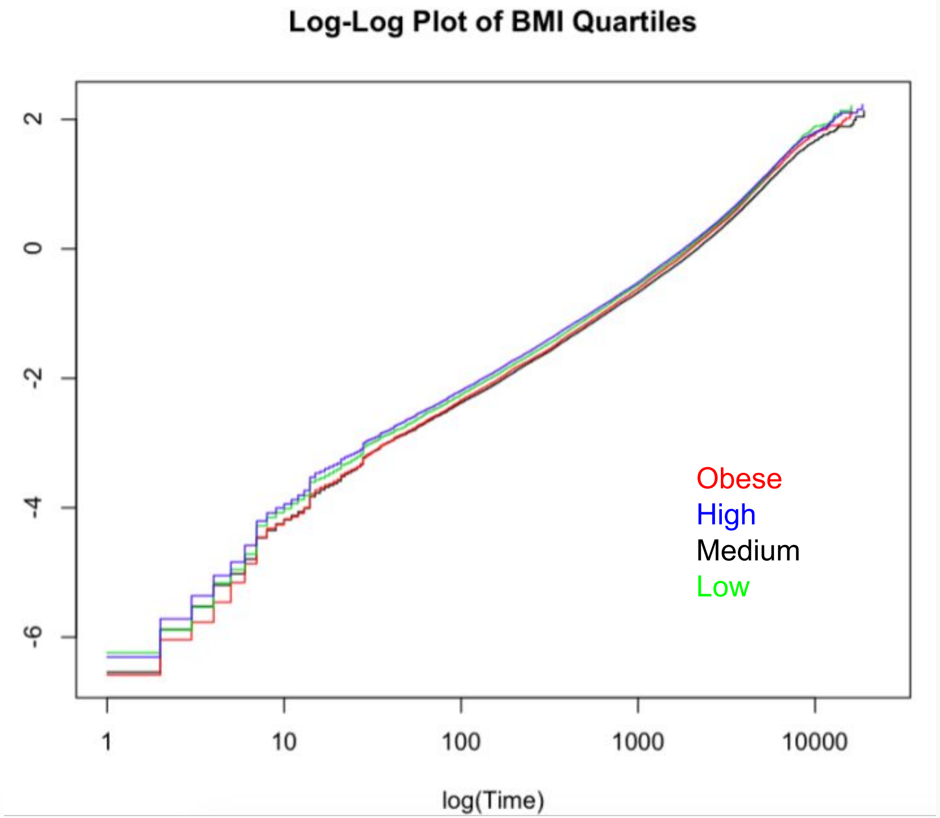
- Schoenfeld Residual Plots for continuous covariates
  - H_0 : $\mathit{PH\ Assumption\ is\ met}$
  - H_α : $\mathit{PH\ Assumption\ is\ not\ met}$
  - High p-values imply horizontal line across entire time span → agrees with assumption
- Log-log plots for categorical/discrete covariates
  - Schoenfeld Residuals yield no insight about alignment with PH assumption with regards to categorical predictors
  - Transforming Kaplan-Meier Estimator (x = Time, y = Survival Prob.) into Log-log plot (x = log(Time), y = log(-log(Survival Prob.))) can help us assess assumption
  - Parallel lines for each risk group implies assumption is met

Schoenfeld Residuals



Log(-Log(Survival)) Plots





Our Stratified Cox Model

- Specifically, socio-economic class did not meet PH assumption when tested numerically
  - Anticipated this to be an important factor → stratified the covariate
- There are 5 different levels of socio-economic class, a Cox model is fit for each level
- The covariates/regression coefficients are **the same** for all 5 strata
  - Only the baseline hazard rate differs across the strata

Our Stratified Cox PH Model

$$h(t) = h_i(t)\exp(0.0261 \cdot age + 0.0216 \cdot bmi + 0.1008 \cdot FS + 0.0015 \cdot MS + 0.0505 \cdot MN) \quad i = 1,2,3,4,5$$

Used the proportionality tests and BIC as our guiding criteria ($BIC = ln(n)k - 2ln(L)$)

