Associations between Fine and Coarse Particles and Mortality in Mediterranean Cities: Results from the MED-PARTICLES Project

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BACKGROUND: Few studies have investigated the independent health effects of different size fractions of particulate matter (PM) in multiple locations, especially in Europe.

OBJECTIVES: We estimated the short-term effects of PM with aerodynamic diameter ≤10 μm (PM_{10}), ≤2.5 μm (PM_{2.5}), and between 2.5 and 10 μm (PM_{2.5–10}) on all-cause, cardiovascular, and respiratory mortality in 10 European Mediterranean metropolitan areas within the MED-PARTICLES project.

METHODS: We analyzed data from each city using Poisson regression models, and combined city-specific estimates to derive overall effect estimates. We evaluated the sensitivity of our estimates to co-pollutant exposures and city-specific model choice, and investigated effect modification by age, sex, and season. We applied distributed lag and threshold models to investigate temporal patterns of associations.

RESULTS: A 10-μg/m^3 increase in PM_{2.5} was associated with a 0.55% (95% CI: 0.27, 0.84%) increase in all-cause mortality (0–1 day cumulative lag), and a 1.91% increase (95% CI: 0.71, 3.12%) in respiratory mortality (0–5 day lag). In general, associations were stronger for cardiovascular and respiratory mortality than all-cause mortality, during warm versus cold months, and among those ≥75 versus <75 years of age. Associations with PM_{2.5–10} were positive but not statistically significant in most analyses, whereas associations with PM_{10} seemed to be driven by PM_{2.5}.

CONCLUSIONS: We found evidence of adverse effects of PM_{2.5} on mortality outcomes in the European Mediterranean region. Associations with PM_{2.5–10} were positive but smaller in magnitude. Associations were stronger for respiratory mortality when cumulative exposures were lagged over 0–5 days, and were modified by season and age.

KEY WORDS: coarse particles, fine particles, Mediterranean, mortality, particulate matter, time series.


Introduction

A large number of epidemiological studies have reported evidence of adverse health effects of airborne particulate matter (Katsouyanni et al. 2009; Pope and Dockery 2006), leading the scientific community to investigate in more detail the role of specific characteristics of particles. Recent studies have attributed previously reported associations with particulate matter with aerodynamic diameter ≤10 μm (PM_{10}) mainly to effects of smaller particles—those with diameter ≤2.5 μm (PM_{2.5}) (Klemm et al. 2000; Laden et al. 2000; Ostro et al. 2006; Zanobetti and Schwartz 2009; Zhou et al. 2011). Potential effects of coarse particles with diameter between 2.5 and 10 μm (PM_{2.5–10}) are still under investigation, although evidence of adverse effects is also accumulating (Brunekreef and Forssberg 2005; Meister et al. 2012; Perez et al. 2009). The great majority of previous studies have been conducted in the United States, including many multicity studies, whereas the few European studies that have been undertaken have been based on single cities (Atkinson et al. 2010; Jiménez et al. 2009; Ostro et al. 2011; Perez et al. 2009). Location-specific characteristics of such studies, such as the higher prevalence of diesel vehicles, particularly passenger cars, and the higher density of the population in European cities compared with North American ones, may result in different exposure patterns. Furthermore, most of the U.S. studies have been based not on daily PM measures, but on PM measures every 3 or 6 days, which could lead to misclassification and possibly an underestimation of the short-term effects of particles on health outcomes (Katsouyanni et al. 2009; Klemm et al. 2011). Data specific to Europe are also needed to inform the revision in air quality standards for Europe that has been announced.

In the framework of the LIFE+ MED-PARTICLES project, which aims to characterize particulate pollution and its health effects across the European Mediterranean countries, we have undertaken the first European multicity investigation of the short-term effects of PM_{2.5} and PM_{2.5–10} exposure on mortality outcomes. Here we report the results of our analysis of acute exposure to PM in 10 metropolitan areas in this region [see Supplemental Material, Figure S1 (http://dx.doi.org/10.1289/ehp.1206124)], including estimated effects by cause of death, and according to age group, sex, and season.
Data and Methods

Data. Data are from 12 cities (Marseille, France; Athens and Thessaloniki, Greece; Bologna, Milan, Modena, Parma, Reggio Emilia, Rome, and Turin, Italy; and Barcelona and Madrid, Spain). These cities represent 10 metropolitan areas in the European Mediterranean region, including the Italian Emilia Romagna (ER) region that comprises Modena, Reggio Emilia, and Parma, three small cities with similar air pollution levels, climate, and population density.

