Module 5: Generalized Additive Models

BIOS 526

Reading

- From Wood, S. *Generalized Additive Models: An Introduction with R, 2nd Edition*: Chapter 4, 5.1.2, 5.3.1, 5.4, 5.5.1, 6.1.2, 6.10, 6.12.
- A nice resource for fitting GAMs: https://wiki.qcbs.ca/r_workshop8.

Concepts

- Generalized additive models (logistic).
- Additive models with multiple covariates
- Using $gam()$ in package $mgcv()$ to fit semiparametric models with parametric (slopes) and nonparametric terms (functions)
- Bivariate splines.
- Interpreting non-linear effects.

Generalized Additive Models

Binary Outcome Example

Recall the example from Module 4:

Dataset: a cohort of live births from Georgia born in the year 2001 (N = 77,340).

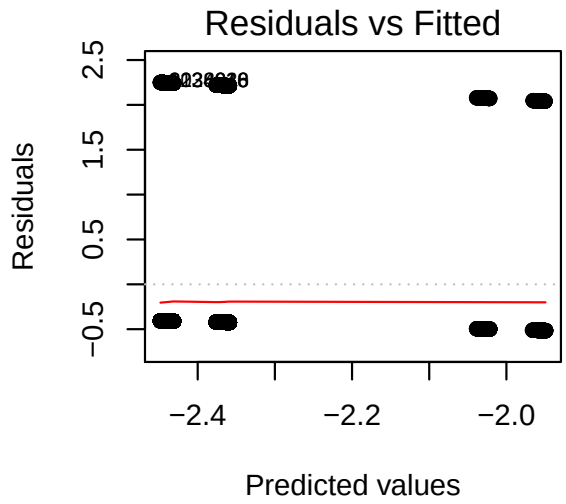
Variables:

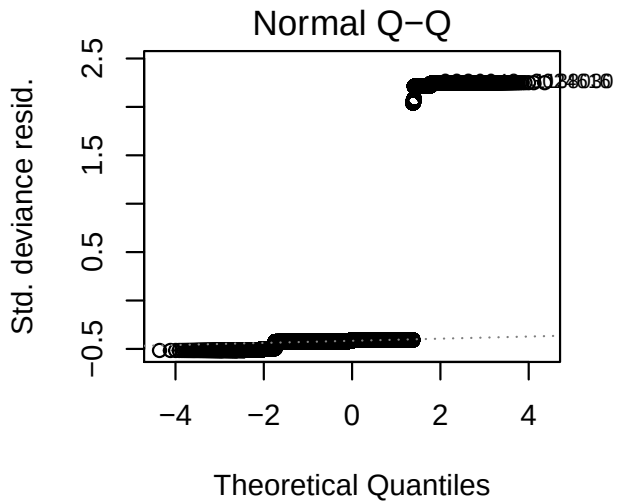
- ptb: indicator for whether the baby from pregnancy i was born preterm ($<$ 37 weeks).
- age: the mother's age at delivery.
- $male$: indicator of the baby's sex (1 = male; 0=female).
- $tobacco$: indicator for mother's tobacco use during pregnancy (1 = yes; 0 = no)

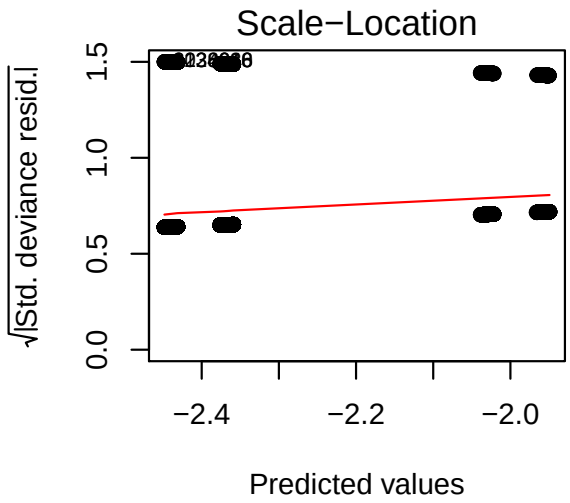
Previous analysis

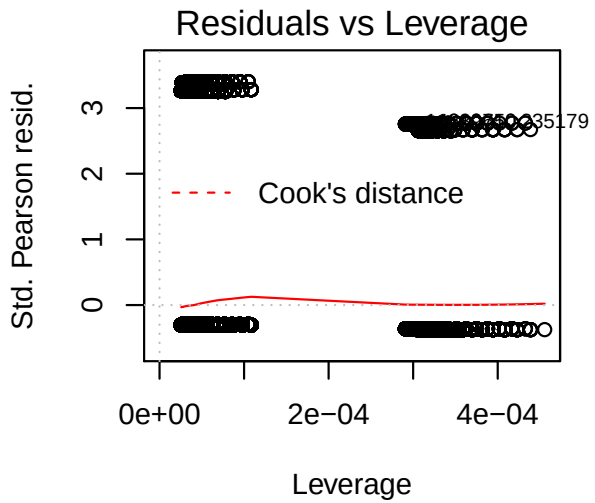
```
### Fit logistic regression model
> fit = glm(ptb~age + male+tobacco, data = dat, family = binomial(link='logit'))
> summary(fit)

Call:
glm(formula = ptb ~ age + male + tobacco, family = binomial(link = "logit"),
    data = dat)

Deviance Residuals:
       Min          1Q      Median          3Q         Max
-0.5159563  -0.4235975  -0.4102807  -0.4087970   2.2499946

Coefficients:
                Estimate   Std. Error   z value   Pr(>|z|)
(Intercept) -2.421266448  0.063135527 -38.35030 < 2.22e-16 ***
age         -0.000629473  0.002159576  -0.29148  0.7706843
maleM        0.072365862  0.025867177   2.79759  0.0051485 **
tobacco      0.409649486  0.053462733   7.66234 1.8258e-14 ***
---
Signif. codes:  0 ?***? 0.001 ?**? 0.01 ?*? 0.05 ?.? 0.1 ? ? 1

(Dispersion parameter for binomial family taken to be 1)

    Null deviance: 44907.564  on 77339  degrees of freedom
Residual deviance: 44845.557  on 77336  degrees of freedom
AIC: 44853.557
```

The plot diagnostics are not very helpful with binary responses:









Generalized Additive Model

To account for non-linear age effect

$$ptb_i \sim \text{Bernoulli } (p_i)$$

$$\log\left(\frac{p_i}{1-p_i}\right) = \beta_0 + \beta_1 male_i + \beta_2 tobacco_i + s(age_i),$$

where $s(age_i)$ is a smooth function of age. The above model is known as a generalized additive model.

GAMs: Generalized Additive Models.

Everything we learned about additive models is directly applicable in this setting!

GAM with logit link

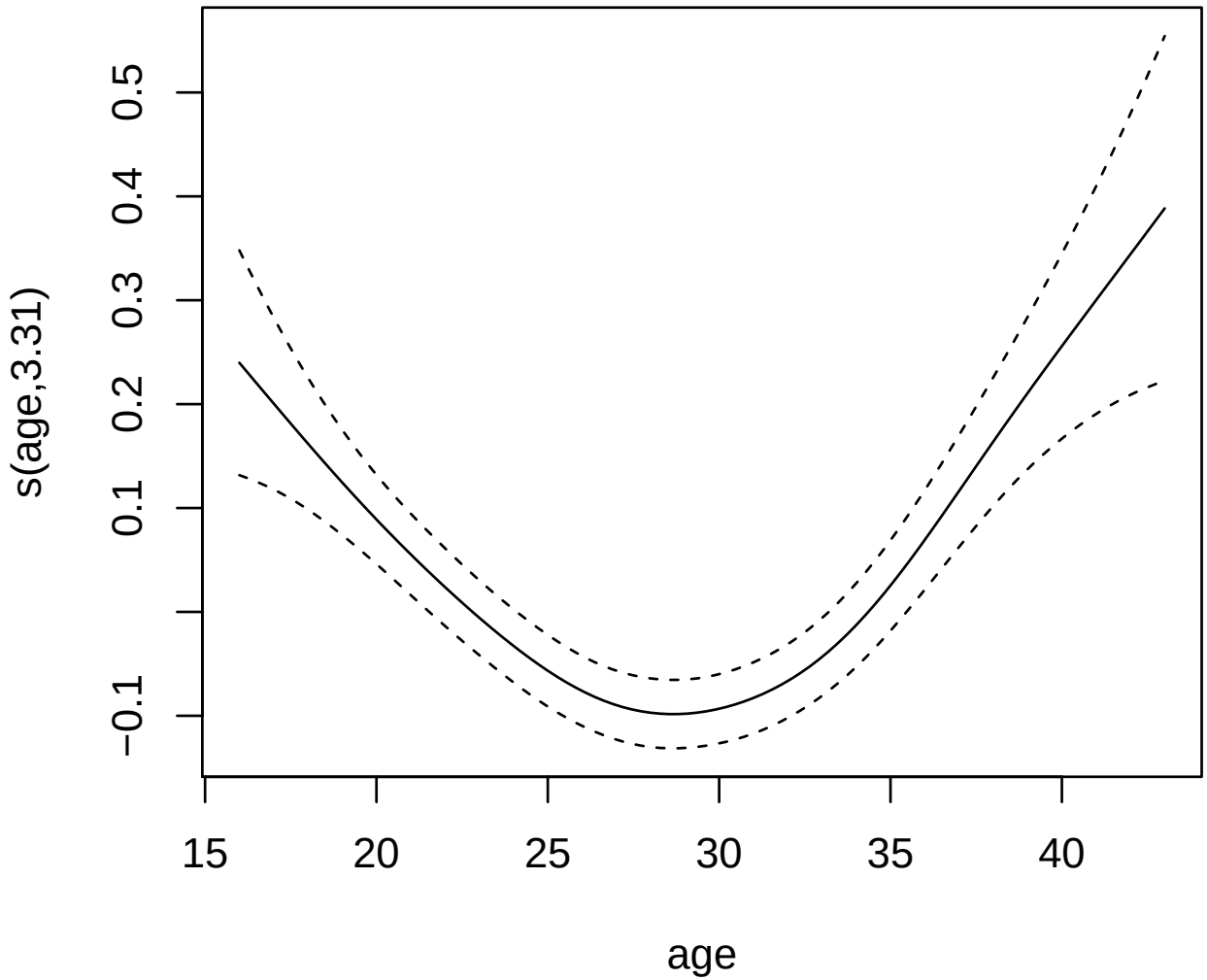
Using the `mgcv::gam` function:

```
> fit.gam = gam(ptb~s(age)+male+tobacco,family=binomial,data=dat)
> summary(fit.gam)

Family: binomial
Link function: logit

Formula:
ptb ~ s(age) + male + tobacco

Parametric coefficients:
            Estimate Std. Error  z value Pr(>|z|)
(Intercept) -2.44226    0.01913 -127.647  < 2e-16 ***
maleM        0.07274    0.02588    2.811  0.00494 **
tobacco      0.39016    0.05356    7.284 3.24e-13 ***
---
Signif. codes:  0 ?***? 0.001 ?**? 0.01 ?*? 0.05 ?.? 0.1 ? ? 1

Approximate significance of smooth terms:
         edf Ref.df Chi.sq  p-value
s(age) 3.314  4.146  70.17 3.85e-14 ***
---
Signif. codes:  0 ?***? 0.001 ?**? 0.01 ?*? 0.05 ?.? 0.1 ? ? 1

R-sq.(adj) =  0.00177   Deviance explained = 0.304%
UBRE = -0.42095  Scale est. = 1         n = 77340
```

GAM diagnostics

```
> gam.check(fit.gam)

Method: UBRE   Optimizer: outer newton
full convergence after 3 iterations.
Gradient range [9.816712095e-07,9.816712095e-07]
(score -0.4209494806 & scale 1).
Hessian positive definite, eigenvalue range [1.285936713e-05,1.285936713e-05].
Model rank =  12 / 12

Basis dimension (k) checking results. Low p-value (k-index<1) may
indicate that k is too low, especially if edf is close to k'.

         k'  edf k-index p-value
s(age) 9.00 3.31    0.94    0.66
```

Generalized Additive Model

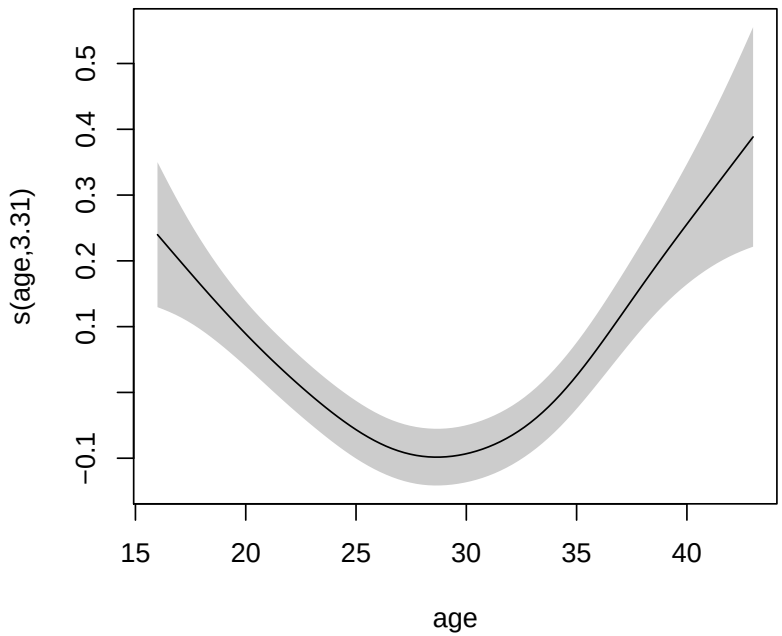


Generalized Additve Model: plots 2

See ?plot.gam for additional options.

Wood suggests coverage probabilities are better with seWithMean=TRUE to include uncertainty in overall mean, particularly if edf=1.

```
plot(fit.gam, shade = TRUE, seWithMean = TRUE, pch = 16, cex = 0.5)
```



Bayesian credible intervals

We are assuming the underlying function is smooth. We can formalize this as a prior in a Bayesian model. We won't get into details, but may return to this topic in M7.

In Bayesian statistics, the parameters $\boldsymbol{\beta}$ are random variables. A ridge penalty corresponds to an improper Gaussian prior:

$$f_{\boldsymbol{\beta}} \propto \exp(-\boldsymbol{\beta}'\mathbf{B}\boldsymbol{\beta}/2).$$

For Gaussian data, this results in a posterior distribution

$$[\boldsymbol{\beta}|\mathbf{y},\lambda] \sim N\left\{\hat{\boldsymbol{\beta}}, \sigma^2(\mathbf{X}'\mathbf{X}+\lambda\mathbf{B})^{-1}\right\}$$

For a general likelihood, we use the Fisher Information matrix (Hessian of the negative log likelihood at $\hat{\boldsymbol{\beta}}$)

$$[\boldsymbol{\beta}|\mathbf{y},\lambda] \sim N\left\{\hat{\boldsymbol{\beta}}, \left(\hat{\mathcal{I}}+\lambda\mathbf{B}\right)^{-1}\right\}$$

Multiply by ϕ for quasi-Poisson.
In particular, the "Bayesian credible intervals" plotted in mgcv::gam have Frequentist coverage probabilities. See Section 6.10 in Wood.

