EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original research article

Pre-admission ambient air pollution and blood soot particles predict hospitalisation outcomes in COVID-19 patients

Stijn Vos, Elien De Waele, Pieter Goeminne, Esmée M. Bijnens, Eva Bongaerts, Dries S. Martens, Robert Malina, Marcel Ameloot, Karolien Dams, Annick De Weerdt, Geert Dewyspelaere, Rita Jacobs, Geert Mistiaen, Philippe Jorens, Tim S. Nawrot

Please cite this article as: Vos S, De Waele E, Goeminne P, *et al*. Pre-admission ambient air pollution and blood soot particles predict hospitalisation outcomes in COVID-19 patients. *Eur Respir J* 2023; in press (https://doi.org/10.1183/13993003.00309-2023).

Pre-admission ambient air pollution and blood soot particles predict hospitalisation outcomes in COVID-19 patients

Stijn Vos[1],* Elien De Waele[2],* Pieter Goeminne[2], Esmée M. Bijnens[1,3], Eva Bongaerts[1], Dries S. Martens[1], Robert Malina[1], Marcel Ameloot[4], Karolien Dams[5], Annick De Weerdt[5], Geert Dewyspelaere[2], Rita Jacobs[5], Geert Mistiaen[2], Philippe Jorens[5], Tim S. Nawrot[1,6]

*authors contributed equally

[1] Centre for Environmental Sciences, Hasselt University, Hasselt, Belgium

[2] VITAZ hospital Sint-Niklaas, Belgium

[3] Department of Environmental Sciences, Faculty of Science, Open University, Heerlen, The Netherlands

[4] Biomedical Research Institute, Hasselt University, Hasselt, Belgium

[5] Antwerp University Hospital, University of Antwerp (LEMP), Edegem, Belgium

[6] Department of Public Health & Primary Care, Occupational & Environmental Medicine, KU Leuven, Leuven, Belgium

Keywords

COVID-19, Disease Severity, SARS-CoV-2, Air Pollution, Particulate Matter

Corresponding author

Tim S. Nawrot, Agoralaan building D, 3590 Diepenbeek, Belgium

E-mail: tim.nawrot@uhasselt.be

ABSTRACT

Background

Air pollutant exposure is one of the major risk factors for aggravation of respiratory diseases. We investigated whether exposure to air pollution and accumulated black carbon particles in blood were associated with COVID-19 disease severity, including the risk for intensive care and duration of hospitalisation.

Methods

From May 2020 until March 2021, 328 hospitalised COVID-19 patients (29% at intensive care) were recruited from 2 hospitals in Belgium. Daily exposure levels (from 2016 to 2019) for particulate matter ($PM_{2.5}$ and PM_{10}), nitrogen dioxide (NO_2) and black carbon were modelled using a high-resolution spatiotemporal model. Blood black carbon particles (internal exposure to nano-sized particles) were quantified using pulsed laser illumination. Primary clinical parameters and outcomes included duration of hospitalisation, and risk of intensive care.

Results

Independent of potential confounders, an interquartile range (IQR) increase in exposure in the week before admission was associated with increased duration of hospitalisation ($PM_{2.5}$:+4.22 (95%CI:0.74-7.69) days;,NO_2:+4.33 (1.30-7.37) days); Similar effects were observed for long-term NO_2 and BC exposure on hospitalisation duration. These effect-sizes for an IQR increase in air pollution on hospitalisation duration were equivalent to the effect of a 10-year increase in age on duration of hospitalisation. Furthermore, for an IQR higher blood black carbon load, the odds ratios for intensive care hospitalisation was 1.36 (1.11-1.70).

Conclusions

In hospitalised COVID-19 patients, higher pre-admission ambient air pollution and blood black carbon levels predicted adverse outcomes. Our findings imply that air pollution exposure influences on COVID-19 severity and therefor the burden on medical care systems during the COVID-19 pandemic.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic presented a challenge for health care burden worldwide. Patients with COVID-19 who are admitted to hospital are usually stratified for risk on the basis of age,[1] obesity,[1, 2] or with underlying diseases such as diabetes mellitus[3] and cardiovascular disease.[4] The burden of morbidity and mortality of COVID-19 has also varied across geographical location which supports a link between environmental factors and severe acute

respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission and COVID-19 susceptibility, severity and outcome.[5]

Ambient air pollution constitutes a serious risk factor not only for the emergence of respiratory and/or viral infections, but also for the development of reduced pulmonary function and/or aggravation of existing pulmonary diseases.[6, 7] During the COVID-19 pandemic, air pollution concentrations were lower than before the pandemic,[8] due to the positive impact of several lockdown related effects such as less traffic and reduced industrial activities on air quality. During the pandemic, the attributable relative risk factor of black carbon exposure levels on human health were significantly lower than before the pandemic.[8] Nonetheless, emerging data from epidemiological studies also suggest that both genetics but also air pollution may modulate the risk of disease by increasing patient susceptibility to infection, including COVID-19 Experimental data supports an important role of the ACE2 receptor, which COVID-19 viruses use to infiltrate target cells, in the pathophysiology of infection.[9] Indeed, studies showed that susceptibility to COVID-19 infection was correlated with ACE2 expression in cell lines.[6, 7, 10–15] Therefore, it is hypothesised that higher ACE2 protein level might be associated with a higher local viral load, and long-term exposure to $PM_{2.5}$ has been shown to increase the expression of angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine type 2 (TMPRSS2), proteins critical to SARS-CoV-2 entry into mice and host cells.[16, 17]

Pathophysiologically, the inhalation of elevated concentrations of air pollution results in inflammation processes of mucus membranes in the pulmonary tract and is a factor that could further influence the process of a COVID-19-infection related lung disease. But the earliest epidemiologic studies p assessing the relationship between air pollution and COVID-19 incidence have been subject to methodologic limitations that may introduce bias and limit causal inference.[5, 18–20] More recently, several studies have demonstrated associations between long-term air pollution and hospitalisation risk, ICU admission risk, and mortality using patient level data.[21–27] Currently, important indicators related not only disease severity, but also pressure on health care systems such has duration of hospitalisation have not been investigated in cohort studies.

Recently, we showed that short-term exposure to particulate and gaseous air pollution prior to hospital admission is an important and modifiable risk factor that prolongs the duration of ventilation in non-COVID critically ill patients.[28] Furthermore, recent evidence demonstrates that air pollution may be associated with COVID-19 disease severity. We therefore investigated whether long-term but also short-term exposure to air pollution prior to hospital admission explains the variable clinical and thus individualised course observed in hospitalised COVID-19 patients by examining duration of hospitalisation and risk of ICU admission, while also using a novel individual marker of BC exposure.

Additionally, we aimed to estimate potential healthcare costs associated with air pollution exposure in this context by making a health-economical translation based on our findings.

METHODS

Study design and participants

In total, we included 328 hospitalised patients with PCR-confirmed COVID-19. 283 were recruited at time of admission to the hospital VITAZ (Sint-Niklaas, Flanders, Belgium): including 233 hospitalised at the general COVID-19 ward and 50 patients who required intensive care soon after admission. Additionally within the same catchment area, 45 intensive care patients from the Antwerp University Hospital were recruited, who had been admitted to the ICU within 24 hours after hospital admission. Patients were recruited between May 2020 and March 2021. To be eligible, patients had to be ≥ 18 years old, and tested positive for COVID-19 by PCR, and not included in other ongoing clinical intervention studies, and not moved during the last 3 years. The participants enrolled in our study were not vaccinated at the time of the study. Based on information in the clinical records of the patients and the available information about dominant SARS-CoV-2 virus variant spread in Belgium and PCR tests, patients infected between May 2020 and February 13th 2021 were affected by the (original) Wuhan variant of the virus, while the majority of the patients recruited from February 14th 2021 until March 2021 were infected by the alfa variant of the virus.

Five patients (1.5%) living outside of Belgium had no information on residential exposure to air pollutants and were therefore excluded from analyses involving modelled air pollution exposures. Written informed consent was obtained from all participants or their closest relatives and ethical approval was given by the ethical committee of VITAZ hospital, Antwerp University hospital (EC20/25/323) and Hasselt University (Registration number: B2020115000006).

Demographic and clinical characteristics, such as ethnicity, sex, age, body mass index, smoking status (active, ex or never) and blood pressure on admission at the hospital were obtained from the medical records. We obtained via questionnaire information on education and occupation.

Educational attainment was assessed as the highest educational level successfully completed using the International Standard Classification of Education. Patients educational level was coded as low, middle, and high. Occupation was assessed using the International Standard Classification of Occupations (ISCO). We chose not to ask participants about personal income because, based on experience in other population-based studies in Belgium, this question is often considered a violation of privacy.[29, 30] Besides the aforementioned individual SES indicators, we determined neighbourhood income (median

annual household income), as this might reflect contextual associations and the geographical dispersion of potential risk factors.[31] More details can be found in supplemental information.

Blood and urine samples were collected at admission to the ward. Subsequently, the values of more general biochemical and haematological measurements were determined at the time of admission (including C-reactive protein (CRP), absolute white blood cell count (WBC) and number of monocytes, eosinophils, lymphocytes, neutrophils, platelets). Primary clinical outcomes used in this study included the duration of hospitalisation (defined as the total number of days that patients remained hospitalised from the date of hospitalisation until the date of hospital discharge), admission to intensive care.

Secondary endpoints included vasopressor usage (noradrenaline, adrenaline or vasopressin, as well as the total duration in days), necessity for invasive ventilation, and blood oxygen saturation (determined in the blood sample at the time of admission to the ward). The arterial partial pressure of oxygen to the fraction of inspired oxygen (PaO_2/FiO_2) on admission was recorded, a validated score to measure the impairment of oxygen uptake in severely impaired lungs.

We also collected data on parameters of comorbidity (Charlson Comorbidity Index[32] and the early warning score,[33–35] a scoring system which assists with the detection of changes in vital signs and may help to identify patients at risk for further clinical deterioration.

Residential ambient air pollution exposure

Daily residential exposure ($\mu g/m^3$) to particulate matter with aerodynamic diameter less than 2.5 µm ($PM_{2.5}$), less than 10 µm (PM_{10}), black carbon (BC), and nitrogen dioxide (NO_2) was estimated using a spatial-temporal interpolation method. Validation statistics of the model indicated that the spatial-temporal variability was explained by 80% for $PM_{2.5}$,[36] 70% for PM_{10}, 74% for BC,[37] and 78% for NO_2.[36] The model was further validated by as study that showed that urinary black carbon load was associated with annual residential modelled concentration.[38] We refer to the supplementary information for more details on the exposure modelling.

Blood black carbon load

The internal black carbon load was quantified in whole blood using a specific and sensitive detection technique based on white light generation of carbonaceous particles under femtosecond pulsed illumination as previously reported.[39] More details can be found in the supplemental information.

Statistical analyses and translation into health care costs

Statistical analyses were performed using R version 4.0.2 (R Core Tea, Vienna, Austria). The threshold for statistical significance was set at the 95% confidence limit (α = 5%). We used multiple linear

regression models to assess the association between predefined outcomes and recent, long-term ambient air pollution as well as the internal black carbon load. We determined Pearson correlation coefficients between the different short-term and long-term air pollution exposures (Table S1). Outcomes were divided into primary and secondary outcomes. Primary outcomes included the duration of hospitalisation, and risk of ICU admission. Secondary outcomes included early warning scores, PaO_2/FiO_2 ratio, blood oxygen saturation at the time of admission

Distributed lag models (DLM, using R package "dlnm" version 2.4.7) were used to estimate day-specific associations between short-term exposure to air pollutants in up to 30 days before admission. More details about the DLM models can be found in the supplemental information.

