

ORIGINAL PAPER

Time-dependent, cumulative and threshold effects of air pollution – RSV interaction: a narrative review

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ABSTRACT

Respiratory syncytial virus (RSV) is a leading cause of respiratory infections in children. An association between air pollution and RSV has received worldwide attention because pollution may contribute to both increased morbidity and disease severity. However, data on this topic are limited, especially in children, and the results may be equivocal because each air pollutant may have a direct effect, the effect may be delayed (lag effect), dependent on threshold level(s) or accumulation of a pollutant, and the pollutants often interact. The objective of this paper was to review the literature in this area, identify knowledge gaps, and present a detailed analysis of the air pollution-RSV interaction with emphasis on time and concentration dependence.

KEY WORDS:

human respiratory syncytial virus, air pollution, particulate matter, infant.

INTRODUCTION

Respiratory syncytial virus (RSV) is one of the most common and important etiologic agents of respiratory tract infections, especially in the field of paediatrics; global assessments of children aged 0–60 months report over 30 million RSV-associated acute respiratory tract infections annually, with approximately 10% of the cases requiring hospital admission and as many as 100,000 children *per year* with a fatal outcome [1]. The highest hospitalisation rate is observed in the youngest patients (i.e. 0–6 months old), in whom about 1.4 million (21%) out of 6.6 million cases are hospitalised, although it must be emphasized that RSV is a common aetiological factor of respiratory infections in patients of all ages, and a recent improvement in access to diagnostic tests, including rapid antigen tests, has changed the paradigm of RSV, affecting only the youngest patients and raised social awareness of the disease [1, 2]. Nevertheless, most data, especially large epidemiological datasets, come from

paediatric studies, mostly based on hospital surveillance or final diagnosis-based hospital reports. Polish data show a hospitalisation rate of 267.5/100,000 children under 5 years of age and 1132.1/100,000 children under one year of age, although these results seem to be underestimated compared to other European countries [3]. Although a fairly stable seasonal pattern of RSV morbidity has been observed in the northern hemisphere, with peak months between December and March, a significant shift in epidemiologic trends was observed after the COVID-19 pandemic, probably related to the use of non-pharmaceutical interventions and their relaxation [3–5].

Air pollution is recognised as a global health threat, and the World Health Organisation (WHO) has identified 6 air pollutants as the most harmful: particulate matter (PM_{2.5} and PM₁₀, i.e. particulate matter with a diameter ≤ 2.5 µm and ≤ 10 µm, respectively), ozone (O₃), carbon monoxide (CO), nitrogen dioxide (NO₂), and sulphur dioxide (SO₂) [6]. Increased RSV morbidity may be related to the influence of air quality, and a significant association

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between exposure to factors such as particulate matter, O₃, CO, NO₂, or benzene has been reported [7–12]. On the other hand, some studies have not only failed to confirm the association between increased air pollution and RSV morbidity, but also have even found an inverse association [13]. The results may be influenced by meteorological conditions, social behavioural patterns, or locally implemented information campaigns advising people to limit outdoor activities when air quality is poor, but also by time dependence, including immediate versus delayed effects of increased air pollutant concentrations. In addition, a significant cumulative effect may be observed, thresholds for some air pollutants may play a role, and an additive effect of mixed air pollution may be expected. This complex relationship needs to be thoroughly investigated to determine the role of air pollution in RSV morbidity. In this narrative review, we aimed to explore the body of evidence on the association between specific air pollutants and RSV morbidity, focusing on time-dependency, cumulative and threshold effects.

MATERIAL AND METHODS

DATA SOURCE

A structured search was performed in 3 databases (PubMed/Medline, Scopus and Cochrane) to answer 2 main questions regarding the interaction between RSV and air pollution: which air pollutants have been associated with increased RSV morbidity, and which time period plays the most important role for RSV disease? In the latter case, 4 types of association were considered: a direct effect of increased concentration of air pollutants (without a lag period), a lagged effect (with different lag periods according to the literature), a cumulative effect, and a threshold effect (i.e. if the effect is observed above a certain concentration of air pollutant).

