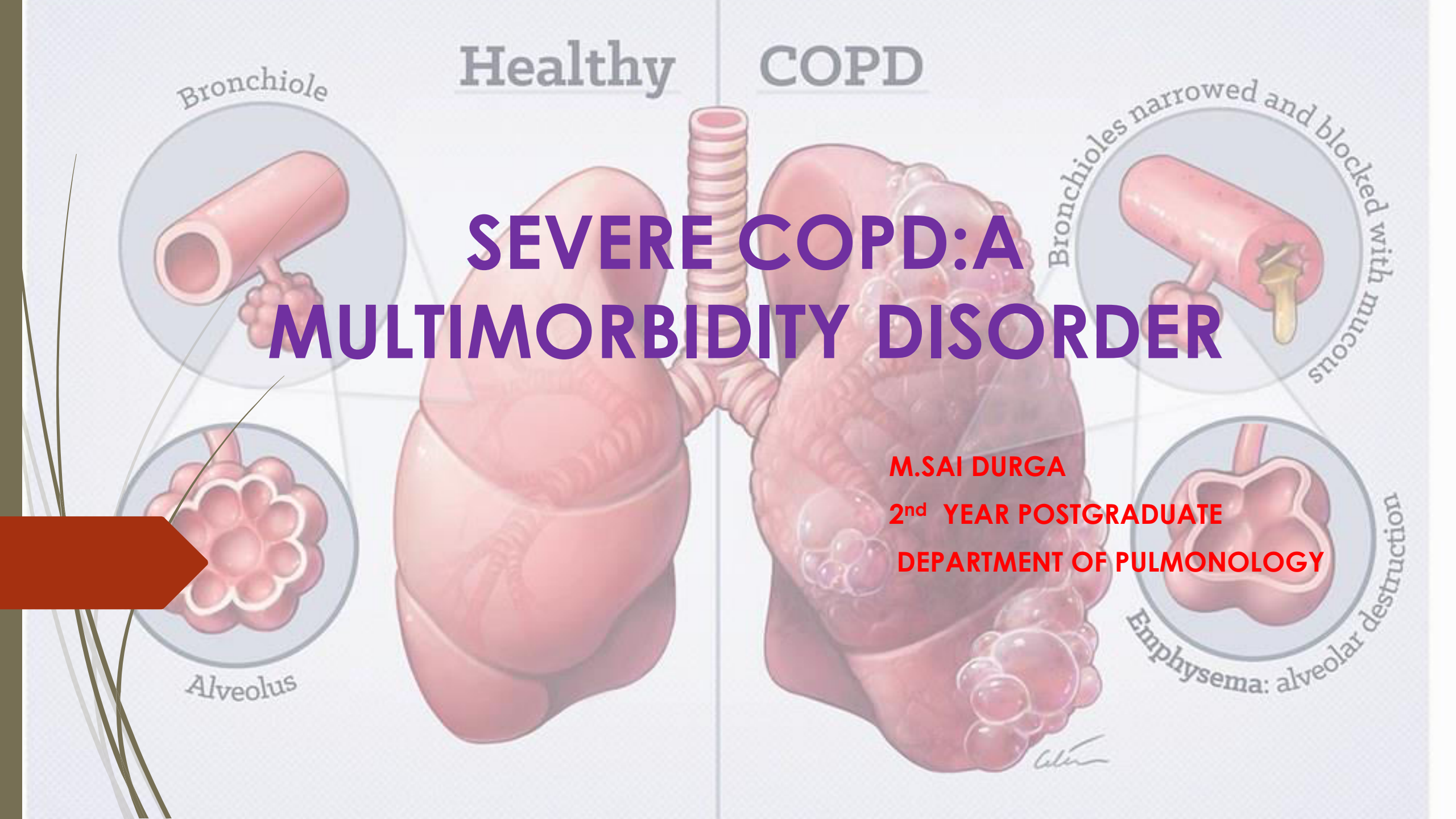


SEVERE COPD:A MULTIMORBIDITY DISORDER

M.SAI DURGA

2nd YEAR POSTGRADUATE

DEPARTMENT OF PULMONOLOGY

COPD:

- Chronic Ostructive Pulmonary Disease is a common,preventable and treatable disease that is characterised by persistant respiratory symptoms and airflow limitation that is due to airway/alveolar abnormalities usually caused by significant exposure to noxious stimuli or gases.

- **WHY COPD IMPORTANT?**
- By 2020: Third leading cause of death in the world and causing
- 6 million deaths annually worldwide due to COPD
- Important cause of multiple morbidties like:Cardiovascular problems
- Pul atretrial hypertension
- Anxiety and Depression
- Osteoporosis
- Obesity and malnutrition
- Diabetes and metabolicsyndrome
- Sleep disturbances
- Anaemia
- Pre-Mture Aging

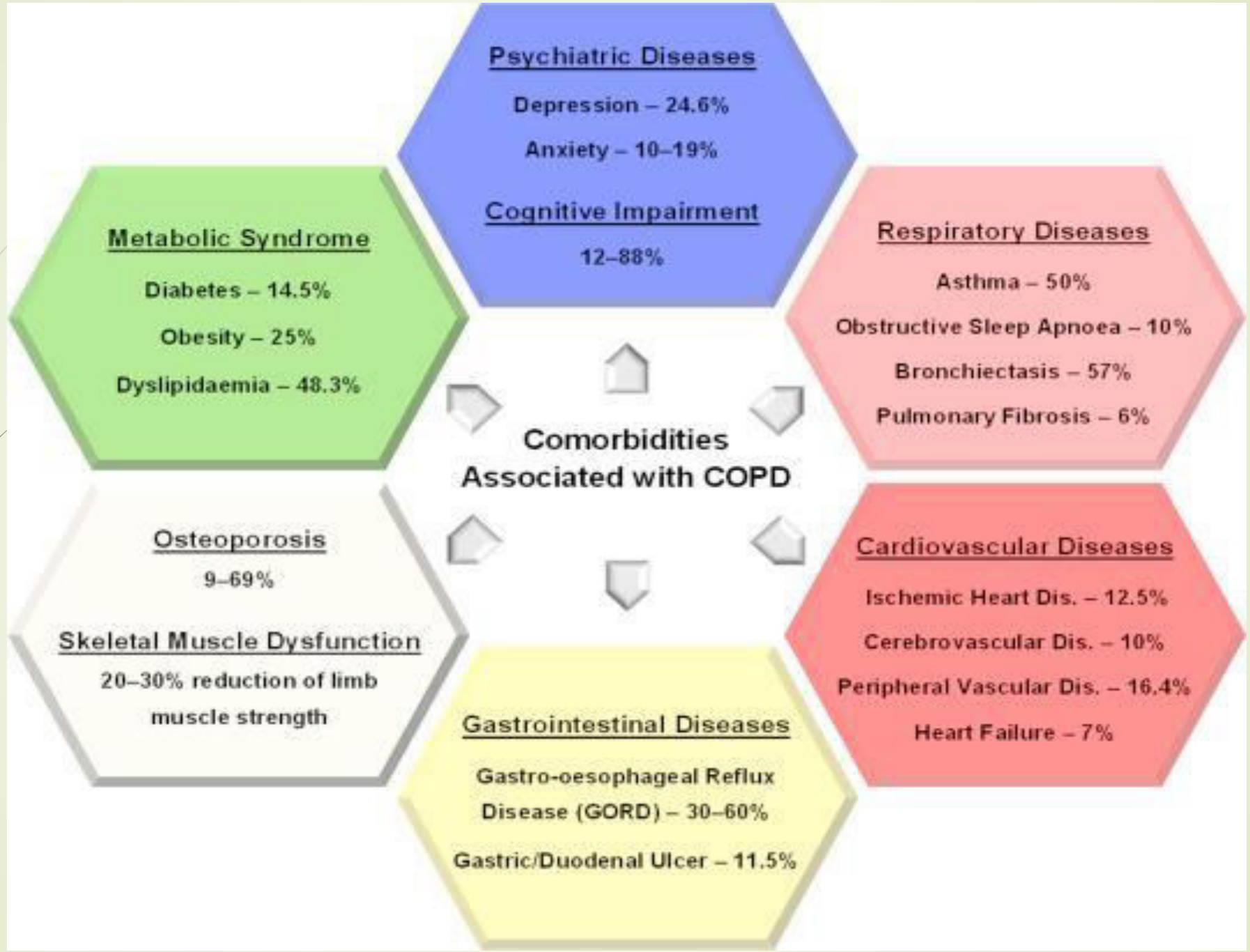

Psychiatric Diseases
Depression – 24.6%
Anxiety – 10–19%
Cognitive Impairment
12–88%
Metabolic Syndrome
Diabetes – 14.5%
Obesity – 25%
Dyslipidaemia – 48.3%
Respiratory Diseases
Asthma – 50%
Obstructive Sleep Apnoea – 10%
Bronchiectasis – 57%
Pulmonary Fibrosis – 6%
Comorbidities Associated with COPD
Osteoporosis
9–69%
Skeletal Muscle Dysfunction
20–30% reduction of limb muscle strength
Cardiovascular Diseases
Ischemic Heart Dis. – 12.5%
Cerebrovascular Dis. – 10%
Peripheral Vascular Dis. – 16.4%
Heart Failure – 7%
Gastrointestinal Diseases
Gastro-oesophageal Reflux Disease (GORD) – 30–60%
Gastric/Duodenal Ulcer – 11.5%

