Metabolic disturbance in COPD

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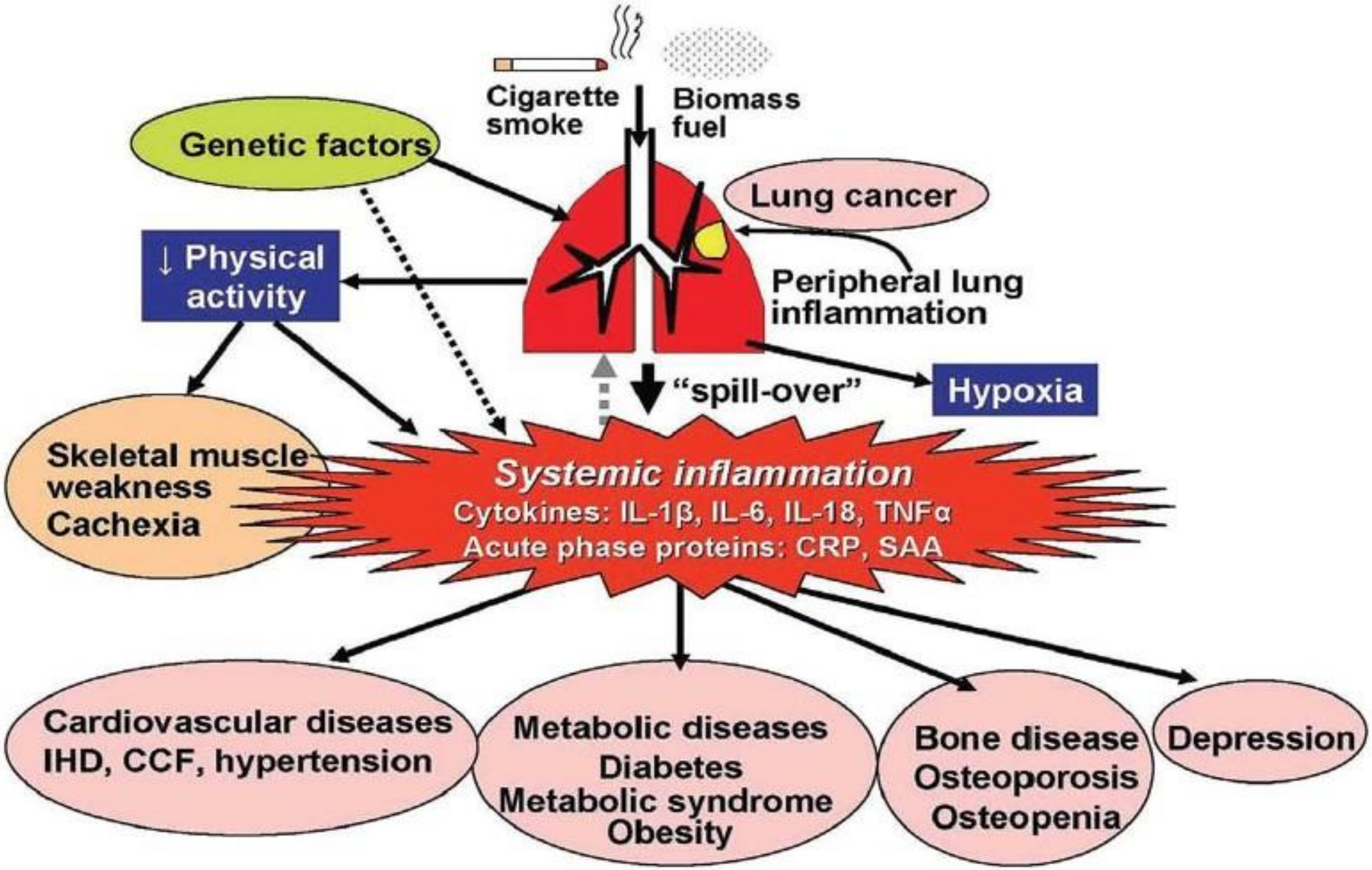
호흡기내과

천식•COPD 센터

이재승

Contents

COPD is systemic disease

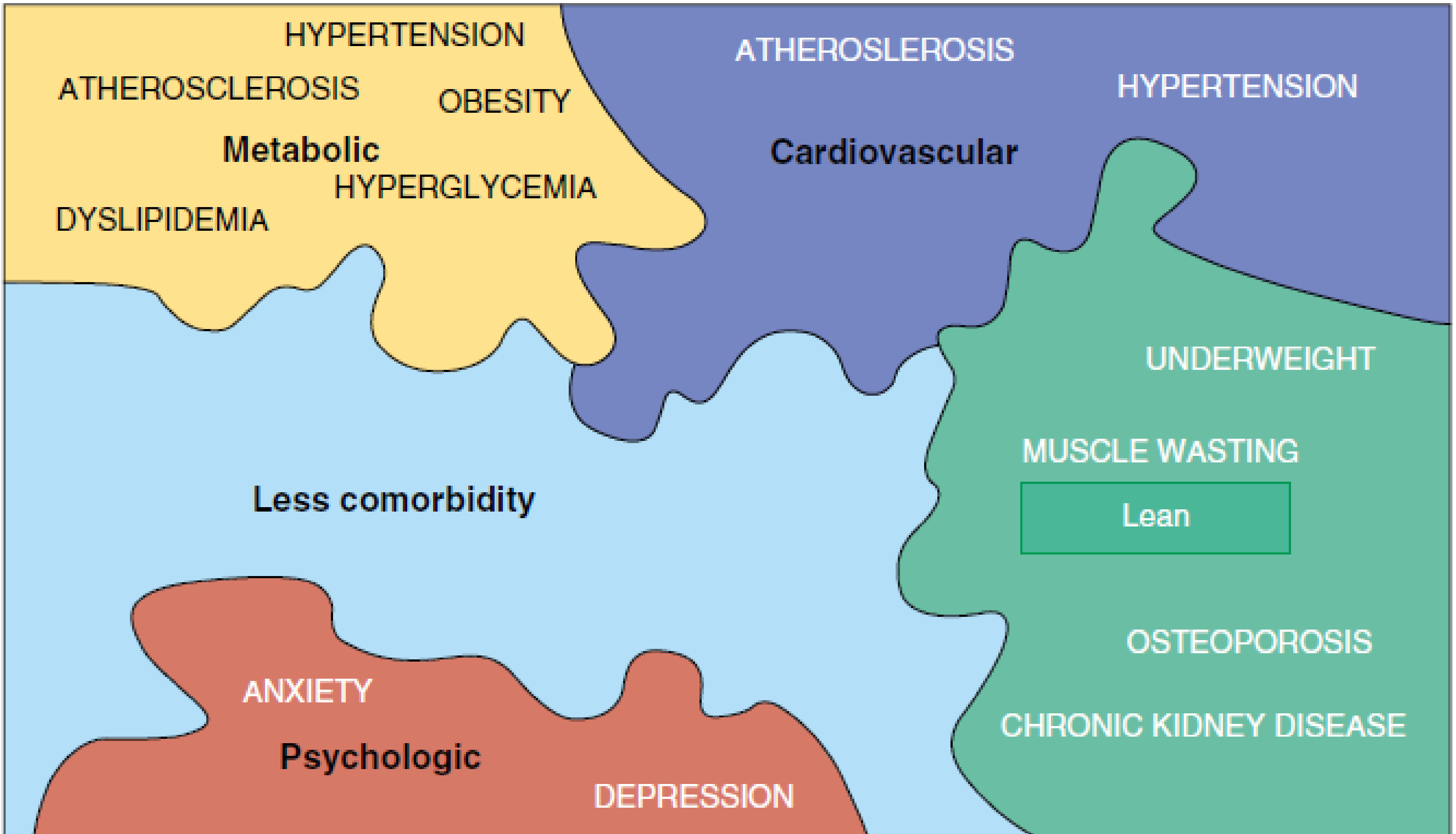


Barnes PJ. Chronic obstructive pulmonary disease. PLoS Med 2010;7e1000220

Pink puffer and blue bloater

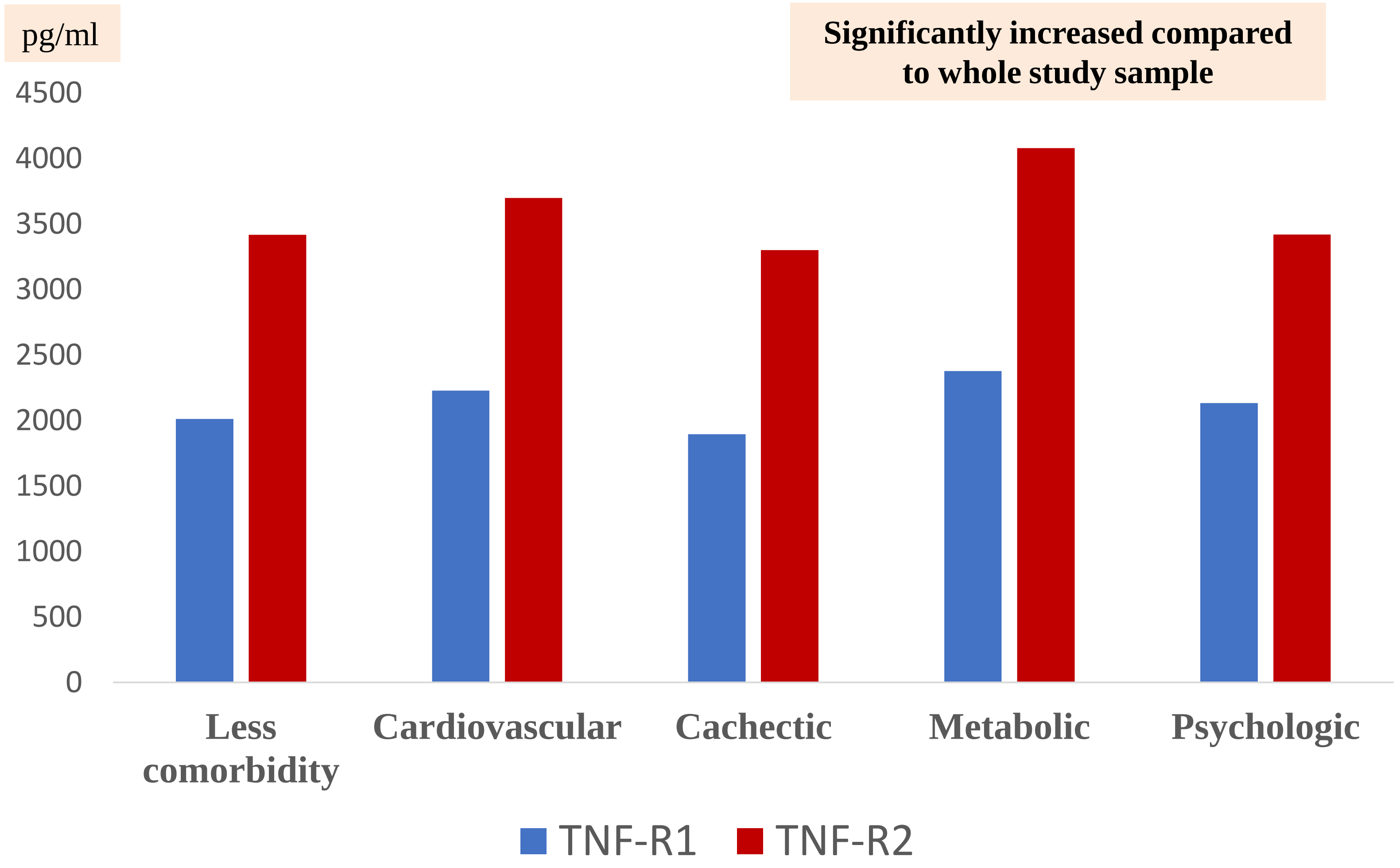
J. G. SCADDING, British Medical Journal 1964;2;1425-1450

Clusters of comorbidity in COPD



Wouters EFM. Ann Am Thorac Soc 2017;14:S389-394

Inflammatory markers among the clusters of comorbidities



Vanfleteren LE, et al. AJRCCM 2013;187(7):728-35.

Metabolic syndrome & COPD in a nationwide survey in Korea

1215 subjects from the 2001 KNHANES

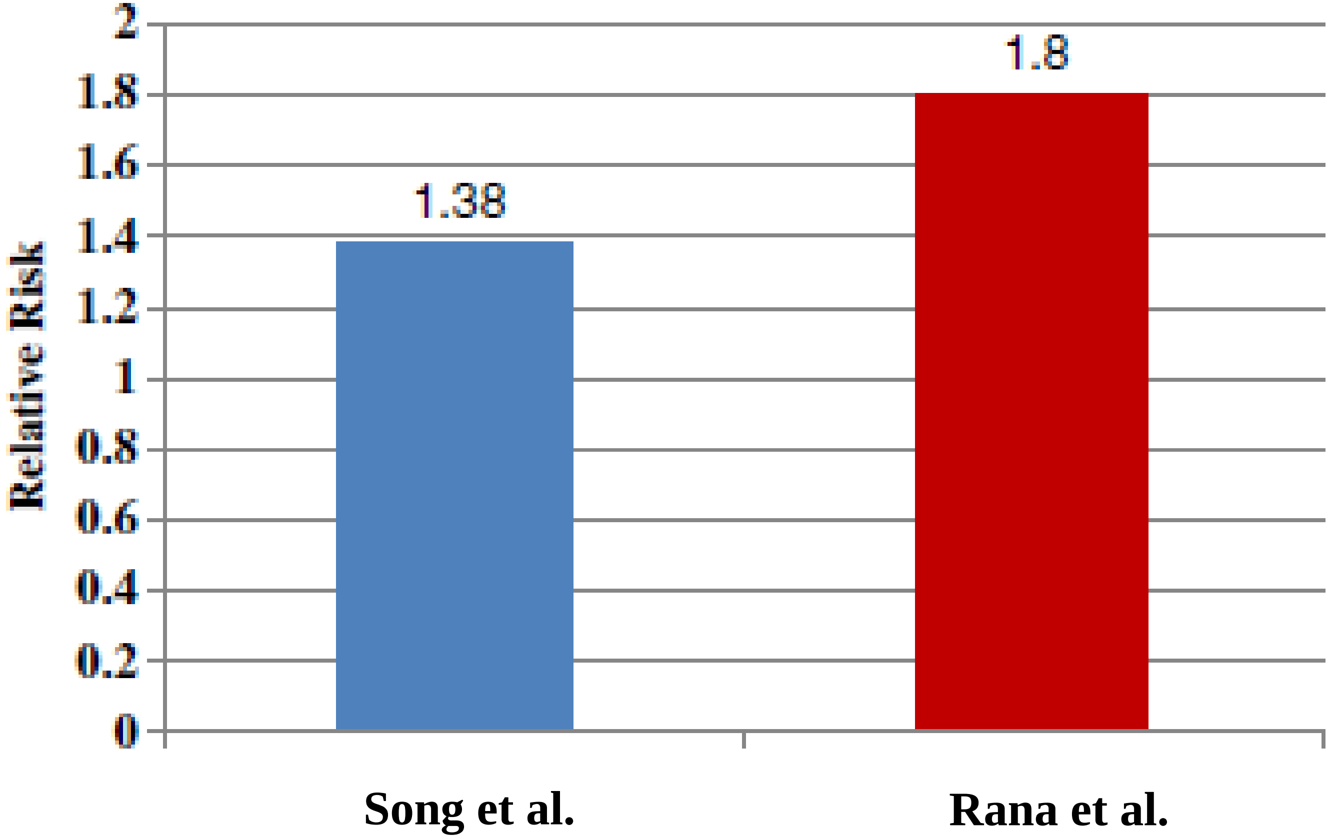
Table 3 Adjusted ORs for chronic obstructive pulmonary disease

	Men		Women	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value
Model 1*				
Metabolic syndrome	1.78 (1.00–3.16)	0.05	1.39 (0.66–2.95)	0.39
Components of metabolic syndrome				
High blood pressure	1.38 (0.81–2.38)	0.24	0.74 (0.32–1.68)	0.47
Abdominal obesity†	1.46 (0.81–2.63)	0.21	1.14 (0.54–2.40)	0.74
High triglyceride‡	1.35 (0.80–2.27)	0.26	1.30 (0.62–2.73)	0.48
Low HDL cholesterol§	1.06 (0.62–1.83)	0.83	0.98 (0.46–2.11)	0.96
High fasting blood glucose¶	1.19 (0.61–2.30)	0.61	0.96 (0.37–2.49)	0.94
Model 2#				
Metabolic syndrome	2.03 (1.08–3.80)	0.03	1.44 (0.62–3.34)	0.40
Components of metabolic syndrome				
High blood pressure	1.40 (0.81–2.41)	0.23	0.72 (0.31–1.65)	0.43
Abdominal obesity†	1.95 (0.93–4.11)	0.08	1.12 (0.43–2.94)	0.82
High triglyceride‡	1.37 (0.81–2.32)	0.24	1.29 (0.61–2.75)	0.51
Low HDL cholesterol§	1.08 (0.62–1.89)	0.78	0.97 (0.45–2.10)	0.94
High fasting blood glucose¶	1.22 (0.62–2.38)	0.57	0.94 (0.36–2.47)	0.90

*After adjustments for age, alcohol intake (never, former and current drinker), education (≤elementary, middle school, high school and ≥college), household income (<US$1000, US$1000–1499, US$1500–2499 and ≥US$2500) and smoking amount (non-smoker, <10 pack-years, ≥10 and <20 pack-years and ≥20 pack-years) in men and for age, education and household income in women.

Park BH, et al. INT J TUBERC LUNG DIS 16(5):694–700

COPD and risk of type 2 DM

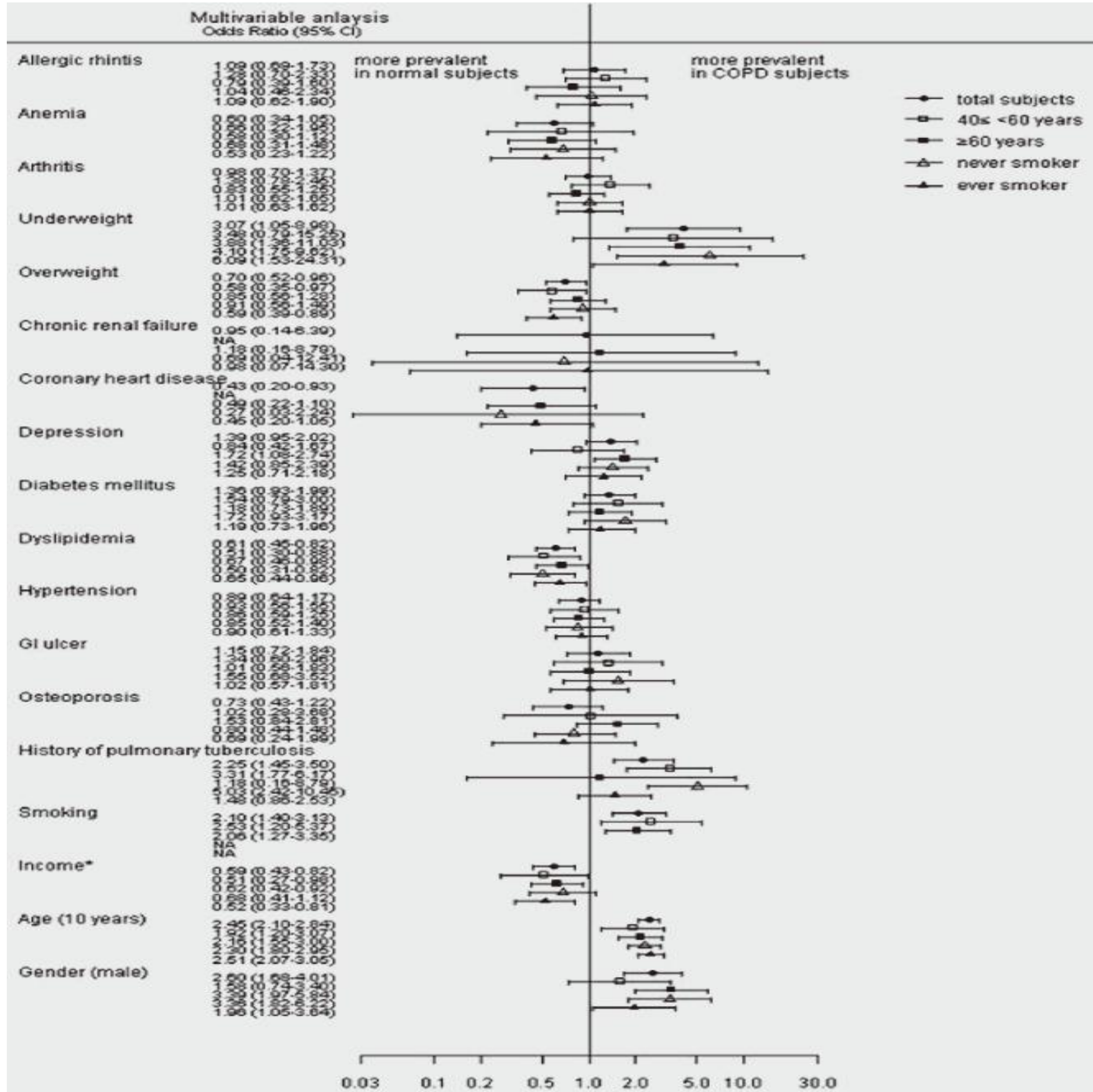


Song Y e tal. Diabetes Res Clin Pract 2010, 90:365–371.