STUDY ELIGIBILITY

All studies that included human subjects younger than 18 years were eligible for review, regardless of study design (retrospective or prospective), number of patients, or type of data analysed, including epidemiologic studies. We included only papers presenting analyses of confirmed RSV cases or presumed RSV cases (with low probability of bias, as in the case of epidemiologic studies based on final hospital diagnosis of RSV disease registered in local/national systems). Exclusion criteria were lack of direct reporting of the association between air pollution and RSV infection, e.g. studies assessing only a general association between air quality and upper/lower respiratory tract infections, including pneumonia, bronchiolitis or bronchitis, unless a separate analysis for RSV upper/lower respiratory tract infection was performed. Prenatal exposure was also not considered, because *in*

utero effects may be very different from postnatal effects and are more likely to be associated with a general increased susceptibility. The results are presented separately for each pollutant (list of 6 WHO-recognised air pollutants, followed by “other” pollutants for which published data are available), and the time-dependency of the association for particulate matter is presented with appropriate comments on the literature. To facilitate reading and understanding, we underline the study group and methodology in each study the first time it is mentioned, but a general suggestion has to be made: while the vast majority of studies are based on hospitalisation data and actually assess the impact of air pollution on RSV hospitalisations, other studies present data from primary care and aim to assess the association with RSV incidence.

RESULTS

PM_{2.5}

Our previous study reviewed data from nearly 50,000 paediatric RSV lower respiratory tract infection hospitalisations, and showed a significant direct effect of elevated PM_{2.5} levels on morbidity; a 10 µg/m³ increase in the PM_{2.5} concentration was associated with an average increase in hospitalisations of 0.134, ranging 0.087–0.16 across study sites (Table 1) [12].

The study by Horne *et al.* assessed general acute lower respiratory infection, but also performed a secondary analysis on laboratory-confirmed RSV cases, showing that the influence of PM_{2.5} is seen mostly in patients aged 0–2 years old, with a lag of 1, 2, and 3 weeks (the peak association was observed within a 2-week lag, followed by a 3-week lag and a 1-week lag, while in those aged 3–17 years old, only a 3-week lag remained statistically significant [14].

In the Italian study, higher PM_{2.5} concentrations were found during the months of peak RSV activity, although the study did not find a direct correlation between mean PM_{2.5} concentrations in the week before hospitalisation for bronchiolitis [10]. A synergistic effect of RSV with a lag of 8 and 10 days in the model explained an increase in respiratory hospitalisations in Chile due to elevated PM_{2.5} concentrations [15].

A study by Ye *et al.* found a weak correlation between RSV concentrations and the number of RSV-positive results (rho = 0.446) in the samples collected at the outpatient clinic in Hangzhou, China; in addition, PM_{2.5} above 150 µg/m³ began to affect RSV rates [7]. However, no significant cumulative effect was found, and the lag period studied (0–5 days) showed a gradual decrease with increasing lag period [7].

An Italian study by Vandini *et al.* found a statistically significant but weak (correlation coefficient, rho = 0.26) correlation between the PM_{2.5} concentrations in the week preceding RSV referral to the emergency unit, while

TABLE 1. A summary of the timing of the PM_{2.5}-respiratory syncytial virus interaction

Direct effect	0–7 days lag	8–14 days lag	Cumulative effect	Threshold
PM _{2.5}				
↑ [12]	↑ 0–5 days lag with gradual decrease [7]	↑ 8 and 10 days lag [15]	x [7]	↑ For PM _{2.5} > 150 µg/m ³ [7]
↑ rho = 0.446 [7]	↑ Lag 1 [13]			
↑ rho = 0.446 [7]	↓ Lag 2, 3, 6, 7 [13]	↓ Lag 8 [13]	↓ 16.3% cumulative decrease [13]	
Weeks lag				
0 weeks	1 week	2 weeks	3 weeks	4 weeks
	↑ 0–2-years-old [14]	↑ 0–2-years-old [14]	↑ 0–2-years-old [14]	
			↑ 3–17-years-old [14]	
x [10]				
x [11]	↑ rho = 0.26 [11]			
	x [9]			
Long-term effect				
1 month	2 months	Life-long	Seasonal	Annual
			↑ [10]	
x [9]	x [9]	x [9]		
			x [16]	
				x Yearly mean of daily maximal [18]

PM_{2.5} – particulate matter of diameter between 0.1 and 2.5 µm, rho – correlation coefficient, yo – years old

Direct effect, lag periods, cumulative effect and threshold level are presented with corresponding literature; a red arrow pointing up indicates positive association, while a blue arrow pointing down indicates negative association, and a green “x” symbol indicates no effect analysed in the study.

there was no significant correlation between the number of RSV cases and mean weekly PM_{2.5} concentrations without a lag period (0 weeks lag) in the group of 327 children under 2 years of age [11].