Binomial logistic regression models were used to estimate the Odds Ratios (OR) for admission to the intensive care unit (ICU), risk of ventilation and vasopressor usage.

All models were adjusted for the following previously reported risk factors and potential confounders: age, sex, body-mass index (BMI), education, neighbourhood median income, smoking status, average temperature at the day of admission, the Charlson comorbidity index, and estimated virus variant (based on dominant virus variant in Belgium at the time of admission). Additionally, we used Generalised Additive Models (GAM) to account for date of admission using a smoothed term for this covariate. Using this smoothed term for date of admission indicated better fitted to the data than adjusting for date of admission as either linear or quadratic terms. Finally, a sensitivity analysis was conducted to exclude a hospital related bias by dropping the smallest patient cohort (patients from University Hospital Antwerp) from the main analysis.

RESULTS

Study population

From May 2020 to March 2021, 328 participants were recruited (Table 1). The patients were on average aged 65.7 years (range: 20.1 to 98.3), included 148 (43.6%) women, 179 (56.6 %) patients with congestive heart failure, 73 (22.3%) with diabetes, and 63 (19.2%) participants with cancer. The mean early-warning score at admission was 3.10 (+-2.2).Most patients obtained a secondary education degree (n = 179, 54.8%), whereas 92 participants (28.0%) obtained a primary education degree or no degree at all and 57 participants (17.4%) obtained a college or university degree. A large proportion of the patients were of Caucasian ethnicity (n = 281, 85.7%). Patients with north-African ethnicity represented the second largest proportion (n = 32, 9.8%). Most patients never smoked (n = 172, 52.4%), whereas 9 patients (2.7%) were active smokers.

The distribution of the average residential exposure to $PM_{2.5}$, PM_{10}, BC and NO_2 (2 days and 7 days before admission, and average chronic exposure from 2016 to 2019) is described in Table 2. The measured black carbon particles in blood were significantly correlated with the modelled chronic exposure levels to black carbon (Spearman $r = 0.48$, $p < 0.01$, Figure S1).

The average duration of hospitalisation was 16.9 days (Table 1). The duration of hospitalisation was significantly associated with several demographic variables. Patient age was the strongest determining demographic factor explaining the duration of hospitalisation (Table S2). While controlling for all other demographic and clinical variables (sex, BMI, education, median neighbourhood income, smoking status, Charlson comorbidity index, average temperature at admission, date of admission and estimated virus variant), each 10-year increase in age, the duration of hospitalisation increased by 2.36 days ($p < 0.01$). Furthermore, men had a longer duration of hospitalisation on average than women (+3.99 days on average, $p = 0.07$). Date of admission was correlated with duration of stay was well ($p < 0.01$). None of the other covariates were significantly correlated with the duration of hospitalisation.

Duration of hospitalisation

Using distributed lag models (DLMs), we investigated day-specific differences in the duration of hospitalisation for increases in exposure to air pollutants 30 days before hospital admission (Figure 2). The DLM model identified the week before hospitalisation as the most significant recent exposure window (for $PM_{2.5}$, PM_{10} and NO_2 exposure) associated with the duration of hospitalisation.

Using average exposures calculated for short-term (2 days, and 7 days before admission) and long-term exposures, we observed that both short- and long-term exposures to $PM_{2.5}$, PM_{10} and NO_2 were associated with increases in the duration of hospitalisation (Table 3). On average, the duration of hospitalisation increased by 3 to 5 days for an interquartile range (IQR) increase in short-term exposure 7 days before admission ($PM_{2.5}$: +4.22 days; 95%CI: 0.74 to 7.69, PM_{10}: +4.46 days; 95%CI: 1.64 to 7.28, NO_2: +4.33 days; 95%CI: 1.30 to 7.37).

We observed a significant moderating effect of patient gender on the association between duration of hospitalisation and air pollutant exposure, with the effect of long- and short-term $PM_{2.5}$ and PM_{10} exposures being more pronounced for men than for women (Figure 1D, p-value interactions < 0.05). Similarly, the effect of short-term (but not long-term) NO_2 exposure was more pronounced in men (p-value interaction = 0.01). Patient BMI and diabetes did not moderate the same associations (p-value interactions > 0.05).

We used co-pollutant models to potentially identify key long-term pollutants (Table S3). We noted that the previously observed effects of long-term NO_2 (+4.39 days, 95%CI: 1.12-6.78) and BC (+3.48 days,

95%CI: 0.61-6.36) exposures on the duration of hospitalisation remained significant in the two-pollutant models that included both PM_{10}, and either NO_2 or BC exposure respectively.

We ran models mutually adjusted for long-term and short-term exposure (Table S4). For the mutually adjusted models, short-term exposure was defined as the average exposure 7 days before admission to the hospital. In the mutually adjusted models, effects for ambient $PM_{2.5}$ and PM_{10} remained significant for the short-term exposure, while for long-term exposure, black carbon exposure remained significant in the mutually adjusted model.

Finally, as sensitivity analysis we additionally adjusted for diabetes and last known occupation. While adjusting for diabetes (Table S5), we observed no notable difference in the previously reported effect estimates. When adjusting for occupation (Table S6), we observed non-significant trends for short-term average $PM_{2.5}$ (+3.40 days, 95%CI: -0.08 – 6.88) and NO_2 (+2.31 days, 95%CI: -0.74 – 5.53) exposures that were significant in the main models. However, effect estimates and overall confidence intervals remained largely comparable. Finally, excluding the smallest patient cohort (Antwerp University hospital) did not alter the aforementioned findings (Table S10).

Risk of admission to intensive care

The distribution of air pollution both long-term exposure to ambient particles (Figure 1A and 1B) and blood carbon particles differed significantly between ICU and non-ICU hospitalised patients.

The odds of admission to intensive care was significantly associated with the blood black carbon particle load (Figure 1C). The odds ratio for an interquartile-range (IQR) increase ($+9.27\times10^5$ particles per mL blood) in measured particles was 1.36 (95%CI:1.11-1.70). Long-term exposure to air pollutants was also associated with the odds of admission to the intensive care unit (Table 4). An IQR increase in long-term BC and NO_2 exposure was associated with an odds ratio of 2.26 (95%CI: 1.66-3.21) and 2.54 (95%CI: 1.81-3.70) respectively.

In addition to the long-term exposure, we observed a significant increase in the odds of admission to the intensive care unit for an IQR increase in the average exposure to NO_2 one week before admission (OR = 2.06, 95% CI:1.38 - 3.15). Sensitivity analysis revealed that excluding the patients recruited from Antwerp university hospital did not alter significantly the aforementioned associations (Table S11).

Secondary outcomes

We observed significant associations between short-term exposure to $PM_{2.5}$, PM_{10} and NO_2, and early warning scores at the time of admission (Table S7). An IQR increase in average PM_{10} exposure 7 days before admission was associated with a 0.32 point increase in the early-warning score on average ($p = 0.05$). The early warning score was not associated with long-term air pollutant indicators. Risk of

ventilation was associated with short-term exposure to NO_2 (OR = 2.08, 95%CI: 1.35 – 3.28, Table S7). In addition, long-term exposure to air pollutants was associated with the risk of ventilation (Figure 1C, Table 4). For an IQR increase in long-term PM_{10}, BC and NO_2 exposure, the odds ratios for the risk of ventilation were 1.34 (95%:1.02–1.83), 1.89 (95%CI:1.41–2.60), and 1.93 (95%CI:1.40-2.72) respectively.

Regarding vasopressor use, short-term NO_2 exposure was associated with higher odds for vasopressor usage (OR=1.97, 95%CI:1.87–2.07, Table 4). Long-term ambient air pollution was associated with increased odds of vasopressor usage (Figure 1C). For an IQR increase in long-term NO_2 and BC exposure, the odds ratios were 3.16 (95%CI:2.02–5.15), and 2.88 (95%CI:1.95-4.43) respectively. Furthermore, an IQR increase in number of BC particles per mL blood ($+9.27\times10^5$ particles) was associated with higher risk of vasopressor usage (OR = 1.38, 95%CI:1.05–1.78).

Long-term BC and NO_2 exposure were associated with lower PaO_2/FiO_2 ratios (Table S8; -30.2, 95%CI:-41.8 to -18.6 and -35.2, 95%CI:-48.6 to -21.8 respectively). Average NO_2 exposure one week before admission was associated with lower PaO_2/FiO_2 ratios as well (-26.7, 95%CI:-44.6 to -9.1).

The odds of vasopressor usage were higher for the same increase in particles per mL blood (OR = 1.23, 95%CI: 0.97-1.57, Table 4). Additionally, we observed a trend toward higher risk of ventilation with increasing black carbon load (OR = 1.19, 95%CI:0.98-1.44).

No associations were found between air pollutant exposure and blood oxygen saturation (Table S9).

DISCUSSION

Inhalation of elevated concentrations of air pollutants results in inflammation processes of mucus membranes in the pulmonary tract and is a factor that could influence the process of SARS-cov-2-infection. In this context, we investigated whether exposure to air pollutants (both recent and long-term exposure as well as ambient and internal markers of exposure including blood load of black carbon) on disease severity and clinical outcomes in phenotypically well -characterised hospitalised COVID-19 patients. We observed associations between short- and long-term $PM_{2.5}$, PM_{10}, and NO_2 exposure and several clinical features during COVID-19 hospitalisation including duration of hospitalisation, ventilation risk, and the risk for admission to the intensive care unit. Our findings show that exposure to air pollutants both recent and long-term exposures at relatively low levels has a significant impact on disease severity and progression for COVID-19 patients. The public health and clinical significance of our findings should not be understated, as we showed that the effect-magnitude of an IQR increase in long-term air pollution (e.g. contrasting NO_2 by 4.16 $\mu g/m^3$) on the duration of hospitalisation was roughly equivalent to the effect on hospitalisation of a 10-year increase in age. The

clinical significance of our findings is further evident from clinical interventions (with Il-6 receptor antagonist,[40] remdesivir,[41] and triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin[42]) on account of the reduction in the number of hospitalisation days, reported to be 5–10 days in these trials. Therefore, based on our observed effects of air pollution exposure on hospitalisation duration, it is clear that for relevant improvements in air quality, even at relatively low concentrations, health gains are in the order of 40 to 80% of the aforementioned proven novel therapies. These findings reinforce the existing call for action to reduce air pollution levels in order to limit the burden of COVID-19 and improve respiratory health worldwide.[43]Our study also confirmed previously identified important factors of COVID disease severity, namely patient gender. Although some studies noted a significant association between BMI and COVID-19 severity in hospitalised patients,[1, 2] others have not observed this effect.[44] In the latter study, it was suggested that the effect of BMI on COVID-19 susceptibility and severity may be mediated through other comorbidities and might be population dependent. We found that patient gender modified the association between short-term $PM_{2.5}$ exposure and the duration of hospital, with more pronounced associations in men than in women. This might be explained by underlying comorbidities that have a higher prevalence in men. However, our results suggest that the effect-modification of gender for COVID-19 disease severity of hospitalised patients by air pollution cannot be explained fully by differences in comorbidities, since we accounted for comorbidity score. Therefore, other susceptibility or biological factors might be involved as well.

