COPD-Related Musculoskeletal Disease

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2017 Update in Internal Medicine

October 20, 2017

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B. Low-dose CT scan
C. Bone densitometry
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B. Low-dose CT scan
C. Bone densitometry
D. Pneumococcal antibody panel testing

Learning Objectives

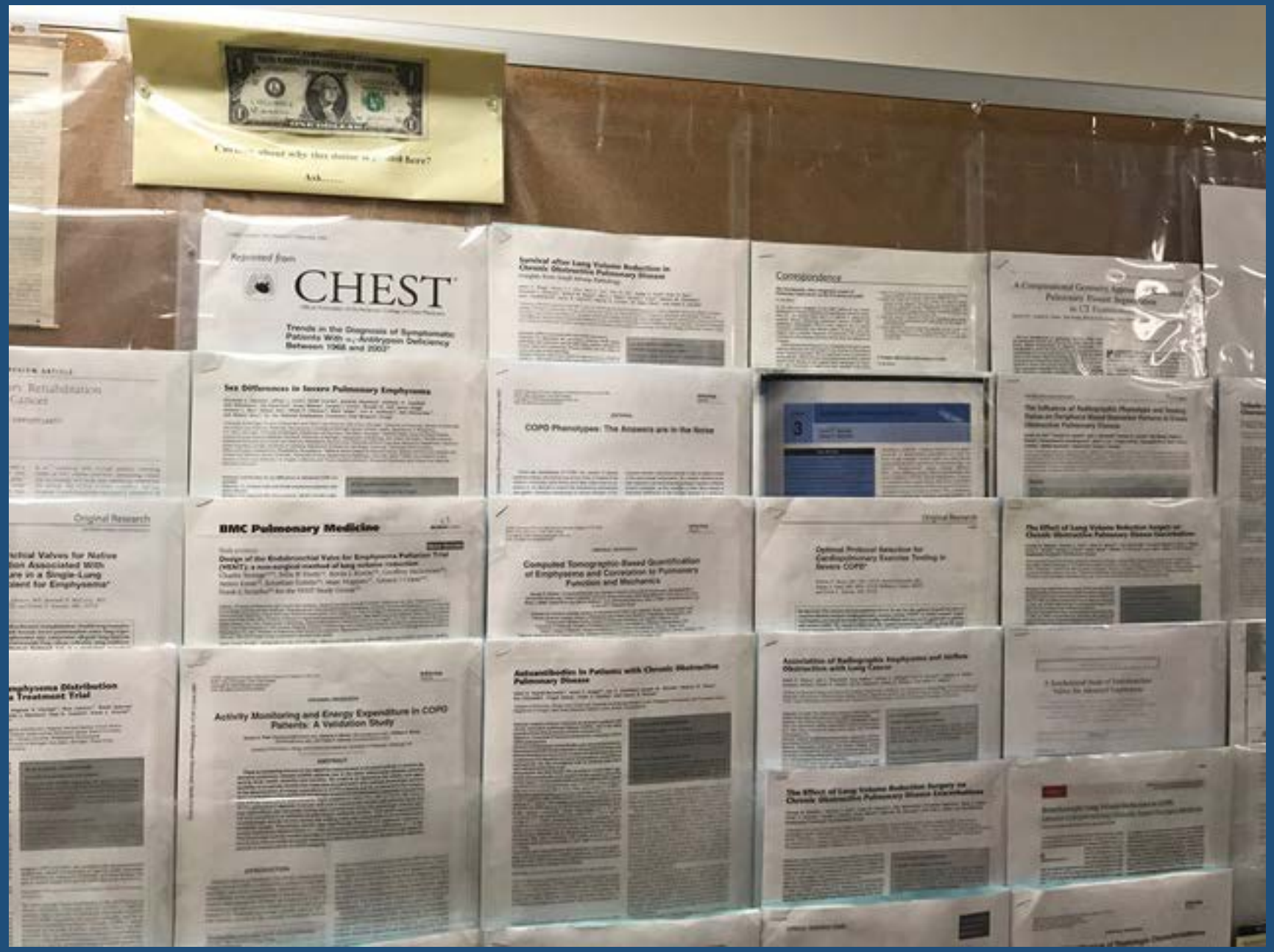
1) To review the epidemiology of COPD-related osteoporosis

2) To recognize both lung-specific and traditional osteoporosis risk factors associated with bone loss in COPD

3) To understand osteoporosis screening guidelines for individuals with COPD

4) To determine appropriate therapy for osteopenia and osteoporosis in individuals with COPD

COPD-Related Osteoporosis Epidemiology


CHEST
Trends in the Diagnosis of Symptomatic Patients With α1-Antitrypsin Deficiency Between 1968 and 2003
Correspondence
Sex Differences in Severe Pulmonary Emphysema
COPD Phenotypes: The Answers are in the Noise
Original Research
BMC Pulmonary Medicine
Computed Tomographic-Based Quantification of Emphysema and Correlation to Pulmonary Function and Mechanics
Activity Monitoring and Energy Expenditure in COPD Patients: A Validation Study
Autoantibodies in Patients with Chronic Obstructive Pulmonary Disease

Prevalence of Low BMD in NHANES III

	Severity of Airflow Obstruction				
	None	Mild	Moderate	Severe	P for Trend
	Number (%) (N=9502)				
Women					
Number of participants	4287	242	235	79	
Osteopenia	1588 (37.0)	102 (42.1)	134 (57.0)	60 (76.0)	0.005
Osteoporosis	327 (7.6)	25 (10.3)	49 (20.9)	19 (24.0)	0.005
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Sin et al. *Am J Med.* 2003; 114:10-14

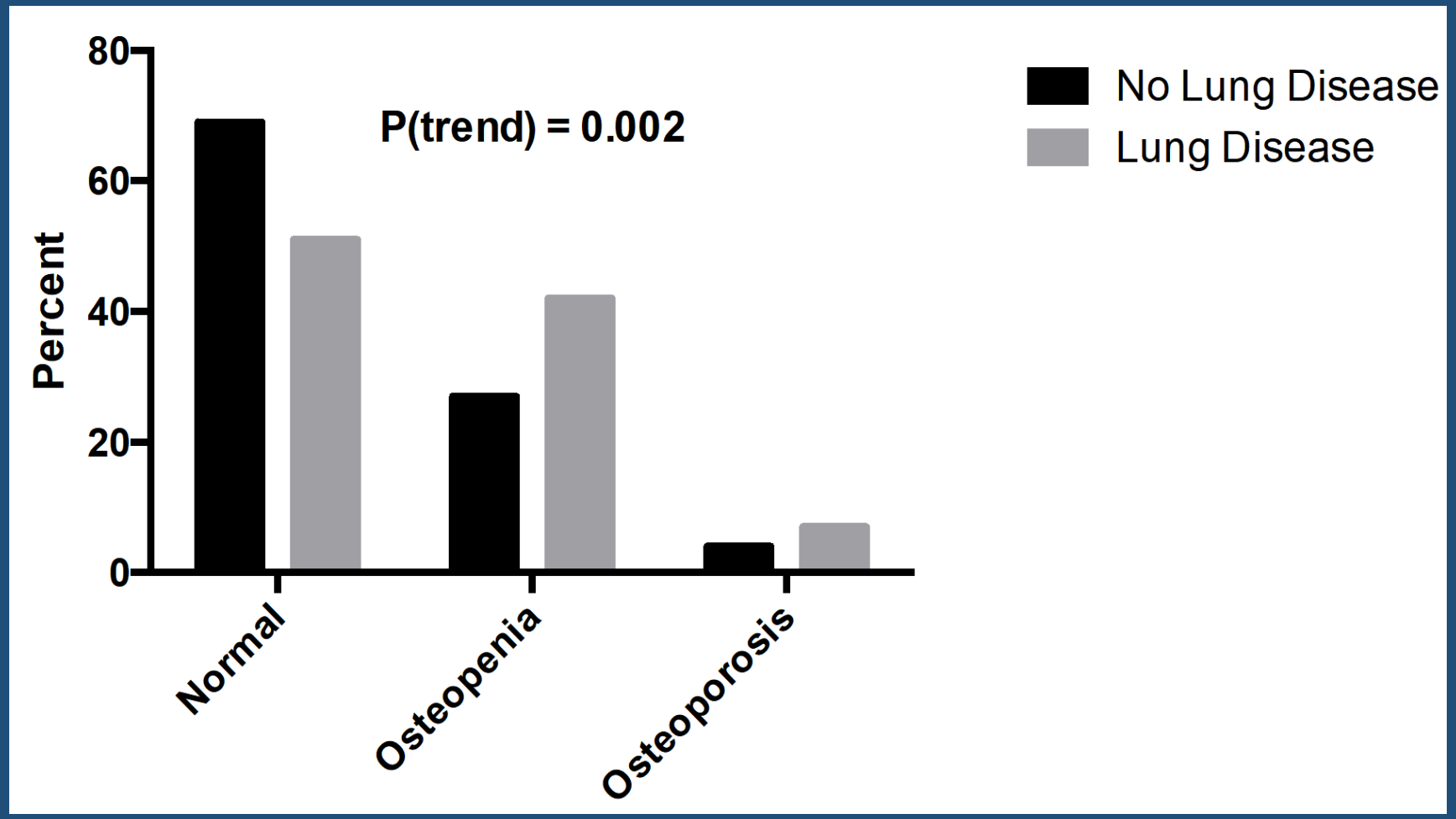
Prevalence of Low BMD in TORCH*

Baseline BMD Values	Total (N=658)
Osteoporosis, BMD T score < -2.5 hip or spine	147 (23%)
Male	66 (18%)
Female	81 (30%)
Osteopenia, T score < -1.0 and ≥ -2.5 hip or spine	272 (42%)
Male	160 (42%)
Female	112 (41%)
Osteoporosis or osteopenia T score < -1.0 hip or spine	419 (65%)
Male	226 (60%)
Female	193 (71%)

