Environmental Research 147 (2016) 415–424

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Air pollution exposure, cause-specific deaths and hospitalizations in a highly polluted Italian region

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ARTICLE INFO

Article history:
Received 23 October 2015
Received in revised form
1 March 2016
Accepted 2 March 2016
Available online 9 March 2016

Keywords:
Air pollution
Mortality
Hospital admissions
Particulate matter
Nitrogen dioxide
Bayesian analysis

ABSTRACT

Background: The Lombardy region in northern Italy ranks among the most air polluted areas of Europe. Previous studies showed air pollution short-term effects on all-cause mortality. We examine here the effects of particulate matter with aerodynamic diameter ≤ 10 μm (PM_{10}) and nitrogen dioxide (NO_2) exposure on deaths and hospitalizations from specific causes, including cardiac, cerebrovascular and respiratory diseases.

Methods: We considered air pollution, mortality and hospitalization data for a non-opportunistic sample of 18 highly polluted and most densely populated areas of the region in the years 2003–2006. We obtained area-specific effect estimates for PM_{10} and NO_2 from a Poisson regression model on the daily number of total deaths or cause-specific hospitalizations and then combined them in a Bayesian random-effects meta-analysis. For cause-specific mortality, we applied a case-crossover analysis. Age- and season-specific analyses were also performed. Effect estimates were expressed as percent variation in mortality or hospitalizations associated with a 10 $\mu g/m^3$ increase in PM_{10} or NO_2 concentration.

Results: Natural mortality was positively associated with both pollutants (0.30%, 90% Credibility Interval [CrI]: −0.31; 0.78 for PM_{10}; 0.70%, 90%CrI: 0.10; 1.27 for NO_2). Cardiovascular deaths showed a higher percent variation in association with NO_2 (1.12%, 90% Confidence Interval [CI]: 0.14; 2.11), while the percent variation for respiratory mortality was highest in association with PM_{10} (1.64%, 90%CI: 0.35; 2.93). The effect of both pollutants was more evident in the summer season. Air pollution was also associated to hospitalizations, the highest variations being 0.77% (90%CrI: 0.22; 1.43) for PM_{10} and respiratory diseases, and 1.70% (90%CrI: 0.39; 2.84) for NO_2 and cerebrovascular diseases. The effect of PM_{10} on respiratory hospital admissions appeared to increase with age. For both pollutants, effects on cerebrovascular hospitalizations were more evident in subjects aged less than 75 years.

Conclusions: Our study provided a sound characterization of air pollution exposure and its potential effects on human health in the most polluted, and also most populated and productive, Italian region, further documenting the need for effective public health policies.

1. Introduction

Northern Italy ranks among the top most polluted areas of Europe (EEA, 2014). The Lombardy region is the geographic and economic epicenter of this area, with more than 10 million residents and the highest gross domestic product per inhabitant of the country (RSY, 2015). Most of its major cities are located in the basin of the Po River, which crosses the entire region. The basin is bordered on three sides by mountains which render air mass exchange very low. Wind speed measured in the Po River plain is among the lowest in Europe, causing frequent phenomena of thermal inversion and trapping of smog and pollution close to the ground. In addition, Lombardy counts many industrial facilities as well as small and medium enterprises for which road transport is an essential component for economic viability (non-industrial combustion plants and road transport represent more than 60% of particulate matter emission sources in the region, Supplementary Table 1). Overall, its unfavorable geographical context, climate

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http://dx.doi.org/10.1016/j.envres.2016.03.003

characteristics, land use and emission sources create a high level of air pollution.

The short-term health effects of exposure to air pollution are well established. Many studies documented, in Europe as well as elsewhere, an association between ground levels of both particulate and gaseous pollutants and health outcomes, measured as deaths and/or hospitalizations (Analitis et al., 2006; Ballester et al., 2006; Biggeri et al., 2004; Samoli et al., 2006; Samoli et al., 2008; Samoli et al., 2013; Stafoggia et al., 2013; WHO, 2013). The 2010 Global Burden of Disease study found that outdoor air pollution in the form of fine particles is the ninth-leading cause of premature death and ill health (IHME, 2015) and ranks first among the environmental risk factors for health (Hanninen et al., 2014). Many health outcomes have been investigated. Respiratory and especially cardiovascular effects (in terms of both mortality and hospital admissions) are supported by the stronger evidence of association with air pollution exposure (Anderson et al., 2012; Mannucci et al., 2015).

Previous studies on particulate matter exposure and all-cause mortality have already addressed the magnitude of the effects of air pollution exposure on human health in Lombardy (Baccini et al., 2011), accounting also for between-city commuting (Baccini et al., 2015). These studies documented a clear effect of PM_{10} exposure on all-cause mortality, with a maximum observed for the capital city of Milan.

In this study we expanded the set of investigated causes and air pollutants considered. We selected the most polluted and densely populated areas of Lombardy, whose exposure to particulate matter with aerodynamic diameter $\leq 10\ \mu m$ (PM_{10}) and nitrogen dioxide (NO_2) is measured by a network of air quality monitoring stations, and examined air pollution short-term effects on all-cause and cause-specific deaths and hospital admissions.