Rana JS, et al. Diabetes Care 2004,27:2478–2484.

Comorbidities of COPD in Koreans

2,177 subjects from the 2008 KNHANES



Underweight
OR 3.07
(95% CI 1.05-8.98)

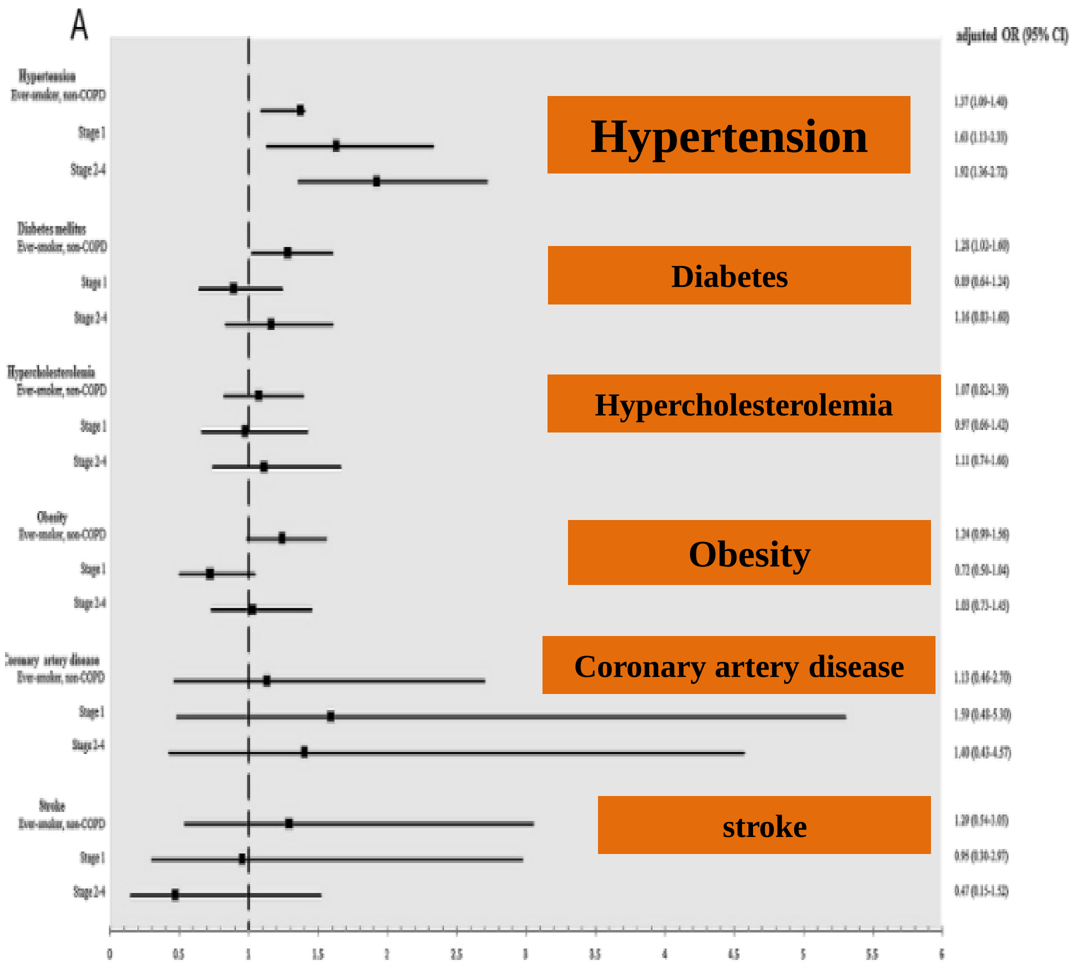
Coronary heart disease
OR 0.43
(95% CI 0.20-0.93)

Dyslipidemia
OR 0.61
(95% CI 0.45-0.82)

Joo H, et al. J Korean Med Sci. 2012;27(8):901-6.

Comorbidities of COPD in Koreans

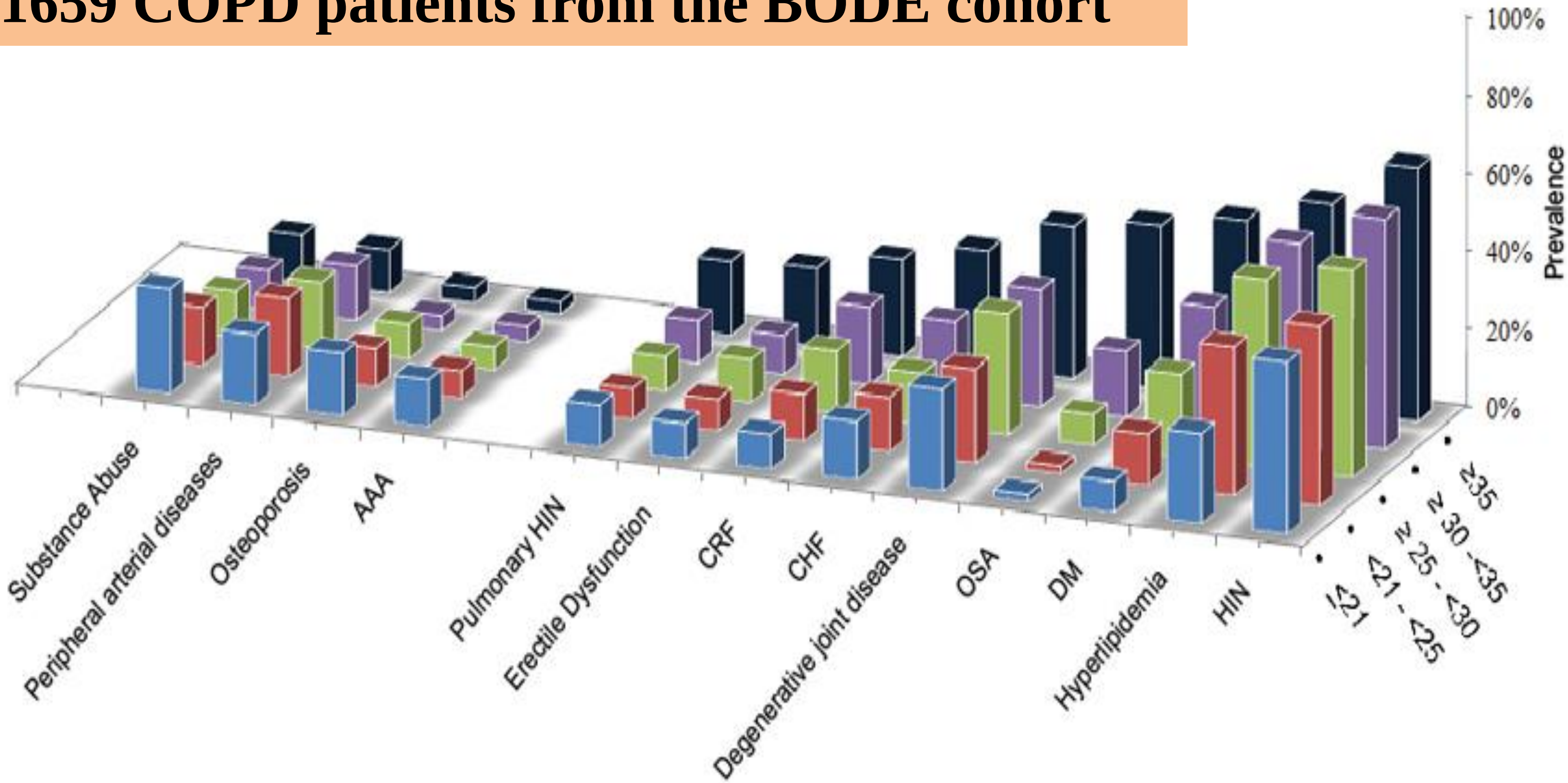
744 COPD and
3313 non-COPD
subjects
from the
KNHANES V
(2010-2012)



Jo YS, et al. Respir Med. 2015 Jan;109(1):96-104.

Comorbidity distribution in COPD patients by BMI

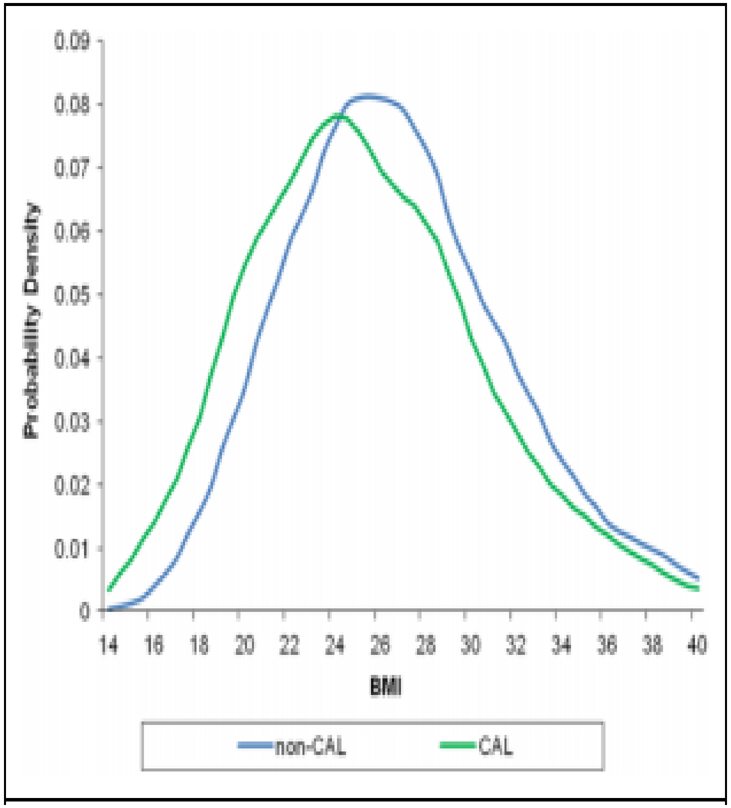
1659 COPD patients from the BODE cohort

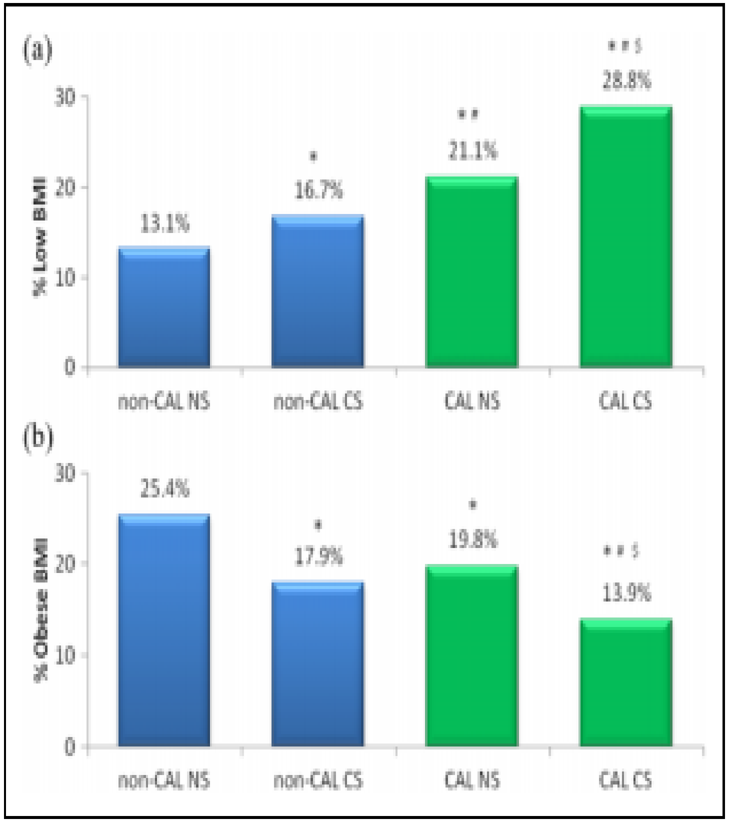


Divo MJ et al. J COPD F. 2014; 1(2): 229-238

BMI in subjects with and without chronic airflow limitation

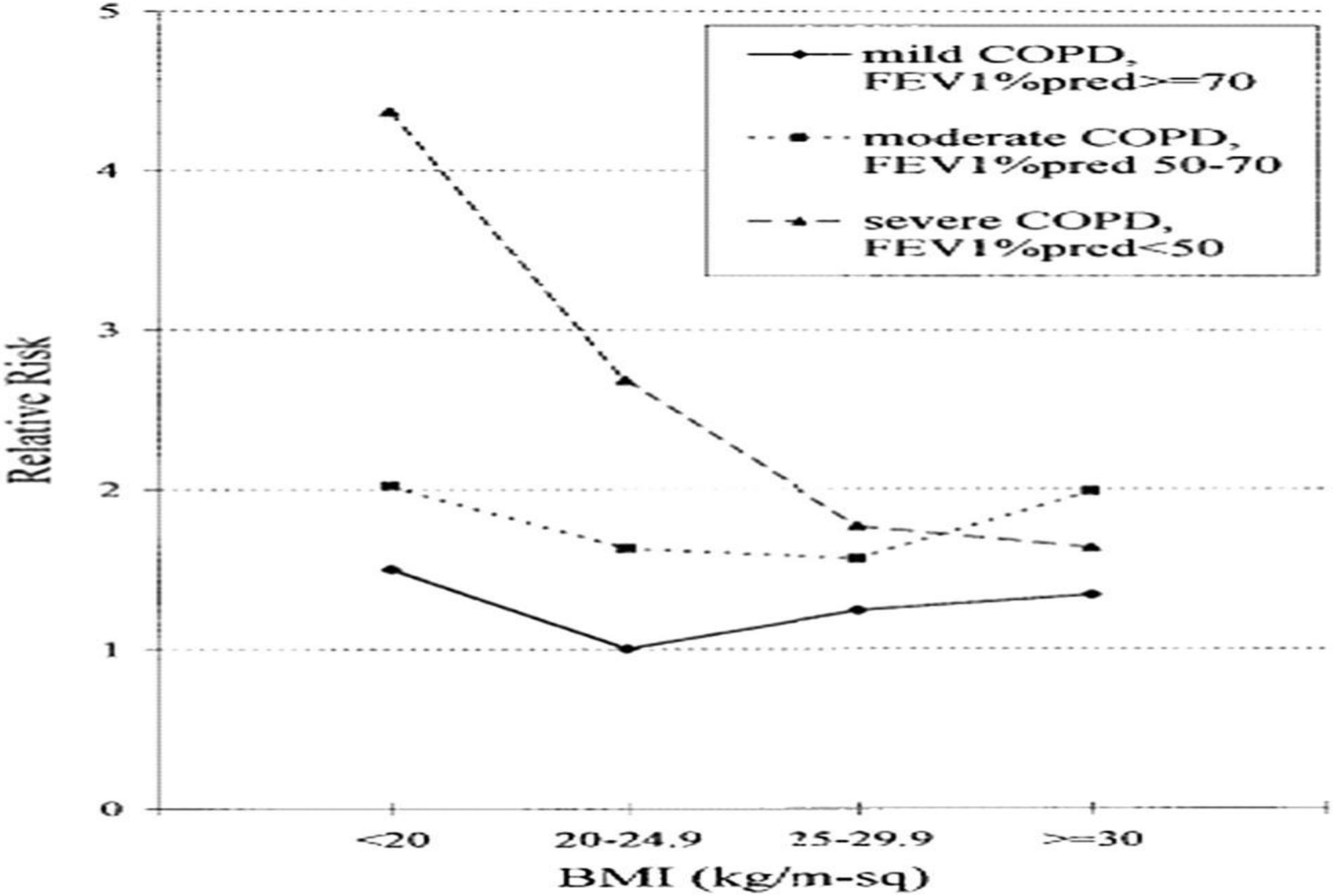
18,606 subjects in the burden of obstructive lung disease (BOLD) initiative





Vanfleteren LE, et al. Chron Respir Dis 2016;13(2):90-101.

