



Short-term effects of particulate matter constituents on daily hospitalizations and mortality in five South-European cities: Results from the MED-PARTICLES project



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ABSTRACT

Background: Few recent studies examined acute effects on health of individual chemical species in the particulate matter (PM) mixture, and most of them have been conducted in North America. Studies in Southern Europe are scarce. The aim of this study is to examine the relationship between particulate matter constituents and daily hospital admissions and mortality in five cities in Southern Europe.

Methods: The study included five cities in Southern Europe, three cities in Spain: Barcelona (2003–2010), Madrid (2007–2008) and Huelva (2003–2010); and two cities in Italy: Rome (2005–2007) and Bologna (2011–2013). A case-crossover design was used to link cardiovascular and respiratory hospital admissions and total, cardiovascular and respiratory mortality with a pre-defined list of 16 PM₁₀ and PM_{2.5} constituents. Lags 0 to 2 were examined. City-specific results were combined by random-effects meta-analysis.

Results: Most of the elements studied, namely EC, SO₄²⁻, SiO₂, Ca, Fe, Zn, Cu, Ti, Mn, V and Ni, showed increased percent changes in cardiovascular and/or respiratory hospitalizations, mainly at lags 0 and 1. The percent increase by one interquartile range (IQR) change ranged from 0.69% to 3.29%. After adjustment for total PM levels, only associations for Mn, Zn and Ni remained significant. For mortality, although positive associations were

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identified (Fe and Ti for total mortality; EC and Mg for cardiovascular mortality; and NO_3^- for respiratory mortality) the patterns were less clear.

Conclusions: The associations found in this study reflect that several PM constituents, originating from different sources, may drive previously reported results between PM and hospital admissions in the Mediterranean area.

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1. Introduction

Dozens of studies link increases in daily particulate matter (PM) levels to increases in mortality and hospital admissions (Brook et al., 2010; Brunekreef and Holgate, 2002), some in the Mediterranean area (Samoli et al., 2013; Stafoggia et al., 2013). However, particulate matter is a location- and season-dependent complex mixture of different components with potentially different toxicity. Several recent investigations have also examined the relationship between concentrations of individual chemical species and mortality or hospital admissions (Bell et al., 2009, 2014; Burnett et al., 2000; Franklin et al., 2008; Ito et al., 2011; Lall et al., 2011; Levy et al., 2012; Lippmann et al., 2006; Mar et al., 2000; Ostro et al., 2007, 2010, 2011; Peng et al., 2009; Sarnat et al., 2008; Son et al., 2012; Zanobetti et al., 2009; Zhou et al., 2011). Most of these studies were conducted in North America, while studies in other parts of the world, where chemical composition may be different, are still limited. In Europe, such studies are scarce and only included one city (Ostro et al., 2011; Andersen et al., 2007; Atkinson et al., 2010). While it seems that some elements such as elemental carbon, nickel, and silicon are among the components most commonly associated with adverse health, the main conclusion derived from existing studies is that there is no sufficient evidence to identify the constituents more closely related to health outcomes (Environmental Protection Agency, 2009; Rohr and Wyzga, 2012; WHO (World Health Organization), 2013).

In this study, we examine the relationship between PM constituents and hospitalizations and mortality in five cities in Southern Europe, a region characterized by high vehicle and population densities, a high proportion of diesel cars, high sea traffic and peculiar meteorology with intense solar radiation, low precipitation and stagnation of regional air masses. These patterns confer to PM distinctive grain size and chemical patterns that are characterized by an important fraction of coarse (2.5–10 μm) PM into PM_{10} and relatively high proportions of mineral (anthropogenic and natural) dust and sulfate (Querol et al., 2009).

2. Methods

2.1. Study population and data

This study, within the context of the MED-PARTICLES project, included five cities, three in Spain (Barcelona, Madrid and Huelva) and two in Italy (Rome and Bologna) (Fig. A.1). City characteristics are provided in the Appendix. The overall period of study was from January 2003 to April 2013, although the different cities contributed to different periods according to data availability. Daily mortality counts for all non-external causes [International Classification of Diseases, 9th Revision (ICD-9) codes 001–799; 10th revision (ICD-10) codes A00–R99] (WHO (World Health Organization), 1999), for cardiovascular causes (ICD-9 codes 390–459, ICD-10 codes I00–I99) and for respiratory causes (ICD-9 codes 460–519, ICD10 codes J00–J99) were collected for all cities using death registries. Daily counts of emergency hospital admissions were collected from the national or regional health information systems. Repeated hospitalizations within 28 days since the previous one and with the same primary diagnosis were eliminated. Cardiovascular and respiratory hospitalizations were defined on the basis of the primary discharge diagnosis using the same ICD codes defined above. Since data were anonymous and collected as daily counts and the analysis was conducted by a public health institute, there was no need for informed consent and approval by an institutional review board.

