Time-series regression for short-term health effects of environmental risk factors in the EMME

Quantifying short-term effects

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Exposure-response and lagged effects

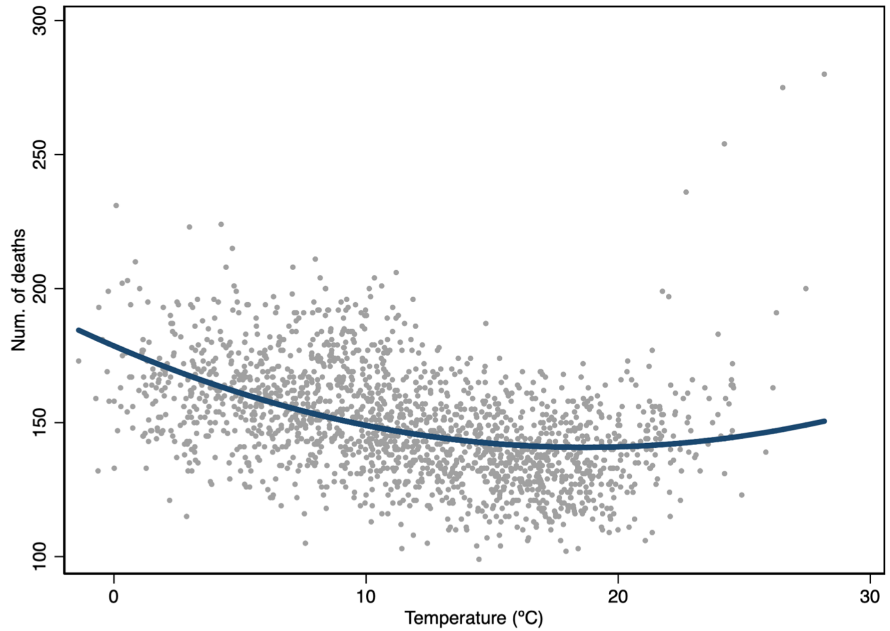
- Associations between environmental exposures and health outcomes can show different **type of shapes**, and are often characterized by **lagged effects**
- We will need to model potentially **complex temporal patterns of risk** due to time-varying exposures
- It requires a **previous knowledge** about the shape of the exposure-response function and the lagged effects

Exposure-response of temperature

- **Quadratic model**

$$Y_t = a + f(t) + b_1 x_t + b_2 x_t^2$$

  - $\mathbf{b_1+2b_2x}$ risk increase for a 1°C rise
  - **Multiple effects**, one for each value of temperature (x)
  - Minimum Mortality Temperature (MMT) at $\mathbf{-b_1/2b_2}$



Exposure-response of temperature

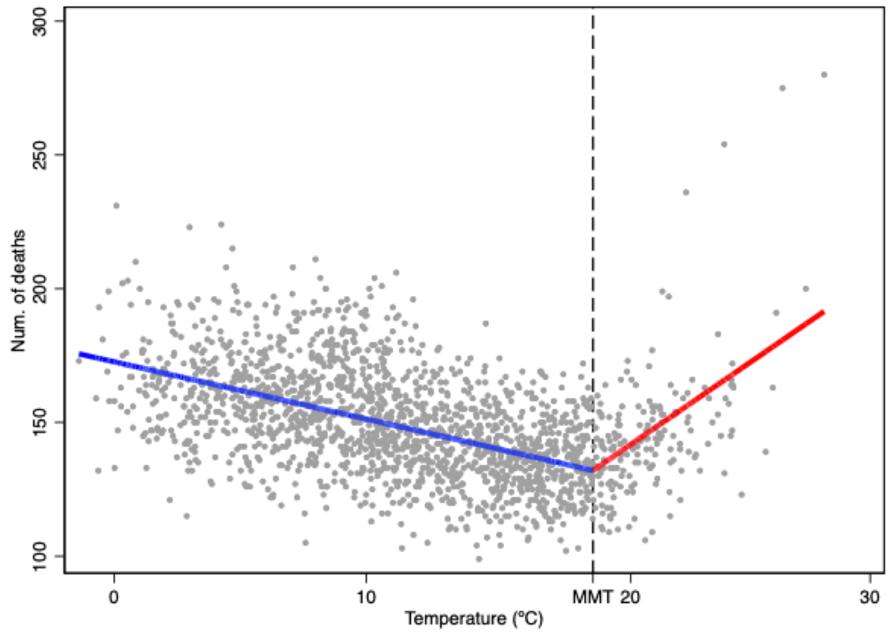
- **Piecewise linear model**

$$Y_t = a + f(t) + b_c x_{ct} + b_h x_{ht}$$

$$x_c = max[(t_c - x_i), 0]$$

$$x_h = max[(x_i - t_h), 0]$$

  - **Cold** effect as $\mathbf{b_c}$ risk decrease for a 1°C rise below MMT
  - **Heat** effect as $\mathbf{b_h}$ risk increase for a 1°C rise over MMT
  - **MMT** identified empirically

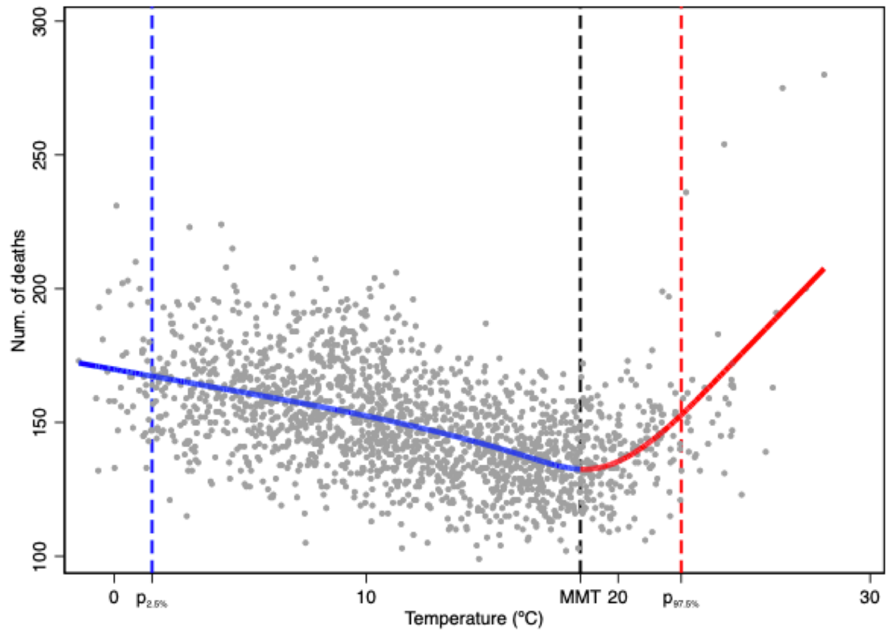


Exposure-response of temperature

- Spline function

$$Y_t = a + f(t) + f(x_t)$$

  - **Cold** effect by comparing the risk at a low temperature (e.g., $p_{2.5\%}$) versus at the MMT
  - **Heat** effect by comparing the risk at a high temperature (e.g., $p_{97.5\%}$) versus at the MMT
  - MMT identified empirically



