



# An association of particulate air pollution and traffic exposure with mortality after lung transplantation in Europe

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**Long-term residential air pollution/traffic exposure associated with CLAD and survival after lung transplantation** <http://ow.ly/lzxj304uA5k>

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**ABSTRACT** Air pollution from road traffic is a serious health risk, especially for susceptible individuals. Single-centre studies showed an association with chronic lung allograft dysfunction (CLAD) and survival after lung transplantation, but there are no large studies.

13 lung transplant centres in 10 European countries created a cohort of 5707 patients. For each patient, we quantified residential particulate matter with aerodynamic diameter  $\leq 10 \mu\text{m}$  (PM<sub>10</sub>) by land use regression models, and the traffic exposure by quantifying total road length within buffer zones around the home addresses of patients and distance to a major road or freeway.

After correction for macrolide use, we found associations between air pollution variables and CLAD/mortality. Given the important interaction with macrolides, we stratified according to macrolide use. No associations were observed in 2151 patients taking macrolides. However, in 3556 patients not taking macrolides, mortality was associated with PM<sub>10</sub> (hazard ratio 1.081, 95% CI 1.000–1.167); similarly, CLAD and mortality were associated with road lengths in buffers of 200–1000 and 100–500 m, respectively (hazard ratio 1.085–1.130). Sensitivity analyses for various possible confounders confirmed the robustness of these associations.

Long-term residential air pollution and traffic exposure were associated with CLAD and survival after lung transplantation, but only in patients not taking macrolides.

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## Introduction

There is a well-established relationship between long-term exposure to particulate matter (particulate matter with aerodynamic diameter  $\leq 2.5 \mu\text{m}$  (PM<sub>2.5</sub>) and  $\leq 10 \mu\text{m}$  (PM<sub>10</sub>)) and mortality in the general and susceptible population.

Lung transplant patients are of particular interest, as they could be extremely vulnerable due to their constant immunocompromised condition. Lung transplantation is the ultimate treatment option for patients with end-stage pulmonary disease, such as emphysema, pulmonary fibrosis or cystic fibrosis (CF) [1]. With a median survival of 5 years, the long-term survival after lung transplantation remains low compared with other solid-organ transplantations [2], mainly due to a higher incidence of chronic lung allograft dysfunction (CLAD) (incidence of 50% at 5 years post-transplant) [3]. Currently, the only treatment able to influence pulmonary function after CLAD diagnosis is macrolide therapy, which reduces/postpones the incidence of CLAD in ~35% of patients [4]. Apart from small single-centre studies, showing an association with CLAD and survival, the role of long-term exposure in lung transplant recipients has not been established [5, 6].

We assessed whether particulate air pollution and traffic exposure were associated with CLAD and mortality in lung transplant patients from 13 major lung transplant centres in 10 European countries. We hypothesised that road density within buffer zones and PM<sub>10</sub> at the home addresses of patients would be associated with CLAD and mortality, but that this would be influenced by the use of macrolides as we previously showed that azithromycin protected against health effects induced by air pollution.

## Material and methods

### Study population

The target population consisted of all subjects having undergone a lung transplantation between 1987 and 2012 in 13 major lung transplant centres (Barcelona, Copenhagen, Essen, Groningen, Hannover, Leuven, Munich, Newcastle, Oslo, Pavia, Utrecht, Vienna and Zurich) from 10 different European countries and with follow-up data available until death or December 31, 2013. This study was approved by the central ethical committee in Leuven and by every participating centre's ethical committee (ML8653). All variables collected by the individual centres were anonymised and sent to the coordinating centre (Leuven) for analysis. Study variables included age, sex, socioeconomic status (occupation), smoking status pre-transplant, home address at the time of transplantation, underlying lung disease, date of transplantation, type of transplantation (single lung, sequential single lung, heart–lung), date of CLAD, date of all-cause mortality and macrolide usage (either azithromycin or clarithromycin). The general protocol for azithromycin usage is 250 mg three times per week and clarithromycin is given daily (500–1000 mg). All data was gathered by retrospective patient chart analysis. CLAD was defined as every irreversible decline in pulmonary function of at least 20% in the absence of an identifiable cause, as evidenced by individual chart analysis of every patient by the treating physician [7]. Given the lack of uniform international criteria and the long period of patient inclusion, we did not subdivide our patients in terms of classical bronchiolitis obliterans syndrome and restrictive CLAD. Socioeconomic status was coded using a scale from low to moderate to high according to the UK Office of Population Censuses and Surveys [8]. Exclusion criteria were the lack of a home address, post-transplant survival <90 days, distance to transplant centre >700 km and lack of key covariate data (online supplementary figure E1).

