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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.

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)], which corresponded to changes in the ratio of the geometric means of the outcome variable (instead of the arithmetic means when outcomes are not log transformed). For the assessment of the association between ambient air pollution (PM2.5 and NO2) and haemodynamics (i.e. PVR, PAP, CI, RAP), only haemodynamic variables were log-transformed. We therefore interpreted the exponentiated regression coefficients as the expected relative changes in haemodyamics per unit increase [exp(beta*Unit increase)] of air pollution concentrations, using a 3-unit and 10-unit increase for PM2.5 and NO2, 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 as the expected relative changes in haemoodynamics when the traffic exposure indicators increased by 1.x fold (or equivalently x% change). In this

case, we assessed the expected change in haemodyamics for a 1.60 fold (or 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				
British	258 (86)	246 (86)	207 (85)	110 (81)
Other White	11 (4)	11 (4)	10 (4)	8 (6)
Other	31 (10)	29 (10)	26 (11)	17 (13)

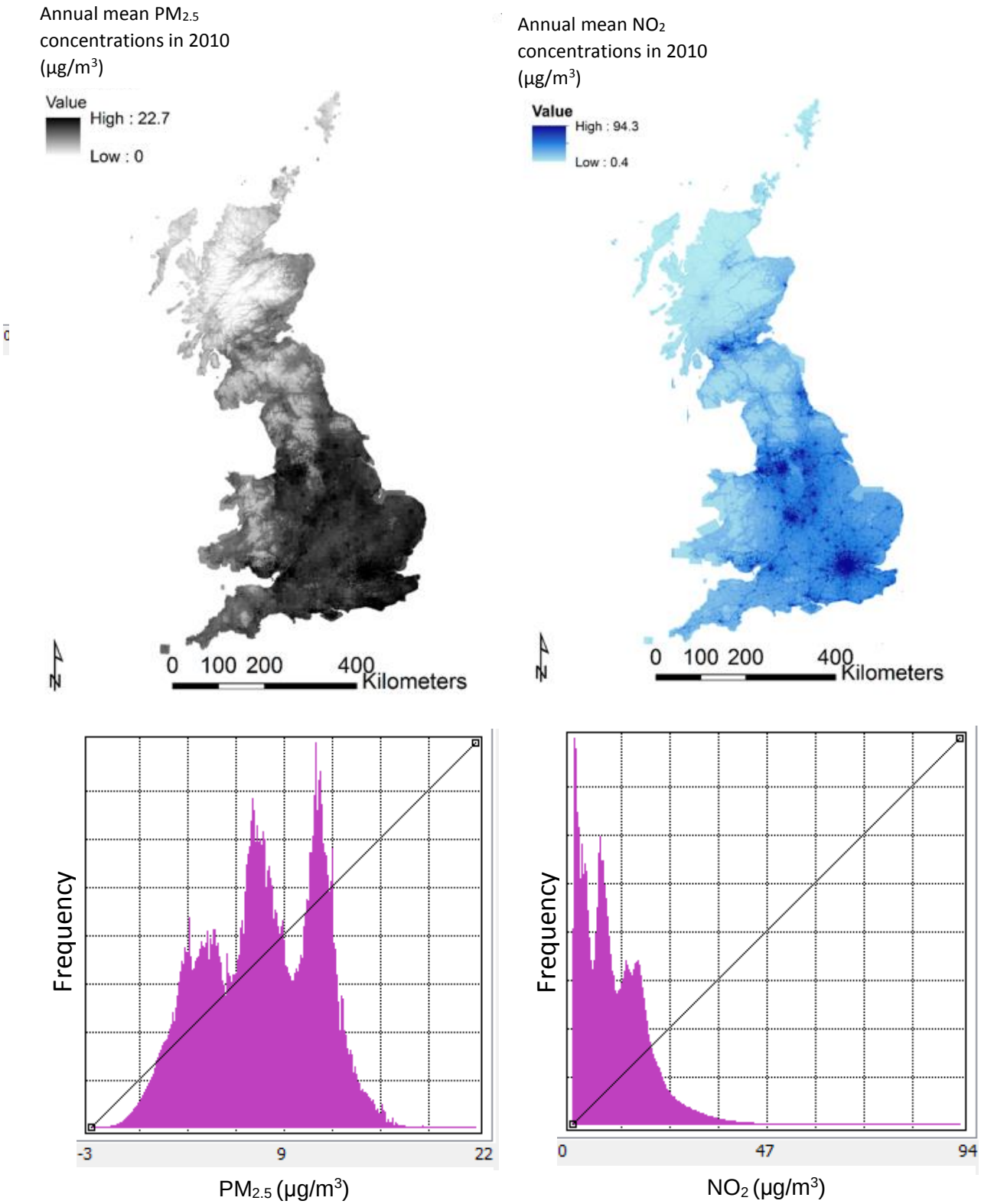
Data are presented as mean±standard deviation, n(%) or median [interquartile range].

