

Environmental Exposures and Long COVID in a Prospective Population-Based Study in Catalonia (COVICAT Study)

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Introduction

Long COVID is a multisystemic condition following acute infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) characterized by symptoms like fatigue, shortness of breath, cognitive dysfunction, pain, digestive symptoms, and/or depression and anxiety persisting for at least 2 months after primary infection and not explained by alternative diagnosis.^{1,2} We previously linked air pollution with the risk of COVID-19 incidence, severity, and lower COVID-19 vaccine response.^{3,4} Similar to others, we found that air pollution was associated with the severity of COVID-19 and that COVID-19 severity was associated with an increased risk of long COVID. In this study, we examine the associations of exposure to air pollution, green spaces, road-traffic noise, and artificial light at night (ALAN) with the risk of long COVID and symptoms persistence.

Methods

The COVICAT cohort is a COVID-19 population-based cohort designed to characterize the health impact of the COVID-19 pandemic on the population in Catalonia, Spain.^{3,5} Baseline data originates from the GCAT cohort, including residents in Catalonia (40–65 years of age) with available health data prior to the pandemic. Online-based questionnaires were administered three times during the pandemic in 2020, 2021, and 2023 to collect self-reported information on COVID-19 symptoms and previous COVID-19 infections⁵ as well as sociodemographic information, including age, sex, education (less than primary school, primary school, secondary school, university, and other), clinical [COVID-19 severity classified according to the World Health Organization (WHO) as asymptomatic, mild/moderate, severe/critical; and chronic disease in 2021, yes/no using a list of 18 diseases], general health status (excellent/great, fine, regular/bad), body mass index (BMI), and vaccination status (number of doses before first infection). Missing data in 2021 and 2023 were replaced using individual information

from the 2020 COVICAT questionnaire. We defined SARS-CoV-2 as follows: *a*) infection self-reported: positive viral detection test (polymerase chain reaction or antigen test), COVID-19 disease, hospitalization, or intensive care unit (ICU) admission due to COVID-19; *b*) identification of a positive test through record linkage with the repository of SARS-CoV-2 tests of the Emergency Electronic Health Records (EHRs); *c*) identification of a diagnosis, hospitalization, or ICU admission due to COVID-19 disease (ICD-10 codes U071, U072, U10, or J1282) through record linkage with EHRs; or *d*) SARS-CoV-2 seropositivity for the subsample with serological testing from any time (2020–2023) based on our antibody data.⁵ The current analysis is restricted to 2,853 individuals with complete information who reported at least one SARS-CoV-2 infection between 2020 and 2023. Among them, we defined long COVID following a modified WHO definition and recent publications^{2,6} as self-report of at least one long COVID symptom, evidence for organ associated dysfunction for a duration of ≥ 3 months, or doctor diagnosis of long COVID. In the subset of participants with long COVID in 2021, we defined persistent long COVID if long COVID had been reported previously and symptoms were still present during the last week before the 2023 interview. Ethical approval for COVICAT was obtained from the Parc de Salut Mar Ethics Committee (CEIM-PS MAR, number 2020/9307/I) and Hospital Universitari Germans Trias i Pujol Ethics Committee (CEI number PI-20-182). All participants provided informed consent.

In 2019, annual averages of particulate matter with diameter $<2.5 \mu\text{g}/\text{m}^3$ (PM_{2.5}), nitrogen dioxide (NO₂), and ozone (O₃) were estimated at each participant's residential address with a spatial resolution of 250 m from the COVAIR-CAT exposure assessment models.⁴ Percent of green space (2005) was available within 300 m buffers and normalized difference vegetation index (NDVI) (2019) at 250 m resolution. Nighttime road-traffic noise was estimated for the nearest road using the strategic noise maps for Catalonia for those with available exposure values within 25 m of residential home location (2012).⁷ Outdoor melanopic illuminance (blue light ALAN) was derived from the International Space Station (2013). Area-level deprivation index was available at census level (2011).⁸

