Meta-analysis of the Italian studies of short term effect of air pollution (MISA), 1990-1999

Meta-analysis of the Italian Studies of Short-term Effects of Air Pollution (MISA), 1990–1999

ANNIBALE BIGGERI, MD, MICHELA BACCINI, MS, PHD, PIERANTONIO BELLINI, MS, BENEDETTO TERRACINI, MD

A meta-analysis of short-term effects of air pollution on health in eight Italian cities from 1990 to 1999 is presented. Death certificates and hospital admission data as well as daily concentrations of pollutants were collected. The same generalized linear model adjusted for age, day of the week, holidays, influenza epidemics, meteorological variables, and seasonality pattern was fitted to the city data. City-specific model selection was not done. In the meta-analysis, for each outcome, the city-specific estimates for each pollutant were combined using fixed and random-effects models. Hierarchical Bayesian models were use to investigate the effects of PM_{10} in detail. Each pollutant (SO_2, NO_2, CO, PM_{10}, O_3) was significantly associated with mortality for natural causes. The effect of PM_{10} on mortality was greater during the warm season and for elderly. A north–south gradient in risk was observed for total natural mortality. The excess risks on hospital admission were modified by deprivation score and by the NO_2/PM_{10} ratio. Results add evidence for an association between air pollution and early mortality or morbidity and support the hypothesis of a synergism between meteorological variables and air pollution. *Key words*: meta-analysis; air pollution; epidemiologic time series.

INT J OCCUP ENVIRON HEALTH 2005;11:107–122

The results of time-series studies conducted in the last decade have shown that exposure to air pollution at levels presently occurring in urban environments, in particular PM_{10} (particles with aerodynamic diameter less than 10 μm), is associated with an increase in mortality and with a variety of health conditions, including emergency room visits and hospital admissions for respiratory and cardiovascular diseases. A quantification of the short-term effects of air pollution comes from large meta-analyses conducted in the United States and in Europe. Risk estimates derived from the NMMAPS[1] and APHEA[2,3] studies have been recently revised due to methodologic concerns related to the statistical modeling procedure used.[4]

Compared with most of the cities that have been investigated in the United States and in Northern and Central Europe, Italian cities experience higher pollution levels due to the large number of circulating vehicles (including diesel-powered cars and commercial vehicles) in areas whose urban infrastructures are not adequate to cope with mass traffic. The lack of enforced restrictive measures to control private traffic in central and densely populated areas, the urban structures with narrow streets and canyons, and the mild weather, which encourages outdoor activities and results in the exposure of more people to air contaminants, make Italian cities of some interest for evaluating the short-term effects of air pollution.

This report summarizes methods and findings of MISA (Meta-analysis of the Italian Studies on Short-term Effects of Air Pollution), a study of short-term effects of air pollution on mortality and hospital admissions in eight Italian cities in the period 1990–1999.

MISA consisted in a two-stage analysis. First, city-specific analyses were carried out using a common protocol. Second, the first-stage results were combined to obtain overall estimates of pollutants' effects. Standard meta-analytic methods were adopted to obtain an overall picture of short-term effects of air pollution in the eight cities, whereas hierarchical Bayesian models were used to investigate the effects of fine particulate matter in detail.

Revised results are presented, based on a fully parametric first-stage modeling approach. Previous results, based on semiparametric city-specific analyses, are reported elsewhere.[5,6]

DATA

Daily Mortality and Hospital-admissions Data

MISA included the cities of Turin, Milan, Verona, (all in Northern Italy), Bologna, Ravenna, Florence, and Rome

Received from the Department of Statistics "G. Parenti," University of Florence, Florence, Italy (AB, MB); and the Department of Statistical Sciences, University of Padua, Padua, Italy (PB); the Unit of Cancer Epidemiology, University of Turin, Turin, Italy (BT); and the MISA group.* MISA was launched on March 2000, within the project Statistics, Environment and Health (GRASPA), funded by the Italian Ministry of Education. Additional support was given by the authorities of the eight participating cities.

Address correspondence and reprint requests to: Annibale Biggeri, MD, Department of Statistics "G. Parenti," University of Florence, Viale Morgagni 59, 50100 Florence, Italy; e-mail: <abiggeri@ds.unifi.it>.

*MISA group members are listed at the end of the article.

TABLE 1 Average Daily Numbers of Deaths and Hospital Admissions for City and Period*

	Causes of Mortality (ICD.9)			Hospital Admissions	
	All Natural < 800	Cardiovascular 390–459	Respiratory 460–519	Cardiac 390–429	Respiratory 460–519
Turin					
1991–94	21.3	9.5	1.2		
1995–98	20.9	8.7	1.4	18.2	12.5
Milan					
1990–94	28.6	11.4	1.9	34.0	15.8
1995–97	29.1	11.4	2.0	44.7	21.9
Verona, 1995–99					6.2
Ravenna, 1991–95				6.5	2.5
Bologna, 1996–98	12.1	4.9	0.9	11.7	7.3
Florence, 1996–98	11.5	4.9	0.8	12.9	5.3
Rome					
1992–94	56.4	23.6	3.0		
1995–97	56.6	23.0	2.9	86.9	43.1
Palermo, 1997–99	14.1	5.6	0.9	31.1	29.3

*Empty cells indicate no available data.

(Central Italy), and Palermo (Southern Italy). Death certificates and hospital-admissions data were obtained, respectively, from local health authorities and from regional files. Mortality data were not available for Ravenna and Verona. For each city, we focused on the daily counts of deaths and hospital admissions of the resident population. Given the purpose of the study, deaths and hospital admissions that occurred outside the city area were excluded from the analysis. Total mortality from all causes excluding external causes (ICD.9: ≤ 800), cardiovascular mortality (ICD.9: 390-459), and respiratory mortality (ICD.9: 460-519) were considered. The same procedure was used for retrieving hospital admissions for cardiac (ICD.9: 390-429) and respiratory (ICD.9: 460-519) acute conditions.

The periods under study and the average numbers of daily health related events in each city are summarized in Table 1. Databases included mortality, hospital admissions, air pollution, and weather data for the second half of the 1990s. For Turin, Rome, and Milan data for the first half of the 1990s were also available: these were included in the study, as a separate dataset, in order to allow for analyses of time trends of the associations. Ravenna participated only with hospital-admissions data for the period 1990–1995. For Verona, only respiratory hospital-admissions data for the period 1995–1999 were available.

Daily Pollutants

Air pollution data were obtained from the Regional Environmental Protection Agencies or from local sources.[5] The monitoring network established in each city provided the results of measurements of air pollutants. Data from monitors with more than 25% missing measurements were excluded from the city datasets. Monitoring stations located in sites largely influenced by local traffic were excluded.[7]

The daily mean concentrations of sulfur dioxide (SO_2), nitrogen dioxide (NO_2), total suspended particles (TSP), and fine particles (PM_{10}) were considered; the daily levels of ozone (O_3) and carbon monoxide (CO) were summarized as the maximum eight-hour moving averages of the hourly measurements.

Daily statistics for pollutant concentrations were considered to be missing when more than 25% of hourly data were not available. For each city, missing data in one monitor were imputed as the average of the data from the remaining monitors, weighted by the ratio between the annual average of the specific monitor and the general annual average of all the selected monitors. Missing data for one day were imputed as the average of data for four days (the preceding and following days, the same day of the previous and following weeks).

In Florence and Palermo, PM_{10} data were available. For the other cities, we applied conversion factors from TSP to PM_{10} (0.6 for Turin and 0.8 for all the other cities), estimated through validation studies.[7] Ozone concentrations were used only when background monitors were available (Turin, Verona, Bologna, and Florence). We avoided O_3 measurements from monitors located near traffic sources, where the scavenger role of nitrogen oxides could have given rise to apparently low levels of ozone. Moreover, the analysis of the effect of O_3 was limited to the warm period of the year (May 1 through September 30).

Meteorologic data (temperature and relative humidity) were collected by the same air-pollution-monitoring networks and completed with data from monitors located in the suburbs or (in Milan and Bologna) in the airports.

Summary statistics of daily concentrations of air pollutants, temperature, and relative humidity are reported in Table 2.

METHODS

City-specific Analysis

In the first stage of the analysis, daily time series of total and cause-specific mortality and morbidity were modeled with respect to each air pollutant separately for each city, using common models defined on the basis of a structured exploratory analysis. City-specific model selection was not done.

The core model consisted in a generalized linear model for Poisson data, with cubic regression splines of time trend to control for seasonal fluctuations of mortality.[8] Analysis was age-adjusted (< 65, 65–74 years, and ≥ 75 years).

For mortality data, indicator variables for season were included in the model for the first two age groups, and a cubic regression spline with 5 degrees of freedom per year was defined for the last age group. For hospital admission data, separate splines of time were specified for the three age classes, whose degrees of freedom varied from 5 to 7 per year. Knots of natural cubic splines were placed evenly throughout the values .

Dummy variables were used to model the confounding effect of day of the week and holidays. The model for morbidity data included interaction terms between day of the week and age class.

