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ORIGINAL RESEARCH ARTICLE

The influence of air pollution on gestational age at delivery and birthweight in patients with or without respiratory allergy: A nested case–control study

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Abstract

Introduction: Air pollution is a current major health issue. The burden of airborne pollutants and aeroallergen levels varies throughout the year, as well as their interaction and consequences. Prenatal exposure during pregnancy has been associated with adverse perinatal outcomes. The aim of this study was to evaluate the impact of air pollutants on perinatal outcomes in patients with or without respiratory allergy.

Material and methods: Nested case–control retrospective study on 3006 pregnant women. Correlations between concentrations of common pollutants in each trimester of pregnancy and on average during the whole pregnancy and both gestational age at delivery and birthweight were studied. Pearson's correlation coefficient and binary logistic regression were used.

Results: In general, pollutants correlated more strongly with birthweight than with gestational age at delivery. Nine-month NO_2, SO_2, CO, and benzene, and second-trimester CO negatively correlated with birthweight, whereas only first-trimester NO_2 showed a very mild correlation with gestational age at delivery. Negative correlations between pollutants and birthweight were much stronger in the respiratory allergy group ($n=43$; 1.4%) than in the non-allergic group. After adjustments, the most significant predictive pollutant of birthweight was SO_2 in both groups. The best predictive model was much stronger in the allergic group for third-trimester SO_2 ($R^2=0.12$, $p=0.02$) than in the non-allergic group for total SO_2 ($R^2=0.002$, $p=0.02$). For each unit that SO_2 increased, birthweight reduced by 3.22% vs. 1.28% in each group, respectively.

Conclusions: Air pollutant concentrations, especially SO_2, negatively influenced birthweight. The impact of this association was much stronger and more relevant in the group of women with respiratory allergies.

Abbreviations: BW, birthweight; CO, carbon monoxide; CO_2, carbon dioxide; GAD, gestational age at delivery; IgE, immunoglobulin E; IVF, in vitro fertilization; LBW, low birthweight; NO_2, nitrogen dioxide; O_3, tropospheric ozone; PM, particulate matter; PTD, preterm delivery; SD, standard deviation; SO_2, sulfur dioxide.

KEYWORDS
air pollution, allergy, birthweight and perinatal outcomes, gestational age at delivery, pregnancy

1 | INTRODUCTION

Air pollution is a current major health issue[1–3] and, in addition to climate change, is a potential driver for the rise of allergic respiratory diseases.[4] Similarly, airborne allergen emissions have also increased, causing airway inflammation, bronchial hyperreactivity, asthma exacerbations, and sensitization to allergen-specific immunoglobulin E (IgE).[4,5]

Due to their small size, composition and transportation, air pollutants easily access the respiratory tract.[1,6] They may cause oxidative stress, induce a pro-inflammatory and pro-thrombotic state,[3,7] and induce a shift towards a T helper type 2 response.[4] Moreover, the interaction between genetic predisposition and environmental factors, such as these pollutants, might explain some epigenetic mechanisms. For instance, DNA methylation has been described as a key factor in the development of allergic diseases,[7,8] and to modify maternal metabolites and metabolic pathways, both leading to adverse pregnancy and birth outcomes.[8,9]

Pregnancy is a vulnerable period, when the impact of environmental exposures can cause damage in the development and growth of the fetus[2,6,8,10] and the placenta.[5,6,8] Each trimester represents a critical window of exposure,[6,8,9] with rapid cell proliferation, immature organ development and metabolic changes that make them more susceptible to these toxic substances.[6,9]

Preterm delivery (PTD) and low birthweight (LBW) represent two of the leading causes of perinatal mortality and morbidity in developed countries,[1,3,7,11–14] and are both considered indicators of perinatal health care.[1,7,9,15] The prevalence varies, ranging from 5% to 13% for PTD and 8% to 16% for LBW, although this depends on the country and the geographical region studied.[1,3,12–14]

Prenatal exposure to air pollutants and high temperatures during pregnancy has been associated with adverse perinatal outcomes,[2,3,9] mostly PTD[3,5,16–18] and LBW.[3,17] These positive associations are predominantly with particulate matter (PM, particles in suspension less than or equal to 2.5 μm [PM2.5] or 10 μm [PM10]), carbon monoxide (CO), ozone and nitrogen dioxide (NO_2).[3,6,17–19]

However, little is known regarding the effects that these environmental factors might have in the different trimesters of pregnancy and during the whole pregnancy in patients with respiratory allergies.

The aim of this study was to evaluate the impact of pollutants on birthweight and gestational age at delivery in patients with or without respiratory allergy.

Key message

Exposure to air pollutants, especially SO_2, negatively influenced birthweight. These associations were much stronger and more relevant in the respiratory allergy group, although other inflammatory mechanisms cannot be ruled out.

2 | MATERIAL AND METHODS

An analytical observational nested case–control population-based retrospective study was performed using data from September 2017 to June 2018 from a tertiary referral center in Madrid, Spain. Demographic information, maternal comorbidities, labor data, and obstetric and perinatal outcomes were obtained from electronic medical records. Medical records with missing data were excluded.

