


ORIGINAL



Pre-admission air pollution exposure prolongs the duration of ventilation in intensive care patients

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Abstract

Purpose: Air pollutant exposure constitutes a serious risk factor for the emergence or aggravation of (existing) pulmonary disease. The impact of pre-intensive care ambient air pollutant exposure on the duration of artificial ventilation was, however, not yet established.

Methods: The medical records of 2003 patients, admitted to the intensive care unit (ICU) of the Antwerp University Hospital (Flanders, Belgium), who were artificially ventilated on ICU admission or within 48 h after admission, for the duration of at least 48 h, were analyzed. For each patient's home address, daily air pollutant exposure [particulate matter with an aerodynamic diameter $\leq 2.5 \mu\text{m}$ ($\text{PM}_{2.5}$) and $\leq 10 \mu\text{m}$ (PM_{10}), nitrogen dioxide (NO_2) and black carbon (BC)] up to 10 days prior to hospital admission was modeled using a high-resolution spatial-temporal model. The association between duration of artificial ventilation and air pollution exposure during the last 10 days before ICU admission was assessed using distributed lag models with a negative binomial regression fit.

Results: Controlling for pre-specified confounders, an IQR increment in BC ($1.2 \mu\text{g}/\text{m}^3$) up to 10 days before admission was associated with an estimated cumulative increase of 12.4% in ventilation duration (95% CI 4.7–20.7). Significant associations were also observed for $\text{PM}_{2.5}$, PM_{10} and NO_2 , with cumulative estimates ranging from 7.8 to 8.0%.

Conclusion: Short-term ambient air pollution exposure prior to ICU admission represents an unrecognized environmental risk factor for the duration of artificial ventilation in the ICU.

Keywords: Air pollution, Intensive care, Artificial ventilation, Mechanical ventilation, Critical care

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Introduction

The usual outdoor traffic-related air polluting suspects comprise gaseous (e.g., nitrogen dioxide (NO₂)) and particulate pollutants generated by combustion processes. Particulate matter (PM) is a heterogenic mixture of solid and liquid particles of organic and inorganic substances, drifting in the air. Mostly, sulfate, nitrates, ammonia, sodium chloride, black carbon, mineral dust and water are present, though heavy metals, polycyclic aromatic hydrocarbons, bacteria, viruses and even pollen can also be found [1]. Relevant to human health, inhalable particles are categorized by aerodynamic diameter: equal or less than (\leq) 10 μm (PM₁₀), ≤ 2.5 μm (PM_{2.5}) or ≤ 0.1 μm (PM_{0.1}). Black carbon (BC), a component of PM_{2.5} formed through incomplete combustion processes, is often used—in addition to NO₂—as a proxy of traffic-related air pollution.

The smaller the particle, the deeper the penetration in the respiratory system, leading to inflammatory reactions on the alveolar level, resulting in cytotoxicity and possible mutagenesis [2, 3]. As such, ambient air pollution constitutes a serious risk factor not only for the emergence of respiratory infections, but also for the development of reduced pulmonary function and/or aggravation of existing pulmonary disease (e.g., asthma, cystic fibrosis, chronic obstructive pulmonary disease [COPD]) [4–7].

In analogy with the recent finding that patient pre-admission medical and sociodemographic characteristics (e.g., medication use, immune status, frailty) can influence the course and outcome and even the degree of respiratory failure during intensive care unit (ICU) admission [8–10], we investigated the association between short-term exposure to residential ambient air pollution and the duration of mechanical ventilation in ICU patients.

Methods

A detailed description of the methods is provided in an electronic supplement.

Study population

We conducted a large-scale cohort study in the 45-bed tertiary ICU of the Antwerp University Hospital (Flanders, Belgium). Medical records of 19,039 patients, admitted from June 6, 2010, up to and including April 15, 2017, were analyzed for all modes of artificial (invasive and noninvasive) ventilation within 48 h of admission. Clinical data were primarily retrieved from the patient data management system (PDMS) (Metavision, iMD-soft, Düsseldorf, Germany), while personal information (e.g., smoking status) was retrieved from other medical

Take-home message

Short-term ambient particulate and gaseous air pollution exposure prior to ICU admission significantly prolongs the duration of mechanical ventilation irrespective of preexisting lung disease or ICU admission diagnosis. This finding suggests that optimizing air quality could influence ICU-related morbidity.

records. Our study was approved by the ethical committee of the University of Antwerp/Antwerp University Hospital (AIRPOLLUTIC trial, 17/12/162). A total of 3191 patients were mechanically ventilated within the first 48 h of admission for the duration of at least 48 h. After exclusion of patients living outside of Belgium ($n=512$), removal of patients with no data on smoking status ($n=414$) and elimination of children (<age 18 years) ($n=262$), our final study population comprised 2003 patients (Fig. 1).

