

COPD School 2021

Redefining of COPD

김우진
강원의대 내과

- Definition

- Risk factor

- Respiratory symptom

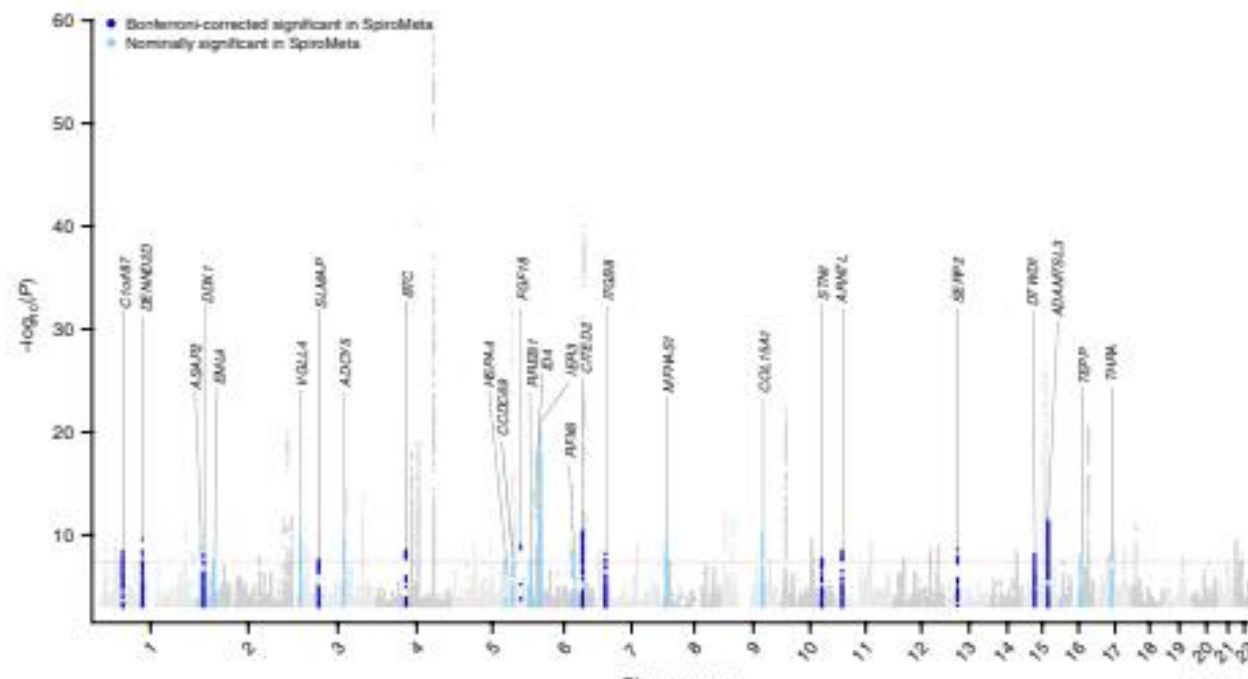
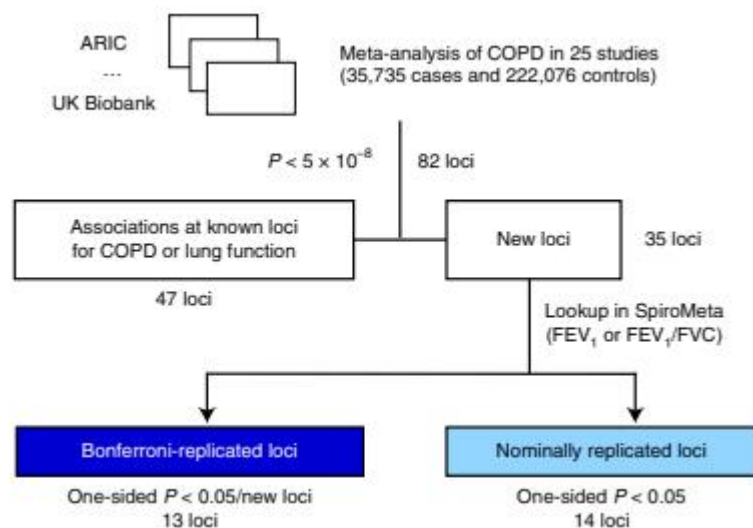
- Structure

- Lung function

COPD definition by GOLD 2021

- Common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases and influenced by host factors including abnormal lung development.

Genetic landscape of chronic obstructive pulmonary disease identifies heterogeneous cell-type and phenotype associations



Associated pathways

Original gene set	Original gene set	Nominal P	False discovery
GO:0048732	gland development	1.22E-07	<0.01
GO:0030323	respiratory tube development	3.12E-07	<0.01
GO:0005604	basement membrane	3.91E-07	<0.01
GO:0035295	tube development	4.31E-07	<0.01
GO:0048729	tissue morphogenesis	4.49E-07	<0.01
GO:0030055	cell-substrate junction	4.79E-07	<0.01
GO:0005925	focal adhesion	6.16E-07	<0.01

