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An approach estimating the short-term effect of NO_2 on daily mortality in Spanish cities

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ABSTRACT

Background: Road traffic is the most significant source of urban air pollution. $PM_{2.5}$ is the air pollutant whose health effects have been most closely studied, and is the variable most commonly used as a proxy indicator of exposure to air pollution, whereas evidence on NO_2 concentrations per se is still under study. In the case of Spain, there are no specific updated studies which calculate short-term NO_2-related mortality.

Objective: To quantify the relative risks (RRs) and attributable risks (ARs) of daily mortality associated with NO_2 concentrations recorded in Spain across the study period, 2000–2009; and to calculate the number of NO_2-related deaths.

Material and methods: We calculated daily mortality due to natural causes (ICD-10: A00 R99), circulatory causes (ICD-10: I00 I99) and respiratory causes (ICD-10: J00 J99) for each province across the period 2000–2009, using data supplied by the National Statistics Institute. Mean daily NO_2 concentrations in μg/m^3 for each provincial capital were furnished by the Ministry of Agriculture & Environment, along with the equivalent figures for the control pollutants (PM_{10}). To estimate RRs and ARs, we used generalised linear models with a Poisson link, controlling for maximum and minimum daily temperature, trend of the series, seasonalities, and the autoregressive nature of the series. A meta-analysis with random effects was used to estimate RRs and ARs nationwide.

Results: The overall RRs obtained for Spain, corresponding to increases of 10 μg/m^3 in NO_2 concentrations were 1.012 (95% CI: 1.010 1.014) for natural-cause mortality, 1.028 (95% CI: 1.019 1.037) for respiratory-cause mortality, and 1.016 (95% CI: 1.012 1.021) for circulatory-cause mortality. This amounted to an annual overall 6085 deaths (95% CI: 3288 9427) due to natural causes, 1031 (95% CI: 466 1585) due to respiratory causes, and 1978 (95% CI: 828 3197) due to circulatory causes.

Conclusion: By virtue of the number of cities involved and the nature of the analysis performed, with quantification of the RRs and ARs of the short-term impact of NO_2 on daily mortality in Spain, 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 at a national level.

1. Introduction

Ambient air pollution was a leading risk factor for the global disease burden in 2015, and its contribution remained relatively stable from 1990 to 2015 (GBD, 2015). The US Environmental Protection Agency, the World Health Organisation (WHO), and a number of literature reviews have shown that long- and short-term exposure to ambient air pollution increases mortality and morbidity due to cardiovascular diseases, respiratory diseases and lung cancer, and shortens life expectancy (Cohen et al., 2017). Motor vehicles are the most significant source of urban air pollution. $PM_{2.5}$ is the air pollutant whose health effects have been most closely studied (Basagaña et al., 2015), and is the variable most commonly used as a proxy indicator of exposure to air pollution, whereas evidence on NO_2 concentrations is still under study. There are several reasons for this but; in essence, it is more difficult to judge the independent effects of NO_2 in studies because, in such research, the correlations between concentrations of NO_2 and other pollutants are often high, so that NO_2 might actually be representing a mix of traffic-related air pollutants.

At this point in time, this fact is particularly important in Europe, since NO_2 concentrations have not been decreasing at the same pace as PM emissions (probably reflecting the impact of the Euro 4 and 5

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vehicle standards on reducing diesel PM). This change in ratio has implications for the interpretation of NO_2 as a quantitative proxy for PM vehicle pollution, and highlights the need to understand the effects of NO_2 per se. Moreover, in Spain -the country which is the focus of this study- statutory and WHO guideline values are currently being complied with in the case of PM but not in that of NO_2 (*Informe de la Calidad del aire en España*, 2016/Report on Air Quality in Spain).

Time-series evidence on NO_2 has increased since the 2005 global update of the WHO Air Quality Guidelines (GBD, 2015). The studies, which were mainly conducted in the WHO Western Pacific Region (which includes China, Europe, the USA and Canada), for the most part used 24-hour average NO_2 concentrations measured at urban background locations. Overall, statistically significant, positive, short-term associations between NO_2 and all-cause and cause-specific mortality (REVIHAAP, 2014) were reported. The robustness of such short-term NO_2 associations to adjustment for particles and other pollutants has been shown by multicity studies undertaken in various geographic locations, including Europe (Katsouyanni et al., 1995; Stafoggia et al., 2013; Samoli et al., 2014).

In Spain, the Spanish Multicentre Study on the Relationship between Air Pollution and Mortality (*Estudio Multicéntrico Español sobre la Relación entre la Contaminación Atmosférica y la Mortalidad/EMECAM*) analysed data on atmospheric concentrations of black smoke, SO_2, NO_2, CO and O_3, temperature and other aspects in 14 Spanish cities, and reported the existence of an association between NO_2 and cardiovascular and all-cause mortality, though based on data from only 7 and 3 cities respectively (Saez et al., 2002). The studies undertaken to date in Spain linking NO_2 exposure to short-term mortality have been rendered obsolete by the fact that they were based on information which dated from the beginning of the 1990s and included only a few cities due to the lack of monitoring data, with no study having yet been conducted that includes all of the country's provinces. This study therefore set out to update the impact of daily mean NO_2 concentrations on population mortality at a national level (Ballester et al., 2005; Ballester et al., 2006).

Accordingly, our aim was: to analyse the short-term association between NO_2 concentrations and all-cause, circulatory-cause and respiratory-cause mortality in all Spanish provinces; and to update the impact and attributable mortality in the country as a whole.

2. Material and methods

2.1. Variables used in the study

We used daily mean NO_2 concentrations measured in $\mu g/m^3$ as the measure of mean population exposure to this pollutant. The readings, as supplied by the Ministry of Agriculture & Environment (*Ministerio de Agricultura, Alimentación y Medio Ambiente/MAGRAMA*), were taken across the period 2000–2009 at monitoring stations, which, according to available data, were validated mainly for urban traffic and were situated in each provincial capital. All the monitors used were of urban type and placed in the capital of the province. When there is more than one station, we calculated the mean of the total monitors. In case of lack of data in one monitor, the missing values were calculated through the rest of the monitors.

As the dependent variable, we used daily mortality due to natural (all causes except accidents) (International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10): A00-R99), circulatory (ICD-10: I00-I99) 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, and were not provincial in scope. These data were furnished by the National Statistics Institute (*Instituto Nacional de Estadística/INE*).

