LYON
5-7 AVRIL 2018
CENTRE DES CONGRÈS

3es JOURNÉES FRANCOPHONES DE LA MUCOVISCIDOSE

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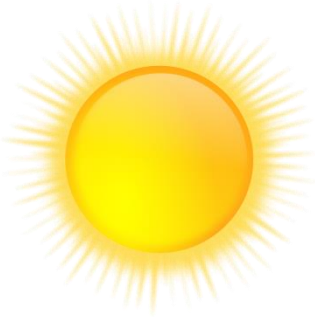
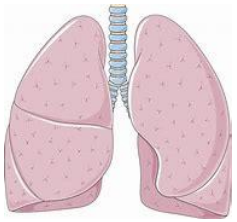
Actualités Mucoviscidose 2017

Adrien Tissot
CHU de Nantes
5 avril 2017






2V125


TV

EUROPEAN RESPIRATORY journal
FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Airway microbiota across age and disease spectrum in cystic fibrosis

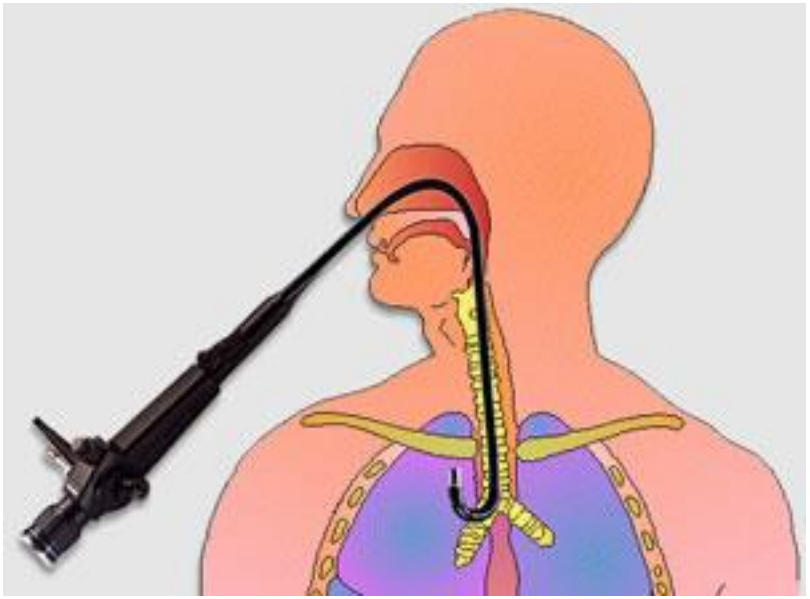
Edith T. Zemanick[1], Brandie D. Wagner[1,2], Charles E. Robertson[1], Richard C. Ahrens[3], James F. Chmiel[4], John P. Clancy[5], Ronald L. Gibson[6], William T. Harris[7], Geoffrey Kurland[8], Theresa A. Laguna[9], Susanna A. McColley[10],

Objectifs:

- caractériser le microbiote de LBA provenant de patients CF
- relation avec l'inflammation et le statut de la maladie

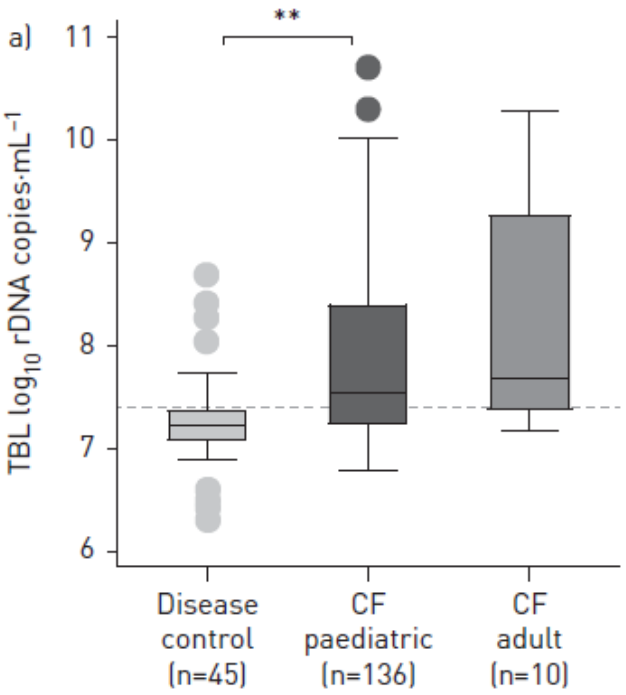
Méthode:

- fibroscopie (indication clinique)
- patients CF âgés de 2 mois à 50 ans / contrôle
- 13 centres US

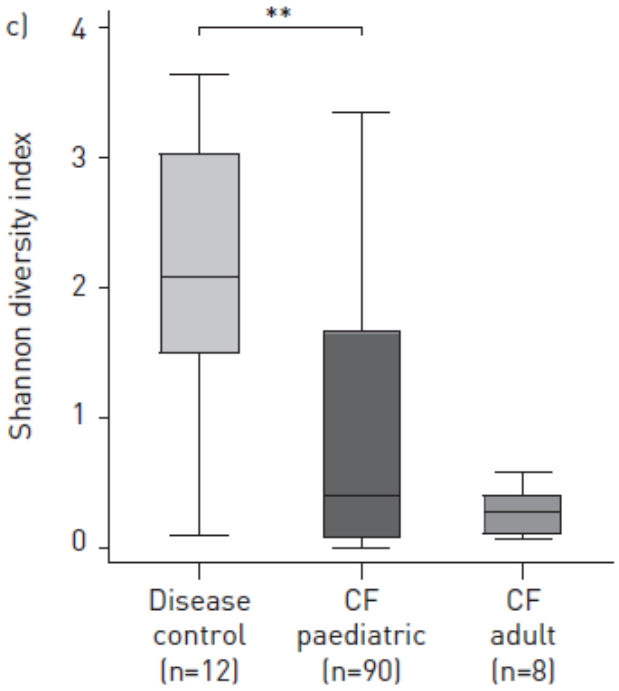


Extraction ADN
Charge bactérienne totale par PCR quantitative
Séquençage ADNr 16S

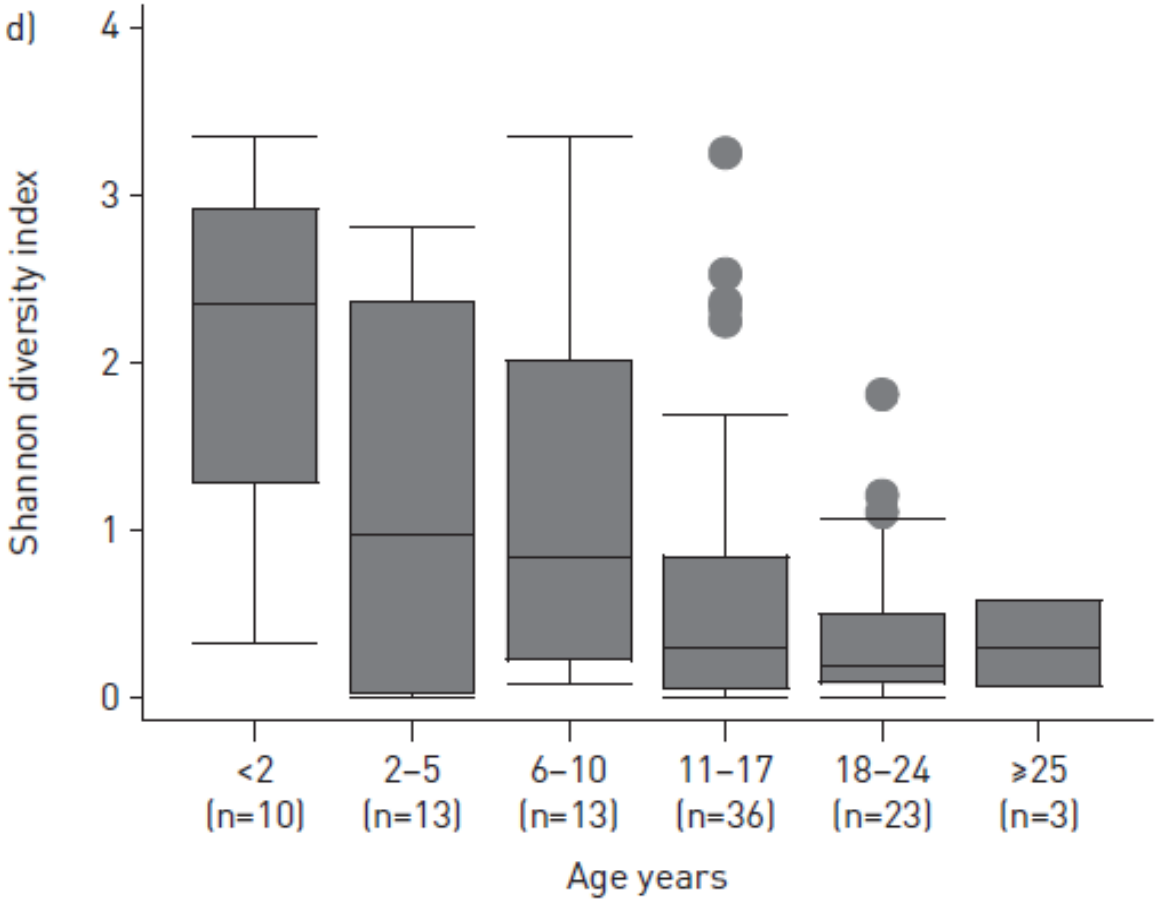
191 échantillons / 136 enfants CF / 10 adultes CF / 45 contrôles



