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# The relationship between ambient particulate matter and respiratory mortality: a multi-city study in Italy

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**Abstract**

The association of air pollutants with natural and respiratory mortality has been consistently reported. However, several aspects of the relationship between particles with an aerodynamic diameter of less than 10 micrometers ($PM_{10}$) and respiratory mortality require further investigation.

**Study question**

To assess the $PM_{10}$ - respiratory mortality association in Italy and to examine potentially susceptible groups.

**Study population and methods**

All natural (n. 276,205) and respiratory deaths (n. 19,629) occurring among 35-plus-year-olds in ten northern, central and southern Italian cities in 2001-2005 were selected. Data for 10-micron particulate matter, nitrogen dioxide and ozone were obtained. A time-stratified case-crossover analysis was carried out. Different cumulative lags were selected to analyse immediate, delayed, prolonged and best-time effects of air pollution. The shape of the exposure-response relationship was analysed. Age, gender, chronic conditions and death site were investigated as potential effect modifiers.

**Results**

We found a 2.29% (IC95% = 1.03; 3.58) increase in respiratory mortality at 0-3 lags. The increase in respiratory mortality was higher in summer (7.57%). The exposure-response curve had a linear shape without any threshold. Gender and chronic diseases modified the relationship between particulate matter and respiratory mortality.

**Answer to the question**

The effect of particulate on respiratory mortality was stronger and more persistent than that on natural mortality. Females and chronic disease sufferers were more likely to die of a respiratory disease caused by air pollution than males and healthy people.

**Key words :** particulate matter, respiratory mortality, case-crossover design, multi-city study.

## Introduction

The effects of particulate air pollution on respiratory health are universally acknowledged, thanks to the results of various studies examining respiratory symptoms, exacerbation of respiratory diseases, decrease in pulmonary function, and mortality in patients with chronic respiratory diseases or due to respiratory causes. The short-term effects on daily mortality of particulate matter with a diameter of less than 10 microns ($PM_{10}$) have been estimated in the range from 0.3 to 1.5 percent per 10 $\mu g/m^3$ $PM_{10}$ [1]. The effects on mortality caused by cardiovascular and respiratory diseases have been found to be generally stronger than for other conditions and the findings contribute to the understanding of the damage mechanisms of air pollution on human health [2].

Although the association between air particles and respiratory mortality has been known for several years, many aspects of the $PM_{10}$ - respiratory mortality relationship, such as the specific form of the exposure-response relationship, the latency interval of the effect and the individual characteristics that can modify the particulate matter effect [3,4], deserve further investigation. The form of the exposure-response relationship has been evaluated for airborne particles and total mortality [5,6], but very few studies have considered the relationship with specific-cause mortality [7,8]; a variable latency interval ranging from 0-1 to 0-6 days has been studied and only a few susceptibility factors have been investigated. For instance, a stronger effect among the elderly has been found in three studies [9-11] and one study only [4] highlights previous heart failure, stroke and diabetes as conditions that increase the effect of PM on respiratory mortality.

We conducted a study (EpiAir) on the short-term effects of air pollution in ten Italian cities during the period 2001-2005. Here we analyse the effects of $PM_{10}$ on respiratory mortality and examine in detail the latency interval of the effect, the shape of the exposure-response relationship and the characteristics of potentially susceptible groups. We also consider the influence of other pollutants ($NO_2$ and $O_3$) and the possible heterogeneity of the $PM_{10}$ effects across the cities.

**Methods**

Health events

All deaths from natural causes in ten northern, central and southern Italian cities from 2001-2005 were selected. Respiratory deaths were identified from the local mortality registry on the basis of underlying cause of death (International Classification of Diseases, 9$^{th}$ revision (ICD-9) codes 460-519). The events under study were further restricted to subjects who had died in their city of residence, to minimise the likelihood of exposure misclassification. We further limited the health series to 35-plus-year-olds and classified the site of death as in hospital or out of hospital, including in the in-hospital group people who died within two days of a hospital discharge; the group of out-of-hospital deaths was further divided into with or without a recent hospitalisation (discharged 28 – 2 days before death) subgroups.

For each subject we collected information on gender, age at death, and hospitalisations in the two preceding years. Information on hospitalisations included all diagnoses appearing in discharge reports and the admission date (retrieved via record linkage with the regional database of hospital discharges). The diseases to be analysed as individual characteristics capable of modifying the impact of $PM_{10}$, were selected on the basis of the existing literature [12-14] and were grouped as acute or chronic conditions according to patients' admission dates and clinical criteria. Conditions were considered acute if they showed clinically characteristics coherent with an acute disease (sudden onset, short course and recovery likelihood) or characteristics coherent with an exacerbation of chronic diseases, provided, in both cases, that they were reported as the primary diagnosis in hospitalisations with admission dates up to 28 days before death. Conditions were considered chronic if they were coherent with the clinical criteria of chronicity and were reported as primary or secondary diagnoses in hospitalisations with admissions from 29 days to 2 years before death (a complete list of these acute and chronic conditions with corresponding ICD-9 codes is provided in Appendix 1).

Data on influenza epidemics were defined on the basis of the weekly data collected at the city level by the National Health Service Sentinel System. A dummy variable was established for each city with an assumed value of "1" for three-week periods of maximum incidence (generally occurring between January and March), and "zero" on all other days.

Environmental data

Air pollution data were provided by the Regional Environmental Agencies, which routinely monitor several pollutants, including particulate matter with an aerodynamic diameter of less than 10 microns ($PM_{10,}$), nitrogen dioxide ($NO_2$) and ozone ($O_3$). Hourly data were available from more than one monitoring station, selected to be representative of the background levels, for each city. A previously defined algorithm [15] was implemented to impute missing values and to derive daily averages for $PM_{10}$ and $NO_2$ and daily maximum 8-hour running means for $O_3$.The missing values for each pollutant on a specific day and at a specific monitoring station was imputed with the average of measurements of that pollutant for that day across the other monitors, weighted by the ratio of the yearly average of that monitor over the yearly average of the other monitoring stations, for the same pollutant. A daily completeness measure of up to 75% per season was used as an inclusion condition for the monitored data.