Table Prevalence of Common Comorbidities in Chronic Obstructive Pulmonary Disease

Comorbidity	Prevalence (%)	Study
Lung cancer	9	Divo et al 2012[11]
Atrial fibrillation	13-14	Divo et al 2012[11]; Mapel et al 2005[17]
Atherosclerosis	53	Vanfleteren et al 2013[14]
Hypertension	40-48	Mannino et al 2008[13]; Vanfleteren et al 2013[14]
Congestive heart failure	16-24	Divo et al 2012[11]; Mapel et al 2005[17]
Coronary artery disease	14-34	Divo et al 2012[11]; Mapel et al 2005[17]; Cazzola et al 2010[20]
Left heart failure	9	Kessler et al 2011[15]
Diabetes	13-19	Mannino et al 2008[13]; Kessler et al 2011[15]; Cazzola et al 2010[20]
Anxiety	21-28	Vanfleteren et al 2013[14]; Di Marco et al 2006[16]
Depression	9-19	Vanfleteren et al 2013[14]; Kessler et al 2011[15]; Di Marco et al 2006[16]
Sleep apnea	8	Kessler et al 2011[15]
Bronchiectasis	57	Martínez-García et al 2013[9]
Pulmonary fibrosis	6	Divo et al 2012[11]
Pulmonary hypertension	50	Thabut et al 2005[18]
Osteoporosis	11-45	Vanfleteren et al 2013[14]; Kessler et al 2011[15]; Jørgensen et al 2007[19]; Cazzola et al 2010[20]

- Common ground for these extrapulmonary manifestation is Chronic Inflammation.

- WHY THESE CO-MORBIDITIES IMPORTANT?
  - All these conditions increases the morbidity of COPD which is they increase the Hospitalisation and Health care costs.
  - Makes management of COPD difficult.
  - Causes death independently of Respiratory Failure.
  - Influences prognosis of patients with COPD.

Co-morbidity	HR (95% CI)*	*P* value
Neoplasm		
Lung cancer†	2.02 (1.63, 2.51)	<.001
Cardiac		
Atrial fibrillation/flutter†	1.56 (1.25, 1.96)	<.001
Congestive heart failure†	1.33 (1.06, 1.68)	.02
Coronary artery disease†	1.27 (1.06, 1.54)	.01
Endocrine		
Diabetes with neuropathy†	1.54 (1.05, 2.27)	.03
Psychiatric		
Anxiety†,‡	13.76 (2.13, 88.63)	.006
Depressive symptoms§	1.07 (1.00, 1.14)	-
Pulmonary		
Pulmonary fibrosis†	1.51 (1.13, 2.03)	.006
Bronchiectasis‖	2.54 (1.16, 5.56)	.02

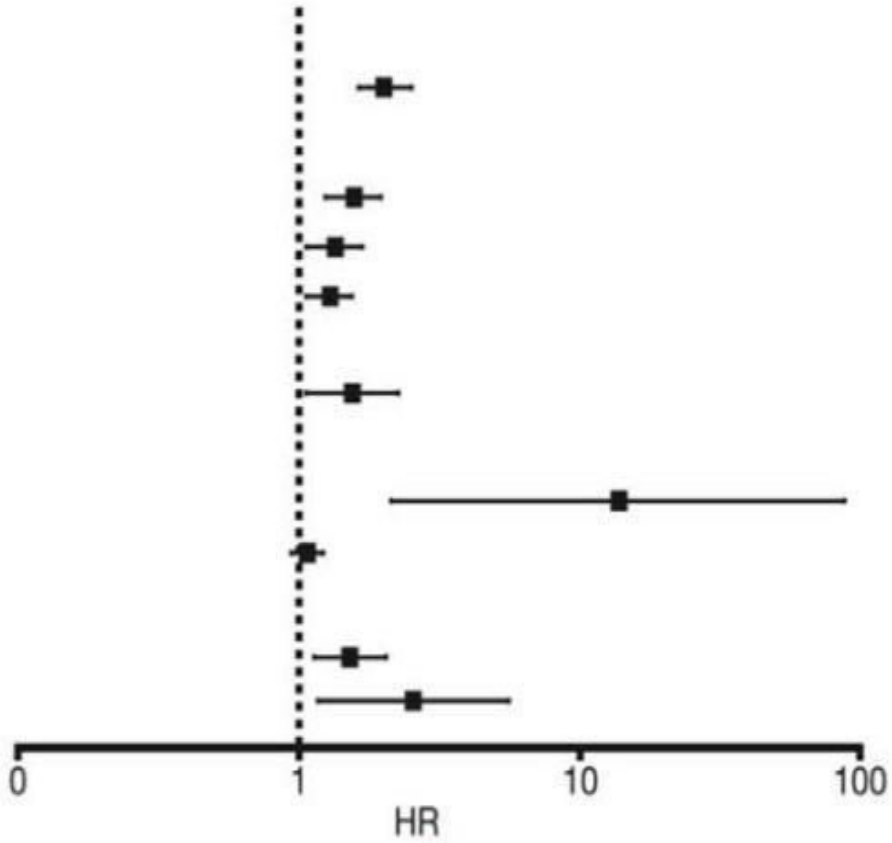


Figure Mortality association of comorbidities in patients with chronic obstructive pulmonary disease.[11]

CI = confidence interval; HR = hazard ratio.

*Multivariate analyses using Cox proportional hazards regression.

†Divo et al 2012.[11]

‡Measured in the female cohort.

§de Voogd et al 2009.[10]

‖Martínez-García et al 2013.[9]