Gene sets significantly enriched at FDR < 0.05 using DEPICT

Lung Development Genes and Adult Lung Function

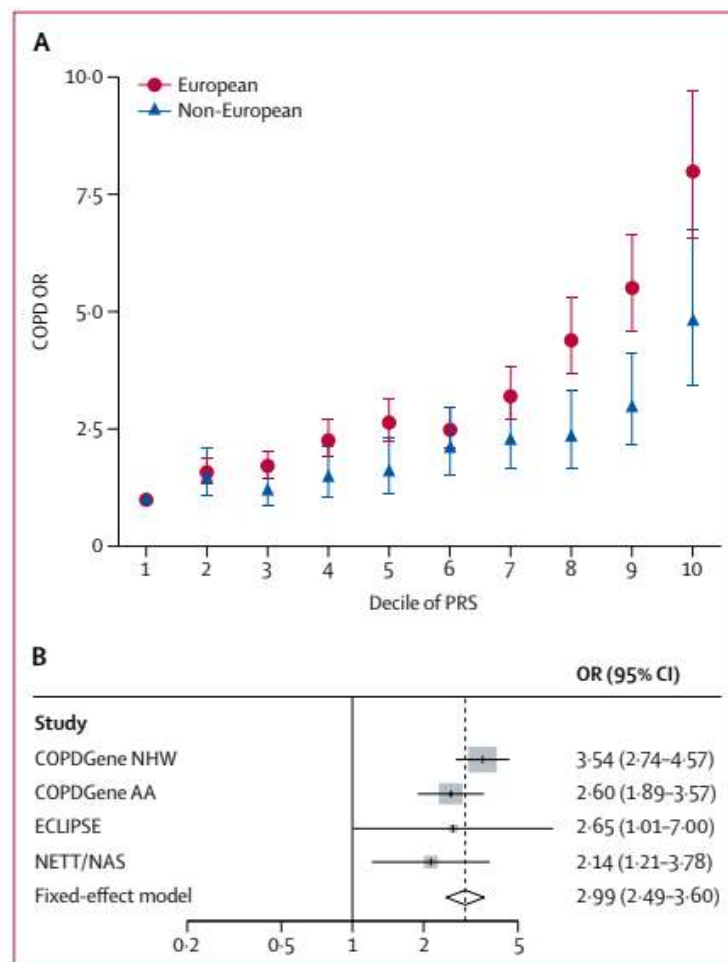
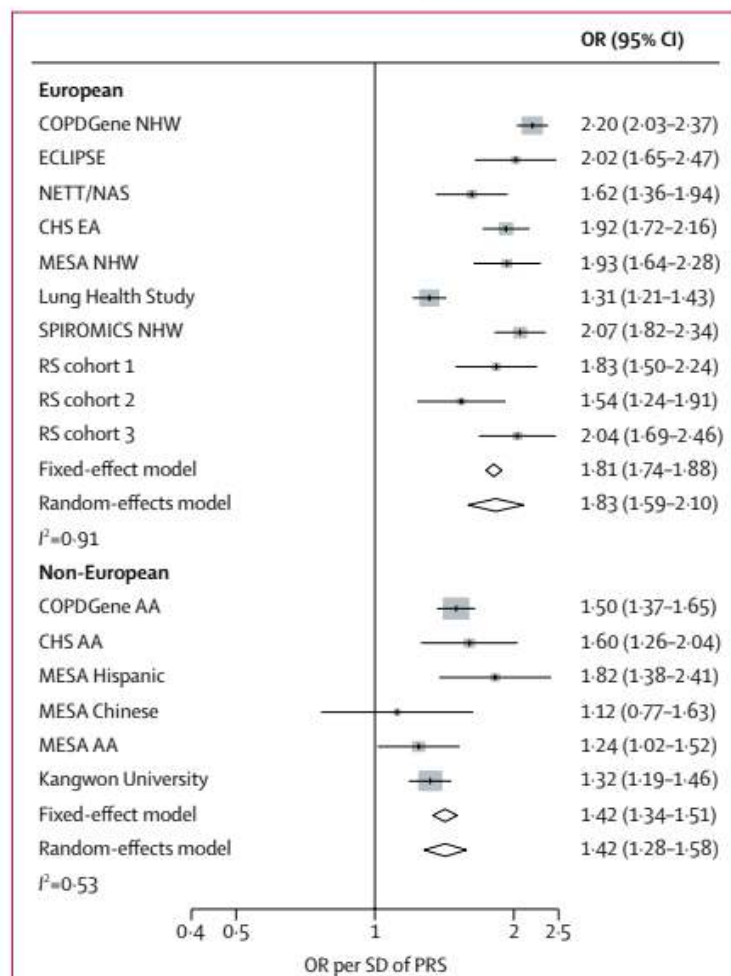
Laura Portas^{1*}, Miguel Pereira^{1,2*}, Seif O. Shaheen³, Annah B. Wyss⁴, Stephanie J. London⁴, Peter G. J. Burney¹, Matthew Hind^{1,5‡}, Charlotte H. Dean^{1,6‡}, and Cosetta Minelli^{1‡}

¹National Heart and Lung Institute, Imperial College London, London, United Kingdom; ²Congenica Ltd., Wellcome Genome Campus, Cambridge, United Kingdom; ³Institute of Population Health Sciences, Queen Mary University of London, London, United Kingdom; ⁴Department of Health and Human Services, National Institute of Environmental Health Sciences, NIH, Research Triangle Park, North Carolina; ⁵Department of Respiratory Medicine, Royal Brompton & Harefield NHS Foundation Trust, London, United Kingdom; and ⁶MRC Harwell Institute, Oxfordshire, United Kingdom

Growth factors					
CSNK2B	Casein kinase 2 β	Ubiquitous protein kinase that regulates metabolic pathways, signal transduction, transcription, translation, and replication			
FGFR3	Fibroblast growth factor receptor 3	Encodes a tyrosine kinase and cell surface receptor for fibroblast growth factors			
FGFR4	Fibroblast growth factor receptor 4	Encodes a tyrosine kinase and cell surface receptor for fibroblast growth factors			
GSK3B	Glycogen synthase kinase 3 β	Encodes a serine-threonine kinase belonging to the glycogen synthase kinase subfamily			
PDGFB	Platelet-derived growth factor subunit B	Encodes a member of the protein family comprised of PDGFs			
ROR2	Receptor tyrosine kinase like orphan receptor 2	Encodes a receptor protein tyrosine kinase and a type I transmembrane protein that belongs to the ROR subfamily of cell surface receptors			
SFRP2	Secreted frizzled related protein 2	Encodes a member of the SFRP family that acts as soluble modulators of Wnt signaling			
TCF7L1	Transcription factor 7-like 1	Encodes a member of the T-cell factor/lymphoid enhancer factor family of transcription factors			
WNT2B	Wnt family member 2	Member of the WNT gene family			
WNT7A	Wnt family member 7A	Member of the WNT gene family			
WNT9A	Wnt family member 9A	Member of the WNT gene family			
			Extracellular matrix		
			ELN	Elastin	Encodes a protein that is one of the two components of elastic fibers
			ITGB5	Integrin subunit β 5	Encodes the integrin β subunit 5 protein
			MMP24	Matrix metalloproteinase 24	Encodes a member of the peptidase M10 family of MMPs
			SERPINC1	Serpin family C member 1	Encodes a plasma protease inhibitor and a member of the serpin superfamily
			SERPING1	Serpin family G member 1	Encodes a highly glycosylated plasma protein involved in the regulation of the complement cascade
			ITGAV	Integrin subunit α V	Encodes a member of the integrin α chain family
			MMP15	Matrix metalloproteinase 15	Encodes a member of the peptidase M10 family and membrane-type subfamily of MMPs
			Oxidative stress and endothelial dysfunction		
			AGER	Advanced glycosylation end-product (AGE) specific receptor	Multiligand receptor; role in chronic vascular injury
Transcriptional regulators			Immune response and surfactant regulation		
GFI1	Growth factor independent 1 transcriptional repressor	Encodes a nuclear zinc-finger protein that functions as a transcriptional repressor	SFTPD	Surfactant protein D	The protein encoded is part of the innate immune response and has a role in surfactant regulation
HOXA1	Homeobox A1	Encodes a DNA-binding transcription factor involved in spatial patterning in development			
HOXB4	Homeobox B4	Encodes a DNA-binding transcription factor involved in spatial patterning in development			
KAT7	Lysine acetyltransferase 7	Encodes a protein that is part of the multimeric HBO1 complex and possesses histone H4-specific acetyltransferase activity; this activity regulates gene transcription (e.g., VEGFR2, by influencing chromatin conformation)			
KAT8	Lysine acetyltransferase 8	Encodes a member of the MYST histone acetylase protein family; the encoded protein regulates gene transcription by influencing chromatin conformation			
NCOR2	Nuclear receptor corepressor 2	Encodes a protein that regulates repression of thyroid-hormone and retinoic-acid receptors			
NFATC3	Nuclear factor of activated T cells 3	Encodes a member of the nuclear factors of activated T cells family of transcription factors			
NR3C1	Nuclear receptor subfamily 3 group C member 1	Encodes glucocorticoid receptor			
PPARD	Peroxisome proliferator-activated receptor delta	Encodes a member of the PPAR family that is believed to function as an integrator of transcriptional repression and nuclear receptor signaling			
RARA	Retinoic acid receptor α	Encodes the retinoic acid receptor α that acts as a ligand-activated transcription factor			
RUNX1	Runt-related transcription factor 1	Encodes for a member of the runt family of transcription factors that regulate hematopoiesis and skeletal development			
RUNX3	Runt-related transcription factor 3	Encodes for a member of the runt family of transcription factors that regulate hematopoiesis and skeletal development			
SOX9	SRY-box 9	The protein encoded is an HMG box DNA-binding protein			

