Pre-COPD : Subtypes and Characteristics

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COPD school 15Jun2024

Lung function criteria

- Defined using postbronchodilator spirometry
  - PRISM (Preclinical Respiratory Syndrome) : FEV1/FVC ≥ 0.7 and FEV1 < 80% predicted
  - GOLD grade 0 : FEV1/FVC ≥ 0.7 and FEV1 ≥ 80% predicted
  - Obstruction : FEV1/FVC < 0.7

Early stages of COPD

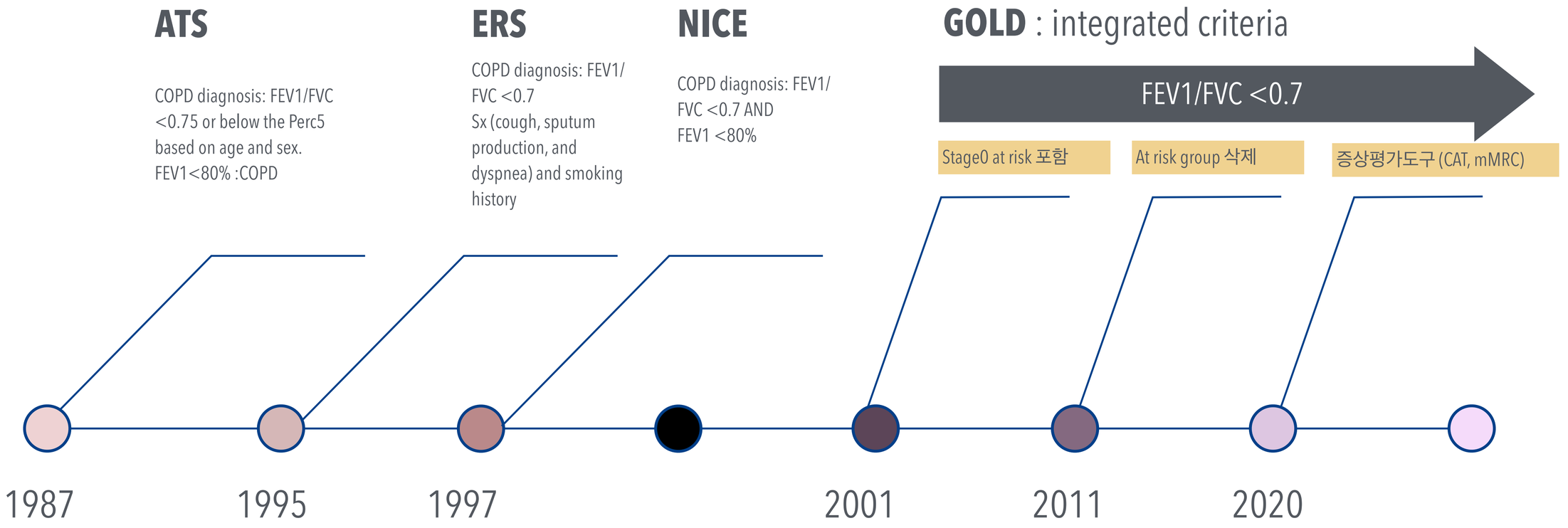
Pre-COPD

- COPD진단기준 미충족, COPD로 진행될 가능성이 있는 초기상태
  - 호흡기 증상이 있지만 폐 기능 검사가 정상인 경우: 이 경우, 흡연 이력이나 다른 위험 요인이 있는 사람들에게 주의 깊은 모니터링이 필요.
  - 폐 기능 저하가 경미한 경우: 정상 범위에 가까운 경계선 상의 폐 기능 저하가 관찰되지만, 아직 COPD 진단 기준에는 도달하지 않는 경우.
- 주로 호흡기 증상과 폐 기능 변화를 기반으로 하는 개념

PRISM

- COPD로 발전할 위험이 높은 환자
  - 단순한 호흡기 증상과 폐 기능 검사 이상을 넘어, 다양한 생물학적 및 임상적 지표를 종합적으로 평가
  - 단순히 증상이나 폐 기능 검사뿐만 아니라, 다양한 생물학적 및 영상 지표를 종합적으로 평가하여 COPD의 조기단계를 찾는 개념
- 보다 세부적이고 연구중심적이며 고도화된 평가법

PFT criteria for COPD



COPD at risk

COPD at risk in 2001 GOLD guideline

정의 :

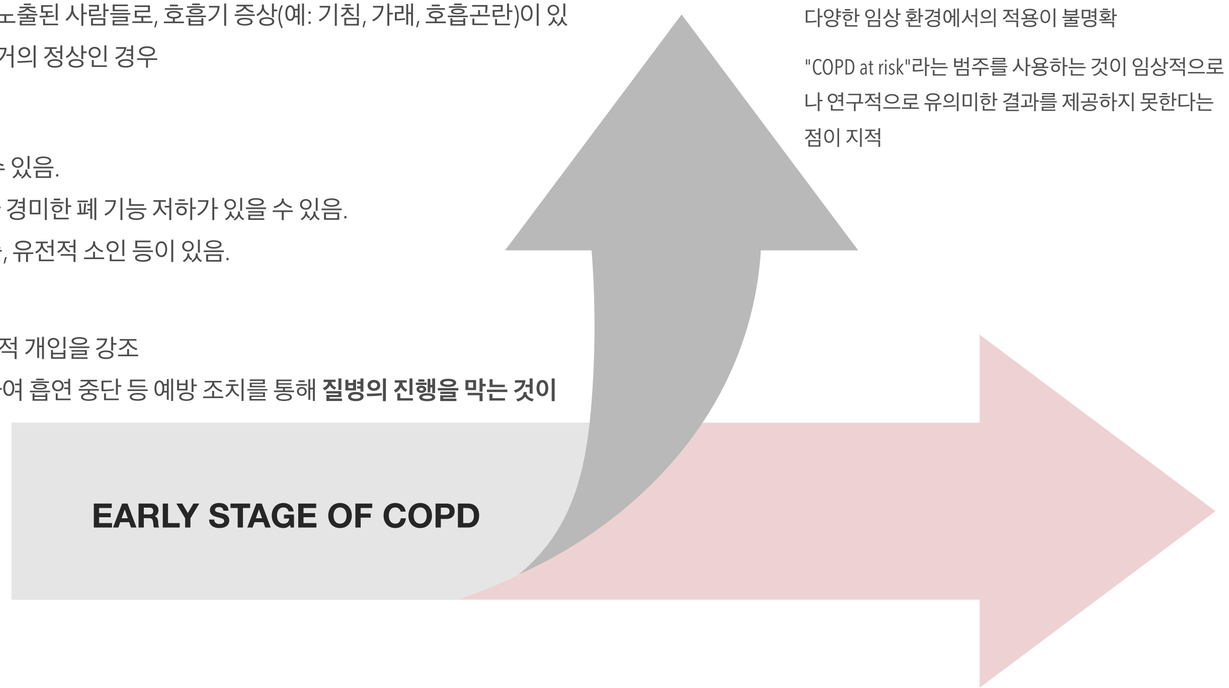
흡연자 또는 환경적, 직업적 요인에 노출된 사람들로, 호흡기 증상(예: 기침, 가래, 호흡곤란)이 있으나 폐 기능 검사에서는 정상 또는 거의 정상인 경우

특징:

증상: 만성 기침 및 가래 등이 있을 수 있음.
폐 기능 검사: 정상 범위 내에 있거나 경미한 폐 기능 저하가 있을 수 있음.
위험 요인: 흡연, 환경적/직업적 노출, 유전적 소인 등이 있음.

의의:

이 범주는 COPD의 조기 진단과 예방적 개입을 강조
흡연자나 고위험군을 조기에 식별하여 흡연 중단 등 예방 조치를 통해 **질병의 진행을 막는 것이 목표**



