Toxic urban waste's assault on cardiovascular risk

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ABSTRACT

A cardiovascular health survey of 1203 persons in households located near the hazardous waste disposal sites and in a reference community, was conducted from 2009 until today to assess whether rates of adverse cardiovascular health outcomes were elevated among persons living near the sites. Data included medical records of reported cardiovascular disease certificates and hospital admission for cardiovascular diseases from hospital database. The study areas appeared similar with respect to mortality, cancer incidence, and pregnancy outcomes. In contrast, rate ratios were greater than 1.5 for 2 of 19 reported diseases, i.e., angina pectoris, and strokes. The apparent broad-based elevation in reported diseases and symptoms may reflect increased perception or recall of conditions by respondents living near the sites. Our study found that cardiovascular risk is associated only with $PM_{2.5}$ concentrations, derived from uncontrolled burning of municipal solid waste in particular sites of our country. Their analysis demonstrated a relationship between increased levels of eventual fine particulate pollution and higher rates of death and complications from cardiovascular and cerebrovascular diseases. Management of solid waste releases a number of toxic substances, most in small quantities and at extremely low levels. Because of the wide range of pollutants, the different pathways of exposure, long-term low-level exposure, and the potential for synergism among the pollutants, concerns remain about potential health effects but there are many uncertainties involved in the assessment. Future community-based health studies should include medical and psychosocial assessment instruments sufficient to distinguish between changes in health status and effects of resident reporting tendency.

1. Introduction

Population-based research has indicated an association between ambient fine particulate matter less than 2.5 μm in aerodynamic diameter ($PM_{2.5}$) and cardiopulmonary mortality and morbidity [1–4]. Most of the studies focused on the effects of $PM_{2.5}$, but very few considered the differential toxicity of $PM_{2.5}$ based on its component species. Since ambient $PM_{2.5}$ consists of species from various sources, including traffic emission, biomass combustion, and crustal origination, the $PM_{2.5}$ species originating from different sources and their mixtures may have greater or lesser toxicity. Nevertheless, recent epidemiologic and toxicological findings have suggested the importance of examining particulate matter species-associated biologic responses and possible underlying mechanisms across the range of cardiopulmonary outcomes [5]. A few studies further examined the association of mortality and morbidity outcomes with seasonal and annual averages of $PM_{2.5}$ species, trying to explain the differential city-to-city $PM_{2.5}$ health risk [6–9]. Secondary particulates such as sulfate and nitrate, as well as trace elements like elemental carbon, organic carbon, and sulfur, have been found most responsible for increased mortality and hospital admission. However, controversy remains regarding the specific $PM_{2.5}$ species associated with adverse health effects across locations and seasons. Differences in sources, chemical characteristics, and meteorology might have contributed to the variations. In Asia, although air quality has improved in many urban areas despite increased combustion of fossil fuels, many cities remain highly polluted. Ongoing research efforts support analyses examining variability in air pollution sources and the geographic, meteorological, and population characteristics of Asian populations [10]. From 1994 to early 2008, in southern Italy, existed under a formal State of Emergency, declared due to the saturation of regional waste treatment facilities. There is growing evidence, including a World Health Organization study of the region, that the accumulation of waste, illegal and legal, and urban and industrial, has contaminated the soil, the water, and the air with a range of toxic pollutants including dioxins. A high correlation between incidences of cancer, cardio-respiratory illnesses, and genetic malformations and the presence of industrial and toxic waste landfills was also found [11]. The most affected zones are the areas of north-east Naples' and south-west Caserta which mark the border between the two provinces. The Campania Mortality Atlas published by the Regional Epidemiological

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Observatory showed that from 1998 to 2001 the first cause of illness was cardiovascular related (40% of men, 50% of women) [12]. In the last phase of the research, the health and environmental data were analyzed to specify the links between contamination from waste and the increase of some health issues. It showed statistically relevant correlations between health and waste, confirming the hypothesis that the high rates of mortality and malformation are concentrated in areas contaminated by waste [12].

2. Methods

2.1. Study site and population

A cardiovascular health survey of 1203 persons in households located near the hazardous waste disposal sites and in a reference community, in Southern Italy, was conducted from year 2009 until 2012 to assess whether rates of adverse cardiovascular health outcomes were elevated among persons living near the sites.

2.2. Data collection

We obtained daily mortality data for urban residents from southern Italy Center for Disease Control and Prevention, with medical records for reported cardiovascular disease certificates and with hospital admissions for cardiovascular diseases from hospital database, for the period between January 1, 2009, and December 31, 2012 (3 years of data). The mortality data were for all causes in all age groups, age-specific groups (0–44 years, 45–64 years, ≥65 years), sex-specific groups (female, male), and all-age cause-specific groups (cardiovascular diseases). The *International Classification of Diseases*, Tenth Revision (ICD-10), codes of mortality were as follows: all natural causes (ICD-10 codes A00–R99), respiratory diseases (ICD-10 codes I00–I98), and cardiovascular diseases (ICD-10 codes I00–I99). We also obtained cause-specific death counts for coronary disease, stroke, and chronic obstructive pulmonary disease. We removed the death counts on December 31 and January 1 of each year, because the daily death counts appeared to be much higher than the average death counts on other days, which likely resulted from the recording of unspecified death counts that had accumulated throughout the year.