2. Materials and methods

2.1. Data

We considered air pollution, mortality and hospital admission data for the period 2003–2006 for 18 areas: 16 cities with more than 50,000 inhabitants, 1 small town, Sondrio (yet the largest in the Alpine administrative province), and all of the municipalities within the agricultural district of Lodi, collapsed into a single epidemiologic time series (Fig. 1). The air quality monitoring network of the Lombardy Regional Environmental Protection Agency (ARPA) provided the daily time series of PM_{10} and NO_2 measurements, temperature, and relative humidity values. The monitoring network provided the background levels of PM_{10} and NO_2. For each area separately we considered the stations not influenced by traffic and located within the municipality boundaries. We then imputed the missing daily values at one of these monitors using concentrations measured by the remaining monitors in the same area, and we obtained a daily time series of pollutant levels for each area by averaging data over the available monitors. A detailed description of the exposure assessment procedure can be found in Biggeri et al. (2005). Death certificates were retrieved from the regional mortality register. We considered mortality from all natural causes, excluding external causes (International Classification of Diseases, Ninth Revision, ICD-9 codes below 800), and we distinguished between cardiovascular mortality (ICD-9 390–459) and respiratory mortality (ICD-9 460–519). For each area, we focused on daily numbers of cause-specific deaths occurring in the

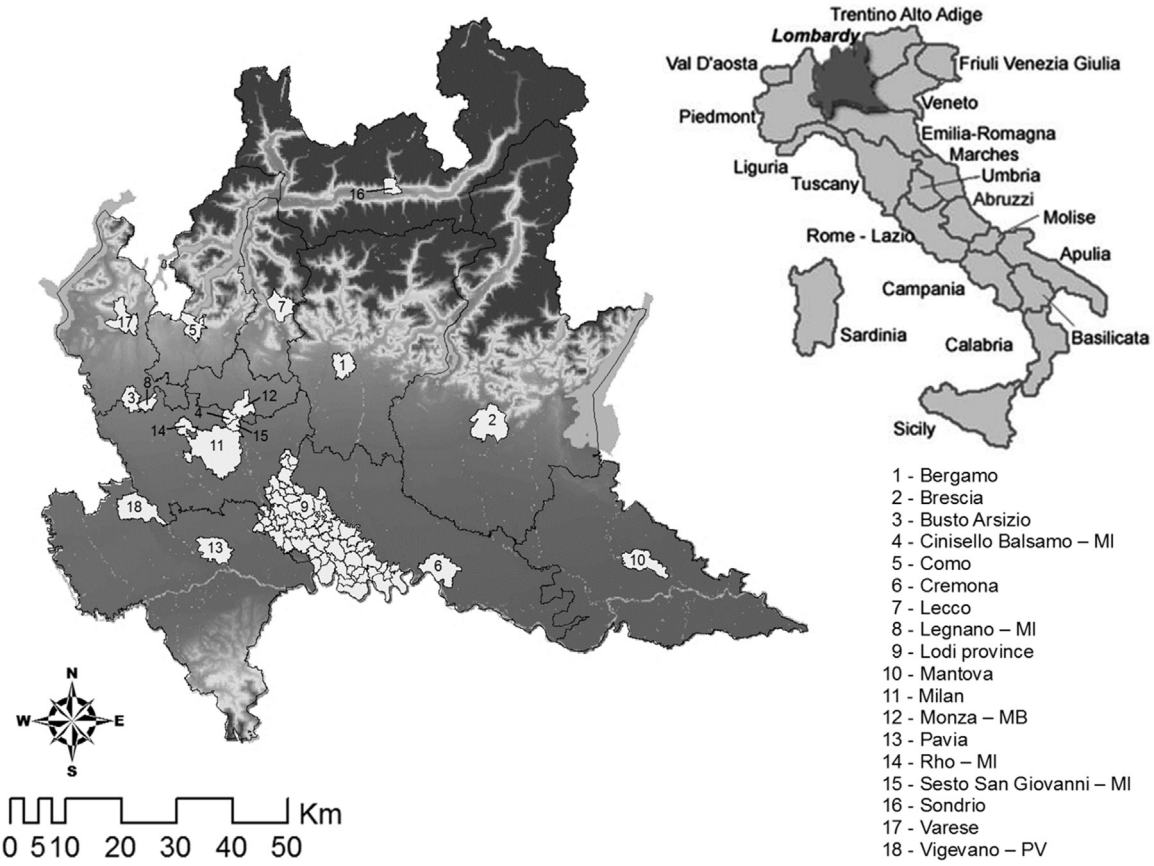

Fig. 1. The Lombardy region of Italy. The study areas included in the analysis of short-term effects of particulate matter $\leq 10\ \mu m$ in diameter (PM_{10}) and nitrogen dioxide (NO_2) are highlighted in white.

resident population inside the areas. Hospital admissions were obtained from the regional hospital admission register. We considered hospital discharge records with cardiac (ICD-9CM 390–429), cerebrovascular (ICD-9CM 430–439), and respiratory diagnoses (ICD-9CM 460–469, 480–519, except 487). For each area, we focused on the daily number of cause-specific hospital admissions occurring among the resident population in hospitals located inside the residence area itself or in municipalities within 10-km from its border.

2.2. Effect estimates

For total mortality and cause-specific hospital admissions, the analysis of short-term effect for PM_{10} and NO_2 has been developed in two steps: at the first stage we obtained the area-specific effect estimates for PM_{10} (13 areas) and NO_2 (18 areas) from a Poisson regression model on the daily number of deaths or hospital admissions; at the second stage we combined these estimates in a Bayesian random-effects meta-analysis. For cause-specific mortality, we could not obtain reliable first-stage estimates using a Poisson regression in those areas where the number of daily events was too small. We thus applied a single overall analysis on the data from all the areas (see Section 2.2.3 for further details).

2.2.1. Area-specific analysis

For each area, we specified Poisson regression models for the daily number of deaths and hospital admissions, following an approach similar to the one used to estimate the short-term effect of atmospheric pollution in Italy (Biggeri et al., 2005, 2004, 2001). The models were age-adjusted (<65, 65–74, ≥ 75 years). In order to remove the confounding effect of medium and long-term time trend and to account for the different influence of seasonality on health outcomes by age, we introduced in the regression model, for daily mortality, an indicator of season for the first two age classes and a regression spline with 5 degrees of freedom per year on calendar day for the elderly. In the hospital admission analysis, we used three different regression splines with 7, 5, and 7 degrees of freedom per year for the three age classes, respectively.

We included in the models a week-day indicator (specific for each age class in case of hospital admissions), to adjust for short-term time trend. We accounted also for holidays with an appropriate dummy variable.

