COPD in smokers and non-smokers

Joo Hun Park, M.D.
Dept. of Pulmonary and Critical Care Medicine
Ajou University School of Medicine

Outline

- Overview of COPD
- smoking COPD and non-smoking COPD

→ Clinical features

→ Comorbidities

→ Mortality

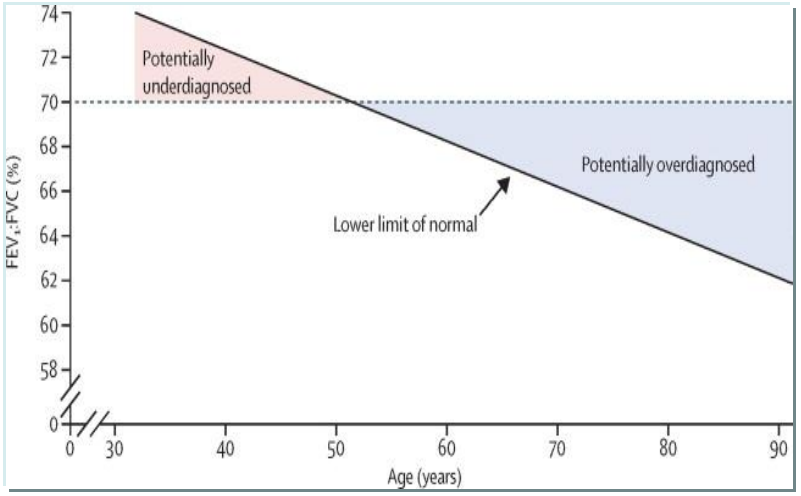
→ Treatment

Overview

Diagnosis

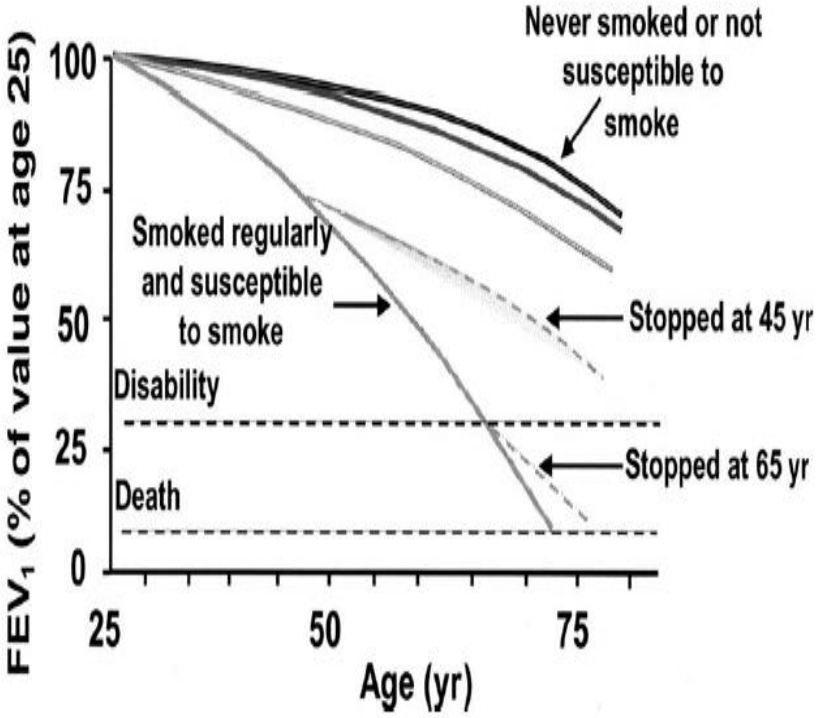
- COPD : post-bronchodilator $FEV_1/FVC < 70\%$
- COPD is accompanied by multiple phenotypes and many co-morbidities.

Han MK et al. AJRCCM 2010; 182: 598-604.
Vanfleteren LE et al. AJRCCM 2013; 187: 728-735.



Lancet 2015; 385: 1778–88

Fletcher's Curve



Summary

A prospective epidemiological study of the early stages of the development of chronic obstructive pulmonary disease was performed on London working men. The findings showed that forced expiratory volume in one second (FEV_1) falls gradually over a lifetime, but in most non-smokers and many smokers clinically significant airflow obstruction never develops. In susceptible people, however, smoking causes irreversible obstructive changes. If a susceptible smoker stops smoking he will not recover his lung function, but the average further rates of loss of FEV_1 will revert to normal. Therefore, severe or fatal obstructive lung disease could be prevented by screening smokers' lung function in early middle age if those with reduced function could be induced to stop smoking. Infective processes and chronic mucus hypersecretion do not cause chronic airflow obstruction to progress more rapidly. There are thus two largely unrelated

Secondly, non-smokers lose FEV_1 slowly and almost never developed clinically significant airflow obstruction. None of the 103 non-smokers in our study had any evidence of even moderate obstruction (p 83[19]).

BMJ 1977; 1: 1645-1648

Risk Factors for COPD in a European Cohort of Young Adults

- In 4636 subjects without asthma (20-44 yr old)
- First survey in 1991-1993

  Second survey in 1999-2002
- 10 European countries

AJRCCM 2011 Apr 1;183(7):891-7.

Risk Factors for COPD in a European Cohort of Young Adults

	IRR (95% CI)		
	GOLD	LLN (Quanjer)	LLN (LuftiBus)
Age (≥ 35 vs. < 35 yr)	2.24 (1.48, 3.39)†	1.25 (0.65, 2.39)	0.92 (0.53, 1.60)
BMI (vs. normal)			
Underweight	3.55 (1.59, 7.93)*	2.35 (0.72, 7.64)	1.14 (0.31, 4.22)
Overweight/obese	0.62 (0.42, 0.91)*	0.78 (0.30, 2.00)	1.03 (0.55, 1.94)
Smoking habits (vs. nonsmoker)			
Quitter/sustained quitter	2.08 (1.34, 3.21)*	1.69 (0.92, 3.10)	1.30 (0.81, 2.09)
Persistent smoker/new smoker/restarter	2.61 (1.62, 4.20)†	2.42 (1.35, 4.33)*	2.43 (1.25, 4.73)*
AHR	3.97 (2.07, 7.65)†	3.89 (1.78, 8.53)†	3.39 (1.72, 6.70)†
IgE sensitization	0.69 (0.44, 1.10)	0.86 (0.46, 1.60)	1.11 (0.68, 1.79)
Respiratory infections in childhood	1.88 (1.02, 3.46)*	1.97 (0.86, 4.54)	2.23 (1.64, 3.04)†
Family history of asthma	1.95 (1.25, 3.04)*	2.24 (1.12, 4.48)*	2.09 (1.26, 3.47)*

IRR = incidence rare ratio
LLN = lower limit of normal

AJRCCM 2011 Apr 1;183(7):891-7.

Risk Factors for COPD in a European Cohort of Young Adults

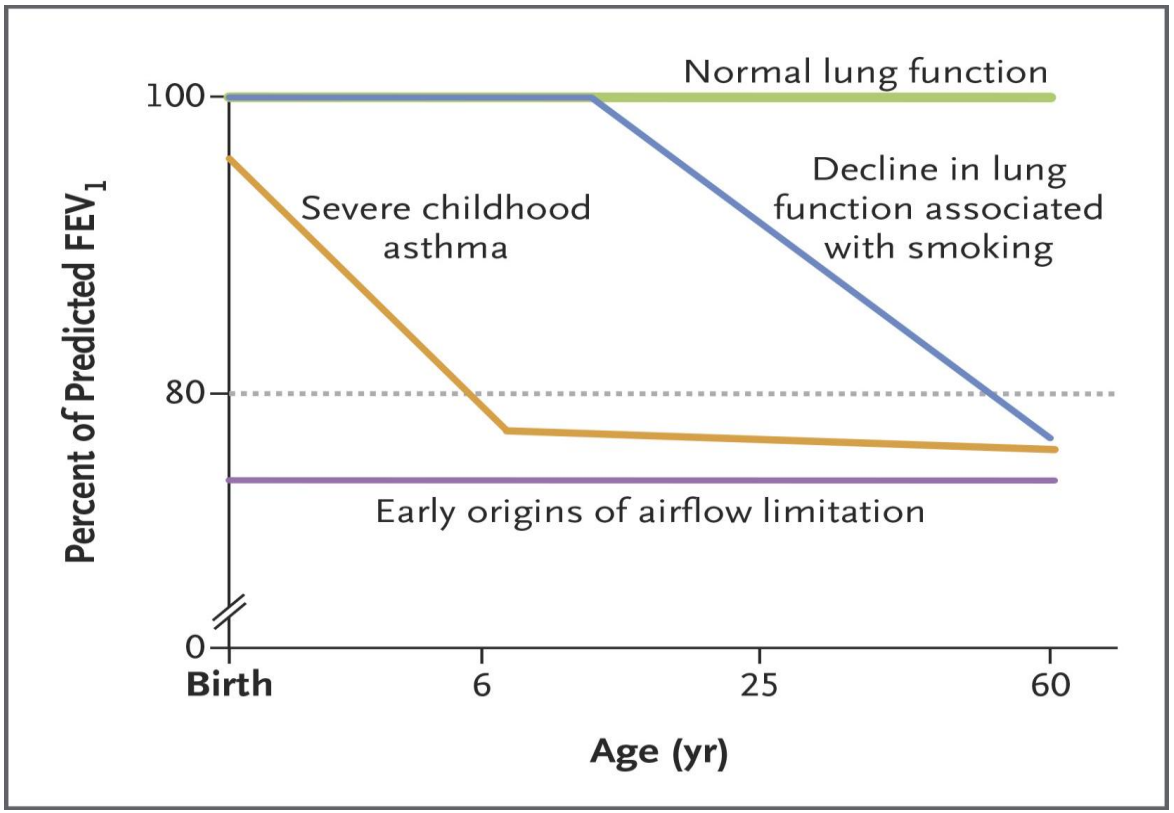
- Cases of COPD due to each factor
- Smoking : 29-39 %
- AHR : 15 %,
- Respiratory infection : 8%

AJRCCM 2011 Apr 1;183(7):891-7.

Risk Factors for COPD in a European Cohort of Young Adults

- COPD may start early in life.
- Airway hyperresponsiveness, a family history of asthma, and respiratory infections in childhood are other important determinants of COPD.

AJRCCM 2011 Apr 1;183(7):891-7.



- Perinatal influences

→ maternal smoking

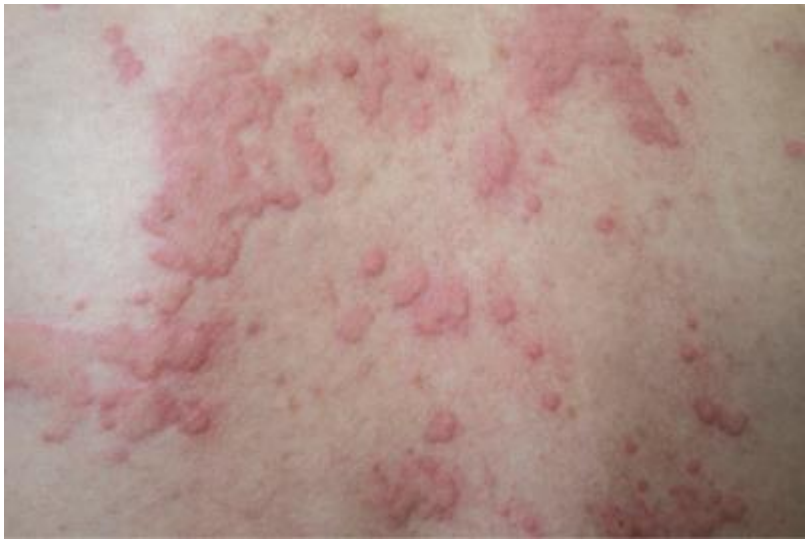
→ premature birth

- Respiratory illness in early life
- Air pollution
- Childhood asthma

Martinez FD, NEJM 2016; 375 : 871 - 878

The Japanese were a disease of the skin, while the communists were a disease of the heart.

Chiang Kai Shek



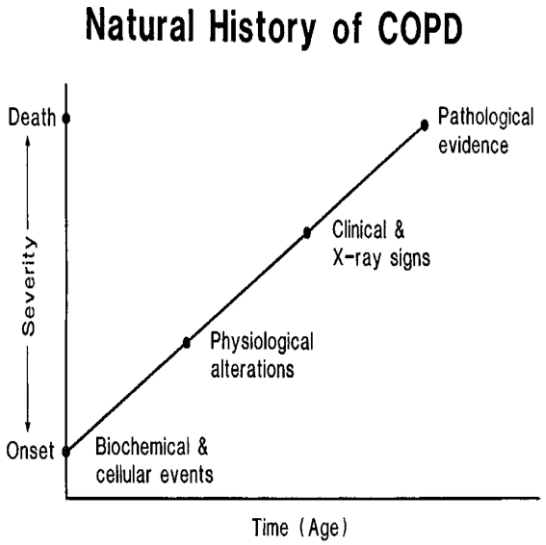
SIR picture

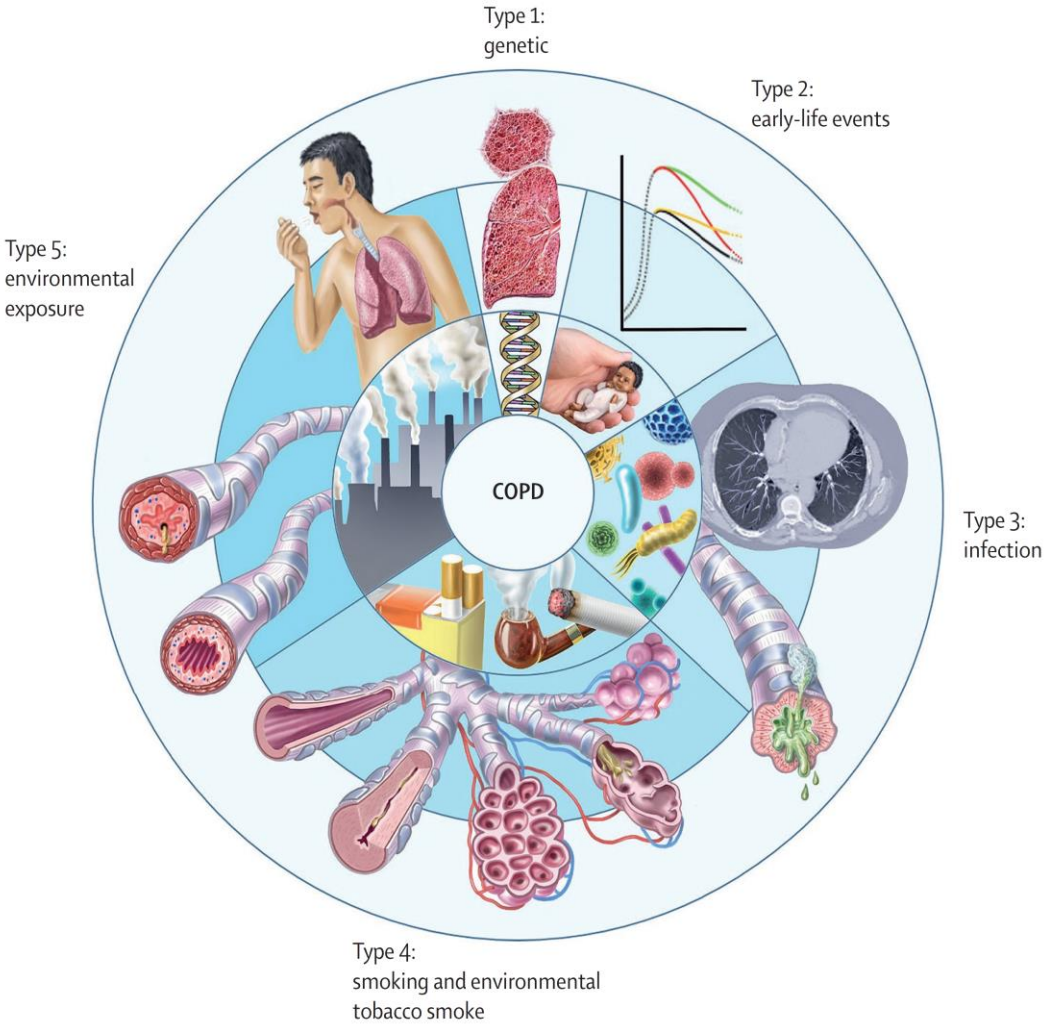
COPD is more like "fever."

- COPD is defined by a single physiologic parameter, reduced expiratory airfow.
- Not so long ago, a great variety of diseases would have been classified as a fever, including tuberculosis, plague, Hodgkin disease, and familial Mediterranean fever.
- COPD and fevers are heterogeneous.

Rennards SI et al. CHEST 2008; 134:623-627

New Classification of COPD





Lancet 2022; 400: 921-72

COPD etiotypes

GOLD 2023	Lancet Commission
COPD-G: genetically determined	Type 1: genetically determined
COPD-D: abnormal lung development	Type 2: early life events
COPD-I: infections	Type 3: infection related
COPD-C: cigarette smoking (and vaping)	Type 4: smoking or vaping
COPD-P: biomass and pollution exposure	Type 5: environmental exposure
COPD-A: COPD and asthma	
COPD-U: unknown cause	

COPD: chronic obstructive pulmonary disease.

Eur Respir J 2023; 61: 2202318

ERJ advances: state of the art in definitions and diagnosis of COPD

Sachin Ananth[1] and John R. Hurst[2]

- Recent changes to the classification of COPD bring much-needed attention to these other exposures.

- There is an absence of evidence for the treatment of COPD related to exposures other than tobacco smoking.

Sachin Ananth[1] and John R. Hurst[2]
Eur Respir J 2023; 61: 2202318

Clinical features

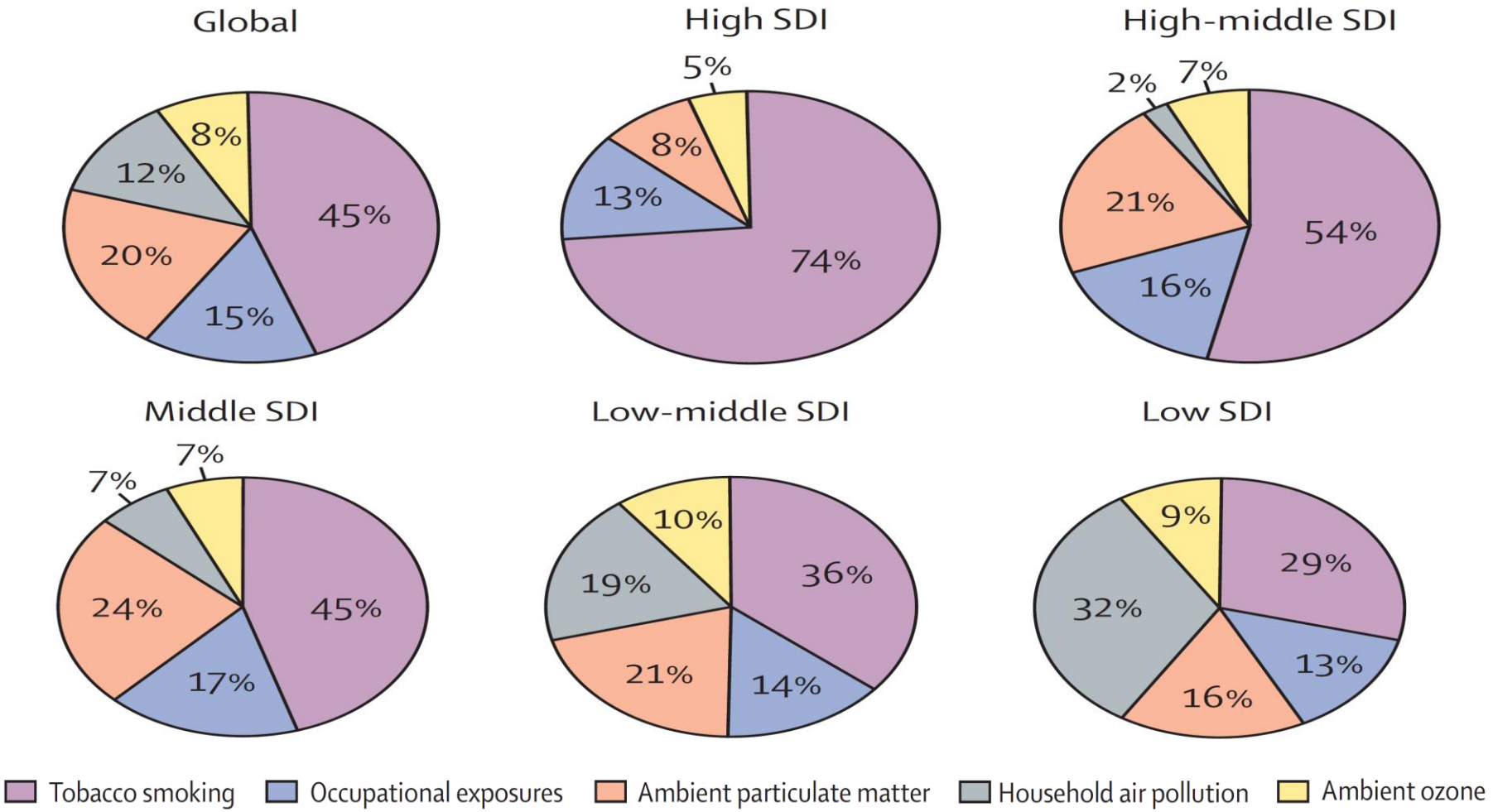
Burden of tobacco smoking in COPD

- Tobacco smoking accounting for COPD

→ over 70% in high income countries

→ non-smoking risk factors now contributing to over 50% of the global burden of COPD in low and middle income countries

Global risk factors associated with COPD according to sociodemographic index (SDI).