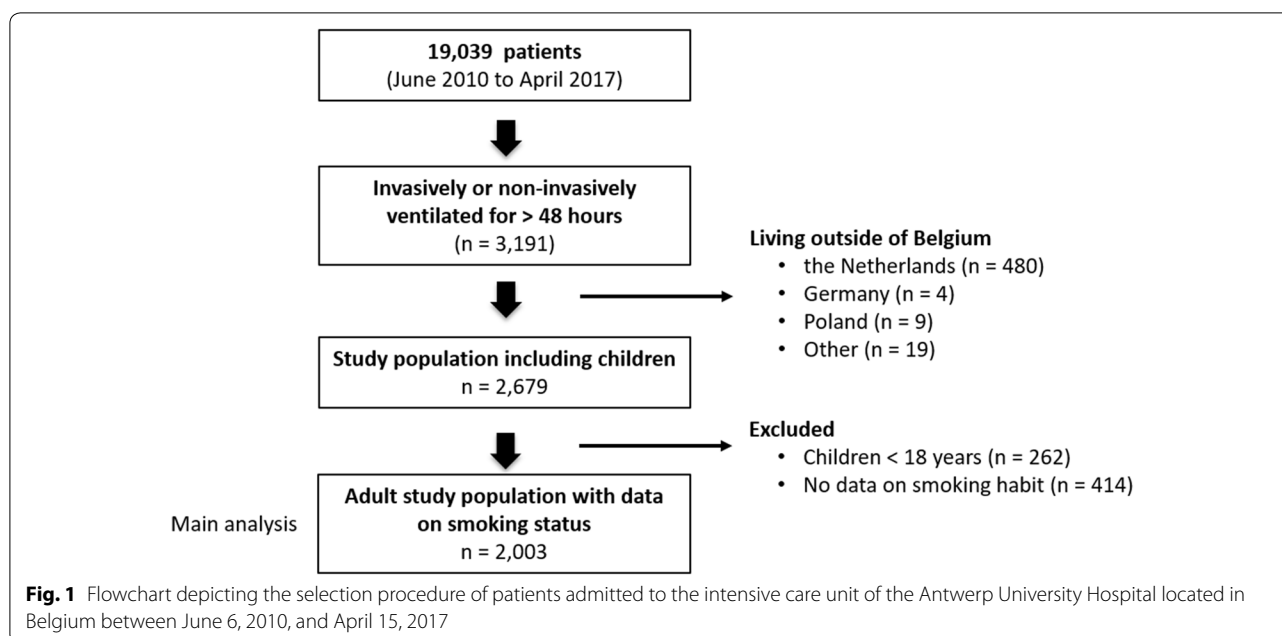
We obtained relevant demographic and clinical data in every patient and used the Simplified Acute Physiology Score (SAPS3) as a validated score for severity of illness [11]. We also obtained information on APACHE IV [12]. Ventilation duration was calculated by summing the duration (in hours) of all consecutive (invasive and noninvasive) ventilation episodes during the same ICU admission and was rounded to the nearest number of whole days.

Ambient air pollution exposure assessment

Residential addresses were geocoded with ArcGIS 10 software. Residential PM_{2.5}, PM₁₀, BC and NO₂ exposure levels ($\mu\text{g}/\text{m}^3$) were modeled for each patient's address using a high-resolution spatiotemporal model [13]. The model takes into account land cover data obtained from satellite images (CORINE land cover data set) and pollution data from fixed monitoring stations in combination with a dispersion model [14]. We calculated the daily concentrations of air pollutants at the patient's residential address up to 10 days before admission (lag0 to lag10, with lag0 representing the day of admission). For a sensitivity analysis, we calculated the annual average air pollution levels (as a proxy for long-term exposure).

Statistical analysis

Short-term health effects of environmental stressors may become apparent only a few or more days after exposure, implying that exposures during several days (lags) before the effect on human health should be considered. Instead of testing associations with lagged exposures in separate models, distributed lag (nonlinear) models [DL(N) Ms] provide a flexible methodology to capture the temporal pattern of the association by entering different lags in one and the same model. The primary study outcome



was the duration of ventilation in days. The association between ventilation duration and air pollution exposure was investigated by negative binomial regression, using a separate model for each of the four pollutants. Potential delayed effects of air pollution on ventilation duration up to 10 days before ICU admission (lag0 to lag10) were allowed by using DLNMs [15], with lag0 representing the day of admission, lag1 the day before admission and so on. The exposure–response function was modeled using a natural cubic spline with 5 df. Seasonality and long-term trends were modeled using a natural cubic spline of time (day of the study period) with 6 df per year. Models were additionally adjusted for indicator variables for day of the week and for known determinants of duration of ventilation such as sex, age (modeled with a natural cubic spline with 3 df), BMI (kg/m^2), disease severity (SAPS3), smoking status (non-smoker/active smoker), origin of the patient before ICU admission (emergency department/other) and admission diagnosis (non-respiratory/respiratory non-infectious/respiratory infectious).

In a secondary analysis, we adjusted our models for APACHE IV. In an effort to account for exposure misclassification in patients who were admitted to the hospital some days before ICU admission (e.g., 6 days at home, 4 days in the hospital, then ICU admission), we performed an analysis where we combined the daily exposure values derived at the home address with the daily exposure values derived at the hospital. Alternatively, we excluded patients coming from another hospital ICU to account for possible exposure misclassification (resulting in $n=1755$). In another secondary analysis, we

accounted for possible confounding due to respiratory comorbidities by excluding all patients with preexisting lung disease including COPD and asthma (resulting in $n=1672$) and by excluding all patients with preexisting respiratory and neuromuscular comorbidities ($n=1463$). We then further restricted the study population to patients who left the ICU alive ($n=1027$) to account for early death. Finally, to differentiate between short- and long-term effects, we added annual average air pollution levels (as a proxy for long-term exposure) to our main model. Reported estimates represent the lag-specific and cumulative (lag0–10 days) percentage change (with 95% confidence intervals [CI]) in ventilation duration for an interquartile range (IQR) increase in air pollution exposure. All analyses were performed with the statistical software R (R Foundation for Statistical Computing, Vienna, Austria) using the “dlm” package [16].