Several mechanism might explain the observation of disease severity of hospitalised COVID-19 and air pollution.[5] First, air pollution might exacerbate comorbidities and other respiratory conditions associated with severe COVID-19. Second, air pollution might modify host susceptibility to infection and/or disease severity through immune response modification. Finally, air pollution might render the host defence mechanisms weakened by promoting host pathogen invasion when damaged by particulate invasion and causes systemic inflammation including oxidative stress,[45–49] influences lung epithelium integrity,[50] and could imbalance the immune system. Severe COVID-19 is associated with high inflammation and elevated levels of inflammatory cytokines. Exposure to ambient pollutants may worsen and/or sustain this inflammatory storm that is triggered by a SARS-CoV-2 infection including interleukins, interferons, tumour necrosis factor, colony stimulating factors, the chemokine family, and growth factors.[45] These inflammatory processes in the mucus membranes of the pulmonary tract which can result in pulmonary dysfunction, which in turn would have a negative impact on the disease progression of a COVID-19 infection.

Complementary to evidence of these plausible pathophysiological mechanisms, epidemiologic data show an association between air quality and the incidence of COVID-19 in the population, the risk for

hospitalisation and regional mortality.[5, 51–58] However, most studies to date, although reporting robust data, have some methodological shortcomings, associating group-level air pollution exposures with aggregate COVID-19 outcomes over a broad area, relying on COVID-19 disease incidence estimated from surveillance data.[5, 52–54, 56–59] or do not include short-term exposures to high concentrations of pollutants, such as might be experienced during a wildfire event.[58] Therefore, our data support the suggestion that studies investigating the relationship between air pollution and COVID-19 incidence could benefit significantly from personal monitoring to estimate individual-level air pollution exposures.[5]

The most important limitation is the limited sample size. Therefore, it is difficult to assess to what extent the study participants were representative for other populations. Further studies are required to substantiate our current observations on hospital related outcomes as well as on the potential role of air pollution on long-COVID. Additionally, studies aiming to obtain more insight in the role of air pollution and the ACE2 receptor in COVID-19 disease progression would be beneficial.. Additionally, we identified the first week before hospital admission as a potentially vulnerable time period for air pollution exposure. In this time period, it may be the case that patients were already showing symptoms of COVID-19, and therefore be self-isolating at home. However, we believe the determined air pollution exposures reflect the indoor pollution levels relatively accurately was well. Studies have previously reported high correlations between indoor and outdoor air pollution, with correlation coefficients ranging between 0.40 and 0.79.[60–62] Furthermore, we would argue that in case most participants self-isolated at home in the time period before hospital admission, this would actually reduce potential exposure misclassification due to participants not being at home 100% of the time and therefore improve our modelled air pollution estimates. Nevertheless, the ambient air concentrations in the current study area are representative for large European areas and our study sample included patients with a social-economic background based on educational level which is in line with the distribution in the general population.

On the other hand, we had well characterised patients, with patient level data about socio-economic status, age, gender, BMI, smoking status, and comorbidities for all participants, which allowed us to account for these potential confounding factors and avoid ecological bias. The participants enrolled in our study were unvaccinated and infected by the contemporary virus strains in the interval from May 2020 to March 2021, and findings were independent of seasonality, the date of admission and meteorological conditions such as the average temperature at the day of admission, which further reduces the risk our findings were confounded by external factors that could be related to both the clinical outcomes and air pollution exposure.

We took several parameters that could explain temporal patterns including date (as smoothed term), season of admission, dominant virus strains, and ambient temperature into account. In addition, the period of this study was before the start of the vaccination campaign in Belgium. For these reasons, we do not believe that temporal effects could have biased our studied outcomes. Further, COVID-19 patients were always transferred to hospitals with sufficient capacity. During this study, patients were only discharged from the hospital if physiological parameters (including hemodynamic characteristics, patient mobility, and a need for oxygen support) were stable. Hospital data showed that the average duration of stay of COVID-19 patients was not significantly shorter during peak months of the pandemic than during other months in the period of this study.

Furthermore, we used validated high-resolution spatiotemporal models to estimate air pollutant exposure. Additionally, we confirmed that external exposure was linked with internal exposure (blood carbon load). Despite the limited sample size, we observed significant and relatively large effects at low levels of air pollution exposure (in 2017, long term $PM_{2.5}$ exposure in Flanders averaged 12.8 $\mu g/m^3$) and therefore representative for large parts of the world.

Overall, our study in COVID-19 patients supports the concept that air pollution even at low levels is one of the factors that determines individualised disease severity or adverse COVID-19 outcomes in hospitalised covid-19 patients, with important consequences on the hospital burden and healthcare costs during the pandemic. Further, improvement in air quality might be in same order of magnitude to 50% of the effect seen by novel clinical medical interventions.[40–42]. Further studies are required to substantiate our current observations on hospital related outcomes as well as on the potential role of air pollution on long-COVID. Additionally, studies aiming to obtain more insight in the role of air pollution and the ACE2 receptor in COVID-19 disease progression would be beneficial.

ACKNOWLEDGMENTS

We would like to thank the team of the pneumology unit of the VITAZ hospital, Ina De Roeck, Karen Lievens, Evi Moestermans, Nienke Van Goeye, Petra Vertongen, and Kaatje Cruysberghs for their help in collecting the samples during the study period.

Role of the funding source

This research was supported by the Flemish administration department Omgeving and Methusalem funding. Dries S. Martens holds a postdoctoral grant from the Research Foundation Flanders (grant 12X9620N). The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or the writing of the report. All the authors had full access to all the data in the study and had final responsibility for the decision to submit the manuscript.

REFERENCES

1. Hendren NS, de Lemos JA, Ayers C, Das SR, Rao A, Carter S, Rosenblatt A, Walchok J, Omar W, Khera R, Hegde AA, Drazner MH, Neeland IJ, Grodin JL. Association of Body Mass Index and Age With Morbidity and Mortality in Patients Hospitalized With COVID-19: Results From the American Heart Association COVID-19 Cardiovascular Disease Registry. *Circulation* United States; 2021; 143: 135–144.

2. Du Y, Lv Y, Zha W, Zhou N, Hong X. Association of body mass index (BMI) with critical COVID-19 and in-hospital mortality: A dose-response meta-analysis. *Metabolism: clinical and experimental* 2021; 117: 154373.

3. Kumar A, Arora A, Sharma P, Anikhindi SA, Bansal N, Singla V, Khare S, Srivastava A. Is diabetes mellitus associated with mortality and severity of COVID-19? A meta-analysis. *Diabetes & metabolic syndrome* 2020; 14: 535–545.

4. Nishiga M, Wang DW, Han Y, Lewis DB, Wu JC. COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives. *Nature reviews. Cardiology* 2020; 17: 543–558.

5. Weaver AK, Head JR, Gould CF, Carlton EJ, Remais J V. Environmental Factors Influencing COVID-19 Incidence and Severity. *Annual review of public health* United States; 2022; 43: 271–291.

6. Paital B, Das K. Spike in pollution to ignite the bursting of COVID-19 second wave is more dangerous than spike of SAR-CoV-2 under environmental ignorance in long term: a review. *Environ Sci Pollut Res Int* 2021; : 1–17.

7. Paital B, Agrawal PK. Air pollution by NO(2) and PM(2.5) explains COVID-19 infection severity by overexpression of angiotensin-converting enzyme 2 in respiratory cells: a review. *Environ Chem Lett* 2021; 19: 25–42.

8. Gupta P, Jangid A & Kumar R. COVID-19-associated 2020 lockdown: a study on atmospheric black carbon fall impact on human health. *Environ Geochem Health* 2022; : 1–14.

9. Gheblawi M, Wang K, Viveiros A, Nguyen Q, Zhong J-C, Turner AJ, Raizada MK, Grant MB, Oudit GY. Angiotensin-Converting Enzym e 2: SARS-CoV-2 Receptor and Regulator of the Renin-Angiotensin System: Celebrating the 20th Anniversary of the Discovery of ACE2. *Circulation research* 2020; 126: 1456–1474.

10. Yan H, Jiao H, Liu Q, Zhang Z, Xiong Q, Wang B-J, Wang X, Guo M, Wang L-F, Lan K, Chen Y, Zhao H. ACE2 receptor usage reveals variation in susceptibility to SARS-CoV and SARS-CoV-2 infection among bat species. *Nature Ecology & Evolution* 2021; 5: 600–608.

11. Jackson CB, Farzan M, Chen B, Choe H. Mechanisms of SARS-CoV-2 entry into cells. *Nature reviews. Molecular cell biology* 2022; 23: 3–20.

12. Fucic A, Aghajanyan A, Druzhinin V, Minina V, Neronova E. Follow-up studies on genome damage in children after Chernobyl nuclear power plant accident. Archives of Toxicology Springer Verlag; 2016. p. 2147–2159.

13. Lan J, Ge J, Yu J, Shan S, Zhou H, Fan S, Zhang Q, Shi X, Wang Q, Zhang L, Wang X. Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. *Nature* England; 2020; 581: 215–220.

14. Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, Somasundaran M, Sullivan JL, Luzuriaga K, Greenough TC, Choe H, Farzan M. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature* 2003; 426: 450–454.

15. Wang Q, Zhang Y, Wu L, Niu S, Song C, Zhang Z, Lu G, Qiao C, Hu Y, Yuen K-Y, Wang Q, Zhou H, Yan J, Qi J. Structural and Functional Basis of SARS-CoV-2 Entry by Using Human ACE2. *Cell* 2020; 181: 894-904.e9.

16. Lin C-I, Tsai C-H, Sun Y-L, Hsieh W-Y, Lin Y-C, Chen C-Y, Lin C-S. Instillation of particulate matter 2.5 induced acute lung injury and attenuated the injury recovery in ACE2 knockout mice. *International journal of biological sciences* 2018; 14: 253–265.

17. Aztatzi-Aguilar OG, Uribe-Ramírez M, Arias-Montaño JA, Barbier O, De Vizcaya-Ruiz A. Acute and subchronic exposure to air particulate matter induces expression of angiotensin and bradykinin-related genes in the lungs and heart: Angiotensin-II type-I receptor as a molecular target of particulate matter exposure. *Particle and fibre toxicology* 2015; 12: 17.

18. Villeneuve PJ, Goldberg MS. Methodological Considerations for Epidemiological Studies of Air Pollution and the SARS and COVID-19 Coronavirus Outbreaks. *Environmental health perspectives* 2020; 128: 95001.

19. Bourdrel T, Annesi-Maesano I, Alahmad B, Maesano CN, Bind M-A. The impact of outdoor air pollution on COVID-19: a review of evidence from in vitro, animal, and human studies. *Eur Respir Rev* England; 2021; 30.

20. Heederik DJJ, Smit LAM, Vermeulen RCH. Go slow to go fast: a plea for sustained scientific rigour in air pollution research during the COVID-19 pandemic. *Eur Respir J* England; 2020; 56.

21. Bozack A, Pierre S, DeFelice N, Colicino E, Jack D, Chillrud SN, Rundle A, Astua A, Quinn JW, McGuinn L, Yang Q, Johnson K, Masci J, Lukban L, Maru D, Lee AG. Long-Term Air Pollution Exposure and COVID-19 Mortality: A Patient-Level Analysis from New York City. *American journal of respiratory and critical care medicine* United States; 2022; 205: 651–662.

