



ERS Webinar

30 jan 2025

Usefulness of chest CT scan in the management of difficult-to-treat and severe asthma

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Conflict of interest disclosure



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- Industry-sponsored grants: Astra Zeneca-MedImmune, Boehringer-Ingelheim, GlaxoSmithKline, Novartis, Sanofi-Regeneron, MSD**
- Consultancies: AstraZeneca-MedImmune, Boehringer-Ingelheim, GlaxoSmithKline, Novartis, Regeneron- Sanofi, Med-in-Cell, Actelion, Celltrion, Areteia, Merck, Roche, Chiesi**
- Investigator/Co-investigator for trials promoted by AstraZeneca-MedImmune, Boehringer-Ingelheim, GlaxoSmithKline, Novartis, Regeneron- Sanofi, Chiesi, Actelion, Merck, Roche, Vertex, Galapagos, Syneos, MSD, Areteia**
- Member of GINA scientific committee**
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- No off-label disclosures**

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Performing HRCT in asthma

- Diagnostic considerations
 - *Does lung imaging help in the work up of asthma diagnosis?*
 - diagnosis of additional conditions in 40% of cases in patients with severe asthma, including bronchiectasis, emphysema and lung nodules.
 - complexity of differentiating asthma from COPD
 - radiological features are incidentally detected (e.g. interstitial lung abnormalities), which may make the diagnosis of asthma a challenge.
- Mechanistic studies
- Therapeutic studies
 - predict future risk of disease exacerbation and lung function decline
 - identify particular phenotypes and predict treatment response
- Sinus CT can not only identify asthma-related comorbidities such as nasal polyposis, but also has the potential to support phenotypic characterization.

Other tests that may be used in diagnosis of asthma – GINA 2024



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Imaging

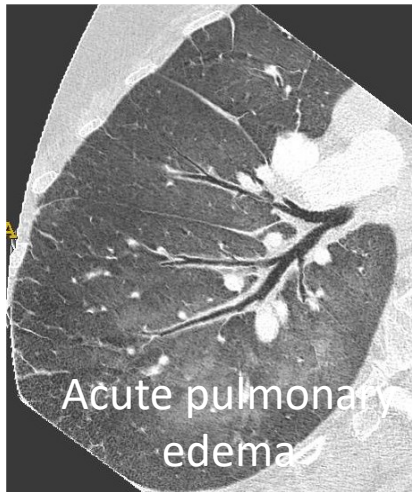
- Imaging studies are **not routinely used in the diagnosis** of asthma, but may be useful to investigate the possibility of **comorbid conditions or alternative diagnoses** in adults with difficult-to-treat asthma.
- Imaging may also be used to **identify congenital abnormalities** in infants with asthma-like symptoms, and **alternative diagnoses** in children with difficult-to-treat asthma.
- High-resolution computed tomography (CT) of the lungs can identify conditions such as bronchiectasis, emphysema, lung nodules, airway wall thickening and lung distension, and may assess airway distensibility.
- The presence of radiographically detected **emphysema** is considered when differentiating asthma from COPD (Box 7-4, p.137), but there is **no accepted threshold**, and these conditions can **coexist**.
- Moreover, **air trapping** (which may be present in asthma, and is also a feature of ageing) can be difficult to distinguish from emphysema.
- Chest imaging **is not currently recommended to predict treatment outcomes** or lung function decline, or to assess treatment response.
- **CT of the sinuses** can identify changes suggestive of chronic rhinosinusitis with or without nasal polyps (p.120), which in patients with severe asthma **may help with choice of biologic therapy** (see Box 8-4, p.144).



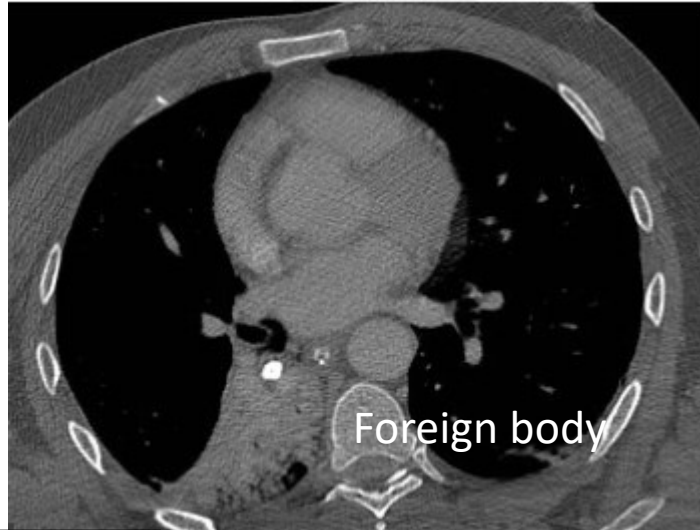
So many differential diagnosis



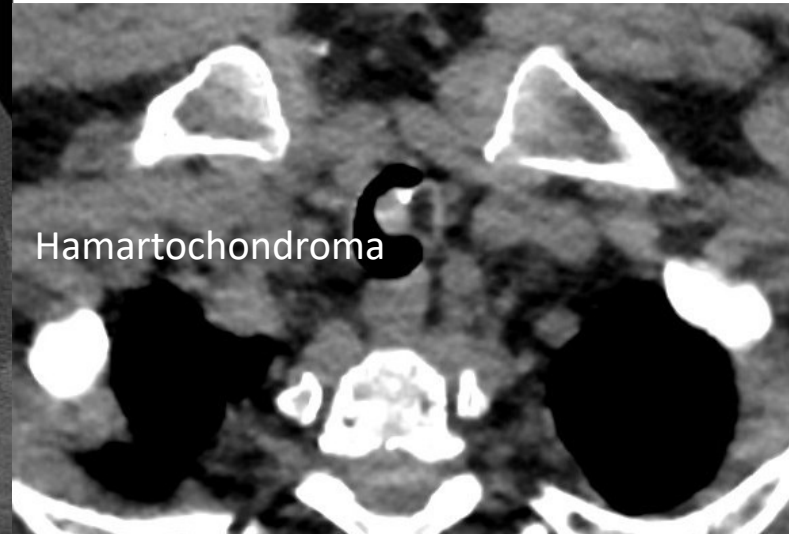
Courtesy of Pr Sebastien Bommart, University of Montpellier



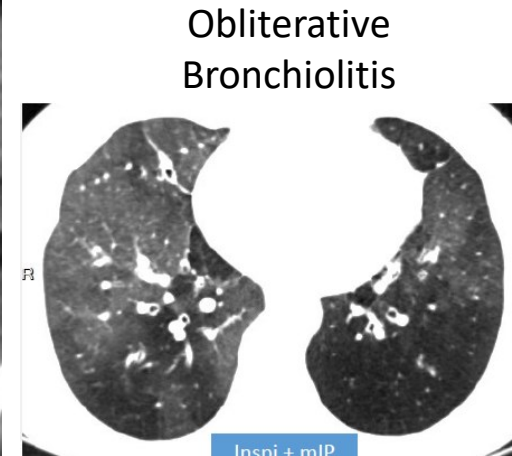
Acute pulmonary edema



Foreign body

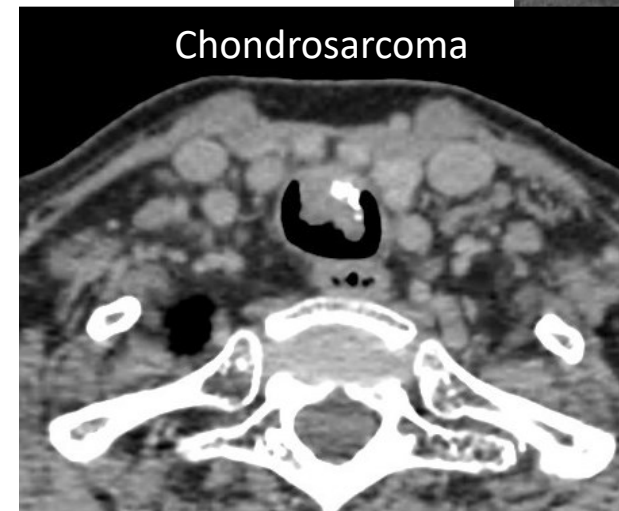


Hamartochondroma



Obliterative Bronchiolitis

Inspi + mIP

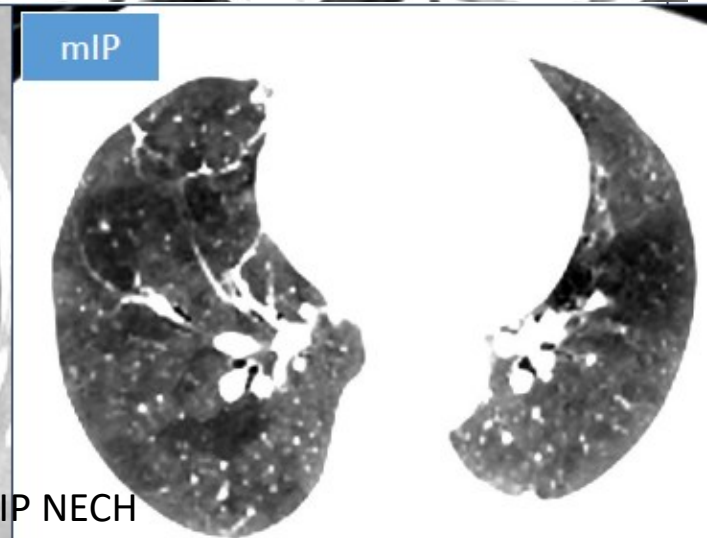


Chondrosarcoma



MIP

DIP NECH



mIP

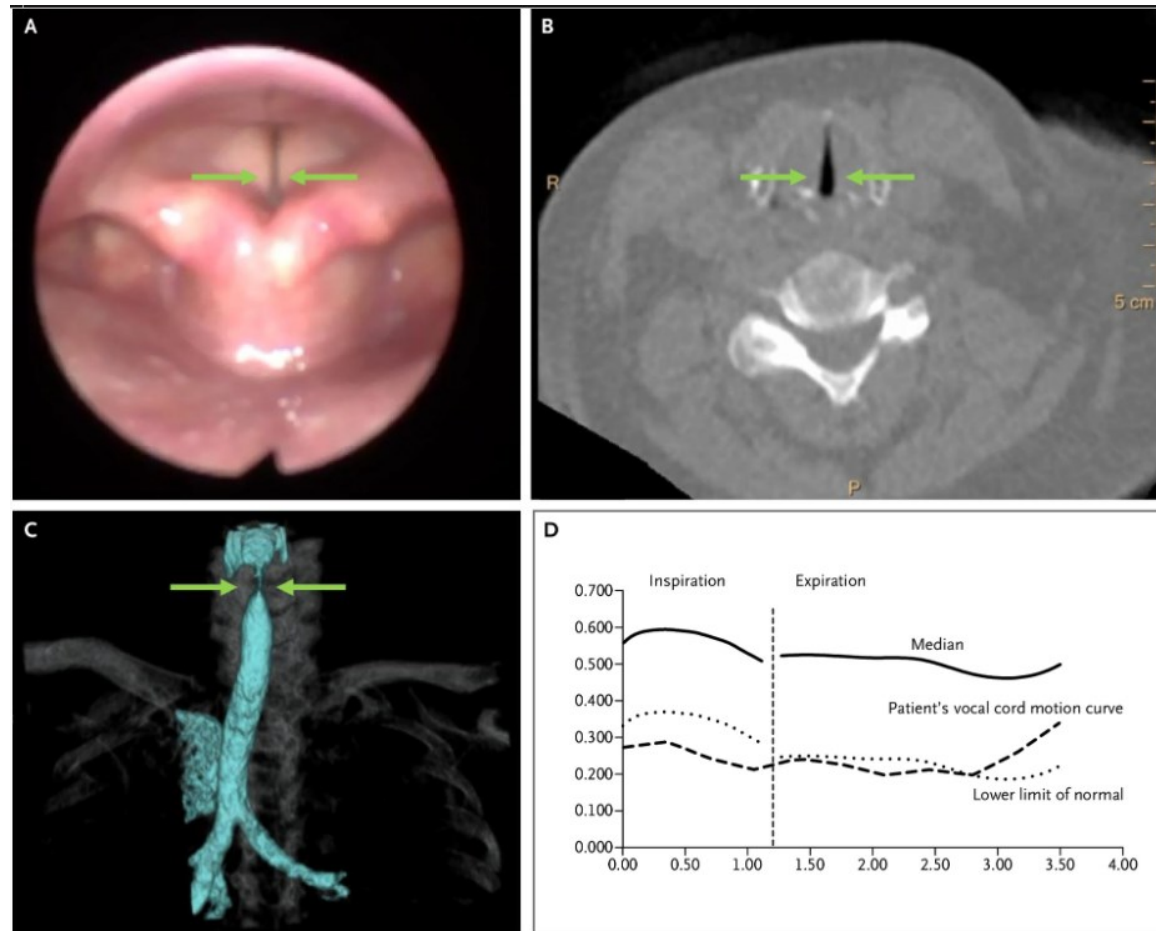


Crohn's

Computed Tomography Imaging of the Larynx for Diagnosis of Vocal Cord Dysfunction

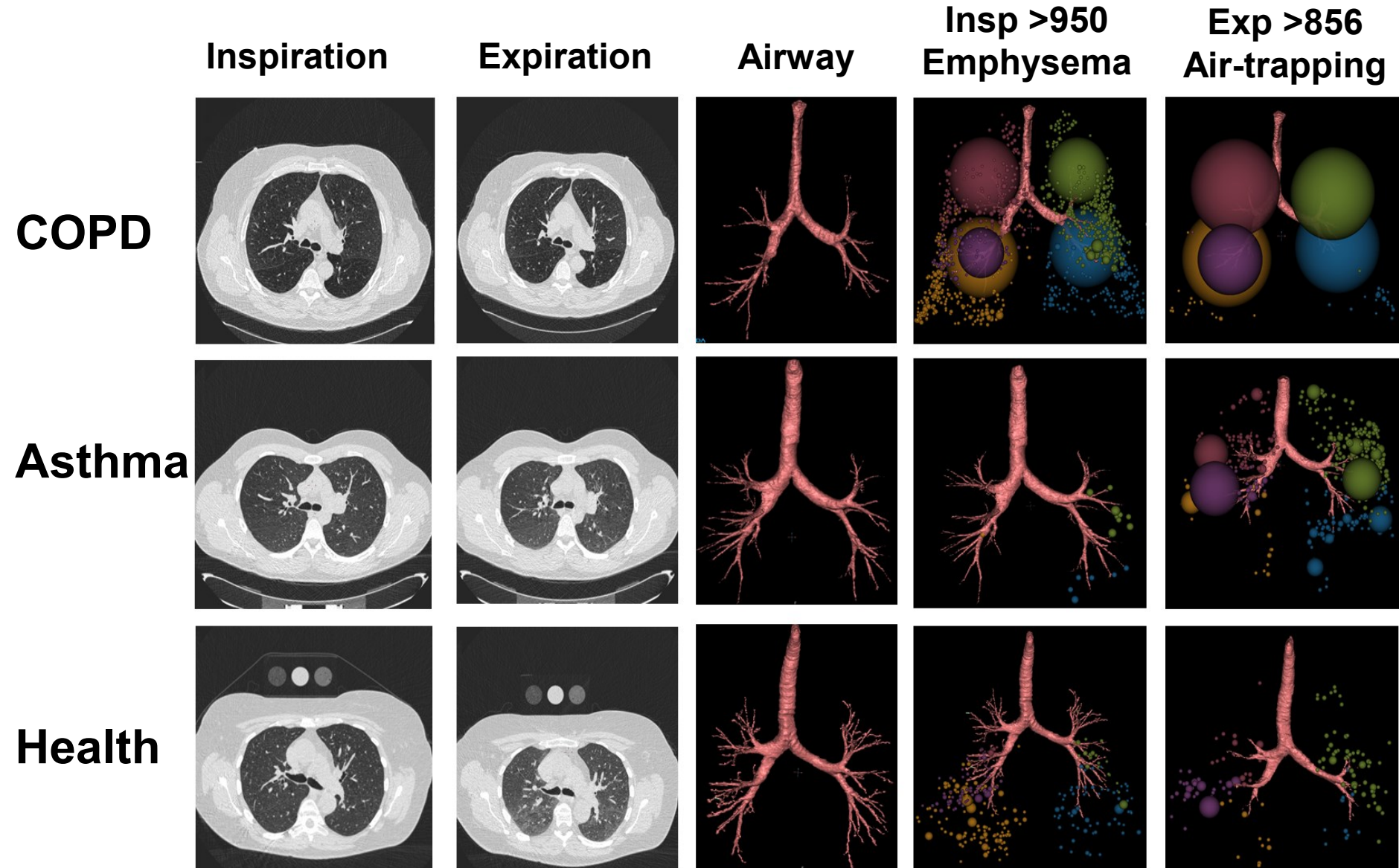
Authors: [Joo H. Koh, M.B.B.S.](#), [Laurence](#)

[E. Ruane, M.Sc.](#), [Debra Phyland, Ph.D.](#), [Kais Hamza, Ph.D.](#), [Risa Fukusho, M.B.B.S.](#), [Elizabeth Leahy, R.N.](#), [Adriana Avram, R.N.](#), +5, and [Philip G. Bardin, Ph.D.](#) philip.bardin@monash.edu [Author Info & Affiliations](#)

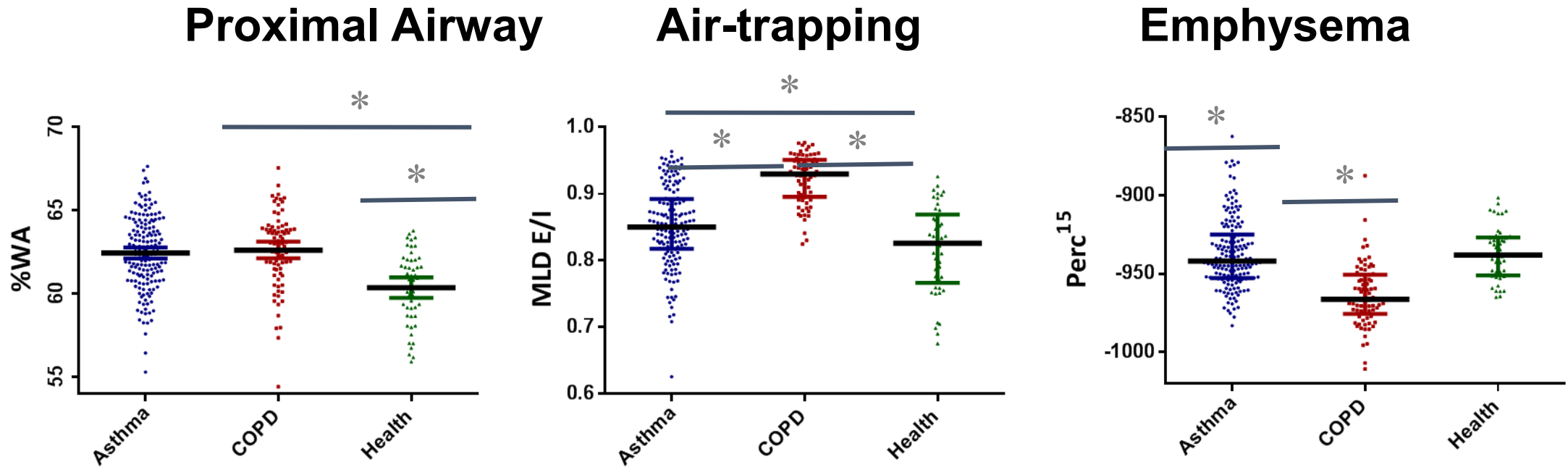


QCT Asthma versus COPD

Hartley et al JACI 2016



QCT Asthma versus COPD



*p<0.05

Bronchiectasis is not a differential diagnosis

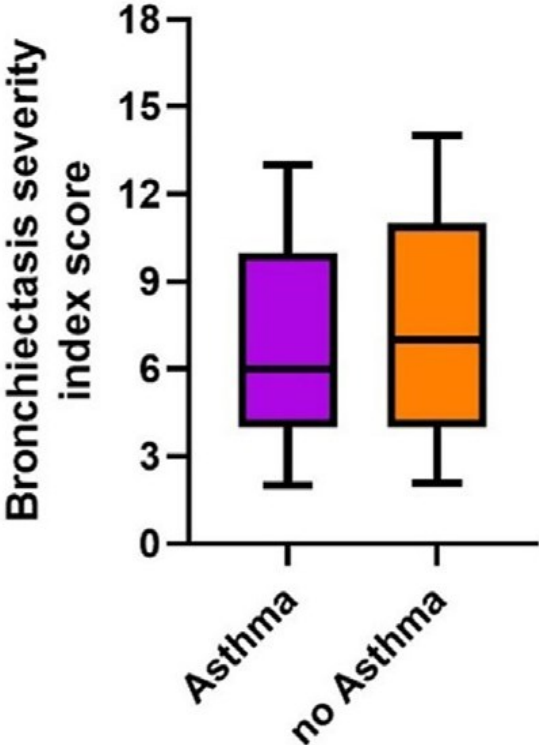
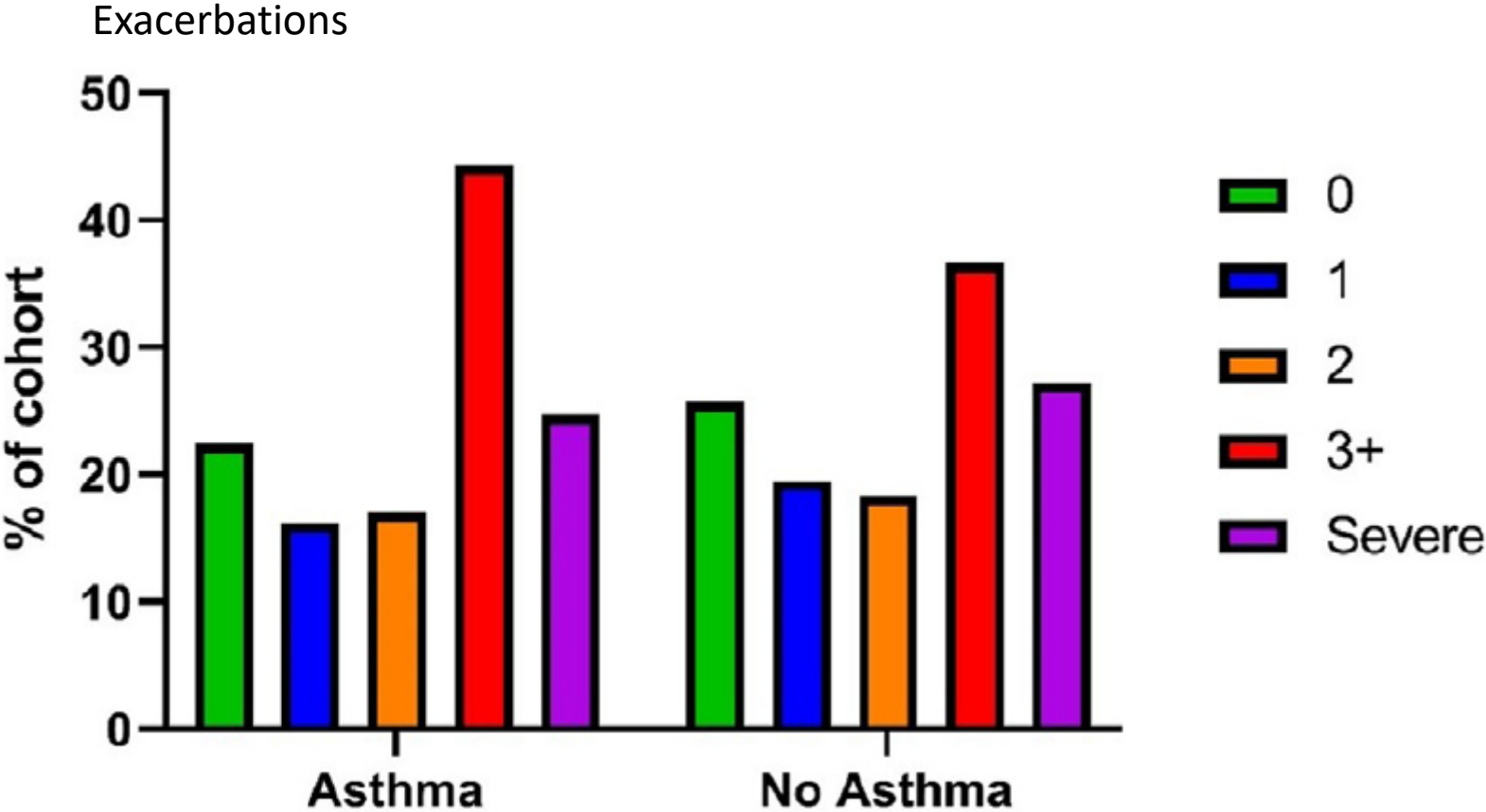
« *Of 16,963 patients with bronchiectasis included for analysis, 5,267 patients (31.0%) had investigator-reported asthma* »

In terms of treatments, **19.7% of patients** with a recorded diagnosis of asthma **were not taking a regular ICS**. Only 387 (7.3%) patients were taking ICSs without an additional treatment. The remaining patients were taking ICSs with at least 1 additional controller medication. There were **410 (7.8%) patients taking oral corticosteroids long term** and **58 (1.1%) patients taking monoclonal antibodies** at baseline.

Asthma was recorded as the underlying cause of bronchiectasis in **1165 patients (6.9%)**.

Parameter	Asthma with bronchiectasis
Any test performed	3456
Elevated peripheral eosinophil count, n/N (%)	574/2804 (20.5%)
IgE groups	2755
<150	1837 (66.7%)
150-300	279 (10.1%)
301-500	193 (7.0%)
501-750	122 (4.4%)
751-1000	71 (2.6%)
1000-2000	121 (4.4%)
>2000	132 (4.8%)
Raised specific IgE to <i>Aspergillus</i>	697/2337 (29.8%)
Diagnostic criteria for ABPA at baseline	265 (7.7%)

EMBARC



Asthmatics with bronchiectasis should be treated...as asthmatics !

TABLE IV. Relationship between reported asthma and clinical outcomes during follow-up

	Unadjusted	Adjusted*	Fully adjusted†
Mortality			
Asthma/ICS use	0.87 (0.73-1.03)	0.76 (0.64-0.90)	0.78 (0.63-0.95)
Asthma/no ICS use	1.09 (0.82-1.44)	1.00 (0.76-1.33)	1.08 (0.81-1.43)
No asthma/ICS use	1.63 (1.41-1.89)	1.12 (0.97-1.30)	1.00 (0.84-1.22)
No asthma/no ICS use	1.00 (reference)	1.00 (reference)	1.00 (reference)
Hospitalizations			
Asthma/ICS use	1.02 (0.92-1.12)	0.92 (0.83-1.02)	0.67 (0.67-0.86)
Asthma/no ICS use	1.53 (1.31-1.78)	1.32 (1.12-1.56)	1.37 (1.16-1.61)
No asthma/ICS use	1.56 (1.42-1.72)	1.01 (0.91-1.02)	0.87 (0.77-0.98)
No asthma/no ICS use	1.00 (reference)	1.00 (reference)	1.00 (reference)
Exacerbations			
Asthma/ICS use	1.24 (1.17-1.32)	1.10 (0.99-1.23)	1.00 (0.92-1.09)
Asthma/no ICS use	1.16 (1.04-1.29)	1.19 (1.11-1.27)	1.08 (0.97-1.21)
No asthma/ICS use	1.58 (1.29-1.47)	1.16 (1.09-1.24)	1.02 (0.94-1.10)
No asthma/no ICS use	1.00 (reference)	1.00 (reference)	1.00 (reference)

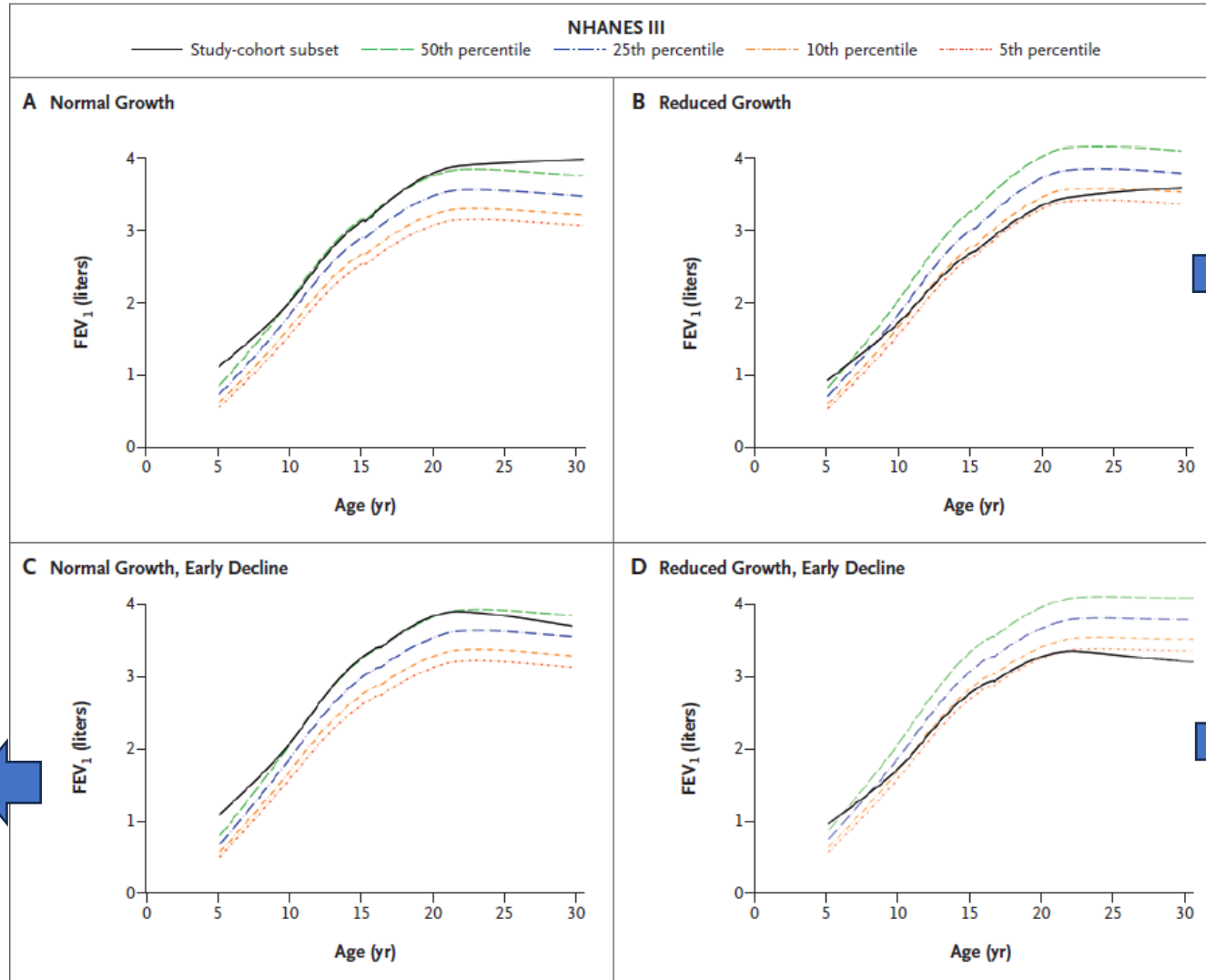
Mortality was analyzed using the Cox proportional hazards regression model, with data presented as hazard ratios with 95% CIs. Hospitalization and exacerbation frequency were analyzed using a negative binomial model, with data presented as rate ratios with 95% CIs.

*Adjusted for BSI and sex.

†Adjusted for age, sex, smoking, cardiovascular disease, diabetes, COPD, radiologic severity, long-acting β -agonists, macrolide use, *P aeruginosa* infection, and country.

