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

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#### 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.

	Low risk	Intermediate risk	High risk
WHO FC	1-11	III	IV
6MWD, m	>440	165-440	<165
BNP, ng⋅L <sup>−1</sup>	<50	50-300	>300
NT-proBNP, ng⋅L <sup>−1</sup>	<300	300-1400	>1400
Right atrial pressure, mmHg	<8	8-14	>14
Cardiac index, L·min <sup>-1</sup> ·m <sup>-2</sup>	≥2.5	2.0-2.4	<2.0
SvO2, %	>65	60-65	<60

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

WHO FC: World Health Organization functional class; BNP: brain natriuretic peptide; NTproBNP: N-terminal fragment of pro-brain natriuretic peptide; SvO<sub>2</sub>: 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<sub>2.5</sub> and NO<sub>2</sub>) 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<sub>2.5</sub> and NO<sub>2</sub>, 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 haemodynamics 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	Non-eligible group	P value
	diagnosis (n=301)	(n=236)	i valuo
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)	0.005
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 m <sup>2</sup>	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).

		Complete dataset with no		Complete Dataset,
	Full initial dataset	missing data for the	Complete Dataset for	limited to cases with
		variables we adjusted for in	disease severity analyses	"nearest monitor" air
	(14-501)	the main (survival analysis)	(N=243)	pollution data
		models (N=286),		(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*				
1-11	44 (15)	41 (14)	34 (14)	17 (13)
111	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 m <sup>2</sup>	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<sub>2.5</sub>: particulate matter with aerodynamic diameter ≤2.5µm3, NO<sub>2</sub>: 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).





Monitors for NO2 2000 2010 2000 2010 2000 2010 1 1 WAR WFEN WIG5 WREX YK11 YW THUR 250 200 150 100 50 0 لبالبانة PLYM PMTH PRES ROCH SEND SHE SOUT STOK SUN2 SWA1 TH2 ويتدافانك 5( LVP MACK MAN3 MID MY1 NCA3 NEWC NOTT OSY OX PEMB 250 200 150 100 50 0 - un b HORE HORS HRL HUL2 INV2 KC1 LEAM LEED LEOM LH LON6 250 200 150 100 50 ه الله GRAN ECCL EX FW GLA4 GLAZ HAR HG1 HIL HM HOPE والملارية B-Mille وبالانطال BUSH CA1 CARD BRT3 CAM CANT CARL CHP CLL2 CWMB DUMF 250 200 150 100 50 matthe ABD ABD7 BAR3 BATH BEL2 BEX BORN BRS8 AH BIL BIR1 250 200 150 100 50 0 2000 2010 2000 2010 2000 2010 2000 2010 2000 2010 2000 2010 Time



# Legend - PM<sub>2.5</sub>: particulate matter with aerodynamic diameter ≤2.5µm<sup>3</sup>, NO<sub>2</sub>: nitrogen dioxide

В.

11





#### Legend

- Main Road network (Motorways, A-roads)
- Buffer zone 100m
  - Buffer zone 200m
- Buffer zone 500m
  - Buffer zone 1km







Survived/Censored



Particulate Matter (PM2.5) - µg/m3

Outcome \ Exposure	Relative change (95% Cl)	P value		
PVR Distance to road (per 200m) - primary Distance to road (per 200m) - crude Road length 1km buffer (per 1.5km) - primary Road length 1km buffer (per 1.5km) - crude Road length 500m buffer (per 0.6km) - primary Road length 500m buffer (per 0.6km) - crude	0.96 (0.94, 0.99) 0.96 (0.93, 0.99) 1.04 (0.99, 1.09) 1.05 (1.00, 1.11) 1.05 (0.99, 1.13) 1.07 (1.00, 1.14)	0.012 0.006 0.126 0.046 0.122 0.064		
PAP mean Distance to road (per 200m) - primary Distance to road (per 200m) - crude Road length 1km buffer (per 1.5km) - primary Road length 1km buffer (per 1.5km) - crude Road length 500m buffer (per 0.6km) - primary Road length 500m buffer (per 0.6km) - crude	0.98 (0.97, 1.00) 0.98 (0.97, 1.00) 1.02 (0.99, 1.05) 1.03 (1.00, 1.06) 1.02 (0.99, 1.06) 1.03 (1.00, 1.07)	0.029 0.022 0.148 0.033 0.191 0.082		
CI Distance to road (per 200m) - primary Distance to road (per 200m) - crude Road length 1km buffer (per 1.5km) - primary Road length 1km buffer (per 1.5km) - crude Road length 500m buffer (per 0.6km) - primary Road length 500m buffer (per 0.6km) - crude	1.01 (1.00, 1.03) 1.01 (1.00, 1.03) 0.99 (0.96, 1.01) 0.99 (0.96, 1.02) 0.98 (0.94, 1.02) 0.98 (0.94, 1.02)	0.106 0.096 0.335 0.399 0.316 0.298		
RAP Distance to road (per 200m) - primary Distance to road (per 200m) - crude Road length 1km buffer (per 1.5km) - primary Road length 500m buffer (per 0.6km) - primary Road length 500m buffer (per 0.6km) - crude	0.98 (0.94, 1.02) 0.98 (0.94, 1.02) 1.00 (0.94, 1.07) 1.00 (0.94, 1.07) 1.04 (0.95, 1.14) 1.04 (0.95, 1.14)	0.249 0.273 0.994 0.988 0.396 0.355		
Expected relative change in outcome (95% CI),				
per 60% increase in exposure				

