Particulate Matter and Daily Mortality

A Case-Crossover Analysis of Individual Effect Modifiers

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Background: Several time-series studies have established the relationship between particulate matter (PM_{10}) and mortality. We adopted a case-crossover design to evaluate whether individual socio-demographic characteristics and chronic or acute medical conditions modify the PM_{10}-mortality association.

Methods: We selected all natural deaths (321,024 subjects) occurring among adult (aged 35+ years) residents of 9 Italian cities between 1997 and 2004. We had access to individual information on socio-demographic variables, location of death, and chronic conditions (hospital admissions in the preceding 2-year period). For in-hospital deaths, we collected information on treatment wards at time of death and acute medical conditions. In a case-crossover analysis we adjusted for time, population changes, and meteorological conditions.

Results: PM_{10} was associated with mortality among subjects age 65 years and older (0.75% increase per 10 $\mu g/m^3$ [95% confidence interval = 0.42% to 1.09%]), with a more pronounced effect among people age 85 and older. A weaker effect was found among the most affluent people. The effect was present for both out-of-hospital and in-hospital deaths, especially among those treated in general medicine and other less specialized wards. PM_{10} effects were stronger among people with diabetes (1.03% [0.28% to 1.79%]) and chronic obstructive pulmonary disease (0.84% [0.17% to 1.52%]). The acute conditions with the largest effect estimates were acute impairment of pulmonary circulation (4.56% [0.75% to 8.51%]) and heart failure (1.67% [0.30% to 3.04%]).

Conclusions: Several factors, including advanced age, type of hospital ward, and chronic and acute health conditions, modify the PM_{10}-related risk of death. Altered pulmonary circulation and heart failure are important effect modifiers, suggesting that cardiac decompensation is a possible mechanism of the fatal PM_{10} effect.

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Short-term increases in daily mortality related to airborne concentrations of particulate matter (diameter ≤ 10 μm [PM_{10}]; or ≤ 2.5 μm [$PM_{2.5}$]) have been well established based on large multicity studies conducted in several parts of the world.[1] However, some aspects of the PM-mortality association are still research priorities[2] and identifying specific subpopulations most sensitive to air pollutants is one of the key questions.[3–7] Several individual characteristics have been indicated as potential effect modifiers of the air pollution-mortality association, including age, sex, socioeconomic status,[8–9] preexisting cardiovascular and respiratory diseases,[4,10,11] diabetes,[12–13] obesity,[14] and use of statins.[15] Recently, the modification of the PM_{10}-mortality association was evaluated by several individual factors in a large case-crossover study of 20 US cities, including socio-demographic variables, location of death, and secondary diagnoses on the death certificate.[16] Although the PM_{10}-mortality association in Europe has been well-described, and some effect modifiers at the population level have been identified,[17–18] no individual-level effect modifiers have been evaluated. Even so, clarification of individual susceptibility to air pollution might be useful to understand the physio-pathologic mechanisms leading to the clinical health effects and to reduce exposure of specific subgroups during periods of increased air pollution.

We aimed to identify various conditions that may render persons more likely to die because of particulate air pollution. In particular, we evaluated whether socio-demographic characteristics, place of death and individual clinical attributes are effect modifiers of the PM_{10}-mortality association in 9 Italian cities. As in a previous study on vulnerability to high temperature,[19–20] extensive record linkage procedures were used to characterize subjects for previous and concurrent morbidity.

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METHODS

The study population consisted of 321,024 subjects aged 35 years or older from 9 Italian cities (in north-south order: Turin, Milan, Mestre, Bologna, Florence, Pisa, Rome, Taranto, and Palermo) who died of natural causes (International Classification of Diseases, 9th revision—ICD IX: 1–799) in one of the above-listed cities between 1997 and 2004. Individual records were retrieved from Regional Registers of Causes of Death, which also record age and sex. Census blocks of residence were collected for 4 centers (Turin, Milan, Bologna, Rome) by record linkage with city-specific population registers. This was used to attribute the median income of the census block of residence to each subject (family income in 1998, provided by the Ministry of Finance), as an area-based indicator of socio-economic status. Income was divided into 4 categories from the city-specific distribution: up to the 20th percentile, 20th–50th percentile, 51st–80th percentile, above 80th percentile.

Individual fiscal codes were used to link records from the city-specific mortality datasets with the Regional Hospital Discharge files (which include hospitalizations in public and private hospitals nationwide of all resident citizens) to retrieve individual information about history of hospitalizations over the past 2 years.

Considering location of death, date of hospitalization and date of death, we could distinguish the following: out-of-hospital deaths (neither admission nor discharge within the last 4-week period), subjects discharged between 2 and 28 days before death, in-hospital deaths, and deaths in a nursing home (information on nursing homes available only for Florence, Milan and Turin). For those who died in-hospital, the number of days since they were hospitalized was considered (0–1, 2–28, more than 28 days). In addition, information about the specific hospital ward where the patient was 2 days before death (general medicine, medical or surgical wards with low-moderate care load, medical or surgical wards with high care load, intensive care units) was available for 4 (Bologna, Milan, Rome, and Turin) of the 9 cities.

