Chronic Obstructive Pulmonary Disease (COPD)

COPD: Outline

- Definition
- Etiology
- Epidemiology
- Pathophysiology
- Clinical Presentation
- Diagnosis
- Prevention
- Treatment

COPD: Definition

Chronic airflow obstruction due to chronic bronchitis and/or pulmonary emphysema

COPD: Definition

Chronic airflow obstruction due to chronic bronchitis and/or pulmonary emphysema

COPD is a chronic disease

- Not acute airflow obstruction
  - Bronchitis/bronchiolitis
  - Asthma attack
- Not (completely) reversible
  - Asthma – reversible airflow obstruction

COPD: Definition

Chronic airflow obstruction due to chronic bronchitis and/or pulmonary emphysema

Airflow Obstruction

- Definition of airflow obstruction
  - $FEV_1/FVC < 0.70$
  - aka “obstructive ventilatory defect”
- Alternative definition
  - $FEV_1/FVC <$ “lower limit of normal”

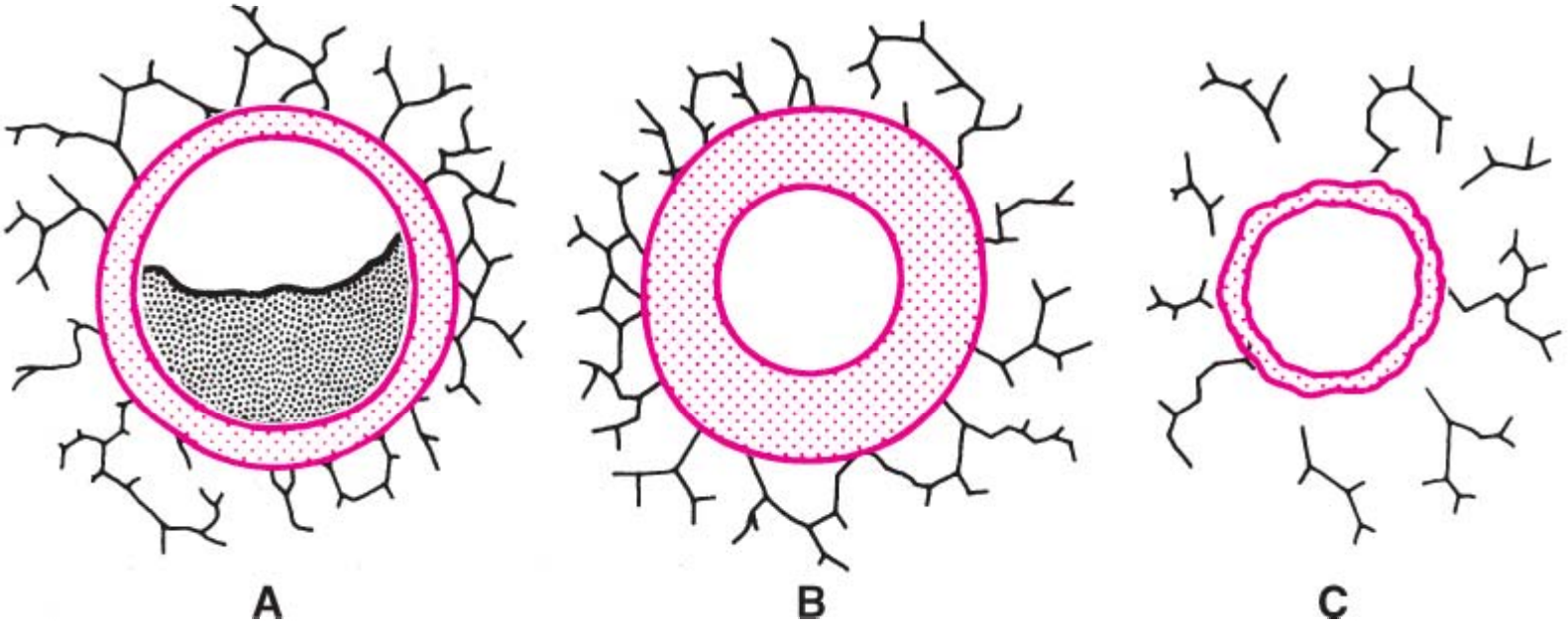
COPD: Definition

Chronic airflow obstruction due to chronic bronchitis and/or pulmonary emphysema

Chronic Bronchitis

- Definition
  - persistent cough and sputum production for at least three months in at least two consecutive years
- Submucosal gland hyperplasia
- Airway edema
- Mucus plugging and airways fibrosis

Types of Airflow Obstruction



Intraluminal:
e.g., Secretions

Intramural:
e.g., Edema

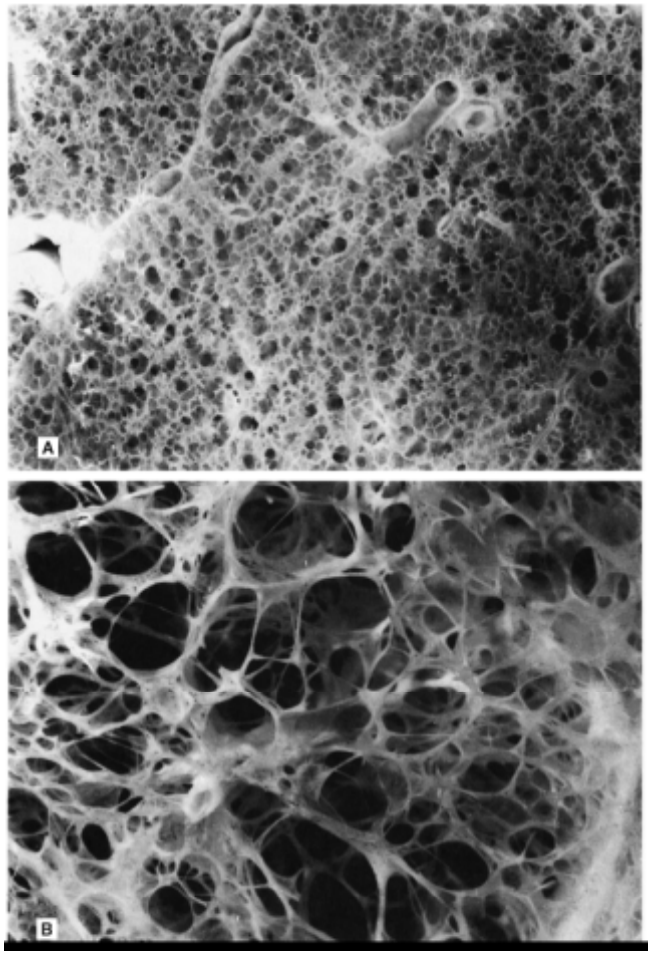
Extraluminal:
e.g., Loss of radial traction

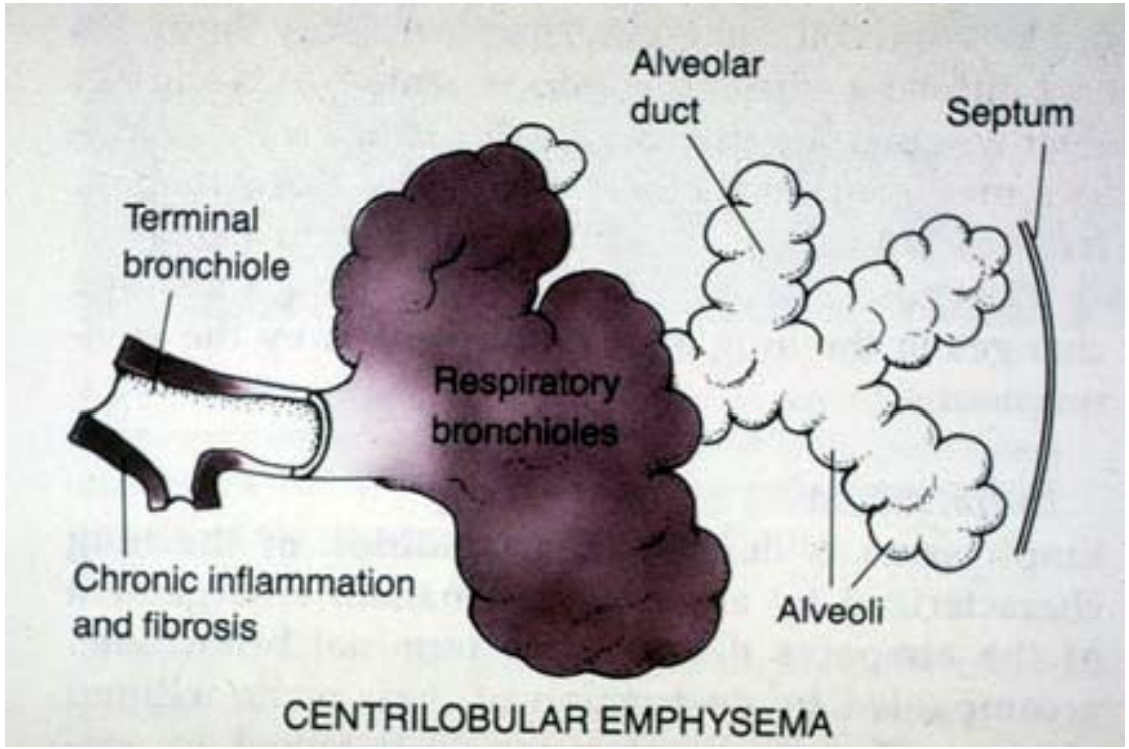
COPD: Definition

Chronic airflow obstruction due to chronic bronchitis and/or pulmonary emphysema

Pulmonary Emphysema

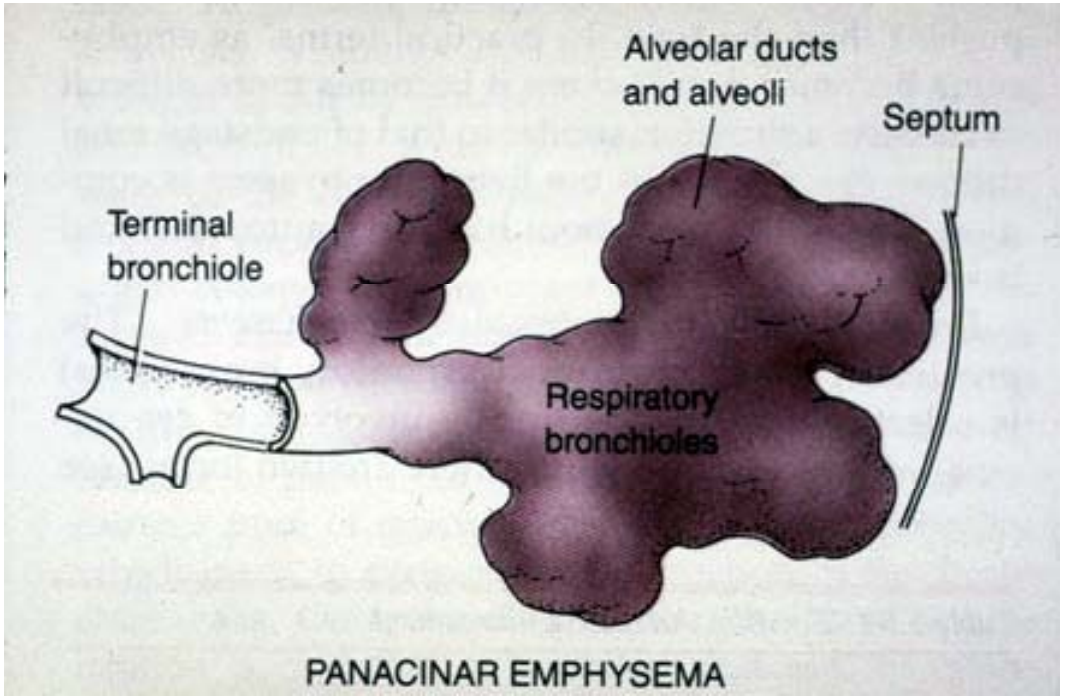
- Destruction of acinar walls
- Physiologic effects
  - Loss of radial traction on airways
  - Increased lung compliance
- Consequences
  - Hyperinflation
  - Poor lung mechanics





