L’apport des grandes cohortes dans la BPCO

Sur la compréhension de la physiopathologie

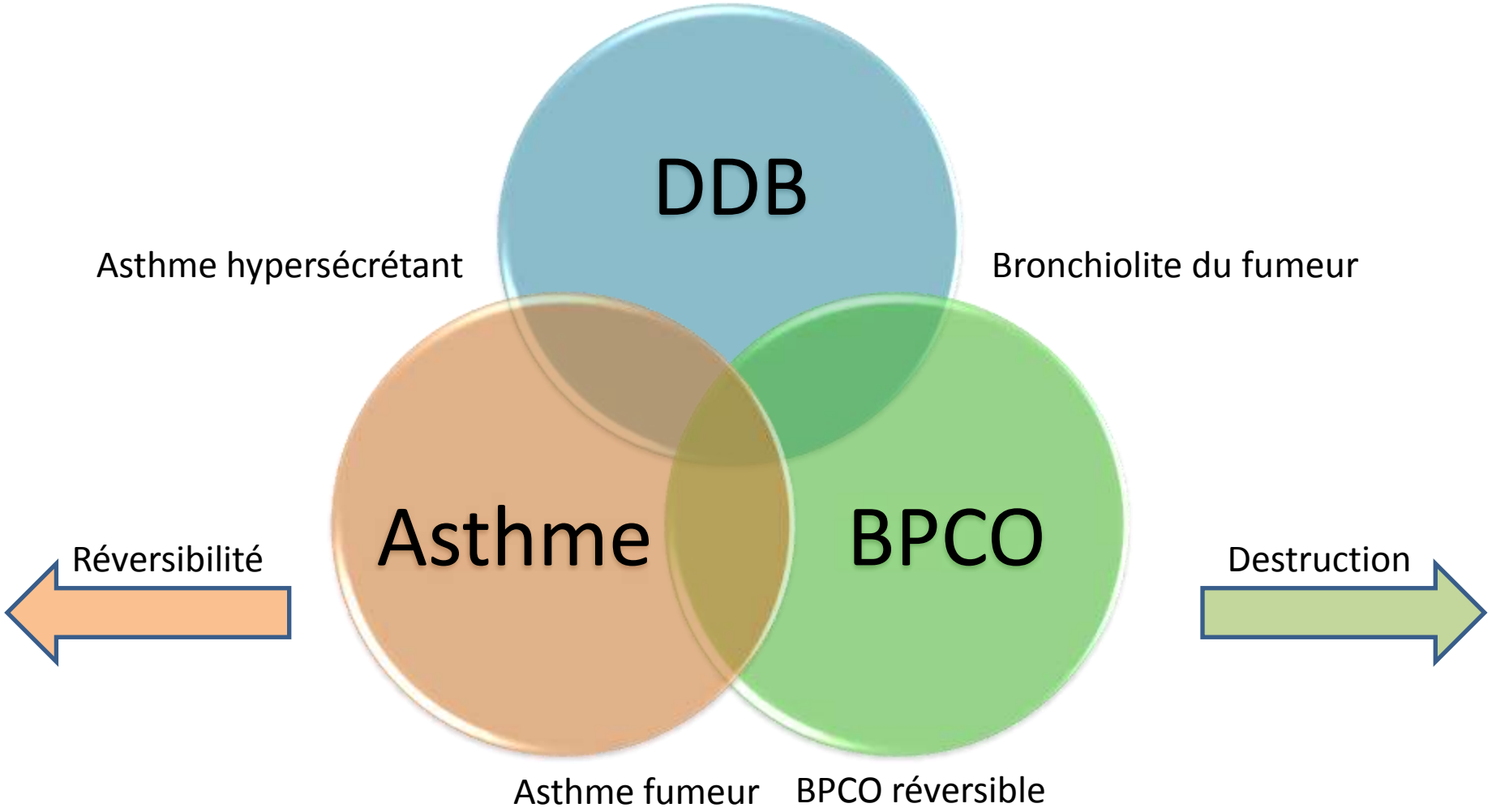
Arnaud BOURDIN (MONTPELLIER)

Déclaration de liens d'intérêts

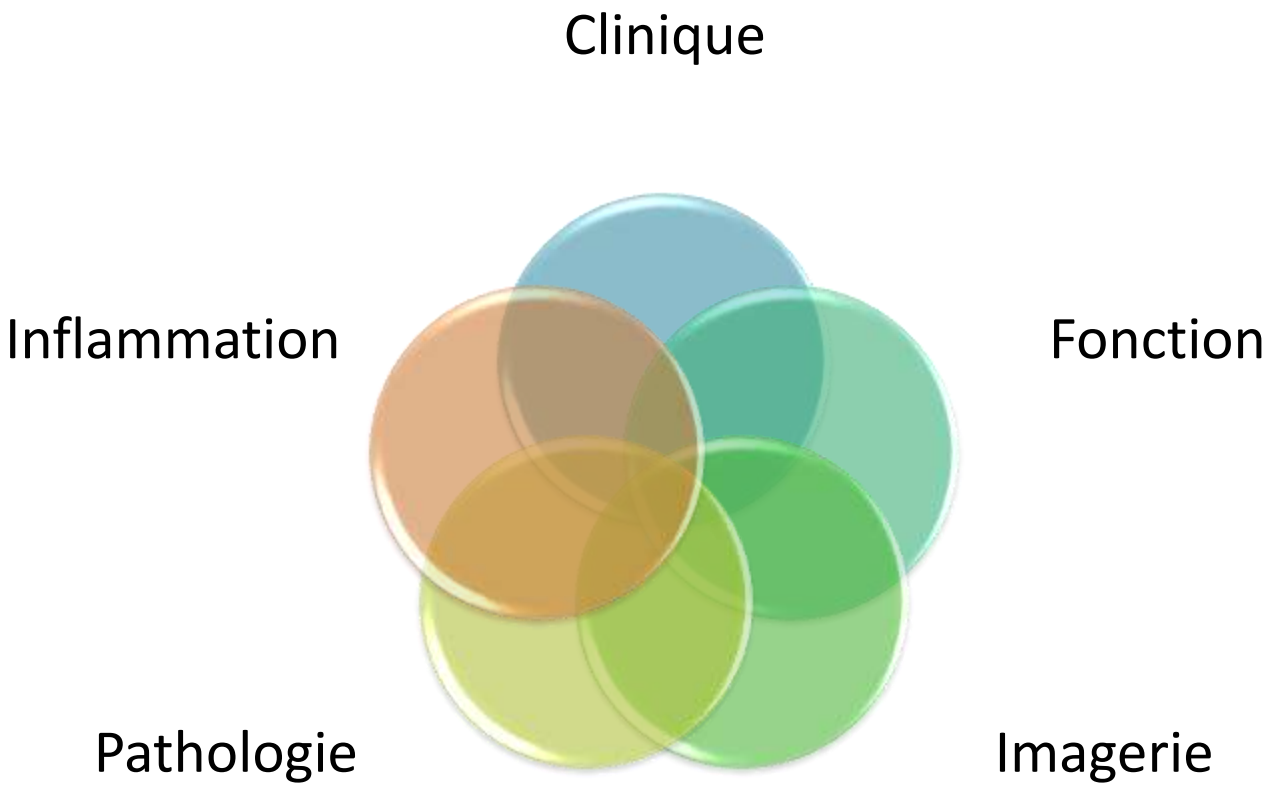
J'ai actuellement, ou j'ai eu au cours des trois dernières années, une affiliation ou des intérêts financiers ou intérêts de tout ordre avec les sociétés commerciales suivantes **en lien avec la santé**.

Actelion
Boston Scientific
Chiesi
Astra Zeneca
MedImmune
Sanofi
Boeringher Ingelheim
Centocor
Kalobios
United Therapeutics
GSK
Novartis
Bayer
Cephalon

Bronchopathies chroniques - nosologie



Bronchopathies chroniques - limites



Bronchopathies chroniques - omics

Protéomique

Epigénomique

Transcriptomique

Microbiomique

Génomique

Comorbidomique

Métabolomique

Grandes cohortes

- Génétique
- Biomarqueurs ?
- Imagerie
- Phénotypes tenant compte de l’hétérogénéité de la maladie

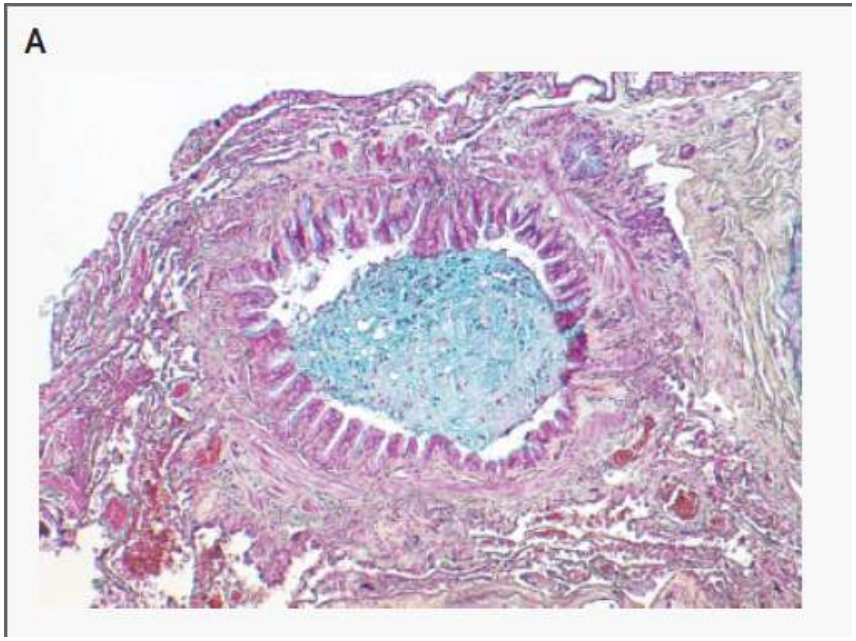
BPCO…ou pas BPCO ?

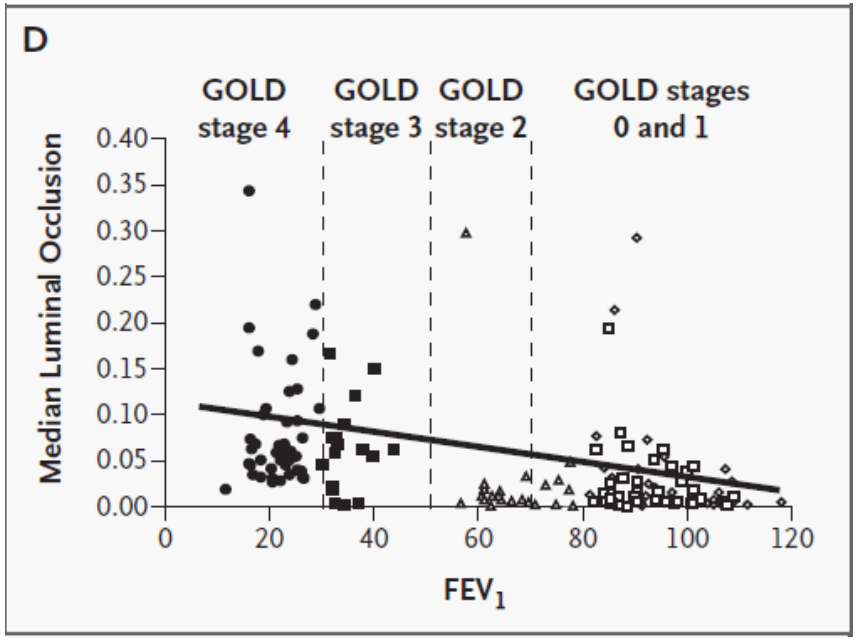
Variable	Participants without ILA	P Value	Participants with Indeterminate HRCT Scans	P Value	Participants with ILA	P Value
Total — no. (%)	1361 (56)		861 (36)		194 (8)	
Demographic characteristics						
Median FEV_1 — % of predicted‡	80 (52–97)	0.02	77 (55–92)	0.03	82 (67–93)	0.15
Median FVC — % of predicted‡	88 (75–100)	0.08	87 (74–99)	0.30	88 (77–98)	0.80
Median FEV_1:FVC %‡	70 (51–79)	0.04	68 (53–76)	0.01	71 (61–77)	0.32
Spirometric restriction — no. (%)§	414 (30)	0.82	266 (31)	0.004	81 (42)	0.002
Cough — no. (%)	473 (35)	0.01	344 (40)	0.87	79 (41)	0.11
Shortness of breath when hurrying on level ground or walking up slight hill — no. (%)	731 (54)	0.04	501 (58)	0.68	115 (60)	0.16
Spirometric measures						
GOLD stage — no. (%)†						
COPD (≥GOLD stage 2)	561 (41)	0.22	378 (44)	0.005	63 (32)	0.02
Unclassified	102 (7)	0.007	94 (11)	0.17	28 (14)	0.002
0	599 (44)		306 (36)		76 (39)	
1	99 (7)		83 (10)		26 (13)	
2	260 (19)		201 (23)		46 (24)	
3	186 (14)		121 (14)		12 (6)	
4	115 (8)		56 (7)		5 (3)	

