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Title: Environmental factors linked to hospital admissions in young children due to acute viral lower respiratory infections: a bidirectional case-crossover study

Short title: Environmental factors associated with viral ALRI in young children

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Abstract

Objective: This study evaluated the association of the short-term exposure to environmental factors (relative humidity, temperature, NO_2, SO_2, O_3, PM_{10}, and CO) with hospital admissions due to acute viral lower respiratory infections (ALRI) in children under two years before the COVID-19 era.

Methods: We performed a bidirectional case-crossover study in 30,445 children with ALRI under two years of age in the Spanish Minimum Basic Data Set (MBDS) from 2013 to 2015. Environmental data were obtained from Spain's State Meteorological Agency (AEMET). The association was assessed by conditional logistic regression.

Results: Lower temperature one week before the day of the event (hospital admission) (q-value=0.012) and higher relative humidity one week (q-value=0.003) and two weeks (q-value<0.001) before the day of the event were related to a higher odds of hospital admissions. Higher NO_2 levels two weeks before the event were associated with hospital admissions (q-value<0.001). Moreover, higher concentrations on the day of the event for SO_2 (compared to lag time of 1-week (q-value=0.026) and 2-weeks (q-value<0.001)), O_3 (compared to lag time of 3-days (q-value<0.001), 1-week (q-value<0.001), and 2-weeks (q-value<0.001)), and PM_{10} (compared to lag time of 2-weeks (q-value<0.001)) were related to an increased odds of hospital admissions for viral ALRI.

Conclusion: Short-term exposure to environmental factors (climatic conditions and ambient air contaminants) was linked to a higher likelihood of hospital admissions due to ALRI. Our findings emphasize the importance of monitoring environmental factors to assess the odds of ALRI hospital admissions and plan public health resources.

Keywords: acute lower respiratory infections; children; environment; pollution; ICD-9-CM; respiratory virus

Introduction

Acute lower respiratory infection (ALRI) is the primary cause of morbi-mortality in young children worldwide [1, 2]. ALRI includes pneumonia, acute bronchiolitis, and bronchitis caused by bacterial and viral infections. However, bacterial ALRI has decreased substantially since 1990 due to preventive measures, access to the health system, and antibiotics [1]. In the last decades, the leading cause of ALRI in young children has been viral infections, including respiratory syncytial virus (RSV, around 60%), influenza virus (around 5%), and other minority viruses such as parainfluenza virus, rhinovirus, and human metapneumovirus [1, 3]. These respiratory viruses may cause severe respiratory failure due to an uncontrolled host immune response damaging the epithelial cells and compromising the respiratory gas exchange [4], resulting in hospitalization and possible death [1]. Therefore, prevention and proper management of viral ALRI could substantially impact clinical outcomes in childhood.

Viral ALRI has a pronounced seasonal pattern related to meteorological conditions [5]. Higher humidity and lower temperatures are often linked to an increased risk of viral transmission and ALRI [2, 6-9]. Outdoor air contamination is a significant environmental hazard for the general population's health worldwide, but even more for developing respiratory diseases in children [10, 11]. The primary outdoor air pollutants that cause particularly adverse respiratory effects include nitrogen dioxide (NO_2), sulfur dioxide (SO_2), ozone (O_3), particulate matter up to 10 µm in size (PM_{10}), and carbon monoxide (CO), among others [12, 13]. Remarkably, short-term exposure to outdoor air contamination has been related to an increased rate of pneumonia in children [14-19].

Meteorological conditions affect outdoor air pollution, but its impact depends on the type of pollutants [20]. For example, temperature affects the movement of air pollution and has a positive correlation with PM_{10} levels. Cold weather is related to increased exhaust from vehicles, chimneys, and smokestacks, leading to elevated NO_2, SO_2, PM_{10}, and CO. Hot weather promotes the emergence of ground-level O_3 while humidity decreases O_3 pollution. The association between environmental factors and viral ALRI may not be consistently uniform, requiring multivariate analysis considering the maximum number of environmental factors.

This study analyzed the relationship between short-term exposure to environmental factors and hospital admissions for viral ALRI in young children under two years of age before the COVID-19 era.

Material and Methods

Study design

We conducted a bidirectional case-crossover study in children under two years of age who had a hospital admission due to viral ALRI in Spain from 2013 to 2015.

