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Impact of air pollution on low birth weight in Spain: An approach to a National Level Study

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ABSTRACT

Background: According to the WHO, low birth weight (< 2500 gr) is a primary maternal health indicator as the cause of multiple morbi-mortality in the short and long-term. It is known that air pollution from road traffic (PM_{10}, NO_2) and O_3 have an important impact on low birth weight (LBW), but there are few studies of this topic in Spain. The objective of this study is to determine the possible exposure windows in the gestational period in which there is greater susceptibility to urban air pollution and to quantify the relative risks (RR) and population attributable risks (PAR) of low birth weight associated with pollutant concentrations in Spain.
Methods: We calculated the weekly average births with low birth weight (ICD-10: P07.0-P07.1) for each Spanish province for the period 2001–2009, using the average weekly concentrations of PM_{10}, NO_2 and O_3, measured in the capital cities of the provinces. The estimation of RR and PAR were carried out using generalized linear models with link Poisson, controlling for the trend, seasonality and auto-regressive character of the series and for the influence of temperature during periods of heat waves and/or cold. Finally, a meta-analysis was used to estimate the global RR and PAR based on the RR obtained for each of the provinces.
Results: The RR for the whole of Spain is 1.104 (CI95%: 1.072, 1.138) for the association between LBW and PM_{10}, and 1.091 (CI95%: 1.059, 1.124) for the association between NO_2 and LBW. Our results suggest that 5% of low birth weight births in the case of PM_{10} and 8% in the case of NO_2 could have been avoided with a reduction of 10 $\mu g/m^3$ in the concentrations of these pollutants.
Conclusions: The impact of the results obtained- with 6105 cases attributable to PM_{10} and up to 9385 cases attributable to NO_2 in a period of 9 study years- suggest the need to design structural and awareness public health measures to reduce air pollution in Spain.

1. Introduction

Low birth weight (LBW), defined by the WHO as newborn infants with a weight of less than 2500 g, has a worldwide prevalence of 15–20% of total births, which means that over 20 million births per year are of infants with low birth weight (UNICEF, WHO, 2004).

Low birth weight is one of the health maternal and child health indicators most used around the world (European health for all database, 2003; MSSSI, 2014) due to its relationship to infant morbidity and mortality. It is not only a part of the 1.1 million deaths due to birth complications per year, it can also result in serious short and long-term consequences, as respiratory diseases (Caudri et al., 2007); more risk of suffering type 2 diabetes and even more risk of mortality (Katz et al., 2013).

According to the OECD (Organization for the Economic Cooperation and Development) the prevalence of low birth weight in OECD countries in 2013 (OECD, 2015) was 6.6% (one in 15) of births. This same report shows an increasing tendency in Spain, a country in which the proportion of births with low birth weight has continued to increase over the past two decades; it was over 5% in 1990, 6.9% in 2000 and 8.2% in 2014 (MSSSI, 2017). It is worth noting that this tendency may be influenced in large part by the elevated number of premature births that occur in Spain, many of which present low birth weight (European Health Perinatal Report, 2014).

In contrast, the number of deaths per 1000 live births has been stable in Spain since the year 2013, at less than 3.0 deaths per 1000 live births (INE), which indicates an adequate quality of prenatal care. All of this means that in developed countries risk factors that are increasing in

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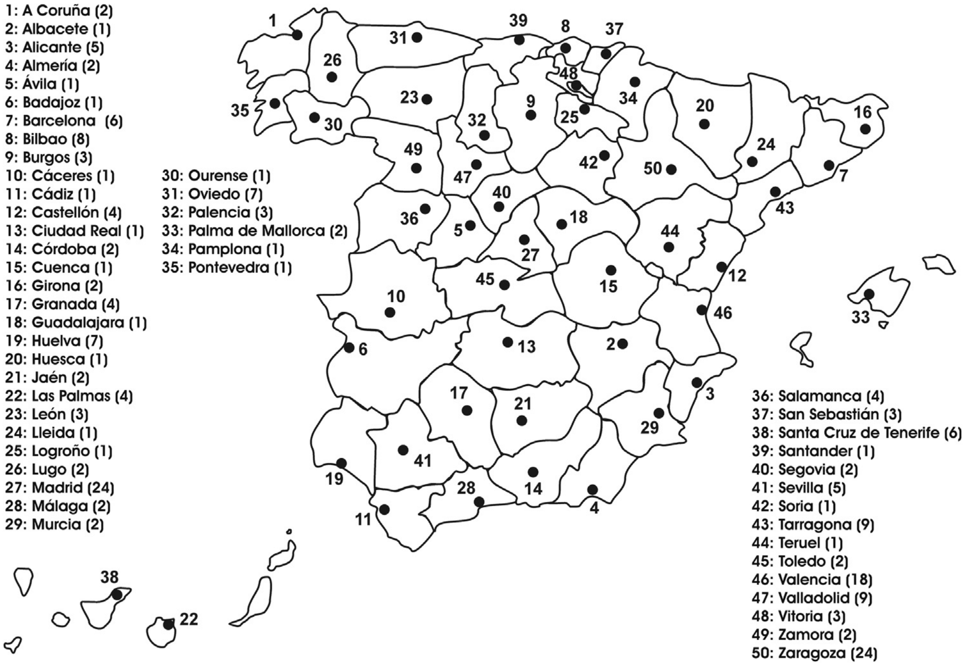

Fig. 1. Location of the air pollution monitors used in the analysis across Spain. The number is the name of the capital province. Among brackets the number of monitors is showed.

our societies play a more active role in the effect on infants' birth weight. (Forouzanfar et al., 2016) This is true for both risk factors directly associated with the mother's habits and state of health and those to which the mother and infant are exposed, primarily air pollution. Exposure to air pollution is an extrinsic risk factor (Backes et al., 2013; Dadvand et al., 2013; Stieb et al., 2012), that can be greater for vulnerable populations. Those populations for which risk factors related to mother's health and habits (obesity, diabetes, high levels of exposure to toxic substances, etc.) also tend to be very present, show an increase in the risk of low birth weight (Makri and Stilianakis, 2008), which can interact with exposure to air pollution (Lakshmanan et al., 2016; Laurent et al., 2014; Pedersen et al., 2014). It has also been shown that there is a relationship and interaction between exposure to air pollution and being of low-medium socioeconomic level (Gray et al., 2014; Laurent et al., 2014; Morelli et al., 2016).

Thus, for several decades the presence of air pollution (Clemente et al., 2016; Iñiguez et al., 2016; Lamichhane et al., 2015), and the distance to road traffic (Dadvand et al., 2014; Laurent et al., 2014) and/or energy plants (Ha et al., 2015) have been focal points as possible environmental risk factors to be taken into account. Because the environment is a made up of a dynamic mix of pollutants, there are multiple and varied hypotheses about how these chemicals affect fetal growth and therefore infants' birth weight.