PM_{10} and $\text{PM}_{2.5}$ data for speciation analysis were available from a single station in each city. Madrid's station was urban while all other were urban background stations. More details about the stations are provided in the Appendix. $\text{PM}_{2.5}$ data were not available for Rome while PM_{10} data were not available for Bologna. The period and frequency of sampling is shown in Table 1. The specific methods used to measure the elements are described in the Appendix.

Only 16 pre-specified PM constituents were included in the association analyses: total carbon (TC), elemental carbon (EC), organic carbon (OC), sulfate (SO_4^{2-}), nitrate (NO_3^-), silica (SiO_2) (calculated as 3 times the alumina concentration in the Spanish cities), calcium (Ca), iron (Fe), potassium (K), magnesium (Mg), zinc (Zn), copper (Cu), titanium (Ti), manganese (Mn), vanadium (V) and nickel (Ni). The list of 16 species was based on their detectability in the included cities and on a review of the literature linking PM constituents and health. If one of the above constituents had more than 20% of values missing or below the limit of detection or quantification in a certain city, the city was excluded from the analysis of that particular constituent. Otherwise, non-detectable values were replaced by half the limit of detection.

Daily average temperature and bank holidays were collected for each city. Information on influenza epidemics was obtained from hospital admission records. The collection of environmental and health data was performed by each partner and each one had its own quality control procedures, described in detail in the project website (www.epidemiologia.lazio.it/medparticles/index.php/en/). They included the use of international reference materials as test samples, and calculation of mass balances between the PM mass and the addition of all the components analyzed.

2.2. Study design and data analysis

In cities with daily data, we used a time-stratified case-crossover study design (Levy et al., 2001), according to which all days from the same year, month and day of the week were grouped in the same stratum. In cities without daily data, a simplified version of the case-crossover approach was adopted: strata were composed of days from the same year and month, and days of the week were modeled separately with indicator variables (Ostro et al., 2011). Since the case-crossover analysis conducts comparisons within strata, seasonal and long-term effects are eliminated and they do not confound the results. Analyses were performed using conditional Poisson regression (Whitaker et al., 2006) and were further adjusted for holidays (different categories for isolated holidays, Christmas and Easter, and periods surrounding Christmas and Easter), summer population decrease (one indicator variable for the 2-week period around 15 August and another for the remaining days between July 16th and August 31st), influenza epidemics, and temperature. To account for non-linearity and for the different lag structures of cold and hot temperatures, we included two separate spline terms for temperature, one for the cold period (temperatures below the annual median) using the average temperature for lags 1–6 and 2 degrees of freedom, and another for the warm period using average temperature for lags 0–1 and 3 degrees of freedom (Stafoggia et al., 2013).

All analyses were conducted separately for each city, and results were combined using random-effects meta-analysis. Lags 0, 1 and 2 of the effect of each pollutant were examined in different models, as models accounting for cumulative lags could not be built in cities without daily data. In cities without daily exposure data, models for different lags are based on non-overlapping sets of mortality days. For example, with PM data collected on time t , lag 0 analyses link these data to

Table 1
Data availability and summary of daily deaths and hospital admissions by city.

City	Date beginning–date end	Number of days	Frequency of sampling	Daily admissions (mean ± standard deviation)		Daily deaths (mean ± standard deviation)		
				Cardiovascular	Respiratory	Total	Cardiovascular	Respiratory
Barcelona	2003/01/01–2010/12/31	736	Twice a week	55.5 ± 10.6	55.1 ± 19.4	41.5 ± 8.6	13.0 ± 4.1	4.4 ± 2.6
Madrid	2007/01/01–2008/02/29	104	Twice a week	127.6 ± 30.3	142.2 ± 45.7	72.1 ± 11.0	21.7 ± 5.0	12.2 ± 4.7
Huelva	2003/01/01–2010/12/31	406	Once a week	1.8 ± 2.3	0.9 ± 1.2	2.9 ± 1.7	1.0 ± 1.0	0.3 ± 0.6
Roma	2005/01/01–2007/12/31	1059	Daily	81.9 ± 18.7	35.5 ± 11.3	57.0 ± 10.5	23.5 ± 6.3	3.5 ± 2.2
Bologna	2011/11/15–2013/02/28	472	Daily	16.8 ± 4.6	9.7 ± 3.7	12.2 ± 3.7	–	–

mortality on day t , lag 1 analyses link them to mortality on day $t + 1$ and lag 2 analyses link them to mortality on day $t + 2$ (Ostro et al., 2011). Results are reported for an interquartile range (IQR) increase in pollutant concentrations.

In order to account for potential confounding for total PM levels, while accounting for the fact that PM constituents are components of PM, we applied the recently proposed constituent residual method (Mostofsky et al., 2012). First, a linear regression model for the constituent as a function of total PM levels was fitted. Then, the residuals for this model, which represent the variation in constituent levels independent of PM, were included as an explanatory variable in the case-crossover model, along with total PM levels. The coefficient for the residuals represents the effect of the constituent while holding PM constant, i.e. the independent contribution of the constituent; and the PM coefficient represents the independent effect of total PM.

