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Environmental factors are associated with hospital admissions for sepsis-related pneumonia: A bidirectional case-crossover design

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Short title: Environmental factors on sepsis-related pneumonia

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Abstract

Objective: Pneumonia is a common cause of morbidity and sepsis worldwide, mainly in the elderly. We evaluated the impact of short-term exposure to environmental factors on hospital admissions for sepsis-related pneumonia in a nationwide study in Spain.

Methods: We conducted a bidirectional case-crossover study in patients who had sepsis-related pneumonia in 2013. Data were obtained from the Minimum Basic Data Set (MBDS) and the State Meteorological Agency (AEMET) of Spain. Conditional logistic regressions were used to evaluate the association between environmental factors (temperature, relative humidity, NO₂, SO₂, O₃, PM₁₀, and CO) and hospital admissions with sepsis-related pneumonia.

Results: A total of 3,262,758 hospital admissions were recorded in the MBDS, of which, 253,467 were patients with sepsis. Among those, 67,443 had sepsis-related pneumonia and zip code information. We found inverse associations [adjusted odds ratio (aOR) values <1] between short-term exposure to temperature and hospital admissions for sepsis-related pneumonia. Moreover, short-term exposure to higher levels of relative humidity, NO₂, SO₂, O₃, PM₁₀, and CO were directly associated (aOR values >1) with a higher risk of hospital admissions for sepsis-related pneumonia. Overall, the impact of environmental factors was more prominent with increasing age, mainly among the elderly aged 65 or over.

Conclusion: Short-term exposure to environmental factors (temperature, relative humidity, NO₂, SO₂, O₃, CO, and PM₁₀) was associated with a higher risk of hospital admissions for sepsis-related pneumonia. Our findings support the role of environmental factors in monitoring the risk of hospital admissions for sepsis-related pneumonia and can help plan and prepare public health resources.

Keywords: environment; pneumonia; sepsis; epidemiology; age; ICD-9-CM

Introduction

Pneumonia is one of the most common causes of morbidity and mortality worldwide, mainly in older adults (Prina et al., 2015). The burden of pneumonia in developed countries is likely to increase due to the aging population (Prina et al., 2015). In Spain, the annual incidence of pneumonia is 4.63 per 1000 persons/year, which increased progressively with age (23.74 per 1000 persons/year in patients older than 90 years) (Gil-Prieto et al., 2011; Rivero-Calle et al., 2016). Moreover, pneumonia is one of the leading causes of sepsis. Sepsis is a dysregulated host response to an infection, which causes life-threatening organ dysfunction (Singer et al., 2016). Sepsis affects millions of people worldwide as the leading cause of death in critical care patients (Collaborators, 2018; Mayr et al., 2014), and it causes a significant economic burden because septic patients require a high expense in hospital resources (Chalupka and Talmor, 2012; Martin, 2012). The incidence of sepsis is higher in children younger than five and people older than 65 (Alvaro-Meca et al., 2018). During the last decades, sepsis diagnosis and its management have improved (Dellinger, 2015), reducing sepsis lethality in most developed countries (Ferrer et al., 2008; Gaieski et al., 2013; Martin, 2012).

Climatic factors are relevant factors in the development of pneumonia (Fares, 2013) since lower temperatures and higher humidity are related to a higher risk of pneumonia (Adegboye et al., 2019; Bunker et al., 2016; Chowdhury et al., 2018; Huh et al., 2020; Lam et al., 2019; Qiu et al., 2016; Sun et al., 2018). However, their impact on the risk of pneumonia is difficult to define, since multiple factors can influence it, such as vitamin D levels, immune system function, pathogen infectivity, and human activity, among others. Moreover, ambient air pollution is one of the leading causes of morbidity and mortality worldwide (WHO, 2016). Short-term exposure to ambient air pollution is linked to an increased rate of hospital admissions for pneumonia (Bergmann et al., 2020; Cheng et al., 2019; Mokoena et al., 2019; Nhung et al., 2017; Nhung et al., 2018; Tian et al., 2019). Specifically, a relationship between air contaminants (nitrogen dioxide (NO₂), ozone (O₃), sulfur dioxide (SO₂), carbon monoxide (CO), and particulate matter up to 10 µm in size (PM₁₀)) and pneumonia have been reported (Bergmann et al., 2020; Cheng et al., 2019; Mokoena et al., 2019; Nhung et al., 2017; Nhung et al., 2018; Tian et al., 2019). However, these associations between environmental factors and pneumonia are not always uniform, since there have been studies that have found significant associations for a specific environmental factor and other reports that do not find it. Besides, to our knowledge, there is little information regarding environmental factors and sepsis-related pneumonia (Rush et al., 2018).

Objective

We aimed to assess whether exposure to environmental factors is related to hospital admissions for sepsis-related pneumonia in a study conducted nationwide in Spain.

Materials and Methods

Study population

We carried out a bidirectional case-crossover (CCO) study in patients who had sepsis-related pneumonia between January 1, 2013, and December 31, 2013, in Spain. Data were obtained from the Spanish Minimum Basic Data Set (MBDS) of the Ministry of Health, Consumption, and Social Welfare (MHCSW).

Data source

The MBDS is an administrative database that provided clinical information at hospital discharge. The data were recorded according to the *International Classification of Diseases, 9th ed, Clinical Modification* (ICD-9-CM). The MBDS includes around 14 discharge diagnoses and 20 procedures completed in the hospital stay. The MBDS also provided epidemiological data (gender, date of birth, date of hospital admission and discharge, and hospital providing the services, among others). Besides, around 70% of the records in MBDS have zip code information.

The Spanish MDDBS covers about 92% of all hospitals, 84.14% of public hospitals, and 15.86% of private hospitals (Subdirección General de Información Sanitaria e Innovación, 2016). The data quality of the MDDBS was ensured by the Spanish MHCSW, establishing protocols for recording data and periodic audits. Patient identifications were encrypted and anonymized.

Ethics statement

The signed informed consent of patients was not necessarily due to the MBDS information is mandatory and an anonymous dataset. The data were treated with full confidentiality according to Spanish legislation. The MHCSW and the Research Ethics Committee (Comité de Ética de la Investigación y de Bienestar Animal) of the Instituto de Salud Carlos III (Madrid, Spain) approved our study.

Environmental data

The State Meteorological Agency (<http://www.aemet.es/>) provided environmental data. The number of stations in Spain was 880, which were distributed throughout the national territory (European Environment Agency, 2014). Data of air quality information reported complies with the regulations of the European Environment Agency, which also collects primary validated assessment data (European Environment Agency, 2018).

For each meteorological station, we had the geolocation of the weather stations (latitude, longitude, and altitude) and daily data of the environmental factors: climatic [temperature (°C) and relative humidity (%)] and ambient air pollutants [SO₂ (µg/m³), CO (µg/m³), NO₂ (µg/m³), O₃ (µg/m³), PM₁₀ (µg/m³)]. Environmental factors of each patient were obtained using the nearest meteorological station to the zip code.

