

## Manuscript Details

<b>Manuscript number</b>	JTH_2017_284_R3
<b>Title</b>	Traffic-related air pollution and solid organ transplant failure in Great Britain: a retrospective cohort study
<b>Short title</b>	A retrospective cohort study
<b>Article type</b>	Review Article

### Abstract

Background Limited evidence suggests that exposure to traffic related air pollution is associated with graft failure among lung transplant recipients. We explored associations between pollution and transplant failure among lung and other solid organ transplant recipients in Great Britain through a retrospective cohort study. Methods All patients who received a lung, heart, liver, or kidney transplant between 2000 and 2008 in Great Britain were included, as recorded in the National Health Service Blood and Transplant (NHSBT) register and followed to March 2015. Using residential addresses at time of transplant we calculated distance to nearest (major) road and modelled annual average exposures to airborne nitrogen oxides and particulate matter of diameter  $\leq 10\mu\text{m}$  and  $\leq 2.5\mu\text{m}$  for each transplant recipient. All-cause mortality or graft failure (kidney) during follow up was the main outcome; median follow-up was around 10 years for each organ type. We fitted Cox regression models with adjustment for age, sex, year of transplant and donor age/smoking status. Results 780 lung, 1213 heart, 3650 liver and 11966 graft kidney transplant patients were analysed. We did not find any consistent associations between mortality or graft failure and any of the analysed air pollutants or road metrics. Although, exposure to particulate matter was associated with renal transplant failure in univariable analyses but not after adjustment for confounders. Conclusions Our analysis does not confirm previously reported associations between traffic-related air pollution exposure and the risk of transplant failure.

<b>Keywords</b>	Transplant(s), air pollution, lung transplant failure, traffic related air pollution.
<b>Taxonomy</b>	Research Methodology Social Sciences, Longitudinal Study, Statistics for Research, Medicine, Action Research
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May 17th 2018

Dear Editor-in-Chief,

Thank you for considering our publication, we are very pleased.

At your suggestion we have:

- Moved Figure 1 to the supplementary materials
- Combined Tables 3a and 3b
- Uploaded the main document and the supplementary materials to your side.

Sincerely,

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## **Comments from the editors and reviewers:**

### **-Editor**

Both reviewers are happy with the revision. However, the paper is rather long (2 figures and 7 tables). Please consider reporting the results of sensitivity analyses (Tables 5 and 6) as supplementary material. Please also consider combining Tables 3a and 3b.

Response: We amended the changes

### **-Reviewer 1**

- Thank your for these remaining clarifications. Although the paper has contradictory findings compared to the accepted literature, I believe the study is now acceptable for publication

Response: Many thanks, we are very pleased

### **-Reviewer 2**

Fascinating research study!

Response: Many thanks, we are very pleased

## Highlights

- Examined the relationship between traffic related air pollution and organ transplant failure using 15 years of data.
- The analysis does not confirm previously reported associations in respect to lung transplants.
- A wider range of solid organ transplants to assess the specificity of earlier reports have also been included.
- Failed to find associations for the other organs too.
- These findings are important; they raise doubts over previous reports and suggest that any advice given to transplant patients should be tempered.

## **Traffic-related air pollution and solid organ transplant failure in Great Britain: a retrospective cohort study**

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## Authorship

L.P. participated in data acquisition, statistical analysis, results interpretation, article writing and critical revision. S.J.S. participated in research design, data acquisition, statistical analysis, results interpretation, article writing and critical revision. D.C. participated in research design, data acquisition, statistical analysis, results interpretation, article writing and critical revision. D.F. participated in the data acquisition, results interpretation, article writing and critical revision. K.D.H. participated in the data acquisition, results interpretation and critical revision. A.L.H. participated in the research design, results interpretation, article writing and critical revision. J.D. participated in the research design, results interpretation and critical revision. P.C. participated in research design, results interpretation, article writing, critical revision and supervision.

Conflict of Interest Disclosures: None

Funding/Support: The work of the UK Small Area Health Statistics Unit is funded by Public Health England as part of the MRC-PHE Centre for Environment and Health, funded also by the UK Medical Research Council.

1 **Traffic-related air pollution and solid organ transplant failure in Great**  
2 **Britain: a retrospective cohort study**

3

4 Abbreviations:

5 BOS, bronchiolitis obliterans syndrome

6 CLAD, chronic lung allograft dysfunction

7 ESCAPE, European Study of Cohorts for Air Pollution Effects

8 LUR, Land Use Regression

9 NHLI, National Heart and Lung Institute

10 NHSBT, National Health Service Blood and Transplant

11 NO<sub>2</sub>, nitrogen dioxide,

12 NO<sub>x</sub>, nitrogen oxides

13 PM<sub>2.5</sub>, particulate matter with diameter ≤2.5µm

14 PM<sub>10</sub>, particulate matter with diameter ≤10µm

15 SAHSU, Small Area Health Statistics Unit

16 SD, standard deviation

17 SES, Socio-economic status

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## 1. Introduction

Traffic-related air pollution is a known risk factor for respiratory and cardiovascular disease <sup>1</sup>; individuals with existing health conditions are particularly susceptible to its negative health effects <sup>2,3</sup>. The association is believed to be mediated by inflammatory pathways. Chronic inflammation is particularly prevalent amongst transplant recipients and a main cause of lung, heart and kidney allograft failure <sup>4,5</sup>. Transplant recipients might therefore be a particularly susceptible group to the adverse health effects of traffic-related air pollution.

Lung transplant recipients have one of the lowest survival rates of those undergoing solid organ transplantation<sup>4</sup>. Chronic lung allograft dysfunction (CLAD), manifest chiefly as bronchiolitis obliterans syndrome (BOS) is the main cause of death in adult lung transplant recipients <sup>6</sup>; the main risk factors for both CLAD and BOS are alloimmune responses and chronic inflammation of the lung due to viral infections. Recent studies, however, suggest that exposure to traffic-related air pollution might also contribute to both CLAD and BOS and consequent mortality <sup>8-11</sup>. In 2011, Nawrot and colleagues published a study of 281 patients (288 transplants) who underwent lung transplantation in Belgium. They reported a strong significant association between proximity to road (a proxy of traffic-related air pollution exposure) and both BOS and all-cause mortality following transplant. On this evidence, the authors suggested that traffic pollution could account for about a third of all lung transplant failures <sup>8</sup>. A subsequent time-series analysis by the same group correlated daily variations in estimated exposures to particulate matter less than or equal to 10 $\mu$ m (PM<sub>10</sub>) with cell counts from bronchoalveolar lavage samples collected from lung transplant patients; the reported associations were confined to patients who were not treated with azithromycin <sup>9</sup>. A more recent analysis of deaths following lung transplant in 13 European centres failed to find a relationship with road proximity but reported significant associations with two different measures of air pollution <sup>10</sup> in patients who had never received treatment

56 with azithromycin. Some support for these observations was provided by a Canadian research  
57 group who reported that in double-lung transplant recipients in Ontario, a high density of local  
58 roads was associated with the development of CLAD <sup>11</sup>.