Centrilobular emphsyema
- Smoking-related
- Upper lobe predominant

Panlobular emphsyema
- alpha-1 antitrypsin deficiency
- Lower lobe (basilar) or diffuse



Causes of Airflow Obstruction

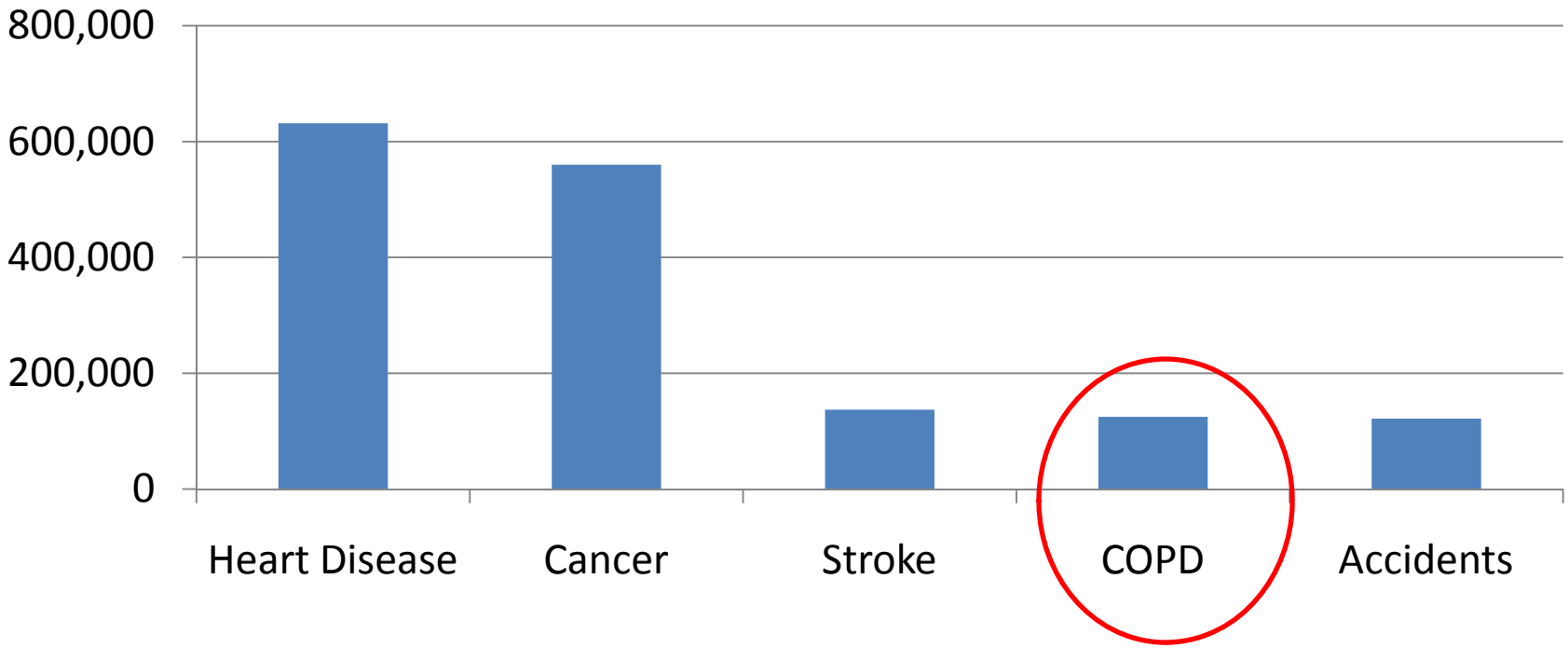
- Upper airway obstruction
- Lower airway obstruction
  - COPD
  - Asthma
  - Bronchiectasis (e.g., cystic fibrosis)
  - Large airway obstruction
    - Tumor, stenosis, foreign body aspiration, et al.
  - Bronchiolitis
  - Pulmonary edema
  - Carcinoid syndrome

COPD: Definition

Chronic airflow obstruction due to chronic bronchitis and/or pulmonary emphysema

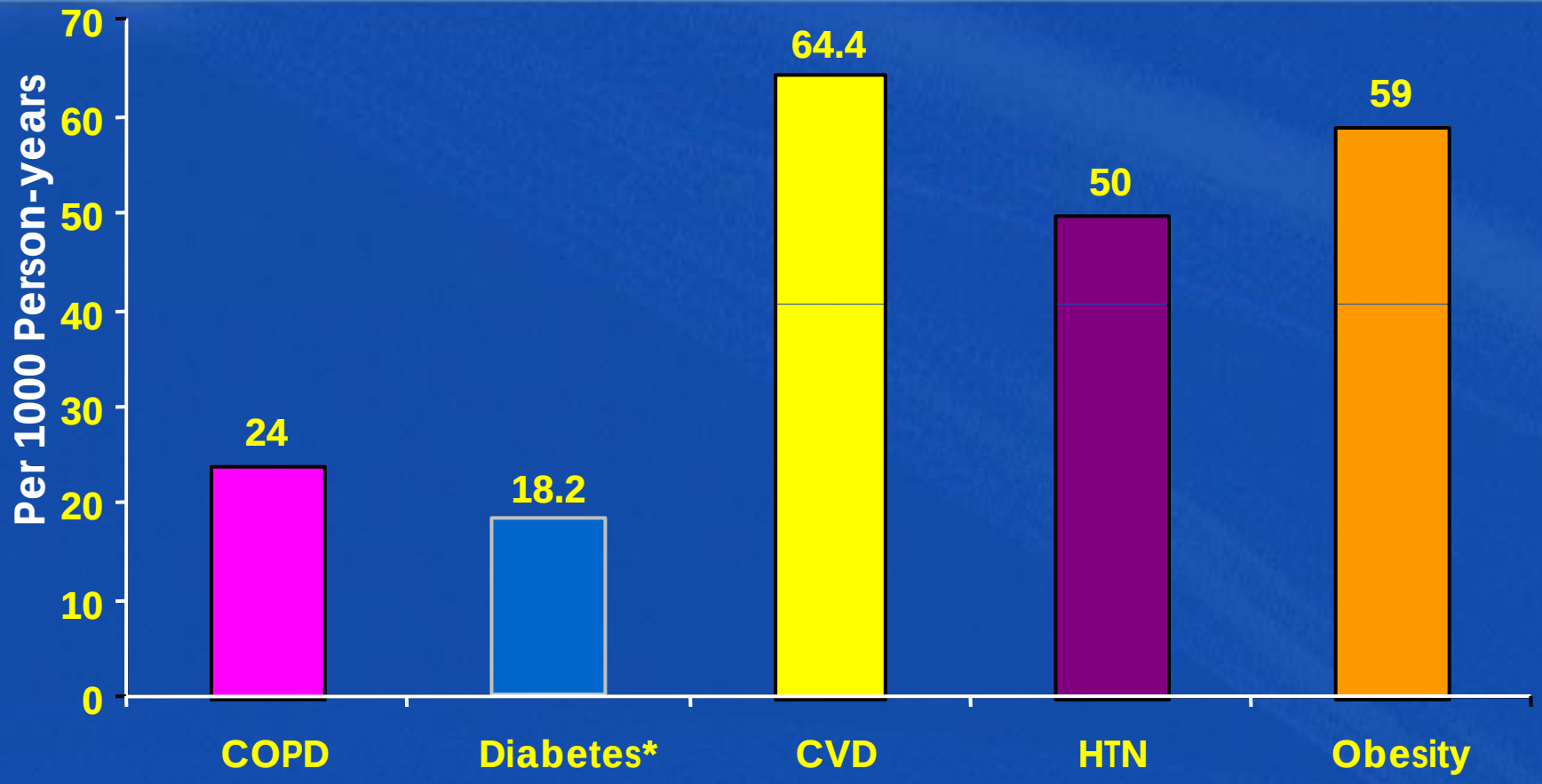
(Persistent post-bronchodilator $FEV_1/FVC < 0.70$ *not due to diseases other than COPD*)