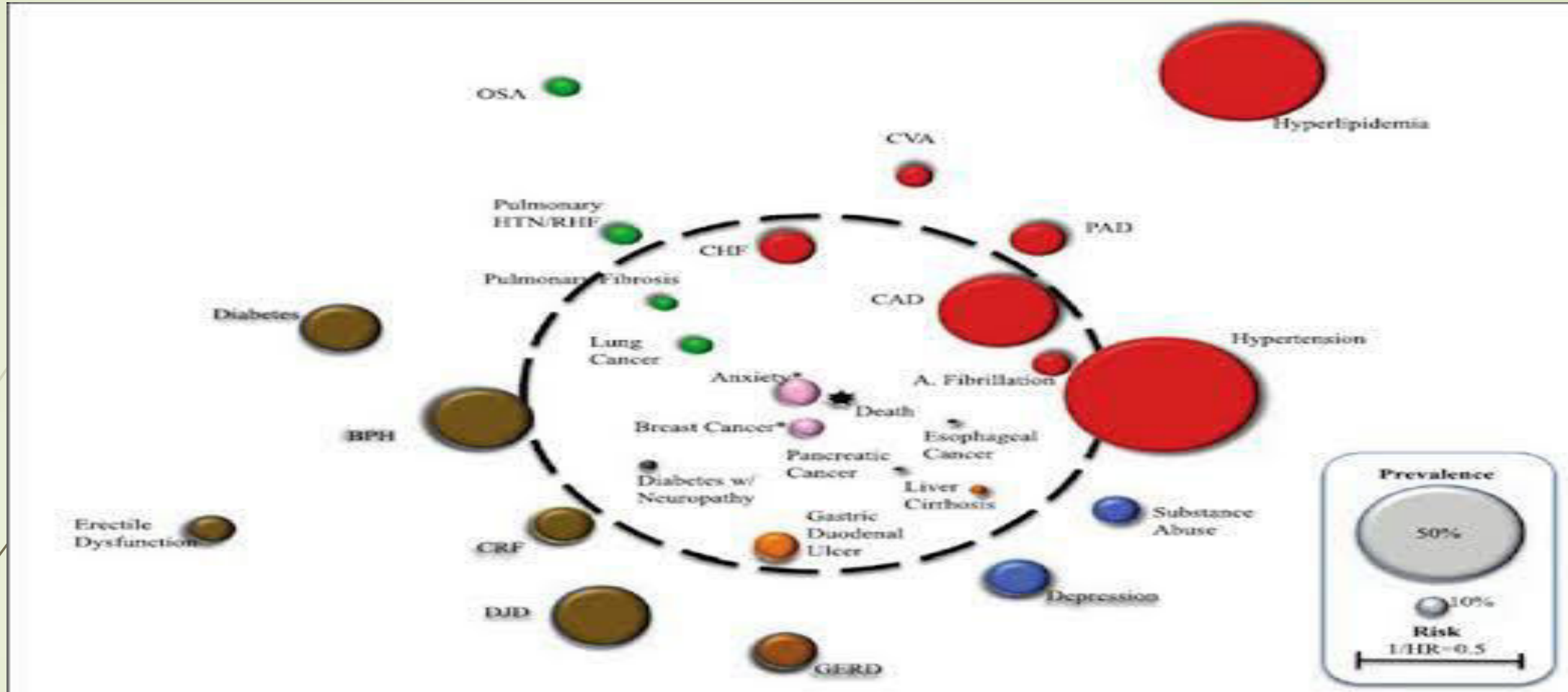


Figure 1. The Cormorbidome: A Graphic Expression of Comorbidities With More Than 10% Prevalence in the Entire Cohort[a]

The *comorbidome* is a graphic expression of comorbidities with more than 10% prevalence in the entire cohort, and those comorbidities with the strongest association with mortality (hazard ratio [HR], .1; 95% confidence interval, .1; P < 0.05). The area of the circle relates to the prevalence of the disease. The proximity to the center (mortality) expresses the strength of the association between the disease and risk of death. This was scaled from the inverse of the HR (1/HR). All bubbles associated with a statistically significant increase in mortality are fully inside the dotted orbit (1/HR ,1). Bubble colors represent organ systems or disease clusters (cardiovascular = red, female-specific comorbidities = pink, pulmonary = green, psychiatric = blue, others = brown and orange).

[a]Reproduced with permission from *American Journal of Respiratory and Critical Care Medicine* [7].

CARDIO VASCULAR CO-MORBIDITIES:

- Vascular and Heart diseases are the most important co-morbidties in COPD cause they have direct impact on Patients survival.
- Mainly mediated by:
- 1) **Endothelial dysfunction**:circulating Endothelial progenitor cells which are responsible for maintaining Endothelial Integrity gets decreased in systemic circulation and increased in pulmonary circulation in COPD patients as a result of Chronic Inflammation and
- 2) **Coagulopathy**:systemic Inflmmation induces PRO-COAGUBLE STATE .In basal state COPD patients high levels of Tissue factor and factor 7a and fibrin is resistant to lysis.Thereby imcreases the risk of stroke.

- 2)Systemic venous thrombo embolism and COPD:

Increases the hospitalistaion stay by 4 days and mortality by 255 if undiagnosed.

Virchows Triad present which increases the risk of SVTE.

Should be suspected when there is chestpain,cough,syncope, ↓pco2.

- 3)Pulmonary artery disease and COPD:

pulmonary artery remodeling leads to Pulmonary artery hypertension.

- Remodelling is due to:Endothelial dysfunction and coagulopathy
- Hypoxic vasoconstriction
- Destruction of pulmonary capillary bed by Emphysema
- Smoking induced inflammatory induction of vascular wall
- Shear stress due to redistribution of blood flow

- Pulmonary artery hypertension:pulmonary artery pressure>25mmHg
- pulmonary artery occlusion pressure >15mmhg
- PVR>3 wood units
- Should suspect when there is :dyspnea,desaturation during 6min walking test,disproptionate reduction in DLCO,clinical/biological signs of RVD not explained by LVF or loud HS in pulmonary area.
- Diagnosis :cardiac cathetarisation
- 2D ECHO;TR velocity>3.5m sec
- Treatment:long term oxygen therapy
- CORONARY ARTERY DISEASE AND COPD:
- Shares common risk factor:smoking
- Presence of symptoms of Chronic Bronchitis increases risk of death due to CAD by 50%

- Presence of obstructive airway disease increases risk of coronary artery event by 30%
- Co-existence of **COPD** and **CAD** worsens prognosis of both diseases.
- Link between **CAD** and **COPD** is independent of any other confounding factor :cholesterol,systemic HTN ,BMI.
- Both are inflammatory diseases leading to clotting abnormalities.
- In COPD due to **Hypoxia,oxidative stress,systemic inflammation,Impaired vasodiltory capacity** in BRONCHIAL ARTERIES causes inflammation and pro-coaguble state.
- Inflammatory cells in **Atherematous plaque** causes increased production of cytokines (**interferon alfa,IL-1,6,TNF,acute inflammatory proteins(fibrinogen,CRP,amyloid protein**) causing CAD.

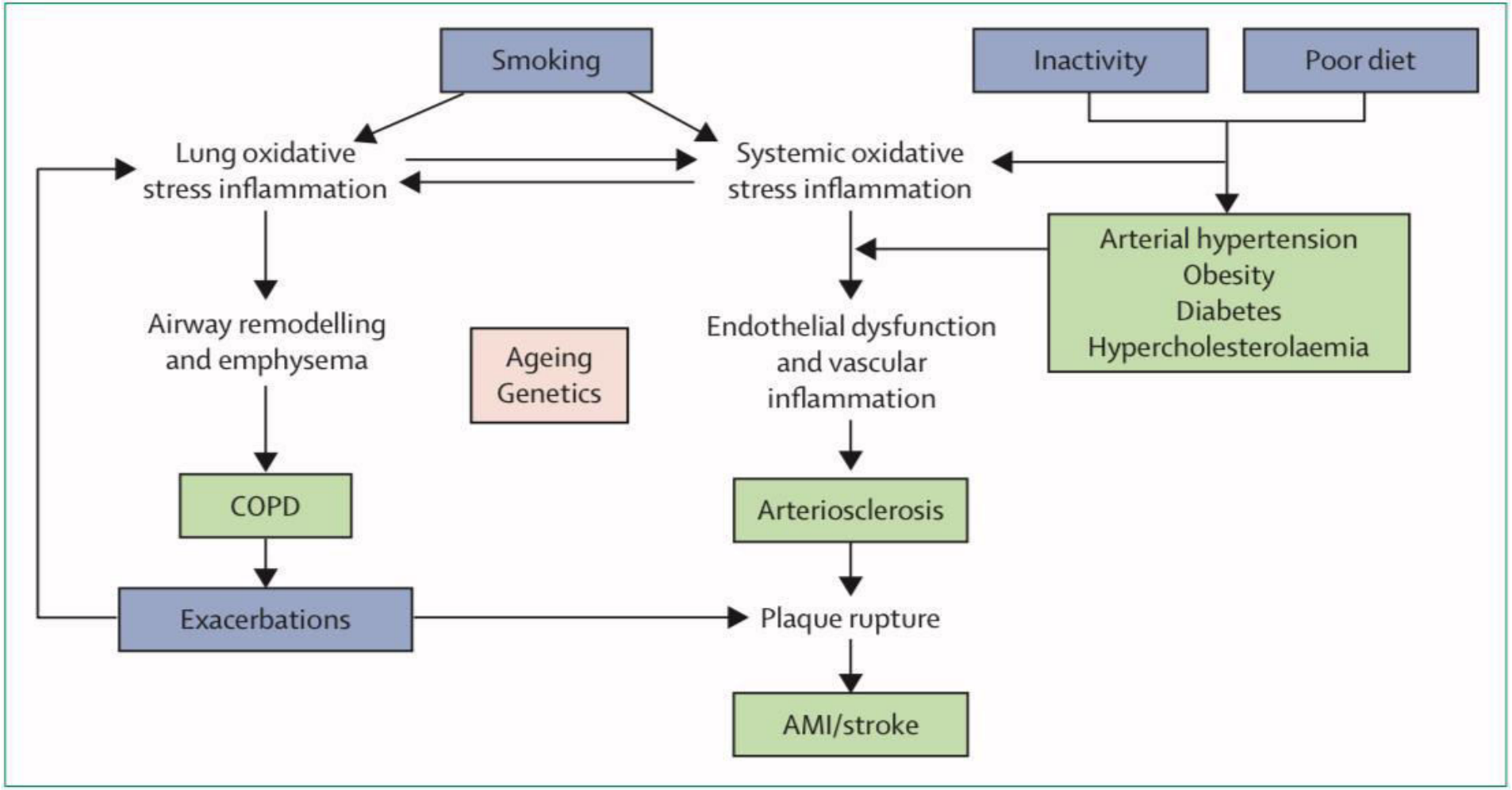


Figure 2: **Associations between COPD and cardiovascular disease**
Ageing and genetics are inherent processes (pink box) that affect all the other mechanisms, whereas smoking, inactivity, poor diet, and exacerbations are modifiable environmental factors (purple boxes). Green boxes represent the diseases (COPD or comorbidities of COPD). COPD=chronic obstructive pulmonary disease. AMI=acute myocardial infarction.

