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Exposure to outdoor air pollution and risk of hospitalization for bronchiolitis in an urban environment: A 9-year observational study

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Abstract

Background: Outdoor air pollution is supposed to influence the course of bronchiolitis, but the evidence is limited. The present study aimed at evaluating the role of outdoor air pollutants on hospitalization for bronchiolitis.

Methods: Infants aged ≤12 months referred for bronchiolitis to our Pediatric Emergency Department in Bologna, Italy, from 1 October 2011 to 16 March 2020 (nine epidemic seasons) were retrospectively included. Daily concentrations of benzene (C_6H_6), nitrogen dioxide (NO_2), particulate matter ≤2.5 μm ($PM_{2.5}$), and ≤10 μm (PM_{10}), and the mean values of individual patient exposure in the week and the 4 weeks before hospital access were calculated. The association between air pollutants exposure and hospitalization was evaluated through logistic regression analysis.

Results: A total of 2902 patients were enrolled (59.9% males; 38.7% hospitalized). Exposure to $PM_{2.5}$ in the 4 weeks preceding bronchiolitis was identified as the main parameter significantly driving the risk of hospitalization (odds ratio [95% confidence interval]: 1.055 [1.010–1.102]). After stratifying by season, higher values of other outdoor air pollutants were found to significantly affect hospitalization: 4-week exposure to C_6H_6 (Season 2011–2012, 4.090 [1.184–14.130]) and $PM_{2.5}$ (Season 2017–2018, 1.282 [1.032–1.593]), and 1-week exposure to C_6H_6 (Season 2012–2013, 6.193 [1.552–24.710]), NO_2 (Season 2013–2014, 1.064 [1.009–1.122]), $PM_{2.5}$ (Season 2013–2014, 1.080 [1.023–1.141]), and PM_{10} (Season 2018–2019, 1.102 [0.991–1.225]).

Conclusion: High levels of $PM_{2.5}$, C_6H_6, NO_2, and PM_{10} may increase the risk of hospitalization in children affected by bronchiolitis. Open-air exposure of infants during rush hours and in the most polluted areas should be avoided.

KEYWORDS
bronchiolitis, children, health effects, hospitalization, infants, outdoor air pollution, particulate matter

1 | INTRODUCTION

Acute bronchiolitis is the first cause of lower respiratory tract infections and the leading cause of hospitalization in infants.[1] It is a viral disease whose main etiological agent is respiratory syncytial virus (RSV).[2] The severity of bronchiolitis can vary from mild, self-limiting symptoms, that can be managed at home, to acute respiratory failure requiring hospitalization.[3] International guidelines agree that the diagnosis is clinical[2,4]: in most cases, laboratory and instrumental tests only play a limited role.[5] The treatment is mainly supportive, based on adequate hydration and, if necessary, oxygen therapy or respiratory support. Severe bronchiolitis is more common in infants aged less than 3 months or with pre-existing risk factors such as prematurity, low birth weight, bronchopulmonary dysplasia, congenital heart disease, immunodeficiency.[6] Other factors that correlate with an increased risk of developing the disease are poor socioeconomic conditions, crowded living environment, having older siblings, maternal asthma, maternal smoking during pregnancy, and passive cigarette smoking.[7,8] Furthermore, many studies have shown that air pollution may increase the prevalence of bronchiolitis and RSV infections,[9,10] and suggest that it may have a role in increasing hospital visits and hospitalizations,[11] but evidence from the literature is limited.[12] In particular, the available studies have shown negative effects of particulate matter (PM), which is divided according to the size of the particles (PM with a size less than or equal to 2.5 μm [$PM_{2.5}$] or 10 μm [PM_{10}]), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), carbon monoxide (CO), ozone (O_3), and benzene (C_6H_6)[13] on human health.

Children are particularly susceptible to the short- and long-term negative effects of atmospheric pollutants[14] due to the immaturity of their lung and immune system, lower efficiency of detoxification of oxidative damage, and because they breathe more air per kg of body weight.[9] The common cellular mechanism through which most pollutants exert their negative effect is promoting oxidative stress and inducing inflammatory responses.[14] In addition, it seems that pollution damages the immune system by reducing its ability to limit the spread of infectious agents, such as RSV; in vivo studies on mice have shown that exposure to pollutants leads to greater susceptibility to RSV infection[15] and enhances the action of the virus.[16]

The purpose of this study was to evaluate the influence of the main atmospheric pollutants on Pediatric Emergency Department (PED) referrals for bronchiolitis and related hospitalizations.