Daily information on temperature, humidity and barometric pressure was provided by the Italian Air Force Meteorological Service. Apparent temperature, was calculated on the basis of air temperature and dew-point temperature, a proxy of relative humidity [16].

Data analysis

All statistical analyses were performed at the city level; city-specific results were then pooled with random-effects meta-analyses. For each pooled estimate, a test for heterogeneity of city-specific associations was performed and reported.

As a first step, a time series analysis was performed in each city to study the association between daily $PM_{10}$ and daily mortality. A Poisson regression was applied, controlling for apparent temperature (lag 0-1, penalized splines) and low temperature (lag 1-6, penalized splines), barometric pressure (lag 0, penalized splines), temporary population decreases in the summer and during holidays (a three-level variable taking into account vacation periods outside the area and decreased health services), and influenza epidemics. In more detail, low temperatures have been controlled for by adding to the model one penalised cubic spline for values of lagged 1-6 air temperature below the median value of each city, as determined over the entire study period distribution, so as to allow a potential non-linear relationship between low temperature and health effects; similarly, high temperatures have been controlled for by adding a penalised cubic spline for values of lagged 0-1 apparent temperature above the median value of each city, with the aim of taking into account the exponential relationship of high temperatures with health effects that increase with increasing temperature. A sensitivity analysis was conducted using the lagged 0-6 apparent temperature above the median value of each city. Long-term trend and seasonality were controlled for by including in regression models a triple interaction of year, month and day of the week. Mortality analysis methods have been fully described in a paper about the effects of ozone [17].

Results are expressed as percentage increases in mortality (and 95% confidence intervals) relative to 10 $\mu g/m^3$ increases in $PM_{10}$.

To explore the lag interval of the $PM_{10}$ effect on respiratory mortality, we fitted single-lag models and cubic polynomial distributed-lag models [18,19] for each city. Six-day lags were explored from 0 to 5 days preceding death. Cumulative lags (unconstrained distributed lags) were also analysed. Three intervals were selected to differentiate between effects defined a priori as “immediate” (up to lag 1), “delayed” (lags 2 to 5), and “prolonged” (lags 0 to 5). A fourth cumulative lag interval was

defined as the best cumulative lag. The criteria for selecting this lag were the strength of the association, the absence of important differences between constrained and unconstrained distributed-lag models, and the lowest heterogeneity between cities in the pooled analysis for that lag interval.

To estimate the net effect of $PM_{10}$ on respiratory mortality, the association was evaluated in bi-pollutant models, including $NO_2$ and $O_3$ in turn, at the same cumulative lag interval used to analyse the $PM_{10}$ effect. The model including $O_3$ was restricted to the hot season.

The shape of the exposure-response relationship between $PM_{10}$ and respiratory mortality was estimated by using the meta-smoothing approach [20]. The relationship was first explored at the city level with city-specific Poisson regression models in which the pollutant was added non-parametrically. The predicted values of the relative risk log of daily death were then computed in each city for 5 $\mu g/m^3$ increments between 10 and 100 $\mu g/m^3$. These predicted values, together with their confidence intervals, were finally combined by using a random-effects meta-analysis.

The second part of the analysis consisted in studying the individual effect modifiers of the $PM_{10}$-respiratory mortality association, using the case-crossover design. Control days were selected by means of the time-stratified approach [21], which divides the study period into monthly strata, selecting control days for each case on the same day of the week in the stratum. Control for season and long-term trend was obtained by design, whereas the other time-varying covariates were adjusted for by modeling with city-specific conditional logistic regression models [13].

The covariates tested as possible effect modifiers were age, gender, recent hospitalisations for selected diseases as an indicator of acute health problems, and hospitalisations in the two previous years as an indicator of chronic conditions. The $PM_{10}$ effect was evaluated in the categories of each individual covariate, and statistical tests were performed to test for effect modification [22,23].

Since age modified the $PM_{10}$-respiratory mortality association, the stratum-specific estimates of the other variables were standardized by age (two groups: 35-84 and 85+ years), using the relative frequencies of the overall age distribution as weights. Effect modification was considered to be clearly present when the p-value of the relative effect modification (REM) was lower than 0.05; it was considered to be suggested when the effect estimate in one stratum was twice that of the referent stratum, and the p-value ranged from 0.05 to 0.20; when a variable had more than two strata (e.g. age groups), an effect modification was also considered to be suggested if a dose-response trend was observed.

All the analyses were conducted with SAS (version 8.2), R (version 2.10.0) and STATA (version 10.0).

**Results**

There were 19,629 respiratory deaths in the study population, which accounted for 7.1% of the natural deaths (n. 276,205). Table 1 shows the number of natural and respiratory deaths in the ten cities for the entire period and during the cold (October to March) season. The respiratory/natural death ratio does not differ among the cities, with the exception of Taranto, whose percentage was a high 11%. Respiratory deaths were more frequent in the cold season, when 57.1% of respiratory deaths occurred. Chronic obstructive pulmonary disease (COPD) and lower respiratory tract infections accounted for 77.8% of the respiratory deaths. An average of 57% of respiratory deaths occurred in hospital; 60% of deceased subjects had been hospitalised in the previous two years, excluding the last 28 days, during which 51% had been hospitalised. Almost 50% had one of the chronic diseases we had selected as potentially susceptible conditions.

The daily concentrations of $PM_{10}$ range from 53.9 $\mu g/m^3$ in Turin to 30.3 $\mu g/m^3$ in Cagliari. $NO_2$ shows a higher variability, with the lowest values in Taranto (26.3 $\mu g/m^3$) and the highest in Milan, Turin and Rome (59.2, 66.0 and 62.4 $\mu g/m^3$) (Table 2). The apparent temperature shows a clear

North-South gradient, with the lowest values in Milan, Mestre and Turin and the highest in Palermo, Taranto and Cagliari. No important differences in humidity or atmospheric pressure were observed among the cities.