Abandon

명확한 기준이 없음
"COPD at risk" 범주는 일관되게 적용하기 어려웠고, 다양한 임상 환경에서의 적용이 불명확

"COPD at risk"라는 범주를 사용하는 것이 임상적으로나 연구적으로 유의미한 결과를 제공하지 못한다는 점이 지적

Pre-COPD

정의: COPD로 진행될 가능성이 높은 초기 상태로, 아직 완전한 COPD 진단 기준을 충족하지 않지만 위험 요인이 존재하는 상태

증상: 만성 기침, 가래, 호흡곤란 등의 호흡기 증상

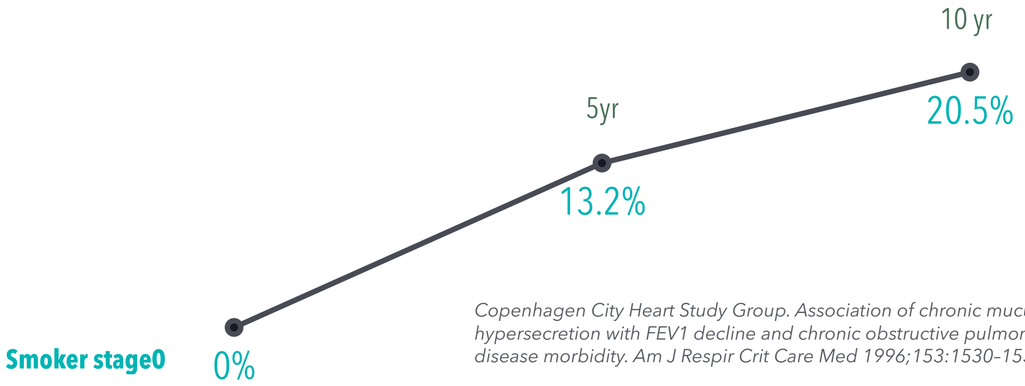
폐 기능 검사: 정상 범위 내에 있거나 경계선 상의 폐 기능 저하

영상 소견: 폐 CT 스캔 등에서 폐 기종 또는 작은 기도 병변 등의 초기 변화

생물학적 지표: 염증 표지자나 다른 생물학적 마커

Pre-COPD

Disease burden

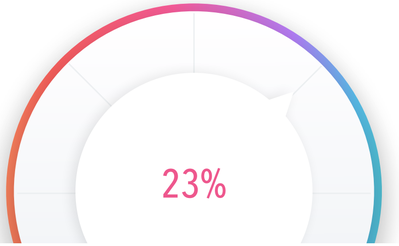


Copenhagen City Heart Study Group. Association of chronic mucus hypersecretion with FEV1 decline and chronic obstructive pulmonary disease morbidity. Am J Respir Crit Care Med 1996;153:1530–1535.

COPENHAGEN

CHRONIC OBSTRUCTIVE PULMONARY DISEASE COPD

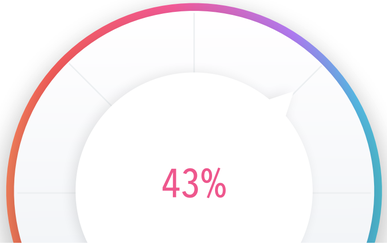
mMRC dyspnea score ≥2



Smoker having Normal FEV1/FVC

Emphysema

Gas trapping



Smoker having Normal FEV1/FVC

Airway wall thickening

COPDGene

Genetic Epidemiology of COPD (COPDGene) Investigators.Clinical and radiologic disease in smokers with normal spirometry. JAMA Intern Med 2015;175:1539–1549.

ARIC (Atherosclerosis Risk in Communities) cohort

ARIC

60% ↑ Mortality

HR, 1.6 for death among participants **at GOLD stage 0** as compared with unobstructed individuals without symptoms

A. Global Initiative on Obstructive Lung Disease (GOLD) classification of lung disease and mortality: findings from the Atherosclerosis Risk in Communities (ARIC) study. Respir Med 2006;100:115–122

Pre-COPD

Symptoms as a Biomarkers of Disease Progression

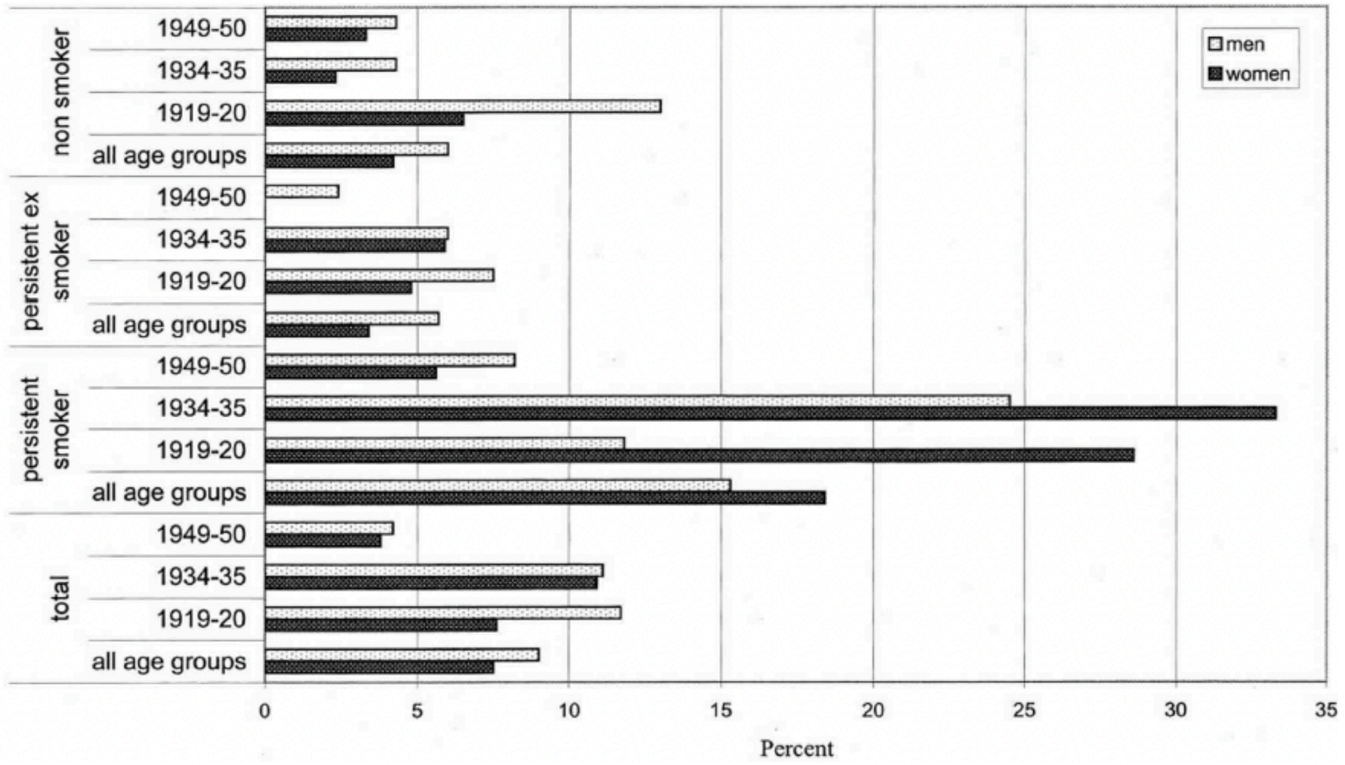
Cough,OR: 1.38

Sputum production, OR:1.24

Chronic productive cough, OR:1.47

Dyspnea, OR: 5.27

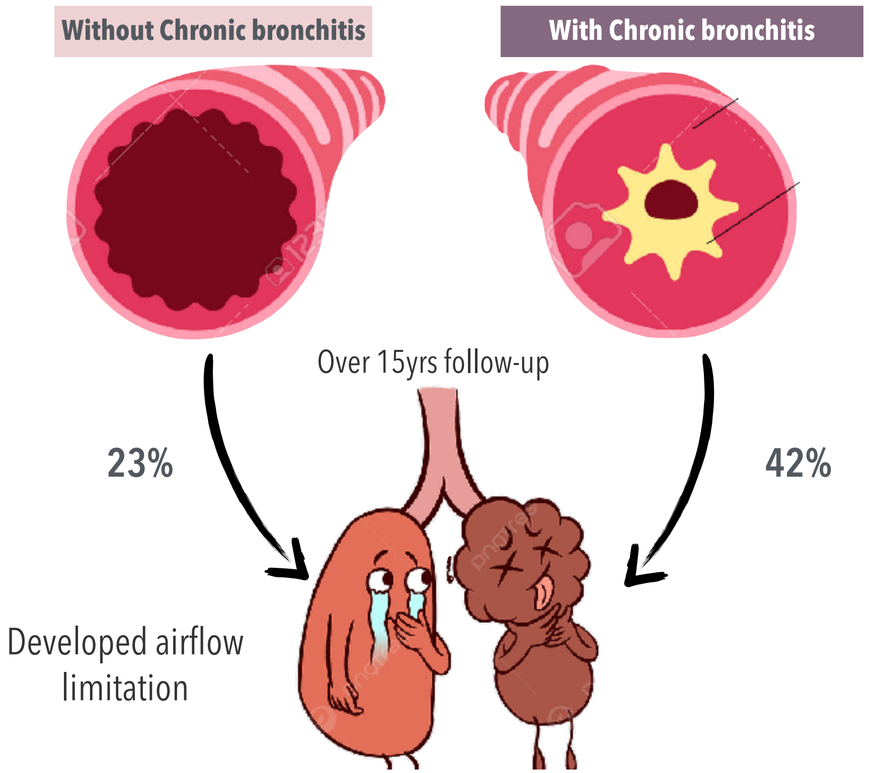
Wheeze,OR: 3.28



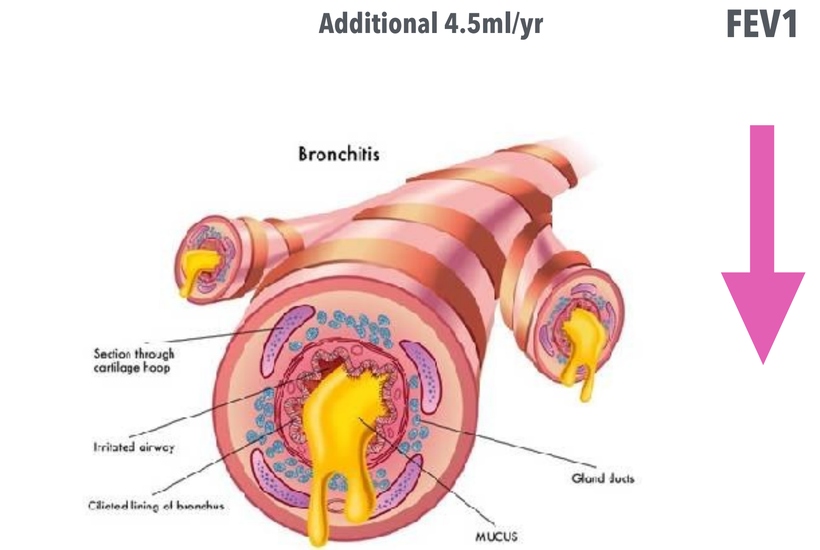
Ten-year cumulative incidence of COPD and risk factors for incident disease in a symptomatic cohort. Chest 2005; 127:1544–1552.

