

# COPD & pre-COPD : screening, etiotypes, and early detection

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- Etiotypes
- Screening and early detection

# Definition

# Definition of terms

1. Early COPD
2. Mild COPD
3. PRISm
4. Young COPD
5. Pre-COPD

# Early COPD

- “Early” refers to the **biological beginning** of the disease process, not necessarily the clinical onset.
- Distinguished from “clinical early,” which involves symptoms, functional limitation, or structural abnormalities.

# Mild COPD

- Mild airflow obstruction” has often been used as a surrogate for “early COPD,” but this is incorrect.
- “Mild” only reflects the **severity of airflow limitation** measured by spirometry, not the disease’s stage or duration.“

# PRISm

- Defined by  $FEV1/FVC \geq 0.7$  with  $FEV1 < 80\%$  predicted (after bronchodilation).
- Prevalence: about 7–11% in population-based studies.
- Common in smokers, females, individuals with high BMI, or multimorbidity.
- Associated with increased risk of respiratory symptoms, cardiovascular disease, metabolic disorders, and mortality.
- Clinically important as a potential precursor or variant of COPD (airway-dominant type)

# PRISm as an independent risk factor for COPD

OLIN COPD Study (1986-1992 -> 1992-1996 -> 2002-2004)

f/u period mean 10.5 (SD 4.0) years

Prevalence of PRISm 18.6%

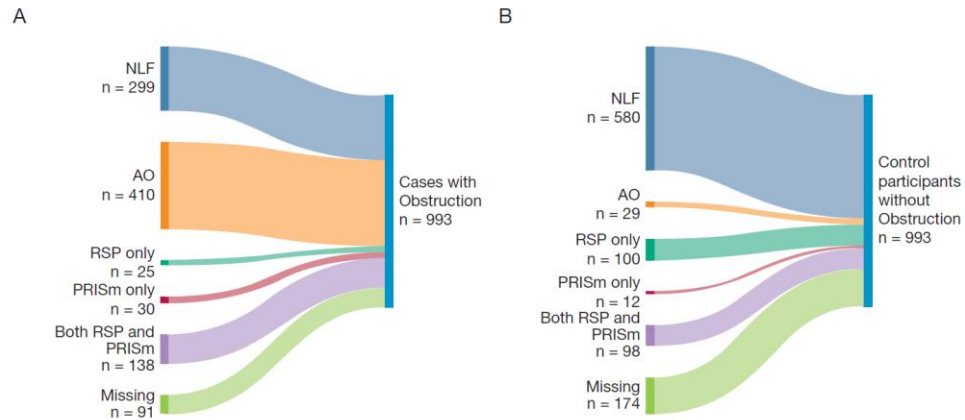
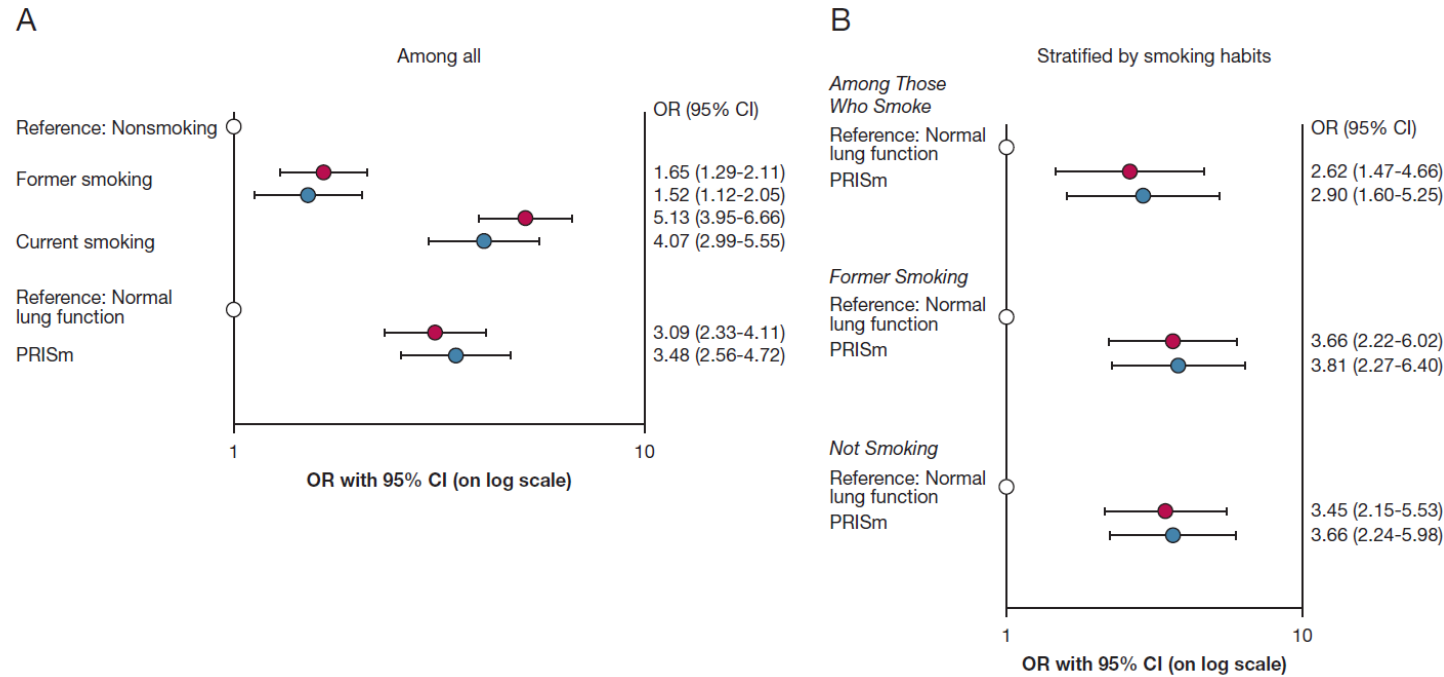


Figure 3 - A, B, Illustrations showing distribution by spirometric pattern among cases (A) and control participants (B): NLF, AO, RSP only, PRISm only, and both RSP and PRISm or missing at first examination. AO = airway obstruction; NLF = normal lung function; PRISm = preserved ratio impaired spirometry; RSP = restrictive spirometric pattern.



# Epigenetic-expression difference between COPD and PRISm

Fig. 1 Venn diagram showing differential methylation sites with or without difference expression



Table 4 The genes that show differential expression

SeqName	Symbol	Base Mean	log2FoldChange	lfcSE	stat	p-value	adj_FDR
ENSG00000101210	EEF1A2	1.3763704	-1.85943	0.442666743	-4.20051842	2.66E-05	0.0488296
ENSG00000104728	ARHGEF10	11.750663	1.631349	0.330964437	4.929077868	8.26E-07	0.00601989
ENSG00000119888	EPCAM	1.5985632	-2.495019	0.441399563	-5.652518503	1.58E-08	0.00034545
ENSG00000132613	MTSS1L	2.375187	-1.146067	0.270609661	-4.235131151	2.28E-05	0.04747611
ENSG00000134824	FADS2	32.683477	-0.646223	0.154318338	-4.18759687	2.82E-05	0.04932518
ENSG00000157423	HYDIN	4.4053575	-0.32203	0.069962611	-4.602886282	4.17E-06	0.01647088
ENSG00000213853	EMP2	3.0398676	-0.818896	0.196103903	-4.175829374	2.97E-05	0.04995083

# PRISm in KHANES

Table 2. Age-standardized prevalence (%) of PRISm.

	All	2010	2011	2012	2013	2014	2015	APC1	2017	2018	2019	APC2
<b>Total</b>	<b>10.4</b>	7.6	8.5	8.9	7.6	7.7	7.5	-1.5	13.9	15.7	14.0	0.4
40–49	10.6	7.6	9.0	10.4	8.2	8.1	9.3	1.3	17.7	18.0	17.7	0.0
50–59	11.8	8.0	10.1	9.1	8.5	9.5	7.0	-2.6	14.3	19.3	15.8	5.1
60–69	9.9	8.8	8.6	8.9	6.7	6.2	5.7	-9.4*	10.9	10.3	10.2	-3.3*
≥70	7.9	5.3	4.5	5.0	5.8	4.8	7.4	5.9	9.6	11.9	9.6	0.0
<b>Male</b>	<b>10.8</b>	8.2	10.0	6.8	8.1	8.0	7.1	-3.4	14.9	18.1	15.6	2.3
40–49	11.7	8.9	10.8	8.9	8.7	8.0	10.2	-0.7	20.9	21.7	21.6	1.7*
50–59	12.1	8.5	12.0	6.2	8.5	8.9	6.2	-6.0	15.1	22.4	16.1	3.3
60–69	10.1	9.4	10.6	7.0	7.7	8.5	4.6	-11.2	11.0	12.4	11.0	0.0
≥70	6.9	3.3	2.1	2.4	6.1	5.2	5.1	18.2	6.5	9.4	9.2	19.0*
<b>Female</b>	<b>10.0</b>	7.0	7.2	10.8	7.2	7.3	7.9	0.7	13.0	13.5	12.5	-1.9
40–49	9.4	6.3	7.2	12.1	7.6	8.2	8.4	4.0	14.3	14.3	13.7	-2.1*
50–59	11.6	7.5	8.1	12.0	8.4	10.1	7.8	1.4	13.5	16.2	15.5	7.2
60–69	9.8	8.2	6.9	10.7	6.0	4.7	6.3	-8.3	10.6	8.7	9.5	-5.3
≥70	8.7	6.5	6.0	6.7	5.3	4.0	9.7	1.6	12.9	14.1	9.7	-13.3

\*APC is significantly different from 0.

APC1 was calculated between 2010 and 2015 and APC2 was calculated between 2017 and 2019.

Age-standardized prevalence was calculated using the 2010 population census data for all South Koreans.

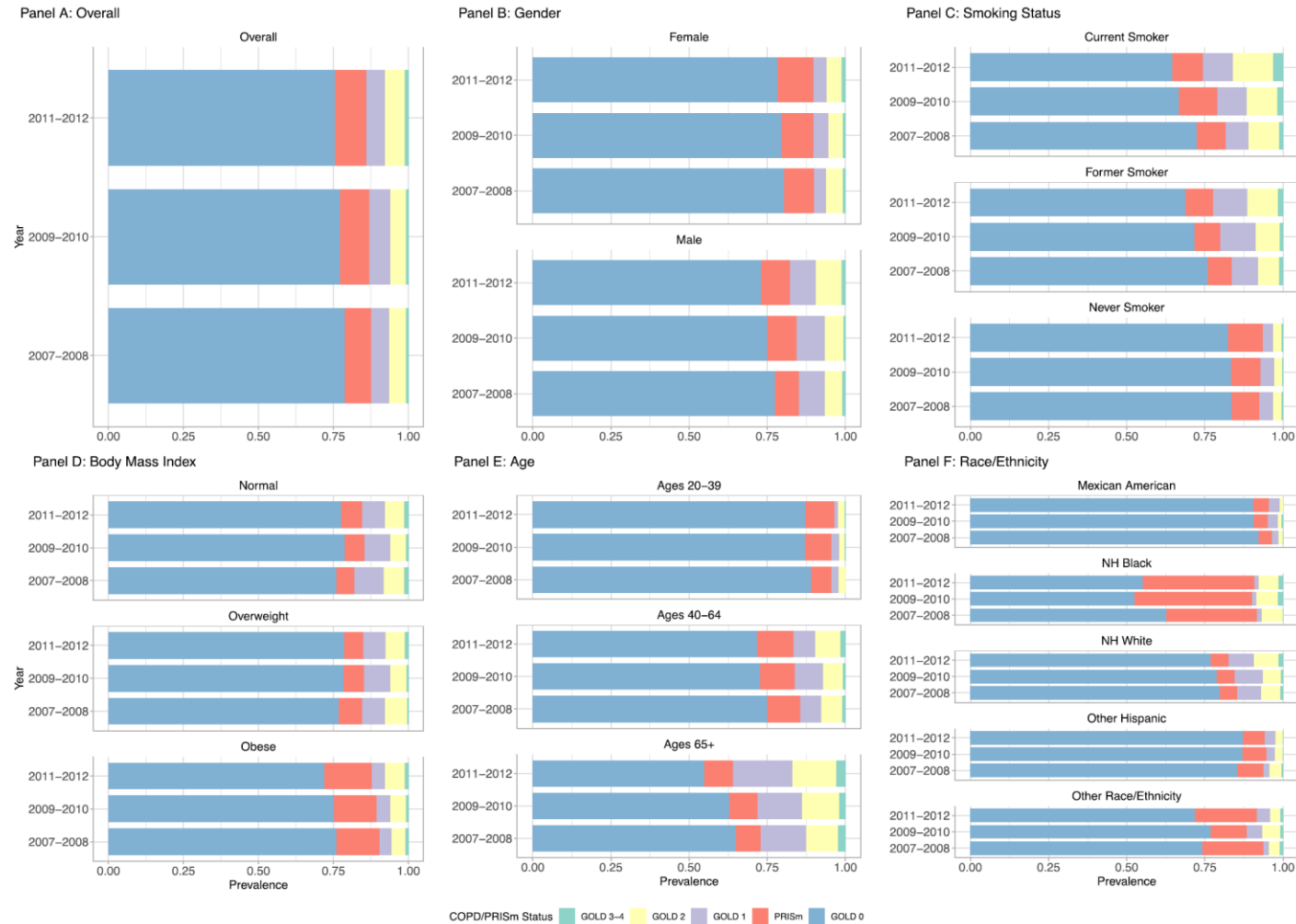
PRISm = preserved ratio impaired spirometry; APC = annual percentage change.

# PRISm in KHANES – metabolic syndrome

Table 4. Multivariable-adjusted model for factors associating PRISm compared to normal spirometry pattern based on the fixed ratio of 0.7 or LLN (5<sup>th</sup> percentile).

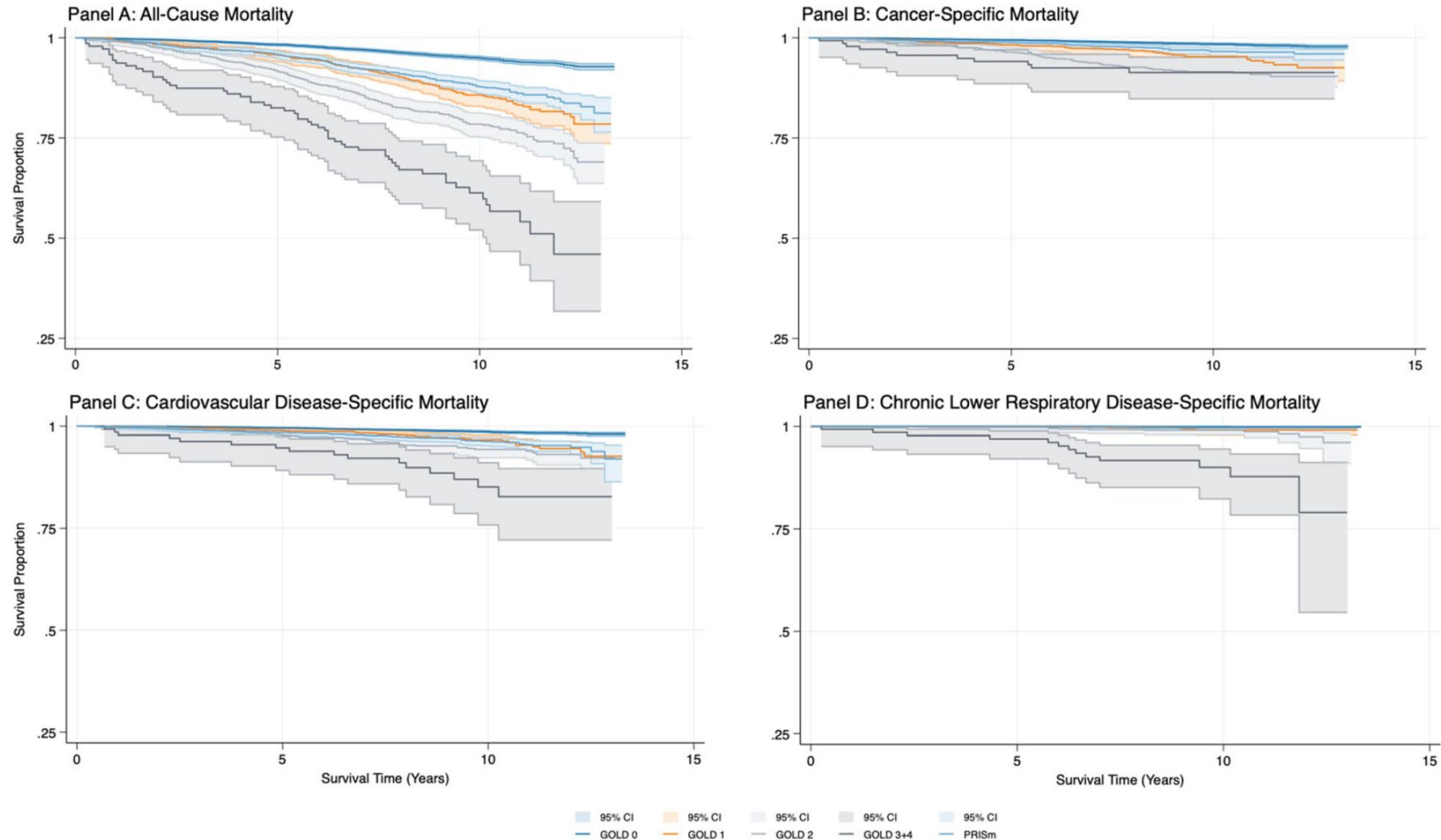
	Fixed ratio		LLN <sup>a)</sup>	
	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
<b>Age</b>		<0.001		<0.001
40–49	<i>Reference</i>		<i>Reference</i>	
50–59	1.10 (0.98–1.24)		0.83 (0.75–0.92)	
60–69	0.87 (0.77–0.99)		0.55 (0.49–0.62)	
≥70	0.68 (0.58–0.79)		0.52 (0.45–0.61)	
<b>Sex</b>		0.746		<0.001
Male	<i>Reference</i>		<i>Reference</i>	
Female	1.02 (0.89–1.18)		5.22 (4.40–6.20)	
<b>Residence</b>		0.328		0.628
Urban	<i>Reference</i>		<i>Reference</i>	
Rural	0.95 (0.85–1.07)		1.03 (0.92–1.15)	
<b>Smoking</b>		0.338		0.741
Never	<i>Reference</i>		<i>Reference</i>	
Former	1.01 (0.87–1.19)		1.08 (0.90–1.30)	
Current	1.08 (0.92–1.26)		0.96 (0.79–1.16)	
<b>BMI (kg/m<sup>2</sup>)</b>		<b>0.034</b>		<0.001
<23	<i>Reference</i>		<i>Reference</i>	
23–24.9	1.01 (0.90–1.14)		1.07 (0.95–1.20)	
≥25	1.13 (1.01–1.26)		1.31 (1.18–1.45)	
<b>Metabolic disorders <sup>b)</sup></b>				
Metabolic syndrome	1.43 (1.29–1.59)	<0.001	1.28 (1.15–1.43)	<0.001
Hypertriglyceridemia	1.25 (1.14–1.37)	<0.001	1.18 (1.07–1.30)	<b>0.001</b>
Abdominal obesity	1.48 (1.31–1.68)	<0.001	1.31 (1.16–1.49)	<0.001
Low HDL-cholesterol	1.10 (1.01–1.21)	<b>0.039</b>	0.98 (0.89–1.07)	0.633
Hypertension	1.27 (1.16–1.39)	<0.001	1.15 (1.05–1.27)	<b>0.003</b>
Diabetes mellitus	1.33 (1.21–1.45)	<0.001	1.22 (1.11–1.34)	<0.001

# PRISm in US from NHANES 2007-2012



Prevalence of COPD and PRISm from 2007-2012 ranged from 13.1%-14.3% and 9.6%-10.2%

# PRISm in US from NHANES 2007-2012



# PRISm in US from NHANES 2007-2012

## - increased mortality risk

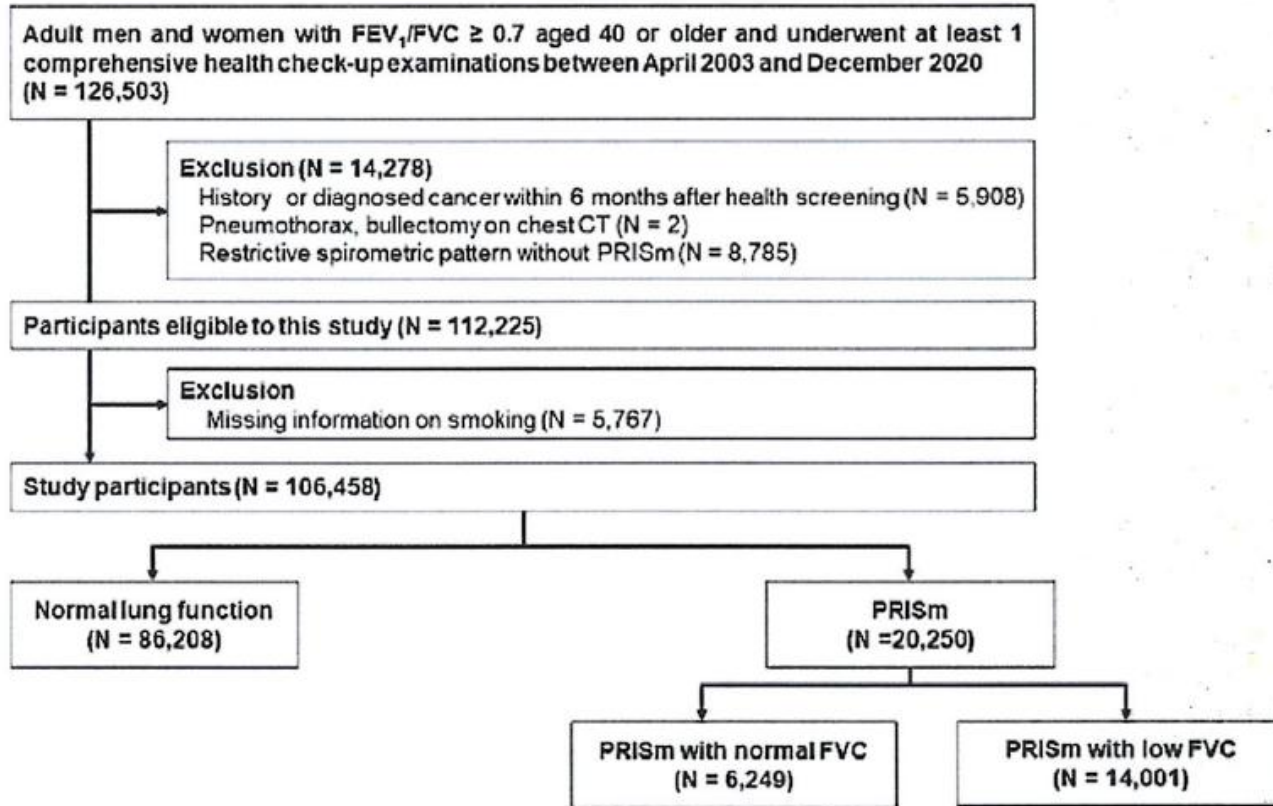
**Table 2** Cox proportional hazard models for all-cause and cause-specific mortality for NHANES 2007–2012

	All-Cause Mortality		Cancer		Cardiovascular Diseases		Chronic Lower Respiratory Diseases	
	Hazard Ratio	95% CI	Hazard Ratio	95% CI	Hazard Ratio	95% CI	Hazard Ratio	95% CI
<b>COPD Status</b>								
GOLD 0	Ref		Ref		Ref		Ref	
PRISm	<b>2.3</b>	<b>(1.9—2.9)</b>	<b>2.0</b>	<b>(1.2—3.2)</b>	<b>2.4</b>	<b>(1.6—3.6)</b>	<b>5.3</b>	<b>(1.1—26.0)</b>
GOLD 1	1.2	(0.9—1.6)	1.4	(0.9—2.4)	0.9	(0.6—1.4)	1.4	(0.4—5.4)
GOLD 2	<b>2.1</b>	<b>(1.7—2.6)</b>	<b>2.0</b>	<b>(1.4—2.8)</b>	<b>2.4</b>	<b>(1.6—3.7)</b>	3.3	(1.0—11.3)
GOLD 3–4	<b>4.2</b>	<b>(2.7—6.5)</b>	1.3	(0.6—2.8)	<b>4.7</b>	<b>(2.3—9.8)</b>	<b>53.2</b>	<b>(14.0—202.0)</b>
<b>Gender</b>								
Female	Ref		Ref		Ref		Ref	
Male	<b>1.7</b>	<b>(1.5—2.0)</b>	<b>1.7</b>	<b>(1.3—2.4)</b>	<b>2.1</b>	<b>(1.5—3.1)</b>	1.6	(0.7—3.6)
<b>Age</b>								
Age 20–39	<b>0.3</b>	<b>(0.2—0.4)</b>	<b>0.1</b>	<b>(0.0—0.3)</b>	<b>0.2</b>	<b>(0.1—0.4)</b>	<b>0.1</b>	<b>(0.0—0.9)</b>
Age 40–64	Ref		Ref		Ref		Ref	
Age 65+	<b>4.7</b>	<b>(4.0—5.5)</b>	<b>4.3</b>	<b>(3.1—6.0)</b>	<b>6.6</b>	<b>(4.9—8.9)</b>	<b>4.3</b>	<b>(1.3—13.7)</b>
<b>Body Mass Index</b>								
Normal	Ref		Ref		Ref		Ref	
Overweight	0.9	(0.7—1.1)	0.8	(0.5—1.3)	1.3	(0.8—2.1)	0.5	(0.2—1.8)
Obese	1.1	(0.9—1.4)	1.0	(0.7—1.4)	<b>1.8</b>	<b>(1.1—2.7)</b>	0.9	(0.2—3.3)
<b>Smoking Status</b>								
Never Smoker	Ref		Ref		Ref		Ref	
Current Smoker	<b>2.1</b>	<b>(1.7—2.6)</b>	<b>2.3</b>	<b>(1.4—3.6)</b>	<b>1.6</b>	<b>(1.1—2.3)</b>	<b>5.8</b>	<b>(1.6—21.7)</b>
Former Smoker	1.2	(0.9—1.4)	1.1	(0.7—1.7)	0.9	(0.7—1.3)	3.0	(0.9—9.9)
<b>Race/Ethnicity</b>								
Non-Hispanic White	Ref		Ref		Ref		Ref	
NH Black	1.0	(0.8—1.2)	0.9	(0.6—1.3)	1.0	(0.7—1.5)	0.4	(0.2—0.9)
Mexican American	0.8	(0.6—1.0)	0.6	(0.4—1.1)	0.9	(0.6—1.5)	0.4	(0.0—3.5)
Other Hispanic	0.8	(0.6—1.1)	0.8	(0.5—1.2)	1.1	(0.6—1.8)	0.1	(0.0—1.1)
Other	<b>0.6</b>	<b>(0.4—0.8)</b>	0.6	(0.3—1.3)	0.6	(0.3—1.0)	1.0	(0.2—4.4)

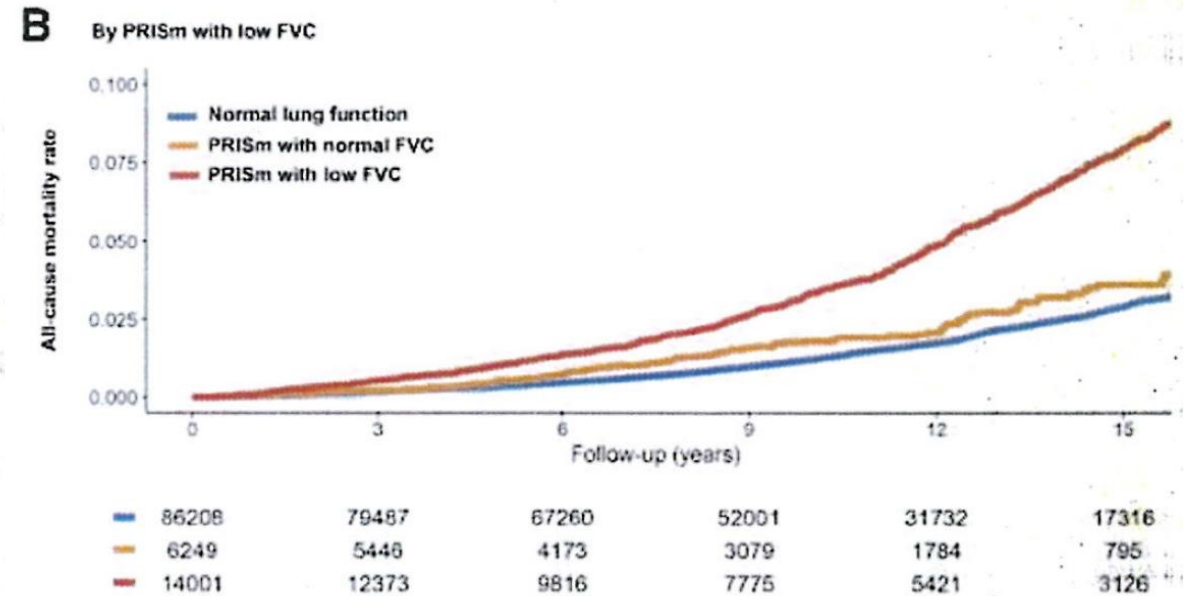
Values in **bold** are statistically significant

All-cause mortality (hazard ratio [HR]: 2.3 95% CI: 1.9—2.9) and various cause-specific deaths (HR ranges: 2.0—5.3)

# PRISm and All-cause mortality ; Korean data



**Figure 1.** Study flow chart. CT = computed tomography; FEV<sub>1</sub> = forced expiratory volume in 1 second; FVC = forced vital capacity; PRISm = preserved-ratio impaired spirometry.



