Eur Respir J 2011; 38: 538–547
DOI: 10.1183/09031936.00093710

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

A. Faustini*, M. Stafoggia*, G. Berti#, L. Bisanti¶, M. Chiusolo#, A. Cernigliaro+, S. Mallone§, R. Primerano^f, C. Scarnato, L. Simonato##, M.A. Vigotti¶¶ and F. Forastiere* on behalf of the EpiAir Collaborative Group++**

ABSTRACT: The association of air pollutants with natural and respiratory mortality has been consistently reported. However, several aspects of the relationship between particulate matter with a 50% cut-off aerodynamic diameter of 10 μm (PM_{10}) and respiratory mortality require further investigation. The aim of the present study was to assess the PM_{10}–respiratory mortality association in Italy and examine potentially susceptible groups.

All deaths from natural (n=276,205) and respiratory (n=19,629) causes among subjects aged ⩾35 yrs in 10 northern, central and southern Italian cities in 2001–2005 were included in the study. Pollution data for PM_{10}, nitrogen dioxide and ozone were also 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 curve was analysed. Age, sex, chronic conditions and death site were investigated as potential effect modifiers.

We found a 2.29% (95% CI 1.03–3.58%) increase in respiratory mortality at 0–3 days lag. The increase in respiratory mortality was higher in summer (7.57%). The exposure–response curve had a linear shape without any threshold. Sex and chronic diseases modified the relationship between particular matter (PM) and respiratory mortality.

The effect of PM 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.

KEYWORDS: Case-crossover design, multi-city study, particulate matter, respiratory mortality

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 of particulate matter with a 50% cut-off aerodynamic diameter 10 μm (PM_{10}) on daily mortality have been estimated to be in the range of 0.3–1.5% per 10 $\mu g \cdot m^{-3}$ PM_{10} [1]. The effects on mortality caused by cardiovascular (CV) and respiratory diseases have been found to be generally stronger than for other conditions, and the findings contribute to our understanding of the damage mechanisms of air pollution in 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 shape of the exposure–response curve, the latency interval of the effect and the individual characteristics that can modify the particular matter (PM) effect [3, 4], deserve further investigation. The shape of the exposure–response curve 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]

This article has supplementary material available from www.erj.ersjournals.com

AFFILIATIONS
*Epidemiology Dept, Regional Health Service of Lazio, Rome,
#Epidemiology Services, Regional Environmental Protection Agency of Piedmont, Turin,
¶Epidemiology Unit, Local Health Authority, Milan,
+Epidemiological Observatory, Regional Health Authority, Palermo,
§Institute for Cancer Prevention, Florence,
^fEnvironmental Engineering and Sustainable Development Dept, Technical University of Bari, Taranto,
**Local Health Authority, Bologna,
##Environmental and Public Health Dept, University of Padua, Padua, and
¶¶Biology Dept, University of Pisa, Pisa, Italy.
++A full list of the EpiAir Collaborative Group members can be found in the Acknowledgements section.

CORRESPONDENCE
A. Faustini
Epidemiology Dept
Regional Health Service of Lazio
V. S. Costanza n 53
00198 Rome
Italy
E-mail: faustini@asplazio.it

Received:
June 17 2010
Accepted after revision:
Dec 04 2010
First published online:
Jan 13 2011

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

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 10 Italian cities during the period 2001–2005. We analysed the effects of PM10 on respiratory mortality and examined in detail the latency interval of the effect, the shape of the exposure–response curve and the characteristics of potentially susceptible groups. We also consider the influence of other pollutants (nitrogen dioxide (NO_2) and ozone (O_3)) and the possible heterogeneity of the PM10 effects across the cities.

METHODS

Health events

All deaths from natural causes in 10 northern, central and southern Italian cities from 2001–2005 were included in the study. Respiratory deaths were identified from local mortality registries on the basis of underlying cause of death (International Classification of Diseases, 9th 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 subjects $\geqslant$35 yrs of age and classified the site of death as in hospital or out of hospital, including in the in-hospital group people who died within 2 days of a hospital discharge; the out-of-hospital death group was further divided into those with or without a recent hospitalisation (discharged 2–28 days before death).

For each subject, we collected information on sex, age at death and hospitalisations in the preceding 2 yrs. 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 PM10 were selected on the basis of the existing literature [12–14], and were grouped as acute or chronic conditions according to the patients' admission dates and clinical criteria. Conditions were considered acute if they showed clinical characteristics consistent with an acute disease (sudden onset, short course and recovery likelihood) or characteristics consistent with an exacerbation of chronic diseases, provided, in both cases, that they were reported as the primary diagnosis on hospitalisations with admission dates $\leqslant$28 days before death. Conditions were considered chronic if they were consistent with the clinical criteria of chronicity and were reported as primary or secondary diagnoses in hospitalisations with admissions from 29 days to 2 yrs before death (a complete list of these acute and chronic conditions with corresponding ICD-9 codes is provided in the online supplementary material).