2 | MATERIALS AND METHODS

2.1 | Study design and setting

The present is an observational, retrospective, monocentric, cohort study. We included all infants under 12 months of age who were diagnosed with acute bronchiolitis from 1 October 2011 to 16 March 2020 in the PED of S.Orsola University Hospital in Bologna, Italy. Among two urban hospitals with pediatric facilities in Bologna, our center is the bigger, consisting of a tertiary-care Pediatric Emergency Unit with a PED, where an average of 24,000 visits per year are performed, a 6-bed short-stay observation unit (SSOU), and a 28-bed ward. A pediatric intensive care unit is also present in the same building, and pediatric intensivist consultations are available as needed. Based on the month of the visit, the studied patients were divided into 9 seasons, considering each season as a 12-month period running from October to September of the following year, except for the ninth season which ended on 16 March 2020 (date of the last enrolled patient) due to the beginning of the SARS-CoV-2 pandemic and the subsequent lockdown that caused a reduced exposure of children to viral illnesses[17] and the consequent absence of cases of bronchiolitis in our pediatric hospital.[18]

2.2 | Data collection and participants

We included the following information for each patient: demographic data (age in months, sex, ethnicity), any eating difficulties, known risk factors for the development of bronchiolitis (e.g., previous episodes of apnea, wheezing, chronic pulmonary disease, congenital heart disease, immunodeficiency, severe neurological or muscle disease, prematurity), any previous PED access for bronchiolitis, vital signs at PED arrival (heart and respiratory rate, body temperature, and oxygen saturation), discharge modality (home, SSOU, or admission to the pediatric ward), complications (especially pneumonia).

Based on the data collected, the severity index of bronchiolitis according to Baraldi et al. (Table S1)—classified as mild, moderate, or severe, considering the respiratory rate, respiratory effort, oxygen saturations, feeding, and apnea[1]—was calculated.

2.3 | Air quality data

For the evaluation of air pollution, we examined daily ground-level mass concentrations of PM_{10} and $PM_{2.5}$ and gaseous pollutants (NO_2, C_6H_6). The daily values of the pollutants were extracted in disaggregated form from the website of the Agency for Prevention, Environmental and Energy of Emilia-Romagna (Arpae).[19] We used data recorded by three monitoring stations located in the urban area of Bologna: two urban background sites, for NO_2, $PM_{2.5}$, and PM_{10}, and one urban traffic site for C_6H_6. The urban background site can be considered representative of population exposure at the urban scale of the city of Bologna, approximately the same one intercepted by users of S.Orsola University Hospital; while the traffic site permits to identify changes in emission rates of traffic-related sources of pollution.[20,21] To standardize the data, the concentrations of C_6H_6 and NO_2 expressed as hourly averages were converted into daily averages, with concentrations of the values expressed in $\mu g/m^3$.

Finally, to analyze the short and medium-term effect of air pollution on hospitalization for bronchiolitis, two different time windows were investigated: the average values of every single pollutant to which individual patients were exposed in the week and the 4 weeks preceding PED referral.

2.4 | Statistical data analysis

The data were collected in a Microsoft Excel® database. The data are presented by the mean and standard deviation for parametric variables, as the median and interquartile range (IQR) for quantitative non-parametric ones, and as a percentage for qualitative variables. The descriptive analysis of the sample was applied to all the variables considered and correlated to establish the different outcomes. Parametric variables were compared by ANOVA and Bonferroni test for multiple comparisons; nonparametric variables with χ^2 test or Mann–Whitney *U* test when appropriate. The association between the values of the pollutants and the risk of hospitalization for acute bronchiolitis was evaluated through logistic regression analysis and the results are presented as odds ratio (OR) and 95% confidence interval (95% CI). Results were deemed as significant for $p \leq .05$. SPSS version 23 software (SPSS Inc.) for Microsoft Windows was used for the analysis.

