Meta-analysis in environmental epidemiology

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Meta-analysis: definition

Meta-analysis is a quantitative synthesis of findings from independent studies performed on the same topic.

Methods for meta-analysis: all quantitative methods which can be used to **combine** and **compare** independent statistical results.

Meta-analysis within multi-centre studies

Today, meta-analysis is widely used in clinical trials, epidemiology and evidence based medicine.

Usually meta-analyses combine results from studies already published.

However it is not unusual that meta-analysis is employed within **multi-center studies** to combine centre-specific results.

Meta-analysis in environmental epidemiology

Planned meta-analysis/multi-centre studies are typical in **environmental epidemiology:**

Short terms effects of air pollution on health
Adverse health effect that a peak in air pollution produces over a short period after exposure (say few days, one week or at most 30 days).

NMMAPS (Samet et al 2000); APHEA (Katsouyanni et al, 2001); HEI (2003); MISA (Biggeri et al, 2004)

Effects of warm and cold ambient temperatures on health
Adverse health effect that heat or cold have over a short period after exposure (say few days, one week or at most 30 days).

PHEWE (Michelozzi et al, 2007; Baccini et al, 2008; Analitis et al, 2008); ISOTHURM (McMichael et al, 2008)

Multi-centre studies in environmental epidemiology

Exposure and health data from different locations (cities) within a geographical region

For each location the following data are available:

- outcome data: daily counts of deaths/hospital admissions over several years (typically more than 3)
- exposure data: daily levels of main urban air pollutants (PM10, CO, NO2, O3); daily temperatures and humidity levels

Multi-centre studies in environmental epidemiology

1. First stage analysis: location-specific analysis

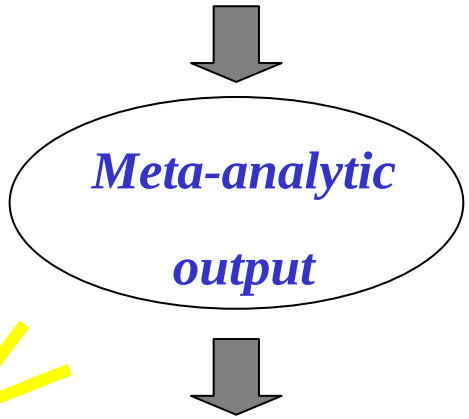
   - Based on regression (GLM or GAM)
   - Common model for each city
   - Basic set of confounders

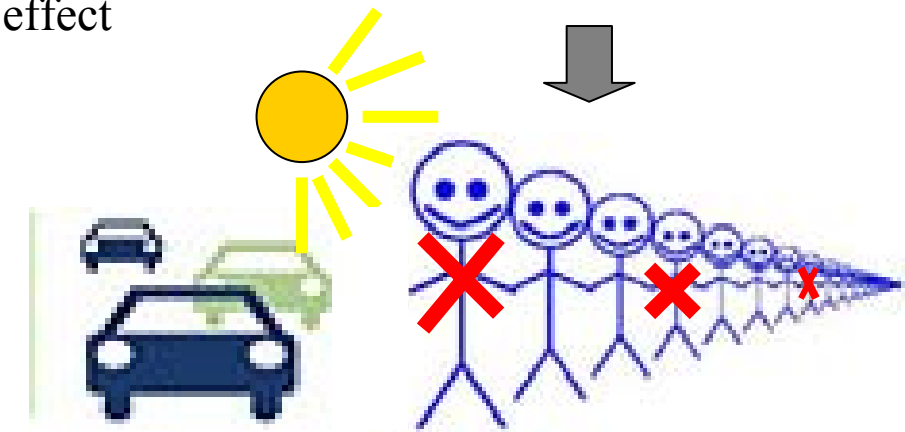
2. Second stage analysis: combined analysis

   - Meta-analysis of the city-specific effect estimates.

3. Health Impact Assessment (HIA)

   - Number of attributable deaths
   - Years of life lost





Aims of meta-analysis

- **Simplify** the statistical analysis
  (two stage analysis instead of a complex multi-level model)

- **Summarize** different findings in an overall result, simplify results communication
  (one effect measure instead of K effects measures)

- **Compare** findings coming from different locations and **investigate heterogeneity** sources

- **Increase the power** by increasing the sample size
  (in some sense the final sample size is $n_1 + n_2 + ... + n_K$)

BUT

larger power is not longer expected if the results to be combined are strongly heterogeneous

Meta-analysis approaches

- Let us suppose that we are interested in an unknown quantity β, for example the regression parameter which expresses the *"air pollutant effect on mortality"*.

- K estimates are available from K different locations (independent studies), with their standard errors

$$(b_1, s_1), (b_2, s_2), ..., (b_K, s_K)$$

- The K independent results can be combined by

Fixed effects meta-analysis
Random effects meta-analysis

Bayesian RE meta-analysis

Fixed effects meta-analysis

ASSUMPTION: The effect is the same in all locations.

The b_is are independent, unbiased estimates of the unique parameter of interest β

Usually, we assume that b_i is Normally distributed with mean β and known variance

$$b_i \sim N\left(\beta, s_i^{\,2}\right)$$

Inference on the fixed effects model: the inverse variance method

The ML estimate of β corresponds to the following weighted mean of the study-specific point estimates:

$$b_{FE} = \frac{\sum b_i w_i}{\sum w_i} \qquad w_i = \frac{1}{s_i^2}$$

Weights are proportional to the inverse of the variances s_i^2 (proportional to the precision $1/s_i^2$)

Small studies contribute less than large studies

Inference on the fixed effects model: the inverse variance method

The precision (1/variance) of the fixed effects estimator is given by the sum of the study-specific precisions:

$$precision_{FE} = \sum w_i = \sum \frac{1}{s_i^2}$$

There is a gain in precision in respect to each single study.

Random effects meta-analysis

ASSUMPTION: The effect is different by location,
i.e. each b_i estimates a different parameter β_i

A two level model is assumed:

$$b_i \left| \beta_i, s_i^2 \sim N\left(\beta_i, {s_i}^2\right) \right.$$

$$\beta_i \left| \beta, \tau^2 \sim N\left(\beta, \tau^2\right) \right.$$

The second level variance, τ^2, expresses the **heterogeneity** among studies

Interpretation of random effects meta-analysis

The first stage inference in the multi-center study is on different parameters (there is not an unique underlying effect!)

The parameter β of the random effects model is a mean of parameters which can be different one each other.

There are two different sources of variability: sampling variability (which is measured within location) and heterogeneity (between location)

Discrepancy among parameters is measured by the heterogeneity variance τ^2

Inference on the RE model: the DL approach

The more widely used method to make inference on the random effects meta-analysis model is the DL approach.

It consists in a two step procedure:

1) Obtain a point estimate of the heterogeneity parameter by the DL estimator (moment estimator)

2) Calculate the RE estimate of β as a weighted mean

Inference on the RE model: the DL approach, stage 1

The DL estimator is a moment-based estimator

$$\tau^2_{DL} = \max\left(\frac{Q-(N-1)}{\sum w_i - \sum w_i^2 / \sum w_i}, 0 \right)$$

where

$$Q = \sum w_i \left(b_i - b_{FE} \right)^2 \qquad w_i = \frac{1}{s_i^2}$$

Only a point estimate of heterogeneity is obtained

Inference on the RE model: the DL approach, stage 2

The random effects estimate of β is obtained as a weighted mean:

$$b_{DL} = \frac{\sum b_i w_i^*}{\sum w_i^*} \qquad w_i^* = \frac{1}{s_i^2 + \tau_{DL}^2}$$

Weights are inversely proportional to the sum of within and between location variances.

