EXCEL IN PULMONOLOGY
the advanced training program in Respiratory Medicine

COPD@ATHENS

3

Respiratory Function and Inflammatory assessment Differences and Similarities with Asthma

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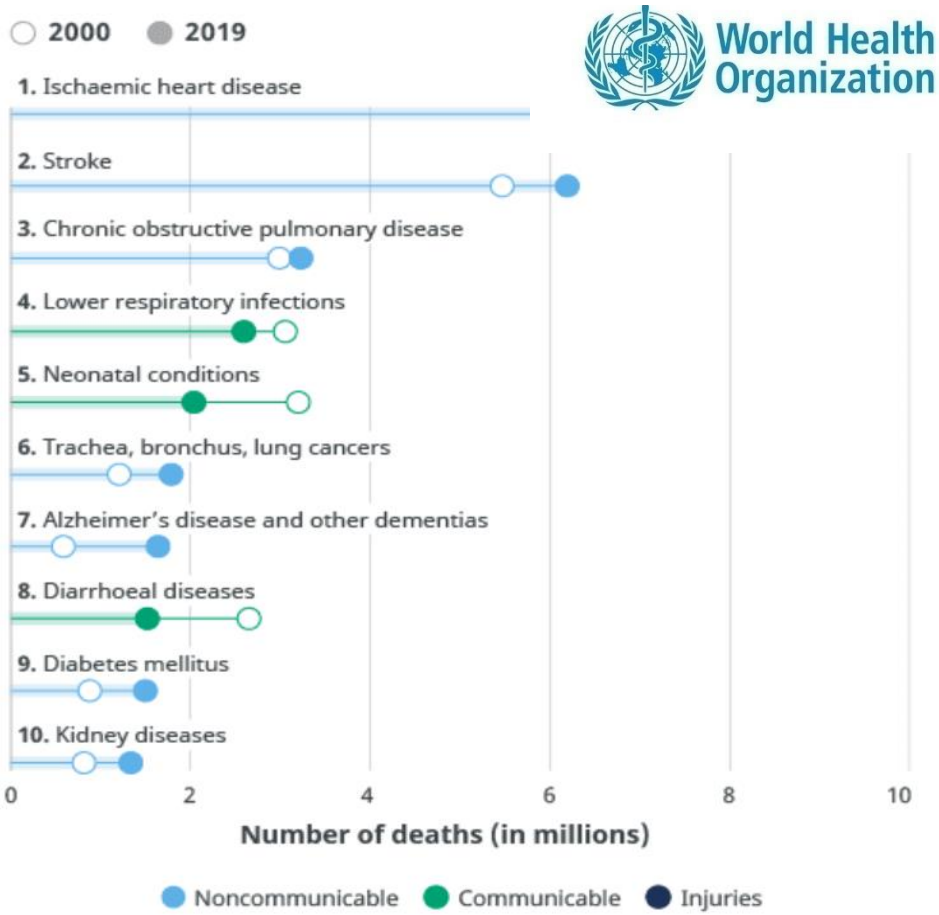
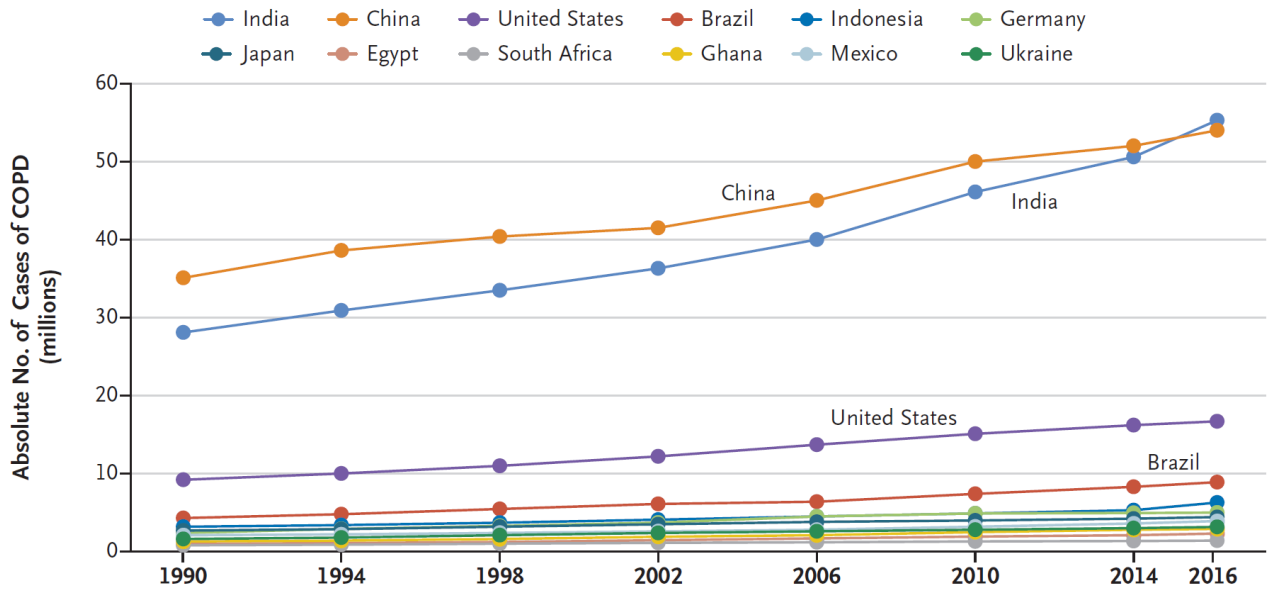
Based on BOLD and other large scale epidemiological studies, it is estimated that the number of COPD cases was 384 million in 2010, with a global prevalence of 11.7% (95% confidence interval (CI) 8.4%-15.0%).[29] Globally, there are around three million deaths annually.[30] With the increasing prevalence of smoking in developing countries, and aging populations in high-income countries, the prevalence of COPD is expected to rise over the next 40 years and by 2060 there may be over 5.4 million deaths annually from COPD and related conditions.[31,32] Data from the Global Burden





Celli BR, Wedzicha JA. *NEJM* 2019; 381: 1257-66.

COPD DEFINITION

Definition

- Chronic Obstructive Pulmonary Disease (COPD) is a heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnea, cough, sputum production, exacerbations) due to abnormalities of the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow obstruction.

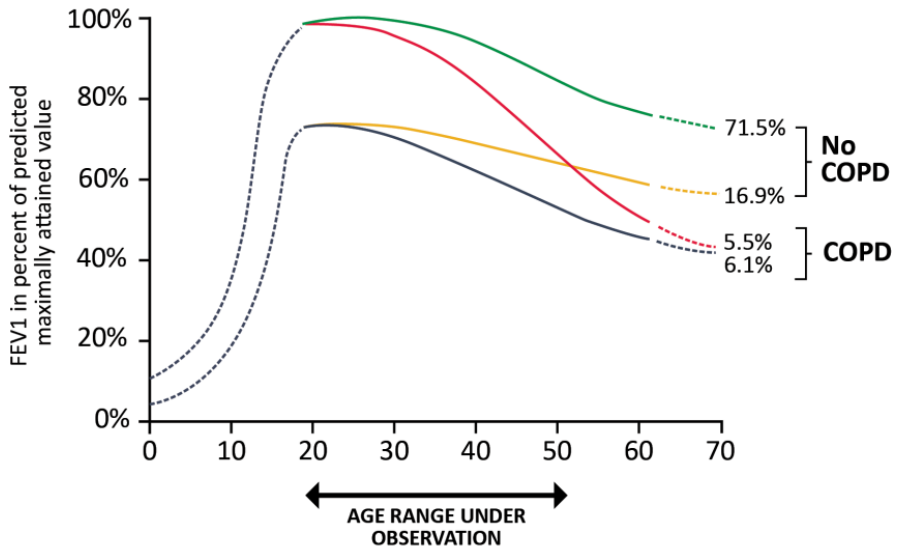
GOLD 2023

Chronic inflammation, Smoking, comorbidities

FEV1 Trajectories

FEV1 Trajectories (TR) Over the Life Course

Figure 1.1



Note: This is a simplified diagram of FEV1 progression over time. In reality, there is heterogeneity in the rate of decline in FEV1 owing to the complex interactions of genes with environmental exposures and risk factors over an individual's lifetime [adapted from Lange et al. NEJM 2015;373:111-22].

CLINICAL DIAGNOSIS

Clinical Indicators for Considering a Diagnosis of COPD

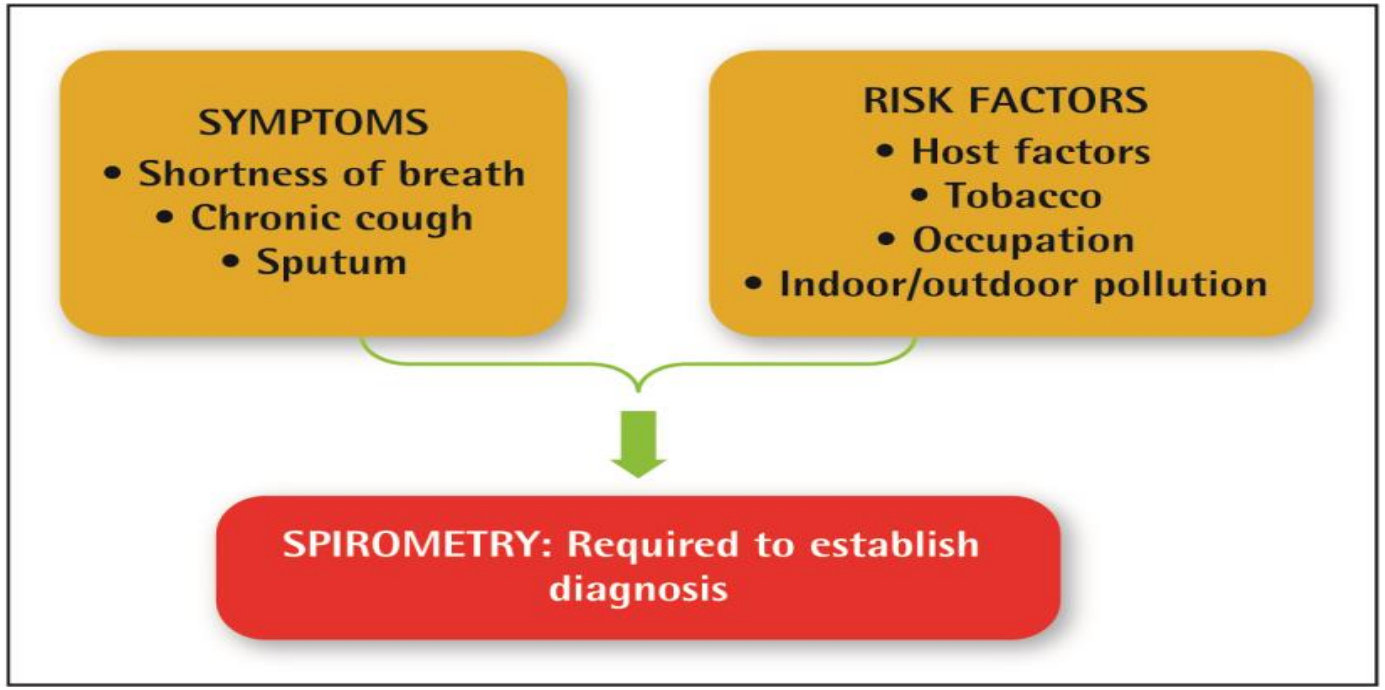
Table 2.1

Consider the diagnosis of COPD, and perform spirometry, if any of these clinical indicators are present:
(these indicators are not diagnostic themselves, but the presence of multiple key indicators increases the probability of the presence of COPD; in any case, spirometry is required to establish a diagnosis of COPD)

Dyspnea that is	Progressive over time Worse with exercise Persistent
Recurrent wheeze	
Chronic cough	May be intermittent and may be unproductive
Recurrent lower respiratory tract infections	
History of risk factors	Tobacco smoke (including popular local preparations) Smoke from home cooking and heating fuels Occupational dusts, vapors, fumes, gases and other chemicals Host factors (e.g., genetic factors, developmental abnormalities, low birthweight, prematurity, childhood respiratory infections etc.)

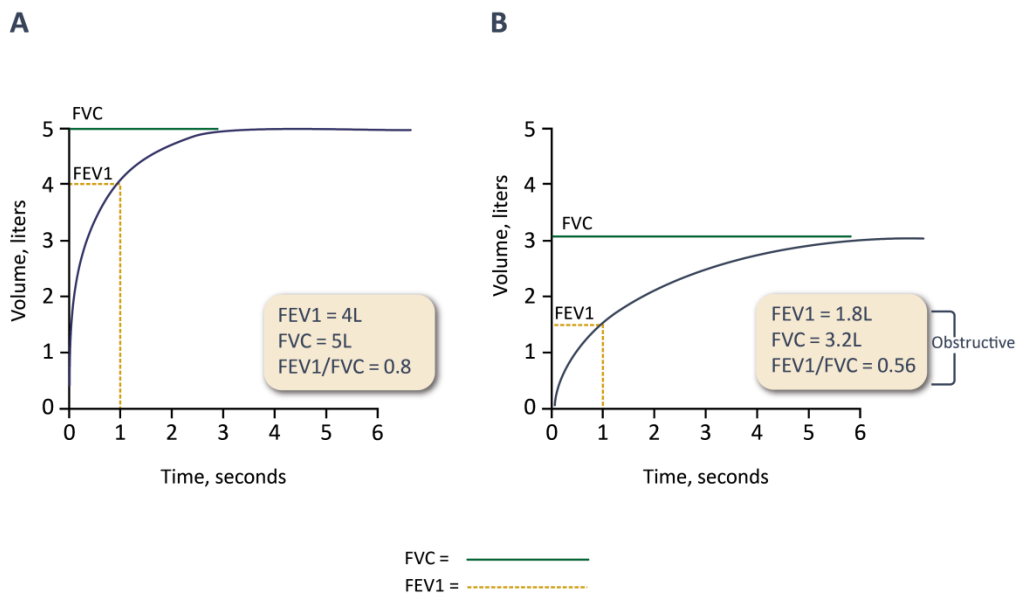
DIAGNOSIS

Figure 2.1. Pathways to the diagnosis of COPD



SPIROMETRY

A. Spirometry - Normal Trace **B. Spirometry - Airflow Obstruction**
Figure 2.1



post broncho
FEV1/FVC < 0.7

Considerations in Performing Spirometry
Table 2.4

PREPARATION	• Spirometers should produce hard copy or have a digital display of the expiratory curve to permit detection of technical errors or have an automatic prompt to identify an unsatisfactory test and the reason for it • The supervisor of the test needs training in optimal technique and quality performance • Maximal patient effort in performing the test is required to avoid underestimation of values and hence errors in diagnosis and management
PERFORMANCE	• Spirometry should be performed following national and/or international recommendations[a] • The expiratory volume/time traces should be smooth and free from irregularities • The pause between inspiration and expiration should be < one second • The recording should go on long enough for a volume plateau to be reached, which may take more than 15 seconds in severe disease • Both FVC and FEV1 should be the largest value obtained from any of three technically satisfactory curves and the FVC and FEV1 values in these three curves should vary by no more than 5% or 150 mL, whichever is greater • The FEV1/FVC ratio should be taken from the technically acceptable curve with the largest sum of FVC and FEV1
BRONCHODILATION	• Possible dosage protocols are 400 mcg short-acting beta$_2$-agonist, 160 mcg short-acting anticholinergic, or the two combined[b]; FEV1 should be measured 10-15 minutes after a short-acting beta$_2$-agonist is given, or 30-45 minutes after a short-acting anticholinergic or a combination of both classes of drugs • Patients already on bronchodilator treatment, in whom spirometry is requested for monitoring purposes do not need to stop their regular treatment for spirometry
EVALUATION	• Spirometry measurements are evaluated by comparison of the results with appropriate reference values based on age, height, sex, and race • The presence of a postbronchodilator FEV1/FVC < 0.7 confirms the presence of non-fully reversible airflow obstruction

[a]Miller *et al.* Eur Respir J 2005; 26(2): 319; [b]Pellegrino *et al.* Eur Respir J 2005; 26(5): 948.