All-cause mortality by BMI in patients with COPD



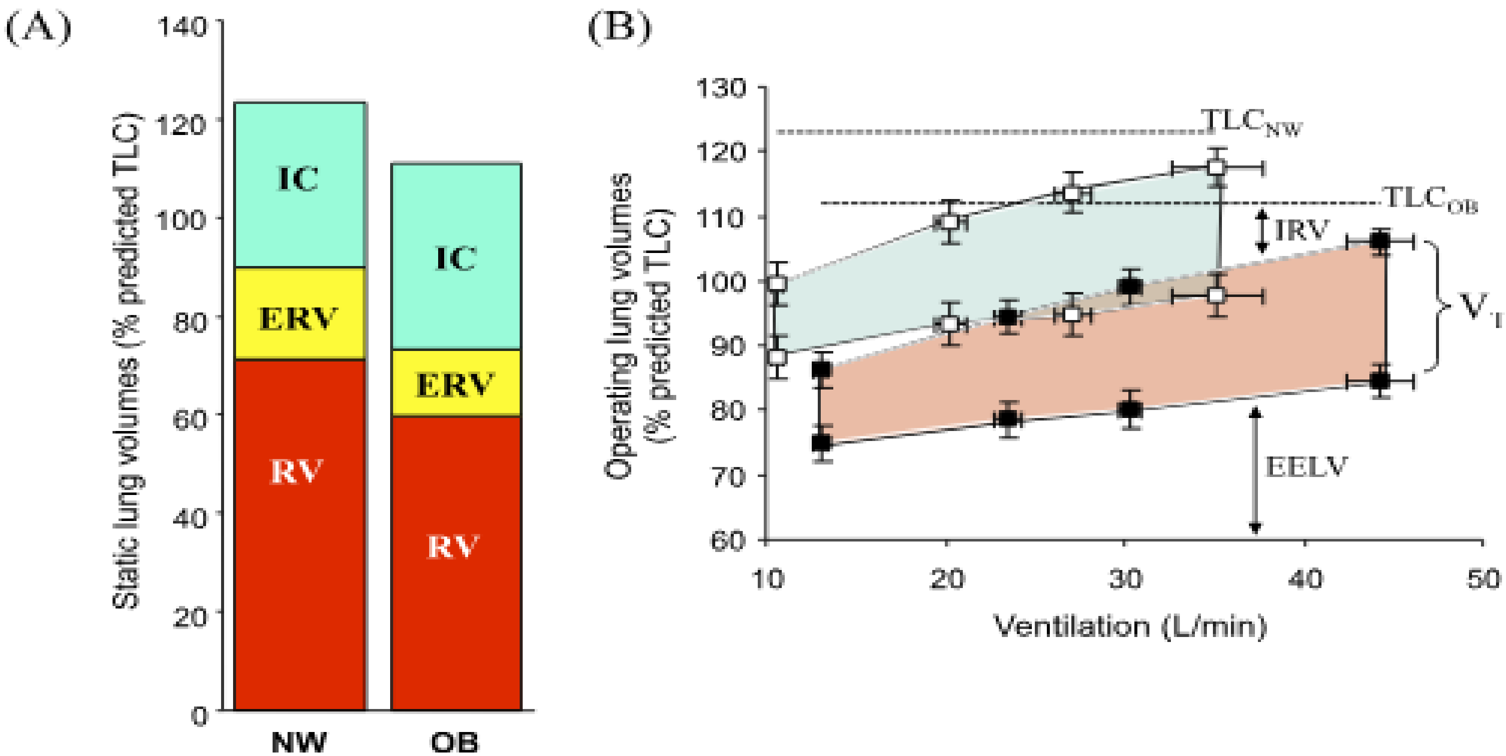
Landbo C, et al. Am J Respir Crit Care Med 160(6):1856–1861

Obesity paradox

- Low FEV_1: restrictive vs obstructive
- **Obesity reduce hyperinflation of lung**
- **Obese COPD patients is related to a low-grade emphysema**
- **BMI vs body composition (Fat-Free Mass; FFM)**
- Other confounders: smoking, cardiorespiratory fitness

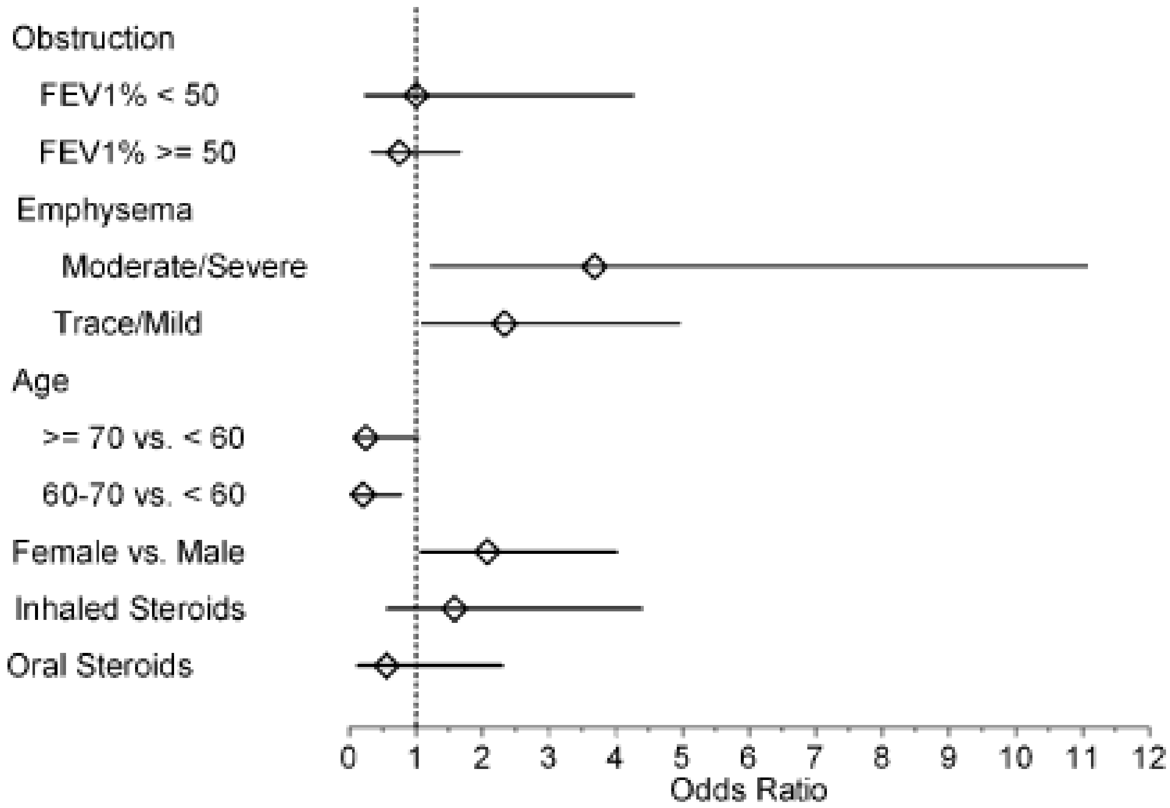
  comorbidity

Obesity and lung volume in patients with COPD



O'Donnell DE, et al. Ann Am Thorac Soc 2014;11:635-644.

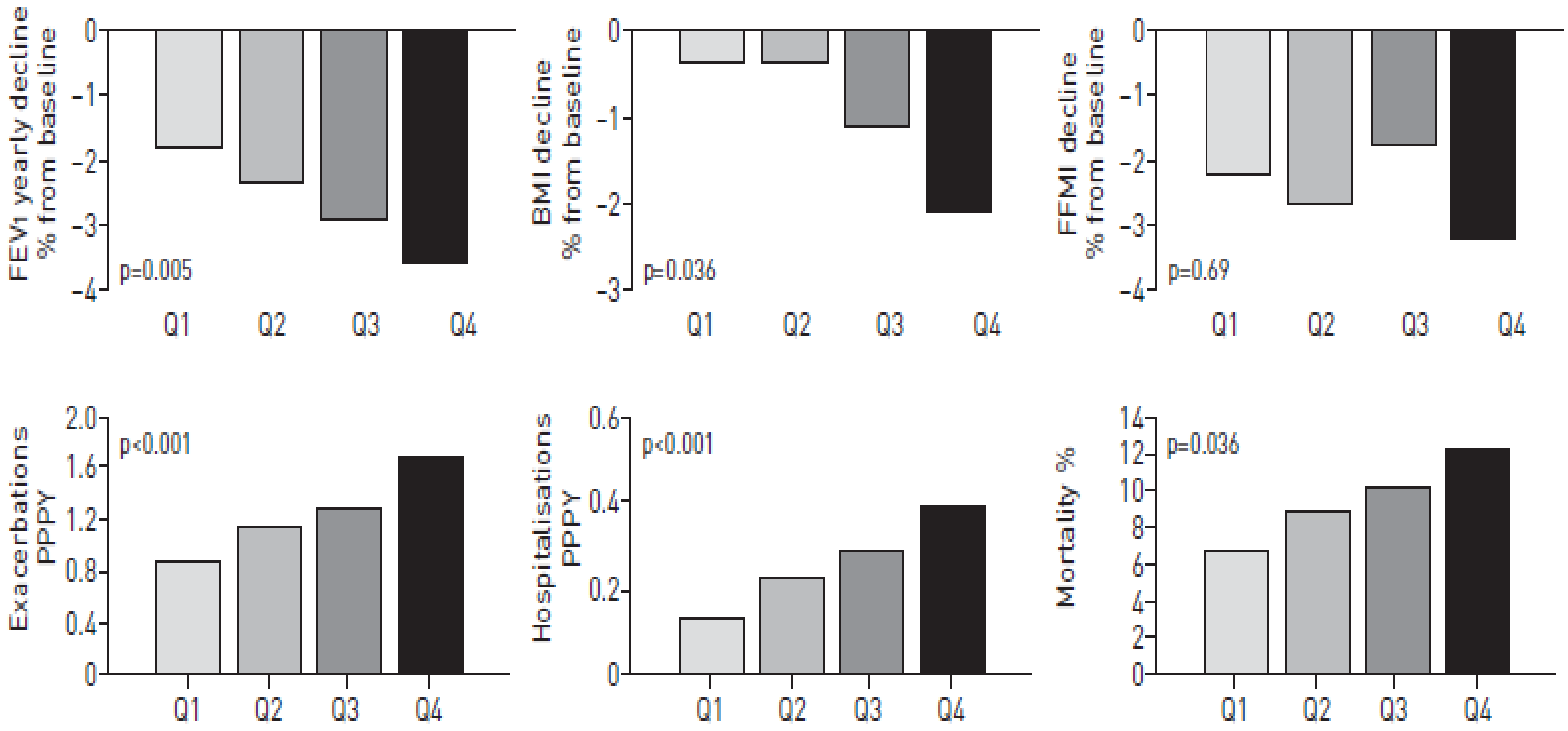
Emphysema predicts low BMI independent of FEV_1



Bon J , et al. Am J Respir Crit Care Med 2011;183:885

Multi-organ loss of tissue (MOLT) COPD phenotype

Longitudinal outcomes in ECLIPSE cohort according to baseline quartiles of CT emphysema



Celli BR, et al. Eur Respir J 2018; 51: 1702146

BMI vs FFMI in COPD

Variables	BMI	FFMI
FFMI	0.04 (0.08)	0.04 (0.08)
FEV_1 %pred	0.005 (0.49)	0.18 (0.001)†
FEV_1/FVC	0.02 (0.12)	0.21 (0.007)†
IC	0.02 (0.15)	0.025 (0.09)
6MWD	0.07 (0.04)†	0.42 (< 0.0001)†
ΔBorg	0.017 (0.07)	0.01 (0.1)
Pao_2	0.005 (0.36)	0.008 (0.4)
$Paco_2$	0.0036 (0.45)	0.008 (0.49)
MRC	0.025 (0.07)	−0.25 (< 0.0001)†
CRQ	0.017 (0.14)	−0.01 (0.18)
Neutrophils	−0.0001 (0.9)	−0.029 (0.09)
LTB_4	−0.02 (0.15)	−0.036 (0.08)

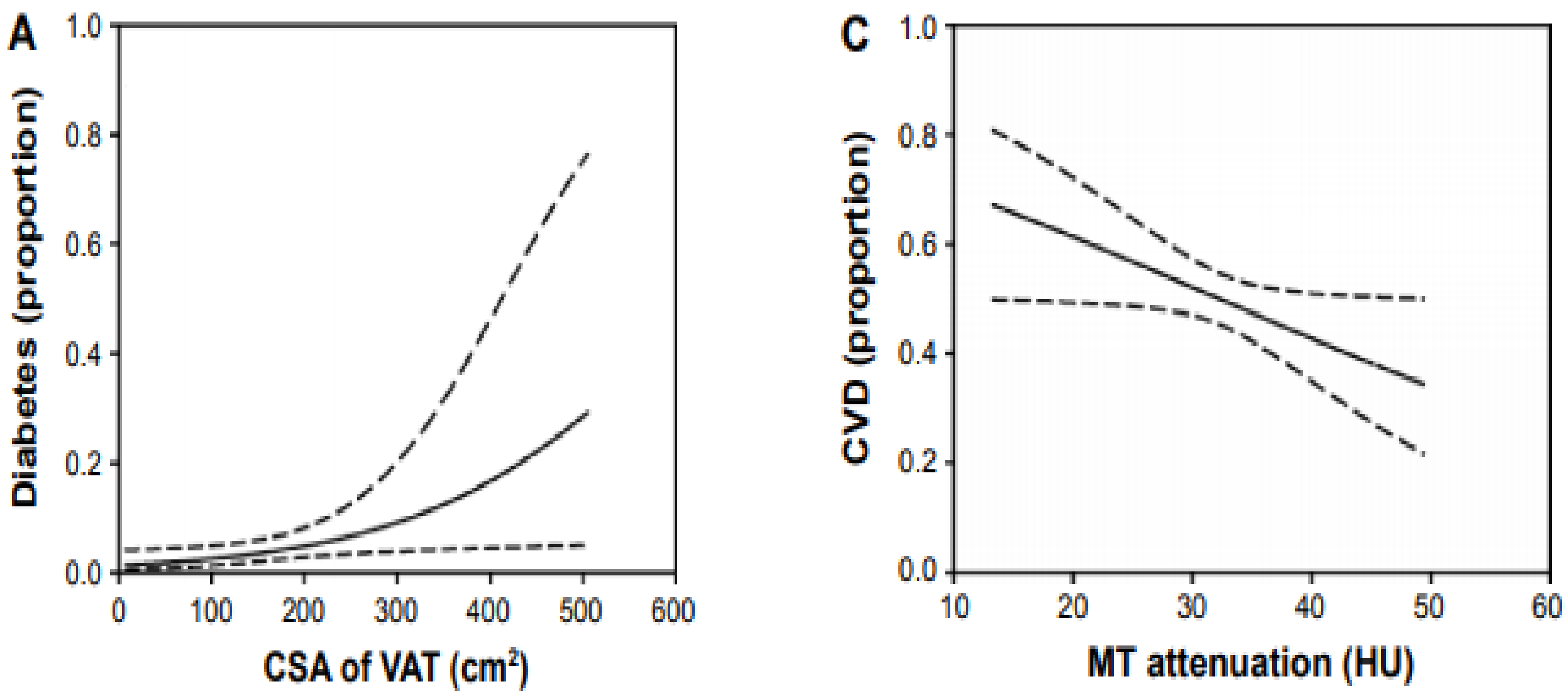
*Data are presented as r^2 (p value).
†Significant correlation.

100 COPD Patients:
GOLD 0-20, GOLD I-20, GOLD II-20, GOLD III-20, GOLD IV-20)

Ischaki E, et, al. CHEST 2007; 132:164-169

Body composition & comorbidities in patients with COPD

From the entire ECLIPSE cohort, we identified 585 subjects with valid CT images at L2–L3 to assess body composition

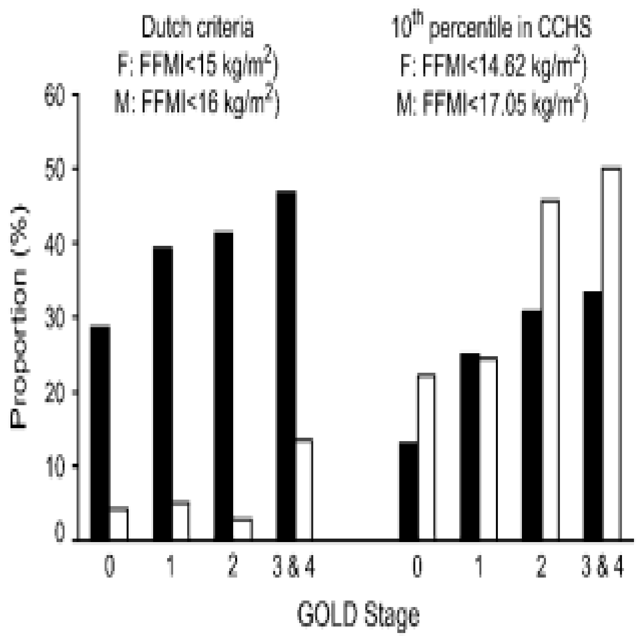


Martin M, et al. International Journal of COPD 2017:12 451–460

BMI vs FFMI in mortality

1,898 patients with COPD from the Copenhagen City Heart Study

Proportion of patients with a low FFMI with normal BMI

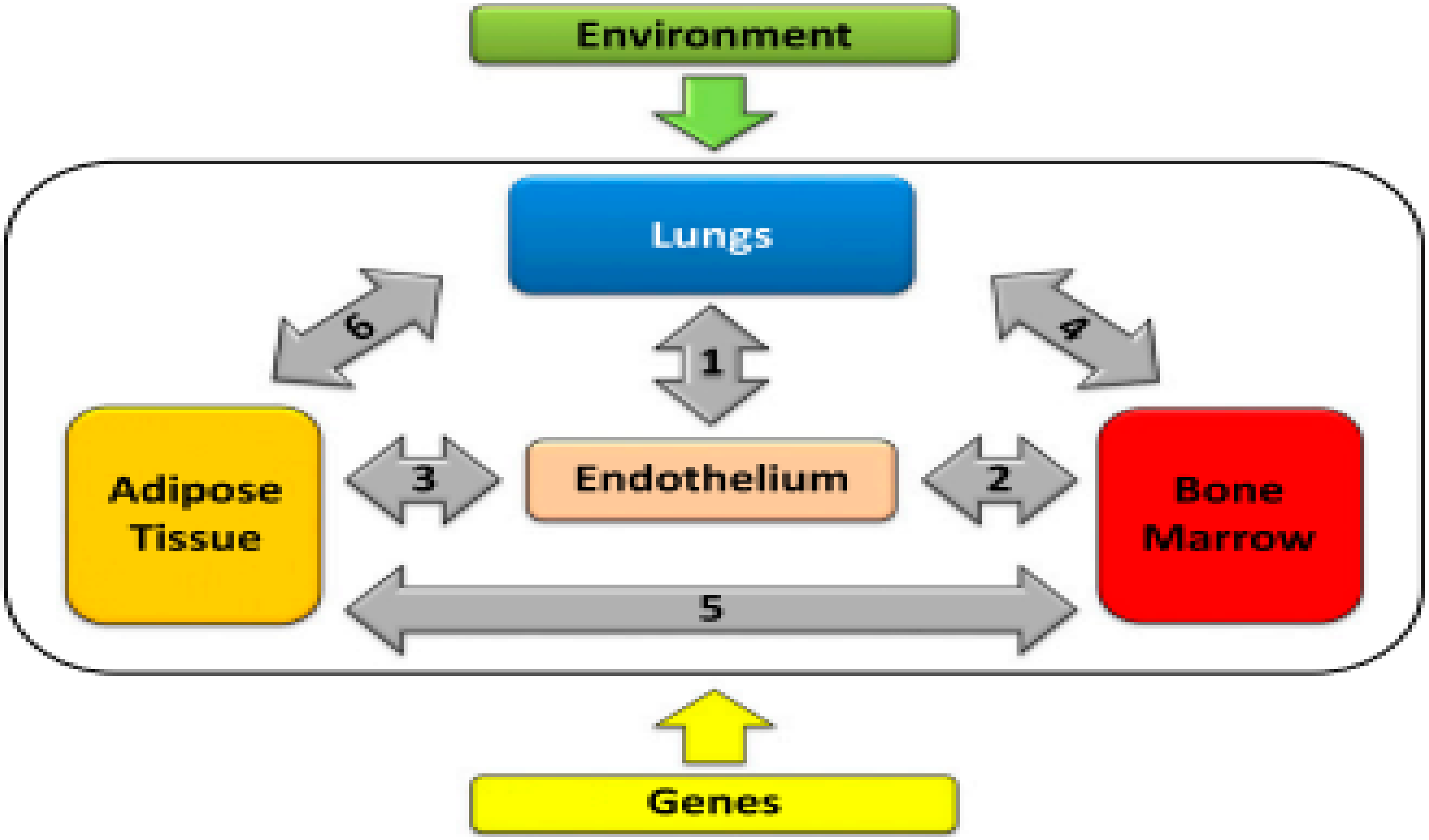


Mortality risk

	Low FFMI[†]	Low BMI[‡]
All subjects with COPD		
Overall mortality	1.5 (1.2–1.8)	1.8 (1.3–2.7)
COPD mortality	2.4 (1.4–4.1)	3.2 (1.5–7.0)
Subjects with normal BMI*		
Overall mortality	1.3 (1.1–1.7)	—
COPD mortality	2.0 (0.9–4.5)	—

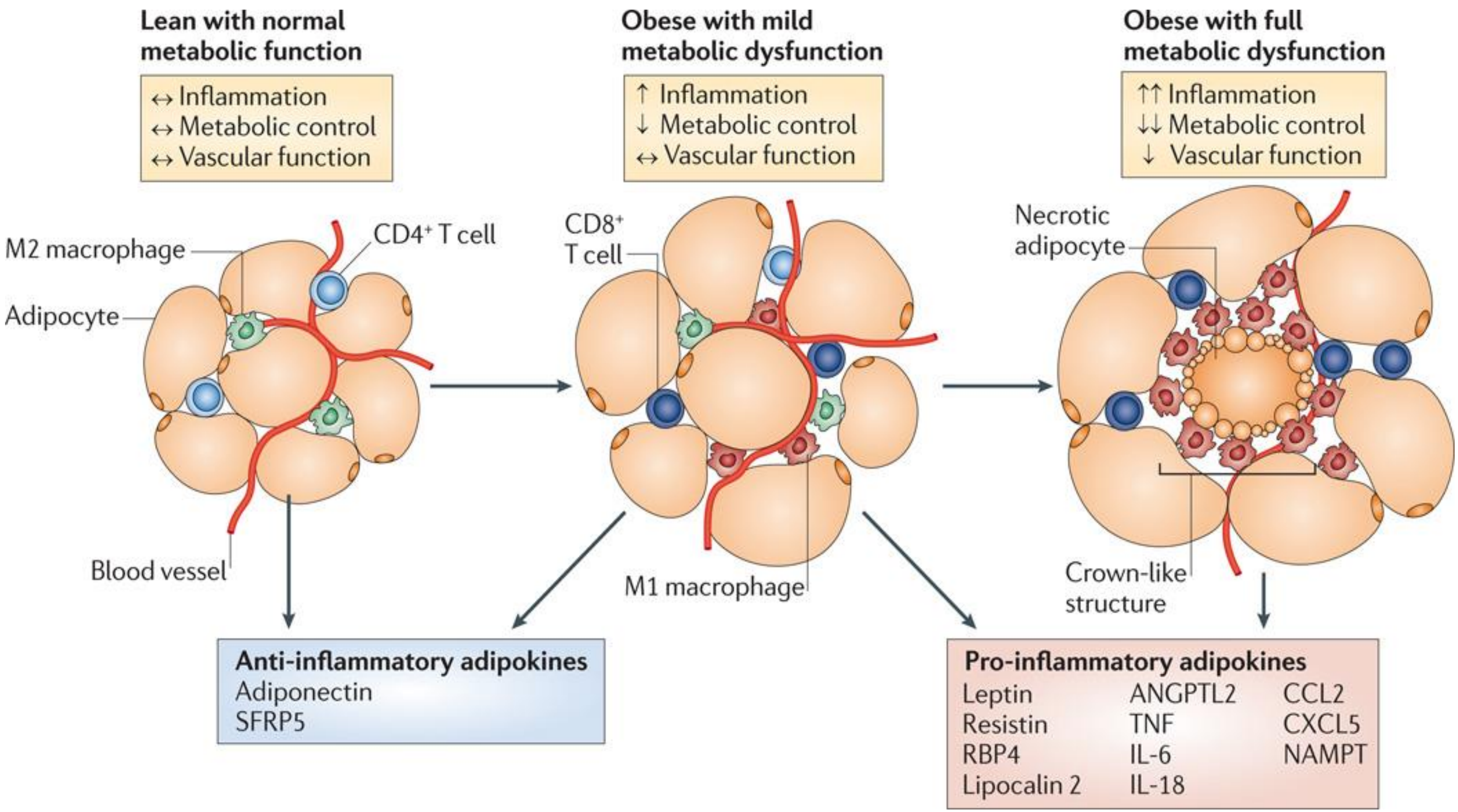
Vestbo J, et al. Am J Respir Crit Care Med. 2006;173(1):79-83.