Inference on the RE model: the DL approach

The precision of the random effects estimate of β is given by:

$$\sum w_i^* = \sum \frac{1}{s_i^2 + \tau_{DL}^2}$$

It is always lower than the precision of the FE estimator (variance RE ≥ variance FE)

If the results are very heterogeneous, the precision of the overall mean can be smaller than in the original results

FE vs RE

The weights of the FE estimator penalize the smallest studies

The weights of the RE estimator are more balanced, in the sense they tend to attribute the same relevance to all results

This effect is evident in presence of "strong" heterogeneity among studies (when the between-study variance is larger than the within study variance)

In presence of low heterogeneity, FE and RE approaches tend to produce similar results (in terms of β)

FE or RE?

A formal test for checking homogeneity exists, but it is characterized by low power (many false-negatives).

Recently use of a relative index, I^2, has been proposed. This index expresses the percentage of the total variability due to heterogeneity (Higgins and Thompson,2002), but it can not be used to select the most appropriate model.

A priori considerations about homogeneity:

FE is justified if we can assume homogeneity of the effect.
Example: meta-analysis of experimental studies which follow a common protocol (randomized clinical trials)

When results from observational studies are combined, the homogeneity assumption is not longer appropriate, due to we can not exclude differences in design, analysis, study population, experimental conditions…In these situations random effects meta-analysis is recommended.

Bayesian RE meta-analysis

The Bayesian formulation of the random effects meta-analysis model, simply requires specification of prior distributions on the iper-parameters β and τ^2

In absence of information, vague priors can be specified:

$$\beta \sim N(0, 105)$$
$$\tau^2 \sim IG(0.001, 0.001)$$

Then, these priors are combined with the empirical evidence (likelihood) to obtain a joint posterior distribution of the model parameters.
MCMC methods can be used for posterior approximation.

Advantages of the Bayesian approach

- The Bayesian approach takes appropriately into account the uncertainty around the heterogeneity variance, while the DL approach only uses the point estimate of the heterogeneity variance!

- A posterior distribution of τ^2 is obtained, making heterogeneity evaluation and investigation more reliable (meta-regression).

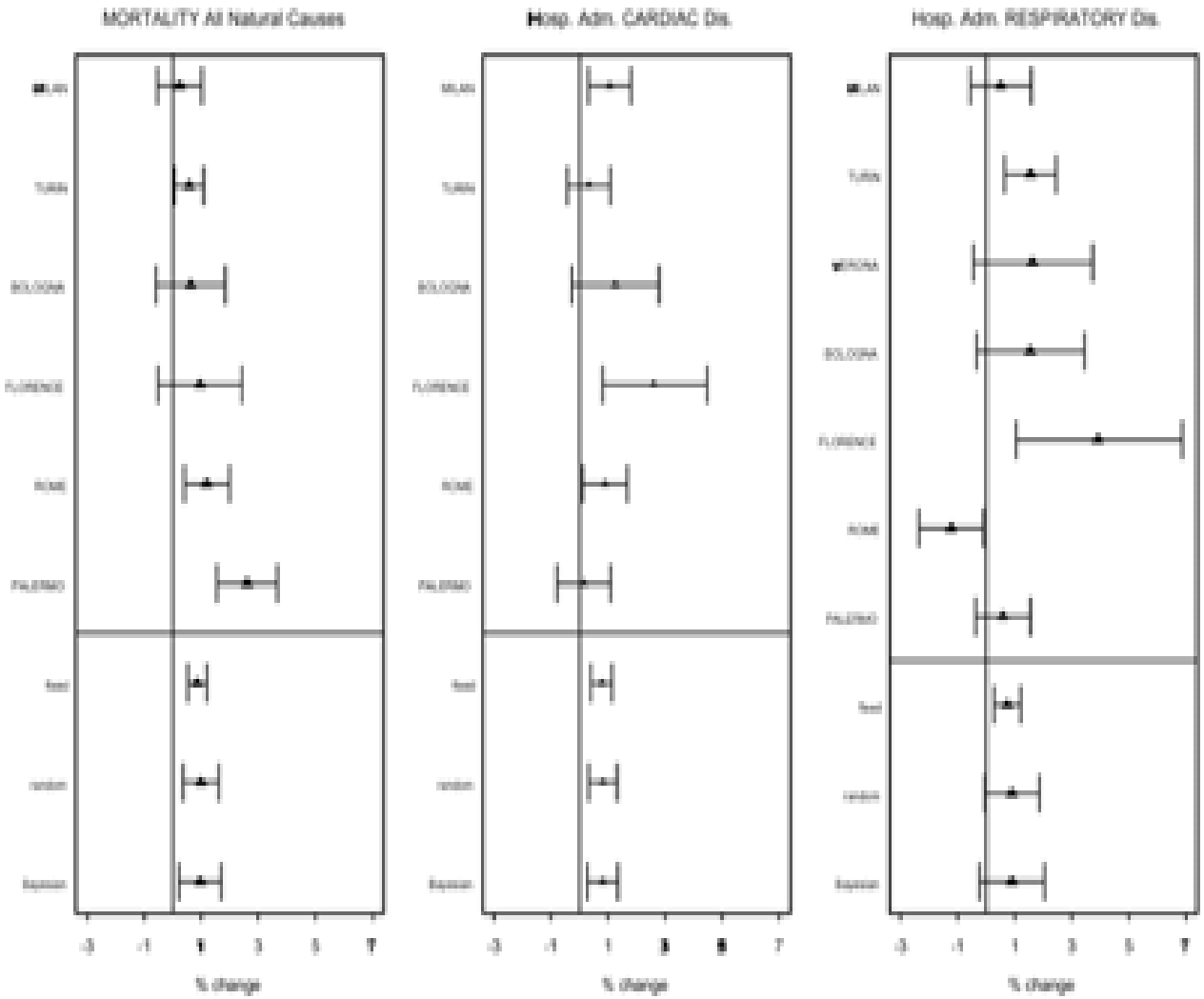


Figure 1—First-stage and overall estimates of PM_{10} effects on total mortality and hospital admissions for cardiac and respiratory diseases by fixed-effects, random-effects and Bayesian models.

Biggeri, Baccini, Bellini et al., IJOEH 2005

Investigating heterogeneity

In general, heterogeneity can be attributable to:

1. ‘true’ variations

Differences in populations, interventions, exposures, outcome measures…

(in some sense, discrepancies have a “biological” explanation)

2. ‘artefactual’ variations

Differences in study design, statistical analysis, confounding control…

(in some sense there is a bias in the estimates we are combining)

Heterogeneity in environmental epid

When the meta-analysis is planned as second step analysis in a multi center study, part of the heterogeneity sources which can affect the results are controlled (common protocol, common methods for the analysis within center)

Then, the observed heterogeneity is likely attributable to “true variations”.

