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Evaluation of short-term mortality attributable to particulate matter pollution in Spain

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ABSTRACT

According to the WHO, 3 million deaths are attributable to air pollution due to particulate matter (PM) world-wide. However, there are no specific updated studies which calculate short-term PM-related cause specific mortality in Spain. The objective is to quantify the relative risks (RRs) and attributable risks (ARs) of daily mortality associated with PM_{10} concentrations, registered in Spanish provinces and to calculate the number of PM-related deaths. We calculated daily mortality due to natural (ICD-10: A00 R99), circulatory (ICD-10: I00 I99) and respiratory causes (ICD-10: J00 J99) for each province across the period 2000–2009. Mean daily concentrations of PM_{10}, NO_2 and O_3 was used. For the estimate of RRs and ARs, we used generalised linear models with a Poisson link. A meta-analysis was used to estimate RRs and ARs in the provinces with statically significant results. The overall RRs obtained for these provinces, corresponding to increases of 10 μ g/m^3 in PM_{10} concentrations were 1.009 (95% CI: 1.006 1011) for natural, 1.026 (95% CI: 1.019 1033) for respiratory, and 1.009 (95% CI: 1.006 1012) for circulatory-cause mortality. This amounted to an annual overall total of 2683 deaths (95% CI: 852 4354) due to natural, 651 (95% CI: 359 1026) due to respiratory, and 556 (95% CI: 116 1012) due to circulatory causes, with 90% of this mortality lying below the WHO guideline values. This study provides an updated estimate of the effect had by this type of pollutant on causes of mortality, and constitutes an important basis for reinforcing public health measures.

1. Introduction

Particulate matter (PM) consists of a complex mix of solid and liquid particles of organic and inorganic substances suspended in the air. The main components of PM are sulphates, nitrates, ammonium, sodium chloride, “black carbon”, mineral dust, organic matter and water (Querol et al., 2012). The respirable particles, PM_{10} (aerodynamic diameter of less than 10 microns) and $PM_{2.5}$ (aerodynamic diameter of less than 2.5 microns), are the types of PM which have the greatest health impact (WHO, 2013). According to a recent WHO study (WHO, 2016), in 2012 some 3 million deaths world-wide were estimated to be attributable to PM-related air pollution, with 193,000 of these occurring in Europe and 7000 in Spain.

The health effects of PM are especially well documented, with a distinction being drawn between two types of effects, short- and long-term. Cohort studies designed to detect the long-term effects on population health, link exposure to PM to an increased risk of death (Dockery et al., 1993; Pope et al., 1995; Miller et al., 2007; Beelen et al., 2008a; Ostro et al., 2010), even for very low $PM_{2.5}$ concentrations (Crouse et al., 2012). Although the principal causes of mortality associated with long-term exposure to PM are some types of cancer (Beelen et al., 2008b), recently the International Agency for Research on Cancer (IARC) classified $PM_{2.5}$ as a carcinogen (Loomis et al., 2013); equally notable are its effects on cardiovascular (Brook et al., 2010; Dominici et al., 2006) and respiratory causes (Dominici et al., 2006; Guaita et al., 2011; Kim et al., 2012), with clearly established physiopathological mechanisms (Brook et al., 2010; Rückerl et al., 2011). Recent studies suggest other types of health outcomes, in which PM is associated with other types of diseases (Rückerl et al., 2011). Hence, PM has been found to have an effect on diabetes (Brook et al., 2008), neurological development in children (Freire et al., 2010) and neurological disorders in adults (Ranft et al., 2009).

There are also numerous studies which associate short-term exposure to PM –both PM_{10} and $PM_{2.5}$- with morbidity and

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mortality due to respiratory and cardiovascular causes (Dominici et al., 2006; EPA, 2009; Maté et al., 2010; Brook et al., 2010; Guaita et al., 2011; Rückerl et al., 2011), with a greater effect being detected in older adults (Zanobetti et al., 2000; Aga et al., 2003; Jiménez et al., 2009, 2010), though there are also effects on the childhood population (Schwartz and Neas, 2000; Barnett et al., 2005; Linares and Díaz 2009; Díaz et al., 2004). Furthermore, PM levels have been associated in the short term with adverse birth variables, including foetal mortality (Arroyo et al., 2016).

Unlike the USA, few multi-city studies have been undertaken in Europe (Samoli et al., 2013). Some of the major studies undertaken in Europe to address the effect of PM on morbidity and mortality have been the APHEA project (Katsouyanni et al., 2001; Atkinson et al., 2001), which focused on 29 towns/cities with the main aim of ascertaining the short-term effect of PM on health, and the APHEIS project (Boldo et al., 2006; Ballester et al., 2008), which analysed the long-term health impact of $PM_{2.5}$ in 23 European towns/cities. More recently, the MEDPARTICLES project sought to analyse the short term effect of PM on morbidity and mortality in 12 towns/cities in Mediterranean Europe (Samoli et al., 2013, 2014; Basagaña et al., 2015).

In Spain, the only multicentre study to analyse the association at short term between morbidity and mortality and chemical air pollution, with data obtained from *in situ* measurements, has been the EMECAM-EMECAS. This study was conducted in 16 Spanish towns/cities using pre-1997 data and total suspended particles (TSP) as the PM indicator (Ballester et al., 2002, 2006). More recently, the SERCA Project was implemented in Spain (Boldo et al., 2011), with the aim of ascertaining $PM_{2.5}$–related mortality for Spain as a whole, though this project also displays limitations. On the one hand, the $PM_{2.5}$ values were the result of modelling based on emission sources, i.e., estimated $PM_{2.5}$ concentrations; and, at an epidemiological level, the dose-response functions used were mainly extrapolated from cohort studies (long term effect) undertaken in the USA. In view of the lack of updated multi-city studies based on measured exposure values, with dose-response functions specifically calculated for each city, we present the following study, whose aim was to analyse the impact of PM on short-term mortality in Spain. Using a times series analysis, based on aggregated natural-, circulatory- and respiratory-cause mortality data for all age groups and air pollution data for each of Spain's provinces across the period 2000–2009, relative risks and PM-related risks were calculated for each province, thereby yielding a closer approximation of the impact of PM on the overall Spanish population and making this the European study with one of the widest coverages at the level of the cities analysed to have ever evaluated the short-term impact of PM on daily mortality due to different causes.

2. Material and methods

2.1. Variables used in the analysis

Dependent variable: as the dependent variable, we used daily mortality due to natural (all causes except accidents) (ICD-10: A00-R99), circulatory (ICD-10: I00I99) and respiratory causes (ICD-10: J00-J99) registered in 52 Spanish provinces across the period 2000–2009. In the case of Madrid, the data corresponded exclusively to the Madrid metropolitan area. These data were furnished by the National Statistics Institute (*Instituto Nacional de Estadística/INE*).