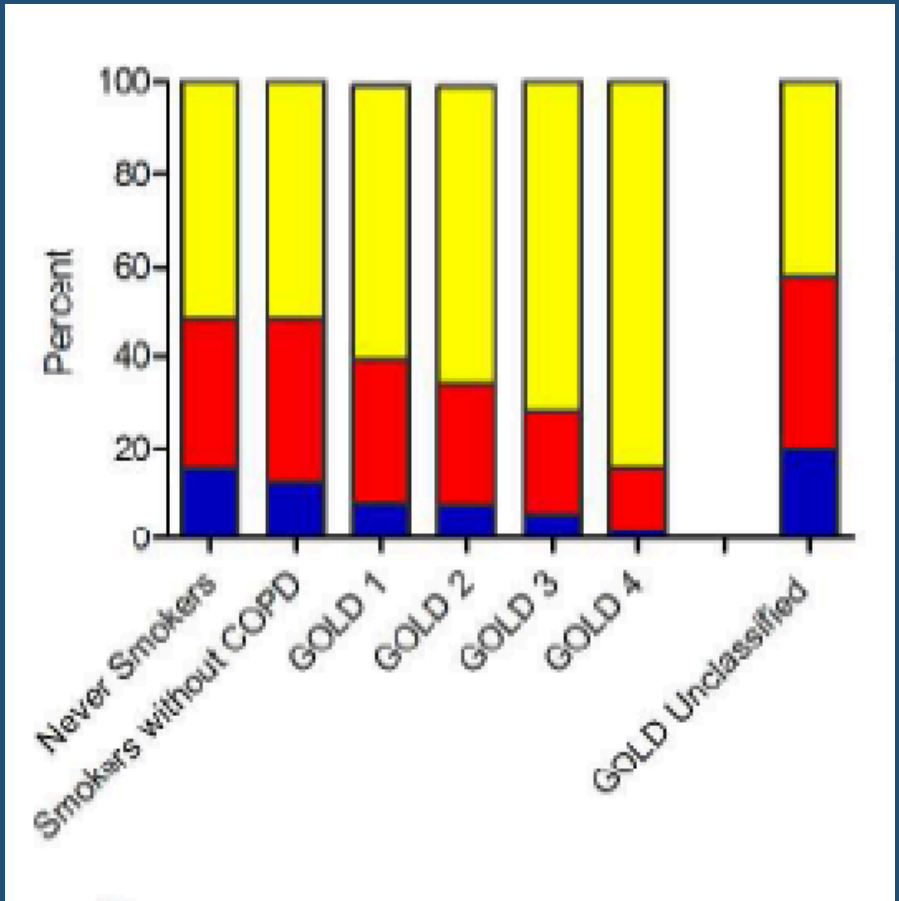
*Mean age 65
*Mean FEV1 44% predicted

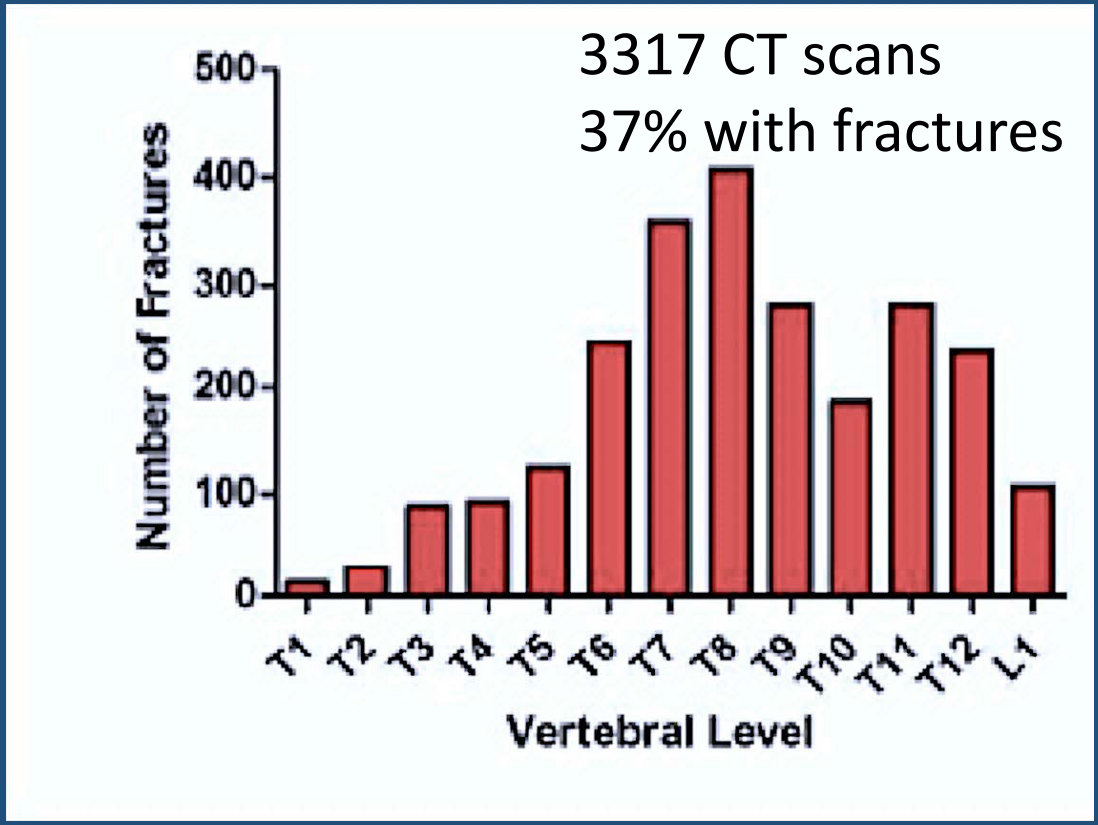
Ferguson et al. *Chest* 2009; 136:1456-1465

Prevalence Low Bone Mineral Density University of Pittsburgh Smoking Cohort (N=388)



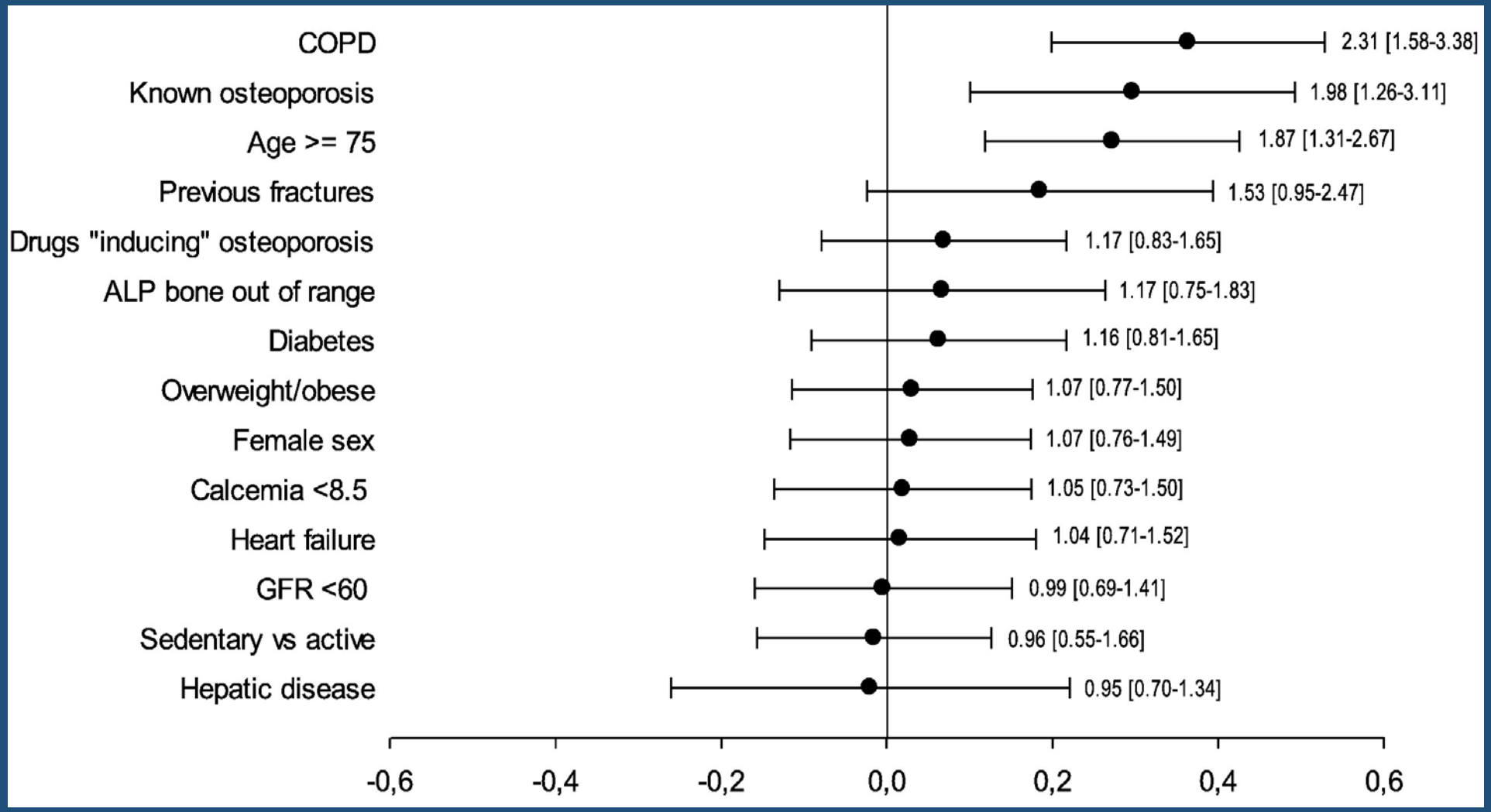
Prevalence of Low Bone Mineral Density and Vertebral Fractures on Chest CT - COPDGene





Jaramillo et al. *AnnalsATS* 2015; 12(5): 648-56.

