Natural History of COPD

동아의대 호흡기 내과
엄수정

Contents

1) Traditional view of COPD progression
2) Factors associated with airflow limitation
3) New paradigm of natural course of COPD
4) Early COPD

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1) **Traditional view of COPD progression**
2) Factors associated with airflow limitation
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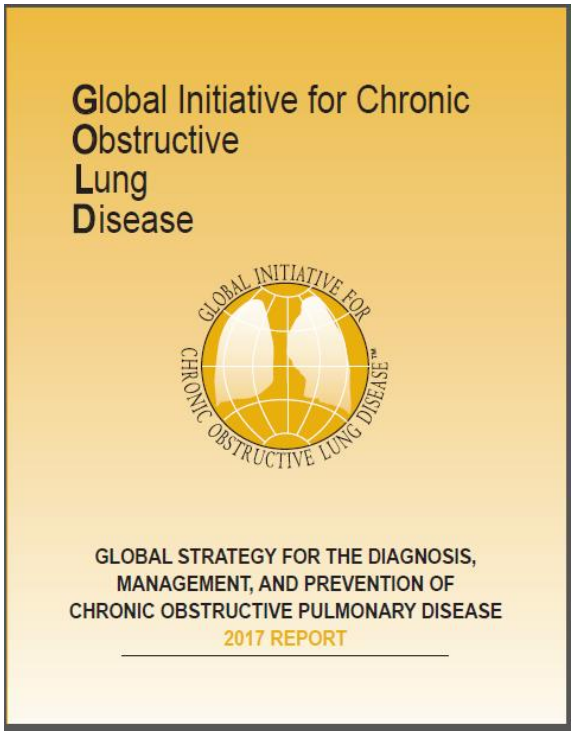
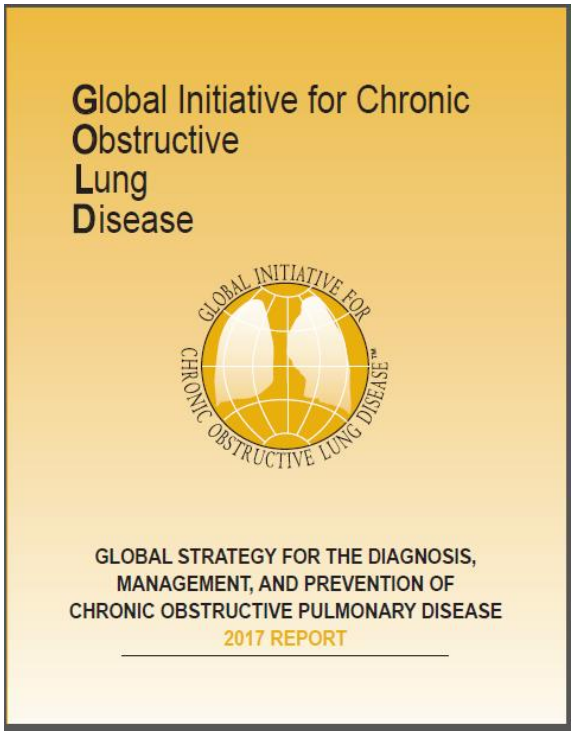


COPD is a common, preventable and treatable disease that is characterized by **persistent respiratory symptoms and airflow limitation** that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases .



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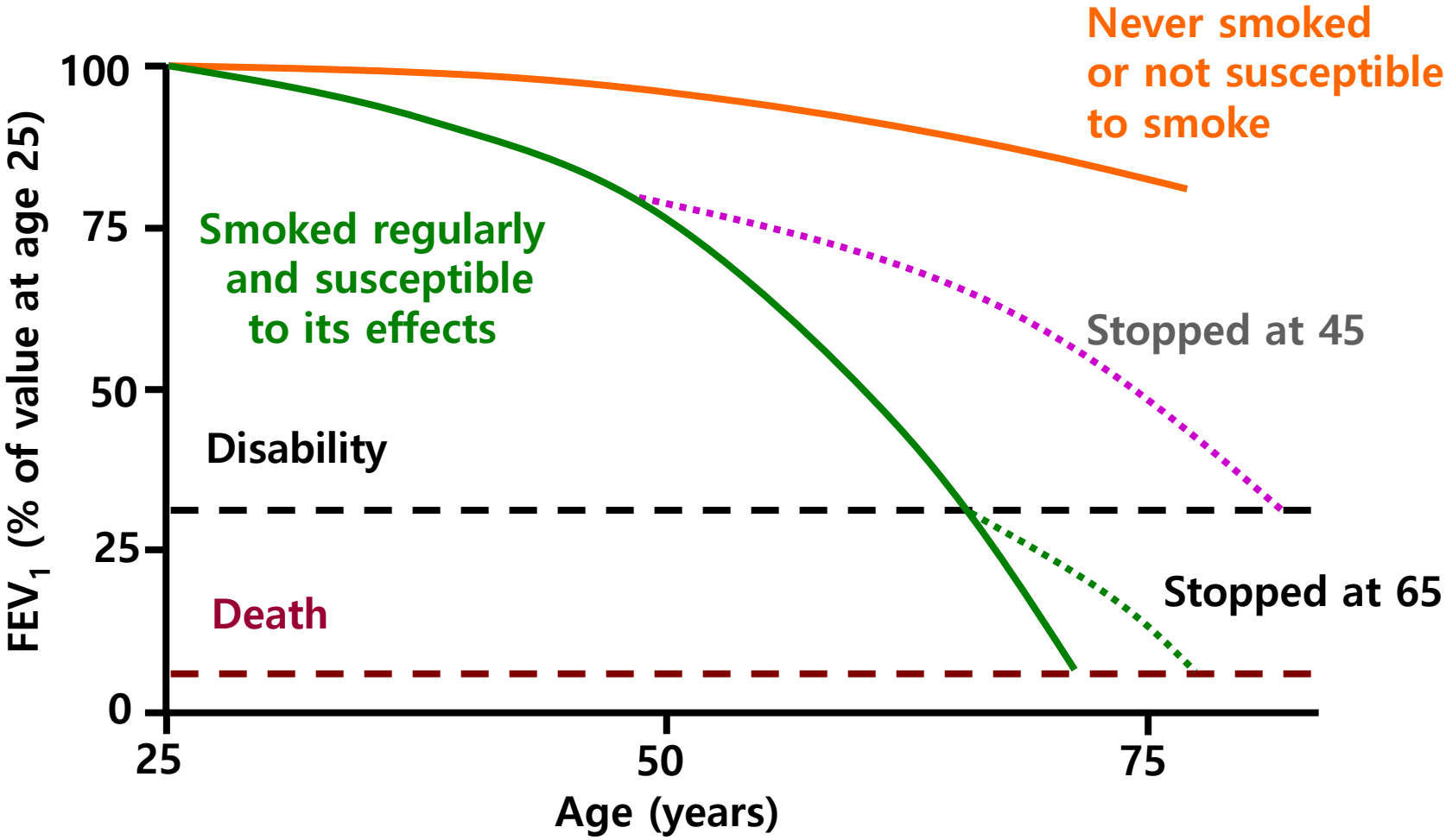
Traditional Paradigm



Fletcher & Peto. Br Med J 1977;1:1645−1648

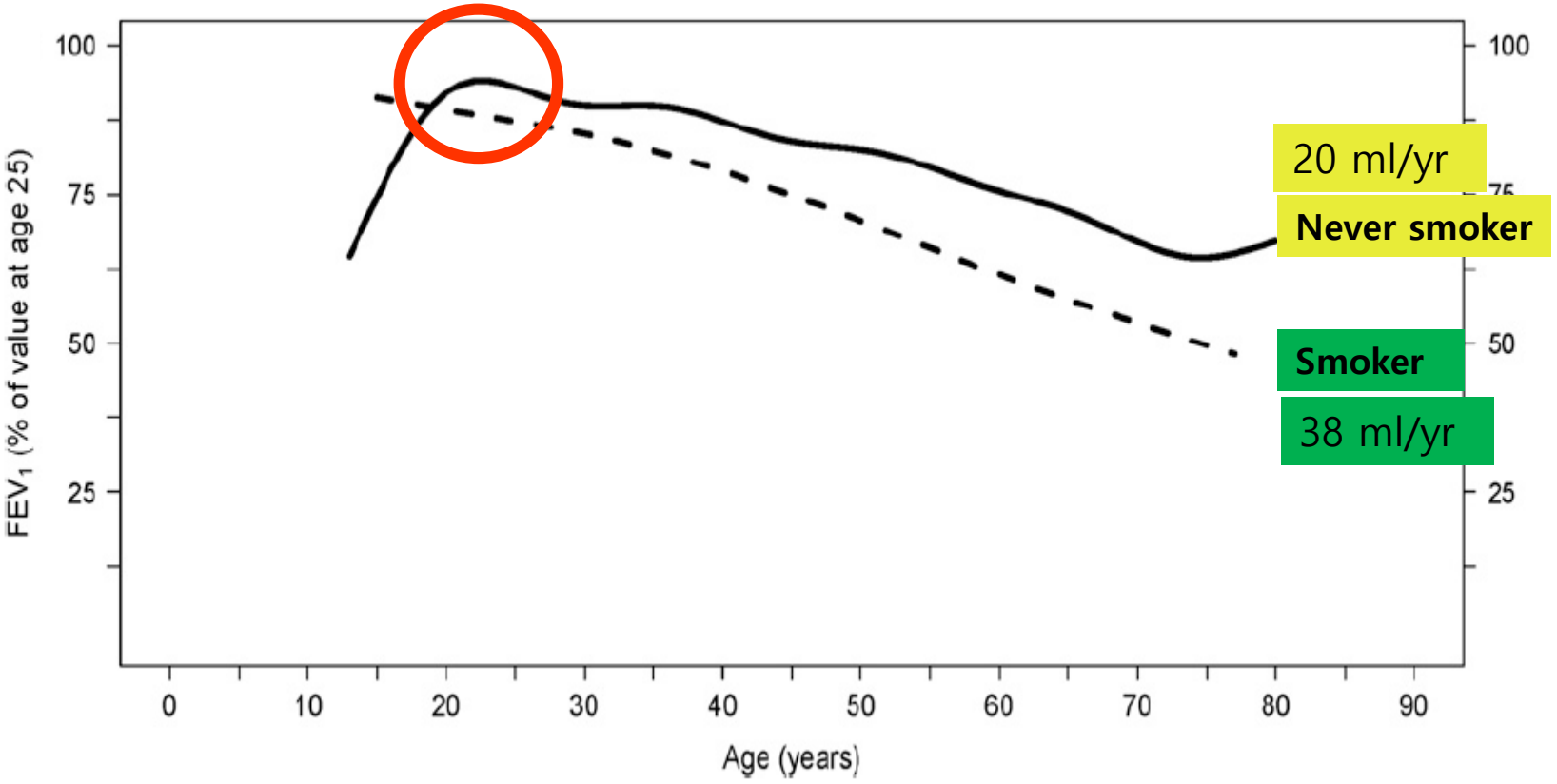
The Natural History of Chronic Airflow Obstruction Revisited

- **Framingham Offspring cohort vs MRC**

1) male and female vs. male
   13-80 yo vs. 30~59 yo
   N=4,391 vs. 1,136
2) Long F/U up to 26 yrs vs. 8 yrs
3) standardized spirometry method

Kohansal R, et al. Am J Respir Crit Care Med 2009; 180: 3–10.

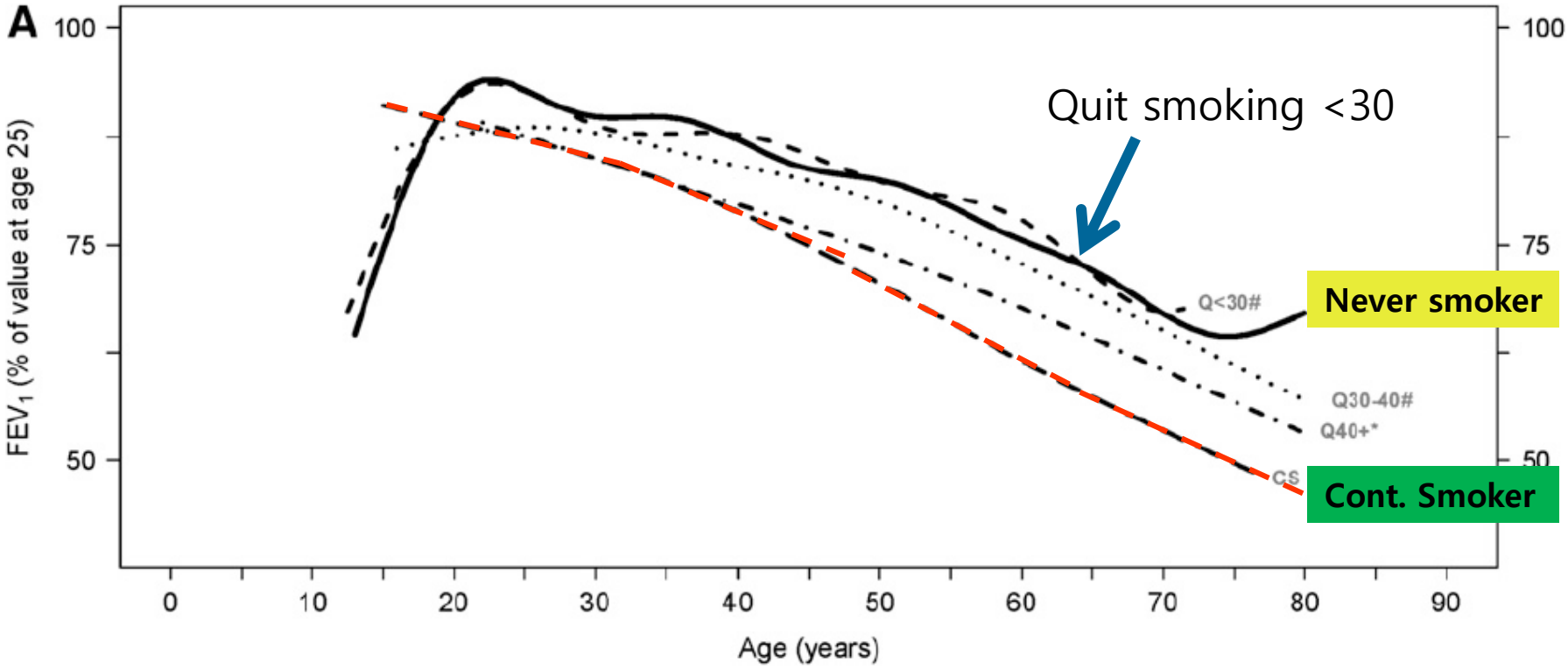
The Natural History of Chronic Airflow Obstruction Revisited



Kohansal R, et al. Am J Respir Crit Care Med 2009; 180: 3–10.