Ian A Yang, Christine R Jenkins, Sundeep S Salvi
Lancet Respir Med 2022; 10: 497–511

	Setting (study name)	Never-smokers (n)	Definition of COPD	Prevalence of COPD in never-smokers	Prevalence of never-smokers among people with COPD
Zhou et al (2009)[7]	China (CESCOPD)	12 471	Post-bronchodilator FEV_1/FVC <0·7	5%	39%
Lamprecht et al (2011)[8]	14 countries (BOLD)	4291	Post-bronchodilator FEV_1/FVC <0·7	12%	28%
Hagsted et al (2012)[9]	Sweden (OLIN)	770	Post-bronchodilator FEV_1/FVC <0·7	7%	20%
Perez-Padilla et al (2012)[10]	Five Latin American cities (PLATINO)	2278	Post-bronchodilator FEV_1/FVC <0·7	4%	26%
Thomsen et al (2013)[11]	Denmark (Copenhagen General Population Study)	26 005	FEV_1/FVC <LLN	6%	22%
Smith et al (2014)[12]	China Kadoorie Biobank	317 000	Pre-bronchodilator FEV_1/FVC <0·7 and <LLN	4% (females); 5% (males)	Not measured
Tan et al (2015)[13]	Canada (CanCOLD)	2295	Pre-bronchodilator FEV_1/FVC <0·7 and <LLN	6%	29%
Lee et al (2016)[14]	Korea (KNHANES IV and V)	8984	Post-bronchodilator FEV_1/FVC <0·7	7%	31%
Terzikhan et al (2016)[15]	The Netherlands (Rotterdam Study)	4997	Post-bronchodilator FEV_1/FVC <0·7	6%	27% (females); 7% (males)
Wang et al (2018)[16]	China (China Pulmonary Health study)	36 429	Post-bronchodilator FEV_1/FVC <0·7	6%	51%
Warkentin et al (2019)[17]	UK Biobank cohort	218 892	FEV_1/FVC <0·7 or FEV_1 <80% of Global Lung Initiative predicted FEV_1 reference value	16%	Not measured

Platino Study

- Cross-sectional population-based study of five Latin American cities
- 2278 never smokers vs. 3036 ever smokers
- Age ≥ 40 years

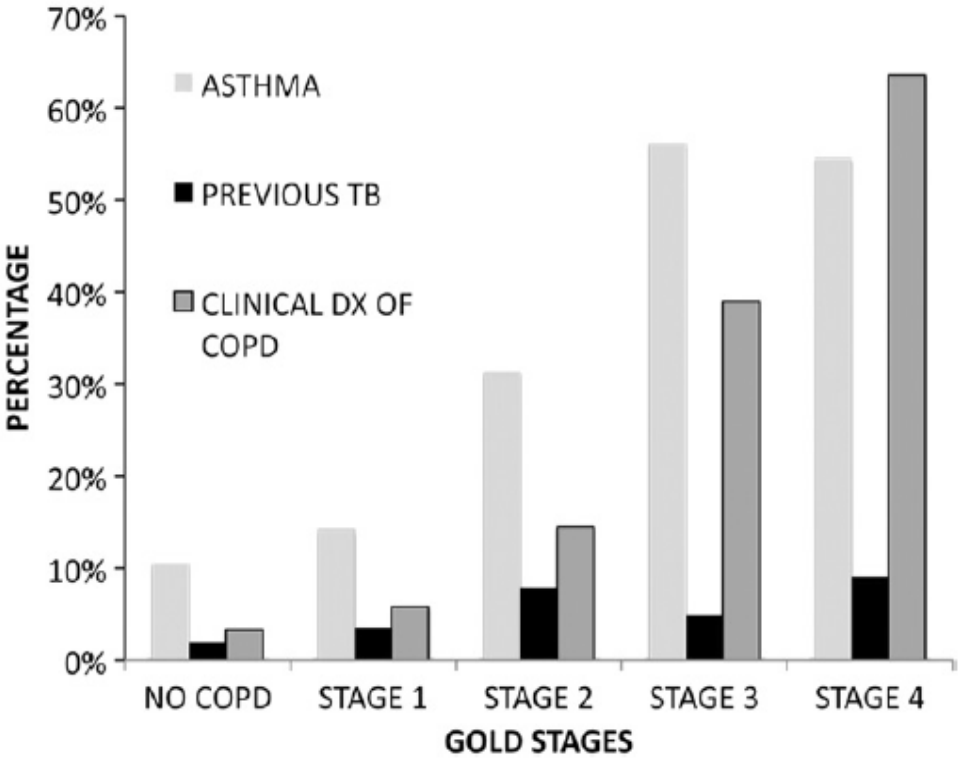
- Never smokers
  → 26% of all individuals with airflow obstruction
  → female & older age
  → asthma or tuberculosis

- COPD prevalence
  → 3.5% of never smokers, 7.5% of ever smokers

Rogelio Perez-Padilla et al

Archives of Medical Research 43 (2012) 159–165

Percentage of self-reported asthma, previous tuberculosis and clinical diagnosis of COPD in never smokers

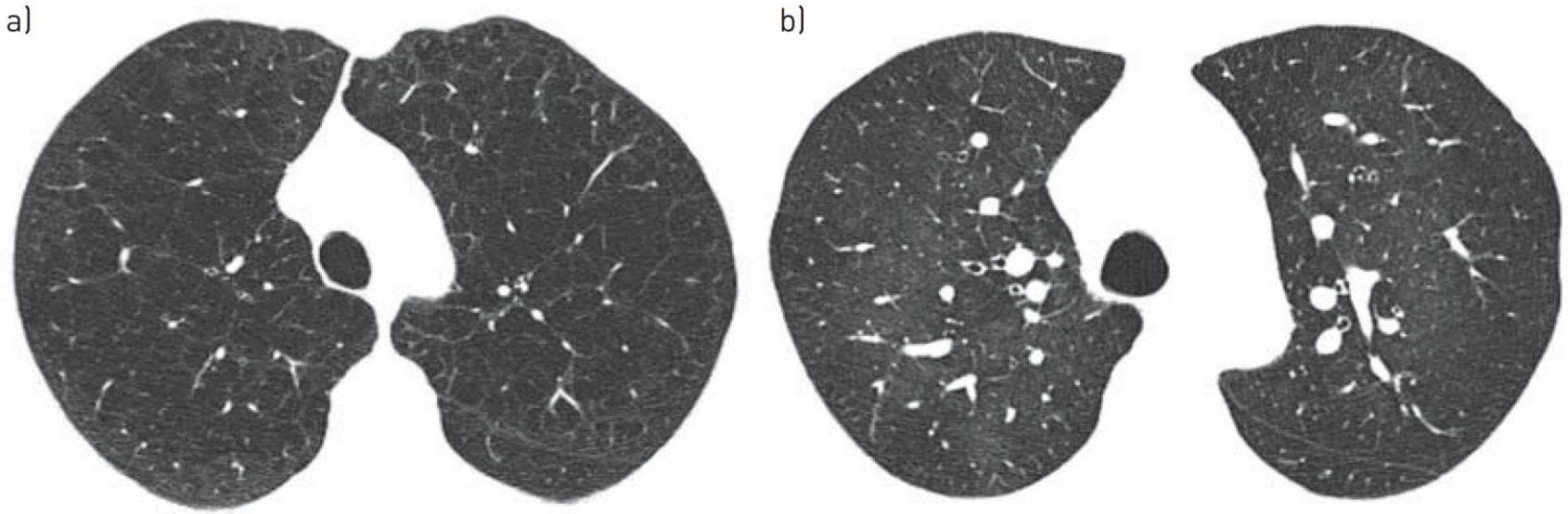


Rogelio Perez-Padilla et al

Archives of Medical Research 43 (2012) 159–165

- Women in the tobacco group (n=22)
  → more emphysema ($p<0.05$)
  (radiologist score 2.3 vs 0.7,
  emphysema on CT 27% vs 19%,
  larger emphysematous space)

- Women in the biomass group (n=21)
  → significantly more air trapping
  → more symptoms & activity limitation,
  → lower oxygen saturation



COPD clinic in Mexico City. Camp et al. ERJ 2014; 3: 725-734

Comparison between NS COPD and S COPD in KOCOSS

Table 5. Comparisons of radiologic features between non-smoking and smoking COPD patients.

	Non-smoking (*N* = 200)	Smoking (*N* = 2277)	*p*-value
Chest X-ray Result			0.06
Abnormal	131 (74.9%)	1327 (67.5%)	
Normal	44 (25.1%)	638 (32.5%)	
Emphysematous change	19 (13.7%)	533 (30.1%)	<0.01
TB destroyed lung	16 (11.5%)	104 (5.9%)	0.01
Airway wall thickening	6 (4.3%)	49 (2.8%)	0.43
Bronchiectasis	21 (15.1%)	94 (5.1%)	<0.01
Chest CT Result			
Abnormal	109 (96.5%)	1132 (91.9%)	0.12
Normal	4 (3.5%)	100 (8.1%)	
Emphysematous change	13 (18.1%)	521 (56.9%)	<0.01
TB destroyed lung	9 (12.5%)	59 (6.4%)	0.09
Airway wall thickening	12 (16.7%)	110 (12.0%)	0.33
Bronchiectasis	21 (29.2%)	114 (12.5%)	<0.01

COPD: JOURNAL OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE
2022, VOL. 19, NO. 1, 174–181

Clinical Characteristics of COPD in never-smokers compared to ever-smokers

	COPD in ever-smokers	COPD in never-smokers
Typical age of onset	>40 years	>30 years
Sex	More males than females affected	Males and females affected equally, or more females than males affected (especially in LMICs)
Symptoms	More cough and dyspnoea (relatively less sputum production)	More cough (relatively less dyspnoea and sputum production)
Respiratory exacerbations	Frequent (and potentially severe)	Frequent (and potentially severe)
Comorbidities	Prevalent	Generally less prevalent
Risk of lung cancer	High	High
Lung physiology	More severe airflow obstruction; greater increase in RV/TLC (hyperinflation); increase in airway resistance; less small airways obstruction; reduced DLCO	Milder airflow obstruction; increase in RV/TLC (hyperinflation); greater increase in airway resistance; more small airways obstruction; normal DLCO
FEV_1 decline	Can be rapid	Usually normal
Lung CT imaging	Less air trapping due to small airways obstruction; more emphysema	More air trapping due to small airways obstruction; less emphysema
Sputum inflammatory cells	Greater increase in neutrophils	Increase in neutrophils; relatively greater increase in eosinophils
Pharmacological responses	Long-acting bronchodilators favoured over inhaled corticosteroids in terms of safety and effectiveness, especially among those with predominant emphysema	Not known

Ian A Yang, Christine R Jenkins, Sundeep S Salvi
Lancet Respir Med 2022; 10: 497–511

TABLE 3. CLINICAL CHARACTERISTICS OF THE SUBJECTS IN THE FIVE CLUSTERS

Clinical Characteristics	Cluster 1: Less Comorbidity	Cluster 2: Cardiovascular	Cluster 3: Cachectic	Cluster 4: Metabolic	Cluster 5: Psychologic
N	67	49	44	33	20
Age, yrs	62.1 ± 6.8*	67.2 ± 5.8†	62.5 ± 7.2	63.1 ± 7.3	62.8 ± 6.8
Male, %	60	65	43*	79†	45
mMRC dyspnea grade	1.99 ± 1.01	2.29 ± 1.21	1.73 ± 0.9*	2.12 ± 1.11	2.84 ± 1.12†
Current smoker, %	30	16*	45†	15	35

Vanfleteren, Spruit, Groenen, *et al.*: Clusters of Comorbidities in COPD

Am J Respir Crit Care Med Vol 187, Iss. 7, pp 728–735, Apr 1, 2013

Prevalence of Symptoms and Risk of Respiratory Exacerbations, According to Study Group.

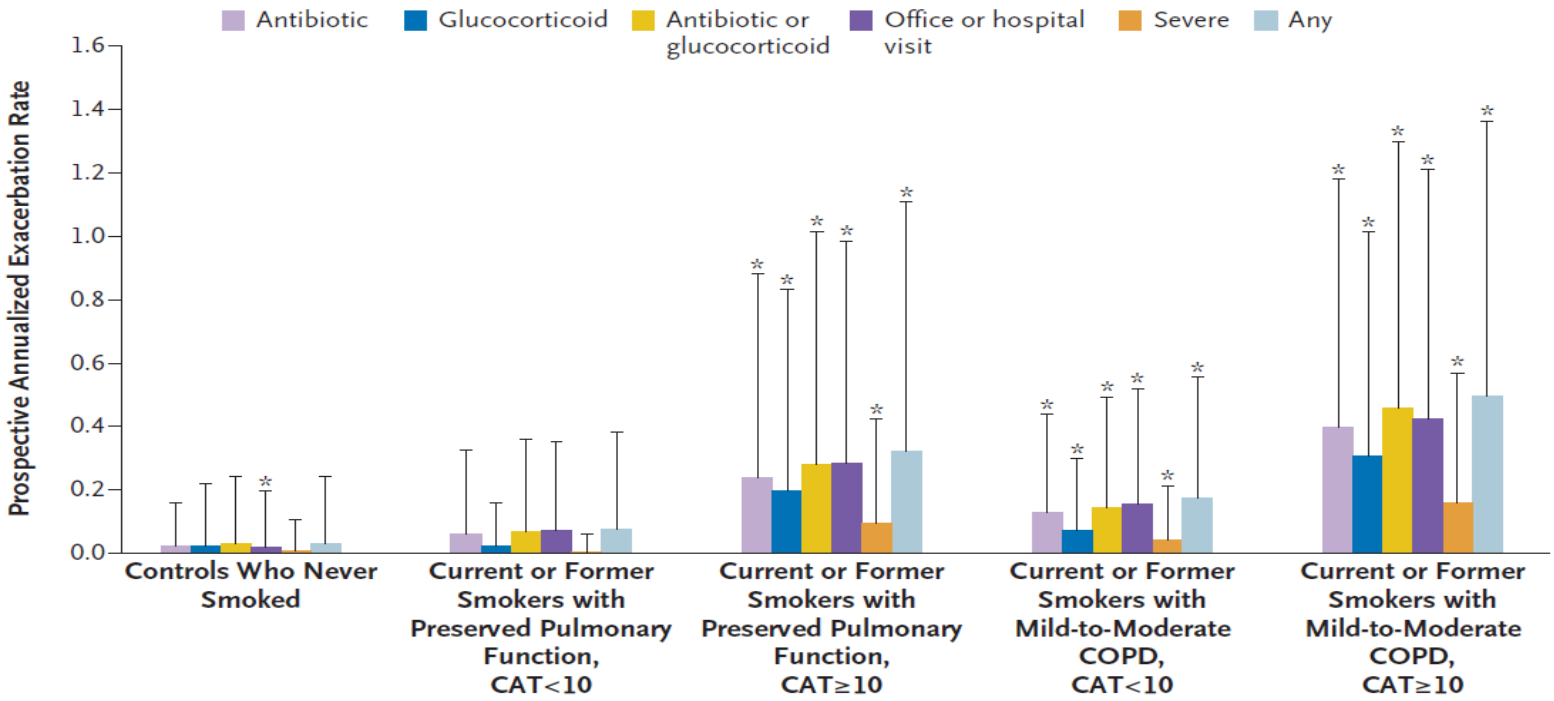


Figure 2. Prevalence of Symptoms and Risk of Respiratory Exacerbations, According to Study Group.

CONCLUSIONS

Although they do not meet the current criteria for COPD, symptomatic current or former smokers with preserved pulmonary function have exacerbations, activity limitation, and evidence of airway disease. They currently use a range of respiratory medications without any evidence base. (Funded by the National Heart, Lung, and Blood Institute and the Foundation for the National Institutes of Health; SPIROMICS

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS

Smoking, Not COPD, as the Disease

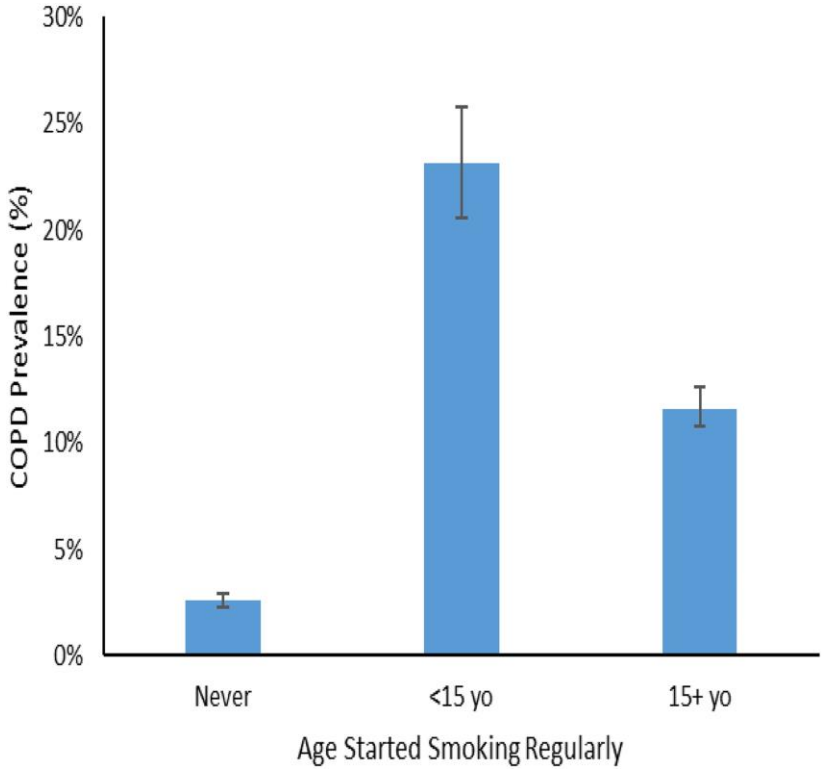
Leonardo M. Fabbri, M.D.