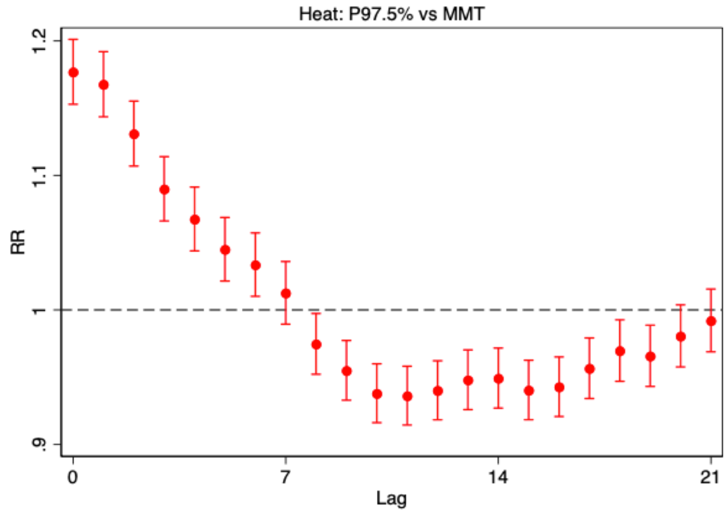
Lagged effects

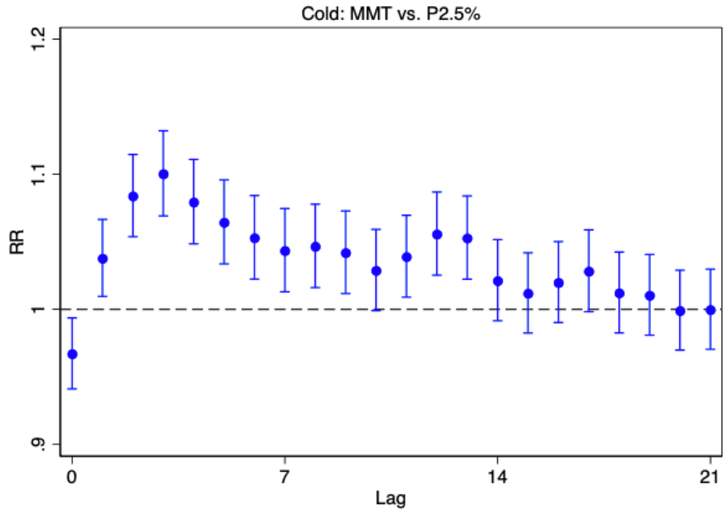
- **Independent model lags**

$Y_t = a + f(t) + b_j x_{t-j}$

for j=0 to k lags

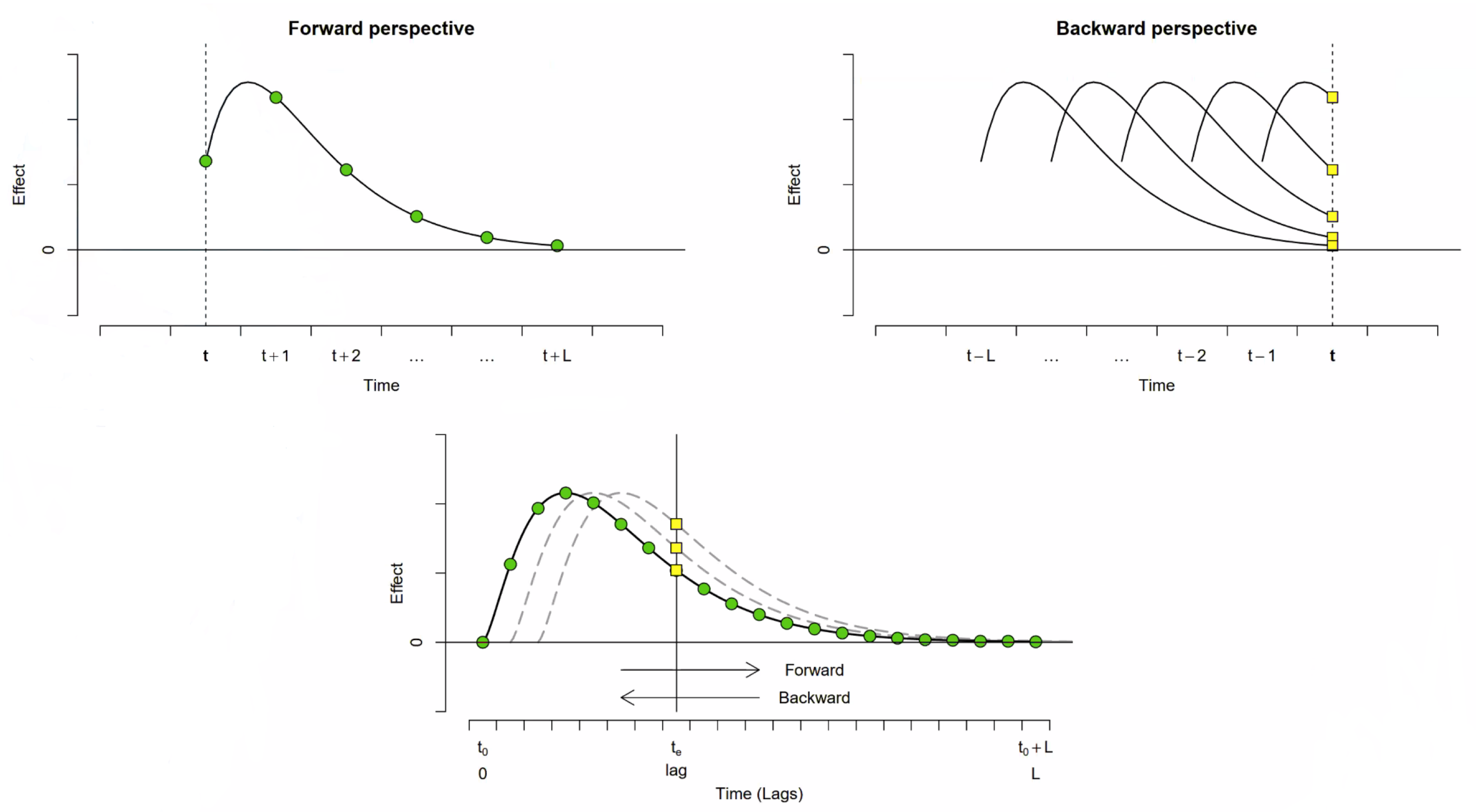
  - A regression model for each lag
  - **Heat** shows short-term effects, up to one week
  - **Cold** shows longer effects, up to almost three weeks