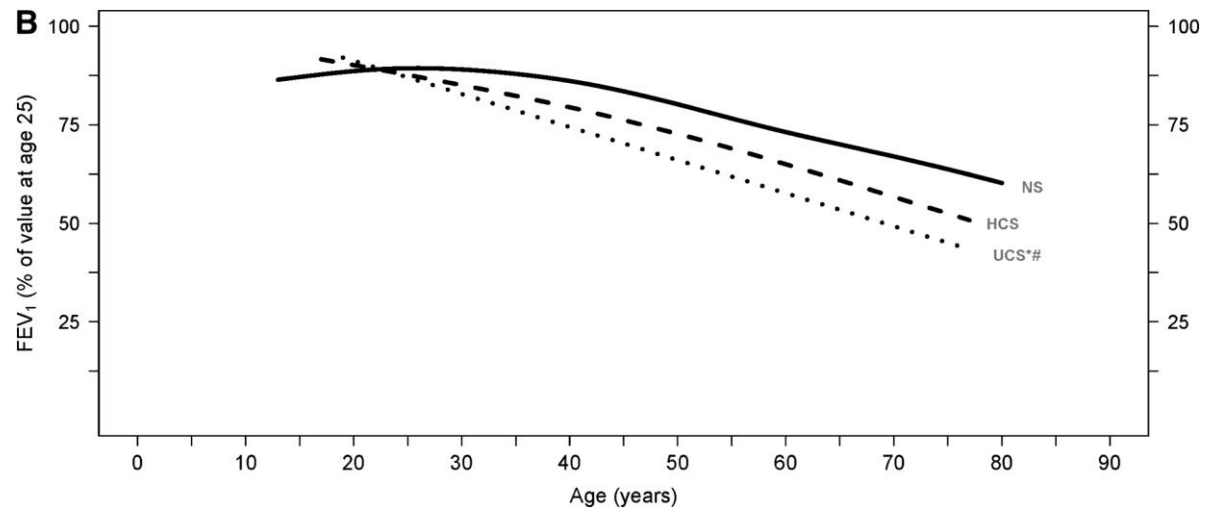
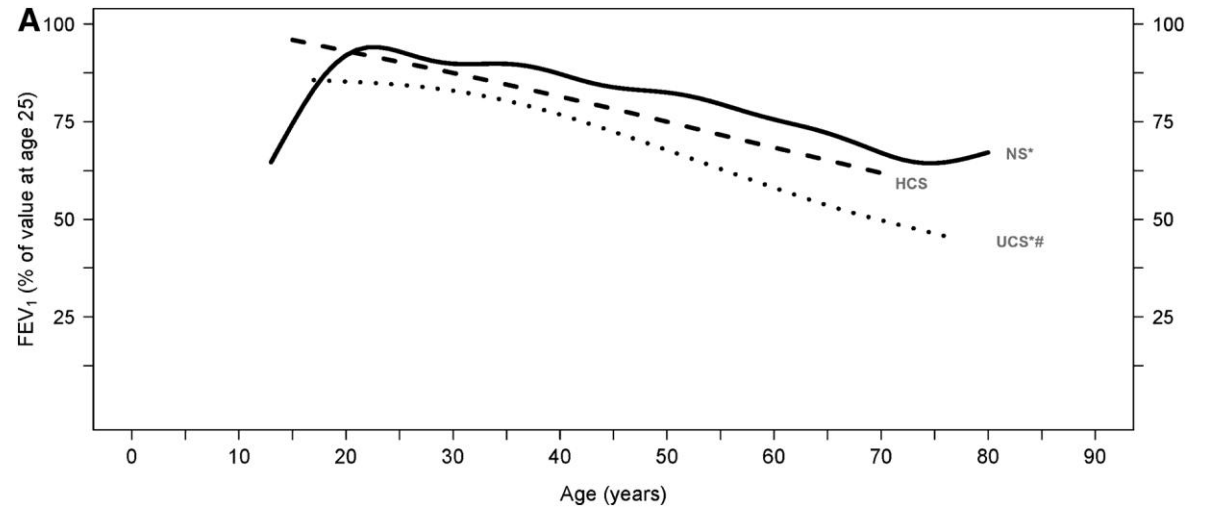
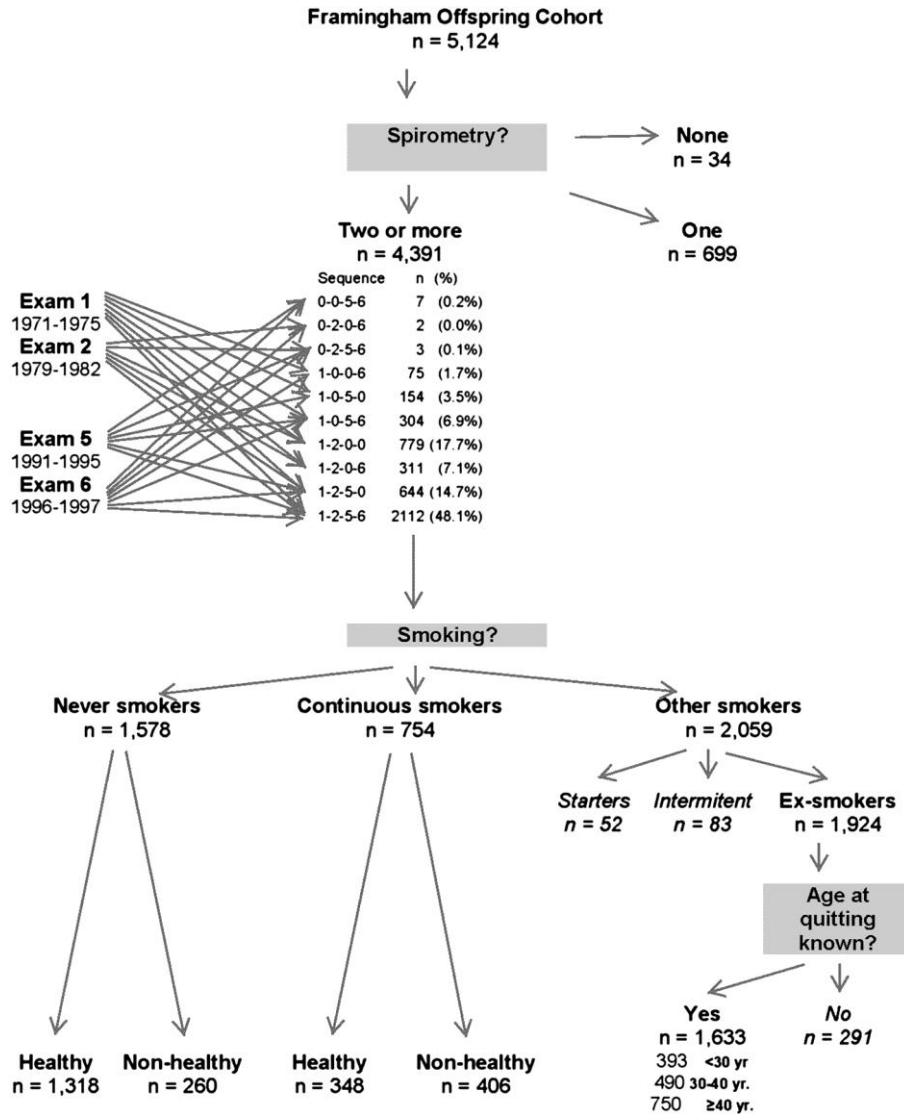
**Table 2.** HRs for all-cause mortality associated with lung function (N = 106,458)

	No. of Deaths (Mortality Rate per 10,000 person-years)	HR (95% CI)	
		Crude	Adjusted*
Normal lung function	1,456 (16)	Reference	Reference
PRISm	763 (39)	2.42 (2.22–2.64)	1.43 (1.31–1.56)
With normal FVC	107 (19)	1.29 (1.06–1.57)	1.25 (1.03–1.52)
With low FVC	606 (47)	2.82 (2.58–3.10)	1.47 (1.33–1.62)

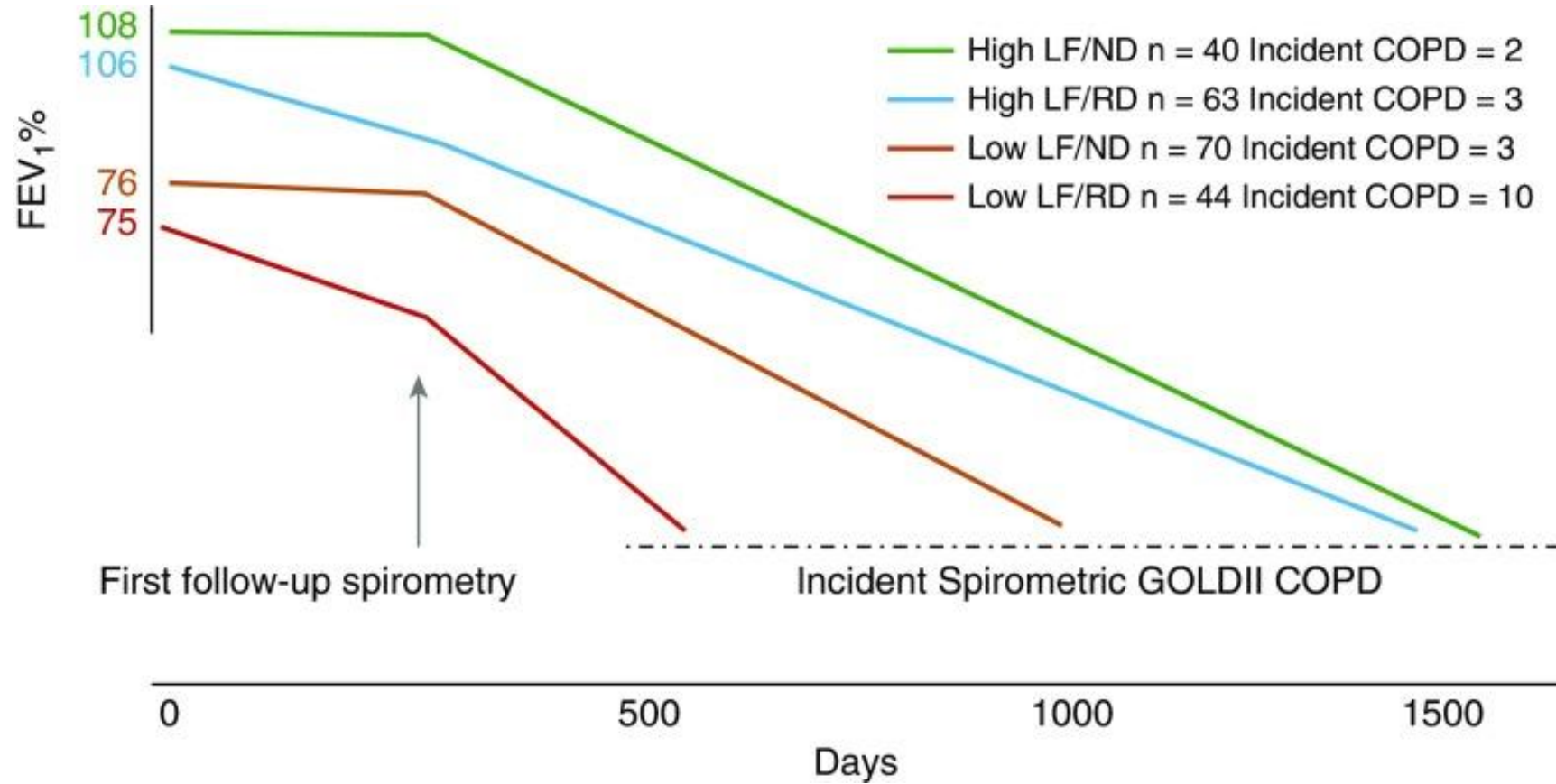
# Young COPD

- Refers to COPD in **younger individuals (20–50 years)**.
- Normal peak lung function followed by an early decline or abnormal early-life lung development.
- Significant structural and functional abnormalities.
- Family history of respiratory disease or early-life respiratory events

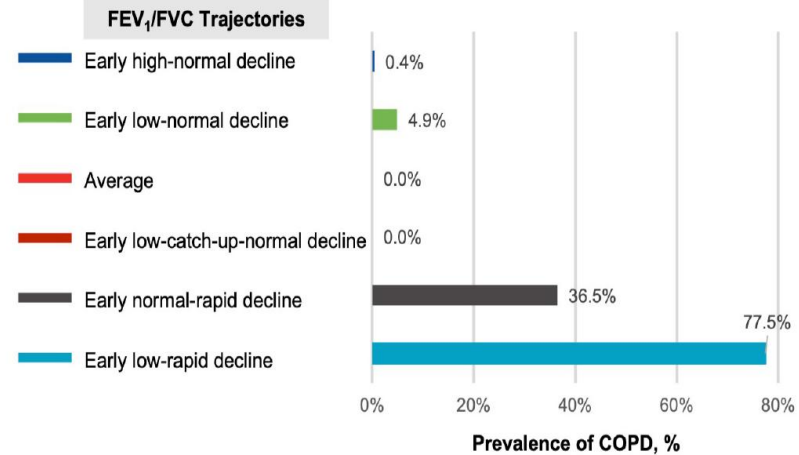
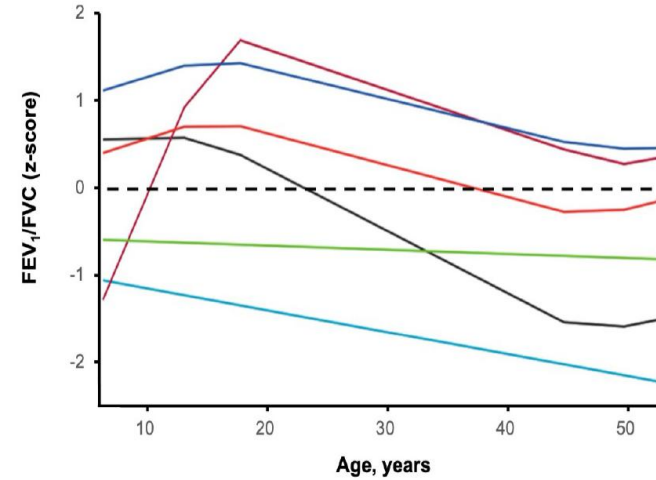
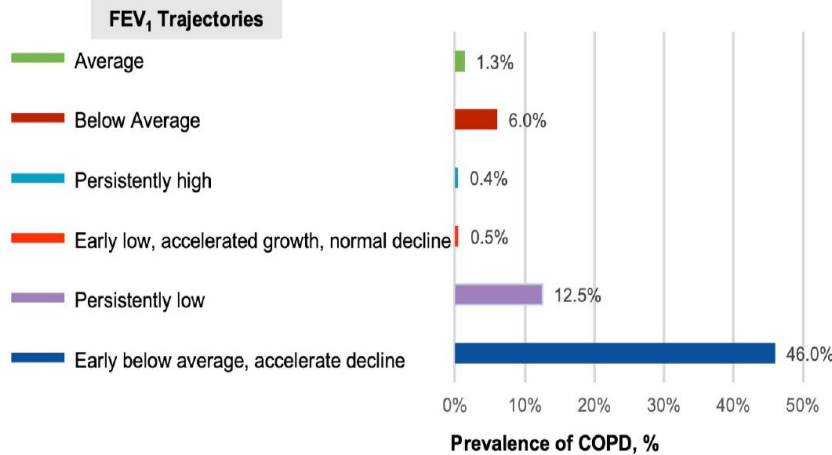
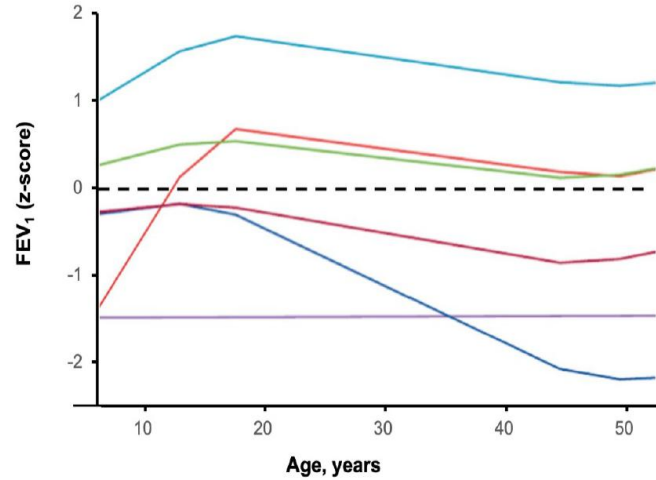
# Natural history of chronic airflow obstruction



# Lung function decline in Lovelace Smokers Cohort (LSC)

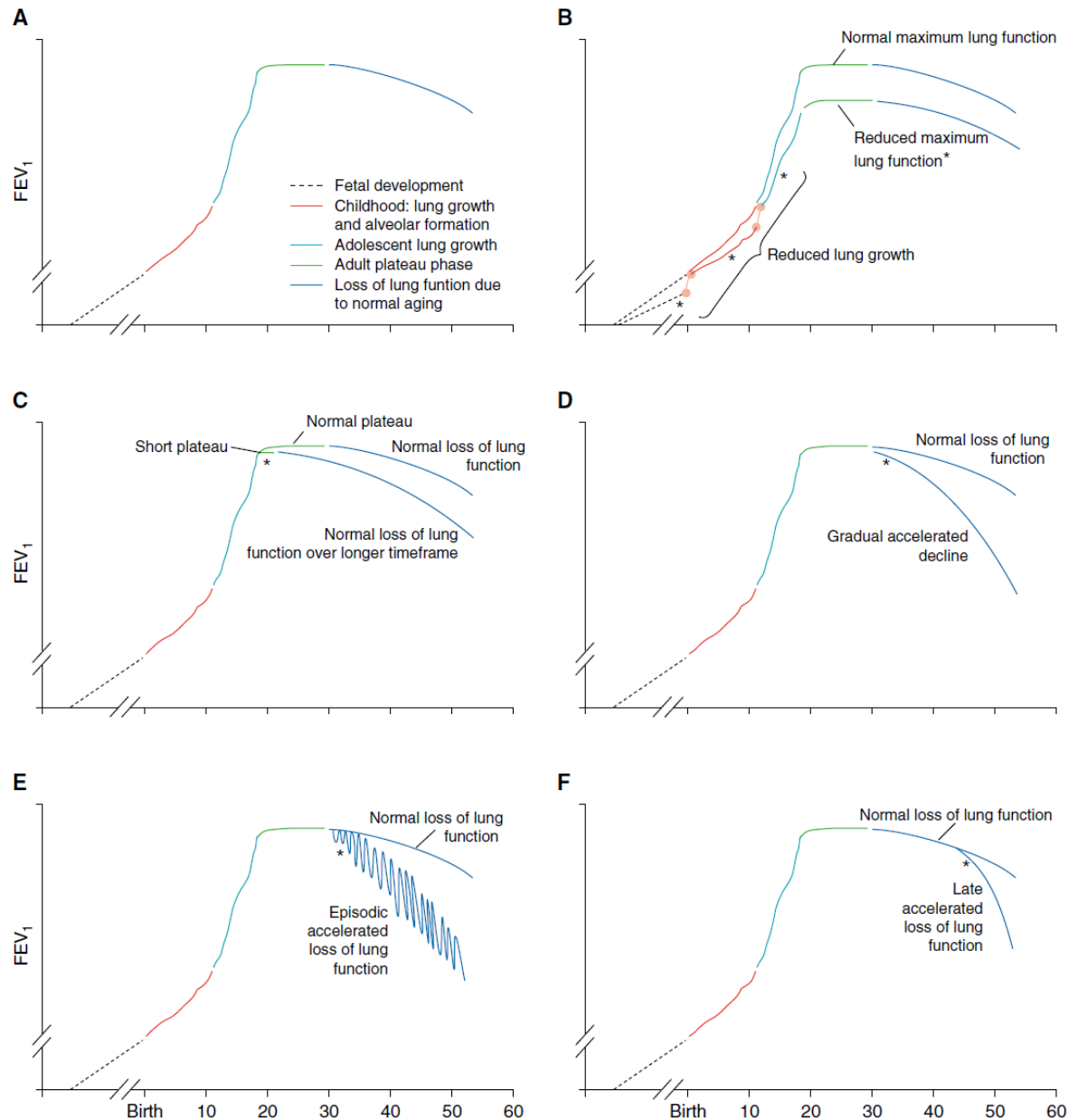


# Trajectories of lung function and COPD : TAHS data



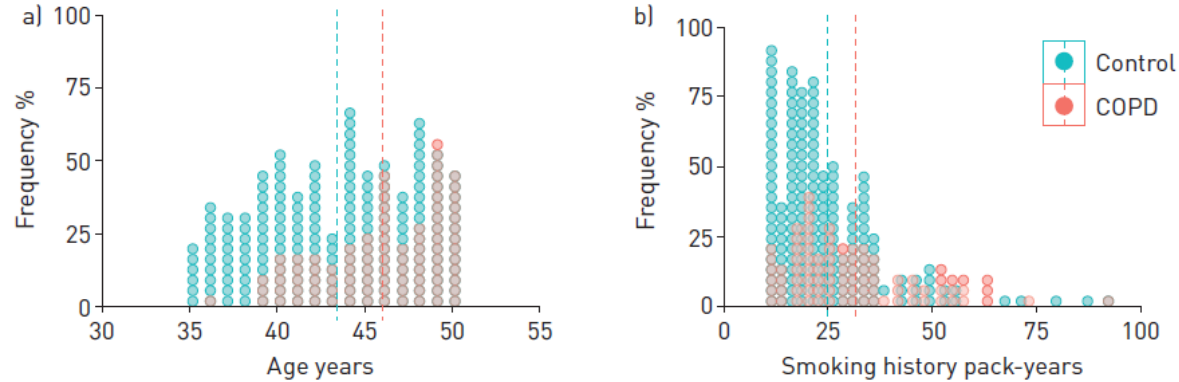
*Respirology.* 2024 Jul;29(7):551-562  
*Lancet Respir Med.* 2018;6:535-44.  
*Lancet Respir Med.* 2023;11:273-82.

# Natural history of chronic airflow obstruction



COPD may result from different trajectories of lung function — either normal growth and accelerated decline or submaximal growth and normal decline

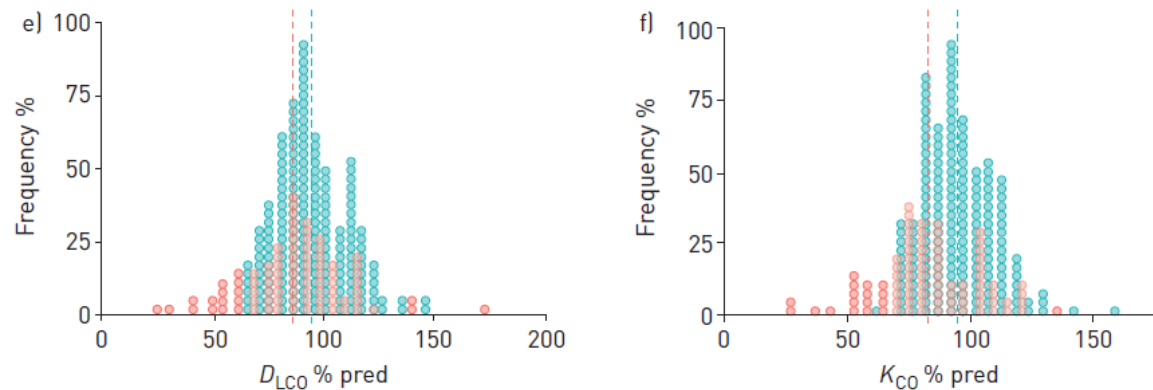
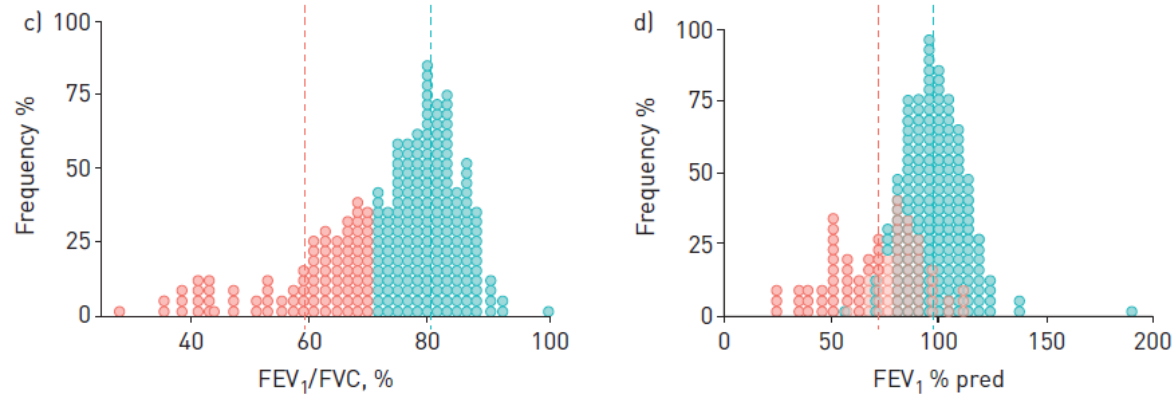
# Clinical characteristics of young COPD patients



Prospective multicenter cohort study of Spain

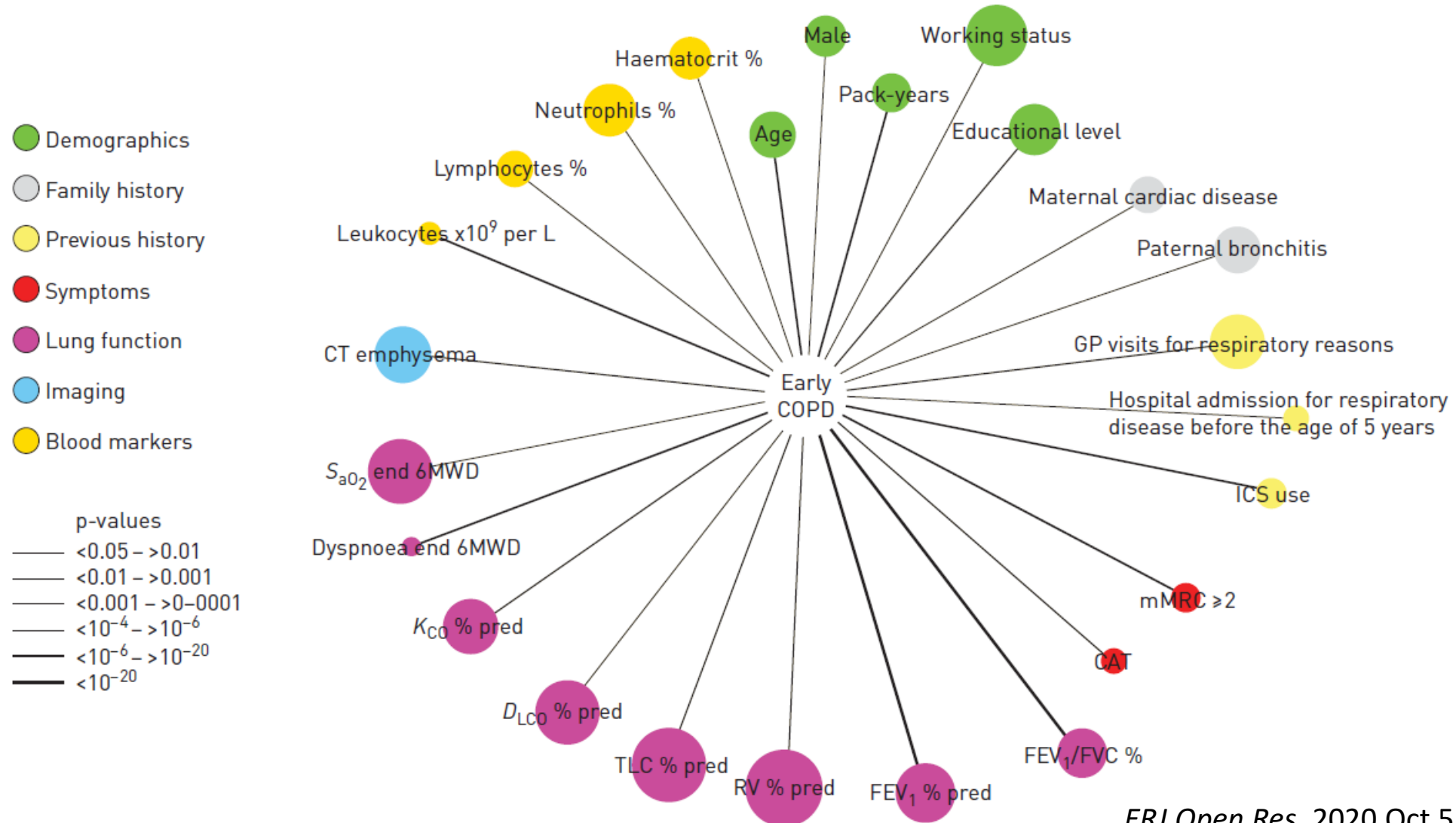
## Early COPD

1. 35–50 years of age
2. Caucasian origin
3. current or former smokers (>10 pack-years)
4. the presence of airflow limitation after bronchodilation ( $FEV_1/FVC < 0.7$ )



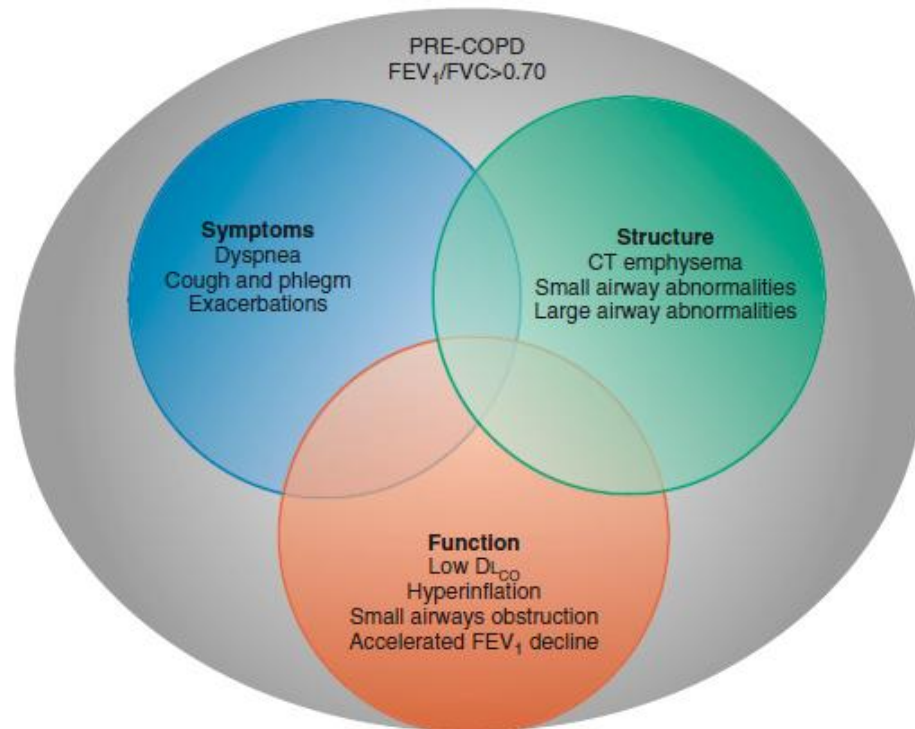
# Variables associated (p<0.05) with the presence of young COPD in the population studied

COPD | B.G. COSÍO ET AL.