Medical records were reviewed and women were classified according to their allergic comorbidities. Respiratory allergy was defined as having rhinoconjunctivitis and/or asthma due to aeroallergen sensitization, and both were physician-diagnosed pre-pregnancy. Pollen sensitization included *Cupressus arizonica*, *Platanus acerifolia*, *Olea europaea*, and Timothy grass. Animal dander included dogs, cats, rabbits, hamsters, horses, and bird feathers. Asthma was classified based on the Global Initiative for Asthma classification.[20] The inclusion criteria for the allergic group needed a confirmed diagnosis of allergy based on clinical history symptoms and either positive skin prick test or the detection of specific IgE in serum for aeroallergens, which were considered positive when ≥0.35 kUA/L.

The number of miscarriages, multiple gestations, the need for in vitro fertilization (IVF), sterility and its causes, type of delivery, gestational age at delivery (GAD), birthweight (BW), and the rates of PTD (<37 weeks of gestation) and LBW (<2500 g) were recorded.

Air pollutants included NO_2, PM (particles in suspension less than or equal to 2.5 μm [PM2.5] or 10 μm [PM10]), sulfur dioxide (SO_2), CO, benzene, and tropospheric ozone (O_3); NO_2, PM10, PM2.5, SO_2, benzene, and O_3 were measured in μg/m^3, CO_2 was measured in mg/m^3. Data were obtained from Madrid's monthly bulletin quality of air published by the city council of Madrid on their official website,[21] which recorded levels using a network of urban background stations located at different points in the health sanitary district related to the University Hospital La Paz. This health sanitary district was defined as the geographical extension that includes patients that have this hospital as a reference for medical care. Data from each station were collected and a mean accumulated exposure for the whole district per month was calculated.

Pollen levels were also evaluated and pollen allergens included *C. arizonica* (CA), *P. acerifolia* (PA), *O. europaea* (OE), and Timothy grass (TG). Data were obtained from the official website of Sociedad Española de Alergología e Inmunología Clínica listing pollen levels,[22] which recorded levels using two pollen stations located at different strategic points of the city. Pollen levels were measured in grains/m^3.

In addition, two meteorological parameters, temperature and monthly precipitation, for this district were also reviewed and included in the analysis. Data were extracted from the Institutional Climatological and Meteorological Archive website.[23] Temperature was measured in degrees Celsius and monthly precipitation was measured L/m^2.

Four composite variables were created, calculating the mean accumulated amount of each air pollutant, each pollen measured, temperature and monthly precipitation in four different periods, measuring the exposure during the whole pregnancy (approximately 9 months) and during the first, second, and third trimesters for each patient based on their labor date and their gestational weeks (1–13, 14–26, and 27 to birth, respectively). As University Hospital La Paz is a tertiary referral center, all pregnant patients referred from other health sanitary areas were excluded from the analysis. Cases of congenital abnormalities were also excluded.

2.1 | Statistical analyses

Qualitative variables were expressed as number and percentages, and Fisher exact and chi-squared tests were used for comparisons. Distribution of numeric variables was evaluated by the Kolmogorov–Smirnov test and the analysis of histograms. Quantitative variables were shown as median and interquartile range in cases of non-parametric distribution. Comparisons were made using Student's *t* test. To evaluate the impact of pollutants on BW and GAD, Pearson's correlation coefficient and linear regression were employed. Statistical significance was set at a 95% level ($p < 0.05$). Analyses were performed with SPSS Statistics software, version 20 (IBM).

2.2 | Ethics statement

The study was approved by the local research Medical Ethical Committee (PI5246) on May 9, 2022. As a retrospective study, we obtained the approval to waiver the consent form.

3 | RESULTS

In total, 3006 pregnant women were included in the study and 43 (1.4%) had a respiratory allergy. Tables 1 and 2 show their clinical characteristics, their obstetric and perinatal outcomes, and their allergy-related comorbidities when applicable.

Maternal median age was 34 years in both groups, and patients were mainly in the age range 25–35 years. Rhinoconjunctivitis and asthma were present in 49 (1.6%) and 97 (3.2%) of the studied

TABLE 1 Clinical characteristics, obstetrics and perinatal outcomes of pregnant patients with or without respiratory allergy ($n = 3006$).

Characteristics, *n* (%)	Pregnant patients with RA *n* = 43	Pregnant patients without RA *n* = 2963	*p* value
Age (years), median (IQR)	34 (30–37)	34 (30–38)	0.28
Age range (y), *n* (%)			0.29
<25	1 (2.3)	280 (9.4)	
≥25 to <35	24 (55.8)	1528 (51.6)	
≥36	18 (41.9)	1154 (38.9)	
Number of miscarriages, *n* (%)	19 (44.2)	1195 (40.3)	0.58
≤3	19 (100)	1163 (97.3)	0.96
>3	0	32 (2.7)	
Multiple gestations, *n* (%)	4 (9.3)	134 (4.5)	0.13
IVF, *n* (%)	3 (7)	80 (2.7)	0.11
Sterility, *n* (%)	3 (7)	68 (2.3)	0.07
Male cause	2 (66.7)	6 (8.8)	0.08
Female cause	3 (100)	62 (91.1)	
Gestational age at delivery (wk), median (IQR)	39.3 (38.5–40.6)	39.3 (38.2–40.2)	0.56
Preterm delivery, *n* (%)	5 (11.6)	260 (8.8)	0.52
Birthweight (g), median (IQR)	3240 (3020–3510)	3200 (2900–3500)	0.21
Low birthweight, *n* (%)	2 (4.7)	218 (7.4)	0.77
Delivery, *n* (%)			0.025
Vaginal delivery	31 (72.1)	2507 (84.6)	
Cesarean section	12 (27.9)	456 (15.4)	

