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Environmental factors are associated to hospital outcomes in COVID-19 patients during lockdown and post-lockdown in 2020: A nationwide study

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A R T I C L E I N F O

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A B S T R A C T

Objective: This study analyzed, at a postcode detailed level, the relation-ship between short-term exposure to environmental factors and hospital ad-missions, in-hospital mortality, ICU admission, and ICU mortality due to COVID-19 during the lockdown and post-lockdown 2020 period in Spain.
Methods: We performed a nationwide population-based retrospective study on 208,744 patients admitted to Spanish hospitals due to COVID-19 based on the Minimum Basic Data Set (MBDS) during the first two waves of the pandemic in 2020. Environmental data were obtained from Copernicus Atmosphere Monitoring Service. The association was assessed by a generalized additive model.
Results: $PM_{2.5}$ was the most critical environmental factor related to hospital admissions and hospital mortality due to COVID-19 during the lockdown in Spain, PM_{10}, NO_2, and SO2and also showed associations. The effect was considerably reduced during the post-lockdown period. ICU admissions in COVID-19 patients were mainly associated with $PM_{2.5}$, PM_{10}, NO_2, and SO2 during the lockdown as well. During the lockdown, exposure to $PM_{2.5}$ and PM_{10} were the most critical environmental factors related to ICU mortality in COVID-19.
Conclusion: Short-term exposure to air pollutants impacts COVID-19 out-comes during the lockdown, especially $PM_{2.5}$, PM_{10}, NO_2, and SO2. These pollutants are associated with hospital admission, hospital mortality and ICU admission, while ICU mortality is mainly associated with $PM_{2.5}$ and PM_{10}. Our findings reveal the importance of monitoring air pollutants in respiratory infectious diseases.

1. Introduction

In December 2019, a new betacoronavirus (SARS-CoV2) emerged in Wuhan, changing life radically as we used to know it (Lu et al., 2020; Xu et al., 2020). In Spain, there were two epidemic waves and more than 2 million cases. Hospitalizations reached up to 200.000 admissions overloading hospital services; mainly, the capacity of Intensive Care Units (ICU) had to be increased to admit more than 18.000 severe cases. More than 42.000 people died in Spain that first year (Equipo COVID-19. Red Nacional de Vigilancia Epidemiológica (RENAVE). Centro Nacional de Microbiología (CNM), 2020; Equipo COVID-19. Red Nacional de Vigilancia Epidemiológica (RENAVE). Centro Nacional de Microbiología

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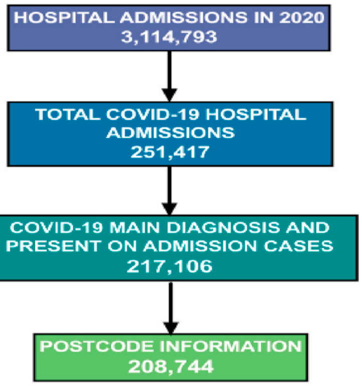


Fig. 1. Diagram of patient selection.

Table 1
Summary of the epidemiological and clinical characteristics of patients with a COVID-19 hospital admission in Spain. Abbreviations: No: Number of patients; ICU: Intensive Care Unit. Values are expressed as number (%) for categorical variable and median (interquartile range) for quantitative variable.

No,	Total	Lockdown period	Post-lockdown period	p-value
	208,744	103,154	105,590	
Gender (male)	117,620 (56.35)	58,217 (56.44)	59,403 (56.26)	0.413
mean Age (years)	69.0 (26.0)	69.0 (25.0)	69.0 (27.0)	0.770
Length of stay (days)	8.0 (8.0)	8.0 (9.0)	8.0 (7.0)	<0.001
In-hospital mortality	34,867 (16.7)	19,317 (18.7)	15,550 (14.7)	<0.001
Charlson Index	1.0 (2.0)	1.0 (2.0)	1.0 (2.0)	<0.001
ICU				
ICU	18,915 (9.1)	9094 (8.8)	9821 (9.3)	<0.001
ICU death	6030 (31.9)	3057 (33.6)	2973 (30.3)	0.270
ICU length of stay	10.0 (16.0)	12.0 (19.0)	9.0 (13.0)	<0.001

(CNM), 2021).

The first measure taken to prevent the virus spread was the confinement of the population that started in Spain on March 15th and lasted until May 10th, 2020 (Boletín Oficial del Estado (67): 25390–25400, 2020). One of the main consequences was the reduction of person-to- person contact, drastically impacting the virus's transmission (Kraemer et al., 2020). Another direct consequence was the reduced traffic, as many people started working remotely from home. This had implications on the levels of environmental conditions, as anthropogenic emission of nitrogen oxides comes mainly from fossil fuels.

In the past two years, many studies on pollution and COVID-19 outcomes have been performed (Zang et al., 2022; Sarmadi et al., 2021; Martelletti and Martelletti, 2020). The main findings suggest short and long-term exposure to NO_2, $PM_{2.5}$, and SO_2 was associated with higher COVID- 19 incidence and long-term exposure to $PM_{2.5}$ with increased COVID-19 mortality. A recent study suggested short and long-term exposure to NO_2, and $PM_{2.5}$ increased COVID-19 hospitalizations and ICU admissions (Chen et al., 2022).

This study analyzed, at a detailed postcode level, the relationship between short-term exposure to environmental factors and hospital admissions, in-hospital mortality, ICU admission, and ICU mortality due to COVID-19 in Spain during the lockdown and post-lockdown 2020 periods.

2. Materials and methods

2.1. Study design

We conducted a nationwide population-based retrospective study in patients hospitalized due to COVID-19 in Spain in 2020. Clinical and administrative data of all patients were collected from the Spanish Minimum Basic Data Set (MBDS), an administrative database provided by the Ministry of Health, which has an estimated coverage of 99.5% for both public and private Spanish hospitals discharges (Subdirección General de Información Sanitaria, 2016). The database includes encrypted patient identification numbers, gender, birth date, hospital admission, and discharge, and admission to Intensive Critical care Units (ICU), and postcode. It also

Includes clinical data, 20 diagnoses, and 20 procedures codes according to the International Classification of Diseases 10th Revision, Clinical Modification (ICD-10-CM), as well as the outcome at discharge (ICD-10-CM, 2022). The MBDS is validated for data quality and overall methodology by the Spanish Ministry of Health, establishing protocols and periodic audits. The data were treated with complete confidentiality according to Spanish legislation. Thus, given the anonymous and mandatory nature of the data, informed consent was not required or necessary. This study was approved by the Ethics Committee of Valladolid East Health Area under the code PI 22–2855.

2.2. Study variables and outcomes

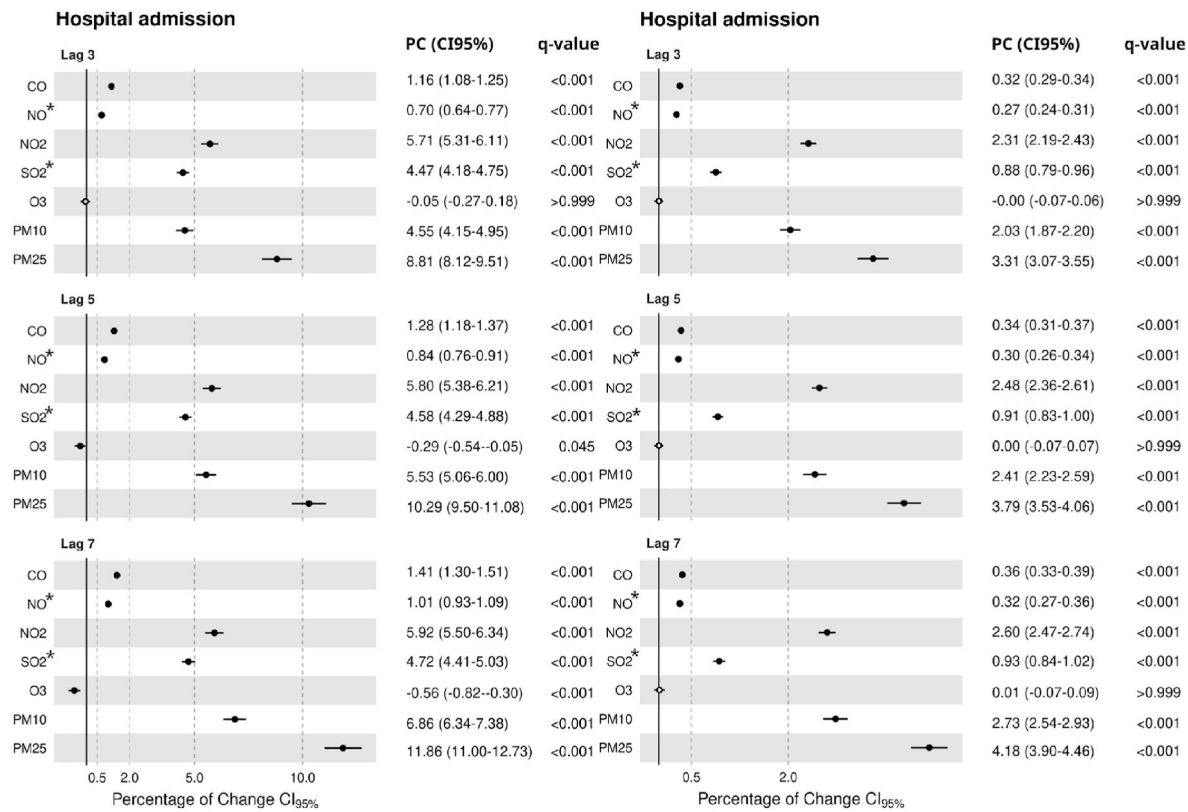
Diagnosis codes included in the MBDS, differentiate between primary and secondary diagnoses at discharge and whether they were present on admission (POA). Hospitalization due to COVID-19 was defined as any hospitalization with codes B97.29 and U07.1, as the principal diagnosis present on admission, from January 1st to December 31st, 2020. Outcomes considered in this study included COVID-19 severity, defined as: a) hospital admission, b) in-hospital mortality, c) ICU admission, and d) ICU mortality. In Spain, the first wave of COVID-19 was marked by the lockdown from March 15th to May 10th that year (Boletín Oficial del Estado (67): 25390–25400, 2020). That had multiple effects, including a considerable reduction in traffic flow, among others (Donzelli et al., 2021). Therefore, the study was divided into two periods: the first, from COVID-19 introduction in Spain until May 10th, 2020; and the second, from May 11th, 2020 until December 31st, 2020.

2.3. Air pollution data

Air pollutant data from January 1st, 2020, to December 31st, 2020 was obtained from Copernicus Atmosphere Monitoring Service (CAMS) European air quality forecasts (METEO FRANCE, 2022). CAMS registers hourly analysis for the European Region at a level of ($0.1^\circ \times 0.1^\circ$) approx. 10 km^2. For the seven main air pollutants, daily averages were calculated and used for analysis, including carbon monoxide (CO) in $\mu g/m^3$, nitrogen monoxide (NO) in $\mu g/m^3$, nitrogen dioxide (NO_2) in $\mu g/m^3$, sulfur dioxide (SO_2) in $\mu g/m^3$, ozone (O_3) in $\mu g/m^3$, particulate matter < 2.5 µm ($PM_{2.5}$) in $\mu g/m^3$, and particulate matter < 10 µm (PM_{10}) in $\mu g/m^3$.

2.4. Meteorological data

Temperature and relative humidity were considered the two main meteorological effects. Data was obtained from Copernicus Climate Change Service, ERA5-Land hourly data from 1950 to the present (Muñoz Sabater, 2022). ERA-5 produces hourly analysis in a regular grid of ($0.1^\circ \times 0.1^\circ$). As Copernicus does not provide precipitation data that might influence pollution levels, relative humidity was used as an indirect method to account for precipitation. To measure air humidity, we computed the daily average temperature of air at 2 m above the ground surface, and the temperature to which the air, at 2 m above the ground



(a) Lockdown period. (b) Post-lockdown period.

Fig. 2. Summary of the association between environmental factors and hospital admissions due to COVID-19. Abbreviations: PC: Percentage of change (%), computed by GAM adjusted for temperature, humidity, and day of the week. (*) Increases of 0.1 μg/m^3 for NO and SO_2. $CI_{95\%}$, 95% of the confidence interval. Lag: Moving average lag effect at 3, 5 and 7 days. q-value: False discovery rate q-value. Note that the x-axes have different scales.

surface, would have to be cooled for saturation to occur. That data, combined with temperature and pressure, can be used to calculate the relative humidity by (Alduchov and Eskridge, 1996):

$$\mathrm{RH} = 100\frac{exp((17.625 * T_D)/(243.04 + T_D))}{\exp((17.625\ * \mathrm{T})/(243.04 + \mathrm{T}))}$$

With T_D as dew point temperature (°C) at 2 m above the surface and T as temperature (°C) of air at 2m above the surface.

