Pollution atmosphérique et *rejet chronique pulmonaire*

5ème Journées francophones de la mucoviscidose, Tours

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Relations d'intérêts

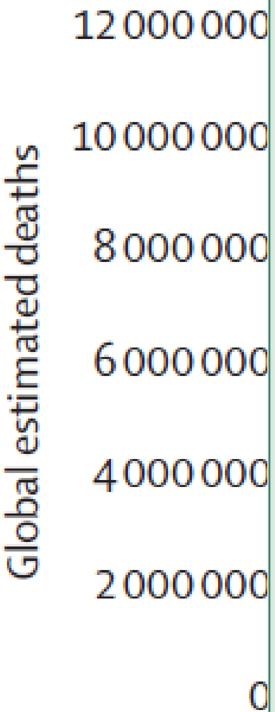
- **Type d'aides et champs**
  - Pr. Ch. Pison, déplacements et inscriptions congrès *via* honoraires FMC, expertises
  - CHUGA, recherche clinique *via* contrat unique

- **Laboratoires, Dispositifs médicaux, SARD**
  - Astra Zeneca
  - Boehringer Ingelheim
  - GlaxoSmithKline
  - Novartis

  - PulmonX, Nuvaira

  - AGIR à Dom, SOS Oxygène

Pollution et santé, mise à jour 2019 GBD



	Female	Male	Total
Total air pollution*	2·92 (2·53–3·33)	3·75 (3·31–4·25)	6·67 (5·90–7·49)
Household air†	1·13 (0·80–1·50)	1·18 (0·79–1·66)	2·31 (1·63–3·12)
Ambient particulate‡§	1·70 (1·38–2·01)	2·44 (2·02–2·83)	4·14 (3·45–4·8)
Ambient ozone‡	0·16 (0·07–0·25)	0·21 (0·09–0·33)	0·37 (0·17–0·56)
Total water pollution*	0·73 (0·40–1·26)	0·63 (0·46–0·95)	1·36 (0·96–1·96)
Unsafe sanitation†	0·40 (0·23–0·68)	0·36 (0·26–0·54)	0·76 (0·54–1·09)
Unsafe source†	0·66 (0·35–1·15)	0·57 (0·39–0·88)	1·23 (0·82–1·79)
Total occupational pollution*	0·22 (0·17–0·28)	0·65 (0·54–0·79)	0·87 (0·74–1·02)
Carcinogens‡	0·07 (0·05–0·09)	0·28 (0·22–0·35)	0·35 (0·28–0·42)
Particulates‡¶	0·15 (0·10–0·21)	0·37 (0·27–0·47)	0·52 (0·42–0·64)
Lead pollution*‡	0·35 (0·19–0·53)	0·56 (0·36–0·77)	0·90 (0·55–1·29)
Total modern pollution*	2·28 (1·86–2·67)	3·55 (3·08–4·04)	5·84 (5·03–6·61)
Total traditional pollution*	1·85 (1·39–2·42)	1·81 (1·36–2·38)	3·66 (2·82–4·63)
Total pollution*	3·92 (3·39–4·47)	5·09 (4·57–5·68)	9·01 (8·12–10·0)

Data are N in millions (95% CI). *Custom aggregate from Institute for Health Metrics and Evaluation corrected for overlap. The totals for air, water, modern, traditional, and all pollution are less than the arithmetic sum of the individual risk factors within each of these categories because their contributions overlap (eg, household air and ambient air pollution each can contribute to the same diseases). †Traditional pollution risk factor. ‡Modern pollution risk factors. §Ambient particulate matter is $PM_{2.5}$. ¶Occupational exposure to respirable, thoracic, or inhalable particulate matter.

Table: **Global estimated pollution-attributable deaths (millions) by type of pollution and sex, 2019**

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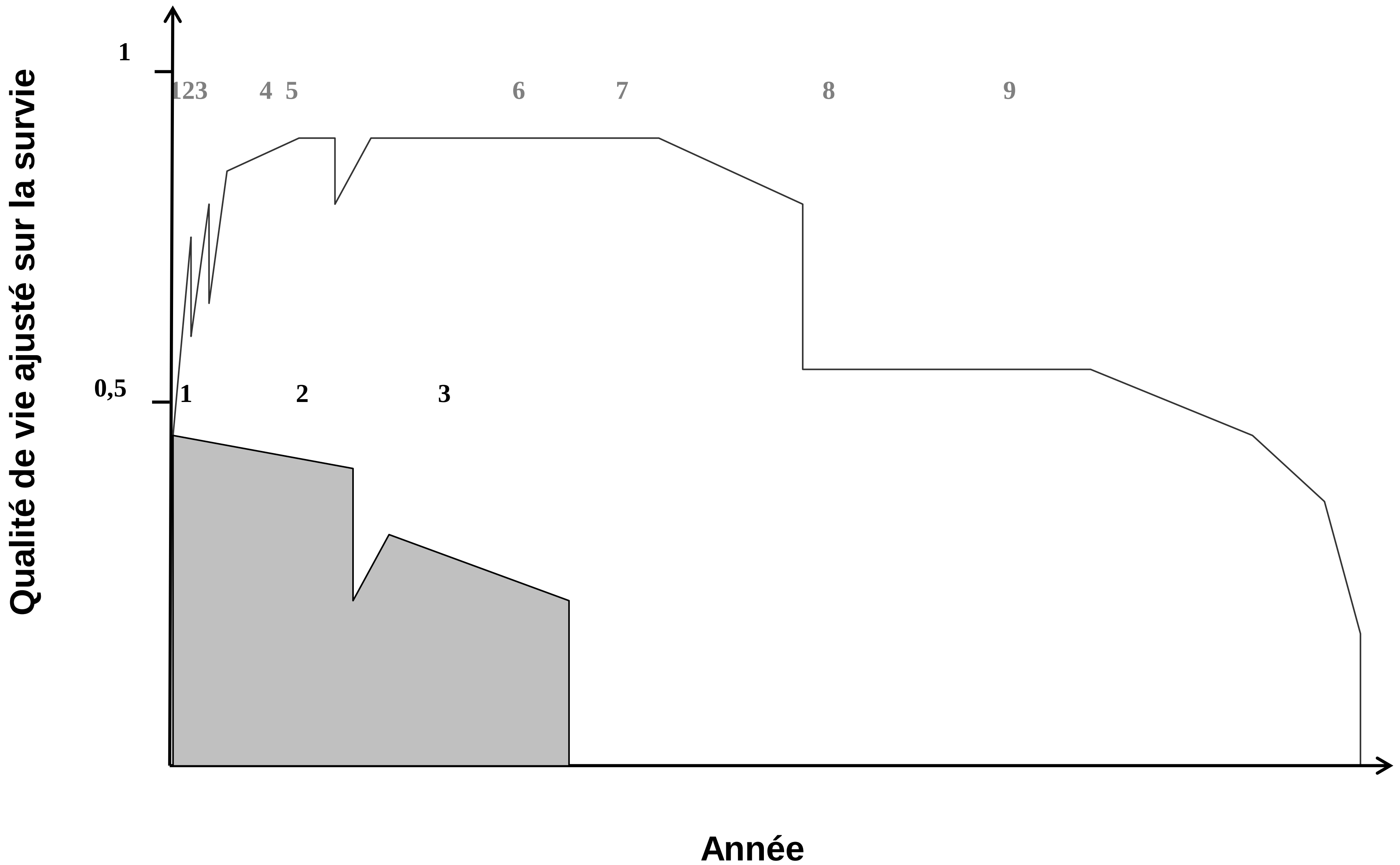
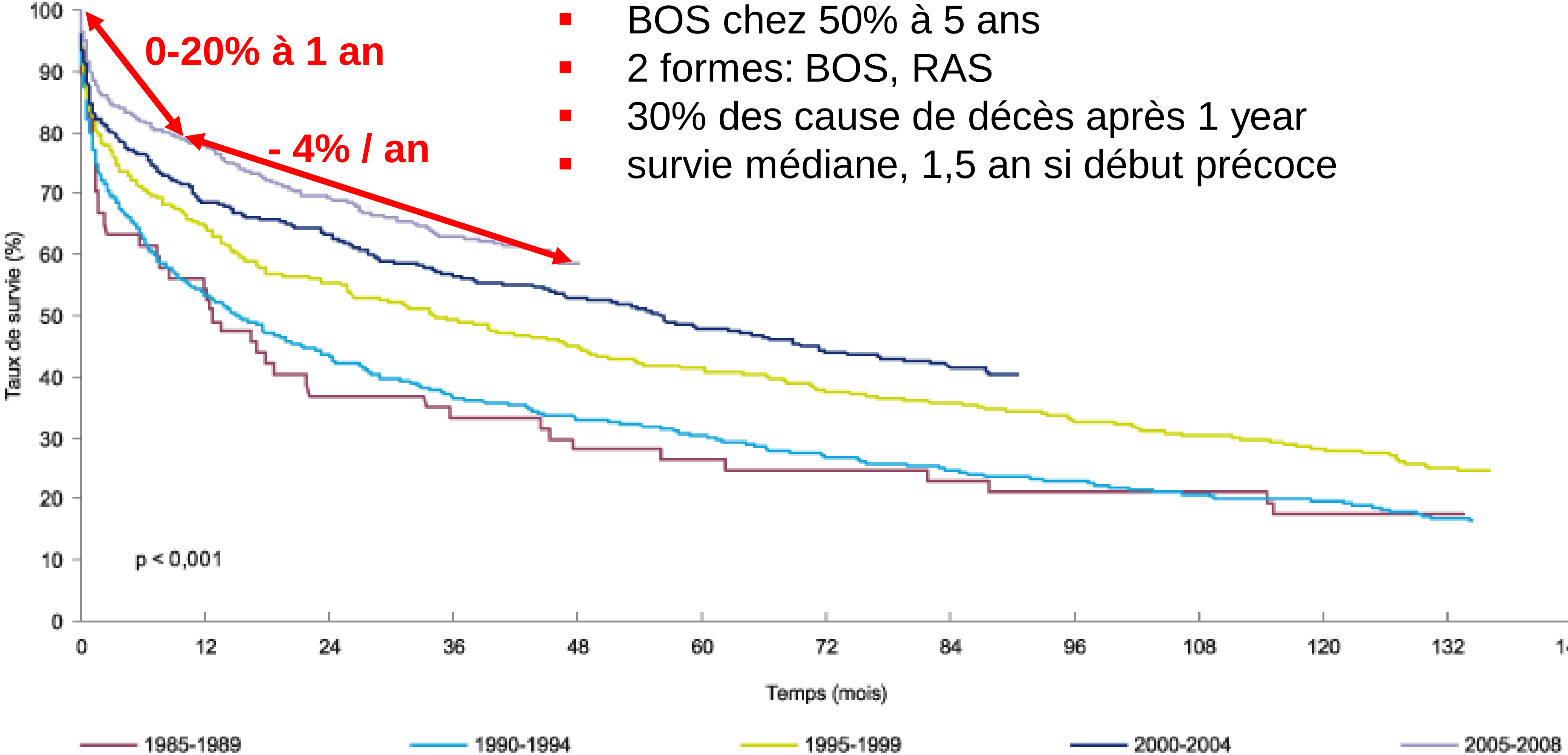
Améliorer la qualité et la durée de vie de patients avec une insuffisance respiratoire chronique grave