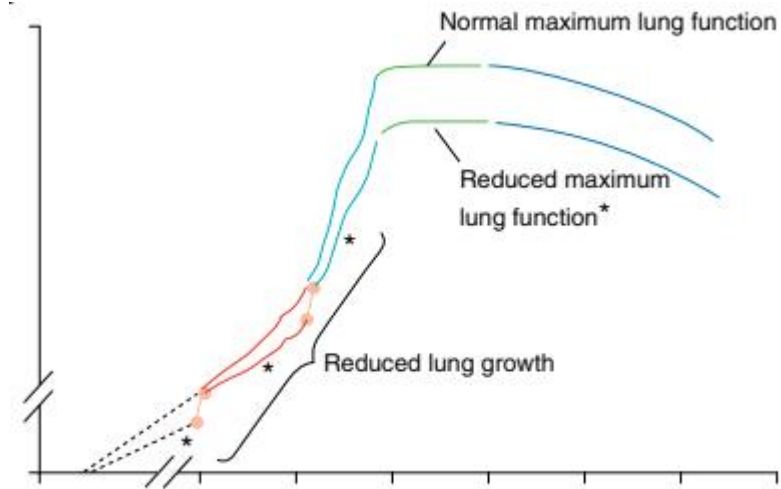
Chronic obstructive pulmonary disease and related phenotypes: polygenic risk scores in population-based and case-control cohorts

Matthew Moll*, Phuwant Sakornsakolpat*, Nick Shrine, Brian D Hobbs, Dawn L DeMeo, Catherine John, Anna L Guyatt, Michael J McGeachie, Sina A Gharib, Ma'en Obeidat, Lies Lahousse, Sara R A Wijnant, Guy Brusselle, Deborah A Meyers, Eugene R Bleeker, Xingnan Li, Ruth Tal-Singer, Ani Manichaikul, Stephen S Rich, Sungho Won, Woo Jin Kim, Ah Ra Do, George R Washko, R Graham Barr, Bruce M Psaty, Traci M Bartz, Nadia N Hansel, Kathleen Barnes, John E Hokanson, James D Crapo, David Lynch, Per Bakke, Amund Gulsvik, Ian P Hall, Louise Wain, International COPD Genetics Consortium†, SpiroMeta Consortium†, Scott T Weiss, Edwin K Silverman, Frank Dudbridge, Martin D Tobin‡, Michael H Cho‡



Risk factors

- Cigarette smoking
- Occupational risk
- Reduced maximal lung function



Characteristics of Patients with Chronic Obstructive Pulmonary Disease Exposed to Different Environmental Risk Factors: A Large Cross-Sectional Study

