



# Osteoporosi e Malattie Respiratorie Croniche



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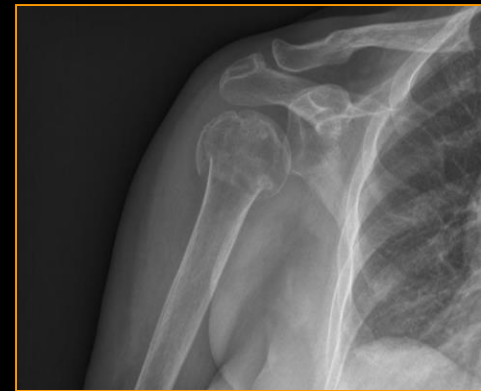


## Some current concepts on Osteoporosis

- Osteoporosis, literally “porous bone”, a disease characterized by weak bone
- A major public health problem, affecting hundreds of millions of people worldwide, mainly but not exclusively postmenopausal women
- Main clinical consequences: bone fractures associated with substantial pain and suffering, disability and even death
- A significant burden on both the individual and the society

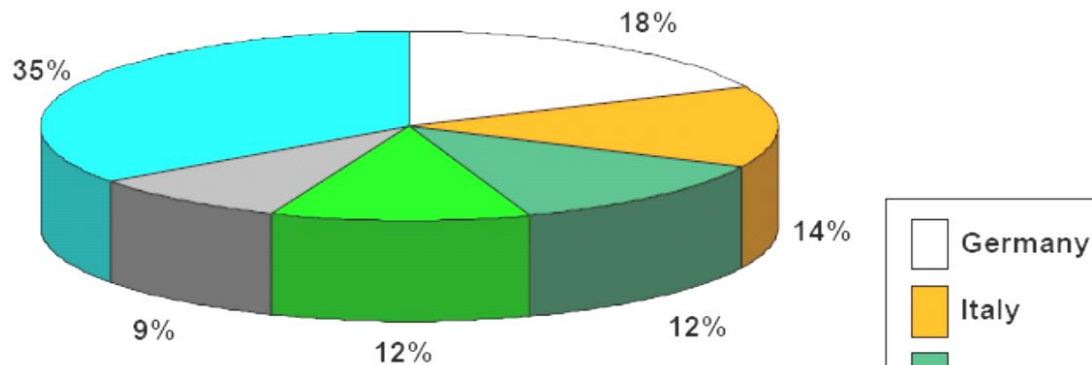
# The conceptual evolution in defining Osteoporosis

- A disease of decreased bone mass (*Consensus Conference, 1996*)
- A disease of decreased bone strength (*Consensus Conference, 2001*)

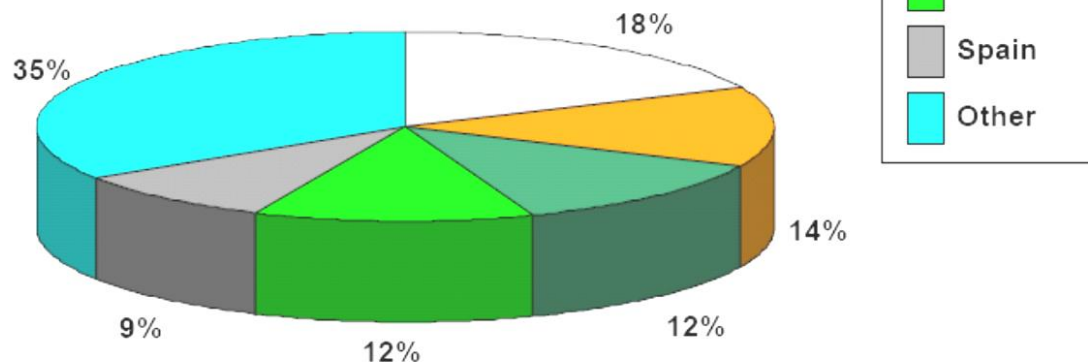


# The prevalence of Osteoporosis in the EU is estimated at 27,6 million in 2010

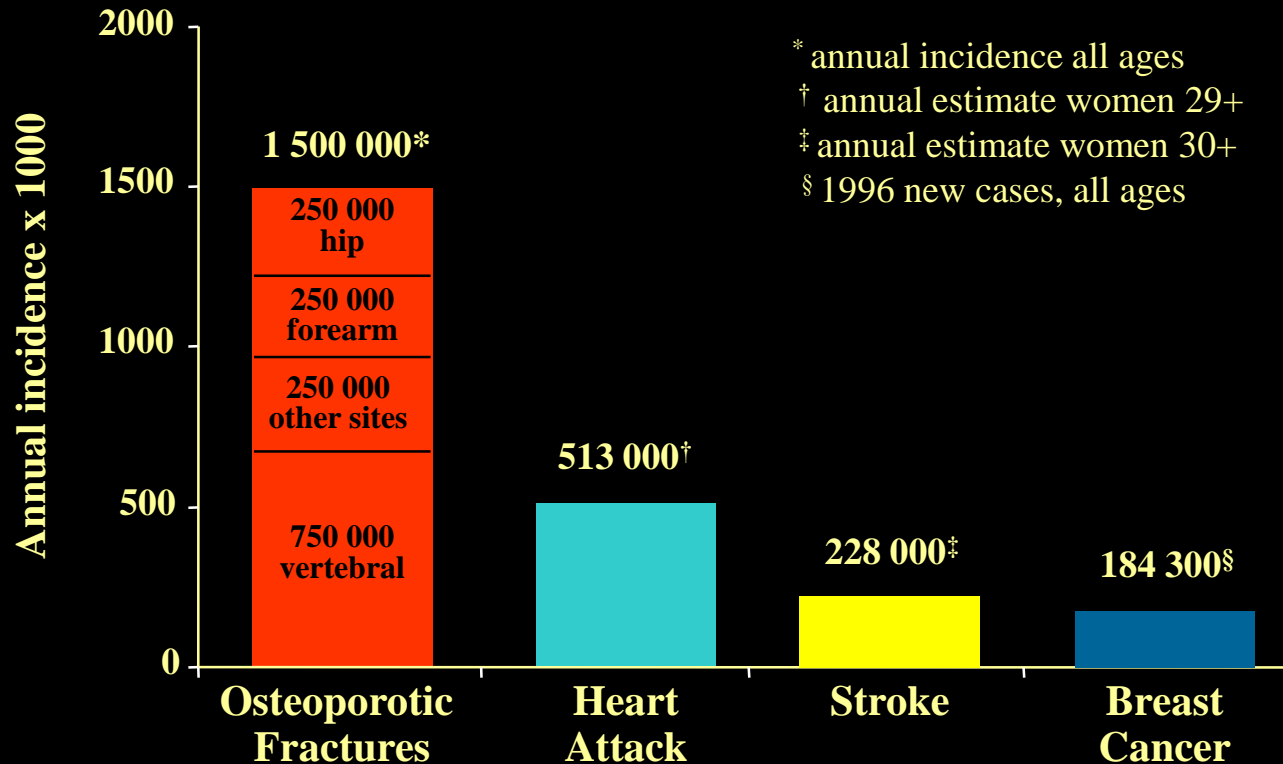
*22.0 million women in the EU have osteoporosis*



*5.6 million men in the EU have osteoporosis*



# Osteoporotic Fractures in Women: Comparison with Other Diseases

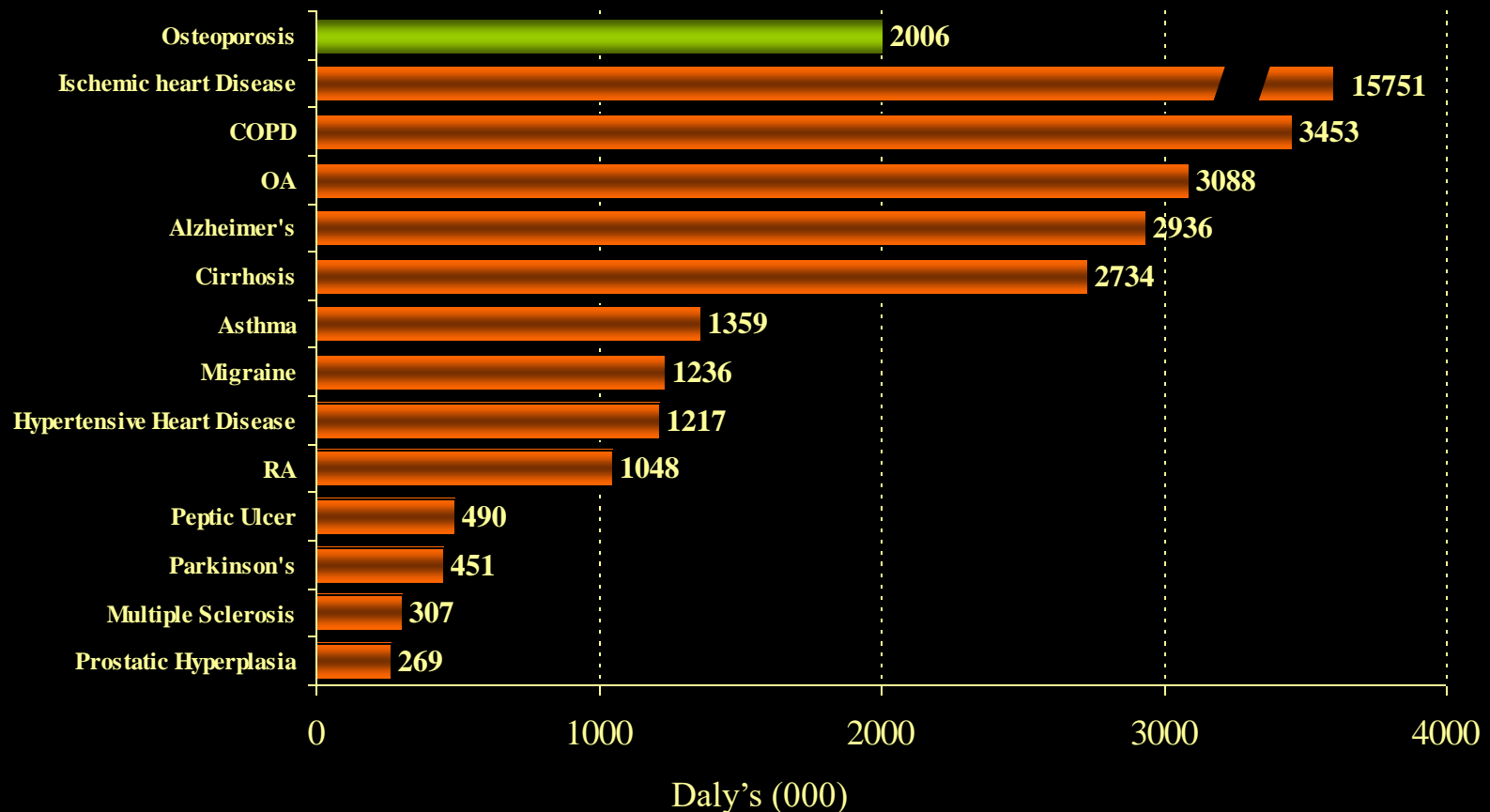


Riggs BL, Melton LJ. Bone 1995  
Heart and Stroke Facts, 1996, American Heart Association  
Cancer Facts & Figures, 1996, American Cancer Society

# Overall estimation of fragility fractures and F/M ratio in Italy ( 2006)

	Total	F/M Ratio in patients older than 65 years		
		65 to 74 years	Older than 75 years	Overall older than 65 years
Hip fractures (M > 65 + F > 65)	87,000	2.48	3.68	3.43
Humeral fractures (M > 65 + F > 45)	48,000	2.99	4.98	4.10
Ankle fractures (M > 65 + F > 45)	36,000	3.15	3.19	3.17
Wrist fractures (M > 65 + F > 45)	85,000	5.01	9.04	6.85
Vertebral fractures (M > 65 + F > 45)	Clinical fractures 47,000 Overall fractures 155,000	2.01	3.27	2.64