59

60 It is argued that the transplanted lung is especially susceptible to the effects of air pollution  
61 because of its direct contact with the environment <sup>8</sup>. In fact there appear to be no studies of  
62 this issue in other, solid-organ transplant patients, although an analysis of 32,000 recipients of  
63 kidney grafts in the United States related the risk of fatal coronary heart disease to ambient  
64 ozone levels <sup>12</sup>. We designed a retrospective cohort study to examine if the findings above could  
65 be replicated in the United Kingdom; and in particular to study whether any effect in lung  
66 transplant patients was specific or could also be observed in recipients of other solid-organ  
67 grafts.

## 68 **2. Materials and Methods**

### 69 2.2 Study population

70 We included all patients in Great Britain who received a first transplant of the lung, heart, liver  
71 or kidney between 1<sup>st</sup> January 2000 and 31<sup>st</sup> December 2008 as recorded in the National Health  
72 Service Blood and Transplant (NHSBT) register. All UK patients who are waiting for an organ  
73 transplant are registered with NHSBT, and for those who receive a transplant, information about  
74 the donor, recipient and transplant procedure is recorded including recipient demographics,  
75 comorbidities and clinical indicators. For each transplant recipient subsequent data are  
76 collected at three and 12 months, and annually thereafter; the final date of follow up was 2<sup>nd</sup>  
77 March 2015. We restricted the cohort to those having a residential address in Great Britain and  
78 linked local air pollution exposure to registry information in three steps. First, NHSBT supplied  
79 a list of the addresses of all patients who received a transplant of the lung, heart, liver or kidney  
80 between 2000 and 2008; in this list, to ensure confidentiality, was concealed an undisclosed

81 number of 'dummy' addresses. On receipt of the list, the Small Area Health Statistics Unit  
82 (SAHSU), Imperial College assigned air pollution measurements to each address and transferred  
83 these back to NSHBT. Finally, the addresses were removed, health variables were attached, and  
84 the anonymised data were transferred to the National Heart and Lung Institute (NHLI), Imperial  
85 College. The health variables included, for the recipient, were sex, age, type of transplant (single  
86 or double lung), date of transplant, date of death – or in the case of kidney transplants, date of  
87 graft failure (the date of return to permanent dialysis) – and, for the donor, age and smoking  
88 status. NHSBT do not collect standardised information on BOS or on treatment with  
89 azithromycin.

90

91 The study was approved by the NRES Ethics Committee, West London and GTAC (reference  
92 14/LO/2042).

93

### 94 2.3 Exposure Assessment

95 We assigned metrics for traffic-related air pollution exposure based on the last recorded  
96 residential address of each transplant recipient; geocoding using Quick Address Software <sup>13</sup> was  
97 successful for 98% of all addresses. We derived both indicators of local traffic and modelled  
98 outdoor air pollution concentrations to assign traffic-related air pollution exposure to transplant  
99 recipients. We derived the inverse distance from each patient's residential address to (i) the  
100 nearest road, and (ii) the nearest major road (defined as roads with traffic intensity > 5,000  
101 vehicles/day). We used the Ordnance Survey Meridian 2 road network, 1: 50,000 (2009) and  
102 assigned traffic count data from the Road Traffic Statistics Branch at the UK Department of  
103 Transport to each road link.

104

105 We estimated exposure to nitrogen dioxide (NO<sub>2</sub>), nitrogen oxides (NO<sub>x</sub>), particulate matter with  
106 diameter ≤10µm (PM<sub>10</sub>) and ≤2.5µm (PM<sub>2.5</sub>). We modelled annual average concentrations for

107 each recipient's address using the standard Land Use Regression (LUR) protocol developed as  
108 part of the European Study of Cohorts for Air Pollution Effects (ESCAPE); details of the models  
109 are provided elsewhere<sup>14,15</sup>. LUR is a standard technique that is widely used in epidemiological  
110 research to investigate possible links between air pollution and health effects<sup>16</sup>. In brief, the LUR  
111 models use measurements of air pollution concentration between January 2010 and January  
112 2011 and spatial predictor variables including traffic indicators, population density and  
113 meteorology. Based on these modelled 2010/2011 concentrations, we back-extrapolated NO<sub>2</sub>,  
114 NO<sub>x</sub>, and PM<sub>10</sub> to each year of transplantation by adjusting for time trends based on daily  
115 monitoring data<sup>17</sup>. We could not back-extrapolate PM<sub>2.5</sub> due to a lack of concentration  
116 measurements in earlier years. As established in the ESCAPE study, we assigned all addresses  
117 more than 400km from Greater London a missing value for particulate (PM<sub>10</sub> and PM<sub>2.5</sub>)  
118 exposures since while estimated concentrations are valid up to 400km from the monitoring zone  
119 (Greater London and the South of England), it is unclear how good they are beyond this area.

120

#### 121 2.4 Socio-economic status (SES)

122 Individual level SES was unavailable and as a proxy we used the area-level 2001 Carstairs Index,  
123 a composite index of SES based on four census variables: percentage of male unemployment,  
124 overcrowded households, households without a car and households with head of household in  
125 low social class<sup>18</sup>. We categorised Carstairs scores across all 218,038 Census Output Areas (COA)  
126 in Great Britain into quintiles and assigned each transplant recipient to a quintile based on the  
127 COA of their residential address.

128

#### 129 2.5 Statistical methods

130 We excluded patients who had more than one transplant within the study period (n=755; Figure  
131 1S), those for whom we had no outcome data (n=514; Figure 1S in supplement) and patients  
132 whose transplant failed within three months of their operation (n=908; Figure 1S). We examined

133 graphical plots for each exposure variables and any extreme values were removed; consequently  
134 37 extreme values of distance to the nearest major or nearest road were removed (Figure 1S).  
135 Our analyses are of the 'complete case' type without imputation of missing data which, for the  
136 variables available to us, were few.