The Natural History of Chronic Airflow Obstruction Revisited

Effect of quitting smoking

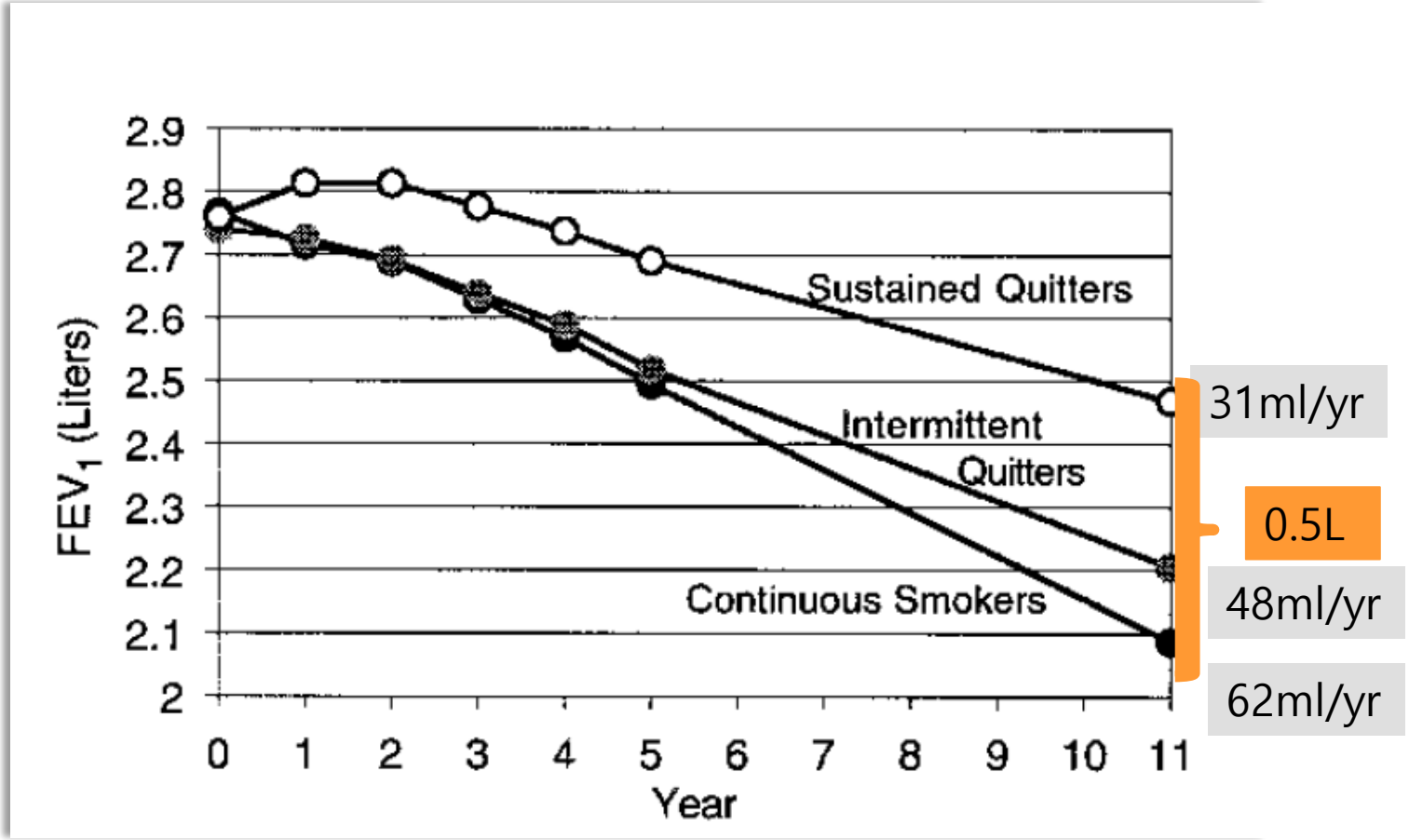


Rate of Lung Function Decline

- **Annualized Rate of Decline**

1) rapid decliners
   annual decline of FEV_1 > 40 mL
2) normal decline
   annual decline of FEV_1 between 20-39.9 mL
3) Non decliner
   annual decline of FEV_1 between 0-19.9 mL

Smoking and Lung Function over 11 yrs
Lung Health Study



Am J Respir Crit Care Med Vol 166. pp 675–679, 2002

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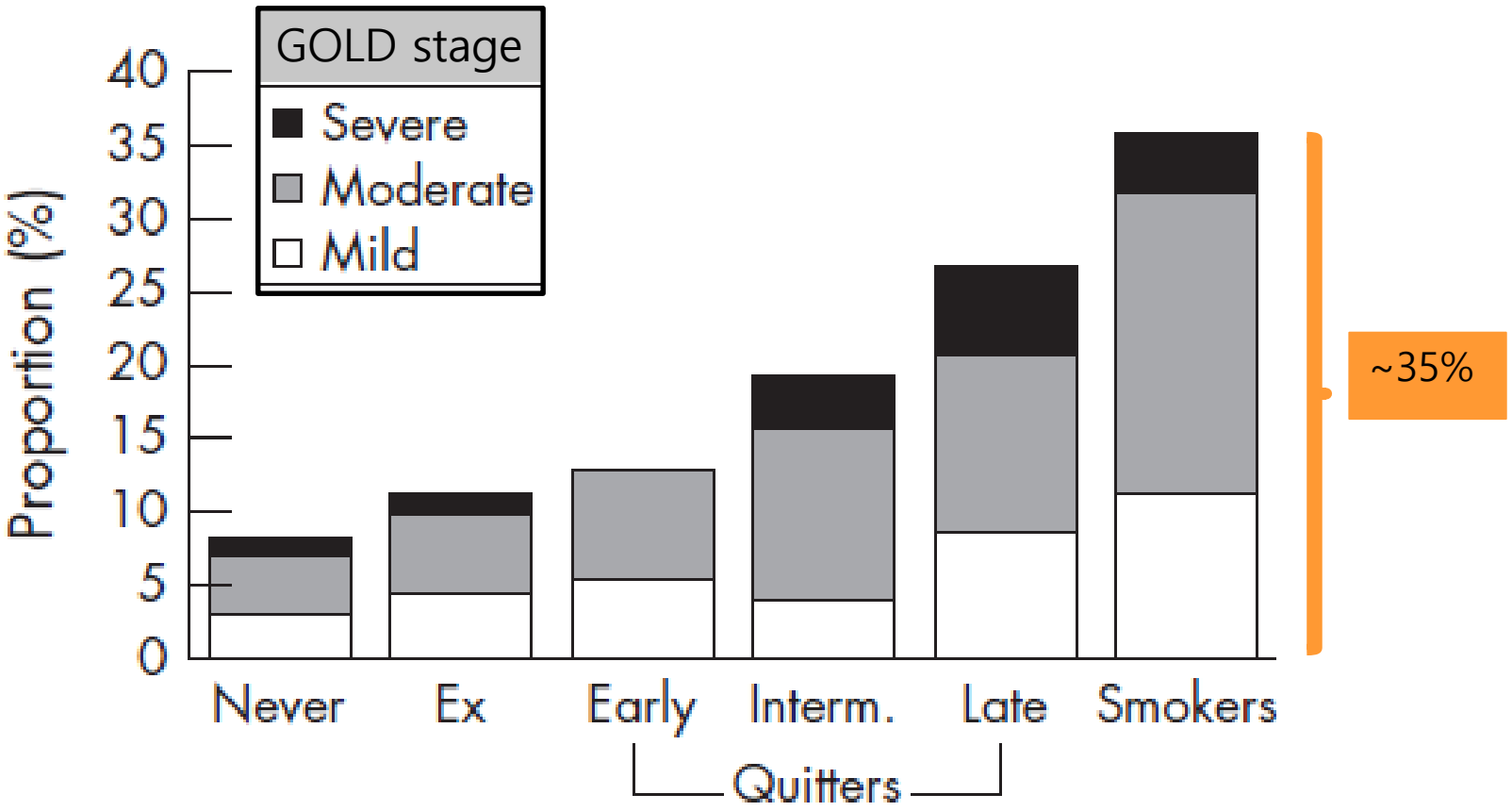
4) Screening in COPD
5) GOLD 0 (Early COPD)

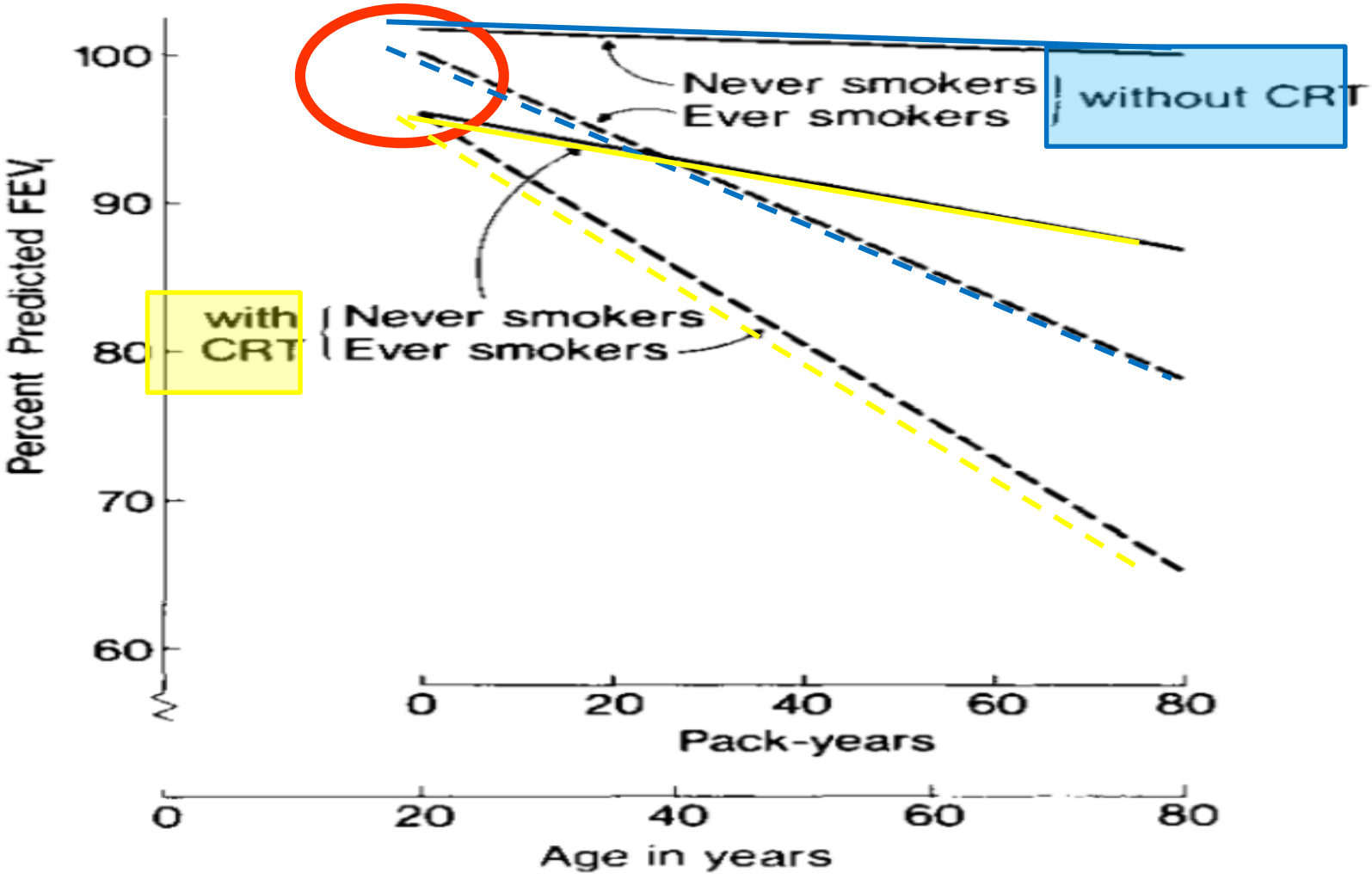
Incidence of COPD among Ever Smokers and Never Smokers

- CCHS cohort



Vestbo J. et al. *Thorax*. 2006; 61(11): 935-939

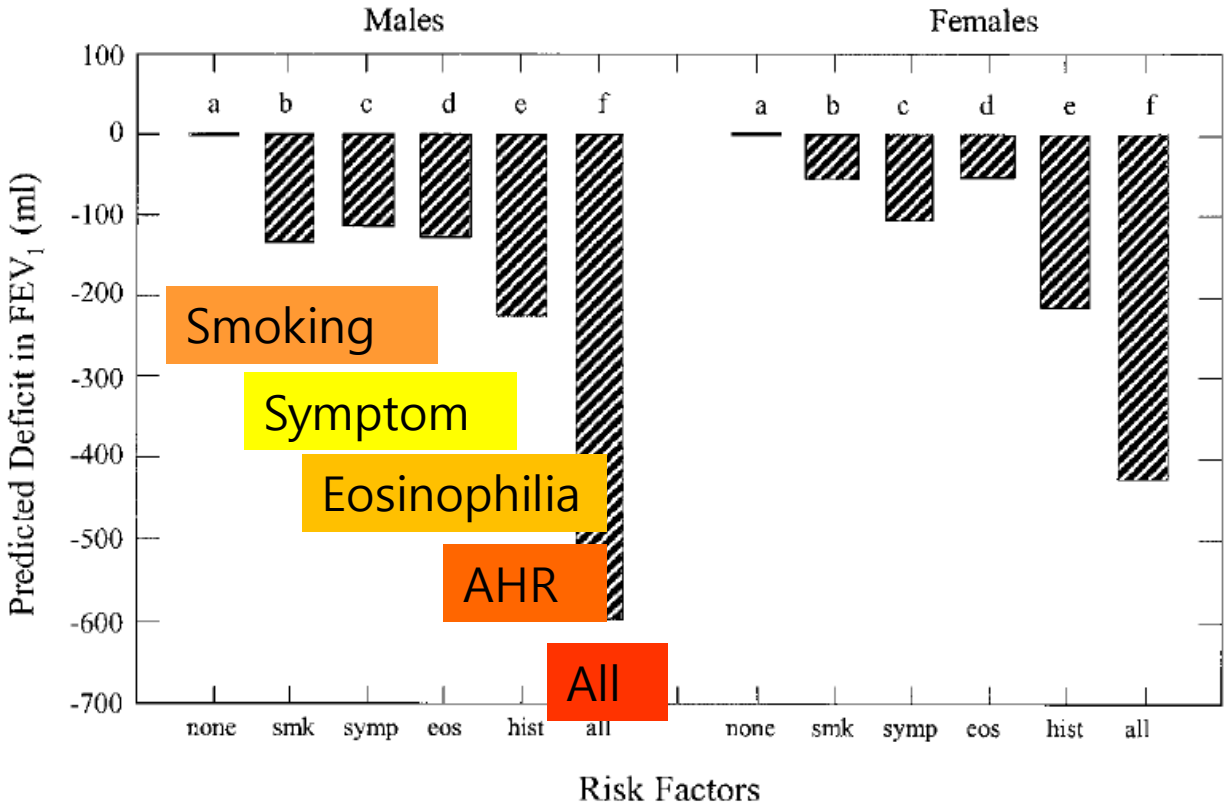
The Relationship of Childhood Respiratory Illness to Adult COPD



Burrows et al. Am Rev Respir Dis 1977;115:751-60

Determinants of Maximally Attained Level of Pulmonary Function

Two Netherlands cohort study
15~35 yo, 1818 males and 1732 females, 24-year F/U



Wang X, et al. Am J Respir Crit Care Med. 2004; 169:941–49.

Factors Associated with the Development of COPD

Risk Factors
Smoking (Active or Passive)
Biomass smoke
Occupational exposure
Air Pollution

Childhood Disadvantage Factors
Intrauterine Growth Disorder
Low birth weight
Severe respiratory infection during childhood

Predisposing Factors
Genetics
Female gender
Low socioeconomic status

Lung Conditions
BHR, Asthma
Chronic mucus hypersecretion
Emphysema detected on HRCT
Recurrent bronchopulmonary infection

1. BMJ. 1991; 303:671–75 2. Thorax. 2013; 68:760–66.
3. Eur J Med Res 2009; 14(suppl 4):27–31 4. Thorax. 2004; 59:295–302.
5. Lancet. 2007; 370:758–64