As control variables, we used different variables related to the designated study objective, namely:

- Daily mean PM_{10} concentrations ($\mu g/m^3$), measured at the same stations as those which obtained the NO_2 values, and likewise supplied by the *MAGRAMA*.
- Maximum temperatures (T_{max}) and maximum 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*).
- 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 (Carlos III Institute of Health).
- Trend of the series and annual, six-monthly, four-monthly and three-monthly seasonalities were taken into account, using the sine and cosine functions of the periods of 365, 180, 120 and 90 days respectively. In addition we also controlled for the autoregressive nature of the dependent variable.

2.2. Parametrisation and creation of new variables

To be properly introduced into impact calculation models, some variables need to be transformed in accordance with the relationship that they maintain with population mortality. For instance, 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 (effect of cold) and the right-hand side to the effect of high temperatures (effect of heat). This effect of temperature on mortality is exacerbated in episodes of heat and cold waves. The importance of heat and cold waves definition for calculating temperature impacts are clearly established (Kent et al., 2014).

Determination of the threshold temperatures ($T_{provincial\_threshold}$) used in the heat- and cold-wave definitions is different in each provincial capital and has recently been updated for each Spanish province in the case of heat (Díaz et al., 2015) and cold waves (Carmona et al., 2016). Bearing this in mind, the variable of maximum daily temperature was parametrised as follows, in order to take account of the effect of heat and cold waves across the study period.

Heat:

$T_{heat} = 0 \quad \text{if } T_{max} < T_{provincial\_threshold}$

$T_{heat} = T_{max} - T_{provincial\_threshold} \quad \text{if } T_{max} > T_{provincial\_threshold}$

Cold:

$T_{cold} = T_{provincial\_threshold} - T_{min} \quad \text{if } T_{min} < T_{provincial\_threshold}$

$T_{cold} = 0 \quad \text{if } T_{min} > T_{provincial\_threshold}$

Furthermore, previous studies indicate that in the case of daily mean NO_2 and PM_{10} concentrations, the functional relationship established with mortality is linear, thus rendering parameterisation unnecessary for their introduction into the models (Ortiz et al., 2017).

2.3. Lags

Many studies in historical reviews targeting air pollution and environmental variables show that the effect on short-term mortality may not be immediate, but may instead be lagged by as much as 5 days in the case of NO_2 and PM_{10}(Díaz et al., 1999; Ortiz et al., 2017). In the case of temperature, the lagged effect on mortality can be up to 4 days for heat waves (Díaz et al., 2015) and until lag 13 for cold waves (Carmona et al., 2016). The effect of heat is direct and immediate. The fact is that this behaviour is related to cardiovascular, and more specifically to cerebrovascular deaths is consistent with the underlying biological mechanism, for this reason the short term effect is considered until four days. Mortality attributable to cold has two impacts, first, for cardiovascular diseases (lags 3 to7) and a second effect longer delay in the case of respiratory diseases (lag 7 to 13) (Alberdi et al., 1998).

The above-mentioned variables were thus introduced into the modelling, lagged in time in accordance with their effect on Spanish population mortality.

2.4. Impact models

To quantify the impact of daily mean NO_2 concentrations on mortality, we constructed generalised linear models (GLMs) with the Poisson regression link, with appropriate control for overdispersion (negative binomial). Bipollutant models (NO_2 and PM_{10}), when it was possible, have been performed. In these models, as indicated above, we included the parametrised variables along with their corresponding lags. The procedure used to determine significant variables was «Backwards-Step», beginning with the model that included all the 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 $p < 0.05$. This methodology makes it possible to calculate the relative risks (RRs) associated with given increases in the significant independent variables, so that in this case the RRs were calculated for every 10 μg/m^3 increase in NO_2 concentrations.

RRs were calculated for natural-, circulatory- and respiratory-cause mortality in each province. The RRs for each province yielded by the Poisson regression models were combined by means of a meta-analysis of random effects, which incorporates an estimate of inter-study variability (heterogeneity) in the weighting (Sterne, 2009), thereby obtaining a measure of the RR (95% CI), not only at an Autonomous Region level, but also at that of all the provinces which proved to be statistically significant.

2.5. Attributable mortality

To ascertain the number of deaths attributable to NO_2 concentrations in each province shown to be statistically significant, we used the methodology published in Tobías et al., 2015. This methodology is based on the fact that the previously calculated value of the attributable risk (AR) represents the percentage increase in daily mortality for every 10 μg/m^3 increase in the pollutant studied. The population attributable risk (AR) is calculated based on the RR associated with this same increase, via the following equation: $AR = ((RR - 1) / RR) \times 100$ (Coste and Spira, 1991).

The percentage increase in daily mortality associated with a given concentration is thus calculated by multiplying it by this AR and dividing by 10. The number of daily deaths attributable to this concentration is then obtained by multiplying this percentage increase in mortality by the number of daily deaths, and dividing by one hundred. In this way, the mortality associated with the concentration of this pollutant (in this case, NO_2) in a given town/city can be calculated for each day.

Finally, to estimate the percentage of attributable mortality due to annual NO_2 concentrations above the WHO recommendations (WHO, 2013) has been calculated considering annual mean with NO_2 concentrations above 20 μg/m^3. This value represent half of the current guideline value of WHO.

The computer software programmes used for all statistical analyses were IBM SPSS Statistics 22 and STATA v 14.1.

3. Results

Table 1 shows the descriptive statistics for NO_2 concentrations in 44 of the 52 Spanish cities analysed across the study period, along with the data on PM_{10} concentrations in 36 such cities. The cities not shown in the table are those that failed to register a sufficiently long and stable series of NO_2 data for analysis purposes.

Table 2 shows the results corresponding to the descriptive statistics for natural-, respiratory- and circulatory-cause mortality in all the provinces analysed. It should be noted that in the case of Madrid, the data refer exclusively to the city of Madrid and not to the province as a whole, thus accounting for Madrid's lower values with respect to other similar cities with a high population density, such as Barcelona.

Table 1
Descriptive statistics of NO_2 and PM_{10} levels (μg/m^3) by city in Spain: 2000–2009. Only cities with valid values for any pollutants are shown. Data provided from Spanish MAGRAMA.

