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

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In hospitalised COVID-19 patients, air pollution exposure predicted duration of stay and ICU admission, which implies that air pollution exposure influences COVID-19 severity and therefore the burden on medical care systems during the COVID-19 pandemic https://bit.ly/3oFfeiS

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Abstract

Background Air pollution exposure is one of the major risk factors for aggravation of respiratory diseases. We investigated whether exposure to air pollution and accumulated black carbon (BC) particles in blood were associated with coronavirus disease 2019 (COVID-19) disease severity, including the risk for intensive care unit (ICU) admission and duration of hospitalisation.

Methods From May 2020 until March 2021, 328 hospitalised COVID-19 patients (29% at intensive care) were recruited from two hospitals in Belgium. Daily exposure levels (from 2016 to 2019) for particulate matter with aerodynamic diameter <2.5 µm and <10 µm ($PM_{2.5}$ and PM_{10}, respectively), nitrogen dioxide (NO_2) and BC were modelled using a high-resolution spatiotemporal model. Blood BC 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 ICU admission.

Results Independent of potential confounders, an interquartile range (IQR) increase in exposure in the week before admission was associated with increased duration of hospitalisation ($PM_{2.5}$ +4.13 (95% CI 0.74–7.53) days, PM_{10} +4.04 (95% CI 1.24–6.83) days and NO_2 +4.54 (95% CI 1.53–7.54) 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 hospitalisation duration. Furthermore, for an IQR higher blood BC load, the OR for ICU admission was 1.33 (95% CI 1.07–1.65).

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

Introduction

The coronavirus disease 2019 (COVID-19) pandemic presented a challenge for healthcare 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 (BC) exposure levels on human health was significantly lower than before the pandemic [8]. Nonetheless, emerging data from epidemiological studies also suggest that not only genetics but also air pollution may modulate the risk of disease by increasing patient susceptibility to infection, including COVID-19. Experimental data support an important role of the angiotensin-converting enzyme 2 (ACE2) receptor, which is used by SARS-CoV-2 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 a 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 ACE2 and transmembrane protease serine type 2, 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. However, the earliest epidemiological studies assessing the relationship between air pollution and COVID-19 incidence have been subject to methodological 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, intensive care unit (ICU) admission risk and mortality using patient-level data [21–27]. Currently, important indicators related not only to disease severity but also pressure on healthcare systems such as 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-19 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 the time of admission to Hospital VITAZ Sint-Niklaas (Sint-Niklaas, 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 Antwerp University Hospital (Edegem, Belgium) were recruited, who had been admitted to the ICU within 24 h after hospital admission. Patients were recruited between May 2020 and March 2021. To be eligible, patients had to be ⩾18 years old, tested positive for COVID-19 by PCR, not included in other ongoing clinical intervention studies and not relocated 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 13 February 2021 were infected by the (original) Wuhan variant of the virus, while the majority of the patients recruited from 14 February 2021 until March 2021 were infected by the alpha 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 Hospital VITAZ, Antwerp University Hospital (EC20/25/323) and Hasselt University (B2020115000006).

Demographic and clinical characteristics, such as ethnicity, sex, age, body mass index (BMI), smoking status (active smoker, ex-smoker or never-smoker) and blood pressure on admission at the hospital were obtained from the medical records.

We obtained information on education and occupation *via* questionnaire. Educational attainment was assessed as the highest educational level successfully completed using the International Standard Classification of Education. Educational level was coded as low, middle and high. Occupation was assessed using the International Standard Classification of Occupations. 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 socioeconomic status indicators, we also 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 the supplementary material.

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, absolute white blood cell count, and number of monocytes, eosinophils, lymphocytes, neutrophils and 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) and ICU admission.

Secondary end-points 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 oxygen tension/inspiratory oxygen fraction (P_{aO_2}/F_{IO_2}) ratio 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 (CCI) [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 ($\mu g \cdot m^{-3}$) to particulate matter with aerodynamic diameter <2.5 µm ($PM_{2.5}$), particulate matter with aerodynamic diameter <10 µm (PM_{10}), BC and nitrogen dioxide (NO_2) was estimated using a spatiotemporal interpolation method. Validation statistics of the model indicated that the spatiotemporal 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 a study that showed that urinary BC load was associated with annual residential modelled concentration [38]. We refer to the supplementary material for more details on the exposure modelling.