For each city, data were collected on daily counts of all-cause mortality (excluding deaths from external causes [International Classification of Diseases, 9th and 10th Revisions (ICD-9, ICD-10)]) (WHO 1999): ICD-9 codes 001–799, ICD-10 codes A00–R99) for all ages and according to sex and age < 75 or ≥ 75 years, in addition to daily counts of cardiovascular mortality (ICD-9 codes 390–459, ICD-10 codes I00–I99). Data from each city covered at least 3 consecutive years during 2001–2010.

Daily PM$_{2.5}$, PM$_{10}$, and gaseous pollutant data (sulfur dioxide (SO$_2$, 24 hr), nitrogen dioxide (NO$_2$, 24 hr), and ozone (O$_3$, 8 hr)) were provided by monitoring networks in each participating city. All measurements were made using the gravimetric method or an equivalent method (beta-attenuation), except for measurements made using the tapered element oscillating microbalance (TEOM) method in Marseille. Because the focus of the analysis was on fine (PM$_{2.5}$) and coarse (PM$_{2.5–10}$) particles, and because PM$_{2.5}$ was estimated as the difference between PM$_{10}$ and PM$_{2.5}$, the study period was selected based on the availability and completeness of PM$_{2.5}$ concentration data. These data were obtained from urban or suburban background sites or, when appropriate as a measure of the exposure of nearby population, from fixed monitors located near traffic. All measurement sites included in the study were required to have at least 75% complete information for the study period. To obtain city-specific exposure estimates, the monitor-specific concentrations were averaged, and missing values from the averaged series were imputed as the average of the values of the remaining stations for that day multiplied by a factor equal to the ratio of the annual mean for the missing station over the corresponding annual mean from the other stations (Katsouyanni et al. 2001). When data were missing from all relevant monitoring stations on a given day, measurements were classified as missing for that day. PM$_{10}$ measurements for all areas except Bologna and Turin were from the same fixed monitoring stations that provided PM$_{2.5}$ measurements, to maintain comparability and allow the calculation of monitor-specific time-series data for PM$_{2.5–10}$. On average, PM$_{2.5}$ and PM$_{2.5–10}$ data were missing on 4% of days during the study (ranging from 0% in Thessaloniki to 12% in Marseille), and PM$_{10}$ data were missing for 2% of study days (ranging from 0% in Thessaloniki to 5% in Bologna). Missing data were at random, as confirmed by local authorities and by data inspection because there were no patterns observed.

Time-series data on daily temperature (degrees Celsius, daily mean) were used to control for the potential confounding effects of weather. External information on influenza epidemics was also collected, if available from hospital admissions records.

Methods. We used a hierarchical modeling approach. First, we fit separate regression models for each city to allow location-specific control for seasonal effects, weather, and other potential confounders. We then used the results of the individual city analysis in a meta-analysis to derive overall estimates.

PM-mortality associations for each city were estimated using Poisson regression models allowing for overdispersion. The city-specific model is of the form:

$$\log E[Y_c^t] = \beta_0 + \beta_1 \times PM_{2.5}^t + \gamma \times (\text{time}^c,\text{df}) + \Sigma \alpha_i \times (x_i^c,\text{df}) + \chi_c$$ [1]

where $E[Y_c^t]$ is the expected value of the Poisson distributed variable $Y_c^t$ indicating the daily mortality count on day $t$ at city $c$ with variance $Var(Y_c^t) = \phi \times E[Y_c^t]$, $\phi$ represents the overdispersion parameter, $x_i^c$ is the value of the $x_i$ meteorological covariate on day $t$ in city $c$, and $PM_{2.5}^t$ is the particulate matter concentration on day $t$ in city $c$. The smooth functions $\phi$ capture the nonlinear relationship between the time-varying covariates, calendar time, and daily mortality using corresponding degrees of freedom (df). We used penalized regression splines as implemented by Wood (2000) in R, with natural cubic splines as basis functions. We chose $k = 50$ basis functions and eight effective degrees of freedom (edfs) per year of available data to control for seasonality and obtain conservative estimates of effect (Katsouyanni et al. 2009; Samoli et al. 2008). To control for weather, the time-series models included smooth terms for temperature on the day of death and the day before death in using a natural spline with 3 df (Katsouyanni et al. 2009). We also included dummy variables for the day of the week, holidays, and influenza epidemics, represented by the vector $X$ in Equation 1. In cities with no influenza data available, we included a dummy variable that was assigned the value of 1 when the 7-day moving average of respiratory mortality was greater than the 90th percentile of the city-specific distribution. Because this method of controlling for influenza was based

on the distribution of respiratory mortality, we adjusted for influenza dummy variable only when modeling all-cause and cardiovascular mortality in these cities (Samoli et al. 2006). Finally, we controlled for the decrease in populations during the summer vacation period (typical of Mediterranean cities) using a three-level ordinal variable assigned a value of 2 during the 2-week period around mid-August, 1 from July 16 to August 31 (with the exception of the aforementioned 2-week period), and 0 (the reference category) on the remaining days (Stafoggia et al. 2010).

