

Functional Form:

Modeling Continuous Predictors

Greenland, 1995
Altman and Royston, 2006

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Lee Example

- Cohort of community-dwelling elders
- Predictors: age, co-morbidities, functional status: > 48 predictors
- Follow-up: mortality over 4 years
- Logistic regression model
- Age is a continuous variable

Lee, SJ et al. JAMA. 2006;295:801-808.

Summary Statistics

summ age, detail

age at time of 1998 interview

	Percentiles	Smallest		
1%	51	50		
5%	53	50		
10%	55	50	Obs	11701
25%	59	50	Sum of Wgt.	11701
50%	66		Mean	67.22169
		Largest	Std. Dev.	10.10853
75%	75	101		
90%	82	101	Variance	102.1825
95%	85	102	Skewness	.4472938
99%	92	103	Kurtosis	2.458463

Distribution of Ages

- Looking for outliers
- Look to see where most values are
90% of ages 53 and 85
- *DONT CARE IF THEIR NORMALLY DIST
doesn't matter*
- *It doesn't.*

Modeling Challenge

Levels of Complexity

- age less than <65
- age 50-60, 60-70, 70-80, 80-90, 90+
- age as a “linear term”
- age + age²
- other transformation (e.g. log)
- smoothing

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Age Cut at 65

Logistic regression

Log likelihood = -3910.362

Number of obs	=	11701
LR chi2(1)	=	592.71
Prob > chi2	=	0.0000
Pseudo R2	=	0.0704

died	Odds Ratio	Std. Err.	z	P> z	[95% Conf. Interval]	
over65	4.829268	.3501685	21.72	0.000	4.189489	5.566749

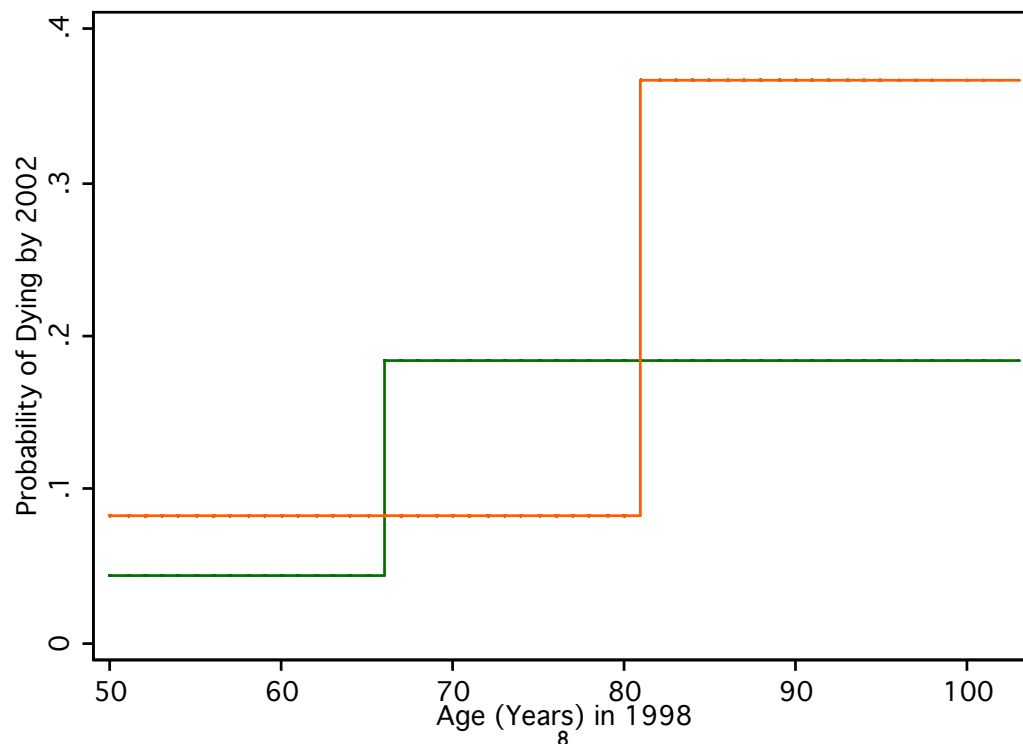
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Odds Ratios

Age 1	Age 2	Odds Ratio
60	64	1
64	66	4.8
71	79	1
79	81	1

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Two Fits



How to Choose Cutpoint

- Strongly discourage making binary variable
- Lose a lot of information
- Cutpoint can be important choice
 - data: no unambiguous choice
 - avoid choosing “most significant” cutpoint

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More Levels

- Cut age at quartiles: 25, 50, 75
ages 59, 66, 75
- Use as a 4-level ordinal categorical variable
- Why use trend test?