Pre-COPD

Symptoms as a Biomarkers of Disease Progression



Chronic bronchitis before age 50 years predicts incident airflow limitation and mortality risk. Thorax 2009;64:894–900



1946 National Survey of Health and Development

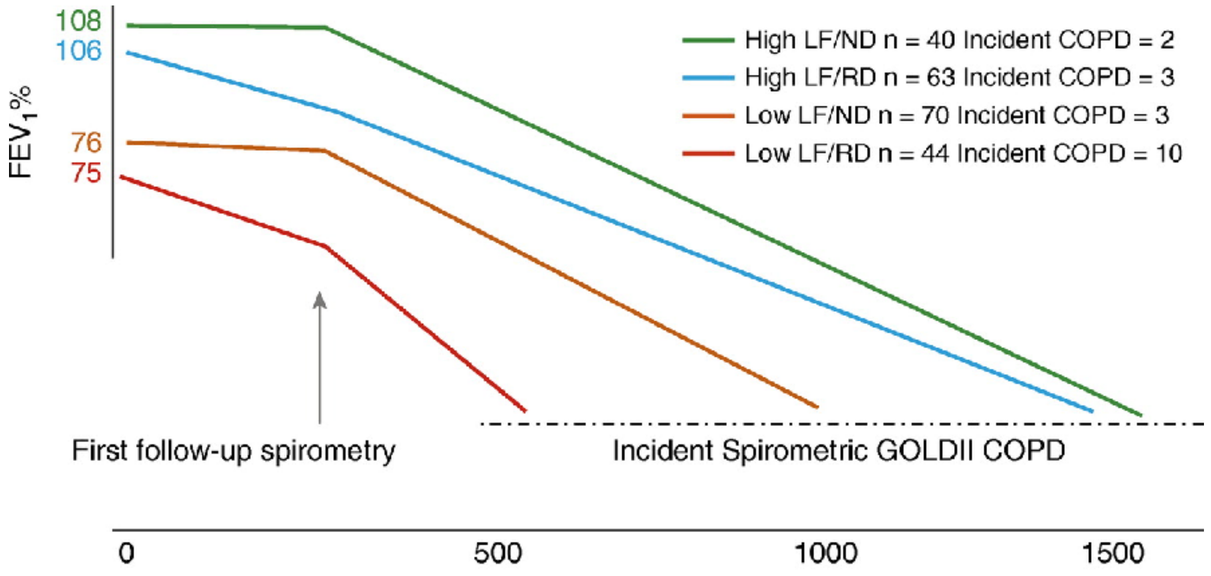
UKRI

The presence of chronic mucus hypersecretion across adult life in relation to chronic obstructive pulmonary disease development. Am J Respir Crit Care Med 2016;193:662–672.

Pre-COPD

Physiologic Measurements as Biomarkers of Disease Progression

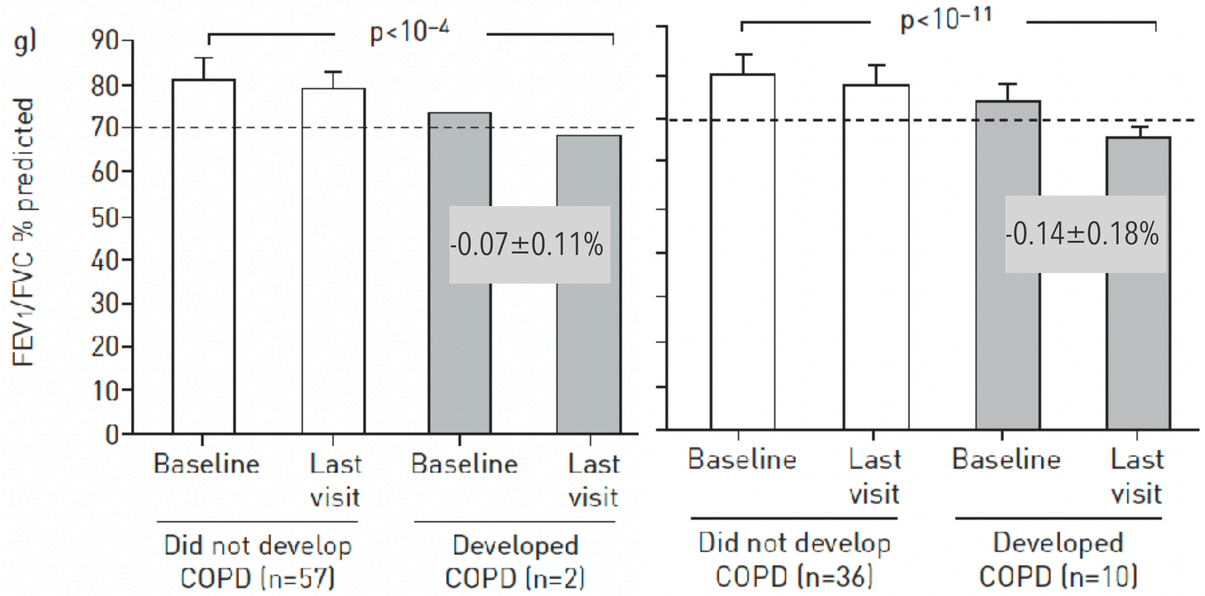
- Incident COPD occurred earlier in subjects with low lung function at baseline
- the hazard ratio was higher in subjects with low LF at baseline and rapid rate of decline



The course of lung function in middle-aged heavy smokers: incidence and time of early onset or chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2018;198:1449-1451

At Baseline
- Normal spirometry
- Normal DIco

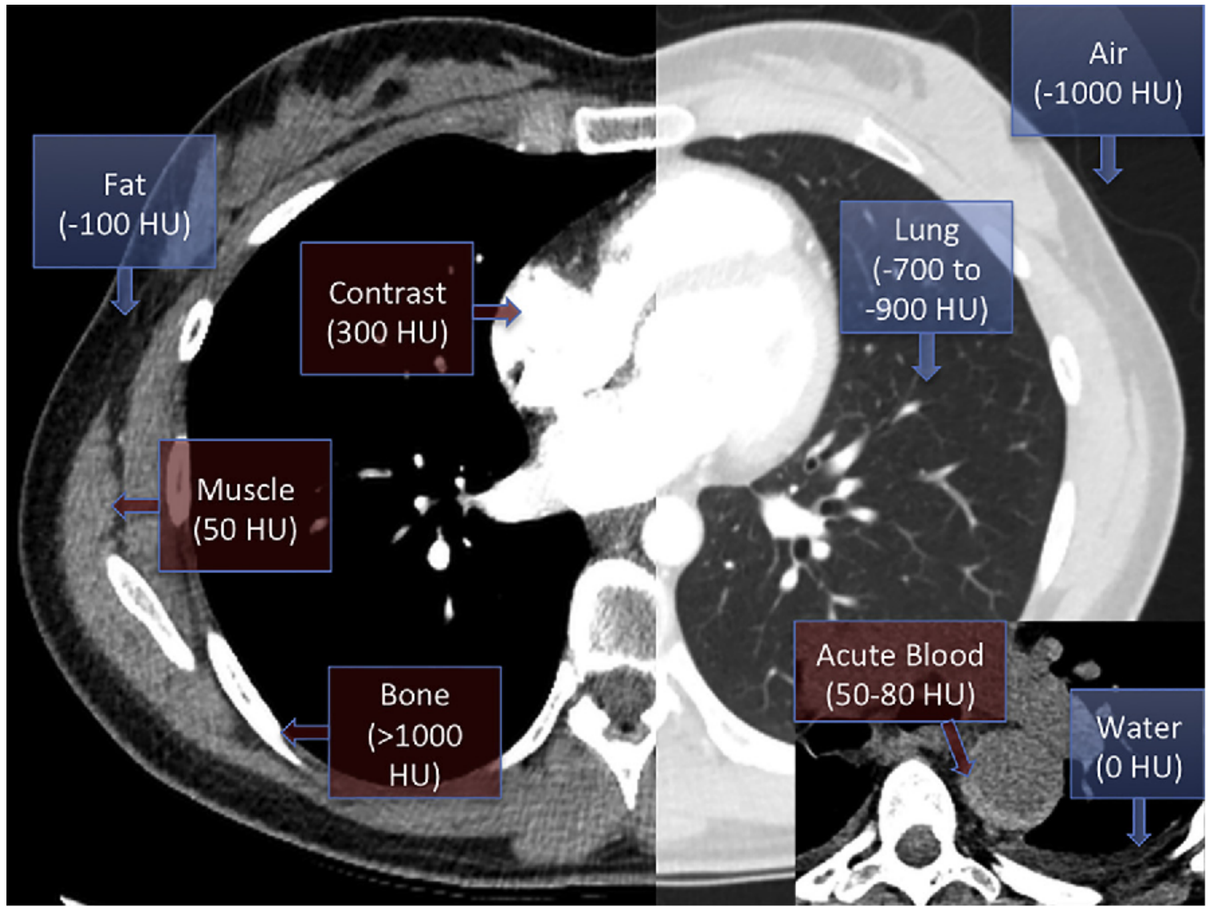
At Baseline
- Normal spirometry
- Low DIco