3 | RESULTS

3.1 | Population

From October 2011 to March 2020, our PED registered 2902 visits with a primary diagnosis of acute bronchiolitis. Of all children, 51.5% ($n = 1495$) were discharged after a visit to the PED, 9.8% ($n = 283$) were admitted to SSOU, and 38.7% ($n = 1124$) were hospitalized in our pediatric ward. The main features of the study population are described in Table 1. The prevalence of males was statistically significant (test χ^2, $p < .0001$) without distinction between the different management modalities (e.g., discharged home, SSOU, or hospitalization). The mean age of the patients was 5.5 ± 3.5 months, and it was significantly lower in the hospitalized group (ANOVA test, $p < .0001$). The lower is the age of the children, the higher were the chances of hospitalization (OR [95% CI]: 0.696 [0.675–0.717]); this relationship remained constant in each season analyzed.

TABLE 1 Characteristics of the 2902 patients who were referred to the Pediatric Emergency Department (PED) of S. Orsola University Hospital in Bologna, Italy, from 1 October 2011 to 16 March 2020 for acute bronchiolitis.

	Total	Discharged from PED	Short-stay observation	Hospitalized
Patients, *n* (%)	2902 (100)	1495 (51.5)	283 (9.8)	1124 (38.7)
Males, *n* (%)	1738 (59.9)	931 (62.3)	170 (60.1)	637 (56.7)
Age mean ± SD, months	5.5 ± 3.5	6.9 ± 3.1	6.7 ± 3.2	3.4 ± 2.8
Ethnicity, *n* (%)				
Caucasian	2137 (73.6)	1136 (76)	201 (71)	800 (71.2)
African	372 (12.8)	152 (10.2)	35 (12.4)	185 (16.5)
Asian	346 (11.9)	186 (12.4)	42 (14.8)	118 (10.5)
Not defined	47 (1.6)	21 (1.4)	5 (1.8)	21 (1.9)
Risk factors[a], *n* (%)	279 (9.5)	24 (1.6)	15 (5.3)	237 (21.1)
Prematurity	214 (7.4)	22 (1.5)	11 (3.9)	181 (16.1)
Eating difficulties	1239 (42.7)	350 (23.4)	108 (38.2)	781 (69.4)
Days from symptoms onset, mean ± SD	4.8 ± 5.9	5 ± 6.3	3.8 ± 4.2	5 ± 5.7
Severity, *n* (%)				
Mild	2278 (78.5)	1413 (94.5)	223 (78.8)	642 (57.1)
Moderate	581 (20)	82 (5.5)	56 (19.8)	443 (39.4)
Severe	43 (1.5)	0 (0)	4 (1.4)	39 (3.5)
Complications				
None	2888 (99.5)	1495 (100)	283 (100)	1110 (98.8)
Pneumonia	459 (15.8)	93 (6.2)	46 (16.3)	320 (28.5)
Other	14 (0.5)	0 (0)	0 (0)	14 (1.2)

[a]Risk factors include: previous apnea, previous wheezing, chronic lung disease, congenital heart disease, immunodeficiency, severe neurological or muscle disease.

The severity of bronchiolitis was classified as mild in 78.5% ($n = 2278$) children, moderate in 20% ($n = 581$), and severe in the remaining 1.5% ($n = 43$). As expected, most moderate and severe cases were hospitalized (76% of moderate and 90% of severe cases were admitted to the pediatric ward). Prematurity and other known risk factors for the development of bronchiolitis were more frequent in the patients hospitalized (respectively, $n = 181$, 16.1% and $n = 237$, 21.1%) than in those discharged from PED (respectively, $n = 22$, 1.5% and $n = 24$, 1.6%) and of those undergoing SSOU (respectively, $n = 11$, 3.9% and $n = 15$, 5.3%).

Bronchiolitis complicated by bronchopneumonia was more frequent in hospitalized subjects (28.5% vs. 16.3% SSOU and 6.2% discharged from PED). Other complications occurred only in hospitalized children (1.2%), five of which were sepsis, three pneumothorax, one pleural effusion, and in five otitis media.