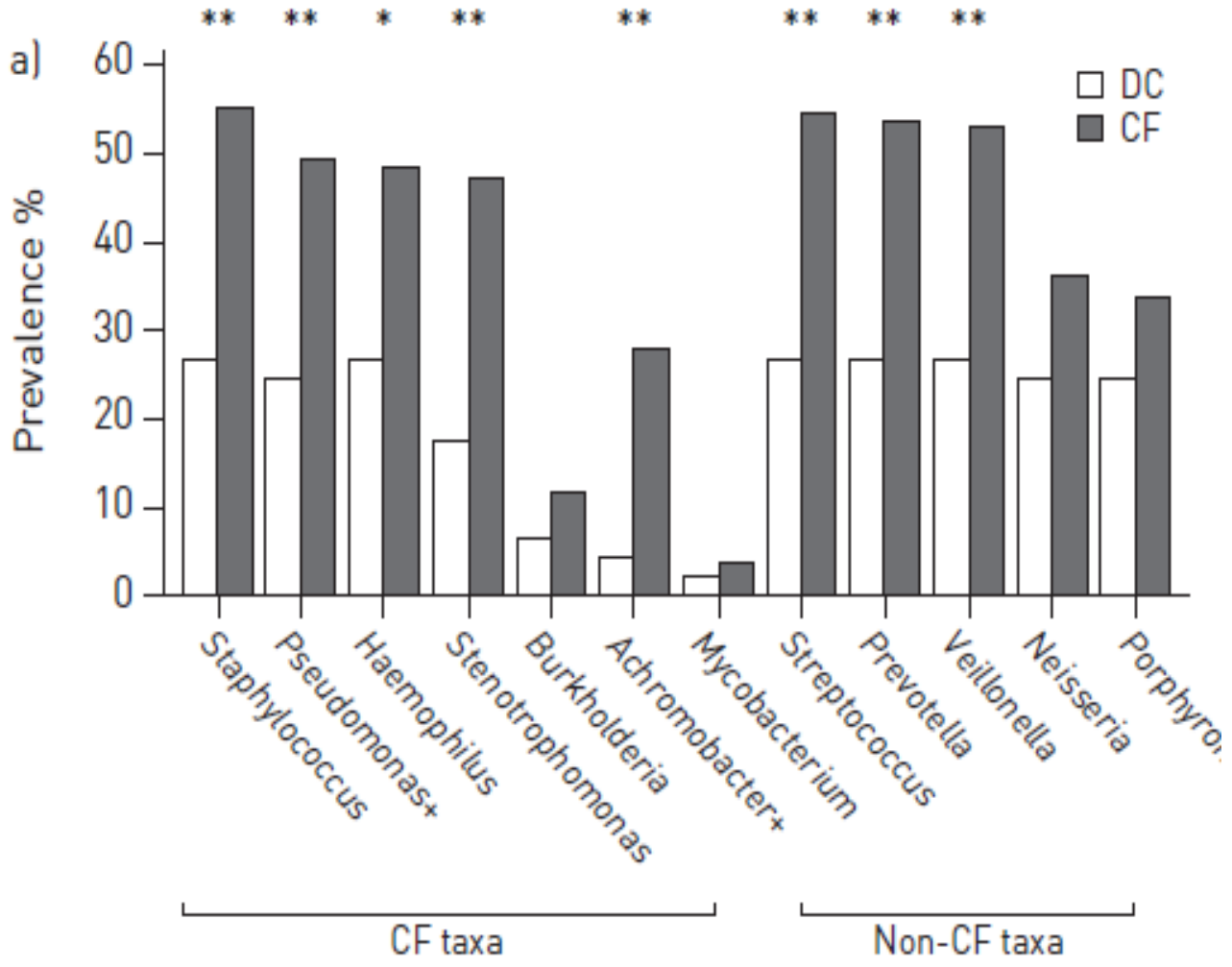
Charge bactérienne élevée

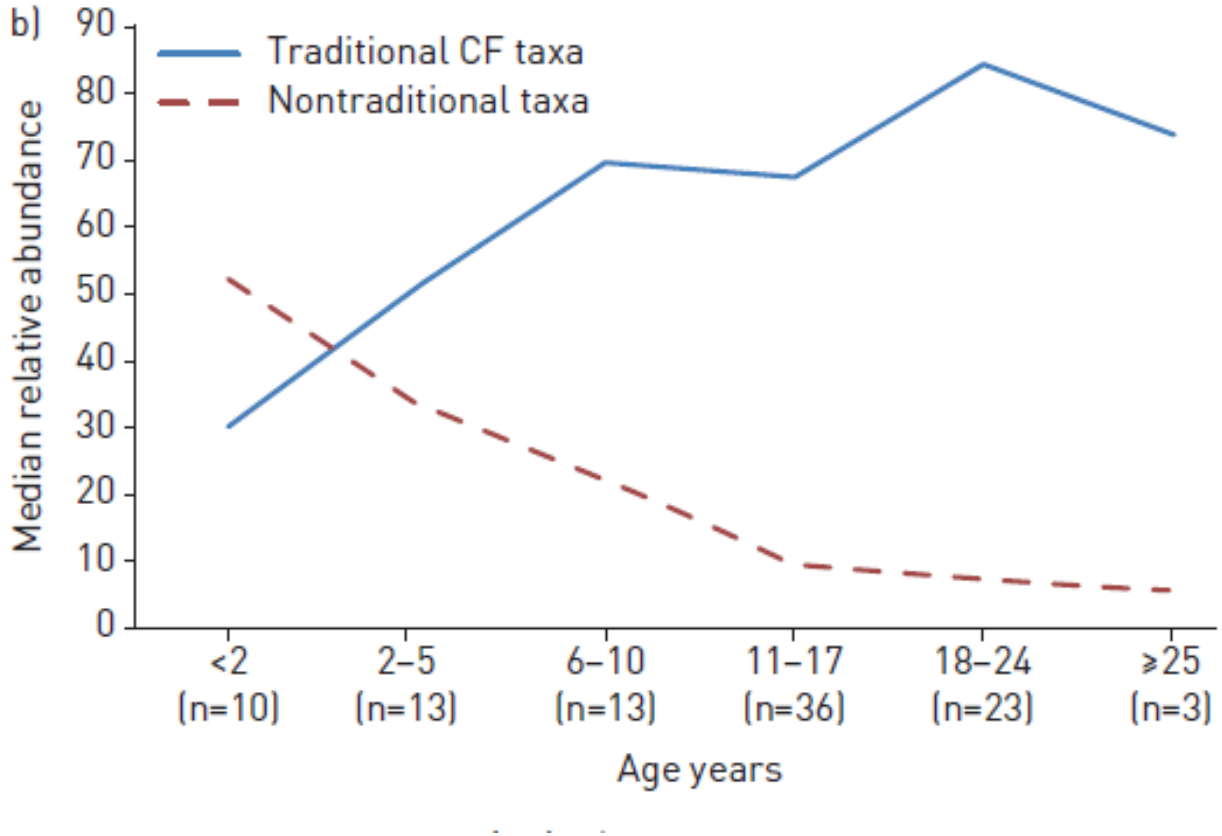


Diversité bactérienne basse



Diversité bactérienne diminue avec l'âge


a)
Prevalence %
60
50
40
30
20
10
0
DC
CF
** ** * ** ** ** ** **
Staphylococcus
Pseudomonas+
Haemophilus
Stenotrophomonas
Burkholderia
Achromobacter+
Mycobacterium
Streptococcus
Prevotella
Veillonella
Neisseria
Porphyro
CF taxa
Non-CF taxa


b)
Traditional CF taxa
Nontraditional taxa
Median relative abundance
90
80
70
60
50
40
30
20
10
0
<2 (n=10)
2–5 (n=13)
6–10 (n=13)
11–17 (n=36)
18–24 (n=23)
⩾25 (n=3)
Age years

EUROPEAN RESPIRATORY journal
FLAGSHIP SCIENTIFIC JOURNAL OF ERS

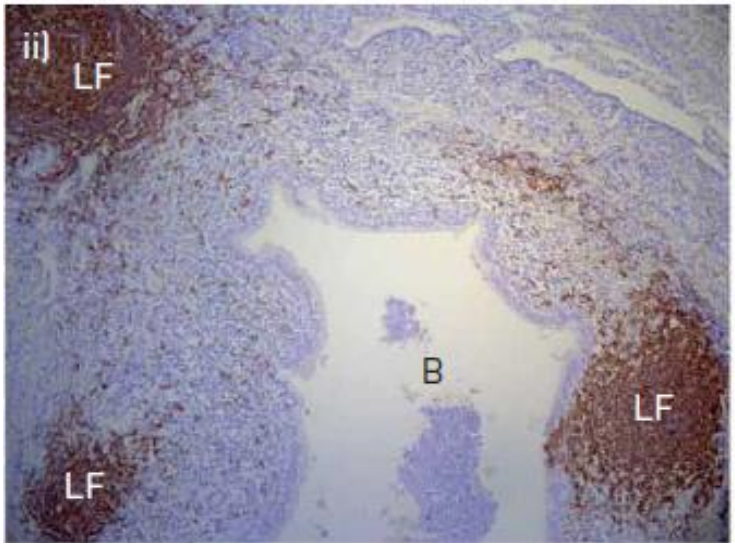
Bacteria-driven peribronchial lymphoid neogenesis in bronchiectasis and cystic fibrosis

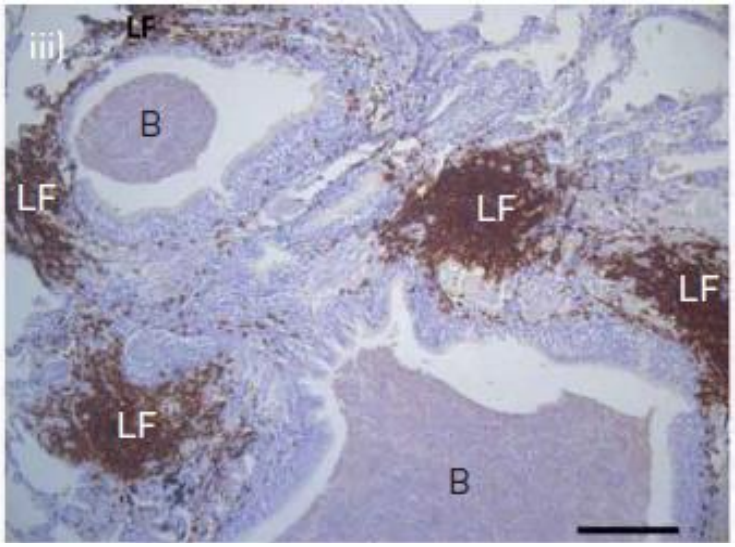
Justine Frija-Masson[1,2,3], Clémence Martin[1,2,3], Lucile Regard[1,2,3], Marie-Noëlle Lothe[1,2,3], Lhousseine Touqui[3], Aurélie Durand[1,4,5], Bruno Lucas[1,4,5], Diane Damotte[1,6], Marco Alifano[1,7], Isabelle Fajac[1,3,8] and Pierre-Régis Burgel[1,2,3]

Contexte:
infection chronique bactérienne -> inflammation VA -> maladie pulmonaire CF
Rôle de l'immunité inné: neutrophiles et macrophages
Rôle de l'immunité adaptative (lymphocyte B et T) ?

