Air pollution and bronchiolitis : a case-control study in Antwerp, Belgium

Reference:
Van Brusselen Daan, De Troeyer Katrien, van Vliet Marinus Pieter, Avonts Dirk, Nemery Benoit, Liesenborghs Laurens, Verhulst Stijn, De Bacquer Dirk.- Air pollution and bronchiolitis : a case-control study in Antwerp, Belgium
European journal of pediatrics - ISSN 0340-6199 - 183(2024), p. 2431-2442
Full text (Publisher's DOI): https://doi.org/10.1007/S00431-024-05493-8
To cite this reference: https://hdl.handle.net/10067/2044490151162165141

Air pollution and bronchiolitis: a case-control study in Antwerp, Belgium.

Daan Van Brusselen MD PhD,[1,3,6] Katrien De Troeyer MD,[2] Marinus Pieter van Vliet MD,[3] Dirk Avonts MD PhD,[4] Benoit Nemery MD PhD,[5] Laurens Liesenborghs MD PhD,[6] Stijn Verhulst MD PhD,[3] Koen Van Herck MD PhD,[7] Dirk De Bacquer MD PhD[8]

[1]Department of Paediatric Infectiology, ZAS Hospitals, Antwerp, Belgium; [2]Department of Family Medicine and Population Health, Antwerp University, Antwerp, Belgium; [3]Department of Paediatrics, Antwerp University Hospital and Lab of Experimental Medicine and Paediatrics, University of Antwerp, Antwerp, Belgium; [4]Chief Editor 'Huisarts Nu', Domus Medica, Antwerp, Belgium; [5]Department of Public Health and Primary Care, University of Leuven, Leuven, Belgium; [6]Department of Clinical sciences, Institute of Tropical Medicine, Antwerp, Belgium; [7]Belgian Cancer Registry, Brussels, Belgium; [8]Department of Public Health and Primary Care, Ghent University, Ghent, Belgium;

Corresponding author:
Dr. Daan Van Brusselen, Department of Paediatric Infectiology, ZAS hospitals, Sint-Vincentiusstraat 20, 2018 Antwerp, Belgium; tel +3232852835; e-mail: daan.vanbrusselen@zas.be

Abstract

Purpose

This case-control study aimed to investigate the association between short-term (1 to 5 days) and medium-term (31 days) exposure to air pollutants ($PM_{2.5}$, PM_{10}, BC, NO_2) at home/daycare and the risk of 'severe bronchiolitis' (defined as 'requiring hospitalization for bronchiolitis') in children under 2 years in Antwerp, Belgium.

Methods

We included 118 cases and 79 controls admitted to three general hospitals from October 2020 to June 2021. Exposure levels were predicted using an interpolation model based on fixed measuring stations. We used logistic regression analysis to assess associations, with adjustment for potential confounders.

Results

There were hardly any significant differences in the day-to-day air pollution values. Medium-term (31 days) exposure to $PM_{2.5}$, PM_{10}, and NO_2 was however significantly higher in cases than controls in univariate analysis. Logistic regression revealed an association between severe bronchiolitis and interquartile range increases in $PM_{2.5}$ and PM_{10} at home and daycare, as well as NO_2 in daycare. Time-adjustment however reduced the odds ratios

significantly, suggesting potential overrepresentation of controls in low pollution periods.

Conclusion

This study suggests a possible link between severe bronchiolitis and medium-term (31 days) air pollution exposure (PM_{10} and NO_2), particularly in daycare. Larger studies are warranted to confirm these findings.

Key words

Bronchiolitis; Air pollution; Respiratory Syncytial Virus; Particulate Matter; Nitrogen dioxide

Abbreviations

BC: Black Carbon; IRCEL: Belgian Interregional Environment Agency; NO_2: Nitrogen Dioxide; $PM_{2.5}$: Particulate matter with a diameter < 2.5µm; PM_{10}: Particulate matter with a diameter < 10µm; RSV: Respiratory Syncytial Virus; USA: United States of America; VITO: Flanders Institute of Technology

What is known?

- Bronchiolitis is a leading cause of hospitalization in infants globally and causes a yearly seasonal wave of admissions in paediatric departments worldwide.
- Existing studies, mainly from the USA, show heterogeneous outcomes regarding the association between air pollution and bronchiolitis.

What is new?

- There is a possible link between severe bronchiolitis and medium-term (31 days) air pollution exposure (PM_{10} and NO_2), particularly in daycare.
- Larger studies are needed to validate these trends.

Acknowledgements

We would like to thank Petra Schelstraete MD PhD, Stefaan De Henauw MD PhD and Patrick Van Der Stuyft MD PhD for their useful comments on the manuscript.

Statement and declarations

Declaration of interests

We declare no competing interests.

Role of the funding source

There was no funding for this study.

Ethics approval

This study was performed in line with the principles of the declaration on Helsinki. The study protocol was approved by the ethics committee of the University of Ghent (number B6702020000754) and those of GZA & ZNA Hospitals.

Author Contributions

DVB and MPV collected and cleaned the data. DVB and KDT performed the statistical analysis, under supervision of KVH and DDB. DVB, MPV, KDT, KVH, BN, DA and DDB have made substantial contributions to the conception and design of the work and interpretation of data for the work; DVB, KDT, KVH, BN, DA, DDB, SV an LL revised the article and approved the final version to be published.

Air pollution and bronchiolitis: a case-control study in Antwerp, Belgium.