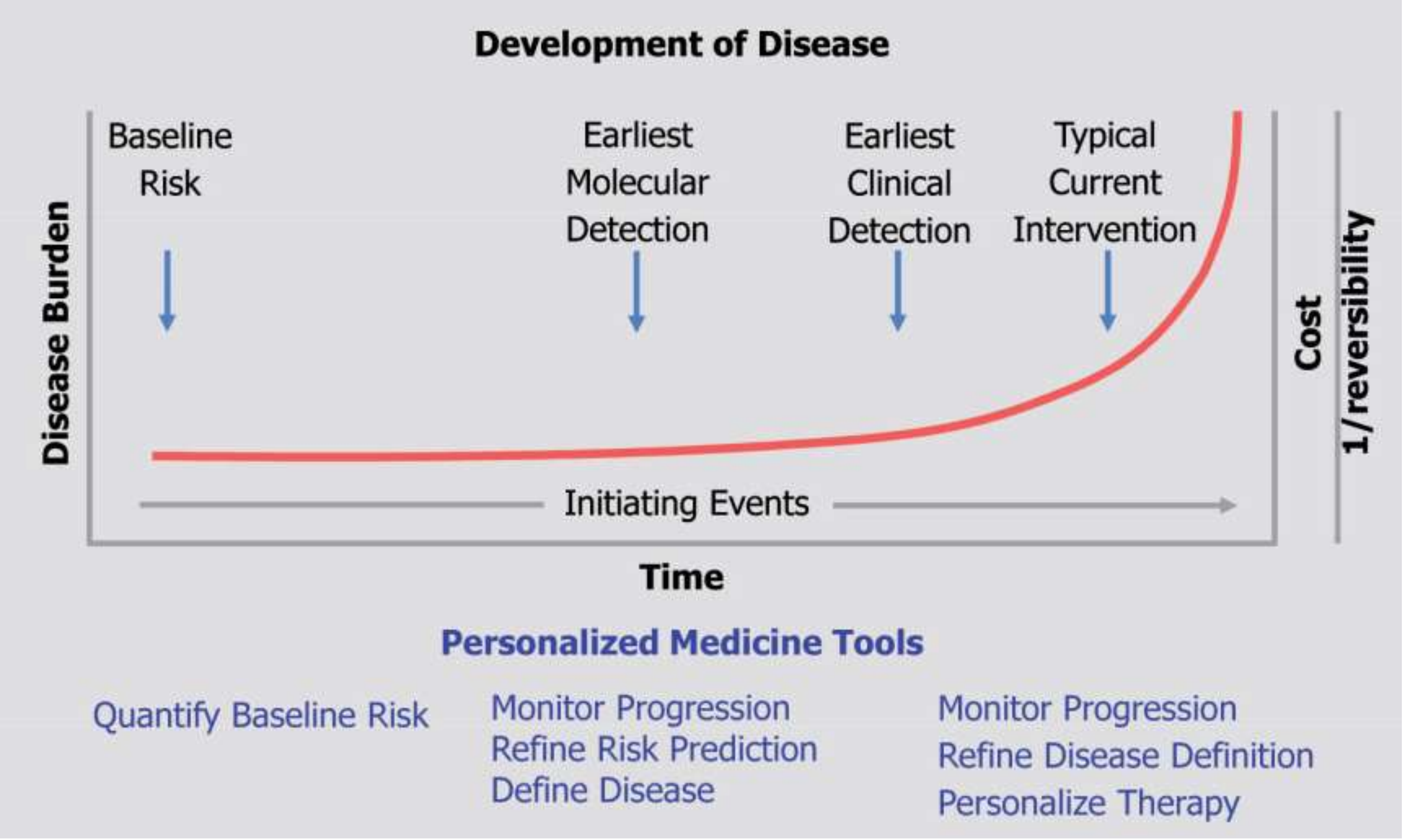
Résultats de la transplantation pulmonaire, S. Quêtant, T. Rochat, C. Pison. ***RMR 2010;*** **27:921-938**

Talons d'Achille de la transplantation pulmonaire

- **Pénurie greffons, Dysfonction Primaire du Greffon**
- **Chronic Lung Allograft Dysfunction - CLAD**
  - BOS chez 50% à 5 ans
  - 2 formes: BOS, RAS
  - 30% des cause de décès après 1 year
  - survie médiane, 1,5 an si début précoce



Cohort Of Lung Tansplantation - COLT
Systems prediction of Chronic Lung Allograft Dysfunction
SysCLAD



Snyderman *et al.* Biotechnol. J. 2012;7:973-9

SysCLAD et COLT

Cohort of lung Transplantation-COLT associating surgeons; anaesthetists – intensivists; physicians; research assistants:
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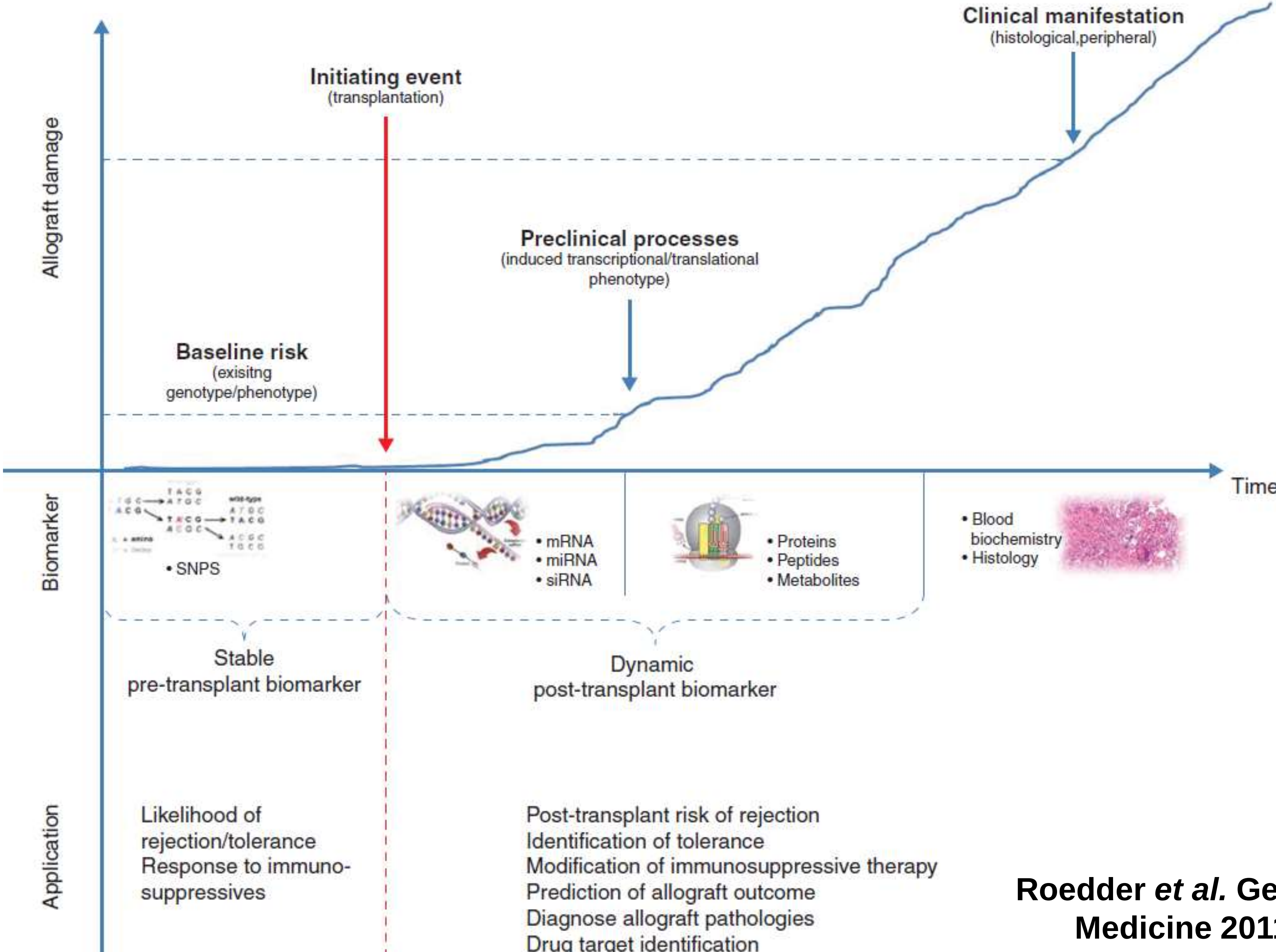

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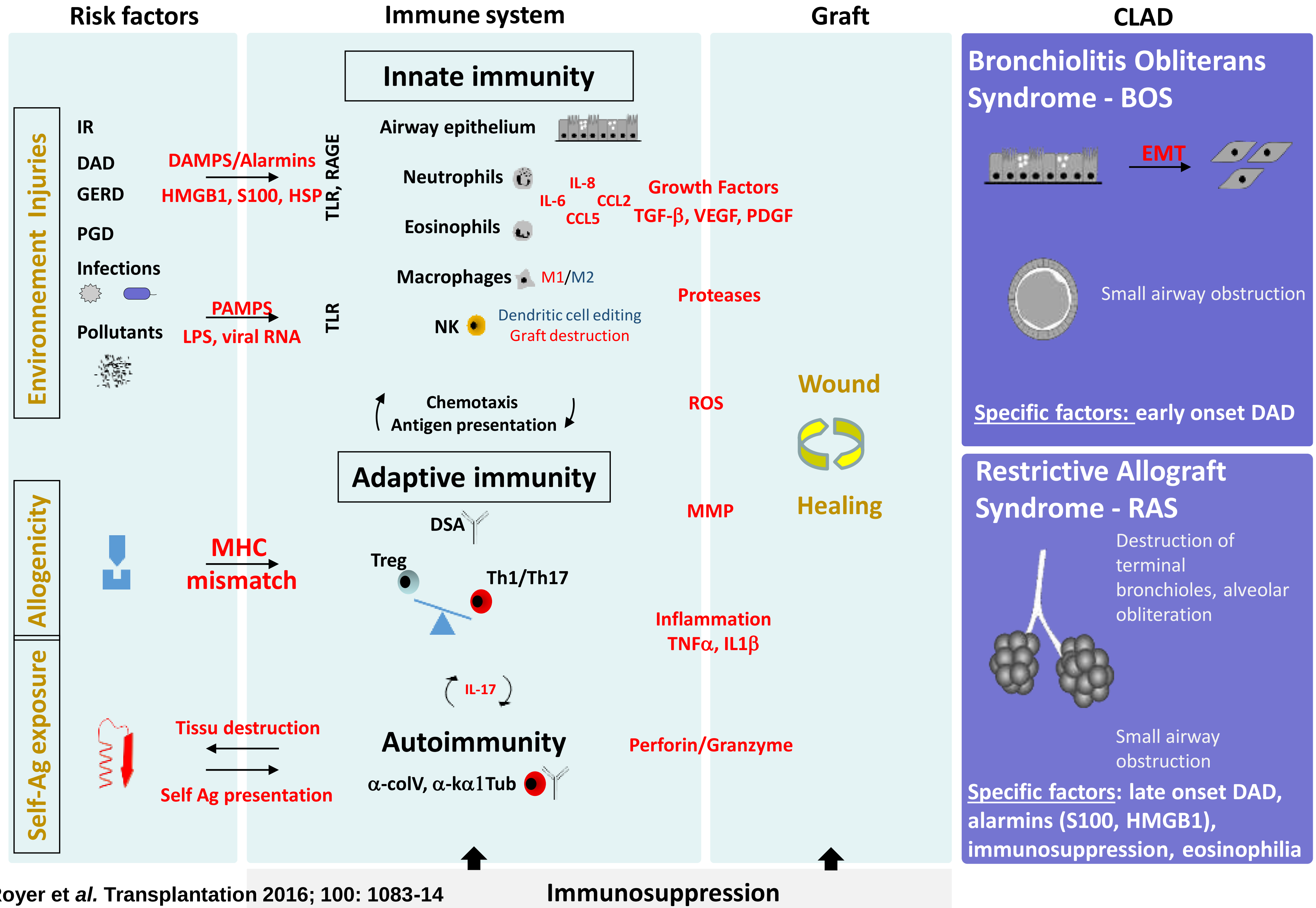