22. Chen Z, Sidell MA, Huang BZ, Chow T, Eckel SP, Martinez MP, Gheissari R, Lurmann F, Thomas DC, Gilliland FD, Xiang AH. 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* United States; 2022; 206: 440–448.

23. Sidell MA, Chen Z, Huang BZ, Chow T, Eckel SP, Martinez MP, Lurmann F, Thomas DC, Gilliland FD, Xiang AH. Ambient air pollution and COVID-19 incidence during four 2020-2021 case surges. *Environ Res* 2022; 208: 112758.

24. Bowe B, Xie Y, Gibson AK, Cai M, van Donkelaar A, Martin RV, Burnett R, Al-Aly Z. Ambient fine particulate matter air pollution and the risk of hospitalization among COVID-19 positive individuals: Cohort study. *Environ Int* 2021; 154: 106564.

25. Chen C, Wang J, Kwong J, Kim J, van Donkelaar A, Martin RV, Hystad P, Su Y, Lavigne E, Kirby-McGregor M, Kaufman JS, Benmarhnia T, Chen H. Association between long-term exposure to ambient air pollution and COVID-19 severity: a prospective cohort study. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne* Canada; 2022; 194: E693–E700.

26. Chen Z, Huang BZ, Sidell MA, Chow T, Eckel SP, Pavlovic N, Martinez MP, Lurmann F, Thomas DC, Gilliland FD, Xiang AH. Near-roadway air pollution associated with COVID-19 severity and mortality - Multiethnic cohort study in Southern California. *Environment international* 2021; 157: 106862.

27. Kogevinas M, Castaño-Vinyals G, Karachaliou M, Espinosa A, de Cid R, Garcia-Aymerich J, Carreras A, Cortés B, Pleguezuelos V, Jiménez A, Vidal M, O'Callaghan-Gordo C, Cirach M, Santano R, Barrios D, Puyol L, Rubio R, Izquierdo L, Nieuwenhuijsen M, Dadvand P, Aguilar R, Moncunill G, Dobaño C, Tonne C. Ambient Air Pollution in Relation to SARS-CoV-2 Infection, Antibody Response, and COVID-19 Disease: A Cohort Study in Catalonia, Spain (COVICAT Study). *Environ Health Perspect* 2021; 129: 117003.

28. De Weerdt A, Janssen BG, Cox B, Bijnens EM, Vanpoucke C, Lefebvre W, El Salawi O, Jans M, Verbrugghe W, Nawrot TS, Jorens PG. Pre-admission air pollution exposure prolongs the duration of ventilation in intensive care patients. *Intensive care medicine* 2020; 46: 1204–1212.

29. Nawrot TS, Staessen JA, Gardner JP, Aviv A. Telomere length and possible link to X chromosome. *Lancet* England; 2004; 363: 507–510.

30. Martens DS, Janssen BG, Bijnens EM, Clemente DBP, Vineis P, Plusquin M, Nawrot TS. Association of Parental Socioeconomic Status and Newborn Telomere Length. *JAMA network open* 2020; 3: e204057.

31. Feldman PJ, Steptoe A. How neighborhoods and physical functioning are related: the roles of neighborhood socioeconomic status, perceived neighborhood strain, and individual health risk factors. *Ann Behav Med* England; 2004; 27: 91–99.

32. Gasparini A. comorbidity: An R package for computing comorbidity scores. *Journal of Open Source Software* 2018; 3: 648.

33. Royal College of Physicians. National Early Warning Score (NEWS) 2: Standardising the assessment of acute-illness severity in the NHS. London; 2017.

34. Kostakis I, Smith GB, Prytherch D, Meredith P, Price C, Chauhan A. The performance of the National Early Warning Score and National Early Warning Score 2 in hospitalised patients infected by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *Resuscitation* Ireland; 2021; 159: 150–157.

35. Lalueza A, Lora-Tamayo J, de la Calle C, Sayas-Catalán J, Arrieta E, Maestro G, Mancheño-Losa M, Marchán-López Á, Díaz-Simón R, García-García R, Catalán M, García-Reyne A, de Miguel-Campo B, Lumbreras C. [The early use of sepsis scores to predict respiratory failure and mortality in non-ICU patients with COVID-19]. *Rev Clin Esp* Spain; 2022; 222: 293–298.

36. Maiheu B, Veldeman B, Viaene P. Identifying the best available large-scale concentration maps for air quality in Belgium. 2012.

37. Lefebvre W, Vercauteren J, Schrooten L, Janssen S, Degraeuwe B, Maenhaut W, Vlieger I, Vankerkom J, Cosemans G, Mensink C, Veldeman N, Deutsch F. Validation of the MIMOSA-AURORA-IFDM model chain for policy support: Modeling concentrations of elemental carbon in Flanders. *Atmospheric Environment - ATMOS ENVIRON* 2011; 45: 6705–6713.

38. Saenen ND, Bové H, Steuwe C, Roeffaers MBJ, Provost EB, Lefebvre W, Vanpoucke C, Ameloot M, Nawrot TS. Children's Urinary Environmental Carbon Load. A Novel Marker Reflecting

Residential Ambient Air Pollution Exposure? *American journal of respiratory and critical care medicine* United States; 2017; 196: 873–881.

39. Bongaerts E, Lecante LL, Bové H, Roeffaers MBJ, Ameloot M, Fowler PA, Nawrot TS. Maternal exposure to ambient black carbon particles and their presence in maternal and fetal circulation and organs: an analysis of two independent population-based observational studies. *Lancet Planet Health* Netherlands; 2022; 6: e804–e811.

40. Gordon AC, Mouncey PR, Al-Beidh F, Rowan KM, Nichol AD, Arabi YM, Annane D, Beane A, van Bentum-Puijk W, Berry LR, Bhimani Z, Bonten MJM, Bradbury CA, Brunkhorst FM, Buzgau A, Cheng AC, Detry MA, Duffy EJ, Estcourt LJ, Fitzgerald M, Goossens H, Haniffa R, Higgins AM, Hills TE, Horvat CM, Lamontagne F, Lawler PR, Leavis HL, Linstrum KM, Litton E, et al. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19. *N Engl J Med* United States; 2021; 384: 1491–1502.

41. Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, Fu S, Gao L, Cheng Z, Lu Q, Hu Y, Luo G, Wang K, Lu Y, Li H, Wang S, Ruan S, Yang C, Mei C, Wang Y, Ding D, Wu F, Tang X, Ye X, Ye Y, Liu B, Yang J, Yin W, Wang A, Fan G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet* England; 2020; 395: 1569–1578.

42. Hung IF-N, Lung K-C, Tso EY-K, Liu R, Chung TW-H, Chu M-Y, Ng Y-Y, Lo J, Chan J, Tam AR, Shum H-P, Chan V, Wu AK-L, Sin K-M, Leung W-S, Law W-L, Lung DC, Sin S, Yeung P, Yip CC-Y, Zhang RR, Fung AY-F, Yan EY-W, Leung K-H, Ip JD, Chu AW-H, Chan W-M, Ng AC-K, Lee R, Fung K, et al. Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. *Lancet* England; 2020; 395: 1695–1704.

43. Mein SA, Annesi-Maesano I, Rice MB. COVID-19 Pandemic: A Wake-Up Call for Clean Air. *Ann Am Thorac Soc* United States; 2021; 18: 1450–1455.

44. Plataki M, Pan D, Goyal P, Hoffman K, Choi JMK, Huang H, Safford MM, Schenck EJ. Association of body mass index with morbidity in patients hospitalised with COVID-19. *BMJ open respiratory research* BMJ Publishing Group; 2021; 8: e000970.

45. Pope CA 3rd, Bhatnagar A, McCracken JP, Abplanalp W, Conklin DJ, O'Toole T. Exposure to Fine Particulate Air Pollution Is Associated With Endothelial Injury and Systemic Inflammation. *Circulation research* 2016; 119: 1204–1214.

46. Peters A, Nawrot TS, Baccarelli AA. Hallmarks of environmental insults. *Cell* United States; 2021; 184: 1455–1468.

47. Laratta CR, Kendzerska T, Carlsten C, Brauer M, van Eeden SF, Allen AJMH, Fox N, Peres BU, Ayas NT. Air Pollution and Systemic Inflammation in Patients With Suspected OSA Living in an Urban Residential Area. *Chest* United States; 2020; 158: 1713–1722.

48. Elbarbary M, Oganesyan A, Honda T, Morgan G, Guo Y, Guo Y, Negin J. Systemic Inflammation (C-Reactive Protein) in Older Chinese Adults Is Associated with Long-Term Exposure to Ambient Air Pollution. *International journal of environmental research and public health* 2021; 18.

49. Sakai M, Sato Y, Sato S, Ihara S, Onizuka M, Sakakibara Y, Takahashi H. Effect of relocating to areas of reduced atmospheric particulate matter levels on the human circulating leukocyte count. *Journal of applied physiology (Bethesda, Md. : 1985)* United States; 2004; 97: 1774–1780.

50. Provost EB, Chaumont A, Kicinski M, Cox B, Fierens F, Bernard A, Nawrot TS. Serum levels of club cell secretory protein (Clara) and short- and long-term exposure to particulate air pollution in adolescents. *Environment international* Netherlands; 2014; 68: 66–70.

51. Chen C, Wang J, Kwong J, Kim J, van Donkelaar A, Martin R V, Hystad P, Su Y, Lavigne E, Kirby-McGregor M, Kaufman JS, Benmarhnia T, Chen H. Association between long-term exposure to ambient air pollution and COVID-19 severity: a prospective cohort study. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne* Canada; 2022; 194: E693–E700.

52. Coker ES, Cavalli L, Fabrizi E, Guastella G, Lippo E, Parisi ML, Pontarollo N, Rizzati M, Varacca A, Vergalli S. The Effects of Air Pollution on COVID-19 Related Mortality in Northern Italy. *Environmental & resource economics* 2020; 76: 611–634.

53. Cole MA, Ozgen C, Strobl E. Air Pollution Exposure and Covid-19 in Dutch Municipalities. *Environmental & resource economics* 2020; : 1–30.

54. Fattorini D, Regoli F. Role of the chronic air pollution levels in the Covid-19 outbreak risk in Italy. *Environmental pollution (Barking, Essex : 1987)* 2020; 264: 114732.

55. Lipsitt J, Chan-Golston AM, Liu J, Su J, Zhu Y, Jerrett M. Spatial analysis of COVID-19 and traffic-related air pollution in Los Angeles. *Environment international* 2021; 153: 106531.

56. Travaglio M, Yu Y, Popovic R, Selley L, Leal NS, Martins LM. Links between air pollution and COVID-19 in England. *Environmental pollution (Barking, Essex : 1987)* 2021; 268: 115859.

57. Zhou X, Josey K, Kamareddine L, Caine MC, Liu T, Mickley LJ, Cooper M, Dominici F. Excess of COVID-19 cases and deaths due to fine particulate matter exposure during the 2020 wildfires in the United States. *Science advances* 2021; 7.

58. Zhu Y, Xie J, Huang F, Cao L. Association between short-term exposure to air pollution and COVID-19 infection: Evidence from China. *The Science of the total environment* 2020; 727: 138704.

59. Wu X, Nethery RC, Sabath BM, Braun D, Dominici F. Exposure to air pollution and COVID-19 mortality in the United States: A nationwide cross-sectional study. *medRxiv : the preprint server for health sciences* Cold Spring Harbor Laboratory; 2020; : 2020.04.05.20054502.

