



A crossroads between the heart and lungs: air pollution and pulmonary hypertension

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Proximity to traffic and particulate pollution may be associated with disease severity and increased mortality in individuals with pulmonary arterial hypertension. Future studies are needed to confirm these findings. <http://bit.ly/2P5QE52>

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While most studies of air pollution health effects have been in the general population, studying subgroups with chronic disease has the potential to define the magnitude of the health effects in sensitive populations and may provide unique insights into the mechanism of pollutant effects. Studies have shown indoor air pollution to be associated with increased chronic obstructive pulmonary disease (COPD) morbidity [1] and outdoor air pollution with increased COPD morbidity and mortality [2]. Recent work in idiopathic pulmonary fibrosis (IPF) has suggested that outdoor air pollution may be associated with steeper rate of lung function decline, risk of IPF exacerbation, and increase in mortality [3–5]. While these and other studies have investigated lung function, exacerbations and mortality, air pollution studies have not previously included assessment of pulmonary vascular effects, as this outcome is not easily accessible. Pulmonary arterial hypertension (PAH) cohorts often include catheterisation data as part of longitudinal assessment of disease course and thus, studies in populations with pulmonary hypertension provide a unique opportunity to link air pollution exposure to physiological effects on the pulmonary circulation.

In this issue of the *European Respiratory Journal*, SOFIANOPOULOU *et al.* [6] report findings from the UK National Cohort Study linking traffic-related pollution to health outcomes among those with underlying PAH. The cohort of ~300 individuals, while relatively small, was well characterised clinically and had right heart catheterisation measurements, providing the ability to investigate associations with physiological end-points. The investigators applied geocoding to assign annual average exposure to particulate matter with a 50% cut-off aerodynamic diameter $\leq 2.5 \mu\text{m}$ (PM_{2.5}) and NO₂ based on 2010 concentrations, which preceded participant entry into the cohort and were selected as indicators of chronic exposure. Proximity of the home residence to roadway and length of roads near the home were also used to represent traffic exposure.

Proximity to traffic was associated with worse disease severity as assessed by cardiopulmonary haemodynamics and by the European Respiratory Society and European Society of Cardiology PAH risk score [7]. However, proximity to traffic was not associated with transplant-free survival. Conversely, chronic PM_{2.5} was associated with reduced transplant-free survival. The magnitude of effect of PM_{2.5} on outcomes was greater than most prior studies with a more than two-fold increased risk of transplant or

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death (HR 2.47, 95% CI 1.12–5.48) per $3 \mu\text{g}\cdot\text{m}^{-3}$ increase in $\text{PM}_{2.5}$. This was in the absence of extraordinarily high particulate matter exposure. In fact, the $\text{PM}_{2.5}$ concentration was generally within regulatory agency recommended ranges, with an ambient $\text{PM}_{2.5}$ concentration median value of $13.7 \mu\text{g}\cdot\text{m}^{-3}$. Unexpectedly, $\text{PM}_{2.5}$ exposure was associated with lower pulmonary vascular resistance (PVR). This was surprising as higher PVR predicts poorer survival in PAH and thus, one would expect an association between long-term $\text{PM}_{2.5}$ exposure and mortality in PAH to be reflected by similar changes in pulmonary haemodynamics. It is possible that the observed association between $\text{PM}_{2.5}$ and outcomes may not be mediated through PVR or that PVR is an inadequate tool to assess this relationship, particularly if the effects of $\text{PM}_{2.5}$ are directed at the right ventricle (RV) rather than the pulmonary vasculature. AARON *et al.* [8] have demonstrated an association between $\text{PM}_{2.5}$ exposure and RV structure and function as assessed by cardiac magnetic resonance imaging (CMR) in the Multi-Ethnic Study of Atherosclerosis (MESA), demonstrating increasing RV mass with increasing particulate matter exposure in healthy adults. Furthermore, prior work in a cohort of PAH demonstrated that more than 25% of patients who experienced improvement in PVR with pulmonary vasodilator therapy had a concomitant decline in RV function as assessed by CMR, suggesting that PVR may be an inadequate measure of RV function [9]. Since $\text{PM}_{2.5}$ may have direct effects on the RV, and RV function is the main determinant of outcomes in PAH, better characterisation of the relationship is needed.

Interestingly, the investigators found no association between NO_2 exposure and disease severity or transplant-free survival. This too was surprising, given prior research demonstrating a strong relationship between NO_2 and RV structure and function. In a separate study from MESA, NO_2 was used as a surrogate for traffic exposure and was associated with increases in RV mass and in end diastolic volume among over 4000 participants [10]. The MESA investigators speculated that traffic-related pollution leads to increases in pulmonary vascular resistance and right heart hypertrophy. While MESA had the advantage of CMR, catheterisation data was not available and the results supported the need to study the effects of pollution on the pulmonary vasculature in potentially susceptible populations [11].

The work of SOFIANOPOULOU *et al.* [6] extends the robust literature demonstrating the association between air pollution and cardiopulmonary health effects in general and susceptible populations [12–14]. Recent evidence from the MESA study has advanced our understanding of air pollution health effects by reporting associations between air pollution exposure and right heart structure and function in the general population [8, 10, 15]. This has led to questions about the potential effect of air pollution on the pulmonary vasculature. The concept that air pollution may provoke changes in the pulmonary vasculature that lead to pulmonary hypertension has biological plausibility given the proximity of pulmonary vasculature to 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. Evidence from animal models suggests that air pollution exposure, including particulate matter and diesel exhaust, results in changes to the pulmonary vasculature [16, 17]. Despite some limitations of the study design, the findings from the UK cohort study represent an important step in addressing gaps in the current understanding of air pollution health effects on the pulmonary vasculature.

Lack of consistency in associations between 1) traffic exposure *versus* $\text{PM}_{2.5}$ and disease severity and 2) the results related to NO_2 exposure and prior studies suggest the study results need to be interpreted with caution. These discrepancies could be an indicator of exposure misclassification, unmeasured confounders, or could represent heterogeneity of effects of the multiple exposures represented by traffic. Individuals spend the majority of their time indoors and those with chronic diseases are even more likely to remain in their homes. Indoor air pollution and other home environmental exposures may be drivers of health effects and these were not measured as part of this study. It is also possible that there was variability in the time of clinical presentation that was driven by participant factors and that this influenced the cross-sectional analysis between air pollution and baseline haemodynamics.

SOFIANOPOULOU *et al.* [6] should be congratulated for their novel application of data from the UK cohort study to address the question of pollutant effects in PAH. Their study suggests that PAH may be a promising model with which to study the effects of air pollution on the pulmonary vasculature. Future studies may include more detailed assessment of indoor and outdoor pollutant exposure and longitudinal design to define the effect of pollution exposure on changes in pulmonary vasculature and right heart over time. While PAH is a relatively rare disease which creates challenges in achieving larger sample sizes, the existence of cohorts that include biological and physiological indicators of disease provides a unique opportunity. The biological rationale that patients with PAH may represent a susceptible subgroup is compelling and the investigators build a strong case for the need for future studies to replicate their findings and advance our understanding on pollution health effects on the pulmonary vasculature in general and in potentially uniquely susceptible patients with PAH.

Conflict of interest: M.C. McCormack reports authorship royalties from UptoDate, outside the submitted work. S.C. Mathai reports personal fees for consultancy from Arena and Actelion, personal fees for consultancy and data monitoring committee work from United Therapeutics, during the conduct of the study; and is a member of the Scientific Leadership Council, Pulmonary Hypertension Association.

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