Multiple Smoothers

Multiple Smooth Terms

Let's consider an additive model for two continuous variables, x_i and z_i:

$$y_i = f_1(x_i) + f_2(z_i) + \epsilon_i\,, \quad \epsilon_i \overset{iid}{\sim} N(0, \sigma^2) \tag{1}$$

where $f_1(\cdot)$ and $f_2(\cdot)$ denote smooth relationships between the response y and predictors x and z.

Again, extends to generalized linear models (binomial, Poisson, etc).

We again express non-linear functions using basis functions:

$$f_1(x_i) = \sum_{m=1}^{M_1} \alpha_m b_{m1}(x_i) \qquad f_2(z_i) = \sum_{m=1}^{M_2} \beta_m b_{m2}(z_i)$$

Induce smoothing by penalizing regression coefficients.
Note we also use smoothers to control for confounders flexibly.

Associations between Mortality and Fine Particulate Matter

Fine particulate matter ($PM_{2.5}$):

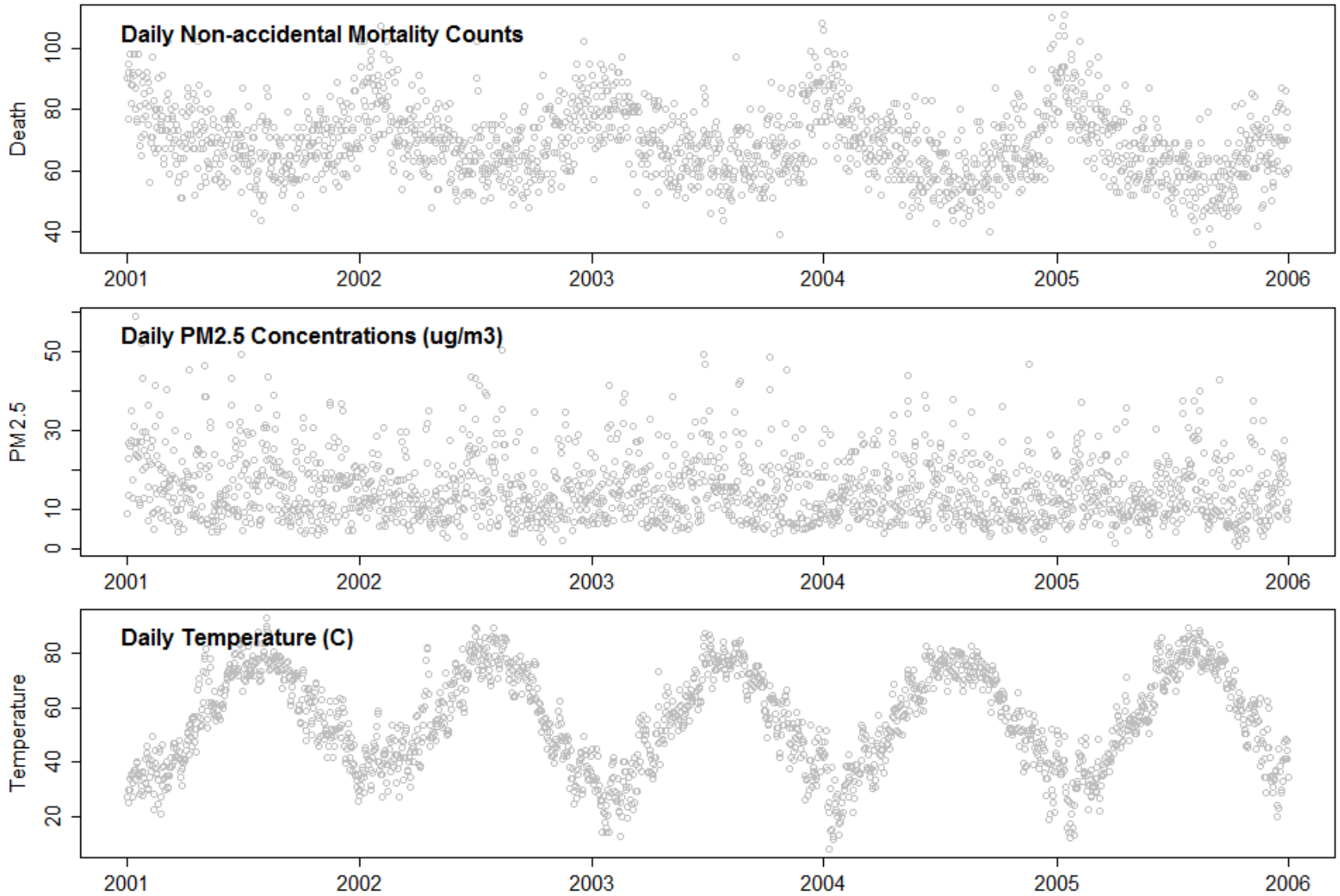
- represents a mixture of solid and liquid particles in the air that are less than 2.5 μm in diameter;
- mainly arises from combustion sources (power generation, vehicle, and industrial operations).

Scientific Question: what is the association between daily mortality counts and daily concentration of outdoor $PM_{2.5}$ air pollution?

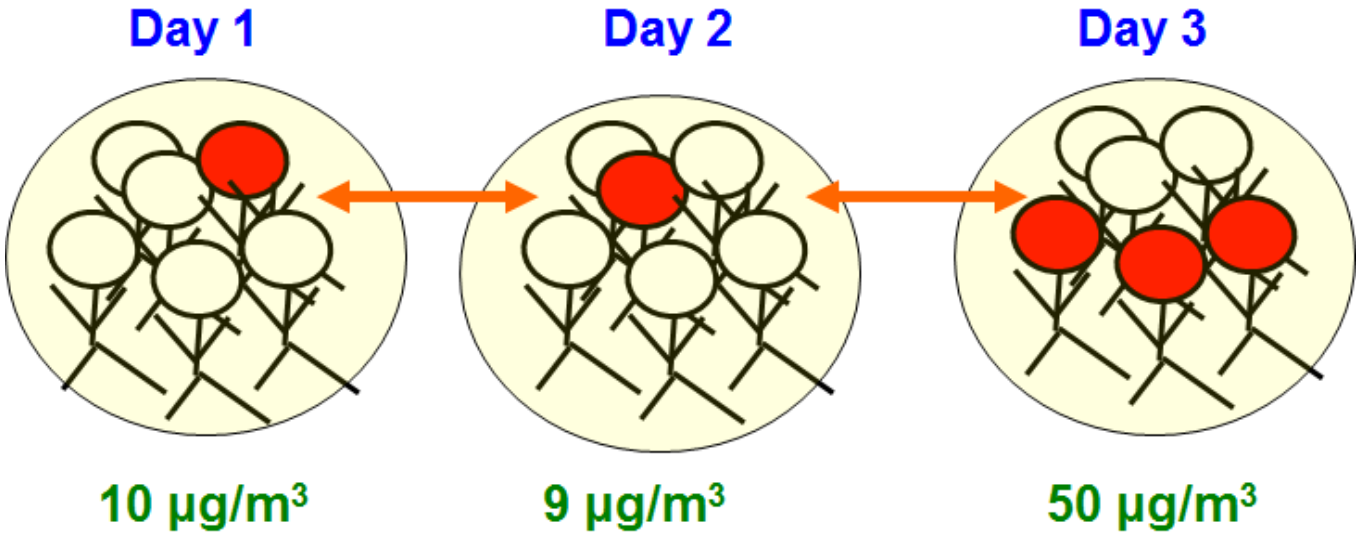
Data Sources:

- Daily counts of non-accidental deaths (age ≥ 65) in the 5-county New York City area (2001-2005) obtained from the National Center for Health Statistics (CDC).
- Daily $PM_{2.5}$ concentrations from Environmental Protection Agency
- Daily meteorology conditions from the National Climatic Data Center (NOAA).

Associations between Mortality and Fine Particulate Matter



Time-Series Health Model



- We are interested in the association between daily variation in mortality counts and daily variation in exposure.
- In a time-series design we view population as the unit of analysis. I.e. outcome = total mortality counts arising from the population.
- Confounders that vary smoothly in time can be easily controlled for by including long-term time trends.

Time-Series Health Model

Let y_t denote the death count on day t, and x_t be the corresponding $PM_{2.5}$ level. Consider the following model:

$$\log y_t = \beta_0 + \beta_1 x_t + \text{confounders} + \epsilon_i \ , \quad \epsilon_i \overset{iid}{\sim} N(0, \sigma^2). \tag{2}$$

Our parameter of interest is β_1. Here we model log-transformed death counts, which can improve normality of residuals.

Confounders to consider:

- Day of the week.
- Seasonality and long-term trends.
- Same-day temperature.
- Same-day dew point temperature.
- Previous day's temperature and dew point temperature.

Data

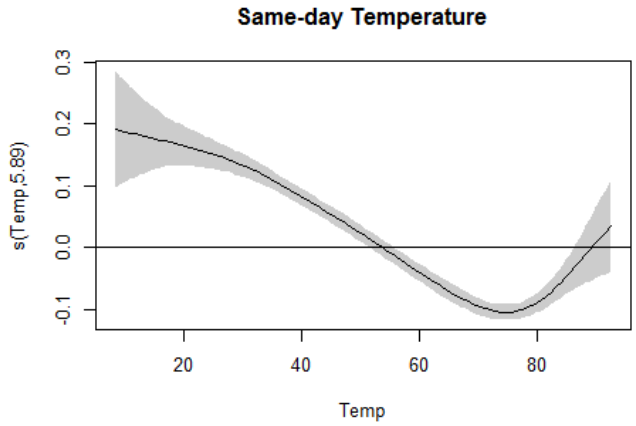
```
> load ("NYC.RData")
> str(health)
'data.frame': 1826 obs. of  12 variables:
 $ date      : Date, format: "2001-01-01" "2001-01-02" "2001-01-03" ...
 $ alldeaths : int  171 198 179 169 201 182 167 167 193 159 ...
 $ age65plus : int  122 146 133 128 145 141 126 116 142 124 ...
 $ cardioresp: int  103 106 109 90 120 101 102 101 115 101 ...
 $ cr65plus  : int  90 92 95 77 98 90 88 82 92 88 ...
 $ dow       : chr  "Monday" "Tuesday" "Wednesday" "Thursday" ...
 $ pm25      : num [1:1826, 1] 8.72 13.39 22.9 26.76 25.89 ...
  ..- attr(*, "dimnames")=List of 2
  .. ..$ : chr  "1" "2" "3" "4" ...
  .. ..$ : NULL
 $ Temp      : num  27.6 25.1 25.3 29.8 29.8 33.9 34.9 35.7 32.3 27.6 ...
 $ DpTemp    : num  14.2 11.8 13.1 15.9 20.5 26.7 22.2 31.2 24.4 11.7 ...
 $ rmTemp    : num  27.7 26.8 26 26.7 28.3 ...
 $ rmDpTemp  : num  17.5 14.3 13 13.6 16.5 ...
```

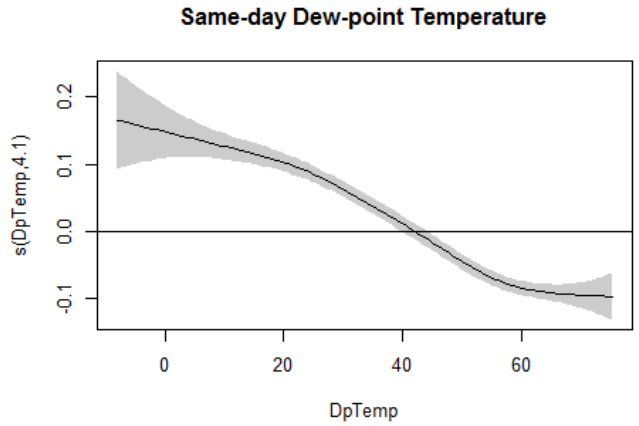
- $DpTemp =$ Dew point temperature.
- rm denotes 3-day running mean of the current day and 2 days prior.
- Note $date$ variable is recorded as the in the Date format. We also create a new date variable $date2$ which takes value 1 to 1827

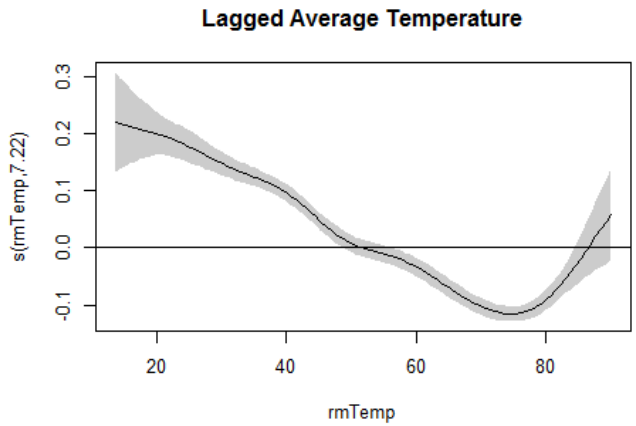
Unadjusted Effects of Meteorology

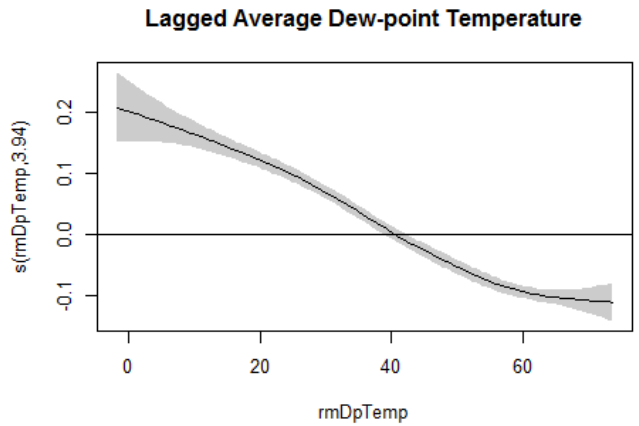
To educational purposes, examine the unadjusted effect of each potential confounder.

```
> fit1 = gam(log(cr65plus)~s(Temp), data = health)
> plot (fit1, rug =F, main="Same-day Temperature", shade=T)
```