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Age by Quartile

```
. xi: logistic died i.age4
i.age4          _Iage4_1-4      (naturally coded; _Iage4_1 omitted)

Logistic regression                                Number of obs   =      11701
                                                    LR chi2(3)       =      949.71
                                                    Prob > chi2      =      0.0000
Log likelihood = -3731.8609                        Pseudo R2       =      0.1129
```

died	Odds Ratio	Std. Err.	z	P> z	[95% Conf. Interval]	
_Iage4_2	2.299158	.2939617	6.51	0.000	1.789523	2.95393
_Iage4_3	3.842798	.4605231	11.23	0.000	3.038359	4.860222
_Iage4_4	12.90059	1.454704	22.68	0.000	10.3425	16.09137

Learn anything about shape?

||

Interpretation

- OR is 12.9 comparing 4th quartile to first often need that 1 number
- Common summary for continuous *especially in NEJM*
- Quartile can be very specific to your data

Odds Ratios

Age 1	Age 2	Odds Ratio
60	64	1
64	66	1.68
71	79	3.34
79	81	1

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Issues

Binary and Categorical

- Con:
 - potentially biased
 - subtle choices
 - residual confounding
- Pro
 - very simple to understand
 - easy to “act” on cutpoints

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Continuous Predictor

```
. logistic died age
```

```
Logistic regression
```

```
Log likelihood = -3632.9744
```

```
Number of obs = 11701
```

```
LR chi2(1) = 1147.48
```

```
Prob > chi2 = 0.0000
```

```
Pseudo R2 = 0.1364
```

died	Odds Ratio	Std. Err.	z	P> z	[95% Conf. Interval]	
age	1.103388	.0034619	31.36	0.000	1.096623	1.110194

Interpretation?

Scale is huge issue here

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Changing Scale

```
lincom 5*age
```

```
( 1) 5 age = 0
```

died	Odds Ratio	Std. Err.	z	P> z	[95% Conf. Interval]	
(1)	1.635463	.0256563	31.36	0.000	1.585942	1.686529

```
lincom 10*age
```

```
( 1) 10 age = 0
```

died	Odds Ratio	Std. Err.	z	P> z	[95% Conf. Interval]	
(1)	2.674738	.08392	31.36	0.000	2.515213	2.84438

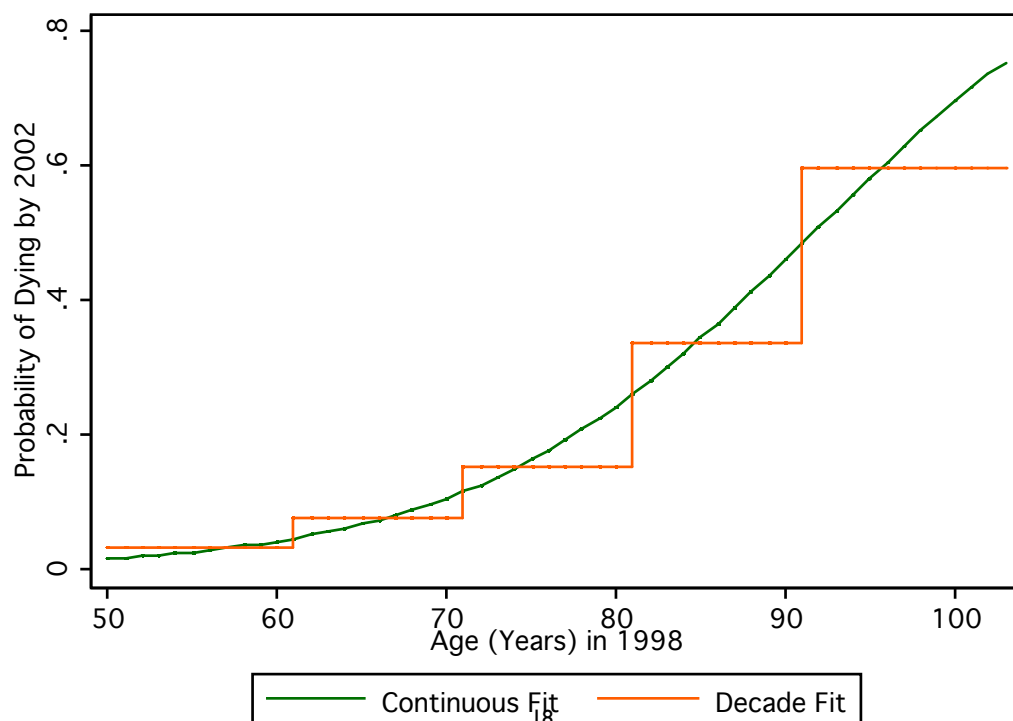
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Induced Odds Ratios