Covariate	Estimated Hazard Rate	95% Confidence Interval
Age	1.0265	[1.0260, 1.0269]
BMI	1.022	[1.0206, 1.0228]
Female Smoker	1.106	[1.0826, 1.1301]
Male Non-Smoker	0.950	[.9384, .9632]
Male Smoker	1.0019	[.9779, 1.0256]

Baseline Hazard Rates for Different Socio-Economic Strata

Time = 1 year

Socio Economic	Hazard Rate
1 (affluent)	0.2281420
2	0.2263601
3	0.2409130
4	0.2549135
5 (deprived)	0.2707321

Time = 3 years

Socio Economic	Hazard Rate
1	0.5564318
2	0.5557649
3	0.5792660
4	0.6067651
5	0.6391335

Time = 5 years

Socio Economic	Hazard Rate
1	0.8963512
2	0.8929580
3	0.9307331
4	0.9454276
5	0.9947118

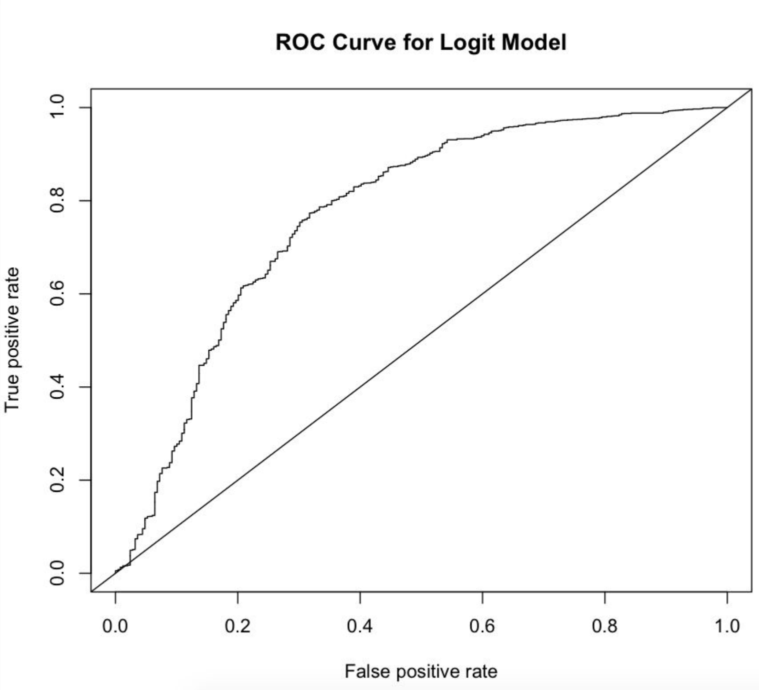
Cross-Validation

Like regression and classification, we wanted to see how robust our Cox model is

- Difficult because we are handling **duration** and **state**
  - First tried to predict duration
- Moved to predicting **state** at 3.5 years
- But the Cox model does not estimate the baseline rate!
  - Tried using the following approximation: $\hat{h}_0(t) = \sum_{t<t^*} h(t)$
  - … With poor results