It is also important to take into account the physiological changes that pregnant women undergo- the increase in their alveolar capacity (Hackley et al., 2007), the physiological increase in inflammatory markers (von Versen-Hoeynck et al., 2009) and greater tendency for oxidative stress (Casanueva and Viteri, 2003)- that can act as facilitating factors for adverse birth outcomes, in addition to the natural vulnerability of the developing fetus (Moore, 2013).

Finally, it is important to signal that air pollution costs annually to European countries hundreds of millions of euros for harm to health and the environment (European Environment Agency, 2014). Therefore, time series studies (Arroyo et al., 2016; Díaz et al., 2016) such as this one can be key instruments, due to the fact that they are less expensive and require less time to carry out than cohort studies. Despite that they have lower statistical power, lack the ability to make causal associations, they are capable of establishing associations in which individual exposure factors do not vary over time (for example, tobacco smoking habits), and thus avoid possible biases. It is therefore possible to detect temporal associations between exposure factors and health events that are statistically significant (Recio et al., 2016). They also have the advantage of being complementary to cohort studies and are therefore useful and cost-effective tools for decision-making in health policy.

The objective of this study was to analyse and quantify the impact of chemical air pollution on low birth weight in different provinces in Spain from January 1, 2001 to December 31, 2009. We also aimed to determine the possible gestational windows for such an impact and to quantify the provincial RR and PAR for each pollutant. The significant RR obtained for each province are grouped by autonomous community and for the whole of Spain. This is one of the few studies that analyse the impact of variables previously considered at a level of a whole country.

2. Materials and methods

2.1. Variables used

2.1.1. Dependent variable

The dependent variable used was the number of daily births with low birth weight (LBW) (birth weight < 2500 g; CIE-10: P07.0-P07.1) registered during the period 2001–2009 for a total of 46 Spanish provinces, except in the case of Madrid, which corresponds only to the metropolitan area of the municipality. The data were obtained from the National Statistics Institute (INE, 2018). Based on this daily distribution, a variable was generated that grouped the average weekly births with LBW.

2.1.2. Independent variables

Based on the average daily values of the concentrations of PM_{10} (mg/m^3), NO_2 (mg/m^3) and O_3 (mg/m^3) particles that were registered in monitoring stations in each province capital in the period (2001–2009) from daily values, the weekly averages were calculated and series were created for average weekly concentrations of each pollutant. These data were provided by the Ministry of Agriculture and

Environment (MAGRAMA, 2015). A map showing the location of monitors has been included as Fig. 1.

The functional relationship that exists between the pollutants PM_{10} (Ortiz et al., 2017) and NO_2 (Linares et al., 2018) for both mortality in all of Spain as well as morbidity (Díaz et al., 1999) is linear and without threshold, therefore no modification of these variables is needed.

2.2. Transformation of the variables

Prior studies (Díaz et al., 1999, 2018) show that tropospheric ozone presents a quadratic relationship- U-shaped curve, with the right arm of this U that implies health effects. The vertex of the parabola varies from one city to another, in the same way as the variable temperature (Carmona et al., 2016; Díaz et al., 2015) varies. This value has recently been determined for the capital city of each Spanish province ($O3_{threshold}$) (Díaz et al., 2018). Therefore, based on the average daily concentrations of ozone, a new variable was created O_{3h} defined in the following way:

$$O_{3h} = 0 \text{ if } O_3 < O_{threshold}$$

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

The daily values of O_{3h} particles were averaged weekly, in the same way as PM_{10} and NO_2.

2.2.1. Control variables

The analysis was controlled for the linear tendency of the series, annual and semestral seasonality using sine and cosine functions for the periods of 52 weeks and 26 weeks, respectively, the autoregressive nature of the series and the influence of temperature in periods of heat and/or cold.

In order to see the effect of temperature on LBW in thermal extremes, new variables were created based on the maximum daily temperature (T_{max}) and the minimum daily temperature (T_{min}), obtained in the observatory station of each province capital. The variables were defined in the following way:

2.2.2. Effect of heat

The daily values of T_{max} determined whether the temperature was greater than the value of the temperature defined as a heat wave in each province ($T_{threshold}$) (Díaz et al., 2015), with the temperature that constitutes a heat wave (T_{heat}) defined in the following way:

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

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

Weekly averages were calculated for the daily variable T_{heat}.

2.2.3. Effect of cold

In the same manner as heat, for cold the variable T_{cold} was created using the temperature definition of cold wave (Carmona et al., 2016) in the following way:

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

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

These daily values of T_{cold} were averaged weekly.

2.2.4. Lagged variable

as per prior analyses carried out (Arroyo et al., 2016) the effect of environmental variables on the variable LBW can be both short and long-term. In order to account for these impacts and other possible associations that could occur throughout a full period of gestation, 37 weeks of gestation (Eds CP Howson et al., 2012), and in the search for possible windows of susceptibility during gestation, a total of up to 37 lagged variables were created related to the delivery date for each of the independent variables.

2.3. Analysis and modeling process

It was necessary to determine the weekly lags for which a statistical significance was established between LBW and the independent variable analysed. The Box-Jenkins methodology was used for this purpose (Makridakis, 1978), to later determine the cross-correlations functions (CCF) between the pre-whitened series for LBW and the corresponding pre-whitened series for PM_{10}, NO_2 and O_3. In this way the CCF were carried out for the control variables T_{max} and T_{min}.

The CCF permit determining the lags in which associations can be established, at the weekly level, with LBW. This methodology has been used successfully in prior studies in the city of Madrid (Arroyo et al., 2016; Díaz et al., 2016).

It should be noted that these lags refer to the week of delivery (birth), and thus when referring to gestational week, it would be necessary to subtract from the 37 weeks of gestation of a full-term birth (Eds CP Howson et al., 2012) the value of the lag with respect to the delivery. Thus, for example, an association in the lag 4 weeks before delivery refers to gestation week 33: 37–4 = 33 week of gestation.

Once the variables that are significant in the CCF carried out with LBW were obtained, with their corresponding lags, they were introduced into the modeling process, along with the control variables described earlier. In the case of the control variable temperature, those variables and their lags that were significant in the CCF carried out with LBW were introduced.

Given the nature of the LBW variable, the Poisson over-dispersion and autoregressive model was used for the analysis (Tobias et al., 2001). Using the backward stepwise regression technique, the least significant explanatory variables were gradually eliminated, to construct the final Poisson model using only those variables that were significant at the p value < 0.05. The RR were calculated for LBW in each province capital for increases of 10 µg/m^3 in the chemical pollutants (PM_{10}, NO_2 and O_3). Thus, if for any of the pollutants the total of data collected without gaps in the time series had a duration of less than 156 weeks, which is equivalent to three years of duration, that series was not introduced into the Poisson model. According to the literature published (Saez et al., 1999), three years is considered the minimum duration that a time series must have in order to be stable in time, without spurious data. This occurred in the case of the variable PM_{10} in Coruna (105 weeks) and with NO_2 in Ciudad Real (99 weeks) and Pontevedra (103 weeks).

Finally, the RR for each province capital were combined in the Poisson regression models using a meta-analysis of random effects that incorporated an estimation of inter-study variability (heterogeneity) in the weighting (Sterne, 2009), which obtained a measure of RR (IC 95%) both at the autonomous community level and at the national level.

