A new modelling framework for multi-location studies in environmental epidemiology

Supplementary materials

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1. Data description

The illustrative application includes 87 cities defined following Eurostat Urban Audit's definition. The full list of cities is shown in Table S1. All metadata attached to cities are shown in Table S2.

Table S1: *List of cities considered in the illustrative example. Observed indicates whether the city is used to fit the second-stage meta-analysis model. Population and mean temperature are inherited from the parent study from which the metadata are extracted.*

Eurostat code	Name	Region	Observed	Population	Mean temperature
IT001C	Rome	Centro	Yes	2,672,838	15.8
IT002C	Milan	Nord-ovest	Yes	3,897,850	13
IT003C	Naples	Sud	No	3,047,442	16.2
IT004C	Turin	Nord-ovest	No	879,331	12.1
IT005C	Palermo	Isole	No	670,213	16.6
IT006C	Genoa	Nord-ovest	Yes	594,860	12.9
IT007C	Florence	Centro	Yes	365,265	13.7
IT008C	Bari	Sud	No	319,627	16.9
IT009C	Bologna	Nord-est	No	377,318	14.3
IT010C	Catania	Isole	No	305,233	18.2
IT011C	Venise	Nord-est	Yes	265,285	14.3
IT012C	Verona	Nord-est	No	256,724	13.5
IT013C	Cremona	Nord-ovest	Yes	71,222	14
IT014C	Trento	Nord-est	Yes	112,731	9.1
IT015C	Trieste	Nord-est	No	205,534	12.4
IT016C	Perugia	Centro	Yes	159,824	13.6
IT017C	Ancona	Centro	Yes	100,772	15.6
IT018C	Pescara	Sud	Yes	119,500	15.1
IT019C	Campobasso	Sud	No	49,892	13.1
IT020C	Caserta	Sud	Yes	76,201	15
IT021C	Taranto	Sud	Yes	199,740	17.4
IT022C	Potenza	Sud	Yes	67,678	11.8
IT023C	Catanzaro	Sud	Yes	91,832	16.2
IT024C	Reggio Di Calabria	Sud	Yes	181,257	15.1
IT025C	Sassari	Isole	Yes	124,625	16.8
IT026C	Cagliari	Isole	No	156,363	17.3
IT027C	Padova	Nord-est	No	208,056	13.9
IT028C	Brescia	Nord-ovest	Yes	191,362	12.7
IT029C	Modena	Nord-est	No	180,668	14
IT030C	Foggia	Sud	No	151,992	16.4
IT031C	Salerno	Sud	No	134,788	15.8
IT032C	Piacenza	Nord-est	Yes	101,375	13.8
IT033C	Bolzano	Nord-est	Yes	104,326	8.9
IT034C	Udine	Nord-est	Yes	98,925	12.2
IT035C	La Spezia	Nord-ovest	Yes	93,062	14.8
IT036C	Lecce	Sud	No	91,773	17.6

IT037C	Barletta	Sud	Yes	94,127	16.6
IT038C	Pesaro	Centro	Yes	94,580	15
IT039C	Como	Nord-ovest	Yes	83,189	11.8
IT040C	Pisa	Centro	Yes	87,945	15.5
IT041C	Treviso	Nord-est	Yes	82,689	13.3
IT042C	Varese	Nord-ovest	Yes	80,460	12
IT043C	Asti	Nord-ovest	Yes	74,811	13.1
IT044C	Pavia	Nord-ovest	Yes	70,380	13.9
IT045C	Massa	Centro	Yes	68,875	13
IT046C	Cosenza	Sud	No	68,131	14.3
IT047C	Savona	Nord-ovest	Yes	60,784	13.2
IT048C	Matera	Sud	No	60,026	15.6
IT049C	Acireale	Isole	No	51,768	16
IT050C	Avellino	Sud	Yes	54,493	13.2
IT051C	Pordenone	Nord-est	Yes	51,067	13.1
IT052C	Lecco	Nord-ovest	Yes	47,404	10
IT053C	Altamura	Sud	Yes	69,760	14.7
IT054C	Bitonto	Sud	Yes	55,456	16
IT055C	Molfetta	Sud	Yes	59,782	16.7
IT056C	Battipaglia	Sud	No	50,611	16.4
IT057C	Bisceglie	Sud	Yes	54,855	16.6
IT058C	Carpi	Nord-est	Yes	68,800	14.3
IT059C	Cerignola	Sud	Yes	57,146	16.3
IT060C	Gela	Isole	Yes	75,040	18
IT061C	Bagheria	Isole	Yes	54,402	17
IT062C	Anzio	Centro	Yes	51,135	17
IT063C	Sassuolo	Nord-est	No	40,495	13
IT064C	Messina	Isole	Yes	242,396	16.8
IT065C	Prato	Centro	No	185,458	13.4
IT066C	Parma	Nord-est	Yes	179,624	13.7
IT067C	Livorno	Centro	Yes	157,938	15.4
IT068C	Reggio Nell'emilia	Nord-est	Yes	160,771	13.5
IT069C	Ravenna	Nord-est	No	151,010	15
IT070C	Ferrara	Nord-est	Yes	132,369	14.7
IT071C	Rimini	Nord-est	Yes	139,996	14.9
IT072C	Siracusa	Isole	No	121,505	18.2
IT073C	Bergamo	Nord-ovest	Yes	116,270	11.7
IT074C	Forlì	Nord-est	Yes	114,818	14.2
IT075C	Latina	Centro	No	118,094	16.4
IT076C	Vicenza	Nord-est	No	111,772	13.1
IT077C	Terni	Centro	Yes	109,317	13.1
IT078C	Novara	Nord-ovest	Yes	102,591	13.2
IT079C	Alessandria	Nord-ovest	No	91,567	13.1
IT080C	Arezzo	Centro	Yes	98,352	13
IT081C	Grosseto	Centro	Yes	80,030	15.7
IT082C	Brindisi	Sud	Yes	87,851	17.5