Leading Causes of Death in the US, 2006



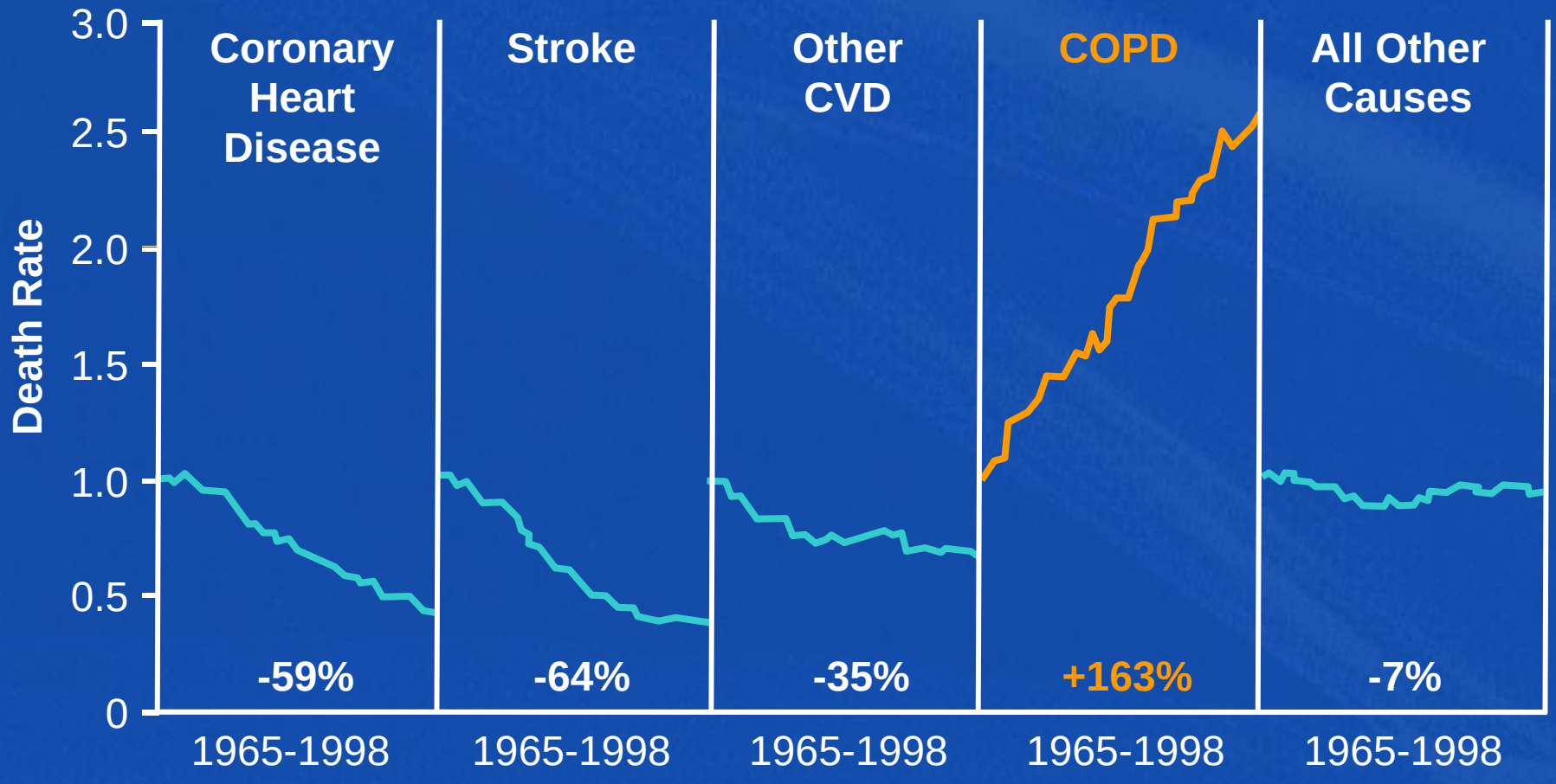
www.cdc.gov

COPD Is as Prevalent as Many Other Chronic Diseases Treated in Primary Care



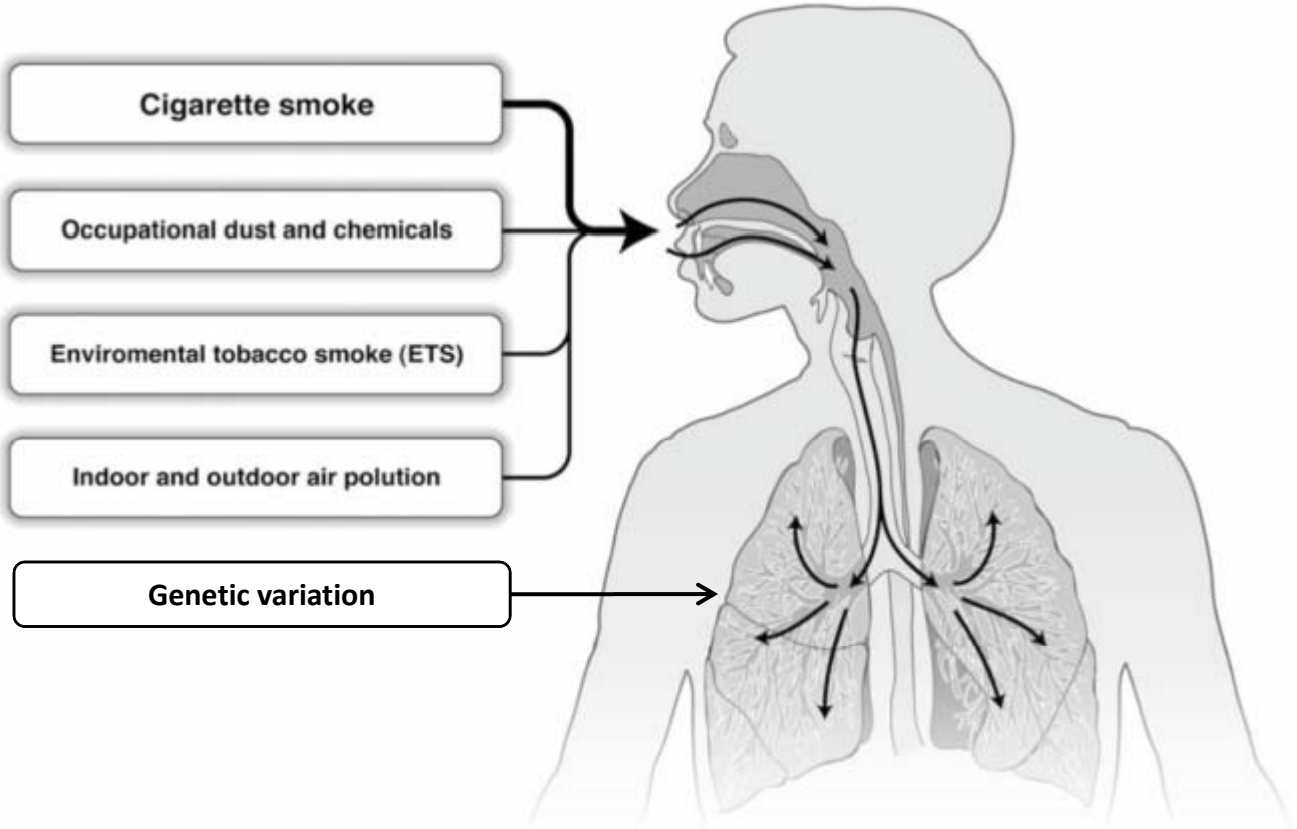
**All About Diabetes.* American Diabetes Association Web site. http://www.diabetes.org. 90% to 95% of Americans with diabetes have type 2 diabetes. AHA. *Heart Disease and Stroke Statistics—2004 Update.* Dallas, TX: AHA; 2003.
Frequently asked questions on overweight and obesity. CDC Web site. http://www.cdc.gov/nccdphp/dnpa/obesity/faq.htm#adults.

Percent Change in Age-Adjusted US Death Rates

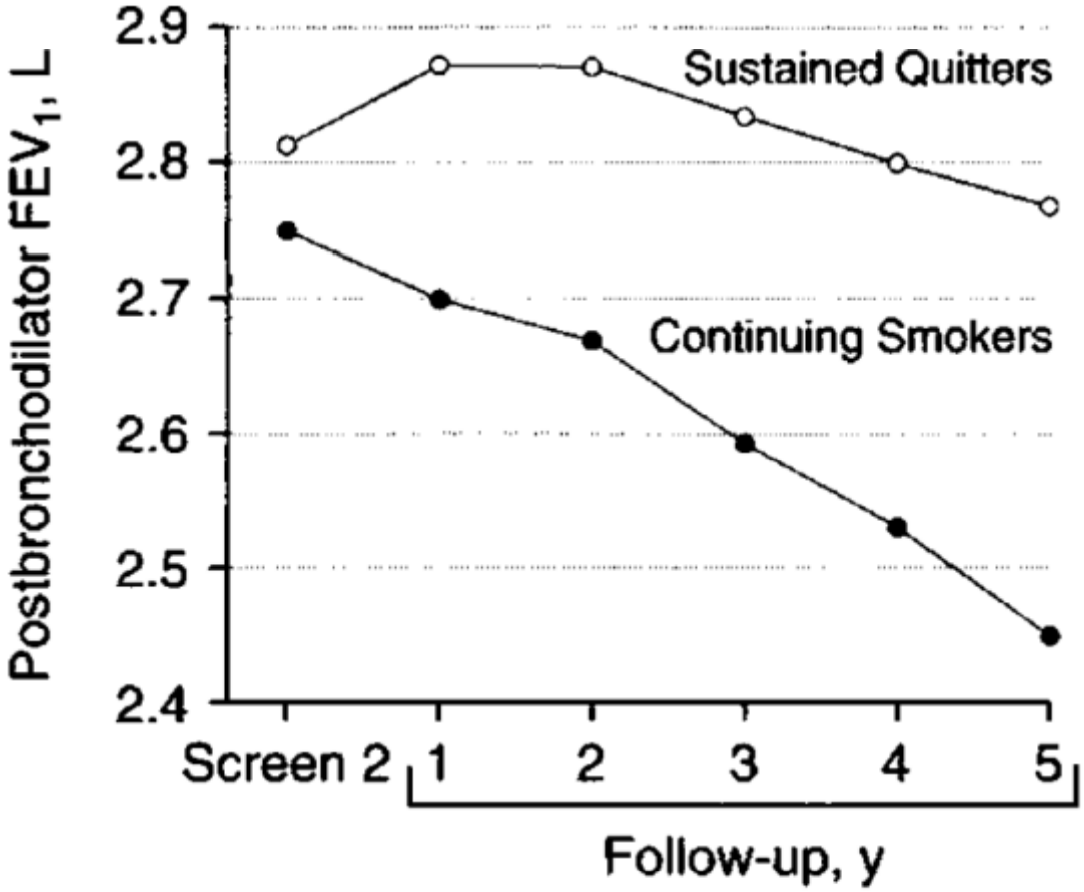


GOLD. Available at: http://www.goldcopd.org/OtherResourcesItem.asp?l1=2&l2=2&intId=969. Accessed July 13, 2006 (A).