2.4. Determination of the attributable impact of chemical pollutants to LBW

The associated population attributable risks (PAR) for each province was calculated based on the RR by applying the following formula: PAR = [(RR-1)/RR] x 100 (Coste and Spira, 1991). PAR was the percentage increase in births with LBW for each 10 µg/m^3 increase in the concentration of the chemical pollutant.

Finally, following the methodology used in prior studies (Díaz et al., 2018; Linares et al., 2018; Ortiz et al., 2017), based on the PAR, the cases of LBW attributable to each pollutant were calculated for increases of 10 µg/m^3.

The software programs used for the statistical analysis were SPSS Statistics v.22 (IBM Company) and STATA/SE 14.1 (StataCorp LP).

3. Results

Table 1 shows the descriptive statistics for the variable low birth weight (LBW) for the 46 province capitals during the nine-year period (470 weeks), from the year 2001–2009. There were no available data

Table 1
Descriptive statistics of low birth weight (< 2500 g) by province capital: Spain 2001–2009 (total days = 3290; weeks = 470).

Province capital		Low birth weight (< 2500 g)					
	Total births	Total	Prevalence (%)	Mean	SD	Min	Max
A Coruña	21,475	1673	7.8	0.4	0.3	0.0	1.4
Albacete	19,941	1597	8.0	0.4	0.3	0.0	1.3
Alicante	37,334	2821	7.6	0.4	0.3	0.0	1.3
Almería	24,575	1938	7.9	0.5	0.3	0.0	1.6
Ávila	6165	474	7.7	0.1	0.1	0.0	0.7
Badajoz	18,201	1344	7.4	0.3	0.3	0.0	1.4
Barcelona	159,488	10,743	6.7	2.7	0.8	0.7	5.6
Bilbao	32,097	2396	7.5	0.6	0.3	0.0	1.7
Burgos	18,180	1269	7.0	0.3	0.2	0.0	1.3
Cáceres	10,529	827	7.9	0.2	0.2	0.0	1.0
Cádiz	11,958	907	7.6	0.2	0.2	0.0	1.0
Castellón	20,869	1489	7.1	0.4	0.3	0.0	1.9
Ciudad Real	8394	618	7.4	0.2	0.2	0.0	0.9
Córdoba	39,145	2730	7.0	0.7	0.4	0.0	2.7
Cuenca	5854	512	8.7	0.1	0.1	0.0	0.7
Granada	26,642	2014	7.6	0.5	0.3	0.0	1.7
Guadalajara	9302	728	7.8	0.2	0.2	0.0	1.0
Huelva	18,884	1341	7.1	0.3	0.2	0.0	1.3
Jaén	14,403	981	6.8	0.2	0.2	0.0	1.1
Las Palmas	40,431	3344	8.3	0.8	0.4	0.0	2.1
León	11,556	842	7.3	0.2	0.2	0.0	0.9
Lleida	16,498	1092	6.6	0.3	0.2	0.0	1.0
Logroño	16,423	1272	7.7	0.3	0.3	0.0	1.6
Madrid	359,835	27,360	7.6	6.9	1.2	3.9	10.0
Málaga	68,945	5684	8.2	1.4	0.6	0.0	3.3
Murcia	56,743	4173	7.4	1.1	0.4	0.1	3.1
Ourense	9455	765	8.1	0.2	0.2	0.0	0.9
Oviedo	19,171	1489	7.8	0.4	0.3	0.0	1.3
Pamplona	22,678	1624	7.2	0.4	0.3	0.0	1.6
P.Mallorca	46,744	3708	7.9	0.9	0.4	0.0	2.3
Pontevedra	8544	643	7.5	0.2	0.2	0.0	1.0
Salamanca	14,380	1106	7.7	0.3	0.2	0.0	1.0
Santander	16,427	1128	6.9	0.3	0.2	0.0	1.1
S.C.Tenerife	22,260	1923	8.6	0.5	0.3	0.0	1.6
Segovia	5405	392	7.3	0.1	0.1	0.0	0.6
Sevilla	85,590	6539	7.6	1.7	0.6	0.3	3.3
Soria	4303	346	8.0	0.1	0.1	0.0	0.6
S.Sebastián	16,932	1162	6.9	0.3	0.2	0.0	1.1
Tarragona	17,539	1318	7.5	0.3	0.3	0.0	1.4
Teruel	3812	280	7.3	0.1	0.1	0.0	0.7
Toledo	9740	705	7.2	0.2	0.2	0.0	0.7
Valencia	88,907	7651	8.6	2.0	0.6	0.3	4.3
Valladolid	28,603	2272	7.9	0.6	0.3	0.0	1.6
Vitoria	23,778	1672	7.0	0.4	0.3	0.0	1.9
Zamora	5752	403	7.0	0.1	0.1	0.0	0.6
Zaragoza	71,104	5919	8.3	1.5	0.6	0.1	3.4

for the province capitals of Girona, Huesca and Lugo, and the data for the province capital of Madrid correspond to the metropolitan area and not to the whole province.

The results of the descriptive analysis of the pollutant variables for the nine-year period (470 weeks) for these 46 province capitals are shown in Table 2. As shown in the case of the pollutants PM_{10} and NO_2, some province capitals lacked sufficient data for a time series without gaps of sufficient length, thus the column corresponding to each pollutant is vacant and not accounted for in the analysis.

Table 3 shows the correlation coefficients established for the three pollutants and highlights the negative coefficients between O_3 and the primary pollutants, and the high positive correlation established between the PM_{10} and NO_2 pollutants.

The possible windows of susceptibility that could exist throughout the gestational period are shown in Table 4. It shows the impact by gestational trimester and the lag in which the statistically significant association ($p < 0.05$) is produced between the variable LBW and the concentrations of any of the three pollutants for each province, after carrying out the corresponding Poisson models. Table 4 also shows the week and month of gestation in which the effect is produced.

Table 4 also shows the 12 provinces in which the PM_{10} concentrations are related to low birth weight, and in seven of them this relationship is produced in the first trimester, and in six it is produced in the third. In contrast, in the case of NO_2 the relationship is established principally in the second and third trimesters, in seven and four respectively, of the 13 provinces in which an association is established. In the case of ozone, the relationship is established in two province capitals, Leon and Pamplona, both in the third trimester of gestation.

Figs. 2 and 3 show, for each province and autonomous community, the resulting meta-analyses of the RR of those province capitals that were significant in the final Poisson models. A global RR for low birth weight was obtained for increases of $10\,\mu g/m^3$ in the case of PM_{10} of 1.104 (1.072, 1.138) (Fig. 1), and of 1.091 (1.059, 1.124) in the case of NO_2 (Fig. 3).

Table 5 presents the values of the population attributable risk for low birth weight in all of Spain for increases of $10\,\mu g/m^3$, with only those province capitals with statistically significant RR. The PAR for low birth weight attributable to PM_{10} is 9.42% and 8.34% for NO_2, that is, in the period of the nine years of the study duration in all of Spain, the PAR of births with low birth weight attributable to PM_{10} and NO_2

Table 2
Descriptive statistics of NO_2, PM_{10} and O_3 levels (μg/m^3), by city: Spain 2001–2009. Only showed cities with valid values in any pollutants.