# Burden of diseases estimated as disability-adjusted life-years (DALYs) lost in Europe

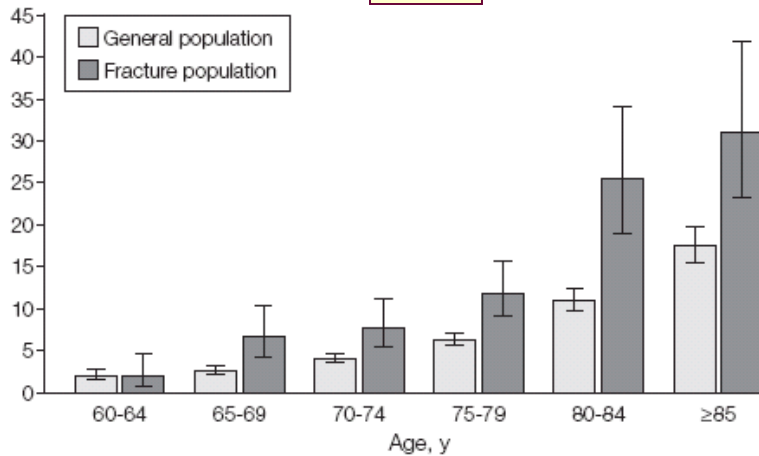


# Mortality rates for the General Population and Fracture Participants according to age

## The Dubbo Osteoporosis Epidemiology Study

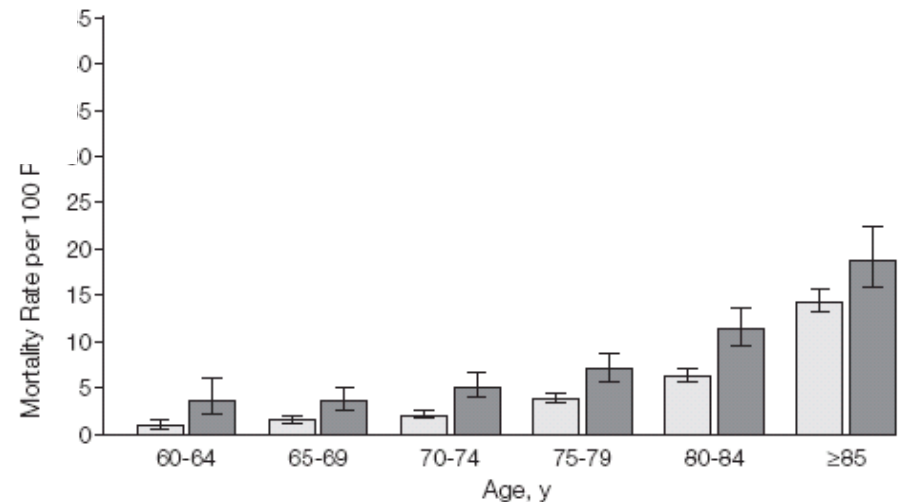
April 1989/ May 2007

### Men



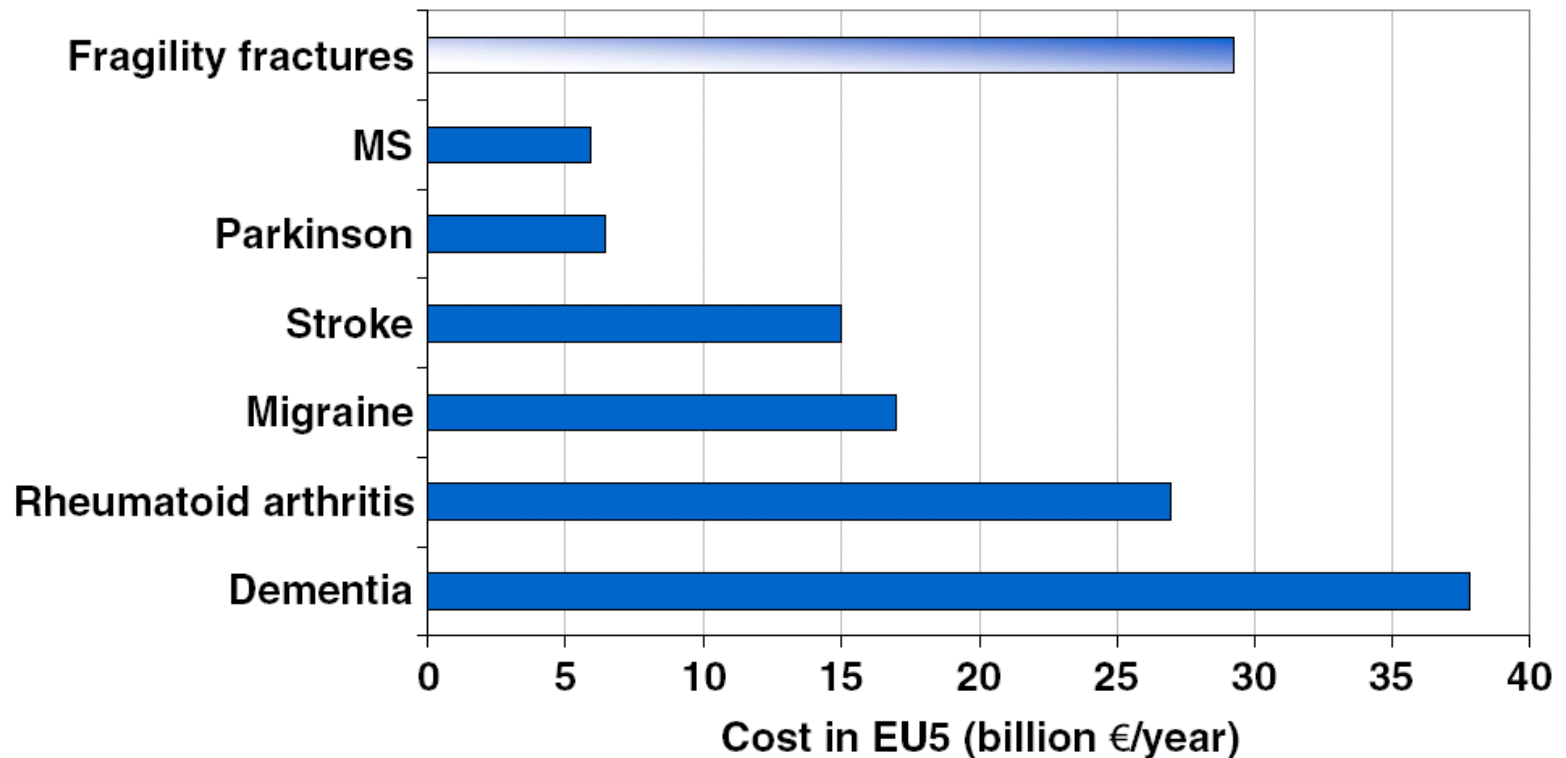
343 low-trauma fractures/ 197 deaths

### Women

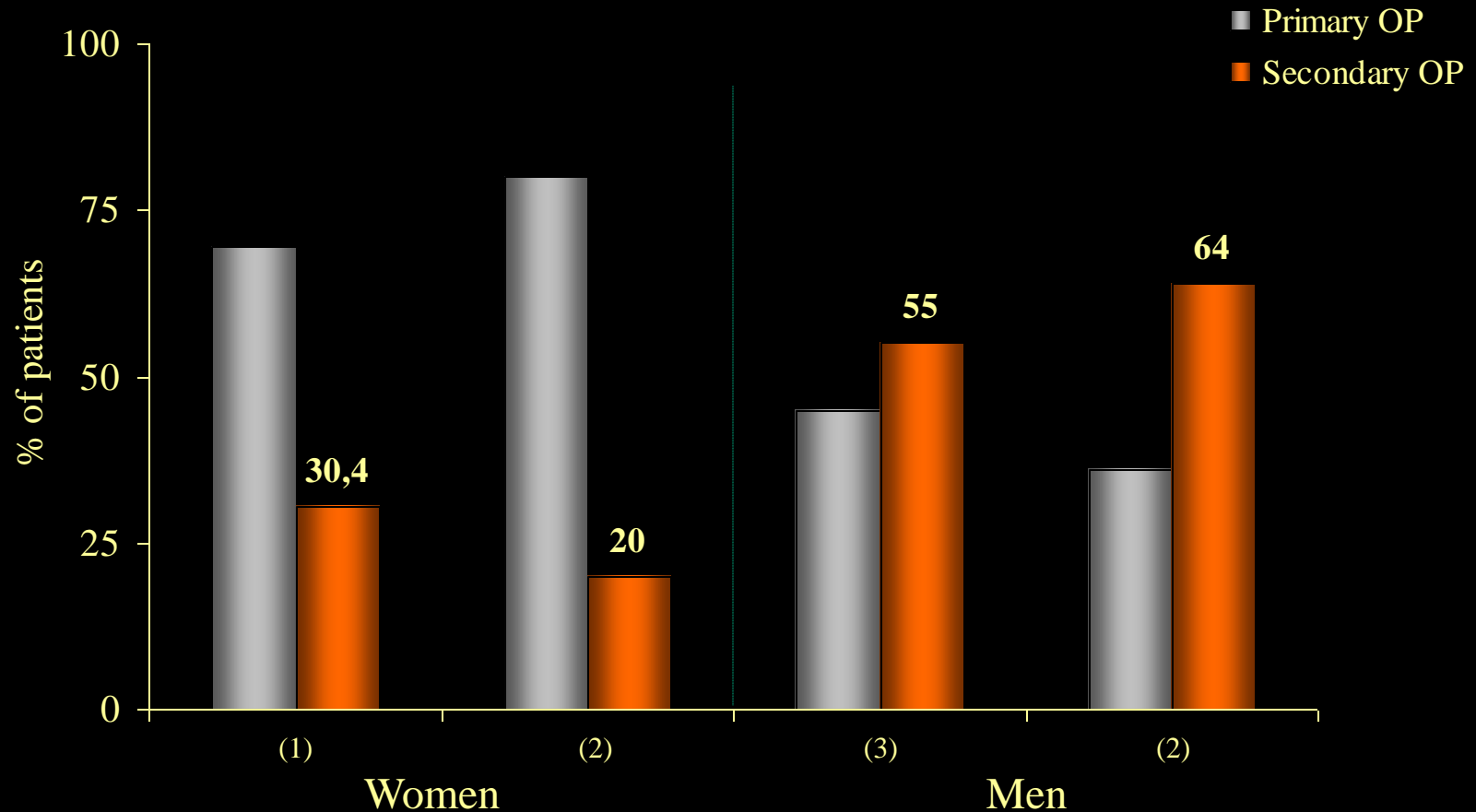


952 low-trauma fractures/ 461 deaths

# Cost of disease in EU5



# Percentage of Primary and Secondary forms of Osteoporosis in men and PM women with a vertebral fracture at presentation



1) *J R Soc Med* 1994

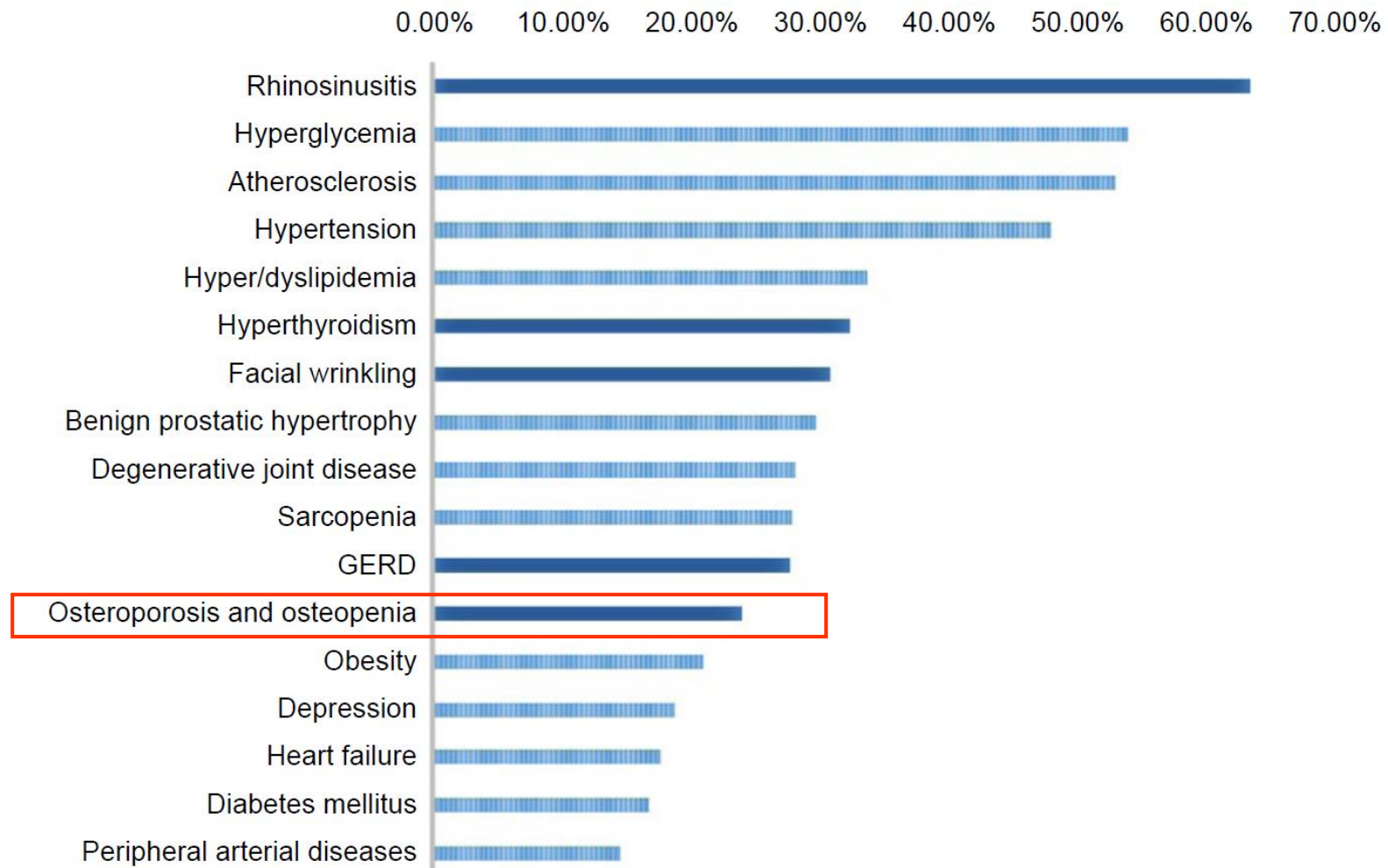
2) *Ann Intern Med* 1995

3) *Baillieres Clin Rheumatol* 1993

# **A link between Osteoporosis and Respiratory Diseases ?**

- **Chronic Obstructive Pulmonary Disease (COPD)**
- **Asthma**
- **Interstitial lung disease**
- **End-stage pulmonary disease**
- **Other chronic respiratory models**

# Underrecognized comorbidities of chronic obstructive pulmonary disease



## Osteoporosis Associated with Chronic Obstructive Pulmonary Disease

Ryo Okazaki, Reiko Watanabe, Daisuke Inoue


*Third Department of Medicine, Teikyo University Chiba Medical Center, Japan*

J Bone Metab 2016;23:111-120

International Journal of COPD

Dovepress

open access to scientific and medical research

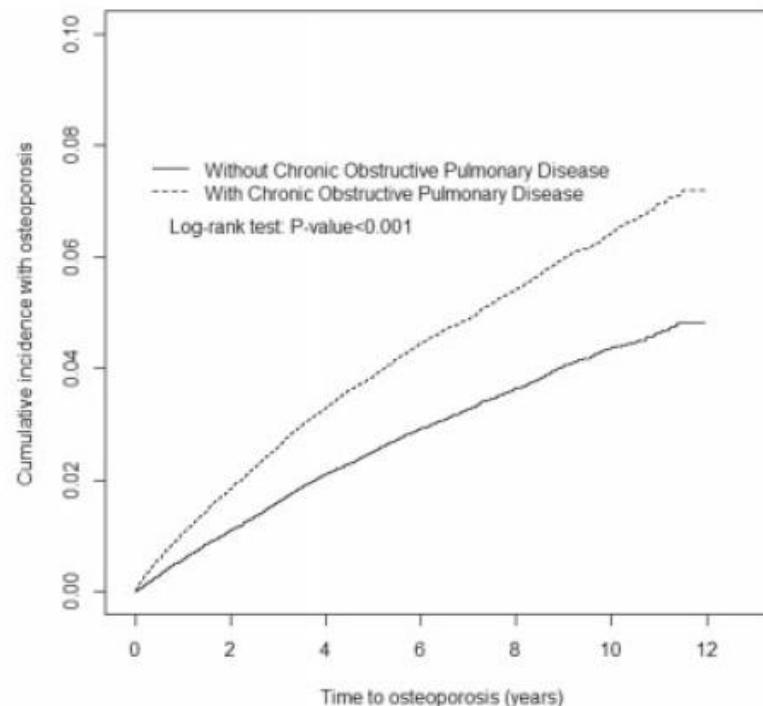
 Open Access Full Text Article

REVIEW

## COPD and osteoporosis: links, risks, and treatment challenges

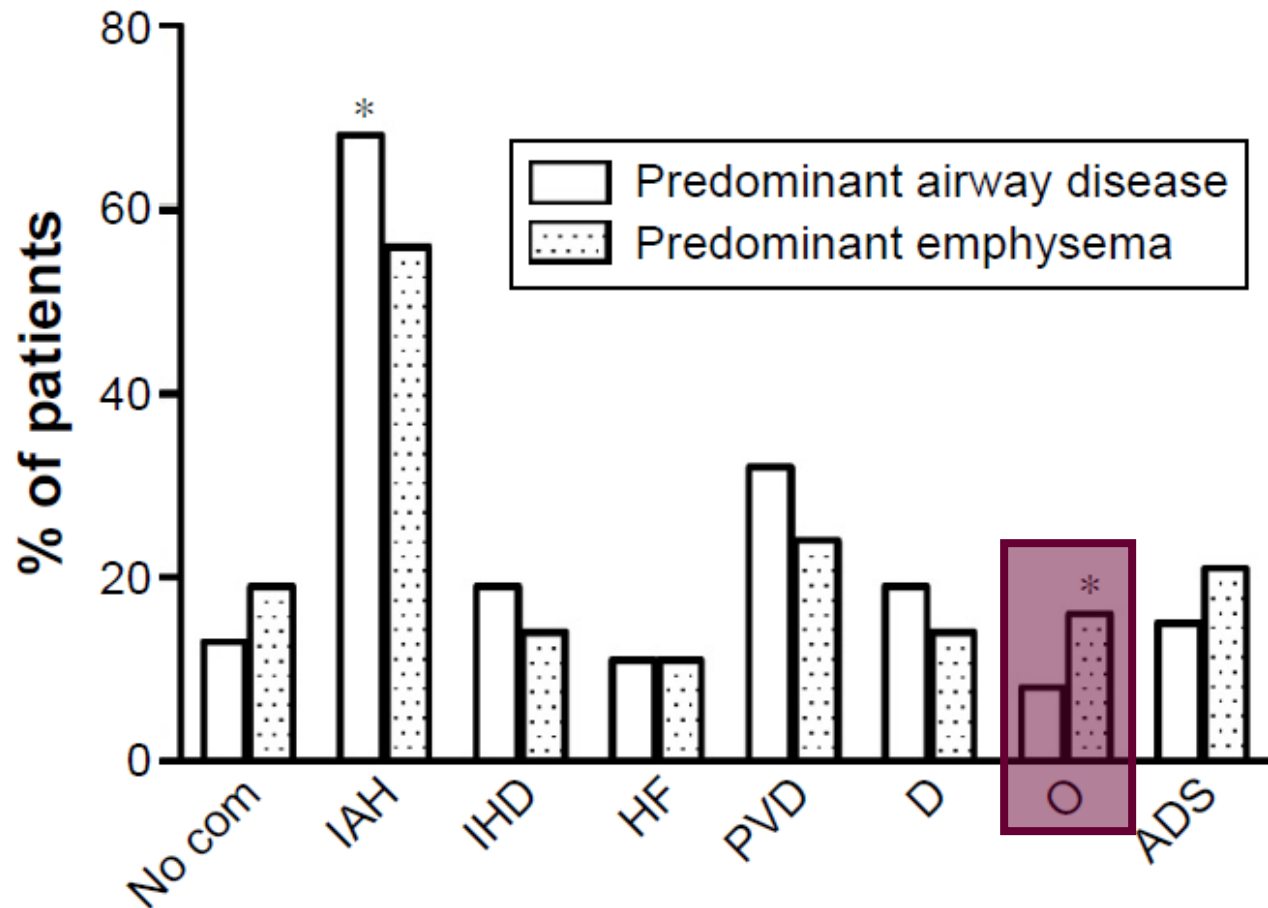
International Journal of COPD 2016;11 637–648

# Cumulative incidence comparison of Osteoporosis between subjects with and without chronic obstructive pulmonary disease



COPD, No.						
At risk	58706	50480	42647	34354	24657	13610
osteoporosis events	0	1020	699	464	297	211
Non-COPD, No.						
At risk	58448	51040	43393	34911	24887	13515
osteoporosis events	0	603	482	334	221	147

# Comparison of the prevalence of each examined comorbidity in 222 patients with a predominant airway disease phenotype and in 190 patients with a predominant emphysema phenotype

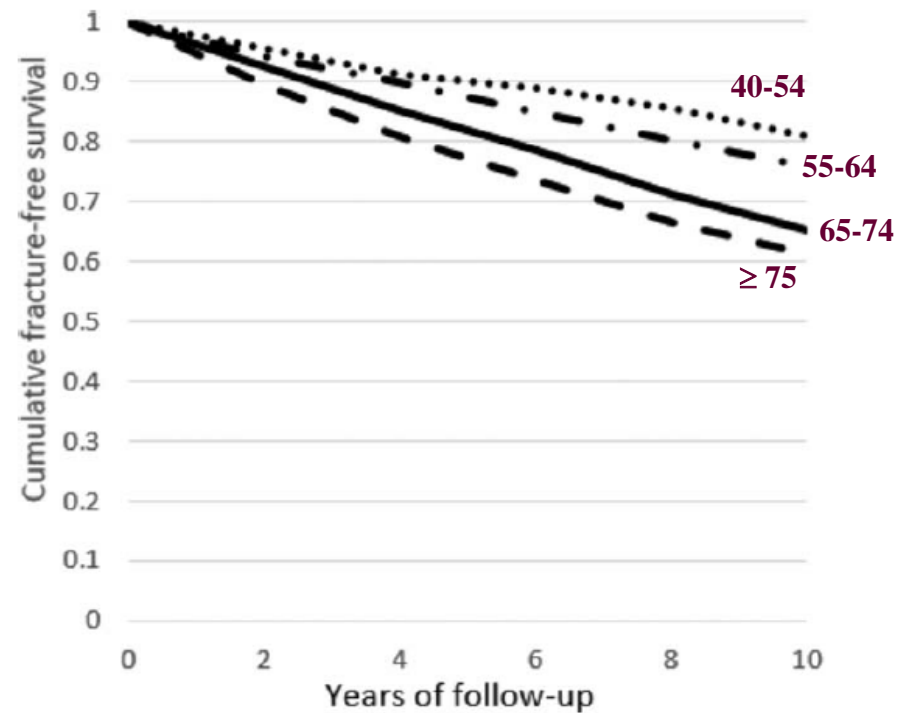
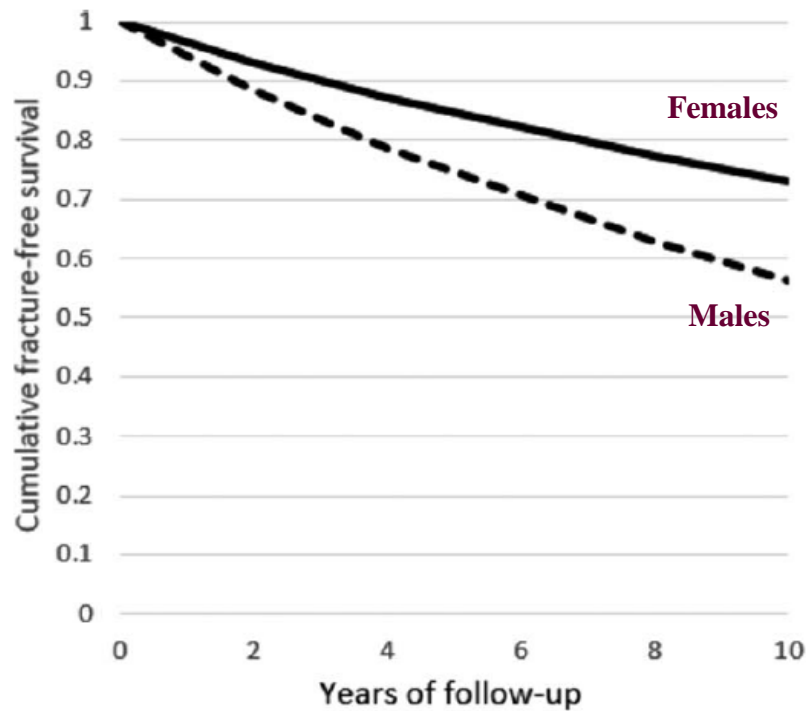


**Abbreviations:** ADS, anxious depressive syndrome; com, comorbidities; D, diabetes; HF, heart failure; IAH, idiopathic arterial hypertension; IHD, ischemic heart disease; O, osteoporosis; PVD, peripheral vascular disease.