Of the 2902 children, 1352 were tested for RSV and 870 (64.3%) were positive.

3.2 | Air pollution and hospitalization

Table S2 reports the average values of the pollutants divided by season and expressed as median and IQR. Logistic regression analysis identified an overall association between higher levels of exposure to $PM_{2.5}$ in the 4 weeks preceding the episode of bronchiolitis and an increased risk of hospitalization (OR [95% CI]: 1.055 [1.010–1.102]).

However, after stratifying by season, other air pollutants were found to significantly affect hospitalization with differences over the years (Figure 1). In the 2011–2012 and 2012–2013 seasons, the only significant identified variable was C_6H_6: in particular, C_6H_6 concentrations during the 4 weeks (OR [95% CI]: 4.090 [1.184–14.130]) and during the week (OR [95% CI]: 6.193 [1.552–24.710]) preceding the access to the PED in the 2011–2012 and 2012–2013 seasons, respectively (Figure 1A,B). In the 2013–2014 season, the exposure to $PM_{2.5}$ and NO_2 in the week preceding the episode of bronchiolitis significantly increased the risk of hospitalization (OR [95% CI]: 1.080 [1.023–1.141] and 1.064 [1.009–1.122], respectively) (Figure 1C,D). In the 2017–2018 season exposure to $PM_{2.5}$ in the 4 weeks before the episode of bronchiolitis influenced hospitalization (OR [95% CI]: 1.282 [1.032–1.593]) (Figure 1E). In the 2018–2019 season, exposure to PM_{10} the week before bronchiolitis affected hospitalization (OR [95% CI]: 1.102 [0.991–1.225], Figure 1F).

4 | DISCUSSION

The present work highlights that high levels of air pollutants such as $PM_{2.5}$, C_6H_6, NO_2, and PM_{10} could increase the risk of hospitalization for bronchiolitis. It is biologically reasonable that air pollutants might increase the probability of severe bronchiolitis, because of known effects on lung function,[22] and airway inflammation, and because children seem to be most vulnerable to the damaging effects of air pollutants.[23] In Table 2, we summarized some representative studies that have been conducted on the impact of air pollution on the development of bronchiolitis and the relative risk of hospitalization although with not always consistent results.

Our data showed an association between higher levels of $PM_{2.5}$ in the 4 weeks preceding the episode of bronchiolitis and an increased risk of hospitalization considering the overall 9-year dataset. This result agrees with the case–control study by Karr et al.,[28] conducted on a sample of 18,595 infants with bronchiolitis aged less than 1 year, which showed that subchronic (30 days) and chronic (from birth) exposure to $PM_{2.5}$ is significantly associated with increased risk of hospitalization. Other similar associations emerge from the study conducted by Yitshak-Sade et al.,[11] which showed a positive association between higher PM levels the week before and hospitalization for bronchiolitis, and from Girguis study,[26] in which higher levels of $PM_{2.5}$ the day before and in the 4 days before the onset of bronchiolitis correlated with an increased risk of hospitalization, especially in preterm infants. Furthermore, the prospective cohort study conducted by Milani et al.,[31] showed a direct association between $PM_{2.5}$ exposure in the few days before and the 2–3 weeks before and the severity of bronchiolitis, and the study conducted by Gallo et al.[25] showed a significant association between $PM_{2.5}$ exposure in the days before the bronchiolitis and an increased risk of presentation to the PED. Terrazas et al.[33] reported a significant correlation between $PM_{2.5}$ levels and hospitalizations for bronchiolitis for a longer exposure than in our study (i.e., 1 year). Moreover, the studies by Nenna et al.[10] and Vandini et al.[9] found correlations between RSV bronchiolitis and $PM_{2.5}$, but this pollutant did not prove to be a proper predictor for hospitalization by applying the regression model. Another study conducted by Karr et al.[29] reported a nonstatistically significant increased risk for RSV bronchiolitis hospitalization associated with $PM_{2.5}$ for acute and chronic time windows of exposure.