Results

Population characteristics

Demographic and clinical characteristics of the 2003 adult patients are summarized in Table 1. 48.3% of our study population were 65 years or older. There were more men (65.3%) than women (34.7%), and nearly one-third (30.7%) of our population were smokers. Approximately 70% of our population was admitted with a non-respiratory diagnosis, only 7.8% with a non-infectious respiratory disease and 22.1% with a respiratory infection. The mean (\pm SD) ventilation duration was 12 (\pm 13) days with

Table 1 Characteristics of the total study population (n = 2003)

Characteristic	Mean \pm SD or n (%)
Age, y	62 \pm 15
BMI, kg/m ²	26.6 \pm 7.6
Sex	
Male	1308 (65.3)
Female	695 (34.7)
Smoking status	
Non-smoker	1389 (69.3)
Smoker	614 (30.7)
Season of admission	
Winter (Dec–Mar)	558 (27.9)
Spring (Mar–Jun)	456 (22.8)
Summer (Jun–Sep)	485 (24.1)
Autumn (Sep–Dec)	504 (25.2)
SAPS3	61.0 \pm 15.8
APACHE IV	40.6 \pm 26.2
Diagnosis	
Non-respiratory	1405 (70.1)
Respiratory non-infectious ^a	156 (7.8)
Respiratory infectious ^b	442 (22.1)
Comorbidities	
COPD	283 (14.1)
Asthma	59 (2.9)
Other respiratory ^c	152 (7.6)
Neuromuscular ^d	73 (3.6)
Mortality	
ICU mortality	635 (31.7)
Hospital mortality	810 (40.4)
28-day mortality	622 (31)
Admission origin	
Emergency department	592 (29.5)
Operating room	518 (25.9)
Other hospital ICU	240 (12)
Conventional ward	424 (21.2)
Medium care unit	169 (8.4)
Other ^e	60 (3)
Ventilation (days)	12.4 \pm 13.4
Episodes of ventilation	1.4 \pm 0.9

^a For example, acute lung injury not related to an infectious disease, non-infectious COPD exacerbation, CO intoxication, lobectomy, lung emboli, pneumonectomy, thoracic trauma, upper airway obstruction

^b For example, acute lung injury in conjunction with a respiratory infection, bronchiolitis, infectious COPD exacerbation, empyema, mediastinitis, pneumonia

^c For example, asbestoses, cystic fibrosis, lung fibrosis, obstructive sleep apnea syndrome, pneumonectomy, etc. (n = 2000)

^d For example, amyotrophic lateral sclerosis, Duchenne muscular dystrophy, Guillain-Barré syndrome, multiple sclerosis, myotonic dystrophy, etc. (n = 1999)

^e Other origin includes maternity ward, coronary catheterization unit, interventional radiology and the recovery room after major surgery

the majority of patients (73.7%) having only one episode of ventilation.

Ambient exposure levels

Median (5th–95th percentiles) daily air pollution exposures up to 10 days before admission were 1.2 (0.4–3.6) $\mu\text{g}/\text{m}^3$ for BC, 11.4 (4.5–37.3) $\mu\text{g}/\text{m}^3$ for PM_{2.5}, 18.9 (9.4–47.0) $\mu\text{g}/\text{m}^3$ for PM₁₀ and 23.5 (8.2–49.5) $\mu\text{g}/\text{m}^3$ for NO₂ (Table 2). The majority of participants lived in the province of Antwerp, relatively close to the Antwerp University Hospital, where we observed the highest levels of PM_{2.5} exposure in Belgium (Figure Electronic supplement)

Main analysis

The lag-specific DLM estimates of the association between ventilation duration and air pollutant exposures up to 10 days before the ICU admission are shown in Fig. 2. The effect of all examined components of air pollution on ventilation duration was found to be acute, with significant effect estimates at lag0 (except for NO₂) and estimates close to zero after lag1. An IQR (1.2 $\mu\text{g}/\text{m}^3$) increment in BC exposure up to 10 days before ICU admission was associated with a 12.4% (95% CI 4.7 to 20.7) longer mechanical ventilation duration (Table 3). The corresponding estimates for PM_{2.5}, PM₁₀ and NO₂ were 7.9% (95% CI 0.5–15.9), 7.8% (95% CI 0.4–15.8), and 8.0% (95% CI 0.02–16.4), respectively.