City	NO_2				PM_{10}			
	Mean	SD	Min	Max	Mean	SD	Min	Max
A Coruña	No data				33.5	15.7	7.0	115.0
Albacete	15.7	8.4	2.0	81.0	46.0	19.4	5.7	190.6
Alicante	34.9	15.4	2.8	103.3	No data			
Almería	40.5	14.0	3.0	94.2	42.1	17.0	9.0	158.0
Ávila	37.6	16.2	1.3	143.1	No data			
Badajoz	11.5	7.4	2.0	60.8	18.4	10.9	3.0	126.0
Barcelona	44.1	19.4	1.4	155.8	No data			
Bilbao	37.5	15.0	0.7	120.8	34.5	17.2	5.8	138.0
Burgos	32.2	15.0	1.0	124.0	30.1	12.0	2.0	106.7
Cáceres	12.0	7.7	1.5	57.0	19.0	9.7	1.0	83.5
Cádiz	No data							
Castellón	20.8	9.9	4.0	78.2	No data			
Ciudad Real	12.8	8.6	2.0	50.0	No data			
Córdoba	35.4	15.1	2.2	121.4	47.6	23.4	6.5	387.1
Cuenca	21.9	10.5	3.0	66.0	30.9	16.7	6.0	139.0
Granada	45.0	17.9	7.1	144.3	42.6	21.7	8.0	338.6
Guadalajara	27.3	14.9	2.0	95.7	29.6	17.8	3.0	247.3
Huelva	20.1	8.4	4.0	69.1	32.7	15.1	6.0	233.0
Jaén	29.7	14.5	4.6	112.3	40.3	23.2	5.0	446.1
Las Palmas	29.5	10.9	6.5	73.1	41.0	39.4	3.0	795.0
León	37.1	17.6	2.1	128.0	39.1	16.3	3.0	135.5
Logroño	15.3	9.1	1.0	51.0	30.3	15.9	2.8	131.0
Lleida	25.6	12.9	1.0	108.6	No data			
Madrid	59.4	17.9	17.6	142.0	32.5	16.1	0.0	149.5
Málaga	36.5	15.9	3.5	95.1	32.0	17.7	4.0	331.0
Murcia	35.8	15.6	5.0	95.1	29.4	12.7	7.7	92.0
Orense	35.5	15.3	10.0	108.0	21.8	13.9	3.0	104.0
Oviedo	45.0	14.7	9.0	105.3	48.2	22.7	7.6	137.0
Pamplona	27.7	16.1	2.0	117.5	32.5	15.0	2.0	161.0
P. Mallorca	43.0	18.3	1.2	158.0	28.6	12.7	1.0	297.0
Pontevedra	26.7	12.0	0.0	73.0	No data			
Salamanca	25.0	11.5	1.0	88.5	31.4	14.9	6.0	129.2
Santander	41.3	15.0	6.0	150.1	33.3	13.9	4.7	118.0
S.C. Tenerife	25.9	15.5	3.0	98.0	54.8	52.2	17.5	919.0
Segovia	46.4	16.6	6.0	130.6	40.4	25.0	1.4	152.2
Sevilla	47.7	16.7	9.0	139.7	40.1	17.0	6.0	202.0
Soria	28.7	12.0	1.0	114.0	29.5	13.7	1.0	132.0
S. Sebastián	38.8	13.2	2.6	123.0	29.7	14.3	6.0	135.0
Tarragona	24.0	10.4	1.5	68.4	No data			
Teruel	No data							
Toledo	25.6	12.9	2.0	129.8	39.6	19.3	2.0	206.7
Valencia	54.4	20.2	5.0	129.4	30.8	13.1	4.0	111.7
Valladolid	38.1	15.1	0.1	149.0	15.3	9.4	1.0	130.4
Vitoria	34.7	14.4	5.3	118.8	27.1	16.6	4.0	149.0
Zamora	42.4	14.8	6.0	132.3	31.2	11.7	7.7	92.3
Zaragoza	47.2	17.1	10.0	107.4	37.8	20.4	1.0	205.5

As stated in the Methodology section above, previous studies have already observed that the functional relationship between daily mortality and daily NO_2 concentrations is linear, without threshold. By way of example, Fig. 1 shows the scatterplot diagram corresponding to the city of Valencia and all-cause mortality across the study period.

Table 3 shows the correlation coefficient between PM_{10} and NO_2 concentrations during the study period. These values vary from 0.6821 for Madrid and 0.1503 for Las Palmas. In general, the coefficients are higher in North and Center of Spain.

Table 4 shows the lags which showed a statistically significant association ($p < 0.05$) between NO_2 concentrations and mortality due to different causes in each province analysed, as a result of the Poisson modelling process. It will be observed that in most cases, the effect of NO_2 concentrations on mortality turned out to be immediate (24 h) or with a short delay (24–48 h) (mainly lags 0 and 1) and that, overall, the strongest associations appear for natural causes as opposed to respiratory and circulatory causes.

Resulting RRs are shown in Fig. 2 for natural causes and Fig. 3a and b for circulatory and respiratory causes respectively. These results

Table 2
Descriptive statistics of mortality due to natural, respiratory and circulatory causes by province in Spain: 2000–2009. The name of the province capital appears on the table. Data provided from National Statistics Institute (INE).

Province	Natural mortality				Respiratory mortality				Circulatory mortality			
	Mean	SD	Min	Max	Mean	SD	Min	Max	Mean	SD	Min	Max
A 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
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
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
Jaén	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
Madrid[a]	60	11	32	109	9	4	0	32	18	5	4	40
Málaga	30	7	9	58	3	2	0	14	12	4	0	30
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
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
Sevilla	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

[a] Daily mortality for metropolitan Madrid only.

constitute a meta-analysis of all the provinces analysed, with the overall value for all provinces and the Autonomous Regions to which they belong, provided, in all cases, that they were statistically significant. The results obtained in this study show a statistically significant association between daily mean NO_2 concentrations and daily natural-cause mortality in 20 of the 44 provinces with valid data analysed, with an overall RR of 1.012 (1.010 1.014). An association was observed with circulatory causes in 16 provinces (overall RR of 1.016 (1.012 1.021)), and with the respiratory causes analysed (overall RR of 1.028 (1.019 1.037)) in 11 provinces.

The results in the above Figures show only the RRs corresponding to the values of the NO_2 concentrations in the final models. The relationship between daily mean NO_2 concentration and mortality proved to be statistically significant and independent of the effect of PM10 and daily maximum and minimum temperatures. Through their transformation into heat and cold waves as indicated in the Methodology section above, these control variables also displayed significance in some of the final models fitted, but only the values for the main pollutant targeted for analysis are shown.

The overall population attributable risk (AR) values, calculated, as indicated, on the basis of the equation $AR = ((RR - 1) / RR) \times 100$ (Coste and Spira, 1991), were as follows: AR for natural causes, 1.18%, AR for circulatory causes, 1.57%, and AR for respiratory causes, 2.72%, for increases of 10 $\mu g/m^3$ in NO_2.

Table 5 shows the calculation of attributable mortality due to the different causes analysed across the study period (10 years), according to the RRs obtained for each province. The highest attributable mortality due to natural causes was observed in Barcelona and Madrid (metropolitan area only), Spain's main urban centres. Total all-cause mortality attributable to NO_2 concentrations for the country as a whole was 60,852 across the study period. A noteworthy finding was the figure of 19,775 for circulatory-cause mortality attributable to NO_2 concentrations for the country as a whole, a figure higher by 10,306 deaths than that found for respiratory-cause mortality.