We also found a cumulative effect of exposure to PM_{10} in the week preceding PED referral for bronchiolitis only for the 2018–2019 season. Other authors evaluated the role of PM_{10} as a risk factor for bronchiolitis. The study conducted by Vandini et al.[9] showed a significant correlation between RSV infections and PM_{10} mean concentration the week before the hospitalization. Carugno et al.[24] found an association between short- and medium-term PM_{10} exposure and increased risk of hospitalization among 2814 infants affected by RSV bronchiolitis in the 2012 and 2013 epidemic seasons in 12 provinces of Lombardy, Northern Italy. Ségala et al.[32] conducted a large retrospective study on 50,857 children less than 3 years of age referred to the PED for bronchiolitis in Paris, France, and identified a correlation between the risk of hospitalization and exposure to PM_{10} in the 5 days before hospital admission. The prospective study conducted by Milani et al.[31] on a cohort of 161 infants with bronchiolitis visited in Milan, Italy, between November 2019 and February 2020, showed an association between PM_{10} exposure and the severity of bronchiolitis. Furthermore, Gallo et al.[25] conducted a retrospective study on 2251 children with a diagnosis of bronchiolitis and presented to the PED in Padova, Italy, and identified a significant association between the PM_{10} exposure in the 4 days

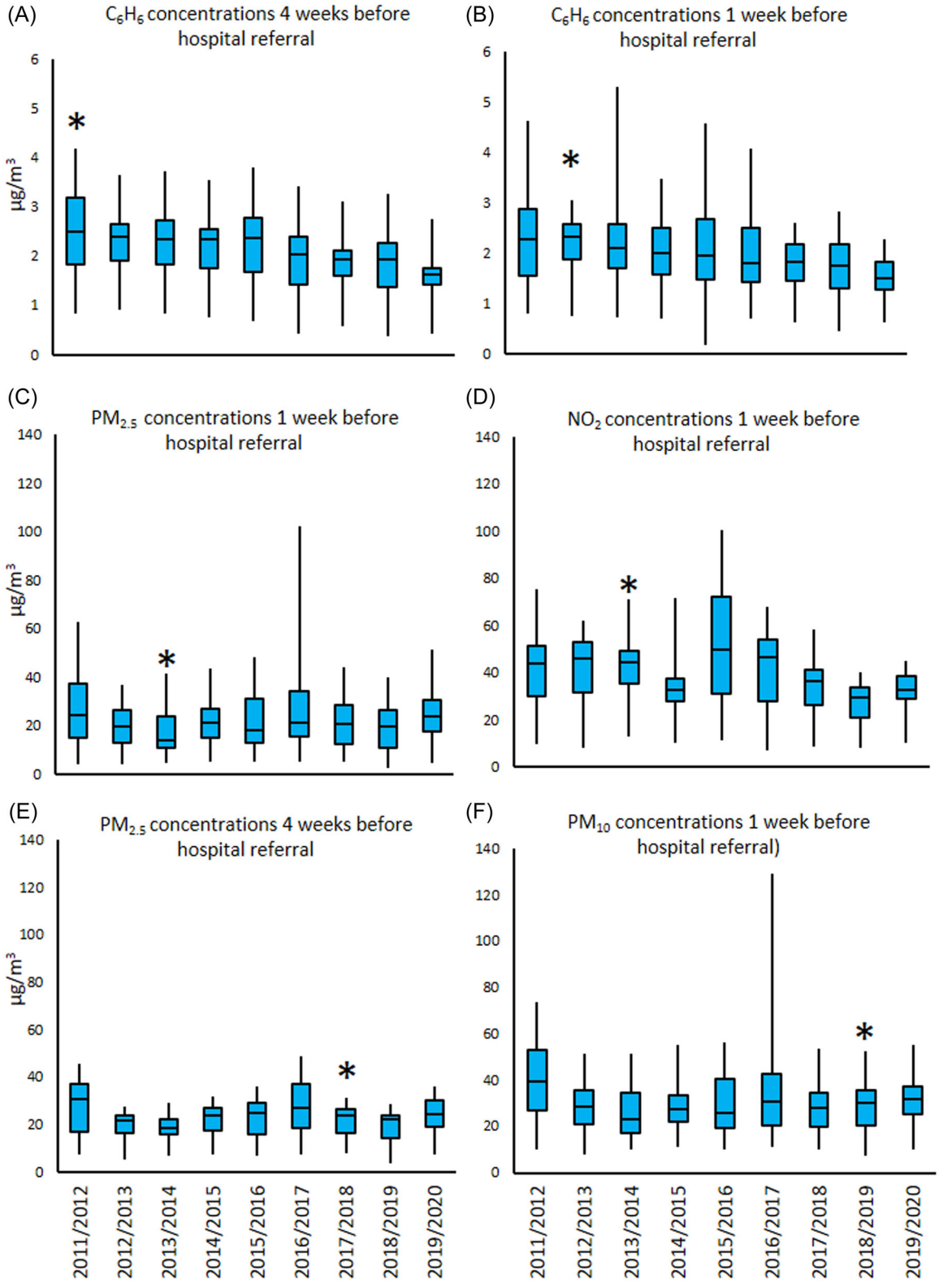

FIGURE 1 Boxplots of the average concentrations of air pollutants to which the patients were exposed in the previous week and in the 4 weeks before the hospital referral and that were shown to significantly influence hospitalization: (A) average concentrations of C_6H_6 in the 4 previous weeks *OR [95% CI]: 4.090 [1.184–14.130]; (B) average concentrations of C_6H_6 in the previous week *OR [95% CI]: 6.193 [1.552–24. 710]; (C) average concentrations of $PM_{2.5}$ in the previous week *OR [95% CI]: 1.080 [1.023–1.141]; (D) average concentrations of NO_2 in the previous week *OR [95% CI]: 1.064 [1.009–1.122]; (E) average concentrations of $PM_{2.5}$ in the previous 4 weeks *OR [95% CI]: 1.282 [1.032–1. 593]; (F) average concentrations of PM_{10} in the previous 1 week *OR [95% CI]: 1.102 [0.991–1.225].

TABLE 2 Main studies on the relationship between air pollutants and bronchiolitis.

Study	Years conducted	Country (region or city)	Time windows of exposure	Pollutants	Significant findings