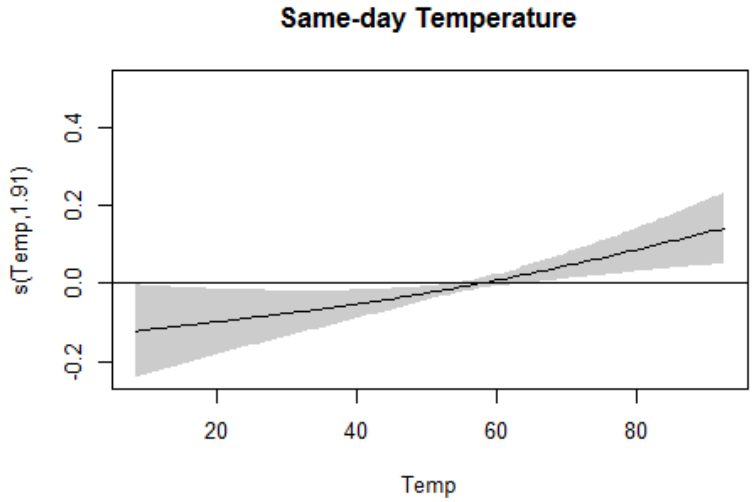


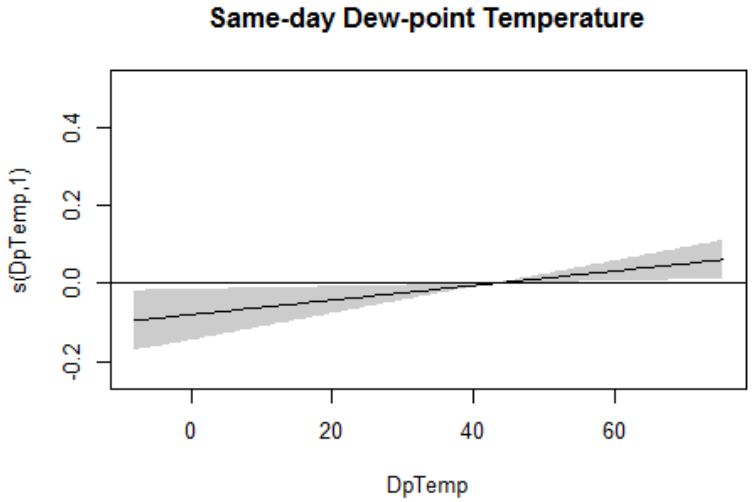


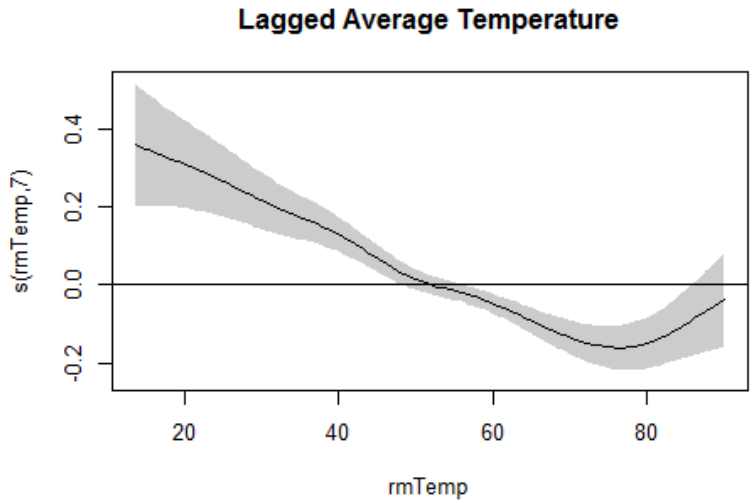


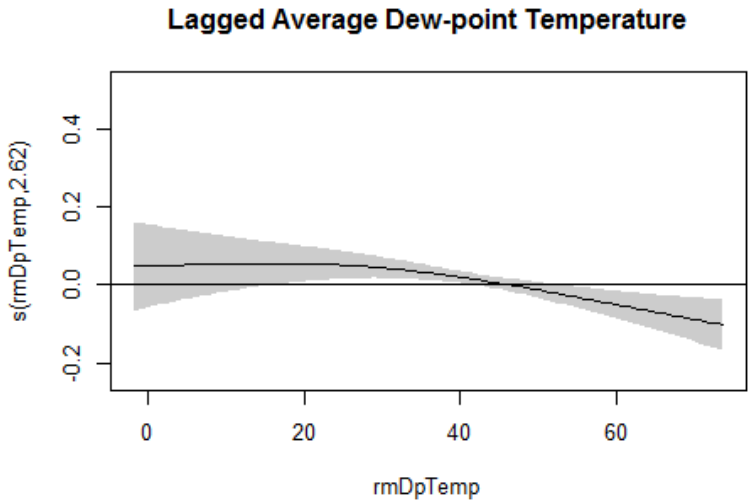
Adjusted Effects of Meteorology

```
> fit = gam(log(alldeaths)~s(Temp)+s(DpTemp)+s(rmTemp)+s(rmDpTemp), data = health)
```







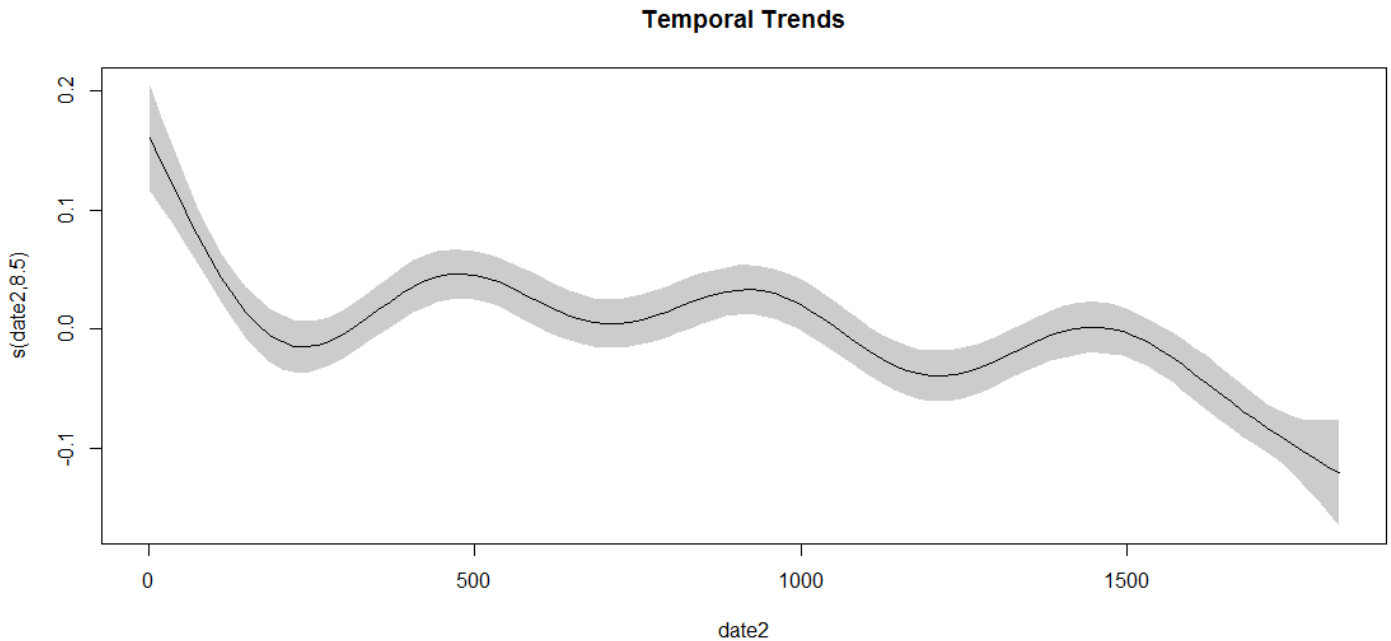


Adjusted Effects of Meteorology

```
> summary(fit)

Parametric coefficients:
            Estimate Std. Error t value Pr(>|t|)
(Intercept) 4.219108   0.003283    1285   <2e-16 ***

Approximate significance of smooth terms:
              edf Ref.df     F  p-value
s(Temp)     1.913  2.509 3.797  0.01485 *
s(DpTemp)   1.000  1.000 6.052  0.01398 *
s(rmTemp)   7.003  8.078 7.826 1.84e-10 ***
s(rmDpTemp) 2.622  3.428 3.707  0.00807 **

R-sq.(adj) =   0.32   Deviance explained = 32.5%
GCV score = 0.019829  Scale est. = 0.019682  n = 1826


### Note the meteorology variables are highly correlated
> round( cor (health[c("Temp", "DpTemp", "rmTemp", "rmDpTemp")]), 2)
          Temp DpTemp rmTemp rmDpTemp
Temp      1.00   0.94   0.97     0.93
DpTemp    0.94   1.00   0.91     0.94
rmTemp    0.97   0.91   1.00     0.96
rmDpTemp  0.93   0.94   0.96     1.00
```

Temporal Trends in Daily Mortality

```
> fit = gam(log(alldeaths)~s(date2), data = health)
> summary(fit)
Parametric coefficients:
            Estimate Std. Error t value Pr(>|t|)
(Intercept) 4.219108   0.003839    1099   <2e-16 ***

Approximate significance of smooth terms:
           edf Ref.df     F p-value
s(date2) 8.502   8.93 15.97  <2e-16 ***

R-sq.(adj) =  0.0704   Deviance explained = 7.47%
GCV score = 0.027059  Scale est. = 0.026918  n = 1826
```



Checking if k is sufficiently large

k-index less than 1 indicates lack of fit.

Similarly, low p-value indicates lack of fit.

```
gam.check(fit)

Method: GCV   Optimizer: magic
Smoothing parameter selection converged after 9 iterations.
The RMS GCV score gradient at convergence was 5.958159e-07 .
The Hessian was positive definite.
Model rank =  10 / 10

Basis dimension (k) checking results. Low p-value (k-index<1) may
indicate that k is too low, especially if edf is close to k'.

          k' edf k-index p-value
s(date2) 9.0 8.5    0.57  <2e-16 ***
```

Maximum Dimension ($option\ s(, k =)$)

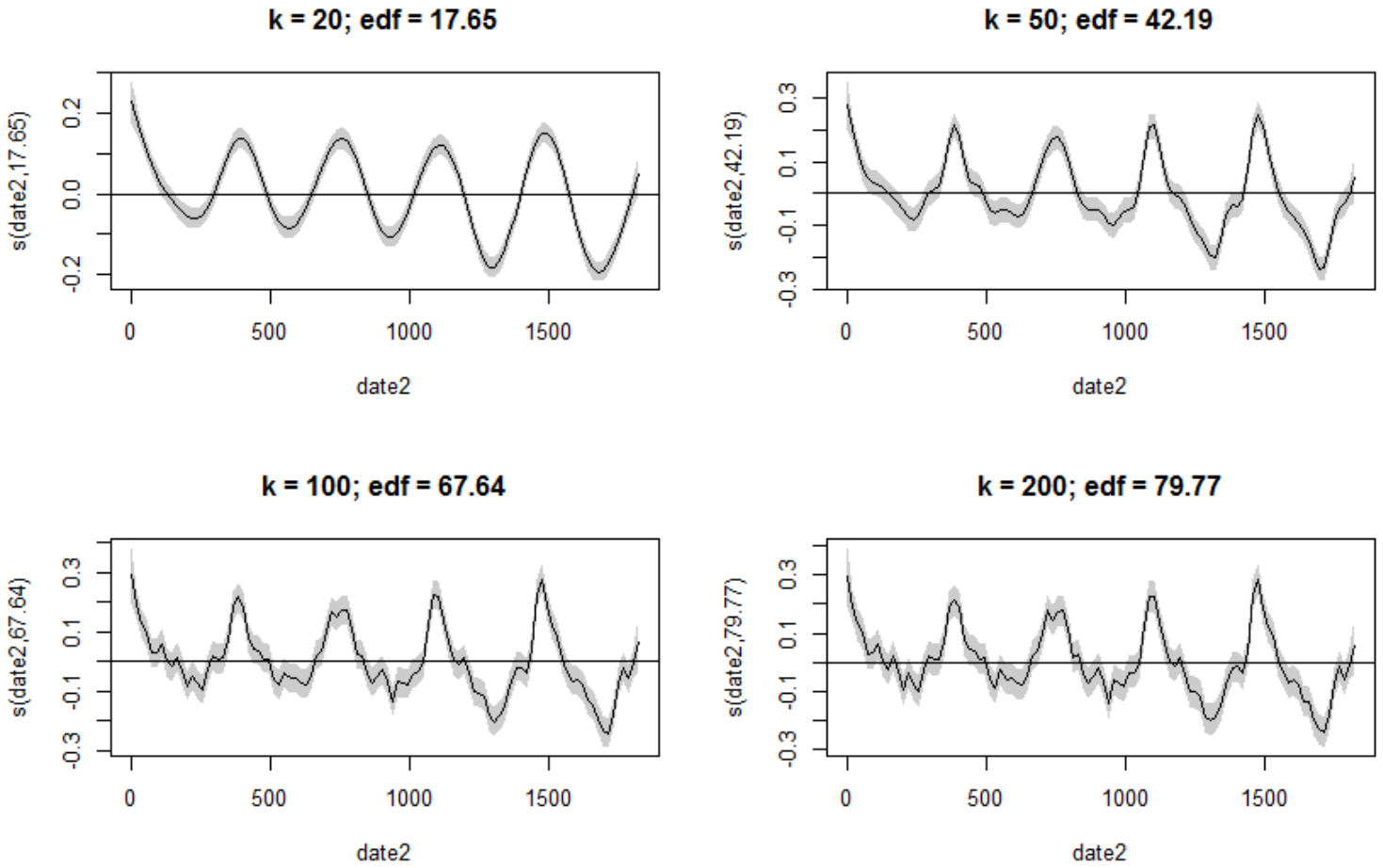
By default $gam()$ assumes the maximum effective degrees of freedom for each smooth effect to be 9. Increase k.

```
> fit = gam(log(alldeaths)~s(date2, k = 20), data = health)

> summary (fit)
Approximate significance of smooth terms:
           edf Ref.df     F p-value
s(date2) 17.65  18.76 55.01  <2e-16 ***

R-sq.(adj) =  0.364   Deviance explained =   37%
GCV score = 0.018602  Scale est. = 0.018412  n = 1826
```

- We increase the adjusted R2 significantly.
- The estimated effective DF (edf $= 17.54$) is still quite close to the upper bound of 20-1. One df is usually lost because of identifiability constraint.

Sensitivity with Maximum Dimension

Because the choice of k is arbitrary, we often need to try different values of k if the estimated edf is close to $k - 1$.