Table 6 shows the natural-, respiratory- and circulatory-cause Attributable Mortality to NO_2 concentrations, for values above 20 $\mu g/m^3$ (WHO, 2013), by province and for Spain at a whole, during the study period. There is only a percentage of 44.5% corresponding to natural

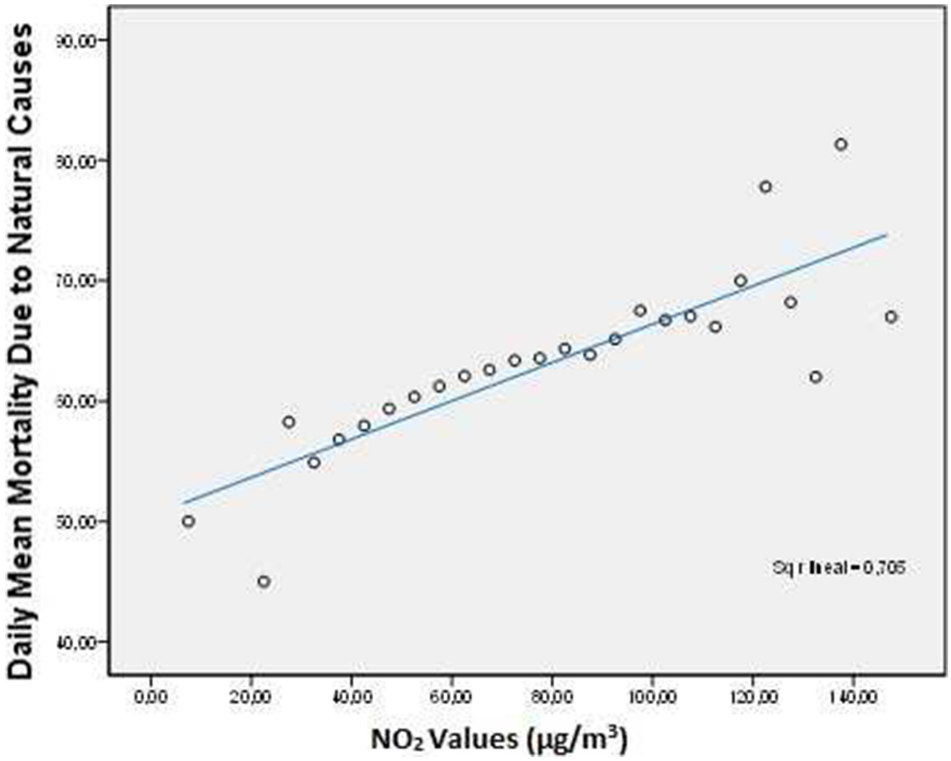

Fig. 1. Scatterplot between daily mean mortality and daily mean concentration of NO_2 in Valencia during 2000–2009.

cause mortality, attributable to NO_2 concentrations, above WHO recommendations.

4. Discussion

The Air Quality in Europe Report issued by the European Environmental Agency (EEA, 2015) reflects the situation of European countries vis-à-vis guideline values for pollutant levels. The situation in Spain is more worrying for NO_2 than for $PM_{2.5}$, both of which are primary pollutants whose principal emission source is road traffic. In the case of NO_2 concentrations, the limit value stipulated by EU legislation is equal to the WHO Air Quality Guideline value, and is set at an annual mean concentration of 40 µg/m^3. From the results obtained, most of the cities (26% of the provinces included), across the study period, exceeded this annual limit (Table 1).

About the correlation coefficient showed in Table 3, in those cities with a lot of monitors such as Madrid and Vitoria showed higher values and they are similar to other European cities (Samoli, 2006). On the other hand, in Spain there are frequently Sahara dust intrusions and advections from biomass combustion. The phenomenon of dust intrusion is above 20% of the days in South provinces and Canary Islands (Díaz et al., 2017). The advections from biomass combustion are especially important in Spanish North-West (Linares et al., 2018). These events can explain also the higher correlation coefficient values obtained in the Center and North of Spain. Probably, if $PM_{2.5}$ and NO_2 coefficient correlation were calculated, the values in general will be higher, because both pollutants are in major relation with diesel exhaust, the type of vehicles majority in Spain (Querol et al., 2014).

This paper only analyses air pollutant data series corresponding to the monitors placed in the capitals of provincial area, considering that in Spain above the 60% of the population lives in the capital (INE, 2017). The research innovation is to calculate for the first time the impact (through the RR and RA) of NO_2 concentrations in Spanish provincial mortality and using specific Spanish data, not another dose-response functions, usually imported from cohort USA studies as those used in previous Spanish papers (Boldo et al., 2011).

Only in the case of Madrid, it has obtained data at the level of the city, not at provincial level, as indicated in Table 2. For this city, the effect of NO_2 on daily mortality, as can be seen in Fig. 2, was RR: 1.009 (CI 95%: 1.006, 1.013). This value was very similar to those obtained at the provincial level for the most densely populated cities in Spain. Such as Barcelona, with a RR: 1007 (CI95%: 1.005, 1.009) or Sevilla with a RR: 1.007 (CI95%: 1.003, 1.011). However, the use of mortality for the whole province may justify the fact that there is no association between NO_2 and daily mortality in cities with a high concentration of NO_2 (as in the case of Valencia and Zaragoza).

About the results obtained, all but 3 of these cities display statistically significant associations with natural-, respiratory-and circulatory-cause mortality, whose quantification can be seen in Figs. 2, 3a and b respectively. However, in addition to the cities that exceed the annual limit, these Figures also show other provinces that display significant RRs for mortality without having exceeded the guideline level, which means a short-term impact of NO_2 concentrations below this threshold. This finding goes hand in hand with the impact of particulate matter on mortality in Spain, published in a recent study based on the same period of analysis (Ortiz et al., 2017), in which the brunt of mortality attributable to PM_{10} concentrations is shown to occur below the WHO threshold.

Our study arose from the need to update the estimates of the short-term effect of NO_2 concentrations on Spain as a whole and, in addition, to include the impact on provinces that were not specifically analysed by the EMECAM project (Saez et al., 2002). In the latter study, conducted across the period 1990–1996, this guideline value was exceeded in 7 of the 8 cities (87%) for which data on mean NO_2 concentrations were available, and was again exceeded in 10 of the 13 cities (77%) in the subsequent EMECAS project (1993–1999) (Ballester et al., 2006). Accordingly, annual mean NO_2 concentrations have been declining in Spain over the last 20 years, thanks mainly to the introduction of statutory air emission control policies and, more recently, as a consequence of the economic crisis and the lower economic and industrial activity that this entailed (Querol et al., 2014). The overall RR obtained in the meta-analysis were an overall RR of 1.012 (1.010 1.014) for natural

Table 3
Correlation coefficients between PM_{10} and NO_2 concentrations during 2000–2009. The name of the province capital appears on the table.

