Online Supplement:

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

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All patients transplanted between 1987 and 2012 in 13 LTx centers (n=7307)

No address/coordinates (n=532)

No extractable pollution parameters (n=146)

Patients with air pollution parameters assessable (n=6629)

Early death (<90 days) (n=673)

Residence >700 km from LTx center (n=225)

Eligible patients (n=5731)

Important covariate missing (n=24)

Total study population (n=5707)

Figure E1: A flow chart of the exclusion of patients within this European cohort of lung transplant patients.

home address

1000 m buffer zone

14216 meter road length
in the 1000 m buffer zone

500 m buffer zone

4565 meter road length in the 500 m buffer zone

200 m buffer zone

629 meter road length in the 200 m buffer zone

100 m bufferzone

323 meter road length in the 100 m buffer zone

50 m bufferzone

162 meter road length in the 50 m buffer zone
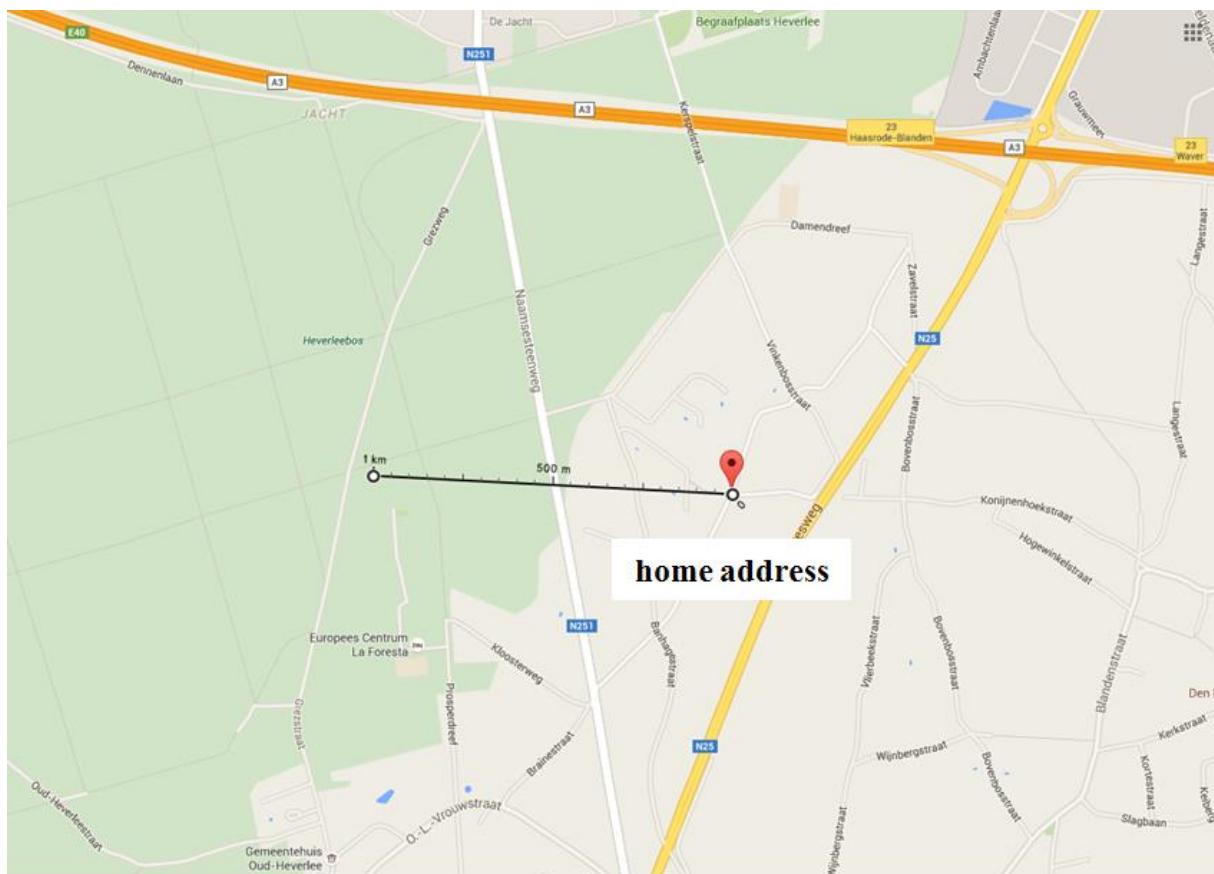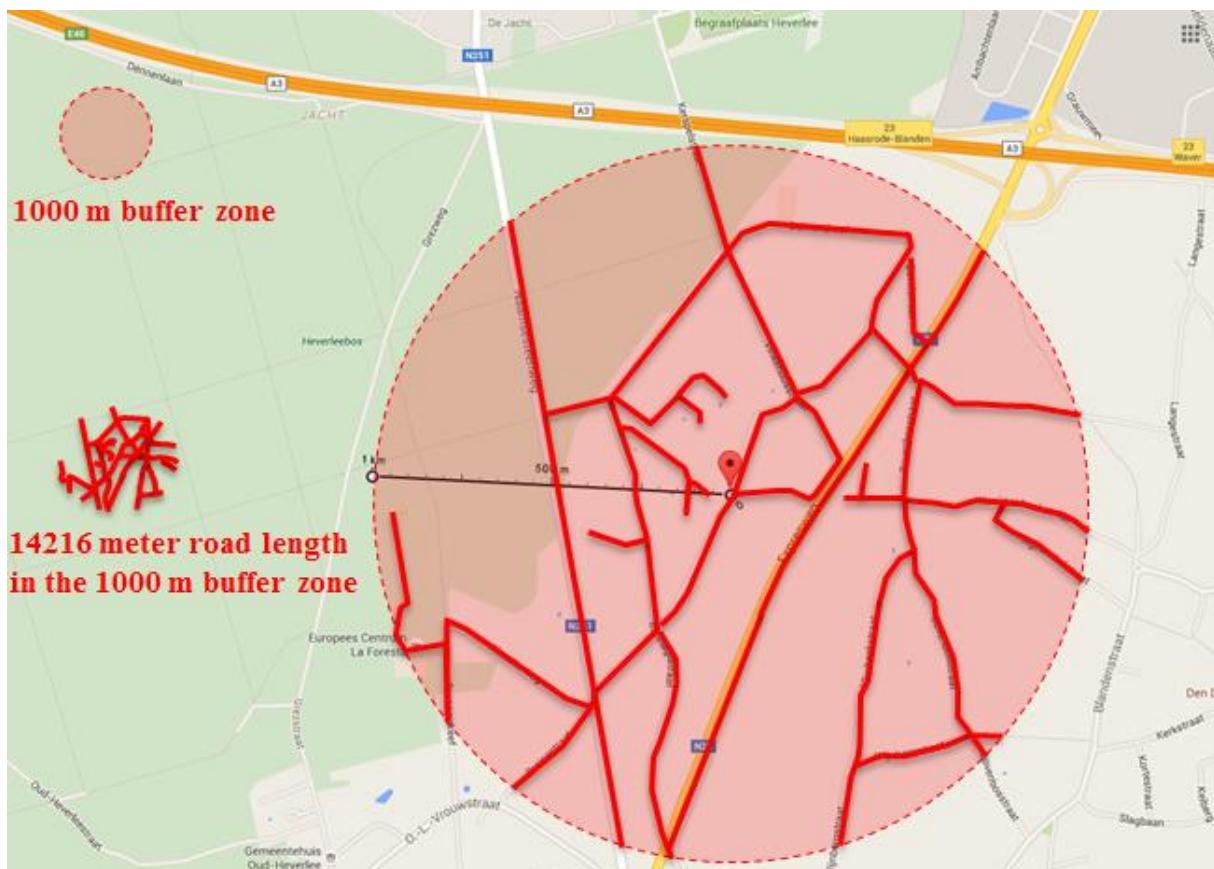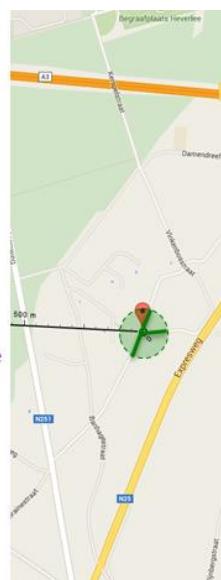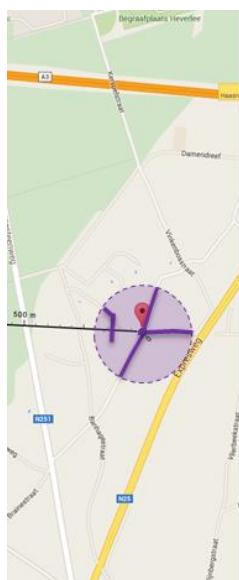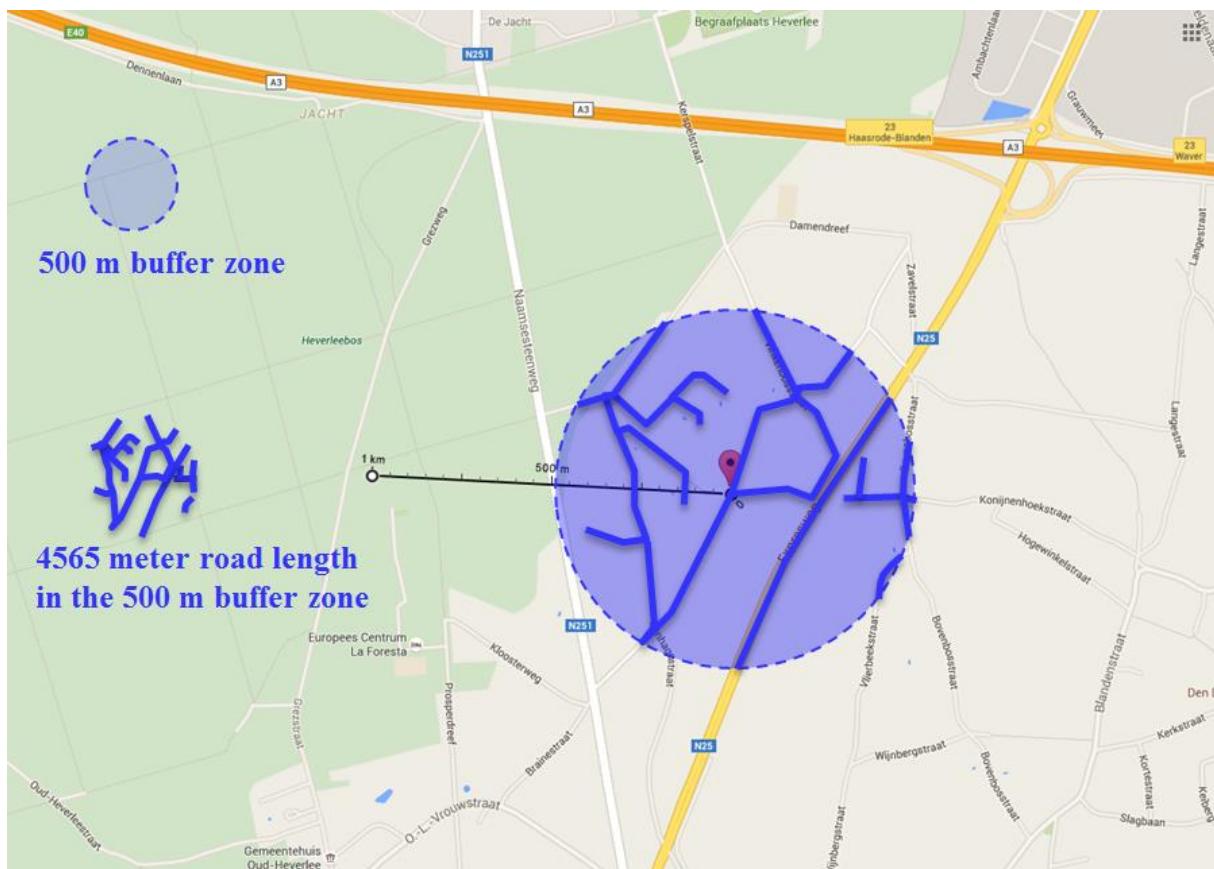
Figure E2: The visual presentation of the buffer zones (50m, 100m, 200m, 500m and 1000m) and their road length around a home address together with the distance to a major road and freeway.
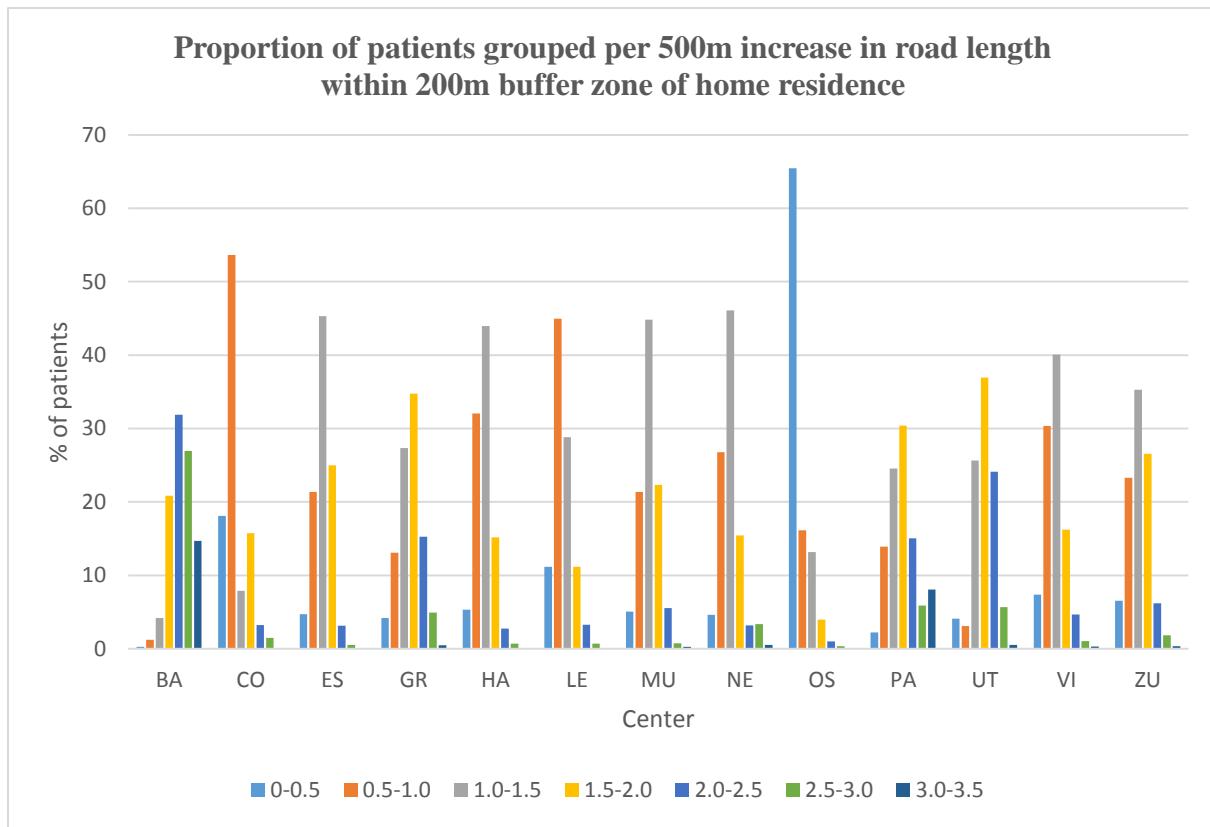
Figure E3: The distribution of the % of patients per center according to the road length in a 200 m buffer zone around patient's residence. Patients are divided into groups having <0.5km of road, 0.5-1.0 km, 1.0-1.5 km, 1.5-2.0 km, 2.0-2.5 km, 2.5-3.0 km and >3.0km within the 200m buffer zone around the