Using Stata 9 to Model Complex Nonlinear Relationships with Restricted Cubic Splines

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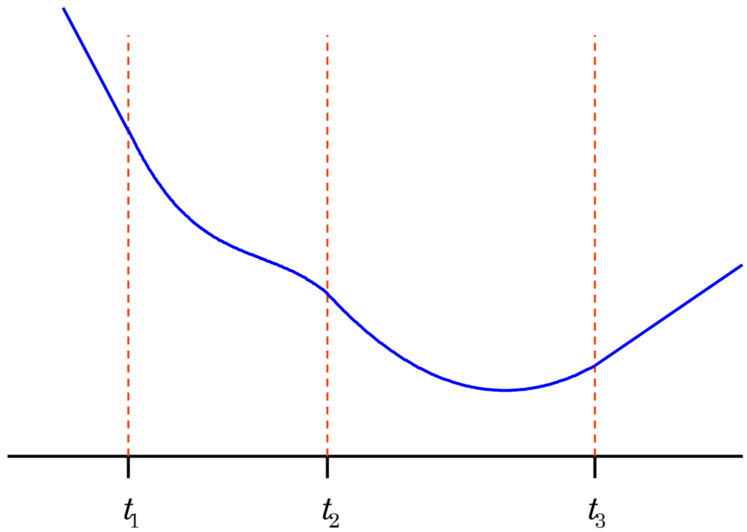
Restricted Cubic Splines (Natural Splines)

Given $\{(x_i, y_i) : i = 1, \cdots, n\}$

We wish to model y_i as a function of x_i using a flexible non-linear model.

In a **restricted cubic spline model** we introduce k knots on the x-axis located at $t_1, t_2, \cdots, t_k$. We select a model of the expected value of y given x that is

- linear before t_1 and after t_k.
- consists of piecewise cubic polynomials between adjacent knots (i.e. of the form $ax^3 + bx^2 + cx + d$)
- continuous and smooth at each knot, with continuous first and second derivatives.



Example of a restricted cubic spline with three knots

Given x and k knots, a restricted cubic spline can be defined by

$$y = \alpha + x_1\beta_1 + x_2\beta_2 + \cdots + x_{k-1}\beta_{k-1}$$

where

$$x_1 = x$$

$$x_j = \left(x - t_{j-1}\right)_+^3 - \frac{\left(x - t_{k-1}\right)_+^3\left(t_k - t_{j-1}\right)}{\left(t_k - t_{k-1}\right)} + \frac{\left(x - t_k\right)_+^3\left(t_{k-1} - t_{j-1}\right)}{\left(t_k - t_{k-1}\right)}$$

for $j = 2, \ldots, k-1$

$$(u)_+ = \begin{cases} u: & u > 0 \\ 0: & u \le 0 \end{cases}$$

These covariates are

- functions of x and the knots but are independent of y.
- $x_1 = x$ and hence the linear hypothesis is tested by $\beta_2 = \beta_3 = \cdots = \beta_{k-1} = 0$.
- Stata programs to calculate $x_1, \cdots, x_{k-1}$ are available on the web. (Run **findit spline** from within Stata.)
- One of these is **rc_spline**

```
rc_spline xvar [fweight] [if exp] [in range]
      [,nknots(#) knots(numlist)]
```

generates the covariates $x_1, \cdots, x_{k-1}$ corresponding to $x =$ **xvar**

nknots(#) option specifes the number of knots (5 by default)

knots(numlist) option specifes the knot locations

This program generates the spline covariates named

_Sxvar1 = **xvar**
_Sxvar2
_Sxvar3
.
.
.

Default knot locations are placed at the quantiles of the x variable given in the following table (Harrell 2001).

Number of knots k	Knot locations expressed in quantiles of the x variable						
3	0.1	0.5	0.9				
4	0.05	0.35	0.65	0.95			
5	0.05	0.275	0.5	0.725	0.95		
6	0.05	0.23	0.41	0.59	0.77	0.95	
7	0.03	0.183	0.342	0.5	0.658	0.817	0.98