IT083C	Trapani	Isole	No	68,439	17.7
IT084C	Ragusa	Isole	Yes	71,276	16.9
IT085C	Andria	Sud	Yes	99,678	15.2
IT086C	Trani	Sud	Yes	55,693	16.5
IT087C	L'aquila	Sud	Yes	69,158	9.2

Table S2: *List of city-level meta-variables. The first group represents the meta-predictors used in the second-stage meta-analysis, and the second represents variables used to compute impact measures.*

Variable	Source	Description
Total population	Urban Audit / Wikipedia	Note: population data were missing for several cities and were added from the Wikipedia pages for each city (Latvia: Valmiera; Belgium: Mechelen, Mouscron, La Louvière, Verviers)
Population above 65	Urban Audit / NUTS3	Percentage
Population density	Urban Audit / Wikipedia	Note: population density data were missing for several cities and were added from the Wikipedia pages for each city (Latvia: Valmiera; Belgium: Mechelen, Mouscron, La Louvière, Verviers; Ireland: Dublin, Limerick, Waterford; Norway: Bergen, Trondheim; UK: Glasgow, North Lanarkshire, Dundee)
Isolation	Urban Audit / NUTS2	Proportion of single-person households
GDP	NUTS3 / Office of National Statistics	GDP per capita. Note: GDP data for UK cities were unavailable in Eurostat and extracted from ONS
Unemployment rate	NUTS2	Among active population (20-64 years old) for all education levels
Education level	NUTS2	Proportion of active population (25-64 years old) with ISCED level >= 5 (higher education)
Deprivation rate	NUTS2	Proportion of population under severe material deprivation condition
Hospital bed rates	NUTS2	Number of hospital beds / inhabitants
Imperviousness	Copernicus High Resolution Layer	Percentage of soil sealing
Tree Cover Density	Copernicus High Resolution Layer	Level of Tree Cover Density (%)
Grassland	Copernicus High Resolution Layer	Proportion of grassland pixels
Water & Wetness	Copernicus High Resolution Layer	Average class between (1) permanent water, (2) temporary water, (3) permanent wetness and (4) temporary wetness
Small Woody Features	Copernicus High Resolution Layer	Small woody features density (%)
Elevation	AWS Terrain Tiles	Elevation at city centre
Coastal region type	Natural Earth	Lowest distance between coastal line and city centre
NDVI	Google Earth Engine - MODIS	
PM25	Atmospheric Composition Analysis Group	https://sites.wustl.edu/acag/datasets/surface-pm2-5/
NO2	Atmospheric Composition Analysis Group	https://sites.wustl.edu/acag/datasets/surface-no2/
Temperature range	Copernicus	Annual temperature range
Mean temperature	Copernicus	Mean annual temperature

Death rate	NUTS3	Death rate within age group
Life expectancy	NUTS2	Life expectancy at age
Population structure	NUTS3	Proportion of the population in age group

