Time series regression: advancements in this new tool for epidemiological analyses.

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LSHTM Feb 2012

Broad themes covered

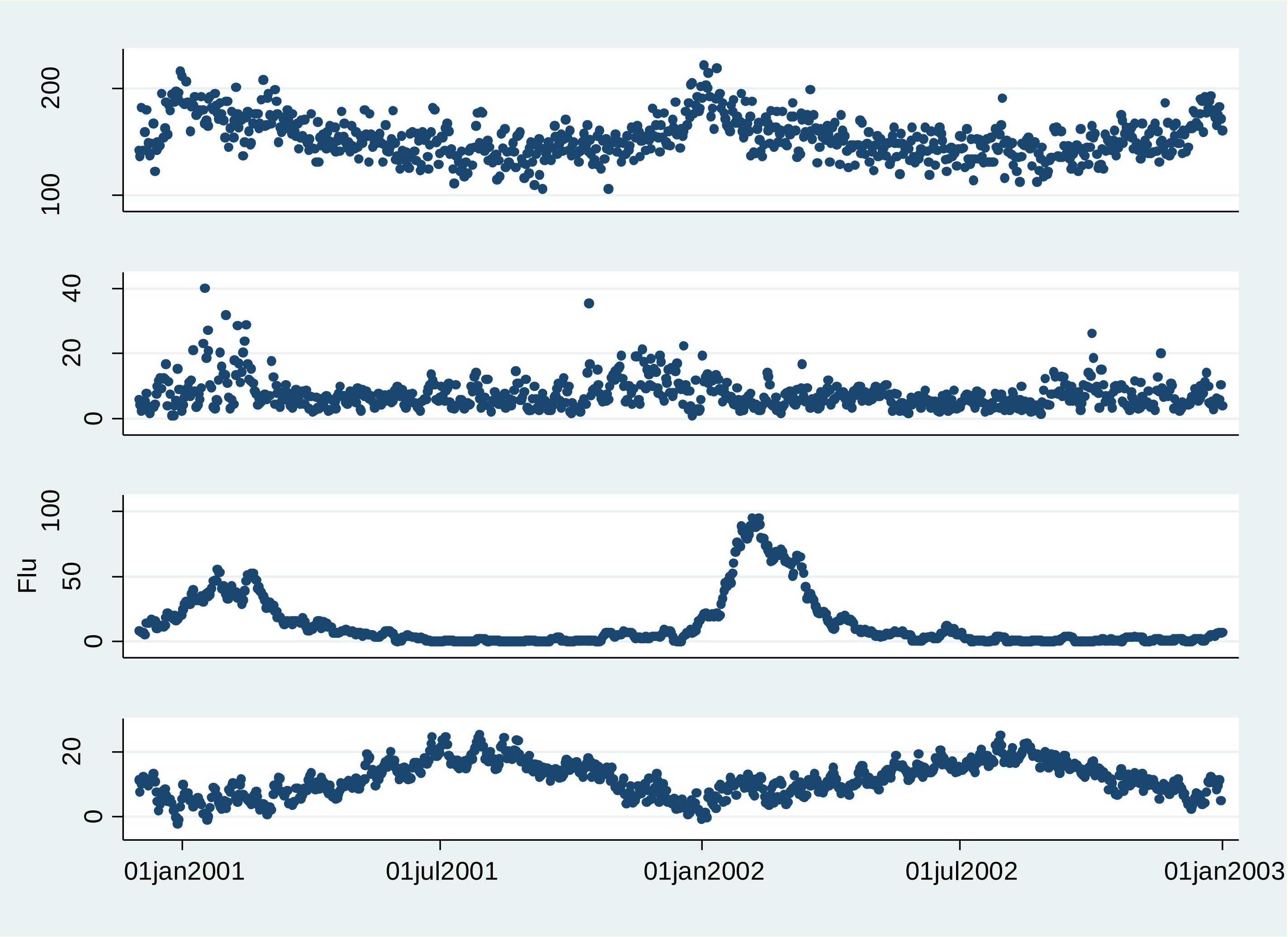
Part 1 (Ben)

1. Introducing time series regression
2. Introducing distributed lag non-linear models (DLNMs)

Part 2 (Antonio)

1. Exploring patterns in DLNMs (& complex patterns generally) across "cities"

Time series regression – the context



Y_i

$x_{1,i}$

$x_{2,i}$

t_i

Time series regressions

What: (Poisson) regression with some time series elements

Why: Find acute effects of time-varying factors

Why not: Effect is chronic or exposure is time invariant

Statistical model needed to allow for:

- Measured time-varying risk factors (flu, pollution, ...)
- Overdispersion
- [Autocorrelation]
- **Unmeasured** smoothly varying risk factors ...
- **Lagged** effects (delay)

Model – general form

Quasi-Poisson regression model with:

$$E(Y_i) = \exp\{ f(t_i, \boldsymbol{\beta}) + [\alpha + \sum_{k=1}^{m} \gamma_{\mathrm{k}} x_{k,i} + \sum_{k=m+1}^{p} S_k(\lambda_k, x_{k,i}) + S_0(\lambda_0, i)]\}$$

$$t_i = temperature\ on\ day\ i$$

$$Y_i = mortality\ count\ on\ day\ i$$

Model – general form

$$E(Y_i) = \exp\{ f(t_i, \boldsymbol{\beta}) + [\alpha + \sum_{k=1}^{m} \gamma_{\mathrm{k}} x_{k,i} + \sum_{k=m+1}^{p} S_k(\lambda_k, x_{k,i}) + S_0(\lambda_0, i)]\}$$