We controlled for the age-specific effect of influenza epidemics, specifying for each city an indicator of days of epidemic. A day of epidemic was defined on the basis of an appropriated smoothing function of daily counts of hospital admissions for influenza or daily counts of deaths from natural causes in the elderly (> 74 years old), which turned out to be a stable indicator of influenza epidemic.[5]

Since the exploratory analysis indicated a typical "v" shape of the relationship between average daily temperature and mortality, we decided to model the effect of current temperature on daily counts of deaths through two linear terms constrained at 21° C, having observed minimum risk around this value in every city. We took into account also the lagged effect of temperature by including in the model a linear term for the difference between current temperature and mean temperature of the previous three days. This term is nearly uncorrelated with the previous ones, assuring more stable estimates. Linear and quadratic terms modeled the effect of relative humidity. For morbidity data, linear terms for current temperature, its difference from lagged temperature, and relative humidity were specified.

All the models included the interaction term between temperature and age class.

Only single-pollutant models were specified. For each pollutant, analyses were conducted separately for all lags from 0 to 3 days and some distributed lags (averages of lags 0–1, 1–2, and 0–3 days). We considered only linear effects of each pollutant.

With regard to the relationship between ozone levels and cause-specific morbidity during the warm season, we included in the model an indicator of the mass departure for the holidays (corresponding to the big industries' closing period) and the lower number of hospital beds available during the summer.

Model adequacy was checked by residual analysis. Sensitivity analyses were performed considering nonlinear pollutant effect and nonlinear confounding effect of temperature. No substantial difference was found (data not shown).

All the city-specific analyses were performed using R 1.8 software (the R Development Core Team, 2003, R Language Version 1.8, ISBN 901167-55-2, <http://cran.r-project.org>).

Combined Analysis

In the second stage of the analysis, the city-specific estimates were combined.

Initially, classical meta-analytic methods were applied to each pollutant and each health outcome. We calculated fixed-effects overall estimates separately for each outcome variable and for each pollution variable. To check the robustness of the results, random-effects models were also specified,[9] even when the homogeneity test Q did not detect significant heterogeneity among cities.

Let $\hat{\lambda}_c$ and $\hat{\sigma}^2_c$, respectively, represent the estimate of log rate ratio and the estimate of its variance for the c-th city ($c = 1, \ldots, C$). Fixed-effects overall estimates were calculated as simple weighted averages of estimated city-specific coefficients $\hat{\lambda}_c$, with weights inversely proportional to the estimated within-cities variability $\hat{\sigma}^2_c$. On the other hand, the random-effects overall means were obtained as weighted averages with weights inversely related to $\hat{\sigma}^2_c + \hat{\tau}^2$. The DerSimonian and Laird estimate of among-cities heterogeneity variance, τ^2, was used here.

We then focused on the effects of particulate matter. Random-effects Bayesian meta-analyses were performed. On one hand, this analysis can be seen as a sensitive analysis of the classical approach to a more accurate estimate of inter-city heterogeneity variance and its uncertainty. On the other hand, the Bayesian approach provides more accurate estimates of the PM_{10} effect, which is our primary interest. It takes into account uncertainty in the heterogeneity variance estimate, including in the analysis the whole posterior distribution of τ^2, rather than a single estimate.

We postulated that the first-stage city-specific estimates were independent realizations from Gaussian populations with mean λ_c and known variance $\hat{\sigma}^2_c$:

TABLE 2 Mean Daily Concentrations of Urban Pollutants and Weather Variables* (Warm Season: May–September)

	SO_2 ($\mu g/m^3$)	NO_2 ($\mu g/m^3$)	CO (mg/m^3)	PM_{10} ($\mu g/m^3$)	O_3† ($\mu g/m^3$)	O^*_3 ($\mu g/m^3$)	Temperature (° C)	Humidity (%)
Turin, 1991–94 (3 monitors)								
Average	32.8	84.0	5.8	77.6	77.8	108.1	14.0	62.8
95° perc.	91.0	134.3	11.5	160.2	164.4		26.3	96.0
Maximum	151.2	256.9	24.7	257.2	219.4	219.4	29.1	100.0
Not available	3	16	3	1	434	49	0	0
Turin, 1995–98								
Average	17.8	74.9	4.0	63.8	66.0	111.7	14.3	61.1
95° perc.	43.7	119.1	7.9	123.8	153.4		25.6	95.0
Maximum	81.4	193.9	19.8	180.0	217.4	217.4	29.2	100.0
Not available	8	4	7	1	201	149	0	0
Milan, 1990–94 (4–5 monitors)								
Average	40.9	105.8	5.9	61.8			13.8	68.2
95° perc.	131.2	180.8	11.4	118.7			26.5	93.7
Maximum	290.8	309.0	26.5	273.0			29.7	99.9
Not available	0	0	0	63			0	3
Milan, 1995–97								
Average	18.4	86.5	4.0	45.2			13.7	65.3
95° perc.	48.9	131.0	8.0	81.4			25.3	97.4
Maximum	90.0	214.0	12.3	126.4			29.1	100.0
Not available	0	0	0	3			0	4
Verona, 1995–99 (4 monitors)								
Average	6.6	57.8	2.5	36.5	73.8	117.6	14.9	76.8
95° perc.	15.7	92.6	4.9	70.1	161.5	176.4	26.7	100.0
Maximum	33.8	161.3	10.2	122.4	226.0	225.6	31.7	100.0
Not available	0	0	0	0	0	0	0	0
Ravenna, 1991–95 (2 monitors)								
Average	19.6	60.5	1.8	59.1			14.3	78.4
95° perc.	46.0	92.0	3.0	116.0			27.0	95.0
Maximum	83.0	175.0	7.0	216.0			30.0	100.0
Not available	378	40	53	550			40	103
Bologna, 1996–1998 (2–3 monitors)								
Average	8.5	60.1	2.4	41.2	75.9	11.2	13.9	69.5
95° perc.	22.1	94.2	5.6	79.3	159.7	172.4	26.0	86.0
Maximum	50.2	120.4	11.1	122.9	215.7	215.6	30.0	95.0
Not available	2	2	7	15	53	9	5	0
Florence, 1996–98 (3–5 monitors)								
Average	7.7	70.1	2.7	40.3	79.5	114.3	15.5	68.6
95° perc.	18.1	103.8	5.4	71.2	147.0	168.8	29.6	88.6
Maximum	40.1	141.4	8.7	182.4	210.7	210.7	29.8	98.0
Not available	0	0	0	4	1	1	8	47
Rome, 1992–94 (3–5 monitors)								
Average	15.9	97.0	6.5	69.7			16.9	61.6
95° perc.	36.3	134.0	11.7	106.2			27.8	80.0
Maximum	22.3	174.6	22.3	158.7			30.5	94.0
Not available	0	0	0	78			0	0
Rome, 1995–97								
Average	8.9	85.8	5.4	59.0			16.6	60.1
95° perc.	18.6	112.7	9.5	79.6			26.7	81.0
Maximum	18.5	150.6	18.5	124.4			29.7	91.0
Not available	27	0	0	125			0	0
Palermo, 1997–99 (6 monitors)								
Average	12.5	61.3	2.1	42.9			18.2	28.5
95° perc.	26.1	88.1	3.8	71.6			26.8	73.6
Maximum	63.8	137.8	8.0	203.3			32.3	83.2
Not available	18	2	2	4			9	25

*Empty cells indicate no available data.
†Warm season: May–September.

$$\hat{\lambda}_c = \lambda_c + \epsilon_c$$

$$\epsilon_c \overset{indep.}{\sim} N(0, \hat{\sigma}^2_c)$$

and that each city-specific effect λ_c was drawn from a Normal population with mean β and variance τ^2:

$$\lambda_c = \beta + u_c$$

$$u_c \overset{indep.}{\sim} N(0, \tau^2)$$

The two random mechanisms ϵ_c and u_c were assumed to be independent. β represents the average effect of pollutant adjusted for the inter-city variation τ^2.

The Bayesian formulation needs to specify prior distributions on hyperparameters β and τ^2. We placed upon these parameters vague proper priors, in particular

$$\lambda \sim N(0, 10^5)$$

$$\tau^2 \sim IG(0.001, 0.001)$$

In this and in the following analyses posterior distributions of parameters have been obtained with WinBUGS.[10] 100,000 iterations (excluding the first 4,000) were retained. To approximate the marginal posteriors, only one sample out of 10 was used. Achieved convergence was assessed using the Gelman and Rubin approach,[11] based on three parallel chains.

Sensitivity Analysis

Since only a small number of cities contributed to the study, information about heterogeneity variance among cities was limited; thus Bayesian inference could be strongly influenced by model assumptions. We considered two aspects of this problem: sensitivity of inference to the choice of heterogeneity variance prior and sensitivity of the results to alternative specifications of random-effects distribution.

First we checked for sensitivity on overall mean estimates, placing alternative priors upon the heterogeneity parameter.[12] We considered extreme cases, specifying on τ normal distributions truncated at zero with variances equal to 1,000 (Model B) and 0.5 (Model C). The first distribution is suitably vague, but it lends more support to high heterogeneity values than Inverse Gamma with small parameter values. The second distribution supports small heterogeneity values, assigning 99% probability to values less than 3.2.

Second, we performed a sensitivity analysis assuming random effects (i.e., λ_c) distributed as a Student's *t* with 4 degrees of freedom (Model D). The Student's *t* distribution with few degrees of freedom admits heavier tails than Normal (the tail behavior being regulated by the degrees of freedom), resulting in more robust inference in the presence of a limited number of outlying observations.[13]

The sensitivity of the overall effect to model choices was measured as calibrated Kullback–Leibler distance between the posterior distribution of β obtained by the original model and the posterior distribution of β obtained by each alternative specification. We assumed the first one as reference distribution, interpreting Kullback–Leibler distance as loss related to use of an alternative distribution, when Inverse Gamma would be the appropriate one (Appendix).