2. Model selection

This section illustrates the model selection performed for the second-stage meta-analysis. Two parameters need to be chosen: i) the specification of the age variable, and ii) the number of composite components representing vulnerability. In a mixed-effect framework, model selection can be performed through the Akaike Information Criterion, following standard likelihood theory. Briefly, the (restricted) likelihood can be extracted from the estimated model, and the number of parameters is the sum of fixed effect coefficients $\boldsymbol{\beta}$ and parameters defining the random effect variance-covariance matrix $\boldsymbol{\Psi}_{\mathrm{i}}$.[1]

Figure S1 shows the ΔAIC, i.e. the difference in AIC with the overall minimum for various specifications. We choose the model with a natural spline and a single knot at age 60, and five composite indices, as the simplest model such that $\Delta AIC \leq 2$, as recommended in the literature.[2]

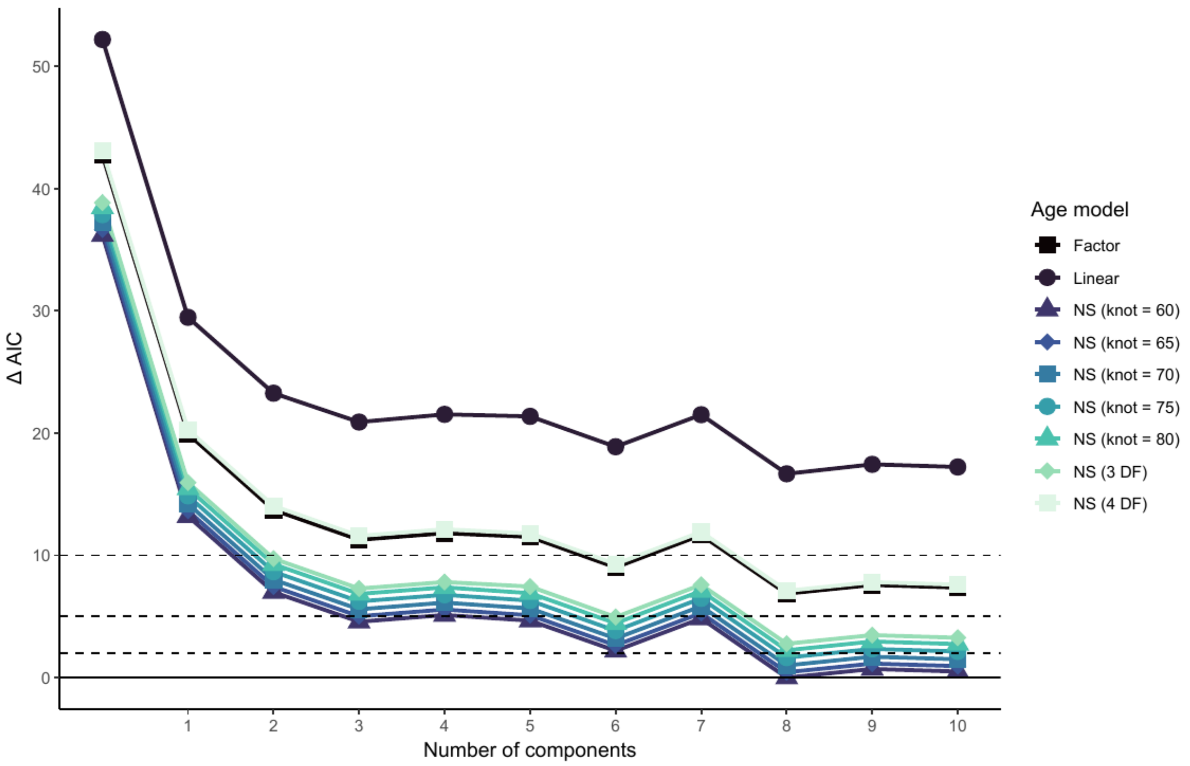


Figure S1: *Comparison of AIC for various number of composite indices and specification of the age term. ΔAIC represents the difference between the model's AIC and the minimum AIC from all models (represented by the thick horizontal black line). Horizontal dashed lines represent values of 2, 5 and 10 for ΔAIC.*