Washko, NEJM 2011

The Nature of Small-Airway Obstruction in Chronic Obstructive Pulmonary Disease

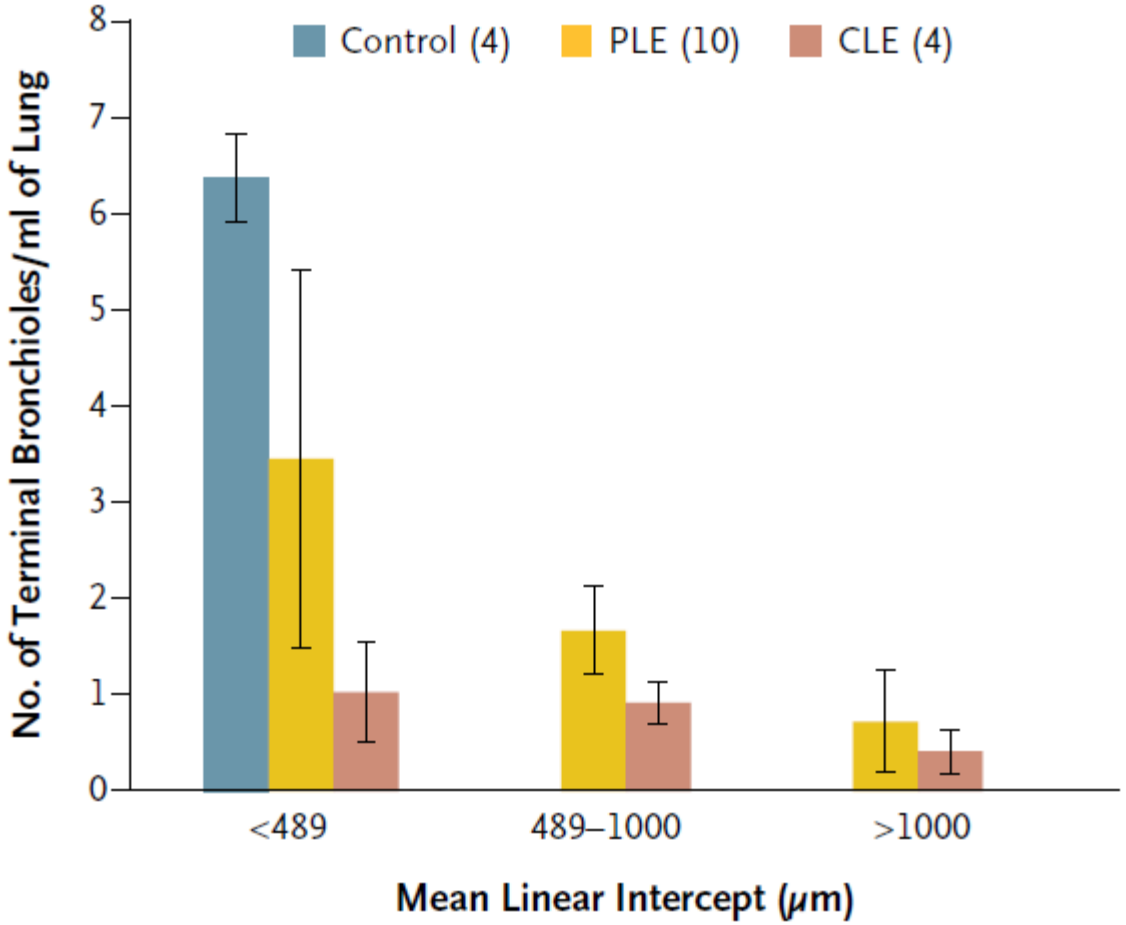
J.Hogg, NEJM 2004

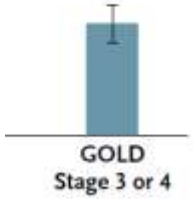


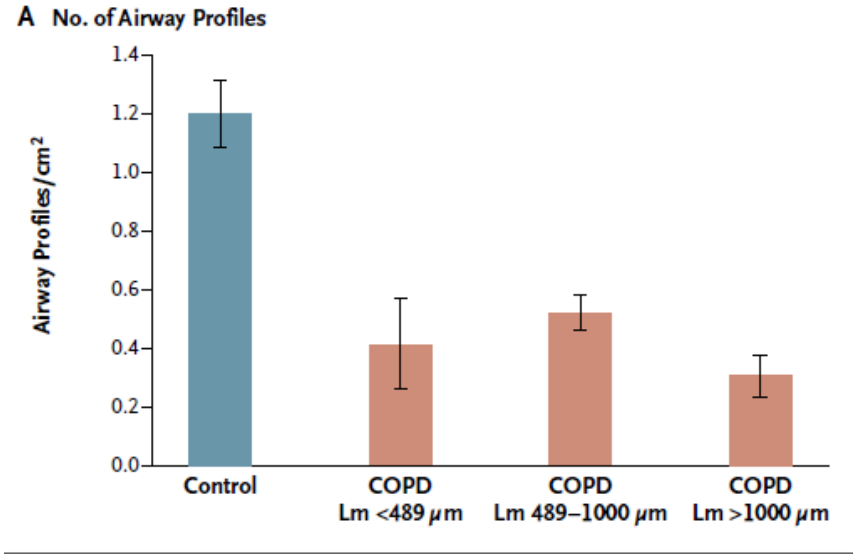


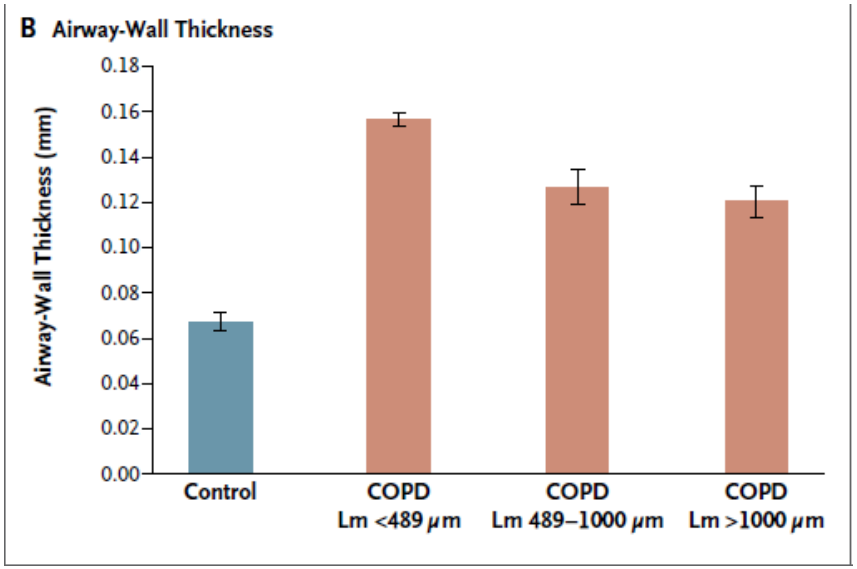
The NEW ENGLAND JOURNAL of MEDICINE

D Terminal Bronchioles

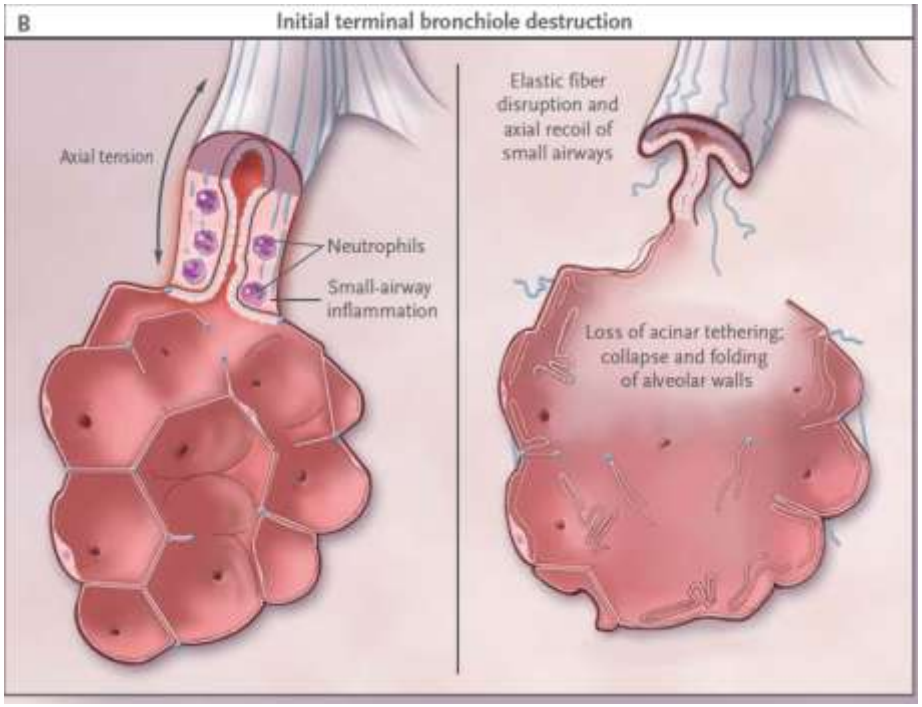





A No. of Airway Profiles
Airway Profiles/cm²
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
Control
COPD Lm <489 μm
COPD Lm 489–1000 μm
COPD Lm >1000 μm

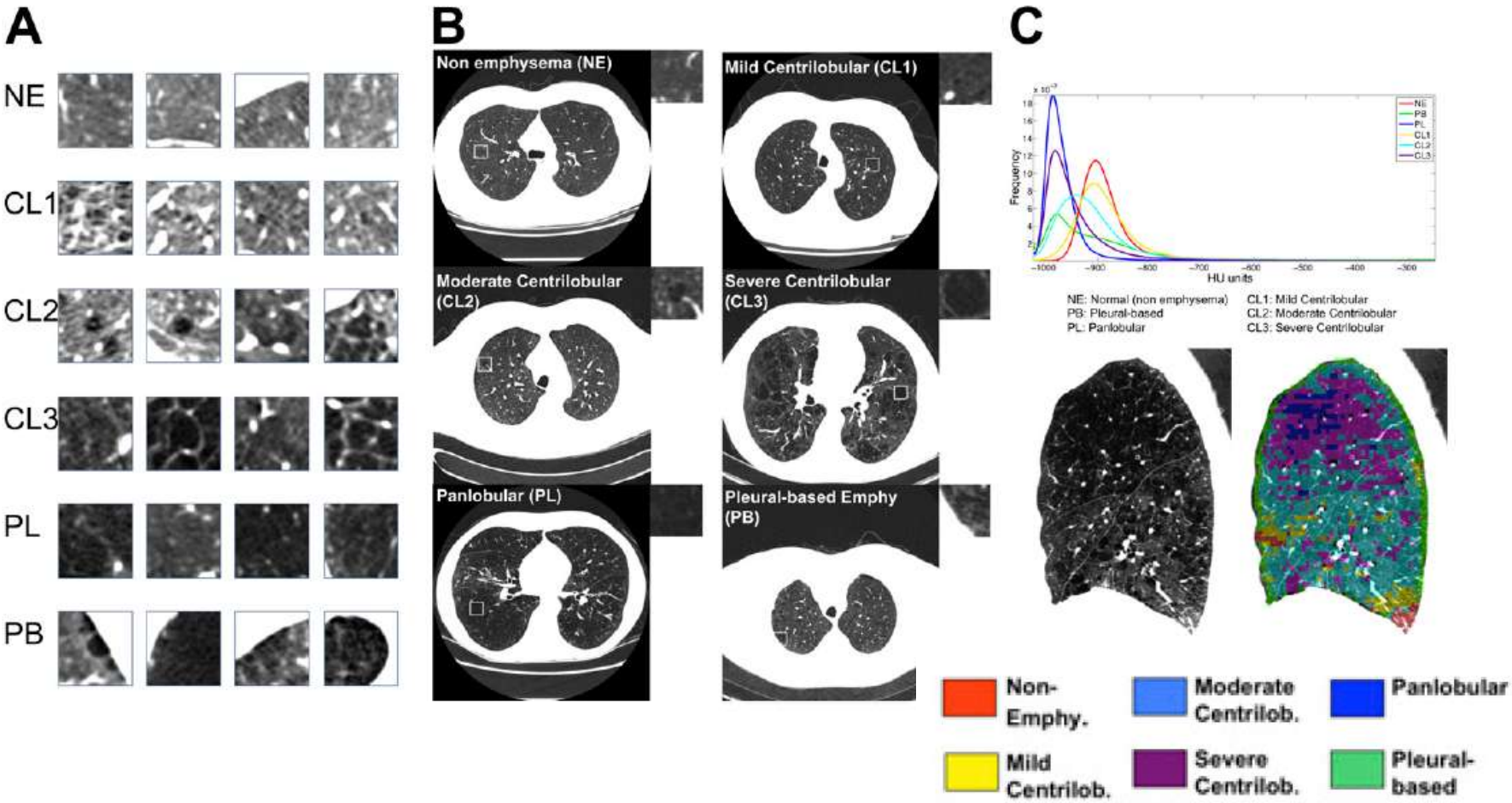

B Airway-Wall Thickness
Airway-Wall Thickness (mm)
0.18
0.16
0.14
0.12
0.10
0.08
0.06
0.04
0.02
0.00
Control
COPD Lm <489 μm
COPD Lm 489–1000 μm
COPD Lm >1000 μm


The NEW ENGLAND JOURNAL of MEDICINE
EDITORIAL
Emphysema — A Disease of Small Airways or Lung Parenchyma?
Wayne Mitzner, Ph.D.