FEV1/FVC ratio vs. LLN

COPD diagnosis: required spirometry with FEV_1/FVC post bronchodilation < 0,70. This cut-off has been criticized that may lead to underdiagnosis in younger age with FEV_1/FVC 0,70-0,74 and to overdiagnosis in patients > 70 y.o with FEV_1/FVC < 0,70 due to lung senescence and not COPD. In such cases the **LLN** has been suggested.

post bronchodilation FEV1/FVC < 0.7

NEW TERMINOLOGY

Young COPD

The term "young COPD" is seemingly straightforward because it directly relates to the chronological age of the patient. Given that lung function peaks at around 20-25 years,[56] we propose to operationally consider "young COPD" in patients aged 20–50 years.[129] Of note, this can include patients who had never achieved normal peak lung function in early adulthood and/or those with shorter *plateau* and/or early lung function decline.[130,131] Young COPD may be associated with significant structural and functional lung abnormalities (i.e., young COPD is not necessarily synonymous with "mild" COPD) that can have a substantial impact on health and, importantly, is frequently not diagnosed and thus not treated. A family history of respiratory diseases and/or early-life events (including hospitalizations before the age of 5 years) is reported by a significant proportion of young patients with COPD, further supporting the possibility of early-life origins of COPD.[127,131]

NEW

Pre-COPD

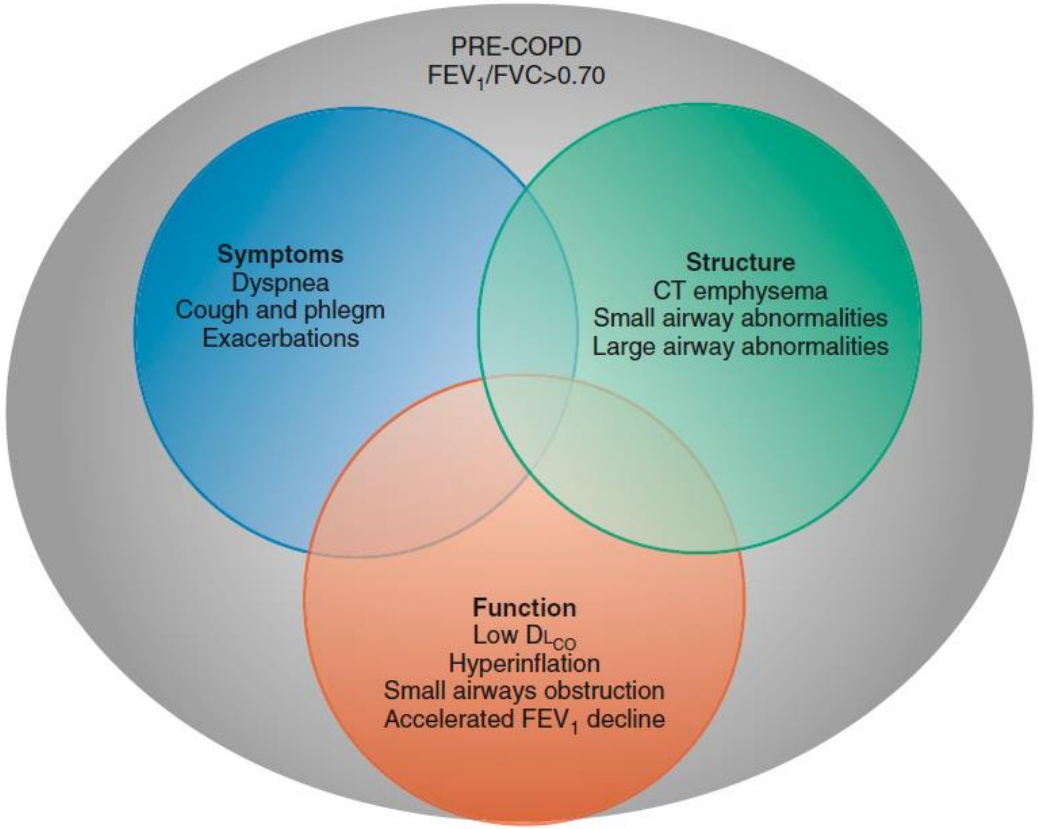
This term has been recently proposed to identify individuals (importantly, of any age) who have respiratory symptoms and/or other detectable structural and/or functional abnormalities, in the absence of airflow obstruction on forced spirometry. These patients may (or not) develop persistent airflow obstruction (i.e., COPD) over time.[132] A very recent publication highlights the need for RCTs, both in patients with 'Pre-COPD', and in young people with COPD.[133]

(FEV1/FVC >=0,.7 post bronchodilation)

GOLD 2023

Pre COPD: Multiple phenotypes

Going further than GOLD stage 0



Han MK et al AJRCCM 2021

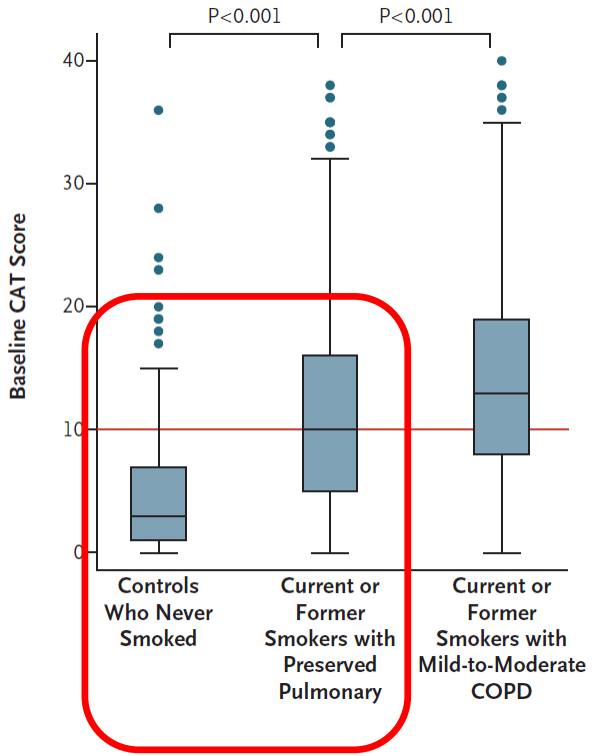
What about PRISm?

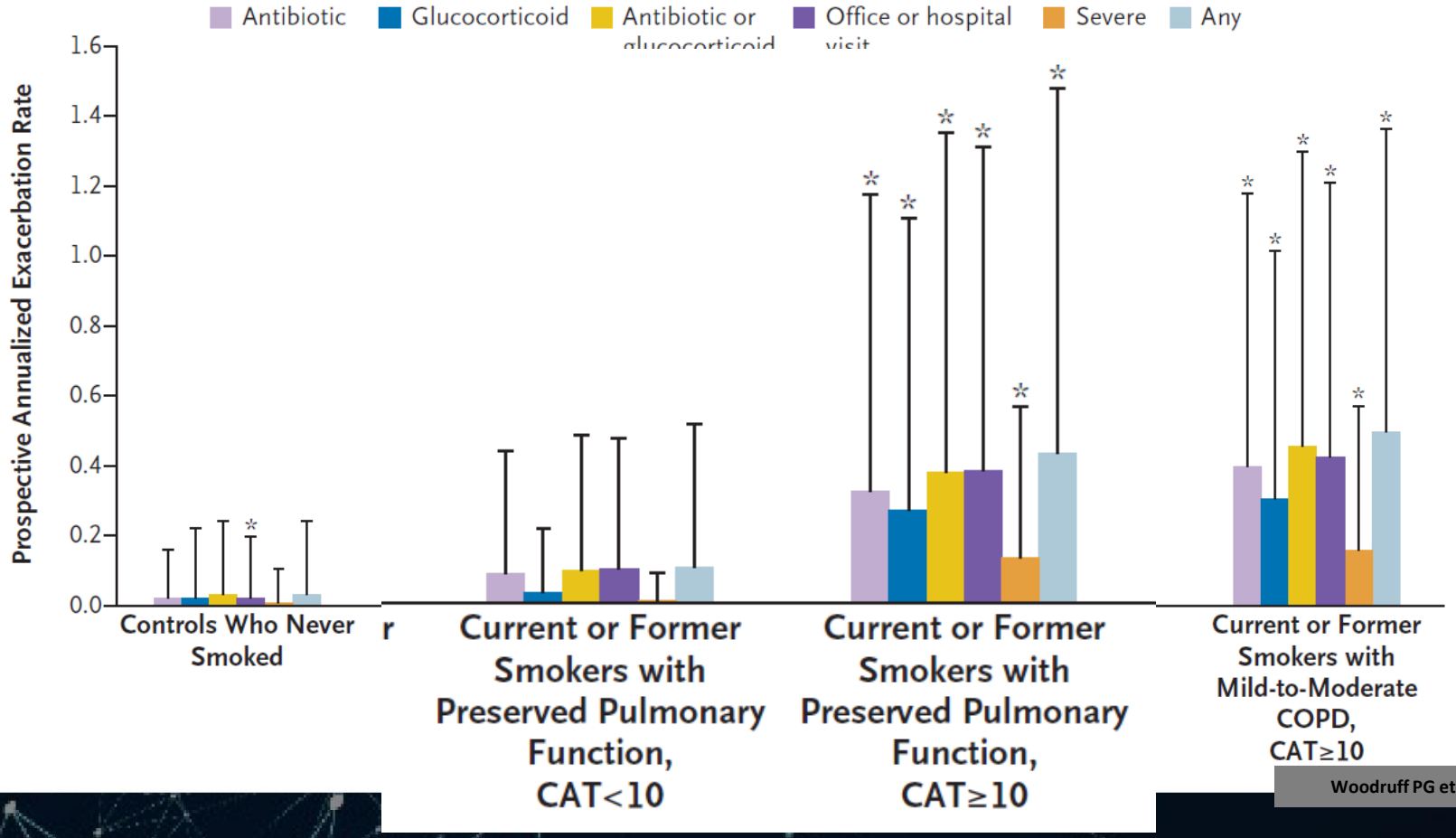
- **P**reserved
  Ratio
  Impaired
  Spirometry
- FEV1/FVC >=0.70
- FEV1 and/or FVC <80% of reference post BD
- Prevalence → 7.1-20.3%
- Important?
  Increased all cause mortality!

GOLD 2023

SYMPTOMS DESPITE PRESERVED LUNG FUNCTION

- N=2736, 40-80 y.o, FEV_1/FVC ≥0.70 pre-broncho and COPD pts
- FVC ≥LLN
- No smokers or current and ex-smokers ≥ 20 pack-years,





Woodruff PG et al NEJM 2016

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Bronchodilators in Tobacco-Exposed Persons with Symptoms and Preserved Lung Function

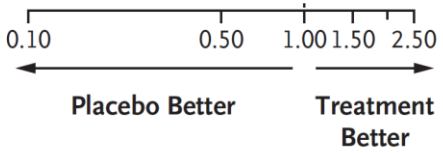
M.K. Han, W. Ye, D. Wang, E. White, M. Arjomandi, I.Z. Barjaktarevic, S.-A. Brown, R.G. Buhr, A.P. Comellas, C.B. Cooper, G.J. Criner, M.T. Dransfield, F. Drescher, R.J. Folz, N.N. Hansel, R.J. Kaner, R.E. Kanner, J.A. Krishnan, S.C. Lazarus, V. Maddipati, F.J. Martinez, A. Mathews, C. Meldrum, C. McEvoy, T. Nyunoya, L. Rogers, W.W. Stringer, C.H. Wendt, R.A. Wise, S.R. Wisniewski, F.C. Sciurba, and P.G. Woodruff, for the RETHINC Study Group*

- **Smokers** ≥ 10 pack years
  CAT score ≥ 10
  FEV_1/FVC ≥ 0.7 and FVC ≥70% post BD
- **Indacaterol (27.5 μg) plus glycopyrrolate (15.6 μg) or placebo** twice daily για 12 weeks
- **Primary outcome: Reduction of at least 4 units (improvement) of SGRQ score without treatment failure (deterioration of symptoms from the lower respiratory tract)**

Han MK, et al. *N Engl J Med* 2022

Shortfall…

Outcome	Placebo (N=244)	Treatment (N=227)	Odds Ratio (95% CI)
	no. of participants/total no. (%)		
Primary outcome			
Overall			
Modified intention-to-treat analysis	144/244 (59.0)	128/227 (56.4)	0.91 (0.60–1.37)
Sensitivity analysis 1	143/242 (59.1)	129/230 (56.1)	0.89 (0.59–1.34)
Sensitivity analysis 2	144/240 (60.0)	124/220 (56.4)	0.87 (0.57–1.33)
Sensitivity analysis 3	115/196 (58.7)	109/192 (56.8)	0.98 (0.61–1.58)
Sensitivity analysis 4	146/249 (58.6)	131/232 (56.5)	0.93 (0.65–1.35)
Per-protocol analysis	110/176 (62.5)	101/170 (59.4)	0.88 (0.65–1.20)
Secondary outcomes			
≥4-point improvement in SGRQ score plus TDI score of ≥1 without treatment failure	60/234 (25.6)	55/220 (25.0)	0.97 (0.60–1.57)
TDI score of ≥1 without treatment failure	80/234 (34.2)	80/220 (36.4)	1.14 (0.82–1.58)
≥2-point improvement in CAT score without treatment failure	166/244 (68.0)	169/227 (74.4)	1.45 (0.96–2.18)



- In the ITT population (471 patients),128 out of 227 (**56.4%)** that received treatment and 144 out of 244 **(59.0%)** that received placebo showed a reduction ≥ 4U in the SGRQ score
- **difference, −2.6 percentage points** 95% confidence interval [CI], −11.6 to 6.3; adjusted odds ratio, 0.91; 95% CI, 0.60 to 1.37; **P = 0.65**

Han MK, et al. *N Engl J Med* 2022

The SPIROMICS cohort Vol 2.0

Model summary for outcomes of interest with estimate of effect size for presence of VO

Model Type	Unadjusted N = 778		Multivariable N = 743	
Outcome	**Effect estimate for VO (95% CI)**	**P-value**	**Effect estimate for VO (95% CI)**	**P-value**
Baseline effect pre-BD FEV_1 % predicted	-8.79% (-10.97%, -6.61%)	<.001	-9.61% (-11.79%, -7.43%)	<.001
Annualized Δ pre-BD FEV_1 % predicted	-0.05% (-0.004, 0.003)	0.785	-0.13% (-0.51%, 0.25%)	0.489
Baseline effect post-BD FEV_1 % predicted	-5.91% (-8.02%, -3.79%)	<.001	-6.60% (-8.73%, -4.48%)	<.001
Annualized Δ post-BD FEV_1 % predicted	-0.53% (-0.90%, -0.15%)	0.006	-0.61% (-0.99%, -0.23%)	0.002
Baseline effect pre-BD FEV_1 (mL)	-162.70 (-274.34, -51.06)	0.004	-225.00 (-298.99, -0.15)	<.001
Annualized Δ pre-BD FEV_1 (mL)	-1.64 (-11.52, 8.24)	0.745	-3.86 (-13.44, 5.72)	0.430
Baseline effect post-BD FEV_1 (mL)	-75.08 (-190.19, 40.03)	0.201	-135.30 (-208.80, -61.80)	<.001
Annualized Δ post-BD FEV_1 (mL)	-14.11 (-23.68, -4.54)	0.004	-16.89 (-26.35, -7.43)	0.001

Summary of physiologic outcome models. Estimate reflects difference for VO compared to no obstruction

- Increased risk for COPD in patients with **pre but not post BD FEV_1/FVC <0,70**.
- Need for change in the spirometry criteria to include those with **pre BD FEV_1/FVC <0,70 ?**

Buhr RJ, et al. *AJRCCM* 2022

DO WE NEED NEW TOOLS ??