Meta-regression

The Bayesian random-effects model was extended to analyze variability across cities in a meta-regression phase. Sources of heterogeneity in short-term effect of fine particles were investigated specifying regression models, where city-specific effects changed according to city-specific explanatory variables. We considered as possible effect modifiers: calendar period (1990–1994, 1995–1999), SMR for total mortality, percentage of elderly, deprivation index, mean temperature, mean level of NO_2, logarithm of mean concentration of fine particles ($\log PM_{10}$) and PM_{10}/NO_2 ratio. Data on selected social–demographic characteristics of the eight cities were obtained from the 1991 Census (Table 3). The deprivation index used is described by Cadum et al.[14] The calendar period was included in each meta-regression. To avoid post hoc data dredging, separate models for the remaining explanatory variables, introduced one at time, were fitted.

Denoting with $\hat{\lambda}_{cj}$ the city-specific estimate in the *j*-th period ($j = 1$ for 1990–1994; $j = 2$ for 1995–1999) and with $\hat{\sigma}^2_{cj}$ the corresponding estimated variance, we assumed:

$$\hat{\lambda}_{cj} = \lambda_{cj} + \epsilon_{cj}$$

$$\epsilon_{cj} \overset{indep.}{\sim} N(0, \hat{\sigma}^2_{cj})$$

Then we expressed the PM_{10} effect in the city *c* during *j* as

$$\lambda_{cj} = \beta_j + u_c$$

or

$$\lambda_{cj} = \beta_j + \alpha \times m^i_{cj} + u_c$$

where m^i_{cj} is the observed value of the effect modifier *i* in the *c*-th city during the *j*-th period and u_c is a city-specific random effect from a Normal distribution with mean zero and variance τ^2. The random mechanisms that generate ϵ_{cj} and u_c were assumed independent. τ^2 expresses the portion of variability among cities that is not explained by covariates, which is usually referred to as residual heterogeneity.

TABLE 3 City-specific Explanatory Variables

	Population	% Population > 65*	Deprivation Index	SMR	Temperature (Mean) (°C)	NO_2 (Mean) ($\mu g/m^3$)	PM_{10} (Mean) ($\mu g/m^3$)	NO_2/PM_{10}
Turin								
1991–94	962,507	16.8	1.8	97.9	14.0	84.0	77.6	1.1
1995–98					14.3	74.9	63.8	1.2
Milan								
1990–94	136,9231	18.2	0.7	97.5	13.8	105.8	61.8	1.7
1995–97					13.7	86.5	45.2	1.9
Verona, 1995–99	255,824	17.8	0.3	95.2	14.9	57.8	36.5	1.6
Ravenna, 1991–95	135,844	18.0	–1.6	84.2	14.3	60.5	59.1	1.0
Bologna, 1996–98	404,378	23.4	0.0	92.6	13.9	60.1	41.2	1.5
Florence, 1996–98	403,294	22.0	–0.1	90.6	15.5	70.1	40.3	1.7
Rome								
1992–94	2,775,250	14.5	–0.1	102.2	16.9	97.0	69.8	1.4
1995–97					16.6	85.8	50.6	1.7
Palermo, 1997–99	698,556	11.4	2.6	122.4	18.2	61.3	42.9	1.4

*As of the 1991 Census.

Non-informative priors were used: vague Normal distributions on regression coefficients and Inverse Gamma with small parameter values on τ^2.

Analysis by Season

The PM_{10}–total mortality rate ratio in 1995–1999 was further studied investigating the effects of particulate matter during cold and warm seasons. First we specified city-specific models where an interaction term between PM_{10} concentration and season was included. Then, a random-effects Bayesian model was used to combine the estimated coefficients $\hat{\lambda}_{cs}$, s denoting season ($s = 1$ for warm season: May–September; $s = 1$ for cold season: October–April).

We specified two different models. The first one assumed that both particle effect and variability among cities were season-dependent. Let λ_{cs} represent the particles effect in the c-th city during the s-th season. We assumed

$$\hat{\lambda}_{cs} = \lambda_{cs} + \epsilon_{cs}$$

$$\lambda_{cs} = \beta_s + u_c + v_{cs}$$

$$\epsilon_{cs} \overset{indep.}{\sim} N(0, \hat{\sigma}^2_{cs})$$

$$u_c \overset{indep.}{\sim} N(0, \tau^2)$$

$$v_{cs} \overset{indep.}{\sim} N(0, v_s^2)$$

where v_{cs} are city–season-interaction random terms introduced to model seasonal differences in heterogeneity among cities (variance heterogeneity in the s-th season being $\tau^2 + v_s^2$). All random mechanisms in the model were assumed independent.

The second model did not include interaction random effects, defining only one heterogeneity parameter:

$$\lambda_{cs} = \beta_s + u_c$$

Vague priors were specified on hyper-parameters:

$$\beta_s \overset{indep.}{\sim} N(0, 10^5)$$

$$\tau^2 \sim IG(0.001, 0.001)$$

$$v_s \overset{indep.}{\sim} IG(0.001, 0.001)$$

Analysis by Age

Identifying possible subgroups of the general population that are more susceptible to short term effects of air pollution is a relevant issue.[15] Age-specific effects of fine particles on total mortality were calculated separately for each city, including age–pollutant interaction terms in the generalized additive model specification. Eventually, several alternative Bayesian hierarchical models were defined to combine the first-stage age-specific estimates. We specified multivariate and univariate meta-analytic models and different linear predictors or correlation structures among age-specific terms. Model selection was performed using the deviance information criterion.[16] The minimum DIC corresponded to the following model:

$$\hat{\lambda}_{ca} = \lambda_{ca} + \epsilon_{ca}$$

$$\lambda_{ca} = \beta_h + u_c + v_{ch}$$

$$\epsilon_{ca} \overset{indep.}{\sim} N(0, \hat{\sigma}^2_{ca})$$

TABLE 4 Overall Estimates (95% CI) of Pollutants'Effect in 1995–99 by Fixed-effects and Random-effects Models

	Mortality			Hospital Admissions	
	All Natural Causes	Cardiovascular Causes	Respiratory Causes	Cardiac Causes	Respiratory Causes
SO_2					
Fixed	1.38 (0.41,2.37)	1.70 (0.14,3.28)	2.52 (–1.27,6.46)	4.00 (2.86,5.16)	0.14 (–1.25,1.55)
Random	1.43 (0.37,2.51)	1.70 (0.14,3.28)	2.52 (–1.27,6.46)	3.97 (2.46,5.50)	0.14 (–1.25,1.55)
NO_2					
Fixed	0.93 (0.58,1.27)	1.31 (0.76,1.85)	1.43 (0.08,2.79)	1.87 (1.50,2.24)	1.53 (1.05,2.01)
Random	0.93 (0.58,1.27)	1.31 (0.76,1.85)	1.42 (0.05,2.81)	1.57 (0.72,2.43)	1.55 (0.87,2.23)
CO					
Fixed	0.93 (0.50,1.36)	1.29 (0.62,1.96)	2.44 (0.74,4.17)	2.92 (2.42,3.43)	1.18 (0.53,1.82)
Random	0.93 (0.50,1.36)	1.29 (0.62,1.96)	2.47 (0.14,4.85)	2.65 (1.11,4.22)	1.53 (0.50,2.56)
PM_{10}					
Fixed	0.85 (0.52,1.18)	0.97 (0.45,1.50)	1.74 (0.44,3.05)	0.77 (0.40,1.15)	0.73 (0.27,1.20)
Random	0.98 (0.35,1.61)	1.21 (0.32,2.10)	1.41 (–1.41,4.32)	0.82 (0.32,1.32)	0.91 (–0.04,1.86)
O_3 (warm season)					
Fixed	0.82 (0.17,1.49)	1.43 (0.36,2.50)	–0.28 (–2.95,2.47)	–0.53 (–1.33,0.27)	0.01 (–0.91,0.94)
Random	0.89 (0.04,1.74)	1.43 (0.36,2.50)	–0.21 (–3.81,3.53)	–0.53 (–1.35,0.29)	0.01 (–0.91,0.94)

$$u_c \overset{indep.}{\sim} N(0, \tau^2)$$

$$v_{ch} \overset{indep.}{\sim} N(0, v_h^2)$$

where a denotes age groups (0–64, 65–74 and ≥ 75); h denotes two age classes less than 65 and more than 65 years. All random mechanisms that express the within- and among-cities variability were supposed to be mutually independent. The model assumes different expected values (β_h) and different variability among cities ($\tau^2 + v_h^2$) of the effects of fine particulate matter on younger (0–64) and older (≥ 65) population.

According to DIC and Kullback–Leibler divergence, a good alternative consisted in the simpler model without v_{ch} interaction random terms (age-independent heterogeneity):

$$\lambda_{ca} = \beta_h + u_c$$

Details of model selection are available in Baccini et al.[17]

Over-dispersed Normal priors were defined on β_h and vague Inverse Gamma, were specified on τ^2 and v_h^2.