- HRCT and airway reactivity in asthma

Patterns of Growth and Decline in Lung Function in Persistent Childhood Asthma



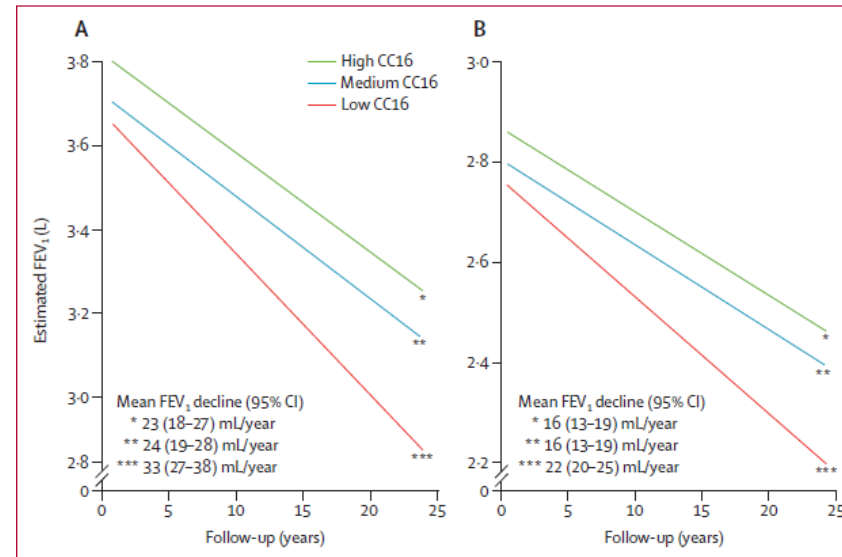
- higher BMI at enrollment (OR 1.39; P = 0.02),
 - maternal cigarette smoking during gestation (OR 2.33; P = 0.04)

- lower FEV1 at enrollment (OR 0.86 per 1% change),
 - lower bronchodilator response (OR 0.91 per 1% change),
 - **AHR (OR 0.61 per unit change);**
 - Male (odds ratio, 8.18; P<0.001);
 - younger at enrollment (OR, 0.55 per year of age);
 - lower level of parental education (OR 0.33; P = 0.002);
 - vitamin D insufficiency (OR 2.15; P = 0.03);
 - more courses of prednisone per year (OR 4.12 for each additional course; P = 0.03).

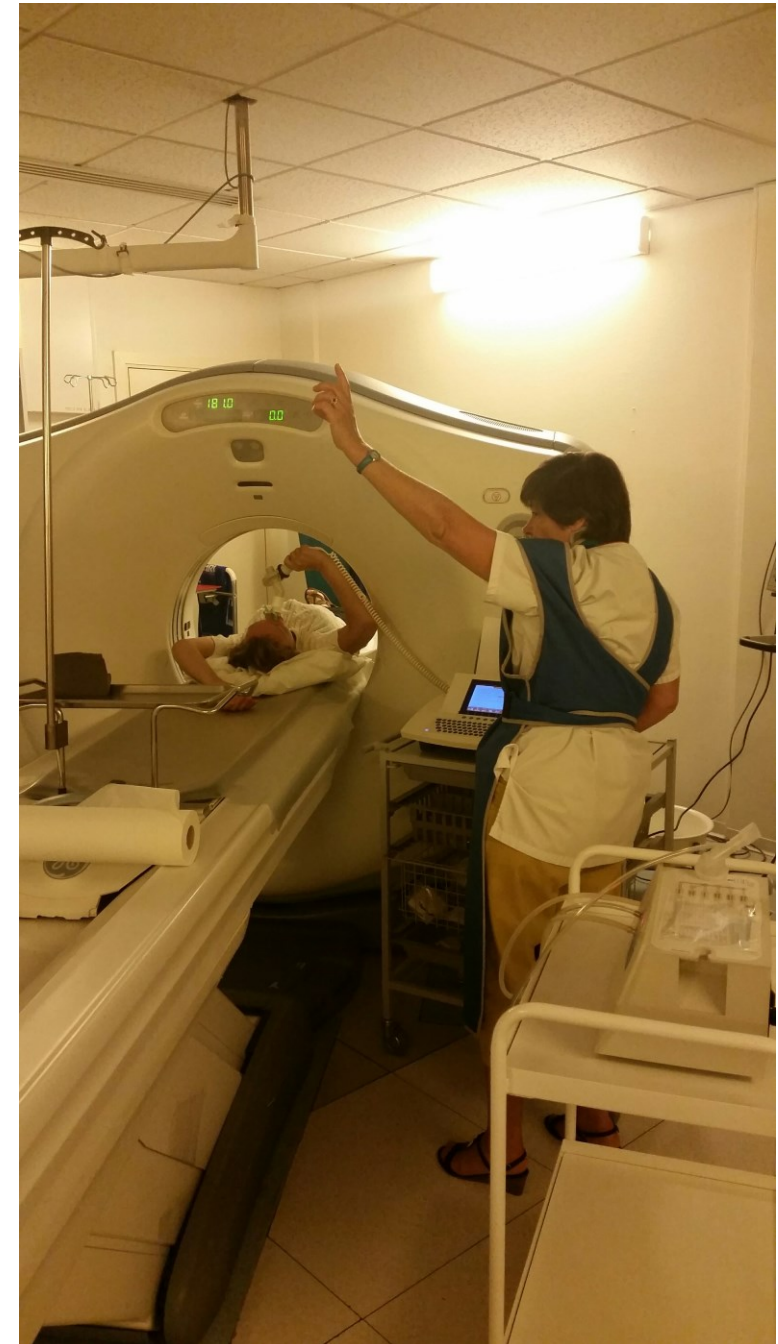
- lower (OR 0.85 per 1% change),
 - lower BDR (OR 0.91 per 1% change)
 - **AHR (OR 0.66 per unit change);**
 - male (OR 3.07);
 - younger at enrollment (OR 0.62 per year of age)
 - lower level of parental education (OR),
 - greater number of positive skin tests (OR for ≥3 positive tests vs.<3, 2.42; P = 0.03),

Relation between circulating CC16 concentrations, lung function, and development of chronic obstructive pulmonary disease across the lifespan: a prospective study

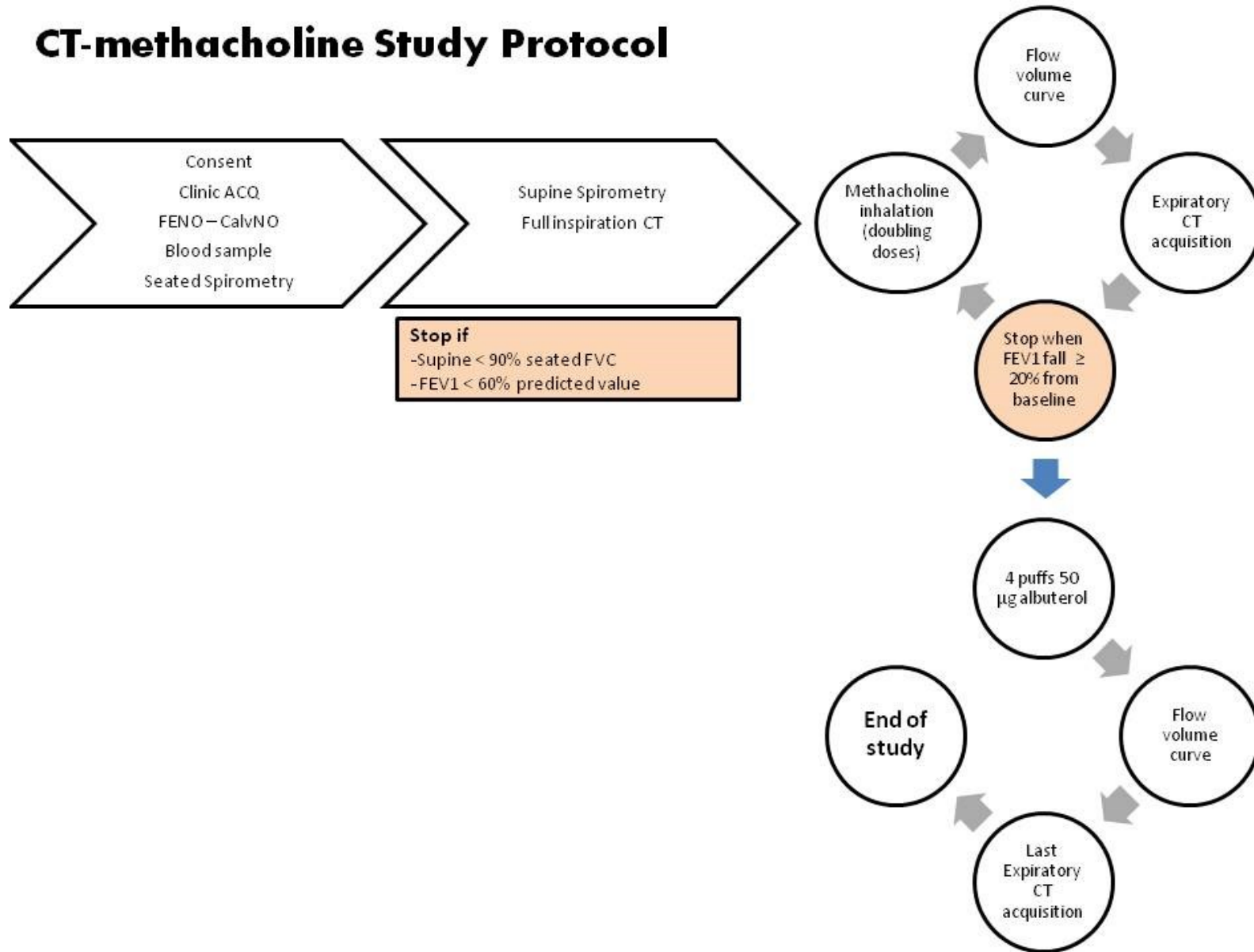
	β coefficient (95% CI) for increase in FEV ₁ decline (mL/year) associated with 1 SD decrease in baseline CC16 concentration*	p value
TESAOD (n=800 with 6114 observations, mean follow-up 16.0 years)†	-4.4 (-7.1 to -1.7)	0.0014
ECRHS-Sp (n=495‡ with 990 observations, mean follow-up 11.5 years)	-2.4 (-4.5 to -0.3)	0.023
SAPALDIA (n=164§ with 328 observations, mean follow-up 8.3 years)	-4.5 (-9.0 to 0.0)	0.052
Meta-analysis	-3.3 (-4.8 to -1.8)	<0.0001



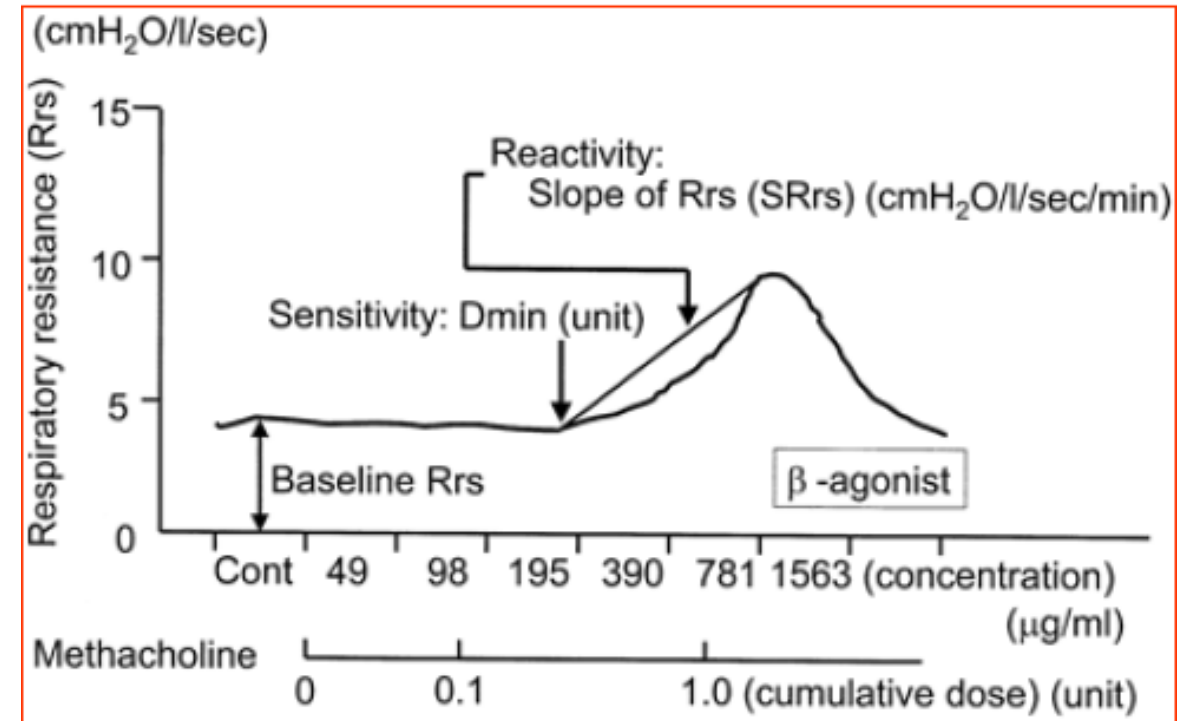
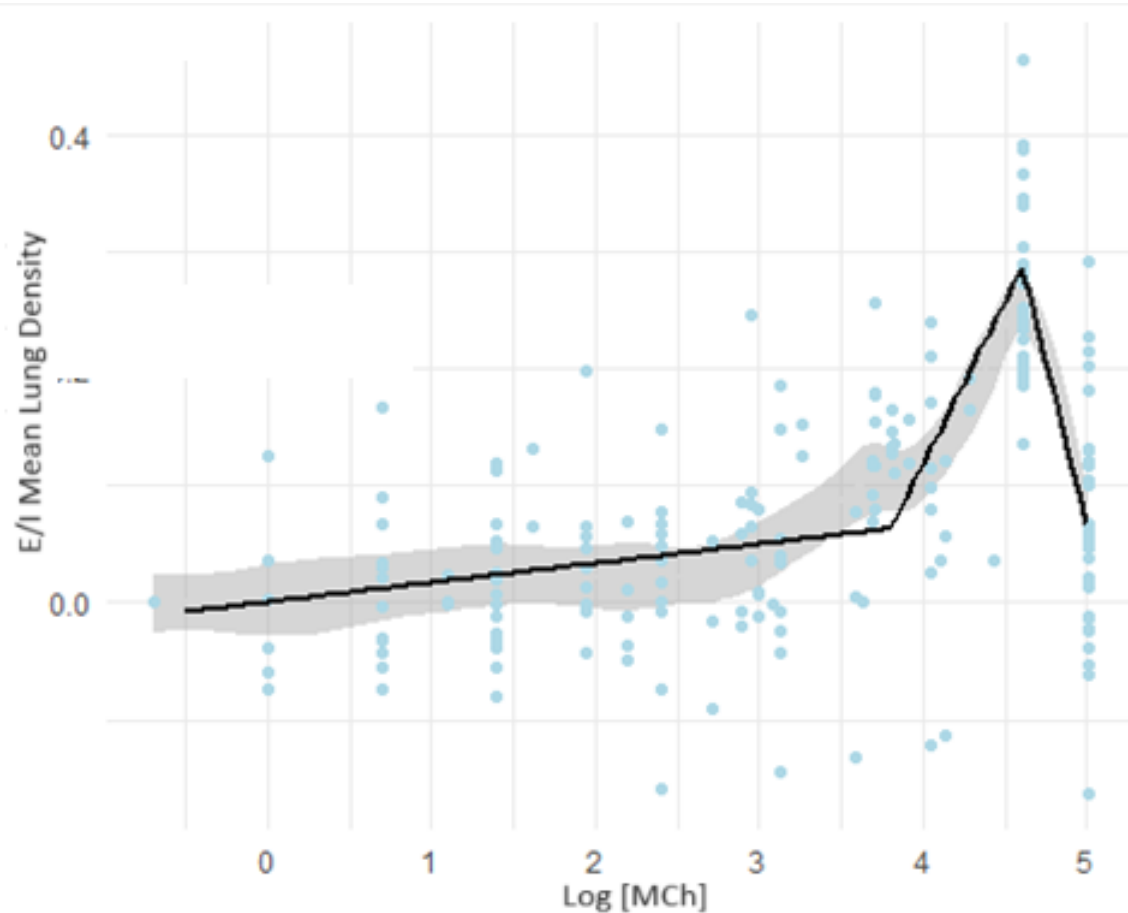
Methacholine challenge at HRCT – *The Scann'air study*



CT-methacholine Study Protocol



Mechanisms of Airway Hyper Reactivity

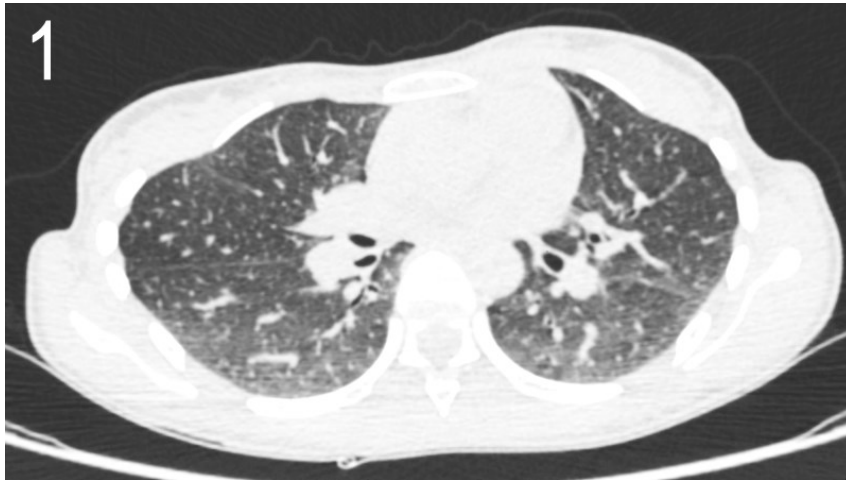


Niimi AJRCCM 2003

The scann'air study

Air trapping during methacholine in asthma patients

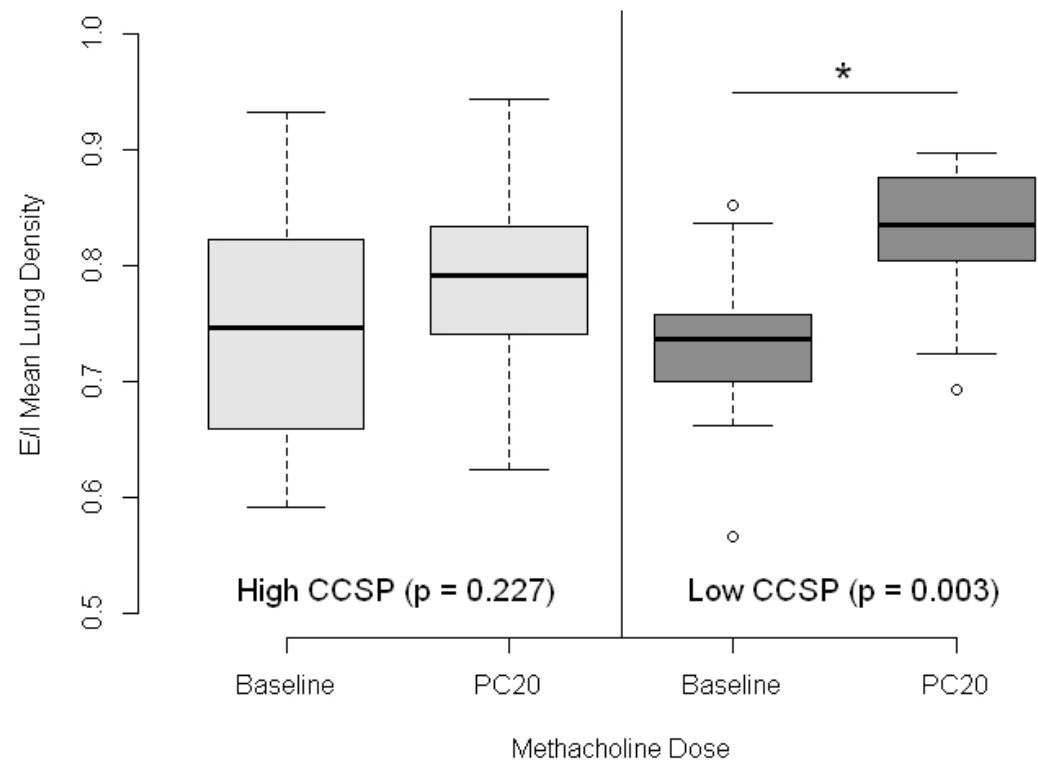
High blood CC16 levels



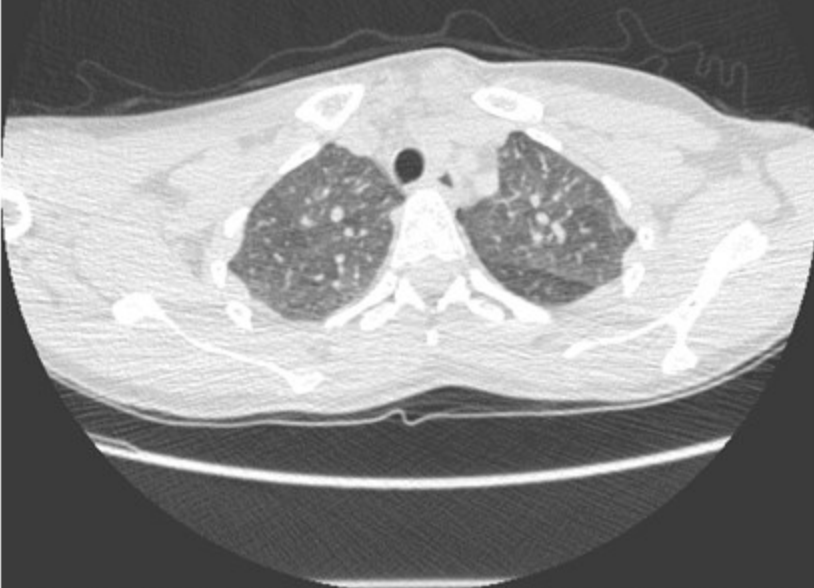
Low blood CC16 levels



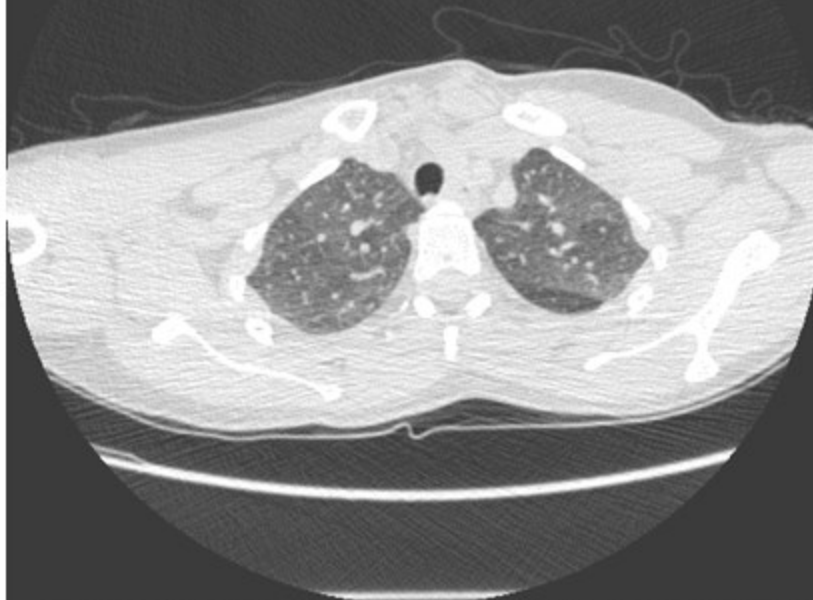
Display in the slideshow mode to start animation



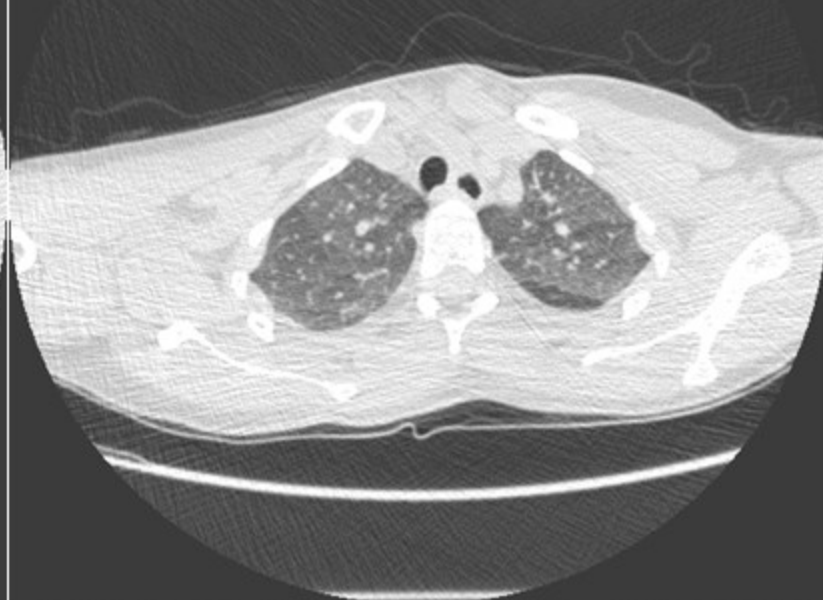
expiration



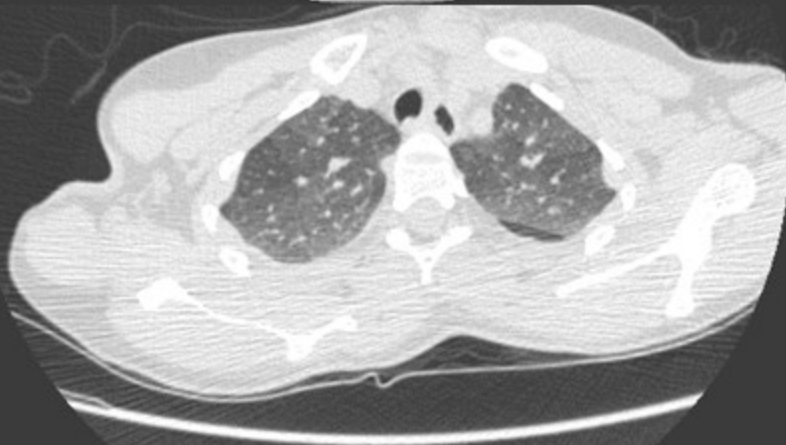
MCh Dose 1



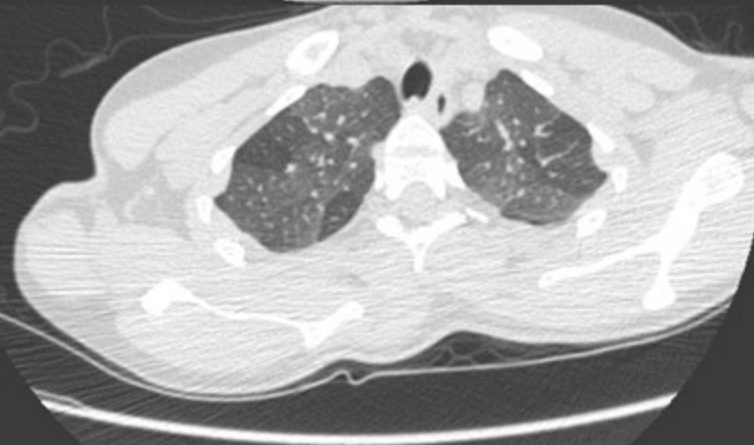
MCh Dose 2



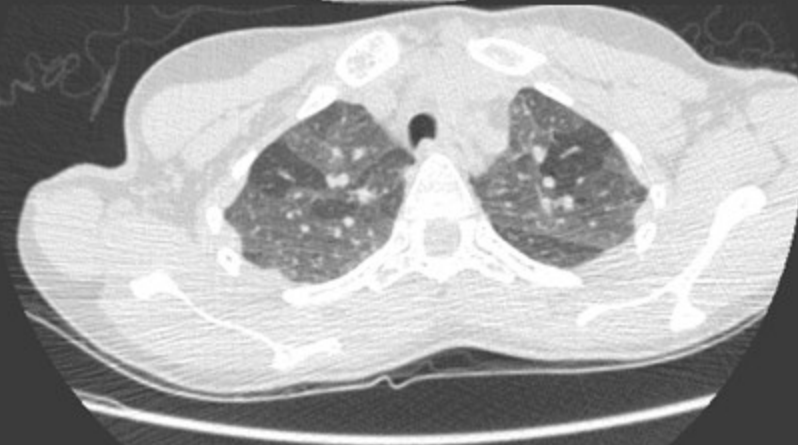
MCh Dose 3



MCh Dose 4



After SABA



expiration



MCh Dose 1



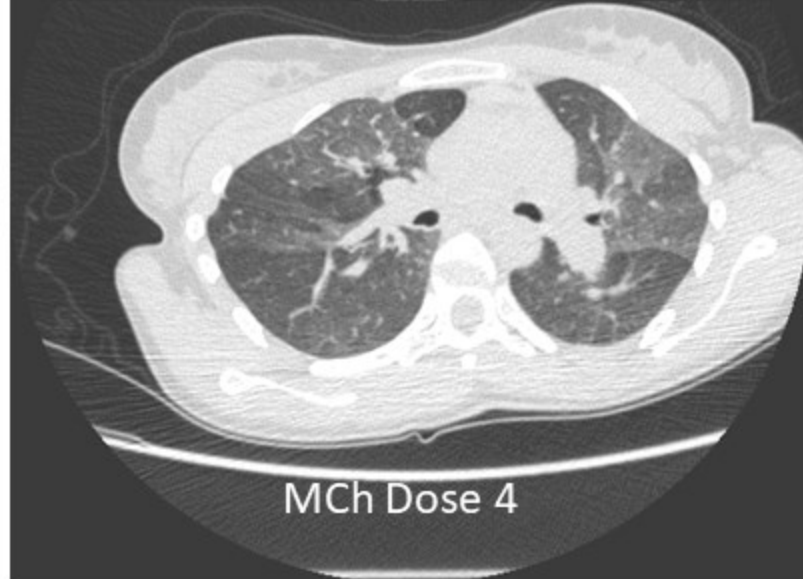
MCh Dose 2



MCh Dose 3



MCh Dose 4



After SABA



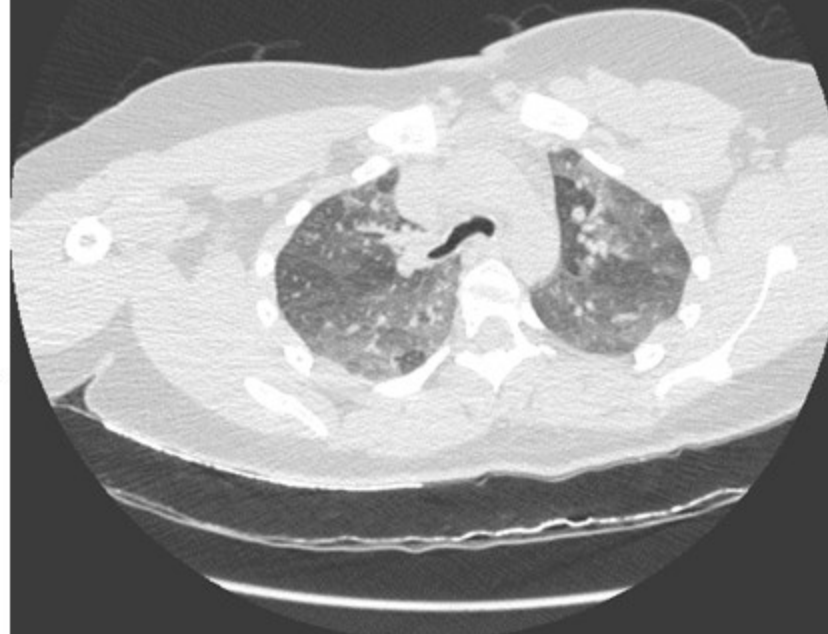
expiration



MCh Dose 1



MCh Dose 2



MCh Dose 3



MCh Dose 4



After SABA



Sequential acquisition in patient #8 belonging to cluster 2 [uniform]; upper lung