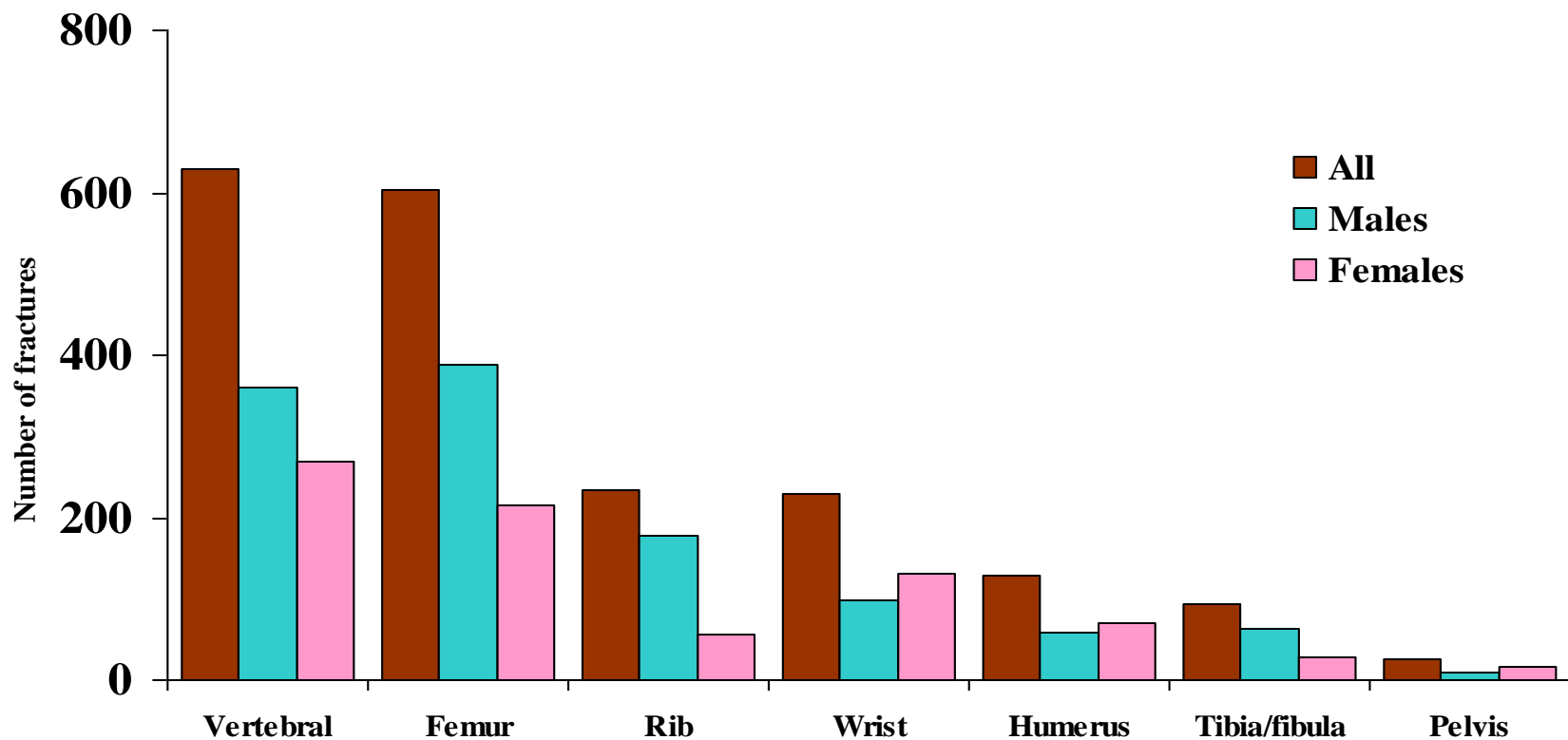
## Risks of all-cause and site-specific fractures among hospitalized patients with COPD

Kuang-Ming Liao, MD<sup>a</sup>, Fu-Wen Liang, PhD<sup>b</sup>, Chung-Yi Li, PhD<sup>b,c,\*</sup>

11,312 patients with COPD.

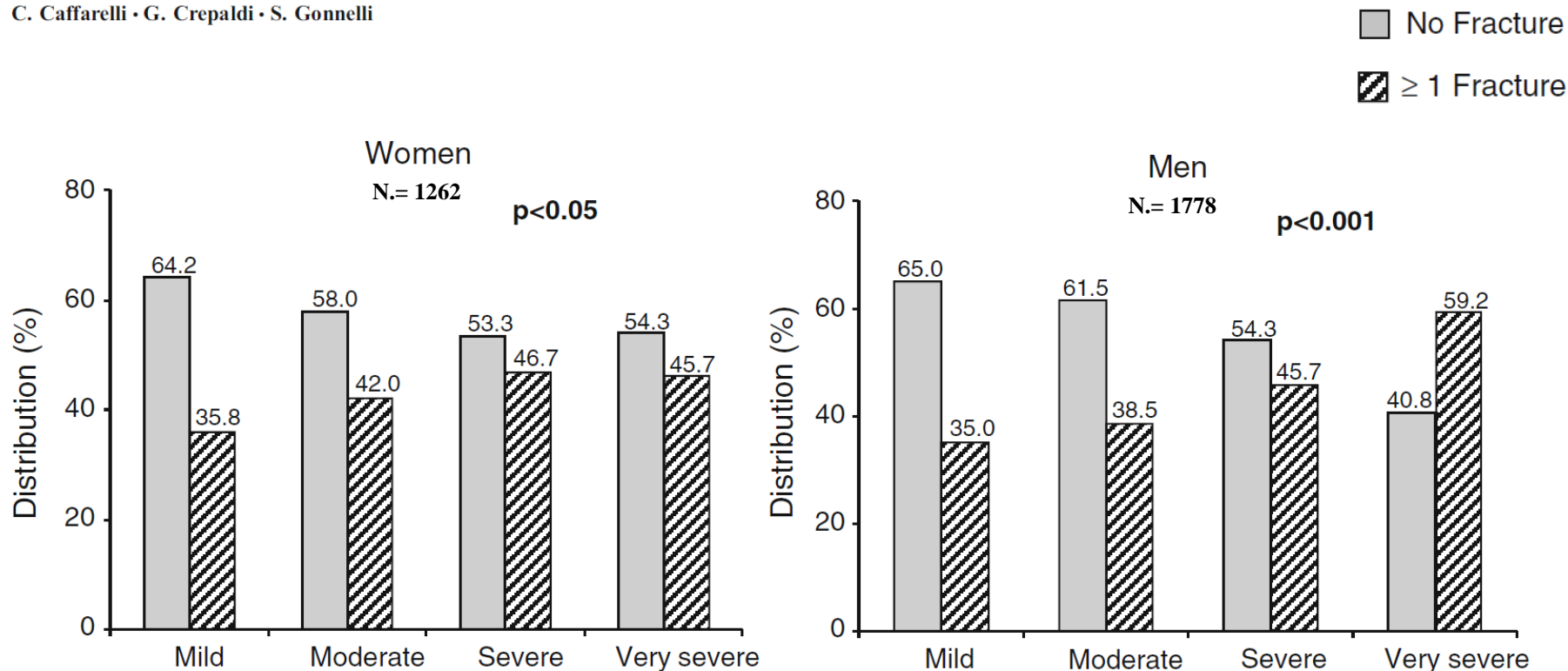


# Site-specific fractures among 11,312 patients with COPD according to gender



## Vertebral fractures in patients with chronic obstructive pulmonary disease: the EOLO Study

R. Nuti • P. Siviero • S. Maggi • G. Guglielmi •  
C. Caffarelli • G. Crepaldi • S. Gonnelli

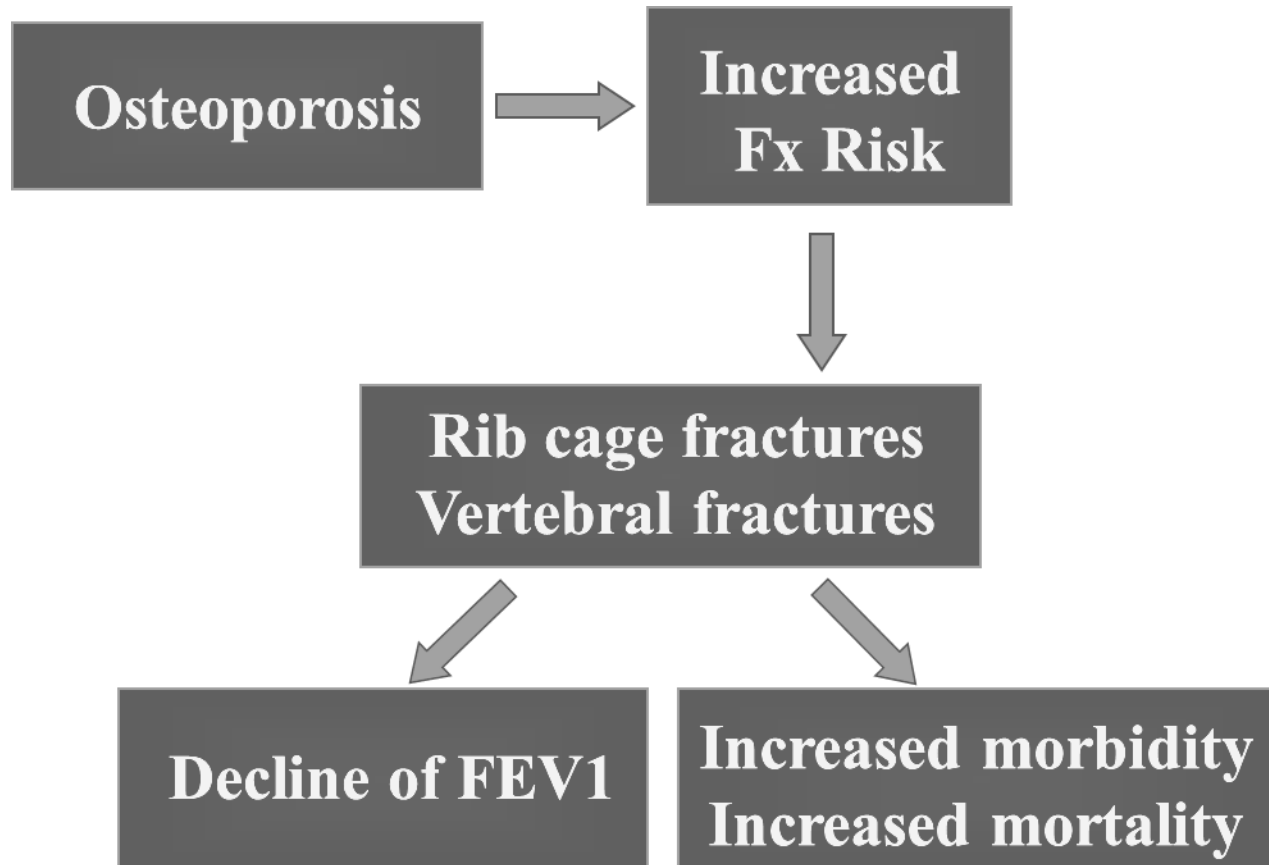


\* COPD severity according to GOLD criteria

# Prevalence of Vertebral Fractures in main observational studies on patients with COPD

Study	N	Sex (M/F)	Mean Age (years)	Vertebral Fx (%)
Graat-Verboom et al.	775	67/33	63	-
Watanabe et al.	136	136/0	71	79
Graat-Verboom et al.	255	158/97	68	37
Ferguson et al.	658	382/276	65	-
Graat-Verboom et al.	133	80/53	69	32
Silva et al.	95	62/33	67	-
Ogura-Tomomatsu et al.	85	78/7	75	35
Hattiholi et al.	102	64/38	66	
Carter et al.	350	350/0	68	52
Jorgensen et al.	62	16/46	63	24
McEvoy et al.	312	312/0	69	66
Papaioannou et al.	127	—	72	27
Nuti et al.	3,030	1,778/1,262	70	41
Kjensli et al.	465	231/234	63	31
Katsura et al.	20	0/20	72	40

# **COPD and Osteoporosis : a challenging vicious circle**



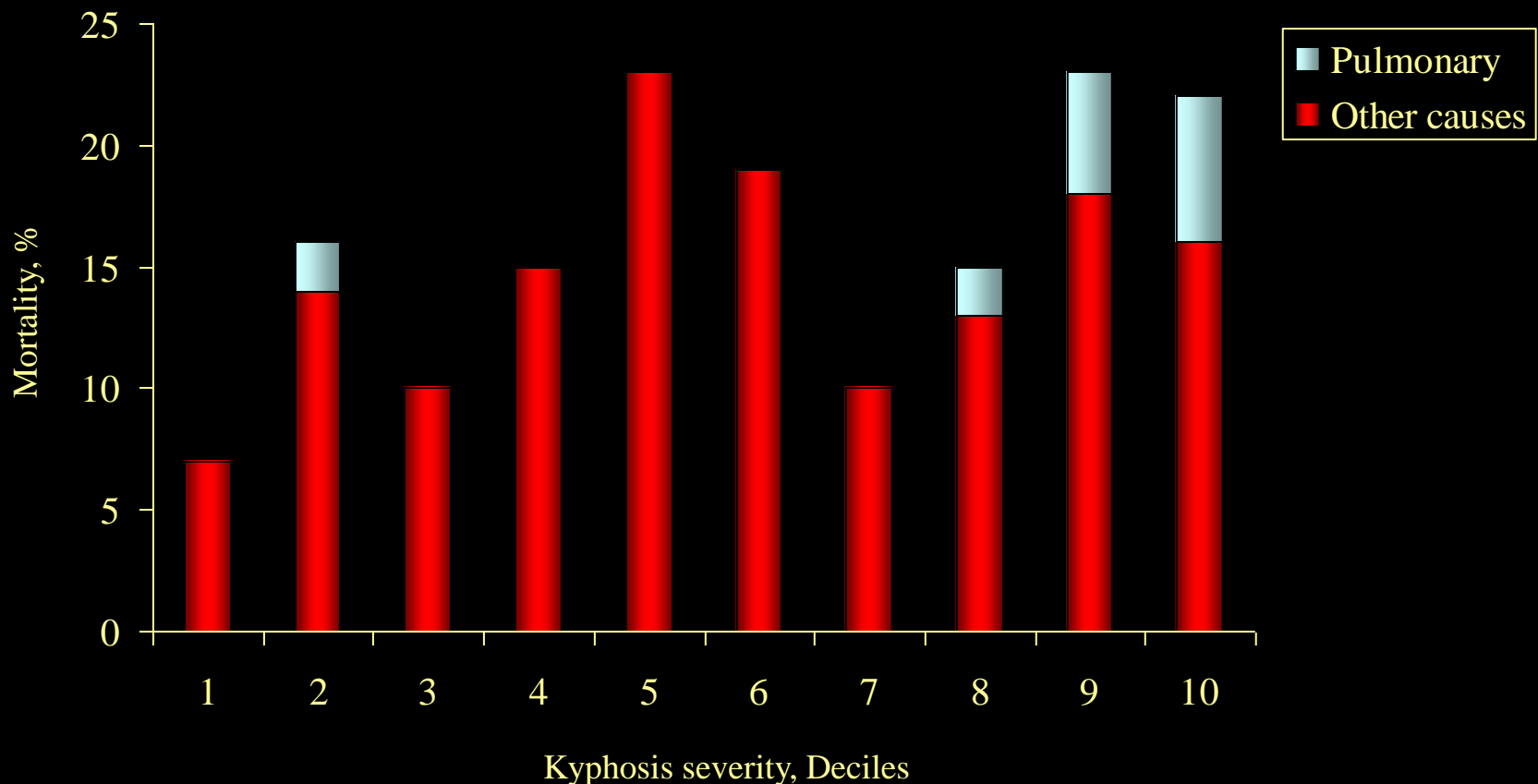
# Osteoporosis-Related Kyphosis and Impairments in Pulmonary Function: A Systematic Review

Robyn A Harrison,<sup>1</sup> Kerry Siminoski,<sup>1,2</sup> Dilini Vethanayagam,<sup>1</sup> and Sumit R Majumdar<sup>1</sup>

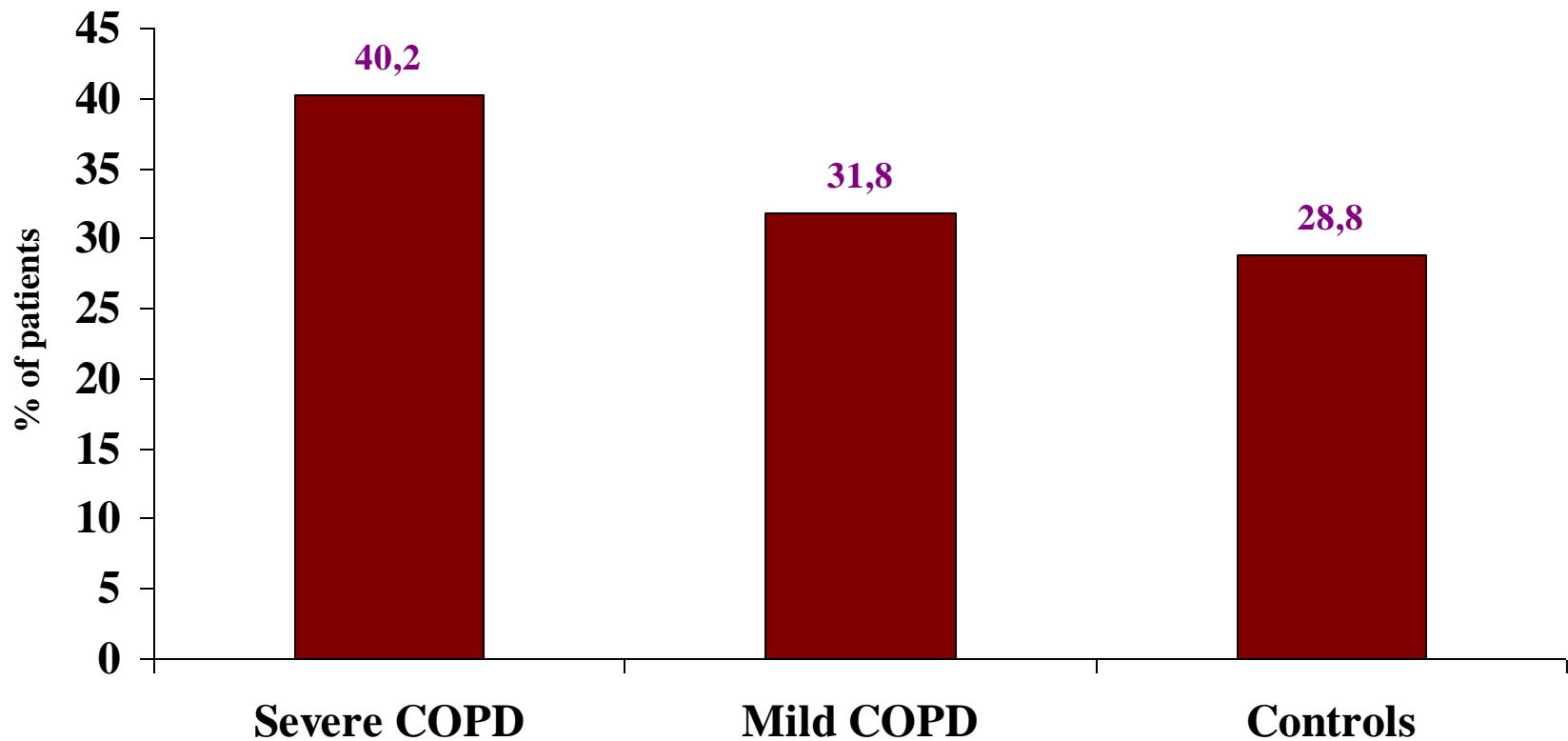
- **The reduction in Vital capacity was quantified as a 9 % reduction in predicted VC per each vertebral fracture**
- **The degree of kyphosis clinically or radiographically correlated with declines in VC**

# Distribution of pulmonary and other deaths by deciles of increasing severity of kyphosis

(9575 women  $\geq 65$  years followed for 8.3 years)



# One-year mortality in 12,646 male patients after hip fracture repair



# **Risk factors for Osteoporosis and fractures in Chronic Obstructive Pulmonary Disease**

- **General risk factors**

- Older age
- Smoking
- Low body weight
- Physical inactivity

- **Disease-specific risk factors**

- Systemic inflammation
- Pulmonary dysfunction
- Vitamin D deficiency
- Glucocorticoid use

