Redefining the diagnosis of COPD

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Financial Disclosure

- Consultant: AstraZeneca, Boehringer Ingelheim, Chiesi, Contrafect, Novartis, Roche-Genentech, GlaxoSmithKline, Merck, Verona, Mylan, Theravance, AbbVie, Kiniksa, BristolMyersSquibb, Galderma, Kamada, Pulmonx, Kinevant, Puretech

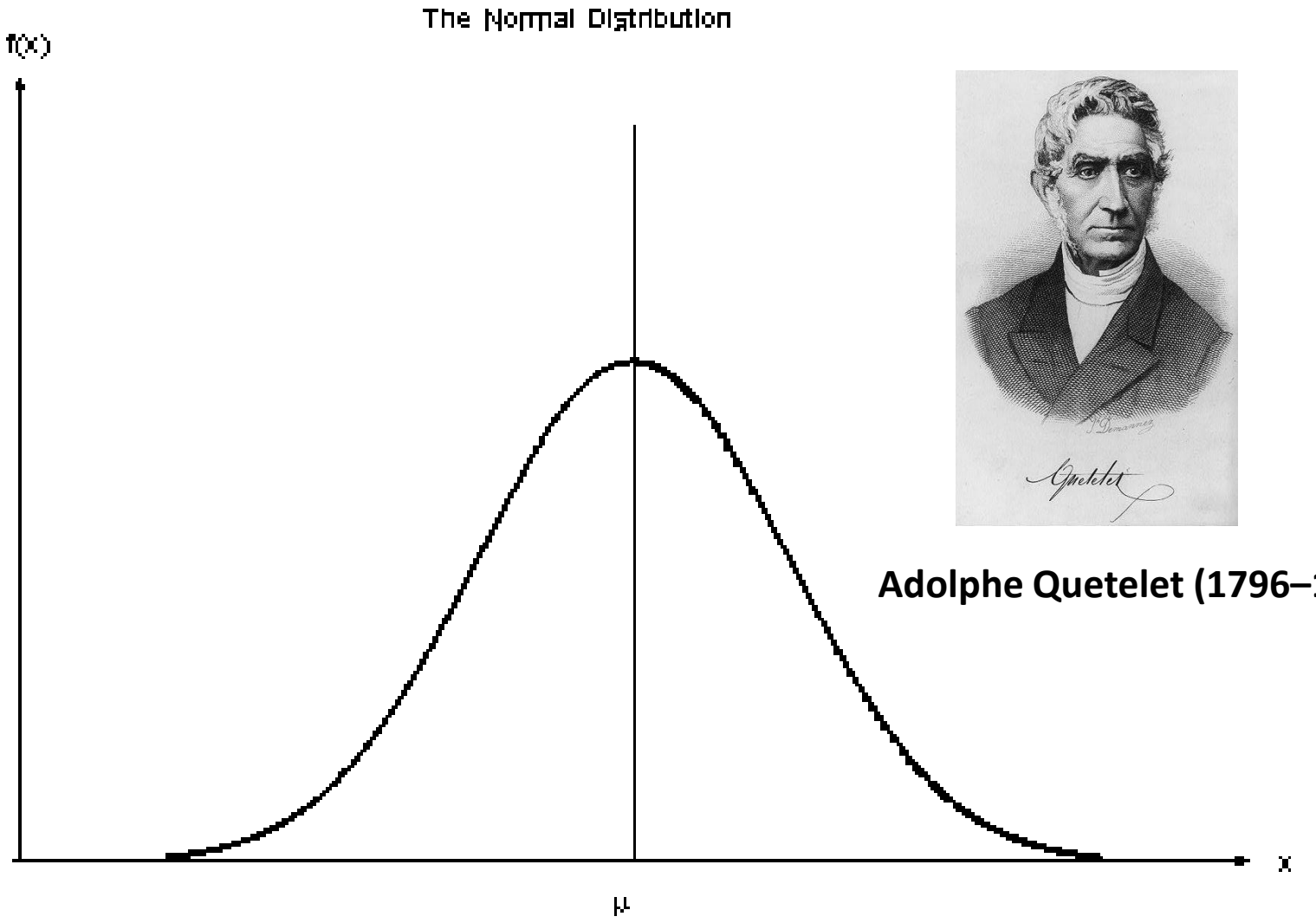
- Advisory Board Member: Arrowhead, Chimerix

- Research grants: AstraZeneca, Sanofi, Boehringer-Ingelheim, Verona

Learning objectives

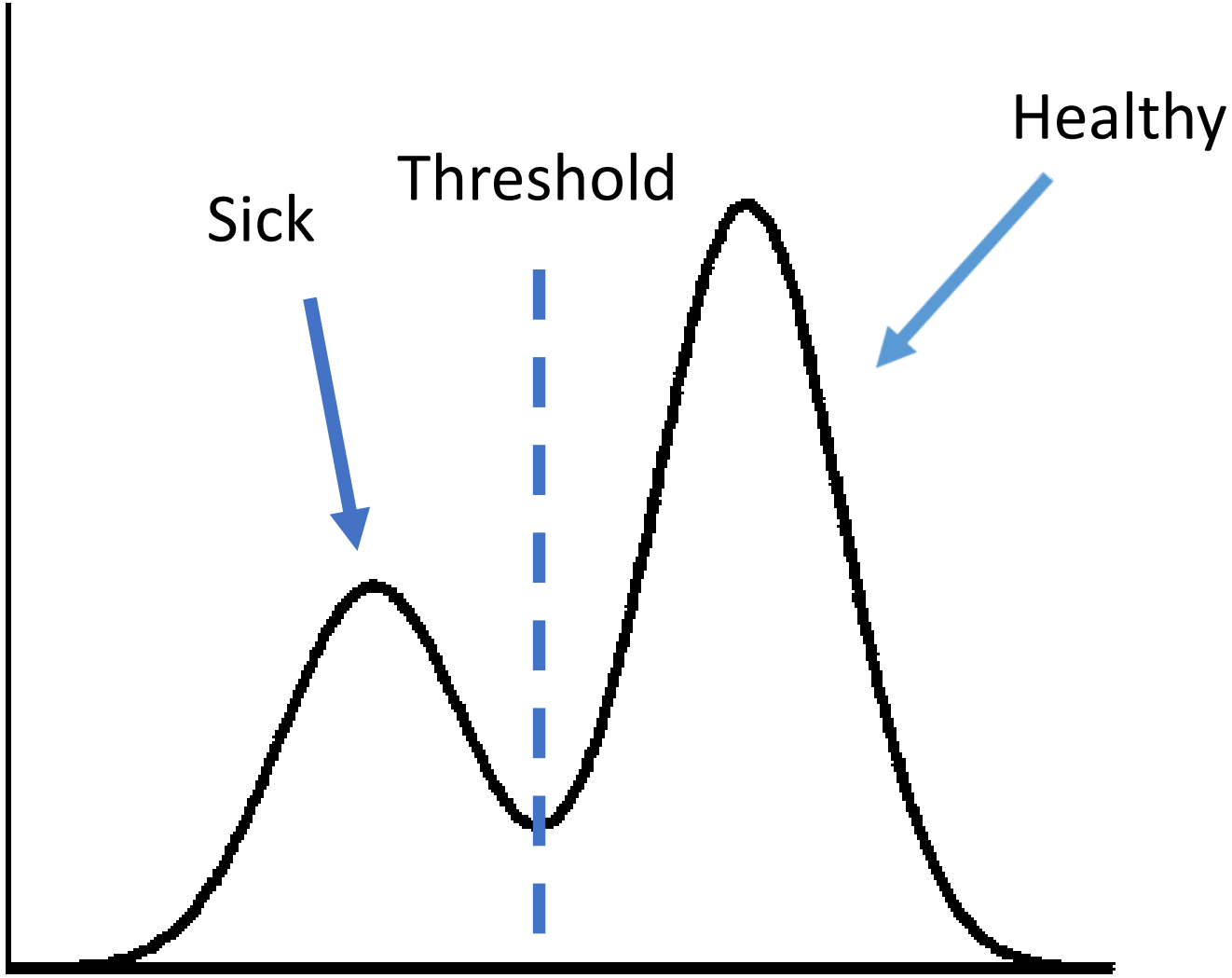
- After completion of this exercise, the participant should be able to distinguish subtypes of chronic lung disease that are not associated with airflow limitation.