- **HEART FAILURE AND COPD** :
- Shares similar risk factors (**smoking**) due to this shares common pathophysiological mechanisms (**inflammation and skeletal muscle alterations.**
- A Meta analysis conducted in2006 from 12 analytical studies defined Heart Failure as combination of **typical clinical symptoms and a Left ventricle ejection fraction of 50%**
- Prevelance of co-existence depends upon the stability of the disease.
- **Effect of COPD in Heart Failure patients**: 1)Independent risk factor for death in compromised Heart Failure patients.
- 2)Co-existence may delay the diagnosis of **HF.**
- 3)Co-existence may worsen **LVD.**
- 4)Due to lack of use Beta blockers due to fear that they worsen airway obstruction therefore denied full benefit of HF treatment .
- Prevalance of HF increases with age worsens prognosis of **COPD.**

- **LUNG CANCER:**
- Prevalance of Lung cancer among COPD patients is 40%-70%.
- Annual incidence of Lung Cancer in COPD patients increases by fourfold compared to general population.
- Patients with COPD at time of Lung cancer has poor prognosis.
- 3year survival rate with COPD is 15% compared to patients without COPD (26%)

- **Pathological mechanisms:**

- **1)Shared genetic links** that predispose tpo both diseases:epigenetic changes common to both are DNA methylation,Deacetylation of histone proteins,protein phosphorylation.

- 2)Role of **chronic inflammation:**epithelial to mesenchymal transition plays an importatnt role in Carcinogenesis.Bronchial inflammation stimulates EMT.

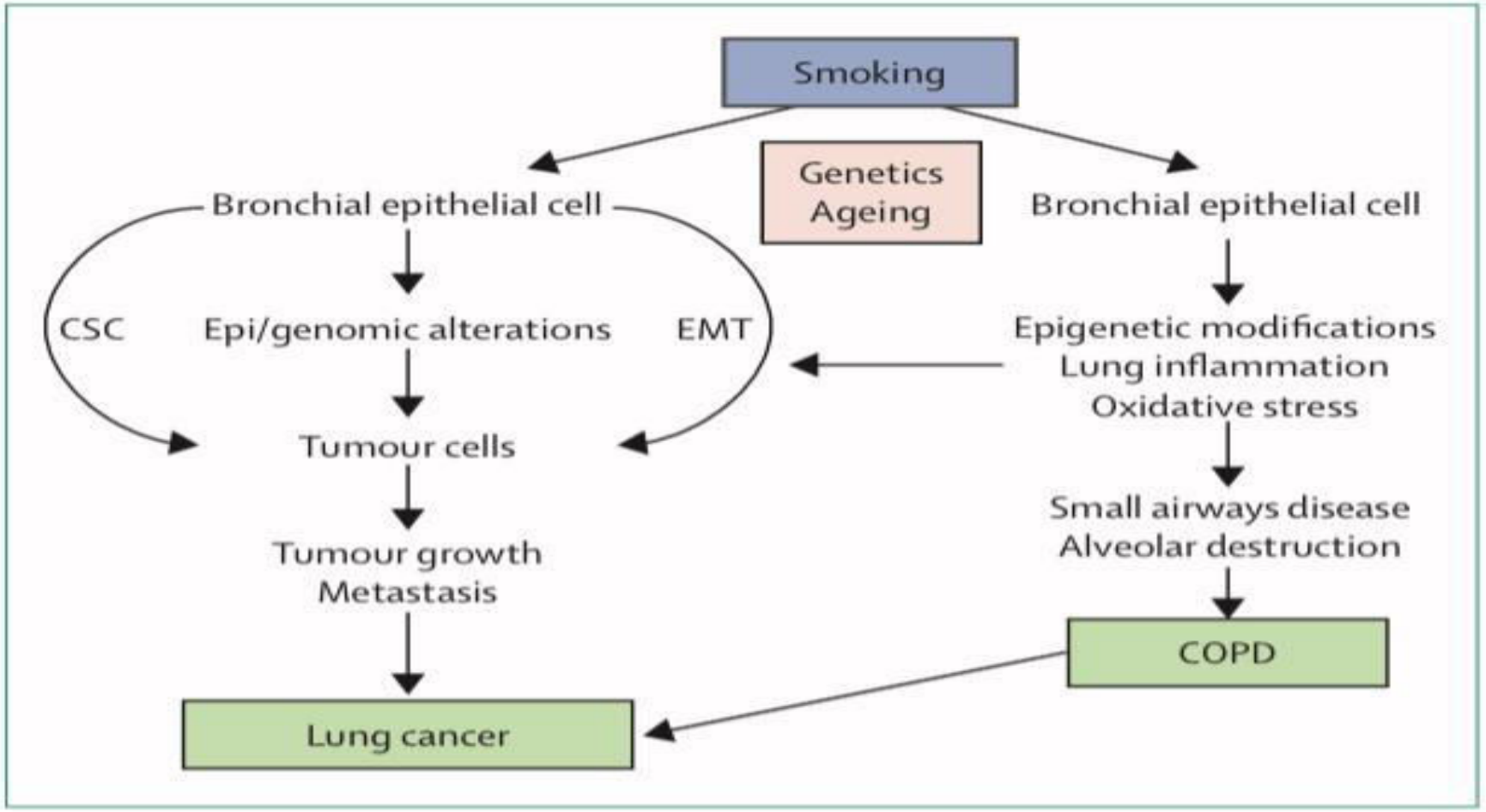


***Figure 4:* Associations between COPD and lung cancer**

Smoking is the main risk factor (environmental factor; purple box), not only for lung cancer, but also for COPD, which combined with ageing and genetics (inherent factors; pink box) contributes to tumorigenesis. Green boxes represent diseases (COPD or comorbidities of COPD). CSC=cancer stem cells. EMT=epithelial-to-mesenchymal transition. COPD=chronic obstructive pulmonary disease.

- **SCREENING:**
- 20% reduction in death due to Lung Cancer in grioup screened by using CT compared to groups screened by radiography in smokers between 55-75years with 30 packyears history.
- **Lung function tests** should be performed at the diagnosis of Lung Cancer (whether localized or locally invasive)because COPD has impact on treatment(lung resection,external beam radiotherapy/radiofrequency ablation depends upon patients lung function,
- PREVENTING LUNG CANCER IN COPD:
- Smoking cessation is one of the corner stone of COPD management
- Prevents progression of COPD and development of Lung Cancer.
- Inhaled corticosteroids and increased physical activity causes increased survival in COPD patients.