Cross-Validation

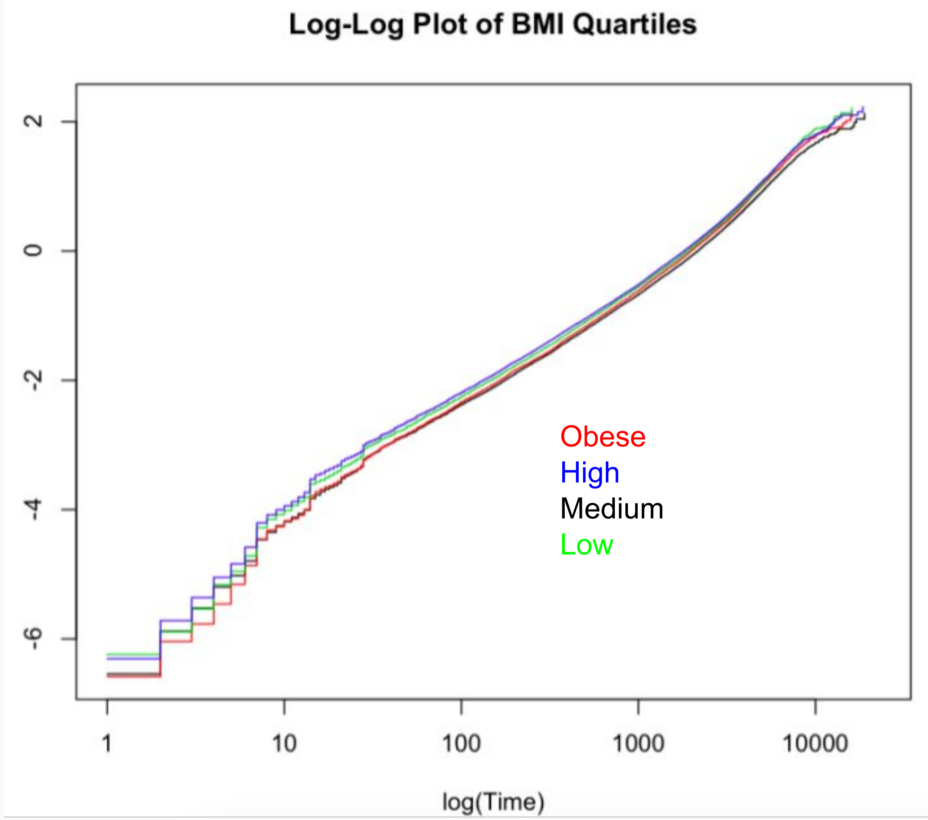
- Took advantage of the fact that we only had one observation/person
- Fit a logistic model on a one-year subset
  - Single train/test split with data between 3 and 4 years
- Used covariates from the Cox PH model
- Area Under the Curve: 77%