Data source

Clinical data at hospital discharge were collected from the Spanish Minimum Basic Data Set (MBDS), an administrative database provided by the Ministry of Health, Consumer Affairs and Social Welfare (MHCSW), which covers about 92% of all hospitals, mostly public hospitals [21]. This database provides gender, date of birth, dates of hospital admission and discharge, the hospital providing the services, and clinical data (14 discharge diagnoses and 20 procedures) according to the 9th revision of the International Statistical Classification of Diseases and Related Health Problems, Clinical Modification (ICD-9-CM). The MHCSW ensures the data quality and consistency of the data collected in the MBDS through data recording protocols and periodic audits.

Environmental data were obtained by the State Meteorological Agency (AEMET; http://www.aemet.es/en/) of Spain. We collected data from 880 meteorological stations distributed in the area under study [22], which provide the geolocation (longitude, latitude, and altitude), climatic data [temperature (°C) and relative humidity (%)] and pollutant factors [NO_2, SO_2, O_3, PM_{10}, and CO; default concentration in μg/m^3]. The AEMET ensures the air quality data according to the European Environment Agency’s European Air Quality Index [23]. More than 70% of the MBDS records had zip code information.

Ethics statement

The Institutional Review Board and the Research Ethics Committee (Comité de Ética de la Investigación y de Bienestar Animal, Instituto de Salud Carlos III, Madrid, Spain) approved this study (Ref. CEI PI 81_2021). They deemed informed consent unnecessary because the MBDS information is anonymous. The nearest meteorological station provided environmental data of each patient according to their zip code. The data were processed with complete confidentiality following Spanish legislation.

ICD-9-CM codes

We selected children under two years of age who had viral ALRI in the Spanish MBDS from 2013 to 2015. That is, those who had a primary diagnosis of viral ALRI [RSV (ICD-9-CM: 079.6, 466.11, and 480.1), influenza (ICD-9-CM: 487.0, 487.1, 488.01, 488.02, 488.11, 488.12, 488.81, and 488.82), viral pneumonia (ICD-9-CM: 480.0, 480.1, 480.2, 480.8, and 480.9), and acute bronchiolitis (ICD-9-CM: 466.11 and 466.19)] or acute respiratory failure (ICD-9-CM: 518.81) along with a secondary diagnosis of viral ALRI. The diagnoses were performed according to standard procedures in each hospital.

Statistical analysis

We used a bidirectional case-crossover design to investigate acute environmental triggers that are potentially causing hospital admissions for viral ALRI. In this design, each one is their control, and all time-invariant confounders were adjusted [24]. Each environmental factor's value was averaged over three days (the study day, one day before, and one after) to alleviate any day with an extreme level. In addition, three short periods were used as control times (lag times of 3 days, 1-week, and 2-weeks) to compare with the patients' exposure at hospital admission. Nevertheless, due to the bidirectional design, the events' exposures were compared to the exposures before and after the event.

The link between environmental factors and hospital admissions due to viral ALRI was assessed by conditional logistic regression, providing the odds ratio (OR) and 95% confidence interval (95%CI) calculated by the exact method. Thus, the odds of hospital admission for a viral ALRI depend on the variation of a specific environmental factor at the date of hospitalization (encoded as "1") and at the control time (encoded as "0"), and only children with variations in environmental exposure were informative [25]. Therefore, aOR values higher than "1" denoted higher odds when the environmental factor is increased at the hospital admission or decreased at the control time (lag time). Conversely, aOR values lower than "1" denoted higher odds when the environmental factor is increased at the control time (lag time) or decreased at the hospital admission. We performed a univariant analysis for each environmental factor and a multivariant analysis for all environmental factors together. Except for the temperature, environmental factors were log_2-transformed because many of them tended to "1". In addition, this log_2-transformation may be interpreted as a doubling of the predictor.

We used the R statistical package version 3.5.2 (GNU General Public License) for statistical analysis [26]. All tests were two-tailed, and *p*-values were corrected using the Benjamini and Hochberg procedure's false discovery rate (*q*-values).

Results

Population characteristics

A total of 44,294 hospital admissions with zip codes were recorded in the MBDS from 2013 to 2015, of which 30,445 were children under two years of age with ALRI. Overall, the mean age was 4.1 months, and 57.9% were males. Almost all the patients had an urgent hospital admission (99.0%), hospital stay was 5.1 days, 55.8% were RSV diagnoses, and 4.2% were influenza virus diagnoses (**Table 1**).