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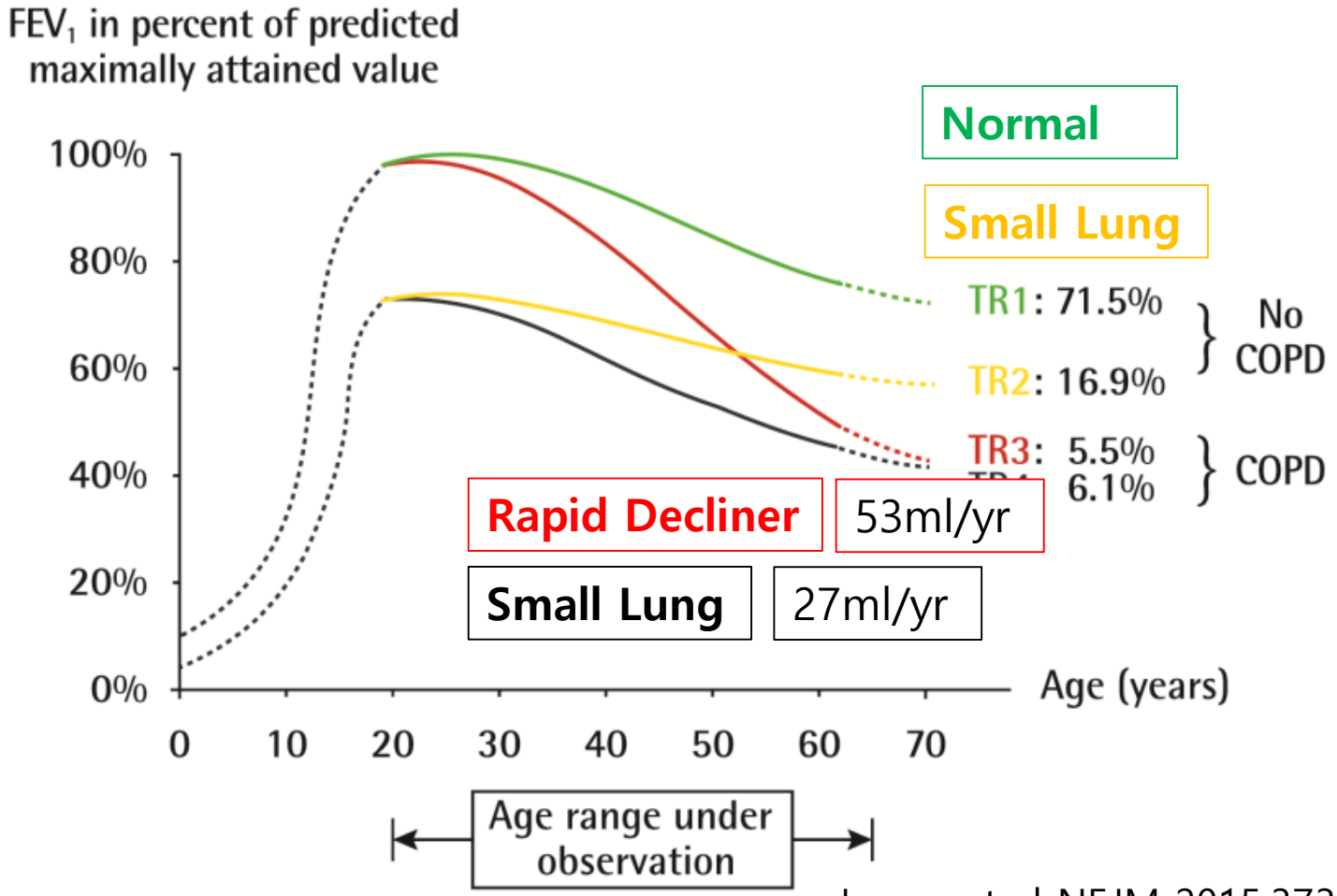
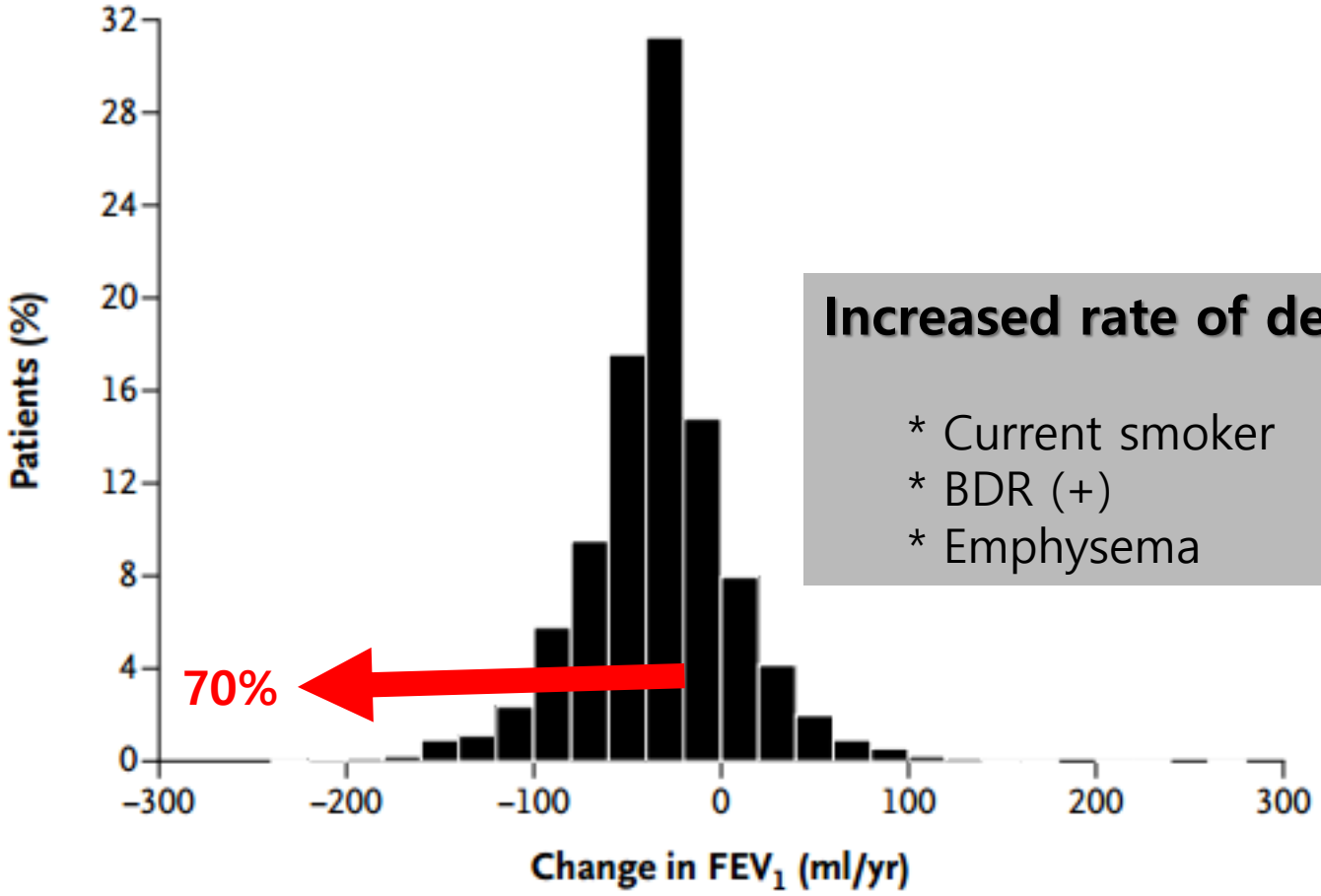
New Paradigm of COPD Progression

Framingham Offspring Cohort. Copenhagen City Heart Study.
Lovelace Smokers Cohort



Lange et al NEJM 2015;373:111-22

Changes in FEV_1 Over Time for 3 yrs ECLIPSE

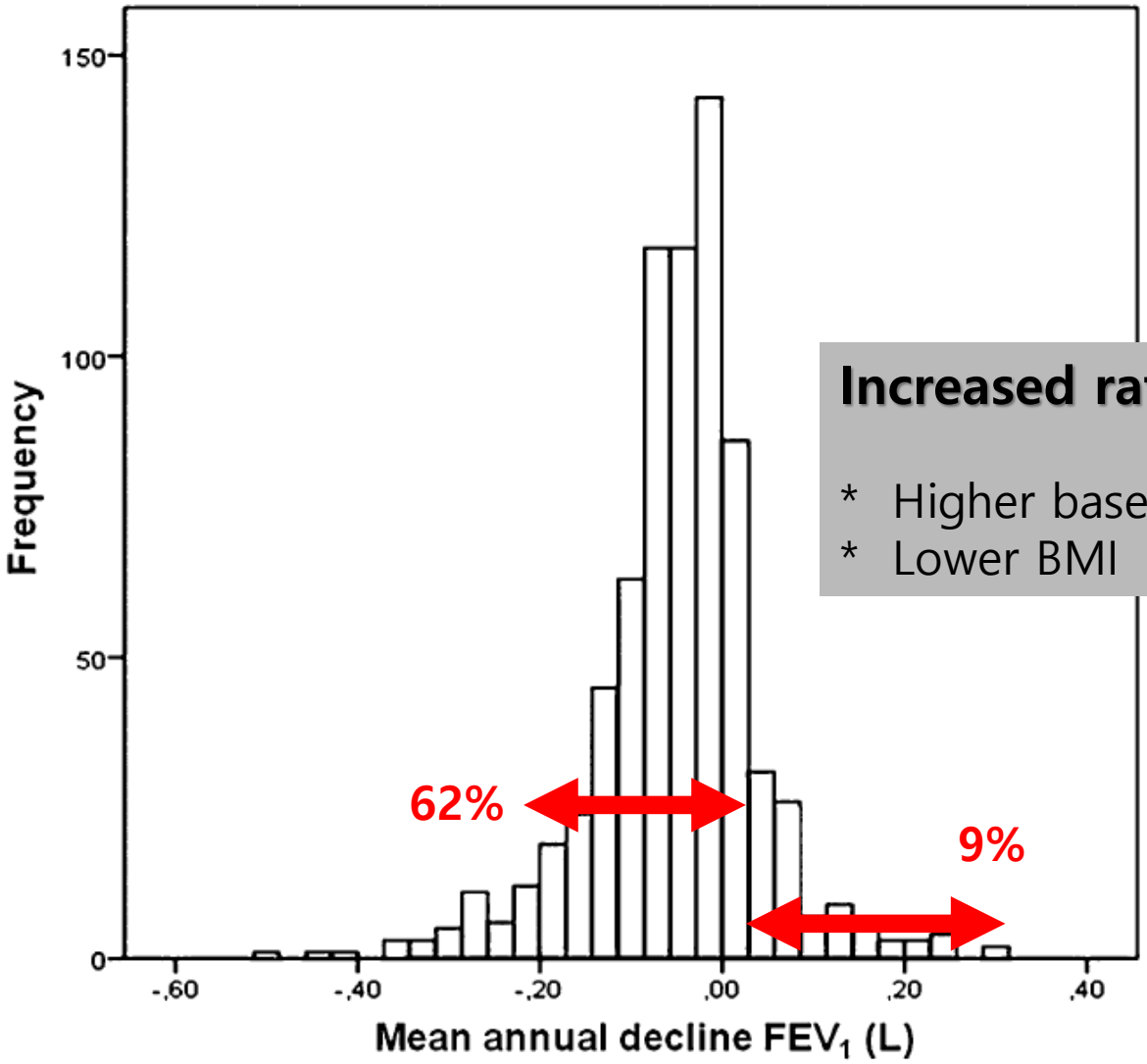


Increased rate of decline

* Current smoker
* BDR (+)
* Emphysema

Vestbo J, et al. N Engl J Med. 2011;365(13):1184–92.

Changes in FEV_1 Over Time for 10 yrs BODE

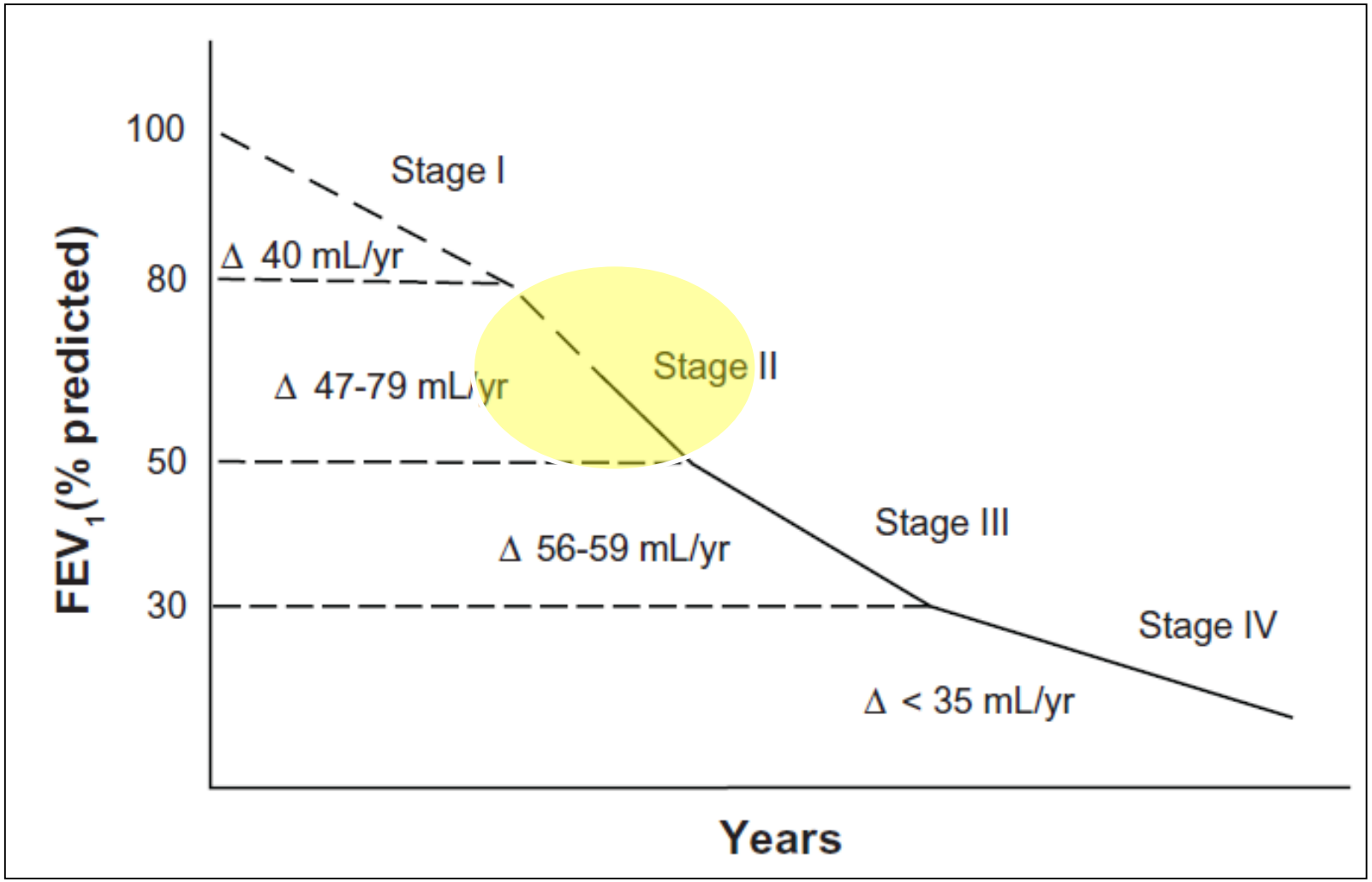


Increased rate of decline

* Higher baseline FEV1
* Lower BMI

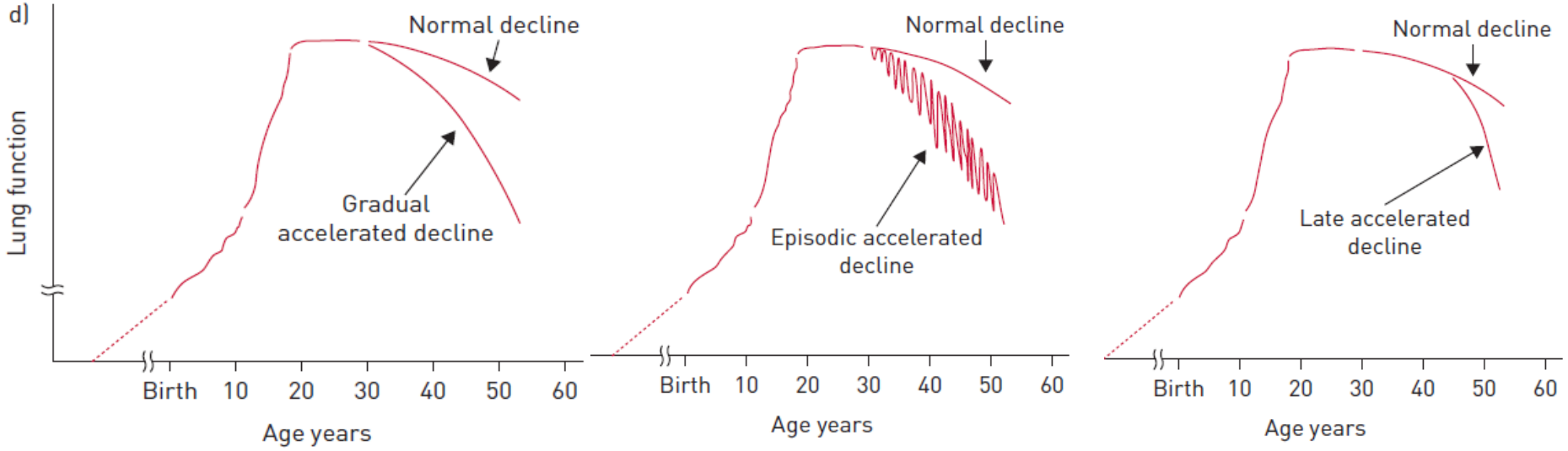
Casanova C, et al. Am J Respir Crit Care Med 2011; 184: 1015–1021.