Normal (Healthy) Population

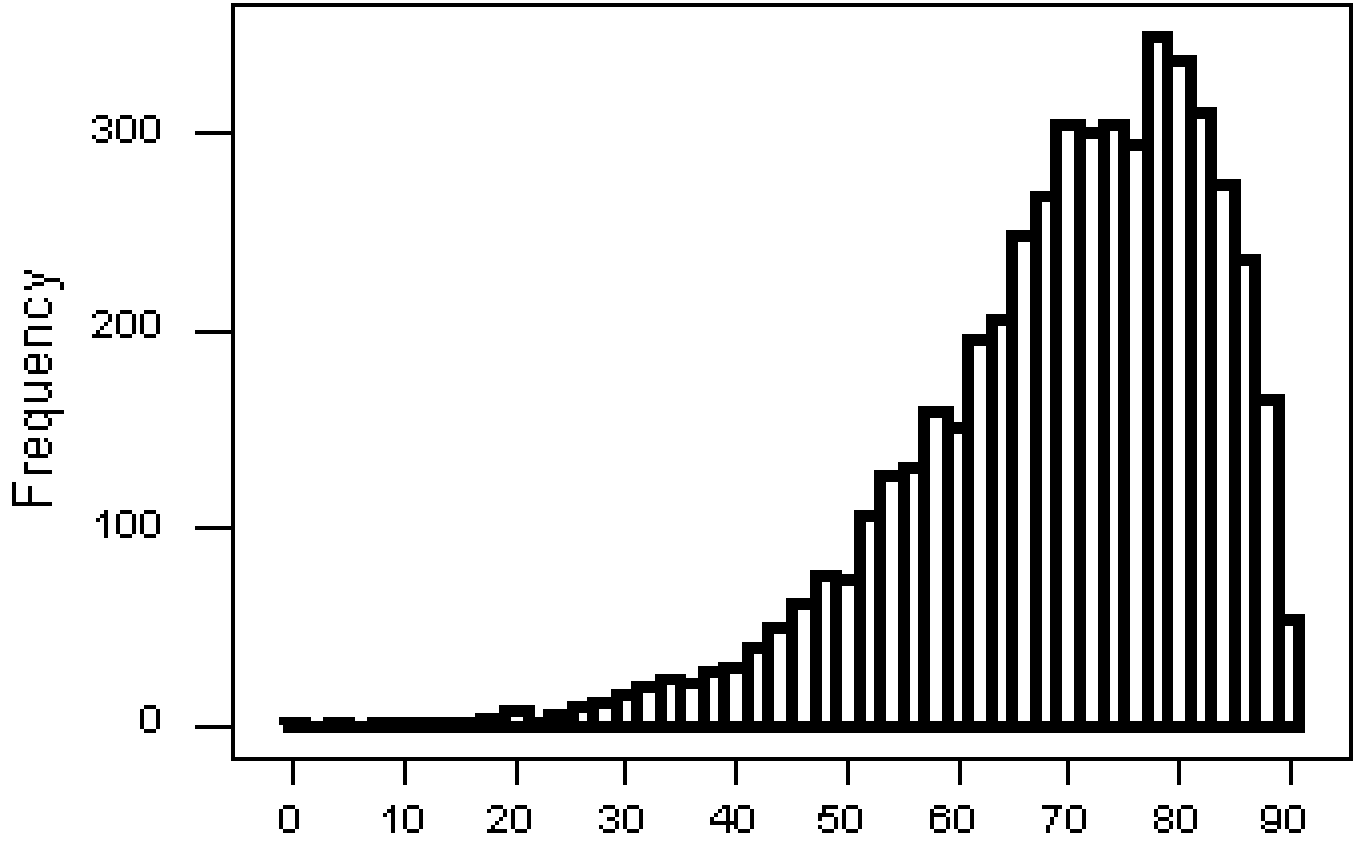


Adolphe Quetelet (1796–1874)