Chronic and acute conditions for all subjects were defined based on the time elapsed between hospitalization and death. For each individual, all hospital admissions in the 2 years preceding death (excluding the last 28 days) were selected, considering both primary causes of admission and secondary contributing diagnoses. Each subject was classified according to a list of 17 groups of diagnoses chosen by adapting the Elixhauser list of comorbidities.[21] The 28-day window was applied to distinguish chronic conditions from suddenly deteriorating health in the few weeks or days before death. Finally, for subjects who died in-hospital, we evaluated the acute clinical factors that contributed to death considering a group of conditions noted as primary diagnoses on the hospital records during the last 28 days.

Environmental Data

Data on PM_{10} from fixed monitoring sites representing concentrations in residential areas were collected for each city according to standard procedures already employed in several European studies of air pollution.[22] Three different methods have been used to measure PM_{10} in Italy: beta automatic, tapered element oscillating microbalance (TEOM) and gravimetric. The beta automatic method is well in agreement with the gravimetric method, whereas TEOM underestimates PM_{10}, especially at high levels of concentrations. Therefore, we applied conversion factors when data from TEOM were available. We obtained hourly or daily values of PM_{10}, according to the different methods of measure, through city-specific air monitoring networks managed by Regional Environmental Protection Agency or local authority. For valid 24-hour mean values, at least 75% of the hourly data for each monitor needed to be present. For each city we estimated a daily average by averaging monitor-specific daily means.[23] Missing data on the aggregate level were replaced using a formula adapted from the APHEA (Air Pollution and Health—A European Approach) method.[22] In particular, when the daily information for a station was missing, it was imputed as a weighted mean of values from other stations. When the daily data of a pollutant were missing for all available stations, the value was left missing. The average of the current and the preceding day means PM_{10} (lag 0–1) was used as the exposure variable on the basis of previous investigations.[17,23]

Daily information on temperature, humidity and barometric pressure were provided by the Italian Air Force Meteorological Service. Apparent temperature[24] (a composite index that takes into account air temperature and humidity at the same time) was calculated. Information on city-specific influenza epidemics were collected from the national surveillance system. Influenza epidemics were defined on the basis of the weekly estimates of influenza incidence, as reported by the Italian National Institute of Health.

Data Analysis

The case-crossover approach[25] was applied to study the effect of PM_{10} (lag 0–1) on all noninjury mortality. This is a special case-control design in which every case serves as its own control, where control records are defined as days on which the subject did not experience the study outcome. Since each case-set is made up of a single subject, all individual time-invariant characteristics are perfectly matched, and this removes the need for adjustment for each potential known or unknown individual confounder. Control-days were selected according to the time-stratified approach, by dividing the study period into monthly strata and matching controls with cases on the same days of the week within each stratum.[26]

A conditional logistic regression was thus applied to each city, while controlling for influenza epidemics, population decreases during vacation periods, holidays, and baro-

metric pressure, while time-trends and day of the week were controlled for by design. Controlling for the confounding effect of apparent temperature was more complex. Many studies have documented the J-shaped relationship between high summer temperatures and total mortality,[19,27–29] while a few have depicted the relationship between cold temperatures and mortality as linear with negative slope.[30] In the present study we combined the 2 components. 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 catch the latent effect of cold temperatures. The central and right side of the curve instead were fitted by superimposing a piecewise linear spline of apparent temperature (lag 0–1) with 2 city-specific inner knots chosen based on visual inspection, AIC, and segmented regression.[31]

For each city, the effect of 10 $\mu g/m^3$ change in PM_{10} (lag 0–1) on daily mortality was studied. Since we were interested in effect modification by several individual conditions, no attempt was made to explore different lags. Because age is the strongest determinant of mortality, and is typically correlated with many of the modifiers examined, we standardized the stratum-specific estimates by age group in the effect-modification analyses. The weights were chosen as the relative frequencies of the age groups 65–74, 75–84 and 85+ years in the total population of people 65+ year old in the 9 cities together.

Finally, a random-effects meta-analysis of the city-specific estimates was performed, using the maximum likelihood method.[32] All results are expressed as percent increase in risk of death and 95% confidence intervals (95% CI) associated with a 10 $\mu g/m^3$ variation in PM_{10} (lag 0–1). Effect modification was tested, and *P* values of the comparisons between the putative effect modifiers and their reference categories are reported. The statistical analyses were performed using R software version 2.3.0,[33] and Stata 8.0.[34]

RESULTS

Table 1 shows the study period in each city, the number of deaths included in the analysis, and the environmental characteristics, including the number of fixed monitoring sites. The period of study varied from a minimum of 3 years (Mestre, Palermo, and Taranto) to a maximum of 7 years (Rome and Turin). Annual PM_{10} levels ranged from an average of 35.1 $\mu g/m^3$ in Pisa to 71.5 $\mu g/m^3$ in Turin. Mean apparent temperature was lower in the northern cities (Milan and Turin), intermediate in central cities (Rome, Florence), and higher in southern cities (Palermo and Taranto).