➡ présence d'organes lymphoïdes tertiaires pulmonaire dans la muco/DDB ?

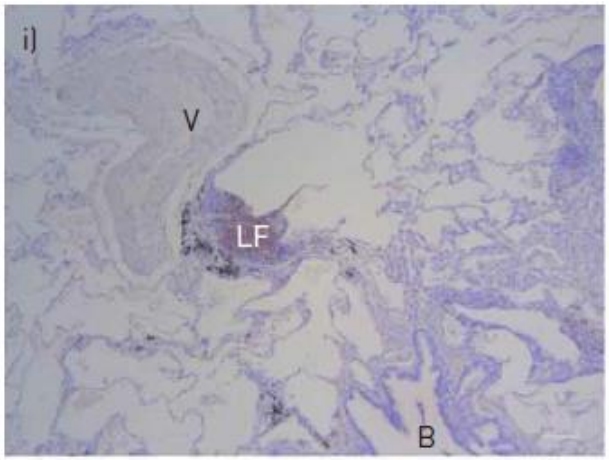
➡ infection chronique responsable néogénèse lymphoïde ?





DDB CF

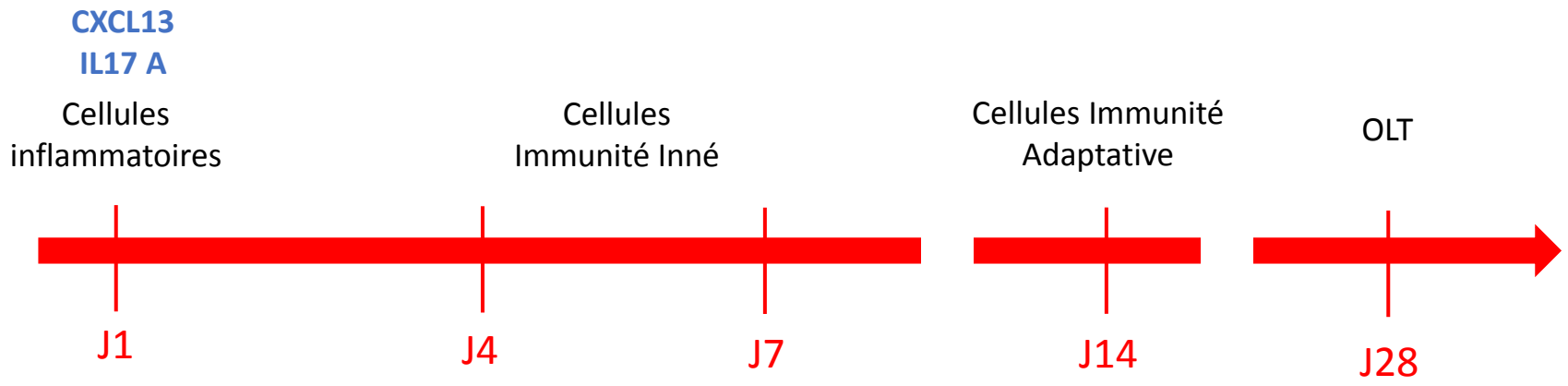
CXCL12
CXCL13
IL17A



contrôle

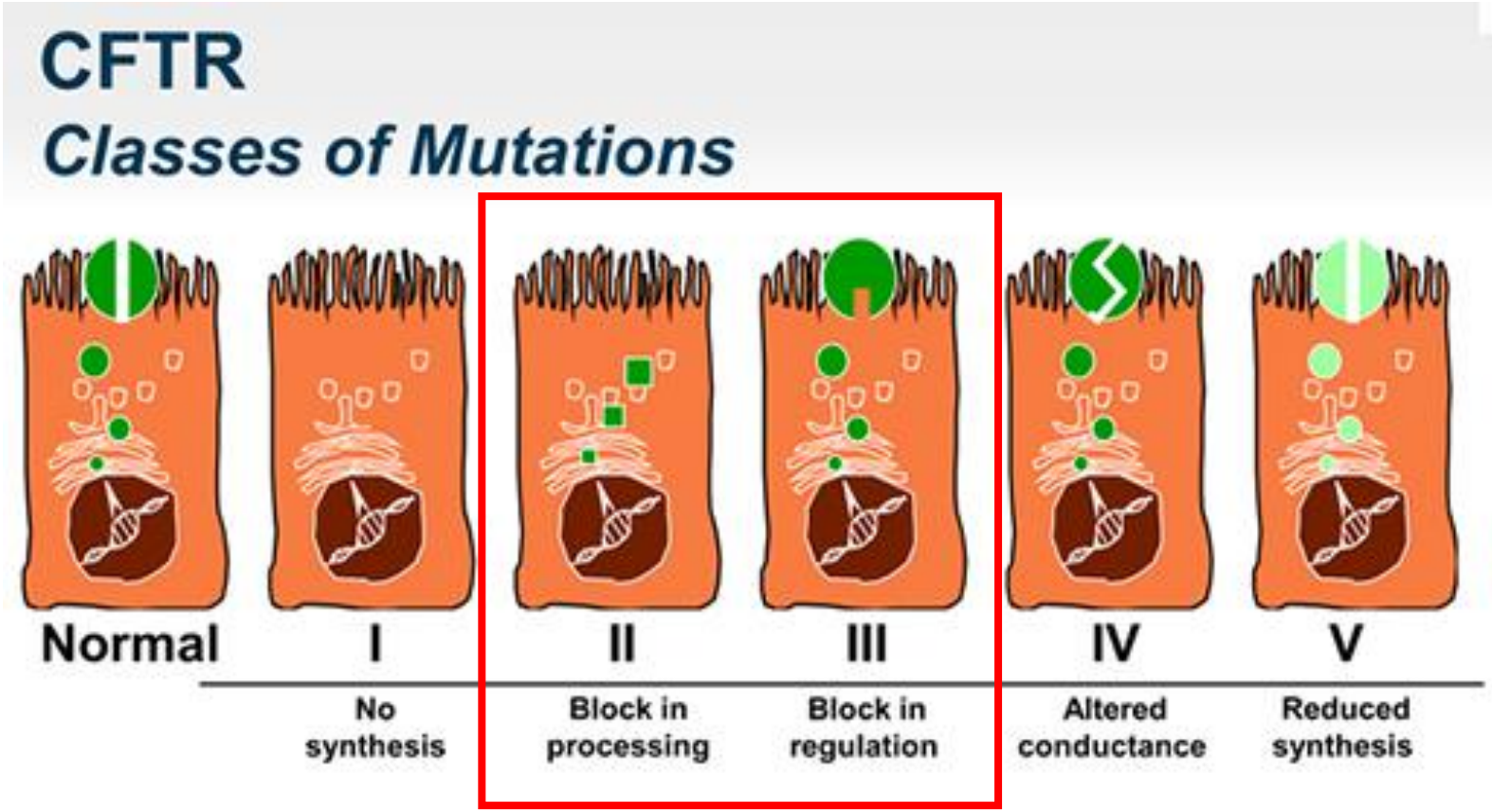
Modèle murin d'infection chronique

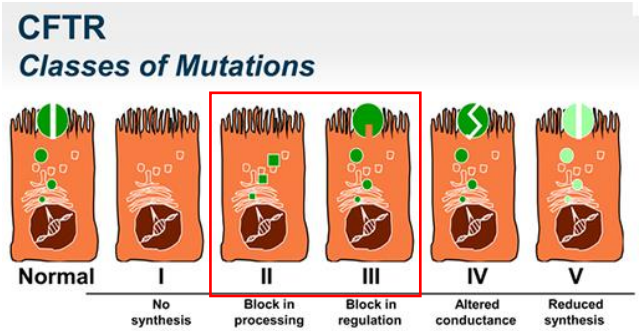
Obtention néogénèse lymphoïde
- + de lymphocyte T
- + de lymphocyte B
- + de cellules dendritiques



The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 NOVEMBER 23, 2017 VOL. 377 NO. 21

Tezacaftor–Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del





Ivacaftor (Potentiator) Plus Lumacaftor (Corrector) in F508del CFTR

TRAFFIC and TRANSPORT

- Diminution de 40% des exacerbations pulmonaires
- Augmentation de 3% du VEMS
- Augmentation de l'IMC moyen
- Amélioration de qualité de vie et des symptômes respiratoires

Mais

- Effets secondaires respiratoires
- Inducteur fort cytochrome P-450-3A = interactions médicamenteuses

Wainwright CE, et al. *N Engl J Med.* 2015;373:220-231.