Province	Correlation coefficient PM_{10} and NO_2
Albacete	0.2226
Almería	0.1981
Badajoz	0.2081
Bilbao	0.4427
Burgos	0.5234
Cáceres	0.2037
Córdoba	0.4382
Cuenca	0.5302
Granada	0.4417
Guadalajara	0.4334
Huelva	0.3916
Jaén	0.4180
Las Palmas	0.1503
León	0.4418
Logroño	0.2252
Madrid	0.6821
Málaga	0.2759
Murcia	0.3109
Ourense	0.3405
Oviedo	0.5163
Pamplona	0.3996
P. Mallorca	0.3396
Salamanca	0.2262
Santander	0.3990
S.C. Tenerife	0.2391
Segovia	0.2717
Sevilla	0.2325
Soria	0.4077
S. Sebastián	0.4232
Toledo	0.2311
Valencia	0.3901
Valladolid	0.2718
Vitoria	0.6759
Zamora	0.2405
Zaragoza	0.1377

Table 4
Lags (days) at which statically significant associations were established between NO_2 concentrations and mortality due to the different causes analysed. The name of the province capital appears on the table. * means no effect.

Province	Natural causes	Respiratory causes	Circulatory causes
A Coruña	*	*	*
Albacete	*	*	*
Alicante	NO_2(2)	NO_2(0)	NO_2(2)
Almería	NO_2(1,5)	NO_2(4)	*
Ávila	*	*	NO_2(5)
Badajoz	*	*	*
Barcelona	NO_2(1)	NO_2(1,5)	NO_2(4)
Bilbao	*	*	*
Burgos	NO_2(1)	NO_2(1)	NO_2(2)
Cáceres	*	*	*
Cádiz	*	*	*
Castellón	*	*	*
Ciudad Real	*	*	*
Córdoba	NO_2(5)	NO_2(5)	NO_2(3)
Cuenca	*	*	*
Granada	NO_2(2)	NO_2(2)	NO_2(2)
Guadalajara	*	*	NO_2(1)
Huelva	NO_2(2)	*	NO_2(3)
Jaén	NO_2(1)	*	*
Las Palmas	*	*	*
León	*	*	*
Logroño	NO_2(2)	NO_2(4)	NO_2(2)
Lleida	*	NO_2(3)	*
Madrid	NO_2(1)	*	*
Málaga	*	*	NO_2(1)
Murcia	*	*	NO_2(2)
Ourense	NO_2(1)	*	*
Oviedo	NO_2(5)	NO_2(3)	*
Pamplona	NO_2(4)	NO_2(0,5)	*
P. Mallorca	*	*	*
Pontevedra	NO_2(4)	$NO_{2(3)}$	
Salamanca	*	*	*
Santander	*	*	*
S.C. Tenerife	*	*	*
S. Sebastián	NO_2(2)	*	NO_2(1)
Segovia	NO_2(0)	*	*
Sevilla	NO_2(1)	*	*
Soria	*	*	*
Tarragona	NO_2(0,3)	NO_2(1)	NO_2(0)
Teruel	*	*	*
Toledo	*	*	*
Valencia	*	*	*
Valladolid	NO_2(1)	*	NO_2(0)
Vitoria	*	*	NO_2(5)
Zamora	NO_2(3)	*	*
Zaragoza	*	*	NO_2(3)

causes, an overall RR of 1.016 (1.012 1.021) for circulatory causes, and an overall RR of 1.028 (1.019 1.037) for respiratory causes. These results obtained showed that the association is stronger than that found at the end of the 1990s by the EMECAM study, in which the combined attributable risk for NO_2 concentrations was 0.6% (95% CI, 0.3–0.8%). The authors are conscious of one of the limitations about the meta-analysis procedure, is only include RR with statically significant associations. This fact may lead to underestimate the real impact of NO_2.

With respect to other European studies, the combined attributable risk of 2.09% (95% CI, 0.96, 3.24) found in the Italian EpiAir study (Chiusolo et al., 2011; Alessandrini et al., 2013) was of a similar magnitude to that obtained by us, though the EpiAir2 project was conducted on adult population (35+ years old). The EpiAir study also reported an even stronger association (AR = 4.64%) in the period from April to September, as well as a stronger association at lags 2–5. However, in another more recent Italian study (Carugno et al., 2016) undertaken in Lombardy, a highly polluted region to the north of Italy (in the words of the authors themselves) in which the annual limit of 40 $\mu g/m^3$ of NO_2 was exceeded in 13 of the 17 cities studied (as opposed to 12 out of 44 in our case), the combined attributable risk was lower (AR = 0.7%, 90% CI 0.20–1.18), similar to that obtained individually in our study for Barcelona (AR = 0.69%, 95% CI 0.45, 0.85).

In the APHEA project (Samoli, 2006), which combines the results of 30 European cities, the resulting attributable risk was even lower than those cited above, 0.34% (95% CI% 0.29, 0.39), though this must be regarded as out of date since it was based on data collected in the 1990s. Outside the confines of Europe, though with a context similar to ours, a study conducted in 12 of Canada's largest cities using a data series that covered 19 years (1981–1999), reported an attributable risk of 2.25% (Burnett et al., 2004), a figure similar to that obtained in our case for respiratory-cause mortality.

In relation to the health effects of exposure to NO_2, a number of reviews and meta-analyses have amply documented the associations between variations in daily NO_2 concentrations and variations in mortality (respiratory, cardiovascular and all-cause). Also an increase in the frequency of hospital admissions (Maté et al., 2010; Linares and Díaz, 2010; REVIHAAP, 2014) and with less expectancy of life (De Keijzer et al., 2017). Insofar as morbidity is concerned, this pollutant has been associated, on the one hand, with respiratory diseases in children (Linares et al., 2006; Esplugues et al., 2007) and adults alike, i.e., acute effects on pulmonary function, asthma and allergic diseases (Rage et al., 2009; Zheng et al., 2015) and lung cancer (Hamra et al., 2015). It has likewise been associated with a higher risk of suffering from cardiovascular diseases, increase in hospitalisations and mortality due to heart failure (Shah et al., 2013), and other diseases such as diabetes mellitus type II (Balti et al., 2014; Eze et al., 2015), depressive episodes (particularly in patients with cardiovascular diseases, diabetes mellitus or asthma) (Cho et al., 2014), acute myeloid leukaemia in