The models accounted for possible peaks of events during flu epidemic days, defined as the days registering a number of influenza-related hospital admissions exceeding a predefined threshold in the entire Lombardy region.

To control for meteorological conditions, we included in the models both temperature and humidity. In the mortality analysis, the temperature effect was modeled by two linear terms for the mean temperature of the previous three days (lag 1–3), constrained to join at 21 °C, and by a linear term for the difference between temperature at lag 1–3 and current day temperature. In the hospital admission analysis, the effect of temperature was modeled by one single linear term for the mean temperature of the current day and the previous three days (lag 0–3). In both cases we considered the interaction between temperature and age. Relative humidity was included in the model through a linear and a quadratic term in the mortality analysis, and through one single linear term in the hospital admission analysis.

To control for the decrease of population at risk during summer plant shutdowns, we included in the models a dummy variable for the period July 15th–August 15th.

Exposure to PM_{10} and NO_2 was measured as mean of the pollutant levels in the current and in the previous day (lag 0–1) for the mortality analysis, and as mean of the pollutant levels in the current and in the previous three days (lag 0–3) for the hospital admission analysis. We modeled both PM_{10} and NO_2 effects using a linear term. Separated models were specified for each of the two pollutants.

The effects of the two pollutants by age class and season (hot season: May 1st–September 30th; cold season: October 1st–April 30th) were also estimated by including suitable interaction terms in the models.

2.2.2. Meta-analysis

At the second stage of the analysis, we combined the area-specific estimates through a Bayesian random-effects meta-analysis (Sutton and Abrams, 2001). Let $\hat{\beta}_i$ be the estimated coefficient expressing the short-term effect of the air pollutant arising from the Poisson model for the area i, and $\hat{\sigma}_i^2$ the corresponding estimated variance. The random-effects meta-analysis model assumes that:

$$\hat{\beta}_i = \beta_i + \varepsilon_i \quad \varepsilon_i \sim N\left(0, \hat{\sigma}_i^2\right)$$

$$\beta_i = \beta + u_i \quad u_i \sim N\left(0, \tau^2\right)$$

$i = 1,2,\ldots n$, where n is the number of the enrolled areas, β is the overall effect, β_i is the mean effect at the area level, τ^2 is the variability of β_i around β (between-area variance), ε_i and u_i are random noises normally distributed and mutually independent. Under the Bayesian approach, we specified *a priori* flat distributions for the overall effect β and the between-area variance τ^2; then we obtained a sample from the joint posterior distribution of β, τ^2 and the area-specific effects β_i, by using WinBUGS software (Lunn et al., 2000).

To evaluate the amount of heterogeneity in the meta-analysis, we calculated the I^2 index, corresponding to the percentage of total variability attributable to between-area variance.

Separated meta-analyses were performed for the effects of PM_{10} and NO_2 on mortality for all natural causes and hospital admissions for cardiac, cerebrovascular and respiratory diseases.

Effect estimates were expressed in terms of percent variation in mortality or hospital admissions associated with a 10 $\mu g/m^3$ increase in PM_{10} or NO_2 concentrations. The posterior distributions of overall effects and area-specific effects arising from the Bayesian meta-analyses were summarized through their posterior mean and their 90% and 50% credibility intervals (i.e. the ranges included between the 5th and 95th percentiles and the 1st and 3rd quartiles of the posterior distribution, respectively) (Louis and Zeger, 2009; Sterne and Davey Smith, 2001). We also obtained the posterior distributions of the heterogeneity statistics I^2 (Higgins and Thompson, 2002).

2.2.3. Case-crossover analysis

In order to estimate the effect of PM_{10} and NO_2 on cause-specific mortality we applied a case-crossover analysis (Hajat, 2003). Within area, for each day we selected controls defined as all other days in the stratum (same day of the week, month, and year as the index day) in which the index day fell. This time-stratified approach allowed us to adjust by design for medium and long-term time trend and day of the week (Janes et al., 2005). Then we specified a conditional logistic regression on the age-specific daily counts. We included in the model an indicator of age class and all terms already included in the Poisson regression specified for total mortality, excluding those used for modeling time-related confounding. The overall air pollutant effect was estimated including in the model a linear term common to all areas. We also estimated the pollutant effect by age class and season, by including suitable interaction terms in the conditional logistic regression model. As a matter of fact, a case-crossover analysis following a time-stratified approach defined as we did is equivalent to a Poisson regression

analysis where seasonality is accounted for through an interaction term between area, year, month and day of the week (Lu and Zeger, 2007). Despite the sparse number of daily events, the model was stable, as based on the entire area information. This approach assumes homogeneity of the effect among areas and returns one single overall estimate.

Effect estimates were thus expressed as percent variation in cardiovascular or respiratory deaths associated with a 10 $\mu g/m^3$ increase in PM_{10} or NO_2 concentrations, with corresponding 90% and 50% confidence intervals.

2.3. Confidence intervals reporting

In the abstract we selected 6 effect estimates over the 12 presented in the paper. Now, while the credibility/confidence intervals given in the body of the text are valid, since they are listed together with all the others, the same cannot be said of the subgroup reported in the abstract. The uncertainty due to the selection process is not accounted for and the nominal coverage probability of each interval does not correspond to the real one. The appropriate correction was suggested by Benjamini and Yekutieli, (2005):

$$\alpha' = R \times \alpha/m.$$

Simply we adjusted the probability level on the basis of R, the number of reported estimates (in our case 6), and m, the total number of estimates (in our case 12) shown in the text (for further detail, see Supplementary material).