Choosing k

Using `gam.check()`,

```
> gam.check(fit3)
...
               k'  edf k-index p-value
s(date2) 99.0 67.6    0.97   0.095 .
---
> gam.check(fit4)
...
                     k'   edf k-index p-value
s(date2) 199.0  79.8    0.99    0.28
> fit5 = gam(log(cr65plus)~s(date2, k = 400), data=health)
> gam.check(fit5)
...
                      k'   edf k-index p-value
s(date2) 399.0  83.4    0.99    0.33
```

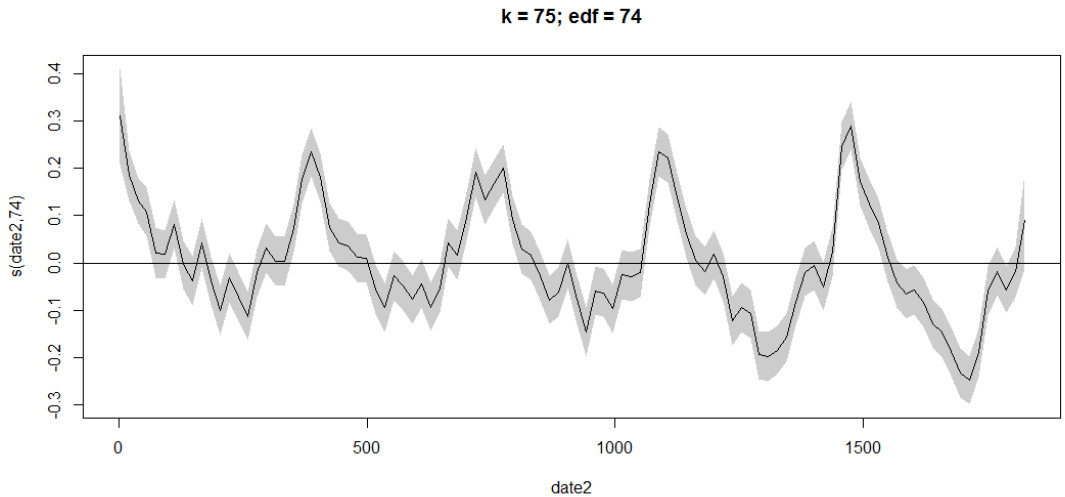
At $k = 100$ (fit3), p-value $>$ 0.05, but less than 0.10. EDF for $k = 200$ (fit4) similar to $k = 400$ (fit5).
General recommendation: err on the side of a smaller k. (Interpretability and guard against overfitting.)

Un-penalized Splines *option* $s(, fx =)$

`s( , fx = TRUE)` fits without penalization.

The results are similar to $k = 200$ with penalization.

```
> fit = gam(log(alldeaths)~s(date2, k = 75, fx=TRUE), data = health)
> summary(fit)
Approximate significance of smooth terms:
          edf Ref.df     F p-value
s(date2)  74     74 19.58  <2e-16 ***

R-sq.(adj) =   0.43   Deviance explained = 45.3%
GCV score = 0.017223  Scale est. = 0.016515  n = 1826
```



Semiparametric Model

Now we examine the linear effect of $PM_{2.5}$ (x_{i1}) on log mortality counts while controlling for DOW_i along with date (x_{i2}), temp (x_{i3}), dew-point temp (x_{i4}), running-mean temp (x_{i5}), and running-mean dew point (x_{i6}):

$$\begin{aligned} y_i &= \beta_0 + \beta_1 x_{i1} + \beta_2 1_{DOW_i=M} + \beta_3 1_{DOW_i=Tu} \cdots + \beta_7 1_{DOW_i=Sa} \\ &\quad + f_1(x_{i2}) + f_2(x_{i3}) + f_3(x_{i4}) + f_4(x_{i5}) + f_5(x_{i6}) + \epsilon_i, \\ \epsilon_i &\overset{iid}{\sim} N(0, \sigma^2), \end{aligned}$$

This is called a semiparametric model because it has a mixture of parameteric terms ($PM_{2.5}$ and day of the week) and nonparametric terms.

One reason we may model $PM_{2.5}$ as a linear effect is because our scientific collaborators prefer it.

Semiparametric Model

```
> fit = gam(log(cr65plus)~pm25+factor(dow)+s(date2, k = 100)+s(Temp)+
                          s(DpTemp)+s(rmTemp)+s(rmDpTemp), data = health)
> summary(fit)
Parametric coefficients:
                  Estimate    Std. Error   t value Pr(>|t|)
(Intercept)    4.2123711446  0.0106328283 396.16657  < 2e-16 ***
pm25          -0.0003667775  0.0004629403  -0.79228 0.428306
fdowMonday     0.0336815611  0.0109374584   3.07947 0.002106 **
fdowSaturday   0.0034936498  0.0109489842   0.31908 0.749701
fdowSunday     0.0111592226  0.0109906188   1.01534 0.310084
fdowThursday   0.0147194486  0.0109224826   1.34763 0.177953
fdowTuesday    0.0107430809  0.0109409288   0.98192 0.326277
fdowWednesday  0.0121661382  0.0109436453   1.11171 0.266417
---
Signif. codes:  0 ?***? 0.001 ?**? 0.01 ?*? 0.05 ?.? 0.1 ? ? 1

Approximate significance of smooth terms:
                  edf    Ref.df        F    p-value
s(date2)    61.221902 73.813250  6.83228 < 2.22e-16 ***
s(Temp)      1.035084  1.065682 13.72623 0.00015877 ***
s(DpTemp)    1.489371  1.853574  3.41795 0.02627890 *
s(rmTemp)    5.550906  6.775753  3.47986 0.00126217 **
s(rmDpTemp)  1.000003  1.000005 12.80124 0.00035572 ***
```

After controlling for meteorology, time trends, and day-of-week, there was no statistical significant association between $PM_{2.5}$ and mortality.

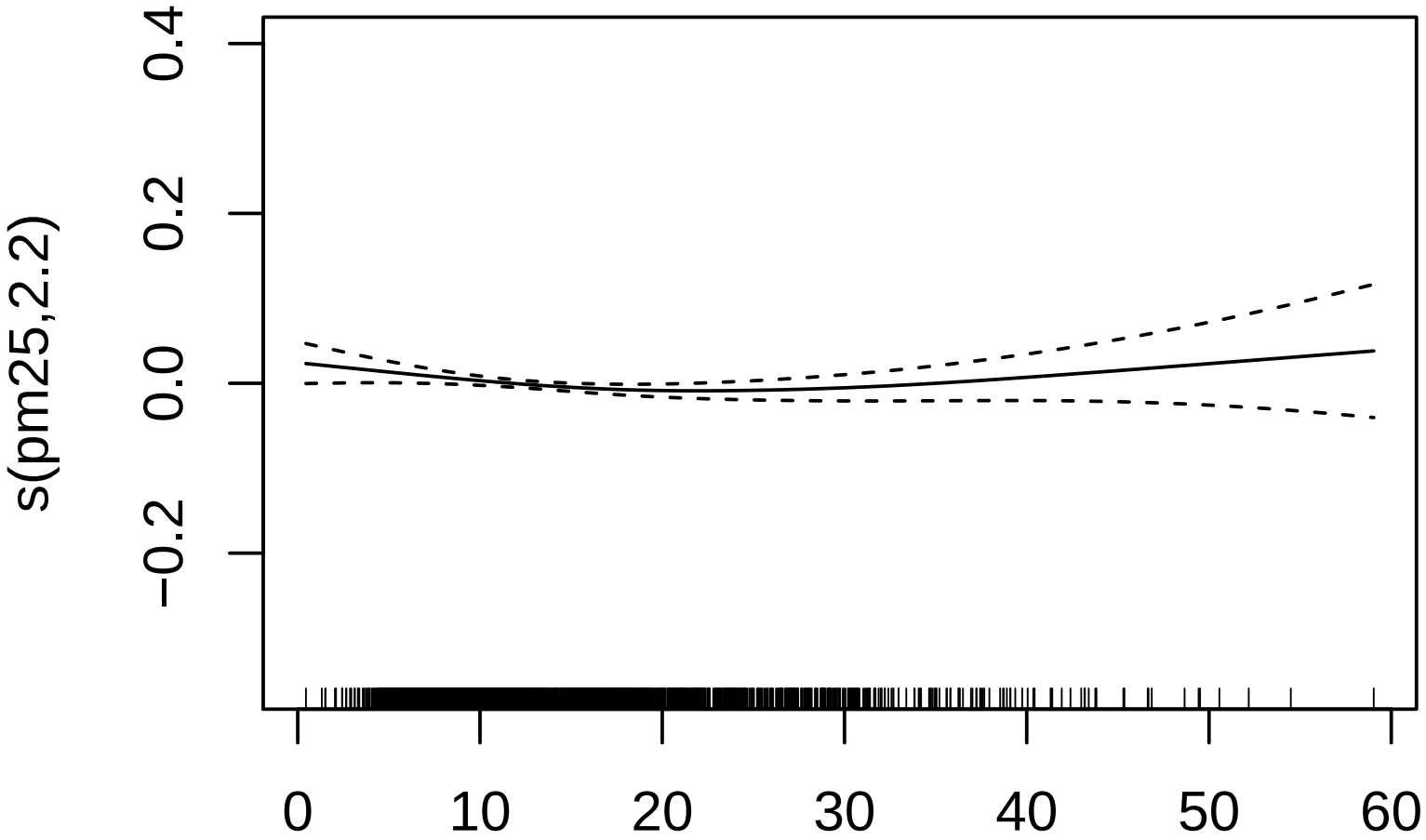
Why did we model PM2.5 as linear?

For the purposes of these slides, we modeled PM2.5 as linear. In general, even if your main effect is not a smooth, you may still want to use smooth terms for confounders.

In practice, we should model PM2.5 with a smooth.

```
   Parametric coefficients:
                Estimate  Std. Error   t value   Pr(>|t|)
(Intercept)   4.207096782 0.007723730 544.69755 < 2.22e-16 ***
fdowMonday    0.033796523 0.010918320   3.09540  0.0019967 **
fdowSaturday  0.003222867 0.010930205   0.29486  0.7681368
...
---
Signif. codes:  0 ?***? 0.001 ?**? 0.01 ?*? 0.05 ?.? 0.1 ? ? 1

Approximate significance of smooth terms:
                  edf    Ref.df         F    p-value
s(pm25)      2.198333  2.795871   2.52742 0.06878491 .
s(date2)    60.957576 73.527967   6.87685 < 2.22e-16 ***
s(Temp)      1.000013  1.000025 17.43434 3.1367e-05 ***
s(DpTemp)    1.523693  1.908105  3.27180 0.03023256 *
s(rmTemp)    5.537556  6.761898  3.44327 0.00141021 **
s(rmDpTemp)  1.000005  1.000009 13.23867 0.00028215 ***
```

Smooth term for PM2.5



Lagged $PM_{2.5}$ Exposure

There is typically a *temporal delay* between exposure and outcome. Let's examine the association between daily mortality and previous-day exposure.

```
> health$pm25.lag1 =  c(NA, health$pm25[1:1825])
> fit = gam(log(alldeaths)~pm25.lag1+factor(dow)+s(date2, k = 75)+s(Temp)+
                           s(DpTemp)+s(rmTemp)+s(rmDpTemp), data = health)
> summary (fit)
Parametric coefficients:
                       Estimate Std. Error t value Pr(>|t|)
(Intercept)           4.2029440  0.0101460 414.248   <2e-16 ***
pm25.lag1             0.0010543  0.0004491   2.347   0.0190 *
factor(dow)Friday    -0.0131336  0.0109570  -1.199   0.2308
factor(dow)Monday     0.0230427  0.0109435   2.106   0.0354 *
*/         some outputs deleted            /*

Approximate significance of smooth terms:
               edf Ref.df      F  p-value
s(date2)    60.138 72.670  6.206  < 2e-16 ***
s(Temp)      1.000  1.000 14.332 0.000158 ***
s(DpTemp)    1.447  1.789  2.037 0.136133
s(rmTemp)    5.827  7.052  2.884 0.005225 **
s(rmDpTemp)  1.000  1.000  9.454 0.002140 **

R-sq.(adj) =  0.463   Deviance explained = 48.6%
GCV score = 0.016212  Scale est. = 0.015524  n = 1825
```

Lagged $PM_{2.5}$ Exposure smooth term

```
> fit = gam(log(cr65plus)~s(pm25.lag1)+fdow+s(date2, k = 100 )+s(Temp)+ s(DpTemp)+s(rmTemp)
> summary(fit)

Family: gaussian
Link function: identity

Formula:
log(cr65plus) ~ s(pm25.lag1) + fdow + s(date2, k = 100) + s(Temp) +
    s(DpTemp) + s(rmTemp) + s(rmDpTemp)

Parametric coefficients:
                Estimate  Std. Error   t value   Pr(>|t|)
(Intercept)   4.205748765 0.007731497 543.97601 < 2.22e-16 ***
fdowMonday    0.036176289 0.010980266   3.29466  0.0010051 **
fdowSaturday  0.004256722 0.010918397   0.38987  0.6966825
....
---
Signif. codes:  0 ?***? 0.001 ?**? 0.01 ?*? 0.05 ?.? 0.1 ? ? 1

Approximate significance of smooth terms:
                   edf    Ref.df        F    p-value
s(pm25.lag1)  1.000040  1.000080  5.50991 0.01902030 *
s(date2)     60.137293 72.669727  6.29239 < 2.22e-16 ***
s(Temp)       1.000002  1.000004 14.33175 0.00015864 ***
s(DpTemp)     1.446148  1.787928  2.05017 0.09521592 .
s(rmTemp)     5.826145  7.051150  2.86630 0.00532417 **
s(rmDpTemp)   1.000004  1.000007  9.45312 0.00214032 **
```

Note on time series data

We should analyze the residuals for evidence of autocorrelation.

If residuals are correlated, e.g., nearby residuals are more similar than distant residuals, our inference is not valid, and p-values tend to be too small.

This is beyond the scope of this course, but a nice tutorial is available at https://petolau.github.io/Analyzing-double-seasonal-time-series-with-GAM-in-R/

Coefficient Interpretation

- Daily counts of non-accidental mortality was positively associated with previous-day $PM_{2.5}$ level among those 65 or above.
- We estimated a 0.00105 (standard error = 0.00045) increase in log death count per unit ($\mu g/m^3$) increase in $PM_{2.5}$ level in the previous day.
- Note that when modeling the outcome on a log-scale

$$\log y_i = \beta_0 + \beta_1 x_i + \epsilon_i,$$

then β_1 is the change in $E[\log y_i]$ per unit change in x_i. Therefore, a 10 unit increase in $PM_{2.5}$ level was associated with an increase in daily death counts by $e^{(0.00105 \times 10)} = 1.0105$, with 95% confidence interval (1.0017, 1.0195).