2.5. Link environmental data with clinical data

A critical task in these studies is the linkage of air pollutant exposures to individuals in the data set. Having the data on a fine grid over Spain, the assignment was performed as follows: first, each patient's centroid postcode was calculated; secondly, the nearest position of the centroid to the grid was searched; and finally, the environmental data were linked according to the date of admission.

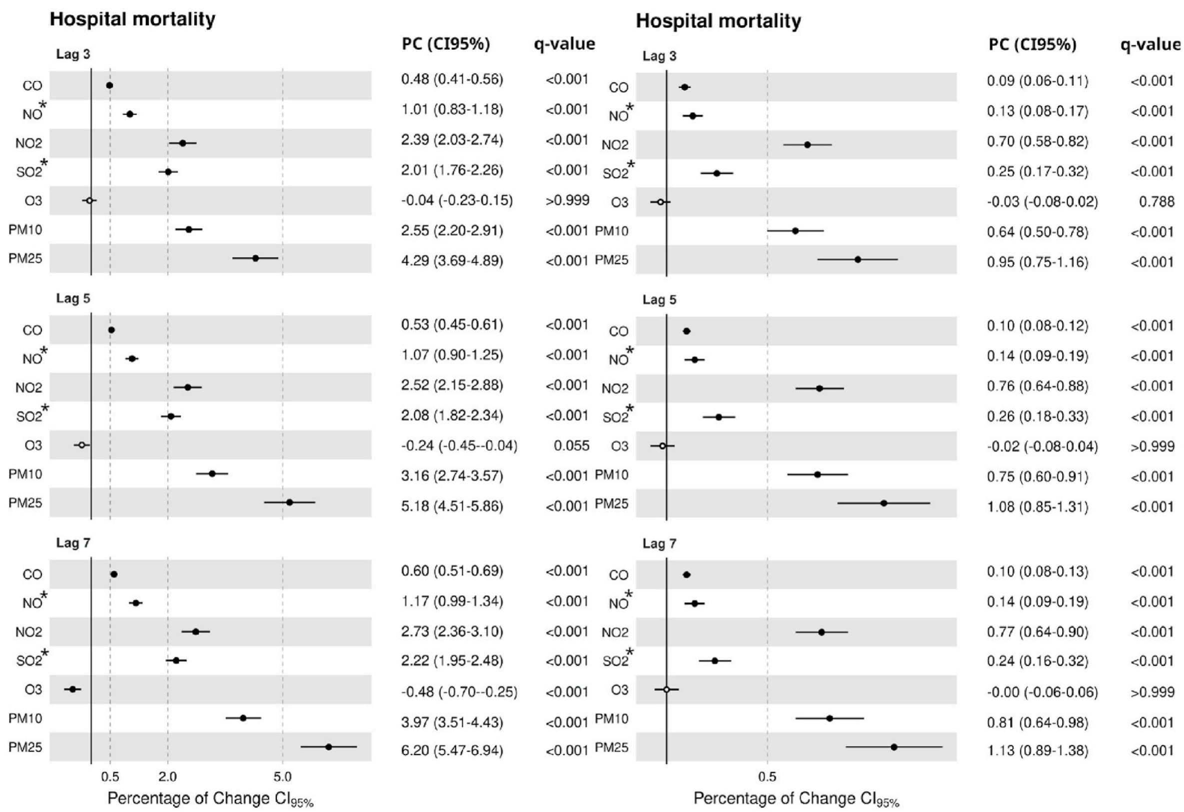
2.6. Statistical analysis

A descriptive study of each environmental factor was carried out in each wave defined. Spearman's rank correlation test was used to study the bivariate relationships between the environmental factors and the outcomes. The incubation period of COVID-19 ranges from 1 to 7 days, so we used a moving average approach to account for the cumulative effect of environ-mental factors. Therefore, the cumulative effects were examined by modeling the moving average lag effect (lag3, lag5, lag7) on the mean environmental factors on daily hospital admission of COVID-19. For example, lag0 represented the concentration of the day of hospital admission. Lag3 represented a 3-day moving average exposure, which was calculated as the average concentration of the day of hospital admission and the three previous days, and so on. We performed separate models by lockdown and post-lockdown period, using a generalized additive model (GAM) (Hastie and Tibshirani, 1990) with a Poisson family distribution and log-link function to estimate the association between the moving average air pollutant concentrations and the daily hospital admission, hospital mortality, ICU admission, and ICU mortality. GAMs were adjusted by temperature, relative humidity, and day of the week. Because there were higher correlations between air pollutants (see Appendix A; Table A1), each model only contains one of them to avoid collinearity. Therefore, the model is defined as follows:

$$\log(y_{it}) = X_{il} + Temp_{il} + RH_{il} + s(day_i) + \varepsilon_{it}$$

where i is the postcode, t is for the date of admission, and $\log(y_{it})$ is the log-transformed cases of hospital admissions, hospital mortality, ICU admission, and ICU mortality for postcode i and date t. X_{il} represents the moving average term (lag0-l) of daily air pollution in postcode i. We controlled by daily mean temperature ($Temp_{il}$), relative humidity, (RH_{il}) and day of the week as $s(day_i)$, which is the basis spline to smooth the data with 4 degrees of freedom. We obtained the percentage of change (%) by exponentiating the effects estimates, subtracting 1, and multiplying by 100. We controlled over-dispersion using quasi-Poisson distribution (McCullagh and Nelder, 1989).

Finally, a sensitivity study was performed on the pollutants that showed an association to establish values at which the pollutants showed a more significant impact on the outcomes studied. For this purpose, and due to the high correlation between different outcomes, we used a multi-output decision tree regression (Dumont et al., 2009) with a



(a) Lockdown period.   (b) Post-lockdown period.

Fig. 3. Summary of the association between environmental factors and hospital mortality due to COVID-19. Abbreviations: PC: Percentage of change (%), computed by GAM adjusted for temperature, humidity, and day of the week. (*) Increases of 0.1 μg/m^3 for NO and SO_2. $CI_{95\%}$, 95% of the confidence interval. Lag: Moving average lag effect at 3, 5 and 7 days. q-value: False discovery rate q-value. Note that the x-axes have different scales.

minimum of 1000 observations per sheet. As regressors, we used the moving averages of each of the pollutants. This was performed with a MANOVA test which allows the degree of correlation between outputs to be taken into account in the segmentation process. The outputs considered were hospital admissions, in-hospital mortality, ICU admission, and ICU mortality. Thus, in each tree, we can find those pollutant values at lag3, lag5, and lag7 for which the mean number of outputs is different. A secondary sensitivity analysis was also carried out to assess environmental factors' impact on the clinical events analyzed, stratifying the population ac-cording to the previous chronic lower respiratory diseases (CLRD) with the ICD-10 codes J40 to J47, which encompasses four major diseases: chronic obstructive pulmonary disease (COPD), chronic bronchitis, emphysema, and asthma.

All analyses were performed using python (version 3.9) and R statistical software (version 4.2.1) with the mgcv package (Wood, 2011) for GAM analysis. All statistical analyses were evaluated using two-sided tests at the 0.05 level of significance. False discovery rates were calculated using the Benjamini-Hochberg method for multiple comparisons.

3. Results

3.1. Population characteristics

A total of 3,114,793 hospital admissions were recorded in Spanish MDBS during 2020, of which 251,417 were admitted with a COVID-19 diagnosis and 217,106 of them with the principal diagnosis and present on hospital admission. Finally, 208,744(96%) hospital admissions with full postcodes were selected Fig. 1.

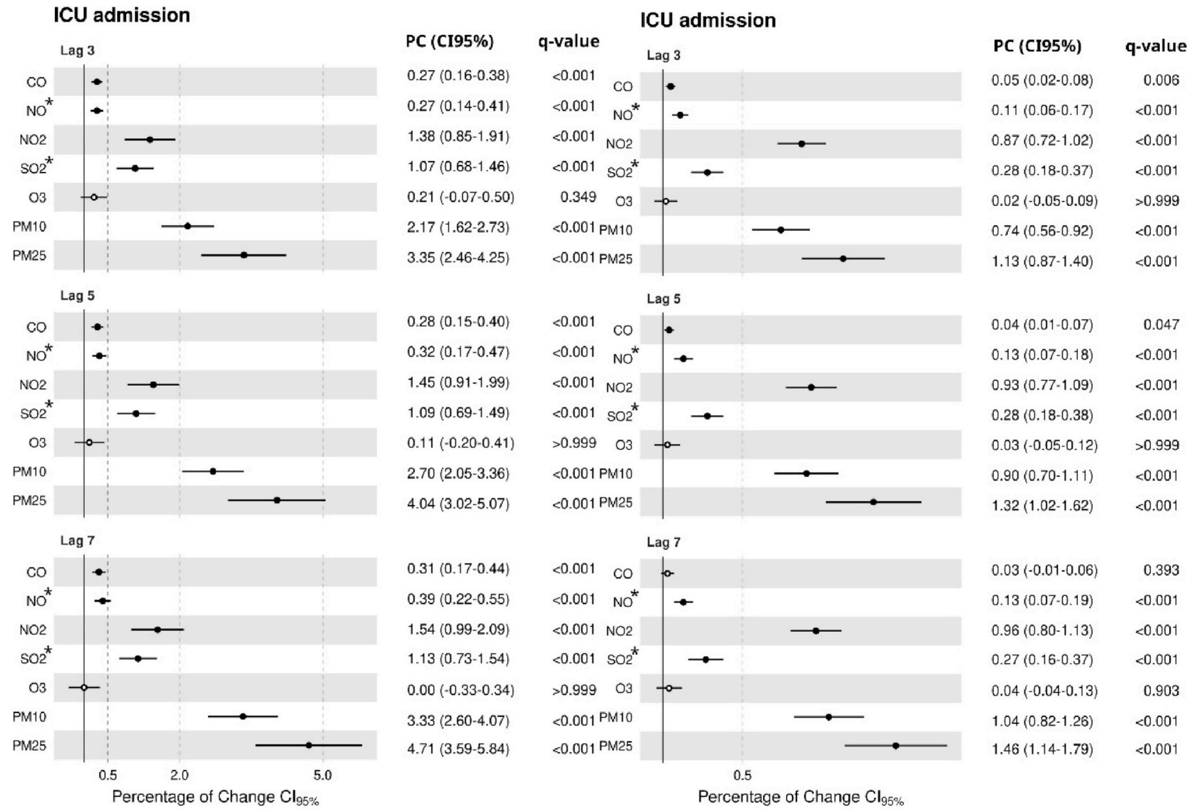
Table 1 shows all patients' clinical and epidemiological characteristics stratified by waves. Overall, the median age was 69 years, and 56% were men. The hospital stay was seven days, in-hospital mortality was 15.9%, ICU admission was 8.8%, and ICU mortality was close to 30%. A difference in in-hospital mortality between waves was found, with the epidemiological characteristics remaining constant.

3.2. Environmental conditions in 2020

During the lockdown in 2020, NO, NO_2, and SO_2 levels were lower and CO, O_3 PM_{10}, and $PM_{2.5}$ levels were higher compared to post-lockdown (Appendix A, Figure A1, and A2). In order to look for a seasonal pattern, the previous year and the year after were also studied. Compared to those years, overall pollution was lower in 2020. However, differences corresponding to lock-down and post-lockdown periods are equally observed. Therefore, a separate analysis of 2020 would be appropriate to discard the seasonal effect.

3.3. Environmental conditions related to COVID-19 hospital admissions

Fig. 2 shows the association between environmental factors and the number of hospital admission. During the lockdown period (Fig. 2a), all air pollutants were positively associated with hospital admissions, except for O_3. $PM_{2.5}$ had the most significant impact on hospital admission, with a percentage of change (PC) greater than 8% for increments of 1 μg/m^3. Exposures to NO_2, PM_{10}, and SO_2 also impacted hospital admissions, with an increase around 5% for every 1 μg/m^3 increase for the first two pollutants and 0.1 μg/m^3 for the third, in the moving average (Fig. 2a).). Although the negative impact of some air pollution was maintained in the post-lockdown period, it was not as high as in the lockdown period. The PC for $PM_{2.5}$ was around 3–4% for increases of 1 μg/m^3 in the moving average (Fig. 2b). Besides, a similar



(a) Lockdown period. (b) Post-lockdown period.