Table 1. Summary of the epidemiological and clinical characteristics of children under two years of age with a hospital admission for viral ALRI in Spain (2013-2015).

Description	All infants
No.	30445
Gender (males), *n* (%)	17647 (57.9)
Age (months), median [IQR]	4.1 [4.1; 4.2]
Urgent admission, *n* (%)	30130 (99.0)
Length of stay (days), median [IQR]	5.1 [5.0; 5.1]
ICU admission	1088 (3.57)
Clinical discharge diagnosis	
Acute lower respiratory infection, *n* (%)	30161 (99.1)
Respiratory syncytial virus, *n* (%)	16988 (55.8)
Influenza, *n* (%)	1276 (4.2)
Viral pneumonia, *n* (%)	919 (3.0)
Acute bronchiolitis, *n* (%)	28241 (92.7)
Acute respiratory failure, *n* (%)	4727 (15.5)

Statistics: Values are expressed as absolute number (percentage) and median [interquartile range]. **Abbreviations**: ALRI, acute lower respiratory infections; ICU, intensive care unit; IQR, interquartile range.

Environmental conditions related to viral ALRI hospital admissions

Figure 1 displays the temporal pattern of ALRI hospital admissions by months and the average levels of environmental factors (temperature, relative humidity, NO_2, SO_2, O_3, PM_{10}, and CO) by day.

Several environmental factors were associated with hospital admissions for ALRI using multivariate models (**Figure 2;** the full description in **Supplementary Table 1**). For climatic factors, lower temperature one week before the day of the event (hospital admission) (*q*-value=0.012) and higher relative humidity one week (*q*-value=0.003) and two weeks (*q*-value<0.001) before the day of the event were related to a higher odds of hospital admissions due to viral ALRI (**Figure 2**). For ambient air contaminants, higher NO_2 levels two weeks before the event were associated with hospital admissions (*q*-value<0.001). Moreover, higher concentrations on the day of the event for SO_2 (compared to lag time of 1-week (*q*-value=0.026) and 2-weeks (*q*-value<0.001)), O_3 (compared to lag time of 3-days (*q*-value<0.001), 1-week (*q*-value<0.001), and 2-weeks (*q*-value<0.001)), and PM_{10} (compared to lag time of 2-weeks (*q*-value<0.001)) were related to an increased odds of hospital admissions for viral ALRI (**Figure 2**).

Figure 1. Summary of the total count of ALRI hospital admissions by months (green bars) and the average levels of environmental factors (temperature, relative humidity, NO_2, SO_2, O_3, PM_{10}, and CO) by day (gray dots) in young children from 2013 to 2015.