137 The outcomes of interest were all-cause mortality (lung, heart and liver transplants) or graft  
138 failure (kidney transplants) and are referred to collectively as 'transplant failure'.

139 Where distance to major road was <5 metres we assigned a value of 5 metres to account for the  
140 fact no addresses fall directly on a road. To assess the assumption of linearity, lowess smoothed  
141 martingale residual plots were assessed for each exposure variable. Where there was evidence  
142 of a violation of the assumption, transformations were applied and used in the models.  
143 Accordingly distance from major and distance from nearest road were  $\log_e$  transformed for  
144 analysis. Distance from major road was also categorised in two ways; as a binary variable using  
145 the lower quartile for each organ type as a cut-off and secondly split into seven categories (<50,  
146 50-100, 100-200, 200-400, 400-700, 700-1000, >1000m) to explore a potential distance decay.

147

148 We present continuous variables by their mean and standard deviation (SD) or median and  
149 interquartile range [IQR] and categorical variables as percentages. Comparisons between groups  
150 were tested using the Kruskal-Wallis test for non-parametric continuous data. Kaplan-Meier  
151 curves were plotted for each binary measure of distance to major road and the log rank test was  
152 used to compare the survival between the different categories. Follow-up time (years) was  
153 calculated using the reverse Kaplan-Meier method <sup>19</sup>.

154

155 We fitted univariable Cox regression models separately for each pollutant to examine their  
156 unadjusted associations with time to transplant failure, censored at last known date alive or  
157 graft failure, for each organ type. Each pollutant was included in the model using an increment  
158 ( $10\mu\text{g}/\text{m}^3$ ,  $20\mu\text{g}/\text{m}^3$ ,  $10\mu\text{g}/\text{m}^3$  and  $5\mu\text{g}/\text{m}^3$  for  $\text{NO}_2$ ,  $\text{NO}_x$ ,  $\text{PM}_{10}$  and  $\text{PM}_{2.5}$  respectively) to derive

159 hazard ratios. In multivariable Cox regression models each pollutant measure was examined  
160 individually after *a priori* adjustment for age, sex, transplant type (single or double lung),  
161 transplant year (to account for temporal improvements in management), SES, donor smoker  
162 and donor age. The assumption of proportional hazards in each final multivariable model was  
163 confirmed using Schoenfeld residuals <sup>20</sup>. Covariates violating the proportional hazard  
164 assumption were stratified in the final models.

165

166 Finally, we performed a series of sensitivity analyses after stratifying the cohort by SES (quintiles  
167 1-3 vs. quintiles 4-5). For lung transplant patients, additional sensitivity analyses were  
168 performed by reducing the median follow time to 2, 3, 4 and 5 years follow up and stratifying  
169 on year of transplant (pre/post 2004) on the grounds that those with more recent  
170 transplants may have been more likely to have been treated with prophylactic azithromycin. In  
171 addition, we ran separate analyses for those exposed to high levels of PM<sub>10</sub> >20µg/m<sup>3</sup>; for those  
172 resident in the south east of England where ambient exposures tend to be higher than in the  
173 rest of the country; and using 'major road length within a 100m buffer' as an exposure surrogate.

174

175 All tests were 2-sided; we used Stata version 14 (STATA Corp., Texas, USA) for all analyses.

### 176 **3. Results**

177 Among those excluded due to missing data (lung n=12 (1.3%), heart n=34 (2.7%), liver n=461  
178 (10.4%), kidney n=2144 (14.7%); Figure 1S ), the median age (years) was significantly lower than  
179 in those included in the analysis for all but lung transplants (heart: 31 vs. 46 years p=0.02, liver:  
180 43 vs.50 p<0.001, kidney 41 vs.45 p<0.001); the proportion of males in excluded liver transplant  
181 patients was also lower (54% vs 59%, p=0.033). There were no differences in the distributions  
182 of socioeconomic status between excluded and analysed patients.

183

184 Table 1: Summary table of the UK transplant dataset (2000 to 2008). Data are presented as  
 185 median (IQR) unless otherwise stated.

	Lung	Heart	Liver	Kidney (graft)
N	780 <sup>a</sup>	1,062	3,355	11,607
Death or graft failure, n (%)	455 (58.3%)	307 (28.9%)	850 (25.3%)	2085 (18.0%)
Age at transplantation (years) , mean (sd)	46.1 (14.7)	39.0 (19.1)	44.4 (18.8)	43.6 (15.9)
Follow-up time (years), median (range)	9.1 (0.3-14.0)	10.0 (0.3-15.0)	9.1 (0.3-15.1)	8.8 (0.3-15.1)
Distance to nearest major road (m)	439.0 (694.4)	406.3 (673.4)	381.8 (627.8)	389.7 (621.4)
Distance to the nearest road (m)	22.4 (23.6)	21.6 (22.7)	21.0 (20.6)	21.3 (22.2)
NO <sub>2</sub> year of transplant (µg/m <sup>3</sup> )	28.2 (13.5)	29.4 (13.0)	30.3 (14.9)	29.2 (13.2)
NO <sub>x</sub> year of transplant (µg/m <sup>3</sup> )	52.5 (26.5)	55.3 (23.8)	56.4 (27.2)	54.8 (25.2)
PM <sub>10</sub> year of transplant (µg/m <sup>3</sup> ) <sup>b</sup>	20.6 (3.5)	20.4 (3.3)	20.6 (3.3)	20.6 (3.4)
PM <sub>2.5</sub> annual average 2010 (µg/m <sup>3</sup> ) <sup>b</sup>	9.9 (1.4)	9.9 (1.3)	10.0 (1.4)	10.0 (1.4)
SES, n(%)				
1 (least deprived)	154 (19.7%)	216 (20.3%)	611 (18.2%)	2367 (20.4%)
2	159 (20.4%)	208 (19.6%)	655 (19.5%)	2290 (19.7%)
3	146 (18.7%)	196 (18.5%)	648 (19.3%)	2278 (19.6%)
4	164 (21.0%)	228 (21.5%)	689 (20.5%)	2293 (19.8%)
5 (most deprived)	157 (20.1%)	228 (21.5%)	752 (22.4%)	2379 (20.5%)

186 <sup>a</sup> single lung n=243, double lung n=537

187 <sup>b</sup> n=720, n=990, n=3240, n=10740 for lung, heart, liver and kidney respectively due to exclusion of patients with  
 188 addresses >400km from the monitoring zone  
 189 IQR - Interquartile range

190

191 In table 1 we summarise baseline and exposure information for each transplant type. After  
 192 exclusions there were 780 lung, 1,062 heart, 3,355 liver and 11,607 kidney transplants for  
 193 analysis. Lung had 43 missing data for donor smoker and 60 for pm25. Heart had 80 missing data  
 194 for donor smoker, 72 for pm25 and 1 for donor age. Liver had 213 missing data for donor smoker,  
 195 115 for pm25 and 1 for donor age. Kidney had 1,598 missing data for donor smoker, 867 for  
 196 pm25 and 1 for donor age. The estimated median follow up time (years) was 9.1, 10.0, 9.1 and  
 197 8.8 for lung, heart, liver and kidney transplants respectively. Both SES and pollution estimates  
 198 were equally distributed across the different organ types. Air pollutant estimates were strongly  
 199 associated with SES, being higher in those from more deprived groups in all transplant patients  
 200 (Table 2).