The effect of PM_{10} increased with age (Table 2), with a null effect on 35–64 year olds and a large effect on 85+ year olds. Therefore, the overall effect on the 65+ year old group was slightly higher (0.75% increase [95%CI = 0.42% to 1.09%]) than the corresponding effect in the 35+ years age group (0.60% increase [0.31% to 0.89%]). Because age was found to be such a significant effect modifier, we restricted all subsequent analyses among the elderly (65+ years) and performed the age adjustment in all effect modification analyses as indicated in the methods. Figure 1 shows the city-specific and combined results of the association between PM_{10} and overall mortality in the 65+ years group. All city-specific point estimates were positive, although they were not homogenous, with the lowest value found in Taranto and the highest in Florence.

Table 2 shows the age-adjusted pooled results of the association between PM_{10} and mortality by sex, area-based-income and location of death; *P* values for the effect modification are also reported. The PM_{10}-mortality association showed very similar effect estimates for men and women.

TABLE 1. Population and Environmental Variables Studied From the 9 Italian Cities, Years 1997–2004

			PM_{10} ($\mu g/m^3$)					Apparent Temperature (°C)	Barometric Pressure (hPa)
City	Period of Study	No. Deaths[a]	No. Monitors	Mean (SD)	5th Percentile	95th Percentile	No. Days Missing	Mean (SD)	Mean (SD)
Bologna	2000–2003	16,612	1	50.4 (31.7)	16.0	114.0	50	13.7 (10.0)	1.016 (7.4)
Florence	2000–2003	14,356	3	37.5 (16.6)	15.8	68.9	38	15.2 (9.2)	1.016 (6.7)
Mestre	1999–2001	5,053	2	48.1 (26.8)	14.3	98.9	12	14.7 (10.4)	1.017 (7.4)
Milan	1999–2004	62,559	1	57.9 (38.0)	19.0	137.0	3	13.5 (9.3)	1.014 (12.3)
Palermo	2002–2004	16,331	7	36.2 (21.7)	19.7	61.5	0	19.0 (7.9)	1.014 (5.5)
Pisa	2000–2003	3,713	3	35.1 (14.9)	16.2	64.3	127	14.8 (8.8)	1.016 (7.0)
Rome	1998–2004	145,845	4	47.3 (19.9)	21.8	84.4	8	15.7 (8.6)	1.015 (6.6)
Taranto	2001–2003	4,309	2	59.6 (18.8)	31.9	90.6	191	16.7 (8.1)	1.016 (5.9)
Turin	1997–2003	52,246	1	71.5 (38.1)	26.0	147.0	70	11.9 (9.4)	1.017 (7.6)

An additional fixed monitor was used in Milan and in Turin to impute missing values when needed.
According to the European Commission Council Directive 1999/30, the annual average PM_{10} standard is 40 $\mu g/m^3$.
[a]Age 35+ years.

TABLE 2. Percent Increase in Risk of Death Associated With a 10 $\mu g/m^3$ Variation in PM_{10} (lag 0–1), by Age, Sex, Median Income, and Location of Death: Age-Adjusted Pooled Estimates of the 9 Cities, Years 1997–2004

Variables	No. (%)	Effect of 10 $\mu g/m^3$ of PM_{10}		
		Percent Increase of Risk	(95% CI)	P[a]
Total no. deaths	321,024[b] (100.0)	0.60	(0.31 to 0.89)	—
Age; yr[b]				
35–64	45,935 (14.3)	−0.20	(−0.77 to 0.37)	—
65–74	66,508 (20.7)	0.51	(0.05 to 0.98)	0.057
75–84	104,698 (32.6)	0.59	(0.20 to 0.97)	0.026
85+	103,877 (32.4)	0.97	(0.53 to 1.42)	0.002
Population aged 65+ yr	275,083 (85.7)	0.75	(0.42 to 1.09)	—
Sex				
Men	127,760 (46.4)	0.72	(0.37 to 1.07)	—
Women	147,312 (53.6)	0.83	(0.33 to 1.33)	0.733
Median income (by census block)[c]				
Low (<20th percentile)	52,419 (19.1)	0.80	(−0.02 to 1.62)	—
Mid-low (20th–50th percentile)	70,518 (25.6)	0.68	(0.25 to 1.12)	0.806
Mid-high (51st–80th percentile)	67,819 (24.7)	0.85	(0.40 to 1.30)	0.919
High (>80th percentile)	45,056 (16.4)	0.30	(−0.25 to 0.86)	0.324
Location of death				
Out-of-hospital	100,621 (36.6)	0.71	(0.32 to 1.11)	—
Discharged 2–28 d before death	22,982 (8.4)	1.34	(0.49 to 2.20)	0.189
In-hospital	140,400 (51.0)	0.65	(0.33 to 0.97)	0.817
Nursing home[d]	11,074 (4.0)	−0.04	(−1.02 to 0.95)	0.168

[a]The P value refers to the effect modification between stratum-specific estimate and the estimate from the reference category.
[b]Totals for variables below do not add to this number because of missing values.
[c]Available only for Bologna, Milan, Rome, and Turin.
[d]Available only for Florence, Milan, and Turin.

