

Air pollution and multiple acute respiratory outcomes

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Abstract

Short-term effects of air pollutants on respiratory mortality and morbidity have been consistently reported but usually studied separately.

Study questions

To more completely assess air pollution effects, we studied hospitalisations for respiratory diseases together with out-of-hospital respiratory deaths.

Study population and methods

A “time-stratified” case-crossover study was carried out in six Italian cities from 2001-2005.

Associations between daily particulate matter (PM₁₀) and nitrogen dioxide (NO₂) and hospitalisations for respiratory diseases (n. 100,690), chronic obstructive pulmonary disease (COPD) (n. 38,577), lower respiratory tract infections (LRTI) among COPD patients (n. 9,886) and out-of-hospital respiratory deaths (n 5,490) were estimated for 35+ year-old residents.

Results

For 10 µg/m³ PM₁₀, we found an immediate 0.59% (lag 0-1) increase in hospitalisations for respiratory diseases and a 0.67% increase for COPD; the 1.91% increase in LRTI hospitalisations lasted longer (lag 0-3) and the 3.95% increase in respiratory mortality lasted six days. Effects of NO₂ were stronger and lasted longer (lag 0-5). Age, gender, and previous ischemic heart disease acted as effect modifiers for different outcomes.

Answer to questions

Analysing multiple more than single respiratory events shows stronger air pollution effects. The temporal relationship between the pollutants’ increases and hospitalizations or mortality for respiratory diseases differs.

Key words: Particulate matter, nitrogen dioxide, air pollutants, respiratory hospitalisations, respiratory mortality, case-crossover design, multi-city study

Introduction

The impact of air pollutants on the respiratory system has been widely and consistently reported in recent years. The short-term effects include decreases in pulmonary function [1], increases in inflammatory markers [2] and respiratory symptoms [3], exacerbations of COPD and infections, [4;5;6-9] increases in respiratory mortality. [10-12]

The risk of dying from respiratory diseases associated with particulate matter (PM, either as PM₁₀ or PM_{2.5}) is close to 1% per 10 µg/m³ in several studies worldwide [13] whereas PM effects on hospitalisations or emergency visits for respiratory diseases tend to be higher (2%-3%) and affect all ages. [4;6-9] Nitrogen dioxide (NO₂) and ozone (O₃) are associated with even larger increases per 10 µg/m³ (near 3%-6% and 5%-6%, respectively) on asthma exacerbations in children. [6;7;14;15;16]

We have recently reported the results of the Italian EpiAir multi-city study on respiratory mortality that had effects ranging from 2.3% per 10 µg/m³ PM₁₀ to 3.5% per 10 µg/m³ NO₂. [17;18] To complete the assessment of PM₁₀ and NO₂ effects on respiratory health, we studied emergency hospitalisations for respiratory diseases and for chronic obstructive pulmonary disease (COPD). We also considered out-of-hospital respiratory mortality since our hypothesis was that the multiple immediate respiratory effects of air pollutants should be considered together to give complete and valid estimates of air pollution effects.

It has been already reported that latency differs with the type of respiratory event: mortality is a prolonged effect of PM (lasting 4-6 days) [19;20] while hospitalisations and emergency visits are immediate (lag 0-1 and up to 3 days, respectively), [7-9] suggesting that subjects' characteristics and patient management may affect the probability of these different events. The stronger increase in out-of-hospital than in-hospital mortality [17;21] and recent studies on the protective effects of drugs against air pollutant effects [22;23] give support to our hypothesis that various respiratory outcomes have to be analysed together as multiple effects of air pollutants.

Methods

Health events

We considered all emergency hospitalizations of 35+ year-old residents of six Italian cities (Bologna, Florence, Milan, Palermo, Rome and Turin), discharged from a hospital in their city, between 1 January 2001 and 31 December 2005. We selected primary diagnoses of all respiratory diseases (International classification of diseases, 9th version (ICD-9) codes 460-519; chronic obstructive pulmonary disease (COPD), (ICD-9 codes 490-492, 494, 496) as primary or secondary diagnosis when respiratory failure (ICD-9 codes 518.5, 518.8, 786.0) was the principal diagnosis, and lower respiratory tract infections (LRTI), (ICD-9 codes 466, 480-487) with COPD as secondary diagnosis; we also considered asthma diagnoses (ICD-9 codes 493). Hospitalisations in the following 28 days with the same discharge diagnosis were excluded. Furthermore, we considered all local deaths (ICD-9 codes 460-519) of 35+ year-old residents of the six cities, during 2001-2005. We selected underlying respiratory causes of death reported in the local mortality registries. We defined out-of-hospital deaths as those that occurred at home, in subjects who had not been hospitalised in the previous two years, or had been discharged at least 28 days before death.

For each subject, gender, age and previous diseases identified from hospital diagnoses in the two preceding years were analysed as potential effect modifiers. The diseases were selected based on the following criteria: (1) diseases related to oxidative stress, systemic inflammation, autonomous nervous system disorders, coagulation disorders and atherosclerosis; (2) heart diseases that may have complicated the natural course of respiratory diseases; (3) chronic diseases that may generally impair vital functions, such as cancer, chronic hepatic conditions, and renal failure.

Data on influenza epidemics were defined, based on National Health Service Sentinel System data, as the three-week period of maximum incidence (generally occurring between January and March) in each city.

Environmental data

Air pollution data were provided by the Regional Environmental Agencies, which in 2001-2005 routinely monitored particulate matter with an aerodynamic diameter of less than 10 microns (PM₁₀) and nitrogen dioxide (NO₂). A previously-defined algorithm [24] was developed to impute missing values and to calculate daily averages for PM₁₀ and NO₂ in each city. For inclusion, monitored data of daily measures per season had to be at least 75% complete.