SUPPORT Study

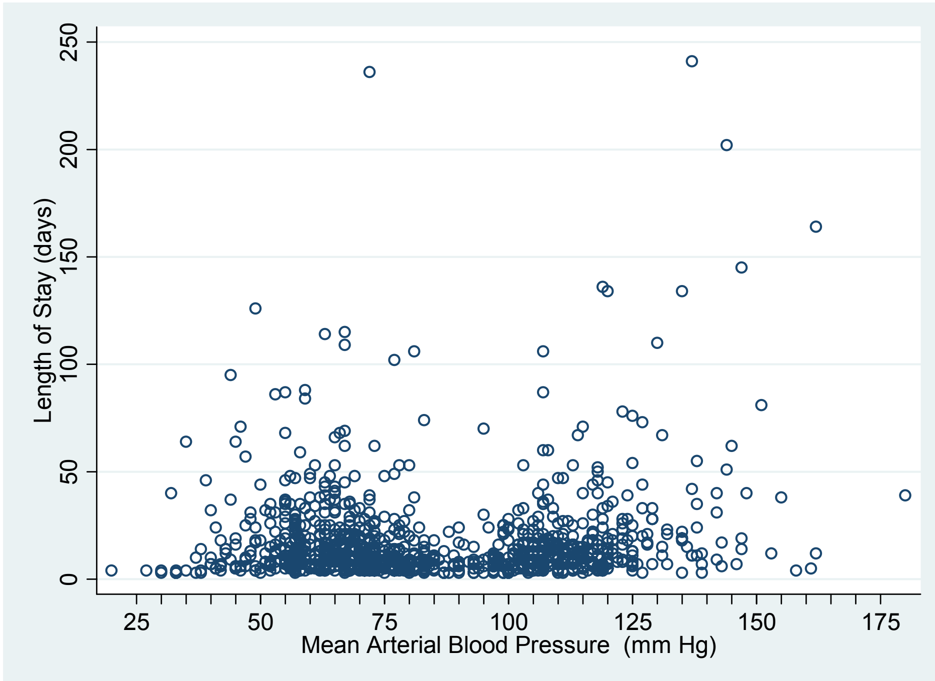
A prospective observational study of hospitalized patients

Lynn & Knauss: "Background for SUPPORT."
J Clin Epidemiol 1990; 43: 1S - 4S.

`los` = length of stay in days.

`meanbp` = baseline mean arterial blood pressure

`hospdead` = $\begin{cases} 1: & \text{Patient died in hospital} \\ 0: & \text{Patient discharged alive} \end{cases}$




```
. gen log_los = log(los)

. rc_spline meanbp
 number of knots = 5
 value of knot 1 = 47
 value of knot 2 = 66
 value of knot 3 = 78
 value of knot 4 = 106
 value of knot 5 = 129
```

Define 4 spline covariates associated with 5 knots at their default locations.

The covariates are named
_Smeanbp1
_Smeanbp2
_Smeanbp3
_Smeanbp4

```
. gen log_los = log(los)

. rc_spline meanbp
 number of knots = 5
 value of knot 1 = 47
 value of knot 2 = 66
 value of knot 3 = 78
 value of knot 4 = 106
 value of knot 5 = 129

. regress log_los _S*
```

Regress **log_los** against all variables that start with the letters **_S**. That is, against
_Smeanbp1
_Smeanbp2
_Smeanbp3
_Smeanbp4

```
      Source |       SS       df       MS              Number of obs =     996
-------------+------------------------------           F(  4,   991) =   24.70
       Model |  60.9019393     4  15.2254848           Prob > F      =  0.0000
    Residual |  610.872879   991  .616420665           R-squared     =  0.0907
-------------+------------------------------           Adj R-squared =  0.0870
       Total |  671.774818   995  .675150571           Root MSE      =  .78512

------------------------------------------------------------------------------
     log_los |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
   _Smeanbp1 |   .0296009   .0059566     4.97   0.000      .017912    .0412899
   _Smeanbp2 |  -.3317922   .0496932    -6.68   0.000    -.4293081   -.2342762
   _Smeanbp3 |   1.263893   .1942993     6.50   0.000     .8826076    1.645178
   _Smeanbp4 |  -1.124065   .1890722    -5.95   0.000    -1.495092   -.7530367
       _cons |    1.03603   .3250107     3.19   0.001     .3982422    1.673819
------------------------------------------------------------------------------
```

```
. test _Smeanbp2  _Smeanbp3 _Smeanbp4

 ( 1)  _Smeanbp2 = 0
 ( 2)  _Smeanbp3 = 0
 ( 3)  _Smeanbp4 = 0

       F(  3,   991) =   30.09
            Prob > F =    0.0000
```

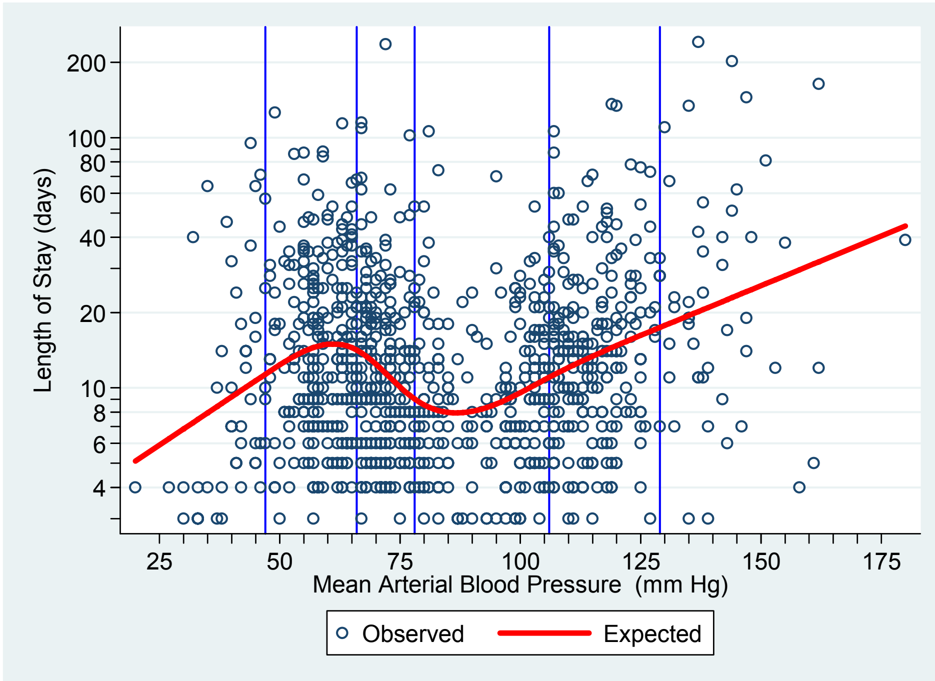
Test the null hypothesis that there is a linear relationship between **meanbp** and **log_los**.

```
. predict y_hat, xb
```