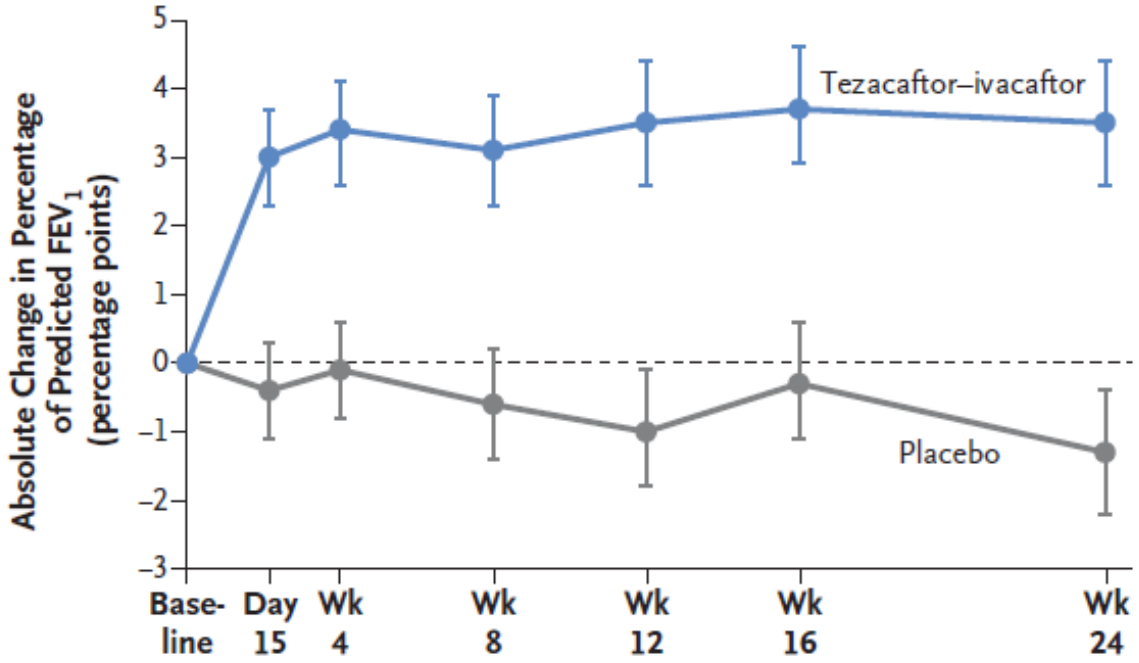
Méthodologie

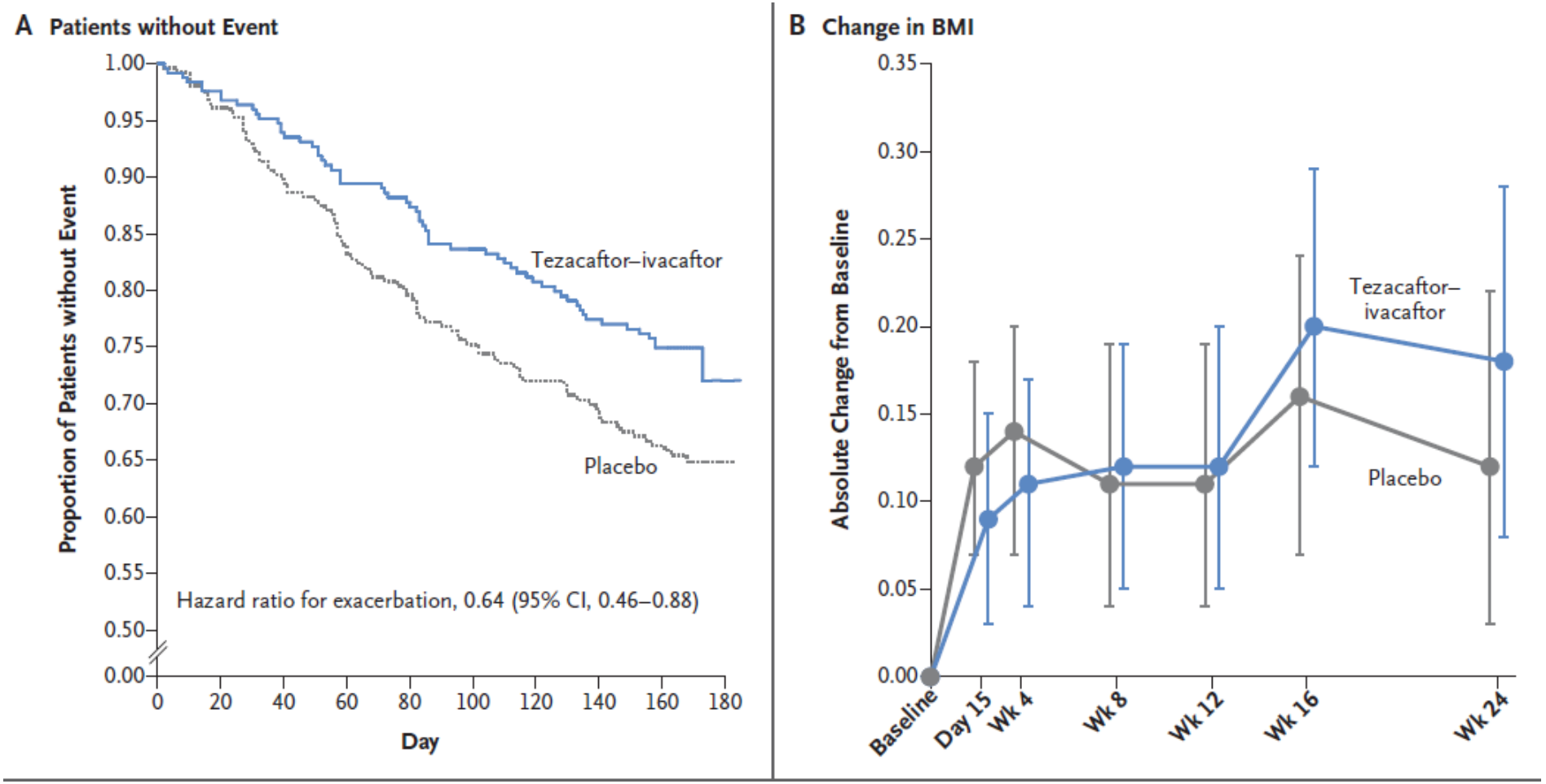
Etude randomisée, contrôlée, contre placebo, double aveugle, multicentrique

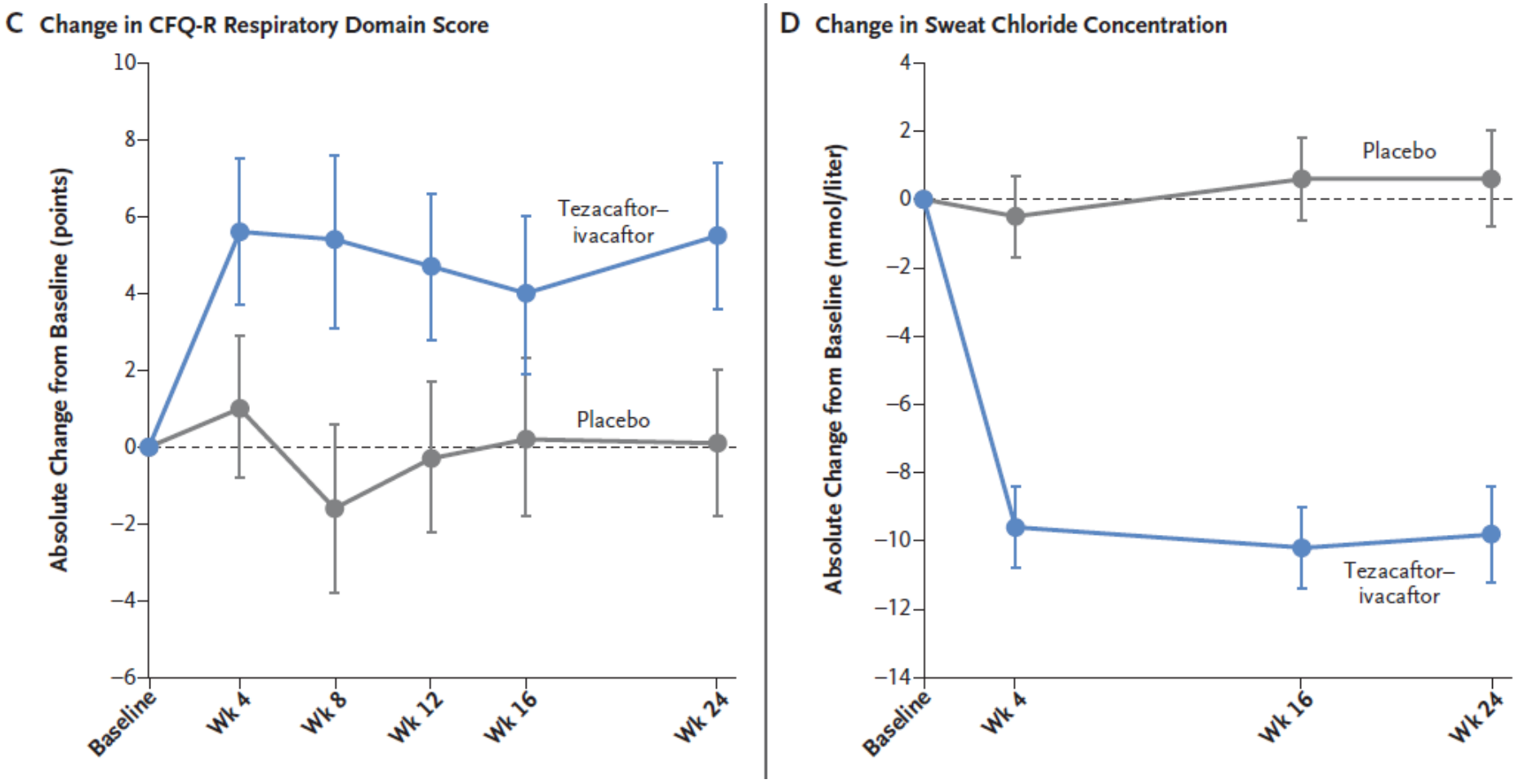
Patients ≥ 12 ans, homozygote mutation CFTR Phe508del
VEMS 40-90%