The effect of $PM_{10}$ on respiratory mortality was prolonged, starting at lag 0 and remaining up to lag 2 (Figure 1); a similar pattern was observed for natural mortality. In contrast, some instability between single-lag, constrained and unconstrained distributed-lag models emerged for the $PM_{10}$ effect on respiratory mortality, on the $5^{th}$ and $6^{th}$ days. The heterogeneity of the effects across the cities remained low up to the $4^{th}$ day but increased significantly for longer latencies (Table 3). Therefore, a 0-3 cumulative lag interval was chosen as the most consistent latency for analysing the effect of $PM_{10}$ on respiratory mortality in further analyses, though the highest cumulative effect was observed at 0-5 days. An increase of 10 $\mu g/m^3$ in $PM_{10}$ was correlated to an increase of 2.29% in respiratory mortality, a greater effect than that for natural mortality (0.80%, IC95% = 0.41; 1.19) at lag 0-2 (Table 3). The sensitivity analysis controlling for the 0-6-lagged apparent temperature above the median (instead of the 0-1 lag) provided very similar results, slightly higher for natural mortality and respiratory mortality overall; in the warm season, however, the effect on respiratory mortality decreased, though very little. The $PM_{10}$-respiratory mortality association was more influenced by COPD (2.02%, 95%CI = 0.18% ; 3.89%) than by pneumonia and acute bronchitis (1.68%, 95%CI = -0.60% to 4.0%) at lag 0-3 (Table 3). No heterogeneity was observed across cities for the effect of $PM_{10}$ on lower respiratory tract infections, whereas it was observed for delayed effects on COPD.

Analysis of $PM_{10}$ - respiratory mortality association by season revealed a 6.2 times greater effect in the warm than in the cold season; it was only 3.7 times greater for natural mortality (table 4). Since both the higher $PM_{10}$ concentration and the influenza epidemics have winter peaks, a sensitivity analysis was carried out of $PM_{10}$ - respiratory mortality association without controlling for influenza epidemics. The respiratory mortality increase only slightly to values of 2.39 (95%CI = 1.13 - 3.66).

This result supports that controlling for influenza cannot explain the seasonal differences observed about the effect of particulate on respiratory mortality.

There was no evidence of a threshold in the exposure-response curve when the effect estimates for all the cities were pooled, and the relationship appeared to be linear (Figure 2). Neither $NO_2$ nor $O_3$ affected the impact of $PM_{10}$ on respiratory mortality in bi-pollutant models, whereas a contemporaneous increase of $NO_2$ reduced the impact of $PM_{10}$ on natural mortality (table 5).

Table 6 shows the combined estimates of the effect of $PM_{10}$ on respiratory mortality in nine cities (Cagliari provided no individual data on effect modifiers), stratified by age group, gender, site of death, recent hospitalisations and chronic diseases, using the 0-3 lag. A suggestion of effect modification was present for females (3.11; 95%CI= 1.15% to 5.11%) as compared to males (1.22; 95%CI= -0.64% to 3.12%, p-REM= 0.175) and for chronic disease sufferers (4.90; 95%CI= 1.09% to 8.87%). Notably high risks of dying from respiratory disease, though without evidence of effect modification, were found in 85-plus-year-olds (3.24%; 95%CI= 1.36% to 5.17%), subjects who died out of hospital (2.97%; 95%CI= 0.52% to 5.47%), those who had been hospitalised between 29 days and 2 years before death (2.46%; 95%CI= 0.75 to 4.19), those who were not hospitalised during their last 28 days (2.62%; 95%CI= 0.69 to 4.59) and those with a chronic pulmonary disease (2.90%; 95%CI= 0.26% to 5.61%).

**Discussion**

We found a greater effect of $PM_{10}$ on respiratory mortality than on all natural-cause mortality. The effect was stronger in the warm than in the cold season. The most consistent effect, not heterogeneous across cities, was observed for the cumulative four-day exposure (lag 0-3). The particulate effect was not influenced by the contemporaneous increase of $NO_2$ or $O_3$ concentration. The effect increased linearly with the $PM_{10}$ concentration without a threshold. Females and subjects

with a previously diagnosed chronic condition were likely to be more susceptible to the effect of $PM_{10}$.

Most previous studies that analysed the short-term effect of increasing PM levels on cause-specific mortality have reported a greater effect on respiratory mortality than on natural or cardiovascular (CV) mortality [9,24-29]. The only exception is a study carried out in the UK [30] which found no effect on either natural, respiratory or cardiovascular deaths. Of three other studies, one found a smaller effect on respiratory mortality than on CV mortality [31], while the other two reported similar effects on respiratory, natural and CV mortality in Europe [32] and in Shanghai [11]. Finally, five of the most recent studies found a PM effect on respiratory mortality twice that on natural or CV mortality, in Europe (Dublin) [33], in the US [4,10,34] and in South-East Asia (Shanghai) [35]. Our results for effect size are thus a confirmation of previous evidence, apart from a study [36] that showed threefold higher estimates of respiratory mortality for specific components of $PM_{2.5}$, such as copper and titanium. This could suggest that studies that use more specific measures of exposure are better at detecting important effects on the respiratory system.

We analysed the effect of $PM_{10}$ separately for the cold and warm seasons. A clear seasonal modification of the PM effect was evident for both natural and respiratory mortality, effects being greater in the warm season than in winter, but the effect on respiratory deaths was twice that on natural deaths. This result seems more noteworthy if we consider that respiratory mortality accounts for a lower proportion of total mortality in warm seasons (6.5%) than in cold (7.8%) and that even the effect of $PM_{10}$ on natural mortality increases during summer. Furthermore, a high heterogeneity across the cities characterized the effect of $PM_{10}$ on respiratory mortality in the heat. Larger risks of dying in summer than in winter as a result of PM increases have been reported in both Europe [26,30] and Asia [29]. Seasonal differences in PM effects on mortality may be due to the interaction of PM with temperature or to behaviour and ventilation patterns, which could also explain the inter-city differences [4, 37]. We controlled for seasonality in our analysis, but we could not control for

behavioural factors. Neither of these factors would, however, have explained the greater impact of PM on respiratory mortality than on natural mortality in the warm season. Further, we considered also the hypothesis of a seasonal misclassification of death respiratory cause versus cardiovascular diseases. Fifteen percent of deaths classified as due to heart failure occurred in chronic respiratory patients, but the higher frequency of this possible miscoding was observed in cold (16%; 95%CI =14.3-17.7) than in hot season (13%; 95%CI=11.3-14.7). Our results suggest that specific problems affect respiratory patients in summer and that the effect varies from city to city.

