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Version: Accepted Version

Article:
Sofianopoulou, E., Kaptoge, S., Gräf, S. et al. (2019) Traffic exposures, air pollution and outcomes in pulmonary arterial hypertension: A United Kingdom cohort study analysis. European Respiratory Journal, 53 (5). 1801429. ISSN: 0903-1936

https://doi.org/10.1183/13993003.01429-2018

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Early View

Original article

Traffic exposures, air pollution and outcomes in pulmonary arterial hypertension: A United Kingdom cohort study analysis

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Please cite this article as: Sofianopoulou E, Kaptoge S, Gräf S, *et al*. Traffic exposures, air pollution and outcomes in pulmonary arterial hypertension: A United Kingdom cohort study analysis. *Eur Respir J* 2019; in press (https://doi.org/10.1183/13993003.01429-2018).

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TRAFFIC EXPOSURES, AIR POLLUTION AND OUTCOMES IN PULMONARY ARTERIAL HYPERTENSION: A UNITED KINGDOM COHORT STUDY ANALYSIS

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In idiopathic pulmonary arterial hypertension, exposure to indirect measures of traffic-related air pollution was associated with hemodynamic severity and ERS/ESC risk score at baseline, whereas exposure to PM2.5 was associated with long-term prognosis.

ABSTRACT

While traffic and air pollution exposure is associated with increased mortality in numerous diseases, its association with disease severity and outcomes in pulmonary arterial hypertension (PAH) remains unknown.

Exposure to particulate matter ≤2.5μm^3 ($PM_{2.5}$), nitrogen dioxide (NO_2) and indirect measures of traffic-related air pollution (distance to main road and length of roads within buffer zones surrounding residential addresses) were estimated for 301 patients with idiopathic/heritable PAH recruited in the UK PAH national Cohort study. Associations with transplant-free survival and pulmonary hemodynamic severity at baseline were assessed, adjusting for confounding variables defined a priori.

Higher estimated exposure to $PM_{2.5}$ was associated with higher risk of death or lung transplant (Unadjusted hazard ratio (HR) 2.68;95%CI 1.11-6.47 per 3μg/m^3,p=0.028). This association remained similar when adjusted for potential confounding variables (HR 4.38;95%CI 1.44-13.36 per 3μg/m^3,p=0.009). No associations were found between NO_2 exposure or other traffic pollution indicators and *transplant-free survival*. Conversely, indirect measures of exposure to traffic-related air pollution within the 500-1000m buffer zones correlated with the ERS/ESC risk categories as well as pulmonary hemodynamics at baseline. This association was strongest for pulmonary vascular resistance.

In idiopathic/heritable PAH, indirect measures of exposure to traffic-related air pollution were associated with disease severity at baseline, whereas higher $PM_{2.5}$ exposure may independently predict shorter transplant-free survival.

Keywords: pulmonary hypertension, pulmonary arterial hypertension, air pollution, traffic pollution, prognosis, pulmonary vascular resistance.

INTRODUCTION

Air pollution is an important contributor to premature deaths with over 7 million deaths per year being attributable to traffic and air pollution exposure worldwide [1]. Enhanced exposure to multiple air pollutants, including nitrogen dioxide (NO_2), sulfur dioxide (SO_2) and fine particulate matter with an aerodynamic diameter of <2.5 μm ($PM_{2.5}$) have been described as independent risk factors for mortality and hospitalisations in the general population [2, 3]. This has also been observed in specific chronic health conditions, including chronic obstructive pulmonary disease [4, 5], pulmonary fibrosis [6-9] and cardiovascular diseases [10]. Of all of these pollutants, $PM_{2.5}$ has the greatest effect on human health [2, 11]. Over two thirds of premature deaths attributable to ambient $PM_{2.5}$ air pollution are due to cardiovascular disease [3, 12]. Both acute and chronic exposure to $PM_{2.5}$ increases the risk of cardiovascular death [2, 13], although long-term effects of $PM_{2.5}$ appear to have a greater impact on cardiovascular mortality [10, 14]. Amongst cardiovascular events, the occurrence of heart failure exhibited the strongest association with $PM_{2.5}$ exposure [13, 15].

Limited data are available regarding the association between air pollution and outcomes in pulmonary arterial hypertension (PAH), a disease characterised by vasoconstriction and obliterative changes in the small pulmonary arteries, leading to right ventricular (RV) failure and death. As for other respiratory diseases, the close relationship between the pulmonary vascular bed and alveolar ventilation makes it highly plausible that air pollution directly affects the pulmonary circulation. Not surprisingly, preclinical studies have suggested that prolonged exposure to particulate and soluble antigens can induce changes in pulmonary arteries [16] and that diesel exhaust exposure induces pulmonary hypertension in mice [17]. Imaging studies also found an association between air pollution and changes in RV mass and function within the general population [18, 19]. Since RV function has been repeatedly shown to represent a major determinant of prognosis in PAH [20], we hypothesized that exposure to air pollution is associated with disease severity and outcomes in PAH.

METHODS

Study population and socioeconomic status

Patients were recruited prospectively from the United Kingdom (UK) national Cohort study of idiopathic and heritable PAH (www.ipahcohort.com), a multicentre prospective study investigating the genetic and environmental causes of PAH *(see online supplement for details)*. Consecutive patients with idiopathic and heritable PAH were then invited to complete a comprehensive epidemiological questionnaire. They were considered eligible if they maintained the same address since diagnosis to minimize the risk of exposure misclassification. Potential confounding due to socioeconomic status [21] was addressed by assigning an area-level deprivation to their residential address for each patient using time-weighted Townsend deprivation quantiles that are available for the UK (https://data.mendeley.com/datasets/389scnndjy/1). Moreover, household income data were collected via questionnaire, taking into account household size and composition [22]. We also accounted for the level of education collected via the epidemiological questionnaire using nine International Standard Classification of Education (ISCED) codes that were collapsed to three categories (Primary & Lower Secondary, Upper & Post-Secondary and Tertiary) as a measure of socioeconomic status. The Regional Ethics Committee approved this study (REC 13/EE/0203) and participants provided written informed consent. Area-level and individual-level deprivation indicators were used in all statistical analyses, given the recognised confounding between deprivation and exposure to air pollution.

Air pollution exposure measures

Each participant's residential address was assigned a geographic coordinate using QGIS v2.18 software (https://qgis.org) in conjunction with the UK geocoding database (http://dx.doi.org/10.5257/census/geoconvert-1). The geocoded patients' residential addresses were linked to average levels of $PM_{2.5}$ and NO_2 annual means using existing 2010 UK-wide maps (**Figure S1**), which were based on routine air pollution monitoring data incorporating satellite-

derived and chemical transport model estimates plus road and land use data [23]. We assessed associations between mortality as well as disease severity with exposure to increases of 3 μg/m^3 for $PM_{2.5}$ and 10 μg/m^3 for NO_2 that correspond to observed interquartile ranges rounded to the nearest integer. We also acquired air pollution monitoring data from the Automatic Urban and Rural Network for the period 01/01/1999–31/12/2017. We obtained hourly data for $PM_{2.5}$ and NO_2 from 59 and 73 monitors, respectively, and computed daily averages (**Figure S2**). To link monitoring data to each residential postal code, we identified the nearest monitoring site within 50 km of the postal code (based on centroid point) and assigned air pollutant measurements to that postal code. If there were no monitoring sites within the 50 km zones, we treated the monitored exposure level as missing and excluded that postal code from the analysis. We estimated cumulative air pollution concentrations at lags of 0, 3, 7 and 14 days to assess short-term effects of air pollution concentrations on pulmonary haemodynamics at the time of diagnosis. Finally, residential proximity to motorways and A-roads, which form the major road network in the country, as well as total length of roads within different buffers (100, 200, 500 and 1000 meters) around patients' home addresses were estimated as indicators of traffic related air pollution (**Figure S3**).

Health outcome measures

The primary outcome measure was transplant-free survival from time of diagnosis. We also assessed whether markers of air pollution correlated with disease severity, using baseline pulmonary hemodynamic data, namely pulmonary vascular resistance (PVR), mean pulmonary arterial pressure (PAP), cardiac index (CI) and right atrial pressure (RAP). We finally assessed whether markers of air pollution are associated with the abbreviated 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) risk stratification strategy, as previously described (**Table S1**) [24].

Statistical analysis

Associations of air pollution exposure estimates with risk of death or lung transplantation were assessed based on hazard ratios (HR) from Cox proportional hazards regression models. In the crude model, we stratified by centre, allowing baseline hazards to be unique for each stratum. In the primary adjustment model, we further adjusted for age, sex and World Health Organisation (WHO) functional class. We fitted a further-adjusted model accounting for additional confounders including area and individual-level deprivation, smoking status at diagnosis (current/former/never), season, body mass index, bone morphogenetic protein receptor type II (BMPR2) gene mutation and whether the patient was incident (diagnosed for <6 months at study entry) or prevalent. The latter adjustment controlled for any potential survivor bias introduced by the inclusion of prevalent cases in the survival analysis. The covariates were chosen a priori on the basis of potential confounding when assessing health effects of air pollution exposures in PAH. The same covariates were also used in models for disease severity associations.

In survival analysis, we added the ERS/ESC risk category and emphysema as covariates, due to their known effect on mortality as well as data completeness. Given the relatively small number of deaths, we consider the crude and primary adjustment models as reasonable, but caution over interpretation of results from the further adjusted model due to overfitting. To minimize the scope for potential survivor bias due to inclusion of prevalent patients, Cox proportional hazards regression models and survival curves were fitted allowing for left truncation arising from the interval between diagnosis and enrolment. Prevalent patients were only included in the risk set from the time of study entry and were excluded if they entered the study more than 10 years after diagnosis.

Linear mixed-effects regression was used to characterise the relationships between air pollution measures and pulmonary haemodynamics, grouping observations by centre. As the haemodynamic outcome variables were natural log-transformed, the estimated regression coefficients ("β-coefficients") were exponentiated (i.e. e^{β}) and more naturally interpreted as the expected relative

(or percentage) change in outcome. The interpretation of results with outcomes modelled on the logarithmic scale is presented in the online supplement. The relationship between air pollution measures and ERS/ESC clinical risk prediction tool (low, intermediate or high-risk categories) was similarly evaluated, using multinomial logistic regression. We excluded the functional class variable from the further-adjusted model, as it is required for the estimation of ERS/ESC risk score at baseline.

In order to make the survival analysis models (crude, primary and further-adjusted) as comparable as possible, we used a complete-case dataset (N=286) with no missing data of all the variables used for adjustment. We further limited this dataset to a complete-case dataset for haemodynamic variables (N=243) for the disease severity analyses. It was considered unreasonable to conduct multiple imputation analysis as haemodynamics were the health outcomes. The variables of the "nearest monitor" exposure analysis were exempted from the complete-case datasets, due to large numbers of missing records on the air pollution time series around the patients' diagnosis dates.

When assessing associations with length of road, we accounted for the absence of a major road within the 500-1000m buffer zones around residences by adding a binary (yes/no) variable on the respective models. We did not model the effect of length of road within the 100-200m buffer zones as only few participants had a major road within these zones. The traffic exposure indicators were log transformed. Therefore log-log regression models were fitted when assessing their association to haemodynamic measures. The exponentiated association estimates were naturally interpreted as expected relative (or percentage) change in haemodynamic outcome for a percent increase in the traffic exposure indicators. Further information on the interpretation of these models is presented in the *online supplement*. Methods used to assess the validity of the models and the robustness of the final results are also presented in the *online supplement*. Data were presented as means ± standard deviation or median [interquartile range] according to data distribution. Analyses were performed using R software, version 3.4.1 (R Project for Statistical

Computing), and STATA software, version 14 (StataCorp, College Station, TX, USA). P values <0.05 were considered as statistically significant.