Data on influenza epidemics were obtained from 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 3-week periods of maximum incidence (generally occurring between January and March) and 0 on all other days.

Environmental data

Air pollution data were provided by Regional Environmental Agencies, which routinely monitor several pollutants, including PM10, NO_2 and 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 used to impute missing values, and derive daily averages for PM10 and NO_2, and daily maximum 8-h running means for O_3. The missing values for each pollutant on a specific day and at a specific monitoring station were 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 $\geqslant$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 for 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 PM10 and daily mortality. A Poisson regression was applied, controlling for apparent temperature (0–1 days lag, penalised splines) and low temperature (1–6 days lag, penalised splines), barometric pressure (0 days lag, penalised splines), temporary population decreases in the summer and during holidays (a three-level variable taking into account holiday periods outside the area and decreased health services), and influenza epidemics. Specifically, low temperatures were controlled for by adding to the model one penalised cubic spline for values of 1–6 days lag air temperature below the median value of each city, as determined over the entire study period distribution, so as to allow a potential nonlinear relationship between low temperature and health effects; similarly, high temperatures were controlled for by adding a penalised cubic spline for values of 0–1 days lag 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 0–6-day lag apparent temperature above the median value of each city. Long-term trend and seasonality were controlled for by including a triple interaction of year, month and day of the week in regression models. The mortality analysis methods used have been fully described in a previous article about the effects of ozone [17].

Results are expressed as percentage increases in mortality (and 95% confidence intervals) relative to 10-$\mu g \cdot m^{-3}$ increases in PM10.

In order to explore the lag interval of the PM10 effect on respiratory mortality, we fitted single-lag models and cubic polynomial distributed-lag models [18, 19] for each city. 6-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 1 day

lag), ''delayed'' (2–5 days lag) and ''prolonged'' (0–5 days lag). 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 across cities in the pooled analysis for that lag interval.

In order to estimate the net effect of PM10 on respiratory mortality, the association was evaluated in bipollutant models, including NO_2 and O_3 in turn, at the same cumulative lag interval used to analyse the PM10 effect. The model including O_3 was restricted to the hot season.

The shape of the exposure–response curve between PM10 and respiratory mortality was estimated by using the metasmoothing approach [20]. The relationship was first explored at the city level with city-specific Poisson regression models in which the pollutant was added nonparametrically. The predicted values of the relative risk log of daily death were then computed in each city for 5-$\mu g \cdot m^{-3}$ increments between 10 and 100 $\mu g \cdot m^{-3}$. 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 PM10–respiratory mortality association, using a 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 seasonal and long-term trend was obtained by design, whereas the other time-varying covariates were adjusted for by modelling with city-specific conditional logistic regression models [13].

The covariates tested as possible effect modifiers were age, sex, recent hospitalisations for selected diseases (as an indicator of acute health problems), and hospitalisations in the previous 2 yrs (as an indicator of chronic conditions). The PM10 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 PM10–respiratory mortality association, the stratum-specific estimates of the other variables were standardised by age (two groups: 35–84 and $\geqslant$85 yrs), 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 <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; SAS Institute, Cary, NC, USA), R (version 2.10.0; Institute for Statistics and Mathematics, WU Wien, Vienna, Austria) and STATA (version 10.0; StataCorp, College Station, TX, USA).

RESULTS

There were 19,629 respiratory deaths in the study population, which accounted for 7.1% of all deaths by natural causes (n=276,205). Table 1 shows the number of natural and respiratory deaths in the 10 cities for the entire period and during the cold (October to March) season. The respiratory/natural death ratio did not differ among the cities, with the exception of Taranto, whose percentage was 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 2 yrs, 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 PM10 ranged from 53.9 $\mu g \cdot m^{-3}$ in Turin to 30.3 $\mu g \cdot m^{-3}$ in Cagliari. NO_2 showed a higher variability, with the lowest values in Taranto (26.3 $\mu g \cdot m^{-3}$) and the highest in Milan, Turin and Rome (59.2, 66.0 and 62.4 $\mu g \cdot m^{-3}$, respectively) (table 2). The apparent temperature shows a clear North–South gradient, with the lowest values in