The lung, bone marrow and adipose tissue network



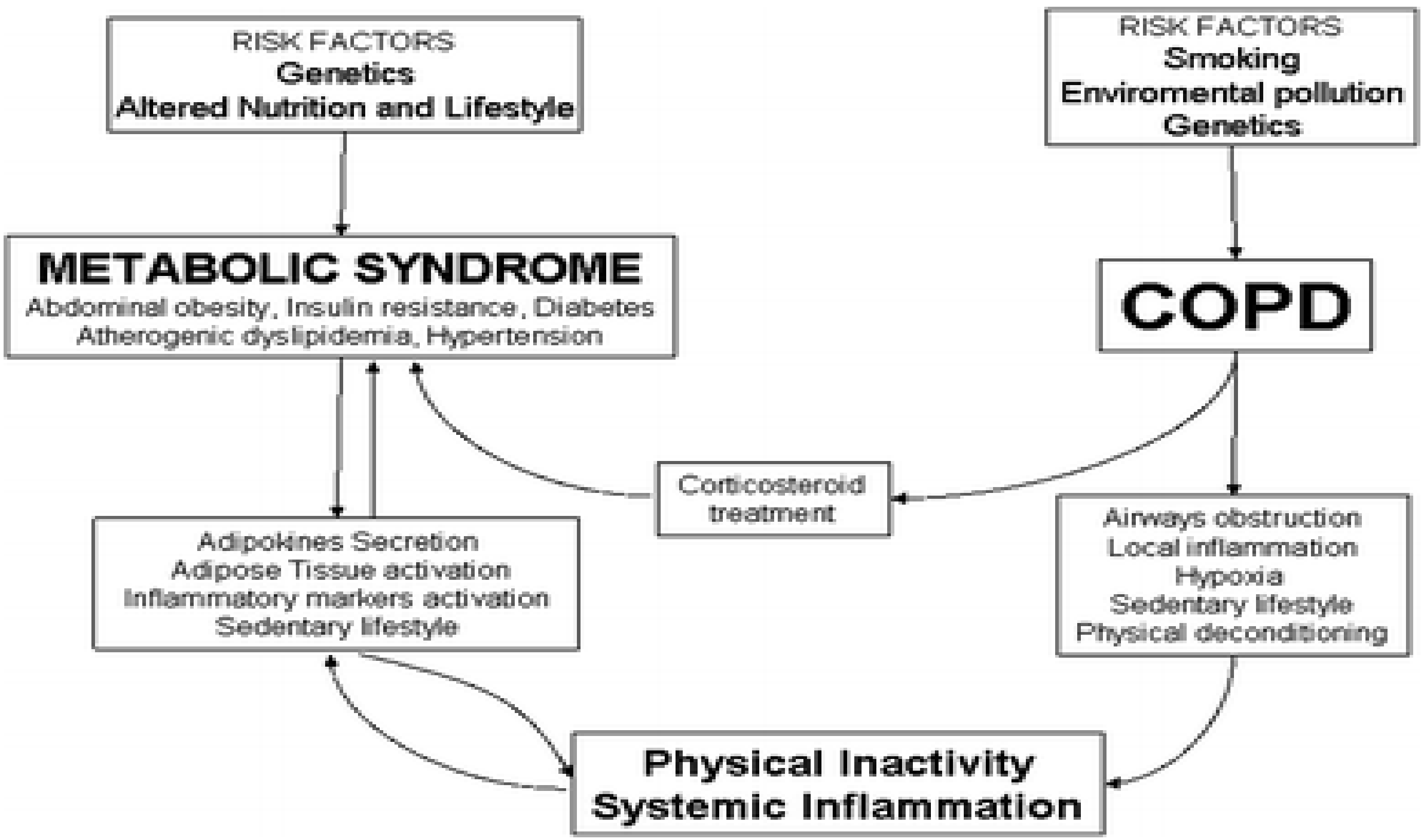
Agusti A, et al. Am J Respir Crit Care Med 2013:188:1396–406

Phenotypic modulation of adipose tissue



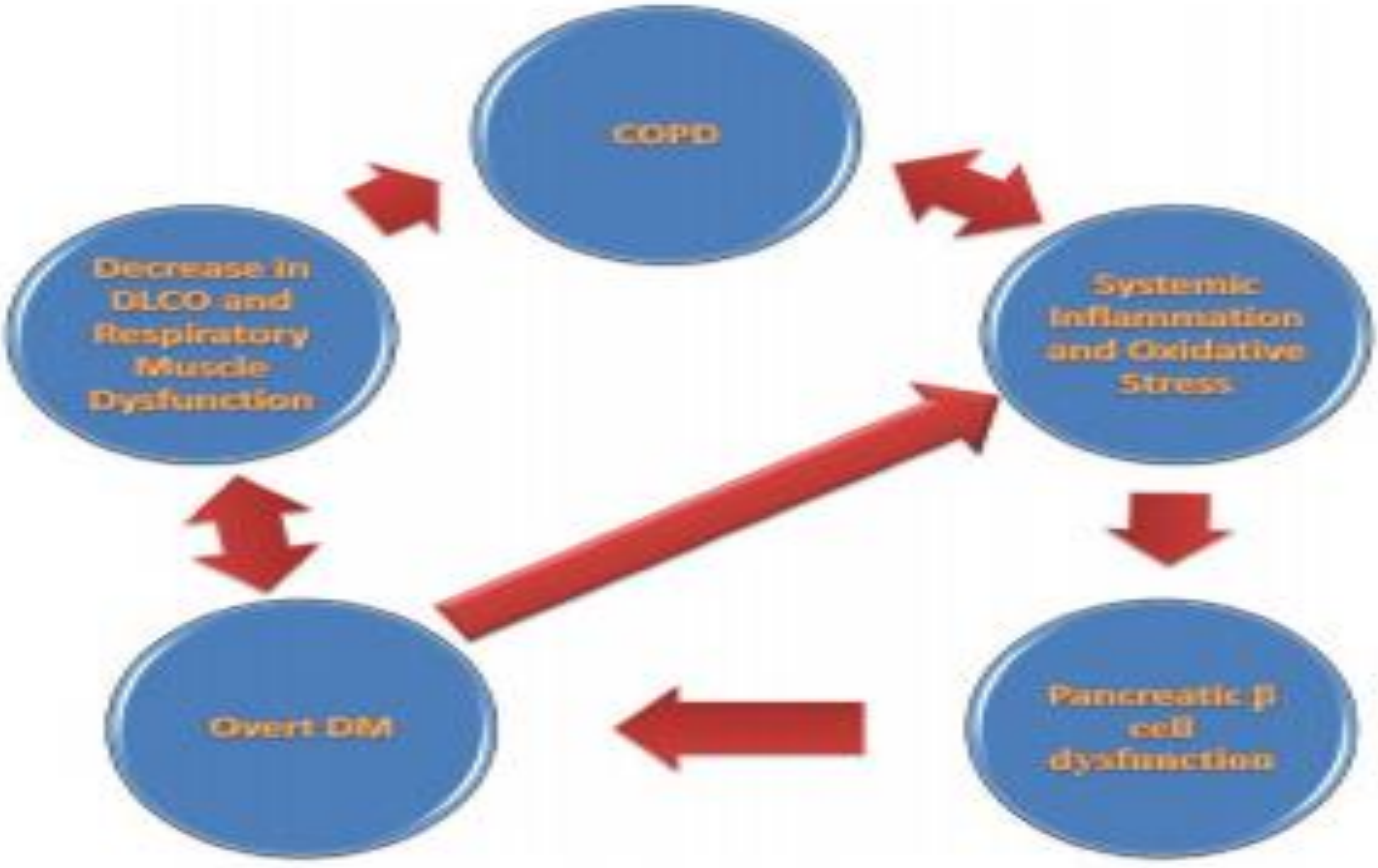
Ouchin N, et al. Nat Rev Immunol 2011;11:85-97

COPD and metabolic syndrome



Clini E, et al. Inern Emerg Med. 2013 Jun;8(4):283-9

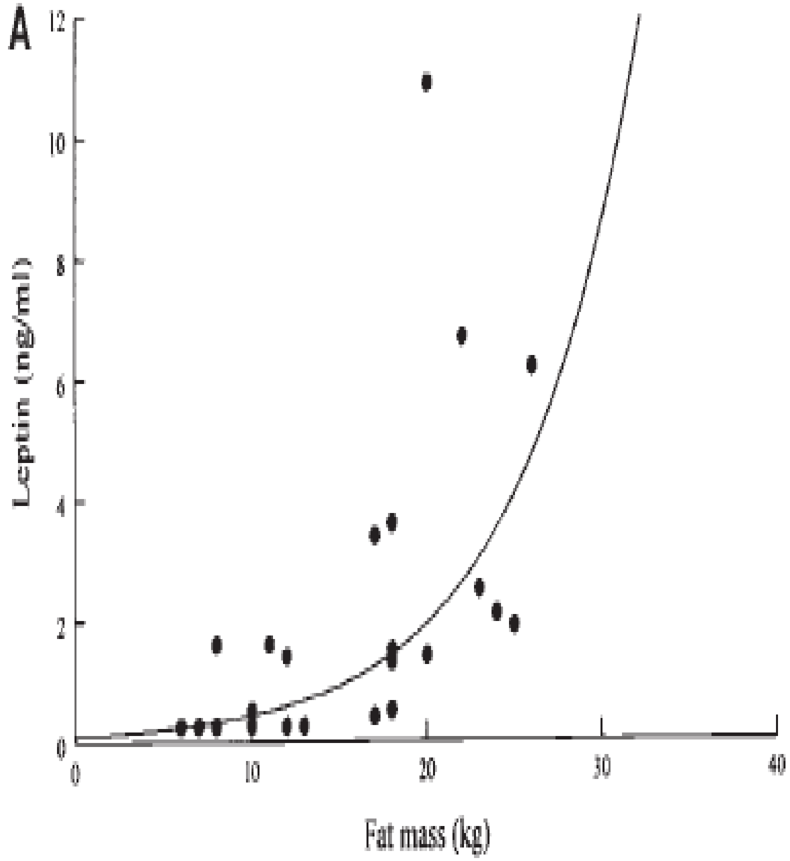
COPD and DM



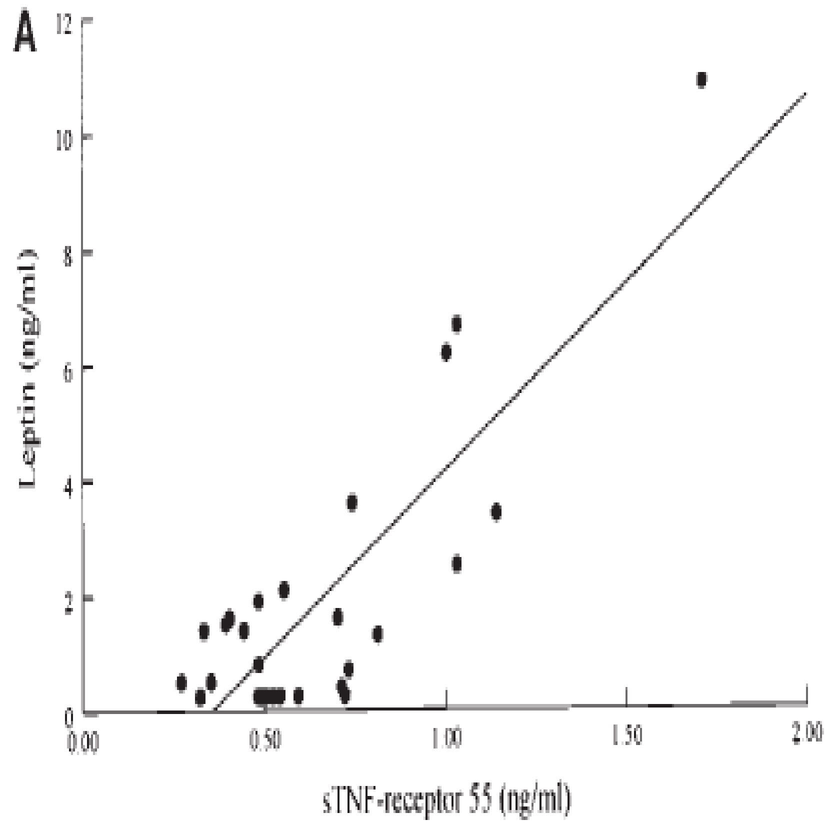
Mirrakhimov AE. Cardiovascular Diabetology 2012, 11:132

Leptin-cytokine link in COPD

R=0.80, P=0.001



R=0.81, P<0.001



Schols AMWJ, et al. AJRCCM 1995;160:1220-26.

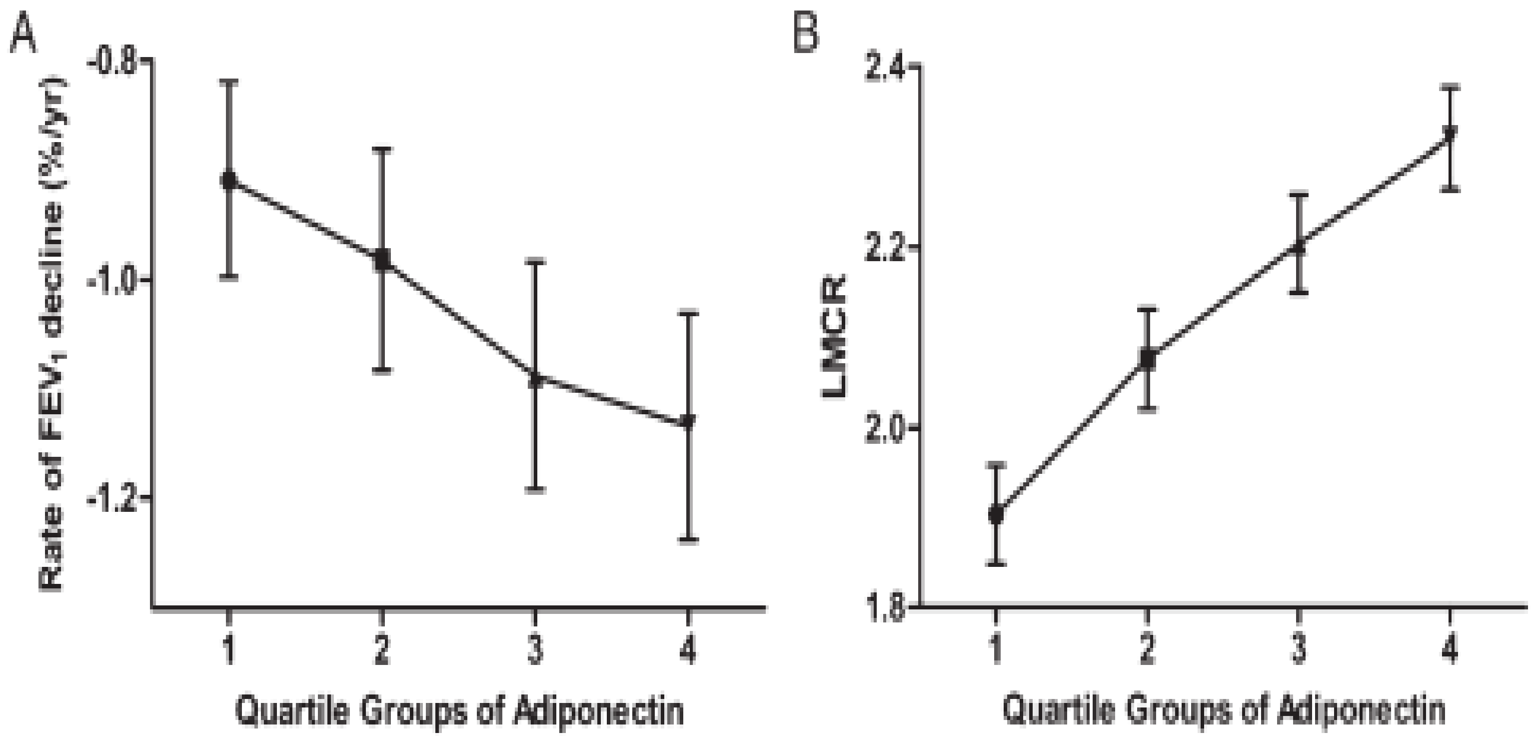
Serum adiponectin and health outcomes

Serum adiponectin was measured in 4,696 LHS participants.