$$or\ \ E(Y_i) = \exp\{< temperature\ effect > + < Other\ effects > \}$$

$$t_i = temperature\ on\ day\ i$$

$$Y_i = mortality\ count\ on\ day\ i$$

Model – general form

Measured Linear — Measured non-linear — Unmeasured smooth in time

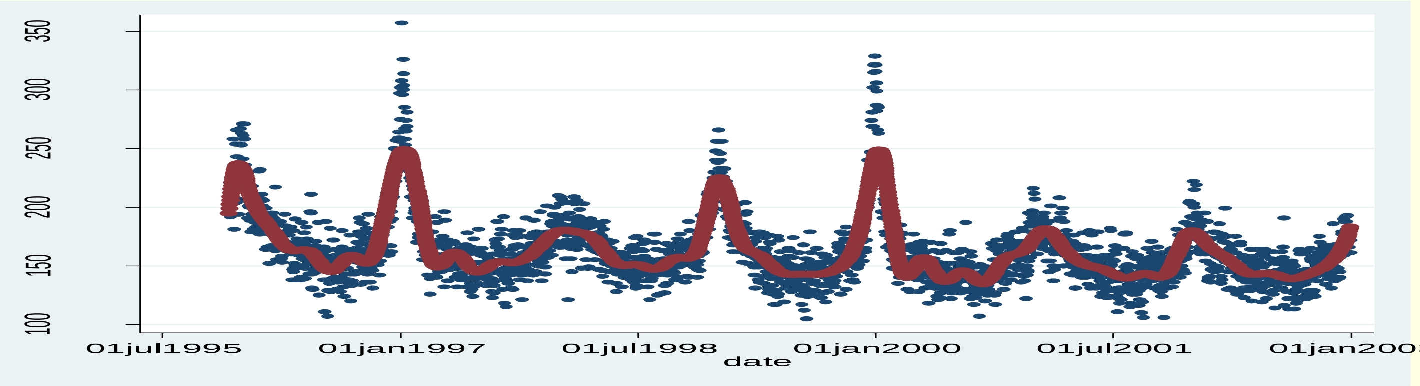
$$E(Y_i) = \exp\{ f(t_i, \boldsymbol{\beta}) + [\alpha + \sum_{k=1}^{m} \gamma_k x_{k,i} + \sum_{k=m+1}^{p} S_k(\lambda_k, x_{k,i}) + S_0(\lambda_0, i)]\}$$

$$or \;\; E(Y_i) = \exp\{< temperature\ effect > + < Other\ effects >\}$$

$$t_i = temperature\ on\ day\ i$$

$$Y_i = mortality\ count\ on\ day\ i$$

… Control for smoothly varying risk factors

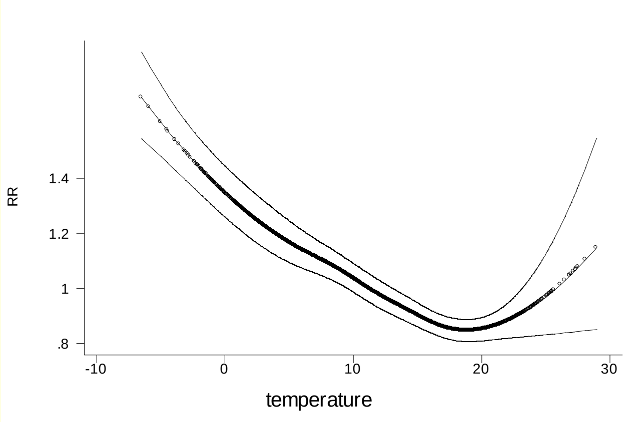


Options:

- Explicitly seasonal
  - Stratification: month (1-12) or week (1-52) indicators
  - Fourier (sine/cosine) functions
- General smooth functions of time
  - Stratification: month(1-72) or week (1-312)
  - Linear
  - Polynomial
  - **Cubic spline (illustrated above with 7 df/y)**
  - Non-parametric (GAM: LOWESS, Penalised spline …)

Impact of confounding

Unadjusted:



Adjusted:

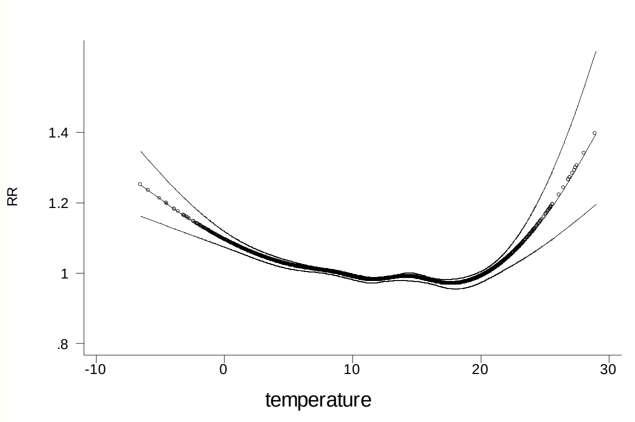
•Time/season smooth curve ,

•Pollution

•Flu

•Day of week

[Air pollution benchmark model]