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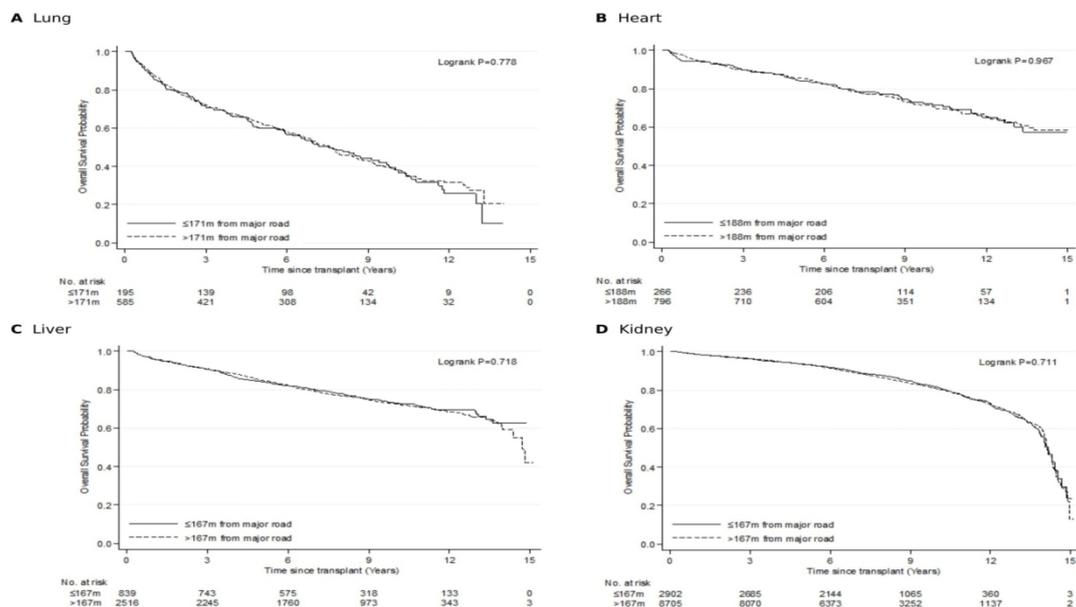
206 Table 2: Association between SES and pollutant estimates in all transplant patients (n=16,804).  
 207 Medians are reported.

Exposure	Socio-economic status					p-value*
	1 (least deprived)	2	3	4	5 (most deprived)	
Distance to nearest major road (m)	547.6	453.5	372.1	366.6	301.2	<0.001
Distance to nearest road (m)	25.5	23.1	20.5	19.3	19.3	<0.001
NO <sub>2</sub> (µg/m <sup>3</sup> )	23.9	26.2	29.4	31.6	36.3	<0.001
NO <sub>x</sub> (µg/m <sup>3</sup> )	44.3	49.8	54.9	59.7	67.8	<0.001
PM <sub>10</sub> (µg/m <sup>3</sup> )	19.7	20.2	20.6	20.8	21.2	<0.001
PM <sub>2.5</sub> annual average 2010 (µg/m <sup>3</sup> )	9.3	9.7	10.0	10.2	10.6	<0.001

208 \*p-values are derived from Kruskal-Wallis tests for differences between groups.

209 The incidence of failure was highest for lung transplants (58%). Unadjusted Kaplan-Meier curves  
 210 suggest that the estimated rate of failure was not significantly different between patients living  
 211 closer to a major road (lower quartile) and those living further away, for any organ (Figure 1).  
 212 Univariable analyses showed no evidence of an association between any of the air pollutant  
 213 measures and lung, heart or liver transplant failures (Table 3). There were significant, unadjusted  
 214 relationships between exposures to PM<sub>10</sub> (year of transplant) or PM<sub>2.5</sub> (2010) and kidney graft  
 215 failure.

216 Figure 1: Kaplan-Meier survival curves stratified by distance to major road (lowest quartile for  
 217 each organ as a cut off); by organ type.



218  
 219 In contrast, the risk of kidney transplant failure was significantly associated with exposure  
 220 estimates for PM<sub>10</sub> and PM<sub>2.5</sub>. Recipient age (lung, heart and liver), SES (heart and kidney), donor

221 age (all organ types) and donor smoker status (lung) were individually associated with transplant  
 222 failure (Table 3 ).  
 223 Table 3: Hazard Ratios (95% CI) from the univariable analyses of organ transplant failure and  
 224 each of the covariates and exposure variables.