Town/City	NO_2					PM_{10}					O_3				
	N	Mean	SD	Min	Max	N	Mean	SD	Min	Max	N	Mean	SD	Min	Max
A Coruña						105	33.5	11.1	17.1	79.9	239	44.1	17.0	4.6	80.3
Albacete	468	15.8	7.4	3.6	61.6	465	46.1	15.2	14.9	113.3	470	87.6	26.9	19.3	153.7
Alicante	459	34.7	12.4	9.5	68.2						467	73.0	17.7	26.7	107.9
Almería	470	40.1	10.3	5.0	66.5	209	40.9	11.5	17.9	94.4	470	73.9	17.4	27.6	112.1
Ávila	411	37.2	12.7	5.8	116.7						414	71.9	26.8	10.9	142.6
Badajoz	407	11.4	6.2	2.2	40.9	416	18.3	8.5	4.6	53.4	157	89.1	21.1	41.1	143.4
Barcelona	470	43.5	14.3	13.2	90.6						470	42.6	19.6	2.1	99.9
Bilbao	470	37.3	10.3	13.2	65.7	301	34.4	12.2	8.0	99.9	470	55.0	19.5	5.6	115.3
Burgos	470	31.4	10.9	5.3	89.0	470	29.5	9.9	3.5	70.8	469	74.0	23.9	16.6	150.8
Cáceres	410	12.0	6.3	2.0	42.0	413	18.9	7.2	5.8	45.2	414	89.6	29.3	26.1	175.6
Cádiz											457	82.0	17.5	34.6	130.9
Castellón	470	20.7	7.1	6.7	49.2						470	75.4	20.7	25.9	121.0
Ciudad Real	99	12.9	6.6	4.4	33.0						105	84.3	21.1	42.0	135.0
Córdoba	467	34.2	12.7	11.6	69.4	470	46.5	18.3	12.4	122.3	470	76.5	30.0	16.1	138.4
Cuenca	102	21.8	7.5	8.8	47.0	105	30.8	11.6	9.1	66.9	104	73.7	25.4	21.6	126.6
Granada	469	44.3	13.5	17.2	95.3	470	41.9	15.6	13.7	123.6	470	73.3	28.6	17.7	133.1
Guadalajara	467	28.1	11.7	2.0	77.9	470	29.5	12.3	8.0	98.2	470	84.3	32.5	7.7	163.3
Huelva	470	19.5	5.7	7.0	40.5	470	32.4	10.9	12.9	93.6	470	80.5	23.1	20.4	134.6
Jaén	348	29.7	11.6	11.1	90.2	347	40.1	15.7	10.9	105.2	348	86.4	26.6	15.7	138.0
Las Palmas	428	42.9	14.6	3.6	87.2	313	28.6	8.4	8.4	73.6	417	56.7	16.4	21.7	110.4
León	466	35.1	14.2	9.1	79.1	466	38.0	13.1	10.6	84.2	466	52.6	24.9	7.0	126.3
Lleida	454	26.4	10.9	2.5	84.6						465	64.7	29.5	3.0	137.1
Logroño	105	15.3	7.8	3.4	38.5	442	30.2	12.4	8.3	88.4	442	71.1	25.7	14.6	142.4
Madrid	470	59.4	12.5	30.1	107.2	470	32.5	10.9	11.1	69.4	470	35.7	16.2	5.4	75.0
Málaga	470	34.9	12.1	5.5	71.5	469	31.4	13.4	7.3	112.7	470	78.3	19.9	21.5	124.0
Murcia	154	36.0	13.5	6.7	69.7	156	29.4	10.2	13.8	74.6	157	77.2	28.6	18.3	133.9
Ourense	105	35.7	12.5	18.4	88.6	105	21.8	11.2	8.1	65.0	103	52.8	22.6	9.0	99.7
Oviedo	470	45.3	11.8	16.6	82.3	418	48.2	20.0	16.3	122.3	470	60.8	19.2	17.0	114.4
Pamplona	465	28.0	12.2	3.0	72.4	468	32.6	10.7	10.9	84.7	470	65.8	23.0	10.9	130.7
P.Mallorca	428	42.9	14.6	3.6	87.2	313	28.6	8.4	8.4	73.6	417	56.7	16.4	21.7	110.4
Pontevedra	103	26.5	9.0	2.9	47.6						209	52.5	19.6	12.1	100.0
Salamanca	470	25.0	8.8	3.0	59.3	470	29.6	12.3	11.3	78.9	470	71.7	26.0	9.0	135.7
Santander	470	39.9	10.7	11.2	88.2	470	32.5	9.3	13.3	70.3	470	59.4	21.8	4.7	123.3
S.C.Tenerife	470	25.5	12.3	6.2	82.8	313	56.8	33.7	24.3	376.0	470	69.8	16.2	33.3	119.3
Segovia	413	46.5	13.6	16.1	112.0	412	36.6	21.0	5.6	105.9	413	67.6	24.7	16.1	140.6
Sevilla	470	46.2	13.0	21.1	114.5	470	40.9	13.7	14.0	95.1	470	58.8	22.0	14.7	114.7
Soria	379	28.7	9.6	3.4	58.4	378	29.5	10.7	3.7	77.2	377	65.9	22.1	5.7	120.0
S.Sebastián	470	38.7	9.5	16.7	72.8	462	29.7	10.5	7.5	75.3	470	47.3	17.3	6.9	98.0
Tarragona	470	24.3	7.5	4.1	53.4						314	75.5	23.7	26.5	121.6
Teruel											440	84.0	23.7	24.3	147.3
Toledo	453	26.6	9.9	2.9	88.1	440	39.9	15.0	8.0	106.7	456	83.3	31.5	13.7	154.9
Valencia	470	53.7	15.8	9.1	106.0	332	30.6	10.4	10.0	65.8	470	46.4	17.3	8.7	92.3
Valladolid	470	36.9	9.8	7.9	68.5	470	15.8	7.5	3.6	59.3	470	65.8	27.7	6.3	146.4
Vitoria	470	34.4	9.9	13.1	74.8	460	27.1	11.5	8.0	74.9	470	61.3	19.3	7.6	124.4
Zamora	409	43.5	11.8	18.2	96.2	409	30.0	9.2	13.0	62.2	410	64.0	23.4	13.1	127.7
Zaragoza	470	45.4	13.1	17.0	79.7	470	38.5	15.7	4.4	90.0	470	40.7	22.5	2.4	108.6

was 6105 (2995–9054) and 9385 (2925–15583) respectively.

The case of O_3, having obtained statistical significance in just 2 of the 46 province capitals analysed (Table 5), leads us to consider that these results lack robustness when it comes to the global meta-analysis for all of Spain. Thus, the results for the whole of Spain appear only for PM_{10} and NO_2.