B
Initial terminal bronchiole destruction
Axial tension
Neutrophils
Small-airway inflammation
Elastic fiber disruption and axial recoil of small airways
Loss of acinar tethering; collapse and folding of alveolar walls

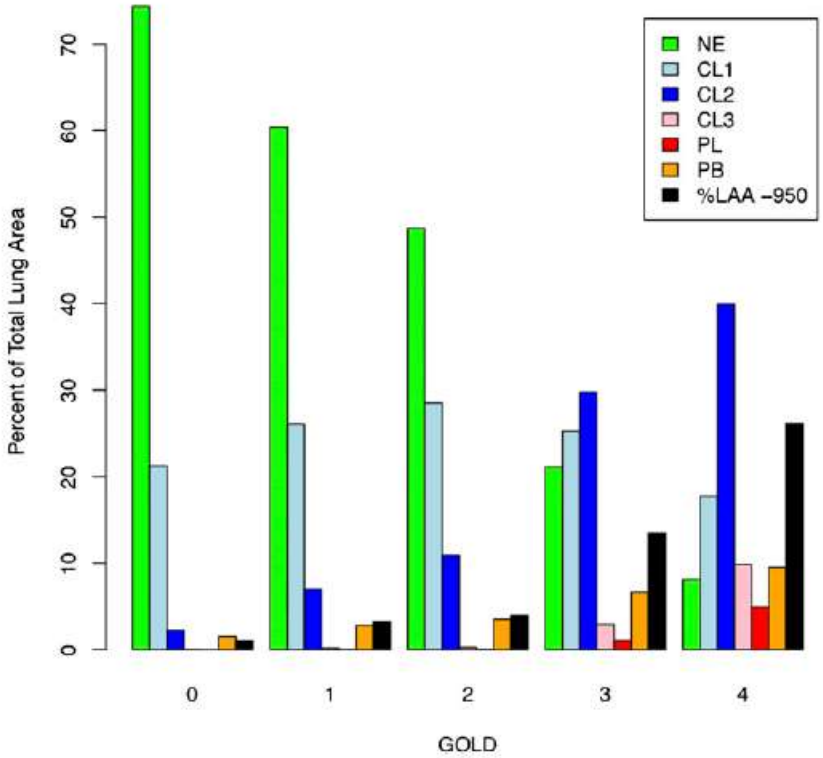
Hétérogénéité tomodensitométrique

Nouvelle méthode automatisée « LHE »

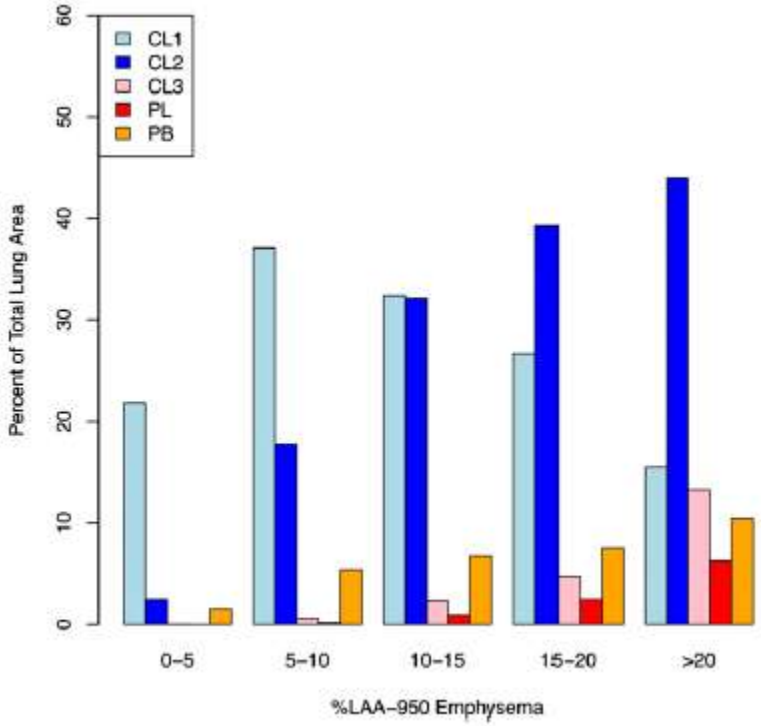


Am J Respir Crit Care Med Vol 188, Iss. 9, pp 1083–1090, Nov 1, 2013

Distribution en fonction de GOLD

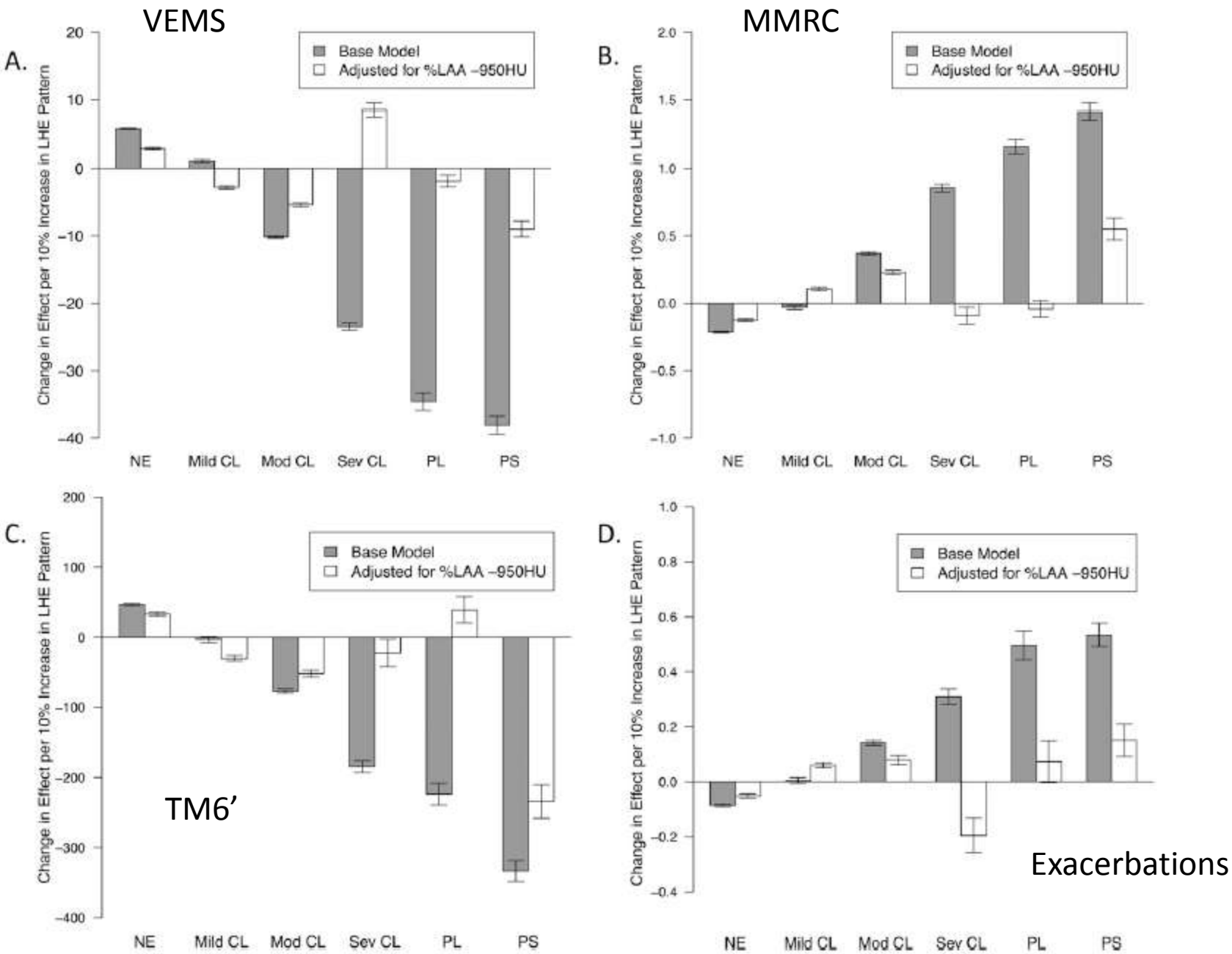


En fonction de GOLD



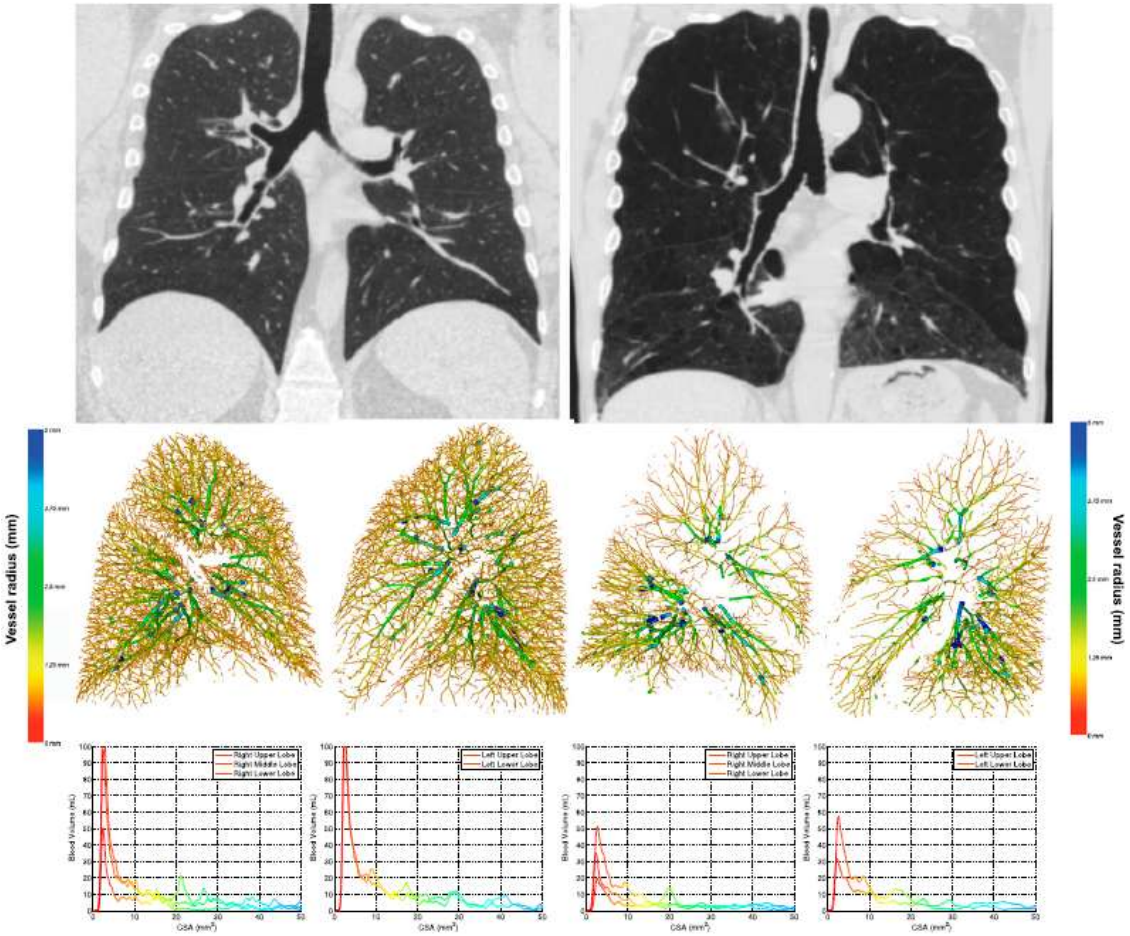
En fonction de la méthode habituelle

Am J Respir Crit Care Med Vol 188, Iss. 9, pp 1083–1090, Nov 1, 2013



Am J Respir Crit Care Med Vol 188, Iss. 9, pp 1083–1090, Nov 1, 2013

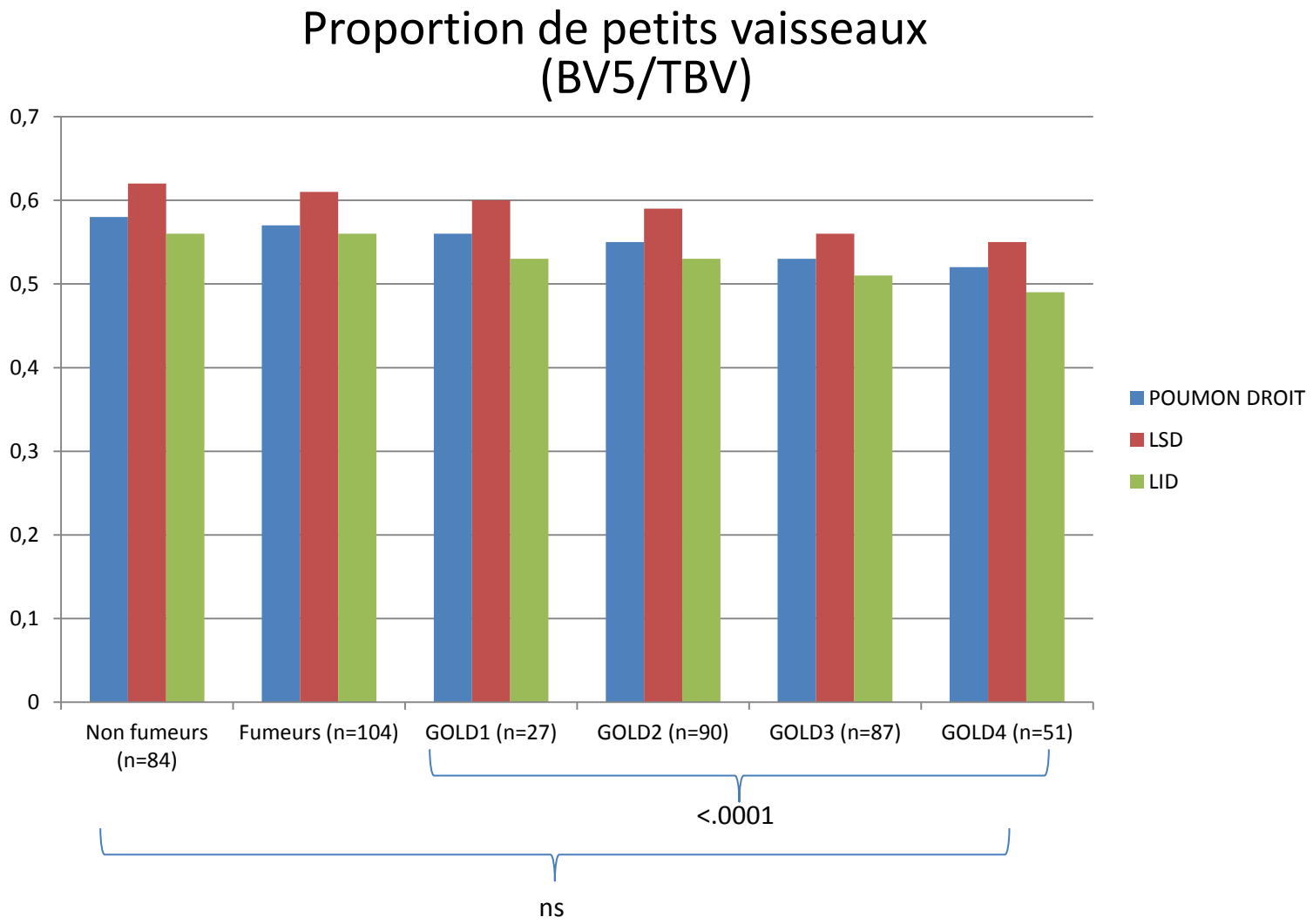
Computed Tomographic Measures of Pulmonary Vascular Morphology in Smokers and Their Clinical Implications