Secondary analysis

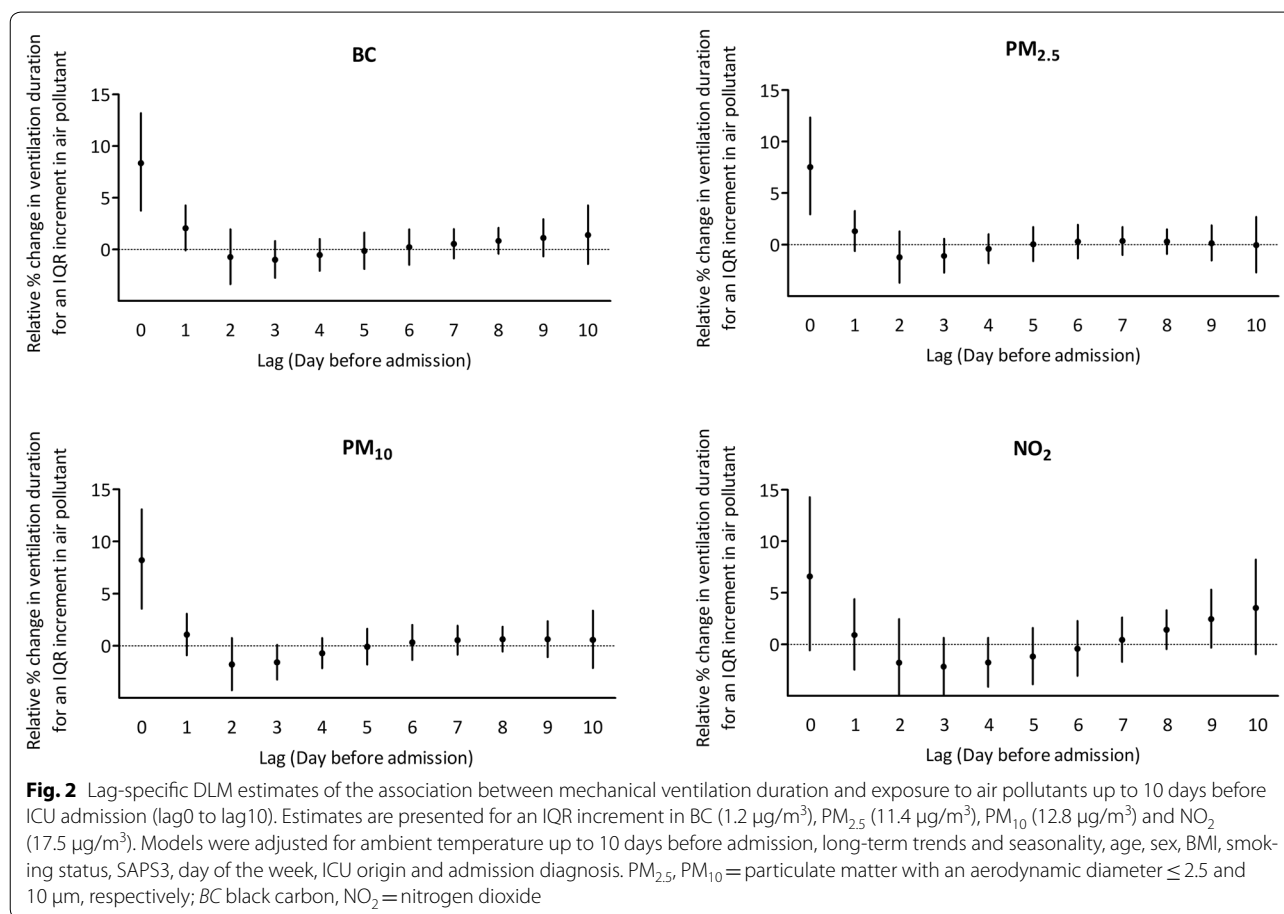
Correcting our models for APACHE IV or using data where we took into account possible exposure misclassification had a little effect on our estimates for all pollutants except that the estimates of PM_{2.5} did not reach significance anymore (Table 3). Excluding patients who had been hospitalized in another hospital ICU, days prior to admission to our ICU, also did not change our effect estimates substantially (Table 3). Restricting our analysis to patients without preexisting COPD and asthma resulted in stronger associations for all pollutants: 16.9% (95% CI 8.1–26.5) for BC, 11.5% (95% CI 2.4–21.5) for PM_{2.5}, 11.4% (95% CI 2.5–21.0) for PM₁₀, and 10.5% (95% CI 1.8–19.8) for NO₂ even after excluding all patients with respiratory and neuromuscular comorbidities. Further restricting the study population to patients without preexisting comorbidities, leaving the ICU alive, resulted in a further increase in cumulative effect estimates for BC and NO₂ and similar (although no longer significant) estimates for PM_{2.5} and PM₁₀. To differentiate between short- and long-term effects, we added annual average air pollution levels

Table 2 Distribution of daily air pollution concentrations and temperature up to 10 days before admission

Pollutant	P ₅	P ₂₅	P ₅₀	P ₇₅	P ₉₅	IQR
BC ($\mu\text{g}/\text{m}^3$)	0.4	0.8	1.2	1.9	3.6	1.2
PM _{2.5} ($\mu\text{g}/\text{m}^3$)	4.5	7.4	11.4	18.8	37.3	11.4
PM ₁₀ ($\mu\text{g}/\text{m}^3$)	9.4	14	18.9	26.8	47	12.8
NO ₂ ($\mu\text{g}/\text{m}^3$)	8.2	15.6	23.5	33.1	49.5	17.5
Temp. ($^{\circ}\text{C}$)	0.3	5.9	10.5	15.5	20.6	9.6

IQR interquartile range

PM_{2.5}, PM₁₀ = particulate matter with an aerodynamic diameter ≤ 2.5 and $10 \mu\text{m}$, respectively, BC black carbon, NO₂ = nitrogen dioxide



(as a proxy for long-term exposure) to our main model but found it not to be associated with the duration of ventilation.

Discussion

In our study of ICU patients, requiring mechanical ventilatory support for a diversity of reasons, ventilation duration was significantly associated with pre-admission exposure to BC, PM_{2.5}, PM₁₀ and NO₂. For an IQR higher air pollution exposure up to 10 days before

admission, the duration of ventilation was estimated to be 7.8–12.4% longer. Our data were obtained in a large and diverse ICU population, and the relationship between air pollution exposure and duration of ventilation was shown irrespective of preexisting lung disease or ICU admission diagnosis.