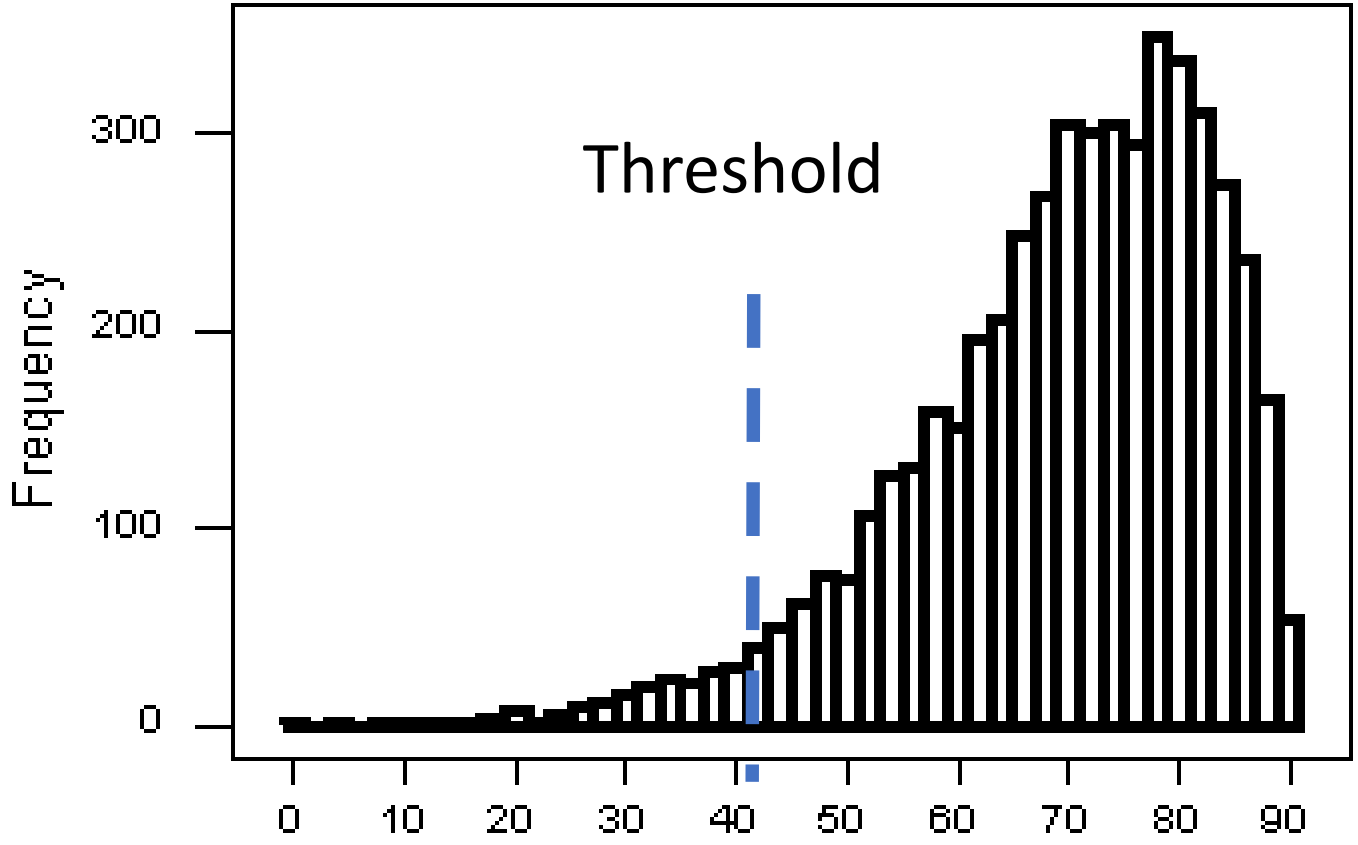
How we (doctors) view the world



How the world really is…



How the world really is. . .



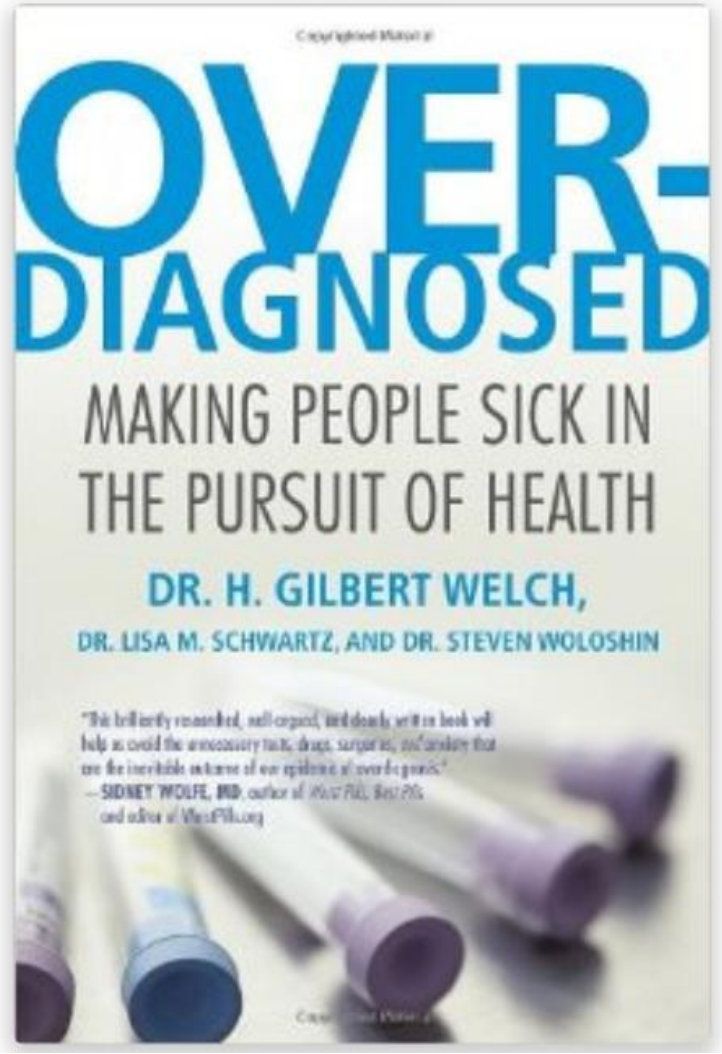
Six definitions of “normal” in common use

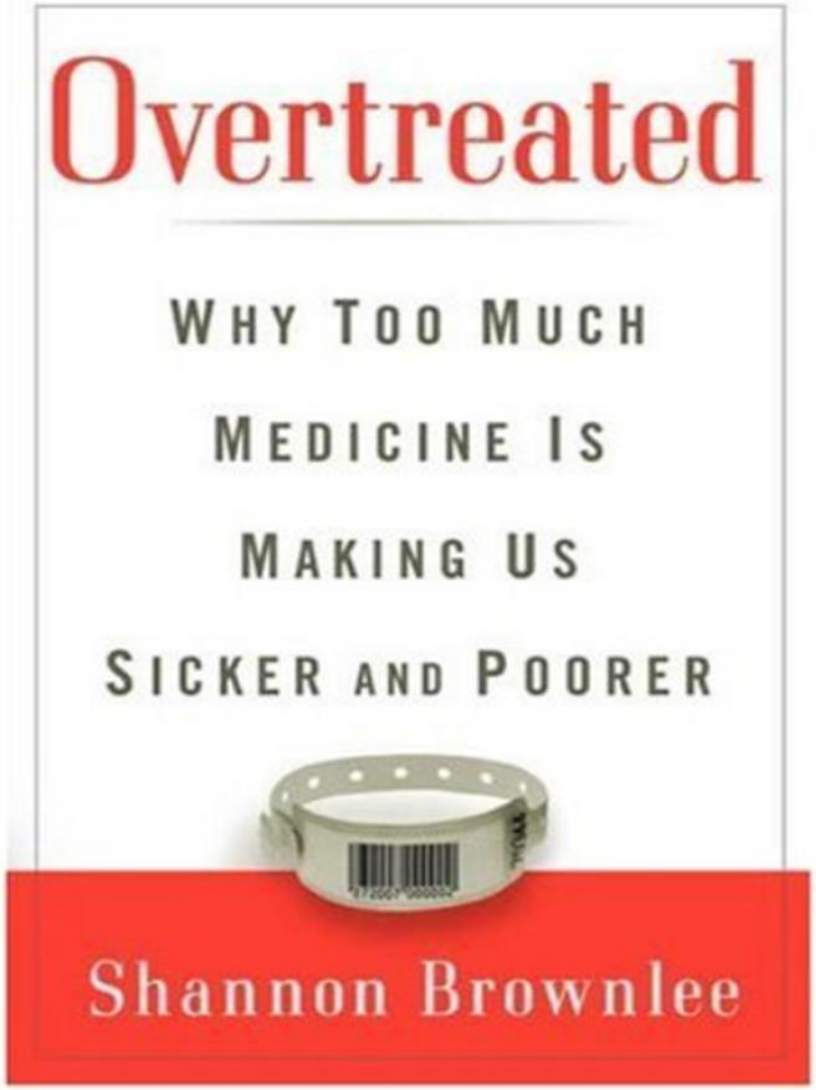
Property	Term
Distribution of diagnostic test results has a certain shape	Gaussian
Lies within a preset percentile of previous diagnostic test results	Percentile
Carries no additional risk of morbidity or mortality	Risk factor
Socially or politically aspired to	Culturally desirable
Range of test results beyond which a specific disease is, with known probability, present or absent	Diagnostic
Range of test results beyond which treatment does more good than harm	Therapeutic

Sackett DL, Haynes RB, Guyatt GH, Tigwell P. *Clinical epidemiology: a basic science for clinical medicine.Boston:Little, Brown:1991:59.*

Selection of threshold of “Sick”