The pollutant was entered in the model using one of three cumulative lags chosen a priori to represent immediate effects (lag 0–1), delayed effects (lag 2–5), and weekly effects (lag 0–5). We also fitted a cubic polynomial distributed lag model over a period of 8 days to investigate the shape of each association (Zanobetti et al. 2002). Further analyses used the cumulative lag that produced the strongest effect estimates for each outcome based on the meta-analytic polynomial distributed lag shape and on the pooled estimates for each lag structure. This strategy was considered an appropriate compromise between a priori definitions and flexibility of lag choice for different exposure/outcome combinations (Stafoggia et al. 2010).

Further analyses of associations with each PM exposure were implemented using the chosen reference lag for each outcome. To evaluate how sensitive our results were to the choice of the degree of smoothing for seasonality control we also applied Poisson models using two alternative methods: a) using penalized splines with the degrees of smoothing for seasonality selected to minimize the absolute value of the sum of the partial autocorrelations of the residuals from lags one to 30 [PACF (partial autocorrelation function) criterion] with a minimum of 3 df per year (Katsouyanni et al. 2009), and b) using a case-crossover approach by modeling the time trend in the Poisson models with a three-way interaction between year, month, and day of death (Lu et al. 2008) that accounted for all possible combinations of year, month, and day of week, without additional adjustment for the day of the week. This is equivalent to the standard case-crossover design with a time-stratified strategy used to select control days on the same day of the week within the same month and year of the event day.

To investigate potential confounding by other pollutants, we used two-pollutant models of associations with PM$_{2.5}$ or PM$_{2.5–10}$ that were adjusted for NO$_2$ (24 hr), SO$_2$ (24 hr), O$_3$ (8 hr), or PM$_{2.5}$ or PM$_{2.5–10}$. We also investigated modification of associations between all-cause mortality and PM by age group (< 75 or ≥ 75 years of age) and sex in separate analyses.
We explored seasonal variation in associations by fitting separate Poisson regression models for cooler months (October–March) and warmer months (April–September) using 4 df/year to adjust for seasonality within each period.

Finally, we carried out threshold analyses to investigate exposure–response relationships between PM$_{2.5}$ or PM$_{2.5–10}$ and all-cause mortality (Samoli et al. 2008). We selected a grid of threshold values in increments of 5 μg/m$^3$ from 0 to 35 μg/m$^3$ for PM$_{2.5}$, and from 0 to 20 μg/m$^3$ for PM$_{2.5–10}$ (i.e., 0, 5, 10 …μg/m$^3$). For each threshold value $h$, we fit a threshold model to the data for the available cities that included the term $x_t - h$ if $x_t > h$ or 0 otherwise, where $x_t =$ PM$_t$ - $h$. PM is the PM concentration on day $t$, and $h$ is the threshold value. We then computed the deviance of the fitted model for all cities for a given threshold value, and the average deviance for that threshold over all cities. We repeated the analysis for all threshold values to identify a possible threshold that minimized the mean deviance.

In the second stage of the analysis, we assumed that city-specific effect estimates were normally distributed around an overall estimate. We derived pooled random-effects estimates with the random variance component estimated by iteratively reweighted least squares (Berkey et al. 1995). We used chi-square tests and the $P$ statistic (Higgins and Thompson 2002) to examine heterogeneity. There was a general agreement between the two measures concerning the amount of observed heterogeneity attributed to the between-cities variability.

All models were fit in R version 15.0 (R Development Core Team, Vienna, Austria). Results are presented as the estimated percent change in the outcome associated with a 10-μg/m$^3$ increase in PM, or an increase in PM equal to the median of the distribution of the city-specific interquartile ranges (IQR) for the exposure being assessed.

Statistical significance was considered at $\alpha < 0.05$.

Results

Table 1 presents descriptive characteristics by metropolitan area. Together, these areas comprise a population of >14 million people. The mean daily total number of deaths ranged from 11 (in Bologna) to 81 (in Athens). For respiratory mortality, daily deaths ranged from 1 (in Bologna and Emilia Romagna) to 10 (in Madrid). All 10 areas provided data for PM$_{2.5}$ with median levels ranging from 13.6 μg/m$^3$ (in Madrid) to 27.7 μg/m$^3$ (in Thessaloniki), whereas for eight areas with available colocated measurements, median PM$_{10}$ and PM$_{2.5–10}$ concentrations ranged from 25.0 μg/m$^3$ and 8.0 μg/m$^3$, respectively, in Marseille, compared with 44.4 μg/m$^3$ and 15.8 μg/m$^3$ in Thessaloniki. There was relatively small variability among cities in the levels of gaseous pollutants and in mean daily temperature.