Diagnostic test	Mechanism	Diagnostic utility
Forced oscillation technique (FOT) [16]	Single-frequency sinusoidal pressure variations in the lungs during tidal breathing	Respiratory system resistance and reactance during spontaneous ventilation, providing information on regional inhomogeneity and lung periphery
Impulse oscillometry (IOS) [15]	Pressure oscillations at varying frequencies during tidal breathing	Airway resistance allowing distinction small airway obstruction from large airway obstruction
Multiple breath washout [17]	Gas mixing efficiency using lung clearing index formula	Ventilation heterogeneity in conducting airways and small airways.
Plethysmography [18]	Assessment of lung volumes	Measurement of air trapping and hyperinflation.
Static lung volumes [19]	Assessment of lung volumes by gas dilution	Air trapping (FRC/TLC) and hyperinflation (RV/TLC)

Takudzwa Mkorombindo et al. *Curr Opin Pulm Med* 2022

ROLE OF SPIROMETRY

Role of Spirometry in COPD

Table 2.5

- **Diagnosis**
- **Assessment of severity of airflow obstruction (for prognosis)**
- **Follow-up assessment**
  - Therapeutic decisions
    - Pharmacological in selected circumstances (e.g., discrepancy between spirometry and level of symptoms)
    - Consider alternative diagnoses when symptoms are disproportionate to degree of airflow obstruction
    - Non-pharmacological (e.g., interventional procedures)
  - Identification of rapid decline

ASSESSMENT OF AIRFLOW OBSTRUCTION SEVERITY

GOLD Grades and Severity of Airflow Obstruction in COPD (based on post-bronchodilator FEV1)

Table 2.6

In COPD patients (FEV1/FVC < 0.7):

GOLD 1:	Mild	FEV1 ≥ 80% predicted
GOLD 2:	Moderate	50% ≤ FEV1 < 80% predicted
GOLD 3:	Severe	30% ≤ FEV1 < 50% predicted
GOLD 4:	Very Severe	FEV1 < 30% predicted

ASTHMA

In clinical practice, once an obstructive defect has been confirmed, variation in airflow limitation is generally assessed from variation in FEV_1 or PEF. *'Variability'* refers to improvement and/or deterioration in symptoms and lung function. Excessive variability may be identified over the course of one day (diurnal variability), from day to day, from visit to visit, or seasonally, or from a reversibility test. *'Reversibility'* (now called 'responsiveness')[24] generally refers to rapid improvements in FEV_1 (or PEF), measured within minutes after inhalation of a rapid-acting bronchodilator such as 200–400 mcg salbutamol,[27] or more sustained improvement over days or weeks after the introduction of treatment such as ICS.[27]

1. HISTORY OF TYPICAL VARIABLE RESPIRATORY SYMPTOMS	
Feature	*Symptoms or features that support the diagnosis of asthma*
Wheeze, shortness of breath, chest tightness and cough (Descriptors may vary between cultures and by age)	• More than one type of respiratory symptom (in adults, isolated cough is seldom due to asthma) • Symptoms occur variably over time and vary in intensity • Symptoms are often worse at night or on waking • Symptoms are often triggered by exercise, laughter, allergens, cold air • Symptoms often appear or worsen with viral infections
2. CONFIRMED VARIABLE EXPIRATORY AIRFLOW LIMITATION	
Feature	*Considerations, definitions, criteria*
1. Documented* excessive variability in lung function* (one or more of the following):	The greater the variations, or the more occasions excess variation is seen, the more confident the diagnosis. If initially negative, tests can be repeated during symptoms or in the early morning.
• Positive bronchodilator (BD) responsiveness (reversibility) test	*Adults*: increase in FEV_1 of >12% and >200 mL (greater confidence if increase is >15% and >400 mL). *Children*: increase in FEV_1 from baseline of >12% predicted. Measure change 10–15 minutes after 200–400 mcg salbutamol (albuterol) or equivalent, compared with pre-BD readings. Positive test more likely if BD withheld before test: SABA ≥4 hours, twice-daily LABA 24 hours, once-daily LABA 36 hours
• Excessive variability in twice-daily PEF over 2 weeks	*Adults*: average daily diurnal PEF variability >10%* *Children*: average daily diurnal PEF variability >13%*
• Increase in lung function after 4 weeks of treatment	*Adults*: increase in FEV_1 by >12% and >200 mL (or PEF† by >20%) from baseline after 4 weeks of ICS-containing treatment, outside respiratory infections
• Positive exercise challenge test	*Adults*: fall in FEV_1 of >10% and >200 mL from baseline *Children*: fall in FEV_1 of >12% predicted, or PEF >15% from baseline
• Positive bronchial challenge test (usually only for adults)	Fall in FEV_1 from baseline of ≥20% with standard doses of methacholine, or ≥15% with standardized hyperventilation, hypertonic saline or mannitol challenge
• Excessive variation in lung function between visits (good specificity but poor sensitivity)	*Adults*: variation in FEV_1 of >12% and >200 mL between visits, outside of respiratory infections. *Children*: variation in FEV_1 of >12% in FEV_1 or >15% in PEF† between visits (may include respiratory infections)
AND	
2 Documented* expiratory airflow limitation	At a time when FEV_1 is reduced (e.g. during testing above), confirm that FEV_1/FVC is also reduced compared with the lower limit of normal (it is usually >0.75–0.80 in adults, >0.90 in children[21])

COPD vs. ASTHMA

- Static volumes

- Diffusing capacity (may be reduced)

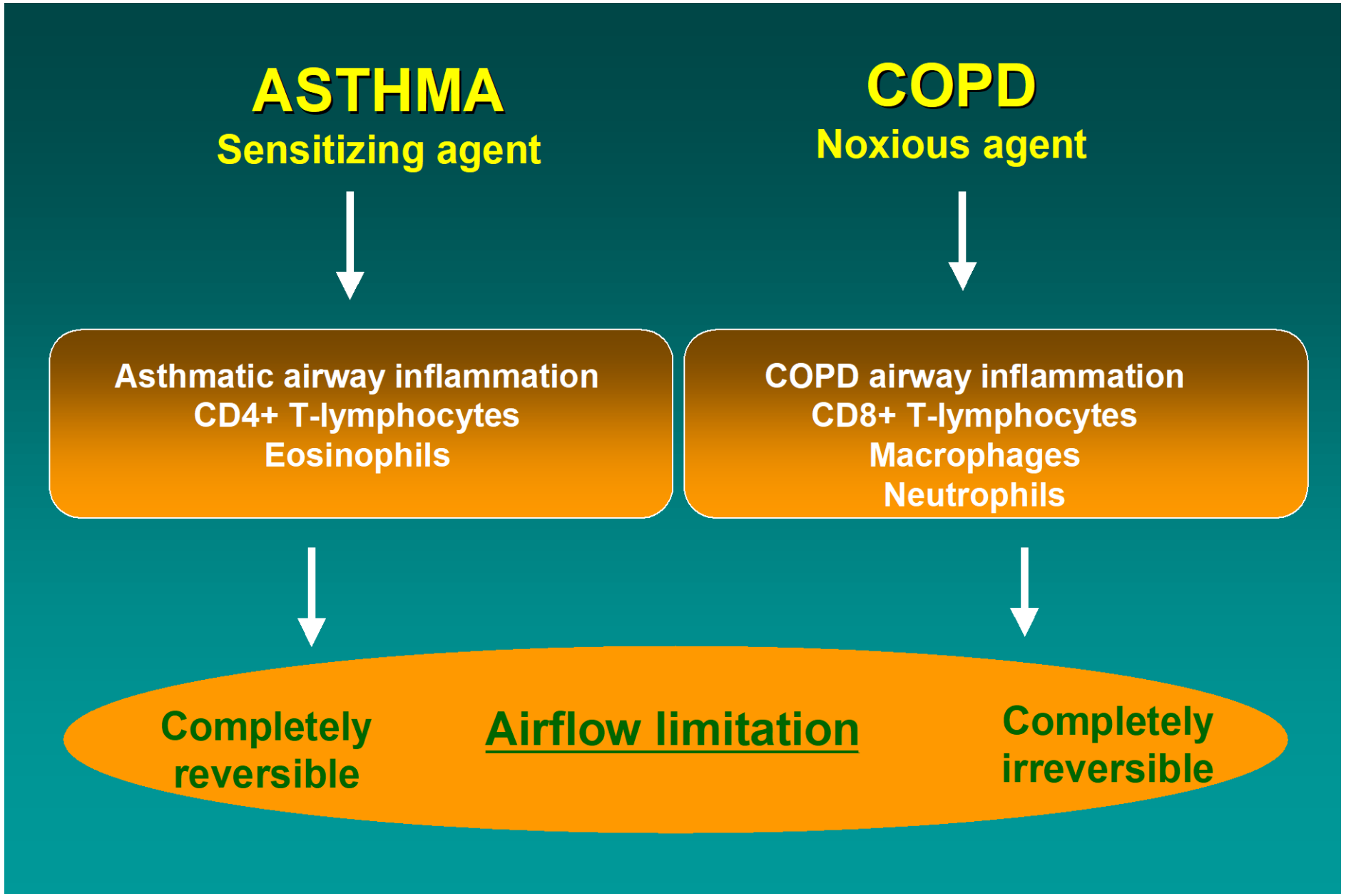
COPD vs. ASTHMA

Differential Diagnosis of COPD

Table 2.3

Diagnosis	Suggestive Features
COPD	Symptoms slowly progressive History of tobacco smoking or other risk factors
Asthma	Variable airflow obstruction Symptoms vary widely from day to day Symptoms worse at night/early morning Allergy, rhinitis, and/or eczema also present Often occurs in children Family history of asthma
Congestive heart failure	Chest X-ray shows dilated heart, pulmonary edema Pulmonary function tests indicate volume restriction, not airflow obstruction
Bronchiectasis	Large volumes of purulent sputum Commonly associated with bacterial infection Chest X-ray/HRCT shows bronchial dilation
Tuberculosis	Onset all ages Chest X-ray shows lung infiltrate Microbiological confirmation High local prevalence of tuberculosis
Obliterative bronchiolitis	Can occur in children Seen after lung or bone marrow transplantation HRCT on expiration shows hypodense areas
Diffuse panbronchiolitis	Predominantly seen in patients of Asian descent Most patients are male and nonsmokers Almost all have chronic sinusitis Chest X-ray & HRCT show diffuse small centrilobular nodular opacities & hyperinflation

These features tend to be characteristic of the respective diseases, but are not mandatory. For example, a person who has never smoked may develop COPD (especially in LMICs where other risk factors may be more important than cigarette smoking).

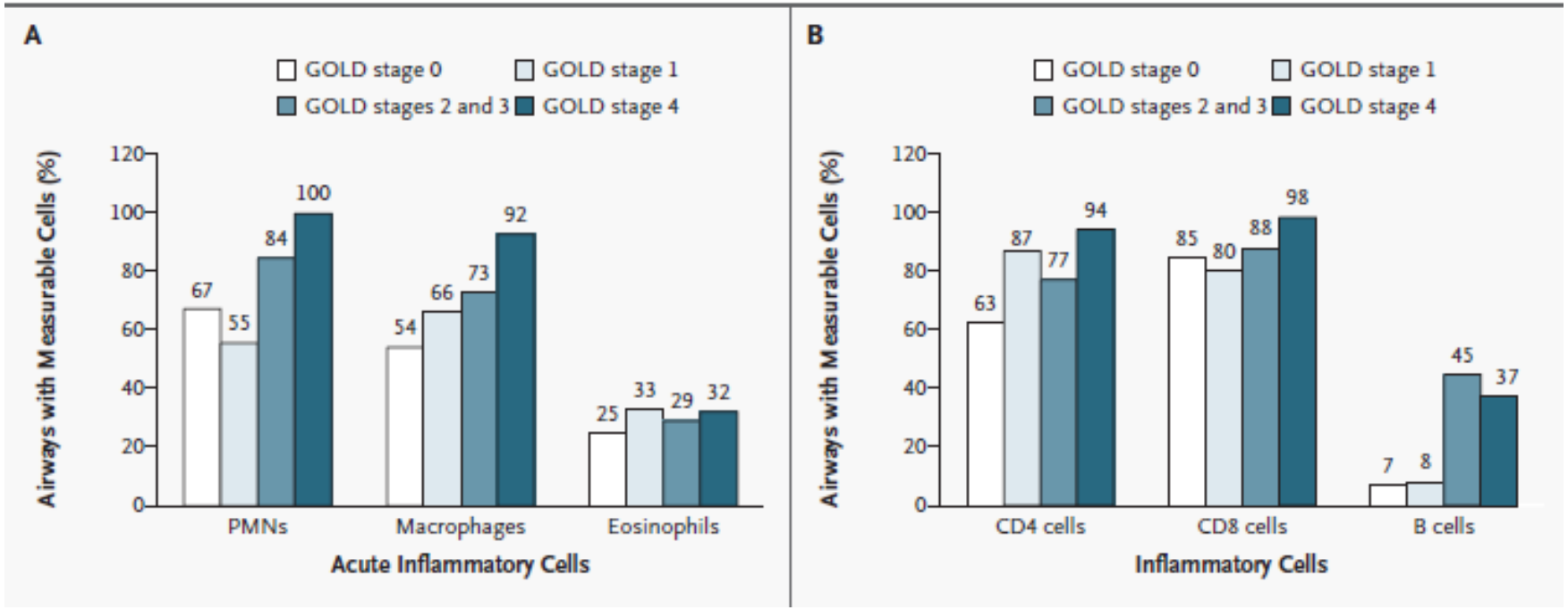

ASTHMA
Sensitizing agent
COPD
Noxious agent
Asthmatic airway inflammation
CD4+ T-lymphocytes
Eosinophils
COPD airway inflammation
CD8+ T-lymphocytes
Macrophages
Neutrophils
Completely reversible
Airflow limitation
Completely irreversible

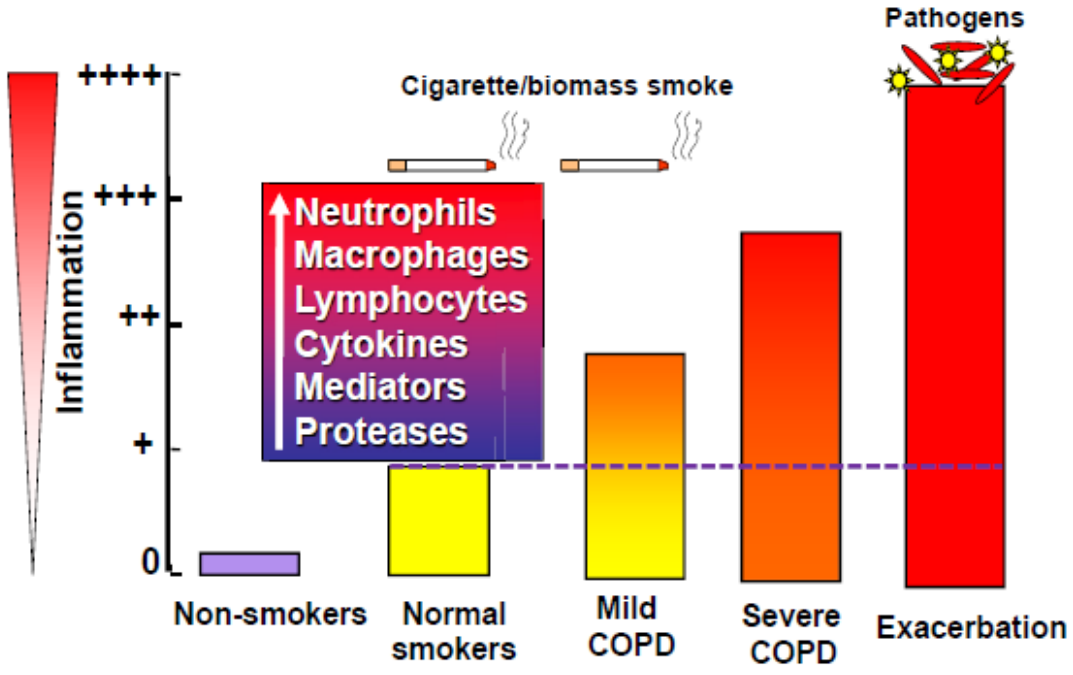
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 24, 2004 VOL. 350 NO. 26