3. Results

Table 1 summarizes the daily number cardiovascular and respiratory hospital admissions and of deaths by natural, cardiovascular and respiratory causes in the five participating cities. Madrid, Rome and Barcelona are large cities with a high number of events, while Bologna and Huelva had lower numbers. Rome and Barcelona were the cities contributing most days to the analyses for PM₁₀ and PM_{2.5}, respectively.

The concentrations of PM₁₀ and PM_{2.5} and of their selected constituents in the five cities are summarized in Table 2. The highest PM₁₀ levels were observed for Barcelona and Madrid, with levels above 40 µg/m³, while Huelva and Rome showed levels between 30 and 35 µg/m³. In terms of PM_{2.5}, the highest levels were found in Barcelona and Bologna, with values above 25 µg/m³, while Madrid and Huelva had values

around 20 µg/m³. The selected species represented between 51% and 65% of the total PM levels depending on the city and fraction. TC, SO₄²⁻, NO₃⁻, SiO₂ and Ca were among the species with the highest contribution in terms of mass, while the other species had much smaller contributions that did not exceed 4% of the mass in any city. Correlations between species and total PM are described in Tables A.1a–e.

Fig. 1 shows the associations between total PM₁₀ and each PM₁₀ component and cardiovascular and respiratory admissions, while Fig. 2 shows the corresponding results for PM_{2.5}. Both total PM₁₀ and PM_{2.5} were associated with cardiovascular admissions at lag 0 and with respiratory admissions at lags 1 and 2. For cardiovascular admissions, we observed increased percent changes for Ca, Fe, Zn, Cu, Ti and Mn from PM₁₀. For PM_{2.5}, we found increased percent changes for EC, SO₄²⁻ and Mn. For respiratory admissions, we found increased percent changes for SO₄²⁻, SiO₂, Zn, V and Ni for PM₁₀; while for PM_{2.5}, increased percent changes were found for EC, Fe, Zn, V and Ni. While most of the effects on cardiovascular hospitalizations were observed at lag 0, the pattern was less clear for respiratory admissions where we found effects at lags 0, 1 and 2. Results from PM₁₀ and PM_{2.5} are not directly comparable, as they did not include the same cities. A comparison between the PM₁₀ and PM_{2.5} results in cities that measured both fractions is shown in Figs. A.2 and A.3. For cardiovascular admissions, associations tended to be stronger for PM₁₀, with the notable exception of EC. Patterns were less obvious for respiratory admissions.

Most of the increased percent changes were around 1% or 2% increase for one IQR increase in pollutant levels, reaching almost 3% for EC from PM_{2.5} for cardiovascular admissions and for EC and Ni from PM_{2.5} for respiratory admissions. The numeric results for all elements are shown in Table A.2. When adjusting for total PM levels using the constituent residual method, only Mn and Zn from PM₁₀ for CV

Table 2
Description (mean ± standard deviation) of PM species^a levels (µg/m³) by city.