Tezacaftor (corrector) / Ivacaftor (potentiator) VS Placebo pendant 24 semaines

➡ **510 patients randomisés**




A Patients without Event
Proportion of Patients without Event
1.00
0.95
0.90
0.85
0.80
0.75
0.70
0.65
0.60
0.55
0.50
0.00
0
20
40
60
80
100
120
140
160
180
Day
Tezacaftor–ivacaftor
Placebo
Hazard ratio for exacerbation, 0.64 (95% CI, 0.46–0.88)
B Change in BMI
Absolute Change from Baseline
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
Baseline
Day 15
Wk 4
Wk 8
Wk 12
Wk 16
Wk 24
Tezacaftor–ivacaftor
Placebo


C Change in CFQ-R Respiratory Domain Score
Absolute Change from Baseline (points)
10
8
6
4
2
0
−2
−4
−6
Tezacaftor–ivacaftor
Placebo
Baseline
Wk 4
Wk 8
Wk 12
Wk 16
Wk 24
D Change in Sweat Chloride Concentration
Absolute Change from Baseline (mmol/liter)
4
2
0
−2
−4
−6
−8
−10
−12
−14
Placebo
Tezacaftor–ivacaftor
Baseline
Wk 4
Wk 16
Wk 24

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 NOVEMBER 23, 2017 VOL. 377 NO. 21

Tezacaftor–Ivacaftor in Residual-Function Heterozygotes with Cystic Fibrosis

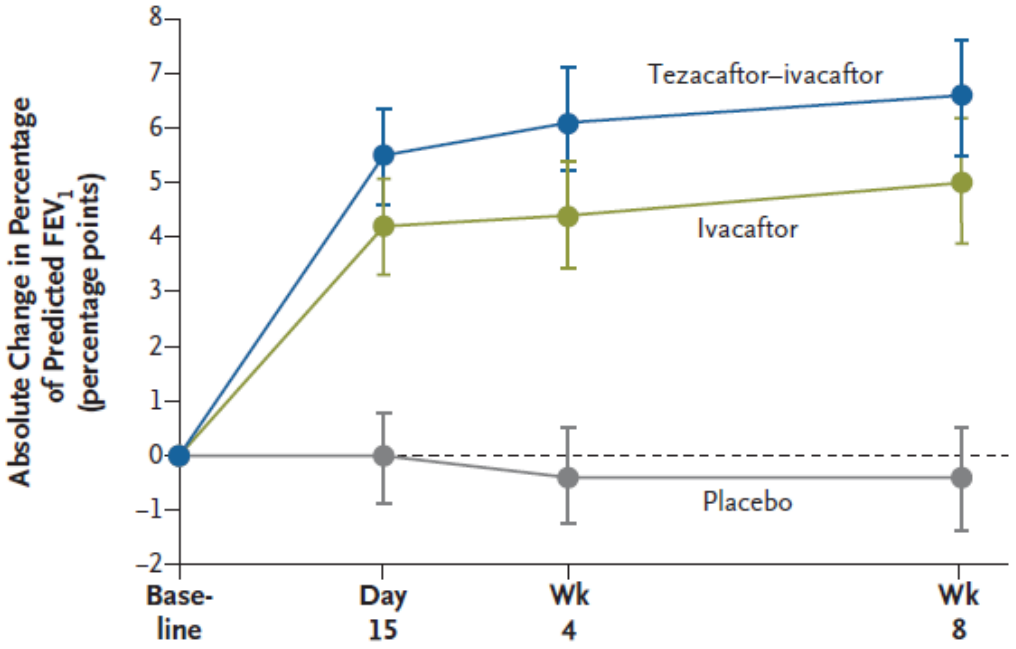
Méthodologie

Etude randomisée, contrôlée, contre placebo, double aveugle, multicentrique

Cross over

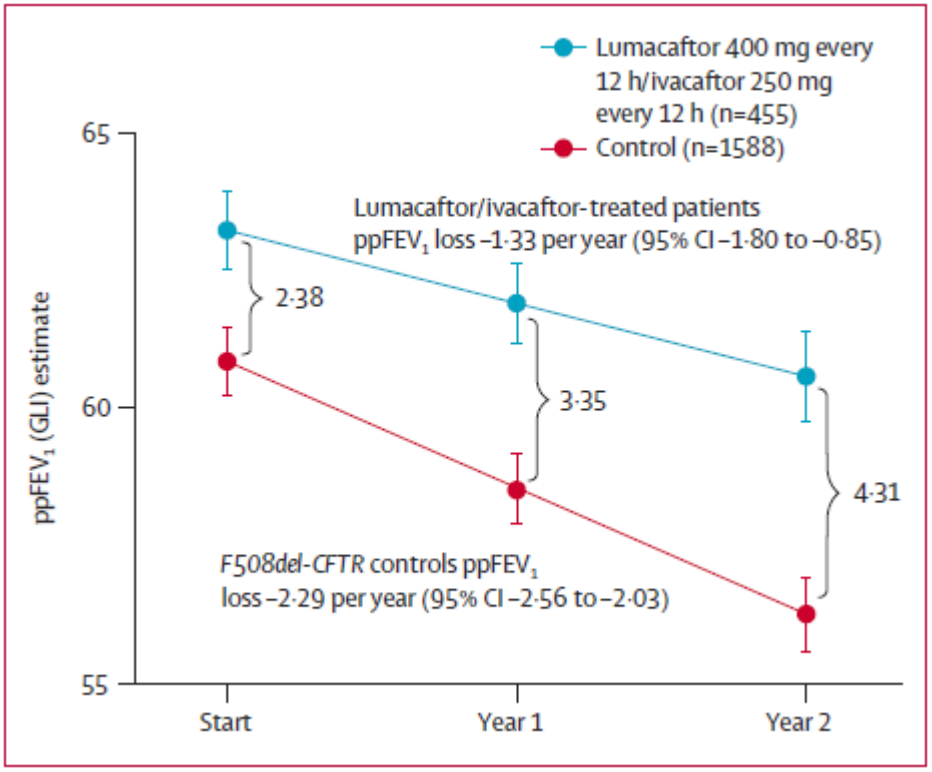
Patients ≥ 12 ans, Phe508del + mutation avec fonction CFTR résiduelle

➡ 248 patients



THE LANCET

Assessment of safety and efficacy of long-term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis homozygous for the *F508del-CFTR* mutation (PROGRESS): a phase 3, extension study



Home Monitoring of Patients with Cystic Fibrosis to Identify and Treat Acute Pulmonary Exacerbations

eICE Study Results

Noah Lechtzin[1], Nicole Mayer-Hamblett[2,3], Natalie E. West[1], Sarah Allgood[1], Ellen Wilhelm[2], Umer Khan[3], Moira L. Aitken[2], Bonnie W. Ramsey[2,3], Michael P. Boyle[1,4], Peter J. Mogayzel, Jr.[1], Ronald L. Gibson[2,3], David Orenstein[5], Carlos Milla[6], John P. Clancy[7], Veena Antony[8], and Christopher H. Goss[2,3]; for the eICE Study Team*

Objectif: évaluer l'efficacité d'une détection précoce des exacerbations par spiromètre à domicile et surveillance des symptômes sur le déclin de la fonction respiratoire

- Etude multicentrique contrôlée randomisée (14 centres US)
- Critère principal: variation du VEMS à 1 an

267 patients
- spiromètre et symptômes x 2 / semaines
- PEC habituelle (cs /3 mois)

	EI Arm (*n* = *135*)	UC Arm (*n* = *132*)	*P* Value*
Participants with at least one acute visit, n (%)	77 (57%)	38 (29%)	<0.001
Distribution of acute visits per subject, n (%)			
0	58 (43%)	94 (71%)	<0.001
1	37 (27%)	20 (15%)	
2–3	30 (22%)	17 (13%)	
⩾4	10 (7%)	1 (1%)	
Total number of acute visits	153	64	0.818
Acute visits missing PE evaluation†, n (%)	16 (10%)	8 (12%)	0.642
Acute visits not meeting protocol-defined PE†, n (%)	29 (19%)	12 (19%)	1.000
Requiring oral antibiotics‡	12 (41%)	4 (33%)	0.734
Requiring intravenous antibiotics	4 (14%)	4 (33%)	0.202
Requiring inhaled antibiotics	4 (14%)	2 (17%)	1.000
Requiring any antibiotics	14 (48%)	8 (67%)	0.325
Requiring hospitalization	5 (17)	4 (33%)	0.408
Acute visits meeting protocol-defined PE†, n (%)	108 (71%)	44 (69%)	0.871
Requiring oral antibiotics‡	72 (67%)	19 (43%)	0.010
Requiring intravenous antibiotics	35 (32%)	23 (52%)	0.027
Requiring inhaled antibiotics	16 (15%)	10 (23%)	0.244
Requiring any antibiotics	91 (84%)	39 (89%)	0.615
Requiring hospitalization	31 (29%)	22 (50%)	0.015

A 3-year prognostic score for adults with cystic fibrosis

Journal of Cystic Fibrosis
The Official Journal of the European Cystic Fibrosis Society

L. Nkam [a,*], J. Lambert [b], A. Latouche [c], G. Bellis [d], PR. Burgel [e,f,1], M.N. Hocine [a,1]

Problématique de la fenêtre thérapeutique transplantation pulmon aire:
Quand adresser ?
Quand faire le bilan pré-greffe?
Quand inscrire?