Independent variable: the principal independent variable was mean daily PM_{10} concentrations ($\mu g/m^3$) recorded at monitoring stations in each provincial capital from 2000 to 2009. All measurements were made using the gravimetric method or an equivalent method (beta-attenuation). All data were validated and comparable, were supplied by the Ministry of Agriculture & Environment (*Ministerio de Agricultura, Alimentación y Medio Ambiente/MAGRAMA, 2016*). For the cities of Madrid, Las Palmas de Gran Canaria and Santa Cruz de Tenerife, $PM_{2.5}$ values were available in addition to those for PM_{10}.

Control variables: in the analysis, we controlled for the different variables related to the designated study objective, namely:

- other pollutants: we controlled for mean daily concentrations ($\mu g/m^3$) of NO_2 and O_3. These pollutants were measured at the same stations as those which obtained the PM_{10} values, and were likewise supplied by the MAGRAMA.
- meteorological variables: we considered the daily maximum temperatures (T_{max}) and minimum temperatures (T_{min}) at each reference observatory situated in each provincial capital. These data were furnished by the State Meteorological Agency (*Agencia Estatal de Meteorología/AEMET*).
- other control variables: we controlled for the presence or absence of influenza epidemics. This variable was introduced dichotomously, with a value = 1 when there was an epidemic and a value = 0 when there was no epidemic. This information was supplied by the National Centre of Epidemiology at the Carlos III Institute of Health.

Similarly, we took into account the trend of the series, day of the week, and annual, six-monthly and three-monthly seasonalities were taken into account, using the sine and cosine functions of the periods of 365, 180 and 90 days respectively. In addition we also controlled for the autoregressive nature of the dependent variable.

2.2. Transformation of variables

Lagged variables: multiple studies have shown that the effect of air pollution on short-term mortality may not be immediate, but that this effect can occur up to 5 days afterwards in the case of PM and NO_2 (Díaz et al., 1999; Maté et al., 2010) and up to 9 days afterwards in the case of O_3 (Díaz et al., 1999). In the case of temperatures, the lagged effect on mortality can be delayed up to 4 days in the case of heat (Alberdi et al., 1998; Díaz et al., 2002, 2015) and up to 13 days in the case of cold (Alberdi et al., 1998; Carmona et al., 2016). To take these impacts into account, we created the corresponding lagged variables for each of the above-mentioned variables.

Non-linear control variables: previous studies have shown that the functional relationship between ozone and mortality is not linear, displaying a U-shaped pattern, with the right-hand side of the U corresponding to the increase in mortality associated with high ozone values (O_{3h}) (Díaz et al., 1999). The minimum value of the quadratic function (U), i.e., the threshold ozone value ($O_{threshold}$), varies from one city to another and was determined for each provincial capital in previous studies (Ortiz et al., 2016). The variable O_3 in each province included in the modelling was therefore parameterised as follows:

$O_3 = 0$ if $O_3 < O_{threshold}$

$O_{3h} = O_3 - O_{threshold}$ if $O_3 > O_{threshold}$

Similarly, it is widely known that temperature displays a U-shaped relationship with mortality (Alberdi et al., 1998), in which the left-hand side corresponds to the effect of low temperatures and the right-hand side to the effect of high temperatures. This effect of heat and cold on mortality is exacerbated in so-called heat and cold waves. Determination of the threshold temperatures

($T_{threshold}$) used in the heat- and cold-wave definitions is different in each provincial capital, with these being established in previous studies undertaken for each Spanish province for heat (Díaz et al., 2015) and cold waves respectively (Carmona et al., 2016). Bearing this in mind, the variable "temperature" was parameterised as follows:

Heat:

$T_{heat} = 0$ if $T_{max} < T_{threshold}$

$T_{heat} = T_{max} - T_{threshold}$ if $T_{max} > T_{threshold}$

Cold:

$T_{cold} = T_{threshold} - T_{min}$ if $T_{min} < T_{threshold}$

$T_{cold} = 0$ if $T_{min} > T_{threshold}$

In the case of NO_2, this variable's functional relationship with mortality is linear (Díaz et al., 1999).

2.3. Process of analysis and modelling

Using different curvilinear adjustments, we first determined the functional relationship existing between the independent variable (PM concentrations) and the dependent variables, choosing the fit with the best Snedecor F-distribution. In any case where the fit was not linear, a transformation was performed. To quantify the impact of PM pollution on mortality, we constructed generalised linear models (GLMs) with the Poisson regression link. This methodology makes it possible to calculate the relative risks (RRs) associated with increases in the independent variable, in this case PM. Based on the RR, we then calculated the attributable risk (AR) associated with this increase via the equation: AR = ((RR-1)/RR)×100 (Coste and Spira, 1991).

In these models, we included both the independent variable with its corresponding lags, and the control variables (already parameterised where this was necessary), along with their corresponding lags. The procedure used to determine significant variables (PM and its corresponding lags, and control variables) was «Backward-Step», beginning with the model that included all the

Table 1
Descriptive statistics of NO_2, O_3 and PM_{10}/$PM_{2.5}$ levels (μg/m^3), by city: Spain, 2000–2009. **Only showed cities with valid values in any pollutants**.