Carugno et al. (2018)[24]	2012–2013	Italy (Lombardy)	Daily and weekly exposure	PM_{10}	Association between short- and medium-term PM_{10} exposure and an increased risk of hospitalization due to RSV bronchiolitis
Gallo et al. (2022)[25]	2007–2018	Italy (Padova)	Daily exposure in the 14 days before	$PM_{2.5}$, PM_{10}, NO_2	Association with an increased risk of PED presentation and hospitalization
Girguis et al. (2018)[26]	2001–2009	United States (Massachusetts)	1 and 4 days before mean	$PM_{2.5}$	Association with an increased risk of hospitalization, especially in preterm infants
Karr et al. (2006)[27]	1995–2000	United States (California)	1 and 4 days before mean	$PM_{2.5}$, CO, NO_2	No increased risk of bronchiolitis after acute exposure, except for modestly increased risk for $PM_{2.5}$ exposure among very prematurely infants
Karr et al. (2007)[28]	1995–2000	United States (California)	30 days before mean and from birth	$PM_{2.5}$, NO_2, O_3, CO	Association between $PM_{2.5}$ exposure and an increased risk of hospitalization
Karr et al. (2009)[29]	1997–2003	United States (Washington State)	7 days, 30 days, 60 days before mean and from birth	$PM_{2.5}$	Non-statistically significant increased risk for RSV bronchiolitis hospitalization associated with $PM_{2.5}$ for all exposure windows evaluated
Leung et al. (2021)[30]	2008–2017	China (Hong Kong)	7 days before mean	PM_{10}, NO_2	Association with an increased risk of hospitalization
Milani et al. (2022)[31]	2019–2020	Italy (Milan)	Daily exposure in 1 month before	$PM_{2.5}$, PM_{10}	Association with an increased severity of bronchiolitis
Nenna et al. (2017)[10]	2004–2014	Italy (Rome)	7 days before mean	$PM_{2.5}$, PM_{10}, NO_2, SO_2, CO, C_6H_6	Association between the mean concentration of C_6H_6 and the hospitalization for RSV positive bronchiolitis
Ségala et al. (2008)[32]	1997–2001	France (Paris)	2 days and 5 days before mean	PM_{10}, NO_2	Association with an increased risk of hospitalization
Terrazas et al. (2019)[33]	2001–2014	Chile	Annual mean	$PM_{2.5}$	Association with an increased risk of hospitalization
Vandini et al. (2013)[9]	2007–2010	Italy (Bologna)	Same week and 1 week before mean	$PM_{2.5}$, PM_{10}	Association between the mean concentration of PM_{10} and the RSV infection
Yitshak-Sade et al. (2017)[11]	2003–2013	Israel (Soroka)	7 days before mean	$PM_{2.5}$, PM_{10}, NO_2	Association with an increased risk of hospitalization