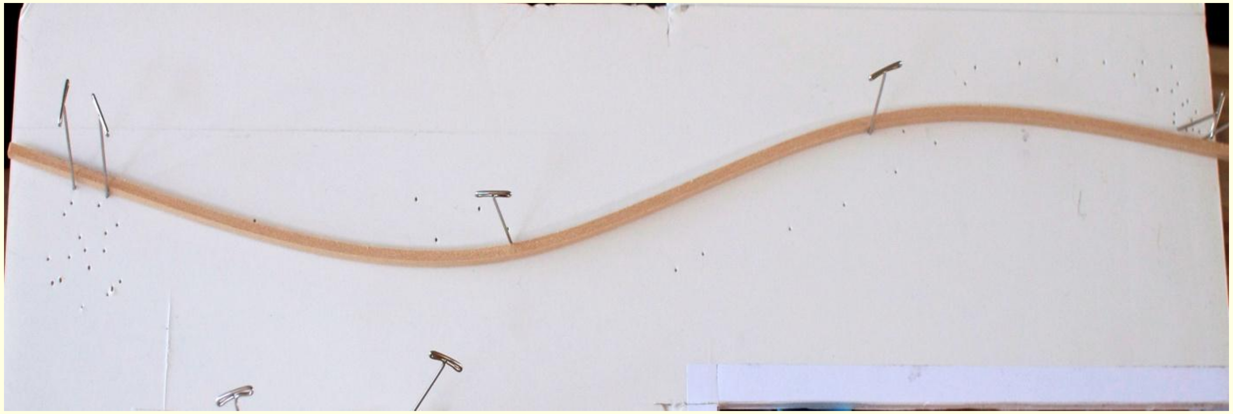
That’s all on confounder control

Functional form of temperature –mortality association

$(f(t_i,\beta))$

Splines: eg natural cubic spline: NCS

1940's

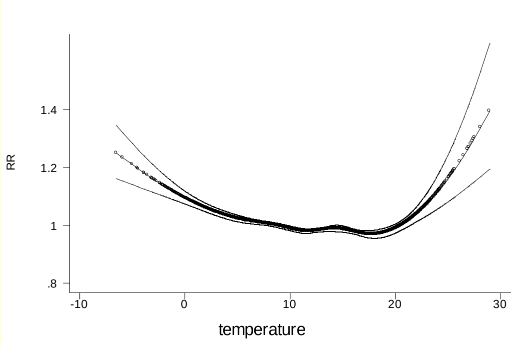


1990's

$$f(t_i, \boldsymbol{\beta}) = \sum_{b=1,k} \beta_b t_{b,i}$$

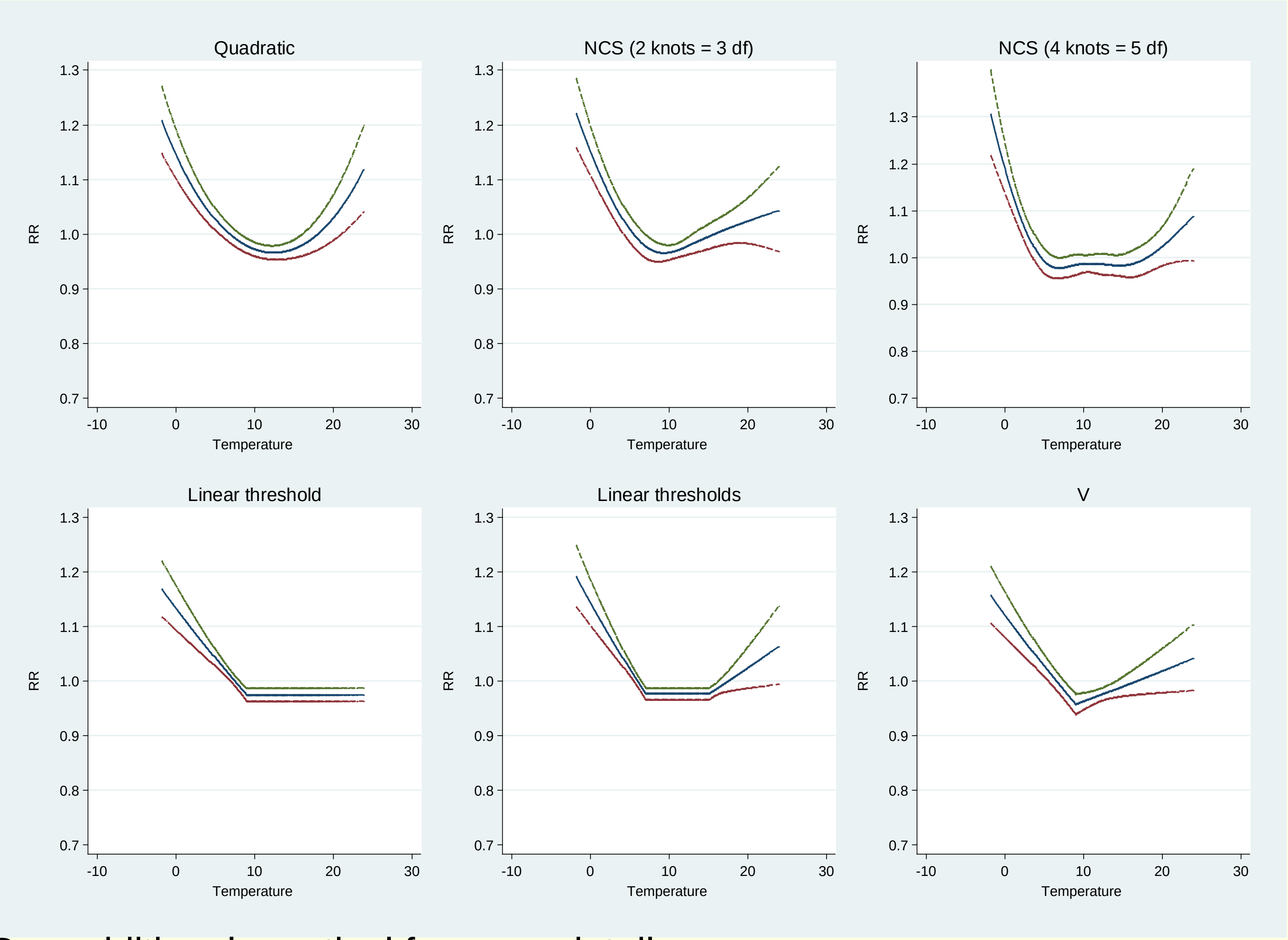
$$t_{b,i} \cong [(t_i - \{knot\}_b)^+]^3$$

"Spline **basis**" variables



(OK geeks – not quite right – but close enough)

Var. of interest: Non-linear options



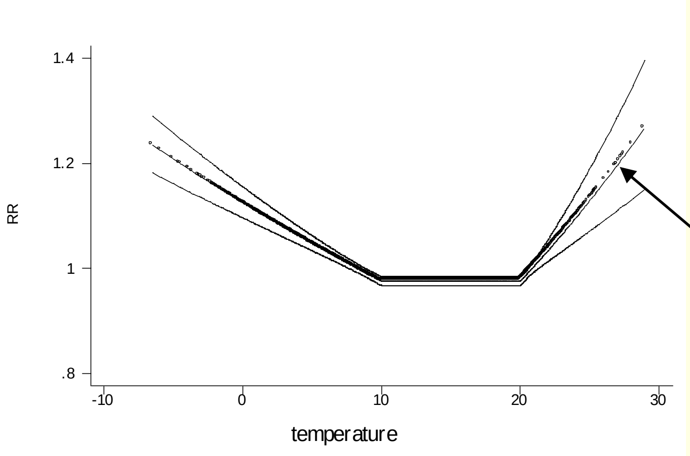
See additional practical for more detail