Fig. 4. Summary of the association between environmental factors and ICU admissions due to COVID-19. Abbreviations: PC: Percentage of change (%), computed by GAM adjusted for temperature, humidity, and day of the week. (*) Increases of 0.1 μg/m^3 for NO and SO_2. $CI_{95\%}$, 95% of the confidence interval. Lag: Moving average lag effect at 3,5 and 7 days. q-value: False discovery rate q-value. Note that the x-axes have different scales.

pattern was observed for NO_2 and PM_{10}. However, SO_2 considerably decreased in this period (Fig. 2b).

3.4. Environmental conditions related to COVID-19 hospital mortality

During the lockdown, the negative impact of $PM_{2.5}$ was present in the hospital mortality with a PC around 5% for increases of 1 μg/m^3 in the moving average at lag 3, 5, and 7 days. Also PM_{10},NO_2, and SO_2, showed a negative impact on hospital mortality with a PC of at least 2% for increases of 1 μg/m^3 (PM_{10} and NO_2), and 0.1 μg/m^3 (SO_2) in the moving average at 3, 5, and 7 days (Fig. 3a). Also, NO presented a PC of at least 1% for increases of 0.1 μg/m^3 in the moving average at lag 3, 5, and 7 days. On.

The contrary, a lesser impact of environmental conditions was observed on hospital mortality during the post-lockdown period (Fig. 3b).

3.5. Environmental conditions related to COVID-19 ICU admissions

The effect of environmental conditions during lockdown showed PM_{10} and PM_{25} had the strongest association with ICU admission, with a PC between 2 and 4% for increases of 1 μg/m^3 in the moving average at lag 3,5 and 7 days. Likewise, NO_2 and SO_2 were associated with ICU admission. By contrast, the impact of pollutants in the post-lockdown was lesser and the strongest association was present for $PM_{2.5}$ with a Pc of 1% for increases of 1 μg/m^3 in the moving average at lag 3,5 and 7 days (Fig. 4a and b).

3.6. Environmental conditions related to COVID-19 ICU mortality

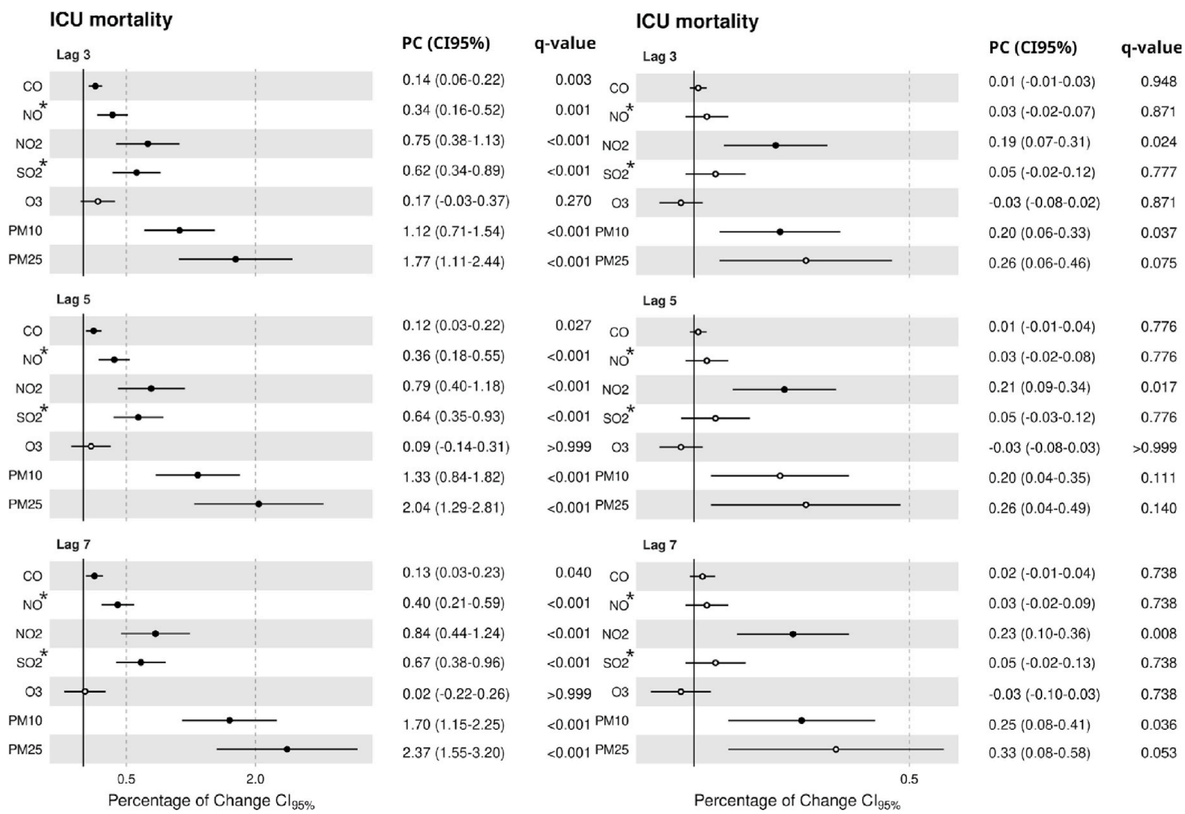
Fig. 5 shows the environmental effect on ICU mortality, but this was evident only during the lockdown for $PM_{2.5}$ and PM_{10} (Fig. 5a). During post-lockdown (Fig. 5b), a different picture from the one previously detected was observed. Only exposures to $PM_{2.5}$ and PM_{10} showed a slight effect on ICU mortality with PC around 0.25% for increases of 1 μg/m^3 in the moving average at lag 3, and 7 days (Fig. 5b).

3.7. Sensitivity analysis

Using the environmental factors that presented an association with the events studied, the sensitivity analysis determined that in the lockdown period, close to 65% of admissions, hospital mortality, ICU admissions, and ICU mortality happened when the moving average at 3 days was over 162 μg/m^3 for CO, over 0.9 μg/m^3 for SO_2, 3.1 μg/m^3 for NO_2, 0.2 μg/m^3 for NO, 9.8 μg/m^3 for PM_{10}, and 8.5 μg/m^3 for $PM_{2.5}$ (Fig. 6).

In the post-lockdown period, the environmental values associated with significant differences in the means of each outcome were similar to those obtained in the lockdown period. However, although the segmentation performed provided cut-offs for which the mean of the number of events was significantly different, the distribution of the events during the post-lockdown is more uniform than that obtained in the lockdown period (see Appendix A Figure A3). Similar patterns were found for lag5 and lag7 days (data not shown).

We stratified the patients according to previous CLRD to analyze the as-sociation between environmental factors and clinical events. When patients did not have CLRD, the association of environmental factors with the out-comes studied remained in the same direction as when the



(a) Lockdown period. (b) Post-lockdown period.

Fig. 5. Summary of the association between environmental factors and ICU mortality due to COVID-19. Abbreviations: PC: Percentage of change (%), computed by GAM adjusted for temperature, humidity, and day of the week. (*) Increases of 0.1 μg/m^3 for NO and SO_2. $CI_{95\%}$, 95% of the confidence interval. Lag: Moving average lag effect at 3,5 and 7 days. q-value: False discovery rate q-value. Note that the x-axes have different scales.

population was not stratified (see Appendix A Table A2). However, when the previous CLRD was considered, the effect of environmental factors was reduced in all clinical events analyzed, particularly in ICU-related clinical events (admission and death) (see Appendix A Table A3).

4. Discussion

This report analyzes the influence of environmental factors on hospital admission, hospital mortality, ICU admission, and ICU mortality in COVID- 19 patients during the lockdown and post-lockdown periods in 2020. Those outcomes were significantly affected mainly by $PM_{2.5}$, NO_2, PM_{10}, and SO_2 specially in the lockdown. Additionally, we determined the values at which an increase in admissions, in-hospital mortality, ICU admissions, and ICU mortality would be observed three days later.

The lockdown in many countries worldwide during the spring of 2020 to prevent the spread of COVID-19 significantly impacted the quality of life in most areas (Choi et al., 2021). As one of the countries most affected by the COVID-19 pandemic, Spain implemented one of the most strict confinement measures (Domínguez-Amarillo et al., 2020). Most studies agree on a global decrease in pollution during the lockdown (Srivastava, 2021). However, a few studies found no differences from previous years (Schiermeier, 2020; Jia et al., 2020; Varotsos et al., 2021). In our study, although 2020 was less polluted, the differences between the lockdown and post-lockdown periods were not as significant as we initially

Expected. Different factors are probably involved in those results. First, after the lockdown, some cities returned rapidly to their usual pollution levels, while in others, levels remained relatively low for a while (Jevtic et al., 2021). And second, meteorological conditions affecting pollution levels are usually repeated year after year.

When comparing both periods (lockdown and post-lockdown), the short-term impact of air pollutants is higher during the lockdown. Still, there are many factors that we must take into consideration. First, the traffic, aviation, industrial activities, and shipping reduction did not recover immediately. Second, home-based work was prolonged for more than a year in many sectors, 2020 summer holiday trips remained local, and mobility restrictions were imposed in Spain in the autumn of 2020 as cases increased dramatically (Gobierno de España, 2020). The use of masks outdoors was also implemented in Spain at the end of June 2020. And third, the confinement from March to May 2020 in Spain involved an intense use of home heating systems, which has previously been described from data all over Europe (Menut et al., 2020).

The difficult task of relating COVID-19 disease with air pollutants has been attempted since the early days of the pandemic (Zang et al., 2022). Those studies have initially established relationships between air pollutants and COVID- 19 transmission, particularly $PM_{2.5}$ (Wang et al., 2020; Tateo et al., 2022), but also PM_{10}, CO, NO_2, and O_3 (Zhu et al., 2020; Copat et al., 2020). Many mortality studies have been performed worldwide (Bozack et al., 2022; Coker et al., 2020; Hendryx and Luo, 2020; Wu et al., 2020), but only a few studies contemplating a short term analysis (Jiang and Xu, 2021; Khorsandi et al., 2021). Those agree that $PM_{2.5}$ is related to higher mortality. Also, $PM_{2.5}$, PM_{10} and O_3 were associated with higher mortality and hospitalization rates (Khorsandi et al., 2021). Our results are aligned with previous findings in which $PM_{2.5}$ was associated with hospitalization, remarking the additional impact of PM_{10} and SO_2 on mortality. Additionally, our results show that NO should be considered in future studies since it has a critical and explainable impact on COVID-19 outcomes. NO and small amounts of NO_2 are generated by traffic, heating, and industrial processes, but the latter mainly derives from NO conversion in the atmosphere. Therefore,