(Armstrong 2006)

Lagged effects



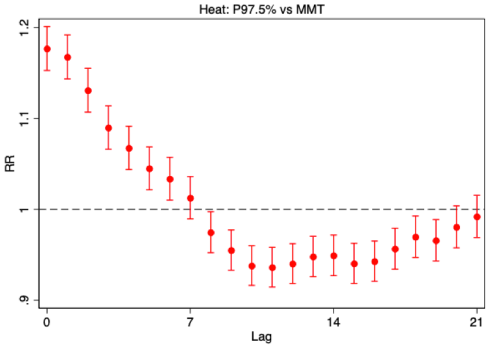
(Courtresy of Antonio Gasparrini)

Lagged effects

- **Independent**

$Y_t = a + f(t) + b_j x_{t-j}$

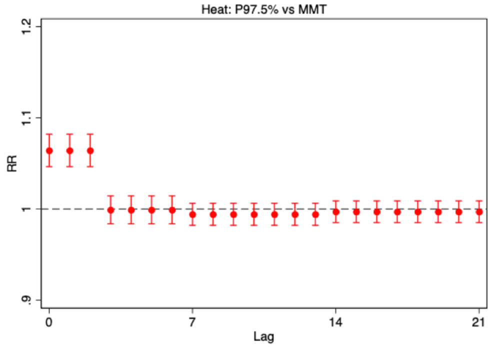
for j=0 to k lags



- **Stratum**

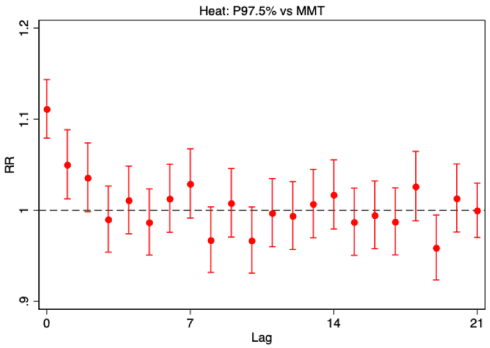
$Y_t = a + f(t) + \sum b_j x_{t-j}$

$b_1 = b_2 = b_3$
$b_4 = b_5 = b_6 = b_7$
$b_8 = \ldots = b_{14}$
$b_{14} = \ldots = b_{21}$



- **Unconstrained**

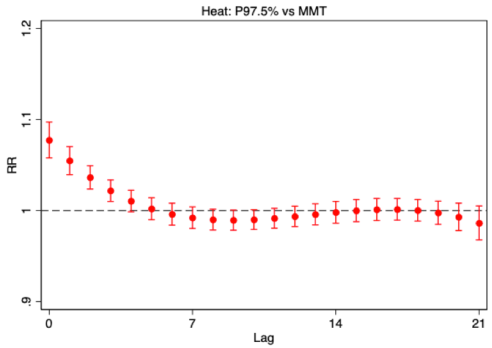
$Y_t = a + f(t) + \sum b_j x_{t-j}$



- **Spline function**

$Y_t = a + f(t) + \sum b_j x_{t-j}$

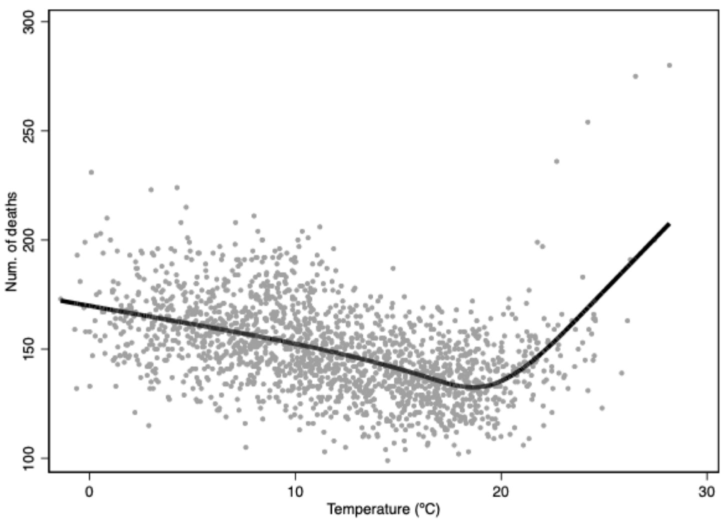
$b_j = f(b,j)$



Distributed lag non-linear models

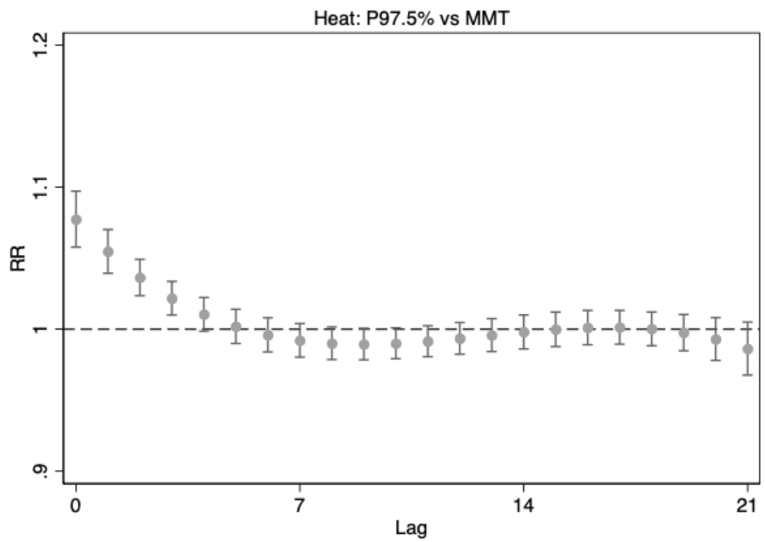
(Gasparrini et al. 2010)