Risk Factors for COPD

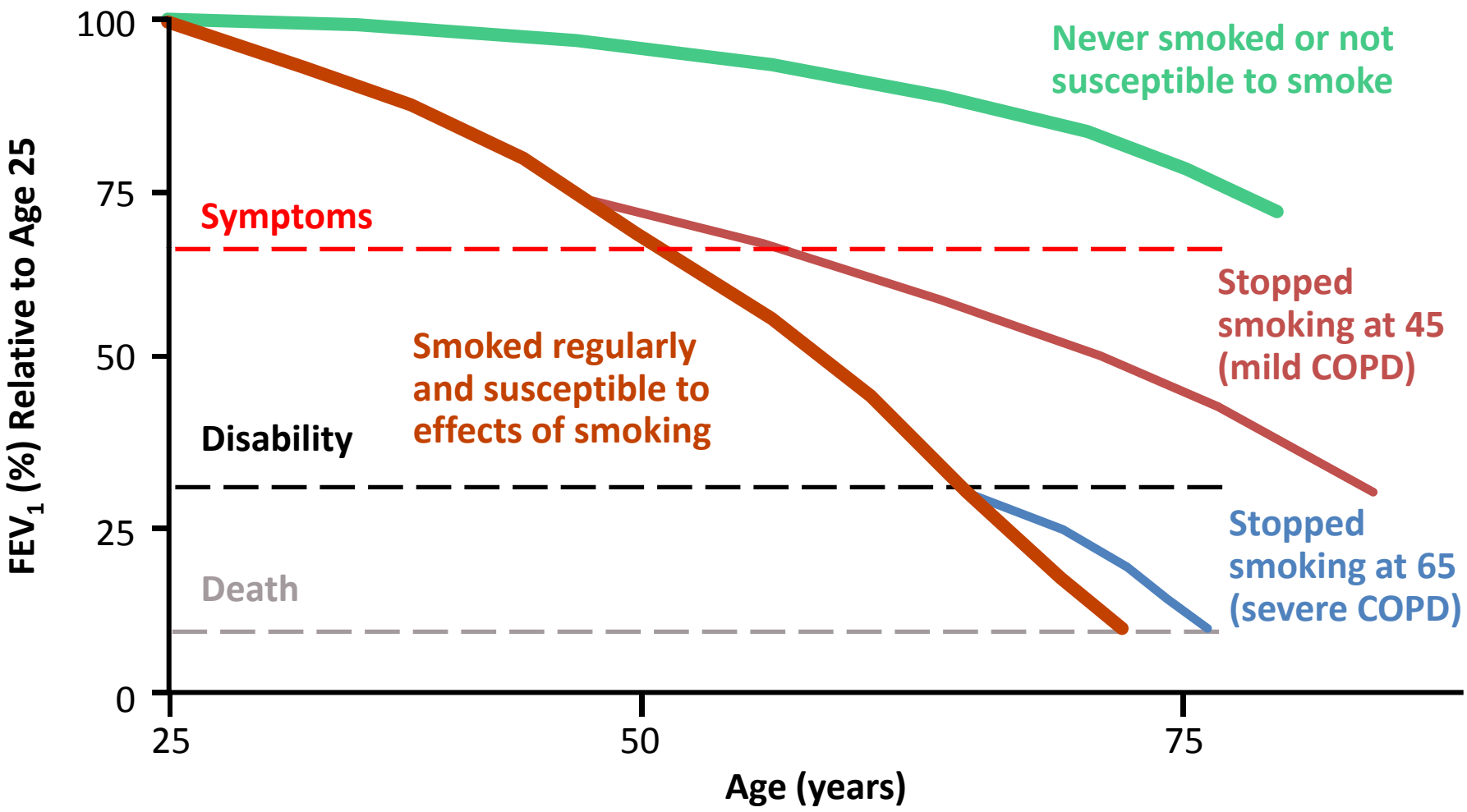


Smoking and Lung Function



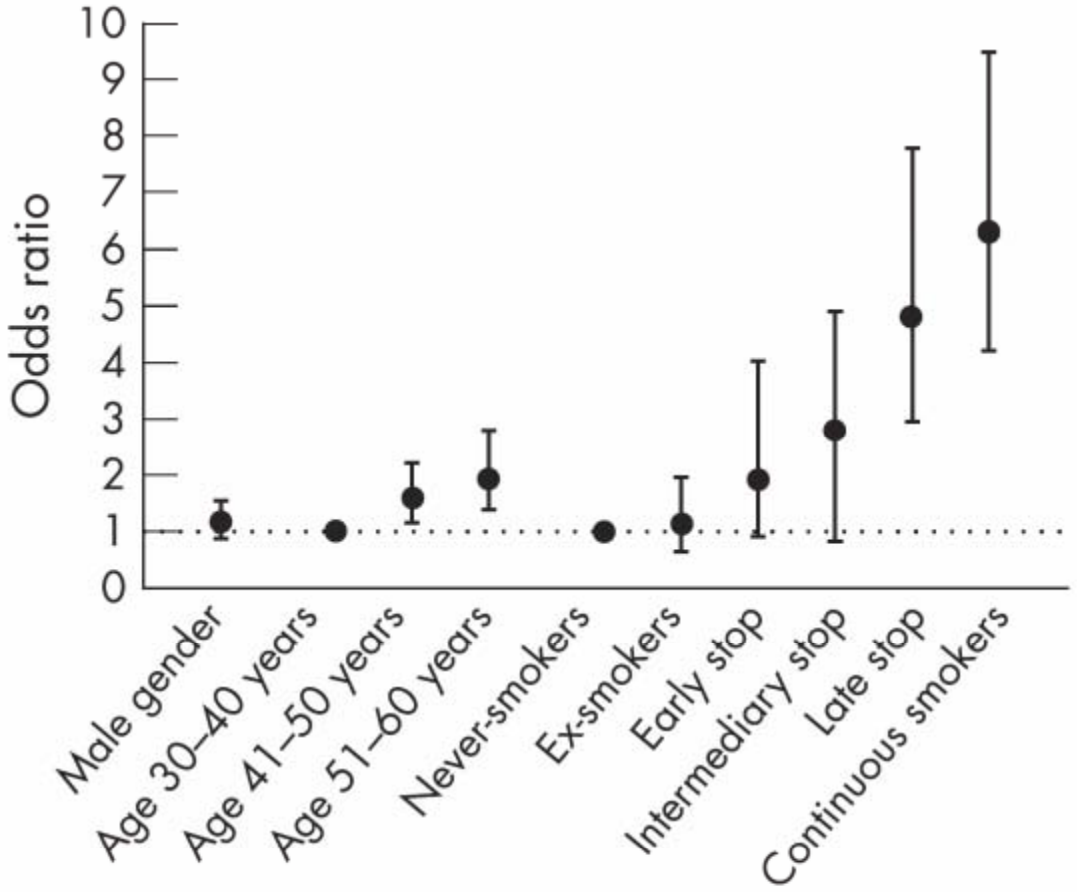
Anthonisen, *JAMA* 1994

Lung Function Over Time



Fletcher *BMJ* 1977

Smoking and COPD risk

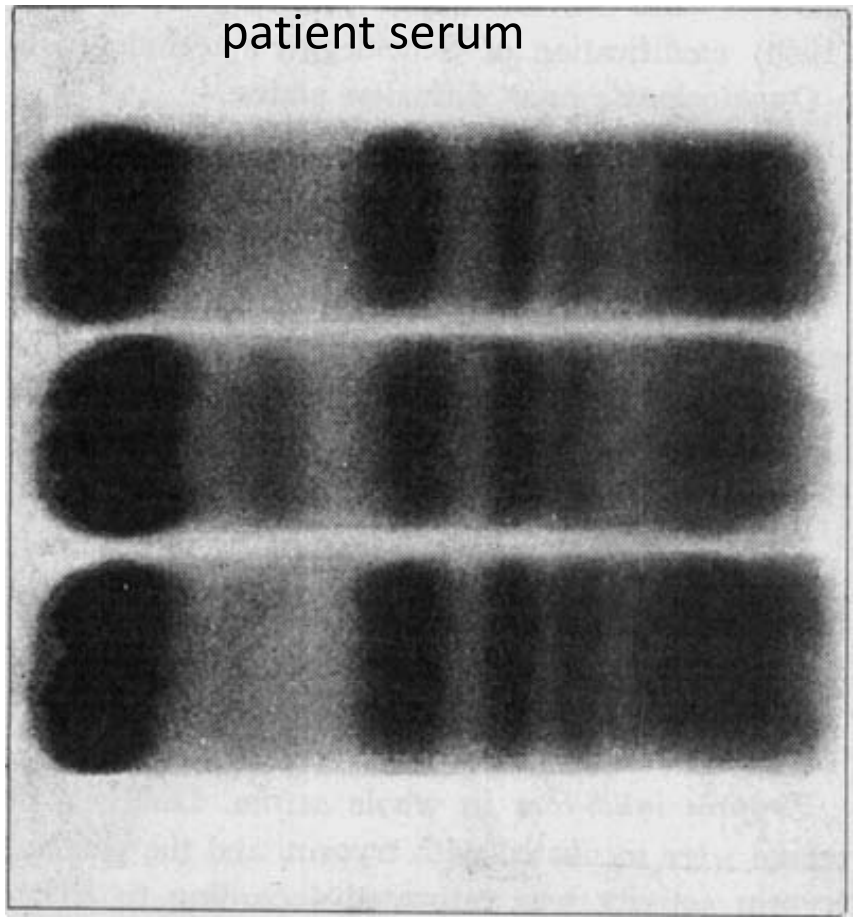


Lokke, *Thorax* 2006

α1-antitrypsin (AAT) Deficiency

- Autosomal co-dominant disorder caused by mutation in the *SERPINA1* gene
- Phenotypes classified by migration in isoelectric pH gradient from A to Z (slowest migration)

Paper electrophoresis of patient serum



Laurell and Eriksson - 1963

AAT alleles

Allele Groups	Examples	Defect
Normal	M X (Glu363Lys)	None
Deficiency	S (Glu264Val) Z (Glu342Lys) M_{malton} (Phe52del)	Intracellular degradation or accumulation
Null	Tyr160X	No mRNA or protein
Dysfunctional	$M_{mineral\ springs}$ Met358Arg	Defective inhibition of elastase

Stoller JK and Aboussouan LS. Lancet 2005.

AAT genotypes and emphysema risk

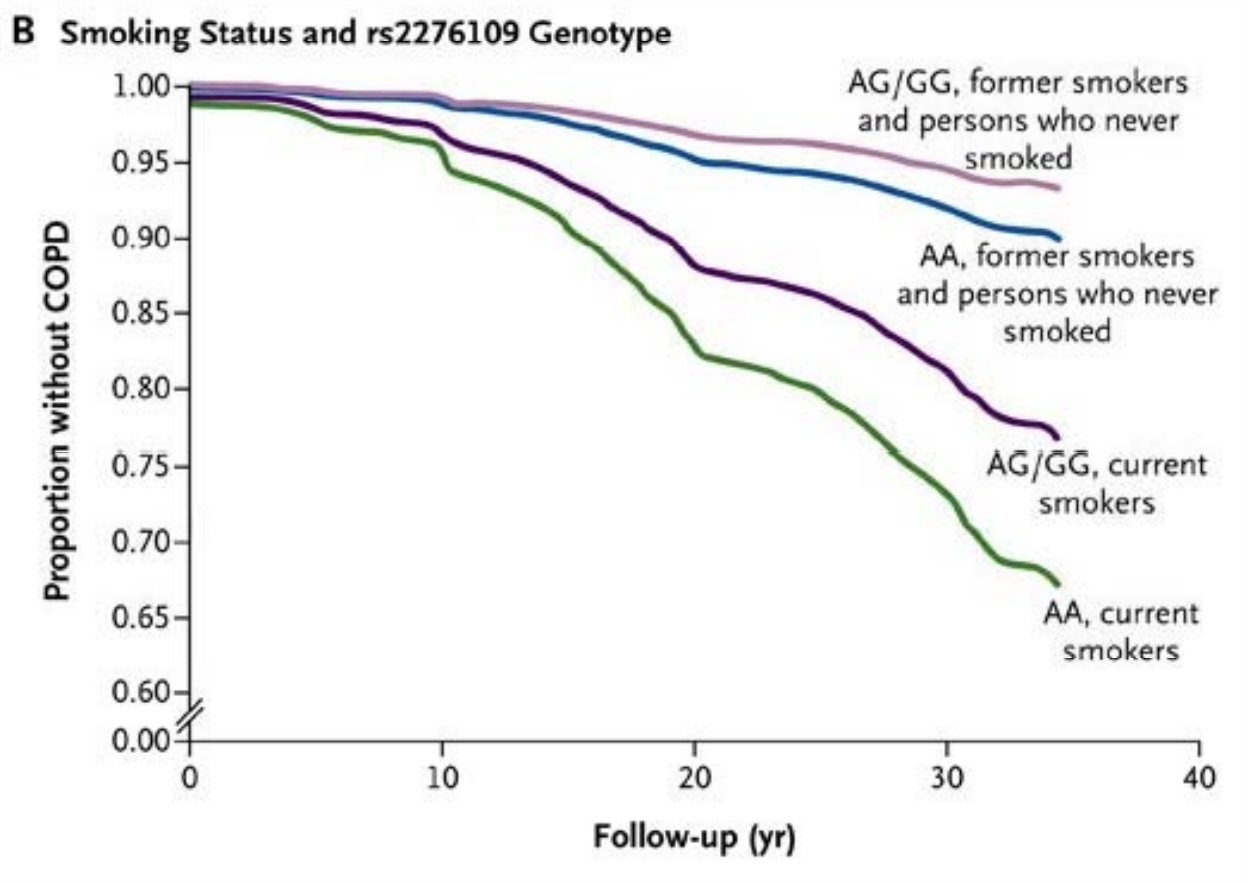
Genotype	Prevalence	A1AT Serum Concentration	Risk of Emphysema
MM	91%	150-350 mg/dL	Background
MS	6%	110-340 mg/dL	Background
MZ	3%	90-210 mg/dL	Background
SS	0.1%	100-200 mg/dL	Background
SZ	0.1%	75-120 mg/dL	20-50%
ZZ	0.02%	20-45 mg/dL	80-100%

Stoller JK and Aboussouan LS. Lancet 2005.

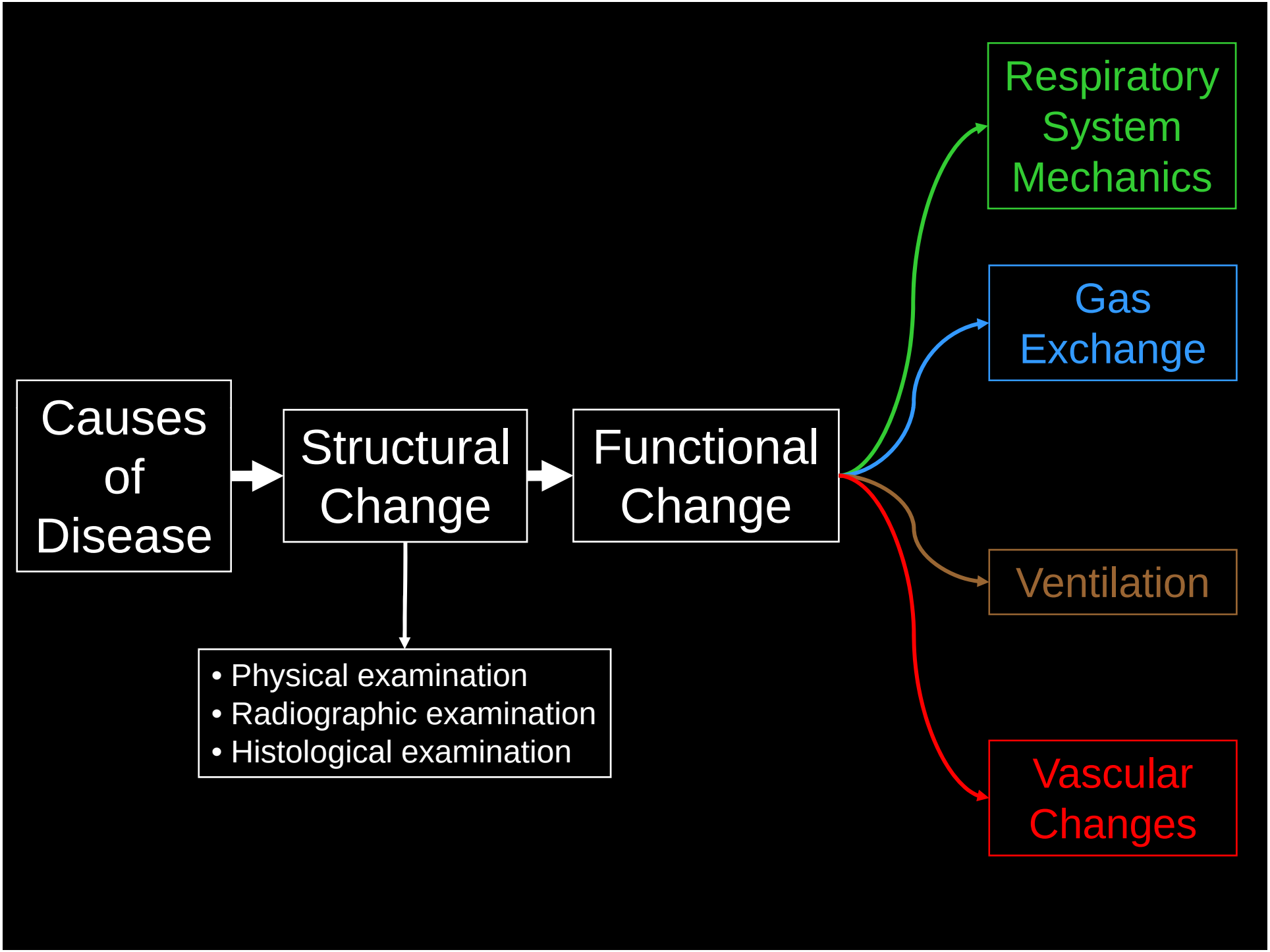
α1-antitrypsin Deficiency (AAT)