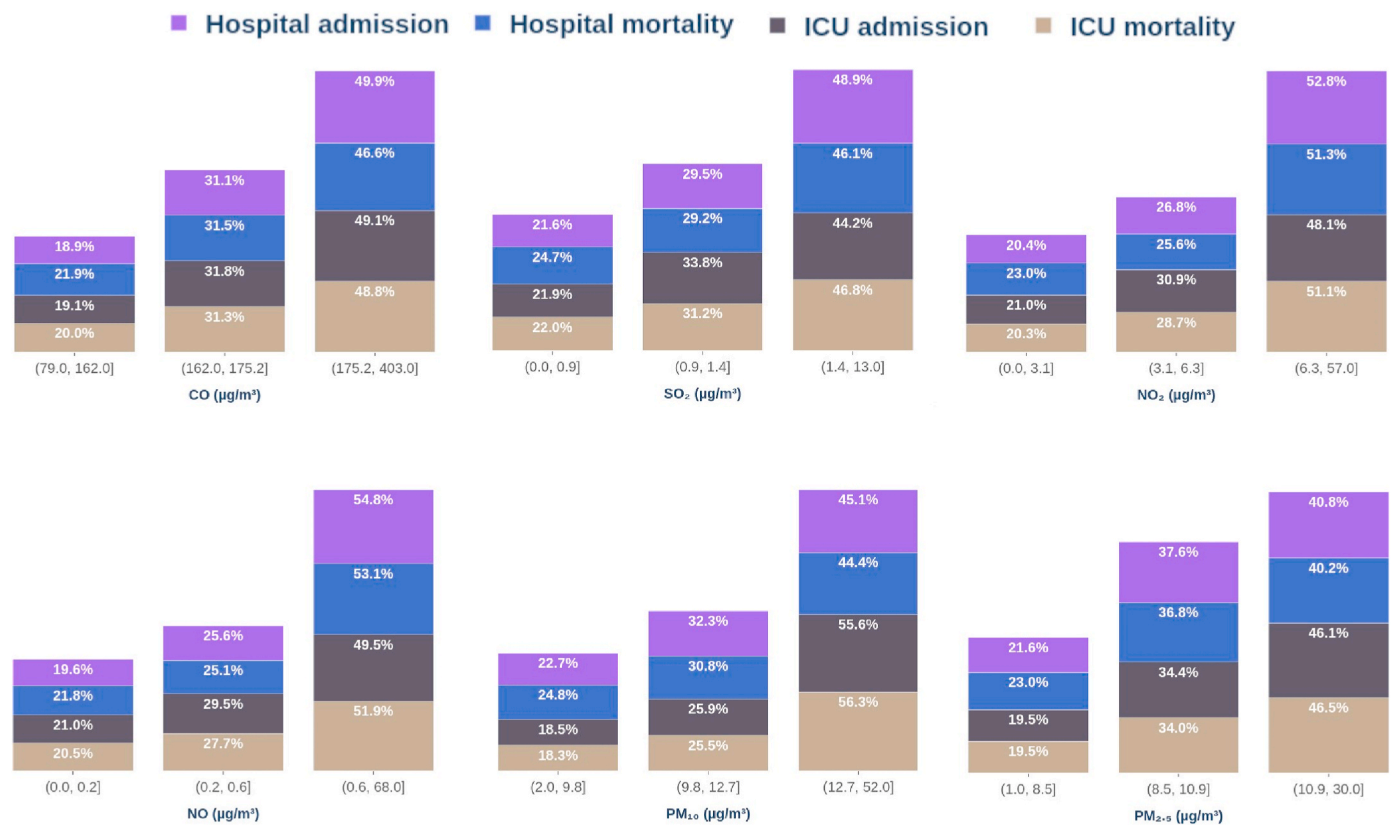


Fig. 6. Summary of the distribution of each pollutant with its cut-off value for each outcome, obtained by multi-output decision tree regression at lag3 days during lockdown.

it is essential not to limit studies to the influence of NO_2 but to broaden them to NO_x (Ayuntamiento de Valladolid, 2022).

It is well-known air pollutants have a short-term and long-term impact on human health. On the one hand, they alter the functions of lung cells, increasing oxidative stress and inflammation and altering the immune responses which favor viral infections (Boningari and Smirniotis, 2016; Copat et al., 2020; Ray and Kim, 2014). Also, a relationship between acute exposure and cardiovascular problems, including stroke, cardiac arrest, and thrombosis, has been described (Robertson and Miller, 2018). On the other hand, those processes

Lead to fibrosis that reduces pulmonary function, mediating the development, maintenance, and exacerbation of obstructive airway diseases and favoring infectious diseases (Feng et al., 2016). The relation between the aforementioned mechanisms and COVID-19 has also been proposed (Bourdrel et al., 2021; Woodby et al., 2020). In fact, those effects have been similarly described for different respiratory viruses (Domingo and Rovira, 2020). Additionally, it has been suggested that pollutant particles could be acting as transporters for SARS-CoV-2 (Martelletti and Martelletti, 2020),a theory that should be carefully studied.

Although not many studies include SO_2 among the air pollutants studied regarding COVID-19, to our knowledge, no evidence has been described before that a positive correlation exists with COVID-19 outcomes. In contrast, a negative correlation between SO_2 and mortality has been found in a couple of studies (Jiang and Xu, 2021; Zhu et al., 2020). Interestingly, the short-term effects of SO_2 were described 25 years ago (Katsouyanni et al., 1997; Stieb et al., 2002, 2003; Sunyer et al., 2003a, b) as a potent irritant contributing to airway inflammation. However, its implications are still controversial, suggesting it could contribute as a co-factor of other pollutants (Kan et al., 2010).

In addition, the cut-off values provided in our study could help us in two directions. On the one hand, it can help us predict when hospital demands will increase if those limits are exceeded the previous 3 days. On the other hand, they can be set as limits of pollution allowed to prevent these events from happening. Although, this has not been performed before, we consider this should be further studied.

A potential bias to consider is that there were changes in patient management during the study period, especially during the first wave. The overflow of patients and the increase in medical personnel with little experience in the management of critical patients could have influenced the outcome of patients with COVID-19. The MBDS database does not have information on the medical staff who care for the patients and their previous experience, so we cannot analyze their real influence on the outcome of these patients.

Overall, we showed associations between four air pollutants ($PM_{2.5}$, PM_{10}, NO_2, and SO_2) and different clinical outcomes, with similar patterns, despite the impact of the post-lockdown period. The short-term exposure with lags (3, 5, 7d) was assessed because the incubation period of COVID-19 ranges from 1 to 7 days. Thus, the relevant role of PM2.5, PM10, NO2, and SO2 could be due to their direct pathological effects on the lower respiratory tract, which could increase the severity of COVID-19. Moreover, three air pollutants (CO, NO, and O_3) did not show a significant short-term impact, but a possible direct or indirect long-term impact cannot be ruled out.

CLRD is a major predictor of severe outcomes in COVID-19 patients. (Beltramo et al., 2021; Gerayeli et al., 2021). We conducted a sensitivity analysis to evaluate the impact of previous CLRD on the relationship between environmental factors and clinical events, finding previous CLRD diluted this association with the clinical events analyzed, particularly in the ICU. It is possible that the impact of environmental contaminants on the clinical outcomes of COVID-19 is more evident in the absence of CLRD and that the presence of CLRD dilutes or cancels this association because it is already a risk factor for severe COVID- 19.

4.1. Limitations of the study

The main limitations are: (i) The retrospective design could introduce biases. (ii) There was no relevant clinical information to interpret the COVID- 19 infection (iii) The accuracy of the MBDS for COVID-19 diagnosis was not evaluated, generating a confusion bias. (iv) Records of ICU admitted patients only include length of stay but not whether it was at the time of admission or later on. (v) We did not have data on indoor air contaminants, which may also influence susceptibility to COVID-19 infection.

Our study also has several strengths that must be considered: (i) This nationwide study covers around 47 million population and all postcodes including all hospitalizations due to COVID-19 in 2020, unlike studies in individual regions or hospitals. (ii) We use data at the postcode level, and exposures were linked in a fine 10 km^2 grid rather than a few stations.

5. Conclusions

Short-term exposure to air pollutants impacts COVID-19 outcomes. During the lockdown, $PM_{2.5}$, PM_{10}, NO_2, but also SO_2, significantly impacted hospital admission, hospital mortality, and ICU admission. ICU mortality was mainly associated with $PM_{2.5}$ and PM_{10} during the same period. The influence of pollutants in COVID-19 outcomes during the post-lockdown period was much lower. Our findings reveal the importance of monitoring air pollutants in respiratory infectious diseases.

Credit author statement

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Consent for publication

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A

Table A1
Spearman's correlation matrix among environmental factors. Abbreviations: CO: Carbon monoxide; NO: Nitrogen monoxide; NO_2: Nitrogen dioxide; SO_2: Sulfur dioxide; O_3: Ozone; PM_{10}: Particulate matter < 10 µm; $PM_{2.5}$:Particulate matter < 2.5 µm; RH: Relative Humidity; Temp: Temperature above 2m surface; *: p-value < 0.001

	CO	NO	NO_2	SO_2	PM_{10}	PM2.5	O_3	RH	Temp
CO	1.00								
NO	0.56*	1.00							
NO_2	0.63*	0.96*	1.00						
SO_2	0.51*	0.73*	0.76*	1.00					
PM_{10}	0.29*	0.47*	0.51*	0.48*	1.00				
PM2.5	0.40*	0.54*	0.59*	0.51*	0.94*	1.00			
O_3	−0.63*	−0.43*	−0.48*	−0.28*	−0.17*	−0.28*	1.00		
RH	0.37*	0.00	0.10*	0.00	0.05	0.09	−0.60	1.00	
Temp	−0.55*	−0.17*	−0.21*	−0.05*	0.12*	0.03*	0.67*	−0.60*	1.00

Table A.2
Summary of the association between environmental factors and clinical out-comes due to COVID-19 in patients without chronic lower respiratory disease. Abbreviations: PC: Percentage of change (%), computed by GAM adjusted for temperature, humidity, and day of the week. (*) Increases of 0.1 µg/m^3 for NO and SO_2. $CI_{95\%}$, 95% of the confidence interval. Lag: Moving average lag effect at 3, 5 and 7 days. q-value: False discovery rate q-value

		Hospital Admission		Hospital Mortality	
		First Wave	Second Wave	First Wave	Second Wave

(continued on next page)

Table A.2 (*continued*)