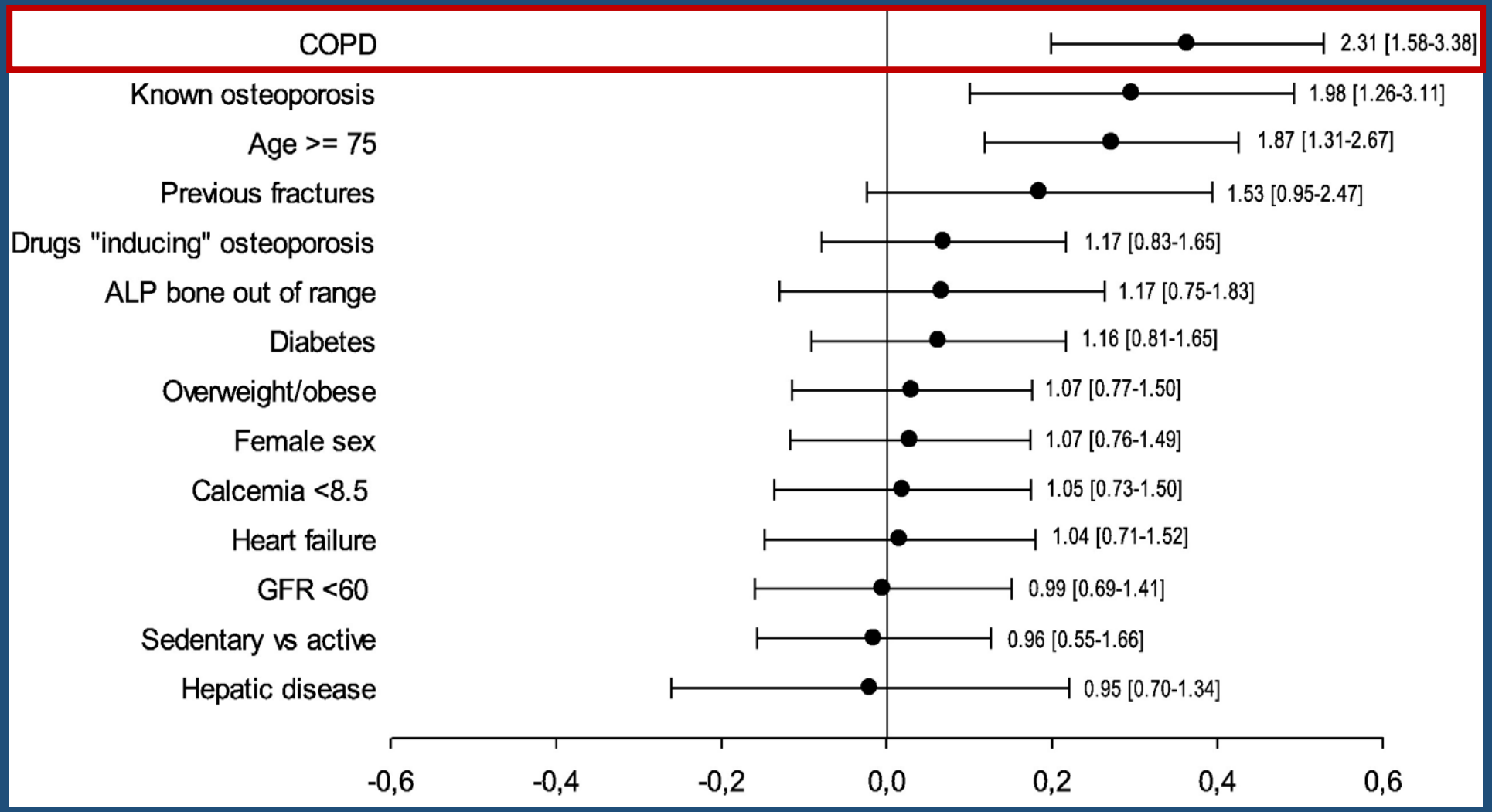
Odds of Vertebral Fracture by Diagnosis



Log odds ratio

Vitali et al. *Bone* 2015; 74:114-120 .

Odds of Vertebral Fracture by Diagnosis



Log odds ratio

Vitali et al. *Bone* 2015; 74:114-120 .

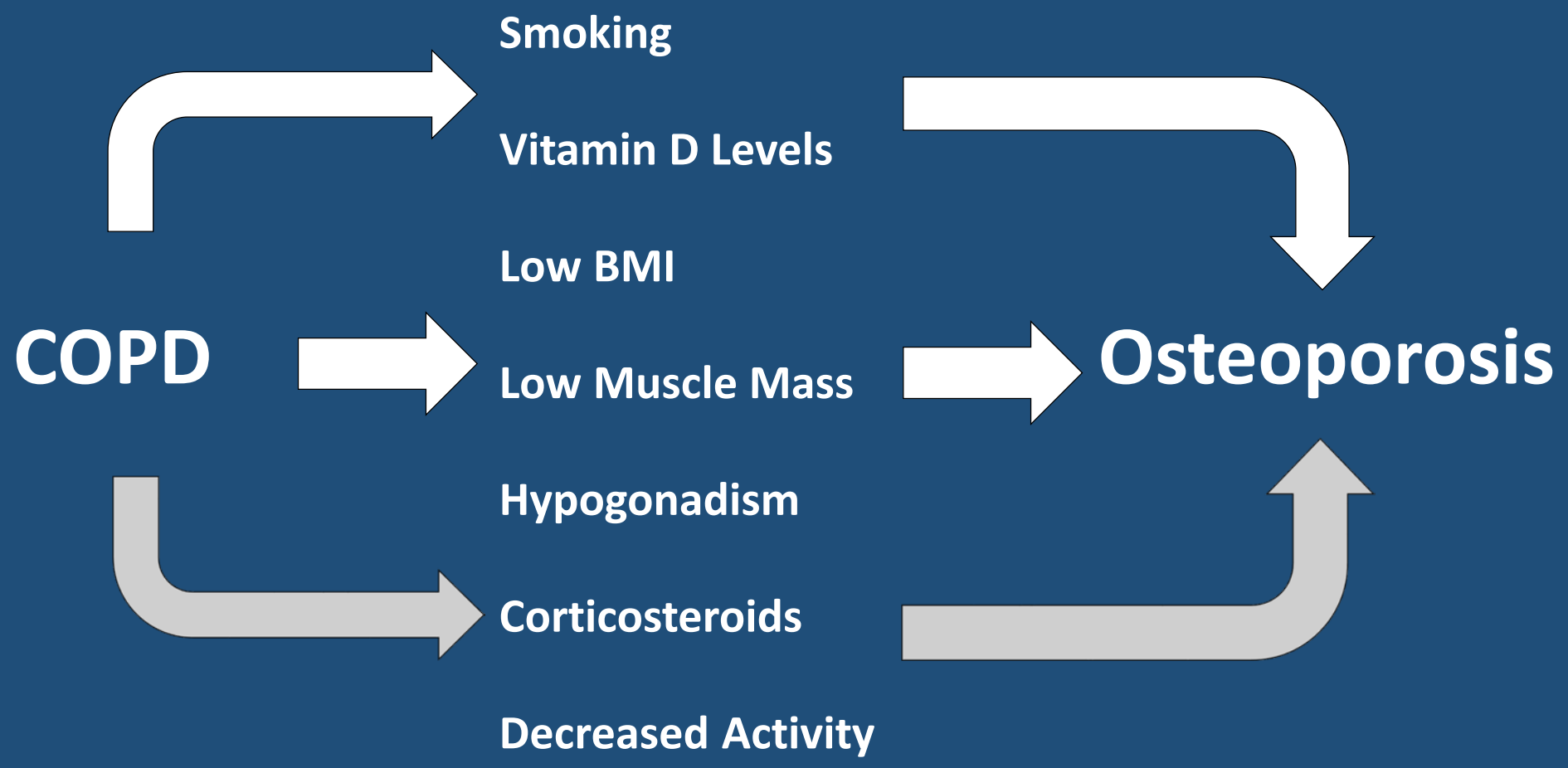
Impact of Fractures in COPD

- 60-70% higher risk of death after hip fracture in COPD patients compared to those without COPD
- High fracture rate with rare BMD assessments (4.4%) and osteoporosis treatment (2.8%) in male veterans with COPD
- Osteoporotic fractures lead to reduced vital capacity and FEV1

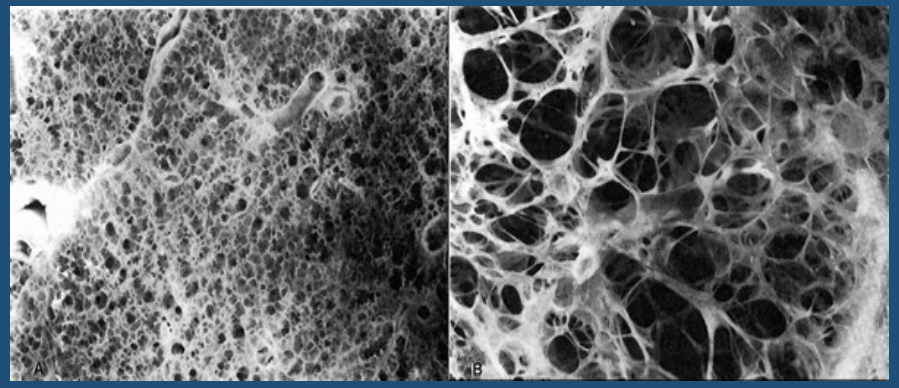
De Luise, *Eur J of Epidem* 2008; 23: 115-122.
Morden, *Osteoporosis Int* 2011; 22:1855-1862.
Lomardi, *Osteoporosis Int* 2005; 16: 1247-1253.