* 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.

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

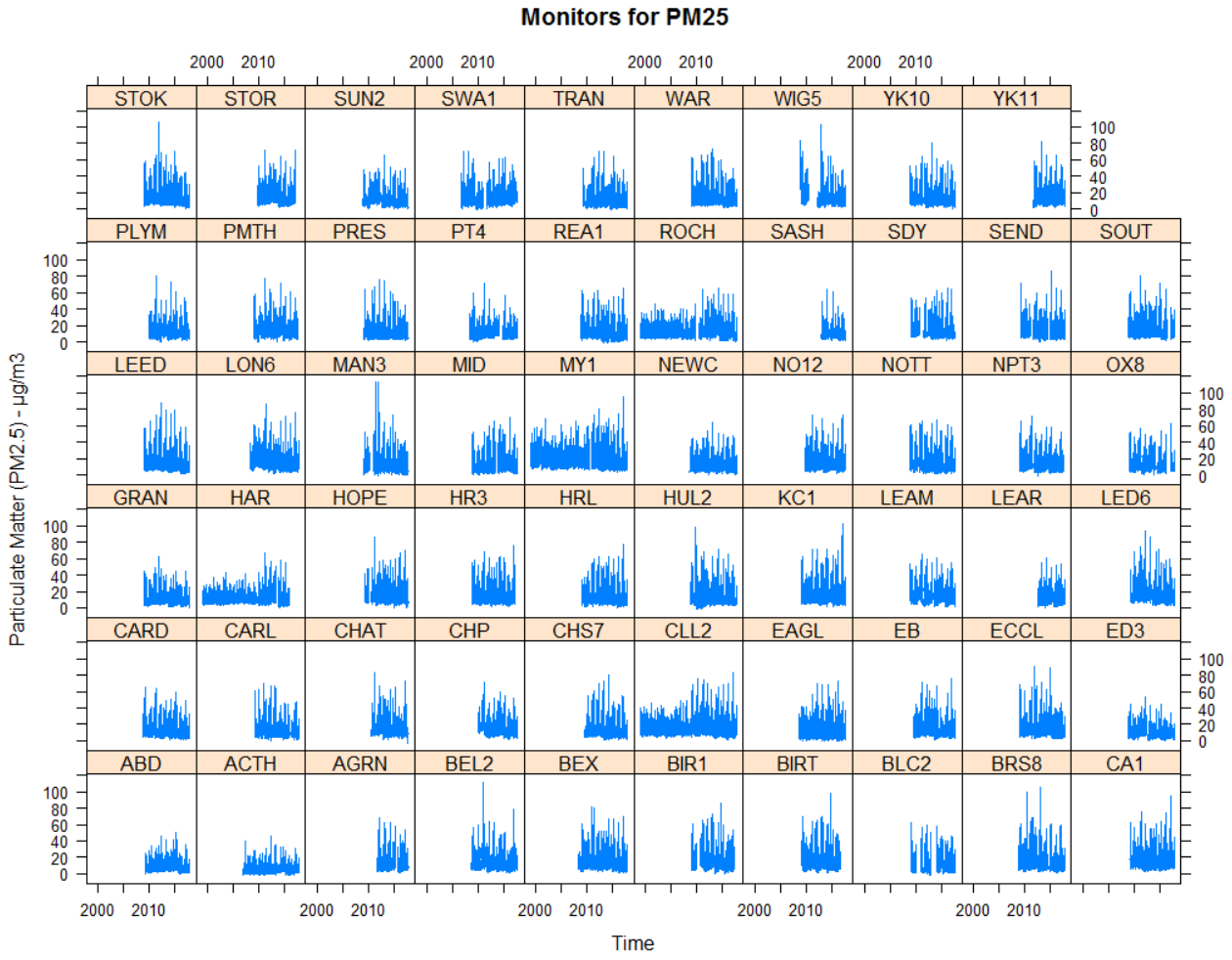
Figure S1. Maps for 2010 annual average (A) particulate matter with aerodynamic diameter ≤2.5µm3 (PM2.5) concentration and (B) nitrogen dioxide (NO2) concentration in Great Britain and respective histograms of pollutants' concentrations.