	<b>Lung</b>	<b>Heart</b>	<b>Liver</b>	<b>Kidney (graft)</b>
<b>Characteristics</b>	<b>Unadjusted HR (95% CI)</b>			
Male	1.03 (0.86-1.24)	1.02 (0.80-1.32)	0.65 (0.56-0.75)	0.97 (0.89-1.06)
Lung transplant type				
single lung	1	-	-	-
double lung	0.67 (0.55-0.80)	-	-	-
Age	1.02 (1.01-1.03)	1.01 (1.00-1.02)	1.03 (1.02-1.03)	1.00 (0.99-1.00)
Transplant year	0.98 (0.94-1.02)	0.95 (0.91-1.00)	0.97 (0.94-1.00)	1.17 (1.14-1.19)
Area-level SES				
1 (least deprived)	1	1	1	1
2	0.98 (0.74 -1.30)	1.62 (1.08-2.43)	1.15 (0.93-1.43)	1.13 (0.97-1.31)
3	0.69 (0.51 -0.94)	1.63 (1.08-2.45)	1.05 (0.84-1.31)	1.39 (1.20-1.60)
4	0.84 (0.63 -1.12)	2.09 (1.42-3.07)	1.11 (0.88-1.38)	1.50 (1.30-1.73)
5 (most deprived)	1.05 (0.79 -1.39)	2.16 (1.46-3.18)	1.05 (0.84-1.30)	1.65 (1.43-1.89)
Donor age	1.01 (1.00-1.02)	1.02 (1.01-1.02)	1.01 (1.01-1.02)	1.02 (1.01-1.02)
Donor smoker status				
No	1	1	1	1
Yes	1.31 (1.08-1.58)	1.21 (0.96-1.52)	1.08 (0.94-1.25)	1.09 (0.99-1.20)
<b>Exposures</b>				
Distance to nearest major road (m)				
>1000	1 (ref)	1 (ref)	1 (ref)	1 (ref)
700-1000	1.05 (0.74-1.47)	1.07 (0.70-1.70)	0.90 (0.67-1.22)	1.06 (0.89-1.25)
400-700	1.12(0.85-1.49)	1.04 (0.73-1.48)	1.12 (0.85-1.48)	1.03 (0.90-1.20)
200-400	0.90 (0.67-1.22)	1.11 (0.78-1.56)	0.88 (0.69-1.11)	1.09 (0.95-1.25)
100-200	1.04 (0.77-1.42)	0.93 (0.62-1.40)	0.94 (0.77-1.16)	1.12 (0.96-1.30)
50-100	0.99 (0.66-1.51)	1.49 (0.94-2.32)	0.96 (0.77-1.19)	1.10 (0.92-1.33)
<50	1.02 (0.67-1.56)	1.09 (0.65-1.82)	0.95(0.73-1.25)	0.89 (0.72-1.10)
Log <sub>e</sub> distance to major road (m)	1.02 (0.95-1.09)	0.97 (0.89-1.06)	1.02 (0.96-1.07)	1.00 (0.96-1.04)
Log <sub>e</sub> distance to the nearest road (m)	1.04 (0.93-1.17)	1.06 (0.91-1.23)	0.97 (0.89-1.07)	1.02 (0.97-1.08)
NO <sub>2</sub> per 10 µg/m <sup>3</sup> increase (year of transplant) <sup>a</sup>	0.96 (0.87-1.06)	1.09 (0.97-1.22)	1.00 (0.94-1.07)	1.00 (0.96-1.05)
NO <sub>x</sub> per 20 µg/m <sup>3</sup> increase (year of transplant) <sup>a</sup>	0.99 (0.91-1.08)	1.08 (0.99-1.19)	1.00 (0.95-1.06)	1.01 (0.97-1.04)
PM <sub>10</sub> : per 10 µg/m <sup>3</sup> increase (year of transplant) <sup>b</sup>	1.16 (0.84-1.60)	0.85 (0.55-1.31)	0.84 (0.66-1.08)	1.27 (1.08-1.49)
PM <sub>2.5</sub> : per 5 µg/m <sup>3</sup> increase (annual average 2010) <sup>b</sup>	0.84 (0.54-1.31)	1.46 (0.84-2.53)	0.88 (0.65-1.19)	1.25 (1.02-1.53)

225 <sup>a</sup> Continuous analysis based on log<sub>e</sub> distance. HR>1 indicates an increased risk of transplant failure per  
 226 log<sub>e</sub> increase of distance to road.

227 <sup>b</sup> n=681, n=911, n=3039, n=9247 for lung, heart, liver and kidney respectively due to exclusion of patients  
 228 with addresses >400km from the monitoring zone.

229  
 230 The findings from our multivariable models in relation to pollution are presented in Table 4. For  
 231 each estimate of traffic-related pollution and for each organ type the risk estimates were close  
 232 to 1.00 and not significant. We observed an elevated risk of lung transplant failure for each 10  
 233 µg/m<sup>3</sup> increase of PM<sub>10</sub>, however this was not statistically significant (HR (95% CI) 1.32 (0.93 to

234 1.86), p=0.12). An analysis using distance to nearest major road expressed as seven consecutive  
 235 categories failed to find any evidence of a trend in risk for any organ (Table 4). We repeated the  
 236 analysis excluding the SES variable (data not shown); the results were similar with the exception  
 237 of an increased risk of kidney graft failure for each 5 µg/m<sup>3</sup> increase in PM<sub>2.5</sub> (HR (95%CI) 1.26  
 238 (1.02 to 1.56), p=0.03).

239 Table 4: Hazards ratios (95% CI) from multivariable models of the association between  
 240 transplant failure and measures of air pollution.

Exposure	Lung n=737		Heart n=981		Liver n=3,142		Kidney n=10,009	
	n	Adjusted HR <sup>a</sup> (95% CI)	n	Adjusted HR <sup>b</sup> (95% CI)	n	Adjusted HR <sup>c</sup> (95% CI)	n	Adjusted HR <sup>d</sup> (95% CI)
Distance to nearest major road (m)								
>1000	157	1 (ref)	197	1 (ref)	602	1 (ref)	1781	1 (ref)
700-1000	83	0.91 (0.64-1.31)	93	0.92 (0.58-1.48)	315	1.04 (0.79-1.37)	1114	1.00 (0.84-1.19)
400-700	155	1.07 (0.80-1.44)	209	0.94 (0.65-1.36)	628	1.03 (0.82-1.29)	2005	0.97 (0.84-1.14)
200-400	140	0.93 (0.68-1.26)	219	0.97 (0.67-1.39)	679	1.02 (0.82-1.27)	2147	0.98 (0.85-1.14)
100-200	107	1.01 (0.73-1.40)	129	0.73 (0.47-1.14)	453	0.93 (0.72-1.20)	1483	1.04 (0.89-1.22)
50-100	50	0.94 (0.62-1.44)	72	1.22 (0.76-1.96)	234	1.14 (0.86-1.53)	790	1.00 (0.83-1.22)
<50	45	0.97 (0.62-1.52)	62	1.00 (0.59-1.69)	231	0.83 (0.60-1.14)	689	0.83 (0.67-1.04)
Log <sub>e</sub> distance to major road (metres) <sup>e</sup>		1.03 (0.95-1.11)		1.00 (0.91-1.10)		1.02 (0.97-1.08)		1.02 (0.98-1.06)
Log <sub>e</sub> distance to the nearest road (metres) <sup>e</sup>		1.04 (0.92-1.17)		1.10 (0.93-1.29)		0.97 (0.88-1.08)		1.05 (1.00-1.12)
NO <sub>2</sub> per 10 µg/m <sup>3</sup> increase (year of transplant)		0.85 (0.64-1.15)		0.99 (0.87-1.12)		0.97 (0.90-1.05)		0.96 (0.91-1.01)
NO <sub>x</sub> per 20 µg/m <sup>3</sup> increase (year of transplant)		0.96 (0.87-1.06)		1.01 (0.90-1.13)		0.98 (0.91-1.04)		0.96 (0.92-1.01)
PM <sub>10</sub> : per 10 µg/m <sup>3</sup> increase (year of transplant) <sup>f</sup>		1.32 (0.93-1.86)		0.74 (0.45-1.21)		0.88 (0.67-1.16)		0.93 (0.77-1.12)
PM <sub>2.5</sub> : per 5 µg/m <sup>3</sup> increase (annual average 2010) <sup>f</sup>		0.82 (0.49-1.36)		0.91 (0.47-1.74)		0.84 (0.58-1.19)		0.86 (0.67-1.09)