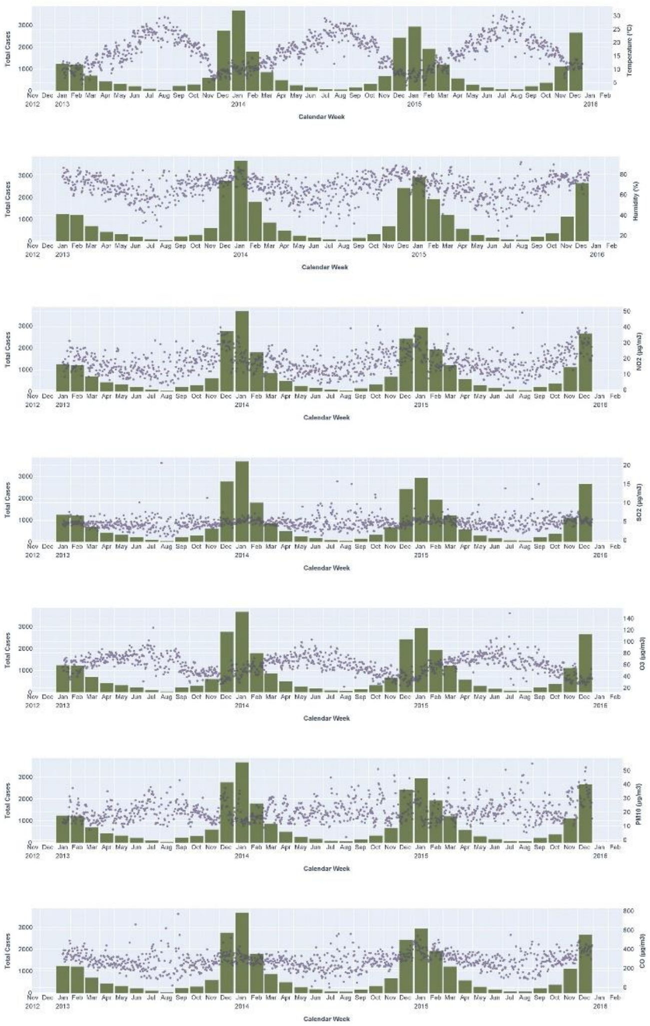
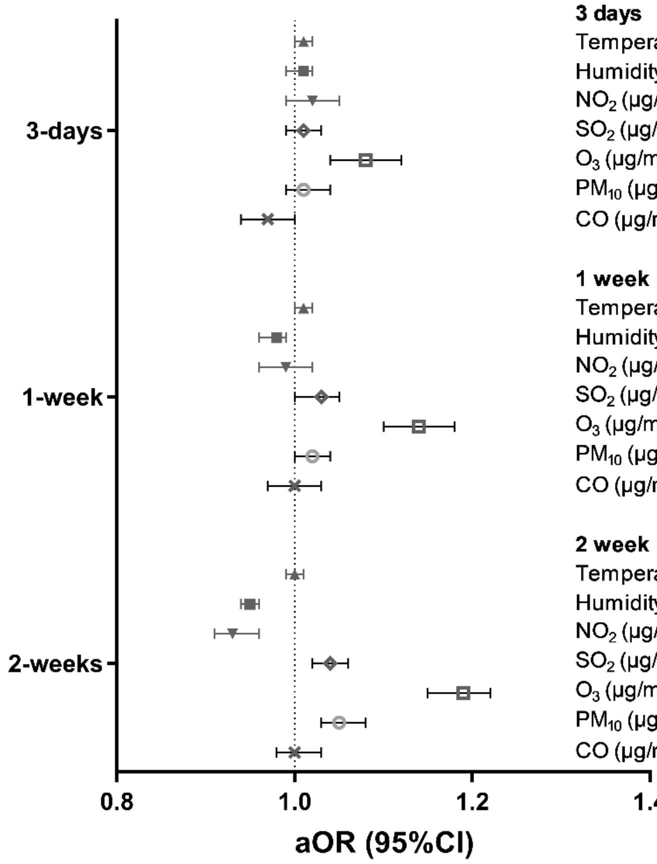


Figure 2. Summary of the association between environmental factors and hospital admissions in young children due to acute lower respiratory viral infection.
Statistic: Association analyses were carried out by conditional logistic regression with three control time points (3-days, 1-week, and 2-weeks). The false discovery rate (Benjamini and Hochberg procedure) was used to correct multiple testing (*q*-values).
Abbreviations: 95% CI = 95% of the confidence interval; aOR = adjusted odds ratio.



	aOR (95% CI)	p-value	q-value
3 days			
Temperature (ºC)	1.01 (1.00; 1.02)	**0.026**	0.091
Humidity (%)	1.01 (0.99; 1.02)	0.292	0.317
NO_2 (μg/m^3)	1.02 (0.99; 1.05)	0.146	0.255
SO_2 (μg/m^3)	1.01 (0.99; 1.03)	0.317	0.317
O_3 (μg/m^3)	1.08 (1.04; 1.12)	**<0.001**	**<0.001**
PM_{10} (μg/m^3)	1.01 (0.99; 1.04)	0.255	0.317
CO (μg/m^3)	0.97 (0.94; 1.00)	**0.050**	0.117
1 week			
Temperature (ºC)	1.01 (1.00; 1.02)	**0.005**	**0.012**
Humidity (%)	0.98 (0.96; 0.99)	**0.001**	**0.003**
NO_2 (μg/m^3)	0.99 (0.96; 1.02)	0.462	0.539
SO_2 (μg/m^3)	1.03 (1.00; 1.05)	**0.015**	**0.026**
O_3 (μg/m^3)	1.14 (1.10; 1.18)	**<0.001**	**<0.001**
PM_{10} (μg/m^3)	1.02 (1.00; 1.04)	0.120	0.168
CO (μg/m^3)	1.00 (0.97; 1.03)	0.912	0.912
2 week			
Temperature (ºC)	1.00 (0.99; 1.01)	0.614	0.716
Humidity (%)	0.95 (0.94; 0.96)	**<0.001**	**<0.001**
NO_2 (μg/m^3)	0.93 (0.91; 0.96)	**<0.001**	**<0.001**
SO_2 (μg/m^3)	1.04 (1.02; 1.06)	**<0.001**	**<0.001**
O_3 (μg/m^3)	1.19 (1.15; 1.22)	**<0.001**	**<0.001**
PM_{10} (μg/m^3)	1.05 (1.03; 1.08)	**<0.001**	**<0.001**
CO (μg/m^3)	1.00 (0.98; 1.03)	0.959	0.959

