Osteoporosi e Malattie Respiratorie Croniche

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Milano

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

Osteoporotic Fractures in Women: Comparison with Other Diseases

Annual incidence x 1000 (y-axis: 0, 500, 1000, 1500, 2000)

* Osteoporotic Fractures — 1 500 000*
  - 250 000 hip
  - 250 000 forearm
  - 250 000 other sites
  - 750 000 vertebral
* Heart Attack — 513 000†
* Stroke — 228 000‡
* Breast Cancer — 184 300§

* annual incidence all ages
† annual estimate women 29+
‡ annual estimate women 30+
§ 1996 new cases, all ages
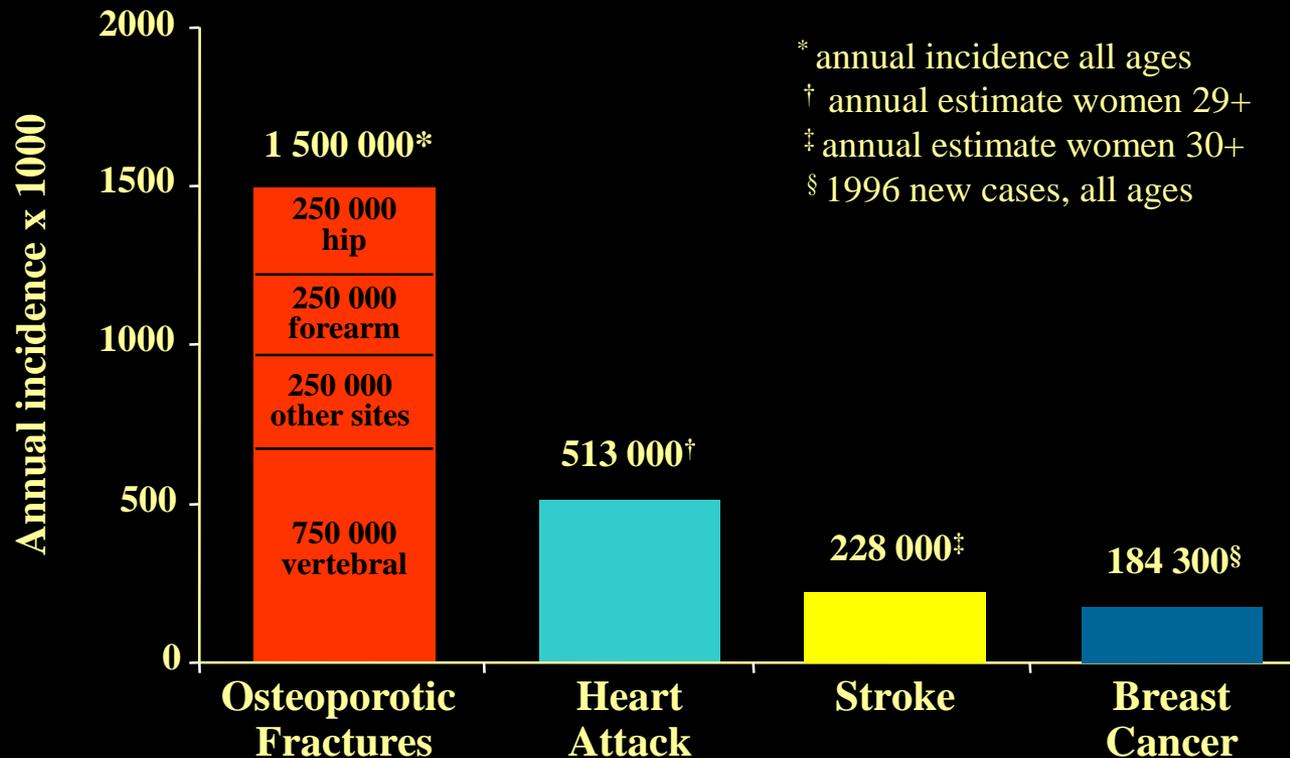
Riggs BL, Melton LJ. Bone 1995
Heart and Stroke Facts, 1996, American Heart Association
Cancer Facts & Figures, 1996, American Cancer Society

Mortality rates for the General Population and Fracture Participants according to age
## The Dubbo Osteoporosis Epidemiology Study
## April 1989/ May 2007

Men
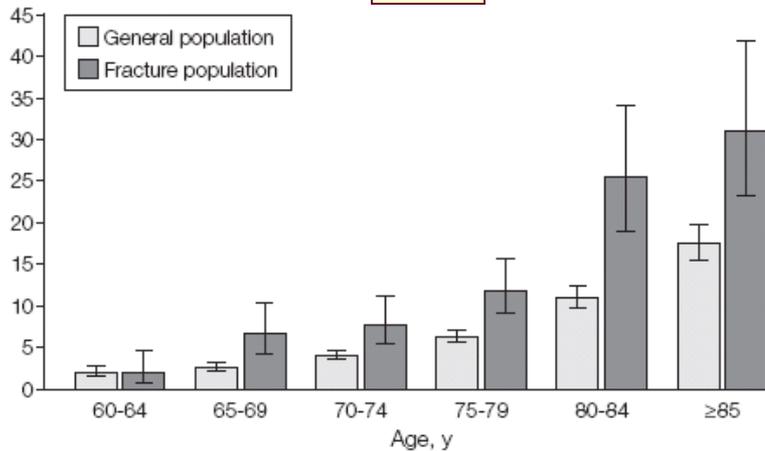
343 low-trauma fractures/ 197 deaths

Women
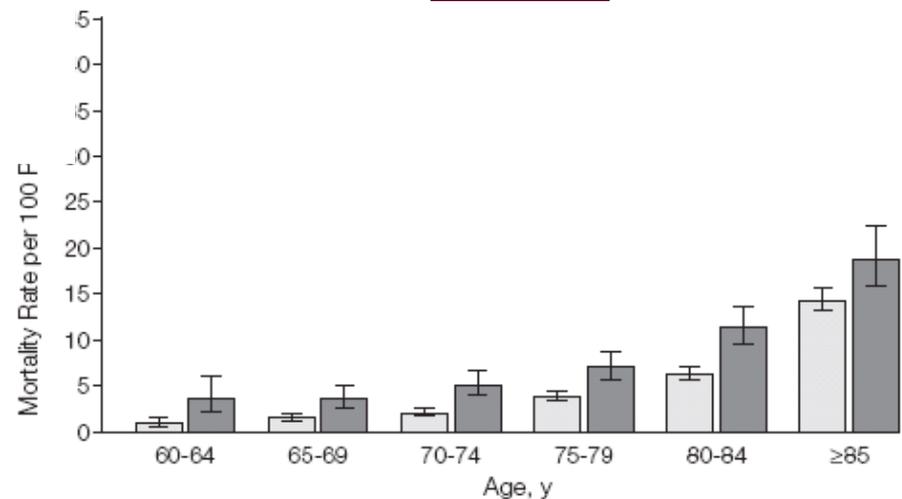
952 low-trauma fractures/ 461 deaths

Bliuc D et al. *JAMA* 2009

Percentage of Primary and Secondary forms of Osteoporosis in men and PM women with a vertebral fracture at presentation
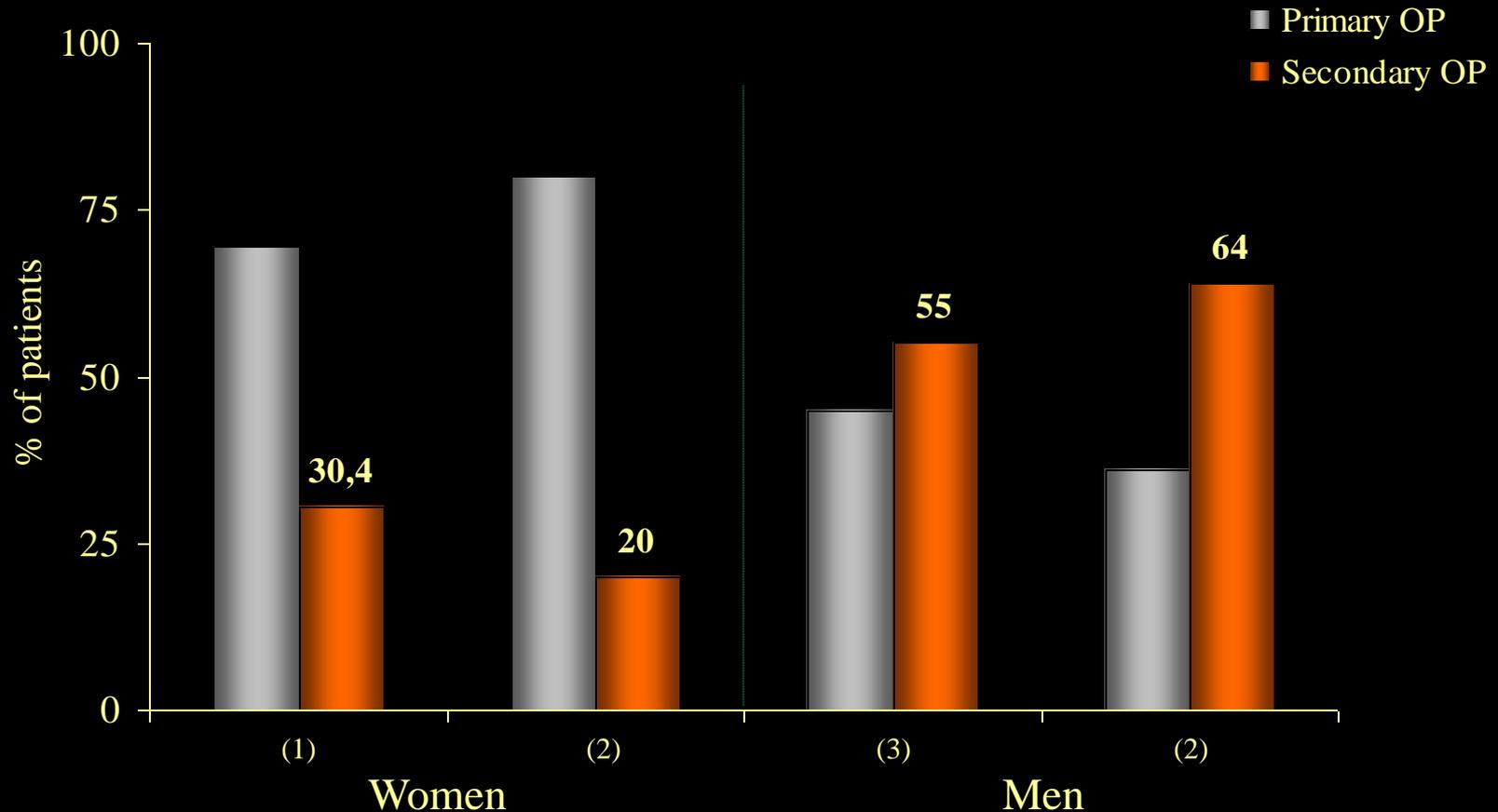
1) *J R Soc Med* 1994
2) *Ann Intern Med* 1995
3) *Baillieres Clin Rheumatol* 1993

# Osteoporosis and Bone Health in Patients with Lung Disease

Marcy B. Bolster, MD

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

Bar chart of comorbidity prevalence. Horizontal axis: 0.00% to 70.00% in 10.00% increments.

- Rhinosinusitis (~63%)
- Hyperglycemia (~52%)
- Atherosclerosis (~51%)
- Hypertension (~46%)
- Hyper/dyslipidemia (~33%)
- Hyperthyroidism (~31%)
- Facial wrinkling (~31%)
- Benign prostatic hypertrophy (~29%)
- Degenerative joint disease (~28%)
- Sarcopenia (~28%)
- GERD (~28%)
- Osteroporosis and osteopenia (~25%)
- Obesity (~22%)
- Depression (~19%)
- Heart failure (~19%)
- Diabetes mellitus (~17%)
- Peripheral arterial diseases (~14%)

Review Article

Osteoporosis Associated with Chronic Obstructive Pulmonary Disease

Ryo Okazaki, Reiko Watanabe, Daisuke Inoue

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

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International Journal of COPD

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REVIEW

COPD and osteoporosis: links, risks, and treatment challenges

Cumulative incidence comparison of Osteoporosis between subjects with and without chronic obstructive pulmonary disease
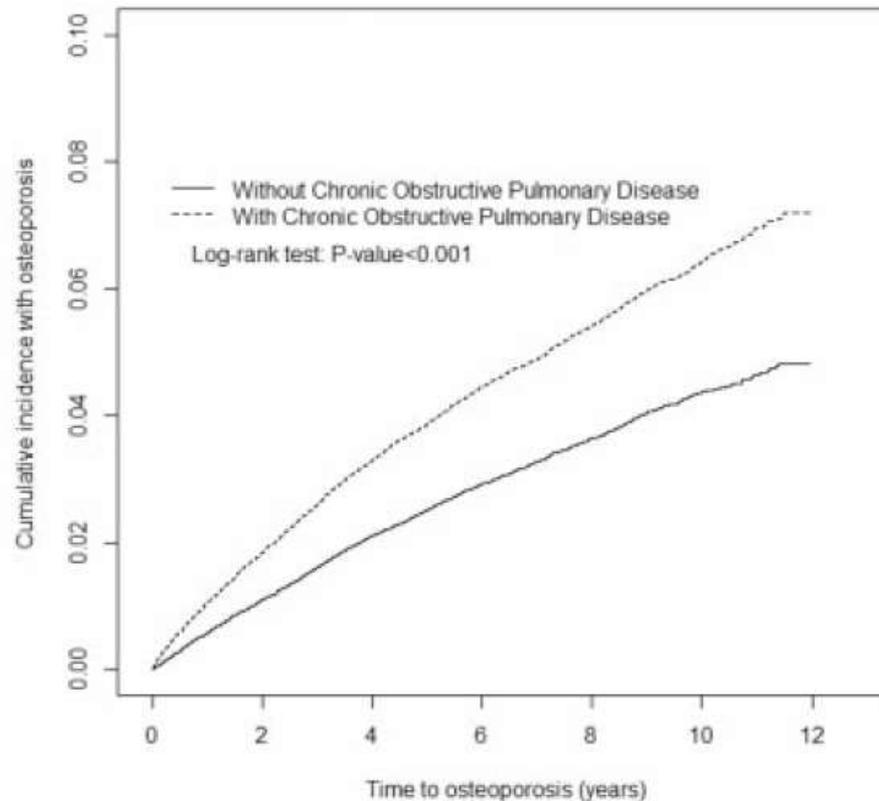
Chen S-J et al *Q J Med* 2015

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

Kuang-Ming Liao, MD[a], Fu-Wen Liang, PhD[b], Chung-Yi Li, PhD[b,c,*]