patients' residence. BA=Barcelona, CO=Copenhagen, ES=Essen, GR=Groningen, HA=Hannover, LE=Leuven, MU=Munich, NE=Newcastle, OS=Oslo, PA=Pavia, UT=Utrecht, VI=Vienna, ZU=Zurich.
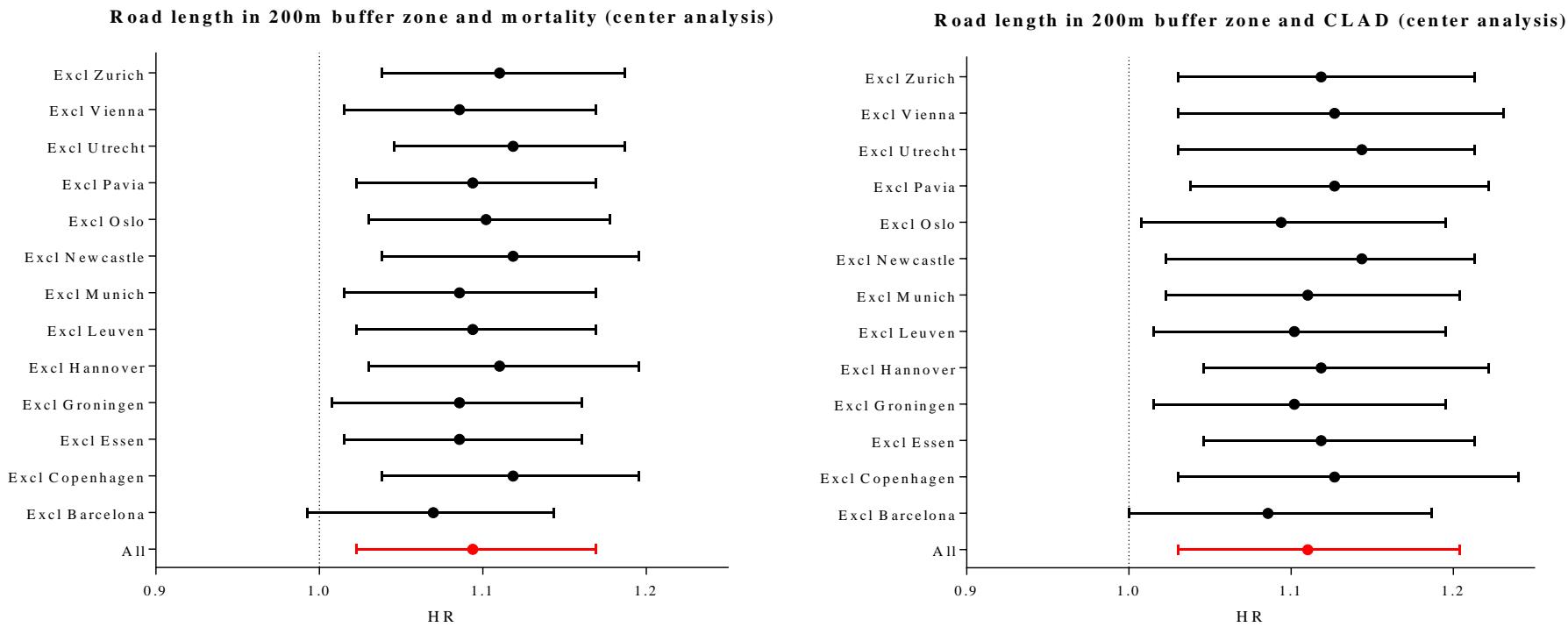
Figure E4: The sensitivity analysis demonstrating the effect of excluding a single center on the association between the road length in a 200 m buffer zone around patients' residence and mortality (left) and CLAD (right). This graph shows the HR and 95% CI of the analysis of the 12 remaining analysis after one-by-one exclusion. We observe that there is no single center that explains the results of our analysis. Exclusion of Barcelona implies the biggest effect as the association of the remaining 12 centers only tends to be significant. This is probably explained by the relatively high pollution in Barcelona contributing a lot of patients to the overall high polluted patients.