Trop tôt
Risque TP > Risque décès lié CF

Trop tard
Etat général, bilan non fait

VEMS < 30%

Méthode

Registre Français de la mucoviscidose
Patients adulte
Entre 2010 et 2013

42 variables testées sur l'évènement décès/TP

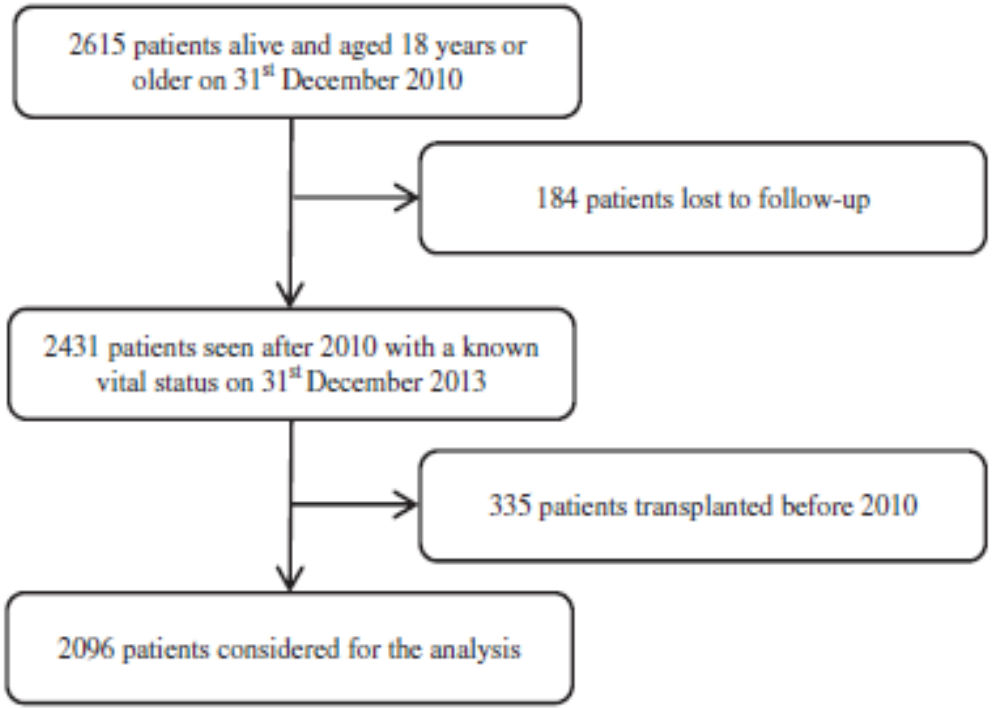
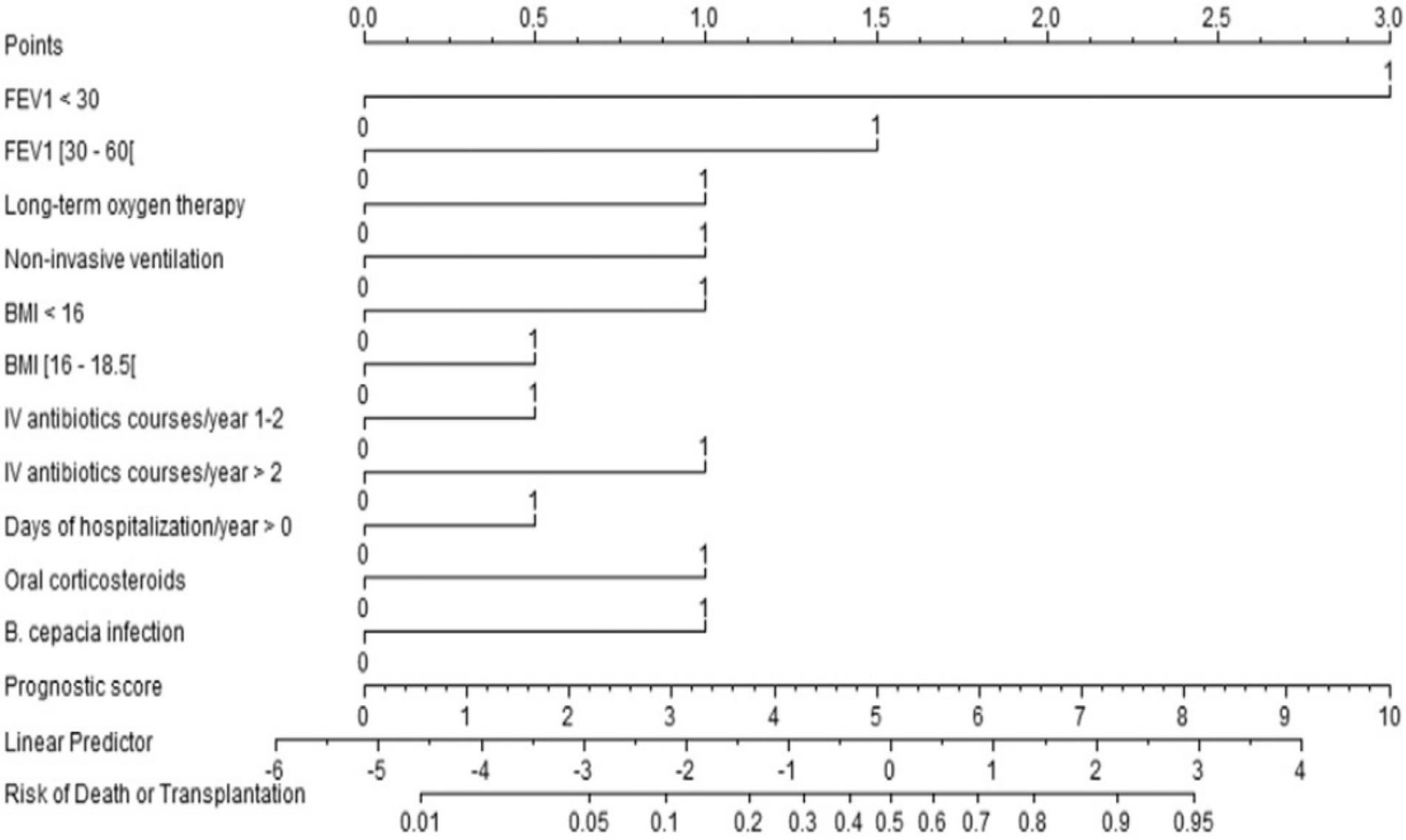
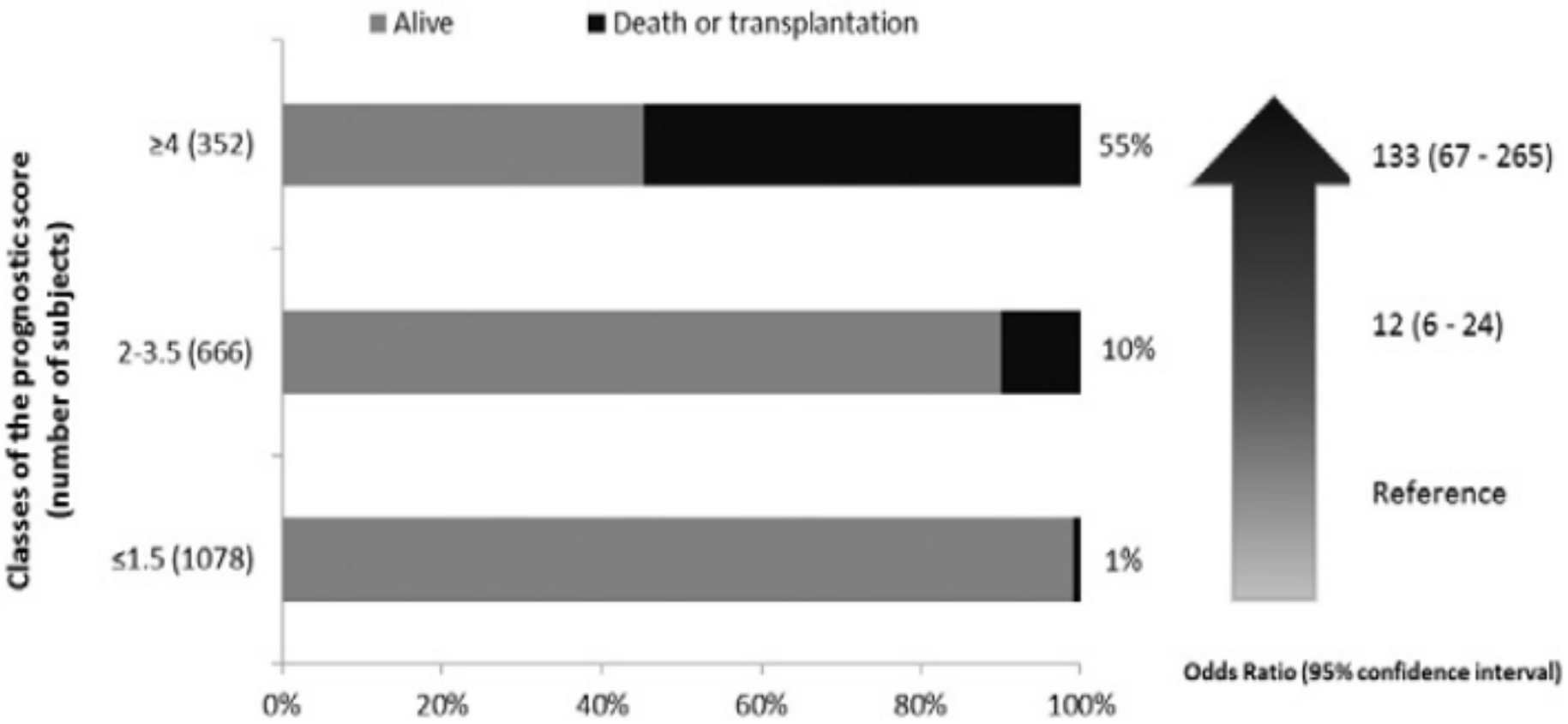


Table 2

Logistic regression model for prediction of within 3-year death or lung transplantation in adults with CF.