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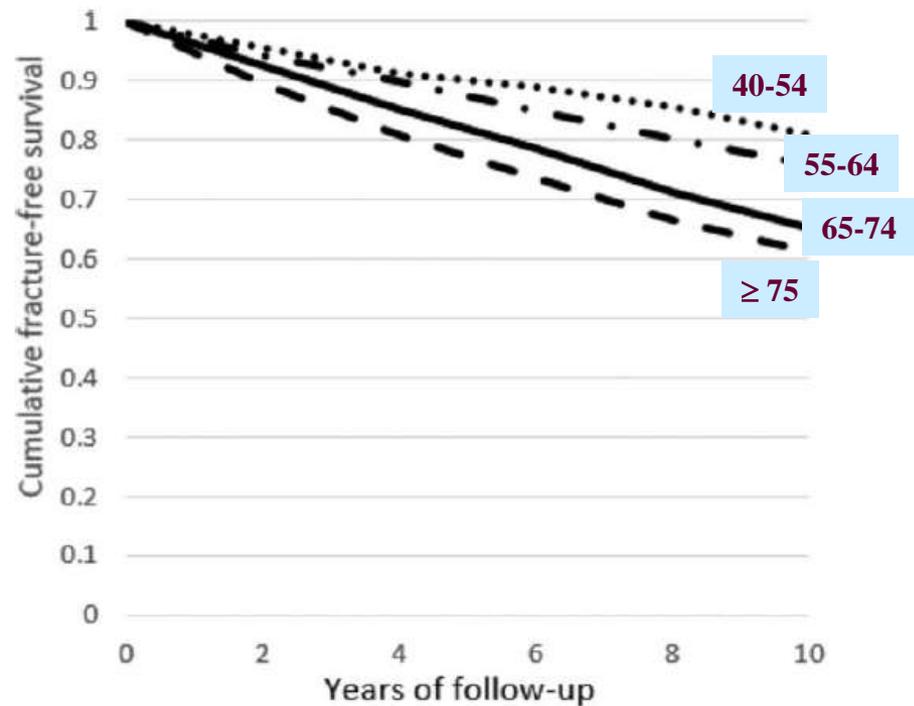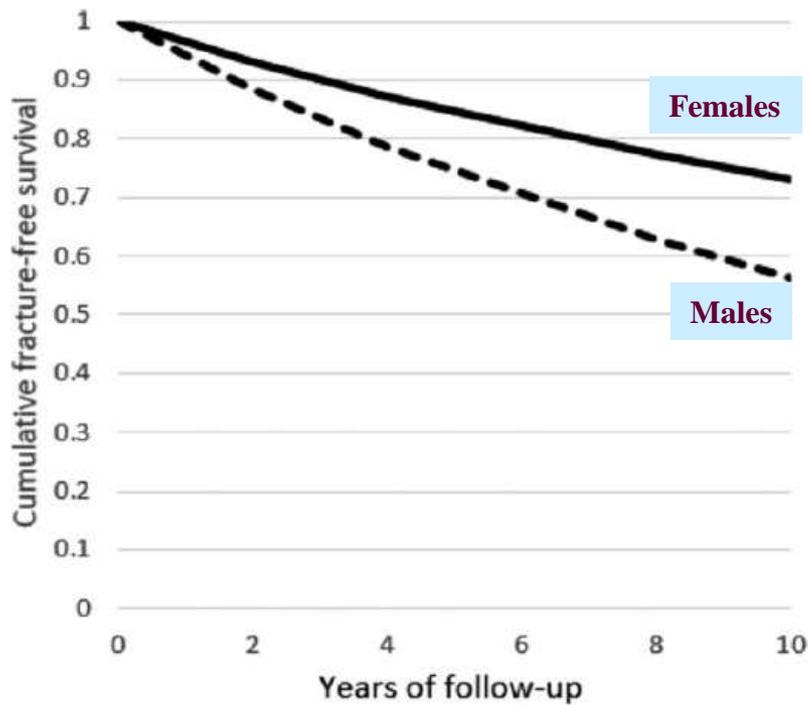
Site-specific fractures among 11,312 patients with COPD according to gender

Liao et al. Medicine (2016) 95:40
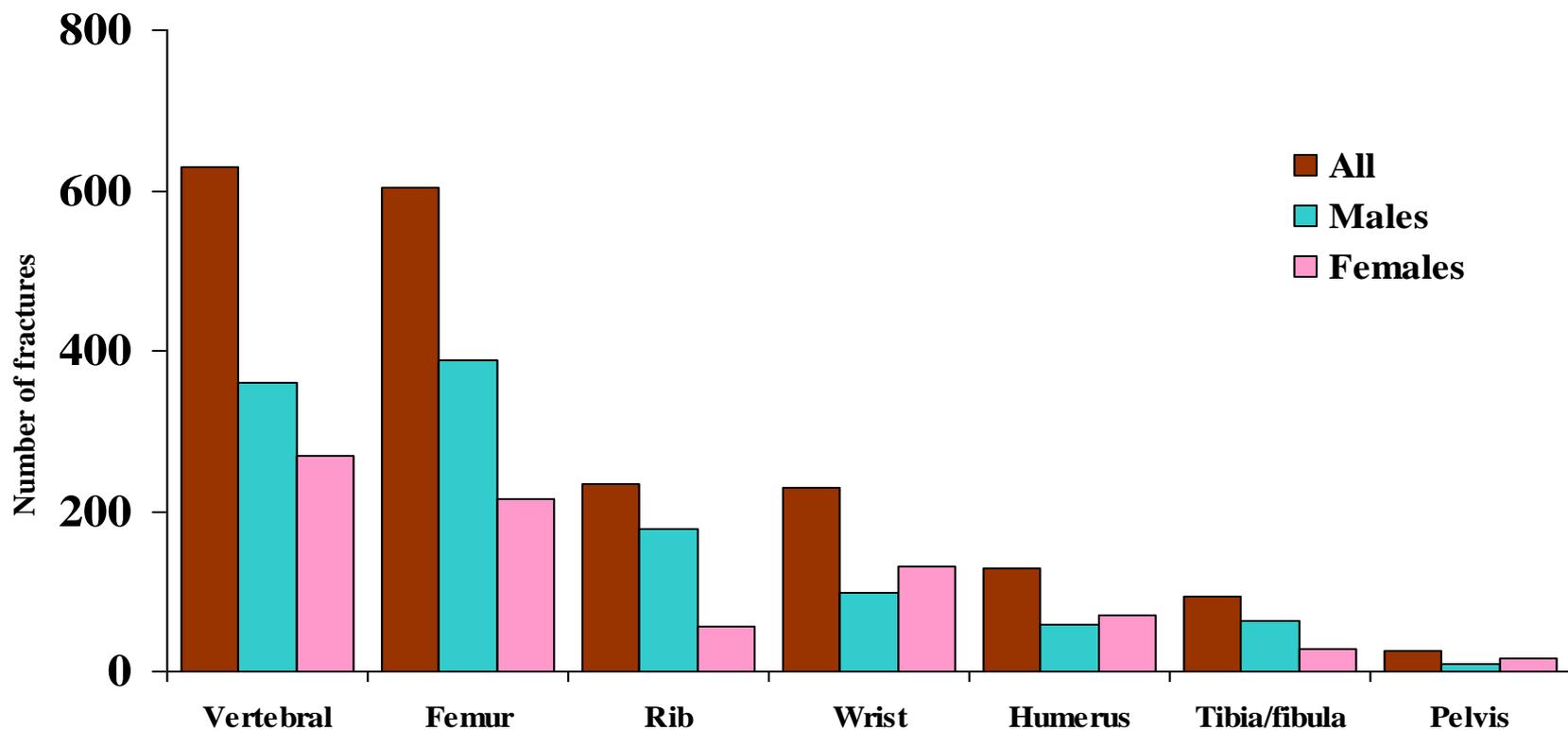
Prevalence of Vertebral Fractures in main observational studies on patients with COPD

| 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

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

Legend: □ No Fracture ▨ ≥ 1 Fracture

Women — N.= 1262 — $p<0.05$

COPD severity	No Fracture	≥ 1 Fracture
Mild	64.2	35.8
Moderate	58.0	42.0
Severe	53.3	46.7
Very severe	54.3	45.7

Men — N.= 1778 — $p<0.001$

COPD severity	No Fracture	≥ 1 Fracture
Mild	65.0	35.0
Moderate	61.5	38.5
Severe	54.3	45.7
Very severe	40.8	59.2

Distribution (%)
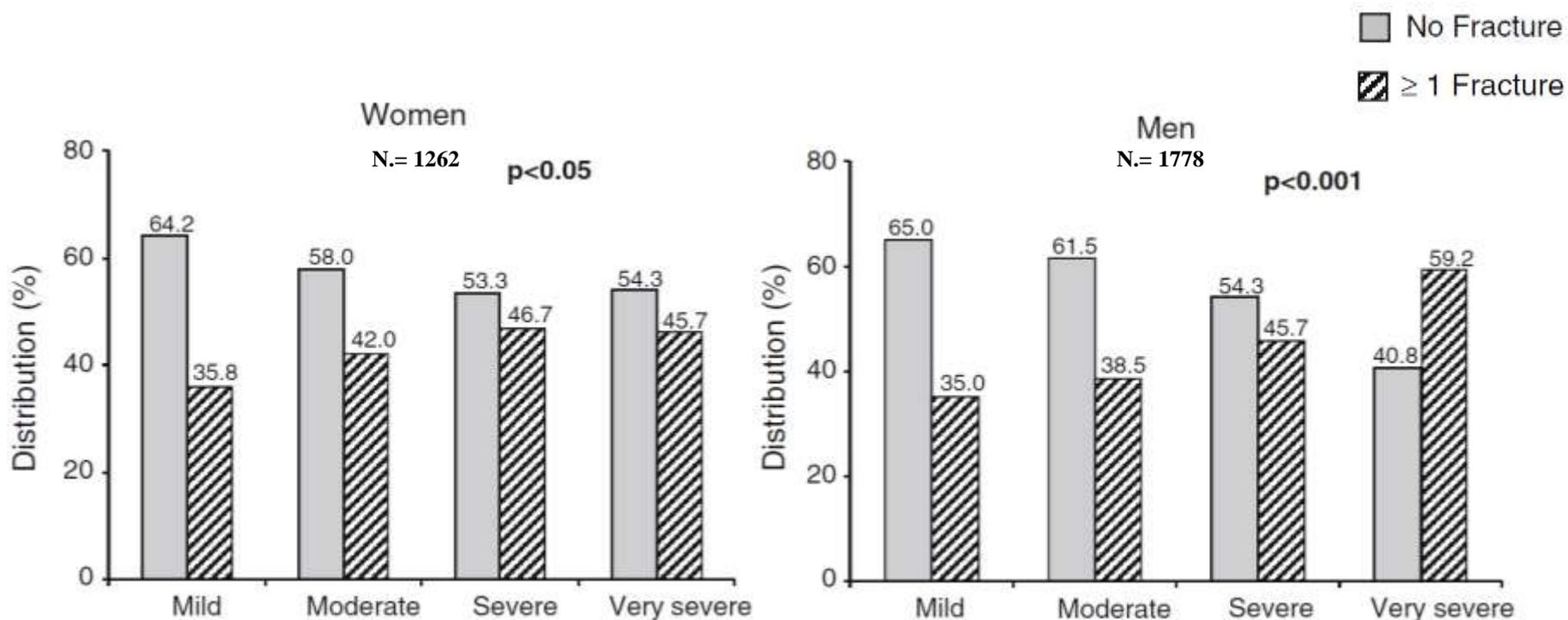
* COPD severity according to GOLD criteria

Nuti R et al. *Osteoporos Int* **2009**

# COPD and Osteoporosis : a challenging vicious circle
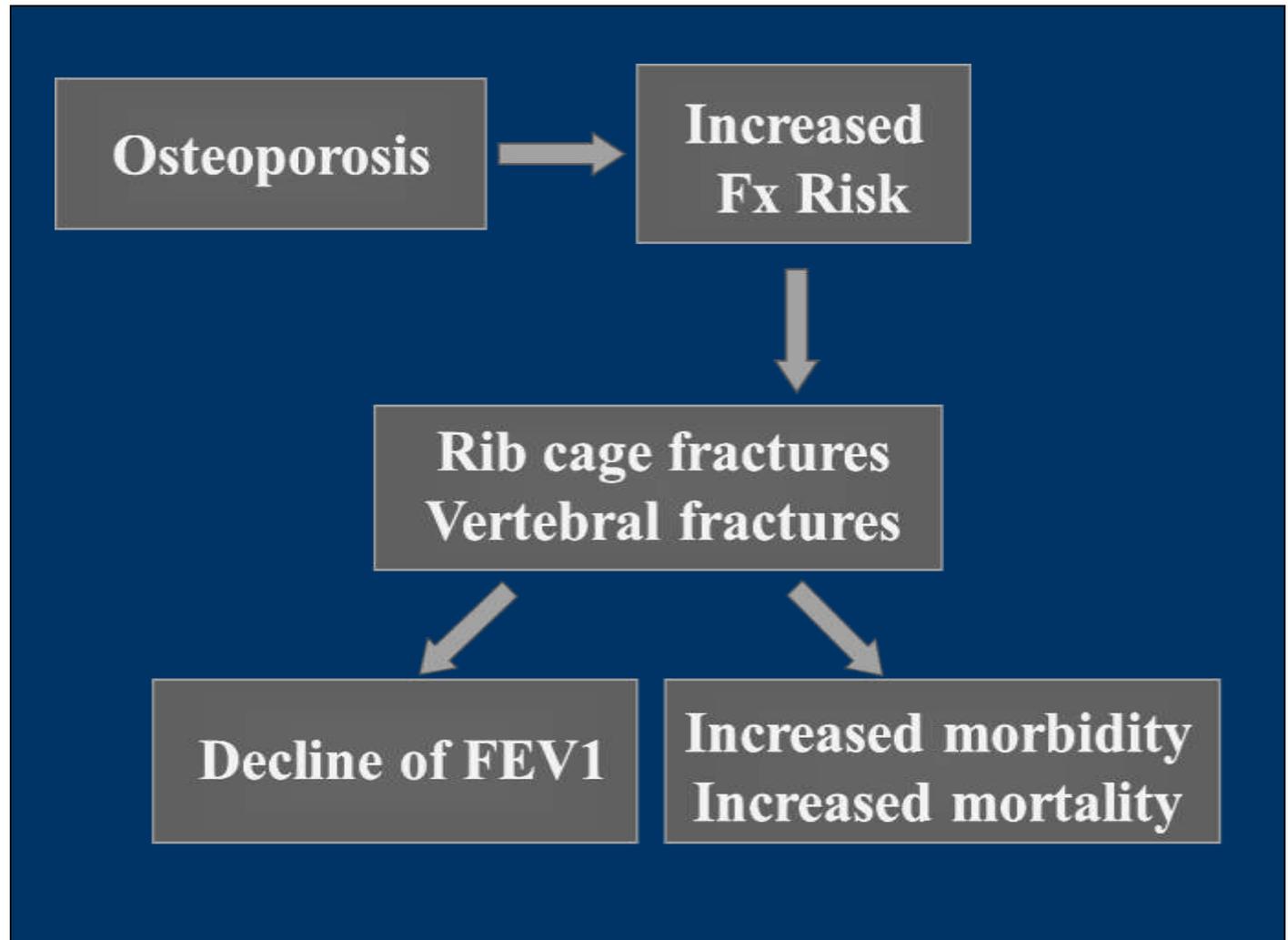
Osteoporosis-Related Kyphosis and Impairments in Pulmonary Function: A Systematic Review

Robyn A Harrison,[1] Kerry Siminoski,[1,2] Dilini Vethanayagam,[1] and Sumit R Majumdar[1]

> ➤ **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**

Harrison RA et al. *J Bone Miner Res* 2007

Distribution of pulmonary and other deaths by deciles of increasing severity of kyphosis
(9575 women ≥ 65 years followed for 8.3 years)