Lags

Lag = delay (in days) between exposure (heat or cold) and death

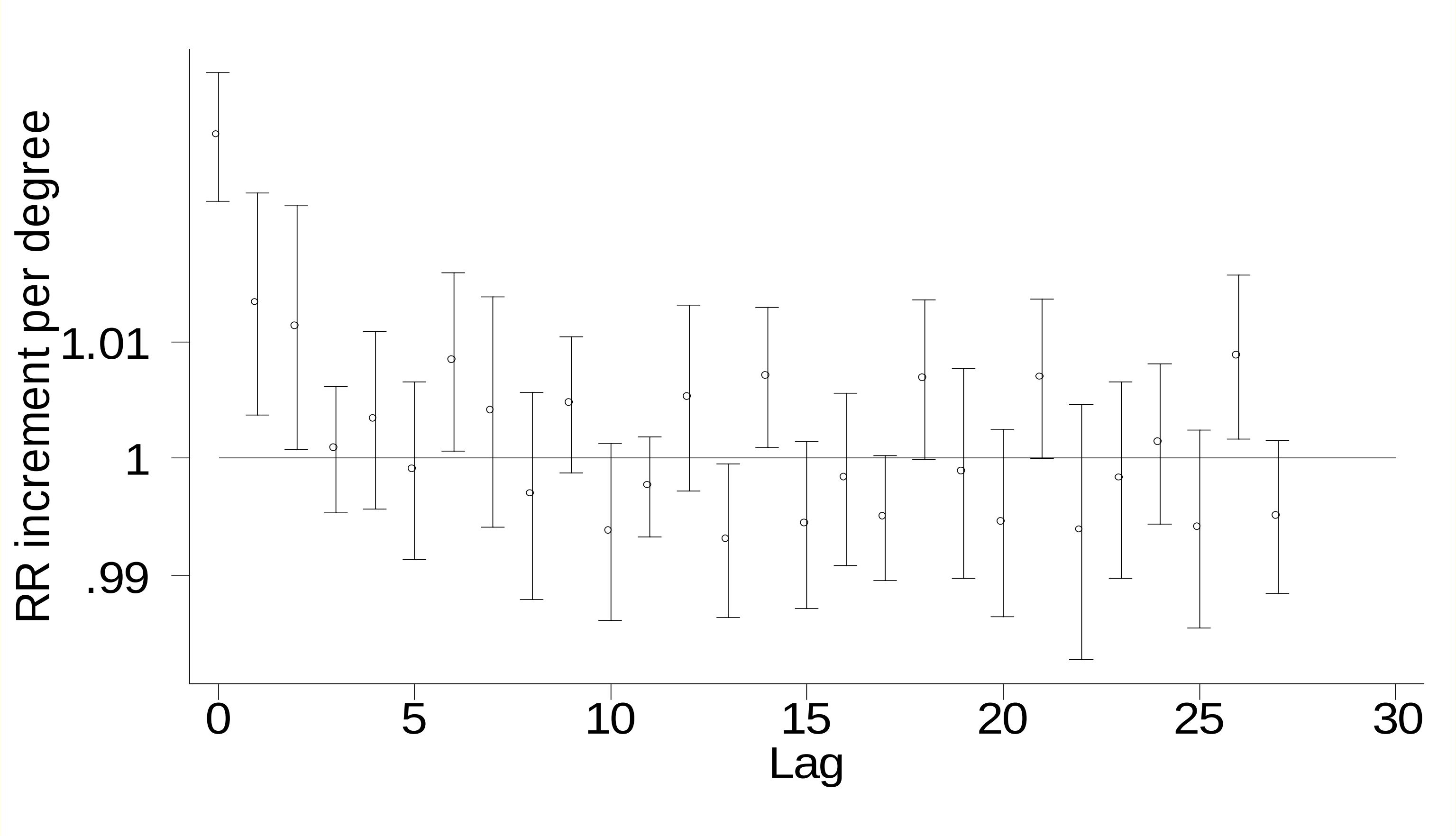
Exploring lagged effects 1:

- Use a linear threshold model
- Fit a **distributed lag model (DLM)** to the heat slope



Heat effects: Different slope for each lag

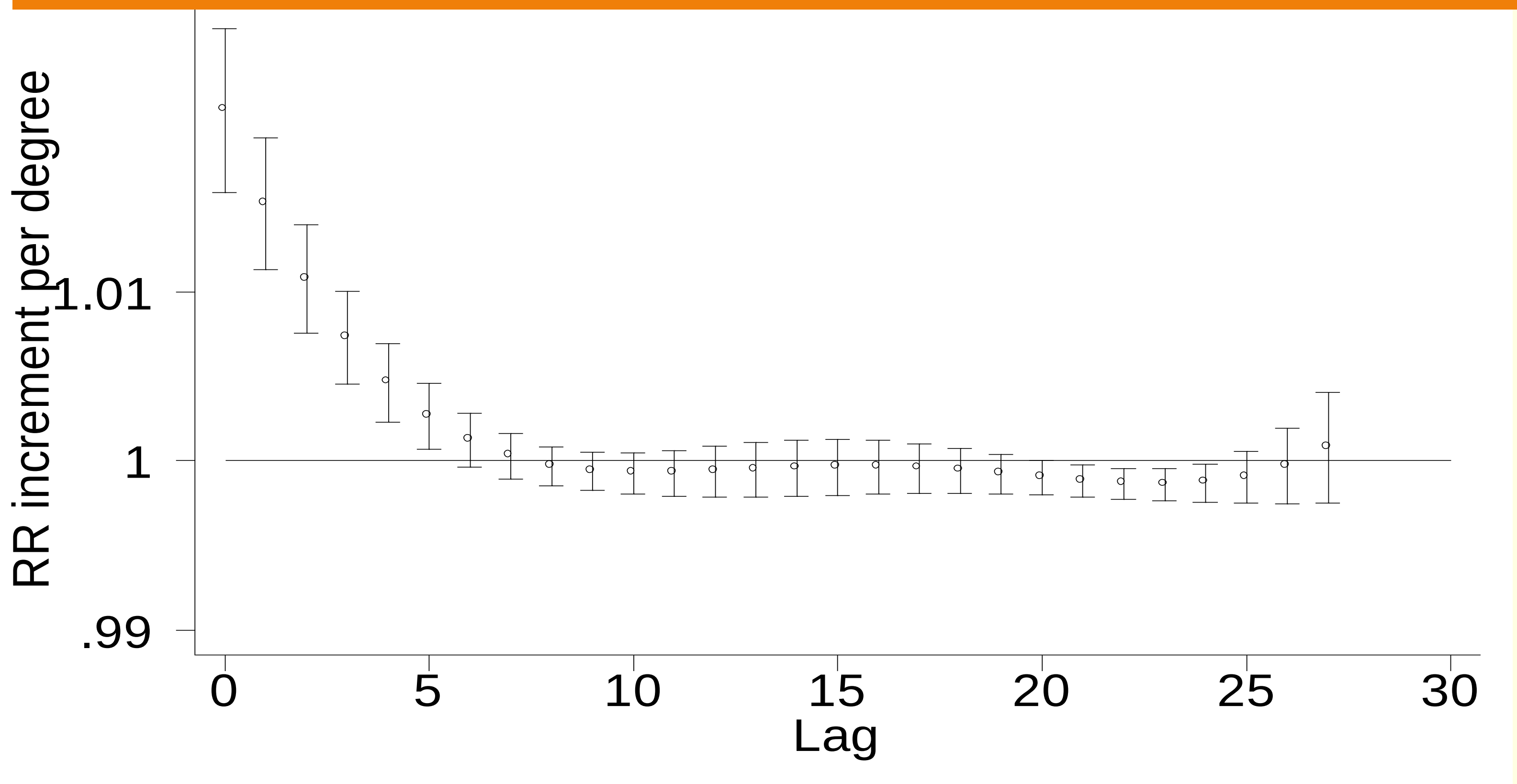
Distributed lags with linear effects – heat (degrees above 20^{o}C)