Sensitivity Analysis

In the above analysis, we selected smoothness parameters for confounders automatically using GCV. However,

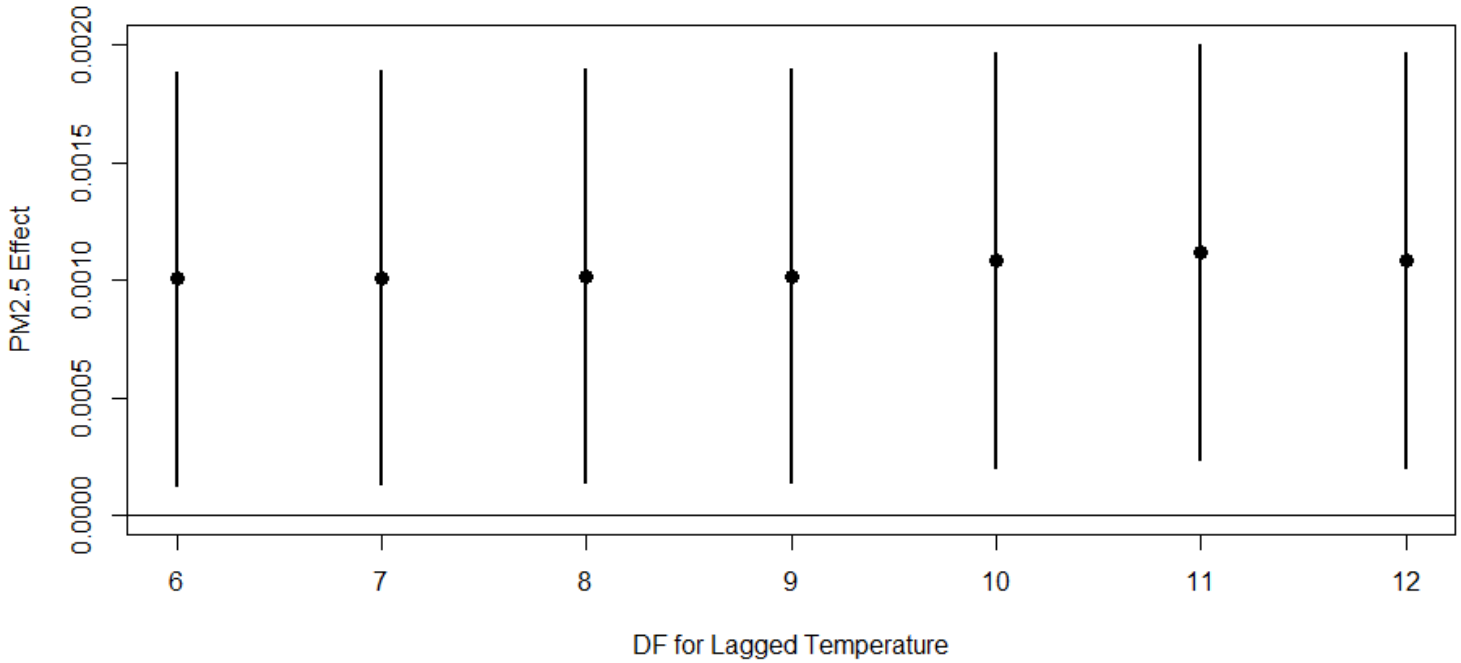
- The GCV criterion used is aimed to maximize prediction performance.
- In a health analysis, our goal is not to construct a model that best predicts the outcome, but to obtain accurate health effect association where confounding is minimized.

Sensitivity Analysis Approach

- Starting with the estimated edf for each confounder, we will increase each of them and refit the model.
- We will examine how the $PM_{2.5}$ estimate changes as we allow more flexible control of confounders.
- We hope to see the effect estimates to be stable and robust against different ways to specific confounder effects.

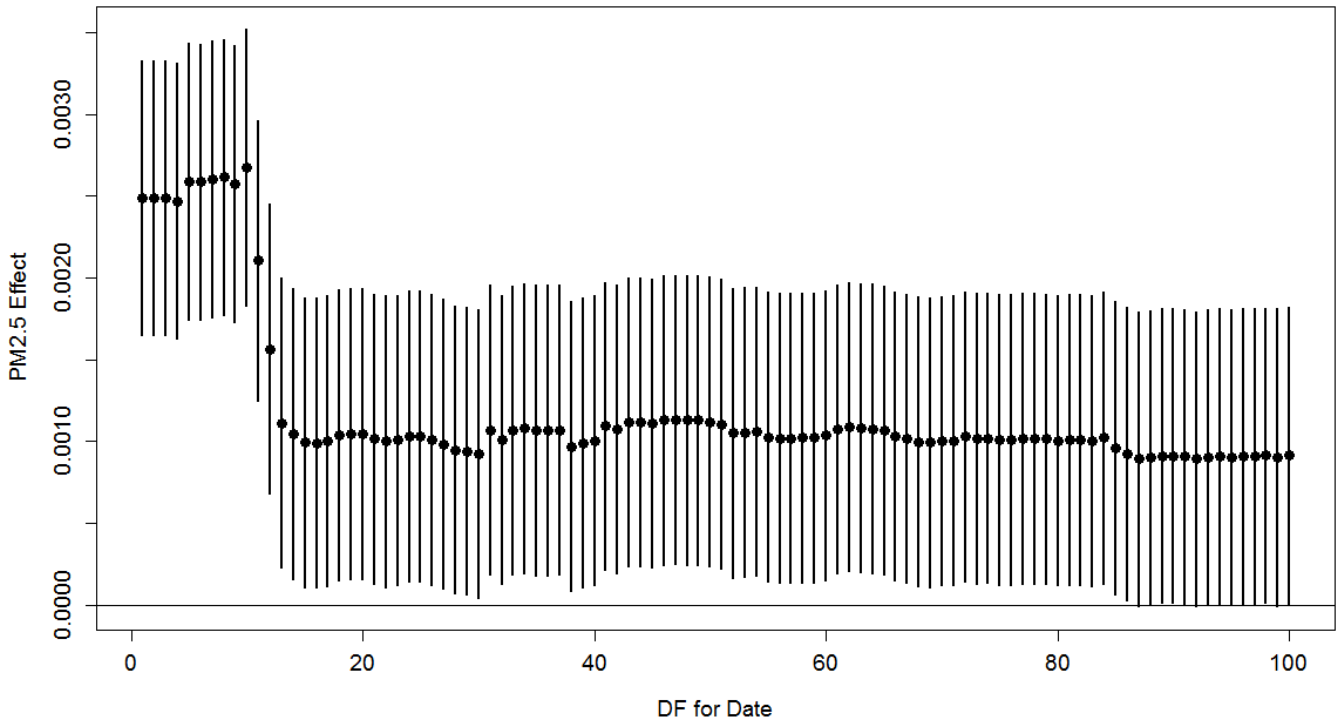
Sensitivity Analysis: Lagged Temperature Effect

```
> Results = NULL
> for (df in 6:12){
    fit = gam(log(alldeaths)~pm25.lag1+factor(dow)+s(date2, k = 100 )+s(Temp)+
                    s(DpTemp)+s(rmTemp, k = df, fx=TRUE )+s(rmDpTemp), data = health)

    #Extract PM2.5 point estimate and standard error
    est = c(summary(fit)$p.coef[2], (fit)[2])

    #Save results
    Results = rbind (Results, est)
 }
```



Sensitivity Analysis: Temporal Trends

- One challenge in time-series analysis is how much control do we need for temporal trend.
- Temporal trend is used to account for unmeasured confounders that vary in time, often at different temporal scales.
- Note below how the estimates *stabilize* after there is sufficient control for temporal trends. Too little temporal control will result in an over-estimate of the $PM_{2.5}$-mortality association.



Bivariate Splines

Bivariate Splines

Under an additive model framework, we can also consider smooth effects of two variables jointly:

$$y_i = f(x_i, z_i) + \epsilon_i, \quad \epsilon_i \ N(0, \sigma^2).$$

We can think of $f(x_i, z_i)$ as a surface.

We can use 2-dimensional splines to model $f(x_i, z_i)$.

Let $\mathbf{s}_i = (x_i, z_i)$ be some pair of covariate values, and let $\mathbf{k}_m = (x_m, z_m)$ denote the m^{th} knot in the domain of x_i and z_i. We can express the smooth function as

$$f(x_i, z_i) = \beta_0 + \sum_{m=1}^{M} \beta_m b_m(\mathbf{s}_i; \mathbf{k}_m).$$

Note that $b_m(\ ,\ )$ is a basis function that maps $\mathbb{R} \times \mathbb{R} \to \mathbb{R}$.

Thin-plate Spline

One popular bivariate basis function uses thin-plate splines, which extends to $\mathbf{s}_i \in \mathbb{R}^d$ and $\partial^l g$ penalties. We consider $d = 2$ and $l = 2$:

$$f(\mathbf{s}_i) = \beta_0 + \beta_1 x_t + \beta_2 z_t + \sum_{m=1}^{M} \beta_{2+m} b_m(\mathbf{s}_i; \mathbf{k}_m)$$

using the radial basis:

$$b_m(\mathbf{s}_i; \mathbf{k}_m) = ||\mathbf{s}_i - \mathbf{k}_m||^2 \log(||\mathbf{s}_i - \mathbf{k}_m||).$$

Here, $||\mathbf{s}_i - \mathbf{k}_m||$ is the Euclidean distance between the covariate $\mathbf{s}_i$ and the knot location $\mathbf{k}_m$.

The radial basis kernel is $r^2 \log r$.

The thin-plate spline is sensitive to the scale of each variable, but invariant to rotation (isotropic).

It is best for variables measured on the same scale (e.g. geographical distance).

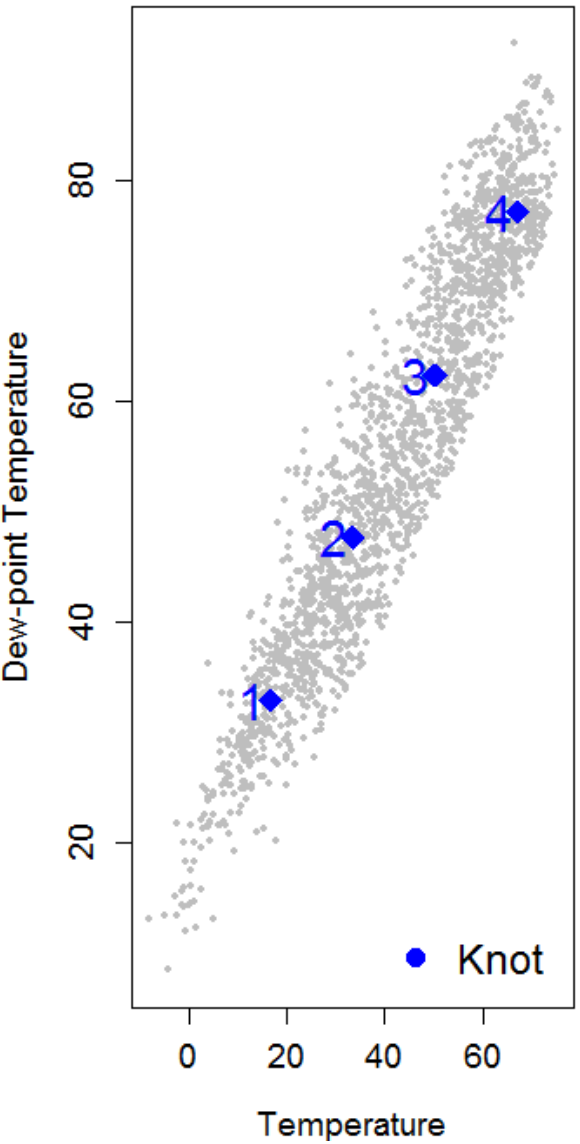
Thin-plate Spline, cont.

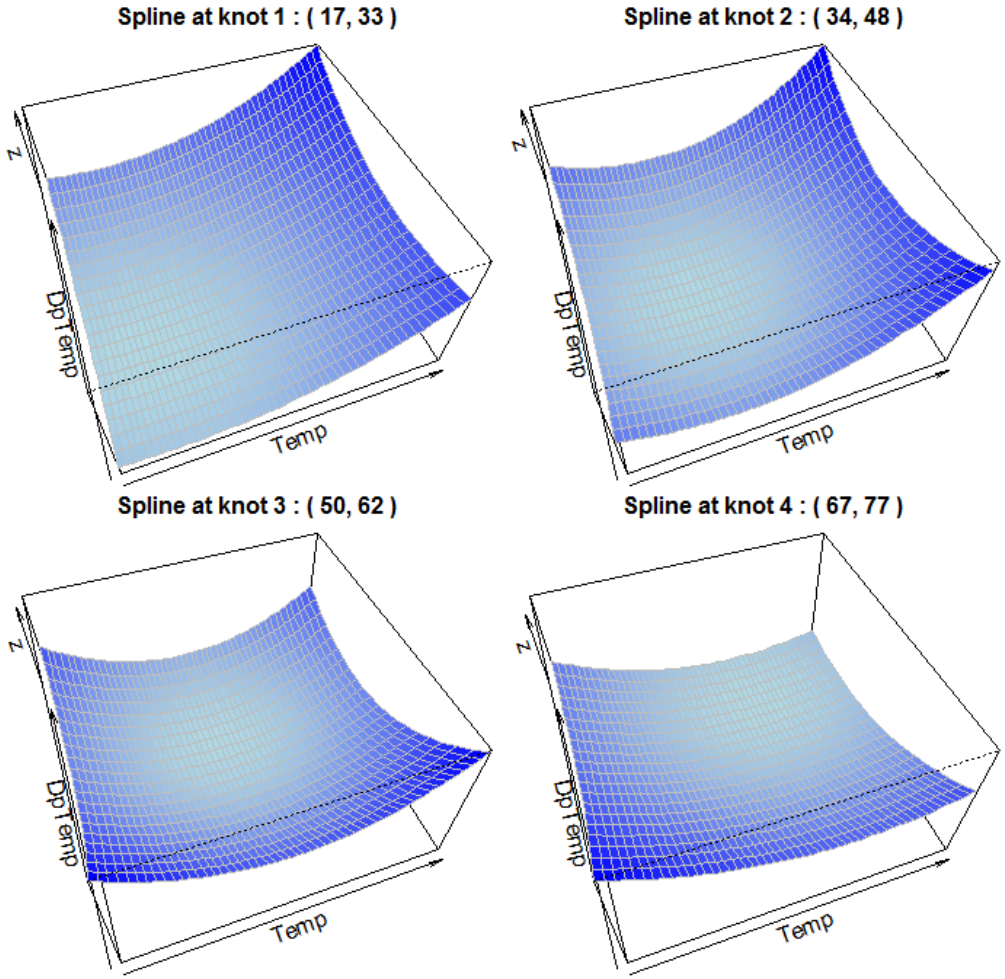
It can be shown that the thin-plate spline function minimizes

$$\sum_{i=1}^{n}\{y_i - f(x_i, z_i)\}^2$$
$$+ \lambda \int \left(\frac{\partial^2 f(x,z)}{\partial x^2}\right)^2 + 2\left(\frac{\partial^2 f(x,z)}{\partial x\, \partial z}\right)^2 + \left(\frac{\partial^2 f(x,z)}{\partial z^2}\right)^2 \, dxdz \; .$$