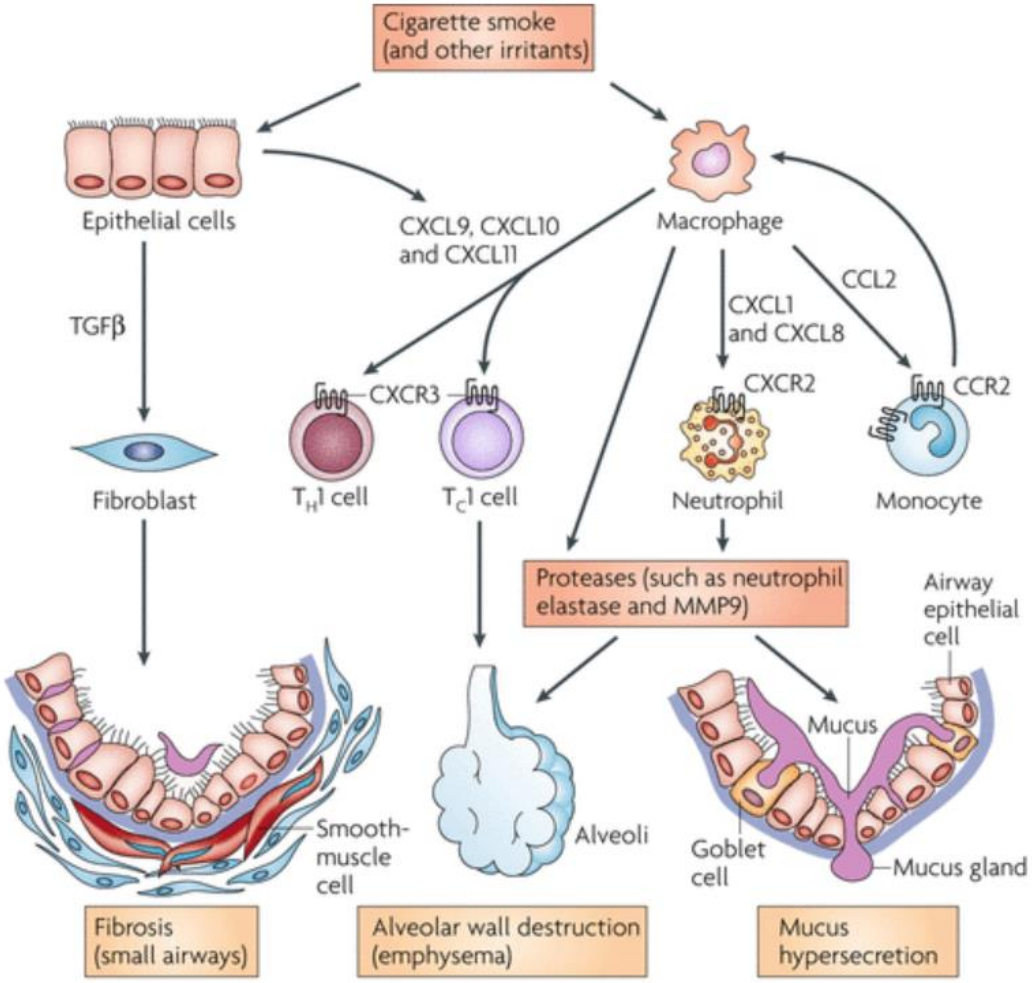
The Nature of Small-Airway Obstruction in Chronic Obstructive Pulmonary Disease

James C. Hogg, M.D., Fanny Chu, B.Sc., Soraya Utokaparch, B.Sc., Ryan Woods, M.Sc., W. Mark Elliott, Ph.D., Liliana Buzatu, M.D., Ruben M. Cherniack, M.D., Robert M. Rogers, M.D., Frank C. Sciurba, M.D., Harvey O. Coxson, Ph.D., and Peter D. Paré, M.D.