		Hospital Admission						Hospital Mortality					
		First Wave			Second Wave			First Wave			Second Wave		
Enviromental factor	Lag	**N.° events**	**PC (CI95%)**	**q-value**	**N.° events**	**PC (CI95%)**	**q-value**	N.° events	PC (CI95%)	**q-value**	N.° events	PC (CI95%)	**q-value**
CO	Lag 3	88,905	1.12 (1.03–1.20)	<0.001	91,280	0.28 (0.25–0.31)	<0.001	16,154	0.44 (0.36–0.51)	<0.001	12,950	0.07 (0.05–0.09)	<0.001
Enviromental factor	Lag	**N.° events**	**PC (CI95%)**	**q-value**	**N.° events**	**PC (CI95%)**	**q-value**	N.° events	PC (CI95%)	**q-value**	N.° events	PC (CI95%)	**q-value**
CO	Lag 3	88,905	1.12 (1.03–1.20)	<0.001	91,280	0.28 (0.25–0.31)	<0.001	16,154	0.44 (0.36–0.51)	<0.001	12,950	0.07 (0.05–0.09)	<0.001
NO*	Lag 3	88,905	2.04 (1.87–2.22)	**<0.001**	91,280	0.25 (0.21–0.29)	**<0.001**	16,154	0.94 (0.76–1.12)	**<0.001**	12,950	0.09 (0.05–0.14)	**<0.001**
NO2	Lag 3	88,905	5.40 (4.98–5.81)	**<0.001**	91,280	2.13 (2.01–2.25)	**<0.001**	16,154	2.13 (1.77–2.50)	**<0.001**	12,950	0.53 (0.42–0.65)	**<0.001**
SO2*	Lag 3	88,905	4.25 (3.96–4.55)	**<0.001**	91,280	0.79 (0.71–0.87)	**<0.001**	16,154	1.81 (1.55–2.07)	**<0.001**	12,950	0.20 (0.12–0.27)	**<0.001**
O3	Lag 3	88,905	0.00 (−0.22–0.23)	>0.999	91,280	0.00 (−0.06–0.06)	>0.999	16,154	0.07 (−0.12–0.26)	>0.999	12,950	−0.02 (−0.07–0.04)	>0.999
PM10	Lag 3	88,905	4.38 (3.97–4.79)	**<0.001**	91,280	1.84 (1.68–2.00)	**<0.001**	16,154	2.34 (1.97–2.70)	**<0.001**	12,950	0.49 (0.36–0.63)	**<0.001**
PM25	Lag 3	88,905	8.38 (7.68–9.09)	**<0.001**	91,280	3.01 (2.78–3.25)	**<0.001**	16,154	3.89 (3.28–4.51)	**<0.001**	12,950	0.71 (0.51–0.92)	**<0.001**
CO	Lag 5	88,905	1.22 (1.12–1.31)	**<0.001**	91,280	0.30 (0.28–0.33)	**<0.001**	16,154	0.47 (0.39–0.56)	**<0.001**	12,950	0.08 (0.06–0.10)	**<0.001**
NO*	Lag 5	88,905	1.97 (1.80–2.13)	**<0.001**	91,280	0.27 (0.23–0.31)	**<0.001**	16,154	1.00 (0.81–1.18)	**<0.001**	12,950	0.11 (0.06–0.16)	**<0.001**
NO2	Lag 5	88,905	5.44 (5.02–5.87)	**<0.001**	91,280	2.28 (2.16–2.41)	**<0.001**	16,154	2.25 (1.87–2.62)	**<0.001**	12,950	0.59 (0.46–0.71)	**<0.001**
SO2*	Lag 5	88,905	4.33 (4.03–4.64)	**<0.001**	91,280	0.83 (0.74–0.91)	**<0.001**	16,154	1.88 (1.61–2.15)	**<0.001**	12,950	0.20 (0.12–0.28)	**<0.001**
O3	Lag 5	88,905	−0.25 (−0.49–0.00)	0.124	91,280	0.01 (−0.06–0.07)	>0.999	16,154	−0.12 (−0.33–0.09)	0.670	12,950	−0.01 (−0.06–0.05)	>0.999
PM10	Lag 5	88,905	5.30 (4.83–5.79)	**<0.001**	91,280	2.20 (2.02–2.38)	**<0.001**	16,154	2.90 (2.48–3.32)	**<0.001**	12,950	0.57 (0.42–0.73)	**<0.001**
PM25	Lag 5	88,905	9.73 (8.93–10.54)	**<0.001**	91,280	3.46 (3.20–3.72)	**<0.001**	16,154	4.72 (4.03–5.42)	**<0.001**	12,950	0.80 (0.57–1.02)	**<0.001**
CO	Lag 7	88,905	1.33 (1.22–1.43)	**<0.001**	91,280	0.32 (0.29–0.35)	**<0.001**	16,154	0.54 (0.44–0.63)	**<0.001**	12,950	0.08 (0.06–0.11)	**<0.001**
NO*	Lag 7	88,905	2.10 (1.92–2.28)	**<0.001**	91,280	0.29 (0.25–0.33)	**<0.001**	16,154	1.08 (0.89–1.26)	**<0.001**	12,950	0.11 (0.05–0.16)	**<0.001**
NO2	Lag 7	88,905	5.54 (5.11–5.98)	**<0.001**	91,280	2.40 (2.27–2.53)	**<0.001**	16,154	2.44 (2.06–2.82)	**<0.001**	12,950	0.59 (0.46–0.72)	**<0.001**
SO2*	Lag 7	88,905	4.45 (4.13–4.77)	**<0.001**	91,280	0.84 (0.76–0.93)	**<0.001**	16,154	2.00 (1.73–2.28)	**<0.001**	12,950	0.19 (0.11–0.27)	**<0.001**
O3	Lag 7	88,905	−0.50 (−0.76–0.23)	**0.001**	91,280	0.01 (−0.06–0.08)	>0.999	16,154	−0.33 (−0.56–0.10)	**0.012**	12,950	0.01 (−0.05–0.07)	>0.999
PM10	Lag 7	88,905	6.57 (6.04–7.10)	**<0.001**	91,280	2.51 (2.32–2.70)	**<0.001**	16,154	3.66 (3.19–4.12)	**<0.001**	12,950	0.63 (0.46–0.79)	**<0.001**
PM25	Lag 7	88,905	11.19 (10.32–12.08)	**<0.001**	91,280	3.84 (3.57–4.12)	**<0.001**	16,154	5.67 (4.93–6.43)	**<0.001**	12,950	0.83 (0.59–1.08)	**<0.001**
ICU Admission ICU Mortality													
CO	Lag 3	7977	0.26 (0.15–0.38)	**<0.001**	8543	0.05 (0.02–0.08)	**0.008**	2623	0.13 (0.05–0.21)	**0.004**	2478	0.00 (−0.02–0.03)	>0.999
NO*	Lag 3	7977	0.65 (0.38–0.92)	**<0.001**	8543	0.10 (0.05–0.16)	**<0.001**	2623	0.31 (0.12–0.49)	**0.004**	2478	0.02 (−0.03–0.06)	>0.999
NO2	Lag 3	7977	1.30 (0.76–1.85)	**<0.001**	8543	0.77 (0.62–0.92)	**<0.001**	2623	0.65 (0.28–1.03)	**0.003**	2478	0.15 (0.02–0.27)	0.114
SO2*	Lag 3	7977	1.01 (0.61–1.41)	**<0.001**	8543	0.25 (0.16–0.35)	**<0.001**	2623	0.55 (0.28–0.83)	**<0.001**	2478	0.03 (−0.04–0.10)	>0.999
O3	Lag 3	7977	0.27 (−0.02–0.55)	0.171	8543	0.03 (−0.04–0.11)	0.984	2623	0.21 (0.02–0.41)	0.087	2478	−0.03 (−0.09–0.02)	>0.999
PM10	Lag 3	7977	2.04 (1.47–2.61)	**<0.001**	8543	0.65 (0.46–0.83)	**<0.001**	2623	1.01 (0.60–1.42)	**<0.001**	2478	0.21 (0.07–0.35)	**0.060**
PM25	Lag 3	7977	3.12 (2.21–4.04)	**<0.001**	8543	0.98 (0.71–1.25)	**<0.001**	2623	1.55 (0.89–2.20)	**<0.001**	2478	0.28 (0.07–0.48)	**0.075**
CO	Lag 5	7977	0.26 (0.13–0.39)	**<0.001**	8543	0.04 (0.01–0.07)	0.068	2623	0.11 (0.02–0.20)	0.054	2478	0.01 (−0.02–0.03)	>0.999
NO*	Lag 5	7977	0.64 (0.37–0.92)	**<0.001**	8543	0.12 (0.06–0.18)	**<0.001**	2623	0.32 (0.13–0.51)	**0.004**	2478	0.02 (−0.03–0.07)	>0.999
NO2	Lag 5	7977	1.33 (0.77–1.90)	**<0.001**	8543	0.83 (0.67–0.99)	**<0.001**	2623	0.66 (0.27–1.05)	**0.004**	2478	0.16 (0.03–0.29)	0.129
SO*2	Lag 5	7977	1.01 (0.60–1.42)	**<0.001**	8543	0.26 (0.15–0.36)	**<0.001**	2623	0.56 (0.27–0.84)	**0.001**	2478	0.02 (−0.05–0.10)	>0.999

(*continued on next page*)

Table A.2 (*continued*)

		Hospital Admission						Hospital Mortality					
		First Wave			Second Wave			First Wave			Second Wave		
Enviromental factor	Lag	**N.° events**	**PC (CI95%)**	**q-value**	**N.° events**	**PC (CI95%)**	**q-value**	N.° events	PC (CI95%)	**q-value**	N.° events	PC (CI95%)	**q-value**
CO	Lag 3	88,905	1.12 (1.03–1.20)	<0.001	91,280	0.28 (0.25–0.31)	<0.001	16,154	0.44 (0.36–0.51)	<0.001	12,950	0.07 (0.05–0.09)	<0.001
O3	Lag 5	7977	0.19 (−0.13–0.50)	0.640	8543	0.04 (−0.04–0.12)	0.794	2623	0.16 (−0.06–0.38)	0.427	2478	−0.03 (−0.09–0.03)	>0.999
PM10	Lag 5	7977	2.50 (1.83–3.17)	**<0.001**	8543	0.80 (0.59–1.00)	**<0.001**	2623	1.15 (0.67–1.64)	**<0.001**	2478	0.20 (0.04–0.36)	0.129
PM25	Lag 5	7977	3.67 (2.62–4.72)	**<0.001**	8543	1.16 (0.86–1.46)	**<0.001**	2623	1.71 (0.95–2.46)	**<0.001**	2478	0.27 (0.04–0.50)	0.132
CO	Lag 7	7977	0.28 (0.14–0.42)	**<0.001**	8543	0.02 (−0.01–0.06)	0.506	2623	0.10 (0.01–0.20)	0.116	2478	0.01 (−0.01–0.04)	>0.999
NO*	Lag 7	7977	0.68 (0.40–0.96)	**<0.001**	8543	0.12 (0.06–0.19)	**<0.001**	2623	0.35 (0.16–0.54)	**0.001**	2478	0.02 (−0.03–0.08)	>0.999
NO2	Lag 7	7977	1.42 (0.85–2.00)	**<0.001**	8543	0.85 (0.69–1.02)	**<0.001**	2623	0.72 (0.32–1.11)	**0.001**	2478	0.18 (0.05–0.32)	0.100
SO2*	Lag 7	7977	1.05 (0.63–1.47)	**<0.001**	8543	0.25 (0.14–0.35)	**<0.001**	2623	0.59 (0.30–0.88)	**<0.001**	2478	0.03 (−0.05–0.11)	>0.999
O3	Lag 7	7977	0.08 (−0.26–0.42)	>0.999	8543	0.05 (−0.04–0.13)	0.760	2623	0.08 (−0.16–0.32)	>0.999	2478	−0.03 (−0.10–0.03)	>0.999
PM10	Lag 7	7977	3.10 (2.35–3.86)	**<0.001**	8543	0.93 (0.71–1.15)	**<0.001**	2623	1.45 (0.91–2.00)	**<0.001**	2478	0.21 (0.04–0.38)	0.100
PM25	Lag 7	7977	4.29 (3.15–5.44)	**<0.001**	8543	1.30 (0.98–1.63)	**<0.001**	2623	1.99 (1.17–2.81)	**<0.001**	2478	0.31 (0.06–0.56)	0.100

Table A.3

Summary of the association between environmental factors and clinical out-comes due to COVID-19 in patients with chronic lower respiratory disease. Abbreviations: PC: Percentage of change (%), computed by GAM adjusted for temperature, humidity, and day of the week. (*) Increases of 0.1 μg/m^3 for NO and SO_2. $CI_{95\%}$, 95% of the confidence interval. Lag: Moving average lag effect at 3, 5 and 7 days. q-value: False discovery rate q-value

		Hospital Admission						Hospital Mortality					
		First Wave			Second Wave								
Enviromental factor	Lag	**N.° events**	**PC (CI95%)**	Enviromental factor	Lag	**N.° events**	**PC (CI95%)**	Enviromental factor	Lag	**N.° events**	**PC (CI95%)**	Enviromental factor	Lag
CO	Lag 3	14,249	0.41 (0.32–0.49)	<0.001	14,310	0.08 (0.05–0.11)	<0.001	3163	0.12 (0.05–0.18)	0.002	2600	0.03 (0.00–0.05)	0.059
NO*	Lag 3	14,249	0.36 (0.27–0.46)	**<0.001**	14,310	0.10 (0.06–0.14)	**<0.001**	3163	0.26 (0.11–0.40)	**0.002**	2600	0.04 (0.00–0.08)	0.092
NO2	Lag 3	14,249	2.00 (1.59–2.42)	**<0.001**	14,310	0.91 (0.78–1.05)	**<0.001**	3163	0.60 (0.29–0.90)	**<0.001**	2600	0.28 (0.18–0.39)	**<0.001**
SO2*	Lag 3	14,249	1.72 (1.42–2.02)	**<0.001**	14,310	0.38 (0.29–0.47)	**<0.001**	3163	0.55 (0.33–0.78)	**<0.001**	2600	0.13 (0.05–0.20)	**0.003**
O3	Lag 3	14,249	0.11 (−0.11–0.33)	0.821	14,310	0.03 (−0.04–0.10)	>0.999	3163	0.01 (−0.15–0.17)	>0.999	2600	−0.00 (−0.05–0.05)	>0.999
PM10	Lag 3	14,249	2.53 (2.11–2.96)	**<0.001**	14,310	1.06 (0.88–1.23)	**<0.001**	3163	1.10 (0.79–1.42)	**<0.001**	2600	0.31 (0.18–0.44)	**<0.001**
PM25	Lag 3	14,249	4.19 (3.49–4.90)	**<0.001**	14,310	1.58 (1.33–1.83)	**<0.001**	3163	1.55 (1.04–2.07)	**<0.001**	2600	0.43 (0.24–0.63)	**<0.001**
CO	Lag 5	14,249	0.44 (0.34–0.54)	**<0.001**	14,310	0.09 (0.05–0.12)	**<0.001**	3163	0.11 (0.04–0.18)	**0.010**	2600	0.03 (0.01–0.06)	**0.024**
NO*	Lag 5	14,249	0.43 (0.32–0.54)	**<0.001**	14,310	0.12 (0.07–0.16)	**<0.001**	3163	0.25 (0.10–0.40)	**0.004**	2600	0.05 (0.01–0.09)	0.065
NO2	Lag 5	14,249	2.05 (1.63–2.47)	**<0.001**	14,310	0.98 (0.84–1.12)	**<0.001**	3163	0.60 (0.29–0.91)	**0.001**	2600	0.30 (0.19–0.41)	**<0.001**
SO2*	Lag 5	14,249	1.75 (1.44–2.07)	**<0.001**	14,310	0.40 (0.30–0.50)	**<0.001**	3163	0.54 (0.31–0.77)	**<0.001**	2600	0.13 (0.06–0.21)	**0.002**
O3	Lag 5	14,249	0.03 (−0.21–0.27)	>0.999	14,310	0.04 (−0.03–0.12)	0.662	3163	−0.06 (−0.23–0.12)	>0.999	2600	0.00 (−0.05–0.06)	>0.999
PM10	Lag 5	14,249	3.14 (2.64–3.64)	**<0.001**	14,310	1.21 (1.01–1.40)	**<0.001**	3163	1.36 (0.99–1.74)	**<0.001**	2600	0.34 (0.19–0.49)	**<0.001**
PM25	Lag 5	14,249	5.08 (4.27–5.90)	**<0.001**	14,310	1.78 (1.51–2.06)	**<0.001**	3163	1.87 (1.28–2.46)	**<0.001**	2600	0.47 (0.26–0.69)	**<0.001**
CO	Lag 7	14,249	0.50 (0.39–0.60)	**<0.001**	14,310	0.09 (0.06–0.12)	**<0.001**	3163	0.12 (0.04–0.20)	**0.008**	2600	0.04 (0.01–0.06)	**0.009**
NO*	Lag 7	14,249	0.52 (0.41–0.64)	**<0.001**	14,310	0.12 (0.08–0.17)	**<0.001**	3163	0.29 (0.14–0.44)	**0.001**	2600	0.05 (0.01–0.09)	**0.050**
NO2	Lag 7	14,249	2.14 (1.71–2.57)	**<0.001**	14,310	1.04 (0.89–1.18)	**<0.001**	3163	0.68 (0.36–1.00)	**<0.001**	2600	0.32 (0.20–0.43)	**<0.001**