ICD-9-CM codes and outcome variables

ICD-9-CM codes defined the clinical status of each patient (see **Supplementary Table 1**). We selected those patients who had sepsis (presence of bacterial or fungal infections and organ dysfunction) from all hospital admissions with ICD-9-CM codes of bacterial or fungal infections (Angus et al., 2001) and diagnosis of acute organ dysfunction (Angus et al., 2001; Dombrovskiy et al., 2007; Shen et al., 2010) (see **Supplementary Table 1**). Next, we selected those patients who had pneumonia (ICD-9-CM codes: 480.x, 481.x, 482.x, 483.x, 484.x, 485.x, 486.x, 487.0). The diagnoses were made using standard procedures in each hospital of the Spanish National Health System.

The clinical outcome was sepsis-related pneumonia, which was defined with the ICD-9-CM codes of the two clinical events defined above, sepsis and pneumonia. First, all patients with sepsis were selected, and from this group of patients, all patients with pneumonia were

selected (**Figure 1**).

Statistical analysis

A bidirectional CCO design was used to evaluate the effect of short-term exposure to environmental factors (temperature, relative humidity, NO₂, SO₂, O₃, CO, and PM₁₀) on hospital admissions for sepsis-related pneumonia. With this design, each individual serves as their control, and all time-invariant confounders are inherently adjusted (Carracedo-Martinez et al., 2010). Besides, in this bidirectional CCO design, two short periods before and after the hospital admission (one-week and two-weeks) were considered as control points to compare the exposure of patients at the time of hospital admission (baseline). Next, we used conditional logistic regression for assessing the association between environmental variables and the outcome variable. This test gives us the odds ratio (OR) and its 95% confidence interval (95%CI) calculated by the exact method. Here, the likelihoods of a clinical event depend on the variation of the level of an environmental variable on the date of hospitalization and the value of that environment variable at the control time (one week and two weeks). The exposure status is encoded as “1” at the time of hospital admission and encoded as “0” at the control time, and only patents with variations in environmental exposure levels are informative (Perz et al., 2006). Thus, an OR >1 indicates higher risk when the analyzed factor increased during the hazard periods (inflated at the time of hospital admission); whereas an OR <1 shows higher risk when the analyzed factor decreased during the hazard periods (diminished at the time of hospital admission).

We performed the statistical analysis stratified by age (≤ 5 , 5-17, 18-44, 45-64, and ≥ 65 years). We used univariant models for each of the environmental factors and multivariant models for all factors together. All environmental factors, except for temperature, were log₂-transformed because many OR values tended to 1, which made their interpretation difficult. Besides, the logarithm to base 2 may be interpreted as an OR associated with a doubling of the predictor.

Statistical analysis was carried out by the R statistical package version 3.5.2 (GNU General Public License) (The R Core Team, 2011). All tests were two-tailed with p-values <0.05 considered significant. The false discovery rate, with the Benjamini and Hochberg procedure, was used for the correction of multiple testing.

Results

Population characteristics

A total of 3,262,758 hospital admissions were recorded in the Spanish MBDS during 2013, of which 253,467 were patients with sepsis. Among them, we found 67,443 hospital admissions of patients who also had sepsis-related pneumonia (**Figure 1**). All selected patients had zip code information in the MBDS.

Table 1 shows the clinical and epidemiological characteristics of all the patients included in the study stratified by age. Overall, the mean age was 72.3 years and 62.2% were men. The hospital stay was 13 days and the Charlson index was 2.4. The mean number of acute failures was 1.35, and 82% had acute dysfunction of the respiratory system (**Table 1**). The specific bacterial strains most frequently found were *Staphylococcus*, *Escherichia coli*, and *Pseudomonas*.

Impact of climatic conditions on hospital admissions

The association between climatic factors and hospital admissions for sepsis-related pneumonia by using multivariate models is presented in **Figure 2** (univariate models in **Supplementary Table 2**). Temperature levels were significantly associated with hospital admissions in the control period of one-week (strata of 45-65 years and ≥ 65 years) and two-week (stratum of ≥ 65 years) (**Figure 2A**). The adjusted odds ratio (aOR) values were less than 1. In the case of the relative humidity (%), we found significant associations with hospital admissions in the control period of one-week (strata of 45-65 years and ≥ 65 years) and two-week (strata of 18-44 years, 45-65 years, and ≥ 65 years) (**Figure 2B**). The aOR values were greater than 1.

Impact of ambient air contaminants on hospital admissions

Figure 3 shows the association between ambient air contaminants and hospital admissions for sepsis-related pneumonia by using multivariate models (univariate models in **Supplementary Table 3**). NO₂ levels were significantly associated with hospital admissions in the control period for one-week (strata of 18-44 years, 45-65 years, and ≥ 65 years) and two-week (strata of 18-44 years, 45-65 years, and ≥ 65 years) (**Figure 2A**). In the case of SO₂, we found significant associations with hospital admissions in all control periods and all age strata (**Figure 2B**). We found O₃ levels were also significantly associated with hospital admissions in the control period for one-week (all age strata) and two-week (all age strata, except strata of 5-17 years) (**Figure 2C**). PM₁₀ levels were significantly associated with hospital admissions in the control period for one-week (strata of 18-44 years, 45-65 years, and ≥ 65 years) and two-week (all age strata, except strata of 5-17 years) (**Figure 2D**). Finally, CO levels were significantly associated with hospital admissions in the control period for one-week (stratum of ≥ 65 years) and two-week (stratum of ≥ 65 years) (**Figure 2E**). Overall, the significant aOR values for ambient air contaminants (NO₂, SO₂, O₃, CO, and PM₁₀) were greater than 1.

Discussion

In this study, we found significant associations between short-term exposure to environmental factors (temperature, relative humidity, NO₂, SO₂, O₃, CO, and PM₁₀) and hospital admissions for sepsis-related pneumonia. These associations varied according to age strata (≤ 5 , 5-17, 18-44, 45-64, and ≥ 65 years), being more prominent with increasing age, mainly among the elderly aged 65 or over.

Climatic factors have an impact on the risk of pneumonia (Fares, 2013). Previous studies have shown that lower temperatures and higher humidity are a significant risk factor for pneumonia (Adegboye et al., 2019; Bunker et al., 2016; Chowdhury et al., 2018; Huh et al., 2020; Lam et al., 2019; Qiu et al., 2016; Sun et al., 2018). In our study, we found an inverse association (aOR <1) between temperature and hospital admissions for sepsis-related pneumonia, indicating that lower values of temperature at baseline increased the risk of the outcome variable. Conversely, we found a direct association (aOR >1) between temperature and hospital admissions for sepsis-related pneumonia, suggesting that higher values of relative humidity at baseline increased the risk of sepsis-related pneumonia. Overall, the infectivity of any pathogen outside the host depends on many environmental factors, including humidity, temperature, dehydration, and ultraviolet light (Sinclair et al., 2008). Of all these, the temperature seems to be the most important because most chemical and physical processes are affected by it (Sinclair et al., 2008). Some pathogens are most stable in high-humidity conditions, which stabilize airborne droplets that can carry pathogens that are transmitted from person to person (Fares, 2013). Thus, the onset of pneumonia can be driven by environmental changes that directly influence pathogen abundance, survival, or virulence (Fisman, 2007).

