Health effects of exposure to residential air pollution in patients with pulmonary arterial hypertension: a cohort study in Belgium

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To the Editor:

We read with interest the paper by Sofianopoulou *et al*. [1]. The authors have significantly contributed to highlighting the potential link between air pollution and health outcomes among pulmonary arterial hypertension (PAH) patients, by showing that exposure to particulate matter with an aerodynamic diameter smaller than 2.5 µm ($PM_{2.5}$) was significantly associated with transplant-free survival, and that traffic-related air pollution was correlated with the European Society of Cardiology (ESC)/European Respiratory Society (ERS) risk categories and haemodynamics at baseline.

In this letter we would like to report our results exploring a potential association between exposure to residential $PM_{2.5}$, PM_{10}, nitrogen dioxide (NO_2), black carbon (BC) and traffic-related air pollution, and parameters related to prognosis, pathophysiology, progression and survival, in a cohort of PAH patients.

Consecutive patients with a haemodynamically proven diagnosis of idiopathic/heritable/anorexigen-associated PAH between January 1995 and September 2018 and long-term follow-up (at least two follow-up visits) at University Hospitals of Leuven (median follow-up of 4.8 years) were included (figure 1a). To assess exposure to air pollution, each residential address at baseline visit was geocoded and linked with annual average levels of $PM_{2.5}$, PM_{10}, NO_2 and BC (year 2015), estimated with land use regression models, as previously described [2]. In addition, traffic-related exposure was determined based on the distance between the residence and the nearest major roads. Multivariate Cox regression was applied to model the association with survival and adverse outcome including pulmonary hypertension-related hospitalisation or treatment with *i.v./s.c.* prostanoids or lung transplantation. We used multivariate linear regression modelling for 6-min walking distance (6MWD), right atrial pressure (RAP), mean pulmonary arterial pressure (mPAP), cardiac index (CI), pulmonary vascular resistance (PVR) and circulating levels of C-reactive protein (CRP) at diagnosis. Multivariate ordinal logistic regression was used for New York Heart Association functional class (NYHA FC) and an abbreviated version of the ESC/ERS risk stratification [3]. We adjusted for age, gender, body mass index, smoking habits and level of obtained education. Additional adjustment for treatment with *i.v./s.c.* prostanoids and presence of bone morphogenetic protein receptor 2 mutations did not modify our results. The patient population was further stratified by 1) age (younger than and older or equal to 65 years at diagnosis), considering that elderly individuals have been exposed for a longer time and may experience greater risk of adverse outcome when exposed to air pollution, and 2) aetiology (only patients with idiopathic PAH and heritable PAH (IPAH and HPAH)). The associations are shown per increase of 10 $\mu g \cdot m^{-3}$ for $PM_{2.5}$, PM_{10} and NO_2, per increase of 1 $\mu g \cdot m^{-3}$ for BC and per interquartile range increase (IQR, 1338 m) for the distance to major roads. To control for type I errors and to adjust for the overall false-positive rate, the p-values were Bonferroni-corrected, accounting for at least five multi-comparisons.

A total of 211 patients (37% male) were studied with median age of 57 years. Patients displayed a severe haemodynamic profile and reduced exercise capacity (figure 1a). During the observation period, 29% of the patients were treated with *i.v./s.c.* prostanoids, 12% underwent a lung transplantation and 53% of the patients died (not mutually exclusive; figure 1a).

Shareable abstract (@ERSpublications)
This cohort study showed that both exercise capacity and ESC/ERS risk assessment were associated with previous exposure to air pollutants in PAH patients. In contrast to previous data, no significant association with adverse outcomes was found. https://bit.ly/3FwhJbz

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a)

Characteristics	Cohort (n=211)
Idiopathic PAH	158 (75)
Heritable PAH	21 (10)
PAH associated with appetite suppressants	32 (15)
Age at diagnosis, years	57 (37–69)
Male sex	78 (37)
RAP, mmHg	9±5
CI, L·min^{-1}·m^{-2}	2.1±0.6
PVR diagnosis, dyn·s·cm^{-5}	988±463
mPAP, mmHg	51±11
BMI, kg·m^{-2}	26±6.7
Smoking habits (n=196)	
Never	120 (61.2)
Active	16 (8.2)
Ex-smokers	60 (30.6)
NYHA FC (n=162)	
I	4 (2.5)
II	41 (25.3)
III	93 (57.4)
IV	24 (14.8)
Level of professional education (n=127)	
No education after high school	85 (66.9)
Short education after high school	34 (26.8)
University education	8 (6.3)
ESC/ERS risk score at diagnosis [3]	
Low risk	49 (23)
Intermediate risk	141 (67)
High risk	21 (10)
6MWD, m	322±146
***i.v.* treatment (n=210)**	61 (29)
Transplantation	25 (12)
Deceased	112 (53)
Survival time, years	4.8 (1.85–11.91)
Yearly level of particulate matter ≤2.5 µm, µg·m^{-3}	12.0 (11.3–12.9)
Yearly level of particulate matter ≤10 µm, µg·m^{-3}	18.3 (17.1–19.8)
Yearly level of nitrogen dioxide µg·m^{-3}	16.9 (13.9–21.7)
Yearly level of black carbon µg·m^{-3}	1.02 (0.9–1.2)
Distance to major road, m	726.9 (33.5–1653.1)