# **Risk factors for Osteoporosis and fractures in Chronic Obstructive Pulmonary Disease**

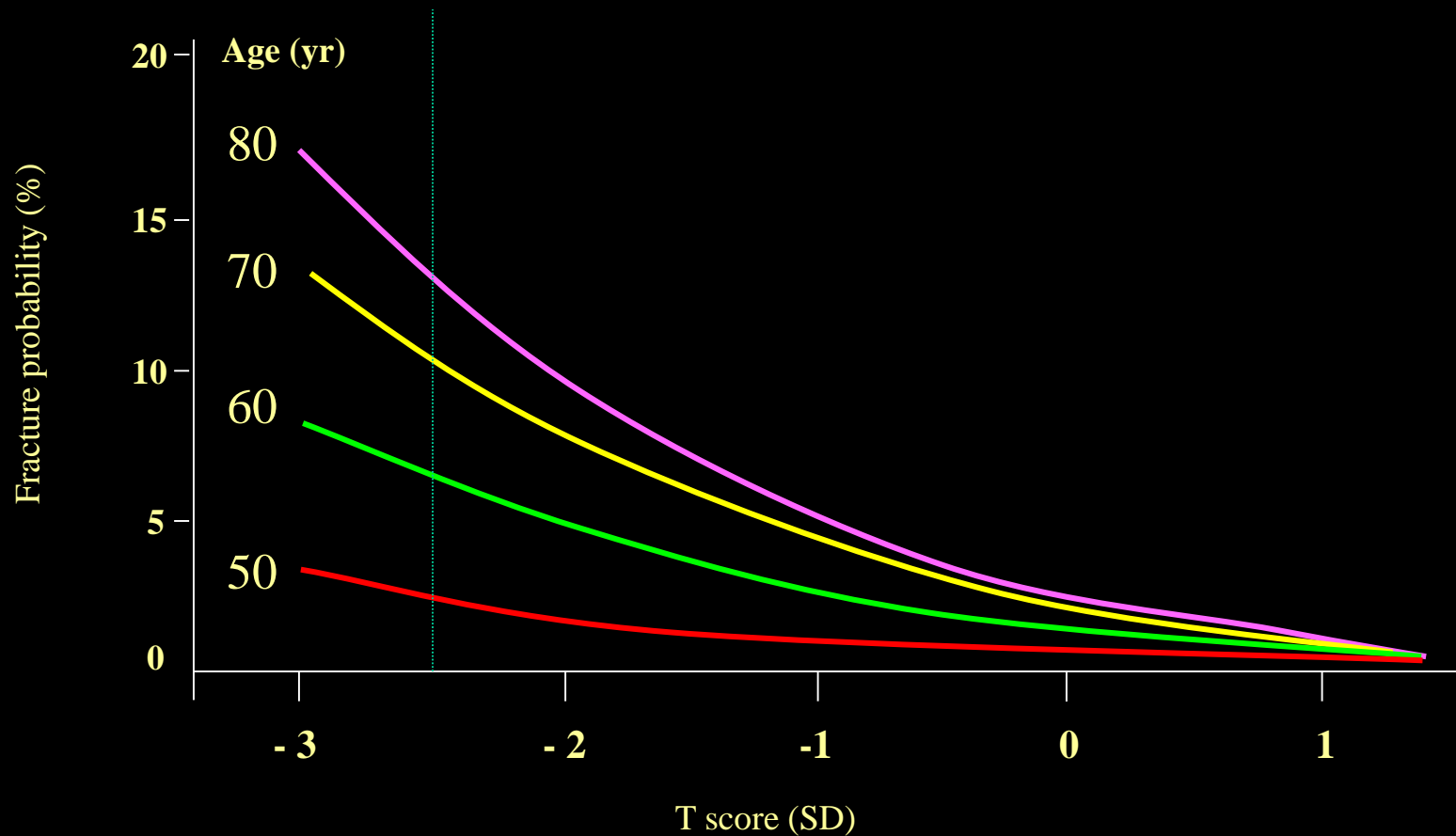
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# Relationship between BMD at the hip and hip fracture probability in women according to age



# Risk factors for Osteoporosis and fractures in Chronic Obstructive Pulmonary Disease

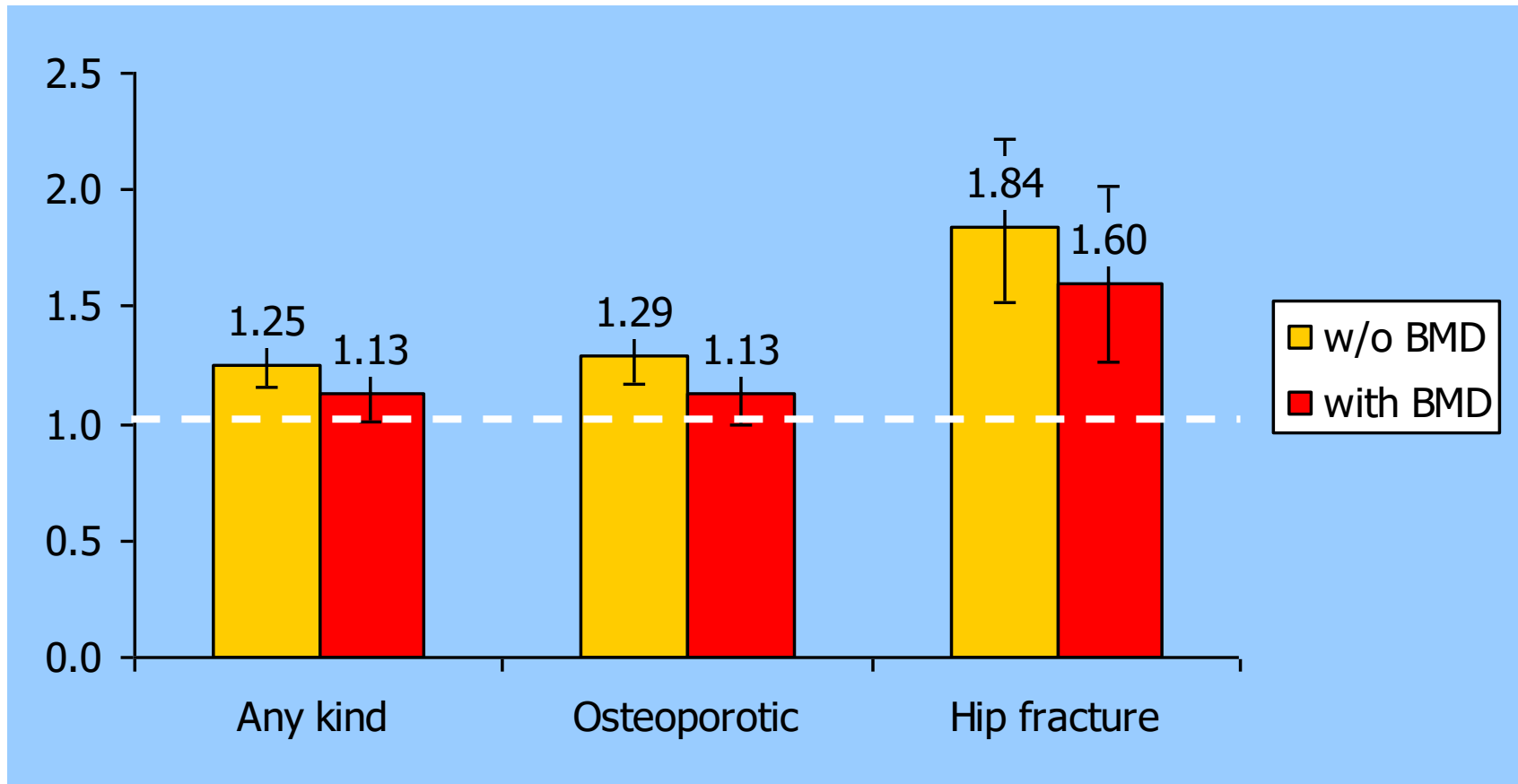
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# Current smoking and risk of any fracture



# Risk factors for Osteoporosis and fractures in Chronic Obstructive Pulmonary Disease

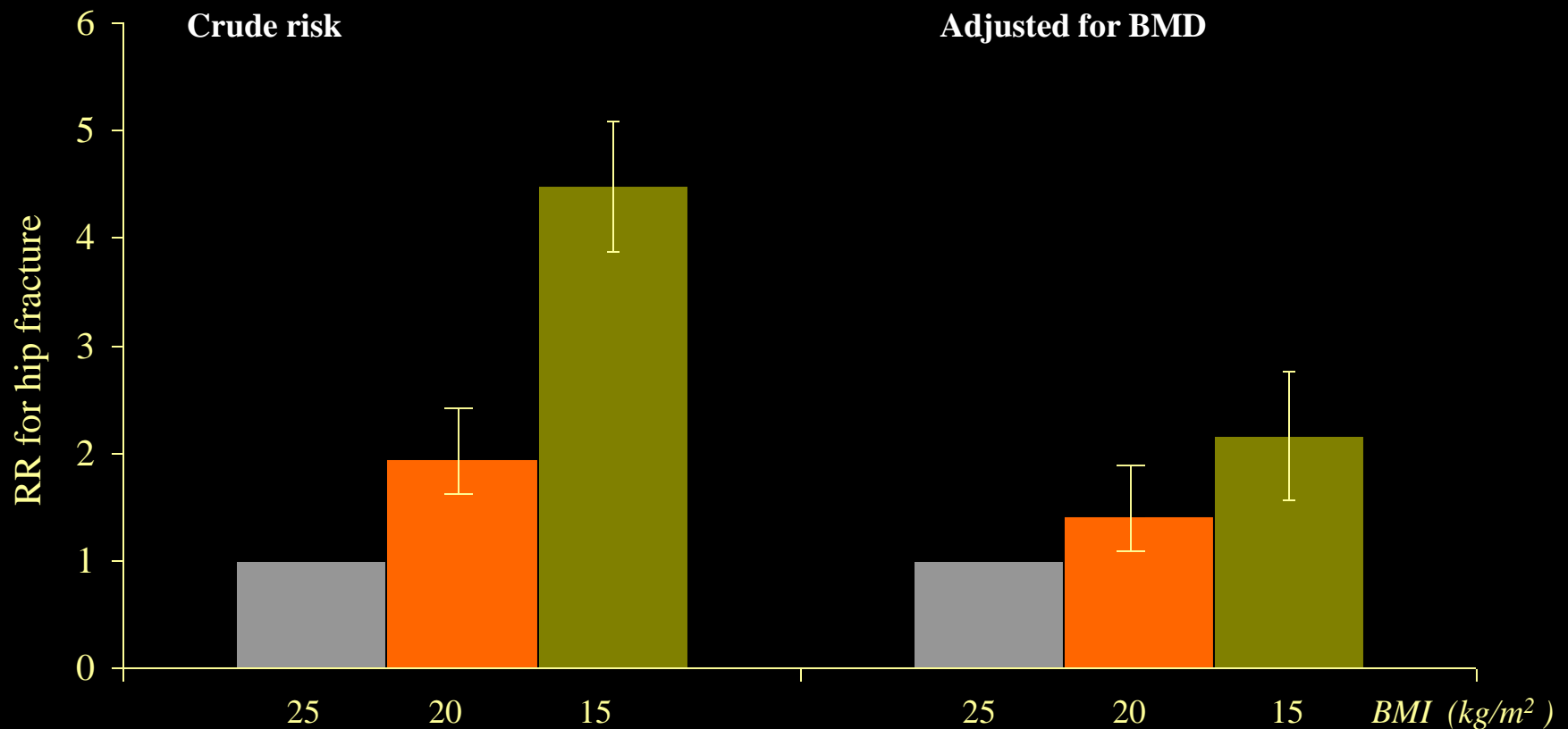
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# A low BMI is a significant risk factor for hip fracture even after adjustment for BMD



# Risk factors for Osteoporosis and fractures in Chronic Obstructive Pulmonary Disease

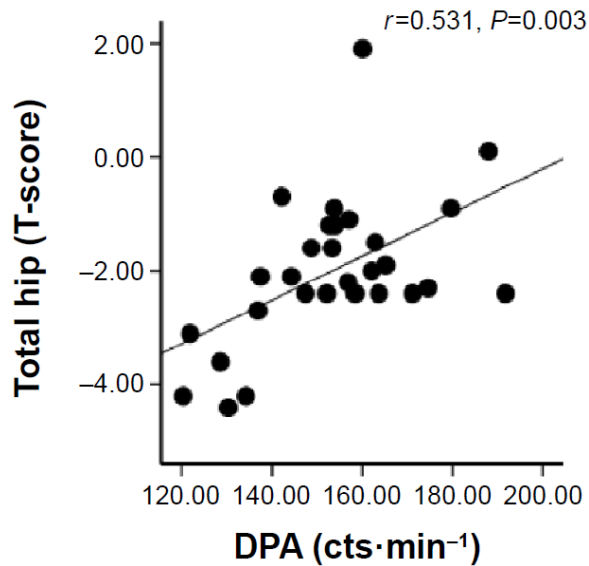
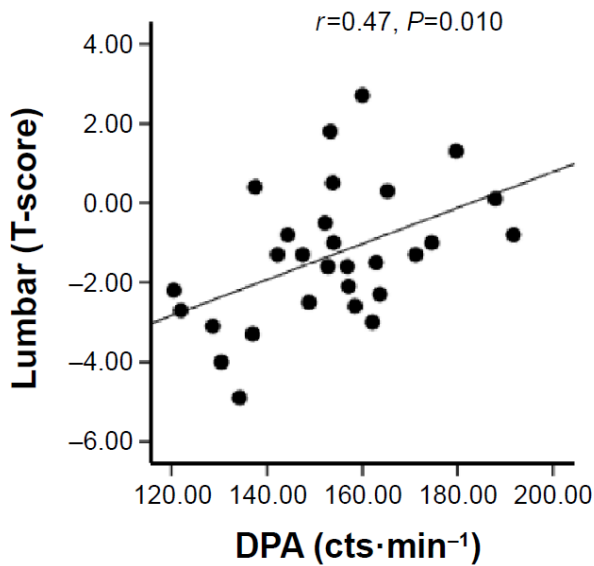
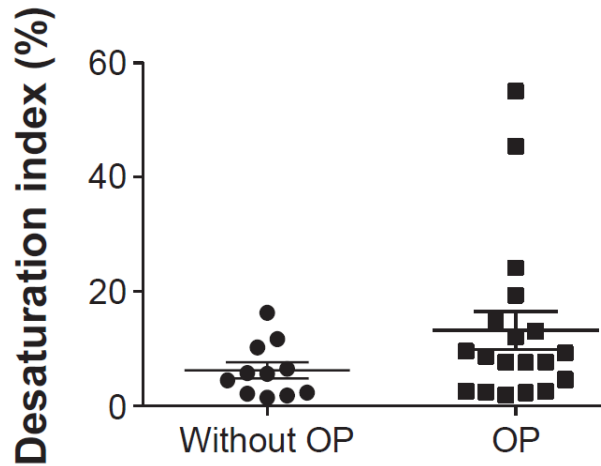
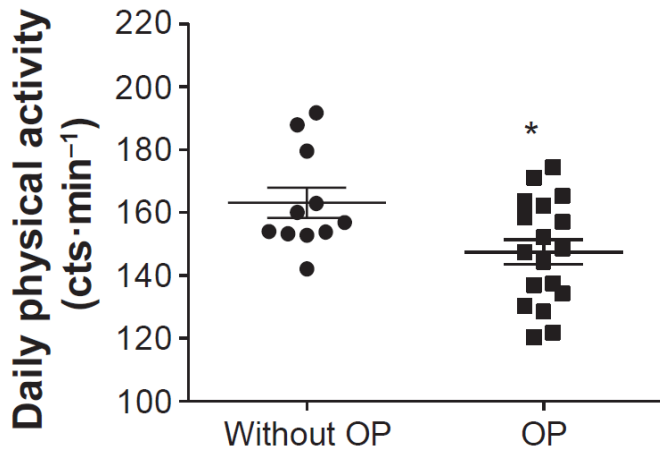
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Low bone mineral density in COPD patients with osteoporosis is related to low daily physical activity and high COPD assessment test scores



# **Risk factors for Osteoporosis and fractures in Chronic Obstructive Pulmonary Disease**

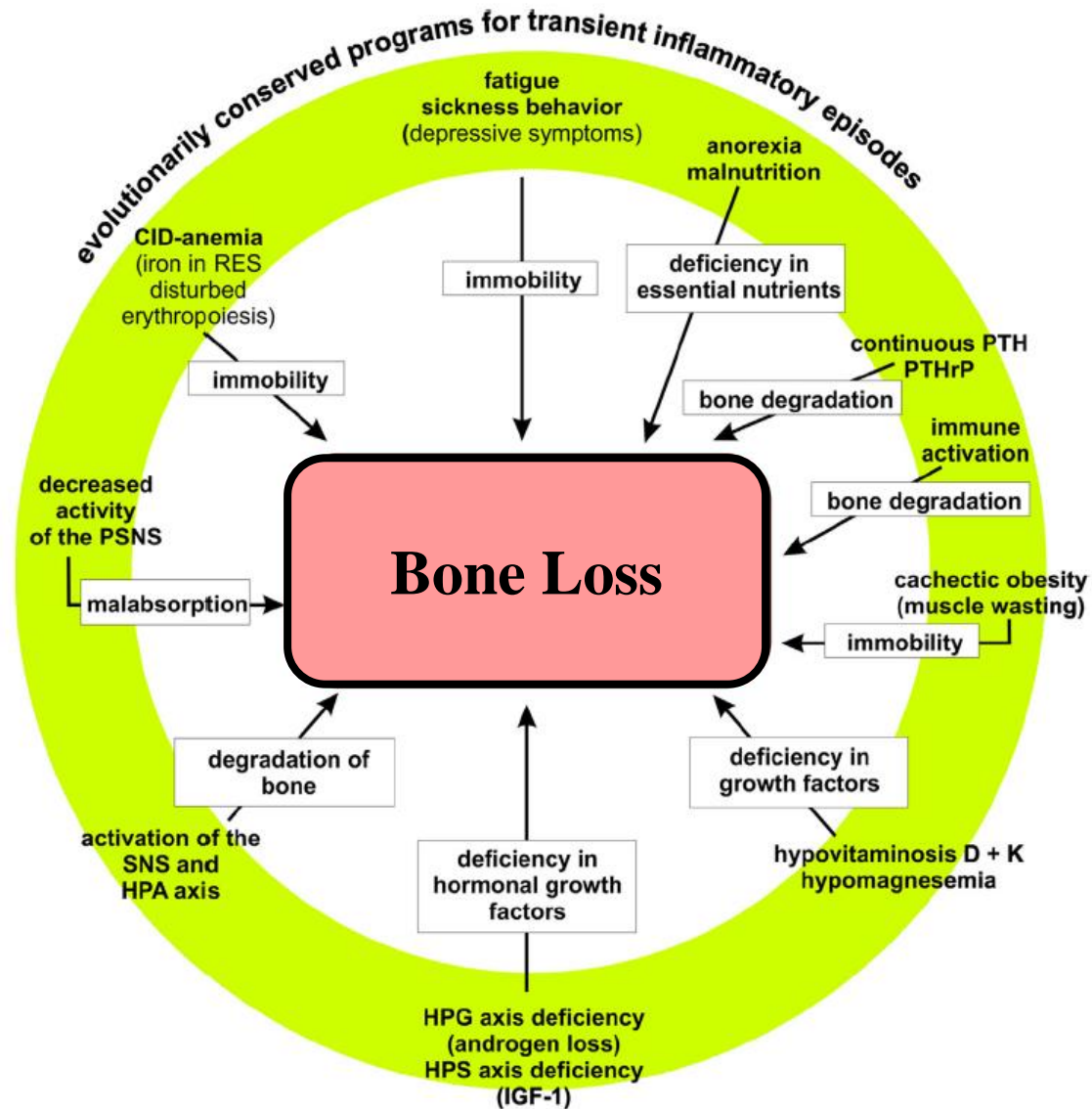
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# Disease sequelae in chronic inflammatory conditions leading to bone loss