Royer et *al.* Transplantation 2016; 100: 1083-14

Méthodes et Objectifs

- **COLT French cohort since 09-2009, 11 centres + Bruxelles**
- **Swiss Transplant Cohort Study, STCS since 2008 in Lausanne- Genève, Zurich**

- **May-2014, 991 + 282: 1273 transplanted**
  422 reached year-3, or displayed CLAD before year-3, or died before year-3

- ***Donors: day 0***
  - **clinics**
  - **HLA**
  - **lung tissue**

- ***Recipients: before Tx, day-0 Tx, M6-M12 post LTx***
  - **Clinics - e.CRF**
  - **Pollution by geolocalization**
  - **Blood: HLA, transcriptomics x 2, proteomics x 2, miRNA x 1, lymphocytes subpopulations, exome sequencing**
  - **BAL: microbiote & macrophages polarization, proteomics x 2**

- **<u>Objective: to predict CLAD @ year-3, as soon as year-1</u>**

Classification
Chronic Lung Allograft Dysfunction

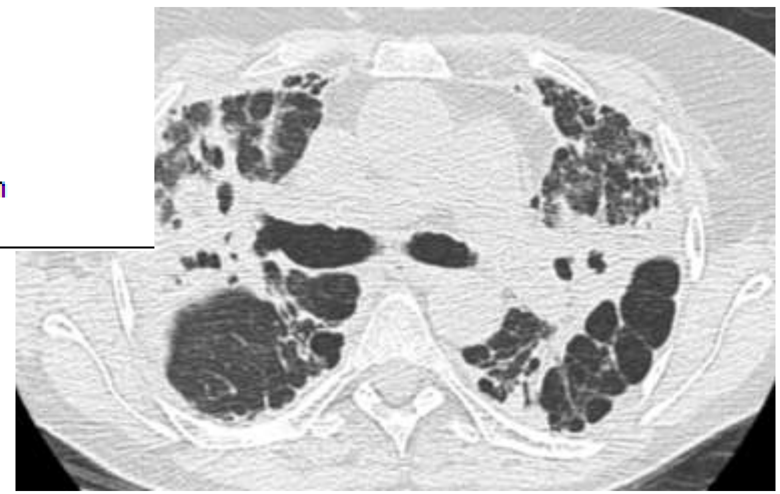
CLAD

BOS

Confounding factors

- Allograft
  - Persistent acute rejection
  - ARAD
  - Infection
  - Anastomotic stricture
  - Disease recurrence
- Extra-allograft
  - Pleural disease
  - Diaphragm dysfunction
  - Native lung hyperinflation
  - Other

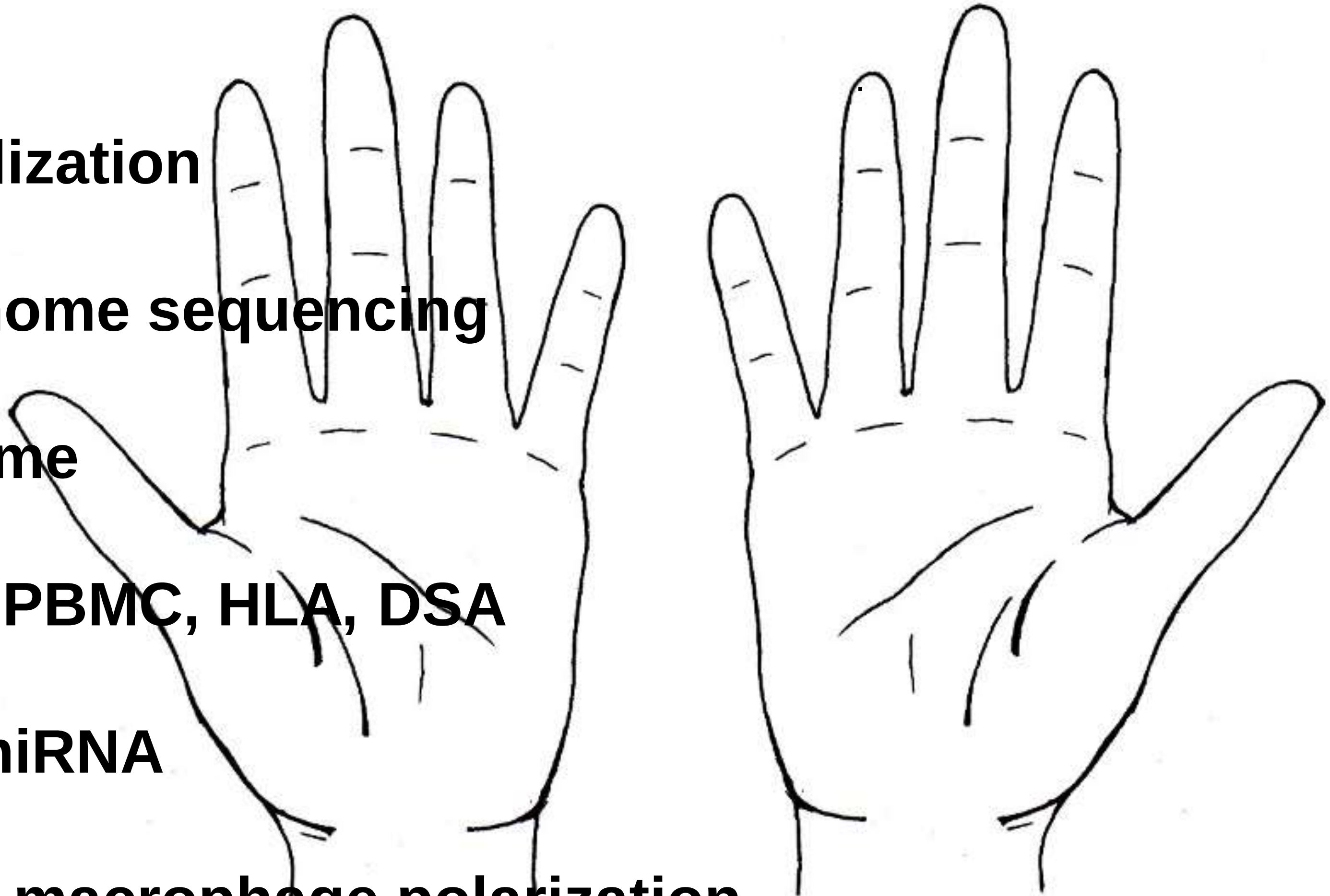
RAS



10 adjudication meetings with 7 experts

Empreintes pour prédire un CLAD

1. Clinicome 1st year
2. Pollution by geolocalization
3. Recipient exome genome sequencing
4. BAL / Plasma proteome
5. Immuno-monitoring, PBMC, HLA, DSA
6. Transcriptome and miRNA
7. Lung microbiote and macrophage polarization

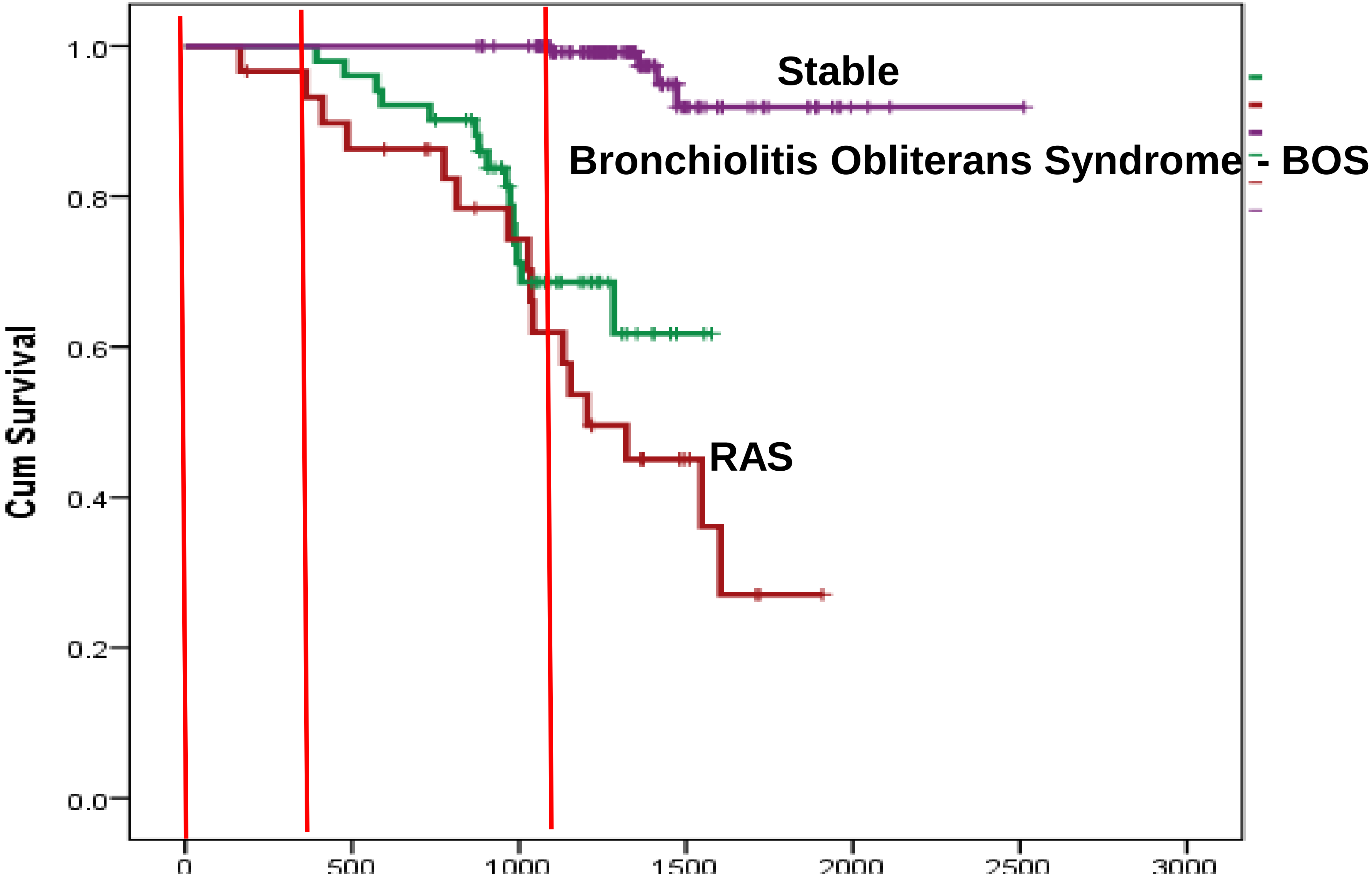


Clinicome, Ac anti-HLA comme prédicteurs à 3 ans

		BOS		RAS	
Variable		**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Underlying diag.	CF	baseline		baseline	
	COPD	1.61 (0.56, 4.61)	0.38	3.86 (1.04, 14.29)	**0.04**
	ILD/IPF	2.44 (0.74, 8.04)	0.14	5.47 (1.48, 20.17)	**0.01**
	Other	2.589 (0.85, 7.91)	0.09	0.23 (0.02, 2.40)	0.22
Immunosuppression	Cyclosporin	baseline		baseline	
	Tacrolimus	3.18 (0.70, 14.36)	0.13	0.67 (0.08, 5.59)	0.71
Induction treatment	Basiliximab	baseline		baseline	
	None	0.54 (0.12, 2.51)	0.43	4.53 (0.89, 23.08)	0.07
	rATG	3.10 (0.68, 14.12)	0.14	2.39 (0.31, 18.67)	0.41
Y1 DSAs II	Yes	3.83 (1.46, 10.04)	**0.006**	6.97 (1.84, 26.38)	**0.004**

