L'EMILIA ROMAGNA VERSO ICAR 2013

Elevata prevalenza e severità dell'enfisema polmonare associata con la morbosità cardiovascolare

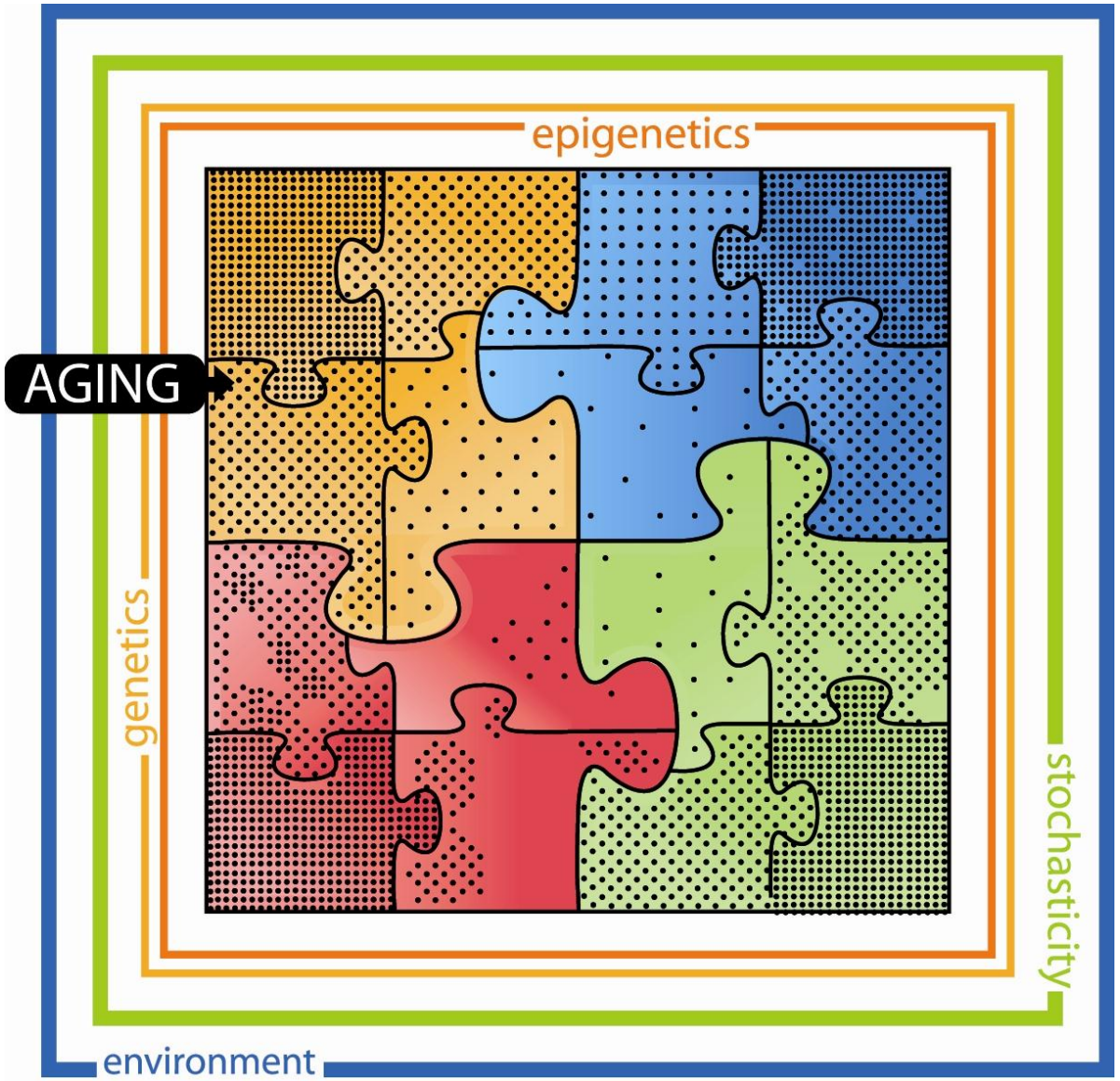
Giovanni Guaraldi

The mosaic of aging

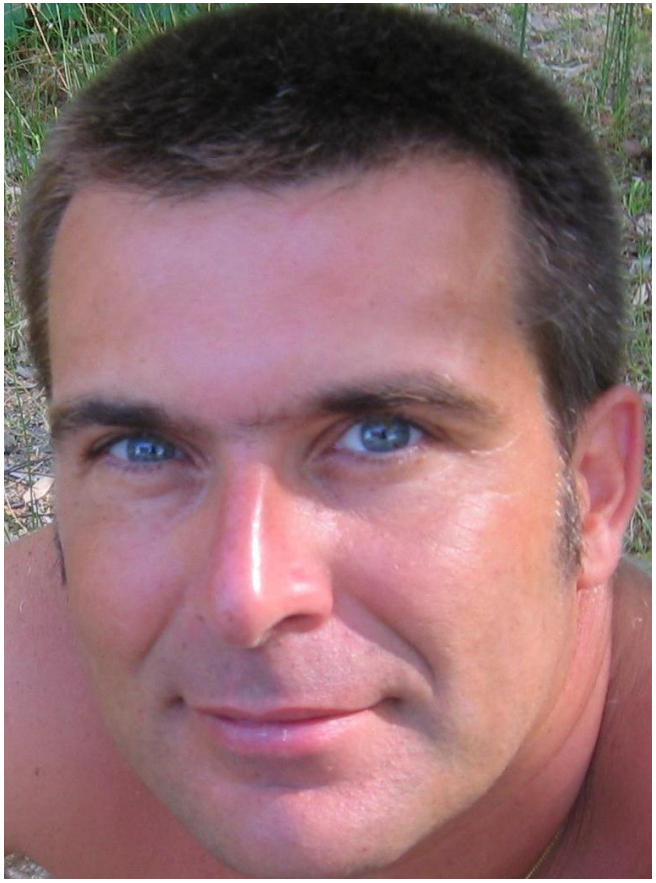
great variability
at all levels
of biological
organization:

- macromolecules
- organelles
- cells
- organs
- individuals
- populations

Expert Opin. Biol. Ther. (2008) 8(9):1393-1405



At an individual level the mosaic of aging is described by frailty



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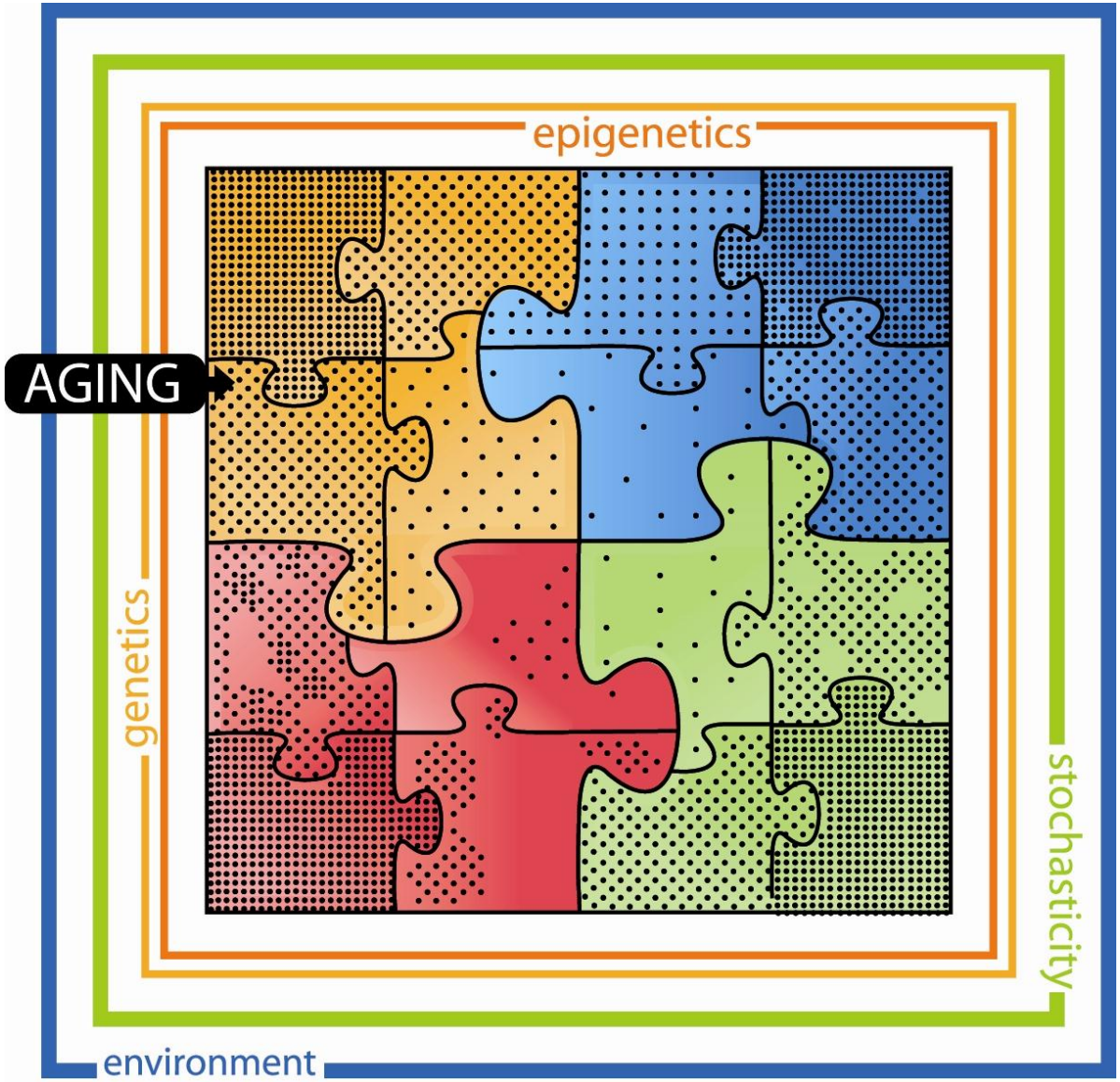

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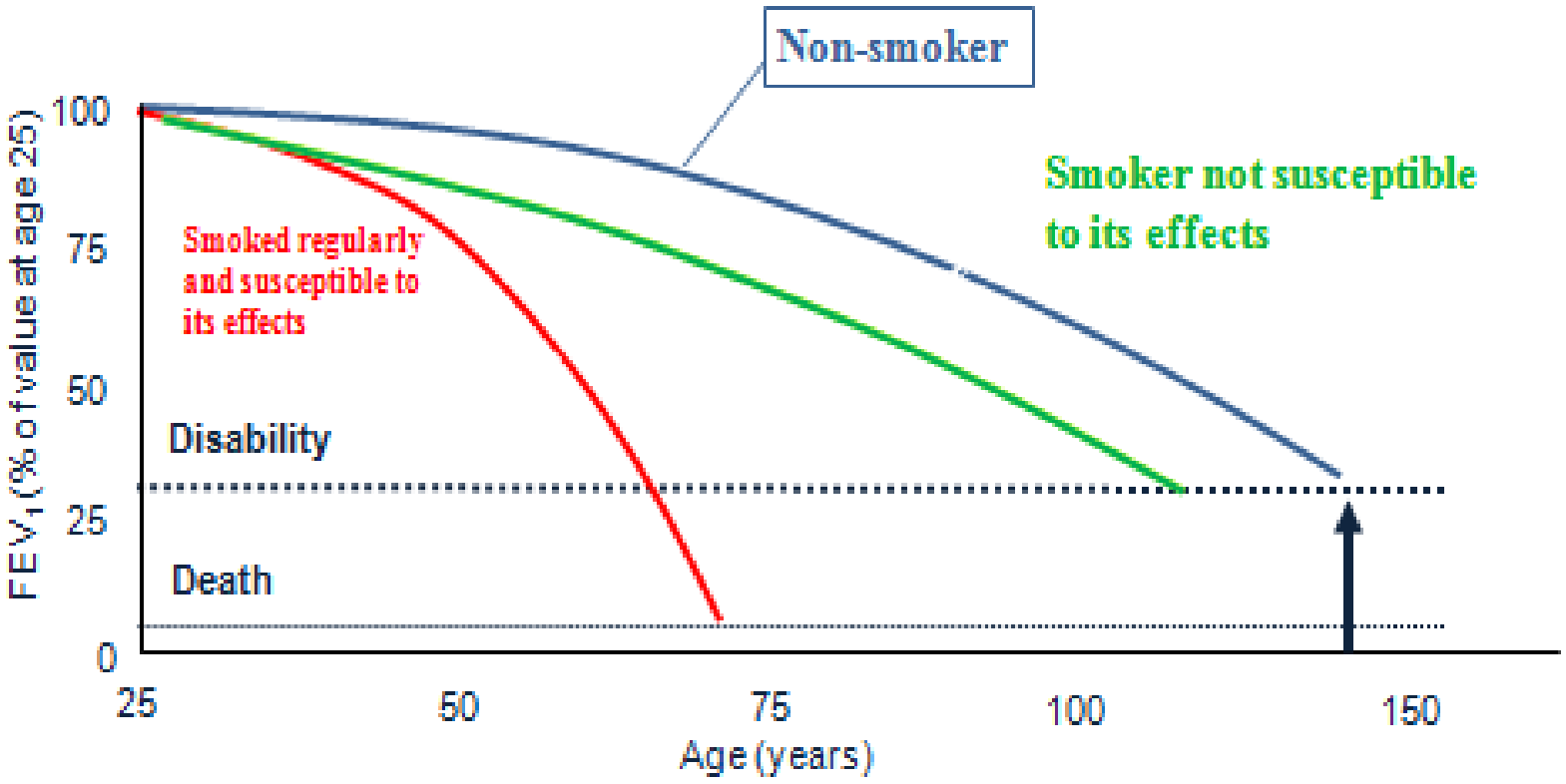
At an organ level the mosaic of aging is described by trajectories of function reserves

