HEI

# SUPPLEMENTARY APPENDIX

## Research Report 220

# Air Pollution in Relation to COVID-19 Morbidity and Mortality: A Large Population-Based Cohort Study in Catalonia, Spain (COVAIR-CAT)

**Cathryn Tonne et al.**

## Appendix A: Supplementary Tables and Figures

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Appendix A was reviewed for spelling, grammar, and cross-references to the main report. It has not been formatted or fully edited by HEI. This document was reviewed by the HEI Review Committee.

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# Appendix A

# Air Pollution in Relation to COVID-19 Morbidity and Mortality: A Large Population-Based Cohort Study in Catalonia, Spain (COVAIR-CAT)

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# Cohort Construction

**Table A1. Databases Used in Cohort Construction**

| Name | Description |
|---|---|
| CMDB-AP | Primary care database |
| CMDB-HA | Hospital discharges database |
| CMDB-URG | Emergency care database |
| ECAP | Primary care source database |
| SUVEC | Epidemiological surveillance emergency service of Catalonia |
| RCA | Catalan Central Registry of Insured Individuals |
| AQuAS | Agency for Health Quality and Assessment of Catalonia |

**Table A2. Variable Definitions**

| Variable | Content | Source | Defined by | Comments |
|---|---|---|---|---|
| Age | Age on 01/01/2020, in years | RCA | Date of birth | Variable provided in categories of 3 years band because of confidentiality. We generated a random integer between the three possibilities to ascertain the final continuous age (e.g., for age category 50-52, we randomly select a number between 50, 51 and 52 |
| Sex | Female / Male | RCA | Sex at birth | |
| Individual income group | Three categories of low (<18,000 euros per year), middle (18,000-100,000 euros) and high (>100,000 euros) | RCA | Co-payment system for drug dispensations | This variable is already categorical. We considered individuals exempt from co-payment (nonworking population or people receiving non-contributory pension) as the low category. |
| Tobacco smoking status | Nonsmoker / Former smoker / Active smoker | ECAP | General practitioner recording | For the main analysis, we considered those missing as nonsmoker. This information was collected in 2015 and 2018; we used the latest available. |
| Health risk group (grupos de morbilidad ajustados, GMA) | Healthy / Low / Moderate / High | RCA | Briefly, the index encompasses multimorbidity and levels of patient complexity, accounting for acute, chronic, or oncological morbidities, if single or multi morbidity, medications, and demand on the health system. | To obtain the health status groups, we used the distribution of the score, as suggested, classifying those Health up to percentile 50th, Low up to 80th, Moderate up to 95th and High above 95th.[1] The index is associated with the use of healthcare resources.[2] |
| Diabetes mellitus | Yes / No | CMDB-AP and CMDB-HA | ICD-09: 250.x0, 250.x2, 357.2, 362.01, 362.02, 362.03, 362.04, 362.05, 362.06, 362.07, 366.41 249*, 250.x1, 250.x3 | Diagnosis up to 01/03/2020 |

| Variable | Content | Source | Defined by | Comments |
|---|---|---|---|---|
| | | | ICD-10: E11*, E12*, E13* | |
| Obesity | Yes / No | CMDB-AP | ICD-10: E66* | Diagnosis up to 01/03/2020 |
| Body mass index | BMI, kg/m$^2$ | ECAP | General practitioner recording | Information collected in 2015 and 2018; we used the latest available. |
| Chronic Obstructive Pulmonary Disorder | Yes / No | CMDB-AP and CMDB-HA | ICD-09: 491.0, 491.1, 491.8, 491.9, 491.20, 491.21, 491.22, 492.0, 492.8, 496*<br>ICD-10: J41*, J42*, J43*, *J44* | Diagnosis up to 01/03/2020 |
| Hypertension | Yes / No | CMDB-AP | ICD-10: I10* | Diagnosis up to 01/03/2020 |
| Other cardiovascular disorders | Yes / No | CMDB-AP and/or CMDB-HA | ICD-09: 410*, 433.x1, 434*<br><br>ICD-10: I10*, I48*, I20*, I21*, I22*, I23*, I24*, I25*, I61*, I63*, G45*,I65*, I66*, I67*, I67.2, I67.8, I67.9, I69*, I70*, I73, I73.9 | Diagnosis up to 01/03/2020. It includes atrial fibrillation, acute myocardial infarction, stroke, other vascular disorders |
| Dyslipidemia | Yes / No | CMDB-AP | ICD-10: E78* | Diagnosis up to 01/03/2020 |
| Nursing home status | Yes / No | SUVEC | Place of residence | Available for COVID-19 cases |
| Urbanicity (Area of residence) | City<br>Town and Suburb<br>Rural | RCA | 1) Cities (Densely populated areas: at least 50% of the population lives in urban centres) 2) Towns and suburbs (Intermediate density areas: less than 50% of the population lives in rural grid cells and less than 50% of the population lives in urban centers), 3) Rural areas (Thinly populated areas: more than 50 % of the population lives in rural grid cells). | The boundaries of the degree of urbanisation areas are derived from the LAU2 2018 boundaries from the European Commission-Eurostat/GISO, based on data from EuroGeographics and the Eurostat 2011 Population grid |

| Variable | Content | Source | Defined by | Comments |
|---|---|---|---|---|
| Small Area Socioeconomic Index | Socioeconomic index at primary care service area level | RCA | | Índex socioeconòmic territorial, based on data from 2017 |
| Deprivation index | Deprivation index at primary care service area level | RCA/Census | | Índice de privación 2011 |
| Percentage of non-Spanish residents | Proportion of non-Spanish residents at census tract | RCA/Census | | From 2018 |
| Gini index | Inequity index at census tract | RCA/Census | | Census 2011 |
| Distance to closest primary care unit | Distance in meters from residence to closest primary care unit | RCA | | 2021 |
| Average weekly TPP | Weekly test-positive proportion at AGA level | AQuaS | Aggregated public data | |
| Clinical COVID-19 diagnosis | Clinical diagnosis | CMDB-AP, CMDB-HA, CMDB-URG | ICD-10: B34.2, B97.2, J12.81, J12.89, U07.1 | |
| Laboratory confirmed COVID-19 diagnosis | RT-PCR or Antigen test for SARS-CoV-2 | SUVEC | Positive RT-PCR / Antigen test | |
| All-cause hospitalization after COVID-19 diagnosis | All-cause hospitalization after 30 days of first COVID-19 (clinical/ laboratory) diagnosis | CMDB-HA | | We also allowed hospitalizations that occurred before 10 days of the diagnosis |
| Cardiovascular-related hospitalization after COVID-19 diagnosis | Cardiovascular cause as main reason of hospitalization after 30 days of first COVID-19 (clinical/ laboratory) diagnosis | CMDB-HA | ICD-10: I* | We also allowed hospitalizations that occurred before 10 days of the diagnosis |
| Respiratory-related hospitalization after COVID-19 diagnosis | Respiratory cause as main reason of hospitalization after 30 days of first COVID-19 (clinical/ laboratory) diagnosis | CMDB-HA | ICD-10: J* | We also allowed hospitalizations that occurred before 10 days of the diagnosis |
| Infection-related hospitalization after COVID-19 | Infection cause as main reason of hospitalization after 30 days of first | CMDB-HA | ICD-10: A* | We also allowed hospitalizations that occurred before 10 days |

| Variable | Content | Source | Defined by | Comments |
|---|---|---|---|---|
| diagnosis | COVID-19 (clinical/ laboratory) diagnosis | | | of the diagnosis |
| Ill defined-related hospitalization after COVID-19 diagnosis | Ill-defined cause as main reason of hospitalization after 30 days of first COVID-19 (clinical/ laboratory) diagnosis | CMDB-HA | ICD-10: R* | We also allowed hospitalizations that occurred before 10 days of the diagnosis |
| ICU admission after COVID-19 diagnosis | ICU admission during the all-cause hospitalization after 30 days of first COVID-19 (clinical/ laboratory) diagnosis | CMDB-HA | | We also allowed hospitalizations that occurred before 10 days of the diagnosis |
| Hospital length of stay | Days of hospitalization during the all-cause hospitalization after 30 days of first COVID-19 (clinical/laboratory) diagnosis | CMDB-HA | | We also allowed hospitalizations that occurred before 10 days of the diagnosis |

# Exposure model

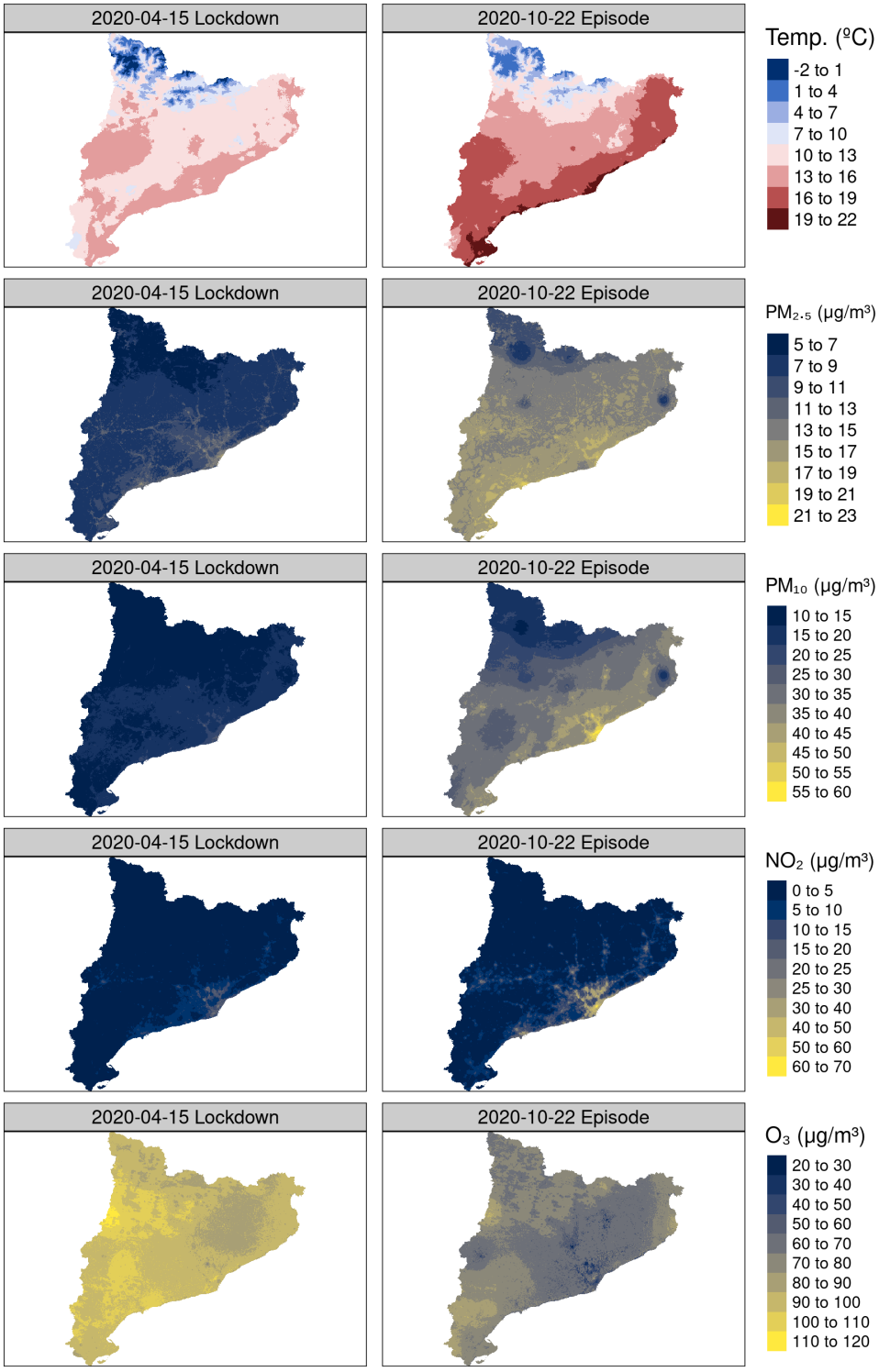



**Figure A1. Model predictions for two selected dates coinciding with COVID-19 lockdown (2020-04-15) and declared air pollution episode in Barcelona due to Saharan dust advection (2020-10-22).**