In our study, we also found a direct association (aOR >1) between short-term exposure to outdoor air contaminants (NO₂, SO₂, O₃, CO, and PM₁₀) and hospital admissions for sepsis-related pneumonia, indicating that higher values of air contaminants are at baseline significant risk factors of sepsis-related pneumonia. Our data are in concordance with previously published reports on exposure to ambient air contaminants and pneumonia (Bergmann et al., 2020; Chen et al., 2019; Cheng et al., 2019; Mokoena et al., 2019; Nhung et al., 2017; Nhung et al., 2018; Pothirat et al., 2019; Tian et al., 2019; Yorifuji et al., 2014). The exposure to air pollution is associated with lower lung function, increased pro-inflammatory response, increased Th₂ and Th₁₇ immune response, and decreased pulmonary immune response to pathogens (Glencross et al., 2020; Laumbach and Kipen, 2012). The ambient air contaminants analyzed cause oxidative stress in lung cells and impair cellular defense and the immune system (Laumbach and Kipen, 2012), increasing susceptibility to infection (Glencross et al., 2020; Shears et al., 2020).

Pneumonia is one of the leading causes of sepsis and is common in older adults (Prina et al., 2015). Our findings show that the risk of hospital admission for sepsis-related pneumonia after short-term exposure to environmental factors increased with age, particularly in elderly patients. During aging, there is a progressive decrease in body function, which leads to greater fragility and vulnerability of elderly subjects (Simoni et al., 2015) who have decreased lung function, which may contribute to higher susceptibility to air pollution and increased risk of pneumonia (Ribeiro Junior et al., 2019). Besides, people over 65 are those at increased risk of developing sepsis (Alvaro-Meca et al., 2018). During sepsis, the host immune response is dysregulated (Rubio et al., 2019), leading to uncontrolled inflammation and life-threatening organ dysfunction (Singer et al., 2016). It should also be noted that short-term exposure to SO₂, O₃, and PM₁₀ were associated with increased risk of hospital admission for sepsis-related pneumonia in those under 18 years of age, particularly in children under five years old. The young child has a maturing immune system and is at risk for many infections (Simoni et al.,

2015). In this regard, children under five years of age in developing countries have also a higher risk of having pneumonia (Liu et al., 2012) and sepsis (Alvaro-Meca et al., 2018).

Limitations of the study

We performed a retrospective study using the Spanish MBDS (administrative database), which carries a series of limitations: (i) We do not have relevant clinical information necessary to fully interpret the disease, such as the cause of hospital admission, treatments, prognostic scores (Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation (APACHE)), nature of pneumonia (community-acquired pneumonia (CAP), hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), and nursing home-associated pneumonia (NHAP)), among others. However, we used a bidirectional case-crossover design. In this design, each individual serves as its control minimizing the impact of the absence of critical variables in the statistical analysis. (ii) We have not evaluated the accuracy of the Spanish MBDS for pneumonia diagnosis, which could cause a confusion bias. On the one hand, we used the "Angus" algorithm to assess sepsis in the MBDS (Angus et al., 2001), but we did not use the ICD-9-CM codes for sepsis (995.9x) nor septic shock (785.52) because they are very troublesome. On the other hand, we did not know the type of pneumonia (CAP, HAP, VAP, and NHAP), although CAP is the most frequently found in epidemiological studies. (iii) We did not have data about indoor air quality, but as mentioned before, each individual serves as its control, which reduces their possible influence through the statistical analysis. (iv) We did not have data of PM_{2.5}, although a high correlation between PM₁₀ and PM_{2.5} have been reported (Janssen et al., 2013; Zhou et al., 2016). (v) Finally, we did not study the mechanism of action related to environmental factors (temperature, relative humidity, NO₂, SO₂, O₃, CO, and PM₁₀) that may be active in these processes. However, the previously reported evidence is consistent with our findings on the association between these environmental factors and hospital admission for sepsis-related pneumonia.

Conclusions

Short-term exposure to environmental factors (temperature, relative humidity, NO₂, SO₂, O₃, CO, and PM₁₀) was associated with a higher risk of hospital admissions for sepsis-related pneumonia. Our findings support the role of environmental factors in monitoring the risk of hospital admissions for sepsis-related pneumonia and can help plan and prepare public health resources.

List of abbreviations

Hospital admission (HA)

Nitrogen dioxide (NO₂)

Ozone (O₃)

Sulfur dioxide (SO₂)

Carbon monoxide (CO)

Particulate matter up to 10 µm in size (PM₁₀)

Minimum Basic Data Set (MBDS)

Ministry of Health, Consumption, and Social Welfare (MHCSW)

International Classification of Diseases, 9th ed, Clinical Modification (ICD-9-CM)

Odds ratio (OR)

95% confidence interval (95%CI)

Adjusted odds ratio (aOR)

Sequential Organ Failure Assessment (SOFA)

Acute Physiology and Chronic Health Evaluation (APACHE)

Community-acquired pneumonia (CAP)

Hospital-acquired pneumonia (HAP)

Ventilator-associated pneumonia (VAP)

Nursing home-associated pneumonia (NHAP)

Declarations

Ethics approval and consent to participate

This study involves the use of patient medical data from the Spanish Minimum Basic Data Set (MBDS) of the Ministry of Health, Consumption, and Social Welfare (MHCSW). The signed informed consent of patients was not necessary due to the MBDS information is mandatory and an anonymous dataset. The data were treated with full confidentiality according to Spanish legislation. The MHCSW and the Research Ethics Committee (Comité de Ética de la Investigación y de Bienestar Animal) of the Instituto de Salud Carlos III (Madrid, Spain) approved our study.

Consent for publication

Not applicable.

Availability of data and material

All relevant data are contained in the paper and Supporting Information files. For additional information, interested readers can contact Dr. Alejandro Alvaro Meca at alejandro.alvaro@urjc.es.

The MBDS dataset is the property of the Ministry of Health, Consumption, and Social Welfare. The environmental data is the property of the State Meteorological Agency from Spain. In both cases, any researcher can request the data related to this article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Conceptualization: AAM and SR.

Formal Analysis: AAM.

Funding Acquisition: ET and SR.

Investigation: AAM, ASL, and SR.

Resources: AAM and SR.

Supervision: ET and SR.

Visualization: AAM, ET, and SR.

Writing – Original Draft Preparation: SR.

Writing – Review & Editing: ASL, RR, ET.

All authors read and approved the final manuscript.