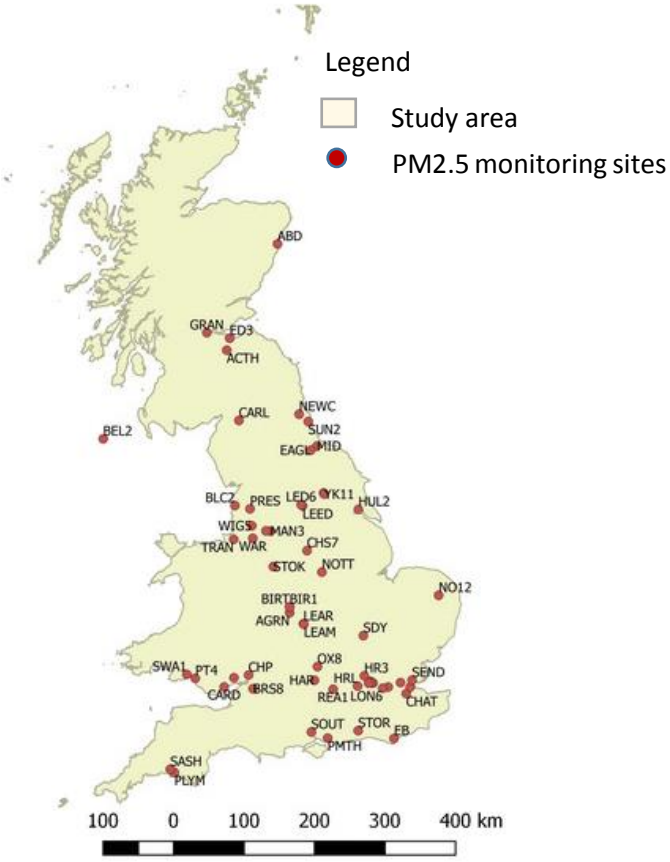


Legend - $PM_{2.5}$: particulate matter with aerodynamic diameter ≤2.5µm3, NO_2: nitrogen dioxide

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.