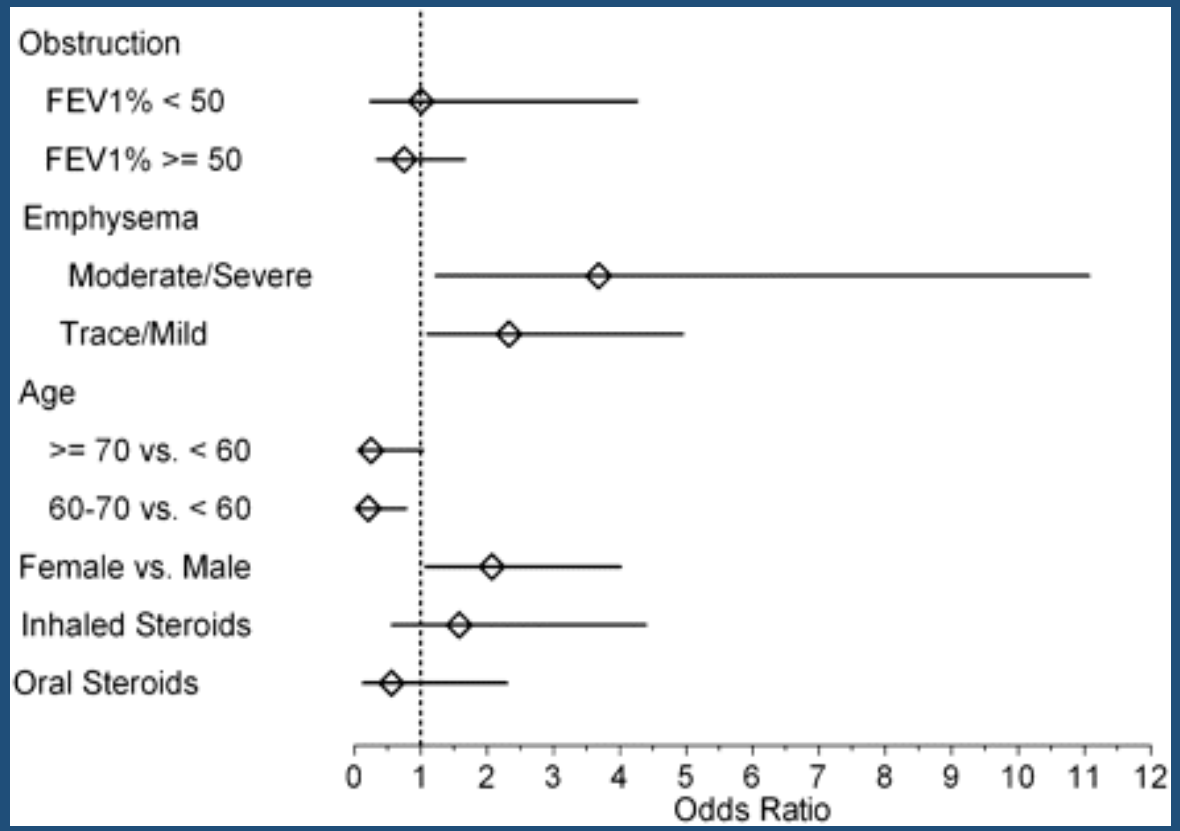
Risk Factors for COPD-Related Low Bone Mineral Density

Mechanisms of COPD-related Bone Mineral Density Loss

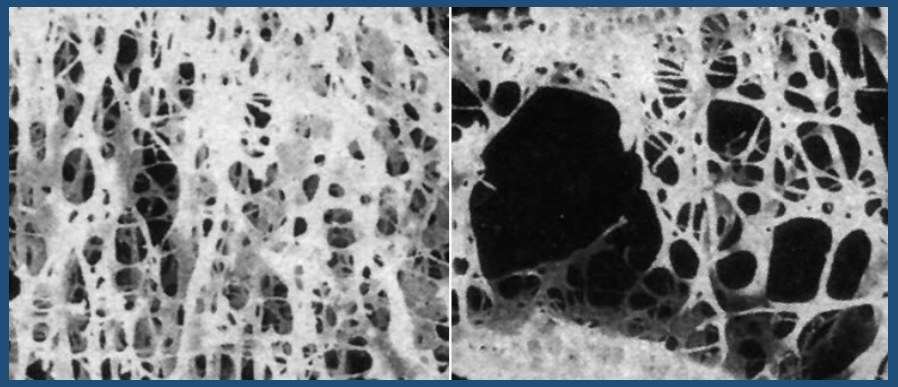


Emphysema and Bone Mineral Density Loss





	Chi Square	p value	Odds* Ratio	95% Confidence Interval
Gender (Male : Female)	24.297	0.00019	1.48	1.27 – 1.74
Race (NHW: AA)	10.08	0.001	1.4	1.14 – 1.72
Current smoking status (Current: Former)	5.65	0.02	1.23	1.03.– 1.46
BMI (Unit Odds)	6.59	0.02	1.02	1.004 – 1.03
QCT-BMD (mg/cc) (Unit odds)	118.67	<0.0001	0.988	0.986 – 0.99
Emphysema (LAA% at -950 HU) (Unit odds)	6.727	0.01	1.01	1.003 – 1.02



Bon et al. *AJRCCM* 2011; 183: 885-90.

Jaramillo et al. *AnnalsATS* 2015; 12(5): 648-56.

TRADITIONAL POPULATION RISK FACTORS PLUS COPD RISK FACTORS MULTIVARIATE MODEL*		
	OR (95% CI)	P value
AGE ENROLLMENT	1.03 (1.02-1.05)	<0.001
CURRENT SMOKER	1.41 (1.07-1.86)	0.016
REPORTED OSTEOPOROSIS	1.65 (1.18-2.31)	0.004
REPORTED HIP FRACTURE	5.87 (3.64-9.46)	<0.001
REPORTED RHEUMATOID ARTHRITIS	1.79 (1.24-2.59)	0.002
REPORTED DIABETES	1.64 (1.20-2.23)	0.002
TOTAL EXACERBATIONS	1.06 (1.04-1.08)	<0.001