Authors' information (optional)

Not applicable.

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Table 1. Summary of the epidemiological and clinical characteristics of patients who had a hospital admission for sepsis-related pneumonia in Spain (2013).

Description	All patients	<5 years	5 - 17 years	18 - 44 years	45 -64 years	>65 years
No.	67443	2261	587	2756	9977	51862
Gender (male)	41934 (62.2%)	1191 (52.7%)	316 (53.8%)	1734 (62.9%)	6832 (68.5%)	31861 (61.4%)
Age (years)	72.29 (20.19)	1.68 (1.56)	10.2 (3.47)	35.7 (6.91)	56.23 (5.65)	81.11 (7.86)
Substances of abuse						
Drugs	7920 (11.7%)	1 (0%)	3 (0.5%)	955 (34.7%)	3278 (32.9%)	3683 (7.1%)
Alcohol	1732 (2.6%)	NA	NA	79 (2.9%)	768 (7.7%)	885 (1.7%)
Tobacco	6819 (10.1%)	NA	2 (0.3%)	804 (29.2%)	2895 (29%)	3118 (6%)
Urgent admission	64526 (95.7%)	2147 (95%)	555 (94.5%)	2567 (93.1%)	9260 (92.8%)	49997 (96.4%)
Length of stay (days)	13.1 (17.08)	10.37 (20.63)	12.81 (19.55)	18.02 (32.97)	17.69 (23.24)	12.08 (13.71)
Charlson index	2.4 (2.19)	0.17 (0.63)	0.66 (1.04)	1.12 (1.65)	2.38 (2.52)	2.59 (2.12)
Surgical condition	4979 (7.4%)	83 (3.7%)	54 (9.2%)	397 (14.4%)	1446 (14.5%)	2999 (5.8%)
In-hospital death	14011 (20.8%)	43 (1.9%)	33 (5.6%)	332 (12%)	1832 (18.4%)	11771 (22.7%)
Acute organ dysfunction						
Average	1.35 (0.68)	1.1 (0.37)	1.24 (0.62)	1.41 (0.79)	1.47 (0.86)	1.34 (0.65)
1	49871 (73.9%)	2088 (92.3%)	490 (83.5%)	2018 (73.2%)	6957 (69.7%)	38318 (73.9%)
2	12940 (19.2%)	131 (5.8%)	66 (11.2%)	479 (17.4%)	1877 (18.8%)	10387 (20%)
>2	4632 (6.9%)	42 (1.9%)	31 (5.3%)	259 (9.4%)	1143 (11.5%)	3157 (6.1%)
Acute organ dysfunction						
Cardiovascular	6053 (9%)	61 (2.7%)	46 (7.8%)	389 (14.1%)	1546 (15.5%)	4011 (7.7%)
Hematologic	3919 (5.8%)	72 (3.2%)	55 (9.4%)	308 (11.2%)	921 (9.2%)	2563 (4.9%)
Hepatic	1164 (1.7%)	5 (0.2%)	8 (1.4%)	114 (4.1%)	463 (4.6%)	574 (1.1%)
Neurologic	2183 (3.2%)	88 (3.9%)	31 (5.3%)	164 (6%)	435 (4.4%)	1465 (2.8%)
Renal	18548 (27.5%)	46 (2%)	42 (7.2%)	505 (18.3%)	2335 (23.4%)	15620 (30.1%)
Respiratory	55273 (82%)	2094 (92.6%)	509 (86.7%)	2247 (81.5%)	8310 (83.3%)	42113 (81.2%)
Metabolic	4058 (6%)	118 (5.2%)	37 (6.3%)	149 (5.4%)	698 (7%)	3056 (5.9%)
Specific bacteria (*)						
Gram-positive (+)	3723 (5.5%)	83 (3.7%)	40 (6.8%)	282 (10.2%)	965 (9.7%)	2353 (4.5%)
<i>Staphylococcus</i>	2407 (3.6%)	48 (2.1%)	32 (5.5%)	155 (5.6%)	605 (6.1%)	1567 (3%)
<i>S. aureus</i>	1646 (2.4%)	21 (0.9%)	18 (3.1%)	109 (4%)	396 (4%)	1102 (2.1%)
<i>Streptococcus</i>	1388 (2.1%)	36 (1.6%)	10 (1.7%)	133 (4.8%)	379 (3.8%)	830 (1.6%)
<i>Enterococcus</i>	669 (1%)	8 (0.4%)	1 (0.2%)	35 (1.3%)	135 (1.4%)	490 (0.9%)
Gram-negative (-)	6175 (9.2%)	125 (5.5%)	35 (6%)	319 (11.6%)	1246 (12.5%)	4450 (8.6%)
Gram-negative NOS	51 (0.1%)	0 (0%)	0 (0%)	5 (0.2%)	11 (0.1%)	35 (0.1%)
<i>Escherichia coli</i>	2234 (3.3%)	29 (1.3%)	3 (0.5%)	81 (2.9%)	332 (3.3%)	1789 (3.4%)
<i>Pseudomonas</i>	2330 (3.5%)	52 (2.3%)	21 (3.6%)	132 (4.8%)	511 (5.1%)	1614 (3.1%)
<i>Klebsiella</i>	995 (1.5%)	21 (0.9%)	6 (1%)	77 (2.8%)	255 (2.6%)	636 (1.2%)
<i>Haemophilus influenzae</i>	183 (0.3%)	25 (1.1%)	3 (0.5%)	8 (0.3%)	40 (0.4%)	107 (0.2%)
<i>Serratia</i>	25 (0%)	0 (0%)	2 (0.3%)	2 (0.1%)	8 (0.1%)	13 (0%)

Values are expressed as absolute number (percentage) and mean (standard deviation). NA, not available. (*), Specific bacteria (not including unknown).

Figures

Figure 1. Flow chart for the selection of patients with hospital admission for sepsis-related pneumonia in Spain (2013).