**Table A3. Model Validation Statistics by Exposure Type and Period Computed Using Nested Cross Validation at the Station Level**

| Exposure | Period | RMSE | $R^2$ | intercept | slope | RMSE spatial | $R^2$ spatial | RMSE temporal | $R^2$ temporal |
|---|---|---|---|---|---|---|---|---|---|
| Temp. (ºC) | 2018-20 | 1.21 | 0.97 | -0.07 | 1.00 | 0.85 | 0.94 | 0.85 | 0.98 |
| | 2018 | 1.20 | 0.98 | -0.05 | 1.00 | 0.88 | 0.94 | 0.83 | 0.99 |
| | 2019 | 1.23 | 0.97 | -0.11 | 1.00 | 0.86 | 0.93 | 0.87 | 0.98 |
| | 2020 | 1.19 | 0.97 | -0.05 | 1.00 | 0.84 | 0.94 | 0.84 | 0.98 |
| $NO_2$ | 2018-20 | 6.69 | 0.78 | 0.18 | 0.98 | 4.86 | 0.78 | 4.53 | 0.78 |
| | 2018 | 7.39 | 0.74 | 0.25 | 0.97 | 5.86 | 0.75 | 4.44 | 0.73 |
| | 2019 | 7.21 | 0.77 | 0.18 | 0.98 | 5.45 | 0.78 | 4.70 | 0.76 |
| | 2020 | 5.55 | 0.81 | 0.17 | 0.97 | 4.13 | 0.77 | 3.84 | 0.83 |
| $PM_{2.5}$ | 2018-20 | 4.29 | 0.59 | -1.02 | 1.07 | 1.68 | 0.71 | 3.98 | 0.54 |
| | 2018 | 3.90 | 0.54 | -1.00 | 1.07 | 1.52 | 0.70 | 3.64 | 0.47 |
| | 2019 | 4.51 | 0.61 | -1.17 | 1.08 | 2.07 | 0.71 | 4.05 | 0.56 |
| | 2020 | 4.32 | 0.55 | -0.91 | 1.06 | 1.82 | 0.53 | 3.95 | 0.55 |
| $PM_{10}$ | 2018-20 | 6.54 | 0.63 | -0.30 | 1.00 | 3.18 | 0.49 | 5.79 | 0.65 |
| | 2018 | 6.25 | 0.51 | 0.32 | 0.97 | 4.08 | 0.41 | 5.17 | 0.51 |
| | 2019 | 6.94 | 0.64 | -0.36 | 1.01 | 3.63 | 0.39 | 5.97 | 0.69 |
| | 2020 | 6.30 | 0.65 | -0.42 | 1.01 | 2.97 | 0.45 | 5.58 | 0.68 |
| $O_3$ | 2018-20 | 9.64 | 0.87 | 0.69 | 1.00 | 5.35 | 0.58 | 8.01 | 0.90 |
| | 2018 | 9.93 | 0.89 | 1.15 | 0.99 | 6.16 | 0.60 | 7.82 | 0.93 |
| | 2019 | 9.70 | 0.87 | 0.49 | 1.00 | 5.39 | 0.67 | 8.08 | 0.90 |
| | 2020 | 9.37 | 0.83 | 0.68 | 0.99 | 5.55 | 0.40 | 7.59 | 0.88 |

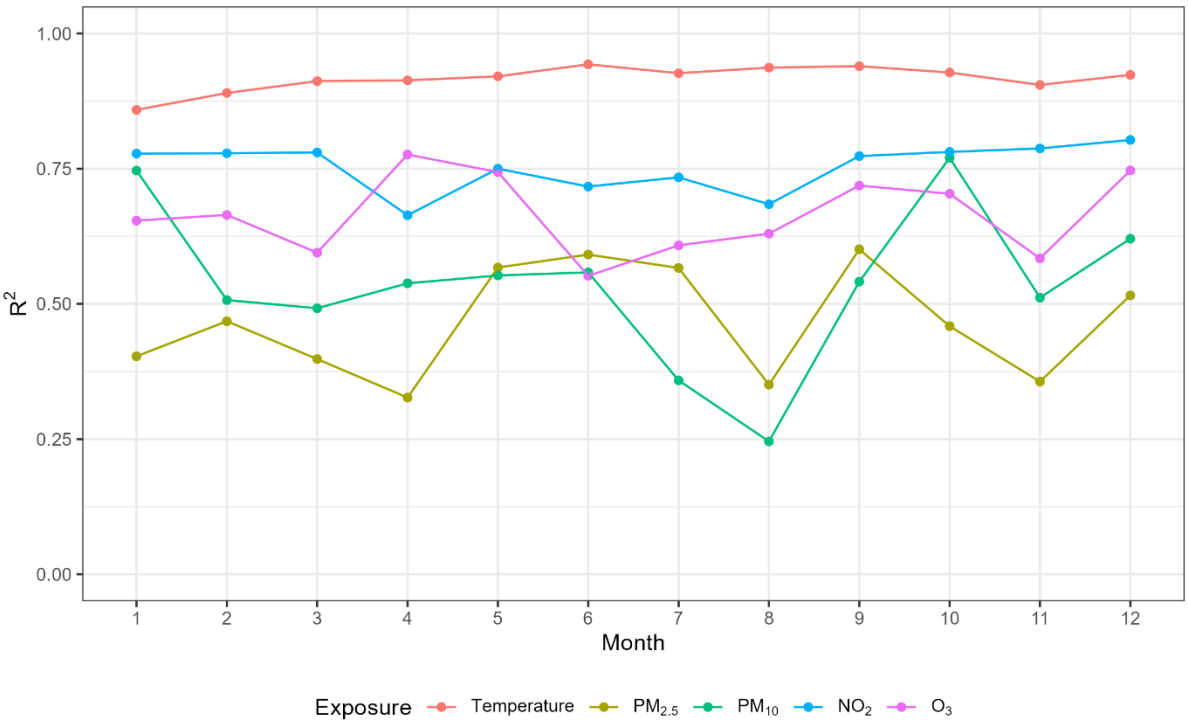



**Figure A2. Monthly $R^2$ between observed and out-of-sample predicted exposures (using nested cross-validation at the station level) by exposure in 2020.**

# Data Analysis

(A)

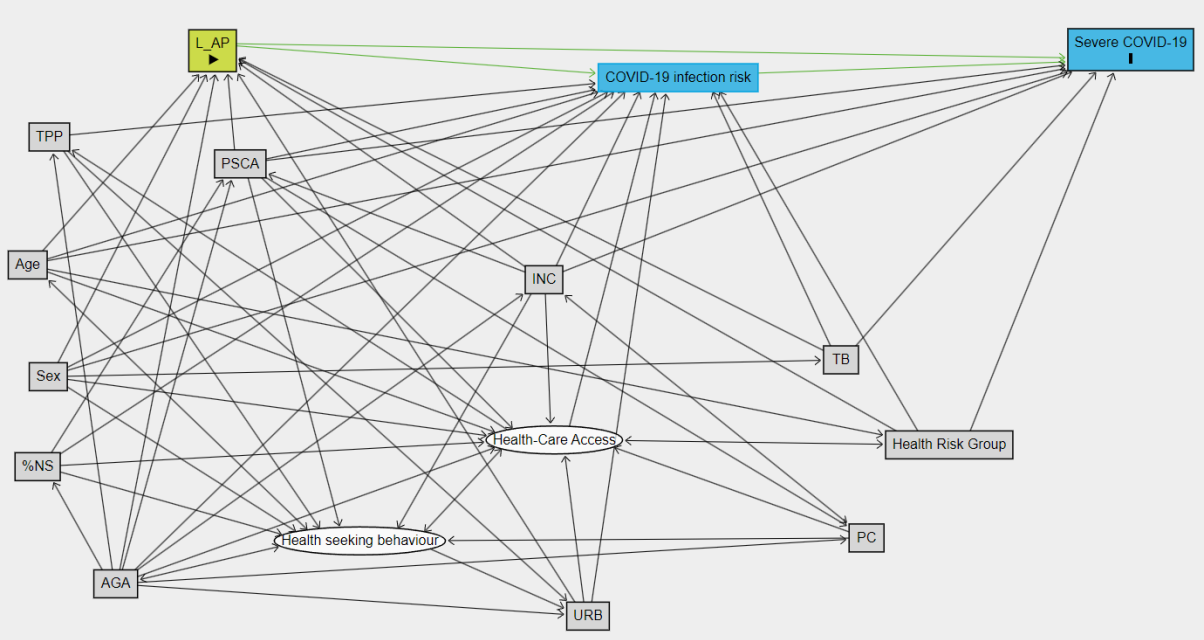
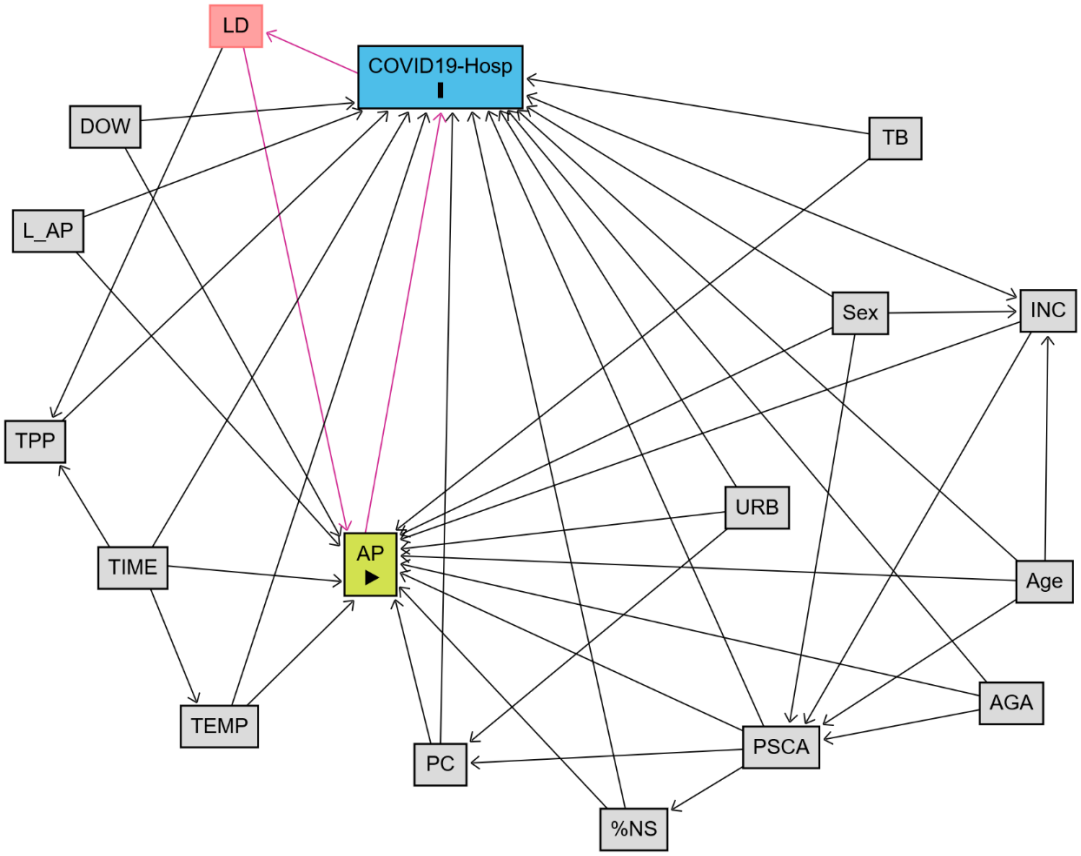
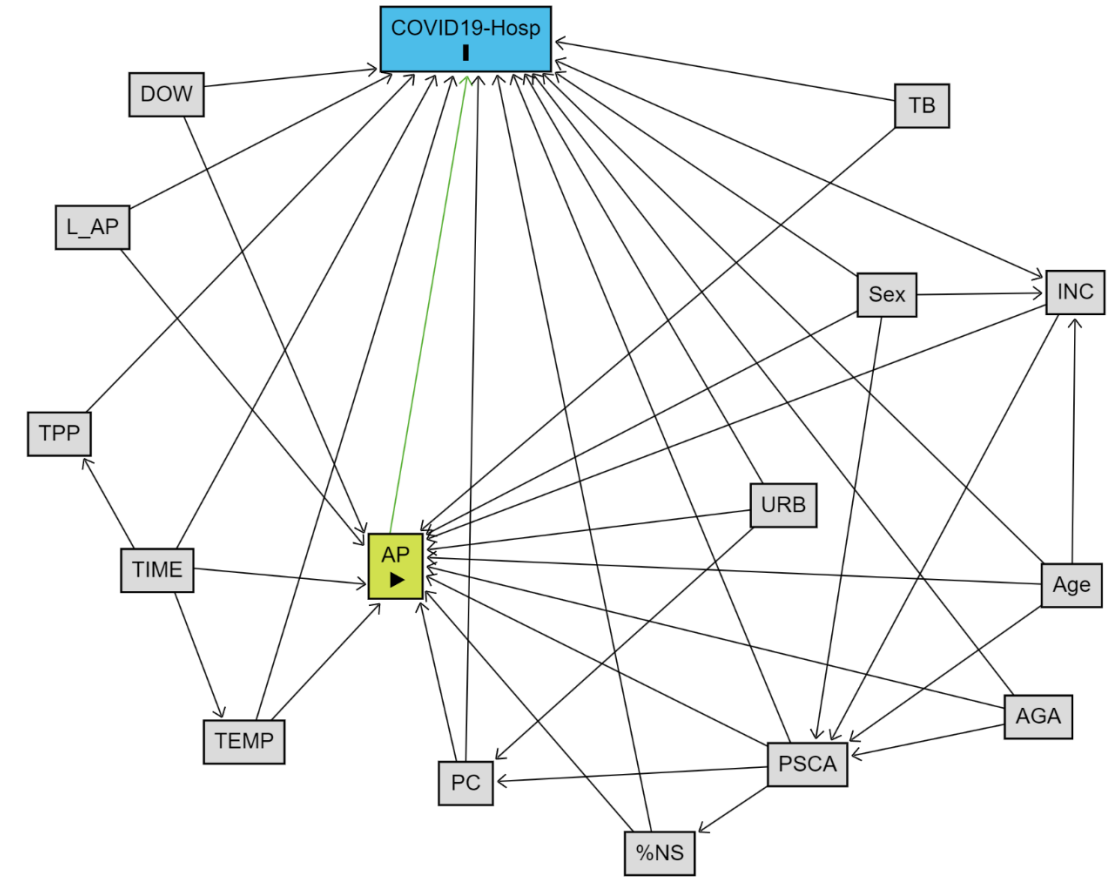



**Figure A3. Directed Acyclic Graphs used for Aim 1 (A) and Aim 2 during the first (B) and second (C) pandemic waves.** *Figure continues next 2 pages. The legend and abbreviations appear on the 3rd page.*

(B)


LD
COVID19-Hosp
DOW
TB
L_AP
Sex
INC
TPP
URB
AP
TIME
Age
AGA
TEMP
PSCA
PC
%NS

(C)




Abbreviations: TPP, test-positive proportion; SES, socioeconomic status; TB, tobacco smoking; INC, individual income; AGA, healthcare management area; PSCA, Small Area Socioeconomic Index; URB, urbanicity; %NS, proportion of non-Spanish nationals; PC, distance to the closest primary care unit; TPP, the weekly average of test-positive proportion at AGA level; L_AP, long-term exposure to air pollution; TEMP, temperature; DOW, day (weekend or not). Created with DAGitty.net (www.dagitty.net).