Introduction

Bronchiolitis is the number one cause of hospitalization among children under 1 year of age worldwide, especially in high income countries. Bronchiolitis is characterized by inflammation of the lower respiratory tract, and mainly affects infants in the first two years of life. Around 90% of cases is caused by the respiratory syncytial virus (RSV), although a few other respiratory viruses are sometimes involved (e.g. influenza, coronavirus, parainfluenza, rhinovirus, human metapneumovirus, and bocavirus). [1] General risk factors of incident bronchiolitis are: age of the child (first year of life), age of the mother (<20 years), having an older sibling, mothers without higher education, no breastfeeding, low (1400-2500g) or very low birth weight (<1400g), birth defects and maternal smoking in pregnancy. [1]

There are only a few studies on air pollution as a risk factor for bronchiolitis, while literature suggests that air pollution could augment inflammation within the lining of the respiratory tract, disrupting normal immune response to pathogens. [2] The limited number of publications on the relationship between air pollution and bronchiolitis has heterogeneous outcome measures and results. Most studies originate from the United Stated of America (USA). In a large case-crossover study, acquiring bronchiolitis was associated with an increased exposure to $PM_{2.5}$ (particulate matter with a diameter < 2.5μm), one and four days before presentation (OR 1.07 and OR 1.04 for every 10 μg/m^3 increase of $PM_{2.5}$, respectively), while no association was seen with exposure 7 days before presentation. [3] In a meta-analysis it was also shown that long-term exposure to $PM_{2.5}$ might be associated with an increased risk of severe bronchiolitis (requiring hospitalization). [4] A recent Italian study demonstrated that bronchiolitis in admitted children is more severe (using 7 degrees of severity) when these children were exposed to higher $PM_{2,5}$ (and PM_{10}, i.e. particulate matter with a diameter < 10μm) levels at day 2, day 5 and day 14-16 before admission. This suggests a mediating role of PM in the severity of bronchiolitis. [5]

The composition of $PM_{2.5}$ differs per region and therefore the effect could be different in Northern Europe. The purpose of our 'BronchiolAir' study was to investigate if $PM_{2.5}$ could also have an impact on bronchiolitis hospitalizations in Antwerp and whether there would also be an impact of NO_2 (nitrogen dioxide), a good indicator of traffic-related pollution, because Antwerp is one of the regions in the world with the highest disease burden because of NO_2. [6]

Our study hypothesis is that children under 2 years of age that are at risk of exposure to a ‘bronchiolitis inducing virus’, using the moment of inclusion in the RSV season as a proxy for this risk of exposure, have a higher probability of developing ‘severe bronchiolitis’ (defined as requiring hospitalization for bronchiolitis) when exposed to short-term (1 to 5 days prior to hospitalization) and medium-term (31 days) air pollution (at home and daycare).

Methodology

We performed a multicentre case-control study in an urban/suburban setting in Antwerp, Belgium, from October 2020 until June 2021.

Participants were recruited in three general hospitals that are part of the Antwerp Hospital Group (ZAS), the largest association of general hospitals in Antwerp. Children <2 years of age were eligible to be included as a case if they presented with severe bronchiolitis, defined as a physician-diagnosed bronchiolitis requiring hospitalization. Controls consisted of infants < 2 years of age, of approximately the same age, who were admitted in the same paediatric hospital ward during the same month for one of the following reasons: a non-respiratory infection (e.g.

gastroenteritis, urinary tract infection, osteomyelitis, skin infection…), trauma, (non-respiratory and non-ENT) surgery (e.g. appendicitis), epilepsy or observation for excessive crying.

After having given their consent to participate, one of the parents/caretakers was interviewed face-to-face on the day of admission or the day after, using a paper questionnaire in Dutch, English or French, about the child's medical history, socioeconomic variables, personal habits (alcohol use, smoking, medication), and residential / occupational exposures. Respondents did not receive a fee or any other benefit for their participation.

Cases and controls were recruited from October 1st 2020 onwards. We included children under 2 years of age that are at risk of exposure to a ' bronchiolitis inducing virus', using the moment of inclusion in the RSV season as a proxy for this risk of exposure. The purpose was to recruit cases during the bronchiolitis season of this autumn/winter (around 6 months), but since the epidemiology of this season was strongly influenced by COVID-19, we continued inclusions until June 2021.[7]

As a measure of exposure, we used predicted values of $PM_{2,5}$, PM_{10}, BC (black carbon) and NO_2 exposure, at the home address, and daycare address of the participant 1 to 5 days prior to hospitalization (considering an incubation period of 2 – 8 days for RSV), as well as the 31 days average of these pollutants before admission. These predicted values were obtained from an interpolation model that is based on fixed measuring stations of the Belgian Interregional Environment Agency, (IRCEL), which are placed throughout Belgium. We used the internationally validated, 'RIO-IFDM (Immision Frequency Distribution) street canyon model', developed by the Flanders Institute of Technology (VITO). This is a geospatial interpolation model which provides urban background concentrations of air pollutants at a resolution of 4x4 km^2 based upon the Belgian Air quality monitoring network. In addition, the model considers Antwerp's building configuration and the city's 'street canyons' to get a more precise estimation at street level. [8, 9] Street canyons are urban roads confined by continuous building-walls with increased pollutant concentrations as ventilation is reduced. [1, 10]

We also calculated a composite variable corresponding to 1/3 of the value in daycare + 2/3 of the value at home (in case the child goes to daycare) and 100% the value at home when the child is only taken care of at home.

Data management and statistical analyses were done with SPSS (version 24.0). Continuous variables were analyzed with a student t-test and categorical variables with Chi-Square or Fisher-exact test for univariate analysis. We performed a standard logistic regression, taking into account possible confounders with a univariate p-value <0.15 (paternal education level and average daily temperature in the 31 days before admission).

The initial aim was to mainly include participants during the winter months. However, because of the COVID-19 pandemic, the 2020-2021 bronchiolitis peak came unexpectedly late. As a result, we recruited a significant number of cases during spring. However, this period is characterized by higher secondary PM concentrations ('spring smog'), arising from high ammonia emissions when farmers clean the stables and spread manure. Participants who are recruited during spring, therefore, are expected to have a higher exposure than those recruited in winter. Because more cases than controls were recruited during spring, we used a time-adjusted model that additionally corrected for the date of hospitalization (transformed into a categorical variable; categories of 2 weeks were used). We expressed the results of the multivariable analyses as increases per interquartile range (IQR), because this takes into account the spread of the dataset.

The study protocol was approved by the ethics committee of the University of Ghent (number B6702020000754) and those of GZA & ZNA Hospitals. We received no funding for this study.