3. Description of Kriging

Kriging was introduced by Georges Matheron [3] in the context of mining, and has since been one of the most popular geostatistical methods, used in a wide variety of applications, including in environmental epidemiology [4,5]. Using a set of n realisations from a spatial process – in our case $\hat{\xi}_i = \hat{\xi}(s_i)$ where s_i represents latitude and longitude – the objective of Kriging is to make a prediction of the process $\hat{\xi}(.)$ in a new location s_0. This prediction takes the form of a linear combination of the observed values:

$$\hat{\xi}(s_0) = \sum_{i=1}^{n} w_i \hat{\xi}(s_i) \tag{1}$$

with the weights w_i summing to one. The best prediction, in the sense of minimising the prediction error variance $Var(\epsilon(s_0))$, can be shown to be:

$$\boldsymbol{w} = [w_1, \dots, w_n]^T = \boldsymbol{C}_n^{-1} \boldsymbol{c}_0 \tag{2}$$

where $\boldsymbol{C}_n$ is the covariance matrix of all observations $\hat{\xi}(s_i)$ and $\boldsymbol{c}_0$ is the vector of covariance between $\hat{\xi}(s_0)$ and all the observations $\hat{\xi}(s_i)$.

Equation (2) highlights the equivalence between Kriging and a classical linear regression with $\hat{\xi}(s_0)$ as the response variable and the $\hat{\xi}(s_i)$ as n predictors. However, in contrast to a classical linear regression in which the covariance can be estimated by having several realisations for each variable ($\boldsymbol{C}_n = \boldsymbol{X}^T\boldsymbol{X}$ and $\boldsymbol{c}_0 = \boldsymbol{X}^T\boldsymbol{y}$), in Kriging we dispose of only one observation. Therefore, we need to assume a parametric covariance function $C(d)$ with d being the distance between two observations.

If the process $\hat{\xi}(.)$ is assumed to be stationary, the covariance function $C(d)$ is estimated from a variogram, a function giving the variance of the difference between two values $Var\left(\hat{\xi}(s_i) - \hat{\xi}(s_j)\right)$ according to their distance d. An empirical variogram $\hat{\gamma}(d)$ can be estimated considering a step δ as

$$\hat{\gamma}(d) = \frac{1}{2N_d} \sum \left(\hat{\xi}(s_i) - \hat{\xi}(s_j)\right)^2 \tag{3}$$

considering all pairs of observations $\hat{\xi}(s_i), \hat{\xi}(s_j)$ with a distance within $d \pm \delta$. From this empirical variogram, a variogram function $\gamma(d)$ following a predefined parametric shape can be fitted and then used to compute the covariances needed in Equation (2). For instance Figure S2 shows the variogram for each element of the BLUP residuals, with a fitted Gaussian model.