Kado DM et al. *Arch Intern Med* 1999
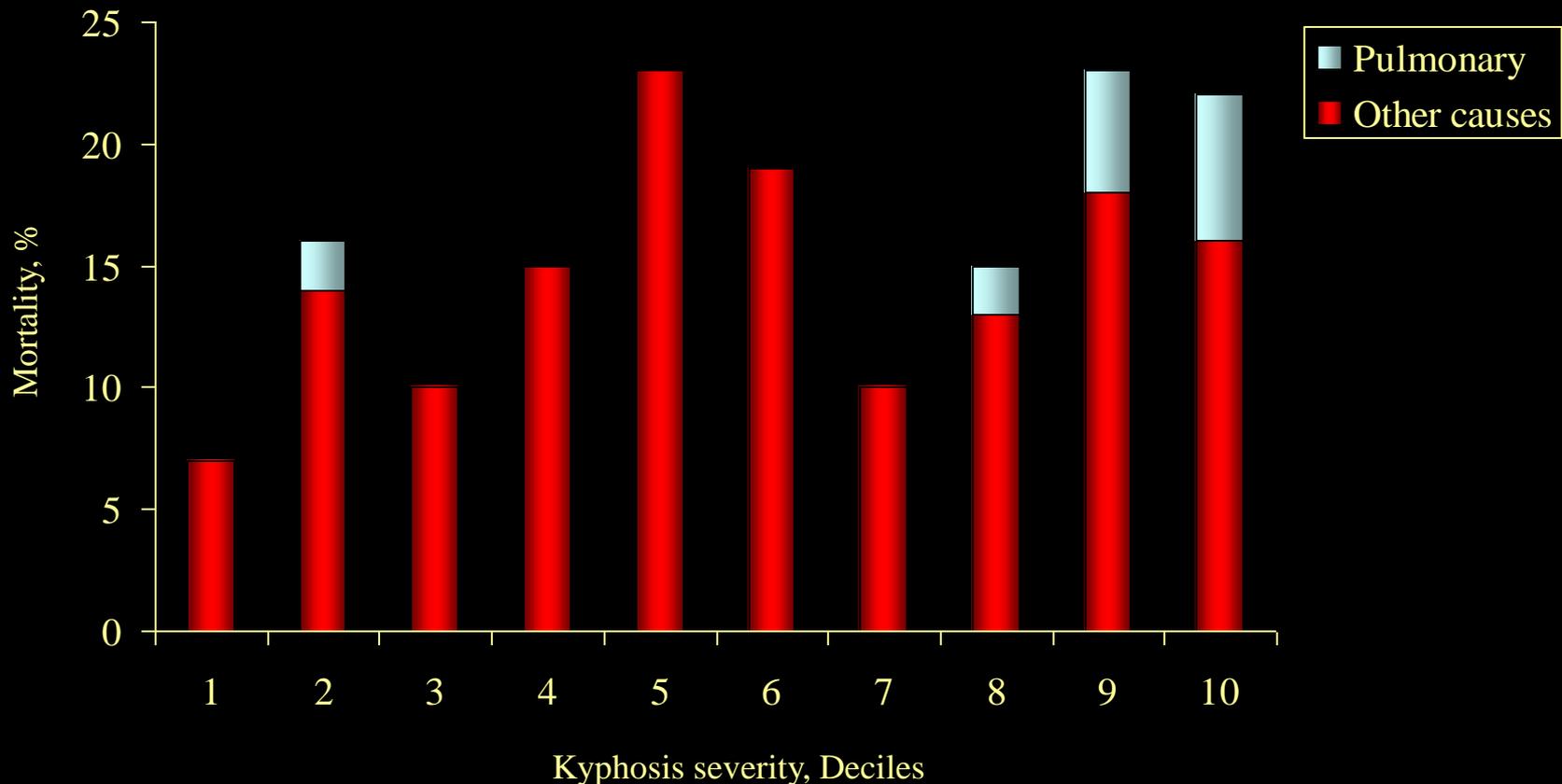
One-year mortality in 12,646 male patients after hip fracture repair
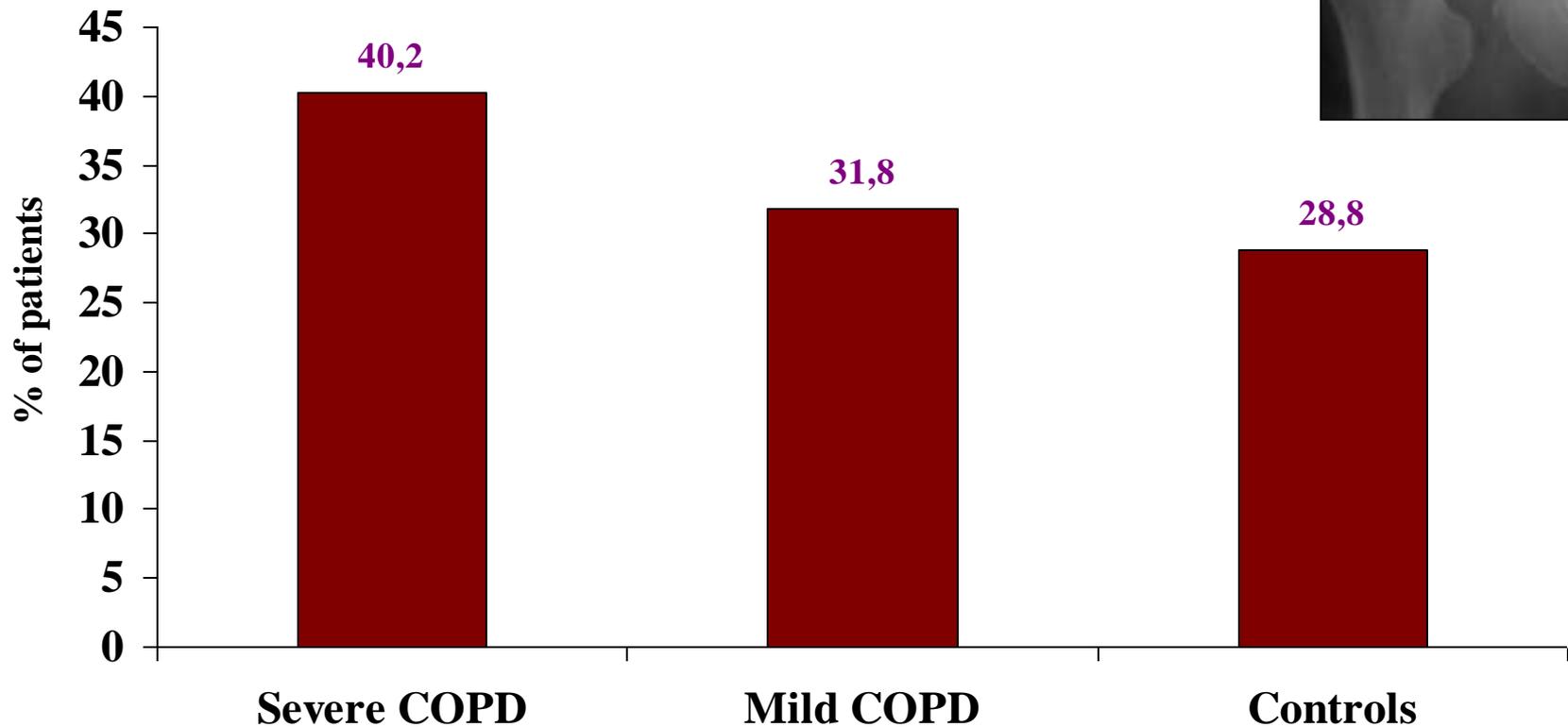
% of patients

Severe COPD	Mild COPD	Controls
40,2	31,8	28,8

Regan EA et al. *Int J COPD* 2013

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**

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Relationship between BMD at the hip and hip fracture probability in women according to age
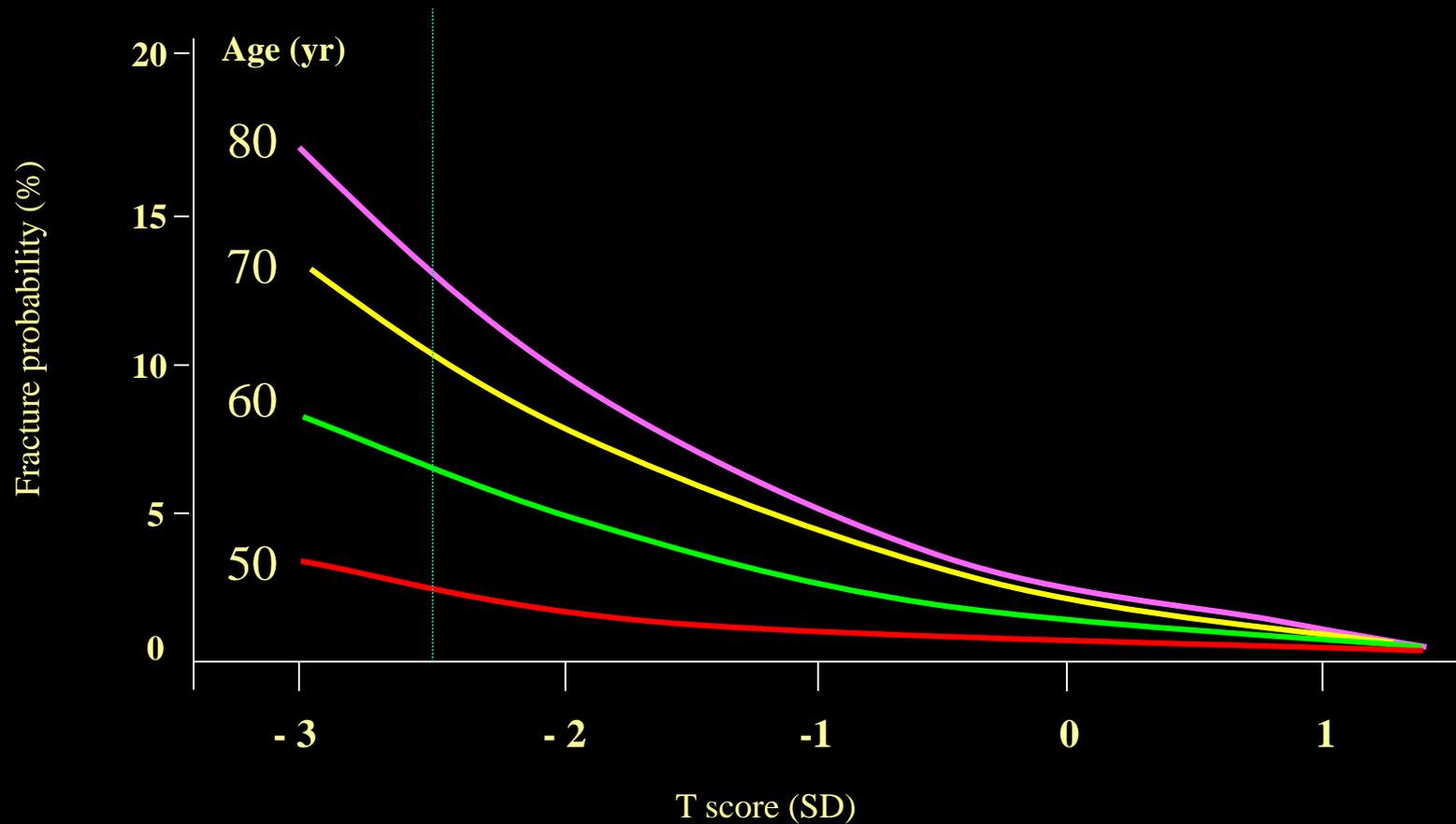
Kanis JA et al. *Osteoporos Int* 2001

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Current smoking and risk of any fracture
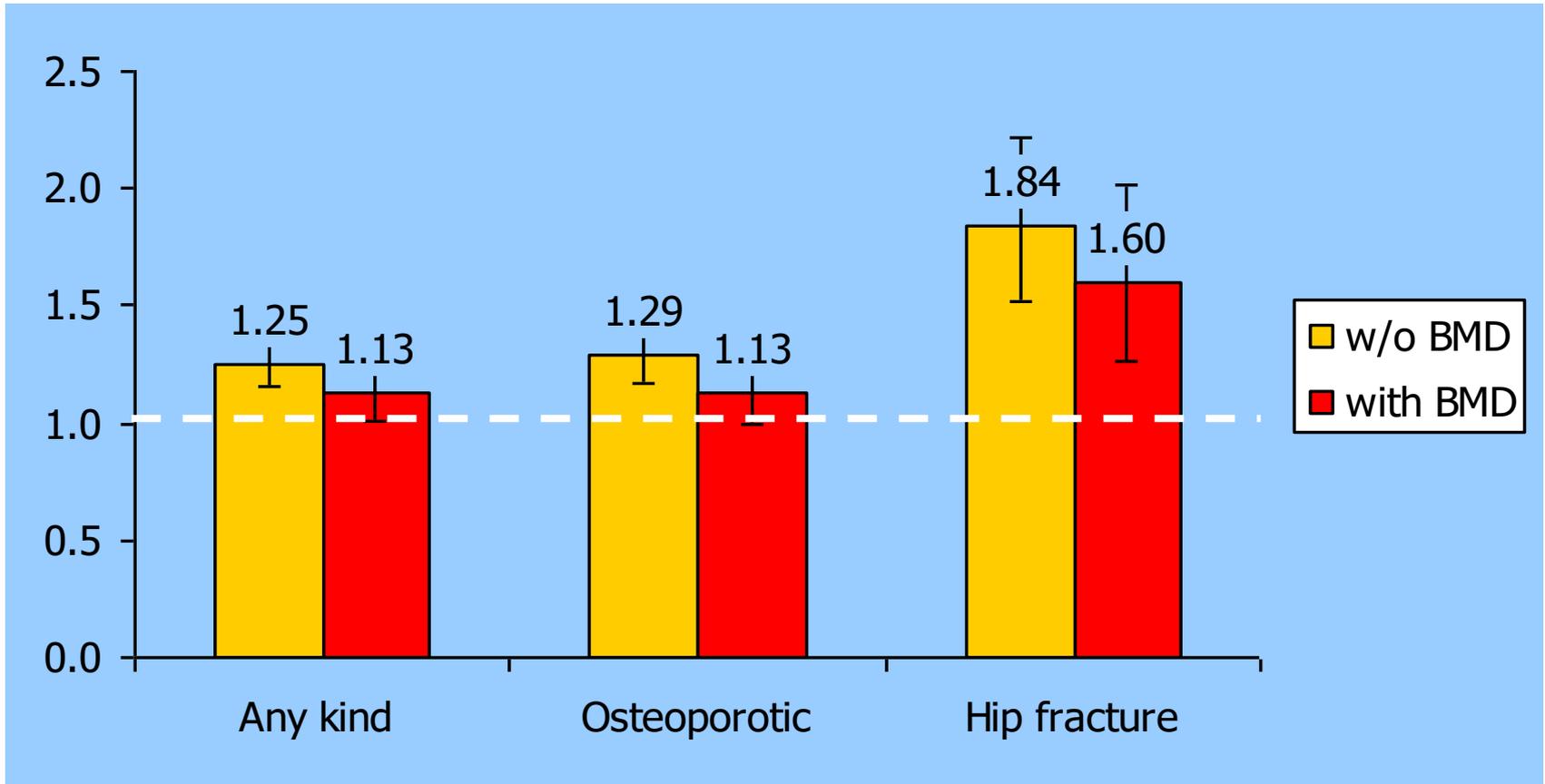
Kanis JA et al. *Osteoporos Int* 2004

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A low BMI is a significant risk factor for hip fracture even after adjustment for BMD
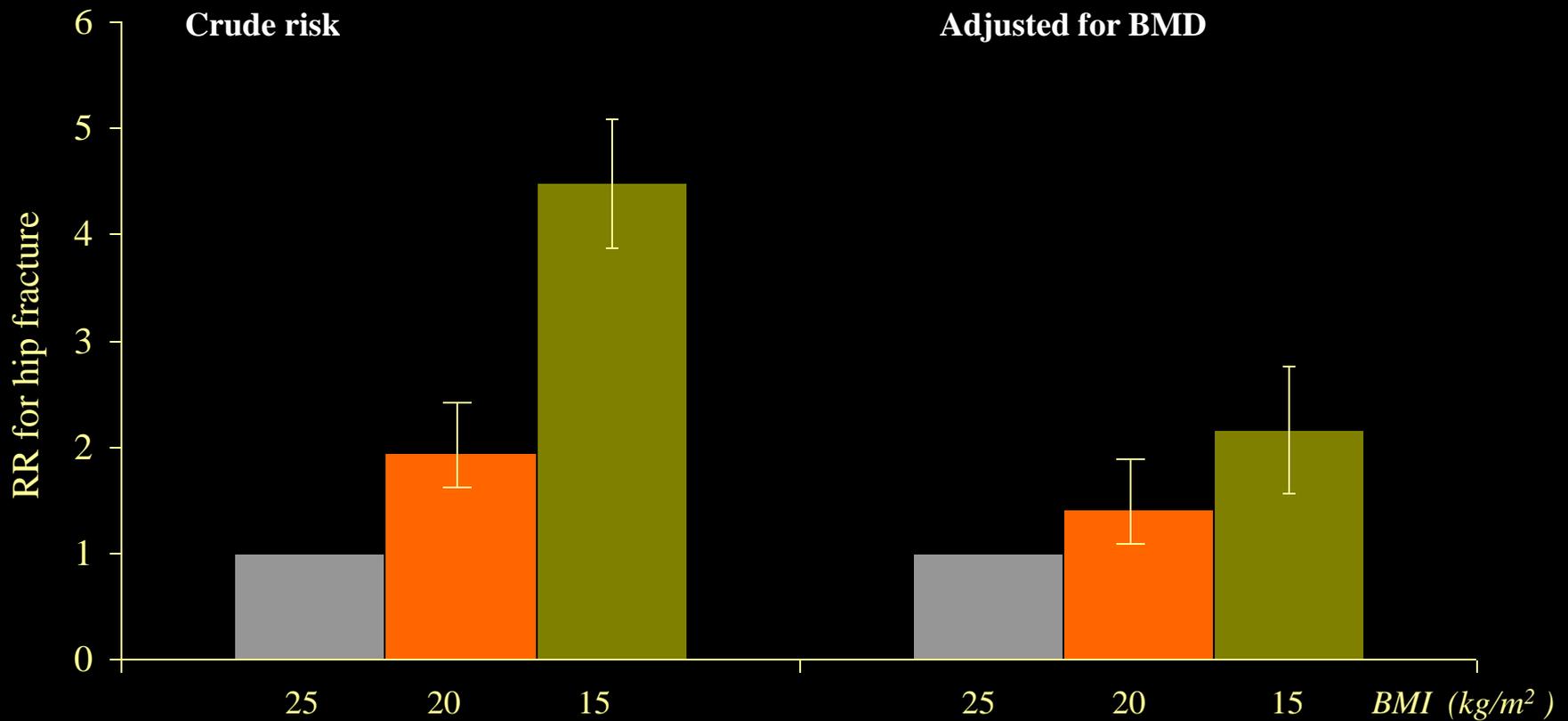
De Laet C et al. *Osteoporos Int* 2005