*41,604 person years follow up; 215 hip fractures

COPDGene *unpublished data*

Systemic Inflammation Linking Lung and Bone

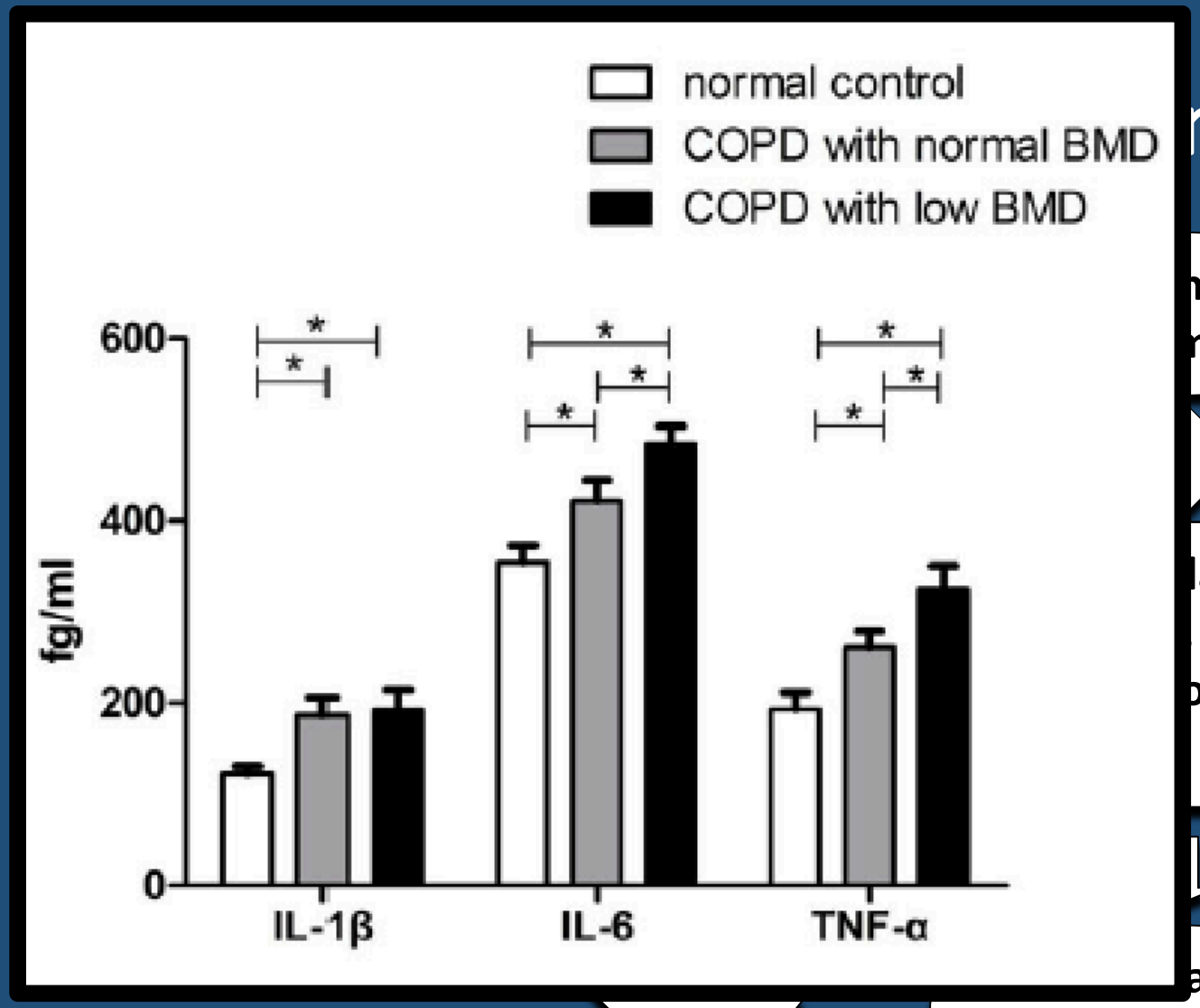
Lung Inflammation

Systemic Inflammation
CRP, IL-6, TNF-α, fibrinogen

Cardiovascular Disease

- Low BMI
- Muscle dysfunction
- Osteopenia
- Diabetes
- Anemia
- Depression

nking Lung and Bone



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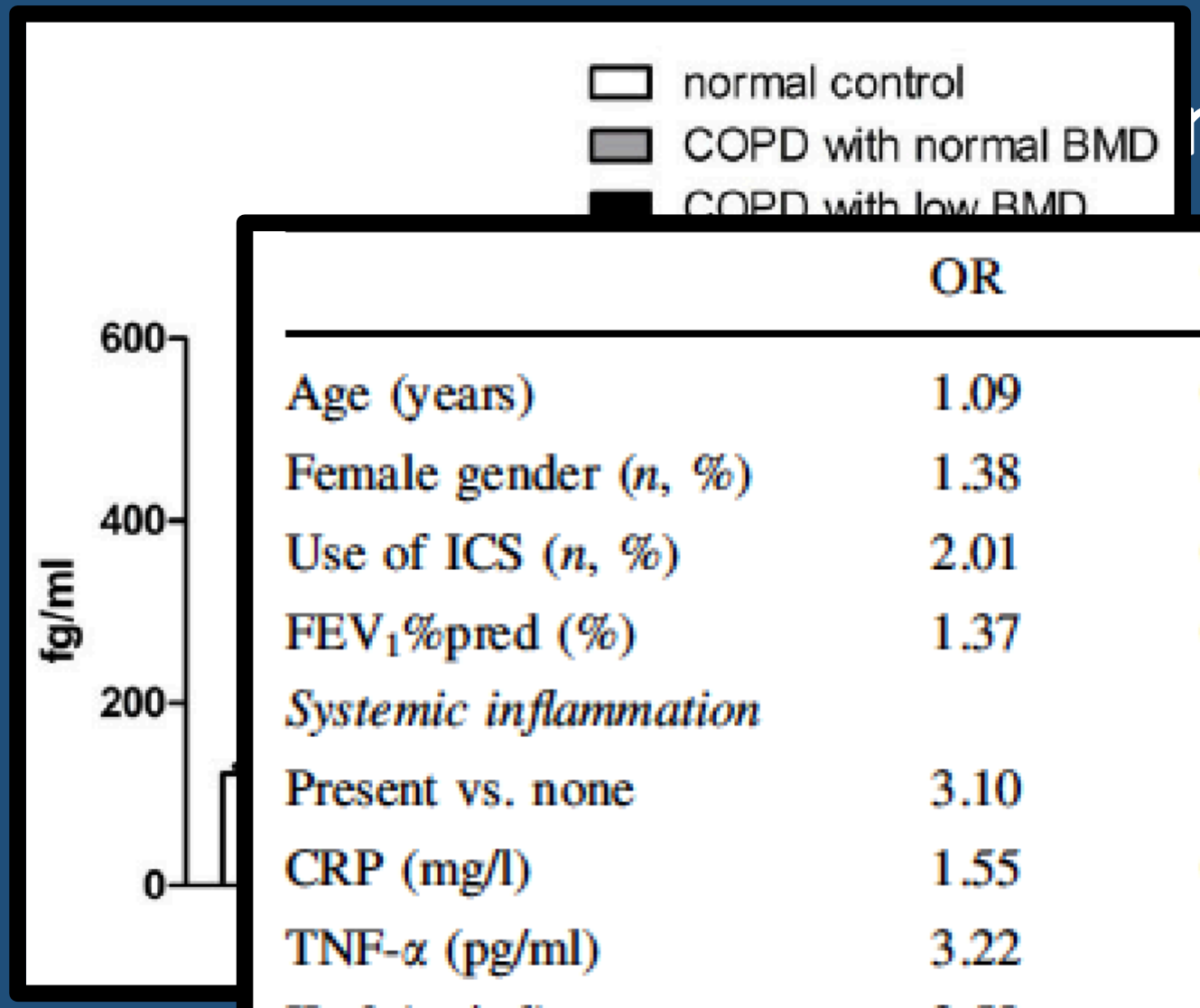

	OR	95% CI	*P* value
Age (years)	1.09	0.61–1.32	0.082
Female gender (*n*, %)	1.38	0.86–2.97	0.098
Use of ICS (*n*, %)	2.01	0.69–3.72	0.26
FEV_1%pred (%)	1.37	0.78–3.24	0.17
Systemic inflammation			
Present vs. none	3.10	1.48–5.06	*0.014*
CRP (mg/l)	1.55	0.92–3.03	0.062
TNF-α (pg/ml)	3.22	1.48–6.77	*0.010*
IL-6 (pg/ml)	2.58	1.32–4.56	*0.023*

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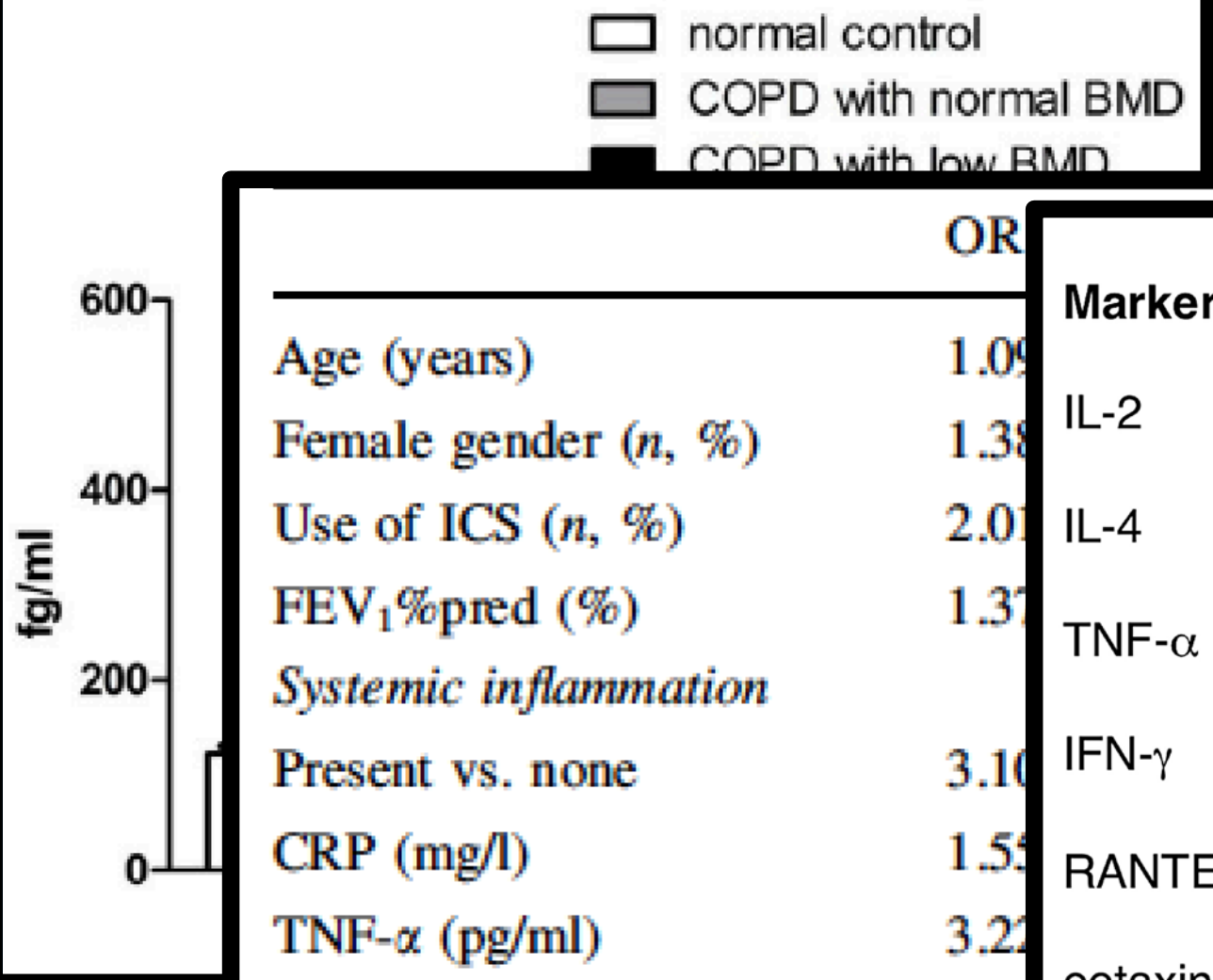
nking Lung and Bone



	OR
Age (years)	1.09
Female gender (*n*, %)	1.38
Use of ICS (*n*, %)	2.01
FEV_1%pred (%)	1.37
Systemic inflammation	
Present vs. none	3.16
CRP (mg/l)	1.55
TNF-α (pg/ml)	3.22
IL-6 (pg/ml)	2.58

Marker	CTx*	P-value	P1NP**	P-value
IL-2	N.S.	0.09	0.11 (+)	0.02
IL-4	0.39 (+)	0.005	0.27 (+)	0.01
TNF-α	0.31 (+)	0.04	0.27 (+)	0.04
IFN-γ	N.S.	0.30	0.10 (+)	0.02
RANTES	0.11(-)	0.01	0.08 (-)	0.02
eotaxin	0.21 (-)	0.003	0.17 (-)	0.02