Abbreviations: IQR, interquartile range; IVF, in vitro fertilization; RA, respiratory allergy.

population, respectively, and an allergic etiology was diagnosed in 43 (87.8%) and 18 (18.6%) of these patients correspondingly. Pollen was the main aeroallergen identified in all of the patients (43; 100%), followed by house dust mite (30; 69.8%).

TABLE 2 Allergy-related comorbidities of pregnant patients with respiratory allergy ($n=43$).

Characteristics, *n* (%)	Pregnant patients with RA
Allergic comorbidities	
Rhinoconjunctivitis	49 (1.6)
Allergic RC	43 (87.8)
Non-allergic RC	6 (12.2)
Asthma	97 (3.2)
Allergic asthma	18 (18.6)
Non-allergic asthma	79 (81.4)
Sensitization aeroallergens	
Pollen	43 (100)
House dust mite	30 (69.8)
Animal dander	5 (11.6)

Note: Pollen sensitization included *Cupressus arizonica*, *Platanus acerifolia*, *Olea europaea*, and Timothy grass. Animal dander included dogs, cats, rabbits, hamsters, horses, and bird feathers.

Asthma was classified based on the Global Initiative for Asthma 2021 classification. The inclusion criteria for the allergic group needed a confirmed diagnosis of allergy based on clinical history symptoms and either positive skin prick test or the detection of specific IgE in serum for aeroallergens, which were considered positive when ≥0.35 kUA/L.

Abbreviations: RA, respiratory allergy; RC, rhinoconjunctivitis.

Analyzing the number of miscarriages, GAD, BW, and the rates of PTD and LBW, no statistical differences were found, except for the type of delivery, where the rate of cesarean section was significantly higher in the respiratory allergy group. Multiple gestations, IVF, and sterility were almost double in the respiratory allergy group. However, these differences were not statistically significant.

Figure 1 shows the mean accumulated measurement of each air pollutant per month throughout the studied period in the health sanitary district of University Hospital La Paz. Figure 2 shows the mean accumulated temperature and monthly precipitation per month in the health sanitary studied, and Figure 3 shows the mean accumulated pollen levels per month from Madrid aeroallergen stations in the health sanitary district of University Hospital La Paz. Air pollution exposures during the whole pregnancy and the three different trimesters for both groups were compared and showed no statistical differences between groups (data shown in Table S1).

Table 3 shows the correlations between pollutants and BW and GAD (considering both variables as continuous), for all the participants, and for non-allergic and allergic patients. Pollutants correlated much more strongly with BW than with GAD. Nine-month NO_2, SO_2, CO, and benzene, and second-trimester CO were negatively correlated with BW, but only first-trimester NO_2 showed a very mild correlation with GAD.

Correlations between temperature and monthly precipitation and BW and GAD were also analyzed for all the participants and for each group. Only temperature during the third trimester showed a significant positive correlation with BW when all the participants were studied, and in the allergic group, a significant negative correlation was found between temperature during the first trimester and BW, and temperature during the second trimester and GAD,