Results

We were able to recruit 118 cases and 79 controls. Cases and controls were found to have similar sociodemographic characteristics, except for paternal education level. (*Table 1A*) The average temperature in the 31 days before hospitalization was lower for cases than for controls. (*Table 1B*) Cases and controls had a similar medical history. (*Table 2A and 2B*)

There were hardly any significant differences in the day-to-day air pollution values in univariate analysis, both at home and at the daycare address. (*Table 3*) The average air pollutant values in the 31 days before admission were however significantly higher in cases than in controls in univariate statistics, both at the home address, and at the daycare address. (*Table 4A and 4B*)

In our analysis it appeared that the daily PM and NO_2 concentrations are generally higher in cases than in controls during the entire month before (but also after) admission. In logistic regression analysis, we modeled cases vs. controls as a binary outcome and assessed potential associations with exposure to different pollutants (*Table 5-8*). In a model that was not time-adjusted we found an OR of 2.00 to be hospitalized for bronchiolitis

(95%CI 1.03-3.85) per interquartile range (IQR) increase of $PM_{2.5}$ at home and OR of 2.40 (95%CI 1.28-5.10) per IQR increase of $PM_{2.5}$ at daycare. Furthermore we found an OR of 2.17 to be hospitalized for bronchiolitis (95%CI 1.23-3.85) per interquartile range (IQR) increase of PM_{10} at home and OR of 2.58 (95%CI 1.26-5.26) per interquartile range (IQR) increase of PM_{10} in daycare. We also found an OR of 1.36 to be hospitalized for bronchiolitis (95%CI 0.79-2.35) per interquartile range (IQR) increase of NO_2 at home and OR of 3.44 (95%CI 1.60-7.41) per interquartile range (IQR) increase of NO_2 in daycare (*Table 5-8*).

In the beginning of the inclusion period, the cumulative percentage of cases included was relatively low, while this increased around the month of March (*Figure 1)*, corresponding to the exceptionally late RSV peak (because of COVID-19) in ‘bronchiolitis season 2020-2021’, but also corresponding to the yearly pollution peak months. [7] Without adjusting for time of admission, this leads to an overrepresentation of controls with lower pollution values. We took this into account by using a ‘time-adjustment’ model: this does reduce the odds ratios of our model significantly (and strongly reduces the significance, especially for $PM_{2.5}$). (*Table 5-8*) Also, after June 1st only controls (N=19) were included. We performed a separate ‘sensitivity analysis’, excluding these 19 cases, but this did not have a signifcant impact on our study results.

Discussion

This case-control study was designed to investigate the effect of short-term (1 to 5 days prior to hospitalization) and medium-term (31 day average) air pollution on 'severe bronchiolitis' (defined as children with bronchiolitis requiring hospitalization). There were hardly any significant differences in the day-to-day air pollution values, both at home and at the daycare address. (*Table 3*) We did however find an association between medium-term (31 days average before admission) exposure to different ambient air pollutants and the risk of a 'severe bronchiolitis', defined as a child <2 years old requiring hospitalization because of bronchiolitis. (*Table 5-8*) This association was however not confirmed for all pollutants in a time-adjusted model (*Table 5-8*), probably related to the fact that our study population is relatively small. However, the effect seems to be the largest in daycare, particularly for NO_2, being the best indicator of spatial variation in outdoor urban air pollution. [11] The fact that we found a larger effect in daycare could be related to daycares being often located in busier streets, but since we do not have traffic data in study, we cannot confirm this hypothesis.

Studies on bronchiolitis and PM in the USA show heterogeneous results.

[3-5] There was at the time of our study only one case-crossover study showing a (short-term) effect of NO_2 on bronchiolitis in Israel, but no effect was shown in a meta-analysis. [1, 4, 12] In our study we aimed to look at the *medium-term (31 days average before admission)* effect of different pollutants on severe bronchiolitis in a European setting.

We aimed to investigate whether children under 2 years of age that are at risk of exposure to a 'bronchiolitis inducing virus' (RSV, Influenza or Sars-Cov-2), using the moment of inclusion in the RSV season as a proxy for this risk of exposure, have a higher probability of developing 'severe bronchiolitis' (defined as requiring hospitalization for bronchiolitis) when exposed to air pollution, as compared to controls hospitalized for a condition that is unlikely to be air pollution related. The pathophysiological explanation for this could be that low-grade inflammation in the respiratory epithelium, provoked by acute or chronic exposure to air pollution in a large European city, increases the risk of hospitalization for bronchiolitis (i.e. 'severe bronchiolitis') in children < 2 years. We only found significant effects in the 31 days average of pollution values, pointing towards a more chronic effect.

A recent case-crossover study from Padua (Italy) also indicated that the cumulative effect of air pollution exposure could be more important than the values at different one-day time lags, especially for NO_2 (high concentrations of NO_2 in the 2-12 days before presentation were associated with a 30% increase in ‘emergency department visits’ for bronchiolitis). [13] This matches with our study results: we did also not see short-term effects, but only an effect in the 31 days average of pollutants.