It has been shown that medical and sociodemographic characteristics [8, 10, 17] already present prior to ICU admission contribute to the occurrence and severity of organ failure including respiratory failure as well as the

Table 3 Effect estimates of the association between ventilation duration (percentage change) and air pollutant exposure up to 10 days before ICU admission

Model	No.	Air pollutant			
		BC (+ 1.2 µg/m ³)	PM _{2.5} (+ 11.4 µg/m ³)	PM ₁₀ (+ 12.8 µg/m ³)	NO ₂ (+ 17.5 µg/m ³)
Main model	2003	12.4 (4.7, 20.7)	7.9 (0.5, 15.9)	7.8 (0.4, 15.8)	8 (0.2, 16.4)
Corrected for APACHE IV instead of SAPS3	2003	12.4 (4.7, 20.6)	7.3 (− 0.8, 16)	7.8 (0.2, 16.2)	8 (0.2, 16.4)
Accounting for exposure misclassification	2003	11 (2.6, 20)	7.1 (− 1.0, 15.8)	7.9 (0.1, 16.4)	8.1 (− 0.9, 17.9)
Excl. patients coming from another ICU	1755	12.2 (4, 21)	7.3 (− 1.3, 16.7)	8.5 (0.1, 17.6)	9.1 (0.7, 18.2)
Excl. COPD, asthma	1672	16.9 (8.1, 26.5)	11.5 (2.4, 21.5)	11.4 (2.5, 21)	10.5 (1.8, 19.8)
Excl. respiratory ^a , neuromuscular comorbidities	1463	16.6 (7, 27)	10 (0.2, 20.8)	10.2 (0.7, 20.7)	10.6 (1.4, 20.6)
Excl. respiratory ^a , neuromuscular comorbidities & deaths	1027	17.9 (6.5, 30.4)	8.4 (− 2.9, 21)	9.1 (− 1.9, 21.3)	12.2 (1.2, 24.4)

The estimates represent the cumulative percentage change in ventilation duration for an IQR (µg/m³) increment in the air pollutant up to 10 days before the ICU admission

All models were adjusted for long-term trends and seasonality, age, sex, BMI, smoking habit, SAPS3, day of the week, ICU origin and admission diagnosis

^a Including preexisting COPD, asthma and all other respiratory comorbidities

PM_{2.5}, PM₁₀ = particulate matter with an aerodynamic diameter ≤ 2.5 and 10 µm, respectively, BC black carbon, NO₂ = nitrogen dioxide

outcome in the critically ill. However, pre-admission environmental factors have hardly been studied in this context, or studies have found no effect (i.e., sunlight exposure prior to ICU admission has been found not to influence the incidence of ICU-acquired delirium) [18]. We are the first to report on the effect of pre-admission air pollution exposure on the duration of mechanical ventilation.

The findings of this study are of critical public health importance because of the ubiquity of ambient air pollution. Short-term ambient particulate air pollution is independently associated with daily all-cause, cardiovascular and respiratory mortality [19, 20]. As such, air pollution has important molecular and physiological effects on the lung, an organ frequently failing in the critically ill. A few recent studies have demonstrated some effects of air pollution on the occurrence of (only) the acute respiratory distress syndrome (ARDS) and associated mortality. Long-term ozone and PM_{2.5} exposure are associated with an increased risk for ARDS among older adults in the USA [21] and in patients at risk for ARDS (e.g., trauma patient, active smoker) [22]. Rush et al. [23] described how chronic exposure to high levels of ozone and PM results in higher mortality rates in ARDS patients, and most recently, Reilly et al. [24] added long-term exposure to low to moderate levels of sulfur dioxide, NO₂ and carbon monoxide to the risk factors for ARDS in trauma patients.

Our results indicate the acute effects of air pollution on ventilation duration. Significant associations were observed for lag0, representing the day of ICU admission, but positive estimates (close to significance for BC and PM_{2.5}) were also observed for lag1. A similar lagged

pattern (lag0 and lag1) has been shown in a recent study investigating the association between the short-term effect of ambient air pollution (PM₁ and PM_{2.5}) and hospital admission for respiratory diseases [25]. The mechanism of this lagged pattern is not completely understood, but (pulmonary and/or systemic) oxidative stress and inflammation might be plausible biological mechanisms. For example, in a prospective panel study, increased blood levels of C-reactive protein and ICAM-1 were observed for an increase in PM₁₀ and ultrafine particles with a delay of 1–2 days [26]. In 3996 individuals of the Framingham Heart Study, elevated exposure to relatively low levels of ambient air pollution for a few days was associated with higher levels of biomarkers of systemic inflammation (including C-reactive protein, interleukin-6 and tumor necrosis factor receptor 2) [27]. Therefore, it is reasonable to assume that acute air pollution-induced inflammation processes occur, at least in the lung, since this is the primary site of inflammation. The effects of air pollutants on the lung originate from extracellular activation of the inflammatory response and/or oxidative stress-mediated inflammation in airway epithelial cells [28].

Known detrimental effects of airway inflammation comprise a reduction in pulmonary function, increased airway reactivity with hypersecretion of mucus and alterations in mucociliary activity [29]. The latter will of course contribute to a protracted exposure of the airway epithelium to toxic particles, thus generating a prolonged inflammatory response. We hypothesize that inflammatory reactions on the alveolar, airway and/or pulmonary capillary level result in gas exchange impairment, thus contributing to the lengthening of ventilation duration.

