



Which specific causes of death are associated with short term exposure to fine and coarse particles in Southern Europe? Results from the MED-PARTICLES project

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ABSTRACT

We investigated the short-term effects of particles with aerodynamic diameter less than 2.5 μm ($\text{PM}_{2.5}$), between 2.5 and 10 μm ($\text{PM}_{2.5-10}$) and less than 10 μm (PM_{10}) on deaths from diabetes, cardiac and cerebrovascular causes, lower respiratory tract infections (LRTI) and chronic obstructive pulmonary disease (COPD) in 10 European Mediterranean metropolitan areas participating in the MED-PARTICLES project during 2001–2010.

In the first stage of the analysis, data from each city were analyzed separately using Poisson regression models, whereas in the second stage, the city-specific air pollution estimates were combined to obtain overall estimates. We investigated the effects following immediate (lags 0–1), delayed (lags 2–5) and prolonged exposure (lags 0–5) and effect modification patterns by season. We evaluated the sensitivity of our results to co-pollutant exposures or city-specific model choice. We applied threshold models to investigate the pattern of selected associations.

For a 10 $\mu\text{g}/\text{m}^3$ increase in two days' $\text{PM}_{2.5}$ exposure there was a 1.23% (95% confidence interval (95% CI): –1.63%, 4.17%) increase in diabetes deaths, while six days' exposure statistically significantly increased cardiac deaths by 1.33% (95% CI: 0.27, 2.40%), COPD deaths by 2.53% (95% CI: –0.01%, 5.14%) and LRTI deaths by 1.37% (95% CI: –1.94%, 4.78%). $\text{PM}_{2.5}$ results were robust to co-pollutant adjustments and alternative modeling approaches. Stronger effects were observed in the warm season. Coarse particles displayed positive, even if not statistically significant, associations with mortality due to diabetes and cardiac causes that were more variable depending on exposure period, co-pollutant and seasonality adjustment.

Our findings provide support for positive associations between $\text{PM}_{2.5}$ and mortality due to diabetes, cardiac causes, COPD, and to a lesser degree to cerebrovascular causes, in the European Mediterranean region, which seem to drive the particles short-term health effects.

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1. Introduction

Adverse health effects of air pollution attributed mainly to airborne particulate matter have been well documented in the last couple of decades (Katsouyanni et al., 2009; Pope and Dockery, 2006; Rückerl et al., 2011). Recent epidemiological research is focused on the identification of the most harmful characteristics of particles, either physical or chemical (Atkinson et al., 2010; Zanobetti and Schwartz, 2009), as well as on the identification of sensitive population groups impacted by particle exposure (Bell et al., 2013; O'Neill et al., 2007). Along these lines most epidemiologic research suggests that short-term effects of particle matter in urban areas are driven by the fine fraction, while the contribution of the coarse fraction is still unclear (Brunekreef and Forsberg, 2005; Meister et al., 2012; Perez et al., 2009; Samoli et al., 2013). Sensitive population subgroups have also been indicated, such as people above 75 years of age (Bell et al., 2013; Katsouyanni et al., 2009) and people with pre-existing conditions such as diabetes (Goldberg et al., 2013; Hoffmann et al., 2012; O'Neill et al., 2007) and heart conditions (Chuang et al., 2008; Goldberg et al., 2013; Wheeler et al., 2006). The rationale for these investigations is driven by the general hypothesis that persons of failing health may be at greater risk for external insults through the failure of regulating physiological set points (Frank and Tankersley, 2002).

Estimates for the associations between particles and cause specific mortality are still sparse, especially from European data, where the corresponding results originate from single-city studies (Forastiere et al., 2005; Guaita et al., 2011; Maté et al., 2010). The LIFE + MED-PARTICLES project aims to characterize particulate pollution and its health effects across the European Mediterranean countries (Samoli et al., 2013). As part of this project, we have undertaken the first European multi-city analysis for the investigation of the short-term effects of $PM_{2.5}$ and $PM_{2.5-10}$ exposure on cause-specific mortality outcomes. According to MED-PARTICLES' protocol mortality outcomes for which there is prior hypothesis of an association were selected (WHO, 2013). Primary outcomes were defined as deaths from diabetes, cardiac and cerebrovascular causes, lower respiratory tract infections (LRTI) and chronic obstructive pulmonary disease (COPD). We subsequently investigated the associations with deaths due to acute coronary effects, arrhythmias and heart failure, as main categories of cardiac mortality.

2. Data and methods

2.1. Data

Initially, 12 cities provided data, namely (in country alphabetical order): Marseille (France), Athens and Thessaloniki (Greece), Bologna, Milan, Modena, Parma, Reggio Emilia, Rome and Turin (Italy), Barcelona and Madrid (Spain). Modena, Reggio Emilia and Parma, three cities in the Italian Emilia Romagna (ER) region were considered as one urban area, because of their small size, similar characteristics (in terms of air pollution levels and climate) and dense population. Hence, the results are reported for the resulting 10 metropolitan areas in the European Mediterranean region.

Data were collected on daily counts of deaths due to the underlying causes of: diabetes (International Classification of Diseases, ICD-9: 250, ICD-10: E10–E14), from cardiac diseases (ICD-9: 390–429, ICD10: I00–I52), cerebrovascular diseases (ICD-9: 430–437, ICD10: I60–I68), LRTI (ICD-9: 466, 480–487, ICD10: J09–J18, J20–J22) and COPD (ICD-9: 490–492, 494, 496, ICD10: J40–J44, J47). We additionally collected data for specific sub-categories of deaths due to cardiac causes, namely for those attributed to acute coronary events (ICD9:410–411, ICD10: I21–I23); including acute myocardial infarction (ICD9:410, ICD10:I21), arrhythmias (ICD9:427, ICD10:I46–I49) and heart failure (ICD9:428, ICD10:I50). Barcelona contributed data only in the analysis of deaths due to acute coronary events and cerebrovascular causes. The data

covered at least three consecutive years for each city within the time period 2001 to 2010. Due to the small counts of deaths under the specific diagnoses for respiratory deaths and sub-categories of cardiac deaths a decision was made not to analyze health outcomes in cities with zero counts on more than 75% of the days.