One of the limitations of our study is that the total number of controls was lower than the number of cases, because the amount of children admitted to paediatric wards for non-respiratory reasons is low in the colder months of the year when other non-essential admissions are often postponed. This made it difficult to include controls evenly with cases (*Figure 1*). Another limitation is the fact that the 2020-2021 RSV season (or better ‘plateau’ in this year) was exceptionally late because of non-pharmaceutical interventions for the COVID-19 pandemic. [7, 14] Indeed, the RSV peak coincided with ‘spring smog’, a period with higher air pollution values (esp. secondary PM), and therefore also with the period in which we included most cases (and less controls). (*Figure 2*) We took this into account by using a time-adjusted model. In this model however, the odds ratios were considerably lower, especially for $PM_{2,5}$. (*Table 5-8*). The spring smog peak however especially counts for PM, and not so much for NO_2, while the most signifcant effect we found was for NO_2 (in daycare; see table 7), which is not so much affected by spring smog, but much more traffic-related. The fact that more people were working at home during the pandemic and that air pollution values changed globally because of the reduction in traffic, is another limitation. For controls we opted for patients who were admitted in the same hospital, but for a non-respiratory illness. This led of course to a strong selection bias. Using hospital controls is, especially in the context of studies with very limited funding, often applied in case-control studies as it is a practical way of finding controls that are representative of the at-risk population and come from the same geographical catchment area. However, as other respiratory diseases are also potentially linked to air pollution, we included only controls who suffered from disease in which air pollution does not play a substantial role: non-respiratory infections (e.g. gastroenteritis, urinary tract infection, osteomyelitis, skin infection…), trauma, (non-respiratory and non-ENT) surgery (e.g. appendicitis), epilepsy or observation for excessive crying. Furthermore, the population at risk in our study should be children exposed to frequent bronchiolitis-inducing viruses (RSV/Influenza/Sars-Cov-2). The lack of funding made it however impossible to swab all controls. A less ideal proxy is to recruit children <2 years as controls during the RSV season (since this is the major pathogen causing bronchiolitis), as we did. Whether or not controls have actually been exposed to the virus is an important variable that we did not measure and which we could therefore not use as a covariate. This leads to a bias towards the null. However, literature suggests that 95% of children have been in contact with RSV (as the major cause of bronchiolitis) in the first 2 years of life: this exposure does happen in the few months that RSV is prevalent. [15] We believe therefore – in our pragmatic view – that controls must have a similar 'risk of exposure' (they were recruited at the moment when the risk of being in contact with RSV was very high), which is one of the reasons why time adjustment is so important in this study. We do recognize however that using timing of inclusion as 'measure of the risk of viral exposure' is a weak proxy for exposure. Last but not least, since biomarkers of chronic exposure to air pollution are lacking, we relied on predicted air pollution values at the home and daycare address to assess exposure. One study suggests that 'urinary black carbon load' could be a specific biomarker of chronic exposure to combustion-related air pollution, possibly providing a more accurate reflection of ambient residential air pollution exposure, but there are not a lot of data yet and this is still expensive. [16]

Our study does also have several strengths. First of all, it is one of the first multicentre studies in Europe that investigates the relationship between air pollution and the risk to be admitted for bronchiolitis systematically. Furthermore we used an internationally validated interpolation model which allowed us to have a very precise estimate of $PM_{2,5}$, PM_{10}, BC and NO_2 exposure, not only at home, but also in daycare. The fact that we performed a multicentre study, also lends strength to our study in different ways. We did not only include hospitalized patients in three of the largest general hospitals in the region, representing the majority of paediatric hospitalization beds in Antwerp, but in this way we also have a good geographic spread of included children; they come from all over the (sub)urban area, including more polluted and less polluted zones. However, because of the fact that cases were overrepresented in 'high pollution months', we still have to interpret the outcomes of this study with caution.

Conclusion

Children hospitalized for bronchiolitis generally appear to be more exposed (during the 31 days before admission) to air pollution, particularly in daycare. The study was however too small to draw definite conclusions. Larger scientific studies are needed to confirm the trends found in our analysis. In a future study on bronchiolitis and air pollution, it could be useful to measure 'urinary black carbon load' as a specific biomarker of chronic exposure to combustion-related air pollution, possibly providing a more accurate reflection of ambient residential air pollution exposure. [16]

Tables

Table 1A							
	Case (n=118)		Number of valid answers	Control (n=79)		Number of valid answers	p value
Child							
Age (months)	7,42	5,65	118	8,08	6,45	79	0,45
Gestational age (weeks)	38,5	1,70	116	38,6	1,59	78	0,60
Birth weight (gram)	3279	490	114	3236	497	78	0,56
Sex			118			79	0,30
male	44	37%	…	36	46%	…	
female	74	63%	…	43	54%	…	
Mother							
Age (years)	31,4	4,5	117	31,2	4,3	78	0,73
Education (high) *	72	61%	118	40	51%	78	0,19
Migration background **	58	50%	117	35	45%	78	0,56

Father							
Age (years)	34,3	6,3	116	33,3	5,0	75	0,24
Education (high)*	64	55%	117	29	39%	74	0,04
Migration	58	50%	116	30	40%	75	0,18
Household							
Smoking			118			78	
parents smoke	26	22%	…	19	24%	…	0,73
inside house	2	2%	…	1	1%	…	1,00
during pregnancy	7	6%	…	2	3%	…	0,32
Breastfed			118			78	
any	94	80%	…	60	77%	…	0,72
<1 month	15	13%	…	13	17%	…	
1-3 months	35	30%	…	19	24%	…	
3-6 months	14	12%	…	13	17%	…	
Household equipment			118			78	
Woodstove	2	2%	…	2	3%	…	0,65
Gas furnace	50	42%	…	33	42%	…	1,00
Going to daycare	69	58%	118	38	48%	79	0,19

Table 1A: Sociodemographic characteristics.
Continuous variables are presented as means (SD) and p-values were based on t-tests. Categorical variables are presented as n (%) and their p-values were based on Chi-Square or Fisher-exact test.
*Education level = high in case the parent followed at least 'short type higher education'.
**Migration background = 'one of the grandparents is not born in Belgium'

Table 1B

	Case (n=118)		Number of valid answers	Control (n=79)		Number of valid answers	p value
Average temperature 31 days before hospitalization (°C)	7,0	2,0	117	9,8	5,1	79	<0,001
Average humidity month before hospitalization (%)	72,1	5,8	117	72,4	6,5	79	0,72

Table 1B: Environmental characteristics.
Continuous variables are presented as means (SD) and p-values were based on t-tests.