End Points	Adiponectin as Continuous Variable (Log Scale)	Adiponectin (Quartiles)			P Value for Trend
		Q2	Q3	Q4	
Death from all causes					
Unadjusted	1.05 (0.91-1.216)	0.96 (0.70-1.31)	1.07 (0.79-1.46)	1.12 (0.83-1.52)	.352
Adjusted	1.10 (0.93-1.29)	0.99 (0.72-1.37)	1.11 (0.80-1.55)	1.17 (0.82-1.67)	.235
Death from cancer					
Unadjusted	1.14 (0.956-1.35)	1.00 (0.68-1.47)	1.10 (0.76-1.60)	1.40 (0.98-2.01)	.054
Adjusted	1.11 (0.92-1.34)	0.92 (0.62-1.37)	1.17 (0.78-1.75)	1.28 (0.84-1.97)	.199
Death from respiratory causes					
Unadjusted	2.07 (1.44-2.97)	2.26 (0.69-7.33)	2.55 (0.80-8.14)	4.94 (1.68-14.52)	.001
Adjusted	2.09 (1.41-3.11)	2.59 (0.77-8.67)	2.31 (0.67-8.00)	5.84 (1.84-18.50)	.002
Hospitalization or mortality due to CHD					
Unadjusted	0.62 (0.55-0.69)	0.60 (0.48-0.75)	0.49 (0.38-0.62)	0.37 (0.28-0.48)	< .001
Adjusted	0.73 (0.62-0.86)	0.61 (0.45-0.81)	0.62 (0.45-0.85)	0.59 (0.41-0.85)	< .001
Hospitalization or mortality due to CVD					
Unadjusted	0.74 (0.67-0.81)	0.74 (0.62-0.89)	0.65 (0.54-0.79)	0.51 (0.42-0.63)	< .001
Adjusted	0.83 (0.73-0.94)	0.83 (0.66-1.05)	0.83 (0.65-1.07)	0.73 (0.55-0.97)	.006

Yoon HI, et al. CHEST 2012; 142(4):893–899

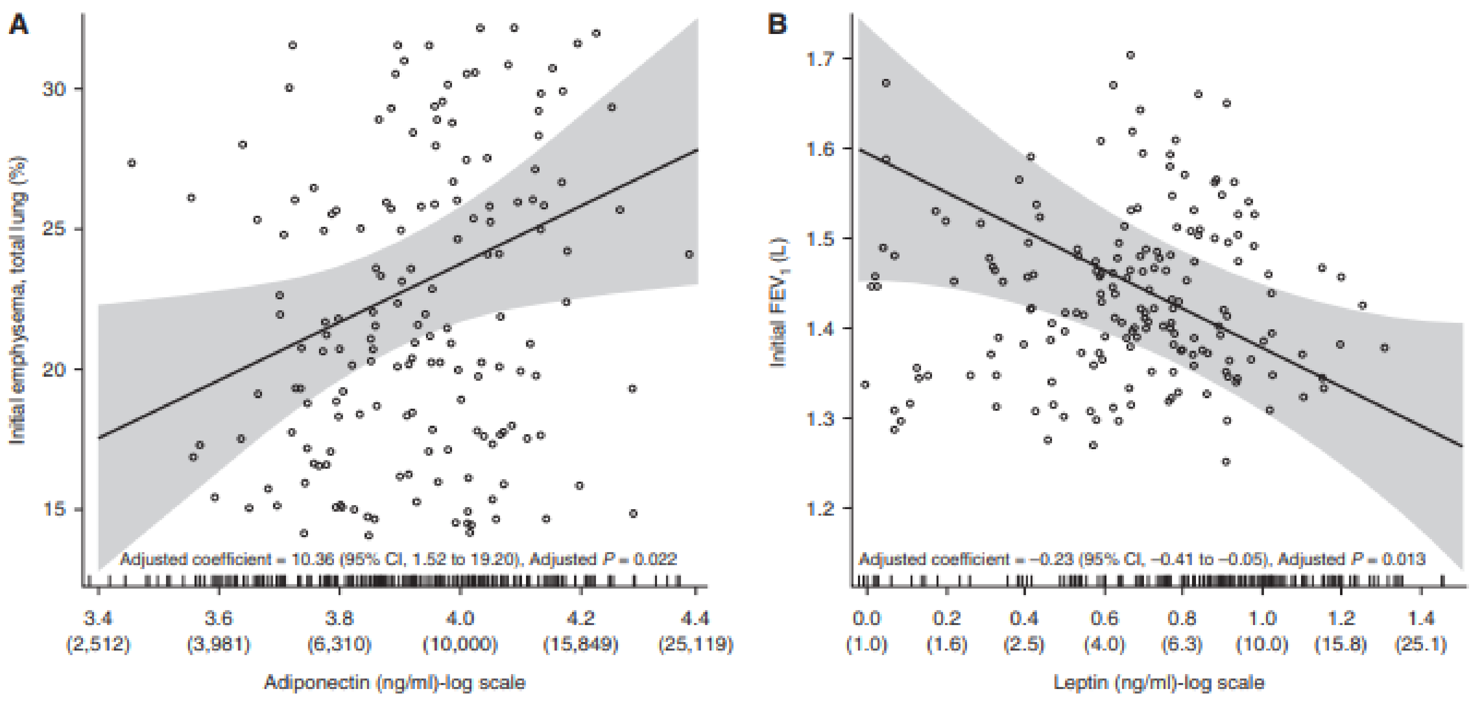
Serum adiponectin and FEV1 decline and bronchial reactivity



Yoon HI, et al. CHEST 2012; 142(4):893–899

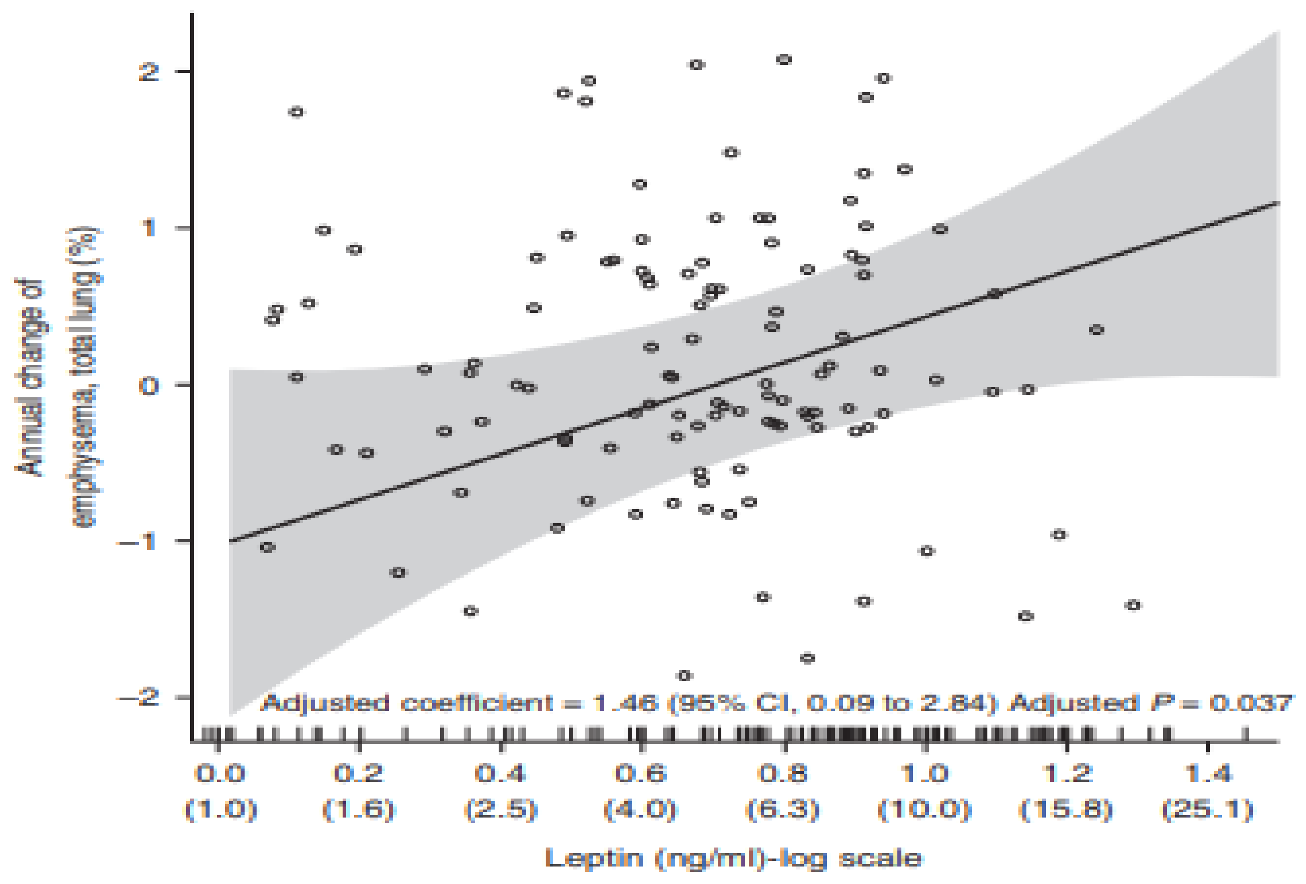
Plasma Adipokines with COPD severity

Plasma leptin and adiponectin levels were measured in 196 subjects with COPD form the KOLD cohort



Oh YM et al. 2015;12(7):1005-12.

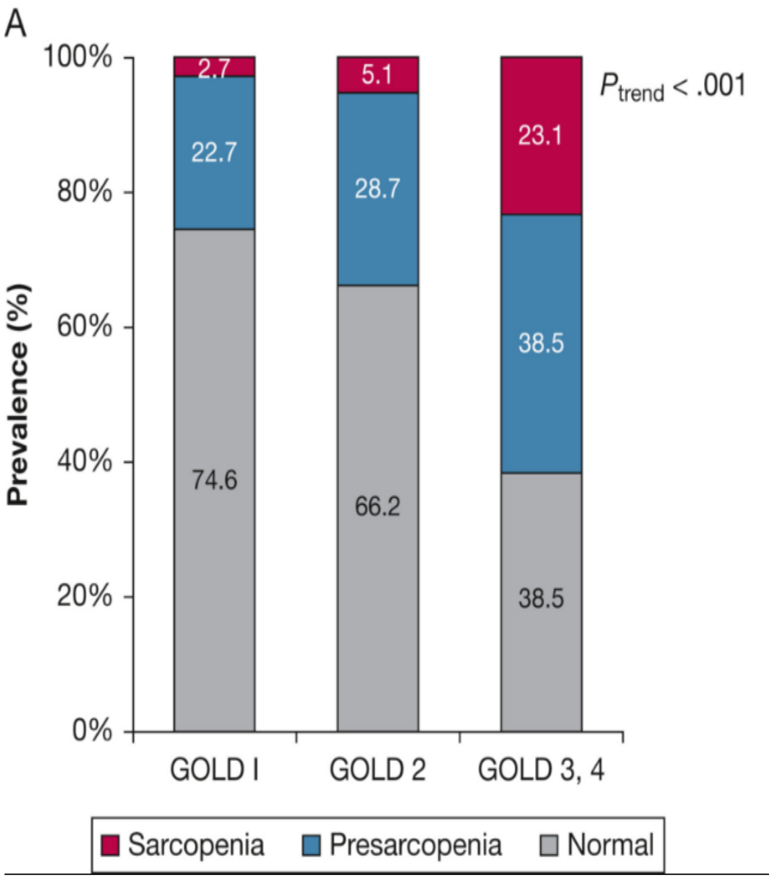
Plasma leptin with emphysema progression

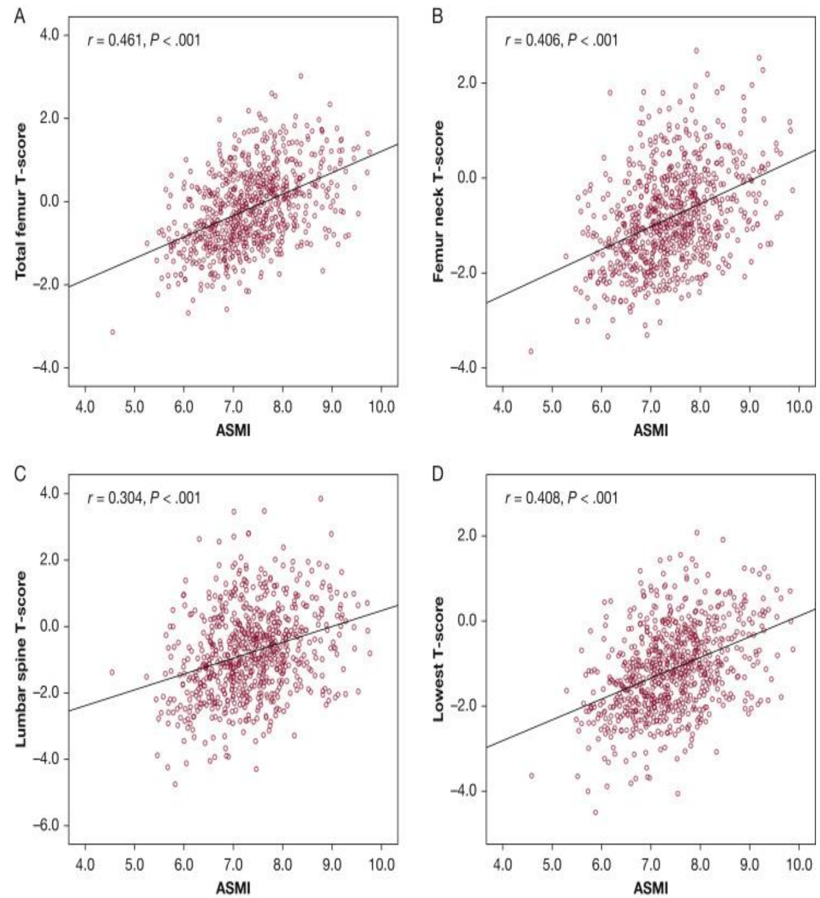


Oh YM et al. 2015;12(7):1005-12.

Sarcopenia in Korean COPD patients

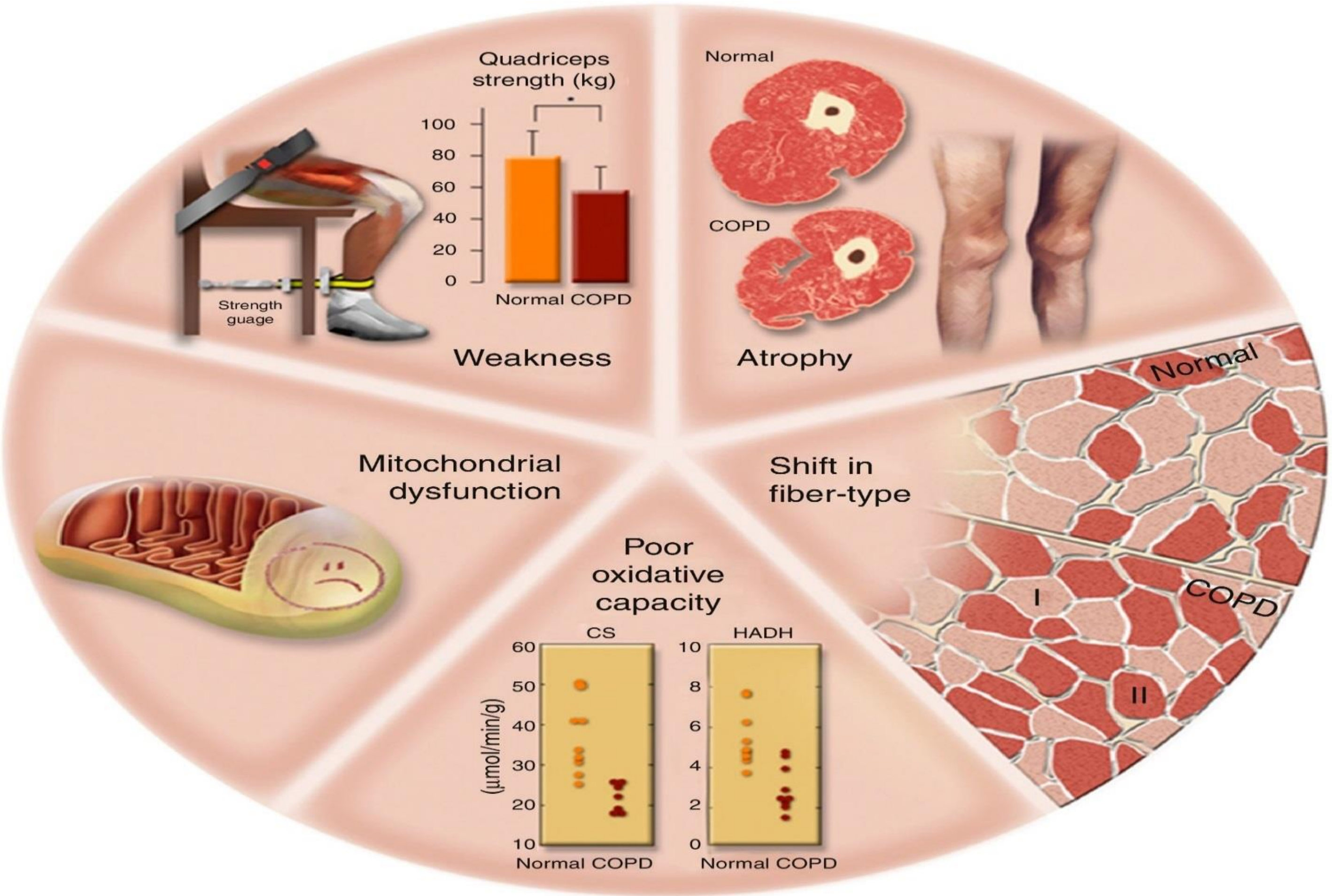
Total of 777 COPD patients from the KNHANES from 2008 to 2011





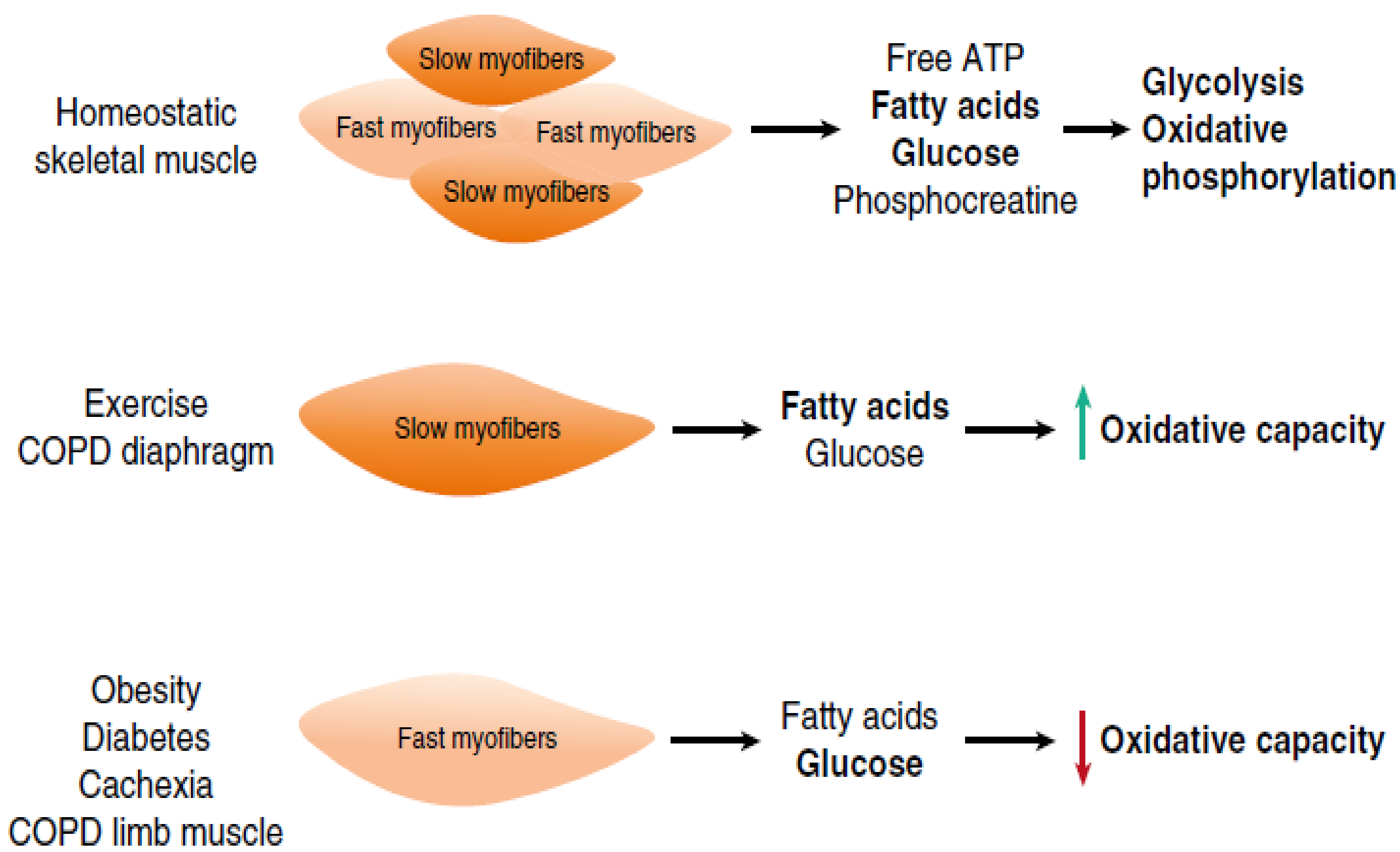
Hwang JA, et al. Chest 2017;151(5):1018-1027