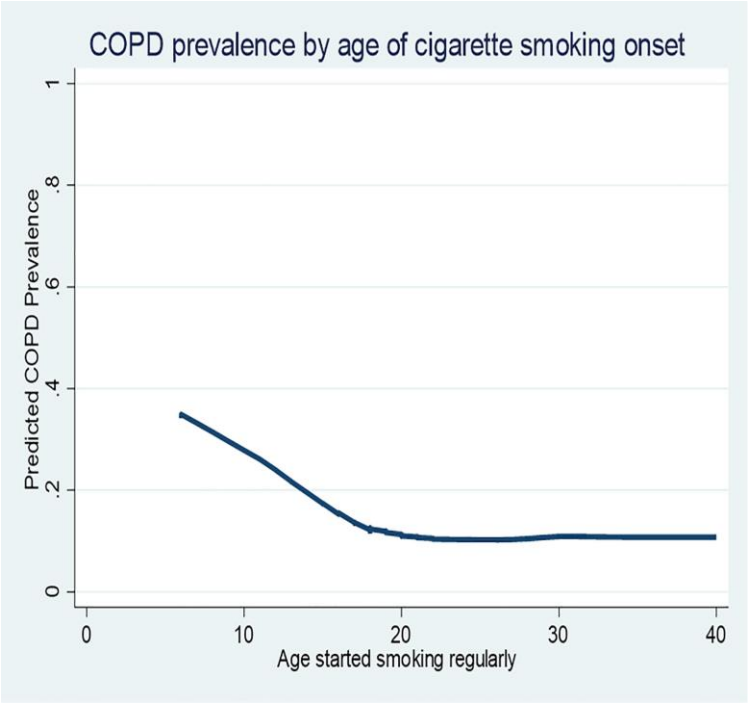
- Even though the effects of smoking are broad and devastating, much smoking-related research traditionally focuses on the lung because the lung is considered to be the primary target organ of smoking.

- Even though COPD is one of the major consequences of smoking, COPD usually does not exist by itself, because it is almost invariably associated with concomitant chronic respiratory and nonrespiratory diseases that contribute to the clinical manifestations and severity of the smoking-induced systemic disease.

Age of Initiating Smoking: An Independent Predictor of COPD in Later Life

Cross-sectional survey in the 2020 National Health Interview Surve
22,374 adults adults ⩾40 years old

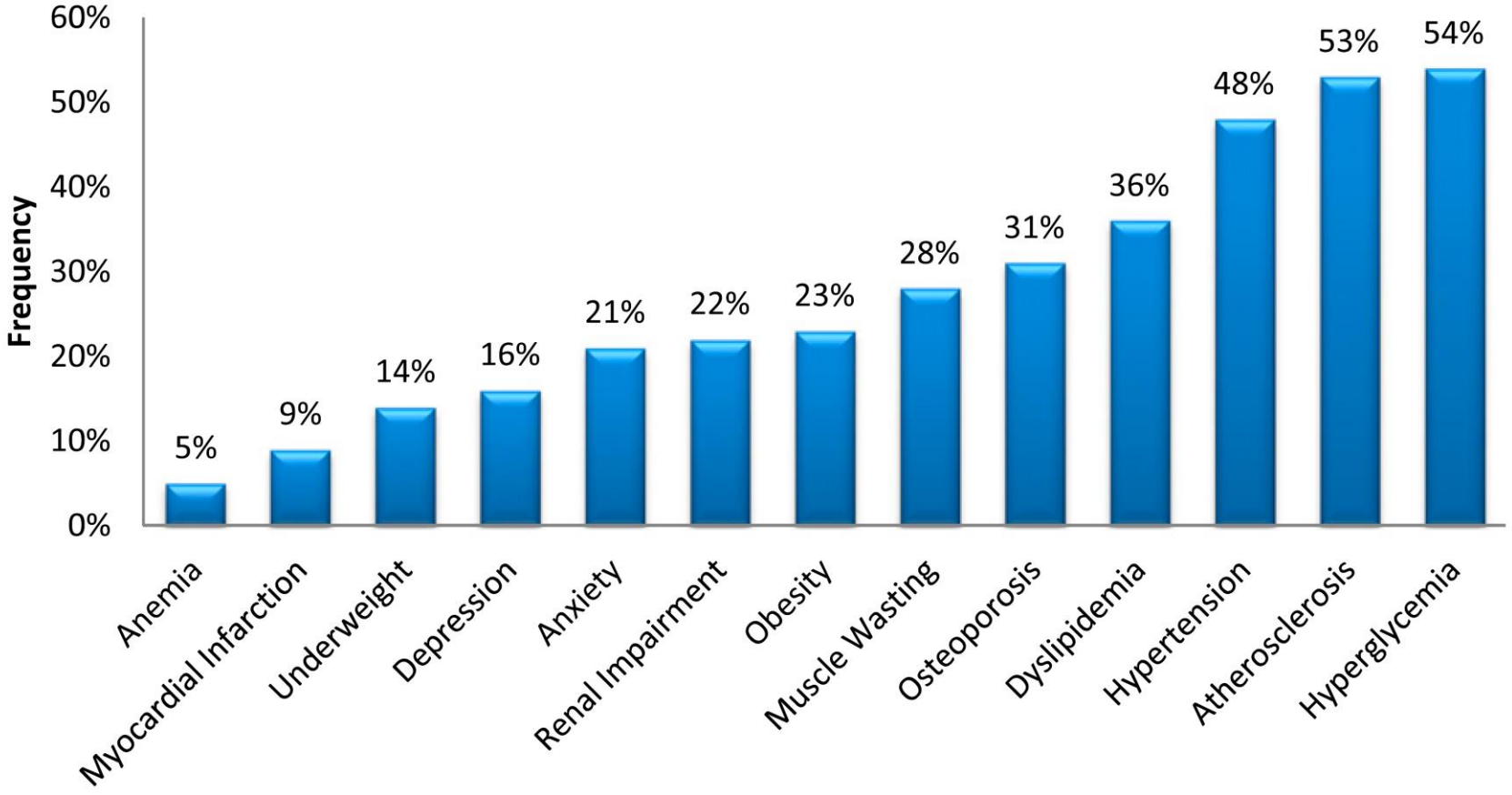




Sargent DJ et al AJRCCM Vol 208, Iss 4, pp 428–434, Aug 15, 2023

Comorbidity

Clusters of Comorbidities Based on Validated Objective Measurements and Systemic Inflammation in Patients with Chronic Obstructive Pulmonary Disease

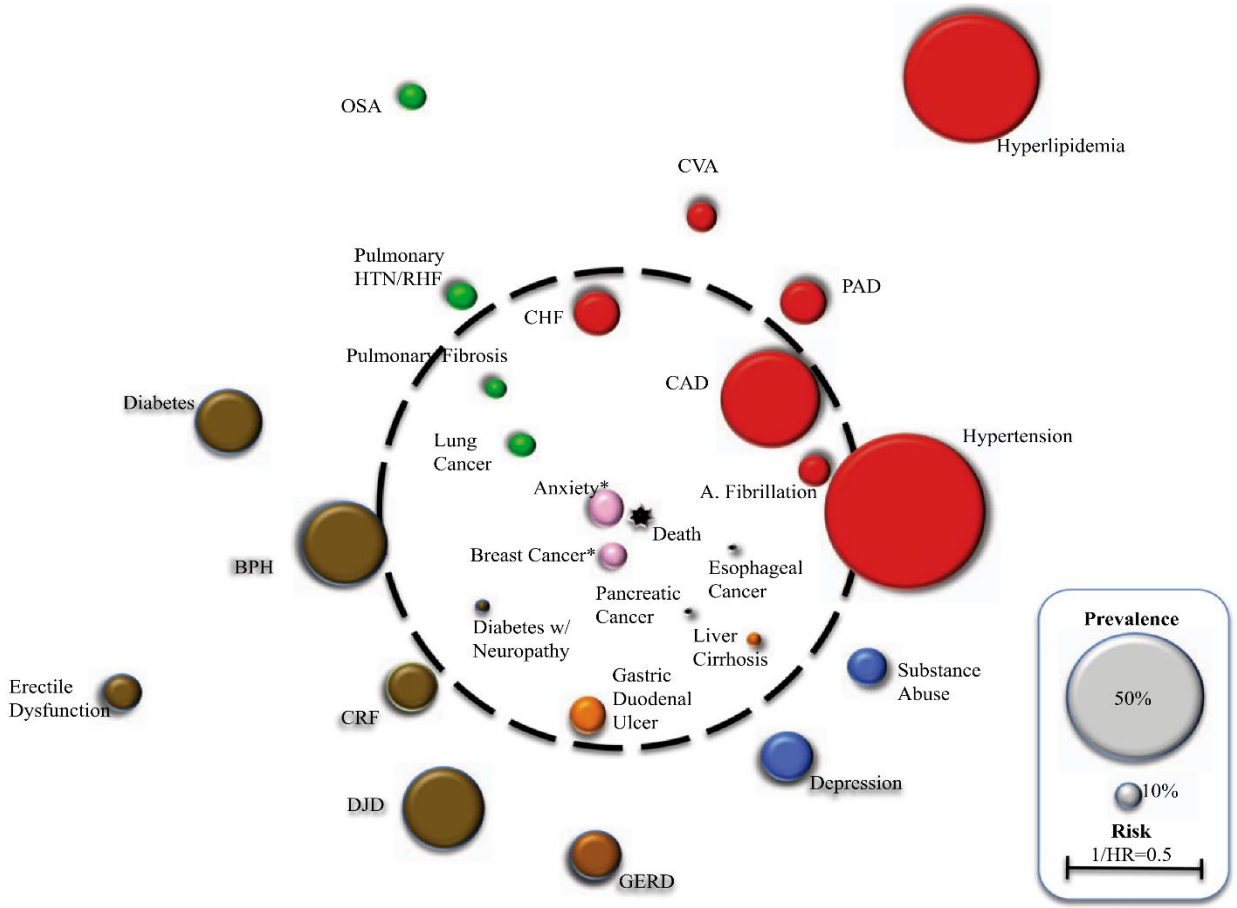


Vanfleteren, Spruit, Groenen, *et al.*: Clusters of Comorbidities in COPD

Am J Respir Crit Care Med Vol 187, Iss. 7, pp 728–735, Apr 1, 2013

Comorbidities and Risk of Mortality in Patients with Chronic Obstructive Pulmonary Disease

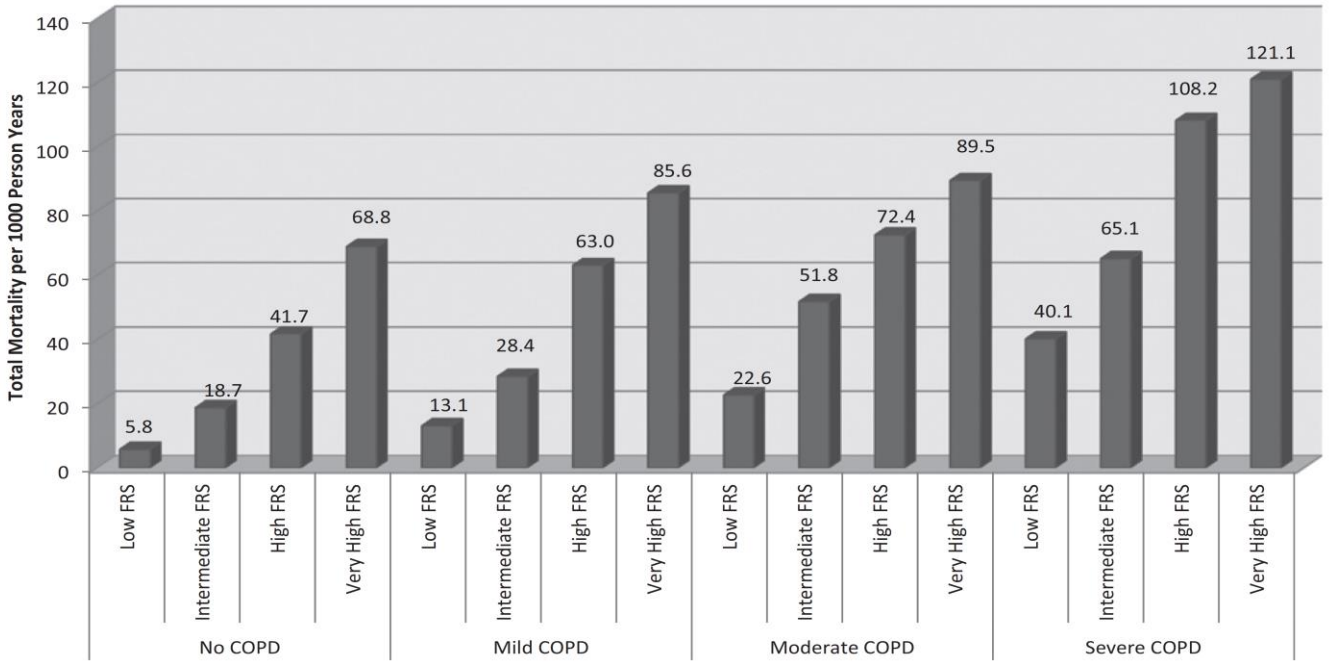
BODE cohort
History of smoking > 10 pack years



Divo M et al Am J Respir Crit Care Med Vol 186, Iss. 2, pp 155–161, Jul 15, 2012

Relation Between COPD Severity and Global Cardiovascular Risk in US Adults

- 6,266 US COPD patients
- Estimated 10-year risk of cardiovascular events
- Framingham Risk Score (FRS) : CV risk estimation



Lee MS et al, chest 2012; 142 : 1118-1125

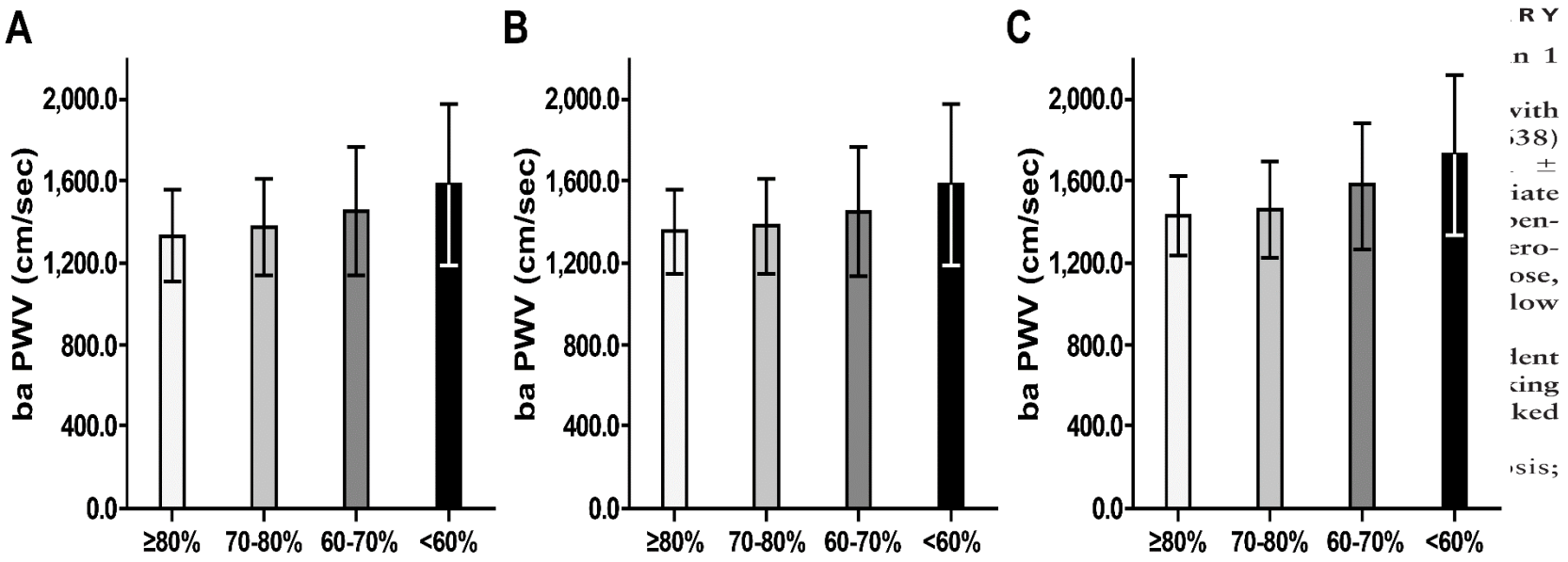
INT J TUBERC LUNG DIS 24(6):000–000

http://dx.doi.org/10.5588/ijtld.19.0457

Airflow limitation as a risk factor for vascular stiffness

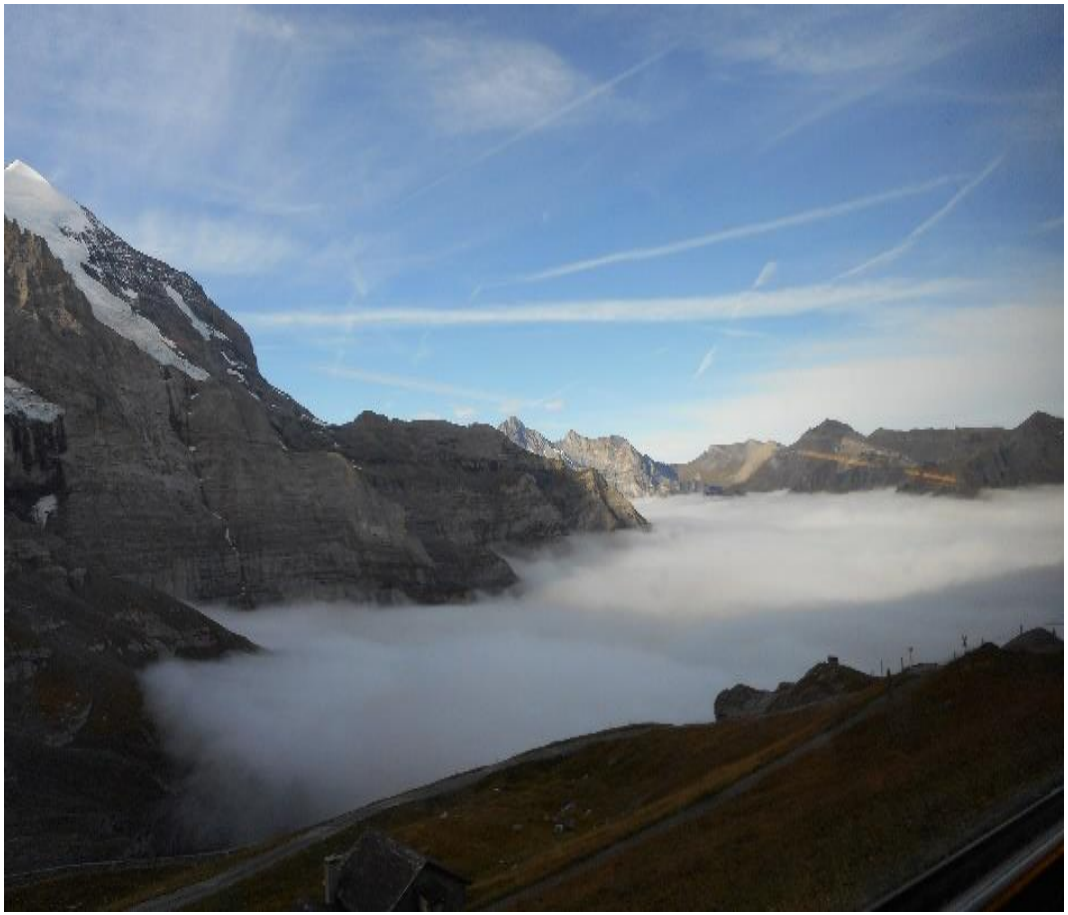
S. S. Sheen,[1] H. J. Kim,[1] D. Singh,[2] S. C. Hwang,[1] K. J. Park,[1] S. V. Ahn,[3] E. Lee,[4] B. Park,[4] J. H. Jung,[4] R. W. Park,[4] J. H. Kim,[5] H-S. Park,[6] J. H. Park[1]