## 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<sup>2</sup>, RAP: right atrial pressure, mm Hg.

Outcome \ Exposure	Ν	Relative change (95% CI)	P value
PVR PM2.5 (annual mean concentrations) - primary PM2.5 (annual mean concentrations) - crude PM2.5 Nearest monitor (0days lag) - primary PM2.5 Nearest monitor (0days lag) - crude PM2.5 Nearest monitor (0days lag) - primary PM2.5 Nearest monitor (0days lag) - primary PM2.5 Nearest monitor (7days lag) - primary PM2.5 Nearest monitor (7days lag) - primary PM2.5 Nearest monitor (14days lag) - primary PM2.5 Nearest monitor (14days lag) - primary PM2.5 Nearest monitor (14days lag) - crude	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	0.90 (0.83, 0.98) 0.90 (0.83, 0.98) 0.97 (0.94, 1.01) 0.97 (0.94, 1.00) 0.98 (0.95, 1.01) 0.97 (0.94, 1.01) 1.00 (0.96, 1.04) 1.00 (0.96, 1.03) 1.01 (0.97, 1.05) 1.01 (0.97, 1.04)	0.018 0.012 0.105 0.072 0.157 0.114 0.995 0.887 0.730 0.791
PAP mean PM2.5 (annual mean concentrations) - primary PM2.5 (annual mean concentrations) - crude PM2.5 Nearest monitor (0days lag) - primary PM2.5 Nearest monitor (0days lag) - crude PM2.5 Nearest monitor (3days lag) - primary PM2.5 Nearest monitor (7days lag) - primary PM2.5 Nearest monitor (7days lag) - primary PM2.5 Nearest monitor (7days lag) - crude PM2.5 Nearest monitor (14days lag) - primary PM2.5 Nearest monitor (14days lag) - primary PM2.5 Nearest monitor (14days lag) - crude	243   243   146   146   152   156   156   156   156   156	$\begin{array}{c} 0.96 & (0.91, 1.00) \\ 0.97 & (0.93, 1.01) \\ 0.98 & (0.97, 1.00) \\ 0.99 & (0.97, 1.01) \\ 0.99 & (0.97, 1.01) \\ 0.99 & (0.97, 1.01) \\ 1.00 & (0.98, 1.02) \\ 1.00 & (0.98, 1.03) \\ 1.01 & (0.99, 1.03) \\ 1.01 & (0.99, 1.03) \end{array}$	0.047 0.189 0.088 0.165 0.259 0.427 0.913 0.655 0.577 0.332
Cl PM2.5 (annual mean concentrations) - primary PM2.5 (annual mean concentrations) - crude PM2.5 Nearest monitor (0days lag) - primary PM2.5 Nearest monitor (0days lag) - crude PM2.5 Nearest monitor (0days lag) - primary PM2.5 Nearest monitor (0days lag) - primary PM2.5 Nearest monitor (0days lag) - primary PM2.5 Nearest monitor (0days lag) - crude PM2.5 Nearest monitor (0days lag) - crude PM2.5 Nearest monitor (0days lag) - primary PM2.5 Nearest monitor (0days lag) - primary PM2.5 Nearest monitor (0days lag) - primary PM2.5 Nearest monitor (0days lag) - crude	2243 243 146 146 152 152 156 156 156 156 156	$\begin{array}{c} 1.03 \; (0.97,  1.09) \\ 1.05 \; (0.99,  1.11) \\ 1.01 \; (0.99,  1.03) \\ 1.01 \; (1.00,  1.03) \\ 1.01 \; (0.99,  1.02) \\ 1.01 \; (0.99,  1.03) \\ 1.00 \; (0.98,  1.02) \\ 1.00 \; (0.98,  1.02) \\ 1.00 \; (0.98,  1.02) \\ 1.00 \; (0.98,  1.02) \\ 1.00 \; (0.98,  1.02) \\ 1.00 \; (0.98,  1.02) \\ 1.00 \; (0.98,  1.02) \end{array}$	0.321 0.113 0.244 0.152 0.387 0.307 0.955 0.733 0.958 0.768
RAP PM2.5 (annual mean concentrations) - primary PM2.5 (annual mean concentrations) - crude PM2.5 Nearest monitor (0days lag) - primary PM2.5 Nearest monitor (0days lag) - crude PM2.5 Nearest monitor (0days lag) - crude	243   243   146   146   152   156   156   156	$\begin{array}{c} 1.00 & (0.87,  1.15) \\ 0.99 & (0.86,  1.13) \\ 0.98 & (0.94,  1.02) \\ 0.98 & (0.94,  1.02) \\ 0.98 & (0.94,  1.02) \\ 0.98 & (0.94,  1.03) \\ 0.99 & (0.94,  1.04) \\ 0.99 & (0.94,  1.05) \\ 1.00 & (0.95,  1.04) \end{array}$	0.971 0.867 0.262 0.271 0.381 0.453 0.678 0.576 0.909 0.824
Expected relative cha	.7 .9 1 1.1 1.3	3 2 (05% CI)	