### Exposure assessment

The residential addresses of all lung transplant patients were geocoded (ArcGIS10; www.esri.com) and linked with average levels of PM<sub>10</sub> ( $\mu\text{g}\cdot\text{m}^{-3}$ ). We used an existing European Union (EU)-wide map of PM<sub>10</sub> modelled on a 100×100 m resolution for 2007 based on land use regression, using predictor variables from EU-wide databases with satellite-derived particulate matter estimates, north–south trend, land use, roads and altitude [9]. Particulate matter data for Switzerland were not available within this

study, although we could quantify all other variables. Residential proximity to major roads or freeways and total length of roads within different buffers (50, 100, 200, 500 and 1000 m) around home addresses of patients were estimated as detailed in online supplementary figure E2.

### Statistical analysis

For the cohort-specific analysis, we performed Cox proportional hazards regression using SAS version 9.3 (SAS Institute, Cary, NC, USA). Censoring was done at the time of death/re-transplantation, loss of follow-up or end of follow-up, whichever came first. All hazard ratio (HR) values shown are given per interquartile range (IQR) increment. Patients with a re-transplantation were censored at the moment of re-transplantation (*i.e.* loss of graft) and the re-transplantation was analysed as a separate event (as the donor organ is different). Particulate matter exposure was analysed as a linear variable, traffic exposure was analysed in each buffer zone, and potential confounders were identified *a priori* (age, sex, type of transplantation, underlying lung disease and date of transplantation) and included in the model. We only included cases where all these data were available in our final model. The effect of lung transplant centre on the Cox model was taken into account as a random effect and separate subanalyses were performed for every centre. Sensitivity subanalyses were performed with lung transplant centre as a fixed effect, omission of each single centre to determine centre effect, re-transplantation status, socioeconomic status, date of lung transplantation, time of macrolide initiation and smoking history. The latter variables were not complete; therefore, the exact number of patients used for analysis is explicitly stated.  $p < 0.05$  was considered significant.

### Results

5707 patients were included in this study and contributed 33 202 patient-years of follow-up, with a median follow-up of 5.6 years. Of these 5707 patients, 2626 (46.0%) developed CLAD and 2577 patients (45.2%) died. Median time to CLAD was 6.4 years, while median survival was 8.9 years; however, patients with early death were excluded from this analysis, which will significantly impact survival. Age, sex, underlying disease and type of transplant were available for all subjects. Concentrations of air pollutants varied between and within study centres (figure 1). Specific characteristics per centre and exposure characteristics are shown in online supplementary table E1. We considered *a priori* that macrolide therapy could modify the relation between air pollution and outcomes, and we therefore divided the patients in two groups, according to whether they had ever (2151 patients (37.7%)) or never (3556 patients (62.3%)) been chronically treated with azithromycin or clarithromycin (table 1). This division was based on previous literature on the beneficial effect of azithromycin in lung transplant patients [4] and the protective effect of azithromycin on air pollution [6]. We also performed analysis without stratification according to macrolide usage, implementing macrolide usage (yes/no) as a covariate (online supplementary table E2); however, these results should be interpreted with caution as we showed significant interaction between macrolides and air pollution variables