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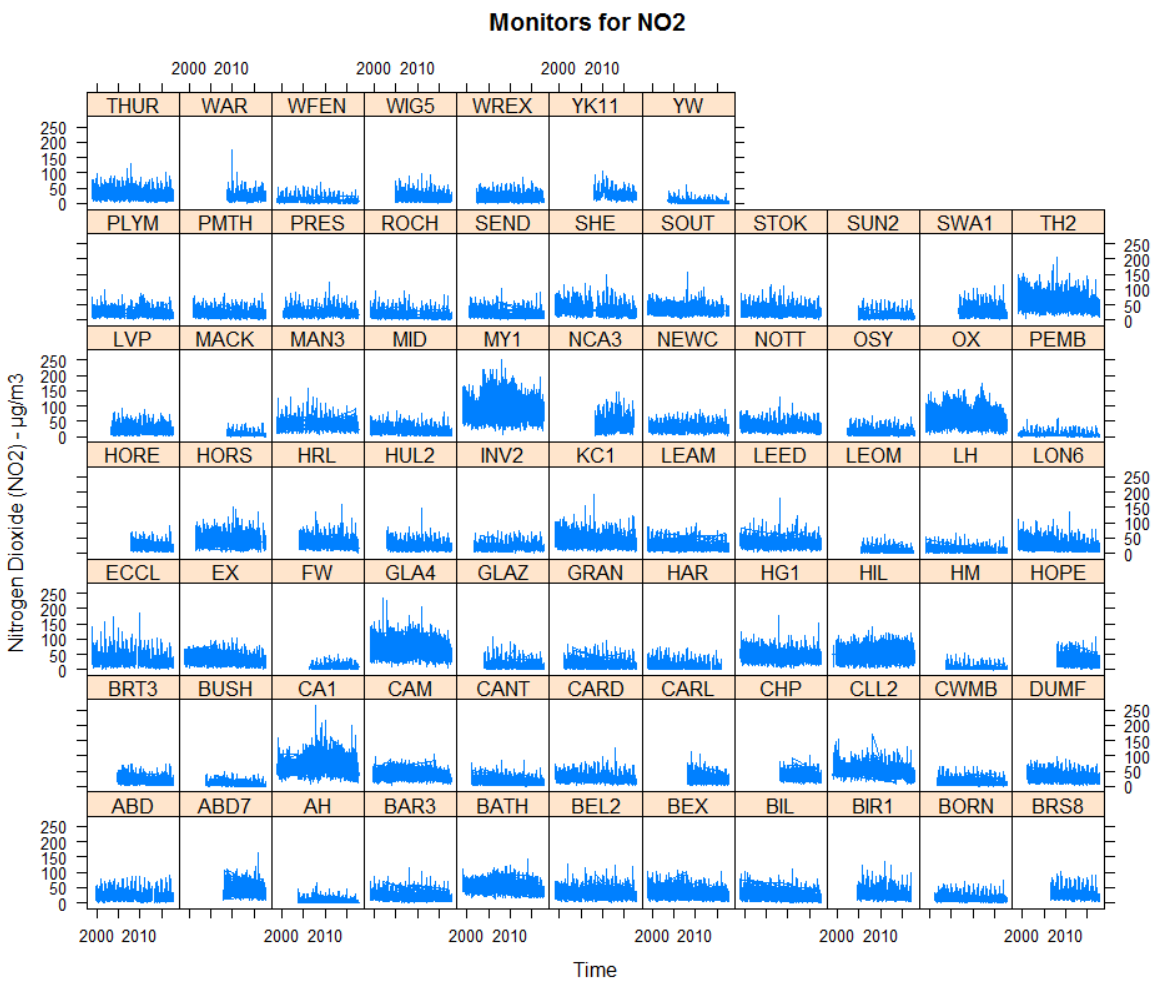