# Pre-COPD

- Describes individuals (any age) with respiratory symptoms and/or structural or functional lung abnormalities but without airflow obstruction on spirometry.
- These individuals may or may not develop COPD later.



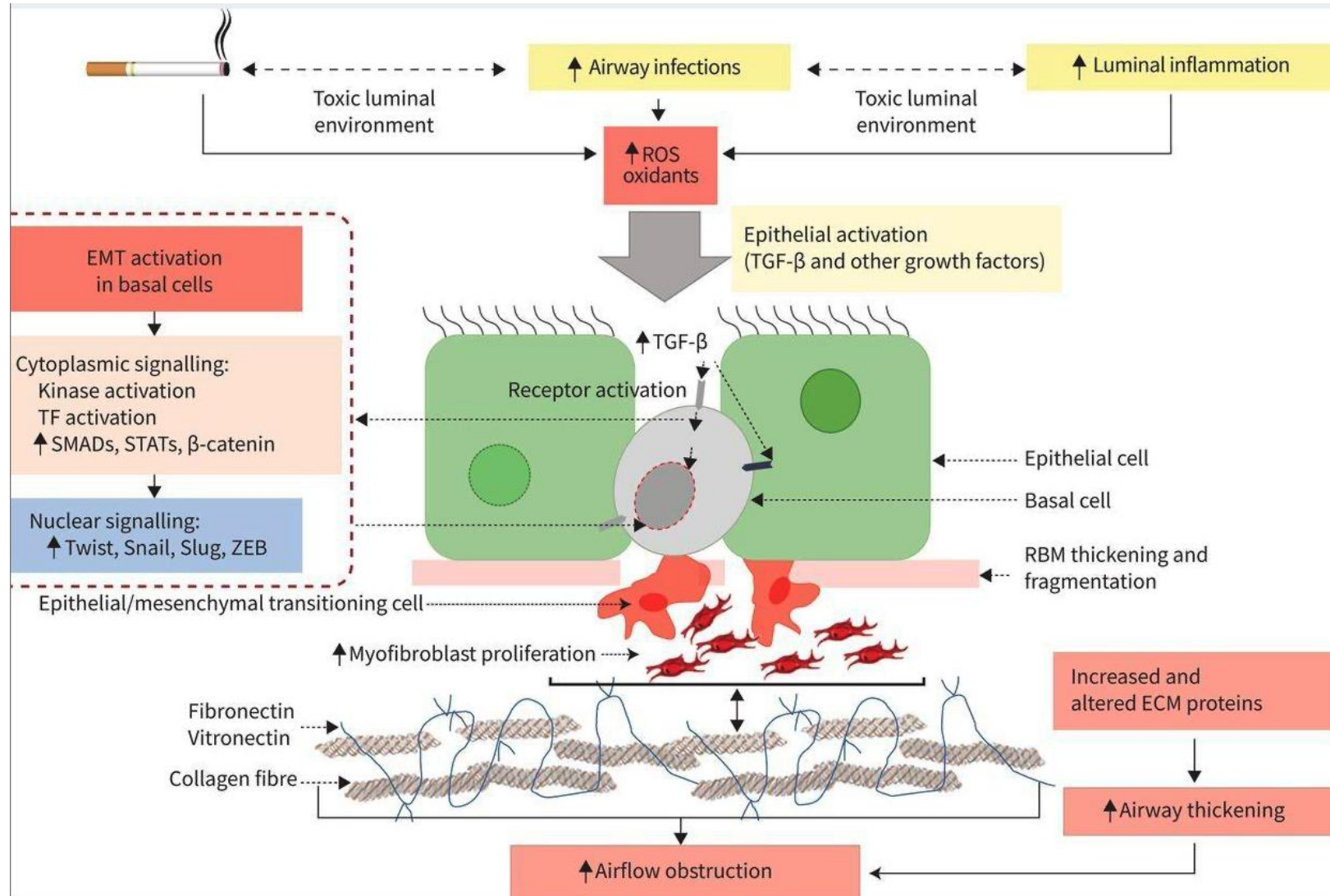
1. Symptoms with normal spirometry (the former GOLD-0 concept)
2. PRISm (normal FEV<sub>1</sub>/FVC but FEV<sub>1</sub> < 80%)
3. Early structural abnormalities on CT
4. Borderline but “normal-range” low lung function

# Pre-COPD - pathophysiology

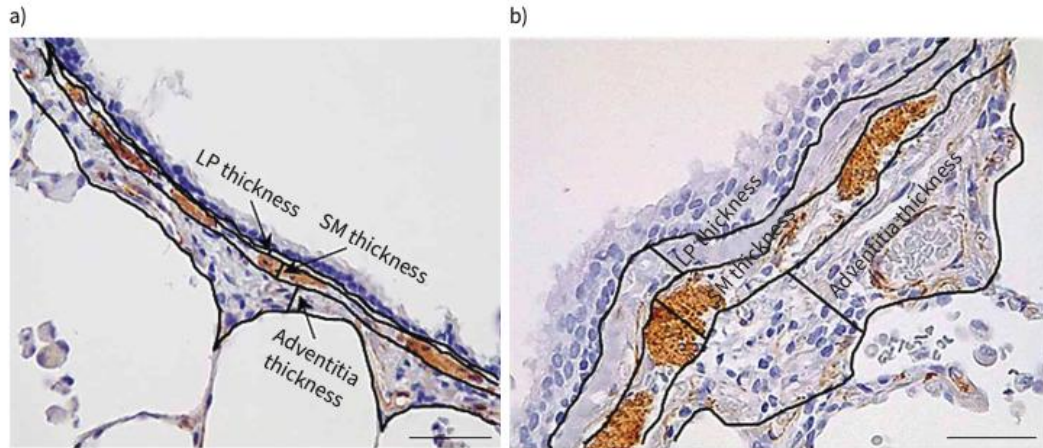
## (1) Epithelial injury and EMT

- Smoking and oxidative stress reprogram basal epithelial cells
- This triggers **epithelial–mesenchymal transition (EMT)** → airway wall thickening, fibrosis, and small-airway obstruction
- Smokers with pre-COPD already show EMT features similar to COPD
- Some regulatory mechanisms (e.g., MAD family factors, blocked  $\beta$ -catenin nuclear translocation) remain partially intact

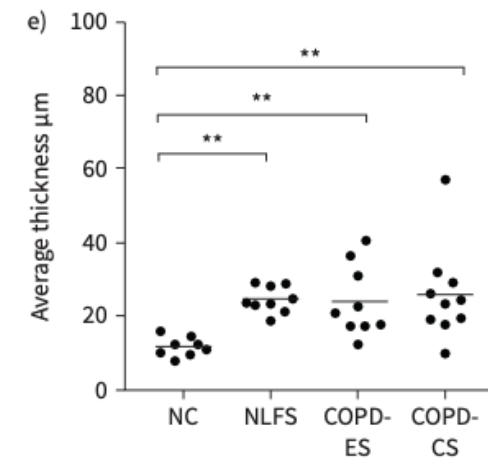
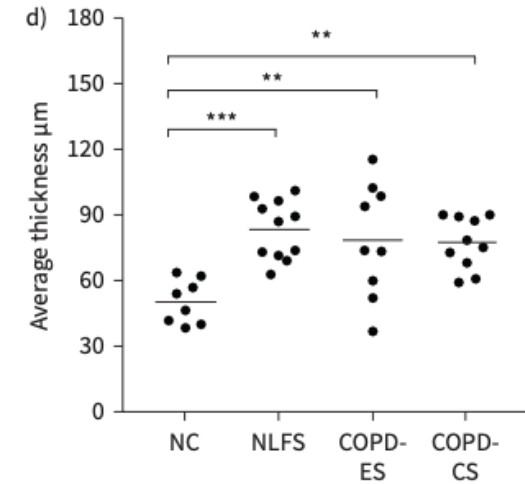
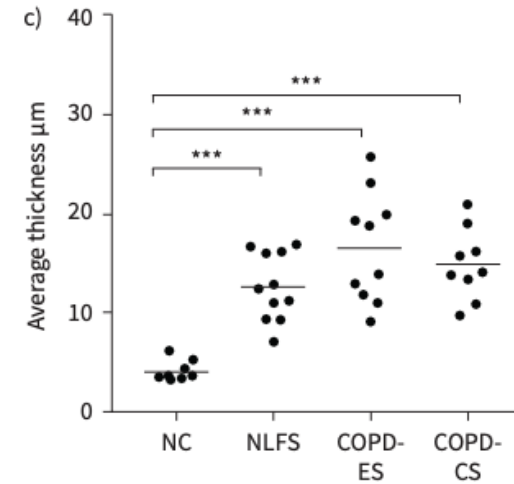
# Pre-COPD - pathophysiology



# Increased myofibroblast in small airways



Increased airway wall thickness and myofibroblast activities in normal lung function smokers

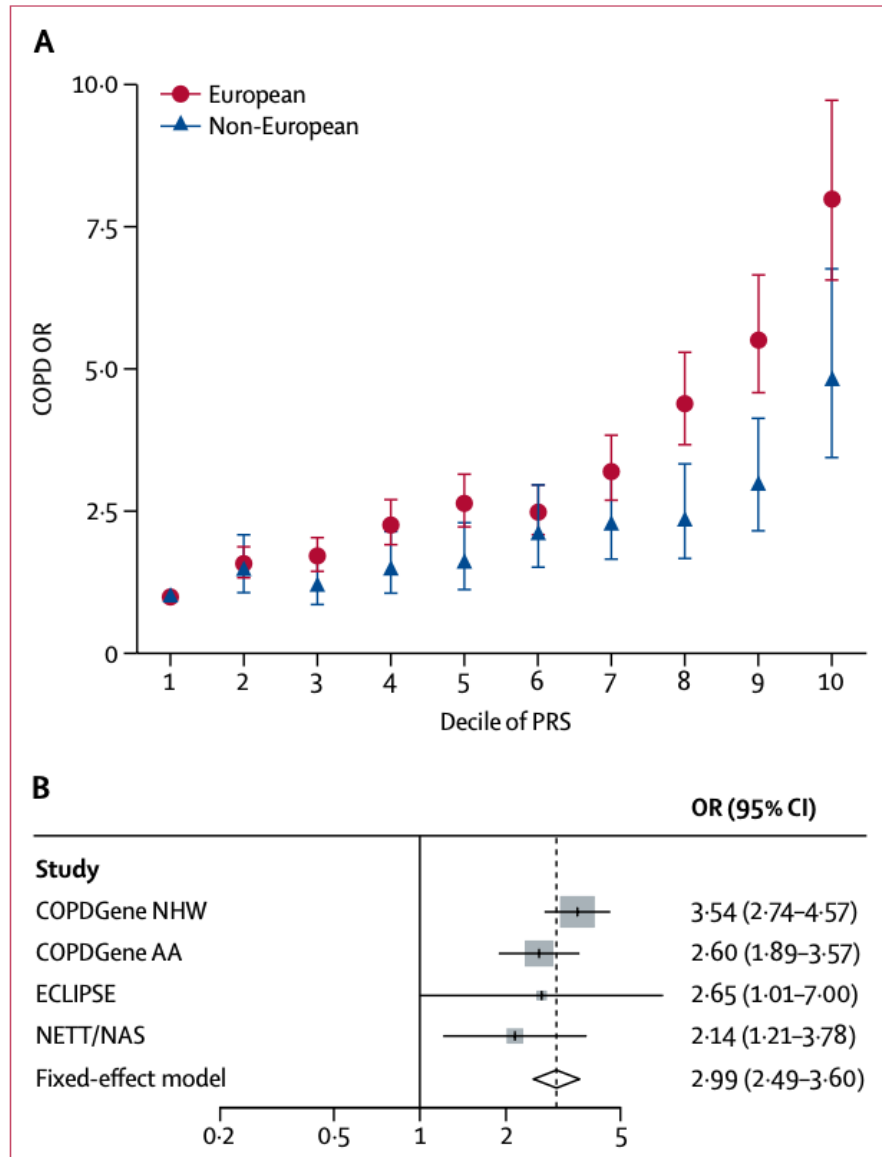


# Pre-COPD - pathophysiology

## (2) Genetic susceptibility

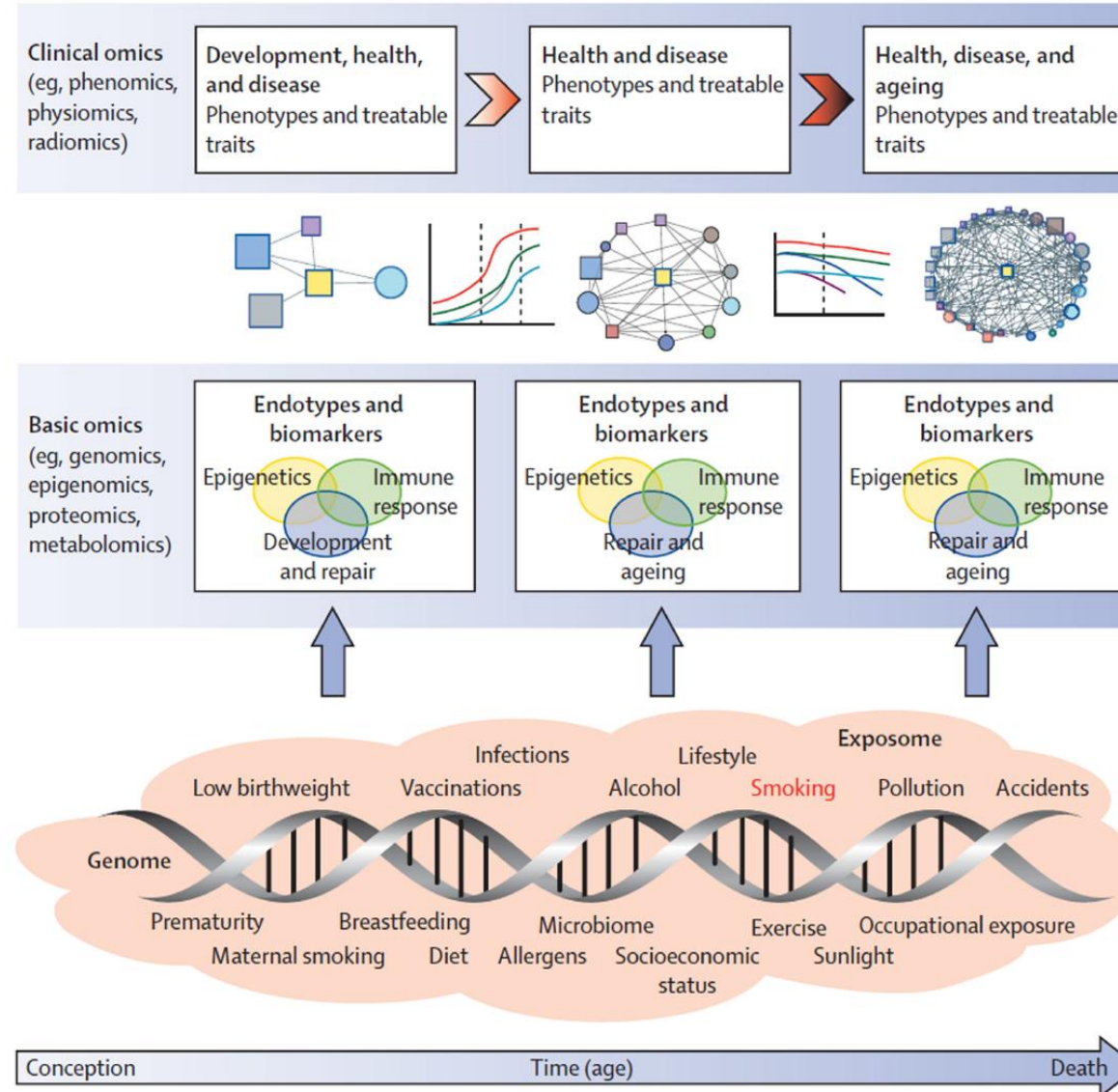
- About 40% of COPD heritable risk comes from common variants
- **Polygenic risk scores** predict low early-life lung function and early airflow limitation
  - Implies genetic contribution to pre-COPD

# Genetic susceptibility of COPD



- GWAS data from **UK Biobank + SpiroMeta**
- Combined PRS =  $0.44 \times \text{PRS}(\text{FEV1}) + 0.59 \times \text{PRS}(\text{FEV1}/\text{FVC})$ .
- Higher PRS related to COPD

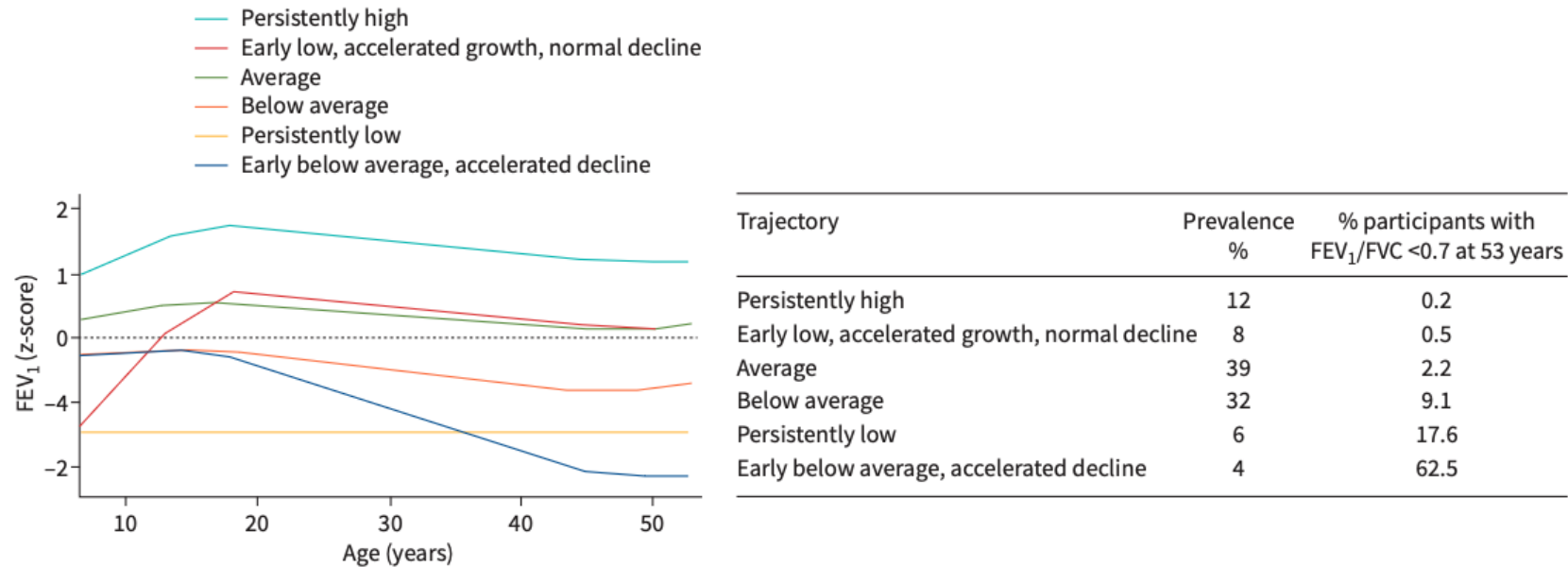
# Pre-COPD - GETomics



# Pre-COPD - pathophysiology

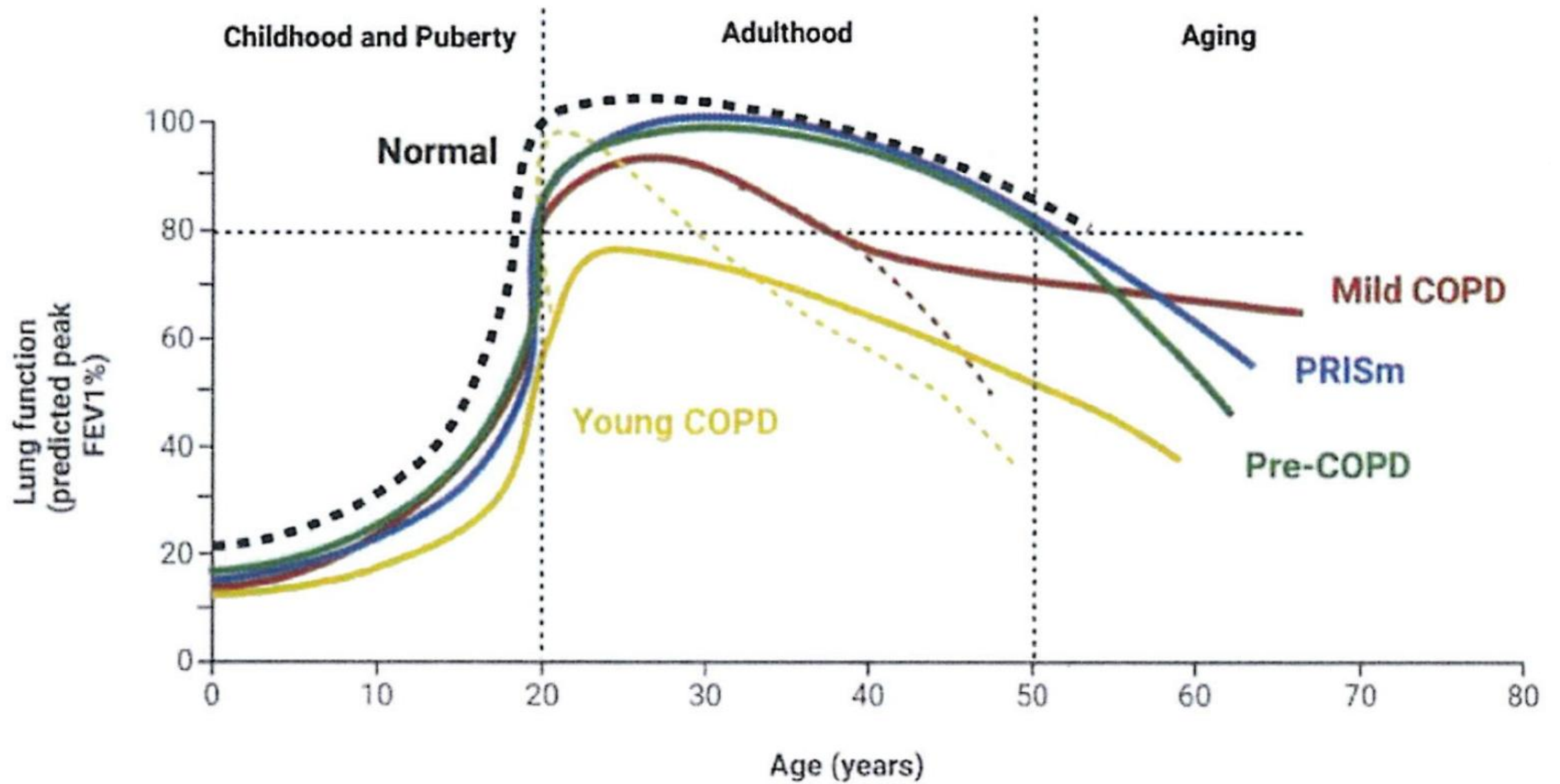
- **(3) Immune/inflammatory markers**
- Biomarkers such as CRP, **CC16**, **CCL19**, **CCL2**, **SP-D**, **sRAGE** are associated with impaired lung function
- DNA methylation patterns differ across lung-function trajectories
- Potential tools for future early detection

# Accelerated decline and biomarkers ; TAHS data

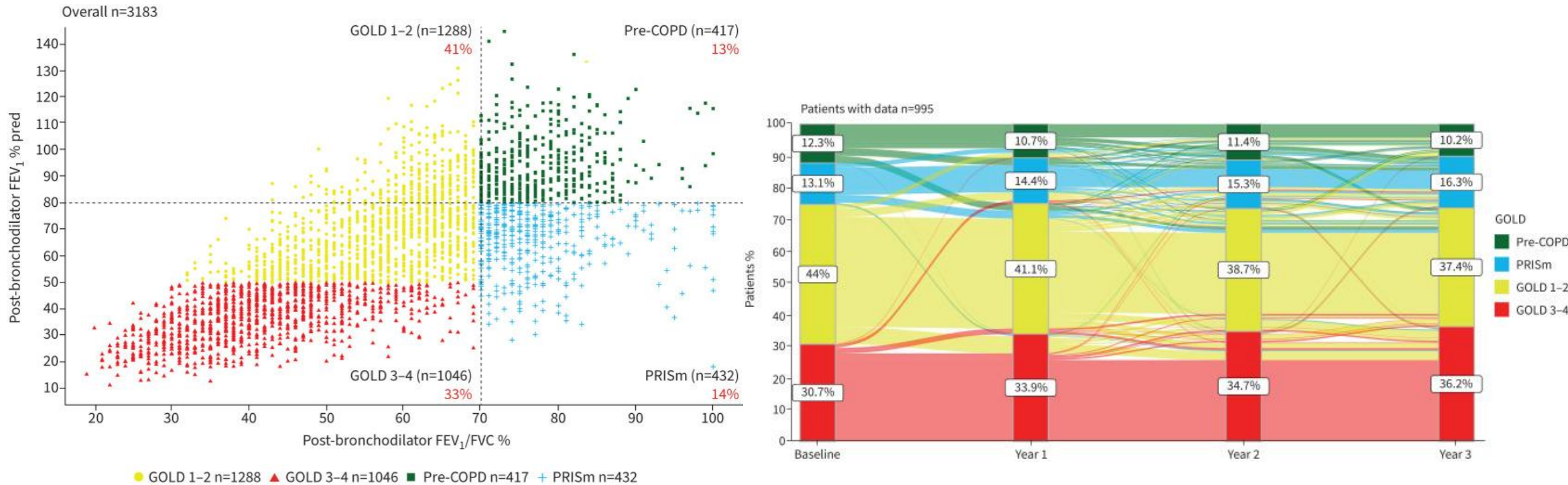


**TABLE 3** Adjusted association between CC16 and C-reactive protein (CRP) levels and the two COPD groups

	COPD with accelerated lung function decline (AD) OR (95% CI) <sup>#</sup>
CC16 levels at 53 years, per unit increase	0.79 (0.63–0.98)*
CC16 levels at 45 years, per unit increase	0.69 (0.52–0.91)**
CRP levels at 53 years, per unit increase	1.07 (1.00–1.13)*
CRP levels at 45 years, per unit increase	1.08 (0.96–1.21)