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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
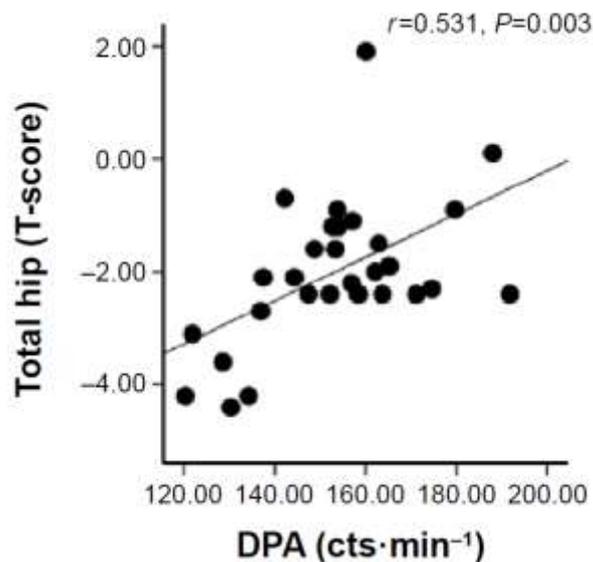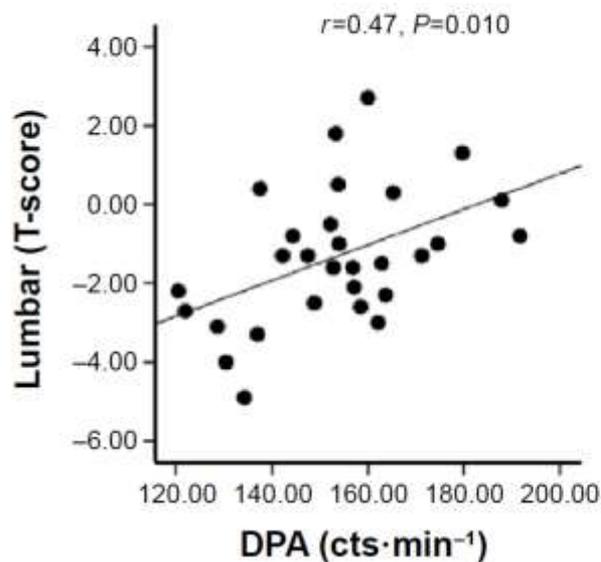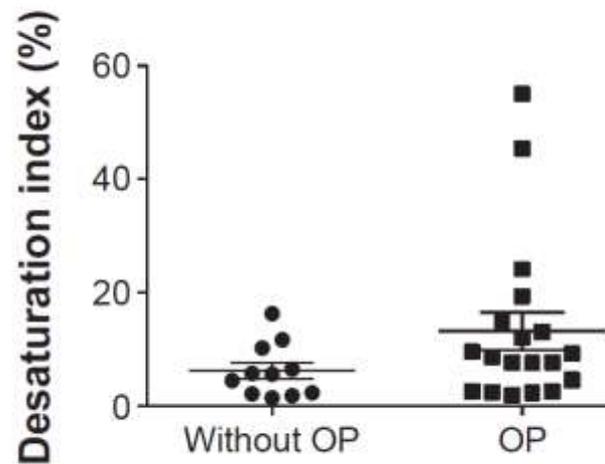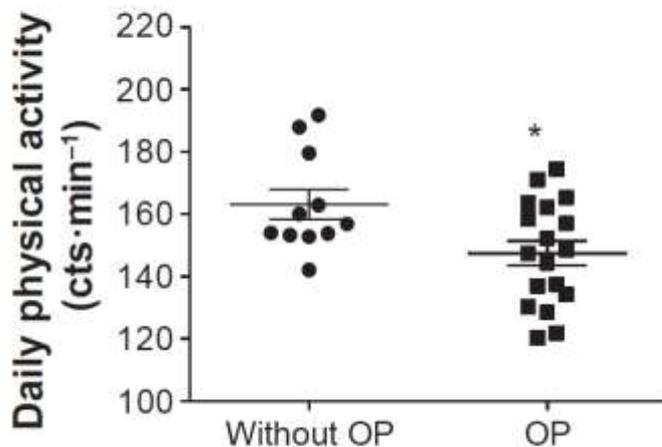
Liu WT et al. *Int J of COPD* 2015

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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 *
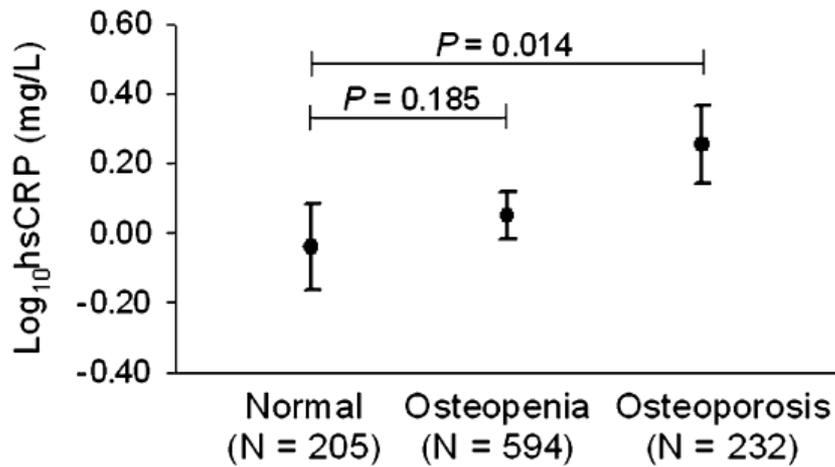
hs-CRP and risk of non-traumatic fractures **
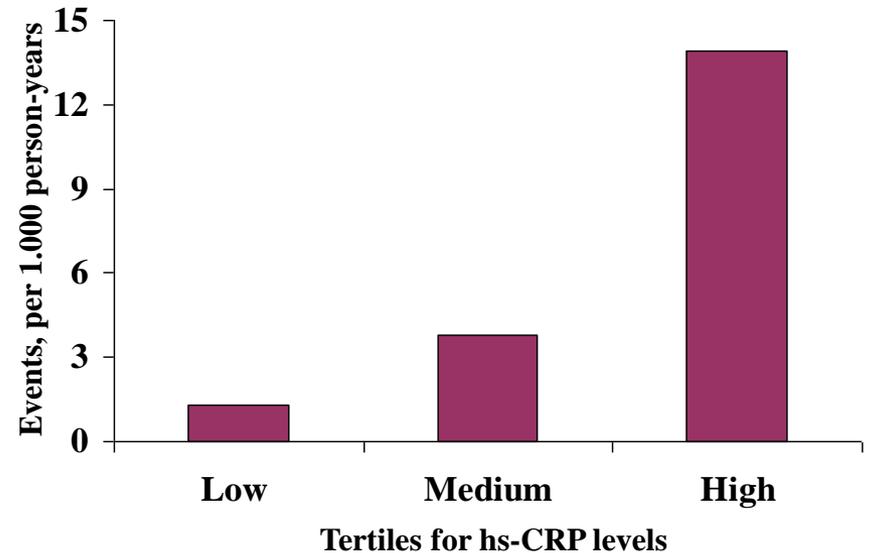
* Koh J-M et al. *Osteoporos Int* 2005
**Schett G et al. *Arch Intern Med* 2006

Signalling in Osteoclasts during inflammation
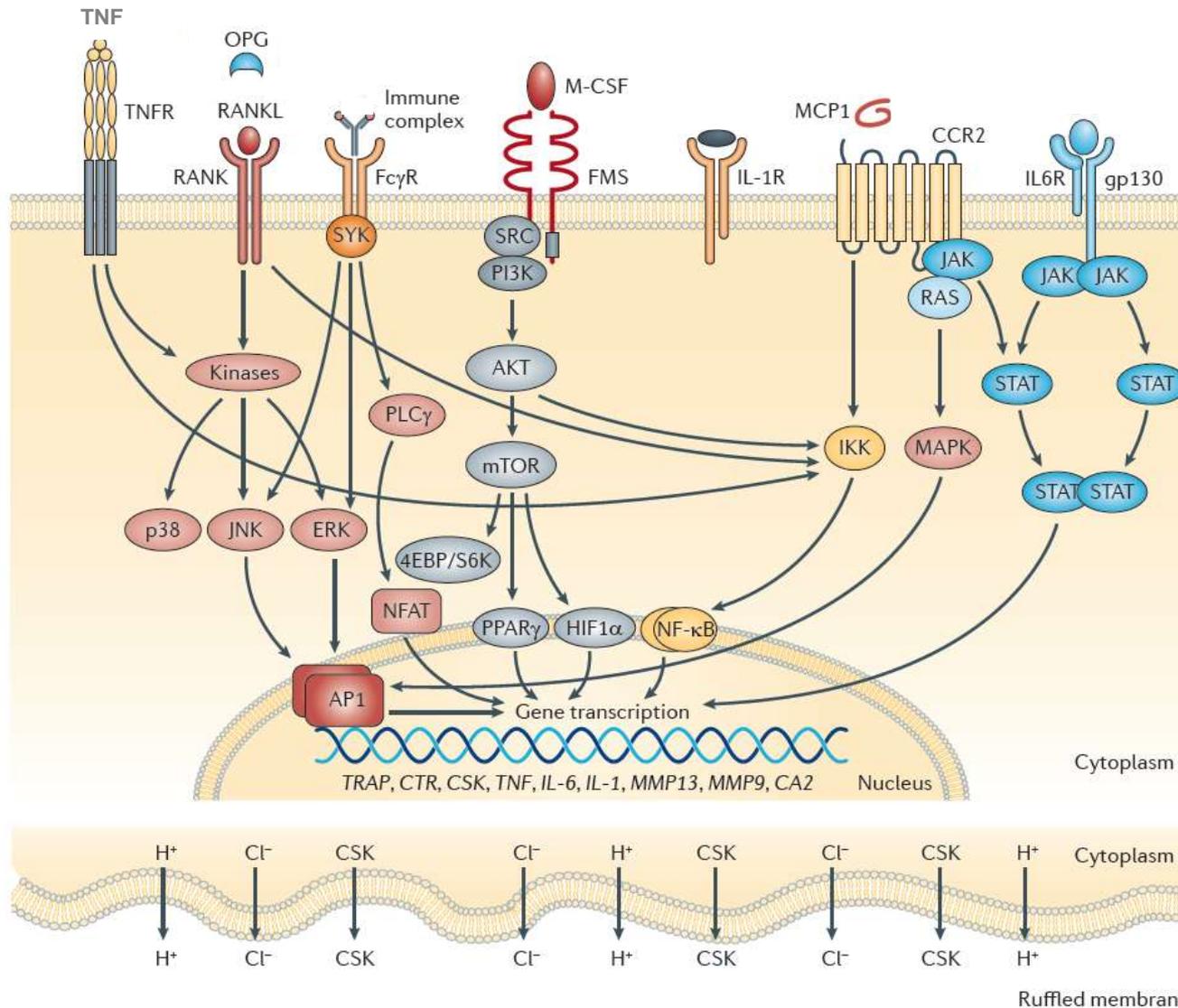
Signalling in Osteoblasts during inflammation
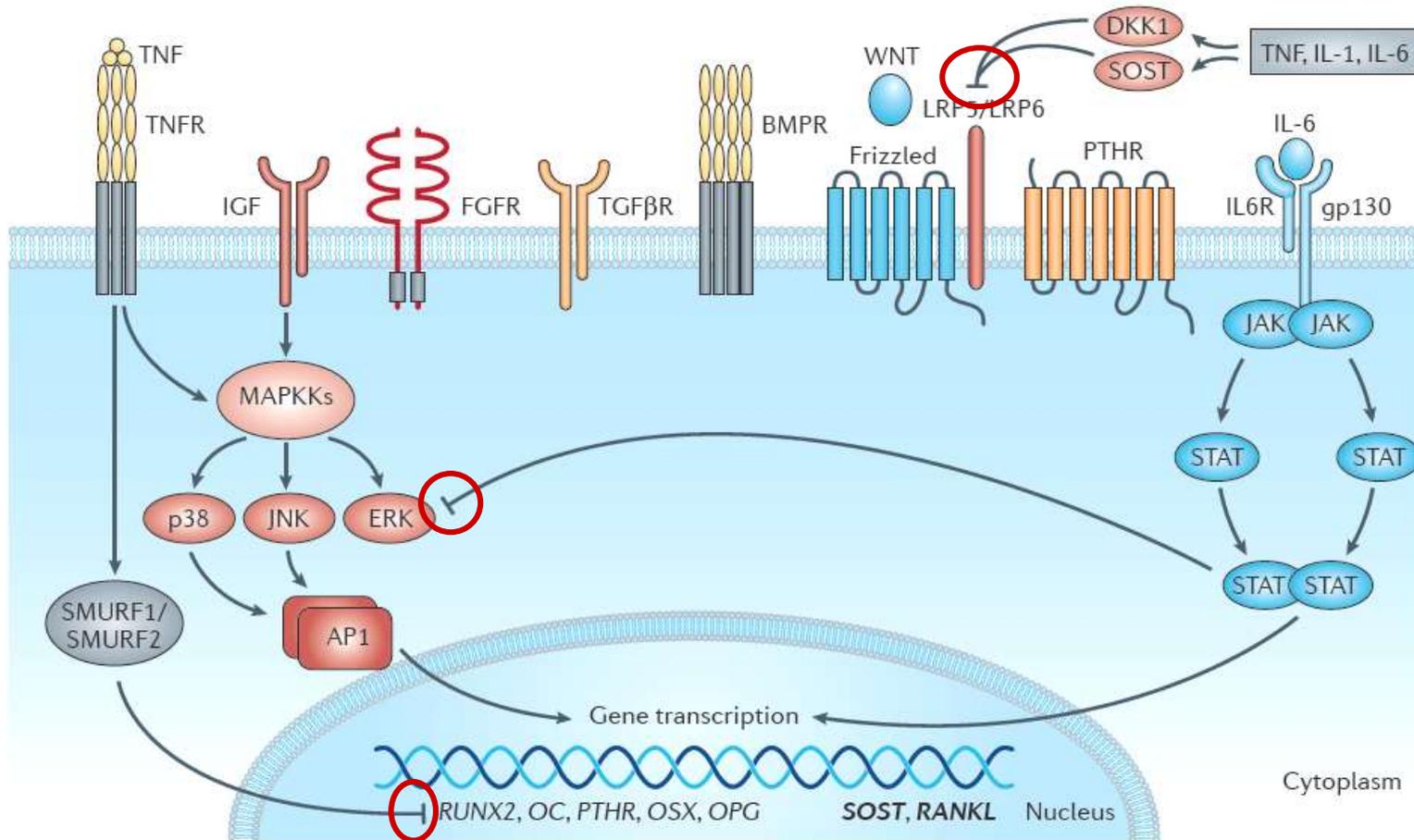
Cytokine-mediated bone destruction in inflammatory diseases
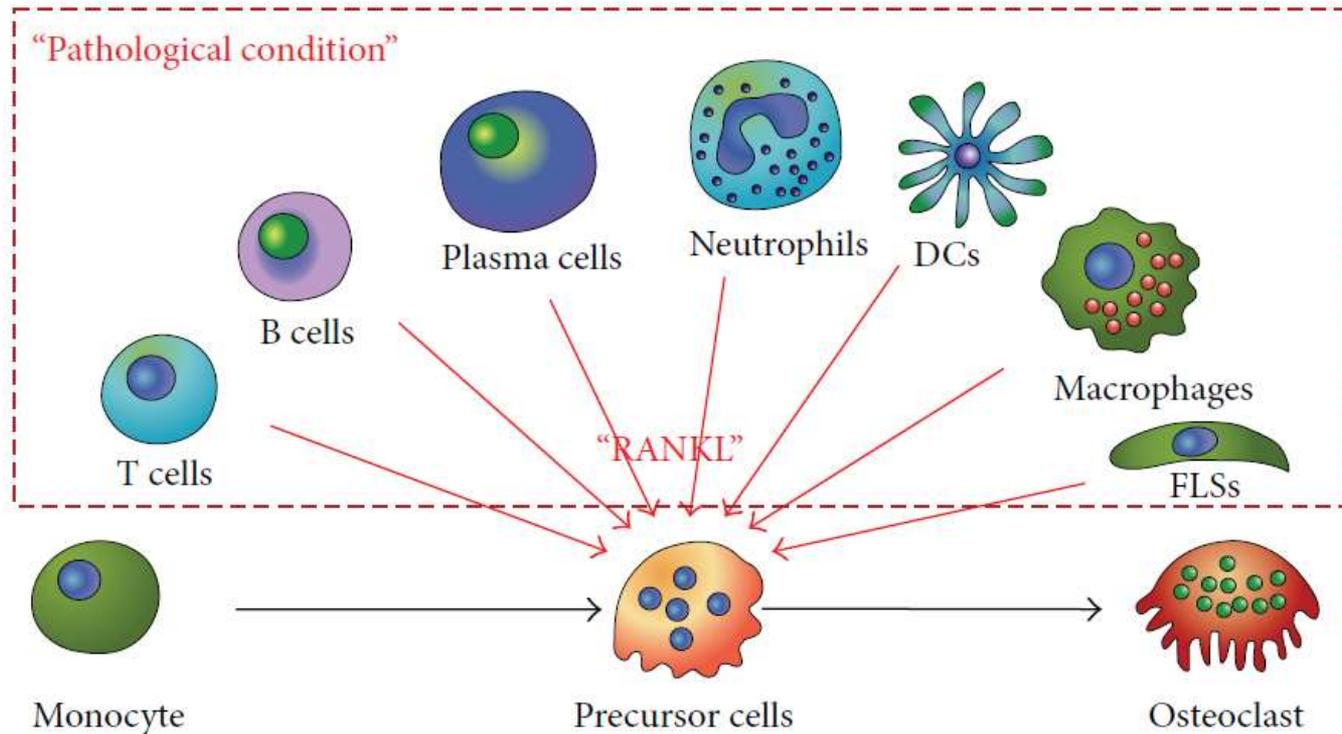
The association of low bone mineral density with systemic inflammation in clinically stable COPD