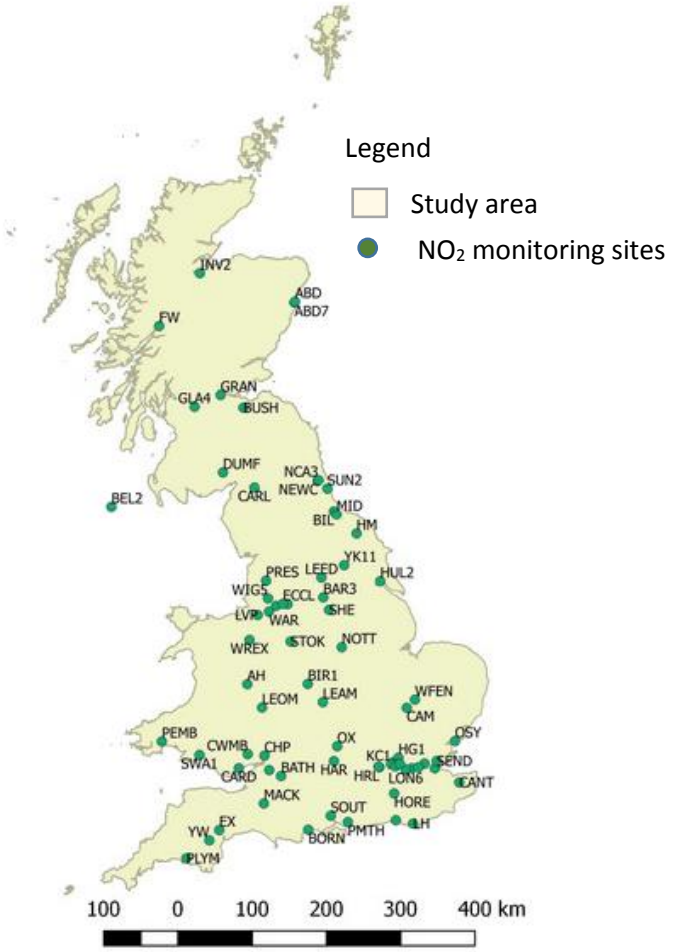
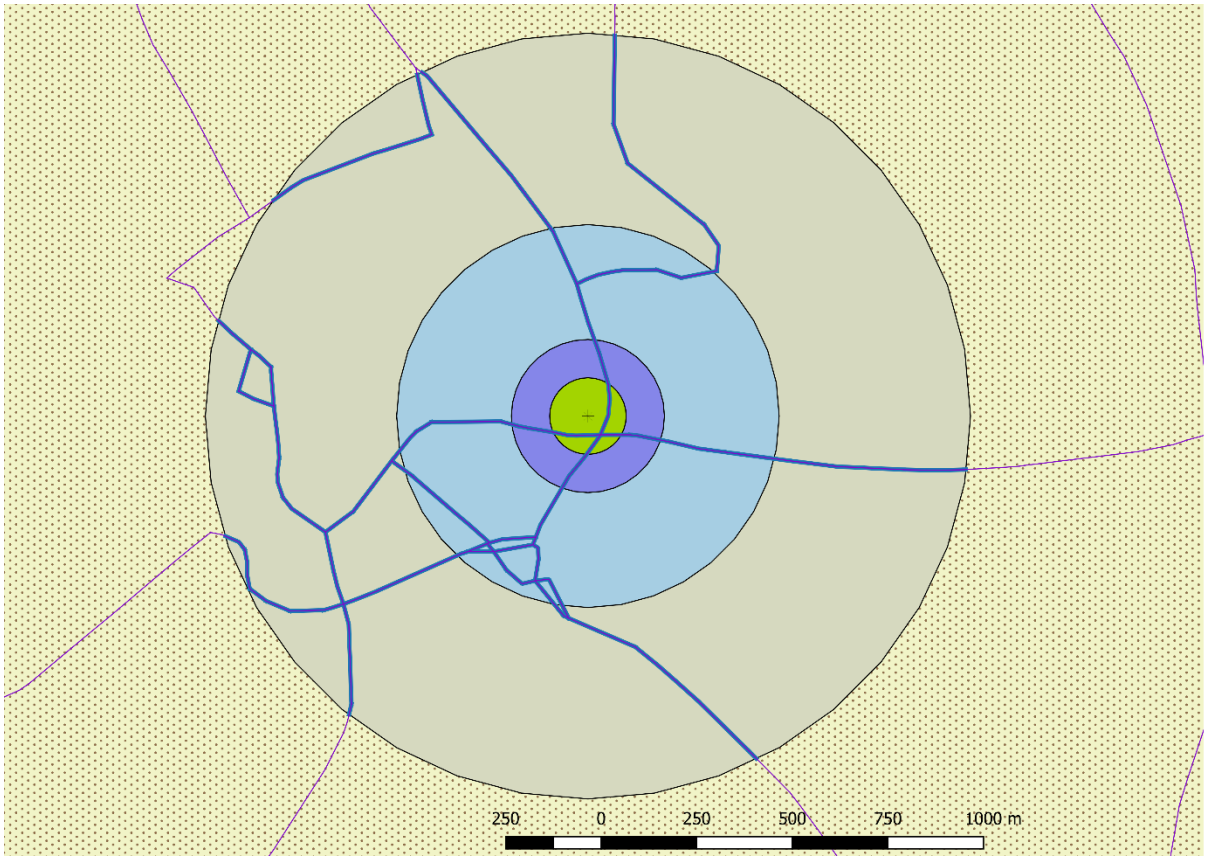
B.