TABLE 1 Study population in 10 Italian cities

	Study period	Age yrs		
		⩾35	⩾65	⩾85
Respiratory deaths				
Milan	2001–2005	4391 (8.5)	4174 (9.2)	2262 (12.2)
Mestre	2001–2005	421 (4.6)	392 (5.0)	168 (5.9)
Turin	2001–2005	2781 (7.6)	2622 (8.3)	1236 (10.4)
Bologna	2001–2005	1719 (8.5)	1656 (9.1)	852 (11.0)
Florence	2001–2005	1450 (8.6)	1402 (9.2)	746 (11.2)
Pisa	2001–2005	361 (8.1)	348 (8.6)	180 (10.9)
Rome	2001–2005	6077 (5.9)	5724 (6.4)	2521 (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	1404 (6.6)	1289 (7.1)	464 (7.4)
Total	2001–2005	19629 (7.1)	18574 (7.8)	8657 (9.6)
Natural deaths				
Total	2001–2005	276205	239624	90070
Cold season#				
Respiratory deaths				
Milan	2001–2005	2572 (9.2)	2446 (10.0)	1331 (13.1)
Mestre	2001–2005	263 (5.3)	247 (5.8)	110 (6.8)
Turin	2001–2005	1578 (8.1)	1499 (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	3467 (6.3)	3272 (6.9)	1475 (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	2001–2005	811 (7.0)	741 (7.5)	264 (7.6)
Total	2002–2005	11202 (7.6)	10615 (8.3)	4987 (10.2)
Natural deaths				
Total	2001–2005	129026	111439	41166

Data are presented as n (%) or n. Estimated percentages over natural-cause mortality are shown. MI: missing information. #: October to March.

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 0 days lag and remaining up to 2 days lag (fig. 1); a similar pattern was observed for natural mortality. Conversely, some instability between single-lag, constrained and unconstrained distributed-lag models emerged for the PM_{10} effect on respiratory mortality on the fifth and sixth days. The heterogeneity of the effects across the cities remained low up to the fourth day but increased significantly for longer latencies (table 3). Therefore, a cumulative lag interval of 0–3 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 $\mu g \cdot m^{-3}$ in PM_{10} was correlated with an increase of 2.29% in respiratory mortality, a greater effect than that for natural mortality (0.80%, 95% CI 0.41–1.19%) at lag 0–2 (table 3). The sensitivity analysis controlling for the 0–6 days lag apparent temperature above the median (instead of the 0–1 days lag) provided very similar results, being slightly higher for natural mortality and respiratory mortality overall; in the warm season, however, the effect on respiratory mortality decreased, although only 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 -0.60–4.0%) at 0–3 days lag (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-fold greater effect in the warm than in the cold season; it was only 3.7-fold greater for natural mortality (table 4). Since both higher PM_{10} concentration and influenza epidemics have winter peaks, a sensitivity analysis was carried out of the PM_{10}–respiratory mortality association without controlling for influenza epidemics. The respiratory mortality increased only slightly to a value of 2.39% (95% CI 1.13–3.66%). This result supports the idea that controlling for influenza cannot explain the seasonal differences observed in the effect of PM on respiratory mortality.

There was no evidence of a threshold in the exposure–response curve when the effect estimates for all of the cities were pooled and the relationship appeared to be linear (fig. 2). Neither NO_2 nor O_3 affected the impact of PM_{10} on respiratory mortality in bipollutant 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, sex, site of death, recent hospitalisations and chronic diseases, using 0–3 days lag. A suggestion of effect modification was present for females (increased risk of respiratory mortality 3.11%, 95% CI 1.15–5.11%) compared with males (1.22%, 95% CI -0.64–3.12%) (REM p=0.175) and for chronic disease sufferers (4.90%, 95% CI 1.09–8.87%). Notably high risks of dying from respiratory disease, although without evidence of effect modification, were found in subjects aged $\geq$85 yrs (3.24%, 95% CI 1.36–5.17%), subjects who died out of hospital

TABLE 2 Pollutant concentrations and meteorological parameters in 10 Italian cities

City	Study period	PM_{10} $\times 10$ $\mu g \cdot m^{-3}$	NO_2 $\times 10$ $\mu g \cdot m^{-3}$	O_3[#] $\mu g \cdot m^{-3}$	Correlation coefficient[¶]		PM_{10}/NO_2	Temperature °C	Relative humidity %	Barometric pressure hPa	Apparent temperature °C
					PM_{10}–NO_2	PM_{10}–O_3					
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	1016±7.4	13.8±10.5
Mestre	2001–2005	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	1016±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	1017±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	1016±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	1016±6.9	14.6±9.3
Pisa	2001–2005	34.2±15.1	29.8±11.3	99±21.3	0.57	0.20	1.23±0.62	15.1±7.1	75.3±12.6	1016±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	1015±6.6	15.7±8.8
Cagliari	2002–2005	30.3±11.0[f]	35.0±16.2[¶¶]	77.9±20.5	0.23[f]	-0.11[f]	1.13±0.84[f]	17.4±16.6	75.1±12.1	1016±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	1016±6.1	16.9±8.4
Palermo	2002–2005	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	1015±6.3	19.4±8.3