- Approach #1: Selection of most accurate classification of health vs disease based on “Gold Standard”
  - Depends upon pre-test probability or prevalence of disease in population, Baye’s theorem
- Approach #2: Selection of classification based on maximization of benefit vs. harm of false classifications
  - Depends upon adverse effects of diagnosis and benefits and costs of treatment
- Approach #3: Arbitrary
  - Something that is easy to remember
  - Something that is not too hard to apply
  - Something that a group of experts agree on


OVER-DIAGNOSED
MAKING PEOPLE SICK IN THE PURSUIT OF HEALTH
DR. H. GILBERT WELCH,
DR. LISA M. SCHWARTZ, AND DR. STEVEN WOLOSHIN


Overtreated
WHY TOO MUCH MEDICINE IS MAKING US SICKER AND POORER
Shannon Brownlee

An epidemic of overdiagnosis

- Overdiagnosis and overtreatment are now major health problems
- Positive average results from trials can mask situations where many patients do not benefit
- Diagnostic tests need to measure clinically meaningful disease rather than positive vs. negative
- Changes to disease definitions do not evaluate harms of overdiagnosis and overtreatment
- Panels are often heavily conflicted

Moynihan R, Henry D, Moons KG. Using evidence to combat overdiagnosis and overtreatment: evaluating treatments, tests, and disease definitions in the time of too much. PLoS Med. 2014 Jul 1;11(7):e1001655.

Conflict of Interests or Confluence of Interests?

- Doctors want to make diagnoses and treat diseases
- Patients want explanatory diagnoses and prescriptions
- Pharmaceutical companies want to develop and market treatments
- Researchers want more funding for their disease targets

Where should we draw the line?

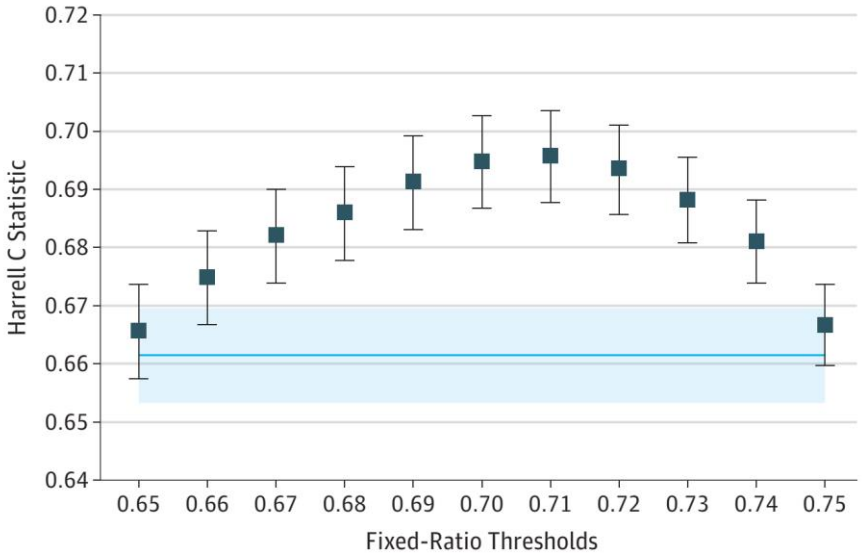
Research

JAMA | Original Investigation

Discriminative Accuracy of FEV_1:FVC Thresholds for COPD-Related Hospitalization and Mortality

Surya P. Bhatt, MD, MSPH; Pallavi P. Balte, PhD, MBBS; Joseph E. Schwartz, PhD; Patricia A. Cassano, PhD; David Couper, PhD; David R. Jacobs Jr, PhD; Ravi Kalhan, MD; George T. O'Connor, MD; Sachin Yende, MD; Jason L. Sanders, MD, PhD; Jason G. Umans, MD, PhD; Mark T. Dransfield, MD; Paulo H. Chaves, MD, PhD; Wendy B. White, PhD; Elizabeth C. Oelsner, MD, MPH

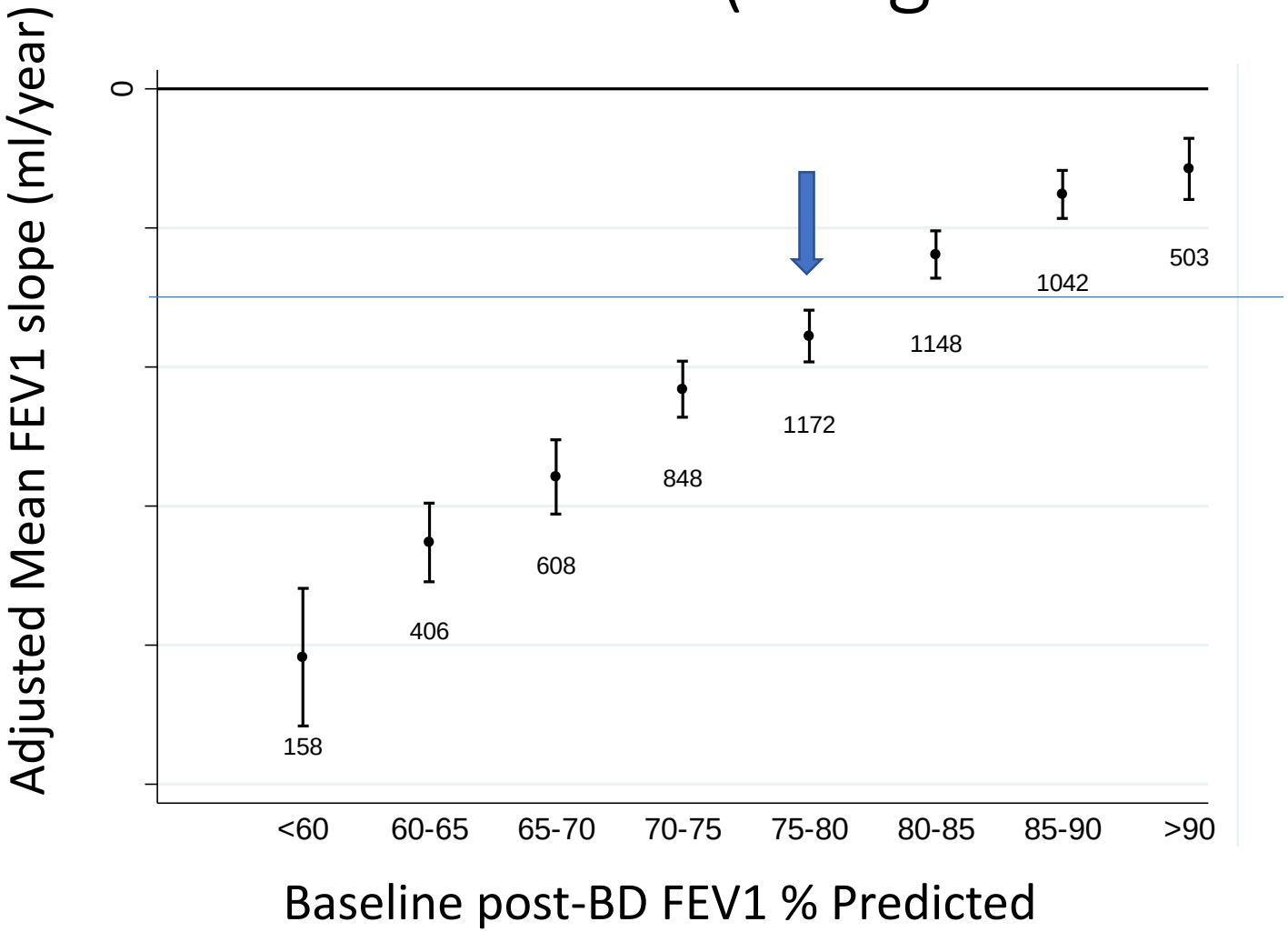
Figure 2. Discriminative Accuracy of Various Fixed FEV_1:FVC Thresholds for Airflow Obstruction With Respect to COPD-Related Hospitalization and Mortality



The C statistics (95% CI) for fixed-ratio thresholds (dots) were estimated separately in unadjusted Cox proportional hazards models that included only 1 dichotomous predictor (ie, whether a participant had a baseline ratio of forced expiratory volume in the first second to forced vital capacity [FEV_1:FVC] that was above or below a given ratio threshold). The C statistic for the lower-limit-of-normal (LLN) threshold is indicated by the solid blue horizontal line (95% CI indicated by blue shading). The optimal threshold based on highest C statistic was 0.71, but C statistics were not significantly different for 0.70 to 0.72. Fixed ratio thresholds 0.66 to 0.74 yielded C statistics that were significantly higher than the LLN threshold (*P* values <.05).