Structural changes in limb muscles in patients with COPD



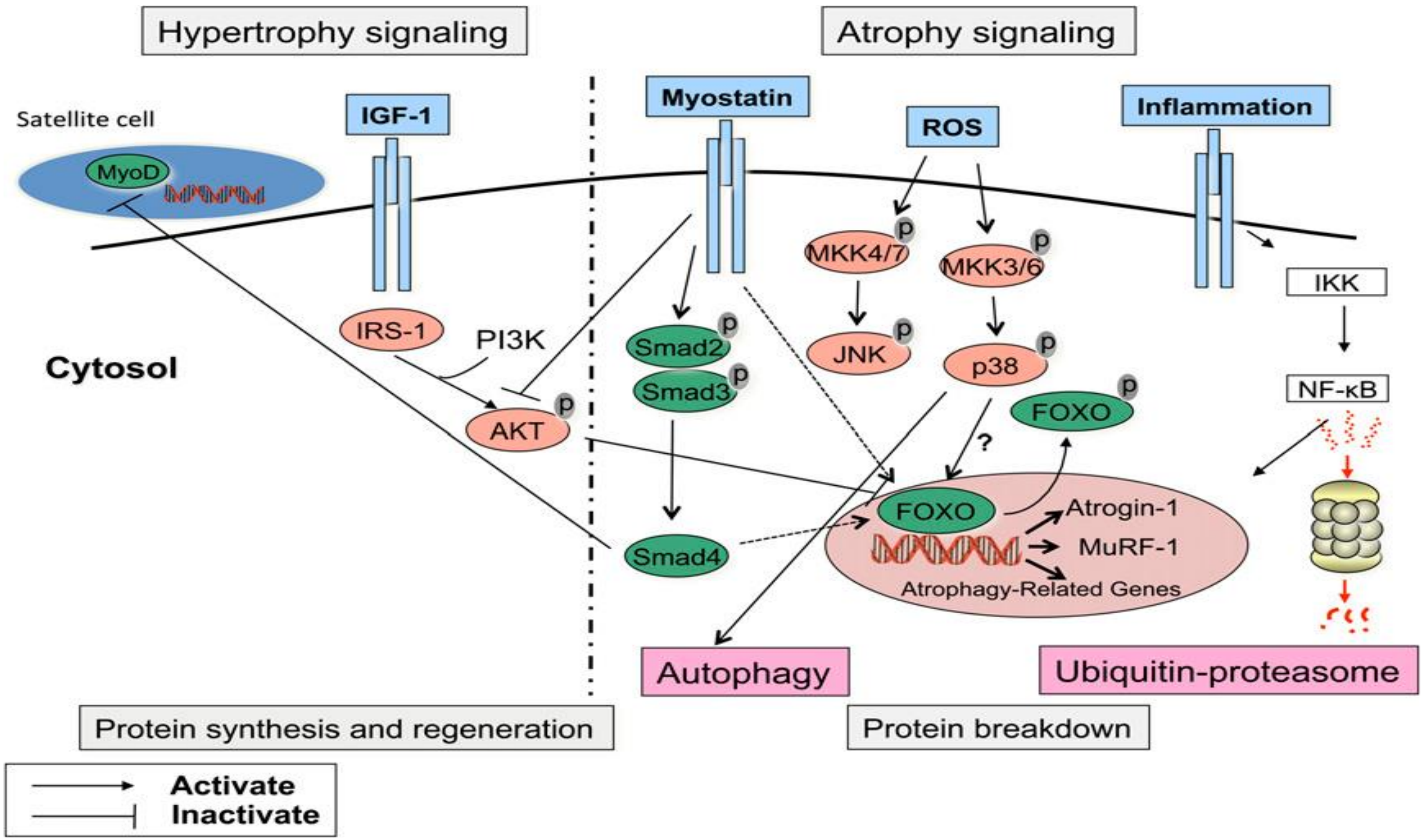
Nyberg A, et al. Ann Am Thorac Soc 2015 Sep;12(9):1269-77

Skeletal muscle fiber type and metabolism



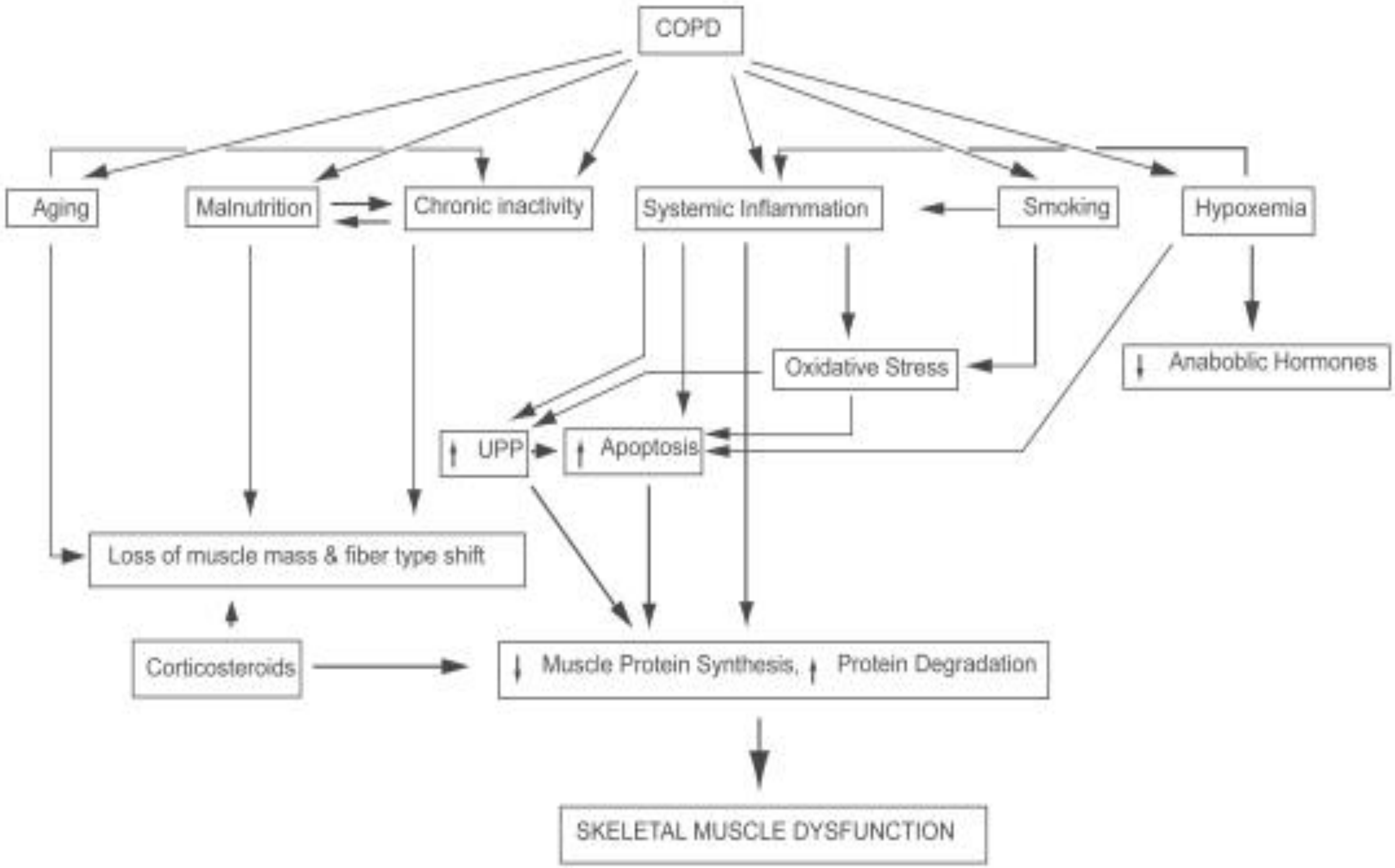
Ceco E, et al. Am J Respir Cell Mol Biol 2017;57:28-34.

Regulation of muscle mass



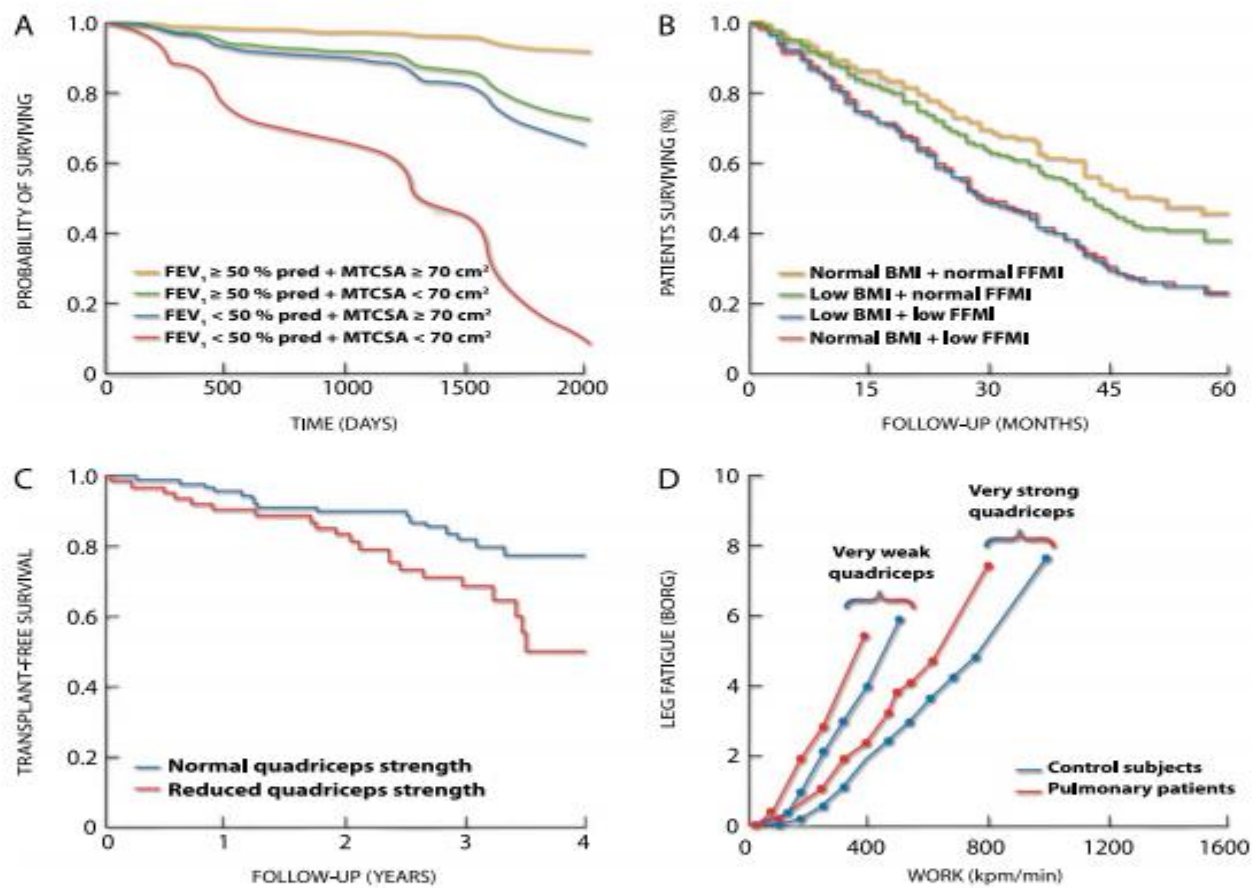
Maltais, et al. Am J Respir Crit Care Med. 2014; 189(9):e15-62.

Proposed mechanisms of skeletal muscle dysfunction in COPD



Kim HC et al. Int J COPD 2008;3(4):637-58.

Relationships between muscle mass and strength and clinical outcomes



Maltais, et al. Am J Respir Crit Care Med. 2014; 189(9):e15-62.

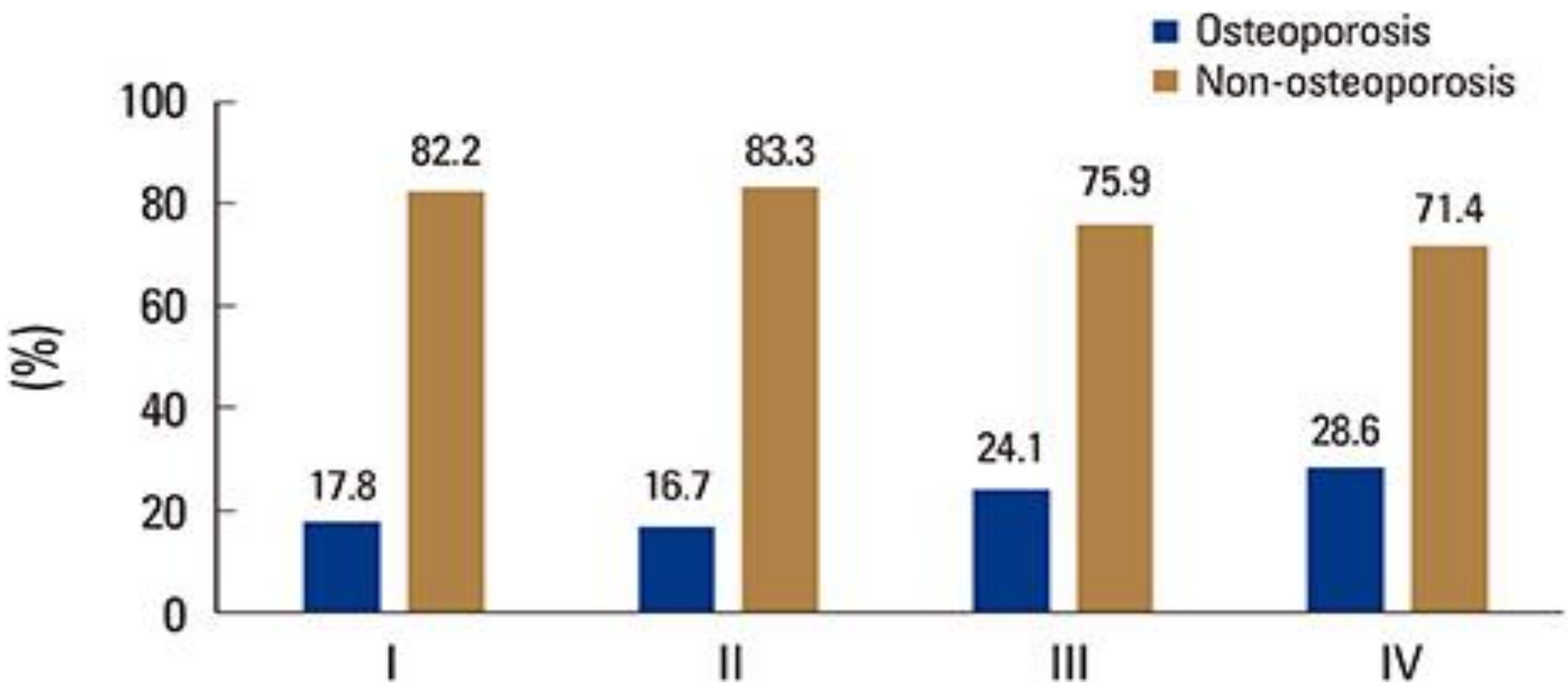
Effects of Treatments for Limb Muscle Dysfunction in COPD

Treatment	Mass	Strength	Exercise tolerance	Survival
Exercise	○	○	○	?
Oxygen	?	?	○	○
Nutrition alone	No	No	No	?
Nutrition with exercise training	○	○	○	?
Nutrition with exercise training and anabolic hormone supplementation	○	○	○	?
Testosteron	○	○	No	?
Growth hormones	○	No	No	?
Ghrelin	?	?	?	?
Megestrol	No	?	No	?
Creatine	?	?	No	?
Vitamin D alone	?	?	?	?
Vitamin D with exercise training	?	?	?	?

Maltais, et al. Am J Respir Crit Care Med. 2014; 189(9):e15-62.

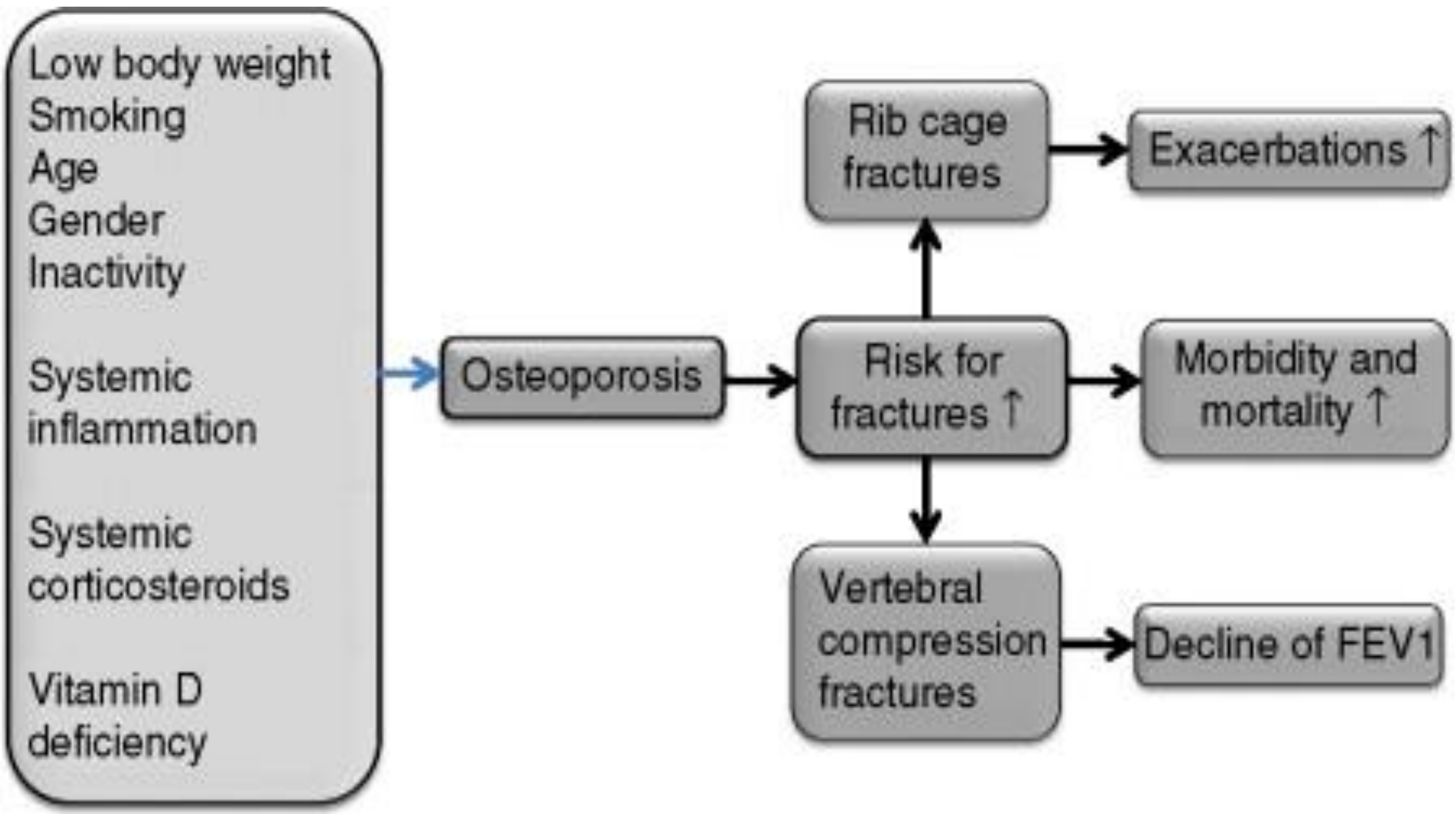
Prevalence of osteoporosis in Korean patients with COPD