	Odds ratio (95% CI)	p value
FEV_1, % predicted	0.94 (0.92–0.95)	<0.001
BMI (kg/m^2)	0.87 (0.81–0.93)	<0.001
Burkholderia cepacia colonization		0.007
Test negative	1	
Test positive	3.15 (1.55–6.41)	
No test	1.17 (0.23–5.93)	
Number of intravenous antibiotics courses/year	1.16 (1.07–1.26)	<0.001
Number of days of hospitalization/year	1.17 (1.06–1.28)	0.001
Oral corticosteroids	2.05 (1.25–3.35)	0.004
Long-term oxygen therapy	2.81 (1.83–4.32)	<0.001
Non-invasive ventilation	1.74 (1.01–3.00)	0.04


Points
0.0 0.5 1.0 1.5 2.0 2.5 3.0
FEV1 < 30
1
FEV1 [30 - 60[
0 1
Long-term oxygen therapy
0 1
Non-invasive ventilation
0 1
BMI < 16
0 1
BMI [16 - 18.5[
0 1
IV antibiotics courses/year 1-2
0 1
IV antibiotics courses/year > 2
0 1
Days of hospitalization/year > 0
0 1
Oral corticosteroids
0 1
B. cepacia infection
0 1
Prognostic score
0 1 2 3 4 5 6 7 8 9 10
Linear Predictor
-6 -5 -4 -3 -2 -1 0 1 2 3 4
Risk of Death or Transplantation
0.01 0.05 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 0.95


Alive
Death or transplantation
Classes of the prognostic score (number of subjects)
≥4 (352)
2-3.5 (666)
≤1.5 (1078)
55%
10%
1%
0%
20%
40%
60%
80%
100%
133 (67 - 265)
12 (6 - 24)
Reference
Odds Ratio (95% confidence interval)

Socioeconomic Status, Smoke Exposure, and Health Outcomes in Young Children With Cystic Fibrosis

PEDIATRICS
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Thida Ong, MD,a Michael Schechter, MD, MPH,b Jing Yang, MS,c Limin Peng, PhD,c Julia Emerson, MD, MPH,a Ronald L. Gibson, MD, PhD,a Wayne Morgan, MD,d Margaret Rosenfeld, MD, MPH,a for the EPIC Study Group

Objectif: comprendre les inégalités en santé des jeunes patients CF

➡ Évaluer l'association entre Niveau Socio Economique et Exposition Fumée Tabac
suivi longitudinal :

1. fonction pulmonaire
2. présence de crépitants/sibilants
3. poids

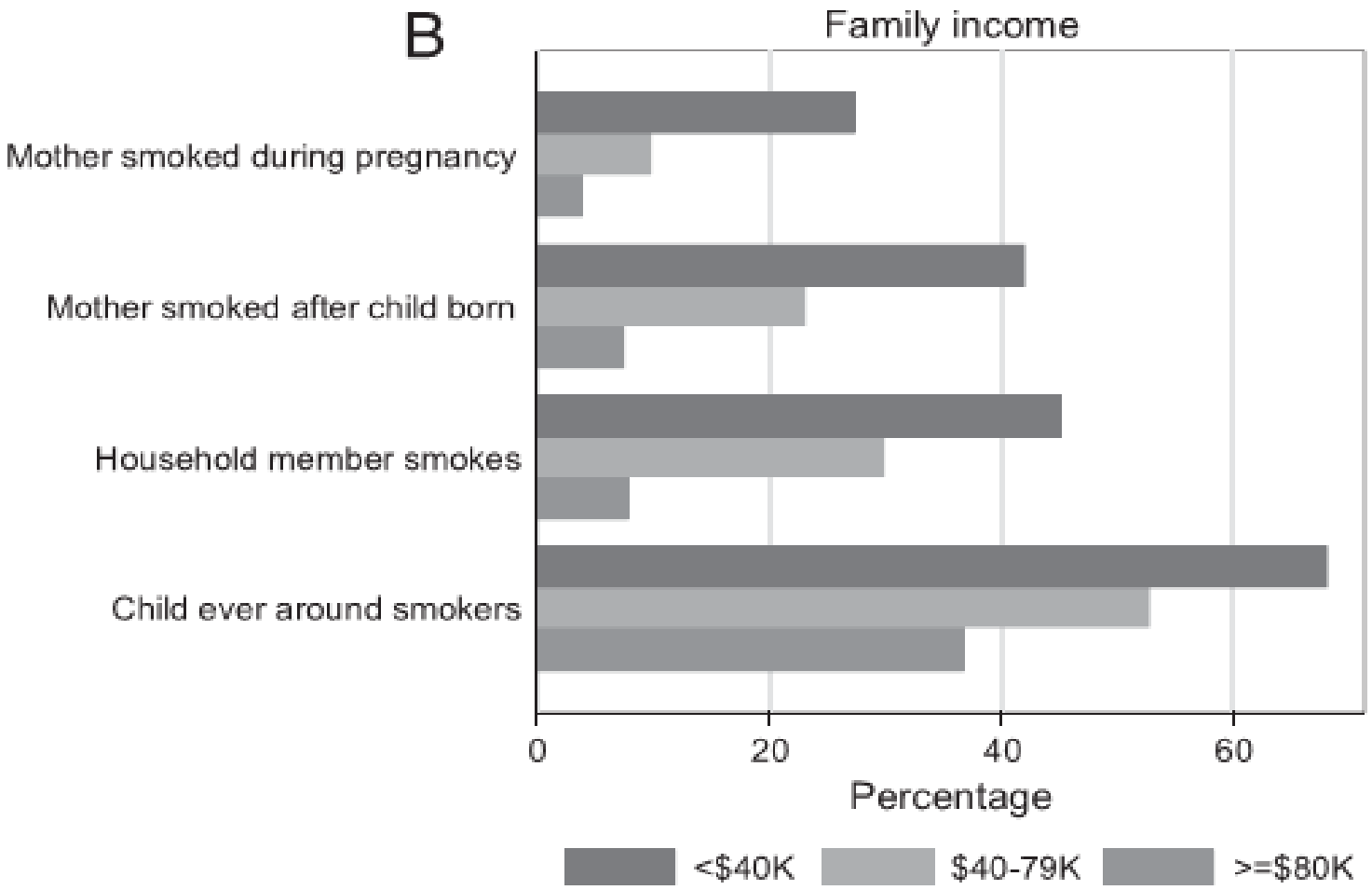
Etude sur cohorte EPIC (Early Pseudomonos Infection Control)

TABLE 1 Characteristics of the Study Cohort at Enrollment (n = 1375)

	n	%
Mother's education		
High school or less	387	28.1
Some college or more	951	69.2
Missing	37	2.7
Annual household income		
<$40 000	368	26.8
$40 000-$79 000	437	31.8
≥$80 000	363	26.4
Missing	207	15.1
Insurance status[d]		
Medicaid or no insurance	602	43.8
Private or other insurance	761	55.3
Missing	12	0.9

TABLE 1 Characteristics of the Study Cohort at Enrollment ($n = 1375$)

	n	%
Mother smoked during pregnancy		
No	1083	78.8
Yes	189	13.7
Unknown	103	7.5
Mother smoked any time after birth of child		
No	974	70.8
Yes	341	24.8
Missing	60	4.4
Household member smokes cigarettes		
No	966	70.3
Yes	400	29.1
Missing	9	0.6
Child around people smoking in past 3 mo		
Ever	720	52.4
Never	631	45.9
Missing	24	1.7



Relation similaire avec le niveau d'éducation maternelle et la couverture maladie

Impact du NSE et tabac sur le VEMS

TABLE 2 Separate Models to Assess Impact of SES and ETS Predictors on $FEV_{1\%}$ Predicted

