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$PM_{2.5}$, PM_{10} and bronchiolitis severity: A cohort study

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Abstract

Background: A few studies suggest that particulate matter (PM) exposure might play a role in bronchiolitis. However, available data are mostly focused on the risk of hospitalization and come from retrospective studies that provided conflicting results. This prospective study investigated the association between PM ($PM_{2.5}$ and PM_{10}) exposure and the severity of bronchiolitis.

Methods: This prospective cohort study was conducted between November 2019 and February 2020 at the pediatric emergency department of the Fondazione IRCCS Ca′ Ospedale Maggiore Policlinico, Milan, Italy. Infants <1 year of age with bronchiolitis were eligible. The bronchiolitis severity score was assessed in each infant and a nasal swab was collected to detect respiratory viruses. The daily PM_{10} and $PM_{2.5}$ exposure in the 29 preceding days were considered. Adjusted regression models were employed to evaluate the association between the severity score and PM_{10} and $PM_{2.5}$ exposure.

Results: A positive association between the $PM_{2.5}$ levels and the severity score was found at day-2 (β 0.0214, 95% CI 0.0011–0.0417, $p = .0386$), day-5 (β 0.0313, 95% CI 0.0054–0.0572, $p = .0179$), day-14 (β 0.0284, 95% CI 0.0078–0.0490, $p = .0069$), day-15 (β 0.0496, 95% CI 0.0242–0.0750, $p = .0001$) and day-16 (β 0.0327, 95% CI 0.0080–0.0574, $p = .0093$).Similar figures were observed considering the PM_{10} exposure and limiting the analyses to infants with respiratory syncytial virus.

Conclusion: This study shows for the first time a direct association between $PM_{2.5}$ and PM_{10} levels and the severity of bronchiolitis.

KEYWORDS
air pollution, bronchiolitis, environment, infants, particulate matter, respiratory syncytial virus, severity

1 | BACKGROUND

The association between air pollution and chronic respiratory diseases is well established in adults and the elderly.[1,2] Increasing data suggest that this association might occur also among children.[3–5] Moreover, a few studies suggest that particulate matter (PM) might be implicated in the development of bronchiolitis in infancy.[6,7] PM exposure might modulate viral infectivity, alter cytokine expression

and impair the phagocytic ability of immune cells, thus enhancing the infection burden on the infant.[8,9]

However, epidemiological studies on PM and bronchiolitis have provided partially conflicting data.[6] A meta-analysis published in 2018 pooled data from 8 studies to verify the association between particulate matter and risk of hospitalization for bronchiolitis and concluded that the effects of PM_{10} were unclear, whereas increased $PM_{2.5}$ levels were not associated with a higher risk of hospitalization.[10]

One of the principal limitations of the available evidence is that it mainly comes from retrospective data or from International Classification of Diseases codes-based studies, and it is mostly focused on the risk of hospitalization.[6,11] Therefore, prospective cohort studies including clinical data from individual patients with different degrees of bronchiolitis severity would be of great importance to gauge the hypothesis of an association between PM and bronchiolitis.

Hence, the aim of this prospective cohort study was the investigate the association between PM ($PM_{2.5}$ and PM_{10}) exposure and the severity of bronchiolitis in infants.

Key Message

Some studies suggested that particulate matter (PM) exposure might play a role in bronchiolitis. However, available data come mainly from retrospective studies and provide conflicting results. Our prospective cohort study showed for the first time a direct association between PM ($PM_{2.5}$ and PM_{10}) exposure and the severity of bronchiolitis.

2 | MATERIALS AND METHODS

2.1 | Study population and procedures

This prospective cohort study was conducted between November 2019 and February 2020 at the pediatric emergency department of the Fondazione IRCCS Ca′ Ospedale Maggiore Policlinico, Milan, Italy, a tertiary emergency department with more than 20,000 patients visited per year.