Mean daily exposure for 7, 30, and 60 days and a life-time period in a matched case-control group of patients analysed in the Karr *et al.* study showed no statistically significant effect on hospitalisation for bronchiolitis (including RSV bronchiolitis), although a trend toward an association was reported [9].

A study conducted in Bogota, Colombia included all children < 2 years of age hospitalised due to bronchiolitis and used a comparative analysis of RSV detection to identify independent factors associated with RSV presence – in this context, PM_{2.5} showed no statistical significance [16]. The authors underline the need for cautious interpretation of these results because misclassification bias may have occurred [16]. Moreover, the study included only children hospitalised due to bronchiolitis, whereas other studies, such as an analysis by Yitshak-Sade *et al.* of bronchiolitis hospitalisations in 4,069 children aged 0–2 years old, showed that air pollution, including PM_{2.5} (OR = 1.04, 95% CI: 1.02–1.06), may increase the risk of hospitalisation for bronchiolitis, so a comparison of RSV versus non-RSV cases may be related to a preselection bias [17].

A Canadian study of climatic and geographic factors influencing RSV hospitalisations included the air

quality health index in general and PM_{2.5} as a covariate in the analysis and found no significant differences in the annual mean of maximum daily PM_{2.5} concentrations in relation to RSV hospitalisations among 1670 diagnosed children matched with 6680 controls [19].

In contrast, the study by Lee *et al.* conducted in Singapore showed that PM_{2.5} is associated with a decreased risk of RSV hospitalisation for certain PM_{2.5} concentrations at 2, 3, 6, 7, and 8 days lag, and with an increased risk only for a limited concentration at 1 day lag [13].

In addition, the cumulative effect of PM_{2.5} concentration (26.2 µg/m³) was associated with a 16.3% cumulative reduction (relative risk [RR] 90%: 0.837, 95% CI: 0.794–0.884) in the risk of RSV infection over 8 days [13]. The authors explain this by the fact that the authorities put a strong emphasis on avoidance/reduction of outdoor exposure during periods of worsened air quality [13].

PM₁₀

A direct effect of PM₁₀ on RSV hospitalisations was shown in Poland; a 10 µg/m³ increase in PM₁₀ levels was associated with a 0.097 increase in RSV hospitalisations, ranging 0.031–0.087 depending on the locations analysed (Table 2) [12].

A correlation between PM₁₀ and the number of RSV-positive cases was significant for the mean PM₁₀

TABLE 2. A summary of the timing of the PM₁₀-respiratory syncytial virus interaction

Direct effect	0–14 days lag		Cumulative effect	Threshold
PM ₁₀				
↑ [12]	↑ Lag 0 to lag 11 [20]		↑ Averaged daily lags from lag 0–1 to 0–28, peak at lag 0–11 and 0–13 [20]	
↑ rho = 0.397 [7]	↑ Harmful after a lag 3 [7]		x [7]	
x [21]	↑ Lag 1–6 and 7–14, peak at lag 5 and 7 [21]		↓ 15% cumulative decrease [13]	
Weeks lag				
0 weeks	1 week	2 weeks	3 weeks	4 weeks
x [11]	↑ rho = 0.34 [11]			
	↑ [20]	↑ [20]	x [20]	x [20]
Long-term effect				
1 month	2 months	Life-long	Seasonal	Annual
			↑ [10]	x No monthly correlation [22]
			x [16]	

PM₁₀ – particulate matter of diameter ≤ 10 µm, rho – correlation coefficient

Direct effect, lag periods, cumulative effect, and threshold are presented with the corresponding literature; a red arrow pointing up indicates a positive association, a blue arrow pointing down indicates a negative association, and a “x” symbol indicates no effect analysed in the study.

concentration in the week before hospitalisation (rho = 0.34), but not in the case of a 0-week lag [11].