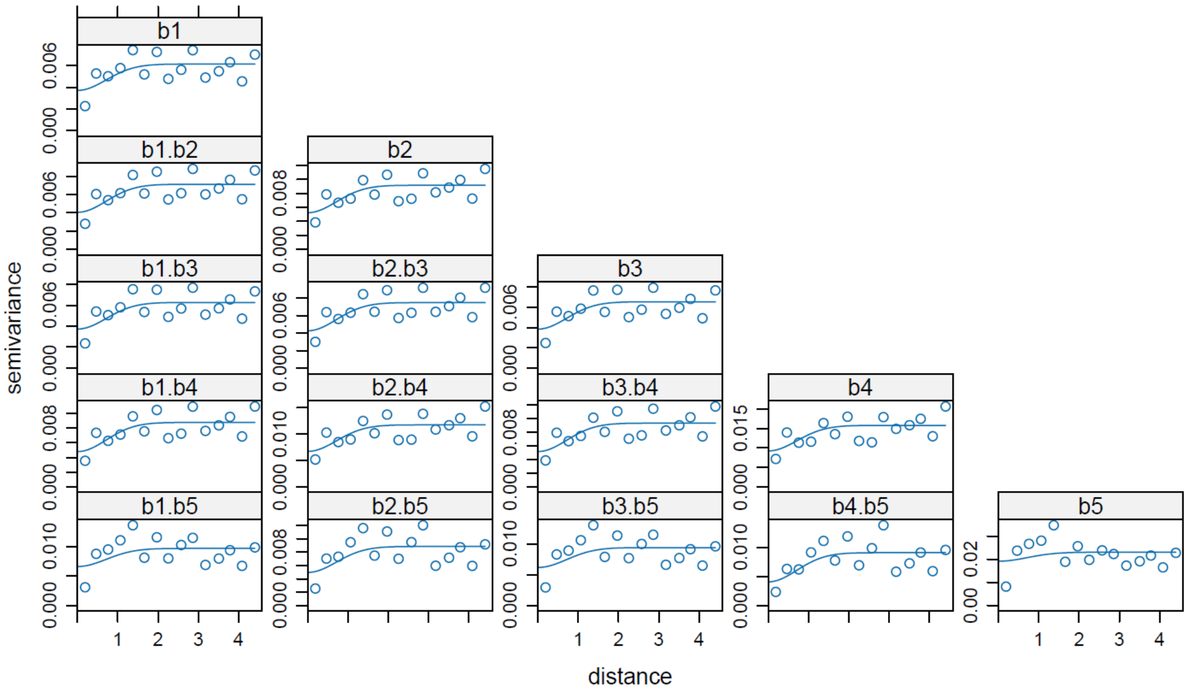