Age 1	Age 2	Odds Ratio
60	64	1.48
64	66	1.22
71	79	2.2
79	81	1.22

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Linear v. Decade Fit



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Linear Fit

- Can give good easy predictions
- Requires only single df: parsimonious
- Avoids overfitting!!
not big concern in this data
- Bias/variance tradeoff
may give better predictor for very old
- Single parameter output
every 10 year increases odds 2.67

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Does the Model Fit

- Maybe the very simple model is missing a pattern
- Multiple categories don't have to give monotone risk
- One way to check: squared term
squared terms have problems

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Quadratic Fit

```
. logistic died age age2
```

Logistic regression

Number of obs = 11701
 LR chi2(2) = 1151.82
 Prob > chi2 = 0.0000
 Pseudo R2 = 0.1369

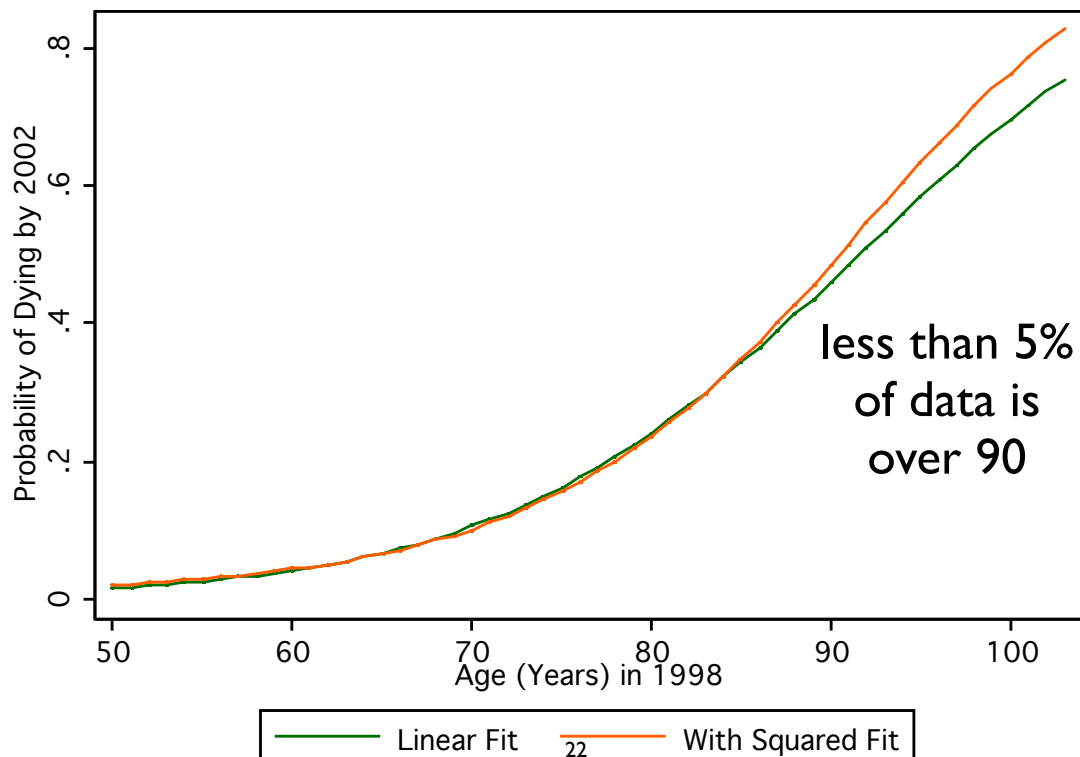
Log likelihood = -3630.8075

died	Odds Ratio	Std. Err.	z	P> z	[95% Conf. Interval]	
age	1.016908	.0397754	0.43	0.668	.9418631	1.097932
age2	1.000557	.0002666	2.09	0.037	1.000034	1.001079