There was a weaker PM_{10} effect (0.30% vs. 0.80%) among the most affluent people (the upper quintile of median income of the census block of residence) compared with the least affluent subjects (lowest quintile), although the interaction term was not statistically significant. There was no clear effect modification of the location of death. The effect of particulate matter on mortality remained strong for those who died in a hospital (0.65% [0.33% to 0.97%]) and was comparable to the effect detected in those who died out-of-the hospital (0.71% [0.32% to 1.11]). The highest risk was found for those who died at home who had been recently discharged from a hospital (1.34% [0.49% to 2.20%]); the lowest risk was for those who died in nursing homes (although the information was limited to 3 cities).

Table 3 displays the combined results of primary and secondary contributing causes of admissions between 29 days and 2 years before death for the 17 groups of diagnoses. The effect estimates were similar for those who were hospitalized in the 2-year period (175,625 subjects) and those who were not (99,458 subjects) (0.63% vs. 0.80% increase). When effect modification was evaluated with a statistical test, no chronic condition seemed to confer a specific susceptibility. However, increased risks were found for patients with diabetes (1.03% [0.28% to 1.79%]), patients with hypertension (0.54% [0.00% to 1.10%]), and with chronic pulmonary diseases (0.84% [0.17% to 1.52%). There were also a number of diseases that showed below average effect estimates (for malignant neoplasms, 0.17% [0.49% to 0.84%]; for coagulation defects: −3.46% [−6.42% to 0.40%]; for other ischemic heart diseases: 0.02% [−0.65% to 0.69%]).

Table 4 reports the results of the analyses restricted to in-hospital deaths (140,400 subjects). The age effect was confirmed, with the highest risk among those 85+years (0.82% [0.27% to 1.37%]). There were no sex differences. There were slight differences in the effect of PM_{10} according to the time elapsed since the hospitalization (0–1 day, 2–28 days, more than 28 days) with a tendency of a stronger effect among those admitted more recently. The effect among people last admitted 2–28 days before death, who were thus inside the hospital when exposed to the lagged PM_{10}, was 0.63% (0.22% to 1.05%). The in-hospital PM_{10} effect was different by ward, ie, it was higher for patients staying in general medicine (0.48%) or "low-load" care units (0.75%), while it was null for those staying in high-load or intensive

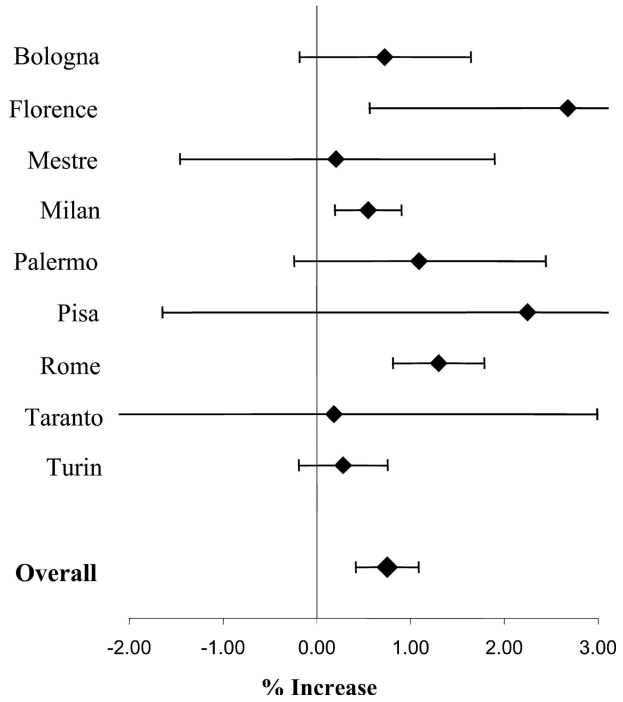

FIGURE 1. Forest plot of city-specific and overall results of the PM_{10}-mortality association for the 65+ year age group: diamonds represent percent increases in risk and horizontal lines represent 95% CIs associated with 10 $\mu g/m^3$ variation in PM_{10} (lag 0–1).

care units (−1.11% and 0.07%, respectively) (*P* values for effect modification = 0.14 and 0.74).

Table 5 shows the results of the analysis conducted among 111,511 subjects who died in-hospital according to the primary diagnosis that led to their last hospitalization (≤28 days before death). The conditions with the largest effect estimates were diseases of pulmonary circulation (acute and chronic pulmonary heart diseases) (4.56% [0.75% to 8.51%]) and heart failure (1.67% [0.30% to 3.04%]). When the analyses of acute conditions were restricted to 86,717 patients admitted to the hospital 2–28 days before death, and who were therefore indoors during the PM_{10} 0–1 lag effect (Table 6), effect modification for pulmonary circulation disorders (4.83% [0.08 to 9.81], *P* value for effect modification = 0.081) and heart failure (2.44% [0.86 to 4.05], *P* value for effect modification = 0.017) was suggested.