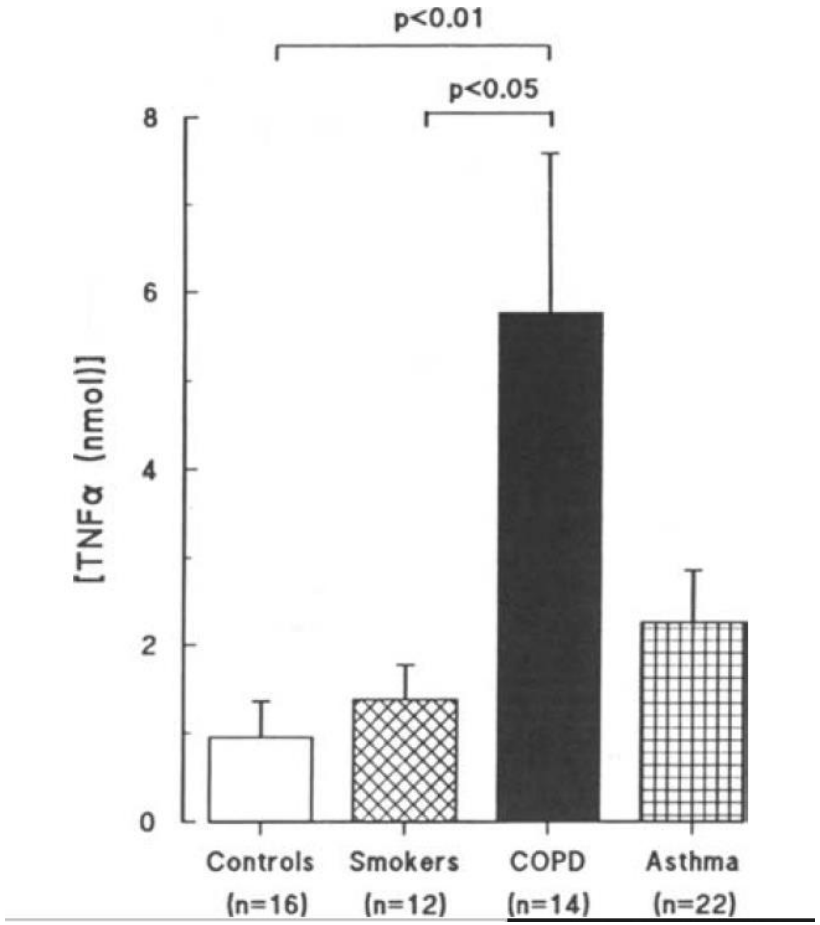


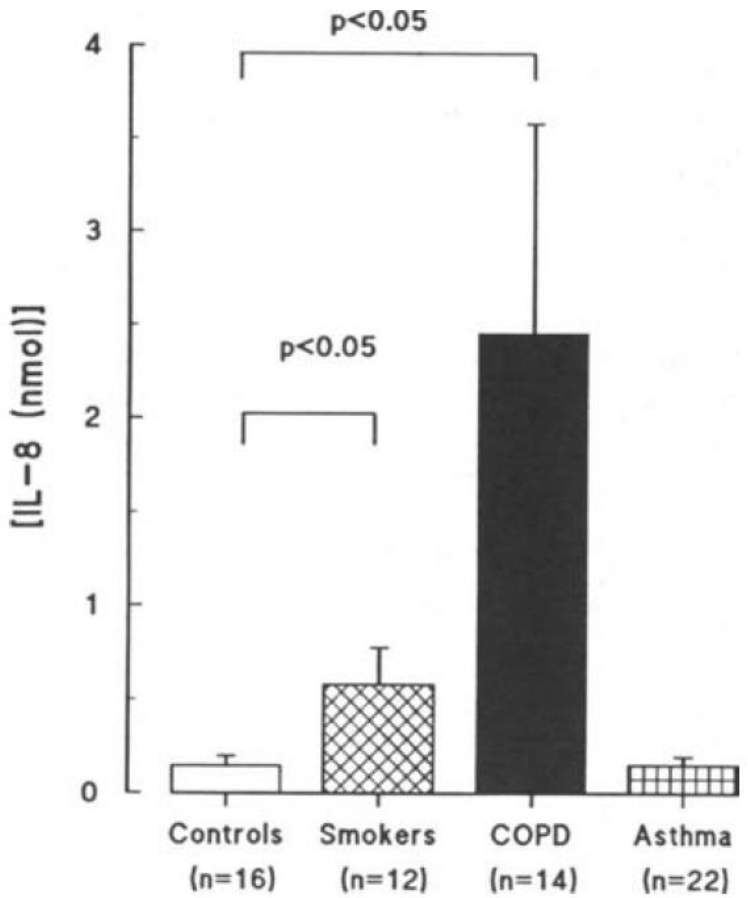


Barnes PJ JACI 2016



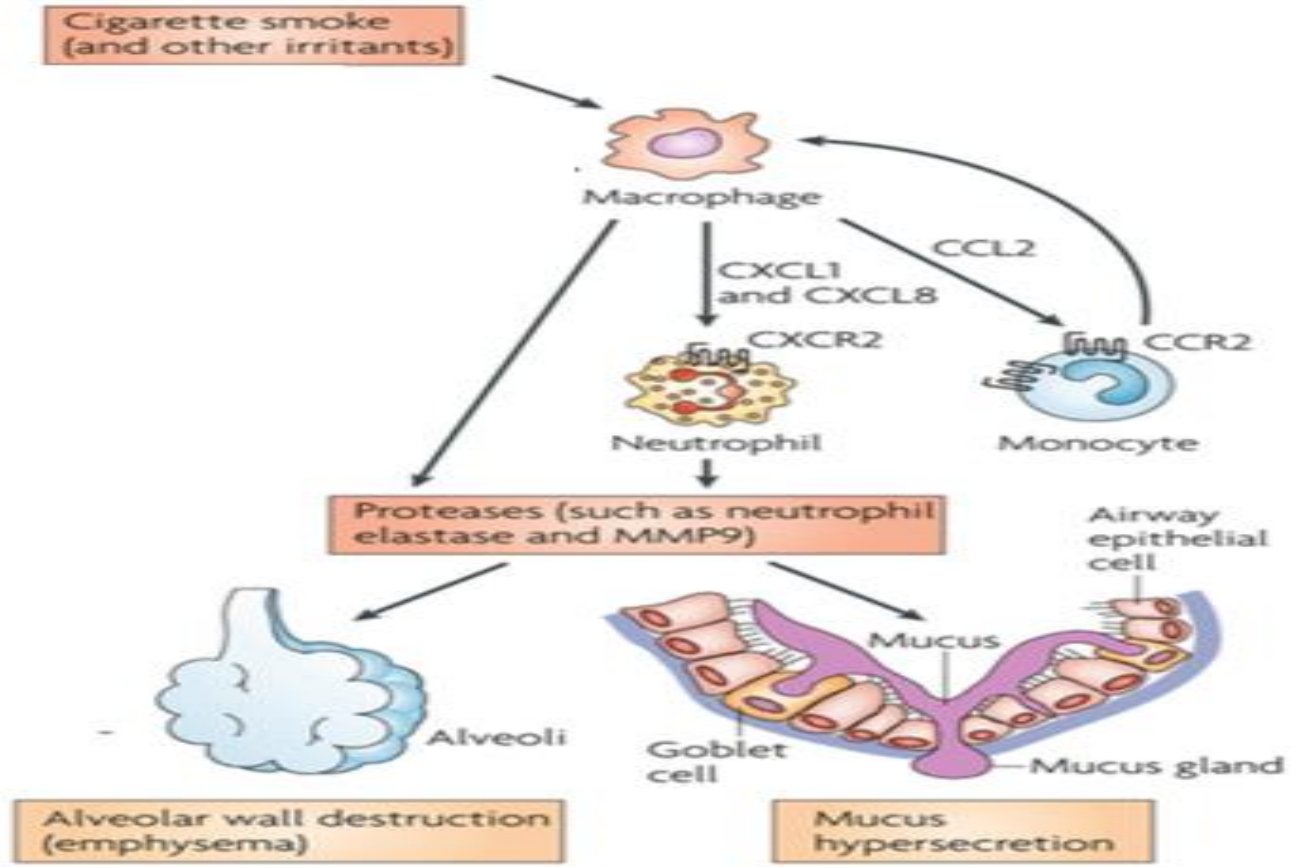
COPD - Macrophages



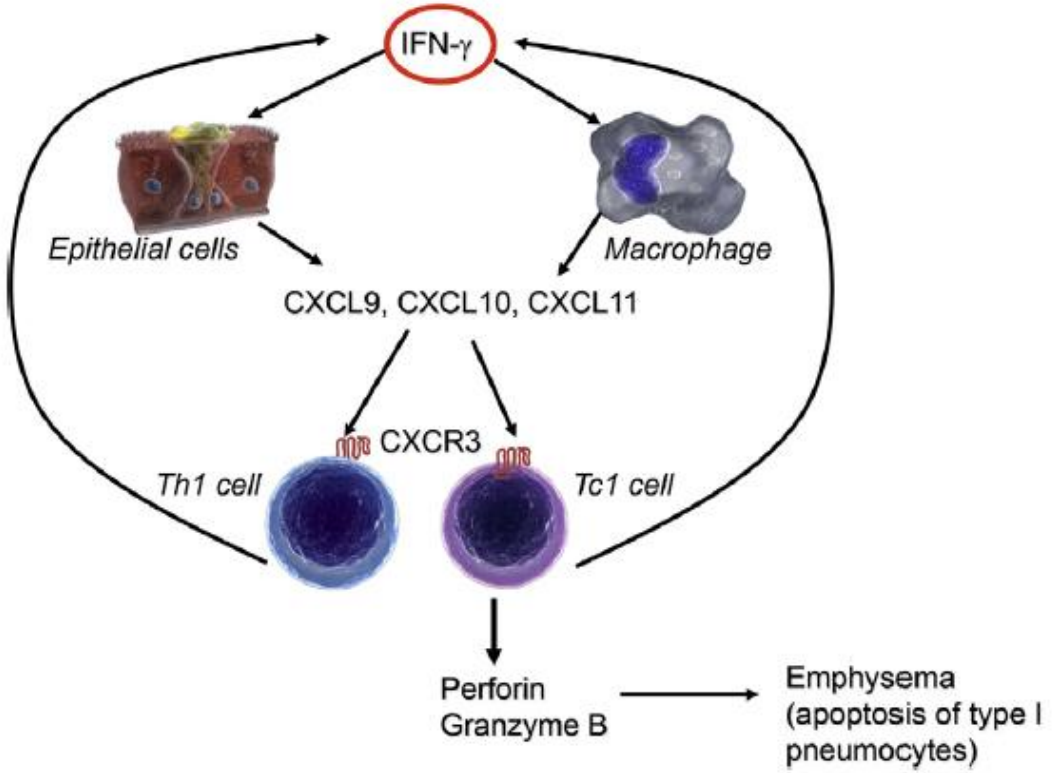


Keatings VM et al AJRCCM 1996

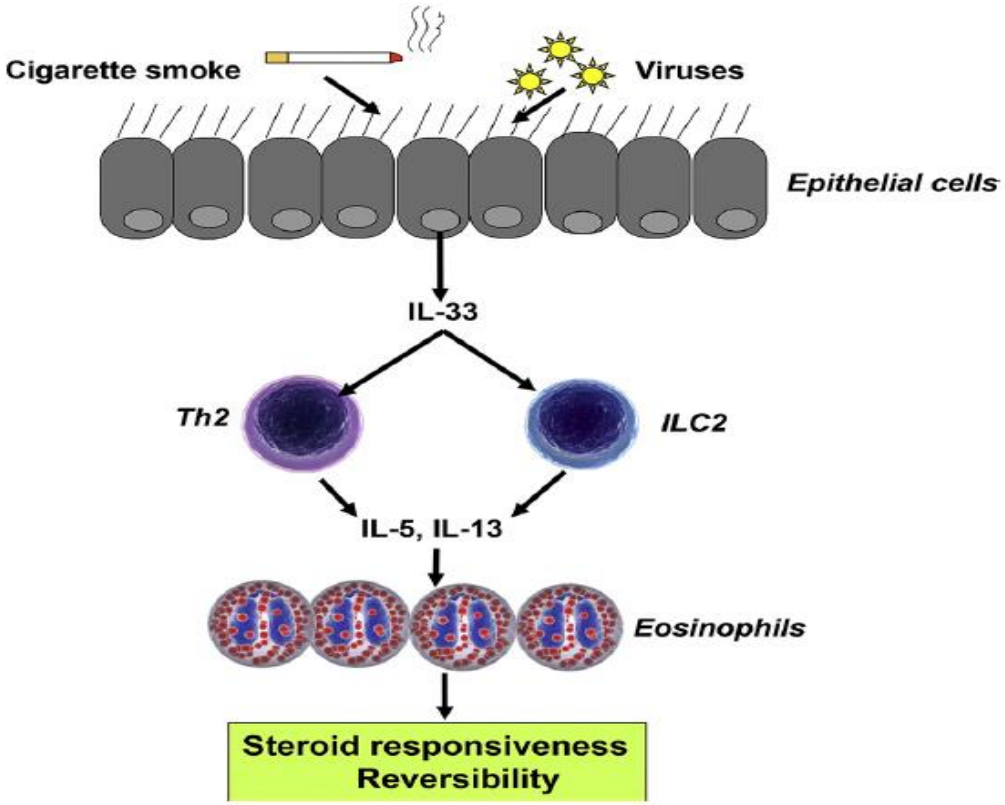
COPD - Neutrophils



COPD - Lymphocytes

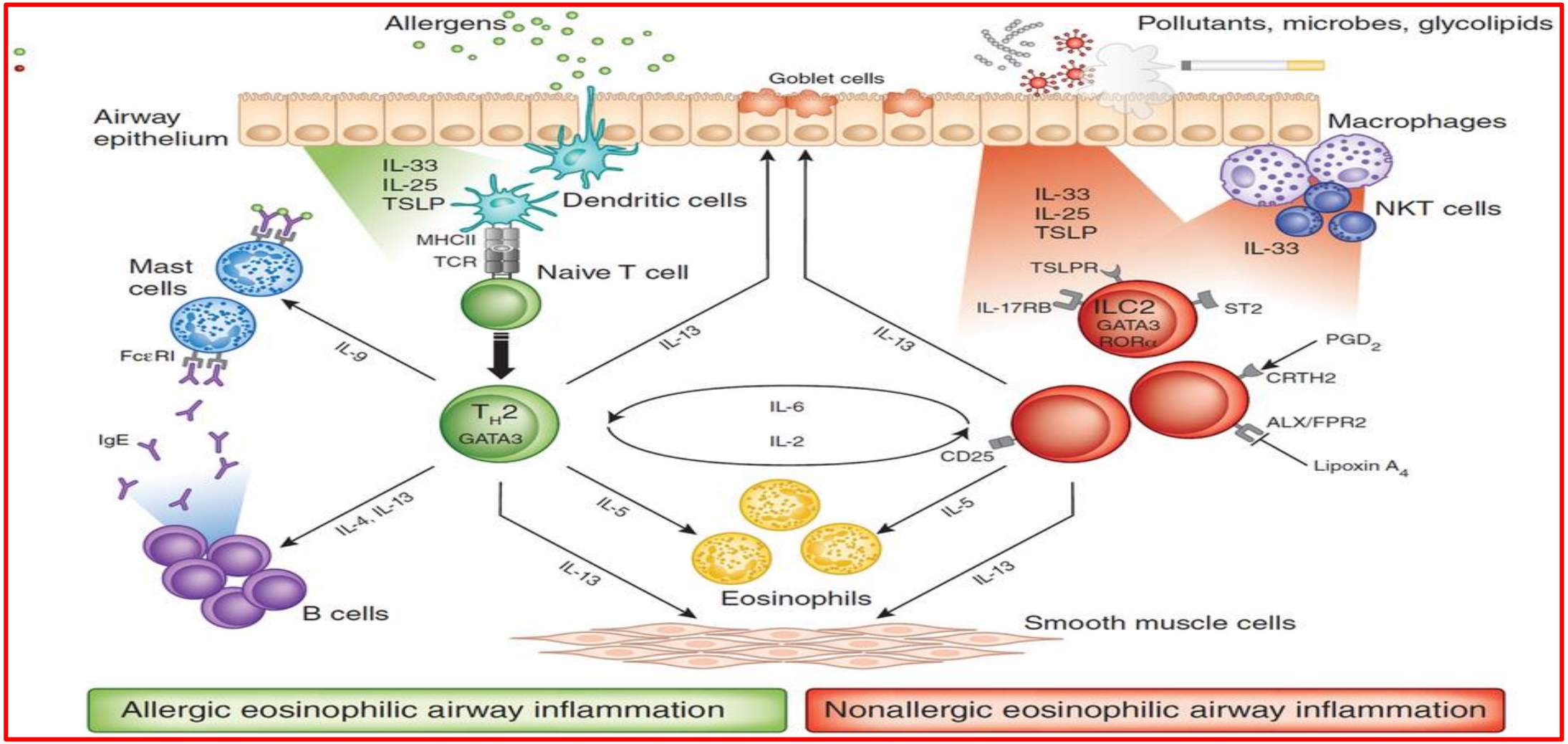


COPD - Eosinophils



Barnes PJ JACI 2016

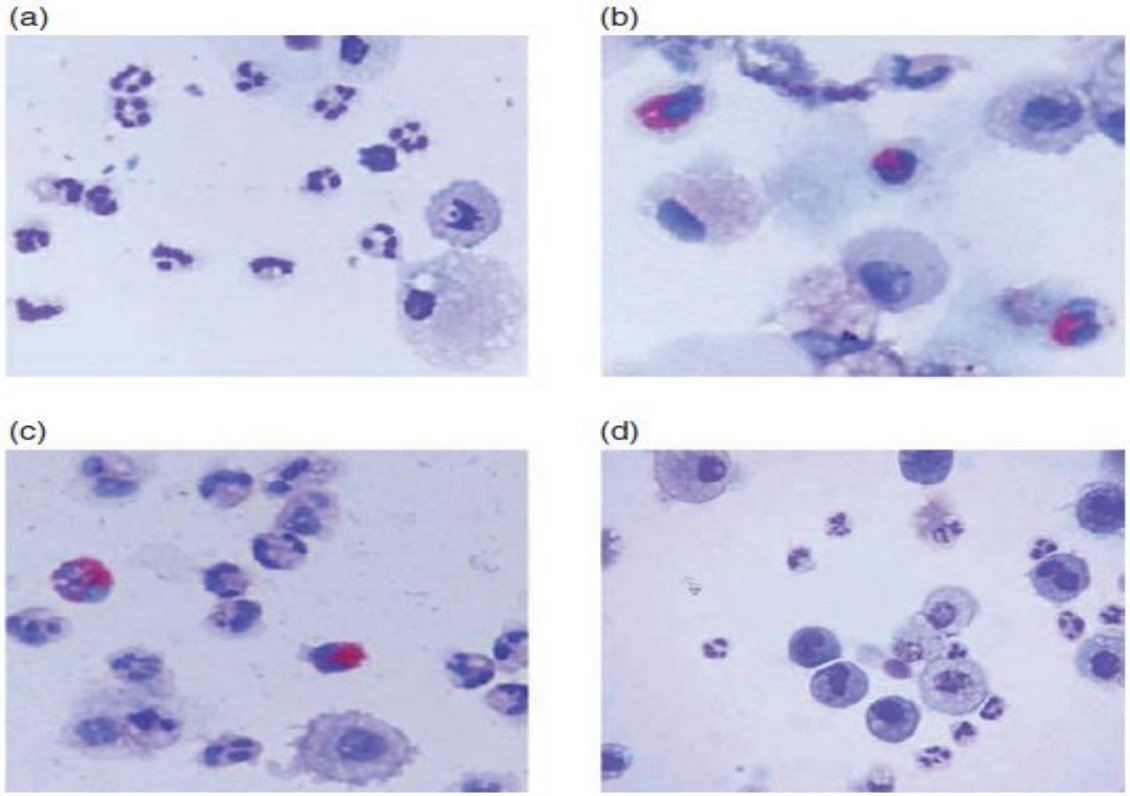
ASTHMA



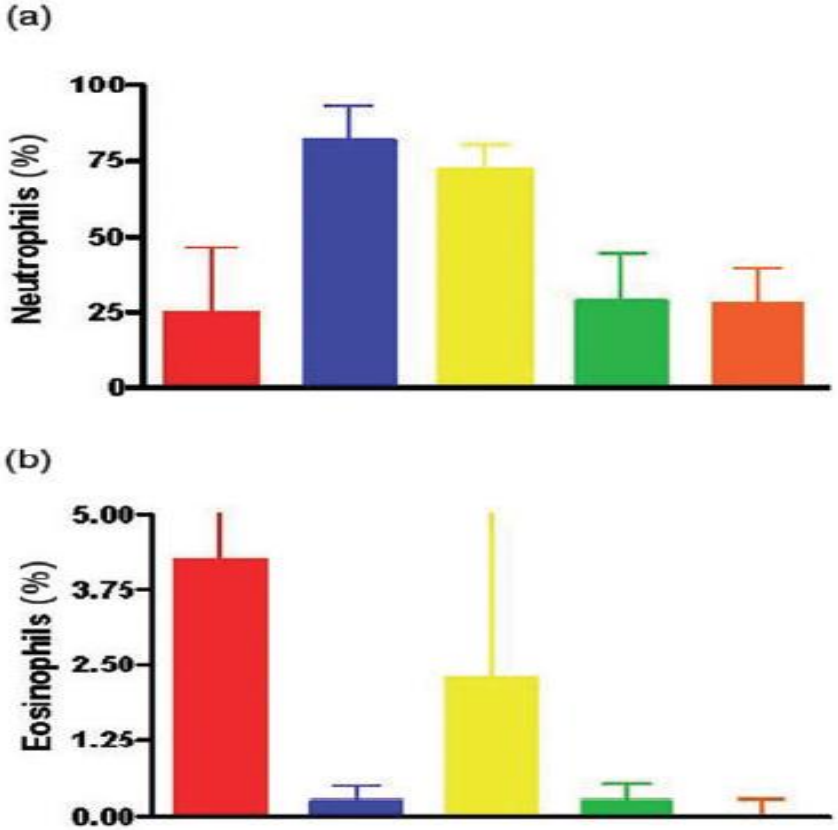
Brusselle G et al, Nat Med 2013

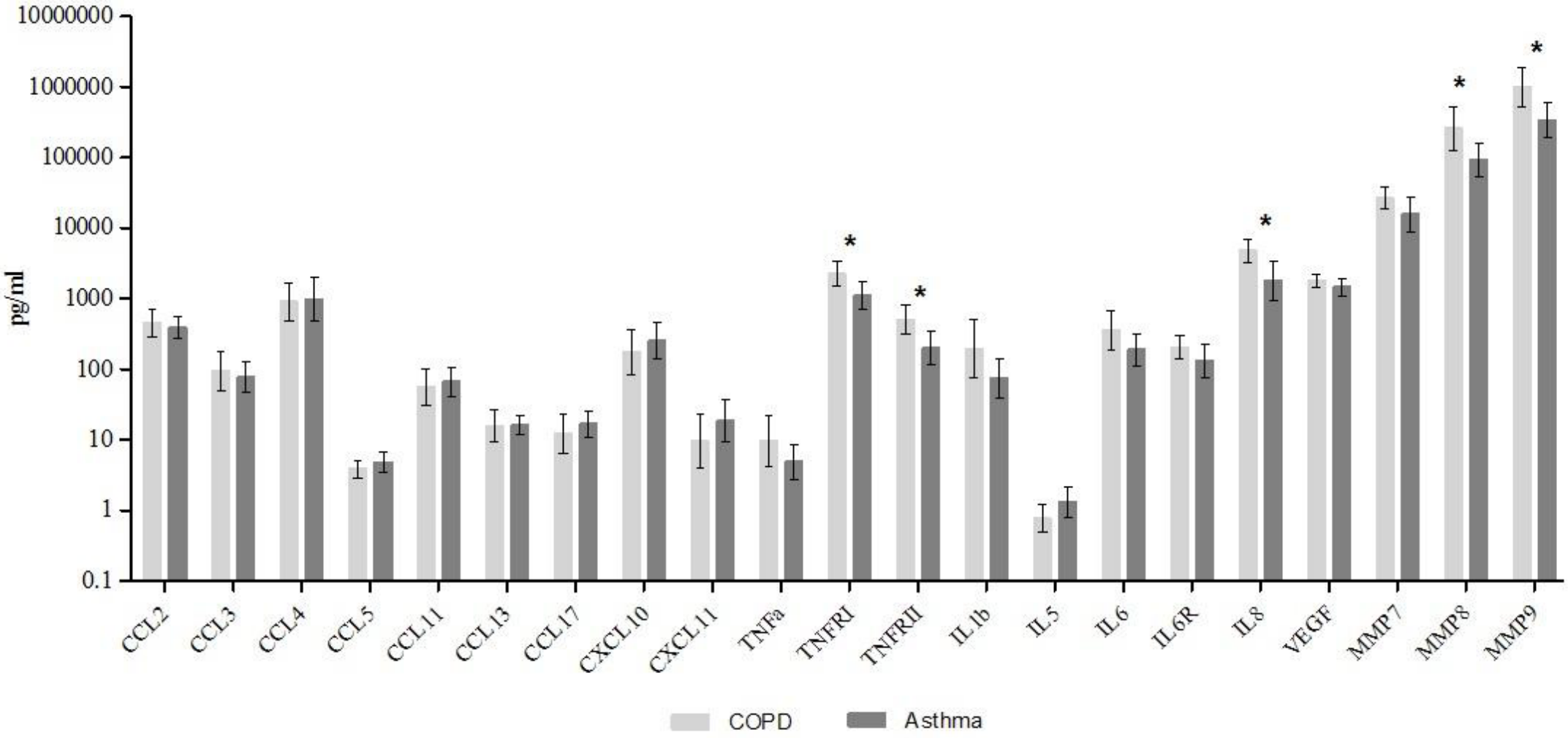
INFLAMMATORY PHENOTYPES IN INDUCED SPUTUM - ASTHMA