(*continued on next page*)

Table A.3 (*continued*)

		Hospital Admission						Hospital Mortality					
		First Wave			Second Wave								
Enviromental factor	Lag	**N.° events**	**PC (CI95%)**	Enviromental factor	Lag	**N.° events**	**PC (CI95%)**	Enviromental factor	Lag	**N.° events**	**PC (CI95%)**	Enviromental factor	Lag
SO2*	Lag 7	14,249	1.82 (1.50–2.14)	**<0.001**	14,310	0.41 (0.31–0.51)	**<0.001**	3163	0.57 (0.34–0.81)	**<0.001**	2600	0.13 (0.06–0.21)	**0.002**
O3	Lag 7	14,249	−0.09 (−0.34–0.17)	>0.999	14,310	0.05 (−0.03–0.13)	0.501	3163	−0.17 (−0.36–0.02)	0.199	2600	0.02 (−0.04–0.07)	>0.999
PM10	Lag 7	14,249	3.86 (3.31–4.42)	**<0.001**	14,310	1.34 (1.13–1.55)	**<0.001**	3163	1.68 (1.27–2.10)	**<0.001**	2600	0.35 (0.20–0.51)	**<0.001**
PM25	Lag 7	14,249	5.98 (5.10–6.87)	**<0.001**	14,310	1.93 (1.63–2.23)	**<0.001**	3163	2.24 (1.60–2.89)	**<0.001**	2600	0.48 (0.25–0.71)	**<0.001**
ICU Admission ICU Mortality													
CO	Lag 3	1117	0.03 (−0.06–0.11)	>0.999	1278	0.00 (−0.02–0.03)	>0.999	434	−0.04 (−0.12–0.03)	>0.999	495	−0.01 (−0.03–0.01)	>0.999
NO*	Lag 3	1117	0.01 (−0.09–0.11)	>0.999	1278	0.04 (0.00–0.09)	0.143	434	0.02 (−0.12–0.16)	>0.999	495	0.00 (−0.06–0.06)	>0.999
NO2	Lag 3	1117	0.13 (−0.26–0.52)	>0.999	1278	0.24 (0.12–0.37)	**0.003**	434	0.07 (−0.24–0.38)	>0.999	495	0.01 (−0.11–0.13)	>0.999
SO2*	Lag 3	1117	0.17 (−0.12–0.46)	>0.999	1278	0.11 (0.03–0.19)	**0.037**	434	0.05 (−0.18–0.28)	>0.999	495	0.05 (−0.02–0.12)	>0.999
O3	Lag 3	1117	0.24 (0.02–0.46)	0.208	1278	−0.02 (−0.08–0.04)	>0.999	434	−0.03 (−0.20–0.14)	>0.999	495	−0.03 (−0.09–0.03)	>0.999
PM10	Lag 3	1117	0.78 (0.34–1.22)	**0.010**	1278	0.27 (0.12–0.41)	**0.004**	434	0.34 (−0.03–0.72)	>0.999	495	0.08 (−0.06–0.22)	>0.999
PM25	Lag 3	1117	1.06 (0.35–1.77)	**0.032**	1278	0.37 (0.15–0.59)	**0.006**	434	0.35 (−0.21–0.92)	>0.999	495	0.07 (−0.14–0.28)	>0.999
CO	Lag 5	1117	0.04 (−0.06–0.14)	>0.999	1278	0.01 (−0.02–0.04)	>0.999	434	−0.02 (−0.10–0.06)	>0.999	495	0.00 (−0.02–0.03)	>0.999
NO*	Lag 5	1117	0.02 (−0.09–0.13)	>0.999	1278	0.04 (−0.01–0.09)	0.311	434	0.04 (−0.10–0.19)	>0.999	495	0.00 (−0.06–0.07)	>0.999
NO2	Lag 5	1117	0.21 (−0.20–0.61)	>0.999	1278	0.24 (0.11–0.38)	**0.008**	434	0.14 (−0.19–0.46)	>0.999	495	0.03 (−0.10–0.16)	>0.999
SO2*	Lag 5	1117	0.22 (−0.08–0.52)	0.704	1278	0.10 (0.02–0.19)	0.083	434	0.09 (−0.14–0.33)	>0.999	495	0.05 (−0.03–0.13)	>0.999
O3	Lag 5	1117	0.22 (−0.03–0.46)	0.491	1278	0.00 (−0.06–0.07)	>0.999	434	−0.06 (−0.24–0.13)	>0.999	495	−0.02 (−0.08–0.04)	>0.999
PM10	Lag 5	1117	1.04 (0.52–1.57)	**0.002**	1278	0.26 (0.09–0.43)	**0.023**	434	0.47 (0.04–0.90)	0.536	495	0.07 (−0.09–0.24)	>0.999
PM25	Lag 5	1117	1.49 (0.68–2.30)	**0.003**	1278	0.35 (0.10–0.60)	**0.036**	434	0.62 (−0.02–1.26)	0.536	495	0.07 (−0.17–0.31)	>0.999
CO	Lag 7	1117	0.05 (−0.05–0.16)	0.948	1278	0.01 (−0.02–0.04)	>0.999	434	−0.01 (−0.10–0.07)	>0.999	495	0.01 (−0.02–0.04)	>0.999
NO*	Lag 7	1117	0.03 (−0.09–0.16)	>0.999	1278	0.04 (−0.01–0.09)	0.431	434	0.05 (−0.10–0.21)	>0.999	495	0.00 (−0.06–0.07)	>0.999
NO2	Lag 7	1117	0.28 (−0.14–0.69)	0.692	1278	0.25 (0.10–0.39)	**0.012**	434	0.15 (−0.18–0.48)	>0.999	495	0.04 (−0.09–0.18)	>0.999
SO2*	Lag 7	1117	0.27 (−0.04–0.58)	0.555	1278	0.10 (0.01–0.19)	0.110	434	0.10 (−0.15–0.34)	>0.999	495	0.06 (−0.02–0.14)	>0.999
O3	Lag 7	1117	0.18 (−0.07–0.44)	0.692	1278	0.01 (−0.06–0.08)	>0.999	434	−0.07 (−0.28–0.13)	>0.999	495	−0.03 (−0.09–0.04)	>0.999
PM10	Lag 7	1117	1.26 (0.68–1.85)	**<0.001**	1278	0.26 (0.08–0.45)	0.052	434	0.58 (0.10–1.06)	0.336	495	0.09 (−0.08–0.27)	>0.999
PM25	Lag 7	1117	1.73 (0.88–2.60)	**0.001**	1278	0.36 (0.09–0.63)	0.055	434	0.62 (−0.05–1.30)	0.635	495	0.13 (−0.13–0.39)	>0.999

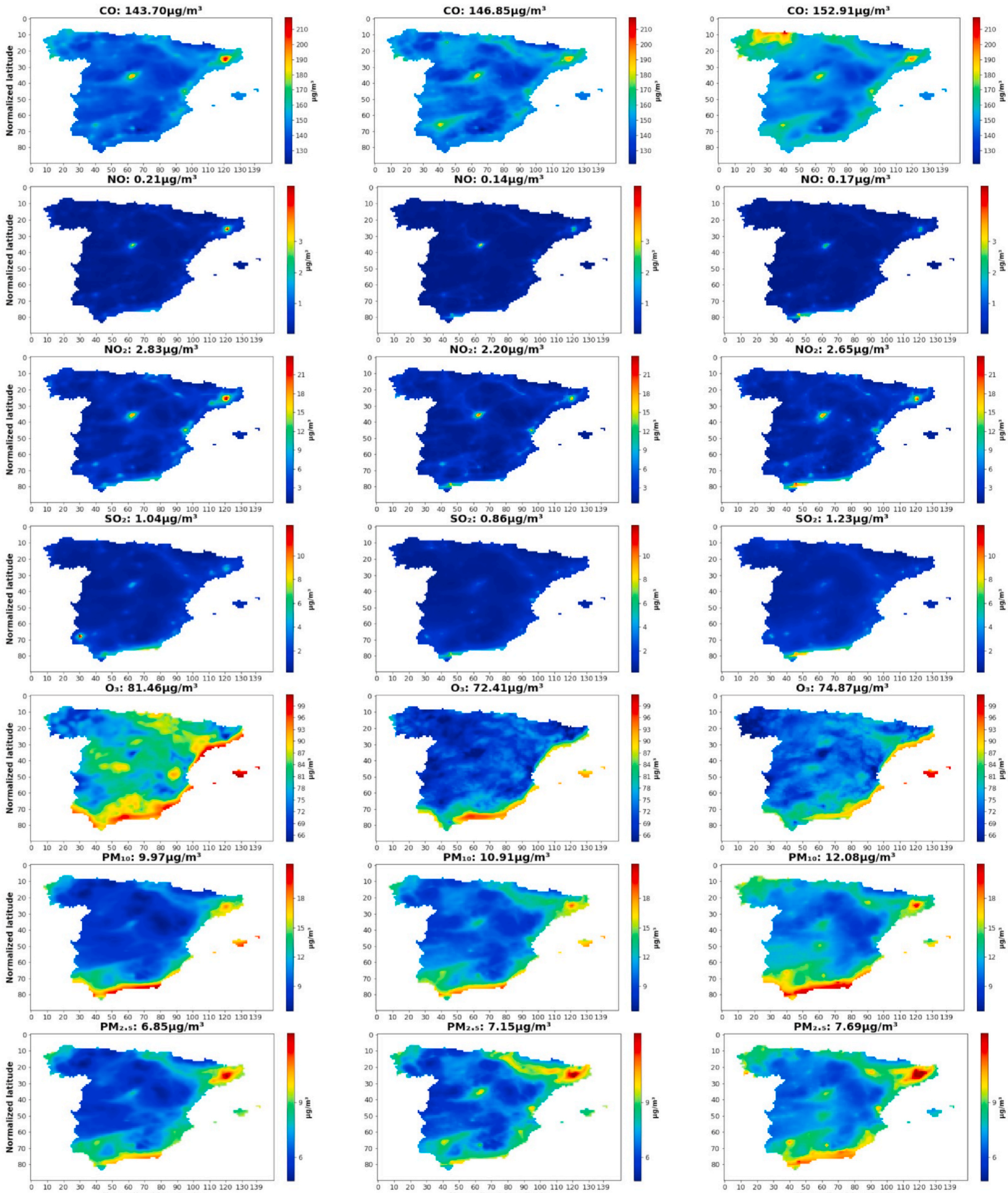

Fig. A.1. Mean of environmental effects in the Lockdown 2020 period (center) compared with the same period in 2019 (left) and 2021 (right)