RESULTS

Of 537 patients recruited in the UK PAH Cohort from Jan 2014 to February 2018, 406 (76%) patients were offered and accepted to complete the questionnaire. One hundred of them were excluded as they moved since diagnosis, and 5 were excluded as coordinates/addresses were missing, leaving 301 patients for analysis (**Figure 1**). These patients were recruited in 7 UK PAH expert centres (**Table S2**). The non-eligible participants were older and more likely to be incident cases (**Table S3**). Characteristics of the study participants are described in **Table 1**, and were comparable to complete-case datasets used for modelling (**Tables S4**). **Table 2** provides summaries of ambient and traffic-related air pollution indicators.

During a mean follow-up of 3.5 years (4.5 years for prevalent cases), 35 (13%) participants died and 5 (2%) were transplanted, resulting in a 1, 3 and 5-year transplant-free survival estimates of 97%, 85% and 67% for incident patients, and 100%, 100% and 88% for prevalent patients, respectively. The distribution of $PM_{2.5}$ exposure, among those participants who died compared to those who did not, is presented in **Figure S4**. Exposure to higher $PM_{2.5}$ annual (2010) mean concentrations was associated with higher risk of death or lung transplant (Unadjusted HR (2.68;95%CI 1.11-6.47 per 3µg/m^3,p=0.028) (**Table 3**). Similar estimates were observed when adjusting for potential confounding variables (HR 4.38;95%CI 1.44-13.36 per 3µg/m^3,p=0.009). Conversely, no associations were found between recent exposure to $PM_{2.5}$ at the time of baseline catheterization (nearest monitoring sites), exposure to NO_2 or traffic-related pollution indicators and mortality. However, increases in the sum of the length of main roads within the 500m-buffer zone were associated with

higher PAH risk score at baseline, increasing the likelihood of being diagnosed within the ESC/ERS high-risk clinical prediction category (**Figure 2**).

Baseline hemodynamic severity correlated with distance to main road and the length of road surrounding the residential addresses for both the crude (**Figure S5**) and the further-adjusted (**Figure 3**) models. The strongest evidence for this association was found between pulmonary vascular resistance and distance to road indicator, with expected relative change of 0.95 (95%CI 0.93-0.98, p=0.001) for a 200m increase. Surprisingly, increased exposure to $PM_{2.5}$ (2010 map) was associated with a lower pulmonary vascular resistance (**Figure 4**). No consistent association was found between pulmonary haemodynamics and NO_2 (**Figure S7-8)**.

DISCUSSION

The main findings of this multicentre UK PAH Cohort are that direct and indirect measures of exposure to air pollution were associated with more severe disease at baseline and poorer transplant-free survival amongst patients with idiopathic and heritable PAH. One exception was that increased annual mean PM2.5 concentrations were associated with lower pulmonary vascular resistance. While estimated exposure to $PM_{2.5}$ was independently associated with the risk of death or transplantation, traffic air pollution indicators at the time of diagnosis correlated with the ESC/ERS risk stratification and baseline hemodynamic severity. These associations should however be interpreted with caution given the limited sample size and the indirect measures used as proxy for air pollution exposure.

Increased air pollution exposure has been documented as an independent risk factor for mortality and hospitalisations in the general population [2, 3], and in several chronic health conditions [4-9, 15]. Evidence suggests that these effects are stronger for cardiovascular mortality than for other causes of mortality [25, 26]. Moreover, $PM_{2.5}$ emissions have been consistently found to have more detrimental health effects compared to gaseous emissions (e.g. NO_2), with cardiovascular events

exhibiting the strongest association with exposure to $PM_{2.5}$ [13, 15]. Particles generated by diesel exhaust are considered particularly toxic since they carry a much larger fraction of toxic compounds [10, 27]. Particulate matter is a mixture of solid particles and liquid droplets suspended in the air. Contrary to larger particles, $PM_{2.5}$ have a diameter that enables particles to penetrate deep into the lungs and permeate the alveolar-capillary epithelium [25]. The size of particles is thus directly linked to their impact to influence human health. Numerous biological mechanisms have been hypothesized to explain the association between $PM_{2.5}$ exposure and cardiovascular diseases. These include the possible direct actions of pollutants reaching the lung and the systemic circulation contributing to oxidative stress, autonomic imbalance [10, 14], epigenetic dysregulation [28], immunomodulation [29] and vascular inflammation [30].

In the Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA Air) long-term ambient $PM_{2.5}$ concentrations were shown to be associated with the progression of intima–media thickness on ultrasound examination [31] and that ambient air pollution was associated with a greater peripheral total pulmonary vascular volume [32]. Interestingly, experimental studies have documented that prolonged exposure to particulate and soluble antigens induces changes in pulmonary arteries [16] and that diesel exhaust exposure induces pulmonary hypertension in mice [17]. Moreover, an echocardiographic study on 81 children living in Mexico also found that outdoor exposure levels of $PM_{2.5}$ were associated with increased pulmonary arterial pressure and with elevated plasma endothelin-1 levels [33], while a chamber study on 18 healthy volunteers showed that diesel exhaust exposure increases pulmonary vascular resistance at high cardiac output [34]. In view of the small numbers of subjects involved in these studies and the limited preclinical experiments on the pulmonary circulation physiology in response to pollutants exposure, the mechanisms underlying the association between indirect measures of air traffic pollution and hemodynamic severity at baseline in the present study remain elusive. Nonetheless, we can speculate that air pollution could contribute to enhanced inflammation, oxidative stress, and endothelial dysfunction that have been involved in PAH development and progression.

Contrary to the scant evidence on the association between pulmonary vascular dysfunction and air pollution in humans, multiple studies confirmed the association between air pollution exposure and heart structure and function. The Multi-Ethnic Study of Atherosclerosis (MESA) confirmed that people living in proximity to roadways had greater left ventricular mass [35]. More recently, the MESA study also confirmed that exposure to higher concentrations of NO_2[36], PM2.5 [37] and PM2.5-10 [19] were associated with greater RV mass and RV end-diastolic volume. The association between chronic past exposure to traffic-related pollutants and RV and left ventricular mass and function were also recently replicated within the UK Biobank Population Imaging Study [18]. Even acute increases in $PM_{2.5}$ exposure were recently shown to induce endothelial dysfunction and influence cardiac function [38]. Since the prognosis of PAH is mostly influenced by the consequences of the increased afterload on the right heart function, the present association between air pollution exposure and PAH outcomes is therefore not unexpected.

To the best of our knowledge, this is the first study that aimed at investigating the association between traffic-related and air pollution exposure and hemodynamic severity and outcomes in PAH. We found strong evidence for the association between pulmonary vascular resistance and distance to the nearest main road. Importantly, despite being exposed at $PM_{2.5}$ concentrations below current air quality standards, $PM_{2.5}$ exposure was associated with increases in the relative risk of mortality. Moreover, this association was robust using different model specifications. Whether this finding is related to influences of pollutant exposure on RV function, PAH progression, comorbidities or a coincidental finding remains to be investigated. It is noteworthy that the magnitude of this association was higher than reported in most observational studies from the general population in which relative increases in mortality were most commonly in the range of 4-15% per 10µg/m^3 of $PM_{2.5}$ concentrations [2, 3]. Subgroups of the general population can be particularly susceptible though to air pollution. In a group of postmenopausal women a 76% increase in the risk of death from cardiovascular disease was observed per 10µg/m^3 of $PM_{2.5}$ concentrations [39]. Although the present study's estimate was imprecise, with wide confidence interval, it remains nonetheless

consistent with the increased risk of death observed in more vulnerable populations [39-41] as with disease-specific mortality [3]. The present results are observed for air pollution levels that meet the current air quality standards, which is also the case with other studies in USA and Europe [2, 42]. These observations thus support current efforts to improve outdoor air quality and meet the WHO reference level for the $PM_{2.5}$ annual mean concentrations (10 $\mu g/m^3$). Intriguingly, previous studies suggested that air pollution exposure correlates not only with pulmonary fibrosis severity, but also its incidence [9]. While low disease awareness was proposed to explain the higher prevalence of PAH in urban regions of France in previous registry data [43], the impact of air pollution cannot be fully excluded.

The present study has several limitations that should be acknowledged. Since evidence suggests that mean $PM_{2.5}$ and NO_2 concentrations minimally fluctuate over the years [15], we estimated individual exposure to air pollution using the 2010 annual average air pollution maps of ambient $PM_{2.5}$ and NO_2 concentrations. We also linked each study participant's residence to the location of the monitoring stations. However, the use of the nearest monitor represents a coarse exposure approach as it does not account for spatial heterogeneity due to land use (i.e. roads) or prevailing winds. Thus, 50km can capture large rural areas as well as urban areas. Moreover, people who live in industrialized countries spend around 90% of their time indoors [44]. Similarly, even if PAH patients are expected to spend more time at home than the general population, many people may spend much of their time at their workplace, which may be far from their home. In addition, smoking and individual level deprivation data only partly captured indoor air quality. Thus, available maps are likely to have led to exposure misclassification for many patients of the present cohort. Intriguingly, enhanced $PM_{2.5}$ exposure using 2010 air pollution maps was associated with poorer survival but lower pulmonary vascular resistance at baseline. The mechanisms underlying these associations remain elusive. It is noteworthy, however, that such discrepancy between specific pollutant exposures and outcomes has been repeatedly observed in other conditions, including chronic obstructive pulmonary disease [4, 5] and pulmonary fibrosis [7-9]. Additionally, in order to minimize exposure

misclassification, a significant proportion of patients were ineligible as they did not maintain the same address since diagnosis. Since moving may not occur randomly, this may have led to selection bias, questioning the external validity of our findings. Moreover, the traffic-related air pollutant exposure has been associated with outcomes in small cohorts of patients with specific cardiorespiratory diseases [7, 8]. However, the present cohort had a smaller sample size than most observational studies evaluating the association between traffic road or air pollutant exposure and outcomes [2, 42]. Whether the observed associations result from sampling error or reflect the vulnerable nature of patients with PAH remains to be determined. The potential for a false positive finding also cannot be excluded, since multiple comparisons increase the possibility for type 1 error in statistical analyses. Finally, as $PM_{2.5}$ is a heterogeneous mixture of solid and liquid particles emitted from a variety of sources and traffic-related air pollution indicators are indirect measures of air pollution, the available data precluded the estimation of the specific constituents and sources of the particles. Given these limitations, the current data should be interpreted with caution until larger studies are available.

In conclusion, traffic-related air pollution and $PM_{2.5}$ exposure may be associated with disease severity and outcomes in PAH. However, our findings require validation and replication in a larger cohort to increase confidence in the reliability of these estimates. The present study thus encourages further investigations on air pollution exposure as a potentially removable risk factor influencing PAH incidence, severity and outcomes.