J Simpson et al, Respirology, 2006

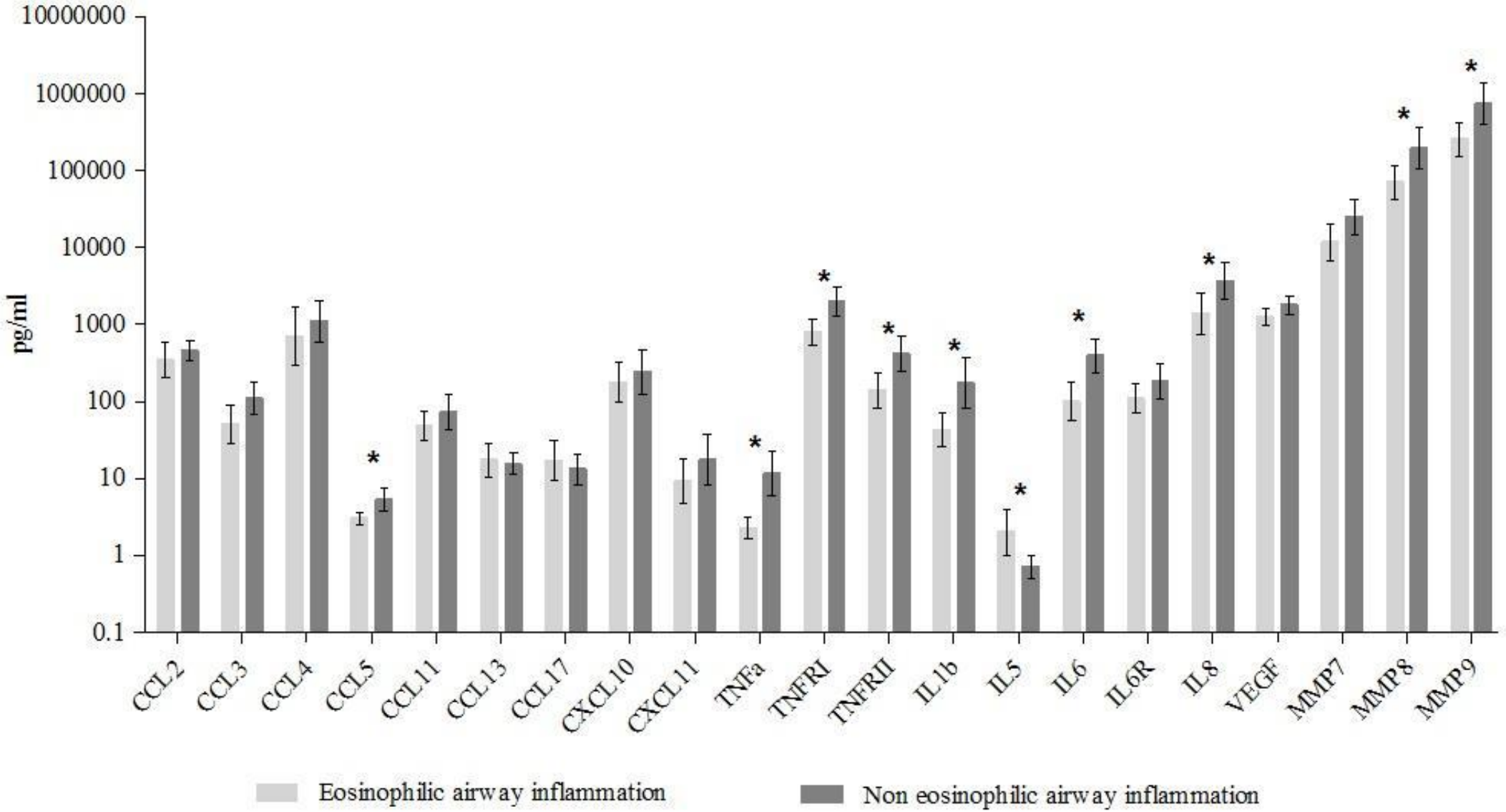


Eos Neut Mixed Pauci Healthy





Bafadhel M et al, Respiration 2012



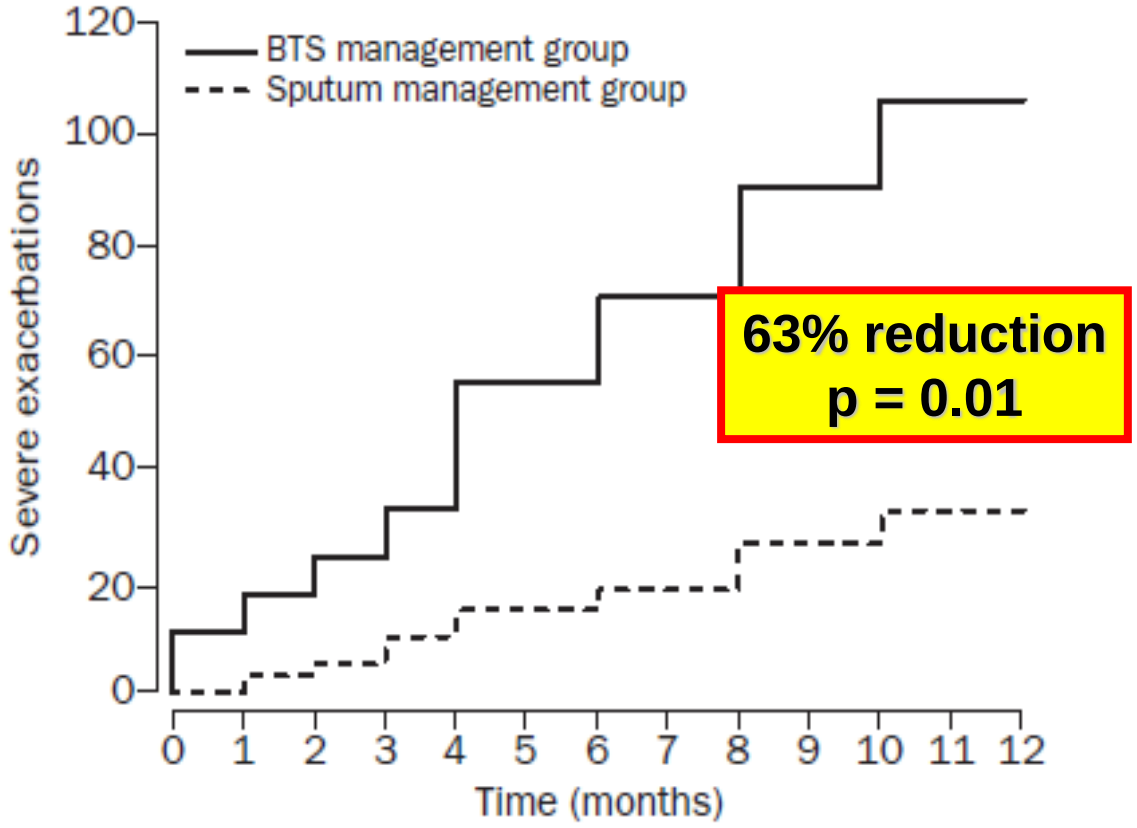
Bafadhel M et al, Respiration 2012

- Within airway inflammatory sub-phenotypes there is a differential pattern of mediator expression that is independent of disease. In other words, these phenotypes were unrelated to the diagnosis of asthma or COPD.

Bafadhel M et al, Respiration 2012

SPUTUM EOSINOPHILS AND ASTHMA MANAGEMENT

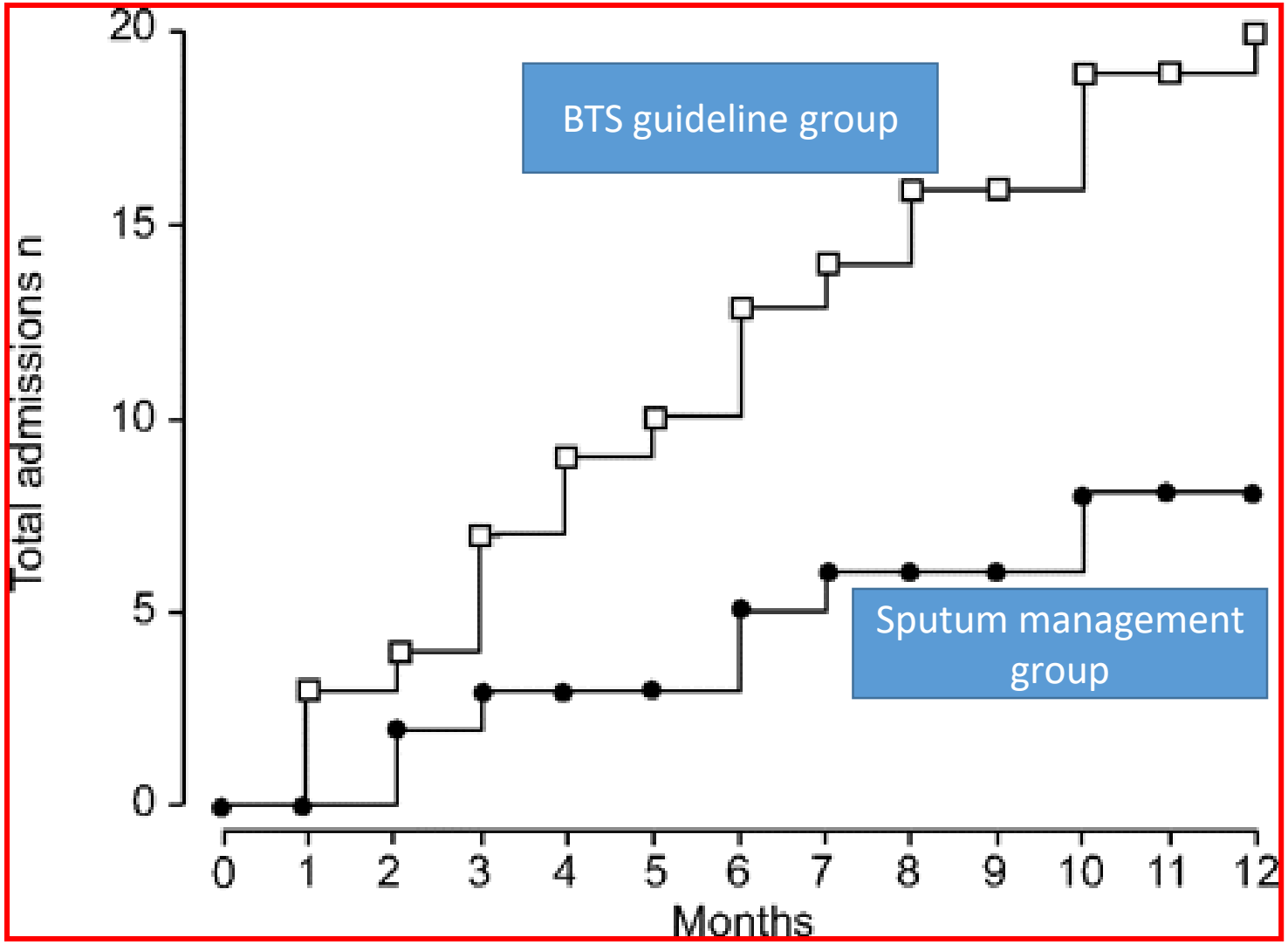
74 patients with moderate to severe asthma from hospital clinics



- **Reduction in exacerbations:**
  - Severe exacerbations: 35 vs. 109 (p=0.01)
  - Hospitalizations: 1 vs. 6 (p=0.047)
- Sputum eosinophil count was 63% lower over 12 months (p=0.002)
- Average daily dose of ICS or oral CS did *not* differ between the two groups

Green RH, Lancet 2002

SPUTUM EOSINOPHILS AND COPD MANAGEMENT

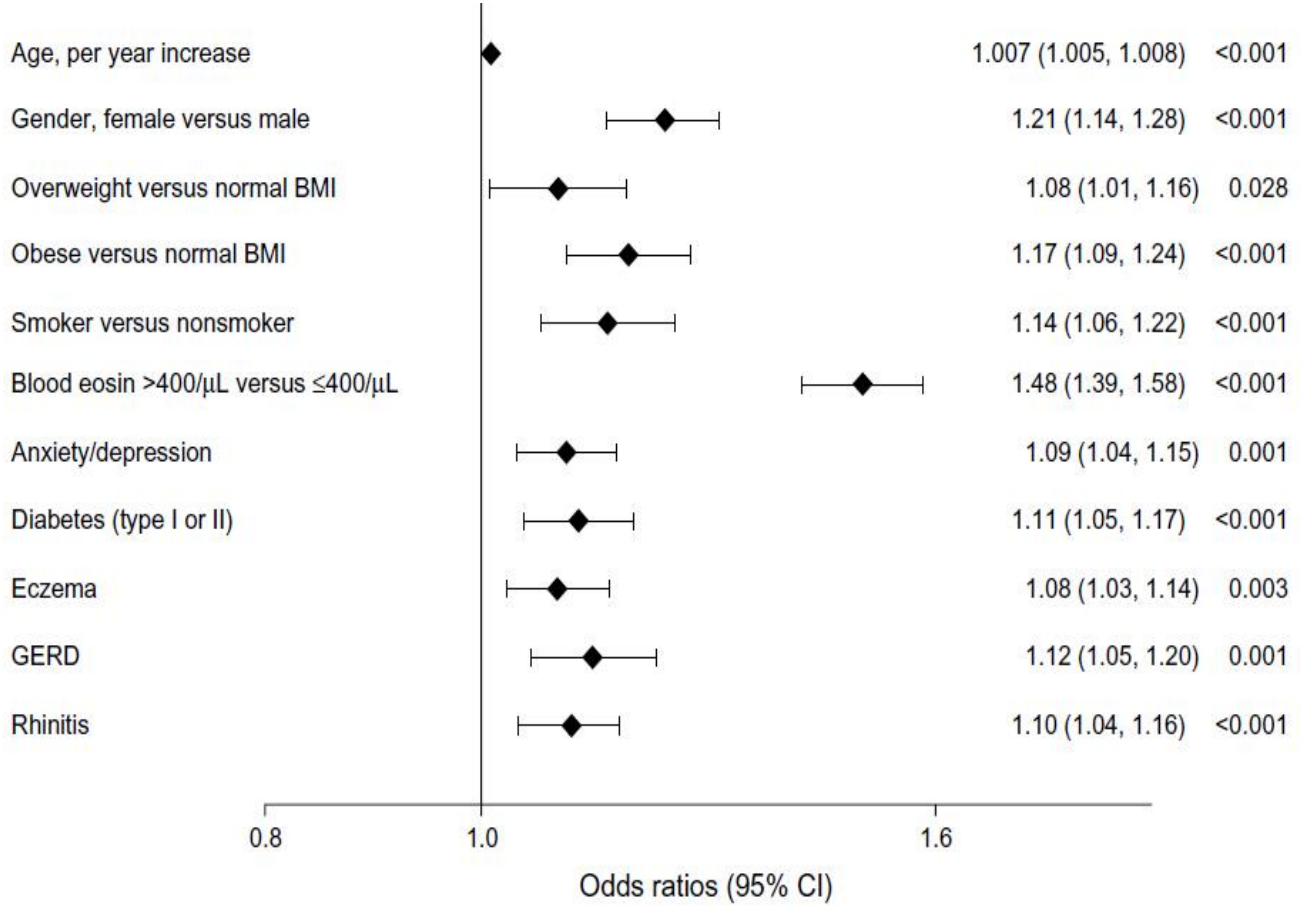


N=82

Siva R et al ERJ 2007

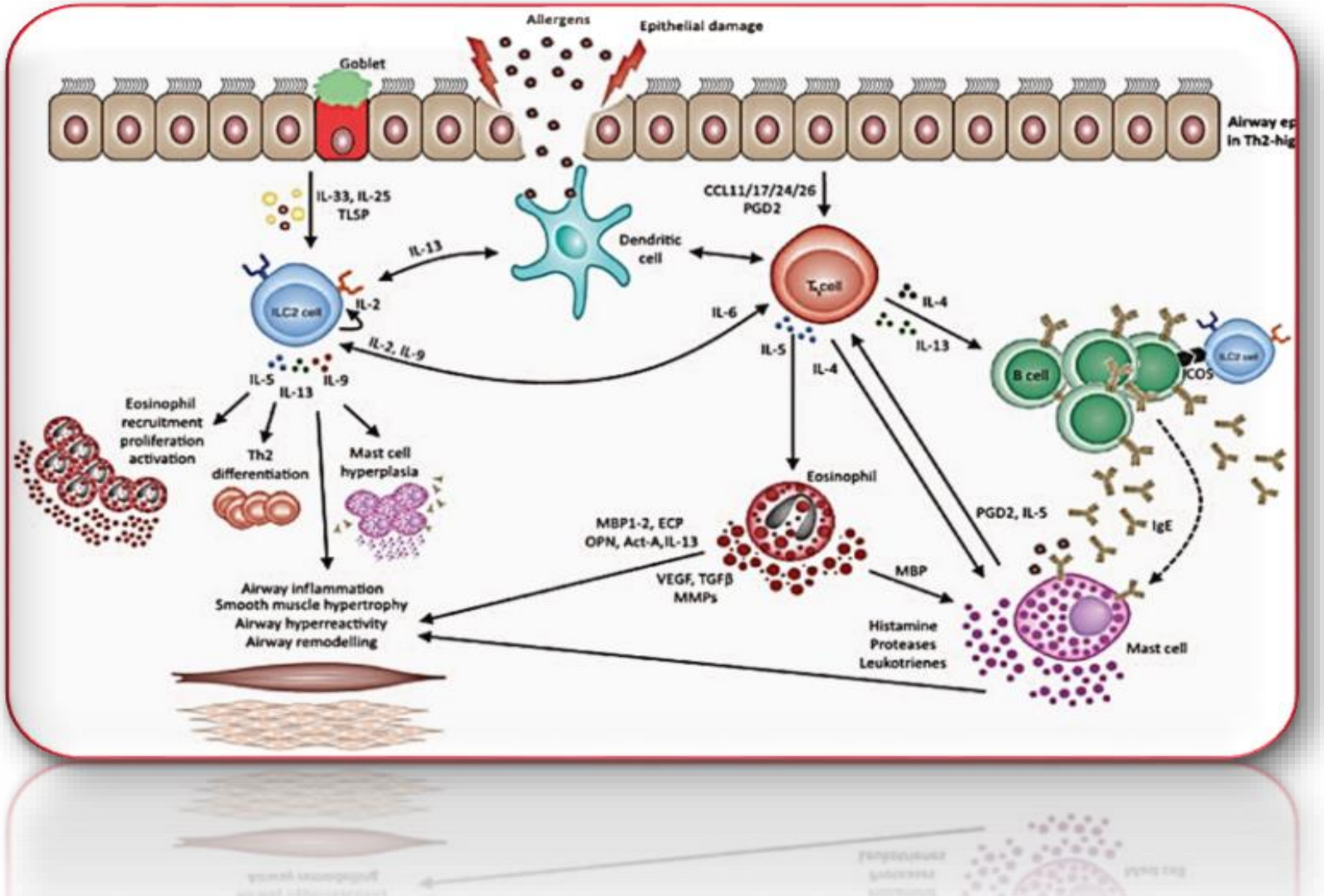
EOSINOPHILS AND EXACERBATIONS IN ASTHMA

Medical record study of 130,547 patients with asthma treated in UK clinical practice, using data obtained from two large, anonymised patient databases: Optimum Patient Care Research Database (OPCRD) and Clinical Practice Research Datalink (CPRD)