Town/City	NO_2				O_3				$PM_{10}/PM_{2.5}$			
	Mean	SD	Min	Max	Mean	SD	Min	Max	Mean	SD	Min	Max
Coruña					44.2	20.2	3.0	107.0	33.5	15.7	7.0	115.0
Albacete	15.7	8.4	2.0	81.0	88.0	29.8	9.0	185.0	46.0	19.4	5.7	190.6
Alicante	34.9	15.4	2.8	103.3	2.9	20.3	6.0	147.0				
Almería	40.5	14.0	3.0	94.2	73.6	20.8	0.0	149.0	42.1	17.0	9.0	158.0
Avila	37.6	16.2	1.3	143.1	72.5	28.6	4.0	171.0				
Badajoz	11.5	7.4	2.0	60.8	89.3	24.5	14.0	162.0	18.4	10.9	3.0	126.0
Barcelona	44.1	19.4	1.4	155.8	42.7	23.6	1.0	119.0				
Bilbao	37.5	15.0	0.7	120.8	54.0	23.2	2.0	156.0	34.5	17.2	5.8	138.0
Burgos	32.2	15.0	1.0	124.0	73.8	26.4	6.0	167.0	30.1	12.0	2.0	106.7
Caceres	12.0	7.7	1.5	57.0	89.8	32.1	2.0	198.0	19.0	9.7	1.0	83.5
Cadiz					82.3	21.3	19.0	175.0				
Castellón	20.8	9.9	4.0	78.2	75.4	23.3	6.0	152.3				
Ciudad Real	12.8	8.6	2.0	50.0	84.3	23.7	15.0	148.0				
Cordoba	35.4	15.1	2.2	121.4	75.9	32.5	4.5	187.5	47.6	23.4	6.5	387.1
Cuenca	21.9	10.5	3.0	66.0	73.7	27.5	3.0	134.0	30.9	16.7	6.0	139.0
Granada	45.0	17.9	7.1	144.3	72.9	31.0	7.0	155.0	42.6	21.7	8.0	338.6
Guadalajara	27.3	14.9	2.0	95.7	84.3	35.9	2.0	192.0	29.6	17.8	3.0	247.3
Huelva	20.1	8.4	4.0	69.1	80.7	26.1	11.0	184.0	32.7	15.1	6.0	233.0
Jaén	29.7	14.5	4.6	112.3	86.4	29.4	7.0	173.0	40.3	23.2	5.0	446.1
Las Palmas	29.5	10.9	6.5	73.1	33.4	17.5	4.0	128.0	41.0/15.2	39.4/13.2	3.0/1.0	795.0/242.0
León	37.1	17.6	2.1	128.0	53.6	26.9	2.0	160.0	39.1	16.3	3.0	135.5
Logroño	15.3	9.1	1.0	51.0	71.0	28.9	4.0	175.0	30.3	15.9	2.8	131.0
Lleida	25.6	12.9	1.0	108.6	65.2	31.7	2.0	154.0				
Madrid	59.4	17.9	17.6	142.0	35.7	18.1	3.7	89.4	32.5/17.1	16.1/7.8	6.9/3.4	149.5/71.4
Malaga	36.5	15.9	3.5	95.1	77.1	23.4	5.5	148.5	32.0	17.7	4.0	331.0
Murcia	35.8	15.6	5.0	95.1	77.4	32.2	4.0	153.0	29.4	12.7	7.7	92.0
Ourense	35.5	15.3	10.0	108.0	53.1	26.2	1.0	129.0	21.8	13.9	3.0	104.0
Oviedo	45.0	14.7	9.0	105.3	59.3	23.0	11.0	149.5	48.2	22.7	7.6	137.0
Pamplona	27.7	16.1	2.0	117.5	63.7	27.1	2.0	158.0	32.5	15.0	2.0	161.0
P.Mallorca	43.0	18.3	1.2	158.0	56.7	19.8	10.0	146.0	28.6	12.7	1.0	297.0
Pontevedra	26.7	12.0	0.0	73.0	52.6	22.3	2.0	137.0				
Salamanca	25.0	11.5	1.0	88.5	72.5	28.2	1.0	168.0	31.4	14.9	6.0	129.2
Santander	41.3	15.0	6.0	150.1	61.4	25.3	2.0	171.0	33.3	13.9	4.7	118.0
S.C.Tenerife	25.9	15.5	3.0	98.0	69.3	20.2	11.0	163.0	54.8/13.6	52.2/15.1	17.5/1.0	919.0/290.8
Segovia	46.4	16.6	6.0	130.6	69.8	27.9	6.0	172.0	40.4	25.0	1.4	152.2
Seville	47.7	16.7	9.0	139.7	58.0	24.4	4.0	129.0	40.1	17.0	6.0	202.0
Soria	28.7	12.0	1.0	114.0	66.0	23.9	1.0	143.0	29.5	13.7	1.0	132.0
S.Sebastián	38.8	13.2	2.6	123.0	47.1	20.6	1.0	124.0	29.7	14.3	6.0	135.0
Tarragona	24.0	10.4	1.5	68.4	75.6	26.9	2.0	162.0				
Teruel					85.2	26.1	10.0	167.0				
Toledo	25.6	12.9	2.0	129.8	83.9	34.7	2.0	188.0	39.6	19.3	2.0	206.7
Valencia	54.4	20.2	5.0	129.4	47.3	20.6	3.0	118.0	30.8	13.1	4.0	111.7
Valladolid	38.1	15.1	0.1	149.0	64.3	30.4	2.0	168.0	15.3	9.4	1.0	130.4
Vitoria	34.7	14.4	5.3	118.8	60.9	23.1	1.5	148.0	27.1	16.6	4.0	149.0
Zamora	42.4	14.8	6.0	132.3	64.7	25.9	5.0	161.0	31.2	11.7	7.7	92.3
Zaragoza	47.2	17.1	10.0	107.4	39.4	24.2	1.0	129.0	37.8	20.4	1.0	205.5

explanatory variables and gradually eliminating those which individually displayed least statistical significance, with the process being reiterated until all the variables included were significant at $p < 0.05$. The RRs were calculated for mortality due to natural and specific causes (circulatory and respiratory) for each province. The increases in the RRs and ARs were calculated for every 10 μg/m^3 rise in PM concentrations. The RRs for each provincial capital yielded by Poisson regression models were combined by means of a meta-analysis of random effects, which incorporated an estimate of inter-study variability (heterogeneity) in the weighting (Sterne, 2009), thereby obtaining a measure of the RR (95% CI) at both a regional (Autonomous Region)and national level.

2.4. Determination of the impact on mortality attributable to PM

To ascertain the impact of PM on mortality, we followed the already published methodology (Tobías et al., 2015), based on the fact that the previously calculated AR value represents the percentage increase in daily mortality for every 10 μg/m^3 rise in PM concentrations. The percentage increase in daily mortality associated with a given concentration of particles is thus obtained by multiplying it by this AR and dividing by 10. To pass from the percentage increase in mortality to the number of daily deaths attributable to this same PM concentration, one only has to multiply this percentage increase in mortality by the number of daily deaths and divide by one hundred. In this way, the mortality associated with this PM concentration in a given town/city can be calculated for each day.

To date, it has been assumed that there is no safety threshold in the effect of PM, i.e., that any increase in PM concentrations is associated with a linear increase in mortality. If one accepts the WHO threshold considered is IT-2 (24 h PM_{10} mean of 50 μg/m^3) (WHO, 2006) and assumes that there are no health effects below it, it is then only necessary to consider the excess in PM concentrations above 50 μg/m^3 and repeat the previous calculations using PM exceedances above 50 μg/m^3. In this study, we calculated the impact of PM on mortality in both cases, with and without the WHO threshold.

The software programmes used were IBM SPSS Statistics 22 and STATA v 14.1.

3. Results

Table 1 shows the descriptive statistics of the NO_2, O_3 and PM_{10} levels for each provincial capital across the period 2000–2009 and the descriptive statistics for the cities of Madrid, Santa Cruz de Tenerife and Las Palmas de Gran Canaria, in which $PM_{2.5}$ levels were available for the study period. As can be seen, in some towns/cities there were no measures for one or more pollutants. In such cases, the column corresponding to the pollutant was left blank and the pollutant was not taken into account for analysis purposes. Of the whole 52 provinces considered, there are no data of PM_{10} or the data series were not enough complete to be considered in the analysis in 16 cities. So, the study has been realized only in 36 cities (see Supplementary Fig. S1).