Data are presented as mean±SD, unless otherwise stated. Means of daily concentrations in the whole period after imputation of missing values are shown. PM_{10}: particular matter with a 50% cut-off aerodynamic diameter of 10 µm; NO_2: nitrogen dioxide; O_3: ozone. [#]: daily maximum 8-h running mean value during hot season (April to September); [¶]: Pearson correlation coefficient (correlation between PM_{10} and O_3 refers to hot season); [+]: for the study period January 1, 2002 to December 31, 2005; [§]: for the study period June 1, 2002 to December 31, 2005; [f]: for the study period January 1, 2003 to December 31, 2004; [##]: for the study period January 1, 2001 to December 31, 2004; [¶¶]: for the study period January 1, 2003 to December 31, 2005.

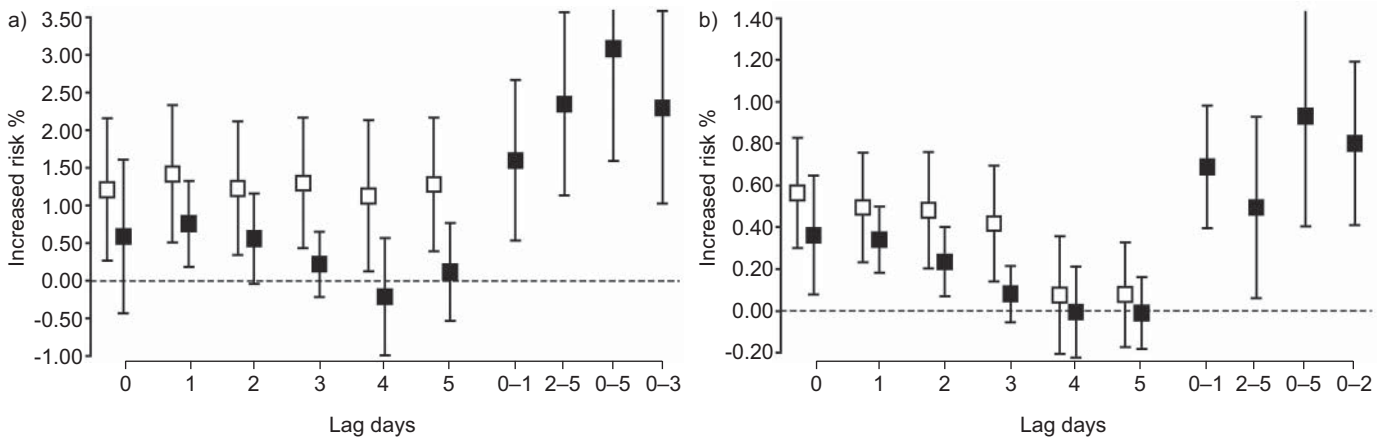

FIGURE 1. Pooled results. Association between particulate matter with a 50% cut-off aerodynamic diameter of 10 μm, and a) respiratory- and b) natural-cause mortality, by cause of death and lag (single-lag and distributed-lag models). Percentage increases of risk are shown with 95% confidence intervals, relative to a 10-μg·m^{-3} increase in the pollutant. Data shown are for 10 Italian cities in 2001–2005. □: single-lag models; ■: distributed-lag models.

(2.97%, 95% CI 0.52–5.47%), those who had been hospitalised between 29 days and 2 yrs prior to death (2.46%, 95% CI 0.75–4.19%), those who were not hospitalised during their last 28 days (2.62%, 95% CI 0.69–4.59%) and those with a chronic pulmonary disease (2.90%, 95% CI 0.26–5.61%).

DISCUSSION

We found a greater effect of PM10 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, which was not heterogeneous across cities, was observed for the cumulative 4-day exposure (lag 0–3 days). The effect of PM10 was not influenced by a contemporaneous increase of NO_2 or O_3 concentration. The effect increased linearly with the PM10 concentration without a threshold. Females and subjects with a previously diagnosed chronic condition were likely to be more susceptible to the effect of PM10.

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 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 CV 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].

TABLE 3 Pooled results: association between particulate matter with a 50% cut-off aerodynamic diameter of 10 μm[#], and natural or respiratory mortality by specific cause of death at different lags in 10 Italian cities

Cause of death	Subjects n	Lag[¶] days	Increased risk % (95% CI)	p-value[+]
Natural	276205	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
Respiratory	19629	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
COPD	9753	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
LRTI[§]	5513	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

Data shown are for the study period 2001–2005. COPD: chronic obstructive pulmonary disease; LRTI: lower respiratory tract infection. [#]: measured as 10-μg·m^{-3} increase in concentration; [¶]: cumulative lags represented immediate (0–1 days), delayed (2–5 days) and prolonged (0–5 days) effects; [+]: heterogeneity test (null hypothesis is perfect homogeneity of city-specific results); [§]: including acute bronchitis and pneumonia.