A comprehensive analysis of the time course of the relationship between PM₁₀ and RSV bronchiolitis hospitalisation was offered by Carugno *et al.* [20]. The authors analysed both single day lags (0–30 days), type of cumulative effect (averaged daily lags in different lag periods from 0–1 to 0–30), and week lags (1–4 weeks) prior to hospitalisation [20]. Individual daily lags were significantly associated with increased risk of hospitalisation between lag 0–11 and were no longer significantly associated from lag 12, with estimated incidence rate ratios (IRRs) ranging 1.03–1.05 for a 10 µg/m³ increase in PM₁₀ concentration [20]. Averaged daily lags increased from IRR = 1.08 (at lag 0–1) to peak values of IRR = 1.15 (at lags 0–11 and 0–13) and then declined to become insignificant at lag 0–28 [20]. In terms of weekly lags, weeks 1 and 2 immediately preceding hospitalisation were associated with an increased IRR of 1.06 and 1.07, respectively [20].

Similarly, a lagged effect of each 10 µg/m³ increase in PM₁₀ was observed in New Zealand (for patients aged 0–19 years) for both shorter (i.e. 1–6 days) and longer (i.e. 7–14 days) lags, whereas no significant effect was observed for lag 0 [21]. The highest percentage increase in RSV hospitalisations was estimated to occur at lag 5 and lag 7, respectively; when all-year data were analysed, the increase reached 2.87% and 3.16%, respectively, while cool-season-only data showed values of 1.8% and 2.09%, respectively [21].

The Chinese study by Ye *et al.* showed a significant but weak correlation between PM₁₀ levels and RSV cases (rho = 0.397); of note, PM₁₀ became harmful after a lag of 3 days and showed no cumulative effect (like PM_{2.5}) [7].

Nenna *et al.* found that PM₁₀ levels, like PM_{2.5} levels, were higher during peak RSV activity months, although again a very important component of seasonality has to be taken into account because a strong negative relationship between temperature and PM₁₀ concentrations was observed [10].

The Korean study examined the association between monthly RSV incidence and levels of air pollutants, including PM₁₀, in a group of 9,113 nasopharyngeal swabs from children under 3 years of age, but found no statistically significant association for PM₁₀ [22].

Similar to PM_{2.5} concentrations, the Colombian study found no significant difference in PM₁₀ concentrations with respect to RSV detection in children hospitalised for bronchiolitis [16].

Similar to PM_{2.5}, an increase in PM₁₀ was found to be negatively associated with RSV hospitalisation in Singapore – at a concentration of 40.4 µg/m³, PM₁₀ was associated with almost a 15% cumulative reduction in the risk of RSV infection [13].

OZONE

Data on the relationship between ozone and RSV are rather scarce and show conflicting results. The Canadian study showed a positive association between elevated O₃ levels and RSV hospitalisations (OR = 1.03, 95% CI: 1.01–1.06) [19]. Conversely, an Italian study by Nenna *et al.* found lower O₃ concentrations in the months of peak RSV activity and increased O₃ levels in the absence of RSV; the inverse correlation may be due to the fact that O₃ concentrations tend to peak in summer

TABLE 3. A summary of the studies on CO-respiratory syncytial virus (RSV), NO₂-RSV, and SO₂-RSV interactions

Parameters	Carbon monoxide	Nitrogen dioxide	Sulfur dioxide
Positive association	↑ Correlation (rho= 0.58) [22]	↑ Direct effect [12]	↑ Correlation (rho= 0.41) [22]
	↑ Correlation (rho = 0.532) [7]	↑ Correlation (rho= 0.4) [22]	↑ Correlation (rho = 0.389) [7]
	↑ Risk gradually decreasing with increasing lag period [7]	↑ Correlation (rho = 0.365) [7]	
		↑ Higher levels during RSV peak season [10]	
Not confirmed association	x Between high and low RSV activity months [10]	x Lifetime exposure average exposure in the month preceding hospitalisation [9]	x Between high and low RSV activity months [10]
		x [13]	x In RSV detection [16]
Negative association	↓ [13]	↓ Lower yearly mean of daily max NO ₂ [19]	↓ 12.2% cumulative decrease [13]
	↓ Independent factor of lower RSV detection [16]	↓ Independent factor associated with lower RSV infection risk [16]	
Lag effect		↑ The greatest increase in RSV RR at lag of 3 days [7]	↑ The greatest risk was observed at 3 days lag [7]
		x Average exposure in the preceding month[9]	
Cumulative effect	↑ Cumulative effect [7]	x No cumulative effect [7]	x No cumulative effect [7]
Threshold level		↑ Association ↓ attenuated for NO ₂ concentrations over 40 µg/m ³ [7]	

CO – carbon monoxide, NO₂ – nitrogen dioxide, SO₂ – sulphur dioxide, rho – correlation coefficient, RR – relative risk

Positive, negative, and unconfirmed associations found in the studies are shown, with special emphasis on lag, cumulative, and threshold effects; a red arrow pointing up indicates a positive association, while a blue arrow pointing down indicates a negative association, and a "x" symbol indicates no effect analysed in the study.

when RSV activity is generally low in the northern hemisphere [10]. The association between ozone levels was also tested in Singapore, which found no significant association, and in the Colombian study, which found no difference in RSV detection [13, 16].