y_hat is the estimated expected value of **log_los** under this model.

Graph a scatterplot of **log_los** vs. **meanbp** together with a line plot of the expected **log_los** vs. **meanbp**.

```
. scatter  log_los meanbp ,msymbol(Oh)                                       ///
>      || line y_hat meanbp                                                  ///
>      ,  xlabel(25 (25) 175) xtick(30 (5) 170) clcolor(red)                 ///
>         clwidth(thick) xline(47 66 78 106 129, lcolor(blue))               ///
>         ylabel(`yloglabel', angle(0)) ytick(`ylogtick')                    ///
>         ytitle("Length of Stay (days)")                                    ///
>         legend(order(1 "Observed" 2 "Expected")) name(knot5, replace)
```

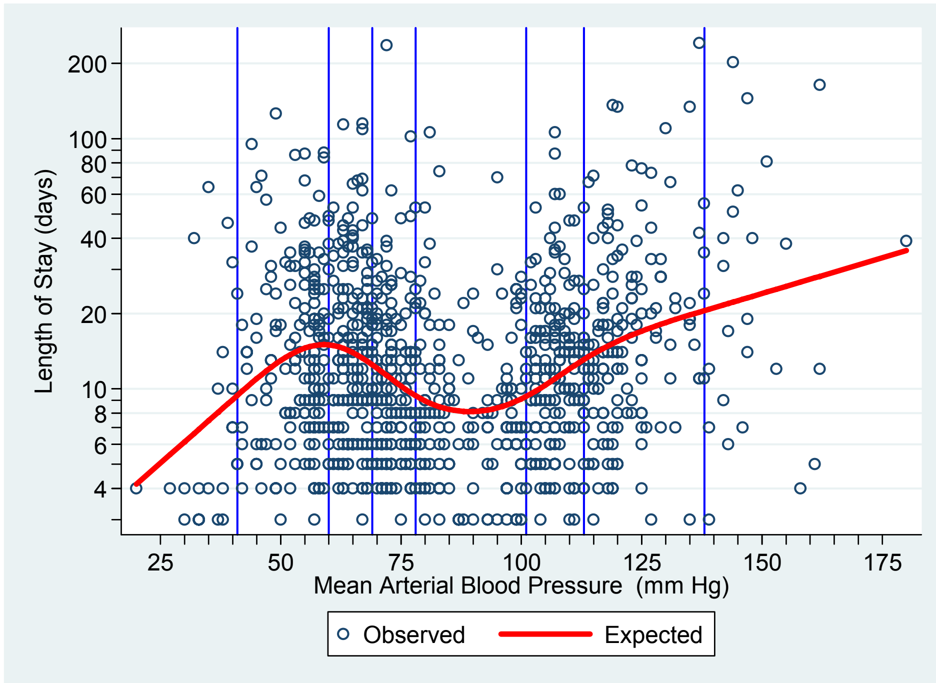



```
. drop _S* y_hat

. rc_spline meanbp, nknots(7)
  number of knots = 7
  value of knot 1 = 41
  value of knot 2 = 60
  value of knot 3 = 69
  value of knot 4 = 78
  value of knot 5 = 101.3251
  value of knot 6 = 113
  value of knot 7 = 138.075

. regress log_los _S*
```

{ Output omitted }

```
. predict y_hat, xb

. scatter  log_los meanbp ,msymbol(Oh)                              ///
>      || line y_hat meanbp                                          ///
>      ,  xlabel(25 (25) 175) xtick(30 (5) 170) clcolor(red)         ///
>         clwidth(thick) xline(41 60 69 78 101 113 138, lcolor(blue)) ///
>         ylabel(`yloglabel', angle(0)) ytick(`ylogtick')            ///
>         ytitle("Length of Stay (days)")                            ///
>         legend(order(1 "Observed" 2 "Expected")) name(setknots, replace)
```

Define **6** spline covariates associated with **7** knots at their **default** locations.