RESULTS

Table 4 summarizes the results by fixed- and random-effects meta-analyses. The results are presented as % change in numbers of deaths, or hospital admissions, associated with a 10 μg/m^3 increase of air-pollutant concentrations (1 mg/m^3 for CO) at lag 0–1 for mortality and at lag 0–3 for hospital admissions. With regard to total mortality and mortality for cardiovascular diseases, all the pollutants, including ozone during the warm season, showed positive and statistically significant associations. For respiratory mortality and hospital admissions, significant increases were found for NO_2 and for CO. In general, the effect estimates were larger for cardiovascular and respiratory-disease mortality than for total mortality. On the other hand, the % increase in hospitalizations for cardiovascular diseases tended to be similar or even higher when compared with hospitalizations for respiratory diseases.

Overall estimates using fixed- or random-effects models tended to be similar with the exception of PM_{10}. In fact, the effects of PM_{10} showed the highest inter-city variability. The homogeneity test Q result was significant for total mortality (Q = 15.2, df = 5), respiratory mortality (Q = 20.5, df = 5), cardiovascular mortality (Q = 12.1, df = 5), and respiratory morbidity (Q = 21.1, df = 6). It did not detect significant inter-city heterogeneity for cardiac morbidity (Q = 7.9, df = 5). Considering the random-effects model, the estimated % changes associated with a 10 μg/m^3 increase in PM_{10} concentration were 0.98 (95% CI: 0.35, 1.61), 1.21 (0.32, 2.10), and 1.41 (–1.41, 4.32) for total, cardiovascular, and respiratory mortality,

TABLE 5 Overall Estimates of PM_{10} Effects on Total Mortality, Mortality for Cardiovascular and Respiratory Diseases, and Hospital Admissions for Cardiac and Respiratory Diseases in 1995-1999 by Fixed-effects, Random-effects and Bayesian Random-effects Models (Percentage Changes and 95% Credibility Intervals)

	Mortality			Hospital Admissions	
	All Natural Causes	Cardiovascular Causes	Respiratory Causes	Cardiac Causes	Respiratory Causes
Fixed effects	0.85 (0.53,1.18)	0.97 (0.45,1.50)	1.74 (0.44,3.05)	0.77 (0.40,1.15)	0.73 (0.27,1.20)
Random effects	0.98 (0.35,1.61)	1.21 (0.32,2.10)	1.41 (–1.41,4.32)	0.82 (0.32,1.32)	0.91 (–0.04,1.86)
Bayesian					
Model A	0.96 (0.24,1.77)	1.13 (0.27,2.25)	1.37 (–2.58,5.22)	0.81 (0.32,1.38)	0.90 (–0.18,2.16)
Model B	0.98 (–0.001,2.01)	1.22 (–0.01,2.60)	1.31 (–3.76,6.16)	0.85 (0.15,1.70)	0.97 (–0.37,2.50)
Model C	0.97 (0.27,1.69)	1.15 (0.34,2.11)	1.71 (0.02,4.66)	0.82 (0.26,1.45)	0.94 (0.04,1.94)
Model D	0.90 (0.21,1.66)	1.11 (0.22,2.19)	1.52 (–2.32,5.12)	0.80 (0.31,1.34)	0.94 (–0.10,2.08)

*Model A: $\tau^2 \sim IG(0.001, 0.001)$; Model B: $\tau \sim N(0, 10^3)$ truncated at 0; Model C: $\tau \sim N(0, 0.5)$ truncated at 0; Model D: random effects $\sim t_{(4)}$.

respectively. The changes in hospital admissions were 0.82% (0.32, 1.32) and 0.91% (–0.04, 1.86) for cardiac and respiratory causes, respectively.

Comparing the results of conventional and Bayesian random-effects meta-analyses (Table 5), the confidence/credibility intervals of overall means were widest with the Bayesian approach, but significance was retained. The estimated % changes with the Bayesian approach were 0.96 (95% CrI: 0.24, 1.77) for total mortality, 1.13 (0.27, 2.25) for cardiovascular mortality and 1.38 (–2.58, 5.22) for respiratory mortality. Percent increases of 0.81 (0.32, 1.38) and 0.90 (–0.18, 2.16) were estimated for cardiac and respiratory hospital admissions, respectively.

The inference on overall means did not appear particularly sensitive to choice of the heterogeneity vari-

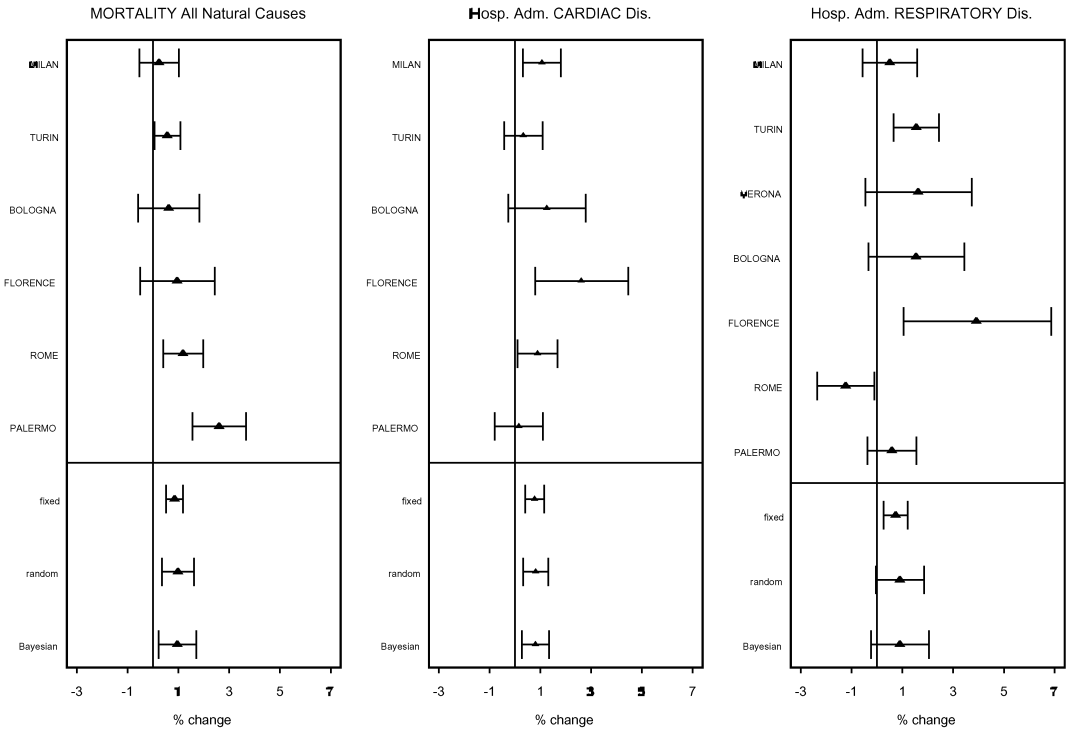


Figure 1—First-stage and overall estimates of PM_{10} effects on total mortality and hospital admissions for cardiac and respiratory diseases by fixed-effects, random-effects and Bayesian models.

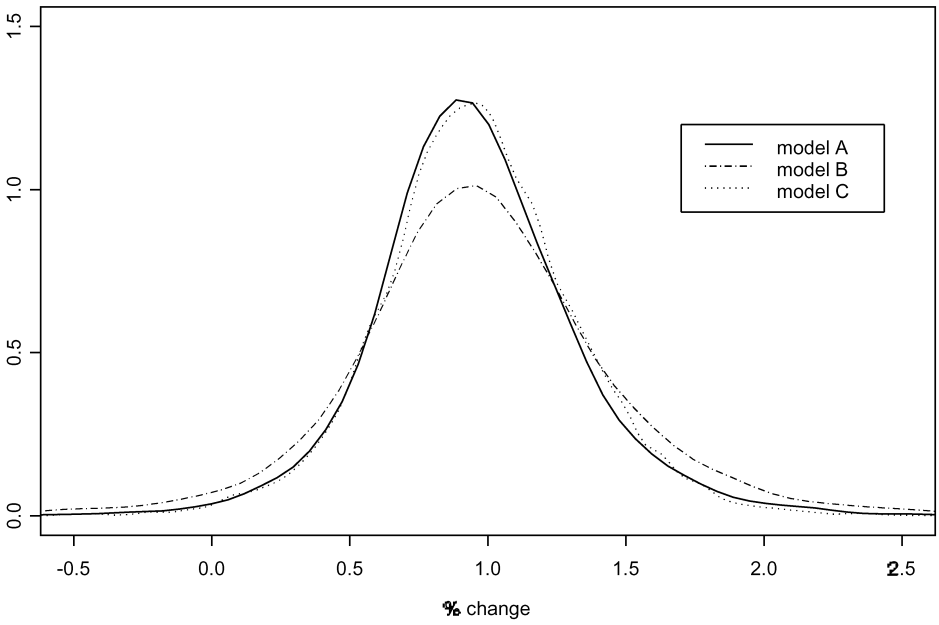


Figure 2—Posterior distribution of % excess of deaths from all natural causes per 10 μg/m³ under alternative specifications of the heterogeneity variance prior.

ance prior (Table 5 and Figure 2). The Kullback–Leibler distances between the posterior distribution of β under the reference model and each of the alternative models were quite small. They were maximum when half-normal distributions with high variance were specified on τ (model B in Table 5). In this case, the calibrated values of the Kullback–Leibler distances (q) were greater than 0.70 for total mortality and cardiac hospital admissions. It should be noticed that the point estimates of the overall effects did not change substantially, while wider credibility intervals were obtained.