We conducted mixed-effect robust Poisson regression models with census tract as random intercept to assess the association between each exposure, separately, and *a*) the risks of long COVID among all infected and *b*) the risk of persistent long COVID (a subset of all long COVID cases). Subjects with COVID-19 infection in 2020, 2021, or 2023 and who never reported long COVID symptoms served as the control group for all analyses. We reported risk ratios (RRs) by interquartile range (IQR) increase of each exposure's distribution in the whole study population. All models were adjusted for (Model 1) age, sex, educational level (as proxy to socioeconomic status), and quintiles of area-level deprivation; in

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Conclusions and opinions are those of the individual authors and do not necessarily reflect the policies or views of EHP Publishing or the National Institute of Environmental Health Sciences.

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Model 2 for general health status and chronic diseases; and in Model 3 for severity of COVID-19 and preinfection vaccination status. Observations with missing exposure values are excluded from the single-exposure models (1,124 were excluded from the L_{night} and 770 from the ALAN analyses). All analyses were restricted to participants with available covariate data for all three models. Nonlinearity in the exposure–response curves were tested using generalized additive models for the four air pollutants (NO_2 , O_3 , PM_{10} , and $\text{PM}_{2.5}$), using the adjustment of Model 2. Statistical analyses were performed using STATA version 18.0. Statistical significance was evaluated at the level $\alpha = 5\%$.

Results

Between 2021 and 2023, the cumulative incidence of long COVID among those infected ($n = 2,853$) was 24.5% ($n = 700$) and 5% for persistent long COVID ($n = 153$). There were small differences in long COVID risk by age. Long COVID risk was more common in women (27.6%, $n = 1,788$) compared to men (19.4%, $n = 1,065$) and in those with primary or lower education (29.2%, $n = 219$) compared to those with university education (22.2%, $n = 1,557$). Prevalence of long COVID was higher among those with prior chronic diseases (33.3%, $n = 1,013$) compared to those without (19.7%, $n = 1,840$) and among those with severe COVID-19 (71.8%, $n = 85$) compared to those with mild/moderate COVID-19 (25.1%, $n = 2,380$) or those asymptomatic (10.3%, 388). Prevalence was lower among those vaccinated prior to first infection (15.4%, $n = 2,003$) compared to those not vaccinated (46.0%, $n = 850$).

No significant association emerged for any of the environmental exposures examined and the risk of ever long COVID (Table 1). For persistent long COVID compared to those without long COVID, we observed a nonstatistically significant association for $\text{PM}_{2.5}$ [RR = 1.14; 95% confidence interval (CI): 0.96, 1.36] and PM_{10} (RR = 1.15; 95% CI: 0.96, 1.39). Similar estimates were observed when additionally adjusting for COVID-19 severity and vaccination prior to first infection. Generalized additive models indicated a linear relationship for the association of particulate matter with persistent long COVID (Figure 1).

Discussion

We did not observe associations between major urban environmental factors and the risk of long COVID, except for particular matter (PM_{10} , $\text{PM}_{2.5}$) showing tendencies toward an increased risk for persistent long COVID. Our findings are in accord with previous limited evidence on air pollutants and long COVID^{9,10}. They are also, to some extent, in accord with prior evidence from the COVICAT population showing an association between air pollution concentrations on the risk of COVID-19^{3,5} but particularly higher risks for severe COVID-19, suggesting complex pathways in the impact of environmental factors on the risk of long COVID. We could speculate that the majority of effect of air pollution on long COVID is indirectly via increasing severity. This hypothesis is supported by the suggestive association between particulate matter and the most severe (persistent) cases of long COVID but not with all cases of long COVID. Further study of long COVID subtypes and symptoms could offer more detailed understanding of the observed associations. These findings contribute to understanding the complex interplay between environmental exposures and long-term COVID-19 outcomes.

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Table 1. Association between environmental exposures and long COVID. Mixed-effect Poisson regression models with census tract as random intercept. Risk ratio estimates reported by IQR unit increase of each exposure's distribution in the study population. Individuals who reported COVID infection but never long COVID are used as control group for all analyses. COVICAT cohort, Catalonia, Spain.