PM$_{2.5}$ monitoring was conducted at a site located in an urban residential area approximately 10 miles (1 mile = 1.6 km) south of Naples and Caserta, southern Italian cities. PM$_{2.5}$ mass and species analyses were conducted at the laboratories of Institute for Environmental Protection and Research, Air Emission Inventory Unit, Rome ITALY. For these analyses, we obtained daily average concentrations of PM$_{2.5}$ mass between January 1, 2009, and December 31, 2012 (3 years of data). Two subsets of PM$_{2.5}$ samples were further analyzed for elements and anions, which were selected mainly on the basis of the results of health effects assessed in previous studies [6]: organic carbon, elemental carbon, sulfur, potassium, calcium, iron, zinc, chlorine, lead, manganese, bromine, cadmium, nickel, chromium, and the water-soluble anions: ammonium, sulfate, and nitrate. Two sub-data sets included one for daily average concentrations of organic carbon, elemental carbon, and other elements from January 1, 2009, to December 31, 2012 (3 years of data), and one for water-soluble anion data from January 1, 2009, to December 31, 2009 (1 year of data). To adjust for the effects of weather on mortality, we obtained information on the daily averaged temperature and the relative humidity for the study period from the Italian State Meteorology Bureau.

2.3. Statistical methods

Because daily counts of mortality data follow a Poisson distribution, we used Poisson regression models to evaluate the associations between mortality and exposure to PM$_{2.5}$ and to specific species. Natural spline functions [13] of calendar time, temperature, and relative humidity were used to adjust for seasonality and long-term trends and to control for the potential confounding effects of weather. Degrees of freedom of natural spline functions were determined by the Akaike Information Criterion [14], generalized cross-validation, and the literature [15]. If there was an over dispersion in the variance, we applied a partial autocorrelation function (PACF) to guide the selection of degrees of freedom until the absolute values of the sum of PACF for lags up to 30 days reached a minimum. Analyses were also adjusted for year and day of the week as dummy variables to control for different baseline mortality rates for each year and each day of the week. Residuals of each model were examined to check whether there were discernible patterns and autocorrelation by means of residual plots and PACF plots, respectively.

We first assessed the mortality risk in association with exposure to PM$_{2.5}$ mass on the same day (lag 0) and up to 6 prior days (lag days 0–6), using an individual-lag model. We fit the following individual-lag model to obtain the estimated pollution-associated relative rate of increased mortality:

$$\text{Log } E(Yt) = \beta Z_{t-n} + \text{ns}(\text{time}, df) + \text{ns}(\text{temperature}, df)$$
$$+ \text{ns}(\text{relative humidity}, df)$$
$$+ \text{day of the week} + \text{year} + \text{intercept},$$

where $E(Y_t)$ is the expected number of deaths at day t; β represents the log-relative rate of mortality associated with a unit increase of air pollutants; Z_{t-n} indicates the pollutant concentrations at day t to n ($n = 0, 1, ..., 6$) to represent concentrations at various lag days; day of the week and year represent the effects of the day of the week and the time over years; and ns(time, df) denotes the natural spline function of calendar time, whereas ns(temperature, df) and ns(relative humidity, df) denote the natural spline functions of temperature and humidity, respectively.

Because most of the significant associations estimated in the individual-lag model occurred across lag days 0–6, we applied a constrained distributed-lag model to investigate the association between mortality risk and cumulative exposures to PM$_{2.5}$ and major species of the previous week, accounting for the daily effect in the prior week. Our distributed-lag model constrains lag-specific regression coefficients to be a step function by including variables that are averages of the same day's and previous 6 days' concentrations.

Finally, because central space heating is operated for a specific set of months each year in Naples and Caserta, we further stratified the whole-year analysis into the heating period (November 15–March 15) and the no heating period (March 16–November 14). We examined the excess relative risk of PM$_{2.5}$ and selected species on all causes of mortality for the whole year, as well as for the heating and no heating periods, using the individual-lag model and the distributed-lag model. We conducted separate regression analyses of the distributed-lag model for each period and examined the heterogeneity of effect estimates across periods.

All results were presented as the percentage change of excess relative risk of mortality and its 95% confidence interval in association with each 10-μg/m^3 or interquartile-range increase in PM$_{2.5}$ and major species. All analyses were performed by using R, version 2.12.1, statistical software available on the Comprehensive R Archive Network [16].