Koutsokera A, Royer PJ, Antonietti JP, Fritz A, Benden C, Aubert JD, Tissot A, Botturi K, Roux A, Reynaud-Gaubert ML, et al. Development of a Multivariate Prediction Model for Early-Onset Bronchiolitis Obliterans Syndrome and Restrictive Allograft Syndrome in Lung Transplantation. *Front Med* (2017) **4**:109. doi: 10.3389/fmed.2017.00109

Clinicome, Ac anti-HLA comme prédicteurs à 3 ans



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Chronic Effects of Air Pollution

PRESS RELEASE

The impact of traffic air pollution on bronchiolitis obliterans syndrome and mortality after lung transplantation

Tim S Nawrot,[1,2] Robin Vos,[3,4] Lotte Jacobs,[2] Stijn E Verleden,[3,4] Shana Wauters,[4] Veerle Mertens,[4] Christophe Dooms,[3] Peter H Hoet,[2] Dirk E Van Raemdonck,[4,5] Christel Faes,[6] Lieven J Dupont,[3,4] Benoit Nemery,[2] Geert M Verleden,[3,4] Bart M Vanaudenaerde[3,4]

Thorax 2011;**66**:748–754. doi:10.1136/thx.2010.155192

Chronic Effects of Air Pollution

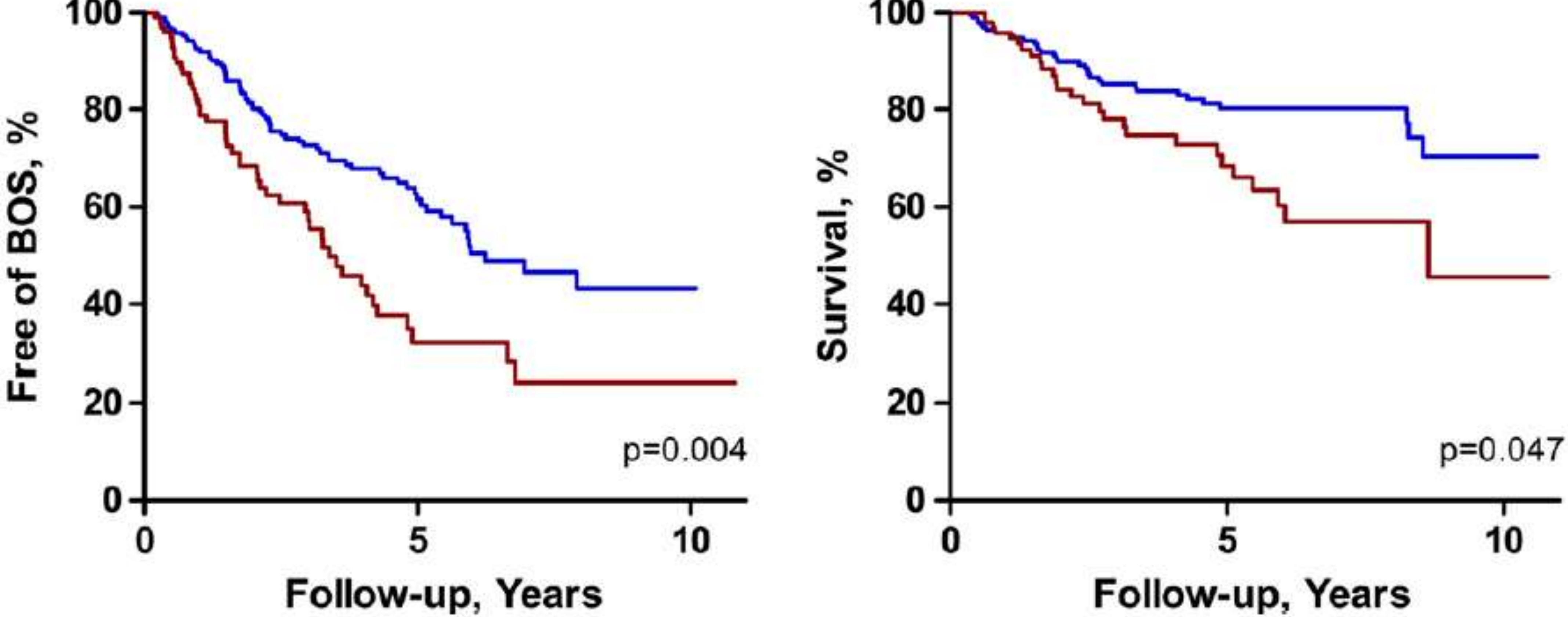

Figure 1 Unadjusted Cox regression in patients after lung transplantation classified according to whether they lived within 171 m of a major road (n=96, lowest tertile, red line) or more than 171 m from a major road (n=192, blue line). BOS, bronchiolitis obliterans syndrome.

- **BOS, double mono -, > 2 RA +, infection CMV +, SES –**
- **Décès, > 2 RA +**

- **PM10, pas de corrélation**

Thorax 2011;**66**:748–754. doi:10.1136/thx.2010.155192

Chronic Effects of Air Pollution

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Air Pollution and the Development of Posttransplant Chronic Lung Allograft Dysfunction

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COPD, chronic obstructive pulmonary disease; DOMI-NO, Dutch OMI NO_2; EOS, Earth Observing System; FEV_1, forced expiratory volume in 1 s; HR, hazard ratio; IPF, idiopathic pulmonary fibrosis; IQR, interquartile range; NAPS, National Air Pollution Surveillance; NO_2, nitrogen dioxide; O_3, ozone; OMI, Ozone Monitoring Instrument; $PM_{2.5}$, particles with aerodynamic diameter $<2.5\ \mu m$; TRAP, traffic-related air pollution

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Introduction/Background

Chronic lung allograft dysfunction (CLAD) is the leading cause of graft failure and mortality for transplant recipients,

Table 2: Hazard ratios (HR) and 95% confidence intervals (95% CI) for the associations of CLAD with different metrics of exposure for ambient air pollution in Ontario, among persons who received bilateral lung transplantation between 1996 and 2009 unadjusted and adjusted for ambient $PM_{2.5}$

Exposure metrics	No. of subjects	CLAD—unadjusted		CLAD—adjusted	
		HR	95% CI	HR	95% CI
Annual concentration of $PM_{2.5}$ averaged between 1996 and 2010, assigned at residential addresses of all subjects (per IQR increment)	397	1.43	0.94, 2.18	–	–
Annual concentration of O_3 average between 1996–2010, assigned at residential addresses of all subjects (in IQR)	397	1.47	0.85, 2.55	1.40	0.79, 2.47
Remote sensed NO_2 for 2005–2009 (IQR)	353	1.51	0.83, 2.71	1.23	0.63, 2.40
Density of major roads within 200 m buffer of residential addresses (IQR)	397	1.30	1.07, 1.58	1.30	1.07, 1.58
Density of major roads within 300 m buffer of residential addresses (IQR)	397	1.27	1.06, 1.52	1.26	1.07, 1.48
Density of major roads within 500 m buffer of residential addresses (IQR)	397	1.26	1.07, 1.50	1.25	1.05, 148
Density of major roads within 1000 m buffer of residential addresses (IQR)	397	1.22	1.03, 1.44	1.20	1.01, 1.43
Distance to major roads					
<100 m	109	1.85	0.85, 4.05	1.96	0.90, 4.29
101–200 m	70	1.94	0.86, 4.41	1.97	0.87, 4.47
201–1000 m	184	1.63	0.77, 3.46	1.72	0.81, 3.65
>1000 m[1]	34	1	–	1	–
Distance to highways					
<100 m	14	4.91	2.22, 10.87	4.72	2.13, 10.47
101–200 m	9	2.72	1.11, 6.65	2.72	1.11, 6.653
201–1000 m	91	1.03	0.69, 1.54	1.05	0.70, 1.57
>1000 m[1]	283	1	–	1	–

ajusté sur âge, sexe D/R, diagnostic, rural/urbain, chômage, quartier, éducation, SES

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

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Ruttens *et al. ERJ* 2017; 49: 1-9

Chronic Effects of Air Pollution

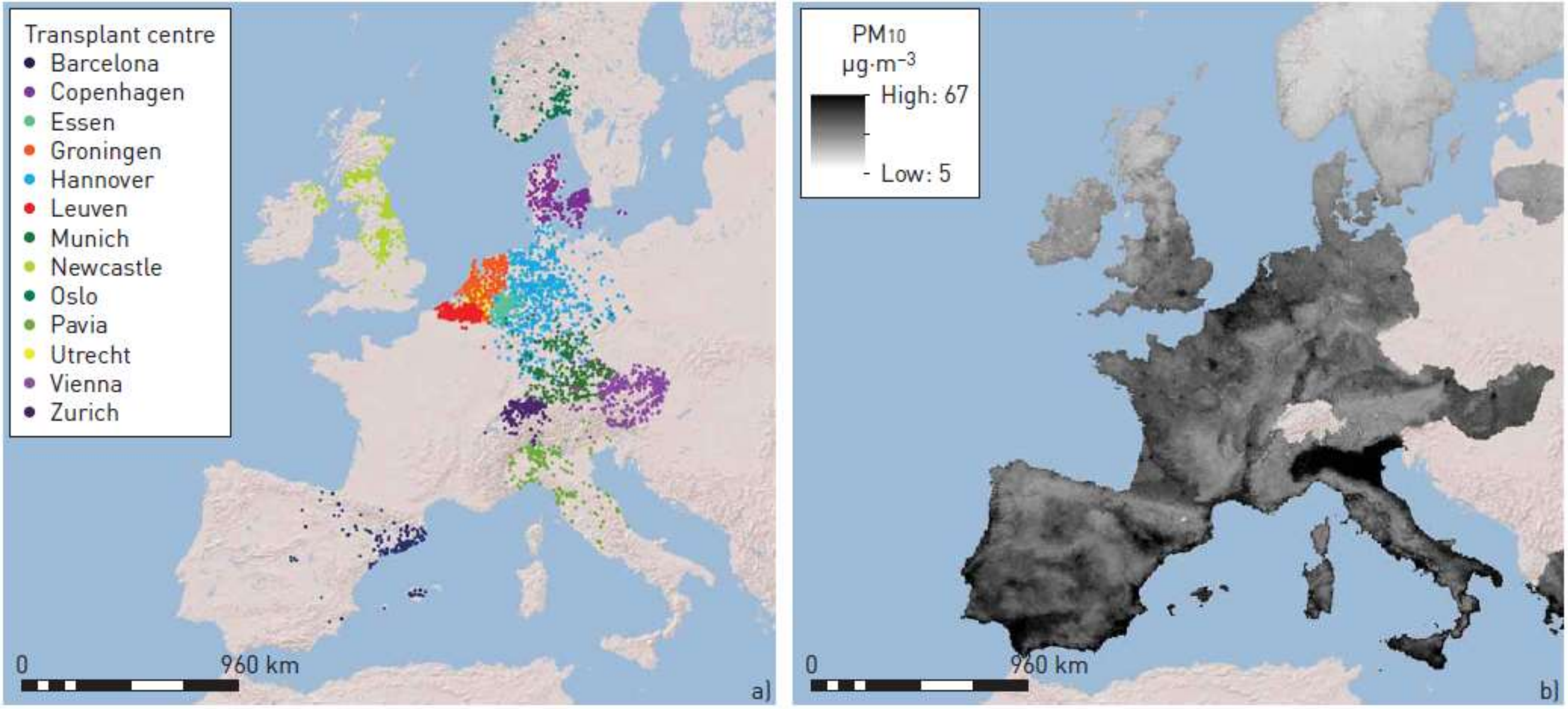

FIGURE 1 a) Geographical distribution of the lung transplant patients from the 13 different lung transplant centres in 10 different European countries. Each point represents a single patient. b) Average particulate matter with aerodynamic diameter ≤10 µm (PM_{10}) concentration in Western Europe. No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

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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#					
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+	1.003 (0.875–1.150)	0.95
200 m	752 m	1.094 (1.030–1.779)	0.0054+	0.978 (0.872–1.094)	0.66
500 m	4092 m	1.085 (1.000–1.130)	0.0356+	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_{10}	$6\ \mu g \cdot m^{-3}$	1.081 (1.000–1.167)	0.049+	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¶					
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+	0.949 (0.872–1.030)	0.21
500 m	4092 m	1.130 (1.042–1.226)	0.0010+	0.960 (0.884–1.085)	0.62
1000 m	15403 m	1.113 (1.031–1.202)	0.0115+	0.970 (0.897–1.063)	0.48
PM_{10}	$6\ \mu g \cdot m^{-3}$	1.093 (0.988–1.208)	0.076	0.886 (0.803–0.976)	0.013+
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_{10}: particulate matter with aerodynamic diameter $\leqslant 10\ \mu m$. #: macrolide-free group n=3556, macrolide group n=2151; ¶: macrolide-free group n=3551, macrolide group n=2150; +: 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).