The Normal–Normal model appeared robust to the presence of outlying city-specific estimates (model D in Table 5 and Figure 3). Defining a heavy tailed distribution on random effects, we obtained no contradictory results in terms of overall estimates. The highest Kullback–Leibler distance between the reference model and the alternative model was calculated for total mortality (q = 0.65). The estimated overall % change was 0.90 under the model with t distributed random effects versus 0.96 under the Normal–Normal model, while the 95% credibility limits were similar.

An interesting inference on the city-specific effects can be based on the posterior distributions of the city-specific parameters. Table 6 presents the first-stage estimates of PM_{10} effects and the posterior distributions of parameters obtained from the Bayesian models by their means and 95% credibility intervals (CrI) for all the outcome variables, showing the improvement in precision and the shrinkage of effect

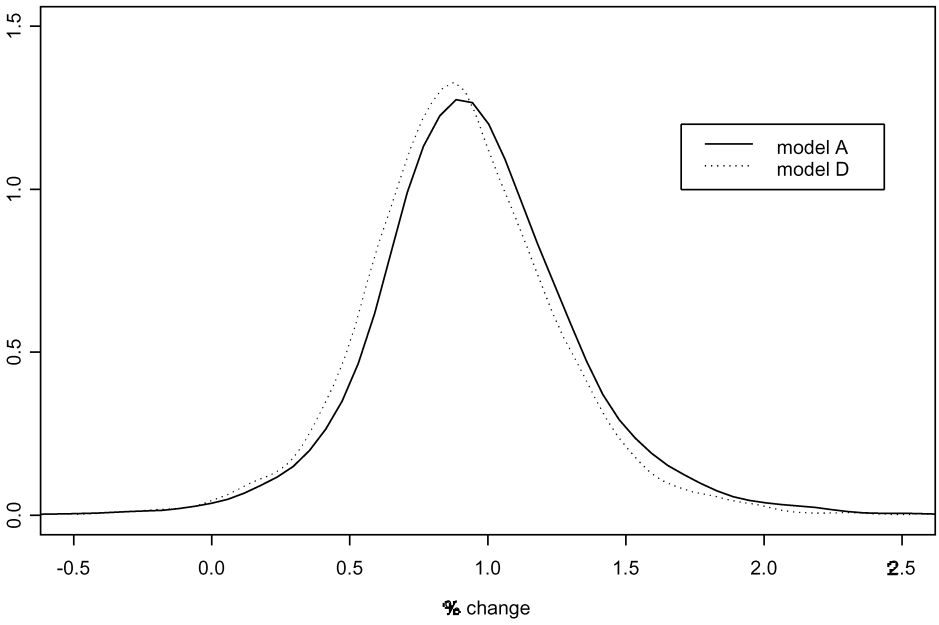


Figure 3—Posterior distribution of % excess of deaths from all natural causes per 10 μg/m³ under alternative specifications of random effects distribution.

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.

estimates toward the overall means introduced by the Bayesian modeling.

A North–South gradient in increase in risk is suggested for mortality by both first-stage estimates and city-specififc posterior estimates (Figure 1, Table 6). However, it is evident that the city of Palermo is an outlier.

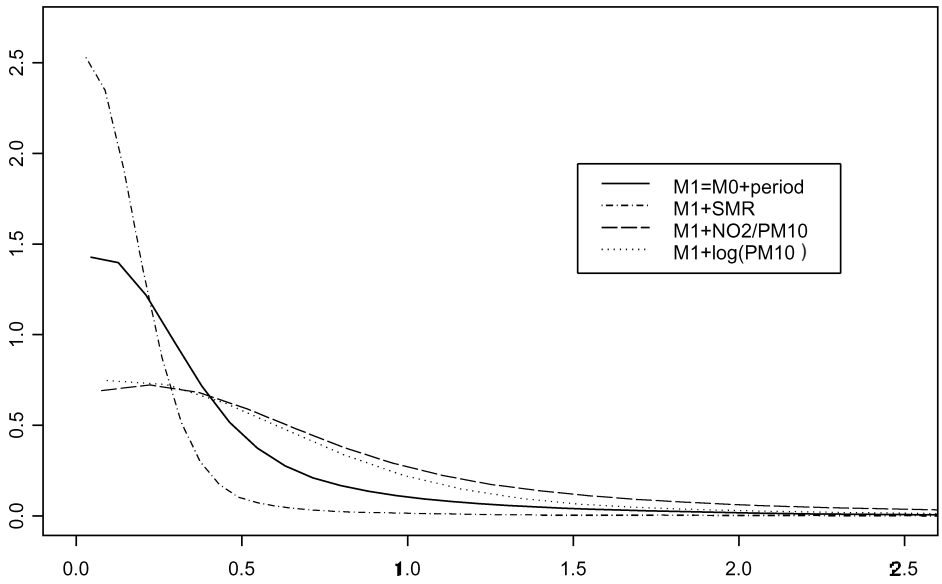
In the Bayesian meta-regressions, the city-specific explanatory variables were considered possible effect modifiers when they explained a substantial part of inter-city variability. Changes in posterior distributions of residual heterogeneity variance indicated that SMR was associated with greater effects of fine particles (Figure 4, Table 7). The overall effect on hospital admissions for cardiac diseases appears slightly modified by the NO_2/PM_{10} ratio. Negative meta-regression coefficients were found for the logarithm of mean PM_{10} concentration, indicating possible nonlinearity of the concentration–response curve (Figure 5). This effect is more evi-

TABLE 7 Results of Bayesian Meta-regressions of PM_{10} Effects on Total Mortality

Model	Coefficient (95% CrI)	One-side Probability	Residual Heterogeneity (95% CrI) ($\times 10^6$)	% Change (95% CrI)	
				1990–94	1995–99
Mortality from all natural causes					
M_0			0.419 (0.001,2.290)	0.78 (0.24,1.54)	
$M_1 = M_0$ + *Period**			0.256 (0.001,1.614)	0.60 (0.14,1.34)	0.90 (0.40,1.52)
M_1 + *SMR*	0.06 (0.02,0.11)	0.99	0.071 (0.001,0.447)		
M_1 + %Pop: > 65	–0.005 (–0.01,0.003)	0.91	0.303 (0.001,1.880)		
M_1 + *depr.index*	0.34 (–0.18,1.01)	0.93	0.516 (0.001,2.218)		
M_1 + NO_2	–0.01 (–0.05,0.05)	0.71	0.438 (0.001,2.730)		
M_1 + log(PM_{10})	–1.61 (–4.99,1.36)	0.89	0.327 (0.001,1.963)		
M_1 + NO_2/PM_{10}	0.56 (–1.69,4.14)	0.64	0.695 (0.002,3.910)		
M_1 + *Temp.*	0.20 (–0.06,0.56)	0.93	0.290 (0.001,1.648)		

*M_0 is the null model.

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



dent for mortality, where we found a posterior probability that the coefficient is less than 0 equal to 0.89. Greater risk estimates were calculated for the calendar period 1995–1999 for total mortality and cardiac morbidity, despite the lower average levels of air pollution observed.

In order to study the effect of fine particulate matter on total mortality by season in 1995–1999, two alternative Bayesian models were considered (see the Discussion), whose results are reported in Table 8. On the basis of the minimum DIC criterion, the most complex model seems to describe the problem better, highlight-

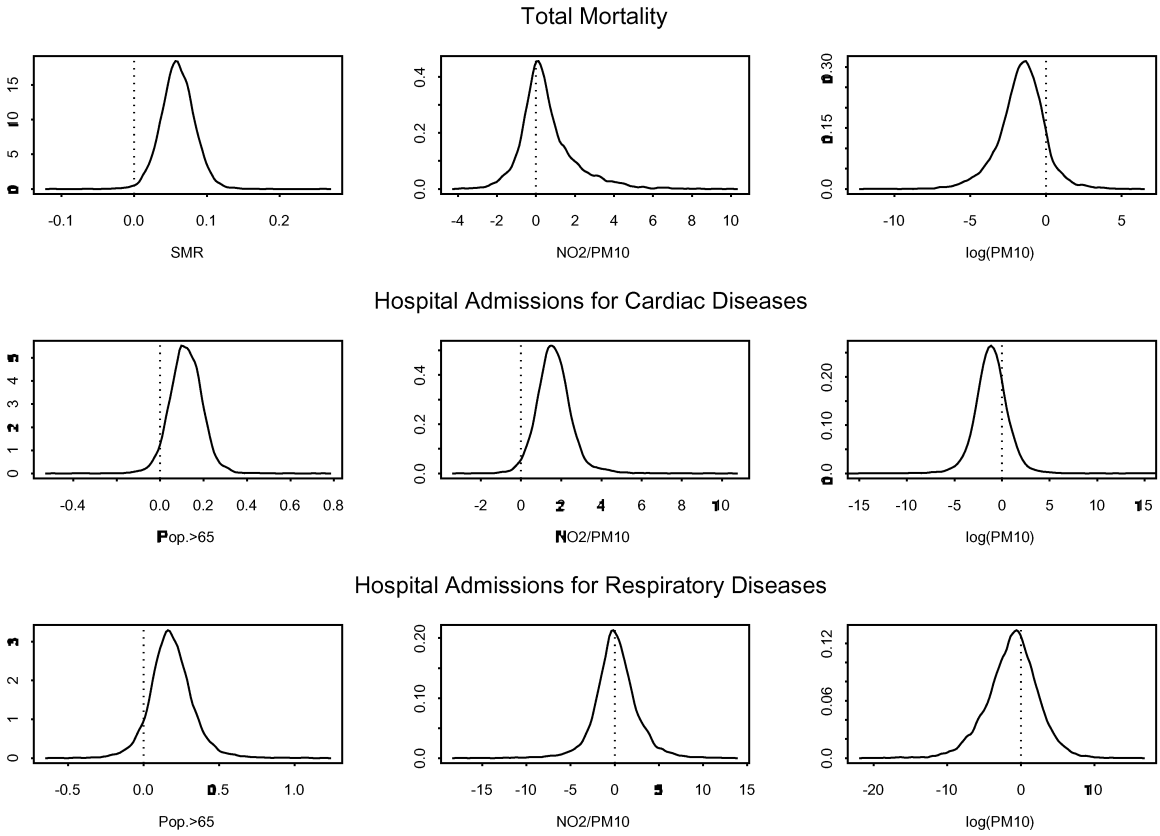


Figure 5—Posterior distributions of meta-regression coefficients of the effect modifiers for total mortality and hospital admissions for cardiac and respiratory diseases.