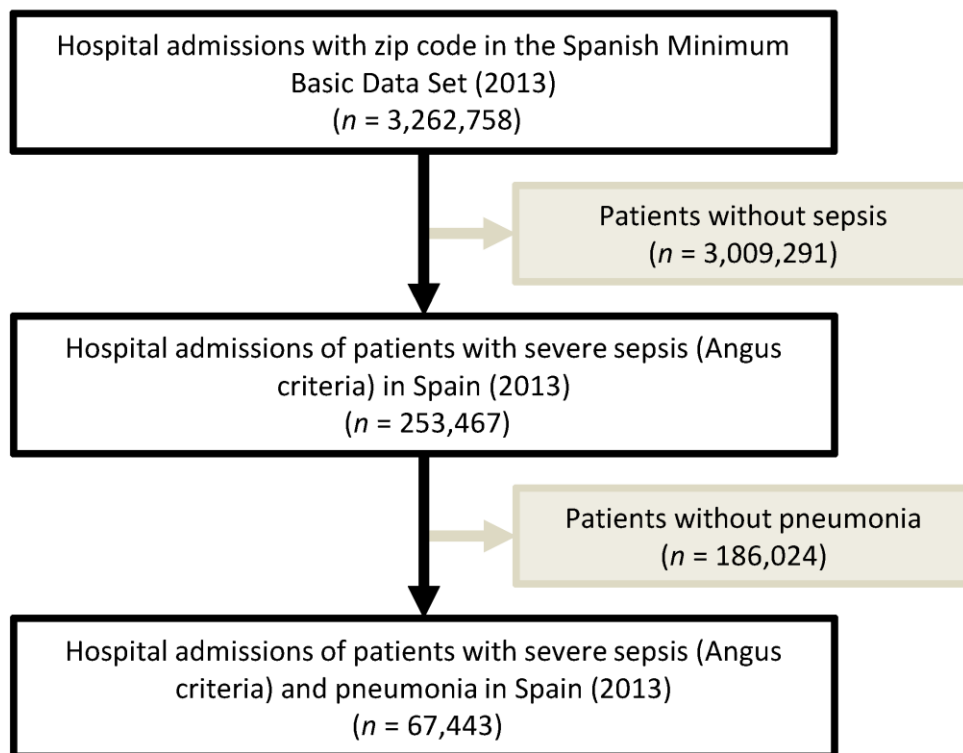


Figure 2. Multivariate analysis between climatic factors (temperature and relative humidity) and hospital admissions for sepsis-related pneumonia, stratified by age (≤ 5 , 5-17, 18-44, 45-64, and ≥ 65 years). **Statistic:** Statistical analysis was performed by conditional logistic regression considering three control timepoints (one-week and two-weeks). P-values were corrected for multiple testing (q-values) using the false discovery rate (FDR) with Benjamini and Hochberg procedure ($n = 15$ inheritance models, multiple comparisons). **Abbreviations:** aOR, adjusted odds ratio; 95% CI, 95% of the confidence interval.

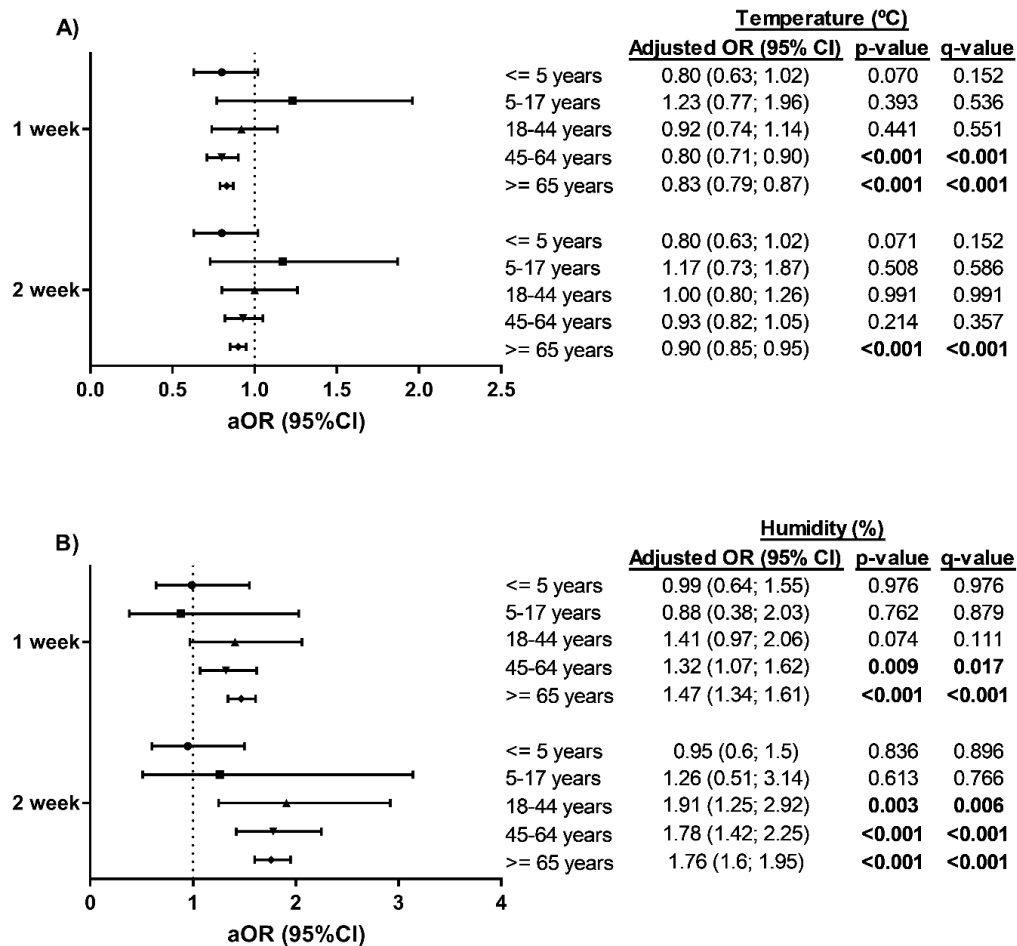
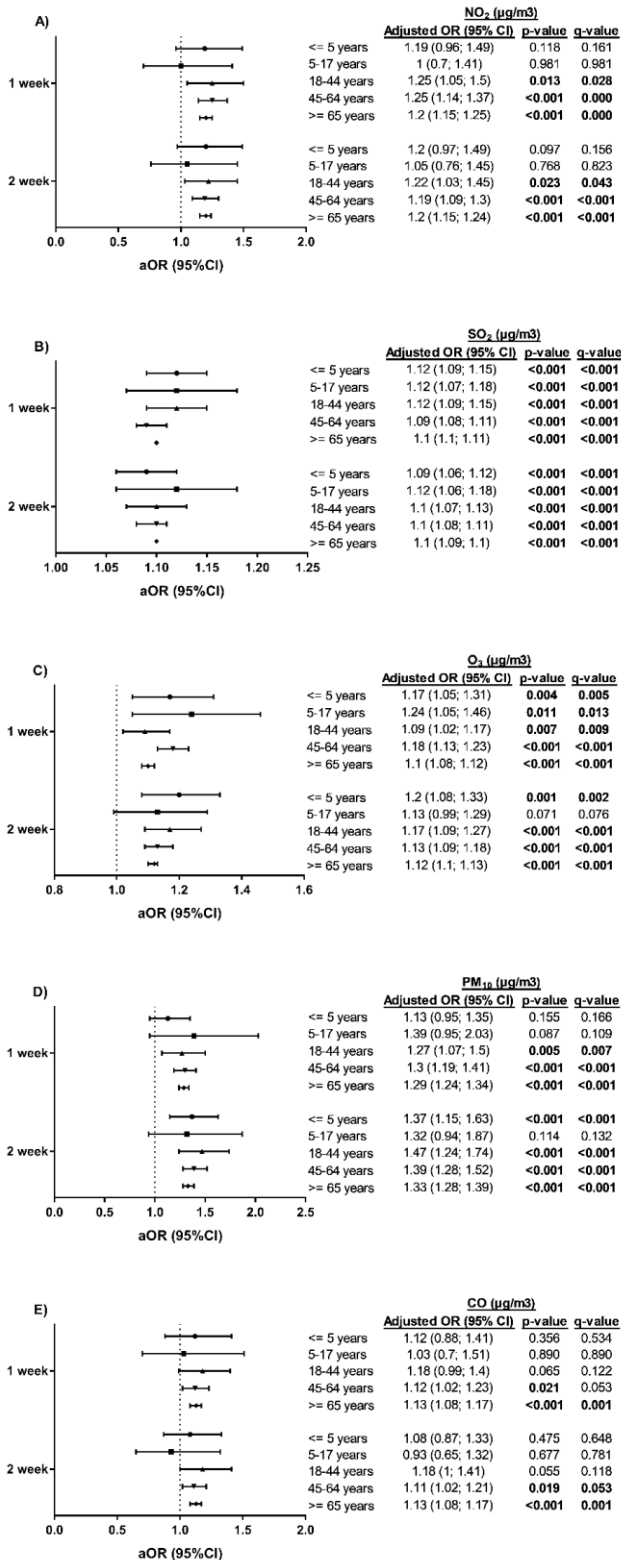