Discussion

Our findings show that climatic factors (temperature and relative humidity) and output air contaminants (NO_2, SO_2, O_3, and PM_{10}) impacted hospital admissions of young children with viral ALRI.

Weather conditions, including humidity and temperature, influence the risk of viral ALRI [5, 6] because they affect respiratory virus infectivity [5, 14, 27]. In our study, lower temperatures and higher relative humidity before hospital admission increased the risk of hospitalization for viral ALRI. The temperature influences most chemical and physical processes, conditioning the pathogen's survival and the host's susceptibility [27]. Thus, low temperatures provide higher stability to the pathogen, increasing its survival and infectivity. Besides, high-humidity conditions increase virus infectivity because the humidity stabilizes airborne droplets that carry the pathogen from person to person [5]. A "wintertime immune suppression" has been associated with bronchoconstriction, increased secretion, and decreased mucociliary clearance, among others [28]. Thus, low temperatures and high humidity has often been associated with a higher risk of viral ALRI in young children [2, 6-9]. Our findings agree with previous ones indicating that viral ALRI hospital admissions are directly influenced by changes in weather [29], which directly affect the abundance, survival, and virulence of pathogens [30]. However, other studies show discordant data on temperature and humidity with our study [31-33]. It could be partly explained by different regions of the world not having the same patterned seasonal peaks or outbreaks of ALRIs. In other words, the circulation of respiratory viruses shows different patterns that vary according to geographic location and altitude, even within communities in the same region [31, 33, 34].

In our study, high air concentrations of SO_2, O_3, and PM_{10} on the day of hospital admission increased the risk of hospitalization due to viral ALRI. This risk was also increased when high NO_2 concentrations were observed two weeks before the day of hospital admission. Our data are consistent with prior reports on exposure to outdoor air pollutants and pneumonia in children [14-19]. Interestingly, some studies did not find an association between indoor NO_2 measurements and ALRI in children [35-37]. It would suggest that NO_2 effects in outdoor ambient on viral ALRI are likely due to the combination with other co-pollutants with similar sources and environmental dynamics (transition metals, organic aerosols, O_3).

O_3 was the most critical environmental factor because it was strongly associated with ALRI hospital admissions in all the lag times, and the strength of this association increased with longer lag times. These results agree with previous studies, which reported significant increases in respiratory hospital admissions due to increased O_3 concentrations [38-40]. However, some studies did not find associations between O_3 and hospital admissions due to ALRI[15, 41]. The differences between published results on the short-term effects of O_3 exposure and the viral ALRI in children may be due to the influence of many factors, such as the different concentrations of O_3, duration and time of exposure, outdoor activities, and the susceptibility to air pollutants.

PM_{10} can be inhaled, causing lung damage by downregulation of antimicrobial peptides [42] and increasing inflammation and airspace epithelial permeability [43]. Several studies agree with our work, finding an association between PM_{10} and hospital admission for severe viral respiratory diseases in young children [44-46], although Nathan et al. did not find a significant association [47]. Moreover, a significant inverse relationship between the short-term exposure to PM10 and respiratory disorders in children was observed in other studies [48-50]. A possible reason could be the linkage of ultraviolet radiation to PM_{10} in specific countries, which attenuate the effect caused by PM_{10}, or differences in ages of the children studied. Finally, Air pollutants, particularly exposure to PM and O_3, trigger oxidative stress in the lung [51]. This oxidative stress causes an increase in the pro-inflammatory, Th2, and Th17 immune responses and a decrease in the antiviral immune response [52, 53], leading to higher susceptibility to lung infection [53, 54].