241 <sup>a</sup> Lung adjusted for age, sex, transplant year, SES, donor age and smoking status and stratified by transplant type  
 242 (single/double)

243 <sup>b</sup> Heart adjusted for recipient age, sex, transplant year, SES, donor age and smoking status

244 <sup>c</sup> Liver adjusted for sex, transplant year, SES, donor age and smoking status and stratified by recipient age  
 245 (quartiles)

246 <sup>d</sup> Kidney adjusted for sex, SES and smoking status and stratified by recipient age (quartiles) and transplant year  
 247 (<2005, ≥2005)

248 <sup>e</sup> Continuous analysis based on log<sub>e</sub> distance. HR>1 indicates an increased risk of transplant failure per log<sub>e</sub> increase  
 249 of distance to road.

250 <sup>f</sup> n=681, n=911, n=3039, n=9247 for lung, heart, liver and kidney respectively due to exclusion of patients with  
 251 addresses >400km from the monitoring zone.

252  
 253 In sensitivity analysis, stratification by SES (table 1S in supplement) did not show any consistent  
 254 patterns of risk associated with exposure for any organ types. Among patients in the SES 1-3  
 255 quintiles, renal graft failure was significantly associated with distance to a major road. When  
 256 looking at differences in the subset of lung transplants performed between 2000 and 2004

257 (Table 2S) we could not observe different median follow up times. (Table 3S ) Sensitivity analyses  
258 restricted to those with estimated exposures  $PM_{10} > 20\mu g/m^3$ , to those resident in the south east  
259 of England and when using 'major road length within a 100m buffer' as an exposure surrogate,  
260 did not show findings different from those of the primary analyses.

#### 261 **4. Discussion**

262 We designed this analysis to test both the consistency and the specificity of previous reports  
263 from Europe and Canada <sup>8,9,11</sup>, arguing that if findings of an association between higher exposure  
264 to air pollution and an increased risk of lung graft failure was truly causal then it would probably  
265 not be seen, at least to the same extent, in transplants of all solid organ types. In the event, in  
266 approximately 17,000 transplants (with 3,700 transplant failures) carried out in the UK between  
267 2000 and 2008, we found no evidence of an association between transplant failure for any organ  
268 group and estimated pollution exposure. An extensive series of sensitivity analyses failed to  
269 identify any groups of transplants which deviated from this conclusion.

270

271 Our findings for lung transplants are in contrast with those reported previously and we have  
272 considered possible explanations for this difference. First, we have no individual information on  
273 treatments following transplantation including, importantly, the use of azithromycin, a drug  
274 which appears to reduce the risk of mortality following BOS<sup>21</sup> and which has been suggested in  
275 analyses by other groups to protect against any adverse associations with air pollution<sup>9,10</sup>,  
276 potentially through its anti-inflammatory properties. Use of this drug for diagnosed BOS has  
277 become routine in UK practice in recent years but an analysis restricted to 2000-2004 failed to  
278 show any era-specific differences in risk, so this may not be the only explanation for our null  
279 findings. We had no consistent information on the frequency and dates of episodes of reversible  
280 graft rejection, including BOS in lung transplants; this may have reduced the statistical power of

281 our analyses but is unlikely to have affected our risk estimates. The address information held  
282 by NHSBT is the latest recorded at clinical interview and may or may not be current at the time  
283 of graft failure. We do not know what proportion of patients move home following transplant  
284 but doubt that this is systematically related to exposure to traffic-related pollutants. We did not  
285 have information on whether the transplanted organ was cadaveric or from a live donor, on  
286 whether the patients were smokers, on the underlying cause of organ failure and on the  
287 medication used after transplant. Each of these may have had an impact on survival although  
288 whether any of them might confound a relationship with ambient air pollution is debatable.  
289 Moreover, information on smoking status after transplant, particularly lung transplant, is  
290 difficult to verify. Finally, while we did not have individual-level SES, we did adjust for SES at the  
291 small area level, which appeared to have very little influence in this setting. To use area-level  
292 SES is a valid and often-used approach in environmental epidemiology, accounting for wider  
293 characteristics of the neighbourhood related to deprivation which might include access to and  
294 quality of healthcare facilities, and other environmental exposures.

295

296 Previous reports, from lung transplants in Belgium (n=288) <sup>8</sup> and in 13 European centres  
297 (n=5707, including the original Belgian cohort) <sup>10</sup> have been inconsistent in their findings. The  
298 first, but not the second, found associations with distance of residence from major road; the  
299 second, but not the first, found associations with PM<sub>10</sub> as well as with road length within 200m  
300 of patients' home address. In the wider analysis <sup>10</sup> the findings were not consistent either  
301 between or within centres, with considerable variation between them; in the single UK centre,  
302 there were no significant associations with either measure of pollution. These discrepancies  
303 may point towards quantitative or qualitative differences between traffic-related exposures in  
304 European regions although we think these are likely to be too small to be important in this  
305 respect. Common to almost all air pollution studies, we used exposure at residence as a proxy

306 for individual-level exposure. This will introduce exposure misclassification due to different  
307 activity patterns that is most likely to bias our risk estimates toward the null.

308

309 Our findings from univariable and multivariable analyses were not importantly different  
310 suggesting that, in the latter, there was probably little residual confounding. We noted a clear  
311 association between SES and most estimates of pollution; while we chose to include both  
312 variables in our final statistical models, omission of SES had no important impact on our risk  
313 estimates.

314

315 The analyses we report here do not show that exposure to traffic-related pollutants has an  
316 adverse effect on (graft) survival after solid organ transplant. However, we were unable to  
317 investigate adequately whether current UK utilisation of azithromycin may have influenced  
318 absence of an observed association. For any environmental exposure, assessment of causality is  
319 based on accumulated evidence from both epidemiological and mechanistic studies. Our study  
320 suggests it is too early to conclude that air pollution affects solid organ transplant survival.