Expected relative change in outcome (95% CI), per 3µg/m3 increase in PM2.5

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  $\mu$ g/m3 (interquartile range rounded to the nearest integer) increase in PM<sub>2.5</sub> 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<sup>2</sup>, RAP: right atrial pressure, mm Hg

Outcome \ Exposurel	Ν	Relative change P (95% Cl) value		
PVR NO2 (annual mean concentrations) - primary NO2 (annual mean concentrations) - crude NO2 Nearest monitor (0days lag) - primary NO2 Nearest monitor (0days lag) - crude NO2 Nearest monitor (3days lag) - primary NO2 Nearest monitor (3days lag) - crude NO2 Nearest monitor (7days lag) - primary NO2 Nearest monitor (7days lag) - crude NO2 Nearest monitor (14days lag) - primary NO2 Nearest monitor (14days lag) - crude	243   243   211   211   214   214   214   214   214   214   217   217	$\begin{array}{cccccc} 0.93 & (0.87, 1.01) & 0.080 \\ 0.94 & (0.87, 1.01) & 0.104 \\ 0.99 & (0.96, 1.01) & 0.351 \\ 0.99 & (0.96, 1.01) & 0.337 \\ 0.99 & (0.97, 1.02) & 0.678 \\ 0.99 & (0.96, 1.02) & 0.550 \\ 0.99 & (0.97, 1.02) & 0.723 \\ 0.99 & (0.96, 1.02) & 0.602 \\ 1.00 & (0.97, 1.03) & 0.906 \\ 0.99 & (0.96, 1.03) & 0.724 \\ \end{array}$		
PAP mean NO2 (annual mean concentrations) - primary NO2 (annual mean concentrations) - crude NO2 Nearest monitor (0days lag) - primary NO2 Nearest monitor (0days lag) - crude NO2 Nearest monitor (3days lag) - primary NO2 Nearest monitor (3days lag) - primary NO2 Nearest monitor (7days lag) - primary NO2 Nearest monitor (7days lag) - crude NO2 Nearest monitor (14days lag) - primary NO2 Nearest monitor (14days lag) - crude	243   243   211   211   214   214   214   214   214   214   217	$\begin{array}{ccccc} 0.98 & (0.94, 1.02) & 0.292 \\ 0.99 & (0.95, 1.03) & 0.756 \\ 1.00 & (0.99, 1.01) & 0.902 \\ 1.00 & (0.99, 1.02) & 0.757 \\ 1.00 & (0.99, 1.02) & 0.801 \\ 1.00 & (0.99, 1.02) & 0.612 \\ 1.00 & (0.99, 1.02) & 0.699 \\ 1.01 & (0.99, 1.02) & 0.525 \\ 1.00 & (0.99, 1.02) & 0.584 \\ 1.01 & (0.99, 1.02) & 0.450 \\ \end{array}$		
Cl NO2 (annual mean concentrations) - primary NO2 (annual mean concentrations) - crude NO2 Nearest monitor (0days lag) - primary NO2 Nearest monitor (0days lag) - crude NO2 Nearest monitor (3days lag) - primary NO2 Nearest monitor (3days lag) - crude NO2 Nearest monitor (7days lag) - primary NO2 Nearest monitor (7days lag) - crude NO2 Nearest monitor (14days lag) - primary NO2 Nearest monitor (14days lag) - crude	243 243 211 211 214 214 214 214 214 214 217 217	$\begin{array}{cccccccccccccccccccccccccccccccccccc$		
RAP NO2 (annual mean concentrations) - primary NO2 (annual mean concentrations) - crude NO2 Nearest monitor (0days lag) - primary NO2 Nearest monitor (0days lag) - crude NO2 Nearest monitor (3days lag) - primary NO2 Nearest monitor (3days lag) - crude NO2 Nearest monitor (7days lag) - primary NO2 Nearest monitor (7days lag) - crude NO2 Nearest monitor (14days lag) - primary NO2 Nearest monitor (14days lag) - crude	243   243   211   211   214   214   214   214   214   217   217	$\begin{array}{ccccc} 0.98 & (0.89, 1.09) & 0.741 \\ 0.96 & (0.87, 1.07) & 0.480 \\ 1.02 & (0.99, 1.05) & 0.249 \\ 1.02 & (0.98, 1.05) & 0.367 \\ 1.03 & (0.99, 1.07) & 0.133 \\ 1.02 & (0.99, 1.06) & 0.209 \\ 1.03 & (0.99, 1.07) & 0.160 \\ 1.02 & (0.98, 1.06) & 0.289 \\ 1.02 & (0.98, 1.07) & 0.301 \\ 1.01 & (0.97, 1.05) & 0.603 \end{array}$		
Expected relative change in outcome (95% CI),				