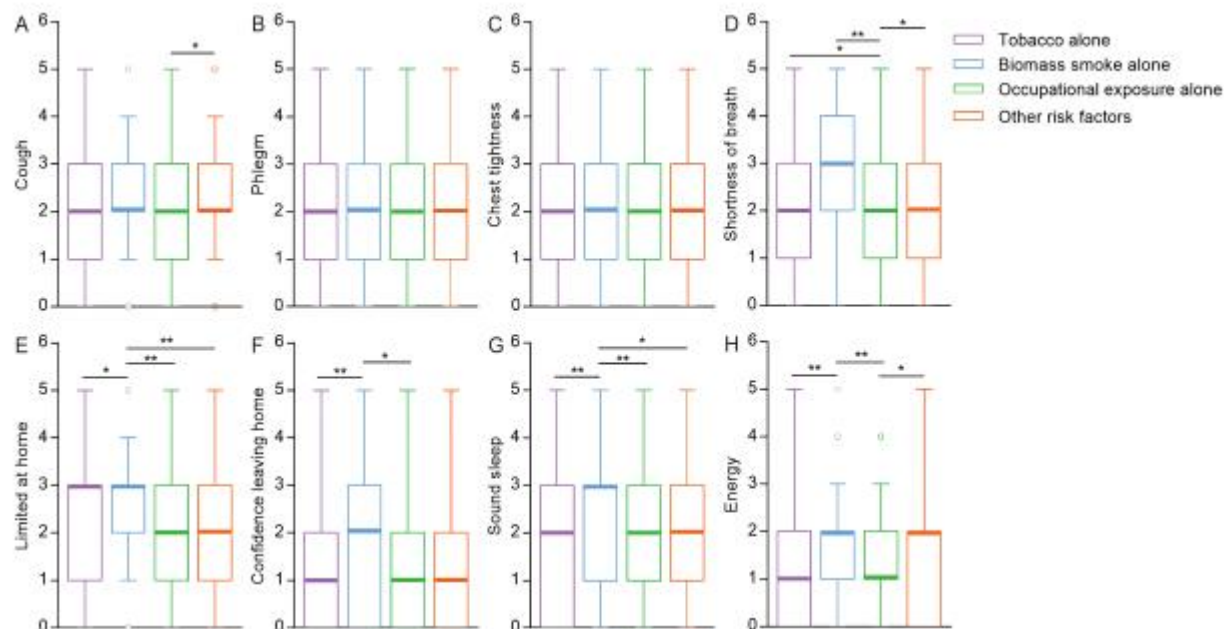


Table 3 Comparison of the Characteristics in the Subgroups of COPD Patients Exposed to Tobacco Alone, Biomass Smoke Alone, Occupational Exposure Alone, and Other Risk Factors

	Tobacco Alone (n = 1520)	Biomass Smoke Alone (n = 423)	Occupational Exposure Alone (n = 527)	Other Risk Factors (n = 545)
Age (years), mean (SD)	64.6 (8.2)	65.8 (8.5) ^a	58.3 (8.9) ^{ab}	63.1 (10.1) ^{abc}
Sex, N (%)				
Male	1498 (98.6)	129 (30.5) ^a	454 (86.1) ^{ab}	302 (55.4) ^{abc}
Female	22 (1.4)	294 (69.5) ^a	73 (13.9) ^{ab}	243 (44.6) ^{abc}
BMI (kg/m ²), N (%)				
< 24	1024 (67.4)	290 (68.6)	362 (68.7)	353 (64.8)
≥ 24	496 (32.6)	133 (31.4)	165 (31.3)	192 (35.2)
Education, N (%)				
Middle school or less	1047 (68.9)	399 (94.1) ^a	465 (88.2) ^{ab}	419 (76.9) ^{abc}
High school or upper	473 (31.1)	25 (5.9) ^a	62 (11.8) ^{ab}	126 (23.1) ^{abc}
Marital status, N (%)				
Unmarried	13 (0.9)	2 (0.5)	7 (1.3)	4 (0.7)
Married	1507 (99.1)	421 (99.5)	520 (98.7)	541 (99.3)
CAT, mean (SD)	15.3 (6.3)	17.5 (6.3) ^a	15.2 (6.3) ^b	16.3 (6.6) ^{abc}
mMRC, N (%)				
0-1	583 (38.4)	109 (25.8) ^a	154 (29.2) ^a	214 (39.3) ^{bc}
2-4	937 (61.6)	314 (74.2) ^a	373 (70.8) ^a	331 (60.7) ^{bc}
Previous exacerbations, N (%)				
< 2	1075 (70.7)	233 (55.1) ^a	275 (52.2) ^a	408 (74.9) ^{bc}
≥ 2	445 (29.3)	190 (44.9) ^a	252 (47.8) ^a	137 (25.1) ^{bc}
FEV ₁ (liter), median (IQR)	1.10 (0.74)	0.87 (0.51) ^a	1.22 (0.83) ^{ab}	0.96 (0.63) ^{abc}
FEV ₁ % predicted (%), median (IQR)	43.2 (27.2)	46.5 (24.9) ^a	46.3 (27.4) ^a	47.1 (27.5) ^a
FVC (liter), median (IQR)	2.46 (1.07)	1.82 (0.86) ^a	2.54 (1.09) ^b	2.00 (0.94) ^{abc}
FVC% predicted (%), median (IQR)	63.6 (25.2)	68.8 (31.2)	80.5 (25.8) ^a	68.1 (36.4)
FEV ₁ /FVC (%), median (IQR)	46.5 (18.4)	48.9 (16.9) ^a	51.6 (17.4) ^a	50.5 (18.5) ^a
ABCD group, N (%)				
A	238 (15.6)	30 (7.1) ^a	69 (13.1) ^b	76 (13.9) ^b
B	837 (55.1)	203 (48.0)	206 (39.1) ^b	332 (60.9) ^{bc}
C	48 (3.2)	29 (5.5) ^a	29 (5.5) ^a	8 (1.5)
D	397 (26.1)	177 (41.8) ^a	223 (42.3) ^a	129 (23.7) ^{bc}

RESEARCH

Open Access



A comparative study of chest CT findings regarding the effects of regional dust exposure on patients with COPD living in urban areas and rural areas near cement plants

Junghyun Kim¹, Bom Kim², So Hyeon Bak³, Yeon-Mok Oh⁴ and Woo Jin Kim^{2*}

Table 3 Comparison of lung function and CT-measurement adjusted for COPD medication and biomass exposure

	Model 1			Model 2		
	CODA	KOLD	P	CODA	KOLD	P
	LSMean ± SE	LSMean ± SE		LSMean ± SE	LSMean ± SE	
CAT score	23.60 ± 2.77	11.30 ± 2.44	<.0001			
Pulmonary function test						
Pre-bronchodilator FEV1 (L)	1.56 ± 0.12	1.27 ± 0.09	0.071			
Pre-bronchodilator FVC (L)	2.63 ± 0.19	2.84 ± 0.14	0.368			
Post-bronchodilator FEV1 (L)	1.68 ± 0.12	1.41 ± 0.09	0.087			
Post-bronchodilator FVC (L)	2.92 ± 0.18	3.00 ± 0.13	0.730			
Post-bronchodilator FEV1/FVC	0.57 ± 0.03	0.47 ± 0.02	0.003			
BDR, bronchodilator response	10.80 ± 2.99	12.40 ± 2.19	0.683			
CT measurement						
Mean wall area (%)	70.30 ± 1.29	67.90 ± 0.95	0.130	70.30 ± 1.25	67.10 ± 0.92	0.041
Emphysema index	6.24 ± 3.16	20.0 ± 2.32	0.001	6.14 ± 2.99	17.60 ± 2.22	0.002
Emphysema index, log-transformed/exponential	4.54 ± 1.29	15.22 ± 1.21	<.001	4.51 ± 1.28	13.20 ± 1.20	0.001
The ratio of mean lung density (expiration/inspiration)	0.95 ± 0.01	0.94 ± 0.01	0.372	0.95 ± 0.01	0.93 ± 0.01	0.088