Table 2 shows the percentage of days on which the WHO threshold (WHO, 2006) for mean daily concentrations of PM_{10} and $PM_{2.5}$ was exceeded. Note should be taken of the high exceedance values in the cities of Oviedo and Cordoba. With regard to the 3 centres for which there were $PM_{2.5}$ values, in the Canary Island cities of Las Palmas de Gran Canaria and Santa Cruz de Tenerife the percentage exceedance of PM_{10} values was higher than that of $PM_{2.5}$, whereas in Madrid, it was the $PM_{2.5}$ exceedances that were slightly higher than those of PM_{10}.

The descriptive statistics corresponding to daily mortality in each Spanish province are those shown in Table 3. It should be noted that in the case of Madrid, the data refer solely to the Madrid metropolitan area.

Table 2
Percentage exceedance of the WHO threshold for PM_{10} (24 h mean of 50 μg/m^3) and $PM_{2.5}$ concentrations (24 h mean of 25 μg/m^3). **Only showed cities with valid values in PM concentrations**.

Town/City	% Days of exceedance of the WHO limit. PM_{10}	% Days of exceedance of the WHO limit. $PM_{2.5}$
Coruña	12.3%	
Albacete	35.8%	
Almería	25.8%	
Badajoz	1.2%	
Bilbao	17.1%	
Burgos	5.8%	
Cáceres	1.1%	
Córdoba	40.0%	
Cuenca	10.2%	
Granada	29.0%	
Guadalajara	10.7%	
Huelva	10.9%	
Jaén	25.0%	
León	20.9%	
Logroño	10.8%	
Madrid	13.5%	14.9%
Málaga	11.8%	
Murcia	6.3%	
Pamplona	11.3%	
Pontevedra		
Ourense	3.7%	
Oviedo	44.4%	
Palma Mallorca	3.9%	
Las Palmas	16.7%	7.9%
Salamanca	12.2%	
Sta. Cruz Ten	32.3%	7.2%
San Sebastián	8,3%	
Santander	11.9%	
Segovia	31.5%	
Sevilla	23.0%	
Soria	6.0%	
Toledo	23.3%	
Valencia	7.3%	
Valladolid	0.9%	
Vitoria	9%	
Zamora	7.3%	
Zaragoza	22.5%	

The functional relationship between daily mortality and daily PM_{10} concentrations was linear and the baseline threshold is the lower value of PM_{10} registered and showed in Table 1 for each capital province.

Table 4 shows that the main result found between PM_{10} concentrations and mortality in Spain, is that only 16 provinces of a total of 36 showed statically significant associations. This table also shows the lags or lags at which the statistically significant associations were established between PM_{10} concentrations and mortality due to the different causes analysed across the study period. Furthermore, the second column lists the control pollutants that also proved statistically significant in the modelling process, along with their corresponding lags. It will be seen that in most cases, the effect of PM_{10} concentrations on mortality was very short term (lags 0 and 1); and that in just a few cities, in addition to this immediate effect, there was another effect at lags 4 and 5. Analysis by specific cause of death showed that, as a general rule, the effect on circulatory-cause mortality occurred earlier than that had on respiratory causes.

The relative risks obtained by Poisson modelling for mortality due to natural, respiratory and circulatory causes are shown in Figs. 1–3, where, in addition to the RRs for each city, the results of the meta-analysis are shown for the individual Autonomous

Table 3
Descriptive statistics of mortality due to natural, respiratory and circulatory causes, by town: Spain, 2000–2009. *Daily mortality only in metropolitan Madrid.

Town/City	Natural-cause mortality				Respiratory-cause Mortality				Circulatory-cause mortality			
	Mean	SD	Min	Max	Mean	SD	Min	Max	Mean	SD	Min	Max
Coruña	31	7	12	59	4	2	0	15	11	4	1	29
Albacete	9	3	1	22	1	1	0	9	3	2	0	12
Alicante	35	8	13	72	4	2	0	15	13	4	2	32
Almería	11	4	1	29	1	1	0	8	4	2	0	12
Ávila	5	2	0	15	1	1	0	6	2	1	0	8
Badajoz	17	5	3	38	2	2	0	10	6	3	0	20
Barcelona	115	20	62	230	12	6	2	49	37	9	15	84
Bilbao	28	6	8	60	3	2	0	17	9	3	1	27
Burgos	9	3	0	24	1	1	0	7	3	2	0	11
Cáceres	10	4	1	26	1	1	0	8	3	2	0	17
Cádiz	23	6	7	48	2	2	0	13	8	3	0	22
Castellón	12	4	3	28	1	1	0	7	5	2	0	15
Ceuta	2	1	0	6	0.2	0.4	0	4	0.5	0.6	0	4
Ciudad Real	13	4	1	32	2	1	0	14	4	2	0	14
Córdoba	19	5	2	49	2	2	0	14	7	3	0	20
Cuenca	5	2	0	14	1	1	0	5	2	1	0	8
Gerona	14	4	3	35	1	1	0	11	5	2	0	15
Granada	20	5	6	48	2	2	0	12	7	3	0	23
Guadalajara	4	2	0	15	1	1	0	5	2	1	0	8
Huelva	11	4	1	28	1	1	0	8	4	2	0	15
Huesca	6	2	0	15	0.6	0.8	0	6	2	1	0	9
Jaen	15	5	2	46	2	2	0	15	5	3	0	17
Las Palmas	16	5	2	35	2	1	0	8	6	3	0	19
León	14	4	3	34	2	2	0	10	5	2	0	15
Logroño	7	3	0	19	1	1	0	6	2	2	0	10
Lleida	10	4	1	29	1	1	0	9	4	2	0	14
Lugo	12	4	1	33	2	1	0	9	5	2	0	19
Madrid*	60	11	32	109	9	4	0	32	18	5	4	40
Malaga	30	7	9	58	3	2	0	14	12	4	0	30
Melilla	2	1	0	7	0.1	0.4	0	3	0.5	0.7	0	4
Murcia	26	6	9	56	3	2	0	16	9	3	1	22
Ourense	12	4	1	28	2	1	0	9	4	2	0	16
Oviedo	33	7	15	63	4	2	0	21	12	4	1	29
Palencia	5	2	0	16	0.5	0.8	0	7	2	1	0	8
Pamplona	13	4	3	31	2	1	0	12	4	2	0	15
P. Mallorca	20	5	6	41	2	2	0	10	8	3	0	21
Pontevedra	21	5	6	45	3	2	0	14	7	3	0	20
Salamanca	10	3	1	26	1	1	0	9	4	2	0	12
Santander	14	4	3	38	2	2	0	12	5	2	0	14
S.C.Tenerife	17	5	4	38	2	1	0	9	6	3	0	16
Segovia	4	2	0	12	0	1	0	4	1	1	0	8
Seville	38	9	14	81	4	2	0	16	16	5	3	40
Soria	3	2	0	12	0	1	0	6	1	1	0	6
S.Sebastián	16	5	4	36	2	2	0	14	5	2	0	16
Tarragona	16	4	4	39	2	1	0	9	5	2	0	17
Teruel	4	2	0	13	0	1	0	5	1	1	0	7
Toledo	14	4	1	34	2	1	0	12	5	2	0	17
Valencia	57	11	30	114	7	3	0	26	20	6	4	47
Valladolid	12	4	2	29	1	1	0	10	4	2	0	14
Vitoria	6	3	0	16	1	1	0	7	2	1	0	10
Zamora	6	3	0	19	1	1	0	6	2	1	0	9
Zaragoza	24	6	7	54	3	2	0	14	8	3	0	21