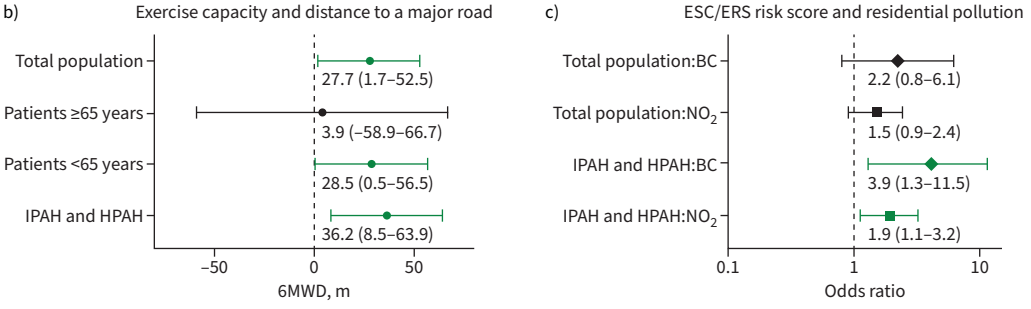

FIGURE 1 a) Summary of patient characteristics at baseline. Values are expressed as mean±SD (for continuous variables), n (%) (for categorical variables) or as median (interquartile range). PAH: pulmonary arterial hypertension; RAP: right atrial pressure; CI: cardiac index; PVR: pulmonary vascular resistance; mPAP: mean pulmonary arterial pressure; BMI: body mass index; NYHA FC: New York Heart Association functional class; ESC/ERS: European Society of Cardiology/European Respiratory Society; 6MWD: 6-min walking distance. b) Association of the 6MWD and the distance to a major road in PAH patients. c) Association of the ESC/ERS risk score and residential pollution in PAH patients. Associations are adjusted for age, gender, BMI, smoking and socio-economic status. Total population, n=211; patients ⩾65 years, n=72; patients <65 years, n=139;

idiopathic PAH (IPAH) and heritable PAH (HPAH), n=179. Results are expressed as beta estimates with 95% confidence intervals per interquartile range increase (1338 m) for the distance to a major road, and expressed as odds ratios with 95% confidence intervals per increase of 10 $\mu g \cdot m^{-3}$ for NO_2 and per increase of 1 $\mu g \cdot m^{-3}$ for black carbon (BC).

Multivariate Cox regression analysis showed that exposure to residential air pollution was not significantly associated with death or with any of the composite endpoints of adverse outcome. Multivariate linear regression modelling for 6MWD, RAP, mPAP, CI, PVR and CRP circulating levels at diagnosis, showed that only 6MWD was significantly associated with the distance from the patients' home to a major road (estimate was 27.7 m, 95% CI 1.7–52.5 per IQR change) (figure 1b). Finally, multivariate ordinal logistic regression revealed additional associations between the ESC/ERS risk score and exposure levels of BC (OR 3.9, 95% CI 1.3–11.5) and NO_2 (OR 1.9, 95% CI 1.1–3.2) in the subgroups of patients with IPAH and HPAH (figure 1c).

The study of Sofianopoulou *et al.* [1] was the first to report that mortality of PAH patients is associated with ambient air pollution. However, we did not confirm this finding in our cohort. The discrepancies between our results and those of Sofianopoulou *et al.* [1] may have various reasons, including: 1) difference in the sample size; 2) inclusion of drug-related PAH, with anorexigen exposure appearing as a potential effect modifier, blurring the association of ESC/ERS risk score with air pollution; 3) a higher proportion of patients with an event, due to longer inclusion and follow-up periods; 4) differences in exposure concentrations and mean distance to major roads.

The concept that air pollution may provoke changes in the pulmonary vasculature, leading to pulmonary hypertension, is biologically plausible given the proximity of the pulmonary vasculature and the alveolar–capillary interface and the potential for pollution to either act directly or through translocation into the circulation to elicit inflammation, oxidative stress and coagulation responses [4–6]. Evidence from animal models and epidemiological cohort studies suggests that air pollution exposure, including particulate matter and diesel exhaust, results in changes to the pulmonary vasculature [7–11]. We showed that living far from a major road may have a beneficial effect on exercise capacity and found a significant association between the ESC/ERS risk score and exposure to NO_2 and BC, pollutants mainly present in vehicle exhaust emissions. The strength of our study is the large cohort of PAH patients with a close follow-up and uniform measures of air pollution exposure. A limitation of the study is the usage of a proxy marker for traffic pollution and the fact that exposure variables do not take into account individual differences in the time spent at home, work or in other environments, although PAH patients may spend more time at home than the general population. In addition, even applying Bonferroni correction, known to decrease type I errors and increase type II errors, associations remained significant.

In conclusion, in contrast to findings by Sofianopoulou *et al.* [1], we found that exposure to $PM_{2.5}$, PM_{10}, NO_2 and BC and residential distance to major roads are not related to adverse outcome or mortality in PAH. Importantly, we did find a significant association between NO_2, BC and ESC/ERS risk score, similarly to the observations in the UK. We also observed an association between improved exercise capacity and living far from a major road. However, we believe that more data need to be collected to better document the compelling debate on air pollution and PAH.

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Conflict of interest: The authors declare that they have no conflict of interest.

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