60. Ozkaynak H, Xue J, Spengler J, Wallace L, Pellizzari E, Jenkins P. Personal exposure to airborne particles and metals: results from the Particle TEAM study in Riverside, California. *J Expo Anal Environ Epidemiol* England; 1996; 6: 57–78.

61. Janssen NA, Hoek G, Brunekreef B, Harssema H, Mensink I, Zuidhof A. Personal sampling of particles in adults: relation among personal, indoor, and outdoor air concentrations. *Am J Epidemiol* United States; 1998; 147: 537–547.

62. Sørensen M, Loft S, Andersen HV, Raaschou-Nielsen O, Skovgaard LT, Knudsen LE, Nielsen IV, Hertel O. Personal exposure to PM2.5, black smoke and NO2 in Copenhagen: relationship to bedroom and outdoor concentrations covering seasonal variation. *J Expo Anal Environ Epidemiol* England; 2005; 15: 413–422.

63. Janssen S, Dumont G, Fierens F, Mensink C. Spatial interpolation of air pollution measurements using CORINE land cover data. *Atmospheric Environment* 2008; 42: 4884–4903.

64. Lefebvre W, Degrawe B, Beckx C, Vanhulsel M, Kochan B, Bellemans T, Janssens D, Wets G, Janssen S, de Vlieger I, Int Panis L, Dhondt S. Presentation and evaluation of an integrated model chain to respond to traffic- and health-related policy questions. *Environmental Modelling & Software* 2013; 40: 160–170.

65. Saenen ND, Bové H, Steuwe C, Roeffaers MBJ, Provost EB, Lefebvre W, Vanpoucke C, Ameloot M, Nawrot TS. Children's Urinary Environmental Carbon Load. A Novel Marker Reflecting Residential Ambient Air Pollution Exposure? *American journal of respiratory and critical care medicine* United States; 2017; 196: 873–881.

66. Gasparrini A, Armstrong B, Kenward MG. Distributed lag non-linear models. *Stat Med* England; 2010; 29: 2224–2234.

Declaration of interests

None of the authors declare any potential conflict of interest.

Supplemental information

Air pollution exposure

Residential addresses of the patients were geocoded, with correction for residential address changes over the 3-year period. In total less than 2% participants had an address change over the last 3-years prior admission.. Daily residential exposure ($\mu g/m^3$) to particulate matter with aerodynamic diameter less than 2.5 µm ($PM_{2.5}$), less than 10 µm (PM_{10}), black carbon (BC), and NO_2 was estimated using a spatial-temporal interpolation method, which integrates the land-cover data obtained from satellite images (CORINE land-cover) [63] and air pollution data of fixed monitoring stations in combination with a dispersion [64]. The dispersion model uses the results from the interpolation method as background and superimposes the effect of industrial point sources and line sources from traffic to calculate the daily concentration at high resolution. Model performance was evaluated by leave-one-out cross-validation and based on 34 monitoring points for $PM_{2.5}$, 58 for PM_{10}, 14 for BC, and 44 for NO_2. Validation statistics of the model indicated that the spatial-temporal variability was explained by 80% for $PM_{2.5}$ [36], 70% for PM_{10}, 74% for BC [37], and 78% for NO_2 [36]. The model was further validated by as study that showed that urinary black carbon load was associated with annual residential modelled concentration [38].

For short term exposure: daily exposures up to 30 days before admission were used to model distributed lag models (DLMs) in order to investigate the associations with clinical outcomes. Lastly, chronic exposure was calculated by averaging the daily exposures over a four-year period (2016-2019). We did not include exposure of recent years (2020-2021) for calculating chronic exposures, due to the fluctuations in air pollution in comparison to the previous years as a consequence of COVID-19 measures. Additionally, the residential distance to major roads, defined as highways and other national roads, was calculated, using Geographic Information System (GIS) functions with ArcGIS 10 software (Esri Inc., US).

Neighbourhood median income

Neighbourhood median income was determined using on the home address of the participants, which were used to assign statistical sectors, the smallest administrative entity for which statistical data are produced by the Belgian National Institute of Statistics. Participants lived in 197 different statistical sectors. The income is calculated on the basis of personal tax declarations and includes taxable professional income, replacement income, pensions, dividends, cadastral income and maintenance payments. It excludes non-taxable income, such as patients benefits and integration income. The reference period of the data used is the 2019 income year, i.e. the 2020 tax year.

Blood black carbon load

To obtain an individual measurement of exposure, the individual internal black carbon load was quantified in whole blood using a specific and sensitive detection technique based on white light generation of carbonaceous particles under femtosecond pulsed illumination as previously reported (6–8). All images were collected at room temperature using a Zeiss LSM880 (Carl Zeiss, Germany) equipped with a femtosecond pulsed laser (810 nm, 120 fs, 80 MHz, MaiTai DeepSee, Spectra-Physics, USA) tuned to a central wavelength of 810 nm using a Plan-Aprochromat 20x/0.8 (Carl Zeiss, Germany). Two-photon induced white light emission by carbonaceous particles was acquired in the non-descanned mode after spectral separation and emission filtering using 400-410 nm and 450-650 nm band-pass filters. Each blood sample was vortexed and aliquoted at 100 µL per imaging chamber constructed by placing a glass coverslip (24x24 mm, #1.5, VWR, The Netherlands) on a microscopic glass slide (75x25, VWR, The Netherlands) merged with 100 µm thick double-sided tape (4959, Tesa, Germany). The blood-filled imaging chambers were air-sealed to prevent drying. Ten by ten tile scans were collected 5 µm inwards from the bottom of the imaging chamber (i.e., 170 µm thick 24x24 mm coverslip). The resulting tile scans had a field of view of 4250.96x4250.96 μm^2 containing 100 images with a 5120x5120 pixel resolution and were recorded with a 1.54 µs pixel dwell time at three different locations in the imaging chamber. To determine the number of BC particles in the images, a peak-find algorithm counting connected pixels above a threshold value of 80% and 20% from the highest pixel intensity of the narrow second harmonic generation channel (400-410 nm) and two-photon excited autofluorescence channel (450-650 nm), respectively, was used. These thresholds resulted in highly reproducible values, which were checked manually using Fiji (ImageJ v2.0, open source software, http://fiji.sc/Fiji). The average amount of particles detected in the different tile scans was normalised to the image volume using the focal volume estimated from the point spread function of the optical system. Finally, the result was expressed as the number of detected BC particles per millilitre blood.

In previous research,[65] we have shown that urinary black carbon load in children (n=289, age 9-12y) is related to chronic modelled BC exposure (1-year average BC). Furthermore, recently we showed that both BC in maternal blood (r=0.57) and cord blood (r=0.68) at delivery was reflective of modelled BC during the entire gestation.[39]

Statistical analysis

Distributed lag models (DLM, using R package “dlnm” version 2.4.7) were used to estimate day-specific associations between short-term exposure to air pollutants in up to 30 days before admission, which allows the simultaneous estimation of a (non-linear) exposure-response association and non-linear effects across lags, the latter termed lag-response association.[66] The exposure-response function was assumed to be linear and the lag structure was modelled using a natural cubic with 5 degrees of

freedom, setting the knots at equally spaced values in the original lag scale (1 to 30). The number of knots was 3, based on Akaike's Information Criterion.[66] Final estimates are presented as the change in duration of hospitalisation for a 5 $\mu g/m^3$ ($PM_{2.5}$, PM_{10}, NO_2) or 0.5 $\mu g/m^3$ (BC) increase in air pollutant exposure.

Tables

Table 1: Description of the demographic and medical study population characteristics (n = 328).

	Mean (+- SD)	Frequency (%)
Demographic characteristics		
Age (years)	65.7 (+- 16.7)	
BMI	28.0 (+- 5.5)	
Sex		
• Male		185 (56.4%)
Ethnicity		
• Caucasian		281 (85.7%)
• North-African		32 (9.8%)
• Middle-Eastern		7 (2.1%)
• Asian		6 (1.8%)
• Black-African		2 (0.6%)
Education		
• Low		92 (28.0%)
• Medium		179 (54.8%)
• High		57 (17.4%)
Smoking status		
• Active		9 (2.7%)
• Ex		146 (44.5%)
• Never		172 (52.4%)
• Passive		1 (0.3%)
Medical characteristics		
Blood oxygen saturation (%)	95.81 (+- 4.05)	
CRP (mg/dL)	77.34 (+- 69.10)	
PaO_2/FiO_2 ratio	286.23 (+- 88.80)	
Neutrophils count	5.65 (+- 3.40)	
Eosinophils count	0.05 (+- 0.26)	
Monocytes count	0.93 (+- 1.81)	
Platelets count	214.71 (+- 83.39)	
Intensive care patients		95 (29.0%)
Patients with vasopressor usage		34 (10.4%)
Patients requiring ventilation		78 (23.8%)
Duration of hospitalisation (days)	16.9 (+- 19.8)	
Early warning score	3.10 (+- 2.16)	
Charlson comorbidity index		
• 0		98 (30.0%)
• 1-2		120 (36.6%)
• 3-4		65 (19.8%)
• >=5		45 (13.7%)

Table 2: Descriptive characteristics of the average exposure to air pollutants (µg/m^3) 2 days before admission, and 7 days before admission, as well as long-term exposure (average exposure from 2016 – 2019).

Air pollutant	Minimum	1st Quartile	Median	3rd Quartile	Maximum	IQR
$PM_{2.5}$						
2 days	3.85	7.20	10.32	10.32	49.35	3.12
7 days	3.79	8.70	11.24	16.08	30.84	7.38
Long-term	10.26	13.20	13.42	13.76	14.24	0.56
PM_{10}						
2 days	8.90	13.90	17.50	29.70	63.15	15.80
7 days	9.39	15.23	19.44	23.09	42.36	7.85
Long-term	15.50	20.87	21.26	21.63	22.75	0.76
BC						
2 days	0.10	0.41	1.03	46.5	294.7	46.1
7 days	0.11	0.49	0.97	50.2	160.2	49.74
Long-term	0.66	0.86	0.91	1.01	1.38	0.15
NO_2						
2 days	4.25	10.24	14.07	19.45	19.45	9.21
7 days	4.03	10.97	13.65	17.13	28.47	6.16
Long-term	10.72	15.97	17.77	20.01	30.43	4.16

Abbreviations: IQR = interquartile range, PM: particulate matter, BC: black carbon, NO_2: nitrogen dioxide.

Table 3: Associations between average air pollutant exposure and blood black carbon load, and the duration of hospitalisation (n = 328).

Exposure	Estimate (days)	95% CI	p-value
$PM_{2.5}$			
2 days	+0.81	-0.05 – 1.68	0.06
7 days	+4.13	0.74 – 7.53	0.02
Long-term	+0.47	-2.05 – 2.99	0.72
PM_{10}			
2 days	+3.63	0.24 – 7.03	0.04
7 days	+4.04	1.24 – 6.83	0.01
Long-term	+1.44		0.12
BC			
2 days	+2.91	-0.48 – 6.30	0.09
7 days	+3.62	-2.44 – 9.67	0.24
Long-term	+2.33	0.216 – 4.40	0.02
NO_2			
2 days	+3.59	0.36 – 6.82	0.03
7 days	+4.54	1.53 – 7.54	<0.01
Long term	+3.21	0.83 – 5.59	0.01
Blood BC load	+0.95	-0.73 – 2.63	0.27

Estimates were determined using linear multiple regression models and are represented for an IQR increase in the exposure. All models were adjusted for age, sex, BMI, education, neighbourhood median income, smoking status, day of admission, average temperature at the day of admission, the Charlson comorbidity index, and estimated virus variant.