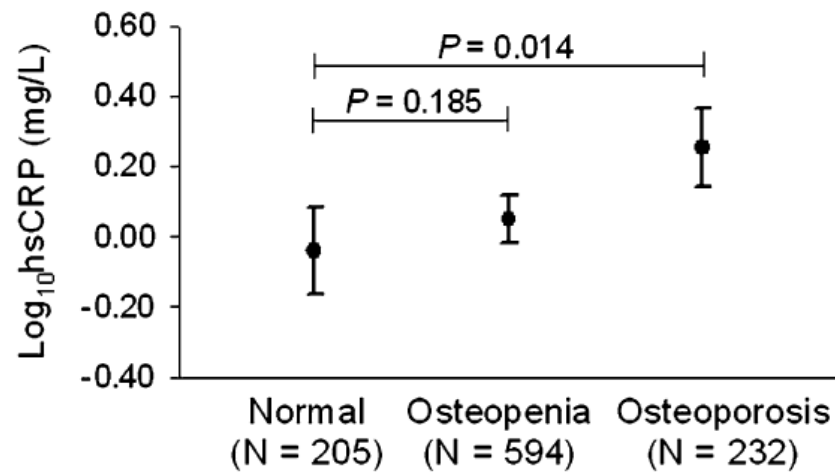


# Inflammation and bone loss

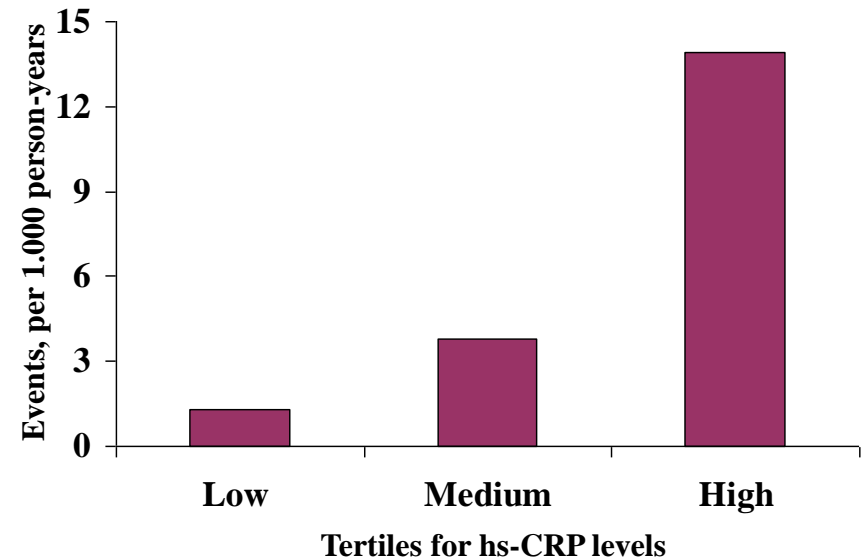
- Rheumatoid Arthritis
- Other chronic inflammatory Rheumatic Diseases
- IBDs , COPD, Asthma etc.
- Inflammatory Osteolysis
- Periodontal bone disease
- LPS-induced bone loss

# Evidences for a link between systemic inflammation and Osteoporosis

## Subclinical inflammation and bone mass in healthy women \*



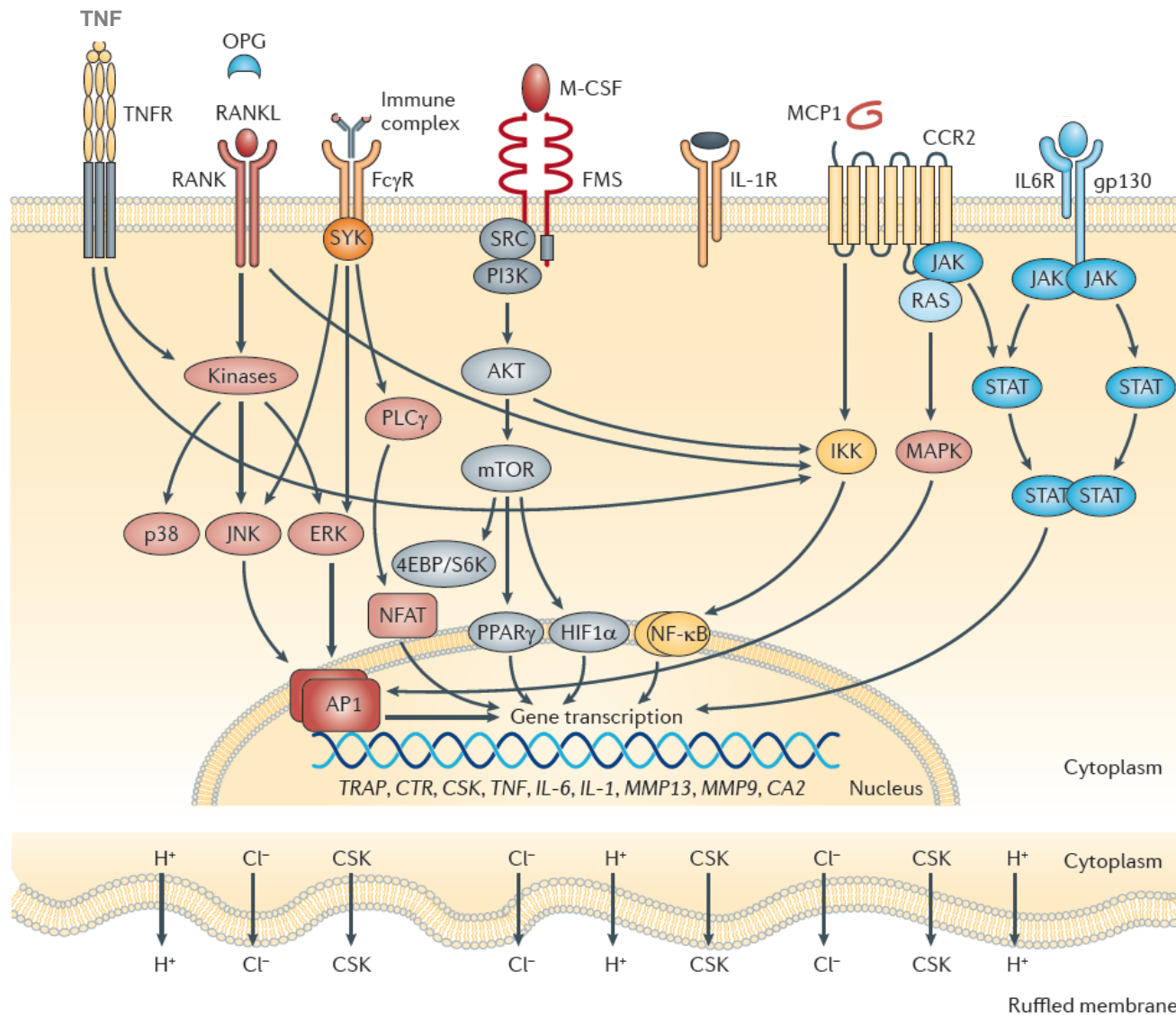
## hs-CRP and risk of non-traumatic fractures \*\*



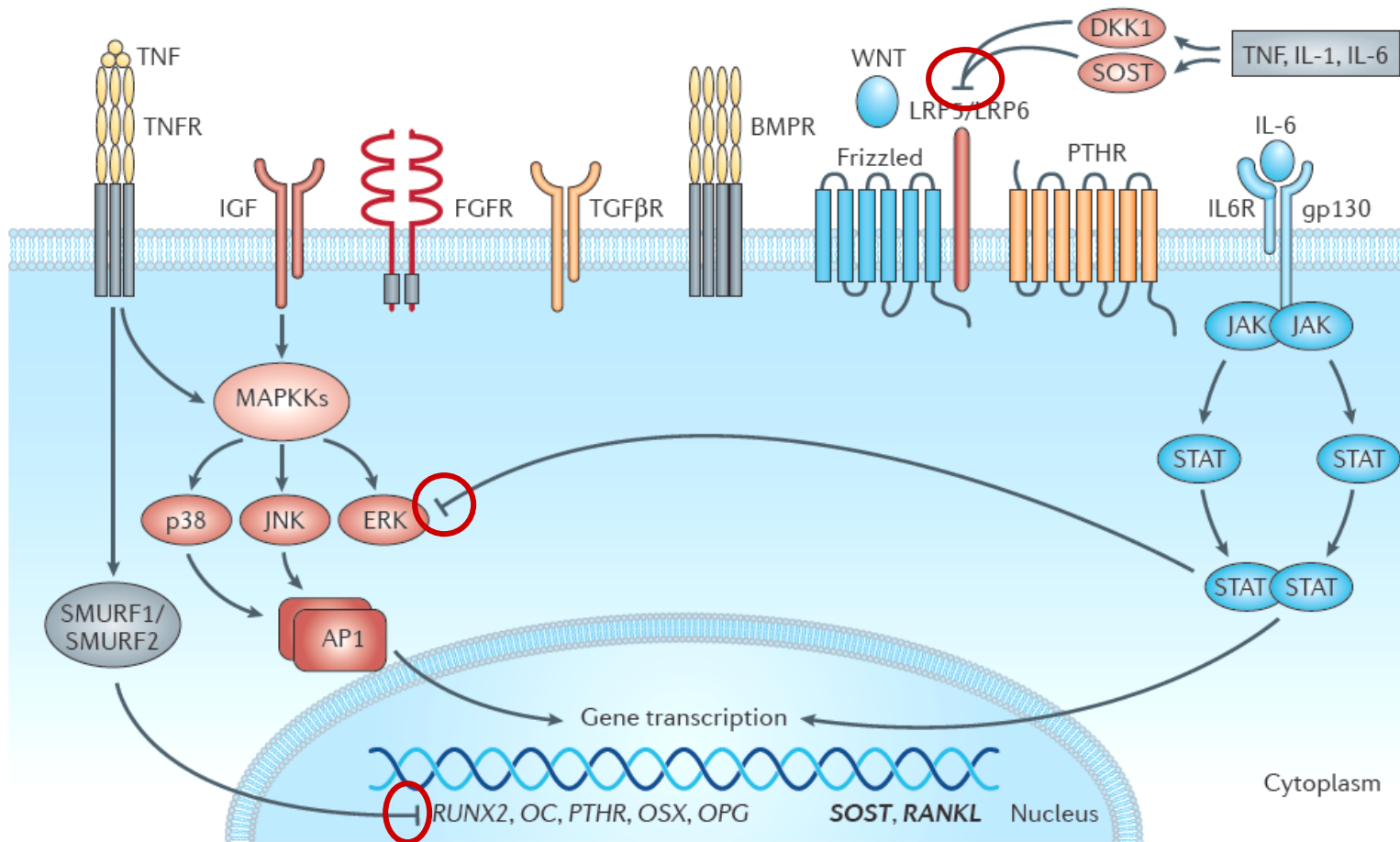
\* Koh J-M et al. *Osteoporos Int* 2005

\*\*Schett G et al. *Arch Intern Med* 2006

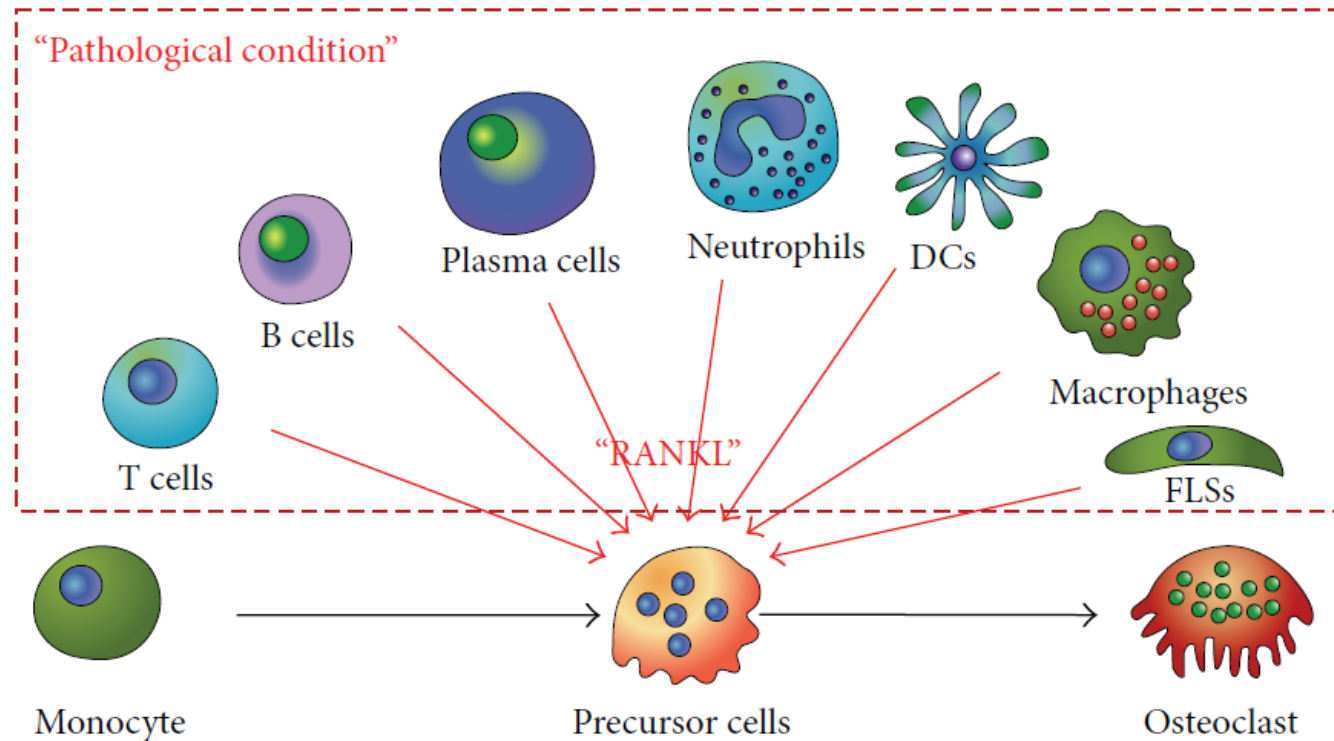
# Signalling in Osteoclasts during inflammation



# Signalling in Osteoblasts during inflammation



# Cytokine-mediated bone destruction in inflammatory diseases



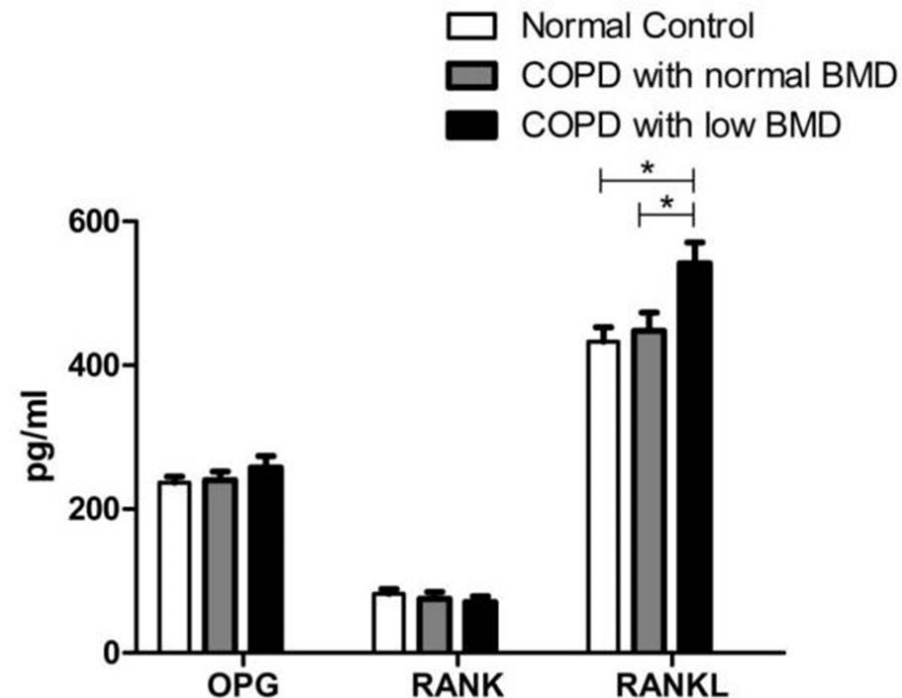
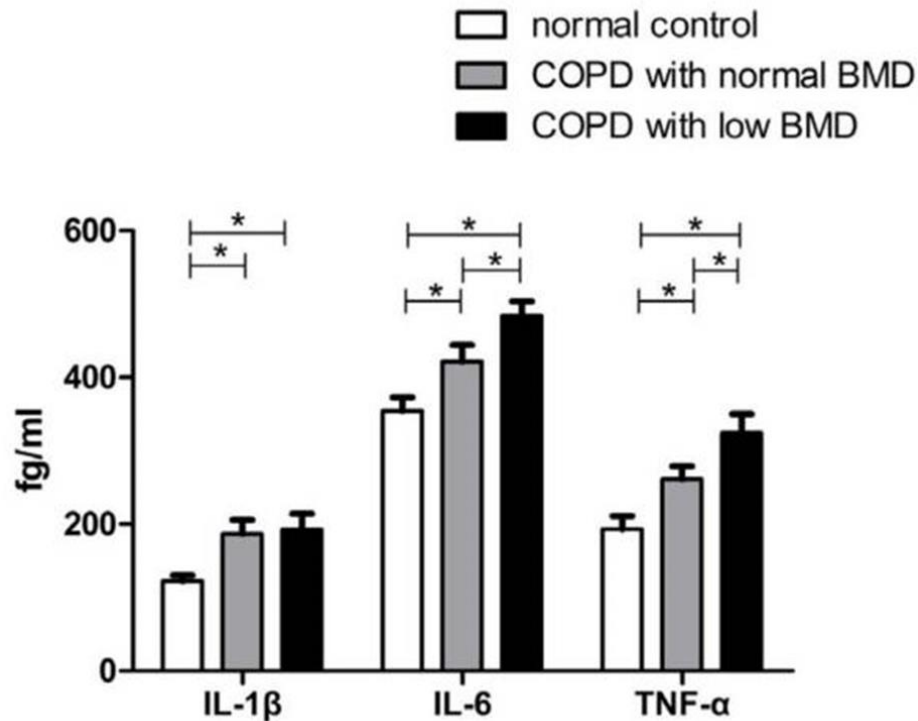
## The association of low bone mineral density with systemic inflammation in clinically stable COPD

Binmiao Liang · Yulin Feng

### Multivariate analysis for low BMD in 672 patients with clinically stable COPD

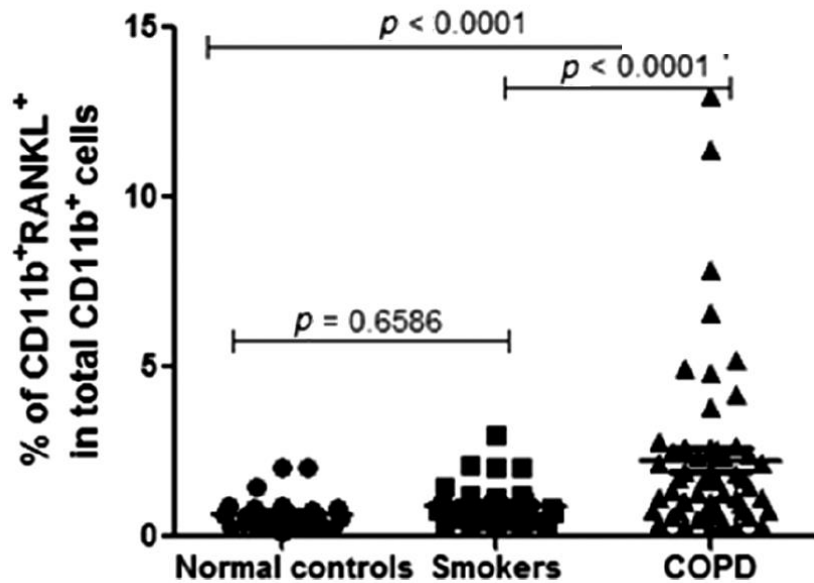
	OR	95% CI	<i>P</i> value
Age (years)	1.09	0.61–1.32	0.082
Female gender ( <i>n</i> , %)	1.38	0.86–2.97	0.098
Use of ICS ( <i>n</i> , %)	2.01	0.69–3.72	0.26
FEV <sub>1</sub> %pred (%)	1.37	0.78–3.24	0.17
<i>Systemic inflammation</i>			
Present vs. none	3.10	1.48–5.06	<i>0.014</i>
CRP (mg/l)	1.55	0.92–3.03	0.062
TNF- $\alpha$ (pg/ml)	3.22	1.48–6.77	<i>0.010</i>
IL-6 (pg/ml)	2.58	1.32–4.56	<i>0.023</i>

# Comparison of serum cytokine levels among COPD patients with low or normal Bone Mineral Density



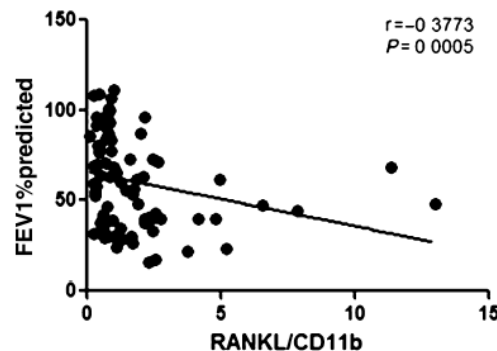
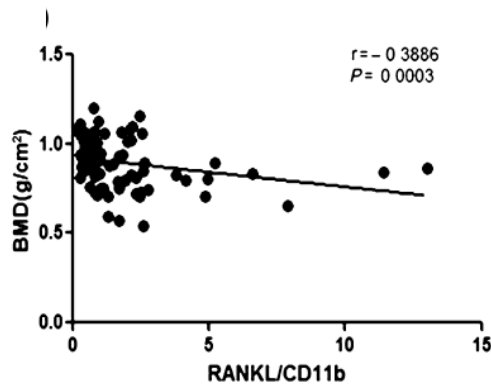
# Expression of RANKL by peripheral neutrophils and its association with bone mineral density in COPD

XIAOLING HU,<sup>1</sup> YONGCHANG SUN,<sup>1,2</sup> WEIHAN XU,<sup>1</sup> TAO LIN<sup>3,4</sup> AND HUI ZENG<sup>3,4</sup>



## SUMMARY AT A GLANCE

Peripheral blood neutrophils from male patients with COPD had enhanced expression of the osteoclast activation factor RANKL (receptor activator of NF- $\kappa$ B ligand), which correlated with bone mineral density and lung function of the patients.