Table 2A

	Case (n=118)		Number of valid answers	Control (n=79)		Number of valid answers	p value
Medical history			118			79	
Immunodeficiency	0	0%		1	1%		0,40
Previous medical problem	18	15%		13	16%		0,84
Chronic medication	18	15%		14	18%		0,70
Clinical characteristics			118			79	
Crepitations	100	85%		1	1%		<0,001
Wheeze	84	71%		1	1%		<0,001
Respiratory distress	106	90%		0	0%		<0,001
Diarrhoea	13	11%		23	30%		0,001
Fever	95	81%		44	56%		<0,001
Investigations and therapy			118			79	
Chest X-ray performed	12	10%		2	3%		0,05
X-ray changes found*	10	8%		0	0%		0,02
Oxygen support	70	59%		1	1%		<0,001
CPAP or Optiflow	16	14%		0	0%		0,001
NG feeding	64	54%		10	13%		<0,001
IV fluids	12	10%		13	16%		0,27
AB	17	14%		31	39%		<0,001
CS	2	2%		0	0%		0,52
Other AID	0	0%		0	0%		NA
Intensive care			118			79	
PICU/NICU	6	5%		0	0%		0,08
Mechanical	1	1%		0	0%		1,00
ECMO	0	0%		0	0%		NA
Inotropic	0	0%		0	0%		NA

Table 2A: General medical data from patient file.
Categorical variables are presented as n (%) and p-values were based on Chi-Ssquare or Fisher-exact test. NA = not applicable. *Radiographic changes compatible with bronchiolitis. Abbreviations: RX = chest radiograph; CPAP = continuous positive airway pressure; NG = nasogastric; AB = antibiotics; CS = corticosteroids; AID = anti-inflammatory drugs; ECMO = extracorporeal membrane oxygenation.

Table 2B

	Case (n=118)		Number of valid answers	control (n=79)		Number of valid answers	p value
Reason of hospitalisation			118			79	<0,001
Bronchiolitis	118	100%		0	0%		
Non-resp. infection				54	68%		
Trauma				4	5%		
Observation				11	14%		
Convulsions				3	4%		
Hyperbilirubineamia				3	4%		
Other				4	5%		
Comorbidities	**18**	**15%**	118	**13**	**16%**	79	0,52
FTT	1	1%		1	1%		
premature	2	2%		0	0%		
CMPA	4	3%		3	4%		
cardiac	3	2%		1	1%		
metabolic	0	0%		2	2%		
recent infection	5	4%		3	4%		
UTI	0	0%		2	2%		
skin	1	1%		1	1%		
chromosomal	1	1%		0	0%		
lupus	1	1%		0	0%		
Viral infection found	**105**	**89%**	118	**4**	**5%**	79	<0,001
Number of children tested	117	99%		71	90%		
RSV	96	81%		0	0%		
SARS-CoV-2	0	0%		2	2%		
Parainfluenza	1	1%		0	0%		
other	2	2%		1	1%		
multiple	6	5%		1	1%		

Table 2B: Reason of hospitalisation, comorbidities and viral screening. Categorical variables are presented as n (%) and p-values were based on Chi-Square or Fisher-exact test. Abbreviations: Non-resp. = non-respiratory infection (e.g. gastroenteritis, osteomyelitis…); FTT = failure to thrive; CMPA = cow milk protein allergy; UTI = urinairy tract infection; RSV = respiratory syncytial virus; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Table 3	Home					Daycare				
	Case (n=118)		Control (n=79)		p value	Case (n=68)		Control (n=36)		p value
PM2,5 (µg/m³)										
Day 0	15,28	10,2	14,48	9,6	0,58	15,08	10,1	12,98	9,1	0,30
Day -1	15,35	9,3	14,26	10,5	0,45	15,32	9,1	13,55	10,8	0,38
Day -2	14,27	7,7	13,18	10,0	0,39	14,37	9,4	14,75	12,9	0,85
Day -3	14,97	9,2	12,61	6,8	0,05	15,03	8,9	13,58	8,1	0,42
Day -4	14,48	9,8	12,97	7,2	0,25	14,43	9,8	14,78	8,4	0,85
Day -5	14,84	10,7	13,51	8,5	0,36	13,21	7,8	13,83	8,8	0,71
PM10 (µg/m³)										
Day 0	26,12	14,7	25,57	13,0	0,79	26,12	14,1	23,24	12,0	0,30
Day -1	26,21	13,6	24,93	14,3	0,53	25,73	12,4	23,80	14,7	0,48
Day -2	24,87	11,4	23,22	14,0	0,36	25,00	11,4	24,80	18,1	0,95
Day -3	26,01	13,6	21,94	9,4	0,01	26,19	14,2	22,75	11,6	0,21
Day -4	24,79	13,3	21,77	8,7	0,06	24,86	14,0	23,53	9,9	0,61
Day -5	25,43	14,5	23,00	11,7	0,20	23,94	12,5	22,93	12,0	0,69
BC (µg/m³)										
Day 0	0,77	0,48	0,85	0,54	0,25	0,80	0,79	0,77	0,82	0,82
Day -1	0,82	0,51	0,81	0,41	0,93	0,89	0,59	0,75	0,57	0,24
Day -2	0,77	0,41	0,84	0,64	0,35	0,81	0,48	0,93	0,82	0,43
Day -3	0,84	0,59	0,75	0,47	0,29	0,89	0,59	0,84	0,57	0,74
Day -4	0,83	0,57	0,74	0,35	0,20	0,86	0,58	0,79	0,38	0,51
Day -5	0,85	0,65	0,78	0,45	0,42	0,81	0,60	0,75	0,42	0,58
NO2 (µg/m³)										
Day 0	23,39	10,8	22,35	11,3	0,52	23,24	10,4	19,98	9,7	0,13
Day -1	22,87	10,6	21,43	11,4	0,37	23,95	10,3	19,47	10,2	0,04
Day -2	22,70	9,9	21,34	11,8	0,39	24,04	11,5	20,76	12,3	0,18
Day -3	23,61	10,4	20,52	11,6	0,04	25,16	12,9	21,08	11,6	0,12
Day -4	23,44	9,9	20,29	10,2	0,03	24,01	11,4	20,77	10,3	0,16
Day -5	24,02	11,2	21,31	10,1	0,09	23,69	11,2	19,48	8,5	0,05

Table 3: Day to day air pollution at both home address and daycare address.
Continuous variables are presented as means (SD) and their p-values were calculated by T-tests
.