Regions and for Spain as a whole. At a qualitative level, NO_2 was the pollutant associated with all-cause mortality in the highest number of towns/cities (17), as compared to PM_{10} (14 towns/cities); it seems to mean that PM is not the main pollutant associated with mortality, and O_3 (13 towns/cities). This finding was reinforced on analysing circulatory causes (NO_2: 17 towns/cities; PM_{10}: 9 towns/cities; and O_3: 14 towns/cities). It was ozone concentrations which displayed the highest number of associations in respiratory-cause mortality (NO_2: 11 towns/cities; PM_{10}: 9 towns/cities; and O_3: 14 towns/cities). Quantitatively, the RRs associated with PM_{10} for natural-cause (RR: 1.009; CI95% (1.006 1.011))- and circulatory-cause (RR: 1.009; CI95% (1.006 1.012)) mortality at a national level were similar, whereas the RR for PM_{10}-related respiratory-cause mortality (RR:1.026; CI95% (1.019 1.033)) was higher than that for the other causes analysed, with this difference being statistically significant.

The RRs associated with increases of 10 $\mu g/m^3$ in $PM_{2.5}$ concentrations for the city of Madrid were: 1.010 (95% CI: 1.002 1018) for natural-cause mortality at lag 2; 1.032 (95% CI: 1.013 1.051) for respiratory-cause mortality at lag 4: and 1.024 (95% CI: 1.010 1037) for circulatory causes at lag 1.

For the city of Santa Cruz de Tenerife, the RRs corresponding to $PM_{2.5}$ concentrations were: 1.014 (95% CI: 1.009 1020) for natural causes at lags 0 and 2, and 1.013 (95% CI: 1.005 1022) for circulatory causes at lag zero, with no association being established between respiratory-cause mortality and $PM_{2.5}$ concentrations. In Las Palmas de Gran Canaria, no statistically significant association was obtained between $PM_{2.5}$ concentrations and daily mortality for any of the causes analysed.

Table 5 shows the mortality attributable to PM_{10} concentrations

Table 4
Lags (days) at which the statistically significant associations between PM_{10} concentrations and mortality due to the different causes analysed were established. The second column shows the control pollutants that also proved significant in the modelling (lags shown in brackets). **Only showed cities with valid statistically significant associations ($p < 0.05$) between air pollutants and mortality.**

Town/City	Natural Causes	Respiratory Causes	Circulatory Causes	Control pollutants (lag)
	Lags with association with PM_{10} ($p < 0.05$)			
Albacete	1			O_{3h}(5)
Alicante				NO_2(2)
Almería				NO_2(1,5)
Burgos				NO_2(1)
Cádiz				O_{3h}(1,6)
Córdoba	1	1		NO_2(5); O_{3h}(1)
Granada				NO_2 (2)
Guadalajara	0; 4	4		
Huelva				NO_2(2); O_{3h}(0,5)
Jaén				NO_2(1); O_{3h}(0)
León	0			
Logroño				NO_2(2); O_{3h}(2)
Madrid	0	1; 4	1	NO_2(1)
Oviedo	2		0	NO_2(5); O_{3h}(1)
Pamplona	2		0	NO_2(4); O_{3h}(0,5)
Pontevedra				NO_2(4)
Salamanca	1		1	O_{3h}(8)
Santander	1	1; 5	4	
Segovia				NO_2(0); O_{3h}(8)
Sevilla		0		NO_2(1)
S. Sebastián	0; 5	2; 5	2	NO_2(2); O_{3h}(0,2,8)
Toledo	1	3	2	O_{3h}(1)
Valencia	0		0	
Valladolid				NO_2(1); O_{3h}(6)
Vitoria	0			
Zamora		3		NO_2(3)
Zaragoza	0			

across the 10-year period analysed for each of the towns/cities in which statistically significant associations were established. This attributable mortality, as indicated under the Methods section, was calculated in two cases: firstly, assuming that there was no safety threshold and, thus, any increase in PM concentrations would be associated with an increase in daily mortality; and secondly, assuming that no effect below the WHO safety threshold would be considered, i.e., mortality would only occur, if the 24-h mean of 50 μg/m^3 was exceeded.

As can be seen, it was in the cities of San Sebastian and Oviedo where natural-cause mortality attributable to PM_{10} was greatest. In Spain as a whole, mortality attributable to PM_{10} accounted for 2683 deaths annually (95% CI: 852 4354); of these, 651 (95% CI: 358 1026) were due to respiratory causes and 556 (95% CI: 116 1012) due to circulatory causes. If PM_{10} only had an effect on mortality above the WHO threshold, it would be reduced to one tenth; that is to say, 90% of mortality associated with PM_{10} concentrations occurs below the WHO guideline values.

4. Discussion

According to European Environmental Agency (EEA) data (EEA, 2014), Spain ranks seventh among the countries least polluted by PM_{10}. The EEA report, which groups 28 Member States, reports that the WHO guideline values were exceeded at 66% of monitoring stations: in the case of Spain, as can be seen in Table 2, the percentage of exceedance was clearly lower.

As a general rule, with the exception of the city of Oviedo, it can be said that the highest percentage exceedance of WHO thresholds occurs in towns/cities in the south and centre of Spain, coinciding with the regions where most Saharan dust advections occur. These advections are an important source of PM of natural origin in this country (Querol et al., 2009). Accordingly, in the south-western, south-eastern and central regions of Spain, Saharan dust advections occur on 25.3%, 30.3% and 18% of days respectively, values much higher than those registered for the north-west, north and north-east, with Saharan dust advections on 9.6%, 10.0% and 15.8% of days respectively During Sahara dust intrusions the mean concentration of PM_{10} in Spain is equal to 46.2 μg/m^3, meanwhile in days without such advections are 31.5 μg/m^3. So, the main source of PM_{10} is anthropic, but when advections of natural source occur, the increments in total concentrations are statically significant (Díaz et al., 2017).

For the Canary Island cities of Las Palmas and Santa Cruz de Tenerife, in which $PM_{2.5}$ concentrations are monitored, exceedances of WHO PM_{10} thresholds are greater than those due to $PM_{2.5}$. This characteristic is unique to the Canary Islands because the same is not applicable to the city of Madrid (for which $PM_{2.5}$ data are also available), possibly due to the fact that diesel vehicle road traffic there is far greater than that found in these two Canary Island towns and constitutes the principal emission source of $PM_{2.5}$ in Spain's capital city (Querol et al., 2012). So, the main source of $PM_{2.5}$ in Madrid is mainly anthropogenic (diesel vehicles) meanwhile, in Canary Island towns, PM_{10} is mainly from natural sources.