The correlation between PM$_{2.5}$ and PM$_{2.5–10}$ ranged from 0.2 (in Barcelona and Marseille) to 0.7 (in Thessaloniki), and the correlation between PM$_{2.5}$ and NO$_2$ ranged from 0.3 (in Barcelona) to 0.8 (in Milan) [see Supplemental Material, Table S1 (http://dx.doi.org/10.1289/ehp.1206124)]. Correlations between PM$_{2.5}$ or PM$_{2.5–10}$ and SO$_2$ and O$_3$ were < 0.4 in all cities except Milan and Turin, where the correlations were around 0.6 in absolute value.

Figure 1 presents estimates from the distributed lag models for all-cause, cardiovascular, and respiratory mortality. In general, the strongest positive associations with respiratory and cardiovascular mortality were delayed compared with associations estimated for all-cause mortality, although associations with respiratory and cardiovascular mortality were highly variable depending on

### Table 1. Descriptive characteristics of the cities in MED-PARTICLES.

<table>
<thead>
<tr>
<th>City</th>
<th>Study period</th>
<th>Population × 1.000</th>
<th>All-cause</th>
<th>CVD</th>
<th>Median no. of deaths per day</th>
<th>PM$_{2.5}$ (μg/m$^3$)</th>
<th>Median (25th–75th percentile)</th>
<th>Mean temperature (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Athens</td>
<td>2007–2009</td>
<td>3,000</td>
<td>81</td>
<td>37</td>
<td>9</td>
<td>21.5 (16.5–27.5)</td>
<td>12.0 (8.0–18.5) 35.0 (26.5–45.5)</td>
<td>45.2 (35.6–56.2) 69.9 (47.1–90.7)</td>
</tr>
<tr>
<td>Barcelona</td>
<td>2003–2009</td>
<td>1,595</td>
<td>38</td>
<td>12</td>
<td>4</td>
<td>22.1 (17.0–29.8)</td>
<td>11.2 (6.6–18.0) 35.4 (26.2–47.0)</td>
<td>38.8 (27.5–50.5) 62.0 (36.1–79.8)</td>
</tr>
<tr>
<td>Bologna</td>
<td>2006–2010</td>
<td>372</td>
<td>11</td>
<td>4</td>
<td>1</td>
<td>20.0 (14.0–32.0)</td>
<td>—</td>
<td>32.0 (24.0–48.0) 49.6 (37.2–62.2)</td>
</tr>
<tr>
<td>Emilia Romagna</td>
<td>2008–2010</td>
<td>530</td>
<td>13</td>
<td>5</td>
<td>1</td>
<td>16.7 (11.7–27.0)</td>
<td>11.3 (8.0–15.7) 29.0 (21.0–34.3)</td>
<td>41.9 (30.6–54.1) 68.6 (27.1–104.9)</td>
</tr>
<tr>
<td>Madrid</td>
<td>2007–2009</td>
<td>3,133</td>
<td>60</td>
<td>18</td>
<td>10</td>
<td>13.6 (9.5–18.8)</td>
<td>14.2 (9.7–20.3) 28.5 (19.9–39.4)</td>
<td>53.0 (39.4–69.7) 46.1 (26.5–60.9)</td>
</tr>
<tr>
<td>Marseille</td>
<td>2001–2008</td>
<td>797</td>
<td>22</td>
<td>7</td>
<td>2</td>
<td>16.0 (11.0–22.0)</td>
<td>8.0 (6.0–12.0) 25.0 (19.0–33.0)</td>
<td>48.8 (37.7–60.5) 80.6 (56.0–103.4)</td>
</tr>
<tr>
<td>Milan</td>
<td>2006–2010</td>
<td>1,300</td>
<td>35</td>
<td>12</td>
<td>3</td>
<td>22.7 (14.0–45.7)</td>
<td>13.1 (7.4–19.3) 35.6 (23.5–60.1)</td>
<td>57.8 (43.5–72.9) 55.0 (18.7–92.2)</td>
</tr>
<tr>
<td>Rome</td>
<td>2006–2010</td>
<td>2,719</td>
<td>58</td>
<td>24</td>
<td>2</td>
<td>17.5 (12.9–24.0)</td>
<td>12.5 (8.5–16.7) 30.5 (23.1–39.5)</td>
<td>59.5 (46.1–70.8) 72.3 (40.4–95.5)</td>
</tr>
<tr>
<td>Thessaloniki</td>
<td>2007–2009</td>
<td>613</td>
<td>18</td>
<td>8</td>
<td>2</td>
<td>27.7 (22.0–34.7)</td>
<td>15.8 (11.3–18.1) 44.4 (35.5–56.5)</td>
<td>43.6 (22.2–56.5) 56.0 (38.9–72.2)</td>
</tr>
<tr>
<td>Turin</td>
<td>2006–2010</td>
<td>908</td>
<td>21</td>
<td>8</td>
<td>2</td>
<td>24.0 (14.0–48.0)</td>
<td>—</td>
<td>37.5 (24.8–65.8) 56.1 (41.3–74.0)</td>
</tr>
</tbody>
</table>

