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Comparison of different exposure settings in a case–crossover study on air pollution and daily mortality: counterintuitive results

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Because of practical problems associated with measurement of personal exposures to air pollutants in larger populations, almost all epidemiological studies assign exposures based on fixed-site ambient air monitoring stations. In the presence of multiple monitoring stations at different locations, the selection of them may affect the observed epidemiological concentration–response (C-R) relationships. In this paper, we quantify these impacts in an observational ecologic case–crossover study of air pollution and mortality. The associations of daily concentrations of PM_{10}, O_3, and NO_2 with daily all-cause non-violent mortality were investigated using conditional logistic regression to estimate percent increase in the risk of dying for an increase of 10 $\mu g/m^3$ in the previous day air pollutant concentrations (lag 1). The study area covers the six main cities in the central-western part of Emilia-Romagna region (population of 1.1 million). We used four approaches to assign exposure to air pollutants for each individual considered in the study: nearest background station; city average of all stations available; average of all stations in a macro-area covering three cities and average of all six cities in the study area ($50 \times 150\,km^2$). Odds ratios generally increased enlarging the spatial dimension of the exposure definition and were highest for six city-average exposure definition. The effect is especially evident for PM_{10}, and similar for NO_2, whereas for ozone, we did not find any change in the C-R estimates. Within a geographically homogeneous region, the spatial aggregation of monitoring station data leads to higher and more robust risk estimates for PM_{10} and NO_2, even if monitor-to-monitor correlations showed a light decrease with distance. We suggest that the larger aggregation improves the representativity of the exposure estimates by decreasing exposure misclassification, which is more profound when using individual stations *vs* regional averages.
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Introduction

Numerous studies have demonstrated associations between day to day variations in ambient pollutants concentrations and corresponding variations in health endpoints such as mortality (WHO, 2006; Pope and Dockery, 2006; Halonen et al., 2009). Health risks have been estimated by means of different methodological approach, primarily time series and case–crossover, and statistical methods. Increasing statistical and methodological sophistication are used in epidemiological studies including for example generalized additive (Hastie and Tibshirani, 1990) and linear models (Ostro et al., 2006), time-varying coefficient models (Lee and Shaddick, 2007), and distributed lag models (Schwartz, 2000), but only little advances have been attained in exposure definition, even though misclassification of exposure has been recognized as a major concern (Koistinen et al., 2001; Kousa et al., 2002).

As a matter of fact, due to practical and theoretical problems associated with an individual exposure assessment to air pollutants, almost all epidemiologic studies, both ecological and analytical, assign exposure according with fixed-site monitoring stations data (Katsouyanni et al., 1996; Samet et al., 2000a, b; Biggeri et al., 2004). Sitting of stations vary between cities and no well-defined criteria to select stations and to evaluate quality and population representativity of the air quality data are available. Even though background stations with good temporal coverage are sometimes used to assign population exposure (for example French cities included in the APHEA study, see Katsouyanni et al., 1996), averaging different monitors within the same urban area has more often been considered (Katsouyanni et al., 1996; Samet et al., 2000a, b; Biggeri et al., 2004). Wilson and Brauer (2006) compared the closest ambient monitoring station and city-average concentration with actually measured personal exposures in a panel study and found that the five station city average represented the ambient exposure component better than the monitoring site located closest to the subject's residence. Sometimes,

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a-posteriori analyses have been carried out to evaluate the effect of some indexes of within-city dishomogeneity of monitoring data (Biggeri et al., 2004).

Exposure assessment is a challenging task. Exposures to air pollutants take place over time and at multiple locations over the daily activities of the population, and accurate exposure estimates for each individual participating in large-scale epidemiological studies is not feasible. Several studies have found significant differences between measured personal exposures to air pollutants and estimates based on central monitor values (Janssen et al., 1998; Hänninen et al., 2004), yielding doubts about findings of epidemiologic studies (Lipfert and Wyzga, 1997). However, much of the variation in exposure resulted between people and the longitudinal correlation between inter-personal averages and ambient levels was found relatively high (Janssen et al., 1998).

The conceptual problem on the impact in epidemiological studies of an assignment of exposure levels to individuals and population by means of monitoring stations has been deeply addressed in the paper of Zeger et al. (2000). The authors showed that risk estimates are affected by three types of errors: (1) differences between individual and population-average exposure; (2) differences between population-average exposures and ambient levels; and (3) difference between measured and true ambient levels including spatial variability and instrument error. The authors argued that the first and third components can be taken as Berkson-type errors (Thomas et al., 1993), resulting in small effects on the relative risk estimates. However, the second component, the difference between the population-average exposure and the ambient concentration, was believed to be a classical error (Carroll et al., 1995) and potentially an important source of bias affecting the magnitude of the observed coefficients.