Modern critical care does not only focus on the prevention of primary ventilation-associated morbidities such as ventilator-associated pneumonia or barotrauma [30, 31] but also tries to prevent long-term sequela related to prolonged mechanical ventilation by the use of short-acting sedatives and daily appraisal of the need for mechanical ventilation. Indeed, duration of ventilation-related conditions such as cognitive impairment, depression, neuro-myopathy and pulmonary function alterations (e.g., reduced diffusion capacity) can persist in the ICU survivor, resulting in a long-term need of medical, psychological and/or physiotherapeutic care, causing considerable economic burden [32, 33]. Our data thus represent a novel and potentially modifiable environmental risk factor, which, if improved, will not only ameliorate the post-ICU quality of life but might also reduce health care costs. The incentive to “clear the air” will gain even more importance in the future, considering the projected increase in an aging [34] population who are even more at risk for air pollution-related respiratory diseases due to an age-related defective mucociliary function in combination with decreased muscle strength, compromising the ability to clear inhaled particles [35, 36].

Our study was conducted in the northern part of Flanders (Belgium), where levels of air pollutants continued to decrease between 2010 and 2017. In 2017, the annual levels of air pollutants in our study population nearly reached the WHO standards for $PM_{2.5}$ (12.8 vs. 10 $\mu\text{g}/\text{m}^3$) and for PM_{10} (20.2 vs. 20 $\mu\text{g}/\text{m}^3$) and even dived under the limit for NO_2 (23.4 vs. 40 $\mu\text{g}/\text{m}^3$) (Table Electronic supplement) [1]. The European Union (EU) air quality directives are less stringent (annual limits 25 $\mu\text{g}/\text{m}^3$ for $PM_{2.5}$, 40 $\mu\text{g}/\text{m}^3$ for PM_{10} and NO_2) than the WHO guidelines. In light of the fact that we found significant effects on duration of ventilation at air pollution levels well below the EU limits, our findings support a further down-revision of the current EU air pollution directives in the direction of the WHO guidelines.

Our findings need to be interpreted within the context of its strengths and limitations. Although we used validated exposure models, there might be some exposure misclassification. For example, we interpolated daily exposure levels at the residence without taking the amount of exposure at the address of employment or the time spent indoors into account. However, considering the higher age and expected preexisting health problems in our study population, we may assume that a considerable portion of time before admission was spent at the home address. Furthermore, a number of patients had been admitted to our hospital some days before ICU admission, thus generating some exposure misclassification. However, it is reasonable to assume that the

exposure misclassification is random, resulting in an underestimation of effect estimates [37, 38]. Moreover, our findings stayed robust after accounting for possible exposure misclassification and excluding patients coming from another hospital ICU. In terms of validity of the exposure model, we showed that the estimated long-term residential exposure correlates with the internal nano-sized carbon load in urine [39].

Secondly, we recognize the multifactorial character of ventilation duration, but we wish to emphasize that the use of short-acting sedatives, lung-protective ventilation and spontaneous breathing trials has been the mainstay of ICU ventilation care in the Antwerp University Hospital before, during and after the study period. Any differences in duration of ventilation are therefore not attributable to physician-specific particularities, but a priori to (preexistent) patient characteristics. Additionally, our findings were robust after adjusting for APACHE IV, excluding all patients with preexisting lung disease (COPD and asthma) or other comorbidities and even after excluding the patients that died in the ICU to account for the competing risk of early mortality. Thirdly, due to patient heterogeneity in the intensive care and random exposure misclassification—which cannot be ruled out in epidemiology—we observed relatively wide confidence intervals around our estimates. Finally, we could not retrieve information on socioeconomic status (SES). Although SES is important in long-term exposure outcomes, it is less likely to be an important confounder in acute exposure studies as no relation between short-term temporal differences in air pollution exposure and SES is expected.

Conclusion

Our results add to the growing body of evidence that links air pollution exposure to respiratory health. Our study is the first to examine the effect of pre-admission ambient air pollution on duration of artificial ventilation in the ICU. Our results suggest that a further optimization of air quality could influence ICU-related morbidity and—although not directly studied—ICU-related health costs. Our study also demonstrates that exposure to “low-level” air pollution prior to mechanical ventilation is clinically relevant.

Electronic supplementary material

The online version of this article (<https://doi.org/10.1007/s00134-020-05999-3>) contains supplementary material, which is available to authorized users.

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Authors' contribution

Annick De Weerd, Bram G. Janssen, Tim S. Nawrot and Philippe G. Jorens designed the study and acquired data. Walter Verbrugge extracted data from the ICU Patient Data Management System, Bram G. Janssen developed the air pollution exposure matrices (with input from Charlotte Vanpoucke and Wouter Lefebvre), Esmée M. Bijnens contributed to the geocoding of the residential addresses, and Omar El Salawi and Margot Jans retrieved additional data from the patient records under the supervision of Annick De Weerd. Annick De Weerd, Bram G. Janssen and Bianca Cox analyzed and interpreted the data. Annick De Weerd, Bram G. Janssen, Philippe G. Jorens wrote the initial version of the manuscript. All authors were involved in constructive criticism of the manuscript and approved the final version.

Compliance with ethical standards

Conflicts of interest

We declare no competing interests.