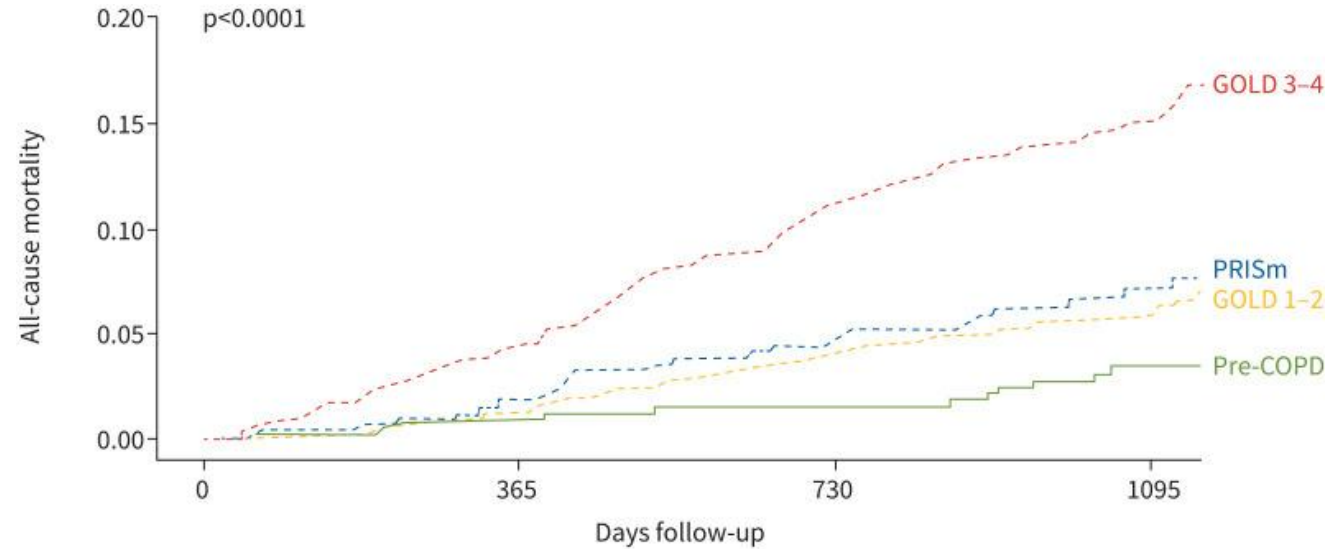
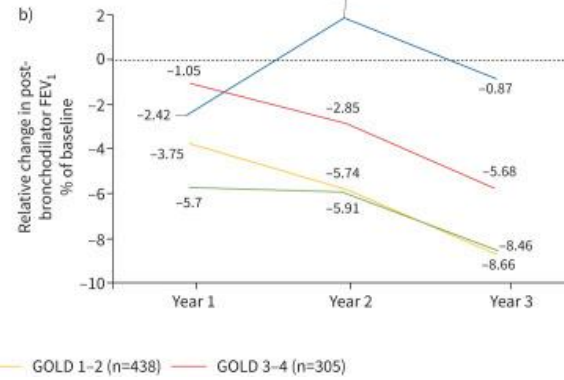
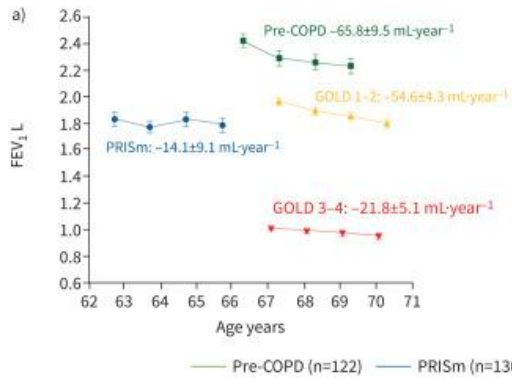


# Pre-COPD, PRISm and COPD in NOVELTY cohort



- 1) COPD GOLD 1-2 (FEV<sub>1</sub>/FVC ratio <0.70 and FEV<sub>1</sub> ≥50% to <80% pred)
- 2) COPD GOLD 3-4 (FEV<sub>1</sub>/FVC ratio <0.7 and FEV<sub>1</sub> <50% pred)
- 3) pre-COPD: diagnosis of COPD with normal spirometry (FEV<sub>1</sub>/FVC ratio ≥0.70 and FEV<sub>1</sub> ≥80% pred)
- 4) PRISm: diagnosis of COPD with FEV<sub>1</sub>/FVC ratio ≥0.70 and FEV<sub>1</sub> <80% pred

# Pre-COPD, PRISm and COPD in NOVELTY cohort



	0	365	730	1095
Pre-COPD	417	401	329	232
PRISm	432	410	339	236
GOLD 1-2	1288	1231	1087	788
GOLD 3-4	1046	962	796	545
<b>0</b>	<b>365</b>	<b>730</b>	<b>1095</b>	

# Definition of terms

**“Early”** = Biological term

**“Mild”** = Airflow limitation level

**“Young”** = Age 20-50

**“Pre”** = Symptom or structural change without airflow obstruction

**“PRISm”** = correlates with metabolic syndrome and elevated all-cause mortality.

Etiotypes

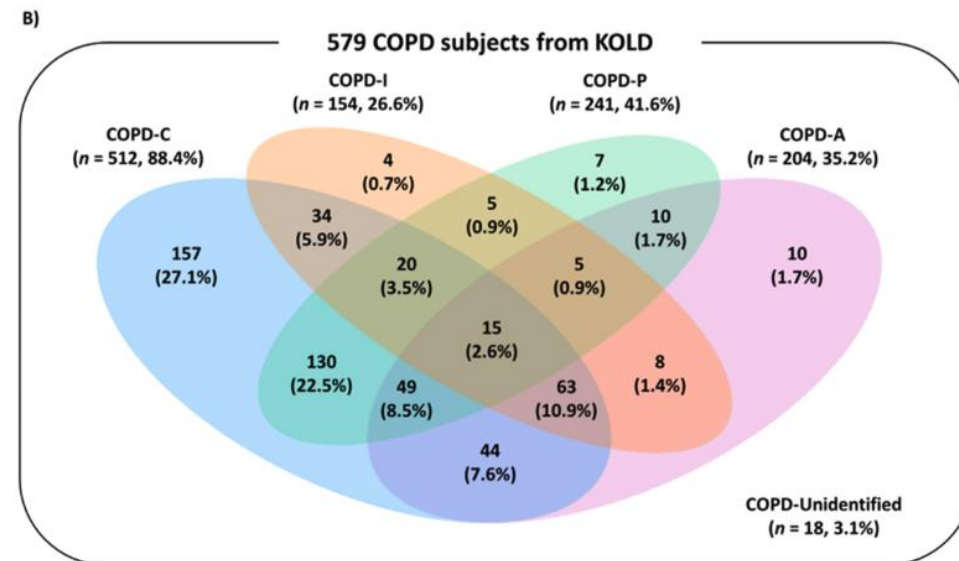
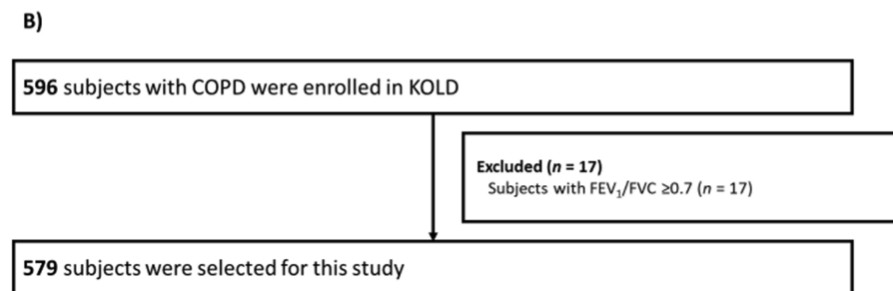
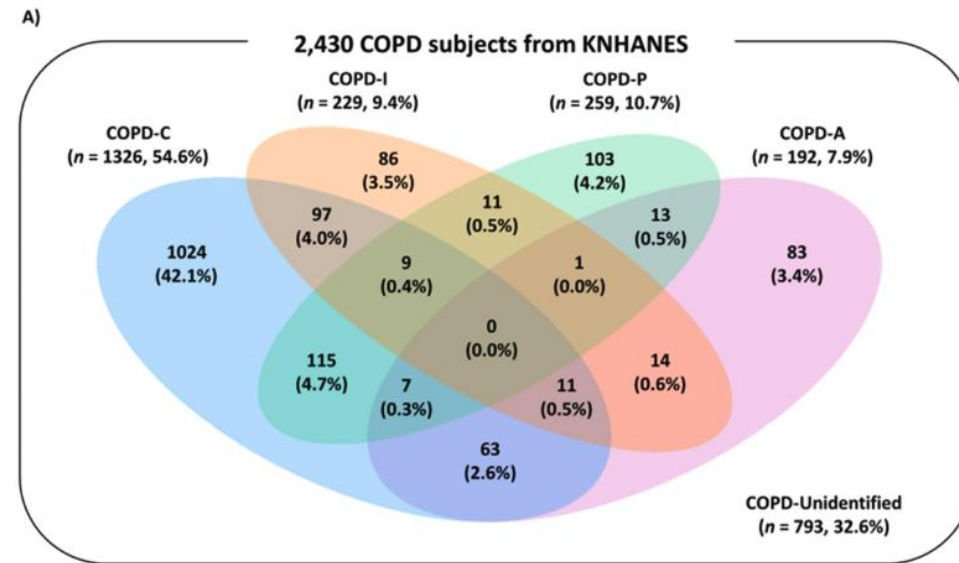
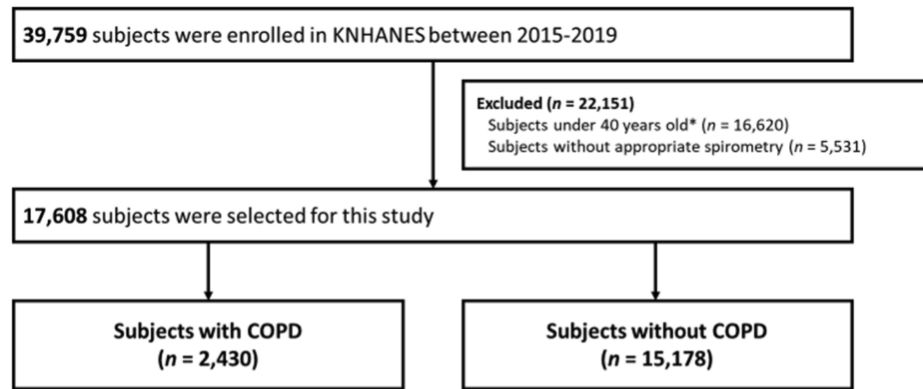
# Proposed Taxonomy (Etiotypes) for COPD

Figure 1.2

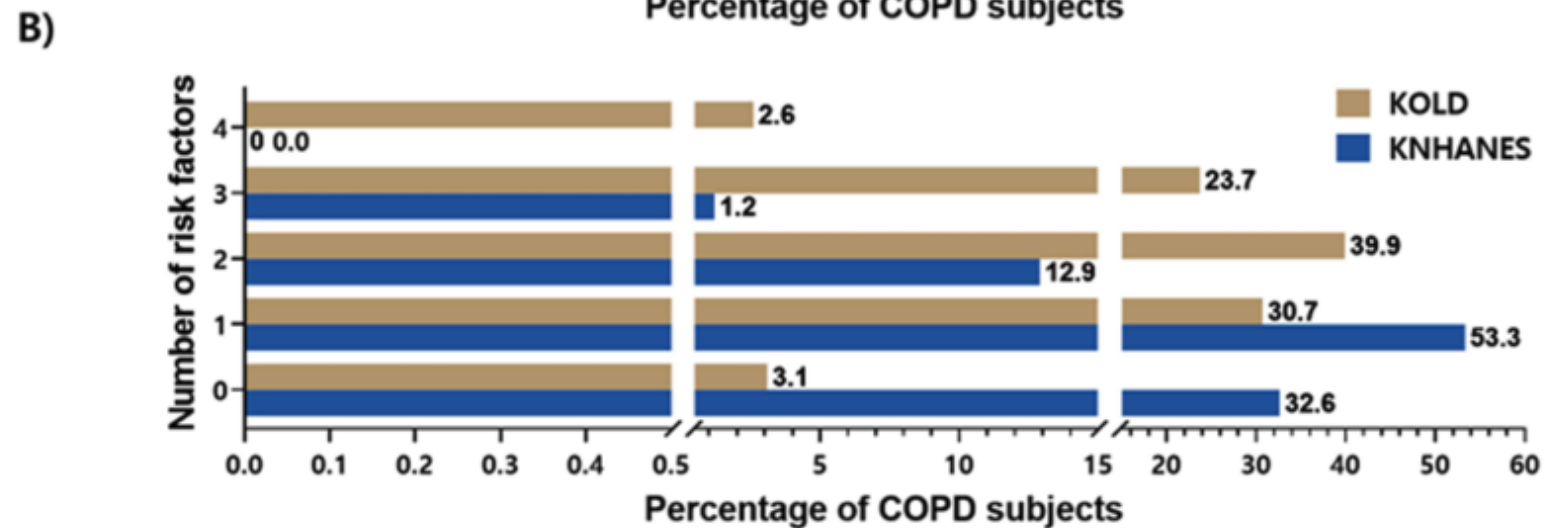
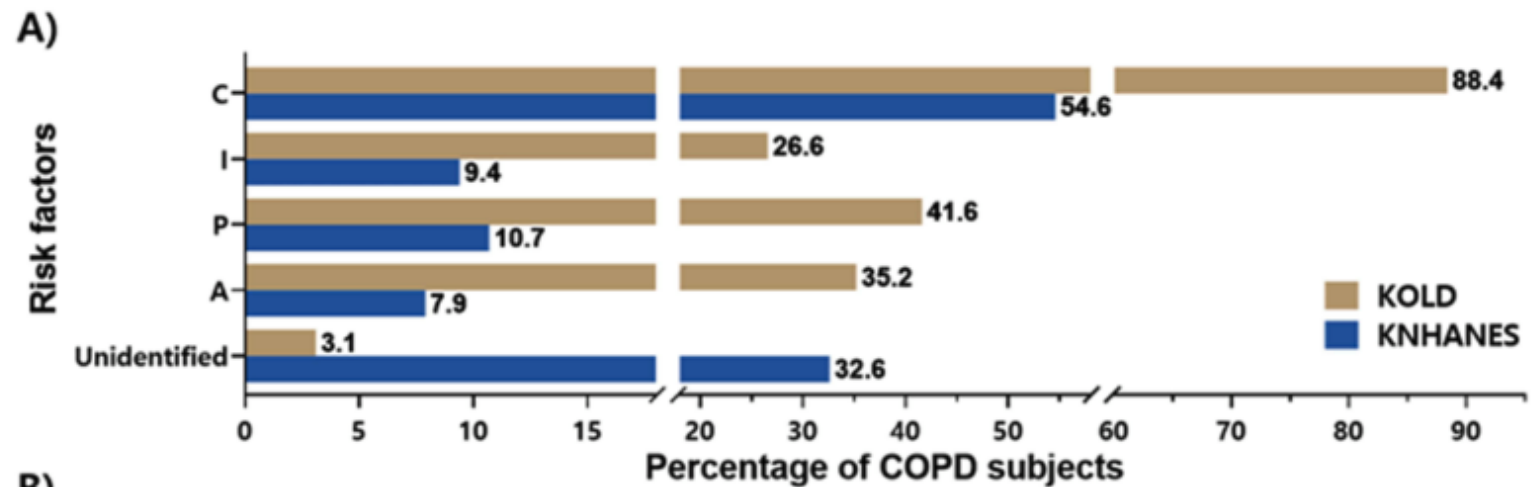
Classification	Description
Genetically determined COPD (COPD-G)	Alpha-1 antitrypsin deficiency (AATD) Other genetic variants with smaller effects acting in combination
COPD due to abnormal lung development (COPD-D)	Early life events, including premature birth and low birthweight, among others
<b>Environmental COPD</b>	
Cigarette smoking COPD (COPD-C)	<ul style="list-style-type: none"><li>• Exposure to tobacco smoke, including <i>in utero</i> or via passive smoking</li><li>• Vaping or e-cigarette use</li><li>• Cannabis</li></ul>
Biomass and pollution exposure COPD (COPD-P)	Exposure to household pollution, ambient air pollution, wildfire smoke, occupational hazards
COPD due to infections (COPD-I)	Childhood infections, tuberculosis-associated COPD, HIV-associated COPD
COPD & asthma (COPD-A)	Particularly childhood asthma
COPD of unknown cause (COPD-U)	

\*Adapted from Celli et al. (2022) and Stolz et al. (2022)

# COPD Risk Factor Profiles in General Population and Referred Patients



# COPD Risk Factor Profiles in General Population and Referred Patients

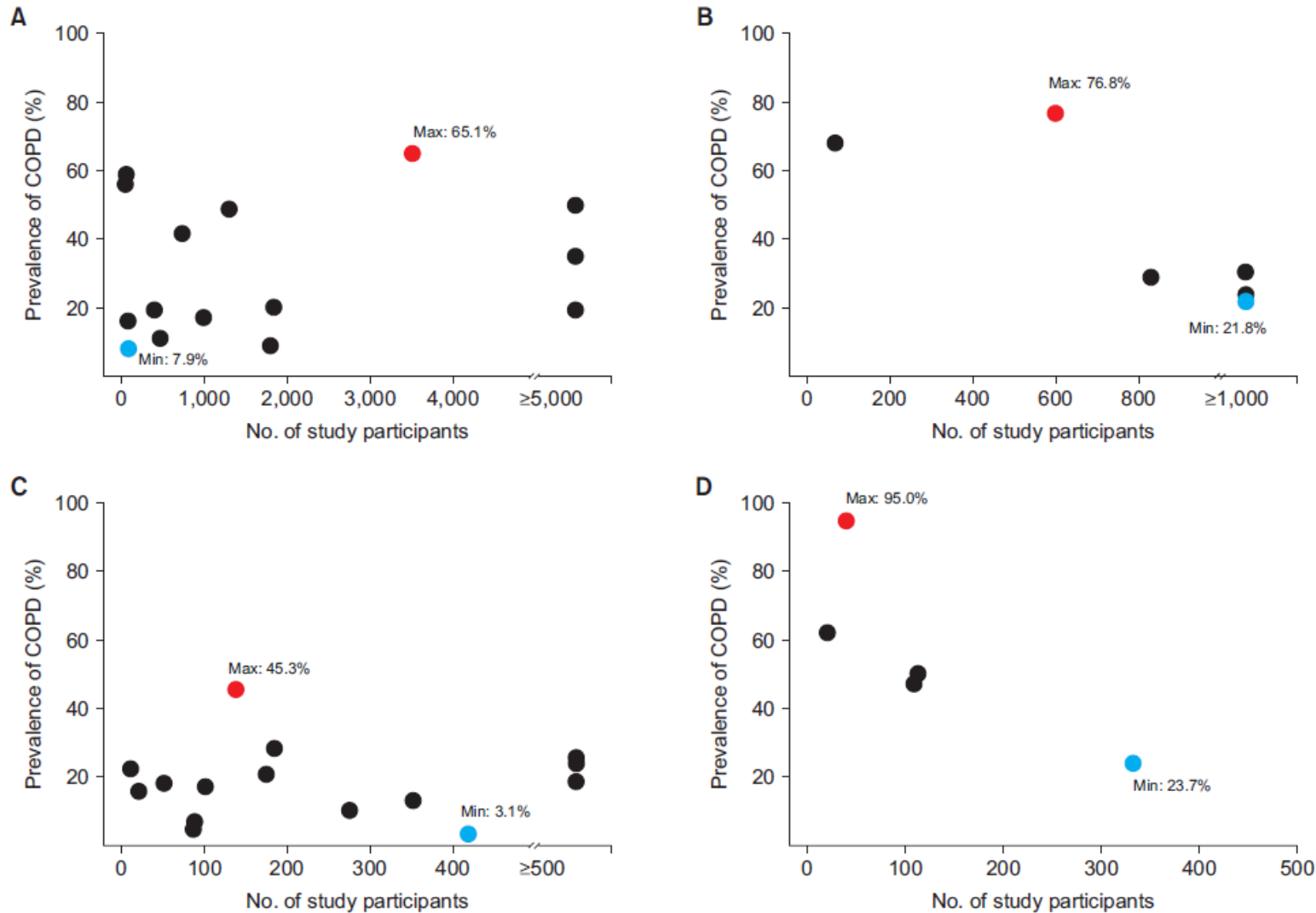


# COPD etiotypes – limitations and controversy

- New definitions - COPD as a heterogeneous, multi-etiological disease group rather than a smoking-related disorder
- This expansion may lead to over-inclusiveness
- How to classify post-TB airflow limitation, bronchiectasis, NTM-PD, anthracofibrosis, and pneumoconiosis?

# Prevalence of COPD-I

**Figure 1.** Prevalence of chronic obstructive pulmonary disease (COPD). (A) Bronchiectasis. (B) Tuberculosis-destroyed lung. (C) Non-tuberculous mycobacterial pulmonary disease. (D) Anthracofibrosis.



COPD prevalence (%)

1) bronchiectasis 7.9-65.1

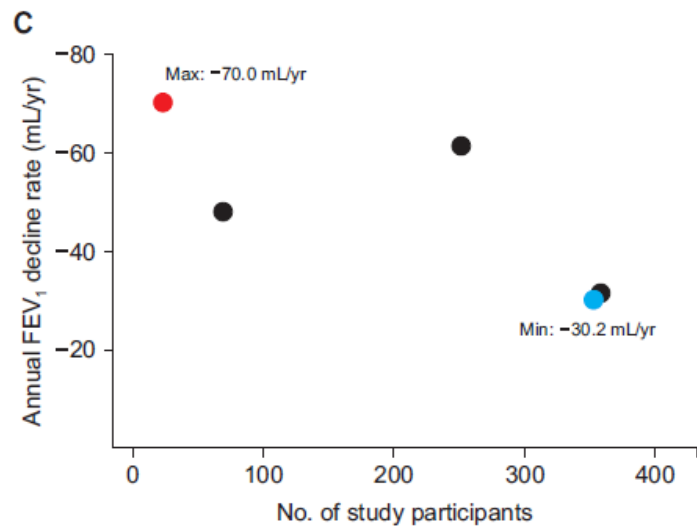
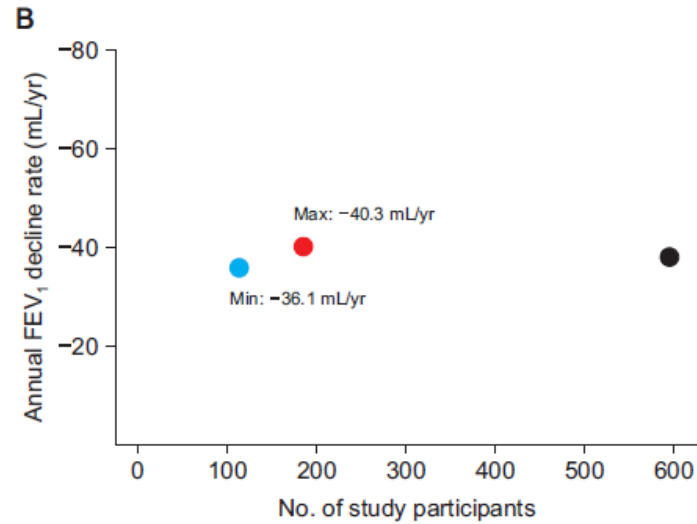
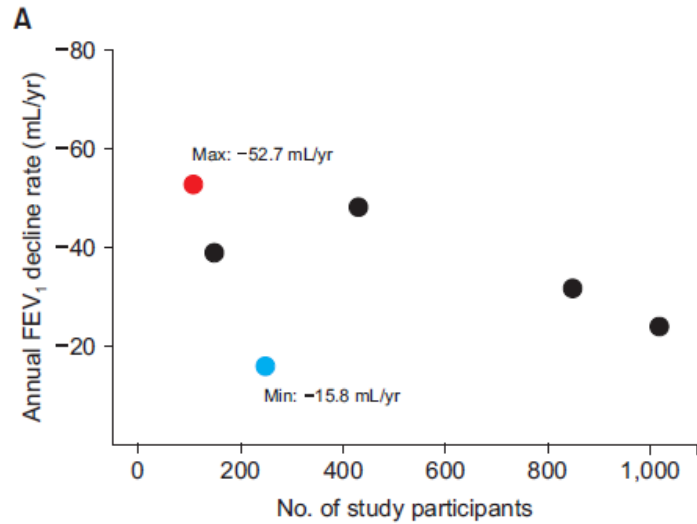
2) TB-D 21.8-76.8

3) NTM-PD 3.1-45.3

4) Anthracofibrosis 23.7-95.0

# Prevalence of COPD-I

**Figure 2.** Annual decline in lung function. (A) Bronchiectasis. (B) Tuberculosis-destroyed lung. (C) Non-tuberculous mycobacterial pulmonary disease. There have been no research results on changes in lung function in anthracofibrosis. FEV<sub>1</sub>: forced expiratory volume in 1 second.



Lung function decline (mL/yr)  
1) bronchiectasis -53 - -16  
2) TB-D -36 --40  
3) NTM-PD -70 - -30

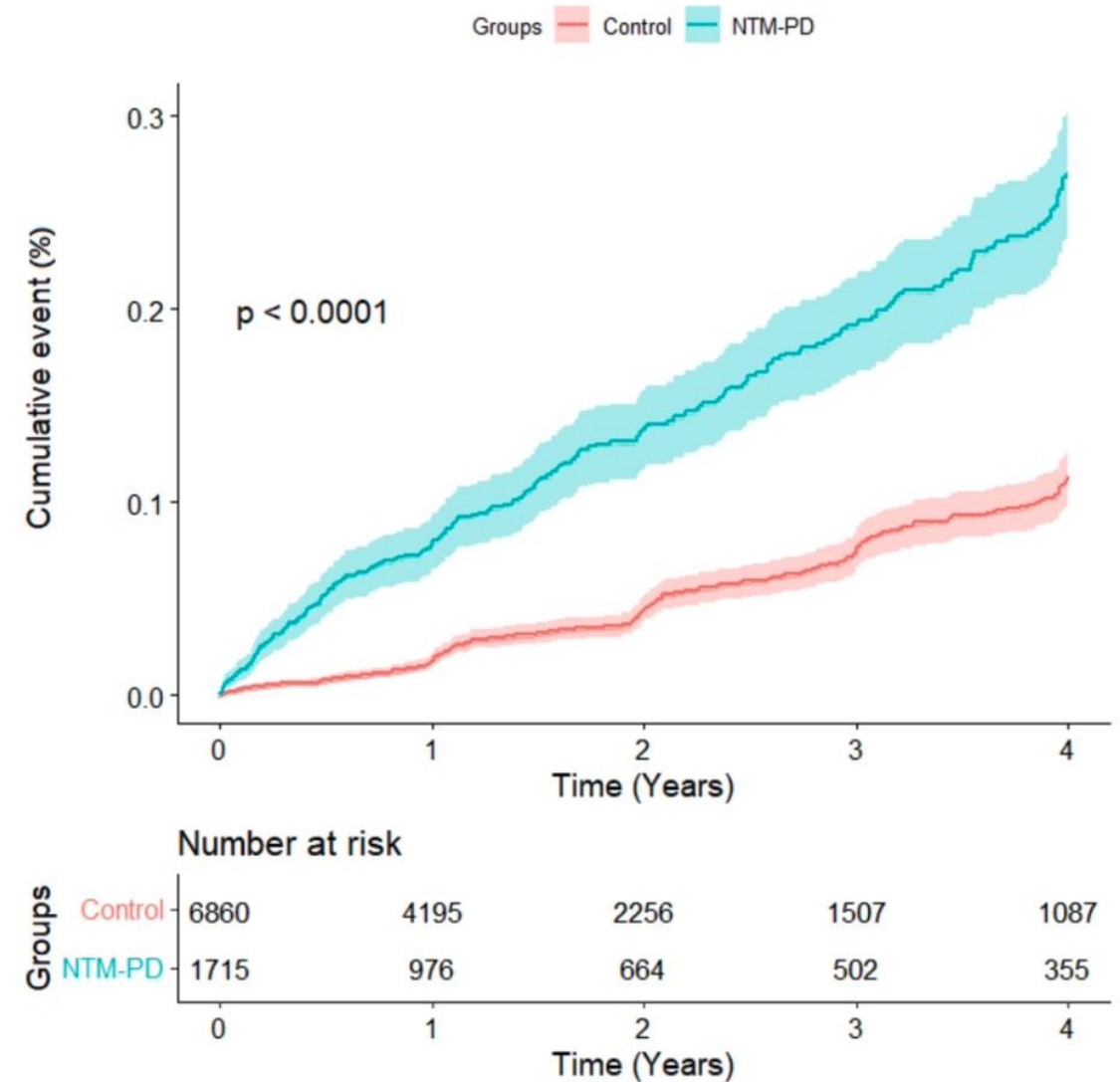
# COPD after NTM-PD

**Table 3** Association between NTM-PD and COPD development

	<i>n</i>	Incident cases of COPD ( <i>n</i> [%])	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)
<b>Before matching</b>				
Control cohort	90,088	2,031 (2.3)	Reference	Reference
NTM-PD cohort	1,715	241 (14.0)	5.46 (4.78–6.24)	1.81 (1.54–2.13)
<b>After matching</b>				
Matched control cohort	6,860	293 (4.3)	Reference	Reference
NTM-PD cohort	1,715	241 (14.0)	3.02 (2.54–3.58)	2.57 (2.15–3.09)
<b>Sex</b>				
<b>Male</b>				
Matched control cohort	2,560	209 (8.2)	Reference	Reference
NTM-PD cohort	735	120 (16.3)	1.84 (1.47–2.30)	1.56 (1.23–1.97)
<b>Female</b>				
Matched control cohort	4,300	84 (2.0)	Reference	Reference
NTM-PD cohort	980	121 (12.3)	5.75 (4.36–7.61)	5.44 (4.11–7.23)
<b>Age</b>				
<b>&lt; 60 years</b>				
Matched control cohort	3,111	48 (1.5)	Reference	Reference
NTM-PD cohort	686	80 (11.7)	7.18 (5.02–10.26)	6.94 (4.84–9.94)
<b>≥ 60 years</b>				
Matched control cohort	3,749	245 (6.5)	Reference	Reference
NTM-PD cohort	1,029	161 (15.6)	2.17 (1.78–2.65)	2.01 (1.63–2.47)