WORLD TRADE CENTER RELATED LUNG DISEASE

Quantitative CT Evidence of Airway Inflammation in WTC Workers and Volunteers with Low FVC Spirometric Pattern

Jonathan Weber¹, Anthony P. Reeves², John T. Doucette³, Yunho Jeon³, Akshay Sood⁵, Raúl San José Estépar⁶, Juan C. Celedón⁷, Rafael E. de la Hoz^{3,4,8}

QCT metric	Comparison	OR	95% CI	OR _{adj}	95% CI
WAP	Low FVC vs. normal	1.32	1.15, 1.52	1.25	1.08, 1.46
	COPD vs. low FVC	1.11	0.87, 1.42	1.13	0.87, 1.47
	COPD vs. normal	1.47	1.17, 1.85	1.41	1.10, 1.80
MLA _{EI}	Low FVC vs. normal	0.74	0.37, 1.48	0.85	0.40, 1.79
	COPD vs. low FVC	6.56	2.69, 16.02	5.64	2.02, 15.76
	COPD vs. normal	4.83	2.43, 9.60	4.77	2.03, 11.20
LAV%	Low FVC vs. normal	0.48	0.14, 1.61	0.53	0.15, 1.87
	COPD vs. low FVC	10.36	2.95, 36.43	7.42	1.94, 28.31
	COPD vs. normal	4.98	2.40, 10.32	3.94	1.58, 9.82

Small airway wall thickening assessed by computerized tomography is associated with low lung function in Chinese carbon black packers

Xue Cao^{1*}, Li Lin^{2*}, Akshay Sood³, Qianli Ma², Xiangyun Zhang⁴, Yuansheng Liu¹, Hong Liu², Yanting Li¹, Tao Wang¹, Jinglong Tang¹, Menghui Jiang¹, Rong Zhang⁵, Shanfa Yu⁶, Zhiqiang Yu⁴, Yuxin Zheng^{1#}, Wei Han^{2#}, and Shuguang Leng^{1,7,8#}

- **Preventable** and treatable disease
 - Cigarette smoking
 - Occupational exposure
 - Biomass exposure
 - Air pollution
 - Maternal exposure of CS, ETS, air pollution
 - Childhood environmental exposure
 - Childhood infection
 - Childhood asthma

Original Research

COPDGene® 2019: Redefining the Diagnosis of Chronic Obstructive Pulmonary Disease

Figure 1. Features Used to Define COPD in the COPDGene® Study

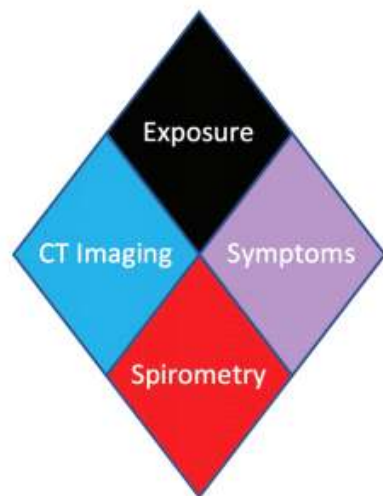


















Table 1. COPDGene® 2019 Categories

Category	Description	Symbol	# of Disease Features
A	Exposure		1
B	Exposure + CT Abnormal		2
C	Exposure + Symptoms		2
D	Exposure + Spirometry Abnormal		2
E	Exposure + Symptoms + CT Abnormal		3
F	Exposure + Spirometry Abnormal + Symptoms		3
G	Exposure + Spirometry Abnormal + CT Abnormal		3
H	Exposure + Spirometry Abnormal + Symptoms + CT Abnormal		4

	Category	Odds of Change >350 ml in FEV ₁ (95% CI) ^a	Hazard Ratio for All-Cause Mortality (95% CI) ^b	COPDGene 2019® Classification
	A	1.0 (ref.)	1.0 (ref.)	NO COPD
	B	1.31 (1.04-1.65)	1.05 (0.76-1.44)	Possible COPD
	C	1.42 (1.07-1.88)	1.55 (1.09-2.19)	
	D	0.92 (0.64-1.30)	1.48 (1.03-2.12)	
	E	1.74 (1.28-2.36)	1.90 (1.33-2.71)	Probable COPD
	F	1.02 (0.66-1.60)	2.62 (1.84-3.72)	
	G	2.11 (1.66-2.68)	1.76 (1.36-2.27)	
	H	2.82 (2.18-3.66)	5.18 (4.15-6.48)	Definite COPD

Original Research

Design of the Redefining Therapy in Early COPD Study

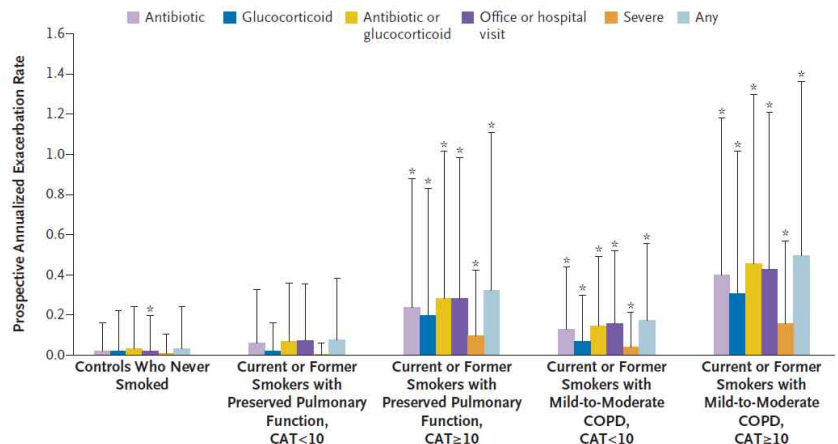
MeiLan K. Han, MD, MS¹ Wen Ye, PhD² Dong-Yun Kim, PhD³ Prescott Woodruff, MD, MS⁴ for the Pulmonary Trials Cooperative Investigators

Redefining Therapy in Early COPD (RETHINC)