Table 4: Odds Ratios for admission to the intensive care unit, risk of ventilation and vasopressor usage in association with average air pollutant exposures and blood black carbon load (n = 328).

	Intensive care unit admission[a]		***On ventilation[b]***		***Vasopressure use[c]***	
Air pollutant	**OR (95 %CI)**	**P-value**	**OR (95%CI)**	**P- value**	**OR (95%CI)**	**P- value**
$PM_{2.5}$						
2 days	0.96 (0.85 – 1.08)	0.51	0.97 (0.86 – 1.10)	0.68	0.90 (0.74 – 1.09)	0.28
7 days	1.02 (0.97 – 1.06)	0.94	1.18 (0.73 – 1.90)	0.50	1.30 (0.63 – 2.69)	0.47
Long-term	0.79 (0.57 – 1.10)	0.16	1.08 (0.75 – 1.54)	0.69	0.68 (0.43 – 1.09)	0.11
PM_{10}						
2 days	0.98 (0.62 – 1.55)	0.93	1.01 (0.62 – 1.65)	0.97	0.76 (0.36 – 1.58)	0.46
7 days	1.17 (0.81 – 1.70)	0.40	1.28 (0.93 – 1.75)	0.23	1.22 (0.71 – 2.10)	0.48
Long-term	1.26 (0.96 – 1.65)	0.09	1.39 (1.03 – 1.89)	0.03	1.42 (0.93 – 2.19)	0.11
BC						
2 days	1.20 (0.79 – 1.84)	0.40	1.21 (0.75 – 1.95)	0.42	1.18 (0.68 – 2.05)	0.56
7 days	0.91 (0.44 – 1.88)	0.81	0.96 (0.45 – 2.05)	0.91	1.65 (0.58 – 4.68)	0.35
Long-term	2.30 (1.64 – 3.22)	<0.01	1.96 (1.43 – 2.70)	<0.01	2.58 (1.70 – 3.92)	<0.01
NO_2						
2 days	1.44 (0.94 – 2.22)	0.09	1.37 (0.86 – 2.17)	0.18	1.75 (0.62 – 4.93)	0.09
7 days	2.05 (1.34 – 3.13)	<0.01	2.12 (1.35 – 3.34)	<0.01	2.99 (1.58 – 5.68)	<0.01
Long-term	2.58 (1.79 – 3.71)	<0.01	1.98 (1.41 – 2.79)	<0.01	2.79 (1.75 – 4.45)	0.08
Blood BC load	1.33 (1.07 – 1.65)	0.01	1.18 (0.96 – 1.45)	0.12	1.37 (1.33 – 1.41)	0.02

Estimates were determined using binomial logistic regression models and are represented for an IQR increase in the exposure. All models were adjusted for age, sex, BMI, education, smoking status, day of admission, average temperature at the day of admission and the Charlson comorbidity index.

[a]n/N (%): 95/328 (29.0%) for intensive care admission

[b]n/N (%): 78/328 (23.8%) for patients on ventilation

[c]n/N (%): 34/328 (10.4%) for patients on 26asopressor use

Table S1: Pearson correlation coefficients between the modelled average exposures.

	$PM_{2.5}$, 2 days	**PM_{10}, 2 days**	**BC, 2 days**	**NO_2, 2 days**	**$PM_{2.5}$, 7 days**	**PM_{10}, 7 days**	**BC, 7 days**	**NO_2, 7 days**	**$PM_{2.5}$, long-term**	**PM_{10}, long-term**	**BC, long-term**	**NO_2, long-term**
$PM_{2.5}$, 2 days	1.00	0.95	0.51	0.77	0.70	0.68	0.42	0.53	0.13	0.07	-0.02	-0.05
PM_{10}, 2 days	0.95	1.00	0.47	0.77	0.64	0.75	0.35	0.54	0.13	0.11	0.03	0.00
BC, 2 days	0.51	0.47	1.00	0.31	0.55	0.46	0.94	0.36	0.10	0.09	0.05	0.05
NO_2, 2 days	0.77	0.77	0.31	1.00	0.42	0.49	0.21	0.64	0.23	0.26	0.23	0.22
$PM_{2.5}$, 7 days	0.70	0.64	0.55	0.42	1.00	0.90	0.53	0.69	0.19	0.16	0.07	0.03
PM_{10}, 7 days	0.68	0.75	0.46	0.49	0.90	1.00	0.40	0.70	0.20	0.22	0.16	0.11
BC, 7 days	0.42	0.35	0.94	0.21	0.53	0.40	1.00	0.35	0.10	0.12	0.10	0.10
NO_2, 7 days	0.53	0.54	0.36	0.64	0.69	0.70	0.35	1.00	0.31	0.45	0.52	0.49
$PM_{2.5}$, long-term	0.13	0.13	0.10	0.23	0.19	0.20	0.10	0.31	1.00	0.86	0.43	0.38
PM_{10}, long-term	0.07	0.11	0.09	0.26	0.16	0.22	0.12	0.45	0.86	1.00	0.71	0.67
BC, long-term	-0.02	0.03	0.05	0.23	0.07	0.16	0.10	0.52	0.43	0.71	1.00	0.98
NO_2, long-term	-0.05	0.00	0.05	0.22	0.03	0.11	0.10	0.49	0.38	0.67	0.98	1.00

Table S2: Associations between patient characteristics and duration of hospitalisation (n = 328).

Explanatory variable	**Estimate**	**95%CI**	**p-value**
Age (+ 10 years)	+2.36	0.82 – 3.9	<0.01
Sex (ref = female)			
• Male	+3.99	-0.38 – 8.35	0.07
BMI (+ 1 unit)	0.14	-0.26 – 0.53-	0.50
Education (ref = Low)			
• Medium	+5.18	-13.5 – 23.9	0.59
• High	+2.95	-16.3 – 22.2	0.76
Neighbourhood median income (+1 IQR = 6261 euro/year)	-4.22	-7.27 - -1.17	<0.01
Smoking status (ref = Active)			
• Ex	9.4	-3.19 – 2.29	0.15
• Never	8.05	-4.78 – 2.16	0.22
• Passive	11.54	-3.09 – 4.97	0.57
Comorbidity index (+ 1 unit)	0.50	-0.59 – 1.60	0.36
Average temp. (+ 1 °C)	+0.48	-0.14 – 1.10	0.37
Date of admission (Linear term)	-27.13	-42.68 - -11.60	<0.01
Date of admission (Quadratic term)	<0.01	<0.01	<0.01

Estimates were determined using linear regression models and are represented in days of hospitalisation with 95%CI.

Table S3: Associations between long-term air pollutant exposure and duration of hospitalisation in co-pollutant models.

Co-pollutant model	Exposure	Estimate	95% CI	p-value
PM_{10} + BC	PM_{10}	-0.26	-2.78 – 2.26	0.84
	BC	3.48	0.61 – 6.36	0.02
PM_{10} + NO_2	PM_{10}	-0.24	-2.62 – 2.14	0.84
	NO_2	4.39	1.12 – 6.78	0.01

Estimates were determined using linear multiple regression models and are represented for an IQR increase in the exposure. All models were adjusted for age, sex, BMI, education, neighbourhood median income smoking status, date of admission, average temperature at the day of admission,the Charlson comorbidity index and estimated virus variant.

Table S4: Associations between air pollution exposure and duration of hospitalization, in models mutually adjusted for short- (average 1 week before admission) and long-term (average 2016 – 2019) air pollution exposure.

Exposure	Exposure window	Estimate	95%CI	p-value
$PM_{2.5}$	Long-term	-1.30	-3.87 – 1.26	0.32
	Short-term	4.53	1.00 – 8.05	0.01
PM_{10}	Long-term	0.37	-1.50 – 2.23	0.70
	Short-term	4.36	1.49 – 7.23	<0.01
BC	Long-term	1.40	-0.39 – 3.79	0.02
	Short-term	-3.89	-8.47 – 0.69	0.10
NO_2	Long-term	1.92	-0.84 – 4.68	0.17
	Short-term	3.16	-0.31 – 6.63	0.08

Estimates were determined using linear multiple regression models and are represented for an IQR increase in the exposure. All models were adjusted for age, sex, BMI, education, neighbourhood median income smoking status, date of admission, average temperature at the day of admission, the Charlson comorbidity index and estimated virus variant. +

Table S5: Associations between average air pollutant exposure and blood black carbon load, and the duration of hospitalisation (n = 328), additionally adjusted for diabetes (yes/no).

Exposure	Estimate (days)	95% CI	p-value
$PM_{2.5}$			
2 days	0.83	-0.04 – 1.71	0.06
7 days	4.27	0.80 – 7.75	0.02
Long-term	-0.54	-3.10 – 2.01	0.68
PM_{10}			
2 days	3.70	0.29 – 7.11	0.03
7 days	4.07	1.27 – 6.87	0.00
Long-term	1.03	-0.82 – 2.89	0.28
BC			
2 days	0.13	-2.69 – 2.96	0.93
7 days	-0.36	-4.57 – 3.85	0.87
Long-term	0.24	-1.85 – 2.32	0.03
NO_2			
2 days	2.58	-0.52 – 5.67	0.10
7 days	3.60	0.61 – 6.58	0.02
Long term	3.08	0.65 – 5.50	0.01
Blood BC load	0.82	-0.88 – 2.52	0.34

Estimates were determined using linear multiple regression models and are represented for an IQR increase in the exposure. All models were adjusted for age, sex, BMI, education, neighbourhood median income, smoking status, day of admission, average temperature at the day of admission,the Charlson comorbidity index, estimated virus variant, and diabetes (yes/no).

Table S6: Associations between average air pollutant exposure and blood black carbon load, and the duration of hospitalisation (n = 328), additionally adjusted last known occupation (ISCO classification).

Exposure	Estimate (days)	95% CI	p-value
$PM_{2.5}$			
2 days	0.65	-0.22 – 1.53	0.15
7 days	3.40	-0.08 – 6.88	0.06
Long-term	-0.71	-3.28 – 1.85	0.59
PM_{10}			
2 days	3.05	-0.37 – 6.47	0.08
7 days	3.45	0.63 – 6.27	0.02
Long-term	0.96	-1.19 – 2.59	0.47
BC			
2 days	1.44	-2.83 – 2.28	0.99
7 days	2.16	-4.91 – 3.56	0.76
Long-term	1.12	-0.40 – 4.00	0.11
NO_2			
2 days	1.60	-1.49 – 4.78	0.30
7 days	1.55	-0.74 – 5.35	0.14
Long term	1.30	0.09 – 5.18	0.04
Blood BC load	0.88	-1.04 – 2.41	0.44

Estimates were determined using linear multiple regression models and are represented for an IQR increase in the exposure. All models were adjusted for age, sex, BMI, education, neighbourhood median income, smoking status, day of admission, average temperature at the day of admission, the Charlson comorbidity index, estimated virus variant, and last known occupation (ISCO classification).

Table S7: Associations between average air pollutant exposure and the blood black carbon load, and the early-warning scores at the time of admission (n = 328).