CARBON MONOXIDE

Jung *et al.* reported a moderate correlation between CO concentrations and RSV activity (rho = 0.58), while Nenna *et al.* found no significant difference when comparing months with high and low RSV activity (Table 3) [10, 22].

The most comprehensive analysis was performed by Ye *et al.* and showed a positive correlation between CO and RSV infection rate (rho = 0.532) [7]. Carbon monoxide was associated with an increased risk of RSV at low concentrations, and the risk increased as CO levels increased [7]. The lag effect played the opposite role, i.e. the risk gradually decreased as the lag period increased [7]. A cumulative effect was also observed with a peak value at CO levels of approximately 1.5 mg/m³ (RR approximately = 2) [7].

However, RSV infection rates were inversely correlated with CO levels (RR 90%: 0.863, 95% CI: 0.801–0.929) in the study by Lee *et al.* [13]. It was also an independent factor associated with lower RSV detection in the trial by Villamil-Osorio *et al.* (OR = 0.99) [16].

NITROGEN DIOXIDE

We previously reported a direct effect of increased NO₂, with an upward shift of 10 µg/m³ corresponding to an average increase in RSV hospitalisations of 0.212 (0.04–0.29 across study sites) [12].

Higher NO₂ levels were found during peak-RSV-activity months compared to low activity season [10]. Similar NO₂-RSV correlation coefficients were found by Jung *et al.* (rho = 0.40) and Ye *et al.* (rho = 0.365); Ye noticed the greatest increase in RSV RR with a lag of 3 days, and the association was attenuated for NO₂ concentrations above 40 µg/m³ [7, 22]. No cumulative effect was observed for NO₂ concentrations [7].

Lifetime exposure to NO₂ and average exposure in the month preceding RSV hospitalisation showed no sta-

tistically significant relationship in the analysis by Karr *et al.* [9].

In the Canadian study, the annual mean maximum daily NO₂ was lower in cases than in controls; the Colombian study also identified NO₂ as an independent factor associated with a lower risk of RSV infection (OR = 0.97) [16, 19]. No effect of increasing NO₂ concentration was found by Lee *et al.* [13].

SULPHUR DIOXIDE

A positive SO₂-RSV correlation coefficient was reported by Jung *et al.* ($\rho = 0.41$) and Ye *et al.* ($\rho = 0.389$) [7, 22]. Similarly to NO₂, there was a lag time and the greatest risk was observed with a 3-day lag, the risk increased gradually with increasing SO₂ levels; and similarly to NO₂, there was no cumulative effect [7]. On the other hand, while no significant differences in SO₂ levels were found between RSV high and low seasons in the study by Nenna *et al.* or with respect to RSV detection in the trial by Villamil-Osorio *et al.*, an increase in SO₂ levels was associated with a 12.2% cumulative decrease in RSV infection (RR 90%: 0.878, 95% CI: 0.807–0.956) in the study by Lee *et al.* [10, 13, 16].

OTHER POLLUTANTS

Benzene was an independent factor associated with RSV incidence (Poisson Regression Model Estimate 0.1736) in the study by Nenna *et al.*, and markedly higher benzene concentrations were observed during the months of peak RSV activity [10].

In addition to benzene, 9 other pollutants have been reported to be associated with an increased risk of RSV infection in a follow-up study of 888 infants (up to age 3 years) that evaluated spatial clusters of lower respiratory tract disease in relation to community-associated risk factors, showing that being in an RSV cluster was associated with exposure to air pollutants [23]. The pollutants included polycyclic organic matter (OR = 2.28), manganese (OR = 2.22), 1,2-dichloropropene (OR = 2.17), benzene (OR = 2.08), butadiene (OR = 2.05), perchloroethylene (OR = 1.96), methylene chloride (OR = 1.77), ethylene oxide (OR = 1.61), mercury (OR = 1.56), and beryllium (OR = 1.53).