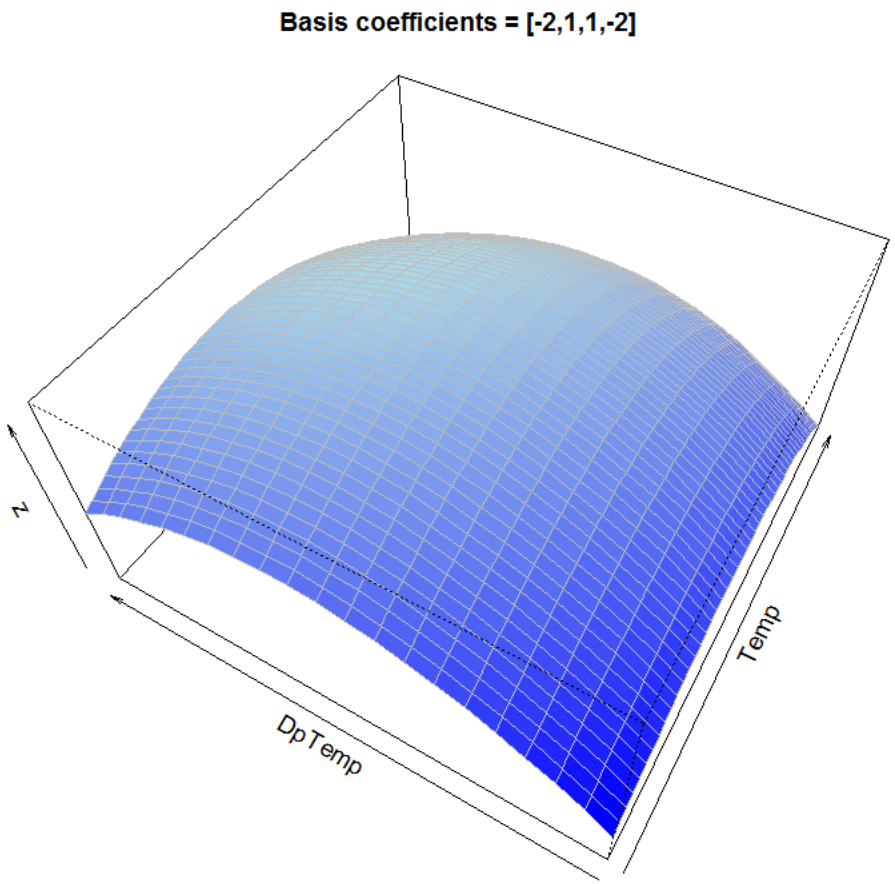
More information is in Wood 2017, pages 215-221, and references therein.

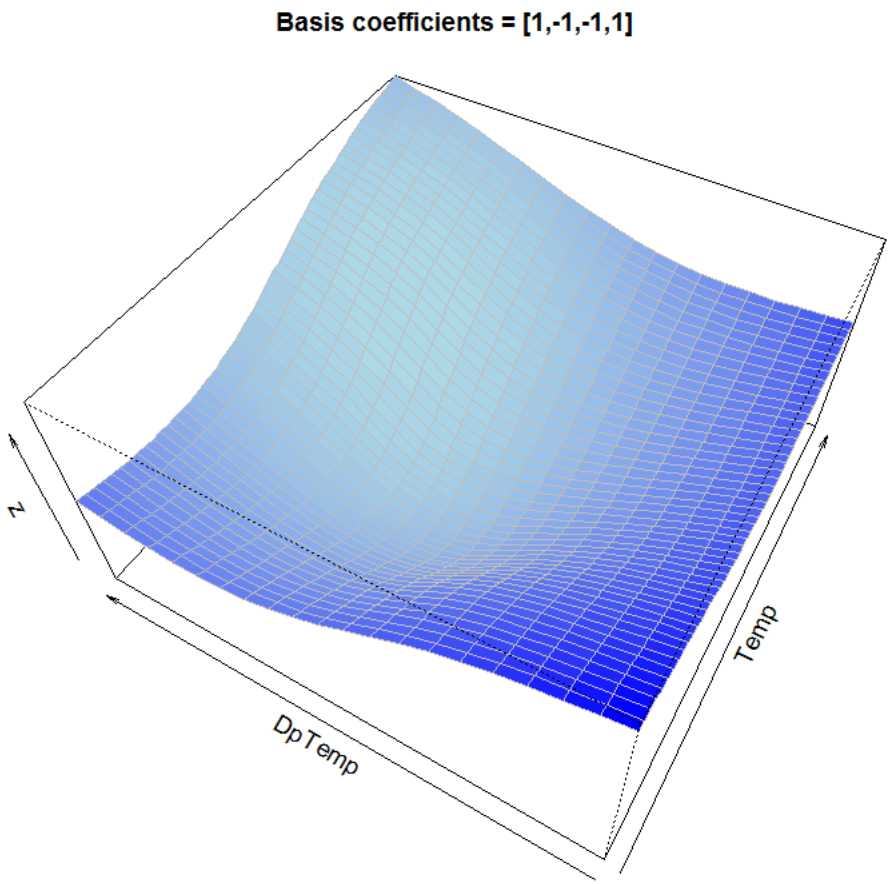
Thin-plate Spline





Thin-plate Spline





Thin-plate regression spline

mgcv::gam uses thin-plate regression splines as the default for smoothers of a single variable (as well as two variables).

This is implemented in a 'knot-free' manner.
This is the general idea.
For $d = 2$, $l = 2$:

1. Construct the $n \times n$ matrix $\mathbf{E}$ from $||\mathbf{s}_i - \mathbf{s}_{i'}||^2 \log(||\mathbf{s}_i - \mathbf{s}_{i'}||)$.
2. Use the singular value decomposition to find a low rank representation, e.g., k leading singular vectors, and use this in place of $\mathbf{X}$ in the penalized objective function.
3. In practice, there are some additional things to worry about to make $\mathbf{1}$ (for the intercept), $\boldsymbol{x}$ and $\boldsymbol{z}$ in the null space of the penalty.
4. Then estimate the β_0, β_1 for $\boldsymbol{x}$, β_2 for $\boldsymbol{z}$ (unpenalized) and $\beta_3, \ldots, \beta_k$ (penalized), which dramatically reduces computation costs.

The formulas for the general case (d dimensions and lth derivative) get a bit complicated; see 5.5 in Wood.

Joint Effects of Temperature and Dew point Temperature

To define a bivariate smoother, simply specify $s(var_1, var_2)$ in the equation formula.

Default in `mgcv:gam` is to use a thin-plate spline.

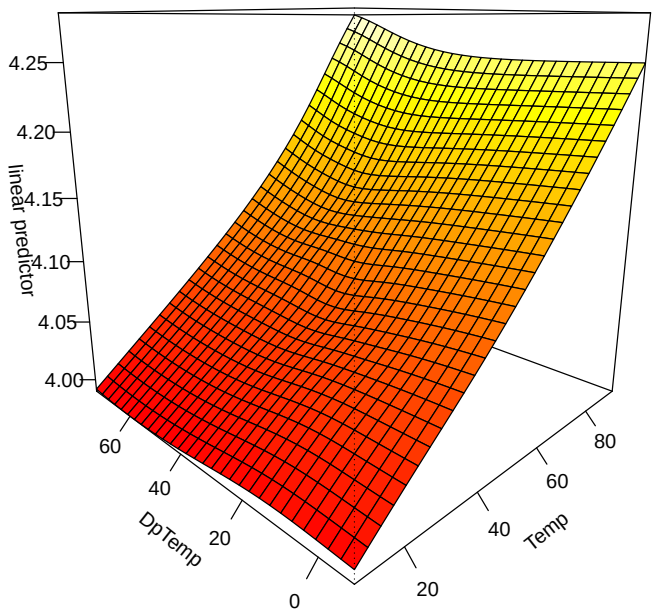
Let's first look at the joint effects of same-day temperature and dew point temperature on log mortality, controlling only for time trends.

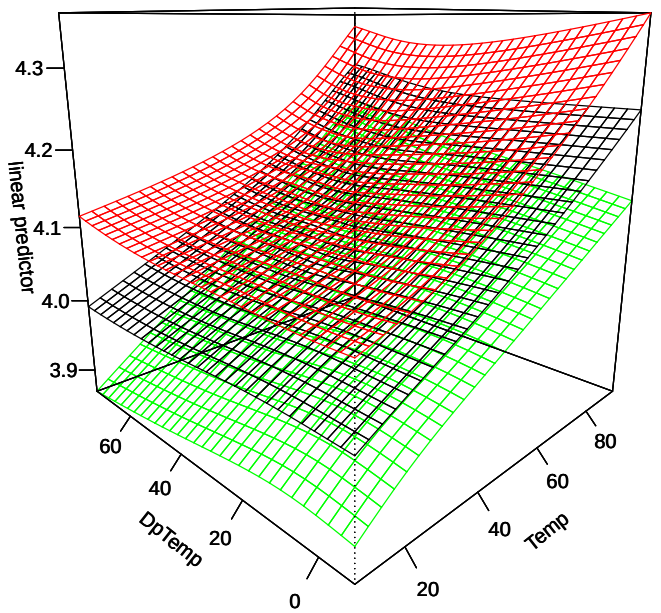
```
> fit1 = gam(log(alldeaths)~s(date2, k=100) + s(Temp, DpTemp, k = 20), data = health)
> summary (fit1)

Parametric coefficients:
            Estimate Std. Error t value Pr(>|t|)
(Intercept) 4.219108   0.002953    1429   <2e-16 ***

Approximate significance of smooth terms:
                 edf Ref.df     F  p-value
s(date2)      69.527 82.144 8.501  < 2e-16 ***
s(Temp,DpTemp)  5.938  8.032 6.407 2.96e-08 ***

R-sq.(adj) =   0.45   Deviance explained = 47.3%
GCV score = 0.016624  Scale est. = 0.015928  n = 1826
```

You should also use `gam.check` (note shown here)

Joint Effects of Temperature and Dew Point Temperature

Perspective Plots from Thin-Plate Spline





red/green are +/− 2 s.e.

Tensor Product

Another way to obtain a 2-D spline is by construction. First consider the effect of a variable x_i specified by M basis functions $b_m(x_i)$

$$f(x_i) = \sum_{m=0}^{M} \beta_m b_{m,x}(x_i).$$

Now assume $f(x_i, z_i)$ is created by allowing each spline coefficient to vary with the second variable z_i: M

$$f(x_i, z_i) = \sum_{m=0} \beta_m(z_i) b_{m,x}(x_i).$$

We can express $\beta_m(z_i)$ also as a smooth function of z_i using N basis functions $b_{n,z}(z_i)$:

$$f(x_i, z_i) = \sum_{m=0}^{M} \sum_{n=0}^{N} \alpha_{m,n} b_{n,z}(z_i) b_{m,x}(x_i).$$

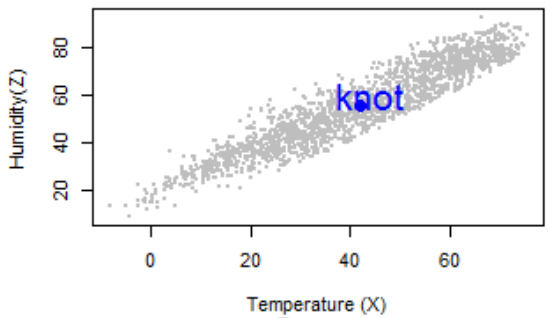
This is equivalent to expressing $f(x_i, z_i)$ as all pairwise basis functions of x_i and z_i:

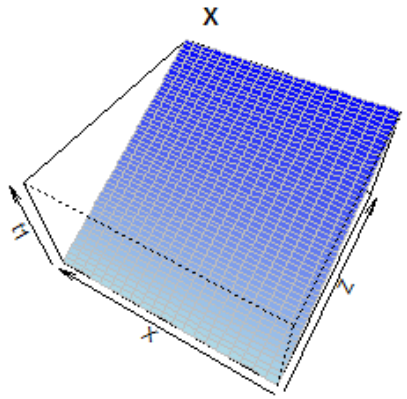
$$f(x_i, z_i) = \sum_{m=0}^{M} \sum_{n=0}^{N} \alpha_{m,n} b_{n,z}(z_i) b_{m,x}(x_i).$$

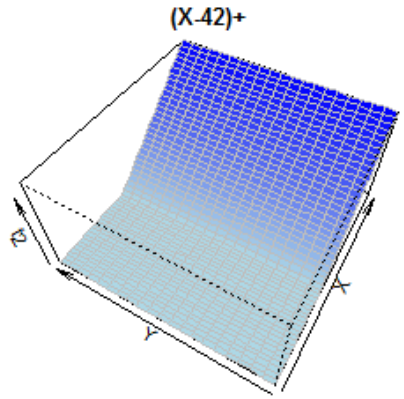
Tensor Product

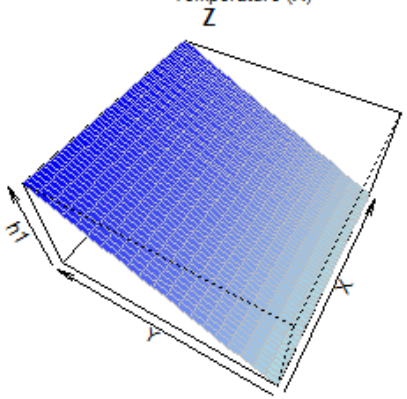
Example with 1 knot: write out all pairwise interactions