Figure 3. Multivariate analysis between ambient air pollutants (NO₂, SO₂, O₃, CO, and PM₁₀) and hospital admissions for sepsis-related pneumonia, stratified by age (≤5, 5-17, 18-44, 45-64, and ≥65 years). **Statistic:** Statistical analysis was performed by conditional logistic regression considering three control timepoints (one-week and two-weeks). P-values were corrected for multiple testing (q-values) using the false discovery rate (FDR) with Benjamini and Hochberg procedure (n= 15 inheritance models, multiple comparisons). **Abbreviations:** aOR, adjusted odds ratio; 95% CI, 95% of the confidence interval; NO₂, nitrogen dioxide; SO₂, sulfur dioxide; O₃, ozone; CO, carbon monoxide; PM₁₀, particulate matter up to 10 μm in size.



Supplementary files

Supplementary Table 1. Summary of ICD-9-CM coding used for baseline comorbidities investigated in this study.

Description	Diagnosis codes (index or prior admissions)
HIV infection	042 or V08
Endocarditis	421.0, 421.1, 421.9
Abuse of alcohol and drugs	
Abuse of drugs	292.x, 304.x, 305.x, and 965.0x
Abuse of alcohol	305.0,303.0,303.9,291.0,291.1,291.2,291.3,291.4,291.5,291.8,291.9,571.0,571.1,571.2,571.3,425.5,535.3,357.5,265.2, V11.3,790.3,980.0
Abuse of tobacco	305.1, V15.82
Conditions influencing in health status	
Surgical conditions	V42, V45
Trauma	E880* to E929*, E950 to E999*
Charlson comorbidities [1]	
Myocardial infarction	410.x, 412.x
Congestive heart failure	428.x
Peripheral vascular disease	443.9, 441.x, 785.4, V43.4, Procedure 38.48
Cerebrovascular disease	430.x-438.x
Dementia	290.x
Chronic pulmonary disease	490.x-505.x, 506.4
Rheumatic disease	710.0, 710.1, 710.4, 714.0-714.2, 714.81, 725.x
Peptic ulcer disease	531.x-534.x
Mild liver disease	571.2, 571.4-571.6
Diabetes without chronic complication	250.0-250.3, 250.7
Diabetes with chronic complication	250.4-250.6
Hemiplegia or paraplegia	344.1, 342.x
Renal disease	582.x, 583-583.7, 585.x, 586.x, 588.x
Any malignancy, including lymphoma and leukemia, except malignant neoplasm of skin	140.x-172.x, 174.x.-195.8, 200.x-208.x
Moderate or severe liver disease	456.0-456.21, 572.2-572.8
Metastatic solid tumor	196.x-199.1
AIDS/HIV	042.x-044.x
Pneumonia	

Viral pneumonia	480.x
Pneumococcal pneumonia	481.x
Other bacterial pneumonia	482.x
Pneumonia due to other specified organism	483.x
Pneumonia in infectious diseases classified elsewhere	484.x
Bronchopneumonia organism unspecified	485.x
Pneumonia organism unspecified	486.x
Influenza with pneumonia	487.0
Organ failure [2-4]	
Cardiovascular	427.5, 458.0, 458.8, 458.9, 785.5, 796.3
Hematologic	286.2, 286.6, 286.9, 287.3, 287.4, 287.5, 790.92
Hepatic	570, 572.2, 573.3, 573.4
Neurologic	293, 348.1, 348.3, 780.01, 780.09, 89.14
Renal	580, 580.0, 580.4, 580.8, 580.81, 580.89, 580.9, 584, 584.5, 584.6, 584.7, 584.8, 584.9, 586, 39.95
Respiratory	518.5, 518.8, 786.03, 799.1, 786.09, 96.7, 96.71, 96.72, 96.04, 93.90
Metabolic	276.2
Site of infection [5,6]	
Nervous	013, 036, 091.81, 098.82, 320, 321, 321.1, 324, 325, 360, 376, 380.14, 383
Circulatory	093, 098.83 – 098.84, 036.4, 391.2, 420.99, 421
Respiratory	010.1, 011, 012, 018, 031.0, 032, 034, 098.6, 112.4, 114.0, 114.2, 115.15, 115.05, 115.95, 117.5, 117.3, 136.3, 461, 462, 463, 464, 465, 475, 480, 481, 482, 483, 485, 486, 487.0, 491.21, 494, 510, 513
Digestive	001, 002, 003, 004, 005, 008, 008.1, 008.2, 008.3, 008.4, 008.5, 009, 014, 129, 522.5, 522.7, 526.4, 527.3, 528.3, 540, 541, 542, 562.01, 562.03, 562.11, 562.13, 566, 567, 569.5, 569.61, 569.83, 572, 572.1, 575
Genitourinary	016, 098.17, 112.2, 590, 599, 601, 604, 614, 615, 616.3, 616.4
Pregnancy	634, 635, 636, 637, 638, 639, 646.6, 658.4, 670, 675.1
Skin, soft tissue, or bone	003.24, 015, 017, 031.1, 035, 036.82, 040.0, 095.5, 098.5, 681, 682, 683, 685, 686, 711, 728.86, 730
Other	790.7, 958.3, 996.6, 998.5, 999.3
Angus algorithm: bacterial and fungal codes [4].	001, 002, 003, 004, 005, 008.0, 008.1, 008.2, 008.3, 008.4, 008.5, 009, 013, 018, 020, 021, 022, 023, 024, 025, 026, 027, 032, 033, 034, 035, 036, 037, 038, 039, 040, 041, 098, 100, 101, 112.0, 112.4, 112.5, 112.8, 114, 115, 116, 117, 118, 320, 321.0, 321.1, 324, 325, 360.0, 376.0, 380.14, 383.0, 420.99, 421, 461, 462, 463, 464, 465, 475, 481, 482, 485, 486, 491.21, 494, 510, 513, 522.5, 522.7, 526.4, 527.3, 528.3, 540, 541, 542, 562.01, 562.03, 562.11, 562.13, 566, 567, 569.5, 569.61, 569.83, 572.0, 572.1, 575.0, 590, 599.0, 601, 604, 614, 615, 616.3, 616.4, 634.0, 635.0, 636.0, 637.0, 638.0, 639.0, 646.6, 658.4, 670, 675.1, 681, 682, 683, 685.0, 686, 711.0, 728.86, 730, 790.7, 958.3, 996.6, 998.5, 999.3
Organism-specific that cause severe sepsis [7,8]	
Gram-positive (+)	038.1, 038.10, 038.11, 038.12, 038.19, 041.1, 041.11, 041.12, 041.10, 041.19, 482.41, and 482.42