4. Discussion

4.1. Descriptive studies

The prevalence of 7.6% births with low birth weight in the years from 2001–2009 (Table 1) is in accordance with the tendency of the time series presented by the MSSSI (MSSSI, 2017) for the same period, which situates it between seven and eight per cent.

In terms of the average values (Table 1), the highest values are in those province capitals that are most densely populated, Madrid and Barcelona, with averages of 6.9 and 2.7 respectively in terms of births with low birth weight, and Valencia and Seville with an average value of 2.0 for the first and 1.7 for the second. The high average value in Madrid is notable, with a difference that is more than double that of Barcelona, the second province capital in terms of population density (INE). This could be due to the fact that the population of the municipality of Madrid is in itself representative of the entire province and concentrates risk factors for low birth weight that are increasing in developed countries (Forouzanfar et al., 2016): obesity, arterial hypertension, socioeconomic inequality, exposure to toxics and high exposure to air pollution and noise (Arroyo et al., 2016) among others. In fact, Madrid is the capital with greatest exposure to NO_2 (Table 2), with an average weekly concentration of around 60 μg/m^3.

It is important to note in Table 1 that the existing differences in the average values of low birth weight among communities present the same variation as presented by poverty and socioeconomic inequality in Spain. There is almost an imaginary central division in which the provinces belonging to the communities in the South of Spain (Valencian Community, Murcia, Extremadura, Castilla-La Mancha, Canarias and Andalusia) (Llano Ortiz, 2017) have higher average values for births with low birth weight. Furthermore, the situation is complicated by the fact that these communities have been exposed to higher concentrations of air pollution (Table 2), possibly due to the interaction

Table 3
Correlation coefficients between NO_2 and PM_{10}, NO_2 and O_3, PM_{10} and O_3 concentrations during 2001–2009. The name of the province capital appears on the table.

Province capital	Correlation coefficient PM_{10} and NO_2		Correlation coefficient PM_{10} and O_3		Correlation coefficient NO_2 and O_3	
A Coruña	–		− 0.1717		–	
Albacete	0.0259		0.3793	**	− 0.3763	**
Alicante	–		–		− 0.2038	**
Almería	0.1019		0.1395	*	− 0.2946	**
Ávila	–		–		− 0.1119	*
Badajoz	0.1468	**	0.1312		− 0.3427	**
Barcelona			–		− 0.1725	**
Bilbao	0.2831	**	− 0.0907		− 0.4111	**
Burgos	0.4901	**	0.2644	**	− 0.2779	**
Cáceres	− 0.0105		0.1366	**	− 0.2368	**
Castellón	–		–		− 0.3339	**
Ciudad Real	–		–		− 0.5527	**
Córdoba	0.4576	**	0.1223	*	− 0.5171	**
Cuenca	0.5294	**	− 0.0575		− 0.5479	**
Granada	0.3586	**	− 0.1407	**	− 0.5515	**
Guadalajara	0.4214	**	0.0324		− 0.4797	**
Huelva	0.2658	**	0.1812	**	− 0.4021	**
Jaén	0.4215	**	− 0.0399		− 0.6171	**
Las Palmas	0.3992	**	− 0.0460		− 0.3343	**
León	0.3148	**	− 0.4078	**	− 0.0772	
Lleida	–		–		− 0.3232	**
Logroño	0.1261		0.0867		− 0.4567	**
Madrid	0.6502	**	− 0.1309	**	− 0.5973	**
Málaga	0.1507	**	0.0672		− 0.4335	**
Murcia	0.2793	**	− 0.0856		− 0.6325	**
Ourense	0.3540	**	− 0.5710	**	− 0.3236	**
Oviedo	0.4836	**	− 0.0829		− 0.4962	**
Pamplona	0.3479	**	− 0.0537		− 0.4778	**
P.Mallorca	0.3992	**	− 0.0460		− 0.3343	**
Salamanca	0.1364	**	− 0.0273		− 0.3800	**
Santander	0.2993	**	0.0033		− 0.0643	
S.C.Tenerife	0.2218	**	− 0.2197	**	− 0.1115	*
Segovia	0.3161	**	0.0626		− 0.4097	**
Sevilla	0.3167	**	0.1111	*	− 0.4208	**
S.Sebastián	0.4083	**	− 0.0451		− 0.4594	**
Soria	0.3197	**	0.1352	**	0.0563	
Tarragona	–		–		− 0.3663	**
Toledo	0.2345	**	0.1505	**	− 0.4432	**
Valencia	0.3843	**	− 0.1158	*	− 0.3819	**
Valladolid	0.2847	**	− 0.1718	**	− 0.3350	**
Vitoria	0.6313	**	− 0.0829		− 0.5108	**
Zamora	0.2342	**	0.0515		− 0.3659	**
Zaragoza	0.0018		0.1707	**	− 0.4325	**

* or ** means statistically significant.

between air pollution exposure and socioeconomic level (Gray et al., 2014; Laurent et al., 2014; Morelli et al., 2016), which could also produce an effect of inequity in environmental health (Deguen and Zmirou-Navier, 2010; Havard et al., 2009).

The positive and significant coefficients (Table 3) among the primary pollutants, PM_{10} and NO_2, are justified by having the same common origin in the urban atmosphere: road traffic (Querol et al., 2012). This gives the elevated relationship between these two pollutants precisely in the provinces of Madrid and Vitoria, which belong to autonomous communities in which there are a great number of traffic-type urban monitors (Melorose et al., 2015). It should also be taken into account that, in a general vision of the whole of Spain (Table 3) high levels are established in the provinces of the Center and North of Spain, because these provinces are affected in an important way by biomass convection advections (Linares et al., 2017) and by dust from the Sahara (Díaz et al., 2017).

The negative correlation coefficients between O_3 and PM_{10} and NO_2 (Table 3) are explained by the fact that O_3 is a pollutant with a secondary nature that is formed based nitrogen oxide (NO_x) and the volatile organic compounds (COV) (Díaz et al., 2018).

4.2. PM_{10}

4.2.1. Findings

The impact of PM_{10} particles has been shown to be present throughout the gestational period (Table 4), as shown in prior studies (Dibben and Clemens, 2015; Pedersen et al., 2013; Stieb et al., 2012), reaching reductions in birth weight of up to 8.9 gr (IC95%: 13.2, 4.6), even after adjusting for socioeconomic condition (Dadvand et al., 2013). The first trimester of gestation is of primary importance in 7 of the 12 capitals in which PM_{10} particle levels were significantly related to LBW, and most markedly in the first and third trimester (Table 4). This relationship is most important in the first trimester of gestation, in 7 of the 12 capitals in which PM_{10} particles had a significant relationship to LBW, and most markedly in the first and third month of gestation (Table 4). Keeping in mind the collinearity that exists between particulate matter $\leq 10\,\mu m$ and ≤ 2.5, an impact of $PM_{2.5}$ in the first trimester was established in combined data from different cities in the USA (Harris et al., 2014) and in the case of New York (Savitz et al., 2014) it was seen in both the first and the third, with reductions of 18.4 g in the first trimester and, even greater, in the third trimester with reductions of 29.7 g. The relationship established in the third trimester in the current study (Table 4) in up to six province capitals, is also important. It's not possible to corroborate the possible relationship that was established in the province capital of Barcelona in prior studies in this study, due to insufficient data (Dadvand et al., 2014). In contrast, other provinces managed to establish only an association with NO_2 and not with PM_{10}, despite having sufficient data (Table 4). This is the case of the municipality of Madrid, for which a study (Díaz et al., 2016) established a similar result and whose global results coincide with those of the current study- first and third month and the last two months of gestation (Table 4).