The functional relationship between PM_{10} concentrations and natural-cause mortality is linear and the baseline threshold is the lower value of PM_{10} registered and showed in Table 1 for each capital province. In other words, any increase in PM_{10} concentrations is associated with an increase in daily mortality, which justifies the fact that in the modelling process both this variable and $PM_{2.5}$ are introduced without the need for parameterisation. From the standpoint of the impact of PM_{10} on mortality, these results question the appropriateness of the WHO guideline values (Linares et al., 2009). This same linear relationship without threshold has been reported in numerous multi-city studies undertaken in recent years (Dominici et al., 2007; Katsouyanni et al., 2009; Samoli et al., 2005) and more recently in those conducted under the European MED-PARTICLES Project (Samoli et al., 2013). Studies conducted in

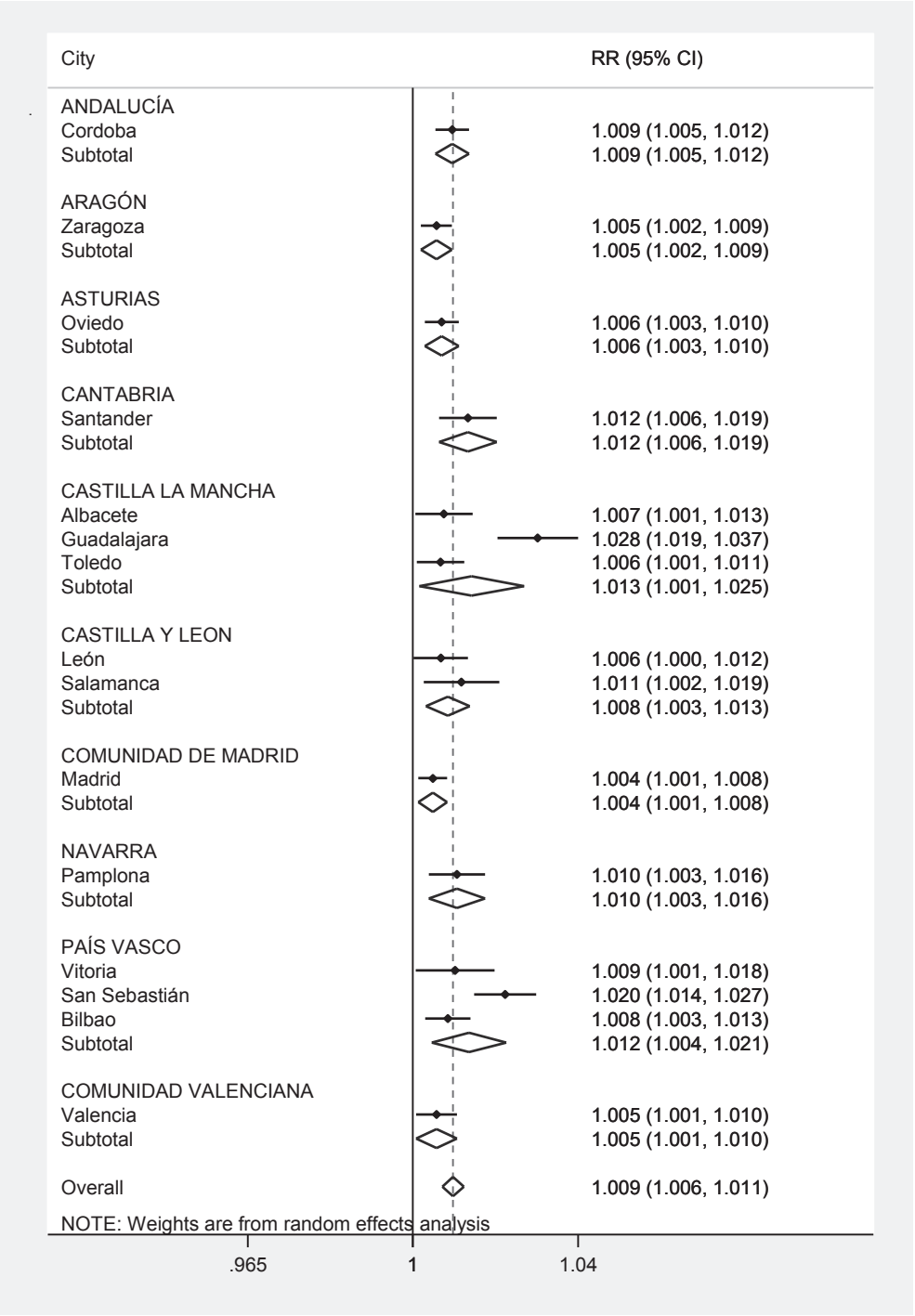

Fig. 1. Relative Risks (RR) calculated for increases of 10 μg/m^3 in PM_{10} levels due to natural causes mortality. **Only showed cities with valid statistically significant associations ($p < 0.05$) between PM and natural mortality causes**.

the USA also support the use of these types of linear relationships, without a threshold between mortality and PM concentrations (Pope et al., 2009).

The results in Table 4 indicate first, that the effect of PM on mortality is found only in 15 provinces of a total of 52. Authors think that this fact is caused mainly by 3 reasons:

1. First, there are no data of PM_{10} or the data series were not enough complete along the time period to be considered in the analysis.
2. The second reason can be that there is an association between PM and mortality but it has not reached the statically significant of $p < 0.05$.
3. Third, in the main cities of Spain (capital provinces), PM_{10} and NO_2 were originated mainly by traffic road (Querol et al., 2012). There is a collinear effect between the two pollutants (Díaz et al., 1999; Maté et al., 2010; Guaita et al., 2011). As we used as air pollution control variable in the models NO_2 concentrations, the effect of the other primary air pollutant considerate in the

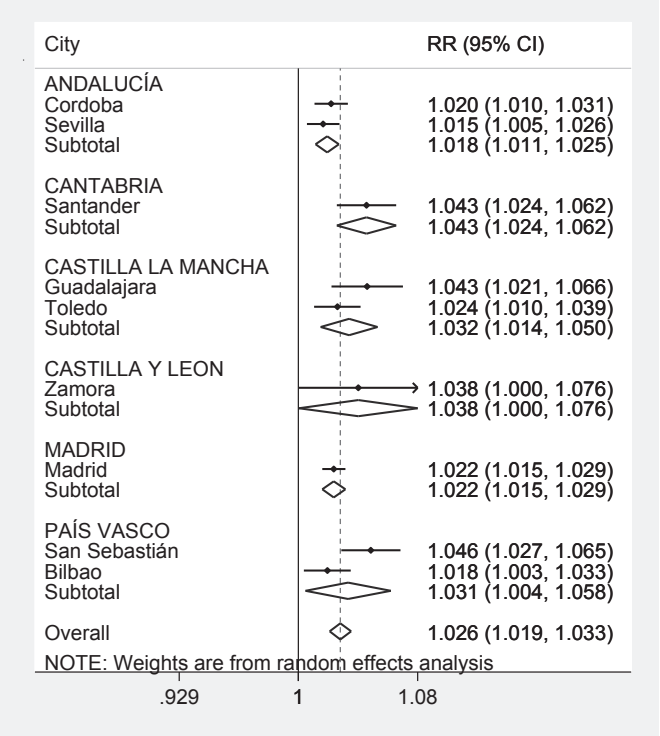

Fig. 2. Relative Risks (RR) calculated for increases of 10 μg/m^3 in PM_{10} levels due to respiratory causes mortality. **Only showed cities with valid statistically significant associations ($p < 0.05$) between PM and respiratory mortality causes**.