	Barcelona (2003–2010)		Madrid (2007–2008)		Huelva (2003–2010)		Rome (2005–2007)	Bologna (2011–2013)	Common IQR	
	PM ₁₀	PM _{2.5}	PM ₁₀	PM _{2.5}	PM ₁₀	PM _{2.5}	PM ₁₀	PM _{2.5}	PM ₁₀	PM _{2.5}
Total PM	40.3 ± 17.4	26.3 ± 12.2	41.5 ± 19.5	20.7 ± 9.2	35.2 ± 15.2	20.8 ± 10.7	30.1 ± 12.6	27.6 ± 19.5	19.6	16.0
Total carbon	6.9 ± 3.7	4.9 ± 2.6	10.4 ± 5.6	7.6 ± 3.9	5.4 ± 3.4	3.9 ± 2.3	10.6 ± 5.2	6.7 ± 4.7	5.2	3.8
OC	3.3 ± 1.8	2.9 ± 1.8	na	6.0 ± 2.7	na	na	8.6 ± 4.2	5.1 ± 3.9	3.4	3.0
EC	1.8 ± 1.2	1.5 ± 1.0	na	3.5 ± 1.5	na	na	2.2 ± 1.3	1.6 ± 1.0	1.4	1.1
SO ₄ ²⁻	3.8 ± 2.6	3.4 ± 2.3	3.2 ± 1.4	2.4 ± 1.1	3.8 ± 3.2	3.3 ± 2.7	3.4 ± 2.0	2.4 ± 1.6	2.7	2.3
NO ₃ ⁻	4.3 ± 3.5	2.4 ± 3.2	2.5 ± 2.1	1.5 ± 1.7	2.7 ± 1.8	1.2 ± 1.2	2.1 ± 1.4	5.1 ± 7.9	2.2	3.0
SiO ₂	3.8 ± 3.6	1.4 ± 1.8	2.2 ± 1.8	1.0 ± 0.8	4.9 ± 4.4	1.4 ± 2.0	1.0 ± 0.9	nd	2.7	1.1
Ca	2.13 ± 1.64	0.60 ± 0.62	2.10 ± 1.35	0.26 ± 0.16	1.16 ± 0.94	0.33 ± 0.52	1.29 ± 0.68	0.10 ± 0.06	1.32	0.27
Fe	0.86 ± 0.54	0.28 ± 0.21	1.67 ± 0.87	0.20 ± 0.15	0.66 ± 0.52	0.18 ± 0.20	0.46 ± 0.26	0.11 ± 0.07	0.63	0.18
K	0.38 ± 0.29	0.20 ± 0.23	0.33 ± 0.22	0.20 ± 0.41	0.41 ± 0.30	0.21 ± 0.20	0.39 ± 0.32	0.18 ± 0.30	0.26	0.15
Mg	0.279 ± 0.165	0.082 ± 0.072	0.225 ± 0.150	0.083 ± 0.084	0.295 ± 0.193	0.084 ± 0.093	0.095 ± 0.098	nd	0.153	0.069
Zn	0.085 ± 0.080	0.059 ± 0.068	0.059 ± 0.044	0.050 ± 0.026	0.049 ± 0.074	0.045 ± 0.084	0.037 ± 0.035	nd	0.047	0.039
Cu	0.056 ± 0.051	0.027 ± 0.036	0.113 ± 0.069	0.019 ± 0.010	0.047 ± 0.078	0.029 ± 0.033	0.040 ± 0.020	nd	0.051	0.021
Ti	0.040 ± 0.033	0.014 ± 0.013	0.040 ± 0.031	0.008 ± 0.014	0.056 ± 0.084	0.020 ± 0.039	0.021 ± 0.023	nd	0.030	0.010
Mn	0.018 ± 0.011	0.009 ± 0.006	0.020 ± 0.011	0.005 ± 0.003	0.013 ± 0.024	0.004 ± 0.004	0.012 ± 0.008	nd	0.011	0.004
V	0.010 ± 0.007	0.008 ± 0.006	0.002 ± 0.001	0.001 ± 0.001	0.005 ± 0.004	0.004 ± 0.003	0.006 ± 0.004	nd	0.005	0.004
Ni	0.005 ± 0.003	0.004 ± 0.003	0.002 ± 0.001	0.004 ± 0.003	0.003 ± 0.003	0.002 ± 0.003	0.005 ± 0.003	nd	0.003	0.004

na: not available.

nd: non-detectable.

^a Ordered by PM₁₀ mass contribution when pooling all cities.