Abbreviations: C_6H_6, benzene; CO, carbon monoxide; NO_2, nitrogen dioxide; O_3, ozone; PED, Pediatric Emergency Department; $PM_{2.5}$, particulate matter with a size less than or equal to 2.5 μm; PM_{10}, particulate matter with a size less than or equal to 10 μm; RSV, respiratory syncytial virus; SO_2, sulfur dioxide.

before and the PED presentation. However, other authors such as Nenna et al.[10] did not find any significant influence of PM_{10} on the risk of hospitalization for bronchiolitis.

After stratifying by season, the analysis allowed to identify associations between hospitalization for bronchiolitis and gaseous pollutants, that is, C_6H_6 and NO_2, generally used as proxy for traffic-related air pollution in the urban environment. A strong association with C_6H_6 concentrations was identified in the first two seasons. In our study, C_6H_6 is measured at an urban traffic site and therefore this result could suggest a potential enhanced contribution of traffic-related sources to the average exposure of the general population at the urban scale of Bologna. To our knowledge, few studies investigated the role of C_6H_6 as a risk factor for hospitalization. The paper by Nenna et al.[10] evaluated the association between weekly exposure to various pollutants (PM_{10}, $PM_{2.5}$, C_6H_6, NO_2, and SO_2) and hospitalization for bronchiolitis, and C_6H_6 was the only one significantly associated with an increased incidence of hospitalization for RSV-positive bronchiolitis.

We also identified an association with higher NO_2 levels in the week preceding the hospitalization for bronchiolitis, potentially indicating higher exposure to traffic-related pollutants. A similar result is also reported in the paper by Yitshak-Sade et al.[11] in which an increase in the IQR (13 $\mu g/m^3$) compared to the average value of NO_2 concentrations in the week before admission, is associated with an increased risk of bronchiolitis (OR 1.36, 95% CI 1.12–1.65). Also, the study by Leung et al.[30] showed that acute exposure to NO_2 was associated with an increased risk of hospitalization for bronchiolitis. Nevertheless, other studies[10,27] do not confirm a significant relationship between acute exposure (7 days) to this pollutant and increased hospitalizations.

These single associations highlighted in the analysis divided by season are based on a reduced number of data (nine different subsets of the entire 9-year dataset), so the consequent conclusions should be taken with caution as they could be more affected by uncontrollable confounding factors related to two main aspects: first, lacking of alternative properties of air pollution/PM as metrics to use to better represent the biologically effective dose linking health effects and air pollution exposure; second, the demographic and socioenvironmental factors (e.g., smoking parents, old-fashioned wood stove nearby, etc.).