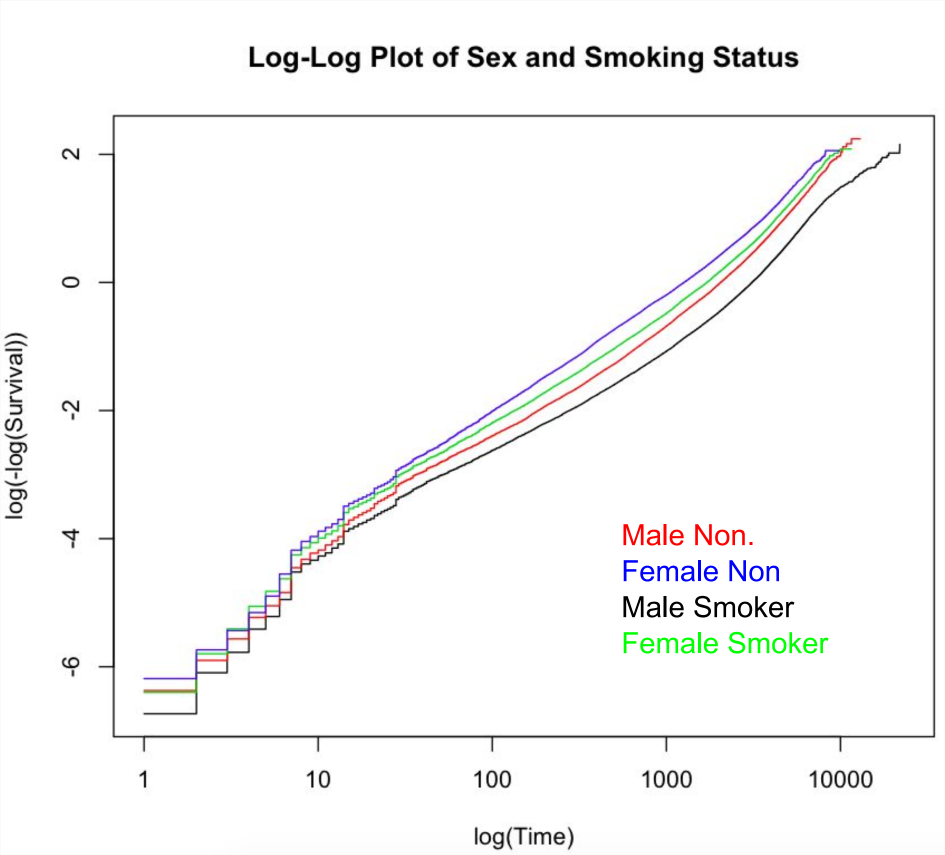
Parameterizing our Model

- Weibull model - Different assumption (Accelerated Failure Times)
    - Test via log-log plots: Linearity of log(-log(Survival Prob.) over log(Time) for each covariate-specific risk group implies assumption is valid
    - Different from PH assumption criterion which seeks parallelism between plotted lines for different risk groups for each covariate
- We also remove observations with duration > 20 years, as advised by Prof. Duncan and Nhan (thank you!)
- Dataset shrinks from 124393 to 123976 observations (- 417 observations)

Evaluating the AFT Assumption



Evaluating the AFT Assumption

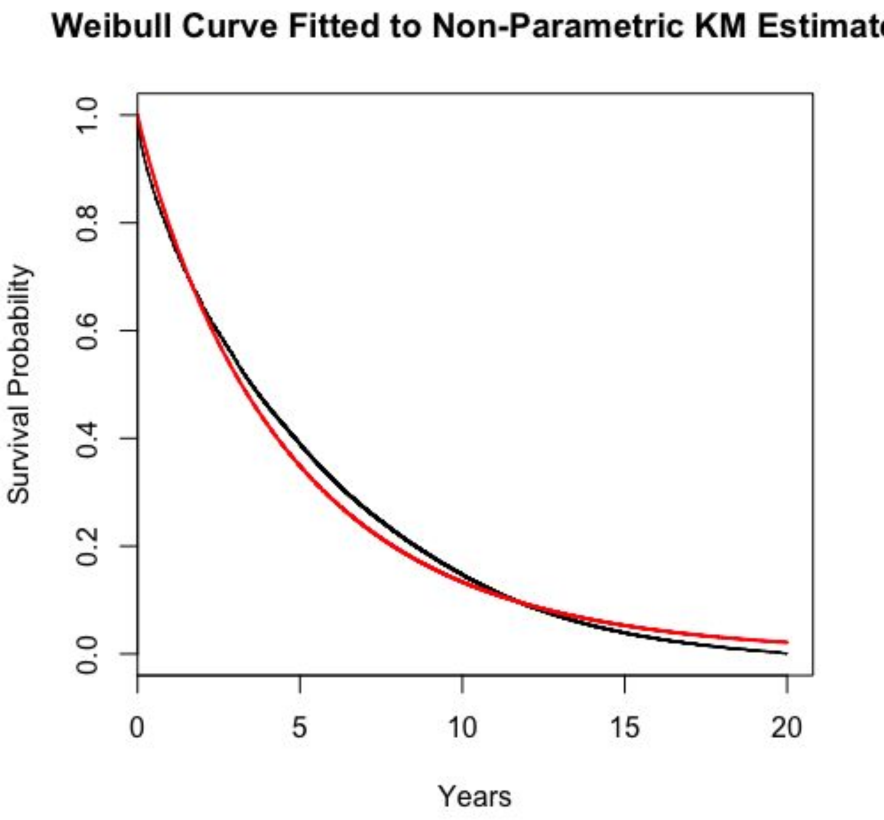


Results From Our Weibull Model

$$h(t) = \lambda^p p t^{p-1} \quad \lambda = \exp(-\sum X_i \beta_i)$$

$$p = 1.0688$$

i	X_i	β_i	Estimated HR
0	Intercept	3.409437	N/A
1	BMI	-.021305	1.021534
2	Start Age	-.024531	1.024834
3	FS	-.100441	1.105658
4	MN	.047097	0.953995
5	MS	-.002017	1.002019