expiration



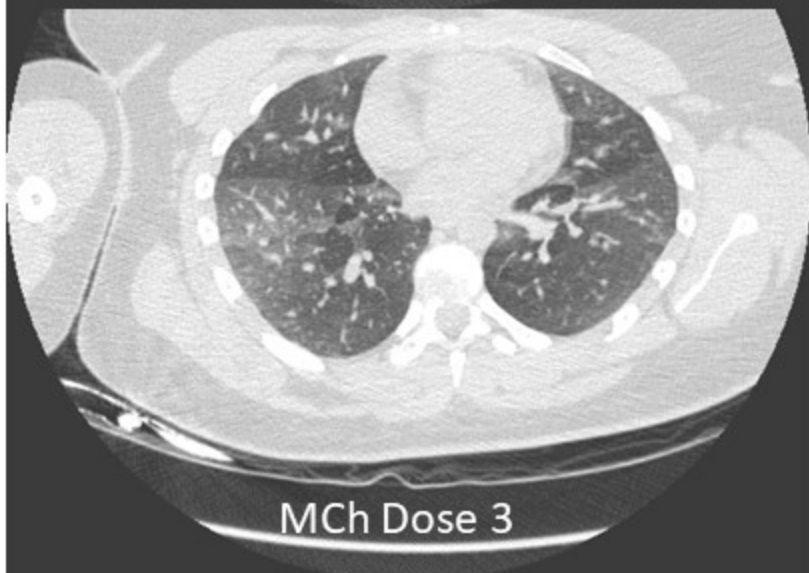
MCh Dose 1



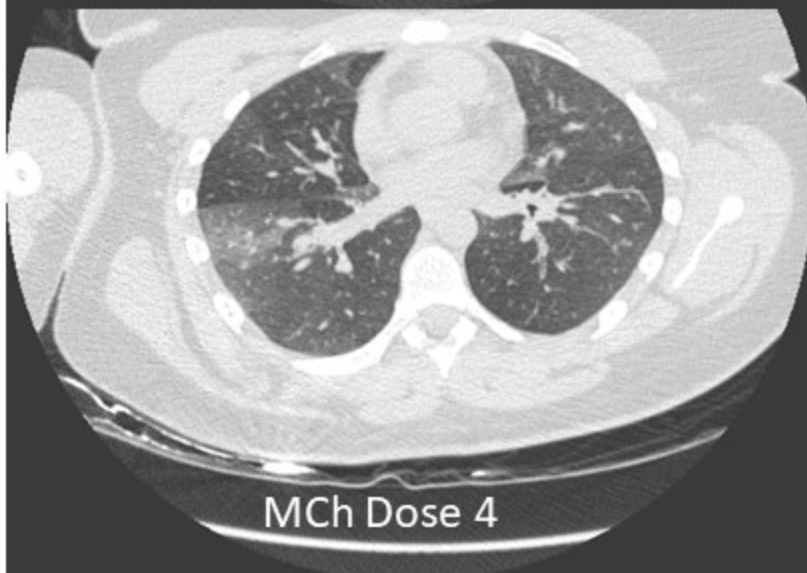
MCh Dose 2



MCh Dose 3



MCh Dose 4

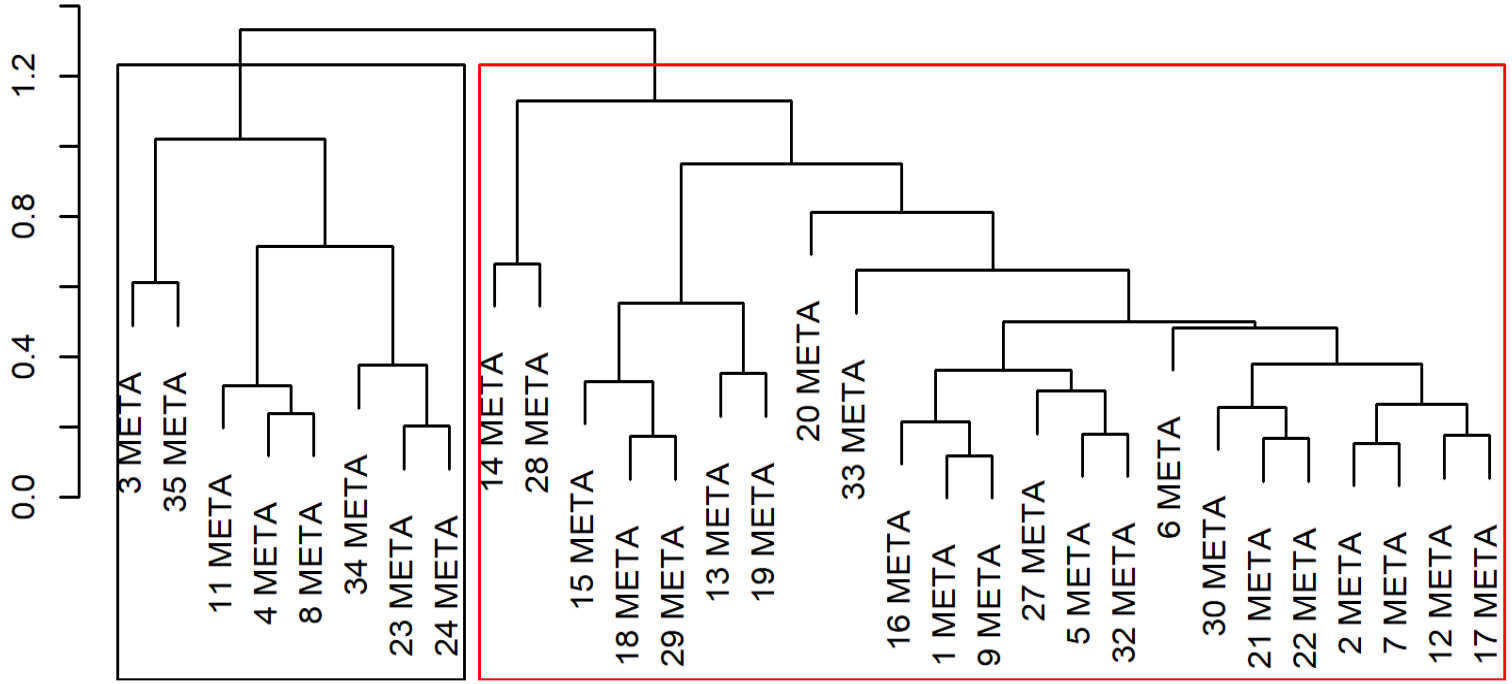


After SABA

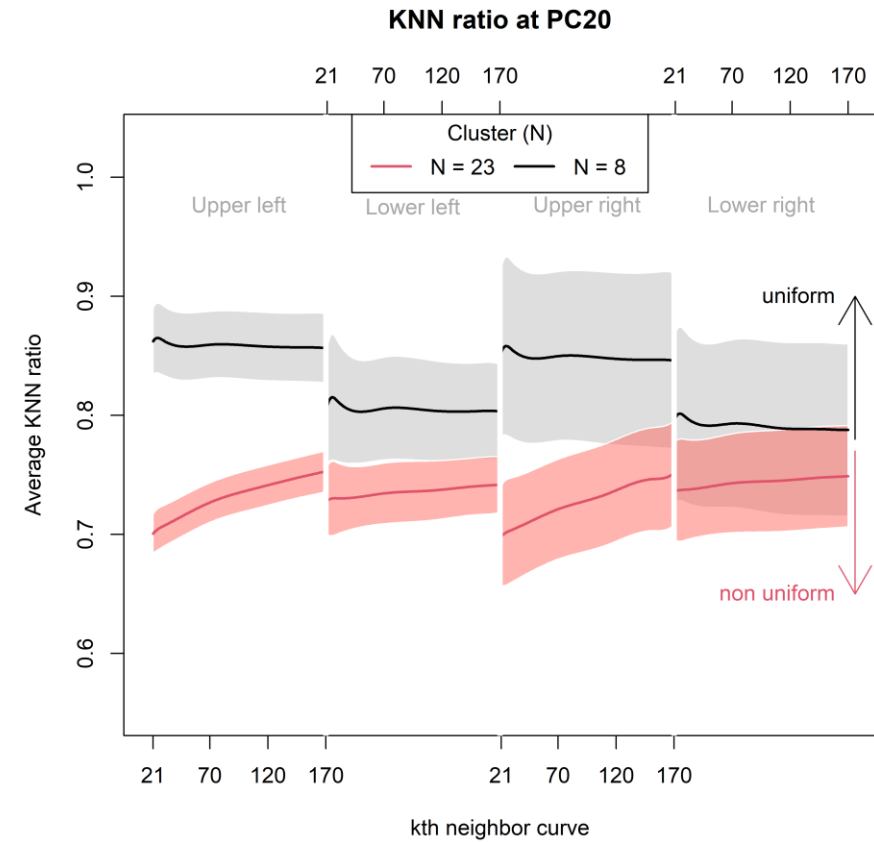
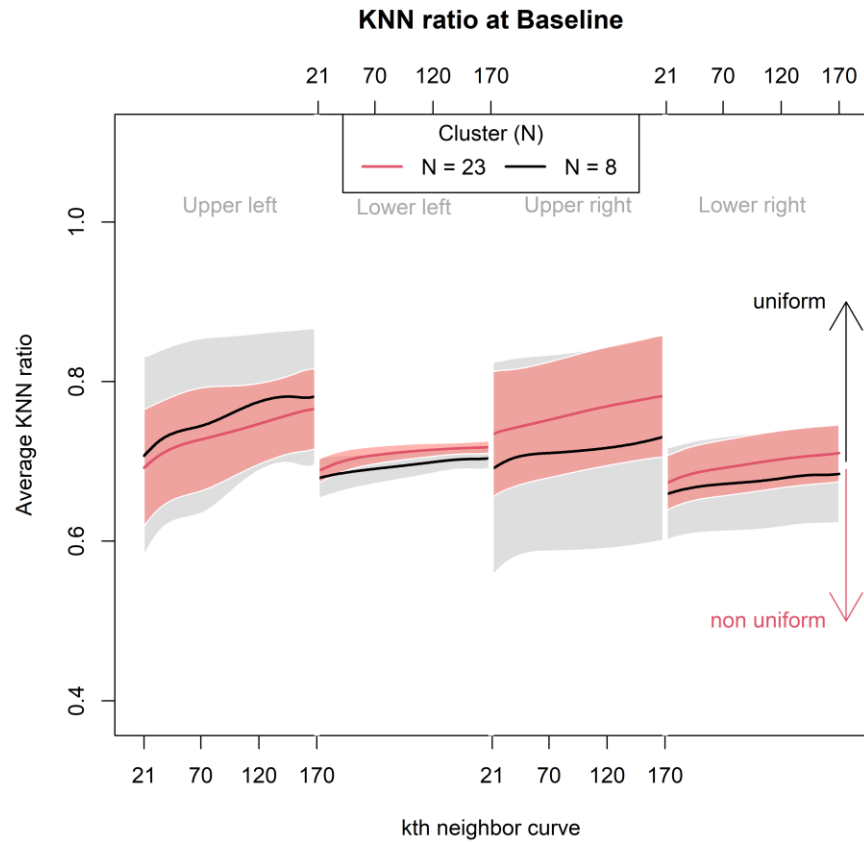


Sequential acquisition in patient #8 belonging to cluster 2 [uniform]; lower lung

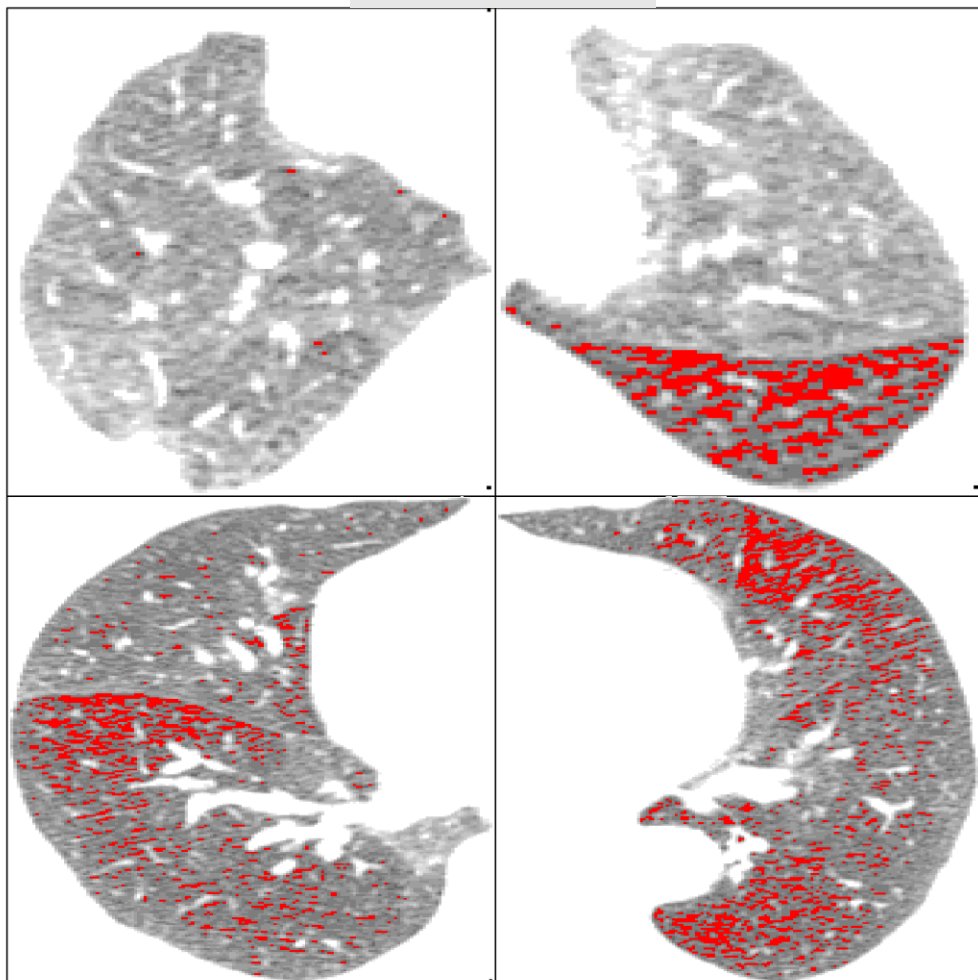
Clustering HRCT patterns during metacholine Challenge



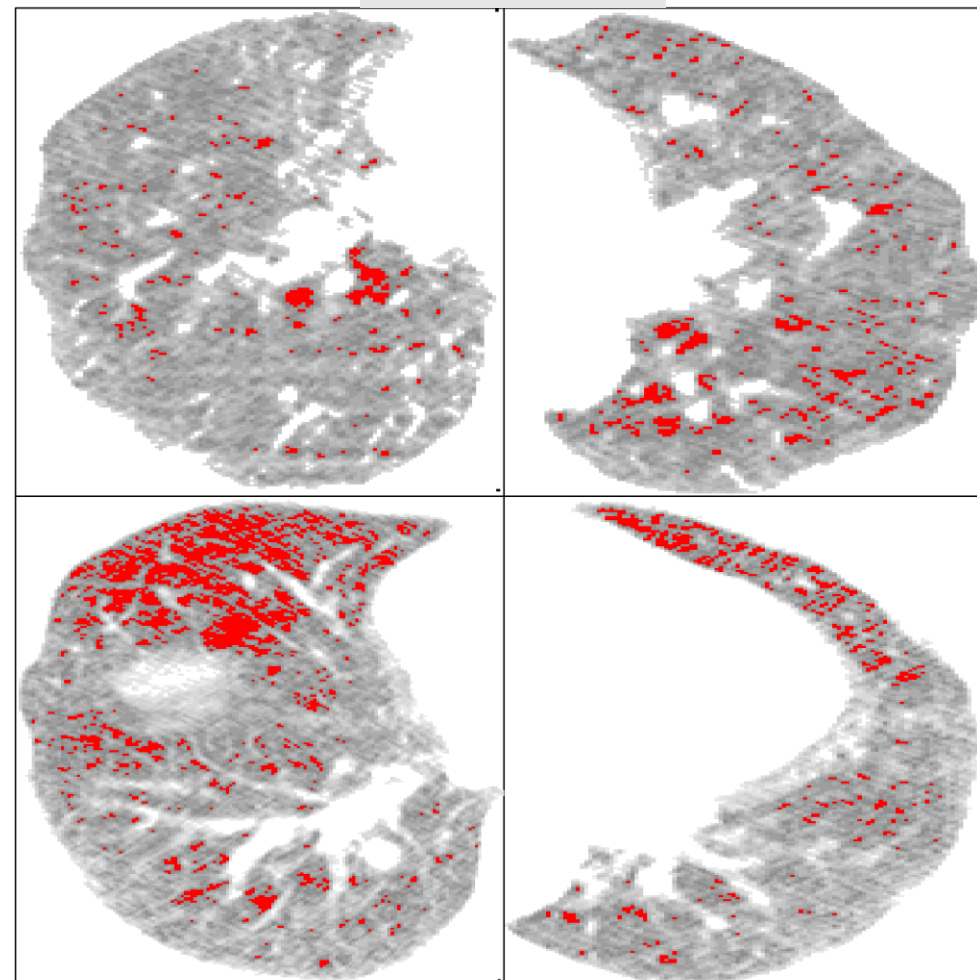
K nearest neighbors

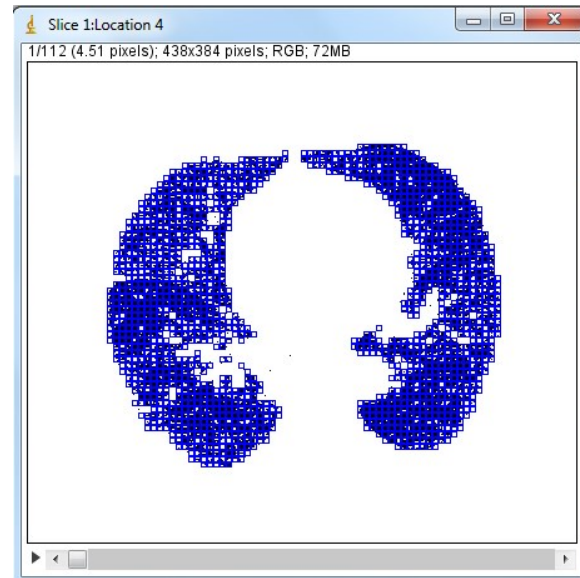
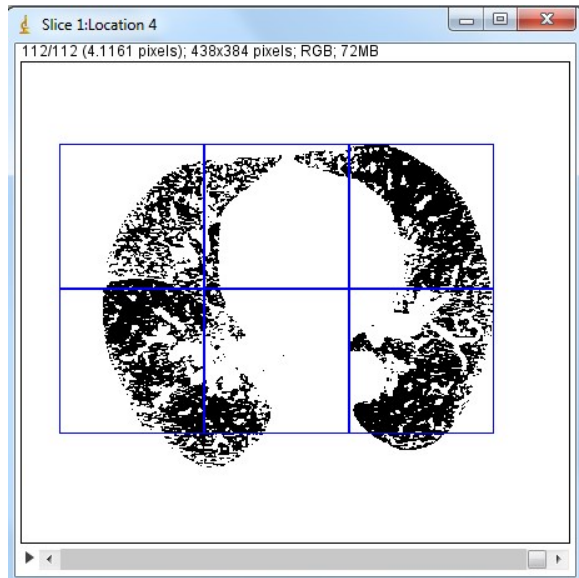


CLUSTER 1



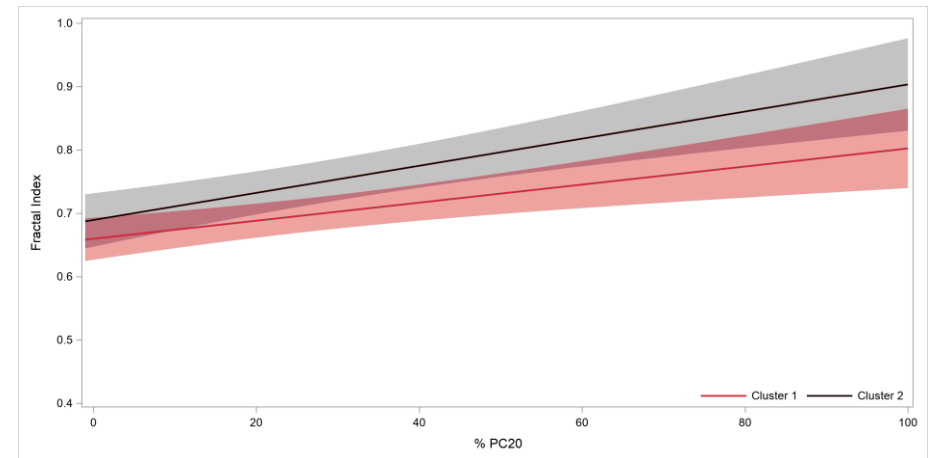
CLUSTER 2



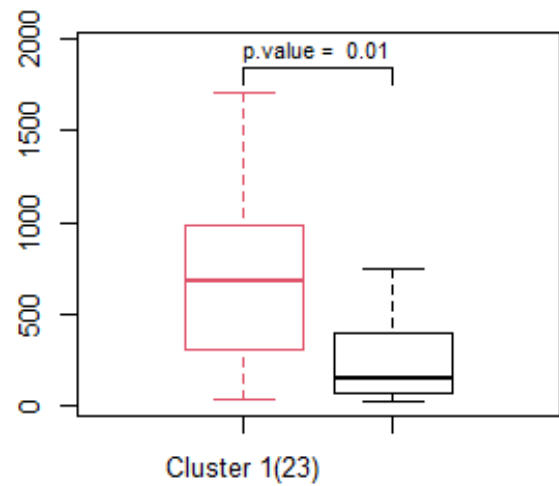


Box counting method for computing FD

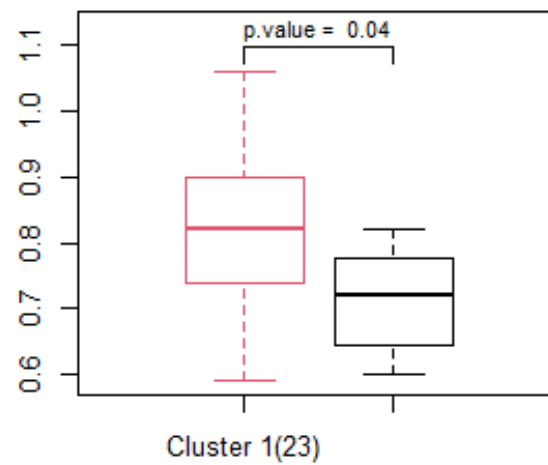
FD progressed with methacholine concentration



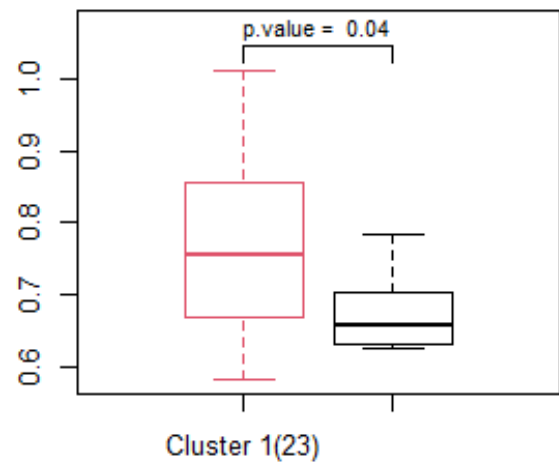
PC20



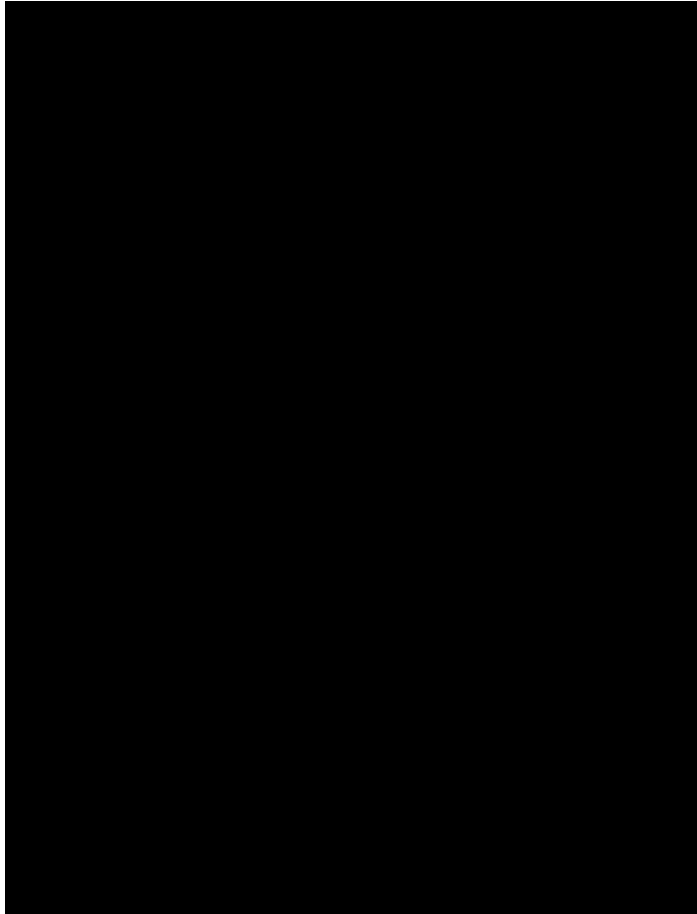
FEV1 at baseline



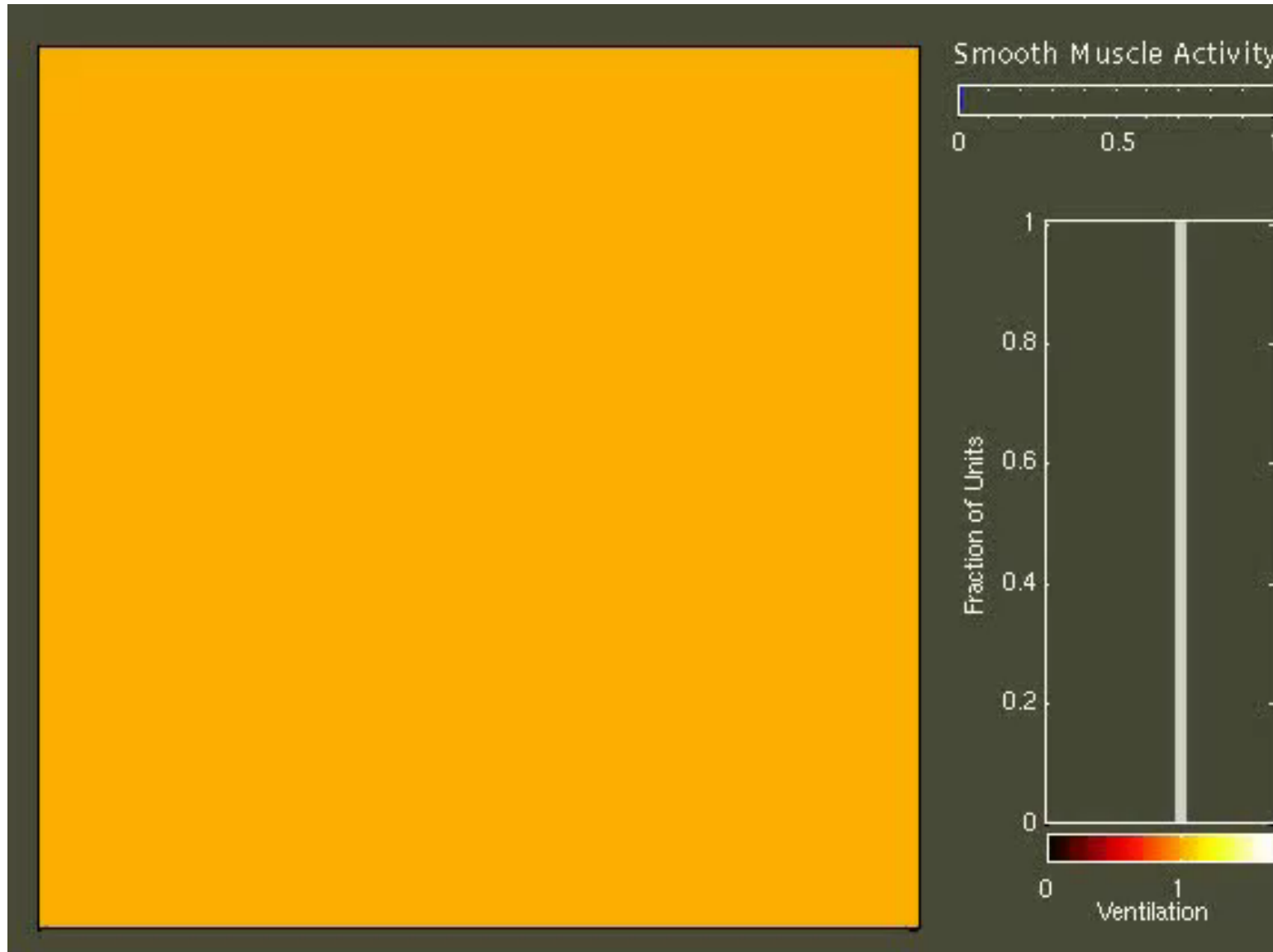
FEV1 post bronchodilator (recovery)