- 2% of COPD pts have severe A1AD
  - 59,000 Americans
  - Only 10,000 are receiving replacement therapy
- AAT inhibits neutrophil elastase
- Panlobular emphysema
- Younger pts with basilar emphysema
- Can also cause liver disease
- Treatment
  - Intravenous pooled plasma α1-antitrypsin
  - May slow the decline in lung function

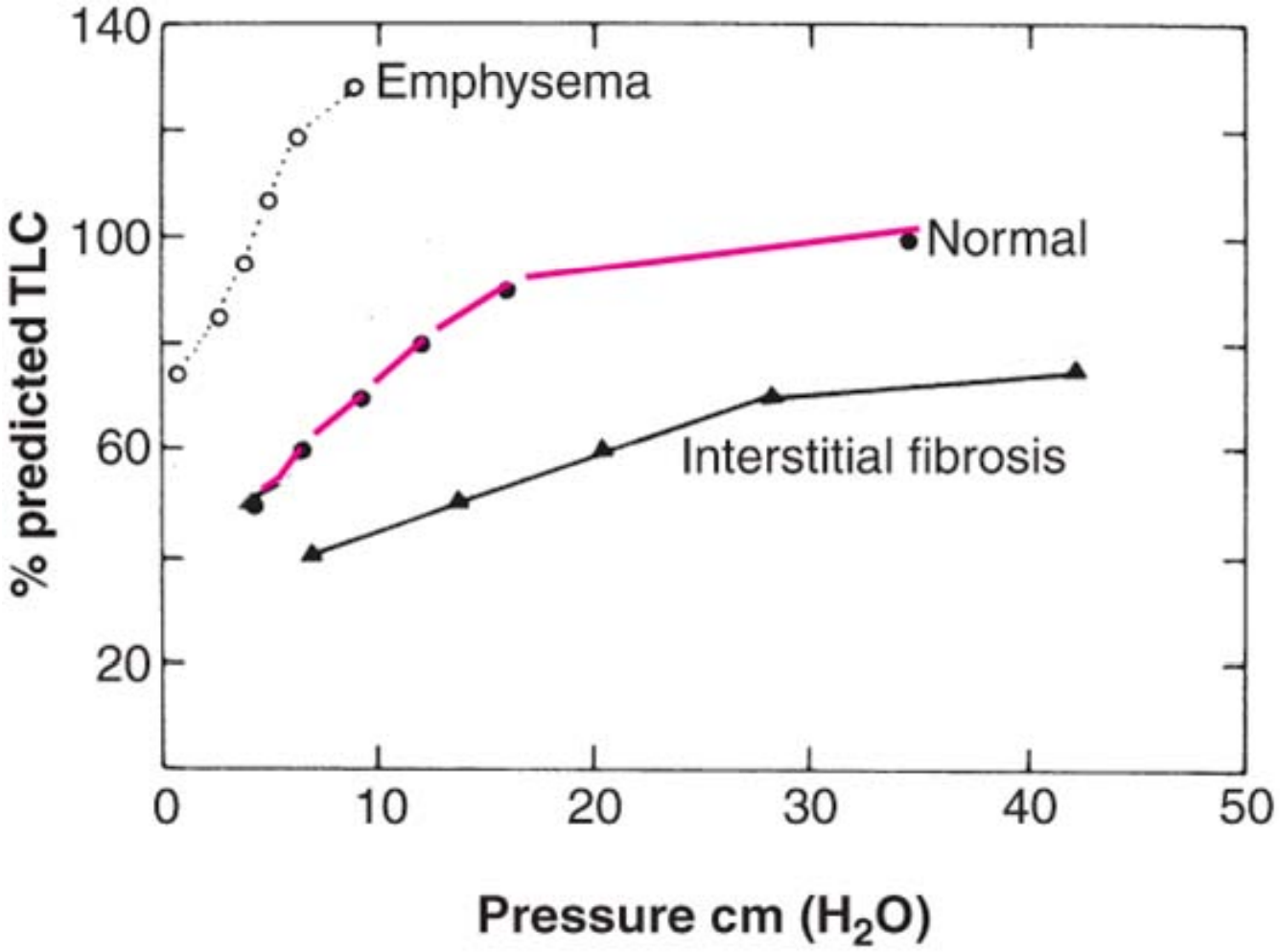
Matrix metalloproteinase-12 and COPD risk



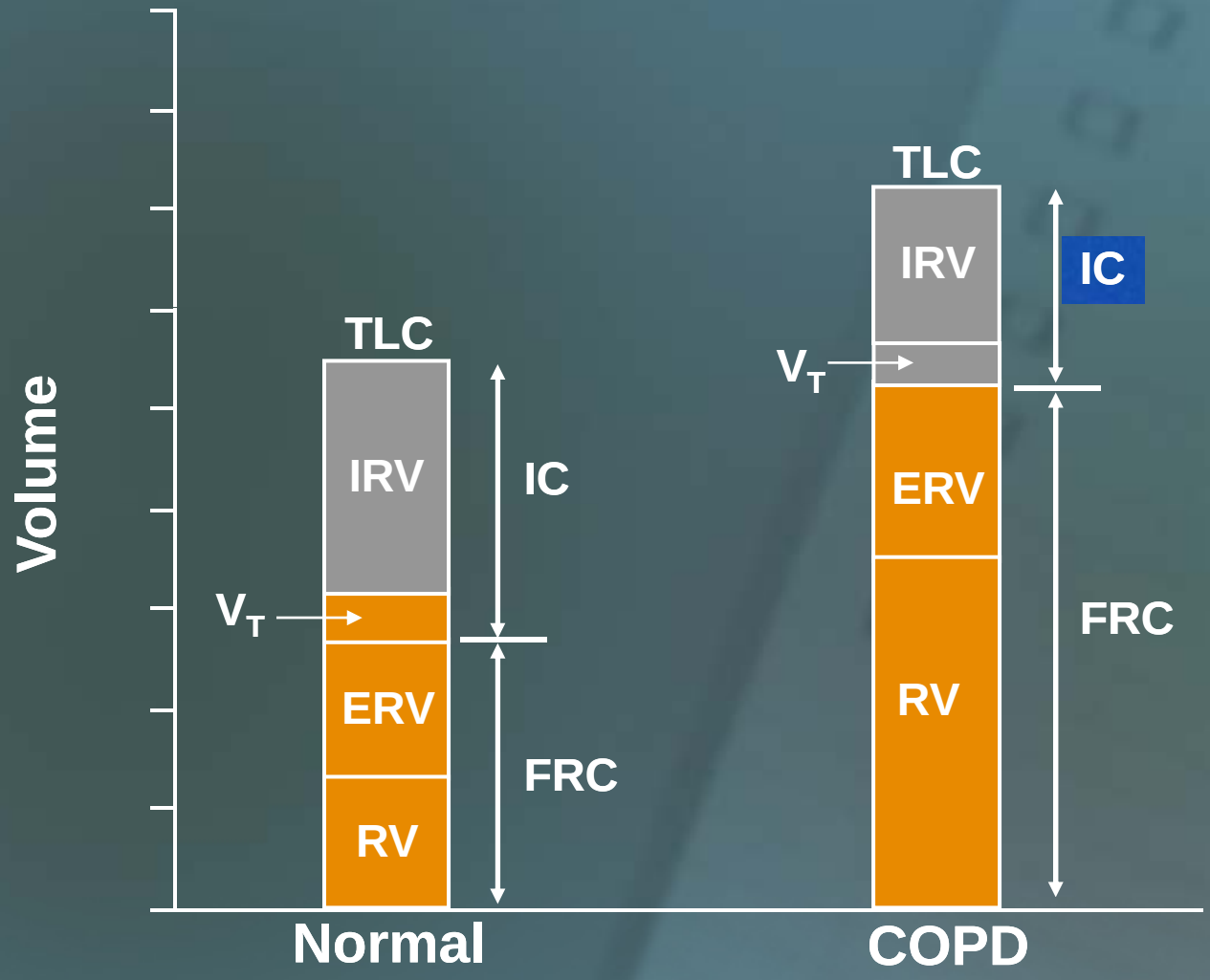
Hunninghake, *NEJM* 2009


Causes of Disease
Structural Change
Functional Change
• Physical examination
• Radiographic examination
• Histological examination
Respiratory System Mechanics
Gas Exchange
Ventilation
Vascular Changes

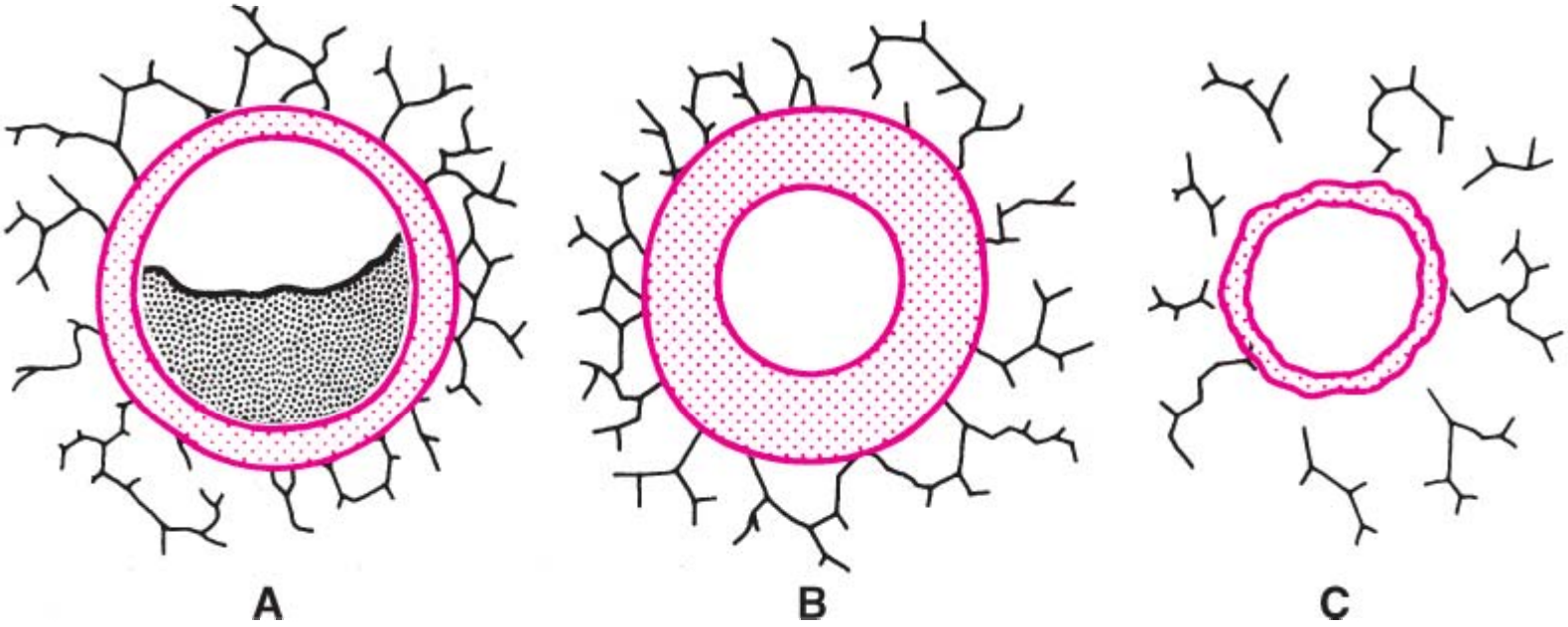
Lung Compliance is Increased in Pulmonary Emphysema