There are factors which interact with the risk factor, and modify the effect:

- Demographic characteristics of the population (percentage of elderly, ethnicity…)
- Behavioral characteristics of the population (air conditioners use, time activity patterns, housing…)
- Environmental conditions (traffic, meteorology, latitude,…)
- Exposure characteristics (particulate composition)

Meta-regression

In presence of heterogeneity, a priority is investigating heterogeneity sources.

If possible, interaction between risk factor and possible effect modifiers should be studied at the first step of the analysis by introducing appropriate interaction terms into the regression model..

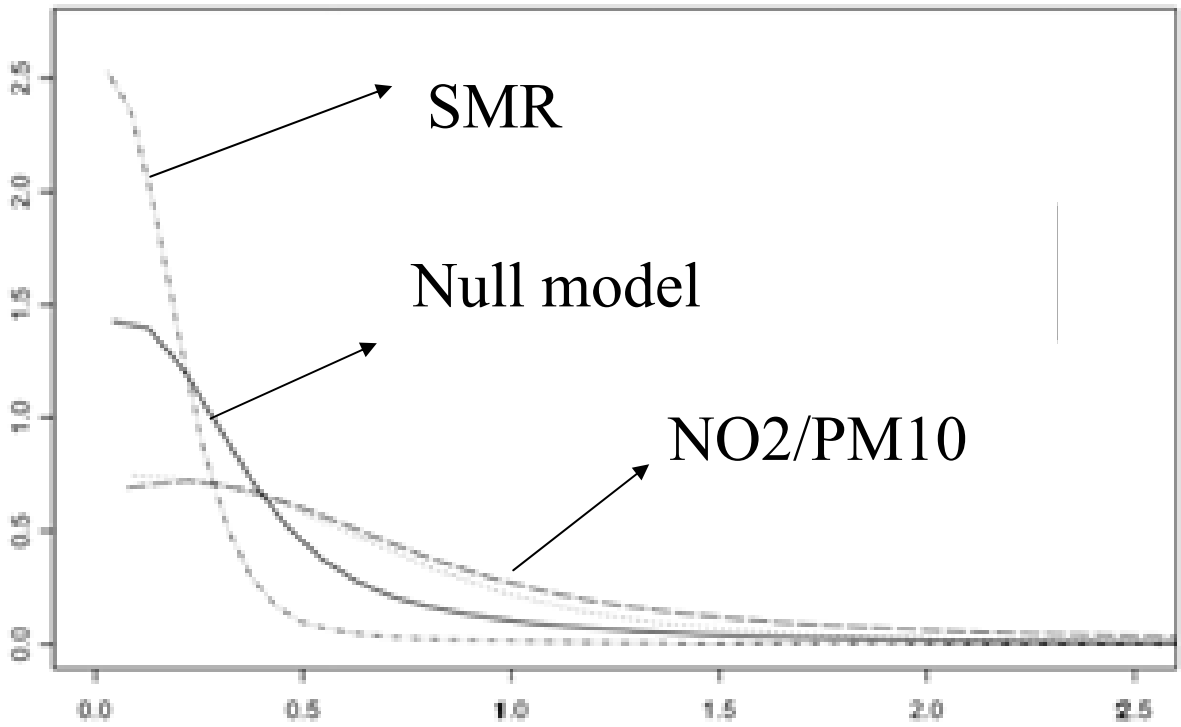
As an alternative, meta-regression can be used to evaluate if study-level covariates explain part of the between location variance:

$$\beta_i = \alpha + \gamma x_i$$

The main drawback of meta-regression is that the results can be affected by ecological bias.

Sometimes, there is not alternative to meta-regression: the interaction can not be investigated at the first stage of the analysis, being the effect modifier constant within location.

Figure 4—Posterior distributions of residual heterogeneity variances from the meta-regression models for total mortality.



- Short terms effect of PM10 on mortality
- Two possible effects modifiers (two meta-regression models):
  - SMR
  - NO2/PM10 as an indicator of trafic

Biggeri, Baccini, Bellini et al., IJOEH 2005

Shrinkage estimates

- In the presence of heterogeneity, shrunken estimates of effect can be calculated. They can be interpreted as updated estimates of the location-specific estimates obtained at the first step of the analysis, given information from all locations.

- Each location-specific estimate is pulled towards the overall effect estimate, proportionally to its precision:

$$\hat{\beta}_i = \frac{s_i^2}{s_i^2 + \tau^2}\hat{\beta} + \left(1 - \frac{s_i^2}{s_i^2 + \tau^2}\right) b_i$$

- Shrunken estimates are a “compromise” between the location-specific estimates obtained at the first step of the analysis and the overall estimate.

- They are more stable than the location-specific estimates (because they borrow strength from all locations) while reflect heterogeneity among locations.

TABLE 6 First-stage Estimates and Bayesian Posterior Means of City-specific PM10 Effects on Total Mortality and Hospital Admissions for Cardiac and Respiratory Diseases in 1995–99*

	Mortality		Hospital Admissions			
	All Natural Causes		Cardiac Causes		Respiratory Causes	
	First Stage (95% CI)	Bayesian (95% CrI)	First Stage (95% CI)	Bayesian (95% CrI)	First Stage (95% CI)	Bayesian (95% CrI)
Milan	0.24 (–0.53,1.02)	0.51 (–0.25,1.17)	1.06 (0.32,1.81)	0.87 (0.37,1.46)	0.51 (–0.57,1.59)	0.60 (–0.36,1.56)
Turin	0.56 (0.05,1.08)	0.66 (0.15,1.13)	0.33 (–0.43,1.09)	0.66 (0.03,1.16)	1.54 (0.65,2.44)	1.37 (0.52,2.26)
Verona					1.62 (–0.46,3.74)	1.22 (–0.22,2.92)
Bologna	0.61 (–0.58,1.83)	0.80 (–0.13,1.68)	1.25 (–0.27,2.79)	0.86 (0.23,1.71)	1.53 (–0.33,3.44)	1.20 (–0.12,2.79)
Florence	0.95 (–0.51,2.43)	0.95 (–0.03,2.00)	2.61 (0.79,4.46)	1.00 (0.35,2.39)	3.91 (1.04,6.86)	1.91 (0.16,4.46)
Rome	1.18 (0.40,1.97)	1.07 (0.44,1.79)	0.88 (0.10,1.68)	0.82 (0.31,1.39)	–1.24 (–2.36,–0.10)	–0.59 (–1.86,0.76)
Palermo	2.61 (1.56,3.67)	1.77 (0.71,3.01)	0.15 (–0.80,1.11)	0.64 (–0.12,1.18)	0.59 (–0.37,1.55)	0.65 (–0.23,1.51)

*Empty cells indicate no available data.

Bayesian Model A 0.96 (0.24,1.77)

Biggeri et al, 2005

Shrinkage estimates and HIA

- Shrinkage estimates of effect are used for HIA purpose.

- When ADs have to be calculated for each location, very-specific information are needed.

- Using the overall meta-analytic estimate could bring to understimation or overestimation of the impact, in particular for locations where the effect is far from the mean.