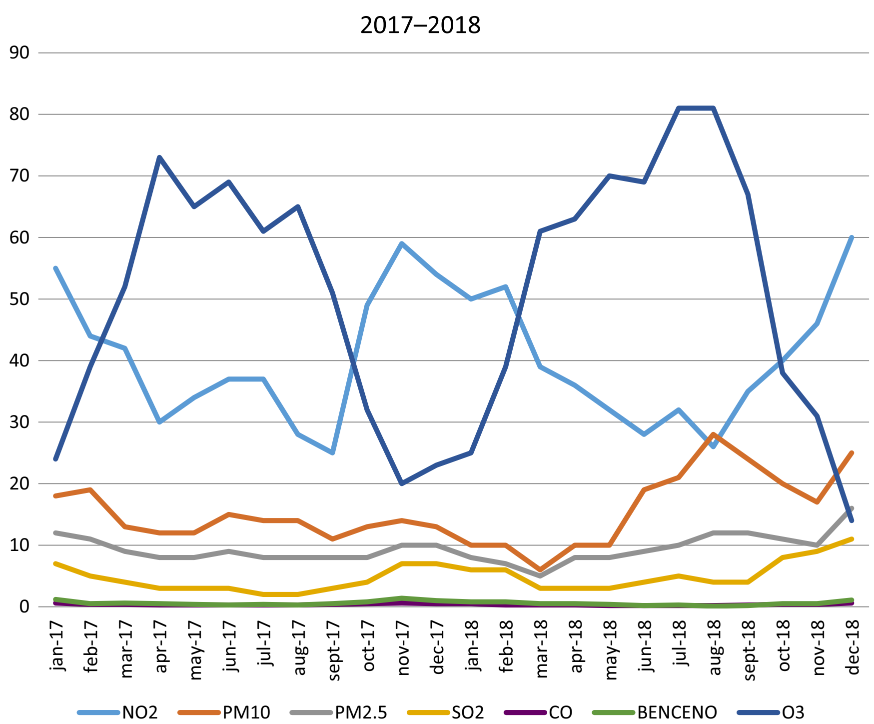


FIGURE 1 Mean accumulated air pollution exposure per month from Madrid's network of urban background stations in the health sanitary district of University Hospital La Paz. NO_2, PM10, PM2.5, SO_2, benzene, and O_3 were measured in μg/m^3. CO was measured in mg/m^3. NO_2, nitrogen dioxide; PM2.5 and PM10, particulate matter (particles in suspension less than or equal to 2.5 μm [PM2.5] or 10 μm [PM10]); CO, carbon monoxide; O_3, tropospheric ozone; SO_2, sulfur dioxide.

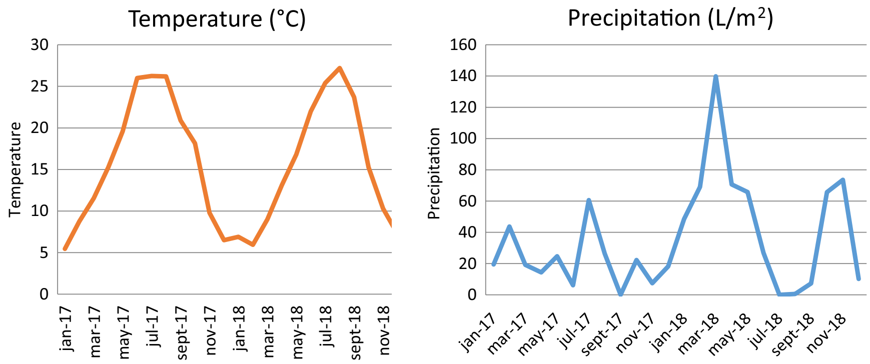
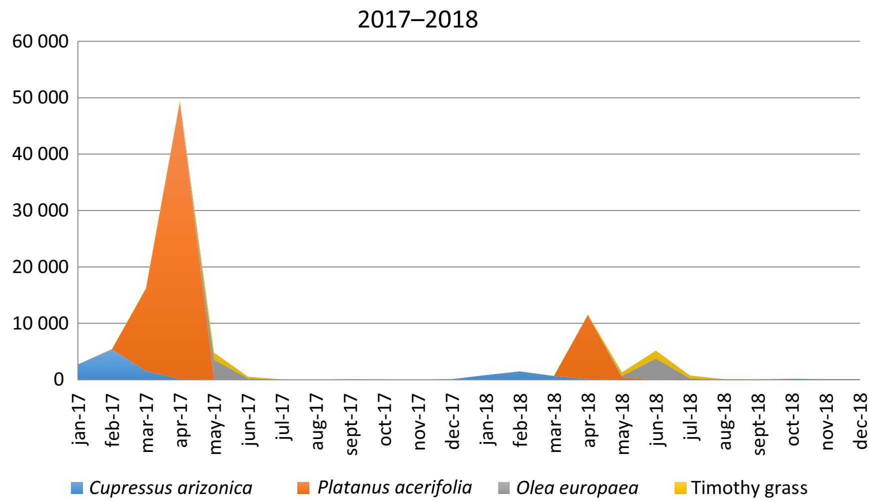


FIGURE 2 Mean accumulated temperature and monthly precipitation per month in the health sanitary district of University Hospital La Paz. Temperature was measured in degrees Celsius and monthly precipitation was measured L/m^2. O_2, PM10, PM2.5, SO_2, benzene, and O_3 were measured in μg/m^3. CO was measured in mg/m^3. CO, carbon monoxide; NO_2, nitrogen dioxide; O_3, tropospheric ozone; PM2.5 and PM10, particulate matter (particles in suspension less than or equal to 2.5 μm [PM2.5] or 10 μm [PM10]); SO_2, sulfur dioxide.

FIGURE 3 Mean accumulated pollen levels per month from Madrid aeroallergen stations in the health sanitary district of University Hospital La Paz. Pollen allergens included *Cupressus arizonica* (CA), *Platanus acerifolia* (PA), *Olea europaea* (OE), and Timothy grass (TG). All aeroallergens were measured in grains/m^3.



although these were very weak ($r=0.039$, $p=0.037$) and weak ($r=-0.305$, $p=0.049$; $r=-0.314$, $p=0.043$), respectively.

With regards to pollen exposure, a significant positive correlation was observed between GAD and 9-month exposure to CA, first-trimester CA, second-trimester PA, OE, and TG, and between BW and 9-month PA, first-trimester CA and PA, and second-trimester OE and TG for all the participants (all considered very weak). Analyzing the non-allergic group, positive correlations were observed between GAD and first-trimester CA and second-trimester TG, and between BW and 9-month PA, first-trimester CA and PA, second-trimester OE and TG (all very weak). Evaluating the allergic group, a negative correlation was observed between GAD and first-trimester OE and TG (both moderate), and none for BW.