**Table A4. AICs for the Different Versions of Distributed Lag Linear and Non-Linear Models (DLM and DLNM, respectively) Tested in Main and Sensitivity Analysis (Bold values indicate models with lowest AIC for each combination of pollutant and wave)**

| Pollutant | Period | DLM (Main model) | | DLNM[a] | | |
|---|---|---|---|---|---|---|
| | | DF[b] for Lag dimension | | DF[b] for Exposure dimension | | |
| | | 4 | 5 | 3 | 4 | 5 |
| $NO_2$ | Wave 1 | **263673.86** | 263675.41 | **263682.65** | 263689.24 | 263688.13 |
| | Wave 2 | 155889.62 | **155879.98** | 155865.75 | **155849.19** | 155859.49 |
| $PM_{2.5}$ | Wave 1 | **261929.39** | 261930.97 | 261925.80 | 261926.02 | **261924.79** |
| | Wave 2 | 156160.21 | **156154.24** | 156152.97 | **156143.42** | 156148.99 |
| $PM_{10}$ | Wave 1 | 263728.36 | **263719.79** | 263720.48 | 263724.69 | **263706.76** |
| | Wave 2 | 156141.63 | **156140.80** | 156141.41 | 156140.90 | **156139.52** |
| $O_3$ | Wave 1 | **263753.00** | 263753.71 | 263724.31 | 263721.80 | **263717.93** |
| | Wave 2 | 156148.17 | **156141.28** | **156145.73** | 156151.60 | 156159.09 |

AIC = Akaike information criteria.

[a]DF=Degrees of Freedom.

[b]DF for Lag dimension in DLNM were set to 5.

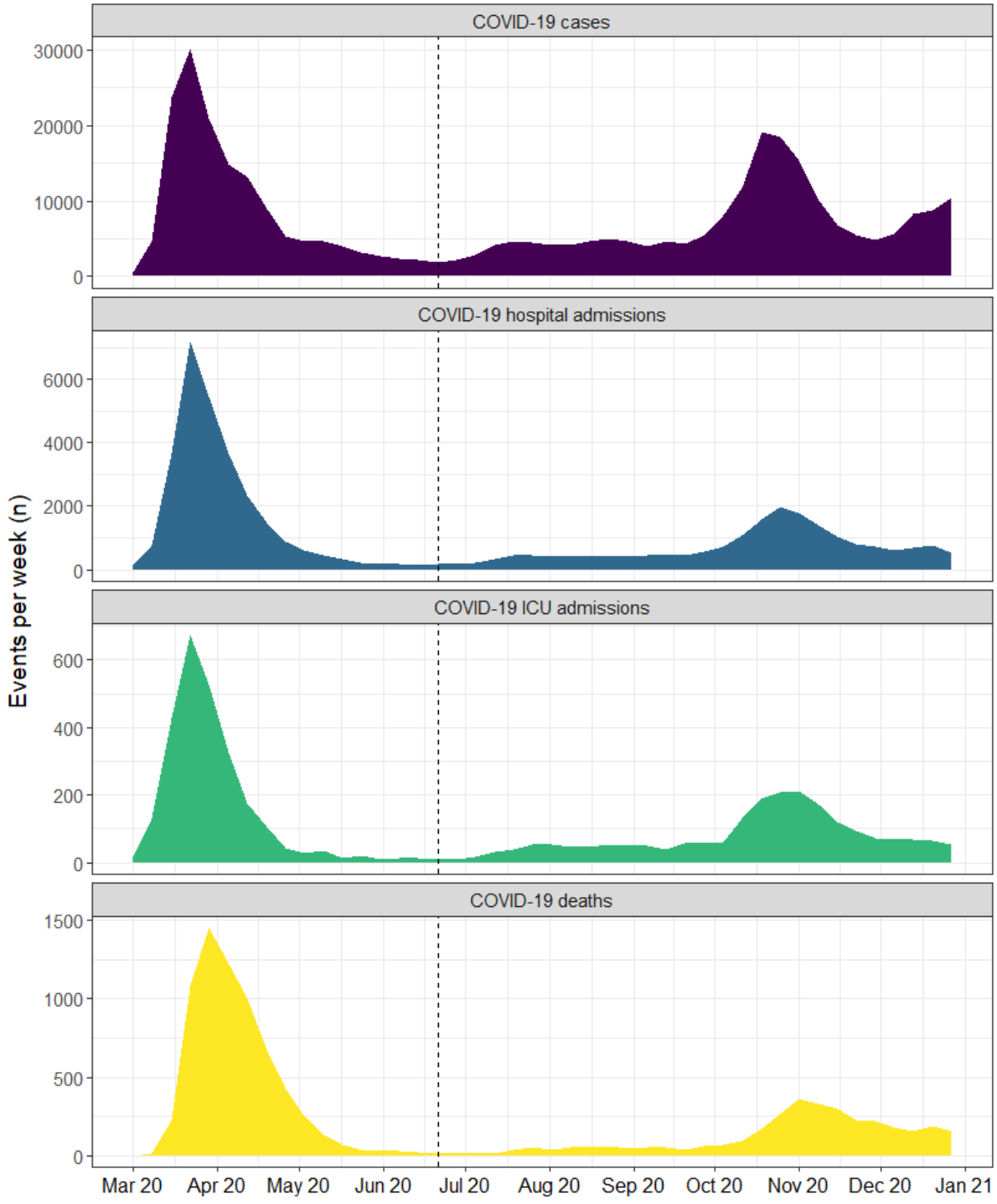



**Figure A4. Weekly COVID-19 cases and severe COVID-19–related events during 2020 in Catalonia, Spain.** The vertical dashed black line refers to the limit between first and second waves (June 21, 2020).

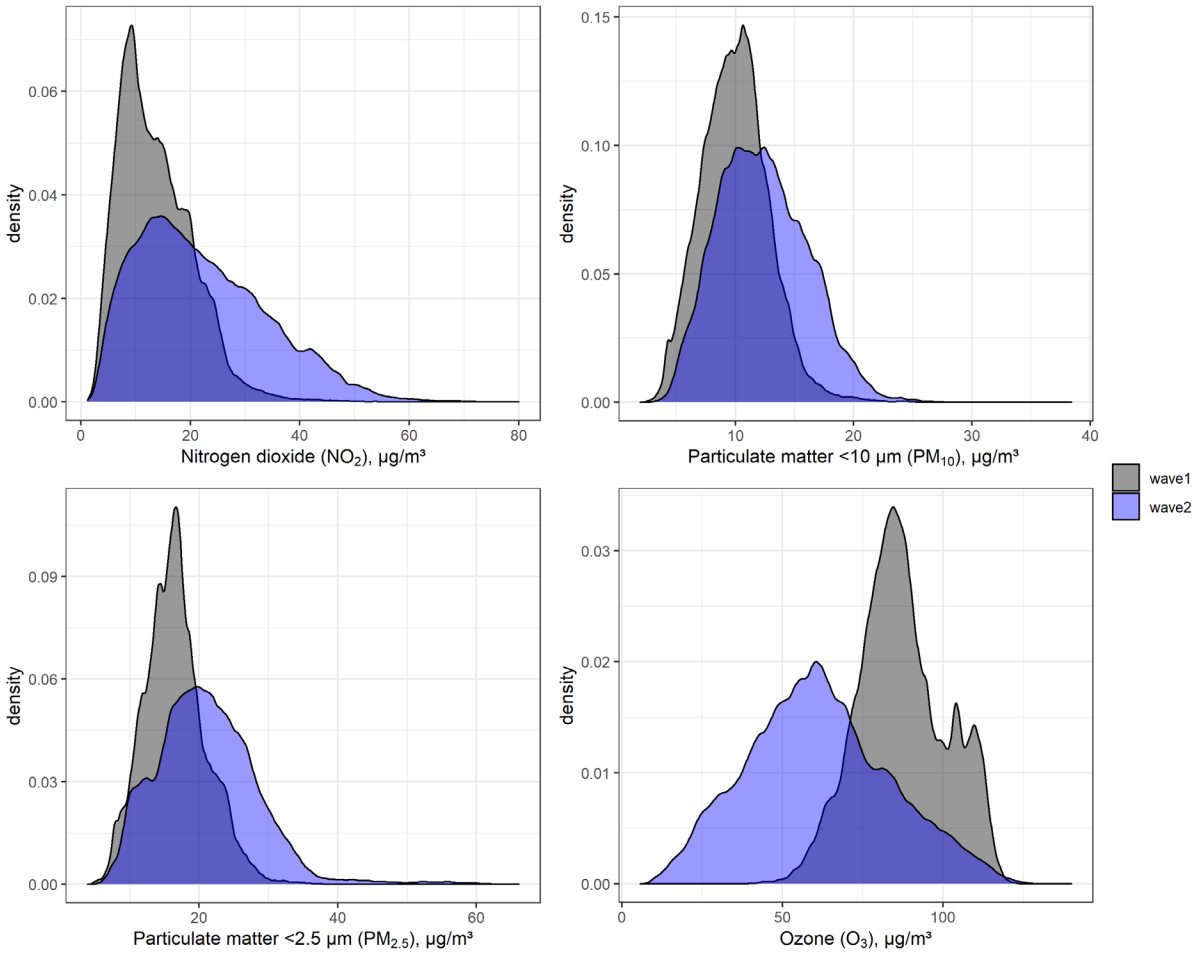



**Figure A5. Distribution of daily air-pollution exposures in person-days of follow-up among individuals diagnosed with COVID-19 in primary care.**

**Table A5. Summary Statistics for Daily Exposure to Ambient Air Pollutants Within Person-Time of Follow-Up**

| Pollutant ($\mu g/m^3$) | Epidemic Wave | Median | 1st Quartile | 3rd Quartile | IQR[a] |
|---|---|---|---|---|---|
| **$NO_2$** | First | 12.58 | 8.56 | 17.99 | 14 |
| | Second | 20.24 | 12.87 | 29.97 | |
| **$PM_{2.5}$** | First | 9.95 | 8.01 | 11.76 | 5 |
| | Second | 12.06 | 9.49 | 14.91 | |
| **$PM_{10}$** | First | 16.28 | 13.53 | 19.07 | 8 |
| | Second | 20.59 | 16.11 | 25.45 | |
| **$O_3$** | First | 85.94 | 77.92 | 96.17 | 31 |
| | Second | 60.14 | 45.74 | 75.51 | |

**Table A6. Spearman Correlations Between (A) Annual Average (2019) and (B) Daily Exposure (2020) from the COVAIR Model**

**(A)**

| | **$NO_2$** | **$PM_{2.5}$** | **$PM_{10}$** | **$O_3$ (warm season)** |
|---|---|---|---|---|
| **$NO_2$** | 1 | | | |
| **$PM_{2.5}$** | 0.89 | 1 | | |
| **$PM_{10}$** | 0.84 | 0.95 | 1 | -0.70 |
| **$O_3$ (warm season)** | -0.82 | -0.76 | | 1 |

**(B)**

| | **$NO_2$** | **$PM_{2.5}$** | **$PM_{10}$** | **$O_3$ (warm season)** |
|---|---|---|---|---|
| **$NO_2$** | 1 | | | |
| **$PM_{2.5}$** | 0.62 | 1 | | |
| **$PM_{10}$** | 0.57 | 0.89 | 1 | |
| **$O_3$ (warm season)** | -0.46 | -0.28 | -0.23 | 1 |