Indeed, PM is generally identified as the key indicator of air quality brought into the air by a variety of natural and human activities and as the main driver of health effects. However, at the center of the scientific debates, there is a growing awareness that most studies are based on PM mass, a metric that is now recognized to be not ideal for representing the toxicologically active dose of PM,[34] because health impacts can vary significantly depending on the blend of particles and gaseous compounds, as well as additional factors such as the mixing state of PM populations, weather conditions, atmospheric dilution, and processing, and so forth. Indeed, $PM_{2.5}$ physicochemical properties vary in space and time and can be affected by a myriad of emission sources. This suggests that exposure to the same mass concentrations (meaning the same value of $PM_{2.5}$ or PM_{10}) can be associated with extremely different toxicological properties and substantially different health outcomes.[35] As pointed out by several authors, a possible recommendation for future studies could be to use alternative metrics to focus on air pollution data for specific types of PM[20] (e.g., Black/Elemental Carbon, Ultrafine PM, ROS species) and/or specific types of sources[36] (e.g., traffic, biomass burning, secondary PM) to be related to specific health/biological outcomes (in vivo or in vitro).[34] On the other hand, some factors other than outdoor air pollutants and pre-existing personal determinants have been shown to influence the course of bronchiolitis. Maternal asthma, maternal smoking during pregnancy, postnatal exposure to cigarette passive smoking, living in a crowded home, and having older siblings have been shown to be important factors in determining the severity of bronchiolitis.[37] A study conducted by Caroll et al.[8] demonstrated that maternal asthma and maternal smoking during pregnancy are independently associated with the development of bronchiolitis in infants with no prior risk factors. Postnatal passive smoking exposure in the family home, mainly when the smoker is the mother,[7] has a large influence on the risk of bronchiolitis in infants, and in particular, as demonstrated by several studies, exposure to cigarette smoking has a significant association with severe bronchiolitis and prolonged hospitalization.[38] Also living in crowded conditions and having older siblings, who often attend school communities, increases the risk of exposure to viral infections and represents a risk factor for the development of severe bronchiolitis.[39] On the contrary, breastfeeding, both exclusive and mixed, results as a protective factor, associated with a lower incidence of bronchiolitis.[40]

The aforementioned demographic and socioenvironmental factors were not considered in our study, nor were other variables such as weather conditions, indoor pollution, or the specific physico-chemical and oxidative properties of PM. These are all potentially confounding factors that were not investigated and this point represents the main limitation of our results. The geographical location of patients was also not included in the analysis; as a tertiary care center, patients may be referred to our hospital from other areas of the Emilia-Romagna region. However, these patients only represent a minority of the population, as, for bronchiolitis, even the most severe cases are usually handled in the local facilities, such as neonatal or general intensive care units of the main cities of the region. The geographical and sociodemographic variables may play a significant role as confounding factors when a limited number of data are used. For this reason, in this monocentric study, the results from the analysis divided by a single year must be considered less robust than those resultant from the entire 9-year dataset.

Nevertheless, we analyzed a long timeseries of pollutants with specific concentrations to which the individual patients were exposed in long and medium time-lag before the development of bronchiolitis. The large sample size and the long observation period are the strengths of our study.

5 | CONCLUSIONS

Our study suggests that infant bronchiolitis may be one of the several adverse effects of ambient air pollution on human health and that high levels of air pollutants, such as $PM_{2.5}$, C_6H_6, NO_2, and PM_{10}, could increase the risk of hospitalization in the affected patients,

implying an increased risk of more severe cases. These considerations reinforce the recommendation to avoid exposing children, especially the youngest ones, during rush hours and in areas characterized by the proximity to strong local sources of air pollution. Policies aimed at reducing air pollution may be successful in decreasing the overall burden of this disease in early childhood. Further studies will be required to define with greater certainty the cause-effect relationships between the exposure of infants to pollutants and bronchiolitis; as well as to identify better metrics for the representation of specific properties of pollutants reflecting more precisely the exposure and biological responses for bronchiolitis.

AUTHOR CONTRIBUTIONS

Arianna Dondi: Conceptualization; investigation; writing—original draft; project administration; methodology; visualization; writing—review and editing; supervision; data curation. **Elisa Manieri**: Writing—original draft; writing—review and editing; investigation. **Ludovica Betti**: Methodology; writing—original draft; writing—review and editing; data curation. **Ada Dormi**: Methodology; software; data curation; formal analysis; validation; writing—review and editing. **Claudio Carbone**: Data curation; validation; visualization; writing—review and editing. **Carlotta Biagi**: Conceptualization; writing—review and editing. **Luca Pierantoni**: Conceptualization; writing—review and editing. **Daniele Zama**: Writing—review and editing; data curation. **Marco Paglione**: Writing—review and editing; data curation. **Marcello Lanari**: Conceptualization; methodology; writing—review and editing; supervision.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The study was conducted in accordance with the Declaration of Helsinki, and it was approved by the Institutional Reviewer Board of our institution (Ethics Committee Area Vasta Emilia Centro, AVEC, study number 1062/2020/Oss/AOUBo).

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SUPPORTING INFORMATION

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

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