Using linear regression analysis, the only pollutant that was significantly predictive for BW was SO_2. However, for non-allergic patients it was whole pregnancy SO_2 exposure ($R^2=0.002$, $p=0.16$ for the model), and for allergic patients it was third-trimester SO_2 with much higher predictive value ($R^2=0.12$, $p=0.02$ for the model; Figure 4). Temperature, monthly precipitation, and the four different pollen exposures studied did not influence the analysis.

We calculated the mathematical equation applied for both models to predict BW. For non-allergic patients, this was "Birthweight = 3354.26−43.636 * SO_2 (approximately 9 months)", which means that for every rise of a unit of SO_2 (μg/m^3) exposed during the whole pregnancy average in the non-allergic group, BW will be reduced 43 g in newborns weighing 3354 g, which represents 1.28% less of its weight. For allergic patients, the equation was "Birthweight = 3779.516−121.731 * SO_2 (third-trimester exposure)". Considering this formula, for every rise of a unit of SO_2 (μg/m^3) exposed in the third-trimester in the allergic group, BW will be reduced 121.73 g in newborns weighing 3779 g, which represents 3.22% less of its weight.

There were too few patients to draw meaningful conclusions on either PTD or LBW, and their subcategories.

4 | DISCUSSION

In the present study, we investigated the influence of air pollutants on GAD and BW in patients with or without respiratory allergy. Whole pregnancy NO_2, SO_2, CO, and benzene exposures, and

TABLE 3 Correlations between air pollutants in the four different periods of gestation studied and, birthweight and gestational age at delivery (All $n = 3006$; Allergic group $n = 43$; Non-allergic group $n = 2963$).

	Birthweight			Gestational age at delivery		
Pollutant	All	Allergy	Non-allergy	All	Allergy	Non-allergy
Whole pregnancy						
NO_2	$r = -0.04$ $p = 0.02$	NS	$r = -0.04$ $p = 0.02$	NS	NS	NS
SO_2	$r = -0.04$ $p = 0.01$	NS	$r = -0.04$ $p = 0.02$	NS	NS	NS
CO	$r = -0.04$ $p = 0.03$	NS	$r = -0.04$ $p = 0.04$	NS	NS	NS
Benzene	$r = -0.045$ $p = 0.017$	NS	$r = -0.044$ $p = 0.021$	NS	NS	NS
1st trimester						
NO_2	NS	NS	NS	$r = -0.04$ $p = 0.04$	NS	$r = -0.04$ $p = 0.03$
SO_2	NS	NS	NS	NS	NS	$r = -0.036$ $p = 0.049$
CO	NS	NS	NS	NS	NS	$r = -0.039$ $p = 0.032$
2nd trimester						
CO	$r = -0.039$ $p = 0.04$	NS	NS	NS	NS	NS
3rd trimester						
NO_2	NS	$r = -0.35$ $p = 0.021$	NS	NS	NS	NS
SO_2	NS	$r = -0.354$ $p = 0.02$	NS	NS	NS	NS
Benzene	NS	$r = -0.301$ $p = 0.05$	NS	NS	NS	NS

Abbreviations: CO, carbon monoxide; NO_2, nitrogen dioxide; NS, not significant; SO_2, sulfur dioxide.

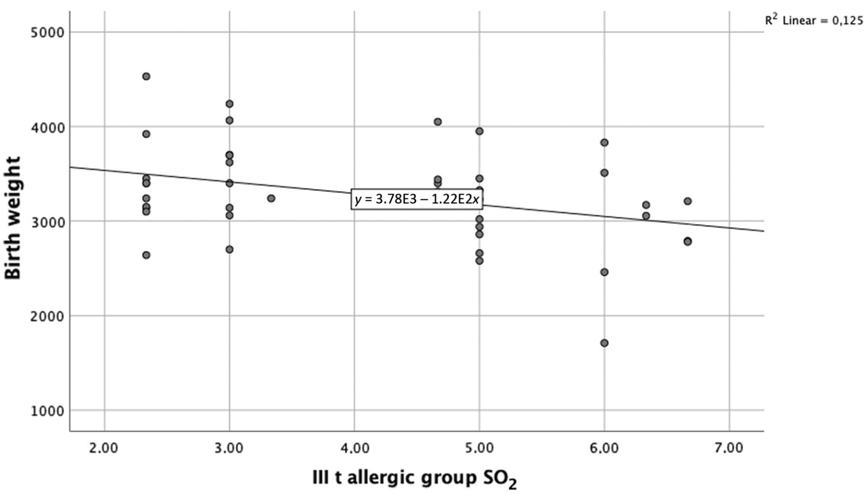


FIGURE 4 Linear regression analysis for third-trimester SO_2 in the allergic group as a significantly predictive variable for birthweight ($R^2 = 0.12$, $p = 0.02$ for the model).

second-trimester CO negatively correlated with BW, but only first-trimester NO_2 showed a very mild correlation with GAD. However, after adjustments, the most significant predictive pollutant of BW was SO_2 for both groups, although the impact of this association was much stronger and relevant in the group of respiratory allergy patients. Temperature, monthly precipitation, and different pollen exposures did not modify the obtained results.