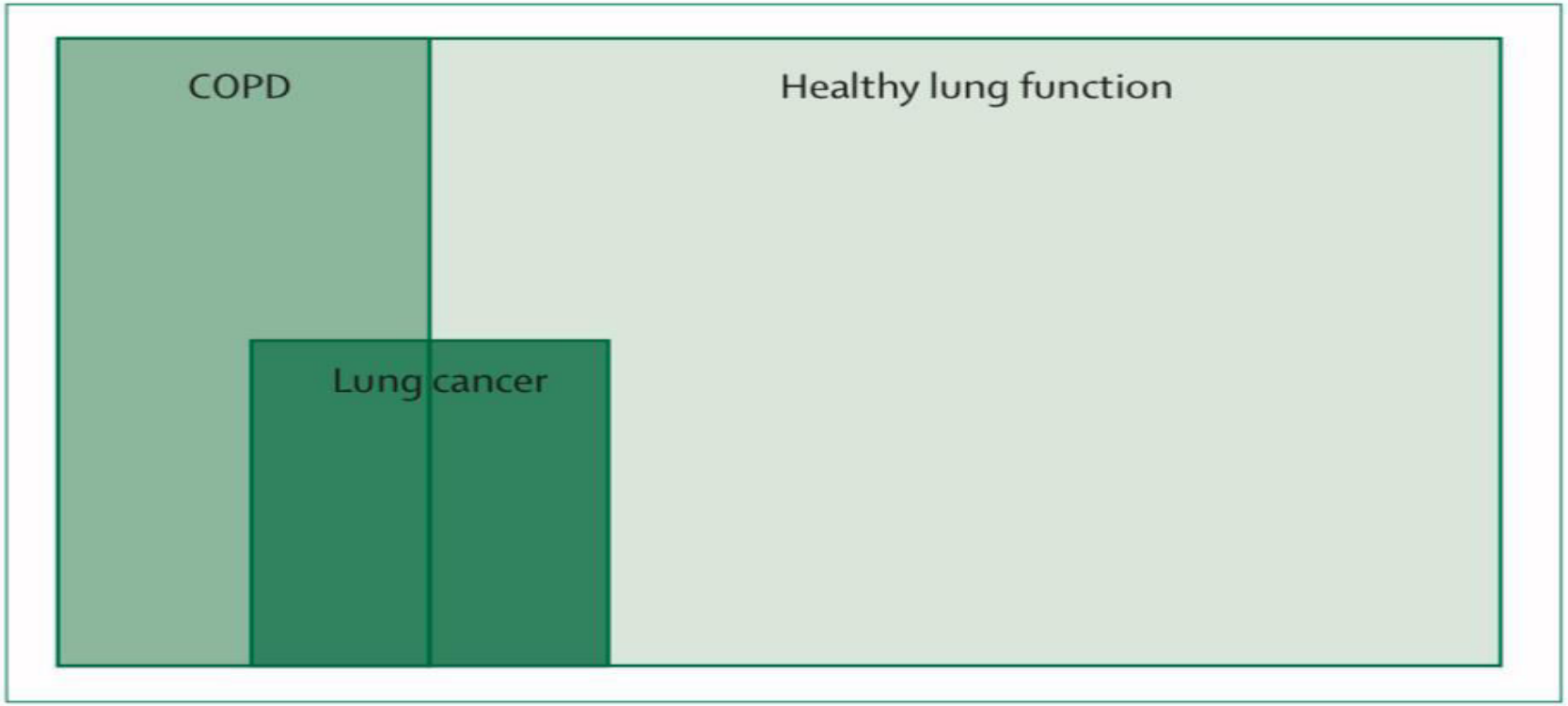


***Figure* 3: Proportion of chronic smokers with COPD and healthy lung function who will get lung cancer**

Relation between lifetime risk of COPD and lung cancer in chronic smokers (n=100). Assuming about 20 (20%) of 100 smokers get COPD and about ten (10%) get lung cancer, and given that 50% of patients with lung cancer have COPD, then five (25%) of 20 with COPD will develop lung cancer, compared with five (6%) of 80 with healthy lung function, accounting for a fourfold increase in incidence rate in patients with COPD. Reproduced from Young and colleagues,[38] by permission of the European Respiratory Society.

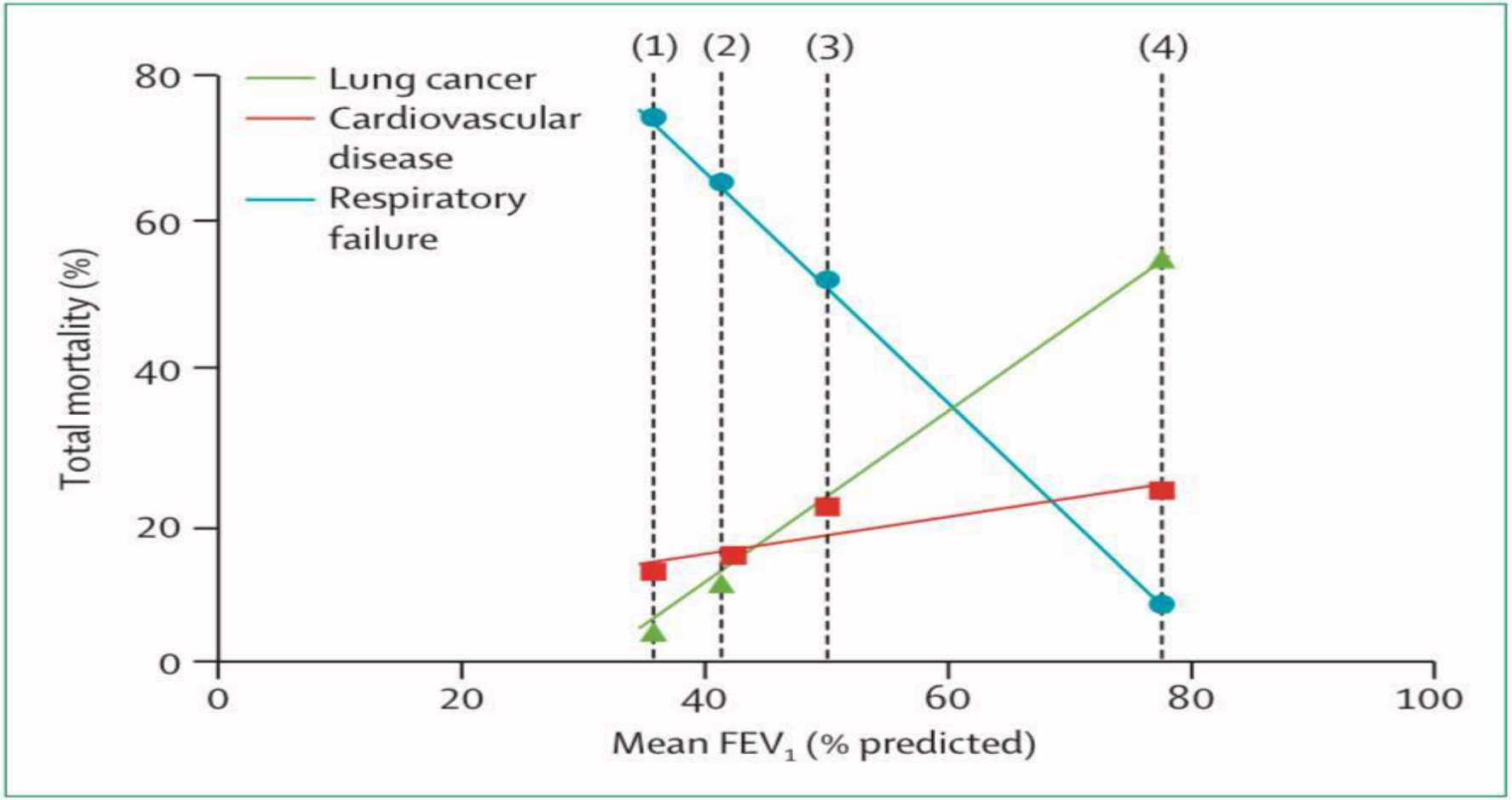


Figure 1: **Relation between lung function and death due to cardiovascular disease, lung cancer, and respiratory failure**

Data are taken from four large cohorts of patients with COPD based on different mean forced expiratory volume in 1 s (FEV_1) values (1–4).[10] Reproduced from Sin and colleagues,[10] by permission of the European Respiratory Society.