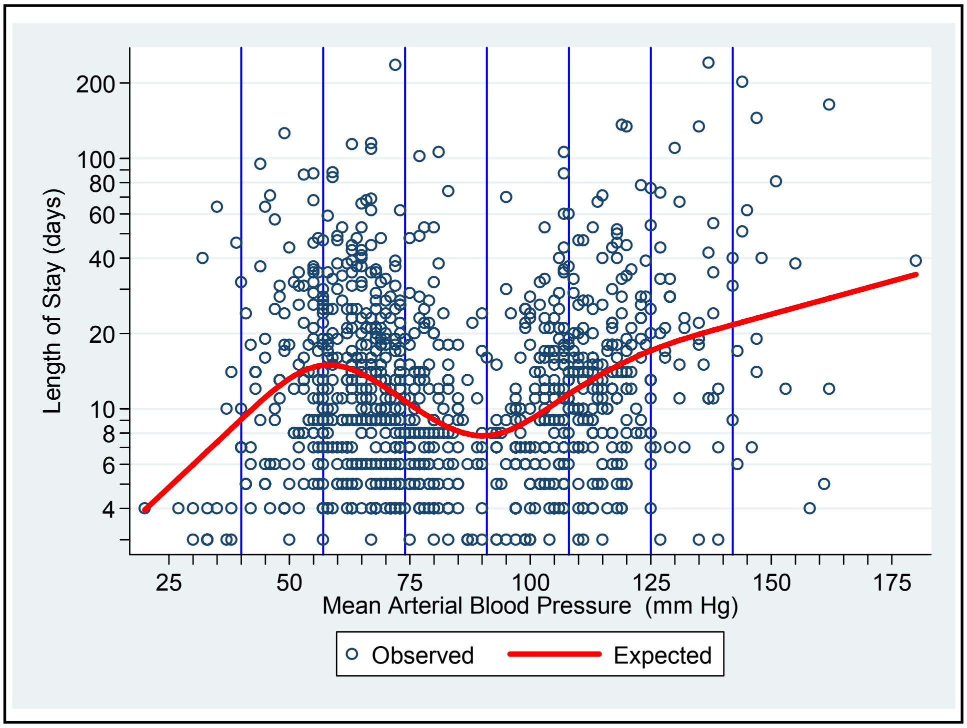

```
. drop _S* y_hat

. rc_spline meanbp, nknots(7) knots(40(17)142)
 number of knots = 7
 value of knot 1 = 40
 value of knot 2 = 57
 value of knot 3 = 74
 value of knot 4 = 91
 value of knot 5 = 108
 value of knot 6 = 125
 value of knot 7 = 142
```

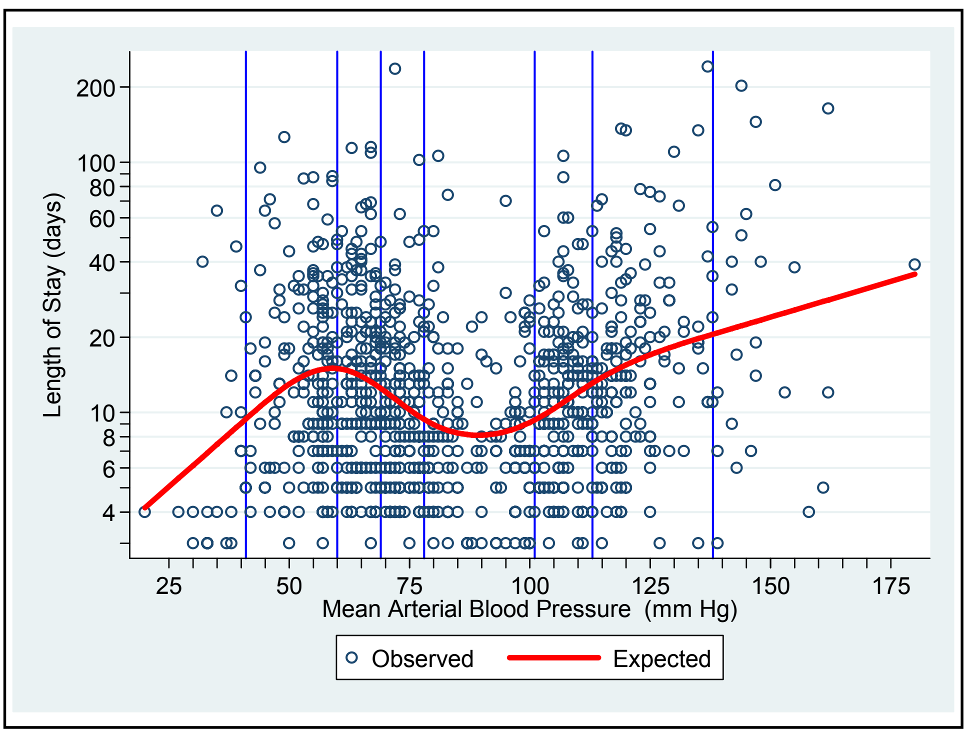
Define **6** spline covariates associated with **7** knots at evenly spaced locations.

```
. regress log_los _S*
```

{ Output omitted }

```
. predict y_hat, xb

. scatter  log_los meanbp ,msymbol(Oh)                                ///
>      || line y_hat meanbp                                           ///
>      ,  xlabel(25 (25) 175) xtick(30 (5) 170) clcolor(red)          ///
>         clwidth(thick) xline(40(17)142, lcolor(blue))                ///
>         ylabel(`yloglabel', angle(0)) ytick(`ylogtick')             ///
>         ytitle("Length of Stay (days)")                             ///
>         legend(order(1 "Observed" 2 "Expected")) name(setknots, replace)
```