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380

# Supplementary tables

Figure 1S: Exclusions from analysis by organ type.

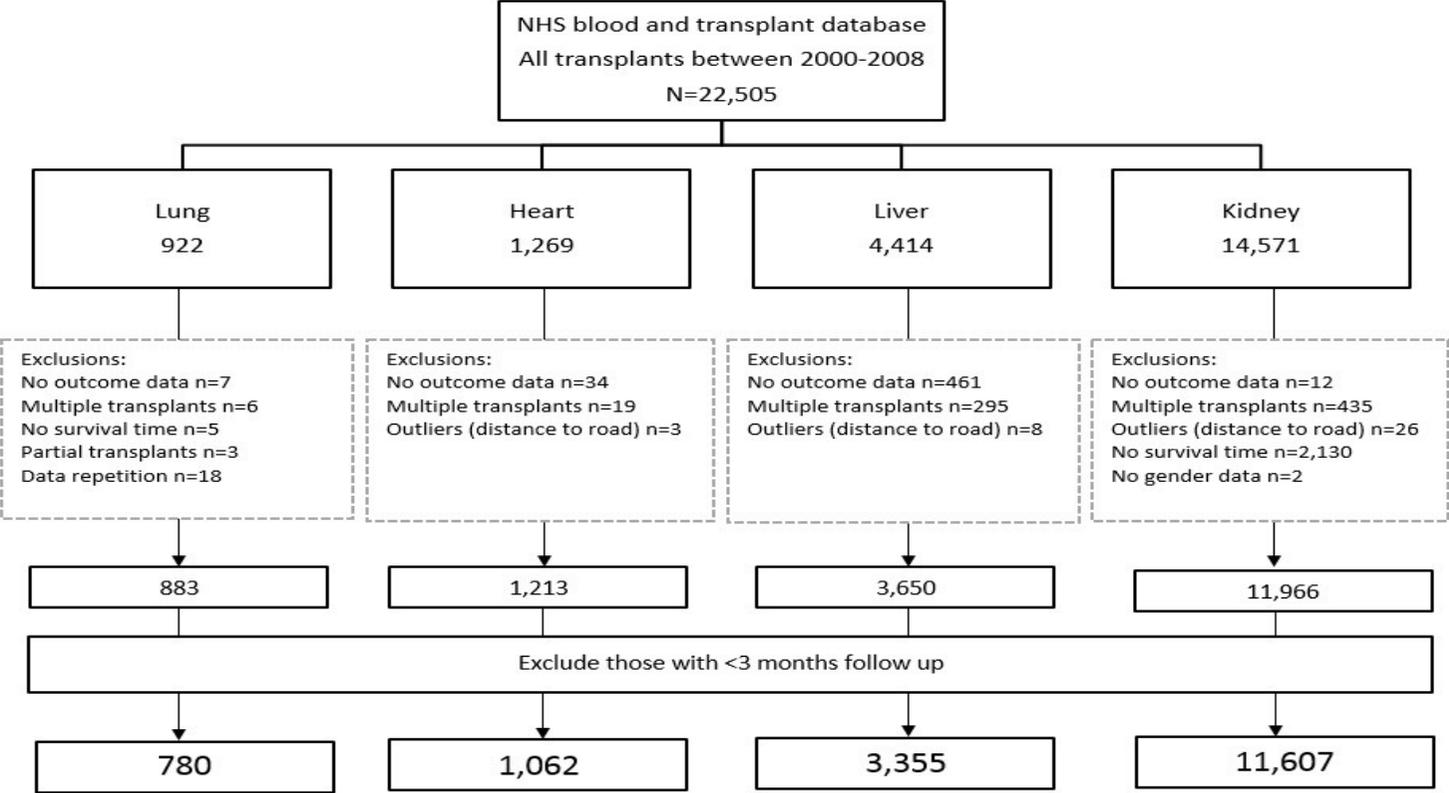


Table 1S: Hazard ratios (95% confidence intervals) from multivariable analyses after stratifying the cohort by SES (quintiles 1-3 and quintiles 4-5).

Pollutants	Lung		Heart		Liver		Kidney	
	Quintiles 1-3	Quintiles 4-5	Quintiles 1-3	Quintiles 4-5	Quintiles 1-3	Quintiles 4-5	Quintiles 1-3	Quintiles 4-5
	Adjusted HR <sup>a</sup> (95% CI)	Adjusted HR <sup>a</sup> (95% CI)	Adjusted HR <sup>b</sup> (95% CI)	Adjusted HR <sup>b</sup> (95% CI)	Adjusted HR <sup>c</sup> (95% CI)	Adjusted HR <sup>c</sup> (95% CI)	Adjusted HR <sup>d</sup> (95% CI)	Adjusted HR <sup>d</sup> (95% CI)
	(n=434)	(n=303)	(n=571)	(n=410)	(n=1788)	(n=1354)	(n=5907)	(n=4102)
Log <sub>e</sub> distance to major road (m) <sup>f</sup>	1.03 (0.94-1.14) p=0.53	1.03 (0.90-1.17) p=0.71	1.00 (0.88-1.13) p=0.98	1.00 (0.86-1.16) p=0.99	1.03 (0.96-1.11) p=0.41	1.03 (0.93-1.13) p=0.60	1.05 (0.99-1.10) p=0.09	1.00 (0.93-1.05) p=0.72
Log <sub>e</sub> distance to the nearest road (m) <sup>f</sup>	1.01 (0.86-1.17) p=0.94	1.10 (0.88-1.38) p=0.39	1.01 (0.81-1.27) p=0.90	1.21 (0.95-1.55) p=0.13	- <sup>e</sup>	- <sup>e</sup>	<b>1.11 (1.03-1.21)</b> <b>p=0.01</b>	0.98 (0.89-1.08) p=0.69
NO <sub>2</sub> per 10 µg/m <sup>3</sup> increase (year of transplant)	0.95 (0.80-1.12) p=0.51	0.89 (0.76-1.04) p=0.13	0.99 (0.81-1.20) p=0.90	1.00 (0.84-1.18) p=0.97	1.02 (0.92-1.13) p=0.71	0.90 (0.81-1.01) p=0.07	<b>0.91 (0.85-0.99)</b> <b>p=0.02</b>	1.00 (0.93-1.07) p=0.94
NO <sub>x</sub> per 20 µg/m <sup>3</sup> increase (year of transplant)	0.99 (0.86-1.15) p=0.92	0.93 (0.81-1.06) p=0.27	1.05 (0.88-1.25) p=0.60	1.00 (0.86-1.15) p=0.94	1.03 (0.94-1.12) p=0.58	0.91 (0.82-1.00) p=0.06	<b>0.92 (0.86-0.99)</b> <b>p=0.02</b>	0.99 (0.94-1.05) p=0.82
PM <sub>10</sub> : per 10 µg/m <sup>3</sup> increase (year of transplant)	1.35 (0.88-2.08) p=0.17	1.25 (0.69-2.28) p=0.46	0.78 (0.40-1.52) p=0.47	0.69 (0.32-1.47) p=0.34	0.92 (0.65-1.29) p=0.62	0.82 (0.52-1.28) p=0.37	0.81 (0.63-1.03) p=0.08	1.16 (0.87-1.54) p=0.31
PM <sub>2.5</sub> : per 5 µg/m <sup>3</sup> increase (annual average 2010)	0.93 (0.45-1.91) p=0.84	0.74 (0.35-1.52) p=0.41	1.08 (0.42-2.73) p=0.88	0.81 (0.32-2.02) p=0.64	1.00 (0.61-1.62) p=0.98	0.65 (0.38-1.10) p=0.11	0.75 (0.53-1.07) p=0.11	0.98 (0.71-1.36) p=0.90