Daily information on temperature, humidity and barometric pressure was provided by the Italian Air Force Meteorological Service. Apparent temperature was calculated from air temperature and dew-point temperature, a proxy of relative humidity. [25]

Statistical analyses

A time-series analysis was performed for each city to study the association between air pollutants and health effects. 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 spent outside the city and decreased health service availability), and influenza epidemics. Long-term trends and seasonality were controlled for by including a triple interaction of year, month and day of the week in the regression models. Increases in hospitalisations and mortality corresponding to 10 µg/m³ increases in PM₁₀ or NO₂ were estimated and reported as percentages with 95% confidence intervals (95%CI). More details about the analysis are reported in previous papers [17;21] and methods used to analyse hospitalisations have been fully described in a paper about the cardiovascular effects of PM₁₀. [26]

To explore the lag interval of the pollutants' effects, we fitted single-lag models and cubic polynomial distributed lag models [27;28] for each city. Six-day lags were explored from 0 to 5 days preceding hospitalisation or death. Cumulative lags were also analysed for three intervals selected a priori to differentiate immediate (up to lag 1), delayed (lag 2-5), and prolonged (lag 0-5)

effects. The cumulative lag interval with the strongest effect and the lowest heterogeneity between cities in the pooled analysis for that lag interval was used in further analysis as the best lag, but lag 0-3 was preferred to lag 0-5 for out-of-hospital mortality to better compare the results with those of total respiratory mortality. [17]

To estimate the net effect of each pollutant on each respiratory event, the association was evaluated in two-pollutant models.

A case-crossover analysis was carried out to investigate the potential modification of the effect of each pollutant on the risk of any respiratory event in each city-specific regression model. A conditional logistic regression was applied, selecting control days with a time-stratified approach [29] (designed to control for season, long-term trend and day of the week), and considering the other covariates as in a Poisson regression approach. Each individual effect modifier was tested by adding to the model an interaction term between each potential effect modifier, one at a time, and the pollutant.

Finally, pooled estimates were obtained from city-specific results by applying a random-effects meta-analysis with maximum likelihood.[30] For each pooled estimate, we estimated the p-values of tests for heterogeneity across cities.

All analyses were carried out using SAS software (Statistical Analysis System, version 8.2, SAS Institute, Inc) and R software (version 2.8.1, R Foundation for Statistical Computing).

Results

There were 100,690 hospitalisations due to respiratory diseases in the study population from 2001 to 2005, 38,577 (39%) were due to COPD (24% of which had a principal diagnosis of respiratory failure) and 9,886 (10%) to LRTI in COPD sufferers. There were 5,490 out-of-hospital respiratory deaths, accounting for 30.7% of all respiratory deaths (n. 17,862). Most hospitalisations for respiratory diseases and COPD, and most out-of-hospital deaths were observed in Rome, Milan and

Palermo, in decreasing order of frequency (Table 1). Hospitalisations for LRTI slightly differed; Florence joined Rome and Milan among the cities with the highest values. Respiratory events were more frequent in the cold seasons (October to March), when 56.6% of hospitalisations and 59.7% of out-of-hospital deaths occurred (Table 1).

There were 185 out-of-hospital deaths related to asthma and 1874 asthma hospitalisations in the six cities over the five-year period.

Daily mean concentrations of PM₁₀ ranged from 53.9 µg/m³ in Turin to 34.8 µg/m³ in Palermo. NO₂ showed greater variability, with the lowest value in Florence (46.1 µg/m³) and the highest in Milan, Turin and Rome (59.2, 66.0 and 62.4 µg/m³). The apparent temperature showed a clear North-South gradient, with the lowest values in Milan, Turin and Bologna (11.5 - 13.8°C) and the highest in Palermo and Rome (15.7 -19.4°C). No important differences in humidity or atmospheric pressure were observed between the cities. Complete data on pollutants and meteorological conditions have been reported in previous papers. [17;21;26]

The effects of both PM₁₀ and NO₂ on hospitalisations for respiratory diseases were immediate (lag 0-1), and notable on hospitalizations for COPD, which increased the same day the pollutants increased and decreased immediately after. Hospitalisations for LRTI increased later, on the second (for PM₁₀) or on the third (for NO₂) day, and reached the strongest values on the fourth day (lag 3) suggesting that COPD patients with pulmonary infections are hospitalised later. Finally, out-of-hospital mortality was prolonged (lag 0-5), increased steadily until the third day and remained high until the sixth day. (Figure 1)

A 10 µg/m³ rise in PM₁₀ increased hospitalisations for all respiratory diseases by 0.59% (95%CI= 0.10-1.08) and for COPD by 0.67% (95%CI= -0.02 to 1.35). Greater increases were observed for LRTI hospitalisations (1.91%; 95%CI= 0.06-3,79) and for out-of-hospital respiratory mortality (3.95%; 95%CI= 1.53-6.43) (Table 2).

A 10 $\mu\text{g}/\text{m}^3$ rise in NO_2 increased hospitalisations for all respiratory diseases by 1.19% (95%CI = 0.23-2.15), and for COPD by 1.20% (95%CI= 0.23-2.15). Greater increases were observed for LRTI (1.79%; 95%CI = -1.16 to 4.83) and for out-of-hospital mortality (6.92%; 95%CI = 3.53-10.42) (Table 2). The heterogeneity of the effects across cities was very low for both pollutants. The effect estimates on asthma hospitalisations were estimated only for Rome (the city with the highest frequency). We found the highest values at lag 0-5 with important but not statistically significant increases (6.59%; 95%CI -2.27 to 16.27 for 10 $\mu\text{g}/\text{m}^3$ PM_{10} and 9.26%; 95%CI -2.66 to 22.64 for 10 $\mu\text{g}/\text{m}^3$ NO_2) (data not shown). The low number of asthma events did not allow further considering them in the analysis.