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TABLE 1. CHARACTERISTICS OF THE STUDY PARTICIPANTS AT DIAGNOSIS

	N=301
Age at Diagnosis, years	51 ± 15
Female sex	199 (66)
PAH subgroup	
Idiopathic	261 (87)
Heritable	40 (13)
WHO functional class*	
I-II	44 (15)
III	219 (73)
IV	38 (13)
Body Mass Index (BMI), kg/m2	30 ± 7
Presence of emphysema on CT scan*	7 (2)
Pulmonary hemodynamics	
Right Atrial Pressure (RAP), mmHg	9 [7]
Mean pulmonary arterial pressure (PAP), mmHg	53 [18]
Cardiac Index (CI), L/min per m^2	2 [1]
Cardiac Output (CO), L/min	4 [2]
Pulmonary Vascular Resistance (PVR), Wood units	11 [8]
Pulmonary capillary wedge pressure (PCWP), mmHg	9 ± 3
Mixed venous oxygen saturation (SvO2), %	64 ± 8
Six-minute walk distance (SMWT), meters	310 [203]
Pulmonary function tests	
Forced expiratory volume in 1 sec (FEV1), %predicted	84 ± 19
Transfer coefficient (KCO), %predicted	74 ± 24
Area-level Deprivation	
q1 (most deprived)	95 (32)
q2	68 (23)
q3	61 (21)
q4	52 (18)
q5	19 (6)
q6 missing category	6 (2)
Household Income	
q1	41 (14)
q2	40 (13)
q3	40 (13)
q4	50 (17)
q5 (most deprived)	28 (9)
q6 missing category	102 (34)
Education	
Primary and Low-Secondary	62 (21)
Upper and Post-Secondary	124 (41)
Tertiary	90 (30)
Missing category	25 (8)

Smoking at diagnosis, n (%)	
Current smoker	22 (7)
Former smoker	92 (31)
Never smoker	46 (15)
Missing category	141 (47)
Ethnicity	
White	271 (90)
Asian	18 (6)
Other ***	12 (4)

Data are presented as mean±standard deviation, n(%) or median [interquartile range].
* The percentages may not add up to 100% due to rounding.
** The presence of emphysema was based on baseline chest computed tomography at the time of diagnosis.
*** The category "Other" includes: Black, Mixed and Prefer not to answer.
†Data were complete for all variables except where indicated by a missing category and further missing data on the continuous variables: BMI 9; RAP, CI 16; PAP 5; CO 10; PVR, PCWP 35; SvO2 27; SMWT 92; FEV1 23; and KCO 46.

PAH: pulmonary arterial hypertension; WHO: World Health Organization.

TABLE 2. SUMMARY OF AIR POLLUTION INDICATORS

Traffic-related air pollution	
Distance to road (km)	0.4 [0.5]
Road length (km) - within 1km buffer zone	2.1 [2.1]
Road length (km) - within 500m buffer zone	0.8 [1]
Ambient Air Pollution	
Mean annual concentrations for $PM_{2.5}$ and NO_2	
Particulate matter 2.5, μg/m^3	13.7 [2.8]
Nitrogen Dioxide, μg/m^3	26 [10.1]
Nearest monitor (<50km) approach for $PM_{2.5}$ and NO_2 at the time of baseline right heart catheterization	
Particulate matter 2.5, μg/m^3	
Lag 0 days *	9.4 [7.9]
Lag 3 days *	9.3 [7.5]
Lag 7 days *	10.2 [7.1]
Lag 14 days *	10.6 [8]
Nitrogen Dioxide, μg/m^3	
Lag 0 days *	29.3 [30.2]
Lag 3 days *	27.3 [28]
Lag 7 days *	28.3 [30.2]
Lag 14 days *	29.2 [27.4]

Data are presented as median [interquartile range].

*Cumulative air pollution concentrations at lags 0, 3, 7 and 14 days preceding the date of diagnosis.

TABLE 3. COX PROPORTIONAL REGRESSION ANALYSIS FOR THE ASSOCIATION BETWEEN ANNUAL (2010) MEAN CONCENTRATIONS OF PARTICULATE MATTER 2.5 EXPOSURE AND RISK OF MORTALITY OR TRANSPLANTATION.

	Complete Dataset for survival analysis (N=268, 40 events) †	
	Hazard Ratio (95% CI)	**P value**
Models		
Crude model*	2.68 (1.11-6.47)	0.028
Primary adjusted model **	2.74 (1.06-7.05)	0.037
Further adjusted model ***	4.38 (1.44-13.36)	0.009

Hazard ratios per 3μg/m^3 increase of PM2.5 exposure.

***** Model is stratified by centre.

** Model adjusted for age, gender, World Health Organisation functional class, stratified by centre.

*** Model adjusted for centre, age, gender, deprivation, income, education, smoking, incident/prevalent, emphysema, European Respiratory Society/European Society of Cardiology risk category and bone morphogenetic protein receptor type II gene mutation, stratified by centre.

†Complete dataset with no missing data for the variables we adjusted for in the main (survival analysis) models (N=286). Due to exclusion criteria related to survival analysis [i.e. prevalent patients who were diagnosed more than 10 years before study entry (n=16) and cases who left before the study initiation (n=2)] the final models comprised of 268 (40 deaths) cases.

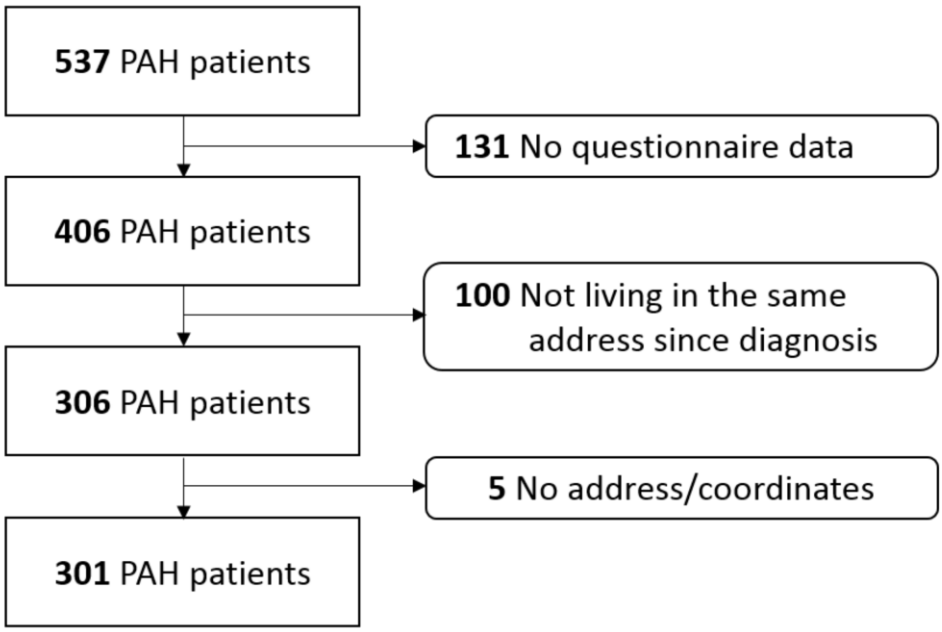


FIGURE 1. FLOW CHART OF THE PATIENT SELECTION

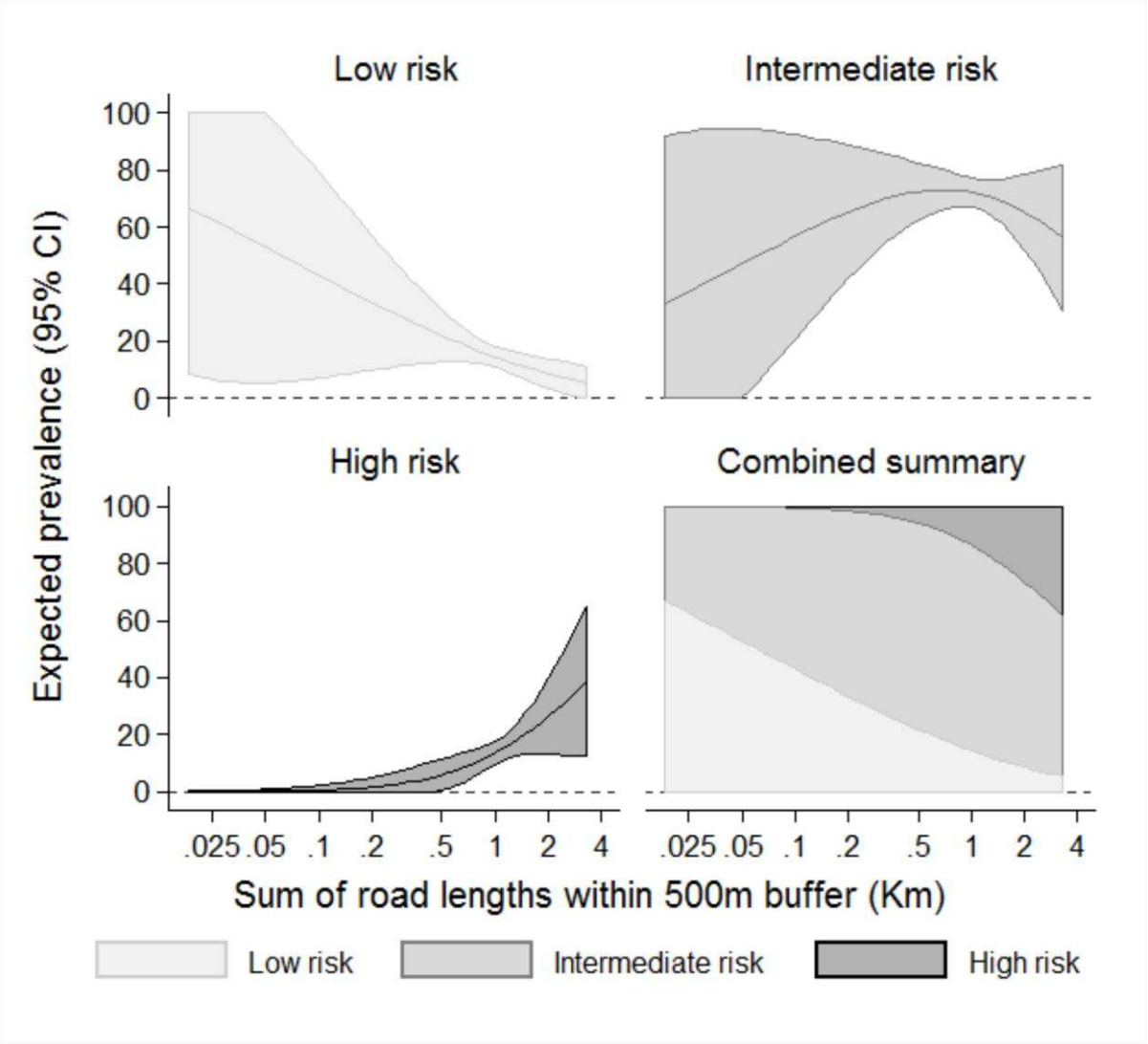


FIGURE 2. MULTINOMIAL LOGISTIC REGRESSION ESTIMATING THE ASSOCIATIONS BETWEEN PULMONARY ARTERIAL HYPERTENSION RISK PROFILE AND LENGTH OF MAIN ROADS WITHIN THE 500M-BUFFER ZONE. First three panels (a, b, c) show the expected risk (and 95%CI) of being diagnosed in low, intermediate and high-risk profile according to the abbreviated ESC/ERS risk score. An increase in length of road was associated with increased probability of having a high-risk score at baseline. Last panel (d) summarises the association between the sum of road lengths within the 500m-buffer zone and the risk of being within the low, medium and high-risk ESC/ERS risk category at diagnosis.