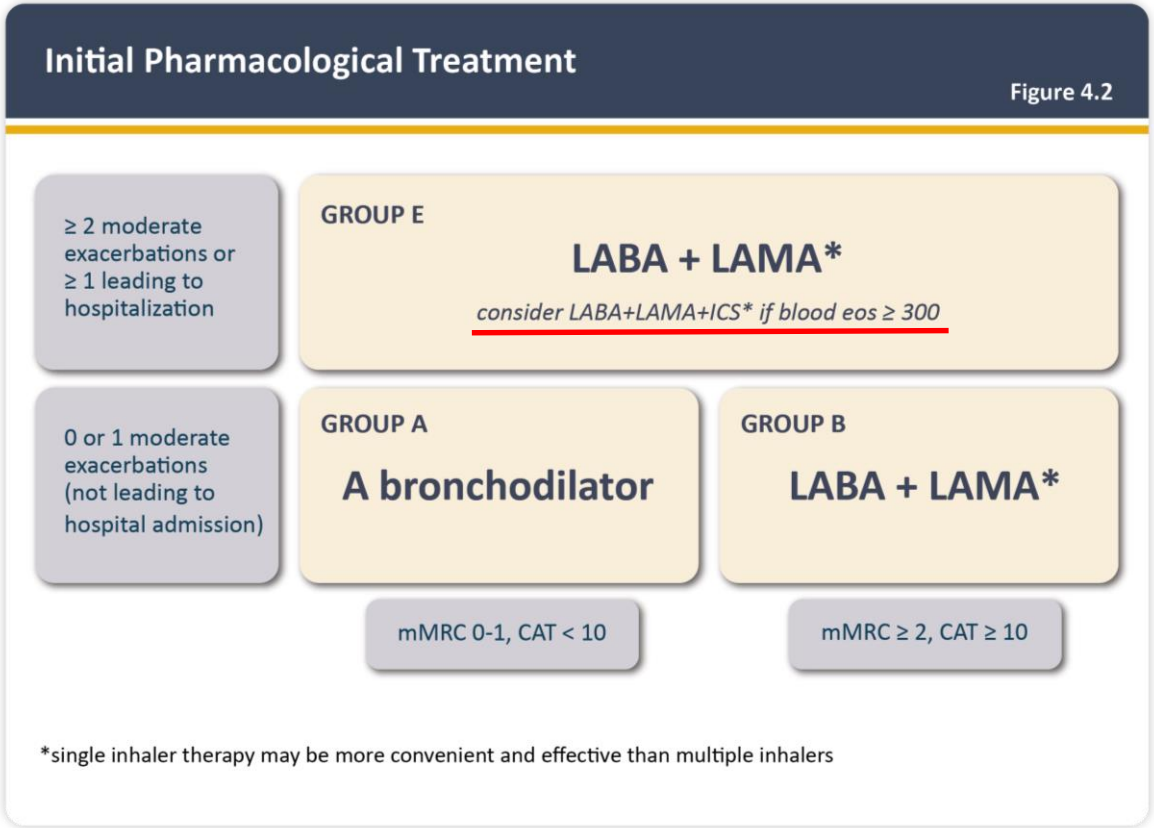


Price D et al. *J Asthma Allergy* 2016;9:1-13

T2 High ENDOTYPE

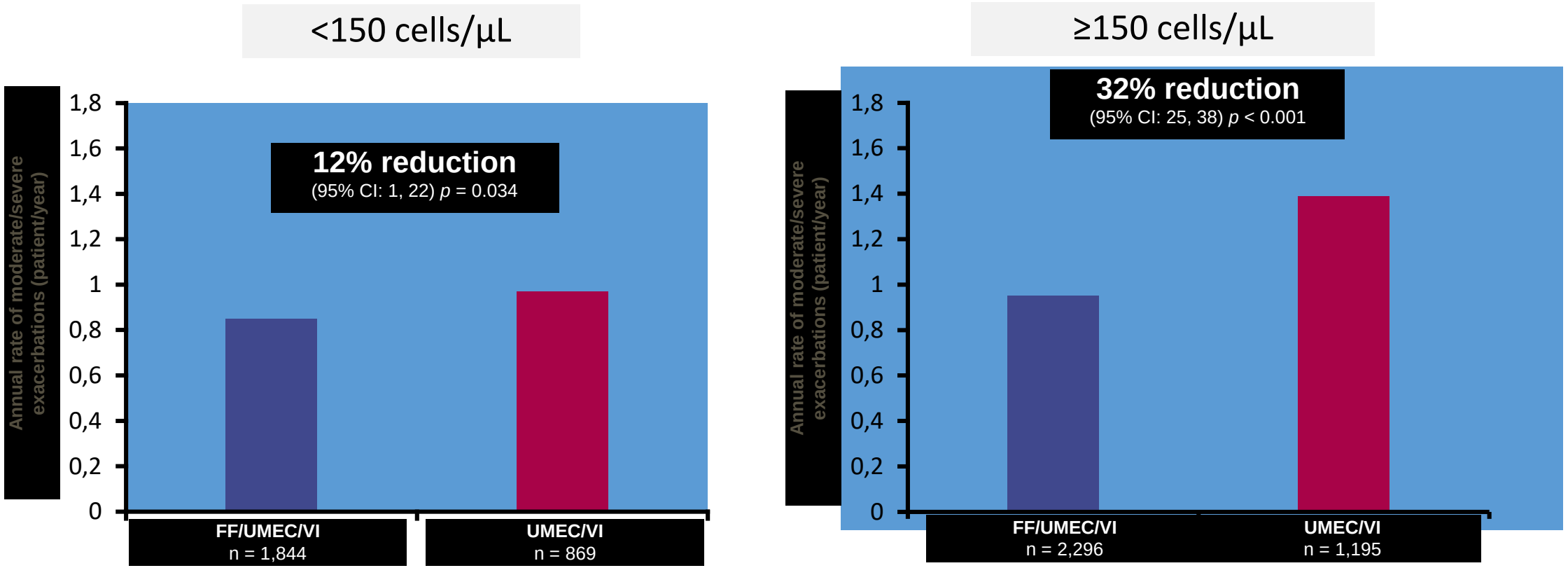


COPD - BRONCHODILATORS



IMPACT: BLOOD EOSINOPHIL COUNT AND REDUCTION OF EXACERBATIONS

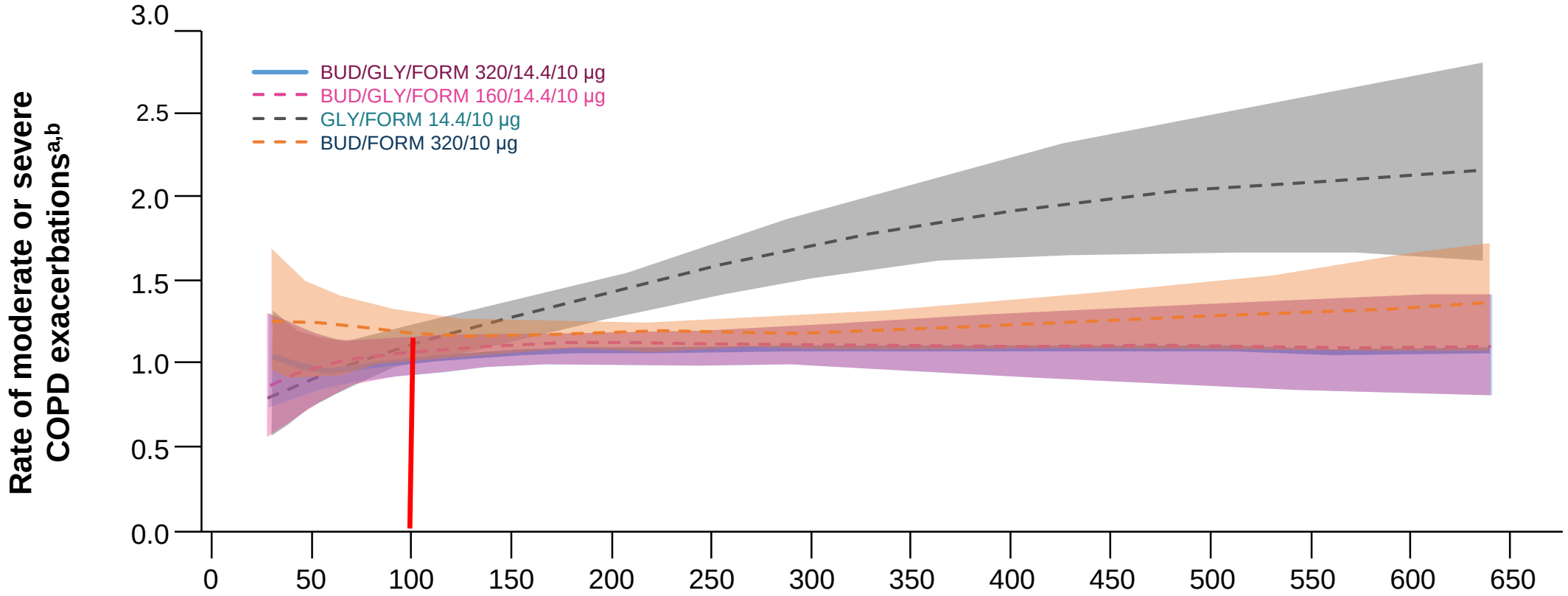
FF/UMEC/VI vs UMEC/VI



IMPACT TRIAL

Lipson DA, et al. *N Engl J Med*. 2018.

ETHOS: Triple combination BUD/GLY/FORM was more beneficious in reducing exacerbations vs. LAMA/LABA as blood eosinophils got higher



Rabe KF et al. *N Engl J Med*. 2020

CHRONIC INFLAMMATION

Anti-Inflammatory Therapy in Stable COPD

Table 3.5

Inhaled Corticosteroids	• An ICS combined with a LABA is more effective than the individual components in improving lung function and health status and reducing exacerbations in patients with exacerbations and moderate to very severe COPD **(Evidence A)** • Regular treatment with ICS increases the risk of pneumonia especially in those with severe disease **(Evidence A)** • Lower blood and sputum eosinophils are associated with greater presence of proteobacteria, notably *Haemophilus*, increased bacterial infections & pneumonia • Independent of ICS use, there is evidence that a blood eosinophil count < 2% increases the risk of pneumonia **(Evidence C)** • Triple inhaled therapy of LABA+LAMA+ICS improves lung function, symptoms and health status, and reduces exacerbations, compared to LABA+ICS, LABA+LAMA or LAMA monotherapy **(Evidence A)**. Recent data suggest a beneficial effect of triple inhaled therapy versus fixed-dose LABA+LAMA combinations on mortality in symptomatic COPD patients with a history of frequent and/or severe exacerbations • Single inhaler therapy may be more convenient and effective than multiple inhalers
Oral Glucocorticoids	• Long-term use of oral glucocorticoids has numerous side effects **(Evidence A)** with no evidence of benefits **(Evidence C)**
PDE4 Inhibitors	• In patients with chronic bronchitis, severe to very severe COPD and a history of exacerbations: ▪ A PDE4 inhibitor improves lung function and reduces moderate and severe exacerbations **(Evidence A)** ▪ A PDE4 inhibitor improves lung function and decreases exacerbations in patients who are on fixed-dose LABA+ICS combinations **(Evidence A)**
Antibiotics	• Long-term azithromycin and erythromycin therapy reduces exacerbations over one year **(Evidence A)** • Treatment with azithromycin is associated with an increased incidence of bacterial resistance **(Evidence A)** and hearing test impairments **(Evidence B)**
Mucoregulators and Antioxidant Agents	• Regular treatment with mucolytics such as erdosteine, carbocysteine and NAC reduces the risk of exacerbations in select populations **(Evidence B)**
Other Anti-Inflammatory Agents	• Simvastatin does not prevent exacerbations in COPD patients at increased risk of exacerbations and without indications for statin therapy **(Evidence A)**. However, observational studies suggest that statins may have positive effects on some outcomes in patients with COPD who receive them for cardiovascular and metabolic indications **(Evidence C)** • Leukotriene modifiers have not been tested adequately in COPD patients

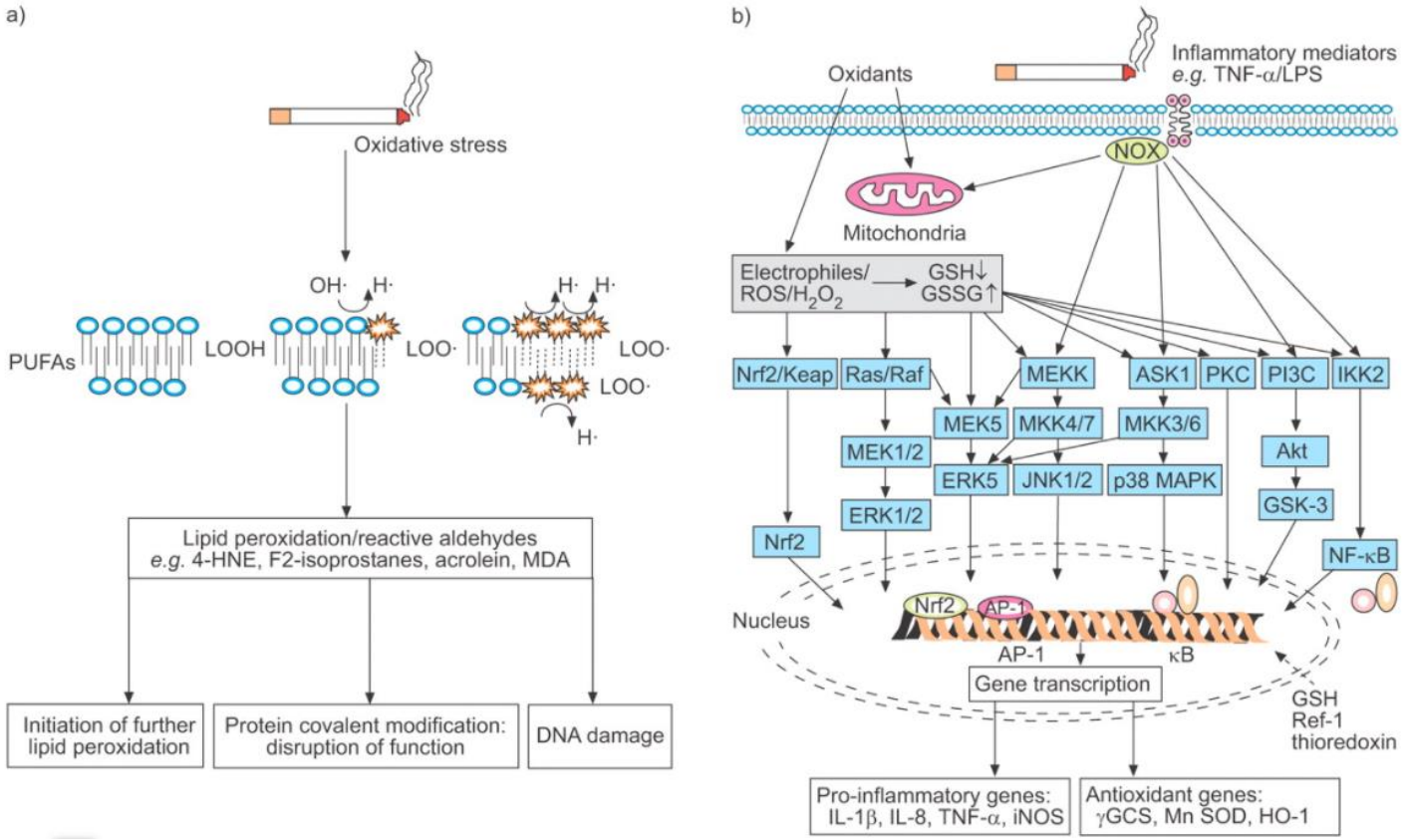
IMPORTANT POINTS

Key Points for the Use of Anti-Inflammatory Agents

Table 4.7

- Long-term monotherapy with ICS is not recommended **(Evidence A)**
- We do not encourage the use of a LABA+ICS combination in COPD. If there is an indication for an ICS the combination LABA+LAMA+ICS has been shown to be superior to LABA+ICS and is therefore the preferred choice. This combination can be given as single or multiple inhaler therapy.
- If patients with COPD have features of asthma, treatment should always contain an ICS
- In patients with severe to very severe airflow limitation, chronic bronchitis and exacerbations the addition of a PDE4 inhibitor to a treatment with long acting bronchodilators with/without ICS can be considered **(Evidence B)**
- Preferentially, but not only in former smokers with exacerbations despite appropriate therapy, macrolides, in particular azithromycin, can be considered **(Evidence B)**
- Statin therapy and/or beta-blockers are not recommended for prevention of exacerbations **(Evidence A)**