Eligible for this study were infants <1 year of age visiting the pediatric emergency department for bronchiolitis. The diagnosis of bronchiolitis was made in infants with a history of acute respiratory tract infection of the upper airways in the previous week, followed by an acute onset of respiratory distress, cough and diffuse crackles on auscultation.[12] Infants with underlying conditions potentially associated with a worse clinical course of bronchiolitis (e.g., infants with bronchopulmonary dysplasia or on chronic treatment with immunosuppressants) were excluded.

At enrollment, all infants underwent a nasal swab by a trained researcher. Once collected, the nasal swabs were stored at −80°C until nucleic acids extraction for the PCR-detection of the respiratory syncytial virus (RSV), the main cause of bronchiolitis in infancy.[13] In addition, the same trained researcher assessed the bronchiolitis severity score according to our standard protocol.[14,15] This score includes the evaluation of the following parameters: ambient air O_2-saturation (>95% = 0; 95–90% = 1; <90% = 2), respiratory rate (<45/min = 0; 45–60/min = 1; >60/min = 2), thoracic retractions (none = 0; present = 1; present and associated with nasal flare = 2) and ability to feed (normal = 0; reduced = 1; strongly reduced = 2). The results of each parameter are summed to define the disease severity as mild (<4), moderate (4–6) or severe (≥7).[12,16] All hospitalized infants were reevaluated every day until their discharge. If hospitalization was not required, mothers were advised to return to the emergency department in case of a worsening condition. A phone call after 7 days was performed to have confirmation that the clinical conditions had not worsened after discharge.

The most severe score assessed in each infant during the bronchiolitis episode was considered for the analyses.

The study was approved by the ethical committee of the Fondazione IRCCS Ca′ Granda Ospedale Maggiore Policlinico, Milan, Italy. Informed consent was obtained by the parents of the infants.

2.2 | Data collection and classification

For each infant, the following information was collected: age, sex, birth weight and length, body weight and height at enrollment, ethnicity, residential address, delivery mode, current breastfeeding, history of antibiotics intake, allergy, daycare attendance, number of siblings and the presence of pets at home.

Moreover, age, educational level, current smoking, the presence of any chronic disease, treatment or allergy of both parents were registered and information on smoking during pregnancy, assumption of antibiotics during pregnancy or during breastfeeding and the result of Group B Streptococcus in vaginal swab at the end of the pregnancy was obtained from the mother.

2.3 | Particulate matter exposure assessment

$PM_{2.5}$ and PM_{10} (i.e., particulate matter with a particle size <2.5 or < 10 μm, respectively), exposure levels were obtained from the Open Data Lombardy Region (https://www.dati.lombardia.it) database, which contains daily mean estimates of municipal aggregate values calculated by the Regional Environmental Protection Agency (ARPA Lombardy). The assessment of the pollutant concentrations was based on the ARIA Regional Modeling (www.aria-net.it), which is a chemical–physical model of air quality that simulates the dispersion and chemical reactions of atmospheric pollutants. It integrates the data measured from the monitoring stations of the ARPA Lombardy air quality network as well as meteorological data,

emissions, concentrations at the beginning of the simulation period, and trends in adjacent areas, covering the whole Lombard territory with a grid of 1×1 km^2 cells and providing daily mean estimates available from the website at municipality resolution. Each subject was assigned the daily PM_{10} and $PM_{2.5}$ concentrations of the municipality of residence in the 29 days (day-1 to day-29) preceding the severity score retained for the analysis and of the Municipality of Milan for the day of recruitment (day-0) or during hospitalization.

2.4 | Laboratory analysis

Viral RNA was extracted from nasal swabs using the QIAamp Viral RNA Mini kit (Qiagen), according to the manufacturer's instructions. The purified RNA was eluted in 50 μl and immediately stored at −80°C. For the quantification of RSV-RNA levels, a commercial real-time RT-qPCR kit was used (PrimerDesign™ genesig; PrimerDesign Ltd., Southampton, Hants, UK) and the qPCR were conducted using a QuantStudio3 real-time PCR system (Applied Biosystem). A standard curve and template negative controls (sterile water) were included on each plate.