Inclusion Criteria

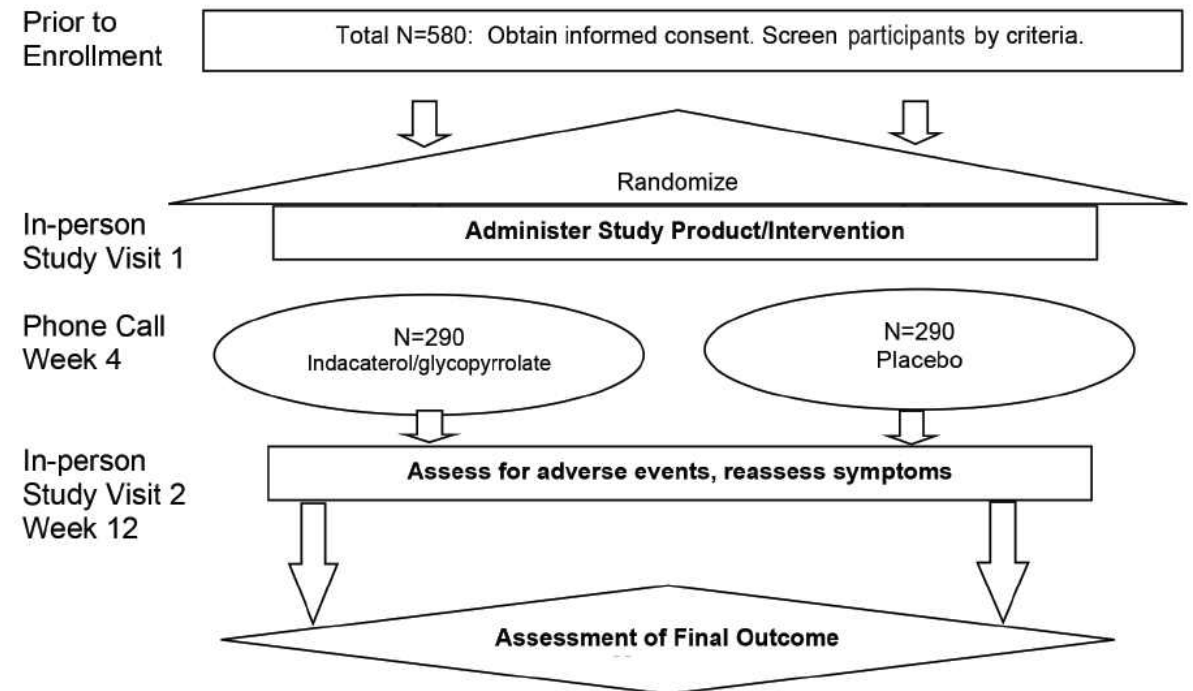
Individuals who meet all of the following criteria are eligible for enrollment as study participants:

1. Subject must be able to understand and provide informed consent
2. Age 40-80
3. ≥ 10 pack-year smoking history
4. Post-bronchodilator FEV₁/FVC ratio ≥ 0.70
5. Baseline CAT ≥ 10



NEJM 2016

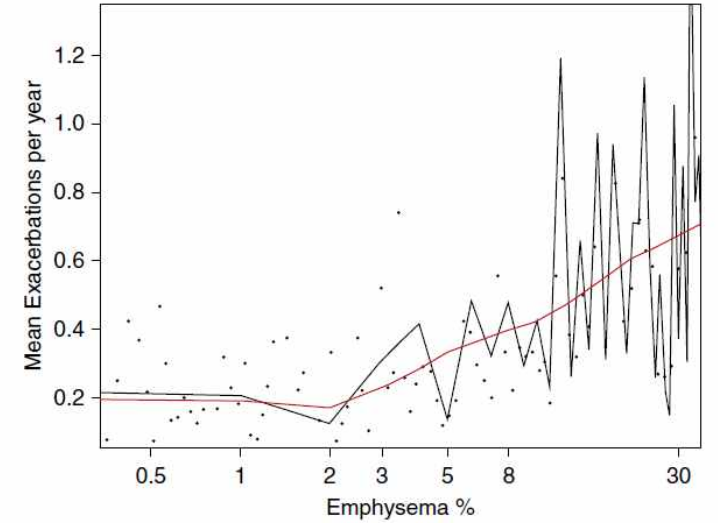
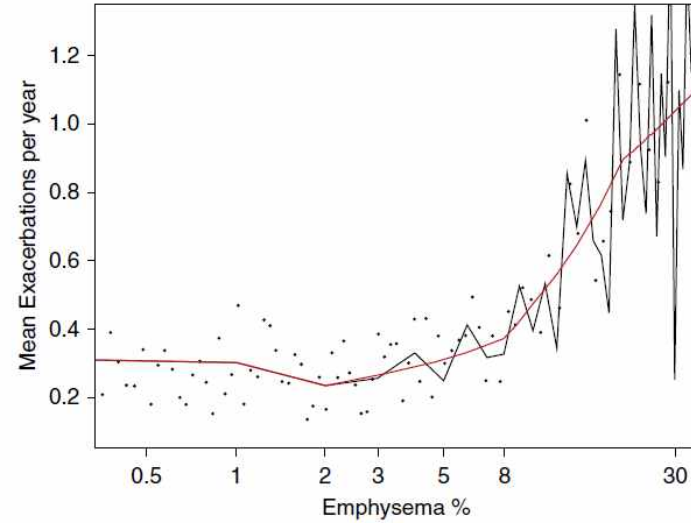
Figure 1. Study Flow Diagram