HIA

città	Overall estimate n. (%)	Overall estimate ICr 80%	Shrinkage estimates n. (%)	Shrinkage estimates ICr 80%
Bologna	95 (2.24)	63,128	109 (2.57)	57,171
Catania	45 (1.69)	30,60	36 (1.35)	3,66
Firenze	55 (1.36)	37,75	44 (1.09)	5,77
Genova	136 (1.75)	91,183	110 (1.41)	33,176
Mestre-Ve	19 (1.13)	12,25	18 (1.07)	5,30
Milano	249 (2.34)	166,335	294 (2.76)	181,425
Napoli	457 (5.23)	305,616	368 (4.21)	236,495
Palermo	99 (1.90)	65,134	97 (1.86)	43,154
Pisa	9 (1.12)	6,13	9 (1.12)	3,16
Ravenna	22 (1.63)	14,29	19 (1.41)	4,33
Roma	583 (2.74)	388,787	885 (4.16)	518,1320
Taranto	19 (1.18)	13,26	18 (1.12)	4,30
Torino	171 (2.28)	114,230	149 (1.98)	56,236
Trieste	14 (0.68)	9,20	13 (0.63)	5,22
Verona	39 (1.91)	26,52	54 (2.64)	27,90
total n.	2012 (2.46)	1339,2713	2223 (2.72)	1180,3341

Deaths attributable to NO2. MISA study (Biggeri et al. 2005)

Effect of heat on mortality: the PHEWE study

15 European cities (1990-2000):

Athens, Barcelona, Budapest, Dublin, Helsinki, Ljubljana, London, Milan, Paris, Praha, Rome, Stockholm, Turin, Valencia, Zurich

Outcome: daily number of deaths

Exposure variable: daily maximum apparent temperature (lag 0-3)

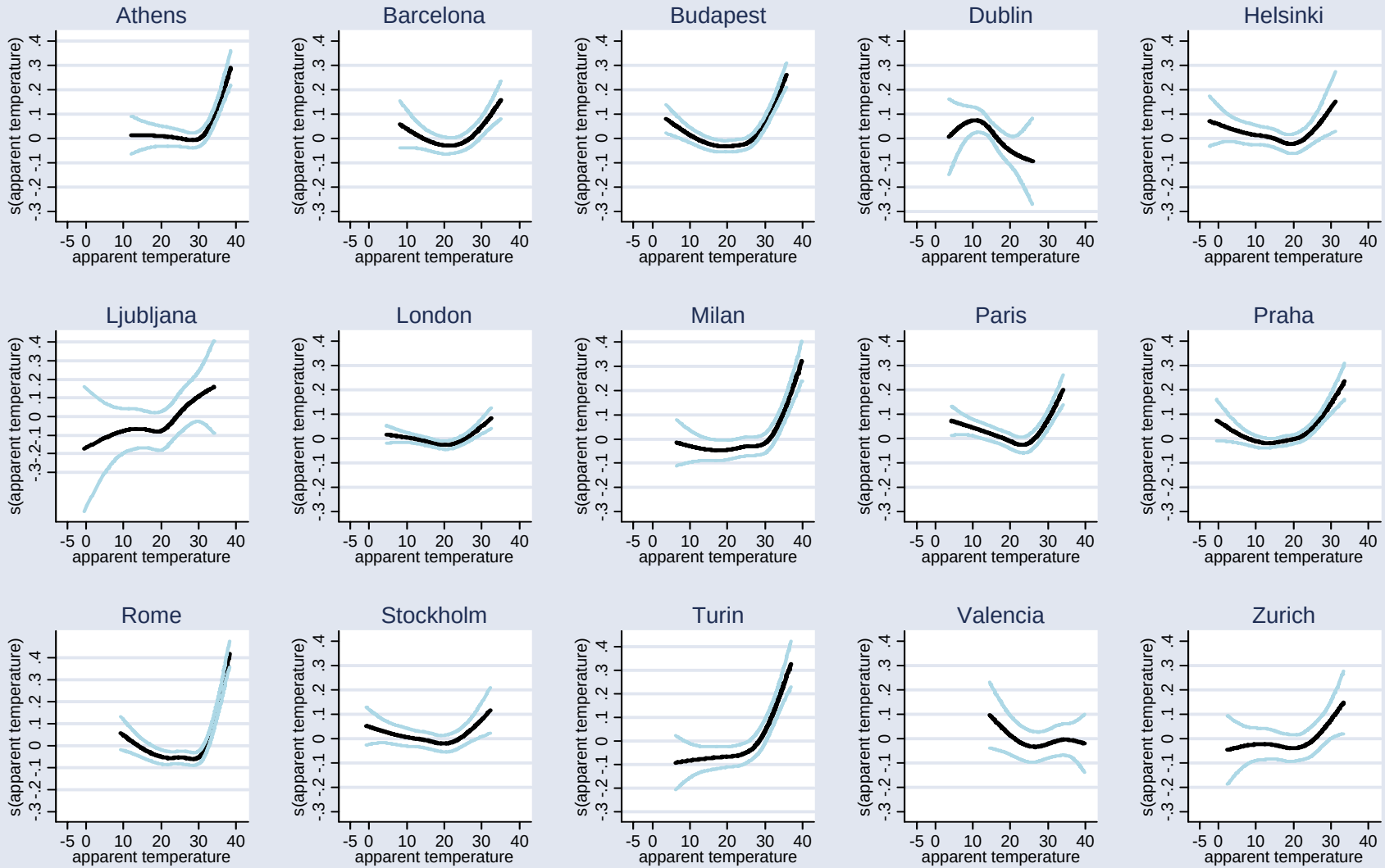
Aim: studying the net effect that warm temperatures have on health, given possible confounders (seasonality, air pollution levels, other meteorological conditions).

(Baccini et al. 2008)

3 - city specific curves (GEE natural cubic spline)

Maximum Apparent Temperature lag 03

All natural deaths - Summer analysis



Threshold and slope model

$$y_{is} \sim Poisson(\lambda_{is})$$

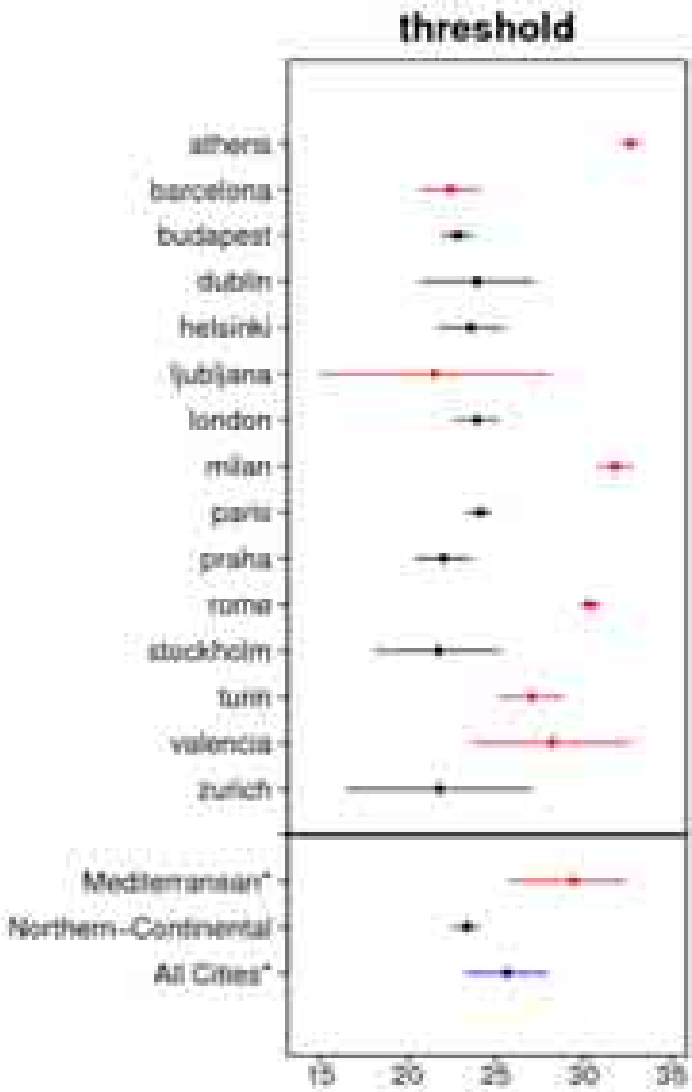
$$\log(\lambda_{is}) = \alpha_s + \beta(AppT_{is})\mathrm{I}(AppT_{is} > \delta) + \sum_k \beta_k x_{kis}$$