Possible biological mechanisms

The respiratory system is the principal entranceway for PM (Kelly and Fussell, 2011; Morakinyo et al., 2016): it is inhaled, crosses the alveolar wall, becomes incorporated into the blood stream and produces a state of oxidative stress (Burton and Jauniaux, 2011; Jauniaux and Burton, 2016), pro-inflammatory (Hertel et al., 2010; Møller et al., 2014) and pro-thrombotic (Martinelli et al., 2012, 2013); this produces maternal hypertension (Babisch and Kamp, 2009) and placental hypoperfusion, which alters the functions of the placenta –exchange and endocrine-, and results in adverse birth outcomes (Erickson and Arbour, 2014). In fact, it has been shown that there is an association between low birth weight and reduced levels of thyroid hormones in the third trimester of gestation due to increases in PM (Janssen et al., 2017a), as also shown in the present study (Table 4).

Oxidative stress produced by exposure to PM can also result in damaged placental DNA, resulting in a decrease in the methylation with increases in exposure to PM (Janssen et al., 2013). This is more marked during the “implantation period” (6–21 days), which is in-line with the results presented here (Table 4), and which has an effect on birth weight, since this period coincides with the development of the placenta (Moore, 2013). PM is also associated with antiangiogenic states (van den Hooven et al., 2012a) and with alterations of the placental vascular morphology (Veras et al., 2008) which make fetal growth difficult and favor low birth weight.

Furthermore, the first trimester of gestation (Table 4) (Janssen et al., 2013) is the trimester with greater susceptibility for congenital damage (Moore, 2013) and thus congenital cardiac alterations that are related to PM are also considered a possible facilitating mechanism for low birth weight (Jacobs et al., 2017; Vrijheid et al., 2011).

It has also been established that the decrease in the proportion of mitochondrial placental DNA is a possible intermediate result that is biologically related to oxidative stress produced by PM and to low birth weight (Gemma et al., 2006; Janssen et al., 2015). The decrease in the third trimester (Janssen et al., 2015), which coincides with the impact window of this study (Table 4), and the increase in larger residential

Table 4

Lags (number of weeks) at which statically significant associations were established between PM_{10}, NO_2 and O_{3h} concentration and low birth weight in Spain (2001–2009). The cells highlighted in gray colour means the effect of PM_{10}, the cells in white colour means the effect of NO_2 and the cells in green colour means the effect of O_{3h}. The name of the province capital appears on the table. * means no effect.

Town/City	First Trimester			Second Trimester			Third Trimester		
	Lags with association	Wk. gest.[a]	Month gest.	Lags with association	Wk. gest.[a]	Month gest.	Lags with association	Wk. gest.[a]	Month gest.
Albacete	*	*	*	NO_2 (lag 19)	18	5	*	*	*
Almería	PM_{10} (lag 35)	2	1	*	*	*	PM_{10} (lag 0)	37	9
Ávila	*	*	*	*	*	*	NO_2 (lag 4)	33	9
Burgos	PM_{10} (lag 35)	2	1	NO_2 (lag 13)	24	6	*	*	*
Cáceres	PM_{10} (lag 30)	7	2	*	*	*	*	*	*
Castellón	*	*	*	*	*	*	NO_2 (lag 8)	29	8
Córdoba	*	*	*	*	*	*	NO_2 (lag 0)	37	9
Granada	*	*	*	NO_2 (lag 21)	16	4	*	*	*
Jaén	PM_{10} (lag 24)	13	3	*	*	*	PM_{10} (lag 5)	32	8
León	*	*	*	*	*	*	O_{3h} (lag 0)	37	9
Madrid	*	*	*	NO_2 (lag 14)	23	6	*	*	*
Murcia	*	*	*	*	*	*	PM_{10} (lag 5)	32	8
Oviedo	*	*	*	*	*	*	PM_{10} (lag 4)	33	9
Pamplona	*	*	*	*	*	*	O_{3h} (lag 5)	32	8
P.Mallorca	NO_2 (lag 36)	1	1	PM_{10} (lag 12)	25	7	PM_{10} (lag 9)	28	7
S.C.Tenerife	PM_{10} (lag 25)	12	3	*	*	*	*	*	*
	PM_{10} (lag 27)	10	3	*	*	*	*	*	*
	PM_{10} (lag 31)	6	2	*	*	*	*	*	*
Soria	*	*	*	NO_2 (lag 16)	21	6	*	*	*
Tarragona	*	*	*	NO_2 (lag 23)	14	4	*	*	*
Valladolid	NO_2 (lag 32)	5	2	*	*	*	*	*	*
	PM_{10} (lag 34)	3	1	*	*	*	*	*	*
Vitoria	*	*	*	NO_2 (lag 19)	18	5	PM_{10} (lag 2)	35	9
Zamora	PM_{10} (lag 36)	1	1	PM_{10} (lag 21)	16	4	NO_2 (lag 0)	37	9
	*	*	*	*	*	*	NO_2 (lag 6)	31	8
Zaragoza	*	*	*	PM_{10} (lag 12)	25	7	*	*	*

distances to primary highways (Janssen et al., 2012), knowing that the intensity of the traffic (Pedersen et al., 2013) and the proximity to road (Dadvand et al., 2014) are two strong predictors of the presence of PM. This may mean that this marker is an important action mechanism. This is even more so the case when there is a possible relationship between the alteration of the genome and the placental hormones that regulate fetal development (Janssen et al., 2017b).

Finally, emphasizing the inflammatory state favored by PM and given that C-reactive protein (Lee et al., 2011) is one of the principal indicators, high levels of C-reactive protein have been established in relation to low birth weight estimates at delivery and in the third trimester (Ernst et al., 2011), which coincides with the window of susceptibility we found (Table 4).

4.3. NO_2

4.3.1. Effects

NO_2 has an effect during the whole duration of pregnancy (Table 4), as has been shown in similar studies carried out in different countries around the world (van den Hooven et al., 2012b; Savitz et al., 2014). These have shown a reduced birth weight of 16.2 g (IC95%: 13.6, 18.8) (Stieb et al., 2016). This has also been shown in European multi-centric studies such as the ESCAPE study, with data from up to 12 countries from 1994 to 2011 (Pedersen et al., 2013) and in meta-analyses and systematic reviews, with 62 included studies, adjusted by socio-economic status (Stieb et al., 2012). At the national level, the INMA study (Iñiguez et al., 2016) is one of the few studies that determines the gestational week and fetal vulnerability in terms of weight, with reduction of 1.6% in weight (IC95%: -3.0,-0.3) between weeks 0 and 12 (first trimester) and of -2.1% (IC95%: -3.7, 0.2) in weeks 20 and 34 (second and third trimesters). These results coincide with the results presented here (Table 4), which establish a greater effect in the second trimester -sixth month (21–24 weeks)- and in the third trimester -eighth month (29–32 weeks) and ninth month (33 weeks-delivery)-, and with the results seen in the municipality of Madrid (Arroyo et al., 2016). Thus we can assure that, despite the presence of studies that seem to show that such an association does not exist (Hjortebjerg et al., 2016), NO_2 has an effect on low birth weight that seems to be accumulative (Estarlich et al., 2011) and more short-term in the case of particulate matter (Table 4).