TABLE 4 Pooled results: association between particulate matter with a 50% cut-off aerodynamic diameter of 10 μm[#], and natural or respiratory mortality by season in 10 Italian cities

Cause of death	Cold season[¶]			Hot season[+]		
	Lag days	Increased risk % (95% CI)	p-value[§]	Lag days	Increased risk % (95% CI)	p-value[§]
All	0–2	0.56 (0.12–1.01)	0.061	0–2	2.05 (1.27–2.85)	0.089
Respiratory	0–3	1.22 (-0.18–2.65)	0.596	0–3	7.57 (2.25–13.17)	0.007

Data shown are for the study period 2001–2005. [#]: measured as 10-μg·m^{-3} increase in concentration; [¶]: October to March; [+]: April to September; [§]: heterogeneity test (null hypothesis is perfect homogeneity of city-specific results).

Finally, five of the most recent studies found a PM effect on respiratory mortality that was twice that on natural or CV mortality, in Europe (Dublin, Ireland) [33], in the USA [4, 10, 34] and in South-East Asia (Shanghai, China) [35]. Our results for effect size are thus a confirmation of previous evidence, apart from a study [36] that showed three-fold 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_{10} 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 characterised the effect of PM_{10} on respiratory mortality in the heat. Greater risks of dying as a result of PM in summer than in winter 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. Furthermore, we also considered the hypothesis of a seasonal misclassification of death by respiratory cause *versus* CV diseases. 15% of deaths classified as due to heart failure occurred in chronic respiratory disease 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 PM increase with death on the same day, a

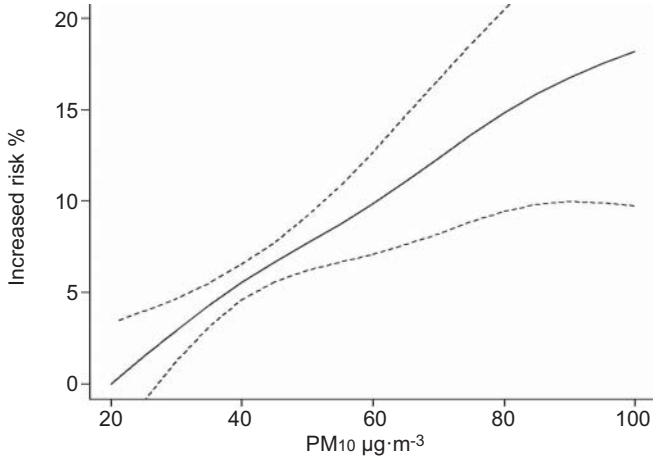

FIGURE 2. Pooled results: exposure–response relationship between particulate matter with a 50% cut-off aerodynamic diameter of 10 μm (PM_{10}) concentration and increased risk respiratory mortality in 10 Italian cities. Data shown are for 10 Italian cities in 2001–2005. —: exposure–response curve; ---: 95% CI.

TABLE 5 Pooled results: association between particulate matter with a 50% cut-off aerodynamic diameter of 10 μm[#], and natural or respiratory mortality[¶] from models adjusted for nitrogen dioxide (NO_2) and ozone (O_3) in 10 Italian cities

	Increased risk % (95% CI)	p-value[+]
Natural 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

Data shown are for the study period 2001–2005. [#]: measured as 10-μg·m^{-3} increase in concentration; [¶]: from unconstrained distributed lag models, using 0–2 days for natural-cause mortality and 0–3 days for respiratory-cause mortality; [+]: heterogeneity test (null hypothesis is perfect homogeneity of city-specific results); [§]: April to September.

TABLE 6 Pooled results: association between particulate matter with a 50% cut-off aerodynamic diameter of 10 μm (PM_{10})[#] and respiratory mortality by demographic characteristics, location of death and chronic conditions in nine Italian cities[¶]

Variable	Subjects[+] n (%)	Increased risk % (95% CI)	p-value	
			REM[§]	Heterogeneity[f]
All subjects	19166			
Age yrs				
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
Sex[##]				
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
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 last 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 yrs 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 ischaemic 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
Chronic conditions[##,¶¶] n				
0	9621 (50.2)	2.19 (0.31–4.11)		0.284
1	2749 (14.3)	4.90 (1.09–8.87)	0.216	0.813
2	2727 (14.2)	0.16 (-3.45–3.91)	0.340	0.783
⩾3	4069 (21.2)	2.30 (-0.65–5.35)	0.951	0.337