TABLE 8 Bayesian meta-analysis results of PM10 effect on total mortality in warm and cold seasons

Model	% Change (95% CrI)	Pr(% Change > 0)	KL (*q*)	Heterogeneity (95% CrI ($\times 10^6$))	DIC
$\lambda_{cs} = \beta_s + u_c + v_{cs}$					
Warm season	2.53 (1.30,3.85)	0.999	*ref.*	1.369 (0.015,6.756)	14.60
Cold season	0.54 (–0.21,1.35)	0.937	*ref.*	0.599 (0.009,3.064)	
$\lambda_{cs} = \beta_s + u_c$					
Warm season	2.43 (1.58,3.30)	≈ 1	0.157 (0.76)	0.436	22.66
Cold season	0.52 (–0.12,1.23)	0.953	0.017 (0.59)	(0.001,2.314)	

ing a significant difference of inter-city variability by season. As a sensitive analysis, we reported also the results of the simplest model, as it is sometimes preferable to estimate a single variance, rather than allowing heterogeneity to vary according to groups, especially when only few estimates are to be combined. The fine-particle effect appeared higher during the warm season (2.53%, 95% CrI: 1.30, 3.85, using the most complex model) than during the cold season (0.54%, 95% CrI: –0.21, 1.35). Figure 6 shows the posterior distributions of % changes associated with a 10 μg/m^3 increase of pollutant level obtained by the most complex model.

Results of the by-age analysis are reported in Table 9 and shown in Figure 7 (they refer to the period 1995–1999). The two models presented (see the Discussion below) are nearly equivalent in terms of DIC. Both of them allow different risks for young (< 65 years) and for elderly people (> 65 years), without making a distinction between the PM_{10} effects in the 65–74 and ≥ 75 year age classes. They provided similar overall effect estimates. Using the most complex model, the estimated % increase in mortality was 0.55 (–0.51, 1.74) for the young and 1.06 (0.21, 1.95) for the old, which suggests that the elderly are more susceptible to the effects of fine particles effect.

DISCUSSION

Methodologic Issues

MISA has been the first attempt to investigate systematically the short-term effects of air pollution in an important segment of the Italian population. It enrolled an overall population of 7 million and included all the major Italian cities, with the exception of Naples. Its originality consisted in the fact that—although the study was based retrospectively on existing databases—city-specific datasets were created through the retrieval of data with standard criteria and the analysis was based on a common protocol derived from a structured exploratory analysis. This allowed

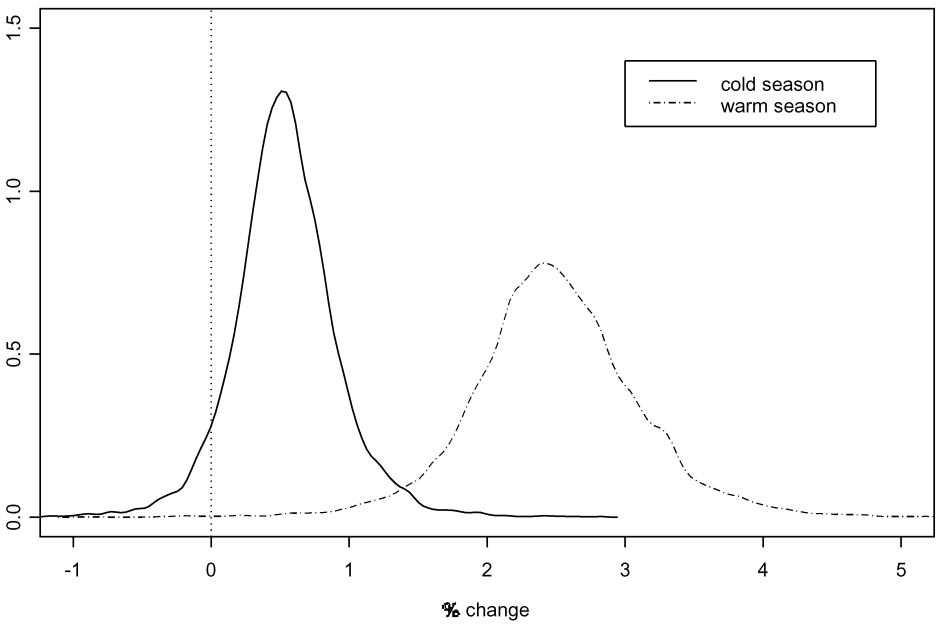


Figure 6—Posterior distributions of PM_{10} effects on total mortality in cold and warm seasons.

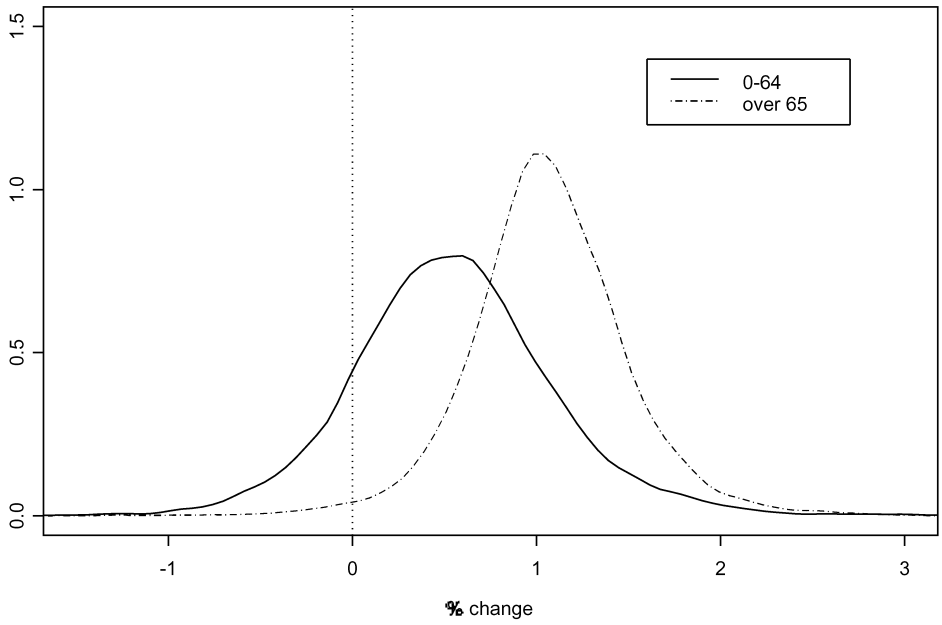


Figure 7—Posterior distributions of PM_{10} effects on total mortality for young (≤ 65 years) and elderly (65+ years) people.

for credible inter-city comparisons and satisfied a major requirement for the reliability of the overall meta-analysis.

A major strength of MISA is that it included cities that had been identified a priori, with unbiased criteria, on the basis of the availability of data and of the interest of local investigators. This has been the case also for two recent major studies based on temporal series, i.e., the European study known as APHEA[3,18] and the NMMAPS study in the United States,[1] as well as for national metanalyses in other countries such as Canada,[19] China,[20] France,[21] Germany,[22] Japan,[23] Korea,[24] The Netherlands,[25] Spain,[26,29] and large cities studies in Brazil[30–33] and Mexico.[34–36]

In order to obtain an overall picture of air-pollution effects for the eight cities included in the study, the classical methods of meta-analysis were used. Given the importance of exposures to fine particulate matter that has been postulated,[37] more detailed analyses were conducted on this pollutant, fitting meta-analytic hierarchical Bayesian models. Finally, particular importance was given to the choice of the models and to sensitivity analyses of the results.

In spite of the attention given to these methodologic features and of the sophistication of the statistical approach, the study—like other comparable metanalyses—may have been affected by a number of sources of imprecision and bias. In the first place, in each city, the number of monitoring stations was small and their representativeness of the actual pollution of the residents' atmosphere was limited. Not all monitoring stations provided data on the atmospheric concentrations of PM_{10}, different analytic methods for this pollutant were used in different cities, and different conversion coefficients were applied. These discrepancies may have contributed to variability of findings between cities.