Center	Barcelona	Copenhagen	Essen	Groningen	Hannover	Leuven	Munich
N-value	400	533	192	406	1087	583	412
Time of lung transplantation	1997-2011	1992-2011	1999-2011	1990-2011	1987-2011	1991-2011	1990-2011
Age mean (SD)	46 (15)	48 (12)	52 (13)	44 (14)	44 (13)	48 (14)	47 (13)
Gender(male) n-value (%)	230 (58)	247 (46)	109 (57)	196 (48)	587 (54)	309 (53)	195 (47)
Double lung transplantation, n-value (%)	285 (71)	232 (43)	180 (94)	325 (80)	938 (86)	439 (75)	245 (59)
Underlying disease n-value (%)							
Emphysema	151 (38)	351 (66)	95 (51)	173 (43)	328 (30)	270 (46)	119 (29)
Cystic fibrosis	63 (16)	76 (14)	33 (17)	100 (25)	250 (23)	94 (16)	57 (14)
Interstitial lung disease	130 (33)	59 (11)	47 (25)	59 (15)	229 (21)	121 (21)	193 (47)
Pulmonary arterial hypertension	18 (5)	28 (5)	5 (3)	43 (11)	115 (11)	50 (9)	14 (3)
Other	38 (10)	19 (4)	9 (5)	31 (8)	165 (15)	48 (8)	29 (7)
Mean (SD) road length (meter) in a specific buffer zone							
50m buffer zone	179 (73)	71 (57)	93 (50)	105 (58)	85 (52)	100 (49)	93 (59)
100m buffer zone	639 (225)	272 (153)	330 (133)	399 (164)	315 (132)	311 (125)	356 (145)
200m buffer zone	2400 (636)	1046 (460)	1237 (442)	1554 (578)	1148 (423)	1017 (463)	1277 (462)
500m buffer zone	13122 (3337)	5791 (2524)	6707 (2368)	8367 (3321)	6099 (2190)	5268 (2535)	6628 (2507)
1000m buffer zone	45375 (14002)	20109 (9552)	23383 (8177)	28893 (12517)	20294 (7932)	18146 (8874)	21615 (9171)
PM_{10} mean (SD)	32 (5)	19 (2)	25 (3)	25 (3)	22 (2)	26 (2)	22 (2)
Distance to freeway mean (SD)	9455 (21120)	16624 (30116)	5051 (6249)	7832 (8435)	12647 (14167)	7025 (6222)	12410 (12074)
Distance major road mean (SD)	2671 (4857)	5785 (7559)	1477 (1601)	3055 (3962)	1716 (2550)	2073 (2280)	2264 (2979)