3. Results

3.1. Population and exposures

The population living in the subset of 13 areas considered in the PM_{10} analysis represents about 25% of the total population of the Lombardy region ($\approx$ 10 million inhabitants), while the population living in the 18 areas for the NO_2 analysis represents 30% of the regional population (Table 1). The capital city of Milan is the largest area and has approximately 1.3 million inhabitants, or 14% of the regional population. During the period 2003–2006, the average PM_{10} level across the 13 areas was 45.4 $\mu g/m^3$, and the areas of Cremona, Lodi, Milan, and Mantova registered annual mean levels higher than 50 $\mu g/m^3$ (Table 2). The overall average level of NO_2 was 52.1 $\mu g/m^3$; Milan, Monza, Cinisello Balsamo and Como reported values higher than 65 $\mu g/m^3$ (Table 2). The correlation coefficients between the daily levels of PM_{10} and NO_2 as well as those between pollutants and meteorological variables were similar across areas, reflecting comparable air pollution and meteorological daily profiles among areas (Supplementary Table 2).

3.2. Effect estimates

Table 3 shows the percent variations in mortality and hospital admissions with their corresponding 90% and 50% credibility/confidence intervals (CrI/CI), for each cause and pollutant (area-specific estimates are reported in Supplementary Figs. 1 and 2 and Supplementary Tables 3 and 4).

3.2.1. Natural mortality

The overall meta-analytic estimate of the percent variation in natural mortality was 0.30 (90%CrI: −0.21; 0.70) for 10 $\mu g/m^3$ increase in PM_{10}. There was little evidence of heterogeneity across zones (I^2=4.33, 90%CrI: 0.11; 28.51), mainly driven by the effect estimate of the Milan area which exhibited an area-specific percent variation twice as high as the overall one (0.63, 90%CrI: 0.28; 1.02; 50%CrI: 0.48; 0.78).

NO_2 percent variation on all-cause mortality was higher (0.70, 90%CrI: 0.20; 1.18); heterogeneity across areas was negligible (median of the I^2 posterior distribution=0.62, 90%CrI: 0.03; 13.84).

Table 1
Annual (and daily) average number of deaths and hospital admissions in the areas included in the study, Lombardy, Italy, 2003–2006.

Study Area	Annual Average Population	Annual (and Daily) Average No. of Deaths From Specific Natural Causes			Annual (and Daily) Average No. of Hospital Admissions From Specific Natural Causes		
		All Natural[a]	Cardiovascular[b]	Respiratory[c]	Cardiac[d]	Cerebrovascular[e]	Respiratory[f]
Bergamo	115,078	1064 (2.9)	401 (1.1)	73 (0.2)	669 (1.8)	228 (0.6)	428 (1.2)
Brescia	190,483	1155 (3.2)	389 (1.1)	109 (0.3)	1726 (4.7)	666 (1.8)	1437 (3.9)
Busto Arsizio	78,305	614 (1.7)	259 (0.7)	54 (0.1)	603 (1.7)	231 (0.6)	399 (1.1)
Cinisello Balsamo	73,204	423 (1.2)	164 (0.4)	44 (0.1)	510 (1.4)	160 (0.4)	505 (1.4)
Como	81,385	698 (1.9)	253 (0.7)	76 (0.2)	627 (1.7)	279 (0.8)	551 (1.5)
Cremona	71,288	723 (2.0)	271 (0.7)	50 (0.1)	626 (1.7)	301 (0.8)	506 (1.4)
Lecco	46,351	422 (1.2)	175 (0.5)	33 (0.1)	379 (1.0)	120 (0.3)	207 (0.6)
Legnano	55,421	414 (1.1)	170 (0.5)	32 (0.1)	337 (0.9)	108 (0.3)	271 (0.7)
Lodi district	209,576	1945 (5.3)	770 (2.1)	166 (0.5)	1417 (3.9)	479 (1.3)	1196 (3.3)
Mantova	47,855	508 (1.4)	221 (0.6)	25 (0.1)	449 (1.2)	201 (0.6)	215 (0.6)
Milan	1,281,781	10,218 (28.0)	3761 (10.3)	909 (2.5)	9130 (25.0)	3332 (9.1)	7991 (21.9)
Monza	121,769	842 (2.3)	314 (0.9)	61 (0.2)	555 (1.5)	267 (0.7)	546 (1.5)
Pavia	71,422	684 (1.9)	250 (0.7)	41 (0.1)	498 (1.4)	182 (0.5)	338 (0.9)
Rho	51,058	349 (1.0)	144 (0.4)	32 (0.1)	401 (1.1)	116 (0.3)	275 (0.8)
Sesto San Giovanni	81,201	427 (1.2)	152 (0.4)	32 (0.1)	623 (1.7)	212 (0.6)	568 (1.6)
Sondrio	21,715	190 (0.5)	68 (0.2)	16 (0)	126 (0.3)	55 (0.2)	100 (0.3)
Varese	81,604	742 (2.0)	296 (0.8)	72 (0.2)	443 (1.2)	218 (0.6)	422 (1.2)
Vigevano	59,271	508 (1.4)	191 (0.5)	33 (0.1)	405 (1.1)	183 (0.5)	331 (0.9)

[a] ICD-9 < 800.
[b] ICD-9 390–459.
[c] ICD-9 460–519.
[d] ICD-9CM 390–429.
[e] ICD-9CM 430–439.
[f] ICD-9CM 460–469, 480–519, except 487.

Table 2
Characteristics of exposure to Particulate Matter ≤ 10 μm in Diameter (PM_{10}), Nitrogen Dioxide (NO_2), and temperature in the areas included in the study, Lombardy, Italy, 2003–2006.