Total of 1,081 COPD patients from the KNHANES from 2008 to 2011



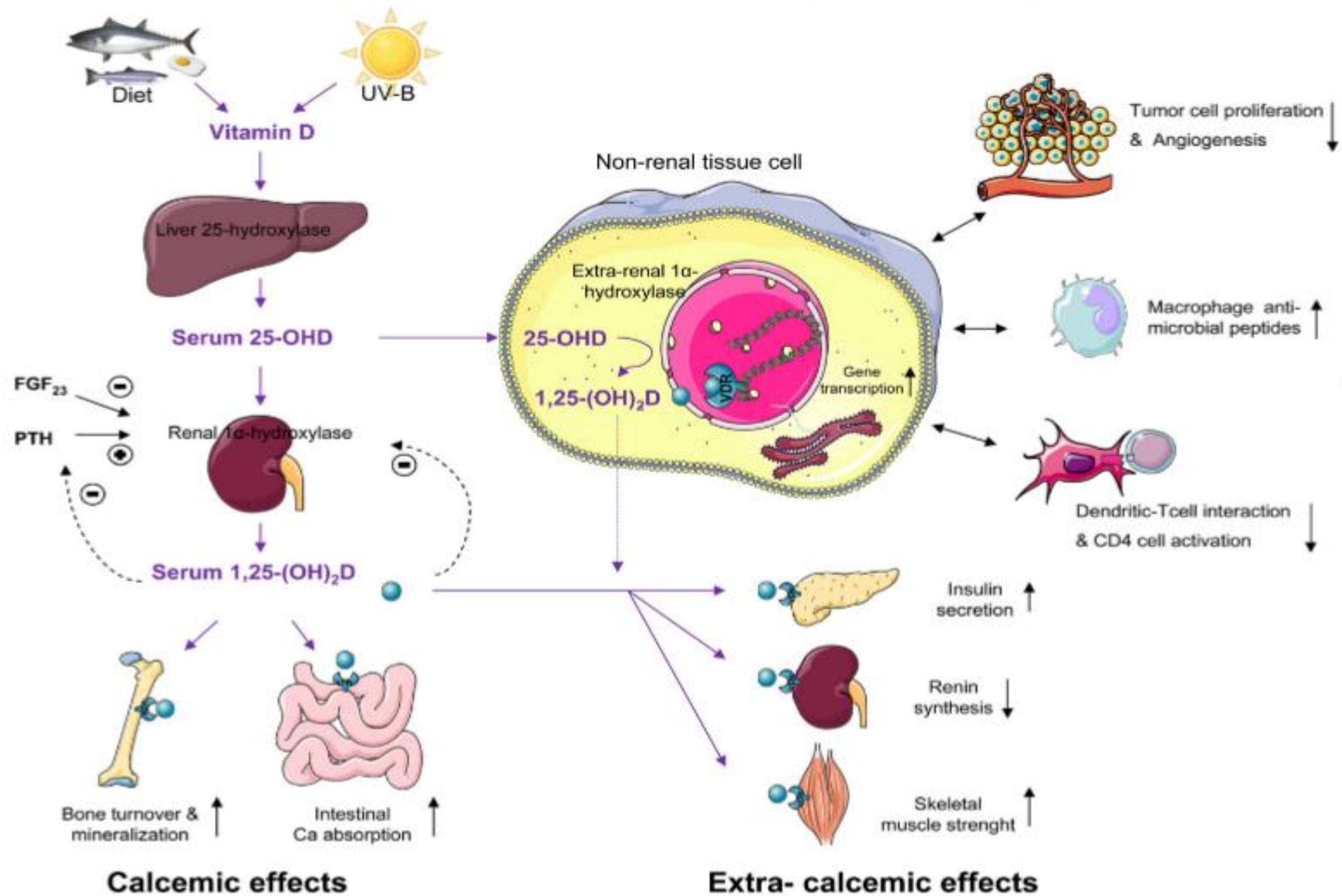
Lee SH & Kwon HY. J Bone Metab. 2017

Risk factors for osteoporosis in COPD



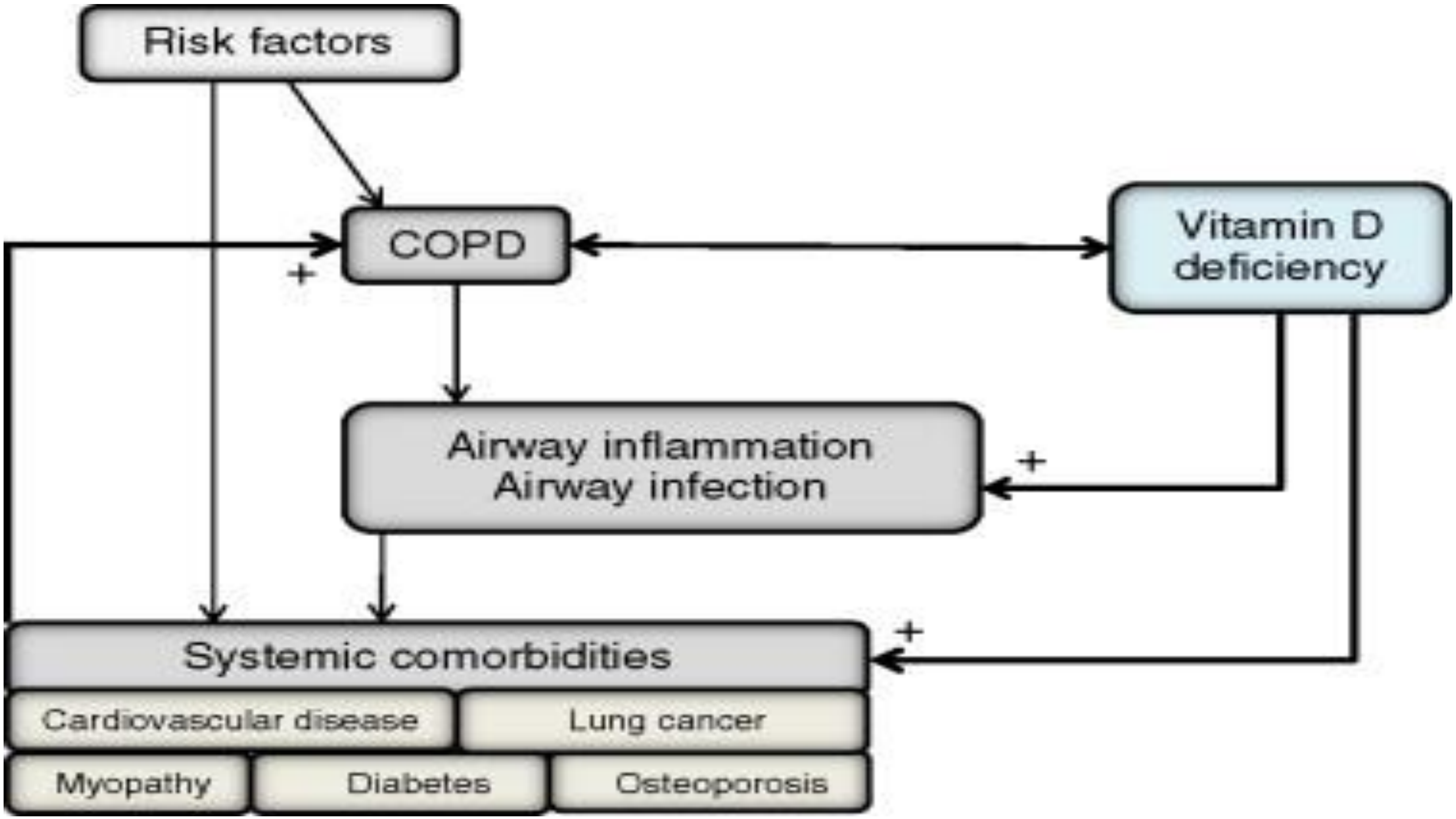
Janssens W et al. Vitamins & Hormones 2011

Vitamin D: beyond bones



Janssens W, et al. Am J Respir Crit Care Med 2009; 179: 630–636

Effect of vitamin D deficiency in COPD



Vitamin D deficiency

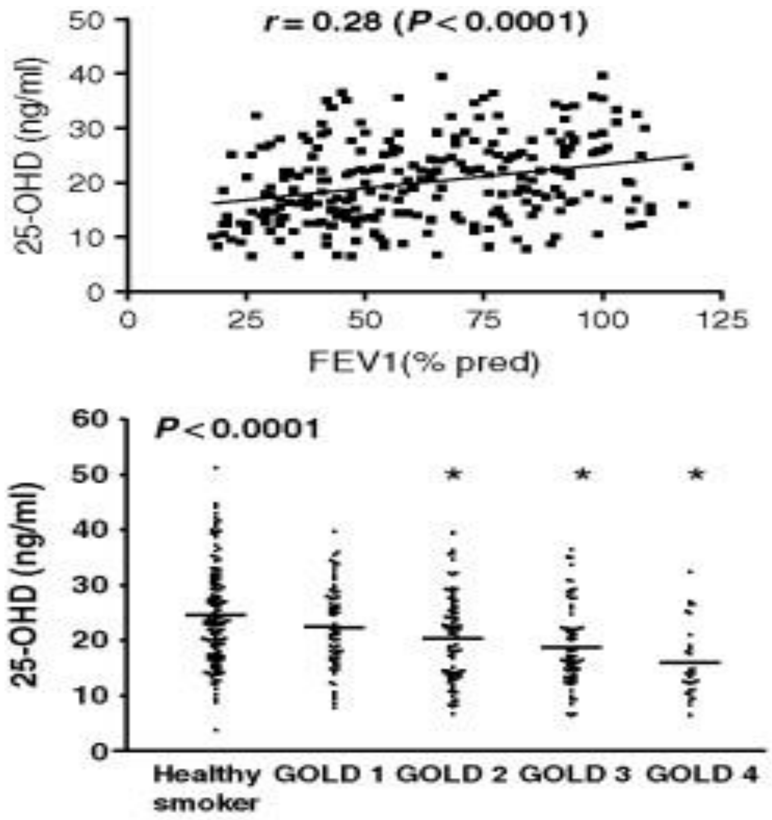
- Because of its long half life, vitamin D status is best measured by total circulating 25-OH vitamin D.

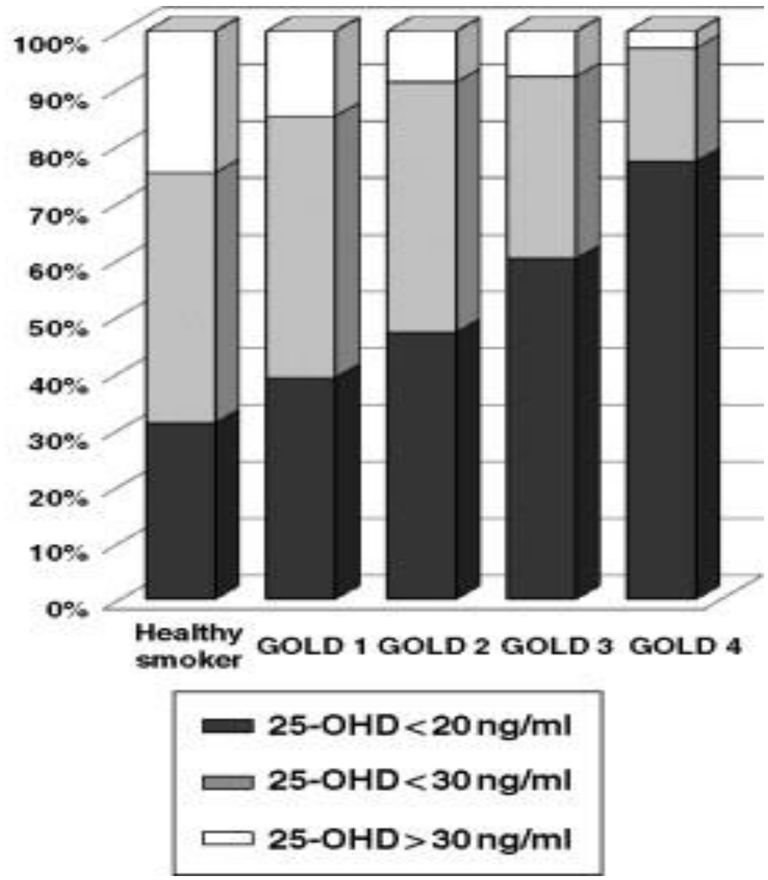
- In view of the calcemic effects, vitamin D insufficiency is best defined as a **25-OH vitamin D level below 20 ng/ml (50 nmol/l).**

- Several experts have suggested that, for **noncalcemic effects, serum levels of at least 30 ng/ml (75 nmol/l)** are required, but so far, intervention studies to support this are lacking.

Prevalence of vitamin D deficiency in COPD

Data from a Belgian patient cohort of 414 smoking individuals





Janssens W et al. Thorax; 2009:65:215-220

ORIGINAL ARTICLE

Relationship of vitamin D status with lung function and exercise capacity in COPD

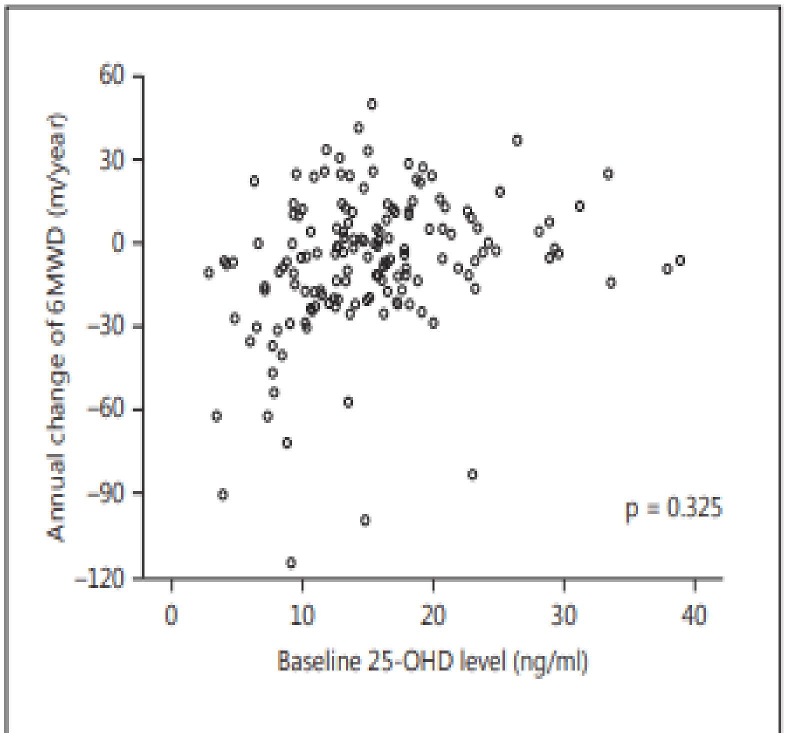
JI YE JUNG,[1] YOUNG SAM KIM,[1] SE KYU KIM,[1] HA YAN KIM,[2] YEON MOK OH,[3] SANG MIN LEE,[4] JOON BEOM SEO,[4] SANG-DO LEE[3] AND KOLD Study

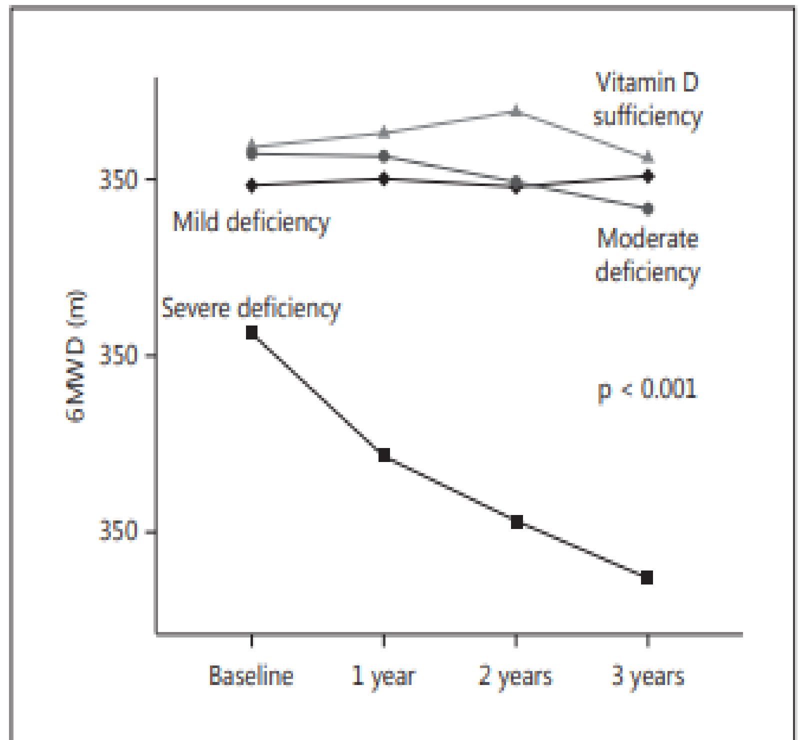
Parameters	Non-deficiency (n = 40)	Deficiency (n = 153)	P-value
Age, years	66.9 ± 5.6	66.1 ± 7.3	0.555
Height, cm	163.6 ± 5.3	165.1 ± 6.2	0.153
BMI, kg/m^2	22.9 ± 3.2	23.4 ± 3.4	0.434
Smoking			
Ever smoker	16 (40.0)	24 (60.0)	0.123
Never smoker	42 (27.5)	111 (72.5)	
Pack-years	51.7 ± 31.5	47.9 ± 25.4	0.434
Follow-up duration, years	3.95 ± 1.55	3.29 ± 1.77	0.032
FEV_1, L	1.69 ± 0.56	1.57 ± 0.52	0.192
FEV_1, % predicted	64.4 ± 19.3	57.9 ± 18.1	0.047
FVC, L	3.26 ± 0.88	3.40 ± 0.75	0.304
FVC, % predicted	88.6 ± 21.9	89.9 ± 17.9	0.694
FEV_1/FVC, %	51.4 ± 10.2	45.8 ± 10.7	<0.001
DLco, % predicted	83.9 ± 24.7	76.9 ± 25.9	0.133
GOLD			
GOLD I	10 (25.0)	14 (9.2)	0.012
GOLD II	23 (57.5)	82 (53.6)	
GOLD III	4 (10.0)	49 (32.0)	
GOLD IV	3 (7.5)	8 (5.2)	
Baseline plasma 25-OH-VitD3, ng/mL	29.4 ± 10.5	12.4 ± 4.3	<0.001
6MW test			
Walking distance, m	467.0 ± 68.4	437.2 ± 80.4	0.035

Respirology 2015 Jul;20(5):782-9

Vitamin D deficiency and decline in exercise capacity

- **156 patients in KOLD cohorts**





Kim C, et al. Respiration 2016;91(5):351-8.

Vitamin D for asthma

- Seven trial involving 435 children and two trials involving 658 adults

Figure 3. Forest plot of comparison: 1 Vitamin D versus placebo (all studies), outcome: 1.1 Rate ratio, exacerbations requiring systemic corticosteroids.

Study or Subgroup	log[Rate Ratio]	SE	Vitamin D Total	Placebo Total	Weight	Rate Ratio IV, Random, 95% CI
Castro 2014	-0.5816	0.2537	201	207	45.3%	0.56 [0.34, 0.92]
Jensen 2016	-0.3857	0.4175	11	11	16.7%	0.68 [0.30, 1.54]
Martineau 2015	-0.3011	0.277	125	125	38.0%	0.74 [0.43, 1.27]
Total (95% CI)			**337**	**343**	**100.0%**	**0.64 [0.46, 0.90]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.58$, df = 2 (P = 0.75); $I^2 = 0\%$
Test for overall effect: Z = 2.59 (P = 0.010)

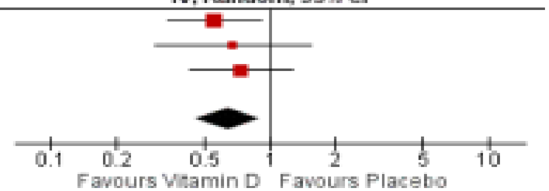
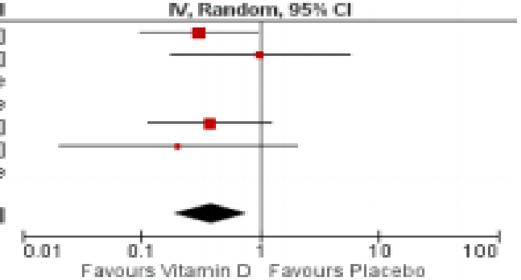


Figure 4. Forest plot of comparison: 1 Vitamin D versus placebo (all studies), outcome: 1.5 People with one or more exacerbations requiring ED visit or hospitalisation or both.