# Figure S7. Linear Regression Estimating the Associations between Pulmonary Haemodynamics and Nitrogen Dioxide (NO<sub>2</sub>) 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<sup>3</sup> (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<sup>2</sup>, RAP: right atrial pressure, mm Hg.

Outcome \ Exposure	Ν		Relative change (95% CI)	P value		
PVR						
NO2 (annual mean concentrations-2010)	243	<b></b>	0.97 (0.88, 1.06)	0.436		
NO2 Nearest monitor (0days lag)	211	+	1.01 (0.98, 1.04)	0.526		
NO2 Nearest monitor (3days lag)	214	+	1.02 (0.99, 1.05)	0.290		
NO2 Nearest monitor (7days lag)	214	+	1.02 (0.99, 1.05)	0.222		
NO2 Nearest monitor (14days lag)	217	+	1.02 (0.99, 1.06)	0.229		
PAP mean						
NO2 (annual mean concentrations-2010)	243	+	1.01 (0.97, 1.06)	0.587		
NO2 Nearest monitor (0days lag)	211	•	1.01 (0.99, 1.02)	0.306		
NO2 Nearest monitor (3days lag)	214	•	1.01 (0.99, 1.03)	0.214		
NO2 Nearest monitor (7days lag)	214	•	1.01 (1.00, 1.03)	0.131		
NO2 Nearest monitor (14days lag)	217	•	1.01 (1.00, 1.03)	0.125		
CI						
NO2 (annual mean concentrations-2010)	243	- <b>-</b> -	1.02 (0.97, 1.08)	0.432		
NO2 Nearest monitor (0days lag)	211	•	1.00 (0.99, 1.02)	0.540		
NO2 Nearest monitor (3days lag)	214	•	1.00 (0.98, 1.02)	0.905		
NO2 Nearest monitor (7days lag)	214	•	1.00 (0.98, 1.02)	0.806		
NO2 Nearest monitor (14days lag)	217	•	1.00 (0.99, 1.02)	0.620		
RAP						
NO2 (annual mean concentrations-2010)	243	<b>_</b> _	0.97 (0.86, 1.10)	0.670		
NO2 Nearest monitor (0days lag)	211	+	1.02 (0.98, 1.05)	0.396		
NO2 Nearest monitor (3days lag)	214	-	1.03 (0.99, 1.07)	0.174		
NO2 Nearest monitor (7days lag)	214	-	1.03 (0.99, 1.08)	0.151		
NO2 Nearest monitor (14days lag)	217	-	1.03 (0.98, 1.07)	0.277		
	<u> </u>		1			
Expected relative ch	Expected relative change in outcome (95% CI)					
	inge i					

#### per 10µg/m3 increase in NO2

### Figure S8. Multivariable Linear Regression Estimating the Associations between Pulmonary Haemodynamics and Nitrogen Dioxide (NO<sub>2</sub>) concentrations, for the furtheradjusted 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<sup>3</sup> (interquartile range rounded to the nearest integer) increase in NO<sub>2</sub> 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<sup>2</sup>, RAP: right atrial pressure, mm Hg, BMPR2: bone morphogenetic protein receptor type II.