$$DLM(heat): \sum_{l=0}^{27} \gamma_p t_{heat,i-p}$$

London CVD 1976-1993

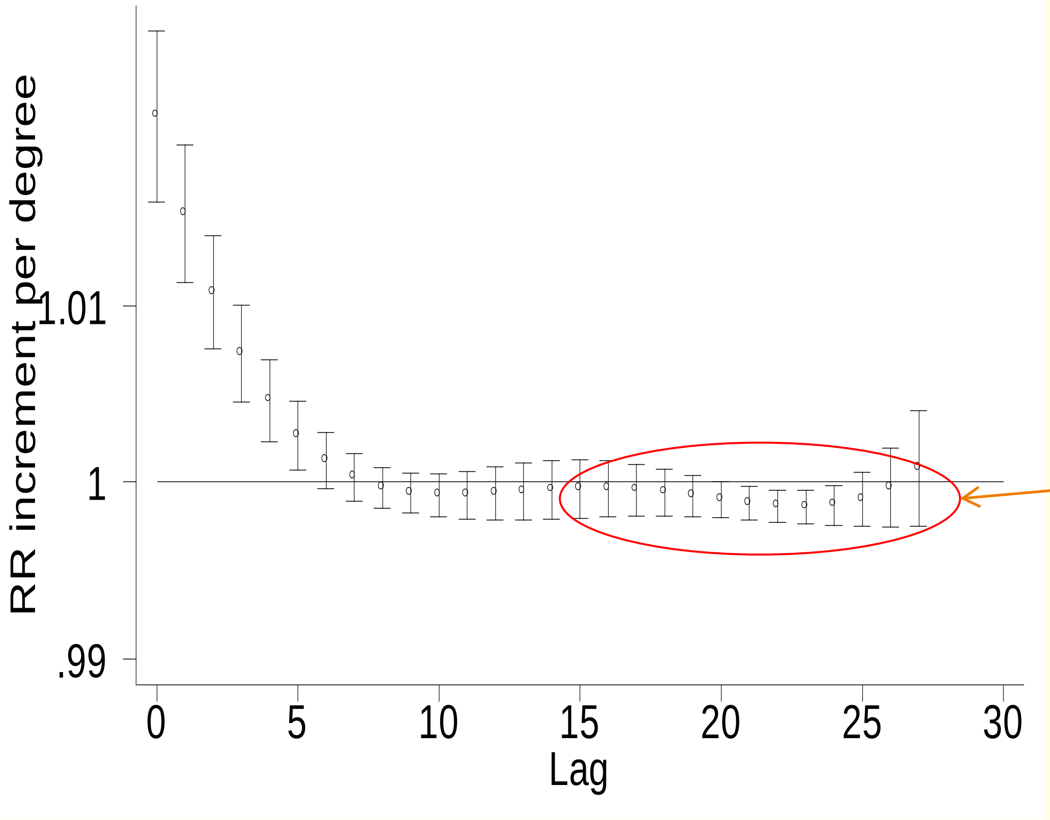
Constrained Distributed lags (degrees above 20^{o}C) Quartic polynomial [Schwartz 2001]



$$DLM(heat): \sum_{p=1}^{P} \gamma_p \overline{t_{heat,p,i}}, \text{ where } \overline{t_{heat,p,i}} = \sum_{l=0}^{L} l_p t_{heat,i-l}$$

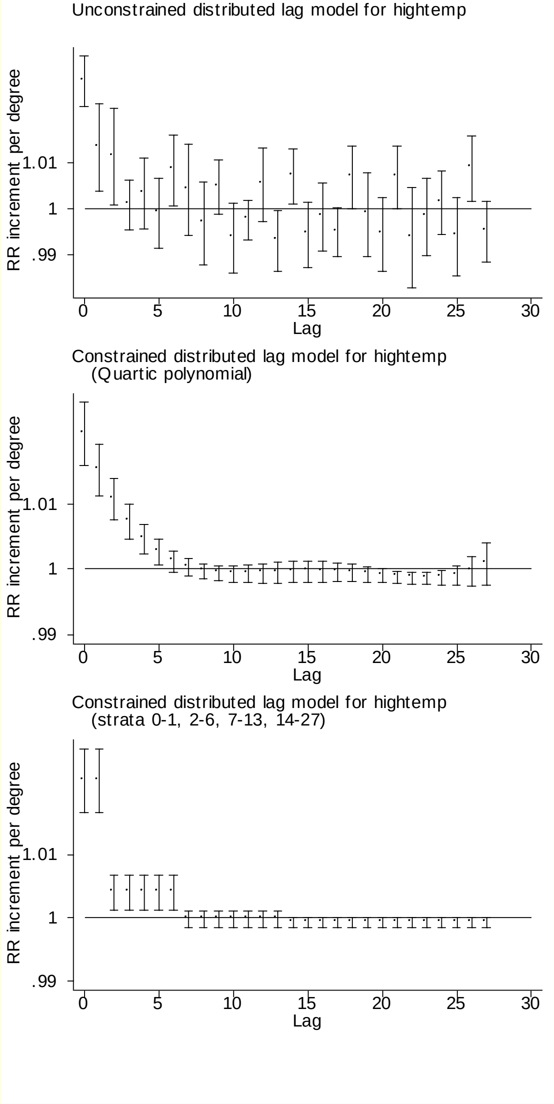
Lag basis variable

Distributed lag models and “harvesting”



Deficit – “harvesting”?