4.3.2. Possible biological mechanisms

Although its mechanism of action is much less known than that of PM, it has also been associated with low birth weight (Clemente et al., 2016) and with the biologically relevant result of a decrease in the proportion of placental mitochondrial DNA in the second and third trimesters, which is similar to the current study (Table 4). This suggests the possibility of a mechanism that is similar to that carried out by PM, being the oxidative stress the principal protagonist.

Furthermore, in a way that is similar to what occurs with PM, a relationship has been shown with vascular anomalies (van den Hooven et al., 2012a; Veras et al., 2008) and with congenital alterations (Chen et al., 2014; Vrijheid et al., 2011).

4.4. O_3

4.4.1. Effects

The results obtained in terms of ozone behavior are of less relevance (Table 4), with a statistical association only in Leon and Pamplona. Despite this, results among populations that are less urban do agree with what has been published, with a greater association between ozone and low birth weight in less urban populations (Tu et al., 2016). This also justifies the few associations found (Table 4), given that the majority of measurement stations used in the current study are in urban areas.

On the other hand, the occurrences in the third trimester of gestation (Table 4) do not agree with what was found in the municipality of Madrid (Arroyo et al., 2016), but they do agree with other studies (Vinikoor-Imler et al., 2014), though results continue to be somewhat inconsistent (Stieb et al., 2012).

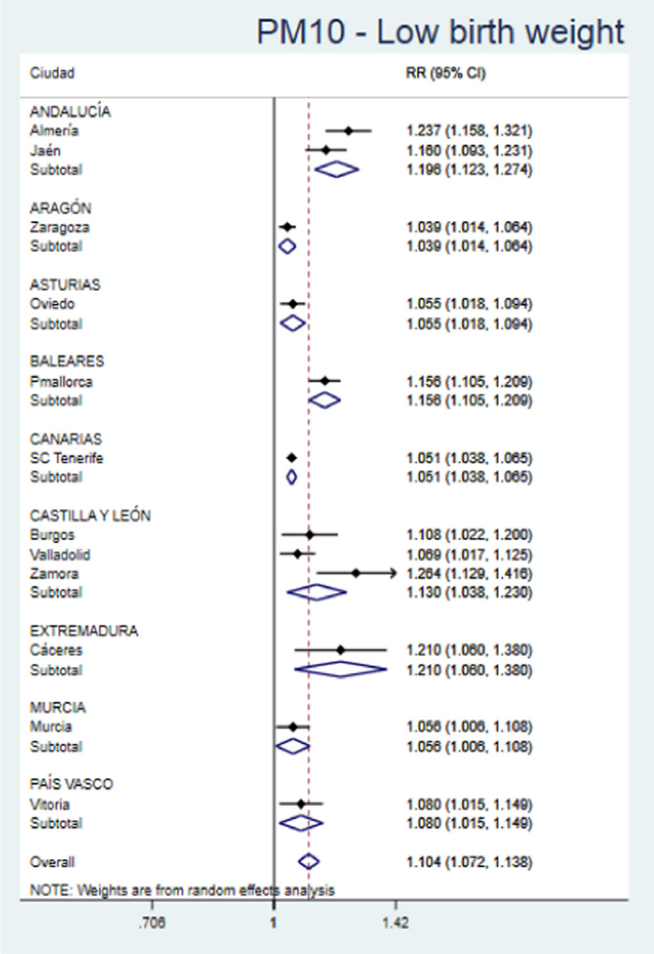

Fig. 2. Relative risks (RR) calculated for increases of 10 μg/m^3 in PM_{10} levels due to low birth weight. Only shows provinces with valid statically significant associations ($p < 0.05$). The name of the provincial capital appears on the table.

4.4.2. *Possible biological mechanisms*

All of this variability in behavior makes it difficult to know the mechanism of action, which differents possible triggers for low birth weight, the decrease in arterial caliber that it can produce (Park et al., 2005) and the increase in resistance at the level of umbilical vessels (Carvalho et al., 2016).

4.5. *Meta-analysis and population attributable risks*

The impact at the macro level shown in the meta-analyses carried out (Figs. 2 and 3) shows that the global risk for low birth weight is greater for PM_{10} than for NO_2, despite the fact that for the latter pollutant there was an additional province capital that showed a statistically significant association. It is probable that this greater effect of particulate matter, seen also in multi-centric studies (Pedersen et al., 2013) and at the local level (Dibben and Clemens, 2015), is due to the great effect it has above all in the first trimester of gestation (Table 4). This is the trimester in which crucial, vital processes occur to support correct fetal development (Moore, 2013) and weight gain.

Table 5 shows that for the whole of Spain the PAR of PM_{10} (RAP: 9.42% (IC95%: 6.72, 19.22)) is greater than that of NO_2 (RAP: 8.34% (IC95%: 5.57, 11.03)), through these differences are not statistically significant. The greater average concentrations of NO_2 compared to those of PM_{10} (Table 2) explain the greater number of cases of LBW attributable to NO_2 (9385 births with low birth weight (IC95%: 2925, 15583)) compared to those of PM_{10} (6105 births with low birth weight (IC95%: 2996, 9054)).