Squared term “adds” to the model $p < 0.05$

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Difference in Fits



Linear v. Quadratic Fit

Age 1	Age 2	OR Linear	OR Quad
60	64	1.48	1.41
64	66	1.22	1.2
71	79	2.2	2.23
79	81	1.22	1.24

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Squared Terms

- Very prone to outliers
outliers become magnified
very non-robust models
can affect fit far from outlying values
- Statistical v. practical significance in model improvement

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Log transformation

- Does not add degrees of freedom per se
- But can handle “non-linear” patterns
- Produces a useful interpretation
- Interpretation in terms of % increase in predictor
- Particularly helpful when measurement is unfamiliar

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Results of Log Fit

```
. logistic died lage
```

Logistic regression

```
Number of obs   =    11701
LR chi2(1)      =    1132.03
Prob > chi2     =    0.0000
Pseudo R2      =    0.1346
```

Log likelihood = -3640.7019

died	Odds Ratio	Std. Err.	z	P> z	[95% Conf. Interval]	
lage	1166.966	270.697	30.44	0.000	740.6419	1838.69

Interpretation problematic

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Results of Log Fit

```
. lincom 0.095*lage
( 1)  .095 lage = 0
```

died	Odds Ratio	Std. Err.	z	P> z	[95% Conf. Interval]	
(1)	1.956008	.0431042	30.44	0.000	1.873324	2.042341

10% increase in age

same as multiplying age by 1.1

same as $\log(1.1) = 0.095$ increase in log age

10% increase in age => HR 1.96

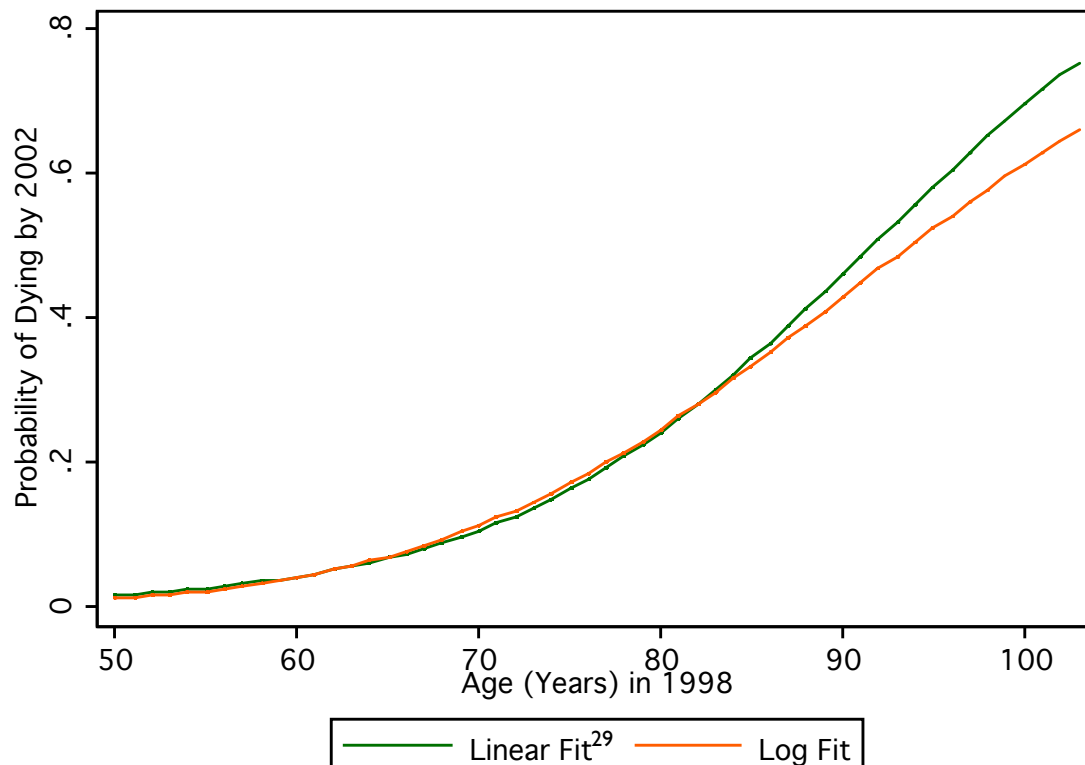
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Log v. Linear Fit