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References

- World Health Organisation (2006) WHO Air quality guidelines for particulate matter, ozone, nitrogen dioxide and sulfur dioxide. WHO, Geneva
- Traboulsi H, Guerrina N, Lu M, Maysinger D, Ariya P, Baglolle CJ (2017) Inhaled pollutants: the molecular scene behind respiratory and systemic diseases associated with ultrafine particulate matter. *Int J Mol Sci* 18:243–262
- Xing YF, Xu YH, Shi MH, Lian YX (2016) The impact of PM_{2.5} on the human respiratory system. *J Thorac Dis* 8:E69–E74
- Collaborators GBDICRD (2017) Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Respir Med* 5:691–706
- Dauchet L, Hulo S, Cherot-Kornobis N, Matran R, Amouyel P, Edme JL, Giovannelli J (2018) Short-term exposure to air pollution: associations with lung function and inflammatory markers in non-smoking, healthy adults. *Environ Int* 121:610–619
- Goeminne PC, Kicinski M, Vermeulen F, Fierens F, De Boeck K, Nemery B, Nawrot TS, Dupont LJ (2013) Impact of air pollution on cystic fibrosis pulmonary exacerbations: a case-crossover analysis. *Chest* 143:946–954
- Ruttens D, Verleden SE, Bijnens EM, Winkelmans E, Gottlieb J, Warnecke G, Meloni F, Morosini M, Van Der Bij W, Verschuren EA, Sommerwerck U, Weinreich G, Kamler M, Roman A, Gomez-Olles S, Berastegui C, Benden C, Holm AM, Iversen M, Schultz HH, Luijk B, Oudijk EJ, Kwakkel-van Erp JM, Jaksch P, Klepetko W, Kneidinger N, Neurohr C, Corris P, Fisher AJ, Lordan J, Meachery G, Piloni D, Vandermeulen E, Bellon H, Hoffmann B, Vienneau D, Hoek G, de Hoogh K, Nemery B, Verleden GM, Vos R, Nawrot TS, Vanaudenaerde BM (2017) An association of particulate air pollution and traffic exposure with mortality after lung transplantation in Europe. *Eur Respir J* 49:1600484
- Chen W, Janz DR, Bastarache JA, May AK, O'Neal HR Jr, Bernard GR, Ware LB (2015) Prehospital aspirin use is associated with reduced risk of acute respiratory distress syndrome in critically ill patients: a propensity-adjusted analysis. *Crit Care Med* 43:801–807
- McKown AC, McGuinn EM, Ware LB, Wang L, Janz DR, Rice TW, Semler MW (2017) Preadmission oral corticosteroids are associated with reduced risk of acute respiratory distress syndrome in critically ill adults with sepsis. *Crit Care Med* 45:774–780
- Muscudere J, Waters B, Varambally A, Bagshaw SM, Boyd JG, Maslove D, Sibley S, Rockwood K (2017) The impact of frailty on intensive care unit outcomes: a systematic review and meta-analysis. *Intensive Care Med* 43:1105–1122
- Moreno RP, Metnitz PG, Almeida E, Jordan B, Bauer P, Campos RA, Iapichino G, Edbrooke D, Capuzzo M, Le Gall JR, Investigators S (2005) SAPS 3—from evaluation of the patient to evaluation of the intensive care unit. Part 2: development of a prognostic model for hospital mortality at ICU admission. *Intensive Care Med* 31:1345–1355
- Zimmerman JE, Kramer AA, McNair DS, Malila FM (2006) Acute Physiology and Chronic Health Evaluation (APACHE) IV: hospital mortality assessment for today's critically ill patients. *Crit Care Med* 34:1297–1310
- Janssen S, Dumont G, Fierens F, Mensink C (2008) Spatial interpolation of air pollution measurements using CORINE land cover data. *Atmos Environ* 42:4884–4903
- Lefebvre W, Vercauteren J, Schrooten L, Janssen S, Degraeuwe B, Maenhaut W, de Vlieger I, Vankerkom J, Cossemans G, Mensink C, Veldeman N, Deutsch F, Van Looy S, Peelaerts W, Lefebvre F (2011) Validation of the MIMOSA-AURORA-IFDM model chain for policy support: modeling concentrations of elemental carbon in Flanders. *Atmos Environ* 45:6705–6713
- Gasparrini A, Armstrong B, Kenward MG (2010) Distributed lag non-linear models. *Stat Med* 29:2224–2234
- Gasparrini A (2011) Distributed lag linear and non-linear models in R: the package dlnm. *J Stat Softw* 43:1–20
- Hofhuis JG, Spronk PE, van Stel HF, Schrijvers AJ, Bakker J (2007) Quality of life before intensive care unit admission is a predictor of survival. *Crit Care* 11:R78
- Simons KS, Workum JD, Slooter AJ, van den Boogaard M, van der Hoeven JG, Pickkers P (2014) Effect of preadmission sunlight exposure on intensive care unit-acquired delirium: a multicenter study. *J Crit Care* 29:283–286
- Liu C, Chen R, Sera F, Vicedo-Cabrera AM, Guo Y, Tong S, Coelho M, Saldiva PHN, Lavigne E, Matus P, Valdes Ortega N, Osorio Garcia S, Pascal M, Stafoggia M, Scortichini M, Hashizume M, Honda Y, Hurtado-Diaz M, Cruz J, Nunes B, Teixeira JP, Kim H, Tobias A, Iniguez C, Forsberg B, Astrom C, Ragettli MS, Guo YL, Chen BY, Bell ML, Wright CY, Scovronick N, Garland RM, Milojevic A, Kysely J, Urban A, Orru H, Indermitte E, Jaakkola JJK, Ryti NRI, Katsouyanni K, Analitis A, Zanobetti A, Schwartz J, Chen J, Wu T, Cohen A, Gasparrini A, Kan H (2019) Ambient particulate air pollution and daily mortality in 652 cities. *N Engl J Med* 381:705–715
- Bein T, Karagiannidis C, Quintel M (2019) Climate change, global warming, and intensive care. *Intensive Care Med*. <https://doi.org/10.1007/s00134-019-05888-4>
- Rhee J, Dominici F, Zanobetti A, Schwartz J, Wang Y, Di Q, Balmes J, Christiani DC (2019) Impact of long-term exposures to ambient PM_{2.5} and ozone on ARDS risk for older adults in the United States. *Chest* 156:71–79
- Ware LB, Zhao Z, Koyama T, May AK, Matthay MA, Lurmann FW, Balmes JR, Calfee CS (2016) Long-term ozone exposure increases the risk of developing the acute respiratory distress syndrome. *Am J Respir Crit Care Med* 193:1143–1150
- Rush B, McDermid RC, Celi LA, Walley KR, Russell JA, Boyd JH (2017) Association between chronic exposure to air pollution and mortality in the acute respiratory distress syndrome. *Environ Pollut* 224:352–356
- Reilly JP, Zhao Z, Shashaty MGS, Koyama T, Christie JD, Lanken PN, Wang C, Balmes JR, Matthay MA, Calfee CS, Ware LB (2019) Low to moderate air pollutant exposure and acute respiratory distress syndrome after severe trauma. *Am J Respir Crit Care Med* 199:62–70
- Zhang Y, Ding Z, Xiang Q, Wang W, Huang L, Mao F (2020) Short-term effects of ambient PM₁ and PM_{2.5} air pollution on hospital admission for