2.5 | Statistical analysis

Summary statistics of study subjects' characteristics were reported in terms of frequency and percentage for categorical variables and in terms of mean and standard deviation or median and first quartile—third quartile as appropriate for continuous variables. The normal distribution of continuous variables was tested by graphical inspection and by Kolmogorov–Smirnov test.

With regards to the effect of PM_{10} and $PM_{2.5}$ on bronchiolitis severity, univariate and multivariable ordinal logistic regression models were fitted. The response variable was the score, using 7 ordinal categories. To evaluate short-term PM exposure, pollutant levels were retrieved as daily means up to 2 days before the day of the enrollment and as averages over 1 week, 2 weeks, 3 weeks and 1 month; we also calculated the average of PM levels in the first, second, third and fourth week. Multivariable analyses were adjusted for age, sex, ethnicity, use of antibiotics during pregnancy and use of antibiotics in the last month. Potential confounders were included in the multivariate model after verifying the presence of an association in a univariate model.

Estimated effects are reported as β and 95% confidence intervals (CI) associated with an increase of 1 μg/m^3 in PM exposure. Statistical analyses were performed with SAS software (version 9.4; SAS Institute Inc.). A two-sided *p*-value of .05 was considered statistically significant.

3 | RESULTS

A total of 161 infants with bronchiolitis visited the pediatric emergency department of Fondazione IRCCS Ca′ Ospedale Maggiore Policlinico, Milan, Italy, during the study period. Thirty-seven were not eligible due to underlying conditions potentially associated with a worse clinical course of bronchiolitis and 14 did not accept to participate. Hence, a total of 110 infants (mean age 6.3 ± 5.5 months, 61% males) with bronchiolitis were finally included. The baseline characteristics of these subjects are given in Table 1. RSV was detected in 64 (58%) of the 110 infants. The bronchiolitis severity score was mild in 75 (68%), moderate in 34 (31%) and severe in one (0.6%) subject. Among infants with RSV, bronchiolitis was mild in 39 (61%) and moderate in 25 (39%) (Figure 1). Data regarding the mother and the father of the included subjects are reported in Table 2. The mean levels of PM_{10} and $PM_{2.5}$ for each time lag preceding the severity peak are given in Table S1.

Results from univariate analyses of variables associated with bronchiolitis severity scores are given in the supplementary online

TABLE 1 Characteristics of the study participants (*N* = 110). For some variables, percentage total slightly differs from 100% due to rounding effect

Characteristics	
Age, months mean ± SD	6.3 ± 5.5
Sex, *N* (%)	
Males	67 (61)
Females	43 (39)
Birth weight, kg mean ± SD	3.204 ± 0.550
Birth length, cm mean ± SD	49.6 ± 2.2
Gestational age, median [Q1–Q3]	38 [38–40]
Weight, kg mean ± SD	7.2 ± 2.2
Length, cm mean ± SD	64.8 ± 10.0
Living area, *N* (%)	
City of Milan	73 (66)
Province of Milan, outside city area	35 (32)
Other provinces	2 (1.8)
Ethnicity, *N* (%)	
Caucasian	87 (79)
African	6 (5.4)
Asian	11 (10)
Multi-ethnic	6 (5.4)
Delivery mode, *N* (%)	
Vaginal delivery	68 (62)
Vacuum	5 (4.6)
Elective cesarean section	25 (23)
Emergency cesarean section	12 (11)
Systemic antibiotic after birth, *N* (%)	
Yes	25 (23)
No	85 (77)
Systemic antibiotic in the last month, *N* (%)	
Yes	6 (5.4)

(Continues)

TABLE 1 (Continued)