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)

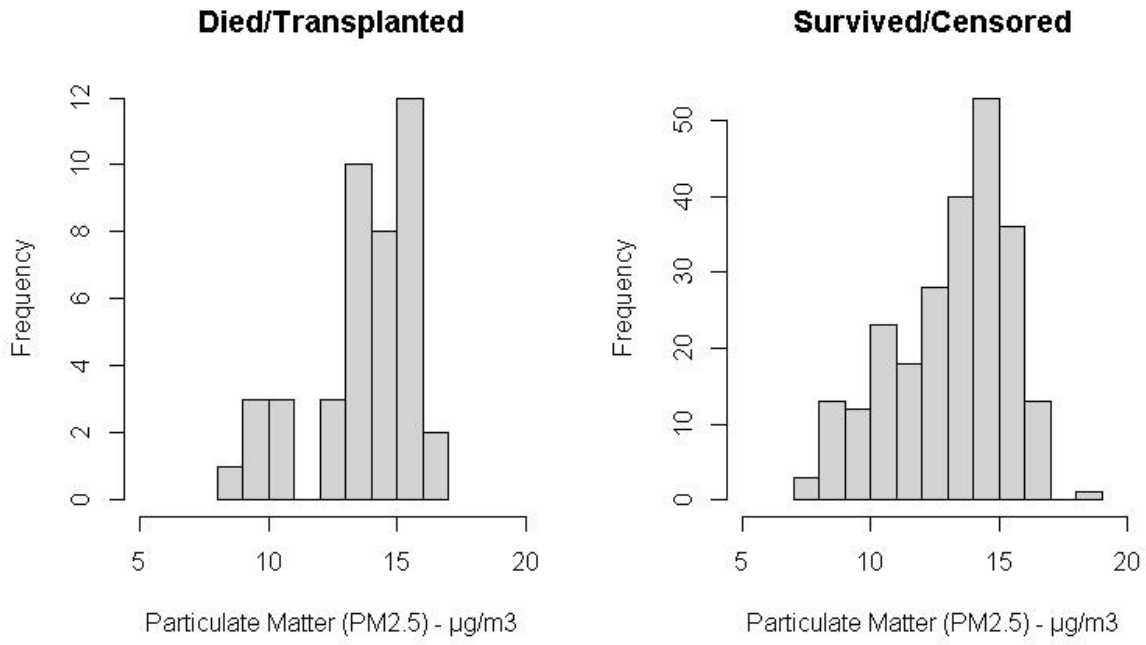
Buffer zone 100m

Buffer zone 200m

Buffer zone 500m

Buffer zone 1km

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



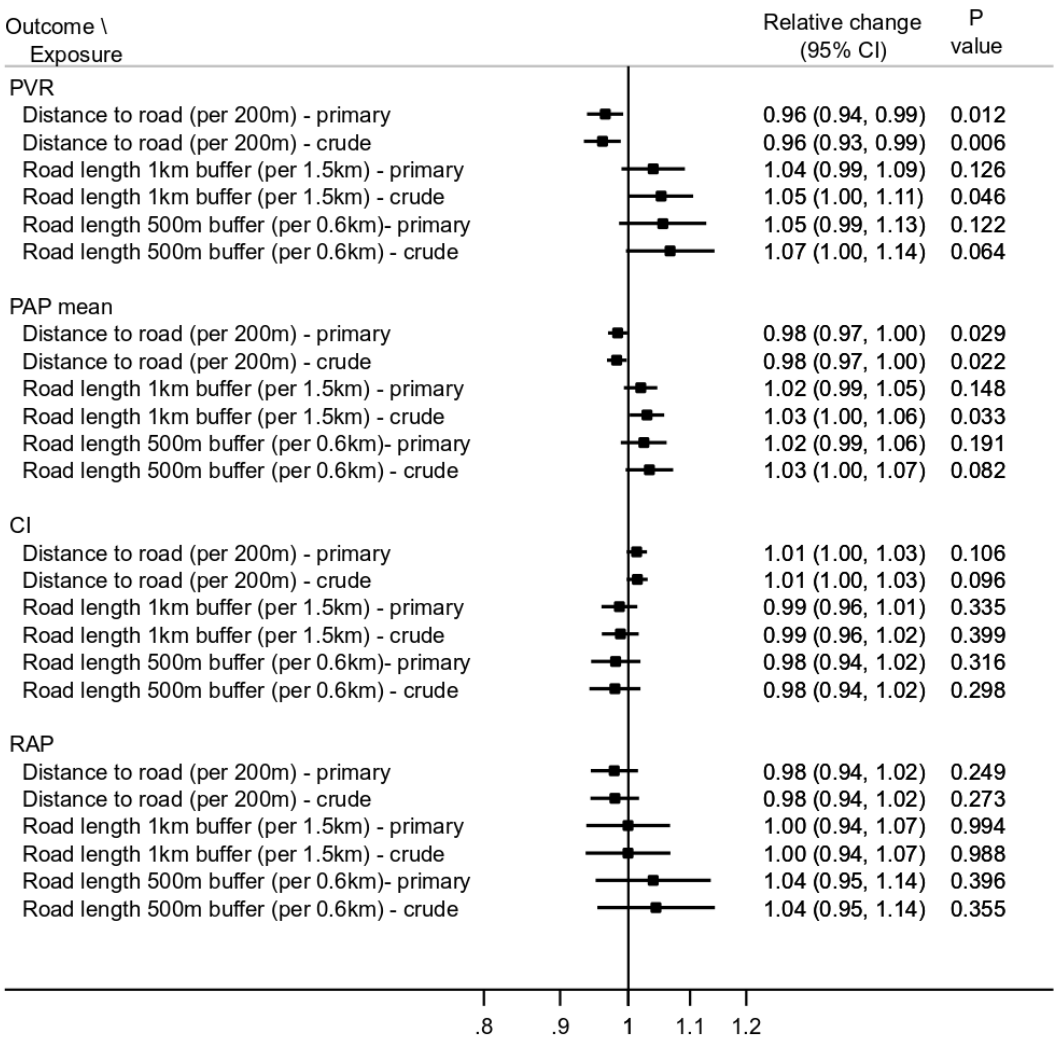


Figure S5. Linear Regression Estimating the Associations between Pulmonary Haemodynamics and Traffic Air Pollution for the crude and primary analysis models.