COPD Progression and GOLD Stage

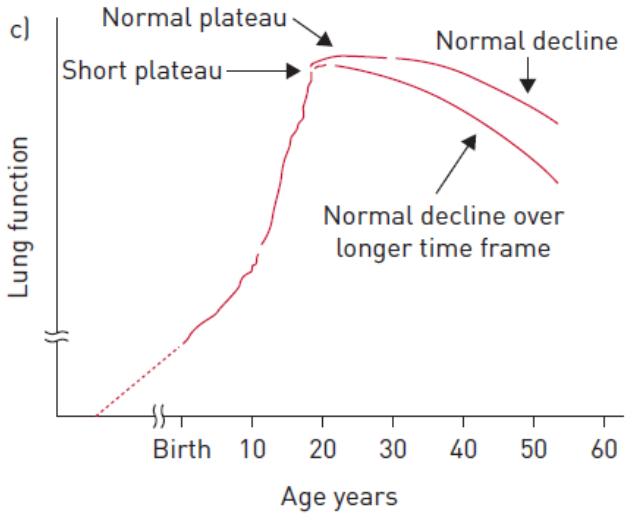


Tantucci et al IJCOPD 2012

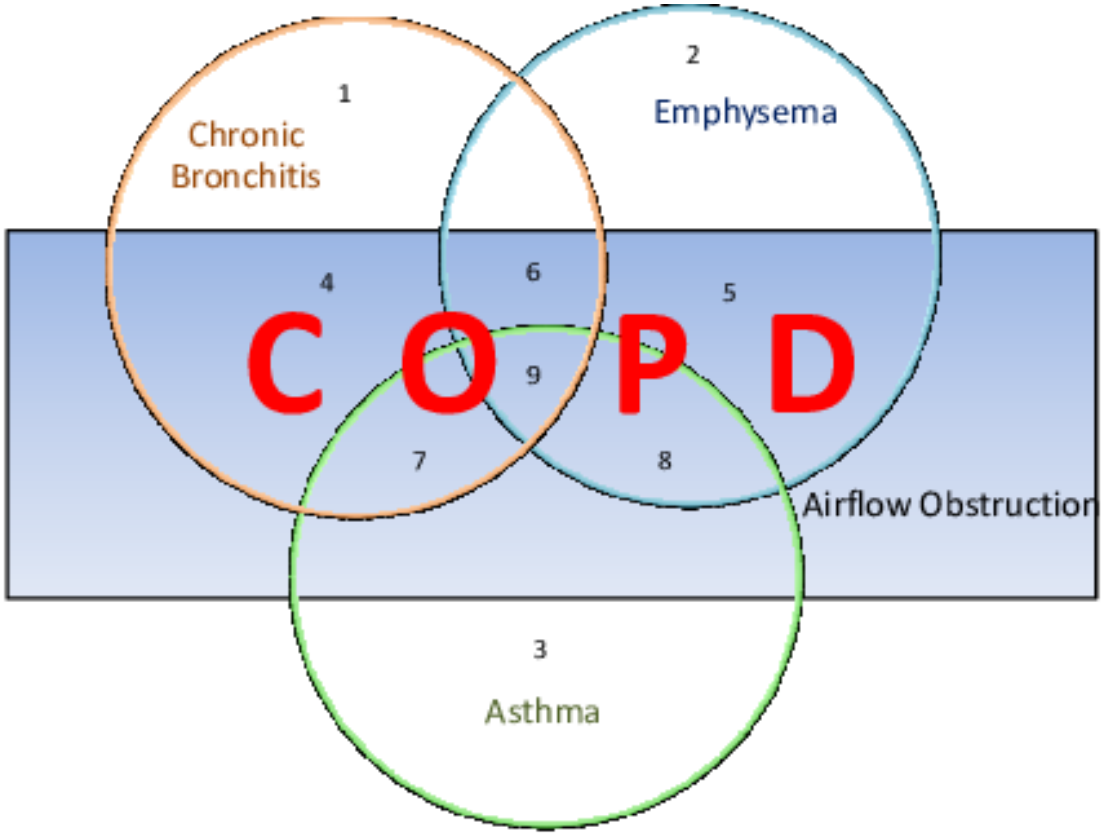
3 Ways For Lung Function Decrease



Short Plateau



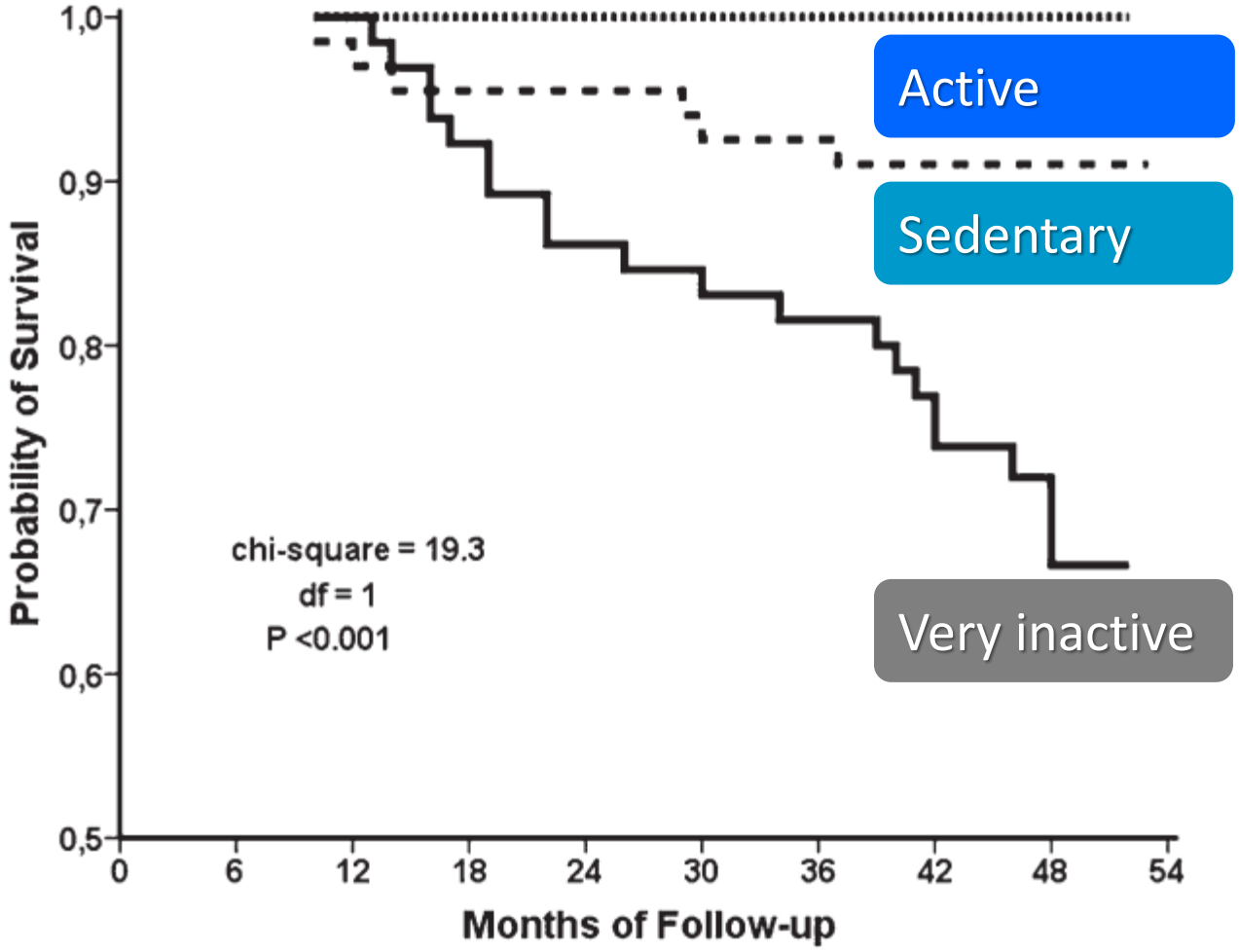
Is COPD Single Disease?



Natural History Beyond FEV_1

- Cough and sputum
- Dyspnoea
- The extrapulmonary features
- Activity level

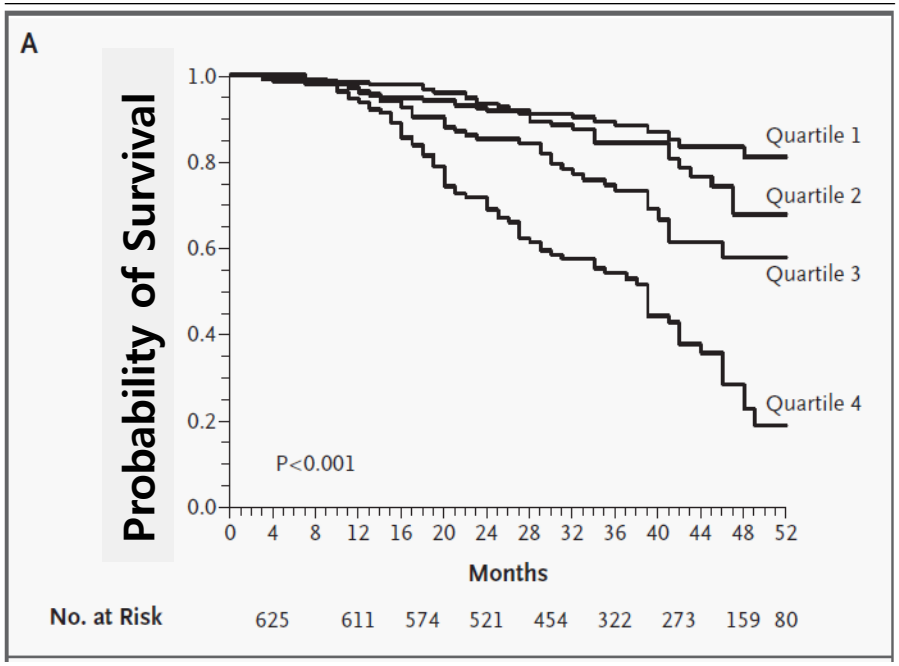
Survival & Physical Activity



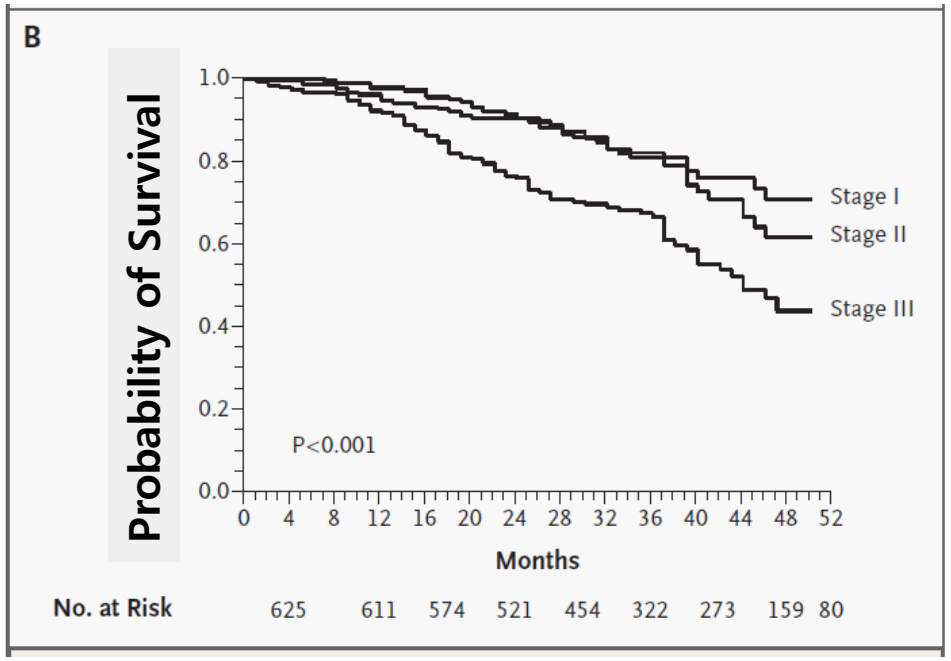
CHEST 2011;140:331-42

BODE Index vs FEV_1

BODE INDEX



GOLD STAGE



- BODE index : FEV_1 , 6MWD, MMRC, BMI

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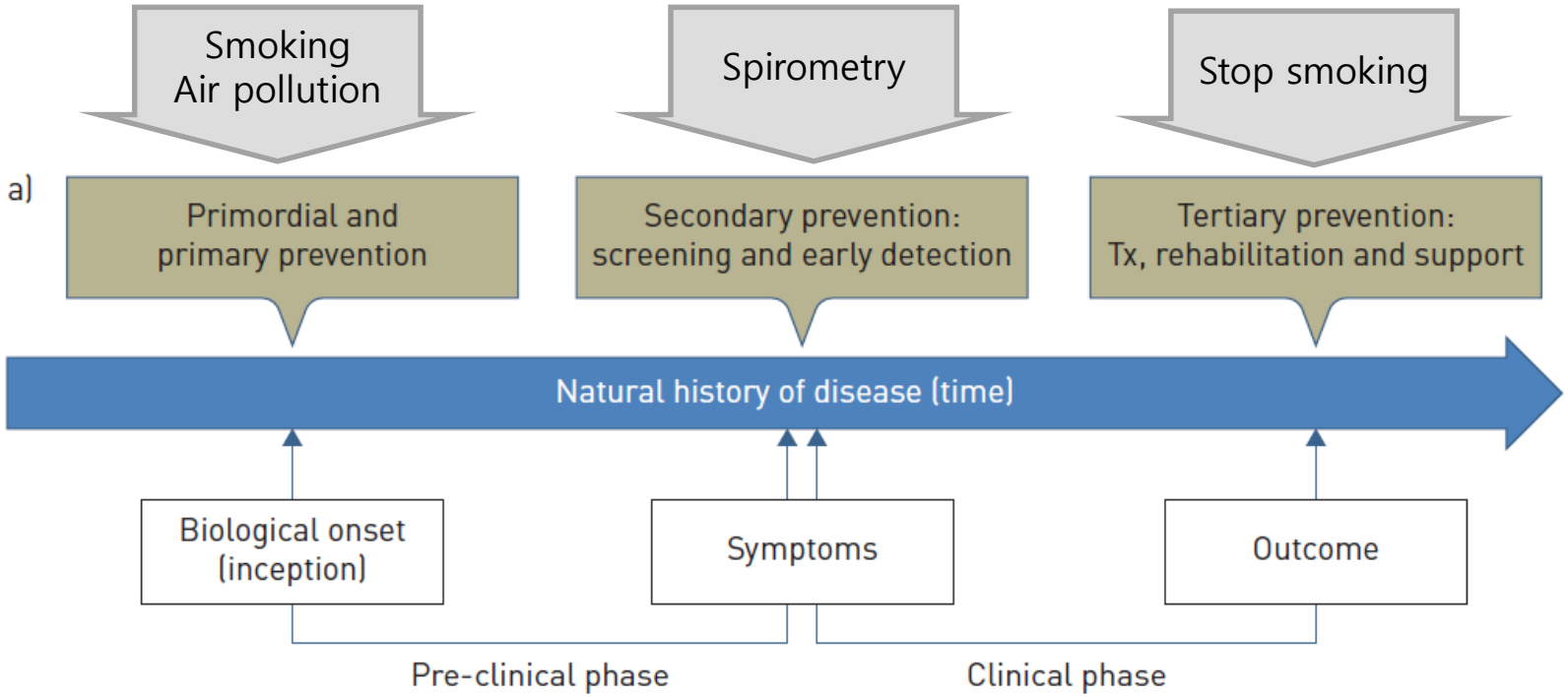
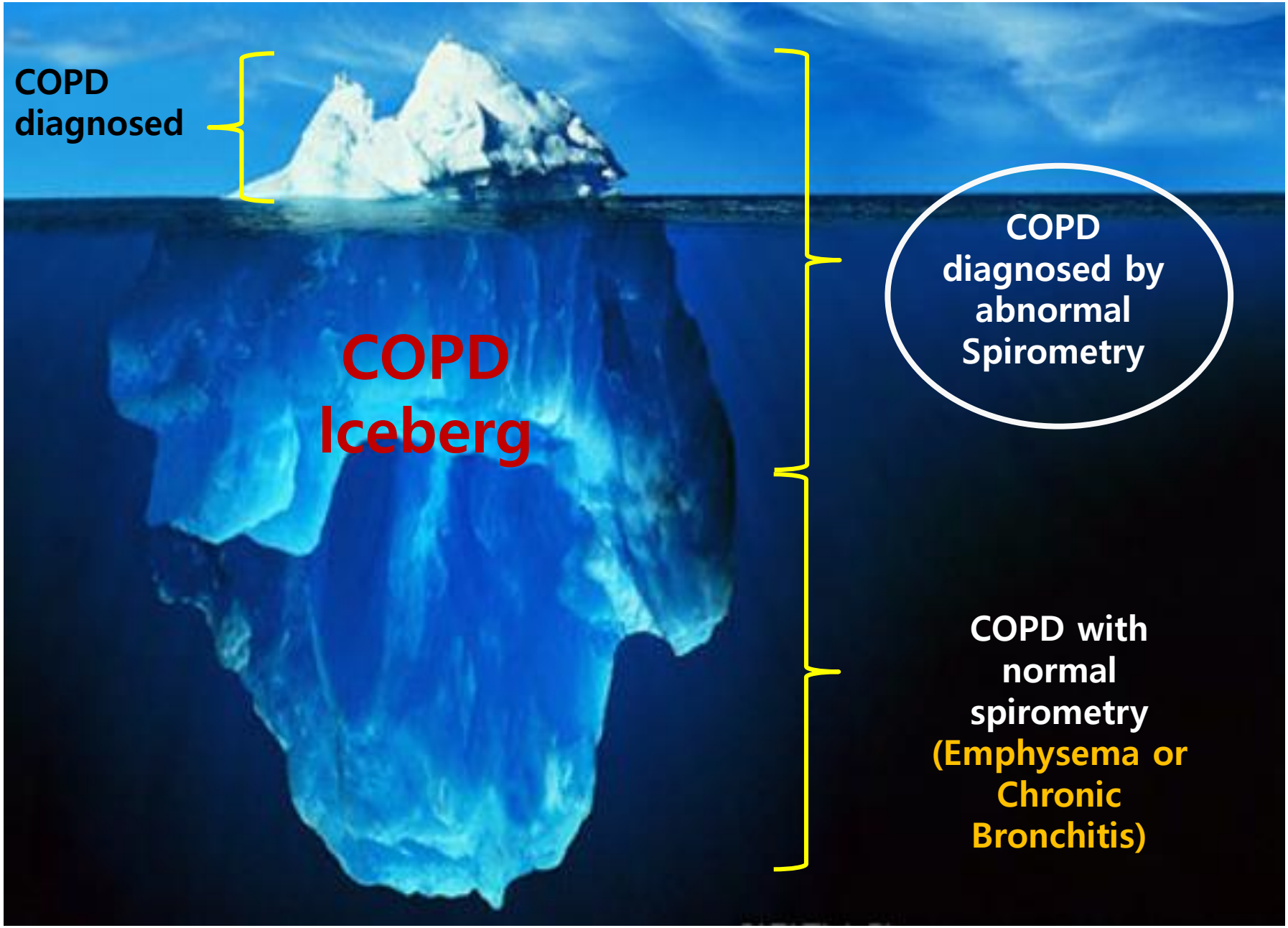
Disease Prevention Model