Because of the limitations in available simultaneous data on ambient levels and personal exposures of large population groups, it is generally nearly impossible to quantify the single error terms and to estimate quantitatively their impacts as a whole. However, it is relatively easy to evaluate the sensitivity of the epidemiological results to the definition of exposure in terms of selecting and aggregating data from ambient monitoring stations.

In this paper, we compare alternative exposure definitions derived from aggregation of fixed-site monitoring station data on different spatial scales and their effect on concentration–response (C-R) relationships. The specific objectives of the work are:

(i) To create four alternative exposure time series for examining the effect of spatial aggregation on the epidemiological C-R model
(ii) and using these time series to calculate case–crossover models for the six cities
(iii) To investigate the observed C-R relationships across the models, and
(iv) To analyze the spatio-temporal relationships among stations and spatial aggregations to understand the observed C-R relationships.

Further, based on the results we discuss the exposure misclassification errors associated with fixed-site monitoring station data in the context of short-term epidemiologic studies on air pollution.

Methods

Air quality monitoring and mortality data from six main cities in the central-western side of Emilia-Romagna region were used in the study (Figure 1). The cities are in the Po Plain, a vast flat area in northern Italy. Total population of the study area is 1,119,200 persons (estimated at 31 December 2006).

According to nearly all epidemiological studies, we defined exposure by means of selection and aggregation of fixed-site monitoring stations data and compared four approaches to assign exposure to air pollutants for each individual considered in the study. The first one is to choose a background reference station in each city. When no background stations were available, we considered stations as little as possible exposed to traffic emissions. The second approach was based on averaging daily data collected by all stations within the city (Table 1). The third method consisted of averaging daily mean concentrations from monitoring stations within each macro-area (macro-area 1: Piacenza, Parma, and Reggio-Emilia; macro-area 2: Modena, Bologna, and Ferrara) and fourth averaged concentrations within the whole study area. Thus, only the first approach is based on using only background stations, whereas all other approaches include also the traffic-oriented stations.

Spatio-temporal association among monitoring stations and among spatial aggregations of monitoring station data have been analyzed in terms of Pearson correlation coefficient, Lin concordance coefficient, and Bland–Altman correlation coefficient (Bland and Altman, 1986; Lin, 1989; Biggeri et al., 2003). The first one indicates the strength and direction of the linear relationship between two variables; the second shows not only the strength of this relationship but also how similar are the absolute values of the two variables, that is characterize the homogeneity of ambient concentrations; the third is the correlation between the difference and the average of each pair of values of variables, that is it shows if and how much differences are related to absolute values.

The epidemiological analysis was based on a case–crossover design that is, together with meta-analysis of time series studies, the most widely used to evaluate short-term effects of air pollution. In particular, the associations of daily concentrations of air pollutants with daily mortality were investigated using a case–crossover design (Maclure, 1991),

Figure 1. Geographical locations of the six cities representing the study area. Macro-area 1 consists of the cities of Piacenza, Parma, and Reggio nell'Emilia, whereas macro-area 2 consists of the cities of Modena, Bologna, and Ferrara.

with a time-stratified approach to represent exposure on control days. Control days were selected from the same day of the week, month, and year as case days. Single pollutant model were used. The association between PM and mortality was estimated by odds ratios with 95% confidence intervals (CIs) using conditional logistic regression, adjusted for apparent temperature (Kalkstein and Valimont, 1986), a composite index that takes into account air temperature and humidity, summer population decrease (8–22 August), bank holiday, flu epidemic week, and heat wave day. Confounding effect of apparent temperature of the day of exposure was controlled following an approach already adopted in Italy in an important country-wide study on health effects of PM_{10} (Forastiere et al., 2008). In particular, the left side of the mortality–temperature curve was approximated by a linear term of the apparent temperature averaged from the previous 6 days (lag 1–6) (up to 9°C) to take into account of the latent effect of cold temperatures. The central and right side of the curve were fitted by superimposing a piecewise linear spline of apparent temperature with an inner knot at 26°C. Heat wave days were defined as days that are at least the third day above a threshold of 30°C of mean apparent temperature. We performed sensitivity analysis to assess the impact of 2003 heat wave and of changing the definition of heat wave days. Estimates for ozone were provided only for the hot season (1 May to 30 September). Estimates focused on hot season were also given for PM_{10} due to the higher level of risks found in many studies (Kousa et al., 2002; Peng et al., 2005; Nawrot et al., 2007).

Air Pollution Data

Population exposure was estimated using the measured concentrations of particulate matter (particles with aero-dynamic diameter $\leq 10\,\mu m$, PM_{10}), ozone (O_3), and nitrogen dioxide (NO_2). We included daily concentration for these pollutants data for 2002–2006 (1826 days) from the

Table 1. Population under study and fixed-site monitoring stations selected for the study.