We chose a cumulative lag of 0-3 days to analyse the effect of $PM_{10}$ on respiratory mortality. Earlier studies have reported an association of particulate increase with death on the same day, a couple of days thereafter and up to a week later. Three of these studies adopted a 0-6 lag interval [9,25,26], but the most frequently adopted interval was the cumulative lag 0-1, chosen on the basis of the effects on natural and CV mortality [10,11, 24, 27-32, 34,35]. Though choosing a common lag for the different mortality outcomes made it easier to compare them, the cumulative lag 0-1 may have resulted in an underestimation of the effect on respiratory mortality. Some studies show differences in the lag structure between PM and cause-specific mortality, with the increasing risk of death after PM exposure declining more slowly for respiratory deaths than for natural and CV deaths [4,28,32]. In two studies, a three-day interval was chosen for analysing respiratory mortality [4,36]. We used other criteria to choose the best lag; our choice of the 0-3 lag was dictated not only by the strength of the association, but also by the absence of heterogeneity across the cities and the consistency between different lag models.

We have not here explored the effects of $PM_{10}$ on respiratory mortality for longer time intervals. Two earlier studies have done so. One of them found a suggestion of harvesting in the second week [33], while the other attributed the apparent displacement of respiratory mortality to the degrees of freedom used in the distributed lag model [28].

We found that the PM effect on respiratory mortality was not influenced by the contemporaneous presence of either $NO_2$ or summer $O_3$ at the same 0-3 lag. Results inconsistent with ours were reported in the only earlier study to perform this analysis: Hoek, in the Netherlands, found an important reduction of the PM effect when nitrogen dioxide was added to the model [26].

Our results for the exposure – response curve are consistent with earlier studies[5,20]. Very few articles are available on specific causes of death [7,8], but most of the studies dealing with the impact of pollutants on total mortality showed not only a similarly shaped exposure – response curve, but also similar differences in the strength of the effects on total and respiratory mortality.

We found that females were likely to be more than twice as susceptible to particulate matter as males, even after adjusting for age. The relevant results in earlier studies have been inconsistent. Two articles report higher risks in females, but only in selected groups, such as black females and very old females. [24,25]. Another study [4] found higher risks of respiratory death in females of all ages, and females were reported to be at a higher risk of hospitalisation for respiratory diseases three days after a peak level of $PM_{10}$ [38]. Only one study [10] found a higher risk of respiratory mortality in males, though females presented a higher risk of total mortality. Further studies will doubtless address the topic of gender susceptibility more thoroughly; however, a higher female susceptibility to air pollution has been postulated because of the greater female reactivity to smoking, and has been justified by differences in the effective dose increasing the final effect in women. Sex differences have been reported for airborne gas adsorption and gas-blood barrier permeability, for vascular transport and organ accumulation of toxic chemicals, and finally for a gender-linked hormonal status which alters the vascular effects of diesel exhaust [39].

We found no effect modification by age, though respiratory mortality was more than twice as high in 85-plus-year-olds than in younger subjects. Our results confirm those found in the literature. Fischer [9] reports an increased risk of dying of COPD or pneumonia only for selected groups of

the elderly, and Franklin [10] found a higher risk of dying of respiratory disease in 75-plus-year-olds than in younger subjects.

This is the first study on respiratory mortality to use previous hospital diagnoses for assessing susceptibility due to chronic diseases. A previous study [4] found an increased effect of PM on respiratory mortality in patients with heart failure, but the disease data were obtained from the concurrent causes reported on death certificates. We found that people who had a chronic disease, but were not hospitalised in their last month, were more susceptible to the particulate matter effect. However, the effect did not increase proportionally to the number of chronic diseases, nor were any specific diseases identified as effect modifiers. A study [23] carried out earlier in the same Italian cities identified recent episodes of heart failure and pulmonary circulation impairment as conditions of susceptibility for all natural deaths. The lower number of respiratory deaths we studied here could justify the negative results in identifying specific diseases that can modify the particulate effect. Alternative explanations are possible for the negative results in patients with two or more diseases: their generally poor condition may have prevented their exposure to air pollution or have played a more important role in causing death.

Finally, the issue of the location of death deserves discussion. We found a higher risk of dying of respiratory disease for subjects who died out of hospital and had not been hospitalised in their last month. Dying in hospital could be interpreted as a consequence of a severe clinical condition; this was the conclusion suggested in a study that found a higher risk of dying among COPD patients who had visited an emergency ward or had been admitted to an intensive-care unit [25]. On the other hand, hospitalisation may constitute a temporary protective factor against air pollution and death, since hospitalised patients might be less exposed or might receive effective treatment for their diseases. A possible interpretation of our data is that the very high $PM_{10}$ - mortality association for people who died out of hospital depended on probable exposure or on being at such a severe stage of disease that they were deemed unable to benefit from intensive treatments and were

consequently not hospitalised; the still high but not statistically significant increased risk for people who died in hospital indicates that they are somehow more protected despite their severe conditions; the very low risk of those who died out of hospital but had recently been discharged may be due to protection given from therapy. Two previous studies specifically analysed the site of death with similar results and a similar interpretation for respiratory diseases [26] and all natural diseases [4].