To compare the effect sizes between the two-pollutants, we estimated the strength of the effects of both pollutants by the inter-quartile-ranges (IQR) of their concentrations (PM_{10} IQR = 24.9 $\mu\text{g}/\text{m}^3$; NO_2 IQR = 25.9 $\mu\text{g}/\text{m}^3$). NO_2 had slightly stronger effects than PM_{10} at the best lag for each pollutant. The effects on respiratory hospitalisations were 1.94% vs. 1.47% at lag 0-1 and 3.10% vs. 1.53% at lag 0-5, respectively. The effects on COPD hospitalisations were 3.13% vs. 1.66% at lag 0-1, those on LRTI hospitalisations were 4.71% vs. 3.75% respectively at 0-5 lag, and those on out-of-hospital deaths were 16.26% vs. 11.25% respectively, at lag 0-5. The complete results are reported in the supplemental material, Table A.

The association between PM_{10} and hospitalisations was stronger in warm than in cold seasons for all respiratory events; it was 12 times stronger for respiratory diseases, 7.5 times stronger for COPD and 5 times stronger for LRTI, indicating that seasons also are an effect modifier (Table B in the supplemental material). Out-of-hospital mortality differed slightly; though it increased 1.7 times in warm seasons, the ratio was much lower than for hospitalisations and no effect modification was statistically supported (Table B in the supplemental material). The pattern of associations between NO_2 and hospitalisations by season was very similar to what has been seen for PM_{10} .

In the two-pollutant models, when both PM₁₀ and NO₂ were considered, the effects remained but were lower, especially for all respiratory diseases and out-of-hospital mortality, and statistical significance was not reached (Table 3). The correlation between NO₂ and PM₁₀ varied between 0.22 and 0.79 across cities, as a result of different sources and dispersion of the pollutants. This could explain the indeterminate results regarding possible independent effects.

Table 4 (and Table C in the supplemental material) shows the pooled estimates of PM₁₀ effects on respiratory hospitalisations and out-of-hospital mortality, stratified by age group, gender and hospital discharge diagnoses in the previous two years. Age was clearly an effect modifier of out-of-hospital mortality, people were more likely to die at home if they were older: risk increased up to 5.07% (95% CI= 1.01-9.30;) for 75-84 year-olds and up to 4.85% (95% CI= 1.81-7.92) for 85+ year-olds. Gender was a mild effect modifier (6.15%; 95%CI= 3.06-9.33); women were more likely to die at home than men (1.98%; 95%CI= -1.32 to 5.40, p-interaction= 0.076); in contrast, cancer patients were less likely to die at home (-5.32%; 95%CI= -16.64 to 7.53; p-interaction= 0.134).

There was a high risk of 85+ year-olds being hospitalised for any respiratory disease (1.24%; 95%CI= 0.25 ; 2-23) compared to younger subjects but the difference was not statistically significant. In contrast, a previous diagnosis of ischemic heart disease increased the risk of hospitalisation, suggesting a possible effect modification on all respiratory diseases (1.59%; 95%CI= 0.41-2.79), COPD exacerbation (1.93%; 95%CI = 0.33-3.55), and LRTI (4.89%; 95%CI= 0.29-9.69) in COPD sufferers. Among non-cardiac diseases, only chronic liver disease possibly increased the likelihood of a hospitalisation for LRTI. We did not find any evidence of modification of the effects of air pollution on respiratory diseases for diseases of pulmonary circulation (ICD-9: 415-417), conduction disorders (ICD-9: 426); arrhythmias (ICD-9: 427), heart failure (ICD-9: 428) and among non-cardiac diseases, for cancer (ICD-9: 140-208), diabetes (ICD-9: 250), cerebrovascular diseases (ICD-9: 430-438), chronic pulmonary diseases (ICD-9: 490-505), or renal failure (ICD-9: 584-588).

Discussion

We found an immediate increase in emergency hospitalisations for respiratory diseases associated with PM₁₀, and even more strongly associated with NO₂. The largest and longest-lasting effect was observed on hospitalisations due to LRTI in COPD sufferers. All effects on hospitalisations were stronger in warm than in cold seasons. Subjects with a previously diagnosed ischemic heart disease showed the strongest effects to PM₁₀. The risk of dying out-of-hospital was much higher than that of being hospitalised, it did not decrease over the cumulative six-day exposure and did not show seasonal differences.

The immediate effect on hospitalisations for respiratory diseases confirms most results from previous studies on adults; [5;8] longer cumulative lags have been consistently reported for respiratory hospitalisations in children. [14;15] The greatest effect has been observed on hospitalisations due to LRTI in COPD sufferers; it lasted longer, up to four or six days for different pollutants, and it was consistent across cities. Since we studied only pneumonia in COPD, we concluded that worsening COPD causes immediate recourse to hospitalisation while pulmonary infections in COPD patients took more time to become serious, resulting in more time elapsed before hospitalisation for COPD patients who developed pulmonary infections. Important increases in hospitalisations for LRTI associated to rises in PM₁₀ or NO₂ were reported both in adults [31;32] and in children. [33] Also, hospitalisations for chronic respiratory diseases (COPD) associated with rising PM₁₀ showed higher increases than those for all respiratory diseases, as has already been reported. [34] Clearly, COPD patients are very likely to be susceptible to the short-term effects of air pollutants. [9;31;35;36;37]

A slightly stronger effect of NO₂ respect to PM₁₀ on respiratory hospitalisations has been reported in some previous studies of both pollutants, [6;14] but the difference was small or not appraisable at all. However, literature shows NO₂ had a stronger effect than PM₁₀ on child morbidity and on adult

mortality, and in our study the NO₂ effects on hospitalisation for respiratory diseases and for COPD were almost twice as large as those due to PM₁₀. While this supports the conclusion that NO₂ has a greater effect on respiratory health, the variability of the correlation between the two-pollutants prevents from drawing a clear conclusion regarding their independent effects.

The warm seasons exacerbate the effects of pollutants, especially those NO₂-related, though a complete explanation for this was still not found in the literature.

The oldest people and those with previous ischemic disease were more likely to be hospitalised following PM increases, but no effect modification was appreciated. The same effect has been previously reported for other cardiac diseases [22] and the oldest ages. [38] It is noteworthy that we did not find any modification with age of the risk of hospitalisations due to specific respiratory diseases (COPD and LRTI), which are likely to be influenced by other factors.