As for outcomes, the mortality data are excellent for deaths from all natural causes and good for deaths from the large groups of cardiovascular and respiratory causes. On the other hand, and although the study protocol was accurate with regard to the selection of hospital admissions for acute conditions, the overall quality of hospital admission data and their comparability throughout Italian regions have not yet been properly assessed in the calendar period covered by our study. In addition, the filing criteria for admissions for acute conditions changed around 1995, so that the credibility of temporal comparisons in Turin, Milan, and Rome is limited. Further, hospital admissions rely on the availability of beds, the offer of which may be restricted during the summer. These factors might explain the fact that the heterogeneity between cities seems to be greater in the analyses of hospital admissions that in the analyses of mortality.

Another limitation of the analysis consists in having fitted models with only one pollutant at a time. On the basis of some results suggesting confounding between NO_2 and PM_{10},[1,18] bipollutant models might have been appropriate for PM_{10}. However, since the pollutants showed high collinearity, the statistical stability of estimates obtained through multivariate analyses would have been compromised. In addition, some reports are reassuring about the existence and extent of confounding.[38]

In the regression models, pollutants were introduced as simple linear terms. The issue of potential nonlinearity of the dose–response curve has not been addressed. On the other hand, for each pollutant, the range of concentrations was not particularly wide and, more important, we tested for nonlinearity in the meta-regression phase. This approach is consistent with previous findings, with which our results are directly comparable.[39–41]

TABLE 9 Bayesian meta-analysis results of PM10 effect on total mortality by age*

Model	% Change (95% CrI)	Pr(% Change > 0)	KL (*q*)	Heterogeneity (95% CrI ($\times 10^6$))	DIC
$\lambda_{cs} = \beta_h + u_c + v_{ch}$					
0–64 years	0.55 (–0.51,1.74)	0.862	*ref.*	0.873 (0.009,4.484)	12.44
65+ years	1.06 (0.21,1.95)	0.987	*ref.*	0.843 (0.021,3.749)	
$\lambda_{cs} = \beta_h + u_c$					
0–64 years	0.51 (–0.47,1.52)	0.852	0.014 (0.58)	0.669	13.40
65+ years	1.08 (0.33,1.92)	0.993	0.015 (0.59)	(0.004,3.299)	

Particular attention has been given to modeling issues. A justification of the methods used in the city-specific analysis is reported elsewhere.[42] In short, natural cubic splines for season were used to assure unbiased estimates of the effects of pollutants and their standard errors instead of generalized additive models via backfitting or penalized likelihood. A sensitivity analysis has been previously reported.[17]

Findings

Beyond these methodologic aspects, results of the Italian meta-analysis definitely provide additional evidence of an association between air pollution and early mortality or morbidity. The meta-analysis has shown a clearcut and statistically significant association between the concentration of each of the five pollutants and most of the endpoints included in the study, i.e., daily mortality for all natural causes, mortality for cardiovascular and for respiratory conditions, hospital admissions for heart conditions and for respiratory conditions. All effects were stronger in the elderly. As for mortality, the only estimates that were not statistically significant regarded the associations between both PM_{10} and ozone and mortality from respiratory causes. As for hospital admissions, only the associations among ozone and the endpoints considered were not statistically significant. Although the concentrations of pollutants were higher in the early 1990s compared with later years, many associations (i.e., the percentage changes of the endpoints associated with unit increments of individual pollutants) were stronger in the latter than in the former period.

Compared with estimates in the United States[4] and in the multicentric APHEA-2 European study (which included countries in both Northern and Southern Europe), the size of the effect seems to be greater in Italy. However, the PM_{10} characterization in MISA is not comparable to that in APHEA.

Interestingly, MISA indicates a North–South gradient in Italy. The nature of the factors that could be responsible for the stronger effect associated with a warmer-climate difference can only be postulated. It has been pointed out that in warmer areas people live a greater number of days with open windows.[5] An effect modification from high temperature (and perhaps other meteorologic features typical of the hot season) is another possibility.

In the present study, the interaction between pollution and seasonality was investigated only for PM_{10} and only for total mortality. Although estimates differed between cities, all showed higher risks during the summer months. The ratio between the effect during the warm months and the corresponding effect during the cold months was highest in cities in Northern Italy.

For all pollutants, the associations with mortality from all natural causes were stronger after 75 years of age than earlier in life. As suggested by others,[43] it is obvious that there are particularly vulnerable segments of the population, and that the elderly are one of these. The test of heterogeneity of a role of age in determining the effects was statistically significant for CO and PM_{10} but not for SO_2 and NO_2.

In the three towns for which comparisons between early and late 1990s were possible, a time-related trend towards decreases in the concentrations of all air pollutants was obvious (Table 2). The decrease was marked (about 50%) for SO_2, and more limited for the other pollutants. In the late 1990s, in the eight cities, the medians of the daily average concentrations of PM_{10} ranged from between 31 μg/cm to 58 μg/cm. Although these values may have been affected by the limits of the analytic methods used, most of them were above the annual average of 40 μg/cm indicated by the EU directive 1999/30/CE of April 22, 1999.

There were some variations in the delays of the appearance of early effects of changes in the concentrations of pollutants. As for mortality, higher and more stable risk estimates were identified with a lag of 1–2 days than with a shorter interval. On the other hand, the greatest effects on hospital admissions were observed in relation to the average concentrations during the three preceding days.

Interpretation and Future Perspectives

Two major limitations of MISA are that the study was based on aggregated data, thus allowing for some sort of ecologic bias, and that the analyses were carried out separately for each of the five pollutants. Nevertheless, most findings were consistent (at least in terms of the sign of the association) between Italian cities, and the results of the Italian meta-analysis are consistent with other European and North American estimates. A 10 μg/cm increment in the concentration of SO_2, NO_2, or PM_{10} and a 1 μg/cm increment for CO are associated with increases of all endpoints ranging between 0.9% and 1.4%. Thus, MISA provides additional and independent evidence of the association between air pollution and the early endpoints considered.

On the other hand, results of a meta-analysis based on data from eight towns are reliable to the extent to which heterogeneity between towns is relatively low. This seems to be the case for most variables related to mortality, with the exception of effects of PM_{10} (which were particularly strong in Palermo). However, most estimates regarding hospital admissions are based on heterogeneous findings, and part of this heterogeneity can be attributed to differences in the quality of the raw data.

In the present analysis, temperature and humidity were considered as possible confounding variables. However, in the association between air pollution and health, their roles might be more complex. The effect of temperature on health is nonlinear, and it might differ between areas with different climates, such as Italian regions. In addition to their obvious impacts on lifestyle (number of hours spent in open spaces), temperature and humidity might physico-chemically modify dusts and their effects.

In conclusion, the methodologic issues raised by MISA and similar studies, the identification of new and hitherto unraveled features of the association between air pollution and health, and the need for a wider knowledge of risks associated with public health in Italy warrant the implementation of larger studies, which in fact are on the way.

Given the uncertainties (not all of which are statistical) of MISA, it was decided not to attempt to estimate the numbers of deaths and other health events attributable to air pollution in the cities included in the study. However, the severity of the problem of air pollution, in terms of public health, can be assessed through a comparison of current levels of individual pollutants and the limits indicated by the 1999 Directive of the European Union. We hope that MISA will contribute to increasing the awareness of Italian health authorities of the need for prompt action.

Appendix

The Kullback–Leibler distance between two distributions $f_0(t)$ and $f_1(t)$, taking $f_0(t)$ as reference, is given by:

$$KL_{f_0}(f_0, f_1) = \int \log \frac{f_1(t)}{f_0(t)} f_0(t)\, dt$$

To obtain a simple approximation of the Kullback–Leibler distance, we supposed that the posterior distribution of the overall effect was Normal. Let f_0 and f_1 represent the posterior distributions of β obtained, respectively, by the reference and the alternative model. We calculated:

$$KL_{f_0}(f_0, f_1) = 0.5 \times \left(\frac{(m_1 - m_0)^2}{s_1^2} + \frac{s_0^2}{s_1^2} - \log \frac{s_0^2}{s_1^2} - 1\right)$$

where m_k and s_k^2 are, respectively, the mean and the variance of f_k $(k = 0; 1)$.

To better appreciate the amount of $KL_{f_0}(f_0, f_1)$ a calibration method was applied.[44] Let $B(p)$ represent the Bernoulli distribution with parameter p. Given a calculated distance d, we calibrated it by the probability q such that:

$$d = KL_{B(0.5)}(B(0.5),\ B(q))$$

$$0.5 \le q \le 1$$

It can be shown that:

$$q = 0.5 + 0.5(1 - \exp^{-2d})^{0.5}$$

Values of q around 0.5 correspond to low sensitivity of inference, and values close to 1 correspond to substantial changes in results.

Italian MISA Group members are Daniele Agostini, Ettore Artioli, Michela Baccini, Emanuela Barletta, Aldo Bellini, Pierantonio Bellini, Giovanna Berti, Roberto Bertollini, Annibale Biggeri, Marco Biocca, Luigi Bisanti, Francesca Bruno, Ennio Cadum, Stefano Cattani, Giulia Cavrini, Elisabetta Chellini, Monica Chiogna, Luisa Cortinovis, Rosanna Cusimano, Moreno Demaria, Marco Deserti, Valeria Fano, Gabriella Filippazzo, Francesco Forastiere, Francesco Fortezza, Catia Gabellini, Claudia Galassi, Pier Carlo Ghiselli, Daniele Grechi, Mauro Grosa, Corrado Lagazio, Gianfranco Lovison, Marco Martuzzi, Paola Michelozzi, Rossella Miglio, Vito Muggeo, Andrea Oliani, Carlo A. Perucci, Giuseppe Rossi, Riccardo Tardiani, Benedetto Terracini, Stefano Tibaldi, Eleonora Verdini, Maria Angela Vigotti, Marcello Vultaggio, and Carlo Zocchetti.