## CONCLUSIONS

1) Respiratory mortality was more affected by $PM_{10}$ than was natural mortality, and the PM effect was slightly longer lasting for respiratory mortality. 2) Females and chronic disease sufferers were likely to be susceptible to the PM effect. 3) Specific problems affect respiratory patients in summer, but the summertime PM effect was heterogeneous across the cities; studying the composition of PM could help to explain both the inter-city differences and the increased effect of PM during the summer. 4) The real effect of PM on respiratory mortality may be even higher than has so far been ascertained; more specific definitions of exposure, as well as an increasing ability in reducing the misclassification of respiratory deaths, should improve the validity of the estimates.

**Appendix 1**

ICD-9 codes for acute conditions analysed as effect modifiers of air pollutants, if reported for the first time as the principal discharge diagnosis up to 28 days before death. Both emergency and scheduled hospitalisations were considered.

| Acute conditions | |
|---|---|
| **Diseases** | **ICD-9 codes** |
| Pulmonary thromboembolism and hypertension | 415-417 |
| Conduction disorders | 426 |
| Arrhythmias | 427 |
| Congestive heart failure | 428 |
| Acute respiratory illness | 460-466, 480-486 |
| Chronic renal failure | 584-588 |

ICD-9 codes for chronic conditions analysed as effect modifiers of air pollutants if reported among the discharge diagnoses before the last 28 days of life and up to 2 years before death. All kinds of hospitalisation were considered.

| Chronic conditions | |
|---|---|
| **Diseases** | **ICD-9 codes** |
| Diabetes | 250 |
| Coagulation disorders | 286-287 |
| Hypertension | 401-405 |
| Acute myocardial infarction | 410, 412 |
| Ischemic heart diseases | 410-414 |
| Pulmonary thromboembolism and chronic pulmonary heart | 415-417 |
| Conduction disorders | 426 |
| Arrhythmias | 427 |
| Congestive heart failure | 428 |
| Cerebro-vascular diseases, including both ischemic and hemorrhagic ictus | 430-438 |
| Chronic pulmonary diseases | 490-505 |

## APPENDIX 2

Italy map and geographical location of the ten cities included into the study.


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**Figure titles and legends**

Figure 1. Pooled results. Association between PM10 and mortality, by cause of death and lag (single lag and distributed lag models): percentage increases of risk, and 95% confidence intervals, relative to 10µg/m3 increase in the pollutant. 10 cities, 2001 – 2005.

Legend

Title of the left diagram : respiratory-cause mortality

Title of the left diagram : natural-cause mortality

In both diagrams :

Abscissa : lag (days)

Ordinate : % increase of risk

White squares = single-lag models

Black squares = distributed-lag models

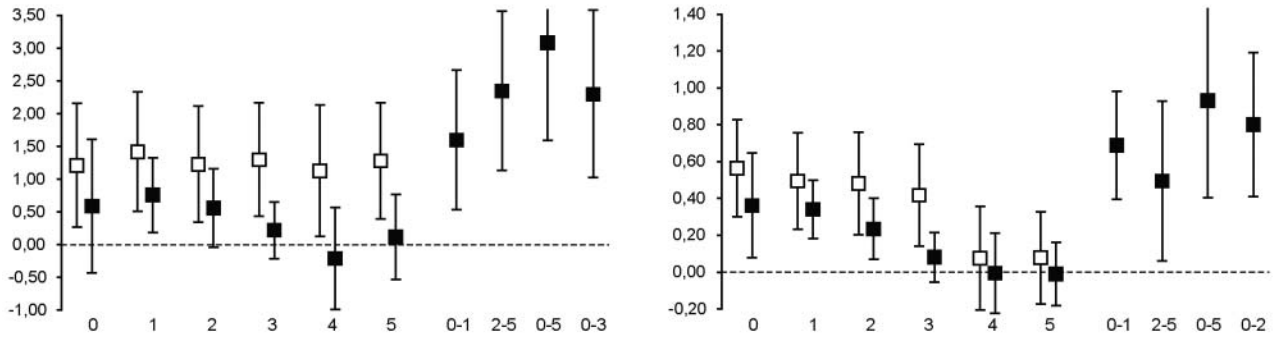


Figure 2 Pooled results. Exposure-response relationship between PM10 concentrations and percentage increase of respiratory mortality, 10 cities, 2001 – 2005

Legend :

abscissa = PM10 (µg/m3)

ordinate = percentage increase of risk

note: dotted lines represent the upper and lower 95% CI of the exposure-response relationship (solid line)