Exposure-response



×

Lagged effects



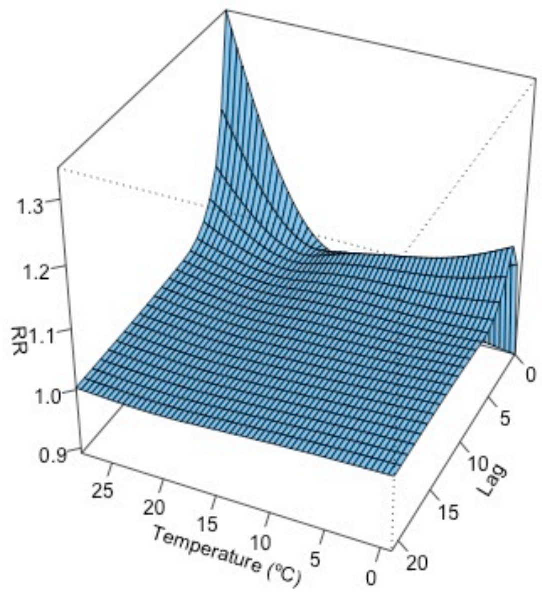
- Function ***f(x)*** for **exposure-response** × function **W(l)** for **lagged** effects

Distributed lag non-linear models

(Gasparrini et al. 2010)

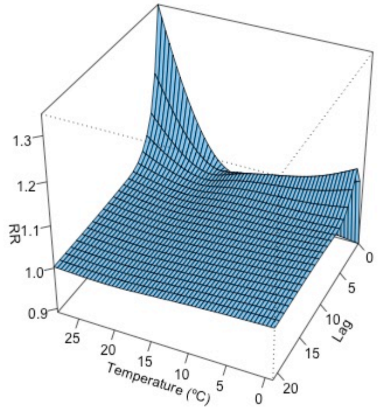
Bi-dimensional **exposure-lag-response**

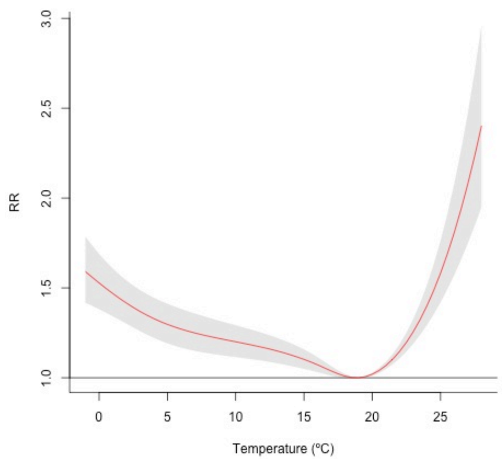
$$\mathbf{Y_t = a + f(t) + \sum \mathit{f \cdot w(x_{t-l}, l)}}$$