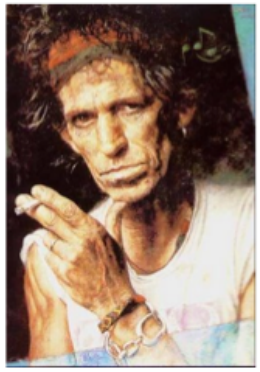
Smoke and premature aging lung



Chronic Obstructive Pulmonary Disease (COPD), is a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients.

Diagnosis requires spirometry:

$$\frac{\text{post-bronchodilator forced expiratory volume in one second } \mathbf{FEV1}}{\text{forced vital capacity } \mathbf{FVC}} \leq 0.7$$



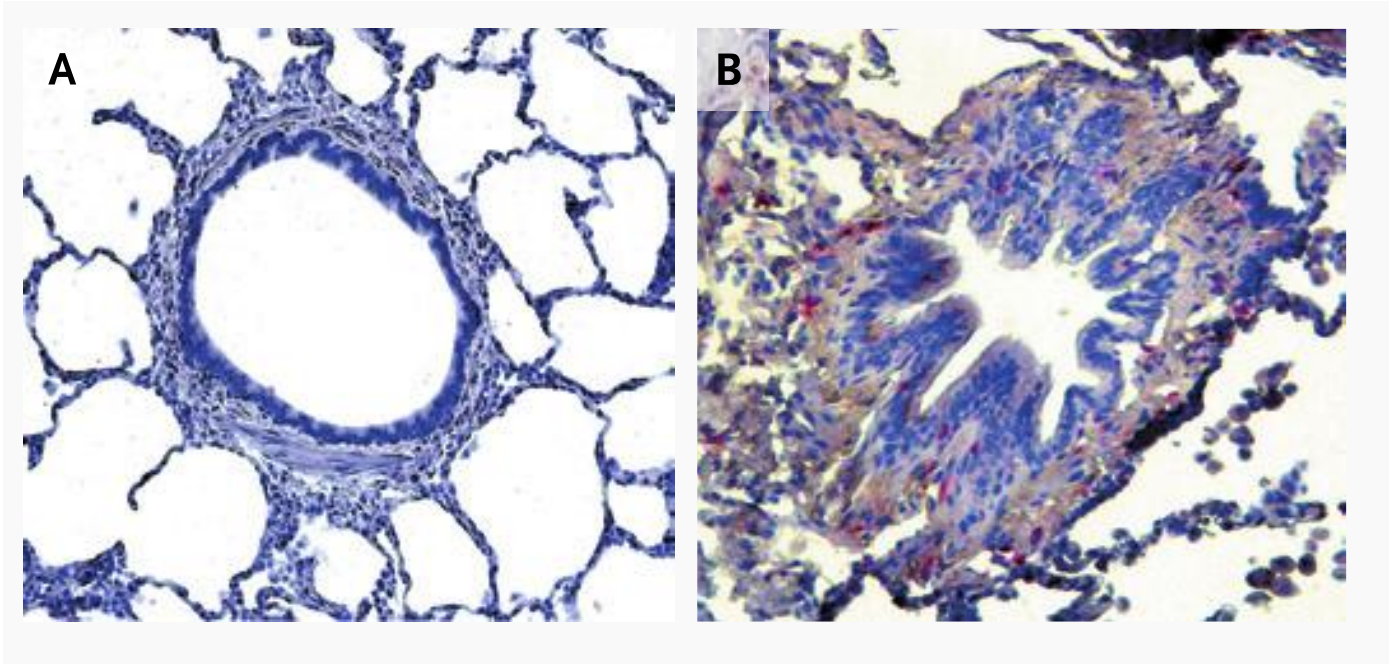
Risk factors

- Smoking
- Socio-economic status
- Occupation
- Environmental pollution
- Recurrent bronchopulmonary infections

Natural history
of COPD is characterized by

- Acute exacerbations
- Chronic inflammation
- **Comorbidities such as chronic heart failure,**
- **metabolic syndrome and others**

Peripheral lung inflammation may cause a spill over of cytochines into the systemic circulation

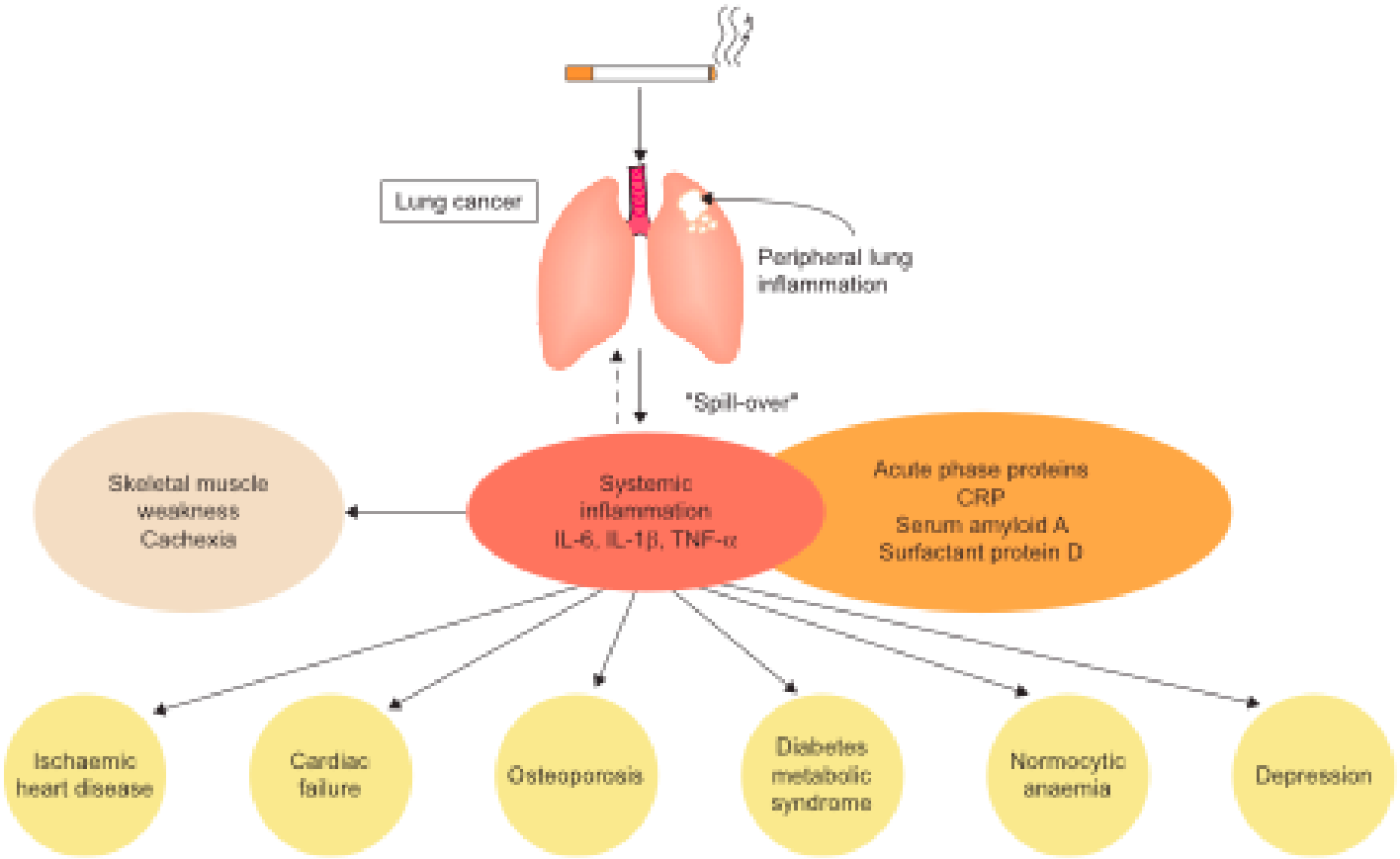


Healthy lung of a nonsmoker

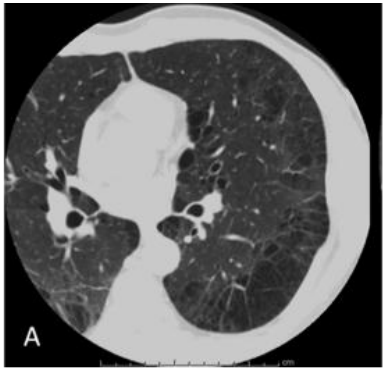
Lung of a smoker with COPD
CD8+ T lymphocytes (in red)
infiltrate the airway wall

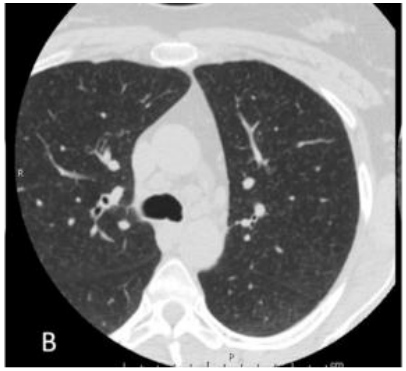
Peripheral lung inflammation may cause a "spill over" of cytokines into the systemic circulation, which may increase acute phase proteins (CRP, IL6, IL4) which may initiate and worsen comorbid conditions and lung cancer

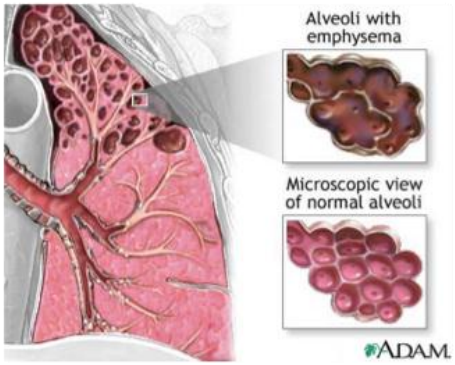
Systemic effects and comorbidities of chronic obstructive pulmonary disease (COPD)



COPD at organ level: CT Imaging





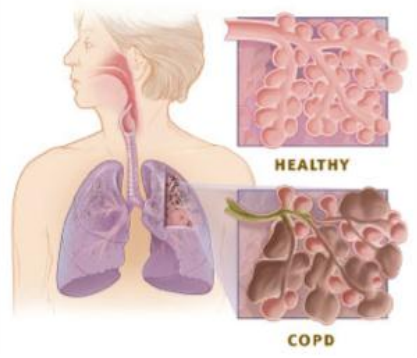


Emphysema:

Abnormal, permanent enlargement of air spaces distal to the terminal bronchioles, accompanied by the destruction of their walls.