Data shown are for the study period 2001–2005. REM: relative effect modification; ICD-9: International Classification of Diseases, 9th revision. [#]: association was assessed at lag 0–3 days, and exposure was measured as an increase of 10 $\mu g \cdot m^{-3}$ in PM_{10}; [¶]: all cities except Cagliari; [+]: the 463 patients from Cagliari are not included here; [§]: 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); [f]: heterogeneity test (null hypothesis is perfect homogeneity of city-specific results); [##]: data standardised by age, with weights equal to relative frequencies of subjects in the age groups 35–84 and ⩾85 yrs from the nine cities analysed; [¶¶]: based on primary or secondary diagnoses from any hospital admission that occurred between 29 days and 2 yrs before death.

couple of days thereafter and up to a week later. Three of these studies adopted a 0–6-day lag interval [9, 25, 26], but the most frequently adopted interval was the cumulative lag of 0–1 days, 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 of 0–1 days 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 3-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-day 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.

Here, we have not 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 displacement of respiratory mortality (known as harvesting) in the second week [33], while the other attributed this apparent phenomenon to the degrees of freedom used in the distributed-lag model [28].

We found that the PM_{10} effect on respiratory mortality was not influenced by the contemporaneous presence of either NO_2 or summer O_3 at the same 0–3 days lag. Results inconsistent with ours were reported in the only earlier study to perform this analysis: in the Netherlands, HOEK and BRÜNEKREEF [26] found an important reduction of the PM effect when NO_2 was added to the model.

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 more than twice as susceptible to particulate matter than males, even after adjusting for age. The relevant results in earlier studies have been inconsistent. Two articles reported higher risks in females, but only in selected groups, such as black females and elderly 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 3 days after a peak level of PM_{10} [38]. Only one study [10] found a higher risk of respiratory mortality in males, although females presented a higher risk of total mortality. Further studies will doubtless address the topic of sex-related 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 females. 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 sex-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 subjects aged $\geqslant$85 yrs than in younger subjects. Our results confirm those found in the literature: FISCHER *et al.* [9] reported an increased risk of dying of COPD or pneumonia only for selected groups of elderly subjects and FRANKLIN *et al.* [10] found a higher risk of dying of respiratory disease in subjects aged $\geqslant$75 yrs 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 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 [4]. We found that people who had a chronic disease, but were not hospitalised in their last month of life, 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 carried out previously in the same Italian cities as the present study identified recent episodes of heart failure and pulmonary circulation impairment as conditions of susceptibility for all natural deaths [23]. The lower number of respiratory deaths we studied here could justify the negative results in identifying specific diseases that can modify the PM_{10} effect. Alternative explanations are possible for the negative results in patients with two or more chronic 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 of life. 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]. However, 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 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 by 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

We are able to draw the following conclusions from the present study. 1) Respiratory mortality was more affected by PM_{10} than was natural mortality and the PM_{10} effect was slightly longer lasting for respiratory mortality. 2) Females and chronic disease sufferers were likely to be susceptible to the PM_{10} effect. 3) Specific problems affect respiratory patients in summer, but the summertime PM_{10} effect was heterogeneous across the cities; studying the composition of PM_{10} could help to explain both the inter-city differences and the increased effect of PM_{10} during the summer. 4) The real effect of PM_{10} 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.

SUPPORT STATEMENT

The analysis of the susceptibility factors for respiratory mortality was funded by the Italian Ministry of Health under the Strategic Programme funded by Ministry of Labour, Health and Welfare, titled ''NHI: health impact associated with residing in polluted areas, near dumps/incinerators or in urban areas with high level of air pollution. Agreement no. 41''. Data collection and analysis of the effects of air pollution on respiratory mortality was funded by the Italian Ministry of Health, Centro Nazionale per la Prevenzione ed il Controllo delle

Malattie under the project title ''Air pollution and Health: Epidemiologic Surveillance and Preventing Measures, EPIAIR''.

STATEMENT OF INTEREST

None declared.