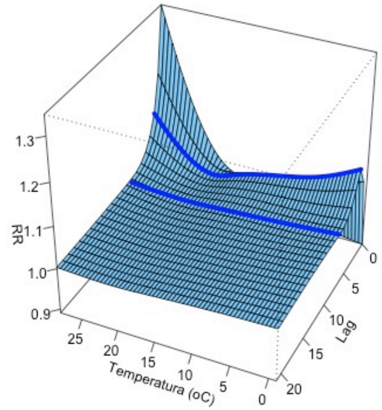
Estimating effects of temperature

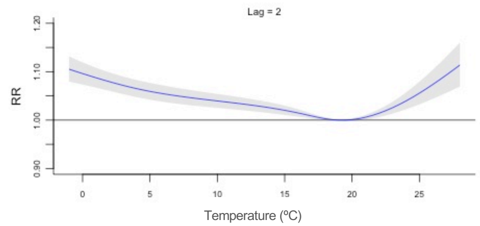
Overall

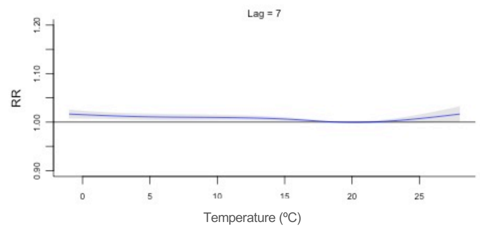




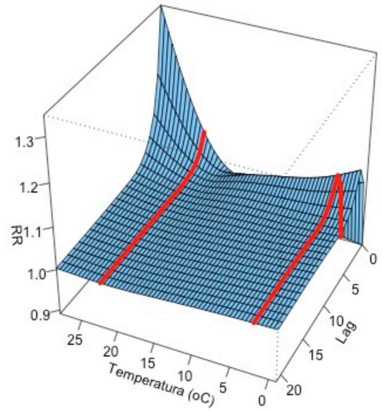
by **lag**

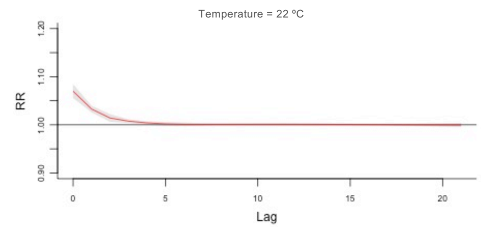


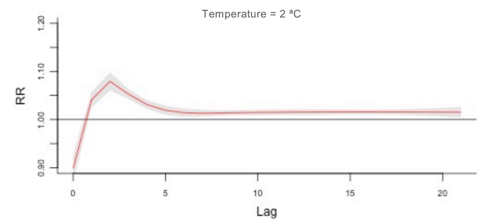




by **temperature**



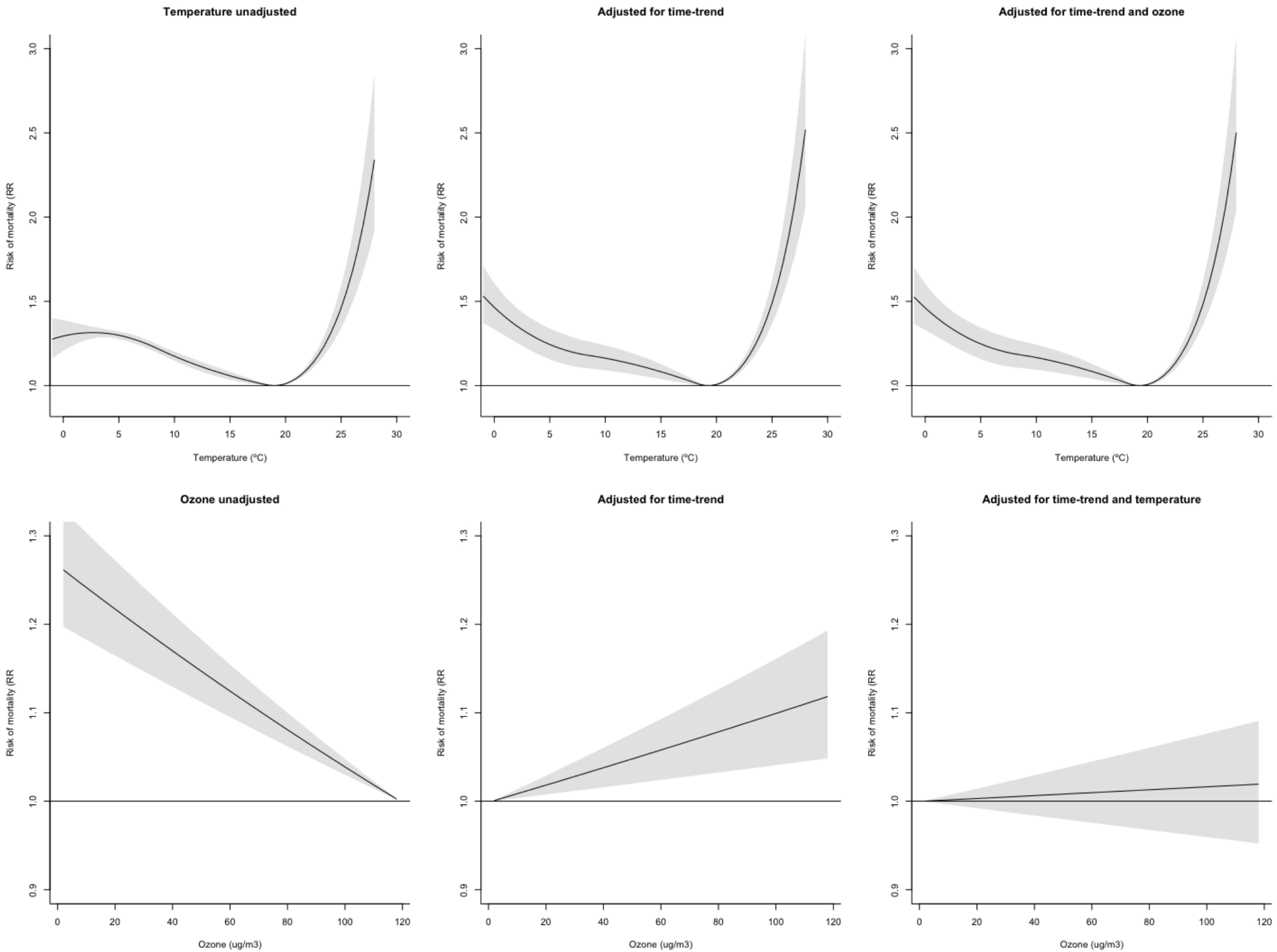




Common environmental exposures

- **Temperature**
  - **Non-linear** association, J- or V-shaped (dlnm)
  - Minimum risk at **MMT**
  - Short-term effects of heat, up to one week, and longer effects for cold, up to 3 weeks
  - Effects **not necessarily confounded** by air pollution *(Buckley et al. 2014)*

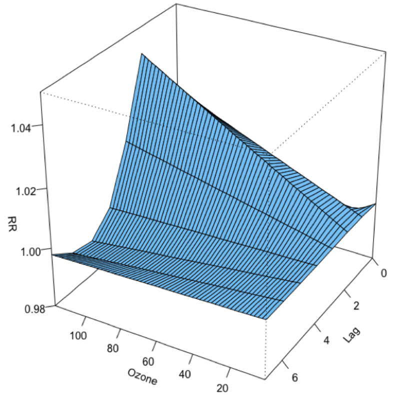
- **Air pollution**
  - **Linear** association (dlm)
  - Minimum risk at **minimum air pollution exposure**
  - Short-term effects, up to 2/3 days
  - Effects are **confounded/modified** by temperature *(Buckley et al. 2014, Analitis et al. 2014)*

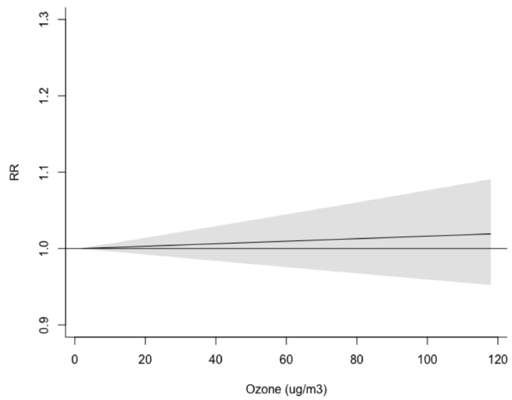


Temperature unadjusted
Adjusted for time-trend
Adjusted for time-trend and ozone
Risk of mortality (RR
Temperature (ºC)
Ozone unadjusted
Adjusted for time-trend
Adjusted for time-trend and temperature
Ozone (ug/m3)