We collected data on $PM_{2.5}$ and PM_{10} , as well as gaseous pollutants (sulfur dioxide (SO_2), nitrogen dioxide (NO_2) and ozone (O_3)). Daily air pollution measurements were provided by the monitoring networks established in each city participating in the project, from urban or suburban background sites and fixed monitors located near traffic (only when they represented the exposure of the population living nearby) with at least 75% complete information for the study period. The focus of the analysis was the investigation of fine ($PM_{2.5}$) and coarse ($PM_{2.5-10}$) particle effects, hence the choice of the study period was based on the availability and completeness of $PM_{2.5}$ concentration data, since $PM_{2.5-10}$ is calculated as the difference between PM_{10} and $PM_{2.5}$. The monitor-specific concentrations were averaged and missing values were imputed by the average of the values of the remaining stations for that day multiplied by the ratio of the annual mean for the missing station over the corresponding annual mean from the other stations (Katsouyanni et al., 2001). For days with missing values in all relevant monitoring stations, the resulting series would also have a missing value on that date. For PM_{10} we used the same fixed monitoring sites that provided $PM_{2.5}$ measurements, to allow for the calculation of the monitor specific time series for the coarse particles ($PM_{2.5-10}$). Eight metropolitan areas (all except Bologna and Turin) provided PM_{10} measurements from the same sites that provided $PM_{2.5}$ measurements so we obtained the corresponding coarse particles' concentrations for these eight areas (Samoli et al., 2013).

Time series data on daily temperature ($^{\circ}C$, daily mean) were used to control for the potential confounding effects of weather. External information on influenza epidemics was also collected, if available.

2.2. Methods

We used a hierarchical modeling approach. First, we fit separate regression models for each city to allow 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 provide overall estimates. Details on the statistical protocol for the analysis have been previously published (Samoli et al., 2013). In short, the particles-mortality associations for each city were investigated using Poisson regression models allowing for overdispersion. We used penalized regression splines with eight effective degrees of freedom (df) per year of available data to control for seasonality. To control for weather, we included a natural spline with 3 degrees of freedom for temperature on the day of death and the day before death. We also included dummy variables for the day of the week effect, holidays, and influenza epidemics. In cities with no influenza data available we included a dummy variable taking the value of "1" when the seven-day moving average of the respiratory mortality was greater than the 90-th percentile of its city-specific distribution (Samoli et al., 2006). Finally, we controlled for the population decrease during the summer vacation periods typical of Mediterranean cities, using a three-level variable assuming value "2" in the 2-week period around mid-August, value "1" from July 16 to August 31 (with the exception of the aforementioned 2-week period), and value "0" (the reference category) on the remaining days (Stafoggia et al., 2010).

The pollutant was entered in the model using, in turn, three cumulative lags chosen a priori to represent immediate effects (lags 0–1), delayed effects (lags 2–5) and prolonged effects (lags 0–5). In accordance with previously published results on broad mortality outcomes (Samoli et al., 2013) we used as lag structure for the extended analysis: for deaths due to diabetes lags 0–1 and for those due to cardiac, cerebrovascular diseases, LRTI and COPD lags 0–5.

Further analyses of each association under investigation were implemented only for the chosen referent lag. Hence, 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: 1) penalized splines with the city-specific choice of final degrees of smoothing for seasonality based on the minimization of the absolute value of the sum of the partial autocorrelations of the residuals from lags one to 30 (PACF criterion), imposing a minimum of three degrees of freedom per year (Katsouyanni et al., 2009), and 2) 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). This is equivalent to the standard case-crossover design with time-stratified strategy for control days' selection, where the control days are selected as the same days of the week within the same month and year of the event day.

To investigate potential confounding effects of the daily levels of other pollutants, we applied two pollutant models, i.e. we included in the model fine or coarse particles and alternatively NO₂ (24 h), SO₂ (24 h) or O₃ (8 h), or coarse/fine particles correspondingly.

We explored the seasonal effects of particles on mortality by defining the winter period from October to March and the summer period from April to September. We performed stratified analyses by the two seasonal periods fitting separate Poisson regression models with 4 df per year for trend confounding control within season.

In the second-stage of the analysis, we assumed the city-specific effect estimates to be normally distributed around an overall estimate. We applied random-effects pooled estimates, where we estimated the random variance component by iteratively reweighted least squares (Berkey et al., 1995). We applied the Cochran's Q test and the I² 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.

Finally, in order to test the linearity of the association, we also carried out threshold analyses to investigate the exposure–response relationship between PM_{2.5} and PM_{2.5–10} and mortality due to cardiac causes (Samoli et al., 2013). We selected a grid of threshold values ranging from 0 to 35 µg/m³ for PM_{2.5} and from 0 to 20 µg/m³ for PM_{2.5–10} in increments of 5 µg/m³ (i.e., 0, 5, 10 ... µg/m³). For each threshold value, we fit a threshold model to the data for the available cities. We computed the deviance value of the fitted model in each city for a given threshold value, and then the average deviance for that threshold over all cities. We repeated the analysis for all threshold values. A possible threshold was set at the value that minimized the mean deviance.

All models were fit in R v.2.15.0 (R development Core Team (2011), ISBN 3-900051-07-0, URL <http://www.R-project.org>). Results in Tables and Figures are presented as percent change associated with 10 µg/m³ increase in particles' concentration and in the text the pooled effects are also presented per an increase equal to the median of the distribution of the city-specific interquartile ranges (IQR) of the corresponding pollutant.