JCOPDF 2020

Structure

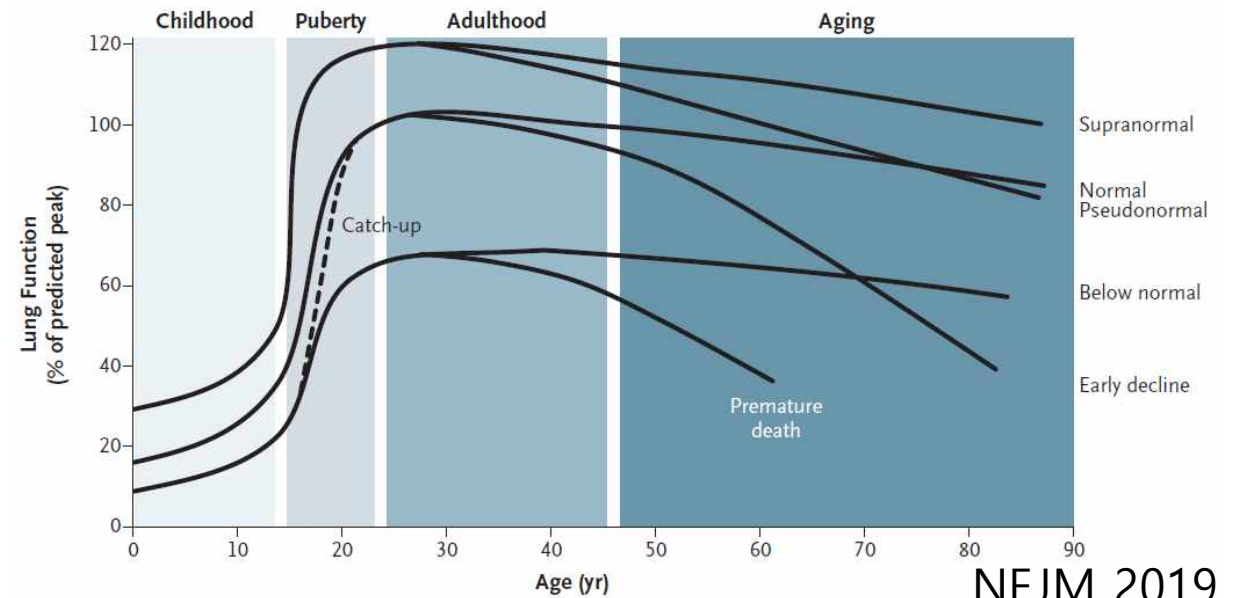
- Emphysema
 - $\geq 5\%$ LAA < -950HU
- Airway wall
 - $Pi10 \geq 2.5\text{mm}$
- Gas-trapping
 - $\geq 15\%$ LAA < -850HU
- Limitation
 - 개별적으로 적용 가능?
 - 임상 시험 부재



	Category	Odds of Change >350 ml in FEV ₁ (95% CI) ^a	Hazard Ratio for All-Cause Mortality (95% CI) ^b	COPDGene 2019 [®] Classification
	A	1.0 (ref.)	1.0 (ref.)	NO COPD
	B	1.31 (1.04-1.65)	1.05 (0.76-1.44)	Possible COPD
	C	1.42 (1.07-1.88)	1.55 (1.09-2.19)	
	D	0.92 (0.64-1.30)	1.48 (1.03-2.12)	
	E	1.74 (1.28-2.36)	1.90 (1.33-2.71)	Probable COPD
	F	1.02 (0.66-1.60)	2.62 (1.84-3.72)	
	G	2.11 (1.66-2.68)	1.76 (1.36-2.27)	
	H	2.82 (2.18-3.66)	5.18 (4.15-6.48)	

Physiology

- Abnormal spirometry
 - Airflow limitation
 - $FEV_1 < 80\%$ predicted and/or $FEV_1/FVC < 0.70$
- Potential novel methods for detect airflow limitation



Early COPD vs. pre-COPD

Required	One or More of the Following:
<50 yr of age ≥10 pack-years smoking history	FEV ₁ /FVC less than lower limit of normal Compatible computed tomography abnormalities (visual emphysema, air trapping, or bronchial thickening graded mild or worse) Evidence of accelerated FEV ₁ decline (≥60 ml/yr)

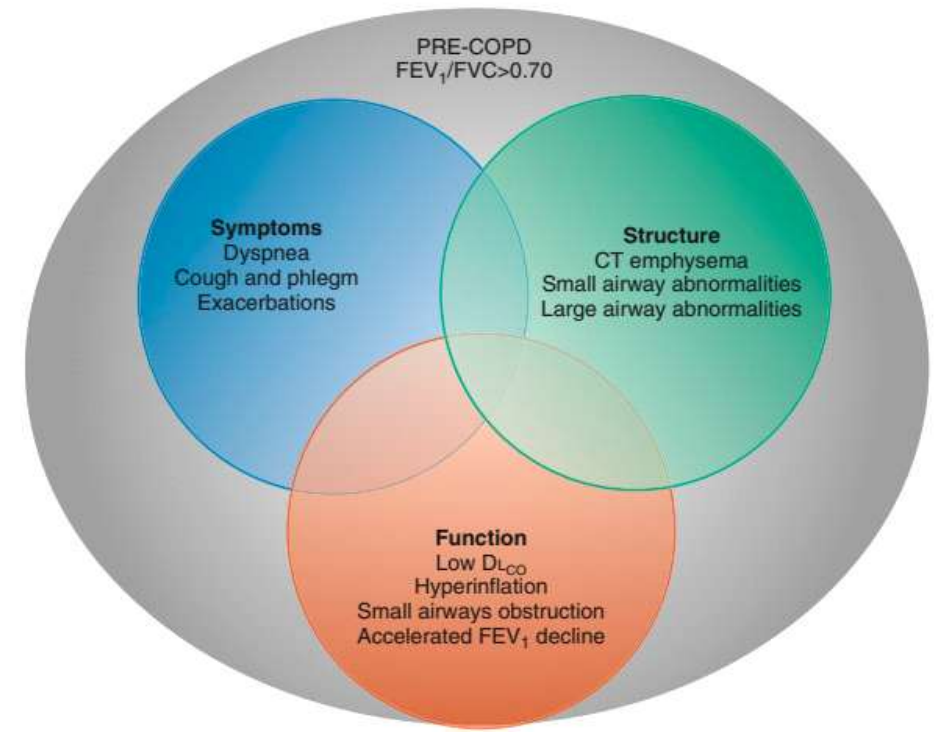
Martinez et al, AJRCCM 2018

- Prognostic marker – treat
- Risk factor – prevention

PULMONARY PERSPECTIVE

From GOLD 0 to Pre-COPD

MeiLan K. Han^{1*}, Alvar Agustí², Bartolome R. Celli³, Gerard J. Criner^{4*}, David M. G. Halpin⁵, Nicolas Roche⁶, Alberto Papi⁷, Robert A. Stockley⁸, Jadwiga Wedzicha^{9*}, and Claus F. Vogelmeier¹⁰