Bhatt SP, et al. Discriminative Accuracy of FEV1:FVC Thresholds for COPD-Related Hospitalization and Mortality. JAMA. 2019 Jun 25;321(24):2438-2447.

Smokers with normal baseline FEV1 do not have accelerated decline in FEV1 (Lung Health Study)



Drummond MB, Hansel NN, Connett JE, Scanlon PD, Tashkin DP, Wise RA. Spirometric predictors of lung function decline and mortality in early chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2012 ;185(12):1301-6.

Emphysema and progressive decline in FEV1

CT emphysema by PRM does not predict decline in FEV1 if there is no airflow obstruction (P = 0.42)

Table 2. Association between PRM Emphysema and fSAD on Change in FEV_1 ml/Year by Baseline GOLD Grade (Estimate, 95% CI, *P* Value)

	PRM^{fSAD}	PRM^{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)

Definition of abbreviations: CI = confidence interval; CT = computed tomography; fSAD = functional small airways disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease; PRM = parametric response mapping; PRM^{emph} = emphysema on parametric response mapping; PRM^{fSAD} = functional small airways disease on parametric response mapping.

Two separate models are shown in rows for the groups GOLD 0 and GOLD 1–4 subjects. Parameter estimates and mean values for respective CT metrics are shown. All models adjusted for age, race, sex, height, current smoking, smoking history in pack-years, baseline FEV_1, baseline FVC, bronchodilator reversibility, and scanner type.

Change in Emphysema in MESA Lung Study

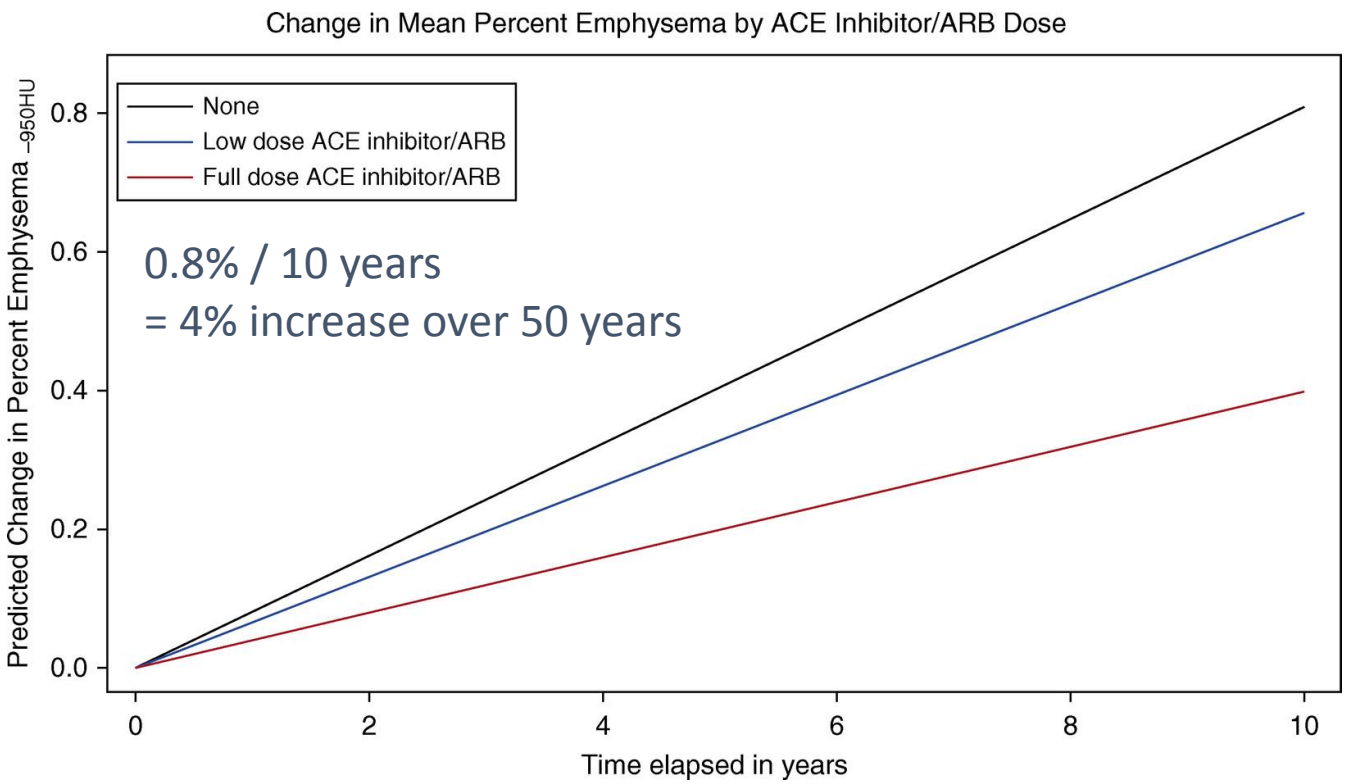
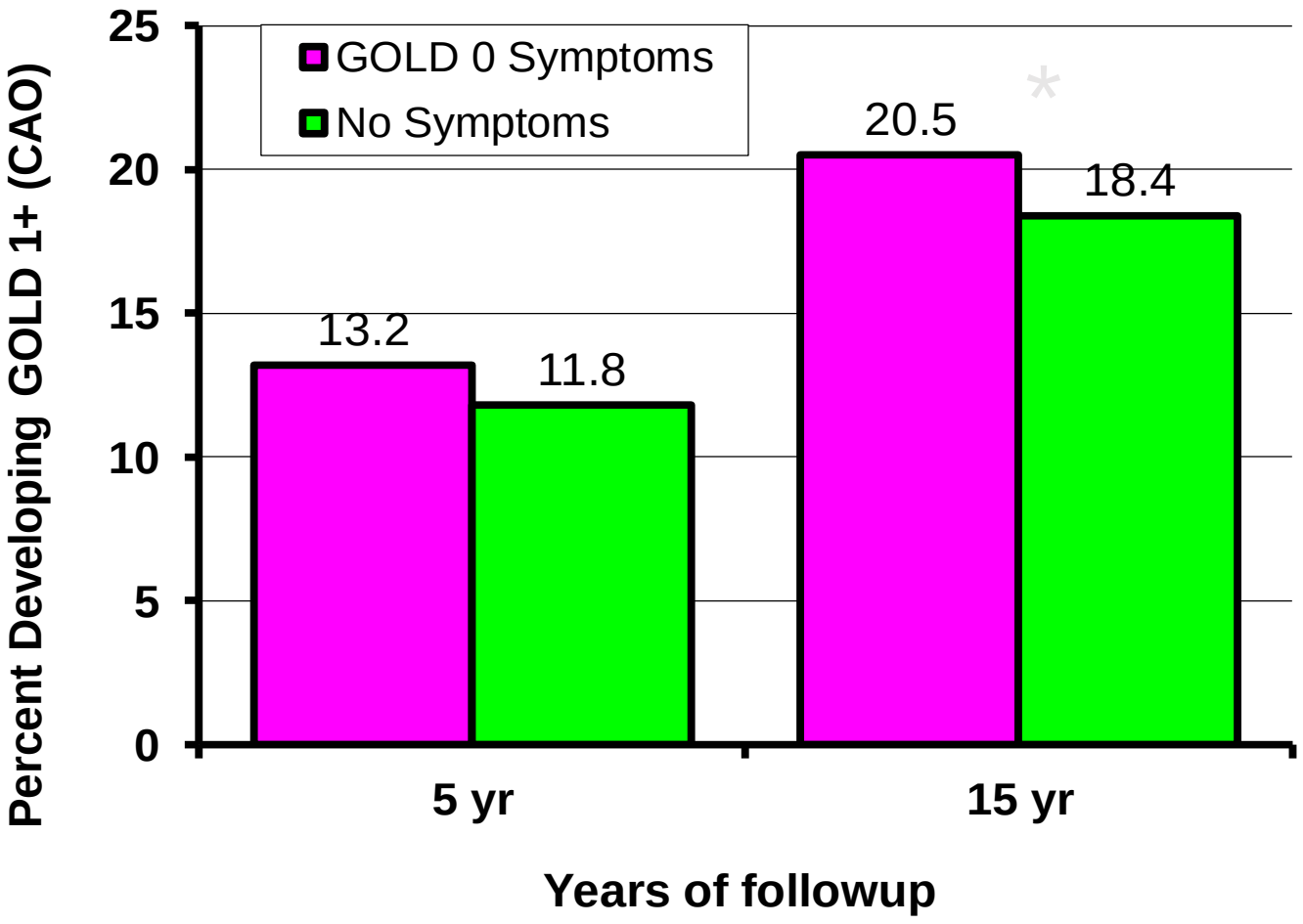