Age 1	Age 2	OR Log	OR Linear
60	64	1.58	1.48
64	66	1.24	1.22
71	79	2.12	2.2
79	81	1.19	1.22

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Linear v. Log Fit



Consider log transform

- Log likelihood reveals no improvement in fit
- In addition, interpretation not helpful
- Sometimes hear “twice your age”
- Generally talk about being 1,5, etc years older
- Additive scale more natural

Splines

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Splines

- A tool for producing smooth functions
- Very amenable to regression models
- Can help in describing complex shape *while adjusting for other variables*
- Similar across regression models

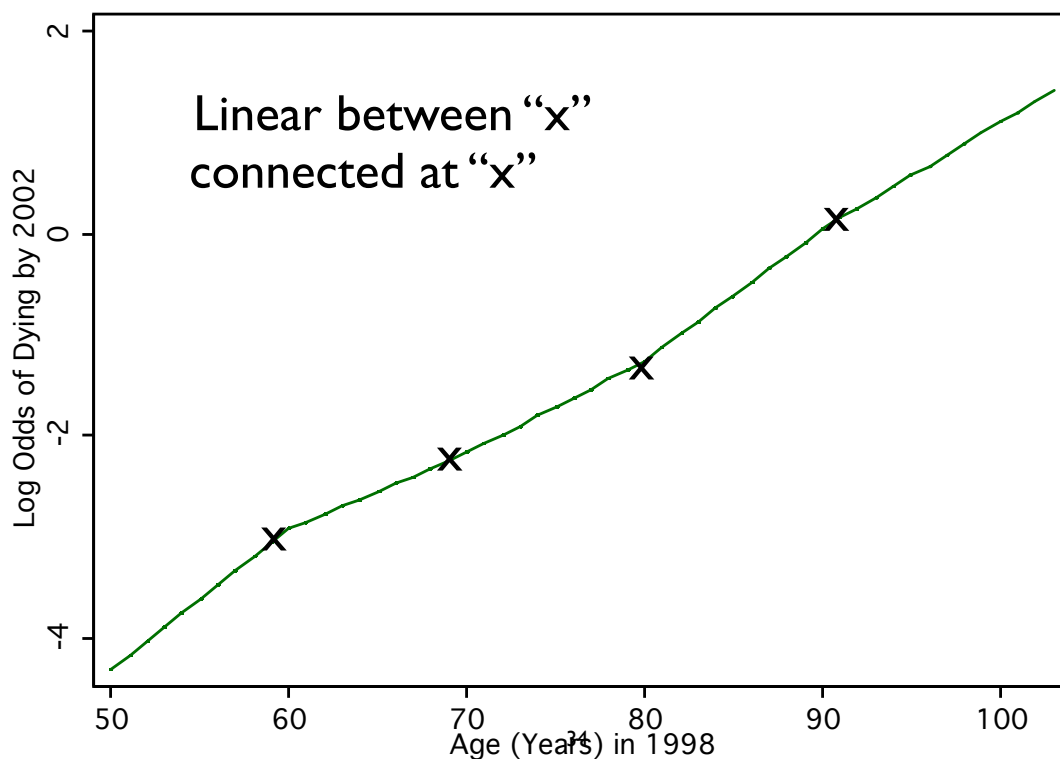
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Heuristic

- Approximate complex function with
- Multiple simple functions
- Simplest example: linear spline
- Suppose use simple lines to approximate effect of age

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Linear Spline



Knots

- “x” are called knots
control how much shape can take
- Where to put knots?
- How many to put down?
- First, not a big effect
- Later can have big effect

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of Knots

- Controls how eccentric curve can be
- $DF = \# \text{ Knots} - 1$
- Too many knots: overfitting
noisy curve
- Too few: bias
- Bias/variance trade off
- 3-5 knots is plenty

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Advantage Over Cutpoint

- Get much more information for df
- Placement of points not as critical
- Extremely flexible methods