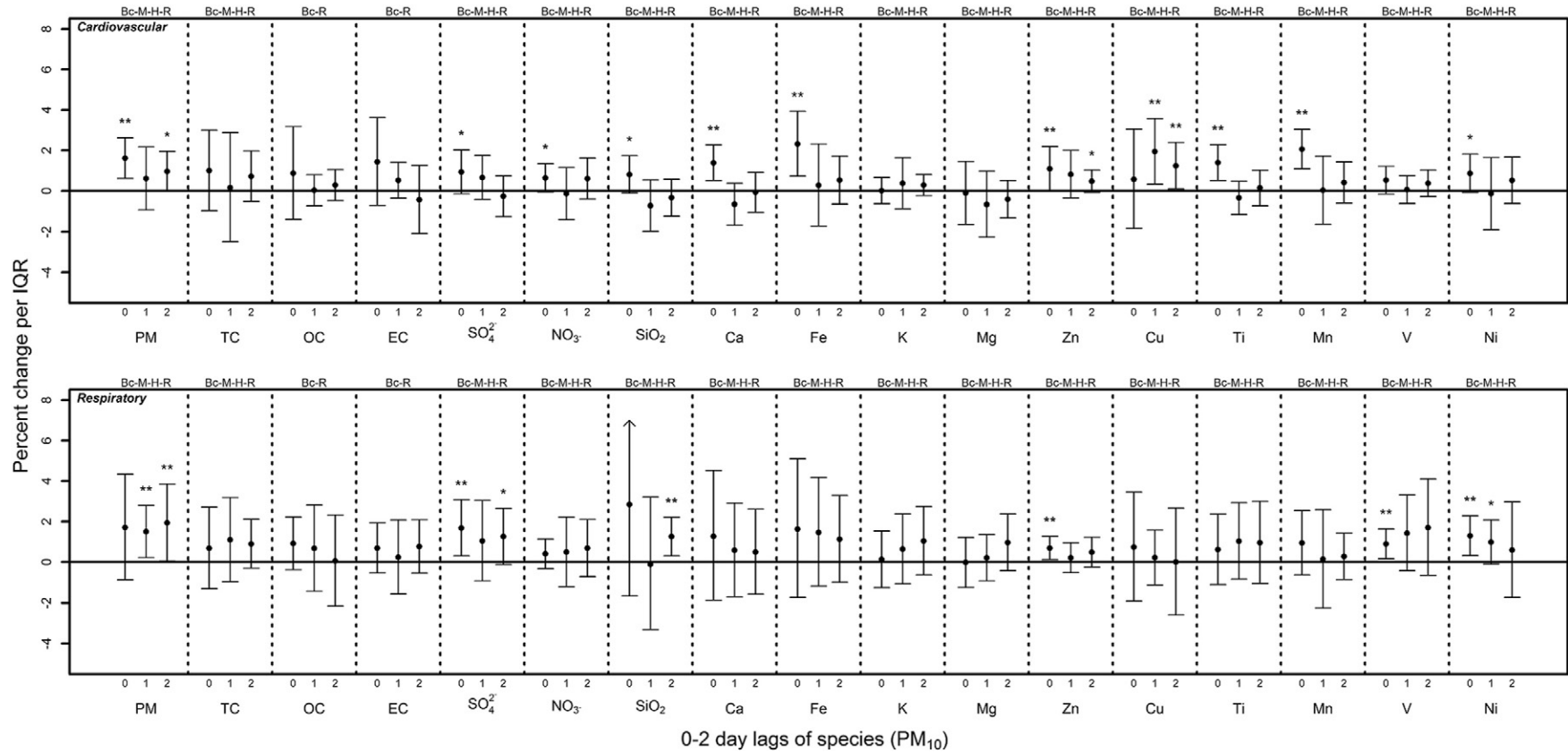


Fig. 1. Association between cardiovascular and respiratory hospital admissions and PM₁₀ constituents for lags 0, 1 and 2, expressed as the percent change in hospital admissions for an interquartile range increase in PM₁₀ constituent levels with 95% confidence intervals. Results were obtained from a meta-analysis combining the city-specific results of the cities with available data on each constituent. The cities contributing to the results for a particular constituent are indicated on top of each graph (Bc: Barcelona, M: Madrid, H: Huelva, R: Rome). (*) indicates a p-value < 0.10, while (**) indicates a p-value < 0.05.