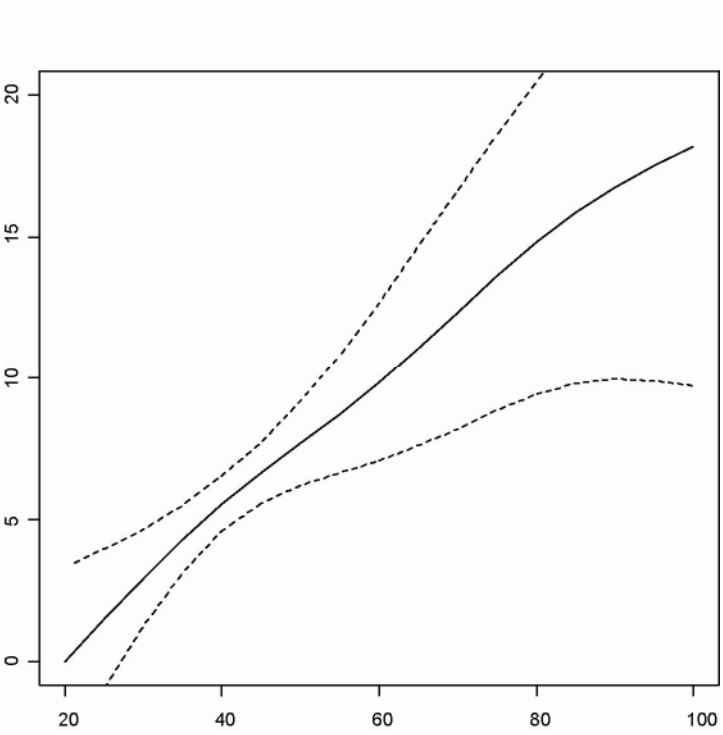

**Table 1. Study population, 10 cities, 2001 – 2005.**

| City | Study period | 35-plus-year-olds | | 65-plus-year-olds | | 85-plus-year-olds | |
|---|---|---|---|---|---|---|---|
| | | N | %* | N | %* | N | %* |
| | | respiratory deaths | | | | | |
| Milan | 2001 - 2005 | 4,391 | 8.5 | 4,174 | 9.2 | 2,262 | 12.2 |
| Mestre | 2001 - 2005 | 421 | 4.6 | 392 | 5.0 | 168 | 5.9 |
| Turin | 2001 - 2005 | 2,781 | 7.6 | 2,622 | 8.3 | 1,236 | 10.4 |
| Bologna | 2001 - 2005 | 1,719 | 8.5 | 1,656 | 9.1 | 852 | 11.0 |
| Florence | 2001 - 2005 | 1,450 | 8.6 | 1,402 | 9.2 | 746 | 11.2 |
| Pisa | 2001 - 2005 | 361 | 8.1 | 348 | 8.6 | 180 | 10.9 |
| Rome | 2001 - 2005 | 6,077 | 5.9 | 5,724 | 6.4 | 2,521 | 7.8 |
| Cagliari | 2002 - 2005 | 463 | 6.7 | 441 | 7.5 | mi | |
| Taranto | 2001 - 2005 | 562 | 11.0 | 526 | 12.2 | 228 | 11.0 |
| Palermo | 2002 - 2005 | 1,404 | 6.6 | 1,289 | 7.1 | 464 | 7.4 |
| **Total** | **2001 - 2005** | **19,629** | **7.1** | **18,574** | **7.8** | **8,657** | **9.6** |
| | | **natural deaths** | | | | | |
| **Total** | **2001 - 2005** | **276,205** | | **239,624** | | **90,070** | |

| City | Study period | 35-plus-year-olds | | 65-plus-year-olds | | 85-plus-year-olds | |
|---|---|---|---|---|---|---|---|
| | | N | %* | N | %* | N | %* |
| | | respiratory deaths in cold season † | | | | | |
| Milan | 2001 - 2005 | 2,572 | 9.2 | 2,446 | 10.0 | 1,331 | 13.1 |
| Mestre | 2001 - 2005 | 263 | 5.3 | 247 | 5.8 | 110 | 6.8 |
| Turin | 2001 - 2005 | 1,578 | 8.1 | 1,499 | 8.9 | 696 | 11.0 |
| Bologna | 2001 - 2005 | 968 | 8.9 | 933 | 9.5 | 478 | 11.3 |
| Florence | 2001 - 2005 | 790 | 8.8 | 765 | 9.5 | 418 | 11.7 |
| Pisa | 2001 - 2005 | 195 | 8.6 | 187 | 9.0 | 94 | 10.6 |
| Rome | 2001 - 2005 | 3,467 | 6.3 | 3,272 | 6.9 | 1,475 | 8.4 |
| Cagliari | 2002 - 2005 | 269 | 9.9 | 259 | 11.1 | mi | |
| Taranto | 2001 - 2005 | 289 | 8.1 | 266 | 8.6 | 121 | 11.2 |
| Palermo | 2002 - 2005 | 811 | 7.0 | 741 | 7.5 | 264 | 7.6 |
| **Total** | **2001 - 2005** | **11,202** | **7.6** | **10,615** | **8.3** | **4,987** | **10.2** |
| | | **natural deaths** | | | | | |
| **Total** | **2001 - 2005** | **129,026** | | **111,439** | | **41,166** | |

mi : missing information
*estimated percentage over natural-cause mortality.
†October to March.

**Table 2. Pollutant concentrations and meteorological parameters, 10 cities, 2001 - 2005**

| City | Study period | $PM_{10}$ (10 □g/m$^3$) Mean | $PM_{10}$ (10 □g/m$^3$) SD | $NO_2$ (10 □g/m$^3$) Mean | $NO_2$ (10 □g/m$^3$) SD | $O_3$ (□g/m$^3$)‡ Mean | $O_3$ (□g/m$^3$)‡ SD | Correlation coefficient+ $PM_{10}$-$NO_2$ | Correlation coefficient+ $PM_{10}$-$O_3$ | $PM_{10}$ / $NO_2$ Mean | $PM_{10}$ / $NO_2$ SD | Temperature (°C) Mean | Temperature (°C) SD | Relative humidity (%) Mean | Relative humidity (%) SD | Barometric Pressure (hPa) Mean | Barometric Pressure (hPa) SD | Apparent Temperature (°C) Mean | Apparent Temperature (°C) SD |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Milan | 2001 - 2005 | 51.5 | 31.7 | 59.2 | 22.8 | 91.1 | 34 | 0.79 | 0.26 | 0.86 | 0.33 | 14.4 | 8.6 | 74.4 | 13.2 | 1,016 | 7.4 | 13.8 | 10.5 |
| Mestre | 2002 - 2005 | 48.0* | 33.2* | 38.2 | 14.2 | 91.4 | 30.3 | 0.66* | 0.49* | 1.19* | 0.60* | 13.8 | 8.0 | 72.8 | 11.4 | 1,016 | 7.4 | 13.2 | 9.8 |
| Turin | 2001 - 2005 | 53.9† | 33.7† | 66.0 | 20.1 | 115.4 | 38.6 | 0.72† | 0.11† | 0.79† | 0.36† | 12.6 | 8.3 | 71.8 | 12.9 | 1,017 | 7.6 | 11.5 | 9.8 |
| Bologna | 2001 - 2005 | 42.5* | 25.3* | 51.7 | 18.3 | 90.8 | 31 | 0.66* | 0.07* | 0.82* | 0.34* | 14.4 | 8.7 | 69.3 | 15.3 | 1,016 | 7.6 | 13.4 | 10.0 |
| Florence | 2001 - 2005 | 38.2 | 17.7 | 46.1 | 18.6 | 95.9 | 23.6 | 0.65 | 0.33 | 0.89 | 0.41 | 15.5 | 7.7 | 66.4 | 12.2 | 1,016 | 6.9 | 14.6 | 9.3 |
| Pisa | 2002 - 2005 | 34.2 | 15.1 | 29.8 | 11.3 | 99 | 21.3 | 0.57 | 0.2 | 1.23 | 0.62 | 15.1 | 7.1 | 75.3 | 12.6 | 1,016 | 6.9 | 14.7 | 8.9 |
| Rome | 2001 - 2005 | 39.4 | 16.0 | 62.4 | 15.6 | 105.1 | 25 | 0.50 | 0.19 | 0.65 | 0.26 | 15.9 | 7.1 | 76.2 | 13.4 | 1,015 | 6.6 | 15.7 | 8.8 |
| Cagliari | 2001 - 2005 | 30.3# | 11.0# | 35.0** | 16.2** | 77.9 | 20.5 | 0.23# | -0.11# | 1.13# | 0.84# | 17.4 | 16.6 | 75.1 | 12.1 | 1,016 | 6.1 | 17.6 | 8.4 |
| Taranto | 2001 - 2005 | 50.3§ | 21.2§ | 26.3 | 10.9 | 80.8 | 21 | 0.19§ | 0.28§ | 2.37§ | 1.30§ | 17.4 | 6.9 | 69.5 | 14.3 | 1,016 | 6.1 | 16.9 | 8.4 |
| Palermo | 2001 - 2005 | 34.8 | 19.9 | 52.1 | 15.6 | 88.3* | 18.2 | 0.22 | -0.03* | 0.71 | 0.61 | 19.4 | 6.5 | 66.8 | 11.1 | 1,015 | 6.3 | 19.4 | 8.3 |