Bronchiolitis :

the airway becomes obstructed from swelling of the bronchiole walls



Both patterns can be present in COPD

Objectives

1. To determine the prevalence of the two major morphologic COPD phenotypes, bronchiolitis and emphysema, using thoracic computed tomography (CT) imaging and to describe risk factors associated with these COPD phenotypes

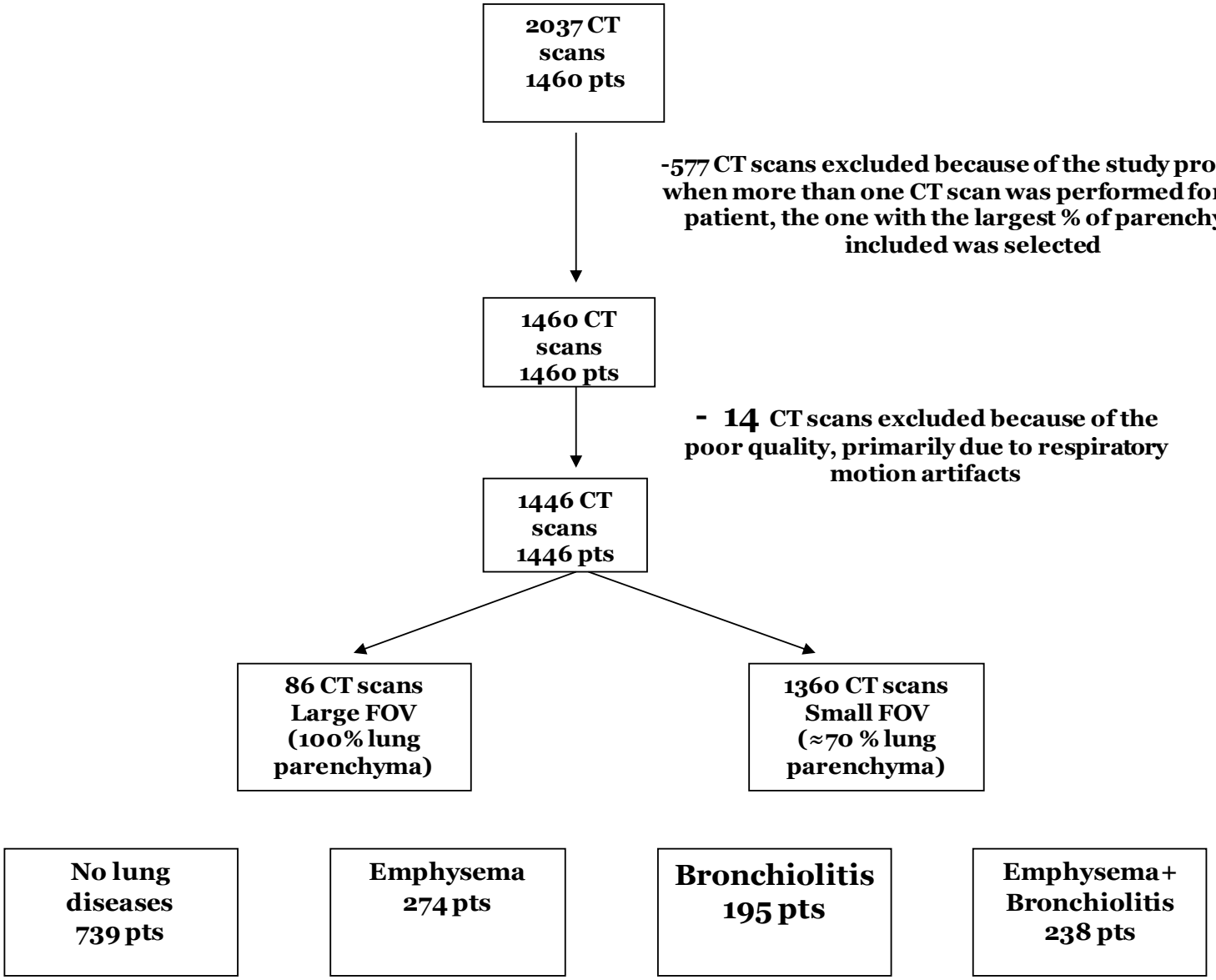
2. To determine the association between emphysema severity and clinical and sub-clinical cardiovascular events (MACE)

3. To study natural history of emphysema in HIV and identify factors associated with emphysema progression (EP), assessed on sequential thoracic CT scans

Methods - 1

- Consecutive chest and abdominal CT of 1446 HIV patients were analyzed for pulmonary findings by two trained observers using a standardized protocol.
- Parenchymal abnormalities were evaluated with a continuous scoring system (with each of 6 lobes scored 0-4 to describe the burden of lung parenchyma showing bullae, centrolobular or paraseptal emphysema or centrilobular micronodules and patchy ground-glass opacity, with or without fine fibrosis.

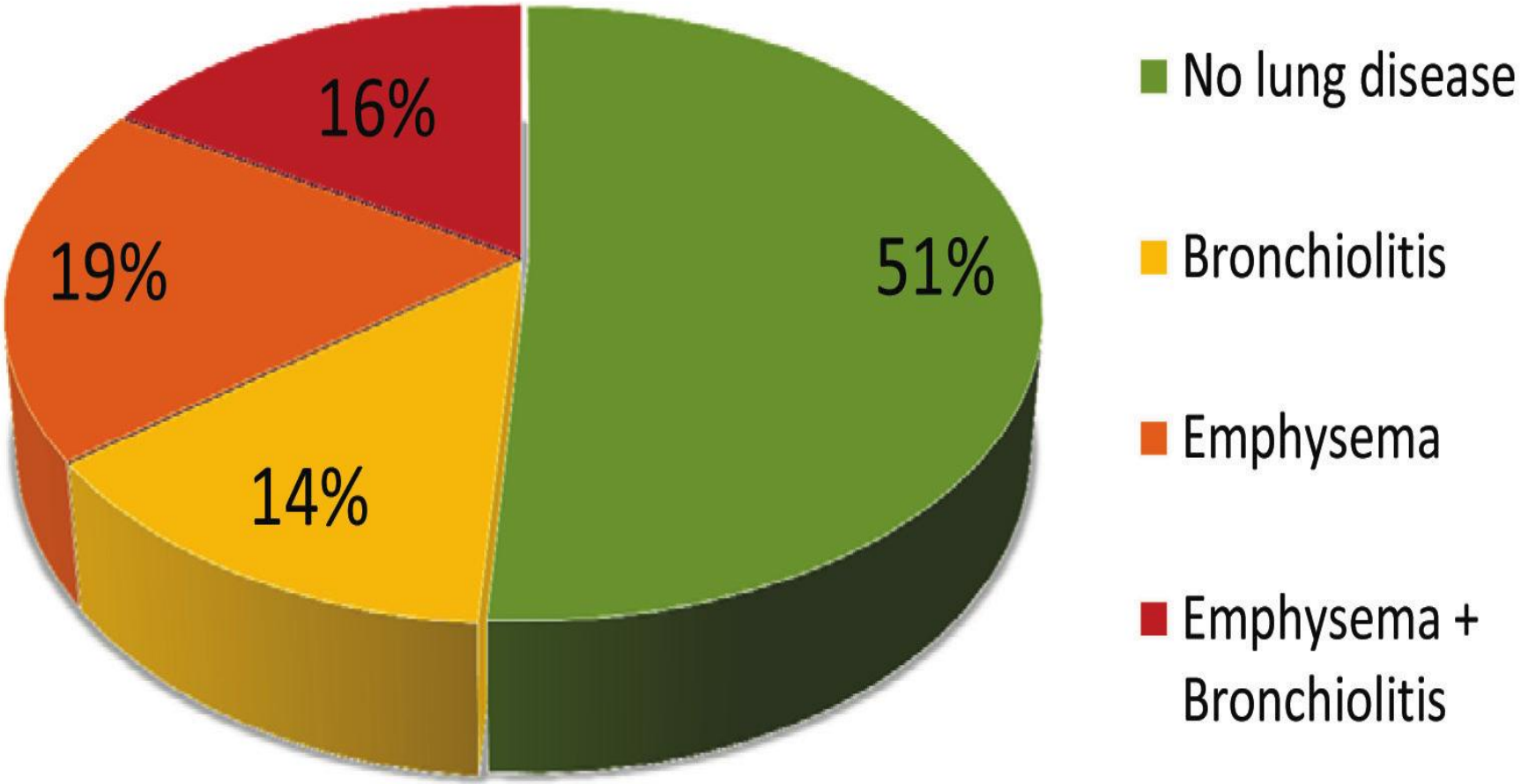
Flow Diagram of Patient Selection



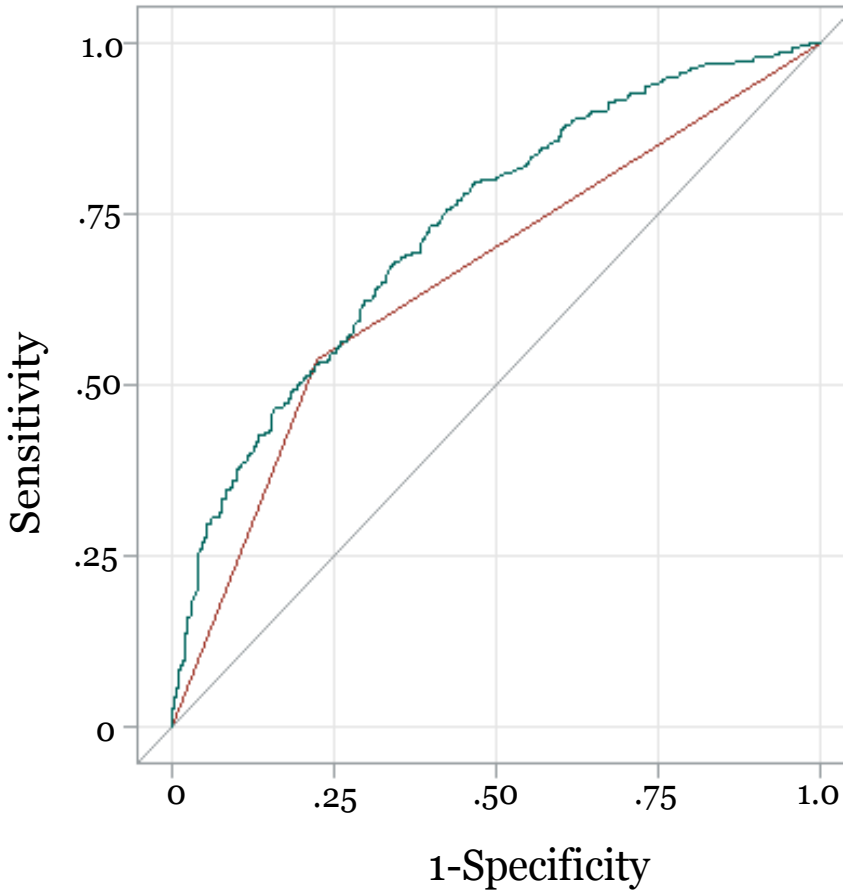
Clinical Characteristics of the 1,446 Consecutive Subjects With HIV Infection According to COPD Changes on CT Scans

Group	No lung disease	Bronchiolitis	Emphysema	Emphysema + Bronchiolitis	Global p value
No of Patients	739 (51%)	195 (13%)	274 (19%)	238 (16%)	<.0001
Age (years)	47.4±7.8	47.1±6.2	51.2±7.8*	49.4±7.1*†	<.0001
Current Smokers	176 (24%)	110 (58%)*	95 (35%)*+	177 (77%)*†+	< .0001
> 10 cigs/day	76 (10%)	61 (31%)+	57 (21%)+	131 (55%)+	< .0001
Intravenous Drug Use	137 (19%)	63 (32%)*	98 (36%)*	105(44%)*	< .0001
HIV exposure (months)	192±76	212±76*	211±68*	217±74*	<.0001
Nadir CD4 (cells/mm^3)	206±152	203±176	175±151*	187±181	0.0309
Body mass index (kg/m^2)	24.1±3.9	23.0±3.4*	23.8±3.7	22.8±3.3*†	< .0001
Visceral Adipose Tissue (cm^2)	132±75	115±58*	147±92*+	125±70†	< .0001
Prior Pneumonia	54 (8%)	25 (15%)*	41 (17%)*	39 (18%)*	0.0001
History of Asthma	5 (1%)	6 (4%)	1 (0%)	3 (1%)	0.0241
CRP (>1.1 mg/L)	322 (46%)	87 (48%)	120 (47%)	130 (59%)*+	0.0138
White blood cell (cells/µL)	5872±1687	6095±1902	6302±1931*	7498±2420*†+	<.0001
Regular Physical activity††	350 (49%)	72 (38%)*	115 (43%)	89 (39%)*	0.0088