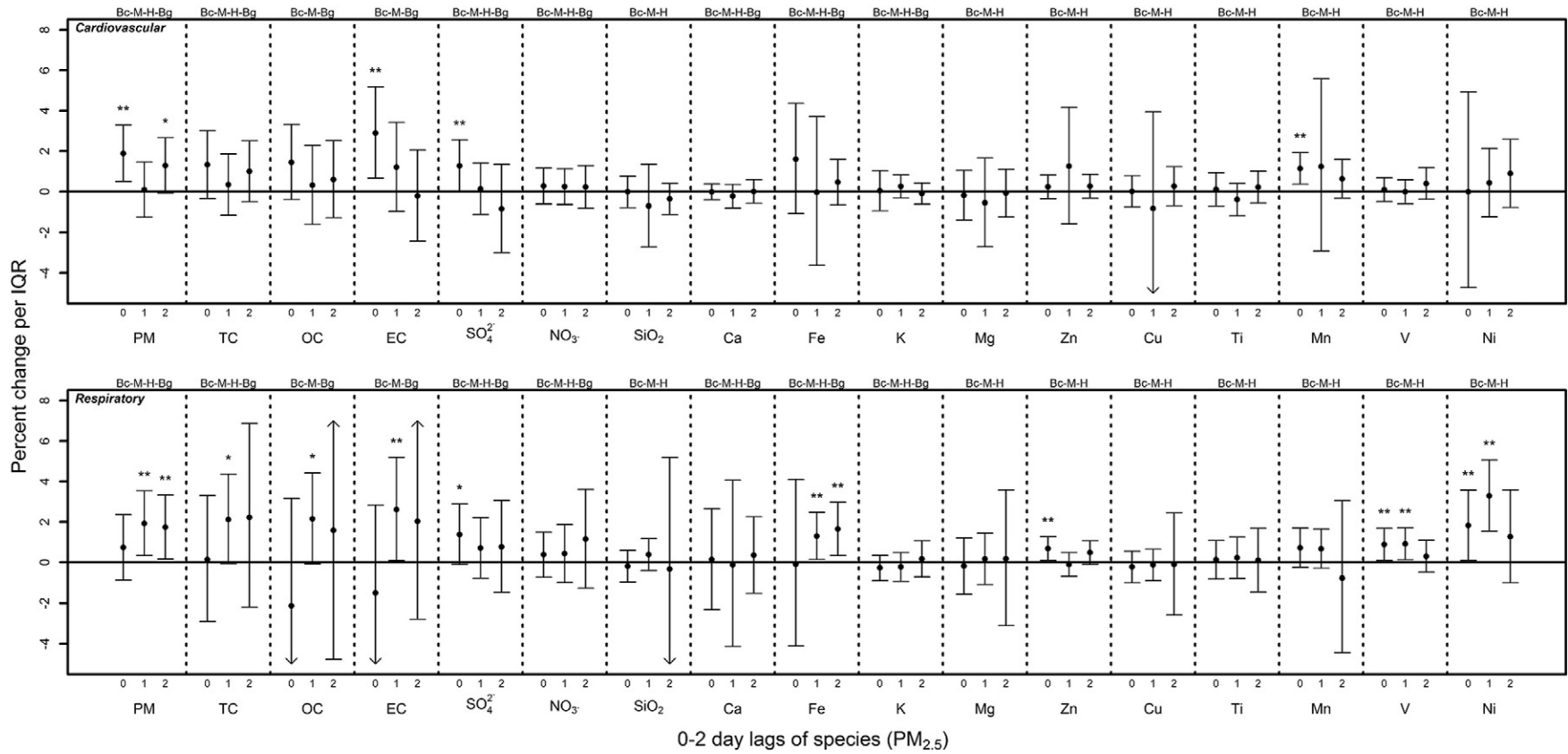


Fig. 2. Association between cardiovascular and respiratory hospital admissions and PM_{2.5} constituents for lags 0, 1 and 2, expressed as the percent change in hospital admissions for an interquartile range increase in PM_{2.5} constituent levels with 95% confidence intervals. Results were obtained from a meta-analysis combining the city-specific results of the cities with available data on each constituent. The cities contributing to the results for a particular constituent are indicated on top of each graph (Bc: Barcelona, M: Madrid, H: Huelva, Bg: Bologna). (*) indicates a p-value < 0.10, while (**) indicate a p-value < 0.05.

admissions and only Ni (PM_{10}) and Ni and Zn ($PM_{2.5}$) for respiratory admissions had 95% confidence intervals not including one and remained with similar magnitude (Table A.4).

We found no increased percent changes in daily mortality in relation to total PM_{10} or $PM_{2.5}$ (Figs. A.4 and A.5). In contrast, when the analysis was performed using complete time series (i.e. using daily data instead of restricting the analyses to days with data on PM species), significant associations with total PM were found (Samoli et al., 2013). We found increased percent changes in mortality for TC, Fe, K and Ti from PM_{10} and for SiO_2 from $PM_{2.5}$ (Figs. A.4 and A.5). For cardiovascular mortality, increased percent changes were found for EC from PM_{10} , and for Mg and Mn from $PM_{2.5}$. For respiratory deaths, we found increased percent changes for EC and Ni from PM_{10} and sulfate from $PM_{2.5}$. We also found some decreased percent changes (TC, OC and NO_3^- for some models). The numerical results of the mortality analyses are presented in Table A.3. Most of the associations ranged from 1 to 2% change per one IQR increase, although for respiratory deaths, the effect of SO_4^{2-} from $PM_{2.5}$ (lag 2) was 5.26% (0.79–9.92) and the effect of EC from PM_{10} (lag 1) was 5.29% (1.37–9.37).

When adjusting for total PM, few associations persisted: SiO_2 , Fe and Ti for total mortality; for cardiovascular mortality, EC and Mg persisted and Ca, SiO_2 and Fe, showed increased percent changes only after adjusting for total PM; and for respiratory mortality, SO_4^{2-} persisted and K showed increased percent changes after adjustment (Table A.5).

The between-city variation in effects and the weight of each city for four selected analyses at lag 0 are illustrated in Fig. A.6. Rome and Barcelona were the cities contributing the most to the total effects.

4. Discussion

This study investigated the relationship between PM_{10} and $PM_{2.5}$ constituents and hospital admissions and mortality in five South-European cities. Several individual PM components showed increased percent changes in hospital admissions and/or mortality. More consistent results were found for hospital admissions, which had increased power due to a greater frequency of the outcome. The highest effects were found for EC and Ni but many other species showed increased percent changes. For mortality, the highest effects were found for respiratory mortality and EC, Ni and SO_4^{2-} . A few other species showed increased percent changes in mortality, and a few of them showed decreased percent changes. Most commonly, increased percent changes were found for hospitalizations at lag 0 and for mortality at lag 1.

The associations found in this study reflect that acute exposure to several PM constituents, originating from different sources, may play a role in the association between PM and health. This general conclusion is in agreement with other reports that reviewed the available evidence (Environmental Protection Agency, 2009; Rohr and Wyzga, 2012; WHO (World Health Organization), 2013). Most of the PM constituents for which we found positive associations are the ones that have been most commonly reported in the literature. Although several epidemiological studies have evaluated the role of specific PM components on health, our study contributes to the gap of knowledge on this topic in Europe (Ostro et al., 2011; Andersen et al., 2007; Atkinson et al., 2010) and in particular in the Mediterranean area.