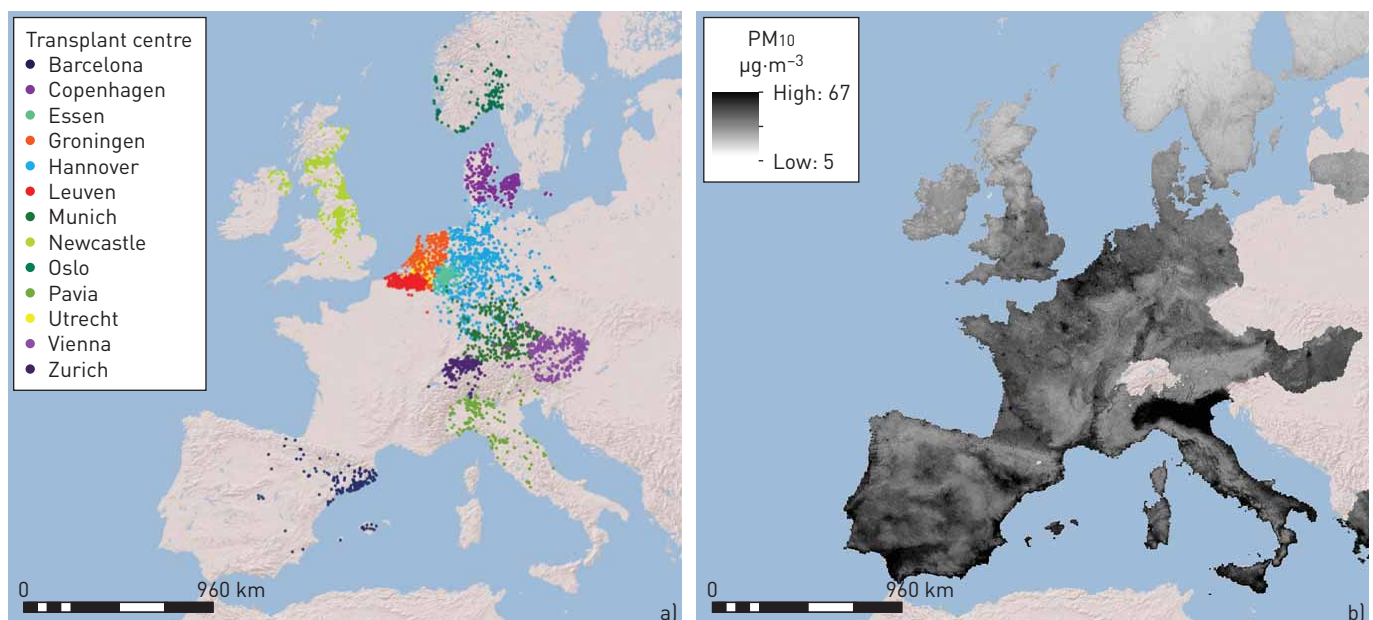


FIGURE 1 a) Geographical distribution of the lung transplant patients from the 13 different lung transplant centres in 10 different European countries. Each point represents a single patient. b) Average particulate matter with aerodynamic diameter  $\leq 10 \mu\text{m}$  ( $\text{PM}_{10}$ ) concentration in Western Europe. No  $\text{PM}_{10}$  values were available for Zurich.

TABLE 1 Characteristics of the lung transplant cohort divided into patients taking macrolides or not

	Macrolide-free group	Macrolide group
<b>Patients</b>	3556	2151
<b>Recipient age years</b>	46.5±14	45.5±13.8
<b>Male</b>	1836 [52]	1146 [53]
<b>Underlying disease</b>		
Emphysema	1535 [43]	798 [37]
Cystic fibrosis	707 [20]	474 [22]
Interstitial lung fibrosis	737 [21]	502 [23]
Pulmonary arterial hypertension	274 [8]	164 [8]
Other	303 [9]	213 [10]
<b>Type of transplantation</b>		
Double or heart-lung	2559 [72]	1652 [77]
Single	997 [28]	499 [23]
<b>Year of transplantation</b>		
1987–1995	479 [14]	94 [4]
1996–2000	710 [20]	254 [12]
2001–2005	936 [26]	644 [30]
2006–2011	1431 [40]	1159 [54]
<b>CLAD</b>		
No	2185 [62]	891 [40]
Yes	1367 [39]	1259 [60]
Unknown	5 [0]	1 [0]
<b>Death or graft loss</b>	1937 [55]	640 [30]

Data are presented as n, mean±SD or n (%). Some of the data do not total 100% due to rounding errors. CLAD: chronic lung allograft dysfunction.

(online supplementary table E3). Macrolides were started at a median (IQR) time of 26 (9–63) months post-transplant and were started as a treatment for CLAD in 782 out of 2107 (37.1%) patients where the start date was available. A total of 640 (29.8%) patients died in the macrolide group and 1937 (54.5%) patients died in the macrolide-free group. No association between pollution variables and mortality could be detected within the cohort of patients treated with macrolides (table 2). An association of all-cause mortality with road length in the 100, 200 and 500 m buffer zones and a trend for the 50 m buffer zone (table 2) were observed. Figure 2a and b shows the HR values for mortality and road length in a 200 m buffer zone and PM<sub>10</sub> for each centre. However, in the macrolide-free group, PM<sub>10</sub> (per IQR increment; HR 1.081, 95% CI 1.000–1.167) was significantly associated with mortality. A 10 µg·m<sup>-3</sup> PM<sub>10</sub> increase was associated with a 13.8% increased risk of mortality. Analysing PM<sub>10</sub> in categories by quintile of exposure (lowest quintile (Q1) as reference) demonstrated that PM<sub>10</sub> >20 µg·m<sup>-3</sup> implied a higher risk of dying (Q3+Q4+Q5 *versus* Q1) (figure 3b). Subdividing the road length in a 200 m buffer zone in quintiles (lowest quintile as reference) showed that it was mainly the patients within the highest quintile of road length who had the highest risk of dying (figure 3a and online supplementary table E4).