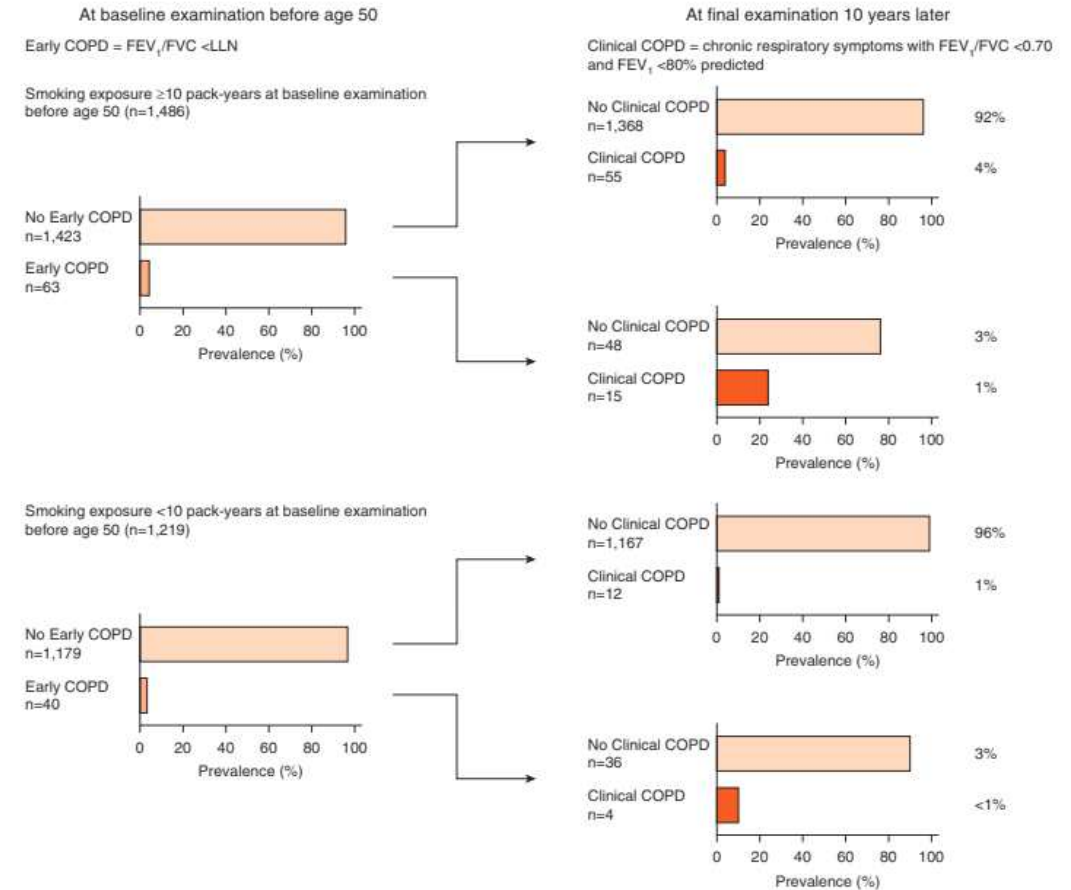
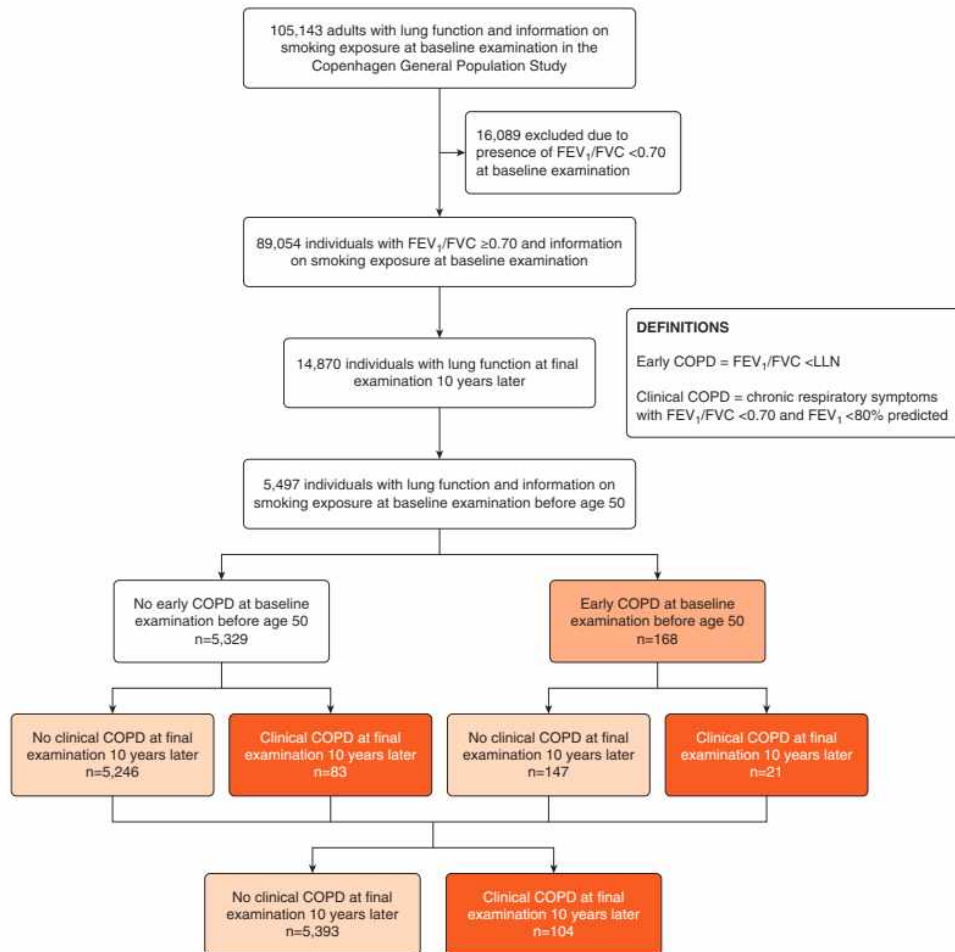


Han et al, AJRCCM 2021

Importance of Early COPD In Young Adults for Development of Clinical COPD

Findings from the Copenhagen General Population Study

Yunus Çolak^{1,2,3}, Shoaib Afzal^{1,2,3}, Børge G. Nordestgaard^{1,2,3}, Peter Lange^{2,3,4,5}, and Jørgen Vestbo⁶



Treatable trait?

- Chronic bronchitis
- PRISM
- Early COPD
- Pre-COPD
- Emphysema

요약

- 최근 definition에서 위험인자에 대한 내용이 업데이트 됨
- 위험인자를 가지고 있으나 폐기능이 현재 definition에 해당하지 않은 경우에도 구조적 또는 기능적 이상 또는 증상이 있는 경우, 향후 COPD의 발병 위험이 높거나 그 자체로 예후가 나쁘다는 것이 보고되고 있음
- COPD 현재 정의에 해당하지 않은 경우에도 치료에 의해 유의미한 결과를 보인다면 향후 정의 및 병기에 대한 업데이트가 필요할 것임