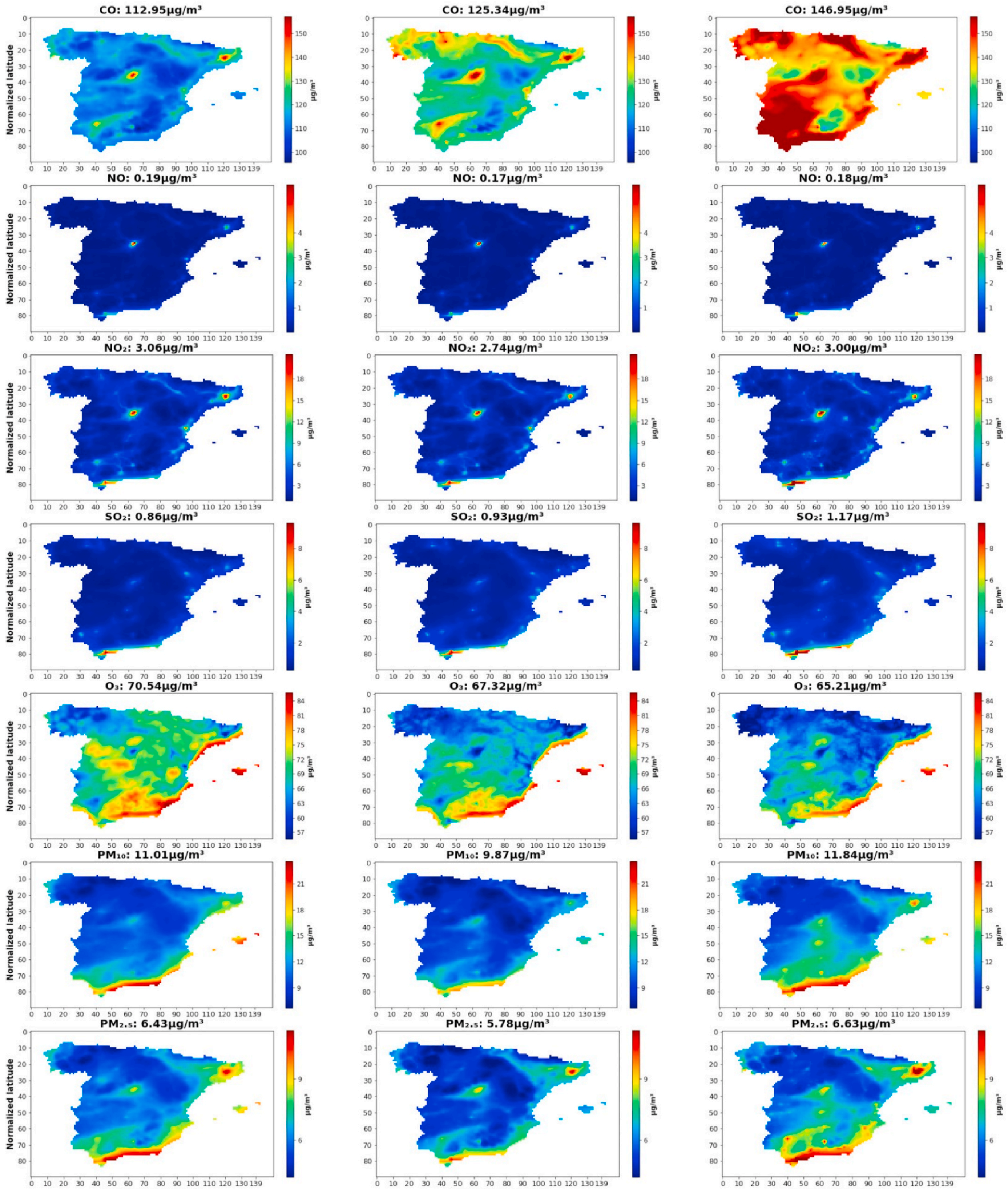

Fig. A.2. Mean of environmental effects in the Post-lockdown 2020 period (center) compared with the same period in 2019 (left) and 2021 (right)

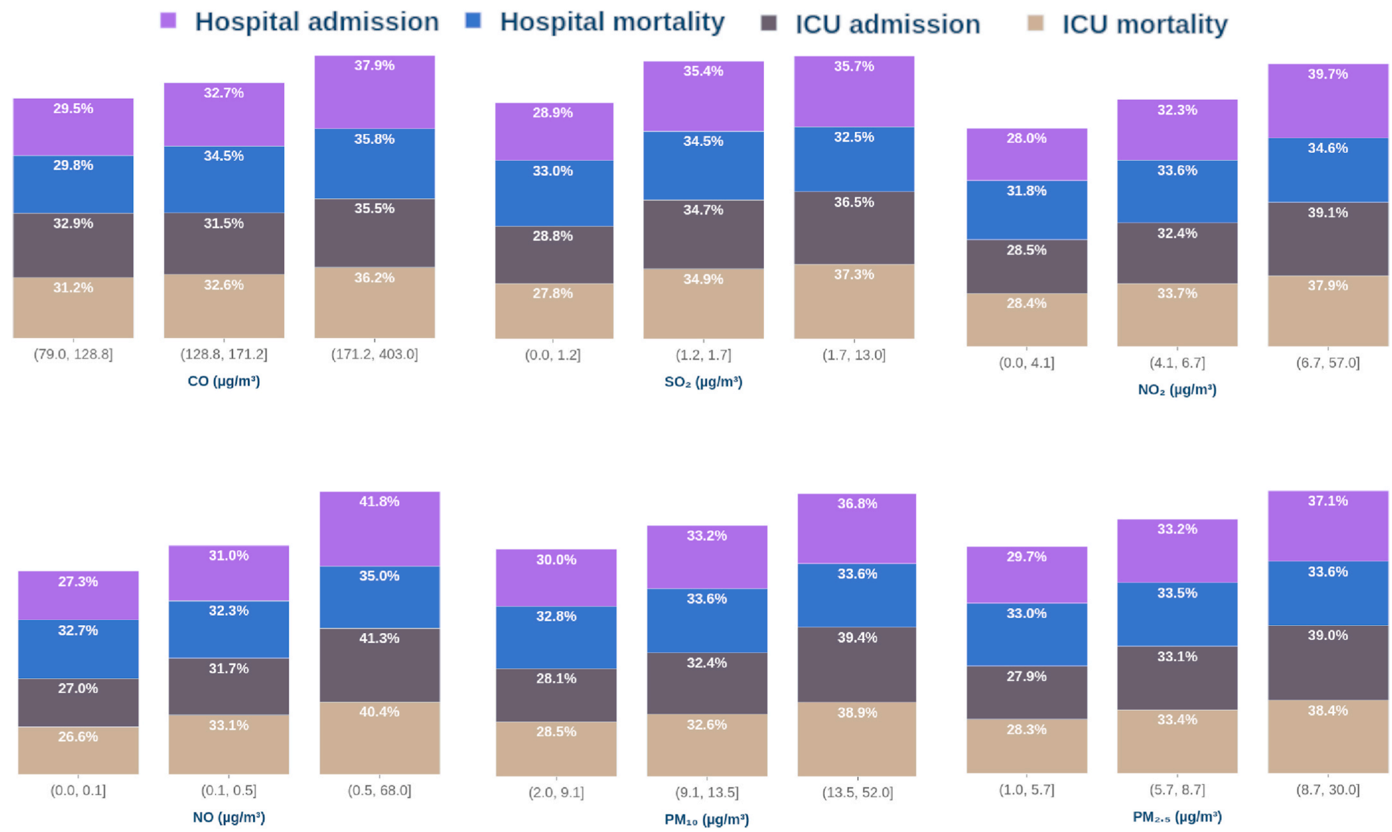

Fig. A.3. Summary of the distribution of each pollutant with its cut-off value for each outcome, obtained by multi-output decision tree regression at lag3 days during post-lockdown

References

Alduchov, O.A., Eskridge, R.E., 1996. Improved magnus form approximation of saturation vapor pressure. J. Appl. Meteorol. Climatol. 35 (4), 601–609. https://doi.org/10.1175/1520-0450(1996)035<0601:IMFAOS>2.0.CO;2.

Ayuntamiento de Valladolid, óxidos de Nitrógeno NO/NO_2. Available at: https://www.valladolid.es/es/rccava/contaminantes/oxidos-nitrogeno-no2–. (Accessed 18 July 2022).

Beltramo, G., Cottenet, J., Mariet, A.-S., Georges, M., Piroth, L., Tubert-Bitter, P., Bonniaud, P., Quantin, C., 2021. Chronic respiratory diseases are predictors of severe outcome in Covid-19 hospitalised patients: a nationwide study. Eur. Respir. J. 58 (6) https://doi.org/10.1183/13993003.04474-2020.

Boletín Oficial del Estado (67): 25390–25400, 2020. 14 de marzo de 2020. ISSN 0212-033X, Real Decreto 463/2020, de 14 de marzo, por el que se declara el estado de alarma para la gestión de la situación de crisis sanitaria ocasionada por el COVID-19. Available at. https://www.boe.es/buscar/doc.php?id=BOE-A-2020-3692. (Accessed 18 July 2022).

Boningari, T., Smirniotis, P.G., 2016. Impact of nitrogen oxides on the environment and human health: Mn-based materials for the NO x abatement. Curr. Opion. Chem. Eng. 13, 133–141. https://doi.org/10.1016/j.coche.2016.09.004.

Bourdrel, T., Annesi-Maesano, I., Alahmad, B., Maesano, C.N., Bind, M.-A., . The impact of outdoor air pollution on covid-19: a review of evidence from "in vitro". Anim Hum stud, Euro- pean Respir.Rev. 30, 200242. https://doi.org/10.1183/16000617.0242-2020.

Bozack, A., Pierre, S., DeFelice, N., Colicino, E., Jack, D., Chillrud, S.N., Rundle, A., Astua, A., Quinn, J.W., McGuinn, L., Yang, Q., Johnson, K., Masci, J., Lukban, L., Maru, D., Lee, A.G., 2022. Long-term air pollution exposure and covid-19 mortality: a patient-level analysis from New York city. Am. J. Respir. Crit. Care Med. 205, 651–662. https://doi.org/10.1164/rccm.202104-0845OC.

Chen, Z., Sidell, M.A., Huang, B.Z., Chow, T., Eckel, S.P., Martinez, M.P., Gheissari, R., Lurmann, F., Thomas, D.C., Gilliland, F.D., Xiang, A.H., 2022. Ambient air pollutant exposures and covid-19 severity and mortality in a cohort of patients with covid-19 in southern California. Am. J. Respir. Crit. Care Med. 206, 440–448. https://doi.org/10.1164/RCCM.202108-1909OC.

Choi, E.P.H., Hui, B.P.H., Wan, E.Y.F., Kwok, J.Y.Y., Tam, T.H.L., Wu, C., 2021. Covid-19 and health-related quality of life: a community based online survey in Hong Kong. Int. J. Environ. Res. Publ. Health 18, 3228. https://doi.org/10.3390/ijerph18063228.

Coker, E.S., Cavalli, L., Fabrizi, E., Guastella, G., Lippo, E., Maria, Parisi, L., Pontarollo, N., Rizzati, M., Varacca, A., Vergalli, S., 2020. The effects of air pollution on Covid-19 related mortality in northern Italy. Environ. Resour. Econ. 76, 611–634. https://doi.org/10.1007/s10640-020-00486-1.

Copat, C., Cristaldi, A., Fiore, M., Grasso, A., Zuccarello, P., Signorelli, S.S., Conti, G.O., Ferrante, M., 2020. The role of air pollution (PM and NO_2) in Covid-19 spread and lethality: a systematic review. Environ. Res. 191, 110129 https://doi.org/10.1016/j.envres.2020.110129.

Domingo, J.L., Rovira, J., 8 2020. Effects of air pollutants on the transmission and severity of respiratory viral infections. Environ. Res. 187 https://doi.org/10.1016/j.envres.2020.109650.

Domínguez-Amarillo, S., Fernández-Agüera, J., Cesteros-García, S., González-Lezcano, R. A., 2020. Bad air can also kill: residential indoor air quality and pollutant exposure risk during the Covid-19 crisis. Int. J. Environ. Res. Publ. Health 17, 7183. https://doi.org/10.3390/ijerph17197183.

Donzelli, G., Cioni, L., Cancellieri, M., Llopis-Morales, A., Morales- Suárez-Varela, M., 2021. Relations between air quality and covid-19 lockdown measures in Valencia, Spain. Int. J. Environ. Res. Publ. Health 18 (5). https://doi.org/10.3390/ijerph18052296.

Dumont, M., Marée, R., Wehenkel, L., Geurts, P., 2009. Fast Multi-Class Image Annotation with Random Subwindows and Multiple Output Randomized Trees, vol. 2, pp. 196–203.

Equipo COVID-19. Red Nacional de Vigilancia Epidemiológica (RENAVE). Centro Nacional de Microbiología (CNM), 2020. Informe n° 32. situación de covid-19 en españa, vol. 5. Instituto de investigación Carlos III (ISCIII). Available at. https://www.isciii.es/QueHacemos/Servicios/VigilanciaSaludPublicaRENAVE/EnfermedadesTransmisibles/Paginas/Informes_Previos_Covid-12_2020.aspx.