3. Results

Table 1 provides a descriptive summary of PM$_{2.5}$ mass and species concentrations, as well as meteorological conditions, in for a northeast Naples and south-west Caserta whole year and for the heating and no heating periods between 2009 and 2012. The average PM$_{2.5}$ concentration during the heating period was approximately 60% higher than that observed during the no heating period. Most PM$_{2.5}$ species, except for calcium and iron, had somewhat higher concentrations during the heating period. However, most proportions of major species

Table 1
Summary statistics of PM$_{2.5}$ and component species concentrations ($\mu g/m^3$), meteorological conditions in Naples and Caserta.

	Whole year		Heating		No heating	
	Mean (SD)	IQR	Mean (SD)	IQR	Mean (SD)	IQR
2009–2012						
Temperature, °C	15.3 (9.8)	16.9	3.9 (4.3)	6.3	20.9 (6.2)	9.9
Relative humidity, %	60.6 (17.4)	28.0	58.7 (17.5)	25.0	61.5 (17.4)	28.0
PM$_{2.5}$	176.7 (103.8)	111.8	235.8 (125.1)	169.3	147.0 (75.5)	88.1
2011–2012						
Organic carbon	28.0 (18.7)	18.2	40.7 (20.8)	27.4	21.7 (13.7)	11.0
Elemental carbon	8.8 (5.2)	6.6	10.8 (5.6)	7.5	7.8 (4.8)	5.8
Sulfur	5.1 (3.4)	4.3	6.7 (4.2)	5.6	4.3 (2.6)	3.6
Potassium	1.8 (1.7)	1.5	2.5 (2.0)	1.6	1.5 (1.3)	1.3
Calcium	2.5 (3.3)	2.4	2.1 (2.1)	2.0	2.7 (3.8)	3.0
Iron	1.6 (1.7)	1.2	1.5 (1.0)	1.0	1.7 (2.0)	1.3
Zinc	1.4 (1.2)	1.2	1.8 (1.3)	1.6	1.3 (1.1)	1.0
Chlorine	1.3 (1.5)	1.5	2.3 (1.9)	2.7	0.8 (1.0)	0.9
Lead	0.49 (0.37)	0.40	0.68 (0.46)	0.57	0.40 (0.27)	0.29
Manganese	0.11 (0.08)	0.09	0.13 (0.08)	0.10	0.10 (0.08)	0.08
Bromine	0.04 (0.05)	0.04	0.05 (0.04)	0.05	0.03 (0.05)	0.03
Cadmium	0.03 (0.05)	0.03	0.03 (0.04)	0.04	0.03 (0.05)	0.03
Nickel	0.01 (0.04)	0.01	0.01 (0.03)	0.01	0.01 (0.05)	0.01
Chromium	0.01 (0.01)	0.01	0.02 (0.01)	0.01	0.011 (0.01)	0.01
2009 only						
Ammonium	11.2 (9.1)	11.7	14.5 (10.8)	15.8	9.6 (7.7)	10.7
Sulfate	38.1 (27.0)	34.6	44.8 (31.3)	44.7	34.8 (24.0)	30.7
Nitrate	16.2 (12.9)	16.2	20.5 (14.2)	21.3	14.0 (11.6)	12.5

Abbreviations: IQR, interquartile range; PM$_{2.5}$, particulate matter less than 2.5 μm in aerodynamic diameter; SD, standard deviation.

did not vary significantly across periods, except for nickel. In north-east Naples and south-west Caserta, the carbonaceous species elemental carbon and organic carbon contributed approximately 5% and 16% to PM$_{2.5}$ mass, whereas the secondary particulate species sulfate, nitrate, and ammonium contributed approximately 22%, 9%, and 6%. We observed the highest correlations among all species between PM$_{2.5}$ and sulfate, nitrate, and ammonium (correlation coefficients (r) ranging between 0.65 and 0.75) and between PM$_{2.5}$ and organic and elemental carbon, sulfur, chlorine, potassium, manganese, and lead (r ranging between 0.65 and 0.8) (Table 2). Table 3 summarizes the daily death counts from 2009 to 2012 averaged for the whole year and for the heating and no heating periods in north-east Naples and south-west Caserta. Death counts due to cardiovascular diseases and respiratory diseases accounted for approximately 46% and 10% of all-cause mortality, respectively, whereas deaths in the ≥65-year group accounted for more than 70% of all-cause mortality. The study areas appeared similar with respect to mortality, cancer incidence, and pregnancy outcomes. In contrast, rate ratios were greater than 1.5 for 2 of 19 reported diseases, i.e., angina pectoris, and strokes. Prevalence odds ratios for 23 symptoms were uniformly greater than 1.0, and 12 symptoms had odds ratios greater than 1.5: the typical anginal pain oppressive or constrictive, deep, frightening, sometimes burning, typically triggered by physical activity dyspnea (shortness of breath) with a feeling of suffocation, the pale skin, the state of anguish and terror of the patient, accompanied by palpitations, faintness, dizziness, marked fatigue, nausea and vomiting. The apparent broad-based elevation in reported diseases and symptoms may reflect increased perception or recall of conditions by respondents living near the sites (Table 4).