Mean = mean of daily concentrations in the whole period after imputation of missing values; SD = standard deviation.

*Study period 01/01/2002 - 31/12/2005.

†Study period 01/06/2002 - 31/12/2005.

§Study period 01/01/2001 - 31/12/2004.

#Study period 01/01/2003 - 31/12/2004.

**Study period 01/01/2003 - 31/12/2005.

‡Ozone, daily maximum 8-hr running mean value, in hot season April to September.

+Pearson correlation coefficient; correlation between PM10 and O3 refers to the hot season.

**Table 3. Pooled results. Association between $PM_{10}$* and natural mortality or respiratory mortality by specific cause of death at different lags, relative to 10mg/$m^3$ increase of pollutant, 10 cities, 2001 – 2005**

| | No | lag# | % | 95% CI | | $p_{HET}$† |
|---|---|---|---|---|---|---|
| **natural mortality** | 276,205 | 0-1 | 0.69 | *0.40* | 0.98 | 0.693 |
| | | 2-5 | 0.49 | *0.06* | 0.93 | 0.001 |
| | | 0-5 | 0.93 | *0.40* | 1.46 | 0.001 |
| | | 0-2 | 0.80 | *0.41* | 1.19 | 0.246 |
| **All respiratory causes** | 19,629 | 0-1 | 1.59 | *0.54* | *2.66* | 0.617 |
| | | 2-5 | 2.34 | *1.13* | *3.57* | 0.022 |
| | | 0-5 | 3.08 | *1.59* | *4.59* | 0.044 |
| | | 0-3 | 2.29 | *1.03* | *3.58* | 0.311 |
| **Chronic obstructive pulmonary disease** | 9,753 | 0-1 | 1.25 | *-0.30* | *2.82* | 0.753 |
| | | 2-5 | 1.94 | *-0.13* | *4.05* | 0.034 |
| | | 0-5 | 2.79 | *0.64* | *4.99* | 0.291 |
| | | 0-3 | 2.02 | *0.18* | *3.89* | 0.465 |
| **Lower respiratory tract infections§** | 5,513 | 0-1 | 1.05 | *-0.84* | *2.98* | 0.475 |
| | | 2-5 | 1.48 | *-0.69* | *3.71* | 0.553 |
| | | 0-5 | 2.30 | *-0.39* | *5.05* | 0.284 |
| | | 0-3 | 1.68 | *-0.60* | *4.00* | 0.668 |

*measured as 10 mg/$m^3$ increase in mass concentration.

#cumulative lags represented immediate (0-1), delayed (2-5) and prolonged (0-5) effects.

†p-value of heterogeneity test (null hypothesis is perfect homogeneity of city-specific results).

§ this includes acute bronchitis and pneumonia.

**Table 4. Pooled results. Association between $PM_{10}$* and mortality due to all natural and only respiratory causes by season, relative to 10□g/m$^3$ increase of pollutant, 10 cities, 2001 – 2005**

| underlying cause of death | the cold season# | | | | | the hot season + | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | lag | %** | 95% CI | | $p_{HET}$† | lag | %** | 95% CI | | $p_{HET}$† |
| **all cause** | 0-2 | 0.56 | *0.12* | *1.01* | 0.061 | 0-2 | 2.05 | *1.27* | *2.85* | 0.089 |
| **respiratory diseases** | 0-3 | 1.22 | *-0.18* | *2.65* | 0.596 | 0-3 | 7.57 | *2.25* | *13.17* | 0.007 |

*measured as 10□g/m$^3$ increase in mass concentration.

†p-value of heterogeneity test (null hypothesis is perfect homogeneity of city-specific results).

+April to September.

#October to March.

**percentage increase in mortality per any 10-μg/m$^3$ increment of $PM_{10}$ concentration.

**Table 5. Pooled results. Association between $PM_{10}$* and mortality by cause of death,[#] from models adjusted for $NO_2$ and $O_3$[§], 10 cities, 2001 – 2005**

| | mortality increase | | | $p_{HET}$[†] |
|---|---|---|---|---|
| | % | 95% CI | | |
| **All natural-cause mortality** | | | | |
| **Single-pollutant model** | 0.80 | *0.41* | *1.19* | 0.246 |
| **Model with $NO_2$** | 0.32 | *-0.08* | *0.73* | 0.363 |
| **Single-pollutant model** [§] | 2.05 | *1.27* | *2.85* | 0.089 |
| **Model with $O_3$**[§] | 2.13 | *1.34* | *2.92* | 0.230 |
| **Respiratory mortality** | | | | |
| **Single-pollutant model** | 2.29 | *1.03* | *3.58* | 0.311 |
| **Model with $NO_2$** | 2.23 | *0.58* | *3.90* | 0.512 |
| **Single-pollutant model**[§] | 7.49 | *2.17* | *13.08* | 0.006 |
| **Model with $O_3$**[§] | 7.45 | *2.17* | *13.00* | 0.013 |

*measured as 10□g/$m^3$ increase in mass concentration.