- Calcul du volume de vaisseaux total (TBV)
- Calcul du volume des petits vaisseaux (BV5; < 5 mm²)
- Mesure de l'emphysème (%LAA -950)
- Volume de tissue non vasculaire (TissuV)

Am J Respir Crit Care Med Vol 188, Iss. 2, pp 231–239, Jul 15, 2013

Computed Tomographic Measures of Pulmonary Vascular Morphology in Smokers and Their Clinical Implications



Am J Respir Crit Care Med Vol 188, Iss. 2, pp 231–239, Jul 15, 2013

Relation avec la BPCO

Models	D_{LCO} Post-bronchodilator ($n = 134$)			Oxygen Saturation ($n = 358$)			6-MWD (*ft*) ($n = 351$)			SGRQ Score Total ($n = 358$)			BODE* ($n = 349$)		
	Beta	*P* Value	R^2	Beta	*P* Value	R^2	Beta	*P* Value	R^2	Beta	*P* Value	R^2	Beta	*P* Value	R^2
RUL															
BVS_{RUL}/TBV_{RUL}	15.20	0.07	0.47	13.44	0.0003	0.46	270.29	0.4877	0.43	14.40	0.4769	0.33	6.1	0.003	0.35
$BVS_{RUL}/T^{issue}V_{RUL}$	−512.6	<0.0001	0.57	−206.5	<0.0001	0.48	−9646.2	0.0335	0.44	58.89	0.0011	0.35	−68.9	0.005	0.35
RLL															
BVS_{RLL}/TBV_{RLL}	24.02	0.0021	0.51	16.51	<0.0001	0.48	730.4	0.0593	0.44	43.17	0.0334	0.33	10.1	<0.0001	0.42
$BVS_{RLL}/T^{issue}V_{RLL}$	−378.4	<0.0001	0.55	−185.1	<0.0001	0.48	14167	0.0003	0.45	83.05	0.0222	0.34	−107.5	<0.0001	0.42
RML															
BVS_{RML}/TBV_{RML}	4.35	0.38	0.48	0.54	0.84	0.44	−336.73	0.2140	0.44	0.28	0.9847	0.33	4.1	<0.0001	0.25
$BVS_{RML}/T^{issue}V_{RML}$	−553.2	<0.0001	0.57	−202.9	<0.0001	0.47	17743	0.0002	0.46	91.41	0.0071	0.34	−95.3	0.0007	0.26
LUL															
BVS_{LUL}/TBV_{LUL}	18.62	0.0136	0.50	10.33	0.0042	0.46	536.4	0.1494	0.44	19.63	0.3128	0.33	7.1	0.0003	0.34
$BVS_{LUL}/T^{issue}V_{LUL}$	−565.2	<0.0001	0.56	−261.7	<0.0001	0.49	11908	0.0191	0.44	38.57	0.0453	0.33	−96.7	0.0008	0.34
LLL															
BVS_{LLL}/TBV_{LLL}	21.26	0.0029	0.51	11.45	0.0006	0.46	600.5	0.0786	0.44	39.41	0.0287	0.33	11.2	<0.0001	0.43
$BVS_{LLL}/T^{issue}V_{LLL}$	−388.7	<0.0001	0.54	−256.6	<0.0001	0.50	10218	0.0177	0.44	86.24	0.4138	0.33	−106.4	<0.0001	0.39
Right lung															
BVS_{Right}/TBV_{Right}	25.42	0.0068	0.50	17.58	<0.0001	0.47	528.65	0.2547	0.44	35.40	0.1373	0.33	8.7	0.0003	0.42
$BVS_{Right}/T^{issue}V_{Right}$	−577.50	<0.0001	0.58	−235.37	<0.0001	0.48	15843	0.0009	0.45	42.65	0.0029	0.34	−103.9	0.0001	0.43
Left lung															
BVS_{Left}/TBV_{Left}	23.14	0.0042	0.51	14.56	0.0002	0.47	725.42	0.0723	0.44	37.78	0.0728	0.33	10.4	<0.0001	0.44
$BVS_{Left}/T^{issue}V_{Left}$	−542.35	<0.0001	0.56	−293.27	<0.0001	0.50	12507	0.0128	0.44	94.03	0.1387	0.33	−81.9	0.004	0.42

Am J Respir Crit Care Med Vol 188, Iss. 2, pp 231–239, Jul 15, 2013

Histoire familiale de BPCO

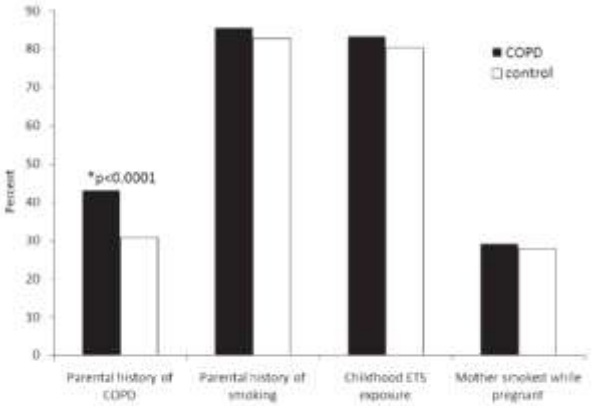


FIGURE 1. Parental history and early life smoke exposures in patients with COPD and control smokers with normal spirometry. ETS = environmental tobacco smoke.

	Full Model[a]	
	OR (95% CI)	*P* Value
Age, per 10 y	2.01 (1.75-2.31)	<.0001
Female sex	0.87 (0.69-1.09)	.22
Black race	0.79 (0.59-1.05)	.11
Lifetime smoking, per 10 pack-years	1.25 (1.18-1.32)	<.0001
Attended college or technical school	0.48 (0.37-0.61)	<.0001
Parental history of COPD[b]	1.73 (1.36-2.20)	<.0001
Parental history of smoking	1.22 (0.82-1.83)	.32
Childhood ETS exposure	0.98 (0.67-1.44)	.91
Occupational exposure to dust, gas, smoke, chemicals, or fumes	…	…

Hersh, Chest 2011

GENETIQUE

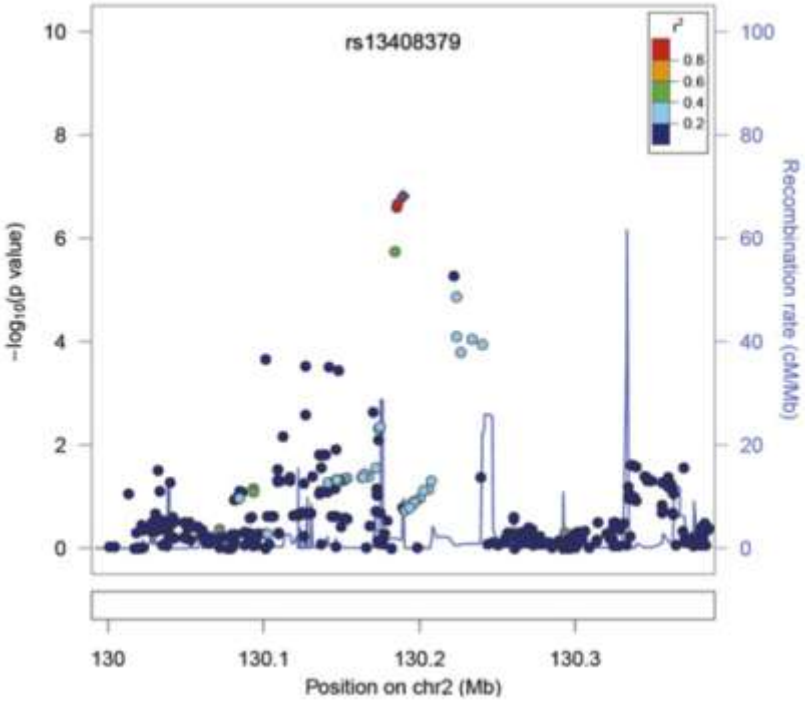
- Association avec le comportement tabagique (sevré vs. persistant)

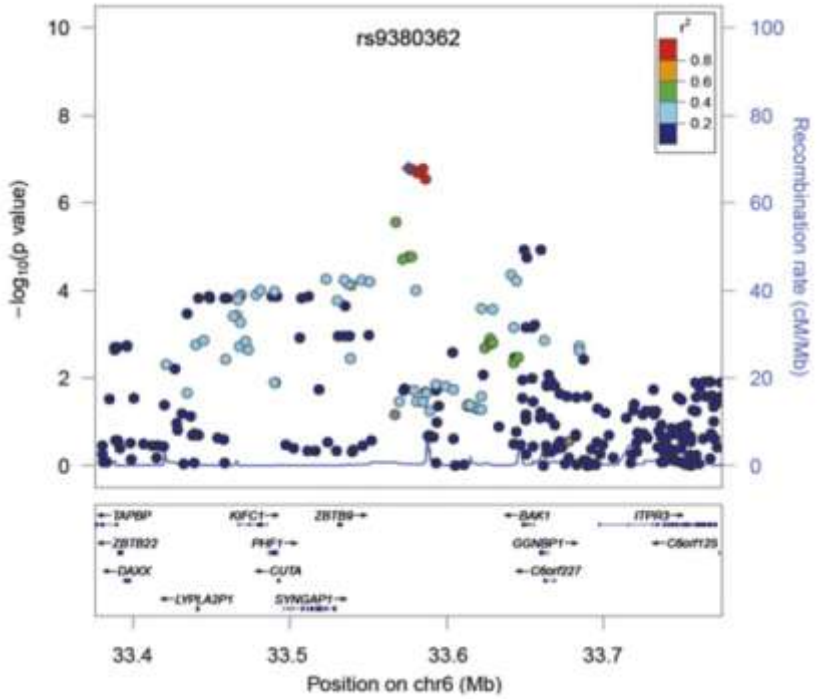
Siedlinski, Thorax 2011

	Cohort			
	NETT n=362*	Norway n=851*	ECLIPSE n=1734*	COPDGene n=494*
Characteristics				
Men*, n (%)	234 (64.6)	511 (60.0)	1160 (66.9)	242 (49.0)
Age in years*, Mean (SD)	67.4 (5.8)	65.5 (10.1)	63.7 (7.1)	64.7 (8.1)
Pack-years smoked*, Mean (SD)	66.1 (30.9)	32.1 (18.6)	50.4 (27.4)	54.8 (26.8)
Post-bronchodilator FEV_1 (% pred.)*, Mean (SD)	29.1 (7.8)	50.7 (17.5)	44.8 (14.7)	48.7 (18.4)
Post-bronchodilator FEV_1/FVC*, Mean (SD)	0.32 (0.06)	0.51 (0.13)	0.45 (0.12)	0.48 (0.13)
Enrolment, Years	1998–2002	2003–2005	2005–2007	2008–2009
Genotyping technology, Chip	Illumina Quad 610	Illumina HumanHap 550 V1, V3, and Duo	Illumina HumanHap 550 V3	Illumina Human Omni1-Quad
Phenotype studied				
Age at smoking initiation				
Mean (SD)	16.6 (3.6)	18.7 (5.1)	16.9 (4.4)	16.8 (4.4)
Number of patients with non-missing phenotype	362	851	1690	494
Lambda inflation factor	0.986	0.989	1.019	0.997
Lifetime average CPD				
Mean (SD)	32.4 (13.5)	15.7 (7.8)	25.5 (12.4)	27.6 (11.8)
Number of patients with non-missing phenotype	361	851	1734	494
Lambda inflation factor	1.002	0.996	1.018	0.996
Smoking cessation				
Current smokers, n (%)	0 (0)	404 (47.5)	610 (35.3)	150 (30.6)
Former smokers, n (%)	362 (100)	447 (52.5)	1120 (64.7)	340 (69.4)
Lambda inflation factor	–	1.000	0.998	0.995
Current CPD†				
Mean (SD)	–	13.1 (6.9)	15.6 (10.8)	18.4 (12.4)
Number of patients with non-missing phenotype	–	398	565	150
Lambda inflation factor	–	0.995	1.005	0.997

Cigarette per day

SNP régionaux associés à l'âge et au comportement tabagique





Loci Identified by Genome-wide Association Studies Influence Different Disease-related Phenotypes in Chronic Obstructive Pulmonary Disease

Sreekumar G. Pillai[1]*, Xiangyang Kong[1], Lisa D. Edwards[2], Michael H. Cho[3], Wayne H. Anderson[1], Harvey O. Coxson[4], David A. Lomas[5], Edwin K. Silverman[3], and ECLIPSE and ICGN Investigators

	ECLIPSE COPD Cases	ICGN	
		Probands	Siblings
Subjects, n	1,609	606	1,285
Age, ± SD	63.8 (± 7.1)	58.4 (± 5.4)	58 (± 9.8)
Female, %	32.5	40.3	49.8
Post-bronchodilator FEV_1, % predicted, ± SD	48.1 (± 15.6)	36.2 (± 12.9)	77.5 (± 25.9)
Post-bronchodilator FEV_1/FVC ratio*, ± SD	0.45 (± 0.11)	0.37 (± 0.12)	0.61 (± 0.15)
Pack-years of smoking, ± SD	50.9 (± 28)	51.5 (± 26.7)	40.5 (± 24.6)
Current smoker, %	35.5	33.83	50.82
Body mass index, ± SD	26.7 (± 5.6)	26.1 (± 6.2)	27.2 (± 6.5)
Fat-free body mass, ± SD[†‡]	50 (± 10.2)		
BODE index, ± SD[†§]	3.2 (± 2.1)		
Frequency of exacerbation in the past 12 mo, ± SD[†]	0.83 (± 1.20)		
Frequency of exacerbation (2-yr follow-up), ± SD[†]	2.12 (± 2.62)		
Quantitative emphysema, −950 HU, ± SD[‖]	18 (± 12)	22.3 (± 14.4)	16.08 (± 10.9)
Radiologist score, % subjects with >5% emphysema	66.7	80.8	39.3
Airway wall thickness, mm, Pi_{10}, ± SD[¶]	3.96 (± 0.21)	4.86 (± 0.43)	4.78 (± 0.44)