Figure 2. Predicted change in percent emphysema over time, by angiotensin-converting enzyme (ACE) inhibitor/angiotensin II receptor blocker (ARB) dose. Low dose is defined as daily intake less than 50% of the maximum recommended dose. Full dose is defined as daily intake of at least 50% of the maximum recommended dose. HU = Hounsfield units.

Published in: Megha A. Parikh; Carrie P. Aaron; Eric A. Hoffman; Joseph E. Schwartz; Jaime Madrigano; John H. M. Austin; Ravi Kalhan; Gina Lovasi; Karol Watson; Karen Hinckley Stukovsky; R. Graham Barr; *Annals ATS* 14649-658.

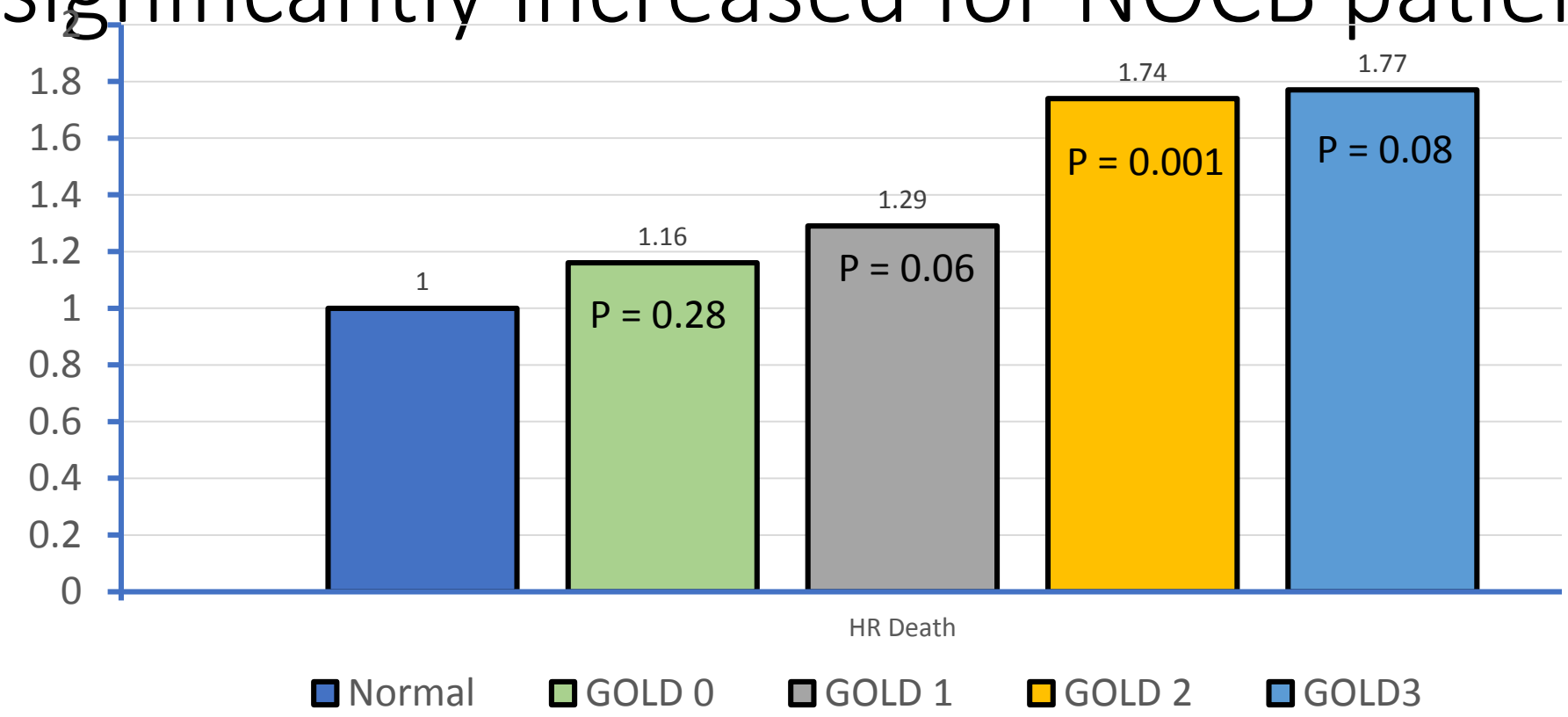
Does cough & phlegm predict smokers at risk for COPD if spirometry is normal?



Copenhagen City Study
16,000 general population
15 year follow-up

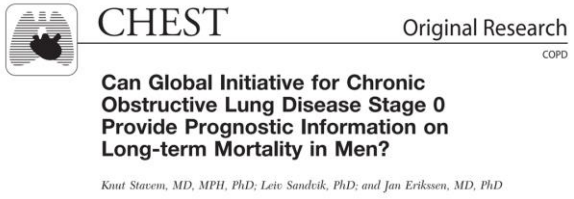
Vestbo & Lange. Can GOLD Stage 0 Provide Information of Prognostic Value in COPD? AJRCCM 166:329-332, 2002

Risk of death in 25 year follow up is <u>not</u> significantly increased for NOCB patients



n = 1,623 Men
Norway cohort
25 year followup
92.4% smokers
GOLD 0 = cough and phlegm with normal spirometry

Stavem K, Sandvik L, Erikssen J. Can global initiative for Chronic Obstructive Lung Disease stage 0 provide prognostic information on long-term mortality in men? Chest. 2006 Aug;130(2):318-25.