Second Dataset

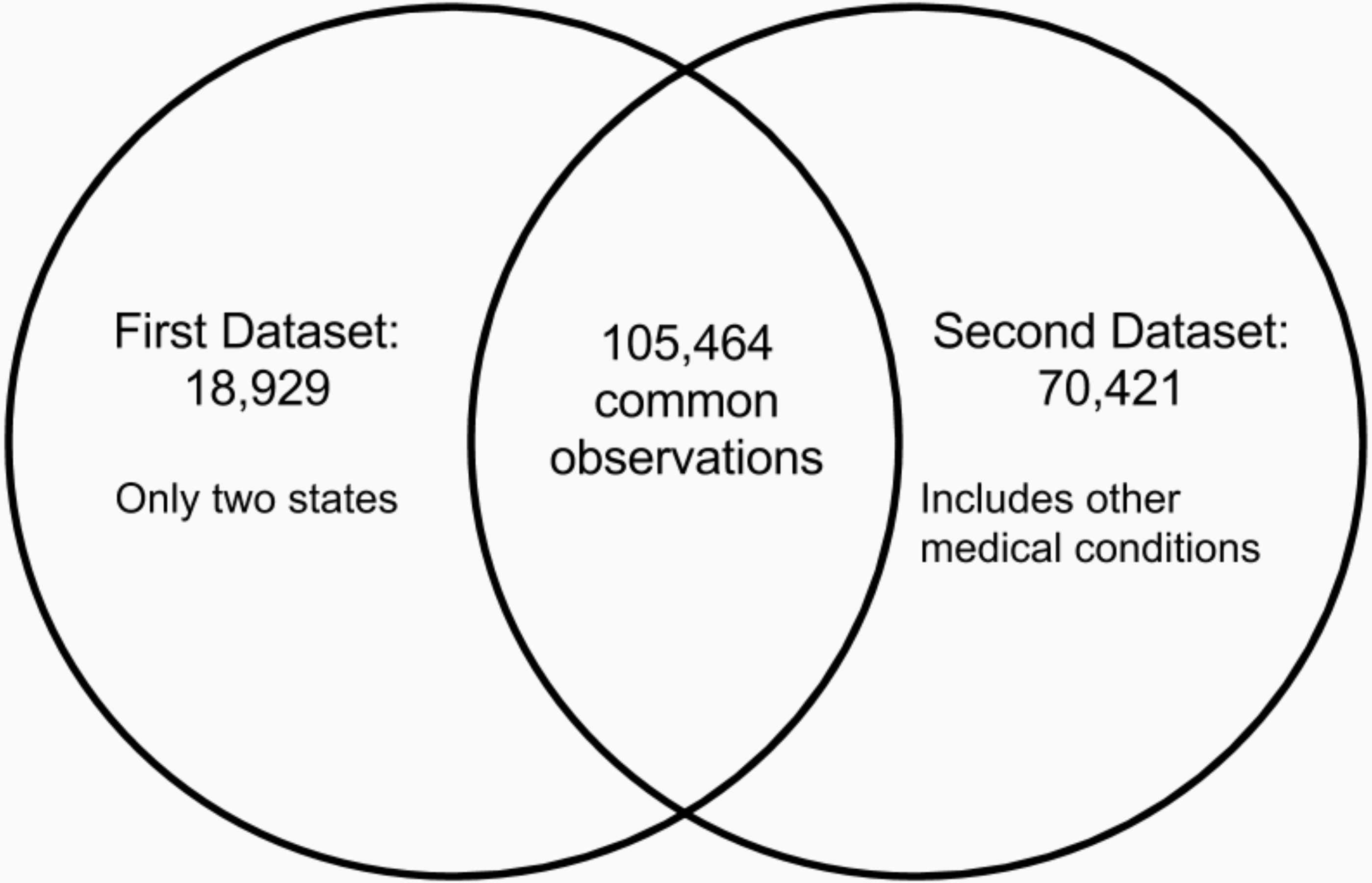
New Variables

Variable Name	Description	Support
diabetes	Binary indicator for diabetes (0: no, 1: yes)	{0,1}
hyperlipidemia	Categorical predictor for hyperlipidemia (0: none, 1: mild, 2: moderate, 3: severe)	{0,1,2,3}

Data Cleaning

Variable	Before Cleaning	After Cleaning
AGE_PRE	[-59, 102]	[8, 103]
BMInew	[0.2, 66000]	[12.1, 98.71]
DURATION (days)	[0, 21850]	(0, 21850]