The high estimates of out-of-hospital mortality we found here for PM₁₀, and even more for NO₂, were consistent with the results we found for total respiratory mortality, [17;18] and confirm the stronger effect of NO₂ with respect to PM reported in other studies. [19;39] However, the higher increases in mortality than in hospitalisations we found for both pollutants contrast the results of most papers which reported higher risks of respiratory hospitalisations than of respiratory mortality. [7-9;13] Though not to exclude the possibility that different habits of recourse to hospitals may explain this disagreement, the more likely explanation is, in our opinion, the shorter lag time (0-1 days) used in most studies in contrast to the prolonged lag (0-5 days) we used here and in previous papers analysing total respiratory mortality. [17;18] Shorter lag times have usually been considered more suited for natural mortality; however previous studies that used 0-6 lag [19;20;39] found higher estimates of respiratory mortality associated with both PM and NO₂. On the other hand, it has been demonstrated that the effect of air pollution on mortality spreads over two days. [27]

Having no previous hospitalizations has been recognised as increasing mortality risk [17-19] since

it assumes hospitalisation functions as a temporary protective factor against air pollution and death, because it reduces exposure and provides effective treatment for chronic diseases. This is the first time that the factors linked to dying out-of-hospital were specifically analysed and the results would suggest that very old people are hospitalised less frequently, while the risk of dying related to air pollution does not seem to be influenced by the presence of chronic diseases.

This study takes a new approach to assess the health effects of air pollution by analysing hospitalisations and out-of-hospital mortality contemporarily as multiple effects. Not having been able to include the emergency visits among the respiratory effects of air pollution is clearly a limit of our analysis, given their importance in assessing air pollutants effects. [7;16;40] This approach however allowed us to obtain a more complete picture of air pollution effects and to detect conditions of susceptibility for different outcomes.

Several conclusions can be drawn from the present study: 1) PM₁₀ and NO₂ increased hospitalizations and mortality for respiratory diseases. 2) Subjects with previous cardiac ischemic diseases were affected more strongly by PM₁₀ than their healthier counterparts. 3) Air pollution effects on hospitalisation in Italy are stronger during the warm period of the year, confirming what has been already observed for mortality. 4) A more complete picture of the short-term respiratory effects of air pollutants is obtained when both hospitalisations and out-of-hospital deaths are examined. Air pollution suddenly aggravates COPD, leading to immediate hospitalisation, and/or promotes respiratory infections that slowly lead to hospitalization or to death at home.

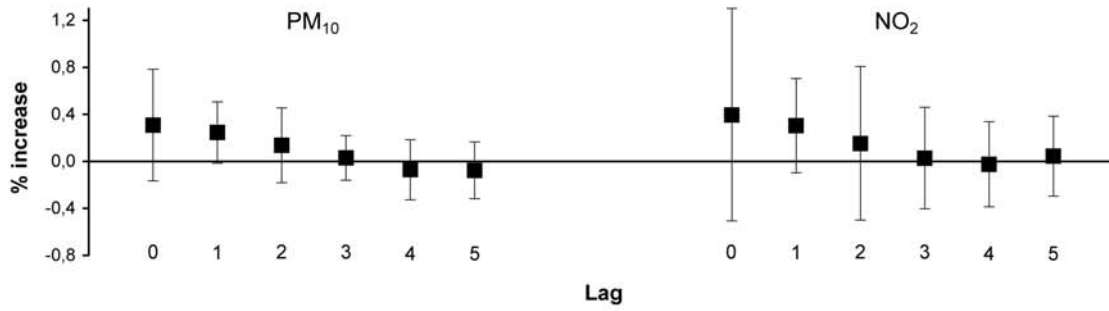
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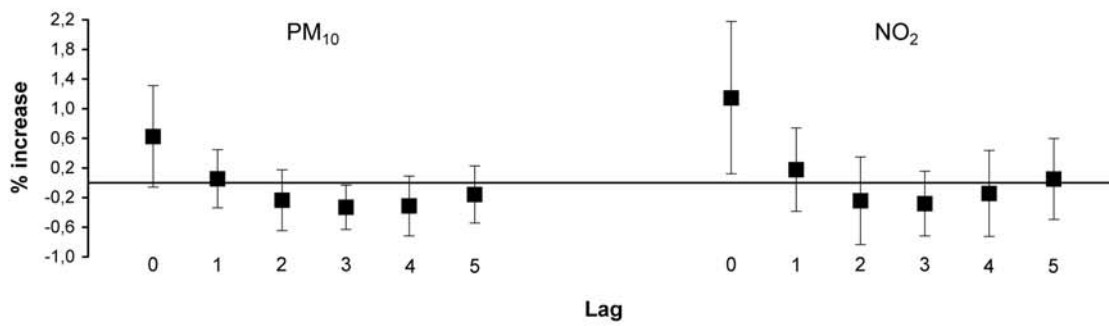
FIGURE LEGEND

Figure 1. Pooled results. Association between multiple respiratory outcomes and PM₁₀ or NO₂, by lag (from constrained distributed lag models) – 6 cities, 2001-2005.