DISCUSSION

The study indicates an overall PM_{10} effect on total mortality similar to what has been reported in the European APHEA study[22] and in a recent meta-analysis.[35] However, there are individual effect modifiers of the PM_{10} effect. Higher estimates were found for very elderly people, and social class differences were suggested, particularly lower effects among the most affluent subjects. The risk was higher in noninstitutionalized people, especially among those recently discharged from the hospital. However, a PM_{10} effect was detected also among hospitalized patients, with the exception of those in more intensive care. Admission to the hospital in the past 2 years was not an important risk modifier. Finally, among recently hospitalized patients, pulmonary heart diseases and acute heart failure clearly increased the PM_{10}-related risk of death.

Several studies have found a stronger effect of PM_{10} on mortality in the elderly,[16,17] and our results confirm that risk increases with age; subjects 85+ years of age had almost double the risk of 65–74 years olds. The cause of this greater susceptibility may be chronic medical conditions or the loss of compensation mechanisms in the cardio-respiratory system.[11] In contrast to previous findings,[36] but in agreement with a large American study,[16] we did not find a sex effect. Previous research has found effect modification by social class when comparing area-specific analyses of low-SES and high-SES communities,[9,37] but there was little evidence of effect modification in a large study in the US[38] that considered national data. Another American study[16] that used individual education level found that risk in low educational groups was almost twice as high as in highly educated people. Similarly, an analysis that classified residents of Rome based on an area-based index of socioeconomic status (SES) did not find a PM_{10} effect on daily mortality in high SES groups but found a strong effect in the other SES groups.[39] Our study indicates that social class modifies the effect of air pollution 2-fold between those in the low (0.80%) and in the high (0.30%) income categories. Differential susceptibility may be the result of disparities in lifestyle factors, such as tobacco and alcohol use, physical activity, and occupational exposure to toxins, as wells as to reduced access to community and hospital care. Differential exposure to air pollution is an additional possibility, although this was not seen in 1 study.[30]

The present study provides new insights regarding place of death as an effect modifier. In North American studies, most of the effect of environmental factors such as air pollution and high temperatures has been observed among people who died outside the hospital[16,40]; a lower effect has been found among in-patients. The use of air filtration and air conditioning in US hospitals has been indicated as the primary explanation. In Italy, air filtration is used only in modern hospitals and the majority did not have air conditioning (until the 2003 heat wave), the exception being intensive care units. In-hospital mortality has been found associated with high temperatures in a study conducted in 4 Italian cities,[19–20] and lack of air conditioning was the likely explanation. Similarly, hospital environments in Italy do not offer protection against air pollution because of the lack of air conditioning, with the exception of specialized and intensive care units where air filtration is common. Usually, windows tend to be open in summer and in the warmers parts of spring

TABLE 3. Percent Increase in Risk of Death Associated With a 10 $\mu g/m^3$ Variation in PM_{10} (lag 0–1), by Primary or Contributing Secondary Cause of the Hospital Admissions in the 2 Years Before Death (Excluding Last 28 Days), Among People Aged 65+ Years: Pooled Estimates of the 9 Cities, Years 1997–2004

		Effect of 10 $\mu g/m^3$ of PM_{10}		
Variables	**No. (%)**	**Percent Increase of Risk**	**(95% CI)**	***P*[a]**
Population aged 65+ yr	275,083 (100.0)	0.75	(0.42 to 1.09)	—
Hospitalization between 29 d and 2 yr before death				
No	99,458 (36.2)	0.80	(0.35 to 1.26)	—
Yes	175,625 (63.8)	0.63	(0.32 to 0.94)	0.528[b]
Groups of diseases as primary or contributing secondary cause of the hospital admission[c]				
Malignant neoplasms (ICD-9: 140–208)	67,275 (38.4)	0.17	(−0.49 to 0.84)	0.064
Disorders of thyroid gland (ICD-9: 240–246)	5,820 (3.3)	1.05	(−0.61 to 2.73)	0.711
Diabetes mellitus (ICD-9: 250)	30,173 (17.2)	1.03	(0.28 to 1.79)	0.457
Anemias (ICD-9: 280–285)	25,511 (14.6)	0.55	(−0.21 to 1.33)	0.656
Coagulation defects (ICD-9: 286–287)	2,442 (1.4)	−3.46	(−6.42 to −0.40)	0.007
Diseases of valves (ICD-9: 394.0–397.1, 424, 746.3–746.6, 093.2)	9,130 (5.2)	0.44	(−0.86 to 1.75)	0.656
Hypertensive disease (ICD-9: 401–405)	52,494 (30.0)	0.54	(0.00 to 1.10)	0.438
Previous acute myocardial infarction (ICD-9: 410, 412)	12,529 (7.2)	0.27	(−0.84 to 1.40)	0.412
Other ischemic heart diseases (ICD-9: 411, 413–414)	35,041 (20.0)	0.02	(−0.65 to 0.69)	0.030
Diseases of pulmonary circulation (ICD-9: 415–417)	4,907 (2.8)	1.29	(−0.63 to 3.25)	0.586
Conduction disorders (ICD-9: 426)	7,106 (4.1)	0.95	(−0.67 to 2.60)	0.808
Cardiac dysrhythmias (ICD-9: 427)	35,743 (20.4)	0.20	(−0.45 to 0.86)	0.117
Heart failure (ICD-9: 428)	29,707 (17.0)	0.53	(−0.18 to 1.24)	0.560
Cerebrovascular diseases (ICD-9: 430–438)	40,151 (22.9)	0.45	(−0.17 to 1.06)	0.323
Diseases of arteries, arterioles, and capillaries (ICD-9: 440–448)	17,300 (9.9)	0.66	(−0.32 to 1.64)	0.876
Pneumonia (ICD-9: 480–486)	16,284 (9.3)	0.43	(−0.47 to 1.34)	0.495
Chronic pulmonary diseases (ICD-9: 490–505)	34,267 (19.6)	0.84	(0.17 to 1.52)	0.773