The burden of airborne pollutants and aeroallergen levels varies throughout the year. Air pollutants can induce physiological and chemical modifications of aeroallergens, acting as adjuvants and changing the immunogenicity, and the amount of allergic proteins released.[4,24] These modifications make patients with respiratory allergies more likely to be affected by them,[4,5] such as allergic rhinitis and/or asthma patients.[5,16] In Madrid, the estimated population affected by one or both conditions is 10%–30% approximately, and mainly individuals between the ages of 25 and 35 years.[24] Currently, this time frame overlaps during the first pregnancy.

In our study, maternal age was similar in both groups, which is also comparable to the mean age of the first pregnancy in Spain according to 2018 data.[12,25] The percentage of pregnant patients included in the age range over 35 is higher than for other studies;[16] however, similar to other European and Chinese data.[6,13,19] These might be influenced by the phenomenon seen in recent decades of Spanish individuals delaying their first pregnancy.[26] The percentage of individuals affected by asthma, rhinoconjunctivitis, and allergic rhinoconjunctivitis in the present study was similar to other published data.[25,27,28] Nevertheless, allergic asthma was lower than expected. There could be multiple reasons for this finding: the retrospective nature of our data, cases missed, and allergic comorbidities not mentioned in the obstetrical evaluation if they are mild and well controlled. Regarding sensitization, pollen was the main allergen due to Madrid's geographical location.[25]

In relation to obstetric and perinatal outcomes, no statistical differences were observed in all the variables studied, except for the delivery mode. The rate of cesarean section was slightly higher than in other series,[27] but lower if compared with other Spanish, European, and US rates.[12,13] This could be related to the population reviewed in this tertiary hospital. It is worth mentioning that the first indication of performing a cesarean section in allergic patients was related to multiple gestations. In addition, higher rates of PTD, multiple gestations, sterility, and use of IVF were seen in the respiratory allergy group, but differences were not statistically significant. This may be due to reduce statistical power for these secondary outcomes. Furthermore, in another study recently published by our group with a higher number of cases, we found significant associations.[29] The rates of PTD and LBW in the present study were similar to other published data, which established the prevalence of both perinatal outcomes to range from 5% to 13% and from 8% to 16%, respectively.[3,6,12–14,18] However, due to the sample size in the allergic group, no meaningful conclusions could be drawn regarding PTD and LBW.

Reviewing the mean accumulated temperature per month during the studied period, there were some fluctuations in the maximum and minimum temperatures varying from 5°C to over 25°C. Comparing these fluctuations with the variability of precipitation, we observed greater precipitation in the winter and spring of 2018, which in turn, highlights the drop in pollen levels observed in the same period compared with the previous decrease during 2017. It seems that this higher precipitation rate during the first half of 2018 had little effect on the levels of air pollutants during 2018.

Analyzing the accumulated air exposure of each group during the whole pregnancy and during their different trimesters, no differences were found. NO_2 is considered a marker for traffic-related ambient air pollution.[7,9,30,31] Madrid's NO_2 concentration varied throughout the seasons, probably showing the relationship between the weather, vacation periods, and forms of commuting by the population in this city. In addition, NO_2 plays a key role in the O_3 formation process. Both curves resemble nearly inverted mirror images.

Air Quality Guidelines recently updated by the World Health Organization have different recommended levels for long-term and short-term exposures to different air pollutants.[1] The annual level of exposure recommended for PM2.5 was 5 $\mu g/m^3$, and for PM10 was 15 $\mu g/m^3$. The recommendation for O_3 was based on the peak season exposure, defined as the six consecutive months of the year with the highest 6-month running-average concentration of this gas, which was 60 $\mu g/m^3$ in the latest guideline.[1] For NO_2, the annual level recommended was 10 $\mu g/m^3$.[1] Only short-term (24-h) levels were given for SO_2 and CO (40 and 4 $\mu g/m^3$, respectively), and no levels for benzene were mentioned.[1] During the study period and using the available data, both groups exceed only the recommendations for PM2.5 exposure. Nevertheless, this air pollutant has been identified in Madrid as having the greatest effect on health in the general population.[3]

In this study, pollutants correlated more strongly with BW than with GAD, and SO_2 exposure was the most significant predictive pollutant for BW. In a systematic review in a Chinese population, SO_2 exposure was consistently associated with PTD and LBW.[10] Another study evaluated BW reduction and gaseous pollutants, and showed unclear results regarding SO_2 exposure.[32] Nonetheless, the current knowledge about the effect of these air pollutants on adverse obstetrical and perinatal outcomes is controversial.[8,10,33] Some studies found no association, inconclusive results or insufficient evidence[10]; and others even reported some of them as protective factors.[3,5,7,34] However, not all studies included all air pollutants, they were mainly based on studies in the USA and China, lacking data for other regions, and their designs were heterogeneous, making comparisons between their results harder. In addition, the reported mean concentrations likely for the whole pregnancy for SO_2 ranged from 1.1 to 12.2 ppb in this umbrella review (approximately 2.98–33.05 $\mu g/m^3$).[10] In our study, the mean average of SO_2 was 4.1 $\mu g/m^3$ (approximately 1.51 ppb), which could have influenced our results.