Table 4A	Home					Daycare				
	Case (n=118)		Control (n=79)		p value	Case (n=68)		Control (n=36)		p value
PM 2,5	15,59	2,22	13,98	2,41	<0,001	15,51	2,17	14,01	2,38	0,002
PM 10	26,71	3,65	24,18	3,95	<0,001	26,57	3,49	23,82	4,21	0,001
BC	0,90	0,19	0,83	0,20	0,01	0,92	0,21	0,84	0,25	0,09
NO2	24,52	5,43	21,92	6,70	0,01	24,97	5,45	20,83	6,35	0,001

Table 4A: Average air pollution during the 31 days before admission to the hospital.
All pollutants (in µg/m^3) are calculated as the mean of the 31 days before hospitalisation. Variables are presented as mean (SD) and p-values were based on t-tests.

Table 4B	Composite value*				
	Case (n=118)		Control (n=79)		p value
PM 2,5	15,50	2,43	13,97	2,42	<0,001
PM 10	26,55	4,02	24,14	3,96	<0,001
BC	0,90	0,19	0,83	0,20	0,018
NO2	24,45	5,57	21,85	6,45	0,003

Table 4B: Average composite air pollution* during the 31 days before admission to the hospital.
All pollutants (in µg/m^3) are calculated as the mean of the 31 days before hospitalisation. Variables are presented as mean (SD) and p-values were based on t-tests.

* The composite variable = 1/3 of the value in daycare + 2/3 of the value at home (in case the child goes to daycare) and 100% the value at home when the child is only taken care of at home

Table 5. Adjusted Odds Ratios (aOR) to be hospitalized for bronchiolitis for an interquartile range (IQR) increase[****] of $PM_{2.5}$, retained in a multivariable logistic regression model with average $PM_{2.5}$ levels in the 31 days before admission at home (N cases = 118; N controls = 79) and in daycare (N cases = 68; N controls = 36).[*]

TIME-ADJUSTED MODEL **			
	aOR (95%CI) average at home	aOR (95%CI) average daycare	aOR (95%CI) Composite ***
$PM_{2.5}$	1.54 (0.51–4.65) p=0.44	2.43 (0.58–10.1) p=0.22	1.57 (0.51–4.78) p=0.43

Nagelkerke R^2 for the time-adjusted model = 0,23 (at home) and 0,13 (in daycare).

Table 6. Adjusted Odds Ratios (aOR) to be hospitalized for bronchiolitis for an interquartile range (IQR) increase of PM_{10}, retained in a multivariable logistic regression model with average PM_{10} levels in the 31 days before admission at home (N cases = 118; N controls = 79) and in daycare (N cases = 68; N controls = 36).[*]

TIME-ADJUSTED MODEL **			
	aOR (95%CI) average at home	aOR (95%CI) average daycare	aOR (95%CI) Composite ***
PM_{10}	2.69 (0.94–7.69) p=0.065	5.13 (1.24–21.28) p=0.024	2.92 (0.99–8.62) p=0.051

Nagelkerke R^2 for the time-adjusted model = 0,25 (at home) and 0,19 (in daycare).

Table 7. Adjusted Odds Ratios (aOR) to be hospitalized for bronchiolitis for an interquartile range (IQR) increase of NO_2, retained in a multivariable logistic regression model with average NO_2 levels in the 31 days before admission at home (N cases = 117; N controls = 79) and in daycare (N cases = 68; N controls = 36).[*]

TIME-ADJUSTED MODEL **			
	aOR (95%CI) average at home	aOR (95%CI) average daycare	aOR (95%CI) Composite ***
NO_2	1.26 (0.69–2.28) p=0.45	3.88 (1.56–9.61) p=0.003	1.41 (0.77–2.57) p=0.27

Nagelkerke R^2 for the time-adjusted model = 0,21 (at home) and 0,23 (in daycare).

Table 8. Adjusted Odds Ratios (aOR) to be hospitalized for bronchiolitis for an interquartile range (IQR) increase of BC, retained in a multivariable logistic regression model with average NO_2 levels in the 31 days before admission at home (N cases = 117; N controls = 79) and in daycare (N cases = 68; N controls = 36).*

TIME-ADJUSTED MODEL **			
	aOR (95%CI) average at home	aOR (95%CI) average daycare	aOR (95%CI) Composite ***
BC	1.13 (0.58–2.22) p=0.71	2.05 (0.83–5.08) p=0.12	1.21 (0.62–2.36) p=0.58

Nagelkerke R^2 for the time-adjusted model = 0,21 (at home) and 0,13 (in daycare).

Legend for Tables 5-8:

* Covariates used in the general model were possible confounders with a bivariate p-value <0.15: paternal education level and the average daily temperature in the 31 days prior to hospitalization