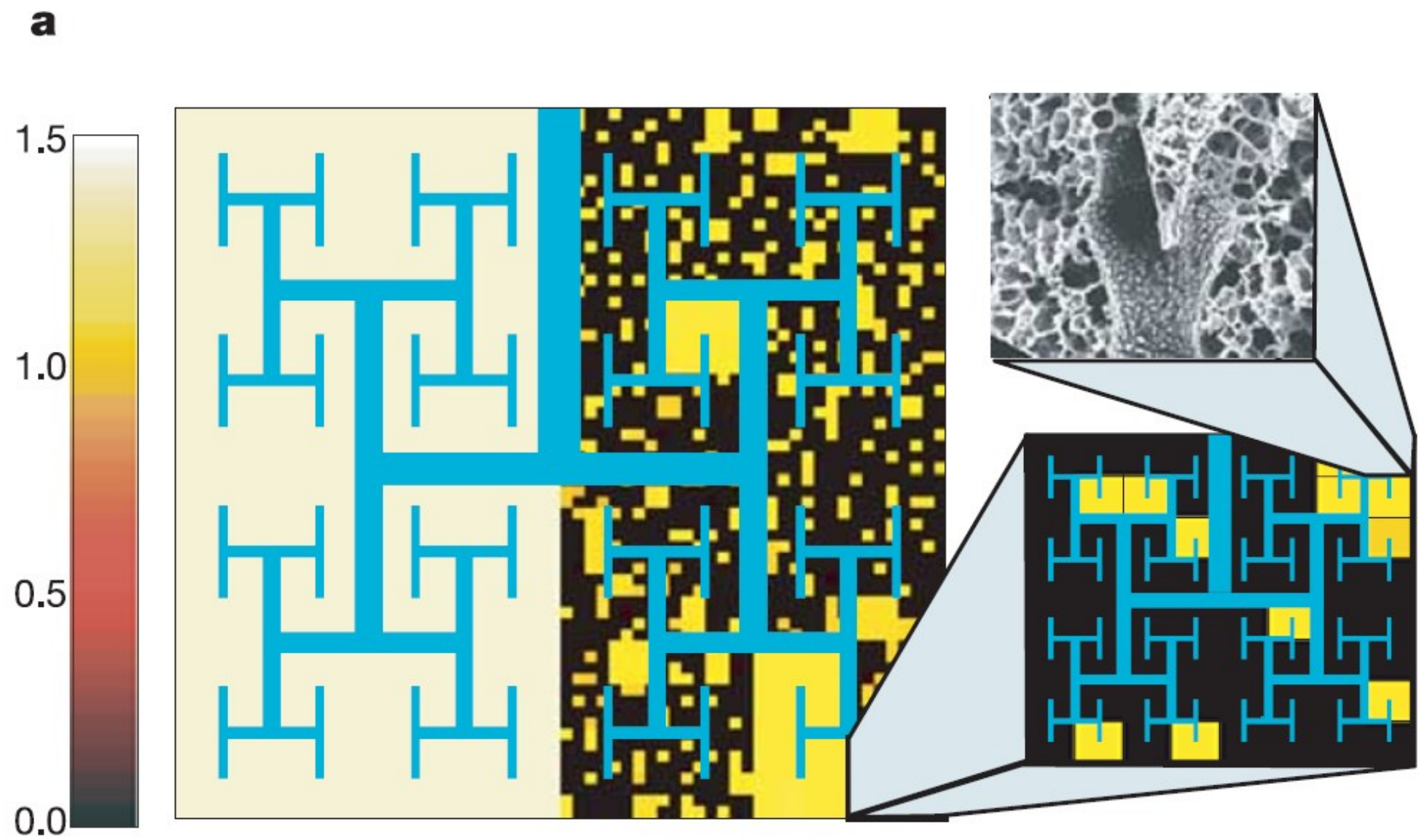


Airway hyper reactivity follows fractal dimensions in the range of chaos



Self-organized patchiness in asthma as a prelude to catastrophic shifts



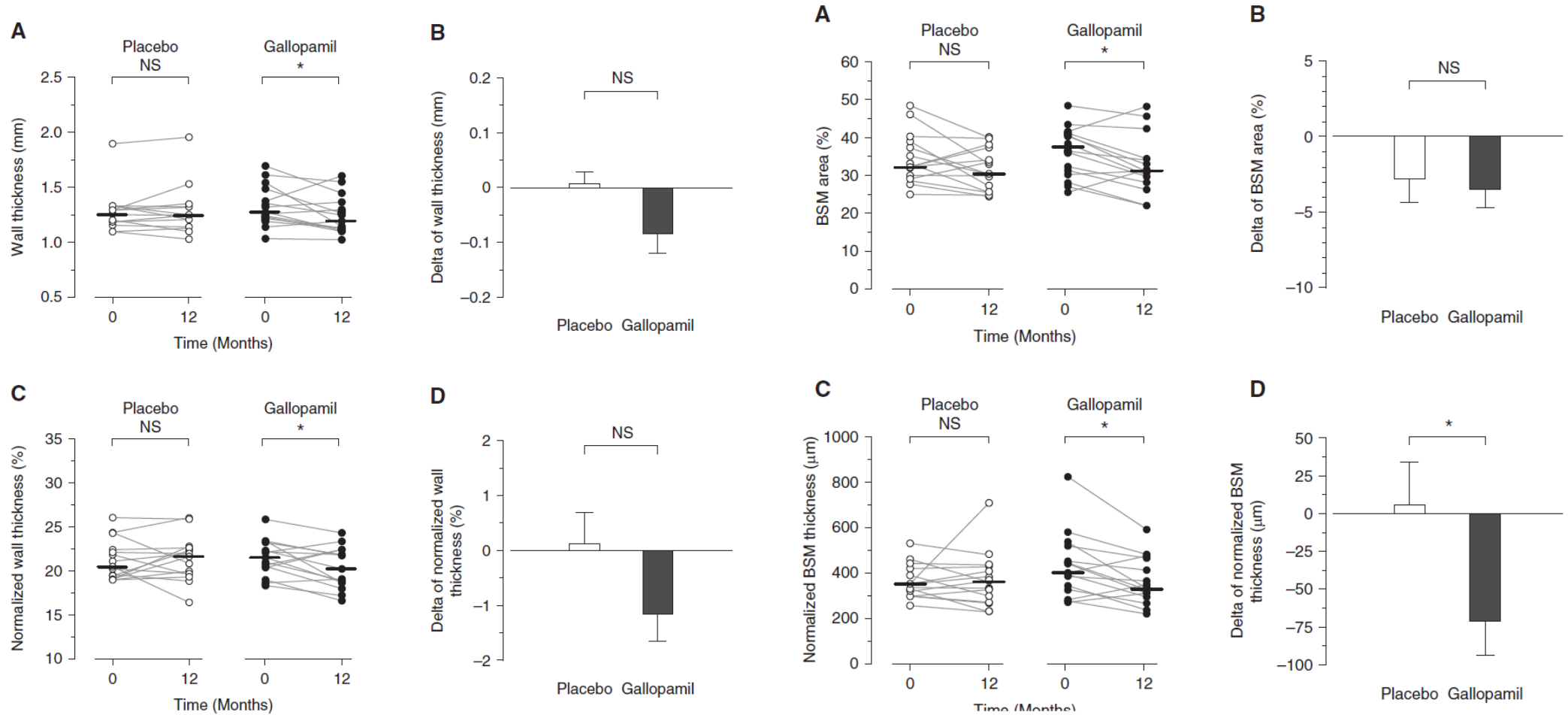


Airway wall

Calcium Channel Blocker Reduces Airway Remodeling in Severe Asthma

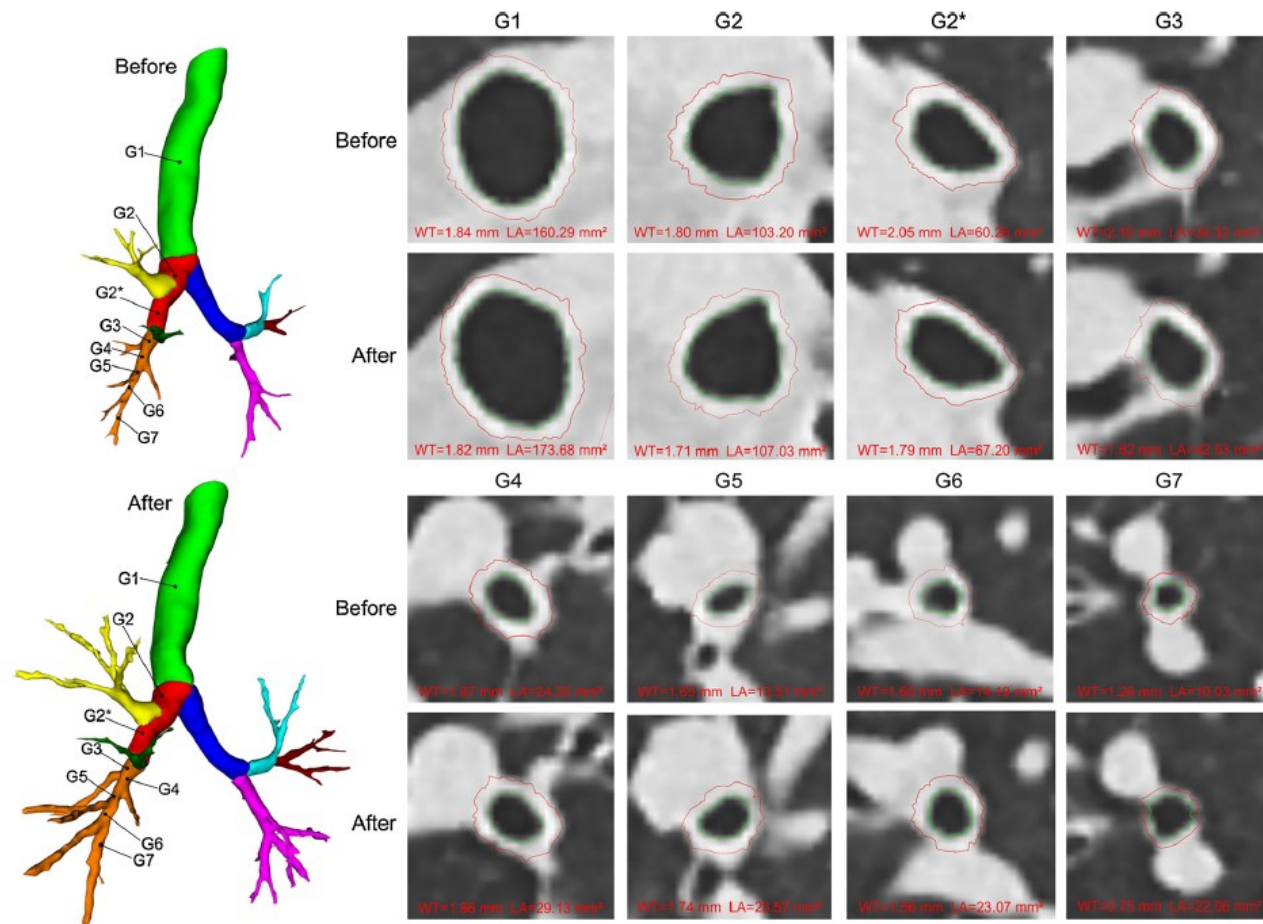
A Proof-of-Concept Study

Pierre-Olivier Girodet^{1,2,3}, Gaël Dournes^{1,2,3}, Matthieu Thumerel^{1,2,3}, Hugues Begueret³, Pierre Dos Santos^{1,2,3}, Annaig Ozier^{1,2,3}, Isabelle Dupin^{1,2}, Thomas Trian^{1,2}, Michel Montaudon^{1,2,3}, François Laurent^{1,2,3}, Roger Marthan^{1,2,3}, and Patrick Berger^{1,2,3}



Quantitative CT detects changes in airway dimensions and air-trapping after bronchial thermoplasty for severe asthma

Philip Konietzke^{a,b,c,*}, Oliver Weinheimer^{a,b,c}, Mark O. Wielpütz^{a,b,c}, Willi L. Wagner^{a,b,c},
 Philine Kaukel^d, Ralf Eberhardt^{b,d}, Claus P. Heussel^{a,b,c}, Hans-Ulrich Kauczor^{a,b,c},
 Felix J. Herth^{b,d}, Maren Schuhmann^{b,d}



	Bronchial thermoplasty	Control
Number of subjects	17	11
Age [years]	55 ± 11	59 ± 12
Sex male/female	6/11	5/6
FEV1 [l/s]	1.43	2.17
FEV1 [%]	49.9	69.9
VC [l]	2.69	3.39
VC [%]	43.3	86.6
Tiffeneau [%] FEV1/FVC	63.47	61.99
RV [l]	3.46	3.31
RV [%]	172.82	156.94
Oral corticosteroids n [%]	12 (70.6)	6 (54.5)
ACT	9.5	8.2
6 MWT [m]	357	391

Airway dimensions in the treatment and the control group.

	Before	After	Δ	Δ%	p
BT					
WT [mm]	1.63 ± 0.49	1.57 ± 0.48	-0.06	-3.94	0.026
WP [%]	57.94 ± 10.51	55.82 ± 9.56	-2.13	-3.67	0.001
LA [mm ²]	39.63 ± 40.92	40.25 ± 40.53	0.62	1.57	0.147
TD [mm]	9.50 ± 3.67	9.53 ± 3.70	0.03	0.36	0.730
Pi10	0.34 ± 0.08	0.32 ± 0.10	-0.02	-5.89	0.050
Controls					
WT [mm]	1.75 ± 0.61	1.76 ± 0.53	0.01	0.73	0.933
WP [%]	55.68 ± 11.70	57.09 ± 8.97	1.42	2.33	0.797
LA [mm ²]	48.26 ± 46.47	42.90 ± 38.04	-5.35	-11.09	0.146
TD [mm]	10.47 ± 3.99	10.18 ± 3.59	-0.29	-2.73	0.230
Pi10	0.31 ± 0.10	0.32 ± 0.07	0.01	0.81	0.577

Changes in air-trapping before and after thermoplasty.

	Before	After	Δ	Δ%	p
TLV [cm ³]	5319 ± 1577	5251 ± 1540	-68	-1.27	0.459
RVC ₈₅₆₋₉₅₀	-0.35 ± 0.16	-0.41 ± 0.19	-0.06	-13.35	< 0.001
E/I MLA	0.94 ± 0.03	0.92 ± 0.04	-0.02	-1.77	< 0.001
A1 [%]	81.81 ± 1.52	79.27 ± 2.69	-2.54	-3.11	< 0.003
A2 [%]	68.63 ± 2.15	64.03 ± 4.53	-4.6	-6.71	< 0.001
A3 [%]	29.87 ± 4.24	26.18 ± 10.26	-3.69	-12.37	< 0.001

Effects of Adding Omalizumab, an Anti-Immunoglobulin E Antibody, on Airway Wall Thickening in Asthma

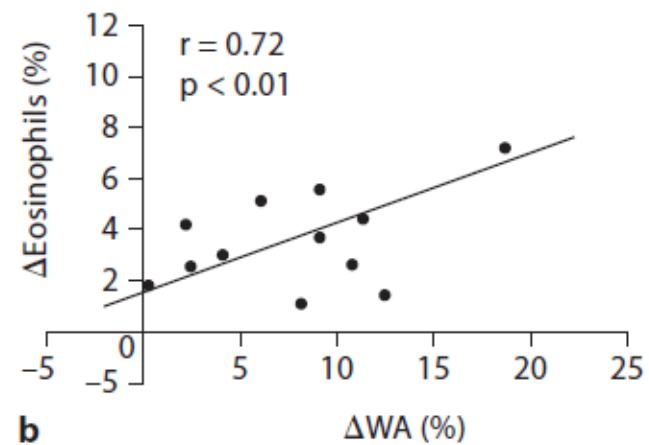
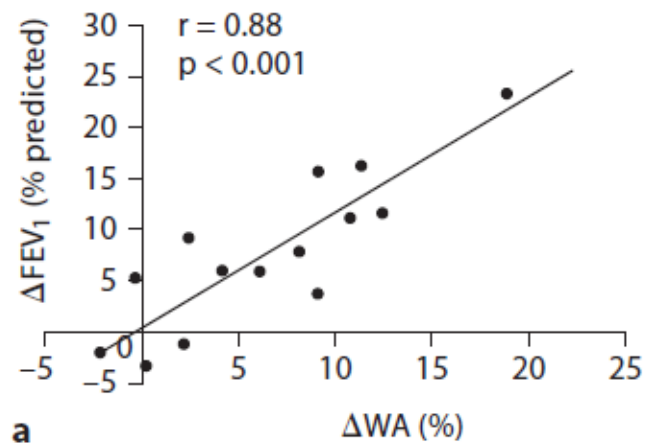
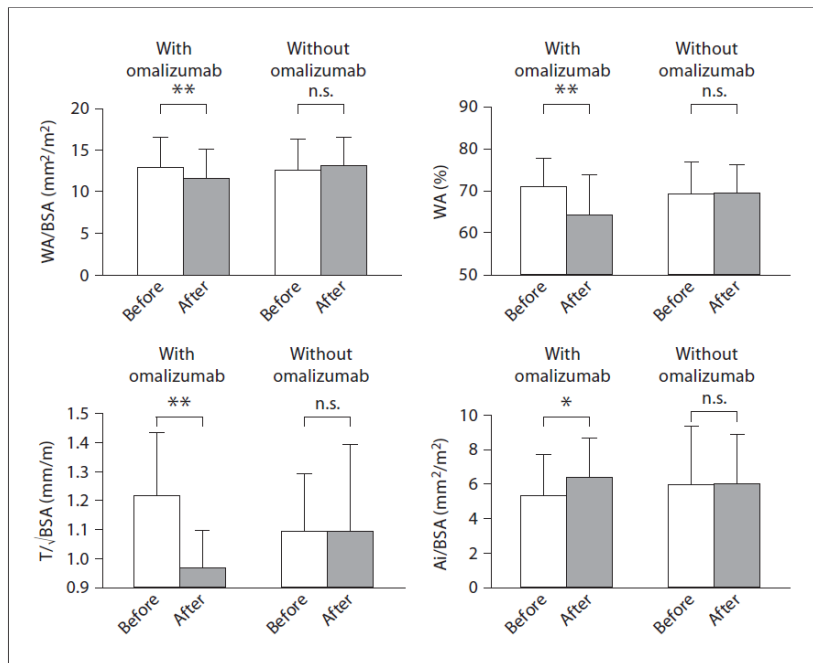
Makoto Hoshino^a Junichi Ohtawa^b

Departments of ^aRespiratory Medicine and ^bRadiology, Atami Hospital, International University of Health and Welfare, Atami, Japan

	Omalizumab (n = 11)	Without omalizumab (n = 16)	p value
Gender, M/F	3/11	4/12	
Age, years	59.2 (11.4)	51.2 (18.7)	0.08
BSA, m ²	1.56 (0.17)	1.59 (0.25)	0.3
Disease duration, years	16.3 (11.5)	10.9 (7.2)	0.07
Serum total IgE, IU/ml	248.0 (170.3)	282.0 (192.5)	0.13
Morning PEF, liters/min	223.6 (116.9)	239.6 (57.3)	0.31
FEV ₁ , % predicted	65.3 (13.9)	68.4 (12.2)	0.26
FEV ₁ , liters	1.32 (0.6)	1.43 (0.41)	0.28
PC ₂₀ , mg/ml	1.64 (1.76)	1.94 (1.66)	0.16
Medication			
ICS, μg/day ¹	791.4 (246.4)	862.5 (305.2)	0.24
LABA, n	14	16	
Antileukotriene, n	10	12	
Theophylline, n	6	7	
Oral corticosteroid, n	4	5	

Data are presented as means and SDs (shown in parentheses). PC₂₀ = Provocation concentration of methacholine causing a 20% fall in FEV₁.

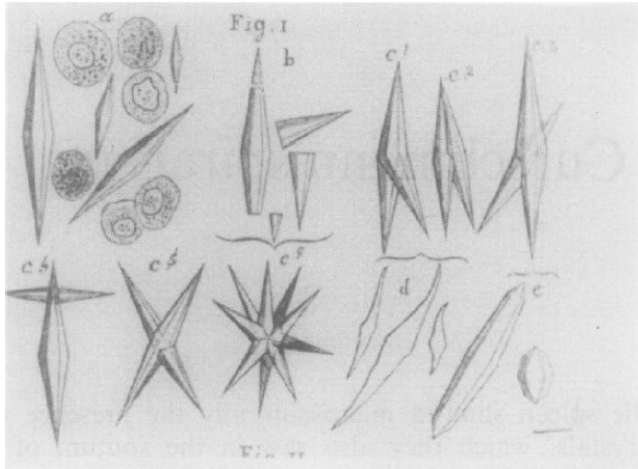
¹ Fluticasone propionate equivalent.



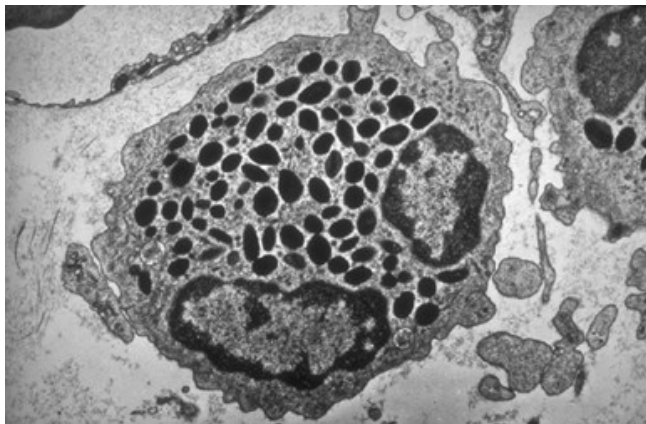
Air trapping and mucus plugs

Epithelial dysregulation in asthma: the missing link

Charcot – Leyden Crystals (1860)

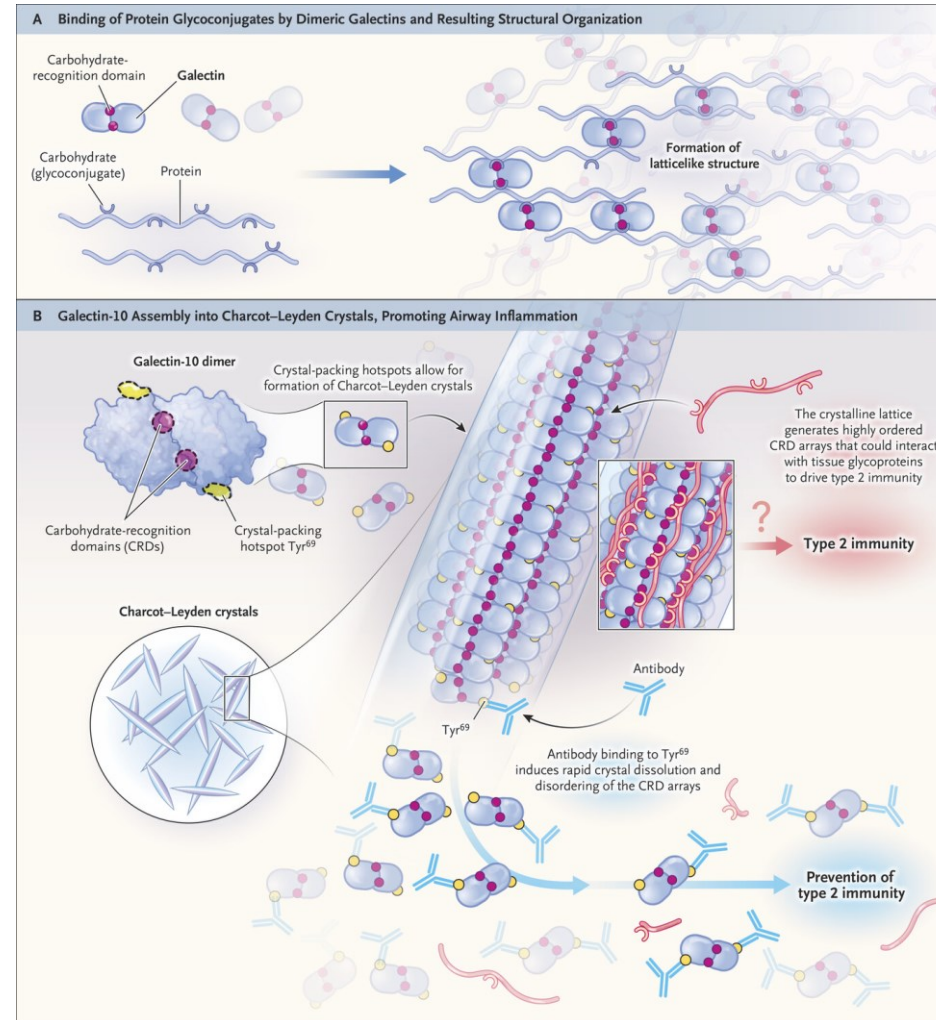


Thorax 1986;41:503–507

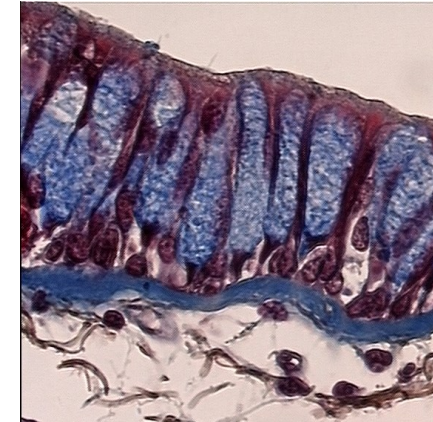


Eosinophils

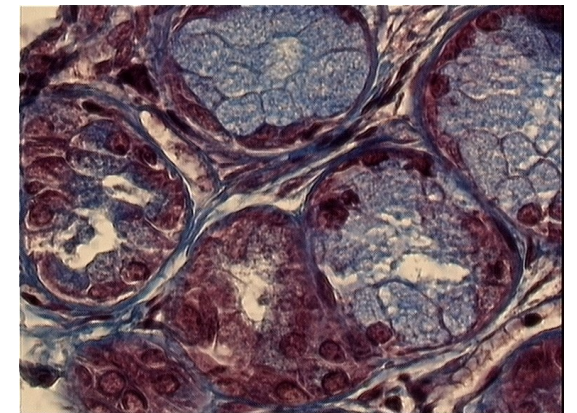
Massive mucus plug



J Fahy NEJM 2023 adapted from B Lambrecht Science 2023



Goblet cell Hyperplasia



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Se: 2
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ACTUEL
Study Date: 16-10-2019
Study Time: 16:34:03



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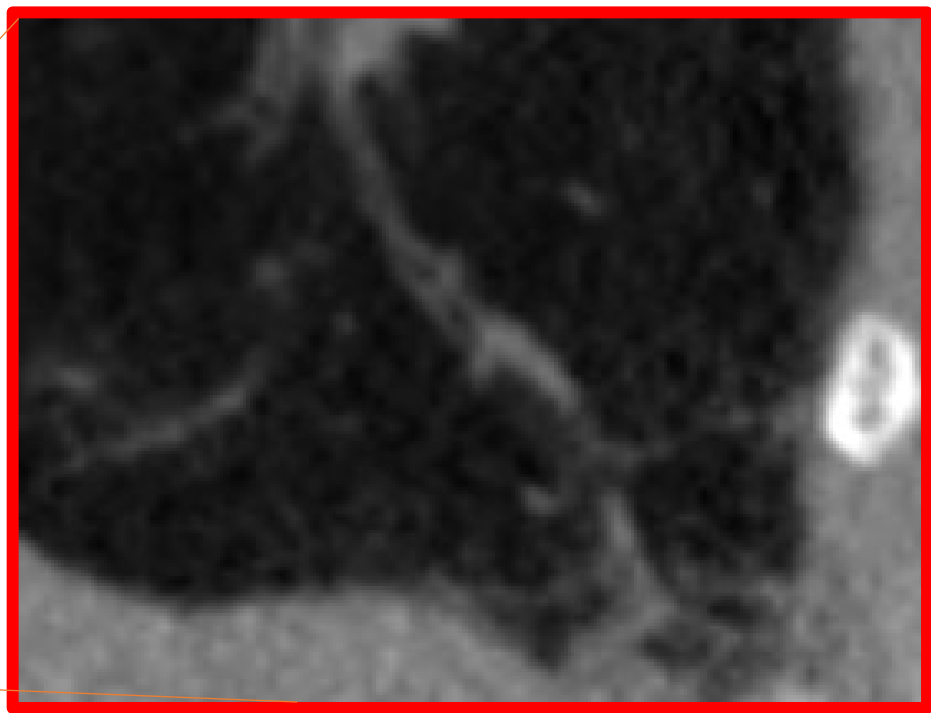
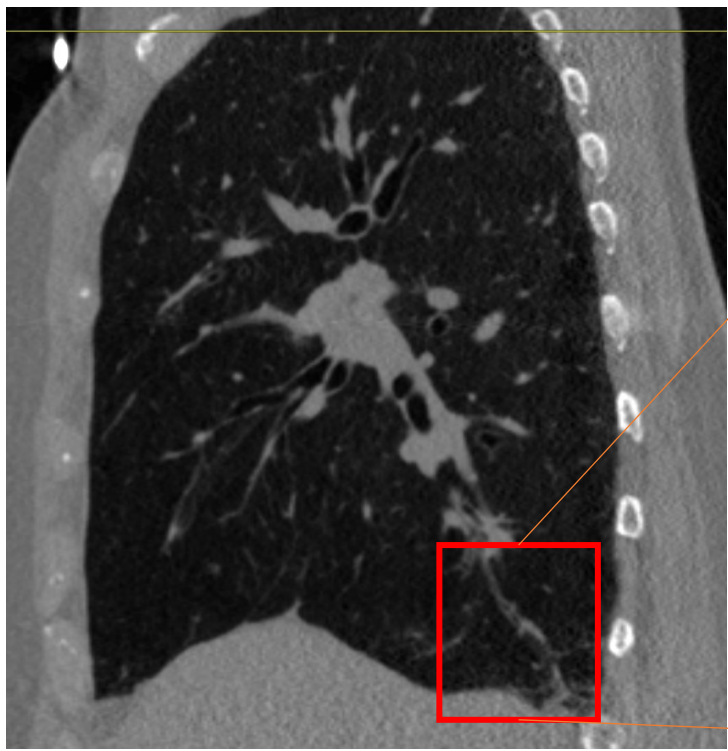
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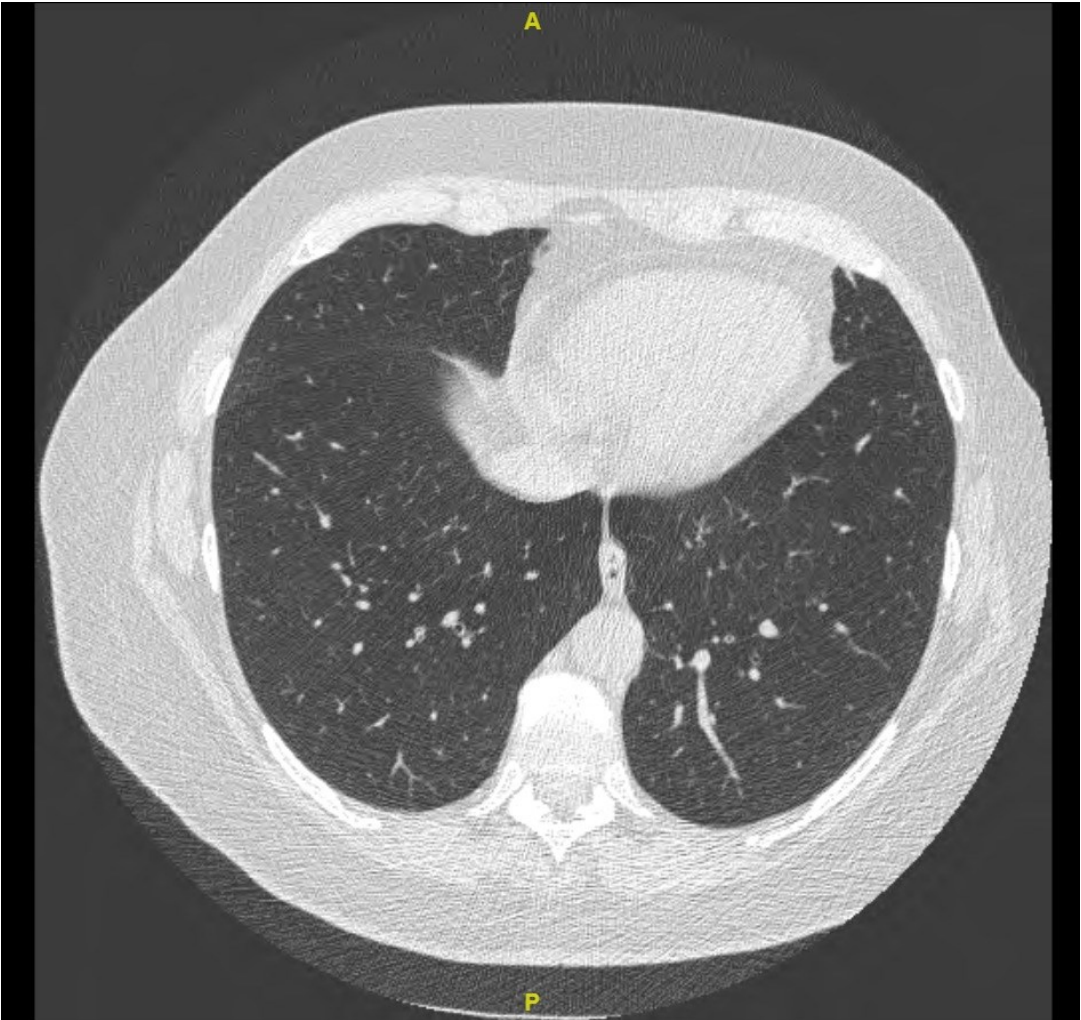
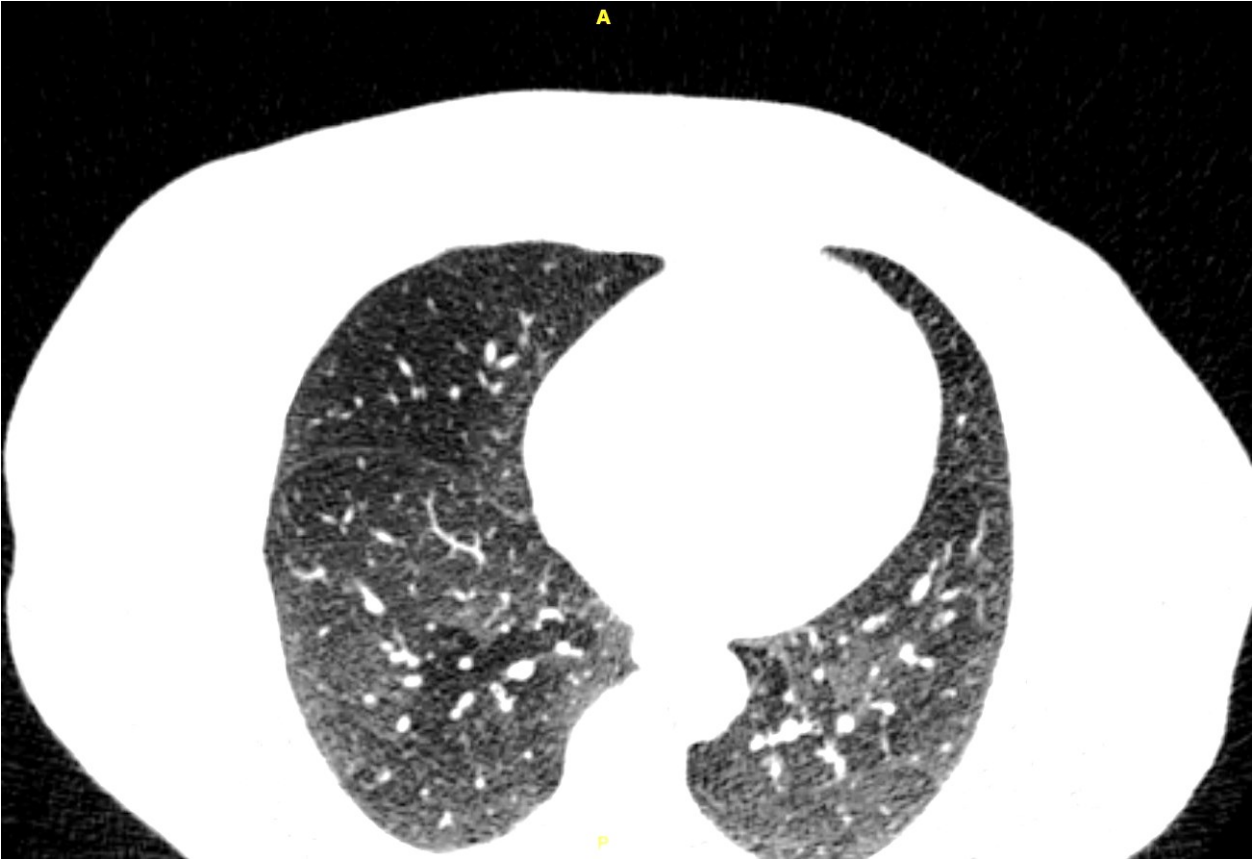
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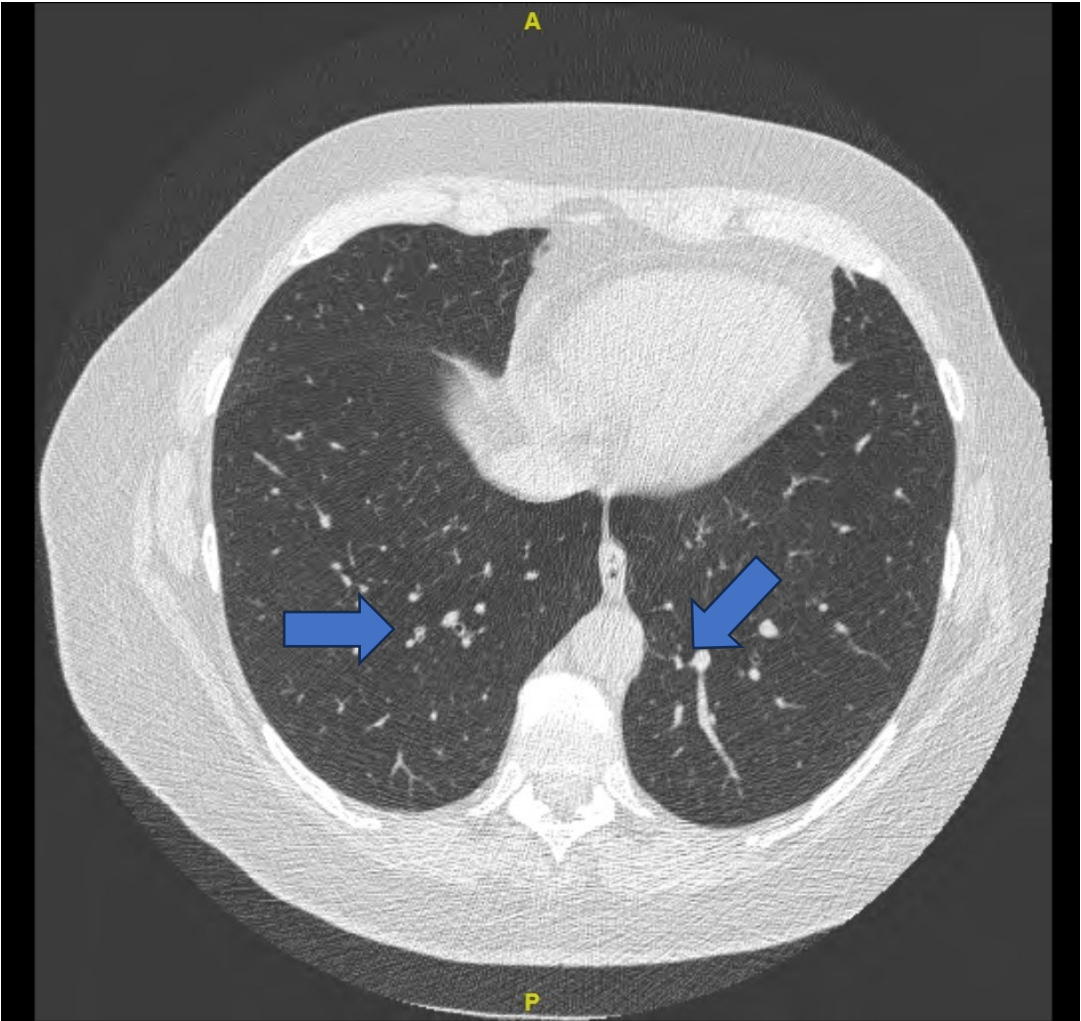
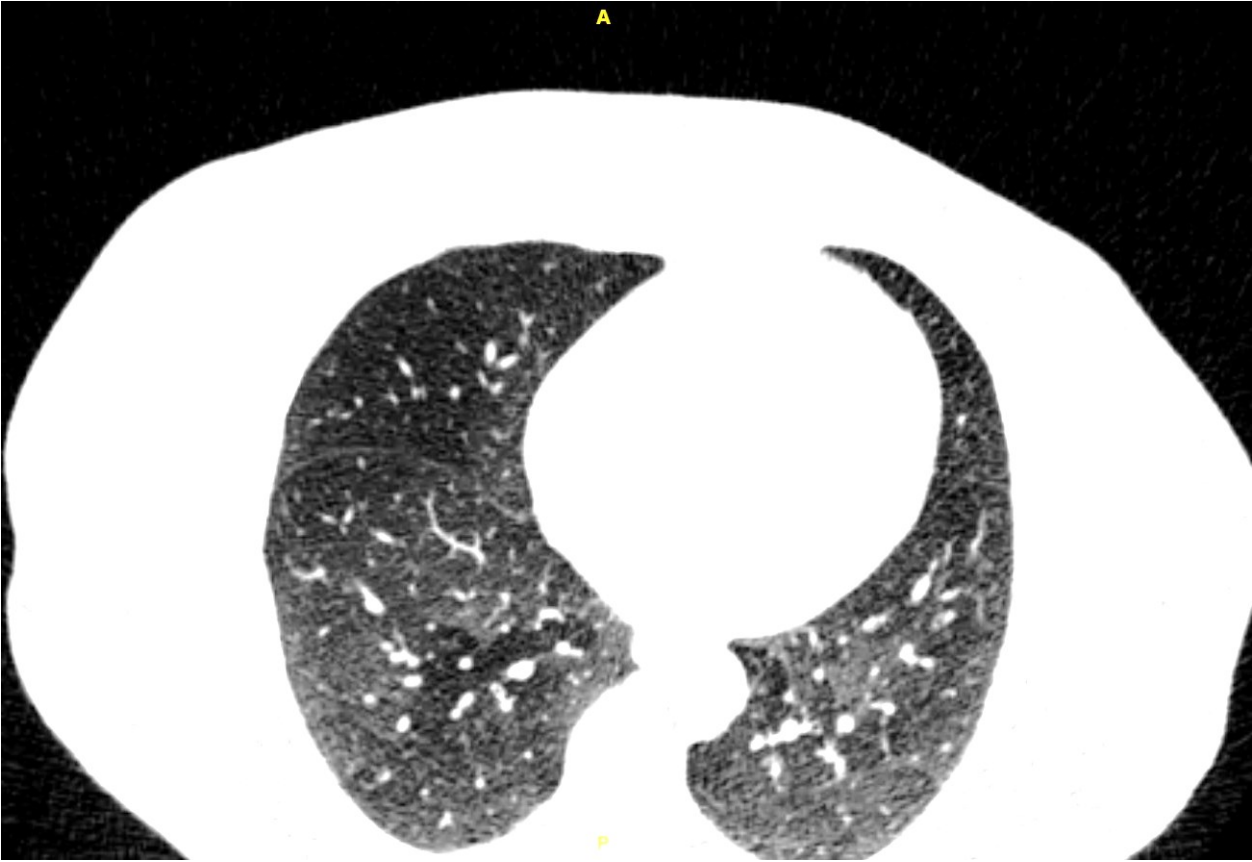