3. Results

Table 1 presents descriptive characteristics for the city-specific data sets. Together, they comprise a population of more than 14 million people. The median daily number of deaths due to cardiac causes presented the greatest variability among the three main mortality diagnoses considered and ranged from three (in Bologna and Emilia Romagna region) to 25 (in Athens). There was a small number of daily deaths due to diabetes with the median equal to two in Rome, one in Athens and Madrid,

Table 1
Characteristics and distribution (number of events and median (25th–75th percentile)) of a) the main health outcomes and b) sub-categories of cardiac causes in MED-PARTICLES cities sorted in descending order according to the city's population size.

(A)												
City	Study period	Population × 1000	Diabetes		Cardiac causes		Cerebrovascular causes		LRTI ^a		COPD ^a	
			N	Median (25th–75th percentile)	N	Median (25th–75th percentile)	N	Median (25th–75th percentile)	N	Median (25th–75th percentile)	N	Median (25th–75th percentile)
Madrid	2007–09	3,133	855	1 (0–1)	13,831	12 (10–15)	4,271	4 (2–5)	3,043	3 (1–4)	2,200	2 (1–3)
Athens	2007–09	3,000	904	1 (0–1)	27,974	25 (21–29)	10,760	10 (7–12)	3 ^b	0 (0–0)	609	0 (0–1)
Rome	2006–10	2,719	3,513	2 (1–3)	31,681	17 (14–21)	9,059	5 (3–7)	965	0 (0–1)	4,374	2 (1–3)
Barcelona	2003–09	1,595	–	–	–	–	7,807	3 (2–4)	–	–	–	–
Milan	2006–10	1,300	1,253	0 (0–1)	15,127	8 (6–10)	5,180	3 (2–4)	2,035	1 (0–2)	2,283	1 (0–2)
Turin	2006–10	908	889	0 (0–1)	8,894	5 (3–6)	4,222	2 (1–3)	1,097	0 (0–1)	1,256	0 (0–1)
Marseille	2001–08	797	1,336	0 (0–1)	12,799	5 (3–6)	3,941	1 (1–2)	1,852	0 (0–1)	785 ^b	0 (0–0)
Thess/ki	2007–09	613	264	0 (0–0)	5,913	5 (4–7)	2,992	3 (1–4)	1 ^b	0 (0–0)	131 ^b	0 (0–0)
Emilia Romagna	2008–10	530	326	0 (0–1)	3,984	3 (2–5)	289	0 (0–0)	291 ^b	0 (0–0)	466	0 (0–1)
Bologna	2006–10	372	492	0 (0–0)	5,254	3 (2–4)	1,528	1 (0–1)	637	0 (0–1)	947	0 (0–1)
Deaths due to:												
City	Acute coronary events				Arrhythmias		Heart failure					
	N	Median (25th–75th percentile)		N	Median (25th–75th percentile)		N	Median (25th–75th percentile)				
(B)												
Madrid	3,528	3 (2–4)		649	0 (0–1)		3,783	3 (2–5)				
Athens	7,561	7 (5–8)		8,530	8 (5–10)		0 ^b	0 (0–0)				
Rome	7,405	4 (3–5)		1,706	1 (0–1)		1,862	1 (0–2)				
Barcelona	4,066	1 (1–2)		–	–		–	–				
Milan	3,355	2 (1–3)		1,271	0 (0–1)		420 ^b	0 (0–0)				
Turin	1,883	1 (0–2)		612	0 (0–1)		264 ^b	0 (0–0)				
Marseille	2,702	1 (0–2)		1,880	0 (0–1)		2,873	1 (0–2)				
Thessaloniki	1,660	1 (1–2)		2,028	2 (1–3)		0 ^b	0 (0–0)				
Emilia–Romagna	828	1 (0–1)		259 ^b	0 (0–0)		163 ^b	0 (0–0)				
Bologna	1,295	0 (0–1)		447 ^b	0 (0–0)		218 ^b	0 (0–0)				

^a LRTI: Lower Respiratory Tract Infections; COPD: Chronic Obstructive Pulmonary Disease.

^b Not included in the analysis due to low counts.

and zero in the remaining six metropolitan areas with available data. Small counts were also observed for deaths from LRTI and COPD (with median ranges from zero in most cities to three in Madrid). Subcategories of deaths due to cardiac causes were analyzed as sensitivity analyses. Deaths due to acute coronary events presented the larger variability, while those attributed to arrhythmias and heart failure ranged from zero in most cities to eight in Athens for the former and three in Madrid for the latter.

All ten areas provided data for PM_{2.5} with median levels ranging from 13.6 µg/m³ (in Madrid) to 27.7 µg/m³ (in Thessaloniki). For eight areas with available collocated measurements, the median for PM₁₀ and PM_{2.5–10} ranged from 25.0 µg/m³ and 8.0 µg/m³ correspondingly (in Marseille) to 44.4 µg/m³ and 15.8 µg/m³ (in Thessaloniki). There was small variability among cities in the levels of daily temperature (see Table 1 in the Supplemental material). The correlation between fine and coarse particles ranged from 0.2 (in Barcelona and Marseille) to 0.7 (in Thessaloniki) and between PM_{2.5} and NO₂ from 0.3 (in Barcelona) to 0.7 (in Milan). The correlation between fine or coarse particles with SO₂ and O₃ was in all cities lower than 0.4 except in Milan and Turin where the correlations were around 0.6 in absolute value (Samoli et al., 2013).