Comparison of Lung Volume Parameters



Airway Resistance is determined by Airway Caliber

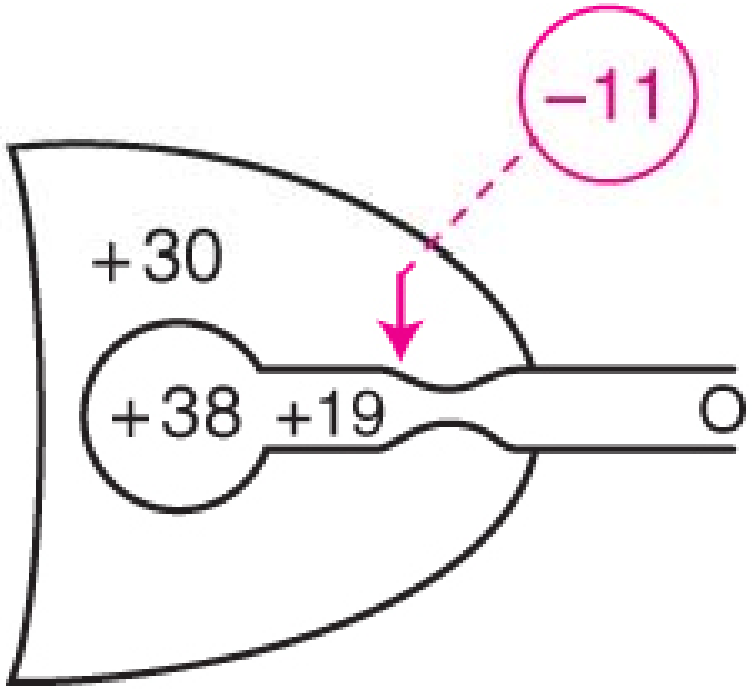


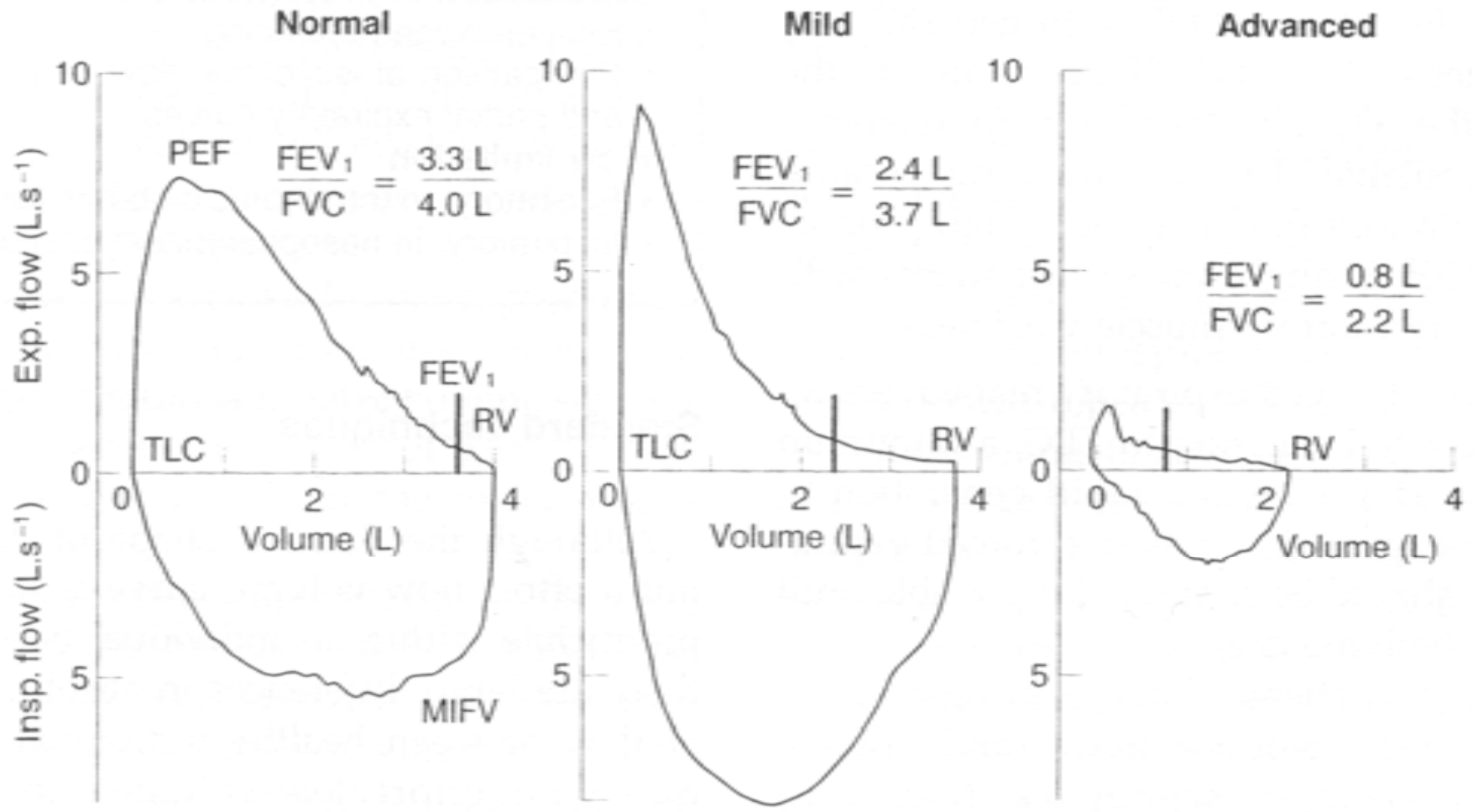
Intraluminal:
e.g., Secretions

Intramural:
e.g., Edema

Extraluminal:
e.g., Loss of radial traction

Dynamic Airway Compression during Forced Expiration




Normal
Mild
Advanced
10
5
0
5
Exp. flow (L.s⁻¹)
Insp. flow (L.s⁻¹)
PEF
FEV₁/FVC = 3.3 L / 4.0 L
FEV₁
RV
TLC
MIFV
0
2
4
Volume (L)
FEV₁/FVC = 2.4 L / 3.7 L
FEV₁/FVC = 0.8 L / 2.2 L

Gas exchange in COPD

- Mild hypoxemia is common
- Severe hypoxemia is rare
- Mechanisms of hypoxemia
  - Increased V/Q mismatch (MAJOR)
  - Alveolar hypoventilation (minor)
- Shunt and diffusion abnormalities do NOT contribute to hypoxemia in COPD

Abnormal Ventilation in COPD

- Increased dead space ventilation
  - Emphysematous regions are poorly perfused
  - Increased work of breathing
- Alveolar hypoventilation
  - Common (but not universal) in advanced disease
  - Worsens during severe “exacerbations” (acute deterioration often in the setting of acute bronchitis)

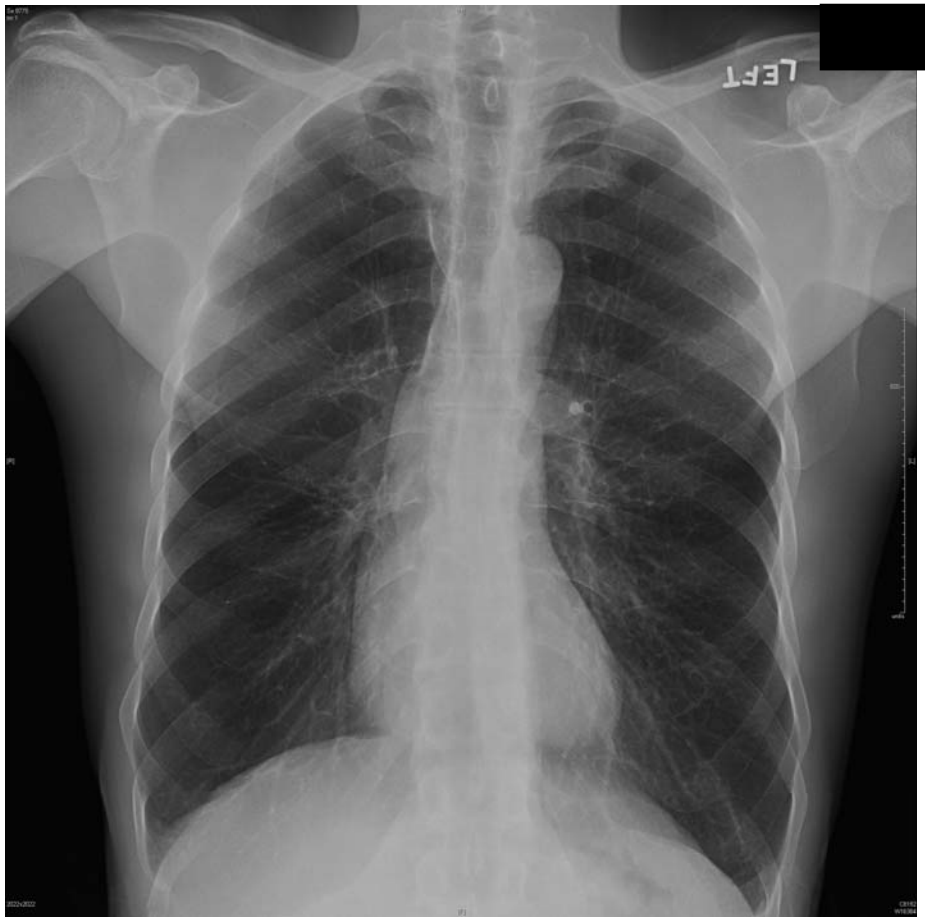
Clinical Presentation of COPD

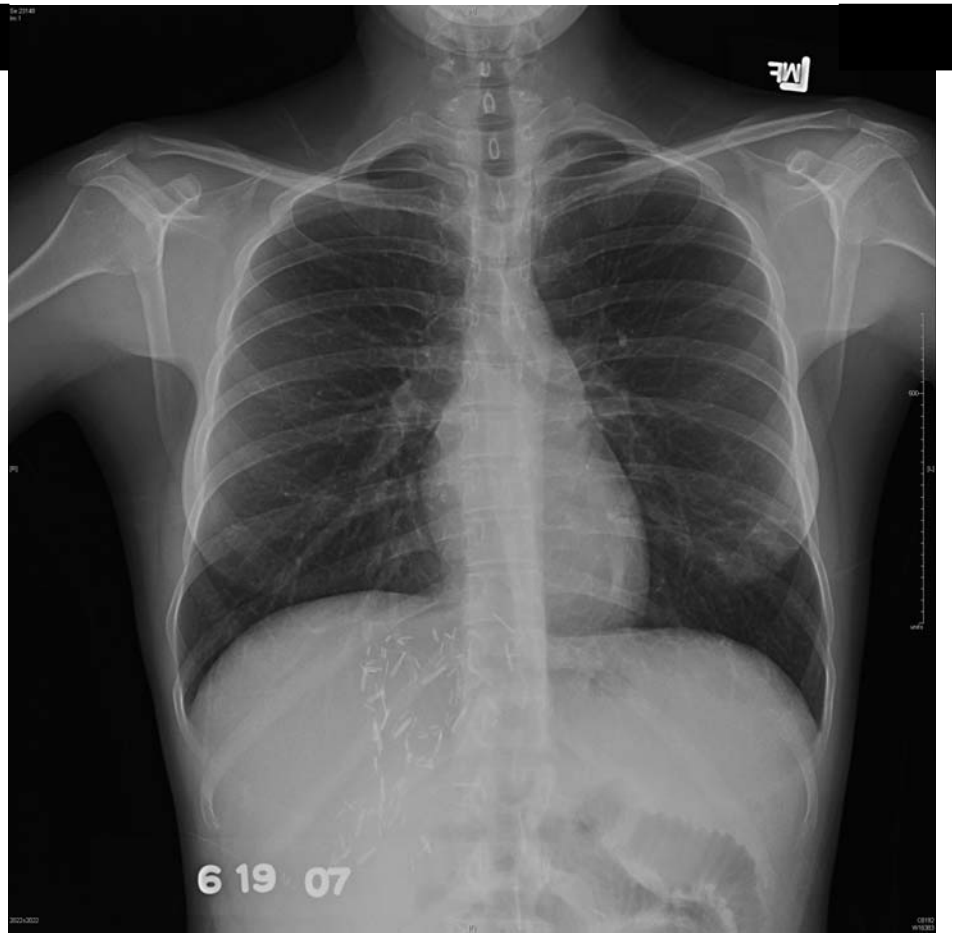
- Millions have early, asymptomatic COPD
- Common symptoms
  - Cough with sputum production (chronic bronchitis)
  - Exertional dyspnea
  - Muscular wasting
- During an exacerbation
  - Change in sputum quantity, color, or consistency
  - Wheezing
  - Increased dyspnea