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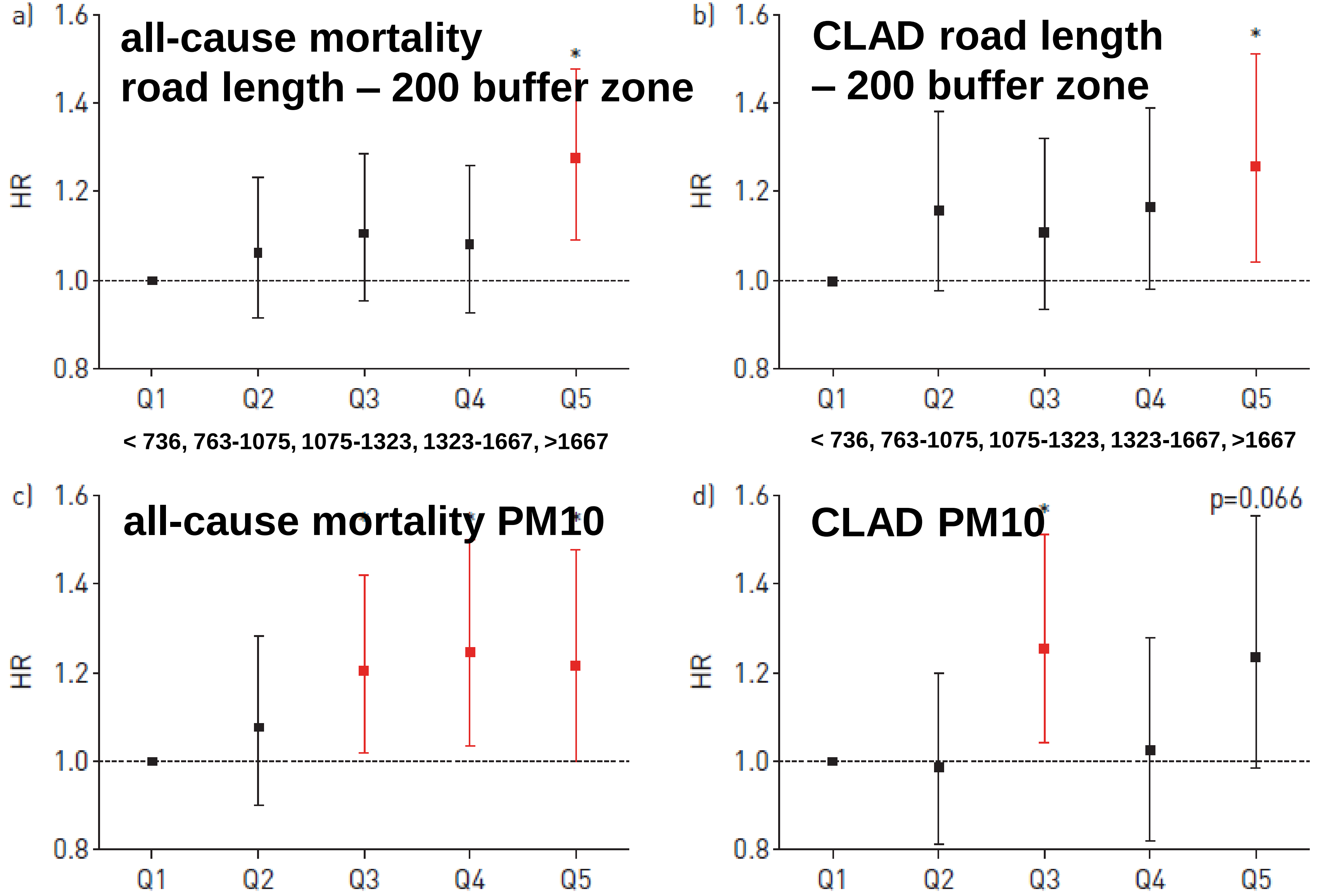

FIGURE 3 Distribution of the hazard ratio (HR) for a) all-cause mortality and b) CLAD associated with quintiles of road length in a 200 m buffer zone around the patient's home address, and c) mortality and d) CLAD associated with quintiles of particulate matter with aerodynamic diameter ≤10 µm (PM_{10}). Quintile 1 (Q1) is used as reference in all these analyses. PM_{10} quintiles are: Q1 <19 µg·m^{-3}; Q2 ≥19 and <21 µg·m^{-3}; Q3 ≥21 and <24 µg·m^{-3}; Q4 ≥24 and <26 µg·m^{-3}; Q5 ≥26 µg·m^{-3}; road length quintiles in a 200 m buffer region are: Q1 <763 m; Q2 ≥763 and <1075 m; Q3 ≥1075 and <1323 m; Q4 ≥1323 and <1667 m; Q5 ≥1667 m. The HR (95%

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Chronic effects of air pollution on lung function after lung transplantation in the Systems prediction of Chronic Lung Allograft Dysfunction (SysCLAD) study

Meriem Benmerad[1,2,3], Rémy Slama[1,2,3], Karine Botturi[4], Johanna Claustre[5,6], Antoine Roux[7], Edouard Sage[7], Martine Reynaud-Gaubert[8], Carine Gomez[8], Romain Kessler[9], Olivier Brugière[10], Jean-François Mornex[11], Sacha Mussot[12], Marcel Dahan[13], Véronique Boussaud[14], Isabelle Danner-Boucher[15], Claire Dromer[16], Christiane Knoop[17], Annick Auffray[18], Johanna Lepeule[1,2,3], Laure Malherbe[19], Frederik Meleux[19], Laurent Nicod[20], Antoine Magnan[4], Christophe Pison[5,6] and Valérie Siroux[1,2,3] on behalf of the SysCLAD consortium[21]

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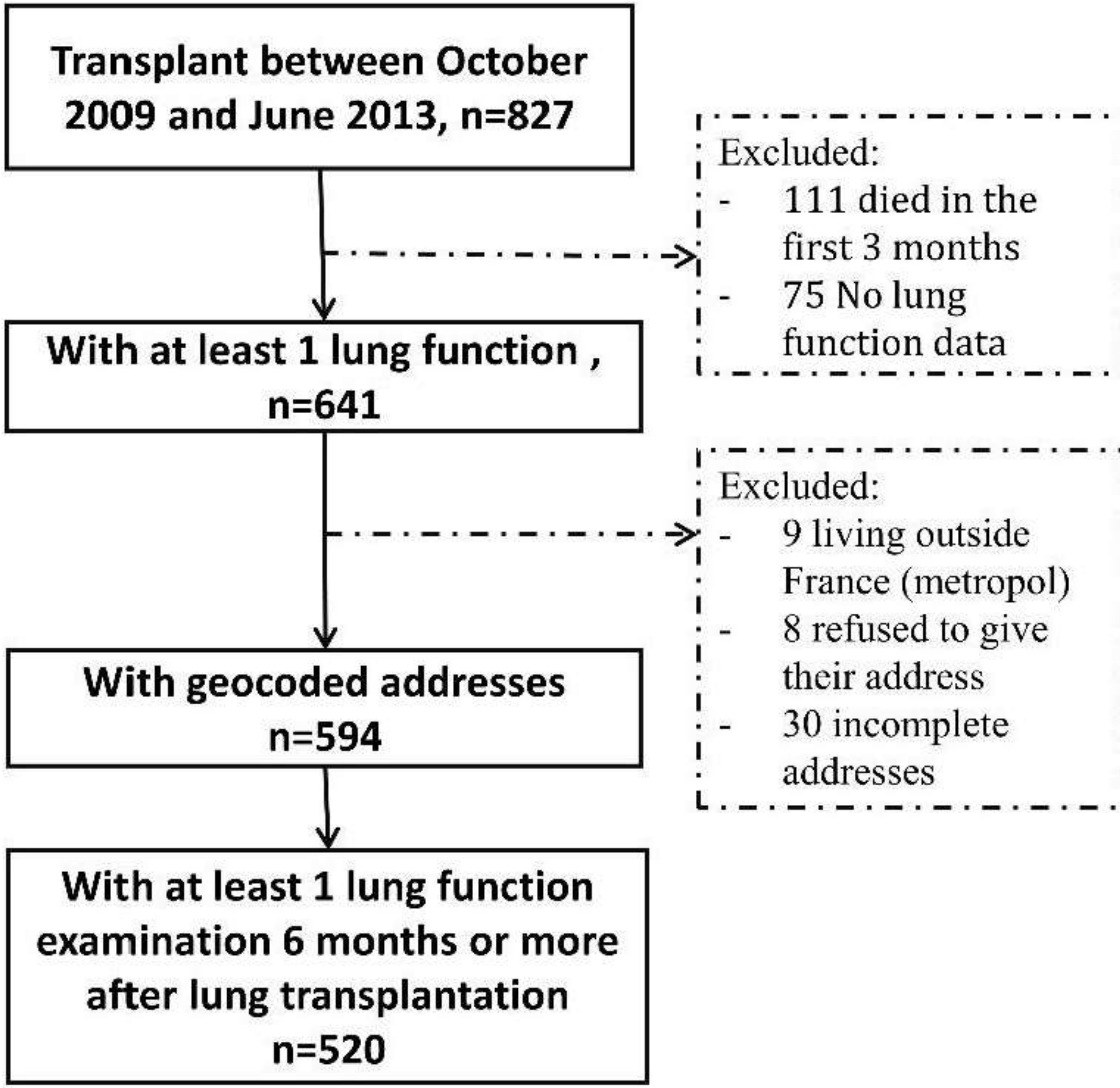