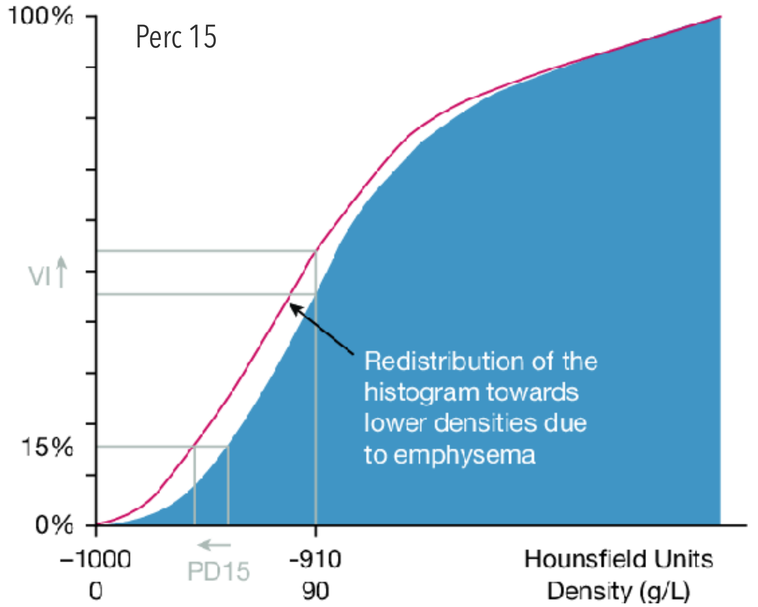


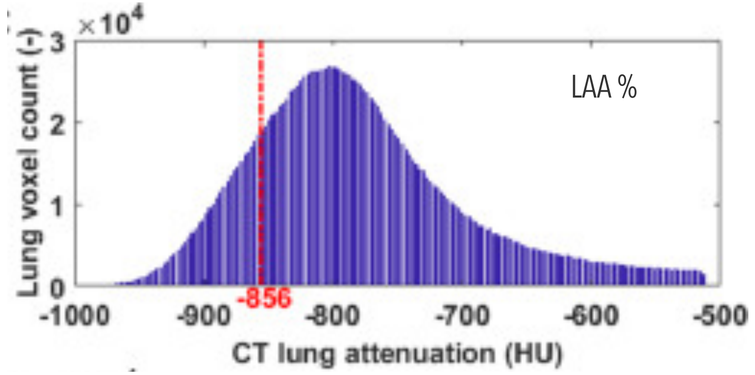
Risk of COPD with obstruction in active smokers with normal spirometry and reduced diffusion capacity. Eur Respir J 2015; 46:1589–1597.

Pre-COPD

Imaging Biomarkers of Disease Progression



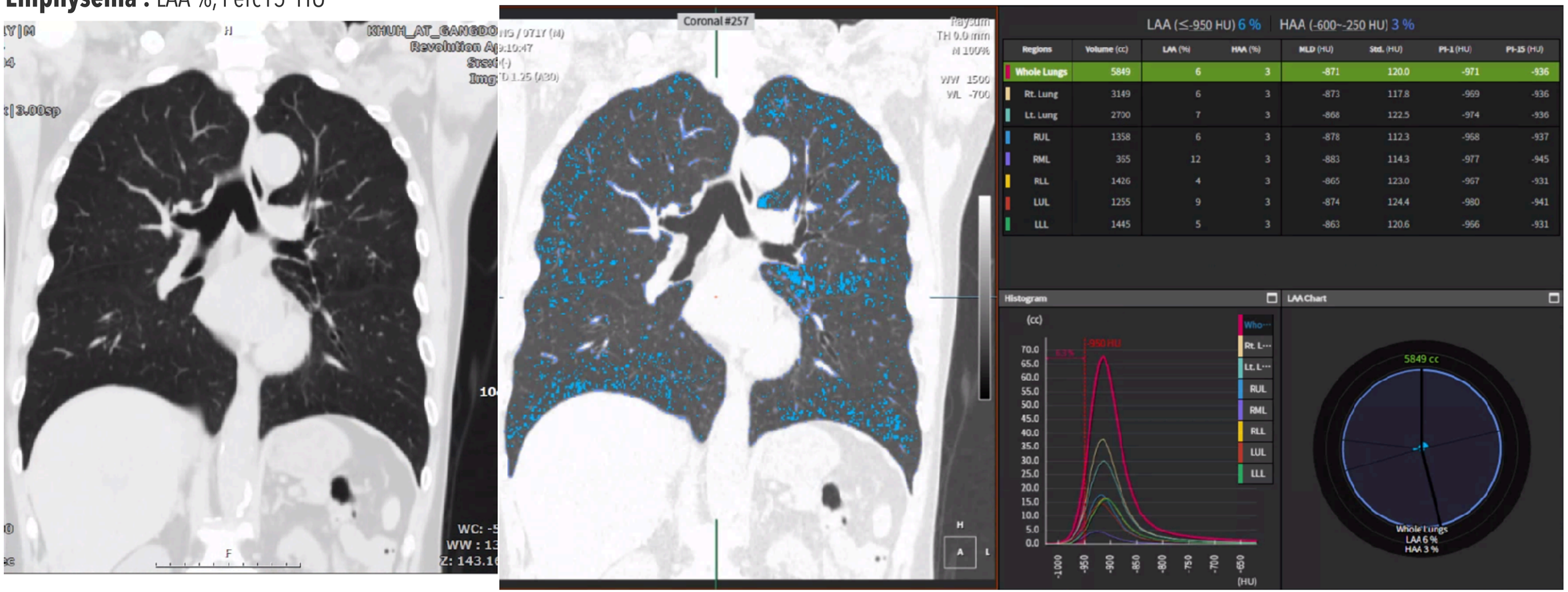




Pre-COPD

Imaging Biomarkers of Disease Progression

Emphysema : LAA %, Perc15 HU



Regions	Volume (cc)	LAA (%)	HAA (%)	MLD (HU)	Std. (HU)	PI-1 (HU)	PI-15 (HU)
Whole Lungs	5849	6	3	-871	120.0	-971	-936
Rt. Lung	3149	6	3	-873	117.8	-969	-936
Lt. Lung	2700	7	3	-868	122.5	-974	-936
RUL	1358	6	3	-878	112.3	-968	-937
RML	385	12	3	-883	114.3	-977	-945
RLL	1426	4	3	-865	123.0	-967	-931
LUL	1255	9	3	-874	124.4	-980	-941
LLL	1445	5	3	-863	120.6	-966	-931

Pre-COPD

Imaging Biomarkers of Disease Progressi

Table 2. Correlation Between FEV_1 and PD15 at Baseline and Decline in FEV_1 and PD15

Subgroup		n	Correlation Between FEV_1 and PD15 at Baseline (95% confidence interval)	*p*-value	Correlation Between Decline in FEV_1 and PD15 (95% confidence interval)	*p*-value
Cohort	DLCST	1178	0.171 (0.115-0.226)	**<0.001**	0.044 (-0.013-0.101)	0.133
	ECLIPSE	970	0.433 (0.381-0.483)	**<0.001**	0.111 (0.049-0.173)	**<0.001**
Sex	Male	1281	0.735 (0.709-0.759)	**<0.001**	0.098 (0.043-0.152)	**<0.001**
	Female	867	0.707 (0.672-0.739)	**<0.001**	0.055 (-0.012-0.121)	0.105
Smoking	Former	1033	0.746 (0.718-0.772)	**<0.001**	0.037 (-0.024-0.098)	0.231
	Current	1115	0.600 (0.561-0.636)	**<0.001**	0.100 (0.042-0.158)	**<0.001**
Spirometric GOLD stage	No	687	0.056 (-0.019-0.130)	<0.144	-0.061 (-0.139-0.017)	0.127
	I	317	0.047 (-0.063-0.157)	<0.400	0.094 (-0.019-0.204)	0.105
	II	630	0.394 (0.326-0.458)	**<0.001**	0.112 (0.037-0.185)	**0.003**
	III	406	0.197 (0.101-0.289)	**<0.001**	0.167 (0.070-0.260)	**<0.001**
	IV	108	0.099 (-0.091-0.283)	<0.306	0.148 (-0.024-0.312)	0.092
All		2148	0.716 (0.694-0.736)	**<0.001**	0.081 (0.038-0.122)	**<0.001**

Correlation between emphysema and lung function in healthy smokers and smokers with COPD. Chronic Obstr Pulm Dis (Miami) 2015;2:204–213.