\*Adjusted for age, sex, BMI, smoking status, and comorbidities (tuberculosis, hypertension, diabetes mellitus, ischemic heart disease, and cerebrovascular disease)

**Abbreviations:** NTM-PD, nontuberculous mycobacterial pulmonary disease; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; CI, confidence interval; BMI, body mass index



# COPD after TB

**Table 2** Incidence Rate and Incidence Rate Ratio of Tuberculosis-Associated Chronic Obstructive Pulmonary Disease Stratified by the Follow-Up Duration Quartile

Follow-up Duration [min-max]	Incidence Rate (1000 PY)	Incidence Rate Ratio	P
Q1 [18–71 months]	40.48	Reference	–
Q2 [72–95 months]	26.58	0.66	0.241
Q3 [96–131 months]	21.89	0.54	0.083
Q4 [132–235 months]	19.61	0.49	0.027

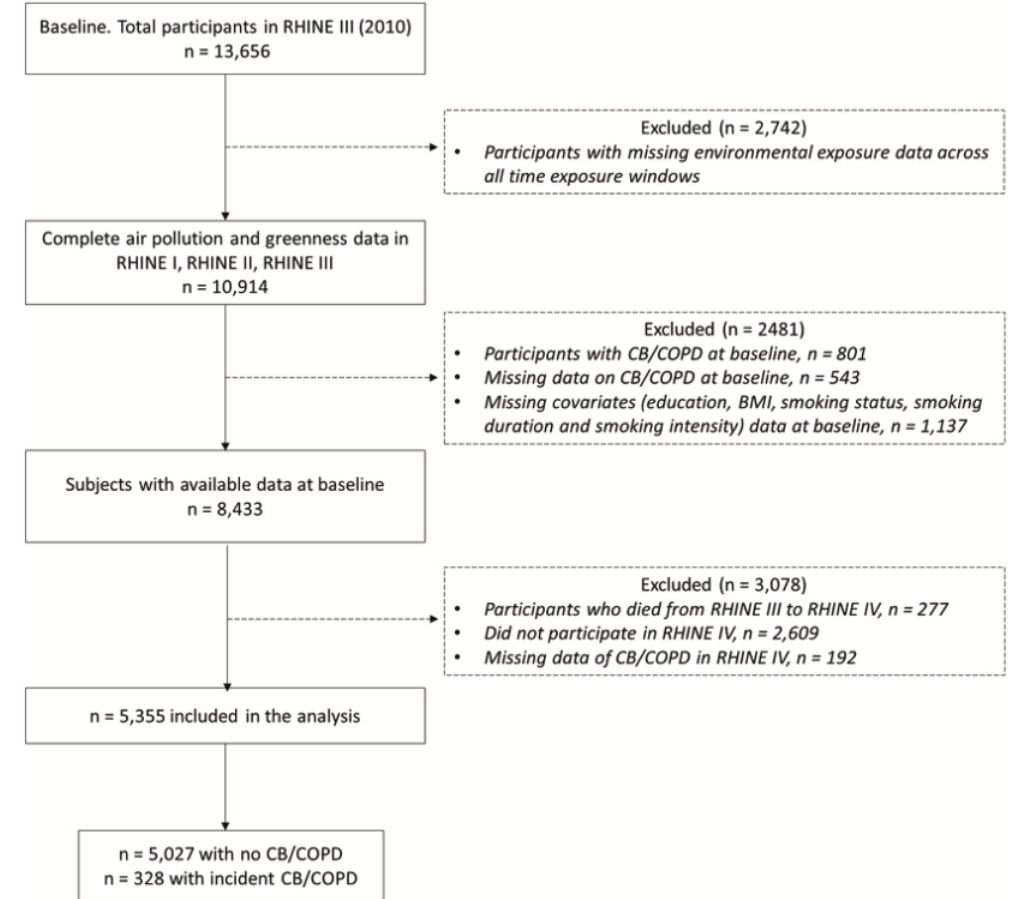
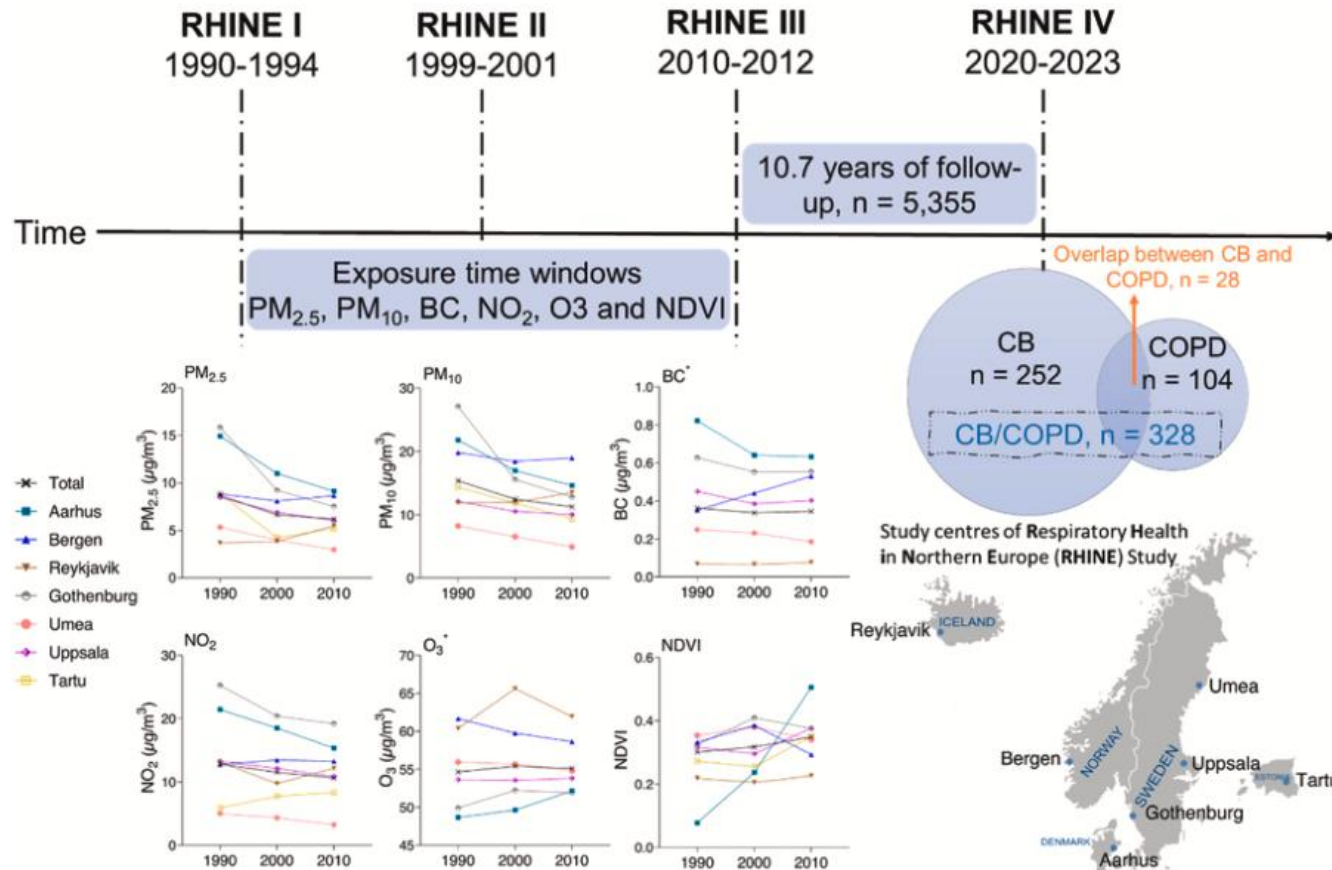
Older age at tuberculosis diagnosis, lower baseline FEV<sub>1</sub> <80%, smoking history, and multilobar involvement were identified as risk factors for tuberculosis-associated COPD

**Table 3** Univariate and Multivariate Logistic Regression Models for the Development of Tuberculosis-Associated Chronic Obstructive Pulmonary Disease

Variables	Univariate Logistic Regression				Multivariate Logistic Regression			
	OR	Lower CI	Upper CI	P	aOR	Lower CI	Upper CI	P
Sex (Ref, Male)	0.60	0.34	1.05	0.073	1.21	0.42	3.48	0.724
Age, year (TB diagnosis)	1.02	1.01	1.05	0.010	1.04	1.01	1.07	0.009
Ever smoker	1.90	1.09	3.32	0.025	3.23	1.14	9.17	0.028
Baseline FEV <sub>1</sub> (%), (Ref, ≥90%)								
80%≤FEV <sub>1</sub> <90%	1.58	0.73	3.38	0.242	1.72	0.68	4.39	0.255
FEV <sub>1</sub> <80%	2.97	1.64	5.39	P <0.001	3.98	1.92	8.24	p <0.001
Endobronchial tuberculosis	2.42	0.97	6.02	0.057	2.58	0.73	9.18	0.142
Multidrug resistant tuberculosis	1.47	0.45	4.75	0.524				
Sputum AFB ≥ 1+	1.84	0.98	3.45	0.059	1.09	0.51	2.33	0.830
Airway stenosis in Radiography	2.32	0.89	6.08	0.085	3.01	0.93	9.79	0.067
Bronchiectasis in Radiography	1.69	0.89	3.19	0.106				
Multilobar involvement in Radiography	1.69	0.98	2.93	0.059	2.04	1.08	3.85	0.028
Pleurisy in Radiography	0.96	0.40	2.29	0.921				
Bronchiolitis in Radiography	1.24	0.66	2.30	0.504				
Volume loss in Radiography	1.61	0.55	4.70	0.380				
Cavity in Radiography	1.12	0.55	2.25	0.759				
Destroyed lung in Radiography	0.79	0.33	1.86	0.591				
Mass in Radiography	1.19	0.56	2.56	0.648				
Bronchial wall thickening in Radiography	1.18	0.24	5.85	0.836				

Abbreviations: AFB, Acid-Fast Bacilli; aOR, adjusted odds ratio; CI, confidence interval; FEV<sub>1</sub>, Forced Expiratory Volume in 1 s; OR, odds ratio; TB, tuberculosis.

# Air pollution and COPD incidence (COPD-P)



328 incident cases of CB/COPD during 2010–2023

# Air pollution and COPD incidence

**Table 2**

Incidence rate ratio (IRR) and 95% CI for the association between air pollutants and greenness and CB/COPD incidence in all subjects (n = 5355).

CB/COPD	Exposure in 1990		Exposure in 2000		Exposure in 2010	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
PM <sub>2.5</sub>	1.00 (0.71–1.40)	0.97 (0.70–1.35)	1.05 (0.66–1.69)	1.12 (0.70–1.79)	1.05 (0.75–1.48)	1.07 (0.76–1.51)
PM <sub>10</sub>	1.01 (0.76–1.37)	1.00 (0.74–1.34)	1.06 (0.71–1.60)	1.11 (0.74–1.67)	1.05 (0.77–1.42)	1.07 (0.79–1.45)
BC*	0.96 (0.76–1.24)	0.97 (0.75–1.24)	1.04 (0.79–1.36)	1.08 (0.82–1.40)	1.12 (0.86–1.47)	1.16 (0.88–1.51)
NO <sub>2</sub>	1.12 (0.90–1.41)	1.13 (0.90–1.41)	1.15 (0.94–1.42)	1.18 (0.96–1.45)	1.13 (0.95–1.34)	1.14 (0.96–1.35)
O <sub>3</sub> *	0.88 (0.70–1.11)	0.87 (0.69–1.10)	0.86 (0.67–1.10)	0.84 (0.66–1.07)	0.89 (0.69–1.14)	0.88 (0.69–1.14)
NDVI	1.02 (0.91–1.14)	1.01 (0.90–1.13)	0.97 (0.89–1.06)	0.96 (0.88–1.05)	1.00 (0.91–1.10)	1.00 (0.90–1.10)

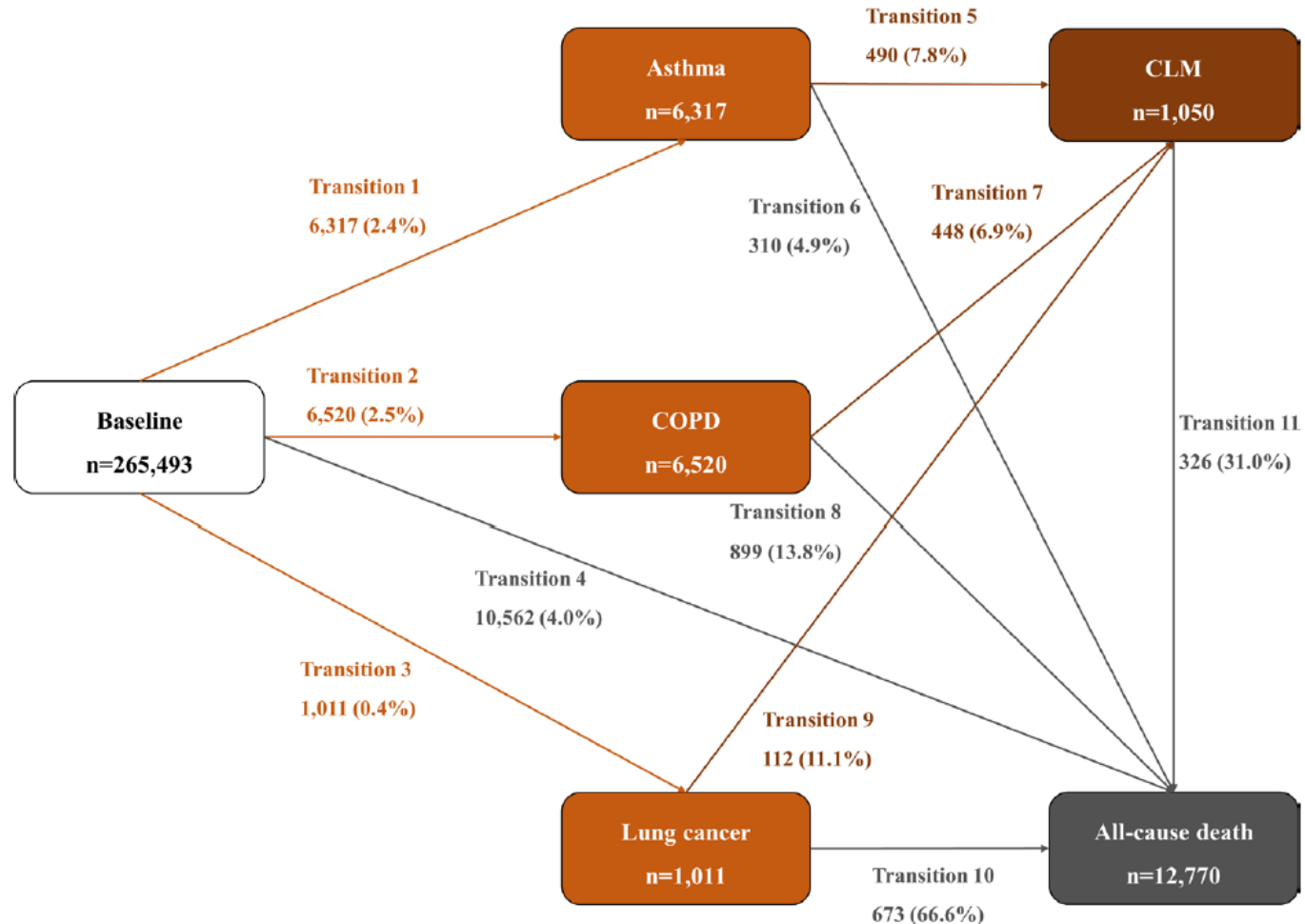
**Table 3**

Incidence rate ratio (IRR) and 95% CI for the relationship between air pollution and greenness with CB/COPD incidence, derived from a **two-exposure model**.

Exposure		Exposure in 1990	Exposure in 2000	Exposure in 2010
		IRR (95% CI)	IRR (95% CI)	IRR (95% CI)
PM <sub>2.5</sub>	+ NDVI	0.98 (0.69–1.39)	1.07 (0.66–1.75)	1.08 (0.75–1.56)
PM <sub>10</sub>	+ NDVI	1.00 (0.74–1.37)	1.07 (0.70–1.64)	1.08 (0.78–1.50)
BC*	+ NDVI	0.97 (0.74–1.27)	1.04 (0.78–1.39)	1.20 (0.89–1.61)
NO <sub>2</sub>	+ NDVI	1.18 (0.90–1.55)	1.17 (0.93–1.46)	1.17 (0.96–1.42)
O <sub>3</sub> *	+ NDVI	0.82 (0.62–1.08)	0.86 (0.66–1.12)	0.85 (0.64–1.12)
NDVI	+ PM <sub>2.5</sub>	1.00 (0.89–1.13)	0.97 (0.88–1.06)	1.00 (0.90–1.12)
NDVI	+ PM <sub>10</sub>	1.01 (0.90–1.13)	0.97 (0.88–1.06)	1.01 (0.90–1.12)
NDVI	+ BC*	1.00 (0.89–1.13)	0.97 (0.88–1.06)	1.04 (0.93–1.15)
NDVI	+ NO <sub>2</sub>	1.05 (0.92–1.9)	0.99 (0.90–1.09)	1.04 (0.93–1.16)
NDVI	+ O <sub>3</sub> *	1.06 (0.93–1.20)	0.98 (0.89–1.08)	1.04 (0.93–1.16)

The association between residential air pollution and COPD incidence was insignificant in this study

# COPD-P - Evidence from UK Biobank data



Median follow-up of 11.9 years, 13,863 participants developed at least one chronic lung disease, 1,055 developed chronic lung multimorbidity and 12,772 died

# COPD-P - Evidence from UK Biobank data

**Table 2** HR (95% CIs) for each transition in transition pattern A by ambient air pollutants

	HR (95% CI), per 5 µg/m <sup>3</sup>				
	PM <sub>2.5</sub>	PM <sub>2.5-10</sub>	PM <sub>10</sub>	NO <sub>2</sub>	NO <sub>x</sub>
Baseline → incident chronic lung disease	<b>1.31 (1.22 to 1.42)</b>	0.94 (0.85 to 1.03)	<b>1.10 (1.05 to 1.15)</b>	<b>1.02 (1.01 to 1.03)</b>	<b>1.01 (1.01 to 1.02)</b>
Incident chronic lung disease → chronic lung multimorbidity	<b>1.27 (1.01 to 1.57)</b>	1.22 (0.88 to 1.68)	1.14 (0.97 to 1.35)	<b>1.05 (1.01 to 1.08)</b>	<b>1.02 (1.00 to 1.04)</b>
Baseline → death	<b>1.32 (1.21 to 1.45)</b>	0.98 (0.88 to 1.09)	<b>1.06 (1.01 to 1.11)</b>	<b>1.02 (1.01 to 1.03)</b>	<b>1.02 (1.01 to 1.02)</b>
Incident chronic lung disease → death	<b>1.24 (1.01 to 1.53)</b>	1.09 (0.85 to 1.41)	<b>1.18 (1.05 to 1.33)</b>	<b>1.03 (1.00 to 1.06)</b>	<b>1.01 (1.00 to 1.03)</b>
Chronic lung multimorbidity → death	<b>1.91 (1.14 to 3.20)</b>	1.17 (0.64 to 2.13)	<b>1.55 (1.13 to 2.11)</b>	<b>1.11 (1.04 to 1.18)</b>	<b>1.04 (1.01 to 1.07)</b>

Bold values denote statistically significant results.

NO<sub>2</sub>, nitrogen dioxide; NO<sub>x</sub>, nitrogen oxides; PM<sub>10</sub>, particulate matter with diameter ≤10µm.

# COPD-P - Evidence from UK Biobank data

171,132 participants free of COPD and asthma at baseline from the UK Biobank, who had data on air pollution and metabolomics.

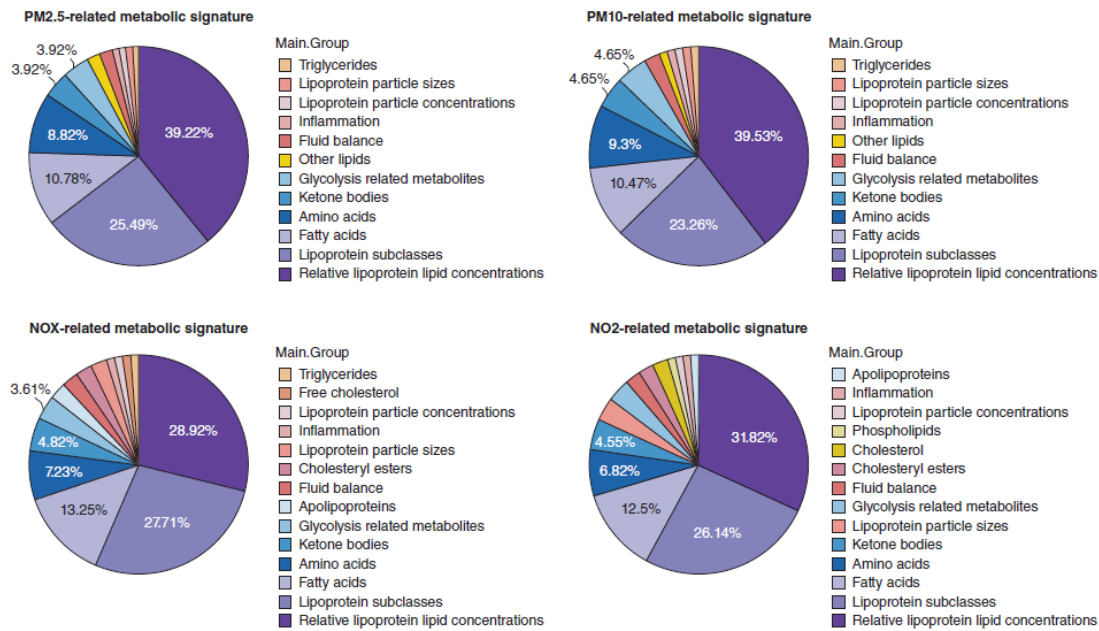
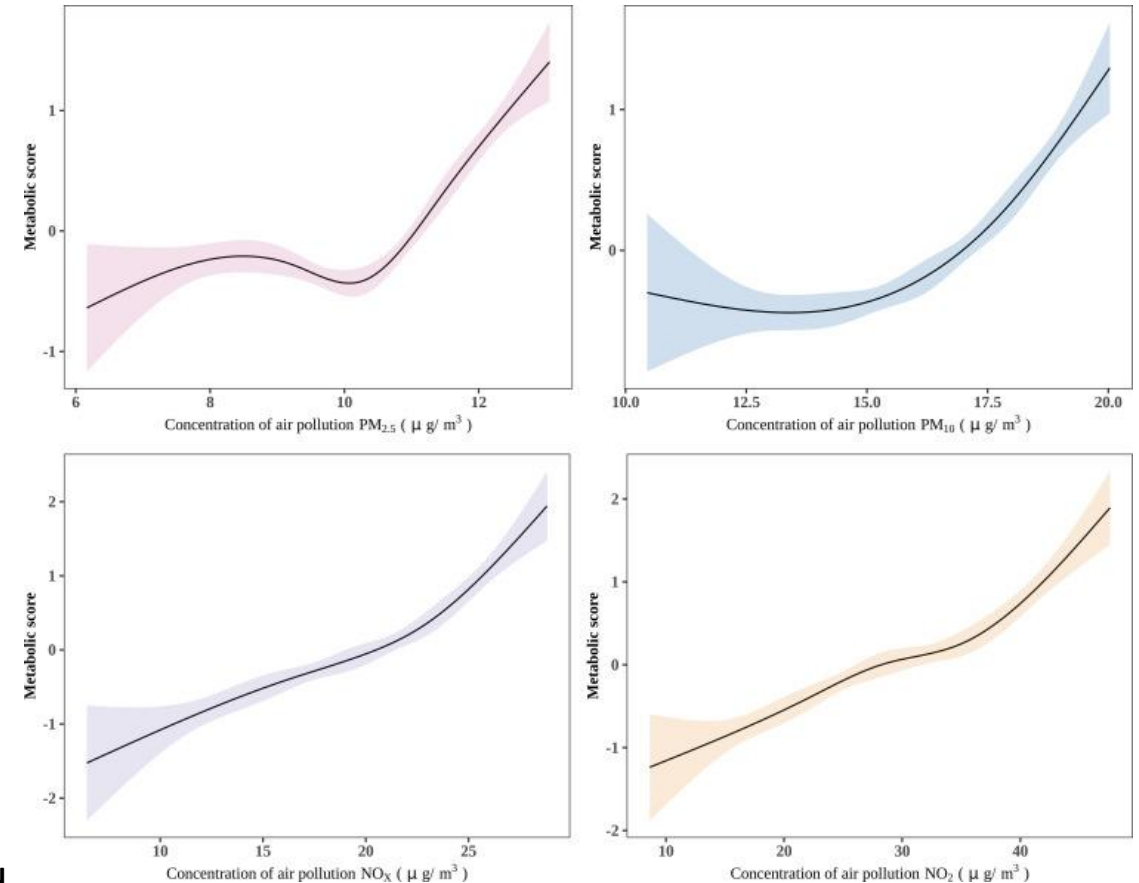


Figure 1 - Composition and distribution of the derived metabolites.  $NO_2$  = nitrogen dioxide;  $NO_x$  = nitrogen oxide;  $PM_{2.5}$  = fine particulate matter with a diameter < 2.5  $\mu m$ ;  $PM_{10}$  = particulate matter with a diameter  $\leq 10 \mu m$ .



Metabolite changes associated with air pollution exposure, and the metabolite signature score increased in proportion to the level of pollution.