SO_2 also causes inflammation and damage of the respiratory mucosa, facilitating virus infection [55]. In addition, young children have an increased risk of having severe bronchiolitis and pneumonia due to their immature immune system that often responds worse to infections [56] and their smaller airways that are easily obstructed by the inflammation process and the accumulation of cellular debris. Although we found significant short-term effects of SO_2 with the increased risk of hospital admissions in children similar to other studies [57, 58], the associations of this air contaminant on LRTI remain controversial [59, 60]. These discrepancies may be due to the measurement of air pollutants in highly populated areas with high traffic (i.e., Asian countries) [61], where the predominant air pollutants are those emitted by vehicles, such as NO_2, CO, and particulate matters [62].

Finally, our study detected some discrepancies between the univariate and multivariate analyses. Multivariate analysis is recommended to simultaneously explore the impact of two or more predictor variables on the outcome variable. The discrepancies were mainly due to the loss of statistical significance (temperature, NO_2, and CO) or their first appearance (SO_2 and PM_{10}). There may be different reasons that justify these discrepancies. One of them is the information provided by each environmental factor in the multivariate analysis. Thus, the variables that achieved statistical significance improved the overall model fit, while those that did not improve the multivariate model became non-significant. Another cause is the multicollinearity between environmental factors because two or more environmental factors provide almost the same information, but we did not find significant correlations between them (data not shown). Another reason is the low statistical power to disentangle their effects adequately, but the sample size of our study was large.

Limitations and strength of the study

The limitations are mainly related to the administrative database we used (Spanish MBDS): (i) The retrospective design could introduce biases. (ii) There was no relevant clinical information to interpret the viral ALRI. (iii) The accuracy of the MBDS for ALRI diagnosis is unknown, generating a confusion bias. (iv) We did not have data on indoor air contaminants, which may also influence susceptibility to viral ALRI. (v) The MBDS is anonymous and makes it difficult to detect whether some children have been hospitalized multiple times.

Our study also has several strengths that must be considered: (i) this is a nationwide study with a very high number of children under two years of age with an ALRI hospital admission, something challenging to achieve with any other database. (ii) We use a bidirectional case-crossover design that minimizes the impact of the absence of fundamental variables in the regression analysis.

Conclusions

Short-term exposure to environmental factors (climatic conditions and ambient air contaminants) was linked to a higher likelihood of hospital admissions due to ALRI. Our findings emphasize the importance of monitoring environmental factors to assess the risk of ALRI hospital admissions and plan public health resources.

List of abbreviations

95%CI = 95% confidence interval

AEMET = State Meteorological Agency

ALRI = Acute lower respiratory infection

aOR = Adjusted odds ratio

CO = Carbon monoxide

ICD-9-CM = 9th revision of the International Statistical Classification of Diseases and Related Health Problems, Clinical Modification

MBDS = Minimum Basic Data Set

MHCSW = Ministry of Health, Consumer Affairs and Social Welfare

NO_2 = Nitrogen dioxide

O_3 = Ozone

PM_{10} = Particulate matter up to 10 μm in size

RSV = Respiratory syncytial virus

SO_2 = Sulfur dioxide

Declarations

Ethics approval and consent to participate

This study involves patient clinical-epidemiological data from the MBDS of the MHCSW, whose information is compulsory and anonymous, and thus, the signed informed consent of the patients was not necessary. The MHCSW and the Research Ethics Committee of the Instituto de Salud Carlos III (Ref. CEI PI 81_2021) approved our study. The data were treated with total confidentiality following Spanish legislation.

Consent for publication

Not applicable.

Availability of data

All relevant data is contained in the article and supplemental files. Those interested can contact Dr. Alejandro Alvaro Meca for additional information at alejandro.alvaro@urjc.es.

The MDBS is the property of the MHCSW and the environmental data of the AEMET. Therefore, any researcher can request the data related to this article from MHCSW and AEMET.

Competing interests

The authors have no competing interests.

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Authors' contributions

Conceptualization: AAM and SR.

Formal Analysis: AAM.

Funding Acquisition: IM and SR.

Investigation: AAM, MCG, and SR.

Resources: AAM and SR.

Supervision: SR.

Visualization: AAM and SR.

Writing – Original Draft Preparation: SR.