Exposure	Estimate	95% CI	p-value
$PM_{2.5}$			
2 days	+0.02	-0.08 – 0.12	0.71
7 days	+0.32	-0.07 – 0.71	0.11
Long-term	+0.22	-0.50 – 0.06	0.13
PM_{10}			
2 days	+0.11	-0.28 – 0.50	0.58
7 days	+0.32	0.01 – 0.64	0.05
Long-term	-0.09	-0.29 – 0.12	0.42
BC			
2 days	0.04	-0.20 – 0.27	0.76
7 days	-0.08	-0.44 – 0.28	0.65
Long-term	-0.02	-0.25 – 0.21	0.88
NO_2			
2 days	+0.12	-0.24 – 0.49	0.51
7 days	+0.22	-0.13 – 0.56	0.21
Long-term	-0.01	-0.27 – 0.25	0.94
Blood BC load	-0.11	-0.30 – 0.08	0.25

Estimates with 95%CI were determined using linear multiple regression models and are represented for an IQR increase in the exposure. All models were adjusted for age, sex, BMI, education, neighbourhood median income, smoking status, day of admission, average temperature at the day of admission,the Charlson comorbidity index, and estimated virus variant.

Table S8: Associations between average air pollutant exposures and blood black carbon load, and the PaO_2/FiO_2 ratio at the time of admission (n = 328).

Exposure	Estimate	95% CI	p-value
$PM_{2.5}$			
2 days	4.13	-0.93 – 9.19	0.11
7 days	11.05	-9.31 – 31.42	0.29
Long-term	0.74	-0.17 – 1.65–	0.11
PM_{10}			
2 days	9.42	-10.70 – 29.53	0.36
7 days	-0.27	-17.33 – 16.78–	0.97
Long-term	-9.72	-20.42 – 0.97	0.08
BC			
2 days	13.13	-3.29 – 29.24	0.12
7 days	15.30	-6.70 – 37.29	0.24
Long-term	-30.19	-48.61 - -21.80	<0.01
NO_2			
2 days	-17.43	-36.75 – 1.88	0.08
7 days	-26.86	-44.64 - -9.07	<0.01
Long-term	-8.77	-48.61 - -21.80	<0.01
Blood BC	-9.93	-20.14 – 0.29	0.06

Estimates were determined using linear regression models and are represented for an IQR increase in the exposure. All models were adjusted for age, sex, BMI, education, neighbourhood median income, smoking status, day of admission, average temperature at the day of admission, the Charlson comorbidity index, and estimated virus variant.

Table S9: Associations between average air pollutant exposures and blood black carbon load, and the saturation of oxygen in blood at the time of admission (n = 328).

Exposure	Estimate	95% CI	p-value
$PM_{2.5}$			
2 days	0.03	0.01 – 0.05	0.80
7 days	-0.32	-1.13 – 0.49	0.44
Long-term	0.00	-0.61 – 0.62	0.99
PM_{10}			
2 days	1.58	0.79 – 2.38	0.70
7 days	-0.18	-0.87 – 0.50	0.60
Long-term	-0.12	-0.59 – 0.34	0.60
BC			
2 days	0.07	-0.64 – 0.77	0.85
7 days	0.14	-1.06 – 1.33	0.83
Long-term	-0.21	-0.85 – 0.44	0.53
NO_2			
2 days	0.13	-0.62 – 0.88	0.73
7 days	-0.46	-1.25 – 0.34	0.26
Long-term	0.24	-0.47 – 0.95	0.51
Blood BC	0.20	-0.25 – 0.54	0.48

Estimates were determined using linear regression models and are represented for an IQR increase in the exposure. All models were adjusted for age, sex, BMI, education, neighbourhood median income, smoking status, day of admission, average temperature at the day of admission, the Charlson comorbidity index and estimated virus variant.

Table S10: Associations between average air pollutant exposure and blood black carbon load, and the duration of hospitalisation (VITAZ hospital patients only, n = 273).

Exposure	Estimate (days)	95% CI	p-value
$PM_{2.5}$			
2 days	0.99	0.21 – 1.78	0.01
7 days	5.66	2.48 – 8.84	<0.01
Long-term	2.51	0.04 – 4.98	0.05
PM_{10}			
2 days	3.65	0.53 – 6.76	0.02
7 days	4.05	1.39 – 6.71	<0.01
Long-term	1.94	0.07 – 3.81	0.04
BC			
2 days	2.52	-0.08 – 5.11	0.06
7 days	5.07	-0.04 – 10.19	0.05
Long-term	2.38	-0.22 – 4.98	0.07
NO_2			
2 days	2.46	-0.38 – 5.30	0.09
7 days	5.80	2.74 – 8.87	<0.01
Long term	2.76	-0.07 – 5.60	0.06
Blood BC load	0.46	-1.13 – 2.05	0.58

Estimates were determined using linear multiple regression models and are represented for an IQR increase in the exposure. All models were adjusted for age, sex, BMI, education, neighbourhood median income, smoking status, day of admission, average temperature at the day of admission,the Charlson comorbidity index, and estimated virus variant.

Table S11: Odds Ratios for admission to the intensive care unit in association with average air pollutant exposure (VITAZ hospital patients only, n = 273)

	Intensive care unit admission[a]	
Air pollutant	**OR (95 %CI)**	**P-value**
$PM_{2.5}$		
2 days	1.03 (0.89 – 1.19)	0.70
7 days	1.33 (0.76 – 2.33)	0.32
Long-term	1.61 (0.95 – 2.73)	0.08
PM_{10}		
2 days	1.17 (0.65 – 2.10)	0.59
7 days	1.23 (0.77 – 1.96)	0.39
Long-term	1.68 (1.07 – 2.63)	0.02
BC		
2 days	1.57 (0.96 – 2.59)	0.07
7 days	1.13 (0.56 – 2.27)	0.74
Long-term	1.84 (1.17 – 2.89)	0.01
NO_2		
2 days	1.22 (0.74 – 2.04)	0.43
7 days	1.77 (1.02 – 3.07)	0.04
Long-term	1.88 (1.16 – 3.01)	0.01
Blood BC load	1.20 (0.95 – 1.52)	0.11

Estimates were determined using binomial logistic regression models and are represented for an IQR increase in the exposure. All models were adjusted for age, sex, BMI, education, smoking status, day of admission, average temperature at the day of admission and the Charlson comorbidity index.

Table S12: Description of demographic and medical characteristics for the additional intensive care patients from the UZA sample (n = 45).

	Mean (+- SD)	Frequency (%)
Demographic characteristics		
Age (years)	58.02 (+- 15.63)	
BMI	28.57 (6.08)	
Sex		
• Male		29 (64.4%)
Ethnicity		
• Caucasian		32 (71.1%)
• North-African		11 (24.4%)
• Middle-Eastern		1 (2.2%)
• Asian		0 (0%)
• Black-African		1 (2.2%)
Education		
• Low		9 (20.0%)
• Medium		27 (60.0%)
• High		9 (20.0%)
Smoking status		
• Active		1 (2.2%)
• Ex		22 (48.9%)
• Never		22 (48.9%)
• Passive		0 (0%)
Medical characteristics		
CRP (mg/dL)	235.72 (+- 105.02)	
PaO2/FiO2 ratio	87.38 (+- 52.64)	
Neutrophils count	9.03 (+- 6.43)	
Eosinophils count	0.02 (+- 0.05)	
Monocytes count	0.69 (+- 1.38)	
Platelets count	236.56 (+- 88.03)	
Charlson comorbidity index		
• 0		25 (55.6%)
• 1-2		15 (33.3%)
• 3-4		4 (8.9%)
• >=5		1 (2.2%)

Table S13: Associations between average air pollutant exposure and black carbon load, and the duration of hospitalisation while adjusting for season of admission instead of date of admission.

Exposure	Estimate	95% CI	p-value
$PM_{2.5}$			0.45
2 days	0.36	-0.57 – 1.29	0.07
7 days	3.38	-0.22 – 6.98	0.59
Long-term	-0.72	-3.32 – 1.87	
PM_{10}			0.27
2 days	2.07	-1.57 – 5.71	0.03
7 days	3.24	0.31 – 6.16	0.26
Long-term	1.09	-0.80 – 2.98	
BC			0.82
2 days	0.35	-2.63 – 3.33	0.76
7 days	0.71	-3.79 – 5.20	0.02
Long-term	2.48	0.38 – 4.59	
NO_2			0.82
2 days	3.61	0.39 – 6.83	0.76
7 days	3.39	0.30 – 6.48	0.02
Long-term	3.35	0.91 – 5.79	
Blood BC	0.91	-0.81 – 2.63	0.30

Estimates were determined using linear multiple regression models and are represented for an IQR increase in the exposure. All models were adjusted for age, sex, BMI, education, neighbourhood median income, smoking status, season of admission, average temperature at the day of admission,the Charlson comorbidity index, and estimated virus variant.

Table S14: Odds Ratios for admission to the intensive care unit in association with average air pollutant exposure while adjusting for season of admission instead of date of admission.

	Intensive care unit admission[a]	
Air pollutant	**OR (95 %CI)**	**P-value**
$PM_{2.5}$		
2 days	0.92 (0.82 – 1.04)	0.20
7 days	0.93 (0.60 – 1.44)	0.75
Long-term	0.74 (0.53 – 1.01)	0.06
PM_{10}		
2 days	0.85 (0.53 – 1.34)	0.48
7 days	1.05 (0.73 – 1.50)	0.80
Long-term	1.21 (0.95 – 1.55)	0.13
BC		
2 days	1.10 (0.78 -1.56)	0.58
7 days	1.13 (0.66 – 1.94)	0.65
Long-term	2.19 (1.58 – 3.02)	<0.01
NO_2		
2 days	1.21 (0.80 – 1.82)	0.37
7 days	1.84 (1.24 – 2.74)	<0.01
Long-term	2.49 (1.75 – 3.53)	<0.01
Blood BC load	1.33 (1.08 – 1.64)	0.01

Estimates were determined using binomial logistic regression models and are represented for an IQR increase in the exposure. All models were adjusted for age, sex, BMI, education, smoking status, season of admission, average temperature at the day of admission and the Charlson comorbidity index.