	038.0, 038.2, 041.0, 041.00, 041.01, 041.02, 041.03, 041.05, 041.09 and 041.2
<i>Staphylococcus</i>	038.1, 038.10, 038.11, 038.12, 038.19, 041.1, 041.11, 041.12, 041.10, 041.19, 482.41, and 482.42
<i>Staphylococcus aureus</i>	038.11, 038.12, 041.11, 041.12, 482.41, and 482.42
Streptococcus	038.0, 038.2, 041.0, 041.00, 041.01, 041.02, 041.03, 041.05, 041.09 and 041.2
<i>Enterococcus</i>	041.04
Gram-negative (-)	008.0, 008.00, 008.01, 008.02, 008.03, 008.04, 008.42, 008.09, 038.4, 038.40, 038.41, 038.42, 038.43, 038.44, 038.49, 041.3, 041.4, 041.5, 041.6, 041.7, 041.85, V01.83, 482.1, 482.0, 482.82,
<i>Gram-negative NOS</i>	038.40
<i>Escherichia coli</i>	008.0, 008.00, 008.01, 008.02, 008.03, 008.04, 008.09, 038.42, 041.4, 482.82, V01.83
<i>Pseudomonas</i>	008.42, 038.43, 041.7, 482.1
<i>Klebsiella</i>	041.3, 482.0
<i>Haemophilus influenzae</i>	038.41, 041.5, 482.2
<i>Serratia</i>	038.44

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Supplementary Table 2. Summary of associations between climatic factors and hospital admissions for sepsis-related pneumonia in Spain (2013).

A) Univariate models

<u>Control period</u>	<u>Temperature (°C)</u>			<u>Humidity (%)</u>		
	<u>OR (95% CI)</u>	<u>p-value</u>	<u>q-value</u>	<u>OR (95% CI)</u>	<u>p-value</u>	<u>q-value</u>
One-week						
≤ 5 years	0.93 (0.75; 1.16)	0.518	0.777	0.9 (0.59; 1.36)	0.605	0.641
5-17 years	1.4 (0.93; 2.11)	0.107	0.229	0.66 (0.3; 1.45)	0.304	0.415
18-44 years	0.99 (0.82; 1.21)	0.956	0.962	1.54 (1.07; 2.2)	0.019	0.032
45-64 years	0.9 (0.81; 1)	0.046	0.115	1.37 (1.12; 1.66)	0.002	0.004
≥ 65 years	0.93 (0.89; 0.97)	0.001	0.005	1.53 (1.4; 1.67)	<0.001	<0.001
Two-week						
≤ 5 years	1.01 (0.81; 1.24)	0.962	0.962	0.9 (0.59; 1.39)	0.641	0.641
5-17 years	1.26 (0.84; 1.88)	0.259	0.486	1.23 (0.53; 2.84)	0.633	0.641
18-44 years	1.09 (0.9; 1.33)	0.361	0.602	1.92 (1.3; 2.85)	0.001	0.003
45-64 years	1 (0.91; 1.11)	0.942	0.962	1.78 (1.43; 2.2)	<0.001	<0.001
≥ 65 years	1 (0.96; 1.05)	0.909	0.962	1.82 (1.66; 2)	<0.001	<0.001

B) Multivariate models

<u>Control period</u>	<u>Temperature (°C)</u>			<u>Humidity (%)</u>		
	<u>OR (95% CI)</u>	<u>p-value</u>	<u>q-value</u>	<u>OR (95% CI)</u>	<u>p-value</u>	<u>q-value</u>
One-week						
≤ 5 years	0.80 (0.63; 1.02)	0.070	0.152	0.99 (0.64; 1.55)	0.976	0.976
5-17 years	1.23 (0.77; 1.96)	0.393	0.536	0.88 (0.38; 2.03)	0.762	0.879
18-44 years	0.92 (0.74; 1.14)	0.441	0.551	1.41 (0.97; 2.06)	0.074	0.111
45-64 years	0.80 (0.71; 0.90)	<0.001	<0.001	1.32 (1.07; 1.62)	0.009	0.017
≥ 65 years	0.83 (0.79; 0.87)	<0.001	<0.001	1.47 (1.34; 1.61)	<0.001	<0.001
Two-week						
≤ 5 years	0.80 (0.63; 1.02)	0.071	0.152	0.95 (0.6; 1.5)	0.836	0.896
5-17 years	1.17 (0.73; 1.87)	0.508	0.586	1.26 (0.51; 3.14)	0.613	0.766
18-44 years	1.00 (0.80; 1.26)	0.991	0.991	1.91 (1.25; 2.92)	0.003	0.006
45-64 years	0.93 (0.82; 1.05)	0.214	0.357	1.78 (1.42; 2.25)	<0.001	<0.001
≥ 65 years	0.90 (0.85; 0.95)	<0.001	<0.001	1.76 (1.6; 1.95)	<0.001	<0.001

Statistics: P-values were calculated 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= 15 inheritance models, multiple comparisons).

Abbreviations: odds ratio; 95% CI, 95% of the confidence interval.

Supplementary Table 3. Summary of associations between ambient air pollutants and hospital admissions for sepsis-related pneumonia in Spain (2013).