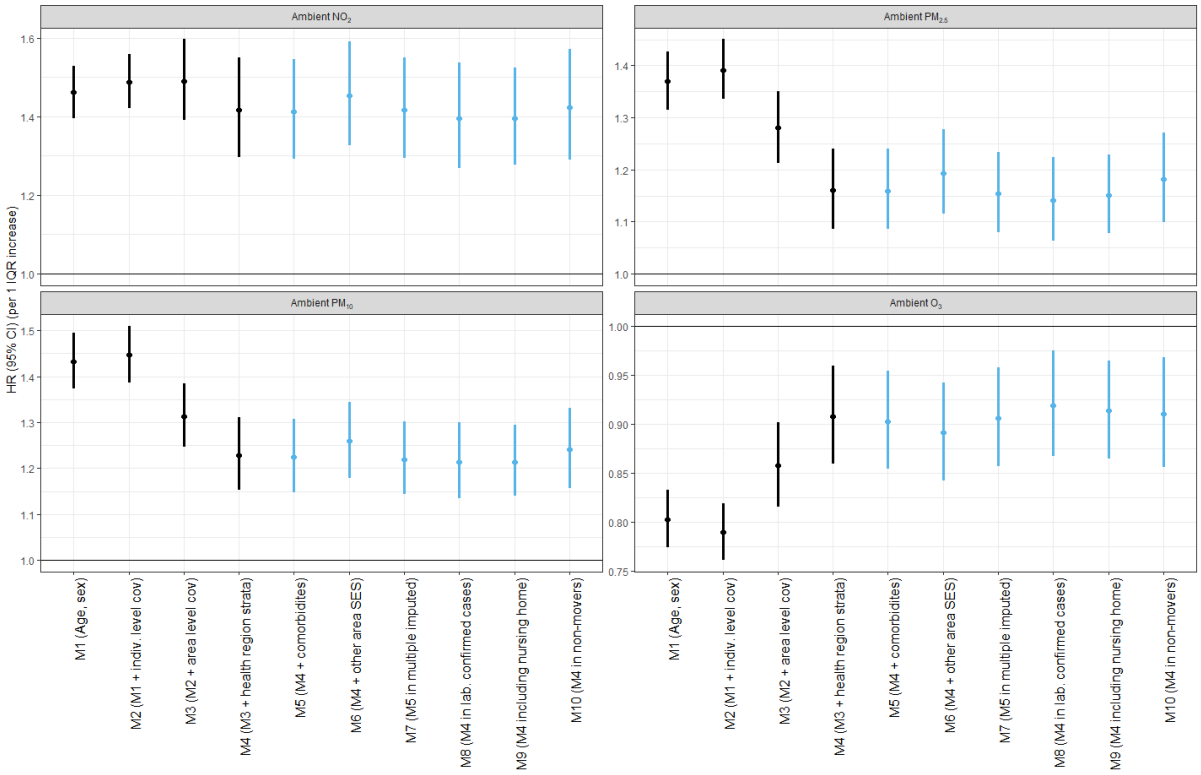



**Figure A6. Sequential adjustment and sensitivity analyses for associations between long-term air pollution exposure and COVID-19–related ICU admission (single-pollutant models).** Main analysis (black); *a priori* sensitivity analysis (blue).

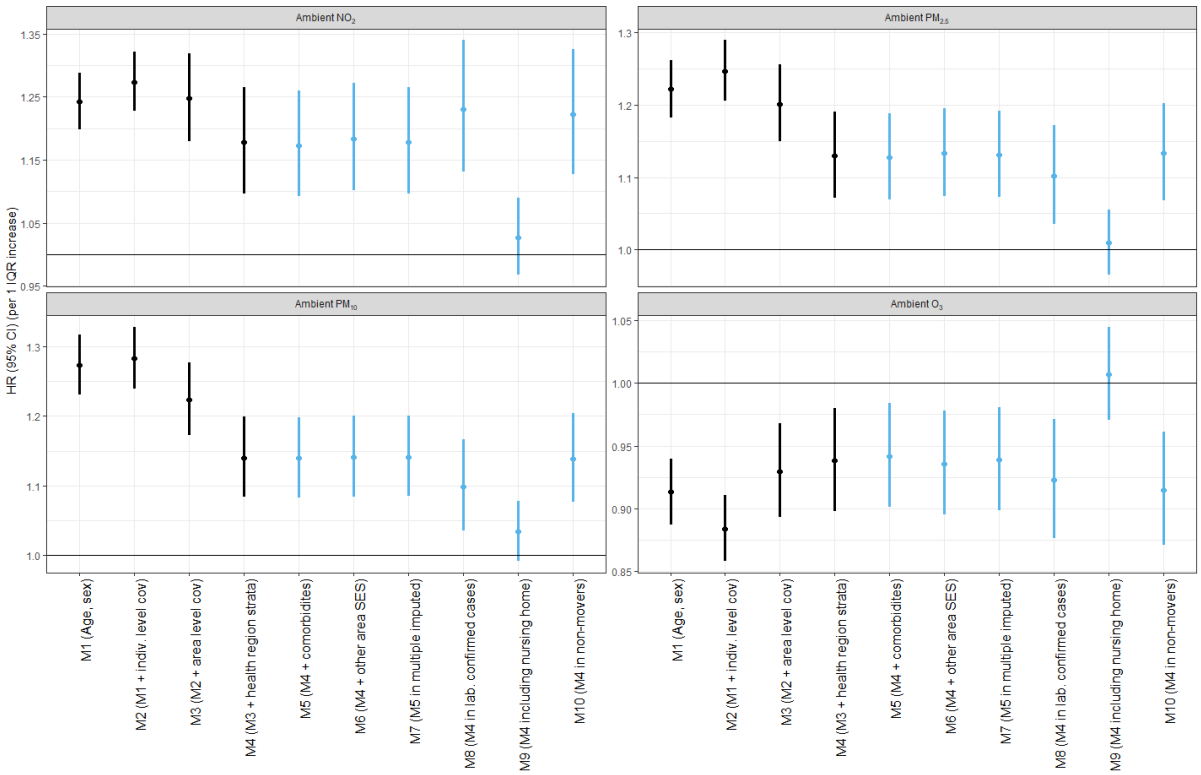



**Figure A7. Sequential adjustment and sensitivity analyses for associations between long-term air pollution exposure and COVID-19–related death (single-pollutant models).** Main analysis (black); *a priori* sensitivity analysis (blue).

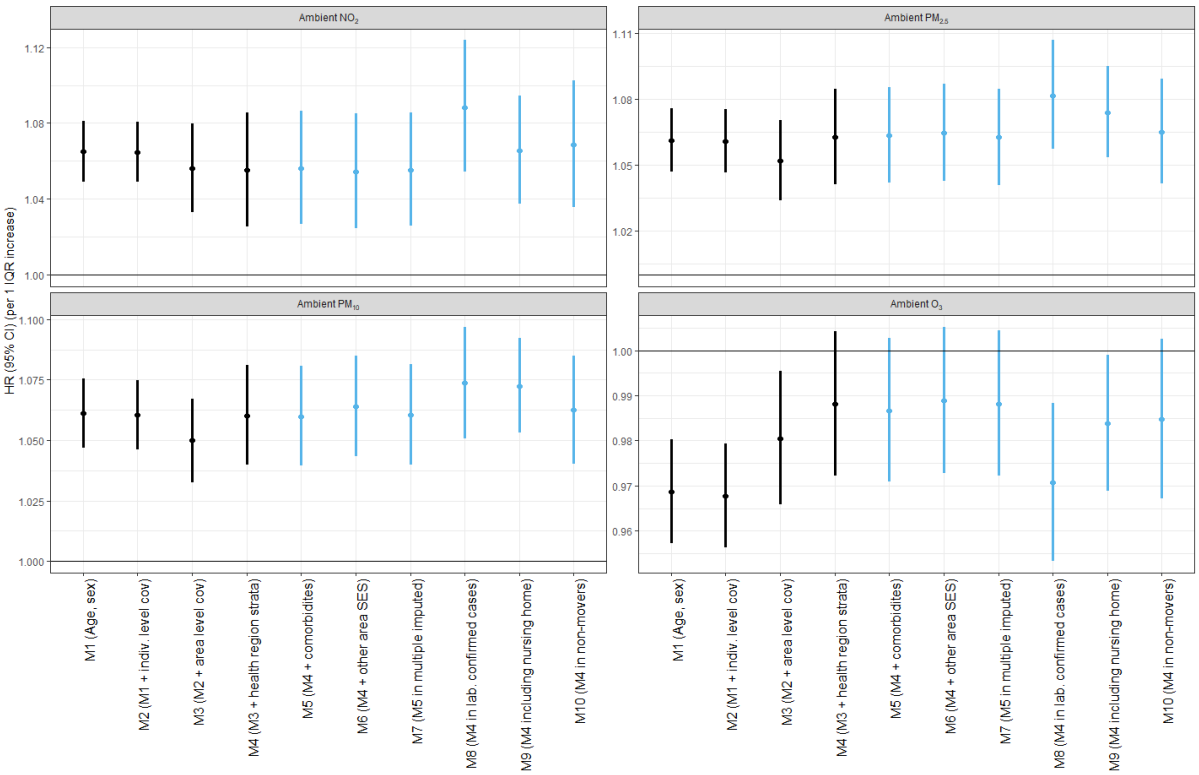



**Figure A8. Sequential adjustment and sensitivity analyses for associations between long-term air pollution exposure and COVID-19–related hospital length of stay (single-pollutant models).** Main analysis (black); *a priori* sensitivity analysis (blue).

**Table A7. Adjusted Long-Term Associations Between Air Pollution and COVID-19–Related Outcomes in Single-Pollutant Models by COVID-19 Wave**

| | | First wave | Second wave |
|---|---|---|---|
| | Exposure | HR (95% CI) | HR (95% CI) |
| **Hospitalization** | | | |
| | **$NO_2$** (IQR increase: 16.1) | **1.32 (1.27-1.37)** | **1.16 (1.11-1.22)** |
| | **$PM_{2.5}$** (IQR increase: 3.2) | **1.25 (1.21-1.28)** | **1.11 (1.07-1.14)** |
| | **$O_3$ (warm season)** (IQR increase: 10.8) | **0.88 (0.86-0.90)** | **0.95 (0.92-0.97)** |
| **ICU admission** | | | |
| | **$NO_2$** (IQR increase: 16.1) | **1.48 (1.32-1.67)** | **1.34 (1.18-1.53)** |
| | **$PM_{2.5}$** (IQR increase: 3.2) | **1.19 (1.09-1.30)** | **1.12 (1.02-1.23)** |
| | **$O_3$ (warm season)** (IQR increase: 10.8) | **0.90 (0.84-0.97)** | **0.92 (0.85-0.99)** |
| **Death** | | | |
| | **$NO_2$** (IQR increase: 16.1) | **1.15 (1.06-1.25)** | **1.25 (1.10-1.41)** |
| | **$PM_{2.5}$** (IQR increase: 3.2) | **1.12 (1.06-1.20)** | **1.14 (1.04-1.25)** |
| | **$O_3$ (warm season)** (IQR increase: 10.8) | **0.94 (0.90-0.99)** | **0.93 (0.86-1.00)** |
| **Hospital LOS** | | | |
| | **$NO_2$** (IQR increase: 16.1) | **1.06 (1.03-1.10)** | 1.03 (0.99-1.06) |
| | **$PM_{2.5}$** (IQR increase: 3.2) | **1.07 (1.04-1.09)** | **1.05 (1.02-1.07)** |
| | **$O_3$ (warm season)** (IQR increase: 10.8) | 0.99 (0.97-1.01) | 0.99 (0.97-1.02) |

Time-stratified Cox model adjusted as Model 4: age (continuous term, penalized spline with 6 df) + sex (strata, 2 categories) + smoking status (factor, 3 categories) + individual income (factor, 3 categories) + health risk group (factor, 4 categories) + Small Area Socioeconomic Index (continuous term) + percentage of non-Spanish nationals (continuous term) + distance to the closest primary care unit (continuous term) + urbanicity (strata, 3 categories) + average weekly of test-positive proportion (continuous term) + health region (strata, 7 categories).

**Table A8. Adjusted Long-Term Associations Between Air Pollutants and COVID-19–Related Hospitalization, in Single- and Two-Pollutant Models, Comparing All-Cause with Cause-Specific Hospitalizations**

| | | **All-cause (n=47,174)** | **COVID-19 or Respiratory[a] (n=36,505)** | **COVID-19[a] (n=33,981)** |
|---|---|---|---|---|
| | Exposure | HR (95% CI) | HR (95% CI) | HR (95% CI) |
| **$NO_2$** (increase: 16.1) | Single-pollutant | **1.25 (1.22-1.29)** | **1.27 (1.23-1.32)** | **1.27 (1.23-1.32)** |
| **$PM_{2.5}$** (increase: 3.2) | Single-pollutant | **1.19 (1.16-1.21)** | **1.21 (1.18-1.24)** | **1.21 (1.18-1.24)** |
| **$NO_2$** (increase: 16.1) | Adjusted for $PM_{2.5}$ | **1.12 (1.08-1.17)** | **1.13 (1.08-1.19)** | **1.12 (1.07-1.18)** |
| **$NO_2$** (increase: 16.1) | Adjusted for $O_3$ | **1.24 (1.19-1.29)** | **1.29 (1.23-1.35)** | **1.26 (1.20-1.32)** |
| **$PM_{2.5}$** (increase: 3.2) | Adjusted for $NO_2$ | **1.12 (1.08-1.15)** | **1.13 (1.09-1.17)** | **1.14 (1.10-1.18)** |
| **$PM_{2.5}$** (increase: 3.2) | Adjusted for $O_3$ | **1.16 (1.13-1.19)** | **1.19 (1.16-1.22)** | **1.18 (1.15-1.22)** |

[a] Defined by the ICD-10 code first position.
Model adjusted as Model 4: age (continuous term, penalized spline with 6 df) + sex (strata, 2 categories) + smoking status (factor, 3 categories) + individual income (factor, 3 categories) + health risk group (factor, 4 categories) + Small Area Socioeconomic Index (continuous term) + percentage of non-Spanish nationals (continuous term) + distance to the closest primary care unit (continuous term) + urbanicity (strata, 3 categories) + average weekly of test-positive proportion (continuous term) + health region (strata, 7 categories).