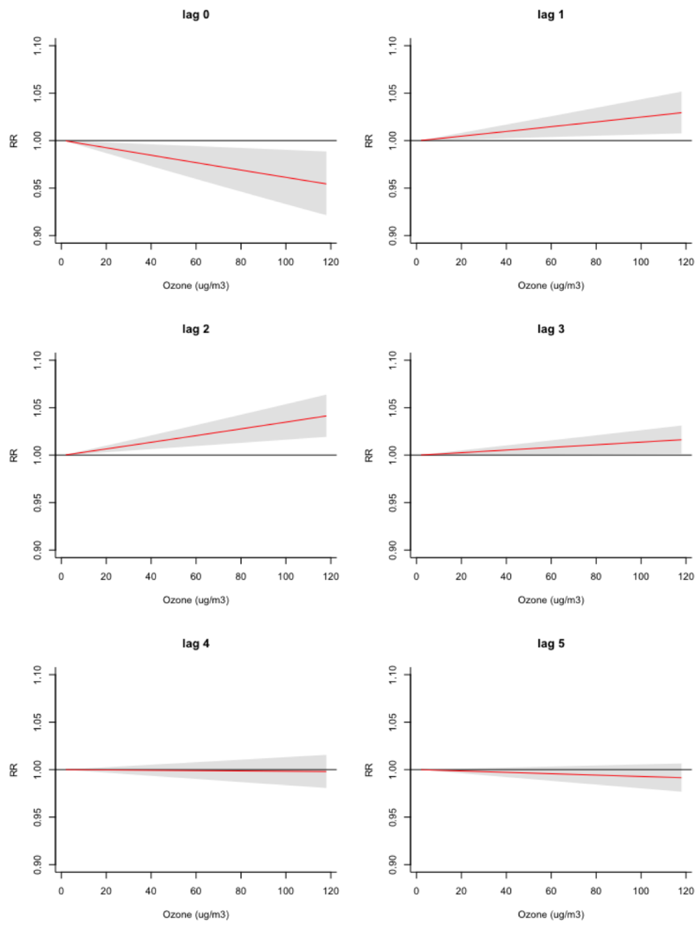
Estimating effects of ozone

Overall

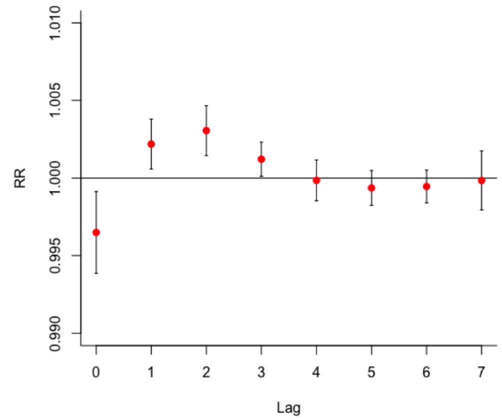




by **lag**



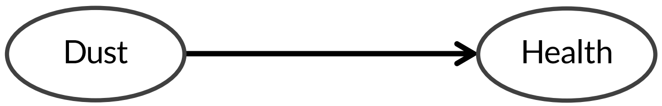
by **10 µg/m^3**



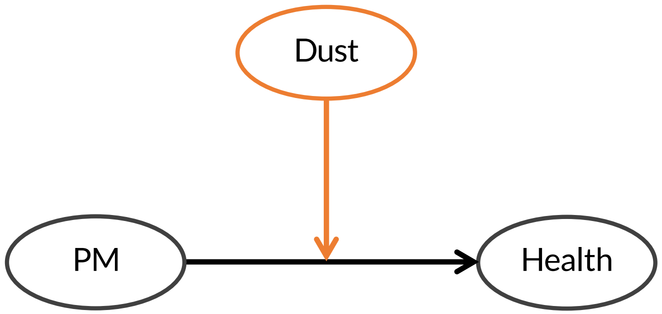
Desert dust exposures

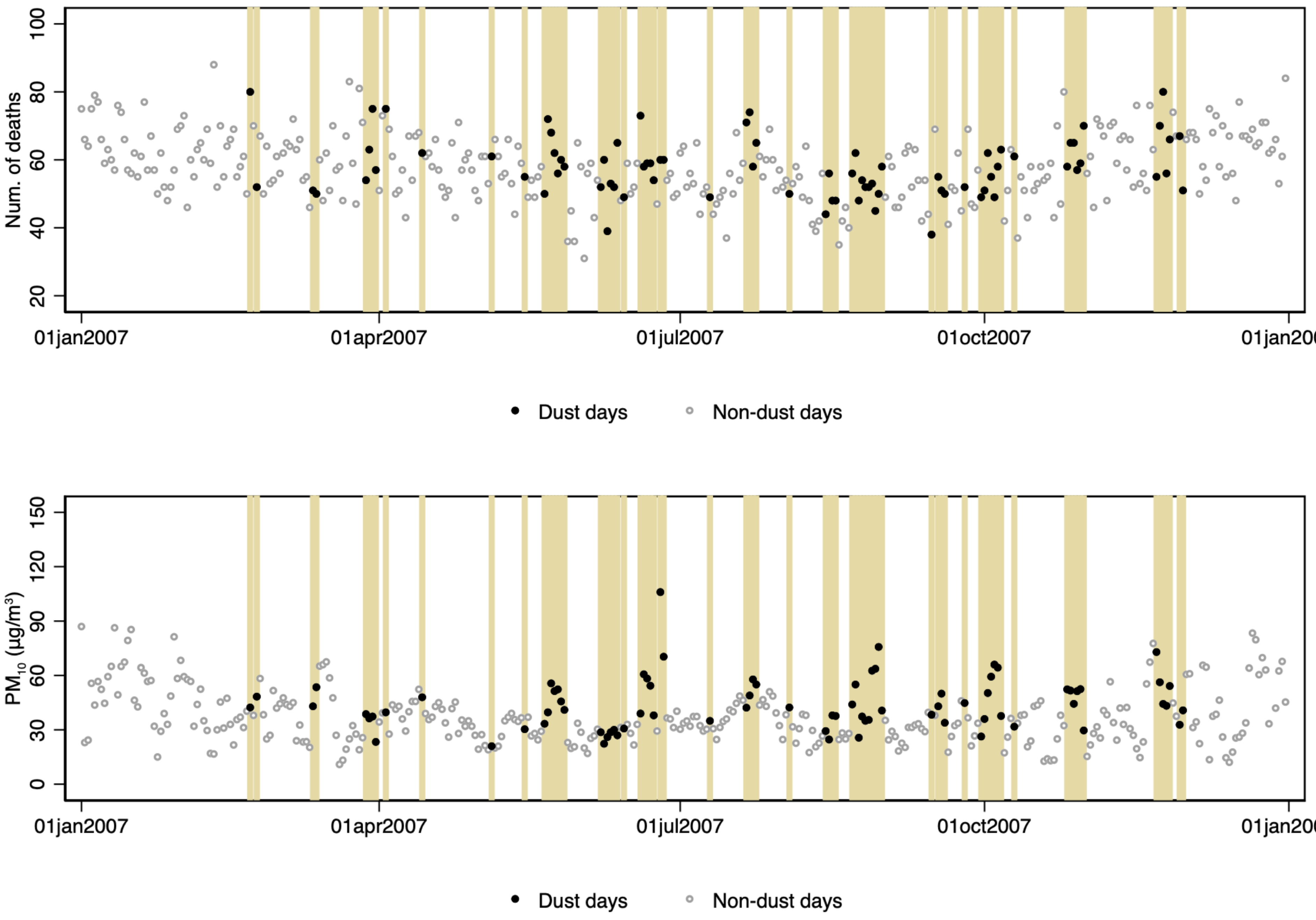
(Tobias & Stafoggia 2020)