- respiratory diseases: case-crossover evidence from Shenzhen, China. *Int J Hyg Environ Health* 224:113418
26. Ruckerl R, Ibalid-Mulli A, Koenig W, Schneider A, Woelke G, Cyrys J, Heinrich J, Marder V, Frampton M, Wichmann HE, Peters A (2006) Air pollution and markers of inflammation and coagulation in patients with coronary heart disease. *Am J Respir Crit Care Med* 173:432–441
 27. Li W, Dorans KS, Wilker EH, Rice MB, Ljungman PL, Schwartz JD, Coull BA, Koutrakis P, Gold DR, Keaney JF Jr, Vasani RS, Benjamin EJ, Mittleman MA (2017) Short-term exposure to ambient air pollution and biomarkers of systemic inflammation: the framingham heart study. *Arterioscler Thromb Vasc Biol* 37:1793–1800
 28. Michael S, Montag M, Dott W (2013) Pro-inflammatory effects and oxidative stress in lung macrophages and epithelial cells induced by ambient particulate matter. *Environ Pollut* 183:19–29
 29. Wright DT, Cohn LA, Li H, Fischer B, Li CM, Adler KB (1994) Interactions of oxygen radicals with airway epithelium. *Environ Health Perspect* 102(Suppl 10):85–90
 30. Ioannidis G, Lazaridis G, Baka S, Mpoukovinas I, Karavasilis V, Lampaki S, Kioumis I, Pitsiou G, Papaiwannou A, Karavergou A, Katsikogiannis N, Sarika E, Tsakiridis K, Korantzis I, Zarogoulidis K, Zarogoulidis P (2015) Barotrauma and pneumothorax. *J Thorac Dis* 7:538–543
 31. Nair GB, Niederman MS (2015) Ventilator-associated pneumonia: present understanding and ongoing debates. *Intensive Care Med* 41:34–48
 32. Desai SV, Law TJ, Needham DM (2011) Long-term complications of critical care. *Crit Care Med* 39:371–379
 33. Sakusic A, Gajic O, Singh TD, O'Horo JC, Jenkins G, Wilson GA, Petersen R, Fryer JD, Kashyap R, Rabinstein AA (2018) Risk factors for persistent cognitive impairment after critical illness, nested case-control study. *Crit Care Med* 46:1977–1984
 34. Eurostat (2019) Ageing Europe—looking at the lives of older people in the EU. Luxembourg
 35. Lowery EM, Brubaker AL, Kuhlmann E, Kovacs EJ (2013) The aging lung. *Clin Interv Aging* 8:1489–1496
 36. Mordukhovich I, Lepeule J, Coull BA, Sparrow D, Vokonas P, Schwartz J (2015) The effect of oxidative stress polymorphisms on the association between long-term black carbon exposure and lung function among elderly men. *Thorax* 70:133–137
 37. Hennekens CH, Buring JE, Mayrent SL (1987) *Epidemiology in medicine*. Little Brown, Boston
 38. Lokken RP, Wellenius GA, Coull BA, Burger MR, Schlaug G, Suh HH, Mittleman MA (2009) Air pollution and risk of stroke: underestimation of effect due to misclassification of time of event onset. *Epidemiology* 20:137–142
 39. Saenen ND, Bove H, Steuwe C, Roeyers M, Provost EB, Lefebvre W, Vanpoucke C, Ameloot M, Nawrot TS (2017) Children's urinary environmental carbon load. A novel marker reflecting residential ambient air pollution exposure? *Am J Respir Crit Care Med* 196:873–881