**Table A9. Adjusted Long-Term Associations Between Air Pollutants and COVID-19–Related Outcomes with Single- and Multi-Year Average Exposure**

| | | COVID-19 hospital admission | COVID-19 ICU admission | COVID-19 Death | Hospital length of stay |
|---|---|---|---|---|---|
| Pollutant | Exposure year | HR (95% CI) | HR (95% CI) | HR (95% CI) | IRR (95% CI) |
| $NO_2$ (increase: 16.1) | 2019 | 1.25 (1.22-1.29) | 1.42 (1.30-1.55) | 1.18 (1.10-1.27) | 1.06 (1.03-1.09) |
| | 2018 | 1.22 (1.19-1.25) | 1.32 (1.21-1.43) | 1.15 (1.08-1.23) | 1.06 (1.04-1.09) |
| | Mean 2018- 2019 | 1.24 (1.20-1.27) | 1.37 (1.26-1.49) | 1.17 (1.09-1.25) | 1.06 (1.03-1.09) |
| $PM_{2.5}$ (increase: 3.2) | 2019 | 1.19 (1.16-1.21) | 1.16 (1.09-1.24) | 1.13 (1.07-1.19) | 1.06 (1.04-1.08) |
| | 2018 | 1.17 (1.14-1.20) | 1.16 (1.08-1.25) | 1.13 (1.07-1.20) | 1.06 (1.04-1.09) |
| | Mean 2018- 2019 | 1.19 (1.16-1.21) | 1.17 (1.09-1.25) | 1.13 (1.07-1.20) | 1.06 (1.04-1.09) |
| $PM_{10}$ (increase: 4.2) | 2019 | 1.21 (1.18-1.23) | 1.23 (1.15-1.31) | 1.14 (1.08-1.20) | 1.06 (1.04-1.08) |
| | 2018 | 1.18 (1.15-1.20) | 1.22 (1.14-1.30) | 1.14 (1.09-1.20) | 1.06 (1.04-1.08) |
| | Mean 2018- 2019 | 1.20 (1.18-1.23) | 1.23 (1.15-1.32) | 1.15 (1.09-1.21) | 1.06 (1.04-1.08) |
| $O_3$ (increase: 10.8) | 2019 | 1.19 (1.16-1.21) | 0.91 (0.86-0.96) | 0.94 (0.90-0.98) | 0.99 (0.97-1.00) |
| | 2018 | 1.17 (1.14-1.20) | 0.90 (0.86-0.95) | 0.92 (0.88-0.96) | 0.98 (0.96-0.99) |
| | Mean 2018- 2019 | 1.19 (1.16-1.21) | 0.90 (0.86-0.95) | 0.93 (0.89-0.97) | 0.98 (0.97-1.00) |

*Model 4: age (continuous term, penalized spline with 6 df) + sex (strata, 2 categories) + smoking status (factor, 3 categories) + individual income (factor, 3 categories) + health risk group (factor, 4 categories) + Small Area Socioeconomic Index (continuous term) + percentage of non-Spanish nationals (continuous term) + distance to the closest primary care unit (continuous term) + urbanicity (strata, 3 categories) + average weekly of test-positive proportion (continuous term) + health region (strata, 7 categories).

**Table A10. Adjusted Long-Term Associations Between Air Pollutants and COVID-19–Related Outcomes in Single Models Stratified by Smoking Status**

| | | COVID-19 hospital admission | COVID-19 ICU admission | COVID-19 Death | Hospital length of stay |
|---|---|---|---|---|---|
| | | HR (95% CI) | HR (95% CI) | HR (95% CI) | IRR (95% CI) |
| $NO_2$ (increase: 16.1) | Main analysis, Model 4* | 1.25 (1.22-1.29) | 1.42 (1.30-1.55) | 1.18 (1.10-1.27) | 1.06 (1.03-1.09) |
| | Among smokers (former and active), Model 4a** | 1.27 (1.20-1.33) | 1.41 (1.21-1.63) | 1.26 (1.11-1.43) | 1.06 (1.01-1.11) |
| | Among non-smokers (no and missing), Model 4a** | 1.25 (1.20-1.29) | 1.43 (1.28-1.60) | 1.14 (1.04-1.24) | 1.06 (1.02-1.09) |
| $PM_{2.5}$ (increase: 3.2) | Main analysis, Model 4* | 1.19 (1.16-1.21) | 1.16 (1.09-1.24) | 1.13 (1.07-1.19) | 1.06 (1.04-1.08) |
| | Among smokers (former and active), Model 4a** | 1.23 (1.19-1.28) | 1.26 (1.12-1.40) | 1.15 (1.05-1.26) | 1.08 (1.04-1.12) |
| | Among non-smokers (no and missing), Model 4a** | 1.17 (1.14-1.20) | 1.11 (1.02-1.21) | 1.12 (1.05-1.19) | 1.06 (1.03-1.08) |
| $PM_{10}$ (increase: 4.2) | Main analysis, Model 4* | 1.21 (1.18-1.23) | 1.23 (1.15-1.31) | 1.14 (1.08-1.20) | 1.06 (1.04-1.08) |
| | Among smokers (former and active), Model 4a** | 1.22 (1.18-1.27) | 1.32 (1.19-1.46) | 1.14 (1.04-1.24) | 1.06 (1.03-1.10) |
| | Among non-smokers (no and missing), Model 4a** | 1.20 (1.17-1.23) | 1.17 (1.08-1.28) | 1.14 (1.07-1.21) | 1.06 (1.04-1.09) |
| $O_3$ (increase: 10.8) | Main analysis, Model 4* | 0.91 (0.89-0.92) | 0.91 (0.86-0.96) | 0.94 (0.90-0.98) | 0.99 (0.97-1.00) |
| | Among smokers (former and active), Model 4a** | 0.90 (0.88-0.93) | 0.86 (0.79-0.95) | 0.91 (0.84-0.98) | 0.99 (0.96-1.02) |
| | Among non-smokers (no and missing), Model 4a** | 0.91 (0.89-0.93) | 0.93 (0.87-1.00) | 0.95 (0.90-1.00) | 0.99 (0.97-1.01) |

*Model 4: age (continuous term, penalized spline with 6 df) + sex (strata, 2 categories) + smoking status (factor, 3 categories) + individual income (factor, 3 categories) + health risk group (factor, 4 categories) + Small Area Socioeconomic Index (continuous term) + percentage of non-Spanish nationals (continuous term) + distance to the closest primary care unit (continuous term) + urbanicity (strata, 3 categories) + average weekly of test-positive proportion (continuous term) + health region (strata, 7 categories).

**Model 4a: age (continuous term, penalized spline with 6 df) + sex (strata, 2 categories) + individual income (factor, 3 categories) + health risk group (factor, 4 categories) + Small Area Socioeconomic Index (continuous term) + percentage of non-Spanish nationals (continuous term) + distance to the closest primary care unit (continuous term) + urbanicity (strata, 3 categories) + average weekly of test-positive proportion (continuous term) + health region (strata, 7 categories).

**Table A11. Cumulative Hazard Ratios[a] (95% CI) Between Air Pollution and Hospital Admission by Lag Among Individuals Diagnosed with COVID-19 in Primary Care Between 1 March and 31 December 2020 (HRs estimated for an Interquartile Range increase in each air pollution from the median)**

| Pollutant | Lag | First Wave | | | Second Wave | | |
|---|---|---|---|---|---|---|---|
| | | HR | 95%CI Low | 95%CI High | HR | 95%CI Low | 95%CI High |
| $NO_2$ | 0 | **1.08** | **1.02** | **1.14** | **1.15** | **1.11** | **1.20** |
| | 0_1 | **1.09** | **1.03** | **1.16** | **1.14** | **1.09** | **1.19** |
| | 0_2 | **1.07** | **1.01** | **1.15** | **1.10** | **1.05** | **1.15** |
| | 0_3 | 1.04 | 0.97 | 1.12 | **1.10** | **1.04** | **1.15** |
| | 0_4 | 1.00 | 0.91 | 1.09 | **1.10** | **1.04** | **1.17** |
| | 0_5 | 0.94 | 0.85 | 1.03 | **1.08** | **1.02** | **1.15** |
| | 0_6 | **0.88** | **0.79** | **0.97** | 1.06 | 0.99 | 1.14 |
| | 0_7 | **0.84** | **0.76** | **0.93** | **1.12** | **1.04** | **1.20** |
| $PM_{2.5}$ | 0 | 0.99 | 0.94 | 1.04 | **1.09** | **1.05** | **1.14** |
| | 0_1 | 0.99 | 0.94 | 1.05 | **1.06** | **1.02** | **1.11** |
| | 0_2 | 1.01 | 0.95 | 1.06 | 1.04 | 0.99 | 1.09 |
| | 0_3 | 1.01 | 0.95 | 1.07 | **1.06** | **1.01** | **1.11** |
| | 0_4 | 1.00 | 0.93 | 1.06 | **1.08** | **1.03** | **1.15** |
| | 0_5 | 0.96 | 0.90 | 1.02 | **1.08** | **1.02** | **1.15** |
| | 0_6 | **0.92** | **0.86** | **0.98** | 1.06 | 0.99 | 1.13 |
| | 0_7 | **0.92** | **0.87** | **0.98** | **1.08** | **1.01** | **1.16** |
| $PM_{10}$ | 0 | 1.02 | 0.97 | 1.07 | **1.07** | **1.04** | **1.10** |
| | 0_1 | 0.98 | 0.94 | 1.03 | **1.06** | **1.03** | **1.10** |
| | 0_2 | 0.97 | 0.92 | 1.03 | **1.04** | **1.01** | **1.08** |
| | 0_3 | 1.01 | 0.95 | 1.07 | **1.04** | **1.00** | **1.08** |
| | 0_4 | 1.03 | 0.96 | 1.11 | **1.05** | **1.01** | **1.10** |
| | 0_5 | 1.00 | 0.92 | 1.08 | **1.06** | **1.01** | **1.11** |
| | 0_6 | 0.94 | 0.86 | 1.02 | **1.07** | **1.01** | **1.12** |
| | 0_7 | 0.97 | 0.88 | 1.06 | **1.09** | **1.03** | **1.15** |
| $O_3$ | 0 | 0.94 | 0.88 | 1.00 | **0.83** | **0.78** | **0.89** |
| | 0_1 | 0.94 | 0.88 | 1.00 | **0.86** | **0.80** | **0.91** |
| | 0_2 | 0.94 | 0.88 | 1.01 | **0.91** | **0.84** | **0.97** |
| | 0_3 | 0.95 | 0.89 | 1.02 | **0.91** | **0.84** | **0.99** |
| | 0_4 | 0.97 | 0.90 | 1.05 | **0.90** | **0.82** | **0.98** |
| | 0_5 | 1.02 | 0.95 | 1.10 | 0.91 | 0.83 | 1.00 |
| | 0_6 | 1.07 | 0.98 | 1.16 | 0.93 | 0.84 | 1.03 |
| | 0_7 | 1.02 | 0.94 | 1.11 | **0.88** | **0.80** | **0.98** |

[a] Predictions were adjusted for: age, sex (stratification variable), tobacco smoking status, individual income, Small Area Socioeconomic Index, proportion of non-Spanish nationals, distance to the closest primary care unit, urbanicity (stratification variable), healthcare management area (AGA), the weekly average of test-positive proportion (TPP) at AGA level, long-term exposure to air pollution, temperature, time and day (weekend or not).

**Table A12. Hazard Ratios for Hospital Admission per Interquartile Range (IQR[a]) Increase in Long-Term Air Pollution in the Main Aim 2 Models**

| Pollutant | Wave | HR | 95%CI Low | 95%CI High |
|---|---|---|---|---|
| **$NO_2$** | First | **1.30** | **1.22** | **1.40** |
| | Second | 0.98 | 0.89 | 1.07 |
| **$PM_{2.5}$** | First | **1.16** | **1.11** | **1.21** |
| | Second | **1.07** | **1.02** | **1.13** |
| **$PM_{10}$** | First | **1.16** | **1.12** | **1.21** |
| | Second | **1.06** | **1.00** | **1.12** |
| **$O_3$** | First | **0.91** | **0.88** | **0.94** |
| | Second | 0.99 | 0.94 | 1.04 |

[a]IQR values for the year 2019. $NO_2$: 16.1; $PM_{2.5}$: 3.2; $PM_{10}$: 4.2; $O_3$: 10.8.