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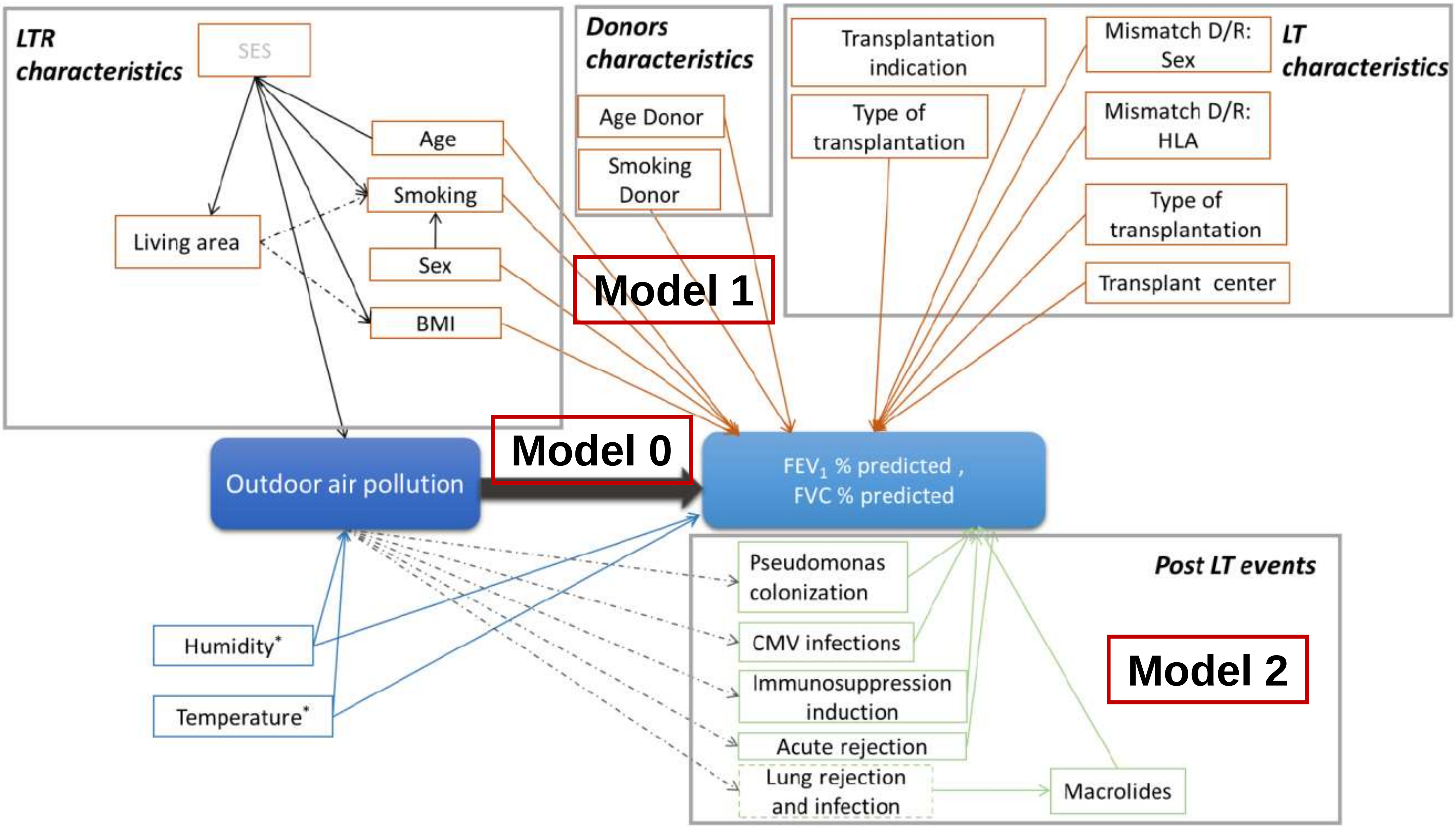

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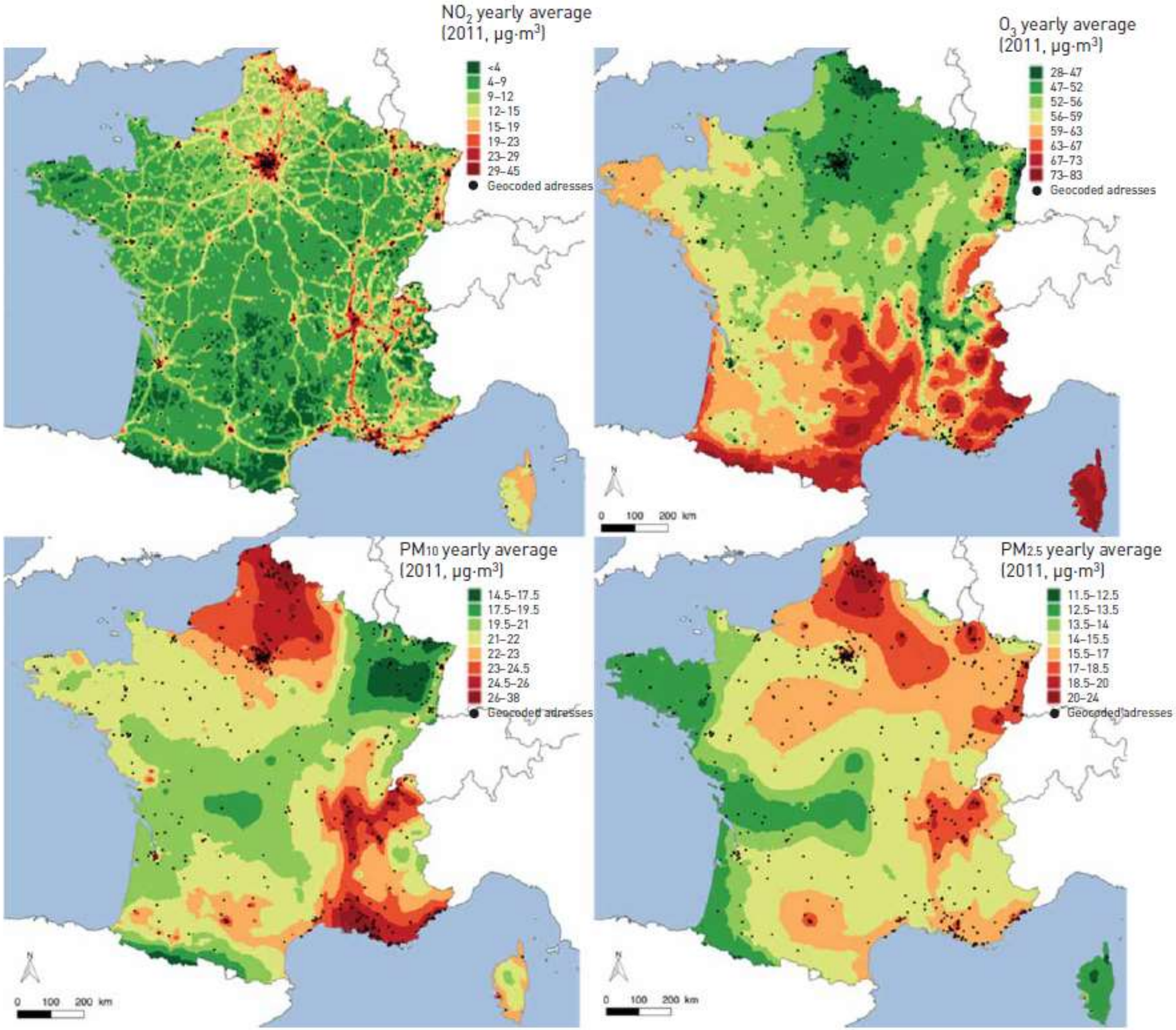

FIGURE 2 Averaged 12-month concentration of particulate matter with an aerodynamic cut-off of 2.5 µm ($PM_{2.5}$) and 10 µm (PM_{10}), NO_2 and O_3 across France in 2011.

Chronic Effects of Air Pollution

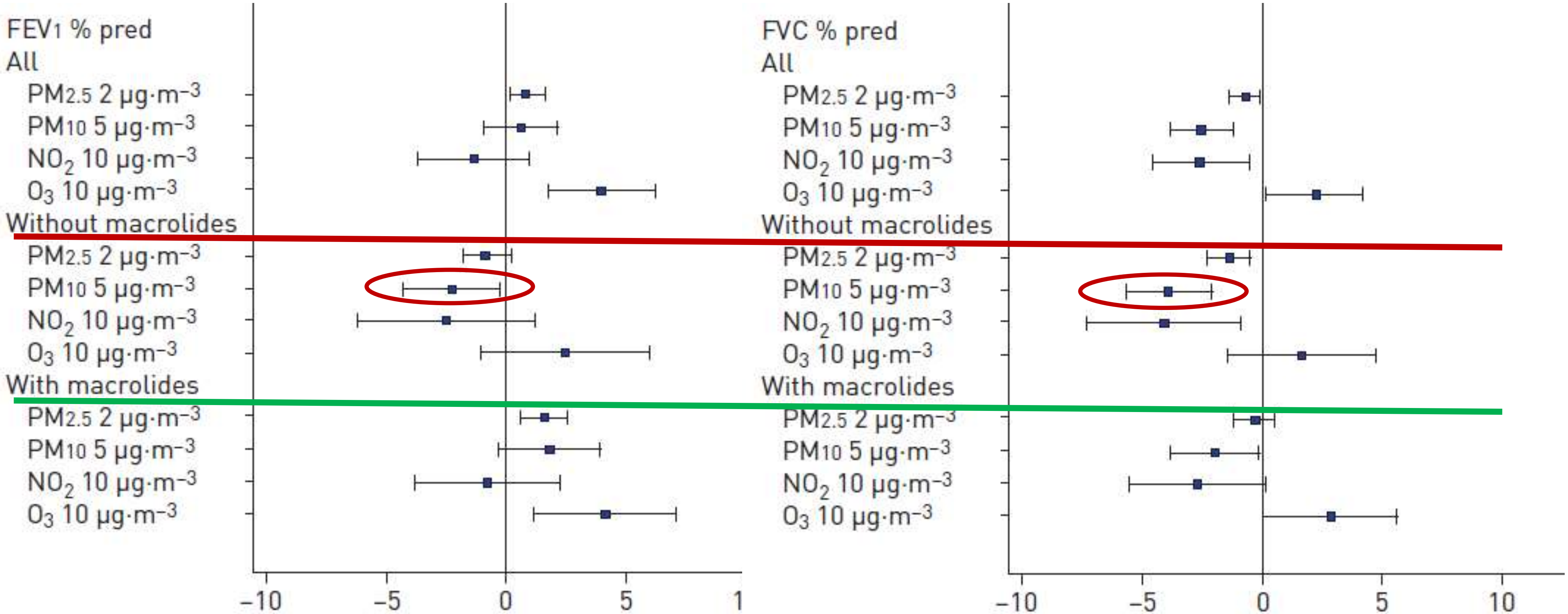

FIGURE 3 Adjusted associations between air pollutants exposure and level of (a) FEV_1 % predicted and (b) FVC % predicted in the whole population and according to the use of macrolides. PM_x: particulate matter with an aerodynamic cross section of x µm.

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Chronic Effects of Air Pollution

Abstract

Rationale: Few studies have examined associations between long-term exposure to fine particulate matter ($PM_{2.5}$) and lung function decline in adults.

Objectives: To determine if exposure to traffic and $PM_{2.5}$ is associated with longitudinal changes in lung function in a population-based cohort in the Northeastern United States, where pollution levels are relatively low.

Methods: FEV_1 and FVC were measured up to two times between 1995 and 2011 among 6,339 participants of the Framingham Offspring or Third Generation studies. We tested associations between residential proximity to a major roadway and $PM_{2.5}$ exposure in 2001 (estimated by a land-use model using satellite measurements of aerosol optical thickness) and lung function. We examined differences in average lung function using mixed-effects models and differences in lung function decline using linear regression models. Current smokers were excluded. Models were adjusted for age, sex, height, weight, pack-years, socioeconomic status indicators, cohort, time, season, and weather.

Measurements and Main Results: Living less than 100 m from a major roadway was associated with a 23.2 ml (95% confidence interval [CI], −44.4 to −1.9) lower FEV_1 and a 5.0 ml/yr (95% CI, −9.0 to −0.9) faster decline in FEV_1 compared with more than 400 m. Each 2 $\mu g/m^3$ increase in average of $PM_{2.5}$ was associated with a 13.5 ml (95% CI, −26.6 to −0.3) lower FEV_1 and a 2.1 ml/yr (95% CI, −4.1 to −0.2) faster decline in FEV_1. There were similar associations with FVC. Associations with FEV_1/FVC ratio were weak or absent.

Conclusions: Long-term exposure to traffic and $PM_{2.5}$, at relatively low levels, was associated with lower FEV_1 and FVC and an accelerated rate of lung function decline.