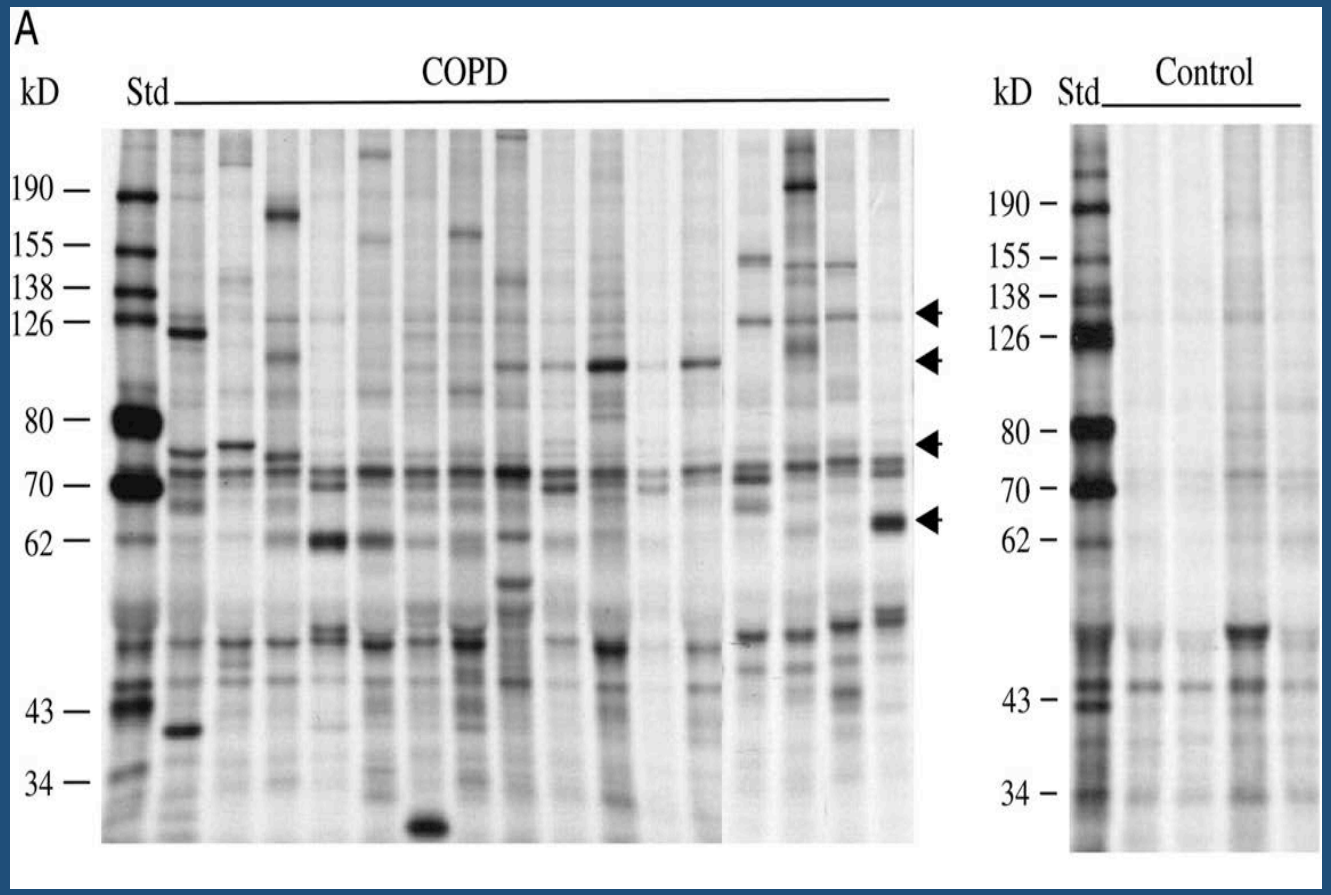
[1]Adjusted for bisphosphonate and steroid use.
*Type I collagen c-telopeptides; R^2 value(direction)
**Procollagen type I amino-terminal propeptide; R^2 value(direction)

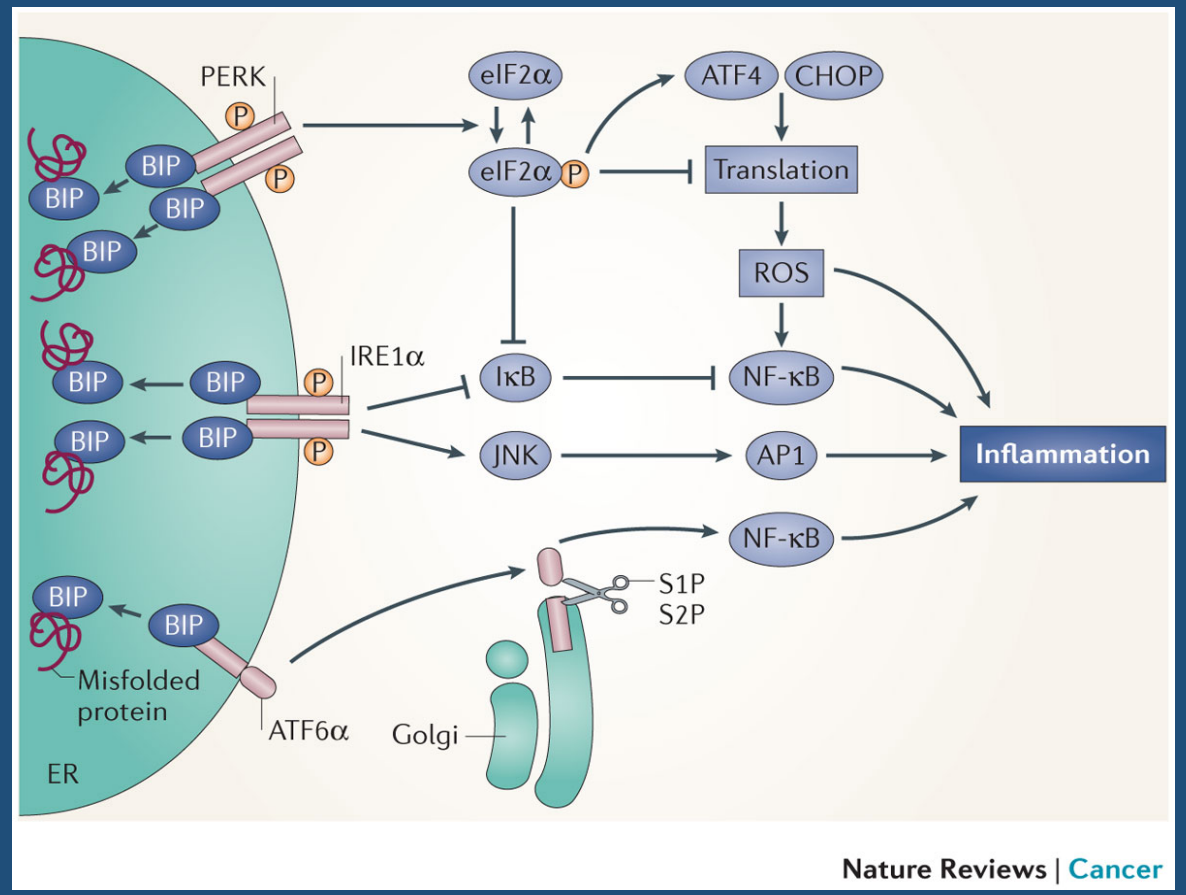
Bai et al. *Respiratory Research* 2011; 12: 157.

Liang et al. *Endocrine* 2012; 42:190-195.

Bon et al. *COPD* 2010; 7(3).:186-91.