Prevalence of CT lung abnormalities



Receiver operating characteristics curve to predict occurrence of COPD phenotypes on thoracic CT scans



Red line represents ROC of cigarette smoking (0.656; 95% CI, 0.631, 0.680)

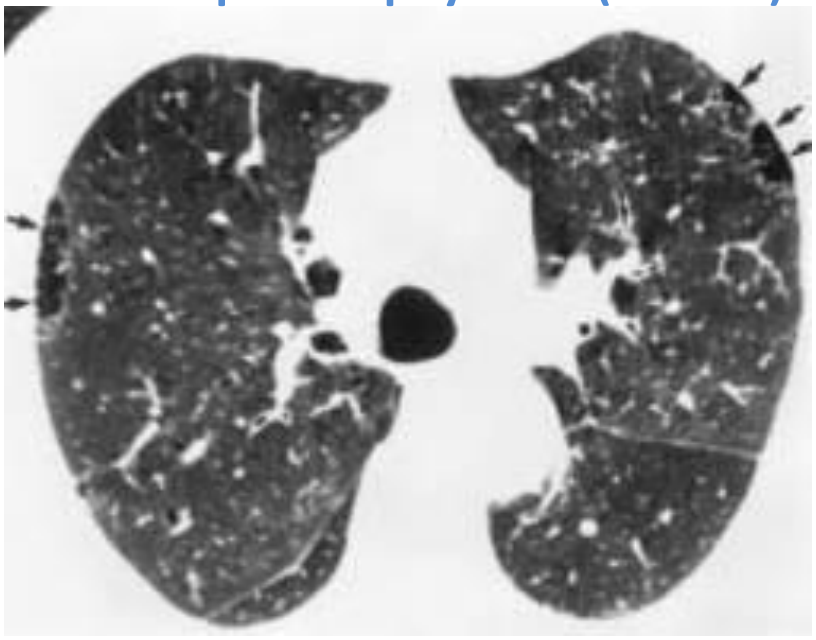
Green line represents ROC of cigarette smoking, peripheral WBC, history of intravenous drug use, and age (0.730; 95% CI, 0.699 to 0.744).

Pulmonary Function Test Results Of 275 HIV Infected Subjects Stratified According To CT Based Lung Abnormalities

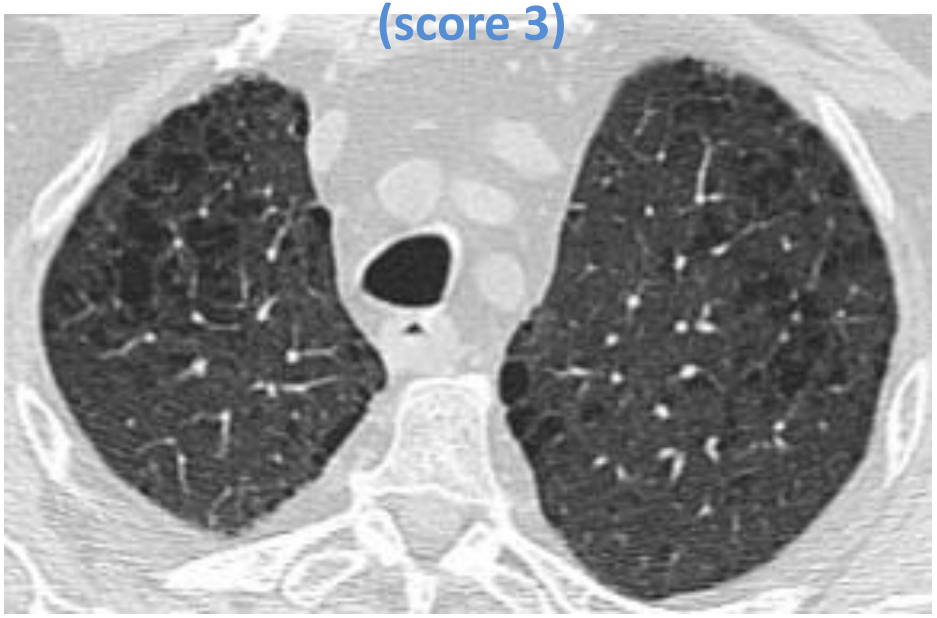
Group	No lung disease	Bronchiolitis	Emphysema	Emphysema + Bronchiolitis	Global p value
No of Patients	113 (41%)	48 (17%)	59 (21%)	55 (20%)	--
FEV1(% predicted)	104.4±13.8	106.2±16.3	105.1±17.5	105.3±20.1	0.9358
FVC (% predicted)	106.3±15.2	108.5±15.9	107.5±18.7	107.9±16.2	0.8539
FEV1/FVC (%)	79.7±6.5	80.1±6.5	78.0±7.5	78.5±6.4	0.2947
RV (% of predicted)	137.0±21.3	142.6±18.0	147.9±29.1	146.2±25.2	0.0174
TLC (% predicted)	113.4±12.3	117.9±15.4	118.0±11.5	116.6±13.2	0.0777
RV/TLC (%)	40.1±7.8	40.8±6.1	40.4±6.7	41.0±7.0	0.8858
DLCO (% predicted)	77.4±16.8	77.2±14.0	73.5±15.7	68.5±15.5	0.0054
DLCO/VA (% predicted)	89.7±18.9	88.4±14.8	83.2±18.0	76.4±20.2	0.0001

Normal lung

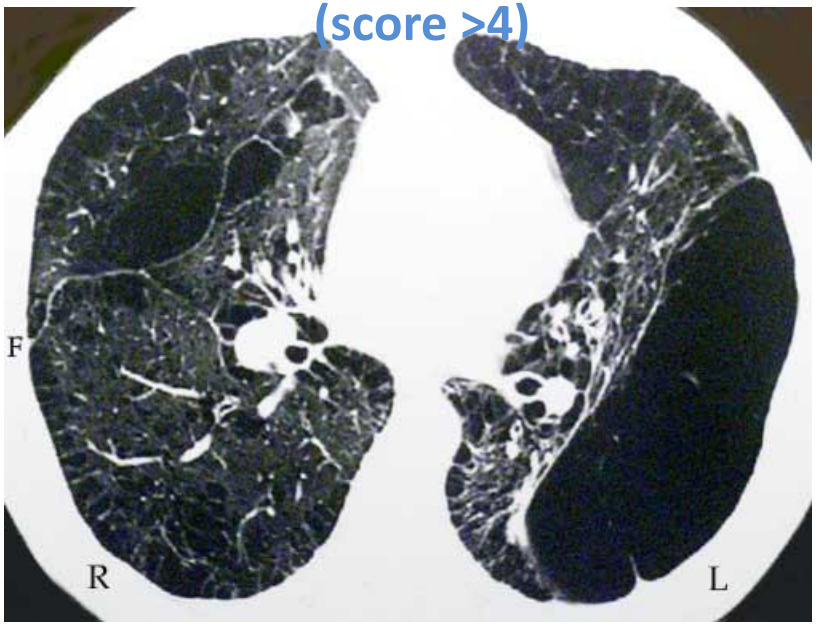
Paraseptal emphysema (score 2)



Paraseptal and centrolobular emphysema (score 3)



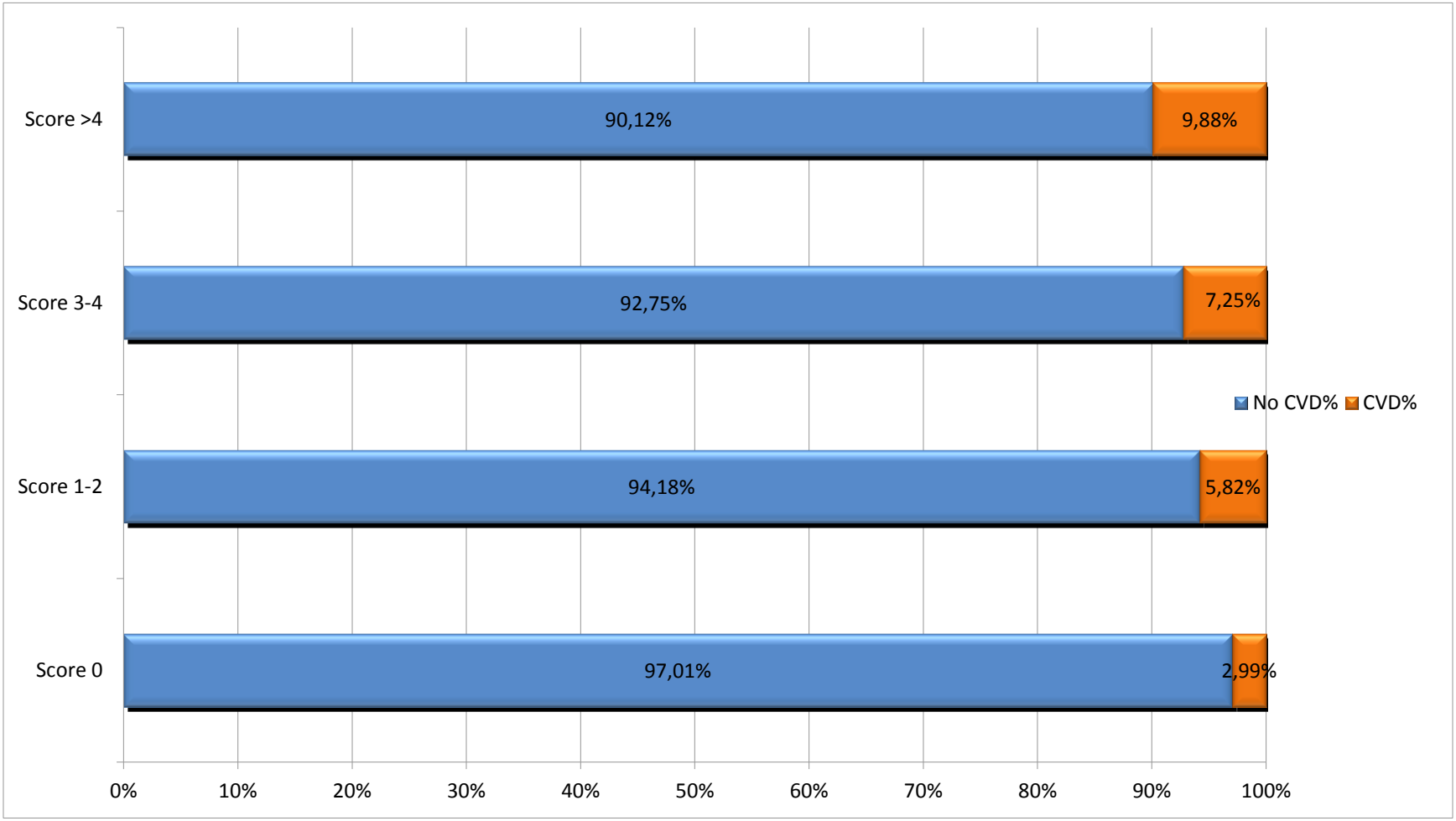
Paraseptal and centrolobular emphysema (score >4)