- Subjects are removed for same reasons:
  - Impossible age, bmi and duration; duplicate IDs
- The size of dataset shrinks from 186,668 to 175,885:
  - 5.78% removed


First Dataset:
18,929
Only two states
105,464
common
observations
Second Dataset:
70,421
Includes other
medical conditions

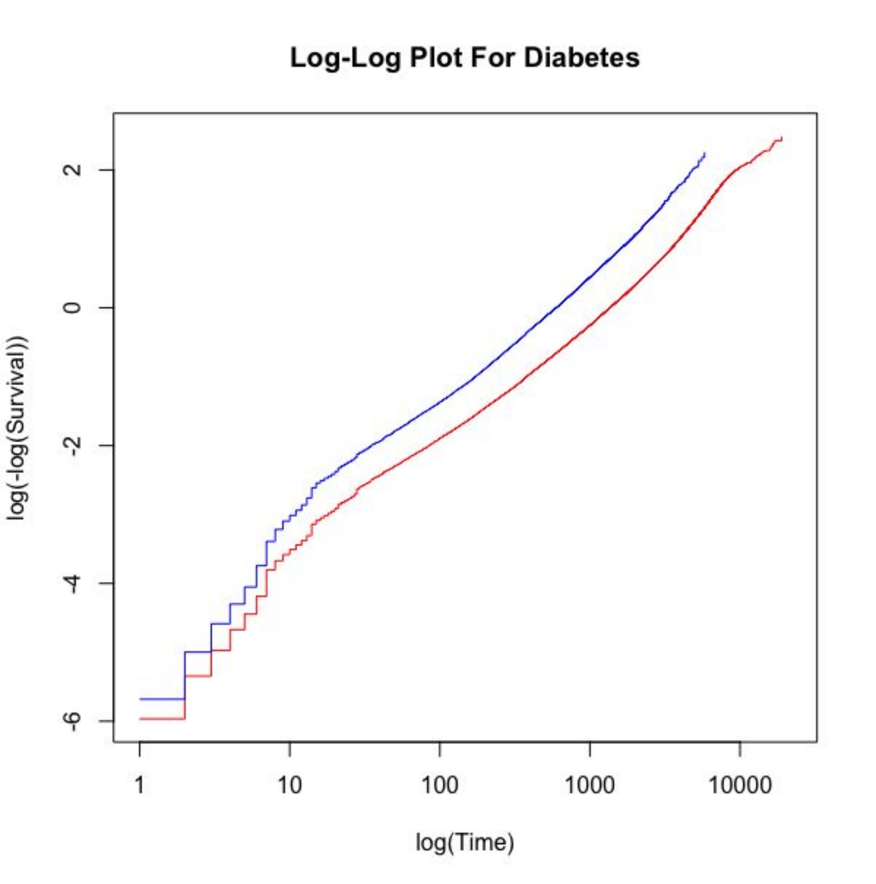
Difficulties - Mo’ Data, Mo’ Problems

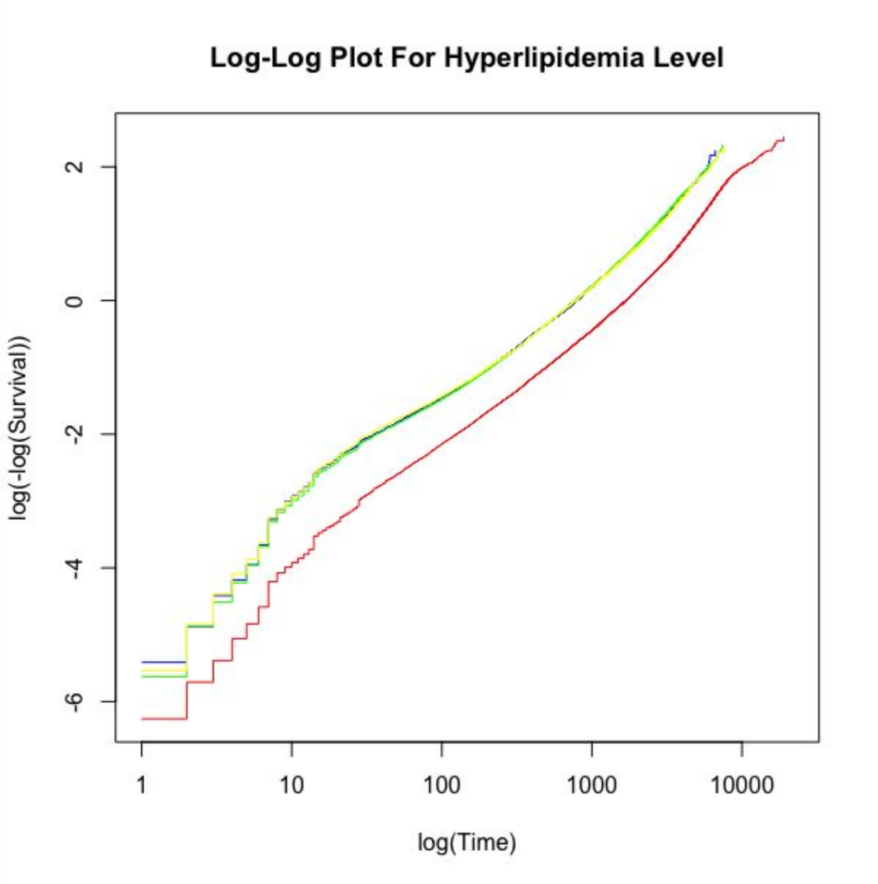
- The two datasets have significant overlap
  - However--seem to be drawn from two separate populations
- Proportional Hazards assumption not met for variables which did satisfy in old dataset - namely, SC failed in our new dataset, but was fine in the old one
- F-tests for variance between old and new datasets:
  - Ratio of variances for BMI: 0.9575417
  - Ratio of variances for duration: 1.29357

Fitting a Model

- We specifically wanted to fit a model using the new predictors for hyperlipidemia and diabetes
- PH assumption met for both hyperlipidemia and diabetes, but not SC
- Natural decision: Build Cox model stratifying on SC, using hyperlipidemia and diabetes as predictors
- 4 levels of SC - 4 differing baseline hazard rates

PH Assumption Verification For New Predictors





Our Second Stratified Model's Results

$$h(t) = h_{sc}(t) \cdot \exp(0.622 \cdot hyper1 + 0.617 \cdot hyper2 + 0.598 \cdot hyper3 + 0.464 \cdot diabete)$$

$$sc = FN, FS, MN, MS$$