City	Population	No. of deaths	Monitoring stations		
			PM_{10}	O_3	NO_2
Piacenza	99,340	4161	2 (1, 0, 1)	1 (1, 0, 0)	2 (1, 0, 1)
Parma	175,789	7004	1 (0, 1, 0)	1 (1, 0, 0)	3 (1, 1, 1)
Reggio-Emilia	157,388	5392	3 (1, 1, 1)	1 (0, 1, 0)	4 (1, 2, 1)
Macro-area 1	432,517	16,557	6 (2, 2, 2)	3 (2, 1, 0)	9 (3, 3, 3)
Modena	180,469	6982	1 (0, 1, 0)	2 (1, 1, 0)	4 (1, 2, 1)
Bologna	373,743	16,803	2 (0, 0, 2)	2 (1, 1, 0)	6 (1, 3, 2)
Ferrara	132,471	6606	2 (0, 1, 1)	1 (0, 1, 0)	3 (0, 2, 1)
Macro-area 2	686,683	30,391	5 (0, 2, 3)	5 (2, 3, 0)	13 (2, 7, 4)
Study area	1,119,200	46,948	11 (2, 4, 5)	8 (4, 4, 0)	22 (5, 10, 7)

The number of urban background, residential background, and traffic stations are listed, respectively, in parentheses.

ISO9001-certified fixed-site monitoring network located within the selected urban areas. These stations were of different types according to their inner city area location, including traffic-oriented stations, as well as residential and urban background stations. Table 1 shows the number and type of the stations in each city included in the analysis. We defined reference stations that were preferably urban background (generally public parks) or as secondary choice, residential background stations. Traffic stations were included only for PM_{10}, due to lack of background stations in Bologna.

With respect to PM_{10}, we considered only stations where particles concentrations were measured by means of β absorption or gravimetric methods. In fact, the β automatic method has been shown to be well in agreement with the gravimetric method (Bureau Veritas, 2006), whereas other methods such as TEOM and optical instruments do not guarantee the same agreement with the reference method.

We included in the analysis and in Table 1 only stations with $>75\%$ of data. Following methods adopted in many studies (Katsouyanni et al., 1996; Samet et al., 2000a, b; Biggeri et al., 2004), missing data were filled by means of procedures based on the hypothesis of fixed ratio between data collected in each station and the average of data collected in the other monitoring sites within the same city. When daily data were missing for all available stations, the value has been kept as missing.

Table 2 shows descriptive statistics of the exposure data obtained with the four above-mentioned approaches, whereas Figure 2 gives a visual inspection of the variability of the 6-year average considering the different methods chosen to define exposure.

Meteorological Data

Daily mean values of temperature and humidity were collected by the regional urban meteorological network. The use of data of a urban network avoids possible biases associated to the use of non-urban monitoring station in multi-city studies (Michelozzi et al., 2006; Zauli Sajani et al., 2008). The area is characterized by a continental climate with cold winters and hot summers (typical monthly mean temperatures ranging from 1°C in January to 26°C in July), and high humidity levels (typical monthly mean relative humidity ranging from 50% in winter to 85% in summer).

Mortality and Flu Epidemics Data

The subjects included in the study consisted of subjects residing and dying from all non-injury causes in the period 1 January 2002 to 31 December 2006 in the study area. Individual mortality records were retrieved from Regional Register of Causes of Deaths. Total number of natural deaths in the study period was 46,948, corresponding to an average of 25.7 deaths/day (Table 1). Influenza epidemics were defined on the basis of the weekly estimates of flu incidence, as reported by the Italian National Institute of Health.

Results

Air pollutant levels for the entire study period (2002–2006) among all stations ranged from 35 to 47 $\mu g/m^3$ for PM_{10}, from 20 to 72 $\mu g/m^3$ for NO_2, and from 58 to 83 $\mu g/m^3$ for O_3 (Figure 2). The differences in air quality between the six cities were quite large; however, the differences of the selected reference stations, preferably representing the urban background air quality, were smaller than the city averages, which reflect to a varying degree variability of concentrations caused by traffic and other sources (Figure 2). These differences between the cities were not explained by simple indicators like total population, population density, total number of vehicles, gross internal product, mean levels of temperature, humidity, and wind levels that were used as

Table 2. Values of 5°, 50°, 95° percentile of daily concentrations for each pollutant for the stations selected as reference in each city (a), and averaged over all stations within each city (b), within the same macro-area (c), and within the whole study area (d).