Agustí A,et al. ERJ Open Res 2017; 3: 00117-2017


COPD diagnosed
COPD Iceberg
COPD diagnosed by abnormal Spirometry
COPD with normal spirometry (Emphysema or Chronic Bronchitis)

JAMA
The Journal of the American Medical Association

5th April, 2016

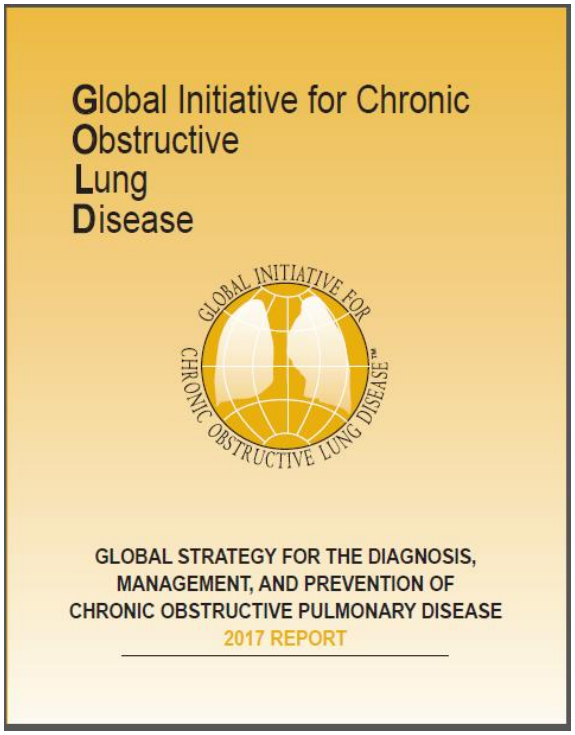
Screening for COPD. Evidence Report and Systematic Review for the US Preventive Services Task Force (USPSTF)

There was no direct evidence available to determine the benefits and harms of screening asymptomatic adults for COPD using questionnaires or office-based spirometry or to determine the benefits of treatment screen-detected populations.

33 studies analyzed

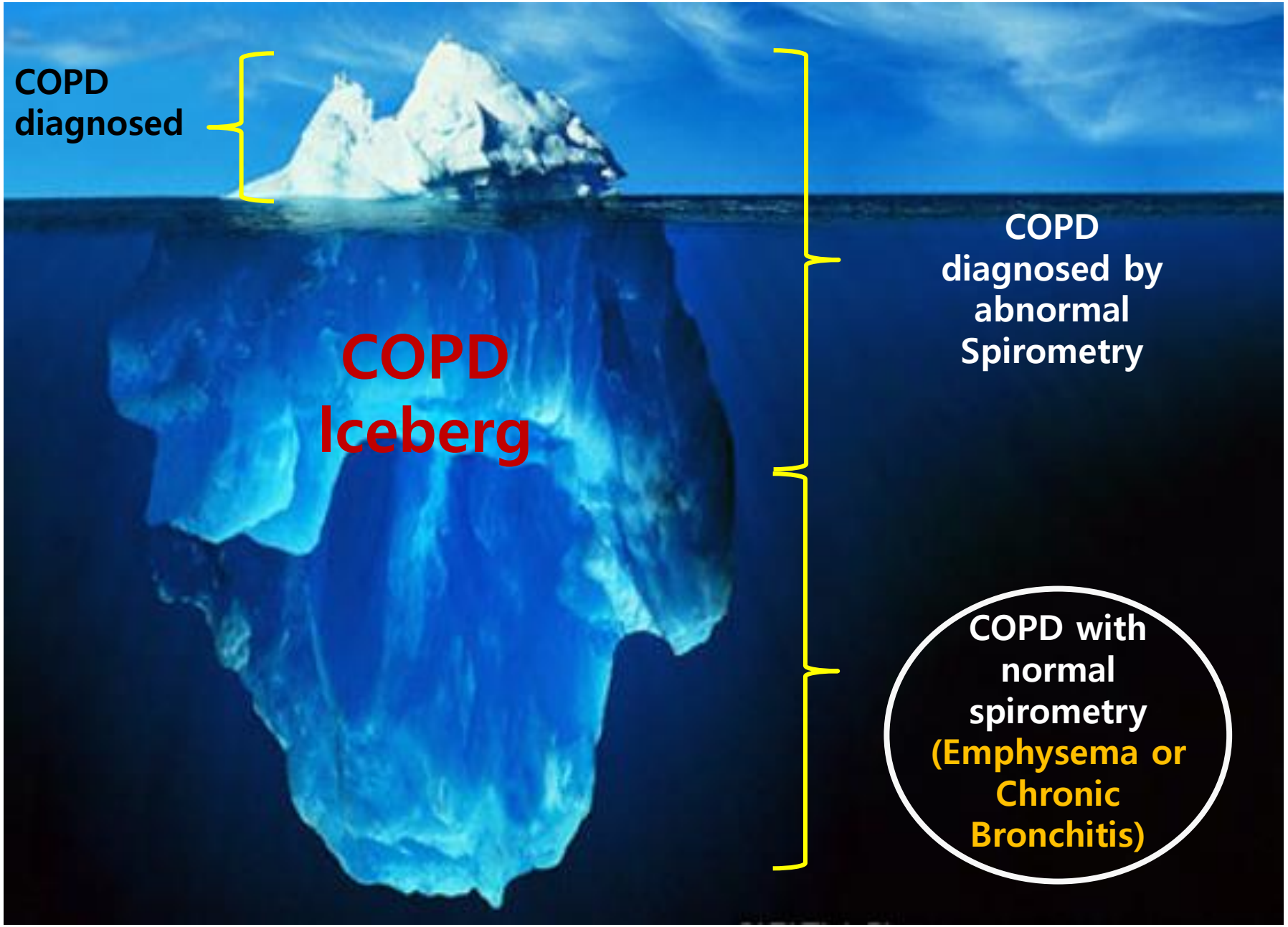
Grade D : Recommends against screening for COPD among asymptomatic adults

(Guirguis-Blake J et al, JAMA 2016;315(13): 1378-1393)



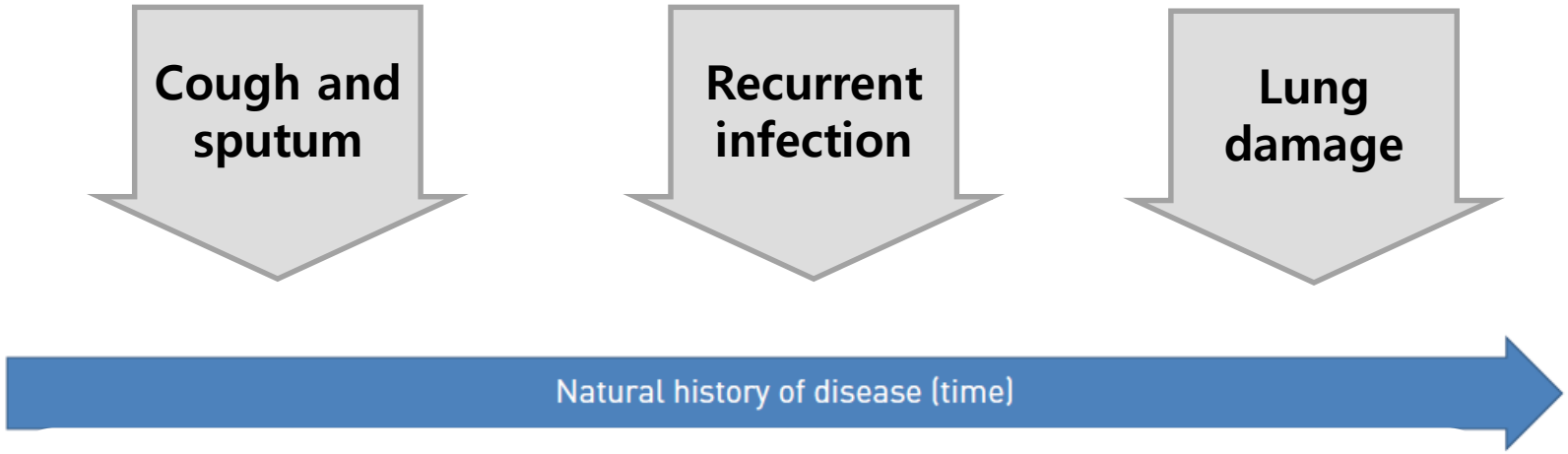
- **Active case finding**

performing spirometry in patients with symptoms and/or risk factors, where the diagnostic yield for COPD is relatively high)
but not routine screening spirometry in asymptomatic individuals without COPD risk factors


COPD diagnosed
COPD Iceberg
COPD diagnosed by abnormal Spirometry
COPD with normal spirometry (Emphysema or Chronic Bronchitis)

Disease Progression Model

Before Peto and Fletcher



Occasional Review

The natural history of chronic airflow obstruction

- two distinct but commonly associated disorders:

① hypersecretory disorder, with mucus hypersecretion and recurrent airways infections – airway disease

② emphysema

- both disorders were favorably affected by smoking cessation, resulting in normalization of the FEV1 decline and remittance of CMH in most quitters.
- <u>mucus hypersecretion should not be regarded as the factor defining susceptibility to future development of airflow limitation</u>

Int J Epidemiol. 1979 Sep;8(3):201-12.

Twelve years spirometric changes among Paris area workers.

Kauffmann F, Drouet D, Lellouch J, Brille D.

Am Rev Respir Dis. 1986 Oct;134(4):688-93.

Is respiratory mucus hypersecretion really an innocent disorder? A 22-year mortality survey of 1,061 working men.

Annesi I, Kauffmann F.

Eur Respir J. 1995 Aug;8(8):1333-8.

Chronic mucus hypersecretion in COPD and death from pulmonary infection.

Prescott E[1], Lange P, Vestbo J.

Am J Respir Crit Care Med. 1996 May;153(5):1530-5.

Association of chronic mucus hypersecretion with FEV1 decline and chronic obstructive pulmonary disease morbidity. Copenhagen City Heart Study Group.

Vestbo J[1], Prescott E, Lange P.

Author information

Abstract

The aim of this study was to examine the association between chronic mucus hypersecretion, and FEV1 decline, and subsequent hospitalization from chronic obstructive pulmonary disease (COPD). We used data from The Copenhagen City Heart Study on 5,354 women and 4,081 men 30 to 79 yr of age with assessment of smoking habits, respiratory symptoms, and spirometry at two surveys 5 yr apart. Information on COPD hospitalization during 8 to 10 yr of subsequent follow-up was obtained from a nationwide register. Chronic mucus hypersecretion was significantly associated with FEV1 decline; the effect was most prominent among men, where chronic mucus hypersecretion at both surveys was associated with an excess FEV1 decline of 22.8 ml/yr (95% confidence interval, 8.2 to 37.4) compared with men without mucus hypersecretion, after adjusting for age, height, weight change, and smoking; in women, the excess decline was 12.6 ml/yr (0.7-24.6). Chronic mucus hypersecretion was associated with subsequent hospitalization due to COPD after adjusting for age and smoking; relative risk was 5.3 (2.9 to 9.6) among men and 5.1 (2.5 to 10.3) among women. After further adjusting for FEV1 at the second survey, the relative risk was reduced to 2.4 (1.3 to 4.5) for men and 2.6 (1.2 to 5.3) for women. Chronic mucus hypersecretion was significantly and consistently associated with both an excess FEV1 decline and an increased risk of subsequent hospitalization because of COPD.

Early COPD

- GOLD 0
  - -2001'GOLD
  - - Chronic Bronchitis or chronic sputum

    & Preserved Lung Function $FEV_1/FVC \geq 0.7$

Can GOLD Stage 0 Provide Information of Prognostic Value in Chronic Obstructive Pulmonary Disease?

Jørgen Vestbo and Peter Lange

Department of Respiratory Medicine, Hvidovre University Hospital, Hvidovre, Denmark

In the recently published guidelines of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) for chronic obstructive pulmonary disease (COPD), the staging system included a Stage 0 for subjects without airways obstruction but with respiratory symptoms, denoting these subjects "at risk" for COPD. Our aim was to validate this staging approach using data from three surveys in The Copenhagen City Heart Study, in which a sample of the general population was examined at baseline and in which, after 5 and 15 years, spirometry was performed at all surveys. Criteria for GOLD Stage 0 was fulfilled by 5.8% of the total adult population and 7.2% of smokers. After 5 and 15 years, 13.2 and 20.5%, respectively, of smokers with GOLD Stage 0 had developed COPD fulfilling criteria for GOLD Stage 1 or worse. This was the case for 11.6 and 18.5%, respectively, of smokers without respiratory symptoms. Further analyses using multivariate logistic regression analysis confirmed that GOLD Stage 0 was not identifying subsequent airways obstruction. When analyzing FEV_1 decline, Stage 0 carried a risk of excess decline. GOLD Stage 0 was not a stable feature, which may explain the lack of predictive value. In the Western world, smoking is still in itself the most important indicator of risk of COPD, and alternative markers of susceptibility in the population must be investigated.

Keywords: COPD; epidemiology; guidelines; prognosis

Global guidelines for chronic obstructive pulmonary disease (COPD), the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, were published in 2001 for the purmost patients with COPD Stage 1+ have "passed through" Stage 0 during the development of their disease.

Because little evidence has been published supporting the use of a Stage 0, we wished to test the usefulness of Stage 0 using data from a large population-based panel study with information available over several years: The Copenhagen City Heart Study.

METHODS

All subjects included in this study participated in the Copenhagen City Heart Study, a prospective epidemiologic study initiated in 1976–1978 (8, 9). A sample of 19,698 individuals, aged 20 years or older, was selected at random after age stratification in 10-year age groups from residents of Copenhagen and invited to all three surveys if still alive. A total of 14,223 attended the first examination from 1976 through 1978 (response rate of 74%); 12,698 attended the second examination from 1981 through 1983 (response rate of 70%), and of these 11,135 had participated in the initial survey and this corresponds to 83.8% of those examined at first survey and alive at the time of the second survey. A total of 10,049 attended the third examination from 1991 through 1994 (response rate of 58%), 7,073 subjects had participated in the initial survey and this corresponds to 70.5% of those examined at first survey and alive at the time of the third survey. Subjects with self-reported asthma at any of the surveys were excluded.