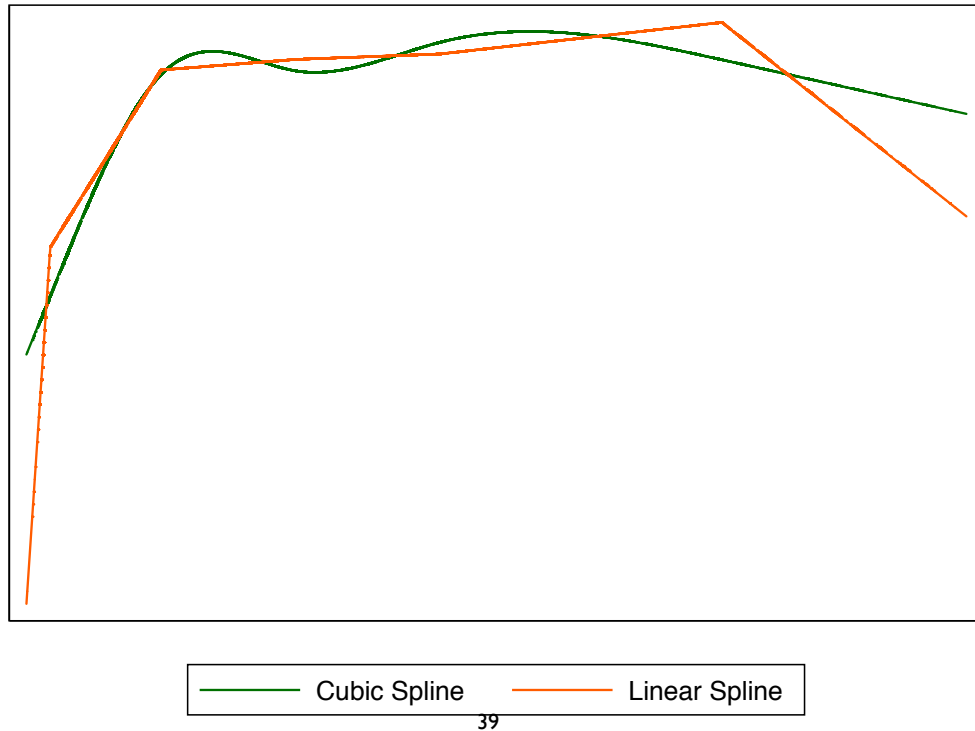
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Cubic Splines

- Type of spline functions
- Fits cubic polynomial between knots
more flexible than a line
- Local function: not susceptible to outliers
- Often need to constrain tails
- Produces nice, smooth looking functions

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Cubic v. Linear Spline



Stata

```
. mkspline cube_age = age, cubic nknots(3) displayknots
```

	knot1	knot2	knot3
age	55	66	82

```
. summ cube_age*
```

Variable	Obs	Mean	Std. Dev.	Min	Max
cube_age1	11701	67.22169	10.10853	50	103
cube_age2	11701	5.493749	7.357163	0	43.18518

Model Fit

```
. logistic died cube_age*
```

Logistic regression

Number of obs = 11701

LR chi2(2) = 1149.94

Prob > chi2 = 0.0000

Pseudo R2 = 0.1367

Log likelihood = -3631.7479

died	Odds Ratio	Std. Err.	z	P> z	[95% Conf. Interval]	
cube_age1	1.084836	.0120655	7.32	0.000	1.061444	1.108743
cube_age2	1.019988	.0128014	1.58	0.115	.9952037	1.045389