Am J Respir Crit Care Med Vol 182. pp 1498–1505, 2010

SNP des 3 gènes déjà associés à la BPCO dans ces deux cohortes

	HHIP rs13118928				*CHRNA* rs8034191				*FAM13A* rs7671167			
	GG (*n* = 270)	GA (*n* = 749)	AA (*n* = 590)	*P* Value	CC (*n* = 270)	CT (*n* = 804)	TT (*n* = 535)	*P* Value	CC (*n* = 343)	CT (*n* = 804)	TT (*n* = 457)	*P* Value
Post-bronchodilator FEV_1	1.399 (0.51)	1.364 (0.53)	1.398 (0.49)	0.058	1.280 (0.47)	1.343 (0.52)	1.383 (0.53)	0.01	1.341 (0.52)	1.338 (0.50)	1.364 (0.54)	0.51
Percent-predicted FEV_1	49.13 (15.41)	48.54 (15.61)	47.06 (15.53)	0.077	46.63 (15.26)	47.43 (15.46)	49.35 (15.88)	0.02	48.3 (14.96)	48.17 (15.59)	47.77 (15.97)	0.53
FEV_1/FVC	46.33 (11.85)	45.66 (11.56)	43.14 (11.18)	1.9×10^{-4}	43.89 (11.44)	44.39 (11.34)	46.03 (11.83)	0.004	45.67 (11.44)	44.83 (11.56)	44.25 (11.58)	0.08
Number of cigarettes smoked per day	25.67 (13.04)	25.96 (12.57)	25.42 (12.43)	0.46	27.95 (12.95)	25.78 (12.62)	24.48 (12.24)	0.0009	25.7 (12.28)	25.63 (12.80)	25.86 (12.5)	0.48
Age started smoking cigarettes	17.54 (4.88)	16.94 (4.32)	16.78 (4.08)	0.18	16.81 (4.08)	17.08 (4.56)	16.59 (4.17)	0.09	16.8 (4.23)	16.99 (4.12)	17.08 (4.78)	0.43
Pack-years of smoking	51.92 (31.27)	50.40 (27.35)	50.94 (27.26)	0.34	56.36 (31.08)	50.35 (27.46)	48.84 (26.84)	0.0016	52.02 (28.05)	50.26 (28.43)	51.02 (27.22)	0.94
Body mass index	26.91 (5.48)	26.96 (5.74)	26.34 (5.59)	0.070	26.54 (5.96)	26.61 (5.69)	26.98 (5.43)	0.15	26.68 (5.58)	26.76 (5.74)	26.69 (5.54)	0.90
Fat-free body mass	51.34 (10.34)	50.40 (10.38)	49.26 (9.70)	0.007	49.28 (9.76)	50.15 (10.42)	50.56 (9.93)	0.09	49.65 (9.67)	50.02 (10.07)	50.71 (10.63)	0.41
Emphysema, −950 HU	17.05 (11.69)	17.66 (12.21)	18.99 (11.95)	0.07	20.34 (12.86)	18.02 (11.79)	16.89 (11.84)	0.0018	16.85 (10.95)	18.17 (12.23)	18.69 (12.42)	0.04
Clinically significant emphysema, radiologist score	64.2	65.1	70	0.006	75.4	67	62	*0.0002*	75.3	74	74	*0.82*
BODE index	*3.13 (1.95)*	*3.18 (2.16)*	*3.17 (2.11)*	*0.78*	*3.45 (2.14)*	*3.21 (2.13)*	*3.00 (2.05)*	*0.03*	3.101 (2.034)	3.13 (2.10)	3.277 (2.15)	*0.08*
Pi_{10}	*3.97 (0.19)*	*3.97 (0.21)*	*3.95 (0.21)*	*0.26*	*3.96 (0.20)*	*3.96 (0.21)*	*3.96 (0.21)*	0.58	3.969 (0.21)	3.967 (0.217)	3.951 (0.20)	0.19

Definition of abbreviations: BODE = body mass index, airflow obstruction, and exercise capacity; COPD = chronic obstructive pulmonary disease; ECLIPSE = Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-point.

Am J Respir Crit Care Med Vol 182. pp 1498–1505, 2010

Analyse multivariée

TABLE 4. MULTIVARIATE ANALYSES INCLUDING *HHIP*, *FAM13A*, AND *CHRNA*3/5 SINGLE-NUCLEOTIDE POLYMORPHISMS OF THE COPD-RELATED PHENOTYPES IN ECLIPSE COPD PATIENTS*

	FEV_1 Percent Predicted			FEV_1/FVC			Quantitative Emphysema		
	Estimate	SE	*P* Value	Estimate	SE	*P* Value	Estimate	SE	*P* Value
rs13118928 (*HHIP*)	1.29	0.56	0.021	1.921	0.412	<0.001	−1.195	0.475	0.012
rs8034191 (*CHRNA*)	−1.341	0.574	0.02	−1.212	0.423	0.004	1.422	0.492	0.004
rs7671167 (*FAM13A*)	0.263	0.558	0.638	0.776	0.411	0.059	−0.963	0.476	0.043
Sex (female)	3.811	0.855	<0.001	2.231	0.63	<0.001	−1.63	0.724	0.024
Pack-years smoking	−0.006	0.014	0.688	−0.007	0.011	0.538	−0.007	0.013	0.57
Age	0.094	0.056	0.093	−0.09	0.041	0.028	0.188	0.048	<0.001
	Fat-Free Body Mass			Body Mass Index					
rs13118928 (*HHIP*)	0.952	0.289	0.001	0.441	0.2	0.028			
rs8034191 (*CHRNA*)	−0.49	0.296	0.098	−0.302	0.206	0.142			
rs7671167 (*FAM13A*)	−0.197	0.287	0.492	0.059	0.2	0.766			
Sex (female)	−13.17	0.441	<0.001	−0.34	0.306	0.267			
Pack-years smoking	0.01	0.008	0.206	0.014	0.005	0.006			
Age	−0.136	0.028	<0.001	−0.033	0.02	0.091			

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; ECLIPSE = Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-point.
* A total of 1,719 subjects from ECLIPSE cohort were used in this analysis.

Am J Respir Crit Care Med Vol 182. pp 1498–1505, 2010

BICD1 et emphysème

	ECLIPSE	Norway	NETT
Subjects, n	1,586	435	362
Age, yr (SD)	63.4 (7.0)	63.8 (9.6)	67.4 (5.8)
Female, %	34.8	37.5	35.4
Post-FEV_1, % predicted (SD)	47.7 (15.7)	52.6 (17.0)	28.1 (7.4)
Pack-years of smoking (SD)	50.7 (27.6)	30.9 (18.1)	66.1 (30.9)
Current smokers, %	35.4	48.7	0
Emphysema −950 (SD)*	18.4 (12.1)	11.5 (11.8)	16.9 (10.8)

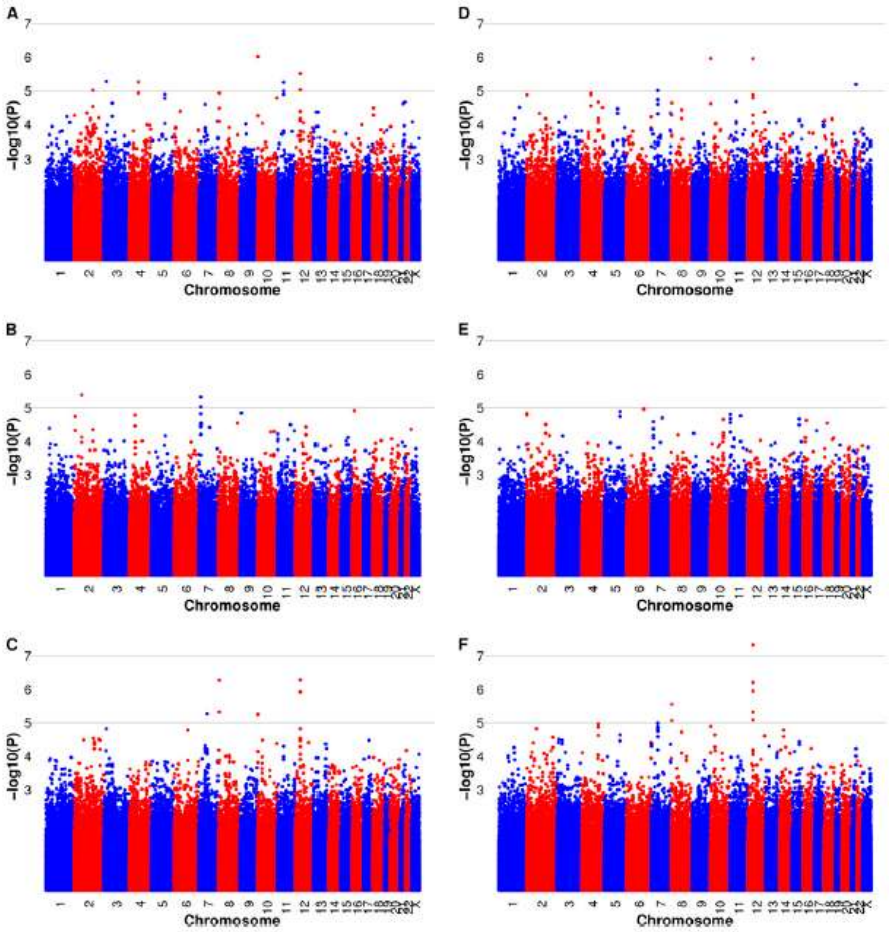
Am J Respir Crit Care Med Vol 183. pp 43–49, 2011

SNP et emphysème

Eclipse

Norway

Meta analyse

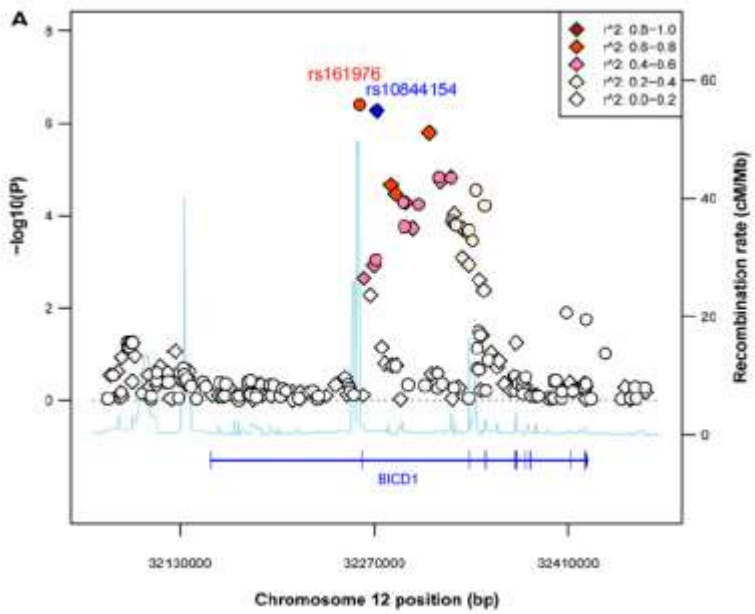


Emphysème < 5%

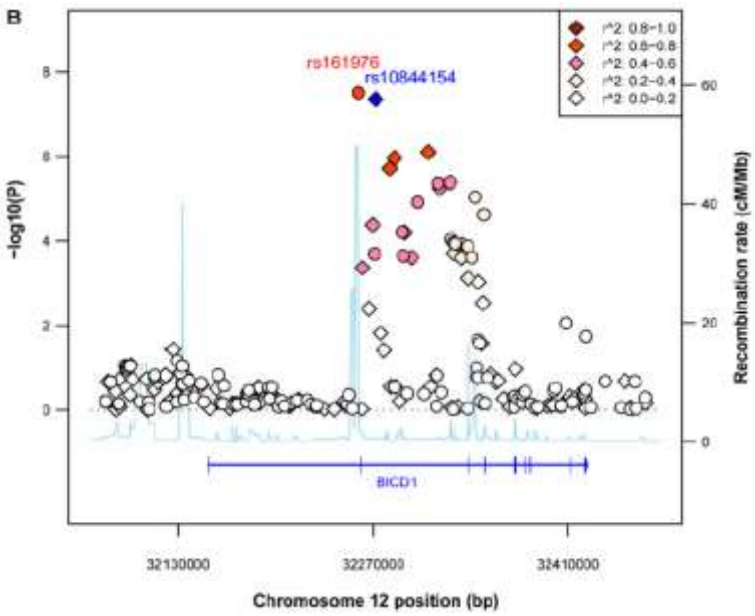
Emphysème > 25%

BICD1: polymorphismes rs161976 et rs10844154

SNP	Chr	Type	Closest Gene	Risk/Nonrisk Allele	Risk Allele Frequency	ECLIPSE OR	ECLIPSE *P* Value	Norway OR	Norway *P* Value	Meta-analysis *P* Value*	Meta-analysis OR (*P* Value)†	Heterogeneity I^2 (%)†
rs10844154	12	Intron	*BICD1*	C/A	0.58	1.50	3.0×10^{-6}	1.35	0.06	5.2×10^{-7}	1.46 (5.5×10^{-7})	0
rs641525	8	Intergenic	*CSMD1*	T/G	0.95	2.17	1.2×10^{-5}	2.24	0.02	5.4×10^{-7}	2.19 (5.3×10^{-7})	0
rs161981	12	Intron	*BICD1*	C/T	0.56	1.47	9.2×10^{-6}	1.37	0.05	1.2×10^{-6}	1.44 (1.2×10^{-6})	0
rs341672	8	Intergenic	*CSMD1*	T/C	0.92	1.82	3.3×10^{-5}	1.71	0.05	4.8×10^{-6}	1.80 (4.7×10^{-6})	0
rs1012036	7	Intergenic	*AC006320.2*	C/T	0.77	1.43	2.1×10^{-4}	1.63	6.0×10^{-3}	5.4×10^{-6}	1.47 (5.23×10^{-6})	0
rs2999399	10	Intergenic	*ADARB2*	T/C	0.76	1.60	9.5×10^{-7}	1.08	0.66	5.6×10^{-6}	1.47 (5.9×10^{-6})	73