Center	Newcastle	Oslo	Pavia	Utrecht	Vienna	Zurich
N-value	546	234	220	195	624	275
Time of lung transplantation	1987-2011	1990-2011	1991-2011	1989-2011	1989-2011	1992-2011
Age mean (SD)	47 (13)	51 (11)	46 (13)	46 (13)	49 (13)	43.8 (16)
Gender(male) n-value (%)	278 (51)	112 (48)	149 (68)	96 (49)	330 (53)	144 (52)
Double lung transplantation, n-value (%)	353 (65)	188 (80)	132 (60)	152 (78)	483 (77)	259 (94)
Underlying disease n-value (%)						
Emphysema	150 (27)	142 (61)	38 (17)	85 (44)	360 (58)	68 (25)
Cystic fibrosis	201 (36)	18 (8)	42 (19)	59 (30)	88 (14)	100 (36)
Interstitial lung disease	102 (19)	24 (10)	70 (32)	34 (17)	107 (18)	64 (23)
Pulmonary arterial hypertension	41 (8)	15 (6)	45 (21)	4 (2)	44 (7)	16 (6)
Other	52 (10)	35 (15)	25 (11)	13 (7)	25 (4)	27 (10)
Mean (SD) road length (m) in a specific buffer zone						
50m buffer zone	96 (48)	234 (49)	127 (68)	116 (58)	88 (59)	94 (62)
100m buffer zone	331 (141)	119 (162)	464 (197)	462 (173)	330 (166)	356 (167)
200m buffer zone	1218 (467)	479 (555)	1563 (660)	1708 (536)	1174 (495)	1303 (553)
500m buffer zone	6498 (2604)	2763 (2830)	7915 (3492)	9621 (2934)	6374 (2854)	7057 (2856)
1000m buffer zone	22164 (9557)	9888 (9493)	26352 (12982)	33729 (11068)	22423 (11532)	23317 (8922)
PM_{10} mean (SD)	19 (3)	13 (2)	33 (7)	27 (2)	24 (4)	/
Distance to freeway mean (SD)	29113 (47812)	50387 (77672)	11716 (15059)	4959 (5232)	10912 (15411)	5436 (7075)
Distance major road mean (SD)	2862 (4058)	1493 (2238)	3959 (6177)	2272 (2728)	2036 (3109)	1595 (2048)