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

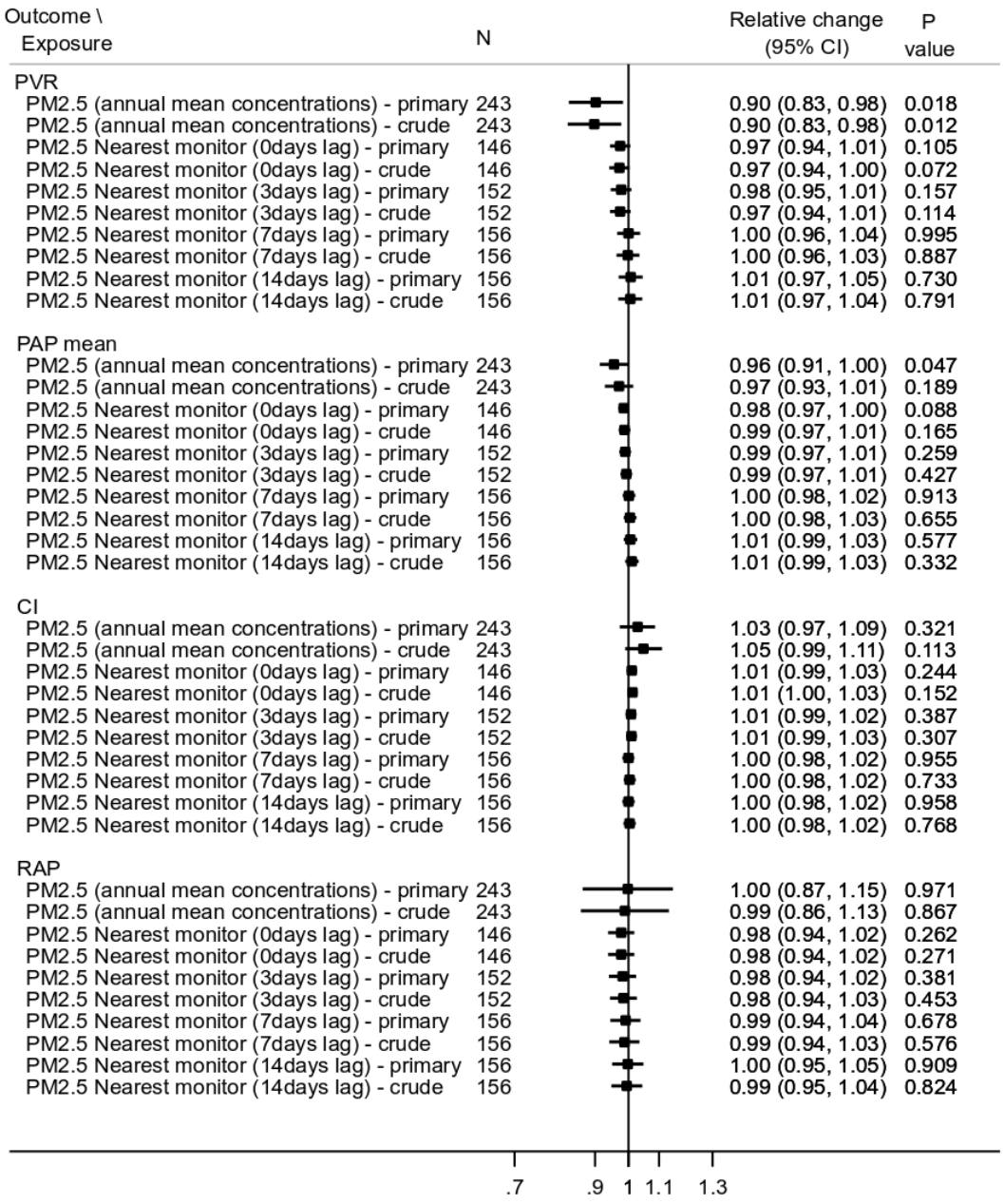


Figure S6. Linear Regression Estimating the Associations between Pulmonary Haemodynamics and Particulate Matter ≤2.5µm (PM2.5) concentrations for the crude and primary analysis models.