200
100
80
60
40
20
10
8
6
4
Length of Stay (days)
25
50
75
100
125
150
175
Mean Arterial Blood Pressure (mm Hg)
Observed
Expected

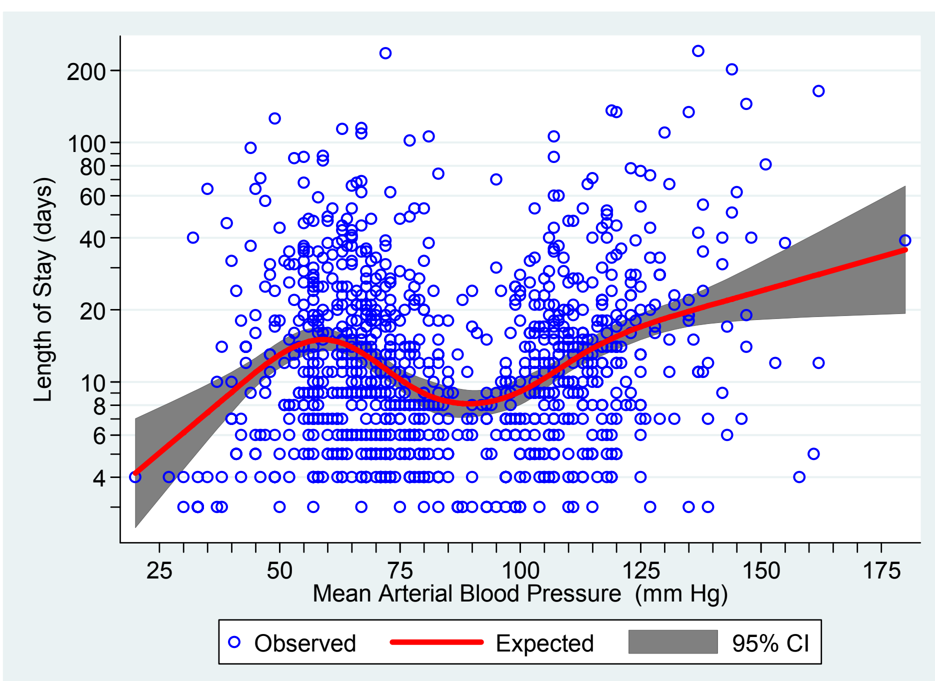

200
100
80
60
40
20
10
8
6
4
Length of Stay (days)
25
50
75
100
125
150
175
Mean Arterial Blood Pressure (mm Hg)
Observed
Expected

```
. drop _S* y_hat

. rc_spline meanbp, nknots(7)

 { Output omitted }

. regress log_los _S*

 { Output omitted }

. predict y_hat, xb

. predict se, stdp

. generate lb = y_hat - invttail(_N-7, 0.025)*se

. generate ub = y_hat + invttail(_N-7, 0.025)*se

. twoway rarea lb ub meanbp , bcolor(gs6) lwidth(none)                 ///
>     || scatter  log_los meanbp ,msymbol(Oh) mcolor(blue)             ///
>     || line y_hat meanbp, xlabel(25 (25) 175) xtick(30 (5) 170)      ///
>        clcolor(red) clwidth(thick) ytitle("Length of Stay (days)")   ///
>        ylabel(`yloglabel', angle(0)) ytick(`ylogtick') name(ci,replace) ///
>        legend(rows(1) order(2 "Observed" 3 "Expected" 1 "95% CI" ))
```

Define **se** to be the standard error of **y_hat**.

Define **lb** and **ub** to be the lower and upper bound of a 95% confidence interval for **y_hat**.

This **twoway** plot includes an **rarea** plot of the shaded 95% confidence interval for **y_hat**.