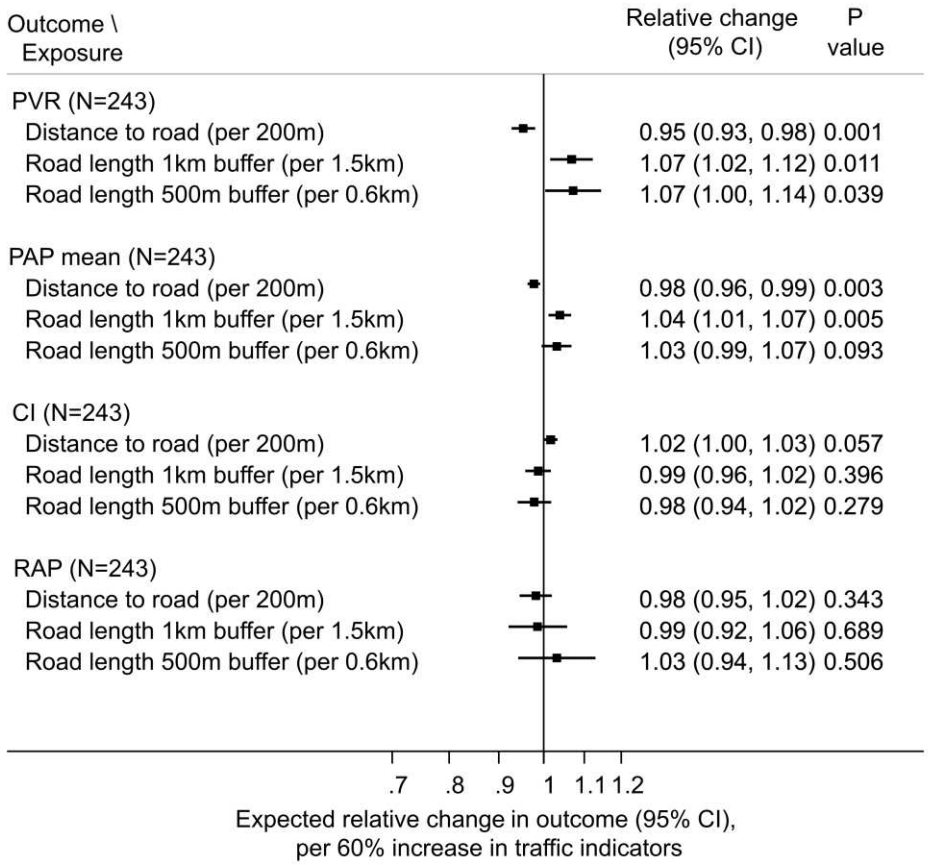


FIGURE 3. MULTIVARIABLE LINEAR REGRESSION ESTIMATING THE ASSOCIATIONS BETWEEN PULMONARY HAEMODYNAMICS AND TRAFFIC AIR POLLUTION The fully adjusted models was adjusted for: age, sex, functional class, smoking status at diagnosis, season, deprivation, income, education, body mass index, prevalent/incident cases, presence of BMPR2 gene mutation and centre. Complete-case dataset with no missing data for the haemodynamics and the variables we adjusted for (N=243).

Both exposure and haemodynamic variables were log-transformed. Therefore, the relative changes represent percentage change of the haemodynamics for a 60% increase in the traffic exposure indicators. A 60% increase in the geometric mean of traffic exposure indicators approximates to 200m increases for distance to road, 0.6km increases for road length (500m buffer zone) and 1.5km increases for road length (1km buffer zone).

N: number of observations in each model, PVR: pulmonary vascular resistance (Wood Units), PAP mean: mean pulmonary arterial pressure, mm Hg (SD), CI: cardiac index, L/min per m^2, RAP: right atrial pressure, mm Hg, BMPR2: bone morphogenetic protein receptor type II.

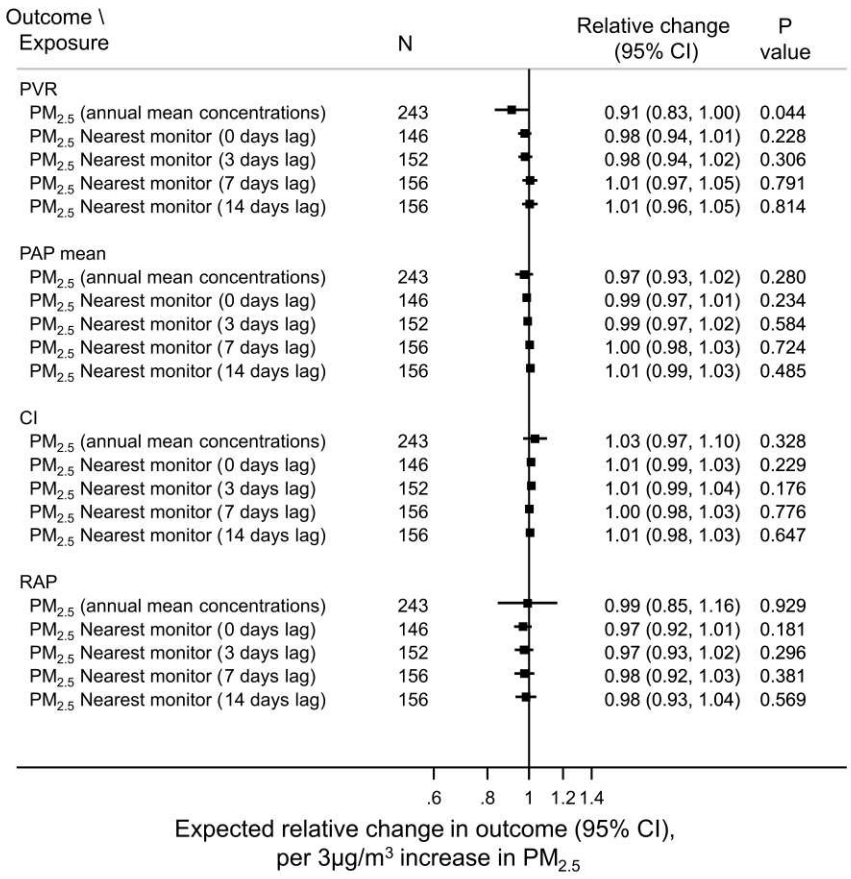


Figure 4. Multivariable Linear Regression Estimating the Associations between Pulmonary Haemodynamics and Particulate Matter ≤2.5μm (PM2.5) concentrations.

The model was fully adjusted for age, sex, functional class, smoking status at diagnosis, season, deprivation, income, education, body mass index, prevalent/incident cases, presence of BMPR2 gene mutation and centre.

Only haemodynamic variables were log-transformed. Therefore, the relative changes represent percentage change in haemodynamics per 3□g/m3 (interquartile range rounded to the nearest integer) increase in PM2.5 exposure.

N: number of observations in each model, PVR: pulmonary vascular resistance (Wood Units), PAP mean: mean pulmonary arterial pressure, mm Hg (SD), CI: cardiac index, L/min per m², RAP: right atrial pressure, mm Hg, BMPR2: bone morphogenetic protein receptor type II.

METHODS

The United Kingdom (UK) National Cohort Study

The PAH cohort study has recruited adult prevalent and incident patients with idiopathic PAH, heritable PAH, and PAH associated with anorexigen exposure, as well as pulmonary veno-occlusive disease since January 2014. Heritable PAH was defined on the basis of a family history or the finding of a known PAH-causing mutation. All cases were diagnosed between January 2000 to February 2018 in seven specialized pulmonary hypertension centres in the UK. The diagnostic algorithm, subsequent treatments and follow-ups were based on contemporary international guidelines [21]. Baseline clinical and hemodynamic characteristics at the time of PAH diagnosis were prospectively entered. Date of diagnosis corresponded to that of confirmatory right heart catheterization.

Abbreviated 2015 European Society of Cardiology/European Respiratory Society risk stratification strategy

The abbreviated version of the 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) risk stratification strategy was used to categorise patients as low, intermediate or high risk (**Table S1**) using the strategy previously proposed [28]. All patients had at least three of the six listed variables available. Briefly, the cut-off values proposed in the guidelines were graded from 1 (low risk), 2 (intermediate risk) and 3 (high risk). For each patient, the sum of all grades was divided by the number of available variables and rounded to the next integer to define the risk group. Calculations were made from baseline assessments and from follow-up assessments between 3 months and 2 years after the initiation of medical therapy for PAH.

Table S1. Variables and cut-off values used for risk stratification

	Low risk	Intermediate risk	High risk
WHO FC	I-II	III	IV
6MWD, m	>440	165-440	<165
BNP, ng·L^{-1}	<50	50-300	>300
NT-proBNP, ng·L^{-1}	<300	300-1400	>1400
Right atrial pressure, mmHg	<8	8-14	>14
Cardiac index, L·min^{-1}·m^{-2}	≥2.5	2.0-2.4	<2.0
SvO_2, %	>65	60-65	<60

WHO FC: World Health Organization functional class; BNP: brain natriuretic peptide; NT-proBNP: N-terminal fragment of pro-brain natriuretic peptide; SvO_2: mixed venous oxygen saturation.

Interpretation of models with logarithmic transformation

When a variable was log transformed (i.e. PVR, PAP, CI, RAP), we interpreted the exponentiated regression coefficients [exp(beta)] and these values corresponded to changes in the ratio of the expected geometric means (instead of the arithmetic means when outcomes are not log transformed) of the original outcome variable. For the interpretation of the effect of ambient air pollution ($PM_{2.5}$ and NO_2) on haemodynamics (i.e. PVR, PAP, CI, RAP), only haemodynamic variables were log-transformed. We therefore assessed the expected change in haemodyamics per unit increase [exp(beta*Unit increase)] of air pollution concentrations, using a 3-unit and 10-unit increase for $PM_{2.5}$ and NO_2, respectively (which corresponded to their interquartile ranges rounded to the nearest integer).

Conversely, for the assessment of the association between traffic exposure indicators (i.e. distance to road, road length surrounding residency) and haemodynamics (i.e. PVR, PAP, CI, RAP), both exposure and haemodynamic variables were log-transformed. We interpreted the exponentiated regression coefficients that correspond to relative changes, as percentage change of the outcome when the traffic exposure indicators increased by x%. In this case, we assessed the expected change in haemodyamics for a 60% percent increase in the

geometric mean of traffic indicators (corresponding to meaningful changes on these indicators). A 60% increase in the geometric mean of traffic exposure indicators approximated to 200m increases for distance to road, 0.6km increases for road length at 500m buffer zone and 1.5km increases for road length at 1km buffer zone. These values fell within the interquartile range of the traffic indicators and are presented in the legend of the respective forest plots.

RESULTS

Table S2. Number of patients recruited per participating centres.