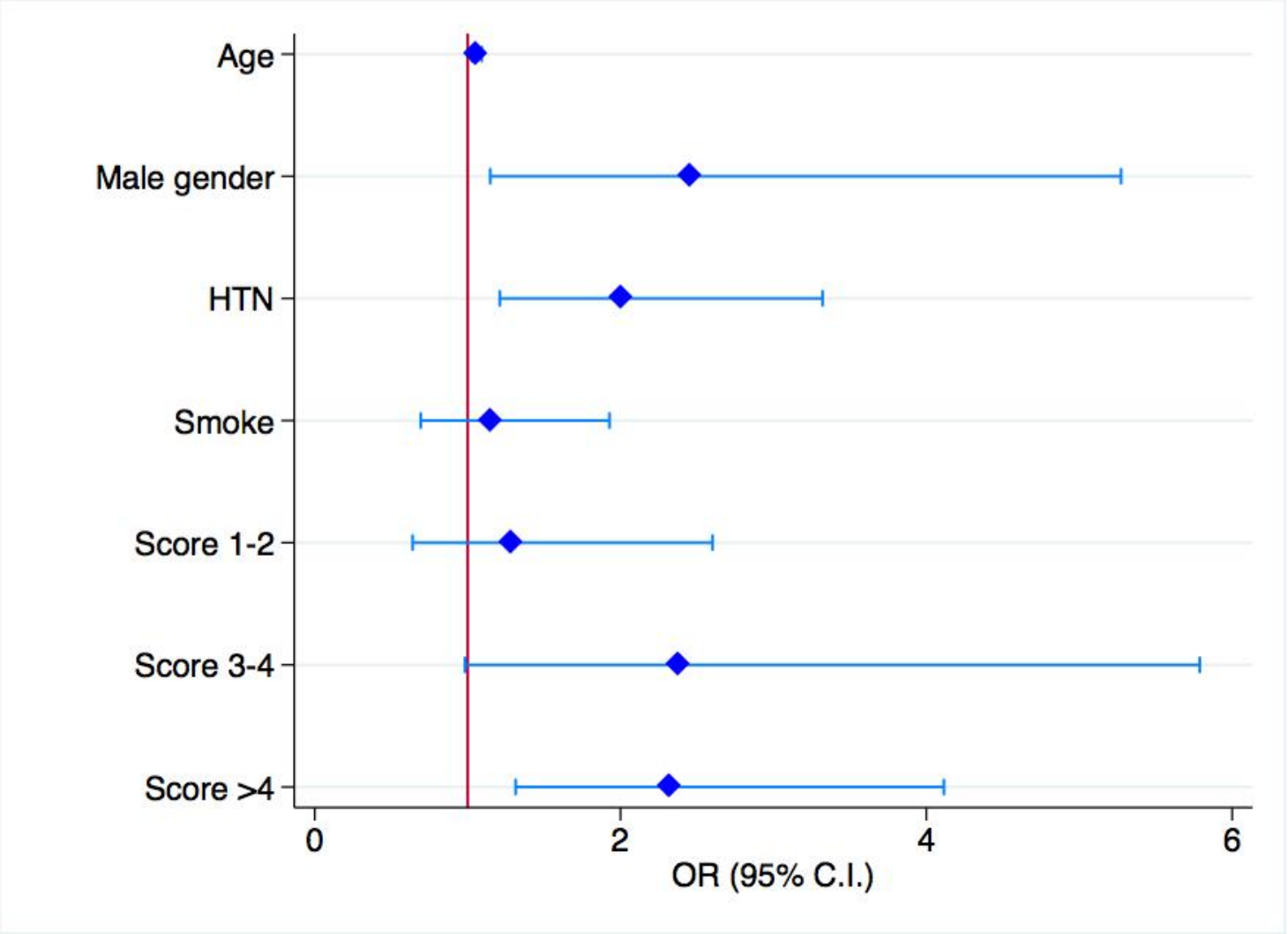
Cardiovascular Risk Factors and Health Outcomes for Emphysema

Emphysema Score (severity)	0 (none)	1-2 (mild)	3-4 (moderate)	>4 (severe)	P value for trend
Triglycerides	173±126	172±116	166±88	185±183	0.4
Cholesterol	195±44	190±44	191±44	192±43	0.3
HDL	47±14	45±13	50±14	44±13	0.0004
LDL	118±35	113±34	115±34	116±35	0.3
Apolipoprotein 1	143±27	138±28	152±26	137±26	0.0001
C-reactive protein	.85±9	.26±.3	0.5±.8	0.3±.3	0.0003
Omocysteine	11.8±11	11.4±5	10.4±4	11.7±6	0.5
D-dimer	309±468	406±1164	551±1091	532±2005	0.3
White Blood Cells	5915±1731	6394±1818	6554±2116	7252±2491	<0.0001
Framingham Risk Score	7.1±5.3	6.7±5.7	7.5±5.6	9.8±6	0.0001
Metabolic Syndrome	127(14%)	32(17%)	12(17%)	33(13%)	0.3
Hypertension	334 (35%)	89(47%)	69(46%)	98(38%)	0.013
T2DM	108(11%)	34(17%)	14(20%)	37(14)	0.02
CAC	34.8±174	50.3±138	78.5±261	67.2±187	0.0001
Major Adverse Cardiac Events	28(2.9%)	11(5.8%)	5(7.25%)	25(9.8)	<.0001

Prevalence of MACE (69 events) according to Emphysema severity score



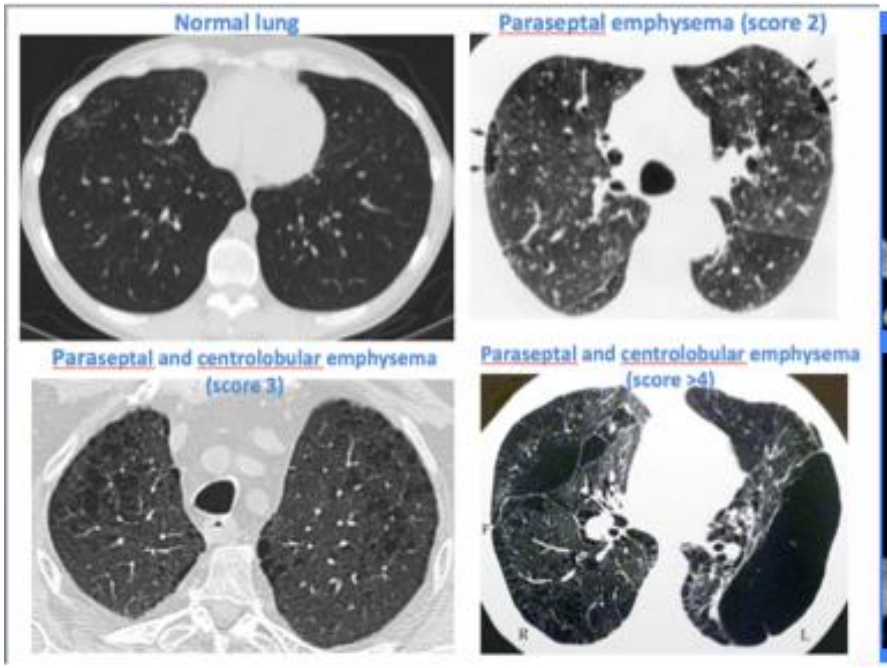
Logistic regression for MACE

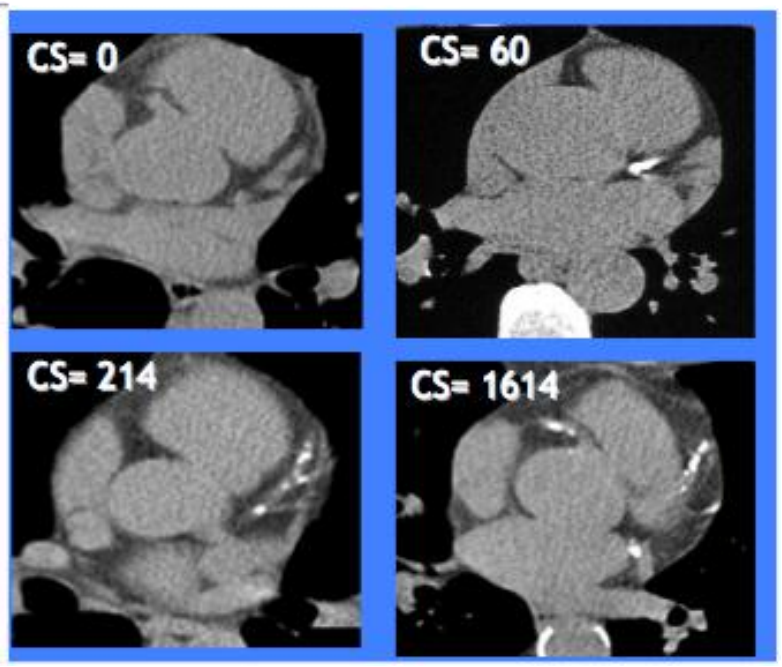


Methods - 2

Emphysema score

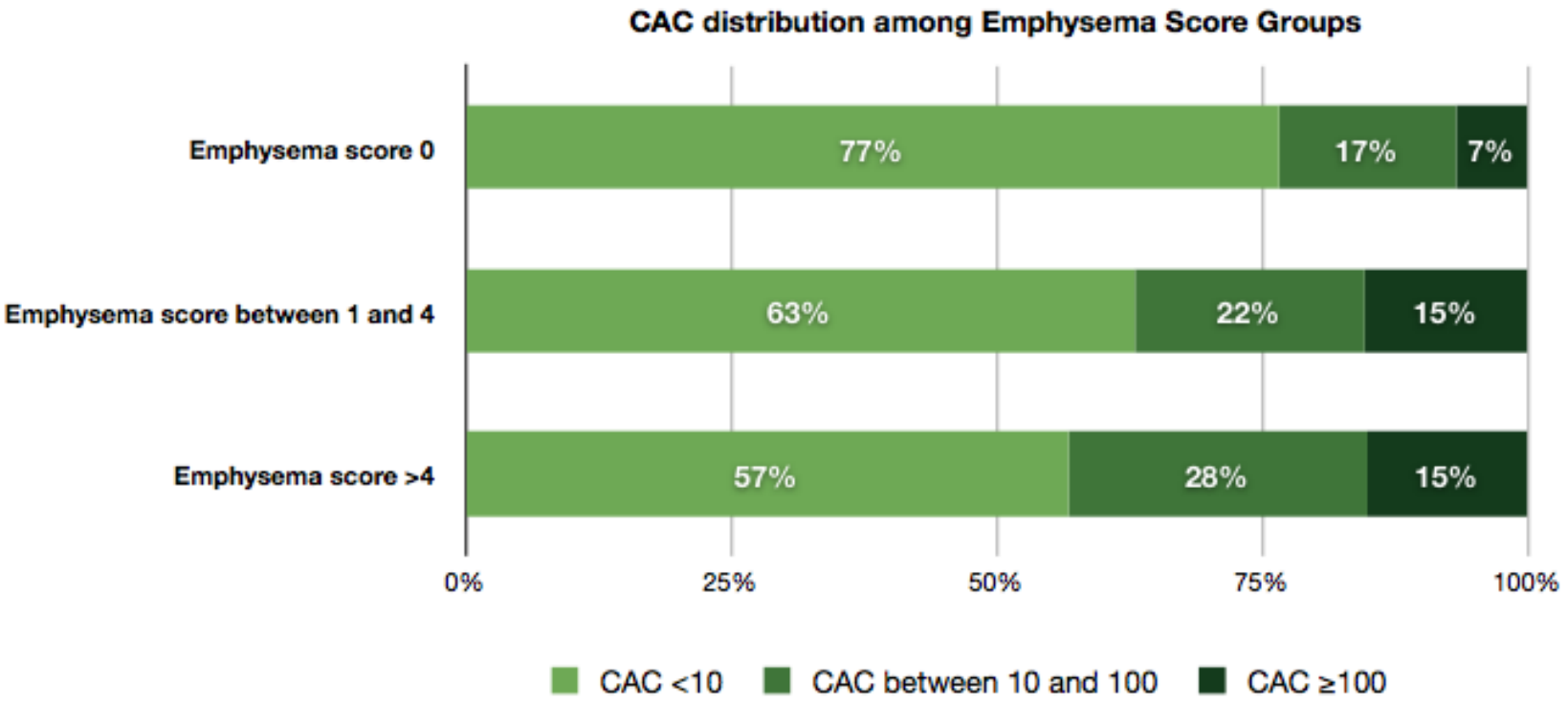
Coronary Calcium Score (CAC)