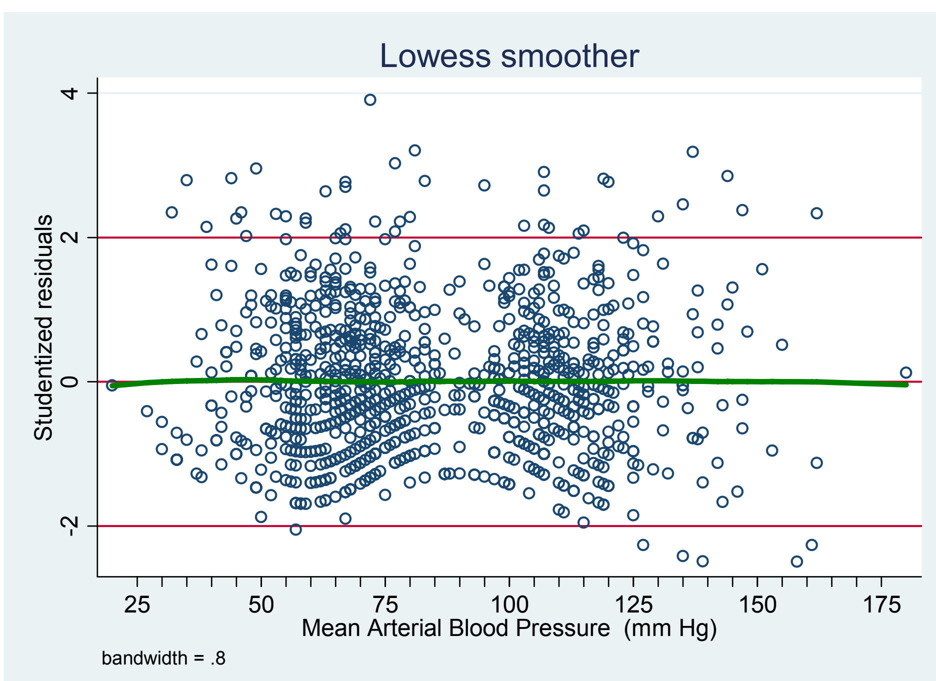


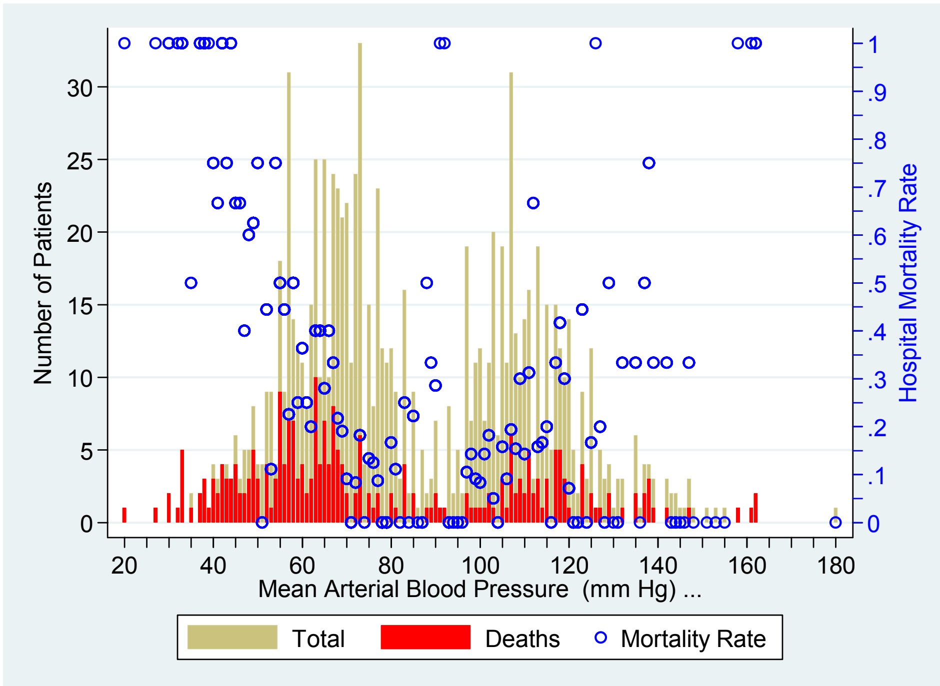
```
. predict rstudent, rstudent
```

Define `rstudent` to be the studentized residual.

Plot a lowess regression curve of `rstudent` against `meanbp`

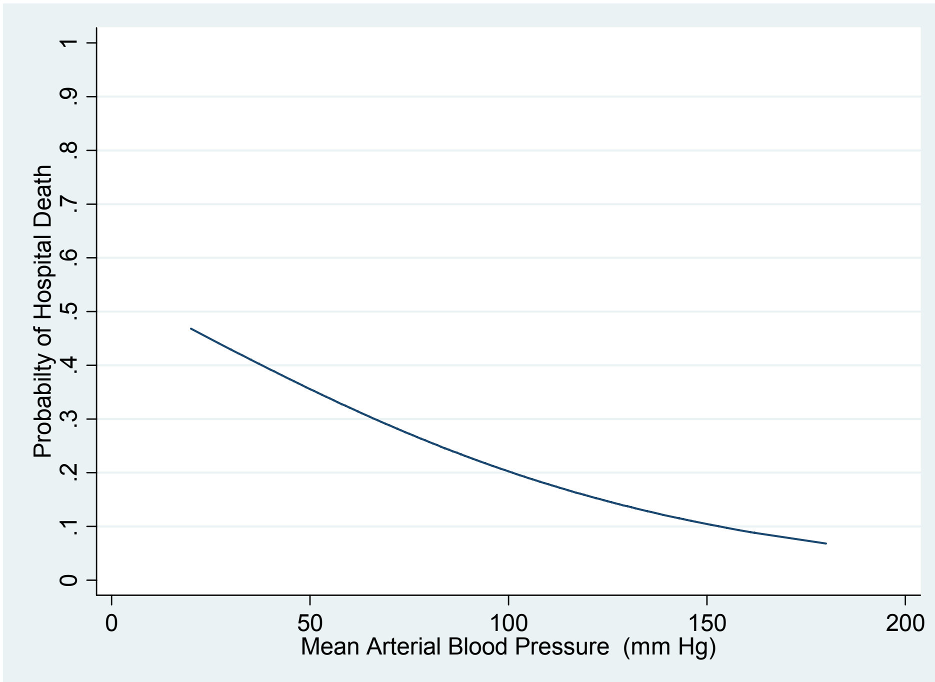
```
. lowess rstudent meanbp                                                  ///
>     , yline(-2 0 2) msymbol(Oh) rlopts(clcolor(green) clwidth(thick))   ///
>     xlabel(25 (25) 175) xtick(30 (5) 170)
```