Table E1: Extended patient characteristics and exposures per lung transplant center

Death			No correction for macrolides			Correction for macrolides		
	IQR	HR	95% CI	P	HR	95% CI	P
Road length in buffer zone							
50 m	**108m**	**1.089**	**1.013-1.169**	**0.0206**	**1.084**	**1.007-1.167**	**0.032**
100 m	279m	**1.097**	**1.028-1.171**	**0.0043**	**1.079**	**1.008-1.156**	**0.028**
200 m	752m	**1.078**	**1.023-1.135**	**0.0068**	**1.062**	**1.007-1.127**	**0.031**
500 m	4092m	**1.003**	**1.042-1.130**	**0.0023**	**1.003**	**1.000-1.085**	**0.020**
1000 m	15403m	**1.080**	**1.016-1.131**	**0.012**	1.047	1.00-1.113	0.081
PM_{10}	6 µg/m³	1.019	0.982-1.106	0.18	1.019	0.982-1.049	0.17
Distance to freeway	1233m	0.976	0.927-1.012	0.55	0.976	0.917-1.050	0.57
Distance to major road	241m	0.976	0.908-1.024	0.32	0.976	0.952-1.000	0.25

CLAD			No correction for macrolides			Correction for macrolides		
Road length in buffer zone							
50 m	108m	1.047	0.972-1.127	0.23	1.050	0.974-1.804	0.20
100 m	279m	1.014	0.943-1.091	0.70	1.022	0.948-1.100	0.57
200 m	752m	1.023	0.972-1.086	0.41	1.030	0.978-1.094	0.28
500 m	4092m	1.042	1.000-1.130	0.063	**1.085**	**1.000-1.130**	**0.034**
1000 m	15403m	1.031	0.970-1.097	0.25	1.047	0.985-1.097	0.17
PM_{10}	6 µg/m³	1.018	0.947-1.093	0.66	1.012	0.941-1.087	0.75
Distance to freeway	1233m	1.038	0.976-1.103	0.32	1.038	0.976-1.103	0.30
Distance to major road	241m	1.000	0.953-1.075	0.99	1.000	0.976-1.024	0.99

Table E2: Analysis of Cox analysis without stratification for macrolide use. We corrected for patient age, patient gender, native disease (COPD vs ILD vs cystic fibrosis and bronchiectasis vs pulmonary hypertension vs others), type of transplantation (single versus sequential single), era of transplantation (1987-1995 vs 1996-2000 vs 2001-2005 vs 2006-2011), macrolides (no correction for macrolides left, correction for macrolides right).