Writing – Review & Editing: MCG, VM, RR, DSC, IM.

All authors read and approved the final manuscript.

Authors' information (optional)

Not applicable.

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Supplementary Table 1. Summary of associations between environmental factors (climatic factors and ambient air pollutants) and hospital admissions for viral lower respiratory tract infections in Spain (2013-2015).

	Univariate			Multivariate		
3 days	**OR (95% CI)**	***p*-value**	***q*-value**	**aOR (95% CI)**	***p*-value**	***q*-value**
Temperature (ºC)	1.01 (1.00; 1.02)	**0.025**	0.058	1.01 (1.00; 1.02)	**0.026**	0.091
Humidity (%)	0.99 (0.98; 1.01)	0.785	0.916	1.01 (0.99; 1.02)	0.292	0.317
NO_2 (μg/m^3)	0.99 (0.97; 1.01)	0.362	0.634	1.02 (0.99; 1.05)	0.146	0.255
SO_2 (μg/m^3)	1.01 (0.98; 1.03)	0.717	0.916	1.01 (0.99; 1.03)	0.317	0.317
O_3 (μg/m^3)	1.07 (1.03; 1.10)	**<0.001**	**0.001**	1.08 (1.04; 1.12)	**<0.001**	**<0.001**
PM_{10} (μg/m^3)	1.01 (0.98; 1.02)	0.980	0.980	1.01 (0.99; 1.04)	0.255	0.317
CO (μg/m^3)	0.96 (0.93; 0.99)	**0.004**	**0.014**	0.97 (0.94; 1.00)	**0.050**	0.117
1 week						
Temperature (ºC)	1.01 (1.00; 1.02)	**0.001**	**0.002**	1.01 (1.00; 1.02)	**0.005**	**0.012**
Humidity (%)	0.96 (0.95; 0.97)	**<0.001**	**<0.001**	0.98 (0.96; 0.99)	**0.001**	**0.003**
NO_2 (μg/m^3)	0.95 (0.93; 0.97)	**<0.001**	**<0.001**	0.99 (0.96; 1.02)	0.462	0.539
SO_2 (μg/m^3)	1.01 (0.99; 1.03)	0.257	0.263	1.03 (1.00; 1.05)	**0.015**	**0.026**
O_3 (μg/m^3)	1.14 (1.11; 1.17)	**<0.001**	**<0.001**	1.14 (1.10; 1.18)	**<0.001**	**<0.001**
PM_{10} (μg/m^3)	0.99 (0.97; 1.01)	0.263	0.263	1.02 (1.00; 1.04)	0.120	0.168
CO (μg/m^3)	0.97 (0.94; 0.99)	**0.010**	**0.014**	1.00 (0.97; 1.03)	0.912	0.912
2 week						
Temperature (ºC)	1.01 (1,01; 1.02)	**0.003**	**0.004**	1.00 (0.99; 1.01)	0.614	0.716
Humidity (%)	0.94 (0.92; 0.95)	**<0.001**	**<0.001**	0.95 (0.94; 0.96)	**<0.001**	**<0.001**
NO_2 (μg/m^3)	0.90 (0.88; 0.92)	**<0.001**	**<0.001**	0.93 (0.91; 0.96)	**<0.001**	**<0.001**
SO_2 (μg/m^3)	1.01 (0.99; 1.03)	0.166	0.194	1.04 (1.02; 1.06)	**<0.001**	**<0.001**
O_3 (μg/m^3)	1.21 (1.18; 1.24)	**<0.001**	**<0.001**	1.19 (1.15; 1.22)	**<0.001**	**<0.001**
PM_{10} (μg/m^3)	0.99 (0.97; 1.01)	0.370	0.370	1.05 (1.03; 1.08)	**<0.001**	**<0.001**
CO (μg/m^3)	0.96 (0.93; 0.98)	**<0.001**	**<0.001**	1.00 (0.98; 1.03)	0.959	0.959

Statistics: Association analyses were performed by conditional logistic regression analysis. *P*-values were corrected for multiple testing (*q*-values) using the false discovery rate (FDR) with Benjamini and Hochberg procedure (n= 21 inheritance models/control time, multiple comparisons). The statistically significant differences are shown in bold.
Abbreviations: 95% CI, 95% confidence interval; aOR, adjusted OR; OR, odds ratio.