# Risk factors for Osteoporosis and fractures in Chronic Obstructive Pulmonary Disease

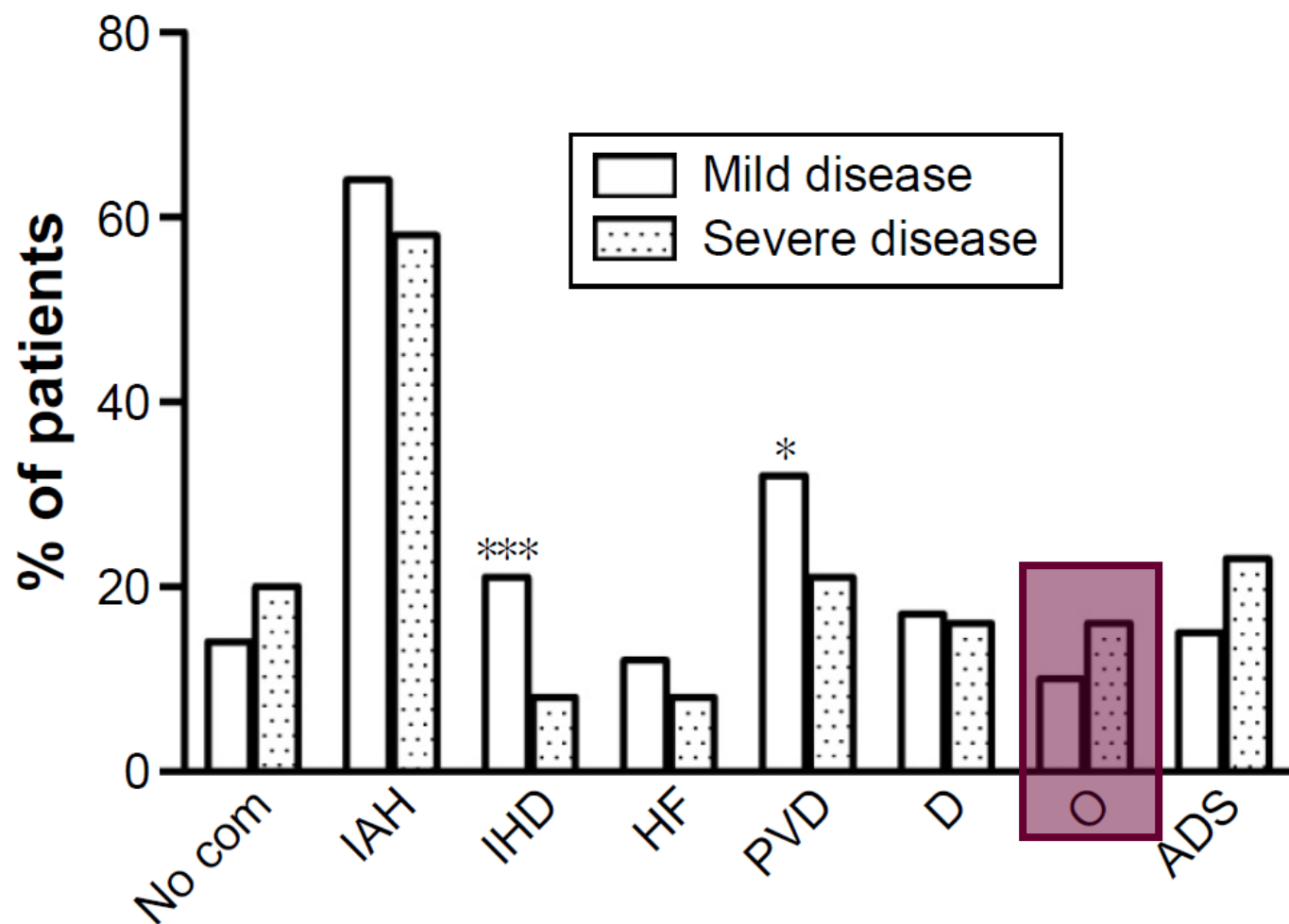
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- **Disease-specific risk factors**

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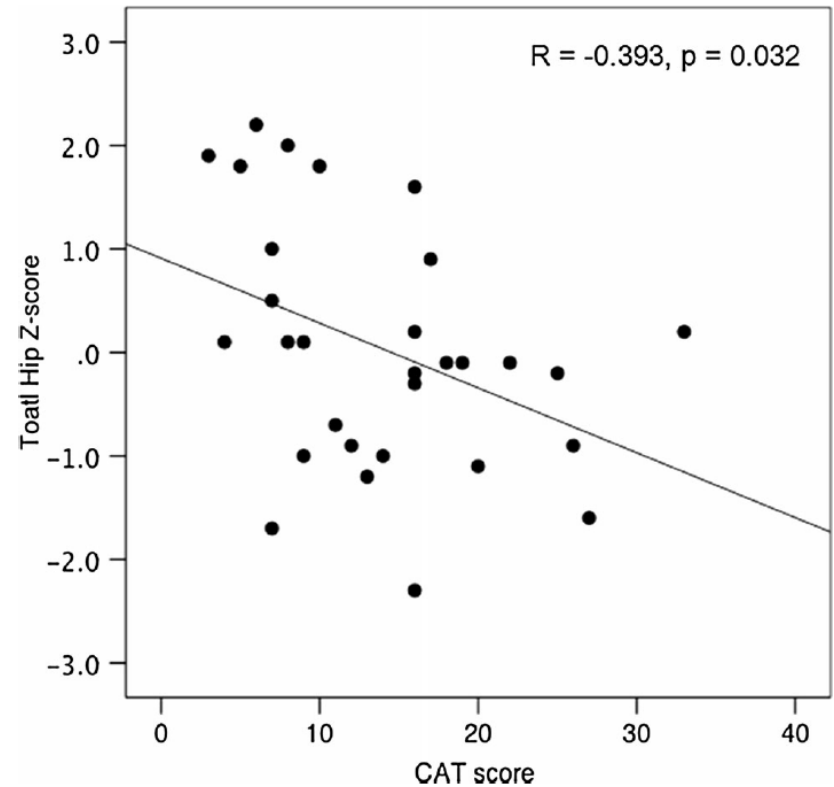
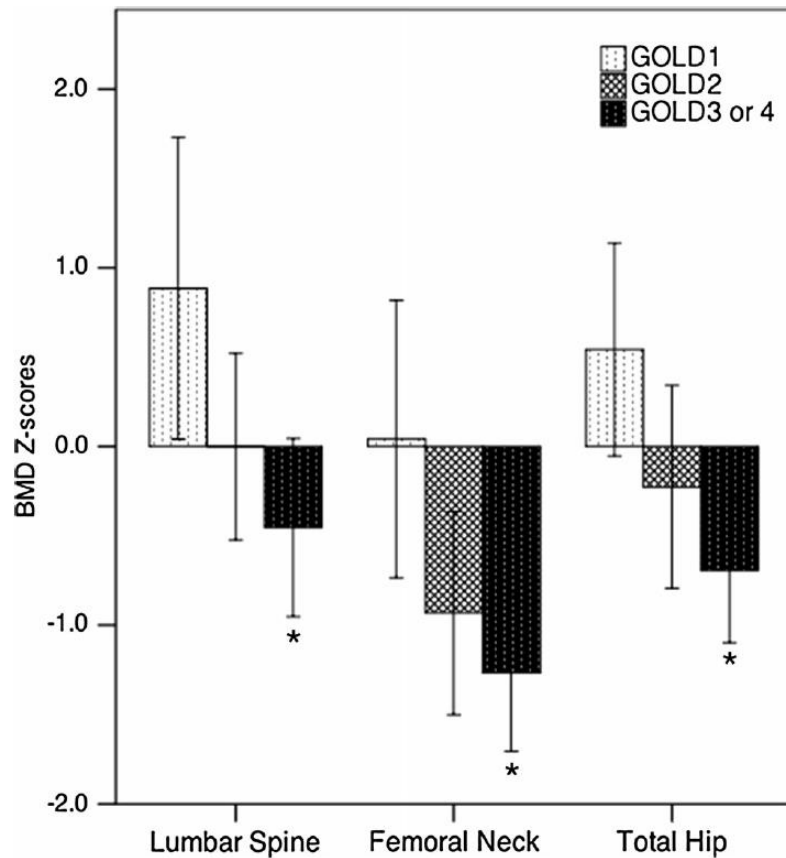
## Prevalence of different comorbidities in 412 outpatients according to mild or severe grade of COPD



**Abbreviations:** ADS, anxious depressive syndrome; com, comorbidities; COPD, chronic obstructive pulmonary disease; D, diabetes; HF, heart failure; IAH, idiopathic arterial hypertension; IHD, ischemic heart disease; O, osteoporosis; PVD, peripheral vascular disease.

# Osteoporosis is highly prevalent in Japanese males with chronic obstructive pulmonary disease and is associated with deteriorated pulmonary function

Reiko Watanabe • Takeshi Tanaka • Keisuke Aita • Masaaki Hagiya •  
Toshiaki Homma • Kyoko Yokosuka • Hisami Yamakawa • Tsutomu Yarita •  
Nobuyuki Tai • Junko Hirano • Daisuke Inoue • Ryo Okazaki



# Risk factors for Osteoporosis and fractures in Chronic Obstructive Pulmonary Disease

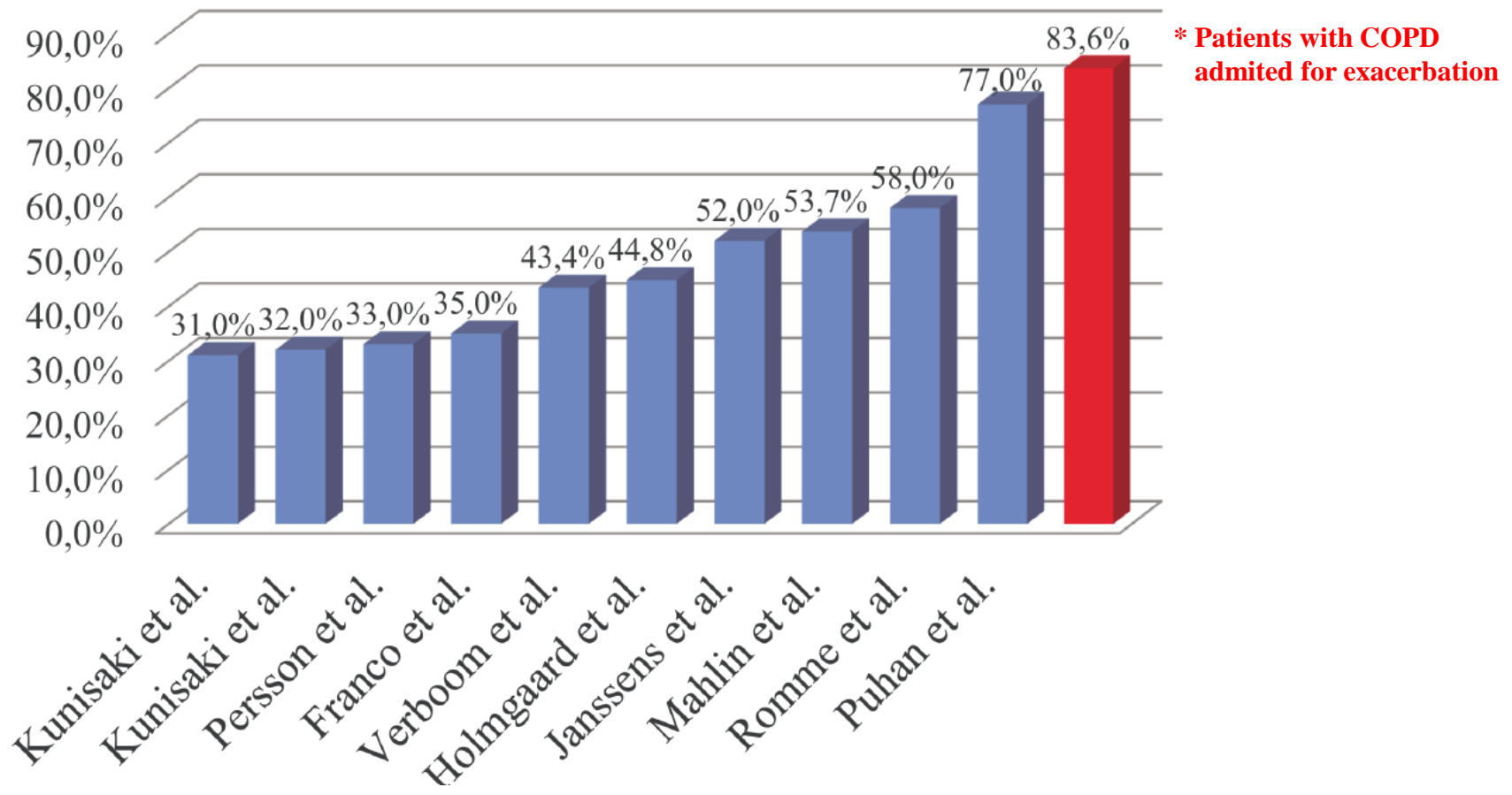
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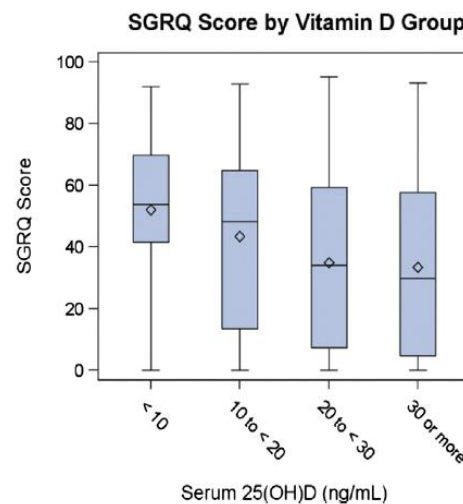
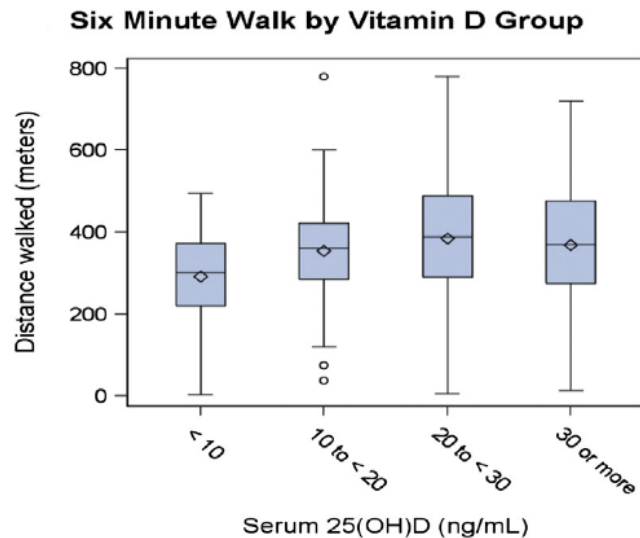
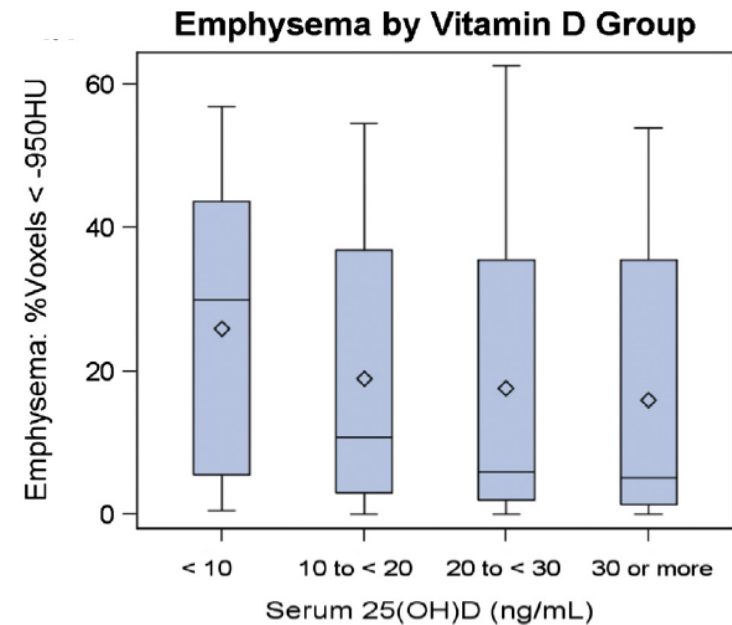
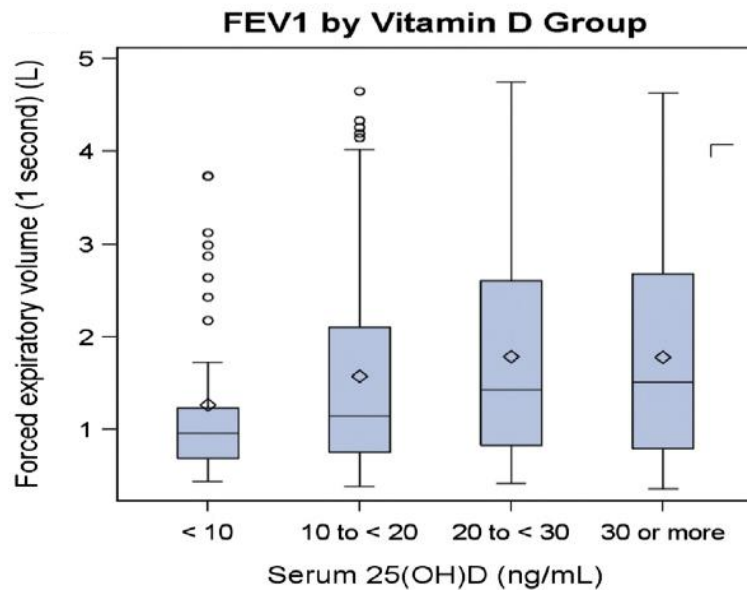
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- Systemic inflammation
- Pulmonary dysfunction
- **Vitamin D deficiency**
- Glucocorticoid use