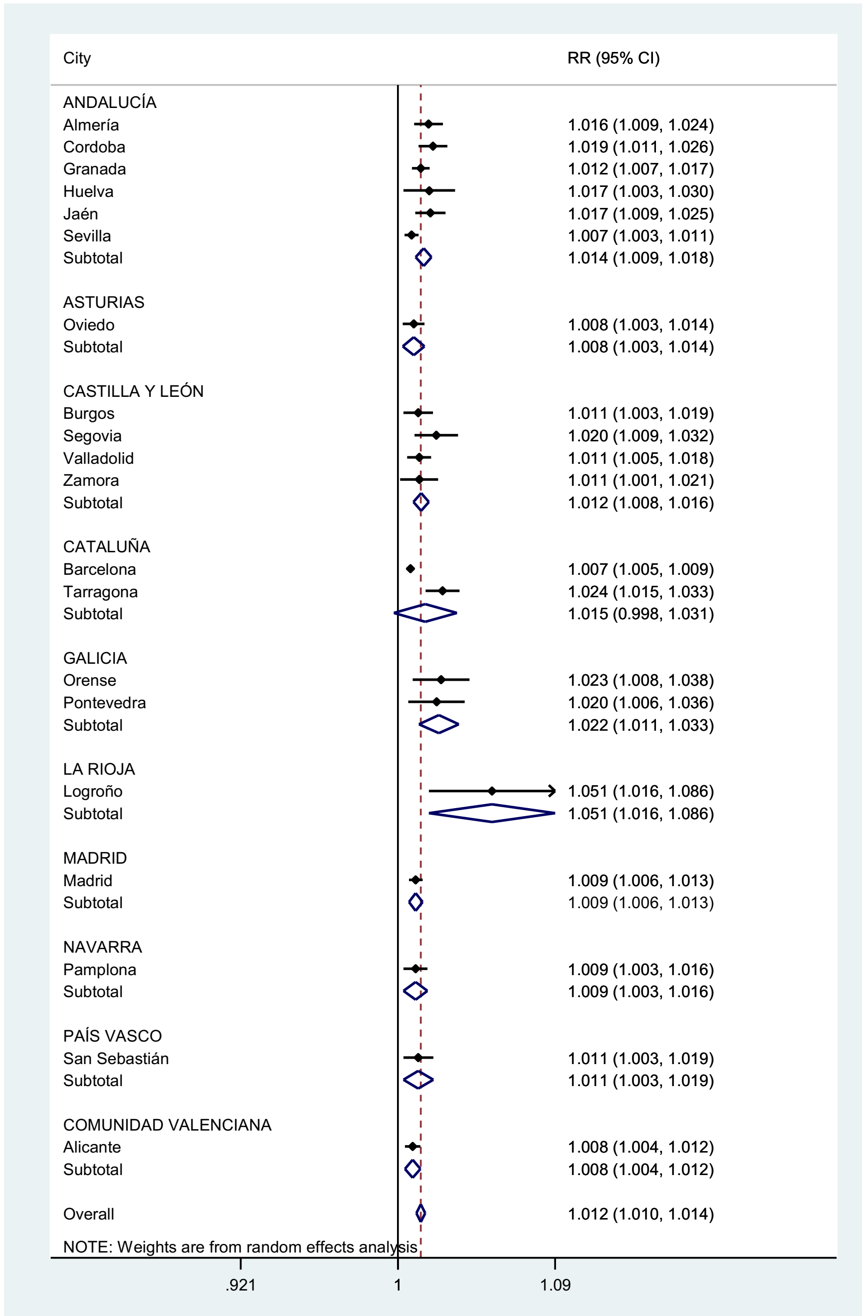

Fig. 2. Relative risks (RR) calculated for increases of 10 μg/m^3 in NO_2 levels due to natural cause ortality. Only showed provinces with valid statically significant associations ($p < 0.05$). The name of the provincial capital appears on the figure.

adults (Raaschou-Nielsen et al., 2016) or breast cancer (Crouse et al., 2010). Among children, congenital exposure to NO_2 has been associated with an increase in the incidence of pre-term births (CARB, 2007; Arroyo et al., 2016), sudden infant death syndrome (Dales et al., 2004), and malformations such as coarctation of the aorta (Chen et al., 2014), in addition to also being associated with a higher frequency of childhood leukaemia (Filippini et al., 2015) and asthmatic symptoms (Weinmayr et al., 2010; Bowatte et al., 2015).

With regard to the relationship between daily mean NO_2 concentrations and mortality found in our study, this follows a linear model, coinciding with other similar studies, with which the lags obtained in our analysis are similarly in line (Burnett et al., 2004; Shin et al., 2012), and which link the short-term impact to the physio-pathogenic mechanisms of NO_2, including its oxidising capacity, whether acting directly on lipids and proteins, or indirectly, by activating intracellular oxidation pathways (Brunekreef and Holgate, 2002).

Furthermore, the overall RRs obtained for the impact of NO_2 concentrations on daily mortality, are comparable to those recently obtained for PM_{10} concentrations for the same time period using the same methodology (Ortiz et al., 2017), though, on the whole, these were slightly higher for NO_2 in all the causes analysed.

If ones focuses on mortality attributable to the two types of pollutants in Spain during the study period, mortality attributable to NO_2 concentrations is also higher, being more than double for NO_2 (6085 annual all-cause deaths) than for PM_{10} concentrations (2683 annual all-cause deaths). Figures which are likewise higher in the case of annual respiratory-cause mortality (1030 versus 651) and are, remarkably,