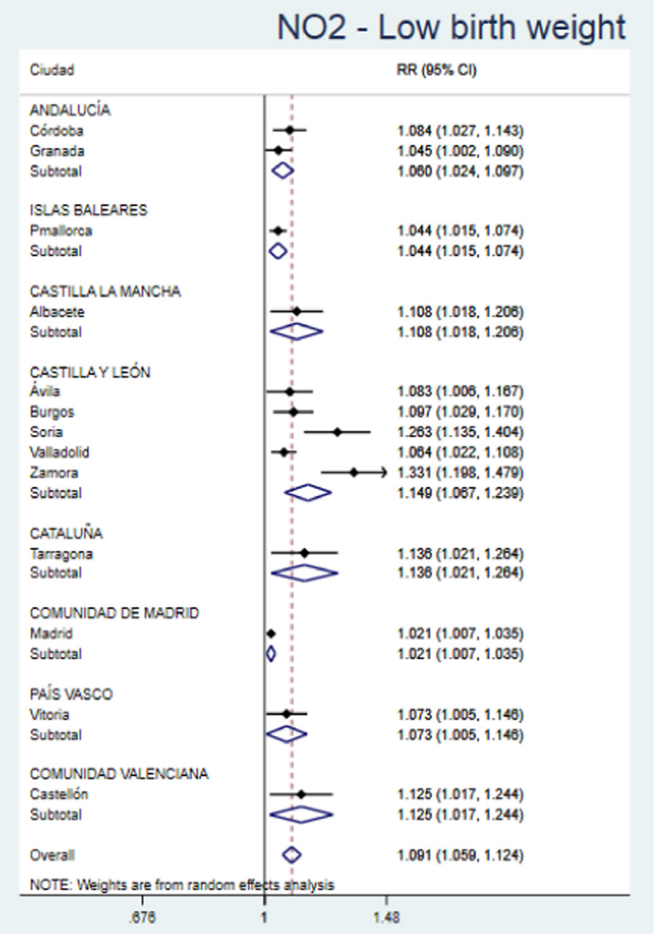

Fig. 3. Relative risks (RR) calculated for increases of 10 μg/m^3 in NO_2 levels due to low birth weight. Only shows provinces with valid statically significant associations ($p < 0.05$). The name of the provincial capital appears on the table.

4.6. *Strengths and limitations*

There are important limitations to this study, including the fact that measurements of pollutants at urban stations could under-estimate the impact of the pollutants (Dibben and Clemens, 2015). Also, the complete absence of data or lack of availability of sufficient data, for some province capitals, impeded carrying out certain models (Table 2).

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.

The threshold temperatures that define T_{heat} or T_{cold} vary among different areas. In the analysis, it is supposed that all people belonging to the same province are exposed to the same temperature threshold; this constituted a limitation of the study. Other papers realized at geographical level less than province showed different patterns in relation to heat exposure (Carmona et al., 2017; López-Bueno et al., 2019). Another limitation about threshold temperatures is that the T_{heat}

Table 5

Population Attributable Risk (PAR) calculated for increases of 10 µg/m^3 in PM_{10}, NO_2 and $O_{3\,h}$ and their Attributable Low Birth Weight, by province and for Spain as a whole: 2001–2009. The name of the province capital appears on the table.

Province capital	PM_{10} - RAP (CI 95%) and Attributable low birth weight			NO_2 - RAP (CI 95%) and Attributable low birth weight			$O_{3\,h}$ - RAP (CI 95%) and Attributable low birth weight		
Albacete	[a]			9.75	(1.81	17.06)	[a]		
	[a]			289	(54	506)	[a]		
Almería	19.16	(13.67	24.31)	[a]			[a]		
	759	(542	963)	[a]			[a]		
Ávila	[a]			7.69	(0.57	14.30)	[a]		
	[a]			127	(9	236)	[a]		
Burgos	9.72	(2.17	16.70)	8.86	(2.80	14.54)	[a]		
	411	(92	706)	407	(129	668)	[a]		
Cáceres	17.33	(5.68	27.54)	[a]			[a]		
	255	(84	406)	[a]			[a]		
Castellón	[a]			11.09	(1.67	19.61)	[a]		
	[a]			413	(62	731)	[a]		
Córdoba	[a]			7.71	(2.65	12.51)	[a]		
	[a]			844	(290	1369)	[a]		
Granada	[a]			4.34	(0.23	8.29)	[a]		
	[a]			449	(24	858)	[a]		
Jaén	13.78	(8.52	18.74)	[a]			[a]		
	480	(297	652)	[a]			[a]		
León	[a]			[a]			16.20	(2.48	27.98)
	[a]			[a]			42	(6	72)
Madrid	[a]			2.07	(0.71	3.42)	[a]		
	[a]			3982	(1366	6580)	[a]		
Murcia	5.29	(0.59	9.77)	[a]			[a]		
	275	(31	508)	[a]			[a]		
Oviedo	5.24	(1.80	8.55)	[a]			[a]		
	398	(137	649)	[a]			[a]		
Pamplona	[a]			[a]			9.43	(1.72	16.54)
	[a]			[a]			86	(16	152)
P.Mallorca	13.50	(9.53	17.31)	4.25	(1.50	6.91)	[a]		
	1162	(820	1489)	737	(260	1198)	[a]		
S.C.Tenerife	4.89	(3.64	6.12)	[a]			[a]		
	432	(322	541)	[a]			[a]		
Soria	[a]			20.79	(11.91	28.78)	[a]		
	[a]			203	(116	281)	[a]		
Tarragona	[a]			11.99	(2.08	20.89)	[a]		
	[a]			457	(79	796)	[a]		
Valladolid	6.49	(1.66	11.09)	5.98	(2.11	9.71)	[a]		
	270	(69	462)	575	(203	934)	[a]		
Vitoria	7.44	(1.52	13.01)	6.83	(0.52	12.73)	[a]		
	380	(78	665)	452	(34	843)	[a]		
Zamora	20.91	(11.43	29.37)	24.86	(16.51	32.37)	[a]		
	258	(141	362)	449	(298	584)	[a]		
Zaragoza	3.72	(1.40	5.99)	[a]			[a]		
	1025	(386	1651)	[a]			[a]		
Spain	9.42	(6.72	19.22)	8.34	(5.57	11.03)	[a]		
	6105	(2996	9054)	9385	(2925	15,583)	[a]		

[a] means no effect.

and the T_{cold} values have been calculated on the daily basis and after that, these values have been calculated on the weekly basis. In Spain, heat waves (Díaz et al., 2015) or cold waves (Carmona et al., 2016) normally last less than a week. The averaged values could be less than the daily values corresponding to Theat and Tcold, so the cold/heat impact on LBW should be smoothed.

Other limitation of 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 such as smoking history, alcohol consumption mother age, number of previous births due to lack of data, which are extremely important determinants of the LBW incidence. These factors may also act as confounders or effect modifiers of relations between air pollution and LBW (Estarlich et al., 2016; 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.

At the same time, this provides the study its principal strength, which is that those time series whose RR were significant (Table 2 y 4) were all of a duration without gaps greater than 3 years, which supports the reliability of these series across time (Saez et al., 1999) and as capable of stabilizing population characteristics (sociodemographic, smoking etc.) and also could be assumed the control of the influence that inter-annual meteorological variability could exert on certain pollutant variables (Eusko Jaurlaritza, 2012).

Another important fact to take into account is that the existing evidence in environmental health continues to present high levels of heterogeneity among studies and even more so in regards to the area of pregnancy and newborns. A possible solution, in addition to continuing to carry out multi-centric studies (Clemente et al., 2016; Iñiguez et al., 2016; Pedersen et al., 2013), would be to try to establish a collective methodology in which time series studies are used as a valid complement to cohort studies, given their cost-effectiveness and capacity to signal windows of susceptibility in fetal development (Table 4).

4.7. Conclusions

The current study shows an important coherence between the biological mechanisms involved and the results obtained in prior published works, which in itself shows that value of the methodology used. On the other hand, the impact of the results obtained- with 6105 cases attributable to PM_{10} and up to 9385 cases attributable to NO_2 in a period of 9 study years- suggest the need to design structural and awareness public health measures to reduce air pollution in Spain.

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, Spain.

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