Study Area	PM_{10}[a] Concentration (μg/m^3)				NO_2 Concentration (μg/m^3)				Average Temperature (°C)
	Mean	5th Percentile	95th Percentile	Number of Monitors	Mean	5th Percentile	95th Percentile	Number of Monitors	
Bergamo	46.1	13.2	105.4	2	42.7	18.0	70.7	3	14.0
Brescia	49.4	14.5	108.7	2	62.5	31.0	97.7	3	12.9
Busto Arsizio	44.7	10.4	103.0	1	44.1	15.8	81.7	2	12.9
Cinisello Balsamo	–	–	–	–	71.3	35.2	108.8	1	14.5
Como	43.6	15.5	93.5	1	68.3	41.9	102.7	1	12.5
Cremona	53.5	20.3	115.2	3	44.3	21.1	77.9	3	13.1
Lecco	38.4	11.0	86.8	2	58.5	26.2	94.6	2	14.0
Legnano	–	–	–	–	53.8	23.7	88.7	1	12.9
Lodi district	52.6	16.1	114.6	6	35.0	16.1	61.6	9	13.1
Mantova	50.6	17.2	102.4	4	29.9	7.3	66.9	5	11.4
Milan	52.5	16.2	120.8	3	65.5	33.1	108.2	8	14.5
Monza	–	–	–	–	75.2	39.1	117.4	1	14.5
Pavia	44.4	12.3	95.4	2	55.0	21.0	102.2	2	16.7
Rho	–	–	–	–	53.5	22.4	93.6	1	14.5
Sesto San Giovanni	–	–	–	–	64.5	27.9	114.5	1	14.5
Sondrio	42.8	11.0	93.6	2	31.4	11.9	62.6	2	12.5
Varese	29.6	11.2	56.2	1	34.7	13.6	59.6	2	13.2
Vigevano	42.2	5.9	100.5	2	47.3	15.1	97.7	1	14.7

[a] PM_{10} data available for 13 areas only.

Table 3
Posterior means and 90% and 50% credibility intervals of the percent variation in mortality and hospital admissions associated with a 10 μg/m^3 increase in the air pollutant level.[a]

Health outcome	Cause of mortality or hospital admission	PM_{10}			NO_2		
		% Change	90% CrI/CI	50% CrI/CI	% Change	90% CrI/CI	50% CrI/CI
Mortality	All natural causes[b]	0.30	(−0.21; 0.70)	(0.14; 0.50)	0.70	(0.20; 1.18)	(0.52; 0.89)
	Cardiovascular diseases[c]	0.30	(−0.21; 0.82)	(0.09; 0.51)	1.12	(0.30; 1.95)	(0.78; 1.45)
	Respiratory diseases[c]	1.64	(0.56; 2.72)	(1.20; 2.08)	0.46	(−1.23; 2.18)	(−0.23; 1.16)
Hospital Admissions	Cardiac diseases	0.14	(−0.31; 0.56)	(−0.03; 0.31)	1.14	(0.51; 1.83)	(0.87; 1.37)
	Cerebrovascular diseases	0.54	(−0.14; 1.23)	(0.25; 0.81)	1.70	(0.60; 2.66)	(1.33; 2.10)
	Respiratory diseases	0.77	(0.31; 1.32)	(0.57; 0.95)	1.20	(0.53; 1.81)	(0.97; 1.45)

Abbreviations: PM_{10}, particulate matter ≤ 10 μm in diameter; NO_2, nitrogen dioxide; CrI, credibility interval; CI, confidence interval.

[a] Results refer to a 10 μg/m^3 increase in the air pollutant level at lag 0–1 for mortality and at lag 0–3 for hospital admissions.

[b] See Baccini et al. (2011).

[c] For cause-specific mortality, we reported the estimated percent change and the corresponding 90% and 50% confidence intervals arising from the conditional logistic regression.

3.2.2. Cause-specific mortality

As regard cardiovascular deaths, we estimated a 0.30% change (90%CI: −0.21; 0.82) per 10 μg/m^3 increase in PM_{10}, and a 1.12% change (90%CI: 0.30; 1.95) per 10 μg/m^3 in NO_2. The magnitude of the percent variations on respiratory mortality almost flipped over, with a 1.64% change (90%CI: 0.56; 2.72) for PM_{10} and a 0.46% change (90%CI: −1.23; 2.18) for NO_2.

3.2.3. Hospital admissions

The overall meta-analytic estimates of percent variation in hospitalizations associated with a 10 μg/m^3 increase in PM_{10} ranged between a minimum of 0.14 (90%CrI: −0.31; 0.56) for cardiac diseases and a maximum of 0.77 (90%CrI: 0.31; 1.32) for respiratory diseases, with a percent increase in hospitalizations for cerebrovascular causes being roughly in between. The order of magnitude of the posterior means of the percent variations in hospital admissions associated with NO_2 exposure was higher, ranging from 1.14 (90%CrI: 0.51; 1.83) for cardiac diseases to 1.70 (90%CrI: 0.60; 2.66) for cerebrovascular diseases. Heterogeneity across areas for all causes and both pollutants was generally low, with posterior medians of I^2 ranging from 0.29 (NO_2 and respiratory hospitalizations) to 0.70 (NO_2 and cardiac hospitalizations) (Supplementary Table 5).

3.2.4. Season and age class analyses

Figs. 2 and 3 depict effects on mortality and hospital admissions, respectively, stratified by season and age class. The posterior means and the credibility intervals of the percent variations are reported in Supplementary Tables 6 and 7.

When stratifying by season, higher effects during summer were observed for all mortality outcomes and both pollutants (with a stronger season-effect for PM_{10}), except for respiratory deaths and NO_2 exposure. We did not find a clear effect increase with increasing age on mortality (Fig. 2).

As regard hospital admissions, a similar difference between summer and winter was observed for all causes, even if the effect on cardiac hospitalizations was less evident. The effect of PM_{10} on hospital admissions for respiratory diseases appeared to increase with age at admission, but the same trend was not observed in other analyses. For both pollutants, effects on cerebrovascular hospitalizations seemed more evident in the first (<65 years) and second (65–74 years) age classes, but not in the highest one (≥ 75 years) (Fig. 3).