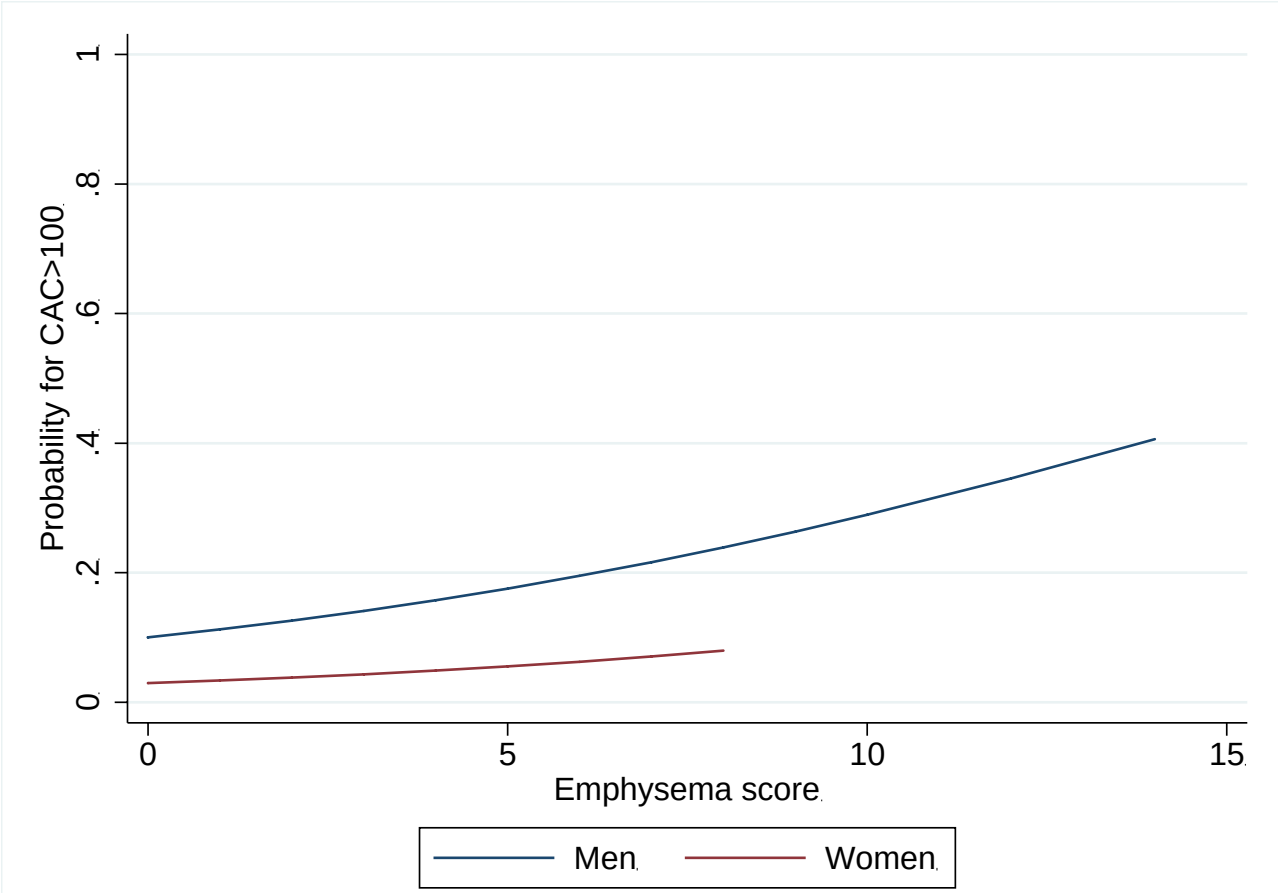
The CAC score was calculated according to the Agatston method

Associacion between CAC score according to Emphysema severity score



Emph. score 0 vs. 1-4 p<0.001
Emph. score 0 vs. >4 p<0.001
Emph. score 1-4 vs. >4 p=0.238

Association between CAC and Emphysema score



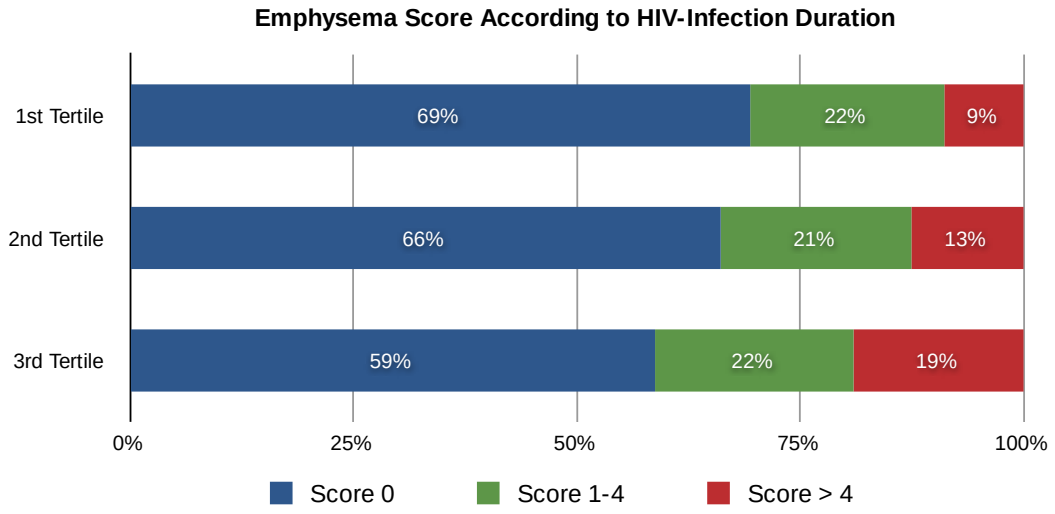
Each point of emphysema score added a 10% risk of CAC>100 (p=0.010)

Methods - 3

- Observational, prospective study of 448 consecutive HIV-infected antiretroviral therapy experienced patients (mean age 47,9 years, 24,1% females, 39,3% smokers) who underwent 2 sequential ECG-gated coronary artery calcium scoring CT scans.
- Images were reviewed by 3 radiologists by consensus to assess lung emphysema by using a visual semi-quantitative score (0 to 4) for each of 6 lobes.
- Emphysema progression was defined as an increase in emphysema score.

Emphysema progression and HIV exposure

B



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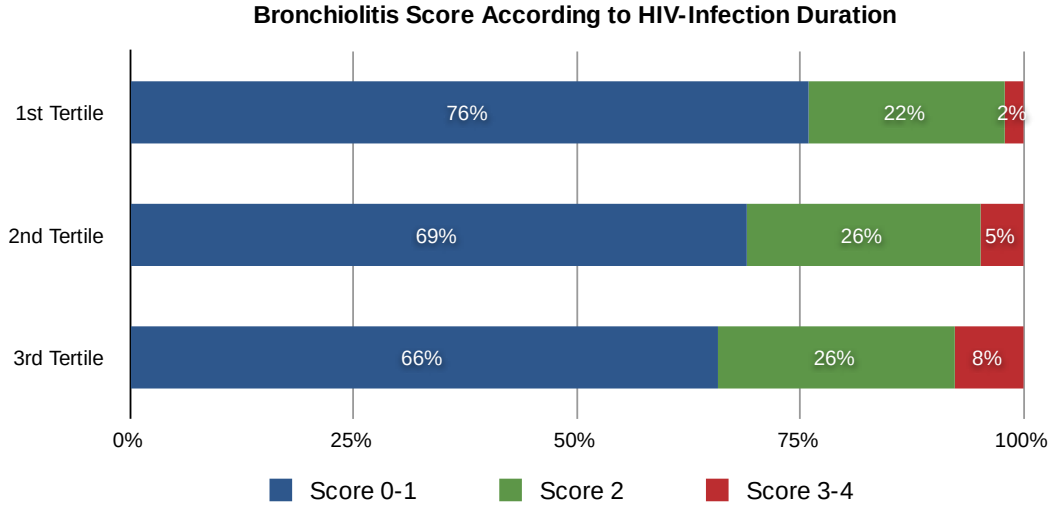


Results

448 patients with repeated scans were included
18 patients a visual progression (frequency of progression 4.02%).

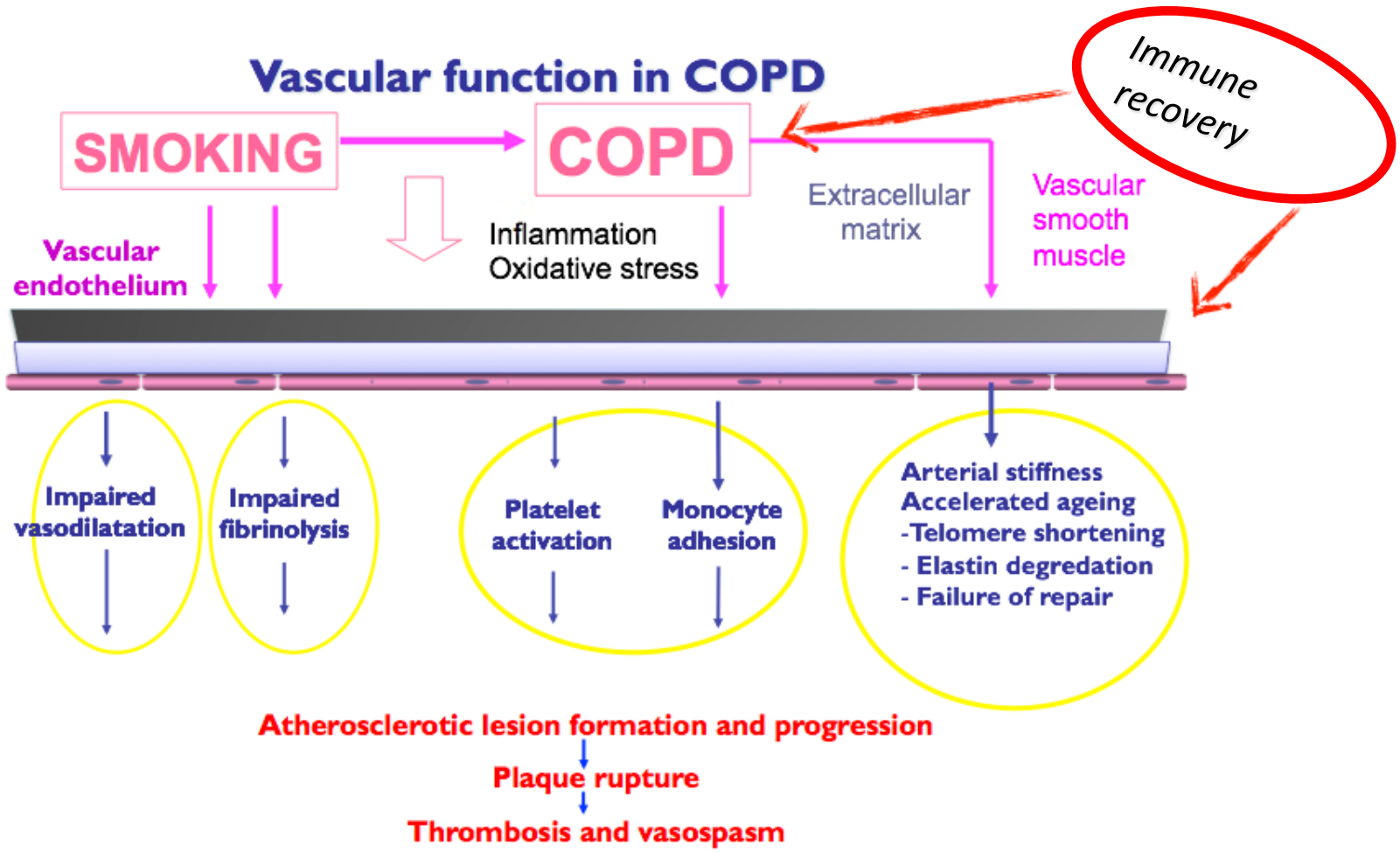
Multivariable analyses to identify redictors of enphysema progression

	OR	p-value
<10 cigarettes per day smoked	2,82	0,14
>10 cigarettes per day smoked	3,36	**0,04**
Time interval between the first and the last scan	1,51	**0,03**
HIV infection duration	1,01	**0,01**

?