Physical Exam in COPD

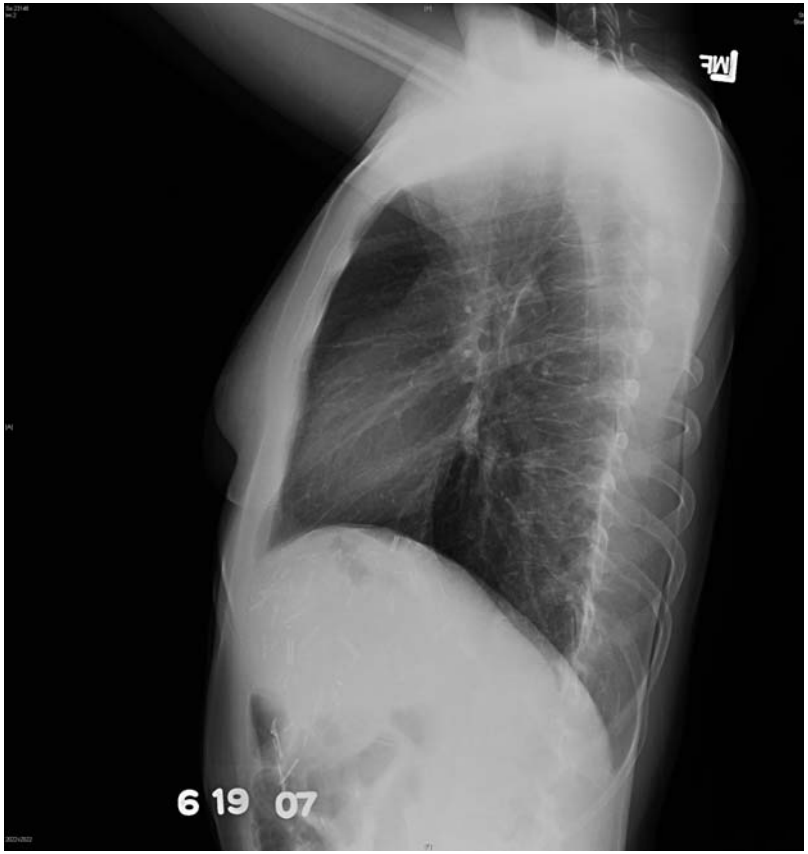
- Early disease = normal exam
- Common findings
  - Increased anteroposterior chest diameter
    - “Barrel chest”
  - Bilaterally diminished breath sounds
  - Muscular wasting
- During an exacerbation
  - Wheezing
  - Rhonchi
  - Cyanosis

COPD VS NORMAL: PA

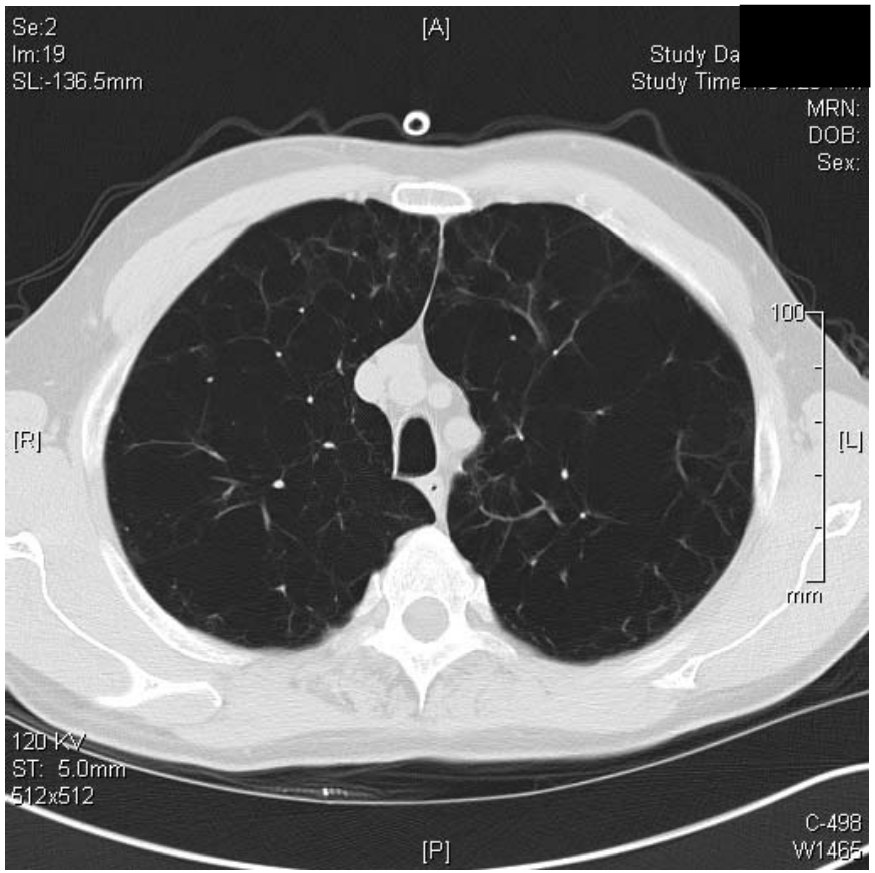


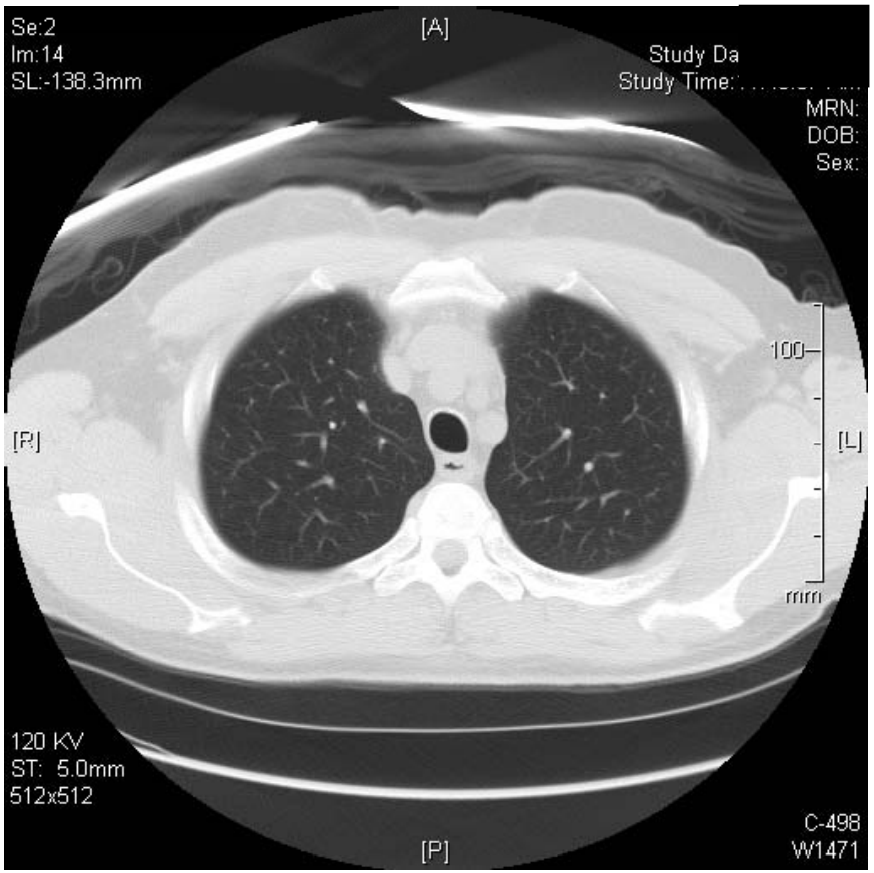


COPD VS NORMAL: LATERAL



COPD VS NORMAL: CT





Diagnosing COPD

- Clinical presentation
- Airflow obstruction without reversibility
- Exclusion of alternative causes
  - Asthma
  - Bronchiecatasis (e.g., cystic fibrosis)
  - Congestive heart failure
  - Tuberculosis
  - Other causes of airflow obstruction

Spirometry is the BEST test for diagnosis and staging of COPD

Stage	FEV_1/FVC	FEV_1	Other
I: Mild	< 0.70	≥80% predicted	
II: Moderate	< 0.70	50 to 79%	
III: Severe	< 0.70	30 to 49%	$PaO_2 \geq 60$ mm Hg, and $PaCO_2 \leq 50$ mm Hg
IV: Very Severe	< 0.70	30 to 49%	$PaO_2 < 60$ mm Hg or $PaCO_2 > 50$ mm Hg
	< 0.70	<30%	

Management by COPD stage

Stage	FEV_1	Consider
I: Mild	≥80%	• Risk factor reduction • Influenza/pneumococcal vaccination • Short-acting inhaled β2 agonists
II: Moderate	50 to 79%	• Long-acting inhaled bronchodilators • Pulmonary rehabilitation
III: Severe	30 to 49%	• Inhaled corticosteroids (if wheezing or repeated exacerbations)
IV: Very Severe	<30%*	• Long-term oxygen therapy • Surgical therapy

Brief Strategies to Help the Patient Willing to Quit Smoking

- ASK — Identify smokers at every visit
- ADVISE — Strongly urge all users to quit
- ASSESS — Determine willingness to quit
- ASSIST — Aid the patient in quitting
- ARRANGE — Schedule follow-up contact

Pharmacologic therapies for tobacco cessation

Agent	Usage	6-month abstinence rate
Nicotine replacement		All about 25%
Nicotine polacrilex (gum)	2-4mg piece every 1-2 hrs x 8-12 weeks	
Nicotine lozenges	1-2mg every hour	
Nasal nicotine spray	0.5 mg inh each nostril hourly x 3-6 months	
Nicotine inhaler	6-16 cartridges/day x 3-6 months	
Transdermal nicotine (patch)	16-24hrs/day x 8 weeks	
Oral medication		
Buproprion sustained release	150mg for 3 days, then 300mg daily x up to 6 months	24%
Varenicline	See next slide	33%

Varenicline

- Orally-available partial agonist at the α4β2 subunit of the nicotinic acetylcholine receptor
- Effects
  - Stimulates nicotinic receptor (reduces withdrawal)
  - Block nicotine from binding (reduces reward)
- Increases the odds of quitting three-fold (33% 6-month quit rate)
- Use:
  - 0.5mg daily x 3 days, then 0.5 mg BID for 4 days, then 1mg BID for 11 more weeks.
  - Quit smoking 1 weeks after initiating varenicline
  - Successful quitters at 12 weeks should continue for 12 more weeks
- Side effects: nausea, insomnia, abnormal dreams
- Concerns: ?suicidal thoughts, aggressive/erratic behavior