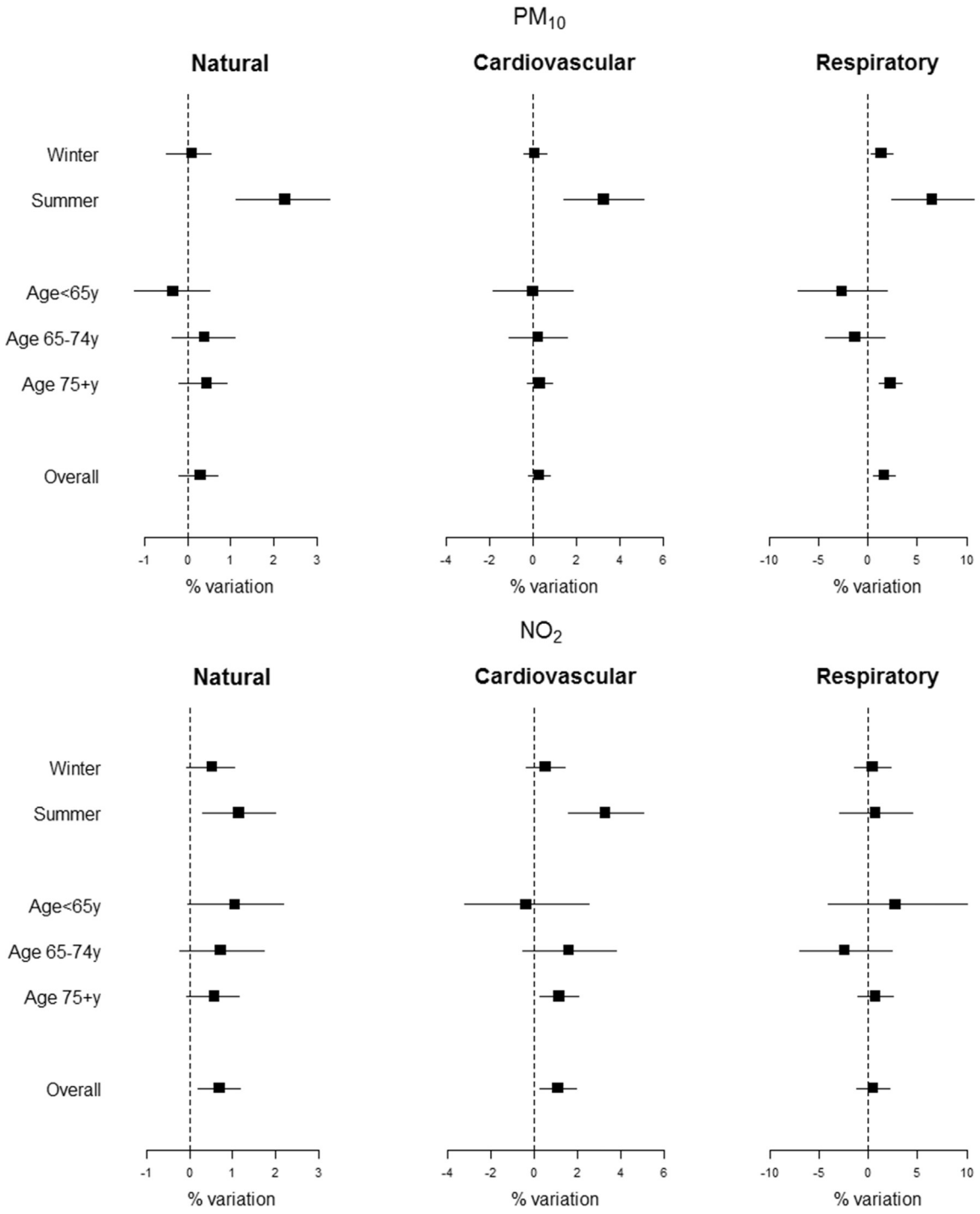

Fig. 2. Posterior means and 90% credibility intervals[*] of the percent variation in mortality associated with a 10 μg/m^3 increase in the air pollutant level (lag 0–1), by season and age at death. (Abbreviations: PM_{10}, particulate matter ≤ 10 μm in diameter; NO_2, nitrogen dioxide. ([*]) For cause-specific mortality, we reported the estimated percent change and the corresponding 90% confidence interval arising from the conditional logistic regression.)

4. Discussion

In this study of short-term effects of PM_{10} and NO_2 exposure at a large regional level, increasing concentrations of air pollution were associated with increased mortality and hospital admissions.

Natural mortality was positively associated with both pollutants. The percent variations were affected by higher heterogeneity when considering PM_{10}, mainly because of the stronger effect of this pollutant in the city of Milan.

The higher effect of PM_{10} on natural mortality in Milan could be partially explained by the different emission sources of the pollutant: in the Milan county, 57% of the total tons of PM_{10} emitted in 2005 were attributable to road traffic alone; in other counties this fraction was much lower (from the highest 37% in Lodi to the lowest 17% in Mantova, Supplementary Table 1). A number of studies have specifically linked traffic-related air pollution to harmful health effects (Baccarelli et al., 2009; Gan et al., 2010; Ghosh et al., 2015; Grahame and Schlesinger, 2010; Hart et al., 2013; Heinrich et al., 2013; Pindus et al., 2015; Zhang and Batterman, 2013). Sandrini and colleagues (Sandrini et al., 2014) showed