Binmiao Liang · Yulin Feng

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

	OR	95% CI	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*

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

Bai P et al. *Respir Res* 2011
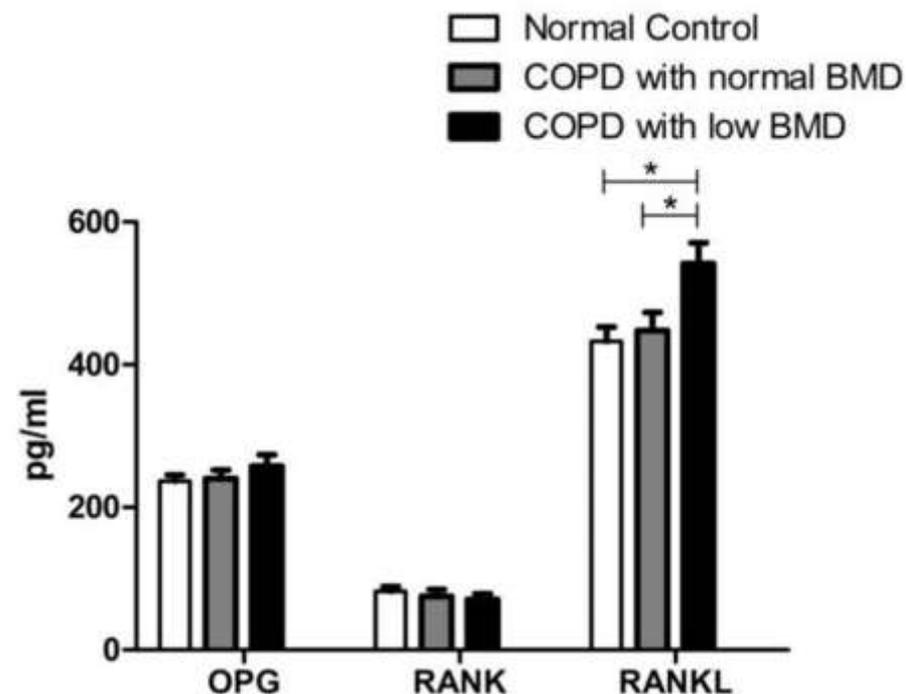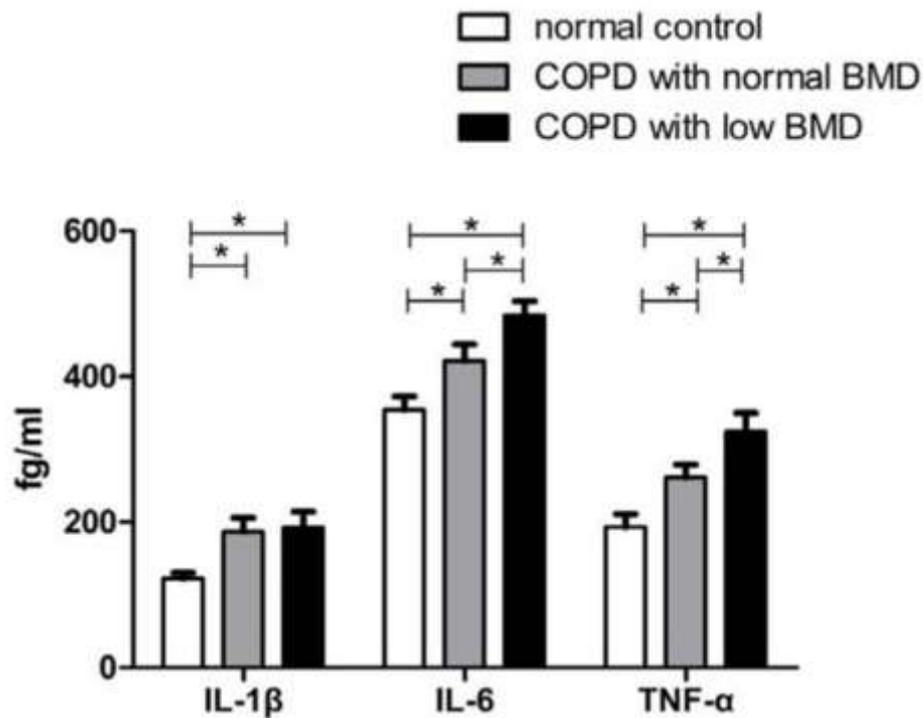
Expression of RANKL by peripheral neutrophils and its association with bone mineral density in COPD

XiaoLing Hu,[1] Yongchang Sun,[1,2] Weihan Xu,[1] Tao Lin[3,4] and Hui Zeng[3,4]
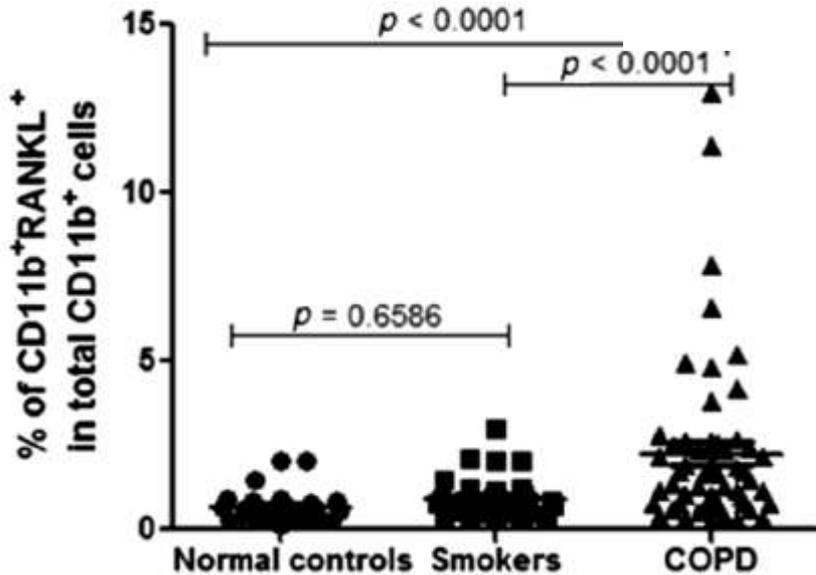
SUMMARY AT A GLANCE

Peripheral blood neutrophils from male patients with COPD had enhanced expression of the osteoclast activation factor RANKL (receptor activator of NF-kB ligand), which correlated with bone mineral density and lung function of the patients.
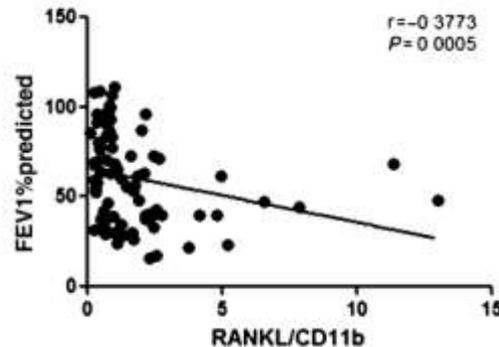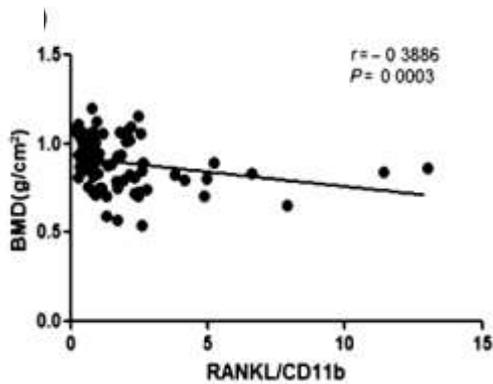
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Prevalence of different comorbidities in 412 outpatients according to mild or severe grade of COPD
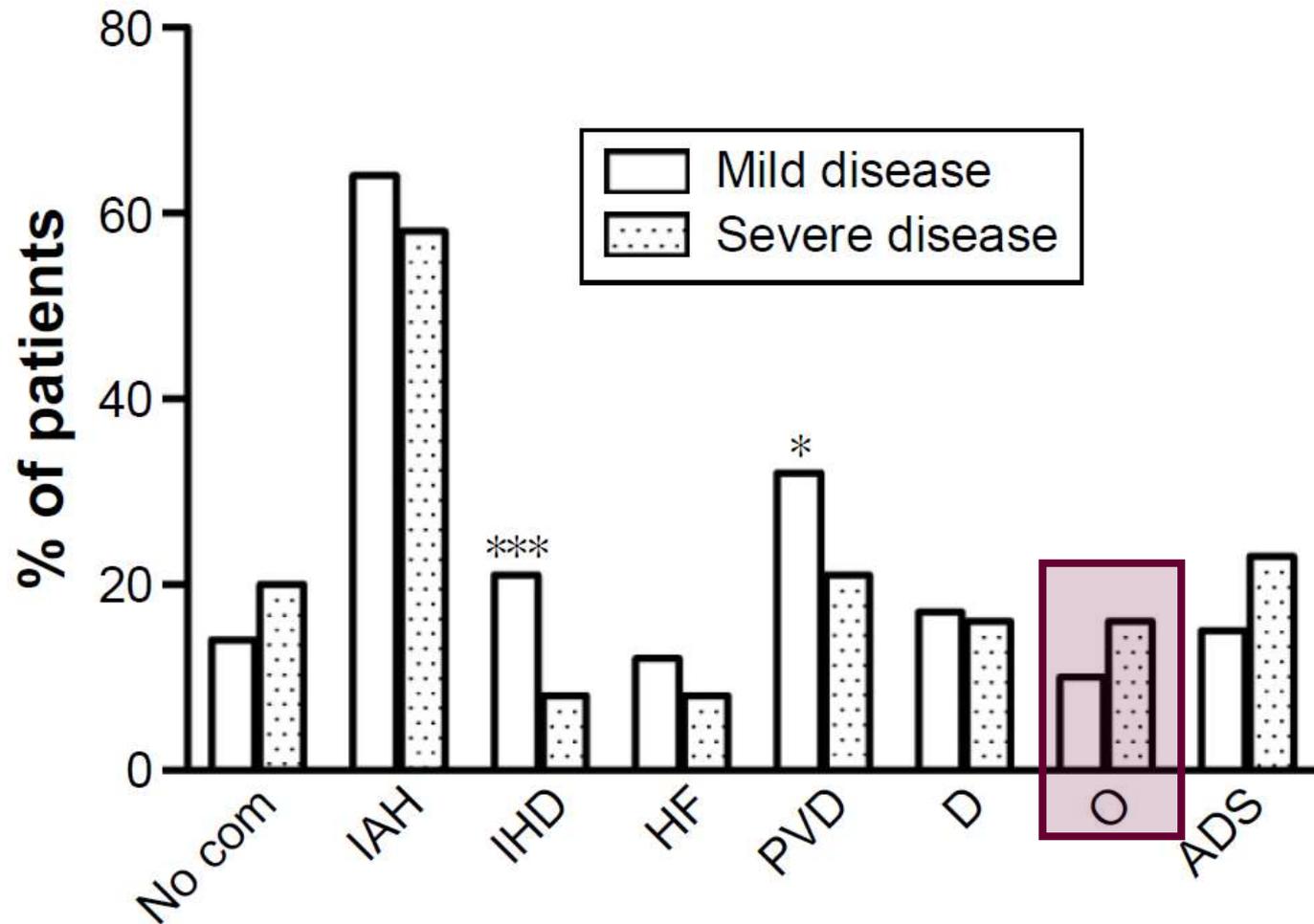
Abbreviations: ADS, anxious depressive syndrome; com, comorbidities; COPD, chronic obstructive pulmonary disease; D, diabetes; HF, heart failure; IAH, idiopathic arterial hypertension; IHD, ischemic heart disease; O, osteoporosis; PVD, peripheral vascular disease.