CHEST Original Research
COPD
Can Global Initiative for Chronic Obstructive Lung Disease Stage 0 Provide Prognostic Information on Long-term Mortality in Men?
Knut Stavem, MD, MPH, PhD; Leiv Sandvik, PhD; and Jan Erikssen, MD, PhD

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

Prescott G. Woo
David Couper, Ph
Richard E. Kanne
Stephen Rennar

Conclusion

Smokers with current respiratory symptoms are more likely to have future respiratory symptoms…

But the risk is small.

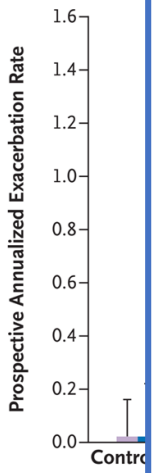


Figure 2. Prevalence of Symptoms and Risk of Respiratory Exacerbations, According to Study Group.
Prospective respiratory exacerbations were defined as respiratory events that were treated with antibiotics or oral glucocorticoids, those associated with health care utilization (office visit, emergency department visit, or hospitalization), those that were considered to be severe exacerbations (i.e., that led to an emergency department visit or hospitalization), or any exacerbation (any of the above). T bars indicate 1 SD. Asterisks indicate a P value of less than 0.05, with Bonferroni correction for multiple comparisons, for the comparison with current or former smokers with preserved pulmonary function and a CAT score of less than 10.