Table 2 presents the percent change in the mortality outcomes for a 10 µg/m³ increase in the particles metrics for the three cumulative lag structures. PM_{2.5} had an adverse association with all mortality outcomes considered, that was also statistically significant for deaths due to cardiac diseases per delayed (lags 2–5, 1.24% increase) and prolonged exposure (lags 0–5 with 1.33% increase). The highest effect estimate of fine particles, at borderline statistical significance (lags 0–5, 2.53% increase, *p* = 0.050), was observed for deaths due to COPD for cumulative exposure after six days. PM_{2.5–10} had a positive association, although not statistically significant, with diabetes and circulatory system mortality outcomes for all lag structures, except for prolonged exposure (lags 0–5) on deaths due to cerebrovascular causes, in which case the association was practically null. The associations between PM_{2.5–10} and respiratory outcomes did not present a consistent pattern since non-significant effect estimates were observed following acute exposure (lags 0–1) on LRTI related deaths but delayed exposure

(lags 2–5) for COPD related deaths. The highest effect estimate of coarse particles was observed on deaths due to diabetes after acute exposure (lags 0–1, 1.30% increase). The lowest effect estimates of all particles metrics were observed on deaths due to cerebrovascular causes. PM₁₀ displayed positive associations, although non-statistically significant, with all mortality outcomes, except following immediate exposure for deaths due to cerebrovascular causes or COPD where the association was null.

There was statistically significant heterogeneity in the effect estimates of particles on daily mortality due to diabetes under most exposure periods considered while there was no statistically significant heterogeneity in the other associations except for coarse particles and cardiac deaths after a weekly exposure (lags 0–5) and on LRTI related deaths after immediate exposure (lags 0–1). For the chosen lags (for deaths due to diabetes lags 0–1 and for those due to other causes lags 0–5) and for an increase equal to the median of the city-specific inter-quartile ranges in PM_{2.5} (13 µg/m³) and PM_{2.5–10} (11 µg/m³) the percent increase in deaths due to diabetes were 1.60% (95% confidence interval (CI): –2.12%, 5.46%) and 1.43% (95% CI: –7.75%, 11.53%) correspondingly; in deaths due to cardiac diseases 1.74% (95% CI: 0.35%, 3.14%) and 0.52% (95% CI: –1.64%, 2.73%), due to cerebrovascular diseases 1.01% (95% CI: –1.12%, 3.19%) and –0.04% (95% CI: –2.48%, 2.46%); for LRTI related deaths the corresponding effect estimates were 1.78% (95% CI: –2.51%, 6.26%) and –1.07% (95% CI: –7.17%, 5.43%) and for COPD related deaths 3.31% (95% CI: –0.01%, 6.73%) and 0.02% (95% CI: –5.39%, 5.73%). In the analysis of diabetes and circulatory system deaths, for which almost all cities were included, when we restricted the analysis of PM_{2.5} effects to the eight areas that also provided the coarse concentrations the effect estimates of fine particles became slightly higher. In particular, the corresponding increases were: 1.64% (95% CI: –4.92%, 8.65%) for deaths due to diabetes, 2.05% (95% CI: 0.59%, 3.54%) for those due to cardiac causes and 2.33% (95% CI: –0.65%, 5.39%) for cerebrovascular causes.

The results from the two pollutant models for the associations under investigation (see Table 3) provided evidence of confounding for fine and coarse particles effect estimates on all three outcomes by mainly SO₂ and to a lesser degree by NO₂ levels. Associations with fine particles

Table 2

Percent change (and 95% confidence intervals (CIs)) in mortality outcomes associated with 10 µg/m³ increase in corresponding particle metrics for different lag structures. Statistically significant results at the 5% level are indicated in bold.

Deaths due to:	Percent change (95% CI) per 10 µg/m ³		
	Lags 0–1	Lags 2–5	Lags 0–5
<i>Diabetes^a</i>			
PM _{2.5}	1.23 (–1.63, 4.17) ^b	1.78 (–0.69, 4.31)	2.02 (–1.51, 5.68)
PM _{2.5–10}	1.30 (–7.07, 10.43) ^b	0.07 (–4.24, 4.56) ^b	0.22 (–10.39, 12.08) ^b
PM ₁₀	0.15 (–2.06, 2.41) ^b	0.92 (–1.01, 2.90)	0.93 (–1.88, 3.82)
<i>Cardiac causes^a</i>			
PM _{2.5}	0.59 (–0.11, 1.30)	1.24 (0.39, 2.09)	1.33 (0.27, 2.40)
PM _{2.5–10}	0.33 (–0.51, 1.18)	0.13 (–0.89, 1.16)	0.48 (–1.49, 2.48) ^b
PM ₁₀	0.35 (–0.13, 0.83)	0.60 (0.11, 1.09)	0.79 (0.08, 1.50)
<i>Cerebrovascular causes^a</i>			
PM _{2.5}	0.32 (–0.64, 1.30)	1.05 (–0.20, 2.31)	0.78 (–0.86, 2.45)
PM _{2.5–10}	0.02 (–1.85, 1.93)	0.09 (–1.53, 1.73)	–0.04 (–2.26, 2.23)
PM ₁₀	–0.08 (–0.73, 0.57)	0.42 (–0.35, 1.19)	0.06 (–0.86, 0.99)
<i>LRTI^{a,c} (6 cities)</i>			
PM _{2.5}	0.31 (–2.08, 2.77)	0.68 (–1.64, 3.06)	1.37 (–1.94, 4.78)
PM _{2.5–10}	0.25 (–5.62, 6.49) ^b	–0.99 (–5.52, 3.77)	–0.97 (–6.54, 4.93)
PM ₁₀	0.14 (–1.37, 1.67)	0.66 (–0.95, 2.29)	0.80 (–1.10, 2.75)
<i>COPD^{a,c} (7 cities)</i>			
PM _{2.5}	1.02 (–0.79, 2.87)	2.53 (–0.33, 5.48)	2.53 (–0.01, 5.14)
PM _{2.5–10}	–1.00 (–4.23, 2.33)	0.88 (–3.17, 5.09)	0.01 (–4.91, 5.20)
PM ₁₀	–0.06 (–1.25, 1.16)	1.43 (–0.39, 3.29)	1.15 (–0.57, 2.90)

^a In cerebrovascular analysis; all areas included; Diabetes and Cardiac: all but Barcelona; LRTI: Bologna, Madrid, Marseille, Milan, Rome, Turin; COPD: all but Marseille and Thessaloniki.