Camiciottoli G et al. *Int J of COPD* **2016**

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
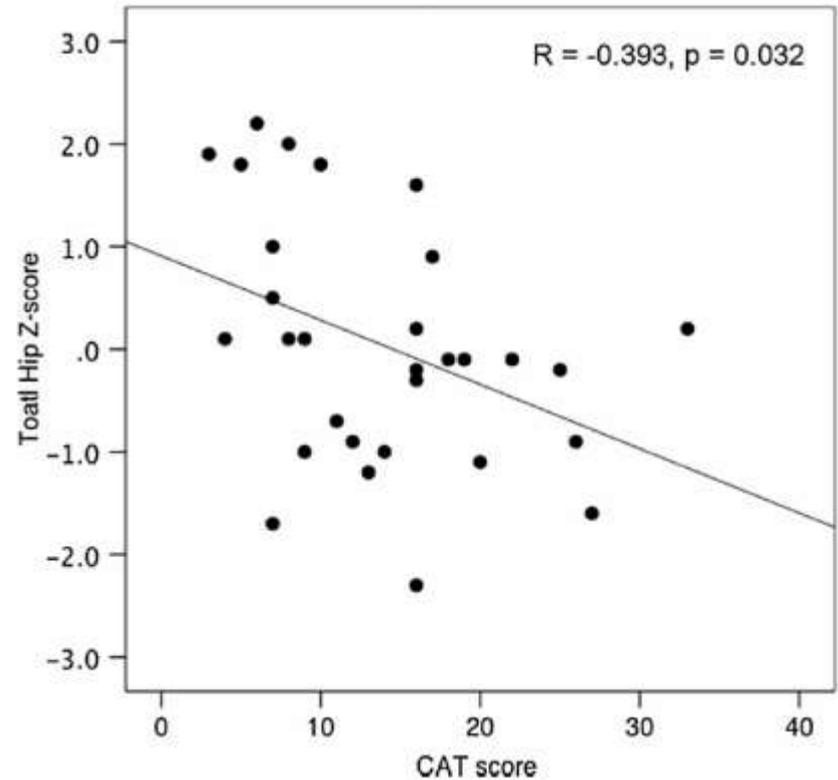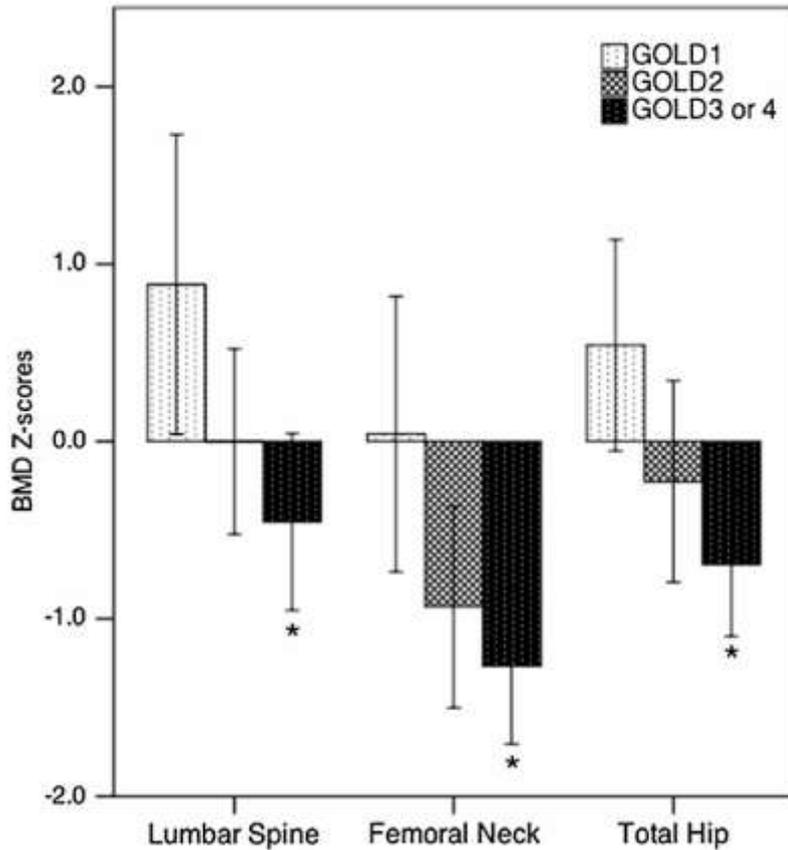
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Prevalence of Hypovitaminosis D in COPD patients

* Patients with COPD admited for exacerbation

Mekov E et al. *PLOS One* **2015**
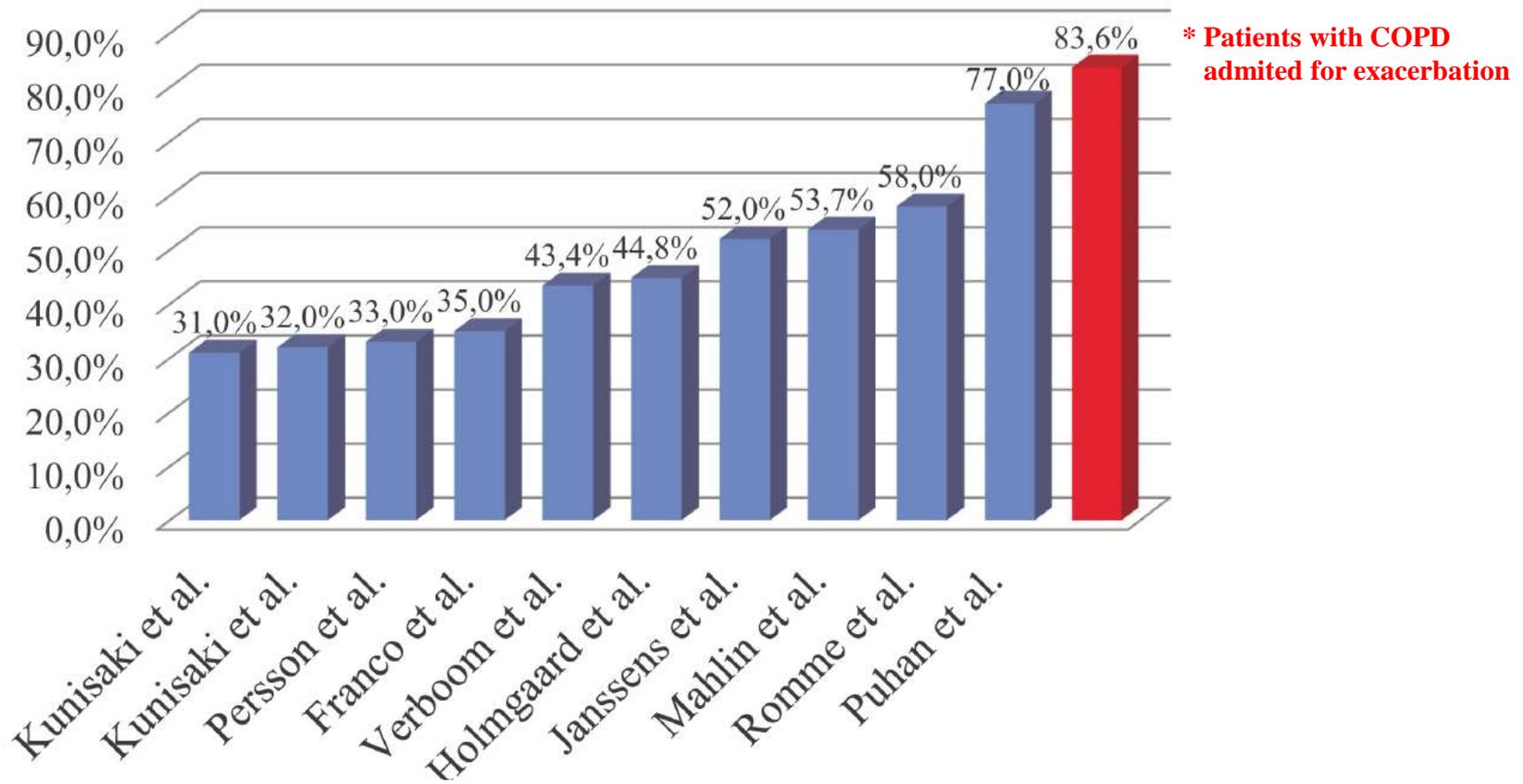
Relationship between FEV1, Emphysema severity, Six Minutes Walk, SGRQ score and serum 25(OH)D in 498 COPD patients (ECLIPSE Study)

Berg I et al *Respir Med* 2013
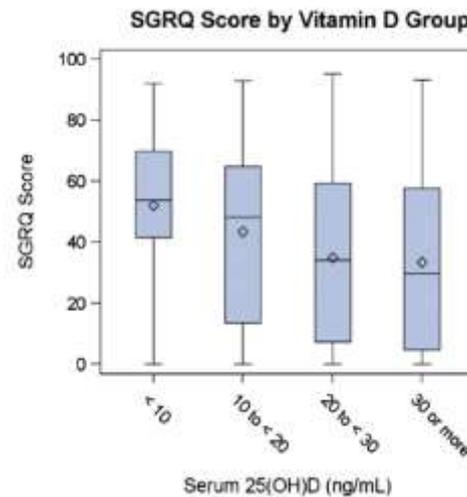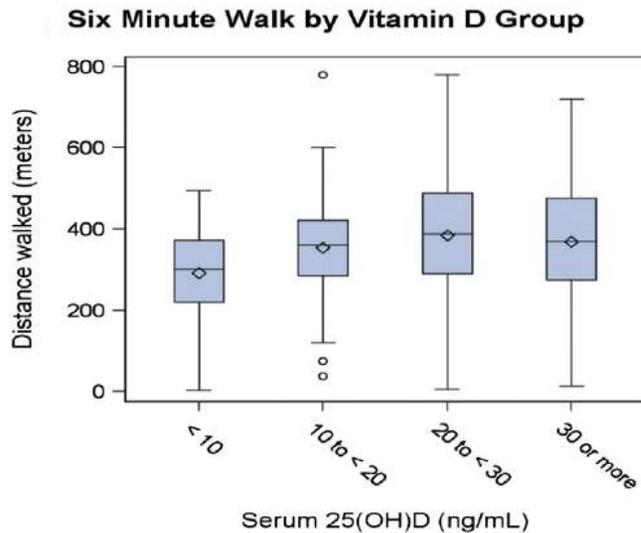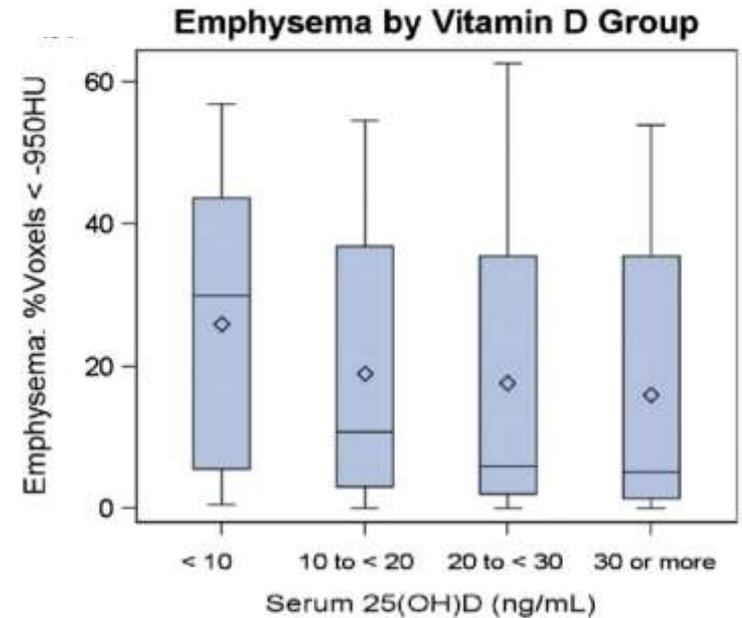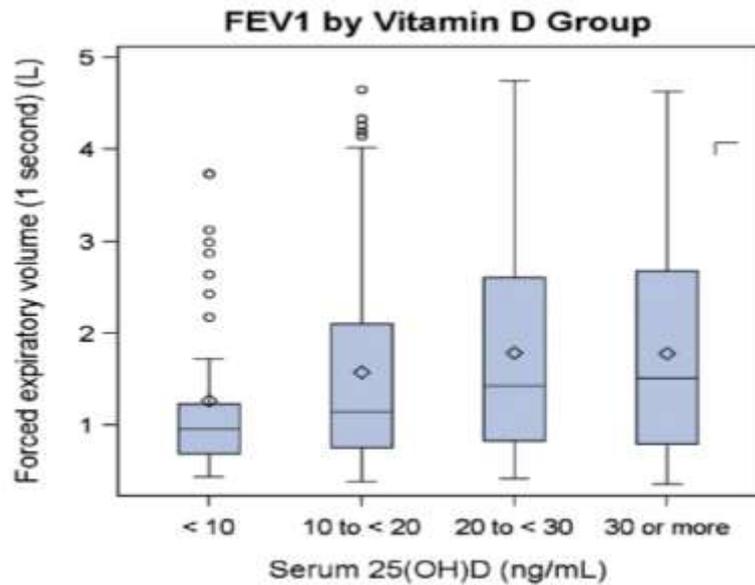
Suggested mapping of the principal Vitamin D –related bone diseases onto the serum 25(OH)D concentration continuum

rickets/osteomalacia

osteoporosis

normal

0	25	50	75	100	125	150

(nmol/L)

Heaney R.P. *Am. J. Clin. Nutr.* 2004
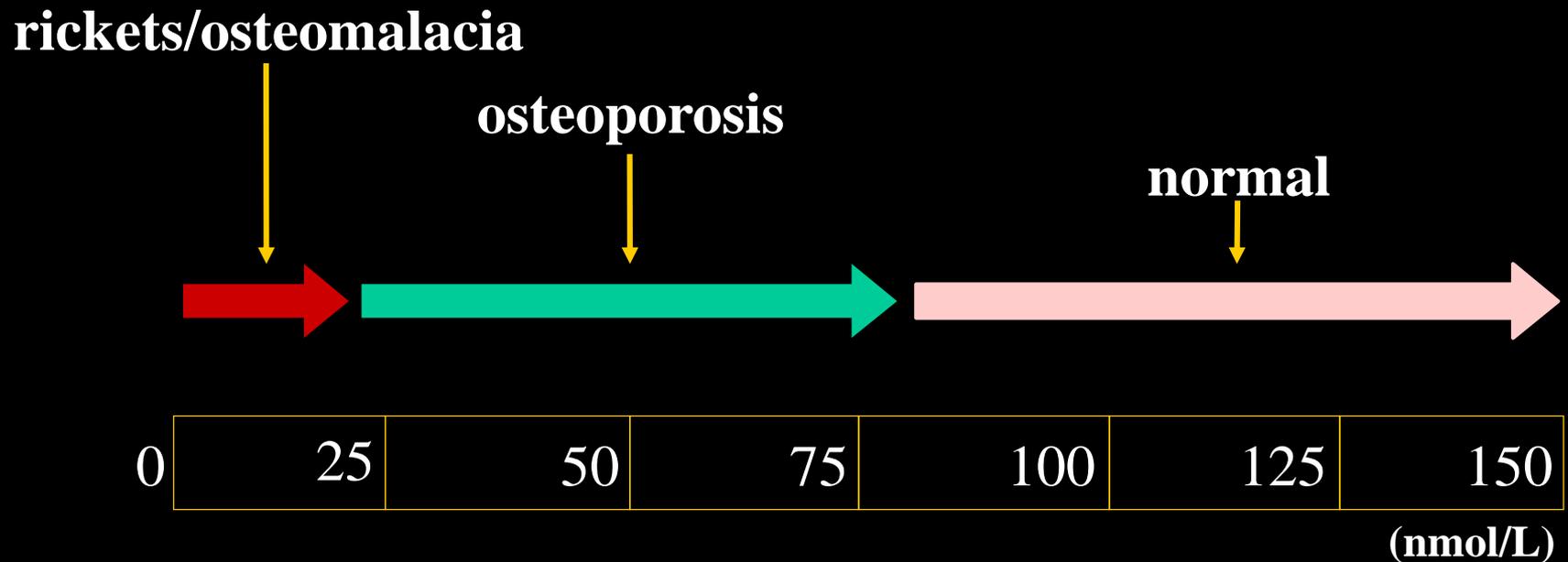
Evolution of Hypovitaminosis D Osteopathy and Osteomalacia

Stage	Clinical features
HVO-I	• **Increased ALP** • **Increased PTH** • **Increased Bone turnover** • **No mineralization defect**
HVO-II	• **Progressive accumulation of unmineralized matrix**
HVO-III	• **Complete cessation of mineralization** • **No tetracycline uptake** • **Frank Osteomalacia**

HVO : Hypovitaminosis D Osteopathy Stage

CrossMark

ORIGINAL ARTICLE

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

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

Rate ratio and 95 % CI

Study

Study	
Chapuy, 1992 [20]	
Chapuy, 2002 [21]	
Dawson-Hughes, 1997 [22]	
Porthouse, 2005 [23]	
Salovaara, 2010 [24]	
Grant, 2005 [25]	
Harwood, 2004 [26]	
Prentice, 2013 [10]ᵃ	