A summary of net effect from distributed lag models



Net RR increment (%) over 28 days per degree above 20 (95% CI):

5.0(3.7,6.3)

4.9(3.6,6.2)

4.9(3.7,6.2)

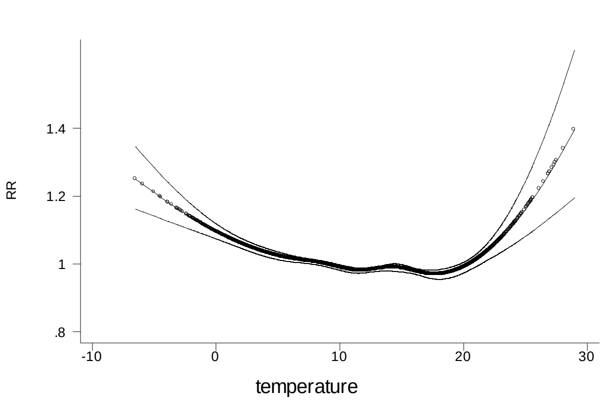
Distributed lag non-linear model

$f(t_i,\beta)$ tweaked again

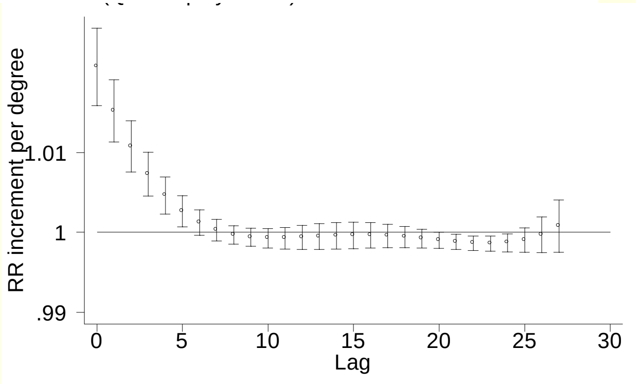
To capture curved associations with non-trivial lag dependence:

Need combined virtues of:

(a) Smooth temp-mort curves



(b) Smooth effects of lag.



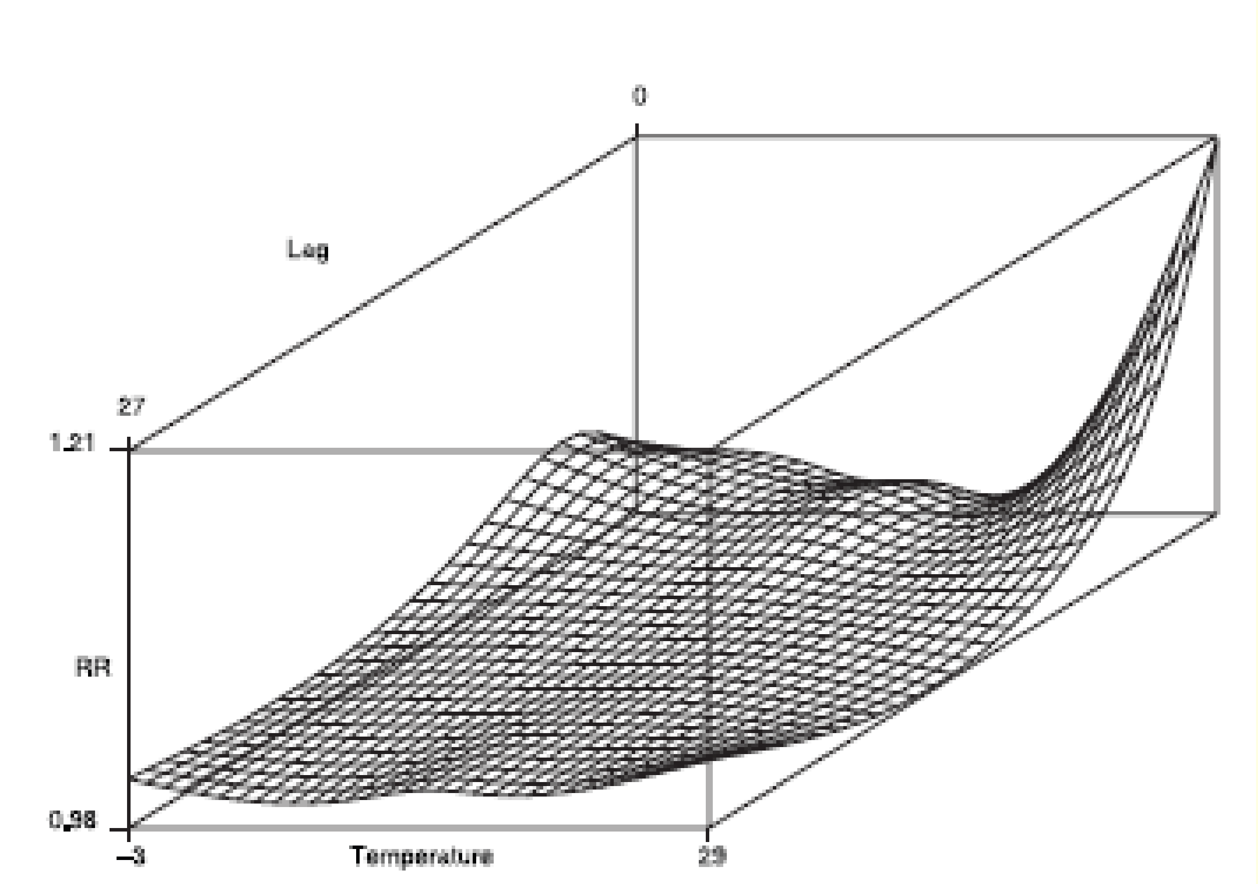
Distributed lag non-linear models (**DLNM**)

Unrestricted choice of:

Shape of temperature-mort graph		**Shape of change with lag**
•Step changes •Thresholds •Cubic splines •...	X	•Step changes •Polynomial •Cubic splines •...