Spatial Relationship between air trapping and mucus plugs



Spatial Relationship between air trapping and mucus plugs





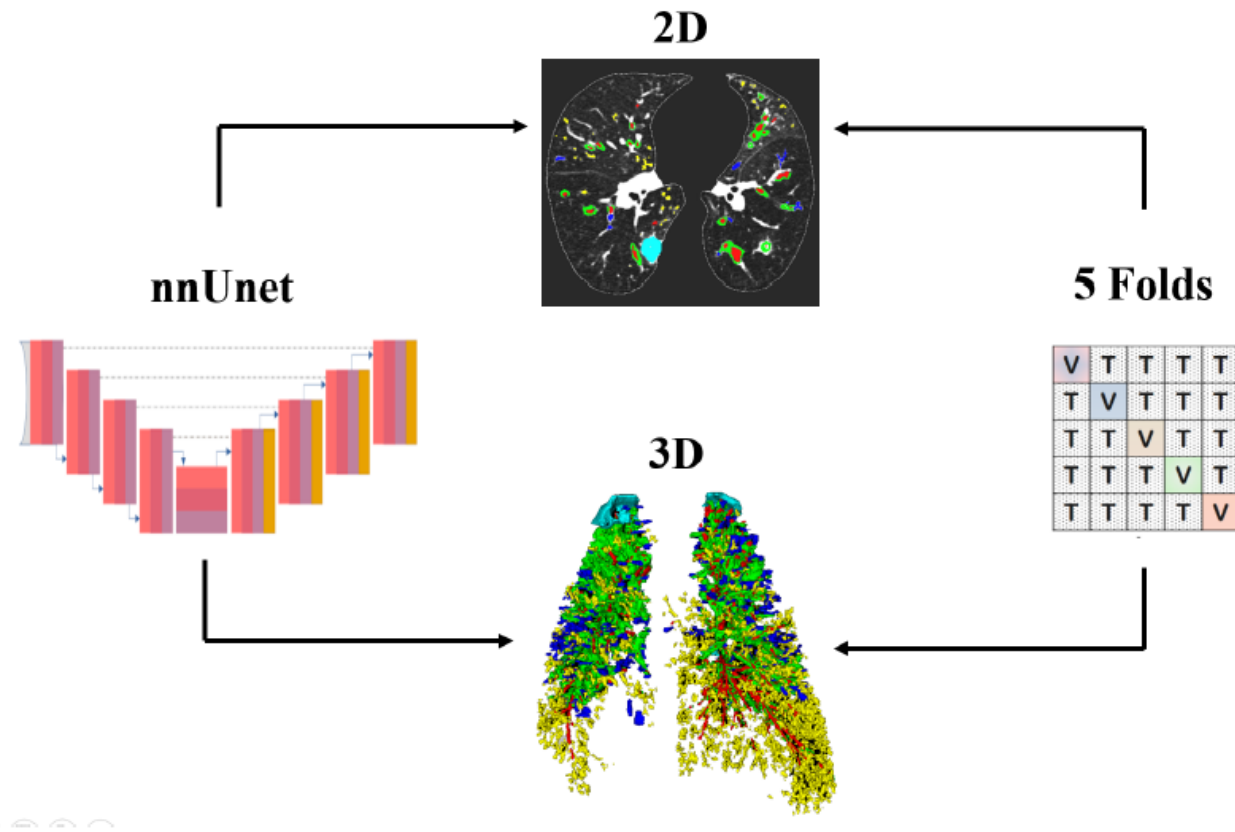


Figure 2 Study methodology. The convolution neural network is nnUnet ; two dimensional (2D) and three dimensional (3D) architectures were trained with databases consisting of CT slices and CT volume. The validation was conducted using a 5-fold cross-validation : The data set is divided into 5 equally folds, the model is trained on 4 of these folds (T) and tested on the remaining one (V).

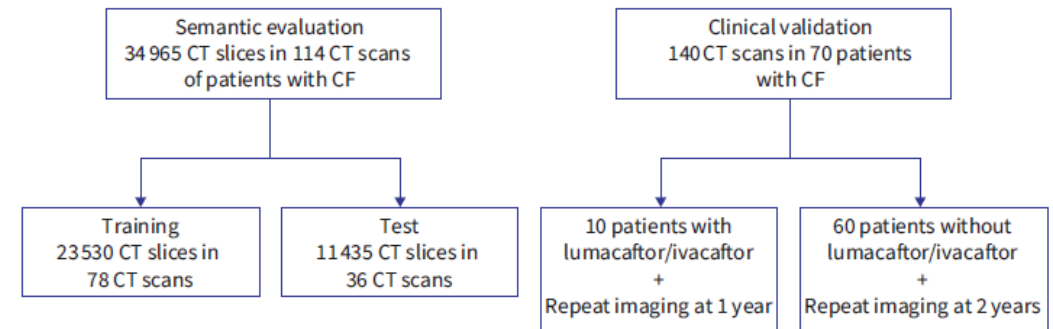
Artificial intelligence in computed tomography for quantifying lung changes in the era of CFTR modulators – G. Dournes

AI training framework

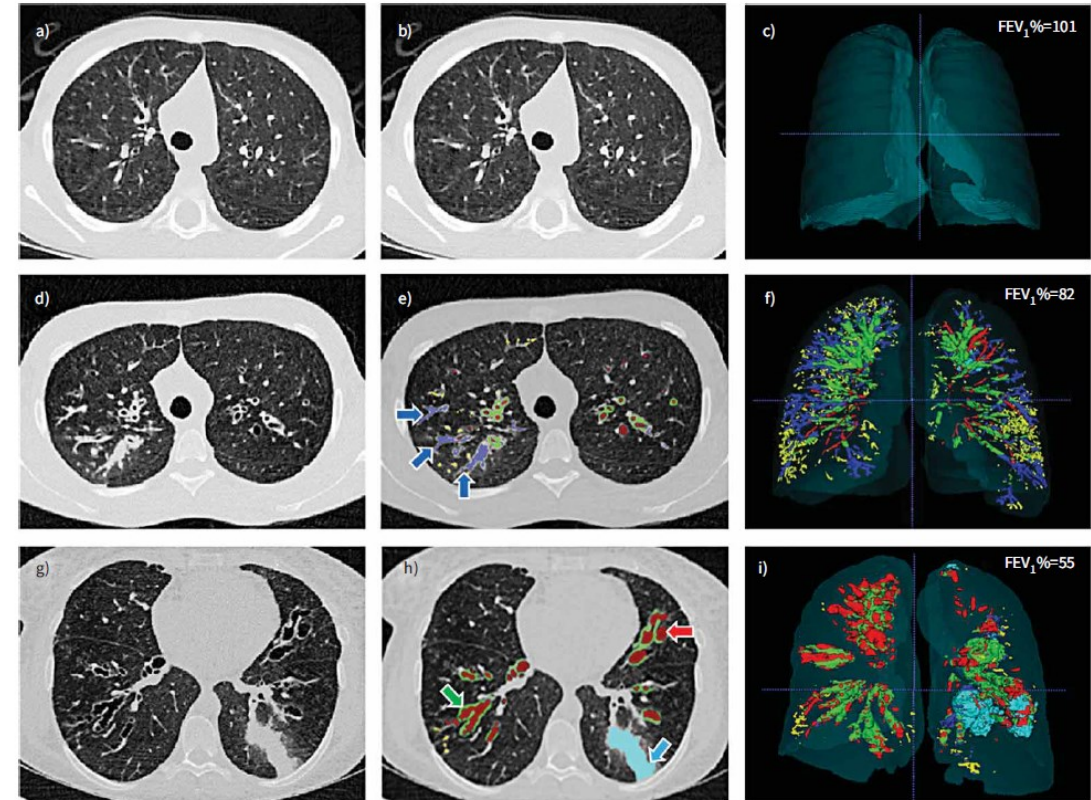
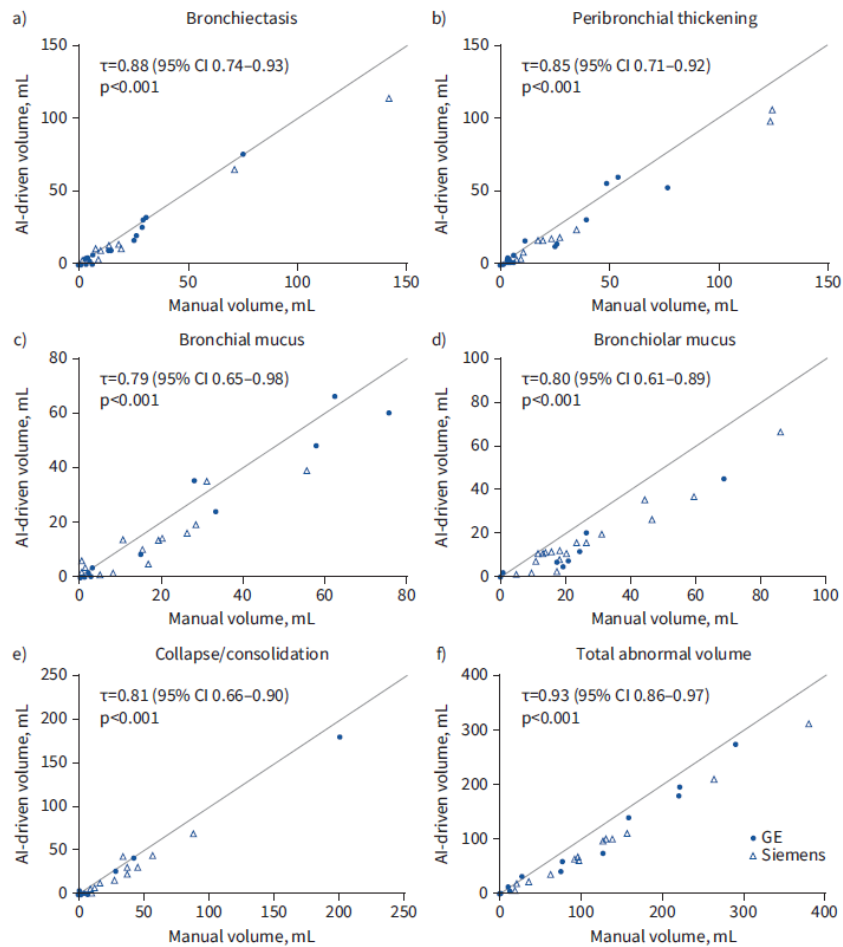
Labels manually completed in the CT axial plane by consensus of three thoracic radiologists on inspiratory CT scans with standard kernels [31] and designated as ground-truth

- bronchiectasis,
- peribronchial thickening,
- bronchial mucus,
- bronchiolar mucus
- and collapse/consolidation.

Three 2D convolutional neural networks (CNNs) were trained utilising the training cohort after data augmentation. A majority vote was performed to complete a final AI-driven multilabel segmentation

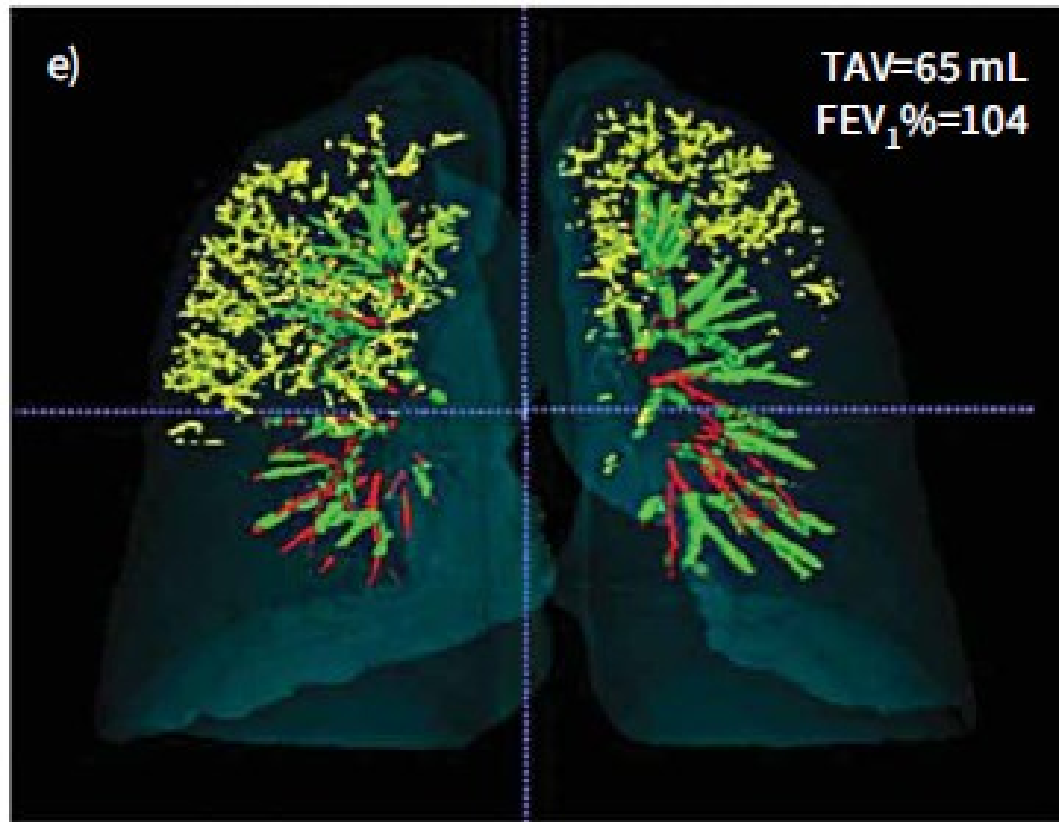


Examples of artificial intelligence (AI)-driven semantic labelling

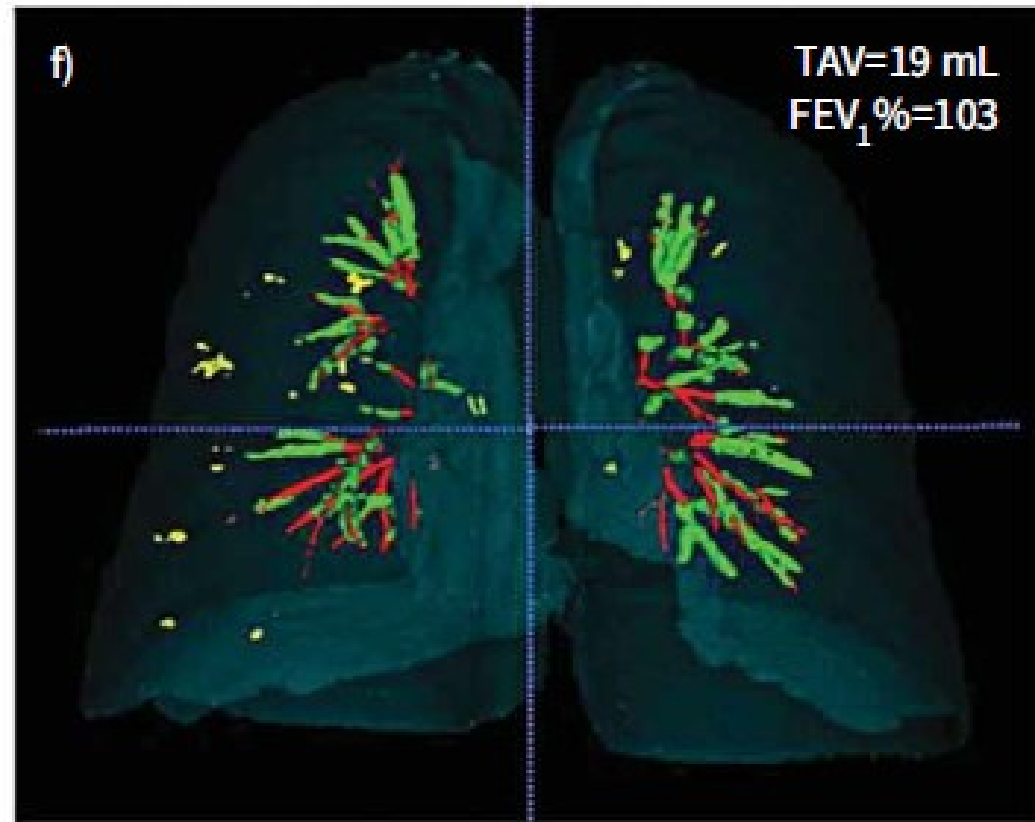


Blue arrows and blue labels highlight areas of central mucus plugs; red arrow and red labels show mucus-free lumen dilatations; green arrow and green labels show peribronchial thickening; cyan arrow and cyan labels show a consolidation

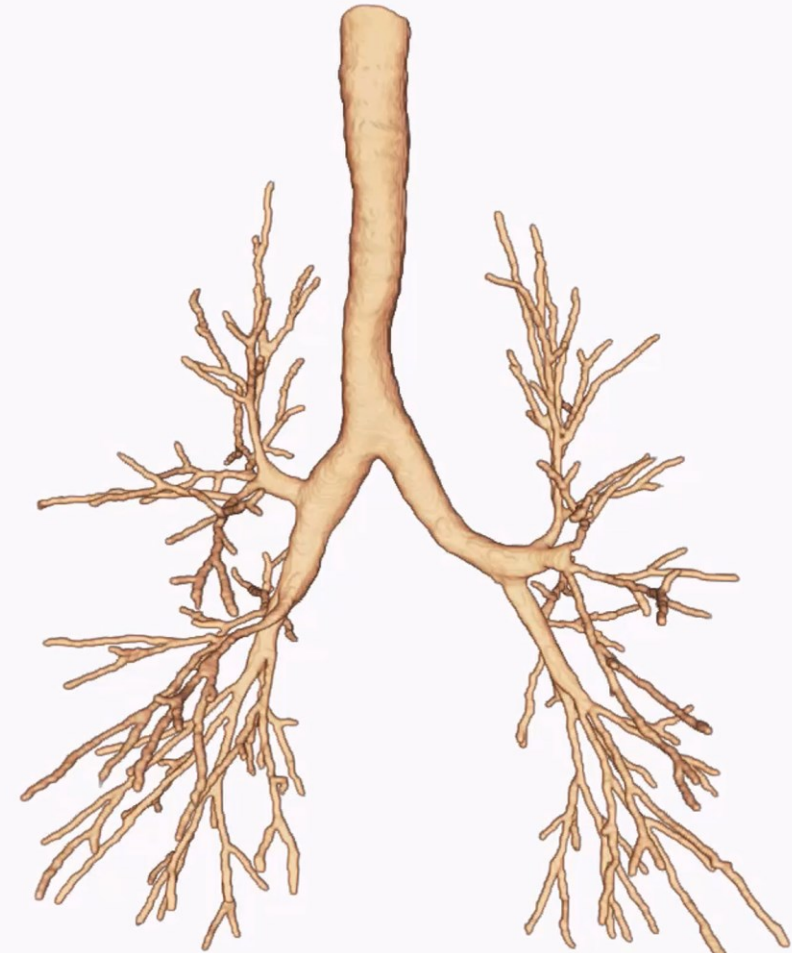
Comparison of artificial intelligence (AI)-driven semantic labelling



before

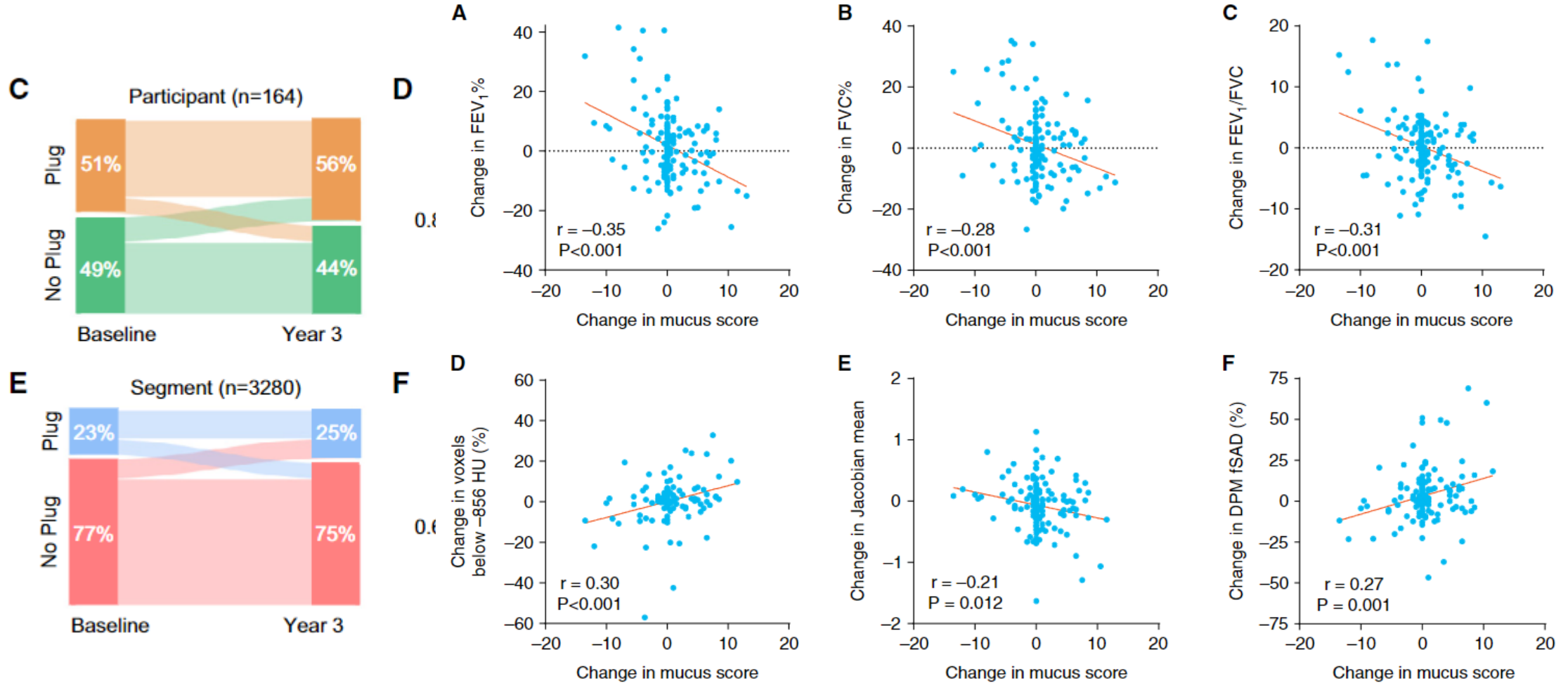


after 1 year of treatment by lumacaftor/ivacaftor

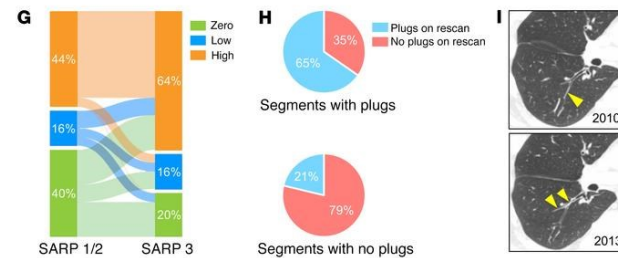
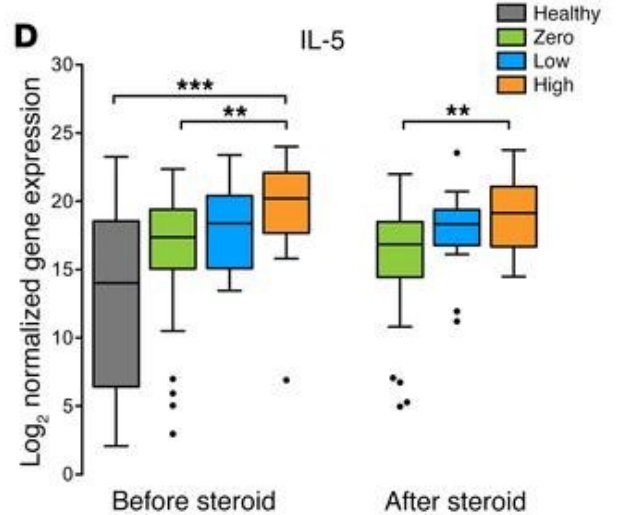
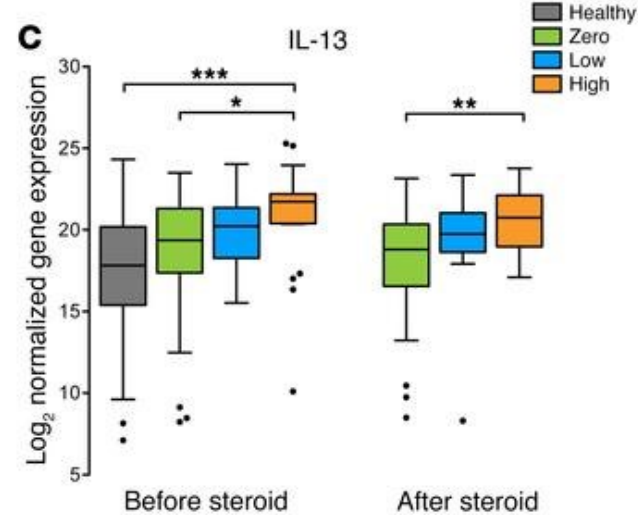
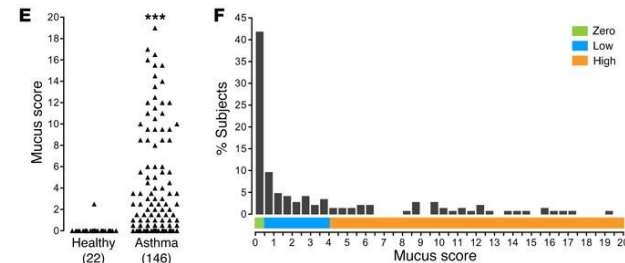
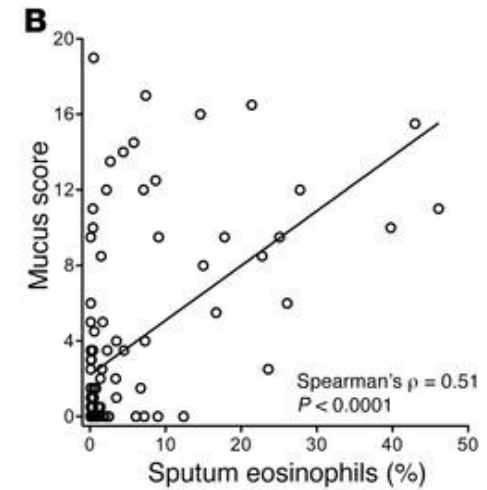
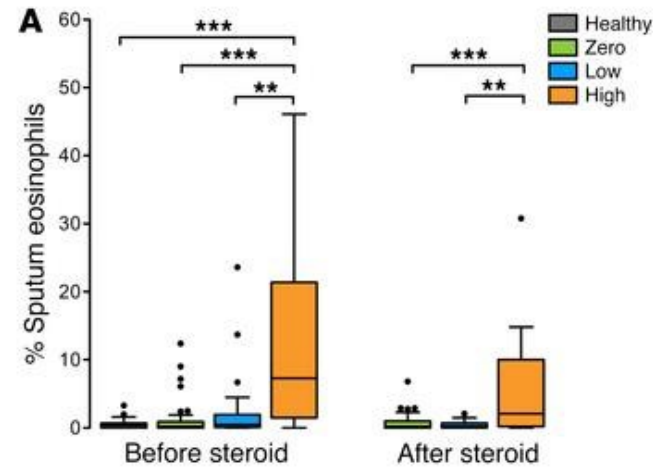
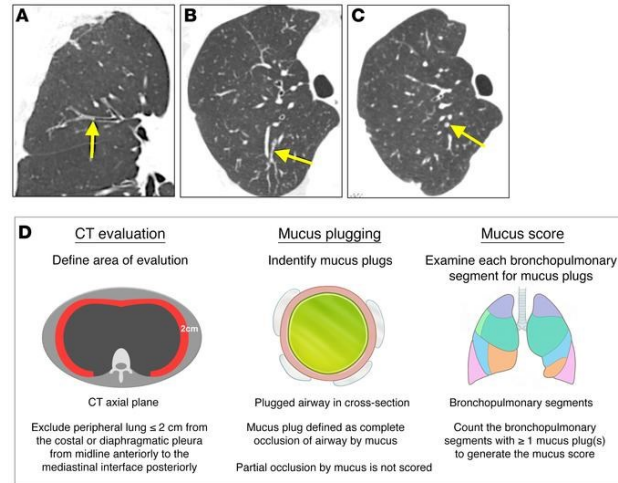