Blood BC load

The internal BC 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 supplementary material.

Statistical analyses

Statistical analyses were performed using R version 4.0.2 (www.r-project.org). 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 BC load. We determined Pearson correlation coefficients between the different short-term and long-term air pollution exposures (supplementary 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, P_{aO_2}/F_{IO_2} ratio and blood oxygen saturation at the time of admission

Distributed lag models (DLMs; using R package “dlnm” version 2.4.7) were used to estimate day-specific associations between short-term exposure to air pollutants up to 30 days before admission. More details about the DLMs can be found in the supplementary material.

Binomial logistic regression models were used to estimate the odds ratios for admission to the ICU, risk of ventilation and vasopressor usage.

All models were adjusted for the following previously reported risk factors and potential confounders: age, sex, BMI, education, neighbourhood median income, smoking status, average temperature at the day of admission, CCI and estimated virus variant (based on the dominant virus variant in Belgium at the time of

admission). Additionally, we used generalised additive models to account for date of admission using a smoothed term for this covariate. Using this smoothed term for date of admission indicated better fit 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 Antwerp University Hospital) 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 20.1–98.3 years) and included 148 (43.6%) women. 179 (56.6%) patients had congestive heart failure, 73 (22.3%) had diabetes and 63 (19.2%) had cancer. The mean±SD early warning score at admission was 3.1±2.2. Most patients obtained a secondary education degree (n=179 (54.8%)), whereas 92 (28.0%) obtained a primary education degree or no degree at all and 57 (17.4%) obtained a college or university degree. A large proportion of the patients were of Caucasian ethnicity (n=281 (85.7%)). Patients of North-African ethnicity represented the second largest proportion (n=32 (9.8%)). Most patients were never-smokers (n=172 (52.4%)), whereas nine 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 presented in table 2. The measured

TABLE 1 Demographic and medical characteristics of the study population (n=328)

Demographic characteristics	
Age (years)	65.7±16.7
BMI ($kg \cdot m^{-2}$)	28.0±5.5
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 smoker	9 (2.7)
Ex-smoker	146 (44.5)
Never-smoker	172 (52.4)
Passive smoker	1 (0.3)
Medical characteristics	
Blood oxygen saturation (%)	95.81±4.05
CRP ($mg \cdot dL^{-1}$)	77.34±69.10
P_{aO_2}/F_{IO_2} ratio	286.23±88.80
Neutrophil count ($\times 10^3\ \mu L^{-1}$)	5.65±3.40
Eosinophil count ($\times 10^3\ \mu L^{-1}$)	0.05±0.26
Monocyte count ($\times 10^3\ \mu L^{-1}$)	0.93±1.81
Platelet count ($\times 10^3\ \mu L^{-1}$)	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)

Data are presented as mean±SD or n (%). BMI: body mass index; CRP: C-reactive protein; P_{aO_2}: arterial oxygen tension; F_{IO_2}: inspiratory oxygen fraction

TABLE 2 Descriptive characteristics of the average exposure to air pollutants 2 and 7 days before admission, as well as long-term exposure (average exposure from 2016 to 2019)

	Minimum	Quartile 1	Median	Quartile 3	Maximum	IQR
$PM_{2.5}$ ($\mu g \cdot m^{-3}$)						
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} ($\mu g \cdot m^{-3}$)						
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 ($\mu g \cdot m^{-3}$)						
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 ($\mu g \cdot m^{-3}$)						
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	20.13	30.43	4.16

IQR: interquartile range; $PM_{2.5}$: particulate matter with aerodynamic diameter <2.5 µm; PM_{10}: particulate matter with aerodynamic diameter <10 µm; BC: black carbon; NO_2: nitrogen dioxide.

BC particles in blood were significantly correlated with the modelled chronic exposure levels to BC (Spearman's r=0.48, p<0.01) (supplementary 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 (supplementary table S2). While controlling for all other demographic and clinical variables (sex, BMI, education, median neighbourhood income, smoking status, day of admission, average temperature at the day of admission, CCI and estimated virus variant), for 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 also correlated with the duration of stay (p<0.01). None of the other covariates were significantly correlated with the duration of hospitalisation.