This simple linear threshold model assumes a log-linear increase in risk above a heat threshold, with the threshold being identified by maximum likelihood estimation (Muggeo, 2003)

TABLE 2. Regional Meta-Analytic Estimates and City-Specific Estimates of Threshold and Percent Change in Natural Mortality Associated With a 1°C Increase in Maximum Apparent Temperature Above the City-Specific Threshold

	Threshold (°C) (95% CrI/CI)*		% Change (95% CrI/CI)*	
Region				
North-continental	23.3	(22.5 to 24.0)	1.84	(0.06 to 3.64)
Mediterranean	29.4[b]	(25.7 to 32.4)	3.12	(0.60 to 5.72)
City				
Athens	32.7	(32.1 to 33.3)	5.54	(4.30 to 6.80)
Barcelona	22.4[c]	(20.7 to 24.2)	1.56	(1.04 to 2.08)
Budapest	22.8	(21.9 to 23.7)	1.74	(1.47 to 2.02)
Dublin	23.9	(20.7 to 27.1)	−0.02	(−5.38 to 5.65)
Helsinki	23.6	(21.7 to 25.5)	3.72	(1.68 to 5.81)
Ljubljana	21.5	(15.0 to 28.0)	1.34	(0.32 to 2.37)
London	23.9	(22.6 to 25.1)	1.54	(1.01 to 2.08)
Milan	31.8	(30.8 to 32.8)	4.29	(3.35 to 5.24)
Paris	24.1	(23.4 to 24.8)	2.44	(2.08 to 2.80)
Praha	22.0	(20.4 to 23.6)	1.91	(1.39 to 2.44)
Rome	30.3	(29.8 to 30.8)	5.25	(4.57 to 5.93)
Stockholm	21.7	(18.2 to 25.3)	1.17	(0.41 to 1.94)
Turin	27.0	(25.2 to 28.9)	3.32	(2.53 to 4.13)
Valencia	28.2	(23.7 to 32.7)	0.56	(−0.35 to 1.47)
Zurich	21.8	(16.5 to 27.0)	1.37	(0.49 to 2.25)