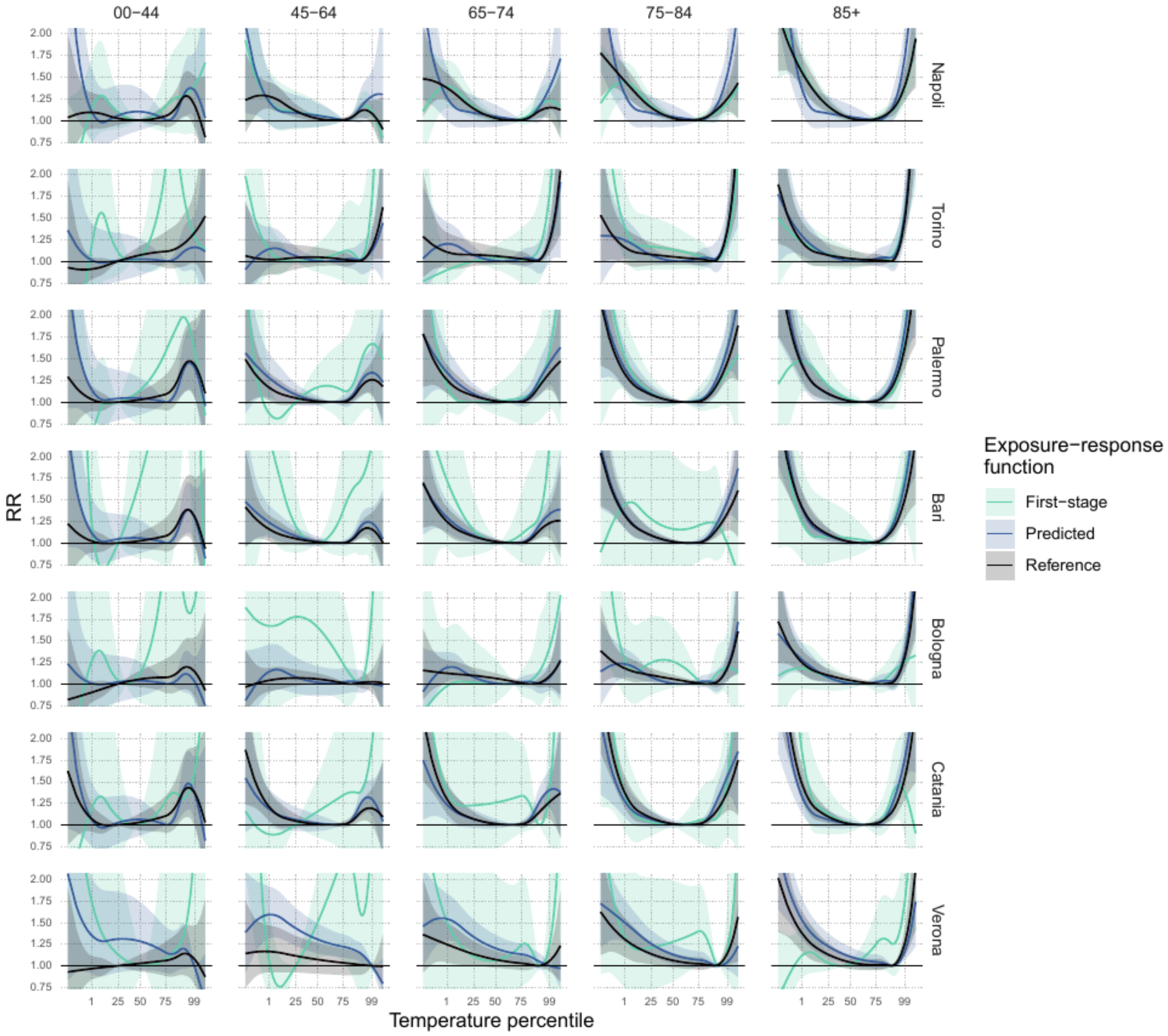
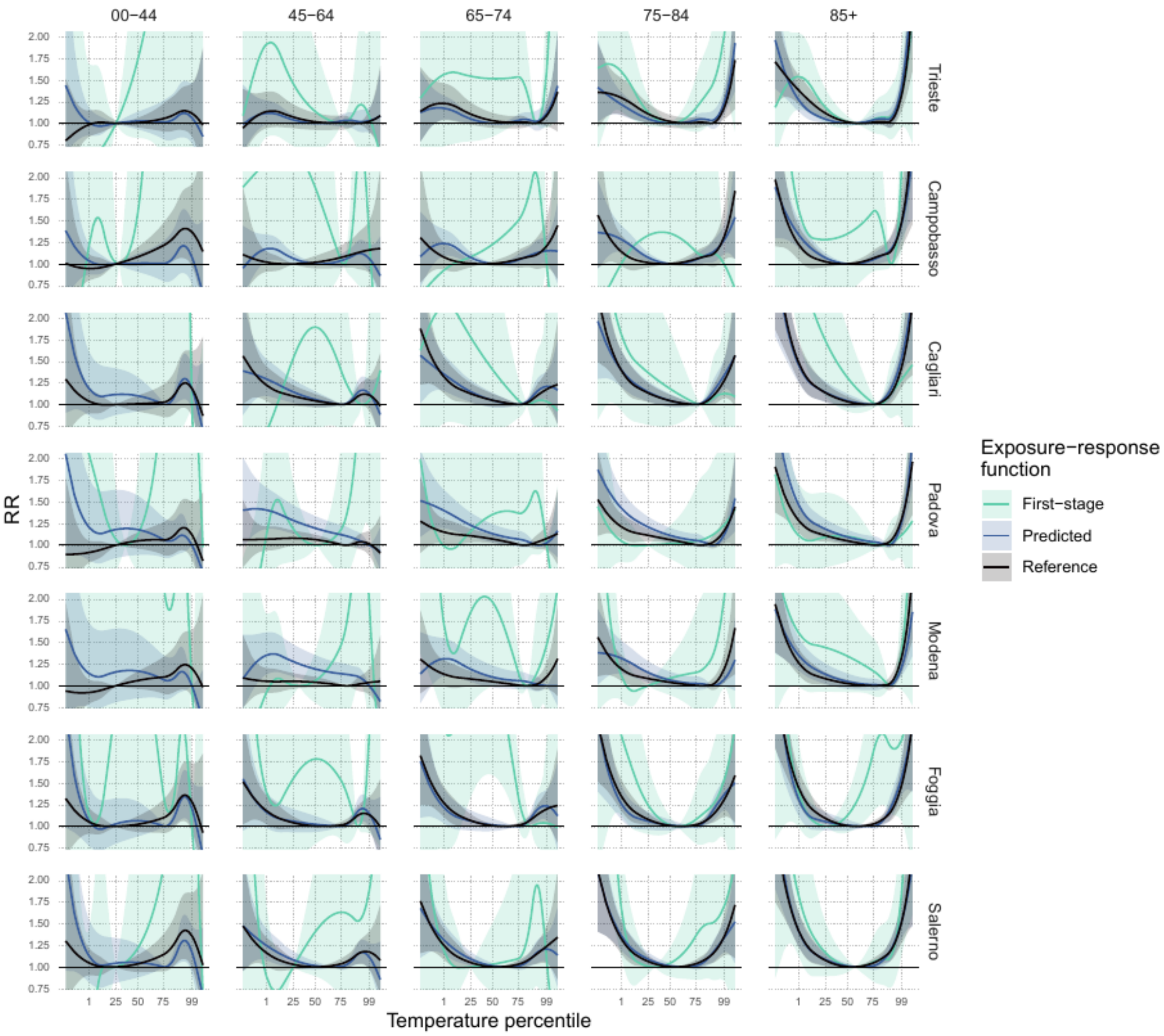