Figures

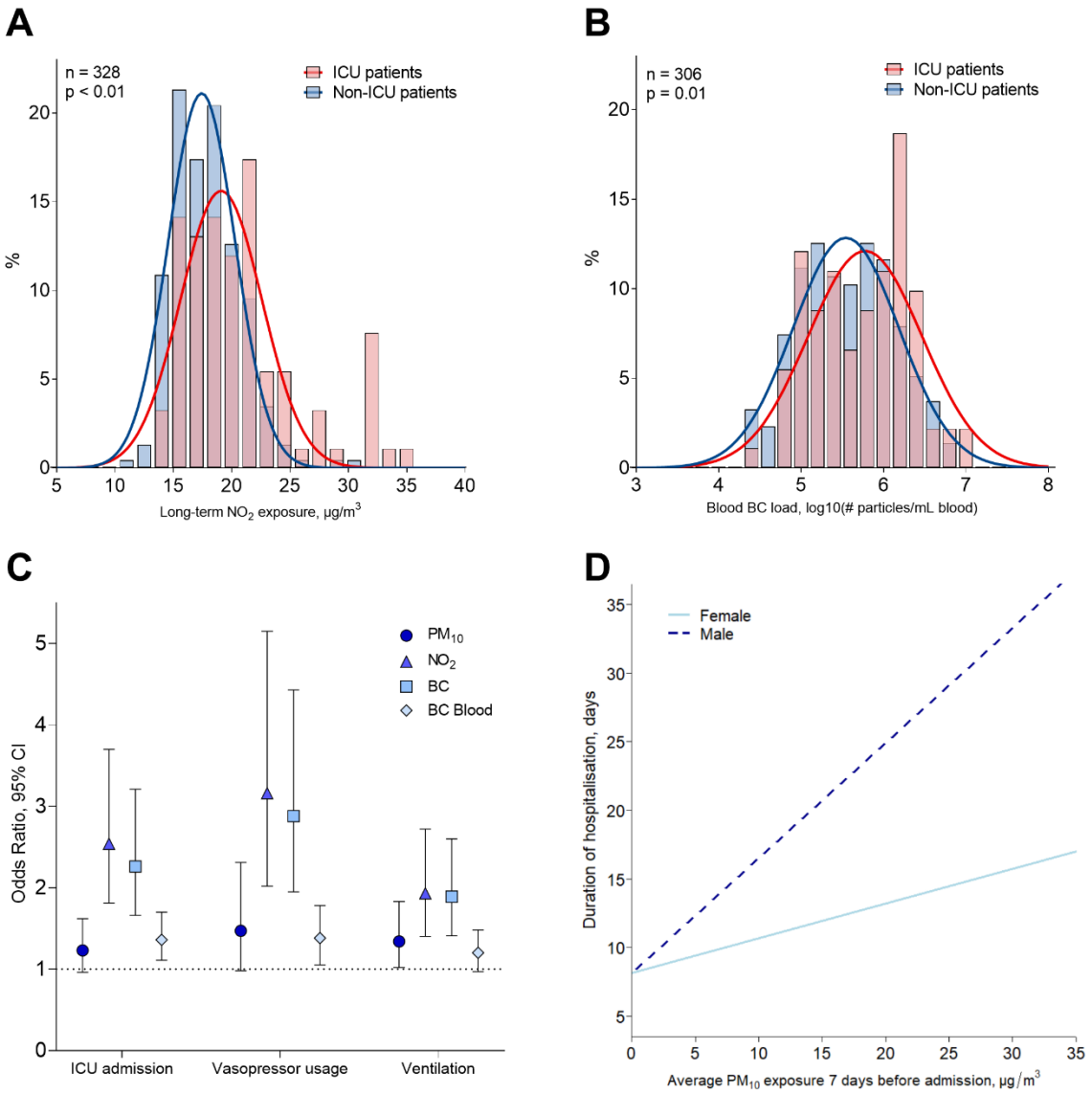

Figure 1: Distribution of pollutant exposure per patient group (ICU versus non-ICU), for long-term exposure to NO_2 (A), and for measured black carbon load in blood (B). Odds-ratios for ICU admission, vasopressor usage and risk of ventilation (C). The brackets represent the 95% confidence interval upper and lower limits. Interaction effect between average exposure to $PM_{2.5}$ one week before admission and patient age (p-value interaction = 0.04) on the duration of hospitalisation (D). Sample size was 308 for blood BC load measurements, since 20 blood samples were missing. Other analysis included all 328 participants (n = 328). All model estimates are represented for an IQR increase in the exposure (long-term PM_{10}: +0.76 µg/m^3, NO_2: +4.13 µg/m^3, BC: +0.15 µg/m^3, Blood BC: +9.27x10^5 particles; short-term $PM_{2.5}$: +0.56 µg/m^3), and were adjusted for age, sex, BMI, education, smoking status, day of admission, average temperature at the day of admission, the Charlson comorbidity index and virus variant.

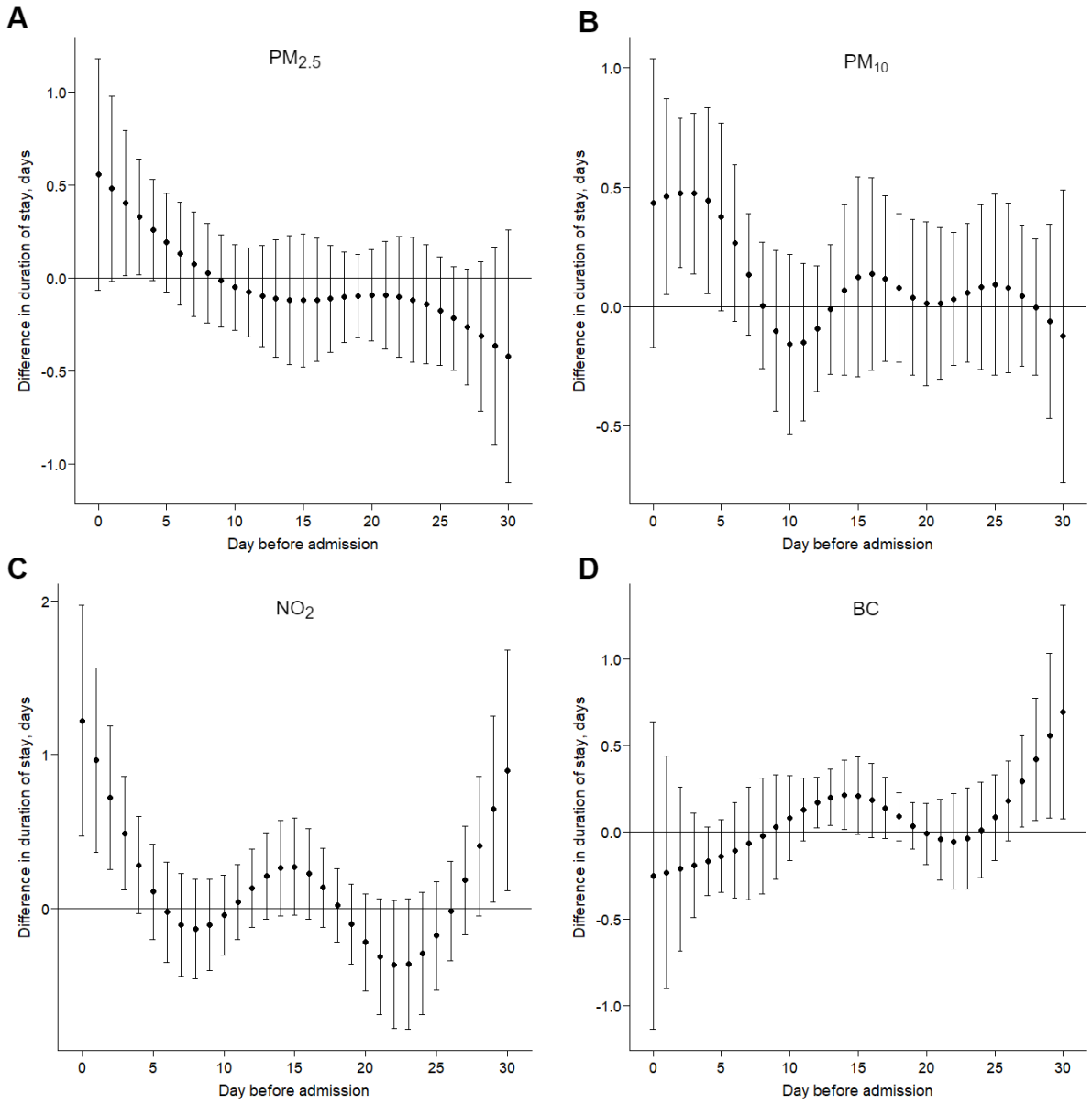

Figure 2: Day-specific estimates for the association between (A) $PM_{2.5}$, (B) PM_{10}, (C) NO_2, and (D) BC exposure and the duration of hospitalisation. The estimates are represented for a 5 μg/m^3 increase in $PM_{2.5}$, PM_{10} and NO_2 exposure, and a 0.5 μg/m^3 increase in BC exposure using distributed lag models. The brackets represent the 95% confidence interval upper and lower limits. All models were adjusted for age, sex, BMI, education, neighbourhood median income, smoking status, day of admission, average temperature at the day of admission, the Charlson comorbidity index, and estimated virus variant.

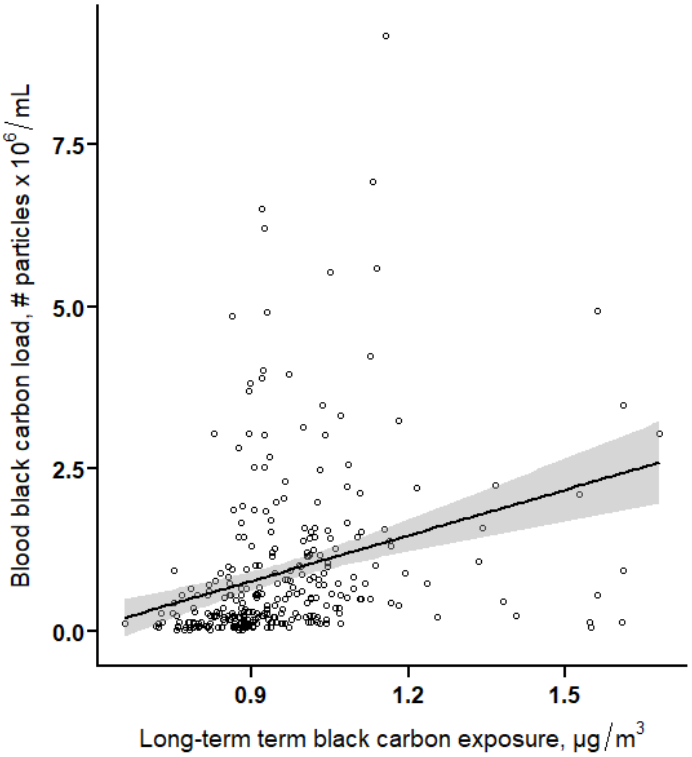

Figure S1: Correlation between the modelled long-term black carbon exposure (µg/m^3) and measured black carbon particles in blood (Spearman's ρ = 0.48, p < 0.01).

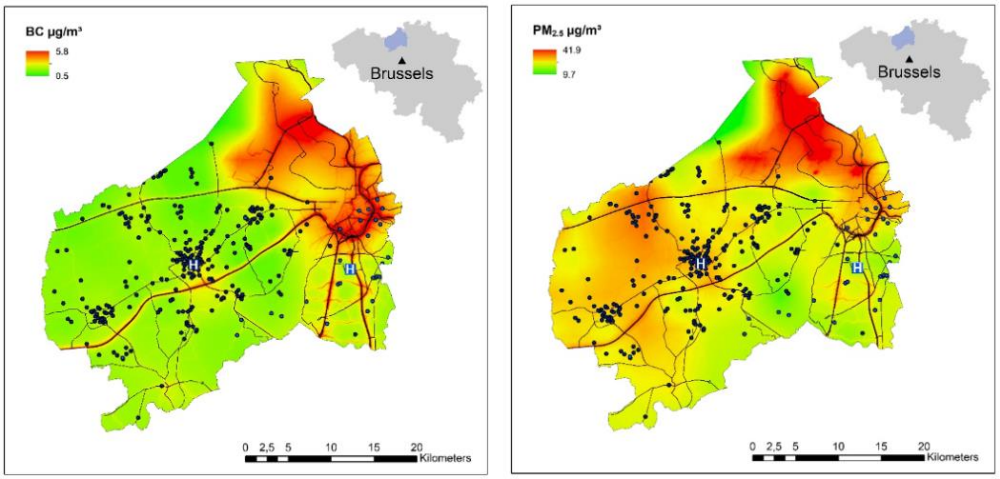

Figure S2: Visual representation of the average BC and $PM_{2.5}$ exposures during 2019 in the study area. The dots represent residential locations of the study participants. The two hospital locations are indicated by the “H” markers.