	Centre	Counts of Patients	Percentage
1	Golden Jubilee National Hospital, Glasgow	45	12%
2	Imperial and Hammersmith Hospital	89	29%
3	Newcastle Freeman Hospital	17	6%
4	Royal Papworth Hospital	51	16%
5	Royal Brompton Hospital	31	12%
6	Royal Free Hospital	17	6%
7	Sheffield Teaching Hospital-- Royal Hallamshire Hospital	51	19%
	Total	301	100%

Table S3. Characteristics of the Study Sample Compared with Excluded Participants, due to lack of residential addresses at diagnosis

	Analysis group Same address since diagnosis (n=301)	Non-eligible group (n=236)	P value
Age at Diagnosis, years	51±15	45±17	<0.001
Female sex	199(66)	167 (71)	0.292
PAH type			
Idiopathic	261 (87)	200 (85)	0.600
Heritable	40 (13)	36 (15)	
WHO functional class			
I-II	44 (15)	52 (22)	0.065
III	219 (73)	149 (63)	
IV	38 (13)	35 (15)	
Transfer coefficient (KCO), %predicted	73±24	71±24	0.355
Pulmonary hemodynamics			
Right Atrial Pressure, mm Hg	9 [7]	8 [6]	0.059
Mean pulmonary arterial pressure, mm Hg	53 [18]	53 [17]	0.984
Cardiac Index,/min per m²	2 [1]	2 [1]	0.287
Cardiac Output, L/min	4 [2]	4 [2]	0.173
Pulmonary Vascular Resistance, WU	11 [8]	11 [9]	0.390
Mixed venous oxygen saturation, %	64 ± 8	65 ± 10	0.263
Prevalent/ incident cases			
Incident	138 (46)	64 (28)	
Prevalent	163 (54)	169 (73)	<0.001
Missing	0 (0)	3 (1)	

Data are presented as mean±SD, n(%) or median [IQR]. Groups were compared using t-test, Mann-Whitney U Test and chi-squared independence test.

Definition of abbreviations: BMPR2 = bone morphogenetic protein receptor type II; SD: standard deviation; WHO: world health organization.

TABLE S4. CHARACTERISTICS OF THE STUDY PARTICIPANTS AT DIAGNOSIS: 1) full dataset with missing data for some of the adjusting variables (N=301); 2) dataset with complete data for adjusting variables used in survival analysis (N=286); 3) dataset with complete haemodynamics and adjusting variables used in disease severity analyses (N=243) and 4) dataset with the nearest monitor analyses data available (N=135).

	Full initial dataset (N=301)	Complete dataset with no missing data for the variables we adjusted for in the main (survival analysis) models (N=286),	Complete Dataset for disease severity analyses (N=243)	Complete Dataset, limited to cases with "nearest monitor" air pollution data (N=135)
Age at Diagnosis, years	51 ± 15	51 ± 15	52 ± 16	53 ± 17
Female sex	199 (66)	189 (66)	161 (66)	88 (65)
PAH subgroup				
Idiopathic	261 (87)	247 (86)	210 (86)	120 (89)
Heritable	40 (13)	39 (14)	33 (14)	15 (11)
WHO functional class*				
I-II	44 (15)	41 (14)	34 (14)	17 (13)
III	219 (73)	211 (74)	183 (75)	105 (78)
IV	38 (13)	34 (12)	26 (11)	13 (10)
Body Mass Index, kg/m2	30 ± 7	30 ± 7	30 ± 7	30 ± 7
Presence of emphysema on CT scan*	7 (2)	6 (2)	5 (2)	3 (2)
Pulmonary hemodynamics				
Right Atrial Pressure, mmHg	9 [7]	8 [7]	8 [6]	8 [6]
Mean pulmonary arterial pressure, mmHg	53 [18]	53 [18]	53 [18]	52 [22]
Cardiac Index, L/min per m²	2 [1]	2 [1]	2 [1]	2 [1]
Cardiac Output, L/min	4 [2]	4 [2]	4 [2]	4 [2]
Pulmonary Vascular Resistance, Wood units	11 [8]	11 [8]	12 [8]	11 [7]
Pulmonary capillary wedge pressure, mmHg	9 ± 3	9 ± 3	9 ± 3	9 ± 3
Mixed venous oxygen saturation, %	64 ± 8	64 ± 8	64 ± 8	64 ± 8
Six-minute walk distance, meters	310 [203]	310 [203]	312 [208]	318 [228]
Pulmonary function tests				
FEV1, %predicted	84 ± 19	84 ± 19	85 ± 18	84 ± 17
Transfer coefficient (KCO), %predicted	74 ± 24	73 ± 24	73 ± 24	70 ± 23

Area-level Deprivation				
q1 (most deprived)	95 (32)	93 (33)	76 (31)	40 (30)
q2	68 (23)	66 (23)	56 (23)	29 (21)
q3	61 (21)	58 (20)	49 (20)	33 (24)
q4	52 (18)	51 (18)	44 (18)	23 (17)
q5	19 (6)	18 (6)	18 (7)	10 (7)
Household Income				
q1	41 (14)	39 (14)	33 (14)	17 (13)
q2	40 (13)	39 (14)	32 (13)	16 (12)
q3	40 (13)	39 (14)	35 (14)	22 (16)
q4	50 (17)	49 (17)	44 (18)	28 (21)
q5 (most deprived)	28 (9)	26 (9)	23 (9)	10 (7)
q6 missing category	102 (34)	94 (33)	76 (31)	42 (31)
Education				
Primary and Low-Secondary	62 (21)	59 (21)	47 (19)	23 (17)
Upper and Post-Secondary	124 (41)	122 (43)	102 (42)	49 (36)
Tertiary	90 (30)	81 (28)	73 (30)	52 (39)
Missing category	25 (8)	24 (8)	21 (9)	11 (8)
Smoking at diagnosis, n (%)				
Current smoker	22 (7)	22 (8)	19 (8)	10 (7)
Former smoker	92 (31)	86 (30)	74 (30)	39 (29)
Never smoker	46 (15)	45 (16)	34 (14)	15 (11)
Missing category	141 (47)	133 (47)	116 (48)	71 (53)
Ethnicity				
White	271 (90)	259 (91)	219 (90)	119 (88)
Asian	18 (6)	16 (6)	15 (6)	11 (8)
Other ***	12 (4)	11 (4)	9 (4)	5 (4)

Data are presented as mean±standard deviation, n(%) or median [interquartile range].

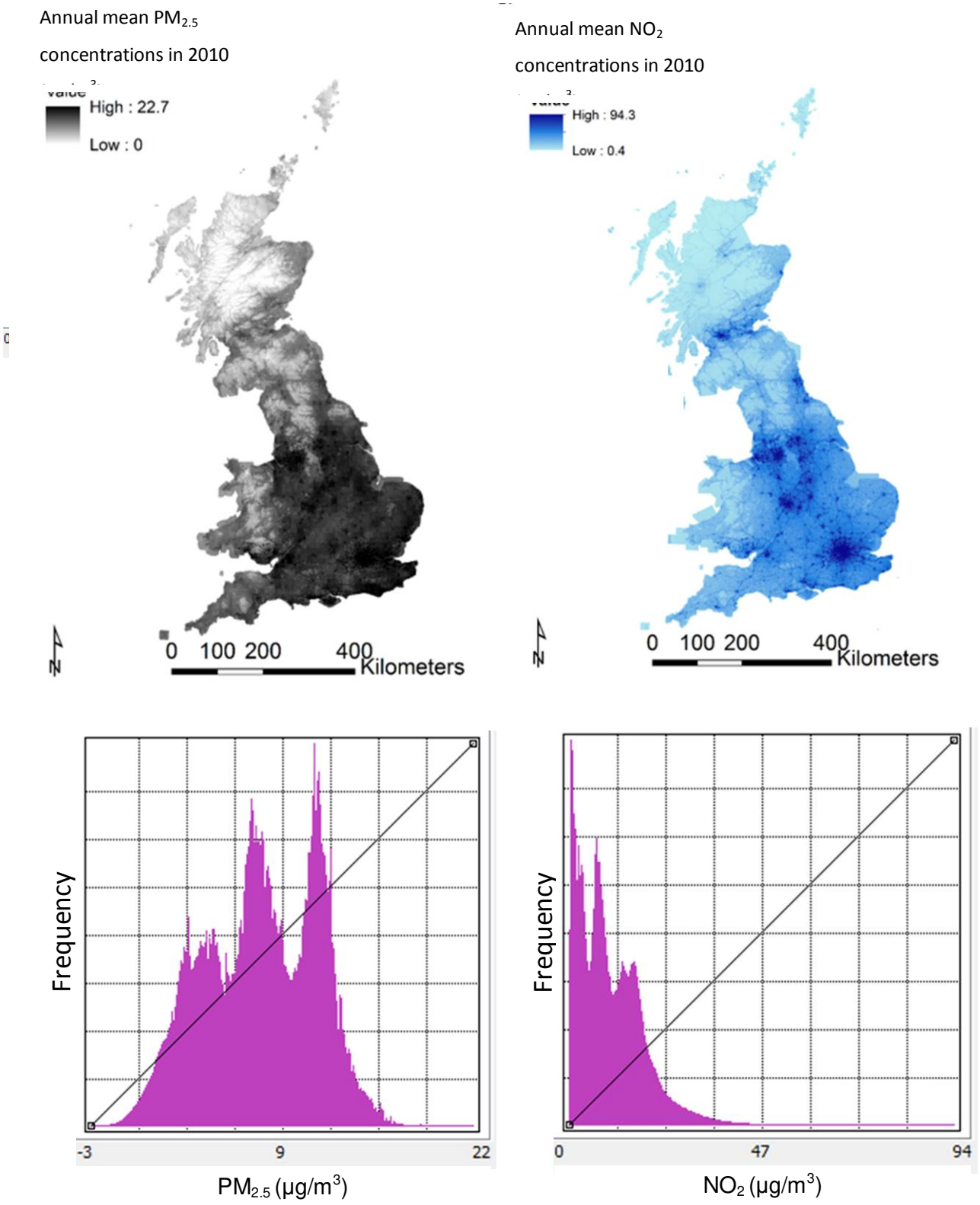
* The percentages may not add up to 100% due to rounding.

** The presence of emphysema was based on baseline chest computed tomography at the time of diagnosis.

*** The category “Other” includes: Black, Mixed and Prefer not to answer

PAH: pulmonary arterial hypertension; WHO: World Health Organization; FEV1: Forced expiratory volume in one second.