ACKNOWLEDGEMENTS

The members of the EpiAir Collaborative Group are as follows. Milan, Italy: L. Bisanti, G. Randi and M. Rognoni (all Epidemiology Unit, Local Health Authority, Milan). Mestre-Venice, Italy: L. Simonato and R. Tessari (both Environmental and Public Health Dept, University of Padua, Padua, Italy). Turin, Italy: G. Berti, E. Cadum and M. Chiusolo (all Epidemiology Service, Regional Environmental Protection Agency of Piedmont, Turin), C. Galassi (Giovanni Battista Hospital and Centre for Cancer Prevention, Turin), and M. Grosa, C. Ivaldi, R. Pelosini and S. Poncino (all Regional Environmental Protection Agency of Piedmont). Bologna, Italy: N. Caranci (Epidemiology Unit, Local Health Authority, Bologna), R. Miglio (Statistical Dept, University of Bologna, Bologna), G. Pace, B. Pacelli, P. Pandolfi and C. Scarnato (Epidemiology Unit, Local Health Authority, Bologna), and G. Zanini (Italian National Agency for New Technologies, Energy and Sustainable Economic Development, Bologna). Florence, Italy: G. Accetta (Institute for Cancer Study and Prevention, Florence), M. Baccini (Dept of Medical Statistics, University of Florence, Florence), A. Barchielli (Epidemiology Dept, Local Health Authority, Florence), A. Biggeri (Dept of Medical Statistics, University of Florence), E. Chellini (Institute for Cancer Study and Prevention), D. Grechi (Regional Environmental Protection Agency of Tuscany, Florence), S. Mallone (Institute for Cancer Study and Prevention) and D. Nuvolone (epidemiology observer; Regional Health Agency of Tuscany). Pisa, Italy: S. Baldacci and G. Viegi (both Epidemiology Unit, National Research Council of Italy, Pisa), and M.A. Vigotti (Biology Dept, University of Pisa, Pisa). Rome, Italy: P. Colais, A. Faustini, F. Forastiere, C.A. Perucci and M. Stafoggia (all Epidemiology Dept, Regional Health Service of Lazio, Rome). Taranto, Italy: S. Minerba (Epidemiology Dept, Local Health Authority, Taranto), M. Serinelli (Regional Environmental Protection Agency of Puglia, Bari, Italy) and M.A. Vigotti. Cagliari, Italy: P. Dessì (Local Health Authority, Cagliari). Palermo, Italy: A. Cernigliaro and S. Scondotto (both epidemiology observers; Regional Health Agency of Sicily, Palermo).

We thank K. Christenfeld (freelance medical editor; Rome) for revising the English and S. Pennisi (Dept of Epidemiology, Regional Health System of Lazio) for her help with the figures.

REFERENCES

1 Pope CA 3rd, Dockery DW. Health effects of fine particulate air pollution: lines that connect. *J Air Waste Manag Assoc* 2006; 56: 709–742.
2 Delfino RJ, Sioutas C, Malik S. Potential role of ultrafine particles in associations between airborne particle mass and cardiovascular health. *Environ Health Perspect* 2005; 113: 934–946.
3 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.
4 Zeka A, Zanobetti A, Schwartz J. Individual-level modifiers of the effects of particulate matter on daily mortality. *Am J Epidemiol* 2006; 163: 849–859.
5 Samoli E, Analitis A, Touloumi G, *et al.* Estimating the exposure–response relationships between particulate matter and mortality within the APHEA multicity project. *Environ Health Perspect* 2005; 113: 88–95.
6 Schwartz J, Coull B, Laden F, *et al.* The effect of dose and timing of dose on the association between airborne particles and survival. *Environ Health Perspect* 2008; 116: 64–69.
7 Qian Z, He Q, Lin HM, *et al.* Association of daily cause-specific mortality with ambient particle air pollution in Wuhan, China. *Environ Res* 2007; 105: 380–389.
8 Pope CA 3rd, Burnett RT, Krewski D, *et al.* Cardiovascular mortality and exposure to airborne fine particulate matter and cigarette smoke: shape of the exposure–response relationship. *Circulation* 2009; 120: 941–948.
9 Fischer P, Hoek G, Brunekreef B, *et al.* Air pollution and mortality in the Netherlands: are the elderly more at risk? *Eur Respir J* 2003; 21: Suppl. 40, 34s–38s.
10 Franklin M, Zeka A, Schwartz J. Association between $PM_{2.5}$ and all-cause and specific-cause mortality in 27 US communities. *J Exp Sci Environ Epidemiol* 2007; 17: 279–287.
11 Kan H, London SJ, Chen G, *et al.* Season, sex, age, and education as modifiers of the effects of outdoor air pollution on daily mortality in Shanghai, China: the public health and air pollution in Asia (PAPA) study. *Environ Health Perspect* 2008; 116: 1183–1188.
12 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.
13 Zanobetti A, Schwartz J. Air pollution and emergency admissions in Boston, MA. *J Epidemiol Community Health* 2006; 60: 890–895.
14 Atkinson RW, Anderson HR, Sunyer J, *et al.* Acute effects of particulate air pollution on respiratory admissions: results from APHEA 2 project. Air pollution and health: a European approach. *Am J Respir Crit Care Med* 2001; 164: 1860–1866.
15 Biggeri A, Bellini P, Terracini B. [Meta-analysis of the Italian studies on short-term effects of air pollution – MISA 1996–2002.] *Epidemiol Prev* 2004; 28: 4–5 Suppl., 4–100.
16 Steadman RG. The assessment of sultriness. Part I: a temperature-humidity index based on human physiology and clothing science. *J Applied Meteorol* 1979; 18: 861–873.
17 Stafoggia M, Forastiere F, Faustini A, *et al.* Susceptibility factors to ozone-related mortality – a population-based case-crossover analysis. *Am J Respir Crit Care Med* 2010; 182: 376–384.
18 Schwartz J. The distributed lag between air pollution and daily deaths. *Epidemiology* 2000; 11: 320–326.
19 Zanobetti A, Wand MP, Schwartz J, *et al.* Generalized additive distributed lag models: quantifying mortality displacement. *Biostatistics* 2000; 1: 279–292.
20 Schwartz J, Zanobetti A. Using meta-smoothing to estimate dose-response trends across multiple studies, with application to air pollution and daily death. *Epidemiology* 2000; 11: 666–672.
21 Levy D, Lumley T, Sheppard L, *et al.* Referent selection in case-crossover analyses of acute health effects of air pollution. *Epidemiology* 2001; 12: 186–192.
22 Stafoggia M, Forastiere F, Agostini D, *et al.* Vulnerability to heat-related mortality: a multicity, population-based, case-crossover analysis. *Epidemiology* 2006; 17: 315–323.
23 Forastiere F, Stafoggia M, Berti G, *et al.* Particulate matter and daily mortality: a case-crossover analysis of individual effect modifiers. *Epidemiology* 2008; 19: 571–580.
24 Ito K, Thurston GD. Daily PM_{10}/mortality association: an investigation of at-risk subpopulations. *J Expo Anal Environ Epidemiol* 1996; 6: 79–95.
25 Sunyer J, Schwartz J, Toblas A, *et al.* 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.
26 Hoek G, Brünekreef B. Daily mortality and air pollution in the Netherlands. *J Air Waste Manage Assoc* 2000; 50: 1380–1389.
27 Omori T, Fujimoto G, Yoshimura I, *et al.* Effects of particulate matter on daily mortality in 13 Japanese cities. *J Epidemiol* 2003; 13: 314–322.
28 Zanobetti A, Schwartz J, Samoli E, *et al.* The temporal pattern and heart disease mortality in response to air pollution. *Environ health perspect* 2003; 111: 1188–1193.