At the first and second examinations, FEV_1 and FVC were measured with an electronic spirometer (model N 403; Monaghan, Littleton, CO), which was calibrated daily with a 1-L syringe and weekly

Vestibo et al. Am J Respir Crit Care Med 2002;166:329-32

Prognostic Value of GOLD 0

TABLE 2. PREVALENCE OF DIFFERENT STAGES OF COPD AFTER 5 AND 15 YEARS IN SUBJECTS WITHOUT COPD AND WITH COPD STAGE 0 AT BASELINE

	No COPD at Baseline		COPD Stage 0 at Baseline	
5-yr follow-up				
COPD Stage 1	364 (4.3%)/239 (4.9%)		5.7%)/26 (5.8%)	
COPD Stage 2	443 (5.3%)/332 (6.7%)	11.7%	6.7%)/33 (7.4%)	13.5%
COPD Stage 3	5 (0.1%)/4 (0.1%)		—/—	
15-yr follow-up				
COPD Stage 1	393 (7.2%)/304 (9.9%)		51 (13.5%)/44 (14.8%)	
COPD Stage 2	317 (5.8%)/260 (8.4%)	18.5%	5.0%)/17 (5.7%)	20.5%
COPD Stage 3	10 (0.2%)/7 (0.2%)		—/—	

Numbers and percentages are given for all subjects/all subjects smoking at baseline.

Prognostic Value of GOLD 0

TABLE 3. RESULTS OF MULTIVARIATE LOGISTIC REGRESSION MODELS WHERE THE OUTCOME WAS PRESENCE OF COPD GOLD STAGE 1+ AT FOLLOW-UP AFTER 5 AND 15 YEARS

	5-yr Follow-Up		15-yr Follow-Up	
Variable	OR	95% CI	OR	95% CI
Age, yr				
< 49 y	1		1	
50–59	1.9	1.6–2.2	2.4	2.1–2.8
60–69	2.9	2.4–3.4	4.3	3.4–5.4
> 70	3.8	2.7–5.3	3.7	1.3–10.3
Sex				
No	1		1	
Yes	1.5	1.3–1.9	2.0	1.6–2.6
Inhalation				
No	1		1	
Yes	1.4	1.2–1.7	2.3	1.9–2.9
Ex-smoking at follow-up				
No	1		1	
Yes	0.8	0.7–1.0	0.7	0.6–0.9
COPD				
None	1		1	
Stage 0	1.1	0.9–1.4	1.2	0.9–1.6

Definition of abbreviations: OR = odds ratio; 95% CI = 95% confidence interval.

2006 GOLD 부터 GOLD 0 없어짐

ORIGINAL ARTICLE

The Presence of Chronic Mucus Hypersecretion across Adult Life in Relation to Chronic Obstructive Pulmonary Disease Development

James P. Allinson[1], Rebecca Hardy[2], Gavin C. Donaldson[1], Seif O. Shaheen[3], Diana Kuh[2], and Jadwiga A. Wedzicha[1]

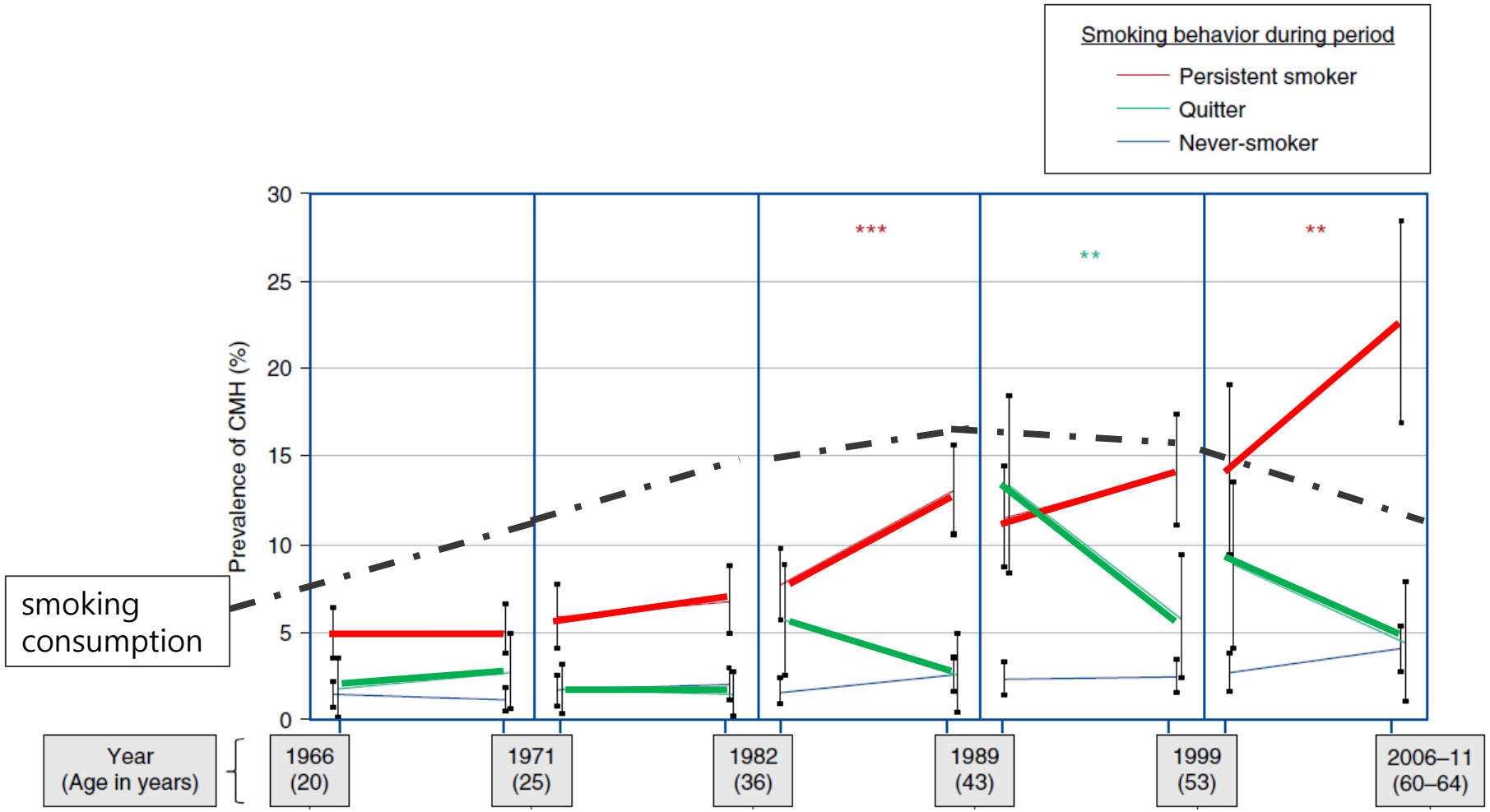
[1]Airways Disease Section, National Heart and Lung Institute, Imperial College London, London, United Kingdom; [2]MRC Unit for Lifelong Health and Ageing at UCL, University College London, London, United Kingdom; and [3]Centre for Primary Care and Public Health, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, United Kingdom

NSHD (National Survey of Health and Development)

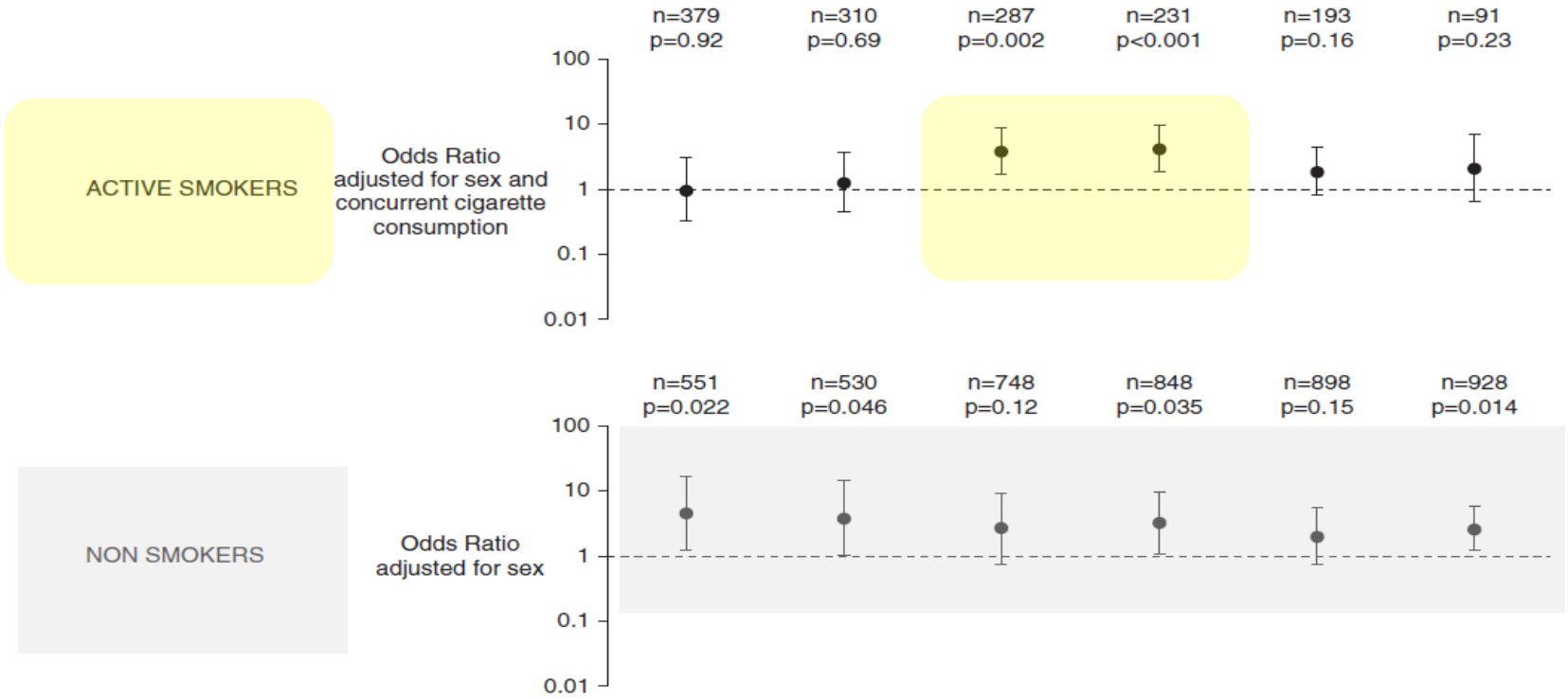
British cohort from 1946 (at birth) ~ N=5,362
Recent data collection 2006~2011 ; 2,856 alive
Prospective observation study between the ages of 20 and 64 years, assessed on six occasions. using a validated questionnaire
2,229 available participants (78%) data analysis

Allinson JP, et.al. Am J Respir Crit Care Med 2016; 193: 662-72

Relationship between Symptoms and Smoking with Age

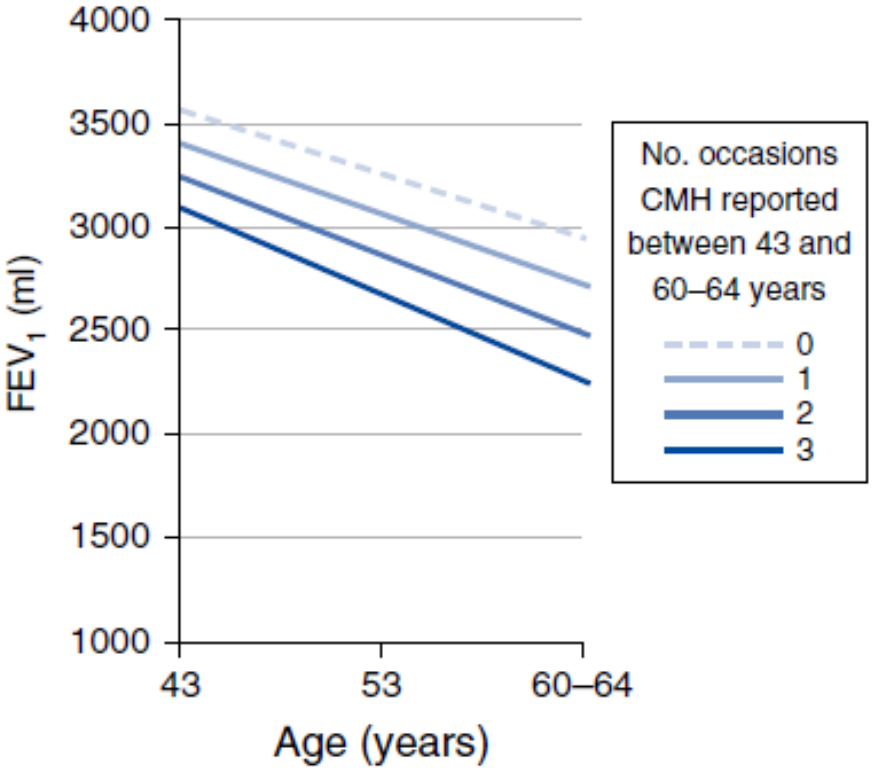


The Relationship between Chronic Symptoms and Airflow Limitation at Age 60–64 Years

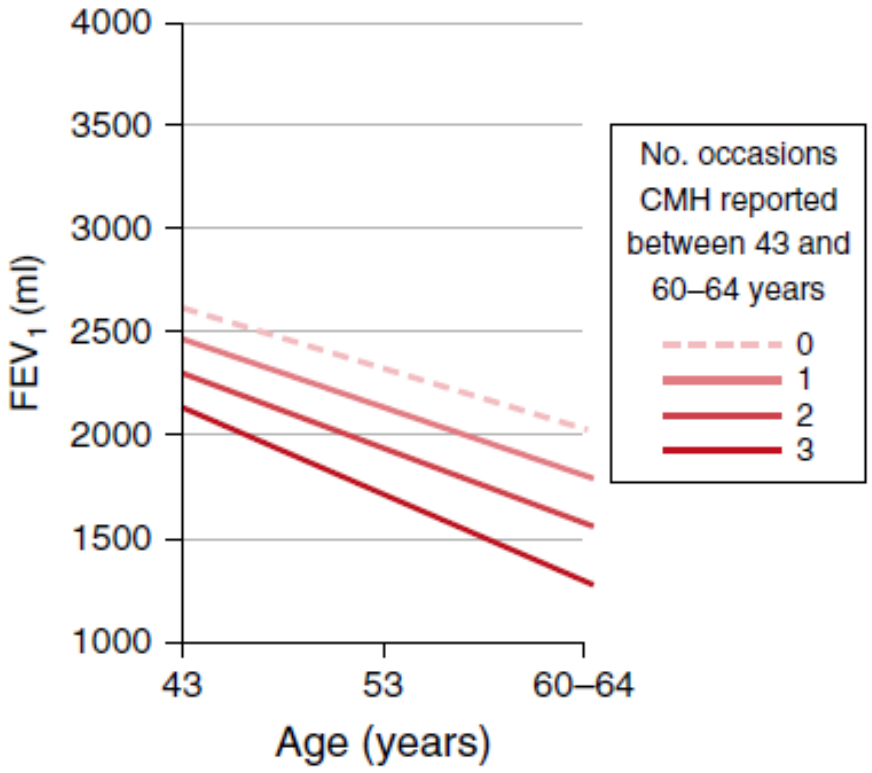


	YEAR (Age in years)	1966 (20)	1971 (25)	1982 (36)	1989 (43)	1999 (53)	2006–11 (60–64)
ACTIVE SMOKERS	Odds Ratio (95% CI)	0.95 (0.32–2.85)	1.24 (0.44–3.52)	3.70 (1.62–8.45)	4.11 (1.85–9.13)	1.82 (0.78–4.23)	2.07 (0.64–4.74)
NON SMOKERS	Odds Ratio (95% CI)	4.64 (1.25–17.22)	3.80 (1.03–14.08)	2.73 (0.78–9.55)	3.29 (1.09–9.92)	2.05 (0.77–5.47)	2.65 (1.22–5.76)

The influence of duration of chronic mucus hypersecretion (CMH) presence on FEV1 decline between ages 43 and 60–64 years.



male



female

ORIGINAL ARTICLE

The Presence of Chronic Mucus Hypersecretion across Adult Life in Relation to Chronic Obstructive Pulmonary Disease Development

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NSHD (National Survey of Health and Development)

- **Cumulative prevalence of CMH among COPD ; 60%**
- **CMH in individuals with normal lung function may precede and augment development of airflow limitation.**

British cohort from 1946 (at birth) ~ N=5,362
Recent data collection 2006~2011 ; 2,856 alive
Prospective observational study between the ages of 20 and 64 years, assessed on six occasions, using a validated questionnaire
2,229 available participants (78%) data analysis

Allinson JP, et.al. Am J Respir Crit Care Med 2016; 193: 662-72

Emphysema and incidence of airflow limitation

Thorax Online First, published on October 26, 2017 as 10.1136/thoraxjnl-2017-210842

Associations between emphysema-like lung on CT and incident airflow limitation: a general population-based cohort study

ABSTRACT

Emphysema on CT is associated with accelerated lung function decline in heavy smokers and patients with COPD; however, in the general population, it is not known whether greater emphysema-like lung on CT is associated with incident COPD. We used data from 2045 adult participants without initial prebronchodilator airflow limitation, classified by $FEV_1/FVC<0.70$, in the Multi-Ethnic Study of Atherosclerosis. Emphysema-like lung on baseline cardiac CT, defined as per cent low attenuation areas$_{<-950HU}$>upper limit of normal. was associated with increased odds of

Using information from the US general population-based Multi-Ethnic Study of Atherosclerosis (MESA), we identified 2045 middle-aged and older adults without prebronchodilator (BD) airflow limitation ($FEV_1/FVC<0.70$) on initial spirometry in 2004–2006. In this group, we tested whether the percentage of emphysema-like lung (voxels <-950 HU (Hounsfield units), or 'percent emphysema') on cardiac CT at cohort baseline (2000–2002) was associated with incident airflow limitation on pre-BD and post-BD spirometry in 2010–2012. Methods for MESA, statistical analyses, and selection and characteristics of participants are described in detail in the online supplementary tables S1–S4 and figure S1.