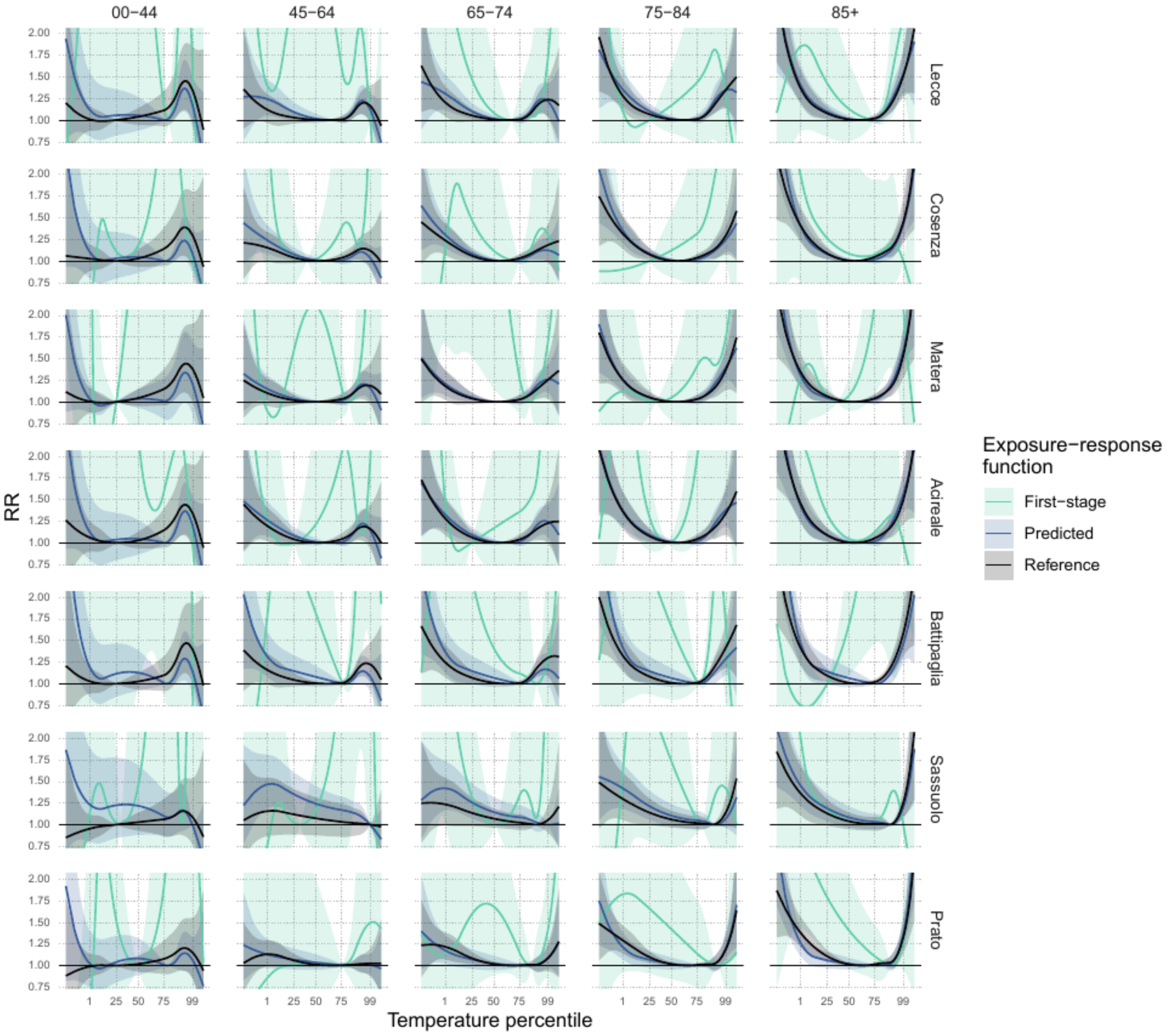