Covariate	Estimated Hazard Rate	95% Confidence Interval
Hyperlipidemia (level 1)	1.862	[1.828, 1.897]
Hyperlipidemia (level 2)	1.853	[1.829, 1.878]
Hyperlipidemia (level 3)	1.814	[1.787, 1.843]
Diabetic	1.590	[1.562, 1.619]

Baseline Hazard Rates for Different Sex-Cigar Strata

Time = 1 year

Sex-Cigar	Rate
FN	0.3666378
FS	0.4207363
MN	0.3512549
MS	0.3915465

Time = 3 years

Sex-Cigar	Rate
FN	0.9009510
FS	0.9957537
MN	0.8334356
MS	0.9027204

Time = 5 years

Sex-Cigar	Rate
FN	1.431580
FS	1.529047
MN	1.308066
MS	1.377740

Future Directions

- The data we used for this project is a subset of a dataset to be used in PSTAT 296 for the upcoming year
  - Recommend carefully checking any new predictors if a new subset is taken
- Change event of interest to diabetes, hyperlipidemia, etc.
  - Use hypertension as predictor
- Include multiple observations per person if possible
  - Better evaluate time-dependency
- Possibly using data from sites such as Kaggle, Reddit, UCI
  - Kaggle hosts datasets from companies and government agencies

Acknowledgements

- Professor Ian Duncan and Shannon Nicponski
  - For advising our team throughout the project
- Terry M Therneau and Thomas Lumley
  - For authoring and maintaining the Survival package
- Tal Galili
  - For publicizing his ggsurv function on R-statistics.com
- Hadley Wickham
  - For authoring the plyr, dplyr, and ggplot2 packages

Q & A

Thank you!