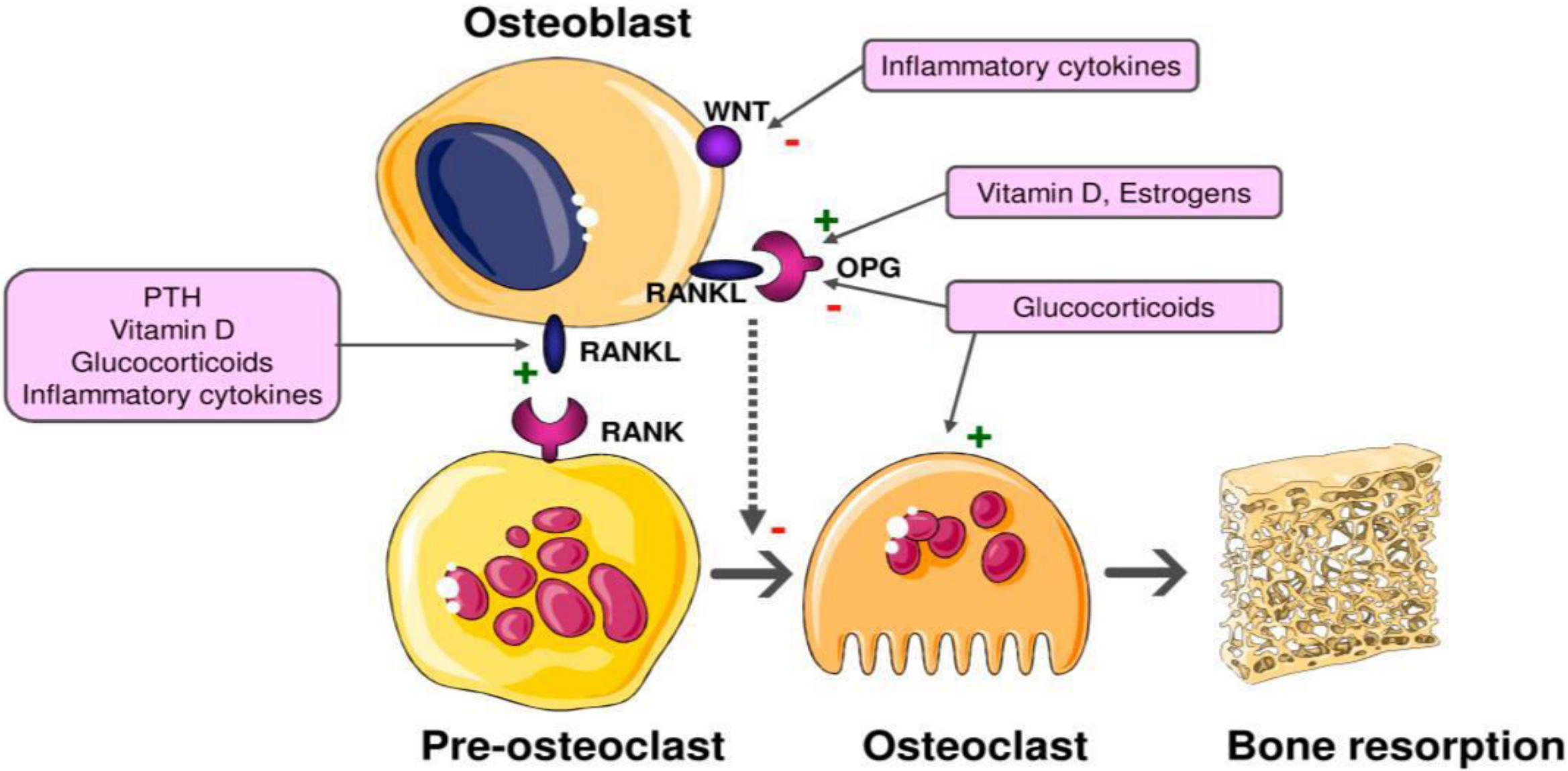
ANXIETY AND DEPRESSIVE DISORDERS:

- ANXIETY:feeling of indefinable insecurity which characterizes psychological component of Anxiety disorders
- .
- DEPRESSION:Illness for some/syndrome for others whose central manifestation is a mental state characterized by marked lassitude,reduced self-esteem and pessimism.
- These two disorders are more common in COPD than in other chronic disorders.
- Dyspnea perceived intensly and deeply and early hospitalization occurs in Depressive patient and morbidity is higher in them.

- **Screening** of COPD in DEPRESSION patients is by HAD scale which is a self questionnaire containing 14 questions should be completed in 10min time .Anxiety score is derived from score of questions 1,4,6,8,10,12,14 and depression from 2,3,5,7,9,11,13.
- **Score >10** high probability of Anxiety and Depression.
- **Treatment** :medical treatment:Anti-depressants
- Therapeutic patient education.
- COGNITIVE IMPAIRMENT:
- Presence of cognitive impairment is an independent risk factor for Mortality.

- **OSTEOPOROSIS:**
- According to WHO prevalence in COPD Patients is 24% to 69%
- Characterised by decreased skeletal resistance through detoiration of microarchitecture of Bone tissue leading to decreased bone mass and reduced mineral content.
- **Consequences:**Bone fragility and increased fracture risk
- BMD more than 2.5D below mean for young adults and fracture primarly effects spine,hips,waist.
- **OSTEOPENIA**: T score between - 2.5 and -1.
- Respiratory complaints of COPD increases in Osteoporosis patients because it exacerebrates pre-existing physical inactivity and increased risk of veretebral farctures with TLC progressively decreased as no.of vertebral fractures increases due to decrease in inhalational movments.

- A study at **MINEO AT AL** evauluated bone density in 40 patients before and after 1year of lung volume reduction surgery for Emphysema :surgery cuases increase ibn Bone Density.
- **Pathophysiology**:3 pathways control interaction between osteoclasts and osteoblasts:
- `1)direct interaction between these 2 cells by **RANKL and RANK** leading to maturation of pre-osteoclasts into osteoclasts.
- **Osteoprotegrin** blocks interaction between RANKL and RANK thereby decreasing bone resorption.
- **Wnt/beta catenin pathway** causing downstream of osteoblast activators.
- Risk Factors;smoking,systemic inflammation,vit D deficiency,oral steroids


Osteoblast
Inflammatory cytokines
WNT
-
Vitamin D, Estrogens
+
OPG
RANKL
-
Glucocorticoids
PTH
Vitamin D
Glucocorticoids
Inflammatory cytokines
RANKL
+
RANK
+
-
Pre-osteoclast
Osteoclast
Bone resorption

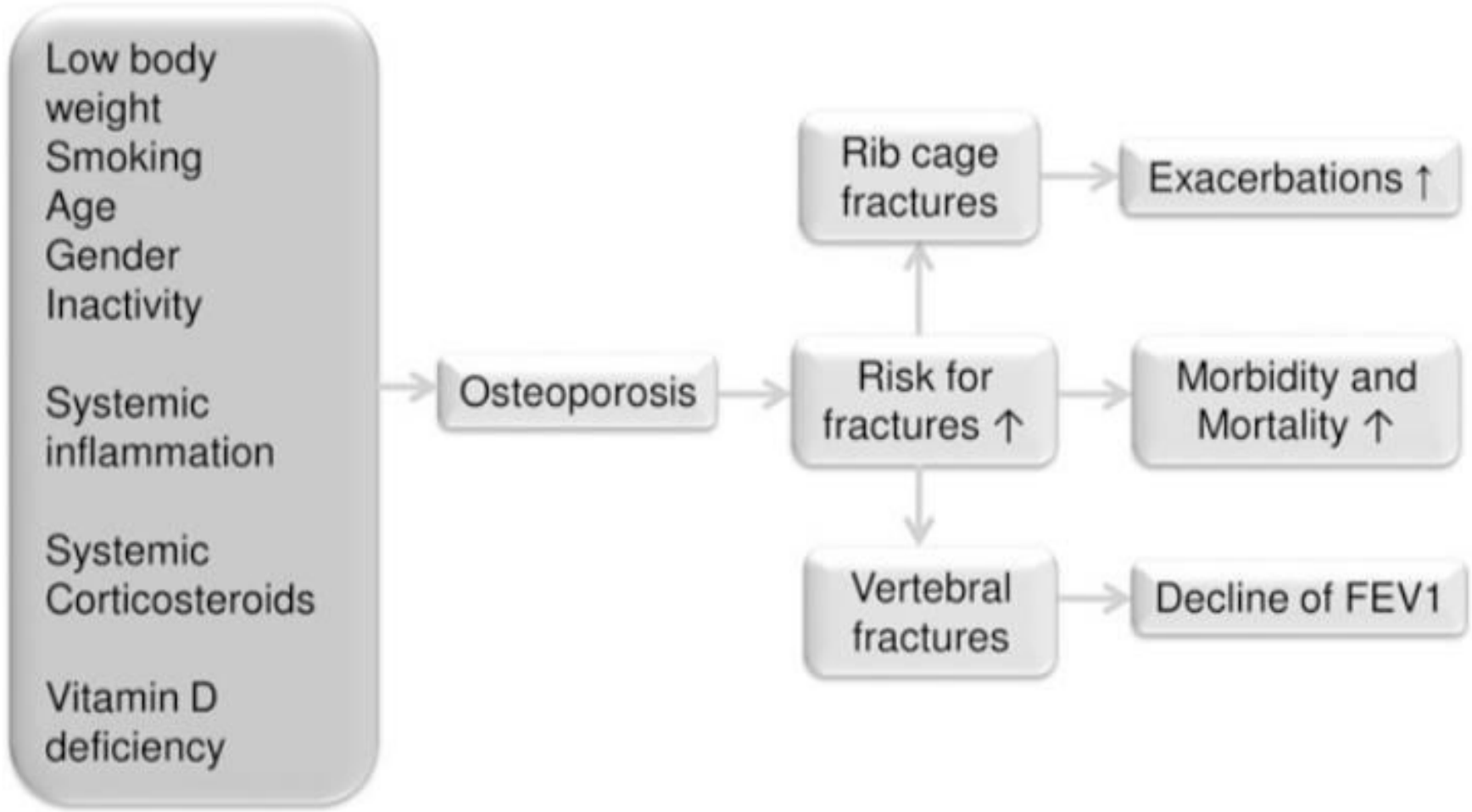


FIGURE 2. COPD-related risk factors for osteoporosis and its functional consequences.