*95% credibility interval for regional meta-analytic estimates and 95% confidence interval for city-specific estimates.
[b]Excluding Barcelona.
[c]Mean apparent temperature.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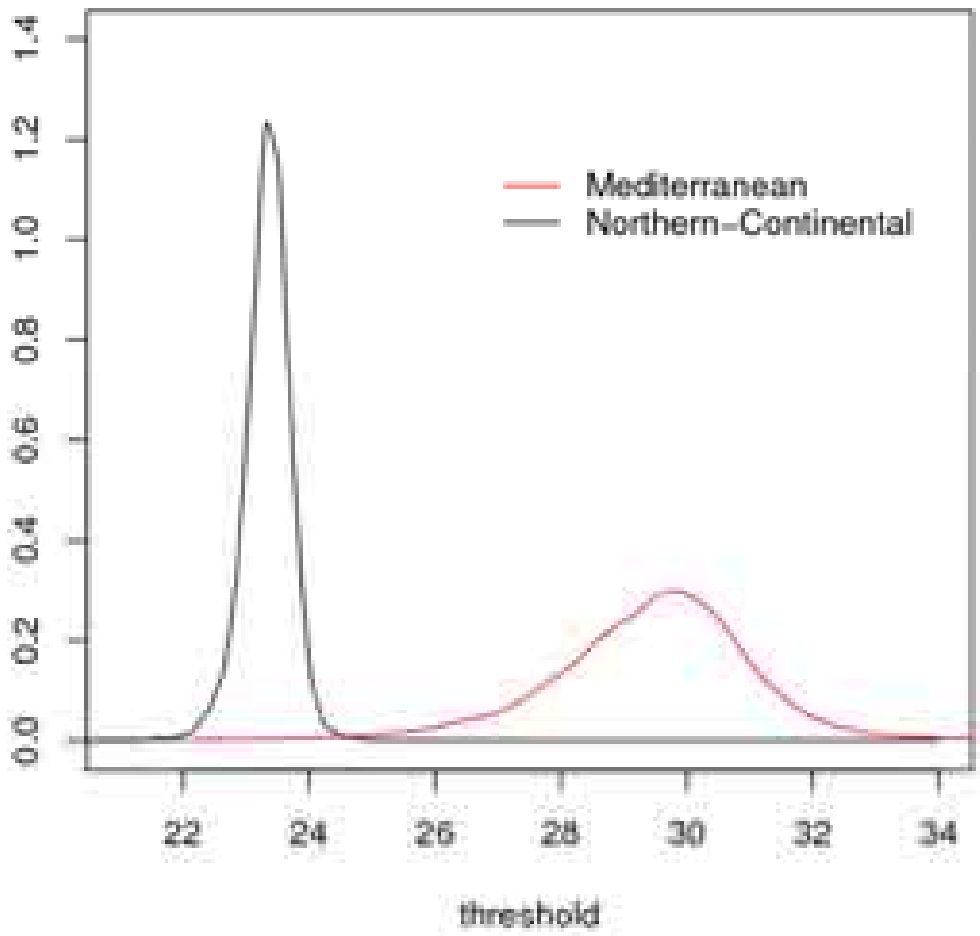
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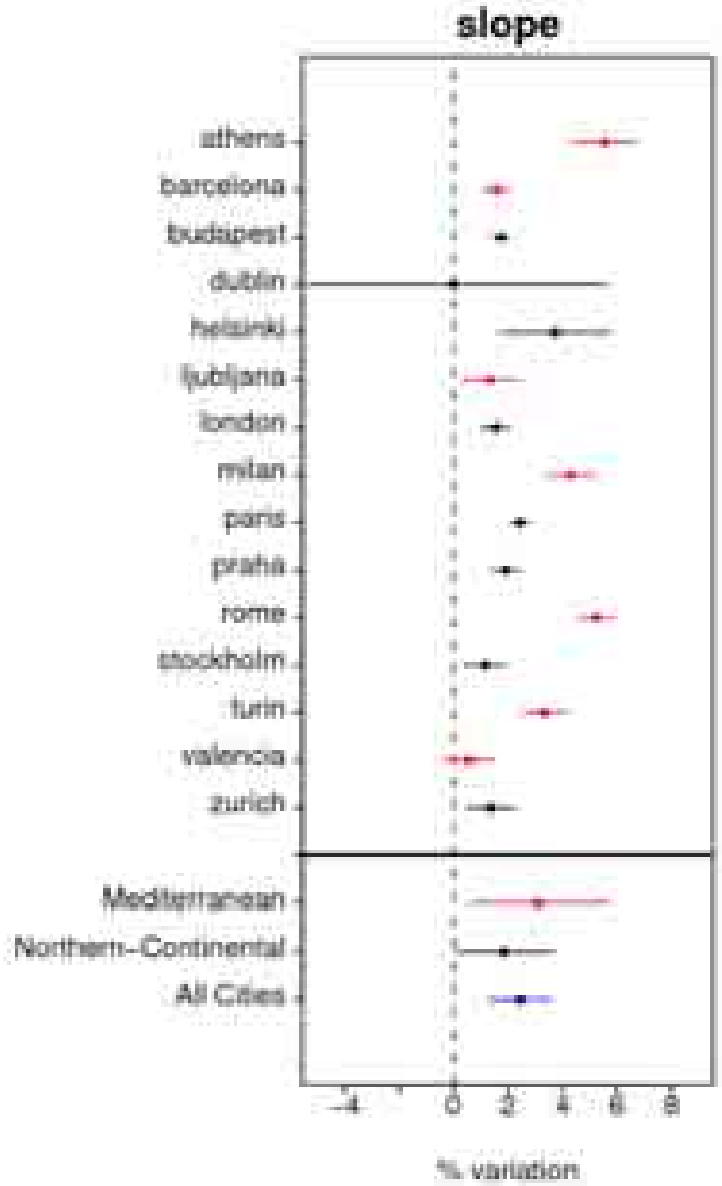