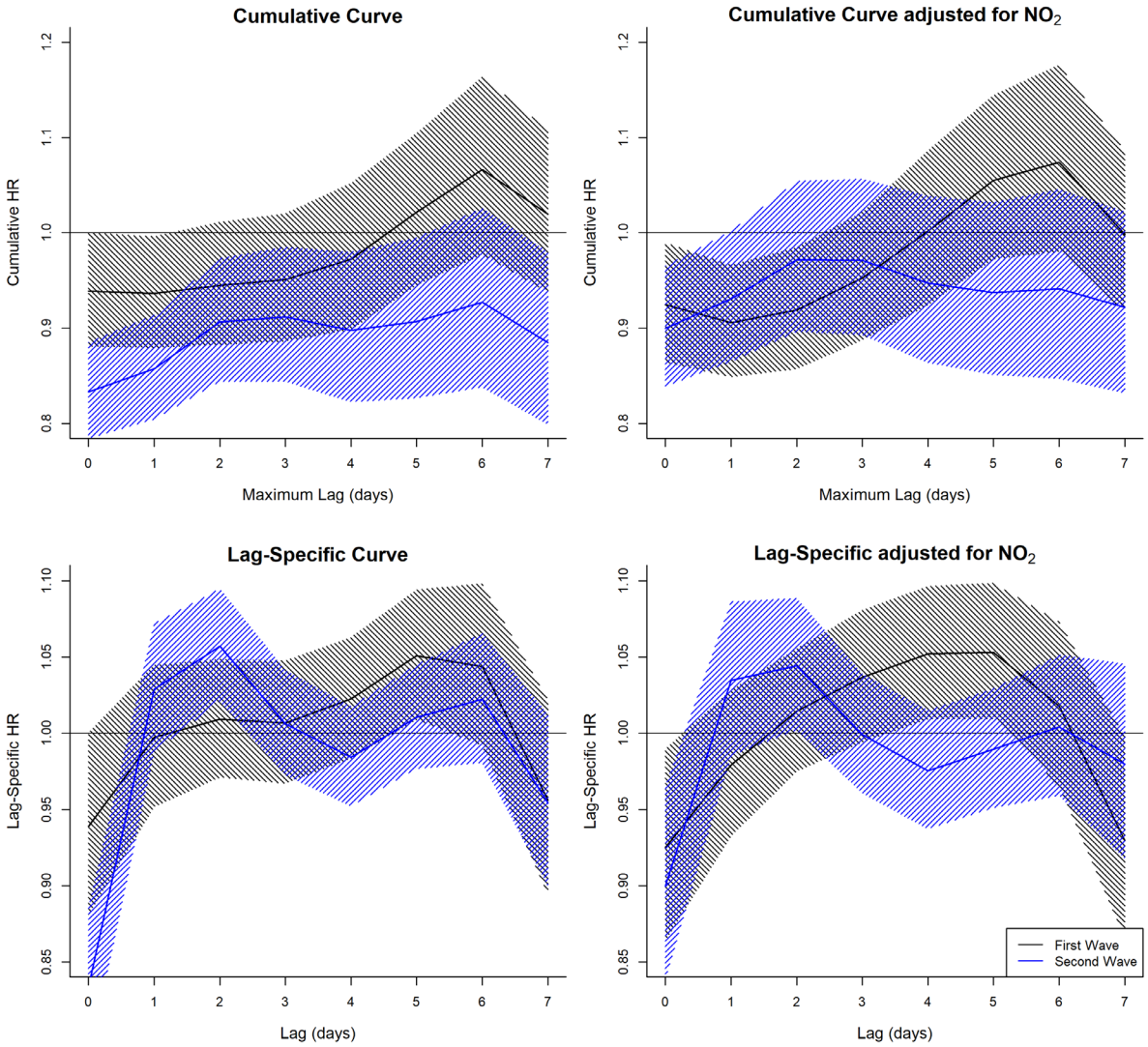



**Figure A9. Cumulative and Lag-Specific Hazard Ratios[a] for hospital admission per IQR increase in ozone ($O_3$) among individuals diagnosed with COVID-19 in primary care (n=240,902) by epidemic wave[b].** Shading represents 95% confidence intervals.

[a]Predictions were adjusted for: age, sex (stratification variable), tobacco smoking status, individual income, healthcare management area (AGA), Small Area Socioeconomic Index, proportion of non-Spanish nationals, distance to the closest primary care unit, urbanicity (stratification variable), the weekly average of test positive proportion (TPP) at AGA level, long-term exposure to air pollution, temperature, $NO_2$, time and day (weekend or not).

[b]Wave 1=1 March to 20 June 2020; Wave 2=21 June to 31 December.

**Table A13. Cumulative Hazard Ratios (95% CI) Between Air Pollution and Hospital Admission at Selected Lags During the Second Wave in Sensitivity Analysis (HRs estimated for an Interquartile Range Increase)**

| Pollutant | Lag | Diagnosed or Test +[a] | Covid 1st cause[b] | Non-movers[c] | Death as competing event[d] | ABS Clustering[e] | Alternative definition of wave[f] | Nonlinearity[g] |
|---|---|---|---|---|---|---|---|---|
| **$NO_2$** | 0 | **1.06 (1.03 to 1.09)** | **1.14 (1.09 to 1.19)** | **1.14 (1.09 to 1.20)** | **1.15 (1.11 to 1.20)** | **1.15 (1.11 to 1.20)** | **1.14 (1.10 to 1.19)** | **1.11 (1.04 to 1.18)** |
| | 0_7 | **1.10 (1.04 to 1.15)** | 1.05 (0.97 to 1.15) | **1.09 (1.01 to 1.18)** | **1.12 (1.04 to 1.20)** | **1.12 (1.03 to 1.21)** | **1.15 (1.07 to 1.23)** | 1.08 (0.99 to 1.19) |
| **$PM_{2.5}$** | 0 | 1.02 (0.99 to 1.05) | **1.09 (1.04 to 1.14)** | **1.09 (1.04 to 1.14)** | **1.09 (1.05 to 1.14)** | **1.09 (1.05 to 1.14)** | **1.10 (1.05 to 1.14)** | **1.08 (1.03 to 1.15)** |
| | 0_7 | **1.05 (1.00 to 1.11)** | **1.10 (1.01 to 1.20)** | **1.09 (1.01 to 1.17)** | **1.07 (1.00 to 1.15)** | 1.08 (0.99 to 1.18) | **1.13 (1.06 to 1.21)** | 1.07 (0.97 to 1.19) |
| **$PM_{10}$** | 0 | **1.02 (1.00 to 1.04)** | **1.06 (1.02 to 1.10)** | **1.07 (1.03 to 1.10)** | **1.07 (1.04 to 1.10)** | **1.07 (1.04 to 1.10)** | **1.08 (1.04 to 1.11)** | **1.06 (1.00 to 1.12)** |
| | 0_7 | **1.07 (1.03 to 1.12)** | **1.09 (1.02 to 1.17)** | **1.10 (1.03 to 1.17)** | **1.08 (1.02 to 1.14)** | **1.09 (1.01 to 1.16)** | **1.12 (1.06 to 1.18)** | 1.06 (0.96 to 1.16) |
| **$O_3$[f]** | 0 | **0.93 (0.89 to 0.97)** | **0.86 (0.79 to 0.92)** | **0.86 (0.80 to 0.92)** | **0.83 (0.78 to 0.88)** | **0.83 (0.78 to 0.89)** | **0.86 (0.81 to 0.91)** | 0.95 (0.83 to 1.08) |
| | 0_7 | 1.01 (0.94 to 1.09) | 0.88 (0.78 to 1.00) | 0.90 (0.80 to 1.01) | **0.88 (0.80 to 0.98)** | 0.88 (0.79 to 1.00) | **0.90 (0.82 to 0.99)** | 0.98 (0.81 to 1.19) |

ABS = primary care service areas.

[a] including individuals who tested positive for COVID-19 infection or were diagnosed in hospital or in emergency care (n=317,714).

[b] considering as outcome of interest only COVID-19 as the main/first cause of hospitalization, defined by the ICD-10 code first position.

[c] excluding people who changed residential address during the period from 2015 to 2021 (n=177,079).

[d] considering death as a competing risk for hospital admission.

[e] considering autocorrelation of model errors among observations in the same primary care service area (Área Básica de Salud, ABS: 378 clusters).

[f] defining end of first epidemic wave as last day of the first lockdown in Catalonia (25 May 2020).

[g] B-spline with 4 df for the exposure-response.

**Table A14. Association Between Ambient $PM_{10}$ and COVID-19 Hospital Admission by Vulnerability Indicators and Their Interaction on Additive and Multiplicative Scales**

| | $PM_{10}$ [a] | | Interaction in Multiplicative Scale | Interaction in Additive Scale | Type of interaction[1] |
|---|---|---|---|---|---|
| | **Low** | **High** | **HR (95% CI)** | **RERI (95% CI)** | |
| **Age, years** | | | | | |
| 23-64 | 1.00 (Reference) | **1.37 (1.32 to 1.41)** | **0.90 (0.87 to 0.94)** | 0.05 (-0.01 to 0.11) | Negative multiplicative zero additive |
| 65+ | **1.77 (1.71 to 1.83)** | **2.18 (2.11 to 2.26)** | | | |
| **Male** | | | | | |
| No | 1.00 (Reference) | **1.28 (1.24 to 1.33)** | 1.02 (0.98 to 1.06) | **0.18 (0.12 to 0.23)** | No multiplicative positive additive |
| Yes | **1.50 (1.46 to 1.55)** | **1.97 (1.90 to 2.03)** | | | |
| **Hypertension** | | | | | |
| No | 1.00 (Reference) | **1.35 (1.31 to 1.39)** | **0.91 (0.88 to 0.95)** | -0.06 (-0.11 to 0.00) | Negative multiplicative zero additive |
| Yes | **1.28 (1.24 to 1.33)** | **1.58 (1.52 to 1.63)** | | | |
| **Diabetes** | | | | | |
| No | 1.00 (Reference) | **1.32 (1.28 to 1.35)** | **0.93 (0.89 to 0.98)** | 0.02 (-0.05 to 0.09) | Negative multiplicative zero additive |
| Yes | **1.46 (1.41 to 1.52)** | **1.80 (1.74 to 1.87)** | | | |
| **Chronic Obstructive Pulmonary Disease** | | | | | |
| No | 1.00 (Reference) | **1.31 (1.27 to 1.34)** | **0.93 (0.88 to 0.99)** | 0.01 (-0.09 to 0.10) | Negative multiplicative zero additive |

| | | | | | |
|---|---|---|---|---|---|
| Yes | **1.43 (1.36 to 1.50)** | **1.74 (1.66 to 1.82)** | | | |
| **Low individual income** | | | | | |
| No | 1.00 (Reference) | **1.25 (1.21 to 1.30)** | **1.05 (1.00 to 1.10)** | **0.07 (0.02 to 0.12)** | Positive multiplicative positive additive |
| Yes | **1.03 (1.00 to 1.07)** | **1.36 (1.31 to 1.41)** | | | |
| **Lower Area-Level Socioeconomic Index** | | | | | |
| No | 1.00 (Reference) | **1.30 (1.26 to 1.34)** | 1.00 (0.96 to 1.04) | 0.04 (-0.01 to 0.09) | No multiplicative zero additive |
| Yes | **1.14 (1.10 to 1.18)** | **1.47 (1.43 to 1.52)** | | | |

[a] $PM_{10}$ categories were defined by the median value (22.8), the low category has a mean of 20.0 (SD=2) while the high category has a mean of 24.8 (SD=1).

**Table A15. Characteristics of Individuals Included in Aim 4 Overall and According to Outcome**

| | All individuals N=4 708 849 (%) | | Influenza or Pneumonia Hospitalization N=17 608 (%) | | Hospitalization for other LRIs[a] N=14 214 (%) | |
|---|---|---|---|---|---|---|
| Mean age (sd), y | 53 | (17) | 72 | (16) | 73 | (15) |
| Age ≥ 65 y | 1 216 876 | (25.8) | 12 482 | (70.9) | 11 278 | (79.3) |
| Male | 2 237 141 | (47.5) | 9 655 | (54.8) | 6 866 | (48.3) |
| *Income* | | | | | | |
| Low | 3 281 718 | (69.7) | 13 880 | (78.8) | 11 561 | (81.3) |
| Middle | 1 399 805 | (29.7) | 3 682 | (20.9) | 2 618 | (18.4) |
| High | 27 326 | (0.6) | 46 | (0.3) | 35 | (0.2) |
| *Smoking Status* | | | | | | |
| Nonsmoker | 3 072 021 | (65.2) | 9 870 | (56.1) | 8 261 | (58.1) |
| Former | 684 531 | (14.5) | 4 152 | (23.6) | 3 321 | (23.4) |
| Active | 952 297 | (20.2) | 3 586 | (20.4) | 2 632 | (18.5) |
| *Comorbidities* | | | | | | |
| Diabetes | 449 752 | (9.6) | 5 496 | (31.2) | 4 754 | (33.4) |
| Hypertension | 1 145 331 | (24.3) | 10 096 | (57.3) | 9 124 | (64.2) |
| COPD | 168 811 | (3.6) | 4 634 | (26.3) | 4 440 | (31.2) |
| Obesity | 1 063 305 | (22.6) | 6 423 | (36.5) | 6 004 | (42.2) |
| Dyslipidemia | 1 264 939 | (26.9) | 8 136 | (46.2) | 6 965 | (49.0) |
| Cardiovascular Disorders | 336 047 | (7.1) | 5 194 | (29.5) | 4 628 | (32.6) |
| Respiratory Disorders | 197 722 | (4.2) | 5 059 | (28.7) | 4 865 | (34.2) |
| *Health risk group* | | | | | | |
| Healthy | 2 356 569 | (50.0) | 2 212 | (12.6) | 1 099 | (7.7) |
| Low Risk | 1 411 953 | (30.0) | 3 861 | (21.9) | 2 462 | (17.3) |
| Moderate Risk | 705 072 | (15.0) | 5 744 | (32.6) | 5 066 | (35.6) |
| High Risk | 235 255 | (5.0) | 5 791 | (32.9) | 5 587 | (39.3) |
| *Urbanicity* | | | | | | |
| Cities | 2 925 072 | (62.1) | 11 384 | (64.7) | 9 602 | (67.6) |
| Towns and Suburbs | 1 374 400 | (29.2) | 4 792 | (27.2) | 3 509 | (24.7) |
| Rural Area | 409 377 | (8.7) | 1 432 | (8.1) | 1 103 | (7.8) |

[a] excluding influenza and pneumonia.