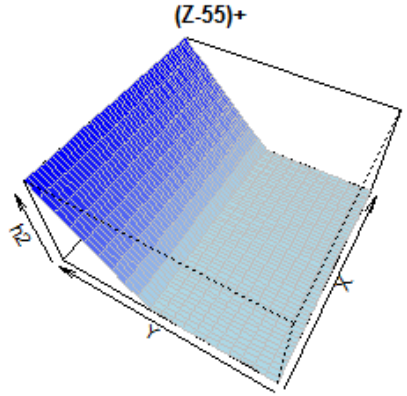
Tensor Product Example

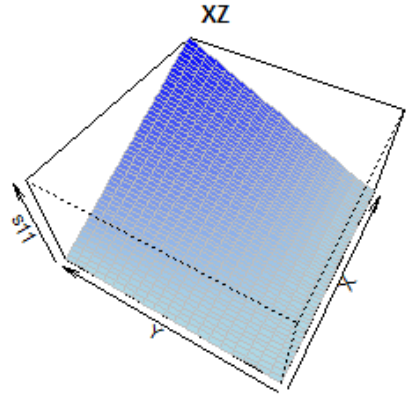


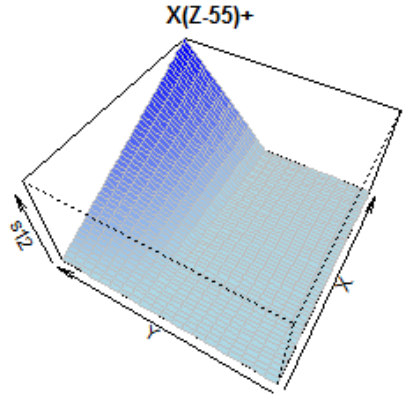


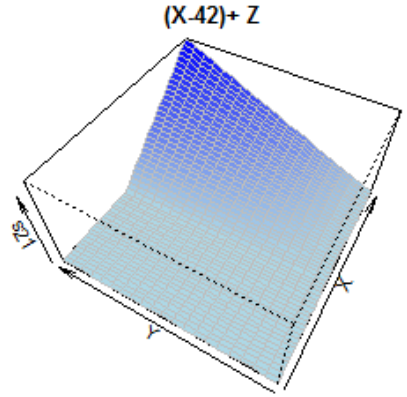


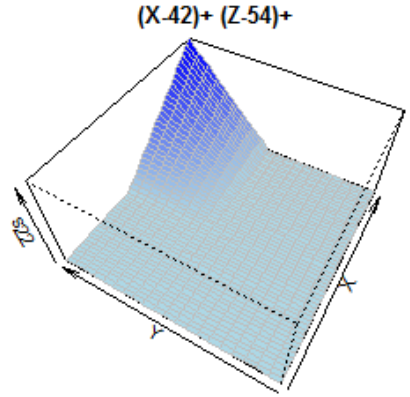












Tensor Product

The roughness penalty optimized by the tensor product is

$$\sum_{i=1}^{n}\{y_i - f(x_i, z_i)\}^2 + \int \lambda_x \left(\frac{\partial^2 f(x,z)}{\partial x^2}\right)^2 + \lambda_z \left(\frac{\partial^2 f(x,z)}{\partial z^2}\right)^2 \, dxdz \; .$$

- Allows penalization in each variable dimension by assigning a smoothing parameter for each marginal smooth effect.
- Choice of basis function and knots also do not need to be the same for each covariate.
- Provides a recipe for constructing flexible multivariate joint effects.
- Often used for modeling interactions where the degree of smoothness may not be the same for all covariates.

Fitting Tensor Product

A bivariate smoother using tensor product is specified by `te( var_1, var_2, bs=‘‘cr’’)` in the equation formula.

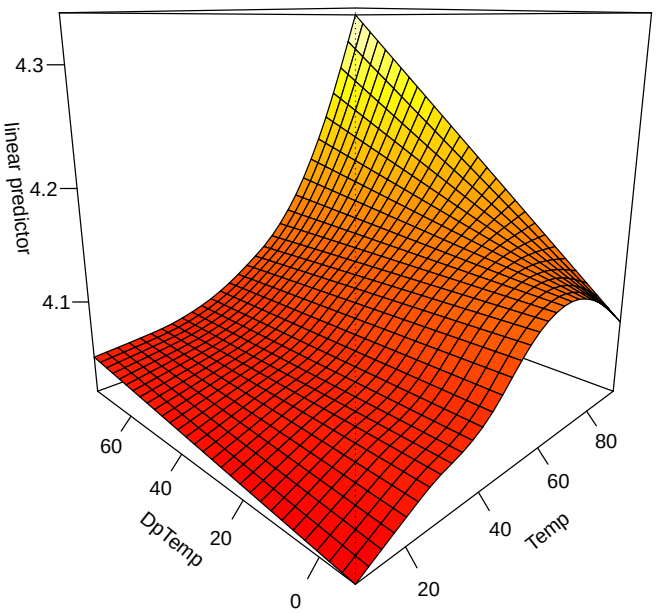
Recommended when scales differ.

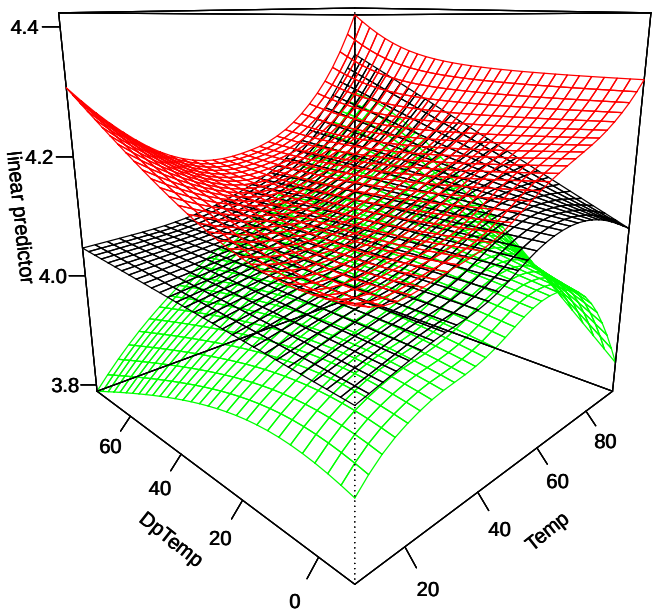
The option `bs = ‘‘cr’’` specifies using cubic spline functions for each covariate .

```
> fit1 = gam (log(alldeaths) ~ s(date2, k = 100) +
        te(Temp, DpTemp, k = 20, bs = "cr") , data = health)

> summary (fit1)

Parametric coefficients:
            Estimate Std. Error t value Pr(>|t|)
(Intercept) 4.219108   0.002952    1429   <2e-16 ***
---
Signif. codes:  0 ’***’ 0.001 ’**’ 0.01 ’*’ 0.05 ’.’ 0.1 ’ ’ 1

Approximate significance of smooth terms:
                   edf Ref.df      F p-value
s(date2)        68.353 81.039  8.343  <2e-16 ***
te(Temp,DpTemp)  6.003  7.391 18.134  <2e-16 ***

R-sq.(adj) =   0.45   Deviance explained = 47.3%
GCV score = 0.016601  Scale est. = 0.015916  n = 1826
```

Joint Effects of Temperature and Dew Point Temperature

Perspective Plots from Cubic Tensor Product Spline



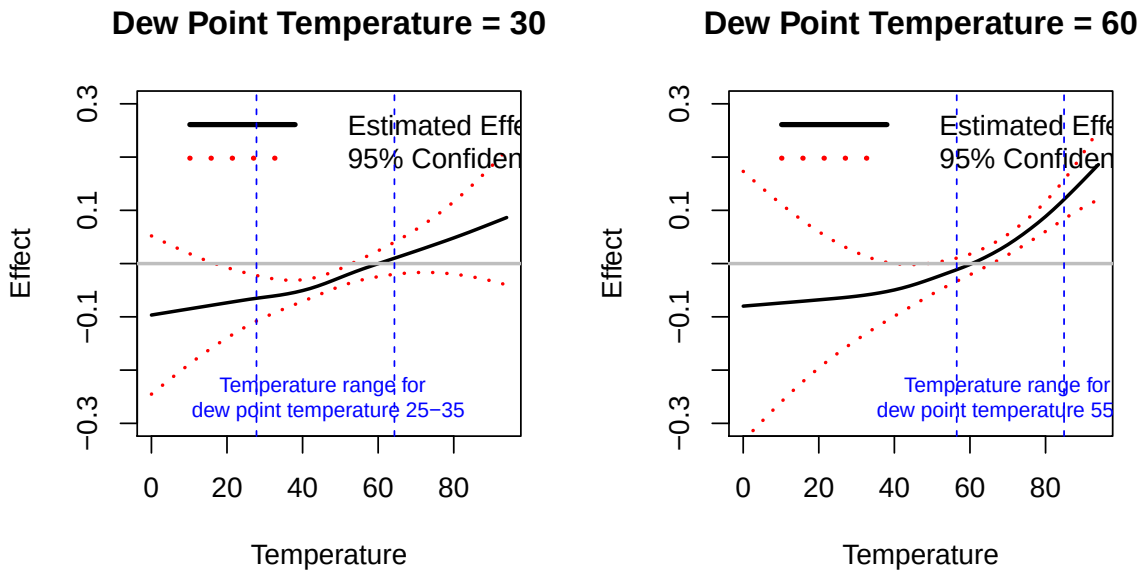


red/green are +/− 2 s.e.

Marginal Effects

By fitting an effect surface, we can obtain slices with respect to a covariate and examine the conditional effect of another covariate.

For example, we can look at the non-linear effect of temperature when dew point temperature $= 30$ versus 60.



$PM_{2.5}$ and Temperature

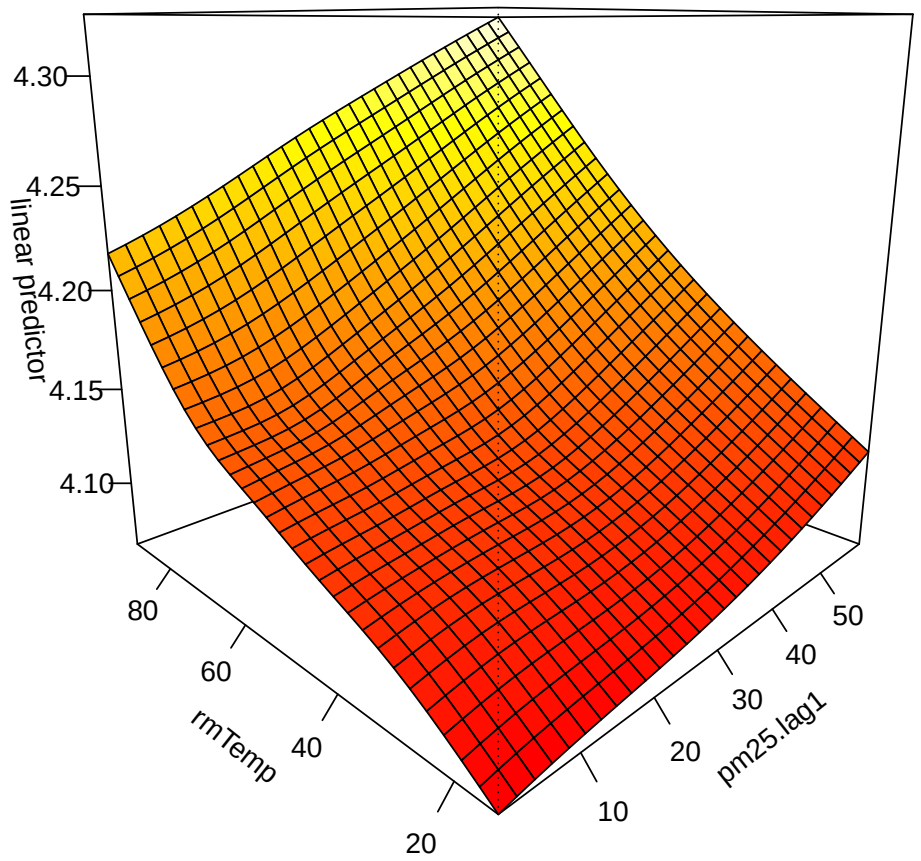
An important research question is whether there is an interaction between air pollution and temperature.

Let's extend our previous model to consider previous-day $PM_{2.5}$ level and 3-day moving average of temperature. Note here we use thin-plate splines, which are much faster to fit than tensor; pm25.lags and rmTemp are very roughly on same scale.

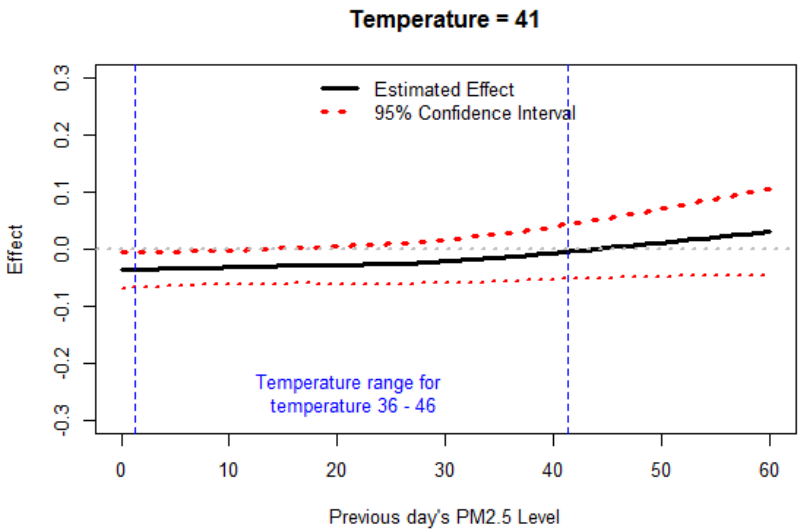
```
> fit = gam(log(alldeaths)~s(pm25.lag1, rmTemp)+factor(dow)+s(date2, k = 75)+
                           s(DpTemp)+s(rmDpTemp), data = health)
> summary (fit)

Parametric coefficients:
                       Estimate Std. Error t value Pr(>|t|)
(Intercept)           4.2191876  0.0077934 541.380   <2e-16 ***
factor(dow)Friday    -0.0142658  0.0110132  -1.295   0.1954
factor(dow)Monday     0.0222996  0.0110146   2.025   0.0431 *
factor(dow)Saturday  -0.0092121  0.0110082  -0.837   0.4028
factor(dow)Thursday   0.0011288  0.0110248   0.102   0.9185

Approximate significance of smooth terms:
                        edf Ref.df      F  p-value
s(pm25.lag1,rmTemp)   5.858  8.381  4.048 6.35e-05 ***
s(date2)             57.808 66.508  6.721  < 2e-16 ***
s(DpTemp)             1.362  1.633 25.075 8.11e-10 ***
s(rmDpTemp)           1.000  1.000 35.085 3.79e-09 ***
```

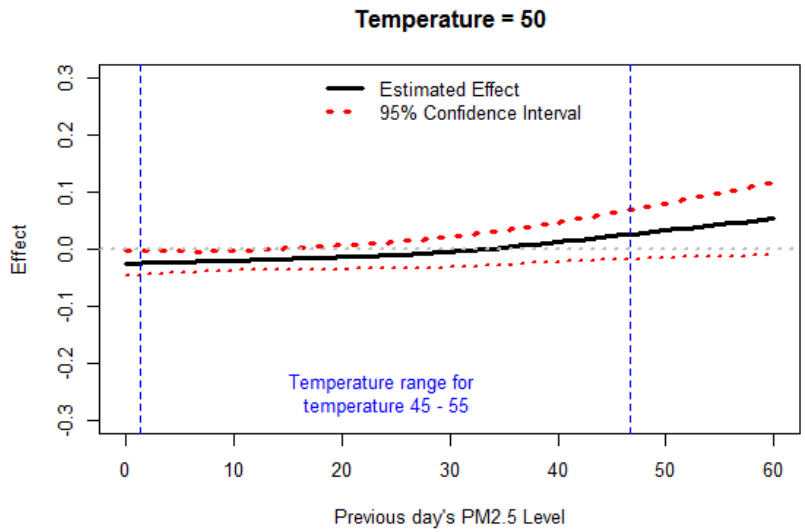
Joint Effects of Temperature and $PM_{2.5}$

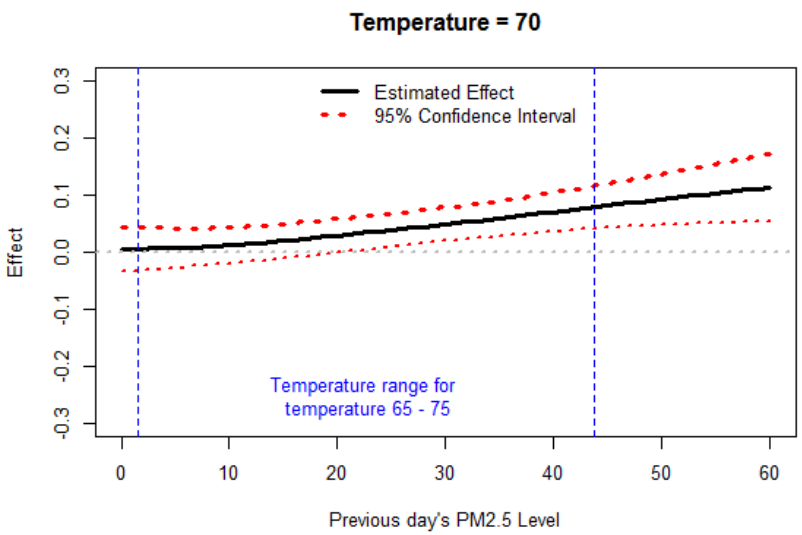
Effect of temperature is more pronounced than $PM_{2.5}$.