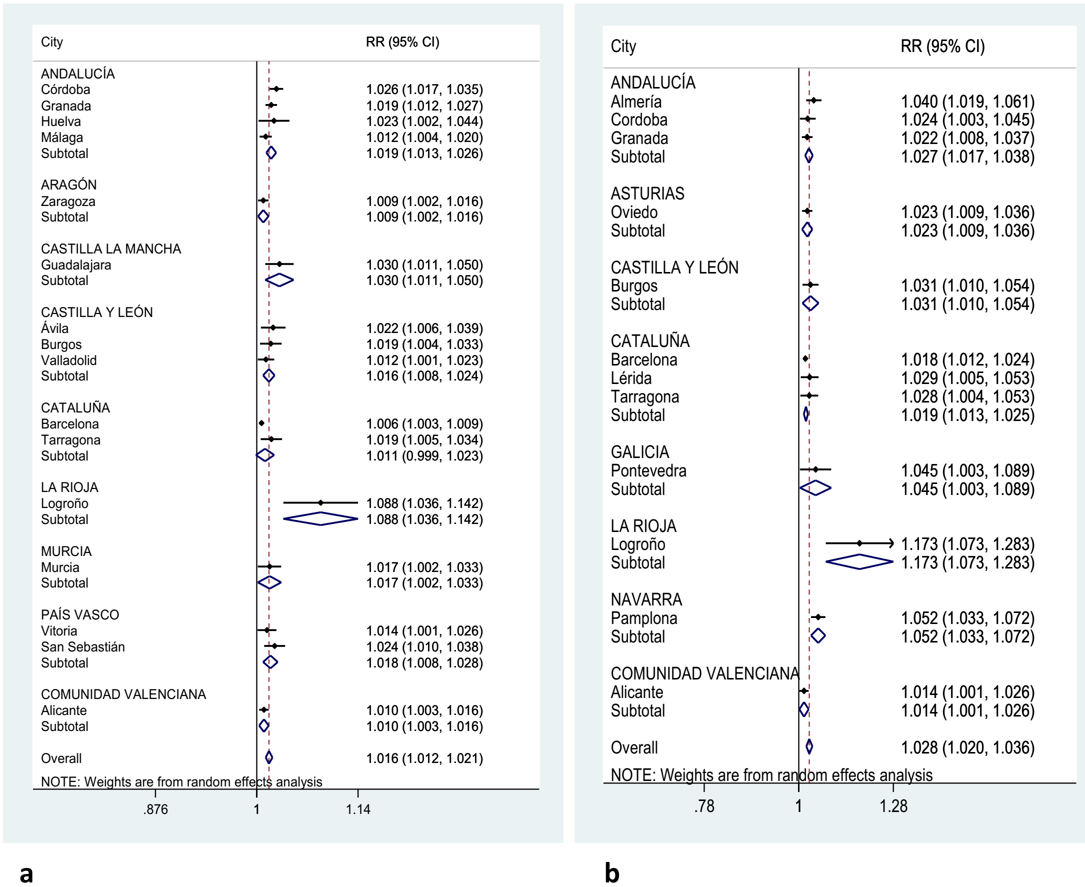

Fig. 3. a/b. Relative risks (RR) calculated for increases of 10 μg/m^3 in NO_2 levels due to circulatory causes of mortality (a) and respiratory causes of mortality (b). Only showed provinces with valid statically significant associations ($p < 0.05$). The name of the provincial capital appears on the table.

more than triple in the case of circulatory causes (1977 versus 556); a finding that goes to underscore what was said above as regards the higher frequency of exceedance of annual guideline levels. The EEA puts air-pollution-related mortality in Spain at 30,000 deaths/year and estimates the health impact assessment attributable to NO_2 in 6740 deaths in year 2014 (EEA, 2015). From our point of view, the discrepancy between these figures is due to the fact that these reports use different concentration-response functions which, though naturally valid, are not specifically calculated for Spain as in our analysis. Moreover, to reach a level of statically significance to conclude that exist an association could minimize the real impact of NO_2 on mortality. In addition, this event is due to different counterfactual levels used and the different impacts obtained from other impacts calculated by EEA for Spain.

Furthermore, the associations obtained between NO_2 concentrations and short–term health effects remain unchanged after adjustment for other pollutants, such as PM10. In other studies, the pollutants used in the adjustments often include PM10, PM2.5, and occasionally, black smoke. Here, bi-pollutant models has been performed and that the interaction of others pollutants, or pollens concentrations, have been not considered. Hence, there is consistent short-term epidemiological evidence and some mechanistic support for causality, particularly for respiratory outcomes. It is reasonable to infer that, apart from other traffic-related air pollutants, NO2 has some direct effects. In addition, we controlled for daily minimum and maximum temperatures, since meteorological conditions can influence impact on mortality. A limitation to our work is that, we had no explanatory variables, a part from sex, age and the address of the subjects, at the individual level. In particular, we cannot control for factors, such as individual socioeconomic data, lifestyles and comorbidities that may differ between the mortality in people in different cities or misclassification of causes of death (Vodonos et al., 2015). These factors may also act as confounders or effect modifiers of relations between air pollution and daily mortality (Barceló et al., 2016). It should likewise be noted that, as this was a longitudinal ecological study, the results cannot be extrapolated at an individual level. The exposure levels used were based on exposures determined on the basis of readings taken by external monitors and then averaged, with the result that they are not measures which represent individual exposure. Another bias from the monitors used can be the heterogeneity in the type, they are mostly urban but occasionally we used background type. Even so, this is a commonly used methodology in these types of studies (Samet et al., 2000). However, much of this residual confusion is controlled by inclusion in the model of variables such as: trend of the series, day of the week, annual, six-monthly and quarterly seasonalities and the autoregressive nature of the series. No specific validation was carried out to assess the representativeness of spatial variability in air pollutants: our study suffered from Berkson-type measurement error, among other biases associated with 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. At all events, most air-pollution studies address the misalignment problem (albeit only implicitly), by using a two-stage modelling procedure, or plug-in approach, where predictions from an exposure model (first stage) are used as covariates in a health-effect model (second stage) (Barceló et al., 2016). Although in a few cases, predictions are obtained from exposure models that explicitly incorporate spatial structure, even in such cases the plug-in approach does not take into account the uncertainty in the exposure predictions. This leads to a complex form of measurement error, resulting in bias of the health effect (Wannemuehler et al., 2009; Ingebrigtsen et al., 2015).

Table 5
Natural-, respiratory- and circulatory-cause Attributable Risk (AR) and Attributable Mortality to NO_2 concentrations by province and for Spain as a whole: 2000–2009. The name of the province capital appears on the table. * means no effect.