CVD, cardiovascular diseases.

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Results from second-stage random-effects models from city-specific polynomial distributed lag models (adjusted for seasonality, temperature, day of the week, holidays, influenza, and summer population decrease) for lags 0–7 presented as percent increase (95% CI) in all-cause (A), cardiovascular (B), and respiratory mortality (C) per 10-μg/m$^3$ increase in PM.
Effects of fine and coarse particles on mortality

Table 2 presents the estimated percent change in all-cause, cardiovascular, and respiratory mortality associated with a 10-μg/m³ increase in PM for cumulative lags of 0–1, 2–5, and 0–5 days. PM₂.₅ had statistically significant positive associations with all mortality outcomes for all lags except for respiratory mortality at lag 0–1, which was positive but not statistically significant. Associations between PM₂.₅ and respiratory and cardiovascular mortality were stronger than associations with all-cause mortality. In general, associations with PM₂.₅ increased for longer cumulative lag periods; for example, a 10-μg/m³ increase in PM₂.₅ on the day of death and the previous day was associated with a 0.55% increase (95% CI: 0.27, 0.84%) in all-cause mortality, whereas a 10-μg/m³ increase in PM₂.₅ 0–5 days before death was associated with a 0.70% increase (95% CI: 0.22, 1.18%).

Associations were positive but not statistically significant for PM₁₀ and all three mortality outcomes, except for associations between respiratory mortality and lag 0–1 exposure, and between all-cause mortality and lag 2–5 exposure, which were essentially null (Table 2). Whereas an association between PM₂.₅ and all-cause mortality was limited to immediate exposure (lag 0–1: 0.30%; 95% CI: −0.10, 0.69%), associations with cardiovascular mortality were similar for all three cumulative lag periods (e.g., lag 0–5: 0.33%; 95% CI: −0.78, 1.46%), and associations with respiratory mortality were limited to the longer cumulative exposure periods (e.g., lag 0–5: 0.76%; 95% CI: −0.70, 2.25%).

PM₁₀ was positively associated with all mortality outcomes, with a statistically significant association for all cause mortality for lag 0–1 (Table 2). For respiratory and cardiovascular mortality, associations were stronger and statistically significant for longer periods of cumulative exposure.

There was no statistically significant heterogeneity observed in the effects of particles on mortality outcomes between the Mediterranean cities (see Supplemental Material, Table S2 [http://dx.doi.org/10.1289/ehp.1206124]), except for the association between PM₁₀ and total mortality after longer periods of exposure.

Table 2. Percent increase (95% CI) in mortality outcomes associated with 10-μg/m² increase in PM for different cumulative lag structures.*

<table>
<thead>
<tr>
<th>Association under investigation</th>
<th>Lag 0–1</th>
<th>Lag 2–5</th>
<th>Lag 0–5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All-cause mortality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PM₂.₅</td>
<td>0.55 (0.27, 0.84)</td>
<td>0.51 (0.07, 0.96)</td>
<td>0.70 (0.22, 1.18)</td>
</tr>
<tr>
<td>PM₂.₅–10</td>
<td>0.30 (−0.10, 0.69)</td>
<td>−0.03 (−0.70, 0.64)</td>
<td>0.07 (−0.75, 0.90)</td>
</tr>
<tr>
<td>PM₁₀</td>
<td>0.32 (0.13, 0.52)</td>
<td>0.19 (−0.18, 0.56)</td>
<td>0.28 (−0.14, 0.71)</td>
</tr>
<tr>
<td><strong>Cardiovascular mortality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PM₂.₅</td>
<td>0.57 (0.07, 1.08)</td>
<td>0.77 (0.20, 1.34)</td>
<td>0.86 (0.15, 1.57)</td>
</tr>
<tr>
<td>PM₂.₅–10</td>
<td>0.29 (−0.37, 0.53)</td>
<td>0.33 (−0.59, 1.26)</td>
<td>0.33 (−0.78, 1.46)</td>
</tr>
<tr>
<td>PM₁₀</td>
<td>0.31 (−0.01, 0.62)</td>
<td>0.41 (0.04, 0.79)</td>
<td>0.54 (0.09, 0.99)</td>
</tr>
<tr>
<td><strong>Respiratory mortality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PM₂.₅</td>
<td>0.72 (−0.11, 1.55)</td>
<td>1.63 (0.62, 2.65)</td>
<td>1.91 (0.71, 3.12)</td>
</tr>
<tr>
<td>PM₂.₅–10</td>
<td>−0.13 (−1.25, 1.01)</td>
<td>0.72 (−0.31, 1.76)</td>
<td>0.76 (−0.70, 2.25)</td>
</tr>
<tr>
<td>PM₁₀</td>
<td>0.23 (−0.39, 0.81)</td>
<td>1.14 (0.28, 2.00)</td>
<td>1.12 (0.29, 1.95)</td>
</tr>
</tbody>
</table>