CLAD was present in 60.1% of the macrolide group and 38.5% of the macrolide-free group. Analysis of the subgroup of patients taking macrolides showed no association of CLAD with any of the studied pollution variables except for PM<sub>10</sub>, which showed an inverse association (table 2). However, in patients not taking macrolides, we observed an association between CLAD and road length in 200, 500 and 1000 m buffer zones around the home addresses of patients (table 2). Figure 2a demonstrates the HR values calculated for CLAD and road length in the 200 m buffer zone per centre. We could not detect an association between CLAD and PM<sub>10</sub>, road length in 50 and 100 m buffer zones, and distance to a major road or freeway, although PM<sub>10</sub> tended to be significant (figure 2d). BHINDER *et al.* [5] previously showed an association between patients living <100 m from a highway and CLAD, but not mortality; we observed a similar association with CLAD, although not significant (HR 1.249, 95% CI 0.994–1.570, p=0.056), but no effect on survival (HR 0.931, 95% CI 0.760–1.140, p=0.49). Subdividing road length in a 200 m buffer zone in quintiles showed that it was mainly patients within the highest quintile of road length who had the highest risk of CLAD (figure 3c); for PM<sub>10</sub> this was mostly Q3 and Q5 (figure 3d). Distance to major road or highway was not associated with any of the outcomes.

Further sensitivity analyses were performed for road lengths in a 200 m buffer zone and for PM<sub>10</sub>; analysis with road length in the 100 and 500 m buffer zones did not change the results. Subanalysis was performed for the possible confounding effect of smoking and socioeconomic status as information was not available for the

TABLE 2 Overview of the main results investigating the association of particulate air pollution and traffic exposure with mortality and chronic lung allograft dysfunction (CLAD) in lung transplant patients

		IQR	Macrolide-free group		Macrolide group	
			HR (95% CI)	p-value	HR (95% CI)	p-value
Death <sup>#</sup>						
Road length in buffer zone						
50 m	108 m	1.055 [0.955–1.112]	0.076	0.989 [0.824–1.047]		0.23
100 m	279 m	1.111 [1.025–1.202]	0.0094 <sup>+</sup>	1.003 [0.875–1.150]		0.95
200 m	752 m	1.094 [1.030–1.779]	0.0054 <sup>+</sup>	0.978 [0.872–1.094]		0.66
500 m	4092 m	1.085 [1.000–1.130]	0.0356 <sup>+</sup>	1.085 [0.960–1.226]		0.15
1000 m	15403 m	1.047 [0.985–1.131]	0.12	1.080 [0.970–1.202]		0.17
PM <sub>10</sub>	6 µg·m <sup>-3</sup>	1.081 [1.000–1.167]	0.049 <sup>+</sup>	0.982 [0.859–1.120]		0.77
Distance to freeway	1233 m	0.987 [0.964–1.012]	0.16	1.000 [0.883–1.025]		0.31
Distance to major road	241 m	1.000 [0.976–1.024]	0.68	0.976 [0.907–1.000]		0.092
CLAD <sup>†</sup>						
Road length in buffer zone						
50 m	108 m	1.025 [0.956–1.099]	0.49	0.997 [0.927–1.073]		0.93
100 m	279 m	1.076 [0.975–1.190]	0.14	0.943 [0.848–1.048]		0.28
200 m	752 m	1.110 [1.023–1.204]	0.0114 <sup>+</sup>	0.949 [0.872–1.030]		0.21
500 m	4092 m	1.130 [1.042–1.226]	0.0010 <sup>+</sup>	0.960 [0.884–1.085]		0.62
1000 m	15403 m	1.113 [1.031–1.202]	0.0115 <sup>+</sup>	0.970 [0.897–1.063]		0.48
PM <sub>10</sub>	6 µg·m <sup>-3</sup>	1.093 [0.988–1.208]	0.076	0.886 [0.803–0.976]		0.013 <sup>+</sup>
Distance to freeway	1233 m	0.988 [0.964–1.012]	0.26	1.012 [1.000–1.038]		0.13
Distance to major road	241 m	1.000 [0.976–1.024]	0.73	1.024 [0.976–1.049]		0.44