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

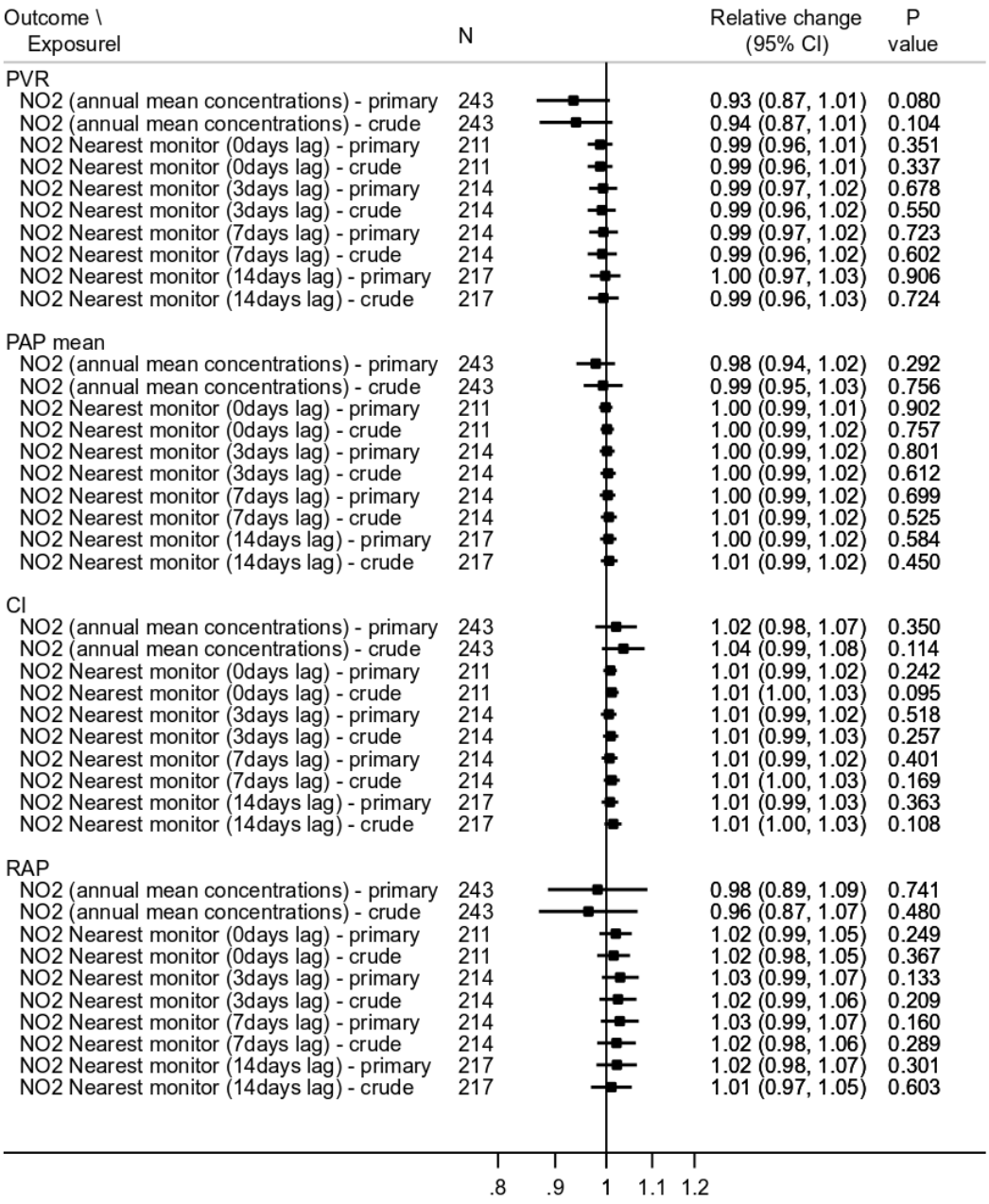


Figure S7. Linear Regression Estimating the Associations between Pulmonary Haemodynamics and Nitrogen Dioxide (NO_2) concentrations for the crude and primary analysis models.

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.

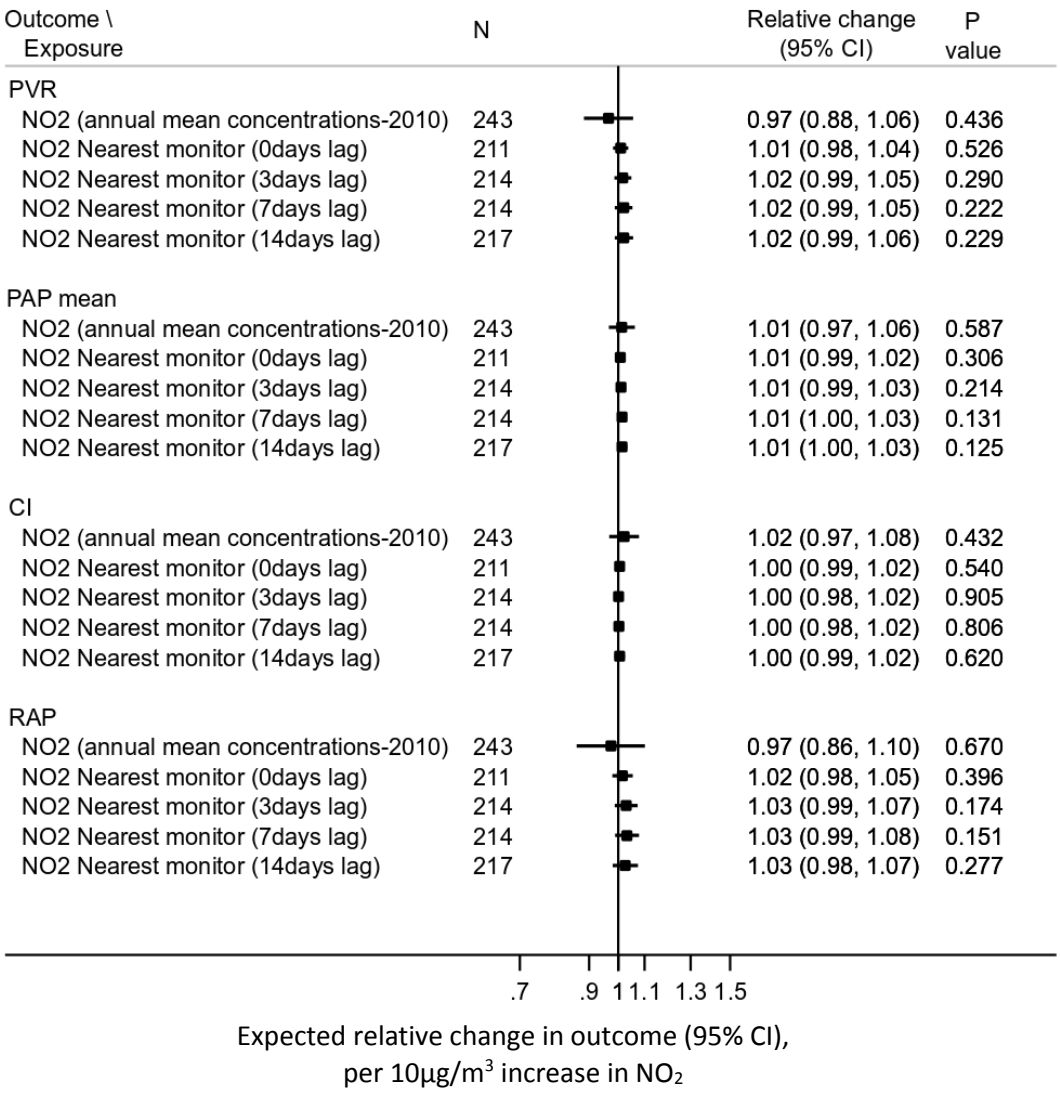


Figure S8. Multivariable Linear Regression Estimating the Associations between Pulmonary Haemodynamics and Nitrogen Dioxide (NO_2) concentrations, for the further-adjusted analysis models.

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.