- **Binary metric (exposure)**
  - **Research question –** *"Is the occurrence of a health outcome higher on dust days compared to non-dust days?"*
    - *All dust events **treated in the same way** not providing information on the exposure-response relationship*



- **Binary metric (modifier)**
  - **Research question –** *"Is the occurrence of a health outcome higher on dust days compared to non-dust days?"*
    - *It is not possible to attribute the health effects to a **given source***



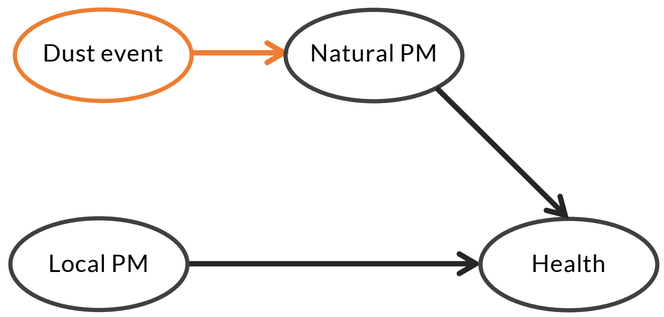


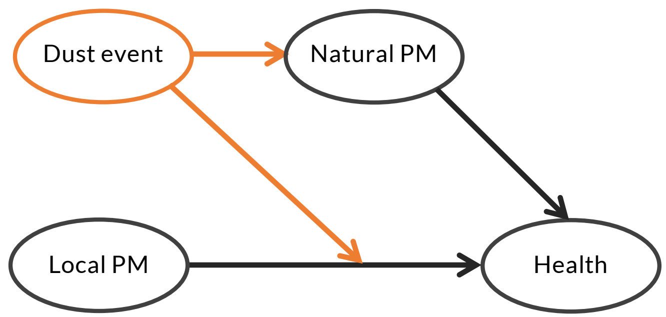
100
80
60
40
20
Num. of deaths
01jan2007
01apr2007
01jul2007
01oct2007
01jan2008
Dust days
Non-dust days
150
120
90
60
30
0
PM10 (μg/m3)
01jan2007
01apr2007
01jul2007
01oct2007
01jan2008
Dust days
Non-dust days

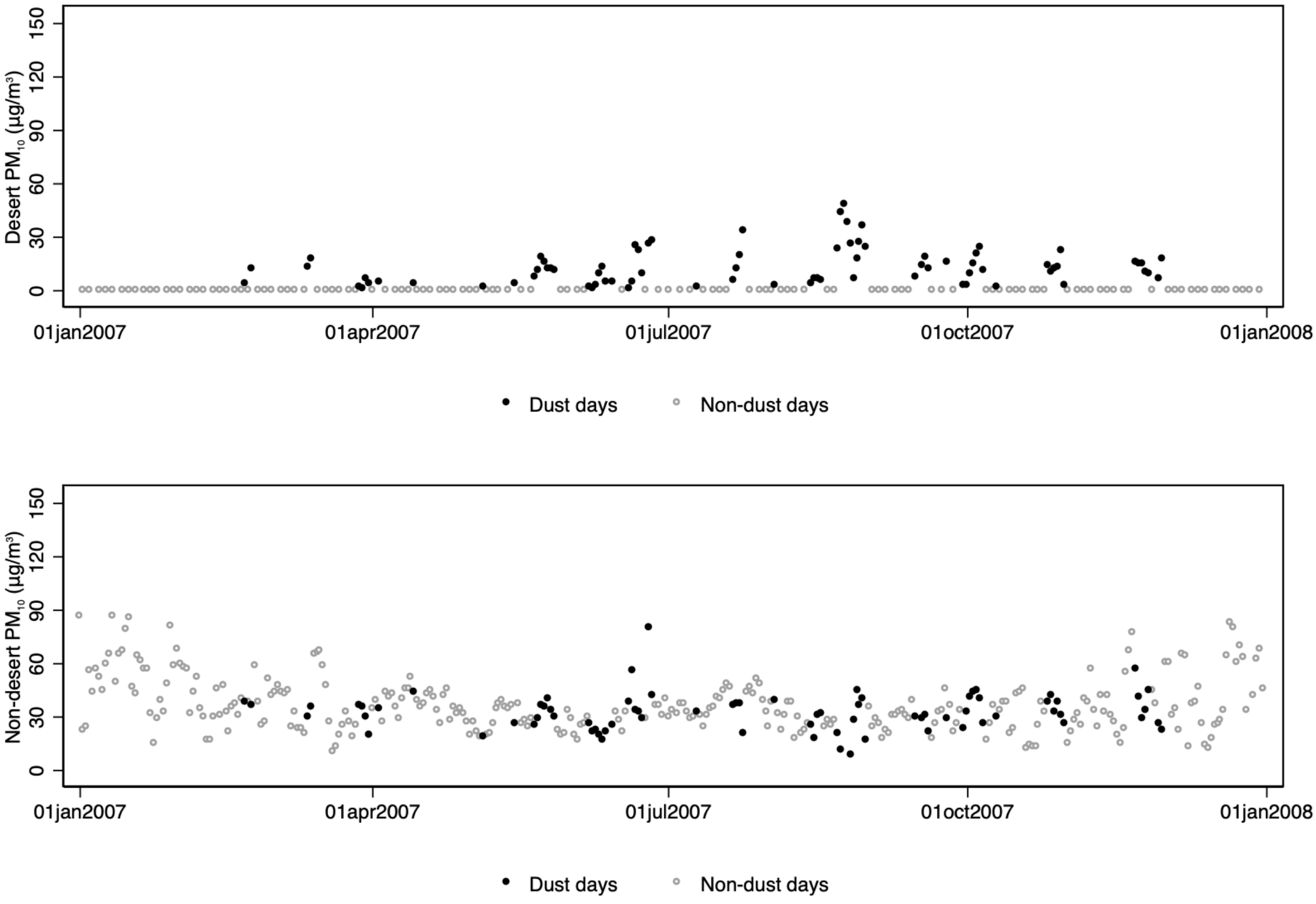
Desert dust exposures

(Tobias & Stafoggia 2020)