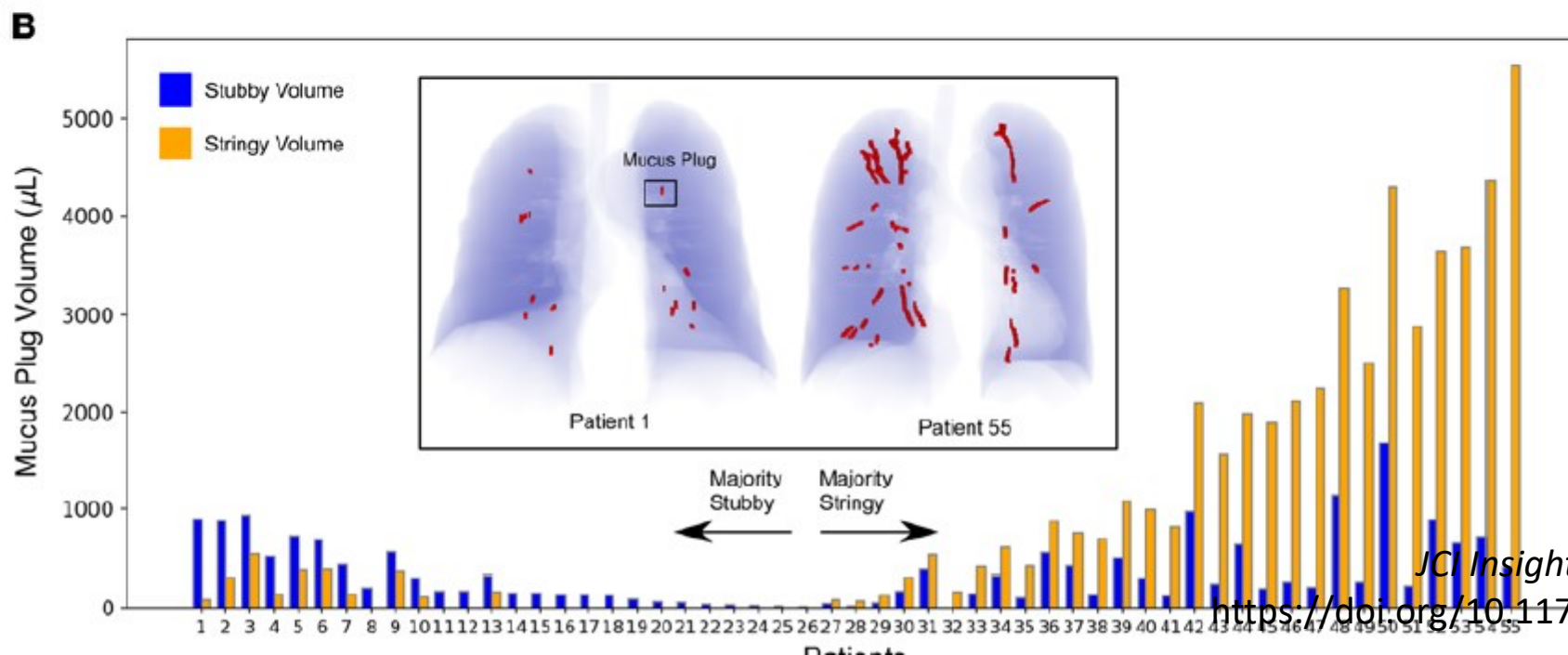
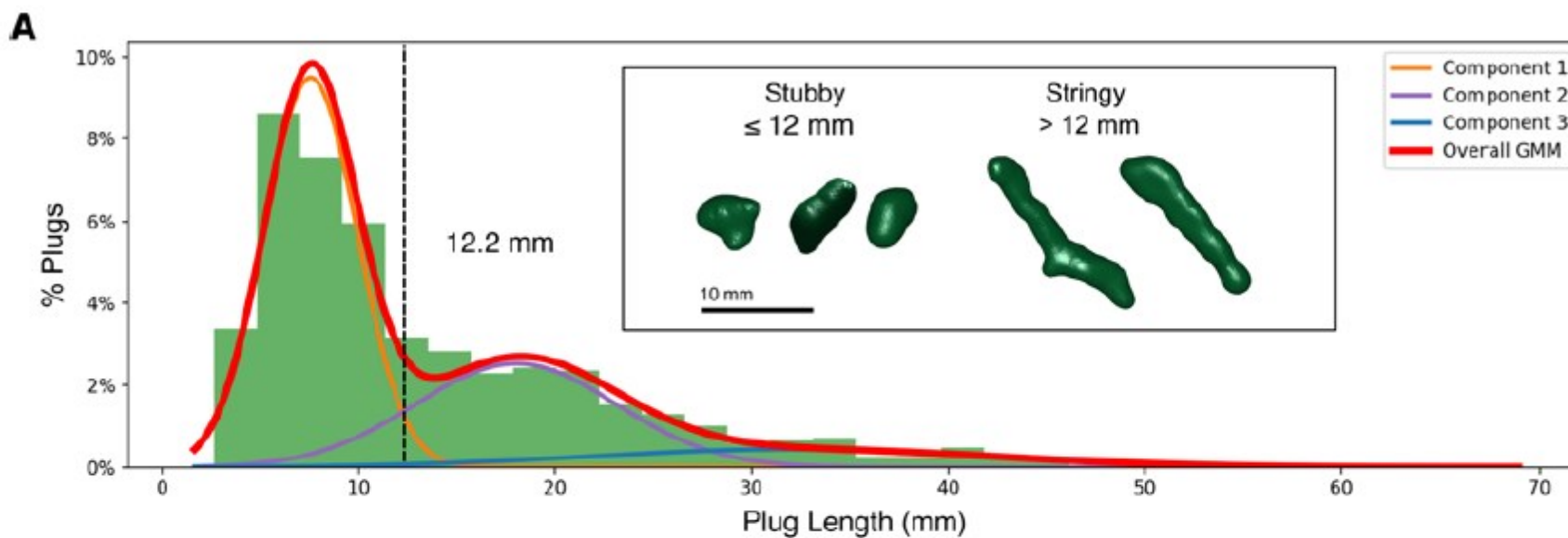
Mucus Plugs Persist in Asthma, and Changes in Mucus Plugs Associate with Changes in Airflow over Time

Monica Tang¹, Brett M. Elicker², Travis Henry³, David S. Gierada⁴, Mark L. Schiebler⁵, Brendan K. Huang¹, Michael C. Peters¹, Mario Castro⁶, Eric A. Hoffman⁷, Sean B. Fain⁷, Samuel Y. Ash⁸, Jiwoong Choi⁶, Chase Hall⁶, Brenda R. Phillips⁹, David T. Mauger¹⁰, Loren C. Denlinger¹¹, Nizar N. Jarjour¹¹, Elliot Israel⁸, Wanda Phipatanakul¹², Bruce D. Levy⁸, Sally E. Wenzel¹³, Eugene R. Bleeker¹⁴, Prescott G. Woodruff^{1,15}, John V. Fahy^{1,15}, Eleanor M. Dunican^{16,17}, and the NHLBI Severe Asthma Research Program-3 (SARP-3)



Mucus plugs in patients with asthma linked to eosinophilia and airflow obstruction





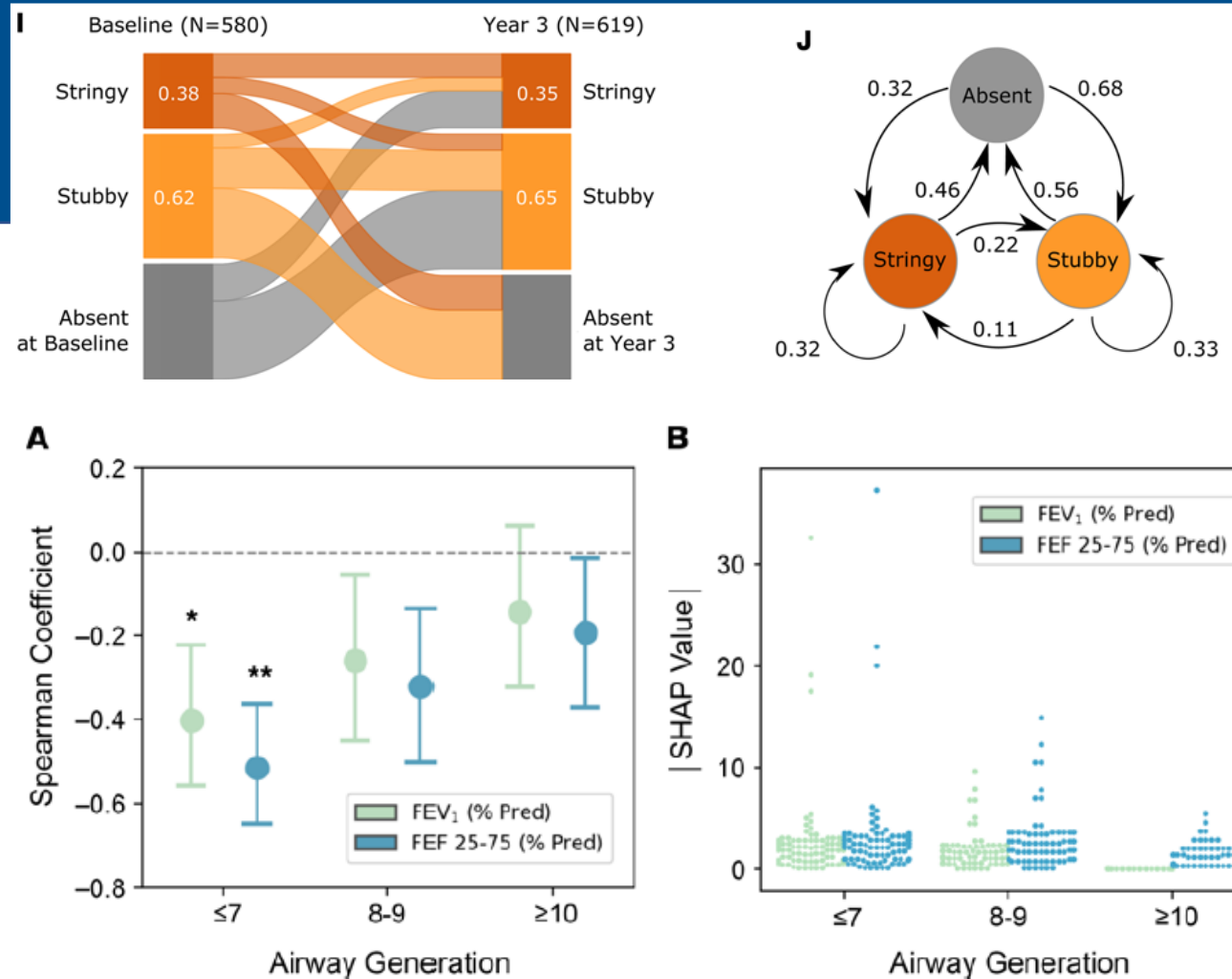
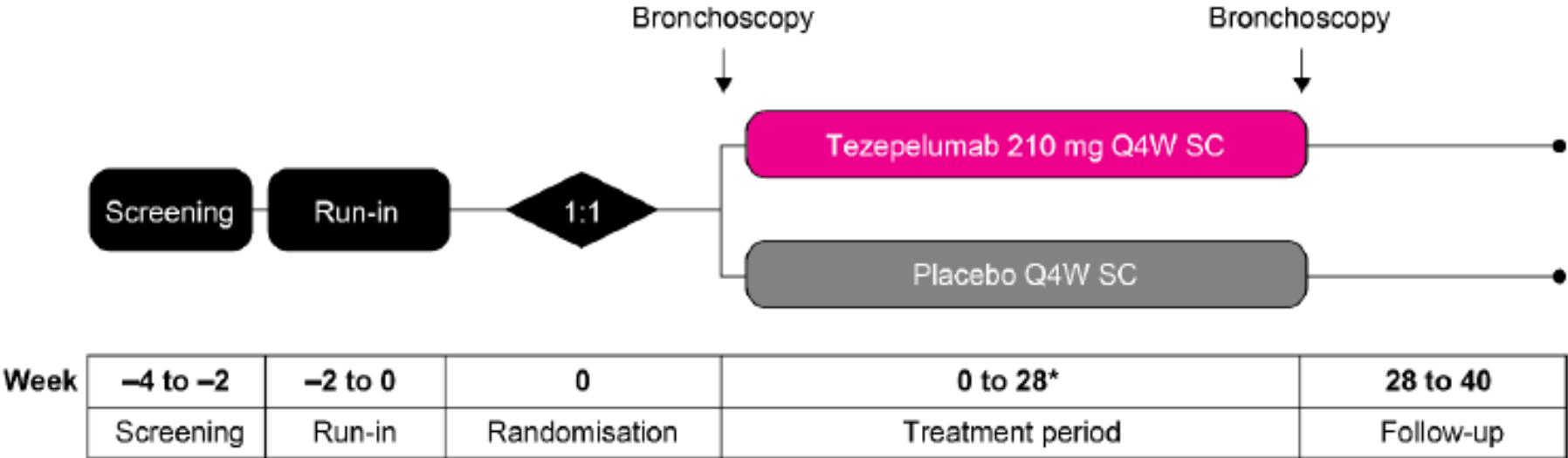


Figure 5. Proximal plugs are more consequential for spirometric measures of airflow obstruction in asthma. (A) Correlation analysis of mucus plugs grouped independently by proximal airway generations (7 or less), intermediate airway generations (8 and 9), and distal airway generations (10 and greater) as well as spirometry measures. The estimated Spearman coefficients for each generation group, which correlate plug count by generation group with FEV₁ and FEF₂₅₋₇₅, are shown for proximal, intermediate, and distal airway generations along with 95% CI. **P* < 0.05, different from distal airway generations for FEV₁ (by bootstrapping). ***P* < 0.01, different from distal airway generation (by bootstrapping). Data presented includes pooled baseline and year-3 follow-up scans (*n* = 97). **(B)** Absolute SHAP values for FEV₁ and FEF₂₅₋₇₅ at proximal, intermediate, and distal airway generations (*n* = 97).

Reversing HRCT changes in asthma

Effect of tezepelumab on airway inflammatory cells, remodelling, and hyperresponsiveness in patients with moderate-to-severe uncontrolled asthma (CASCADE): a double-blind, randomised, placebo-controlled, phase 2 trial

Sarah Diver, Latifa Khalfaoui*, Claire Emson*, Sally E Wenzel, Andrew Menzies-Gow, Michael E Wechsler, James Johnston, Nestor Molfino, Jane R Parnes, Ayman Megally, Gene Colice†, Christopher E Brightling†, on behalf of the CASCADE study investigators‡*



	Baseline		EOT		Change from baseline	
	Tezepelumab 210 mg Q4W (N=54)	Placebo (N=56)	Tezepelumab 210 mg Q4W (N=54)	Placebo (N=56)	Tezepelumab 210 mg Q4W (N=54)	Placebo (N=56)
Lung function						
n	54	56	53	51	53	51
FEV ₁ , L	2.21 (0.70)	2.34 (0.54)	2.42 (0.74)	2.57 (0.67)	0.21 (0.37)	0.22 (0.36)
FEV ₁ predicted, %	68.8 (14.3)	69.4 (11.8)	75.756 (15.606)	75.381 (14.110)	6.8 (11.6)	6.0 (10.1)
FVC, L	3.48 (0.98)	3.83 (0.98)	3.65 (1.04)	3.95 (0.99)	0.17 (0.54)	0.11 (0.36)
FEF ₂₅₋₇₅ (L/s)	1.26 (0.68)	1.25 (0.51)	1.53 (0.80)	1.54 (0.65)	0.27 (0.49)	0.28 (0.41)
Large airway quantitative CT parameters						
n	35	41	33	40	33	40
Airway lumen area, mm ²						
Generation 3	12.2 (4.0)	14.1 (3.9)	12.9 (4.3)	13.9 (4.3)	5.4% (12.3%)	0.5% (9.2%)
Generation 4	7.6 (2.8)	8.2 (2.5)	8.0 (2.7)	8.1 (2.7)	5.0% (13.6%)	0.5% (8.8%)
Generation 5	6.5 (2.5)	6.7 (2.2)	6.5 (2.2)	6.6 (2.3)	6.4% (15.9%)	0.3% (10.8%)
Airway wall area, mm ²						
Generation 3	18.3 (3.3)	20.3 (3.0)	18.9 (3.6)	20.1 (3.3)	2.9% (6.7%)	0.3% (4.1%)
Generation 4	13.8 (2.7)	14.9 (2.8)	14.3 (2.8)	14.8 (3.0)	3.0% (7.8%)	0.3% (4.1%)
Generation 5	11.5 (2.7)	12.5 (3.0)	11.9 (2.8)	12.1 (2.8)	4.0% (9.7%)	0.9% (5.1%)
Airway wall area, %						
Generation 3	60.7 (4.3)	59.8 (3.7)	60.1 (3.9)	60.1 (3.6)	-0.4% (3.5%)	0.1% (2.2%)
Generation 4	65.0 (3.6)	64.5 (2.9)	64.5 (3.6)	64.7 (2.8)	-0.7% (2.6%)	0.0% (2.0%)
Generation 5	65.9 (3.4)	65.9 (2.4)	65.9 (3.0)	66.2 (2.6)	-0.4% (3.1%)	0.1% (2.4%)
Airway wall thickness, mm						
Generation 3	1.14 (0.08)	1.18 (0.08)	1.15 (0.09)	1.18 (0.08)	1.2% (4.4%)	0.1% (2.3%)
Generation 4	1.03 (0.08)	1.05 (0.09)	1.04 (0.09)	1.05 (0.08)	1.1% (4.1%)	0.3% (1.9%)
Generation 5	0.92 (0.10)	0.95 (0.11)	0.94 (0.12)	0.96 (0.10)	2.2% (4.9%)	1.0% (2.8%)
Airwave oscillometry						
n	53	56	51	54	50	54
R5-R20, kPa.s/L*	0.13 (0.16)	0.15 (0.12)	0.14 (0.14)	0.13 (0.11)	0.01 (0.17)	-0.02 (0.11)
Reactance area, kPa/L	2.22 (2.57)	1.77 (2.05)	2.62 (3.37)	1.56 (1.89)	0.32 (3.13)	-0.24 (2.03)
Small airway quantitative CT parameters						
n	35	41	32	40	32	40
DPM ^{BSAD} , %	29.5 (18.3)	23.8 (14.2)	28.6 (20.2)	23.5 (13.0)	-2.1 (17.6)	-0.5 (10.1)
n	34	41	31	40	31	40
Air trapping index, % less than -856 HU	9.6 (9.3)	13.5 (11.4)	9.4 (9.3)	12.6 (11.2)	-0.8 (4.5)	-1.0 (6.9)
n	31	38	28	37	28	37
Expiratory to inspiratory ratio of mean lung density	0.84 (0.07)	0.84 (0.06)	0.84 (0.07)	0.83 (0.06)	-0.01 (0.04)	-0.01 (0.04)

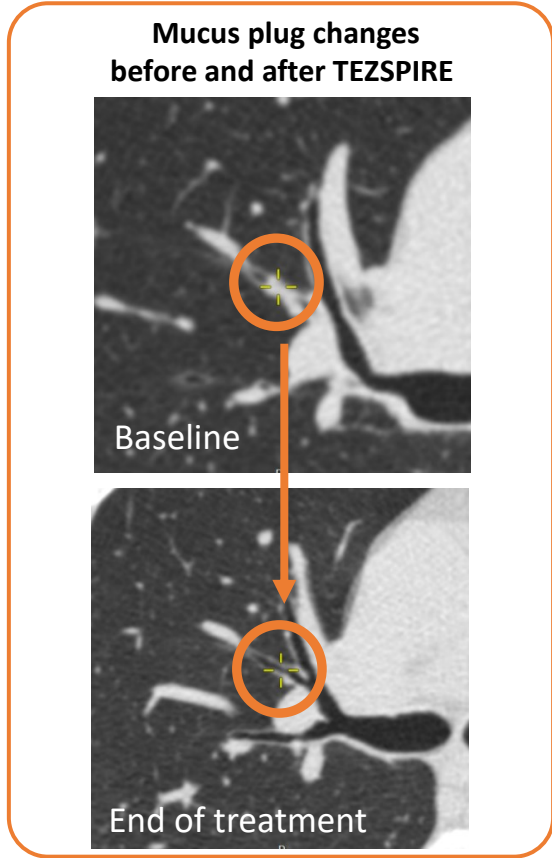
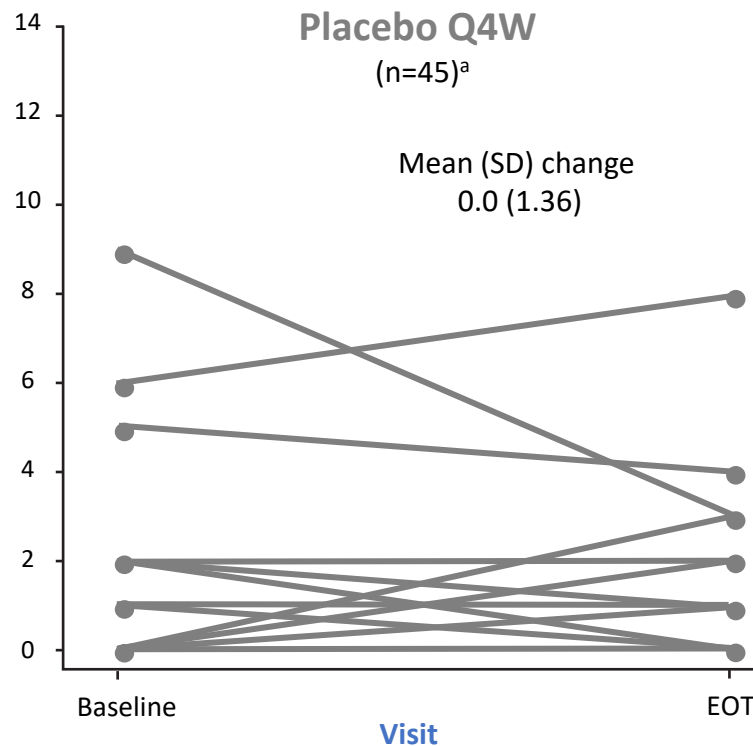
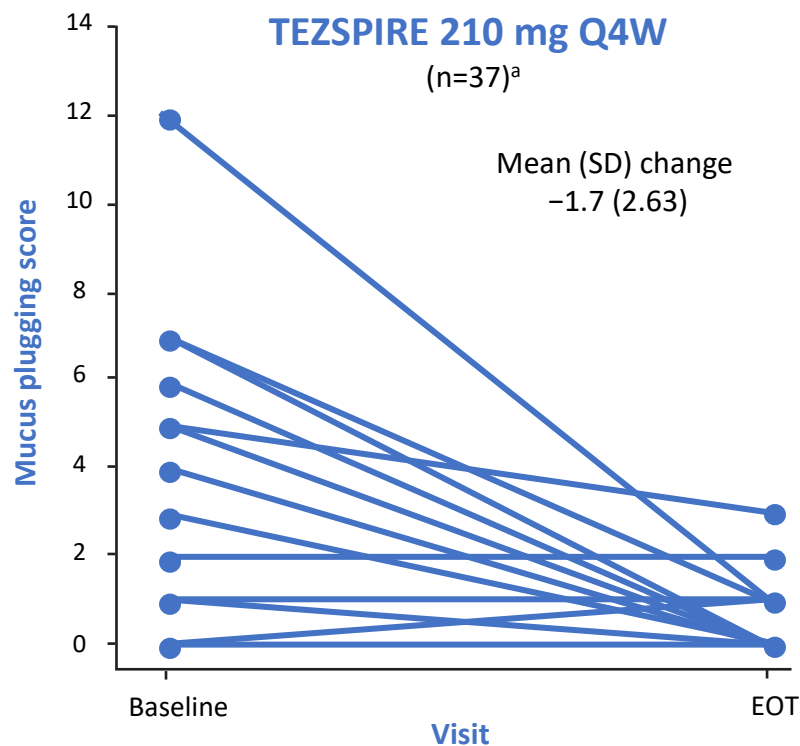
Data are mean (SD). For large airway quantitative CT parameters, values and change are calculated as the median across airways in the same generation; airway lumen area and wall area have been normalised according to BSA and airway wall thickness according to $\sqrt{\text{BSA}}$.

BSA=body surface area. CT=computed tomography. DPM^{BSAD}=disease probability mapping (functional small airways disease). EOT=end of treatment. FEF₂₅₋₇₅=forced expiratory flow at 25-75% of the forced vital capacity. FEV₁=forced expiratory volume in 1 second. FVC=forced vital capacity. HU=Hounsfield units. Q4W=every 4 weeks. SD=standard deviation.

*R5-R20 is a measure of peripheral airway resistance defined as the difference in resistance between 5 Hz (R5, total respiratory system resistance) and 20 Hz (R20, central resistance).