[a]The *P* value refers to the effect modification between those with and without a hospitalization for each group of diseases.
[b]The effect modification is relative to those never admitted to a hospital between 29 days and 2 years before death.
[c]Percentages are calculated on the total number of subjects (175,625) aged 65+ years and hospitalized at least once between 29 days and 2 years before death.

and fall. In our study people recently discharged from a hospital had a higher PM_{10} effect (1.34% increase). The reasons for such high vulnerability should be studied.

We were expecting our detailed search of chronic conditions using previous hospital admissions to allow us to single out the specific clinical factors associated with vulnerability to PM_{10}. Some conditions were strong candidates. For instance, studies[41–43] have reported hypertension as a modifier of the effects of air pollution. A similar phenomenon may occur in subjects with chronic obstructive pulmonary disease (COPD); Sunyer et al,[44] De Leon et al,[45] and Forastiere et al[46] have reported higher risks of circulatory deaths in subjects with COPD. Finally, there are suggestions that the association between particulate matter and health effects is stronger in persons with increased baseline systemic inflammation and oxidative stress, such as patients with diabetes, obese individuals, and people not using statins.[15,47] Contrary to those findings, we were not able to detect specific conditions with particularly high effect estimates, based on previous hospital admissions. In general, the strength of the PM_{10} effect was the same for those who had been hospitalized in the 2 preceding years and those who had not. It should be noted, however, that the PM_{10} effects were robust among people previously hospitalized for diabetes, hypertension and COPD. Overall, the results suggest that the associated effects of PM_{10} are widespread and not necessarily limited to persons with severe conditions requiring hospital care. On the other hand, cardiovascular, respiratory and metabolic diseases are highly prevalent in the general population and do not always require hospital admission. Although our work did

TABLE 4. Percent Increase in Risk of Death Associated With a 10 $\mu g/m^3$ Variation in PM_{10} (lag 0–1), by Age, Sex, Period of the Last Hospital Admission, and Hospital Ward, Among People Aged 65+ Years Who Died in the Hospital: Pooled Estimates of the 9 Cities, Years 1997–2004

		Effect of 10 $\mu g/m^3$ of PM_{10}		
Variables	**No. (%)**	**Percent Increase of Risk**	**(95% CI)**	***P*[a]**
Population aged 65+ yr died in hospital	140,400 (100.0)	0.65	(0.33 to 0.97)	—
Age; yr				
65–74	38,186 (27.2)	0.26	(−0.35 to 0.87)	—
75–84	56,843 (40.5)	0.80	(0.29 to 1.31)	0.184
85+	45,371 (32.3)	0.82	(0.27 to 1.37)	0.182
Sex				
Men	69,729 (49.7)	0.66	(0.18 to 1.13)	—
Women	70,668 (50.3)	0.63	(0.17 to 1.09)	0.934
Period of the last hospital admission (days before death)				
0–1	24,794 (17.7)	0.75	(0.00 to 1.51)	0.696
2–28	86,717 (61.8)	0.63	(0.22 to 1.05)	0.831
>28	28,889 (20.6)	0.54	(−0.17 to 1.26)	—
Hospital ward (relative to 2 d before death)[b]				
General medicine, geriatry, psychiatry, rehabilitation	38,079 (27.1)	0.48	(−0.04 to 1.00)	—
Low-load care units	19,089 (13.6)	0.75	(−0.07 to 1.58)	0.577
High-load care units	4,487 (3.2)	−1.11	(−3.13 to 0.95)	0.142
Intensive care units	7,711 (5.5)	0.07	(−2.28 to 2.47)	0.743

[a]The *P* value refers to the effect modification between stratum-specific estimates and the reference category.
[b]Available only for Bologna, Milan, Rome, and Turin.

not specifically address the issue of mortality displacement, our results may suggest that the association between particulate matter and mortality does not involve only an advance in the timing of death by few days in a selected group of frail individuals.[48]

The observation that people with a previous diagnosis of cancer, coagulation defects or other ischemic heart diseases were not affected by air pollution should be noted; there was statistical evidence of effect modification. We have no ready explanation for these findings, although one may speculate that the diseases themselves or their treatments may interfere with the effects of airborne particles. Patients with malignant cancer are at high risk of death and they usually receive chemotherapy and radio-therapy that produce very high oxidative stress, so that the additional strain produced by air pollution may be not important. Recent literature[49] suggests that air pollution is associated with changes in global coagulation function with a tendency towards hyper-coagulability after short-term exposure to air pollution. People who already have coagulation problems may be less susceptible to this mechanism especially if chronic coagulation interfering drugs are used. Finally, people with chronic ischemic heart diseases may be taking antithrombotic drugs (eg, aspirin) and agents that lower cholesterol (eg, statins) that would modify their risk profile. These findings need confirmation.