Autoimmunity Linking Lung and Bone

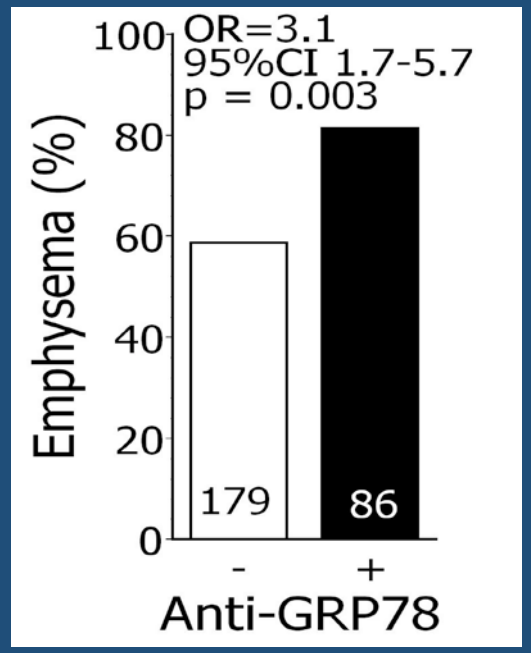


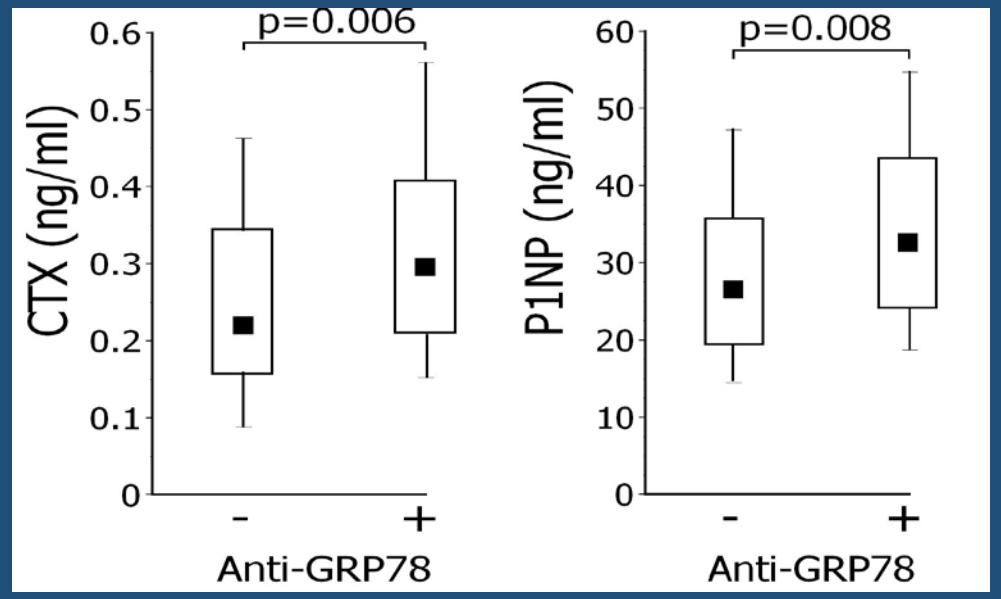


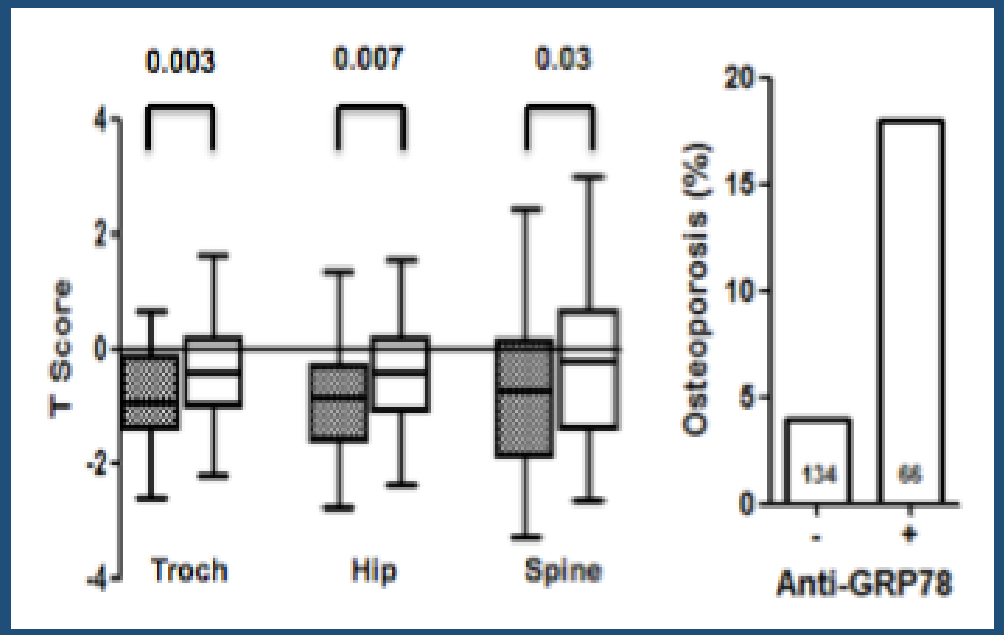
Carol A. Feghali-Bostwick et al. *Am J Respir Crit Care Med* **2008,** 177, 156-163.

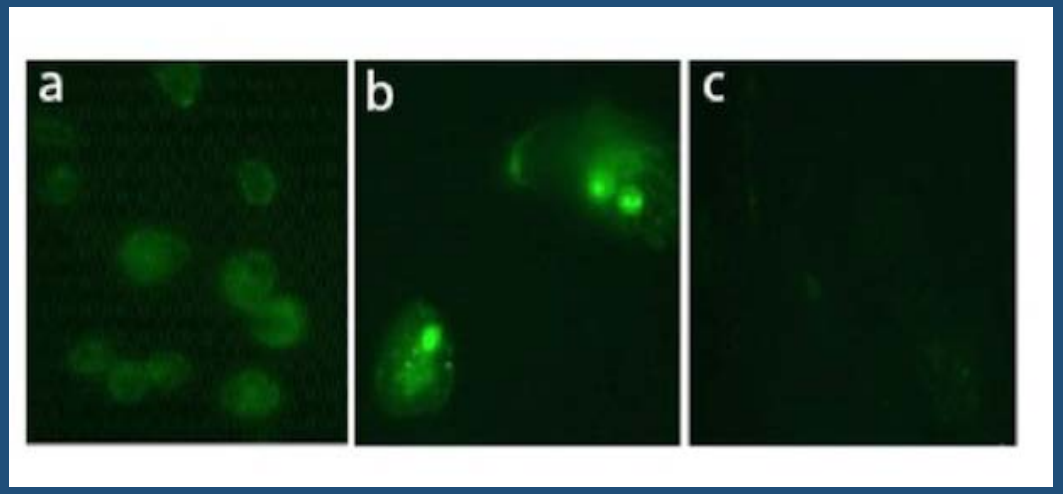
Wang et al., *Nature Reviews Cancer* **14**, 581–597 (2014)

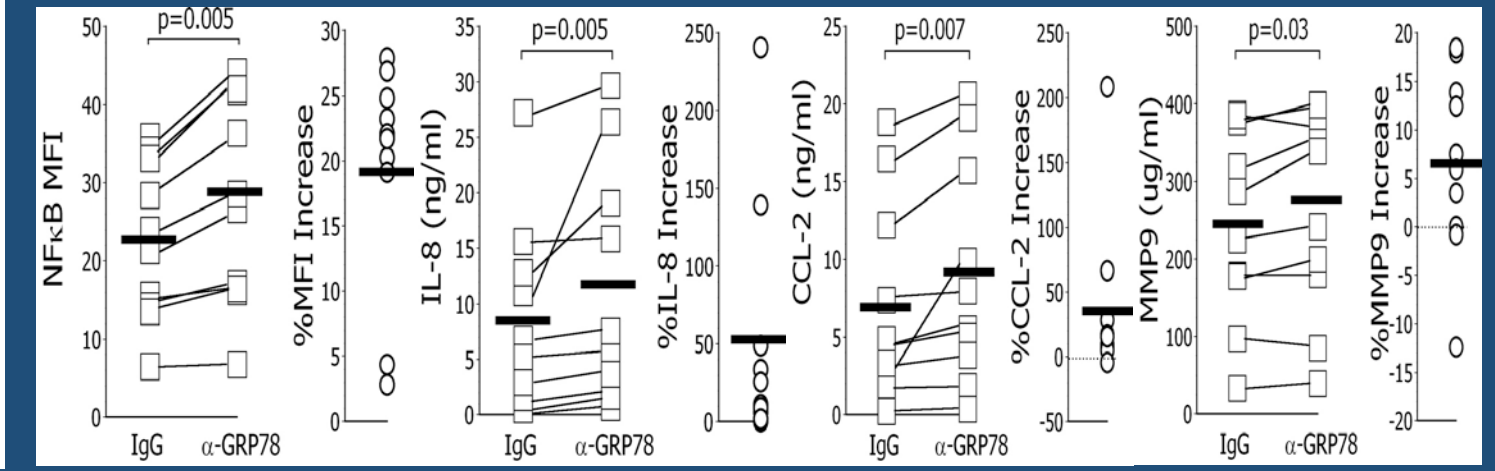
Prevalence of Emphysema and Low BMD Increased with anti-GRP78 Autoantibody Positivity











Bon et al. *PLoS One* 2014; 9(9).

Osteoporosis Screening in COPD

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C. Bone densitometry
D. Pneumococcal antibody panel testing

Annals of Internal Medicine | CLINICAL GUIDELINES

Screening for Osteoporosis: An Update for the U.S. Preventive Services Task Force

Heidi D. Nelson, MD, MPH; Elizabeth M. Haney, MD; Tracy Dana, MLS; Christina Bougatsos, BS; and Roger Chou, MD

Women ≥ 65 or < 65 if risk factors; "current evidence is insufficient to assess the balance of benefits and harms of screening for osteoporosis in men. "

CLINICAL GUIDELINES | ACP Clinical Practice American College of Physicians GUIDELINES

Screening for Osteoporosis in Men: A Clinical Practice Guideline from the American College of Physicians

Amir Qaseem, MD, PhD, MHA; Vincenza Snow, MD; Paul Shekelle, MD, PhD; Robert Hopkins Jr., MD; Mary Ann Forciea, MD; and Douglas K. Owens, MD, MS, for the Clinical Efficacy Assessment Subcommittee of the American College of Physicians*

"Data are insufficient in men to determine whether the presence of respiratory disease……increase the risk for low-BMD mediated fracture."

- Osteoporosis is a major comorbidity that is often under-diagnosed and associated with poor health status and prognosis.
- Osteoporosis is often associated with emphysema, decreased body mass index, and low fat-free mass. Low bone mineral density and fractures are commonly in COPD patients even after adjustment for steroid use, age, pack-years of smoking, current smoking, and exacerbations.
- Osteoporosis should be treated according to usual guidelines.