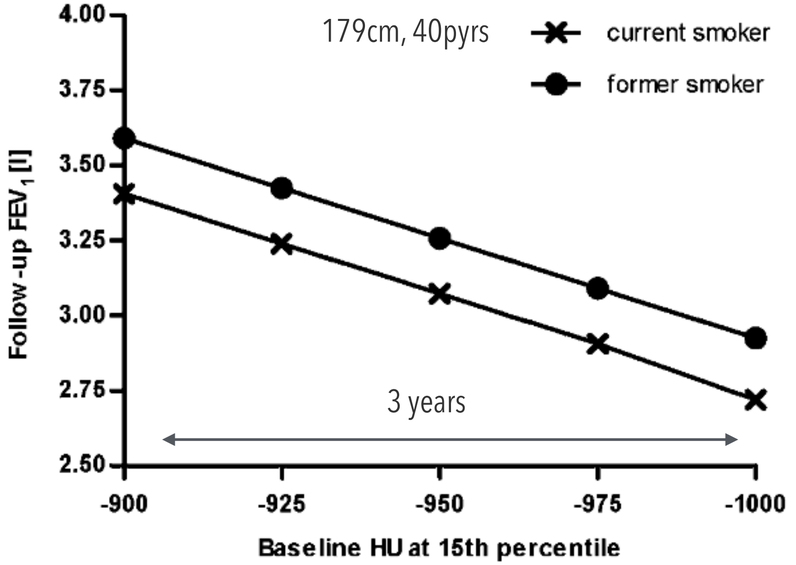


Table 3 Results of linear mixed models analysis for the cohort (change in FEV_1 per unit change in covariable)

Estimated effects of specified increments in covariables: changes in FEV_1 (ml)				
Covariate	**Increment or comparison**	**Change in FEV_1 per unit change in covariable**	**95% CI**	**p Value**
Study centre	Utrecht vs Groningen	+43.5	−100 to 13.8	0.137
Years in study	Plus 1 year	−65.6	− 69.4 to −61.6	<0.001
Smoking status	Current vs former	−186.7	−241.0 to −132.2	<0.001
Age (years)	Plus 1 year	−36.2	−41.3 to −31.1	<0.001
Height (cm)	Plus 1 cm	+38.6	34.7 to 42.7	<0.001
Pack-years	Plus 1 year	−5.16	−6.62 to −3.68	<0.001
HU 15th percentile at CT	Decrease of 1 HU	−4.75	−3.30 to −6.10	<0.001

FEV_1, forced expiratory volume in 1 s; HU, Hounsfield Unit.

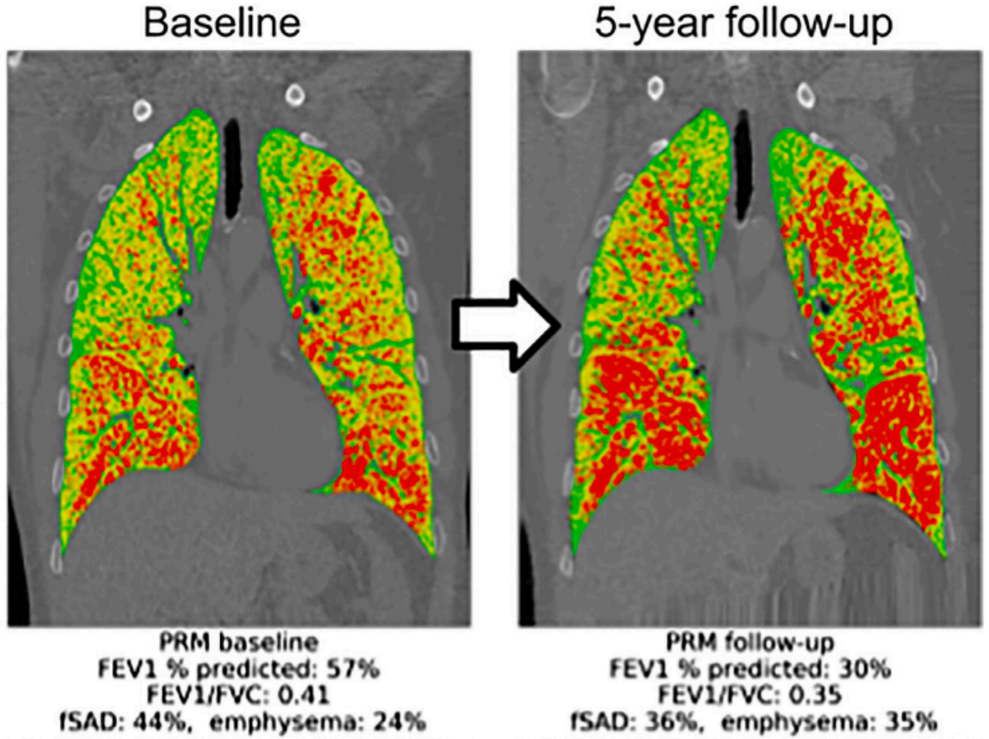
CT-quantified emphysema in male heavy smokers: association with lung function decline. Thorax 2011;66: 782–787

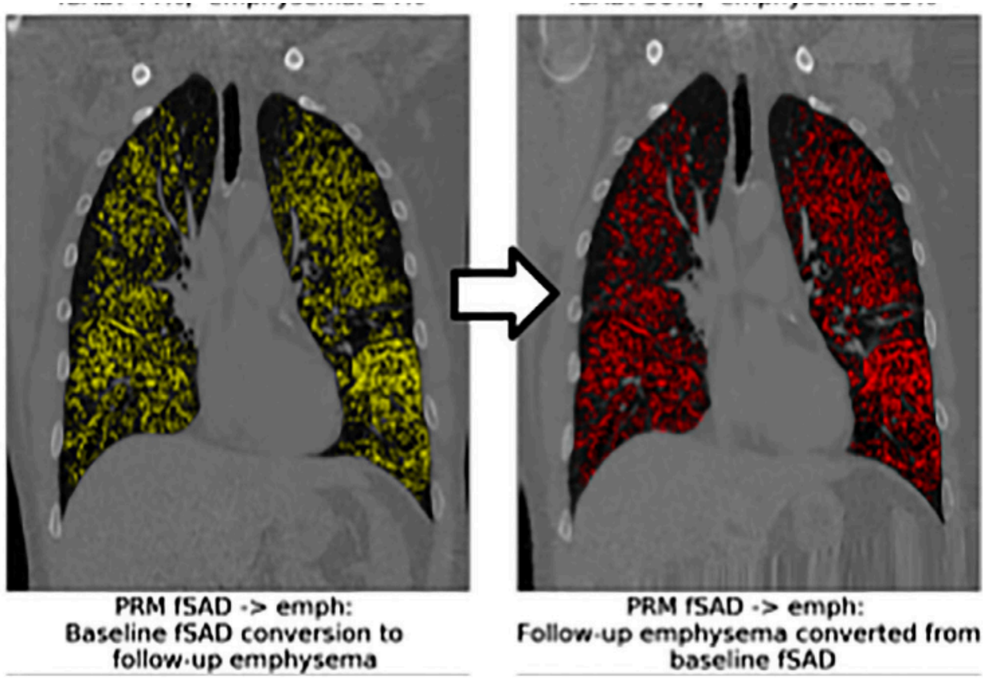
Pre-COPD

Imaging Biomarkers of Disease Progression

AIR-TRAPPING : < -856 HU on the expiration scan were classified as PRM^{fSAD} (functional small airway disease)

- normal lung parenchyma (green), functional small airway disease (fSAD; yellow) and emphysema (red)