Table 2
Spearman correlations of PM$_{2.5}$ mass and anions in north-east Naples and south-west Caserta, Campania, Italy, 2009.

	PM$_{2.5}$	Ammonium	Sulfate	Nitrate
PM$_{2.5}$	1.00	0.66	0.69	0.76
Ammonium		1.00	0.96	0.89
Sulfate			1.00	0.85
Nitrate				1.00

PM$_{2.5}$: particulate matter less than 2.5 μm in aerodynamic diameter.

3.1. Mortality effects estimated by the individual-lag model

Table 5 presents the percent change of adjusted excess relative risk of all-cause and cause-specific mortality, per 10-$\mu g/m^3$ and interquartile-range increases in PM$_{2.5}$ concentrations averaged over a 1–2 day lag, estimated by an individual-lag model. In the whole-year analyses, all-cause mortality and cardiovascular mortality were significantly increased by 0.20% (95% confidence interval (CI): 0.07, 0.33) and 0.27% (95% CI: 0.08, 0.46), per 10-$\mu g/m^3$ increase in PM$_{2.5}$ concentration, with adjustment for weather and time-varying effects. Sensitivity analyses showed that, per 10-$\mu g/m^3$ increase, the risk estimates for PM$_{2.5}$ on all-cause mortality remained significant and robust when extremely high values were removed. Individual-lag-day effects of PM$_{2.5}$ exposure on all-cause, cardiovascular, and respiratory mortality in a whole year and during the heating and no heating periods are presented in Fig. 1. Increased all-cause mortality was found to be associated with exposure to PM$_{2.5}$ for the whole year. Specifically, increased all-cause and cardiovascular mortality risks were associated with exposures to secondary aerosols (sulfate, nitrate, ammonium) and combustion species (elemental carbon and sulfur) with lags of 0–3 days for the whole year and with greater risks observed during the heating period.

Table 3
Summary statistics of daily mortality counts in Naples–Caserta, 2009–2012.

	Death counts, mean (SD)		
	Whole year	Heating	No heating
All causes			
All ages	25.8 (9.6)	28.6 (10.4)	24.4 (8.9)
0–44 years	2.5 (1.9)	2.7 (1.9)	2.5 (1.9)
45–64 years	5.3 (3.1)	5.6 (3.1)	5.1 (3.0)
≥65 years	18.0 (7.6)	20.3 (8.3)	16.8 (6.9)
Sex			
Female	10.2 (4.8)	11.5 (5.2)	9.6 (4.5)
Male	15.6 (6.4)	17.1 (6.9)	14.8 (6.1)
Cardiovascular	11.8 (5.8)	13.9 (6.4)	10.8 (5.1)
Coronary	6.2 (3.6)	7.5 (4.0)	5.6 (3.1)
Stroke	4.5 (2.7)	5.2 (2.9)	4.2 (2.6)
Respiratory	2.6 (1.9)	3.1 (2.2)	2.4 (1.8)
COPD	0.9 (1.0)	1.2 (1.2)	0.8 (0.9)

Abbreviations: COPD, chronic obstructive pulmonary disease; SD, standard deviation.

Table 4

Symptom prevalence odds ratios and 95% confidence intervals, high exposed versus comparison area.

Symptom	Prevalence odds ratio	95% CI	
Chest pain oppressive or constrictive	5.95	1.85	19.16
Headache	4.97	1.82	13.63
Fatigue or tired	4.92	1.90	12.77
Nervousness	4.28	1.43	12.73
Sinus congestion	4.27	1.43	12.73
Irritated eyes	3.86	1.72	8.68
Sore throat	2.78	1.17	6.70
Palpitations	2.70	1.02	4.30
Allergies	2.64	1.15	6.04
Difficulty sleeping	2.64	1.25	5.59
Feeling of suffocation	2.28	0.77	6.73
Nausea and vomiting	2.10	1.02	4.30
Stomach pain	2.01	0.95	4.25
Diarrhea	2.01	0.67	6.04
Pale skin	1.89	0.93	3.88
Poor concentration	1.70	0.78	3.68
Faintness	1.68	0.81	3.47
Loss of appetite	1.66	0.63	4.33
State of anguish and terror	1.62	0.77	3.41
Dizziness	1.62	0.79	3.28
Dyspnea (shortness of breath)	1.04	0.51	2.11
Numbness	0.78	0.32	1.91
Earaches	0.64	0.29	1.86

However, the confidence intervals of the effect estimates for sulfate, nitrate, and ammonium are also large, which likely was due to small sample sizes (1 year of daily data). Further, several elements (bromine, chlorine, chromium, nickel, zinc, and lead) showed stronger associations with increased mortality at various lag days in the heating period.