We found evidence that the PM_{10} risk is doubled among patients with heart failure and quadrupled among those with disorders of pulmonary circulation. Heart failure due to left-ventricular systolic dysfunction is usually associated with pulmonary hypertension. Increased blood pressure in lung vessels is also secondary to pulmonary embolism and COPD, leading to right heart failure and cor pulmonale. The prevalence of these conditions in the general population is relatively high, especially among the elderly (5%–10% above 65 years).[50] Very few studies have been able to consider clinical events in the last day or days before death as possible effect modifiers of the air pollution-mortality association, and suggestive indications are available for heart failure. Goldberg et al[4,11] estimated the association between daily mortality and daily concentrations of particles in the ambient air of Montreal, Quebec among individuals with cardiovascular and respiratory conditions diagnosed before death. People who had acute lower respiratory diseases and congestive heart failure shortly before death had a particulate matter-associated mortality about twice that found over the entire study population. Kwon et al[51] selected a cohort of congestive heart failure patients from the medical insurance files of a hospital among residents of Seoul, South Korea. Effects attributable to PM_{10} among the ill cohort appeared larger than among the general population and a stronger effect of urban particles

TABLE 5. Percent Increase in Risk of Death Associated With a 10 $\mu g/m^3$ Variation in PM_{10} (lag 0–1), by Primary Cause of the Hospital Admissions in the Last 28 Days before Death, Among People Aged 65+ Years Who Died in the Hospital: Pooled Estimates of the 9 Cities, Years 1997–2004

		Effect of 10 $\mu g/m^3$ of PM_{10}		
Variables	**No. (%)**	**Percent Increase of Risk**	**(95% CI)**	***P*[a]**
People hospitalized within the last 28 d before death	111,511 (79.4)	0.66	(0.30 to 1.02)	0.405[b]
Groups of diseases as primary cause of the hospital admission[c]				
Malignant neoplasms (ICD-9: 140–208)	27,902 (25.0)	0.86	(−0.05 to 1.78)	0.677
Diabetes mellitus (ICD-9: 250)	993 (0.9)	−1.54	(−6.27 to 3.42)	0.375
Anemias (ICD-9: 280–285)	1,202 (1.1)	−1.10	(−7.56 to 5.82)	0.609
Hypertensive disease (ICD-9: 401–405)	803 (0.7)	−4.06	(−11.98 to 4.57)	0.275
Acute myocardial infarction (ICD-9: 410)	6,774 (6.1)	−0.07	(−1.53 to 1.42)	0.328
Other acute ischemic heart diseases (ICD-9: 411)	692 (0.6)	−0.70	(−6.59 to 5.55)	0.662
Diseases of pulmonary circulation (ICD-9: 415–417)	1,319 (1.2)	4.56	(0.75 to 8.51)	0.043
Cardiac dysrhythmias (ICD-9: 427)	5,715 (5.1)	−0.77	(−2.67 to 1.18)	0.135
Heart failure (ICD-9: 428)	9,569 (8.6)	1.67	(0.30 to 3.04)	0.123
Cerebrovascular diseases (ICD-9: 430–438)	15,040 (13.5)	0.41	(−0.84 to 1.67)	0.677
Diseases of arteries, arterioles, and capillaries (ICD-9: 440–448)	2,828 (2.5)	1.89	(−1.40 to 5.29)	0.466
Pneumonia (ICD-9: 480–486)	5,875 (5.3)	0.51	(−1.18 to 2.23)	0.868
Chronic pulmonary diseases (ICD-9: 490–505)	2,608 (2.3)	1.19	(−1.49 to 3.95)	0.704
Renal failure (ICD-9: 584–588)	2,608 (2.3)	−0.21	(−2.59 to 2.23)	0.478

[a]The *P* value refers to the effect modification between those with and without a hospitalization for each group of diseases.
[b]The effect modification is relative to those never admitted to a hospital during the last 28 days before death.
[c]Percentages are calculated on the total number of subjects (111,511) aged 65+ years who died in-hospital and hospitalized at least once within the last 28 days before death.

was found in patients for whom a shorter period (<1 month) had elapsed since the index hospitalization than among patients who had survived the first month. Finally, in a large investigation of daily hospital admission rates from 1999 to 2002 in 204 US counties,[52] the largest $PM_{2.5}$ effect was found on heart failure.