Carbonaceous particles are emitted from burning fossil fuels and biomass, as well as from the oxidation of natural and anthropogenic volatile organic compounds (VOCs) and from bioaerosols. Total carbon, EC and OC in urban areas have been used as markers for traffic emissions, and EC is considered to be a good marker of diesel vehicle emissions. OC is made of a highly complex mixture of compounds from combustion and non-combustion, anthropogenic and natural, and primary and secondary compounds (Jimenez et al., 2009). EC levels in $PM_{2.5}$ were between 1.5 and 3.5 $\mu g/m^3$ in the studied cities, higher than those found in most cities in the US (average 0.7 $\mu g/m^3$ with range 0.3–1.7) (Bell et al., 2009), and somewhat similar to those reported for Seoul (Korea) (2.2 $\mu g/m^3$) (Son et al., 2012). We found consistent

increased risks of mortality and hospitalizations associated with EC. Other epidemiological studies have found associations with EC with total (Zhou et al., 2011) and cardiovascular mortality (Ito et al., 2011; Mar et al., 2000; Ostro et al., 2007; Zhou et al., 2011) and other with cardiovascular (Bell et al., 2009; Ito et al., 2011; Levy et al., 2012) and respiratory admissions (Bell et al., 2009). In fact, and especially for cardiovascular outcomes, most of the studies on mortality or hospital admissions, the studies on systemic biomarkers and the few controlled human exposure studies report significant associations with either EC or OC (or both) (Rohr and Wyzga, 2012). Positive results have also been found for respiratory outcomes, but less consistently.

Toxicological studies have described several pathways responsible for adverse health outcomes produced by diesel engine emissions. One of the main mechanisms involves production of an inflammatory response mediated by the induction of oxidative stress and the release of pro-inflammatory cytokines, but other mechanisms include changes in the bioavailability of NO within the vascular system, migration of leukocytes into bronchial tissue and effects on the immune system (Grahame et al., 2014). This evidence suggests a deleterious effect of carbon-containing particles, although the WHO (World Health Organization) (2012) stated that EC may not be a directly toxic PM component but may act as a carrier for a wide range of chemical compounds of varying toxicity, such as aromatic polycyclic hydrocarbons, organic acids, and metals. Some animal studies found associations between carbon particles and increased heart rate, reduced heart rate variability, increased blood pressure but no inflammatory response (WHO (World Health Organization), 2013). However, studies in humans have linked EC and OC to inflammatory biomarkers (Delfino et al., 2009), and it has been suggested that the oxidative stress and inflammation associated with carbon particles may be due to the semivolatile organic fraction on the carbon particle core (WHO (World Health Organization), 2013; Cassee et al., 2013).

We studied two secondary inorganic aerosol species, NO_3^- and SO_4^{2-} . We found increases in respiratory mortality and hospitalizations and in cardiovascular hospitalizations associated with SO_4^{2-} . In the mortality literature, SO_4^{2-} has been linked to total and cardiovascular deaths (Burnett et al., 2000; Franklin et al., 2008; Ito et al., 2011; Ostro et al., 2011; Anderson et al., 2001), but respiratory effects of SO_4^{2-} have been reported when looking at hospital admissions (Sarnat et al., 2008; Atkinson et al., 2010). A review of all the available evidence for SO_4^{2-} reported mixed results (Rohr and Wyzga, 2012). It has been suggested that SO_4^{2-} may act as a marker for other harmful constituents from oil and coal combustion, and in addition it can increase the toxic effects of Fe by increasing its solubility (WHO (World Health Organization), 2013; Cassee et al., 2013). For NO_3^- , we did not find consistent results and few studies have reported adverse effects (Rohr and Wyzga, 2012; WHO (World Health Organization), 2013). The available toxicological evidence does not support a causal association between SO_4^{2-} or NO_3^- and health risk (Cassee et al., 2013).

We found health effects of several metals. In particular, we found effects for a set of metals composed by SiO_2 , Ca, Fe and Ti that were highly correlated in all participating cities. In addition, we also increased percent changes for K, Mg and Mn, which were highly correlated with the previous set in some but not all the cities. Most of the previous metals have mineral origin and have been apportioned to road dust and mineral factors in Southern European cities (Ostro et al., 2011; Amato et al., 2009). The infrequent rainfall favors the accumulation of road dust in the roads, which is then resuspended by traffic, a phenomenon particularly relevant in the Mediterranean area (Karanasiou et al., 2014). In this area, road dust, apart from having substances emitted by vehicle exhaust and wear, contains a large fraction of mineral dust, coming, for example, from construction work (Ostro et al., 2011; Amato et al., 2009; Querol et al., 2004). A recent review included Si and K among the group of elements that have been most frequently associated with health effects, along with Ni and V (discussed in the next paragraph), and Zn and Cu (Rohr and Wyzga, 2012), for which we also detected

increased percent changes in hospital admissions. However, a proper assessment of the results in the literature is difficult, as not all studies included the same elements. Although not included in the top list by the review, it is worth noting that, as in our study, several epidemiological studies have found effects for Fe (Burnett et al., 2000; Ostro et al., 2007, 2009, 2010; Cakmak et al., 2009), and Mn (Lall et al., 2011; Ostro et al., 2007; Zanobetti et al., 2009; Cakmak et al., 2009). There exists toxicological evidence for the deleterious effects of metals, but they are not believed to account for all the health effects of PM (WHO (World Health Organization), 2013). For example, Mn and Fe have been related to oxidative stress markers in exposed human epithelial cells, and Cu and Zn have been linked to decrease in spontaneous beat rate, vasoconstriction and vasodilatation (Lippmann et al., 2013; Zhang et al., 2009).