References

1. Samet JM, Zeger SL, Dominici F, et al. The national morbidity, mortality, and air pollution study. Part II: Morbidity and mortality from air pollution in the United States (with discussion). Res Rep Health Effects Institute. 2000;94:5-79.
2. Atkinson RW, Anderson HR, Sunyer J, et al. Acute effects of particulate air pollution on respiratory admissions: results from APHEA 2 project. Air pollution and health: a European approach. Am J Respir Crit Care Med. 2001;164:1860-6.
3. Katsouyanni K, Touloumi G, Samoli E, et al. Confounding and effect modification in the short-term effects of ambient particles on total mortality: results from 29 European cities within the APHEA2 project. Epidemiology. 2001;12:521-31.
4. HEI Health Effect Institute. Revised Analyses of Time Series Studies of Air Pollution and Health. Health Effect Institute Special Report, Boston, MA, 2003.
5. Biggeri A, Bellini P, Terracini B. Meta-analysis of the italian studies on short-term effects of air pollution. Epidemiologia e Prevenzione. 2001;25:2 suppl: 1-72.
6. Biggeri A, Baccini M, Accetta G, Lagazio C. Estimates of short-term effects of air pollutants in Italy. Epidemiologia e Prevenzione. 2002;26:203-5.

7. Cattani S, Galassi C, Gruppo ITARIA. Database of air pollution and air quality indicators for the principal Italian cities: the ITARIA-WHO project. Annali dell'Istituto Superiore di Sanit´a. 2000;36:275-83.
8. Dominici F. Air pollution on health: what can we learn from an hierarchical approach? Invited Commentary, Am J Epidemiol. 2002;155:1-5.
9. DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled Clinical Trials. 1986;7:177-88.
10. Spiegelhalter DJ, Thomas A, Best NG, Gilks WR. BUGS: Bayesian Inference Using Gibbs Sampling. Medical Research Council Biostatistics Unit, Cambridge, England, 1996.
11. Gelman A, Rubin DR. Inference from iterative simulation using multiple sequence (with discussion). Statistical Science. 1992;7: 457-511.
12. Sutton AJ, Abrams KR. Bayesian methods in meta-analysis and evidence synthesis. Statistical Methods Med Res. 2001;10:277-303.
13. Gaver DP, O'Muircheartaigh IG. Robust empirical Bayes analyses of event rates. Technometrics. 1987;29:1-15.
14. Cadum E, Costa G, Biggeri A, Martuzzi M. Deprivazione e mortalitá. Epidemiologia e Prevenzione. 1999;23:175-87. [In Italian]
15. Goldberg MS, Bailar JC, Burnett RT, et al. Identifying subgroups of the general population that may be susceptible to short term increase in particulate air pollution: a time series study in Montreal, Quebec. Research Report HEI. 2000;97:1-126.
16. Spiegelhalter DJ, Best NG, Carlin BP, van der Linde A. Bayesian measures of model complexity and fit (with discussion). J Royal Statistical Society. 2002;B.64:583-639.
17. Baccini M, Biggeri A, Accetta G, Lagazio C, Lertxundi A, Schwartz J. Estimates of the short term effects of air pollution in Italy using alternative modelling techniques. In: Biggeri, Dreassi, Lagazio, Marchi (eds). Statistical Modelling. Florence, Italy: Firenze University Press, 2004; 301-5.
18. Katsouyanni K, Schwartz J, Spix C, et al. Short term effects of air pollution on health: a European approach using epidemiologic time series data: the APHEA protocol. J Epidemiol Community Health. 1996;50:(suppl 1):S12-S18.
19. Burnett RT, Cakmak S, Brook JR. The effect of the urban ambient air pollution mix on daily mortality rates in 11 Canadian cities. Can J Public Health. 1998;89:152-6.
20. Aunan K, Pan X-C. Exposure-response functions for health effects of ambient air pollution applicable for China—a meta-analysis. Science of the Total Environment. 2004;329:3-16.
21. Zeghnoun A, Eilstein D, Saviuc P, et al. Monitorig of short-term effects of urban air pollution on mortality. Results of a pilot study in 9 French cities. Rev Epidemiol Sante Publique. 2001; 49:3-12.
22. Wichmann H-E, Spix C, Tuch T, et al. Daily Mortality and Fine and Ultrafine Particles in Erfurt, Germany. Part I: Role of Particle Number and Particle Mass. Research Report 98. Health Effects Institute, Cambridge, MA, 2000.
23. Omori T, Fujimoto G, Yoshimura I, Nitta H, Ono M. Effects of particulate matter on daily mortality in 13 Japanese cities. J Epidemiol. 2003;13:314-22.
24. Lee JT, Kim H, Hong YC, Kwon HJ, Schwartz J, Christiani DC. Air pollution and daily mortality in seven major cities of Korea, 1991–1997. Environ Res. 2000;84:247-54.
25. Hoek G, Brunekreef B, Verhoeff A, van Wijnen J, Fischer P. Daily mortality and air pollution in The Netherlands. J Air Waste Management Association. 2000;50:1380-9.
26. Ballester Diez F, Saez Zafra M, Perez-Hoyos et al. The EMECAM project: a discussion of the results in the participating cities. Estudio Multicentrico Espanol sobre la Relacion entre la Contaminacion Atmosferica y la Mortalidad. Revista Espanola de Salud Publica. 1999;73:303-14.
27. Ballester F, Saez M, Perez-Hoyos S, et al. The EMECAM project: a multicentre study on air pollution and mortality in Spain: combined results for particulates and for sulfur dioxide. Occup Environ Med. 2002;59:300-8.
28. Ballester F, Iniguez C, Saez M, et al. Short-term relationship between air pollution and mortality in 13 Spanish cities. Med Clin North Am. 2003;121:684-9.
29. Saez M, Ballester F, Barcelo MA, et al. A combined analysis of the short term effects of photochemical air pollutants on mortality within the EMECAM project. Environ Health Perspect. 2002;110:221-8.
30. Brilhante OM, Tambellini AM. Particulate suspended matters and cases of respiratory disease in Rio de Janeiro city (Brazil). Int J Environ Health Res. 2002;12:169-74.
31. Lin CA, Amador Pereira LA, de Souza Conceicao GM, et al. Association between air pollution and ischemic cardiovascular emergency room visits. Environ Res. 2003;92:57-63.
32. Daumas RP, Mendonca GA, Ponce de Leon A. Air pollution and mortality in the elderly in Rio de Janeiro: a time-series analysis. Cad Saude Publica. 2004;20:311-9.
33. Martins MC, Fatigati FL, Vespoli TC, Martins LC, Pereira LA et al. Influence of socioeconomic conditions on air pollution adverse health effects in elderly people: an analysis of six regions in Sao Paulo, Brazil. J Epidemiol Community Health. 2004;58:41-6.
34. Loomis DP, Borja-Aburto VH, Bangdiwala SI, Shy CM. Ozone exposure and daily mortality in Mexico City: a time-series analysis. Research Report 75. Health Effects Institute, Boston, MA, 1996. 1-37; discussion 39-45.
35. Borja-Aburto VH, Loomis DP, Bangdiwala SI, Shy CM, Rascon-Pacheco RA. Ozone, suspended particulates, and daily mortality in Mexico City. Am J Epidemiol. 1997;145:258-68.
36. O'Neill MS, Loomis D, Borja Aburto VH, Gold D, Hertz-Picciotto I, Castillejos M. Do associations between airborne particles and daily mortality in Mexico City differ by measurement method, region, or modeling strategy? J Expo Anal Environ Epidemiol Epub ahead of print doi:10.1038/sj.jea.7500341, 2004.
37. National Research Council. Research Priorities for Airborne Particulate Matter: IV. Continuing Research Progress. Washington, DC, National Academy Press, 2004.
38. Sarnat JA, Schwartz J, Catalano PJ, Suh HH. Gaseous pollutants in particulate matter epidemiology: confounders or surrogates? Environ Health Perspect. 2001;109:1053-61.
39. Schwartz J, Zanobetti A. Using meta-smoothing to estimate dose-response trends across multiple studies, with application to air pollution and daily death. Epidemiol. 2000;11:666-72.
40. Daniels MJ, Dominici F, Samet JM, Zeger SL. Estimating particulate matter–mortality dose–response curves and threshold levels: an analysis of daily time-series for the 20 largest US cities. Am J Epidemiol. 2000;152:397-406.
41. Schwartz J, Ballester F, Saez M, et al. The concentration response relation between air pollution and daily deaths. Environ Health Perspect. 2001;109:1001-6.
42. Saez M, Baccini M, Biggeri A, Lertxundi A. Parametric and semi-parametric approaches in the analysis of short-term effects of air pollution on health. In: Biggeri, Dreassi, Lagazio, Marchi (eds). Statistical Modelling, Florence, Italy: Firenze University Press, 2004, 58-62.
43. Schwartz J. What are people dying of on high air pollution days? Environ Res. 1994;64:26-35.
44. McCulloch R. Local model influence. J Am Statistical Assoc. 1989;84:473-8.