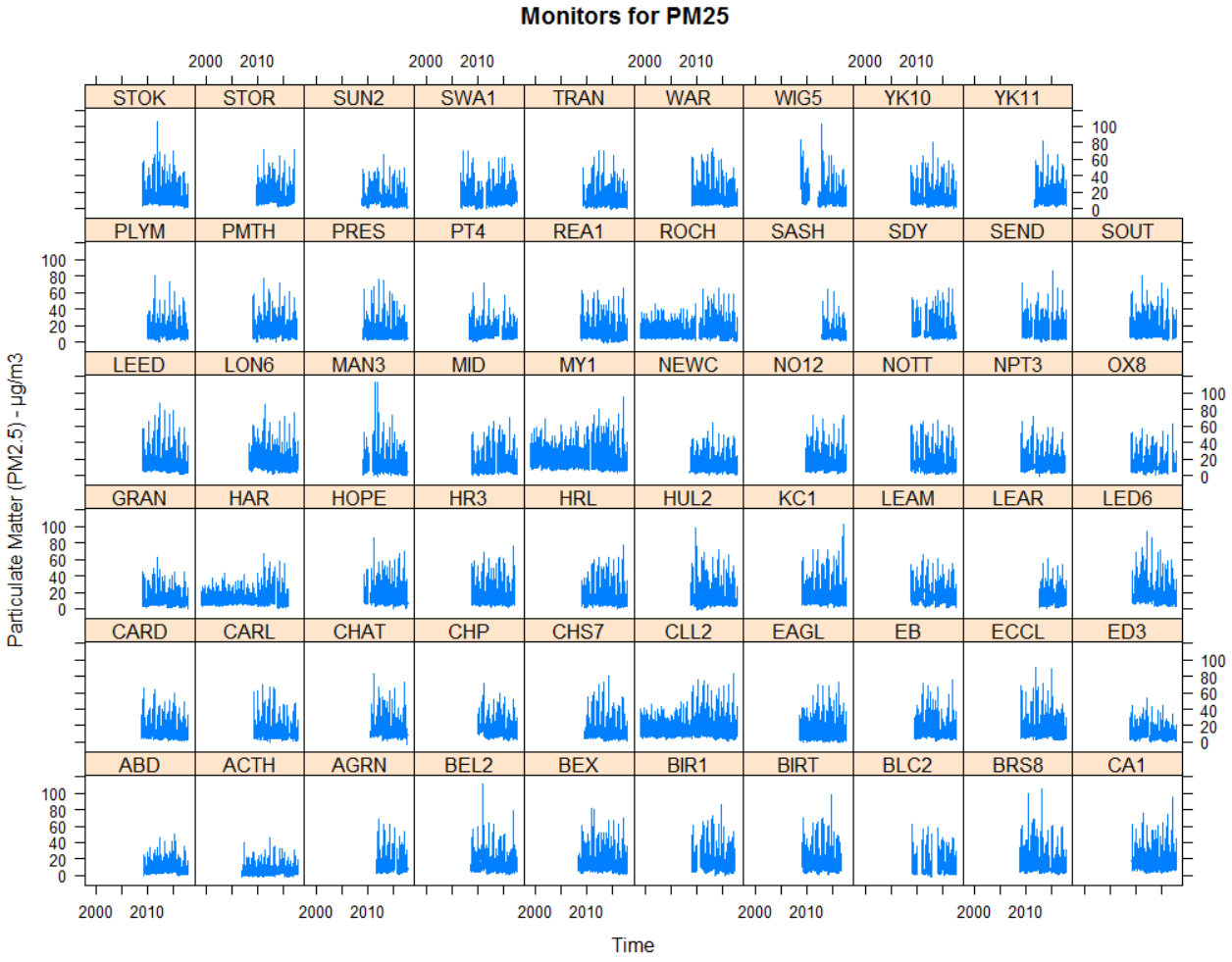
Figure S1. Maps for 2010 annual average (A) particulate matter with aerodynamic diameter ≤2.5µm3 (PM2.5) concentration and (B) nitrogen dioxide (NO2) concentration in Great Britain and respective histograms of pollutants' concentrations.

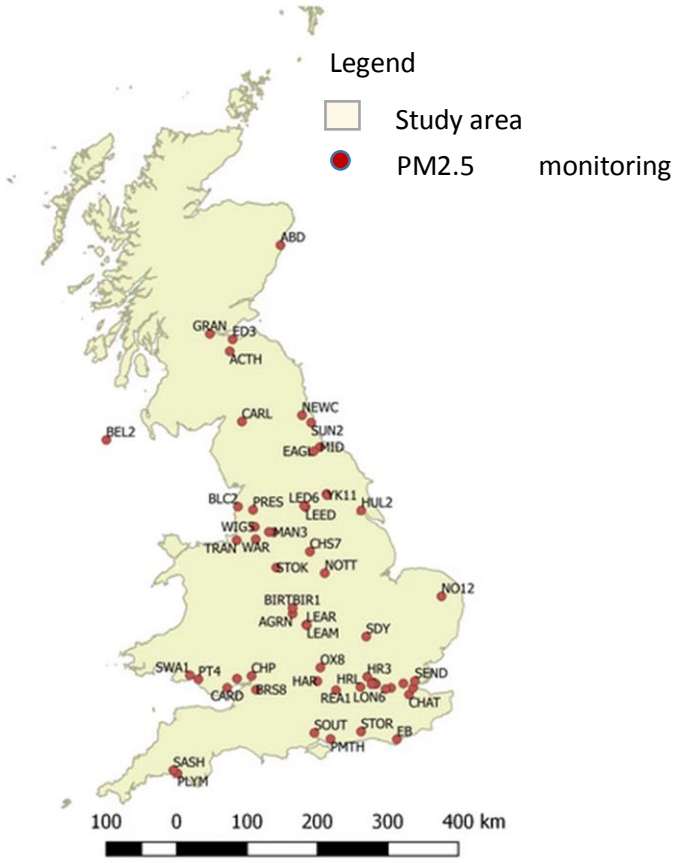


Legend - $PM_{2.5}$: particulate matter with aerodynamic diameter ≤2.5µm3, NO_2: nitrogen dioxide

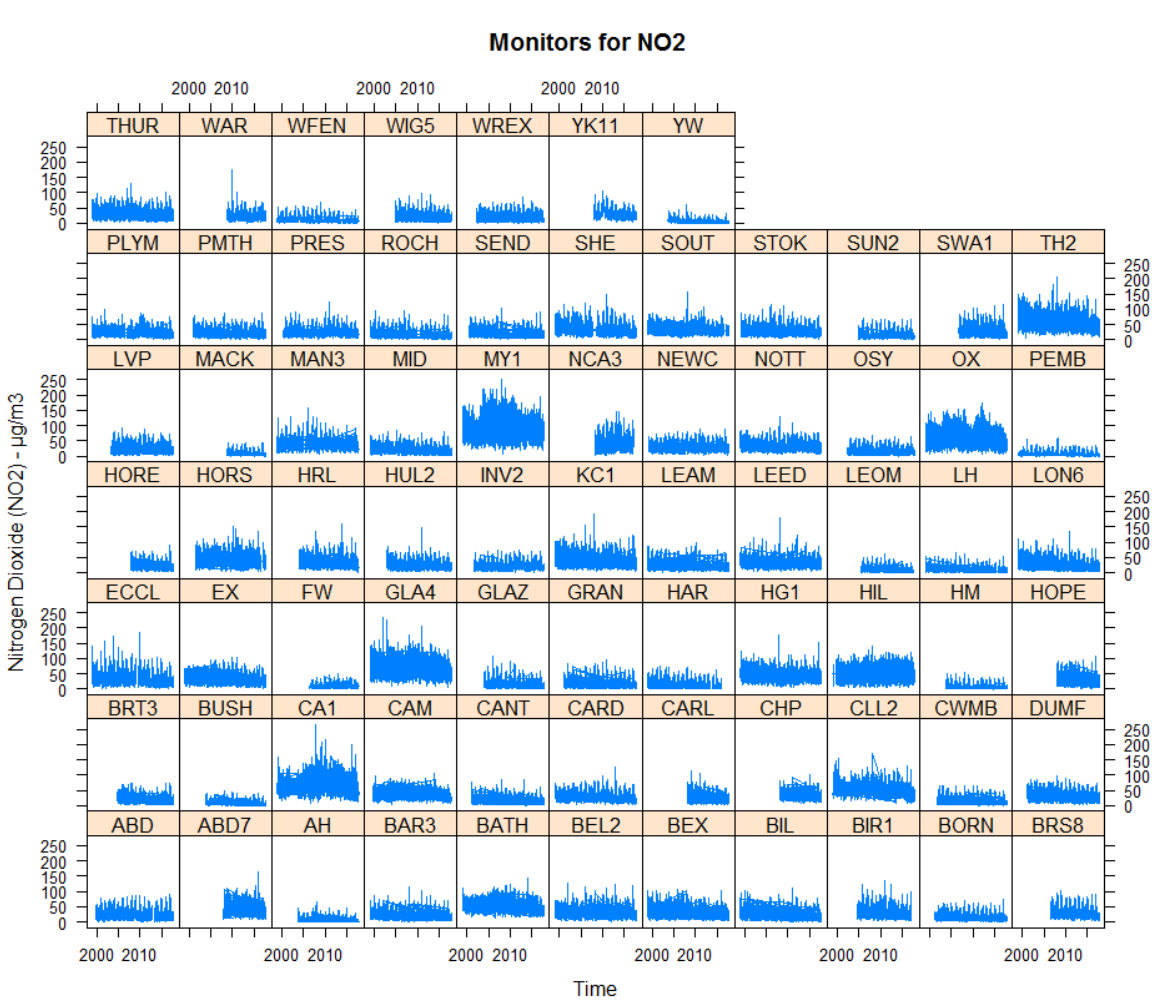
Figure S2. Time series and Location of Automatic Urban and Rural Network data for (A) Particulate Matter ≤2.5µm3 (PM2.5) and (B) Nitrogen Dioxide (NO2).

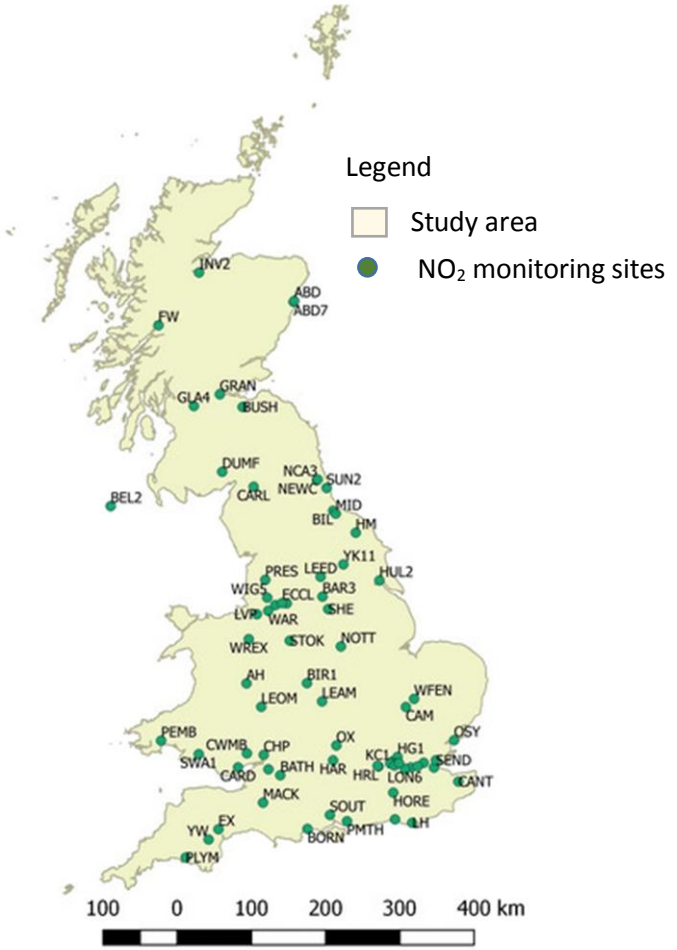
A.