29 Wong C-M, Vichit-Vadakan N, Kan H, *et al.* Public health and air pollution in Asia (PAPA): a multicity study of short-term effects of air pollution on mortality. *Environ health perspect* 2008; 116: 1195–1202.

30 Anderson HR, Bremner SA, Atkinson RW, *et al.* Particulate matter and daily mortality and hospital admissions in the West Midlands conurbation of the United Kingdom: associations with fine and coarse particles, black smoke and sulphate. *Occup Environ Med* 2001; 58: 504–510.

31 Le Tertre A, Quénel P, Eilstein D, *et al.* Short-term effects of air pollution on mortality in nine French cities: a quantitative summary. *Arch environ health* 2002; 57: 311–319.

32 Analitis A, Katsouyanni K, Dimakopoulou K, *et al.* Short-term effects of ambient particles on cardiovascular and respiratory mortality. *Epidemiology* 2006; 17: 230–233.

33 Goodman PG, Dockery DW, Clancy L. Cause-specific mortality and the extended effects of particulate pollution and temperature exposure. *Environ Health Perspect* 2004; 112: 179–185.

34 Zanobetti A, Schwartz J. The effect of fine and coarse particulate air pollution on mortality: a national analysis. *Environ Health Perspect* 2009; 117: 898–903.

35 Kan H, London SJ, Chen G, *et al.* Differentiating the effects of fine and coarse particles on daily mortality in Shanghai, China. *Environ Int* 2007; 33: 376–384.

36 Ostro B, Feng WY, Broadwin R, *et al.* The effects of components of fine particulate air pollution on mortality in California: results from CALFINE. *Environ Health Perspect* 2007; 115: 13–19.

37 Stafoggia M, Schwartz J, Forastiere F, *et al.* Does temperature modify the association between air pollution and mortality? A multicity case-crossover analysis in Italy. *Am J Epidemiol* 2008; 167: 1476–1485.

38 Luginaah IN, Fung KY, Gorey KM, *et al.* Association of ambient air pollution with respiratory hospitalisation in a government-designated ''area of concern'': the case of Windsor, Ontario. *Environ Health Perspect* 2005; 113: 290–296.

39 Clougherty JE. A growing role for gender analysis in air pollution epidemiology. *Environ Health Perspect* 2010; 118: 167–176.