Keywords: air pollution; respiratory function tests; particulate matter; chronic obstructive pulmonary disease; asthma

Rice** et al. **AJRCCM 2015;191:656-64

Chronic Effects of Air Pollution

	Mean (SD) or %
Demographics	
Age, yr	50.4 (12.4)
Male sex, %	46.2
Body mass index, kg/m^2	27.7 (5.5)
Smoking status, %	
Never	55.6
Former	44.4
Pack-years	
Never smokers	0 (0)
Former smokers	17.4 (18.0)
Education, %	
$<$High school	1.8
High school	18.6
Some college	28.5
College graduate school	49.8
Missing education	1.3
Median census tract household income, $	65,118 (21,927)
Pulmonary outcomes	
FEV_1, L	3.18 (0.85)
FVC, L	4.19 (1.06)
FEV_1/FVC, %	75.7 (7.06)
Obstruction, $FEV_1/FVC < 0.7$	16.4
Asthma diagnosis, ever	15.4
Wheeze in past 12 mo	16.1
Cough $\geq$3 mo in past year	5.1

Data calculated from 10,686 observations (among 6,339 participants).

Rice *et al. AJRCCM 2015;191:656-64*

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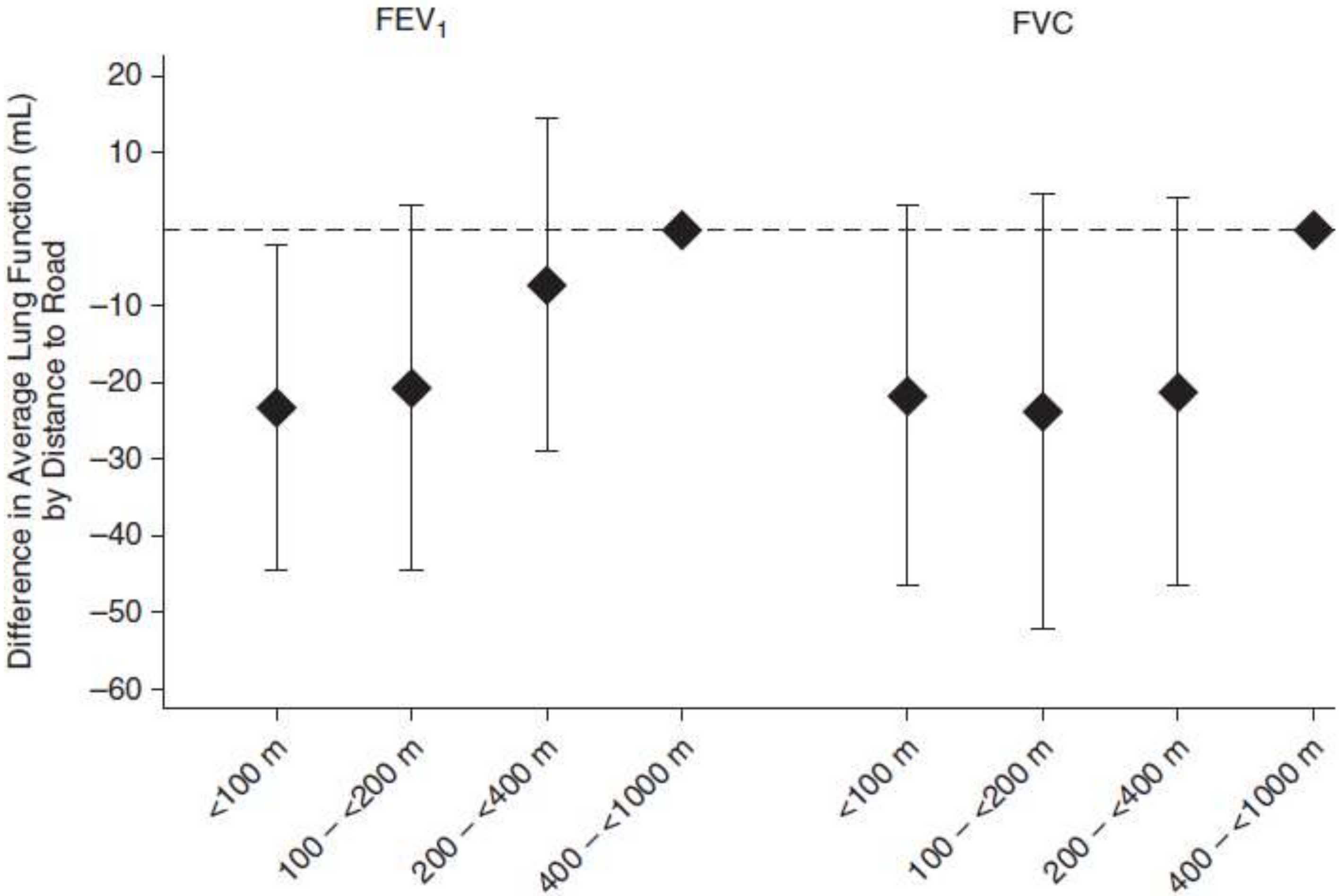

Figure 1. Differences in average lung function (and 95% confidence intervals) by distance-to-roadway category compared with the 400- to 1,000-m reference group. Adjusted for sex, age, height, weight, pack-years, education (no high school diploma, completed high school, some college, college degree or higher), median household income from 2000 census tract, cohort, date of examination, weekday, season (as a sine and cosine function of date), and relative humidity and temperature the day before the examination.

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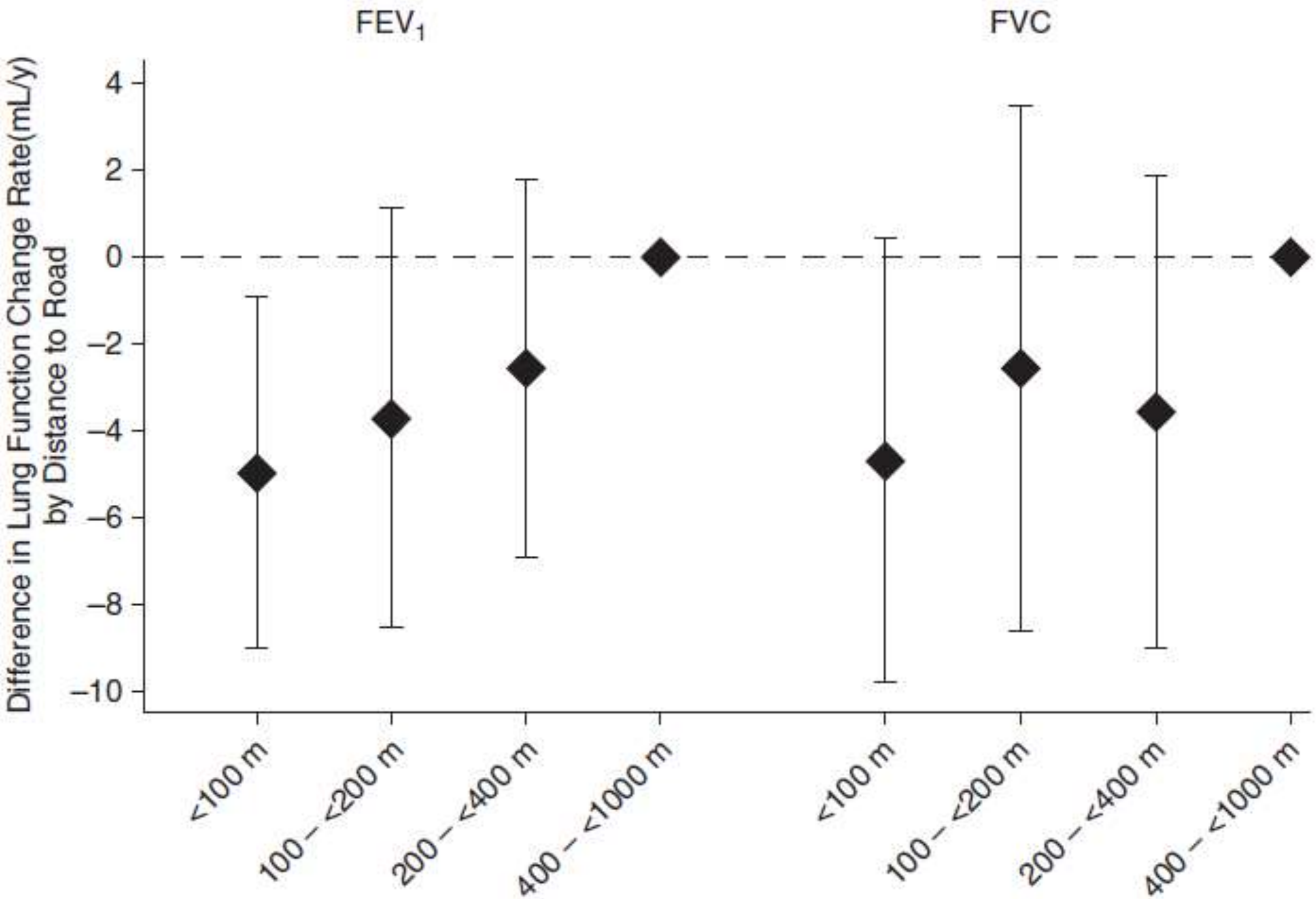

Figure 2. Differences in the rate of change in lung function (and 95% confidence intervals) by distance-to-roadway category compared with the 400- to 1,000-m reference group. Adjusted for sex, age, height, weight, pack-years, education (no high school diploma, completed high school, some college, college degree or higher), median household income from 2000 census tract, cohort, date of examination, weekday, season (as a sine and cosine function of date), and relative humidity and temperature the day before the examination.

Rice *et al. AJRCCM 2015;191:656-64*

Chronic Effects of Air Pollution Reduction

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Reduced Exposure to PM_{10} and Attenuated Age-Related Decline in Lung Function

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Jean-Pierre Zellweger, M.D., Thierry Rochat, M.D., Joel Schwartz, Ph.D.,
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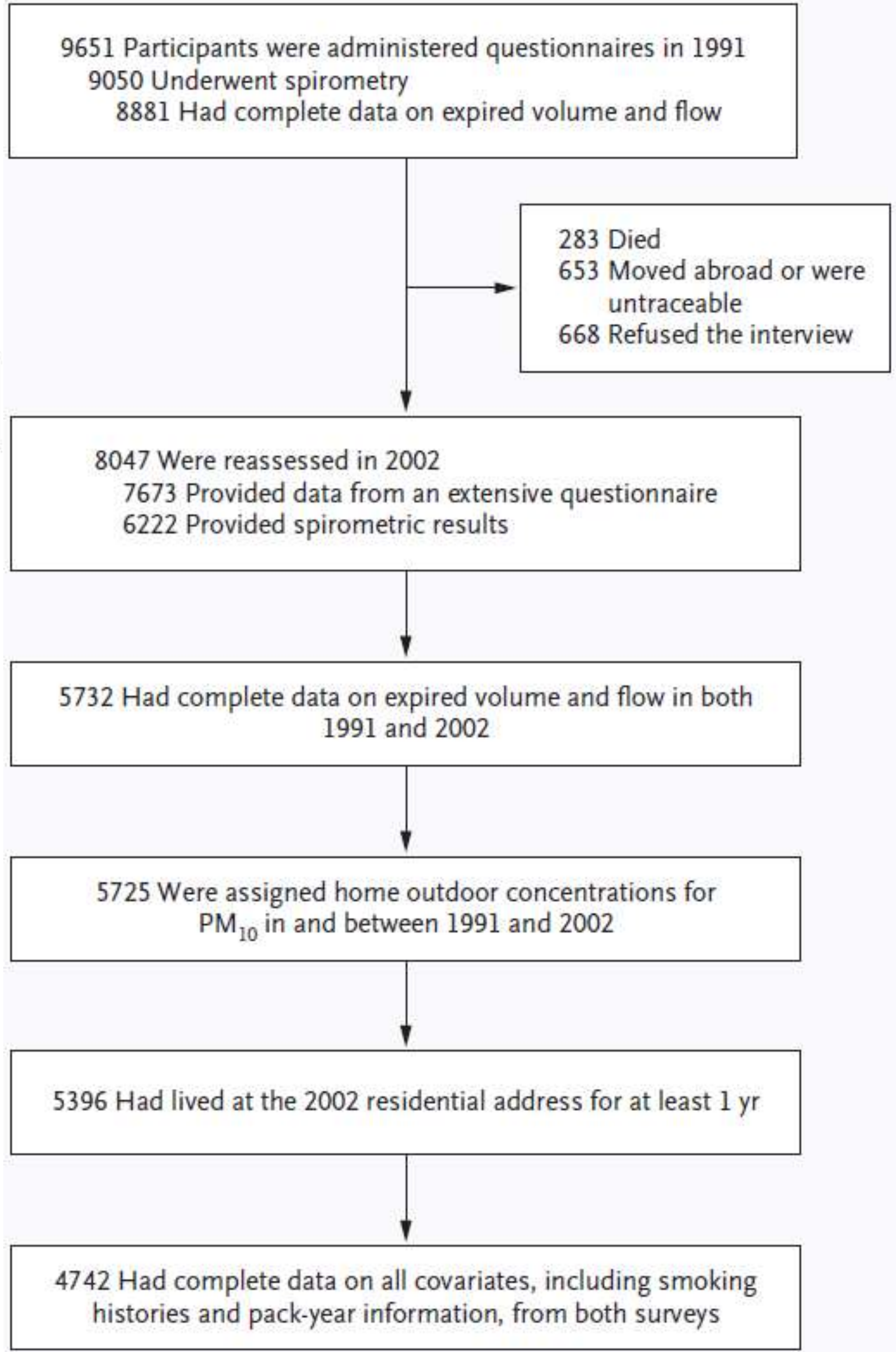