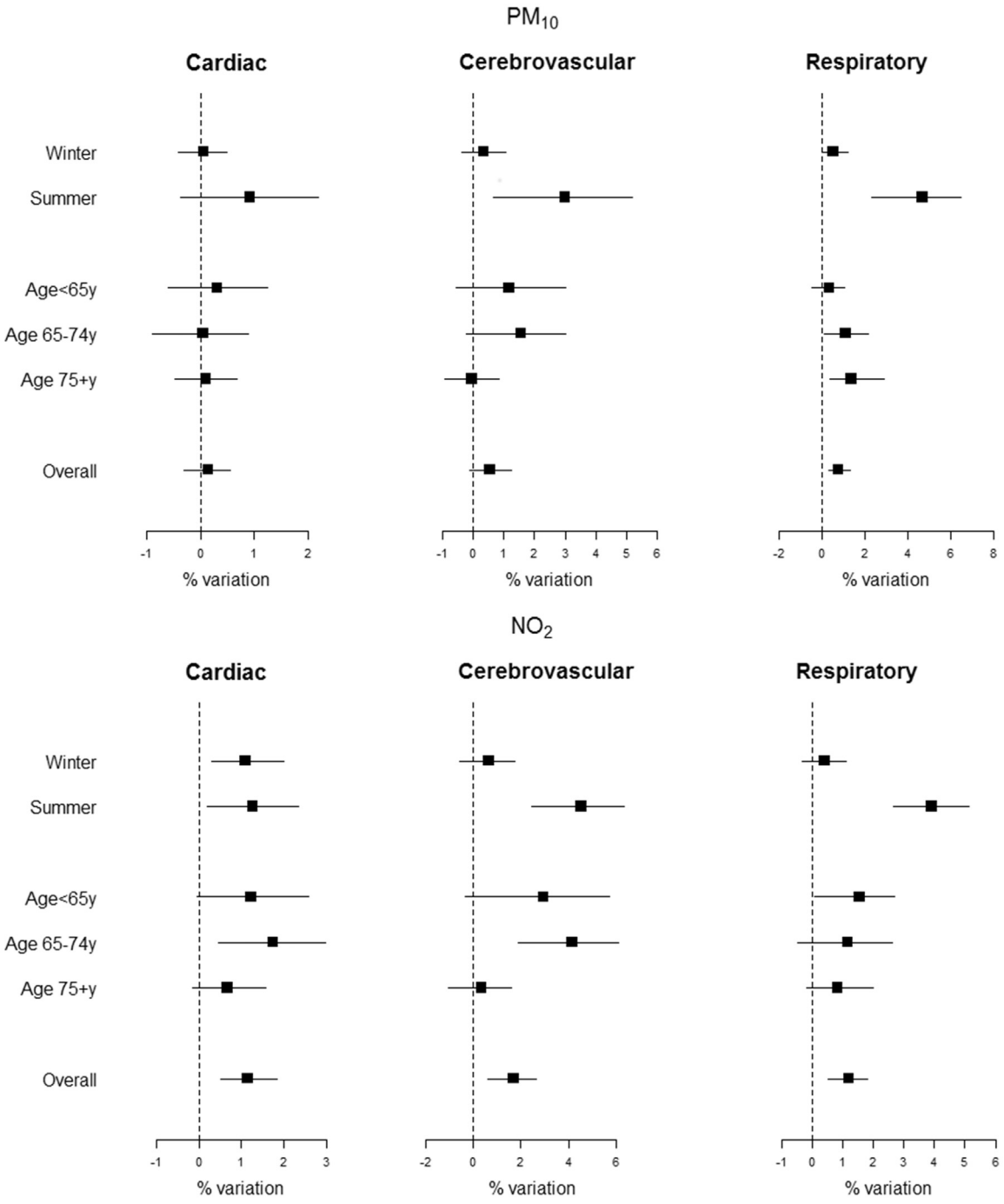

Fig. 3. Posterior means and 90% credibility intervals of the percent variation in hospital admissions associated with a 10 μg/m^3 increase in the air pollutant level (lag 0–3), by season and age at admission. (Abbreviations: PM_{10}, particulate matterv ≤ 10 μm in diameter; NO_2, nitrogen dioxide.)

that Milan particulate matter is richer in elemental carbon, a valuable proxy for PM from combustion sources, especially from diesel exhaust (Janssen et al., 2011).

Many studies documented an association between air pollution exposure and deaths related to cardiovascular as well as respiratory diseases (Li et al., 2015; Samoli et al., 2006; Stafoggia et al., 2009; Zeka et al., 2005). The estimated percent variation for cardiovascular deaths was higher in association with NO_2, and the one for respiratory mortality was higher in association with PM_{10}. The findings on cardiovascular deaths are roughly comparable with a recent study conducted in eight Chinese cities, where an increase of 10 μg/m^3 in 2-day moving average concentrations of PM_{10} and NO_2 was found to be significantly associated with increases of 0.36% and 1.30%, respectively, in daily coronary heart disease mortality (Li et al., 2015). Similar results for respiratory mortality were observed in the EpiAir study, a large multicity investigation conducted on 24 Italian cities (Stafoggia et al., 2009).

The effect of both pollutants was more evident in the summer season, consistently with previous investigations (Biggeri et al., 2004; Chiusolo et al., 2011). It has been shown that both temperature and period of the year might play a role as effect modifiers (Nawrot et al., 2007). Another likely explanation is that during the summer season the concentrations measured by the monitoring stations better represent the real exposure: people, actually, spend more time outdoor in the summer season, and keep windows open thus allowing ambient air pollutants to enter

their homes. The higher effects observed in the warm season might also be related to the lower background mortality during the summer, with a consequential increase in the number of susceptible subjects (Huynen et al., 2001).

A trend in mortality with increasing age classes was not that clear, even if the effects of PM_{10} on natural mortality seemed lower in the first age category (<65 years). This finding might simply uncover the fact that higher ages correspond, on average, to a greater prevalence of risk factors for all-cause and cause-specific mortality which make individuals more susceptible to the effect of fine particles exposure (Bateson and Schwartz, 2004).

The presence of an association with air pollution was evident for hospital admissions as well. The percent variations were stronger for NO_2, similarly to what already observed in other investigations conducted in Italy (Biggeri et al., 2004; Colais et al., 2009; Scarinzi et al., 2013). All the meta-analytic estimates of percent variation were generally affected by low heterogeneity.

Even for hospital admissions, the effect was more evident during the summer.

We found that the effect of PM_{10} on respiratory hospital admissions increased with age. Some inflammatory markers, such as C-Reactive Protein and D-dimer, have been found to increase with age (Rumley et al., 2006) and also to be predictive of respiratory outcomes such as pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension (Quarck et al., 2009). In addition, PM_{10} has been shown to produce oxidative stress and increase inflammatory markers in exposed subjects (Yang et al., 2015). PM_{10} and aging related increased levels of inflammatory markers may contribute to explain the observed trend of respiratory hospital admissions. Moreover, as for mortality, higher age classes correspond, on average, to categories of subjects with high prevalence of respiratory risk factors which can act as effect modifiers for PM_{10} (Bentayeb et al., 2012).