Duration of hospitalisation

Using DLMs, we investigated day-specific differences in the duration of hospitalisation for increases in exposure to air pollutants 30 days before hospital admission (figure 1). The DLM 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 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 3–5 days for an interquartile range (IQR) increase in short-term exposure 7 days before admission ($PM_{2.5}$ +4.13 (95% CI 0.74–7.53) days, PM_{10} +4.04 (95% CI 1.24–6.83) days and NO_2 +4.54 (95% CI 1.53–7.54) days).

We observed a significant moderating effect of patient sex on the association between the 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 (p-value for interactions <0.05) (figure 2d). Similarly, the effect of short-term (but not long-term) NO_2 exposure was more pronounced in men (p-value for interaction 0.01). Patient BMI and diabetes did not moderate the same associations (p-value for interactions >0.05).

We used co-pollutant models to potentially identify key long-term pollutants (supplementary table S3). We noted that the previously observed effects of long-term NO_2 (+4.39 (95% CI 1.12–6.78) days) and BC (+3.48 (95% CI 0.61–6.36) days) 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.

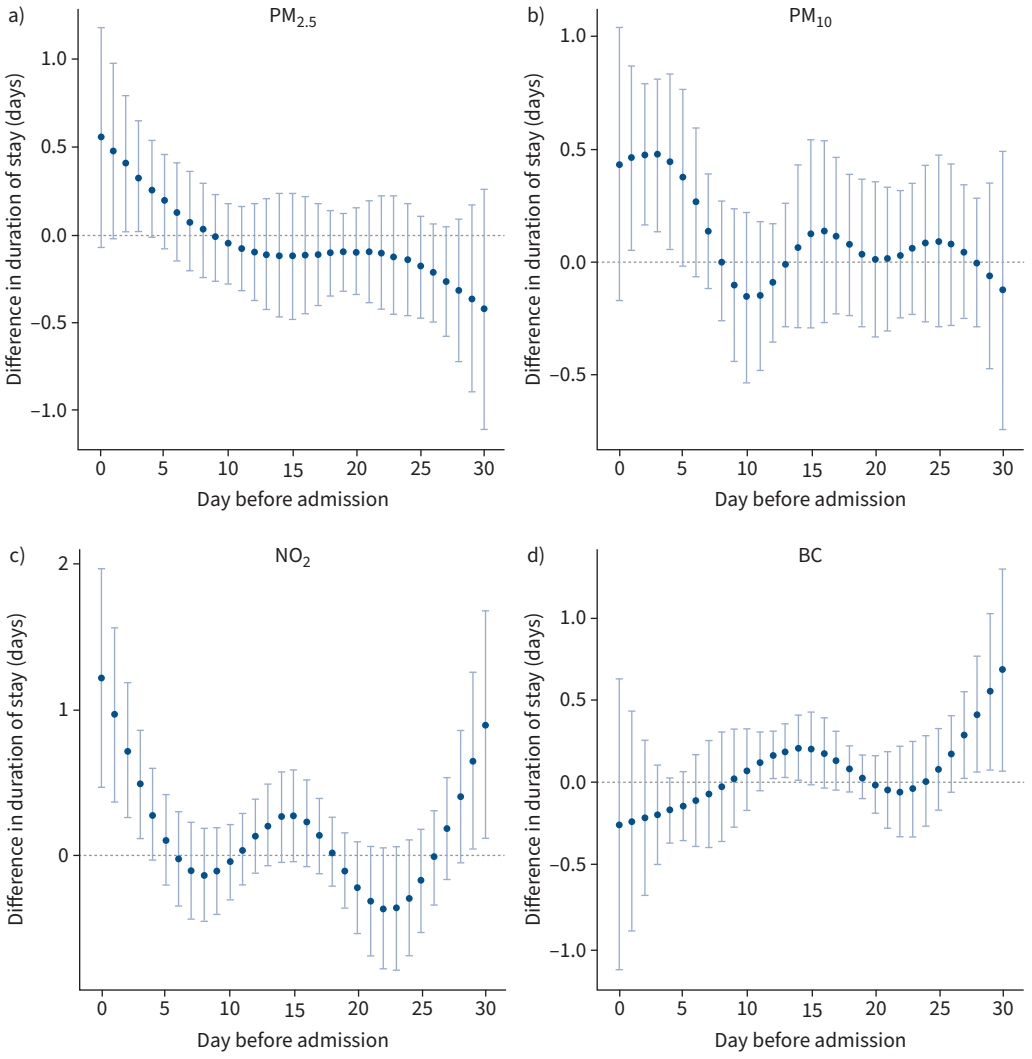

FIGURE 1 Day-specific estimates for the association between a) particulate matter with aerodynamic diameter <2.5 µm ($PM_{2.5}$), b) particulate matter with aerodynamic diameter <10 µm (PM_{10}), c) nitrogen dioxide (NO_2) and d) black carbon (BC) exposure and the duration of hospitalisation. The estimates 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 95% confidence interval upper and lower limits are shown. All models were adjusted for age, sex, body mass index, education, neighbourhood median income, smoking status, day of admission, average temperature at the day of admission, Charlson Comorbidity Index and estimated virus variant.

We ran models mutually adjusted for long-term and short-term exposure (supplementary 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 short-term exposures, while for long-term exposures, BC exposure remained significant in the mutually adjusted model.

Finally, as a sensitivity analysis we additionally adjusted for diabetes and last known occupation. While adjusting for diabetes (supplementary table S5), we observed no notable difference in the previously reported effect estimates. When adjusting for occupation (supplementary table S6), we observed non-significant trends for short-term average $PM_{2.5}$ (+3.40 (95% CI −0.08–6.88) days) and NO_2 (+1.55 (95% CI −0.74–5.35) days) 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 (supplementary table S10).

TABLE 3 Associations between average air pollutant exposure and blood black carbon (BC) load and the duration of hospitalisation (n=328)