Implemented in R package dlnm AG (and clutzy stata code - BA)

RR by temperature (NCS) and lag(NCS)



Temperature-mortality models: recap

$$f(t_i, \boldsymbol{\beta}) =$$

$$Thresholds: \quad \beta_{cold} t_{cold,i} + \beta_{heat} t_{heat,i}$$

$$Spline(gen): \sum_{b=1}^{B} \beta_b t_{b,i}$$

$$DLM(heat): \sum_{p=1}^{P} \gamma_p \overline{t_{heat,p,i}}, \text{ where } \overline{t_{heat,p,i}} = \sum_{l=0}^{L} l_p t_{heat,i-l}$$

Temperature-mortality models: +1

$$f(t_i, \boldsymbol{\beta}) =$$

$$Thresholds \quad : \beta_{cold} t_{cold,i} + \beta_{heat} t_{heat,i}$$

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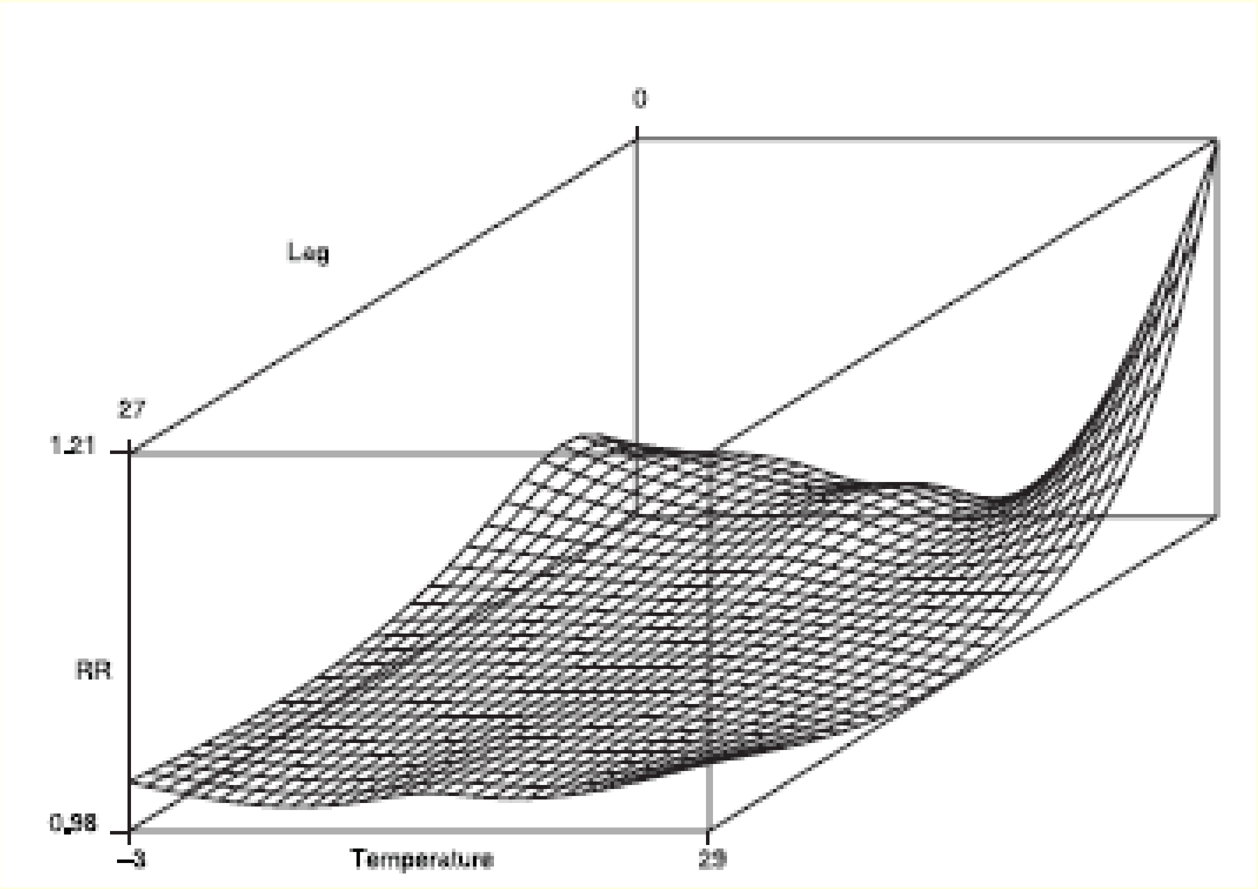
$$DLNM(gen) \; : \sum_{b=1}^{B} \sum_{p=1}^{P} \eta_{b,p} \overline{\overline{\mathbf{t_{b,p,i}}}}, \; where \; \overline{\overline{t_{b,p,i}}} = \sum_{l=0}^{L} l_p t_{b,i-l}$$

Temperature **basis**
(B df)
+
Lag **basis**
(P df)

=
"Cross" **basis**
(BXP df)

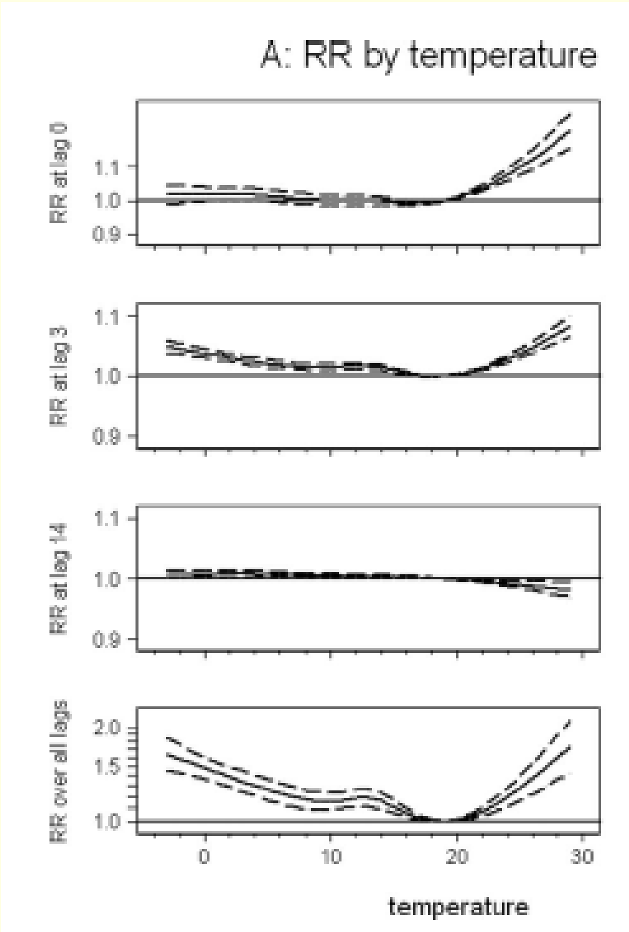
Armstrong 2006

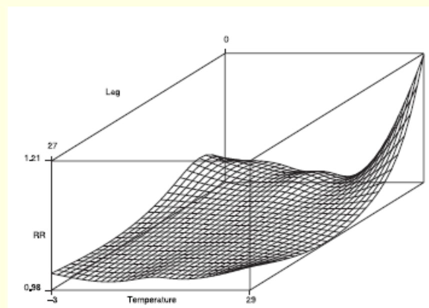
RR by temperature (NCS) and lag(NCS)