3.2. Mortality effects estimated by the distributed-lag model

Table 6 presents the adjusted mortality risk estimated by the distributed-lag model, per interquartile-range increases in $PM_{2.5}$ exposure averaged for the prior week. A distributed-lag model may underestimate the acute exposure effect that occurred in recent days, such as the same day and 1 or 2 days, by summing up the cumulative effects. Distributed-lag model results estimated an increase of 1.83% (95% CI: 0.29, 3.39) for all-cause mortality and a greater increase of 3.46% (95% CI: 0.78, 6.20) in the cold months, per interquartile-range increases in $PM_{2.5}$ concentrations. We also observed greater mortality risk in the elderly (≥ 65 years), in males, in the heating period for cardiovascular disease. In sequential period-stratified, distributed-lag model analyses

Table 5

Excess relative risk of mortality per 10 µg/m^3 and IQR increases in $PM_{2.5}$ concentration averaged for lag 1–2 days estimated by individual-lag model, in Naples–Caserta, Italy, 2009–2012.

Mortality	Per 10 µg/m^3		Per IQR	
	Excess relative risk, %[a]	95% CI	Excess relative risk, %[a]	95% CI
All causes				
All ages	0.20	0.07, 0.33	2.29	0.83, 3.76
0–44 years	0.23	−0.18, 0.63	2.55	−2.02, 7.33
45–64 years	0.25	−0.04, 0.53	2.80	−0.43, 6.14
≥65 years	0.18	0.03, 0.34	2.09	0.35, 3.85
Sex				
Female	0.25	0.05, 0.45	2.83	0.53, 5.19
Male	0.17	0.00, 0.34	1.92	0.06, 3.83
Cardiovascular	0.27	0.08, 0.46	3.08	0.94, 5.26
Coronary	0.39	0.14, 0.65	4.48	1.53, 7.52
Respiratory	0.19	−0.20, 0.59	2.17	−2.24, 6.77

Abbreviations: CI, confidence interval; IQR, interquartile range of $PM_{2.5}$ averaged for lag 1–2 days: 103.0 µg/m^3; $PM_{2.5}$, particulate matter less than 2.5 µm in aerodynamic diameter.

[a] Excess relative risk is adjusted for temperature, relative humidity, day of the week, and time trend.

of $PM_{2.5}$ species-associated risk for cardiovascular mortalities in all age groups (Table 7), in general, secondary aerosols (sulfate and ammonium), combustion species (elemental carbon, sulfur, and chlorine), and transition metals (chromium, lead, nickel, and zinc) appeared the most responsible for increased risk, particularly in the cold months.

4. Discussion

One of the main problems in dealing with studies on landfill sites is the distinction between sites for municipal solid wastes and sites for other wastes. The definition of different types of waste is far from being standardized across the world. The terms hazardous, special, toxic, industrial, and commercial, are variously applied in different countries and time periods to designate non-household wastes. In addition to causing lung damage, air pollution is now also recognized as a threat to cardiovascular health. Pope et al. examined long-term health data to compare increases in air pollution levels with incidence of death [17]. According to these authors, our study discovered that when air pollution levels suddenly increased, in addition to expected increases in deaths from asthma, pneumonia, and emphysema, there was an unexpected increase in the number of deaths related to heart attacks and stroke. Most surprising was the finding that when air pollution levels rose, so did deaths from all causes, not just those related to the heart and lungs. One possible explanation for the increase in cardiovascular-related deaths is that air pollution causes oxidative stress generated by the organic and metallic compounds adsorbed onto their surface that, in turn, triggers an inflammatory response in the lungs that leads to the release of chemicals that impair heart function and blood pressure [17]. Another mechanism implicated in air pollution-related heart failures involves bone marrow and atherosclerotic plaques.