Apart from the metals mentioned above, we also found effects of Ni and V on respiratory admissions and of Ni on respiratory mortality. Ni and V are typical markers for fuel oil combustion (Viana et al., 2008). Ni has been the metal most commonly linked with health effects, mainly for cardiovascular outcomes (WHO (World Health Organization), 2013). A few studies have also reported effects of Ni on respiratory outcomes (Bell et al., 2009, 2014; Cakmak et al., 2009). V has also been associated with cardiovascular and respiratory admissions (Bell et al., 2009, 2014; Lippmann et al., 2006). Multiple toxicological studies in animals have reported effects of Ni, including acute changes in heart rate variability; delayed hypothermia, bradycardia and arrhythmogenesis; respiratory carcinoma induction; expression of several genes involved in oxidative stress response, inflammation, repair/remodeling and vascular function; and apoptosis of ovary cells and T cell hybridoma cells (Zhang et al., 2009). V can induce expression of genes involved in injury/inflammation and vascular function, and has been shown to produce adverse reactions in human airway epithelial cells (Zhang et al., 2009).

We attempted to separate the effect of PM constituents and total PM levels by using the constituent residual method. For hospital admissions, only results from Mn, Zn and Ni were robust to adjustment for total PM. An assessment of the results in the literature regarding models adjusted for PM or models including more than one constituent is difficult, as not all studies fitted such models or included the same constituents. EC has been shown to be robust in multi-pollutant models and is suggested to have a stronger effect than total PM (Grahame et al., 2014). In our study, even though EC effects lost statistical significance, point estimates were only slightly reduced. Ni has also shown some robustness in multi-pollutant models in some studies (Rohr and Wyzga, 2012). When adjusting for total PM in the mortality analyses, associations remained significant in some models for SiO₂, Fe, Ti, EC, Mg, SO₄²⁻ and some associations were only significant after adjustment for PM, as it was the case for Ca and K. It is important to note, though, that PM mass was not associated with mortality in single pollutant models. We believe that this may be due to a lack of power, since an association for total PM was detected when using daily PM values (including days without speciation data) (Samoli et al., 2013). Therefore, our mortality analyses should be interpreted with caution.

The study of the health effects of PM components is hindered by the large number of elements present in the PM mixture and the correlations between them. In our study, we found 95% confidence intervals not including 1 in 8.3% of the comparisons, a higher percentage than what would be expected by chance, and all but six associations were positive. Although this supports the likelihood of harmful effect of some PM constituents, chance associations can be expected. The fact that the components found in this study are the ones most commonly reported in the literature gives more confidence in our results. The correlation between PM constituents is also problematic. We found effects for different constituents that were highly correlated. In such instances, even if a single responsible pollutant exists, it is hard to single it out. Models with multiple constituents were not fitted to avoid collinearity.

Our study suffered from additional limitations. Data were available for a single monitoring station in each city and they might not be good representatives of all the population. This introduces Berkson-type

measurement error, as is common in most time-series studies of air pollution, which leads to no or little bias but decreases statistical power (Mostofsky et al., 2012). The multiple components of PM have different spatial distributions, and how well outdoor levels reflect indoor levels also varies by component. This leads to different degrees of measurement error – and therefore, of power – for each of them, and this may influence which associations are detected (Mostofsky et al., 2012). The study is also limited in not having daily data for some cities. This may preclude an adequate correction for time trends, but also it prevented the use of models combining the effects of multiple lags. Finally, our data were heterogeneous in terms of years and PM fractions used in each city and this may introduce some extra uncertainty in the meta-analysis results. Rome, a city with important weight in the analysis, did not have PM_{2.5} data. It is interesting to note, though, that there was a moderate concordance in the results for PM₁₀ and PM_{2.5} in cities with both fractions available.

A better understanding of which elements, and therefore which sources, are the most harmful for health is very important from the policy point of view. In order to confirm these results, future studies should develop specific studies with a stronger focus on PM speciation, with ad-hoc long term campaigns of daily data in several locations and using the same protocols for data collection. Future studies should also explore the role of combined effects of several PM constituents, as toxicological studies have provided some evidence on interactions (e.g. between C and Fe, or between Ni and V) and other interactive biological effects have been suggested (e.g. secondary inorganic components influencing the bioavailability of metals) (WHO (World Health Organization), 2013; Cassee et al., 2013; Zhang et al., 2009).

This study examined the effects of PM constituents on hospitalizations and mortality in five Southern European cities. Our study suggests that several PM constituents are associated with increases in daily hospitalizations and mortality. Such elements come from different sources and some of them are highly correlated and therefore it is difficult to attribute effects to a particular constituent. Studies with larger datasets and daily data are needed to confirm these results in the Southern Europe.

Conflict of interest statement

The authors have no conflicts of interest to disclose.

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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.2014.11.011>.

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