	Never long COVID (control)			Ever long COVID			Persistent long COVID ^a		
	Exposure ^b		Exposure <i>n</i> = 700 [median (IQR)]	Model 1 ^c		Model 3 ^e	Model 1 ^c		Model 3 ^e
	<i>n</i> = 2,153 [median (IQR)]	Total (<i>n</i>)		RR (95% CI)	RR (95% CI)		RR (95% CI)	RR (95% CI)	RR (95% CI)
% Green space (300 m)	9.9 (16.4)	2,853	10.8 (18.6)	1.04 (0.97, 1.11)	1.04 (0.98, 1.11)	1.02 (0.97, 1.08)	1.00 (0.85, 1.18)	1.00 (0.86, 1.16)	1.00 (0.89, 1.13)
NDVI (median)	0.2 (0.1)	2,852	0.2 (0.1)	1.05 (0.98, 1.12)	1.05 (0.98, 1.12)	1.04 (0.98, 1.10)	1.05 (0.89, 1.25)	1.05 (0.90, 1.24)	1.05 (0.91, 1.19)
NDVI (mean)	0.2 (0.1)	2,852	0.2 (0.1)	1.05 (0.98, 1.13)	1.06 (0.99, 1.13)	1.04 (0.98, 1.11)	1.04 (0.88, 1.25)	1.05 (0.89, 1.23)	1.04 (0.91, 1.20)
NO_2	33.3 (11.6)	2,852	33.3 (10.0)	1.03 (0.95, 1.12)	1.02 (0.94, 1.11)	1.03 (0.95, 1.11)	1.07 (0.89, 1.29)	1.06 (0.89, 1.27)	1.07 (0.90, 1.26)
O_3 (warm season)	88.8 (12.7)	2,852	89.4 (10.1)	1.05 (0.95, 1.16)	1.06 (0.96, 1.16)	1.03 (0.95, 1.13)	1.09 (0.88, 1.37)	1.11 (0.88, 1.38)	1.06 (0.87, 1.29)
PM_{10}	23.9 (3.7)	2,852	23.9 (3.6)	1.01 (0.93, 1.10)	1.00 (0.92, 1.08)	1.00 (0.92, 1.08)	1.17 (0.96, 1.42)	1.16 (0.96, 1.39)	1.15 (0.98, 1.35)
$\text{PM}_{2.5}$	15.0 (2.8)	2,852	15.0 (2.5)	1.01 (0.94, 1.09)	1.01 (0.93, 1.09)	1.01 (0.94, 1.08)	1.15 (0.97, 1.37)	1.15 (0.97, 1.36)	1.14 (0.97, 1.33)
Transportation noise at night (L_{night})	55.0 (9.0)	1,760	55.0 (9.0)	0.90 (0.81, 1.01)	0.92 (0.82, 1.02)	0.94 (0.85, 1.03)	1.08 (0.78, 1.50)	1.09 (0.81, 1.47)	1.07 (0.87, 1.31)
Blue light ALAN	0.2 (0.2)	2,102	0.2 (0.2)	0.98 (0.91, 1.06)	0.97 (0.90, 1.05)	1.01 (0.94, 1.08)	1.00 (0.85, 1.17)	0.99 (0.84, 1.16)	1.10 (0.93, 1.29)

Note: ALAN, artificial light at night (blue light spectrum); CI, confidence interval; IQR, interquartile range; L_{night} , average noise level during the night period (2200 to 0600 hours) in decibels; NDVI, normalized difference vegetation index; NO_2 ; nitrogen dioxide; O_3 , ozone; PM_{10} , particulate matter with diameter $< 10 \mu\text{g}/\text{m}^3$; $\text{PM}_{2.5}$, particulate matter with diameter $< 2.5 \mu\text{g}/\text{m}^3$. Overall, 1,124 missing observations were excluded from the analyses for L_{night} (264 for ever long COVID) and 770 for ALAN (166 for ever long COVID).