Van Eeden et al. found that exposure to high levels of air pollution stimulates bone marrow to release leukocytes and platelets that accumulate preferentially in pulmonary capillaries. In addition to causing damage to lung tissues, the researchers also observed that inhalation of particulate pollution causes changes in atherosclerotic plaque lesions that make the deposits more vulnerable to rupture [18]. Diabetics are particularly susceptible to cardiovascular damage caused by airborne pollution. Zanobetti et al. found that diabetics were twice as likely as non-diabetics to be admitted to a hospital with a cardiovascular problem caused by airborne particulate pollution. They also found that persons 75 years of age and older also faced a higher risk of cardiovascular injury [19]. Our study showed that the relationship between urban pollution and ischemic heart disease seems to affect all age groups. There is little information as to whether certain populations such as elderly persons [20] and subjects with a history of heart failure or arrhythmia [21] or high plasma fibrinogen levels [22] may be more sensitive to the ischemic effects of pollution. One study found that excess risk was constantly higher in women than in men, whatever the multivariate statistical model used [23]; this finding deserves to be confirmed by further studies. The risk appears to be higher in patients who had previously been hospitalized for cardiorespiratory diseases [19] or who had already had myocardial infarction [24]. Numerous methodological factors hamper the comparability and power of the our study: difficulty of comparing risks for particles of different aerodynamic diameter which do not have the same health impact (on the respiratory tree in particular), absence of measurement of other traffic-related toxic compounds (PAHs, metallic organic compounds adsorbed onto ultrafine particles), extrapolation of measurements taken by fixed monitors which do not take into account the movement of individuals nor the level of indoor pollution. A disturbance of cardiac autonomic nervous activity could be a complementary harmful mechanism: particular pollution has in fact been associated with decreased heart rate variability [25–27], elevated pulse rate [28], and increased incidence of cardiac arrhythmia [29]. Among the gaseous pollutants, NO and O_3, which are powerful oxidizing agents, may also trigger an inflammatory pulmonary
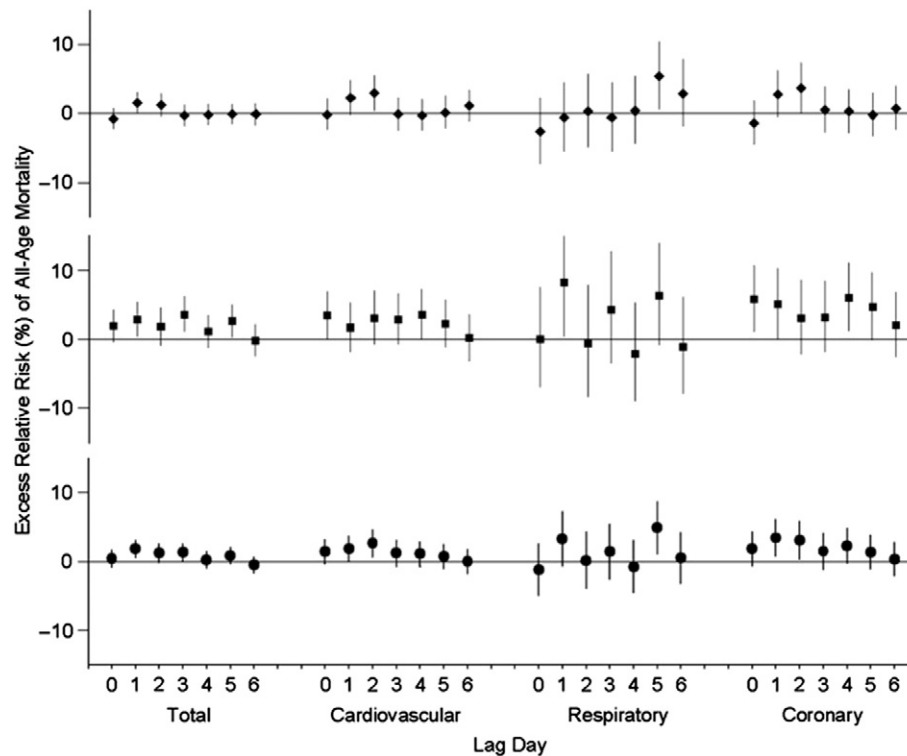
Fig. 1. Individual-lag-day effects of PM[2.5] exposure on all-cause, cardiovascular, and respiratory mortality in a whole year and during the heating and no heating periods.

[30], then systemic reaction with an increase of blood coagulability, fibrinogen, and platelets [31]. An arrhythmic [29] and vasoconstrictor effect [32] has also been previously demonstrated. The role of SO2 itself in the effects observed is unclear. At the present time, its cardiovascular toxicity appears to be related above all to sulfates, pollutants which are combustion by-products and can be adsorbed onto the particular surface [31]. CO, which binds very strongly to hemoglobin to form carboxy hemoglobin, reduces the capacity of hemoglobin to transport oxygen and to deliver it to peripheral tissues, thus contributing to tissue hypoxia. It may also lead to the production of oxidizing agents [33]. Traffic-related air pollution plays a major part in the exposure of the urban population to fine PM, NO, and CO. Ozone is formed for the most part by the interaction between solar radiation and primary pollutants (NO, CO, volatile hydrocarbons) which are present in exhaust fumes. Ozone levels increase at a distance from the points of emission, often in peripheral urban areas, which explains the widely different results observed. Our study on air pollution and cardiovascular disease stresses

that our understanding of the biological mechanisms responsible is still incomplete. Nevertheless, it emphasizes the knowledge acquired: short-term exposure to a high level of particles is associated with increased risk of cardiovascular mortality, and an increased mean level of particles is associated with a marked increase of hospital admissions for several cardiovascular diseases. Dominici et al. confirmed a significant increase of 0.44 (0.02–0.86) in hospital admission rates for ischemic heart diseases (patients aged _65) per 10 mg/m3 increase of PM[2.5]. In addition, it also pointed to higher risk for heart failure: 1.28 (0.78–1.78) and heart rhythm: 3.8 (3.3–4.2). The life expectancy of subjects with prolonged exposure to elevated PM levels could be reduced by some years [34]. Even if the RR levels associated with urban atmospheric pollution are much lower than those of other known cardiovascular risk factors, this does not mean that their impact on health is only a minor one. Pope et al. estimated that the all-cause mortality risk associated with pollution by PM[2.5] is comparable to the risk of cardiovascular mortality associated with moderate obesity (body mass index

Table 6
Excess relative risk of mortality per IQR increases in PM[2.5] estimated by constrained distributed-lag model, in Naples–Caserta, 2009–2012.