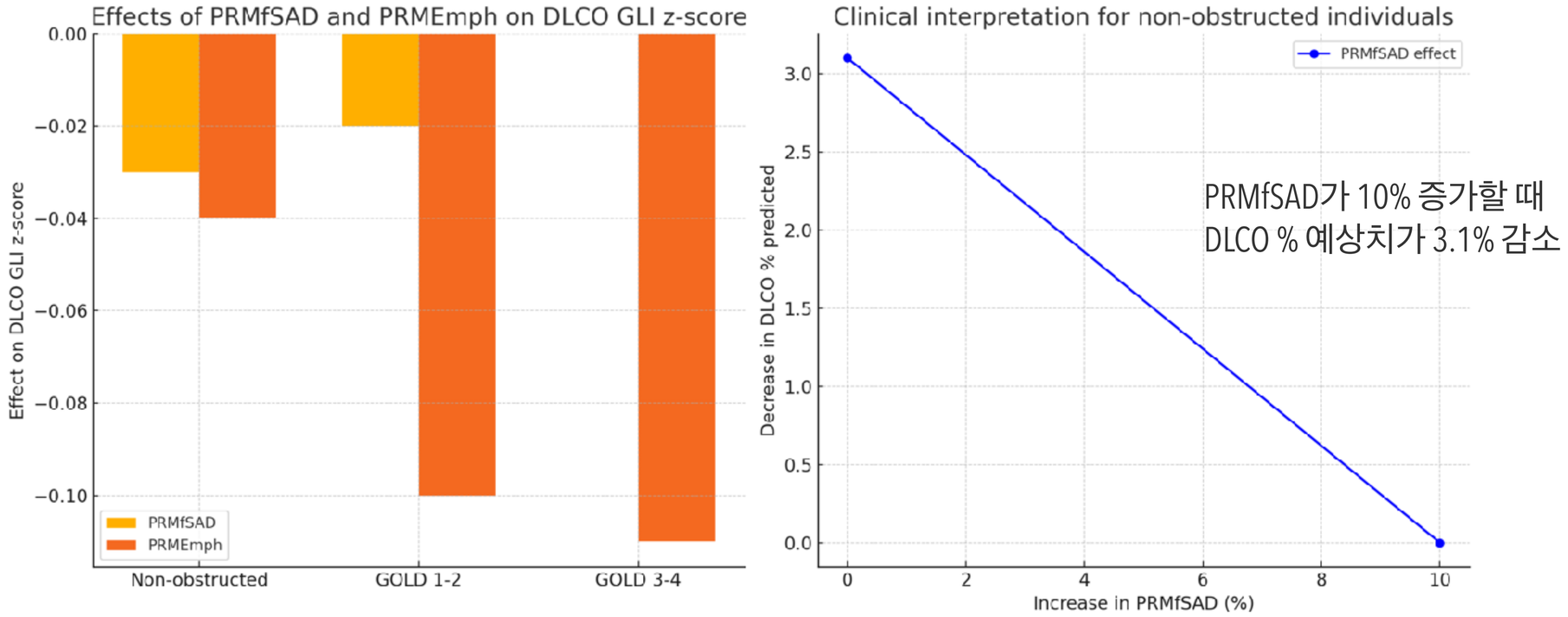


Voxel-wise longitudinal parametric response mapping analysis of chest computed tomography in smokers. Acad Radiol 2019;26: 217–223.

Pre-COPD

Imaging Biomarkers of Disease Progression

AIR-TRAPPING : < -856 HU on the expiration scan were classified as PRM^{fSAD} (functional small airway disease)



Relationship between diffusion capacity and small airway abnormality in COPDGene. Respir Res 2019;20:269.

Pre-COPD

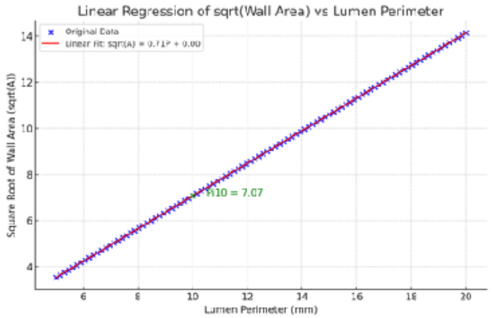
Imaging Biomarkers of Disease Progression

내강의 둘레측정

- 기도협착 : 내강의 둘레가 줄면 기관지가 좁아졌다는 것을 의미
- 환기평가 : 내강의 둘레= 기도 개방정도

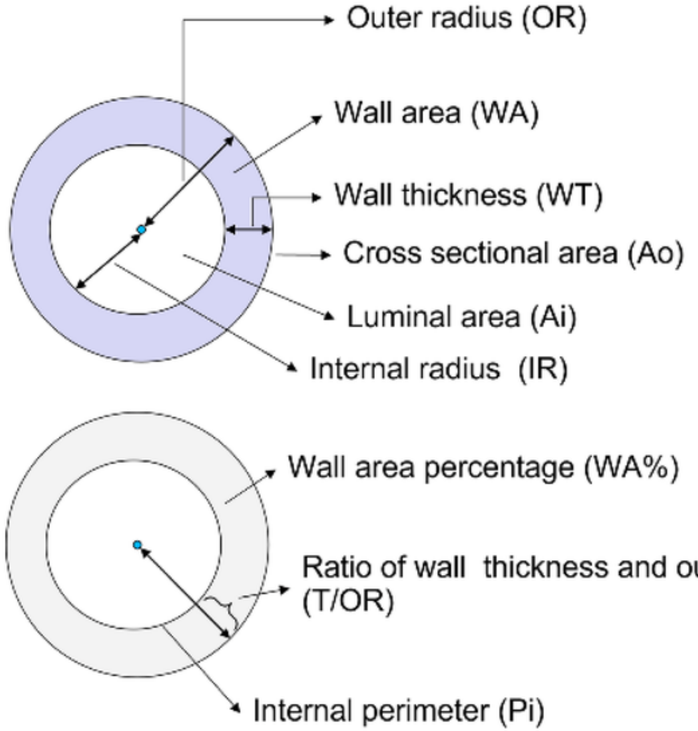
기관지벽두께 측정

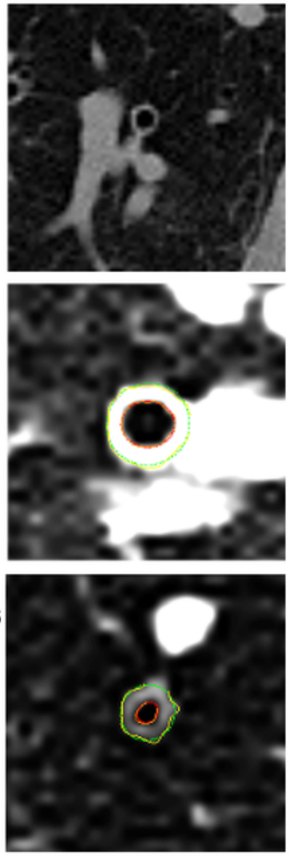
- 기관지벽 비후 : 염증및 섬유화의 징후



Pi10

- as a measurement of airway wall thickness.
- 벽 두께와 내강 둘레 사이의 관계를 선형화하기 위해 벽 면적의 값을 제곱근으로 변환
- (벽 면적 자체는 단면의 기하학적 특성에 따라 큰 변동을 보임)
- 내강의 둘레가 10mm일때 벽면적 제곱근 : 기관지벽의 두께를 일관되게 비교평가
- 값이 클수록 airway wall thickness 증가





Pre-COPD

Imaging Biomarkers of Disease Progression

Covariable	Increment or comparison	Changes in FEV_1 after follow-up per unit change in covariable β	95% CI	p-value
Years in study	+1 year	−38 mL	−60–−16	0.001
Baseline FEV_1	−10 mL	−8.8 mL	−8.6–−9.0	<0.001
Smoking status	Current *versus* former	−55 mL	−77–−33	<0.001
Age years	+1 year	−5 mL	−7–−3	<0.001
Height cm	+1 cm	+3 mL	1–5	0.006
Pack-years	+10 pack-years	−10 mL	−15–−5	<0.001
Pi_{10} mm	+1 mm	−34 mL	−56–−12	0.002
$Perc_{15}$ Hounsfield Units	10 Hounsfield Units lower	−10 mL	−15–−5	0.006

Pi_{10}: square root of wall area of a 10-mm lumen perimeter; $Perc_{15}$: 15th percentile method.