Death	$P_{interaction}$	CLAD	$P_{interaction}$
Road length in buffer zone		Road length in buffer zone	
50m	0.013	50m	0.033
100m	0.47	100m	0.45
200m	<0.0001	200m	0.0049
500m	<0.0001	500m	0.25
1000m	<0.0001	1000m	0.39
PM_{10}	0.005	PM_{10}	0.041
Distance to freeway	0.61	Distance to freeway	0.39
Distance to major road	0.0008	Distance to major road	0.081

Table E3: Within the Cox analysis we corrected for patient age, patient gender, native disease (COPD vs ILD vs cystic fibrosis and bronchiectasis vs pulmonary hypertension vs others), type of transplantation (single versus sequential single), era of transplantation (1987-1995 vs 1996-2000 vs 2001-2005 vs 2006-2011), macrolides (yes-no) and the interaction term between macrolides and the predictive variable. P values shown are for the interaction between macrolides and the predictive variable reflecting air pollution.

quintiles	mortality and road length (200m)		P-value	CLAD and road length (200m)		P-value
	HR	95% CI		HR	95% CI	
Q1	REF	Overall	0.029	REF	Overall	0.17
Q2	1.063	0.916-1.235	0.43	1.063	0.916-1.235	0.21
Q3	1.107	0.952-1.287	0.17	1.107	0.952-1.287	0.13
Q4	1.084	0.930-1.263	0.59	1.173	0.983-1.401	0.13
Q5	1.279	1.092-1.480	0.0033	1.265	1.046-1.524	0.012
	mortality and PM_{10}			CLAD and PM_{10}		
Q1	REF	overall	0.10	REF	Overall	0.014
Q2	1.077	0.904-1.283	0.41	0.988	0.813-1.200	0.91
Q3	1.206	1.022-1.422	0.027	1.257	1.043-1.257	0.016
Q4	1.246	1.035-1.501	0.020	1.024	0.82-1.278	0.83
Q5	1.217	1.003-1.476	0.046	1.238	0.985-1.550	0.066

Table E4: Hazard ratio's for both mortality and CLAD comparing the quintiles of particulate matter (PM_{10}) versus the lowest quintile which is used as reference value (Q1).

	mortality				CLAD			
	N	HR	95% CI	P-value	N	HR	95% CI	P-value
200 m road length (+752m)								
Main model	3556	1.094	1.030-1.779	**0.0054**	3551	1.11	1.023-1.204	**0.0114**
Sensitivity analysis for SES								
Subgroup	1199	1.119	1.008-1.249	**0.037**	1198	1.127	0.985-1.295	0.087
Subgroup+SES	1199	1.119	1.008-1.249	**0.042**	1198	1.135	0.985-1.305	0.079
SES (REF=high)								
SES moderate	1199	1.321	0.943-1.852	0.11	1198	0.808	0.564-1.158	0.23
SES low	1199	1.253	0.919-1.708	0.15	1198	0.822	0.597-1.132	0.25
Sensitivity analysis for smoking								
Subgroup	1159	1.24	1.119-1.383	**<0.0001**	1157	1.222	1.062-1.413	**0.0060**
Subgroup+smoking	1159	1.24	1.119-1.383	**<0.0001**	1157	1.222	1.062-1.403	**0.0063**
Smoking	1159	1.074	0.872-1.323	0.50	1157	0.903	0.681-1.197	0.48
PM_{10} (+6µg/m³)								
Main Model	3556	1.081	1.000-1.167	**0.049**	3551	1.093	0.988-1.208	0.076
Sensitivity analysis for SES								
Subgroup	1068	1.012	0.886-1.160	0.84	1067	1.16	0.982-1.371	0.083
Subgroup+SES	1068	1.012	0.886-1.160	0.84	1067	1.16	0.982-1.371	0.079
SES (REF=high)								
SES moderate	1068	1.198	0.861-1.666	0.28	1067	0.824	0.565-1.201	0.31
SES low	1068	1.226	0.858-1.751	0.26	1067	0.815	0.580-1.145	0.24
Sensitivity analysis smoking								
Subgroup	1152	1.055	0.936-1.201	0.38	1150	1.222	1.030-1.451	**0.020**
Subgroup+smoking	1152	1.055	0.936-1.201	0.34	1150	1.222	1.030-1.451	**0.022**
Smoking	1152	1.065	0.864-1.313	0.55	1150	0.932	0.702-1.236	0.66