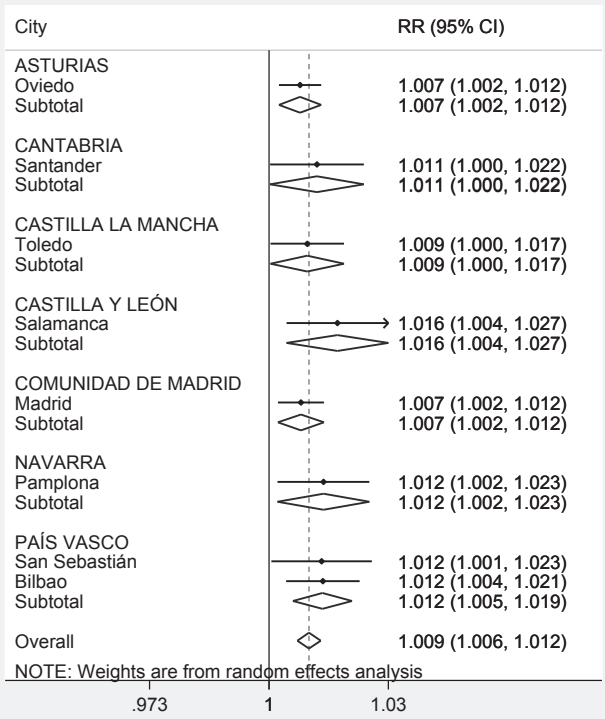

Fig. 3. Relative Risks (RR) calculated for increases of 10 μg/m^3 in PM_{10} levels due to circulatory causes mortality. **Only showed cities with valid statistically significant associations ($p < 0.05$) between PM and circulatory mortality causes**.

analysis, can be higher depending on the capital considered. This fact can be observed in the second column of Table 4.

Another finding observed in Table 4 is that the effect of NO_2 on mortality is to be seen in a higher number of towns/cities than that of PM. Furthermore, this effect is generally at later lags. This common source is what accounts for fact that there is a high collinearity between these two primary pollutants with a very high correlation (Díaz et al., 1999; Maté et al., 2010; Guaita et al., 2011), and that in the modelling process it is either PM or NO_2 concentrations which are significant but never both at the same lag. However, the effects of NO_2 on mortality tend to be more lagged than those of PM (Díaz et al., 1999), which would explain the lags at which the observed associations are established with the different causes of mortality.

Furthermore, non-compliance levels with WHO guideline values in Spain are higher for NO_2 than for PM10 (EEA, 2014), i.e., NO2 pollution levels in Spain are higher than those of PM if the WHO guideline levels are taken as reference, which would explain the former's greater effect on mortality.

Ozone, being a secondary pollutant whose precursor is (among others) NO_2, has a negative correlation with the latter (Díaz et al., 1999; Maté et al., 2010; Guaita et al., 2011) and thus also with PM. The lags at which the associations are established are in line with those observed by other studies (Díaz et al., 1999; Maté et al., 2010; Guaita et al., 2011).

The effect of PM_{10} on natural-cause mortality is manifested at two points in time, one immediate (lags 0 and 1) and the other at lags 4 and 5. Generally, the effect of PM_{10} at lags 0 and 1 would be related to circulatory-cause mortality whereas the more lagged effect would be due to respiratory causes. The biological mechanisms implicated in mortality due to circulatory causes and related diseases, cause mortality more immediately (Maté et al., 2010). The presence of PM in pulmonary alveoli induces a local inflammatory process, which, coupled with an increase in oxidative stress, has systemic repercussions, through the release into the blood stream of inflammatory mediators (Peters et al., 2001; Danesh et al., 1998; Utell et al., 2002) and pro-thrombotic factors and platelets (Schwartz, 2001; Ghio et al., 2003; Zeka et al., 2006), thereby also causing a reduction in platelet stability. The result of these processes (pro-inflammatory and pro-thrombotic) is twofold: among patients with atheromatous plaques there is a risk, which may be more or less acute, of peripheral thrombosis, both arterial (including coronary arteries) and venous, with the additional possibility of erosion and even fragmentation of the atheromatous plaque (Nemmar et al., 2002; Zeller et al., 2006). The biological processes implicated in respiratory-cause mortality are not as clear, and the associated diseases appear at a later point in time (Guaita et al., 2011). The biological mechanisms indicate that PM concentrations cause oxidative stress reactions in the interior of alveolar epithelial cells (Xia et al., 2006), triggering an immediate inflammatory response, which is responsible for the exacerbation of episodes of asthma, chronic obstructive pulmonary disease (COPD) and respiratory failure. On the other hand, these same particles are also able to depress pulmonary defence mechanisms through the production of defence-immunoglobulin-specific antigens (Zanobetti et al., 2000; Svendsen et al., 2007). This state of "immunodepression" causes an increase in the incidence of upper and lower tract respiratory infections (pneumonias, bronchitis).

From a quantitative point of view, the magnitude of the RRs found in this study, is very similar to that reported by more recent studies undertaken in Europe under the MED-PARTICLES Project (Samoli et al., 2013). In our analysis, the ARs for Spain as a whole for increases of 10 μg/m^3 in PM_{10} concentrations were 0.89% (95% CI: 0.59, 1.09) for natural-cause mortality (Fig. 1), 2.53% (95% CI: 1.86 3.19) for respiratory-cause mortality (Fig. 2), and 0.89% (95% CI:

Table 5
Natural-, respiratory- and circulatory-cause mortality attributable to PM_{10} and $PM_{2.5}$ concentrations by provincial capital and for Spain as a whole, across the study period, 2000–2009, with and without considering the WHO guideline values at a national level. *(PM_{10} limit value = 50 μg/m^3; $PM_{2.5}$ limit value = 25 μg/m^3). **Only showed cities with valid statistically significant associations ($p < 0.05$) between PM and natural, respiratory and circulatory mortality causes**.