The mechanism by which air pollutants affect perinatal outcomes is not clear. Experimental studies have suggested several mechanisms, such as oxidative stress, inflammatory responses, endocrine disruption, DNA damage, mitochondrial damage of placental tissue, interference with nutrient transportation, and reduced oxygenation in maternal blood.[5,6,8–10] All of these mechanisms could induce a systemic response in the mother and enhance the possibility of other great obstetrical syndromes, which are a common cause of PTD and LBW.[5,7,8,11] We did not evaluate other disorders in the present study because of its sample size, which could have influenced the results.

Additionally, the developing fetus and the placenta are known to be highly susceptible to pollutants.[5,6,8,9] Furthermore, these exposures might be critical during some specific windows.[3,7,18,19,30,31,33]

Nevertheless, some published data suggested that windows of exposure might not correlate with clinical trimesters only,[9,18] and that further evaluation should focus on models, which combine exposures to multiple pollutants.[5,9,15]

The results of our study have limitations, such as the retrospective design, the low number of patients enrolled in the respiratory allergy group that could have led to reduced statistical power and that only one hospital was used as study setting. In addition, we have only evaluated a specific period of time in which there were few variations in the concentrations of some of the air pollutants studied. Measurement errors could have also affected the station collectors, such as sample preparation or timing of collection, but the use of repeated measurements and standardized tools mitigate these possible biases. Also, the patients included lived in the health sanitary district of the hospital, but we did not use postal codes to determine a specific exposure based on each individual's housing, residential proximity to traffic, nor did we consider indoor pollutants or home environmental factors, such as parental smoking, mold/damp stains, window pane condensation, and redecoration inside the house. We did not evaluate other socioeconomic variables that could have acted as confounding factors. However, the present study is one of the first European studies to evaluate these outcomes using medical records instead of ecological studies or studies based on general health and birth registry data.

5 | CONCLUSION

To our knowledge, this is one of only a few studies based on medical records that investigate the influence air pollutants on BW and GAD in pregnant patients with or without respiratory allergy. In the present study, pollutants correlated more strongly with BW than with GAD, and these correlations were stronger in the respiratory allergy group.

Further studies with more samples are needed to reach definite conclusions regarding the clinical relevance of short- and long-term exposures to these modifiable air pollutants in both mother and child. Nevertheless, there is sufficient evidence to suggest that a reduction in their exposure is beneficial. Investigations and assessments are a key target for public health in order to promote a healthier environment, prevent future diseases and improve as well as guide prenatal care.

AUTHOR CONTRIBUTIONS

IB and JLB wrote the first draft of the manuscript, created the tables and participated in the design. MF, MC, EMB, NMS, and JLB reviewed and edited the manuscript. All authors contributed to the article and approved the submitted version.

CONFLICT OF INTEREST STATEMENT

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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REFERENCES