Take home messages

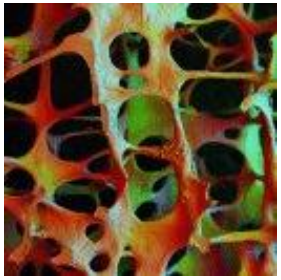
1. Morphologically diagnosed COPD is present in 50%, of HIV infected patients who were not evaluated for respiratory complaints
2. This high disease burden and rapid progression suggest that smoke related lung disease in HIV could be included among the HIV Associated Non AIDS (HANA) conditions describing a premature aging lung process
3. COPD is an independent risk factor for clinical and subclincal cardiovascular disease
4. There is an urgent need to tackle the enormous burden of lung disease: COPD prevention, diagnosis and treatment must be developed in PLWH


Vascular function in COPD
SMOKING
COPD
Immune recovery
Vascular endothelium
Inflammation
Oxidative stress
Extracellular matrix
Vascular smooth muscle
Impaired vasodilatation
Impaired fibrinolysis
Platelet activation
Monocyte adhesion
Arterial stiffness
Accelerated ageing
-Telomere shortening
- Elastin degredation
- Failure of repair
Atherosclerotic lesion formation and progression
Plaque rupture
Thrombosis and vasospasm

HIV Associated Non AIDS (HANA) Conditions

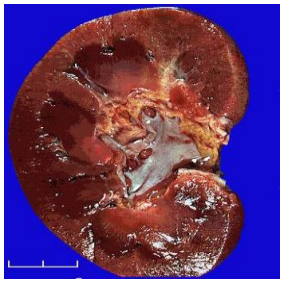
Cardiovascular

Infectious and
Non infectious Cancers



Osteopenia
Osteoporiosis

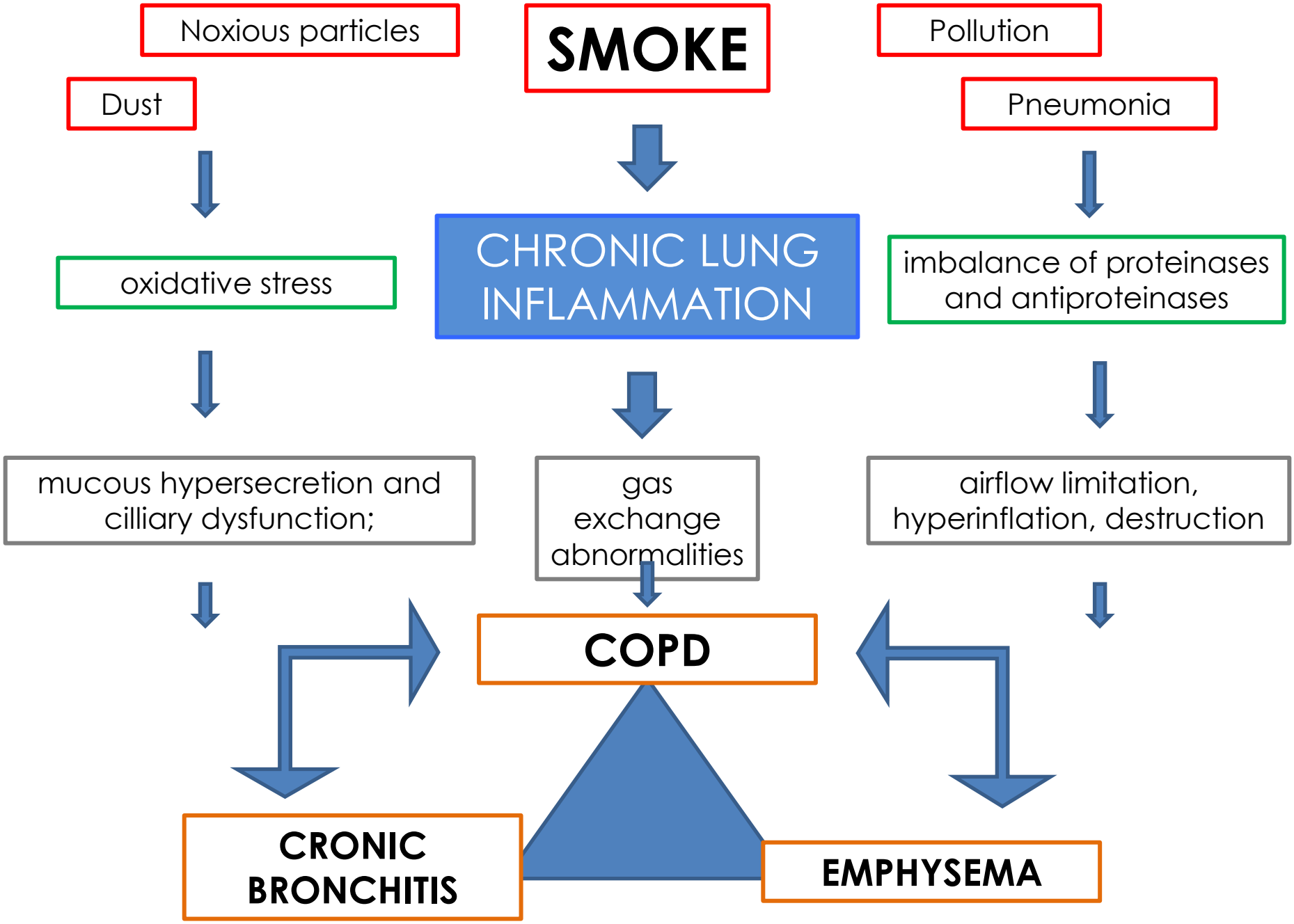
Liver diseases



Renal Diseases

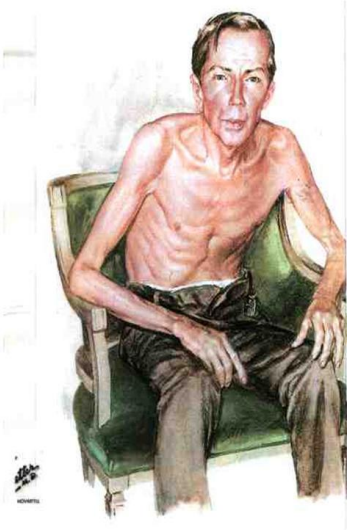
Neurocognitive decline

- ✓ Are associated with advancing age an chronic inflammations
- ✓ After adjustment for established risk factors, association with HIV remains
  - Compare to demographically and behaviorally similar uninfected controls
  - Weaker (<2 fold) associations may be due to inadequate adjustment for risk factors



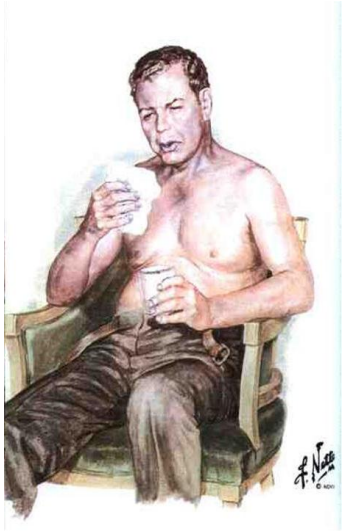
Celli, MacNEe Eur Respir J 2004; 23: 932–946

In the past anthropometric characteristics were used to differentiate emphysema patients from chronic bronchitis patients (1)

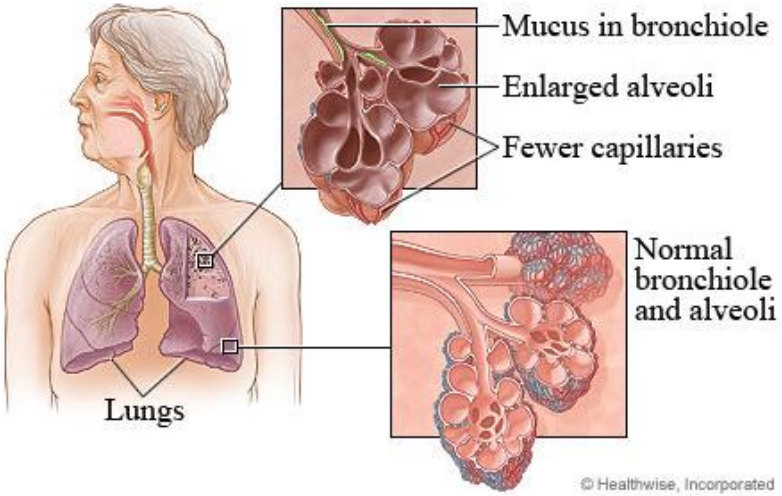


The **'pink puffer'** (emphysematous type) was characterized as being thin in appearance with frequent major weight loss

The**'blue bloater'** (chronic bronchitic type) was frequently obese with no marked weight loss, except occasionally in terminal stages

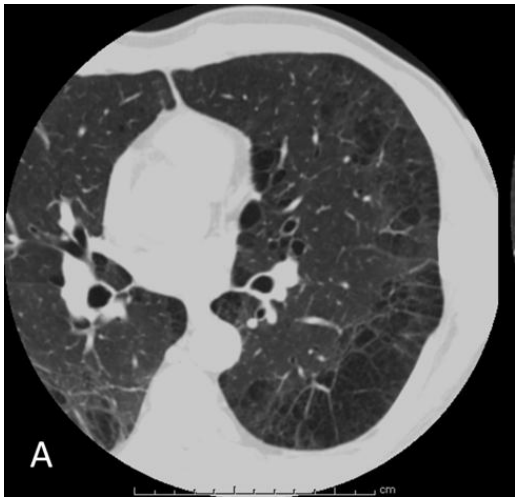


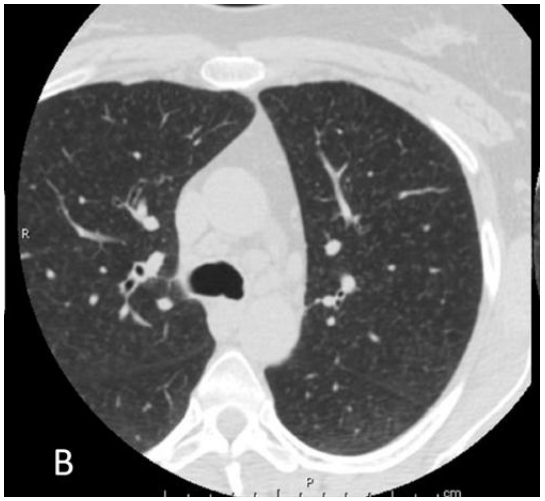
Now we know that COPD comprises pathological changes in four different compartments of the lungs (central airways, peripheral airways, lung parenchyma and pulmonary vasculature), which are variably present in individuals with the disease

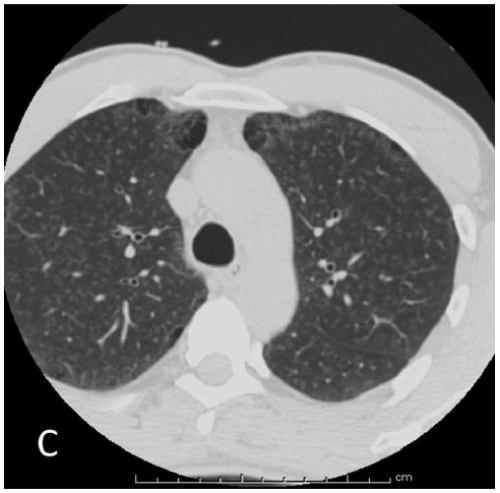


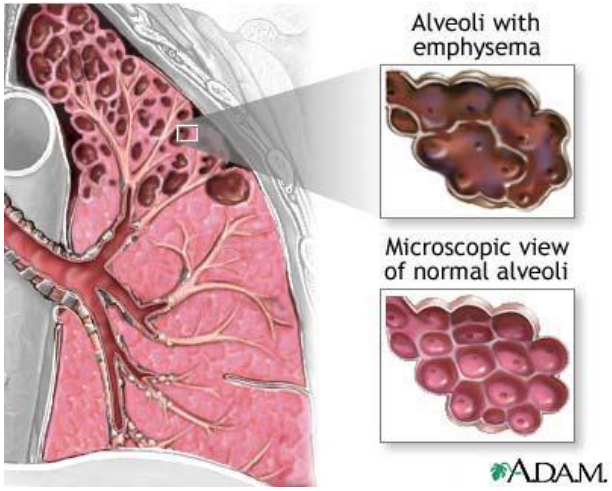
Airway abnormalities and emphysema interact in a complex fashion in the development of airflow limitation in COPD

(1)Filley G F, et al. Chronic obstructive bronchopulmonary disease. 2. Oxygen transport in two clinical types. Am J Med 1968; 44:26-38
(2)M.G. CosioEur Respir J 2001; 18: Suppl. 34



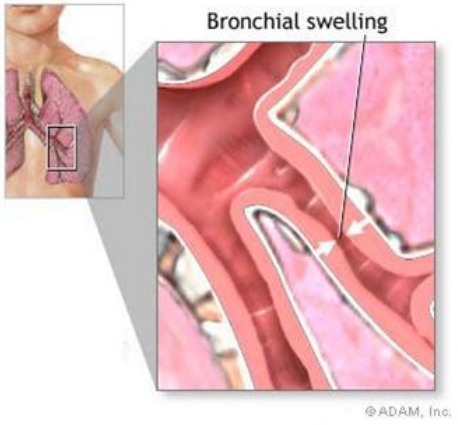






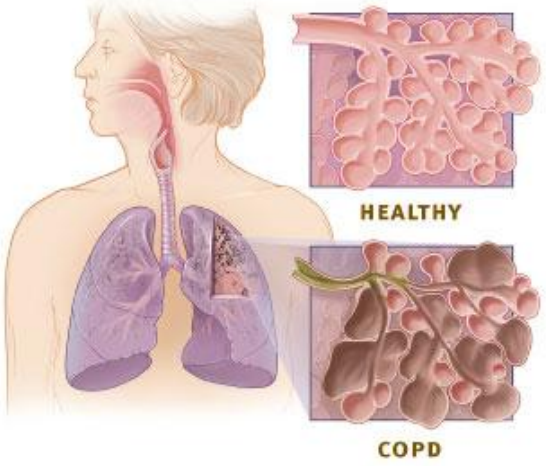
Emphysema:

Abnormal, permanent enlargement of air spaces distal to the terminal bronchioles, accompanied by the destruction of their walls.