Town/City		Attributable mortality without WHO threshold*	95% CI Attributable mortality without WHO threshold*	Attributable mortality with WHO threshold*	95% CI Attributable mortality with WHO threshold*
Spain		26,830	(8525–43,538)	2292	(882–3820)
Natural	Albacete	975	(79–1864)	119	(10–278)
Causes	Bilbao	1551	(553–2544)	107	(43–267)
	Córdoba	2790	(1608–3967)	469	(270–667)
	Guadalajara	1328	(905–1748)	84	(57–111)
	León	1247	(37–2449)	96	(3–189)
	Madrid PM_{10}	2798	(771–4818)	155	(43–267)
	Madrid $PM_{2.5}$	2281	(489–4060)	17	(4–31)
	Oviedo	2963	(1221–4699)	541	(223–858)
	Pamplona	1523	(550–2489)	74	(27–121)
	Salamanca	1244	(278–2202)	50	(11–88)
	Santander	2116	(417–3304)	92	(18–143)
	San Sebastián	3110	(2074–4138)	134	(89–178)
	Sta. Cruz Tenerife $PM_{2.5}$	1065	(654–1473)	114	(78–158)
	Toledo	1109	(158–2055)	106	(15–196)
	Valencia	1858	(252–3457)	50	(7–93)
	Vitoria	488	(32–940)	29	(2–55)
	Zaragoza	1729	(590–2864)	186	(64–309)
Spain		6509	(3581–10,256)	499	(266–781)
Respiratory	Bilbao	362	(69–651)	26	(5–47)
Causes	Córdoba	835	(412–1253)	145	(72–218)
	Guadalajara	272	(132–410)	21	(10–32)
	MadridPM_{10}	1720	(1460–2845)	100	(85–166)
	Madrid $PM_{2.5}$	1117	(465–1578)	9	(4–14)
	Santander	963	(548–1371)	48	(27–68)
	Sevilla	785	(271–1292)	61	(21–100)
	San Sebastián	774	(462–1080)	39	(23–54)
	Toledo	551	(224–872)	54	(22–85)
	Zamora	247	(3–482)	5	(1–11)
Spain		5558	(1159–10,123)	472	(116–827)
Circulatory	Bilbao	777	(249–1300)	53	(17–88)
Causes	Madrid	717	(203–1231)	42	(12–72)
	Oviedo	1173	(380–1962)	218	(71–365)
	Pamplona	626	(98–1149)	29	(5–549
	Salamanca	635	(165–1100)	26	(7–45)
	Santander	619	(15–1217)	28	(1–55)
	San Sebastián	562	(26–1091)	24	(1–46)
	Sta Cruz Tenerife $PM_{2.5}$	342	(129–553)	41	(16–67)
	Toledo	449	(23–1073)	52	(2–102)

0.59 1.19) for circulatory-cause mortality (Fig. 3). In the MED-PARTICLES Project the ARs, in the models adjusted for O_3, were 0.46% (95% CI: 0.16 0.76) for natural causes, 2.54% (95% CI: 0.94 3.97) for respiratory causes, and 0.94% (95% CI: 0.16 1.73) for circulatory causes. Perhaps, the greatest difference between both studies is to be seen in the ARs associated with natural-cause mortality, though this difference is not statistically significant. This may be due to the fact that the PM indicator in our study was PM_{10}, whereas in MED-PARTICLES it was $PM_{2.5}$, and the effect on natural-cause mortality due to PM_{10} is less than that found for $PM_{2.5}$ in this European study (Samoli et al., 2013).

On the other hand, an acknowledged limitation of all studies of ambient data is that measurements from stationary outdoors monitors may not represent individual exposure, although relatively crude, ambient measures are often the most feasible measure of exposure in terms of cost and burden to the study participant (Samet et al., 2000). No specific validation was done within the project to assess representativeness of spatial variability in air pollutants our study suffered from Berkson-type measurement error, between others bias associated to an ecological exposure, as is common in most time-series studies of air pollution, which leads to no or little bias but decreases statistically power.

The estimated annual natural-cause mortality attributable to PM pollution for Spain as a whole amounts to 2683 deaths (95% CI: 852 4354), a figure lower than that established by the WHO, i.e., 6860 deaths (95% CI: 1210 11,062), though the difference is not statistically significant.

There may be three reasons for this difference; on the one hand, in the WHO report there was no control for other variables such as temperature, which have a clear effect on daily mortality, particularly in the summer months (Díaz et al., 2015); and secondly, there was no adjustment for NO_2 which, by virtue of its collinearity with PM is of special importance, as explained above. Furthermore, the WHO report (WHO, 2016) uses global dose-response functions, not calculated specifically for these provinces or even for the country. In our analysis, the dose-response functions were calculated for each province. Furthermore, the mortality calculated by the WHO also includes long-term effects of PM, something that is not present in our estimate. Moreover, our analysis is done for each capital city and only there are statically significant results for 15 cities.

The only recent study on the effect of PM on mortality in Spain was the SERCA Project (Boldo et al., 2011). This study, which was based on emission levels modelled for the calculation of immission rather than on measured values (Lumbreras et al., 2012), and which, moreover, used dose-response functions calculated for the USA rather than Spain (Pope et al., 2002; Laden et al., 2006),

established that reductions of up to 4μg/m^3 in $PM_{2.5}$ concentrations could prevent around 1500 deaths annually. If one bears in mind that the mean PM_{10} value for Spain as a whole is 34.5 mg/m^3 and of this, 0.59 is $PM_{2.5}$ (Linares & Díaz 2009), one would be talking of an annual attributable mortality of 7500 deaths. Although this figure is similar to that of the WHO, it is nevertheless subject to an important degree of bias because, apart from the failure to use dose-response functions calculated *ad hoc,* it is based on simulated instead of measured values. Furthermore, in our study, mortality attributable to PM corresponds to short-term effects, whereas in the SERCA project short- and long-term effects were combined in the dose-response functions used.

With respect to the $PM_{2.5}$–related mortality values shown in Table 5, it should be noted that these values are very similar to those obtained in the latest evaluation of the impact of $PM_{2.5}$ on mortality in Madrid (Tobías et al., 2015), despite the fact that in this latter study control was also made for traffic noise.

From analysis of Table 5, it is clear that 90% of mortality attributable to PM is below the guideline values considered "safe by the WHO", so that these guidelines values should be revised downwards. This fact is even clearer in relation to the WHO values for $PM_{2.5.}$.

5. Conclusions

By virtue of the number of towns/cities involved and the nature of the analysis performed, this study, with its calculation of RRs and ARs for each Spanish province, controlling for other confounding variables, can be viewed as a reliable, updated estimate of the short-term impact of PM on mortality in Spain. The magnitude of annual PM-related mortality calls for urgent implementation by public administrations of measures designed to reduce PM concentrations of anthropic origin in towns/cities where the principal emission source is road traffic.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.envpol.2017.02.037.

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