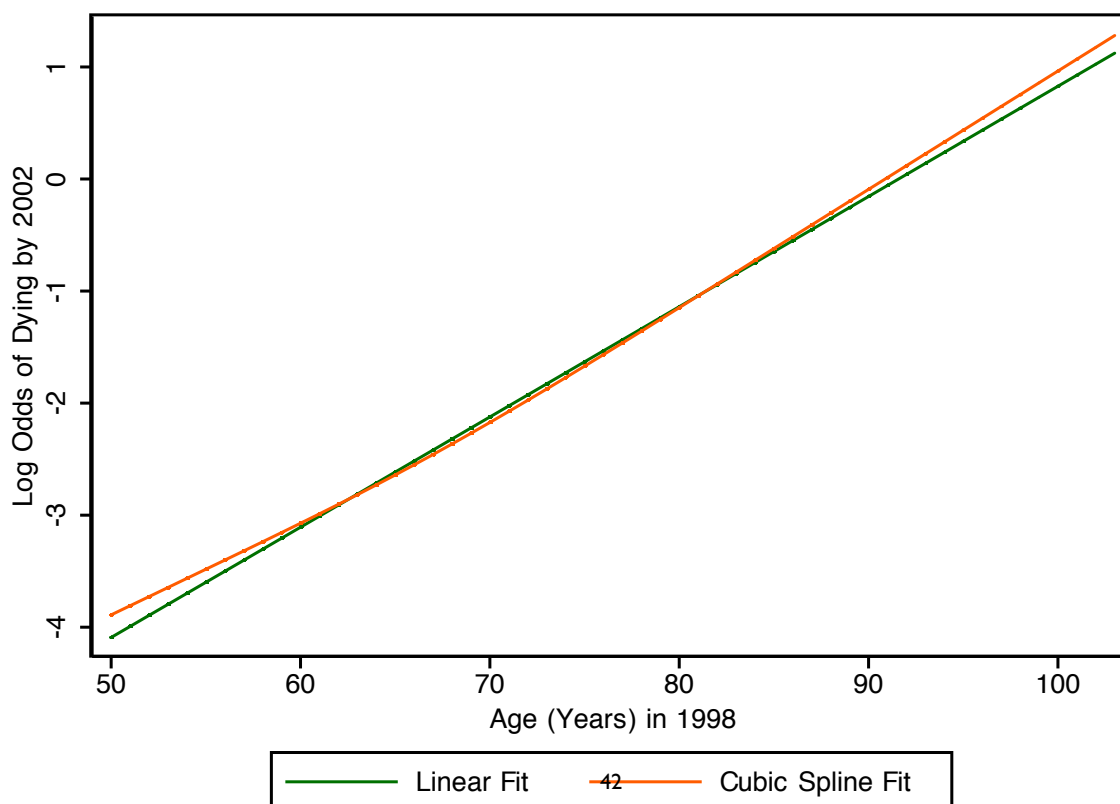
coefficient not interpretable

extract prediction

```
predict out_cubic
```

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Spline Fit



How to test splines

flexible test for non-linear effects

- Fit spline model
`logistic died cube_age1 cube_age2`
- Store results
`est store splineresults`
- Fit model with linear effect
`logistic died age`
- Apply likelihood ratio test
`lrtest splineresults`
- LR test works because spline model always nested

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How to test splines

simpler alternative for cubic splines

- Fit spline model
`logistic died cube_age1 cube_age2`
- Note, “first” term is the linear effect
first term: `cube_age1`
- Subsequent terms allow for non-linearity
here cubic there is only `cube_age2`
- Test that subsequent terms 0
`test cube_age2 = 0`

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Two Tests

Likelihood Ratio Test

```
. lrtest splineresults
```

```
Likelihood-ratio test                                LR chi2(1)  =      2.45  
(Assumption: . nested in splineresults)           Prob > chi2 =    0.1173
```

Wald Test

```
. test cube_age2=0
```

```
( 1)  [died]cube_age2 = 0  
  
      chi2( 1) =      2.49  
      Prob > chi2 =    0.1148
```

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Adjusted Splines

- Predicted outcome (prob, mean) by cts predictor
- All other variables “held constant”
- Race adjusted mortality: requires we specify racial composition of ref. population
- Requires that we margin race out of predictions
- According to mix in reference population

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Race in Sample

race/ethnicity	Freq.	Percent	Cum.
white, non-hisp	9,467	80.99	80.99
black, non-hisp	1,225	10.48	91.47
other, non-hisp	225	1.92	93.40
hisp	772	6.60	100.00
Total	11,689	100.00	

I set reference population to resemble this: 81% white, 10% black, 2% other, 6% latino

Choice is *arbitrary* -- could have chose race mix for those under 65. Or the pop of California

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Adjusted Model

```
. logistic died cube_age* i.raceeth
```

```
Logistic regression               Number of obs   =       11689
                                LR chi2(5)        =       1165.06
                                Prob > chi2       =        0.0000
Log likelihood = -3618.6447       Pseudo R2    =        0.1387
```

died	Odds Ratio	Std. Err.	z	P> z	[95% Conf. Interval]	
cube_age1	1.086678	.0121674	7.42	0.000	1.06309	1.110789
cube_age2	1.018119	.0128472	1.42	0.155	.9932481	1.043613
raceeth						
2	1.416758	.1341638	3.68	0.000	1.176762	1.7057
3	.9241177	.22599	-0.32	0.747	.5722275	1.492402
4	.9216928	.1313255	-0.57	0.567	.6971151	1.218619
_cons	.0003029	.0002135	-11.49	0.000	.0000761	.0012061