RESULTS

Mean age was 58.4 years at baseline, 54.0% were female, and 75.5% were

table S5). There was no evidence of effect measure modification by age, sex or race/ethnicity ($p>0.2$).

Sensitivity analyses

Results were similar in never smokers and ever smokers, and multiplicative interaction terms with smoking status were not statistically significant (see online supplementary table S6). Among ever smokers with 30+ pack-years, per cent emphysema was associated with adjusted ORs of 2.98 (per SD, 95% CI 1.63 to 5.41) and 5.45 (per SD, 95% CI 1.59 to 18.69) for incident pre-BD and post-BD airflow limitation, respectively.

Associations were not substantially altered by adjustment for education, site, self-reported emphysema and asthma, second-hand smoke, exposure to fumes, coronary artery calcium score, initial FEV_1/FVC, or fine particulate matter, nor

- From US general population cohort (MESA)
- 2045 participants without initial preBD airflow limitation
- Non-smoker : 50%
- 5yr F/U

Table 1 Emphysema-like lung on CT and incidence of airflow limitation at 5-year follow-up

Model*	Cases/at risk	Per cent emphysema>upper limit of normal (dichotomous)† OR (95% CI)‡	p Value	Per cent emphysema log transformed (continuous) OR per SD (95% CI)‡	p Value
Incident prebronchodilator airflow limitation§	224/2045				
Unadjusted		1.86 (1.12 to 3.09)	0.016	1.64 (1.39to 1.94)	<0.001
Minimally adjusted		2.07 (1.22 to 3.51)	0.007	1.48 (1.23 to 1.77)	<0.001
+age, sex, race/ethnicity					
Fully adjusted		2.62 (1.47 to 4.67)	0.001	1.92 (1.55 to 2.38)	<0.001
+height, weight, CT scanner, smoking history, initial FEV_1					
Extended		2.41 (1.32 to 4.40)	0.004	1.61 (1.28 to 2.03)	<0.001
+initial FEV_1/FVC					
Incident postbronchodilator airflow limitation§	53/1915				
Unadjusted		2.47 (1.03 to 5.94)	0.043	1.91 (1.35 to 2.69)	<0.001
Minimally adjusted		2.56 (1.05 to 6.25)	0.040	1.79 (1.23 to 2.60)	0.003
+age, sex, race/ethnicity					
Fully adjusted		4.38 (1.63 to 11.74)	0.003	2.59 (1.65 to 4.08)	<0.001
+height, weight, CT scanner, smoking history, initial FEV_1					
Extended		4.63 (1.71 to 12.53)	0.003	2.36 (1.47 to 3.79)	<0.001
+initial FEV_1/FVC					

*Logistic regression models were sequentially adjusted. The minimally adjusted model includes study baseline age, sex and race/ethnicity. The fully adjusted model additionally includes height, weight, CT type, smoking status, pack-years, urinary cotinine and FEV_1 per cent predicted at the initial spirometry exam. The extended model also includes initial

11%

- Emphysema was independent risk factor for incidence of airflow limitation among general population

Mortality by Level of Emphysema and Airway Wall Thickness

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Rationale: There is limited knowledge of the prognostic value of quantitative computed tomography (CT) measures of emphysema and airway wall thickness (AWT) on mortality.
Objectives: To examine 8-year mortality in relation to CT-measured emphysema and AWT, and assess if potential impact of these predictors remained after adjustment for lung function.
Methods: In the Norwegian GenKOLS study of 2003–2005, 947 ever-smokers (49% with COPD) aged 40–85 years performed spirometry and CT examination. Mortality data from 2003–2011 were gathered from the Norwegian Cause of Death Registry. CT emphysema % low-attenuation areas (%LAA) and standardized measure for AWT (AWT-Pi10) were main predictors. We performed Laplace regression for survival

AT A GLANCE COMMENTARY

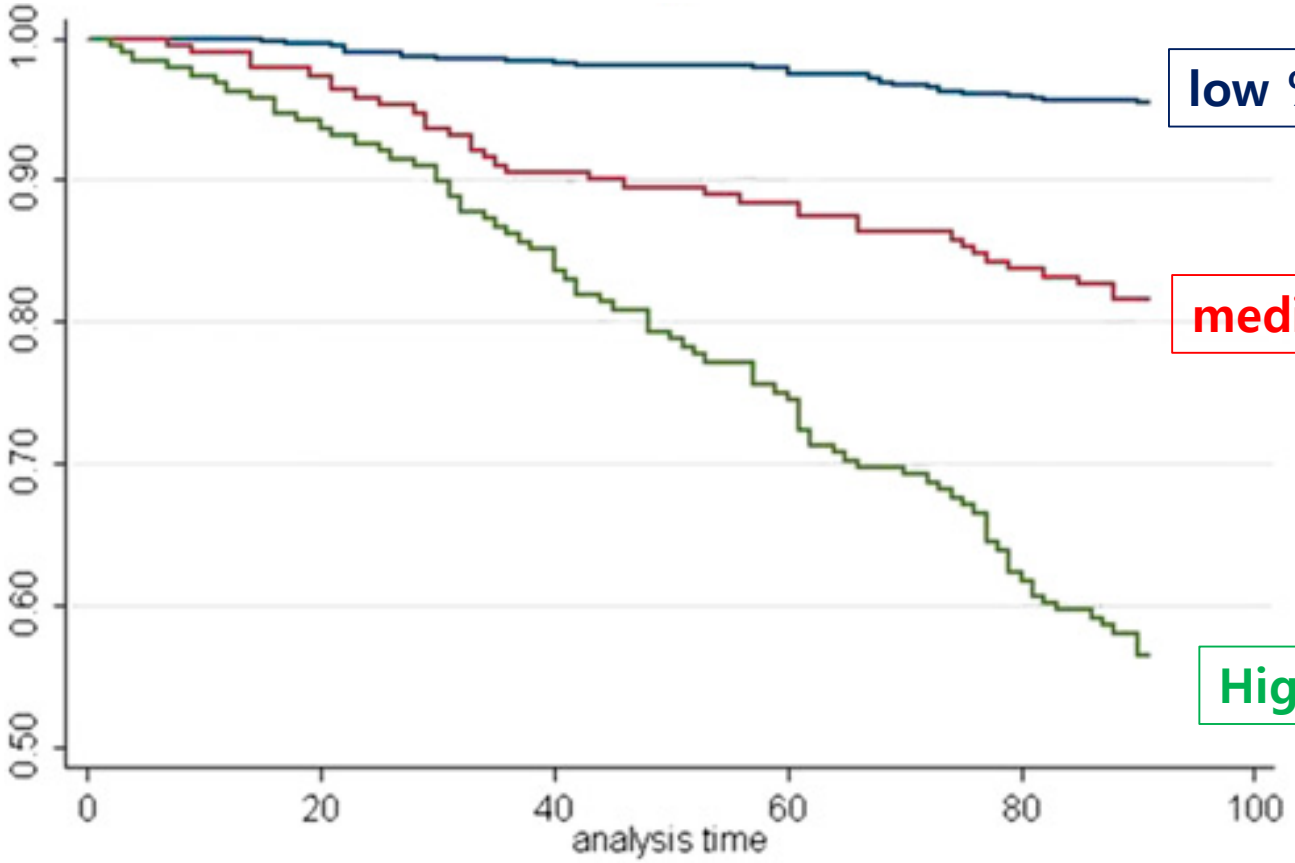
Scientific Knowledge on the Subject

Chest computed tomography makes it group patients with chronic obstructive pu (COPD) into predominantly emphysema disease phenotypes. So far, however, mo COPD are assessed through spirometry al available as to how level and distributio predicts mortality in subjects with modera

- From Norwegian community-based cohort (GenKOLS)
- 462 COPD cases and 485 subjects without COPD examined with a quantitative CT scan
- Ever smokers (≥ 2.5PY)
- 8 year mortality

Emphysema predicts all-cause mortality

- **ALL CAUSE MORTALITY**



Am J Respir Crit Care Med 2013;187:602–608

CHARACTERISTICS OF SYMPTOMATIC, UNOBSTRUCTED INDIVIDUALS

Original Investigation

Clinical and Radiologic Disease in Smokers With Normal Spirometry

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Regan EA et al. JAMA Intern.Med 2015; 175: 1539-49

Clinical Characteristics
COPDGene

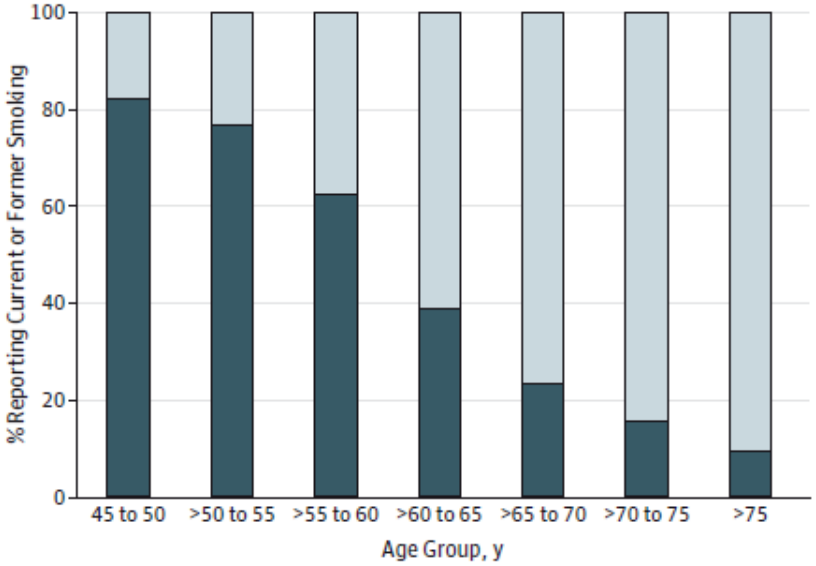
Table 3. Smokers With Symptoms or Impairments, Including Individuals With Self-reported Asthma

Variable	No. (%) Never Smokers (n = 108)	GOLD 0 (n = 4388)	GOLD 1 (n = 794)
Individual Scores			
Chronic bronchitis, by criteria	0	552 (12.6)	125 (15.7)
History of ≥1 severe exacerbation	0	190 (4.3)	39 (4.9)
St George's Respiratory Questionnaire total score >25	4 (3.7)	1143 (26.0)	226 (28.5)
Six-minute walk distance <350 m	4 (3.7)	674 (15.4)	109 (13.7)
Modified Medical Research Council dyspnea score ≥2	4 (3.7)	1029 (23.5)	175 (22.0)
Emphysema >5%	9 (8.3)	428 (9.8)	273 (34.4)
Gas trapping >20%	11 (10.2)	536 (12.2)	319 (40.2)
Sums			
Any impairment	26 (24.1)	2375 (54.1)	585 (73.7)
6 Impairments	0	8 (0.2)	6 (0.8)
5 Impairments	0	32 (0.7)	17 (2.1)
4 Impairments	0	156 (3.6)	65 (8.2)
3 Impairments	1 (0.9)	414 (9.4)	92 (11.6)
2 Impairments	4 (3.7)	690 (15.7)	204 (25.7)
1 Impairment	21 (19.4)	1089 (24.8)	201 (25.3)
No impairment	82 (75.9)	1990 (45.4)	209 (26.3)

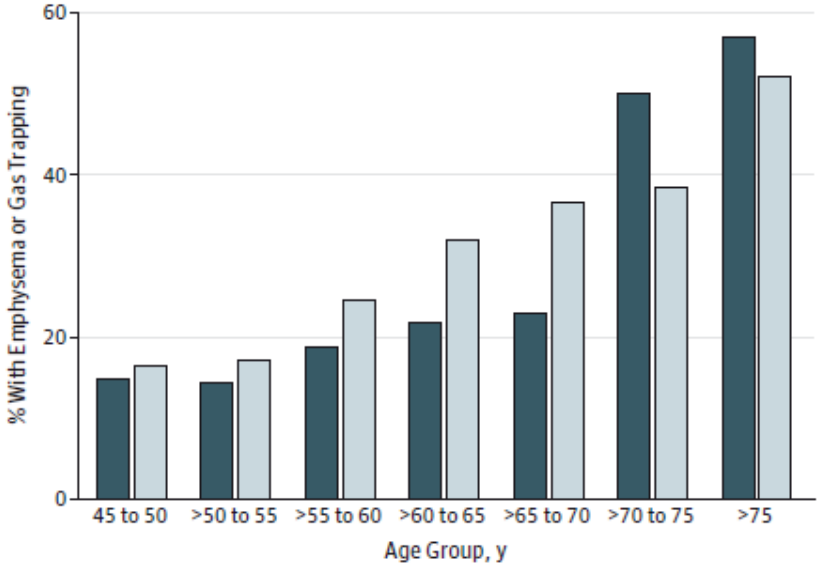
Radiographic Characteristics in GOLD 0 COPDGene

42.3%(127 of 300) of the GOLD 0 group had CT evidence of emphysema or airway thickening.