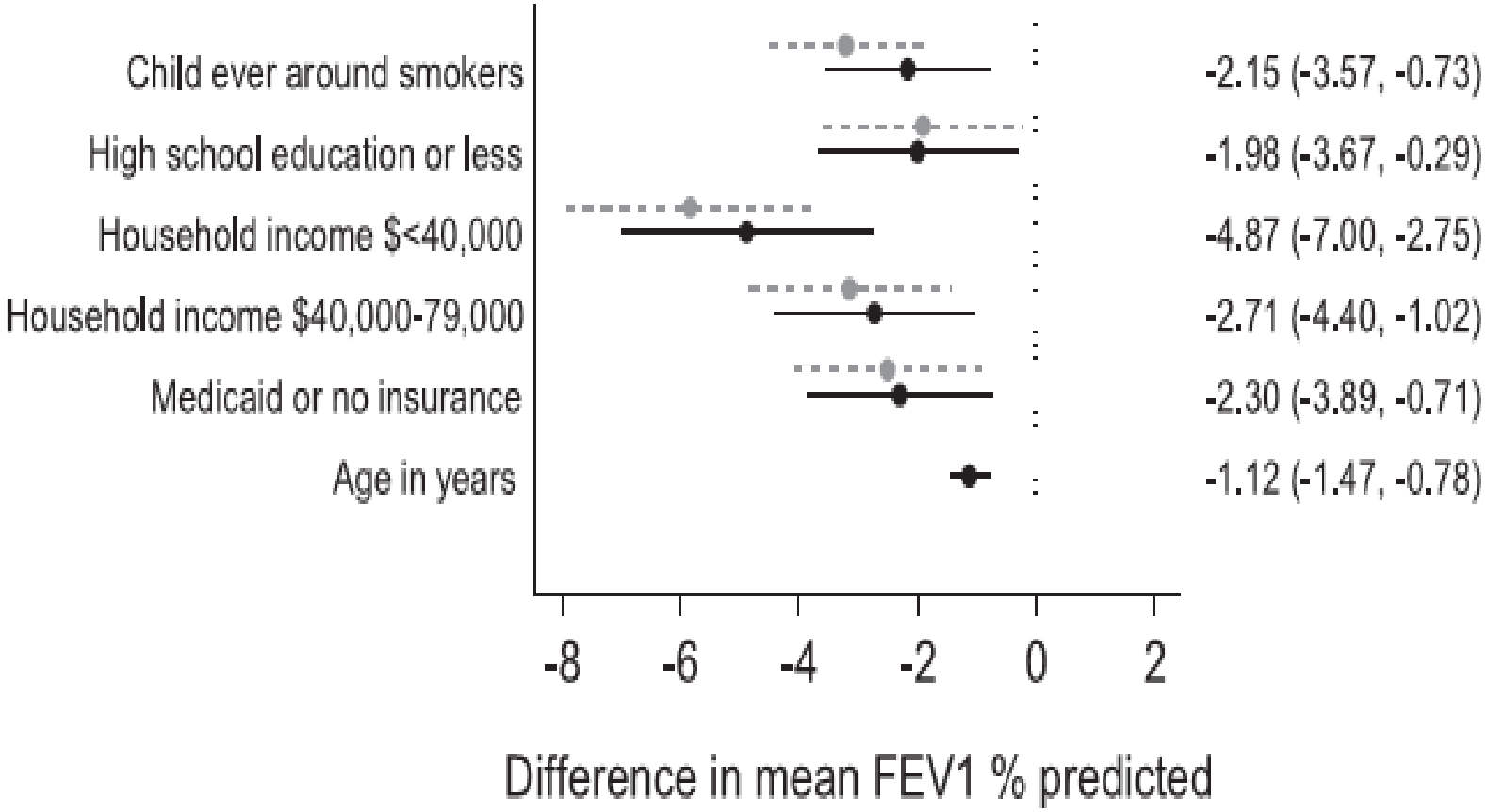
Exposure Variable	*n*/Observation[a]	Coefficient[b]	95% CI	*P*
SES model[c]	1050/18 416			
High school education or less		−1.90	−3.60 to −0.19	.03
Household income <$40 000		−5.82	−7.94 to −3.71	<.0001
Household income $40 000–79 000		−3.14	−4.83 to −1.44	.0003
Medicaid or no insurance		−2.49	−4.09 to −0.89	.0024
Age, y		−1.11	−1.46 to −0.76	<.0001
ETS model 1	1160/20 056			
Mother smoked during pregnancy		−4.59	−6.43 to −2.74	<.0001
Age, y		−1.10	−1.44 to −0.77	<.0001
ETS model 2	1197/20 743			
Mother smoked after child's birth		−5.98	−7.44 to −4.52	<.0001
Age, y		−1.11	−1.44 to −0.78	<.0001
ETS model 3	1240/21 607			
Household member smokes		−2.60	−4.03 to −1.16	.0004
Age, y		−1.11	−1.43 to −0.78	<.0001
ETS model 4	1224/21 321			
Child ever around smokers in past 3 mo		−3.21	−4.48 to −1.93	<.0001
Age, y		−1.11	−1.43 to −0.78	<.0001

NSE

Tabac

Argent ou tabac ?

Analyse multivariée



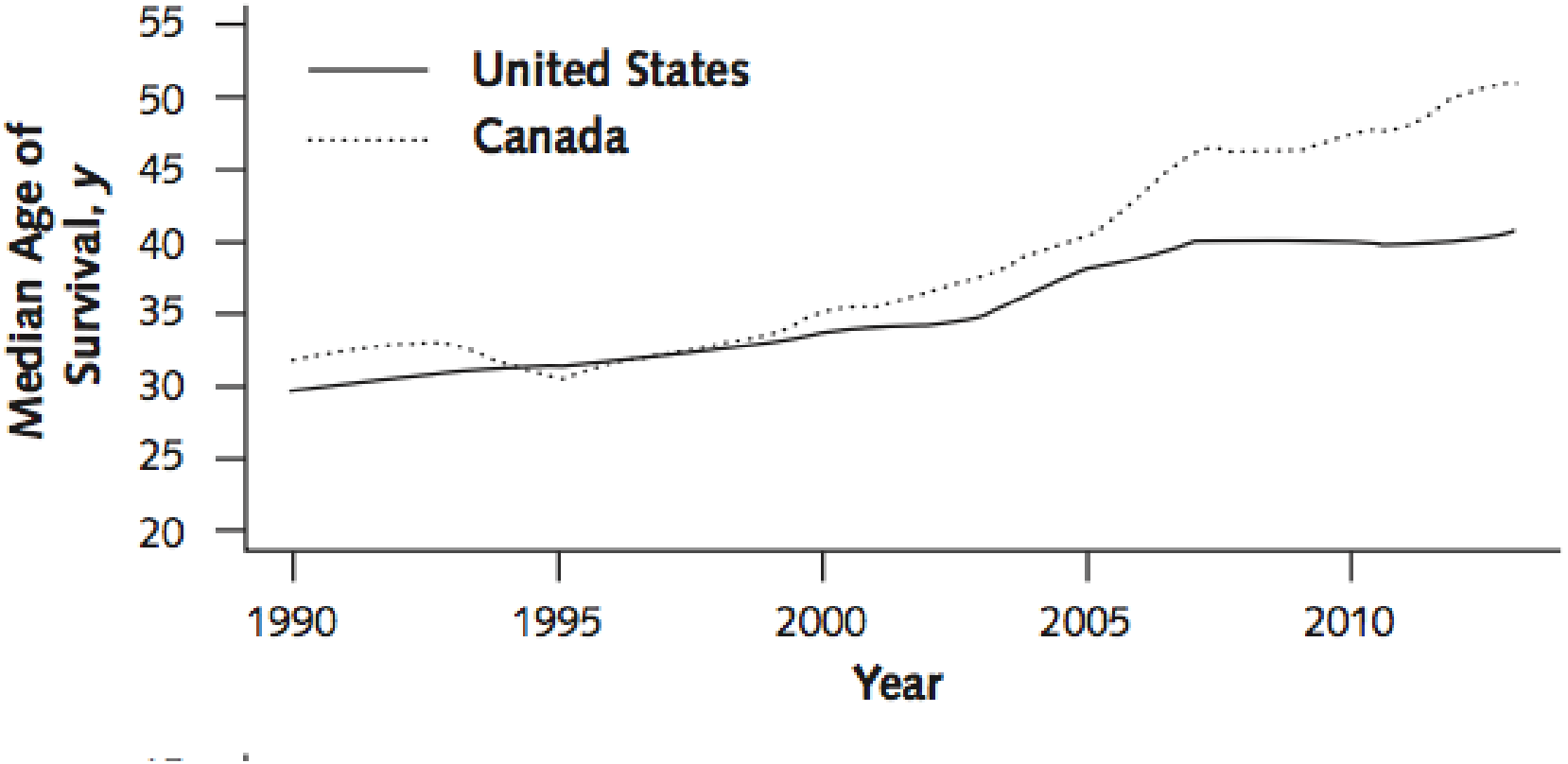
Les 2 !

Annals of Internal Medicine

Survival Comparison of Patients With Cystic Fibrosis in Canada and the United States

A Population-Based Cohort Study

Anne L. Stephenson, MD, PhD; Jenna Sykes, MMath; Sanja Stanojevic, PhD; Bradley S. Quon, MD, MSc; Bruce C. Marshall, MD; Kristofer Petren, BA, BSc; Josh Ostrenga, MSc; Aliza K. Fink, DSc; Alexander Elbert, PhD; and Christopher H. Goss, MD, MSc



Variable	Patients, *n* (%)†		*P* Value‡
	Canada (*n* = 4662)	United States (*n* = 32 699)	
Vital status			
Censored at follow-up	4421 (94.8)	30 525 (93.4)	
Died	241 (5.2)	2174 (6.6)	<0.001
Did not receive transplant	147 (61.0)	1699 (78.2)	<0.001
Median age at death (range), *y*	31.9 (0.3–79.3)	26.9 (0.3–76.9)	<0.001
Cause of death			
Cardiorespiratory	164 (68.0)	1462 (67.2)	0.176
Other	51 (21.2)	578 (26.6)	
Unknown	26 (10.8)	134 (6.2)	
Transplantation‖			
No	4182 (89.7)	30 572 (93.5)	
Yes	480 (10.3)	2127 (6.5)	<0.001
Insurance status			
Continuous Medicaid/Medicare	0 (0)	7971 (24.4)	
Intermittent Medicaid/Medicare use	0 (0)	10 814 (33.1)	
Other insurance	0 (0)	13 131 (40.2)	
None/unknown	0 (0)	783 (2.4)	
Canadian health care	4662 (100)	0 (0)	

- plus de diabétiques
- plus de staphylocoque METI R, de pyocyanique et Mycobactéries atypiques
- moins de Burkholderia cepacia et d'aspergillus
- plus de mucolytiques
- plus d'azithromycine
- moins de visites médicales (4,2 vs 3,8 mois)

Messages

Sur place ou à emporter

Evolution du microbiote respiratoire avec l'âge (quantité et en qualité)

Rôle de l'immunité adaptative dans la maladie pulmonaire

Intégration Tezacaftor dans la stratégie thérapeutique

Développement de la médecine personnalisée

Importance du système de soins et du niveau socio-économique

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Merci pour votre attention !