Simple logistic regression of **hospdead** against **meanbp**

```
. logistic hospdead meanbp

Logistic regression                               Number of obs   =        996
                                                  LR chi2(1)      =      29.66
                                                  Prob > chi2     =     0.0000
Log likelihood = -545.25721                       Pseudo R2       =     0.0265

------------------------------------------------------------------------------
    hospdead | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
      meanbp |   .9845924   .0028997    -5.27   0.000     .9789254    .9902922
------------------------------------------------------------------------------

. predict p,p

. line p meanbp, ylabel(0 (.1) 1) ytitle(Probabilty of Hospital Death)
```




```
. drop _S* p

. rc_spline meanbp
 number of knots = 5
 value of knot 1 = 47
 value of knot 2 = 66
 value of knot 3 = 78
 value of knot 4 = 106
 value of knot 5 = 129

. logistic hospdead _S*, coef

Logistic regression                               Number of obs   =        996
                                                  LR chi2(4)      =     122.86
                                                  Prob > chi2     =     0.0000
Log likelihood = -498.65571                       Pseudo R2       =     0.1097

------------------------------------------------------------------------------
    hospdead |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
   _Smeanbp1 |  -.1055538   .0203216    -5.19   0.000    -.1453834   -.0657241
   _Smeanbp2 |   .1598036   .1716553     0.93   0.352    -.1766345    .4962418
   _Smeanbp3 |   .0752005   .6737195     0.11   0.911    -1.245265    1.395666
   _Smeanbp4 |  -.4721096   .6546662    -0.72   0.471    -1.755232    .8110125
       _cons |   5.531072    1.10928     4.99   0.000     3.356923    7.705221
------------------------------------------------------------------------------
```

Logistic regression of **hospdead** against spline covariates for **meanbp** with 5 knots.

Spline covariates are significantly different from zero

```
. test _Smeanbp2 _Smeanbp3 _Smeanbp4

 ( 1)  _Smeanbp2 = 0
 ( 2)  _Smeanbp3 = 0
 ( 3)  _Smeanbp4 = 0

           chi2(  3) =   80.69
         Prob > chi2 =    0.0000
```

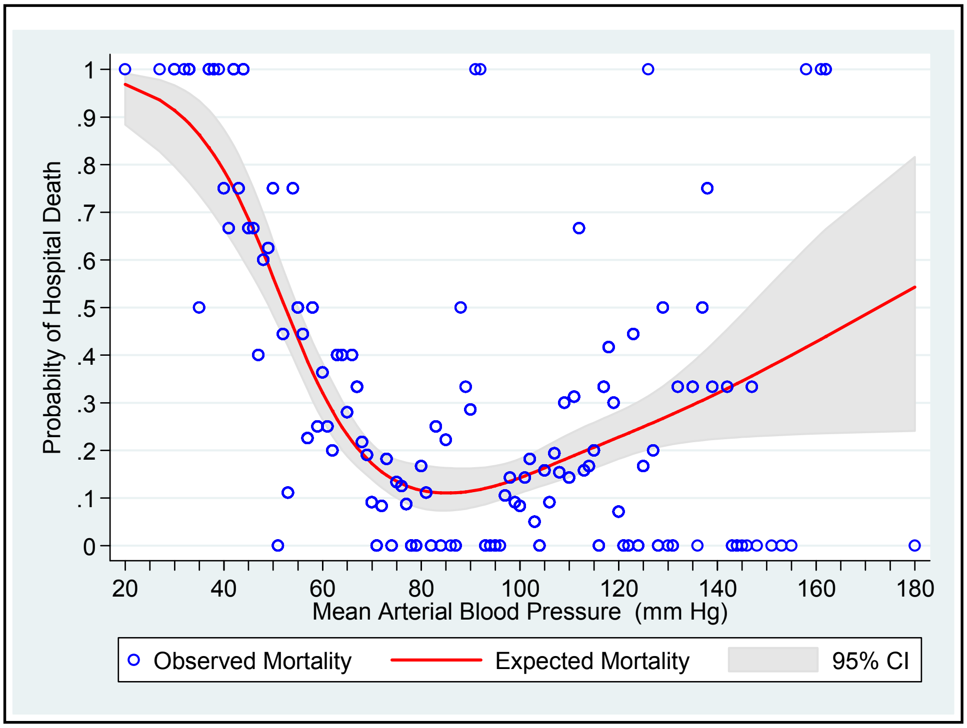
We reject the null hypothesis that the log odds of death is a linear function of mean BP.