Pollutant (μg/m^3)	City	Ref. station (a)			City (b)				Macro-area (c)			Study area (d)		
		Percentile			Percentile				Percentile			Percentile		
		5°	50°	95°	5°	50°	95°		5°	50°	95°	5°	50°	95°
PM_{10}	Piacenza	9	35	95	6	32	90							
	Parma	11	37	89	11	37	89	Macro-area 1	12	34	88			
	Reggio-Emilia	12	38	97	13	33	84					15	35	89
	Modena	12	39	105	12	39	105							
	Bologna	15	36	93	18	38	95	Macro-area 2	15	37	96			
	Ferrara	10	34	101	10	33	98							
O_3	Piacenza	2	64	160	2	64	160							
	Parma	6	73	159	6	73	159	Macro-area 1	6	72	158			
	Reggio-Emilia	9	73	155	9	73	155					7	68	149
	Modena	5	64	159	4	60	151							
	Bologna	4	65	147	4	56	132	Macro-area 2	7	67	146			
	Ferrara	10	81	153	10	81	153							
NO_2	Piacenza	10	32	59	16	42	69							
	Parma	14	31	57	27	48	74	Macro-area 1	26	46	72			
	Reggio-Emilia	18	40	78	28	49	82					28	50	78
	Modena	23	51	94	31	59	96							
	Bologna	17	41	74	33	62	95	Macro-area 2	30	53	87			
	Ferrara	17	37	74	19	39	72							

predictors in a multiple regression model ($R^2 = 0.02$; $P = 0.8$). Increasing aggregation to the macro-area level decreased the variability further, leaving deviations from the mean equal to 3%, 4%, and 8% for PM_{10}, O_3, and NO_2, respectively.

To quantify the spatial deviation in air quality due to increasing distance between the monitoring stations, the Pearson correlations of daily concentrations were analyzed. Correlations were quite high for PM_{10} and O3, ranging 0.6–0.9 and 0.85–0.95, respectively, but somewhat lower for NO_2 (0.35–0.9). The correlations decreased slightly with increasing distances (Figure 3) with slopes of -0.066/100 km for PM_{10} (CI: -0.109, -0.022; $P<0.01$), -0.017/100 km for O_3 (CI: -0.051, 0.017; $P=0.313$), and -0.051/100 km for NO_2 (CI: -0.086, -0.015; $P<0.01$). Correlation coefficients are still quite high also at a distance equal to about 150 km (about 0.75 for PM_{10}, about 0.9 for O_3 and 0.6 for NO_2).

Even stronger Pearson correlations were found between the two macro-areas (0.98, 0.99, and 0.96 for PM_{10}, O_3, and NO_2, respectively). Nearly identical values were found for Lin concordance coefficients for PM_{10} and O_3. Only for NO_2, Lin coefficient was somewhat lower (0.89). Pearson correlations between city's averages within the same macro-areas were similar to the correlations between stations within the same city (Table 3). In particular, inter-city Pearson correlations are, on average, higher for NO_2 (0.77 *vs* 0.67, mean values), almost equal for O_3 (0.94), and lower for PM_{10} (0.81 *vs* 0.87), with respect to intra-city correlations. The analysis in terms of Lin correlation coefficients showed similar results. The highest differences between Pearson and Lin coefficients were found for NO_2 (0.67 *vs* 0.54) and the lowest for PM_{10} (0.87 *vs* 0.82). Bland–Altman coefficients showed a decrease toward the null enlarging spatial aggregations for PM_{10} (0.25, 0.13, 0.07 for mean values of between stations, between cities, and between macro-areas coefficients, respectively) and O_3, (0.39, 0.21, 0.16). On the contrary, a marked increase was found for NO_2 (0.19, 0.20, and 0.34).

The main objective of this study was to look at how the C-R coefficients react to the aggregation of the concentration measures. Hypothetically, the aggregation of concentrations would decrease the non-representative variation due to individual monitoring locations, but would simultaneously introduce a spatial error term by including results from further distance. The net effect of these counteracting factors were quantified by calculating the case–crossover epidemiological analysis for the same all-cause mortality data (excluding violent causes) using four levels of spatial aggregation in the exposure indicator. The observed effects of different exposure indicators on estimated mortality risk associated with unit increase of pollutant concentrations were similar for PM_{10} and NO_2, but much smaller for ozone (Table 4).

For PM_{10}, the local background station approach yielded a 0.14% increase in daily mortality per 10 μg/m^3 (95% CI:

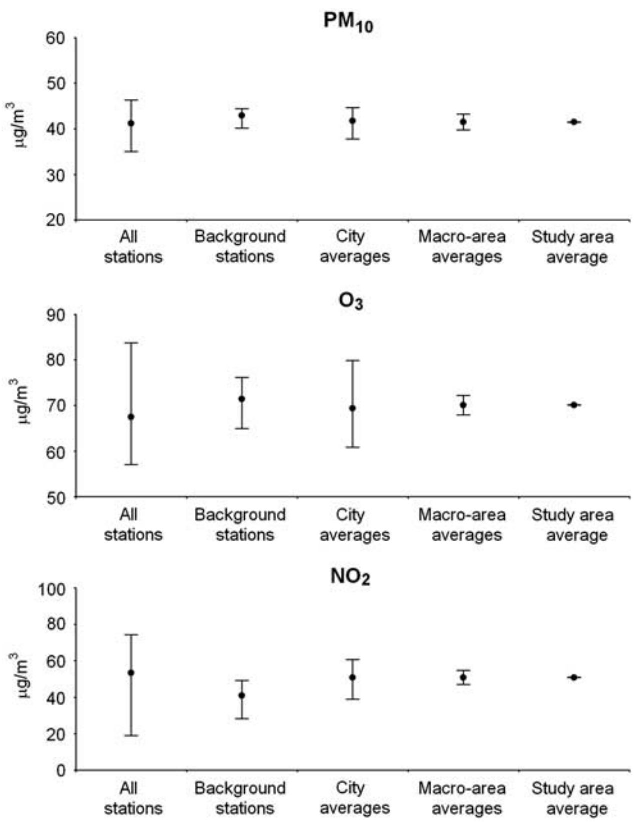

Figure 2. Ranges of the 2002–2006 averages of daily concentrations for each pollutant calculated among all stations (all stations), among the stations selected as reference in each city (background stations), and among spatial averages over all stations within each city (city averages), within the same macro-area (macro-area averages), and within the whole study area (study-area averages).

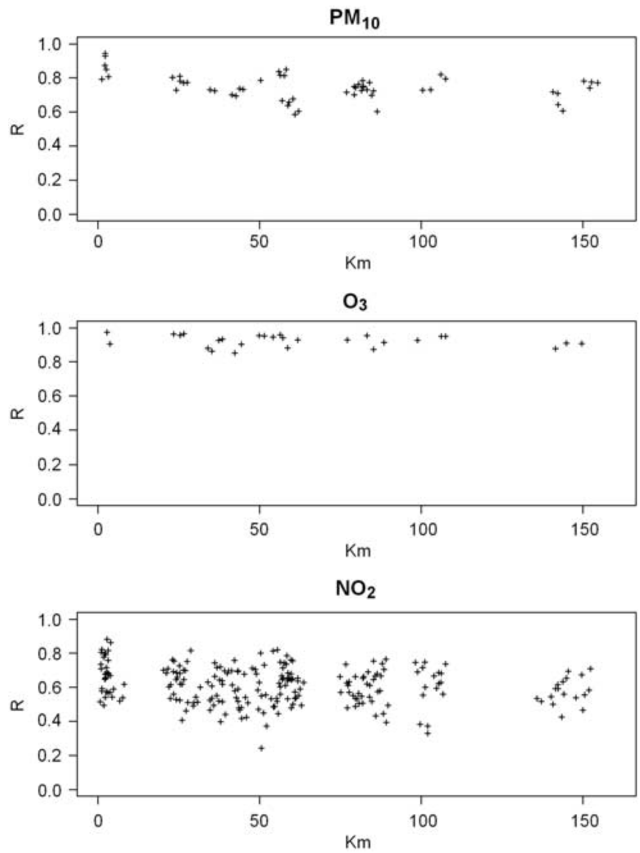

Figure 3. Pearson correlations between each couple of stations *vs* their distance.

−0.32–0.60). Using all city monitoring stations, including the traffic-oriented sites where applicable, for each city, the second approach yielded a corresponding 0.18% increase in daily mortality (representing 28% increase in the C-R function, even though the CIs are overlapping). Three-city-average (macro-area) estimate is 0.32% (228% of the local background station based estimate) and aggregating all six cities the estimate is 0.42% (300%, respectively; CIs reported in Table 4). Thus, although all the results remain statistically insignificant, the trend within the current study area is clear, and the increasing aggregation level increases the C-R slope, indicating that even at a three-city level, the random variation between ambient levels and population exposures biases the epidemiological model toward null. The limitation of the study area size did not allow for finding the dimension, where the increasing aggregation level would start to work toward lowering the estimates again.

For NO_2, the local background station approach yielded a 0.17% increase in daily mortality per 10 $\mu g/m^3$ (95% CI: −0.72–1.07). For city averages, the estimate increased to 0.23% (35% increase), and the corresponding values for three cities (macro-areas) and six cities (study area) were 0.38% (223%) and 0.74% (435%), respectively. From the relative increase of the slope, it can be seen that a manifold underestimation can take place due to the exposure misclassification when using a single reference station approach.

For PM_{10}, models applied separately to the hot season only gave the highest C-R relationship, with percent increase of risk ranging from 0.26% (95% CI: −1.39–1.93) using the local background station approach to 2.95% (0.67–5.27) using the six city study-area average concentrations (Figure 4; Table 4).

No increase in C-R relationship was found for ozone in relation to the enlargement of the spatial scale of exposure; the results for local reference station *vs* city average were almost identical and the C-R function slightly decreased with the two larger aggregations (Table 4).