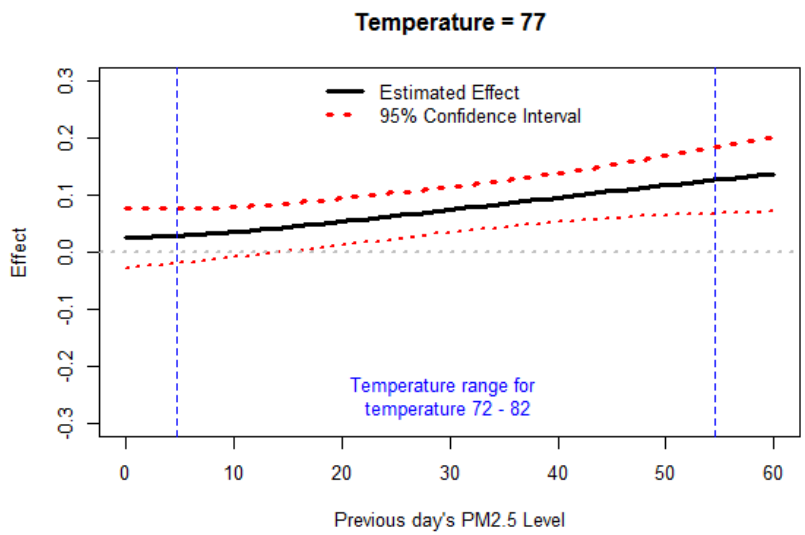


$PM_{2.5}$ Effect Modification by Temperature?









Extracting Effects from Smooth Function

- Let's say we are interested in the difference in $f(x_i)$ when x_i increases from value a to value b:

$$\hat{f}(b)-\hat{f}(a) = \sum_{m=1}^{M} \hat{\beta}_m b_m(b) - \sum_{m=1}^{M} \hat{\beta}_m b_m(a) = \sum_{m=1}^{M} \hat{\beta}_m \{b_m(b)-b_m(a)\}.$$

  The covariance matrix is given by $Cov(\mathbf{B}'_{b-a}\hat{\boldsymbol{\beta}}) = \mathbf{B}'_{b-a} Cov(\hat{\boldsymbol{\beta}}) \mathbf{B}_{b-a}$, where

$$\mathbf{B}_{b-a} = [b_1(b) - b_1(a), b_2(b) - b_2(a), \ldots, b_M(b) - b_M(a)]'.$$

- However $b_m()$'s are basis functions and $b_m(b) - b_m(a) \neq b_m(b-a)$. We will need to construct the new covariate vector $\mathbf{B}$ ourselves.

Extracting Effects from a Smooth Function

We want to estimate the effect of a 10 $\mu g/m^3$ increase in $PM_{2.5}$ levels from 40 to 50 $\mu g/m^3$ when temperature $=$ 70F.

```
> X1 = predict(fit, data.frame(pm25.lag1 = 40, rmTemp=70,
+           DpTemp=0, rmDpTemp = 0, dow = "Sunday", date2=0),type= "lpmatrix")
> X2 = predict(fit, data.frame(pm25.lag1 = 50, rmTemp=70,
+           DpTemp=0, rmDpTemp = 0, dow = "Sunday", date2=0),type= "lpmatrix")

> X.diff = X2 - X1
> dim (X.diff)
[1]   1 128
> Est = X.diff %*% coef (fit)  ## Estimate
> se = sqrt( X.diff %*% vcov (fit) %*% t(X.diff) ) ## Standard Error
> Est; se
        [,1]
1 0.02213508
          1
1 0.01096592
```

So our estimate is 0.022 (95%CI 0.001, 0.044).

The same effect of a 10-unit increase in $PM_{2.5}$ levels from 20 to 30 $\mu g/m^3$ is 0.020 (95%CI 0.004, 0.036).

These two estimates are very similar because the $PM_{2.5}$ effect appears to be quite linear.

Inference in models with smoothing splines

For parametric terms, the inference is identical to purely parametric model.

You can use the t-statistics from `summary(fit)`.

```
> fit.full = gam(log(cr65plus)~s(pm25.lag1, rmTemp)+fdow+s(date2, k = 100)+s(DpTemp)+s(rmDp
> summary(fit.full)

Family: gaussian
Link function: identity

Formula:
log(cr65plus) ~ s(pm25.lag1, rmTemp) + fdow + s(date2, k = 100) +
    s(DpTemp) + s(rmDpTemp)

Parametric coefficients:
               Estimate Std. Error t value Pr(>|t|)
(Intercept)    4.219093   0.007784 541.997   <2e-16 ***
fdowFriday    -0.014166   0.011001  -1.288   0.1980
fdowMonday     0.022352   0.011002   2.032   0.0423 *
fdowSaturday  -0.009111   0.010995  -0.829   0.4074
fdowThursday   0.001261   0.011012   0.114   0.9089
fdowTuesday   -0.001689   0.011002  -0.153   0.8780
fdowWednesday  0.000470   0.011012   0.043   0.9660
---
Signif. codes:  0 ?***? 0.001 ?**? 0.01 ?*? 0.05 ?.? 0.1 ? ? 1
```

Inference in models with smoothing splines

For overall effect of `fdow`, use `anova`:

```
> anova(fit.full)

Family: gaussian
Link function: identity

Formula:
log(cr65plus) ~ s(pm25.lag1, rmTemp) + fdow + s(date2, k = 100) +
    s(DpTemp) + s(rmDpTemp)

Parametric Terms:
     df     F p-value
fdow  6 2.154  0.0448
```

Inference in models with smoothing splines

For smoothed terms, the inference is approximate because the distribution of the test statistics is impacted by the penalization.

The idea is to jointly test the significance of the $\hat{\boldsymbol{\beta}}_j$ for the coefficients corresponding to the spline of the jth smooth term.

There is some discussion of these approximate p-values in `?summary.gam`. For detailed discussion, see Wood 2017 p.304.

Approximate inference for smooth effects:

```
Approximate significance of smooth terms:
                        edf Ref.df      F  p-value
s(pm25.lag1,rmTemp)   5.433  7.738  4.246 6.30e-05 ***
s(date2)             62.047 74.627  6.118  < 2e-16 ***
s(DpTemp)             1.210  1.379 29.260 2.89e-09 ***
s(rmDpTemp)           1.000  1.000 34.655 4.68e-09 ***

R-sq.(adj) =  0.458   Deviance explained =   48%
GCV = 0.016377  Scale est. = 0.015688  n = 1825
```

Inference in models with smoothing splines

Should we use a bivariate spline for pm25.lag1 and rmTemp, or two univariate splines? Don't do this:

```
> anova(fit.reduced2,fit.full,test='F')
Analysis of Deviance Table

Model 1: log(cr65plus) ~ s(pm25.lag1) + s(rmTemp) + s(date2, k = 100) +
    fdow + s(DpTemp) + s(rmDpTemp)
Model 2: log(cr65plus) ~ s(pm25.lag1, rmTemp) + fdow + s(date2, k = 100) +
    s(DpTemp) + s(rmDpTemp)
  Resid. Df Resid. Dev        Df     Deviance F Pr(>F)
1 1734.9095  27.353616
2 1733.2552  27.428321 1.6542684 -0.074705162
```

What happened here?

Models are not nested. Works better with tensor spline, which we can construct in a special way to make nested. Then we can recast the problem as testing for an interaction.

Inference in models with smoothing splines

Before testing for interaction, let's do an approximate anova for date2.

```
> fit.nodate2 = gam(log(cr65plus)~s(pm25.lag1,rmTemp)+fdow+s(DpTemp)+s(rmDpTemp), data = he
> anova(fit.nodate2,fit.full,test='F')
Analysis of Deviance Table

Model 1: log(cr65plus) ~ s(pm25.lag1, rmTemp) + fdow + s(DpTemp) + s(rmDpTemp)
Model 2: log(cr65plus) ~ s(pm25.lag1, rmTemp) + fdow + s(date2, k = 100) +
    s(DpTemp) + s(rmDpTemp)
  Resid. Df Resid. Dev     Df Deviance      F    Pr(>F)
1    1798.9     34.854
2    1733.3     27.428 65.639   7.4257 7.2111 < 2.2e-16 ***
> ((34.854 - 27.428)/(1798.9-1733.3)) / (27.428 / 1733.3)
[1] 7.1537
```

Testing for an interaction

To test for an interaction between pm25.lag1 and rmTemp, we can construct the tensor spline in a special way such that the univariate splines are in the null space of the penalty of the tensor spline. See pages 243 and the example on page 343-346.

```
fit.full.tensor = gam(log(cr65plus)~s(pm25.lag1,bs='cr')+s(rmTem
summary(fit.full.tensor)
anova(fit.full.tensor)
```

Testing for an interaction

```
> anova(fit.full.tensor)

Family: gaussian
Link function: identity

Formula:
log(cr65plus) ~ s(pm25.lag1, bs = "cr") + s(rmTemp, bs = "cr") +
    ti(pm25.lag1, rmTemp, bs = "cr") + fdow + s(date2, k = 100) +
    s(DpTemp) + s(rmDpTemp)

Parametric Terms:
     df    F p-value
fdow  6 2.24  0.0371

Approximate significance of smooth terms:
                         edf Ref.df      F p-value
s(pm25.lag1)           1.000  1.001  4.147  0.0418
s(rmTemp)              5.301  6.480  2.524  0.0171
ti(pm25.lag1,rmTemp)   1.000  1.000  3.463  0.0629
s(date2)              59.917 72.436  6.143  <2e-16
s(DpTemp)              1.000  1.000 41.860  <2e-16
s(rmDpTemp)            1.000  1.000 31.651  <2e-16
```

H_0: $g_{xz}(x_i, z_i)$ does not improve model fit over $g_x(x_i)$ and $g_z(z_i)$.
p=0.06.

Inference in models with smoothing splines

Let's refit the model with pm25.lag1 as a linear term.

```
> fit.reduced3 = gam(log(cr65plus)~pm25.lag1+s(rmTemp)

+s(date2, k = 100)+fdow+s(DpTemp)+s(rmDpTemp), data = health)
> summary(fit.reduced3)

Family: gaussian
Link function: identity

Formula:
log(cr65plus) ~ pm25.lag1 + s(rmTemp) + s(date2, k = 100) + fdow +
    s(DpTemp) + s(rmDpTemp)

Parametric coefficients:
               Estimate Std. Error t value Pr(>|t|)
(Intercept)    4.203e+00  1.018e-02 412.689   <2e-16 ***
pm25.lag1      1.073e-03  4.508e-04   2.381   0.0174 *
fdowFriday    -1.478e-02  1.099e-02  -1.345   0.1789
fdowMonday     2.249e-02  1.098e-02   2.048   0.0407 *
fdowSaturday  -9.026e-03  1.098e-02  -0.822   0.4110
fdowThursday   5.425e-04  1.100e-02   0.049   0.9607
fdowTuesday   -1.433e-03  1.098e-02  -0.130   0.8962
fdowWednesday  9.336e-05  1.100e-02   0.008   0.9932
...
R-sq.(adj) =  0.459   Deviance explained = 48.2%
GCV = 0.016324  Scale est. = 0.015642  n = 1825
```

GAM or linear?

It may seem like we can test for whether or not to include a smooth term versus linear term using anova. However, the anova test can produce funny results when the EDF is approximately one, as the change in DF is very small. So, I suggest not doing this:

```
> anova(fit.reduced2,fit.reduced3,test='F')
Analysis of Deviance Table

Model 1: log(cr65plus) ~ s(pm25.lag1) + s(rmTemp) + s(date2, k = 100) +
    fdow + s(DpTemp) + s(rmDpTemp)
Model 2: log(cr65plus) ~ pm25.lag1 + s(rmTemp) + s(date2, k = 100) + fdow +
    s(DpTemp) + s(rmDpTemp)
  Resid. Df Resid. Dev       Df   Deviance      F Pr(>F)
1    1734.9     27.354
2    1734.9     27.353 0.016157 0.00029882 1.1824 0.0325 *
---
Signif. codes:  0 ?***? 0.001 ?**? 0.01 ?*? 0.05 ?.? 0.1 ? ? 1
```

GAM or linear?

When you have an effect that is close to linear, your interpretation is very similar whether or not you use a gam, and when EDF=1, then the approximate p values are equivalent to refitting with a linear term.

To determine whether or not to include a smooth or linear effect, I suggest looking at the EDF. If it is greater than 1, than it seems reasonable to use a smooth term.

There is not really any disadvantage to modeling with a smooth term, except for some extra work we need to do for interpretation.

One approach to test for a non-linear effect is to construct a special spline that separates the linear and non-linear parts:
https://stats.stackexchange.com/questions/449641/is-there-a-hypothesis-test-that-tells-us-whether-we-should-use-