IQR: interquartile range; HR: hazard ratio; PM<sub>10</sub>: particulate matter with aerodynamic diameter ≤10 µm. <sup>#</sup>: macrolide-free group n=3556, macrolide group n=2151; <sup>†</sup>: macrolide-free group n=3551, macrolide group n=2150; <sup>+</sup>: statistically significant (p<0.05). All parameters were analysed for every IQR increase. In the Cox analysis we corrected for patient age, patient sex, native disease (chronic obstructive pulmonary disease *versus* interstitial lung disease *versus* cystic fibrosis and bronchiectasis *versus* pulmonary hypertension *versus* others), type of transplantation (single *versus* sequential single) and date of transplantation (1987–1995 *versus* 1996–2000 *versus* 2001–2005 *versus* 2006–2011).

entire cohort. This analysis is shown in online supplementary table E5, and demonstrates that both smoking and socioeconomic status did not influence the association between mortality/CLAD and either road length or PM<sub>10</sub>. The time of macrolide initiation could be an important confounder; consequently, we subdivided our cohort of macrolide users into macrolide users at/after CLAD diagnosis (n=782) and contrasted these patients with macrolide users before CLAD diagnosis or never developing CLAD (n=1325), with 44 patients not having the exact date of macrolide initiation recorded. Stratification demonstrates that the deleterious effect of air pollution in macrolide users is absent in patients taking macrolides before CLAD or not developing CLAD, while a trend towards an association is observed in patients who started with macrolide therapy at/after CLAD diagnosis (*i.e.* no protective effect on CLAD development was possible as diagnosis was made at/after initiation and therefore macrolides were started “too late”). A model without transplant centres, to prevent overcorrection for macrolide strategy, demonstrated that air pollution increased the risk of CLAD and death in patients who started macrolides at/after CLAD diagnosis (online supplementary table E6). As macrolide therapy can be started any time after transplant, we also analysed macrolide usage as a time-dependent variable (online supplementary table E7), confirming the increased risk of death and CLAD in patients not taking macrolides. Finally, we performed an analysis where we censored CLAD and mortality for date of macrolide initiation, which confirmed that air pollution variables are associated with CLAD-free (HR 1.005, 95% CI 1.000–1.011) and overall survival (HR 1.012, 95% CI 1.003–1.021).

The distribution of road lengths varied between centres (online supplementary figure E3). A subsequent sensitivity analysis for centre as an indicator variable (fixed effect) instead of a random effect variable demonstrated that the association between road length in the 200 m buffer zone and either mortality (HR 1.086, 95% CI 1.015–1.161) or CLAD (HR 1.110, 95% CI 1.023–1.204) remained unchanged, although there was a pronounced difference in mortality and CLAD rate across the centres (p<0.0001). Additional analysis to exclude an effect by a specific centre was performed by removing one centre at a time and performing the analysis with the 12 remaining centres. These analyses confirmed the consistency of our results (online supplementary figure E4).

We excluded patients living >700 km from their transplant centre, as it may be a confounder, given that worse survival has been demonstrated for patients living further from their transplant centre after kidney and stem cell transplantation [10, 11]. Analyses of different thresholds are shown in online supplementary