^aPersistent long COVID cases are a subset of ever long COVID cases that had symptoms both in 2021 and 2023 (see Methods).

^bAll summary exposure values are reported as the median (IQR) unless otherwise noted.

^cModel 1: Adjusted for age, sex, educational level, and quintiles of area-level deprivation.

^dModel 2: Model 1 + health status and chronic diseases (2021).

^eModel 3: Model 2 + COVID severity + number of vaccine doses.

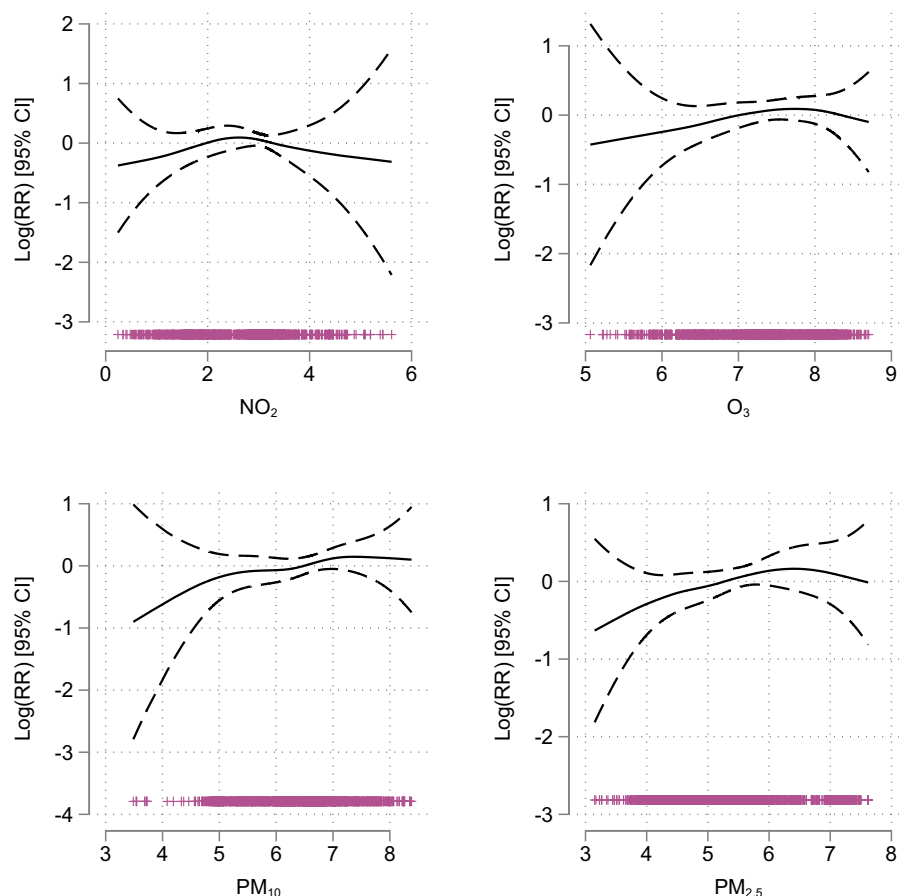


Figure 1. Generalized additive models showing the dose–response relationship of air pollutants with persistent long COVID. The x-axis represents the levels of exposure for each specific pollutant per unit increase in population interquartile range (IQR). The y-axis represents the prediction for the risk of persistent long-COVID in the log-scale. 95% confidence intervals are displayed with dotted lines. The bar at the bottom of each figures represents the exposure (IQR) distribution in the study population. Note: COVICAT Cohort (Catalonia, Spain), $n = 2,306$. NDVI, normalized difference vegetation index; NO_2 , nitrogen dioxide; O_3 , ozone; PM_{10} , particulate matter with diameter $< 10 \mu\text{g}/\text{m}^3$; $\text{PM}_{2.5}$, particulate matter with diameter $< 2.5 \mu\text{g}/\text{m}^3$; RR, risk ratio.

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