A) Univariate models

Control	NO₂ (µg/m³)			SO₂ (µg/m³)			O₃ (µg/m³)			PM₁₀ (µg/m³)			CO (µg/m³)		
	OR (95% CI)	p-value	q-value	OR (95% CI)	p-value	q-value	OR (95% CI)	p-value	q-value	OR (95% CI)	p-value	q-value	OR (95% CI)	p-value	q-value
One-week															
≤ 5 years	1.28 (1.07; 1.52)	0.007	0.010	1.12 (1.1; 1.15)	<0.001	<0.001	1.12 (1.01; 1.23)	0.025	0.031	1.14 (0.98; 1.33)	0.087	0.093	1.25 (1.04; 1.49)	0.016	0.024
5-17 years	1.15 (0.84; 1.58)	0.377	0.377	1.13 (1.08; 1.19)	<0.001	<0.001	1.23 (1.05; 1.43)	0.010	0.015	1.39 (1.01; 1.92)	0.045	0.052	1 (0.73; 1.38)	0.982	0.982
18-44 years	1.41 (1.21; 1.65)	<0.001	0.000	1.12 (1.09; 1.14)	<0.001	<0.001	1.07 (1.01; 1.13)	0.020	0.027	1.34 (1.16; 1.54)	<0.001	<0.001	1.32 (1.15; 1.53)	<0.001	<0.001
45-64 years	1.34 (1.24; 1.45)	<0.001	0.000	1.1 (1.08; 1.11)	<0.001	<0.001	1.13 (1.09; 1.17)	<0.001	<0.001	1.33 (1.23; 1.43)	<0.001	<0.001	1.22 (1.13; 1.32)	<0.001	<0.001
≥ 65 years	1.32 (1.27; 1.36)	<0.001	0.000	1.1 (1.1; 1.11)	<0.001	<0.001	1.07 (1.06; 1.09)	<0.001	<0.001	1.37 (1.32; 1.41)	<0.001	<0.001	1.25 (1.21; 1.29)	<0.001	<0.001
Two-week															
≤ 5 years	1.32 (1.11; 1.57)	0.001	0.002	1.1 (1.07; 1.12)	<0.001	<0.001	1.13 (1.03; 1.23)	0.008	0.013	1.33 (1.15; 1.54)	<0.001	<0.001	1.17 (0.99; 1.38)	0.072	0.098
5-17 years	1.15 (0.86; 1.53)	0.349	0.374	1.12 (1.07; 1.18)	<0.001	<0.001	1.13 (1; 1.28)	0.050	0.054	1.42 (1.05; 1.92)	0.023	0.029	0.98 (0.72; 1.33)	0.888	0.951
18-44 years	1.44 (1.24; 1.67)	<0.001	0.000	1.11 (1.09; 1.14)	<0.001	<0.001	1.14 (1.06; 1.22)	<0.001	<0.001	1.51 (1.3; 1.74)	<0.001	<0.001	1.24 (1.08; 1.42)	0.002	0.004
45-64 years	1.35 (1.26; 1.46)	<0.001	0.000	1.1 (1.09; 1.12)	<0.001	<0.001	1.09 (1.05; 1.13)	<0.001	<0.001	1.42 (1.32; 1.53)	<0.001	<0.001	1.22 (1.14; 1.31)	<0.001	<0.001
≥ 65 years	1.34 (1.29; 1.38)	<0.001	0.000	1.1 (1.1; 1.11)	<0.001	<0.001	1.08 (1.07; 1.1)	<0.001	<0.001	1.41 (1.36; 1.45)	<0.001	<0.001	1.25 (1.21; 1.29)	<0.001	<0.001

B) Multivariate models

Control	NO₂ (µg/m³)			SO₂ (µg/m³)			O₃ (µg/m³)			PM₁₀ (µg/m³)			CO (µg/m³)		
	OR (95% CI)	p-value	q-value	OR (95% CI)	p-value	q-value	OR (95% CI)	p-value	q-value	OR (95% CI)	p-value	q-value	OR (95% CI)	p-value	q-value
One-week															
≤ 5 years	1.19 (0.96; 1.49)	0.118	0.161	1.12 (1.09; 1.15)	<0.001	<0.001	1.17 (1.05; 1.31)	0.004	0.005	1.13 (0.95; 1.35)	0.155	0.166	1.12 (0.88; 1.41)	0.356	0.534
5-17 years	1 (0.7; 1.41)	0.981	0.981	1.12 (1.07; 1.18)	<0.001	<0.001	1.24 (1.05; 1.46)	0.011	0.013	1.39 (0.95; 2.03)	0.087	0.109	1.03 (0.7; 1.51)	0.890	0.890
18-44 years	1.25 (1.05; 1.5)	0.013	0.028	1.12 (1.09; 1.15)	<0.001	<0.001	1.09 (1.02; 1.17)	0.007	0.009	1.27 (1.07; 1.5)	0.005	0.007	1.18 (0.99; 1.4)	0.065	0.122

45-64 years	1.25 (1.14; 1.37)	<0.001	0.000	1.09 (1.08; 1.11)	<0.001	<0.001	1.18 (1.13; 1.23)	<0.001	<0.001	1.3 (1.19; 1.41)	<0.001	<0.001	1.12 (1.02; 1.23)	0.021	0.053
≥ 65 years	1.2 (1.15; 1.25)	<0.001	0.000	1.1 (1.1; 1.11)	<0.001	<0.001	1.1 (1.08; 1.12)	<0.001	<0.001	1.29 (1.24; 1.34)	<0.001	<0.001	1.13 (1.08; 1.17)	<0.001	0.001
Two-week															
≤ 5 years	1.2 (0.97; 1.49)	0.097	0.156	1.09 (1.06; 1.12)	<0.001	<0.001	1.2 (1.08; 1.33)	0.001	0.002	1.37 (1.15; 1.63)	<0.001	<0.001	1.08 (0.87; 1.33)	0.475	0.648
5-17 years	1.05 (0.76; 1.45)	0.768	0.823	1.12 (1.06; 1.18)	<0.001	<0.001	1.13 (0.99; 1.29)	0.071	0.076	1.32 (0.94; 1.87)	0.114	0.132	0.93 (0.65; 1.32)	0.677	0.781
18-44 years	1.22 (1.03; 1.45)	0.023	0.043	1.1 (1.07; 1.13)	<0.001	<0.001	1.17 (1.09; 1.27)	<0.001	<0.001	1.47 (1.24; 1.74)	<0.001	<0.001	1.18 (1; 1.41)	0.055	0.118
45-64 years	1.19 (1.09; 1.3)	<0.001	<0.001	1.1 (1.08; 1.11)	<0.001	<0.001	1.13 (1.09; 1.18)	<0.001	<0.001	1.39 (1.28; 1.52)	<0.001	<0.001	1.11 (1.02; 1.21)	0.019	0.053
≥ 65 years	1.2 (1.15; 1.24)	<0.001	<0.001	1.1 (1.09; 1.1)	<0.001	<0.001	1.12 (1.1; 1.13)	<0.001	<0.001	1.33 (1.28; 1.39)	<0.001	<0.001	1.13 (1.08; 1.17)	<0.001	0.001

Statistics: P-values were calculated 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= 15 multiple comparisons per column).

Abbreviations: μ, micro; m, meter; NO₂, nitrogen dioxide; SO₂, sulfur dioxide; O₃, ozone; PM₁₀, particulate matter up to 10 μm in size; CO: carbon monoxide; OR, odds ratio; aOR, adjusted odds ratio; 95% CI, 95% of the confidence interval.