# COPD-P - Evidence from UK Biobank data

Follow-up of 12.51 years, 8,951 and 5,980 incident COPD and asthma

TABLE 2 ] Associations of Air Pollution and Metabolomic Signature Scores With CRD

Air Pollutants	CRD		COPD		Asthma	
	HR (95% CI) <sup>a</sup>	P Value	HR (95% CI) <sup>a</sup>	P Value	HR (95% CI) <sup>a</sup>	P Value
<b>PM<sub>2.5</sub></b>						
Basic <sup>b</sup>	1.14 (1.11-1.16)	< .001	1.14 (1.11-1.17)	< .001	1.15 (1.11-1.19)	< .001
MV <sup>c</sup>	1.09 (1.06-1.13)	< .001	1.07 (1.04-1.11)	< .001	1.14 (1.10-1.18)	< .001
MV + mutual adjustment <sup>d</sup>	1.09 (1.06-1.12)	< .001	1.06 (1.03-1.10)	< .001	1.14 (1.09-1.18)	< .001
<b>PM<sub>2.5</sub>-related metabolomic signature score</b>						
MV <sup>c</sup>	1.11 (1.09-1.14)	< .001	1.16 (1.13-1.19)	< .001	1.02 (0.99-1.05)	.161
MV + mutual adjustment <sup>d</sup>	1.11 (1.08-1.13)	< .001	1.15 (1.13-1.18)	< .001	1.02 (0.99-1.05)	.169
<b>PM<sub>10</sub></b>						
Basic <sup>b</sup>	1.15 (1.12-1.18)	< .001	1.17 (1.14-1.20)	< .001	1.15 (1.11-1.19)	< .001
MV <sup>c</sup>	1.09 (1.06-1.12)	< .001	1.08 (1.04-1.11)	< .001	1.12 (1.08-1.17)	< .001
MV + mutual adjustment <sup>d</sup>	1.08 (1.05-1.11)	< .001	1.07 (1.03-1.10)	< .001	1.12 (1.08-1.17)	< .001
<b>PM<sub>10</sub>-related metabolomic signature score</b>						
MV <sup>c</sup>	1.13 (1.11-1.16)	< .001	1.17 (1.14-1.20)	< .001	1.04 (1.01-1.07)	.019
MV + mutual adjustment <sup>d</sup>	1.13 (1.10-1.15)	< .001	1.17 (1.14-1.20)	< .001	1.03 (1.00-1.06)	.042
<b>NO<sub>x</sub></b>						
Basic <sup>b</sup>	1.20 (1.17-1.22)	< .001	1.27 (1.24-1.30)	< .001	1.14 (1.11-1.18)	< .001
MV <sup>c</sup>	1.09 (1.06-1.12)	< .001	1.12 (1.08-1.15)	< .001	1.08 (1.05-1.12)	< .001
MV + mutual adjustment <sup>d</sup>	1.08 (1.06-1.11)	< .001	1.11 (1.07-1.14)	< .001	1.08 (1.04-1.12)	< .001
<b>NO<sub>x</sub>-related metabolomic signature score</b>						
MV <sup>c</sup>	1.15 (1.12-1.17)	< .001	1.18 (1.15-1.21)	< .001	1.04 (1.01-1.07)	.012
MV + mutual adjustment <sup>d</sup>	1.14 (1.12-1.17)	< .001	1.17 (1.14-1.20)	< .001	1.04 (1.01-1.07)	.022
<b>NO<sub>2</sub></b>						
Basic <sup>b</sup>	1.20 (1.17-1.22)	< .001	1.27 (1.24-1.30)	< .001	1.14 (1.11-1.17)	< .001
MV <sup>c</sup>	1.09 (1.07-1.12)	< .001	1.12 (1.09-1.15)	< .001	1.08 (1.05-1.12)	< .001
MV + mutual adjustment <sup>d</sup>	1.09 (1.06-1.12)	< .001	1.11 (1.08-1.15)	< .001	1.08 (1.05-1.12)	< .001
<b>NO<sub>2</sub>-related metabolomic signature score</b>						
MV <sup>c</sup>	1.08 (1.06-1.11)	< .001	1.10 (1.08-1.13)	< .001	1.02 (0.99-1.05)	.318
MV + mutual adjustment <sup>d</sup>	1.08 (1.06-1.10)	< .001	1.10 (1.07-1.13)	< .001	1.01 (0.98-1.04)	.452

# Etiotypes of COPD

- COPD has multiple Etiotypes
- Post-infectious etiotypes (TB, NTM-PD, bronchiectasis) show relatively high COPD prevalence, incidence and faster lung-function decline
- The expanded etiology model improves understanding but risks over-inclusion in complex diseases

# Early detection & Screening

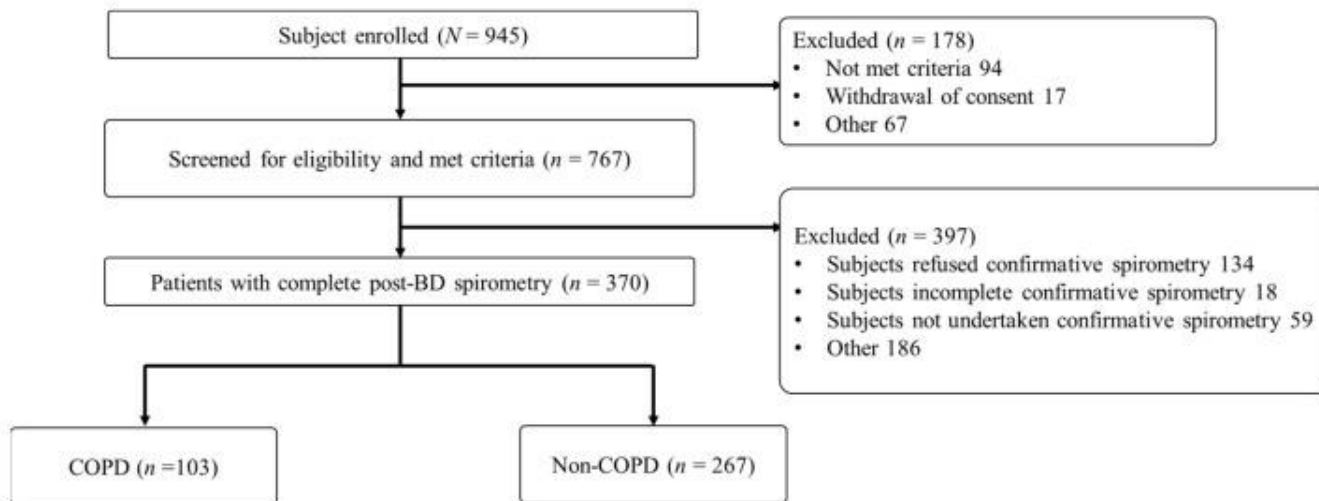
# Pre-COPD – Prevention and Screening

## **Primary prevention**

- Prematurity, childhood asthma, pneumonia, and smoking are key drivers of pre-COPD lung-function trajectories
- Preventing these early-life risk factors is essential

# Novel App-Based Portable Spirometer for the Early Detection of COPD

- Age of  $\geq 40$  years
- $\geq 10$  pack-years of smoking
- Chronic respiratory symptoms (cough, phlegm, or dyspnea)



## Spirobank Smart

MIR Spirobank Smart and Smart Oxi

Remote respiratory monitoring the smart way with optional pulse oximetry

[Watch Video](#)

The image shows the Spirobank Smart device, a white and orange portable spirometer, and a smartphone displaying the app interface with a graph showing respiratory volume over time.

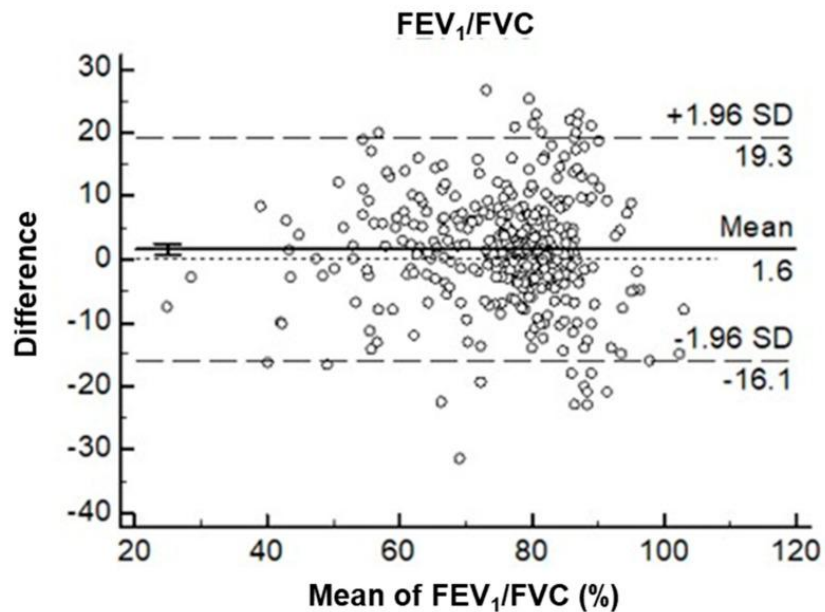
The image shows the Spirobank Smart device and a smartphone displaying the app interface. The app shows various respiratory parameters:

- FVC: 4,69 L
- FEV1: 4,10 L
- PEF: 640 L/s
- FEV6: 4,69 L
- FEF2575: 4,12 L
- FEV1/FVC: 87%
- EVC: 4,79 L
- IC: 3,46 L
- SET: 4 L

The app also displays a table of results:

Time	FVC	FEV1	PEF	FEV1/FVC	PEF/FVC	
14:45:53	4,33	4,30	4,33	88	5,85	640
14:46:19	4,69	3,86	4,69	82	4,32	596

# Novel App-Based Portable Spirometer for the Early Detection of COPD

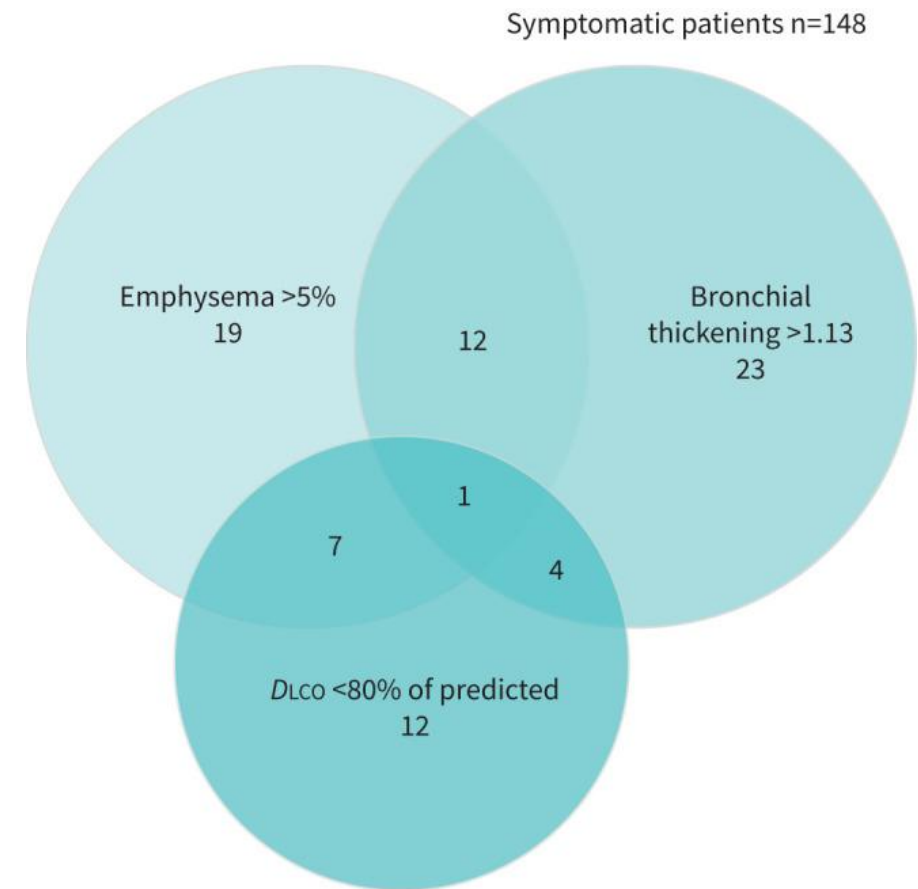
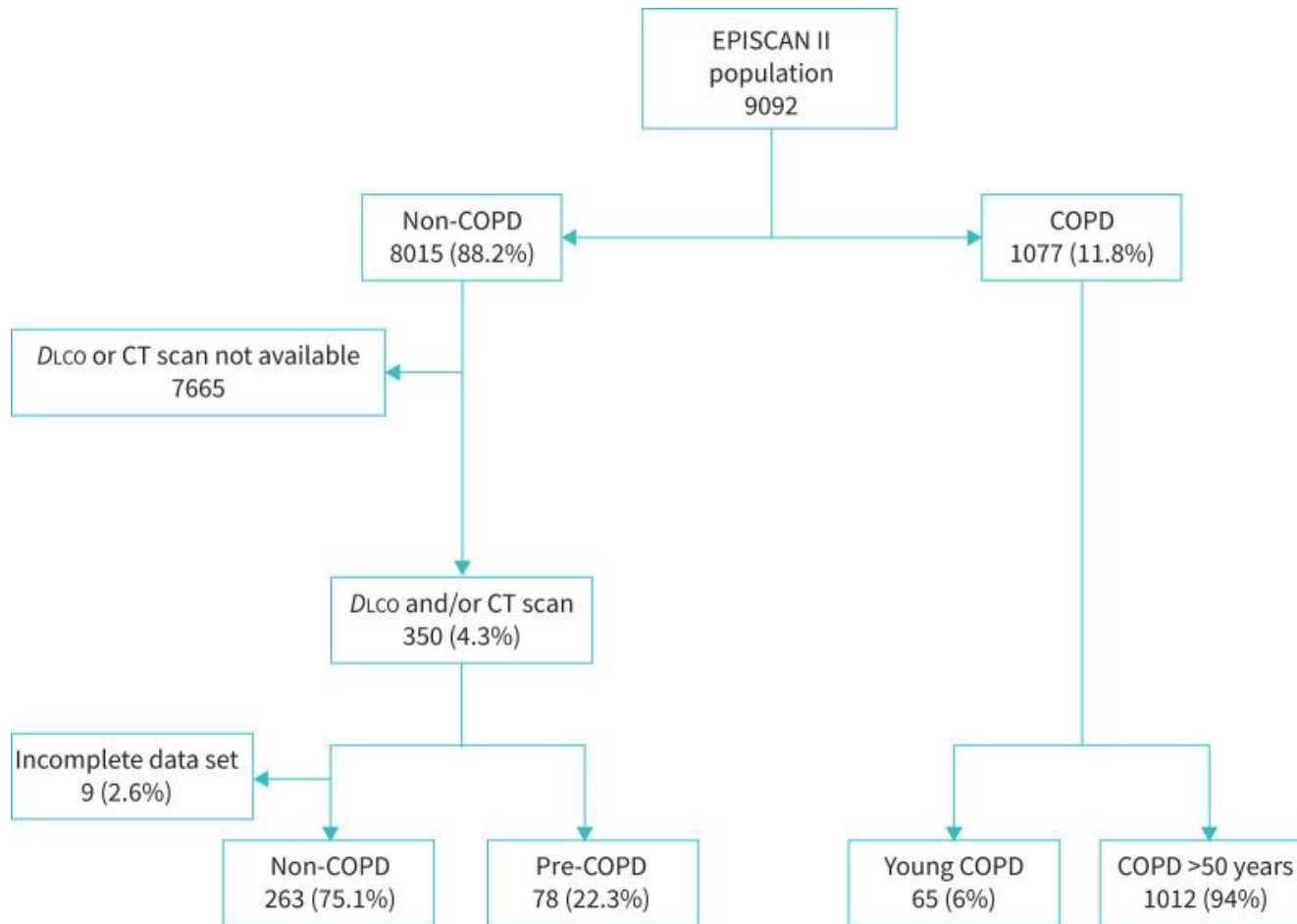


GOLD Grade	Diagnostic Spirometer		Spirobank Smart	
	<i>n</i> (%)	CAT Score	<i>n</i> (%)	CAT Score
GOLD I	25 (24.3%)	10 ± 5	16 (15.5%)	10 ± 4
GOLD II	53 (51.5%)	12 ± 7	59 (57.3%)	11 ± 6
GOLD III	22 (21.3%)	11 ± 6	22 (21.4%)	13 ± 8
GOLD IV	3 (2.9%)	21 ± 19	6 (5.8%)	18 ± 12
Total	103 (100%)	12 ± 7	103 (100%)	12 ± 7

# Young COPD and pre-COPD in general population

- The EPISCAN II study
- COPD in Spain in subjects  $\geq 40$  years
  1. Pre-COPD definition
    - emphysema  $> 5\%$
    - and/or bronchial thickening in CT
    - and/or DLCO  $< 80\%$  and FEV1/FVC  $> 0.7$
  2. Young COPD definition
    - FEV1 /FVC  $< 0.70$  in age  $\leq 50$  years

# Young COPD and pre-COPD in general population



# Young COPD and pre-COPD in general population

**TABLE 1** Differential demographic and clinical characteristics of young COPD (YC) and pre-COPD (PC) subjects compared to COPD (C) and non-COPD (NC) populations

	C	YC	PC	NC	p-value					
					C versus YC	NC versus YC	C versus PC	NC versus PC	PC versus YC	
<b>Subjects</b>	1012	65	78	263						
<b>General characteristics</b>										
Age, years, mean±SD, median (interquartile range)	67.8±9.9, 68.0 (59.0–75.0)	45.8±2.6, 46.0 (43.0–48.0)	63.5±11.6, 65.0 (54.0–72.0)	59.3±10.1, 59.0 (51.0–67.0)	<0.0001	<0.0001	0.003	0.0002	<0.0001	
Females	418 (41.3%)	30 (46.2%)	44 (56.4%)	163 (62.0%)	0.44	0.02	0.009	0.37	0.22	
BMI, kg·m <sup>-2</sup>	27.4±4.6	27.4±7.0	28.0±4.8	26.7±4.5	0.88	0.49	0.31	0.06	0.52	
<b>Smoking status</b>										
Active smokers	301 (29.7%)	32 (49.2%)	14 (17.9%)	58 (22.1%)	0.004	<0.0001	0.009	0.59	0.0002	
Former smokers	433 (42.8%)	20 (30.8%)	31 (39.7%)	90 (34.2%)						
Never-smokers	278 (27.5%)	13 (20%)	33 (42.3%)	115 (43.7%)						
Smoking exposure, pack-years	29.2±30.1	22.2±21.35	18.5±25.6	13.1±17.9	0.06	0.0005	0.002	0.04	0.35	
<b>Education level</b>										
No studies	41 (4.1%)	0	1 (1.3%)	2 (0.8%)	0.15	0.03	0.23	0.27	0.56	
Primary education	270 (26.7%)	14 (21.5%)	17 (21.8%)	52 (19.8%)						
Secondary education	243 (24.0%)	19 (29.3%)	17 (21.8%)	45 (17.1%)						
University or vocational training	454 (44.9%)	31 (47.7%)	42 (53.8%)	164 (62.4%)						
<b>Clinical characteristics</b>										
mMRC dyspnoea scale					0.14	0.0009	0.32	<0.0001	0.01	
Grade 0	499 (49.2%)	42 (64.6%)	30 (38.5%)	223 (84.8%)						
Grade 1	355 (35.1%)	18 (27.7%)	36 (46.2%)	36 (13.7%)						
Grade 2	113 (11.2%)	3 (4.6%)	9 (11.5%)	3 (1.1%)						
Grade 3	39 (3.9%)	2 (3.1%)	3 (3.8%)	1 (0.4%)						
Grade 4	6 (0.6%)	0	0	0						
CAT	9.1±6.8	9.1±6.4	11.3±6.1	5.7±5.1	0.98	<0.0001	0.004	<0.0001	0.03	
Cough and phlegm <sup>#</sup>	621 (66.3%)	37 (58.7%)	78 (100.0%)	70 (28.0%)	0.21	<0.0001	<0.0001	<0.0001	<0.0001	
Asthma	163 (16.1%)	19 (29.2%)	5 (6.4%)	24 (9.1%)	0.006	<0.0001	0.02	0.45	0.0003	
Charlson Comorbidity Index	0.7±1.1	0.6±1.7	0.5±0.9	0.3±0.8	0.71	0.01	0.22	0.01	0.63	
COTE index	1.2±2.4	1.4±2.8	1.7±2.8	0.9±2.1	0.44	0.12	0.10	0.01	0.62	
Exacerbations last year	114 (11.3%)	5 (7.7%)	2 (2.6%)	9 (3.4%)	0.37	0.12	0.01	0.70	0.15	
<b>Treatments</b>										
Any respiratory treatment	641 (63.3%)	28 (43.1%)	39 (50.0%)	86 (32.7%)	0.001	0.11	0.01	0.005	0.40	
Treatment with short-acting β-agonist	251 (24.8%)	17 (26.2%)	4 (5.1%)	8 (3.0%)	0.80	<0.0001	<0.0001	0.37	0.0004	
Treatment with anticholinergics	159 (15.7%)	4 (6.2%)	2 (2.6%)	5 (1.9%)	0.03	0.06	0.001	0.71	0.28	
Treatment with inhaled corticosteroids	189 (18.7%)	10 (15.4%)	4 (5.1%)	9 (3.4%)	0.50	0.0002	0.002	0.48	0.03	

Data are presented as mean±SD or n (%), unless otherwise stated. BMI: body mass index; mMRC: modified Medical Research Council; CAT: COPD Assessment Test; COTE: COPD-specific comorbidity test. <sup>#</sup>: European Coal and Steel Community questionnaire.

# Young COPD and pre-COPD in general population

**TABLE 2** Differential functional, inflammatory and imaging characteristics of young COPD (YC) and pre-COPD (PC) subjects compared to COPD (C) and non-COPD (NC) populations

	C	YC	PC	NC	p-value				
					C versus YC	NC versus YC	C versus PC	NC versus PC	PC versus YC
<b>Subjects</b>	1012	65	78	263					
<b>Lung function</b>									
FVC, % of predicted	99.3±18.5	99.8±14.8	101.2±16.5	104.9±13.3	0.83	0.02	0.39	0.11	0.60
FEV <sub>1</sub> , % of predicted	80.6±18.8	80.3±16.2	103.6±18.0	105.3±13.7	0.08	<0.0001	<0.0001	0.33	<0.0001
6MWT distance, m	477.1±108.1	525.5±121.0	467.3.0±114.8	527.2±87.8	0.09	0.94	0.47	<0.0001	0.07
D <sub>LCO</sub> , % of predicted	88.6±23.1	108.9±19.5	90.9±19.4	101.5±17.4	0.001	0.11	0.40	<0.0001	0.001
BODE index <sup>#</sup>	1.5±1.2	1.1±0.8	1.4±0.9	0.9±0.4	0.13	0.30	0.24	<0.0001	0.22
BODEx index <sup>†</sup>	1.4±1.0	1.3±0.9	1.2±0.6	0.9±0.3	0.19	<0.0001	0.01	<0.0001	0.31
<b>Biomarkers</b>									
Eosinophils per µL	191±123, 175 (101–249)	233±169, 182 (168–227)	158±95, 140 (89–215)	159±120, 128 (88–198)	0.22	0.02	0.03	0.98	0.02
CRP, mg·dL <sup>-1</sup>	1.9±4.0, 0.4 (0.1–2.0)	2.1±4.1, 0.2 (0.1–1.0)	1.6±2.8, 0.6 (0.1–1.5)	1.3±2.7, 0.4 (0.1–1.1)	0.93	0.33	0.46	0.43	0.60
Fibrinogen, g·L <sup>-1</sup>	3.9±0.9, 3.7 (3.3–4.5)	3.3±0.8, 3.0 (2.7–4.0)	3.9±1.1, 3.9 (3.2–4.5)	3.7±0.8, 3.6 (3.1–4.3)	0.02	0.07	0.995	0.10	0.04
<b>Imaging</b>									
Emphysema >5%	160 (59.7%)	3 (27.3%)	39 (50.0%)	55 (20.9%)	0.03	0.61	0.12	<0.0001	0.15
Bronchiole thickness, mm	1.1±0.1, 1.1 (1.0–1.1)	1.1±0.1, 1.1 (1.1–1.2)	1.1±0.2, 1.1 (1.0–1.2)	1.0±0.2, 1.1 (1.0–1.1)	0.67	0.21	0.03	0.0001	0.69

Data are presented as mean±SD or mean±SD, median (interquartile range), unless otherwise stated. FVC: forced vital capacity; FEV<sub>1</sub>: forced expiratory volume in 1 s; 6MWT: 6-min walk test; D<sub>LCO</sub>: diffusing capacity of the lung for carbon monoxide; BODE: body mass index, obstruction, dyspnoea, exercise; BODEx: simplified BODE; CRP: C-reactive protein; IQR: interquartile range. #: out of 10; †: out of 9.

# Screening and early diagnosis of COPD

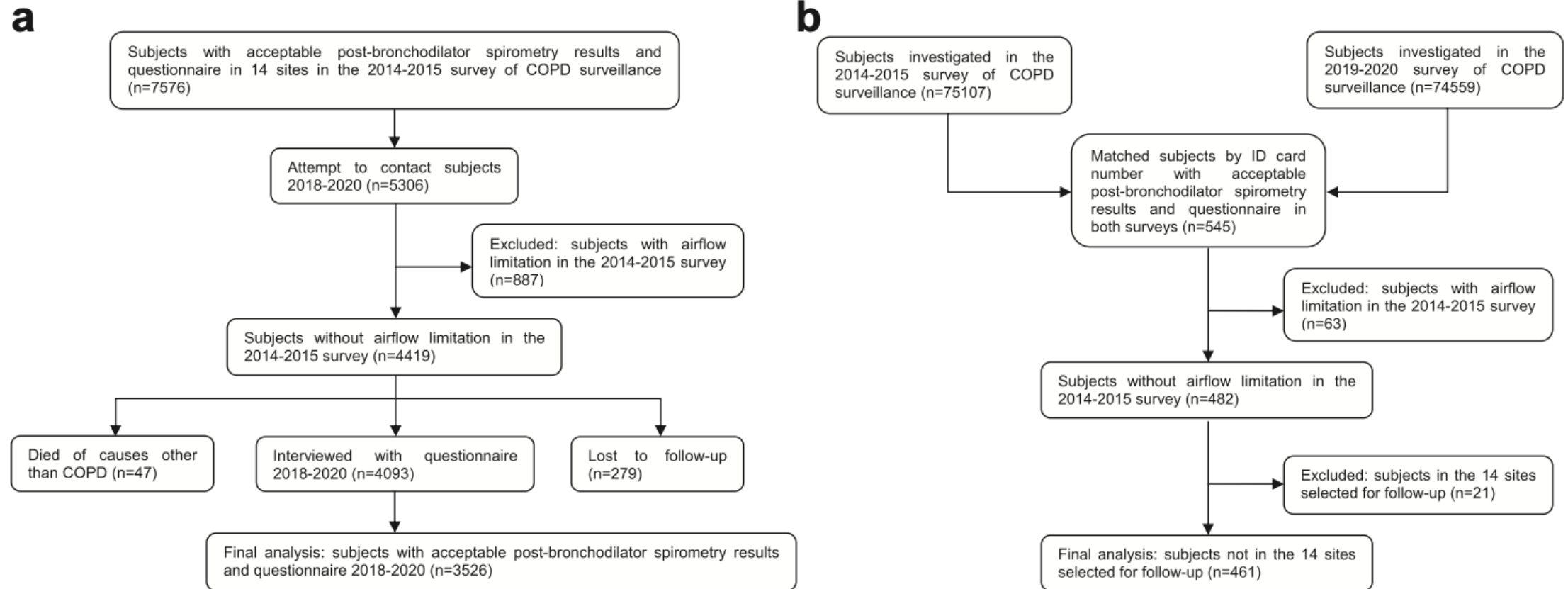
**Table 1** COPD screening questionnaire

Questions	Options and scoring criteria
Your age (years)	20–49(0), 50–59(3), 60–69(7), ≥ 70(10)
Your consumption of cigarettes (packs per year)	0–14(0), 15–30(1), ≥ 30(2)
Your BMI (Kg/m <sup>2</sup> )	< 18.5(7), 18.5–23.9(4), 24.0–27.9(1), ≥ 28.0(0)
Do you cough often when you do not have a cold?	Yes (3), No (0)
Do you usually feel shortness of breath?	No (0), feeling shortness of breath when walking quickly on level ground or climbing gentle slopes (2), feeling shortness of breath when walking at a normal pace on level ground (3)
Do you currently use coal stoves or firewood for cooking or heating?	Yes (1), No (0)
Is there a family history of bronchial asthma, or COPD	Yes (2), No (0)

**Table 5** Analysis of influencing factors for pulmonary function grading in COPD high-risk groups - Multivariate ordinal multi-classification logistic regression analysis

Variables	Coefficient	OR value	95% confidence interval for the OR value	t value	P value
Gender male	0.561	1.753	(1.114,2.777)	2.412	0.016
Age 50–59 years	0.192	1.211	(0.636,2.324)	0.581	0.561
Age 60–69 years	0.795	2.215	(1.133,4.383)	2.308	0.021
Age ≥ 70 years	0.808	2.244	(1.113,4.573)	2.245	0.025
Consumption of cigarettes (packs per year) 15–30	-0.008	0.992	(0.577,1.702)	-0.029	0.976
Consumption of cigarettes (packs per year) ≥ 30	0.16	1.174	(0.739,1.866)	0.679	0.497
BMI 18.5–23.9	0.217	1.242	(0.731,2.116)	0.801	0.423
BMI 24.0–27.9	0.305	1.357	(0.734,2.515)	0.972	0.331
Feeling shortness of breath when walking at a normal pace on level ground	-2.414	0.089	(0.057,0.138)	-10.671	<0.001
Feeling shortness of breath when walking quickly on level ground or climbing gentle slopes	-4.163	0.016	(0.002,0.066)	-5.061	<0.001
Use of firewood, grass, and coal stoves	-0.579	0.561	(0.364,0.861)	-2.643	0.008

# Pre-COPD indicators in association with COPD development



**Fig. 1:** Flowchart of study participants. a) the 3526 study participants in the training cohort; b) the 461 study participants in the validation cohort. **\*\*235(6.7%)\*** COPD cases (post-BD FEV1/FVC < 70%) among 3,526 participants

# Pre-COPD indicators in association with COPD development

	Crude HR (95% CI)	Model 1 <sup>a</sup>		Model 2 <sup>b</sup>		Model 3 <sup>c</sup>	
		Adjusted HR (95% CI)	P	Adjusted HR (95% CI)	P	Adjusted HR (95% CI)	P
Chronic bronchitis	2.89 (1.40–5.93)	1.80 (0.85–3.85)	0.1274	2.84 (1.38–5.84)	0.0046	2.94 (1.43–6.04)	0.0035
PRISm	1.63 (1.08–2.47)	1.57 (1.03–2.40)	0.0361	0.87 (0.56–1.36)	0.5385	0.76 (0.48–1.19)	0.2270
Low PEF	1.75 (1.32–2.32)	1.66 (1.25–2.21)	0.0005	1.28 (0.94–1.75)	0.1115	1.22 (0.90–1.68)	0.2055
sSAD	2.86 (2.21–3.70)	2.69 (2.07–3.49)	<0.0001	2.74 (2.07–3.61)	<0.0001		
Low MMEF	3.26 (2.50–4.25)	2.93 (2.24–3.83)	<0.0001			2.38 (1.65–3.43)	<0.0001
Low FEF50	2.58 (1.99–3.34)	2.46 (1.89–3.19)	<0.0001			1.42 (0.98–2.06)	0.0622
Low FEF75	1.98 (1.44–2.71)	2.37 (1.73–3.26)	<0.0001			1.23 (0.86–1.76)	0.2598

Definition of abbreviations: CI = confidence interval; PRISm = preserved ratio impaired spirometry; PEF = peak expiratory flow; sSAD = spirometric small airway dysfunction; MMEF = maximal midexpiratory flow; FEF50 = forced expiratory flow at 50% of FVC exhaled; FEF75 = forced expiratory flow at 75% of FVC exhaled. <sup>a</sup>Model 1: included each one of chronic bronchitis, PRISm, low PEF, sSAD, low MMEF, low FEF50, and low FEF75 respectively, adjusted for sex, age, smoking status, exposure to dust or chemicals in the workplace, indoor exposure to coal, and indoor exposure to biomass. <sup>b</sup>Model 2: included chronic bronchitis, PRISm, low PEF, and sSAD. <sup>c</sup>Model 3: included chronic bronchitis, PRISm, low PEF, low MMEF, low FEF50, and low FEF75.