^b Statistically significant heterogeneity as indicated by *p* < 0.10 from Cochran's Q and I² > 50%.

^c LRTI: Lower Respiratory Tract Infections; COPD: Chronic Obstructive Pulmonary Disease.

Table 3
Percent change (95% CIs) in selected mortality outcomes associated with 10 $\mu\text{g}/\text{m}^3$ increase in particle metrics for selected lags per association. Results from two-pollutant models. Statistically significant results at the 5% level are indicated in bold.

Controlling for	Deaths attributed to:				
	Diabetes (lags 0–1) ^a	Cardiac causes (lags 0–5) ^a	Cerebrovascular causes (lags 0–5) ^a	LRTI (lags 0–5) ^{a, c}	COPD (lags 0–5) ^{a, c}
No other pollutant	PM _{2.5} 1.23 (–1.63, 4.17) ^b	1.33 (0.27, 2.40)	0.78 (–0.86, 2.45)	1.37 (–1.94, 4.78)	2.53 (–0.01, 5.14)
SO ₂	–0.05 (–3.06, 3.06)	0.99 (–0.53, 2.52)	0.60 (–1.94, 3.20)	3.09 (–1.53, 7.92)	1.95 (–3.67, 7.91)
NO ₂	0.55 (–3.71, 5.00) ^b	1.03 (–0.20, 2.27)	0.84 (–1.33, 3.05)	0.31 (–4.50, 5.36)	1.67 (–1.55, 4.99)
O ₃	1.19 (–1.80, 4.27)	1.41 (0.30, 2.54)	0.98 (–0.90, 2.89)	1.76 (–1.69, 5.32)	2.60 (–0.09, 5.36)
PM _{2.5–10}	1.07 (–1.87, 4.10)	2.06 (0.84, 3.30)	1.51 (–0.64, 3.71)	4.03 (–3.50, 12.14) ^b	5.27 (1.37, 9.32)
No other pollutant	PM _{2.5–10} 1.30 (–7.07, 10.43) ^b	0.48 (–1.49, 2.48) ^b	–0.04 (–2.26, 2.23)	–0.97 (–6.54, 4.93)	0.01 (–4.91, 5.20)
SO ₂	0.00 (–4.72, 4.95)	0.09 (–1.44, 1.64)	–1.23 (–5.64, 3.39) ^b	–4.76 (–13.35, 4.68)	–3.97 (–10.83, 3.42)
NO ₂	1.23 (–7.55, 10.84) ^b	–0.22 (–1.63, 1.20)	0.01 (–2.89, 2.99)	–0.21 (–8.24, 8.52)	–2.24 (–7.86, 3.73)
O ₃	1.71 (–7.58, 11.93) ^b	0.57 (–1.62, 2.82) ^b	0.22 (–2.74, 3.27)	–0.11 (–6.76, 7.02)	–0.71 (–5.81, 4.66)
PM _{2.5}	1.68 (–3.22, 6.83)	–0.81 (–2.22, 0.62)	–0.48 (–2.72, 1.81)	–1.04 (–9.85, 8.63)	–4.05 (–9.63, 1.88)

^a In cerebrovascular analysis: all areas included; Diabetes and Cardiac: all but Barcelona; LRTI: Bologna, Madrid, Marseille, Milan, Rome, Turin; COPD: all but Marseille and Thessaloniki.

^b Statistically significant heterogeneity as indicated by $p < 0.10$ from Cochran's Q and $I^2 > 50\%$.

^c LRTI: Lower Respiratory Tract Infections; COPD: Chronic Obstructive Pulmonary Disease.

were less affected from possible confounding effects. Interestingly, their effect estimates on deaths from all analyzed causes except diabetes were increased after controlling for coarse particles and even reached statistical significance in the association with COPD related deaths (p -value = 0.007). In all cases, the effect estimates of PM_{2.5} remained positive except for deaths due to diabetes after controlling for SO₂ when the association was reduced to null.

We further investigated the association between particles' exposure and deaths due to acute coronary events, arrhythmias and heart failure, as presented in Table 4, in order to identify the driving causes of death behind the association identified with cardiac related mortality. We found positive associations of PM_{2.5} with deaths due to acute coronary events after delayed (lags 2–5) or prolonged exposure (lags 0–5), and deaths due to arrhythmias but there was no association with heart failure related deaths. The only statistical significant association was with acute coronary related deaths for delayed lags 2–5 exposure (1.97%, 95% CI: 0.49%, 3.48%). Nevertheless, the highest effect estimate of fine particles was observed on arrhythmia related deaths after prolonged exposure (lags 0–5, 2.39%, 95% CI: –0.39%, 5.24%). PM_{2.5–10} exposure was associated (not statistically significantly) with deaths due to acute coronary events for all periods considered and with those due to arrhythmias but only after immediate (lags 0–1) exposure. Following the patterns identified before, PM₁₀ exposure was associated, but not significantly with acute coronary events and arrhythmia related deaths.