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Key Code

```
gen adjlogodds = _b[_cons] + _b[cube_age1]*cube_age1 +  
_b[cube_age2]*cube_age2 + _b[1.raceeth]*0.80 _b[2.raceeth]*0.10 +  
_b[3.raceeth]*0.02 + _b[3.raceeth]*0.07
```

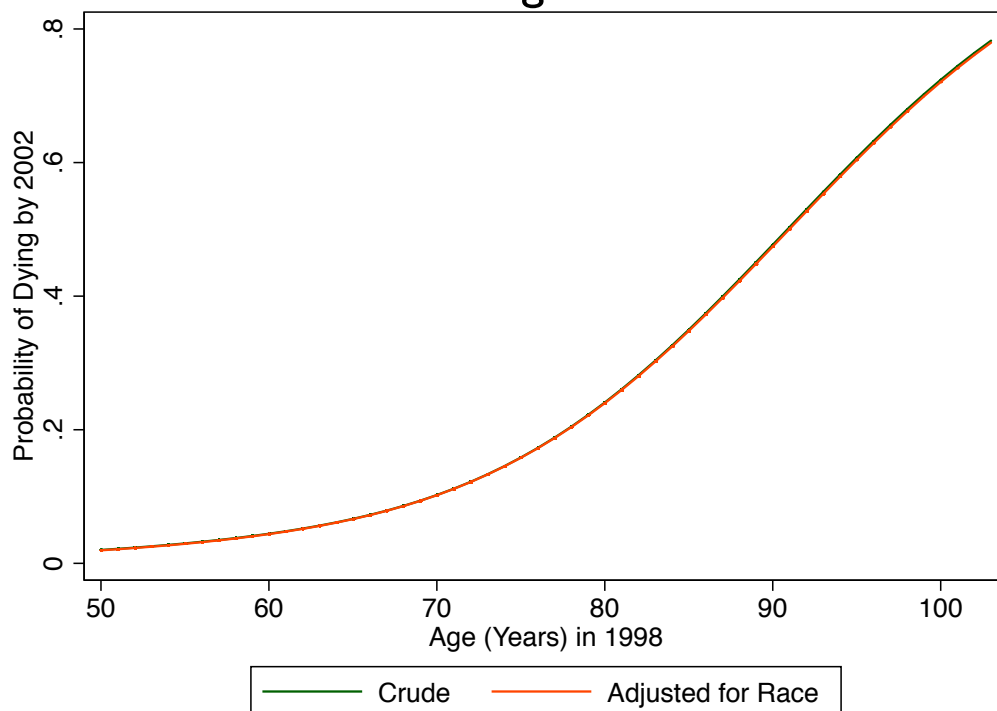
Calculates Logs Odds for the Reference Population

```
gen adjprob = exp( adjlogodds ) / (1+ exp( adjlogodds ))
```

Converts to a Predicted Probability

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Crude v. Adjusted Indistinguishable



Cutpoint Approach

- Binary cutpoint approach always inferior.
Can always do better
- Multiple cutpoints: better
- Dilemma: flexibility v. degrees of freedom
- Discontinuous: difficult for statisticians
- Groups: appeals to clinicians
- Choice of cutpoint: difficult and important
- Residual confounding is an issue

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Transformations: Polynomial

- Two df but only moderate flexibility
- Very susceptible to outliers
- Outlier can affect curve far away
- Mathematically complex: need to graph
- Statistical v. practical significance

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Transformations:

Log Transformation

- Pulls in outliers
- Can produce useful interpretation
especially for exotic assays
- Mathematically complex
- Don't need to graph
- Can't handle negative values
- No easy test for linear v. log

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Linear Fit

- Parsimonious
- No worry about overfitting
optimizing bias/variance tradeoff
- Often “good enough”
especially to get rid of confounding
- Need to be careful about the scale
- Usually produces good interpretation
in the eye of the beholder

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Spline: Pros

- Flexible method
- Knot placement not critical
- Can be fit in any regression model
- Allows for check on linear fit
- Potential rich information
especially for degrees of freedom spent

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Spline: Cons

- Knot number is important issue
- Too many knots can lead to overfitting
could use cross-validation to choose
- Can only be conveyed in a plot
difficult when adjusting other variables
- Useful when predictor is of HIGH interest

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Balance

- overfitting (-)
- residual confounding (-)
- flexibility (+)
- interpretation (+)

Purpose of regression very important