Characteristics	
No	104 (95)
Allergy, *N* (%)	
Yes	3 (2.8)
No	107 (97)
Daycare attendance, *N* (%)	
Yes	26 (24)
No	84 (76)
Siblings, *N* (%)	
Yes	80 (73)
No	30 (27)
Number of siblings, *N* (%)	
0	31 (28)
1	50 (45)
2	23 (21)
3	6 (5.5)
Siblings attending daycare/school, *N* (%)	
Yes	83 (75)
No	27 (25)
Pets at home, *N* (%)	
Yes	25 (23)
No	85 (77)
Current breastfeeding, *N* (%)	
Characteristics	
Yes	69 (63)
No	41 (37)

tables (Tables S2 and S3). $PM_{2.5}$ was positively associated with the bronchiolitis severity score on day-2 (β 0.0214, 95% CI 0.0011–0.0417, $p = .0386$), on day-5 (β 0.0313, 95% CI 0.0054–0.0572, $p = .0179$), on day-14 (β 0.0284, 95% CI 0.0078–0.0490, $p = .0069$), on day-15 (β 0.0496, 95% CI 0.0242–0.0750, $p = .0001$) and on day-16 (β 0.0327, 95% CI 0.0080–0.0574, $p = .0093$). PM_{10} was positively associated with the bronchiolitis severity score on day-2 (β 0.0171 95% CI 0.0015–0.0326, $p = .0317$), on day-5 (β 0.0268, 95% CI 0.0067–0.0469, $p = .0091$), on day-14 (β 0.0220, 95% CI 0.0062–0.0379, $p = .0065$), on day-15 (β 0.0356, 95% CI 0.0167–0.0545, $p = .0002$) and on day-16 (β 0.0230, 95% CI 0.0049–0.0412, $p = .0128$).

Adjusted models returned very similar results (Table 3). A significant association with the $PM_{2.5}$ and PM_{10} mean levels during the third week before the assessment and the bronchiolitis severity score was observed (β 0.0426, 95% CI 0.0173–0.0679, $p = .0010$; β 0.0478, 95% CI 0.0159–0.0797, $p = .0034$, respectively). Similar figures were observed considering only $PM_{2.5}$ and PM_{10} exposure and bronchiolitis severity score of infants with bronchiolitis due to RSV infection (Table S4).

4 | DISCUSSION

Bronchiolitis is the main cause of hospitalization in infants. Although a few risk factors (e.g., pre-existing pulmonary diseases) are recognized, most cases occur in previously healthy infants without predisposing risk factors.[17] This prospective cohort study showed for the first time a significant association between $PM_{2.5}$ and PM_{10} levels and the severity of bronchiolitis.