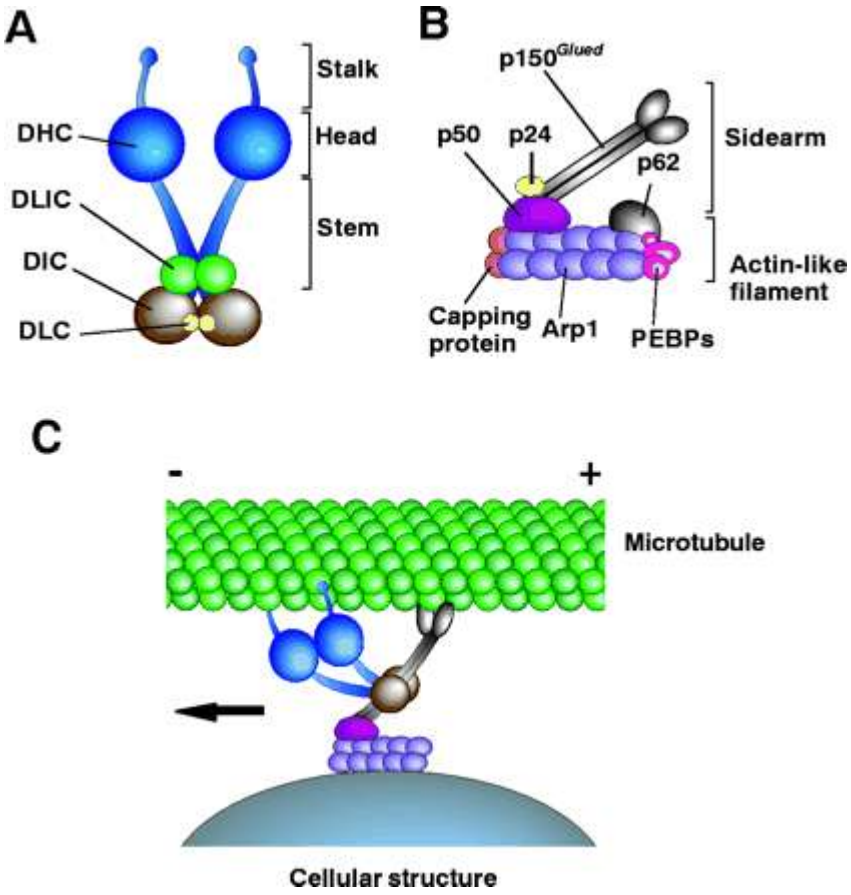
Emphysème > 5%



Emphysème > 25%

BICD1: interaction dynéine - dynactine

- BICD1 is one of two human homologs of Drosophila bicaudal-D (BicD). The function of BICD protein has been well characterized—it forms a complex with dynein–dynactin and plays a critical role in mediating dynein function. Dynein is involved in many cellular processes, including mitosis, nuclear migration and mRNA transport, and transport of a variety of axonal and dendritic vesicles. The second exon of BICD1 encodes the sequence located in the coiled-coil domain at the N terminus of the protein, which directly interacts with dynein



JCS **November 15, 2003vol. 116 no. 22 4501-4512**

En résumé

Gene studies	
Smoking history	Suggestive associations identified for age at smoking initiation (chromosomes 2q21 and 6p21), lifetime mean number of cigarettes per day (CHRNA3/CHRNA5 and CYP2A6), current number of cigarettes smoked per day (CYP2A6) and smoking cessation (DBH)[30]
COPD susceptibility	Several genomic regions associated with COPD susceptibility (FAM13A, HHIP, CHRNA3/CHRNA5/IREB2 and a region on chromosome 19). Others (ADAM19, FGF7 and SP-D) need replication in other populations
COPD subtypes	CHRNA3/5 significantly associated with pack-years, emphysema and airflow limitation[42]; HHIP not associated with pack-years but related to FEV_1/FVC, lean body mass and exacerbation.[42]
Emphysema	Borderline genome-wide significant association with BICD1[43]
Cachexia	Suggestive association of BMI and FFMI with FTO gene.[46] The latter also related to FEV_1[46]
Blood biomarkers	Genome-wide significant associations identified only for CC16 (chromosome 11) and SP-D (SFTPD and SNPs on chromosomes 6 and 16)[47]

BMI, body mass index; COPD, chronic obstructive pulmonary disease; DBH, dopamine beta-hydroxylase; ECLIPSE, Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points; FEV_1, forced expiratory volume in 1 s; FFMI, fat-free mass index; FVC, forced vital capacity; HHIP, hedgehog interacting protein; SNP, single nucleotide polymorphism; SP-D, surfactant protein D.

Faner R, *et al*. *Thorax* 2013;**0**:1–7.

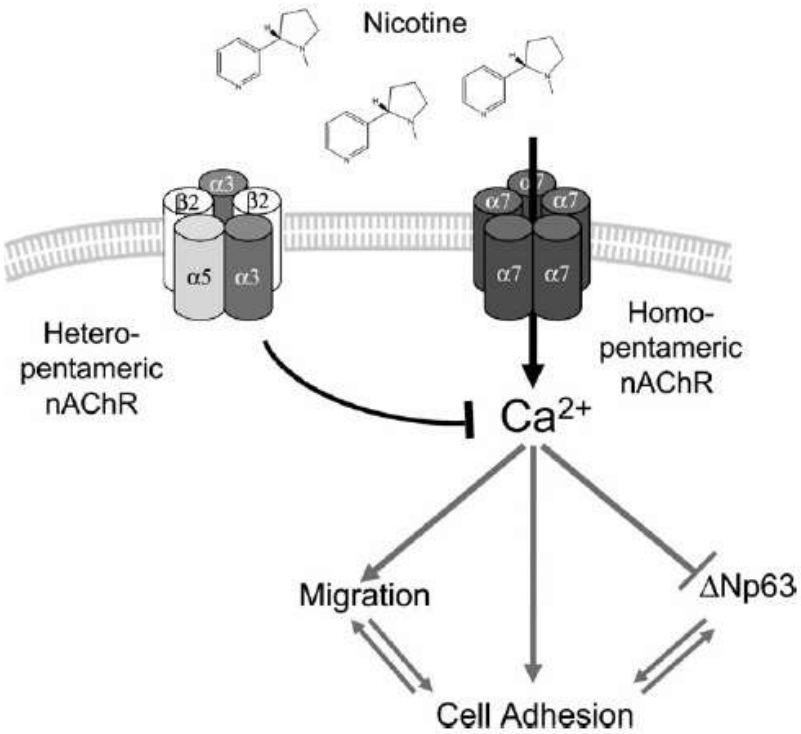
FAM13A

- Association de polymorphismes génétiques avec
  - BPCO
  - Cancer bronchique
  - Sibilants dans l'enfance

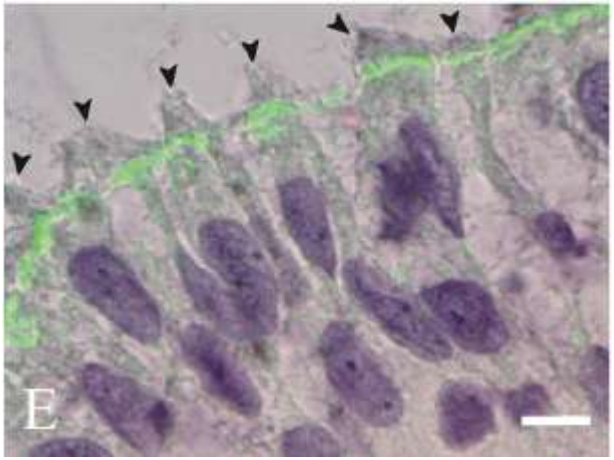
Respirology. 2014 Jan 6
J Thorac Dis. 2013 Oct;5(Suppl 5):S454-S462
PLoS One. 2013 Jul 30;8(7):e70220.
Clin Biochem. 2013 Nov;46(16-17):1683-8.
J Allergy Clin Immunol. 2014 Jan;133(1):68-76.e4
Hum Genet. 2013 Apr;132(4):431-41.
Am J Respir Cell Mol Biol. 2012 Aug;47(2):203-8
Hum Mol Genet. 2012 Feb 15;21(4):947-57.
Biochem Biophys Res Commun. 2011 Nov 18;415(2):284-7.
Allergol Int. 2011 Sep;60(3):253-8.
Appl Clin Genet. 2010 Dec 22;4:1-10.
Am J Respir Crit Care Med. 2010 Dec 15;182(12):1498-505.
Nat Genet. 2010 Mar;42(3):200-2.

- *FAM13A* (also known as *FAM13A1*) has a putative role in signal transduction, and our most statistically significant SNPs lie in an intronic region downstream of a Rho GTPase–activating protein (RhoGAP) domain. Although little is known about *FAM13A* function, gene expression analyses in cell lines from several tissues (not including the lung) have shown a consistent increase of expression in response to hypoxia. Differences in respiratory epithelial cell expression of*FAM13A* have been noted during differentiation into pulmonary type II cells *in vitro* and in individuals with mild as compared to severe cystic fibrosis