[1]Department of Pulmonary and Critical Care Medicine, Ajou University School of Medicine, Suwon, South Korea; [2]Division of Infection, Immunity and Respiratory Medicine, School of Biological Sciences, Faculty of Biology, Medicine and Health, Manchester Academic Health Science Centre, The University of Manchester and University Hospital of South Manchester NHS Foundation Trust, Manchester, UK; [3]Department of Health Convergence, Ewha Woman's University, Seoul, Departments of [4]Biomedical Informatics, [5]Gastroenterology, and [6]Allergy and Clinical Immunology, Ajou University School of Medicine, Suwon, South Korea



2. Value of ba PWV based on FEV_1/FVC
A. Never-smokers, p<0.001
B. Former-smokers, p<0.001
C. Current-smokers, p<0.001

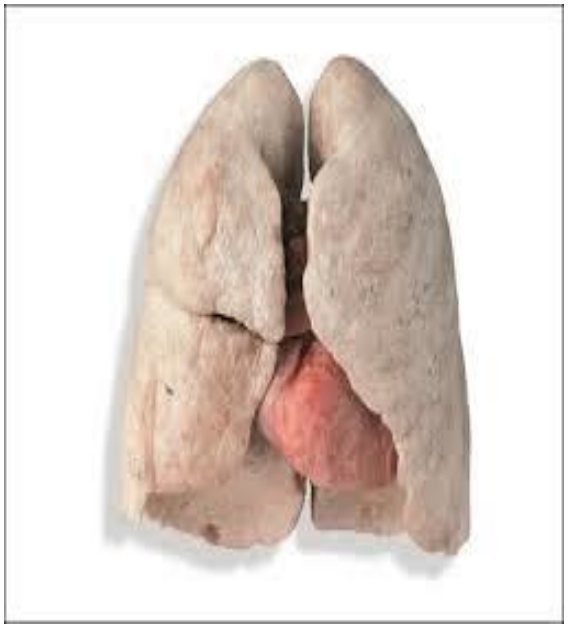
COPD & lung cancer

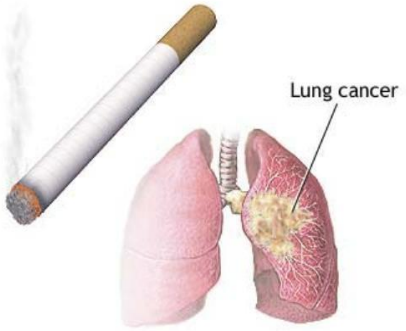


Average adult inhales about 10,000 L/day.
Carcinogens present in the air at low concentrations are of concern as a risk factor for lung cancer.

Murray & Nadel 5 th edition p1081

Past ⟹ Present ⟹ Future





Risk Factors of Lung Cancer in COPD

- Smoking
- Air pollution
- Emphysema

  Am J Respir Crit Care Med 2011, 184:866-867

  Chest 2021;159(5):1812-1820

- TB destroyed lung

  Ann Am Thorac Soc. 2022 Apr;19(4):640-648.

- Severity of airflow obstruction

  Chest 2010, 138:1295-1302

  Arch Intern Med 2003, 163:1475-1480

  Ann Am Thorac Soc 2017; 14:392

Carcinogenesis in the airways

- Retention of airborne carcinogens because of airflow limitations
- Chronic inflammatory processes
- Genetic backgrounds common to both COPD and the development of lung cancer

Yuichi Takiguchi, Ikuo Sekine, Shunichiro Iwasawa, Ryota Kurimoto, Koichiro Tatsumi
World J Clin Oncol 2014 October 10; 5(4): 660-666

Detection of COPD in the SUMMIT Study lung cancer screening cohort using symptoms and spirometry

Methods 16 010 current or former smokers aged 55–77 years attended a lung health check as part of the SUMMIT Study. A respiratory consultation and spirometry were performed alongside LCS eligibility

	Univariate		Multivariate	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age				
Per increasing year	1.08 (1.05–1.11)	<0.001	1.05 (1.02–1.09)	0.002
Sex				
Male	1		1	
Female	1.50 (1.05–2.15)	0.028	1.39 (0.95–2.01)	0.089
Pack-years				
Per increasing pack-year	1.01 (1.00–1.01)	0.037	1.00 (1.00–1.01)	0.179
Personal history of cancer				
No	1			
Yes	2.11 (1.38–3.21)	<0.001	1.77 (1.15–2.72)	0.009
Family history of lung cancer				
No	1		1	
Yes	2.08 (1.41–3.05)	<0.001	2.02 (1.36–2.99)	<0.001
Emphysema presence?				
No	1		1	
Yes	2.01 (1.40–2.88)	<0.001	1.43 (0.97–2.10)	0.069
Airflow obstruction?				
No	1		1	
Yes	3.24 (2.13–4.94)	<0.001	2.45 (1.57–3.83)	<0.001
Symptomatic airflow obstruction?				
No airflow obstruction	1		1	
Asymptomatic	1.94 (1.00–3.73)	0.049	1.61 (0.82–3.16)	0.163
Symptomatic	3.66 (2.38–5.61)	<0.001	2.74 (1.73–4.34)	<0.001
Previous diagnosis?				
No airflow obstruction	1		1	
Asymptomatic	1.94 (1.00–3.73)	0.049	1.61 (0.82–3.16)	0.163
Undiagnosed symptomatic airflow obstruction	3.83 (2.40–6.13)	<0.001	2.79 (1.67–4.64)	<0.001
Diagnosed symptomatic airflow obstruction	3.44 (2.08–5.68)	<0.001	2.61 (1.15–5.91)	0.022

Eur Respir J 2022; 60: 2200795

Pulmonary Tuberculosis and the Incidence of Lung Cancer among Patients with COPD

- Health screening examination cohort
- 13,165 Koreans with COPD
- Age : 50 — 84 years
- Matched for age, sex, smoking, and PTB
- HR (95% CI) for lung cancer in those with pulmonary TB history

→ 1.24 (1.03-1.50)

HY Park et al, Ann ATS 2022 Apr;19(4):640-648.

The Bidirectional Gut–Lung Axis in Chronic Obstructive Pulmonary Disease

Lei Wang[1,3*], Yang Cai[2*], Johan Garssen[1,4], Paul A. J. Henricks[1], Gert Folkerts[1], and Saskia Braber[1]

Am J Respir Crit Care Med Vol 207, Iss 9, pp 1145–1160, May 1, 2023

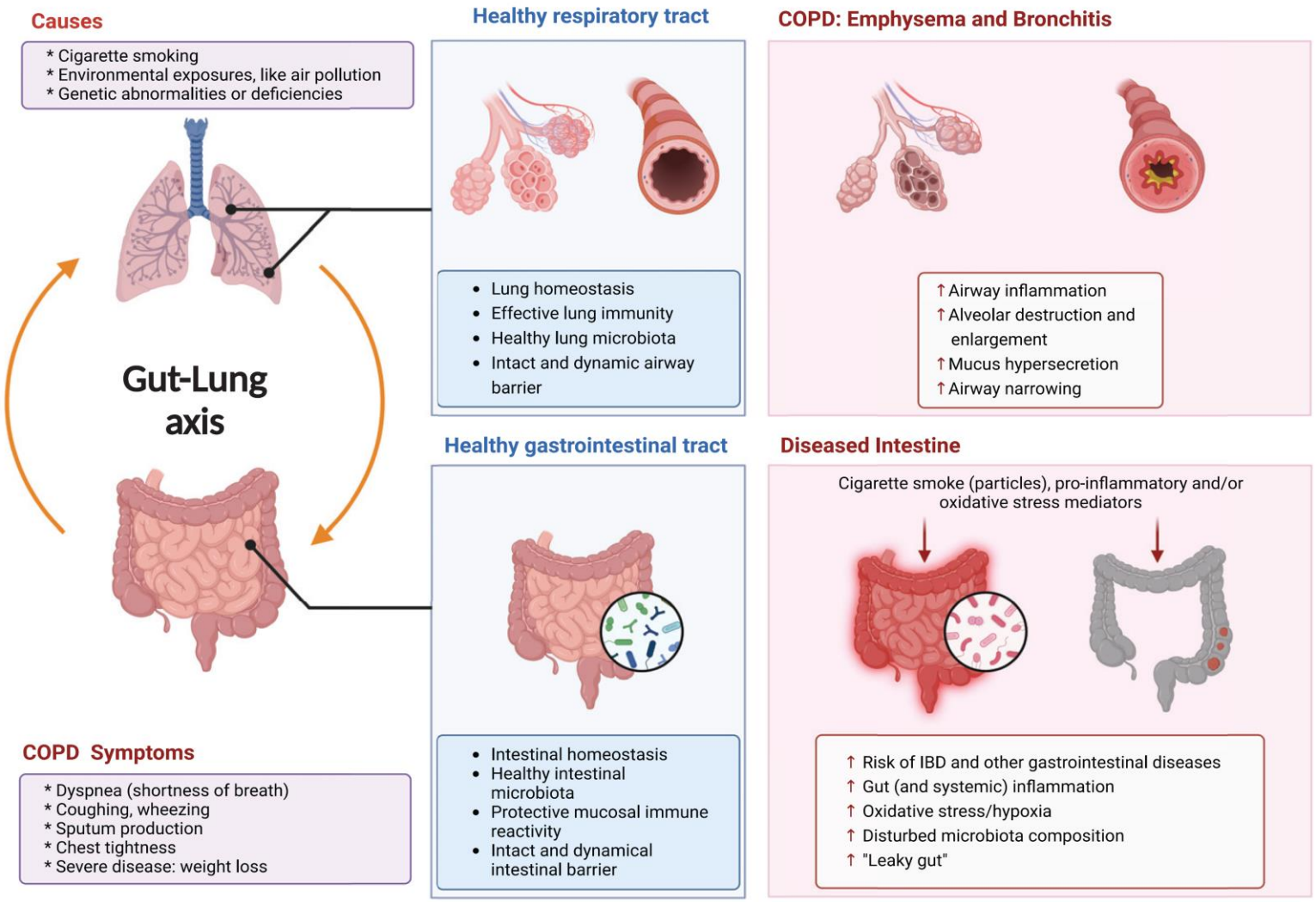


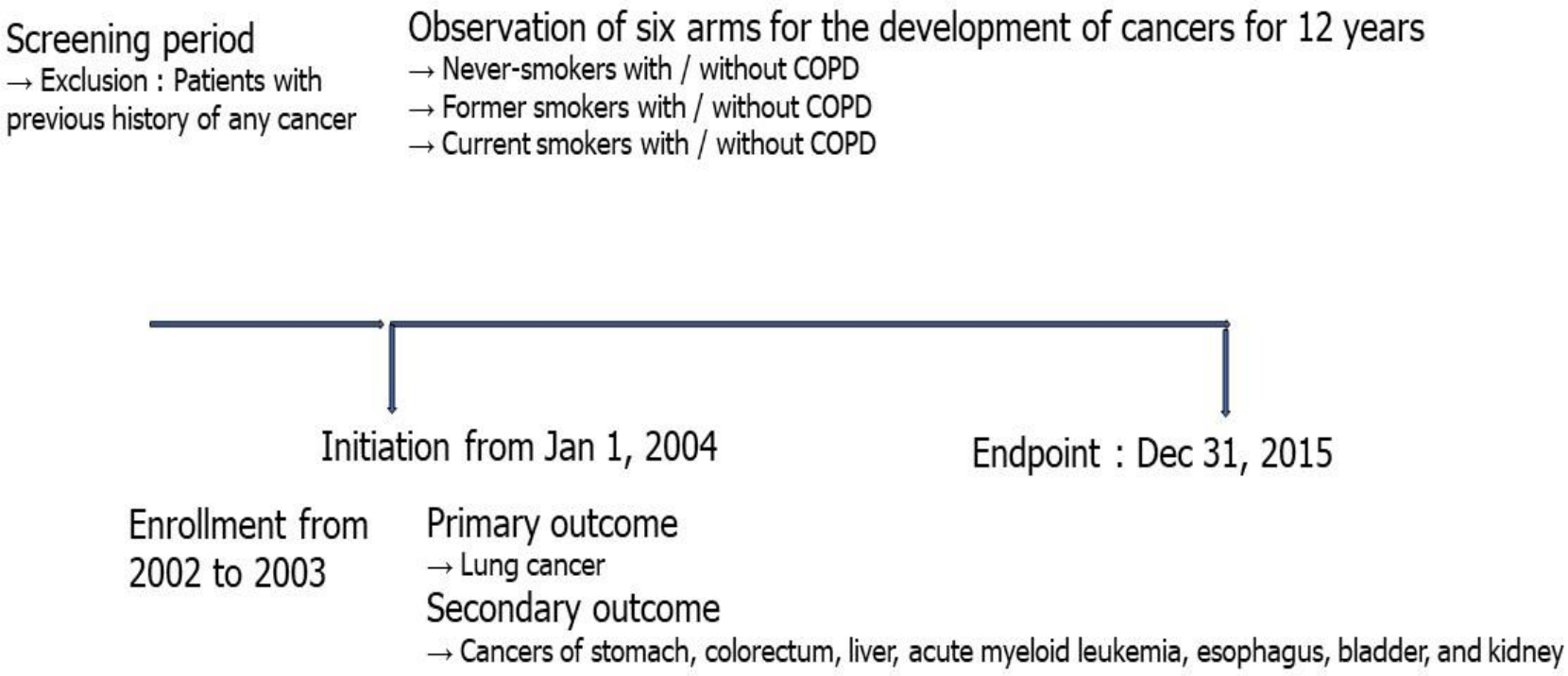
Table 1. Clinical Evidence for Gut–Lung Axis in Chronic Obstructive Pulmonary Disease

Target Subjects	Study Design	Effects on Intestine/Mortality	References
Patients with COPD Non-COPD control subjects	Population of Québec, 2001–2006	The incidence of CD and ulcerative colitis was 55% and 30% higher in patients with COPD than in the general population, respectively The highest incidence rate for COPD cohort was at ages 50–59 yr	7
COPD Asthma–COPD Non-COPD control subjects	Health databases in Québec, age ⩾ 65 yr, without a private drug plan as control Residents received one or more prescriptions for a specific respiratory medication from 1990 to 2007, age ⩾ 41 Newly developed IBD in patients with COPD/ asthma–COPD	In patients with asthma–COPD, IBD increased the risk of mortality from respiratory conditions In patients with COPD, IBD increased the risk of death of digestive conditions	17
Patients with COPD Non-COPD control subjects	National Health Insurance Database of Korea Patients received prescriptions for COPD medications at least twice in 2009	The prevalence of GERD in patients with COPD was 28% GERD increased the risk of hospitalization in patients with COPD	30
Patients with COPD Non-COPD control subjects	Smokers, former smokers, and nonsmokers of the Korean population in 2002; ages 40–79 yr	Higher incidence of colorectal cancer in patients with COPD regardless of smoking status	27

27. Ahn SV, Lee E, Park B, Jung JH, Park JE, Sheen SS, *et al.* Cancer development in patients with COPD: a retrospective analysis of the National Health Insurance Service–National Sample Cohort in Korea. *BMC Pulm Med* 2020;20:170.

Cancer development in patients with COPD: a retrospective analysis of the National Health Insurance Service-National Sample Cohort in Korea

Figure 2



27. Ahn SV, Lee E, Park B, Jung JH, Park JE, Sheen SS, *et al.* Cancer development in patients with COPD: a retrospective analysis of the National Health Insurance Service–National Sample Cohort in Korea. *BMC Pulm Med* 2020;20:170.

Cancer development in patients with COPD: a retrospective analysis of the National Health Insurance Service-National Sample Cohort in Korea

- Independent factors associated with the development of lung cancer

→ Old age, male sex, smoking, COPD

→ Lower BMI

→ Low exercise level

→ Diabetes mellitus

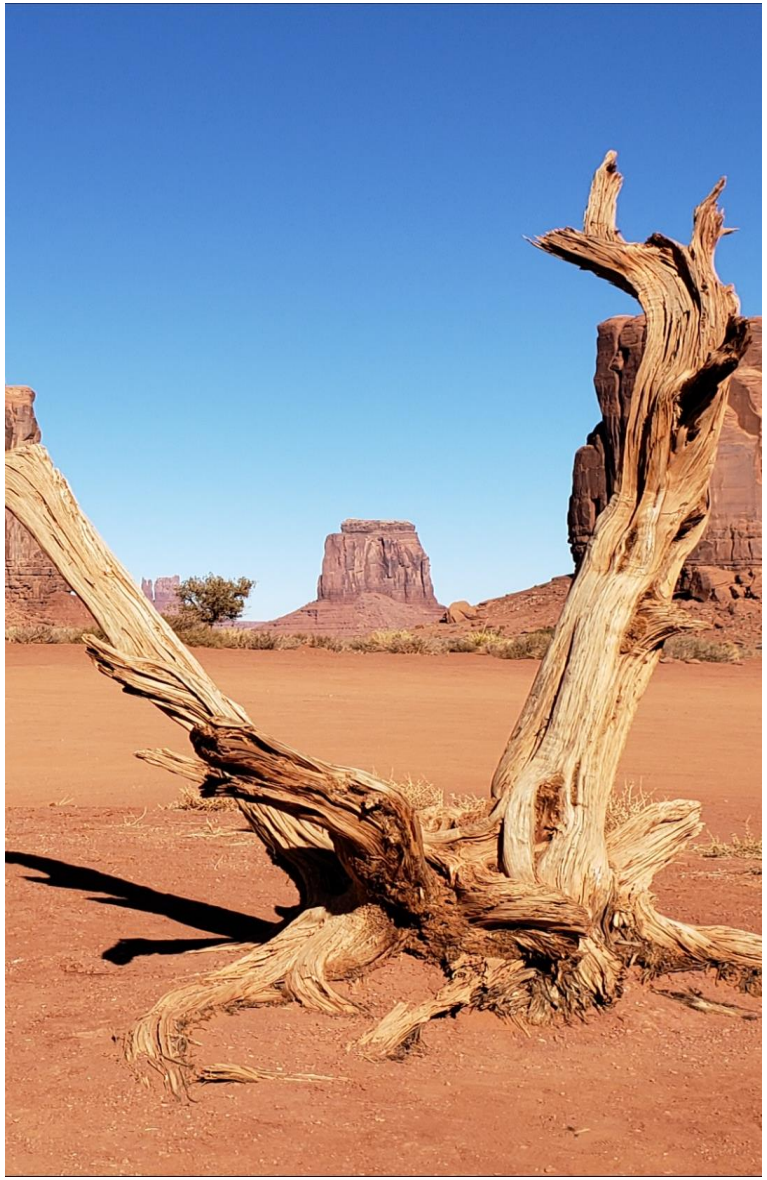
- Regardless of smoking status, COPD was an independent risk factor for