Figure S2: *Empirical variogram with fitted variogram model for all elements of the BLUP residuals* $\hat{\boldsymbol{\xi}}_i$, *including their covariance*.

4. Additional validation results




00−44
45−64
65−74
75−84
85+
Trieste
Campobasso
Cagliari
Padova
Modena
Foggia
Salerno
RR
2.00
1.75
1.50
1.25
1.00
0.75
1
25
50
75
99
Temperature percentile
Exposure−response function
First−stage
Predicted
Reference



00−44
45−64
65−74
75−84
85+
Lecce
Cosenza
Matera
Acireale
Battipaglia
Sassuolo
Prato
RR
2.00
1.75
1.50
1.25
1.00
0.75
1
25
50
75
99
Temperature percentile
Exposure−response function
First−stage
Predicted
Reference

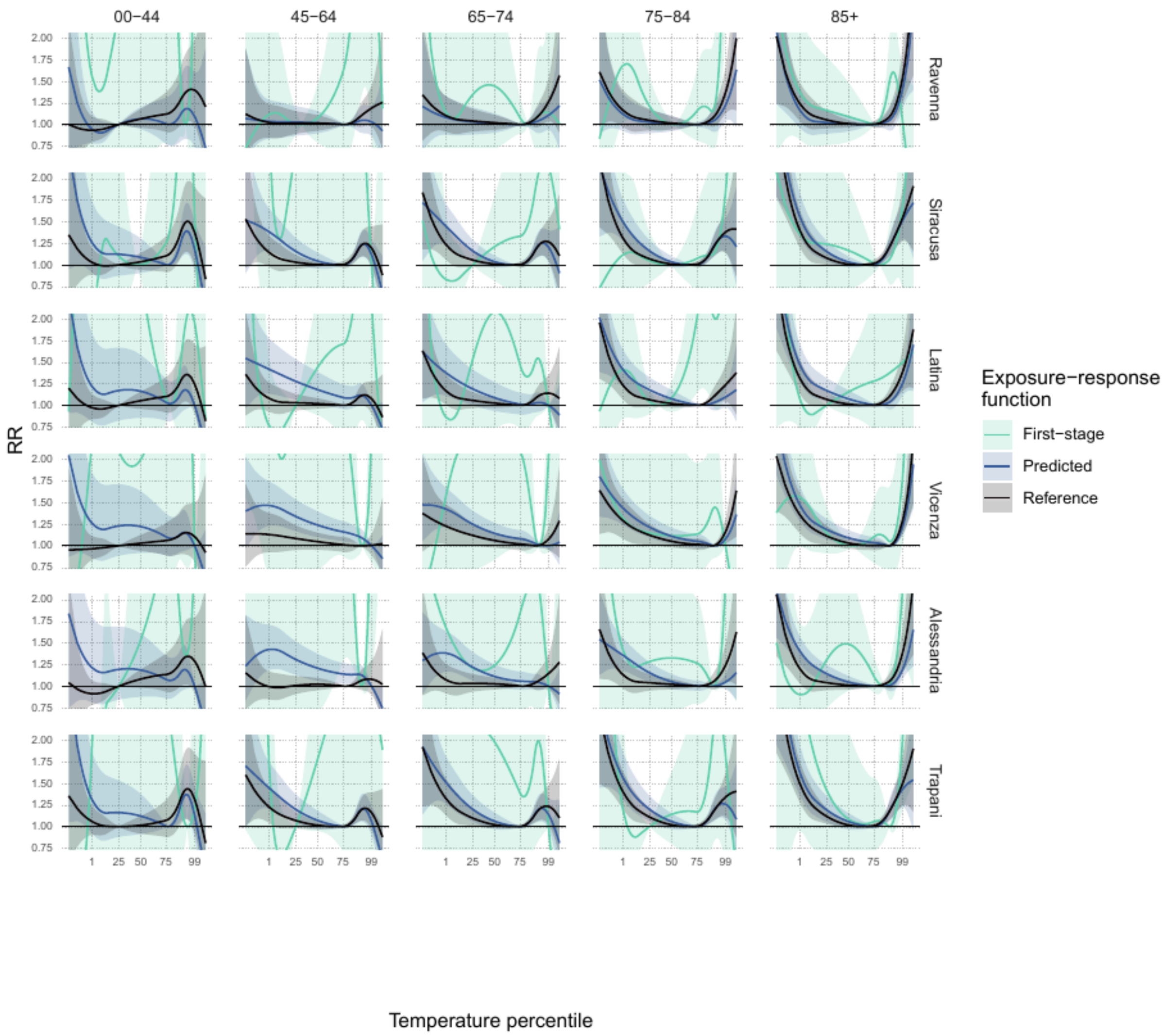


Figure S3: *Age-group and city-specific first-stage, predicted and reference exposure-response functions for the 27 unobserved cities. "First-stage" indicates estimate from a location and age-specific model applied on these cities' mortality series, "Predicted" is the prediction from the framework, and "Reference" corresponds to the BLUP from a meta-regression model hat includes the unobserved cities.*

References

1. Sera F, Armstrong B, Blangiardo M, et al. An extended mixed-effects framework for meta-analysis. *Stat Med* 2019; 38: 5429–5444.

2. Burnham KP, Anderson DR. Multimodel Inference: Understanding AIC and BIC in Model Selection. *Sociol Methods Res* 2004; 33: 261–304.

3. Matheron G. Principles of geostatistics. *Econ Geol* 1963; 58: 1246–1266.

4. Hoek G, Beelen R, de Hoogh K, et al. A review of land-use regression models to assess spatial variation of outdoor air pollution. *Atmos Environ* 2008; 42: 7561–7578.

5. Ignaccolo R, Mateu J, Giraldo R. Kriging with external drift for functional data for air quality monitoring. *Stoch Environ Res Risk Assess* 2014; 28: 1171–1186.