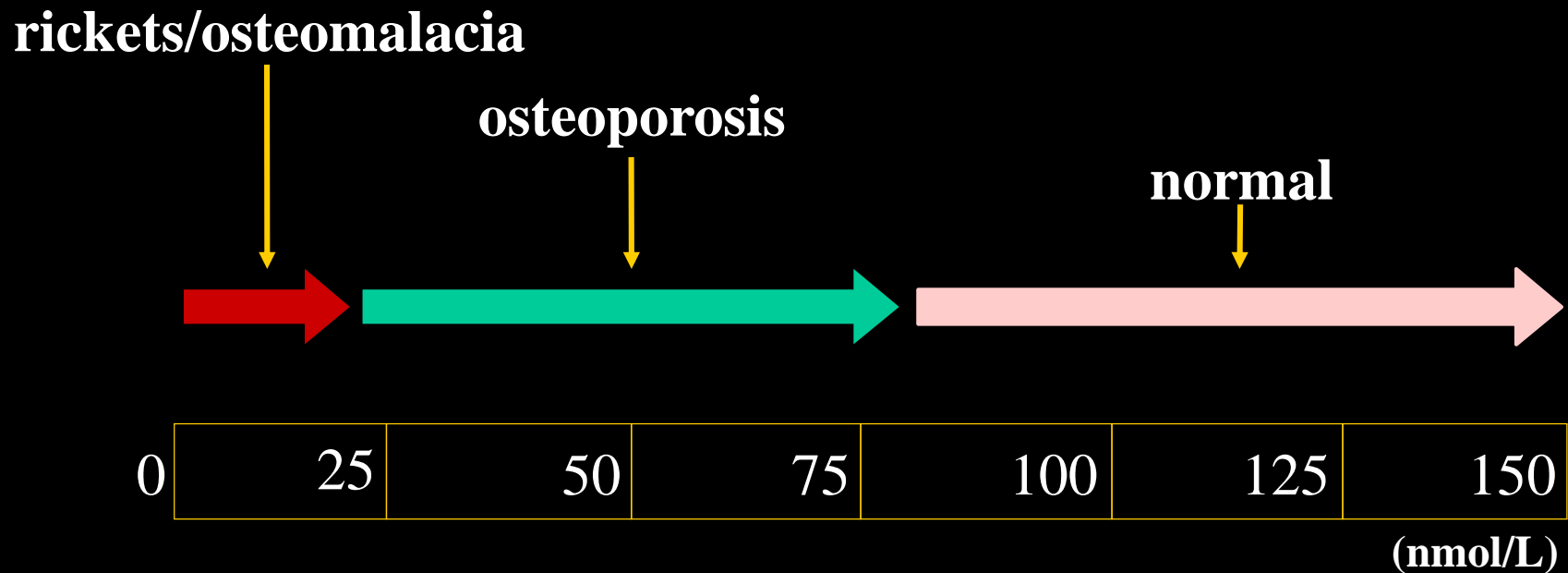
# Prevalence of Hypovitaminosis D in COPD patients



# Relationship between FEV1, Emphysema severity, Six Minutes Walk, SGRQ score and serum 25(OH)D in 498 COPD patients (ECLIPSE Study)



# Suggested mapping of the principal Vitamin D –related bone diseases onto the serum 25(OH)D concentration continuum



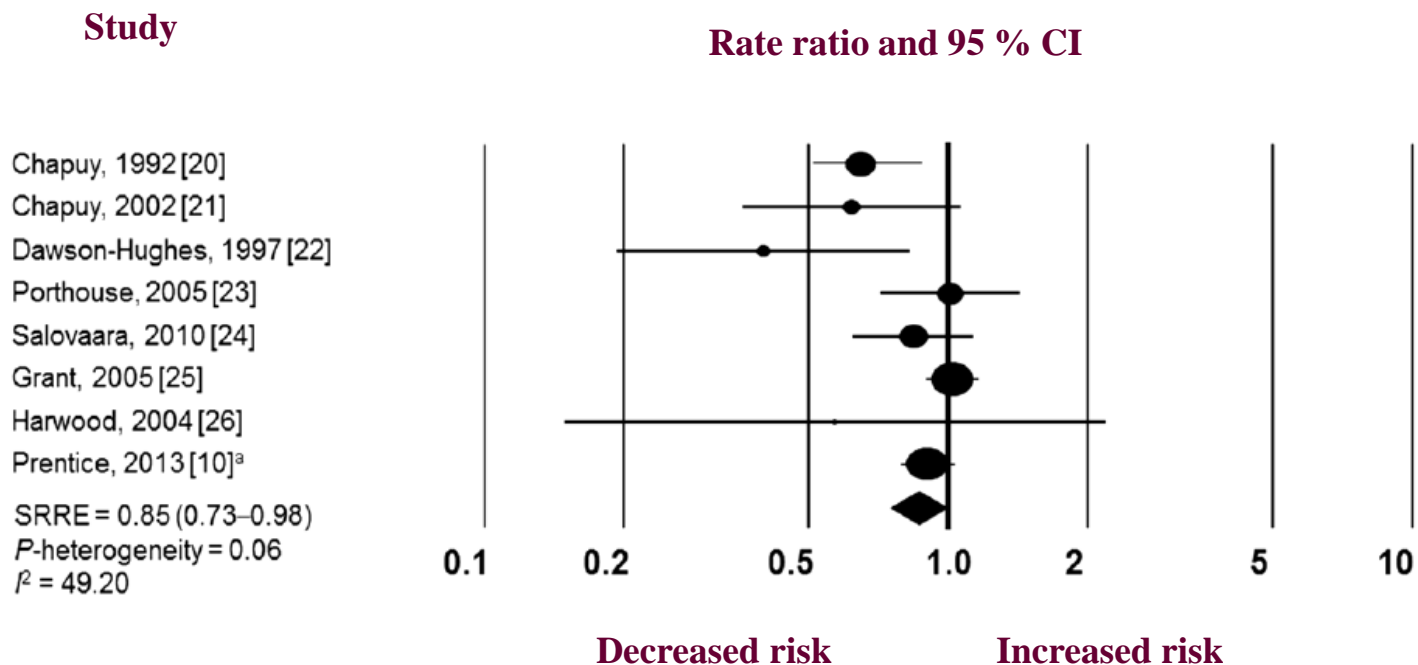
# Evolution of Hypovitaminosis D Osteopathy and Osteomalacia

Stage	Clinical features
<b>HVO-I</b>	<ul style="list-style-type: none"><li>• Increased ALP</li><li>• Increased PTH</li><li>• Increased Bone turnover</li><li>• No mineralization defect</li></ul>
<b>HVO-II</b>	<ul style="list-style-type: none"><li>• Progressive accumulation of unmineralized matrix</li></ul>
<b>HVO-III</b>	<ul style="list-style-type: none"><li>• Complete cessation of mineralization</li><li>• No tetracycline uptake</li><li>• Frank Osteomalacia</li></ul>

**HVO : Hypovitaminosis D Osteopathy Stage**

# Calcium plus vitamin D supplementation and risk of fractures: an updated meta-analysis from the National Osteoporosis Foundation

C. M. Weaver<sup>1</sup> • D. D. Alexander<sup>2</sup> • C. J. Boushey<sup>3</sup> • B. Dawson-Hughes<sup>4</sup> • J. M. Lappe<sup>5,6</sup> • M. S. LeBoff<sup>7</sup> • S. Liu<sup>8</sup> • A. C. Looker<sup>9</sup> • T. C. Wallace<sup>10,11</sup> • D. D. Wang<sup>12</sup>



# Risk factors for Osteoporosis and fractures in Chronic Obstructive Pulmonary Disease

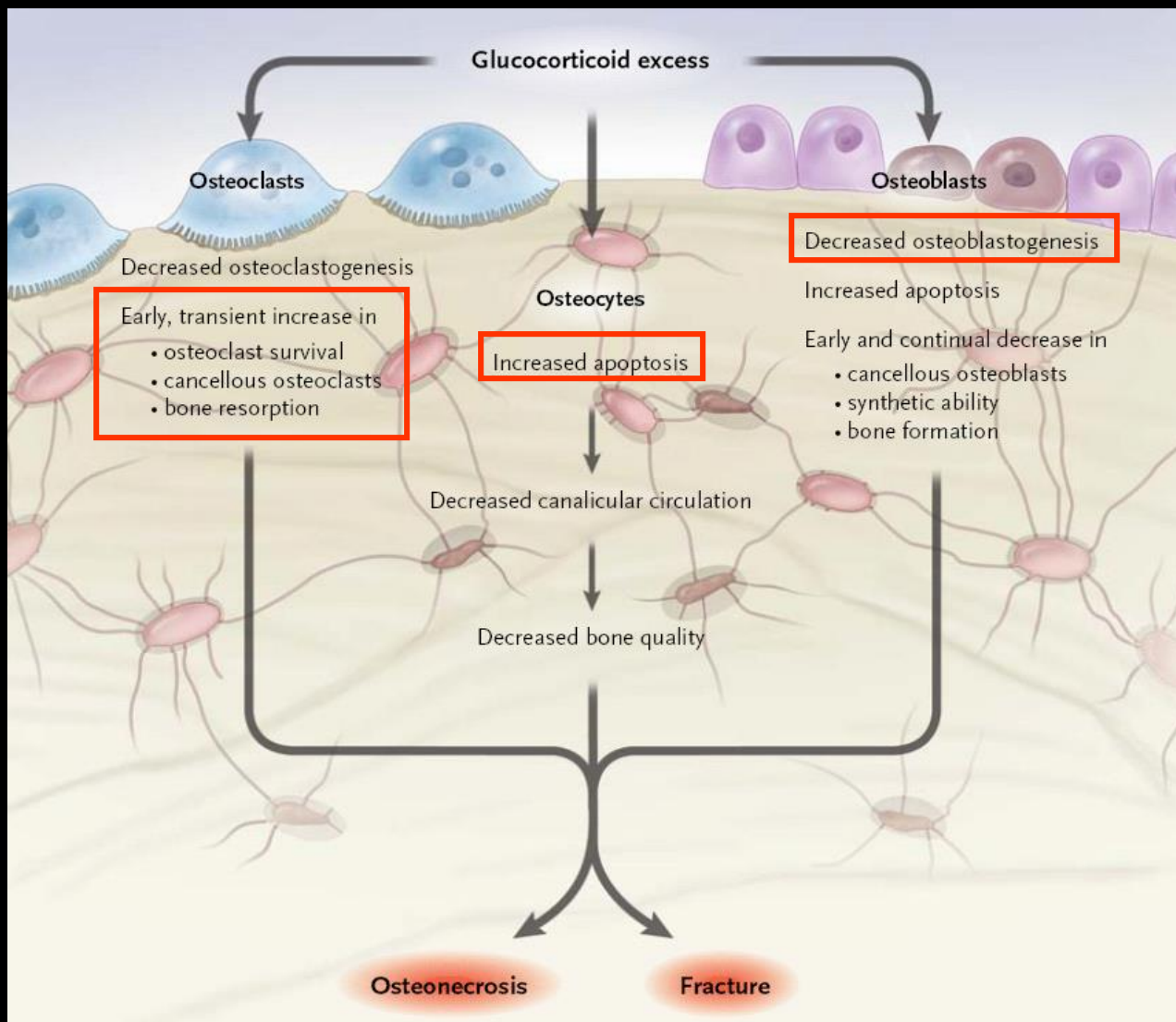
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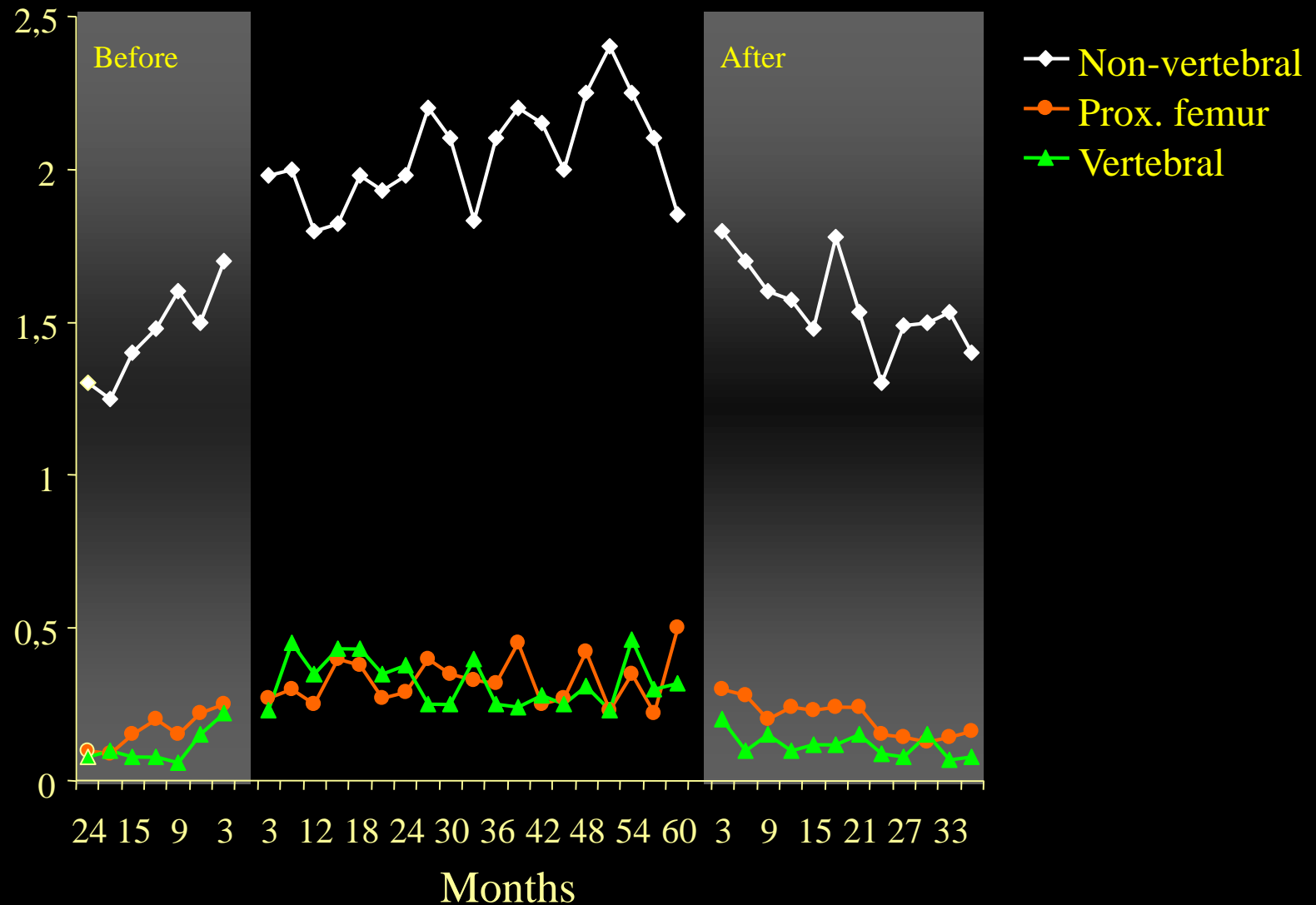
- **Disease-specific risk factors**

- Systemic inflammation
- Pulmonary dysfunction
- Vitamin D deficiency
- **Glucocorticoid use**