Tezepelumab and Mucus Plugs in Patients with Moderate-to-Severe Asthma

Exploratory analysis of CASCADE

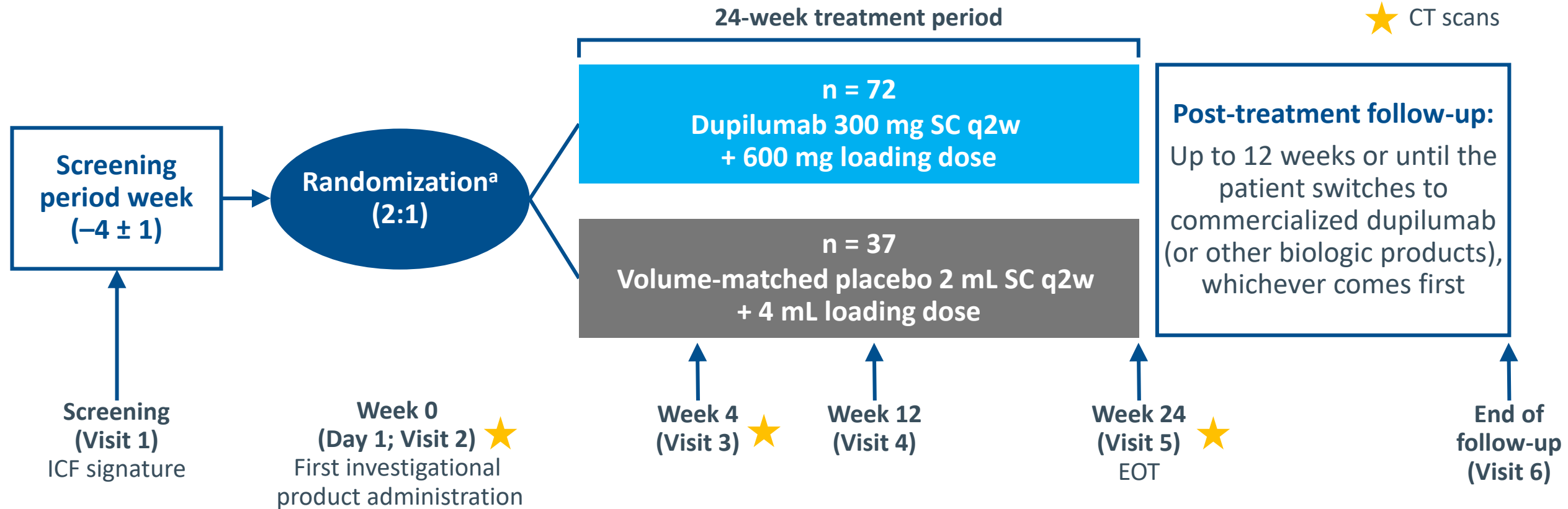


^aData are from the evaluable analysis set. Each line may represent more than one patient. Change from baseline in mucus score reduction was compared between treatment groups using a Wilcoxon rank sum test, nominal p=0.0007

EOT = End of Treatment; Q4W = Every 4 Weeks; SD = Standard Deviation

VESTIGE phase 4 study design

★ CT scans



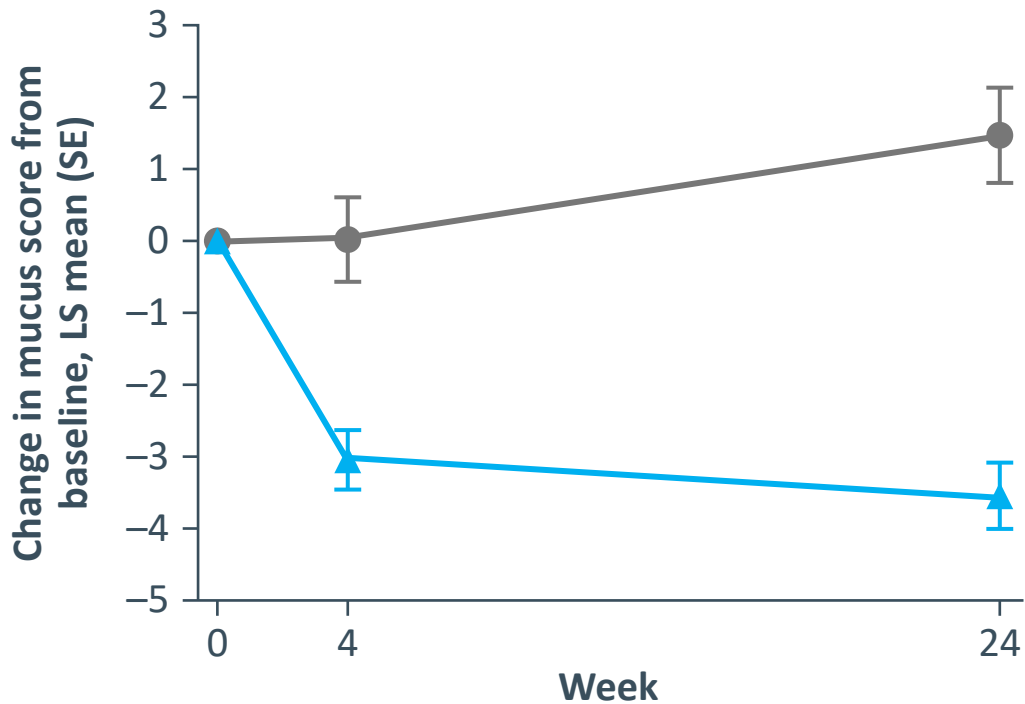
Patients were randomized 2:1 to receive add-on dupilumab 300 mg or matched placebo for 24 weeks

The Vestige phase IV trial

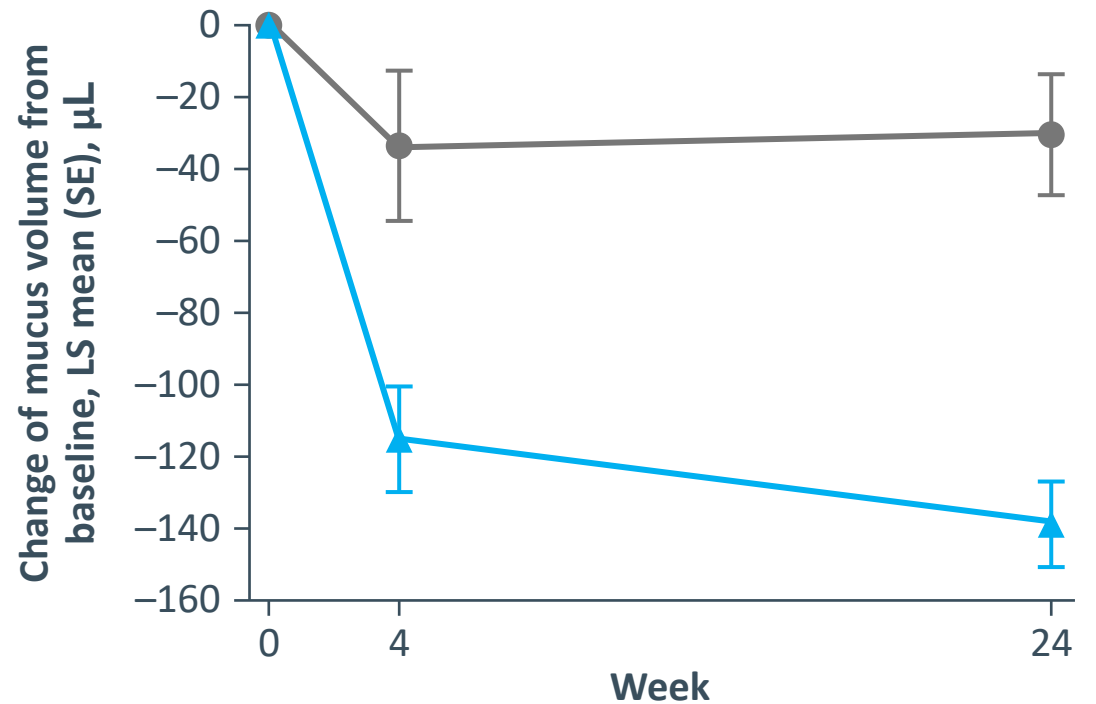
Dupilumab reduced both mucus score and volume

● Placebo q2w ▲ Dupilumab 300 mg q2w

A) Mucus score



B) Mucus volume



Porsbjerg C Dupilumab Reduces Mucus Plugging and Volume: Phase 4 VESTIGE Trial

Placebo

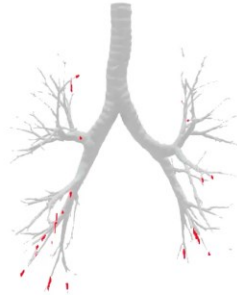
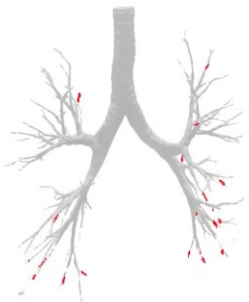
MUCUS VOLUME - AVERAGE PLACEBO



BASELINE

WEEK 4

WEEK 24



 MUCUS PLUGS

Dupilumab

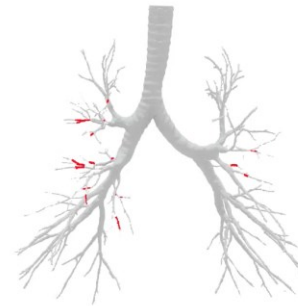
MUCUS VOLUME - AVERAGE TREATED



BASELINE

WEEK 4

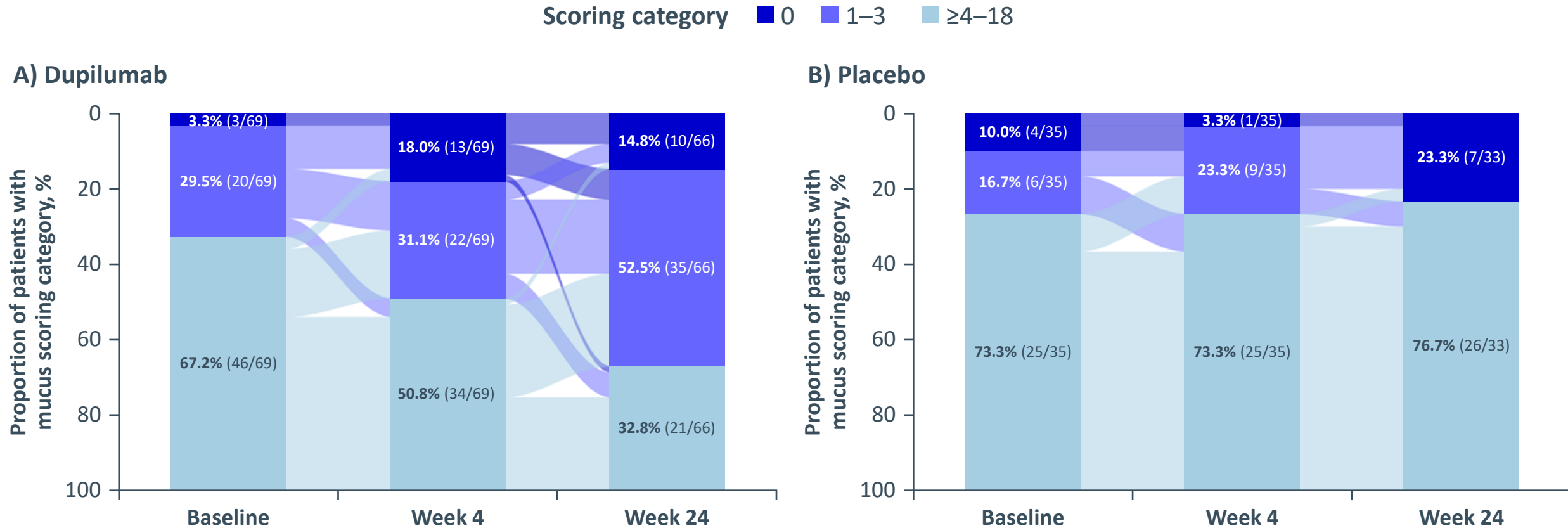
WEEK 24



 MUCUS PLUGS

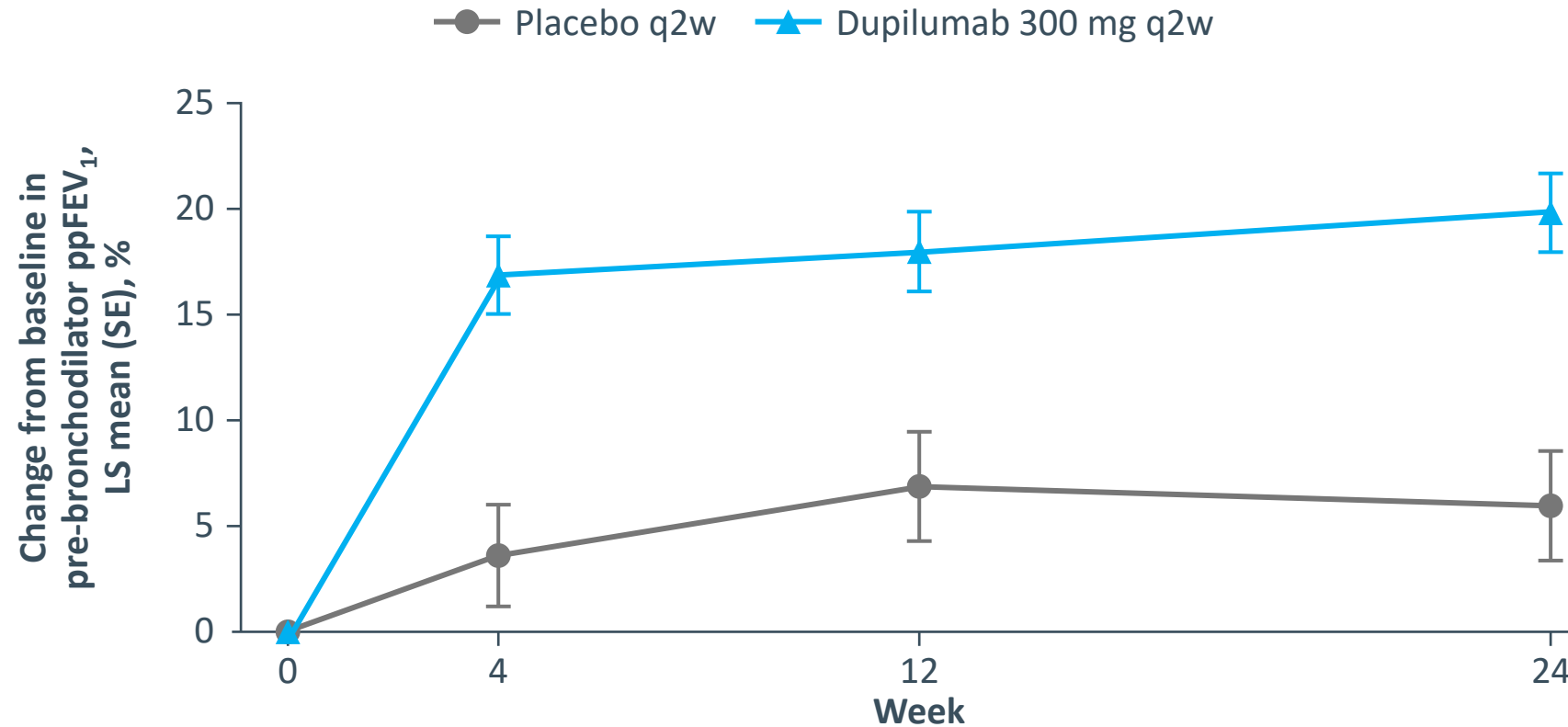
Results – Mucus score

By Week 24, 67.3% of the dupilumab group (A) had a mucus score of <4 (low or no burden) compared with 23.3% of the placebo group (B)



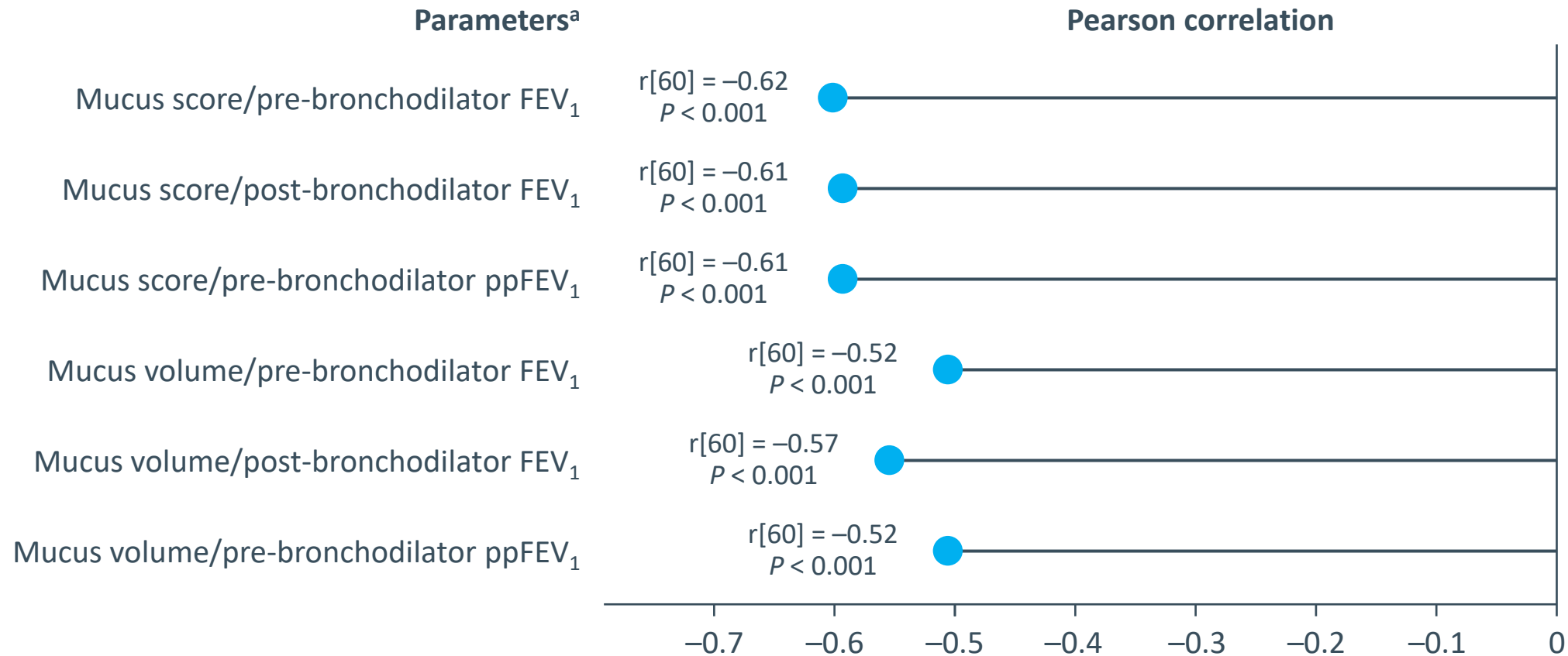
Results – Lung function

Patients receiving dupilumab vs placebo showed a greater improvement in pre-bronchodilator ppFEV₁



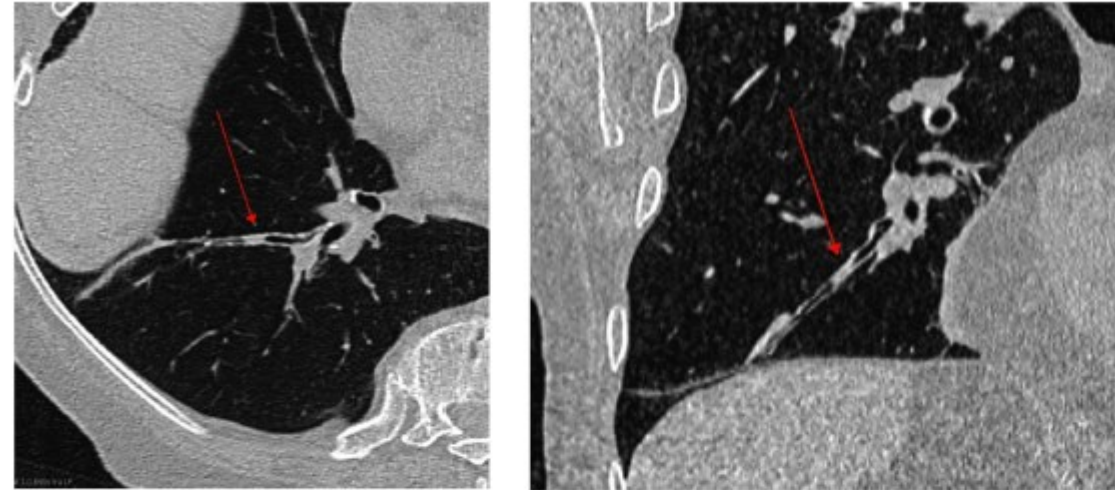
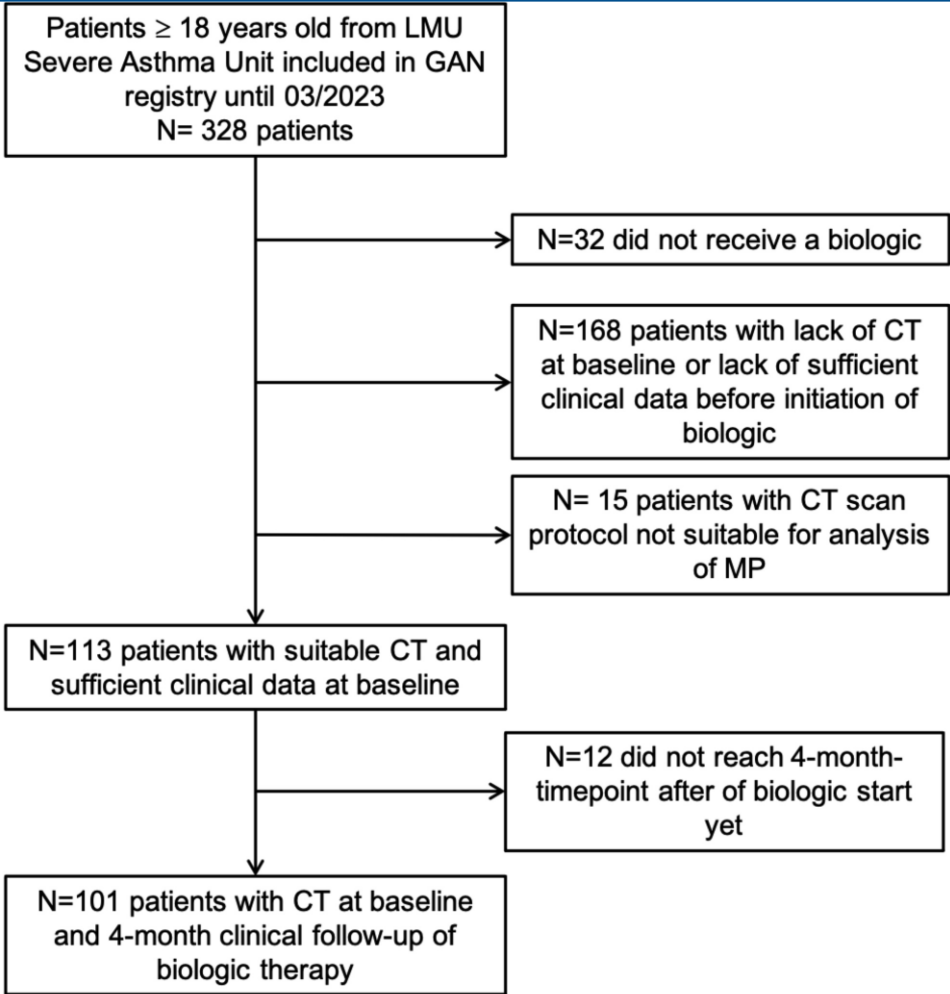
Results – Lung function and mucus scores

In the dupilumab group, improvements from study baseline to Week 24 in lung function and mucus scoring or mucus volume were significantly correlated

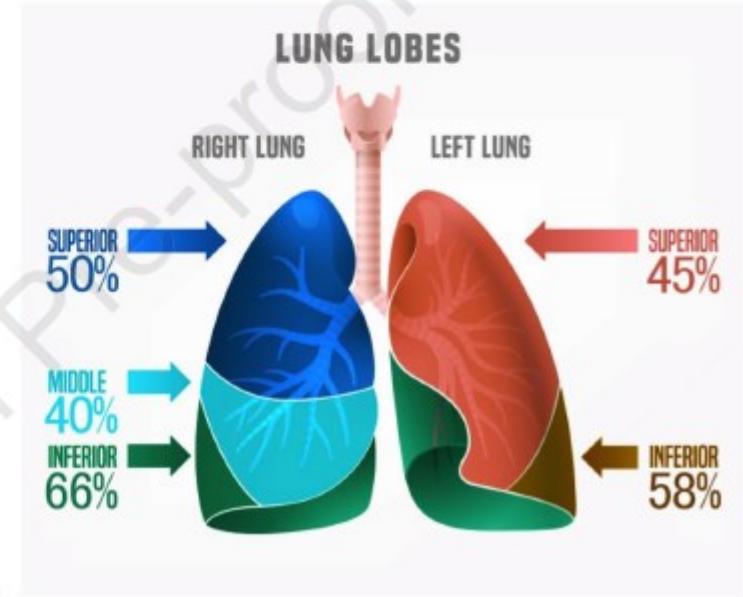
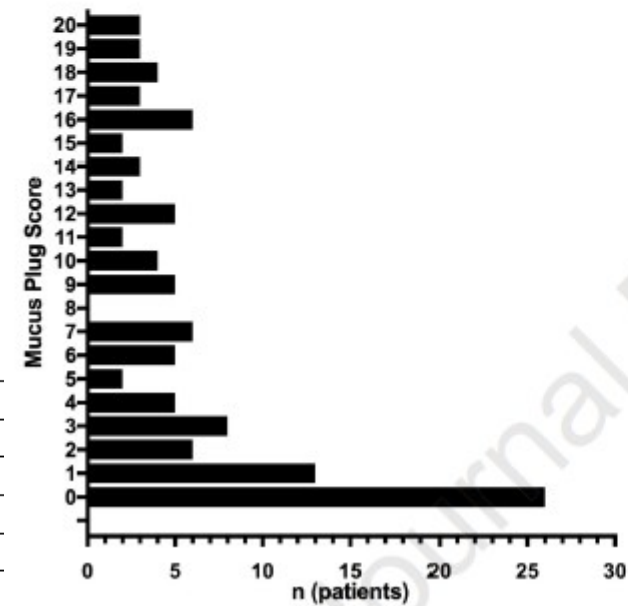


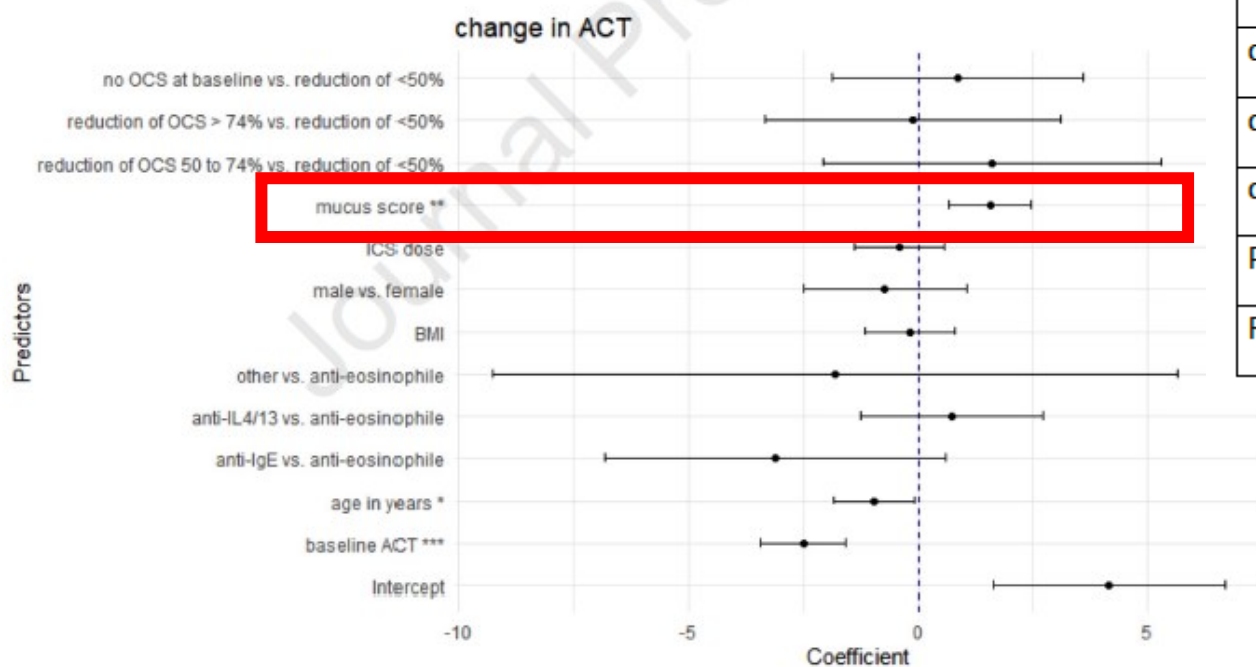
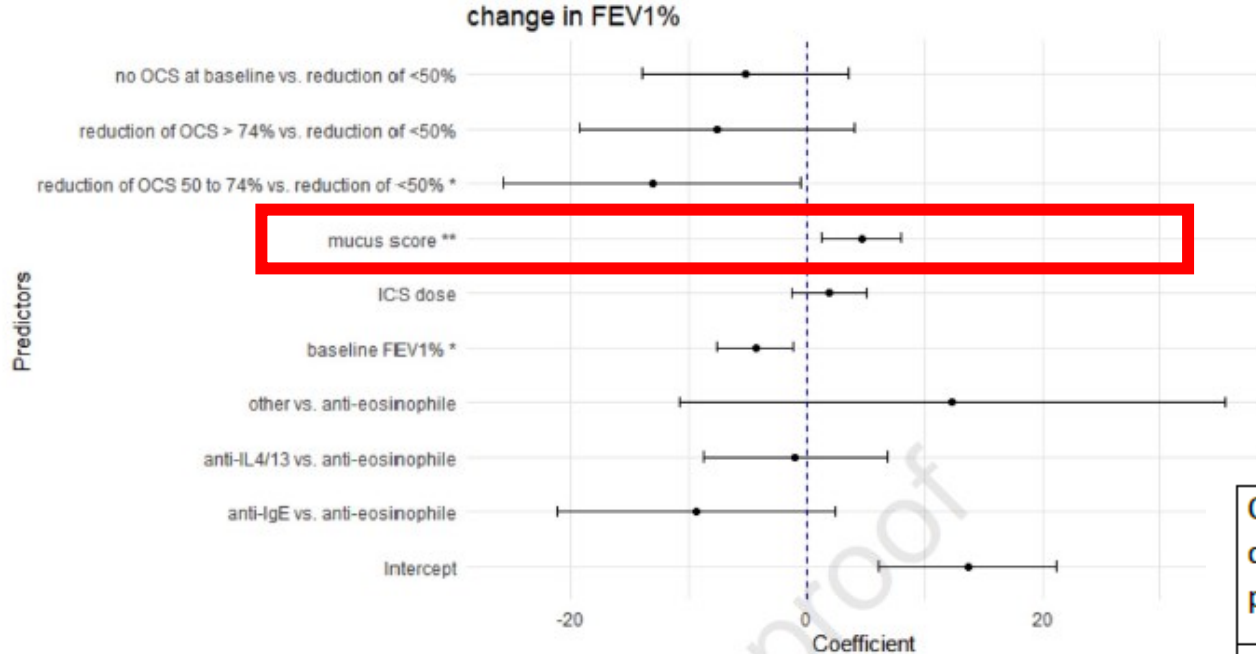
^a Parameters measured are change from study baseline to Week 24
FEV₁, forced expiratory volume in 1 second; ppFEV₁, percent predicted forced expiratory volume in 1 second.

Usefulness of CT for predicting
benefits of biologics in asthma



Biological therapy started after baseline			
	n (%)		
Dupilumab	n (%)	29 (25.7)	25 (24.8)
Omalizumab	n (%)	10 (8.8)	8 (7.9)
Benralizumab	n (%)	42 (37.2)	38 (37.6)
Mepolizumab	n (%)	30 (26.5)	28 (27.7)
Reslizumab	n (%)	1 (0.9)	1 (1.0)
Tezepelumab	n (%)	1 (0.9)	0





Correlation of MPS baseline with delta (follow-up – baseline) parameter	Spearman r	P (two-tailed)	n
BARS	0.3128	0.0012	104
ACT	0.4871	<0.0001	72
delta FEV1 % predicted	0.3266	0.0008	102
delta FVC % predicted	0.2525	0.0109	101
delta FEV1/FVC	0.2267	0.0226	101
PEF % predicted	0.1046	0.3003	100
R % predicted	-0.1933	0.0528	101

The *Benraliscan* study (NCT03976310)

Unrestricted grant from AZ paid to our institution

CHU Montpellier promotor

Bicentric Montpellier – Marseille

Open label one arm

National ethic committee – regulatory approval

FPFV 20th jun 2019 – LPLV 9th Jun 2023



Patients characteristics (Per protocol)

n = 44

Age : 56y
Women : 57%
BMI : 27 Kg/m²
Former smoker < 10 yr : 57%

Asthma for 24y

3.4 exacerbations/yr
Former ICU admission : 32%
ACQ-5 : 2.8
FEV1 : 71%
BD Reversibility : 8%

LTOCS : 27%
Former biologic : 43%
≥ High dose ICS + LABA : 100%

Typical characteristics of
very severe asthmatics:

Highly eosinophilic

High OCS ICS exposure

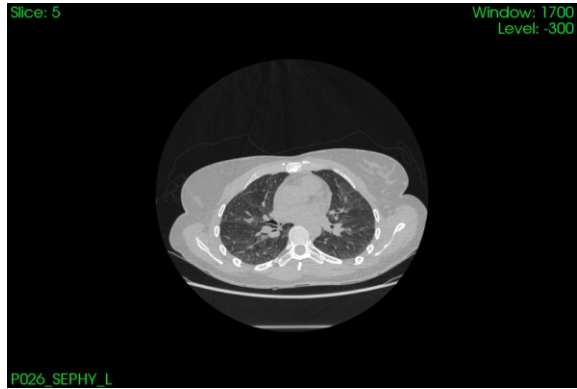
High comorbidities

CRSwNP 66% / NP surgery : 45%
Allergic : 59%
Urticaria : 23%
Atopic Dermatitis : 13%
Allergic Conjunctivitis : 23%
Aspirin ERD : 23%

Diabetes : 4%
Osteoporosis : 23%
Cardiovascular : 39%

Highest BEC : 1410/mm³
BEC at entry : 513/mm³

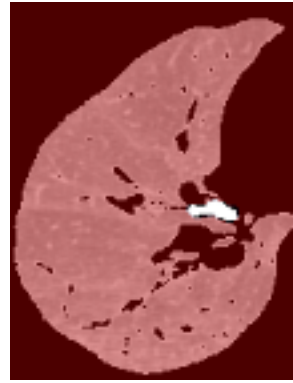
Expiratory/Inspiratory Mean Lung Density



acquisition



segmentation



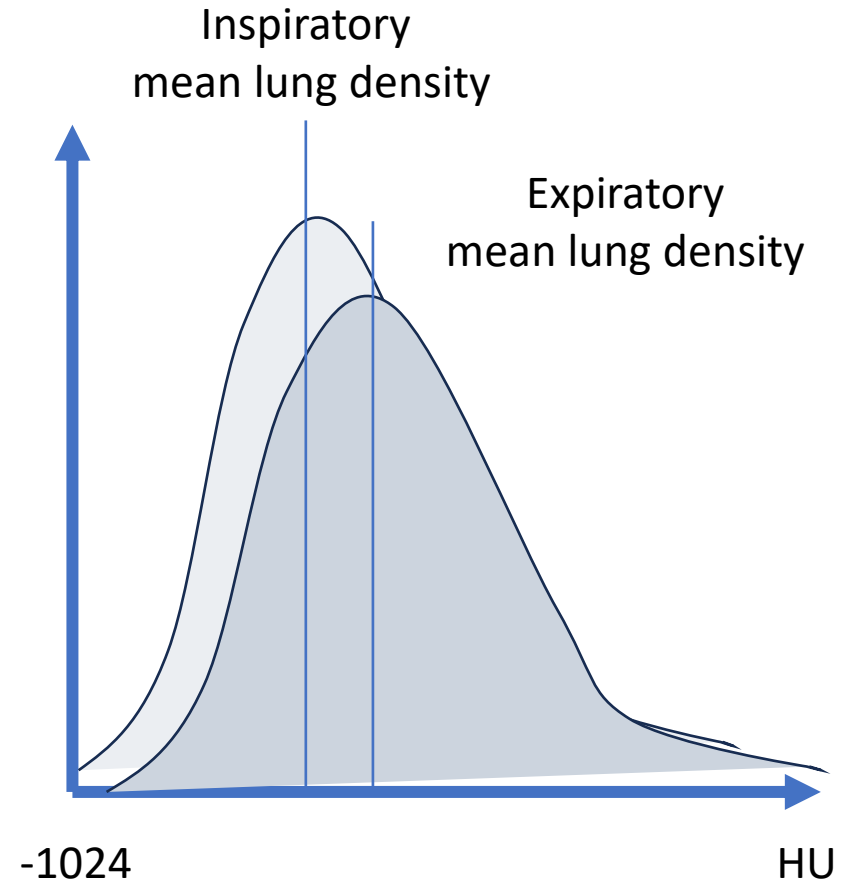
optimisation



Inspiration



Expiration



Parametric Response Map (PRM)