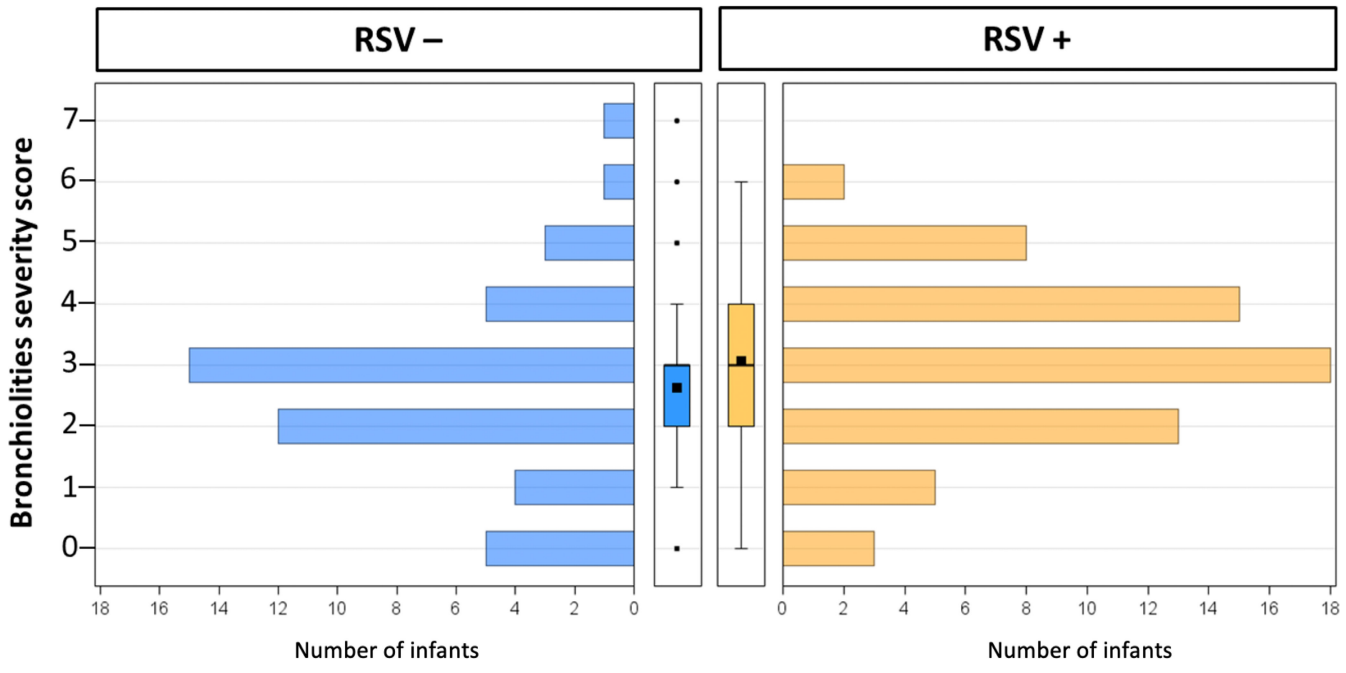

FIGURE 1 Bronchiolitis severity score in infants with and without respiratory syncytial virus (RSV)

TABLE 2 Characteristics of parents of the study participants ($N = 110$). For some variables, percentage total slightly differs from 100% due to rounding effect

	Mothers	Fathers
Age, years, mean ± SD	34.8 ± 5.6	37.1 ± 6.3
Education, *N* (%)		
Elementary school	5 (4.6)	1 (0.9)
Junior high school	14 (13)	18 (16)
High school	29 (27)	38 (35)
University	62 (56)	53 (48)
Smoking, *N* (%)		
Yes	10 (9.2)	41 (37)
No	100 (91)	69 (63)
Maternal smoking during pregnancy, *N* (%)		
Yes	7 (6.4)	–
No	103 (94)	–
Chronic diseases, *N* (%)		
Yes	31 (28)	13 (12)
No	79 (72)	97 (88)
Allergy, *N* (%)		
Yes	43 (39)	30 (27)
No	67 (61)	80 (73)
Systemic antibiotics during pregnancy, *N* (%)		
Yes	27 (25)	–
No	83 (75)	–
Systemic antibiotics during breastfeeding, *N* (%)		
Yes	12 (11)	–
No	98 (89)	–
Vaginal swab for Group B Streptococcus, *N* (%)		
Positive	14 (14)	–
Negative	89[a] (86)	–

[a]Information was not available for 7 mothers.

Previous retrospective studies investigating the association between the risk of hospitalization or number of clinical encounter for infants with bronchiolitis and exposure to PM ended with inconsistent results. A study performed in the United States on ~20,000 infants found very limited support for a link between the acute increase of $PM_{2.5}$ and bronchiolitis hospitalization.[18] A further study conducted in Canada on approximately 11,000 infants found that exposure to PM_{10} and $PM_{2.5}$ had no association with inpatient or outpatient clinical encounter for bronchiolitis.[19] On the other hand, studies conducted in Italy, Israel and France found a positive association between the risk of hospitalization and exposure to PM ≤10 μm in infants with bronchiolitis.[6,20–22] This association was also observed in a study conducted in Hong Kong on >29,000 subjects.[23] Finally, a study conducted on about 12,000 infants hospitalized for RSV bronchiolitis found that exposure to $PM_{2.5}$ and PM_{10}, together with other air pollutants might explain >20% of the hospitalizations.[24] In this study, which includes individual data of all infants visiting the pediatric emergency department, we were able to observe a positive association between the exposure to $PM_{2.5}$ and PM_{10} and bronchiolitis severity thus confirming the potential role of PM in bronchiolitis. Moreover, such association was observed in the few days before the severity score assessment or about 2 to 3 weeks before. These observations deserve some consideration.