→ Lung cancer

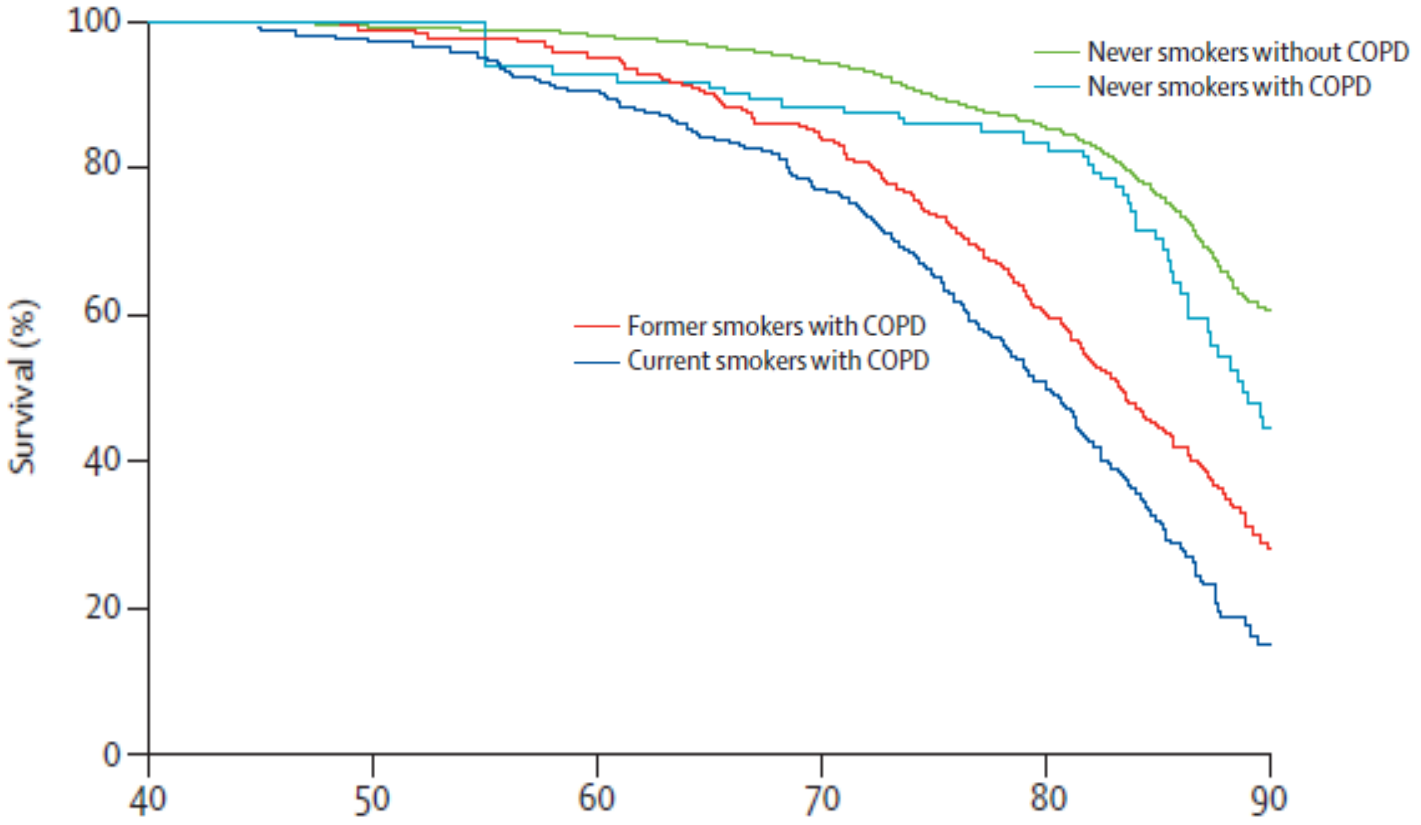
→ Colorectal cancer and liver cancer among other major cancers

27. Ahn SV, Lee E, Park B, Jung JH, Park JE, Sheen SS, *et al.* Cancer development in patients with COPD: a retrospective analysis of the National Health Insurance Service–National Sample Cohort in Korea. *BMC Pulm Med* 2020;20:170.

Mortality



Mortality Based on Smoking in COPD



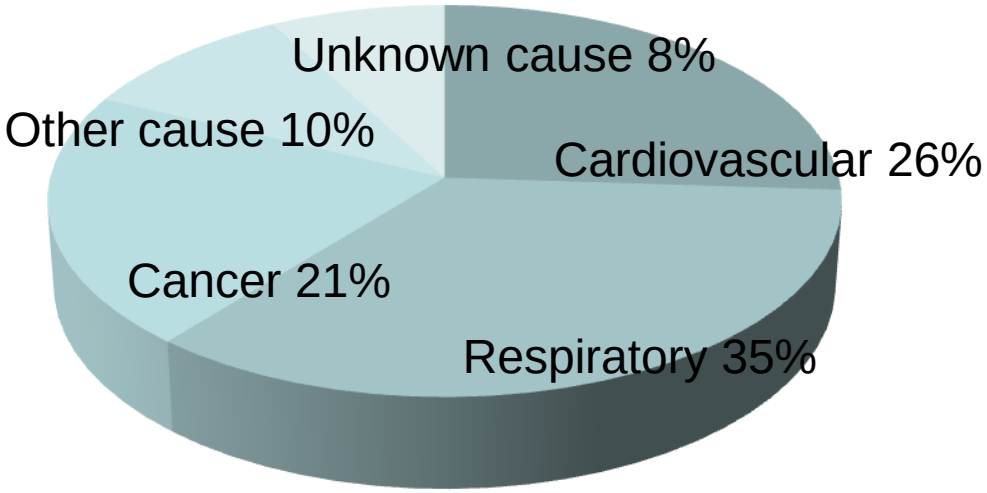
Tomsen et al. Lancet repsir med 2013; (7) ; 543-550

The BODE index is better than FEV1 at predicting the risk of death from any and respiratory causes in COPD

FEV_1 (% of predicted)†
Distance walked in 6 min (m)
MMRC dyspnea scale‡
Body-mass index§

B Celi et al, NEJM 2004;350:10

Causes of Death in COPD (Torch Study)



- Current or former smokers with at least 10 PY
- 40 to 80 years of age
- COPD, preBD FEV1 <60%

McGarvey et al, Thorax 2007;62:411–415
Calverley PM et al N Engl J Med 2007; 356: 775-789.

Mortality in COPD

- 32,535 spirometry-determined Taiwanese COPD

→ increase of all-cause mortality : HR ratio of 1.44

→ loss of 6.0 years in life expectancy

→ Two thirds (65%) of the causes of deaths : extra-pulmonary, such as cardiovascular disease, diabetes, cancer and kidney diseases

Chin-Chung Shu[1,4], June-Han Lee[2,4], Min-Kuang Tsai[2], Ta-Chen Su[1,3]✉ & Chi Pang Wen[2]✉
Scientific Reports | (2021) 11:21674

Air pollution and mortality

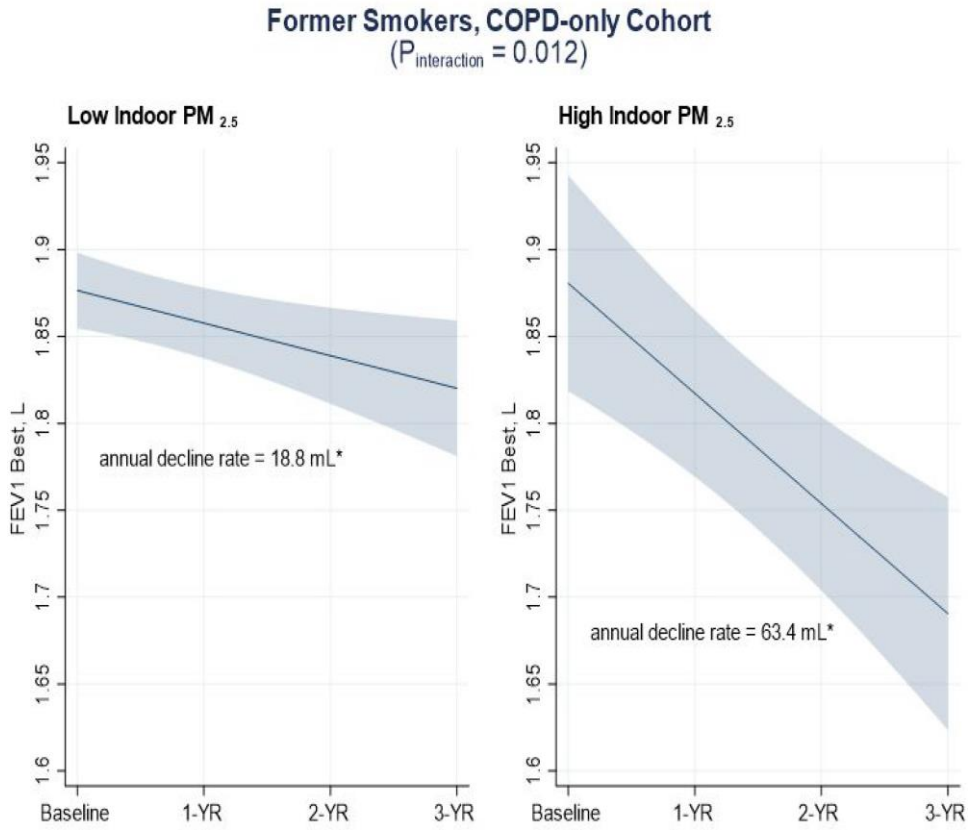
- A Systematic Review and Meta-analysis of 12 studies

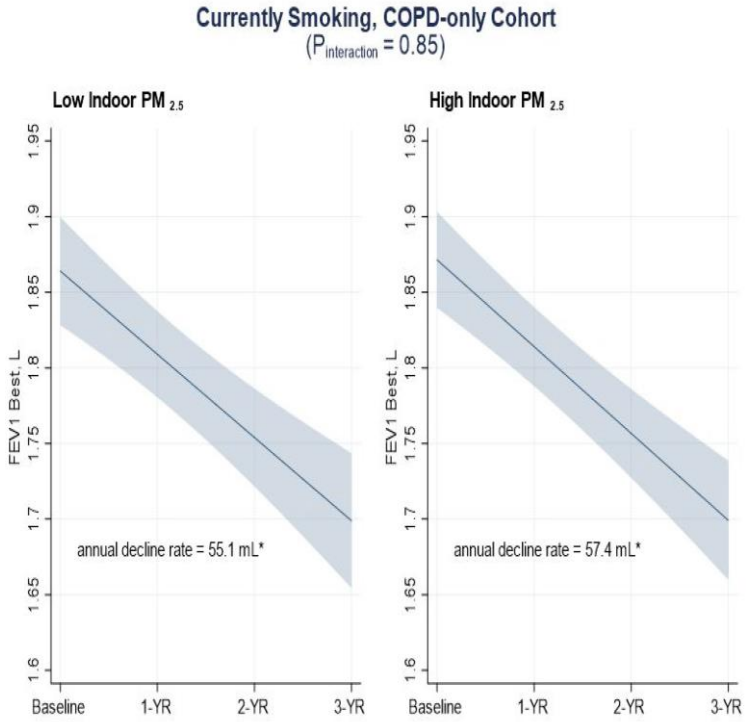
A 10-μg/m^3 increment of ambient PM2.5

→ 3.1% increase in COPD hospitalization

→ 2.5% increase in mortality

Li MH et al. Chest 2016 Feb;149(2):447-458





- an average rate of FEV_1 decline

→ currently smoker : 60.3 mL/year

→ former smoker : 35.2 mL/year

- every 10 μg/m^3 increase in indoor PM

→ former smokers : additional 10 mL/year decline in FEV_1 (p=0.044)

→ among current smokers, FEV_1 decline did not differ by indoor PM.

Hanzel NA AJRCCM 2023 Jul 31.

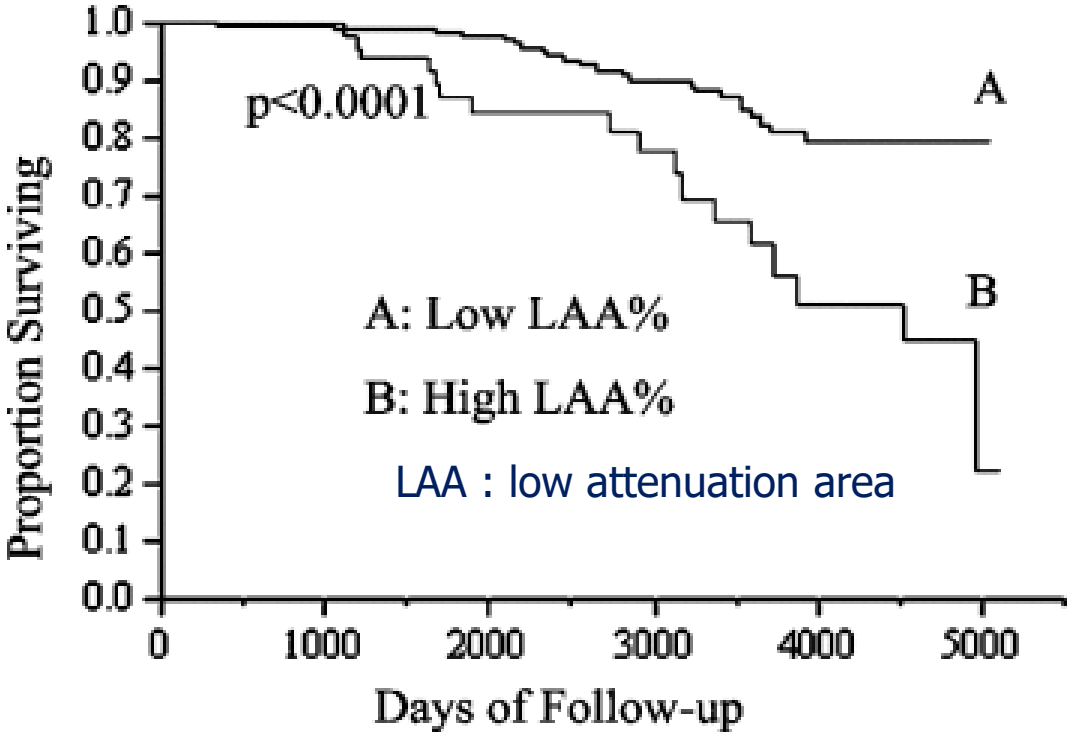
An association between air pollution and mortality in six U.S. cities.

Cause of Death	Percentage of Total	Current Smokers†	Former Smokers‡	Most vs. Least Polluted City
		rate ratio (95% CI)		
All	100	2.00 (1.51–2.65)	1.39 (1.10–1.75)	1.26 (1.08–1.47)
Lung cancer	8.4	8.00 (2.97–21.6)	2.54 (0.90–7.18)	1.37 (0.81–2.31)
Cardiopulmonary disease	53.1	2.30 (1.56–3.41)	1.52 (1.10–2.10)	1.37 (1.11–1.68)
All others	38.5	1.46 (0.89–2.39)	1.17 (0.80–1.73)	1.01 (0.79–1.30)

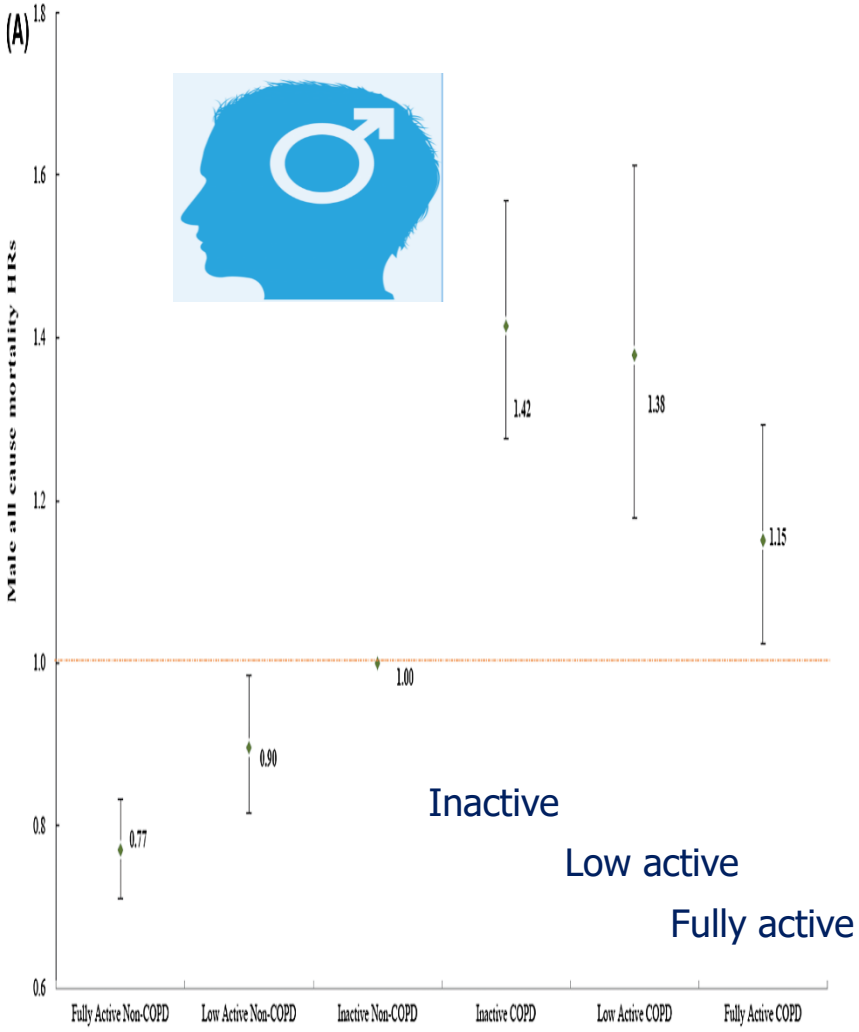
Dockery DW et al, N Engl J Med 1993 Dec 9;329(24):1753-9..