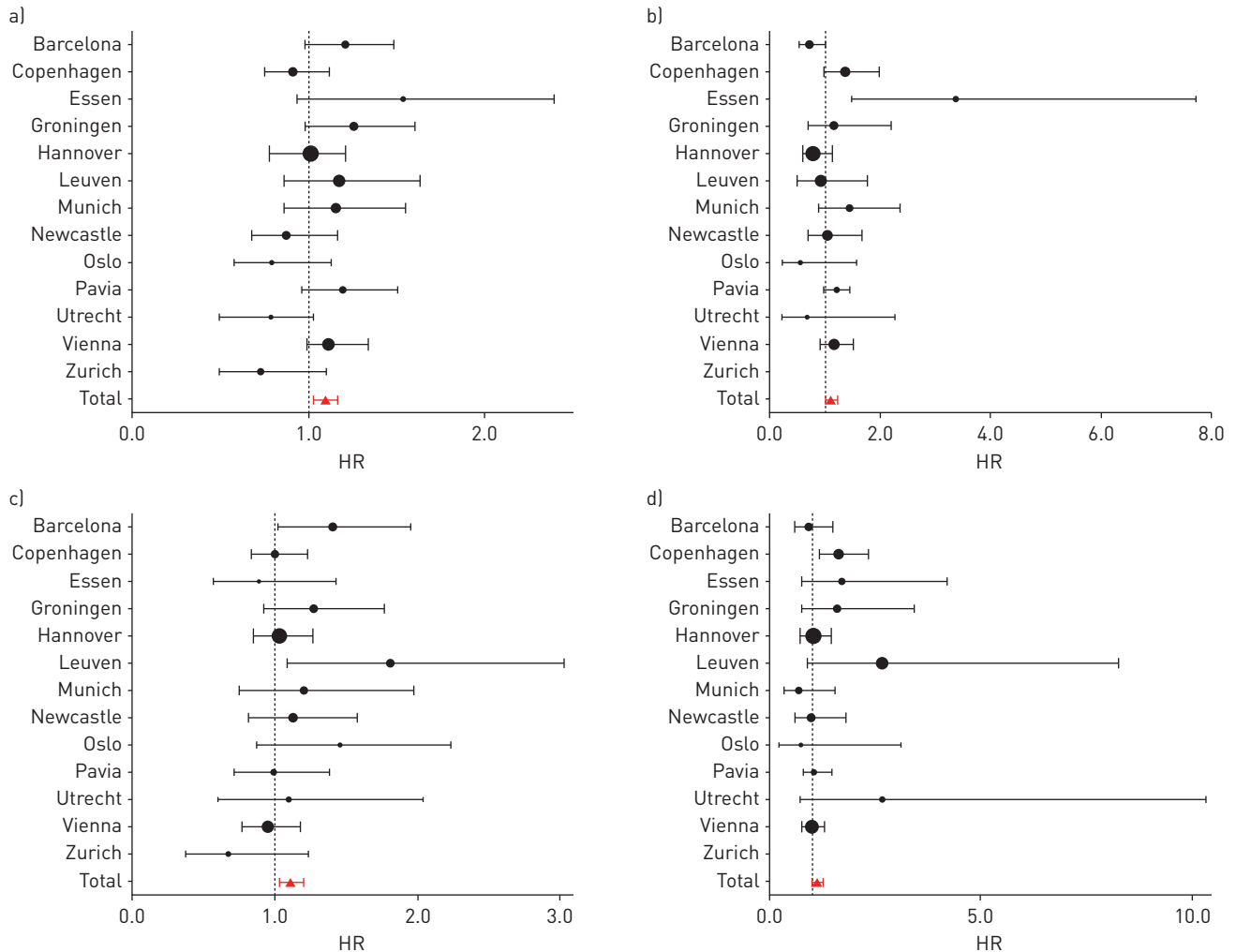


FIGURE 2 Hazard ratio (HR) values for a) all-cause mortality and road length within a 200 m buffer zone around the patient's home address, b) all-cause mortality and particulate matter with aerodynamic diameter  $\leq 10 \mu\text{m}$  (PM<sub>10</sub>), c) CLAD and road length in a 200 m buffer region, and d) CLAD and PM<sub>10</sub>. Each HR is per interquartile range increase. The HR values shown are from the macrolide-free group and are corrected for date of lung transplantation, type of transplantation, underlying disease, sex and age. No PM<sub>10</sub> values were available for Zurich. The size of the signal reflects the number of subjects and the lines represent the 95% confidence interval.

table E8. In order to include as many patients as possible, we decided to use a threshold of 700 km from the transplant centre.

Sensitivity analysis was also performed using only patients transplanted after 1997 as we used PM<sub>10</sub> maps of 2007. In patients not taking macrolides ( $n=2959$ ), the association between road length and overall survival (HR 1.013, 95% CI 1.003–1.024,  $p=0.011$ ) and CLAD-free survival (HR 1.014, 95% CI 1.001–1.027,  $p=0.035$ ) persisted, while there was no association in macrolide users.

Regarding re-transplantation, we omitted all data regarding the second transplantation from those patients ( $n=58$ ) and considered the moment of re-transplantation as death (as the graft is lost), and demonstrated that road length in the 200 m buffer zone remained associated with both survival (HR 1.093, 95% CI 1.023–1.169) and CLAD (HR 1.119, 95% CI 1.030–1.213).

The World Health Organization (WHO) recommends limiting the annual mean exposure to PM<sub>10</sub> to a maximum of  $20 \mu\text{g}\cdot\text{m}^{-3}$ ; therefore, we analysed the effect of road length in buffer zones around home addresses separately for patients not taking macrolides experiencing PM<sub>10</sub>  $<20$  or  $\geq 20 \mu\text{g}\cdot\text{m}^{-3}$ . The road length in the 200 m buffer zone was only associated with mortality in patients exposed to PM<sub>10</sub>  $\geq 20 \mu\text{g}\cdot\text{m}^{-3}$  (2605 patients; HR 1.119, 95% CI 1.038–1.204) and not in patients exposed to PM<sub>10</sub>  $<20 \mu\text{g}\cdot\text{m}^{-3}$  (951 patients; HR 0.941, 95% CI 0.808–1.094). Similarly, for CLAD an association was only present for the patients exposed to PM<sub>10</sub>  $\geq 20 \mu\text{g}\cdot\text{m}^{-3}$  (2598 patients; HR 1.119, 95% CI 1.015–1.231) and no association was observed for the patients exposed to PM<sub>10</sub>  $<20 \mu\text{g}\cdot\text{m}^{-3}$  (945 patients; HR 0.993, 95% CI 0.832–1.187).