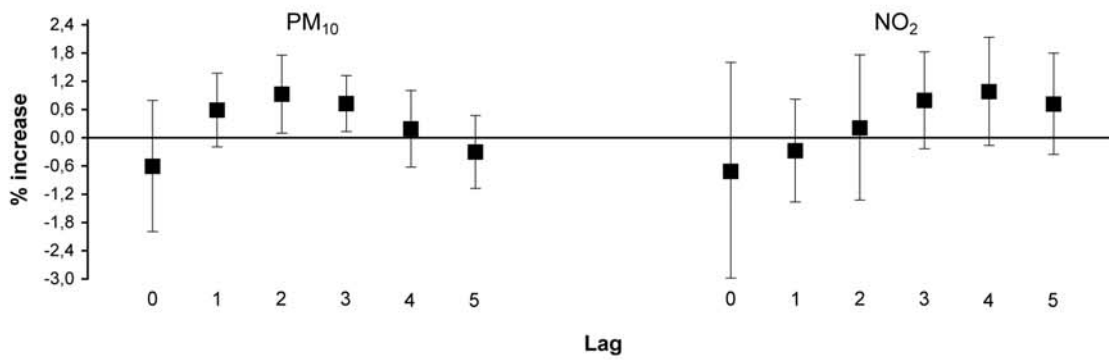
hospitalisations for respiratory diseases



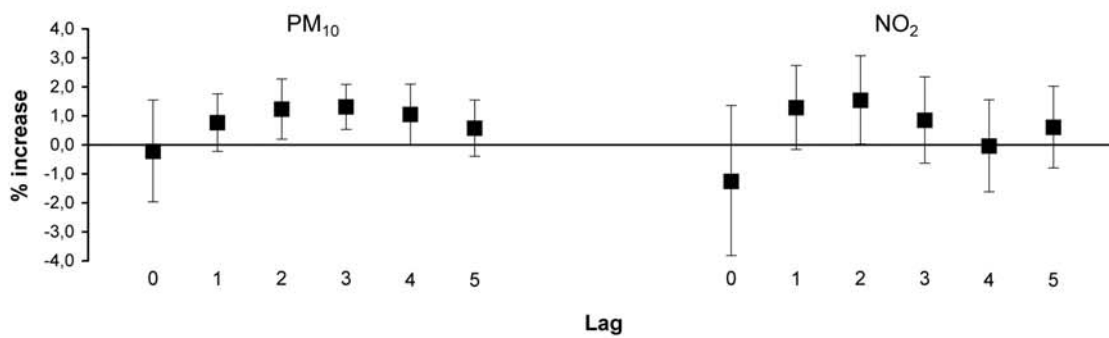
hospitalisations for COPD



hospitalisations for LRTI in COPD



Out-of-hospital respiratory deaths



Diagrams' titles

(from top to bottom)

hospitalisations for respiratory diseases

hospitalisations for COPD

hospitalisations for LRTI in COPD patients

out-of-hospital respiratory deaths

In each diagram

Abscissa : lag

Ordinate : % increase of respiratory outcome,

legends : Black squares = constrained distributed-lag models

Notes:

Data are percent increases of risk, and 95% confidence intervals, relative to a $10 \mu\text{g}/\text{m}^3$ increase in PM_{10}
In distributed lag models, a third-degree polynomial constrain for lags from 0 to 5 has been applied.

REFERENCES

1. Lagorio S, Forastiere F, Pistelli R et al. Air pollution and lung function among susceptible adult subjects: a panel study. *Environ Health*, 2006 5: 11 doi:10.1186/1476-069X-5-11.
2. Zeka A Zanobetti A, Schwartz J. Individual-level modifiers of the effects of particulate matter on daily mortality. *Am J Epidemiol*. 2006; 163: 849-59.
3. Delfino RJ, Gong H Jr, Linn WS et al. Asthma symptoms in Hispanic children and daily ambient exposures to toxic and criteria air pollutants. *Environ Health Perspect* 2003; 111: 647-656.
4. Schwartz J. Air pollution and hospital admissions for respiratory disease. *Epidemiol* 1996; 7:20-28.
5. Atkinson RW, Anderson HR, Sunyer J et al. Acute effects of particulate air pollution on respiratory admissions. Results from APHEA 2 Project. *Am J Respir Crit Care Med* 2001; 164: 1860-1866.
6. Barnett AG, Williams GM, Schwartz J et al. Air pollution and child respiratory health: a case-crossover study in Australia and New Zealand. *Am J Respir Crit Care Med*. 2005;171:1272-1278.
7. Peel J, Tolbert PE, Klein M et al. Ambient air pollution and respiratory emergency department visits. *Epidemiology* 2005; 16: 164-174
8. Medina-Ramón M, Zanobetti A, Schwartz J. The effect of ozone and PM10 on hospital admissions for pneumonia and chronic obstructive pulmonary disease: a national multicity study. *Am J Epidemiol* 2006; 163: 579-586
9. Dominici F, Peng RD, Bell ML et al. Fine particulate air pollution and hospital admission for cardiovascular and respiratory diseases. *JAMA* 2006; 295: 1127-1134.
10. Dominici F, Mc Dermott A, Daniels M, Zeger SL, Samet JM. Revised analyses of the National Morbidity, Mortality, and Air Pollution Study: mortality among residents of 90 cities. *J Toxicol Environ Health A*. 2005; 68:1071-92

11. Katsouyanni K, Touloumi G, Samoli E et al. Confounding and effect modification in the short-term effects of ambient particles on total mortality: results from 29 European cities within the APHEA2 Project. *Epidemiology* 2001; 12:521-531.
12. Ostro B, Feng WY, Broadwin R, Green S, Lipsett M. The effects of components of fine particulate air pollution on mortality in California: Results from CALFINE. *Environ Health Perspect* 2007;114:13-19.
13. Pope CA 3rd, Dockery DW. Health effects of fine particulate air pollution: lines that connect. *J Air Waste Manag Assoc.* 2006; 56: 709-42.
14. Galán I, Tobías A, Banegas JR, Aránguez E. Short-term effects of air pollution on daily asthma emergency room admissions. *Eur Respir J.* 2003;22:802-808.
15. Babin SM, Burkom HS, Holtry RS et al. Pediatric patient asthma-related emergency department visits and admissions in Washington, DC, from 2001-2004, and associations with air quality, socio-economic status and age group. *Environ health* 2007; 21 March 6:9 doi:10.1186/1476-069X-6-9.
16. Strickland MJ, Darrow LA, Klein M, Flanders WD, Sarnat JA, Waller LA, Sarnat SE, Mulholland JA, Tolbert PE. Short-term associations between ambient air pollutants and pediatric asthma emergency department visits. *Am J Respir Crit Care Med.* 2010; 182: 307-316.
17. Faustini A, Stafoggia M, Berti G, Bisanti L, Chiusolo M, Cernigliaro A, Mallone S, Primerano R, Scarnato C, Simonato L, Vigotti MA, Forastiere F; EpiAir Collaborative Group. The relationship between ambient particulate matter and respiratory mortality: a multi-city study in Italy. *Eur Respir J.* 2011; 38: 538-547
18. Chiusolo M, Cadum E, Stafoggia M, Galassi C, Berti G, Faustini A, Bisanti L, Vigotti MA, Dessì MP, Cernigliaro A, Mallone S, Pacelli B, Minerba S, Simonato L, Forastiere F on behalf of the EpiAir Collaborative Group. Short-Term Effects of Nitrogen Dioxide on