It has been speculated that the air pollutants and especially PM might play a key role in the viral spread and transmission.[25,26]

It is known that after the infection, bronchiolitis symptoms peak occurs roughly within 2 weeks.[6,27] The positive association between the levels of $PM_{2.5}$ and PM_{10} about 2 weeks preceding the symptoms peak corroborates the hypothesis that high levels of PM might increase the viral load reaching the patient's airways.[25,26] Growing evidence points out that $PM_{2.5}$ and PM_{10} cause airways inflamation[28,29] by stimulating the release of pro-inflammatory- cytokines (e.g., IL-1, IL-6, IL-8 and IL-33).[29–31] High levels of airways inflammation are associated with severe bronchiolitis, in turn.[32,33] These data might explain the positive association found in this study between the severity of bronchiolitis and the levels of $PM_{2.5}$ and PM_{10} exposure also in the few days preceding the severity peak. Overall, this study suggests a mediating role of PM in different stages of bronchiolitis (Figure 2).

Based on our data, we speculate that personalized preventive measures might be developed for infants at risk of severe bronchiolitis. In particular, strategies to limit the spread of respiratory viruses (e.g., limiting the time spent in potentially contagious settings) or to reduce airways inflammation (e.g., preventively using inhaled anti-inflammatory molecules) might be performed in the days following high levels of $PM_{2.5}$ and PM_{10} exposure. These hypotheses should be tested in future prospective studies.

It is recognized that climate has an impact on air pollutant concentrations.[34] Recent observations suggest that climate change and especially increased temperatures are associated with PM peaks in the atmosphere.[35,36] The results of this study and the current context of global warming point out that increasing efforts should be addressed to raise awareness among parents, healthcare providers and public authorities on the possible role of PM on infant health and to limit its production.

This study has some limitations: first, it included only infants with bronchiolitis visiting the emergency department. Therefore, infants managed by primary care physicians or by pediatricians in private practice were not considered. Second, the study included a limited number of patients from a single center. Finally, we did not evaluate the possible role of chronic exposure to $PM_{2.5}$ and PM_{10}. Yet, the study has important strengths. All clinical data were prospectively collected. Several confounding factors for bronchiolitis severity were controlled. Furthermore, the study was conducted immediately before the COVID-19 outbreak in Italy and therefore there was no potential confounding effect of exceptional preventive measures (e.g., homebound, social distancing, use of facial masks or school closure) applied during the first wave of the pandemic.[37]

In conclusion, this study shows a direct association between $PM_{2.5}$ and PM_{10} levels and the severity of bronchiolitis. Levels of

TABLE 3 Association between exposure to $PM_{2.5}$ and PM_{10} and bronchiolitis severity score ($N = 110$ case of bronchiolitis)