	Estimate (95% CI) (days)	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 (−0.38–3.26)	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 (0.22–4.40)	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 interquartile range increase in the exposure. $PM_{2.5}$: particulate matter with aerodynamic diameter <2.5 µm; PM_{10}: particulate matter with aerodynamic diameter <10 µm; NO_2: nitrogen dioxide. All models were adjusted for age, sex, body mass index, education, neighbourhood median income, smoking status, day of admission, average temperature at the day of admission, Charlson Comorbidity Index and estimated virus variant.

Risk of admission to the ICU

The distribution of air pollution long-term exposure to both ambient pollutants and blood BC particles differed significantly between ICU and non-ICU hospitalised patients (figure 2a and b).

The odds of admission to the ICU were significantly associated with the blood BC particle load (figure 2c). The OR for an IQR increase (+9.27×10^5 particles per mL blood) in measured particles was 1.33 (95% CI 1.07–1.65). Long-term exposure to air pollutants was also associated with the odds of admission to the ICU (table 4). An IQR increase in long-term BC and NO_2 exposure was associated with an OR of 2.30 (95% CI 1.64–3.22) and 2.58 (95% CI 1.79–3.71), respectively.

In addition to long-term exposure, we observed a significant increase in the odds of admission to the ICU for an IQR increase in the average exposure to NO_2 1 week before admission (OR 2.05 (95% CI 1.34–3.13)). Sensitivity analysis revealed that excluding the patients recruited from Antwerp University Hospital did not significantly alter the aforementioned associations (supplementary 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 (supplementary 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 2.12 (95% CI 1.35–3.34)) (table 4). In addition, long-term exposure to air pollutants was associated with the risk of ventilation (figure 2c and table 4). For an IQR increase in long-term PM_{10}, BC and NO_2 exposure, the ORs for the risk of ventilation were 1.39 (95% CI 1.03–1.89), 1.96 (95% CI 1.43–2.70) and 1.98 (95% CI 1.41–2.79), respectively.

Regarding vasopressor use, short-term NO_2 exposure was associated with higher odds for vasopressor usage (OR 2.99 (95% CI 1.58–5.68)) (table 4). Long-term ambient air pollution was associated with increased odds of vasopressor usage (figure 2c). For an IQR increase in long-term NO_2 and BC exposure, the ORs were 2.79 (95% CI 1.75–4.45) and 2.58 (95% CI 1.70–3.92), respectively. Furthermore, an IQR increase in number of BC particles (+9.27×10^5 particles per mL blood) was associated with higher risk of vasopressor usage (OR 1.37 (95% CI 1.33–1.41)).