Bronchiolitis :

the airway becomes obstructed from swelling of the bronchiole walls



Both patterns can be present in COPD

Copd in HIV

George MP et al. 2009
Prevalence of airway obstruction 6.8%.
Age , pack-year smoking history , previous bacterial pneumonia, and HAART use are independent predictors of decreased FEV_1/FVC.

Drug use

Bacterial pr

Risk of COPD among patients infected with HIV

HAART medications?

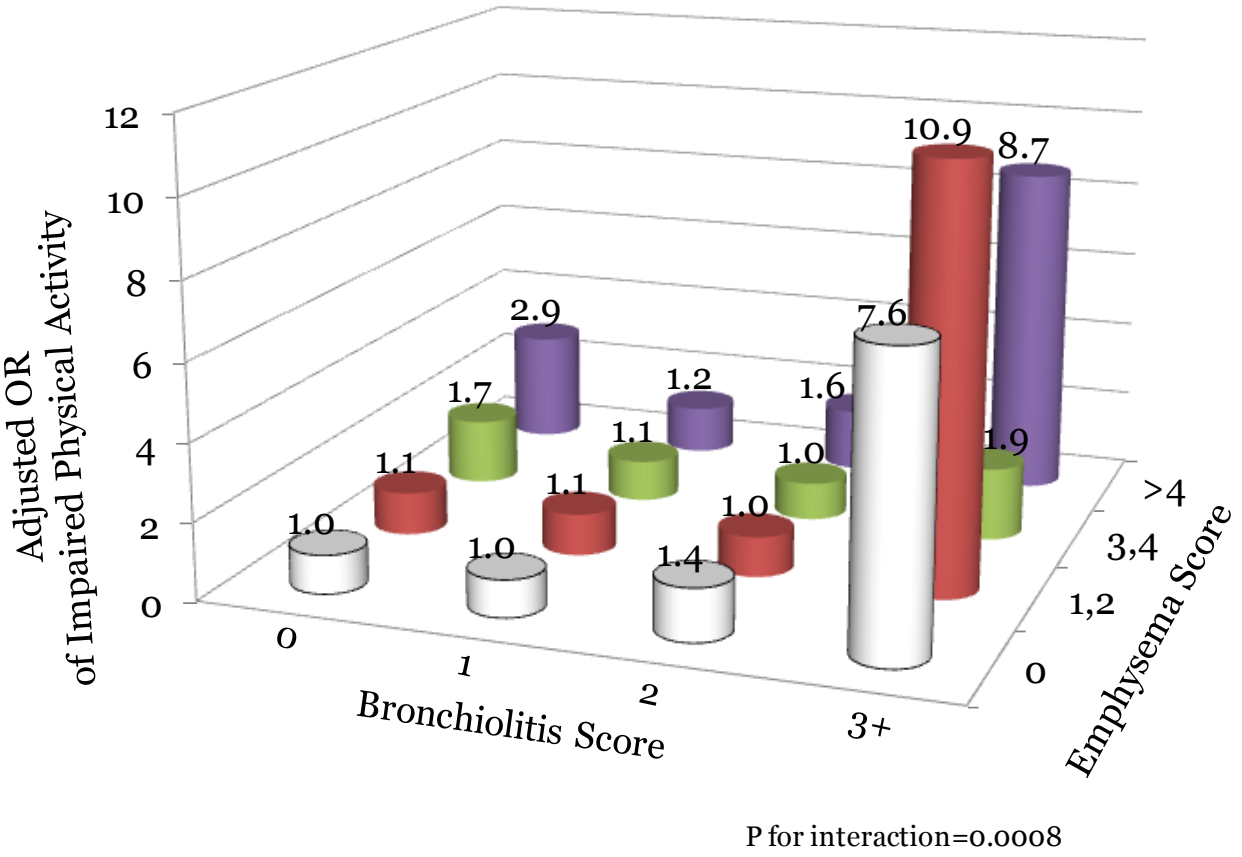
HIV replication?

PCP colonisation

Crothers et al. 2011
Case-control: 3707 HIV patients. Pulmonary conditions diagnosos based on ICD-9 codes. HIV infectionis independently associated with a significantly higher risk of COPD).

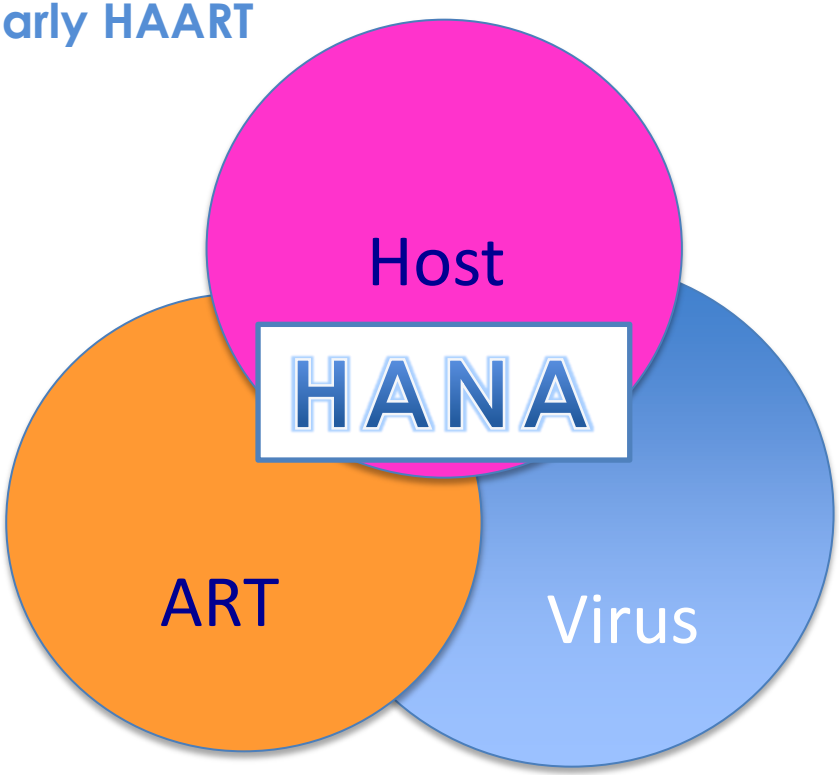
Drummond et al 2010
the prevalence of airway obstruction was 15.5%.No influence of HIV status

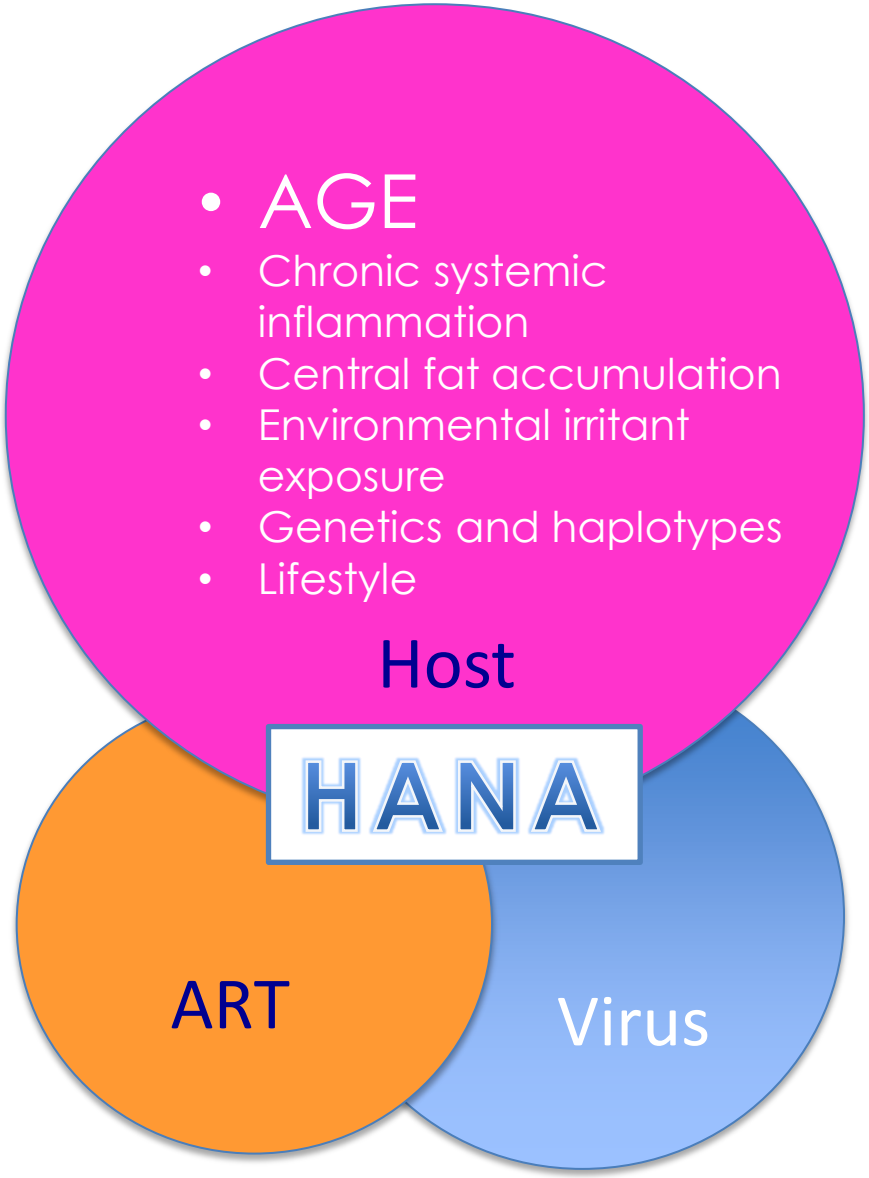
The Synergistic Interaction of Emphysema with Bronchiolitis Scores on The Risk of No Regular Physical Activity



P for interaction=0.0008

Early HAART

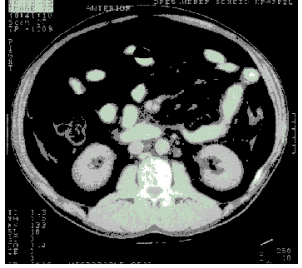




Late HAART
…ops
Immune-recovery Era

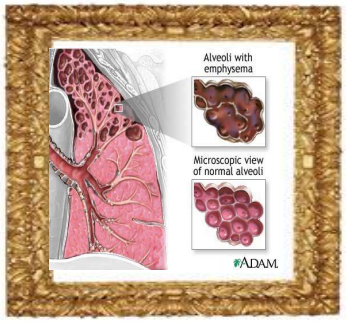
Glucose metabolism impairment

Dyslipidaemia



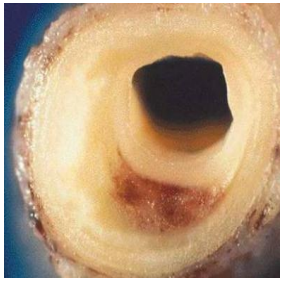
Abnormalities of body composition

LIPODYSTROPHY and Non-infectious Co-morbidities WILL CONTINUE TO DEPICT the HIV specific Ageing phenotypes



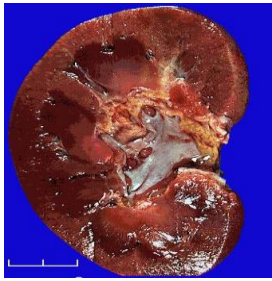
COPD

HAND



CVD

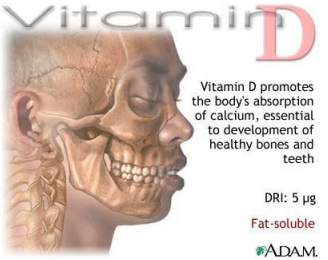
Hepatic steatosis



Bone & Kidney disease

Depression

HT



Vit D

T2D

Cancer

Sexual Dysfunction