We applied several sensitivity analyses with regard to the number of cities included in the pooled estimates in order to identify the degree to which these were driven by specific cities (see Table 2 in the Supplemental material). Hence we restricted analyses to the three cities (Madrid, Marseille and Rome) that contributed to all health outcomes (except to COPD for Marseille) and to the six cities that were common to most outcomes (excluding the two Greek cities, Barcelona and Emilia-Romagna). The results differed in magnitude from the main ones with no specific pattern, but the general conclusions indicating associations between fine particles and diabetes, cardiac and COPD deaths remained unaltered. The exclusion of the two Greek cities affected the associations with cerebrovascular and acute coronary deaths, since they contributed a large number of counts in these diagnoses.

Fig. 1 presents annual and seasonal pooled percent change in cause-specific deaths associated with 10 $\mu\text{g}/\text{m}^3$ increase in PM_{2.5}, PM_{2.5–10}, and PM₁₀, respectively, following immediate exposure (lags 0–1) for diabetes related deaths and prolonged exposure (lags 0–5) for the rest of the outcomes. Associations between PM_{2.5} and all cause-specific deaths (except for LRTI in the warm period) were positive irrespective of period. Substantially higher adverse health effect estimates were observed in the warm period as compared with the cold one, except for the association with LRTI that presented the opposite pattern. Nevertheless, due to the considerably lower number of respiratory events in the warm period, the estimates are less robust. The great majority of the city-specific

Table 4
Percent change (and 95% confidence intervals (CIs)) in mortality due to specific cardiac causes associated with 10 $\mu\text{g}/\text{m}^3$ increase in corresponding particle metrics for different lag structures.

Deaths due to:	Percent Increase (95% CI) per 10 $\mu\text{g}/\text{m}^3$		
	Lags 0–1	Lags 2–5	Lags 0–5
<i>Acute coronary events^a</i>			
PM _{2.5}	–0.29 (–1.50, 0.93)	1.97 (0.49, 3.48)	1.43 (–0.34, 3.24)
PM _{2.5–10}	0.56 (–1.05, 2.19)	0.52 (–1.41, 2.49)	1.07 (–1.35, 3.56)
PM ₁₀	0.06 (–0.75, 0.87)	0.87 (–0.09, 1.83)	0.96 (–0.19, 2.13)
<i>Arrhythmias^a</i>			
PM _{2.5}	1.74 (–0.57, 4.11)	1.69 (–0.59, 4.02)	2.39 (–0.39, 5.24)
PM _{2.5–10}	1.25 (–0.70, 3.24)	–0.21 (–2.70, 2.35)	0.10 (–2.87, 3.17)
PM ₁₀	1.07 (–0.33, 2.49)	0.56 (–0.76, 1.90)	1.20 (–0.42, 2.84)
<i>Heart failure^a</i>			
PM _{2.5}	–2.43 (–6.23, 1.51)	–2.67 (–8.38, 3.39)	–4.88 (–11.44, 2.17)
PM _{2.5–10}	–4.56 (–9.02, 0.11)	–3.12 (–11.78, 6.40)	–6.52 (–17.44, 5.84) ^b
PM ₁₀	–2.47 (–4.98, 0.10)	–2.01 (–5.90, 2.04)	–3.70 (–8.47, 1.32)

^a In Acute Coronary Events analysis: all areas included; Arrhythmias: all but Barcelona, Bologna and Emilia-Romagna; Heart Failure: Madrid, Marseille, Rome.

^b Statistically significant heterogeneity as indicated by $p < 0.10$ from Cochran's Q and $I^2 > 50\%$.

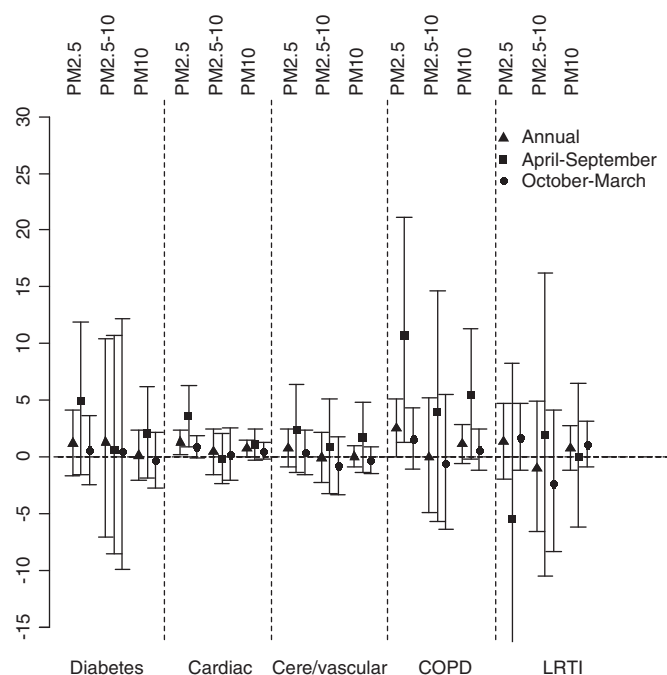


Fig. 1. Annual and seasonal pooled percent increase in cause specific mortality per $10 \mu\text{g}/\text{m}^3$ increase in particles metrics for the main lag structures per outcome, lags 0–1 for diabetes and lags 0–5 for the rest.

results followed the seasonal pattern displayed in the pooled results, whereas small cities like Marseille and Thessaloniki deviated from the general pattern. On the other hand, coarse particles' effects displayed less variability between periods as compared with fine particles' effects, but more cities displayed varying patterns, including bigger cities like Milan and Rome.

The results from alternative modeling approaches used to test the sensitivity of our estimates provided evidence that the latter were rather conservative estimates of the associations under investigation (results not shown). Sensitivity analysis on seasonality control using PACF criterion resulted in using df per year in all cases (due to the absence of seasonality in the analyzed deaths) and provided higher effect estimates for the associations under investigation (e.g. a $10 \mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ associated with 1.93% (95% CI: -0.64% , 4.57%) increase in diabetes deaths and 2.06% (95% CI: 1.06% , 3.07%) increase in cardiac ones). The case crossover analysis provided higher estimates to our main analyses results, except for deaths due to diabetes (1.05% (95% CI: -2.56% , 4.79%) for $10 \mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$). Both alternative models confirmed the statistically significant effect estimates of fine particles on cardiac and COPD related deaths.