1. World Health Organization. 2022. https://www.who.int
2. Roos N, Kovats S, Hajat S, et al. Maternal and newborn health risks of climate change: a call for awareness and global action. *Acta Obstet Gynecol Scand*. 2021;100:566-570.
3. Arroyo V, Díaz J, Carmona R, Ortiz C, Linares C. Impact of air pollution and temperature on adverse birth outcomes: Madrid, 2001-2009. *Environ Pollut*. 2016;218:1154-1161.
4. Sedghy F, Varasteh AR, Sankian M, Moghadam M. Interaction between air pollutants and pollen grains: the role on the rising trend in allergy. *Rep Biochem Mol Biol*. 2018;6:219-224.
5. Lavigne E, Yasseen AS 3rd, Stieb DM, et al. Ambient air pollution and adverse birth outcomes: differences by maternal comorbidities. *Environ Res*. 2016;148:457-466.
6. Liu X, Ye Y, Chen Y, et al. Effects of prenatal exposure to air particulate matter on the risk of preterm birth and roles of maternal and cord blood LINE-1 methylation: a birth cohort study in Guangzhou, China. *Environ Int*. 2019;133:1-12.
7. Arroyo V, Linares C, Díaz J. Premature births in Spain: measuring the impact of air pollution using time series analyses. *Sci Total Environ*. 2019;660:105-114.
8. Inoue K, Yan Q, Arah OA, et al. Air pollution and adverse pregnancy and birth outcomes: mediation analysis using metabolomic profiles. *Curr Environ Health Rep*. 2020;7:231-242.
9. Klepac P, Locatelli I, Korošec S, Künzli N, Kukec A. Ambient air pollution and pregnancy outcomes: a comprehensive review and identification of environmental public health challenges. *Environ Res*. 2018;167:144-159.
10. Nyadanu SD, Dunne J, Tessema GA, et al. Prenatal exposure to ambient air pollution and adverse birth outcomes: an umbrella review of 36 systematic reviews and meta-analyses. *Environ Pollut*. 2022;1(306):1-25.
11. Arroyo V, Díaz J, Ortiz C, Carmona R, Sáez M, Linares C. Short term effect of air pollution, noise and heat waves on preterm births in Madrid (Spain). *Environ Res*. 2016;145:162-168.
12. Hidalgo-Lopezosa P, Jiménez-Ruz A, Carmona-Torres JM, Hidalgo-Maestre M, Rodríguez-Borrego MA, López-Soto PJ. Sociodemographic factors associated with preterm birth and low birth weight: a cross-sectional study. *Women Birth*. 2019;32:538-543.
13. European Health Perinatal Report. 2015. [Cited February, 28th 2022]. https://www.europeristat.com/index.php/reports/european-perinatal-health-report-2015.html
14. Chawanpaiboon S, Vogel JP, Moller AB, et al. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. *Lancet Glob Health*. 2019;7(1):37-46.
15. Zahran S, Weiler S, Mielke HW, Pena AA. Maternal benzene exposure and low birth weight risk in the United States: a natural experiment in gasoline reformulation. *Environ Res*. 2012;112:139-146.
16. Lavigne E, Gasparrini A, Stieb DM, et al. Maternal exposure to aeroallergens and the risk of early delivery. *Epidemiology*. 2017;28:107-115.
17. Díaz J, Arroyo V, Ortiz C, Carmona R, Linares C. Effect of environmental factors on low weight in non-premature births: a time series analysis. *PloS One*. 2016;11:1-14.
18. Wang Q, Benmarhnia T, Zhang H, et al. Identifying windows of susceptibility for maternal exposure to ambient air pollution and preterm birth. *Environ Int*. 2018;121(Pt 1):317-324.
19. Stieb DM, Lavigne E, Chen L, Pinault L, Gasparrini A, Tjepkema M. Air pollution in the week prior to delivery and preterm birth in 24 Canadian cities: a time to event analysis. *Environ Health*. 2019;18:1-11.

20. Global Initiative for Asthma (GINA) guidelines. 2022. https://ginasthma.org
21. Portal Web de Calidad del Aire del Ayuntamiento de Madrid. 2022. https://www.mambiente.madrid.es/opencms/calaire/consulta/boletin_mensual.html
22. SEAIC pollen levels official website. SEAIC Niveles ambientales de Pólenes. (Sociedad Española de Alergología e Inmunología Clínica). 2022. https://www.polenes.com/es/home
23. Archivo Climatológico y Meteorológico Institucional. Arcimis. AEMet (Agencia Estatal de Meterología) and Gobierno de España. 2023. https://repositorio.aemet.es
24. Reinmuth-Selzle K, Kampf CJ, Lucas K, et al. Air pollution and climate change effects on allergies in the Anthropocene: abundance, interaction, and modification of allergens and adjuvants. *Environ Sci Technol*. 2017;51:4119-4141.
25. Dordal Culla MT. Capítulo 3. Rinoconjuntivitis. *Alergológica 2015*. SEAIC- Faes Farma; 2015:122-142.
26. Instituto Nacional de Estadística. INE. 2022. https://www.ine.es/jaxiT3/Datos.htm?t=1580
27. Trønnes H, Wilcox AJ, Markestad T, Tollånes MC, Lie RT, Moster D. Associations of maternal atopic diseases with adverse pregnancy outcomes: a national cohort study. *Paediatr Perinat Epidemiol*. 2014;28:489-497.
28. Somosköví Á, Bártfai Z, Tamási L, Kocsis J, Puhó E, Czeizel AE. Population-based case-control study of allergic rhinitis during pregnancy for birth outcomes. *Eur J Obstet Gynecol Reprod Biol*. 2007;131:21-27.
29. Bartha I, de la Fuente M, de la Calle M, Martin Boado E, Martinez-Sanchez N, Bartha JL. The influence of maternal respiratory allergy on obstetrics and perinatal outcomes: a nested case-control study. *Int J Gynaecol Obstet*. 2023;161:509-516.
30. Lu C, Zhang W, Zheng X, Sun J, Chen L, Deng Q. Combined effects of ambient air pollution and home environmental factors on low birth weight. *Chemosphere*. 2020;240:124836.
31. Lu C, Cao L, Norbäck D, Li Y, Chen J, Deng Q. Combined effects of traffic air pollution and home environmental factors on preterm birth in China. *Ecotoxicol Environ Saf*. 2019;184:109639.
32. Stieb DM, Chen L, Eshoul M, Judek S. Ambient air pollution, birth weight and preterm birth: a systematic review and meta-analysis. *Environ Res*. 2012;117:100-111.
33. Lu C, Deng M, Norbäck D, Zijing L, Murithi R, Deng Q. Effect of outdoor air pollution and indoor environmental factors on small for gestational age. *Building Env*. 2021;206:108399.
34. Protano C, Scalise T, Orsi GB, Vitali M. A systematic review of benzene exposure during pregnancy and adverse outcomes on intrauterine development and birth: still far from scientific evidence. *Ann Ig*. 2012;24:451-463.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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