Downs *et al. NEJM 2007;357:2338-47*

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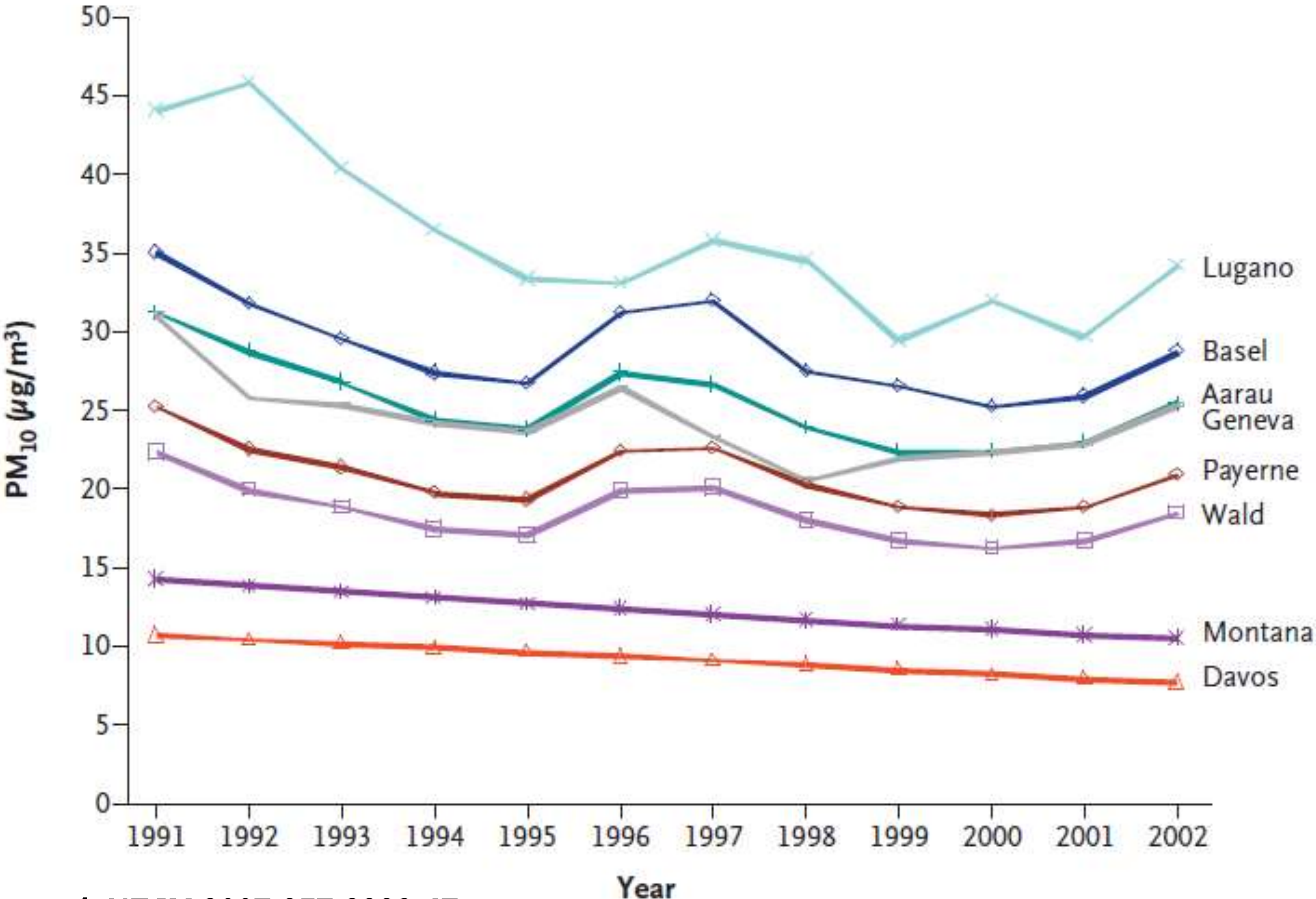

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Table 2. Estimated Effect of Change in PM_{10} and of Interval Exposure to PM_{10} on Annual Change in Lung Function.*

Variable	No. of Participants	Decrease in PM_{10} of 10 $\mu g/m^3$ between 1991 and 2002		Decrease in Interval Exposure of 109 $\mu g/m^3$-yr	
		Effect (95% CI)	P Value	Effect (95% CI)	P Value
All participants	4742				
FVC (ml)		−0.2 (−4.3 to 3.9)	0.91	5.3 (−1.1 to 11.7)	0.10
FEV_1 (ml)		3.1 (0.03 to 6.2)	0.045	6.9 (2.1 to 11.7)	0.005
FEV_1 as a percentage of FVC		0.06 (0.01 to 0.12)	0.02	0.05 (−0.04 to 0.13)	0.27
FEF_{25-75} (ml/sec)		11.3 (4.3 to 18.2)	0.001	14.0 (3.1 to 24.8)	0.01
All participants who never smoked	2213				
FVC (ml)		2.2 (−3.4 to 7.9)	0.43	9.9 (1.3 to 18.4)	0.02
FEV_1 (ml)		4.2 (−0.3 to 8.5)	0.06	9.3 (2.6 to 16.0)	0.006
FEV_1 as a percentage of FVC		0.05 (−0.03 to 0.13)	0.18	0.03 (−0.08 to 0.15)	0.59
FEF_{25-75} (ml/sec)		11.3 (1.4 to 21.2)	0.03	15.4 (0.2 to 30.6)	0.047

* Estimates were made after controlling for baseline PM_{10}, age, age squared, sex, height, parental smoking status, sine and cosine function of day of examination to control for seasonal effects, level of education in 1991, change in level of education, nationality, self-reported occupational exposure to dust or fumes in 1991 and in 2002, smoking status in 2002 (never smoked, former smoker, or current smoker), pack-years up to 1991, pack-years between 1991 and 2002, number of cigarettes per day in 1991 and in 2002, presence or absence of atopy, body-mass index (BMI) in 1991, change in BMI between 1991 and 2002, and clustering within area. FEF_{25-75} denotes forced expiratory flow between 25% and 75% of forced vital capacity (FVC), FEV_1 forced expiratory volume in 1 second, and PM_{10} particulate matter with an aerodynamic diameter of less than 10 μg.

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Chronic Effects of Air Pollution Reduction

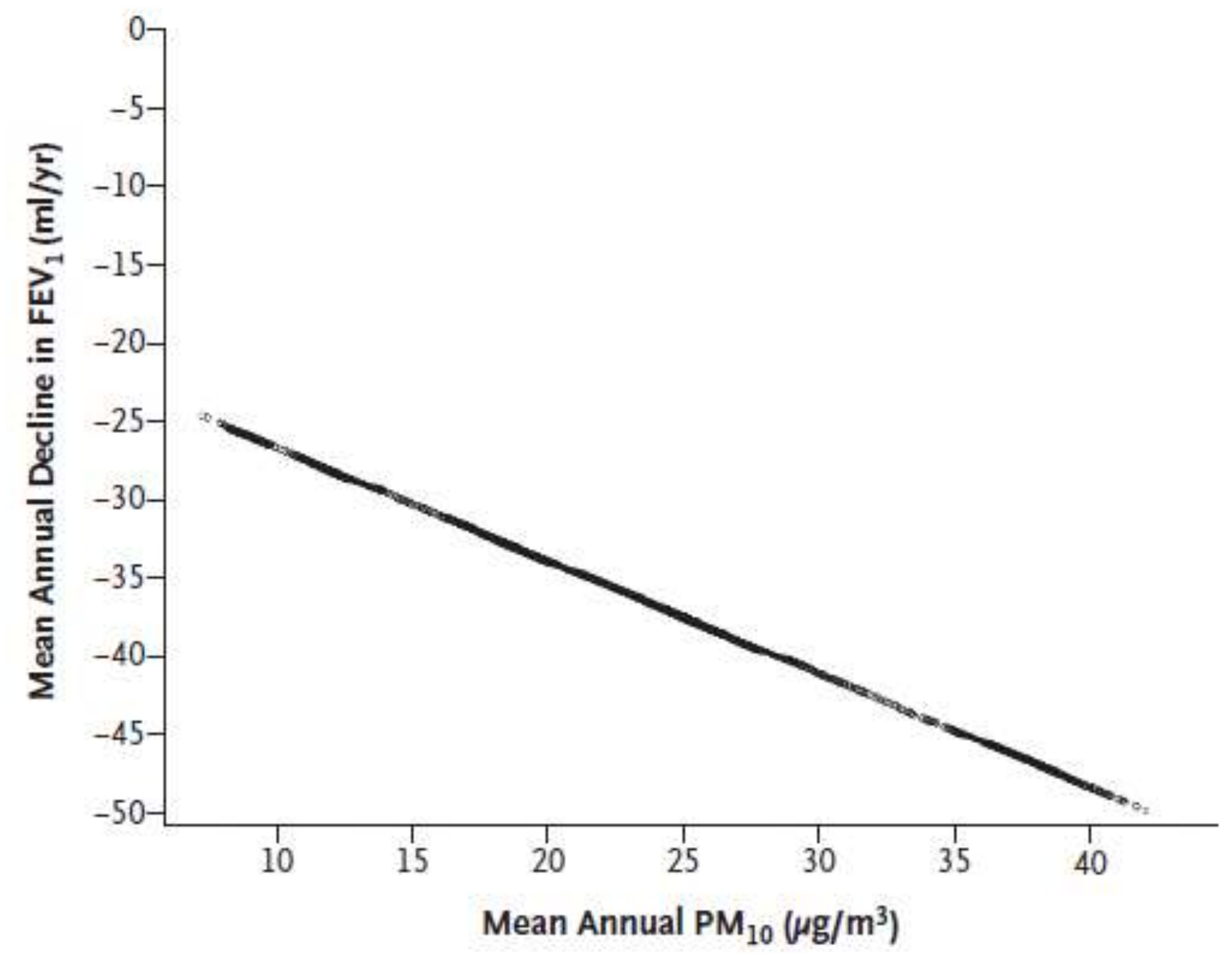

Figure 3. Estimated Effect of Interval Exposure between 1991 and 2002 (Expressed as Mean Annual PM_{10}) on Mean Annual Decline in FEV_1.

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