Amplitudes of CIs of estimates systematically increased enlarging the spatial scale of exposure, even if the amount of this increase is quite low. CIs ranged from 0.92 to 1.07 for PM_{10} and from 1.79 to 2.23 for NO_2. CIs obtained for ozone and PM_{10} for the hot season ranged from 1.54 to 1.72, and from 3.33 to 4.60, respectively.

Table 3. Summary statistics of Pearson correlation coefficients, Lin concordance coefficient, and Bland–Altman correlation coefficients computed between each couple of stations within the same city, between couple of city averages within the same macro-area, and between macro-area averages within the study area.

		Between stations within the same city			Between cities within the same macro-area			Between macro-areas within the study area		
		PM_{10}	O_3	NO_2	PM_{10}	O_3	NO_2	PM_{10}	O_3	NO_2
Pearson	Mean	0.87	0.94	0.67	0.81	0.94	0.77	0.98	0.99	0.96
	Min	0.80	0.91	0.50	0.75	0.90	0.70			
	Max	0.95	0.98	0.89	0.86	0.97	0.82			
Lin	Mean	0.82	0.87	0.54	0.77	0.92	0.63	0.98	0.98	0.89
	Min	0.73	0.82	0.16	0.63	0.77	0.42			
	Max	0.89	0.92	0.88	0.85	0.97	0.76			
Bland–Altman	Mean	0.25	0.39	0.19	0.13	0.21	0.20	0.07	0.16	0.34
	Min	0.09	0.36	0.03	0.00	0.01	0.01			
	Max	0.47	0.43	0.52	0.32	0.49	0.45			

Table 4. Percent increase of death associated with a 10 $\mu g/m^3$ variation in PM_{10} (lag 1) by different definition of exposure to PM_{10}, NO_2, and O_3.

	Reference station		City		Macro-area		Study area	
	Percent increase of risk	95% CI	Percent increase of risk	95% CI	Percent increase of risk	95% CI	Percent increase of risk	95% CI
PM_{10}	0.14	−0.32 to 0.60	0.18	−0.30 to 0.66	0.32	−0.19 to 0.84	0.42	−0.11 to 0.96
NO_2	0.17	−0.72 to 1.07	0.23	−0.68 to 1.14	0.38	−0.63 to 1.39	0.76	−0.35 to 1.89
PM_{10} summer	0.26	−1.39 to 1.93	0.36	−1.38 to 2.14	2.26	0.17 to 4.39	2.95	0.67 to 5.27
O_3 summer	0.32	−0.4 to 0.10	0.37	−0.45 to 1.19	0.12	−0.70 to 0.93	0.24	−0.61 to 1.11

Discussion

The analyses showed the impact of different approaches in individual exposure definition in a case–crossover study of air pollution and mortality. Spatial aggregation of monitoring station data lead to higher risk estimates for PM_{10} and NO_2 even if monitor-to-monitor correlations showed a slight decrease with distance. Exposure definition at the regional level yielded risk estimates similar to national (Biggeri et al., 2004) and international estimates (WHO, 2003; Anderson et al., 2004). The Italian meta-analysis estimated the increases in natural mortality associated with 10 $\mu g/m^3$ increase of PM_{10} and NO_2 as 0.31% and 0.59%, respectively. A European meta-analysis (Anderson et al., 2004) and APHEA 2 (Samoli et al., 2006) estimated corresponding increases to be 0.6% for PM_{10} and 0.30% for NO_2. These values are closest to the results obtained with exposure defined on regional scale for PM_{10} (0.42%) and on macro-area scale for NO_2 (0.38%). The Italian meta-analysis estimate for ozone (0.27%) is well in agreement with our regional-scale estimate (0.24%) even if the estimates obtained with the alternative exposure definitions were not very far from this value. The Italian meta-analysis estimate for PM_{10} obtained for the hot season was 1.95%, also well in agreement with our macro-scale and regional estimates (2.26% and 2.95%).

The reason why spatial detail in exposure definition lead to lower estimates is probably related to the different types of errors and approximations existing in assigning exposure by means of fixed-site monitoring stations. It is useful to discuss the issue in the framework of the already mentioned paper by Zeger et al. (2000).

The first type of error defined by Zeger et al. (2000), the difference between personal exposure and population average personal exposure, is believed to have no influence in the explanation of the effect highlighted in this work.