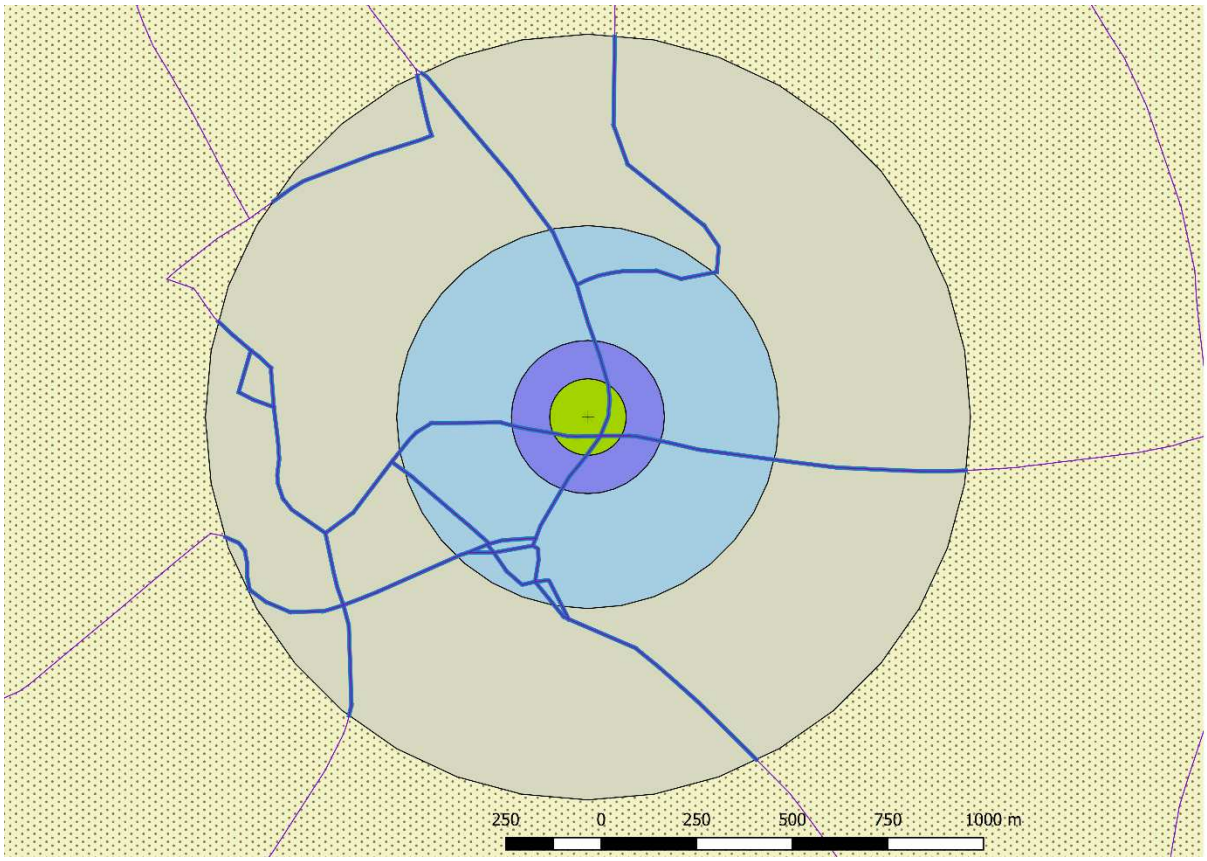
B.





Legend - $PM_{2.5}$: particulate matter with aerodynamic diameter ≤2.5µm^3, NO_2: nitrogen dioxide

Figure S3. Sum of length of road, surrounding the residential addresses



Legend

Main Road network (Motorways, A-roads)

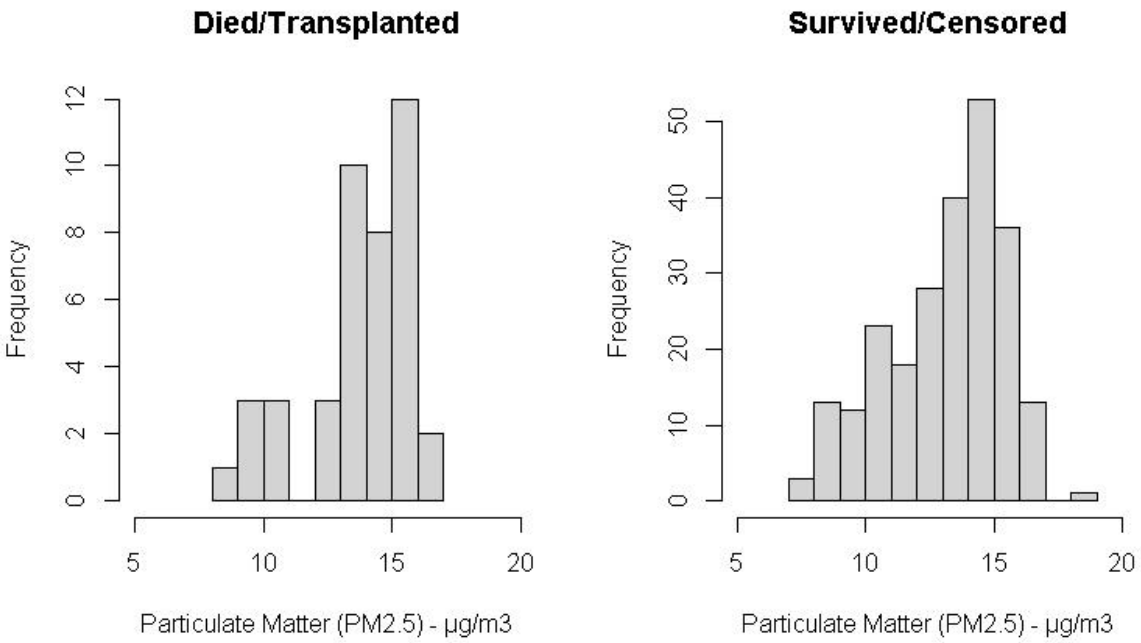
Buffer zone 100m

Buffer zone 200m

Buffer zone 500m

Buffer zone 1km

Figure S4 Distribution of Particulate Matter ($PM_{2.5}$), by outcome in survival analysis



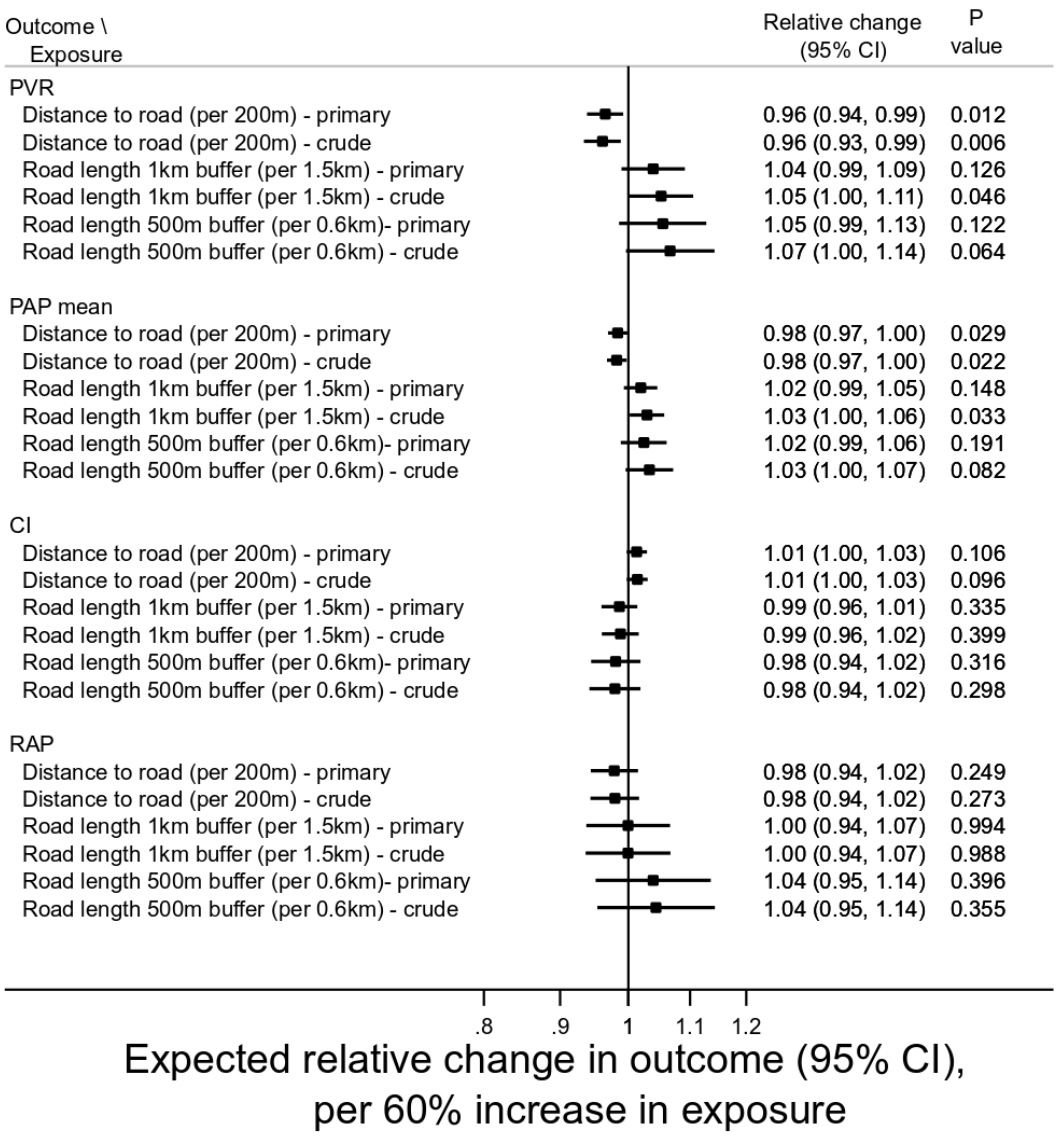


Figure S5. Linear Regression Estimating the Associations between Pulmonary Haemodynamics and Traffic Air Pollution for the crude and primary analysis models.

Primary adjusted model: The model was adjusted for age, sex, functional class, and centre. Complete dataset with no missing data for the haemodynamics and the variables we adjusted for (N=243).

Both exposure and haemodynamic outcomes were log-transformed. Therefore, the relative changes represent percentage change in the haemodynamics for a 60% increase in the traffic exposure indicators. A 60% increase in the geometric mean of traffic exposure indicators approximates to 200m increases for distance to road, 0.6km increases for road length (500m buffer zone) and 1.5km increases for road length (1km buffer zone).

N: number of observations in each model, PVR: pulmonary vascular resistance (Wood Units), PAP mean: mean pulmonary arterial pressure, mm Hg (SD), CI: cardiac index, L/min per m^2, RAP: right atrial pressure, mm Hg.