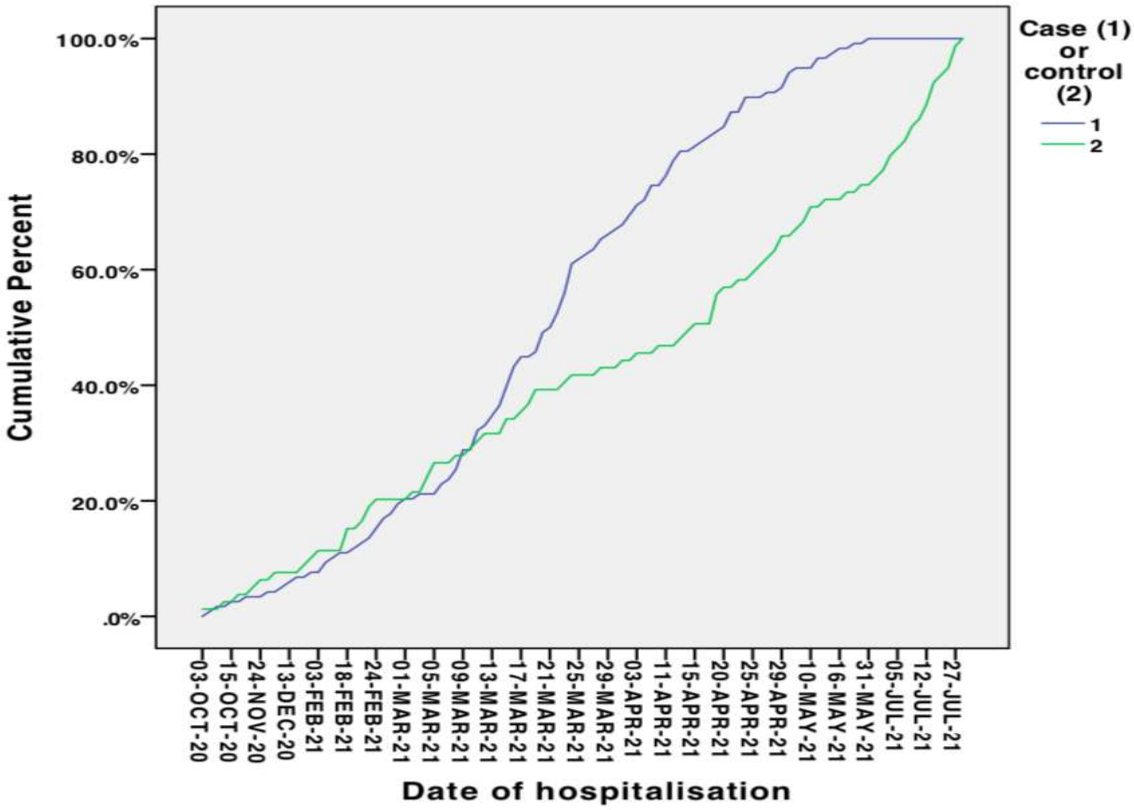
** Because more cases than controls were included in 'high pollution months', we used a time-adjusted analysis not only taking into account paternal education and daily temperature, but also the date of hospitalisation (transformed into a categorical variable) as a confounder.

*** The composite variable = 1/3 of the value in daycare + 2/3 of the value at home (in case the child goes to daycare) and 100% the value at home when the child is only taken care of at home

**** The interquartile ranges were 4.2 (3.8 in daycare) µg/m^3 for $PM_{2.5}$, 6.5 (6.0 in daycare) µg/m^3 for PM_{10}, 0,27 (0.26 in daycare) µg/m^3 for BC and 9.6 (9.4 in daycare) µg/m^3 for NO_2.

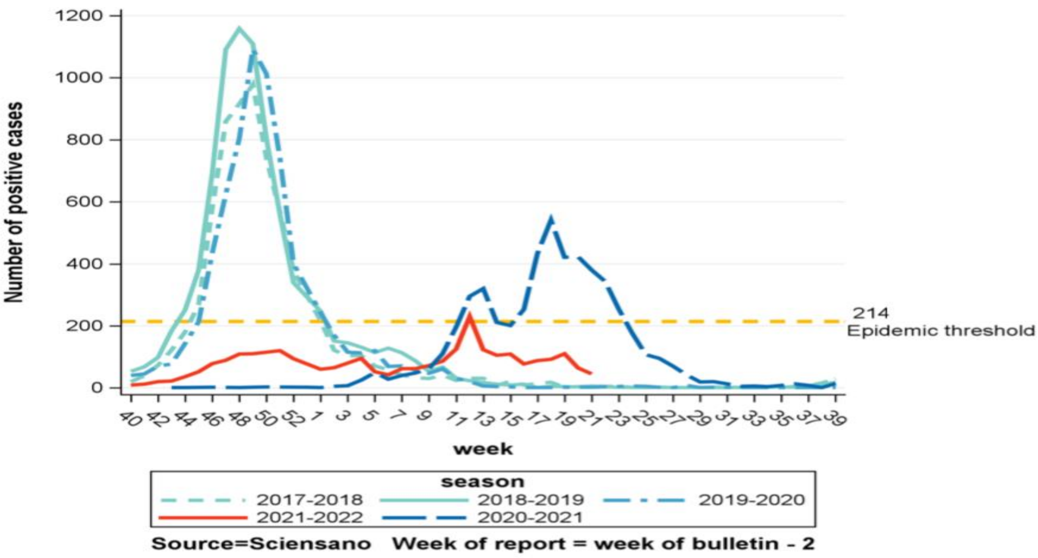
Figures

Figure 1. Cumulative percentage * of inclusions (cases vs. control) according to date of admission. **



* The absolute amount of cases included per month was always higher than the absolute amount of controls included (because of logistical reasons – see text). In the beginning of the inclusion period, the cumulative percentage of cases included was relatively low, while this became higher around the month of March, corresponding to the exceptional RSV peak in ‘bronchiolitis season 2020-2021’ (disturbed by ‘non-pharmaceutical interventions’ for the COVID-19 pandemic – see *‘Figure 2’*)
** After June 1st only 19 more inclusions were done. All were controls. Because seasonal pollution values are lower this time of the year; we included a time-adjusted model in order to prevent an overrepresentation of controls with lower pollution data.

Figure 2. Number of RSV infections (as main cause of bronchiolitis) in Belgian reference centres in previous years and the year of inclusion.



* The 2020-2021 RSV season was exceptional because of 'non-pharmaceutical interventions' for the COVID-19 pandemic.[7, 14] The RSV peak moment (in which we included most cases) coincided with the 'spring smok peak,' a period with (especially) higher secondary PM concentrations – *see 'Figure 1'*. This made the interpretation of our data more difficult.