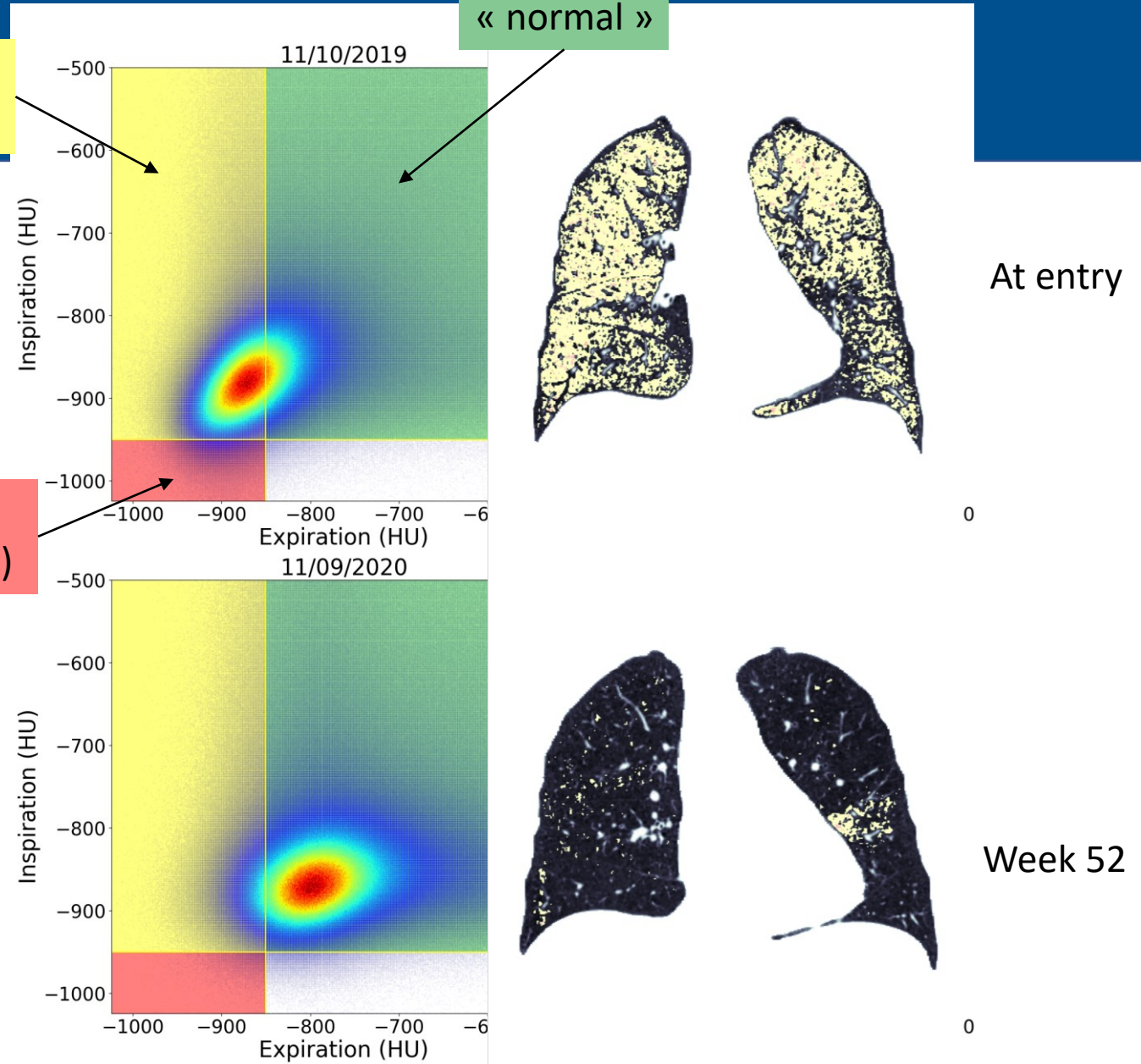
Air trapping
(PRM fSAD)

Emphysema
(PRM fEMPH)

« normal »

PRM considers anatomical deformation of the chest

- Analyzes voxel value as during respiratory phases, evaluating voxel's value during inspiration before considering its value during expiration
- Differentiates emphysema from air trapping



Secondary objectives

Identify predictors of response at week 52

- +1 : 0 or 1 mild unadmitted exacerbation
- +1 : Change in Pre BD FEV1 between week 0 and week 52 > 300 ml
- +1 : Change in ACQ5 between week 0 and week 52 > 0.5

Composite clinical response score

NON RESPONDERS

- 0 : Non responder
- 1 : Limited response

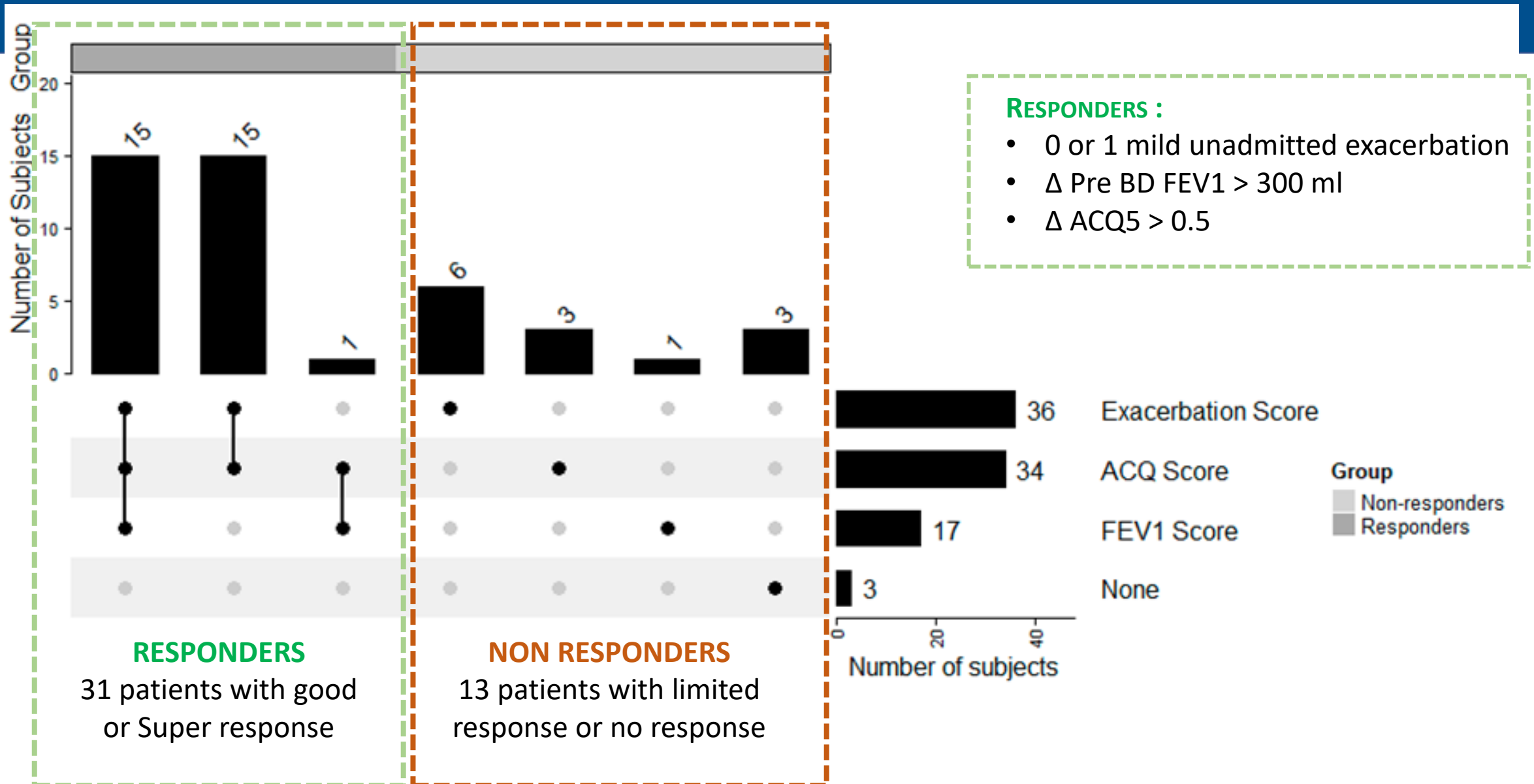
vs

RESPONDERS

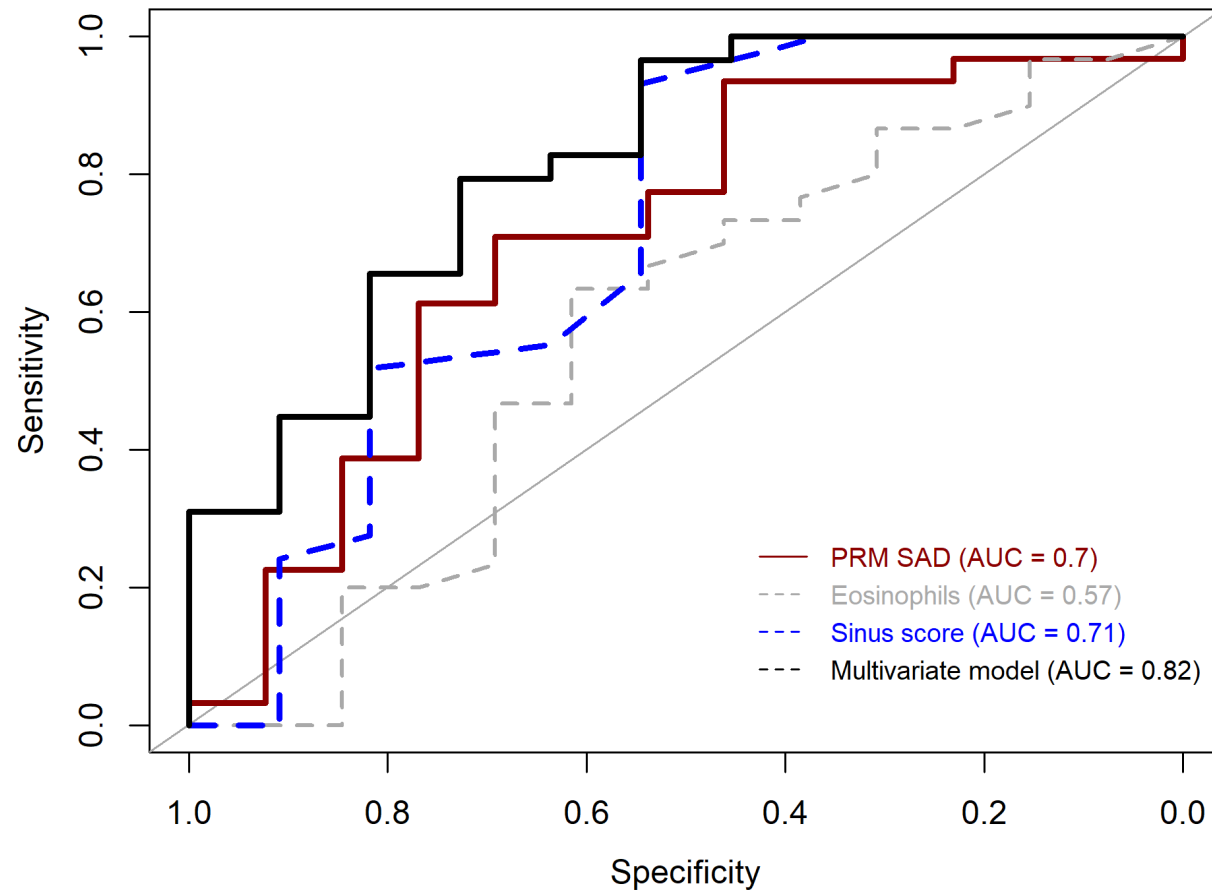
- 2 : Good response
- 3 : Super response

Assess HRCT changes over time

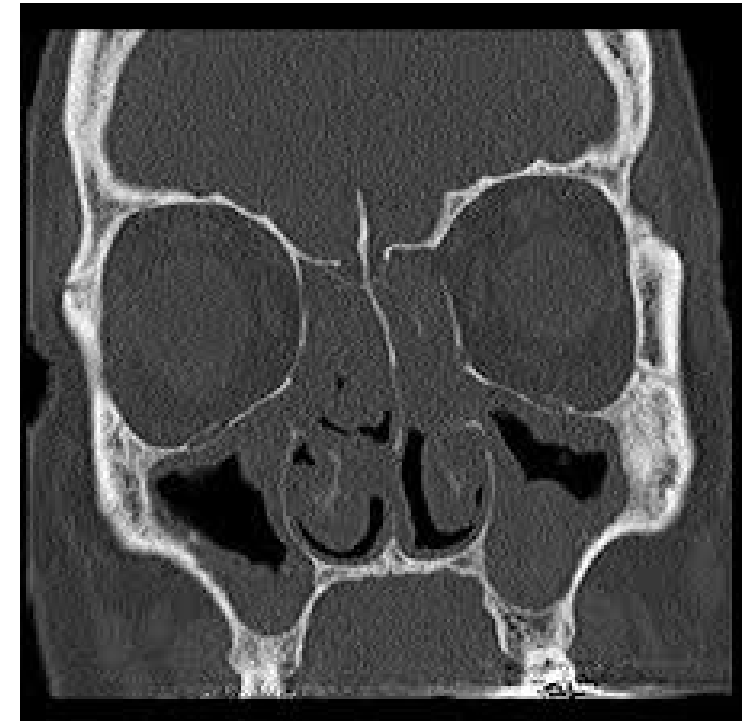
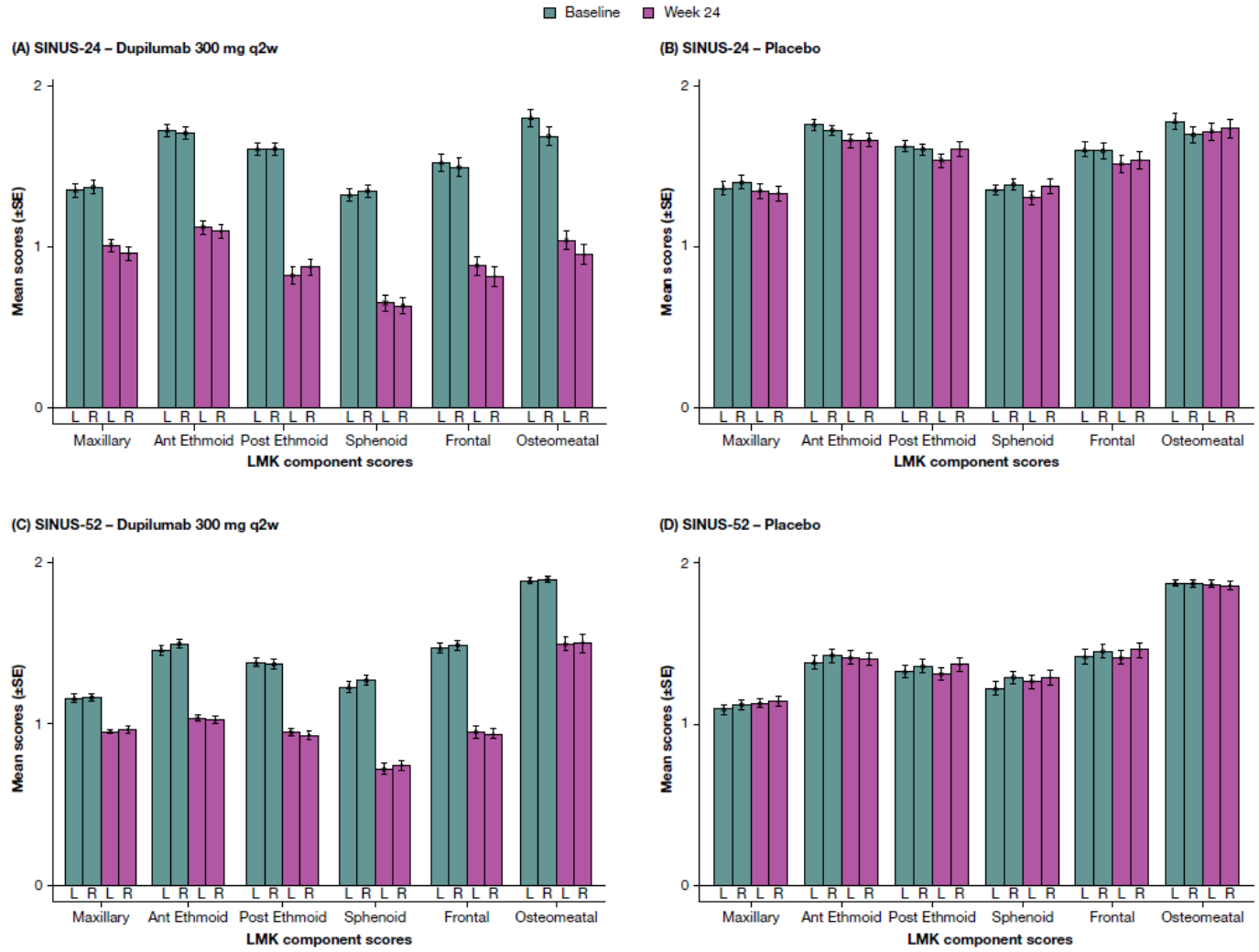
Composite Clinical response

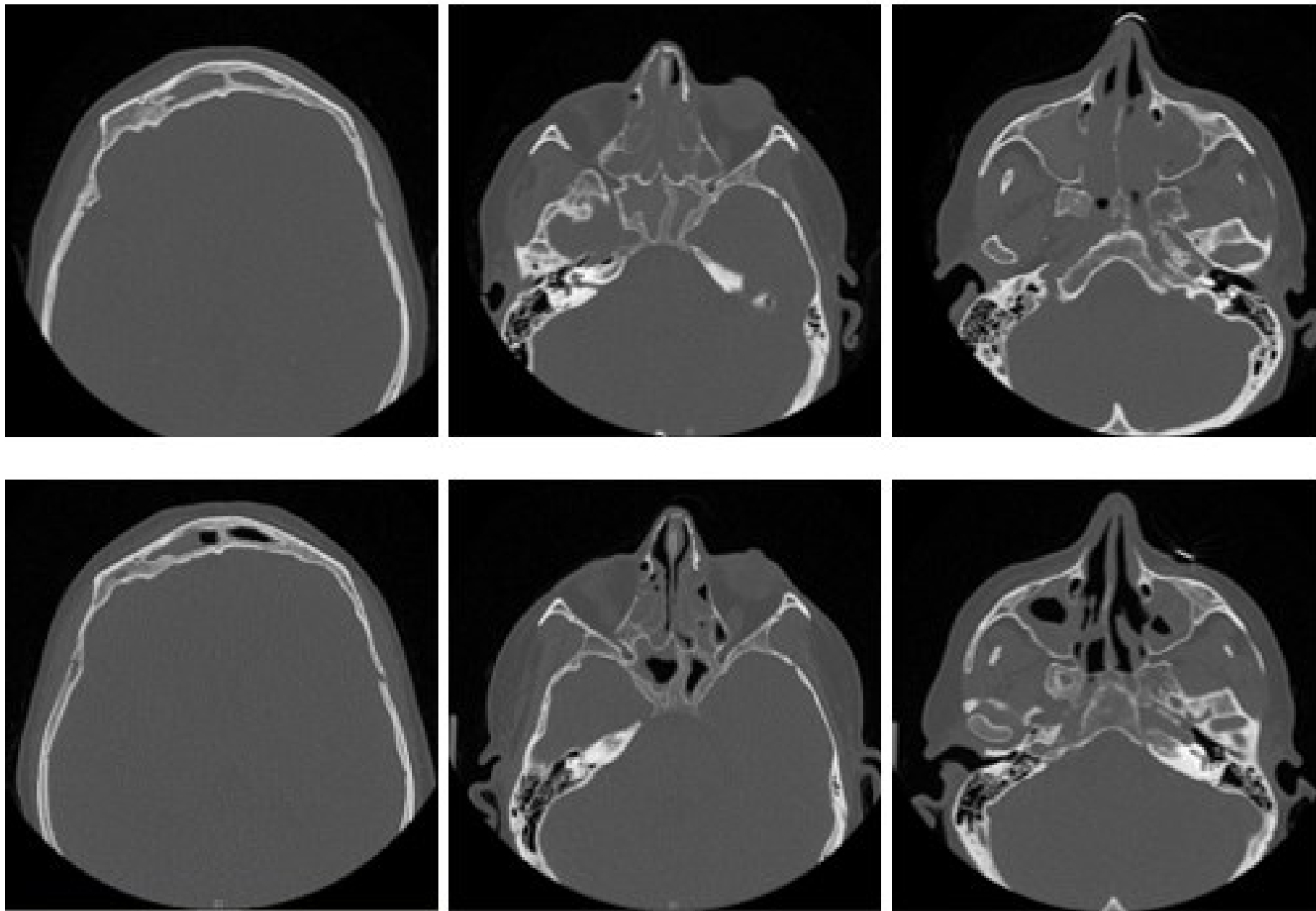


Predicting composite clinical responders (good and super) vs. non responders



Mean Lund-Mackay CT score at baseline and week 24 in SINUS-24 and SINUS-52



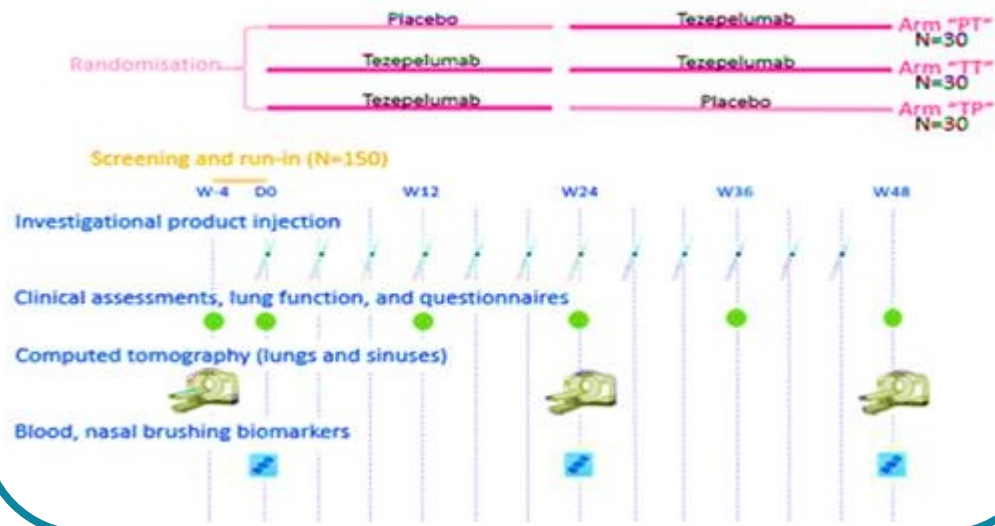


The Benraliscan study

REVERsing airway Remodelling with Tezepelumab (REVERT): a prospective, multi-centre, parallel-arm, placebo-controlled, randomized controlled trial



Study design



Hypothesis

Tezepelumab treatment is capable of at least partially reversing bronchial remodelling as detected on computed-tomographic (CT) scan.

Study setting

The French initiative CRISALIS organized within the F-CRIN network will be the basis for this study with multiple sites in France.

Study Population^{1,2}

- Age 18-75 years, asthmatic
- at least 1 severe or 2 moderate exacerbations in the previous 12 months
- Maximal inhaled therapy including high dose ICS and at least a second controller
- ACQ-6 ≥ 1.5
- % wall area index at the B1 and B8 bronchi >65% at CT scan
- Post-bronchodilator FEV1 predicted values must be at 25-90%

NCT05651841²
Status: Recruiting

Primary endpoint^{1,a}

- To compare the change from baseline on CT-scan in the wall-area index* at bronchial levels

Secondary endpoint^{1,a}

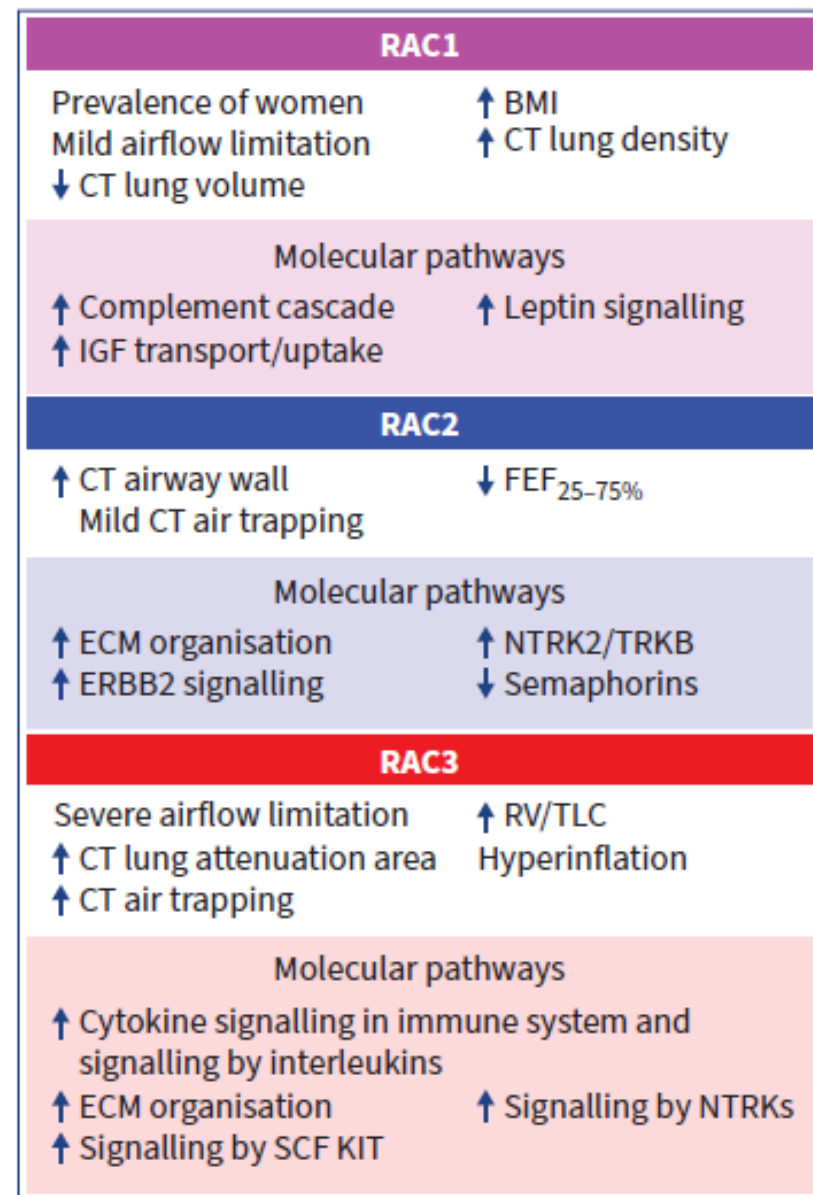
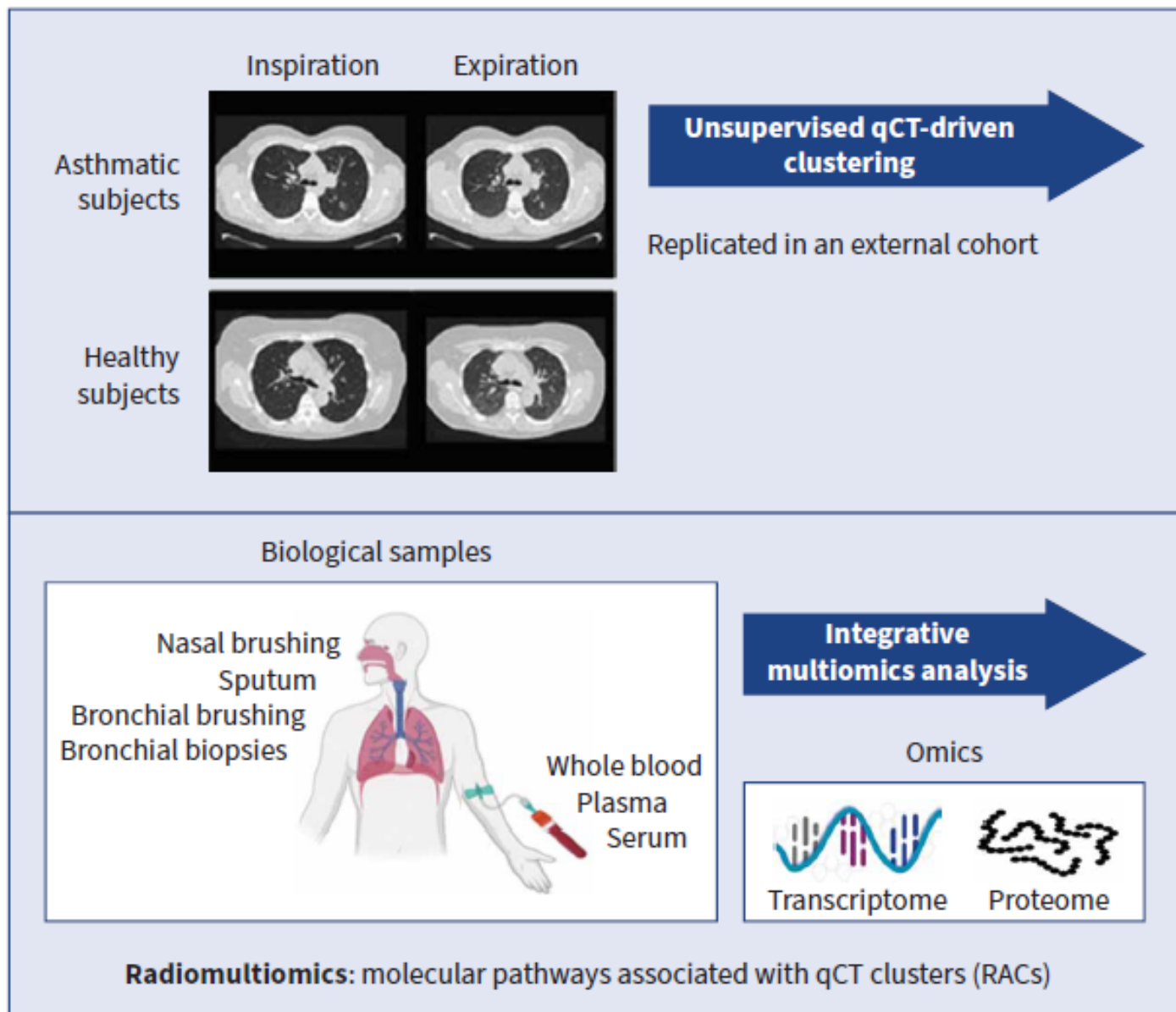
- Further imaging outcomes
- Clinical outcomes : AAER, hospitalization, ACQ-6, SGRQ, SNOT-22, BCSS...
- Bloodwork
- Nasal brushing analyses
- Single cell analyses
- Safety

* (%WA = (wall area (mm²)/ (wall area (mm²) + lumen area (mm²)) $\times 100$

^a The following vector of measures will be taken and used as a repeated measure at baseline, 6 months and 12 months: the %WA at the B1 and B8 bronchi, generations 3, 4 and 5. The primary analysis will be performed at 6 months and will compare the change in mean %WA between arms.

CRISALIS (Clinical Research Initiative in Severe Asthma: a Lever of Innovation & Science, www.crisalis-network.org); F-CRIN network (www.fcrin.org); 1 Bourdin A et al. REVERsing airway Remodelling with Tezepelumab (REVERT): a protocol for a double-blind randomized controlled trial for patients with asthma. 16 December 2022; 2 Bourdin A et al. REVERsing Airway Remodelling With Tezepelumab (REVERT). clinicaltrials.gov/study/NCT05651841

CT as an endotypic marker ?



Conclusions

- Imaging in asthma
 - Is not only for improving confidence in asthma diagnosis and in the assessment of severity
 - Is improving our understanding of asthma mechanisms, including AHR and impaired lung function
 - Is progressively improving prediction of benefits of a biologic
 - But not yet whether this will inform which biologic should be initiated first
- Insights from the upper airway level
 - Nasal polyposis is a great predictor of biologics success, probably the strongest T2 marker
 - Clearer understanding of upper-lower airway is needed
 - « Welcome to the T2 club ! »