- a larger FEV1 decline or will develop airflow limitation.
- Pi10 (standized wall thickness) ∝ Development of airflow limitation
- both emphysema and airway wall thickness are independently associated with a lower FEV1 after an average 3-year follow-up period

Airway wall thickness associated with forced expiratory volume in 1 second decline and development of airflow limitation. Eur Respir J 2015;45:644–65

- early changes in airway morphology predict
- risk of chronic lower respiratory disease and that Pi10 and other CT measures of large airway dimensions at 5-year follow-up

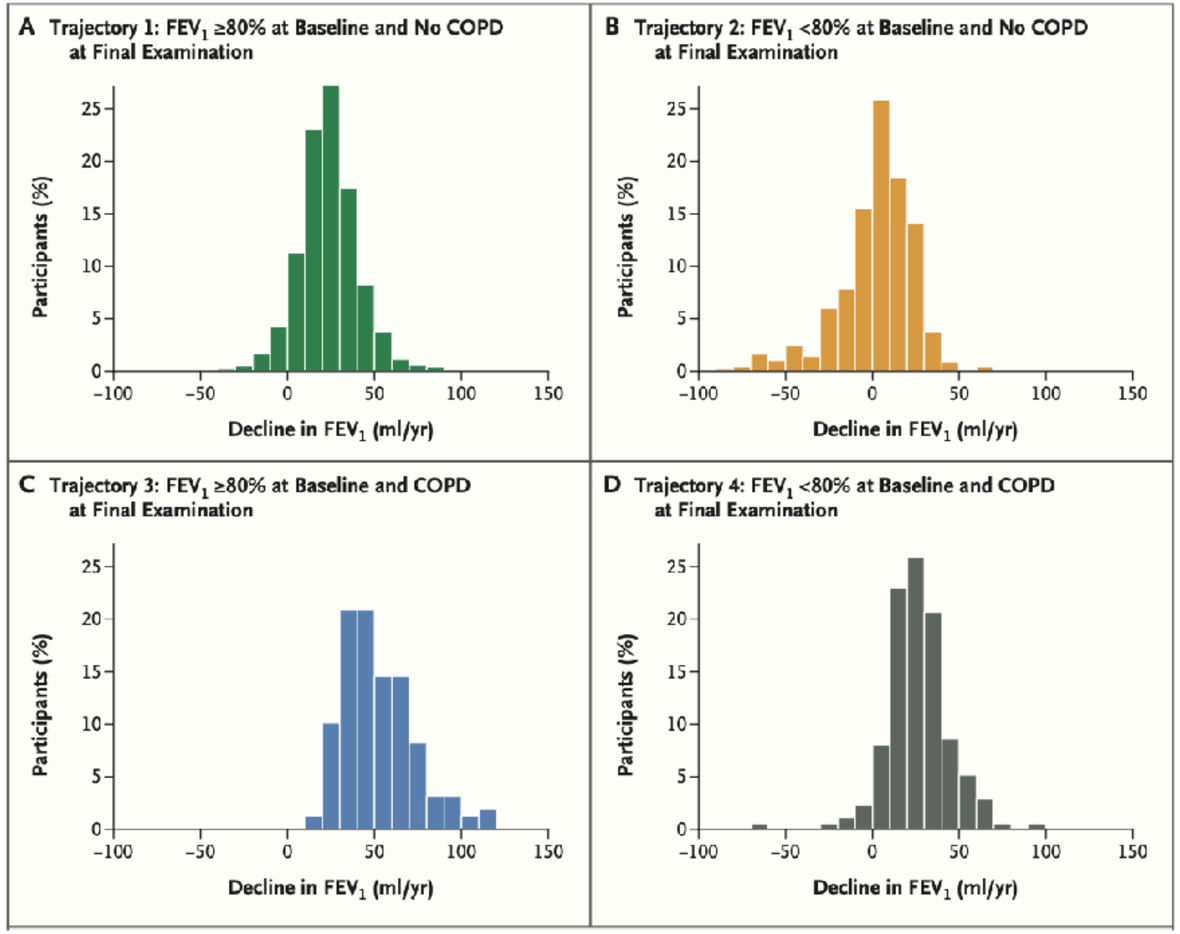
Prognostic significance of large airway dimensions on computed tomography in the general population: the Multi-Ethnic Study of Atherosclerosis (MESA) lung study. Ann Am Thorac Soc 2018;15:718–727.

	Annual Change in FEV_1* (*ml*) (*n* = 1,830)		Incident COPD† (*n* = 1,717) Cases (*n* = 40 [2.3%])		CLRD Hospitalization/Mortality‡ (*n* = 6,029) Events (*n* = 84 [1.4%])	
Model	B per SD§ (95% CI)	*P* Value	OR per SD§ (95% CI)	*P* Value	HR per SD§ (95% CI)	*P* Value
Pi10, sequential adjustment‖						
Unadjusted	−2.46 (−4.32, 0.60)	0.010	1.49 (1.11, 2.01)	0.009	1.33 (1.17, 1.52)	<0.001
Partially adjusted	−2.45 (−4.26, −0.64)	0.008	1.71 (1.24, 2.35)	0.001	1.30 (1.13, 1.50)	<0.001
Fully adjusted	−2.47 (−4.28, −0.66)	0.008	1.87 (1.26, 2.78)	0.002	1.38 (1.20, 1.60)	<0.001
Genetic risk adjusted	−2.66 (−4.54, −0.79)	0.005	2.21 (1.47, 3.33)	<0.001	1.41 (1.22, 1.63)	<0.001
FEV_1 adjusted	−2.45 (−4.36, −0.55)	0.0118	2.22 (1.43, 3.45)	<0.001	1.57 (1.00, 2.45)	0.0496
Directly measured airway dimensions, fully adjusted¶						
Lumen diameter	−0.58 (−2.64, 1.48)	0.582	0.37 (0.25, 0.56)	<0.001	0.75 (0.59, 0.96)	0.023
AWT	−1.95 (−3.98, 0.07)	0.059	1.97 (1.25, 3.10)	0.004	1.34 (1.01, 1.78)	0.040

Pre-COPD

Patterns of Progression: Lung Function Trajectories

- Mean decline in FEV1 : 23ml/yr

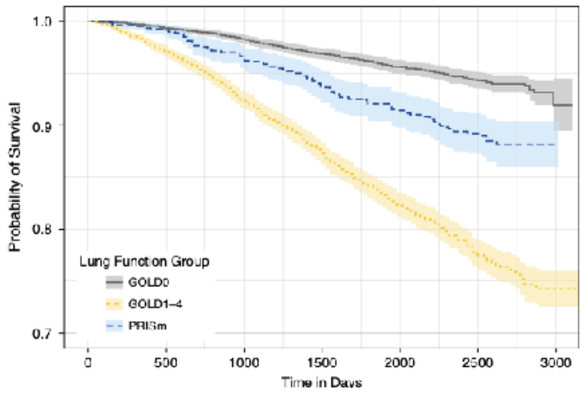


- Mean decline in FEV1 : 2ml/yr
- Mean decline in FEV1 : 53ml/yr
- Mean decline in FEV1 : 27ml/yr

Lung-function trajectories leading to chronic obstructive pulmonary disease. N Engl J Med 2015;373:111–122.

Pre-COPD

Patterns of Progression: Lung Function Trajectories



A

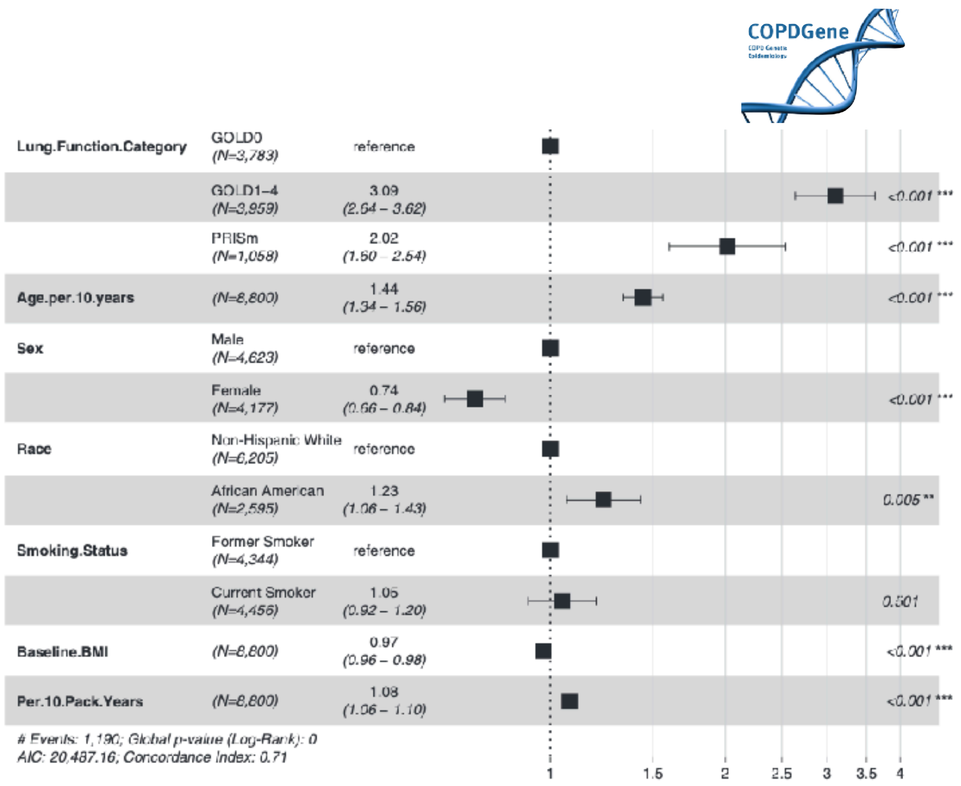
Phase 1*	Phase 2*	N	%
PRISm	GOLD 0	152	22.2%
	COPD (GOLD 1–4)	172	25.1%
	PRISm	360	52.6%