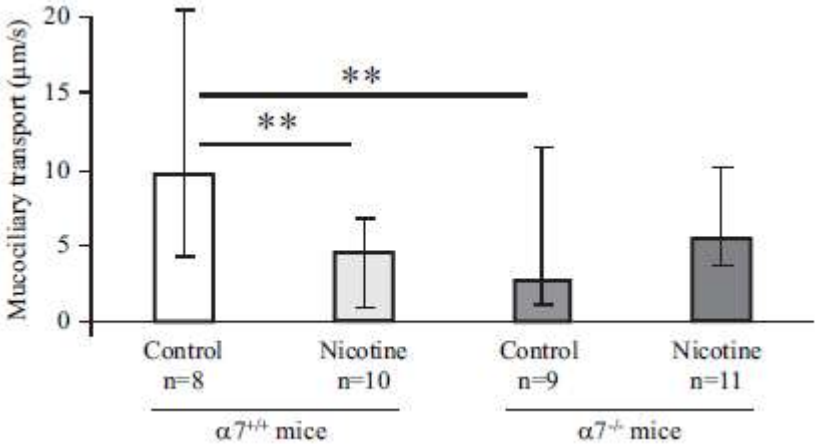
CHRNA3/5



Carcinogenesis vol.32 no.9 pp.1388–1395, 2011

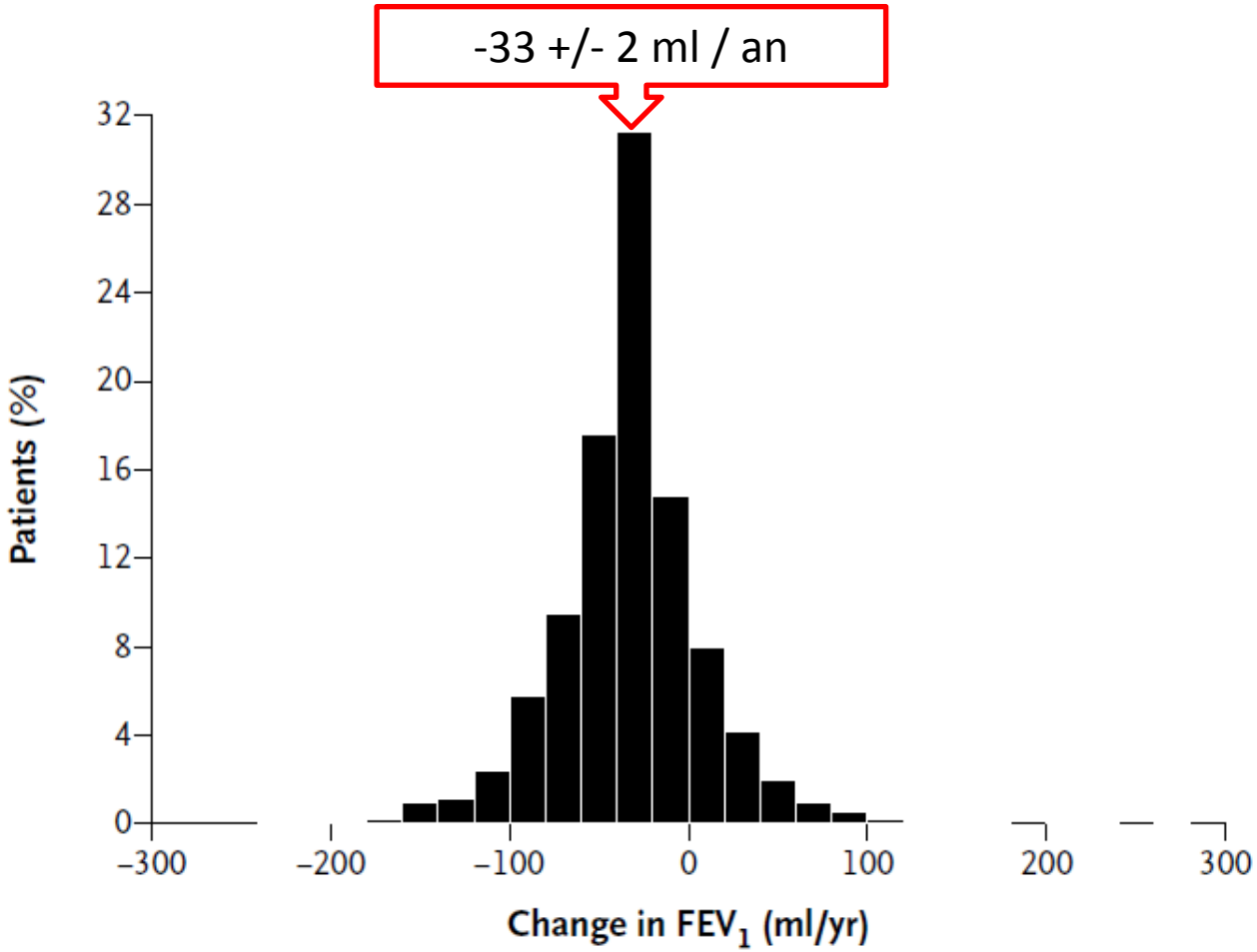


Alpha7 subunit



PNAS | March 5, 2013 | vol. 110 | no. 10 | 4099–4104

Déclin de la fonction respiratoire

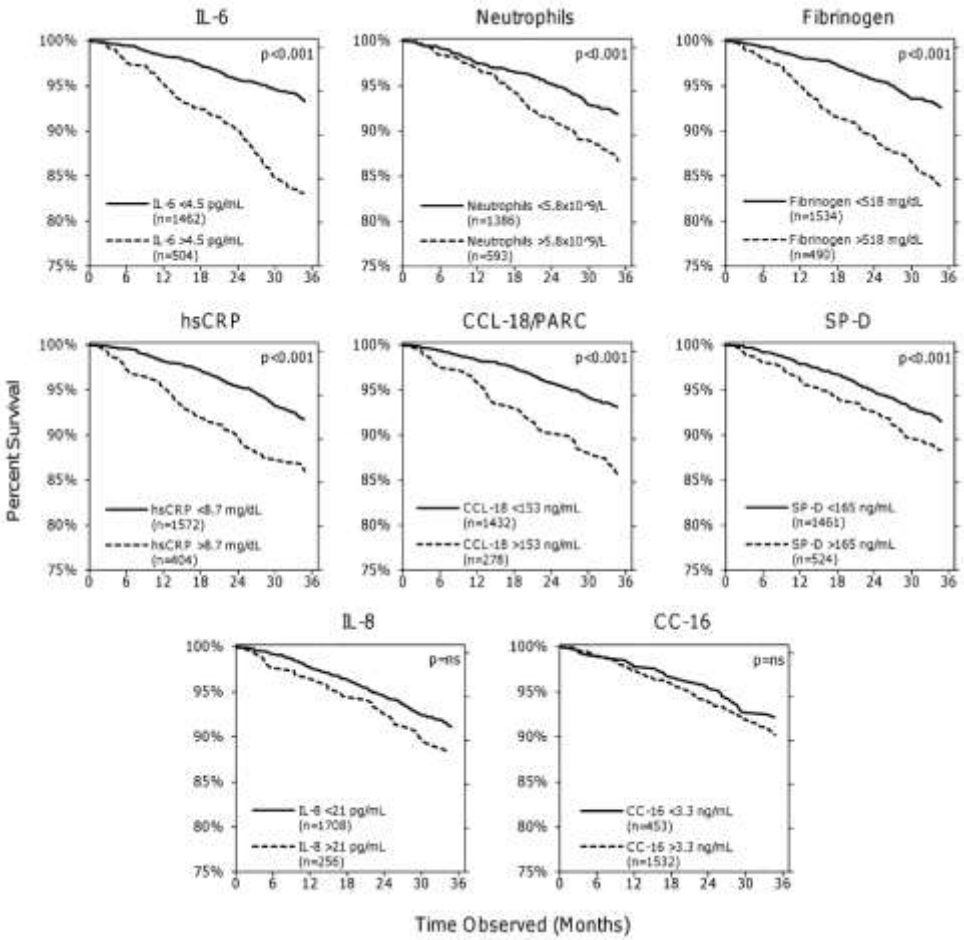


Vestbo, NEJM 2011

Biomarqueurs prédictifs du déclin

Biomarker†	Effect on Baseline FEV_1 *ml*	P Value‡	Effect on Annual Rate of Change in FEV_1 *ml/yr*	P Value‡
Fibrinogen	−93±10.6	<0.001	−1±2.1	0.63
Interleukin-6	0±10.0	>0.99	1±2.3	0.52
Interleukin-8	20±9.9	0.04	−2±2.0	0.36
TNF-α	1±9.9	0.89	0±1.8	0.84
C-reactive protein	−23±10.3	0.037	4±2.1	0.07
CC-16	33±10.8	0.002	4±2.2	0.04
Surfactant protein D	0±10.3	0.96	−3±2.1	0.18

Un biomarqueur qui prédit la survie ?



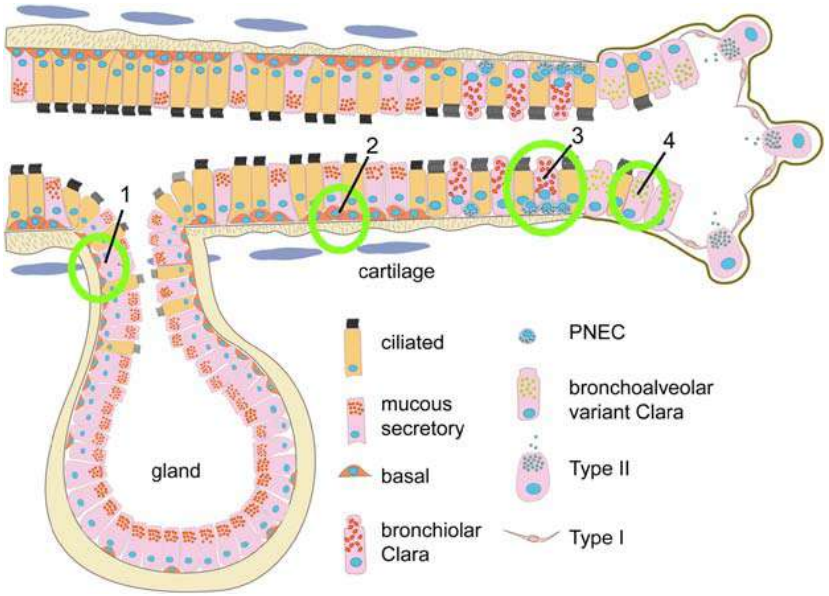
Celli, AJRCCM 2012

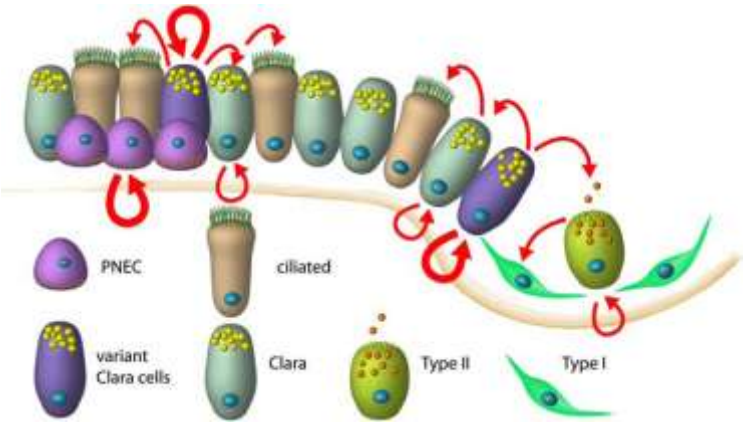
C-statistique: capacité à prédire

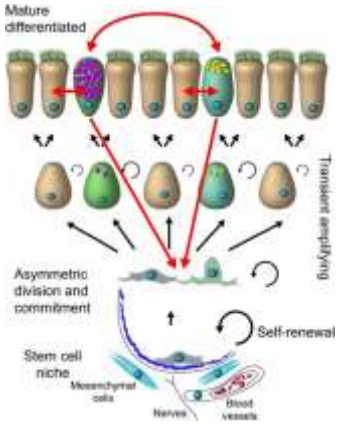
Model	C Statistic	Difference from Base	95% Confidence Interval for Difference from Base Model	*P* Value Versus Reference
Age + BODE + COPD Hosp	0.686			
+ IL-6	0.708	0.023	(0.003 to 0.043)	0.027
+ Neutrophils	0.699	0.013	(−0.001 to 0.028)	0.078
+ White blood cells	0.698	0.012	(−0.003 to 0.028)	0.119
+ CRP	0.697	0.012	(−0.005 to 0.028)	0.168
+ Fibrinogen	0.698	0.012	(−0.007 to 0.031)	0.207
+ SP-D	0.692	0.006	(−0.006 to 0.018)	0.309
+ IL-8	0.690	0.005	(−0.005 to 0.013)	0.371
+ All biomarkers	0.726	0.041	(0.014 to 0.067)	0.003
Sensitivity Model (n = 1,579)				
Age + BODE + COPD Hosp	0.697			
+ CCL-18/PARC	0.706	0.009	(−0.008 to 0.026)	0.294
+ All biomarkers	0.742	0.045	(0.010 to 0.079)	0.011

Celli, AJRCCM 2012

Airway Epithelial Stem Cells

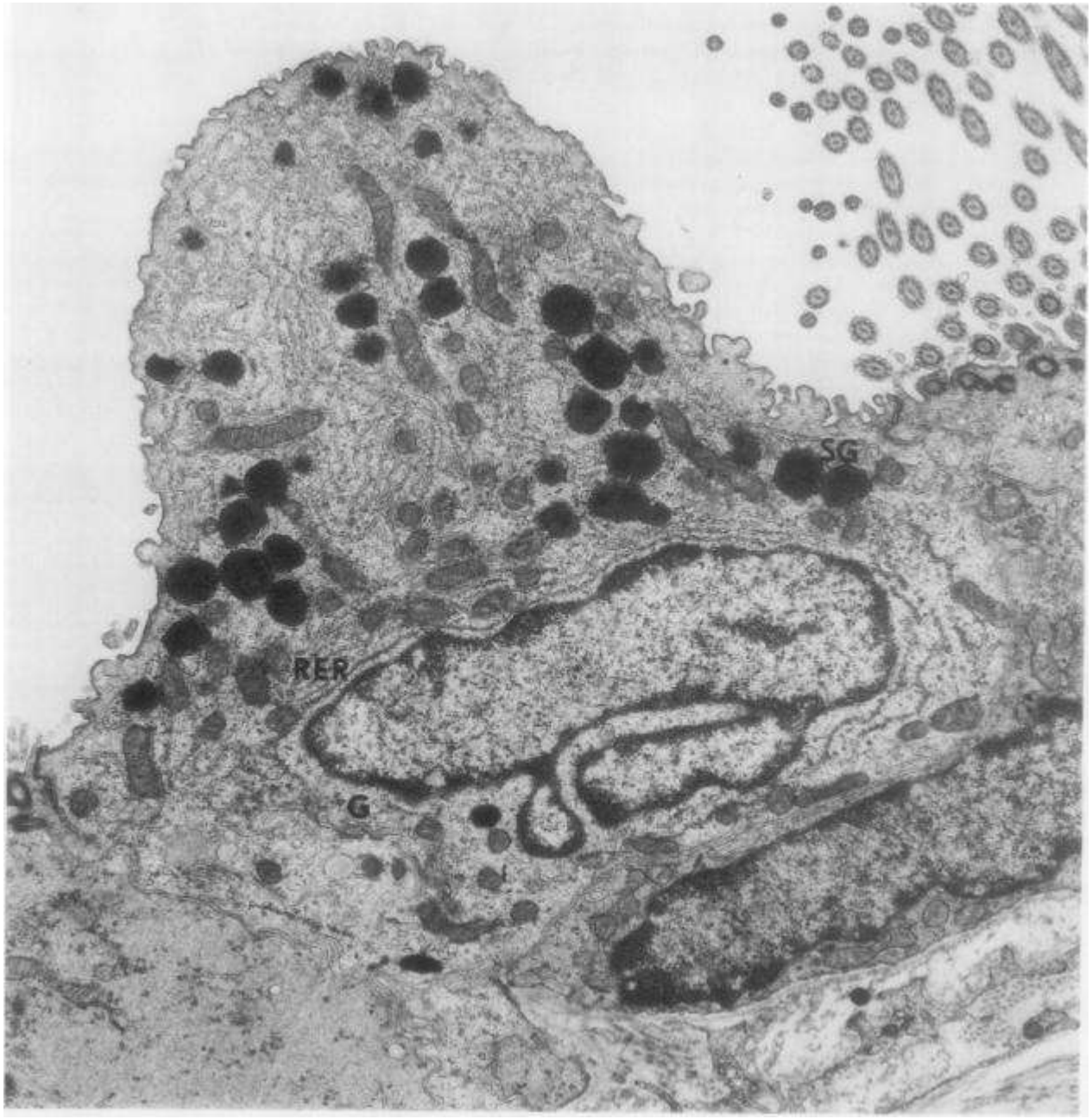






- « Typical »: CC10+ and morphology
- « Variant »: CC10+, associated with PNEC
- BASCs CC10+ Sca1+ CD34+ SPC+

Randell, PATS 2006



Massaro, JCI 1976

Non-Invasive Assessment of Small Airway Remodelling in Smokers

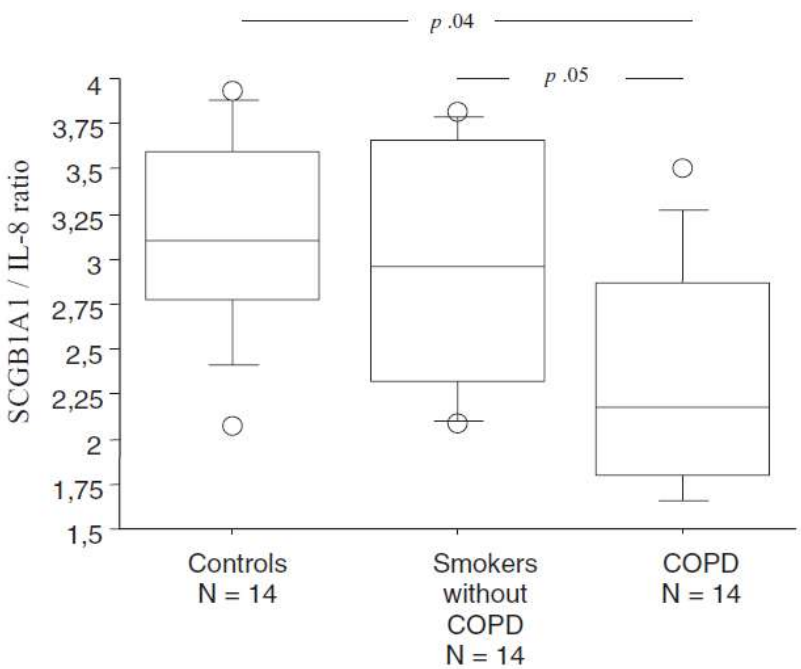


Figure 1. Box-plot comparison for log-transformed IS SCGB1A1 / IL8 ratio in controls, smokers and COPD patients.