Province	Natural causes AR (CI 95%) Attributable mortality	Respiratory causes AR (CI 95%) Attributable mortality	Circulatory causes AR (CI 95%) Attributable mortality
A Coruña	*	*	*
Albacete	*	*	*
Alicante	0.79 (0.40 1.19) 3384 (1627–5133)	1.38 (1.00 2.53) 606 (61–1144)	1.00 (0.30 1.57) 1572 (527–2608)
Almería	1.57 (0.89 2.34) 2651 (1405–3887)	3.80 (1.19 5.75) 841 (415–1257)	*
Ávila	*	*	2.15 (0.58 3.75) 460 (118–796)
Badajoz	*	*	*
Barcelona	0.69 (0.50 0.89) 12,218 (8443–15,983)	1.77 (1.09 2.34) 3530 (2349–4703)	0.51 (0.30 0.89) 3788 (2033–5537)
Bilbao	*	*	*
Burgos	1.09 (0.30 1.86) 1128 (314–1934)	3.00 (1.00 5.12) 394 (124–658)	1.86 (0.40 3.19) 619 (145–1086)
Cáceres	*	*	*
Cádiz	*	*	*
Castellón	*	*	*
Ciudad Real	*	*	*
Córdoba	1.86 (1.09 2.53) 4442 (2634–6236)	2.34 (0.30 4.30) 738 (90–1373)	2.53 (1.67 3.32) 2289 (1500–3070)
Cuenca	*	*	*
Granada	1.19 (0.69 1.67) 3955 (2417–5184)	2.15 (0.74 3.66) 805 (307–1294)	1.87 (1.19 2.12) 2386 (1453–3311)
Guadalajara	*	*	2.41 (0.30 4.76) 443 (167–713)
Huelva	1.67 (0.30 2.91) 1332 (238–2410)	*	2.55 (0.20 4.21) 725 (76–1360)
Jaén	1.67 (0.89 2.43) 1912 (1018–2798)	*	*
Las Palmas	*	*	*
León	*	*	*
Logroño	4.85 (1.57 7.92) 410 (137–674)	14.75 (6.80 22.06) 144 (67–215)	8.11 (3.47 12.1) 234 (100–360)
LLeida	*	2.81 (0.50 5.030) 337 (60–607)	*
Madrid	0.89 (0.58 1.28) 11,042 (6770–15,297)	*	*
Málaga	*	*	1.86 (0.40 2.53) 1826 (576–3066)
Murcia	*	*	1.67 (0.20 3.19) 620 (59–1171)
Orense	1.87 (0.79 3.67) 696 (241–1144)	*	*
Oviedo	0.79 (0.30 1.38) 4411 (1374–7431)	2.25 (0.89 3.47) 1349 (536–2150)	*
Pamplona	0.89 (0.30 1.57) 1251 (398–2097)	4.14 (3.19 6.79) 898 (573–1216)	*
Palma de Mallorca	*	*	*
Pontevedra	1.96 (0.58 3.47) 840 (229–1442)	4.31 (0.30 8.17) 230 (17–434)	*
Salamanca	*	*	*
Santander	*	*	*
S.C. Tenerife	*	*	*
San Sebastián	1.09 (0.30 1.87) 2439 (665–4199)	*	2.34 (0.99 3.66) 1651 (692–2595)
Segovia	1.96 (0.89 3.10) 1199 (523–1865)	*	*
Sevilla	0.69 (0.30 1.09) 4809 (2287–7320)	*	*
Soria	*	*	*
Tarragona	2.34 (1.47 3.19) 3280 (2039–4508)	2.72 (0.40 5.03) 434 (62–797)	1.86 (0.01 2.34) 898 (240–1546)
Teruel	*	*	*
Toledo	*	*	*
Valladolid	1.09 (0.50 1.77) 1913 (23–2996)	*	1.09 (0.79 2.34) 731 (309–1985)
Vitoria	*	*	1.38 (0.79 2.53) 309 (31–583)
Zamora	1.09 (0.79 2.06) 924 (99–1740)	*	*
Zaragoza	*	*	0.89 (0.20 1.52) 1224 (254–2186)
Spain	1.19 (0.99 1.30) 60,852 (32881–94,278)	2.72 (1.86 3.57) 10,306 (4661–15,848)	1.57 (1.19 2.57) 19,775 (8280–31,973)

Table 6
Natural-, respiratory- and circulatory-cause Attributable Mortality to NO_2 concentrations, for values above 20 $\mu g/m^3$, by province and for Spain as a whole: 2000–2009. The name of the province capital appears on the table. * means no effect.

Province	Natural causes Attributable mortality	Respiratory causes Attributable mortality	Circulatory causes Attributable mortality
A Coruña	*	*	*
Albacete	*	*	*
Alicante	1503 (571 2440)	503 (365 641)	709 (21 1411)
Almería	1292 (733 1850)	284 (89 480)	*
Ávila	*	*	276 (74 479)
Badajoz	*	*	*
Barcelona	6980 (5058 8872)	1869 (1150 2580)	1660 (976 2341)
Bilbao	*	*	*
Burgos	437 (120 760)	134 (44 222)	206 (44 366)
Cáceres	*	*	*
Cádiz	*	*	*
Castellón	*	*	*
Ciudad Real	*	*	*
Córdoba	1986 (1164 2891)	263 (34 490)	995 (394 1599)
Cuenca	*	*	*
Granada	2170 (1260 3080)	392 (135 646)	1195 (760 1635)
Guadalajara	*	*	128 (16 242)
Huelva	7 (1 14)	*	4(1 8)
Jaén	877 (472 1302)	*	*
Las Palmas	*	*	*
León	*	*	*
Logroño	*	*	*
LLeida	*	56 (10 102)	*
Madrid	7680 (5090 10,270)	*	*
Málaga	*	*	1344 (289 1061)
Murcia	*	*	466 (110 812)
Orense	383 (133–640)	*	*
Oviedo	2378 (904 3852)	821 (325 1324)	*
Pamplona	325 (111 550)	232 (179 288)	*
Palma de Mallorca	*	*	*
Pontevedra	406 (298 514)	195 (62 328)	*
Salamanca	*	*	*
Santander	*	*	*
S.C. Tenerife	*	*	*
San Sebastián	1197(330 2064)	*	802 (340 1260)
Segovia	756 (343 1169)	*	*
Sevilla	2649 (1153 4140)	*	*
Soria	*	*	*
Tarragona	444 (279 612)	79 (12 145)	136 (1 272)
Teruel	*	*	*
Toledo	*	*	*
Valladolid	864 (396 1335)	*	288 (208 370)
Vitoria	*	*	148 (85 220)
Zamora	535 (486 554)	*	*
Zaragoza	*	*	706 (160 1252)
Spain	32,879 (19,202 54,211)	4828 (2405 7010)	9063 (3479 14,640)

In despite of some important limitations of this study: the city levels of pollutants used were representative of the whole province; the meta-analysis included only positive results and not included other causes of differences in mortality. We feel that NO_2-related air pollution represents an important environmental risk for public health in Spain, as is borne out by the attributable mortality figures shown in Table 5, with 60,852 deaths across the study period attributable to all causes, 19,775 to circulatory causes, and 10,306 to respiratory causes. Respect the results obtained in Table 6, only remark that the 55.5% of the mortality attributable to NO_2 due to natural causes, was below the recommendation value considered" (WHO, 2013).

Accordingly, there is a pressing need to implement pollution control measures, aimed in particular at preventing episodic situations in which high NO_2 levels are reached, a relatively frequent phenomenon in Spanish cities with a high traffic density and prolonged periods of atmospheric stability.

Disclaimer

This paper reports independent results and research. The views expressed are those of the authors and not necessarily those of the Carlos III Institute of Health.

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