- Treatment and prevention:1)**non-pharmacological:**smoking cessation and respiratory rehabilitation.
- 2)**Pharmacological**:VIT-D and Calcium supplementation both have immunomodulatory effect and improves muscle function.
- **Criteria**: T score<1
- **Presence of any 3 minor RF**:BMI<21kg./m2,age >65y,hip and rib fracture,menopause,sedentary life style,smoking,chronic alcoholism,FEV1<50% predicted.
- **Presence of one major RF:**systemic corticosteroids >3mnths/yr,Previous vertebral compression fracture

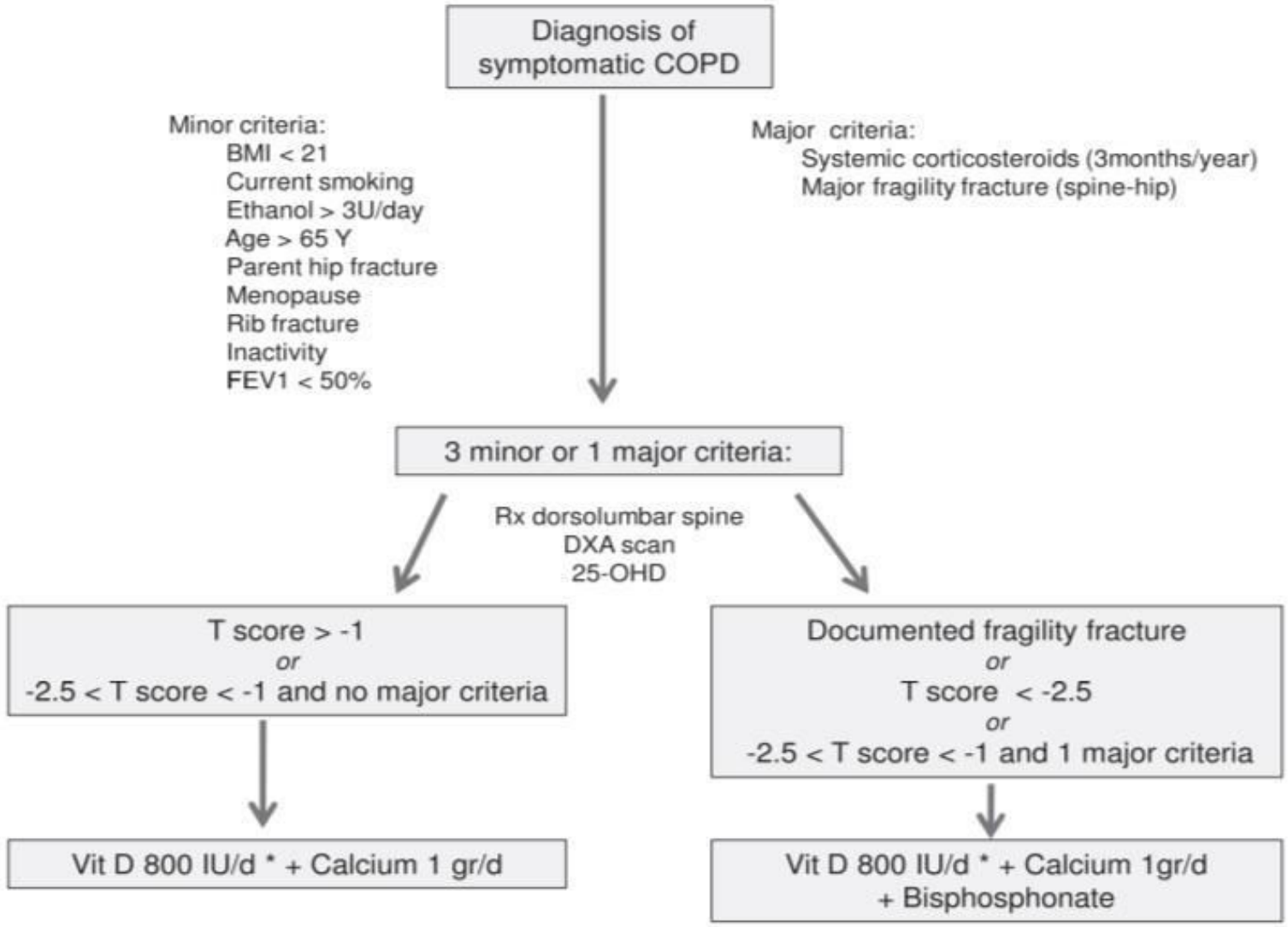


FIGURE 3. Flow diagram summarizing risk assessment, diagnosis, and therapy of osteoporosis in COPD
*25-OHD < 10 ng/mL: start high dose vitamin D supplements with control of 25-OHD after 3 months.
25-OHD = 25 hydroxyvitamin D; DXA = dual-energy x-ray absorptiometry; Vit D = vitamin D.

MALNUTRITION:

- In COPD ,patients are malnourished when BMI <20kg/m2.
- Evaulated by dual energy absorptionometry and biometrical impedance analysis.
- **Malnutrition profile in COPD**:1)underweight with lean body mass
- 2)underweight with normal body mass
- 3)stable body weight with lean body mass.
- Its importance is underlined by prognostic power of BODE index
- **Pathophysiology:**imbalance between energy intake and energy consumption(increased work of breathing,smoking,increased protein catabolism,hypoxia,hypoandrogenism,medications)
- Prevalanceof grade 2 COPD in pts with BMI<18.5kgm2 is 0-5% and grade 4 is 15-30%