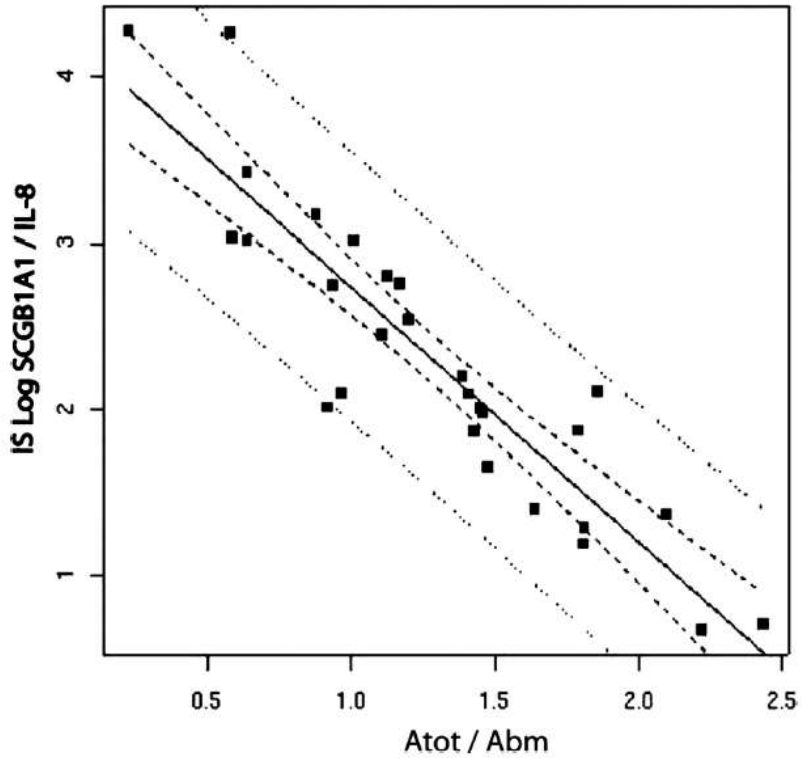
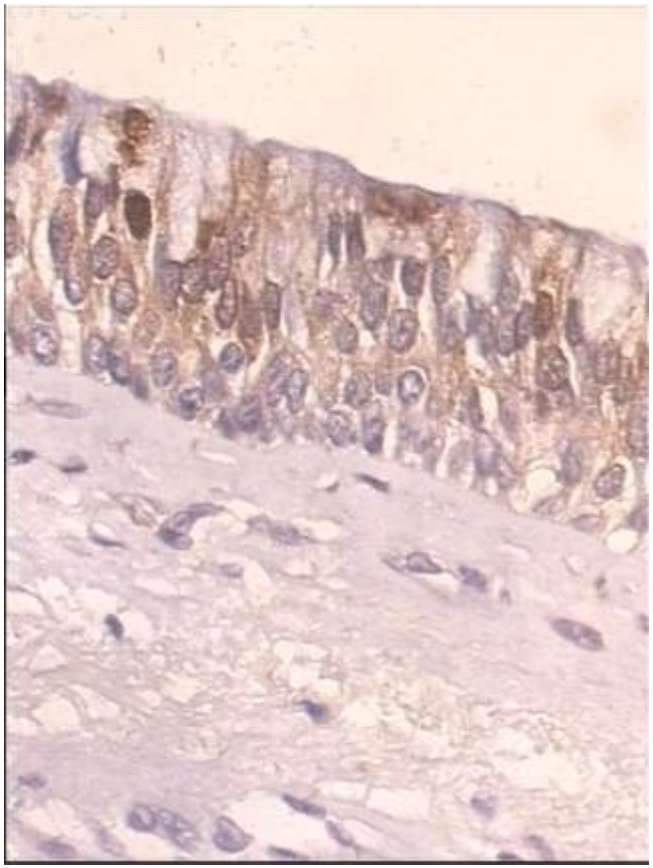


Figure 2. Correlation between SCGB1A1/IL-8 ratio and the wall thickness of the airways assessed by morphometry.

Bourdin, COPD 2010

Il existe des cellules CCSP+ dans les voies aériennes proximales

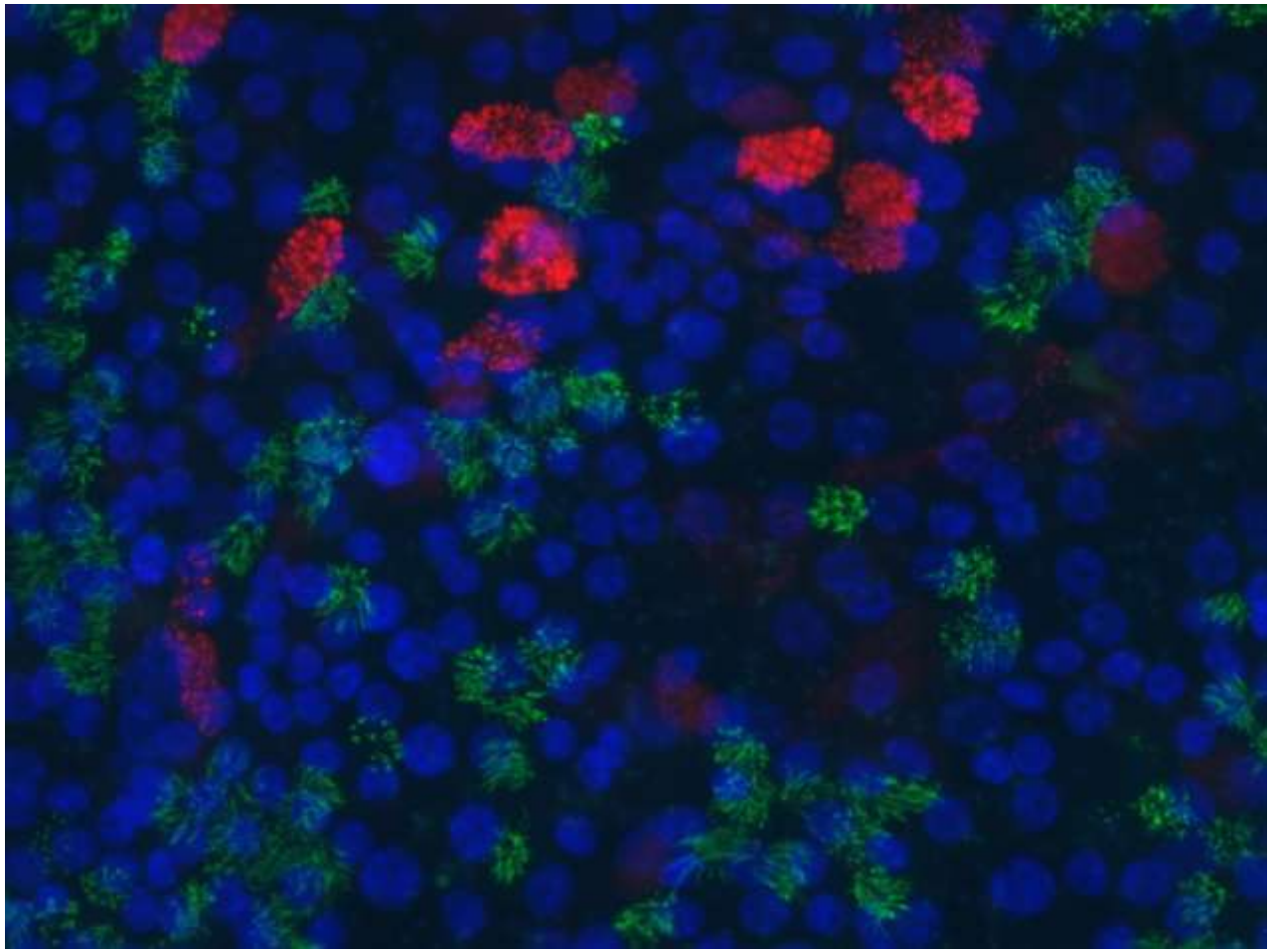
	Pourcentage d'aire marquée
BPCO (n=6)	6,29%
Fumeurs (n=5)	4,58%
Témoins (n=5)	11,43%
p-value	0,133



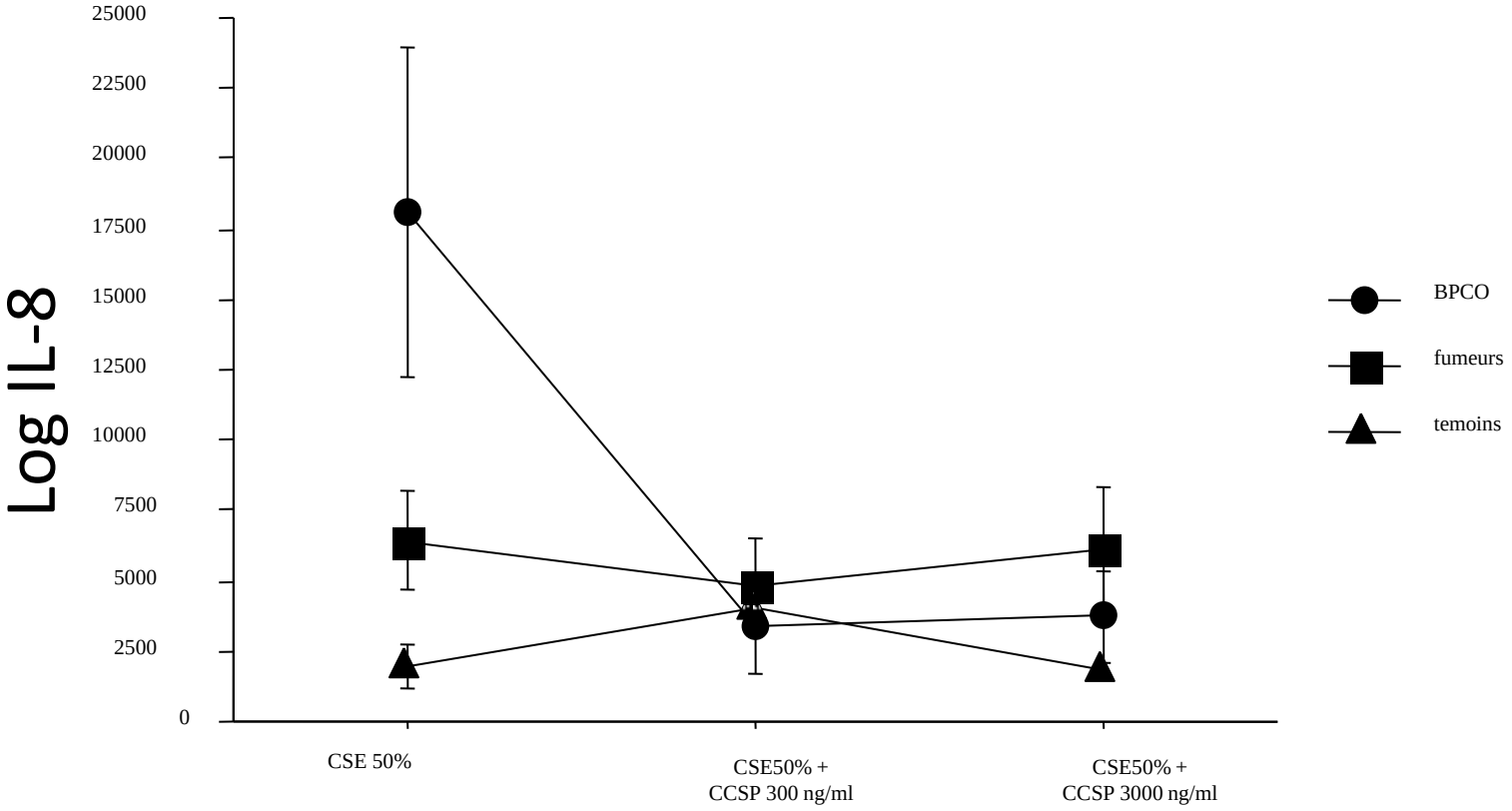
Coefficient de corrélation linéaire IHC/sécrétion CCSP r^2= 0,71

Gamez, Gras, Vachier, Chanez et Bourdin, ERS 2010

CCSP+ en cultures ALI



rhCCSP decreases COPD specific CSE-induced IL-8 release in ALI cultures



Gamez AS, ERS 2010

Conclusion

- La meilleure compréhension de la physiopathologie de la BPCO grâce aux études longitudinales
  - N'est pas encore acquise
  - Montre la grande hétérogénéité et sans doute l'urgente nécessité de modifier les critères diagnostiques
  - Montre l'intérêt de l'imagerie pour comprendre
  - Une communauté de genes de susceptibilité en particulier autour du récepteur nicotinique semble de plus en plus solide
- La caractérisation clinique des patients reste donc le point critique