Study or Subgroup	log[Odds Ratio]	SE	Vitamin D Total	Placebo Total	Weight	Odds Ratio IV, Random, 95% CI
Castro 2014	-1.194	0.5806	201	207	38.6%	0.30 [0.10, 0.95]
Jensen 2016	0	0.8864	11	11	16.6%	1.00 [0.18, 5.68]
Majak 2009 (1)	0	0	18	18		Not estimable
Majak 2011 (2)	0	0	24	24		Not estimable
Martineau 2015	-0.9671	0.6058	125	125	35.4%	0.38 [0.12, 1.25]
Tachimoto 2016	-1.6032	1.1762	54	35	9.4%	0.20 [0.02, 2.02]
Urashima 2010 (3)	0	0	51	59		Not estimable
Total (95% CI)			**484**	**479**	**100.0%**	**0.39 [0.19, 0.78]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.63$, df = 3 (P = 0.65); $I^2 = 0\%$
Test for overall effect: Z = 2.65 (P = 0.008)



Cochrane Database Syst Rev. 2016

Annals of Internal Medicine | ORIGINAL RESEARCH

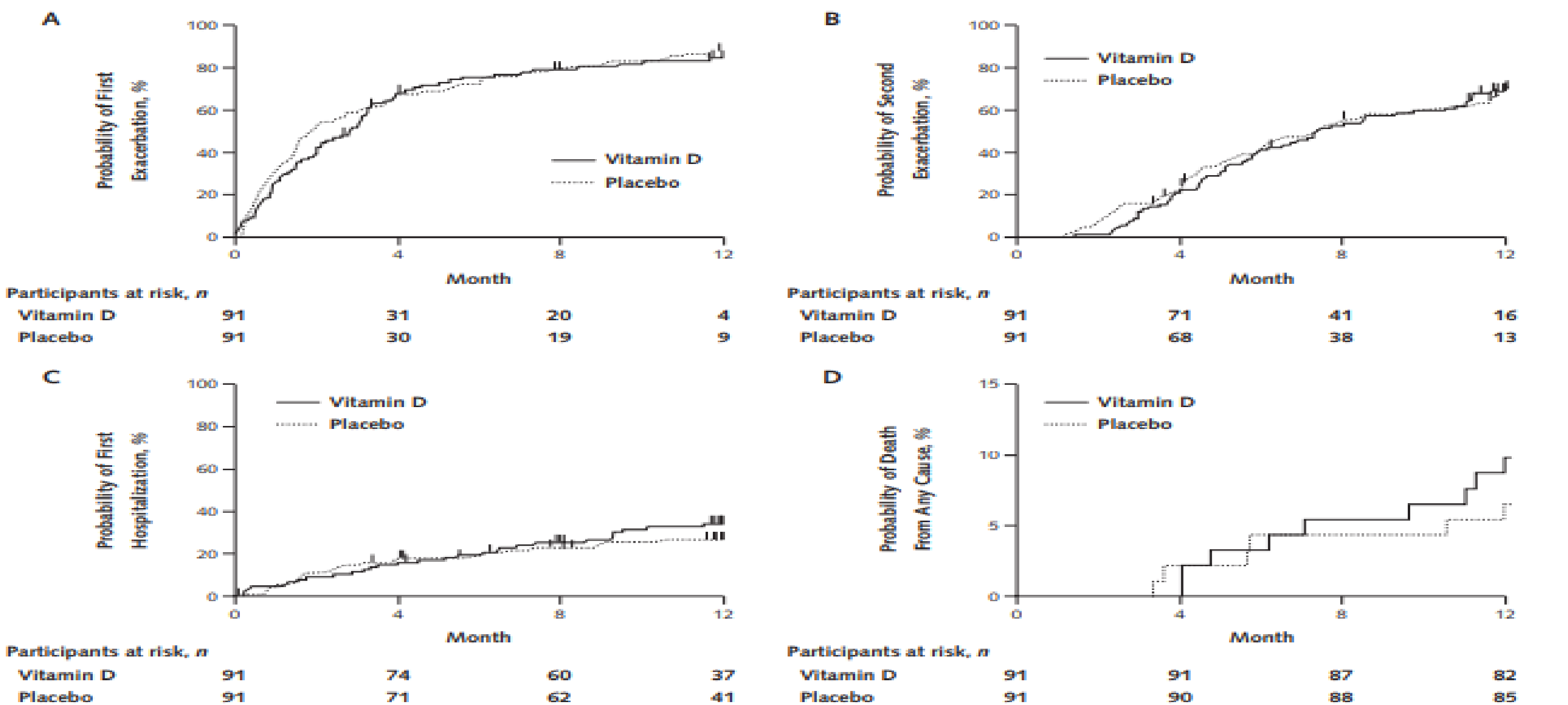
High Doses of Vitamin D to Reduce Exacerbations in Chronic Obstructive Pulmonary Disease

A Randomized Trial

Patients: 182 patients with moderate to very severe COPD and a history of recent exacerbations.

Intervention: 100000 IU of vitamin D or placebo every 4 weeks for 1 year

Primary outcome: time to first exacerbation



Ann Intern med. 2012; 17;156(2):105-14.

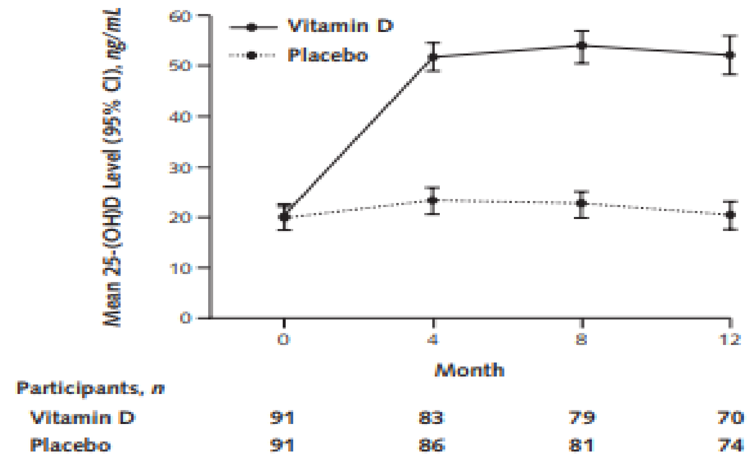
Annals of Internal Medicine | Original Research

High Doses of Vitamin D to Reduce Exacerbations in Chronic Obstructive Pulmonary Disease

A Randomized Trial

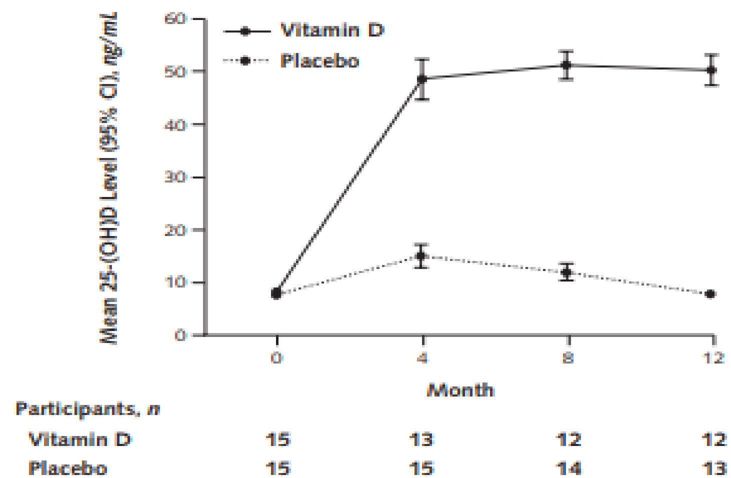
A. ITT Population

Variable	Vitamin D (*n* = 91)	Placebo (*n* = 91)	Difference or RR (95% CI)	*P* Value
Mean 25-(OH)D level (SD), *ng/mL*				
At baseline	20 (12)	20 (11)	0.2 (–3 to 4)	0.90
During study	52 (16)	22 (13)	30 (27 to 33)	<0.001
COPD exacerbations per patient-year, *n*	2.8	2.9	0.94 (0.76 to 1.16)	0.57



C. Subgroup With Severe Vitamin D Deficiency

Variable	Vitamin D (*n* = 15)	Placebo (*n* = 15)	Difference or RR (95% CI)	*P* Value
Mean 25-(OH)D level (SD), *ng/mL*				
At baseline	8 (2)	7 (2)	0.57 (–1 to 2)	0.36
During study	50 (15)	12 (8)	38 (33 to 44)	<0.001
COPD exacerbations per patient-year, *n*	1.84	3.45	0.57 (0.33 to 0.98)	0.042

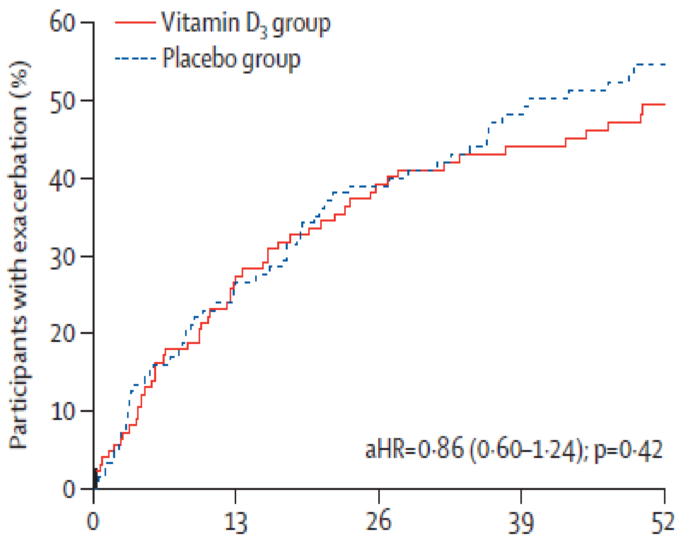


Ann Intern med. 2012; 17;156(2):105-14.

Vitamin D_3 supplementation in patients with chronic obstructive pulmonary disease (ViDiCO): a multicentre, double-blind, randomised controlled trial

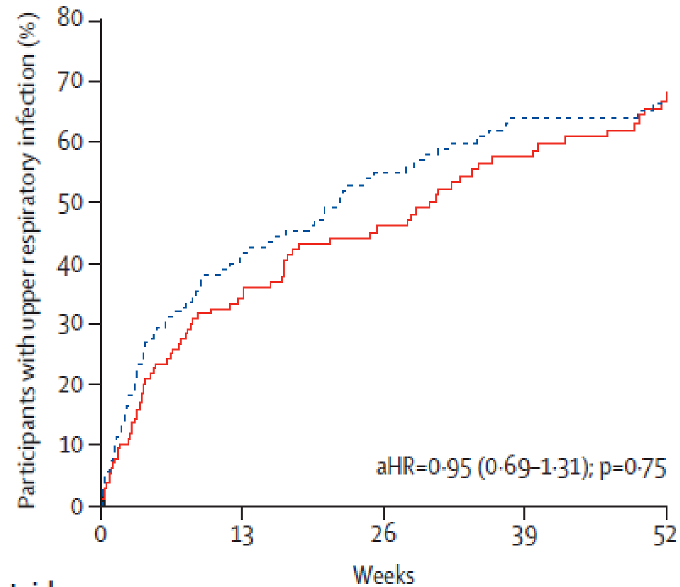
Patients: 240 patients with COPD
Intervention: 120000 IU of vitamin D or placebo every 2 months for 1 year
Co-primary outcome: time to first moderate or severe exacerbation
time to first upper respiratory tract infection

A



Number at risk	0	13	26	39	52
Vitamin D_3 group	122	84	65	55	46
Placebo group	118	80	64	50	40

B



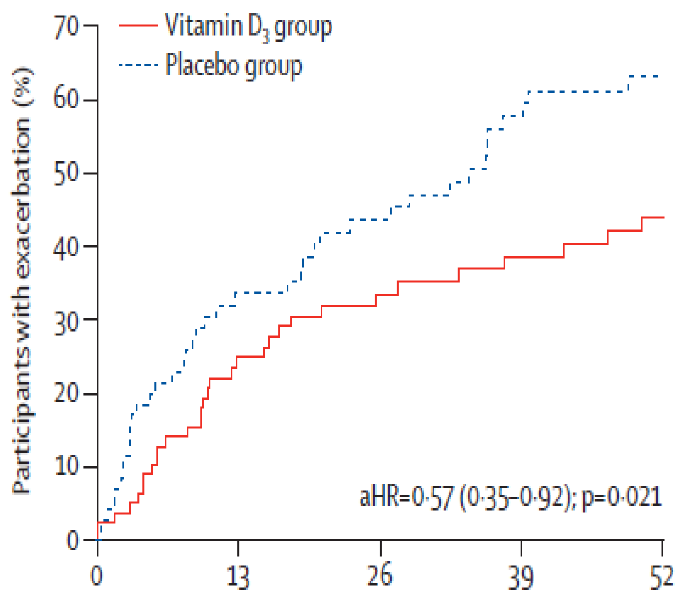
Number at risk	0	13	26	39	52
Vitamin D_3 group	122	75	54	39	28
Placebo group	118	64	47	34	29

Martineau ARM, et al. Lancet Respir Med **2015;3: 120 - 30**

Vitamin D_3 supplementation in patients with chronic obstructive pulmonary disease (ViDiCO): a multicentre, double-blind, randomised controlled trial

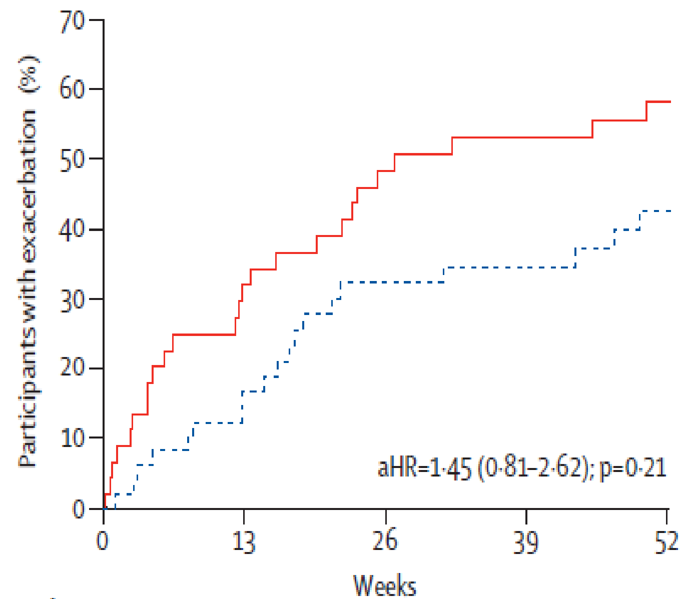
Pre-specified subgroup analysis by baseline vitamin D status

Vitamin D< 50 nmol/L



Number at risk	0	13	26	39	52
Vitamin D_3 group	78	55	43	35	31
Placebo group	70	41	34	24	20

Vitamin D > 50 nmol/L



Number at risk	0	13	26	39	52
Vitamin D_3 group	44	29	22	20	15
Placebo group	48	39	30	26	20

Martineau ARM, et al. Lancet Respir Med 2015;3: 120 - 30

2015 대한골대사학회 권고안

50세 이상의 남성과 폐경 여성에게 칼슘 및 비타민 D의 적절한 공급은 골다공증 및 골절의 예방과 치료를 위해 필수적이다.

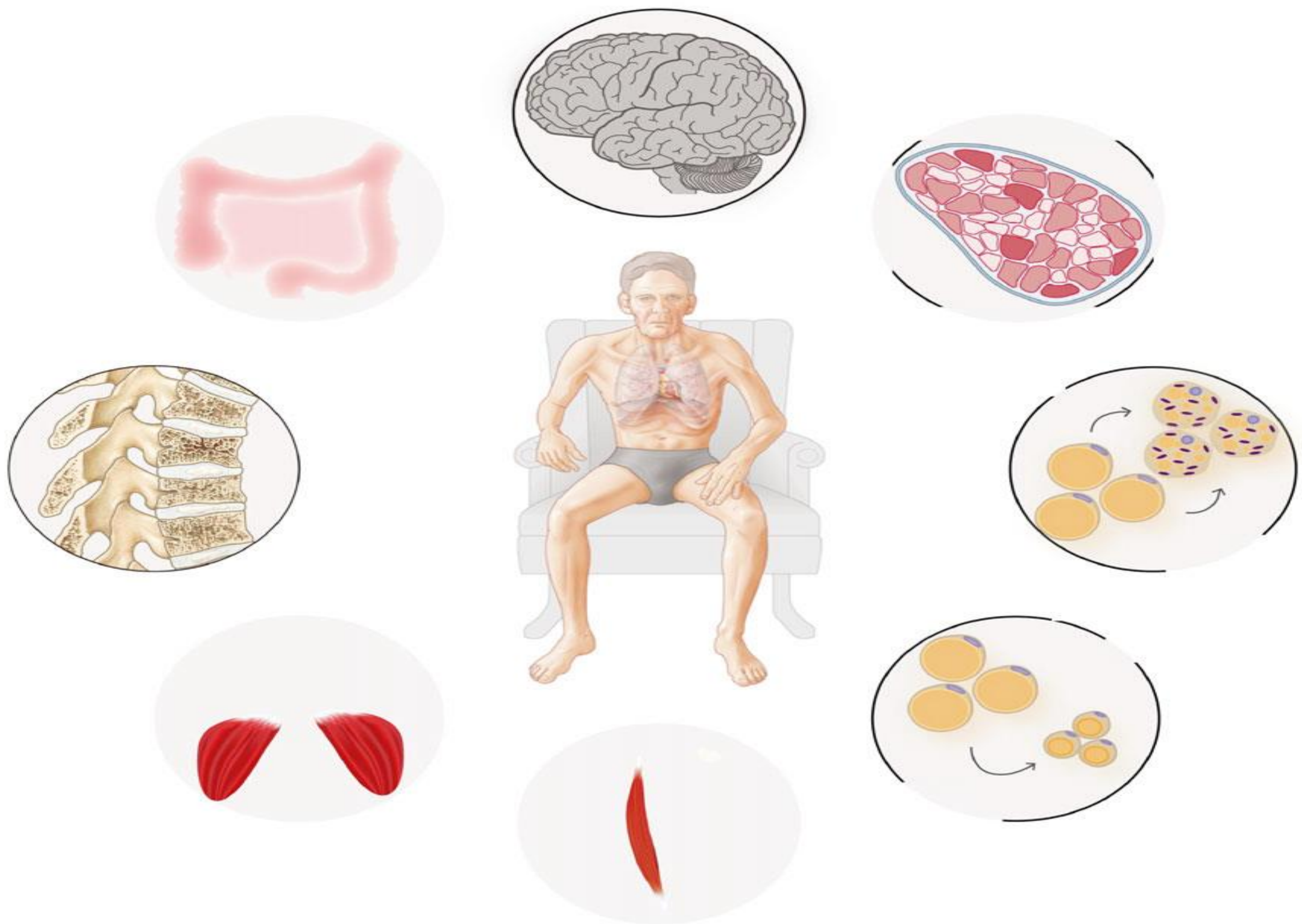
1) 칼슘은 일일 800~1,000 mg 섭취를 권장한다.

한국인의 일일 칼슘 섭취량은 권장량에 비해 부족하기 때문에 음식으로 칼슘 섭취를 증가시키는 것이 일차적으로 필요하며, 음식을 통한 칼슘 섭취가 용이하지 않은 경우에는 보충제의 사용을 권장한다.

2) 비타민 D는 일일 800 IU 섭취를 권장한다.

비타민 D 결핍이 의심될 경우에는 혈액 25(OH)D 농도 측정이 필요하다.
골다공증의 예방을 위하여 혈액 25(OH)D 농도는 최소 20 ng/mL 이상을 유지하도록 한다. 골다공증의 치료, 골절 및 낙상의 예방을 위해서는 30 ng/mL 이상이 필요할 수도 있다.

Pulmonary and extra-pulmonary cross-talk in COPD



Sanders KJC, et al. Journal of Cachexia, Sarcopenia and Muscle 2016; 7