*Results from second-stage random-effects models pooling estimates from city-specific Poisson models adjusted for seasonality, temperature, day of the week, holidays, influenza, and summer population decrease. *Statistically significant heterogeneity as indicated by p < 0.10 from Cochran’s Q and I² > 50%.

Based on these findings, for all PM exposures, further analyses of all-cause mortality focused exposure on the same day and the previous day (lag 0–1), whereas cumulative exposure through the previous 5 days (lag 0–5) was used for respiratory and cardiovascular mortality. Increases in lag 0–1 exposure equal to the median of the city-specific interquartile ranges for PM₂.₅ (13 μg/m³) and PM₂.₅–10 (11 μg/m³) were associated with estimated increases in all-cause mortality of 0.72% (95% CI: 0.35, 1.09%) and 0.33% (95% CI: −0.10, 0.76%), respectively. The same cumulative increases in PM₂.₅ and PM₂.₅–10 over the same day and previous 5 days (lag 0–5) were associated with 1.11% (95% CI: 0.19, 2.04%) and 0.37% (95% CI: −0.86, 1.61%) increases in cardiovascular mortality, and 2.49% (95% CI: 0.92, 4.07%) and 0.84% (95% CI: −0.77, 2.48%) increases in respiratory mortality. When analyses were restricted to the eight areas that also provided PM₁₀ data (i.e., excluding Turin and Bologna) estimated increases associated with a 13-μg/m³ increase in exposure were 0.76% (95% CI: 0.31, 1.20%) for all-cause mortality (lag 0–1) and 1.50% (95% CI: 0.42, 2.58%) and 3.82% (95% CI: 1.77, 5.91%) for cardiovascular and respiratory mortality, respectively (lag 0–5).

Figure 2 presents city-specific and pooled effects estimated as the percent change in mortality outcomes associated with a 10-μg/m³ increase in PM₂.₅, PM₂.₅–10, and PM₁₀, respectively. Although the single city estimates are less precise and are often not statistically significant, associations with PM₂.₅ exposures were generally higher in larger metropolitan areas (see also Supplemental Material, Table S3 [http://dx.doi.org/10.1289/ehp.1206124]).

Estimates from two-pollutant models (Table 3) provided evidence of confounding for associations between PM₂.₅–10 and mortality. Associations with fine particles were less affected by adjustment for
other pollutants, although there was some indication of confounding by NO$_2$ and SO$_2$. When the three cities with correlations > 0.70 between PM$_{2.5}$ and NO$_2$ were excluded [Bologna, Milan, and Turin; see Supplemental Material, Table S1 (http://dx.doi.org/10.1289/ehp.1206124)], the NO$_2$-adjusted association between PM$_{2.5}$ and all-cause mortality increased (0.40% increase; 95% CI: –0.25, 1.06%, compared with 0.28%; 95% CI: –0.12, 0.68% when all cities were included, lag 0–1). Associations between PM$_{2.5}$ and mortality increased with adjustment for PM$_{2.5-10}$ (Table 3). As for PM$_{2.5}$ and PM$_{2.5-10}$, associations between PM$_{10}$ and mortality (data not shown) also decreased when adjusted for NO$_2$ or SO$_2$ (0.13%; 95% CI: –0.11, 0.37% and 0.10%; 95% CI: –0.22%, 0.43%, for total mortality respectively, compared with 0.32%; 95% CI: 0.13, 0.52% without adjustment).