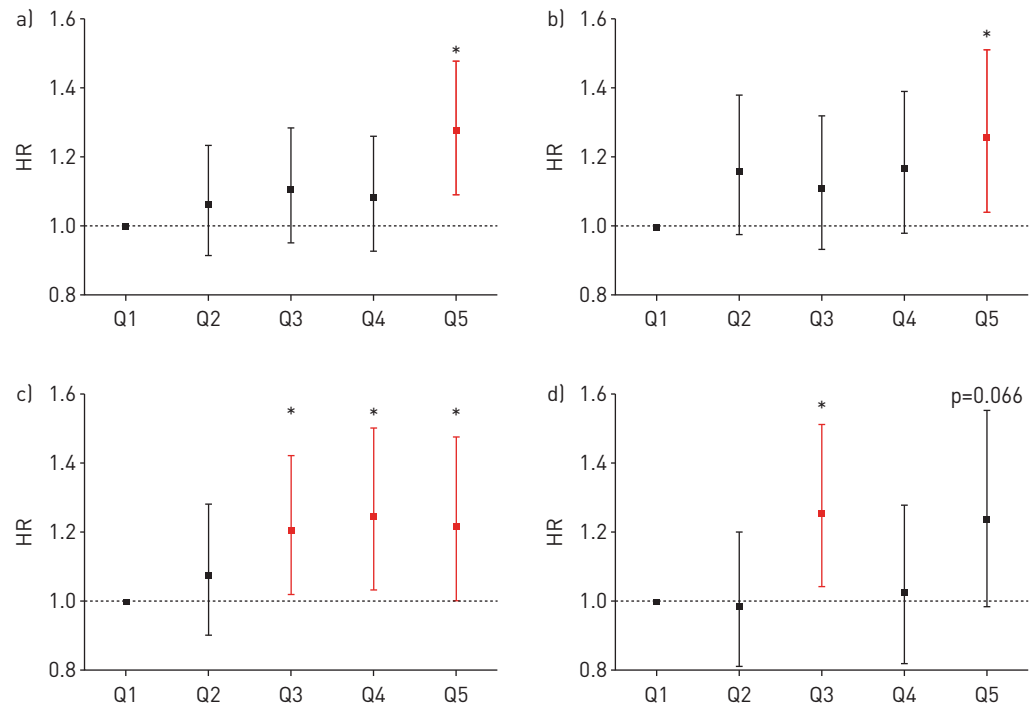


FIGURE 3 Distribution of the hazard ratio (HR) for a) all-cause mortality and b) CLAD associated with quintiles of road length in a 200 m buffer zone around the patient's home address, and c) mortality and d) CLAD associated with quintiles of particulate matter with aerodynamic diameter  $\leq 10 \mu\text{m}$  (PM<sub>10</sub>). Quintile 1 (Q1) is used as reference in all these analyses. PM<sub>10</sub> quintiles are: Q1  $< 19 \mu\text{g}\cdot\text{m}^{-3}$ ; Q2  $\geq 19$  and  $< 21 \mu\text{g}\cdot\text{m}^{-3}$ ; Q3  $\geq 21$  and  $< 24 \mu\text{g}\cdot\text{m}^{-3}$ ; Q4  $\geq 24$  and  $< 26 \mu\text{g}\cdot\text{m}^{-3}$ ; Q5  $\geq 26 \mu\text{g}\cdot\text{m}^{-3}$ ; road length quintiles in a 200 m buffer region are: Q1  $< 763$  m; Q2  $\geq 763$  and  $< 1075$  m; Q3  $\geq 1075$  and  $< 1323$  m; Q4  $\geq 1323$  and  $< 1667$  m; Q5  $\geq 1667$  m. The HR (95% CI) values are shown in online supplementary table E2. \*: statistically significant ( $p < 0.05$ ).