Use of kerosene as a cooking fuel was another identified risk factor for the first episode of RSV lower respiratory tract infection in a prospective surveillance of infants and children under 5 years of age in Indonesia; the patients underwent weekly visits aimed at screening for lower respiratory tract infection signs, and in case of infection, RSV test was performed [24]. The effects of kerosene might be mediated by other air pollutants, since combustion of kerosene is related to the emission of particulate matter (including PM_{2.5}), CO, SO₂ or nitric oxide [25].

Nitric oxide (NO) has been linked with the risk of RSV infection in *in vitro* studies, although the concentrations used were high; the study by Mohammed *et al.* performed on 208 hospitalised children showed no significant association for either single-day lags (0 to 6 days lag) or average NO concentration of different lag periods (0–1 to 0–6 days) [26].

DISCUSSION

The study shows the complexity of the interaction between air pollution and RSV and its susceptibility to potential confounding factors, and the existing body of knowledge requires further studies to draw definitive conclusions; however, some important conclusions need to be underlined. PM_{2.5} and PM₁₀ have been studied most extensively, and although there are some conflicting results, both PM_{2.5} and PM₁₀ appear to be associated with increased RSV risk with some time-specific differences.

PM_{2.5} appears to be associated with RSV disease both in the short and medium term; the studies from China, Chile and Poland confirm the direct effect or the influence of PM_{2.5} with a delay of a few days, while the American study shows the importance of a delay of 1–3 weeks [7, 12, 14, 15]. However, the trial from Singapore reported an inverse correlation, but the results of this study, as underlined by the authors, could raise some concerns about the influence of local government advice to limit outdoor time when air pollution levels are high [13]. PM_{2.5} may be associated with some kind of a threshold effect, i.e. higher PM_{2.5} concentrations may play a more important role [7]. A cumulative effect of PM_{2.5} was estimated in one study and was related to a cumulative decrease in Singapore [7, 13]. The long-term effects of PM_{2.5} would also require further confirmation because existing studies do not support this theory [9].

PM₁₀ also appears to be associated with RSV infection in both the short and medium term, and the lag period is of great importance. While a direct effect of elevated PM₁₀ concentrations has been reported, other studies show the importance of the lag, with lag times varying 1–14 days, and peaks observed on days 1, 3, 5, or 7 [7, 12, 20, 21]. Consistent with the daily lag period are estimates of the weekly lag, which show that week 1 or week 1 and 2 are significantly associated [11, 20]. A role of cumulative effect might be expected because the averaged daily lags played a role up to 0–28 days lag (with peaks at 0–11 and 0–13 lag), although a cumulative decrease was also observed [13, 20]. No confirmation of threshold level or long-term effects was found.

Previous studies in human models indicated the highest deposition fraction of PM₁₀ in the head/throat region, followed by the tracheobronchial (TB) and pulmonary (P) regions; the highest PM_{2.5} deposition in sleeping or sitting children was observed in the P region, followed

by the head and TB [27]. This could be a plausible explanation for the differences in the lag periods of $PM_{2.5}$ and PM_{10} effects, because PM_{10} may mainly promote upper respiratory tract infection, i.e. make it easier to contract the disease, whereas $PM_{2.5}$ may increase the severity of the disease due to high deposition in the lower respiratory tract. Thus, the time needed to observe the effects of increased PM_{10} levels would be longer compared to the time needed to observe the effects of $PM_{2.5}$. It should be underlined that differences in the proportion of ambient aerosol as well as the composition of aerosol, including variations in its chemical content, may lead to different PM deposition in the human body and different health effects [28–30]. Moreover, although the deposition of PM_{10} in the respiratory tract appears to be similar in adults and children (i.e. deposition in the head of the respiratory tract, followed by the TB region and the lung region), the fraction of PM_{10} that penetrates into the TB and P region is higher in children compared to adults [27]. The average deposition of $PM_{2.5}$ is about 2 times higher in children than in adults [27]. This raises awareness of the increased susceptibility of the paediatric population to air pollutants; the structure and physiology of the respiratory tract not only favours the deposition of smaller particles in children, but these particles are more toxic relative to body mass [31].