Estimates from our primary analyses, which used penalized regression splines with 8 df/year to adjust for seasonal variation, were conservative relative to estimates from models that controlled for seasonality using the PACF criterion or a case-crossover analysis (Table 4), except for the estimated association between PM$_{10}$ and respiratory mortality under the case-crossover model. In addition, associations between PM$_{2.5-10}$ and all-cause mortality were statistically significant based on both alternative models, and were increased from the primary model estimates to a greater extent than the corresponding estimates for PM$_{2.5}$. All associations were substantially stronger for exposures during warm months (April–September) compared with colder months (October–March) (Table 4).

Table 3 presents associations with all-cause mortality according to age group (< 75 or ≥ 75 years) and sex. Associations between a 10-μg/m$^3$ increase in PM$_{2.5}$ and mortality appeared to be limited to the older age group (0.77%; 95% CI: 0.43, 1.10% compared with 0.02%; 95% CI: –0.51, 0.55% for those < 75, p = 0.02). In contrast, the opposite pattern was observed for PM$_{2.5-10}$ (0.10%; 95% CI: –0.47, 0.68% among those ≥ 75 years vs. 0.76%; 95% CI: 0.03, 1.49% for those < 75 years, p = 0.16). All associations were slightly stronger in males than in females, but differences were not statistically significant (p = 0.59–0.83).

Threshold models for all-cause mortality in association with a 10-μg/m$^3$ increase in PM$_{2.5}$ or PM$_{2.5-10}$ (lag 0–1) did not support the presence of a threshold because the best-fitting models (with the lowest deviance values) were those that did not assume a threshold [see Supplemental Material, Table S4 (http://dx.doi.org/10.1289/ehp.1206124)].

### Discussion

We investigated associations between mortality outcomes and fine and coarse particles in 10 European Mediterranean metropolitan areas participating in the MED-PARTICLES project. This is the first European multicity analysis to report on these associations using complete daily time-series data on PM$_{2.5}$ and PM$_{2.5-10}$.

PM$_{2.5}$ was statistically significantly associated with all-cause, cardiovascular, and respiratory mortality. Associations estimated for our study populations are slightly weaker but generally consistent with those previously reported for single-city studies in Europe and studies from the U.S. (Atkinson et al. 2010; Klemm et al. 2000; Laden et al. 2000; Ostro et al. 2006; Zanobetti and Schwartz 2009). Specifically, for a 10-μg/m$^3$ increase in PM$_{2.5}$ on the same day and the previous day (lag 0–1) we estimated a 0.55% increase in all-cause mortality and a 0.57% increase in cardiovascular mortality. For respiratory mortality, we estimated an increase of 1.91% in association with cumulative exposures over the same day and 5 previous days, suggesting...
Effects of fine and coarse particles on mortality

that the elderly are the most susceptible population subgroup. Finally, there was no statistically significant heterogeneity observed in our results due to the similar characteristics between the areas.

Associations between short-term PM$_{2.5}$ exposures (lag 0–1) and all-cause mortality appeared to be confounded by NO$_x$ and SO$_2$, although positive associations persisted when adjusted for other individual pollutants. Since both PM$_{2.5}$ and NO$_x$ are primarily traffic-derived pollutants (Querol et al. 2012) that are highly correlated, it is difficult to estimate their independent effects. In contrast with all-cause mortality, associations between PM$_{2.5}$ (lag 0–5) and respiratory mortality increased when adjusted for other pollutants, which may reflect delayed effects of PM$_{2.5}$ compared with effects of other pollutants on respiratory deaths. The associations between PM$_{2.5}$ and all three outcomes were stronger when adjusted for PM$_{2.5-10}$ but estimates from these models were unstable because of the high correlation between the two pollutants. Zanobetti and Schwartz (2009) reported no evidence of confounding between fine and coarse particles.