## Discussion

This is the first study investigating the effect of air pollution and traffic exposure in a large multicentre cohort of lung transplant patients geographically dispersed over almost the entire European continent. Interestingly, the effect of air pollution was not limited to mortality and we also found an association with CLAD. However, this was only observed in patients not taking macrolides, suggesting a protective role of macrolides against air pollution.

This seemingly protective effect of macrolides on air pollution is not unexpected as these drugs are known to reduce innate (neutrophilic) immune activation in many chronic respiratory disorders, such as chronic obstructive pulmonary disease (COPD) [12], CF [13], non-CF bronchiectasis [14], severe asthma [15] and CLAD [4, 16]. More indirect evidence to support a protective effect of macrolides originates from a randomised placebo-controlled trial that demonstrated maintenance azithromycin therapy is able to prevent COPD exacerbations [12], which are also linked with short-term exposure to air pollution [17]. Moreover, in lung transplantation patients, PM<sub>10</sub> was associated with airway inflammation on transbronchial biopsies and lavage samples, but again only in those patients not taking azithromycin [18]. It might be counter-intuitive that there was a higher CLAD rate in the macrolide group; however, current guidelines propose to start azithromycin as soon as possible after CLAD diagnosis [12]. This explains why the majority of the patients in the macrolide group suffer from CLAD. Stratification of our macrolide cohort according to the time of macrolide initiation provided further support for the protective effect of macrolides. We acknowledge that macrolide usage is an important confounder in this analysis; however, adding macrolide usage to our model binary, as a time-dependent variable, censoring for macrolide start data and stratified analysis according to timing of macrolide start relative to CLAD data all proved that the observed associations are robust.

Our findings corroborate the proposed WHO limit for air pollution, as the effect of long-term air pollution exposure was only found among those patients with exposure to PM<sub>10</sub>  $\geq 20 \mu\text{g}\cdot\text{m}^{-3}$ . Two-thirds of our lung transplant patients were exposed to PM<sub>10</sub> values above the WHO (annual) standard of  $20 \mu\text{g}\cdot\text{m}^{-3}$ . Based on our data, a reduction of the PM<sub>10</sub> concentrations below the WHO recommendation could potentially prevent 9.9% of the observed mortality in lung transplant recipients not taking macrolides. Our observed associations regarding mortality (13.8% increased risk per  $10 \mu\text{g}\cdot\text{m}^{-3}$  PM<sub>10</sub> increase; 6.7% increased risk per

5  $\mu\text{g}\cdot\text{m}^{-3}$  PM<sub>10</sub> increase) are somewhat more pronounced than in other similar studies. The ESCAPE (European Study of Cohorts for Air Pollution Effects) study found a 4% increased risk in mortality for every 5  $\mu\text{g}\cdot\text{m}^{-3}$  increase in PM<sub>10</sub> [19]. Similarly, a recent study in the Netherlands showed an 8% increased risk of nonaccidental mortality for every 10  $\mu\text{g}\cdot\text{m}^{-3}$  increase in PM<sub>10</sub> [20].

The strength of our study is the unique, large cohort of lung transplant patients spread over a large geographical area and the close follow-up of these patients in combination with uniform measures of air pollution exposure. A limitation of the study is the incomplete data for some variables (e.g. socioeconomic status and smoking status); however, when sensitivity analyses were restricted to cohorts for which this information was available, the estimates were robust. Although we used a single EU-wide exposure model, exposure misclassification might be cohort-specific due to differences in model performance for different areas across Europe [21]. We used modelled data on PM<sub>10</sub> from 2007 and applied these to home addresses of patients at baseline (for some patients even 20 years earlier), based on evidence showing that the spatial distribution of particulate air pollution is stable over a decade [22]. Indeed, four separate studies have demonstrated that the distribution of particulate air pollution is stable over a decade and that existing land use regression models are good predictors of historical spatial contrasts [22–24]. We conducted a sensitivity analysis using a more recent cohort of patients transplanted after 1997 and saw similar associations. Nevertheless, there have been changes in clinical practice and outcome that could confound our analysis. It would be of interest to associate PM<sub>2.5</sub> with incidence of CLAD and mortality given its important effects in respiratory diseases, but unfortunately this data was not available. Finally, diagnosis of CLAD remains subjective and this might cause bias in a multicentre study [25]. We opted not to subphenotype our patients as there are no uniform diagnostic criteria and, even so, using these on a large retrospective cohort is very difficult.

In conclusion, our findings suggest that a significant association exists between air pollution and mortality/CLAD in lung transplant patients. Additionally, the possible protective effect of macrolide therapy against the detrimental effects of air pollution warrants further investigation.

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