Table E5: The sensitivity analysis showing the association of mortality and CLAD with the road length in a 200m buffer zone and PM_{10} after correction for pre-transplant smoking (Yes/No) and SES coded according to pre-transplant occupation (low-moderate-high).

	macrolides before CLAD or no CLAD (n=1325)			macrolide at/after CLAD (n=782)		
	HR	95% CI	P-value	HR	95% CI	
death and road length 200m buffer*	0.980	0.958-1.002	0.075	1.012	0.992-1.032	0.25
CLAD and road length *	0.987	0.969-1.006	0.18	1.010	0.998-1.023	0.11
death and road length no center	0.992	0.974-1.009	0.35	1.025	1.007-1.043	0.0052
CLAD and road length no center	0.982	0.967-0.997	0.019	1.014	1.003-1.026	0.017

* In the Cox analysis we corrected for patient age, patient gender, native disease (COPD vs ILD vs cystic fibrosis and bronchiectasis vs pulmonary hypertension vs others), type of transplantation (single versus sequential single), era of transplantation (1987-1995 vs 1996-2000 vs 2001-2005 vs 2006-2011).

Table E6: Sensitivity analysis for time of macrolide initiation stratifying according to the time of macrolide initiation being either macrolides before CLAD diagnosis or never developing CLAD (n=1325, possible protective effect) vs. patients treated with macrolides at CLAD diagnosis or after CLAD diagnosis (n=782, no possible protective effect since CLAD is already diagnosed).

	Never macrolide therapy			Ever macrolide therapy		
	HR	95% CI	P-value	HR	95% CI	P-value
death and road length 200m buffer	1.130	1.063-1.201	0.0001	0.924	0.838-1.018	0.11
CLAD and road length 200m buffer	1.120	1.050-1.194	0.0006	0.776	0.699-0.861	0.0001

* In the Cox analysis we corrected for patient age, patient gender, native disease (COPD vs ILD vs cystic fibrosis and bronchiectasis vs pulmonary hypertension vs others), type of transplantation (single versus sequential single), era of transplantation (1987-1995 vs 1996-2000 vs 2001-2005 vs 2006-2011) and azithromycin as a time-dependent variable.

Table E7: Time-dependency of macrolide therapy

mortality and road length in 200m buffer					CLAD and road length in 200m buffer				
cut-off	N	HR	95% CI	P-value	N	HR	95% CI	P-value	
500 km	3387	1.114	1.045-1.188	**0.0014**	3377	1.118	1.029-1.205	**0.0072**	
700 km	3556	1.094	1.030-1.779	**0.0054**	3544	1.11	1.023-1.204	**0.011**	
1000 km	3664	1.091	1.022-1.363	**0.0063**	3650	1.083	1.007-1.172	**0.037**	
No cut-off	3731	1.075	1.015-1.147	0.012	3717	1.075	1.000-1.155	0.053	

mortality and PM_{10}					CLAD and PM_{10}				
cut-off	N	HR	95% CI	P-value	N	HR	95% CI	P-value	
500 km	3243	1.093	1.012-1.187	**0.028**	3234	1.093	0.988-1.215	0.084	
700 km	3412	1.081	1.000-1.167	**0.049**	3400	1.093	0.988-1.208	0.076	
1000 km	3517	1.068	0.994-1.153	0.082	3504	1.081	0.982-1.194	0.11	
No cut-off	3583	1.055	0.976-1.139	0.17	3570	1.087	0.988-1.194	0.088	

Table E8: The effect of investigating the association between pollution parameters and CLAD/mortality stratified according to different proposed cut-off values for distance from transplant center. We introduced this as an inclusion criterion as patients living further from their transplant center are more likely to be lost to follow-up or more rarely visit out-patient clinic. A relationship between inferior outcome and distance from transplant center has been previously demonstrated after allogeneic hematopoietic stem cell transplantation and kidney transplantation (Abou-nassar et al. 2011 and Axelrod et al. 2010). Indeed, in our database the 225 patients living >700 km from transplant center tended to experience worse survival (p=0.073, HR 1.186; 0.984-1.430), which can introduce bias in our analysis. This table alternatively also shows the association when patients living >500 km and >1000 km from the transplant center were excluded from the analysis from the main model, while also showing the results when nu cut-off is used. This clearly demonstrates the bias that including those patients will cause.