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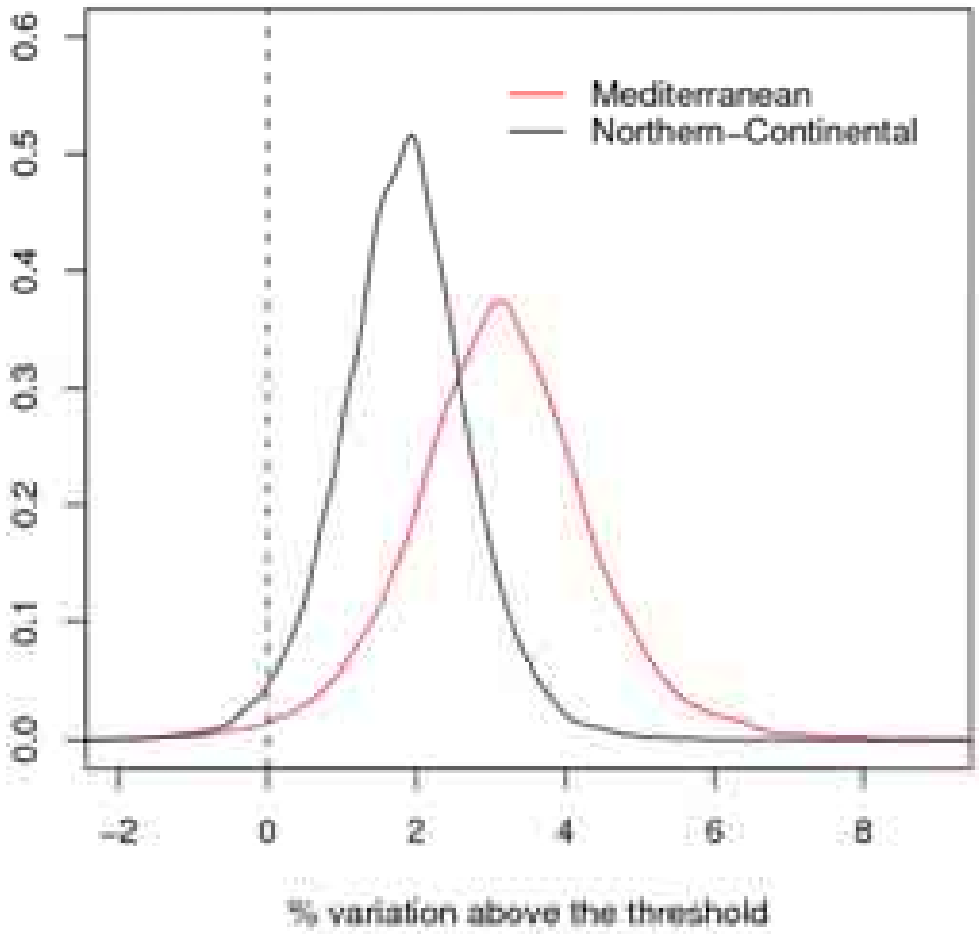
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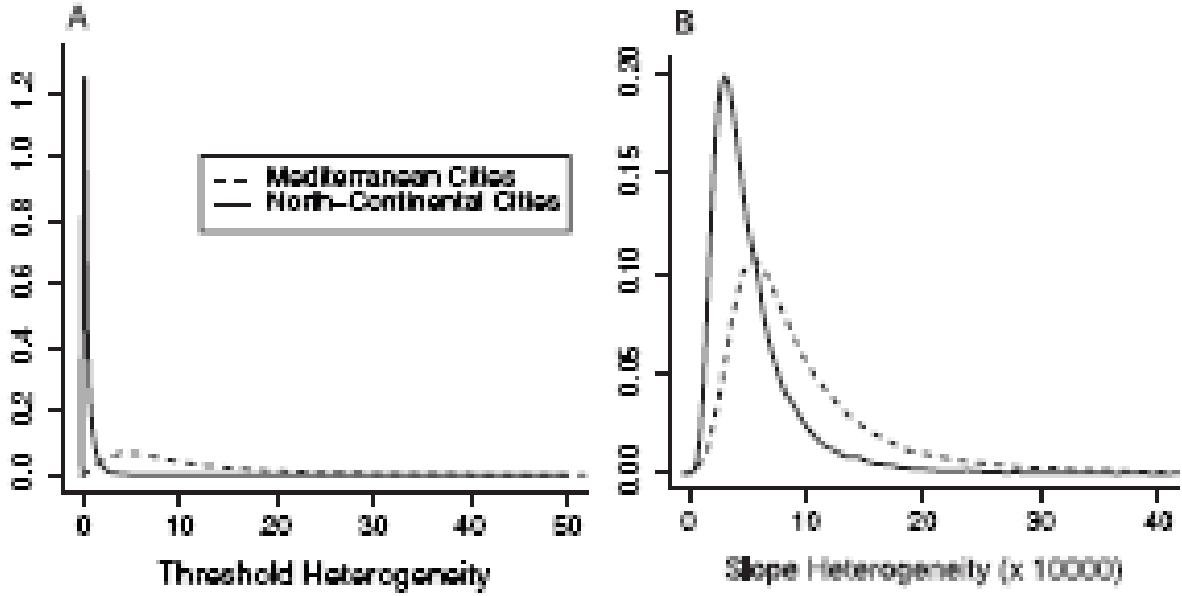
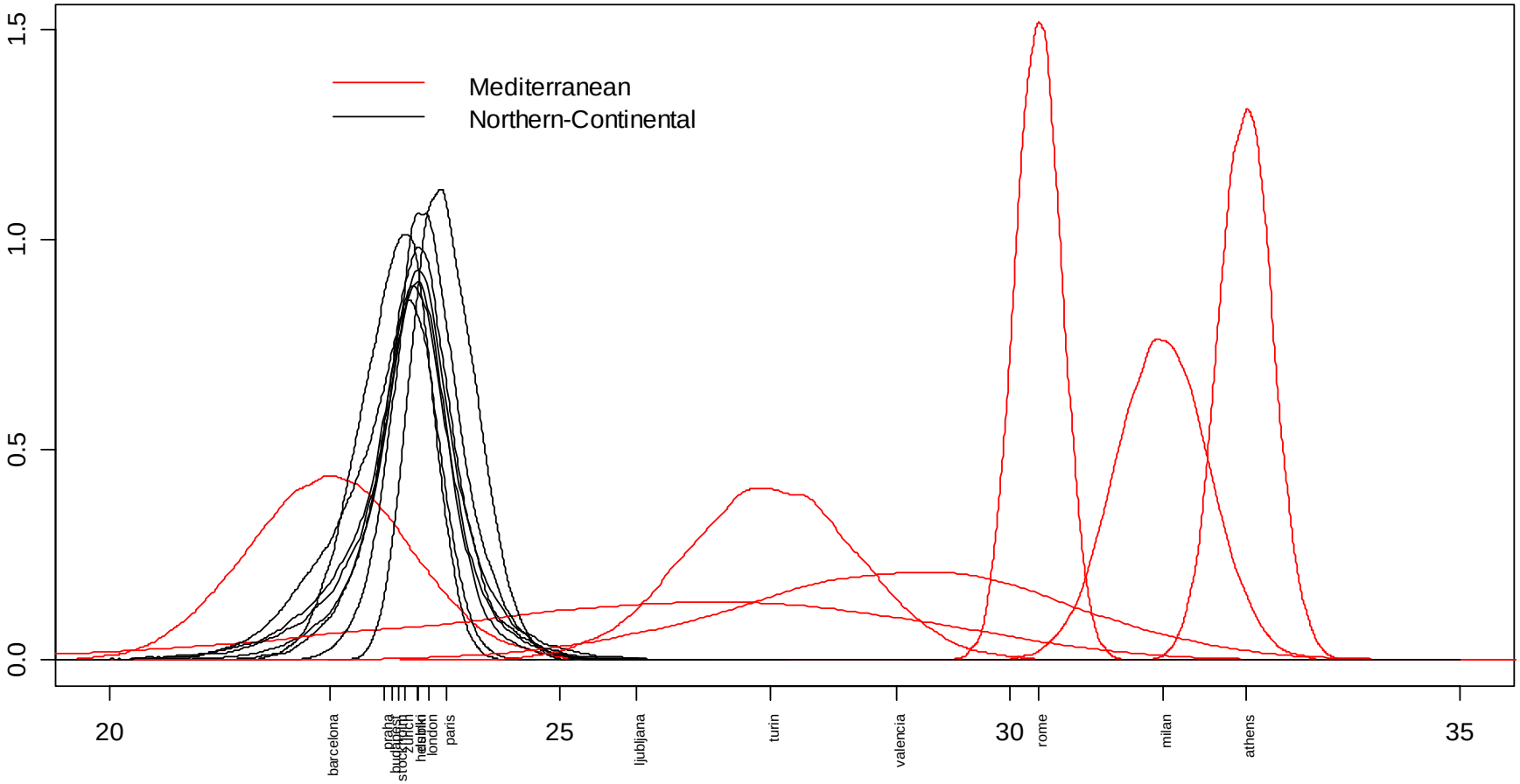
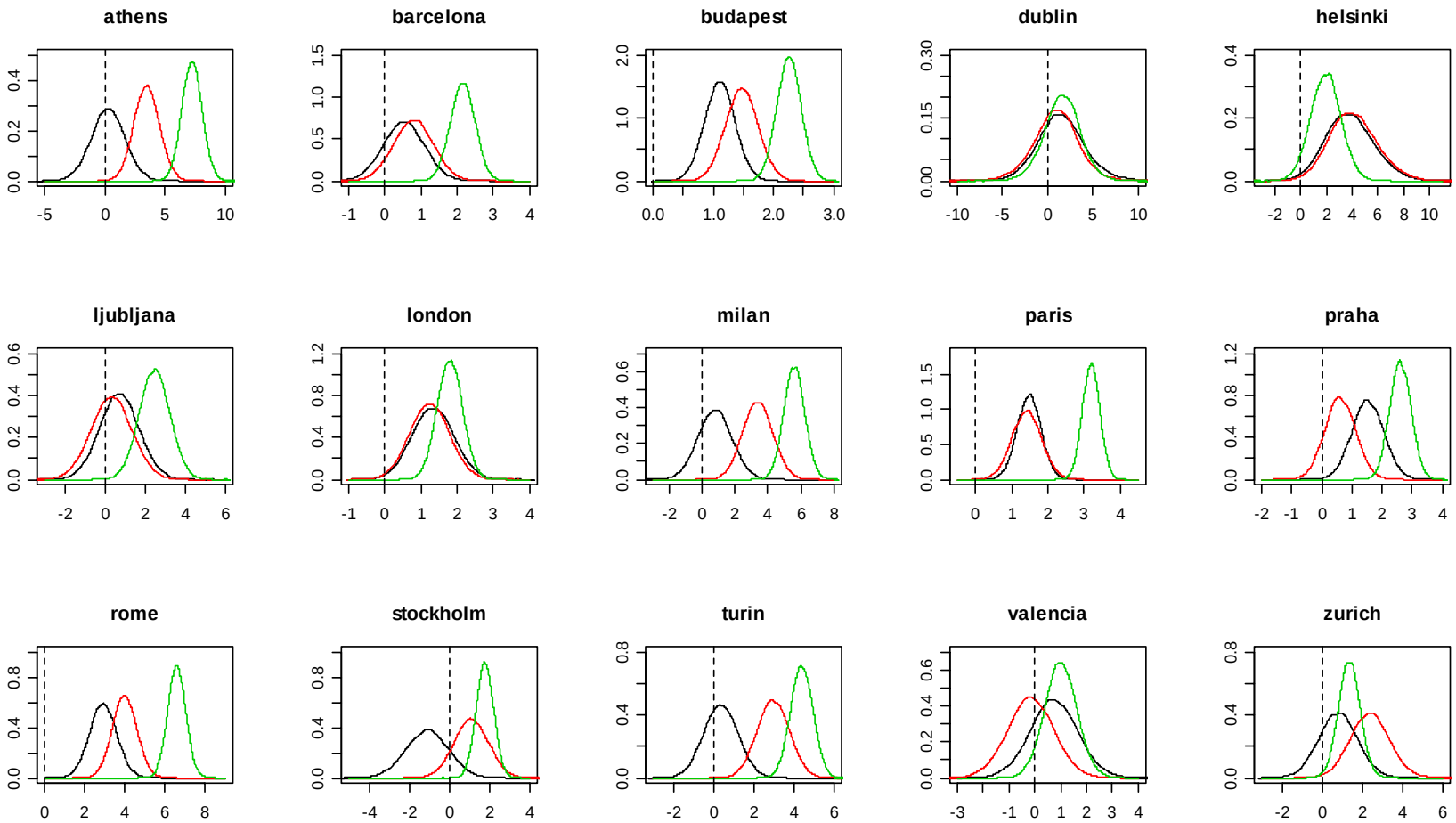