For both pollutants, effects on cerebrovascular hospitalizations were more evident in subjects aged less than 75 years. While the evidence assessing the association between air pollution and cardiovascular outcomes has become sound, fewer studies have investigated cerebrovascular outcomes and the evidence of an association with air pollutants is less consistent (Lai et al., 2013; Shah et al., 2015). Our findings are coherent with what observed in other recent studies (Leiva et al., 2013; Zheng et al., 2013). Nonetheless, a greater effect of both PM_{10} and NO_2 exposure in subjects younger than 75 years appear as a finding that needs further clarification. It might indicate an anticipation of the effect of pollutant exposure in a highly exposed population (Schwartz, 2001).

Several studies have tried to explain the potential biological mechanisms underlying the retrieved associations between air pollution exposure and health effects. For both PM_{10} and NO_2, *in-vitro* (Quay et al., 1998; Silbajoris et al., 2011) and *in-vivo* (Rutowski et al., 1998; Sandstrom et al., 1991) investigations documented an increase in reactive oxygen species, inflammatory cells and cytokines after exposure to the pollutants, that might partly explain the relationship between air pollution exposure and respiratory effects. As regards PM, human (Chuang et al., 2007; Ruckerl et al., 2006) and animal (Nemmar et al., 2003; Nemmar et al., 2002) studies suggested that acute exposures might entail changes in coagulation and platelet activation, thus providing a more proximal link between PM and cardiovascular disorders.

We found generally higher percent variations for NO_2 than for PM_{10}. In interpreting this difference, we should account for the ranges of the daily levels of the two pollutants. Therefore, to properly compare the effects of PM_{10} and NO_2 we can express the percent variations per standard deviation (SD) increase in the pollutant concentration (Basagana et al., 2015). From the overall data, we obtained SD=28.7 for PM_{10} and SD=13.0 for NO_2. If we take, as an example, the effect estimates on natural mortality, the percent variations in all-cause deaths per one SD increase are approximately 0.86 ($0.30 \times 1/10 \times 28.7$) for PM_{10} and 0.91 ($0.70 \times 1/10 \times 13.0$) for NO_2. This way of reporting the results suggests that the difference between the effects of the two pollutants might be less remarkable.

Different areas were included in the PM_{10} and NO_2 analyses (13 areas vs. 18 areas), hence potentially leading to scarce comparability of the effects obtained for each pollutant. To verify whether the inclusion of 5 more areas in the NO_2 analysis had influenced our results, we conducted a sensitivity analysis on NO_2-related outcomes by excluding those areas without available PM_{10} measurements. The analysis on the subset of 13 areas returned results that were very similar to the ones obtained on the full set of areas (Supplementary Table 8). This finding, partly expected due to the low heterogeneity among areas, suggests that our conclusions are robust to the unavailability of the 5 areas with missing PM_{10} data.

Limited to the effect of PM_{10} on mortality from all natural causes, we conducted an additional sensitivity analysis by specifying area-specific Poisson models which accounted for overdispersion. Overall, there was no evidence of relevant overdispersion, and the standard errors of the estimates were slightly smaller than those obtained without accounting for overdispersion. These differences, already negligible, became irrelevant after meta-analysis (results not reported); in fact, the reduced within-area variances were completely balanced by a larger between-area heterogeneity.

This study suffers from some limitations. Small numbers of cause-specific deaths prevented meta-analytic estimates of cause-specific mortality. When performing case-crossover analysis on the overall dataset, we could not consider heterogeneity between areas. Residual confounding by age cannot be completely ruled out, due to the relatively wide age categories. In addition, specific analyses on small susceptible subgroups (e.g. newborns and extreme elderly people) could not be performed. Air pollution measurements were averaged over each study area, thus assuming that all subjects living in one area shared the same levels of environmental exposure. Potential non-linear effects of PM_{10} and NO_2 exposures were not investigated. Lastly, temperature was thoroughly taken into account as confounder in our models, but its role as potential effect modifier of the association between air pollution and health outcomes was not investigated in detail.

Our investigation also has methodological strengths. First, results on all-cause mortality and cause-specific hospitalizations were derived from Bayesian meta-analytic techniques that are capable of providing stable estimates, since they take advantage of the overall information while reflecting the differences among areas (Sutton and Abrams, 2001). Where not applicable, we conducted a case-crossover analysis with a time-stratified approach, which allowed to control by design for most confounders involved in time-series studies on air pollution exposure (i.e. seasonality, long-term trend and day of the week) (Janes et al., 2005). Secondly, the cities we selected represent a non-opportunistic sample of the entire regional territory. The great majority of Lombardy residents live in urban areas and air pollution measures in cities smaller than the ones we included are often unavailable or imprecise. Our results can thus be used with a good level of confidence to make inference on the effects of air pollution exposure in the entire region. Lastly, our exposure data are derived from fixed monitoring stations that are not affected by uncertainties that are typical of dispersion models (Holnicki and Nahorski, 2015).

5. Conclusions

In conclusion, our study provided a sound characterization of air pollution exposure and its potential effects on human health in

a large highly polluted Italian region. In the wider framework of Health Impact Assessment, our results offer important information on which to base public health policies and interventions.

Conflicts of interest

None declared.

Acknowledgements

The authors thank the Air Quality Unit of the Lombardy Regional Environment Protection Agency (ARPA Lombardia) and the Health Directorate of the Lombardy Regional Government for providing the data that made this work possible.

This work was supported by the Lombardy Regional Government (research grant "Regione Lombardia Ricerca Indipendente 2012: ESSIA-Effetti Sulla Salute degli Inquinanti Aerodispersi in Regione Lombardia") and the Italian Ministry of Education, University and Research (Grant PRIN 20072S2HT8).

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.envres.2016.03.003.

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