Equipo COVID-19. Red Nacional de Vigilancia Epidemiológica (RENAVE). Centro Nacional de Microbiología (CNM), 2021. Informe n° 60. situación de covid-19 en españa, vol. 1. Instituto de investigación Carlos III (ISCIII). Available at. https://www.isciii.es/QueHacemos/Servicios/VigilanciaSaludPublicaRENAVE/EnfermedadesTransmisibles/Paginas/Informes_Previos_Covid-12_2021.aspx.

Feng, S., Gao, D., Liao, F., Zhou, F., Wang, X., 2016. The health effects of ambient pm2.5 and potential mechanisms. Ecotoxicol. Environ. Saf. 128, 67–74. https://doi.org/10.1016/j.ecoenv.2016.01.030.

Gerayeli, F.V., Milne, S., Cheung, C., Li, X., Yang, C.W.T., Tam, A., Choi, L.H., Bae, A., Sin, D.D., 2021. Copd and the Risk of Poor Outcomes in Covid-19: A Systematic Review and Meta-Analysis, vol. 33. https://doi.org/10.1016/j.eclinm.2021.100789.

Gobierno de España, 2020. Crisis sanitaria COVID-19: normativa e información útil. Estado de alarma 25 de octubre 2020. Available at. https://administracion.gob.es/pag_Home/atencionCiudadana/Crisis-sanitaria-COVID-19.html.

Hastie, T., Tibshirani, R., 1990. Generalized Additive Models. Wiley Online Library. https://doi.org/10.1201/9780203753781.

Hendryx, M., Luo, J., 2020. Covid-19 prevalence and fatality rates in association with air pollution emission concentrations and emission sources. Environ. Pollu. 265 (10) https://doi.org/10.1016/J.ENVPOL.2020.115126.

ICD-10-CM, 2022. Diagnosis codes. Available at: www.icd10data.com. (Accessed 18 July 2022).

Jevtic, M., Matkovic, V., van den Hazel, P., Bouland, C., 2021. Environment lockdown, air pollution and related diseases: could we learn something and make it last? Eur. J. Publ. Health 31. https://doi.org/10.1093/eurpub/ckab157 iv36–iv39.

Jia, C., Fu, X., Bartelli, D., Smith, L., 2020. Insignificant impact of the "stay- at-home" order on ambient air quality in the Memphis metropolitan area. u.s.a., Atmosphere 11 (2020), 630. https://doi.org/10.3390/ATMOS11060630. Page 630 11.

Jiang, Y., Xu, J., 2021. The association between covid-19 deaths and short-term ambient air pollution/meteorological condition exposure: a retrospective study from Wuhan, China. Air Qual. Atmos. Health 14, 1–5. https://doi.org/10.1007/s11869-020-00906-7.

Kan, H., Wong, C.-M., Vichit-Vadakan, N., Qian, Z., , the PAPA Project Teams, Vajanapoom, N., Wong, H.K.C., Thach, T., Chau, P., Chan, K., Chung, R., Ou, C., Yang, L., Thomas, G., Lam, T., Hedley, A., Wong, T., Kan, S.H., Chen, B., Zhao, N., Zhang, Y., Yang, N., Wuhan, D.Z., 2010. Short-term association between sulfur dioxide and daily mortality: the public health and air pollution in Asia (papa) study † project teams by location: Bangkok-n. vichit-vadakan and. Environ. Res. 110, 258–264. https://doi.org/10.1016/j.envres.2010.01.006.

Katsouyanni, K., Touloumi, G., Spix, C., Schwartz, J., Balducci, F., Medina, S., Rossi, G., Wojtyniak, B., Sunyer, J., Bacharova, L., Schouten, J.P., Ponka, A., Anderson, H.R., 1997. Short term effects of ambient sulphur dioxide and particulate matter on mortality in 12 European cities: results from time series data from the aphea project. BMJ 314, 1658. https://doi.org/10.1136/bmj.314.7095.1658, 1658.

Khorsandi, B., Farzad, K., Tahriri, H., Maknoon, R., 2021. Association between short-term exposure to air pollution and Covid-19 hospital admission/mortality during warm seasons. Environ. Monit. Assess. 193, 426. https://doi.org/10.1007/s10661-021-09210-y.

Kraemer, M.U.G., Yang, C.-H., Gutierrez, B., Wu, C.-H., Klein, B., Pigott, D.M., null, null, du Plessis, L., Faria, N.R., Li, R., Hanage, W.P., Brownstein, J.S., Layan, M., Vespignani, A., Tian, H., Dye, C., Pybus, O.G., Scarpino, S.V., 2020. The effect of human mobility and control measures on the covid-19 epidemic in China. Science 368 (6490), 493–497. https://doi.org/10.1126/science.abb4218.

Lu, R., Zhao, X., Li, J., Niu, P., Yang, B., Wu, H., Wang, W., Song, H., Huang, B., Zhu, N., Bi, Y., Ma, X., Zhan, F., Wang, L., Hu, T., Zhou, H., Hu, Z., Zhou, W., Zhao, L., Chen, J., Meng, Y., Wang, J., Lin, Y., Yuan, J., Xie, Z., Ma, J., Liu, W.J., Wang, D., Xu, W., Holmes, E.C., Gao, G.F., Wu, G., Chen, W., Shi, W., Tan, W., 2020. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus ori- gins and receptor binding. Lancet 395 (10224), 565–574. https://doi.org/10.1016/S0140-6736(20)30251-8.

Martelletti, L., Martelletti, P., 2020. Air pollution and the novel Covid-19 disease: a putative disease risk factor. SN Compr Clin. Med. 2, 383–387. https://doi.org/10.1007/s42399-020-00274-4.

McCullagh, P., Nelder, J., 1989. Generalized Linear Models. Chapman & Hall CRC. https://doi.org/10.1201/9780203753736.

Menut, L., Bessagnet, B., Siour, G., Mailler, S., Pennel, R., Cholakian, A., 2020. Impact of lockdown measures to combat covid-19 on air quality over western europe. Sci. Total Environ. 741 (11) https://doi.org/10.1016/J.SCITOTENV.2020.140426.

Meteo France, 2022. Institut national de l'environnement industriel et des risques (Ineris), Aarhus University, Norwegian Meteorological Institute (MET Norway), Jülich Institut für Energie- und Klimaforschung (IEK), Institute of Environmental Protection National Research Institute (IEP-NRI), Koninklijk Nederlands Meteorologisch Instituut (KNMI), Nederlandse Organisatie voor toegepast natuurwetenschappelijk onderzoek (TNO), Swedish Meteorological and Hydrological Institute (SMHI), Finnish Meteorological Institute (FMI), Italian National Agency for New Technologies, Energy and Sustainable Economic Development (ENEA) and Barcelona Supercomputing Center (BSC), CAMS European air quality forecasts, ENSEMBLE data. Copernicus Atmosphere Monitoring Service (CAMS) Atmosphere Data Store (ADS). Available at: (Accessed 18 July 2022).

Muñoz Sabater, J., 2022. ERA5-Land Hourly Data from 1950 to 1980. Copernicus Climate Change Service (C3S) Climate Data Store (CDS). https://doi.org/10.24381/cds.e2161bac. (Accessed 18 July 2022).

Ray, S., Kim, K.-H., 2014. The pollution status of sulfur dioxide in major urban areas of Korea between 1989 and 2010. Atmos. Res. 147–148, 101–110. https://doi.org/10.1016/j.atmosres.2014.05.011.

Robertson, S., Miller, M.R., 2018. Ambient air pollution and thrombosis. Part. Fibre Toxicol. 15 https://doi.org/10.1186/s12989-017-0237-x.

Sarmadi, M., Moghanddam, V.K., Dickerson, A.S., Martelletti, L., 2021. Association of Covid-19 distribution with air quality, sociodemographic factors, and comorbidities: an ecological study of us states. Air Qual. Atmos.Health 14, 455–465. https://doi.org/10.1007/s11869-020-00949-w.

Schiermeier, Q., 2020. Why pollution is plummeting in some cities but not others. Nature 580, 313. https://doi.org/10.1038/d41586-020-01049-6, 313.

Srivastava, A., 2021. Covid-19 and air pollution and meteorology-an intricate relationship: a review. Chemosphere 263 (1). https://doi.org/10.1016/J.CHEMOSPHERE.2020.128297.

Stieb, D.M., Judek, S., Burnett, R.T., 2002. Meta-analysis of time-series studies of air pollution and mortality: effects of gases and particles and the influence of cause of death, age, and season. J. Air Waste Manag. Assoc. 52, 470–484. https://doi.org/10.1080/10473289.2002.10470794.

Stieb, D.M., Judek, S., Burnett, R.T., 2003. Meta-analysis of time-series studies of air pollution and mortality: update in relation to the use of generalized additive models. J. Air Waste Manag. Assoc. 53, 258–261. https://doi.org/10.1080/10473289.2003.10466149.

Subdirección General de Información Sanitaria e Innovación, Registro de Actividad de Atención Especializada RAE-CMBD. Available at. https://www.sanidad.gob.es/estadEstudios/estadisticas/cmbdhome.htm–. (Accessed 18 July 2022).

Sunyer, J., Atkinson, R., Ballester, F., Tertre, A.L., Ayres, J.G., Forastiere, F., Forsberg, B., Vonk, J.M., Bisanti, L., Anderson, R.H., Schwartz, J., Katsouyanni, K., 2003a. Respiratory effects of sulphur dioxide: a hierarchical multicity analysis in the aphea 2 study. Occup. Environ. Med. 60, 2. https://doi.org/10.1136/oem.60.8.e2.

Sunyer, J., Ballester, F., Tertre, A.L., Atkinson, R., Ayres, J.G., Forastiere, F., Forsbergg, B., Vonk, J.M., Bisanti, L., Tenías, J.M., Medina, S., Schwartz, J., Katsouyanni, K., 2003b. The association of daily sulfur dioxide air pollution levels with hospital admissions for cardiovascular diseases in Europe (the aphea-ii study). Eur. Heart J. 24, 752–760. https://doi.org/10.1016/S0195-668X(02)00808-4.

Tateo, F., Fiorino, S., Peruzzo, L., Zippi, M., De Biase, D., Lari, F., Melucci, D., 2022. Effects of environmental parameters and their interactions on the spreading of sars-cov-2 in north Italy under different social restrictions. a new approach based on multivariate analysis. Environ. Res. 210, 112921 https://doi.org/10.1016/j.envres.2022.112921.

Varotsos, C., Christodoulakis, J., Kouremadas, G.A., Fotaki, E.-F., 2021. The signature of the coronavirus lockdown in air pollution in Greece. Water, Air, Soil Pollut. 232, 119. https://doi.org/10.1007/s11270-021-05055-w.

Wang, B., Liu, J., Li, Y., Fu, S., Xu, X., Li, L., Zhou, J., Liu, X., He, X., Yan, J., Shi, Y., Niu, J., Yang, Y., Li, Y., Luo, B., Zhang, K., 2020. Airborne particulate matter, population mobility and covid-19: a multi- city study in China. BMC Publ. Health 20 (12). https://doi.org/10.1186/s12889-020-09669-3.

Wood, S.N., 2011. Fast stable restricted maximum likelihood and marginal likelihood estimation of semiparametric generalized linear models. J. Roy. Stat. Soc. B 73 (1), 3–36. https://doi.org/10.1111/j.14679868.2010.00749.x.

Woodby, B., Arnold, M.M., Valacchi, G., 2020. Sars-cov-2 infection, covid-19 pathogenesis, and exposure to air pollution: what is the connection? Ann. N. Y. Acad. Sci. https://doi.org/10.1111/nyas.14512.

Wu, X., Nethery, R.C., Sabath, M.B., Braun, D., Dominici, F., 2020. Air pollution and Covid-19 mortality in the United States: strengths and limitations of an ecological regression analysis. Sci. Adv. 6 (11) https://doi.org/10.1126/sciadv.abd4049.

Xu, X., Chen, P., Wang, J., Feng, J., Zhou, H., Li, X., Zhong, W., Hao, P., 2020. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human trans- mission. Sci. China Life Sci. 63 (3), 457–460. https://doi.org/10.1007/s11427-020-1637-5.

Zang, S.-T., Luan, J., Li, L., Yu, H.-X., Wu, Q.-J., Chang, Q., Zhao, Y.-H., 2022. Ambient air pollution and covid-19 risk: evidence from 35 observational studies. Environ. Res. 204, 112065 https://doi.org/10.1016/j.envres.2021.112065.

Zhu, Y., Xie, J., Huang, F., Cao, L., 7 2020. Association between short-term exposure to air pollution and covid-19 infection: evidence from China. Sci. Total Environ. 727 https://doi.org/10.1016/j.scitotenv.2020.138704.