SRRE = 0.85 (0.73–0.98)
P-heterogeneity = 0.06
I^2 = 49.20

0.1   0.2   0.5   1.0   2   5   10
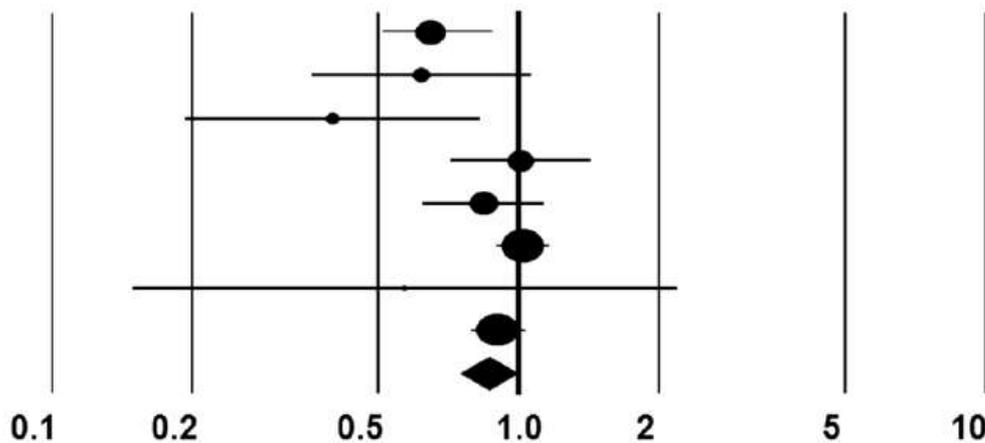
Decreased risk   Increased risk

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Glucocorticoids are bad for bone
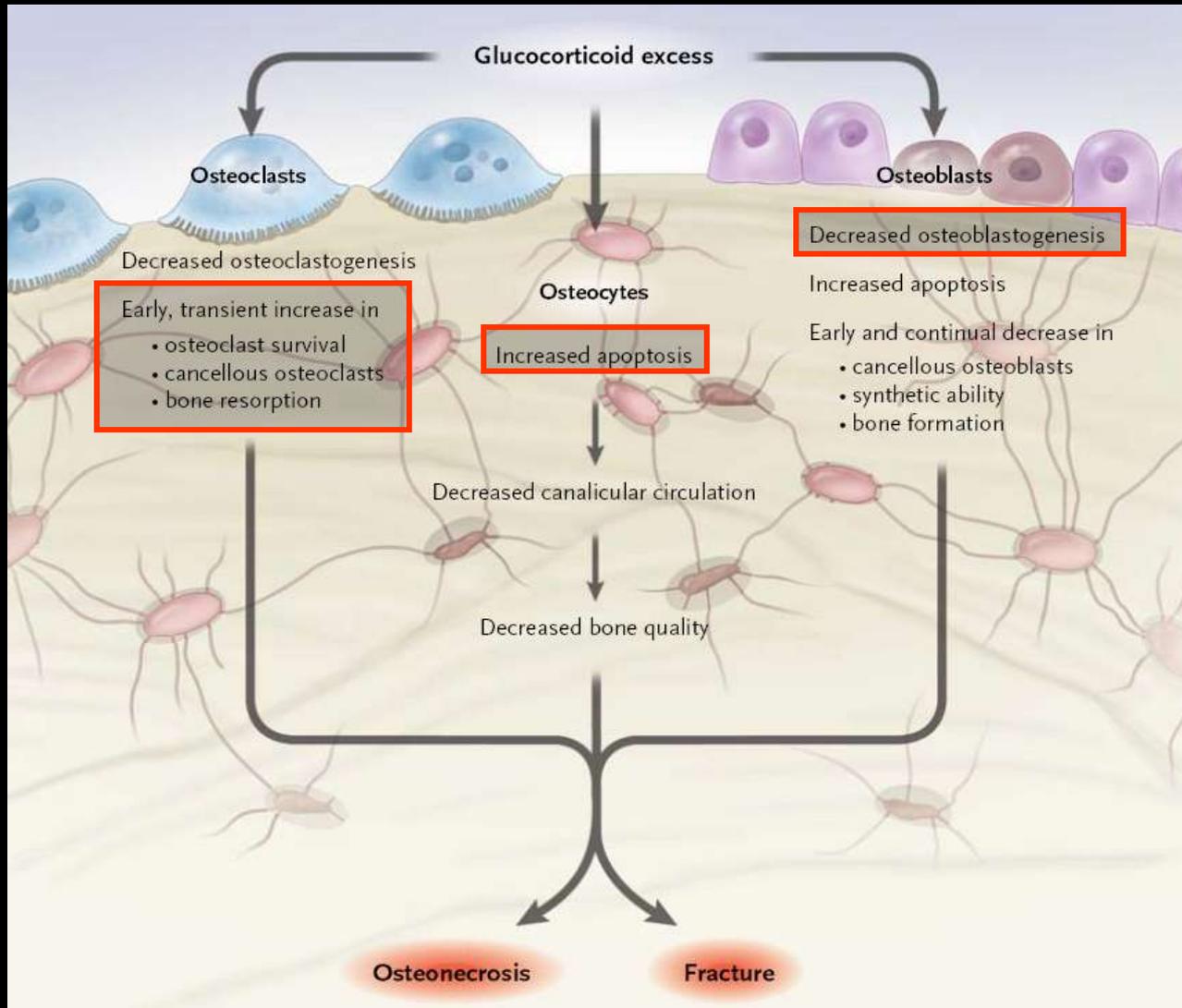
Fracture incidence before, during and after Glucocorticoid treatment

Van Staa TP et al. *JBMR* 2000
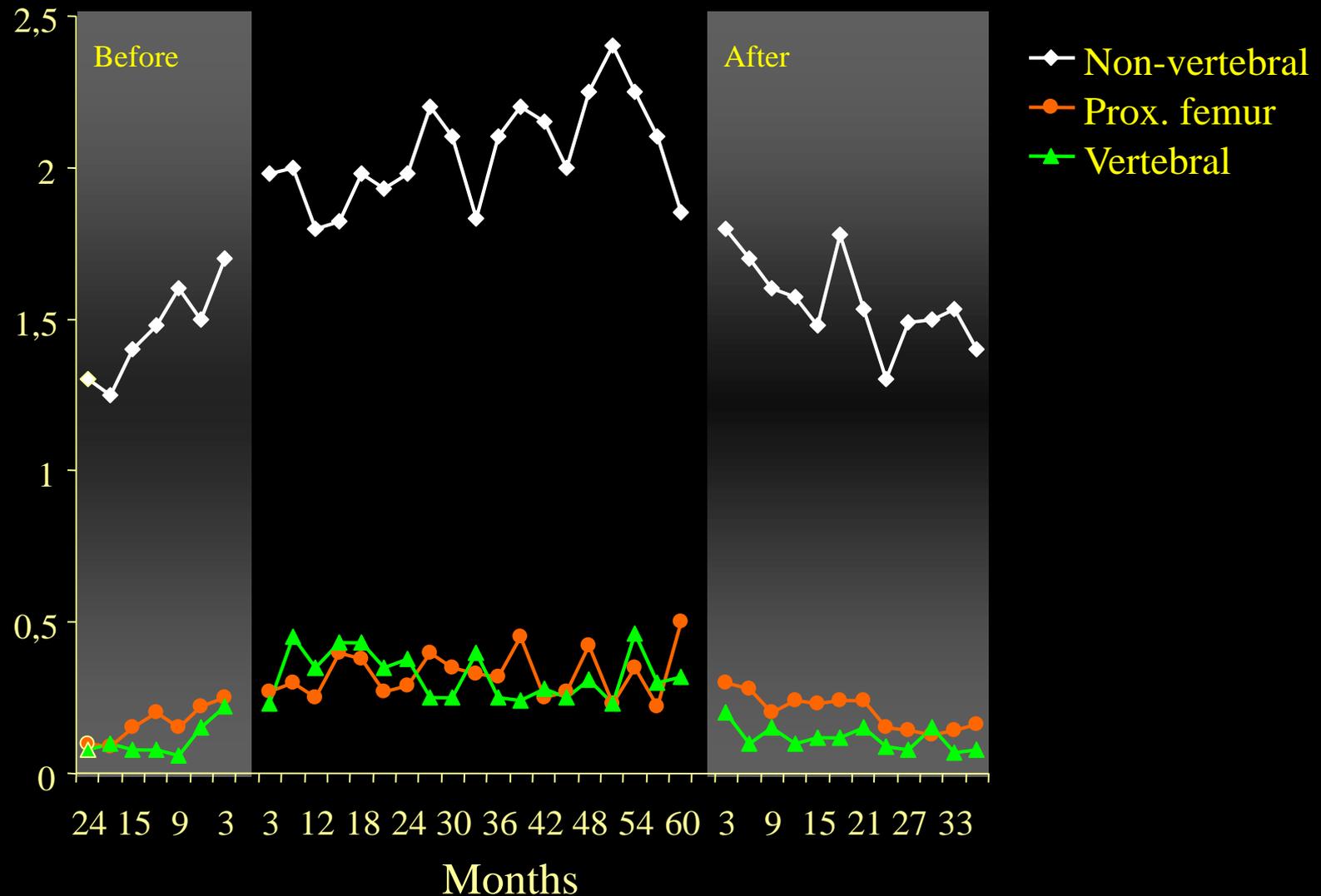
Adjusted * prevalence of asymptomatic vertebral fractures in 551 post-menopausal women treated with GCs
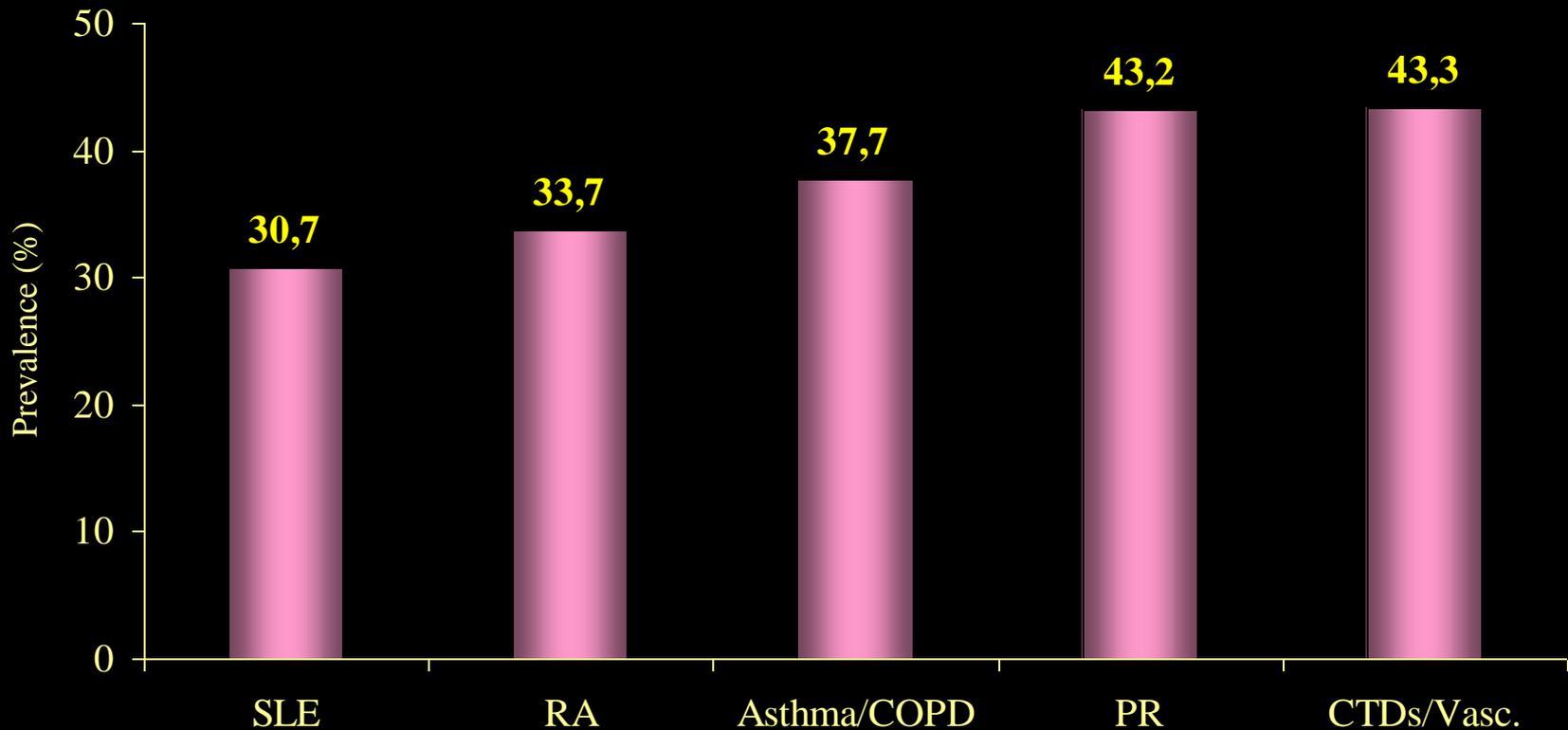
* Adjusted for age, GC cumulative dose,
treatment duration and personal history of fxs

Angeli A et al. *Bone* 2006

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

Prevalence or one or more vertebral fractures

McEvoy et al. *Am J Respir Crit Care Med* 157:704, 1998
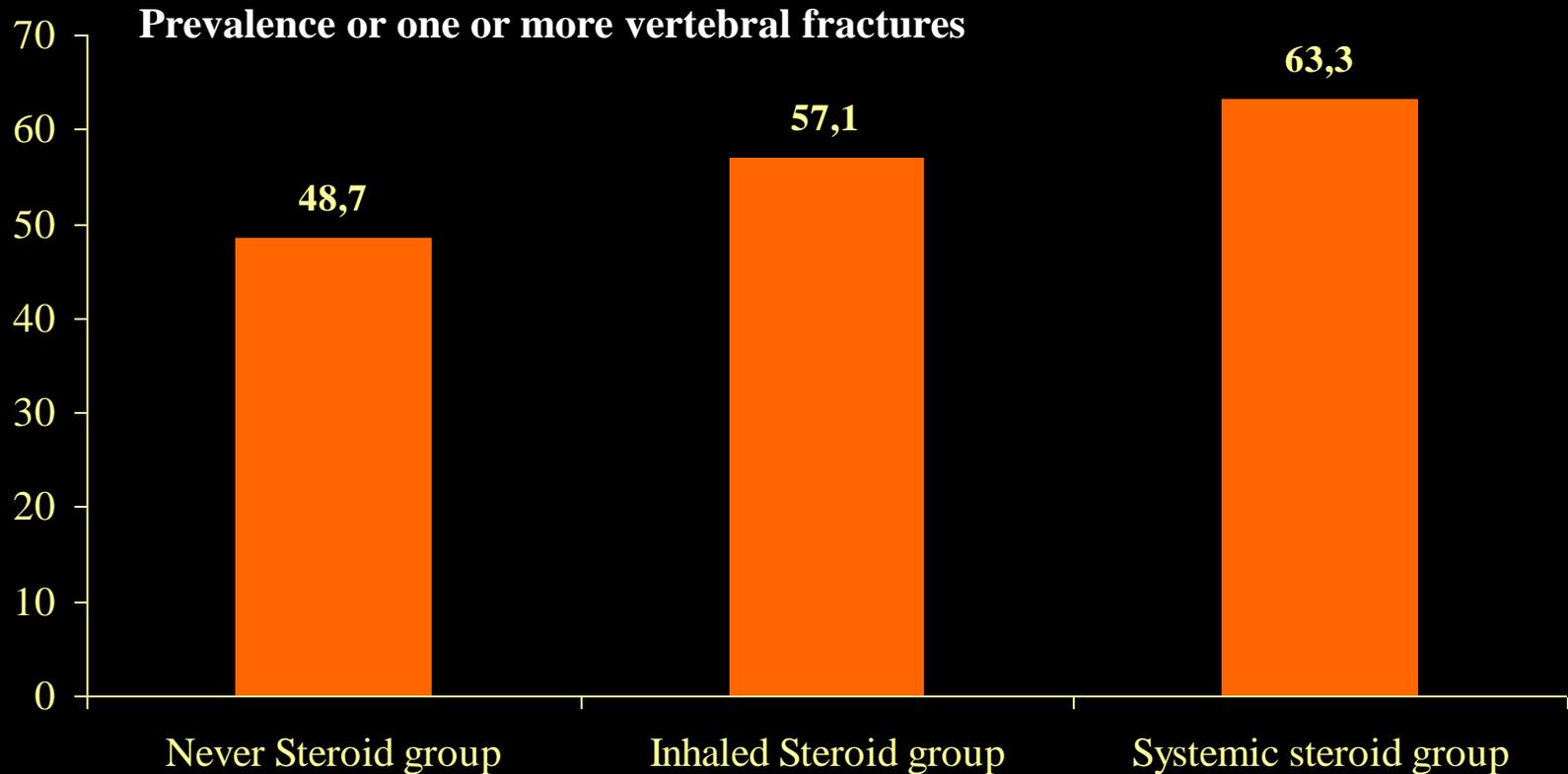
Use of inhaled corticosteroids and risk of fractures : a retrospective cohort study on 170,818 inhaled steroid users