- Mortality and Susceptibility Factors in 10 Italian Cities: The EpiAir Study. *Environ Health Perspect* 2011; 119: 1233–1238
19. Hoek G, Brünekreef B. Daily mortality and air pollution in the Netherlands. *J Air Waste Manage Assoc* 2000; 50:1380-1389.
 20. Analitis A, Katsouyanni K, Dimakopoulou K, Samoli E, Nikoloulopoulos AK, Petasakis Y, Touloumi G, Schwartz J, Anderson HR, Cambra K, Forastiere F, Zmirou D, Vonk JM, Clancy L, Kriz B, Bobvos J, Pekkanen J. Short-term effects of ambient particles on cardiovascular and respiratory mortality. *Epidemiology*. 2006; 17: 230-3.
 21. Stafoggia M, Forastiere F, Faustini A, Biggeri A, Bisanti L, Cadum E, Cernigliaro A, Mallone S, Pandolfi P, Serinelli M, Tessari R, Vigotti MA, Perucci CA; EpiAir Group. Susceptibility factors to ozone-related mortality: a population-based case-crossover analysis. *Am J Respir Crit Care Med*. 2010 Aug 1;182(3):376-84.
 22. Barclay JL, Miller BG, Dick S, Dennekamp M, Ford I, Hillis GS, Ayres JG, Seaton A. [A panel study of air pollution in subjects with heart failure: negative results in treated patients](#). *Occup Environ Med* 2009; 66: 325-334.
 23. Qian Z, Lin HM, Chinchilli VM, Lehman EB, Stewart WF, Shah N, Duan Y, Craig TJ, Wilson WE, Liao D, Lazarus SC, Bascom R. Associations between air pollution and peak expiratory flow among patients with persistent asthma. *J Toxicol Environ Health A*. 2009; 72: 39-46.
 24. Biggeri A, Bellini P, Terracini B. Metanalisi italiana degli studi sugli effetti a breve termine dell'inquinamento atmosferico 1996-2000. *Epidemiol Prev* 2004; 28 (4-5).
 25. Steadman RG. The assessment of sultriness. Part I: a temperature-humidity index based on human physiology and clothing science. *J Applied Meteorol*. 1979;18:861.73.
 26. Colais P, Faustini A, Stafoggia M, Berti G, Bisanti L, Cadum E, Cernigliaro A, Mallone S, Pacelli B, Serinelli M, Simonato L, Vigotti MA, Forastiere F. Particulate Air Pollution and Hospital Admissions for Cardiac Diseases in Potentially Sensitive Subgroups. *Epidemiology*. 2012 May;23(3):473-481.

27. Schwartz J. The distributed lag between air pollution and daily deaths. *Epidemiology* 2000; 11:320-326.
28. Zanobetti A Wand MP, Schwartz J, Ryan LM. Generalized additive distributed lag models: quantifying mortality displacement. *Biostatistics* 2000;1:279-92.
29. Levy D, Lumley T, Sheppard L, Kaufman J, Checkoway H. Referent selection in case-crossover analyses of acute health effects of air pollution. *Epidemiology* 2001; 12:186–192.
30. Normand SL. Meta-analysis: formulating, evaluating, combining and reporting. *Stat Med* 1999; 18: 321-59
31. Zanobetti A, Schwartz J, Gold D. Are there sensitive subgroups for the effects of airborne particles ? *Environ Health Perspect* 2000; 108: 841-845.
32. Zanobetti A, Schwartz J. [Air pollution and emergency admissions in Boston, MA.](#) *J Epidemiol Community Health.* 2006; 60: 890-895.
33. Lin M, Stieb DM, Chen Y. Coarse particulate matter and hospitalization for respiratory infections in children younger than 15 years in Toronto: a case-crossover analysis. *Pediatrics.* 2005; 116: e235-240
34. Belleudi V, Faustini A, Stafoggia M, Cattani G, Marconi A, Perucci CA, Forastiere F. Impact of fine and ultrafine particles on emergency hospital admissions for cardiac and respiratory diseases. *Epidemiology* 2010; 21: 414-423.
35. Sunyer J, Schwartz J, Tobias A, Macfarlane D, Garcia J, Antó JM. Patients with chronic obstructive pulmonary disease are at increased risk of death associated with urban particle air pollution: a case-crossover analysis. *Am J Epidemiol* 2000; 151: 50-56.
36. Bateson TF, Schwartz J. Who is sensitive to the effects of particulate air pollution on mortality?. A case-crossover analysis of effect modifiers. *Epidemiology* 2004; 15: 143-149.
37. Faustini A, Stafoggia M, Cappai G, Forastiere F. [Short-term effects of air pollution in a cohort of patients with chronic obstructive pulmonary disease.](#) *Epidemiology* (accepted on 22-04-2012)

38. Halonen JJ, Lanki T, Yli-Tuomi T, Kulmala M, Tiittanen P, Pekkanen J. Urban air pollution, and asthma and COPD hospital emergency room visits. *Thorax* 2008; 63: 635-641.
39. Fischer P, Hoek G, Brunekreef B, Verhoeff A, van Wijnen J. Air pollution and mortality in The Netherlands: are the elderly more at risk? *Eur Respir J Suppl.* 2003;40: 34s-38s.
40. Stieb DM, Szyszkowicz M, Rowe BH, Leech JA. Air pollution and emergency department visits for cardiac and respiratory conditions: a multi-city time-series analysis. *Environ Health.* 2009 Jun 10;8:25.