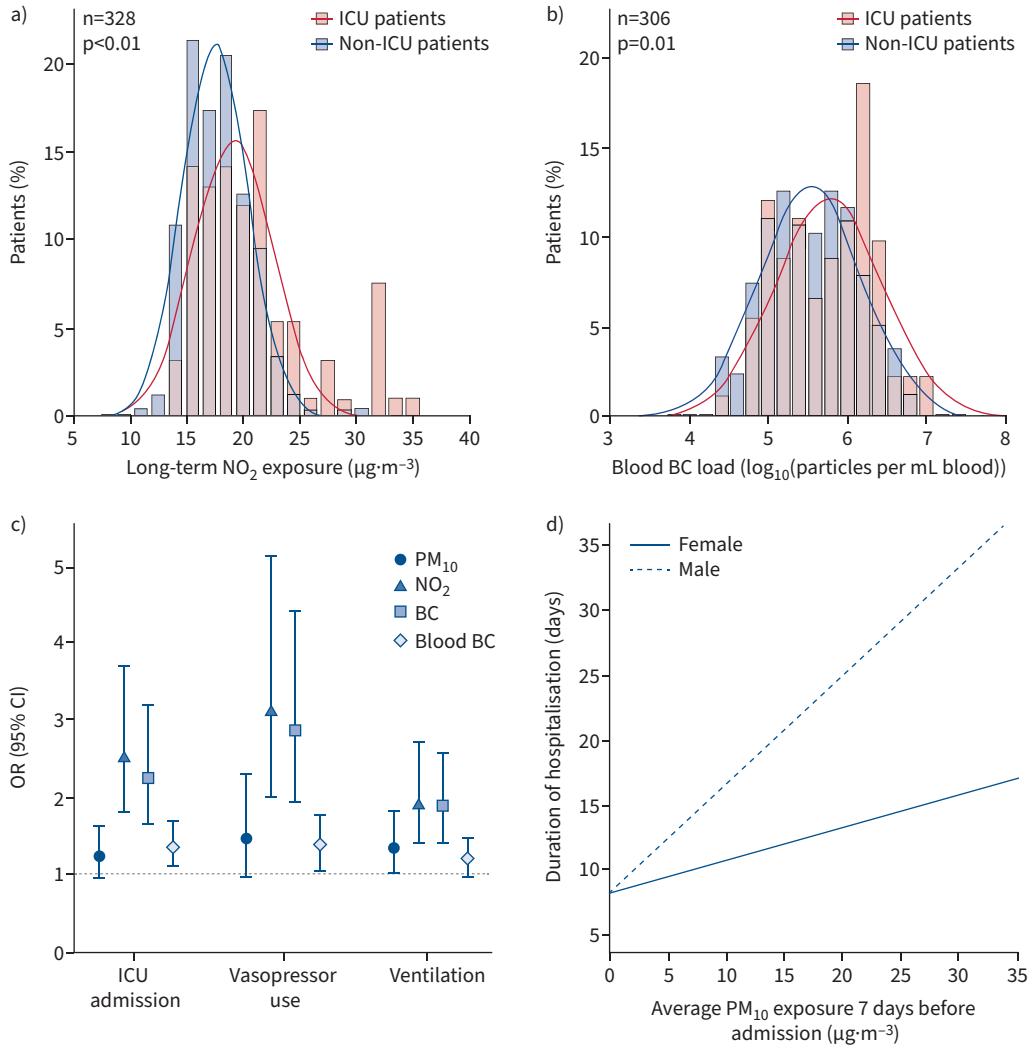

FIGURE 2 Distribution of pollutant exposure per patient group (intensive care unit (ICU) *versus* non-ICU) for a) long-term exposure to nitrogen dioxide (NO_2) and b) measured black carbon (BC) load in blood. c) Odds ratios (95% CI) for ICU admission, vasopressor usage and risk of ventilation for particulate matter with aerodynamic diameter <10 µm (PM_{10}), NO_2, BC and blood BC load. d) Interaction effect between average exposure to particulate matter with aerodynamic diameter <10 µm (PM_{10}) 1 week before admission and patient sex (p-value for interaction 0.04) on the duration of hospitalisation. Sample size was 308 for blood BC load measurements, since 20 blood samples were missing. Other analyses included all 328 participants (n=328). All model estimates are represented for an interquartile range increase in the exposure (long-term PM_{10} +0.76 µg·m^{-3}, NO_2 +4.16 µg·m^{-3}, BC +0.15 µg·m^{-3} and blood BC +9.27×10^5 particles per mL blood; short-term $PM_{2.5}$ +0.56 µg·m^{-3}), and were adjusted for age, sex, body mass index, education, smoking status, day of admission, average temperature at the day of admission, Charlson Comorbidity Index and virus variant.

Long-term BC and NO_2 exposures were associated with lower P_{aO_2}/F_{IO_2} ratios: −30.2 (95% CI −41.8– −18.6) and −35.2 (95% CI −48.6– −21.8), respectively (supplementary table S8). Average NO_2 exposure 1 week before admission was also associated with lower P_{aO_2}/F_{IO_2} ratios (−26.9 (95% CI −44.6– −9.1)).

Finally, we observed a trend toward higher risk of ventilation with increasing BC load (OR 1.18 (95% CI 0.96–1.45)).

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

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

Air pollutant	ICU admission (n=95 (29.0%))		On ventilation (n=78 (23.8%))		Vasopressor use (n=34 (10.4%))	
	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 interquartile range increase in the exposure. $PM_{2.5}$: particulate matter with aerodynamic diameter <2.5 µm; PM_{10}: particulate matter with aerodynamic diameter <10 µm; NO_2: nitrogen dioxide. All models were adjusted for age, sex, body mass index, education, smoking status, day of admission, average temperature at the day of admission and Charlson Comorbidity Index.

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 BC load) was associated with 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 risk for admission to the ICU. 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.* an increase in NO_2 by 4.16 µg·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 interleukin (IL)-6 receptor antagonist [40], remdesivir [41], and the triple combination of interferon (IFN)-β1b, 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 of the order of 40–80% 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-19 disease severity, namely patient sex. 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 by Plataki *et al.* [44], 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 sex modified the association between short-term $PM_{2.5}$ exposure and the duration of hospitalisation, 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 sex for COVID-19 disease severity of hospitalised patients by air pollution cannot be