The second error term is the difference between average personal exposures and the true ambient concentration and is believed to be non-Berksonian. Personal exposure derives either from indoor or outdoor sources. Exposures to pollution of indoor origin take place only indoors. If daily exposures from indoor sources are approximately independent of daily concentrations across time (Wallace, 1996; Wilson and Suh, 1997), the lack of indoor data will not

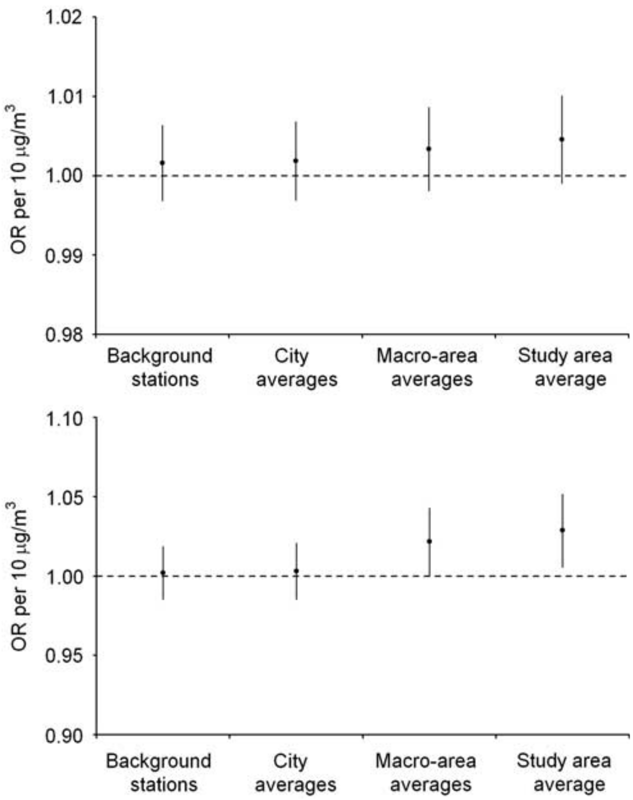

Figure 4. Results of the PM_{10}-mortality association for the whole study period (upper panel) and for the summer periods (1 May to 30 September; lower panel) for the four approaches in the definition of exposure. Percent increases and 95% confidence intervals associated with 10 $\mu g/m^3$ variation in PM_{10} are shown.

introduce bias in the estimation of mean risk. On the other hand, exposures to pollution of ambient origin both take place directly outdoor and as a result from the penetration of ambient pollution indoors. This penetration is generally expressed by a coefficient, which results in an attenuation of the association between exposure and health effects. Pollutant concentrations from indoor sources are not correlated with outdoor concentrations and should have only a minor effect in a time series study on the observed C-R relationship due to the additional exposure variance. It is also theoretically possible that indoor environment filters out some spatio-temporal variability in comparison to outdoor concentration at the same location, but this effect has never been showed in literature.

The third error represents the problems related to assessment of the true ambient levels by means of fixed-site monitoring stations. In the paper by Zeger et al., it was stated that this type of error is close to be of Berkson type and would be cancelled out by spatial averaging across multiple unbiased ambient monitors in a region. We think that this term should be deeply investigated and could be strictly related to our findings. In fact, assessment of true ambient concentrations of pollutants is affected by several problems. First of all, ambient levels are variable across urban areas. Our data suggested that within-city spatial variability is pollutant specific and the deviation from the city average is estimable on annual scale equal to about 15% for PM_{10}, 20% for O_3, and to 60% for NO_2. These differences were much greater on daily scale: up to 50% for PM_{10}, 70% for O_3, and to 120% for NO_2. Temporal correlations among different measuring sites were coherent with literature findings (Ito et al., 2001, 2005), with value ranging from about 0.7 and 0.9 for PM_{10}, from 0.9 to 0.95 for O_3, and from 0.6 to 0.8 for NO_2. Pearson correlation properties, together with the analyses in terms of Lin and Bland–Altman coefficients, showed from low to medium spatial homogeneity of pollutant concentrations within urban areas. These data reflect true spatio-temporal variability in daily levels within urban areas but also experimental errors that perturb the real relationships between different measuring sites.

In fact, measurement errors are the second important issue in view of estimating true ambient levels and population exposure. Monitoring stations are complicated instruments. Errors sometimes are due to intrinsic properties and limits of the experimental methods (for example volatile components for TEOM), but often the problems rely in some components not properly working thus affecting the measure. Measurement errors are either random or systematic and a quantitative estimate of contributions of these two different kinds of errors is in general not available. Systematic errors could be time dependent. Figure 5 shows an example of a sudden change in relative concentrations between two stations (PM_{10}) and a slow drift (NO_2). These are only examples of errors that are difficult to control although quite frequent in air quality data. In addition, these situations are important because not only classical stochastic-type errors with normal distribution bias the mortality–pollution association toward the null, but also time-varying biases between stations.

In many regions, there are quite accurate data quality control, also certified by quality control accurate procedure. However, quality control is generally carried out by inspections of technical personnel, who are trained to identify only macroscopic anomalies. Quality control by means of reference instruments are available only as periodic (for example annual) check. Slow drifts and low entity sudden change in concentrations are generally not considered good reason to invalidate data. In fact, often these situations are to be considered as almost normal.