Current or Former Smoking Status



Emphysema and Gas trapping for each patient



Current smoker

Former smoker

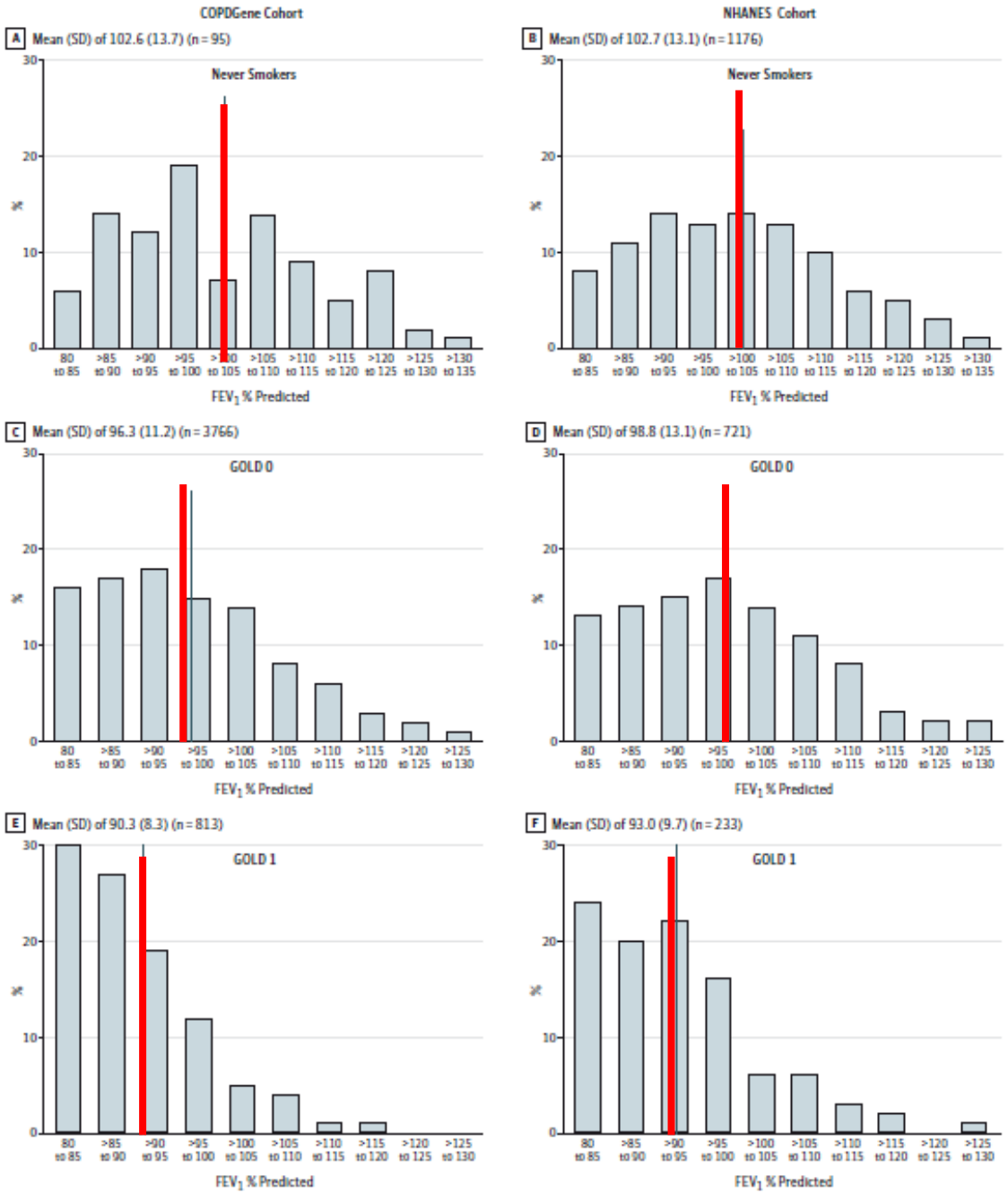
Mean FE

Never Smoker

Gold 0

Gold 1

Figure 2. Evidence of Occult Obstructive Disease in the Global Initiative for Obstructive Lung Disease (GOLD) 0 Group



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 12, 2016 VOL. 374 NO. 19

Clinical Significance of Symptoms in Smokers with Preserved Pulmonary Function

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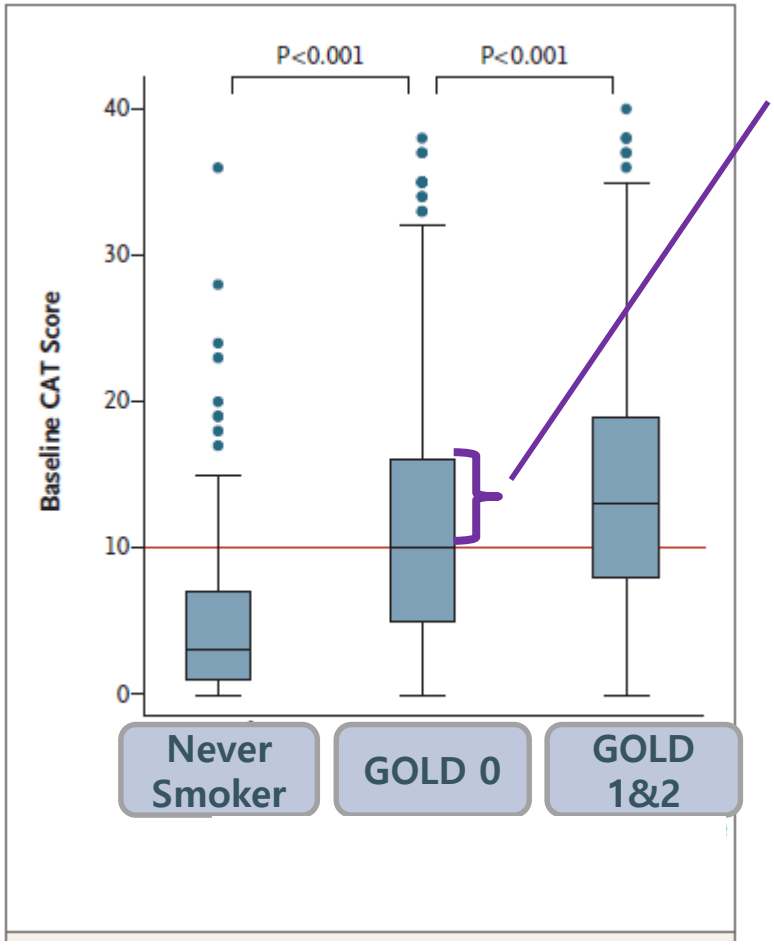
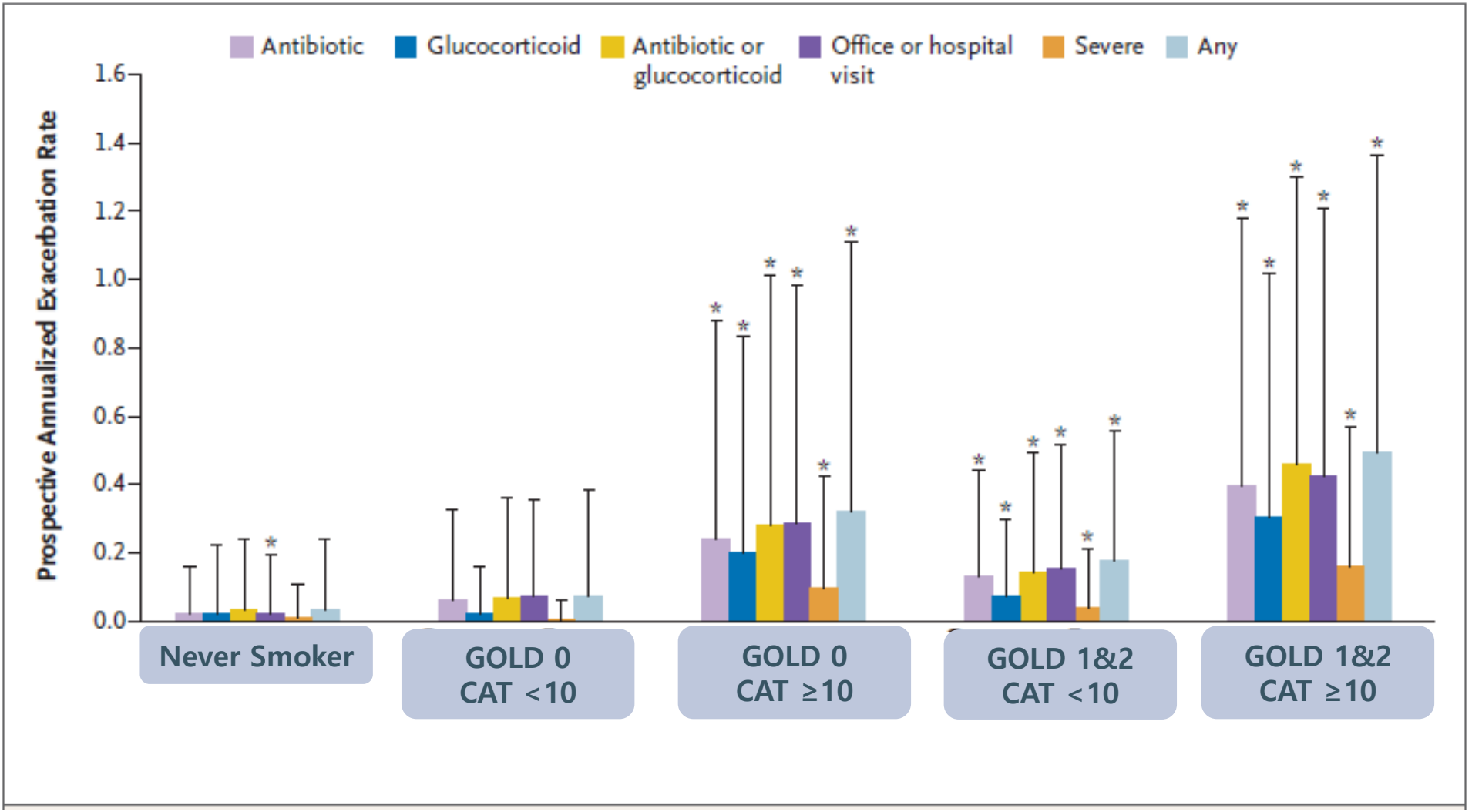
Prevalence of Respiratory Symptoms, According to Study Group



Smokers with Preserved lung function **AND ≥CAT 10**

- respiratory exacerbations,
- shorter 6MWD
- Evidence of occult airway disease (e.g., FEV1↓, FVC↓, and inspiratory capacity↓)
- airway wall thickening

Prospective Annualized Exacerbation Rate



Association between Functional Small Airway Disease and FEV_1 Decline in Chronic Obstructive Pulmonary Disease

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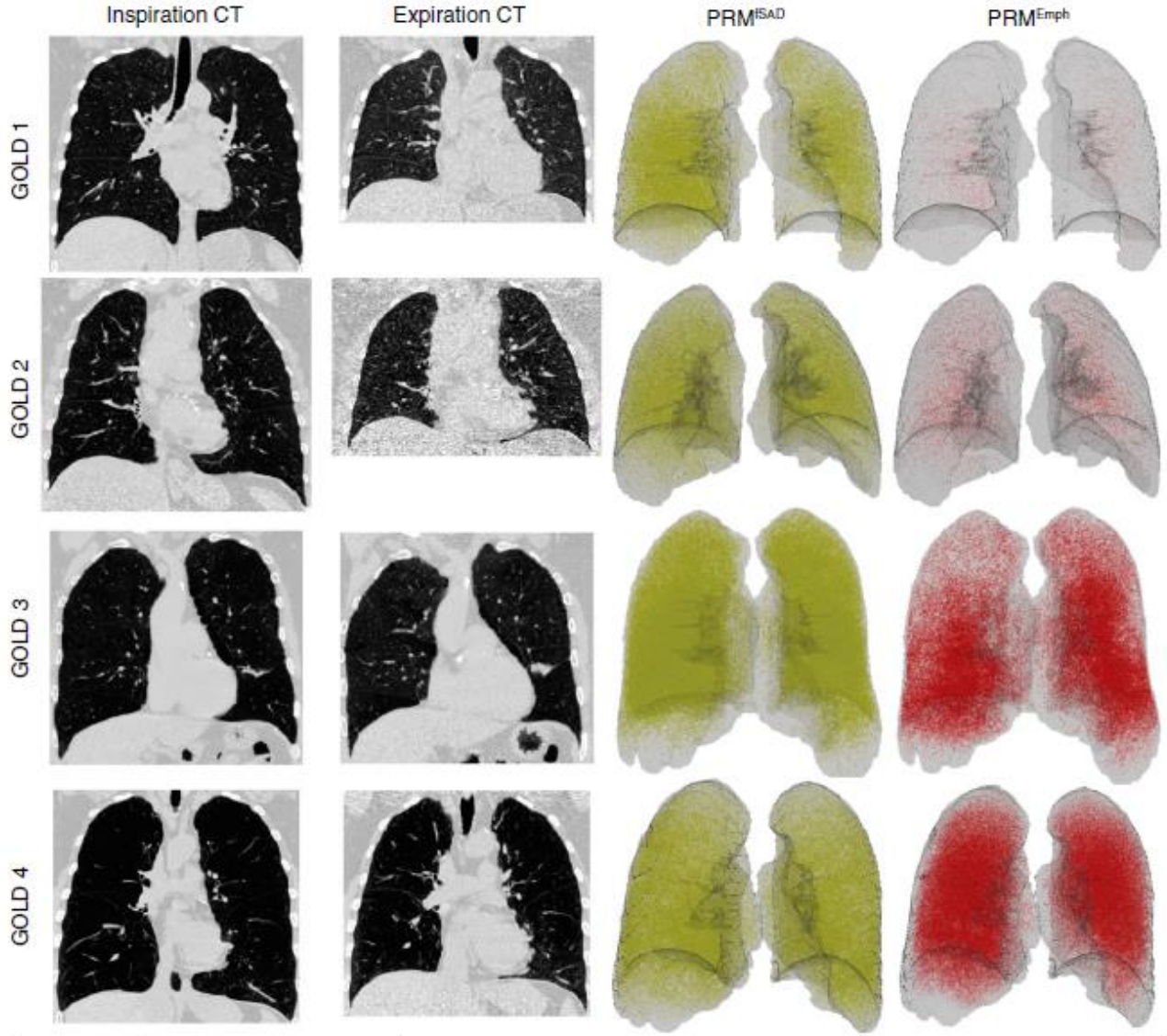

	PRM Normal (%)	PRM Functional Small Airways Disease (%)	PRM Emphysema (%)
GOLD 1	78.8	18.5	0.8
GOLD 2	44.9	41.6	7.0
GOLD 3	28.8	40.8	25.1
GOLD 4	21.8	26.9	43.2

Total number of subjects (*N* = *1,508*)	GOLD Spirometry Grade				
	0 (*n* = *751*)	1 (*n* = *150*)	2 (*n* = *356*)	3 (*n* = *192*)	4 (*n* = *59*)
Age, yr	58.2 (8.6)	63.8 (8.1)	63.3 (8.4)	64.1 (7.9)	62.8 (7.6)
Sex, n (% female)	395 (52.6)	66 (44.0)	161 (45.2)	87 (45.3)	29 (49.2)
Race, n (% African American)	245 (32.6)	28 (18.7)	79 (22.2)	36 (18.8)	5 (8.5)
Height, cm	169.5 (9.2)	169.7 (10.1)	170.9 (9.3)	169.9 (10.3)	169.6 (9.0)
FEV_1, L	2.8 (0.7)	2.6 (0.7)	1.9 (0.5)	1.2 (0.3)	0.68 (0.2)
$FEV_{1\%}$ predicted	97.7 (11.4)	91.6 (8.6)	65.0 (8.3)	40.9 (5.9)	23.6 (4.1)
FVC, L	3.6 (0.9)	4.1 (1.0)	3.3 (0.9)	2.7 (0.8)	2.3 (0.6)
FVC % predicted	96.2 (11.3)	108.5 (11.2)	87.4 (13.4)	72.4 (12.8)	59.1 (11.6)
FEV_1/FVC	0.79 (0.1)	0.64 (0.04)	0.47 (0.08)	0.44 (0.09)	0.31 (0.05)
Smoking pack-years	37.2 (20.0)	40.0 (49.2)	37.9 (48.6)	55.4 (24.8)	57.8 (28.6)
Current smokers, n (%)	364 (48.5)	60 (40.0)	135 (37.9)	60 (31.3)	10 (16.9)
Bronchodilator reversibility, n (%)*	68 (9.1)	42 (28.0)	136 (38.2)	80 (41.7)	19 (32.2)
Exacerbations in the prior year	0.13 (0.49)	0.13 (0.37)	0.43 (0.95)	0.71 (1.15)	1.14 (1.50)
Follow-up time, mo	63.9 (4.5)	63.7 (4.2)	64.1 (4.2)	64.0 (4.1)	65.0 (5.1)
Emphysema, %LAA <−950 HU_{ins}	2.7 (3.0)	6.9 (6.4)	8.4 (8.4)	17.9 (12.6)	26.6 (13.6)
Gas trapping, %LAA <−856 H	11.8 (9.9)	23.4 (12.1)	29.9 (15.4)	48.7 (16.3)	60.9 (12.2)
PRM functional small airways	12.4 (9.7)	22.2 (10.7)	26.6 (11.6)	36.3 (10.0)	39.2 (9.9)
PRM emphysema, %	0.6 (1.4)	3.3 (4.4)	5.6 (7.4)	15.2 (12.9)	24.7 (14.7)

fSAD

Emph

Association Between Emphysema and Functional Small Air Way Disease On FEV_1 Decline

	PRM^{fSAD} fSAD	PRM^{emph} Emph
GOLD 0 (n = 751)		
Parameter estimate per 5% (ml/yr)	−2.2 (95% CI, −4.2 to −0.1; $P = 0.04$)	5.5 (95% CI, −8.0 to 19.1; $P = 0.42$)
Mean value CT metric (%)	12.4 (9.7)	0.6 (1.4)
GOLD 1–4 (n = 757)		
Parameter estimate per 5% (ml/yr)	−4.5 (95% CI, −6.3 to −2.6; $P < 0.001$)	−3.5 (95% CI, −5.6 to −1.4; $P = 0.001$)
Mean value CT metric (%)	29.2 (12.3)	9.1 (11.4)

Summary

- COPD is heterogenous and there are heterogeneous pathway to airflow limitation
- The concept that COPD is always progressive and worsens universally is not tenable
- Mild COPD seems to progress more rapidly
- Symptoms and emphysema in unobstructed smokers are associated with higher risk for the future development of airflow limitation