ADDENDUM TO BRONCHIOLAIR STUDY

Questionnaire 'BronchiolAir'

1. What is your exact address? (street, number and postal-code):
   ………………………………………………………………………

2. Where is your child during the day? At home or daycare?
   (e.g. 'grandparents' or 'neighbors' can be listed as daycare) (max. 1 answer!)
   ○ Home ○ Daycare or other

   What is the exact address of daycare? (street, number and postal-code)
   ………………………………………………………………………

3. Did you move to a new home/location in the last 2 years?
   ○ Yes ○ No

   If yes, what was your previous address? (street, number and postal-code):
   ………………………………………………………………………

4. What is the age of both parents?
   ….. (Mother) and ….. (father of co-parent) in years

5. What is the occupation of the mother? (max. 1 answer!)
   ○ Laborer (blue collar) ○ Servant (white collar)
   ○ Middle class
   ○ Upper class ○ Self-employed

6. What is the occupation of the father or co-parent? (max. 1 anwer!)
   ○ Laborer (blue collar) ○ Employee (white collar)
   ○ Middle management
   ○ Upper management ○ Self-employed

7. What is the highest level of education of the mother?
   ○ Primary school ○ Lower secondary school
   ○ Higher secondary ○ Higher education (short type)
   ○ Higher education (long type)

8. What is the highest level of education of the father or co-parent?
   - ○ Primary school ○ Lower secundary
   - ○ Higher secundary ○ Higher education (short)
   - ○ Higher education (long type)

9. Does one or both of the parents smoke?
   - ○ Yes ○ No

10. Do people smoke inside the house?
    - ○ Yes ○ No

11. Did the mother smoke during pregnancy?
    - ○ Yes ○ No

12. Was your child breastfed? If yes, for how long?
    - ○ No ○ <1month ○ 1-3months
    - ○ 3-6months ○ >6 months

13. Does the mother have a migration background?
    (e.g. is one of the grandparents not born in Belgium?)
    - ○ Yes ○ No

14. Does the father or co-parent have a migration background?
    (e.g. is one of the grandparents not born in Belgium?)
    - ○ Yes ○ No

15. Do you use a woodstove at home?
    - ○ Yes ○ No`

16. Do you use a gas stove at home?
    - ○ Yes ○ No

17. How do you travel with your child?
    - ○ car ○ bike ○ on foot
    - ○ public transport

18. What is the distance between home and daycare?
    - ○ <1km ○ 1-5km ○ 5-20km
    - ○ >20km
    - ○ no daycare

19. How many siblings (bothers or sisters) does the child have?
….. (answer with a number)

20. How many other people (apart from siblings) live in your home?
(e.g. parents or other family) …..

21. Does your child have any congenital syndrome / disease?
O Yes O No

If yes, please describe shortly: ………………………….

1. Koehoorn M, Karr CJ, Demers PA, Lencar C, Tamburic L, Brauer M. Descriptive epidemiological features of bronchiolitis in a population-based cohort. Pediatrics. 2008;122(6):1196-203.
2. Monoson A, Schott E, Ard K, Kilburg-Basnyat B, Tighe RM, Pannu S, et al. Air pollution and respiratory infections: the past, present, and future. Toxicological sciences : an official journal of the Society of Toxicology. 2023;192(1):3-14.
3. Girguis MS, Strickland MJ, Hu X, Liu Y, Chang HH, Kloog I, et al. Exposure to acute air pollution and risk of bronchiolitis and otitis media for preterm and term infants. Journal of exposure science & environmental epidemiology. 2018;28(4):348-57.
4. King C, Kirkham J, Hawcutt D, Sinha I. The effect of outdoor air pollution on the risk of hospitalisation for bronchiolitis in infants: a systematic review. PeerJ. 2018;6:e5352.
5. Milani GP, Cafora M, Favero C, Luganini A, Carugno M, Lenzi E, Pistocchi A, Pinatel E, Pariota L, Ferrari L, Bollati V. PM2.5, PM10 and bronchiolitis severity: a cohort study. Pediatr Allergy Immunol 2022;33e13853.
6. Khomenko S, Cirach M, Pereira-Barboza E, Mueller N, Barrera-Gómez J, Rojas-Rueda D, et al. Premature mortality due to air pollution in European cities: a health impact assessment. The Lancet Planetary health. 2021;5(3):e121-e34.
7. Van Brusselen D, De Troeyer K, Ter Haar E, Vander Auwera A, Poschet K, Van Nuijs S, et al. Bronchiolitis in COVID-19 times: a nearly absent disease? European journal of pediatrics. 2021;180(6):1969-73.
8. Janssen S., Dumont G., Fierens F., & Mensink C. Spatial interpolation of air pollution measurements using CORINE land cover data. Atmospheric Environment 2008; 42(20): 4884–4903.
9. Lefebvre W, Van Poppel M, Maiheu B, Janssen S, Dons E. Evaluation of the RIO-IFDM-street canyon model chain. Atmospheric Environment 2013 (77:); 325–337.
10. Berkowicz R, Hertel O, Larsen SE, Sørensen NN, Nielsen M. Modelling traffic pollution in streets. National Environmental Research Institute, 1997.
11. Levy I, Mihele C, Lu G, Narayan J, Brook JR. Evaluating multipollutant exposure and urban air quality: pollutant interrelationships, neighborhood variability, and nitrogen dioxide as a proxy pollutant. Environmental health perspectives. 2014;122(1):65-72.
12. Yitshak-Sade M, Yudovitch D, Novack V, Tal A, Kloog I, Goldbart A. Air Pollution and Hospitalization for Bronchiolitis among Young Children. Annals of the American Thoracic Society. 2017;14(12):1796-802.
13. Gallo E, Bressan S, Baraldo S, Bottigliengo D, Geremia S, Acar AS, et al. Increased risk of emergency department presentations for bronchiolitis in infants exposed to air pollution. Risk analysis : an official publication of the Society for Risk Analysis. 2022.
14. https://www.sciensano.be/nl/gezondheidsonderwerpen/respiratoir-syncytieel-virus-rsv/rol (accessed, Feb 1st 2023).
15. Raes M, Daelemans S, Cornette L, Moniotte S, Proesmans M, Schaballie H, et al. The burden and surveillance of RSV disease in young children in Belgium-expert opinion. European journal of pediatrics. 2022:1-10.
16. Saenen ND, Bové H, Steuwe C, Roeffaers MBJ, Provost EB, Lefebvre W, et al. Children's Urinary Environmental Carbon Load. A Novel Marker Reflecting Residential Ambient Air Pollution Exposure? American journal of respiratory and critical care medicine. 2017;196(7):873-81.