Finally, the findings from this study related to ozone require some specific remarks. In this case, the increase in spatial scale of aggregation of monitoring station data did not lead to higher risk estimates. This is probably due to its well-known strong spatial homogeneity, which is mainly related to its nature of secondary pollutant, and to the measurement method for ozone, which is in general less affected by errors with respect to PM_{10} or NO_2. The risk estimate obtained

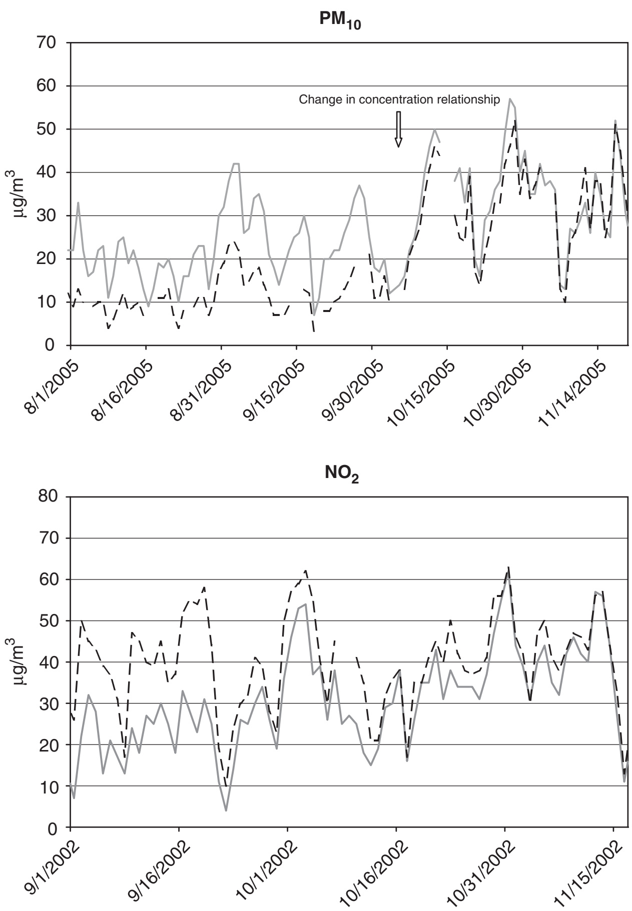

Figure 5. Time-varying relationships between concentrations measured by monitoring stations showing: (upper panel) an example of a sudden change in concentration relationship for two PM_{10} monitoring stations; (lower panel) a slow decrease of the difference in concentrations between two stations measuring NO_2.

using the whole study area for the exposure definition, was very close to the results of the Italian meta-analysis MISA (0.24% *vs* 0.27% increase in total mortality for $10\,\mu g/m^3$ increase in daily mean concentrations). The risk estimate obtained using the macro-areas for the exposure definition was very close to the results of NMMAPS estimate (0.12% *vs* 0.13%) (Bell et al., 2004).

Conclusions

The effect of four levels of increasing spatial aggregation of ambient air pollution data was investigated on epidemiological short-term C-R relationships for PM_{10}, ozone, and NO_2. The results showed higher C-R coefficients and statistical significance for effects of air pollution on mortality for larger spatial scale on which exposure was defined as the mean of fixed-site monitoring stations. This effect was evident for PM_{10} and NO_2 but not for O_3. It is likely that local variability at individual stations, caused by measurement errors and traffic emissions affecting especially PM_{10} and NO_2, is not representative of the variability of the population exposures and leads to exposure misclassification error biasing the C-R relationships toward nil. Averaging of several stations filters out such non-representative local variability at the individual monitoring stations and captures thus better the effective average population exposures. Our findings lead to the unexpected and counterintuitive conclusion that it is more useful to define exposure over larger area rather than at the usually adopted spatial scale of a city where monitoring stations are more correlated and most intuitively linked to the typical ranges of movements of the people. Selecting monitoring stations over larger area reduces the problems related to variations at specific monitoring locations. The current data showed only increasing C-R coefficients for increasing spatial aggregation, thus not reaching the scale where the opposite development begins. It is clear that the aggregation works only when the study area is sufficiently uniform from topographical and meteorological point of view.

For PM_{10} moving from single city to multi-city aggregations, the summer time C-R coefficient increased fivefold from below 0.4% to 2–3% per $10\,\mu g/m^3$; if this increase is taken as a true finding regardless of the limitation of the statistical significance, it would suggest that the short-term mortality effects of PM_{10} could be much higher than previously assumed. On the other hand, the fine PM fraction of PM_{10} has much more stable spatial distributions, and it could be that the aggregated levels represent this fraction; nevertheless, the observed C-R relationship is higher than reported in most time series studies.

There is still a lack of information in the literature about exposure and its surrogate measures, and a comprehensive and quantitative discussion of the effect we found in this study could be undertaken only if more data on the different types of experimental and theoretical errors involved in assigning exposures by means of fixed-site monitoring stations were available.

Conflict of interest

The authors declare no conflict of interest.

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