Suggested approach to smoking cessation

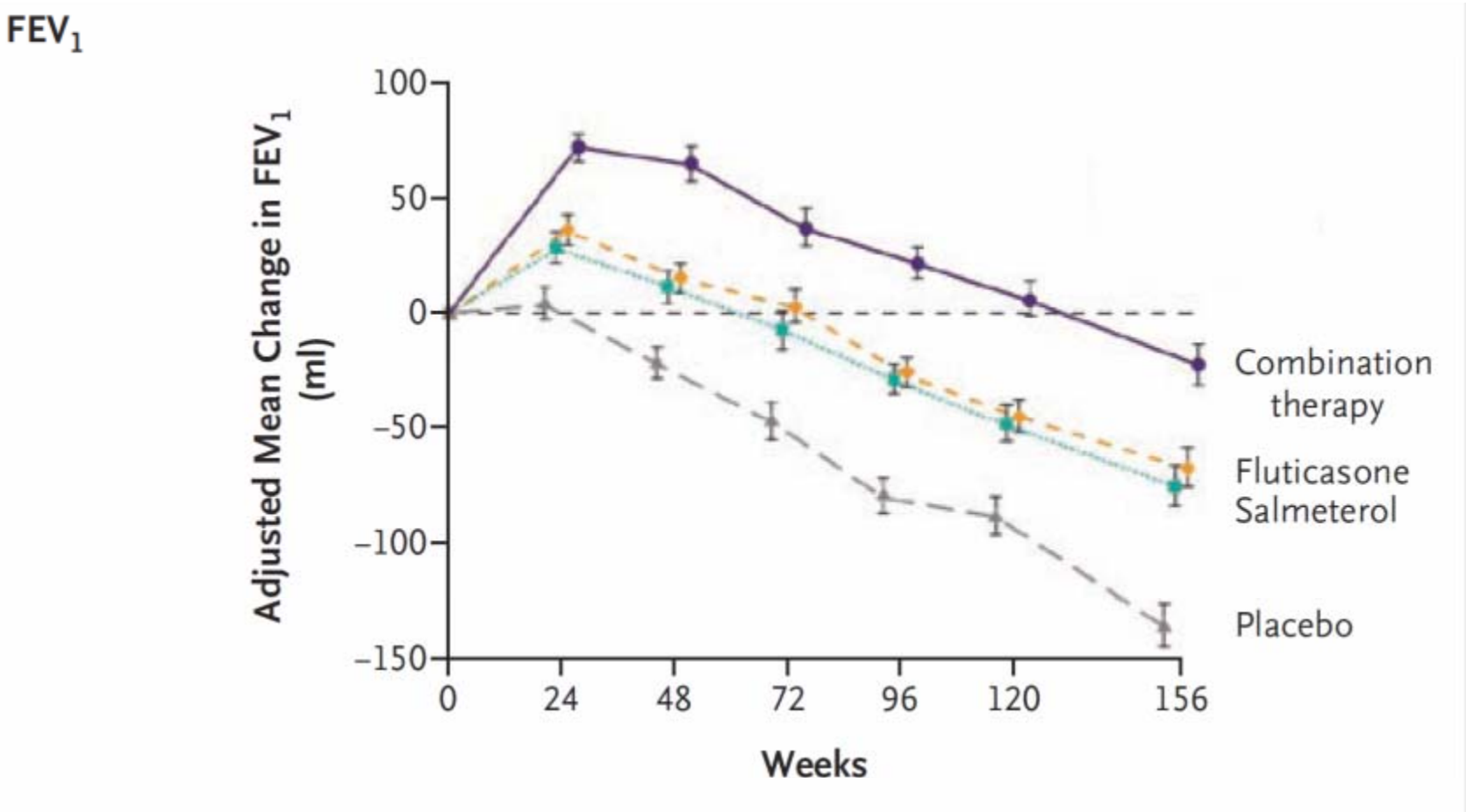
- Use the 5 A's
- Dual approach
  - Counseling
  - Pharmacologic therapy
    - Varenicline most effective
    - May be combined with nicotine replacement
- Tailor therapy to the individual
  - Comorbidities
  - Preferences

Selected Inhaled Medications for COPD

Type of Drug	Drug	Trade Names
Short-acting β2-agonist (SABA)	Albuterol	Ventolin
	Terbutaline	Brethine
	Pirbuterol	Maxair
	Levalbuterol	Xopenex
Long-acting β2-agonist (LABA)	Formoterol	Foradil
	Arformoterol	Brovana
	Salmeterol	Serevent
Anticholinergic	Ipratropium (short-acting)	Atrovent
	Tiotropium (long-acting)	Spiriva
SABA/Anticholinergic	Fenoterol/Ipratropium	Duovent
	Albuterol/Ipratropium	Combivent
Glucocorticoid	Becolmethasone	Beclovent, Vanceril
	Budesonide	Pulmicort
	Fluticasone	Flovent
	Flunisolide	AeroBid
	Mometasone	Asmanex
	Triamcinalone	Azmacort
LABA/Glucocorticoid	Formoterol/Budesonide	Symbicort
	Salmeterol/Fluticasone	Advair

*Do not memorize this Table. It is provided for future reference, only

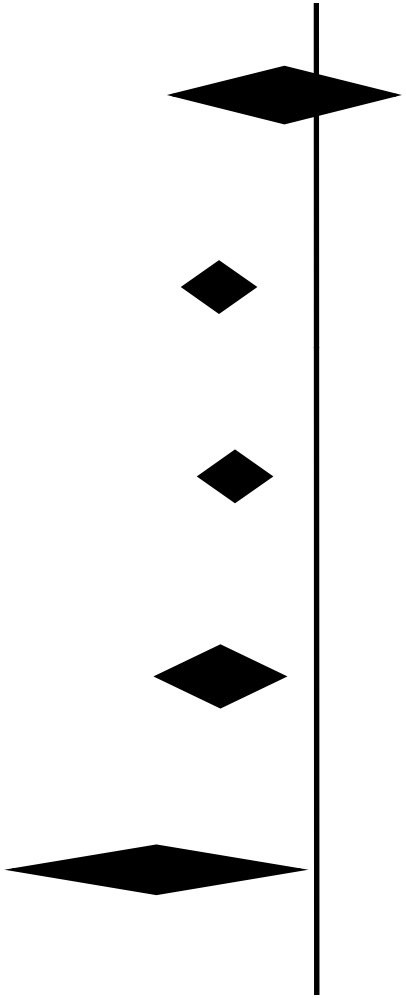
TORCH study: LABAs and ICS improve lung function in COPD



Calverley, NEJM 2007

Relative risk of COPD exacerbation: Inhalational treatment vs. placebo

Inhalation treatment	RR (95% CI)	RR	*P*	*n**
Ipratropium	0.95 (0.78-1.15)		0.60	4
Tiotropium	0.84 (0.78-0.90)		<0.001	4
LABA	0.87 (0.82-0.93)		<0.001	17
Corticosteroids	0.85 (0.75-0.96)		0.01	8
Combined LABA/ corticosteroids	0.77 (0.58-1.01)		0.06	4

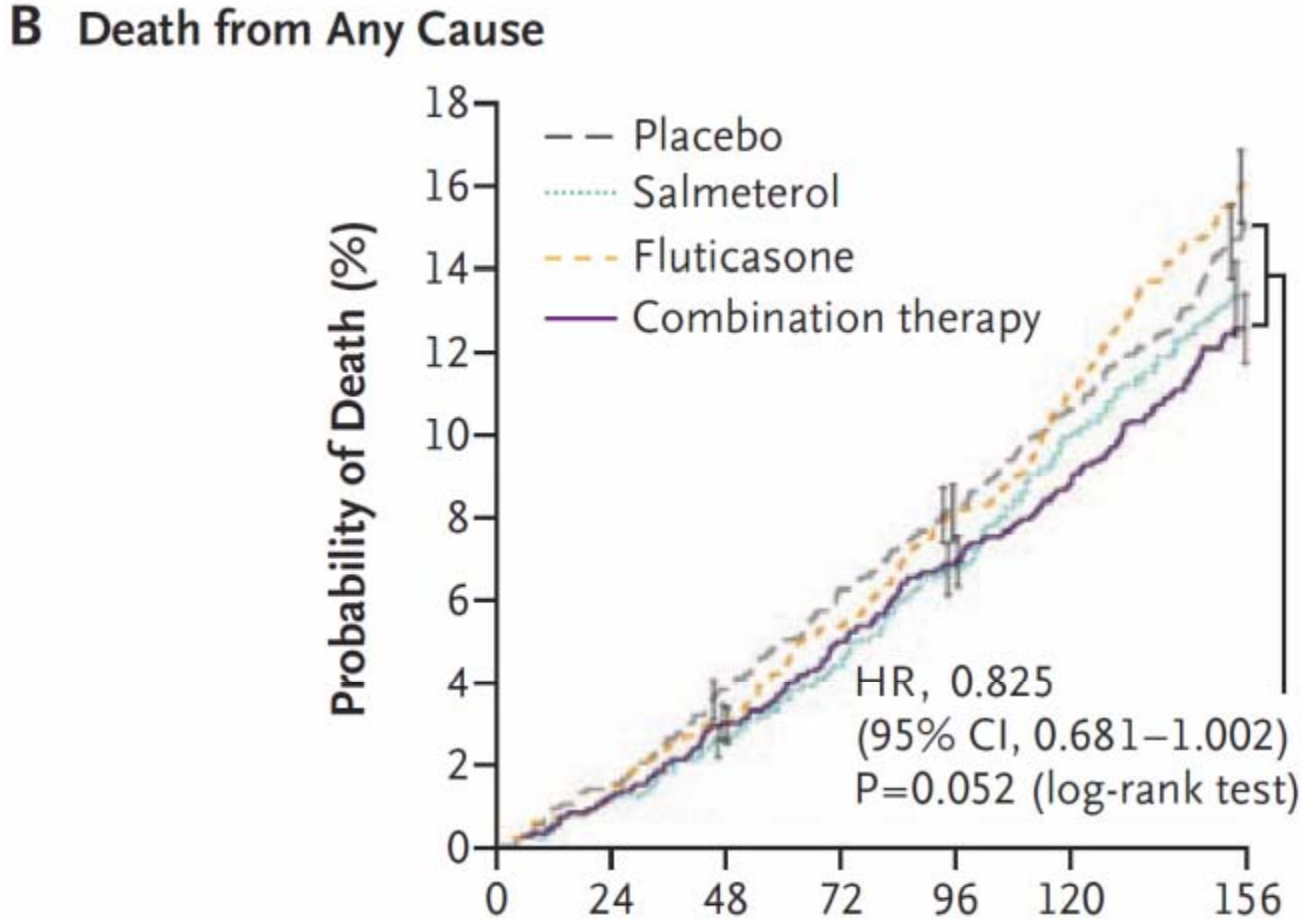


Key: Ipratropium, short acting anticholinergic
Tiotropium, long-acting anticholinergic
LABA, long-acting β-agonist

n = number of trials

Modified from: Wilt et al., *Annals Internal Med.* 147:639, 2007

TORCH study: Reduced mortality with combination therapy?



Calverley, NEJM 2007

Side effects of inhaled medications

- β2-agonists
  - Tremor
  - Tachycardiac
  - Hypokalemia
  - Hypoglycemia (rare)
  - LABA: Increased risk of asthma mortality?
- Anti-cholinergics
  - Dry mouth
  - Cardiovascular events? (conflicting evidence)
- Inhaled glucocorticoids
  - Oropharngeal thrush (gargle & rinse to prevent)
  - Cataracts
  - Osteoporosis
  - Increased risk of pneumonia in COPD pts?

Surgical therapy for COPD

- Lung Volume Reduction Surgery (LVRS)
  - Resection of the upper 25% of both lungs
  - Improves lung compliance, symptoms, and outcomes
- Lung transplantation
  - Replacement of one or both lungs with lungs from a deceased donor
  - 50% mortality at 5 years
- Selected candidates only!!