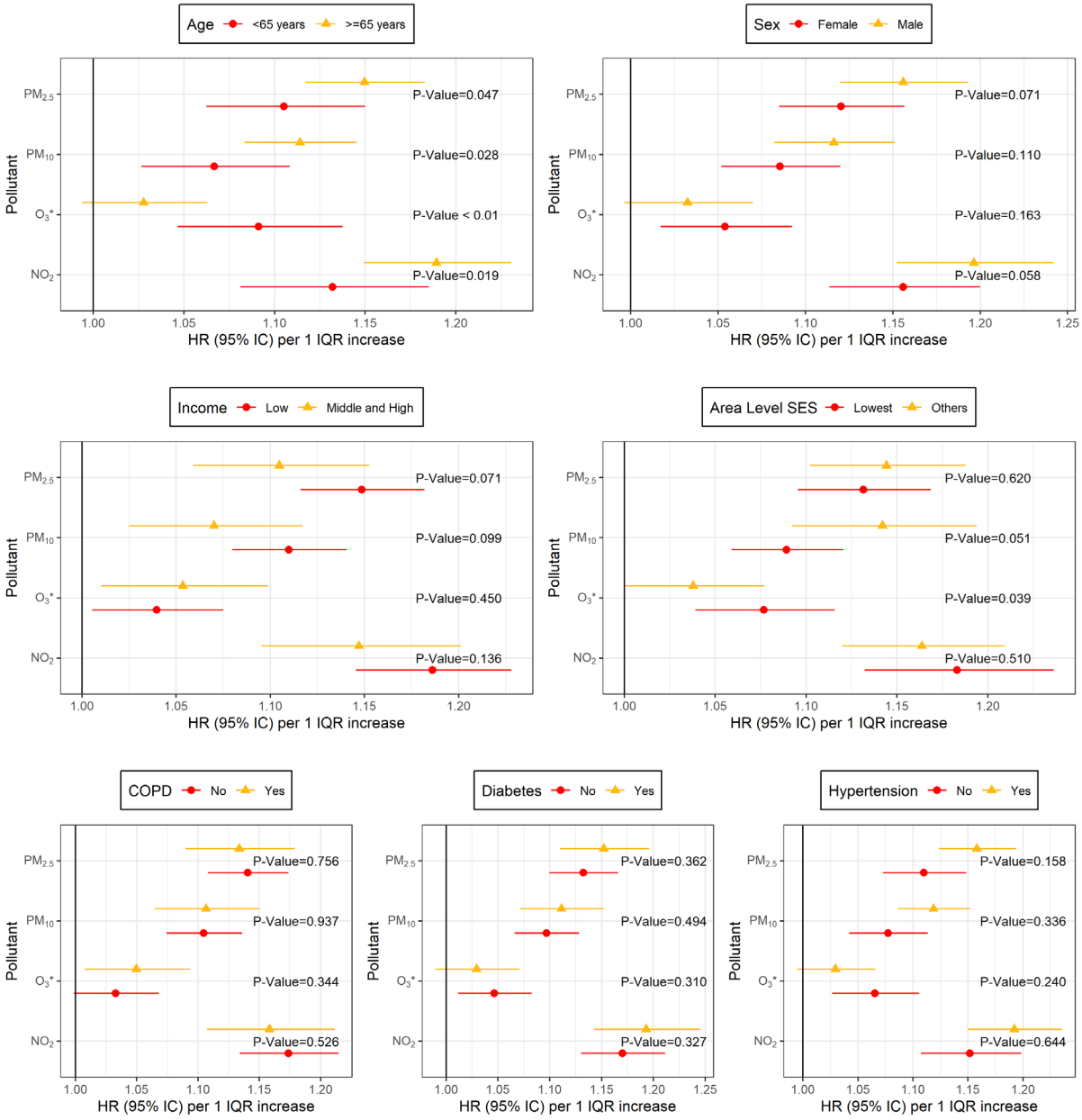



**Figure A10. Associations between long-term exposure to air pollution and hospital admission for lower respiratory infections according to vulnerability indicators.** P-values for interaction between continuous air pollution exposures and vulnerability indicator.

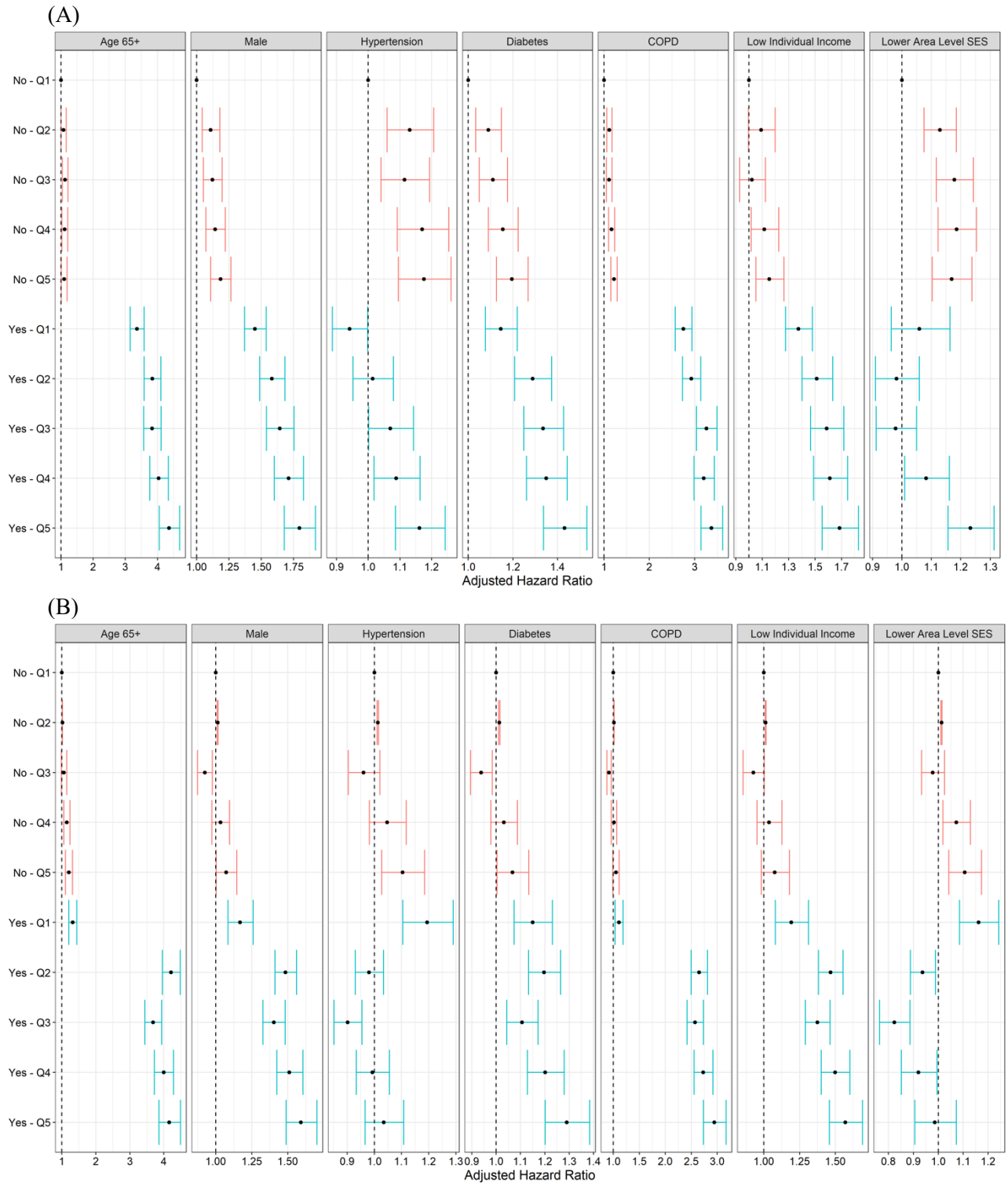



**Figure A11. Combined effects of long-term ambient (A) $PM_{10}$ and (B) $O_3$ and vulnerability indicators on the risk of hospital admission for lower respiratory infections.**

**Table A16. Association Between $NO_2$ and Hospital Admission for Lower Respiratory Infections by Vulnerability Indicators and Their Interaction on Additive and Multiplicative Scales**

| | $NO_2$ [a] | | Interaction in Multiplicative Scale | Interaction in Additive Scale | Type of interaction |
|---|---|---|---|---|---|
| | **Low** | **High** | **HR (95% CI)** | **RERI[b] (95% CI)** | |
| **Age, years** | | | | | |
| 22-64 | 1.00 (Reference) | 1.03 (0.97 to 1.09) | **1.09 (1.03 to 1.15)** | **0.38 (0.24 to 0.52)** | Positive multiplicative positive additive |
| 65+ | **3.43 (3.29 to 3.58)** | **3.84 (3.65 to 4.05)** | | | |
| **Male** | | | | | |
| No | 1.00 (Reference) | **1.06 (1.01 to 1.11)** | 1.02 (0.98 to 1.07) | 0.06 (0.00 to 0.12) | No multiplicative zero additive |
| Yes | **1.45 (1.40 to 1.51)** | **1.58 (1.50 to 1.65)** | | | |
| **Hypertension** | | | | | |
| No | 1.00 (Reference) | **1.06 (1.01 to 1.11)** | 1.02 (0.98 to 1.07) | 0.02 (-0.03 to 0.07) | No multiplicative zero additive |
| Yes | **0.93 (0.90 to 0.97)** | 1.01 (0.96 to 1.06) | | | |
| **Diabetes** | | | | | |
| No | 1.00 (Reference) | **1.08 (1.03 to 1.12)** | 0.99 (0.94 to 1.04) | 0.00 (-0.06 to 0.06) | No multiplicative zero additive |
| Yes | **1.19 (1.14 to 1.23)** | **1.27 (1.21 to 1.33)** | | | |
| **Chronic Obstructive Pulmonary Disease** | | | | | |
| No | 1.00 (Reference) | **1.08 (1.04 to 1.13)** | 0.97 (0.92 to 1.02) | 0.04 (-0.10 to 0.19) | No multiplicative zero additive |
| Yes | **2.81 (2.70 to 2.93)** | **2.94 (2.79 to 3.09)** | | | |

| | | | | | |
|---|---|---|---|---|---|
| **Low individual income** | | | | | |
| No | 1.00 (Reference) | 1.04 (0.98 to 1.11) | 1.04 (0.98 to 1.10) | **0.07 (0.00 to 0.14)** | No multiplicative positive additive |
| Yes | **1.41 (1.35 to 1.47)** | **1.53 (1.45 to 1.62)** | | | |
| **Lower area-level SES** | | | | | |
| No | 1.00 (Reference) | **1.06 (1.02 to 1.11)** | 1.05 (0.98 to 1.11) | 0.04 (-0.02 to 0.10) | No multiplicative zero additive |
| Yes | **0.92 (0.87 to 0.97)** | 1.02 (0.97 to 1.07) | | | |

[a]categories defined by the median value (27.1), the low category has a mean of 17.1 (SD=6) while the high category has a mean of 33.6 (SD=6).
[b]RERI = relative excess risk due to interaction.