Investigation of the exposure–response relationship between $\text{PM}_{2.5}$ or $\text{PM}_{2.5-10}$ and mortality due to cardiac causes in MED-PARTICLES did not support the presence of a threshold. Although the best fitting models were observed from the threshold model at $25 \mu\text{g}/\text{m}^3$ and $15 \mu\text{g}/\text{m}^3$, the difference with the linear model was not statistically significant ($p > 0.920$). Threshold analysis was not applied for other outcomes due to limited power issues.

4. Discussion

We have previously reported associations between exposure to particles and main mortality outcomes within the MED-PARTICLES project (Samoli et al., 2013). According to the recent WHO project “Review of evidence on health aspects of air pollution” (WHO, 2013) although data from main mortality causes tend to be more reliable than data from more rare causes of death, cause-

specific assessments are defensible and proposed in order to elucidate the application of epidemiological study results to the EU population since air pollution is not related to all causes of death. Under this perspective we undertook an analysis of cause-specific mortality in the 10 European Mediterranean areas participating in the MED-PARTICLES project. We found positive associations between $\text{PM}_{2.5}$, $\text{PM}_{2.5-10}$ and PM_{10} with deaths due to diabetes after immediate exposure and cardiac causes, LRTI and COPD after prolonged exposure. Fine particles' exposure was also associated with deaths due to cerebrovascular diseases. PM_{10} effect estimates seem to be reflecting the associations with fine particles.

$\text{PM}_{2.5}$ displayed positive associations with all three main mortality outcomes analyzed that reached the nominal level of statistical significance for cardiac deaths. $\text{PM}_{2.5}$ effect estimates were larger than the ones for $\text{PM}_{2.5-10}$ and seemed to drive the associations with PM_{10} . Compared with previous findings from the MED-PARTICLES project on the fine particles' effects on broad mortality outcomes (Samoli et al., 2013), the effect estimates on the cause-specific outcomes presented here are higher, since for the same concentration increase a 0.55% increase in total and 0.86% in cardiovascular mortality has been previously reported. Nevertheless, effect estimates for mortality sub-categories with smaller daily counts are expected to exhibit larger variation, as also the magnitude of negative estimates is larger. During the last decade there has been an increasing interest among the environmental epidemiology community on the link between air pollution and diabetes (Brook et al., 2008; Liu et al., 2013; Maynard et al., 2007), although most epidemiological findings assess long-term exposures effects (Andersen et al., 2012; Coogan et al., 2012; Kramer et al., 2010) or indicate people with diabetes as a sensitive population group (Laumbach et al., 2010; O'Neill et al., 2005, 2007). Our estimate for the association between fine particles and diabetes mortality is smaller than previously reported in Quebec (7.6%, Goldberg et al., 2001), which may be attributed to the use of estimated and not measured particles' concentrations in Canada. Besides, higher air pollution health effects have been consistently reported in Canada as compared to the U.S.A. and Europe (Katsouyanni et al., 2009). Maynard et al. (2007) reported a non-statistically significant increase of 5.7% in diabetes deaths associated with an interquartile increase in traffic particles short-term exposure in Boston, U.S.A., which may be considered relevant to $\text{PM}_{2.5}$ that are mainly traffic originated, while Ostro et al. (2006) reported a statistically significant 2.4% increase in diabetes mortality in nine California counties, where more diabetes-driven deaths were reported compared to the MED-PARTICLES cities. Hence, although our estimate is lower to the one reported in the U.S.A., the corresponding figures get closer when the same lag structure and particles' index are considered or after exclusion of small areas in MED-PARTICLES, since exclusion of Emilia-Romagna and Bologna resulted in 2.24% (95% CI: 0.07% , 4.46%) increase in diabetes deaths. There was significant amount of heterogeneity between the area-specific effect estimates of fine particles on diabetes deaths ($I^2 = 42\%$, $p\text{-value} = 0.09$), mainly attributed to the significantly lower associations detected in the small areas of Emilia-Romagna and Marseilles, and to a smaller extent in the Italian cities, as compared with the high effect estimates in the Greek cities and Madrid.

We found a statistically significant 1.3% increase in cardiac deaths following a $10 \mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ and a non-statistically significant 0.78% increase in cerebrovascular deaths. Although several authors have addressed the effects of fine particles on deaths from specific cardiovascular diseases, no report has directly addressed cardiac deaths. Most reports have focused on hospital admissions related to the causes considered in our analysis (due to the largest power in the morbidity as compared to the mortality analysis) and have reported significant associations. Le Tertre et al. (2002) reported an increased risk of cardiac hospital admissions associated with PM_{10} and black smoke exposure in eight European cities, and suggested that these effects were likely to be mainly attributable to diesel exhaust – which is a major source of fine

particles. Likewise, Von Klot et al. (2005) reported an increased risk of hospital cardiac readmission among myocardial infarction survivors in five European cities with increased levels of air pollution and Peters et al. (2004) reported that transient exposure to traffic increased the risk of myocardial infarction in susceptible persons. Our results regarding PM_{2.5} effects on specific cardiac outcomes are in accordance with those previously reported in Madrid (Maté et al., 2010), where a delayed effect was also noted. Regarding cerebrovascular deaths, Valdés et al. (2012) found a significant 1.13% increase for 10 µg/m³ increase in fine particles in Santiago, Chile, and Perez et al. (2009) reported a significant effect for very fine particles (PM₁). Our analysis on specific major categories of cardiac deaths indicated a non-significant association with deaths from acute coronary events and arrhythmias, but the absence of association with heart failure. The former finding is in accordance with Zanobetti and Schwartz (2009) who reported an association with myocardial infarction deaths that are part of the acute coronary deaths.