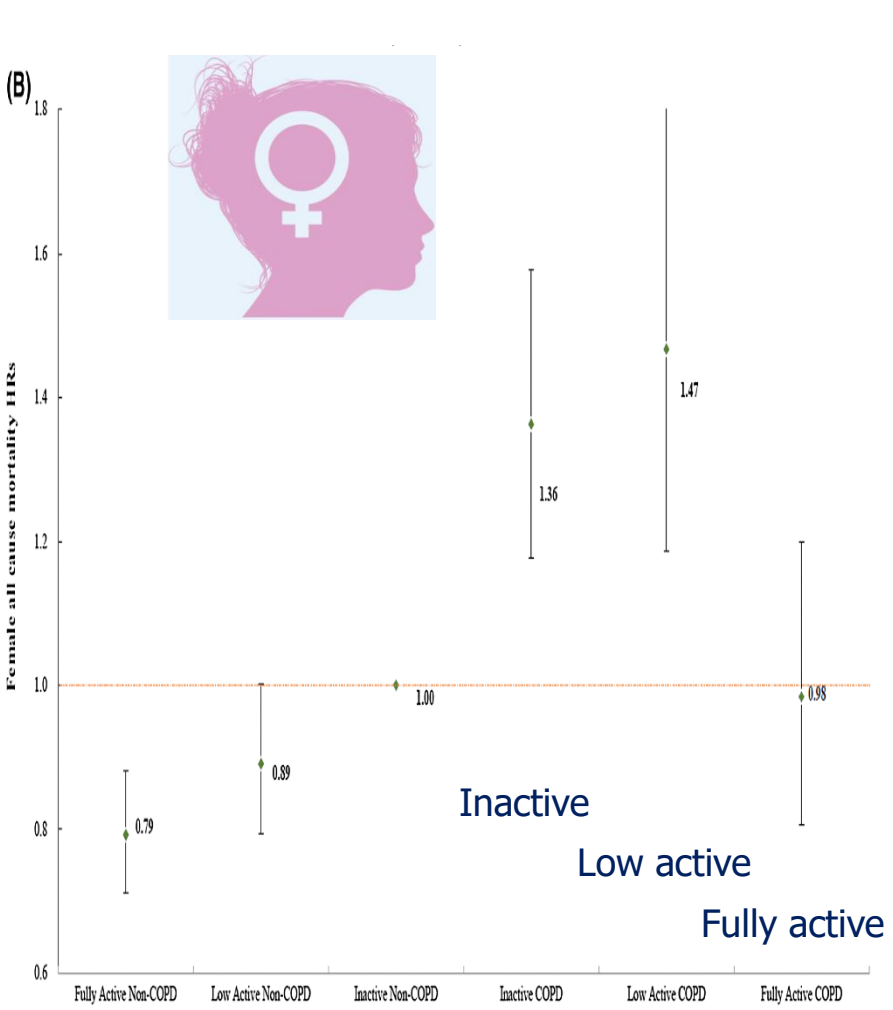
Emphysematous change predicts respiratory mortality in outpatients with various stages of COPD

- 251 outpatients with stable COPD
- Median follow-up time was 8 years



Haruna A et al. CHEST 2010; 138(3):635–640





Inactive

Low active

Fully active

Inactive

Low active

Fully active

Chin-Chung Shu[1,4], June-Han Lee[2,4], Min-Kuang Tsai[2], Ta-Chen Su[1,3]✉ & Chi Pang Wen[2]✉

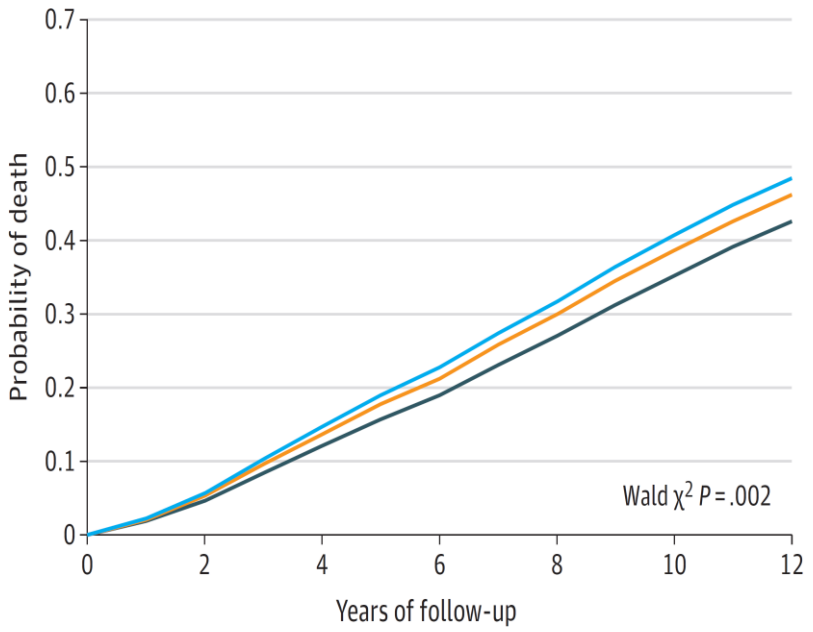
Scientific Reports | (2021) 11:21674

Airway-Occluding Mucus Plugs and Mortality in COPD

Table 2. Association Between Mucus Plug Score and All-Cause Mortality in Participants With COPD

	No.	Mucus plug score (No. of lung segments with mucus plugs)				
		0 (n = 2585)	1-2 (n = 953)		≥3 (n = 825)	
Mortality rate, % (95% CI)		34.0 (32.2-35.8)	46.7 (43.5-49.9)		54.1 (50.7-57.4)	
Unadjusted mortality rate difference, % (95% CI)			1-2 vs 0: 12.7 (9.1-16.4)		≥3 vs 0: 20.1 (16.2-24.0)	
Model		HR (95% CI)	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Unadjusted model	4363	1 [Reference]	1.51 (1.34-1.69)	<.001	1.98 (1.76-2.22)	<.001
Adjusted model[a]	4166	1 [Reference]	1.15 (1.02-1.29)	.02	1.24 (1.10-1.41)	<.001
Plus coronary artery disease[b]	4166	1 [Reference]	1.16 (1.03-1.30)	.02	1.26 (1.11-1.43)	<.001
Plus chronic bronchitis[c]	4166	1 [Reference]	1.15 (1.02-1.30)	.02	1.25 (1.10-1.42)	<.001
Plus current asthma[d]	4166	1 [Reference]	1.15 (1.02-1.30)	.02	1.25 (1.10-1.41)	<.001
Plus exacerbations per year[e]	3759	1 [Reference]	1.10 (0.96-1.25)	.17	1.20 (1.05-1.38)	.008
Plus BODE index[f]	4060	1 [Reference]	1.14 (1.01-1.29)	.03	1.21 (1.06-1.37)	.004

B Adjusted probability of death by mucus plug score



No. at risk

Mucus plug score							
0	2585	2337	2126	1860	1587	1339	792
1-2	953	859	763	643	526	411	237
≥3	825	730	613	481	372	299	167

JAMA. 2023;329(21):1832-1839.

Mortality of COPD beyond FEV1 and BODE index

- Smoking (Lancet repsir med 2013; (7) ; 543-550)
- Comorbidities

- Heart failure (Resp Res 2020; 21:54)
- Pneumonia (Respiration 2011;82(4):320-7)

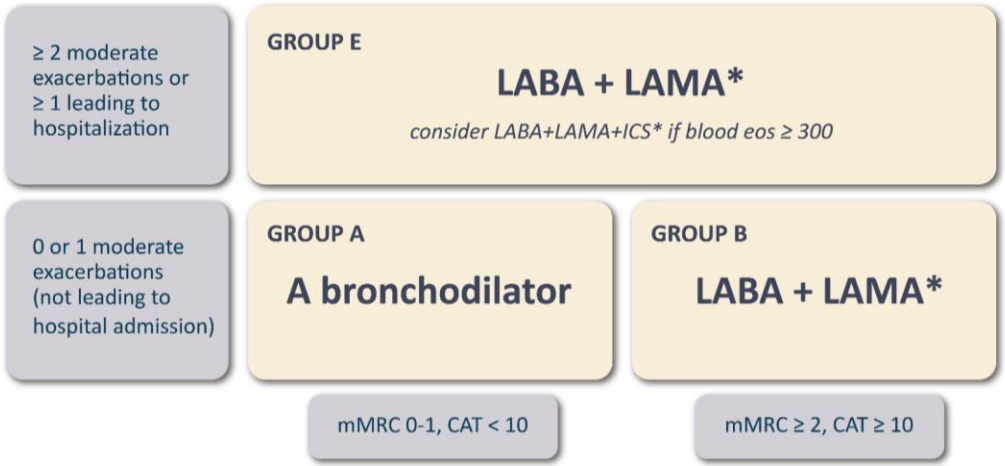
- Emphysema (CHEST 2010; 138(3):635–640)
- Airways responsiveness (JACI 2016;138(6):1571-1579)
- Mucus plug (JAMA 2023 ;329 : 1832-1839)
- Low body-mass index (BMI ≤21)
- Air pollution (Chest 2016;149(2):447-458)
- Inactivity (Sci Rep 2021;11: 21674)
- Nutrition & anemia (IJCOPD 2018:13 1599–1605)

Treatment

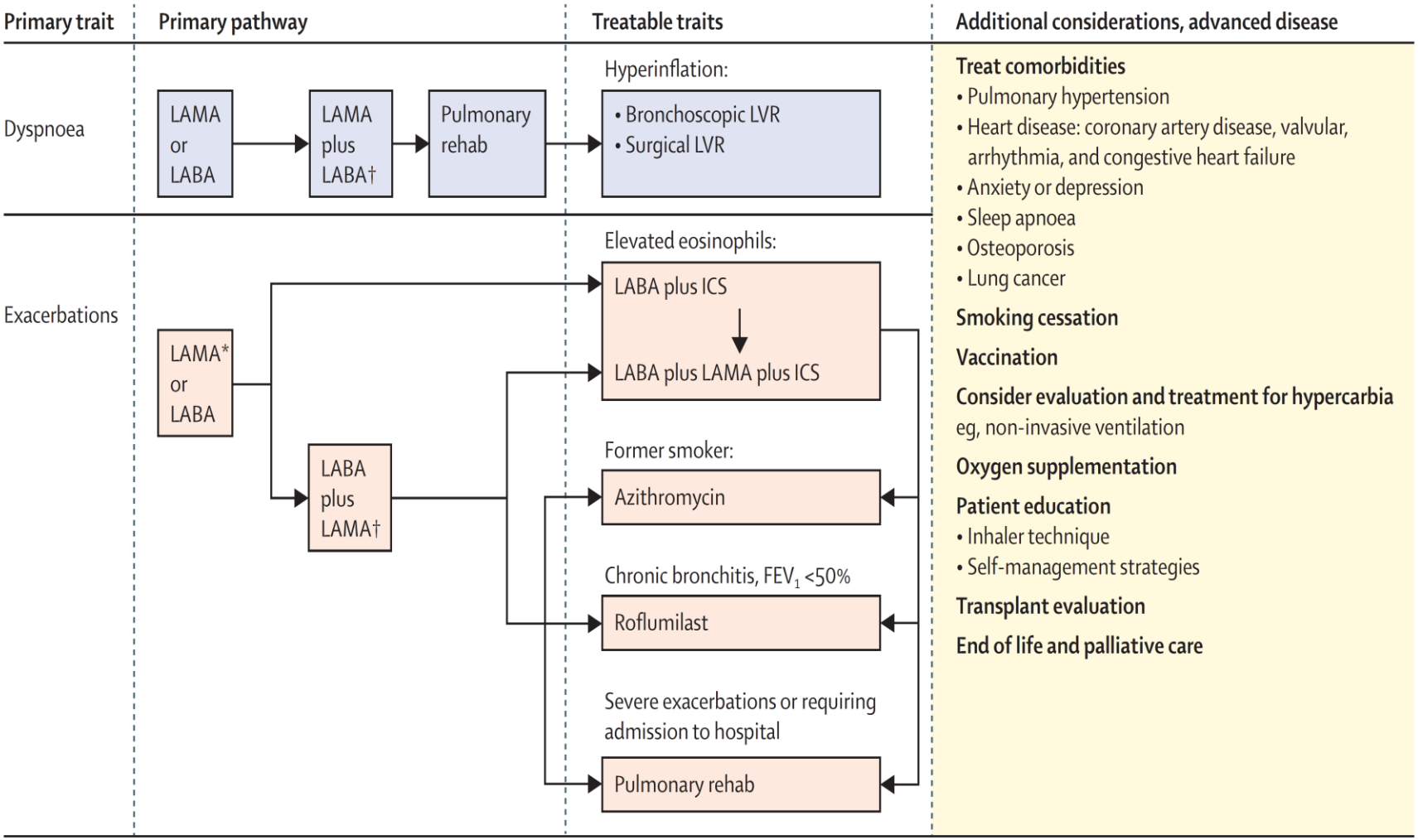
2023
Teaching
Slide Set

Initial Pharmacological Treatment

Figure 4.2



*single inhaler therapy may be more convenient and effective than multiple inhalers
Exacerbations refers to the number of exacerbations per year



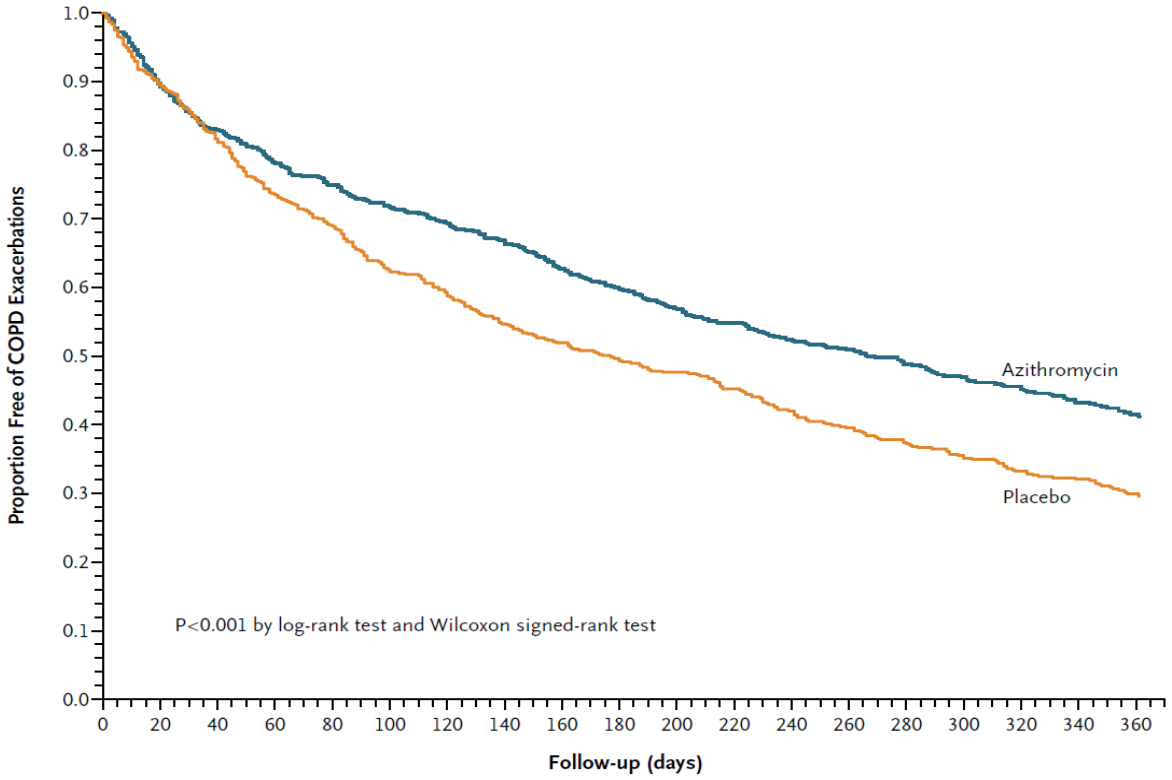
Lancet 2022; 399: 2227–42

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 25, 2011 VOL. 365 NO. 8

Azithromycin for Prevention of Exacerbations of COPD

Richard K. Albert, M.D., John Connett, Ph.D., William C. Bailey, M.D., Richard Casaburi, M.D., Ph.D., J. Allen D. Cooper, Jr., M.D., Gerard J. Criner, M.D., Jeffrey L. Curtis, M.D., Mark T. Dransfield, M.D., MeiLan K. Han, M.D., Stephen C. Lazarus, M.D., Barry Make, M.D., Nathaniel Marchetti, M.D., Fernando J. Martinez, M.D., Nancy E. Madinger, M.D., Charlene McEvoy, M.D., M.P.H., Dennis E. Niewoehner, M.D., Janos Porsasz, M.D., Ph.D., Connie S. Price, M.D., John Reilly, M.D., Paul D. Scanlon, M.D., Frank C. Sciurba, M.D., Steven M. Scharf, M.D., Ph.D., George R. Washko, M.D., Prescott G. Woodruff, M.D., M.P.H., and Nicholas R. Anthonisen, M.D., for the COPD Clinical Research Network



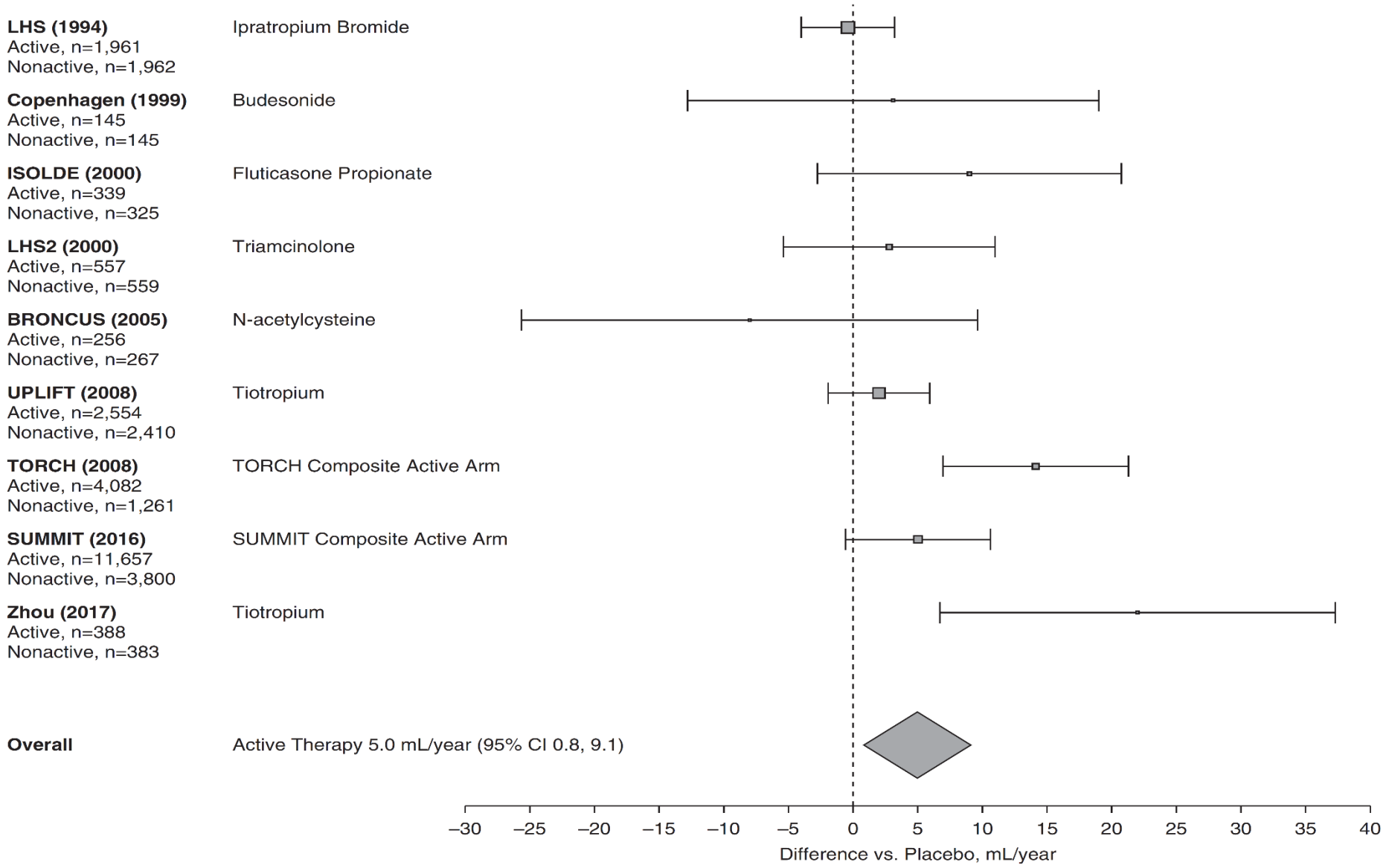
Azithromycin for Prevention of COPD AE

- Azithromycin with better treatment response

→ Effective in reducing AECOPD (P = 0.0002)