The findings regarding heart failure and pulmonary heart conditions may help in understanding the mechanisms of the PM_{10} effect. Goldberg et al[11] have already suggested that ambient particles may affect the heart indirectly by modifying endothelin homeostasis in the lungs. He speculated that elevated circulating endothelins, associated with oxidative stress linked to particulate matter exposure, exacerbate congestive heart failure, precipitate ischemic heart disease, promote infarct extension, and also possibly affect individuals with conditions involving endothelial dysfunctions such as diabetes and atherosclerosis. Endothelin-1, an endothelium-derived mediator, has fibrogenic and inflammatory properties, is a potent vasoconstrictive agent, has inotropic and mitogenic actions, modulates salt and water homeostasis and plays an important role in maintaining vascular tone and blood pressure. Consequently, endogenous endothelin-1 contributes to the pathophysiology of conditions associated with sustained vasoconstriction, such as heart failure[53] and unregulated pulmonary hypertension.[54]

Several strengths of the present study deserve consideration. This study involved 9 cities and more than 300,000 deaths. The overall results are robust and the case-crossover analysis gives estimates consistent with those obtained in the APHEA study[17] and in a previous Italian time-series analysis.[23] Linking individual data records offered the opportunity to exploit individual information that is rarely available in other European countries. Adjusting for age in evaluating effect modification allowed us to assess the independent role of several factors that are linked to age.

Some limitations must also be taken into account. Chronic clinical conditions are based on hospital admissions and suffer from the limits of accuracy of the source used.[55] In addition, simple hospital discharge summaries provide only an approximation of acute illnesses or exacerbations of chronic diseases. We tried to increase the sensitivity of the definition of chronic conditions by using all hospital admissions in the period of 29 days to 2 years before death and by considering both primary and contributory causes. Studying the clinical conditions that characterized the subjects in the few weeks before death is more complex. The information

TABLE 6. Percent Increase in Risk of Death Associated With a 10 $\mu g/m^3$ Variation in PM_{10} (lag 0–1), by Primary Cause of the Hospital Admissions in the 2–28 Days Before Death, Among People Aged 65+ Years Who Died in the Hospital: Pooled Estimates of the 9 Cities, Years 1997–2004

		Effect of 10 $\mu g/m^3$ of PM_{10}		
Variables	**No. (%)**	**Percent Increase of Risk**	**(95% CI)**	***P*[a]**
People last hospitalized within the last 2–28 d before death	86,717 (61.8)	0.63	(0.22 to 1.05)	—
Groups of diseases as primary cause of the hospital admission[b]				
Malignant neoplasms (ICD-9: 140–208)	24,578 (28.3)	0.61	(−0.37 to 1.60)	0.916
Diabetes mellitus (ICD-9: 250)	792 (0.9)	0.64	(−5.86 to 7.60)	0.993
Anemias (ICD-9: 280–285)	1,065 (1.2)	−0.62	(−6.45 to 5.58)	0.689
Hypertensive disease (ICD-9: 401–405)	664 (0.8)	−3.86	(−14.71 to 8.38)	0.459
Acute myocardial infarction (ICD-9: 410)	4,519 (5.2)	0.20	(−1.68 to 2.12)	0.674
Other acute ischemic heart diseases (ICD-9: 411)	617 (0.7)	−1.55	(−7.95 to 5.29)	0.528
Diseases of pulmonary circulation (ICD-9: 415–417)	972 (1.1)	4.83	(0.08 to 9.81)	0.081
Cardiac dysrhythmias (ICD-9: 427)	3,542 (4.1)	−2.05	(−5.06 to 1.05)	0.083
Heart failure (ICD-9: 428)	7,509 (8.7)	2.44	(0.86 to 4.05)	0.017
Cerebrovascular diseases (ICD-9: 430–438)	12,630 (14.6)	0.47	(−0.76 to 1.71)	0.797
Diseases of arteries, arterioles, and capillaries (ICD-9: 440–448)	2,025 (2.3)	1.08	(−2.27 to 4.54)	0.789
Pneumonia (ICD-9: 480–486)	4,924 (5.7)	0.49	(−1.55 to 2.58)	0.922
Chronic pulmonary diseases (ICD-9: 490–505)	2,254 (2.6)	0.62	(−2.40 to 3.74)	0.999
Renal failure (ICD-9: 584–588)	2,254 (2.6)	−0.08	(−2.72 to 2.63)	0.608

[a]The *P* value refers to the effect modification between those with and without a hospitalization for each group of diseases.
[b]Percentages are calculated on the total number of subjects (86,717) aged 65+ years who died in-hospital and who was last hospitalized between 2 and 28 days before death.

from the last hospitalization was used, which in most cases ended in death, and, to increase the specificity of the definition, the analysis was restricted to primary causes only. Additional data could have been useful to better define chronic susceptibility (individual habits, smoking status, obesity, etc.) but, unlike in the study conducted by Goldberg et al,[11] we did not have access to other databases from healthcare services outside the hospital, or to filled drug prescriptions. Finally, despite the large size of the study, we had limited statistical power to detect effect modification.

In conclusion, we found that the greatest risk of death associated with high concentrations of PM_{10} was among the elderly, among people of lower socio-economic status, and among in-patients not in intensive care and with altered pulmonary circulation and heart failure.

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