with

ars

rs

with

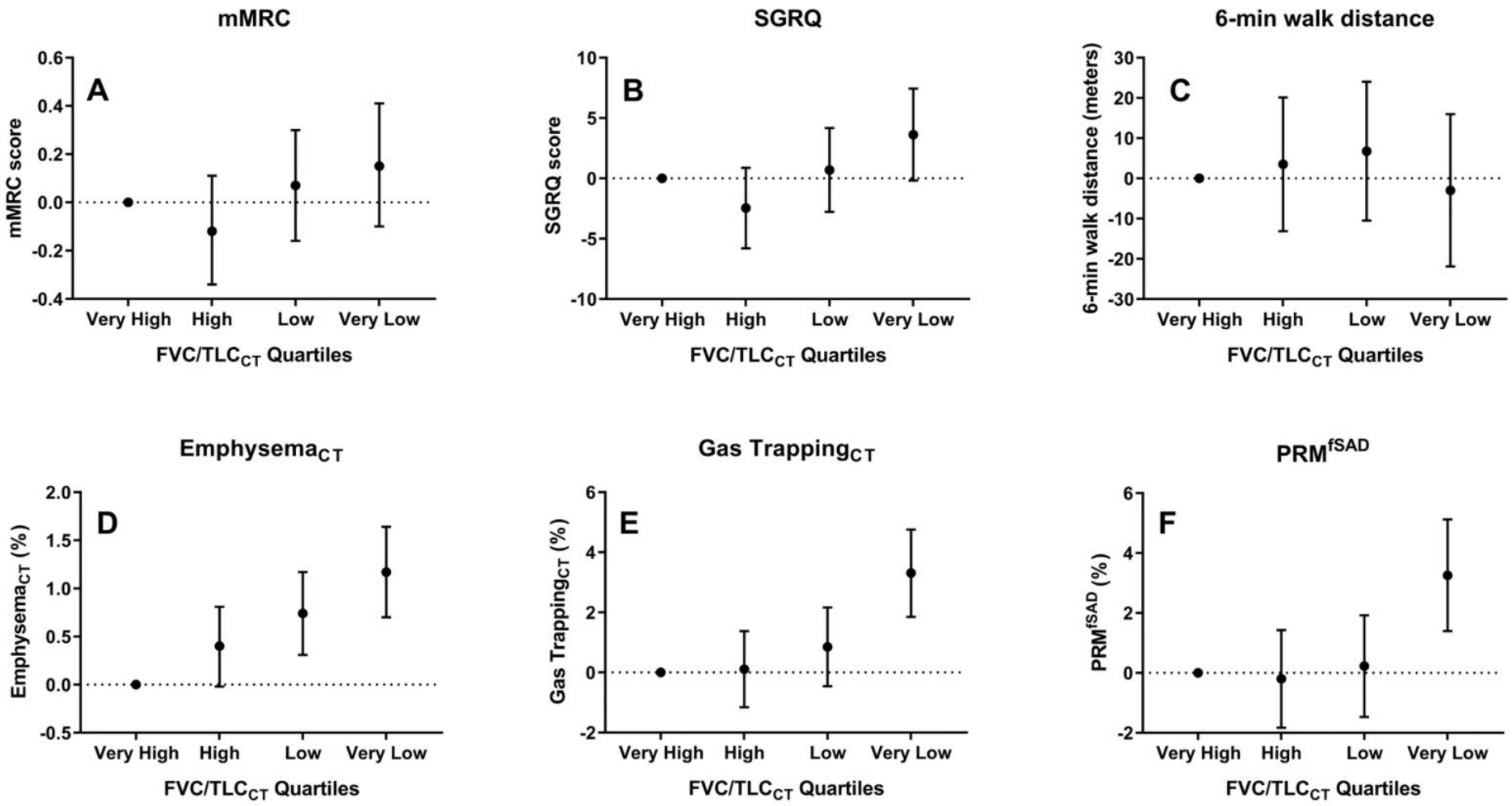
n 2.5 years

n 0.5 – 1 year

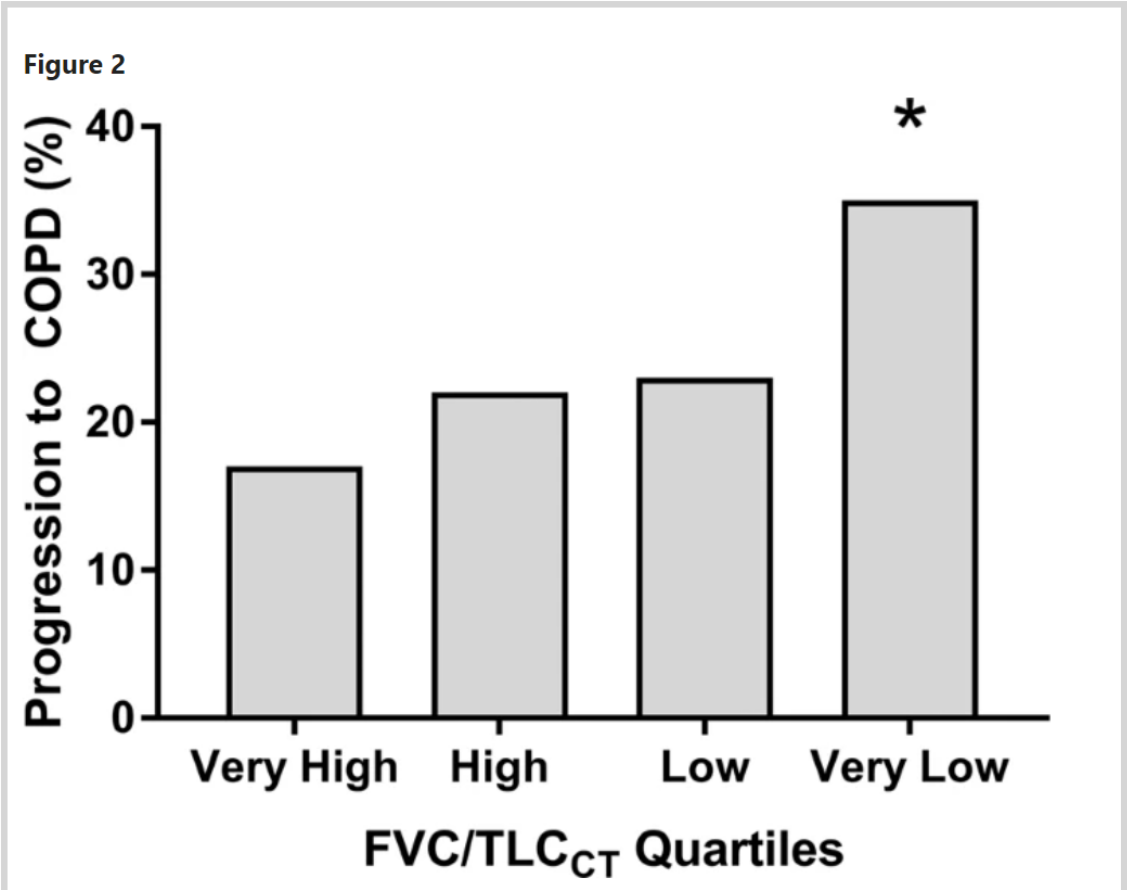
“Non-specific” PFT -- PRISm

- Low FVC with [presumed] normal TLC and FEV1/FVC
- Must have elevated RV
- Also known as:
  - Air trapping
  - Small airway disease
  - “Non-specific” PFT
  - Pseudo-restriction

Are people with “PRISm” sick?

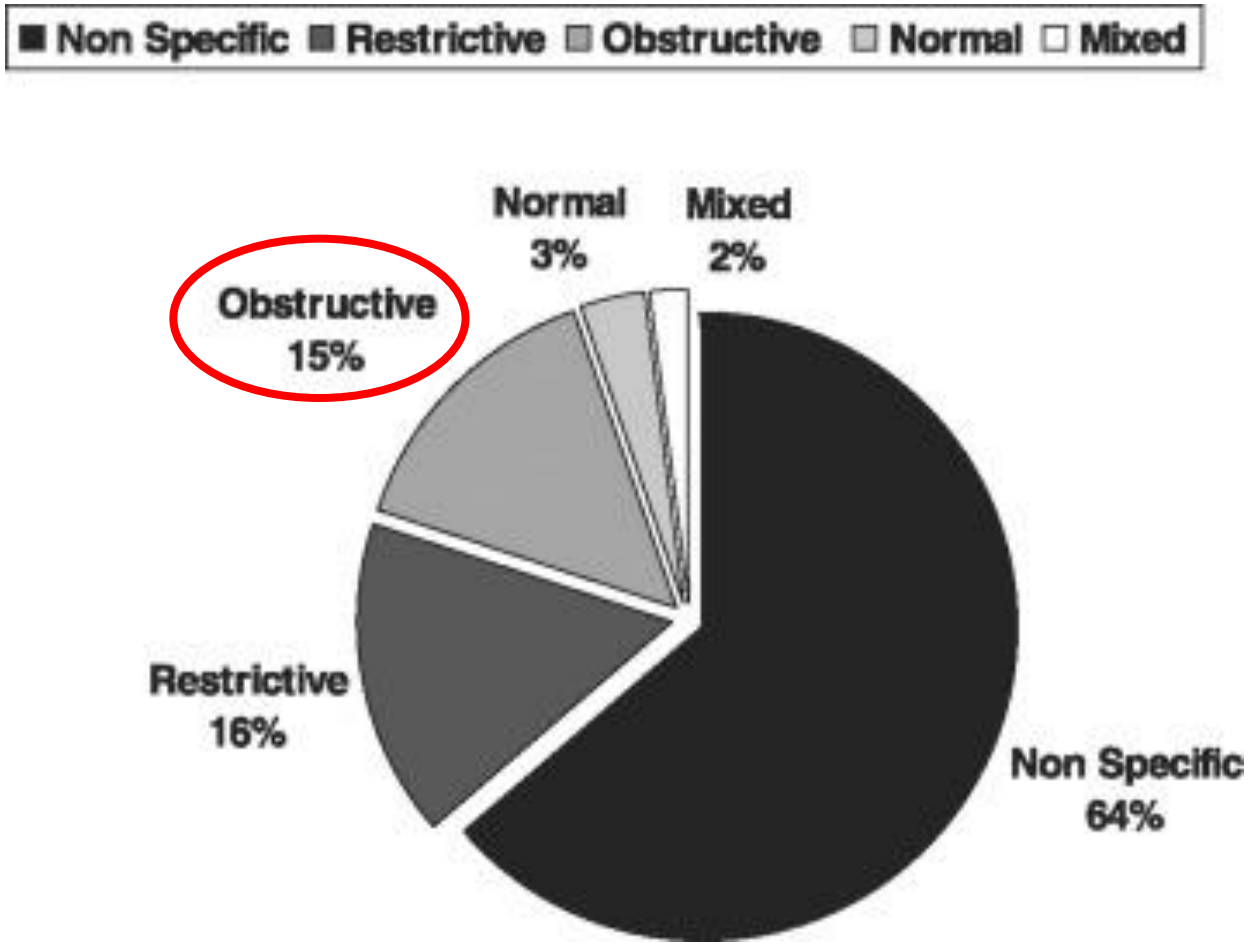


Some patients with PRISm do develop COPD but not many



Fortis, S., Comellas, A., Kim, V. et al. Low FVC/TLC in Preserved Ratio Impaired Spirometry (PRISm) is associated with features of and progression to obstructive lung disease. Sci Rep 10, 5169 (2020).

What happens to PRISm over ≥ 5 years



Conclusions: The NS pattern is a distinct and stable PF test pattern with roughly two-thirds of patients continuing to show this pattern on follow-up testing. Current interpretation guidelines erroneously label the NS pattern as representing obstruction and need to be changed to reflect these data.

N = 1284 patients with NS pattern

Iyer VN, Schroeder DR, Parker KO, Hyatt RE, Scanlon PD. The nonspecific pulmonary function test: longitudinal follow-up and outcomes. Chest. 2011 Apr;139(4):878-886.

Conclusions

- Our current definition of COPD based on airflow obstruction is robust and comprehensive
- Couth and phlegm in the absence of airflow obstruction does not predict significant morbidity in most patients.
- The presence of emphysema in the absence of airflow obstruction is not a significant predictor of decline in FEV1
- PRISm or non-specific PFT pattern is associated with air-trapping but does not predict development of airflow obstruction in most patients.

“Never ask a barber if you need a haircut.”

— Warren Buffett

Definition of GOLD 0

Medical Definition of **GOLD-0**

GOLD-0 is stage **0** in the **GOLD** classification of **COPD** and indicates "at risk" for **COPD**. **GOLD-0** is characterized by chronic cough and sputum production. Lung function, as measured by spirometry (a test of the air capacity of the lungs),is still normal.

Definition of GOLD-0 - MedicineNet

https://www.medicinenet.com/script/main/art.asp?articlekey=39634