**Table 2: Crude and adjusted hazard ratios of COPD development for potential indicators for pre-COPD.**

**Definition of sSAD (2 of 3)  
MMEF (FEF25–75%) < LLN  
FEF50 < LLN  
FEF75 < LLN**

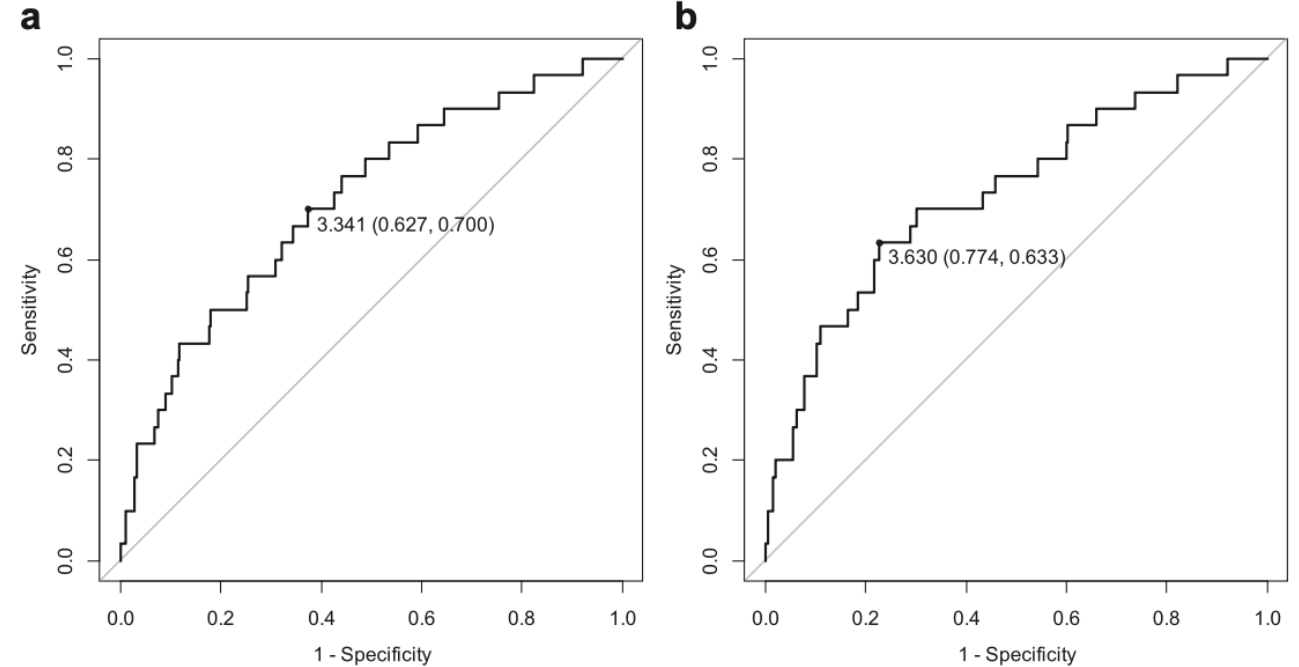
Concurrent **chronic bronchitis and sSAD/low MMEF** indicating pre-COPD optimally require more high attention

# Screening and early diagnosis of COPD

	Model 4			Model 5		
	Coefficient	SE	P	Coefficient	SE	P
Age	0.0382	0.0069	<0.0001	0.0394	0.0069	<0.0001
Male	0.9977	0.1400	<0.0001	0.9206	0.1419	<0.0001
sSAD	0.9953	0.1325	<0.0001			
Low MMEF				0.7552	0.1812	<0.0001
Low FEF50				0.4541	0.1762	0.0100
Indoor exposure to biomass	0.6932	0.1393	<0.0001	0.7169	0.1387	<0.0001
Internal validation						
Dxy	0.534			0.541		
C	0.7670 <sup>a</sup>	0.0171		0.7704 <sup>b</sup>	0.0170	
AIC	3184.793			3180.358		
Corrected Dxy	0.527			0.532		
Corrected C	0.7635 <sup>c</sup>	0.0228		0.7660 <sup>d</sup>	0.0229	
Temporal validation						
AUC	0.715 <sup>e</sup>	0.049		0.730 <sup>f</sup>	0.050	
X-squared of HL test	1.7459		0.9878	2.8828		0.9415

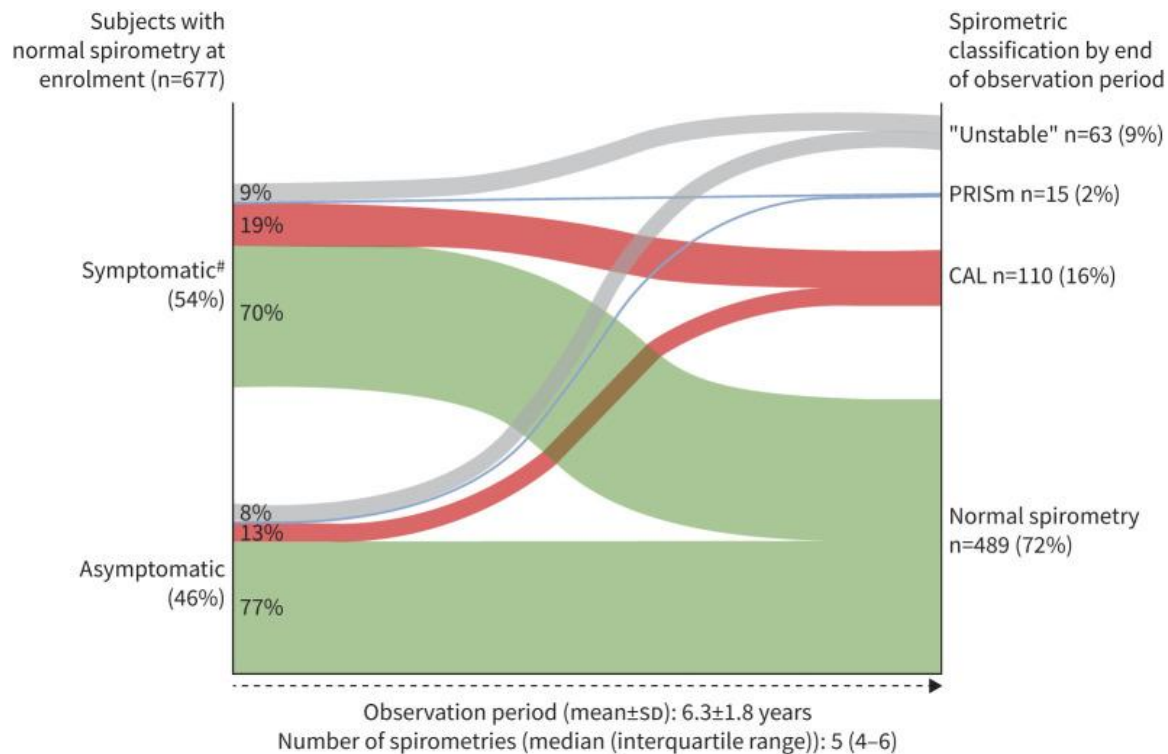
Definition of abbreviations: sSAD = spirometric small airway dysfunction; MMEF = maximal midexpiratory flow; FEF50 = forced expiratory flow at 50% of FVC exhaled; AIC = akaike information criterion; AUC = area under the receiver operating characteristic curve; HL test = Hosmer-Lemeshow test; SE = standard error. <sup>a</sup>95% Confidence Interval: 0.7335-0.8005. <sup>b</sup>95% Confidence Interval: 0.7371-0.8037. <sup>c</sup>95% Confidence Interval: 0.7188-0.8082. <sup>d</sup>95% Confidence Interval: 0.7210-0.8110. <sup>e</sup>95% Confidence Interval: 0.6190-0.8110. <sup>f</sup>95% Confidence Interval: 0.6320-0.8280.

**Table 4:** Cox regression analysis results and performance metrics for the internal and temporal validation of the prediction models for COPD development.



**Fig. 3:** Receiver operating characteristic curves for the temporal validation of the prediction models for COPD development. a) Model 4: The cut-off value of prognostic index was 3.341 to discriminate individuals at a high or low risk of COPD, at which the sensitivity and the specificity was 0.700 and 0.627 respectively and the positive and negative predictive value was 0.117 and 0.967 respectively. The area under the curve was 0.715; b) Model 5: The cut-off value of prognostic index was 3.630 to discriminate individuals at a high or low risk of COPD, at which the sensitivity and the specificity was 0.633 and 0.774 respectively and the positive and negative predictive value was 0.165 and 0.968 respectively. The area under the curve was 0.730. For example for the usage of the cut-off value in model 5, a 65 year-old ( $65 \times 0.0394$ ) man (0.9206) with low MMEF (0.7552), but without low FEF50 (0) and indoor exposure to biomass (0) presents a prognostic index of 4.2368 indicating a high risk of COPD.

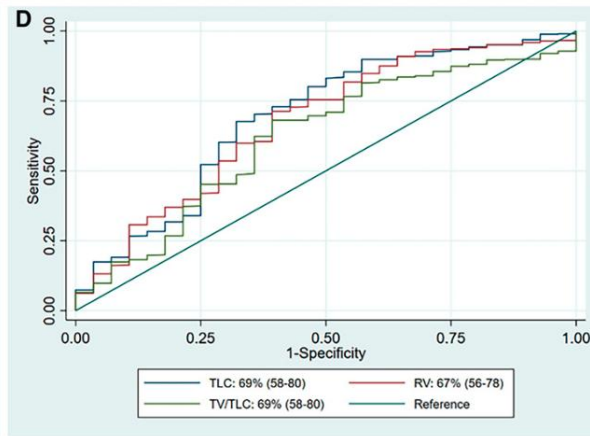
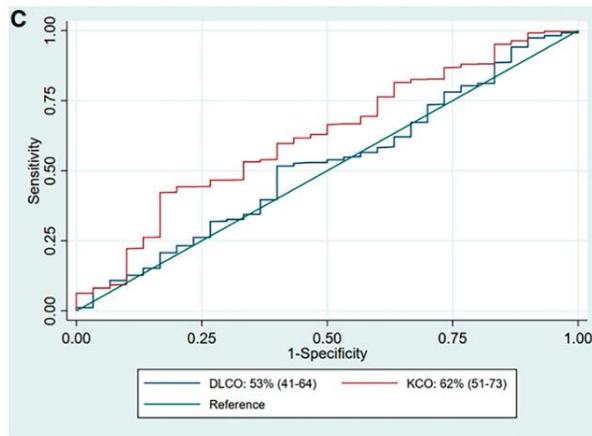
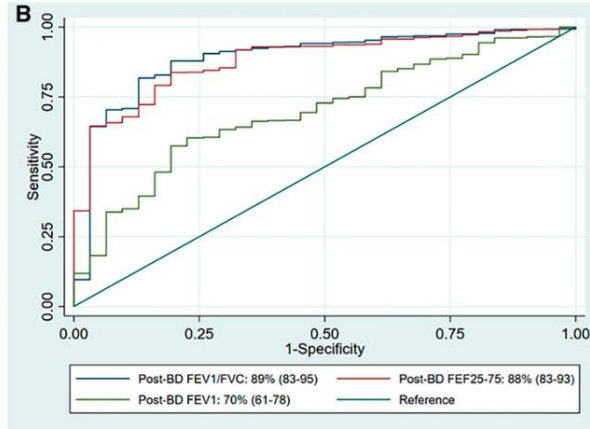
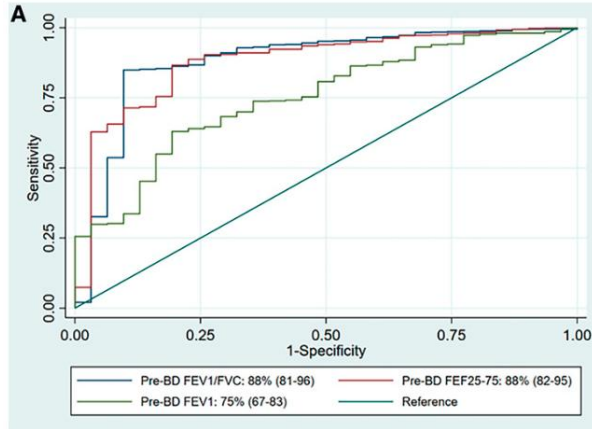
# SLIM risk calculator ; pre-COPD to COPD



	FEV <sub>1</sub> /FVC <0.75	≥30 pack-years	BMI ≤25 kg·m <sup>-2</sup>	Chronic bronchitis (yes)	Probability of incident CAL (%)	Probability maintaining normal lung function (%)
					85%	15%
					76%	24%
					71%	29%
					63%	37%
					56%	44%
					48%	52%
					42%	58%
					28%	72%
					27%	73%
					17%	83%
					14%	86%
					10%	90%
					8%	92%
					6%	94%
					4%	96%
					2%	98%

Among 2273 Lovelace Smokers' Cohort (LSC) participants 677 with normal spirometry, current and ex-smoker

# Pre-COPD to COPD; according to TAHS data



	z-Score	Percentile	Sensitivity	Specificity	LR <sup>+</sup>	LR <sup>-</sup>	Y <sub>Max</sub>
Pre-BD FEV <sub>1</sub> /FVC	-1.264	<10th	88% (71, 96)	87% (84, 89)	6.79 (5.40, 8.52)	0.14 (0.05, 0.38)	0.75
Pre-BD FEF <sub>25-75</sub>	-1.328	<9th	79% (60, 90)	88% (86, 90)	6.76 (5.13, 8.89)	0.24 (0.12, 0.50)	0.67
Pre-BD FEV <sub>1</sub>	-0.535	<30th	73% (54, 86)	67% (64, 70)	2.20 (1.71, 2.83)	0.41 (0.22, 0.75)	0.40
Post-BD FEV <sub>1</sub> /FVC	-0.701	<24th	81% (63, 92)	84% (81, 86)	5.09 (3.99, 6.49)	0.22 (0.10, 0.49)	0.65
Post-BD FEF <sub>25-75</sub>	-0.775	<21st	73% (55, 86)	86% (83, 88)	5.23 (3.93, 6.97)	0.31 (0.17, 0.58)	0.59
Post-BD FEV <sub>1</sub>	-0.113	<46th	79% (61, 90)	61% (58, 65)	2.04 (1.65, 2.53)	0.34 (0.17, 0.71)	0.40
DL <sub>CO</sub>	+0.366	<64th	60% (41, 76)	49% (46, 53)	1.18 (0.86, 1.53)	0.81 (0.51, 1.30)	0.09
K <sub>CO</sub>	+0.505	<69th	81% (63, 92)	40% (36, 43)	1.35 (1.11, 1.64)	0.47 (0.21, 1.05)	0.21
TLC*	+0.623	>73rd	56% (37, 73)	66% (63, 70)	1.65 (1.15, 2.37)	0.67 (0.43, 1.04)	0.22
RV*	+1.015	>84th	52% (34, 70)	71% (67, 75)	1.82 (1.23, 2.69)	0.76 (0.45, 1.01)	0.23
RV/TLC*	+1.061	>86th	58% (40, 75)	69% (66, 72)	1.90 (1.36, 2.64)	0.60 (0.39, 0.94)	0.27

**Pre-BD FEV<sub>1</sub>/FVC z-score < -1.264**  
 - 36-fold increased risk of developing COPD  
 - Sensitivity 88%, and Specificity 87%

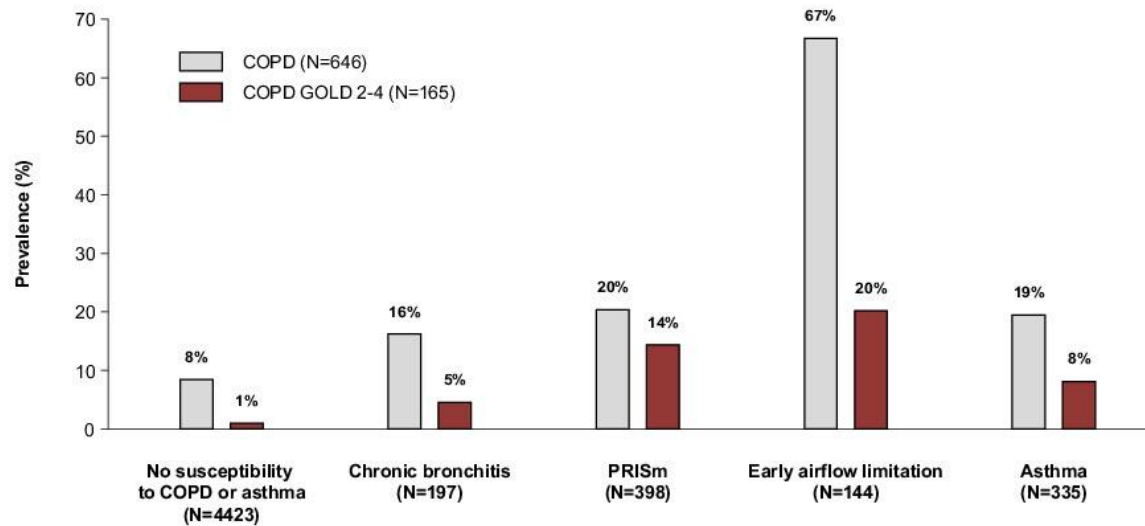
# Susceptible Young Adults and Development of COPD

- Copenhagen General Population Study from 2003 ( $N = 5,497$ ) and the Copenhagen City Heart Study from 1976-1978 ( $N = 2,609$ )
- For 10 and 25 years
- **Susceptible group**
  1. Chronic bronchitis
    - FEV<sub>1</sub>/FVC  $\geq 0.70$  &  $\geq$ LLN
    - FEV<sub>1</sub>, FVC  $\geq 80\%$  predicted
  2. PRISm
    - FEV<sub>1</sub>/FVC  $\geq 0.70$  &  $\geq$ LLN
    - FEV<sub>1</sub> or FVC  $< 80\%$  predicted
  3. Early airflow limitation
    - FEV<sub>1</sub>/FVC  $\geq 0.70$  &  $<$ LLN
  4. Asthma
  5. Active smoking history
- Development of **COPD (FEV<sub>1</sub>/FVC  $< 0.70$ )** and COPD GOLD 2-4 (FEV<sub>1</sub>  $< 80\%$  pred).

# Susceptible Young Adults and Development of COPD

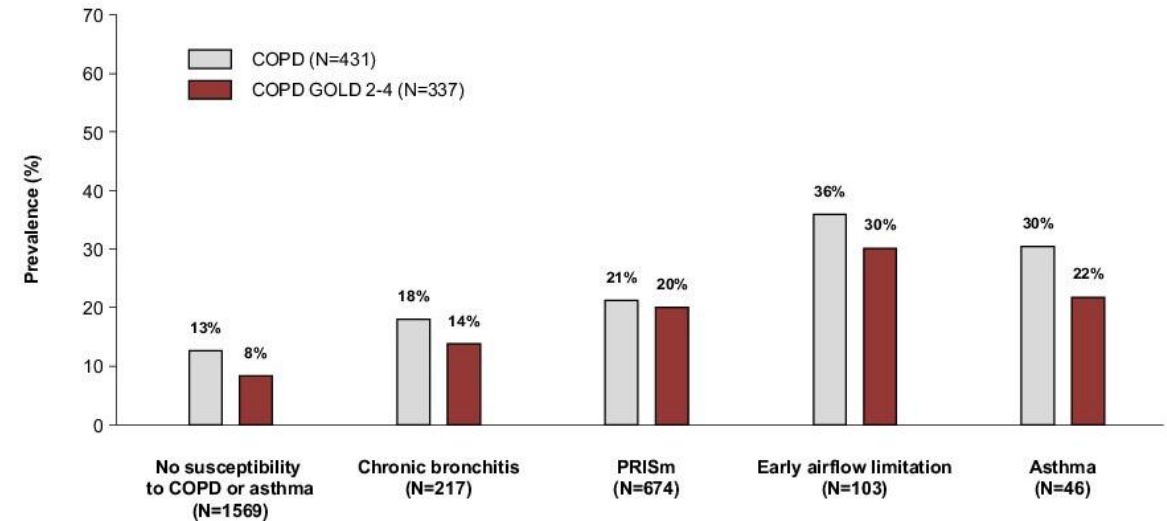
## The Copenhagen General Population Study

Prevalence of COPD at final examination 10 years later



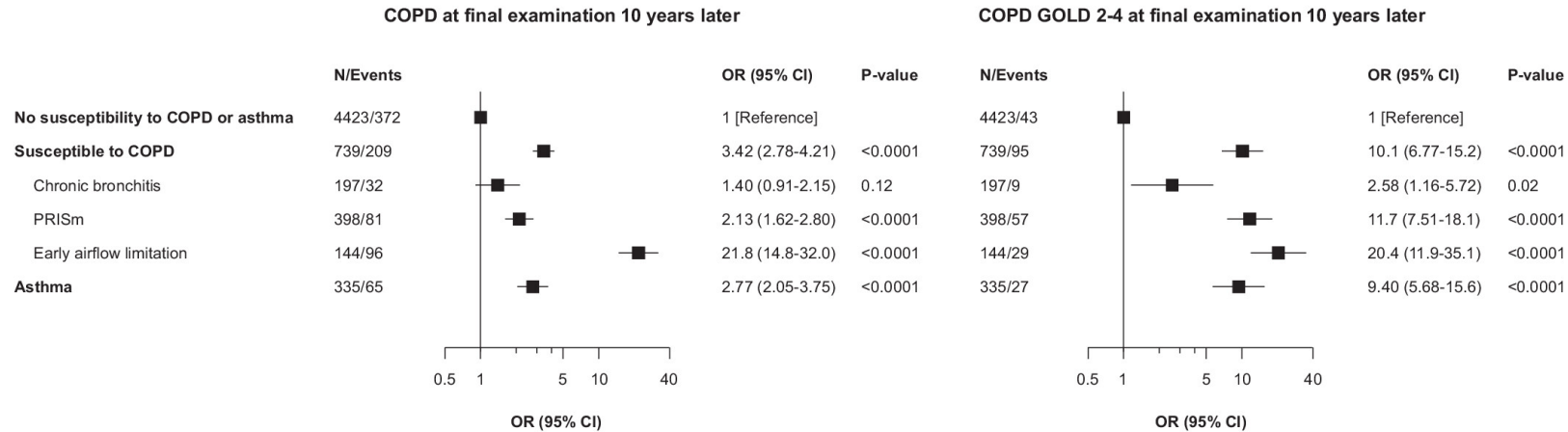
## The Copenhagen City Heart Study

Prevalence of COPD at final examination 25 years later

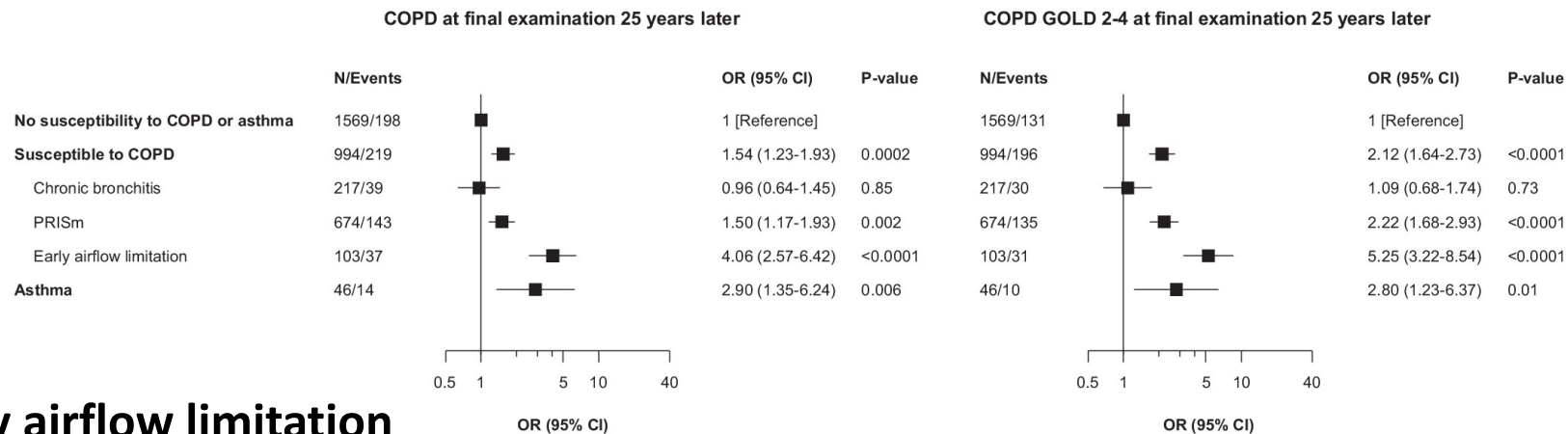


# Susceptible Young Adults and Development of COPD

## The Copenhagen General Population Study



## The Copenhagen City Heart Study



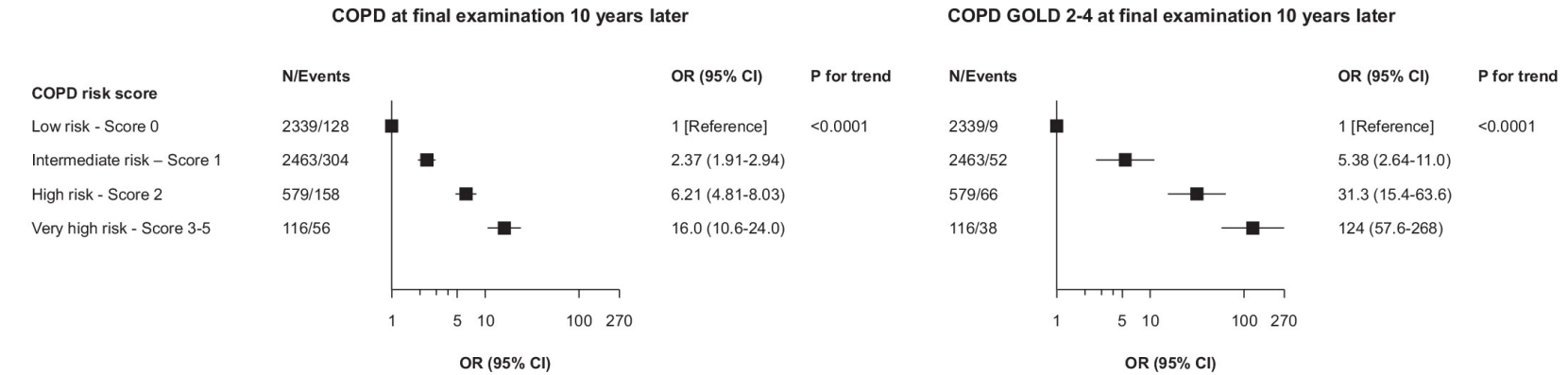
**PRISm and Early airflow limitation related to development of COPD**

# Susceptible Young Adults and Development of COPD

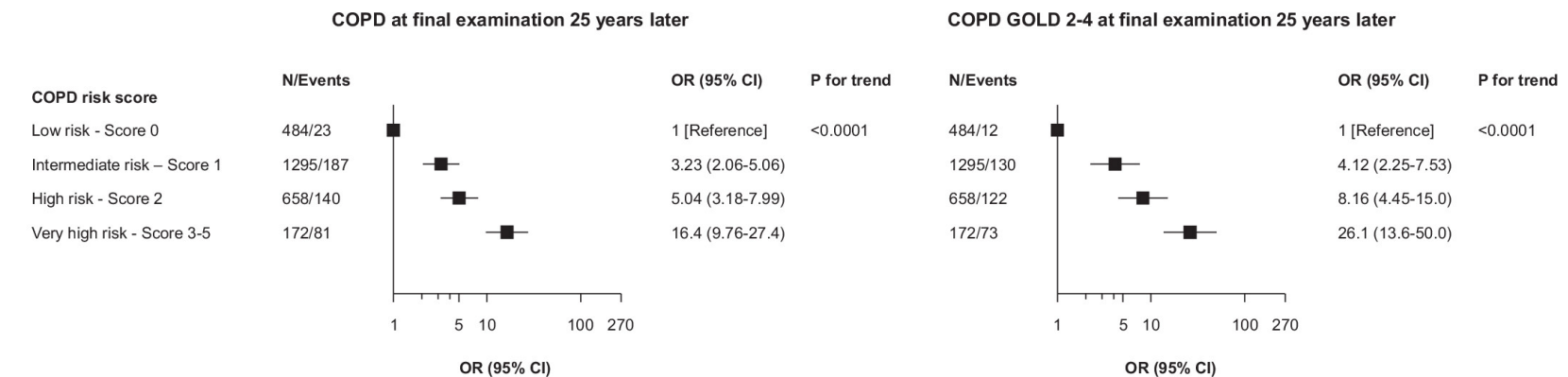
## Risk factors used for calculating COPD risk score