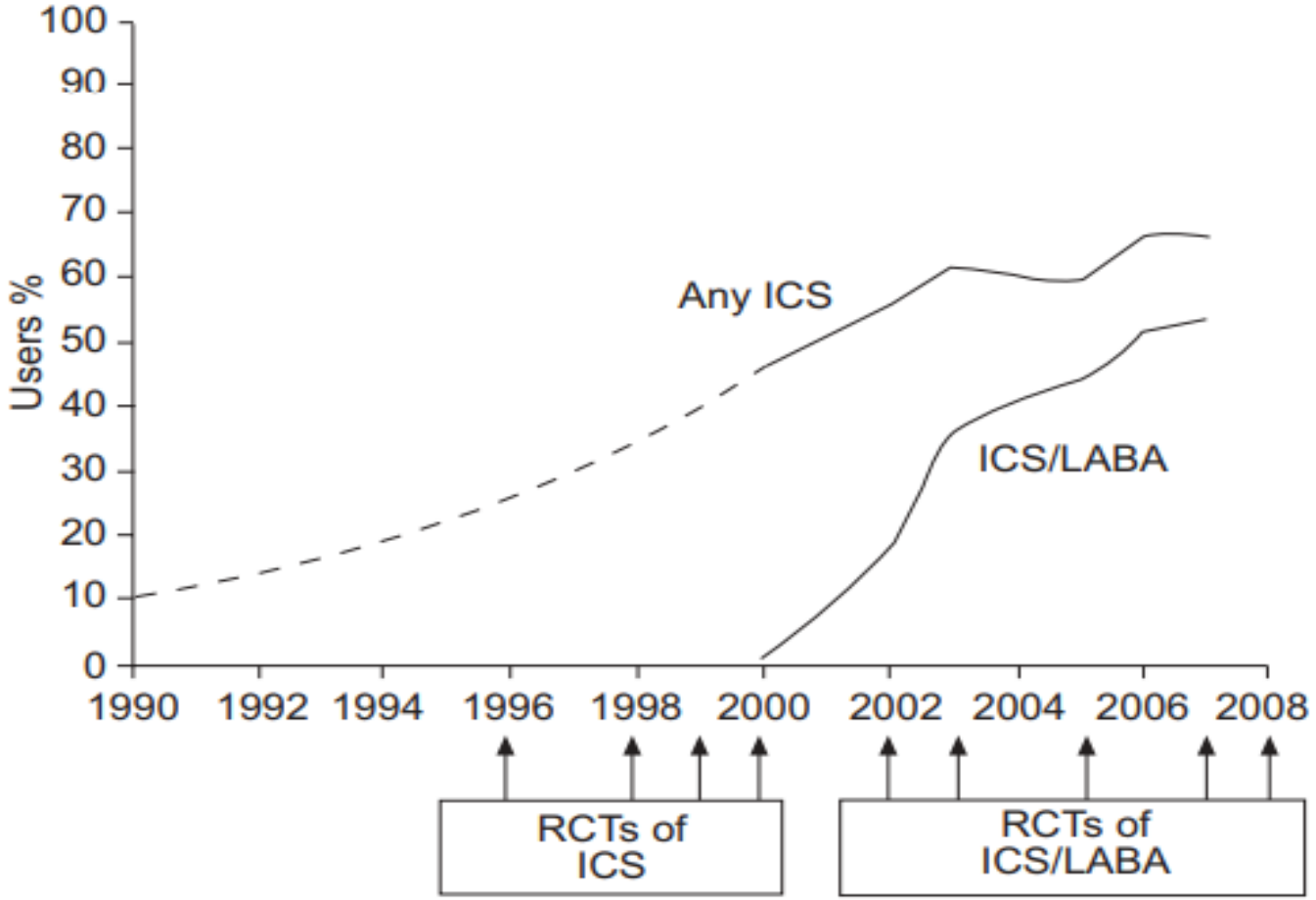
→ Did not reduce exacerbation in current smokers (HR= 0.99; 95%CI 0.71-1.38; P = 0.95).

Han MK et al Am J Respir Crit Care Med 2014;189(12):1503-8



B Celi al, AJRCCM 2021;203(6):689-698 185: 44 - 52

Overuse of ICS in COPD



S. Suisa and PJ Barnes. Eur Respir J 2009; 34: 13–16

International Journal of Chronic Obstructive Pulmonary Disease Dovepress
open access to scientific and medical research
Open Access Full Text Article ORIGINAL RESEARCH

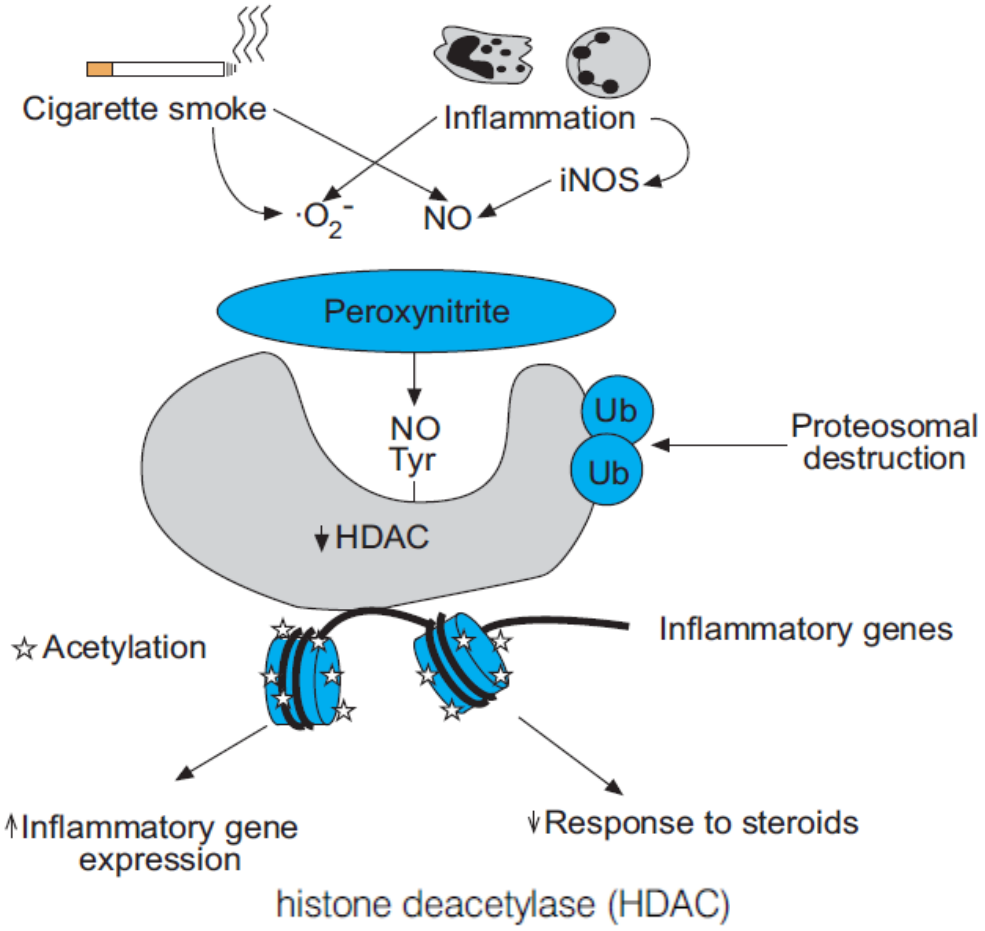
The Impact of Inhaled Corticosteroids on the Prognosis of Chronic Obstructive Pulmonary Disease

Ji Won Park[1,*], Yoonki Hong[2,*], Chin Kook Rhee[3], Hye Sook Choi[4], Kyungjoo Kim[3], Kwang Ha Yoo[5], Ki-Suck Jung[6], Joo Hun Park[1]

Methods: We examined 978 COPD patients registered in the Korean National Health and Nutrition Examination Survey (KNHANES) database and with their data linked to Health Insurance and Review Assessment (HIRA) data. The outcome measures were ascertained by HIRA from January 1, 2009, to December 31, 2012. This study enrolled two arms; ICS users (N = 85, mean age = 66.7 ± 8.9 years) and non-ICS users (N = 893, mean age = 63.7 ± 9.7 years).

Results: Compared to the non-ICS users, the ICS users had a higher rate of pneumonia, tuberculosis, and acute exacerbations ($P<0.05$). Hospitalization due to respiratory causes was also higher among ICS users ($P<0.05$). Multivariate analysis showed that acute exacerbation was independently associated with the development of pneumonia ($P<0.05$), whereas ICS therapy had a tendency to be associated with pneumonia. Another multivariate analysis demonstrated that old age, FEV_1, ICS therapy, and pneumonia were independently associated with the occurrence of acute exacerbation ($P<0.05$). The concomitant pneumonia (HR = 3.353, $P = 0.004$) was independently associated with higher mortality ($P<0.05$).

Steroid Resistance in Smokers



Barnes PJ Eur Respir J. 2005 Mar;25(3):552-63.

Factors to Consider when Initiating ICS Treatment

Figure 3.1

2023 Teaching Slide Set

Factors to consider when adding ICS to long-acting bronchodilators:

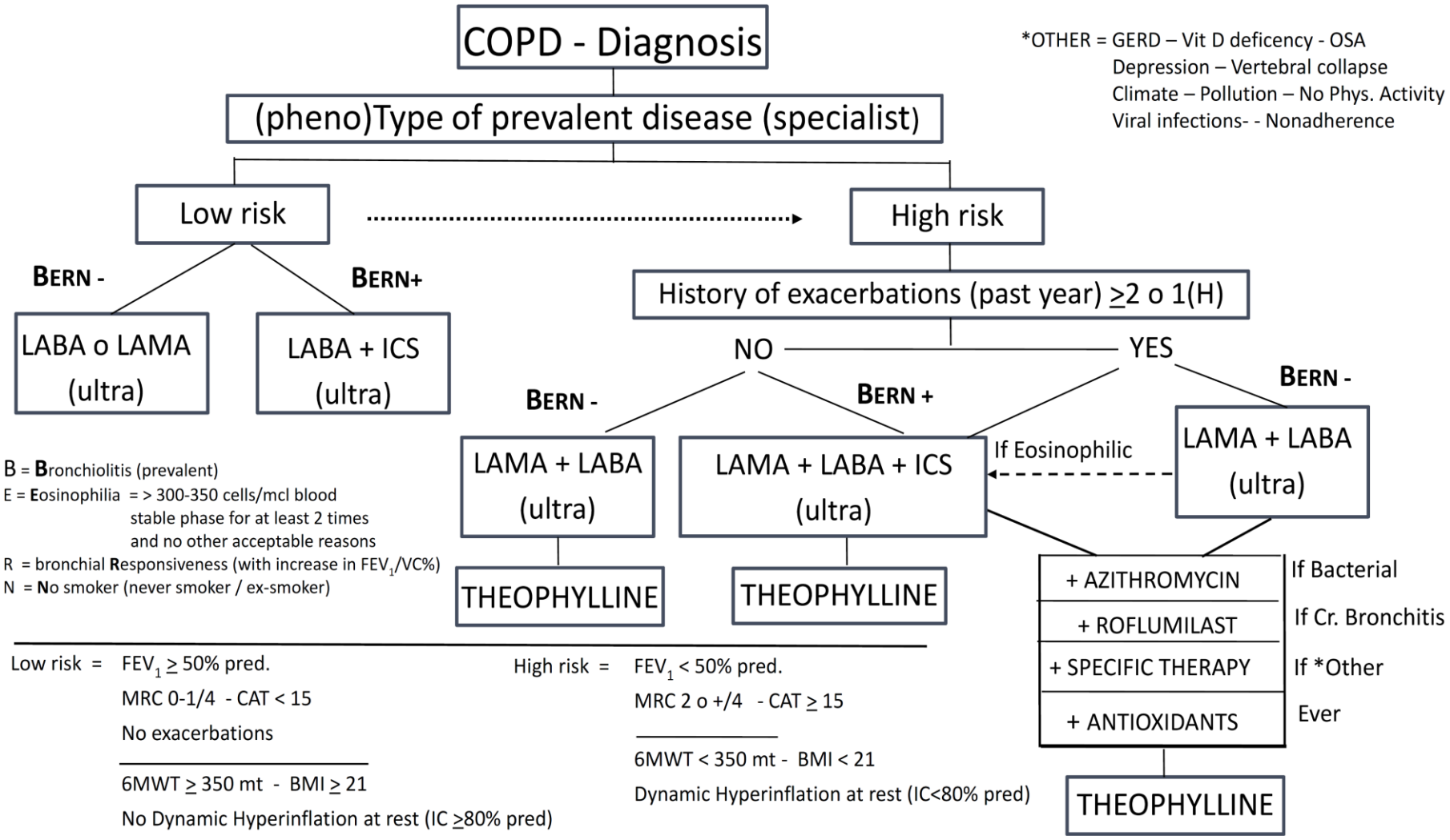
(note the scenario is different when considering ICS withdrawal)

STRONGLY FAVORS USE	History of hospitalization(s) for exacerbations of COPD[#]
	≥ 2 moderate exacerbations of COPD per year[#]
	Blood eosinophils ≥ 300 cells/µL
	History of, or concomitant asthma
FAVORS USE	1 moderate exacerbation of COPD per year[#]
	Blood eosinophils 100 to < 300 cells/µL
AGAINST USE	Repeated pneumonia events
	Blood eosinophils < 100 cells/µL
	History of mycobacterial infection

[#]despite appropriate long-acting bronchodilator maintenance therapy (see Table 3.4 and Figure 4.3 for recommendations);
*note that blood eosinophils should be seen as a continuum; quoted values represent approximate cut-points; eosinophil counts are likely to fluctuate.

Adapted from & reproduced with permission of the © ERS 2019: *European Respiratory Journal 52 (6) 1801219; DOI: 10.1183/13993003.01219-2018 Published 13 December 2018*

Inhaled Corticosteroids in COPD



Claudio Tantucci et al IJCOPD 2020 Apr 20;15:821-829

Take these findings of IMPACT and FLAME with a grain of salt

Indacaterol–Glycopyrronium versus Salmeterol–Fluticasone for COPD

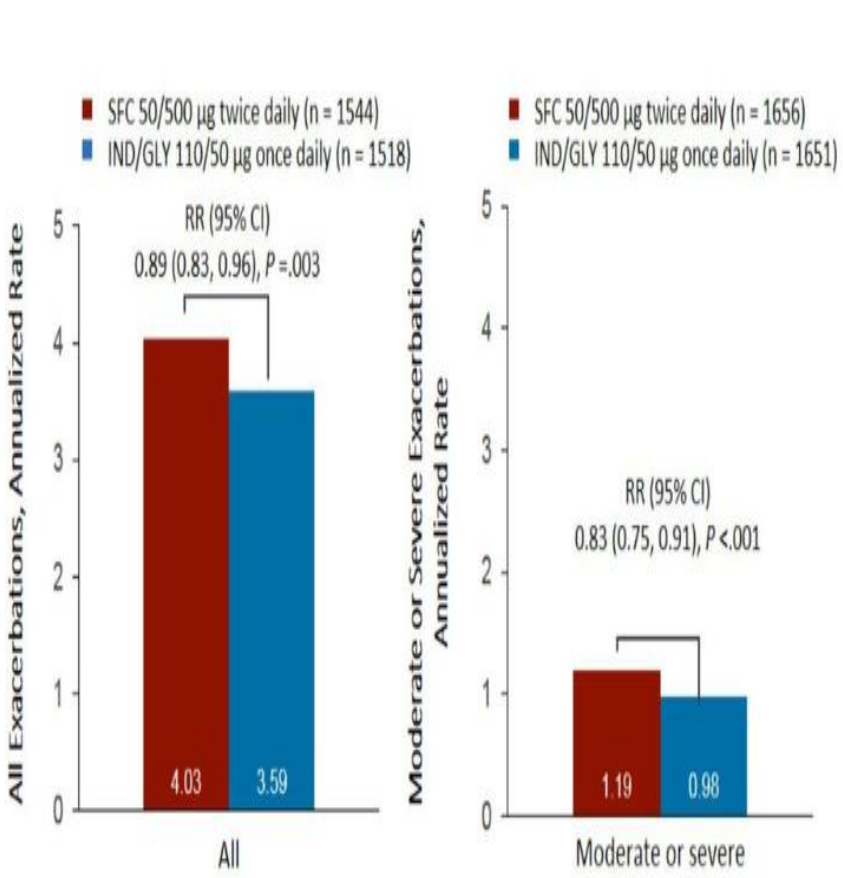
Jadwiga A. Wedzicha, M.D., Donald Banerji, M.D., Kenneth R. Chapman, M.D., Jørgen Vestbo, M.D., D.M.Sc., Nicolas Roche, M.D., R. Timothy Ayers, M.Sc., Chau Thach, Ph.D., Robert Fogel, M.D., Francesco Patalano, M.D., and Claus F. Vogelmeier, M.D., for the FLAME Investigators*

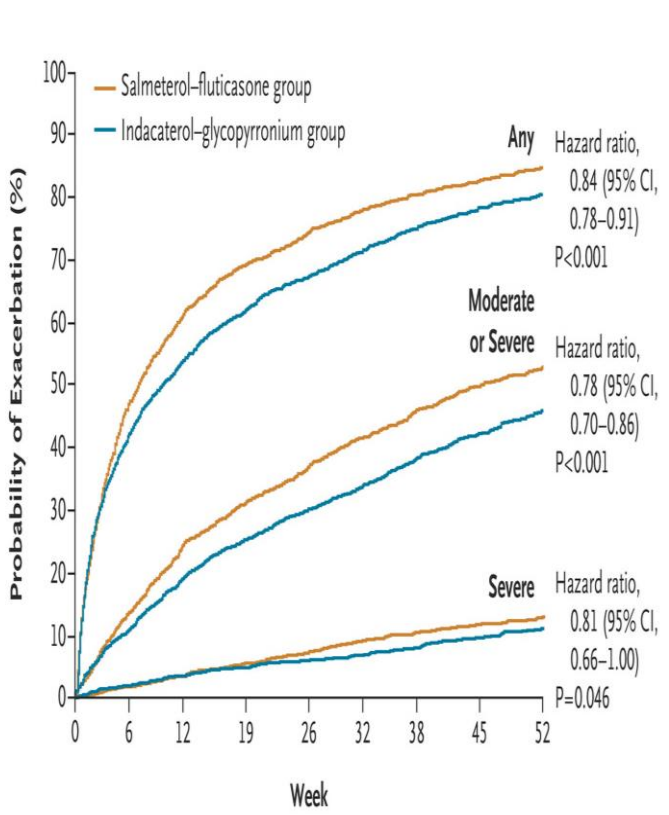
- Patients : ≥ one COPD AE during previous year
- Current or ex-smokers with a smoking history of at least 10 pack-years

N ENGL J MED 374;23 NEJM.ORG JUNE 9, 2016

COPD exacerbations in the FLAME study

The primary outcome: annual rate of all COPD exacerbations.