Estimated Statistics at Given Mean BP

- `p` = probability of death
- `logodds` = log odds of death
- `stderr` = standard error of logodds
- (`lodds_lb`, `lodds_ub`) = 95% CI for `logodds`
- (`ub_l`, `ub_p`) = 95% CI for `p`

```
. predict p,p

. predict logodds, xb

. predict stderr, stdp

. generate lodds_lb = logodds - 1.96*stderr

. generate lodds_ub = logodds + 1.96*stderr

. generate ub_p = exp(lodds_ub)/(1+exp(lodds_ub))

. generate lb_p = exp(lodds_lb)/(1+exp(lodds_lb))

. by meanbp: egen rate = mean(hospdead)

. twoway rarea lb_p ub_p meanbp, bcolor(gs14)                         ///
>     || line p meanbp, clcolor(red) clwidth(medthick)                ///
>     || scatter rate meanbp, msymbol(Oh) mcolor(blue)                ///
>     ,  ylabel(0 (.1) 1, angle(0)) xlabel(20 (20) 180)               ///
>        xtick(25 (5) 175) ytitle(Probabilty of Hospital Death)       ///
>        legend(order(3 "Observed Mortality"                          ///
>            2 "Expected Mortality"  1 "95% CI") rows(1))
```

`rate` = proportion of deaths at each blood pressure



We can use this model to calculate mortal odds ratios for patients with different baseline blood pressures.

```
. list _S*                                                                    ///
>     if (meanbp==60 | meanbp==90 | meanbp==120) & meanbp ~= meanbp[_n-1]

     +-------------------------------------------+
     | _Smean~1    _Smean~2    _Smean~3    _Smean~4 |
     |-------------------------------------------|
178. |       60      .32674           0           0 |
575. |       90    11.82436    2.055919    .2569899 |
893. |      120    56.40007    22.30039    10.11355 |
     +-------------------------------------------+
```

Logodds of death for patients with **meanbp** = 60

```
. lincom (5.531072 +        60*_Smeanbp1 +    .32674*_Smeanbp2          ///
>                  +         0*_Smeanbp3 +         0 *_Smeanbp4)        ///
>                                                                       ///
>       -(5.531072 +        90*_Smeanbp1 + 11.82436*_Smeanbp2           ///
>                  + 2.055919*_Smeanbp3 + .2569899*_Smeanbp4)
```

Logodds of death for patients with **meanbp** = 90

```
 ( 1) - 30 _Smeanbp1 - 11.49762 _Smeanbp2 - 2.055919 _Smeanbp3 -
> .2569899 _Smeanbp4 = 0

------------------------------------------------------------------------------
    hospdead | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |    3.65455   1.044734     4.53   0.000     2.086887    6.399835
------------------------------------------------------------------------------
```

Mortal odds ratio for patients with **meanbp** = 60 vs. **meanbp** = 90.

```
. lincom (5.531072 +      120*_Smeanbp1 + 56.40007*_Smeanbp2             ///
>                   + 22.30039*_Smeanbp3 + 10.11355*_Smeanbp4)           ///
>                                                                        ///
>        -(5.531072 +       90*_Smeanbp1 + 11.82436*_Smeanbp2            ///
>                   + 2.055919*_Smeanbp3 + .2569899*_Smeanbp4)

 ( 1)  30 _Smeanbp1 + 44.57571 _Smeanbp2 + 20.24447 _Smeanbp3 + 9.85656
> _Smeanbp4 = 0

------------------------------------------------------------------------------
    hospdead | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         (1) |   2.283625   .5871892     3.21   0.001     1.379606    3.780023
------------------------------------------------------------------------------
```

Mortal odds ratio for patients with **meanbp** = 120 vs. **meanbp** = 90.

Stone CJ, Koo CY: Additive splines in statistics *Proceedings of the Statistical Computing Section ASA*. Washington D.C.: American Statistical Association, 1985:45-8.

Stata Software

Goldstein, R: srd15, Restricted cubic spline functions. 1992; *STB*-10: 29-32. *spline.ado*

Sasieni, P: snp7.1, Natural cubic splines. 1995; *STB*-24. *spline.ado*

Dupont WD, Plummer WD: *rc_spline* from SSC-IDEAS http://fmwww.bc.edu/RePEc/bocode/r

General Reference

Harrell FE: *Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression, and Survival Analysis*. New York: Springer, 2001.

Cubic B-Splines

de Boor, C: *A Practical Guide to Splines.*
New York: Springer-Verlag 1978

- Similar to restricted cubic splines
- More complex
- More numerically stable
- Does not perform as well outside of the knots

Software

Newson, R: sg151, B-splines & splines parameterized by values at ref. points on x-axis. 2000; *STB*-57: 20-27.
bspline.ado

nl – Nonlinear least-squares regression

- Effective when you know the correct form of the non-linear relationship between the dependent and independent variable.
- Has fewer post-estimation commands and `predict` options than `regress`.

Conclusions

- Restricted cubic splines can be used with any regression program that uses a linear predictor – e.g. `regress, logistic, glm, stcox` etc.
- Can greatly increase the power of these methods to model non-linear relationships.
- Simple technique that is easy to use and easy to explain.
- Can be used to test the linearity assumption of generalized linear regression models.
- Allows users to take advantage of the very mature post-estimation commands associated with generalized linear regression programs to produce sophisticated graphics and residual analyses.