Table 1. Multiple respiratory health events in 35+ year-olds, by city and season, 2001-2005

City	hospitalisations for respiratory diseases						out-of hospital respiratory deaths [‡]	
	all respiratory diseases		COPD		LRTI in COPD		N	%**
	N	%	N	%*	N	%*		
Milan	19,479	19.3	6,538	6.5	1,960	1.9	1,147	20.9
Turin	10,100	10.0	3,695	3.7	1,060	1.1	409	7.4
Bologna	8,716	8.7	3,883	3.9	859	0.9	457	8.3
Florence	8,725	8.7	2,740	2.7	1,419	1.4	426	7.8
Rome	37,692	37.4	14,713	14.6	3,238	3.2	2,400	43.7
Palermo	15,978	15.9	7,008	7.0	1,350	1.3	651	11.9
Total	100,690	100.0	38,577	38.3	9,886	9.8	5,490	100.0
	in warm seasons [†]						in warm seasons [†]	
Milan	8,376	19.2	2,654	6.1	840	1.9	432	19.5
Turin	4,168	9.5	1,423	3.3	409	0.9	169	7.6
Bologna	3,653	8.4	1,578	3.6	350	0.8	187	8.5
Florence	3,617	8.3	1,040	2.4	587	1.3	181	8.2
Rome	16,751	38.3	6,231	14.3	1,444	3.3	981	44.4
Palermo	7,147	16.4	3,039	7.0	568	1.3	261	11.8
Total	43,712	100.0	15,965	36.5	4,198	9.6	2,211	100.0
COPD = chronic obstructive pulmonary disease, identified as principal diagnosis of COPD or respiratory failure with COPD as secondary diagnosis.								
LRTI = lower respiratory tract infections (bronchitis and pneumonia) identified as principal diagnosis with COPD as secondary diagnosis.								
‡ deaths of people without hospitalisations in the previous two years or with hospitalisation but discharged at least 28 days before death. *percentage over all respiratory diseases.								
**estimated percentages over all respiratory deaths. †April to September								

Table 2. Pooled results. Increased risk (IR) in multiple respiratory health effects in 35+ year-olds associated with 10µg/m³ increase in PM₁₀ and NO₂ at different lags, 6 Italian cities, 2001 – 2005

	hospitalisations for											out-of-hospital respiratory deaths [‡] (n. 5490)					
	all respiratory diseases (n.100690)				COPD (n. 38577)			LRTI in COPD (n. 9886)									
	lag	% IR	95% CI		p _{HET} [†]	% IR	95% CI		p _{HET} [†]	% IR	95% CI		p _{HET} [†]	% IR	95% CI		p _{HET} [†]
PM ₁₀	0	0.53	0.09	0.96	0.597	0.67	-0.02	1.35	0.580	0.28	-1.10	1.68	0.837	1.13	-0.62	2.90	0.898
	0-1	0.59	0.10	1.08	0.718	0.23	-0.54	1.02	0.817	0.57	-0.95	2.12	0.880	1.85	-0.17	3.90	0.376
	0-3	0.60	0.01	1.20	0.634	-0.14	-1.07	0.80	0.475	1.91	0.06	3.79	0.655	3.95	1.53	6.43	0.437
	2-5	0.35	-0.21	0.92	0.330	-0.76	-1.73	0.22	0.184	1.64	-0.31	3.63	0.154	4.50	2.19	6.86	0.517
	0-5	0.61	-0.07	1.30	0.651	-0.43	-1.50	0.65	0.424	1.49	-0.65	3.68	0.585	4.38	1.57	7.26	0.639
NO ₂	0	0.67	0.03	1.31	0.522	1.20	0.17	2.23	0.574	-0.14	-2.10	1.86	0.589	0.15	-2.47	2.84	0.767
	0-1	0.75	0.03	1.46	0.987	0.98	-0.16	2.13	0.736	-0.67	-2.83	1.55	0.853	1.14	-1.80	4.17	0.820
	0-3	1.09	0.24	1.95	0.729	0.86	-0.50	2.23	0.724	1.13	-1.48	3.81	0.820	3.54	-0.04	7.25	0.264
	2-5	0.73	-0.36	1.83	0.033	-0.01	-1.27	1.27	0.413	2.56	-0.72	5.96	0.118	6.92	3.53	10.42	0.194
	0-5	1.19	0.23	2.15	0.837	0.82	-0.70	2.37	0.766	1.79	-1.16	4.83	0.714	5.99	1.92	10.22	0.521

COPD = chronic obstructive pulmonary disease, identified as principal diagnosis of COPD or respiratory failure with COPD as secondary diagnosis.

LRTI = lower respiratory tract infections (bronchitis and pneumonia) identified as principal diagnosis with COPD as secondary diagnosis.

‡ deaths of people without hospitalisations in the previous two years or with hospitalisation but discharged at least 28 days before death.