In contrast to particulate matter, there are pollutants that show balanced contradictory results, as in the case of ozone, while SO_2 and NO_2 , for example, appear to be harmful in terms of RSV infections, and the data (although still inconsistent) show that they may act in a very similar way, with a peak lag effect on day 3 and no cumulative effect [7]. On the other hand, a cumulative effect has been reported for CO, although some conflicting results must be emphasised, as 2 studies conducted at different sites found a negative association between CO levels and RSV, while others confirmed the expected positive association [7, 13, 16, 22]. In general, the lack of a positive or negative association, regardless of the pollutant studied (CO , SO_2 , or NO_2), was most often reported in studies comparing longer time periods, such as high versus low RSV activity seasons or lifetime exposure, but also in studies looking at minute differences, such as RSV detection in hospitalized bronchiolitis patients [9, 10, 16]. Taken together, these discrepancies indicate the complexity of the problem and the need for further studies. And the results presented above refer to the 6 most harmful pollutants (according to the WHO), while other pollutants, although each of them deserves in-depth analysis, have been studied in single studies.

The body of knowledge is limited by several factors impeding comparisons. First, it must be emphasized that due to limited RSV testing, the vast majority of studies are based on data from hospitalisations (where RSV testing is much more frequent due to higher availability), so the time frames of the relationship between air pollution

and RSV may be somewhat blurred. The results in this review are presented with respect to the source data, but the true timing may be shifted because RSV hospitalisations usually occur after a few days and not at the onset of signs/symptoms, as in the case of RSV bronchiolitis, which tends to require hospitalisation after 3–5 days of illness [32]. As a result, the authors use different time-dependency strategies to assess the influence of air pollution on RSV morbidity. Even if all data were adjusted for the first day of signs/symptoms, there would still be room for bias, because the most important question is not whether air pollution increases RSV morbidity, but whether it increases the risk of RSV severity, which would lead to hospitalisation, for example. Second, the results themselves are often inconsistent or even contradictory, especially in the case of the less studied contaminants. These issues can only be resolved by studies involving large numbers of patients and conducted under similar conditions. Reproducibility of studies also requires comparable study settings, including the social perspective, the problem raised by Lee *et al.* who unexpectedly found an inverse relationship between some of the pollutants and RSV disease [13]. The authors discussed the possible explanatory effect of local policies that emphasised deteriorating air quality and advised citizens to limit outdoor activities [13]. In fact, environmental risk perception is crucial for the range of exposure to pollution, and personal differences between patients might be expected; the study conducted in London showed significant differences in air pollution exposure depending on the mode of transport used by primary school children [33, 34]. There are other aspects that make direct comparisons between studies difficult, such as meteorological factors that affect air pollution levels, inter-seasonal differences, or differences between study sites. In addition, some authors include meteorological factors as variables while others do not, which introduces an additional risk of misinterpretation.

Understanding the molecular mechanisms underlying the interaction between air pollution and RSV is essential to understanding the timing. While certain pollutants may promote RSV infection itself, others may increase viral load leading to a prolonged disease course, or result in an enhanced/prolonged inflammatory response, or even cause airway hyperresponsiveness, which would show clinical effects after longer lag times [35]. As shown above, PM_{10} may promote RSV infection itself, and molecular studies show that RSV entry into epithelial cells may be facilitated in the presence of PM_{10} ; on the other hand, the inflammatory response may also be enhanced by PM_{10} , leading to delayed clinical effects [36].

There are some limitations of the review that need to be emphasised. In addition to the above-mentioned limitations and inconsistencies in the source papers, we have not presented (due to lack of data) the results of interactions between air pollutants, which could be

significant and might more accurately reflect the conditions in the real environment, since a mixture of pollutants affects humans rather than single molecules [12]. We did not assess the quality of the data presented nor the power of the studies (e.g., assessed by the number of participants) in order to present all available literature on the topic. Third, methodological differences make it difficult to compare results directly, and although some studies did not confirm the relationship, or even found an inverse one, the results of these studies may differ from those of other studies due to different study settings or social behaviour (as mentioned above).

CONCLUSIONS

It would appear that there is a positive association between air pollution and RSV morbidity, mostly assessed in hospital-based studies, but the range of pollutants varies widely in terms of the available evidence: while the majority of studies show an association between PM_{2.5} and/or PM₁₀ and RSV, this relationship is not as clear for NO₂, SO₂ or CO, and is even less clear for ozone or nitric oxide. The complexity of the relationship, including likely interactions between pollutants, makes conclusions regarding time and concentration dependence a challenge for future studies, which are guaranteed.

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4. Conflicts of interest: None.

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