Regarding the association between fine particles' exposure and deaths due to respiratory causes we found an association with COPD deaths significant at the 10% level and a non-significant association with LRTI-related deaths. Previous studies have reported an association between COPD mortality and PM₁₀ exposure (Braga et al., 2001; Romieu et al., 2012; Zeka et al., 2005) or have addressed hospital admissions (Atkinson et al., 2001; Dominici et al., 2006; Faustini et al., 2013). A recent review by Schikowski et al. (2014) that focused on the long term association between air pollution and COPD concluded that acute and long term effects on the development of the underlying patho-physiological changes are not easily distinguished from each other under the epidemiological designs evaluated, and that evidence was suggestive though not conclusive. There have been contradictory reports as to whether COPD diagnosis characterizes sub-population groups sensitive to air pollution effects (Bateson and Schwartz, 2004; Sunyer et al., 2000). Fewer studies have studied the association with LRTI deaths and particles, mainly reporting associations with hospital admissions (Dominici et al., 2006; Faustini et al., 2013).

Effects of fine particles seemed to be mainly confounded by SO₂ and NO₂ levels, while control for coarse particles in cardiovascular and respiratory endpoints increased the relevant estimates. Confounding by SO₂ may reflect a wind direction effect since a main source of SO₂ in the Mediterranean cities is shipping and this source may co-emit other pollutants such as NO_x, sulphate, elemental carbon, vanadium and nickel among others. Nevertheless the interpretation of results from two pollutants models is restricted by their inherent instability because of the pollutants correlations. Higher effect estimates during the warm season (detected, except for LRTI where there is lack of power) are in accordance with previous findings on air pollution health effects (Samoli et al., 2013; Stafoggia et al., 2013), as higher associations may be attributed to better exposure characterization of the populations by the fixed monitoring sites' measurements. Alternatively the PM mixture may vary in the chemical composition by season due to differential sources.

We found positive, though non-statistically significant, associations of PM_{2.5–10} with deaths from diabetes and cardiac causes, the latter possibly driven by the association identified with acute coronary events. Only the association between coarse particles and diabetes remained in two-pollutant models, which presented heterogeneity attributed to the higher effect estimates reported in the larger cities. The lack of power may inhibit the identification of an association with specific causes of deaths that have low counts, as is the case with diabetes and respiratory outcomes, especially when these are addressed in small regions. Literature on coarse particles' effects is more limited, hence we were not able to trace any studies that investigated the associations with our cause-specific mortality outcomes. Nevertheless, Zanobetti and Schwartz (2009) reported no association between coarse particles and myocardial infarction, a main sub-category of cardiac deaths, either

overall 112 U.S.A. cities analyzed or restricted to cities characterized by a Mediterranean climate.

The investigation of the concentration-response relationship between fine and coarse particles and deaths from cardiac causes (for which sufficient power was available) revealed no evidence for a threshold, consistent with previous findings for the effects of particles on broader mortality outcomes (Katsouyanni et al., 2009; Samoli et al., 2013). Nevertheless, since research on particles' effects is targeting more specific outcomes it is important when possible, to address the issue of the concentration-response in such cases as well, in order to provide valuable information for health impact assessment and targeted policy measures.

There is considerable toxicological support for the adverse health effects of particles, especially those of smaller diameter, on cardiovascular and respiratory endpoints (Brook et al., 2004; Gurgueira et al., 2002; Schulz et al., 2005). Regarding short-term effects, plausible mechanistic pathways for cardiovascular effects include enhanced coagulation, a propensity for arrhythmias, acute arterial vasoconstriction and systemic inflammatory responses. In accordance with our findings that cardiovascular effects are mainly fine particles-driven, are the results by Tong et al. (2010) reporting that exposure of mice to coarse PM resulted in pulmonary toxicity, while ultrafine PM enhanced cardiac ischemia and reperfusion injury. Several links have also been proposed for the association between long-term exposure to fine particles and diabetes, such as endoplasmic reticulum stress-induced apoptosis, in brown adipose tissue dysfunction and decreased expression of UCP1 in brown adipose tissue (Liu et al., 2013), or increase of sICAM-1 (soluble intercellular adhesion molecule-1) and sVCAM-1 (soluble vascular adhesion molecule 1) (O'Neill et al., 2007).

The main limitations of our study are the exposure measurement error that is inherent in the time-series design, and to a lesser degree the misclassification of cause-specific mortality outcomes, as there may be differences in death certificates coding practices between countries. Regarding the former, exposure error was imposed within MED-PARTICLES by the limited number of monitors per city, and by the indirect estimation of PM_{2.5–10} that was not directly measured; attributing part of its variability to measurement error in both PM₁₀ and PM_{2.5}. Moreover, PM_{2.5–10} mass concentrations were generally lower than PM_{2.5} ones, which combined with the expected larger spatial heterogeneity for PM_{2.5–10} within cities, may have also resulted in larger measurement error. On the other hand, the combination of large and full time-series of exposure data on particles coming from multiple locations similar in topography is a major advantage of our study. Furthermore, analysis of cause-specific outcomes is hindered by diagnosis misclassification, as well as different diagnostic practices between countries.

As knowledge on the health effects of particles' exposure is expanded there is a growing need to identify specific health outcomes as compared with broad mortality categories. The results from the MED-PARTICLES project, the first multi-country European project on the investigation of short-term effects of size-fractionated particulate pollution on health, provide evidence of associations, mainly of fine particles, with deaths from cardiac causes and COPD, and also indicate a possible association with deaths from diabetes.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.envint.2014.02.013>.

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