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

Table 3. Pooled results. Increased risk (IR) in respiratory health effects associated[#] with 10µg/m³ increase in PM₁₀ or NO₂ from models adjusted for other pollutants, 6 Italian cities, 2001 – 2005.

	hospitalisations for respiratory diseases										out-of-hospital respiratory deaths					
	all respiratory diseases				COPD			LRTI in COPD			% IR	95% CI	p HET [†]			
	% IR	95% CI	p HET [†]		% IR	95% CI	p HET [†]		% IR	95% CI				p HET [†]		
Single-PM₁₀ model	0.59	<i>0.10</i>	<i>1.08</i>	0.718	0.67	<i>-0.02</i>	<i>1.35</i>	0.580	1.91	<i>0.06</i>	<i>3.79</i>	0.655	3.95	<i>1.53</i>	<i>6.43</i>	0.437
Model with NO₂	0.45	<i>-0.12</i>	<i>1.01</i>	0.422	0.54	<i>-0.41</i>	<i>1.49</i>	0.250	2.14	<i>-0.74</i>	<i>5.11</i>	0.194	2.93	<i>-0.14</i>	<i>6.09</i>	0.636
Single-NO₂ model	1.19	<i>0.23</i>	<i>2.15</i>	0.837	1.20	<i>0.17</i>	<i>2.23</i>	0.574	1.79	<i>-1.16</i>	<i>4.83</i>	0.714	5.99	<i>1.92</i>	<i>10.22</i>	0.521
Model with PM₁₀	0.86	<i>-0.30</i>	<i>2.02</i>	0.576	1.02	<i>-0.45</i>	<i>2.51</i>	0.184	2.01	<i>-1.78</i>	<i>5.94</i>	0.386	3.00	<i>-2.04</i>	<i>8.30</i>	0.967

[#]The following lags were used in PM₁₀ models: 0-1 for respiratory hospitalisations; 0 for COPD and 0-3 for LRTI hospitalisations and out-of-hospital deaths. In NO₂ models lag 0-5 was used for all the outcomes apart from COPD hospitalisations which were analysed at lag 0.

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

Table 4. Pooled results. Percentage increased risk (IR) in respiratory disease hospitalisations and out-of-hospital respiratory deaths associated with 10 µg/m³ increase in PM₁₀, in 35+ year olds, by demographic characteristics and previous diseases, 6 Italian cities, 2001 - 2005.

	hospitalisation for all respiratory diseases						hospitalisations for COPD							
	N.	%	% IR [§]	95% CI		p HET [‡]	p inter [†]	N.	%	% IR [§]	95% CI		p HET [‡]	p inter [†]
Total	100,690	100	0.59	<i>0.10</i>	<i>1.08</i>	0.718	-	38,577	100	0.67	<i>-0.02</i>	<i>1.35</i>	0.580	-
Age (years)														
35-64	22,572	22.4	0.05	<i>-0.86</i>	<i>0.97</i>	0.984	-	5,939	15.4	0.20	<i>-1.24</i>	<i>1.66</i>	0.748	-
65-74	26,093	25.9	0.54	<i>-0.52</i>	<i>1.61</i>	0.111	0.513	11,640	30.2	1.17	<i>-0.60</i>	<i>2.97</i>	0.019	0.230
75-84	34,492	34.3	0.79	<i>0.06</i>	<i>1.52</i>	0.813	0.205	15,092	39.1	0.71	<i>-0.28</i>	<i>1.70</i>	0.235	0.537
85+	17,533	17.4	1.24	<i>0.25</i>	<i>2.23</i>	0.541	0.131	5,906	15.3	0.05	<i>-1.49</i>	<i>1.61</i>	0.689	0.642
Gender														
men	56,647	56.3	0.50	<i>-0.08</i>	<i>1.09</i>	0.310	-	23,000	59.6	0.93	0.02	1.85	0.320	-
women	44,043	43.7	0.79	<i>0.14</i>	<i>1.44</i>	0.740	0.473	15,577	40.4	0.22	<i>-0.73</i>	<i>1.18</i>	0.964	0.371
Heart diseases in the previous 2 years														
Ischemic heart diseases (ICD-9: 410-414)*	12,495	12.4	1.59	<i>0.41</i>	<i>2.79</i>	0.697	0.074	5,466	14.2	1.93	0.33	3.55	0.388	0.068
	hospitalisation for LRTI in COPD						out-of-hospital respiratory deaths							
	N.	%	% IR [§]	95% CI		p HET [‡]	p inter [†]	N.	%	% IR [§]	95% CI		p HET [‡]	p inter [†]
Total	9,886	100	1.91	<i>0.06</i>	<i>3.79</i>	0.655	-	5,490	100	3.95	<i>1.53</i>	<i>6.43</i>	0.344	-
Age (years)														
35-64	1,563	15.8	0.78	<i>-3.41</i>	<i>5.15</i>	0.827	-	288	5.2	<i>-5.38</i>	<i>-14.10</i>	<i>4.22</i>	0.397	-
65-74	2,569	26.0	0.77	<i>-2.23</i>	<i>3.86</i>	0.501	0.883	575	10.5	4.00	<i>-2.98</i>	<i>11.48</i>	0.707	0.120
75-84	3,726	37.7	2.42	<i>-0.19</i>	<i>5.10</i>	0.432	0.504	1,682	30.6	5.07	<i>1.01</i>	<i>9.30</i>	0.704	0.049
85+	2,028	20.5	3.78	<i>0.45</i>	<i>7.22</i>	0.660	0.243	2,944	53.6	4.82	<i>1.81</i>	<i>7.92</i>	0.468	0.047
Gender														
men	6,344	64.2	2.46	<i>0.41</i>	<i>4.56</i>	0.879	-	2,550	46.4	1.98	<i>-1.32</i>	<i>5.40</i>	0.098	-
women	3,542	35.8	1.27	<i>-1.36</i>	<i>3.96</i>	0.296	0.486	2,940	53.6	6.15	<i>3.06</i>	<i>9.33</i>	0.395	0.076
Heart diseases in the previous 2 years														
Ischemic heart diseases (ICD-9: 410-414)*	1,227	12.4	4.89	<i>0.29</i>	<i>9.69</i>	0.755	0.192	476	8.7	3.42	<i>-3.40</i>	<i>10.72</i>	0.943	0.820

[§] risk estimated at the best lag: hospitalisations for respiratory diseases (lag 0-1), for COPD (lag 0), for LRTI in COPD (lag 0-3), out-of-hospital mortality (lag 0-3).

[‡] p-value of heterogeneity test (null hypothesis is perfect homogeneity of city-specific results). [†] p-value derived from the model with the interaction term (for each condition, the reference category is the group of subjects without the disease). *discharge diagnosis in the period 29 days - 2 years before death