PM_{10}	β	SE	95% CI		*p*-value	$PM_{2.5}$	β	SE	95% CI		*p*-value
Day 0	0.0099	0.0090	−0.0077	0.0275	.2684	Day 0	0.0067	0.0110	−0.0148	0.0283	.5399
Day −1	0.0131	0.0078	−0.0022	0.0283	.0932	Day −1	0.0116	0.0092	−0.0065	0.0297	.2089
Day – 2	**0.0175**	**0.0083**	**0.0013**	**0.0338**	**.0347**	**Day – 2**	**0.0214**	**0.0104**	**0.0011**	**0.0417**	**.0386**
Day −3	0.0051	0.0074	−0.0094	0.0197	.4876	Day −3	0.0070	0.0099	−0.0124	0.0263	.4802
Day −4	0.0125	0.0086	−0.0044	0.0295	.1462	Day −4	0.0112	0.0100	−0.0083	0.0308	.2601
Day – 5	**0.0333**	**0.0114**	**0.0109**	**0.0557**	**.0036**	**Day – 5**	**0.0313**	**0.0132**	**0.0054**	**0.0572**	**.0179**
Day −6	0.0088	0.0094	−0.0097	0.0272	.3504	Day −6	0.0040	0.0115	−0.0185	0.0265	.7279
Day −7	0.0049	0.0096	−0.0139	0.0237	.6101	Day −7	−0.0032	0.0120	−0.0267	0.0204	.7929
Day −8	0.0067	0.0095	−0.0119	0.0252	.4813	Day −8	0.0035	0.0109	−0.0180	0.0249	.7506
Day −9	0.0061	0.0096	−0.0128	0.0249	.5287	Day −9	0.0047	0.0122	−0.0192	0.0285	.7009
Day −10	0.0067	0.0087	−0.0103	0.0237	.4387	Day −10	0.0097	0.0106	−0.0110	0.0304	.3589
Day −11	0.0021	0.0075	−0.0126	0.0168	.7799	Day −11	0.0029	0.0097	−0.0162	0.0220	.7652
Day −12	0.0136	0.0082	−0.0025	0.0297	.0985	Day −12	0.0143	0.0100	−0.0053	0.0339	.1520
Day – 13	**0.0205**	**0.0095**	**0.0018**	**0.0392**	**.0321**	Day −13	0.0190	0.0114	−0.0034	0.0414	.0962
Day – 14	**0.0268**	**0.0089**	**0.0093**	**0.0443**	**.0026**	**Day – 14**	**0.0284**	**0.0105**	**0.0078**	**0.0490**	**.0069**
Day – 15	**0.0477**	**0.0107**	**0.0268**	**0.0686**	**<.0001**	**Day – 15**	**0.0496**	**0.0130**	**0.0242**	**0.0750**	**.0001**
Day – 16	**0.0336**	**0.0101**	**0.0139**	**0.0534**	**.0008**	**Day – 16**	**0.0327**	**0.0126**	**0.0080**	**0.0574**	**.0093**
Day – 17	**0.0234**	**0.0109**	**0.0021**	**0.0447**	**.0315**	Day −17	0.0250	0.0137	−0.0019	0.0518	.0681
Day −18	0.0139	0.0088	−0.0034	0.0311	.1154	Day −18	0.0145	0.0110	−0.0071	0.0361	.1890
Day −19	0.0179	0.0104	−0.0025	0.0383	.0855	Day −19	0.0204	0.0130	−0.0051	0.0459	.1176
Day −20	0.0193	0.0103	−0.0010	0.0395	.0621	Day −20	0.0238	0.0134	−0.0024	0.0500	.0754
Day −21	0.0059	0.0097	−0.0130	0.0249	.5381	Day −21	0.0049	0.0125	−0.0196	0.0293	.6956
Day −22	0.0033	0.0091	−0.0144	0.0211	.7134	Day −22	−0.0030	0.0124	−0.0273	0.0213	.8091
Day −23	−0.0006	0.0092	−0.0186	0.0175	.9510	Day −23	0.0021	0.0122	−0.0219	0.0260	.8656
Day −24	0.0044	0.0093	−0.0139	0.0227	.6373	Day −24	0.0046	0.0118	−0.0185	0.0278	.6952
Day −25	0.0056	0.0090	−0.0120	0.0232	.5344	Day −25	0.0092	0.0113	−0.0129	0.0313	.4146
Day −26	0.0033	0.0086	−0.0135	0.0202	.6975	Day −26	−0.0019	0.0109	−0.0232	0.0195	.8641
Day −27	−0.0041	0.0089	−0.0215	0.0134	.6479	Day −27	−0.0033	0.0111	−0.0251	0.0185	.7675
Day −28	0.0079	0.0080	−0.0077	0.0235	.3225	Day −28	0.0122	0.0105	−0.0085	0.0329	.2473
Day −29	0.0056	0.0091	−0.0122	0.0234	.5381	Day −29	0.0095	0.0114	−0.0129	0.0319	.4078
-1st week AVG (Day 0–6)	**0.0235**	**0.0117**	**0.0005**	**0.0466**	**.0449**	-1st week AVG (Day 0–6)	0.0235	0.0143	−0.0046	0.0516	.1012
-2nd week AVG (Day −7 -13)	0.0151	0.0119	−0.0082	0.0384	.2040	-2nd week AVG (Day −7 -13)	0.0150	0.0147	−0.0138	0.0438	.3064
-3rd week AVG (Day – 14 -20)	**0.0426**	**0.0129**	**0.0173**	**0.0679**	**.0010**	**-3rd week AVG (Day – 14 -20)**	**0.0478**	**0.0163**	**0.0159**	**0.0797**	**.0034**
-4th week AVG (Day −21 -27)	0.0032	0.0110	−0.0184	0.0248	.7688	-4th week AVG (Day −21 -27)	0.0030	0.0143	−0.0251	0.0311	.8327
−2 week AVG (Day 0–13)	**0.0284**	**0.0143**	**0.0003**	**0.0565**	**.0473**	−2 week AVG (Day 0–13)	0.0289	0.0177	−0.0058	0.0635	.1025
−3 week AVG (Day 0–20)	**0.0425**	**0.0154**	**0.0122**	**0.0728**	**.0059**	−3 week AVG (Day 0–20)	0.0051	0.0094	−0.0133	0.0234	.5890
−4 week AVG (Day 0–27)	**0.0318**	**0.0151**	**0.0023**	**0.0614**	**.0348**	−4 week AVG (Day 0–27)	0.0336	0.0191	−0.0038	0.0709	.0782