explained fully by differences in comorbidities, since we accounted for the CCI. Therefore, other susceptibility or biological factors might also be involved.

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 SARS-CoV-2 infection, including ILs, IFNs, tumour necrosis factor, colony-stimulating factors, the chemokine family and growth factors [45]. These inflammatory processes in the mucus membranes of the pulmonary tract can result in pulmonary dysfunction, which in turn would have a negative impact on disease progression of COVID-19 infection.

Complementary to evidence of these plausible pathophysiological mechanisms, epidemiological data show an association between air quality and the incidence of COVID-19 in the population, the risk for hospitalisation and regional mortality [5, 25, 51–57]. 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, 51–53, 55–58] or not including short-term exposures to high concentrations of pollutants, such as might be experienced during a wildfire event [57]. 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 of our study 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 on 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 self-isolating at home. However, we believe the determined air pollution exposures reflect the indoor pollution levels relatively accurately. Studies have previously reported high correlations between indoor and outdoor air pollution, with correlation coefficients ranging between 0.40 and 0.79 [59–61]. Furthermore, we would argue that in the case that 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 socioeconomic 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 socioeconomic status, age, sex, 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 into account, including date (as smoothed term), season of admission, dominant virus strains and ambient temperature. 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. Furthermore, 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 haemodynamic characteristics, patient mobility and need for oxygen support) were stable. Hospital data showed that the average duration of stay of COVID-19 patients was not significantly shorter during the peak months of the pandemic than during the 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 BC 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 $\mu g \cdot m^{-3}$) 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 hospital burden and healthcare costs during the pandemic. Furthermore, improvement in air quality might lead to health effects comparable to 50% of the effect seen with novel clinical medical interventions (IL-6 receptor antagonist, remdesivir, and the triple combination of IFN-β1b, lopinavir–ritonavir and ribavirin) [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 on the role of air pollution and the ACE2 receptor in COVID-19 disease progression would be beneficial.

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