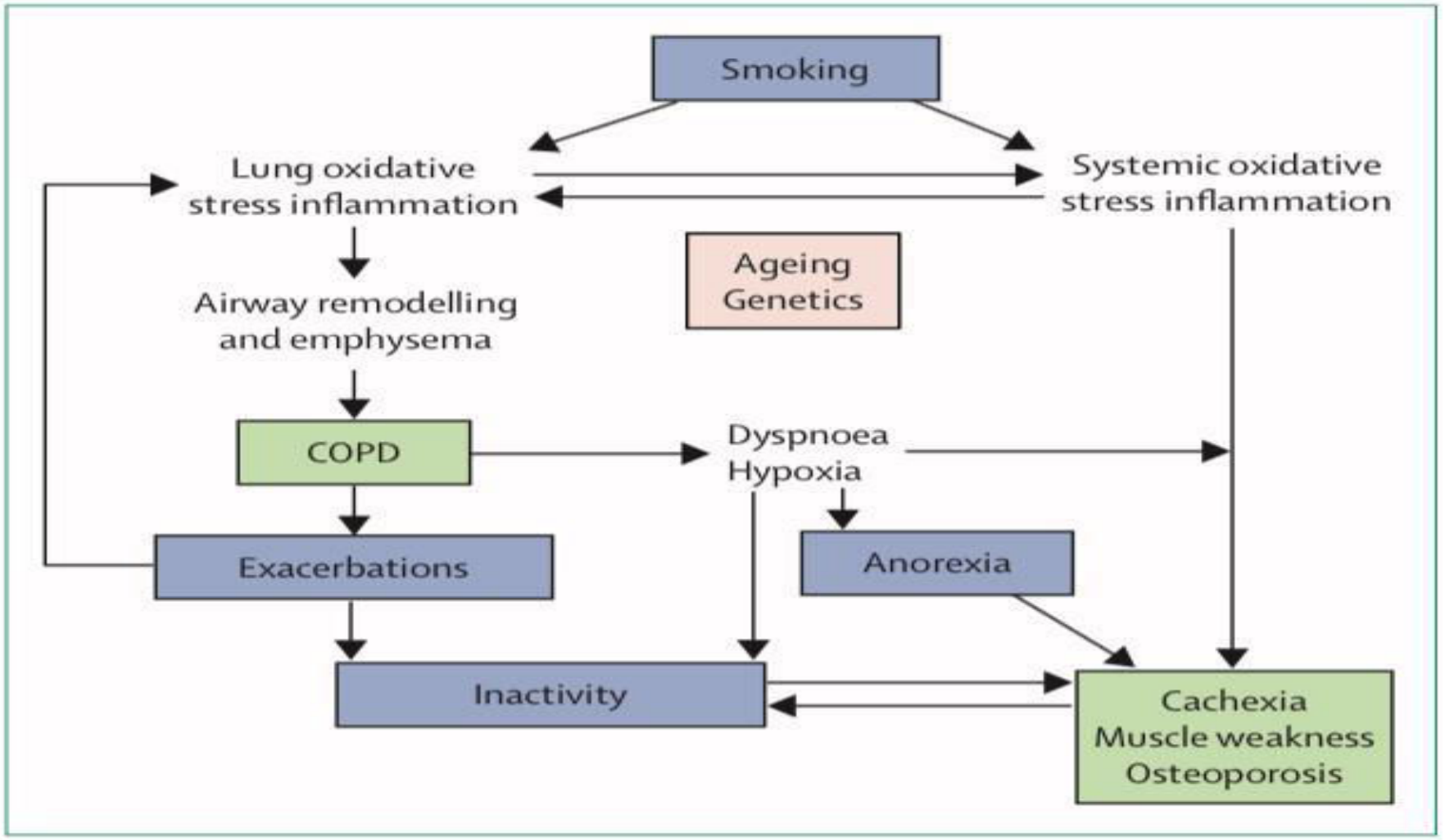


***Figure 5:* Associations between COPD and body composition**

Ageing and genetics are inherent processes (pink box) that affect all other mechanisms, whereas smoking, inactivity, anorexia and exacerbations are modifiable environmental factors (purple boxes). Green boxes represent diseases (COPD or comorbidities of COPD). COPD=chronic obstructive pulmonary disease.

- **Treatemnt** :physical exerecises as a part of rehabilitation
- 2)increased caloric,protein and PUFA supplementation
- 3)anabolic steroids. These 3 integrated as **NUTRITIONAL REHABILITATION.**
- **OBESITY:**
- Increased risk of death in morbid obese patients (BMI>40kgm2)and should be investigated for **OSA/OHS.**

METABOLIC SYNDROME AND DIABETES:

- Common co-morbidities of COPD.
- DM:polyuria and polydipsia syndrome
- **Clinical signs**:Blood Glucose>11.1mmol/L
- FBS>7mmol/l
- 2hr PPBG >11.5mmol/
- HBA1C.6.5%
- Incidence of DM is 12.6 -14.5% in COPD
- Incidence of Metabolic syndrome is 53% in grade 2 COPD
- 37% in grade 3 COPD
- 44% in grade 4 COPD

TABLE 1
Criteria for Clinical Diagnosis of the Metabolic Syndrome[13]

Measure	Cut Points
Elevated waist circumference	Population & country-specific
Elevated triglycerides (or on therapy for hypertriglyceridemia)	⩾ 150 mg/dL
Reduced HDL-C (or on therapy for reduced HDL-C)	< 40 mg/dL in males < 50 mg/dL in females
Elevated blood pressure (or on therapy with known history of HTN)	SBP ⩾130 and/or DBP ⩾ 85 mm Hg
Elevated fasting glucose (or on therapy for hyperglycemia)	⩾ 100 mg/dL

- **Pathophysiology** :hypoxia,smoking and bronchial obstruction stiamulate enzyme cascade in adipose tissue leading to production of cytokines(TNF alfa,IL-1,IL-6) causing decrease in adiponectin and increase in adiposity.
- These changes causes increased insulin resistance,increased circulating levels of free radicals leading to inflammation and DM
- **ASIAN COHORT STUDY** :strong link between central obesity and airway obstruction.
- MECHANISMS:abdominal obesity(increased intra abdominal SC tissue)causing ;1)decreased pulmonary elasticity through non enzymatic glycosylation of tissue proteins
- 2)loss of inspiratory muscle strength
- 3)diaphragmatic compromise due to diabetic neuropathy.
- **TREATMENT**:metformin for **DM** and statins for **DYSLIPIDEMIA**

SLEEP DISTURBANCES:

- Impaired sleep quality common in severe **COPD** patients.
- Sleep studies confirmed that total sleep period,total sleep time,NREM sleep time reduced and
- Sleep latency,arousals ,no.of sleep state changes increases.
- **MECHANISM:**
- 1)distension and increased work of breathing potentiated when lying down
- 2)respiratory symptoms(dyspnea,cough,expectoration)causes arousal
- 3)anxiety and depression causes sleep disturbances.
- 4) presence of **OSAS** exacrerbrates sleep disturbances.

- TREATMENT OF INSOMNIA IN COPD;
- 1)restricting time spent in bed
- 2)stimulus control and relaxation
- 3)cognitive behavioural therapy
- 4)short term hypnotics

- **OSAS AND COPD:**
- According to **MONICA2**: prevalence of OSAS in COPD is 17%
- **OSAS** is suspected when there is Typical nocturnal clinical signs(snoring,breathing pauses,poor sleep) and
- Day time signs(non restorative sleep,headache on awakening ,excessive daytime sleepiness) and impaired gas exchange
- Diagnosis by **POLYSOMNOGRAPHY**

- **OSAS AND COPD COMBINATION CONSEQUNECES:**
- 1)reduced sleep quality
- 2)increased nocturnal hypoxemia
- 3)nocturnal desaturation
- 4)more frequent day time hypercapnea
- 5)pul artery HTN and RHF
- 6)Increased frequency of exacerebration and hospitalization.
  - **TREATMENT:**CPAP and OXYGEN THERAPY if LTOT criteria met

ANAEMIA:

- Prevalance in COPD is 12.3-23%
- In **COPD** which causes chronic inflammation leading to increased production of IL-1,6,TNF alfa which have harmful effect on erythropoiesis.
- CONFOUNDING FACTORS:age,malnutrition,CVS
- **IMPACT OF ANAEMIA IN COPD:**
- 1)dyspnea score is higher
- 2)exercise capacity is lower
- 3)decreased survival rate
- 4)Negative imapact on prognosis of patient
- 5)interferes with management
- **TREATMENT:**blood transfusion and Erythropoietin

LUNG FIBROSIS:

- **Smoking** is a risk factor for Lung Fibrosis and COPD.
- **Combined Pulmonary Fibrosis and Emphysema(CPFE)** is a clinical syndrome associated with Smoking.
- These patients have **Normal spirometry** which is secondary to association of Bronchus obstruction and Collapse in Emphysema and inversely airway traction by Peribronchial Fibrosis.
- And reduction of vascular surface in Emphysema and the alveolar membrane thickening due to fibrosis leads to Impaired gaseous exchange.
- CT is characterized by upperlobe Emphysema and lower lobe pulmonary fibrosis.**Bullous,paraseptal and centrilobular** emphysema noted in upper lobes.In Lower lobes **Honey combing,reticular intralobular opacities** and traction bronchiectasis seen.

- PH is the important morbidity of CPFE.It is more severe and frequent in **CPFE** patients than IPF alone.
- On **Right Heart Cathetarisation** reduced cardiac index or an elevated PVR were predictors of poor prognosis.
- LUNG CANCER was associated with CPFE and its prevalence is higher in them.
- CPFE patients have significantly **lower survival rates** than COPD patients alone.Median survival rate is **6 years**.

PRE-MATURE AGING:

- Accelerated aging has been examined as a pathological mechanism, of many chronic diseases like **COPD.**
- Some studies conducted to know whether **COPD** is associated with Pre mature aging by studying two harmones DEHYDROEPIANDROSTERONE(DHEA) AND GROWTH HARMONE(GH) known to be characteristic biological markers of aging.
- In this study difference in **DHEA** between **COPD** patients and control group was**30.2**microgram grams/L indicating that the biological age of a **COPD** patient is on average about 24 years older than that of a controls of same age.
- Similarly the difference in **GH** was **0.42**microgram/L indicating biological age of **COPD** patient is on average about 13.1 years older than that of control group.
- The biological age could vary from **13** to **23** years older than Non-COPD patients.
- **HEAD** and **GH** were significantly and negatively correlated with age in **COPD** patients.

CONCLUSION:

From the above discussion it showed thatCOPD is frequently associated with other diseases.These Exacerebrations have a negative impact in COPD patients in terms of **Quality of life,Exacerebration and mortality.**Thus Dianosis and Management of Co-Morbidities is an important challenge for the COPD patient.As it is not easy to diagnose the Co-Existing illness as these can be asymptomatic or the symptoms may not be specific in COPD patients.Thus systematic reaseach of Co-Morbidities is done.BMI,HAD SCALE,ECG,Chest X ray,6min walk test are easy to obtain in Medical practice and should be regularly used to asessCOPD patients.Transthoracic Echocardiography,CT,Bone Mineral Density Asessment also performed for clinically significant COPD or when lother risk factors are associated.

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Thank
you!