**Table A17. Association Between $PM_{2.5}$ and Hospital Admission for Lower Respiratory Infections by Vulnerability Indicators and Their Interaction on Additive and Multiplicative Scales**

| | $PM_{2.5}$ [a] | | Interaction in Multiplicative Scale | Interaction in Additive Scale | Type of Interaction |
|---|---|---|---|---|---|
| | **Low** | **High** | **HR (95% CI)** | **RERI[b] (95% CI)** | |
| **Age, years** | | | | | |
| 22-64 | 1.00 (Reference) | 1.03 (0.98 to 1.09) | **1.06 (1.00 to 1.12)** | **0.30 (0.17 to 0.42)** | Positive multiplicative positive additive |
| 65+ | **3.48 (3.34 to 3.63)** | **3.81 (3.63 to 3.99)** | | | |
| **Male** | | | | | |
| No | 1.00 (Reference) | **1.06 (1.01 to 1.10)** | 1.04 (0.99 to 1.09) | **0.08 (0.02 to 0.15)** | No multiplicative positive additive |
| Yes | **1.44 (1.39 to 1.50)** | **1.58 (1.52 to 1.65)** | | | |
| **Hypertension** | | | | | |
| No | 1.00 (Reference) | **1.07 (1.02 to 1.11)** | 1.02 (0.97 to 1.07) | 0.01 (-0.03 to 0.06) | No multiplicative zero additive |
| Yes | **0.93 (0.90 to 0.97)** | 1.01 (0.97 to 1.06) | | | |
| **Diabetes** | | | | | |
| No | 1.00 (Reference) | **1.07 (1.03 to 1.11)** | 1.02 (0.96 to 1.07) | 0.03 (-0.03 to 0.09) | No multiplicative zero additive |
| Yes | **1.17 (1.13 to 1.22)** | **1.27 (1.22 to 1.33)** | | | |
| **Chronic Obstructive Pulmonary Disease** | | | | | |
| No | 1.00 (Reference) | **1.08 (1.04 to 1.13)** | 1.00 (0.95 to 1.06) | **0.15 (0.01 to 0.29)** | No multiplicative positive additive |

| | | | | | |
|---|---|---|---|---|---|
| Yes | **2.75 (2.64 to 2.879** | **2.98 (2.85 to 3.12)** | | | |
| **Low individual income** | | | | | |
| No | 1.00 (Reference) | **1.05 (1.00 to 1.12)** | 1.03 (0.97 to 1.09) | **0.07 (0.00 to 0.13)** | No multiplicative positive additive |
| Yes | **1.42 (1.36 to 1.49)** | **1.54 (1.47 to 1.62)** | | | |
| **Lower area-level SES** | | | | | |
| No | 1.00 (Reference) | **1.07 (1.03 to 1.11)** | 1.03 (0.97 to 1.09) | 0.03 (-0.03 to 0.08) | No multiplicative zero additive |
| Yes | **0.93 (0.88 to 0.98)** | 1.03 (0.98 to 1.07) | | | |

[a] $PM_{2.5}$ categories defined by the median value (13.8), the low category has a mean of 12.3 (SD=1) while the high category has a mean of 14.9 (SD=1).
[b] Relative Excess Risk due to Interaction.

**Table A18. Association Between $PM_{10}$ and Hospital Admission for Lower Respiratory Infections by Vulnerability Indicators and Their Interaction on Additive and Multiplicative Scales**

| | $PM_{10}$[a] | | Interaction in Multiplicative Scale | Interaction in Additive Scale | Type of Interaction |
|---|---|---|---|---|---|
| | Low | High | HR (95% CI) | RERI[b] (95% CI) | |
| **Age, years** | | | | | |
| 22-64 | 1.00 (Reference) | 1.02 (0.97 to 1.07) | **1.08 (1.02 to 1.14)** | **0.32 (0.20 to 0.44)** | Positive multiplicative positive additive |
| 65+ | **3.45 (3.30 to 3.59)** | **3.78 (3.62 to 3.96)** | | | |
| **Male** | | | | | |
| No | 1.00 (Reference) | **1.04 (1.00 to 1.08)** | **1.05 (1.00 to 1.10)** | **0.10 (0.04 to 0.16)** | Positive multiplicative positive additive |
| Yes | **1.43 (1.38 to 1.48)** | **1.57 (1.51 to 1.63)** | | | |
| **Hypertension** | | | | | |
| No | 1.00 (Reference) | **1.05 (1.00 to 1.09)** | 1.04 (0.99 to 1.09) | 0.03 (-0.01 to 0.08) | No multiplicative zero additive |
| Yes | **0.92 (0.89 to 0.96)** | 1.00 (0.96 to 1.05) | | | |
| **Diabetes** | | | | | |
| No | 1.00 (Reference) | **1.07 (1.03 to 1.10)** | 1.01 (0.96 to 1.06) | 0.02 (-0.03 to 0.08) | No multiplicative zero additive |

| | | | | | |
|---|---|---|---|---|---|
| Yes | **1.17 (1.13 to 1.22)** | **1.26 (1.21 to 1.32)** | | | |
| **Chronic Obstructive Pulmonary Disease** | | | | | |
| No | 1.00 (Reference) | **1.07 (1.04 to 1.11)** | 1.00 (0.95 to 1.06) | 0.13 (-0.01 to 0.26) | No multiplicative zero additive |
| Yes | **2.76 (2.64 to 2.87)** | **2.95 (2.83 to 3.09)** | | | |
| **Low individual income** | | | | | |
| No | 1.00 (Reference) | **1.05 (0.99 to 1.11)** | 1.02 (0.96 to 1.08) | 0.05 (-0.01 to 0.12) | No multiplicative zero additive |
| Yes | **1.43 (1.36 to 1.49)** | **1.53 (1.46 to 1.61)** | | | |
| **Lower area-level SES** | | | | | |
| No | 1.00 (Reference) | **1.06 (1.02 to 1.09)** | **1.06 (1.00 to 1.12)** | 0.05 (-0.01 to 0.11) | Positive multiplicative zero additive |
| Yes | **0.91 (0.87 to 0.96)** | 1.02 (0.98 to 1.06) | | | |

[a] $PM_{10}$ categories defined by the median value (22.8), the low category has a mean of 20.5 (SD=2) while the high category has a mean of 24.4 (SD=1).
[b] Relative Excess Risk due to Interaction.

**Table A19. Association Between $O_3$ and Hospital Admission for Lower Respiratory Infections by Vulnerability Indicators and Their Interaction on Additive and Multiplicative Scales**

| | $O_3$[a] | | Interaction in Additive Scale | Interaction in Multiplicative Scale | Type of Interaction |
|---|---|---|---|---|---|
| | **Low** | **High** | **RERI[b] (95% CI)** | **HR (95% CI)** | |
| **Age, years** | | | | | |
| 22-64 | 1.00 (Reference) | **1.16 (1.10 to 1.22)** | 0.07 (-0.07 to 0.21) | **0.92 (0.87 to 0.97)** | No multiplicative positive additive |
| 65+ | **3.74 (3.58 to 3.89)** | **3.96 (3.76 to 4.17)** | | | |
| **Male** | | | | | |
| No | 1.00 (Reference) | **1.12 (1.07 to 1.17)** | 0.00 (-0.07 to 0.06) | 0.96 (0.92 to 1.01) | No multiplicative zero additive |
| Yes | **1.50 (1.45 to 1.55)** | **1.62 (1.55 to 1.70)** | | | |
| **Hypertension** | | | | | |
| No | 1.00 (Reference) | **1.13 (1.08 to 1.19)** | -0.05 (-0.10 to 0.00) | 0.96 (0.91 to 1.00) | No multiplicative zero additive |
| Yes | **0.96 (0.93 to 1.00)** | 1.04 (0.99 to 1.09) | | | |
| **Diabetes** | | | | | |
| No | 1.00 (Reference) | **1.10 (1.06 to 1.14)** | 0.02 (-0.04 to 0.08) | 1.00 (0.95 to 1.05) | No multiplicative zero additive |
| Yes | **1.18 (1.14 to 1.22)** | **1.30 (1.24 to 1.36)** | | | |
| **Chronic Obstructive Pulmonary Disease** | | | | | |
| No | 1.00 (Reference) | **1.09 (1.05 to 1.14)** | **0.22 (0.08 to 0.37)** | 1.02 (0.97 to 1.08) | Positive multiplicative zero additive |
| Yes | **2.73 (2.63 to 2.84)** | **3.04 (2.90 to 3.20)** | | | |

| | | | | | |
|---|---|---|---|---|---|
| **Low individual income** | | | | | |
| No | 1.00 (Reference) | **1.13 (1.06 to 1.20)** | 0.01 (-0.06 to 0.08) | 0.97 (0.91 to 1.03) | No multiplicative zero additive |
| Yes | **1.47 (1.41 to 1.53)** | **1.61 (1.53 to 1.69)** | | | |
| **Lower area-level SES** | | | | | |
| No | 1.00 (Reference) | **1.09 (1.04 to 1.13)** | 0.05 (-0.01 to 0.11) | **1.06 (1.00 to 1.13)** | No multiplicative positive additive |
| Yes | **0.89 (0.86 to 0.92)** | 1.03 (0.97 to 1.08) | | | |

[a] $O_3$ categories defined by the median value (94.2), the low category has a mean of 88.9 (SD=7) while the high category has a mean of 99.2 (SD=3).
[b] Relative Excess Risk due to Interaction.

**Table A20. Summary of Individual-Level Cohort Studies of Long-Term Air Pollution Exposure and Severe COVID-19 Outcomes**

| Population | Exposures | Outcomes | Reference increase | Findings |
|---|---|---|---|---|
| **COVID-19 positive** | | | | |
| 1,128 COVID-19 patients diagnosed at University of Cincinnati healthcare system (UC Health) (Mendy, Resp Med 2021) [2] | $PM_{2.5}$ | COVID-19 hospitalization | OR per 1μg/m$^3$ in average and maximal $PM_{2.5}$ | 0.99 (0.79-1.23) for average $PM_{2.5}$<br>0.95 (0.81-1.11) for maximal $PM_{2.5}$ |
| 2,112 COVID-19 hospitalized patients in Catalonia, Spain (Marquès, EI 2022) [3] | $PM_{10}$<br>$NO_2$ | Severe COVID-19<br>Death | OR for categorical (High vs Low) exposure to pollutants according to WHO: ≥20 for $PM_{10}$ and ≥40 for $NO_2$ | 1.65 (1.32-2.06) for Severe COVID $PM_{10}$<br>2.37 (1.71-3.32) for Death $PM_{10}$<br><br>0.75 (0.57-0.99) for Severe COVID $NO_2$<br>0.77 (0.54-1.10) for Death $NO_2$ |
| 169K COVID-19 diagnosed US Veterans (Bowe, Environ Int 2021) [4] | $PM_{2.5}$ | COVID-19 hospital admission | RR per IQR (1.9 μg/m$^3$) annual avg $PM_{2.5}$ | 1.10 (1.08, 1.12) |
| 6,524 COVID hospitalized individuals in NYC (Bozack, AJRCCM 2021) [4] | $PM_{2.5}$, $NO_2$, BC | Mortality, ICU admission and Intubation | RR per 1 μg/m$^3$ annual avg $PM_{2.5}$ | 1.11 (1.02, 1.21) mortality<br>1.13 (1.00, 1.28) ICU<br>1.05 (0.91, 1.20) Intubation<br>No associations for $NO_2$ or BC |
| 75,000 COVID diagnosed individuals in Kaiser Permanente, California (Chen, AJRCCM 2022) [5] | $PM_{2.5}$, $NO_2$, $O_3$ | COVID hospital admission<br>ICU admission<br>Ventilation (IRS)<br>Mortality | RR per SD (1.5 μg/m$^3$) in 1 yr $PM_{2.5}$ | 1.24 (1.16, 1.32) hospital admis (30d)<br>1.33 (1.20,1.47) IRS<br>1.32 (1.16, 1.51) ICU<br>1.14 (1.02, 1.27) Mortality (60d)<br><br>Null association with $NO_2$ |
| 150,000 COVID-diagnosed individuals in Ontario | $PM_{2.5}$, $NO_2$, $O_3$ | COVID hospital | RR per IQR (1.7 | 1.06 (1.01, 1.12) hospital admis |

| Population | Exposures | Outcomes | Reference increase | Findings |
|---|---|---|---|---|
| (Chen, CMAJ 2022) [6] | | admission<br>ICU admission<br>Mortality | µg/m$^3$) $PM_{2.5}$ | 1.09 (0.98, 1.21) ICU<br>1.00 (0.90, 1.11) Mortality<br><br>Null association with $NO_2$<br>Positive association with $O_3$ |
| 3,139,804 individuals with COVID-19 in California (English, EA 2022) [7] | $PM_{2.5}$ | Death | RR for 1-unit $PM_{2.5}$<br>RR for PM quintiles | 1.04 (1.03-1.05) per 1-unit<br>1.18 (1.11-1.25) for lowest quintile (9.9-11.2 µg)<br>1.56 (1.43-1.71) for highest quintile (16.2-18.8 µg) |
| **Non-COVID cohort** | | | | |
| Selected population | | | | |
| 9,605 individuals in Catalonia (Kogevinas, EHP 2021) [8] | $PM_{2.5}$, $NO_2$, BC, $O_3$ | Severe COVID (Hospital admission/ ICU/ Oxygen) | RRR per IQR $PM_{2.5}$<br>RRR per IQR $NO_2$ | 1.51 (1.06, 2.16) for $PM_{2.5}$<br>1.26 (0.89, 1.79) for $NO_2$ |
| 424,721 individuals in England (UK-Biobank) (Sheridan, EP 2022) [9] | $PM_{2.5}$, $PM_{10}$, $NO_2$ | COVID-19 hospitalization<br>COVID-19 deaths | OR per IQR $PM_{2.5}$ (1.27)<br>OR per IQR $PM_{10}$ (1.75)<br>OR per IQR $NO_2$ (9.93) | 1.01 (0.95-1.09) Hosp for $PM_{2.5}$<br>1.02 (0.94-1.11) Hosp for $NO_2$<br>1.00 (0.89-1.11) Death for $PM_{2.5}$<br>1.03 (0.90-1.16) Death for $NO_2$<br>Similar results for $PM_{10}$ |
| General population | | | | |
| 1,594,308 aged 30+ residents in Rome (Nobile F, ERJ 2022) [10] | $PM_{2.5}$, $NO_2$ | COVID-19 death | HR per IQR $PM_{2.5}$ (0.92)<br>HR per IQR $NO_2$ (9.22) | 1.08 (1.03, 1.13) for $PM_{2.5}$<br>1.09 (1.02, 1.16) for $NO_2$ |

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