Note: β (95% CIs) at different time lags (from the day of the nasal swab to the previous 30 days) and for different 7-day moving average are calculated for a 1 $\mu g/m^3$ increase in PM. Beta regression coefficients were estimated from multivariate continuous ordinal regression models adjusted for age, sex, ethnicity, assumption of systemic antibiotics during pregnancy and assumption of systemic antibiotics in the last month.

Significant associations are reported in bold.

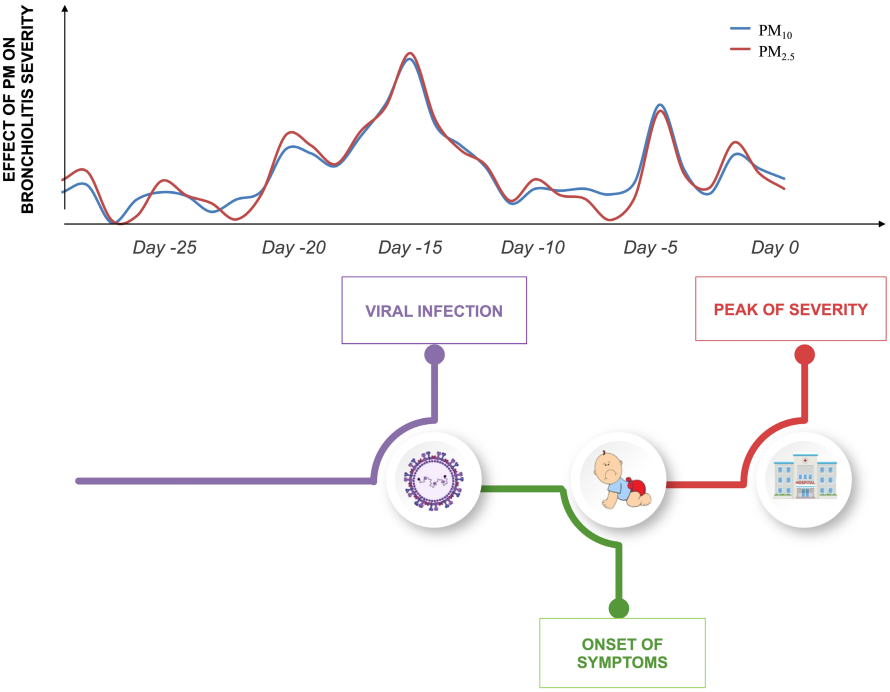

FIGURE 2 Hypothesis linking PM exposure and bronchiolitis severity

PM might modulate the viral load and the airways inflammation. Future studies should investigate whether preventive strategies, applied to very high-risk infants in the days following high levels of $PM_{2.5}$ and PM_{10} exposure might reduce the burden of this disease.

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CONFLICT OF INTEREST

None.

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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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