<sup>a</sup> Lung adjusted for age, sex, transplant year, SES, donor age and smoking status and stratified by transplant type (single/double)

<sup>b</sup> Heart adjusted for recipient age, sex, transplant year, SES, donor age and smoking status

<sup>c</sup> Liver adjusted for sex, transplant year, SES, donor age and smoking status and stratified by recipient age (quartiles)

<sup>d</sup> Kidney adjusted for sex, SES and smoking status and stratified by recipient age (quartiles) and transplant year (<2003, 2003-2005, >2006)

<sup>e</sup> The exposure violated the assumption of proportional hazards.

<sup>f</sup> Continuous analysis based on log<sub>e</sub> distance. HR>1 indicates an increased risk of transplant failure per log<sub>e</sub> increase of distance to road.

Table 2S: Hazard ratios (95% confidence intervals) from multivariable analyses restricting year of lung transplant to 2000-2004.

Pollutants	Lung (n=360)	
	Adjusted HR <sup>a</sup> (95% CI)	p value
Log <sub>e</sub> distance to major road (m) <sup>c</sup>	1.06 (0.95-1.18)	0.29
Log <sub>e</sub> distance to nearest road (m) <sup>c</sup>	1.07 (0.91-1.25)	0.44
NO <sub>2</sub> per 10 µg/m <sup>3</sup> increase (year of transplant)	0.91 (0.79-1.05)	0.20
NO <sub>x</sub> per 20 µg/m <sup>3</sup> increase (year of transplant)	0.94 (0.83-1.06)	0.32
PM <sub>10</sub> : per 10 µg/m <sup>3</sup> increase (year of transplant) <sup>b</sup>	1.21 (0.72-2.03)	0.48
PM <sub>2.5</sub> : per 5 µg/m <sup>3</sup> increase (annual average 2010) <sup>b</sup>	0.70 (0.36-1.33)	0.28

<sup>a</sup> Lung adjusted for age, sex, transplant year, SES, donor age and smoking status and stratified by transplant type (single/double)

<sup>b</sup> n=333

<sup>c</sup> Continuous analysis based on log<sub>e</sub> distance. HR>1 indicates an increased risk of transplant failure per log<sub>e</sub> increase of distance to road.

Table 3S: Hazard ratios (95% confidence intervals) from multivariable analyses for i) restricted to those with PM<sub>10</sub> exposure >20µg/m<sup>3</sup>, ii) using major road length within a 100m buffer as exposure and iii) restricted to those resident in the south east of England.

	Lung		
	PM <sub>10</sub> >20µg/m <sup>3</sup>	length within a 100m buffer'	Resident in the South east of England
	Adjusted HR <sup>a</sup> (95% CI) (n=439)	Adjusted HR <sup>a</sup> (95% CI) (n=737)	Adjusted HR <sup>a</sup> (95% CI) (n=156)
<b>Pollutants</b>			
Major road		1.00 (0.98-1.01) p=0.58	
Log <sub>e</sub> distance to major road (m) <sup>b</sup>			1.07 (0.85-1.34) p=0.67
Log <sub>e</sub> distance to nearest road (m) <sup>b</sup>			1.06 (0.78-1.43) p=0.71
NO <sub>2</sub> per 10 µg/m <sup>3</sup> increase (year of transplant)			1.00 (0.98-1.02) p=0.99
NO <sub>x</sub> per 20 µg/m <sup>3</sup> increase (year of transplant)			1.00 (0.99-1.01) p=0.79
PM <sub>10</sub> : per 10 µg/m <sup>3</sup> increase (year of transplant)	1.04 (0.99-1.10) p=0.15		1.00 (0.92-1.09) p=0.99
PM <sub>2.5</sub> : per 5 µg/m <sup>3</sup> increase (annual average 2010)			0.97 (0.77-1.22) p=0.76

<sup>a</sup> Lung adjusted for age, sex, transplant year, SES, donor age and smoking status and stratified by transplant type (single/double)

<sup>b</sup> Continuous analysis based on log<sub>e</sub> distance. HR>1 indicates an increased risk of transplant failure per log<sub>e</sub> increase of distance to road.

### Funding/Support

The Authors did not receive any specific funding for this work

The work of the UK Small Area Health Statistics Unit is funded by Public Health England as part of the MRC-PHE Centre for Environment and Health, funded also by the UK Medical Research Council.

We the undersigned declare that this manuscript is original, has not been published before and is not currently being considered for publication elsewhere.

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Susie Schofield	Susie Schofield	19/09/2017	There is no conflict of interest.
Dave Collett	Dave Collett	19/09/2017	There is no conflict of interest.
Daniela Fecht	Daniela Fecht	19/09/2017	There is no conflict of interest.
Kees De Hoogh	Kees De Hoogh	19/09/2017	There is no conflict of interest.
Anna L Hansell	Anna L Hansell	19/09/2017	There is no conflict of interest.
John Dark	John Dark	19/09/2017	There is no conflict of interest.
Paul Cullinan	Paul Cullinan	19/09/2017	There is no conflict of interest.

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