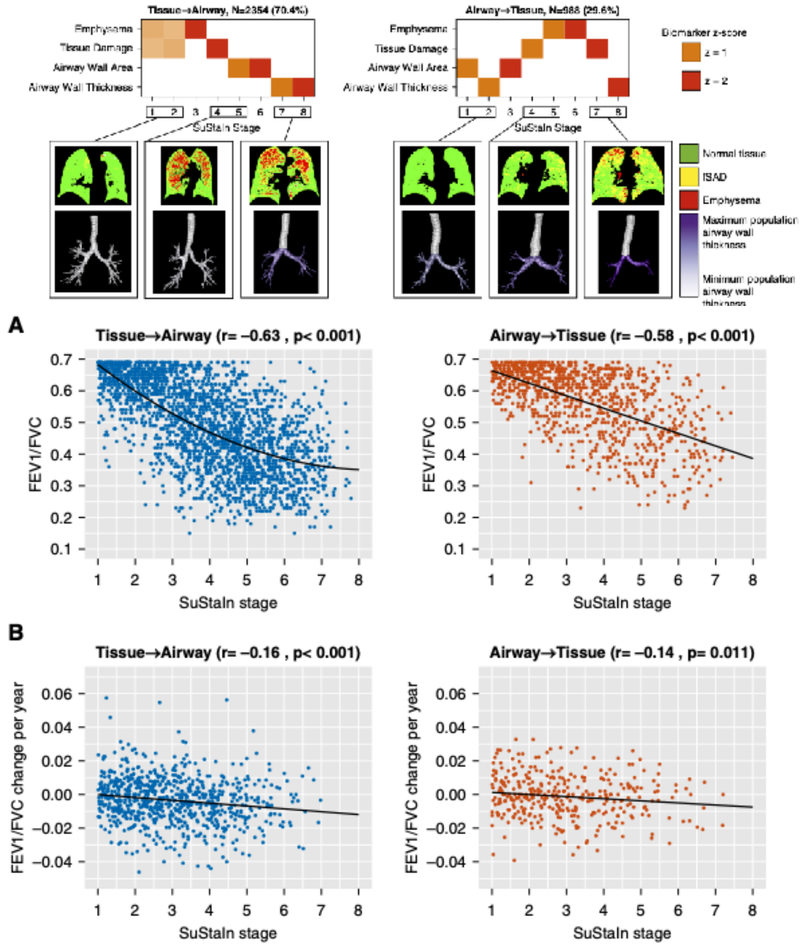
*Among participants with lung function data at both Phase 1 and Phase 2

B

Phase 1*	N	%	Phase 2*
PRISm	360	51.9%	PRISm
GOLD 0	223	32.1%	
COPD (GOLD 1–4)	111	16%	

*Among participants with lung function data at both Phase 1 and Phase 2





Pre-COPD

From GOLD Stage 0 to Pre-COPD

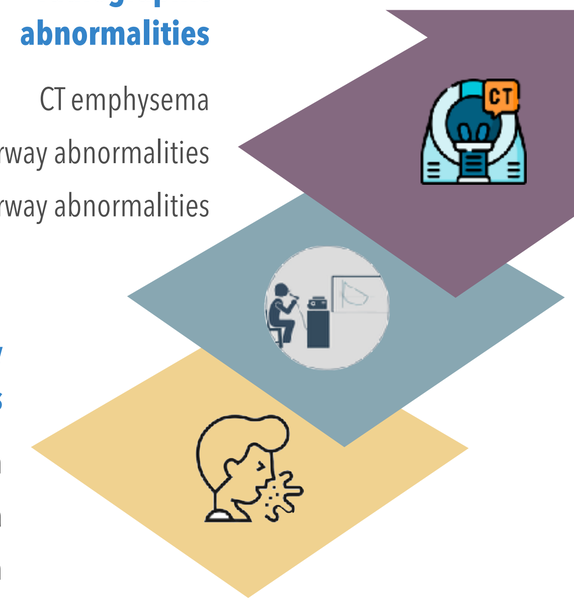
Pre-COPD

radiographic abnormalities

CT emphysema

Small airway abnormalities

Large airway abnormalities



Respiratory symptoms

Cough with sputum production

Dyspnea

Exacerbation

physiologic abnormalities

Low DLCO

Hyperinflation

Small airways obstruction

Accelerated FEV1 decline

GOLD stage 0

Pre-COPD

Key Takeaways

- Current COPD Definition
  - It may not capture early disease abnormalities.
  - Sensitivity Issues: Early-stage COPD may not show reduced FEV1/FVC ratio.
- Introduction of Pre-COPD
  - Pre-COPD refers to individuals without airflow obstruction detectable by spirometry but at risk of developing COPD.
  - Early identification is crucial for disease management and prevention.
- Importance of Recognizing Pre-COPD
  - Symptoms in pre-COPD and NOCB are significant.
  - Recognizing these conditions can lead to better patient outcomes.
- Biomarkers in Pre-COPD
  - CT :
    - small airway disease and early emphysema detection
    - Airway wall thickening and gas trapping
  - PFT : DIco

Multi-faced assessment for diagnosis

임상평가

- Sx assessment
- Risk factor identification : smoking, environment

PFT

- Spirometry
- Lung Volume : TLC,RV
- Diffusion capacity : DIco

Biomarker

- Blood test : Eosinophil, CRP, fibrinogen, inflammatory markers
- Exhaled breath analysis: FENO
- Genetic test : genetic predispositions, polymorphisms

CT image

- 폐의 작은 기도 병변, 초기 폐기종, 기타 실질 변화 등의 구조적 변화를 감지

Advanced Tools:

- BFS : airway, tissue biopsy
- Sputum analysis : for inflammatory cells, pathogens

Clinical assessment

CAT (COPD Assessment Test)

- COPD 환자의 증상과 삶의 질을 평가하기 위한 도구,
- 환자의 건강 상태를 객관적으로 파악하고 치료 계획을 세우는 데 도움
- CAT 점수는 총 8개의 질문으로 구성
- 각 질문은 0점(문제 없음)에서 5점(매우 심각함)까지의 점수로 평가

자신감 감소
집밖에서 활동할때
얼마나 자신감이 있는지 평가

수면곤란
밤에 잘자는지
수면에 어려움이 있는지 평가

집안활동곤란
집안일이나 청소등 일상활동을 할때
얼마나숨이 차는지 평가

기침
기침의 빈도와 심각도를 평가

숨가쁨
언덕을 오르거나 계단을 오를때
숨이 얼마나 가쁜지 평가

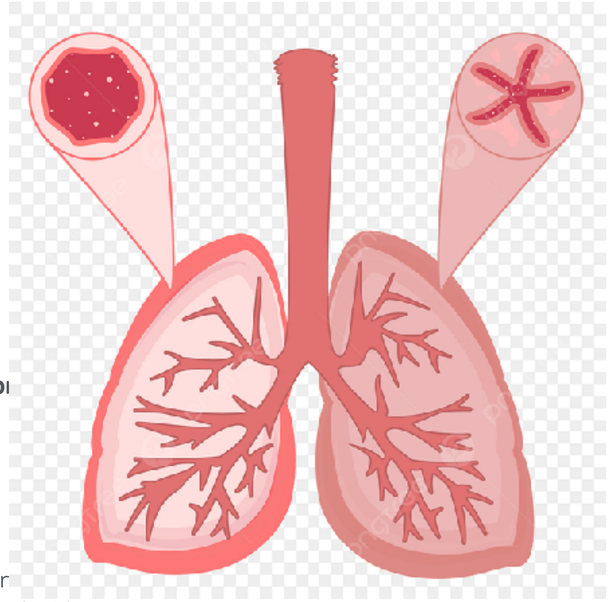
가래
가래의 양과 그로 인한 불편감을 평가

가슴답답함
가슴이 얼마나 답답한지

에너지저하
하루종일 얼마나 에너지가 있는지 평가

- **1-10점 (경증):** 증상이 경미하고 환자의 일상 생활에 미치는 영향이 적음
- **11-20점 (중등도):** 증상이 중등도이며 일상 생활에 어느 정도 영향을 미침.
- **21-30점 (중증):** 증상이 중증이며 환자의 일상 생활과 활동에 큰 영향을 미침.
- **31-40점 (매우 중증):** 증상이 매우 중증이며, 환자의 삶의 질에 심각한 영향을 미침

Symptom phenotypes of COPD



ARIC (Atherosclerosis Risk in Co

ARIC

HR, 1.6 for death among par
GOLD stage 0 as compared with
unobstructed individuals without symptoms

A. Global Initiative on Obstructive Lung Disease (GOLD) classification of lung disease and mortality: findings from the Atherosclerosis Risk in Communities (ARIC) study. Respir Med 2006;100:115–122