FIGURE 3. Posterior distribution of the heterogeneity variance for (A) threshold and (B) slope above the threshold among Mediterranean cities (excluding Barcelona) and north-continental cities. Values of the posterior density function on y-axis.



Shrinkage distributions of the apparent temperature thershold corresponding to the minimum mortality risk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	Attributable fraction of deaths (%) (absolute number of attributable deaths per year*)			
	Age class			
	35-64	65-74	75+	All classes of age (35+)
Athens	0.64 (9)	1.16 (82)	2.52 (178)	1.88
Barcelona	1.76 (20)	2.28 (30)	5.86 (240)	4.43
Budapest	2.02 (71)	2.62 (81)	3.95 (247)	3.10
Dublin	0.03 (0)	0.02 (0)	0.02 (0)	0.02
Helsinki	0.49 (3)	0.52 (3)	0.25 (4)	0.36
Ljubljana	0.78 (2)	0.75 (2)	1.60 (9)	1.16
London	0.44 (21)	0.40 (24)	0.59 (97)	0.52
Milan	0.54 (5)	1.56 (16)	2.60 (74)	1.98
Paris	1.27 (68)	1.16 (42)	2.64 (313)	2.03
Prague	0.92 (11)	0.40 (7)	1.56 (53)	1.13
Rome	2.17 (40)	3.03 (68)	5.10 (279)	4.05
Stockholm	0.63 (4)	0.28 (3)	0.41 (14)	0.41
Turin	0.86 (6)	2.96 (24)	4.54 (91)	3.48
Valencia	2.55 (13)	2.87 (14)	2.89 (44)	2.70
Zurich	1.01 (4)	2.17 (8)	1.22 (17)	1.35

$$AD_t = Y_t \frac{RR_i - 1}{RR_i}$$

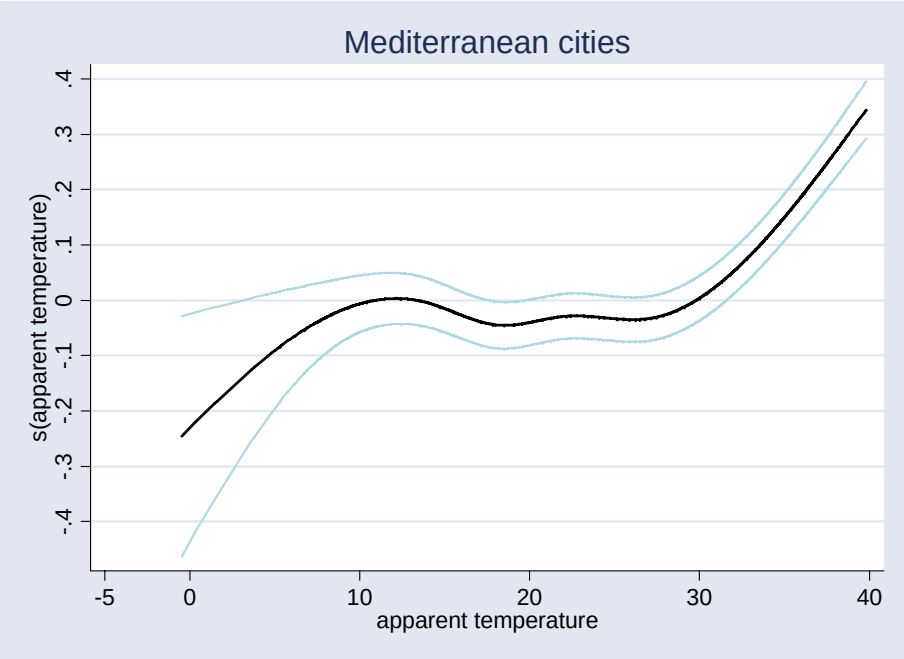
Future developments of meta-analysis in environmental epidemiology

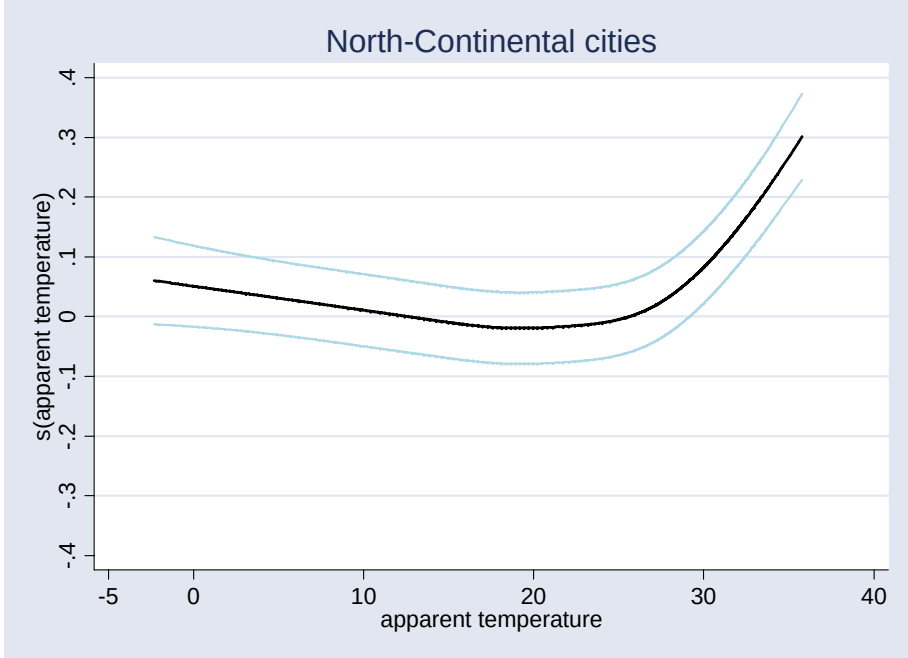
- They are mainly related to the Bayesian model.
- Due to the possibility of approximating the posterior joint distribution by MCMC methods, close formulas are not required and different distributions can be assumed for the random effects in a natural way.
- For example, in the presence of few outlying results, both heterogeneity evaluation and shrinkage as arising from the NN model are inappropriate. Assuming a t distribution with few df on the random effects could be a better choice.
- Mixture of Normal distributions, Polya tree.

meta-analytic curve

Maximum Apparent Temperature lag 03

All natural deaths - Summer analysis





References

- General aspects: Normand StatMed - 99
- Meta-regression: Thompson e Sharp StatMed - 99
- Bayesian meta-analysis: Sutton e Abrams SMMR - 01