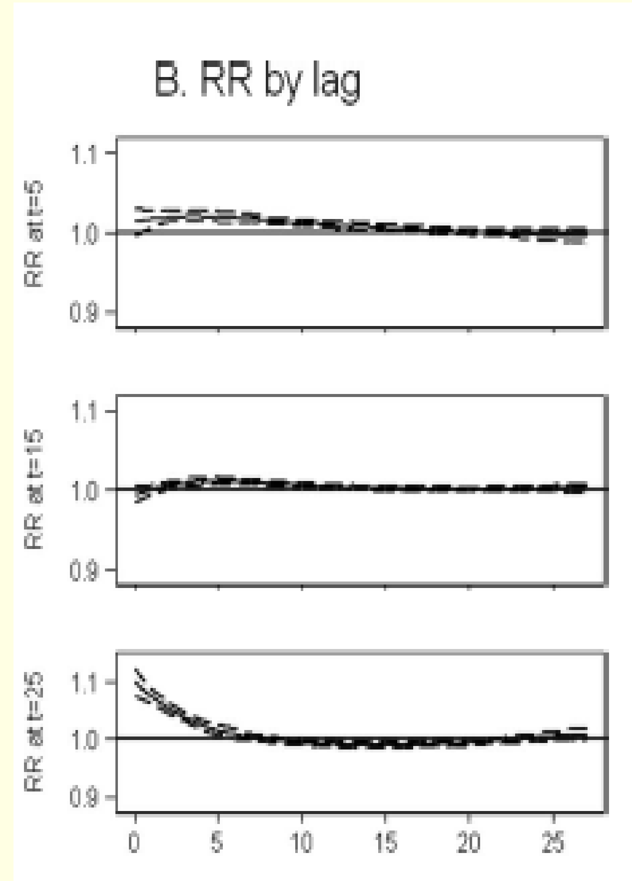


5df temp X 4df lag = 20 df

Ways of looking at DLNMs





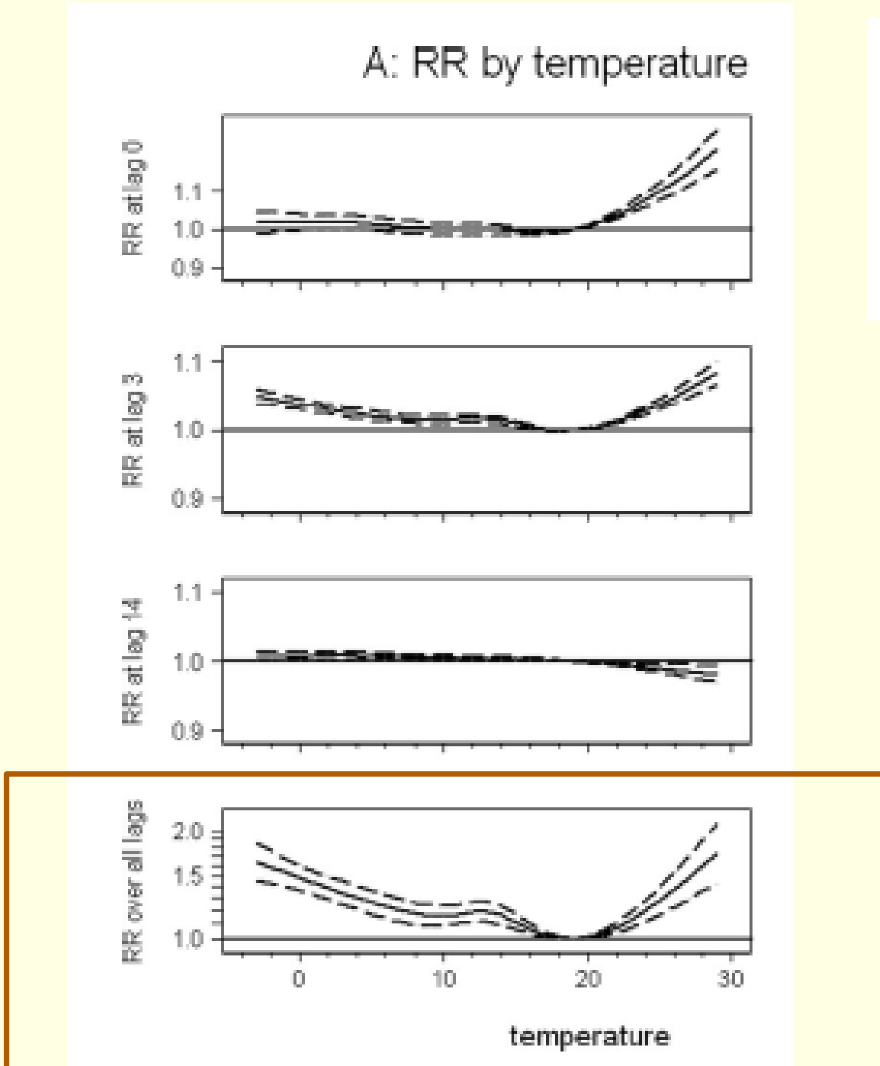


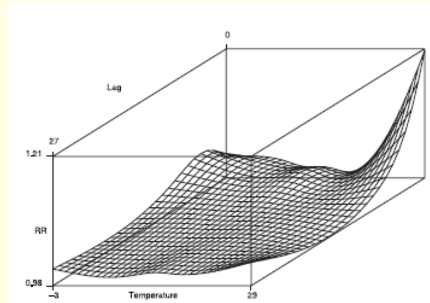
RR by temperature for given lag

RR vs 20^{oC}

RR by lag for given temperature

- Adding graph of total (28 day) effect





Part 1 wrap-up

- Time series regression allows investigation of acute effects; many applications:
  - *Air pollution -> health outcomes*
  - *Weather -> health (incl. infectious diseases)*
  - *Circulating viruses -> mortality/admissions*
  - *Policy changes ->health (interrupted time series)*
  - -...
- DLNMs allow flexible modelling of delayed effects with possibly non-linear exposure-response.

Ecol TS: Counts, proportions, means;
+Panel studies, cohorts, case-control, ...