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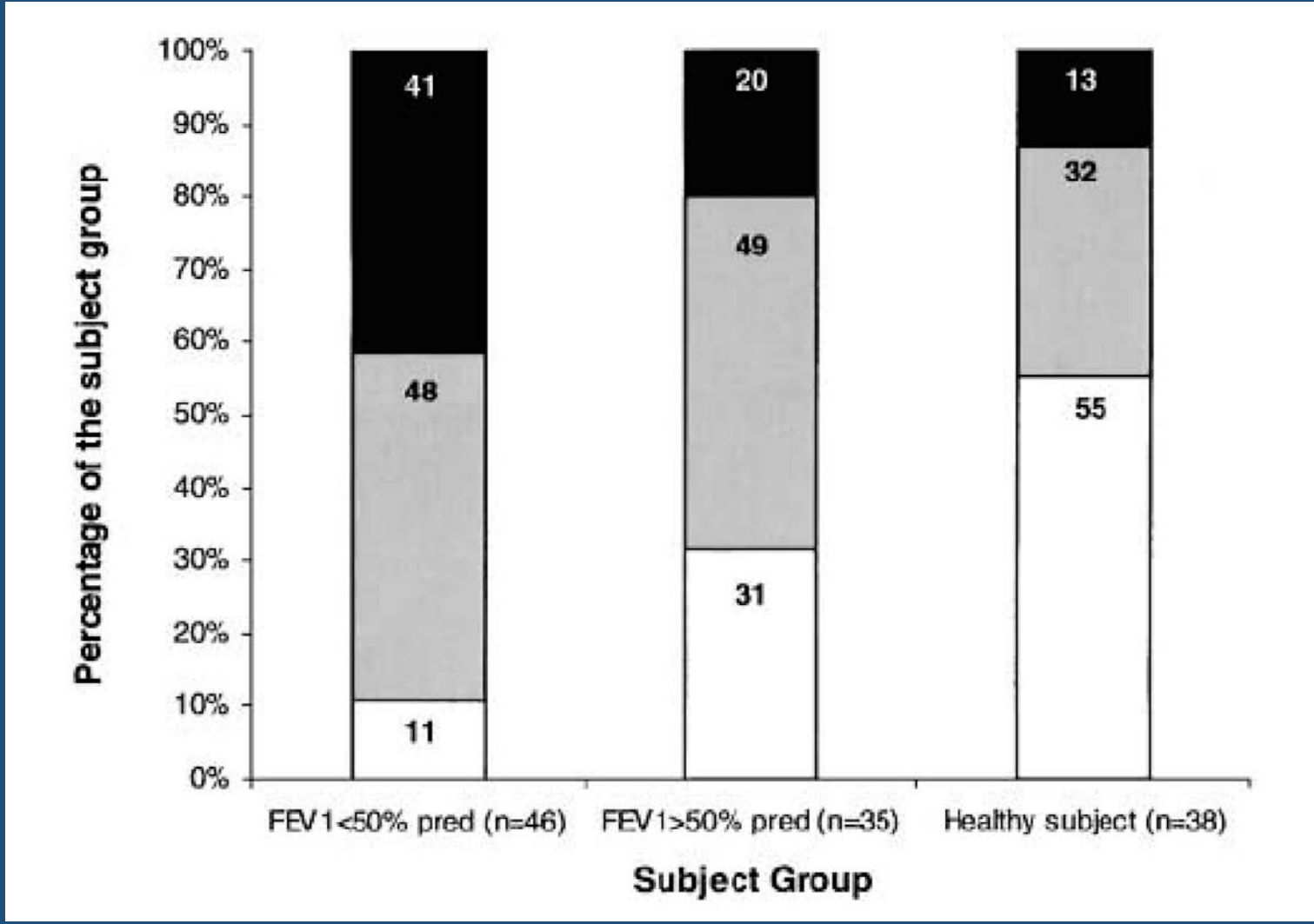
Prevalence of Low BMD by Obstruction Severity



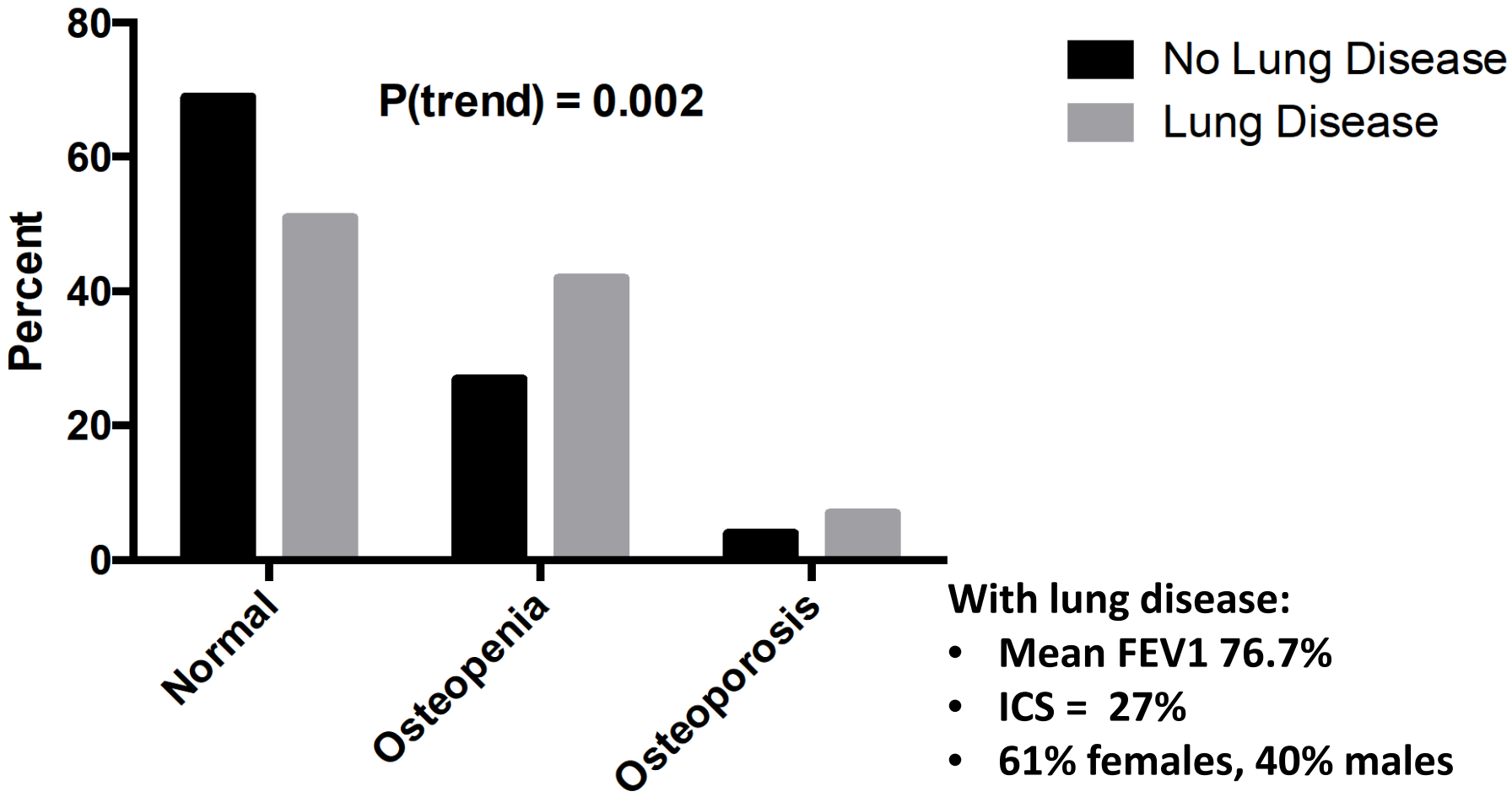
osteoporosis

osteopenia

normal BMD

Bolton et al. *Am J Respir Crit Care Med* 2004; 170:1286-93..

Prevalence Low BMD UofPitt Smoking Cohort



With lung disease:

- **Mean FEV1 76.7%**
- **ICS = 27%**
- **61% females, 40% males**

(My) Approach to Screening

- All COPD patients ≥ 65 years of age (men and women)
- All COPD patients with history of fracture
- COPD patients 50 - 64 years of age with any of the following:
  - Severe airflow obstruction (FEV1 < 50% predicted)
  - Chronic oral steroid use (rare)
  - Frequent acute exacerbations of COPD requiring short courses of systemic steroids
  - Significant radiographic emphysema detected on chest imaging

Treatment of COPD-Related Osteopenia and Osteoporosis

Who to treat?

Country: US (Caucasian) Name/ID: About the risk factors

Questionnaire:

1. Age (between 40 and 90 years) or Date of Birth
   Age: Date of Birth: Y: M: D:
2. Sex ◯ Male ◯ Female
3. Weight (kg)
4. Height (cm)
5. Previous Fracture ◉ No ◯ Yes
6. Parent Fractured Hip ◉ No ◯ Yes
7. Current Smoking ◉ No ◯ Yes
8. Glucocorticoids ◉ No ◯ Yes
9. Rheumatoid arthritis ◉ No ◯ Yes
10. Secondary osteoporosis ◉ No ◯ Yes
11. Alcohol 3 or more units/day ◉ No ◯ Yes
12. Femoral neck BMD (g/cm^2)

Select BMD

Clear Calculate

- T score $\leq$ -2.5 or fragility fracture
- FRAX score with 10-year probability of hip fracture or combined major osteoporotic fracture of $\geq$ 3 or $\geq$ 20 percent, respectively

How to Treat

- Lifestyle modifications
  - Weight-bearing exercise
  - Avoid smoking, excess alcohol intake
- Assure adequate calcium and vitamin D intake
  - Calcium 1000 – 1200 mg daily
  - Vitamin D supplementation 600 to 800 IU/day, check levels
- Treatment of secondary causes (hypogonadism in men)
- Bisphosphonate therapy (first-line)
- Denosumab
- Teriparatide (severe osteoporosis)
- SERMs (raloxifene)

Summary

- Osteoporosis is prevalent in COPD, occurs independently of traditional osteoporosis risk factors, and contributes significantly to morbidity and mortality
- Multiple mechanisms, including systemic inflammation and autoimmunity, likely contribute to bone loss in COPD
- Future research efforts should focus on delineating mechanisms of bone loss, establishing disease-specific screening guidelines, and assessing response to therapy