Mortality	Whole year		Heating		Non heating	
	Excess relative risk, %[a]	95% CI	Excess relative risk, %[a]	95% CI	Excess relative risk, %[a]	95% CI
All causes						
All ages	1.83	0.29, 3.39	3.46[*]	0.78, 6.20	0.28	−1.74, 2.34
0–44 years	1.88	−2.95, 6.95	−2.50	−10.4, 6.09	2.44	−3.83, 9.12
45–64 years	2.52	−0.91, 6.07	3.21	−2.73, 9.51	0.00	−4.33, 4.53
≥65 years	1.61	−0.23, 3.48	4.28[**]	1.08, 7.58	0.06	−2.37, 2.55
Sex						
Female	2.54	0.10, 5.05	2.83	−1.35, 7.18	2.54	−0.73, 5.92
Male	1.35	−0.63, 3.36	3.88[**]	0.43, 7.45	−1.15	−3.70, 1.46
Cardiovascular	2.97	0.69, 5.29	4.90	1.00, 8.95	1.72	−1.34, 4.87
Coronary	4.83	1.67, 8.09	8.72[**]	3.26, 14.46	1.90	−2.33, 6.31

Abbreviations: CI, confidence interval; IQR, interquartile range of PM[2.5] averaged for lag 0–6 days: 78.9 μg/m3 (whole year), 104.0 μg/m3 (heating period), and 59.7 μg/m3 (no heating period); PM[2.5], particulate matter less than 2.5 μm in aerodynamic diameter.
[*] P = 0.05–<0.10 (significant difference existed between heating and no heating periods).
[**] P < 0.05 (significant difference existed between heating and no heating periods).
[a] Excess relative risk is adjusted for temperature, relative humidity, day of the week, and time trend.

Table 7
Excess relative risk of all-age cardiovascular mortality per IQR increases in selected $PM_{2.5}$ species estimated by constrained distributed-lag model, in Naples–Caserta, 2009–2012.

$PM_{2.5}$ Species	Whole year		Heating		No heating	
	Excess relative risk, %[a]	95% CI	Excess relative risk, %[a]	95% CI	Excess relative risk, %[a]	95% CI
Organic carbon	1.77	−2.03, 5.71	3.43	−3.41, 10.76	2.28	−1.13, 5.80
Elemental carbon	3.00	−0.96, 7.11	10.17[**]	5.26, 15.30	1.53	−3.45, 6.78
Sulfur	0.52	−2.89, 4.05	7.76[*]	1.66, 14.23	0.96	−2.91, 4.99
Bromine	0.92	−2.21, 4.15	1.96	−5.06, 9.49	−0.07	−2.90, 2.83
Chlorine	4.16	−0.12, 8.61	10.04	3.22, 17.32	6.29	1.51, 11.30
Chromium	0.22	−1.64, 2.11	3.78[**]	0.42, 7.25	−0.76	−3.05, 1.58
Potassium	0.91	−2.36, 4.28	0.33	−3.49, 4.30	−0.30	−4.48, 4.07
Nickel	0.07	−0.69, 0.85	2.04[**]	0.90, 3.20	0.00	−1.35, 1.37
Lead	−1.26	−4.34, 1.92	5.26	−1.12, 12.05	2.32	−1.59, 6.38
Zinc	−0.99	−3.96, 2.08	4.48	−0.89, 10.14	1.32	−1.79, 4.53
Ammonium	3.29	−1.97, 8.14	2.55	−7.91, 14.2	−8.03	−19.02, 4.45
Sulfate	4.22	−0.49, 9.24	2.22	−8.43, 14.11	−4.78	−15.82, 7.71
Nitrate	6.32	−1.91, 8.52	4.91	−7.11, 18.48	−0.27	−9.52, 9.92

Abbreviations: CI, confidence interval; IQR, interquartile range; $PM_{2.5}$, particulate matter less than 2.5 μm in aerodynamic diameter.
[*] $P = 0.05$–<0.10 (significant difference existed between heating and no heating periods).
[**] $P < 0.05$ (significant difference existed between heating and no heating periods).
[a] Excess relative risk is adjusted for temperature, relative humidity, day of the week, and time trend.