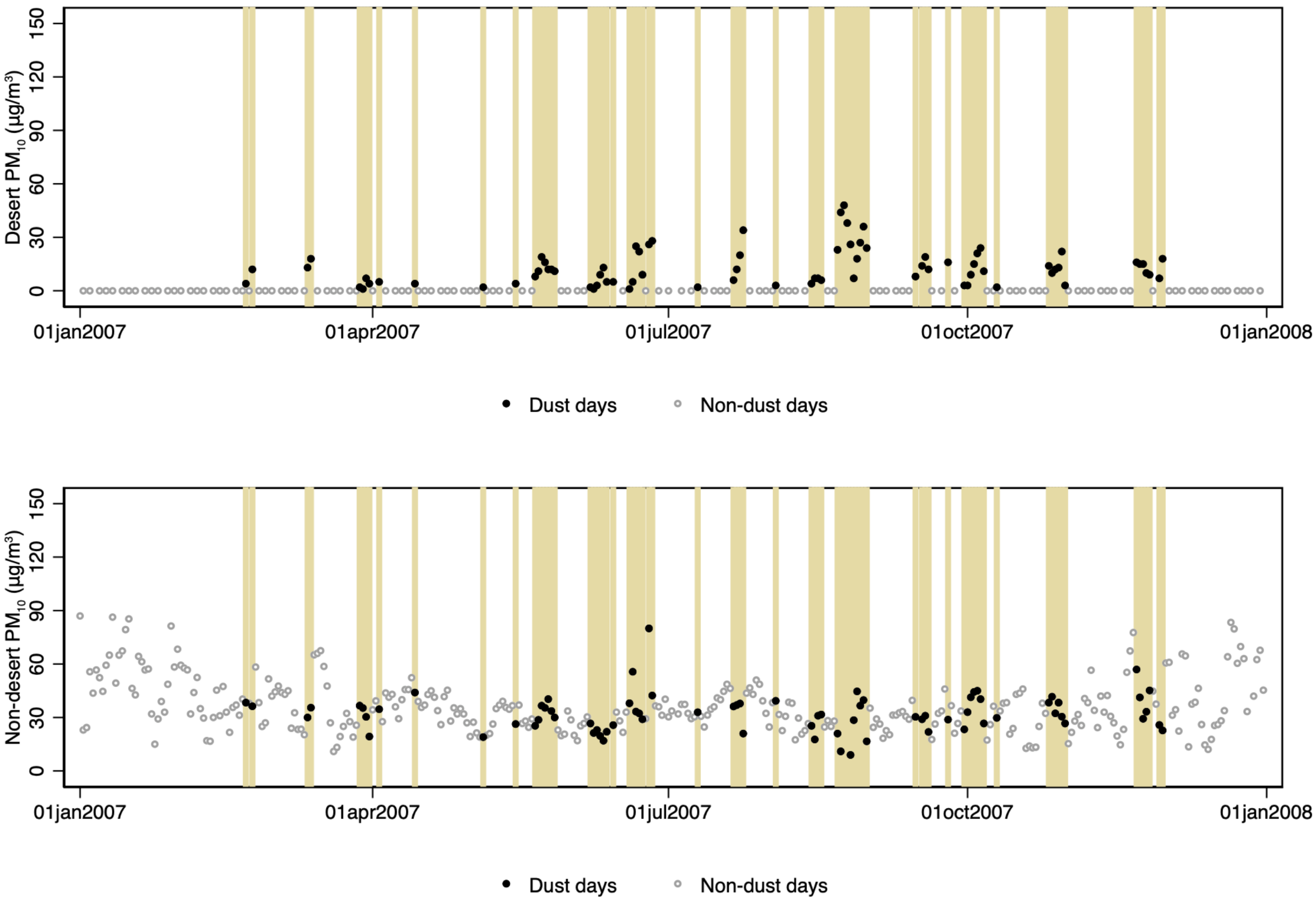
- **Continuous metric (2 sources)**
  - **Research question –** *"Are natural and local sources of PM independently associated with a health outcome?"*
    - *Allows to estimate* ***exposure-response functions****, useful for HIA*
- **Continuous metric (3 sources)**
  - **Research question –** *"… and is the association between local sources of PM with a health outcome different between dust and non-dust days?"*
    - ***PM mixture*** *of natural and local sources, even within the dust days. But may not be useful in hot-spots, with high local pollution*







Desert PM10 (µg/m³)
0
30
60
90
120
150
01jan2007
01apr2007
01jul2007
01oct2007
01jan2008
Dust days
Non-dust days
Non-desert PM10 (µg/m³)
0
30
60
90
120
150
01jan2007
01apr2007
01jul2007
01oct2007
01jan2008
Dust days
Non-dust days



Desert PM$_{10}$ (µg/m^3)
0
30
60
90
120
150
01jan2007
01apr2007
01jul2007
01oct2007
01jan2008
Dust days
Non-dust days
Non-desert PM$_{10}$ (µg/m^3)
0
30
60
90
120
150
01jan2007
01apr2007
01jul2007
01oct2007
01jan2008
Dust days
Non-dust days

Summary

- Time-series studies provide evidence on short-term associations between environmental exposures and health outcomes
- Time-series regression is similar in principle to any regression analysis but with some specific features
  - Residual autocorrelation
  - Controlling for time-trends and time-varying confounders
- Be aware of the different shapes of exposure-response and lagged effects of environmental risk factors based on the epidemiological literature

Useful references

- Gasparrini et al. Distributed lag non-linear models. **Stat Med** 2010;29:2224-34.
- Gasparrini. Distributed lag non-linear models in R: the package dlmn. **J Stat Software** 2011;43:1-20.
- Armstrong. Models for the relationship between ambient temperature and daily mortality. **Epidemiology** 2006;17:624-31.
- Peng and Dominici. Statistical Methods for Environmental Epidemiology with R – A Case Study in Air Pollution and Health. Springer: New York, 2008.
- Buckley et al. Does air pollution confound studies of temperature? **Epidemiology** 2014;25:242-245.
- Tobías and Stafoggia. Modeling desert dust exposures in epidemiologic short-term health effects studies. **Epidemiology** 2020;31:788-795.