PM$_{2.5-10}$ exposures were positively, but not significantly, associated with all-mortality outcomes (for example, a 10-μg/m$^3$ increase at lag 0–1 was associated with a 0.30% increase in all-cause mortality). Stronger associations were estimated for some metropolitan areas (e.g., Rome) possibly reflecting less measurement error and better characterization of population exposure in these areas. Zanobetti and Schwartz (2009) reported statistically significant associations of a similar magnitude between PM$_{2.5-10}$ and total or cardiovascular mortality in 47 U.S. cities, but did not find an association in the analysis of the subset of cities characterized by a Mediterranean climate. However, in a multicity study in California, Malig and Ostro (2009) estimated statistically significant associations of PM$_{2.5-10}$ with all-cause and cardiovascular mortality. Regarding previously reported European results, there was no indication of an association in the United Kingdom (Atkinson et al. 2010; Brunekreef and Forberg 2005), but Perez et al. (2008) reported nonsignificant associations in Barcelona; Meister et al. (2012) reported a stronger and statistically significant association with all-cause mortality in Stockholm (1.68%); and Halonen et al. (2009) reported positive associations with respiratory mortality. When we applied alternative methods for seasonality control in the present analysis, we estimated slightly higher and statistically significant associations with all-cause and cardiovascular mortality. Nevertheless, after adjusting for PM$_{2.5}$ in the alternative models, the associations decreased and became nonsignificant (0.41% increase; 95% CI: –0.51, 1.35%) for all cause mortality using the PACF, and 0.18% increase; 95% CI: –0.65, 1.01% using the case-crossover approach), thus supporting the possibility that health effects of PM are driven mainly by effects of fine particles. As was the case with estimates of effect for fine particles, we found stronger associations between PM$_{2.5-10}$ and mortality during winter months, consistent with findings reported for the U.S. (Zanobetti and Schwartz 2009) but not Stockholm (Meister et al. 2012). Differences may be attributable partly to different sources of coarse particles, such as desert dust transported from the Sahara region to Mediterranean areas, which is more evident in spring and early autumn (Pey et al. 2013). An unexpected finding was the stronger association between PM$_{2.5-10}$ and mortality among those < 75 versus ≥ 75 years of age in the Mediterranean study populations, in contrast with stronger associations with PM$_{2.5}$ in the elderly. One possible explanation might be differences in time–activity patterns according to age and season, combined with greater penetration of fine particles into indoor environments compared with coarse particles. Hence, if the effect of both particle fractions is encountered mainly in the warm period (which is representative of the Mediterranean climate), younger people who spent more time outdoors may be more affected by coarse particles, and older people, who spend comparably more time indoors, may be more affected by fine ones. Still the absence of effect of fine particles among the younger age group requires further investigation.

The nonsignificant positive associations between PM$_{2.5-10}$ and mortality became essentially null when we controlled for other pollutants, which indicate that health effects of PM are a consequence of traffic-related pollution, because the coarse fraction of PM is dominated by dust. Alternatively, because within-city spatial variation is greater for PM$_{2.5-10}$ (due to traffic non-tailpipe emissions) than for PM$_{2.5}$ (Canepari et al. 2008), there is more exposure measurement error for PM$_{2.5-10}$ possibly biasing their effects.

Associations between PM$_{10}$ and mortality in the Mediterranean populations included in

Table 5. Percent increase (95% CI) in mortality associated with 10-μg/m$^3$ increase in particles: effect modification by age and sex of the associations between particles (lag 0–1) and all-cause mortality.*

<table>
<thead>
<tr>
<th>All-cause mortality</th>
<th>PM$_{2.5}$</th>
<th>$p$-Value for interaction</th>
<th>PM$_{2.5-10}$</th>
<th>$p$-Value for interaction</th>
<th>PM$_{10}$</th>
<th>$p$-Value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ages, both sexes</td>
<td>0.55 (0.27, 0.84)</td>
<td>0.02</td>
<td>0.30 (−0.10, 0.69)</td>
<td>0.16</td>
<td>0.31 (0.10, 0.52)</td>
<td>0.24</td>
</tr>
<tr>
<td>By age (years)</td>
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<td></td>
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<tr>
<td>≤ 75</td>
<td>0.02 (−0.51, 0.55)</td>
<td>0.76 (0.03, 1.49)</td>
<td>0.14 (−0.21, 0.50)</td>
<td>0.41 (0.17, 0.63)</td>
<td>0.83</td>
<td></td>
</tr>
<tr>
<td>≥ 75</td>
<td>0.77 (0.43, 1.10)</td>
<td>0.10 (−0.47, 0.68)</td>
<td>0.40 (0.17, 0.63)</td>
<td>0.83</td>
<td></td>
<td></td>
</tr>
<tr>
<td>By sex</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Male</td>
<td>0.51 (0.08, 0.94)</td>
<td>0.69 (−0.19, 1.59)</td>
<td>0.38 (0.09, 0.67)</td>
<td></td>
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</tr>
<tr>
<td>Female</td>
<td>0.44 (0.10, 0.79)</td>
<td>0.40 (−0.20, 1.00)</td>
<td>0.34 (0.06, 0.61)</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

*Results from second-stage random-effects models pooling estimates from city-specific subgroup analysis by the level of the corresponding effect modifier using single-pollutant Poisson models adjusted for seasonality, temperature, day of the week, holidays, influenza, and summer population decrease.
were stronger during warmer months, but associations with fine particles appeared to be limited to those ≥ 75 years of age, whereas associations with coarse particles were stronger among those < 75 years.

References