$30–31.9\ kg/m^2$) [17]. For the combustion and traffic markers elemental and organic carbon in according to Viana et al. and Hammond et al. [35, 36], we observed significant association between elemental carbon and all-cause and cardiovascular diseases mortality, mostly in the heating period. Yet, our findings were consistent with those of previous studies in which the seasonal variation of elemental carbon effects varied with locales and sources. Ostro et al. [2] observed an association between elemental carbon and all-cause mortality in the cold period (October–March) but not in the whole year. Zhou et al. [7] reported that elemental carbon had higher concentrations and stronger effects in the warm period (April–September) in Detroit, while showing higher levels in the cold period (October–March) in Seattle. Ito et al. [8] demonstrated that elemental carbon was significantly associated with cardiovascular mortality in the warm period and nearly significant in the cold period in New York City. For the transition metals, nickel, zinc, chromium, and lead were found mostly associated with all-cause and cardiorespiratory mortality in the heating period. Chromium, nickel, and zinc were reported from industrial and combustion processes and found to be associated with daily mortality in a multicity analysis conducted in Canada [37]. Recent studies provided further evidence that exposure to nickel was related to acute cardiovascular outcome changes [7]. In the current study, we observed approximately 20%–50% concentration increases of major chemical species in $PM_{2.5}$ in the cold months, whereas the proportions of most species remained similar across periods. The overall stronger mortality effects of combustion and secondary aerosols observed in the heating period may not be interpreted as independent influences of coal combustion and traffic alone but uncontrolled burning of municipal solid waste in particular sites of our region, too. Potential seasonal influence and effect modifiers for $PM_{2.5}$ and species-associated health effects warrant further investigation. An important strength of our study is the application of the distributed-lag model in assessing cumulative effects, rather than using models that may estimate the effects of a single day or several days at a particular lag period alone. In our study, the key results of $PM_{2.5}$ and species-associated mortality effects, obtained by both the individual-lag model and the distributed-lag model, are largely in agreement with each other. The distributed-lag model approach better summarized the cumulative effects in association with exposure to $PM_{2.5}$ and species in proceeding days and allowed us to assess the heterogeneity of effects between cold and warm periods. Our results added to previous findings in several ways. First, the relatively high level of $PM_{2.5}$ mass and species observed in southern Italy increased the study power to detect small changes and statistically significant associations. Second, with four years of daily $PM_{2.5}$ mass and 1–3 years of subsets of species data, we were able to assess the seasonal distribution of $PM_{2.5}$ species and the associated

mortality effect over time, which has been rarely studied in the Italian population. Third, our results were consistent with previous findings on combustion-derived species associated with cardiorespiratory mortality and morbidity risk [38,39]. However, the association patterns over time were not always consistent with previous findings, which suggested that $PM_{2.5}$ toxicity may be largely determined by its component species from various sources of the local environment and, thus, the overall $PM_{2.5}$-related effects might be modified by some of its species that differ across locations. Finally, the distinct seasonal pattern of $PM_{2.5}$ species mortality effects observed in our study provided an important rationale to further examine how time-varying factors, such as personal activity and weather conditions, may modify the mortality effects of $PM_{2.5}$ and species [40]. Thus, the interpretation of our results could be limited by the uncertainties with regard to the influence of relative exposure errors on the observed associations across the species. In summary, we observed a significant cardio mortality and cardio morbidity associations with exposure to $PM_{2.5}$ and species from combustion, vehicle emission, and industry process sources and overall from uncontrolled burning of municipal solid waste. The differential seasonal association pattern across species indicated that $PM_{2.5}$-related effects are not sufficiently explained by mass alone. Although understanding the biologic causal mechanism of the $PM_{2.5}$ mortality effect remains challenging, our study, along with the related work of others, provides evidence that primary $PM_{2.5}$ species, as well as time-varying factors, might play important roles in modifying the $PM_{2.5}$ cardio-mortality and morbidity association. More studies examining source-specific health evidence of $PM_{2.5}$ will be critical for developing a comprehensive air control strategy at local and regional scales.

5. Conclusion

In terms of public health, air pollution may be considered as a cardiovascular risk factor which requires urgent action. This study may provide physicians, and cardiologists in particular, with arguments for the recognition of urban pollution as a new risk factor for coronary disease. This risk appears to exist in both the short term (time-series, case cross-over studies) and the long term (cohort studies). It is present even for pollutant concentrations which are below regulation levels. Although the mean cardio-mortality or morbidity risk related to urban atmospheric pollution is low compared with that associated with other better-known risk factors, its impact on health is nevertheless major because of the large number of people who are exposed. The present study has detected a tendency towards clustering of several cardiovascular mortality and morbidity in a fairly well defined area encompassing the northern part of Naples and the southern part of Caserta Provinces.

These results have been adjusted for the possible confounding effect of socioeconomic deprivation, corresponding to the part of southern Italy where most of the illegal practices of dumping toxic wastes took place over time. The adopted study design was not aimed at evaluating cause–effect relationships, since it does not take into account the different possible risk factors, like smoking, life style, and occupation, but rather at pursuing a better knowledge of the spatial distribution of the diseases of interest in an area in which a long-lasting practice of illegal waste management had taken place. This approach represents a step in the construction of an epidemiological framework. Causal relations will then be evaluated integrating epidemiological, clinical and toxicological sources of evidence. Environmental monitoring and epidemiological surveillance might continue in the area, where priorities for environmental reclamation and health investigations can now be selected with more confidence.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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