	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**

Van Staa TP et al. *JBMR* 16:581 2001

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
Non Vertebral	1.11 (1.03-1.20)	1.16 (1.07-1.26)	1.28 (1.15-1.42)
Hip	0.95 (0.67-1.34)	1.06 (0.80-1.40)	1.77 (1.31-2.40)
Vertebral	1.31 (0.89-1.92)	1.39 (0.95-2.04)	2.50 (1.63-3.83)
	< 300 μg per day	*300-700 μg per day*	*< 700 μg per day*

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

Study or Subgroup	ICS Events	ICS Total	No ICS Events	No ICS Total	Weight	Peto OR Peto, Fixed, 95% CI
4.2.1 ICS-LABA vs LABA						
Anzueto SCO100250 2009	3	394	0	403	1.0%	7.60 (0.79 to 73.27)
Calverley SCO30003 2007	78	1546	61	1542	43.0%	1.29 (0.92 to 1.81)
Calverley SFCB3024 2003	3	358	0	372	1.0%	7.73 (0.80 to 74.55)
Ferguson SCO40043 2008	3	394	3	388	1.9%	0.98 (0.20 to 4.90)
Hanania SFCA3007 2003	1	178	0	177	0.3%	7.35 (0.15 to 370.30)
Kardos SCO30006 2007	1	507	1	487	0.6%	0.96 (0.06 to 15.39)
Mahler SFCA3006 2002	0	165	0	160		Not estimable
SCO100470 2006	1	518	0	532	0.3%	7.59 (0.15 to 382.72)
SCO40041 2008	1	92	1	94	0.6%	1.02 (0.06 to 16.46)
Tashkin 2008	1	845	1	284	0.5%	0.27 (0.01 to 6.52)
Wouters SCO40002 2005	5	189	5	184	3.2%	0.97 (0.28 to 3.41)
Subtotal (95% CI)		5186		4623	52.5%	1.34 (0.99 to 1.82)
Total events	97		72			

Heterogeneity: $\chi^2=7.54$, df=9 (p=0.58); $I^2=0\%$
Test for overall effect: Z=1.86 (p=0.06)

4.2.2 ICS alone vs Placebo						
Burge FLTB3054 2000	4	376	7	375	3.5%	0.57 (0.17 to 1.89)
Calverley SCO30003 2007	65	1552	57	1544	38.0%	1.14 (0.79 to 1.64)
Calverley SFCB3024 2003	2	374	1	361	1.0%	1.88 (0.20 to 18.17)
FLTA3025 2005	3	434	0	206	0.8%	4.39 (0.39 to 49.66)
Hanania SFCA3007 2003	0	183	1	185	0.3%	0.14 (0.00 to 6.90)
Johnell 2002	5	322	3	331	2.6%	1.70 (0.42 to 6.87)
Mahler SFCA3006 2002	1	168	0	181	0.3%	7.98 (0.16 to 403.44)
Paggiaro FLIT97 1998	1	142	0	139	0.3%	7.23 (0.14 to 364.68)
SFCT01 2005	1	131	0	125	0.3%	7.06 (0.14 to 356.10)
Tashkin 2008	1	275	0	300	0.3%	8.09 (0.16 to 409.34)
Subtotal (95% CI)		3957		3747	47.5%	1.19 (0.86 to 1.64)
Total events	83		69			

Heterogeneity: $\chi^2=7.62$, df=9 (p=0.57); $I^2=0\%$
Test for overall effect: Z=1.05 (p=0.29)

Total (95% CI)		9143		8370	100.0%	1.27 (1.01 to 1.58)
Total events	180		141			

Heterogeneity: $\chi^2=15.43$, df=19 (p=0.69); $I^2=0\%$
Test for overall effect: Z=2.07 (p=0.04)
Test for subgroup differences: $\chi^2=0.28$, df=1 (p=0.60), $I^2=0\%$

0.05 0.2 1 5 20
ICS safe   ICS harmful

Loke YK et al *Thorax* 2011

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

Loke YK et al *Thorax* 2011
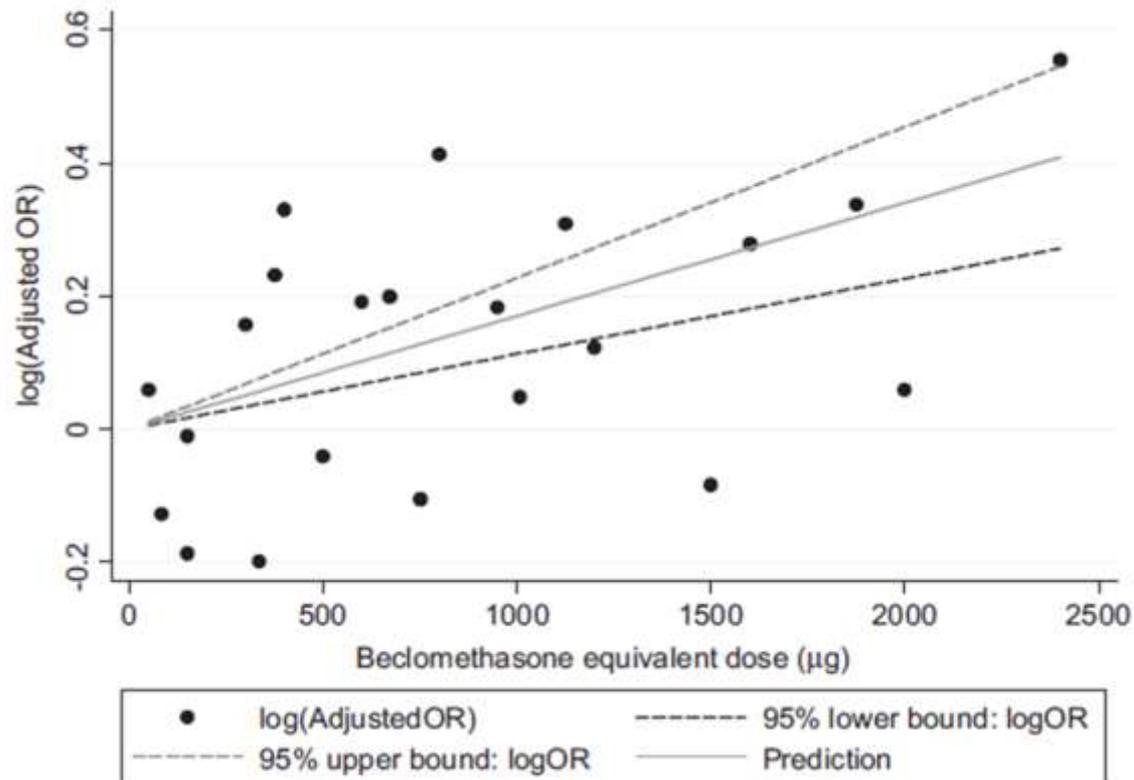
Effects of Asthma on bone

- 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

Osteoporosis in Lung Transplantation Candidates: Association With 6-minute Walking Test and Body Mass Index

M.K. Balci[a,*], E. Ari[b], M. Vayvada[a], C. Salturk[c], E. Asicioglu[d], A. Yeginsu[a], and C.A. Kutlu[a]

	COPD (n = 36)	DPLD (n = 55)	Bronchiectasis (n = 43)	Cystic Fibrosis (n = 8)	Silicosis (n = 18)	Others (n = 14)
Age (mean ± SD)	53 ± 10	49 ± 11	34 ± 11	25 ± 11	37 ± 9	41 ± 17
Gender, female, n (%)	5 (13.5)	30 (55.6)	21 (46.7)	4 (50)	1 (5.6)	7 (50)
Ex-smoker, n (%)	33 (89.2)	18 (33.3)	4 (8.9)	2 (25)	14 (78.8)	6 (43.9)
Nonsmoker	4 (10.8)	36 (66.7)	41 (91.1)	6 (75.0)	4 (22.2)	8 (57.1)
$PaCO_2$, mean ± SD	49 ± 14	43 ± 10	49 ± 10	53 ± 13	44 ± 11	37 ± 11
PaO_2/FiO_2, median (25%–75%)	93 (60–175)	76 (55–113)	72 (62–143)	73 (57–79)	74 (70–97)	80 (60–138)
BMI, mean ± SD	24 ± 4	24 ± 5	21 ± 5	17 ± 2	21 ± 4	24 ± 4
6MWD (m), median (25%–75%)	162 (140–270)	210 (150–340)	263 (150–370)	246 (110–296)	210 (152–296)	181 (90–351)
BMD, n (%)						
Osteoporosis	19 (52.8)	21 (38.9)	21 (48.8)	7 (87.5)	7 (38.9)	5 (35.7)
Osteopenia	11 (30.6)	20 (37)	19 (44.2)	1 (12.5)	6 (33.3)	3 (21.4)
Normal	6 (16.7)	14 (25.9)	3 (7)	0	5 (27.8)	6 (42.9)
PAP, median (25%–75%)	42 (33–55)	40 (25–55)	35 (30–60)	38 (35–55)	45 (25–60)	65 (54–90)
Disease duration (y), median (25%–75%)	7 (4–10)	4 (2–6)	20 (10–25)	20 (14–23)	5 (3–5)	4 (2–6)
NIMV treatment, n (%)	13 (27.1)	9 (18.8)	18 (37.5)	4 (8.3)	3 (6.2)	1 (2.1)

NUOVA NOTA 79

GAZZETTA UFFICIALE
DELLA REPUBBLICA ITALIANA

20/05/2015

Prevenzione primaria

Femmine in postmenopausa e maschi di età ≥ 50 anni

- Trattamento in corso di blocco ormonale adiuvante in F con CA mammella e M con CA Prostatico

- **T score ≤ -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 ≤ -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

Lidwien Graat-Verboom [a,b,*], Martijn A. Spruit [c], Ben E.E.M. van den Borne [b], Frank W.J.M. Smeenk [b], Elisabeth J. Martens [d,e], Ragnar Lunde [c,f], Emiel F.M. Wouters [a,c], On behalf of the CIRO Network [g]
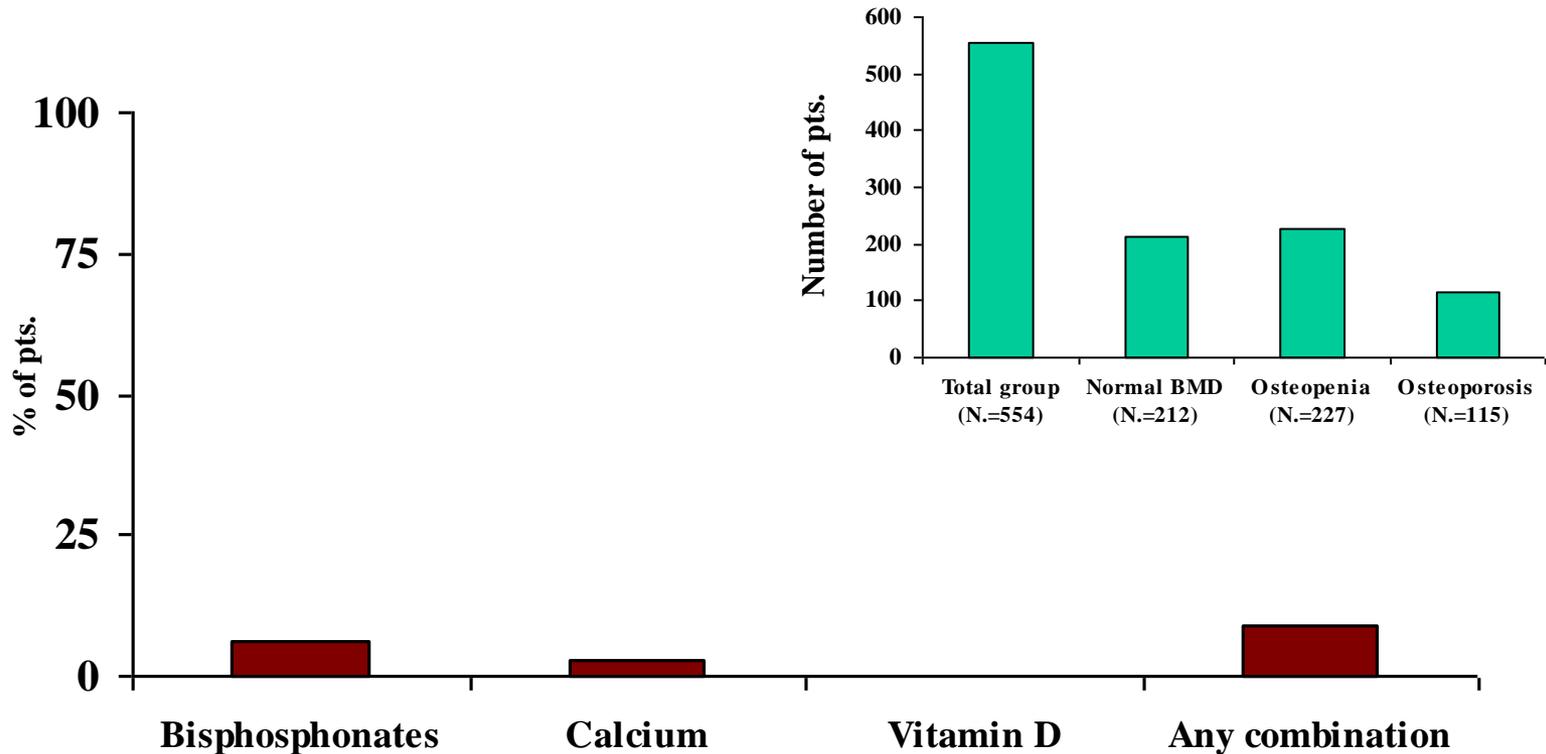
The golden rules for Osteoporosis treatment

- Correct or prevent vitamin D insufficiency ($\geq$800 IU/day)
- Ensure dietary calcium intake ~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 estabilished vertebral and non vertebral fracture efficacy reduce mortality

Study	Treatment n/N	Control n/N	Relative Risk [95% Confidence Interval]	Weight (%)
Alendronate				
Black 1996	24/1022	21/1005	1.12 [0.63, 2.01]	3
Cummings 1998	37/2214	40/2218	0.93 [0.59, 1.44]	5
Total	61/3236	61/3223	1.00 [0.70, 1.41]	P=0.98
Risedronate				
Harris 1999	15/813	16/815	0.94 [0.47, 1.89]	2
Reginster 2000	11/407	17/407	0.65 [0.31, 1.36]	2
McClung 2001	114/3162	127/3184	0.90 [0.71, 1.16]	17
Total	140/4382	160/4406	0.88 [0.70, 1.10]	P=0.27
Strontium				
Meunier 2004	29/826	21/814	1.36 [0.78, 2.37]	3
Reginster 2005	142/2526	159/2503	0.88 [0.71, 1.10]	21
Total	171/3352	180/3317	0.94 [0.77, 1.15]	P=0.54
Zoledronic acid				
Black 2007	130/3862	112/3852	1.16 [0.90, 1.48]	15
Lyles 2007	101/1054	141/1057	0.72 [0.56, 0.91]	19
Total	231/4916	253/4909	0.90 [0.76, 1.08]	P=0.26
Denosumab				
Cummings 2008	70/3902	90/3906	0.78 [0.57, 1.06]	12
Total	70/3902	90/3906	0.78 [0.57, 1.06]	P=0.11
Total	673/19788	744/19761	0.90 [0.81, 1.00]	P=0.044

Test for heterogeneity: I² = 23%, P=0.23

0.5 0.7 1 1.4 2
Favors treatment   Favors control