[#]The following lags (from unconstrained distributed lag models) were used: 0-2 for natural-cause mortality; 0-3 for respiratory-cause mortality.

[§]April to September period.

[†] p-value of heterogeneity test (null hypothesis is perfect homogeneity of city-specific results)

**Table 6. Pooled results. Association between PM10 (lag 0-3) and respiratory mortality,* by demographic characteristics, location of death and chronic conditions, 9 cities[+], 2001 - 2005.**

| | No.[#] | % | mortality increase % | 95% CI | | p REM[†] | p HET[‡] |
|---|---|---|---|---|---|---|---|
| **Variables** | 19166 | | | | | | |
| **age (years)** | | | | | | | |
| 35-64 | 1033 | 5.4 | 1.39 | *-4.63* | *7.79* | - | 0.608 |
| 65-74 | 2522 | 13.2 | 0.11 | *-3.48* | *3.82* | 0.727 | 0.222 |
| 75-84 | 6953 | 36.3 | 1.72 | *-0.44* | *3.93* | 0.921 | 0.816 |
| 85+ | 8657 | 45.2 | 3.24 | *1.36* | *5.17* | 0.578 | 0.916 |
| **Gender§** | | | | | | | |
| males | 9890 | 51.602 | 1.22 | *-0.64* | *3.12* | - | 0.400 |
| females | 9276 | 48.398 | **3.11** | ***1.15*** | ***5.11*** | **0.175** | **0.588** |
| **Location of death§** | | | | | | | |
| out of hospital | 6183 | 32.3 | 2.97 | *0.52* | *5.47* | - | 0.120 |
| out of hospital, with last discharge 2-28 days before death | 1121 | 5.8 | 0.39 | *-6.25* | *7.50* | 0.493 | 0.925 |
| in hospital | 10822 | 56.5 | 1.52 | *-0.22* | *3.30* | 0.349 | 0.992 |
| nursing home | 1040 | 5.4 | 1.81 | *-3.53* | *7.46* | 0.708 | 0.472 |
| **Hospital admission in the 0-28 days before death§** | | | | | | | |
| no | 9441 | 49.3 | 2.62 | *0.69* | *4.59* | - | 0.386 |
| yes | 9725 | 50.7 | 1.96 | *0.13* | *3.81* | 0.629 | 0.858 |
| **Hospital admission from 29 days to 2 years before death§** | | | | | | | |
| no | 7665 | 40.0 | 1.76 | *-0.35* | *3.91* | - | 0.274 |
| yes | 11501 | 60.0 | 2.46 | *0.75* | *4.19* | 0.618 | 0.610 |
| **Chronic conditions** § ** | | | | | | | |
| Diabetes (ICD-9: 250) | 1699 | 8.9 | 3.63 | -1.87 | 9.44 | 0.556 | 0.151 |
| Hypertension (ICD-9: 401-405) | 3625 | 18.9 | 3.07 | -0.16 | 6.40 | 0.531 | 0.791 |
| Myocardial infarction (ICD-9: 410, 412) | 619 | 3.2 | 4.52 | -5.22 | 15.26 | 0.654 | 0.798 |
| Cardiac ischemic diseases (ICD-9: 410-414) | 2547 | 13.3 | 1.02 | -2.73 | 4.91 | 0.508 | 0.498 |
| Diseases of pulmonary circulation (ICD-9: 415-417) | 1127 | 5.9 | 0.87 | -8.03 | 10.63 | 0.823 | 0.908 |
| Dysrhythmias (ICD-9: 427) | 2590 | 13.5 | 0.70 | -3.01 | 4.56 | 0.430 | 0.728 |
| Heart failure (ICD-9: 428) | 2514 | 13.1 | 1.41 | -2.68 | 5.67 | 0.775 | 0.047 |
| Cerebrovascular diseases (ICD-9: 430-438) | 2763 | 14.4 | 1.95 | -1.53 | 5.56 | 0.979 | 0.255 |
| Chronic pulmonary diseases (ICD-9: 490-505) | 5964 | 31.1 | 2.90 | 0.26 | 5.61 | 0.644 | 0.103 |
| **Number of chronic conditions** § ** | | | | | | | |
| none | 9621 | 50.2 | 2.19 | *0.31* | *4.11* | - | 0.284 |
| one | 2749 | 14.3 | **4.90** | ***1.09*** | ***8.87*** | **0.216** | **0.813** |
| two | 2727 | 14.2 | 0.16 | *-3.45* | *3.91* | 0.340 | 0.783 |
| three or more | 4069 | 21.2 | 2.30 | *-0.65* | *5.35* | 0.951 | 0.337 |

*Association was assessed at lag 0-3; esposure was measured as an increase of 10□g/m$^3$ in $PM_{10}$; effect was measured as percentage increase in respiratory mortality.

[+] all cities except Cagliari.

[#] the 463 patients from Cagliari are not included here.

[†] p-value of relative effect modification (REM), derived from the difference between the coefficient of the stratum and the coefficient of the reference category; for each chronic condition, the reference category is the group of subjects without the disease.

‡ p-value of heterogeneity test (null hypothesis is perfect homogeneity of city-specific results).

§ Results standardized by age, with weights equal to relative frequencies of subjects in the age groups 35-84, and 85+ years, from the 9 cities analyzed.

|| Data available only for Bologna, Milan, Rome and Turin which account for 77% (n.14,797) of people studied.

** Chronic conditions are based on primary or secondary diagnoses from any hospital admission that occurred between 29 days and two years before death.