Risk factors	Point on COPD risk score	
	0	1
Chronic bronchitis	no	yes
FEV1 and FVC	>=80	<80
FEV1/FVC	>=LLN	<LLN
Active smoking history	No	Yes
Asthma	No	Yes
Risk management	COPD risk score	
Low	0	
Intermediate	1	
High	2	
Very High	>=3	

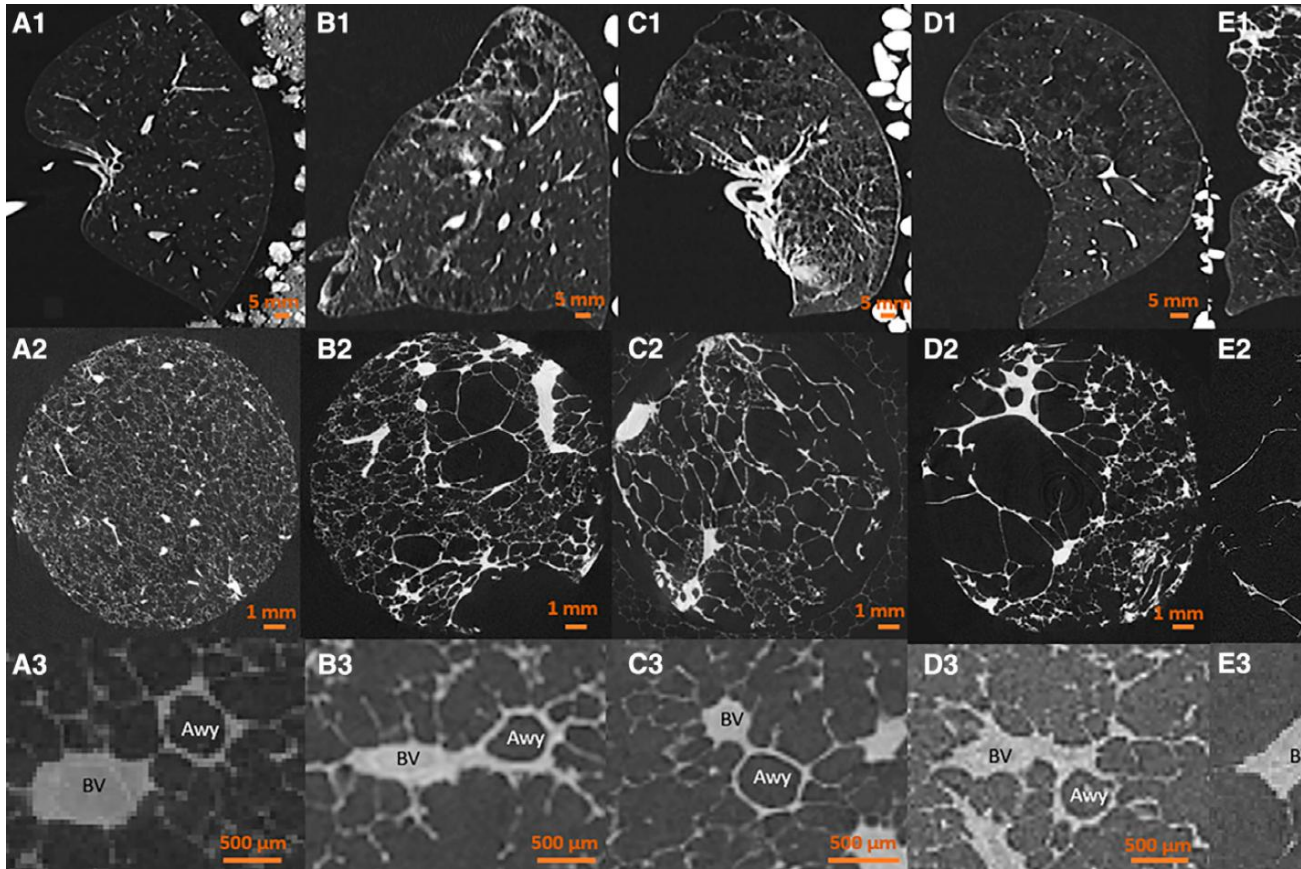
## The Copenhagen General Population Study



## The Copenhagen City Heart Study



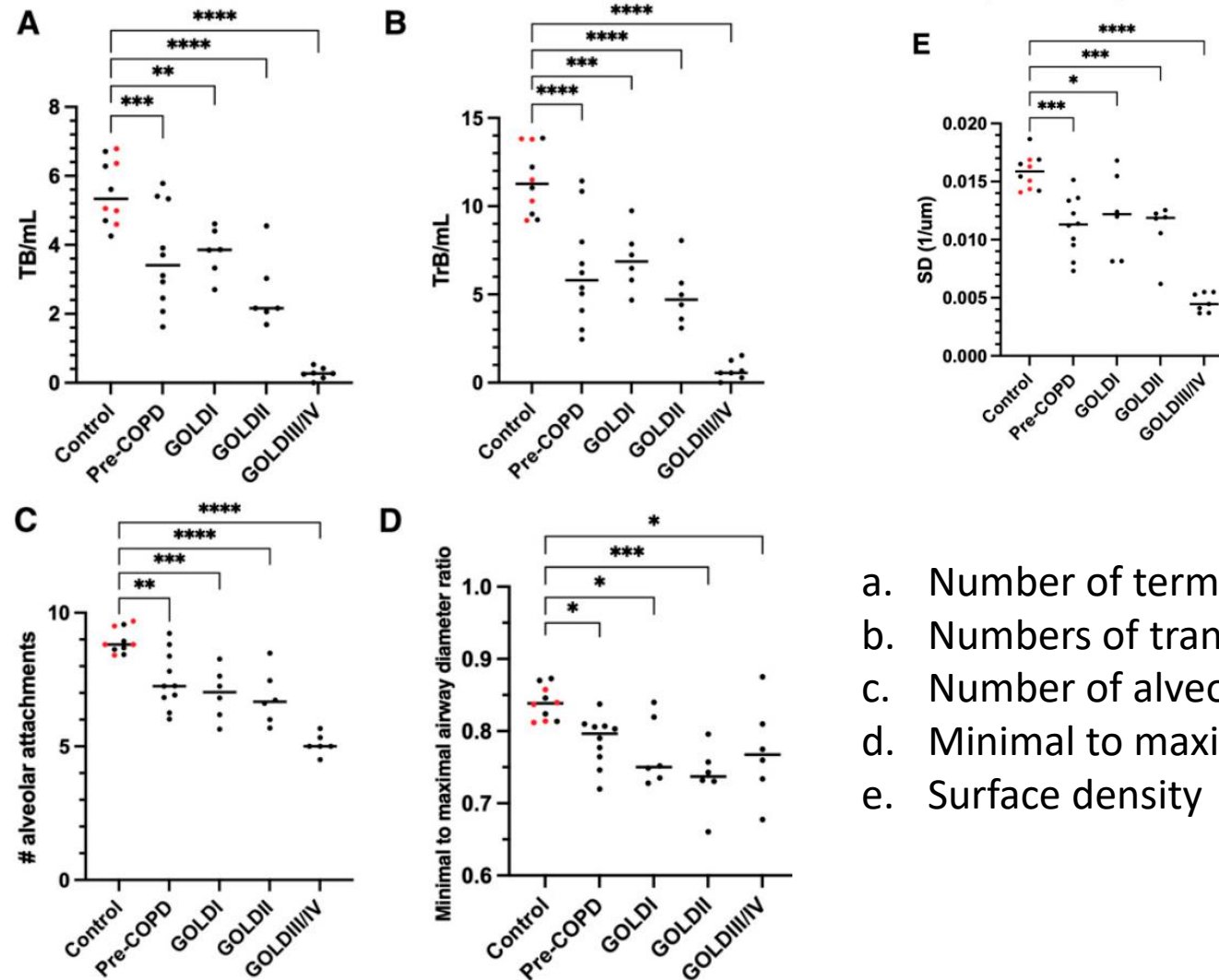
# SAD in pre-COPD with emphysema - microCT



**Table 2.** Summary of ex vivo Computed Tomography Scoring

	Control	Pre-COPD	GOLD I	GOLD II	GOLD III/IV	Correlation (R) with Second Observer
Emphysema, %	1.3 ± 1.9	22.0 ± 16.9	22.9 ± 16.0	31.3 ± 12.7	85.2 ± 11.2	0.87 (0.75 to 0.93)
Bronchiectasis, %	4.3 ± 4.1	3.5 ± 3.0	4.2 ± 3.6	2.3 ± 1.5	1.7 ± 1.4	0.44 (0.13 to 0.67)
Airway wall thickening, %	4.7 ± 2.8	7.8 ± 6.1	9.7 ± 6.4	5.7 ± 1.9	10.5 ± 3.3	0.22 (-0.12 to 0.51)
Mucus plugging, %	0.0 ± 0.0	1.7 ± 4.4	0.0 ± 0.0	0.5 ± 1.3	1.4 ± 1.3	0.17 (-0.17 to 0.47)
Tree-in-bud changes, %	2.5 ± 7.9	6.1 ± 9.4	4.0 ± 7.6	0.7 ± 1.6	1.4 ± 2.5	0.15 (-0.19 to 0.46)

# SAD in pre-COPD with emphysema - microCT

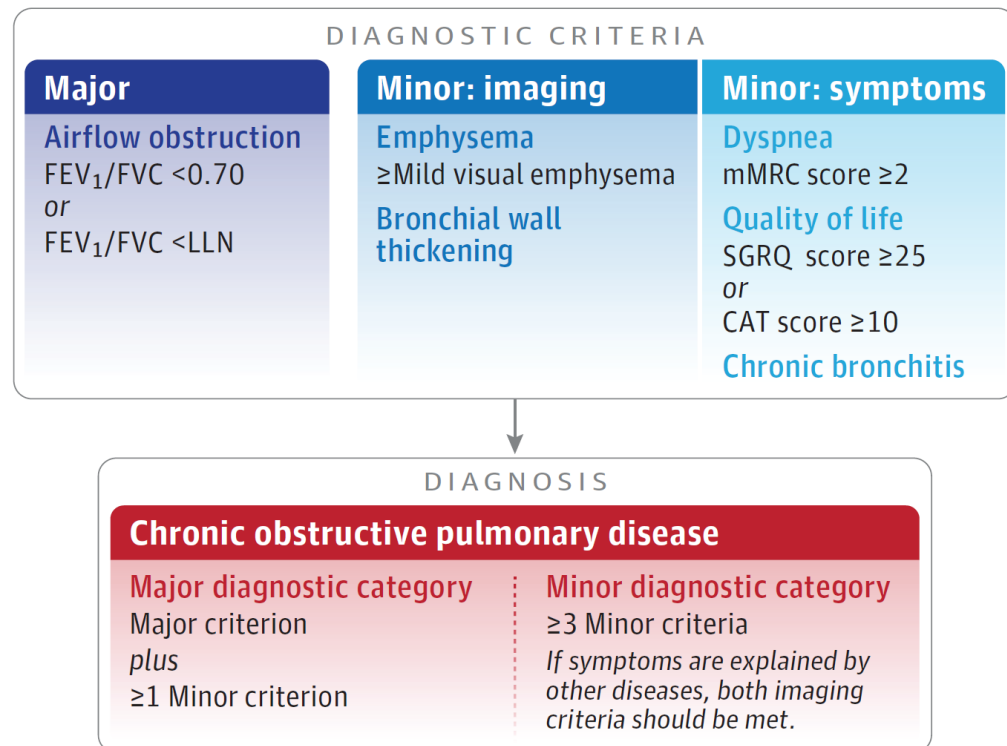


- a. Number of terminal bronchioles per milliliter
- b. Numbers of transitional bronchioles per milliliter
- c. Number of alveolar attachments
- d. Minimal to maximal airway diameter
- e. Surface density

# Expanding COPD diagnostic criteria

## COPDgene & CanCOLD

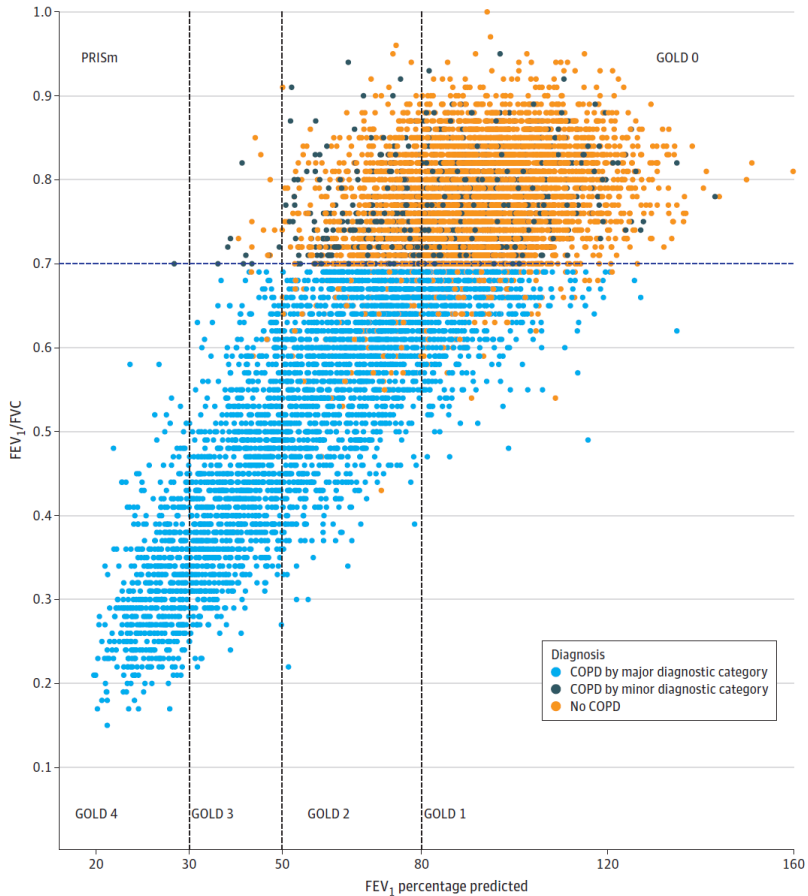
Figure 1. Diagnostic Schema for Chronic Obstructive Pulmonary Disease (COPD) Using Major and Minor Criteria



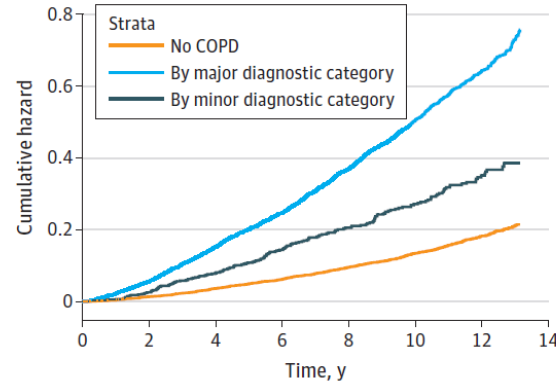
### Reclassification overall (N = 9416)

COPD by both old and new diagnostic schemas (n = 3884)	No airflow obstruction but COPD present according to new diagnostic schema (n = 811)	Airflow obstruction but no COPD according to new diagnostic schema (n = 282)	No COPD by both old and new diagnostic schemas (n = 4439)

# Expanding COPD diagnostic criteria

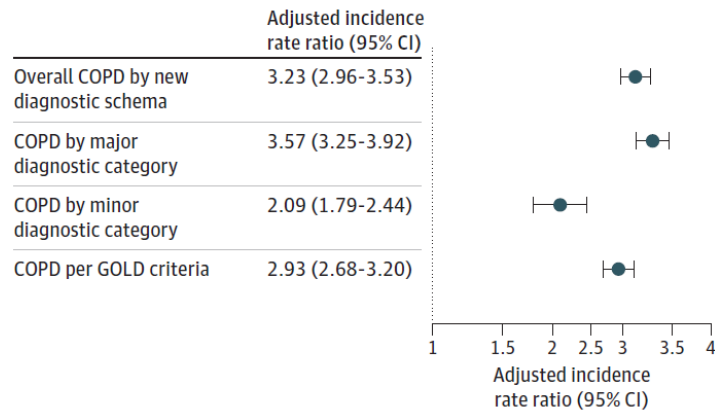


**A** Multivariable cumulative hazards plot of all-cause mortality by COPD category

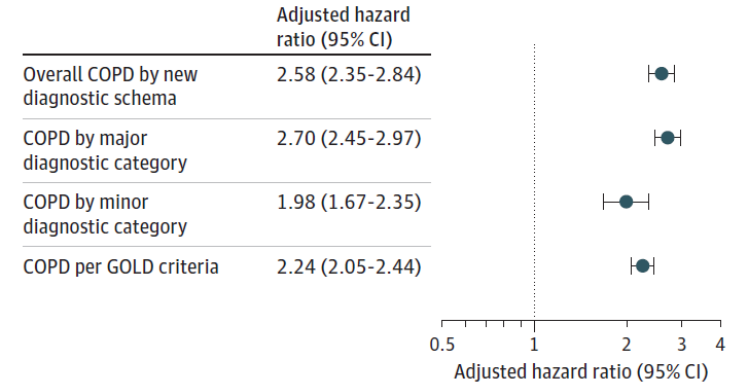


No. at risk	4721	4183	3986	3612	3276	2932	1820
No COPD	4721	4183	3986	3612	3276	2932	1820
By major diagnostic category	3884	3495	3100	2626	2160	1763	1015
By minor diagnostic category	811	670	598	517	423	354	201

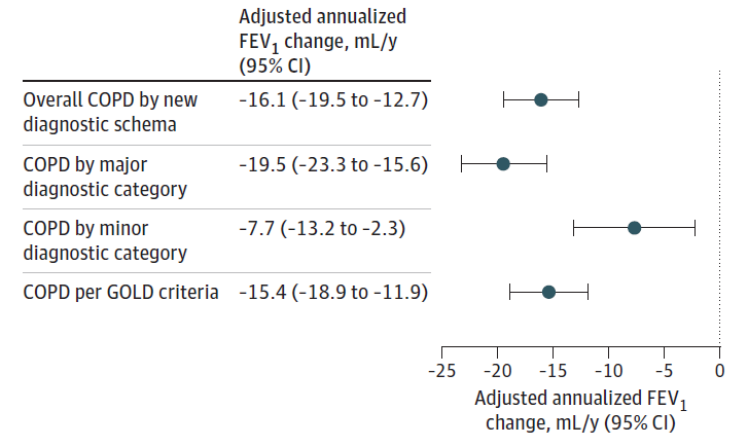
**C** Adjusted incidence rate ratio for exacerbations



**B** Adjusted hazard ratio for all-cause mortality by COPD category



**D** Adjusted annualized change in FEV<sub>1</sub>



# Screening of pre-COPD or COPD risk group

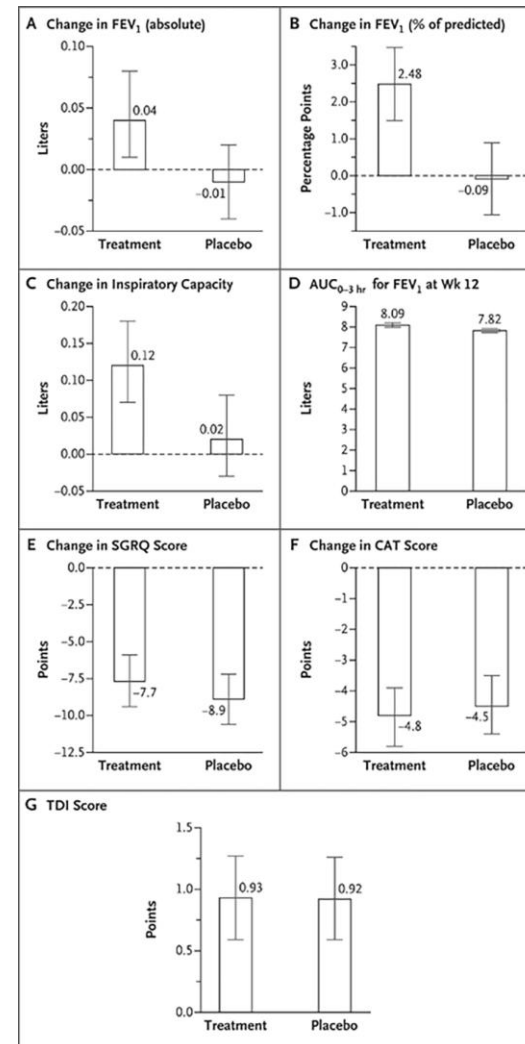
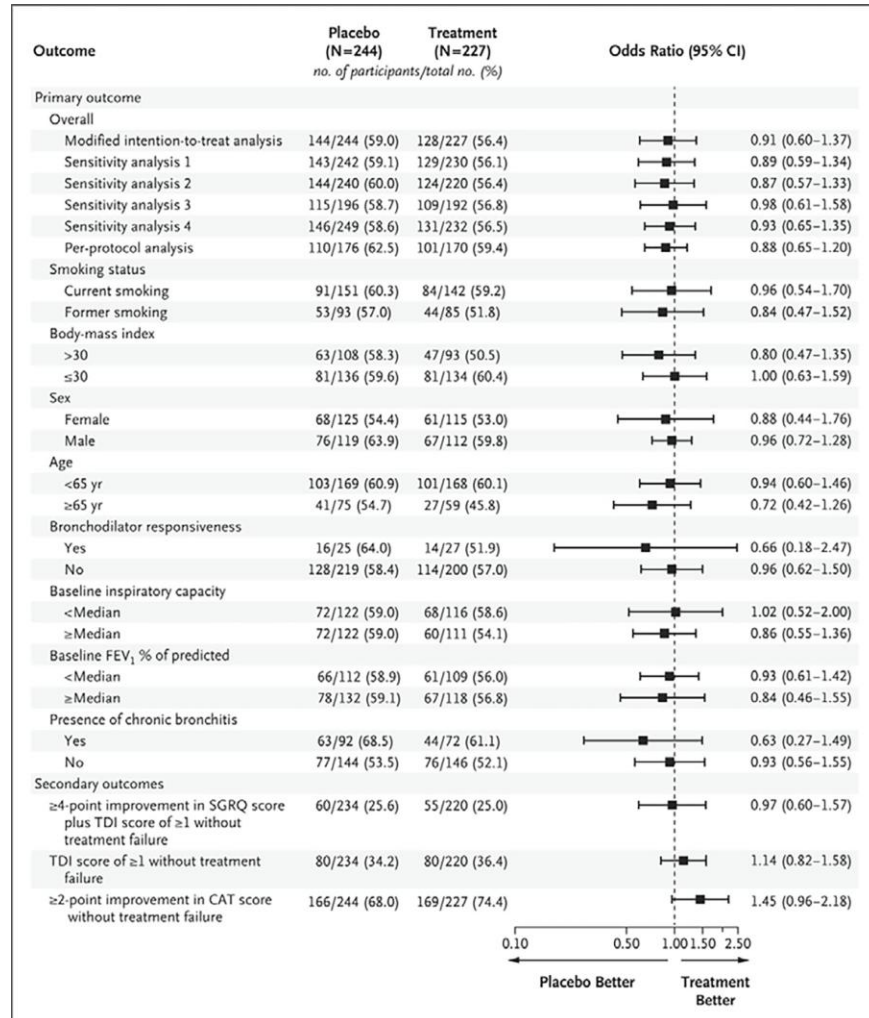
- Respiratory symptom - Chronic bronchitis or asthma identified via questionnaire
- Spirometry data - Evidence of small airway disease or PRISm
- Radiologic findings – Presence of emphysema or small airway disease
- Potential blood biomarkers – CC16, hsCRP

# Pre-COPD – early treatment strategies

## Secondary prevention

- Attempts to slow progression from pre-COPD to COPD have produced mixed results:
  - **12-week trial:** no improvement in symptoms
  - **1-year trial:** improved gas diffusion and small-airway metrics
- A large trial (PRE-TREAT) of triple therapy is underway
- Non-pharmacologic strategies (physical activity, smoking cessation) also matter
- Addressing “treatable traits” (airflow limitation, bronchitis, inactivity, mental health) may help

# Bronchodilators in Tobacco-Exposed Persons with Symptoms and Preserved Lung Function



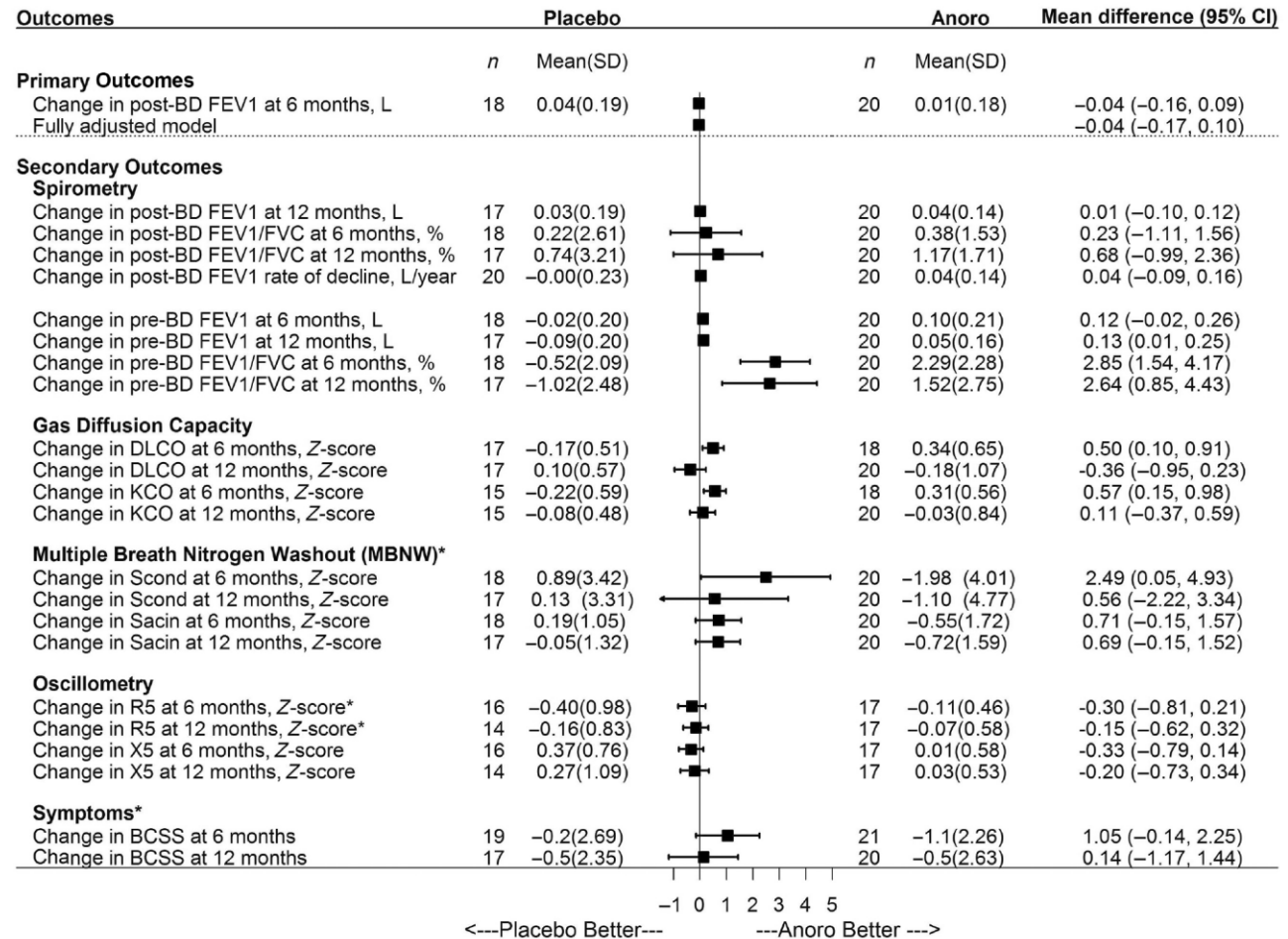
- No significant difference in clinically meaningful symptom improvement
- The treatment group showed a small but favorable change in lung function, and inspiratory capacity

# Dual bronchodilator treatment for prevention of COPD in at-risk smokers

Dual BD therapy would reduce lung function decline in smokers with small airways dysfunction (abnormal multiple nitrogen breath washout) and normal spirometry.

No differences between the study arms were found in change from baseline post-BD FEV1 at 6 months

Mean difference of primary and secondary outcomes between treatment arms



\* Note: Mean difference calculated as Anoro versus Placebo, except for MBNW, Oscillometry (R5 only) and Symptoms, which are Placebo versus Anoro

# Future direction of screening & intervention

## **1. Early Screening**

- Target individuals with family history of COPD, childhood respiratory infections, early abnormalities on imaging or PFTs, or respiratory symptoms without COPD diagnosis.
- Use CT, PFT, and risk-score–based surveillance for early detection
- Lung function tracking strategy

## **2. Intervention in PRISm Groups**

- Manage metabolic comorbidities and promote weight reduction to improve respiratory outcomes.

## **3. Treatment Approaches for Pre-COPD**

- Consider early therapeutic strategies, including inhaler therapy, to prevent progression to COPD.

# Summary

- COPD develops through multiple etiologies, including impaired lung growth, infections, genetics, and environmental exposures.
- Pre-COPD and PRISm are early abnormal states with meaningful symptom burden, faster decline, and increased mortality
- Early identification of high-risk markers (chronic bronchitis, small-airway dysfunction, PRISm) enables timely intervention and may prevent progression to COPD.

Thank you for listening