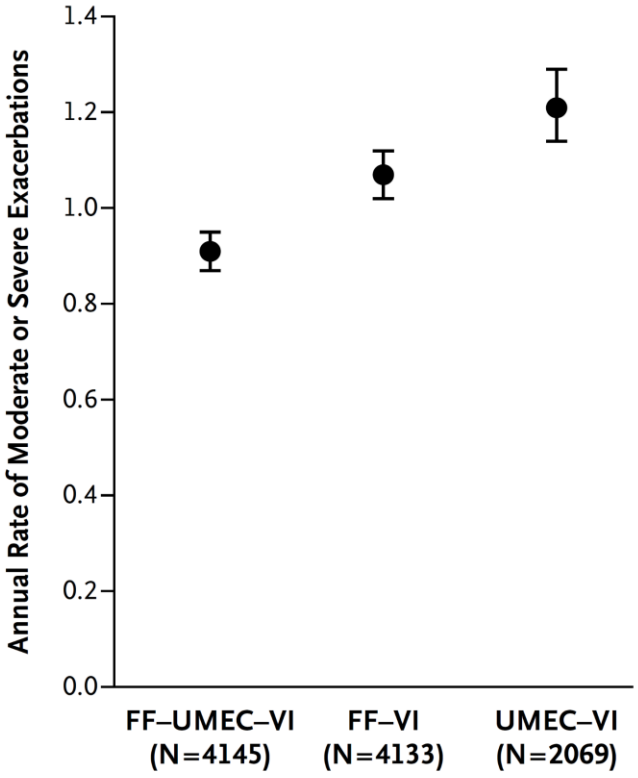
Wedzicha JA, et al. N Engl J Med 2016; 374:2222-2234

The NEW ENGLAND JOURNAL of MEDICINE

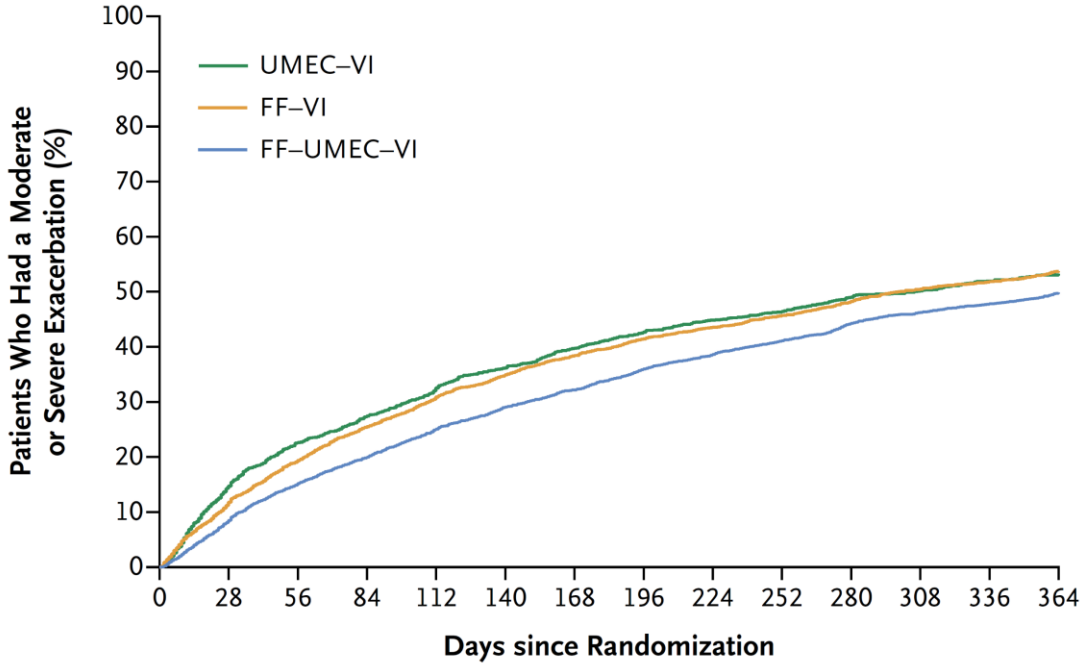
ESTABLISHED IN 1812 MAY 3, 2018 VOL. 378 NO. 18

Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD

A Model-Estimated Rate



B Time-to-First-Event Analysis



No. at Risk

UMEC–VI	2070	1721	1516	1406	1301	1201	1123	1059	1001	971	917	884	851	642
FF–VI	4134	3554	3133	2838	2620	2410	2250	2120	2004	1823	1823	1729	1671	1228
FF–UMEC–VI	4151	3758	3408	3186	2954	2752	2614	2457	2324	2216	2085	1988	1919	1419

N Engl J Med 2018;378:1671-80.
DOI: 10.1056/NEJMoa1713901

The IMPACT versus the FLAME study

	IMPACT	FLAME
Enrolled patients	10,355	3,362
Asthma	Previous history of asthma : eligible	Any history of asthma : excluded
GOLD Group	FEV1<50 % : 64% GOLD D : 75.9%	GOLD B: 24.4% GOLD D: 74.8%
AE in previous year	1: 45%, ≥2: 55%	1: 81%, ≥2: 19%
ICS use at screen	71.6%	56.3%
Treatment during run-in	Current COPD medicine	Tiotropium

Mismatch between RCT and a real-life setting

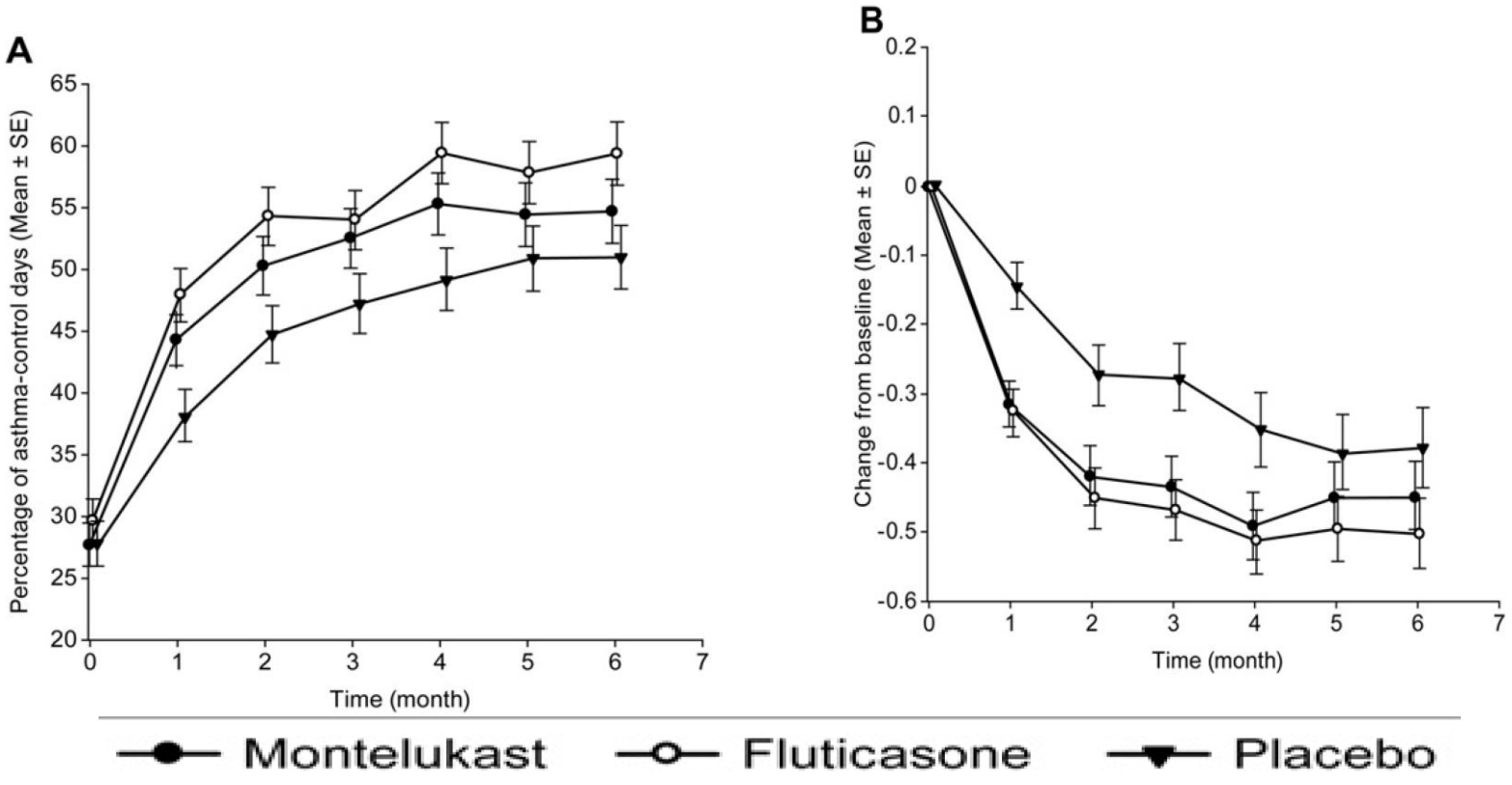
- Over COPD subjects in the community who were taking medication, 5% (median) met inclusion criteria for the major RCTs.

  Resp med 2007 Jun;101(6):1313-20

- In real-life settings, more than 80% of COPD subjects are currently treated based on results of RCTs for which they would not have been eligible.

  Respiration 2014; 87(1) : 11-7

Active cigarette smokers (age :18-55 years)
Randomized in 131 sites of 29 countries between 2006.5 and 2010.4
→ 347 (montelukast), 336 (fluticasone), and 336 (placebo)
Mean percentage of days with asthma control over 6 months of treatment
→ 45% (montelukast, P < .05 vs placebo)
49% (fluticasone, P < .001 vs placebo)
39% (placebo)



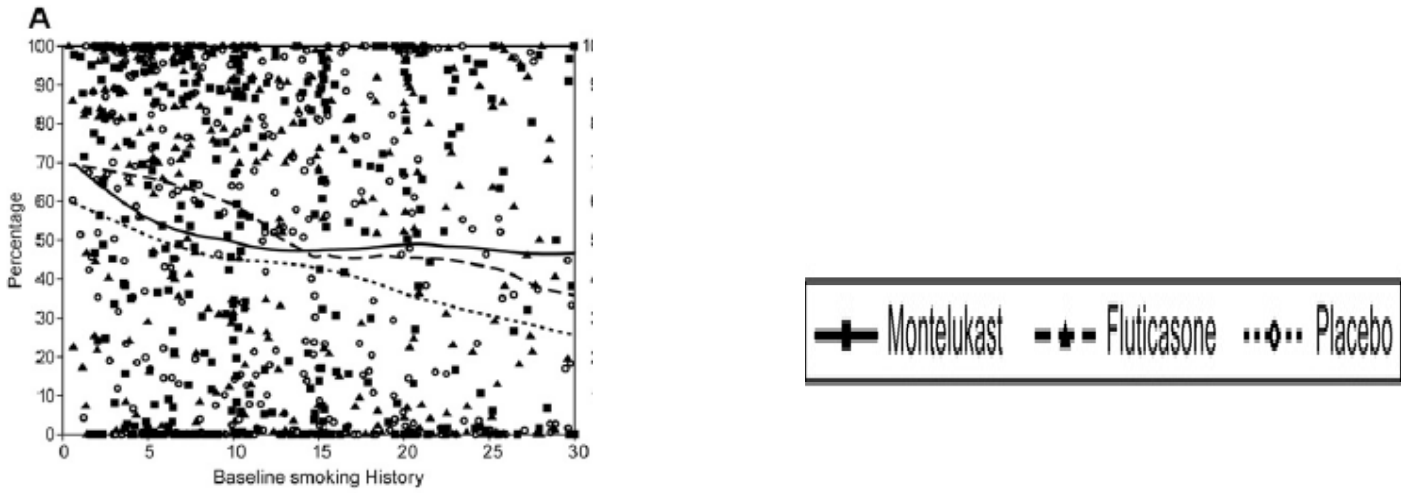
David Price et al J Allergy Clin Immunol 2013;131:763-71

- smoking history of <11 pack years :

→ more benefit with fluticasone

- smoking history of >11 pack years :

→ more benefit with montelukast.



David Price et al J Allergy Clin Immunol 2013;131:763-71

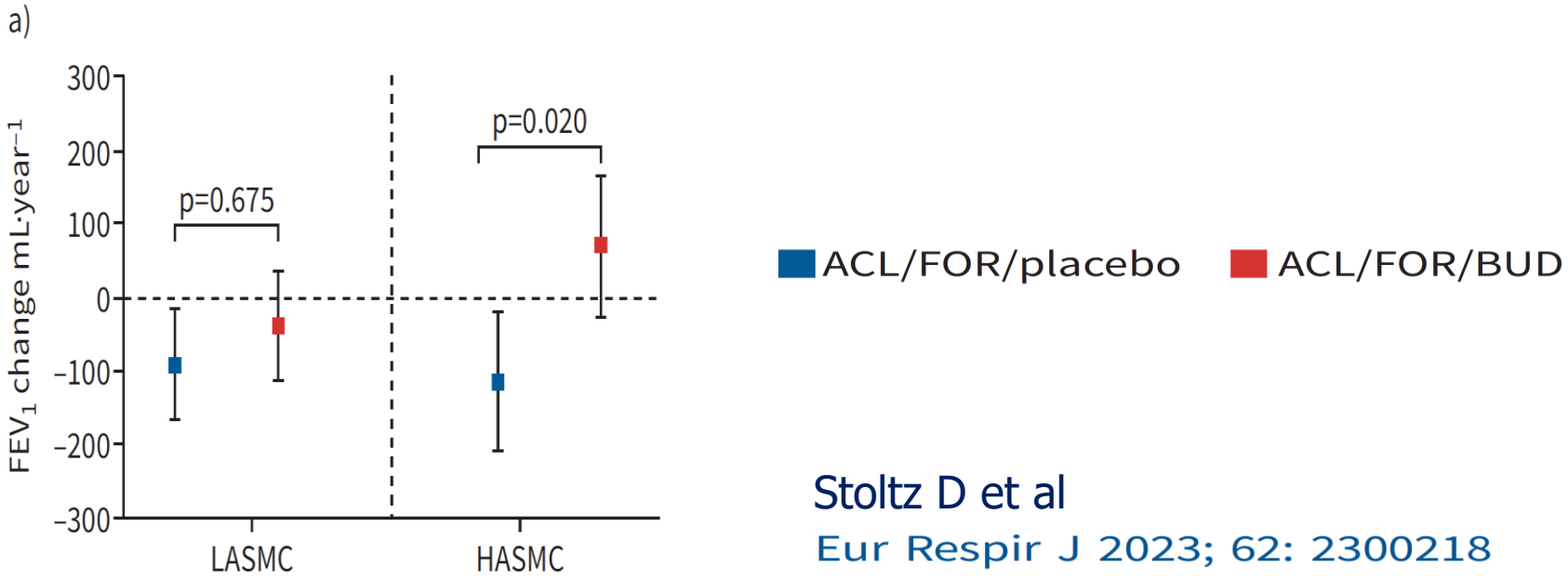
Airway smooth muscle area to predict steroid responsiveness in COPD patients receiving triple therapy (HISTORIC):

- 190 COPD patients : bronchoscopic biopsy
- GOLD stage B–D, ≥ 10 pack year smoking

→ HASMC : >20% of bronchial airway smooth muscle cell

→ LASMC: ⩽20% of ASMC

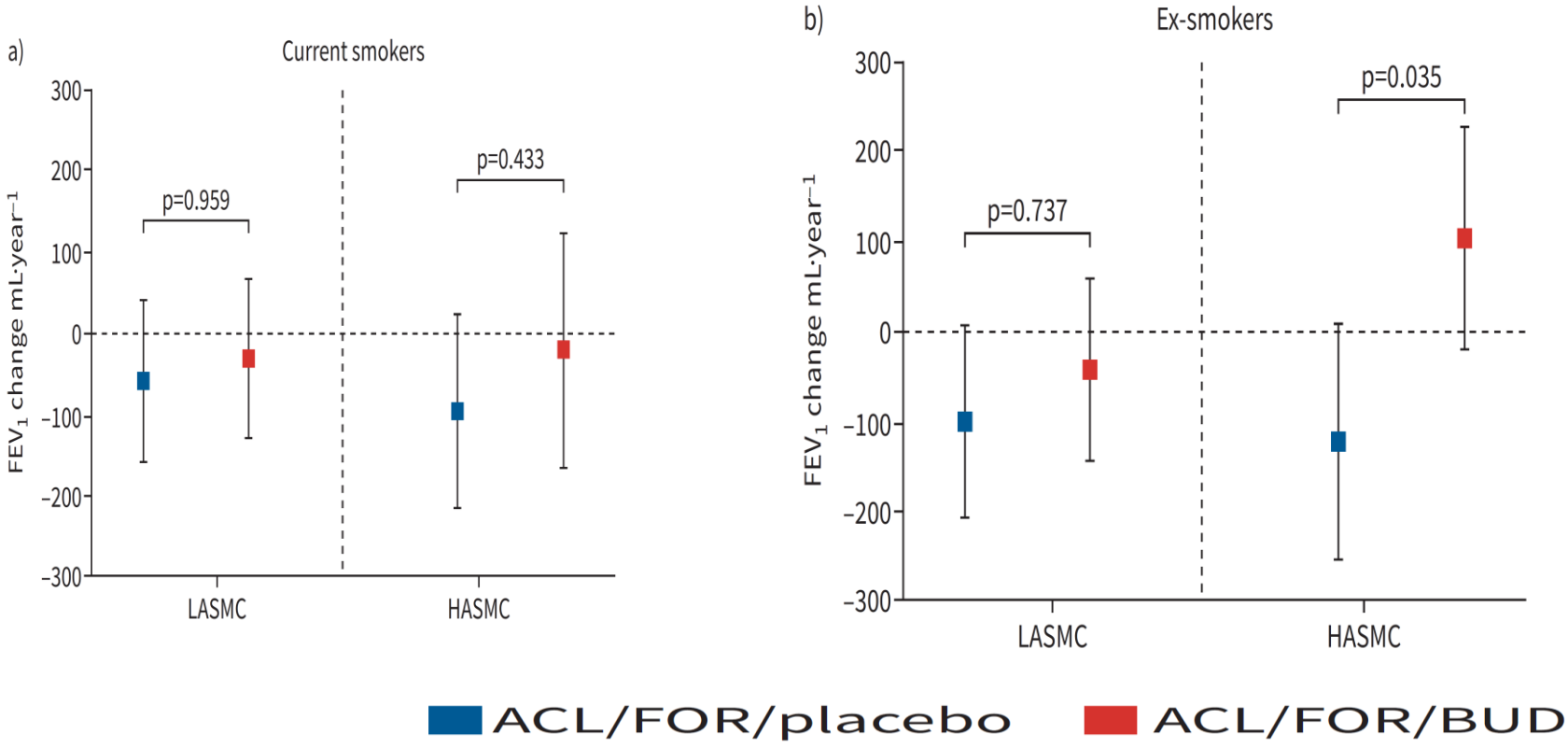
- Run-in period of 6 weeks, followed for 12 months



Stoltz D et al

Eur Respir J 2023; 62: 2300218

Airway smooth muscle area to predict steroid responsiveness in COPD patients receiving triple therapy (HISTORIC):

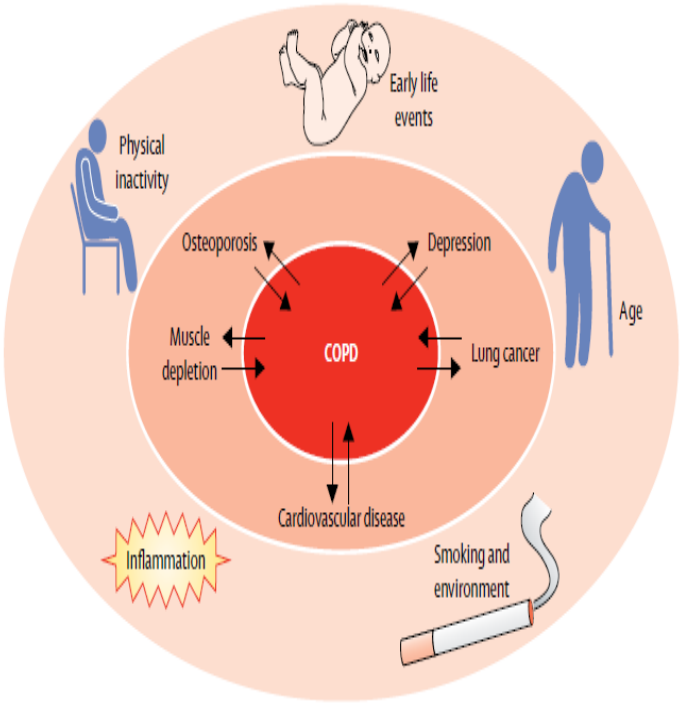


Stoltz D et al

Eur Respir J 2023; 62: 2300218

Summary

Summary



Lancet 2017; 389: 1931–40

- COPD stems not only from smoking but a lso from asthma, infection, air pollution, and poor growth in childhood.
- Prevention of COPD should have high priority.
- Compared to ever-smokers with COPD, never-smokers with COPD have more air-trapping, less emphysema, and fewer comorbidities. They still have a higher risk of lung cancer and exacerbations.
- Treatment of never-smokers with COPD requires further researches.

Thank you for your attention