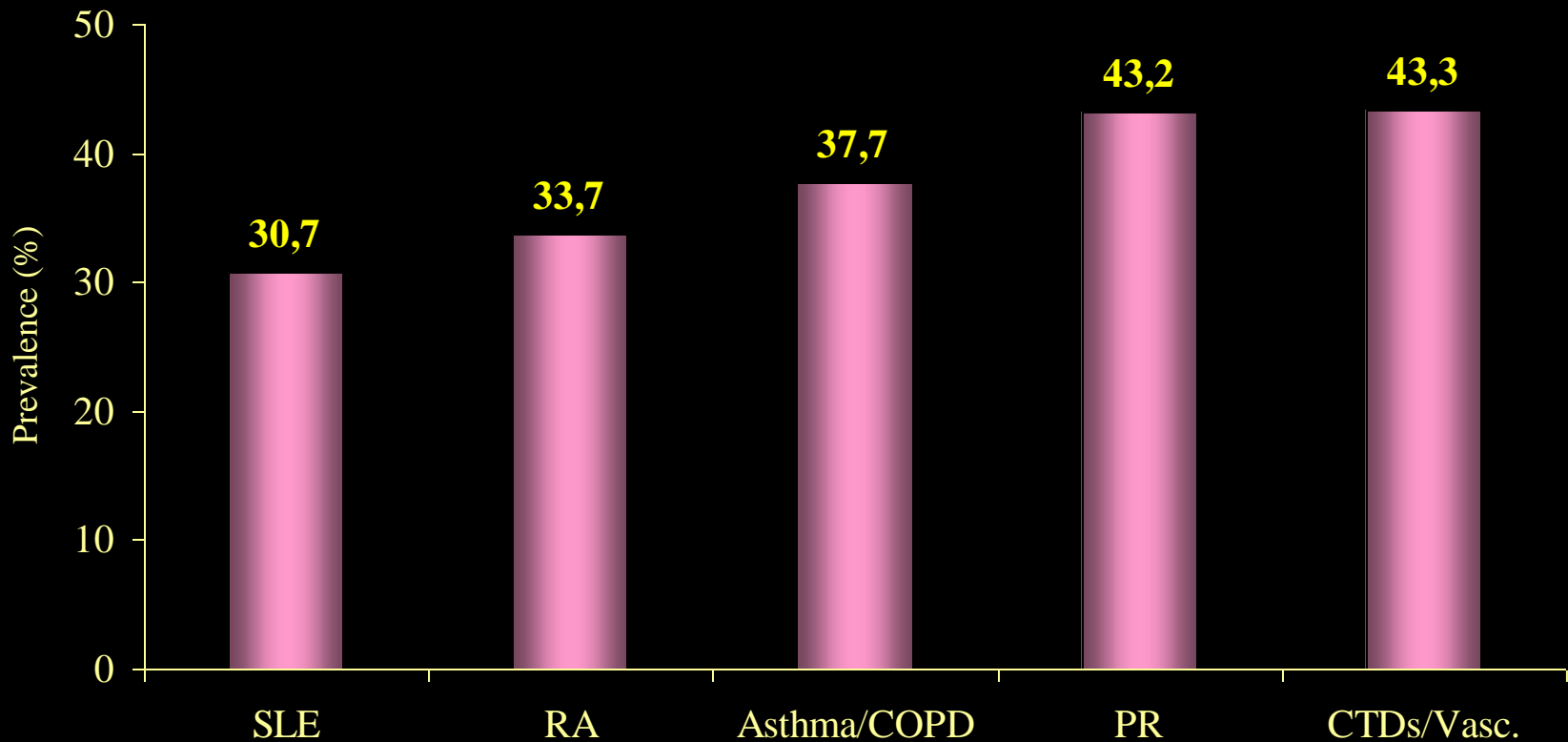
# Glucocorticoids are bad for bone



# Fracture incidence before, during and after Glucocorticoid treatment



# Adjusted \* prevalence of asymptomatic vertebral fractures in 551 post-menopausal women treated with GCs

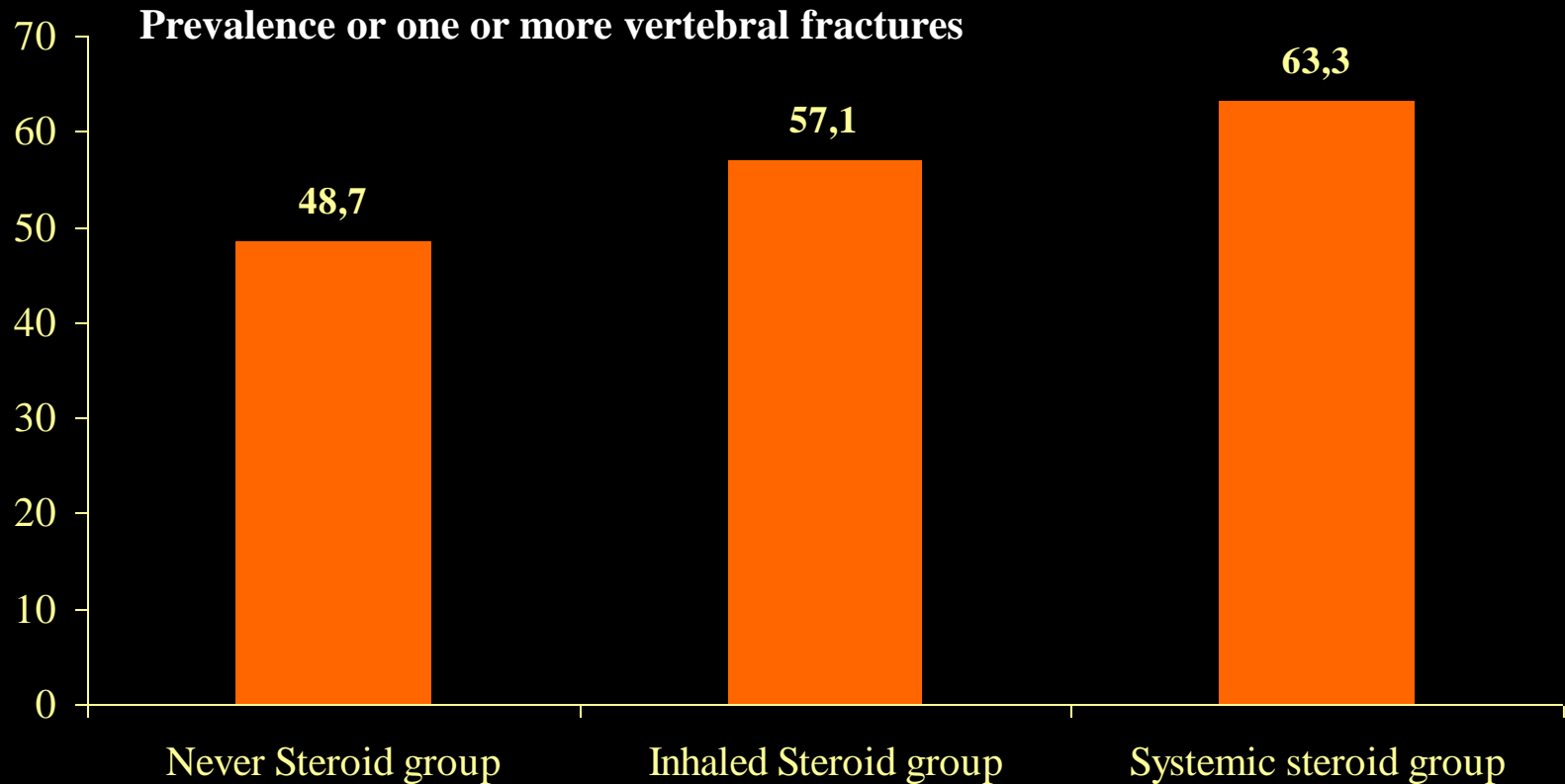


\* Adjusted for age, GC cumulative dose, treatment duration and personal history of fxs

# Some key points about Glucocorticoid-induced Osteoporosis

- High burden of early onset, dose-dependent multiple fractures
- Incidence of fractures largely independent on BMD
- Underlying disease and menopausal status as major determinants
- GC-induced bone loss:
  - Biphasic
  - Partially reversible after withdrawal
  - Dose-dependent (daily vs cumulative)
- Low doses detrimental
- Inhaled CS harmful as well
- Persisting barriers to GIOP prevention and treatment

## Association between Corticosteroid use and vertebral fractures in older men with COPD



## Use of inhaled corticosteroids and risk of fractures : a retrospective cohort study on 170,818 inhaled steroid users

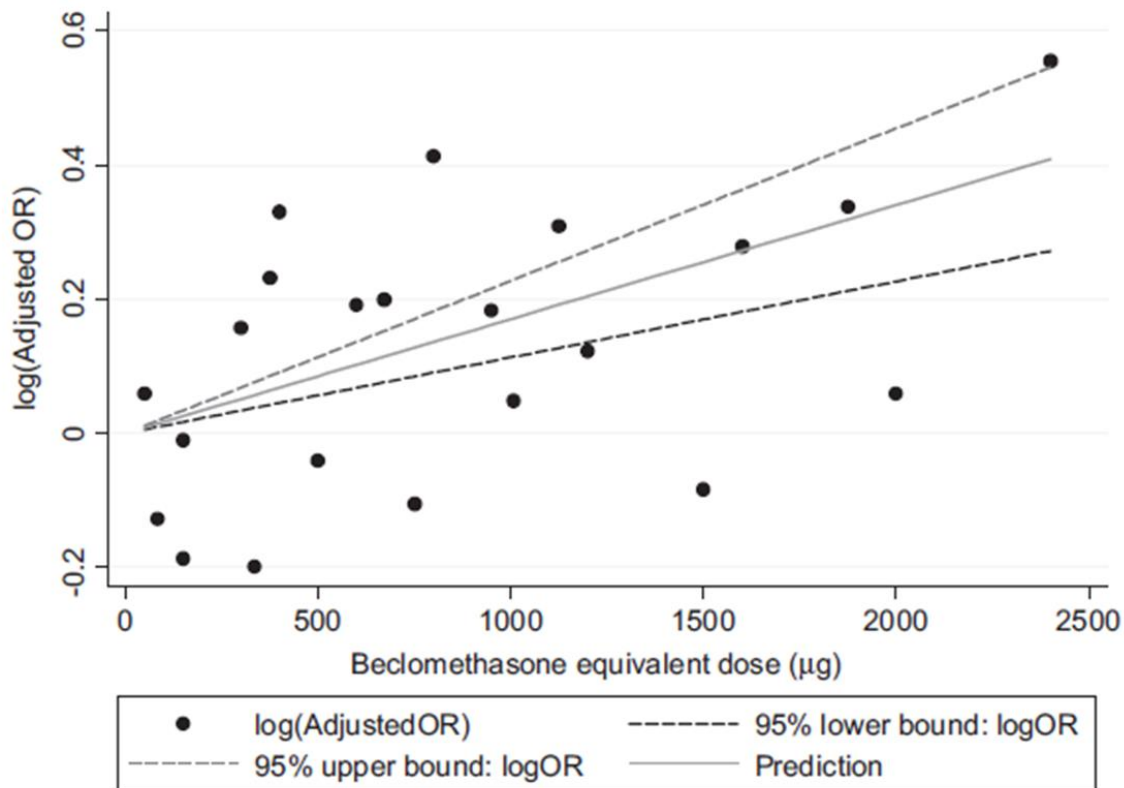
	Relative rate	95 % CI
Non vertebral fractures	1.15	1.10-1.20
Hip fractures	1.22	1.04-1.43
Vertebral fractures	1.51	1.22-1.85

# Incidence of fractures according to inhaled corticosteroid dose

	Low Dose ( n= 46,797)	Medium dose (n = 43,070)	High dose (n= 28,815)
	Inhaled CS vs Control Group	Inhaled CS vs Control Group	Inhaled CS vs Control Group
<b>Non Vertebral</b>	<b>1.11</b> (1.03-1.20)	<b>1.16</b> (1.07-1.26)	<b>1.28</b> (1.15-1.42)
<b>Hip</b>	<b>0.95</b> (0.67-1.34)	<b>1.06</b> (0.80-1.40)	<b>1.77</b> (1.31-2.40)
<b>Vertebral</b>	<b>1.31</b> (0.89-1.92)	<b>1.39</b> (0.95-2.04)	<b>2.50</b> (1.63-3.83)

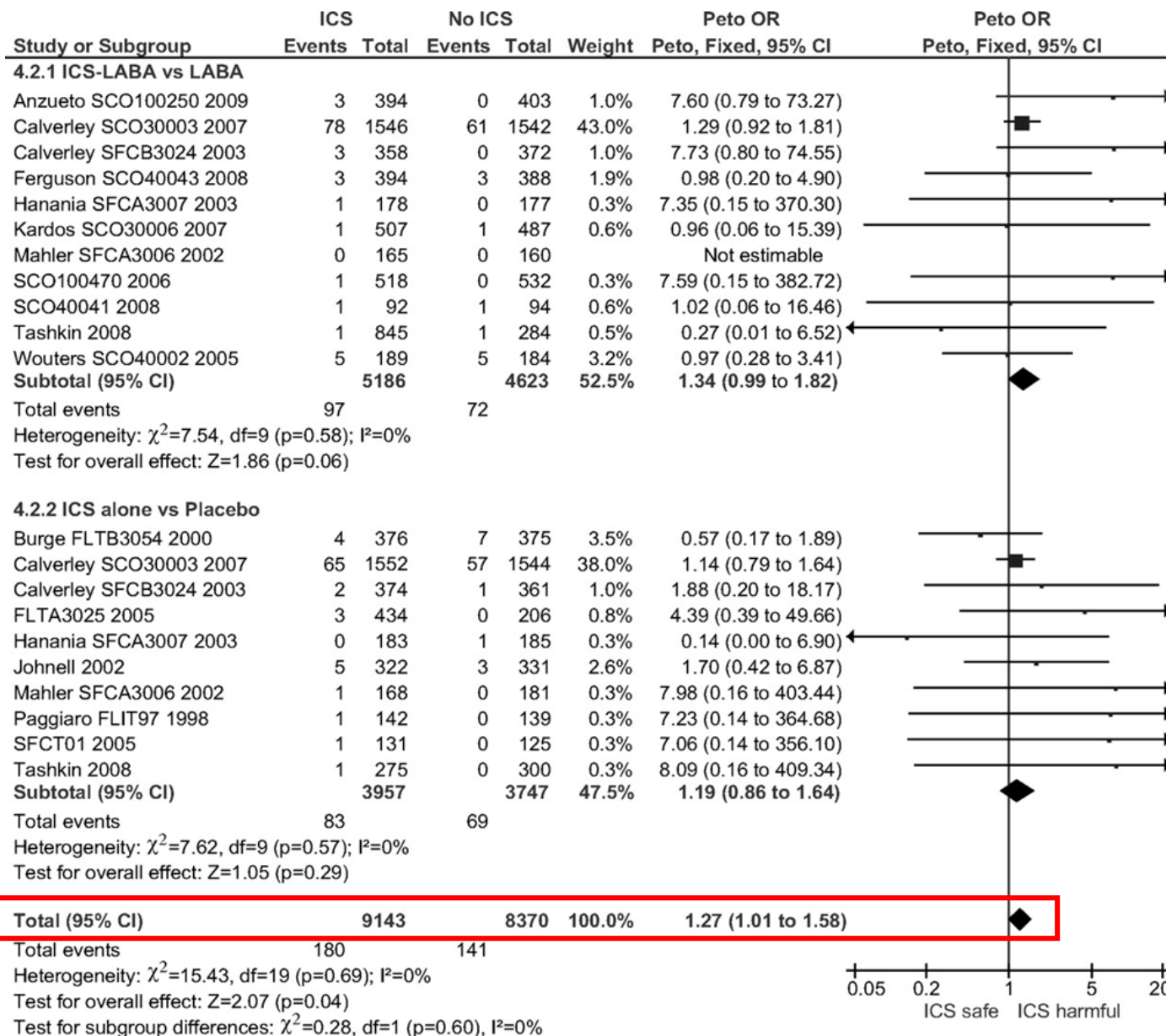
*< 300 µg per day*
*300-700 µg per day*
*< 700 µg per day*

# Meta-analysis of inhaled Corticosteroids versus controls for fractures in observational studies in COPD patients



# Meta-analysis of odds of fracture with inhaled Corticosteroids (ICS) exposure trials of patients with COPD

THORAX



# Effects of Asthma on bone

- Impact on physical activity
  - Severe asthma may affect prepubertal growth
  - Severe asthma may delay the onset of puberty
  - Severe asthma may decrease peak bone mass
- 
- Bone mineral density reduced in children as compared to healthy controls

Konig et al. *J Pediatr* 122:219, 1993

- BMD not reduced in asthmatics who used inhaled CS but duration of use correlated negatively with spinal BMD

Laatikainen et al. *Am J Respir Crit Care Med* 159:1179, 1999

# NUOVA NOTA 79



**20/05/2015**

## Prevenzione primaria

*Femmine in postmenopausa e maschi di età  $\geq 50$  anni*

- Trattamento in corso di blocco ormonale adiuvante in F con CA mammella e M con CA Prostatico
- **T score  $\leq -3$  + almeno 1 fattore di rischio**: familiarità per frattura vertebrale o femorale, comorbidità (AR o altre connettiviti, diabete, **BPCO**, IBD, Parkinson, AIDS, sclerosi multipla, grave disabilità motoria)

## Estensione della prevenzione secondaria

- Pazienti con pregressa **frattura non vertebrale non femorale** e valori di T score  $\leq -3$

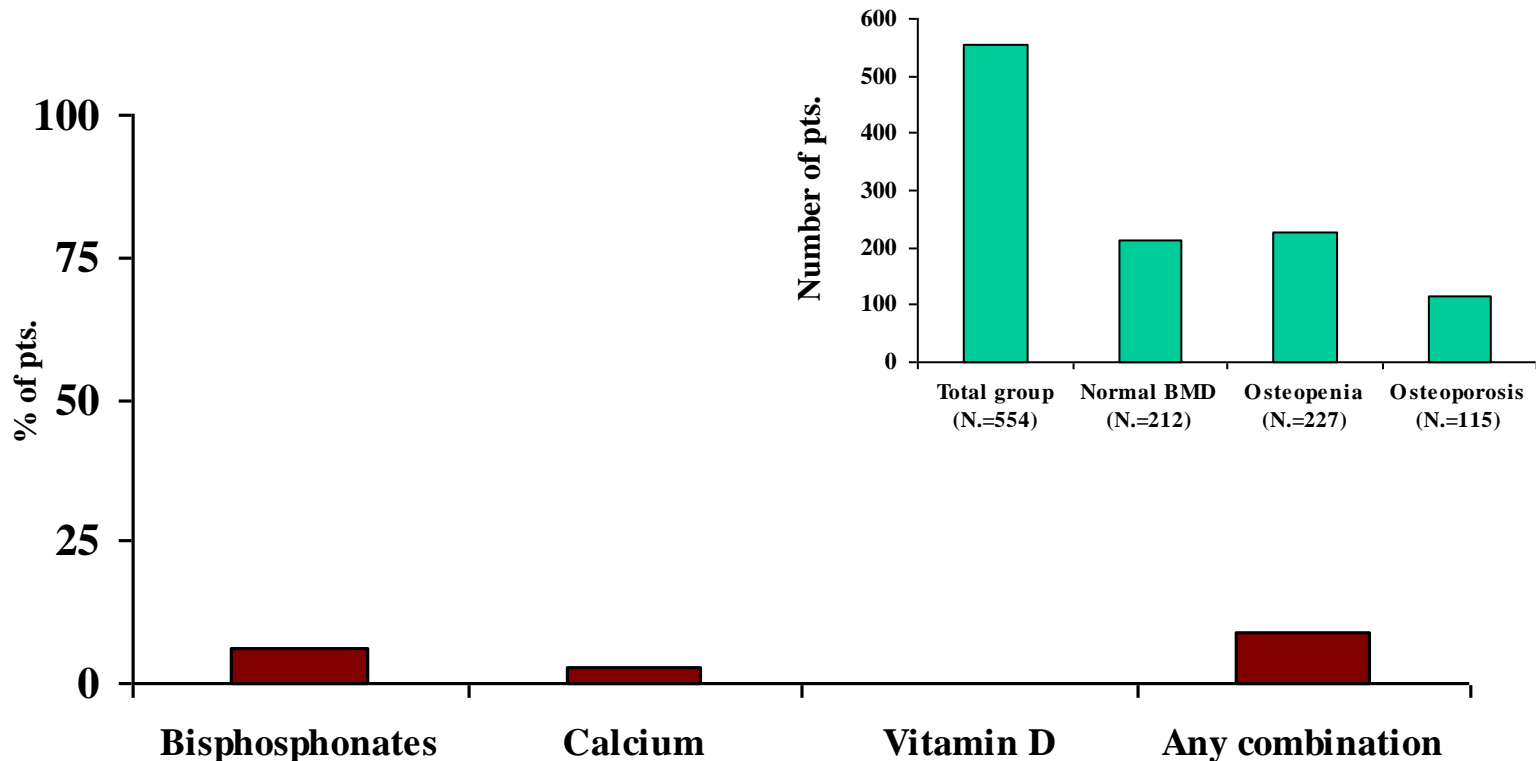
# Evidence for fracture reduction for FDA-approved bone active agents

Drug	Vertebral Fracture	Nonvertebral Fracture	Hip Fracture
Calcitonin (Miacalcin, Fortical)	✓	No effect demonstrated	No effect demonstrated
Raloxifene (Evista)	✓	No effect demonstrated	No effect demonstrated
Ibandronate (Boniva)	✓	No effect demonstrated	No effect demonstrated
Alendronate (Fosamax)	✓	★	✓
Risedronate (Actonel, Atelvia)	✓	✓	★
Zoledronic acid (Reclast)	✓	✓	✓
Denosumab (Prolia)	✓	✓	✓
Teriparatide (Forteo)	✓	✓	No effect demonstrated

★ Evidence for effect but not an FDA-approved indication.

# Correlates of osteoporosis in chronic obstructive pulmonary disease: An underestimated systemic component

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# The golden rules for Osteoporosis treatment

- Correct or prevent vitamin D insufficiency ( $\geq 800$  IU/day)
- Ensure dietary calcium intake  $\sim 1000$  mg/day
- Ensure adequate dietary protein intake  $\geq 1$  g/kg body wt/day
- Promote weight-bearing physical exercise
- Treat any disease that might be causing bone loss
- Reduce the risk of falls
- Reduce consequences of fall (hip protectors)
- Prescribe pharmaceutical treatment when indicated by risk assessment
- Provide adequate counselling and treatment explanation
- Follow-up patients with enquiries of persistence
- Re-evaluate therapeutic options after 3 years

# Treatments for Osteoporosis with established vertebral and non vertebral fracture efficacy reduce mortality