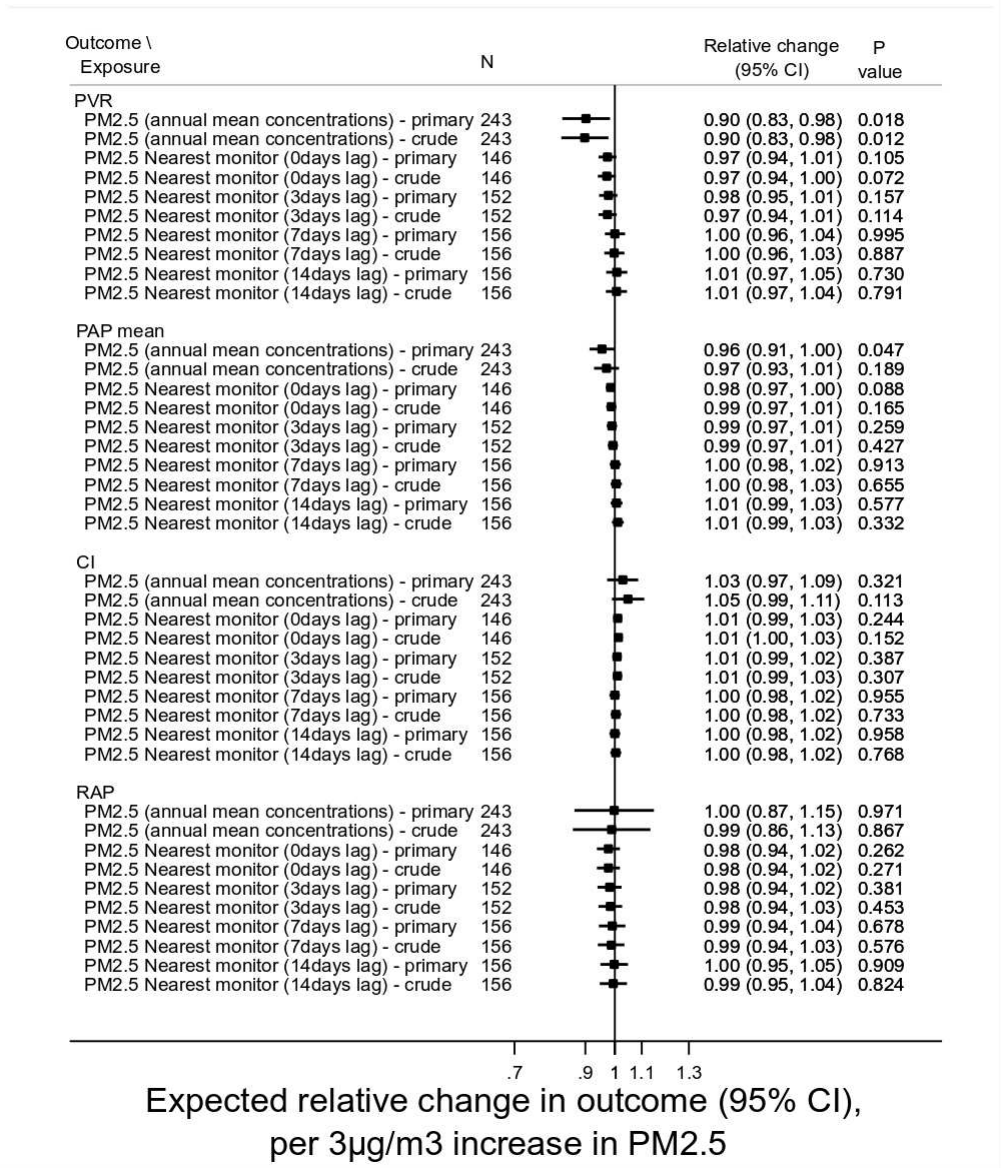


Figure S6. Linear Regression Estimating the Associations between Pulmonary Haemodynamics and Particulate Matter ≤2.5µm3 (PM2.5) concentrations for the crude and primary analysis models.

Primary adjusted model: The model was adjusted for age, sex, functional class, and centre.

Log-transformed outcome variables (haemodynamics). The relative changes represent percentage change in haemodynamics per 3 µg/m3 (interquartile range rounded to the nearest integer) increase in $PM_{2.5}$ exposure.

N: number of observations in each model, PVR: pulmonary vascular resistance (Wood Units), PAP mean: mean pulmonary arterial pressure, mm Hg (SD), CI: cardiac index, L/min per m^2, RAP: right atrial pressure, mm Hg

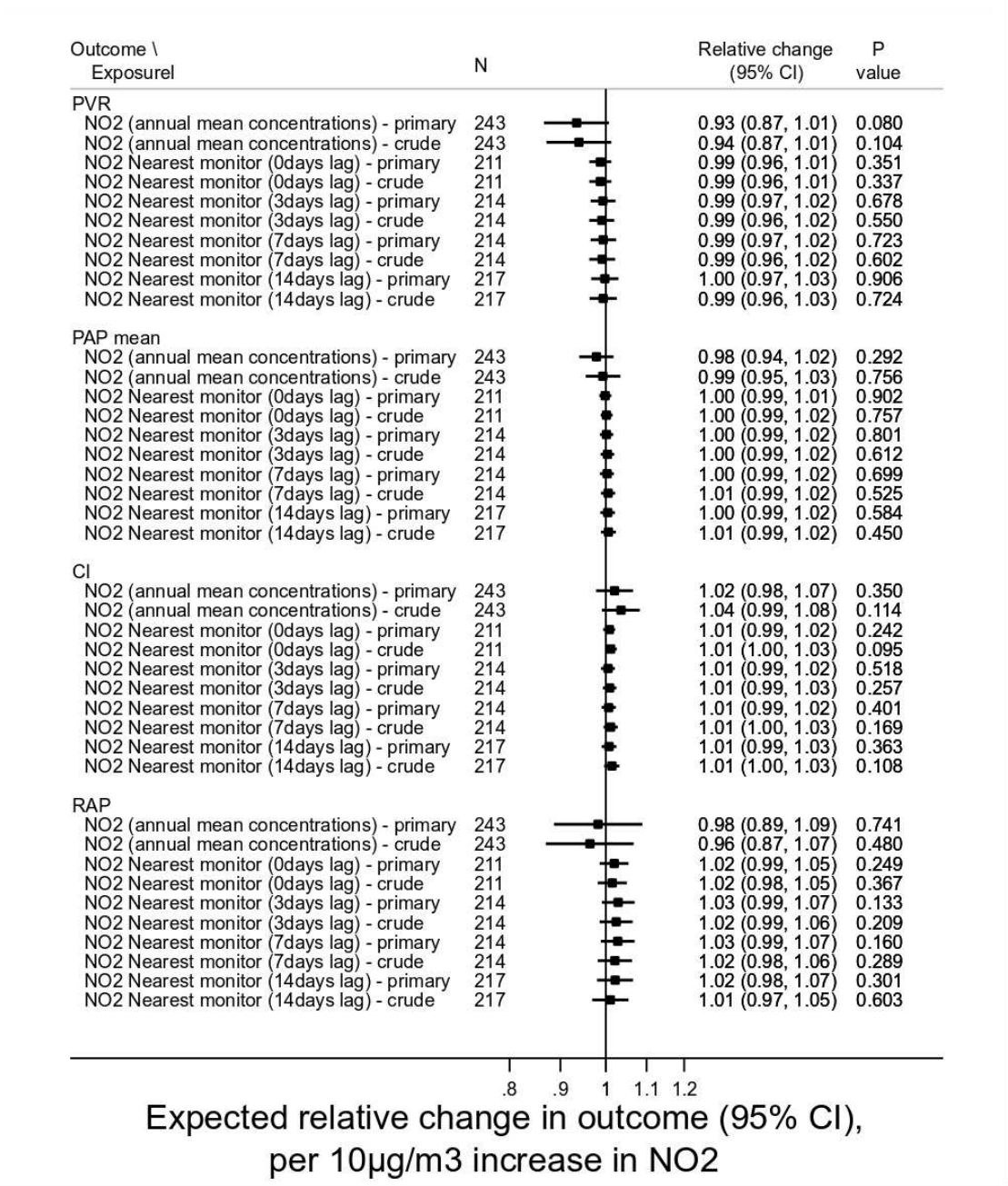


Figure S7. Linear Regression Estimating the Associations between Pulmonary Haemodynamics and Nitrogen Dioxide (NO_2) concentrations for the crude and primary analysis models.

Primary adjusted model: The model was adjusted for age, sex, functional class, and centre.

Log-transformed outcome variables (haemodynamics). The relative changes represent percentage change in haemodynamics per 10 $\mu g/m^3$ (interquartile range rounded to the nearest integer) increase in NO2 exposure.

N: number of observations in each model, PVR: pulmonary vascular resistance (Wood Units), PAP mean: mean pulmonary arterial pressure, mm Hg (SD), CI: cardiac index, L/min per m^2, RAP: right atrial pressure, mm Hg.

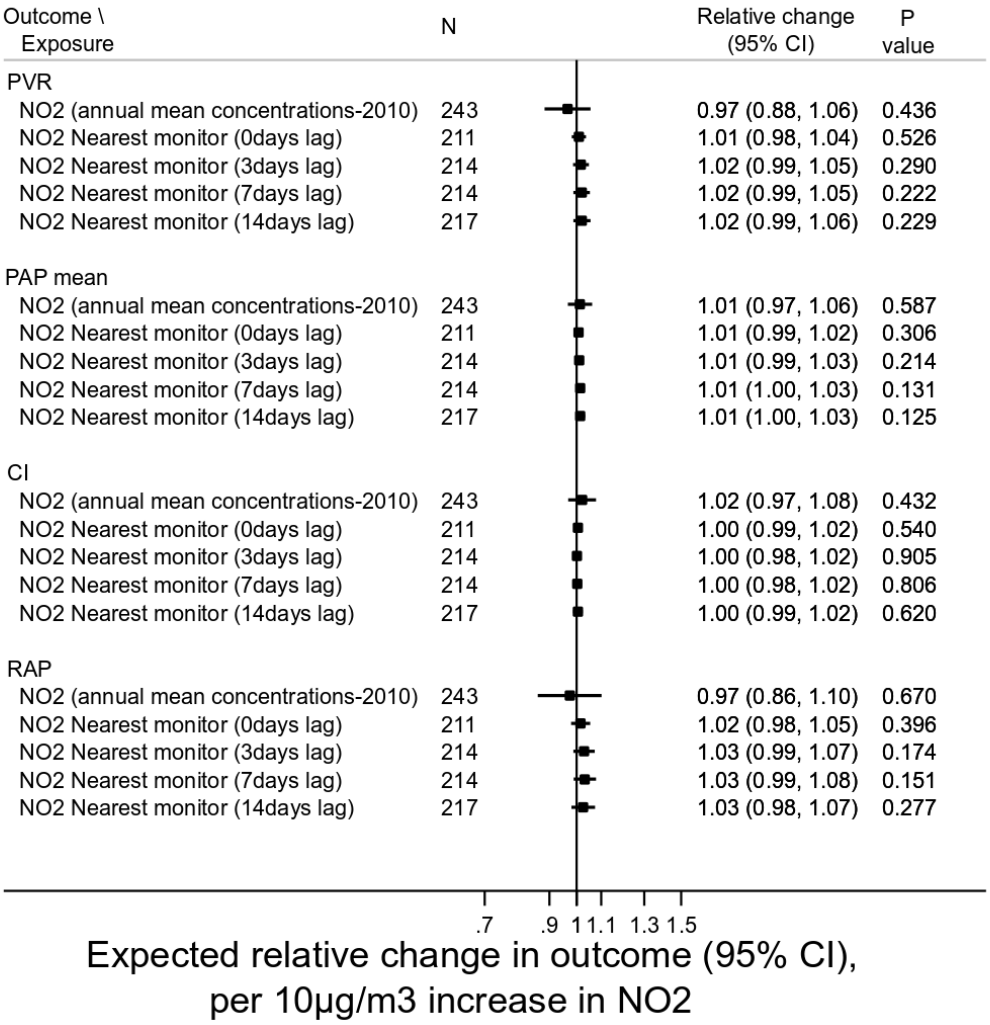


Figure S8. Multivariable Linear Regression Estimating the Associations between Pulmonary Haemodynamics and Nitrogen Dioxide (NO_2) concentrations, for the further-adjusted analysis models.

Further-adjusted model: The model was adjusted for age, sex, functional class, smoking status at diagnosis, season, deprivation, income, education, body mass index, prevalent/incident cases, presence of BMPR2 gene mutation and centre.

Log-transformed outcome variables (haemodynamics). The relative changes represent percentage change in haemodynamics per 10 $\mu g/m^3$ (interquartile range rounded to the nearest integer) increase in NO_2 exposure.

N: number of observations in each model, PVR: pulmonary vascular resistance (Wood Units), PAP mean: mean pulmonary arterial pressure, mm Hg (SD), CI: cardiac index, L/min per m^2, RAP: right atrial pressure, mm Hg, BMPR2: bone morphogenetic protein receptor type II.