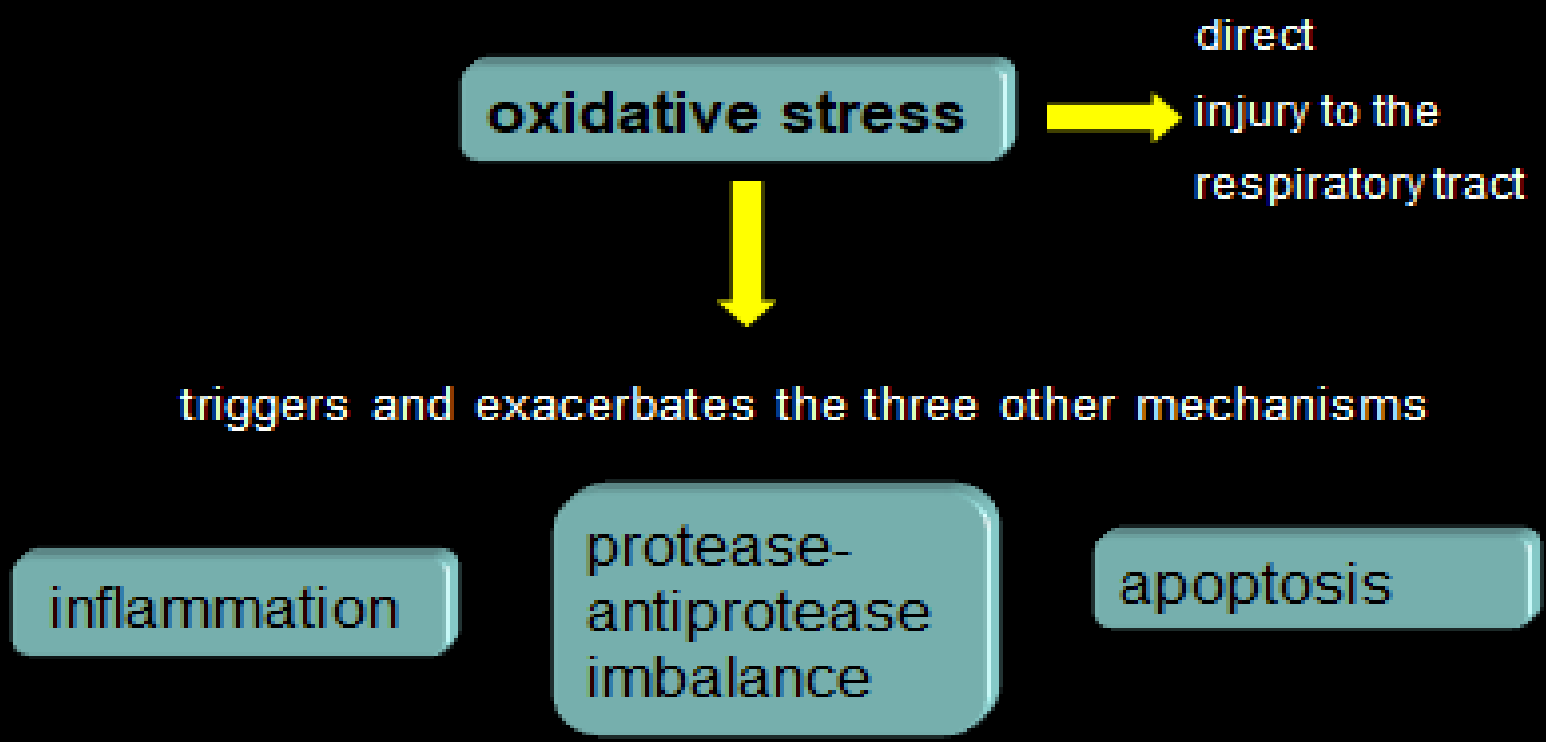
Oxidative stress promotes inflammation



Activation of transcription factors

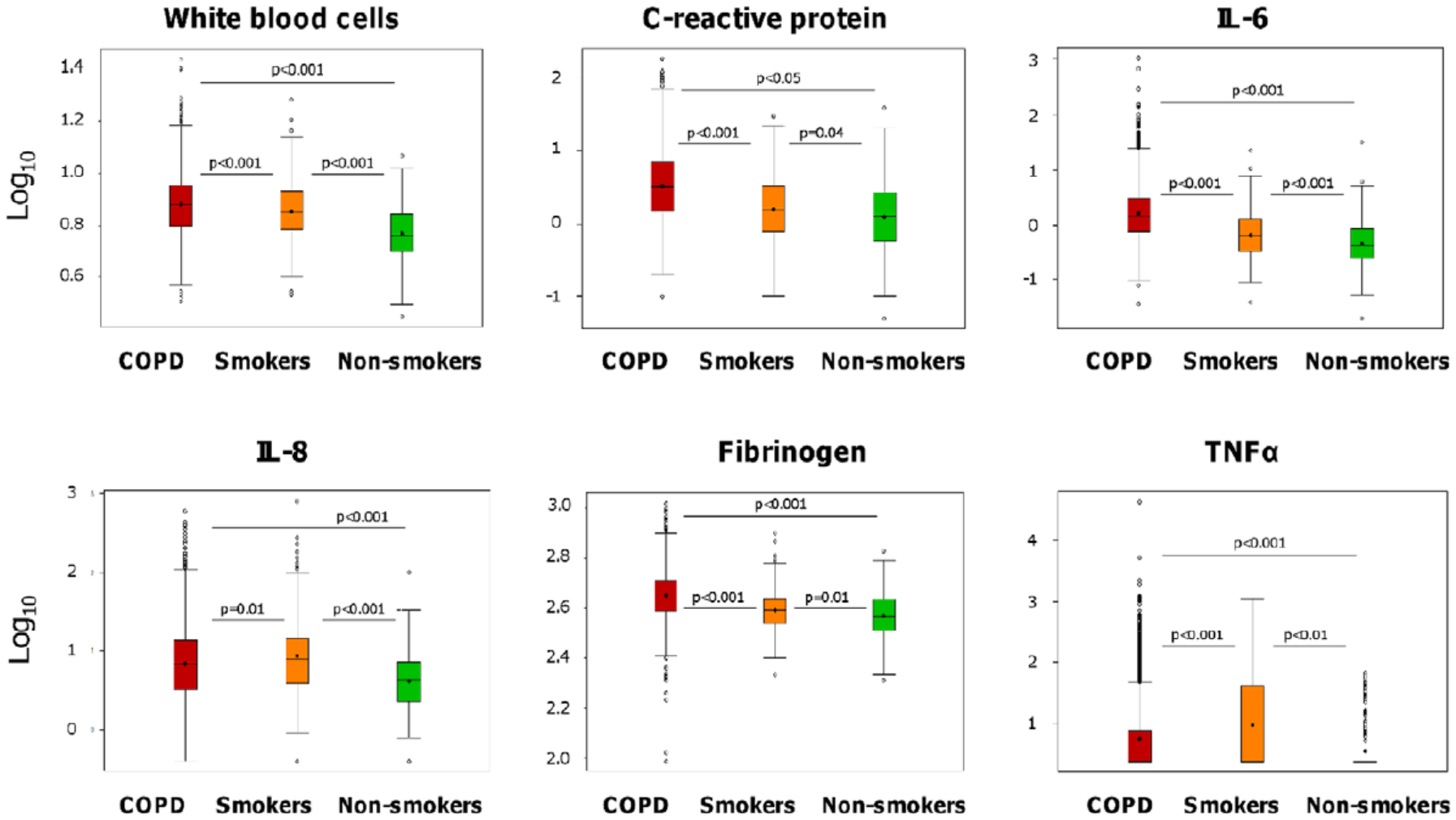
Production of inflammatory and antioxidative molecules

Principal mechanisms responsible for the alterations observed in COPD



MacNee W. *Proc Am Thorac Soc* 2005; 2: 258-66.

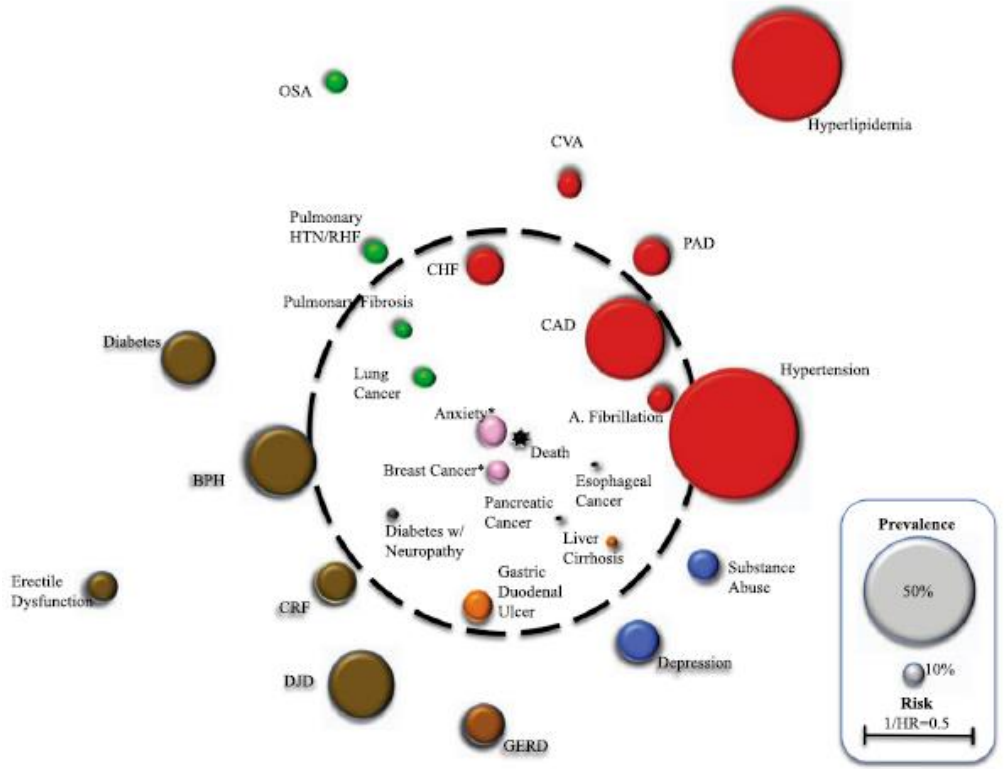
Systemic inflammation in COPD



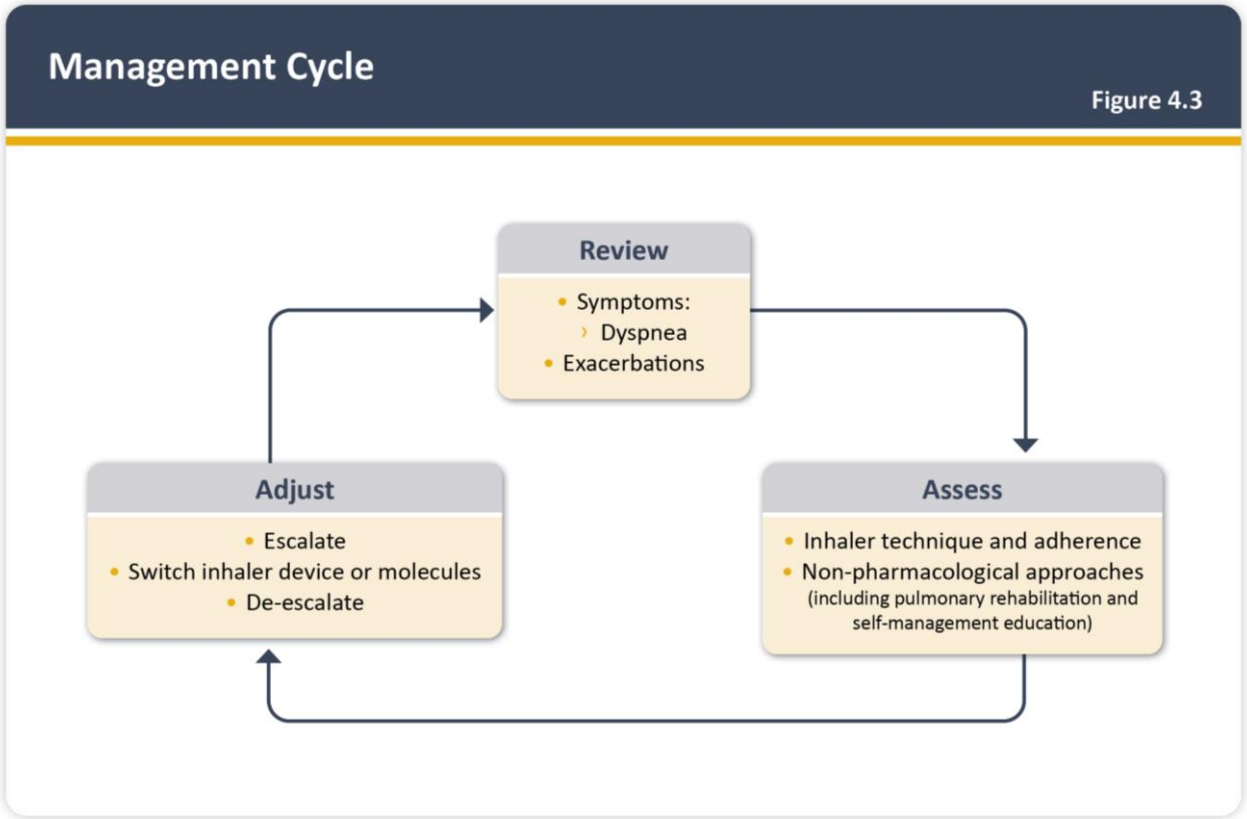
Agusti A et al PLOSone 2012

Comorbidities and Risk of Mortality in Patients with Chronic Obstructive Pulmonary Disease

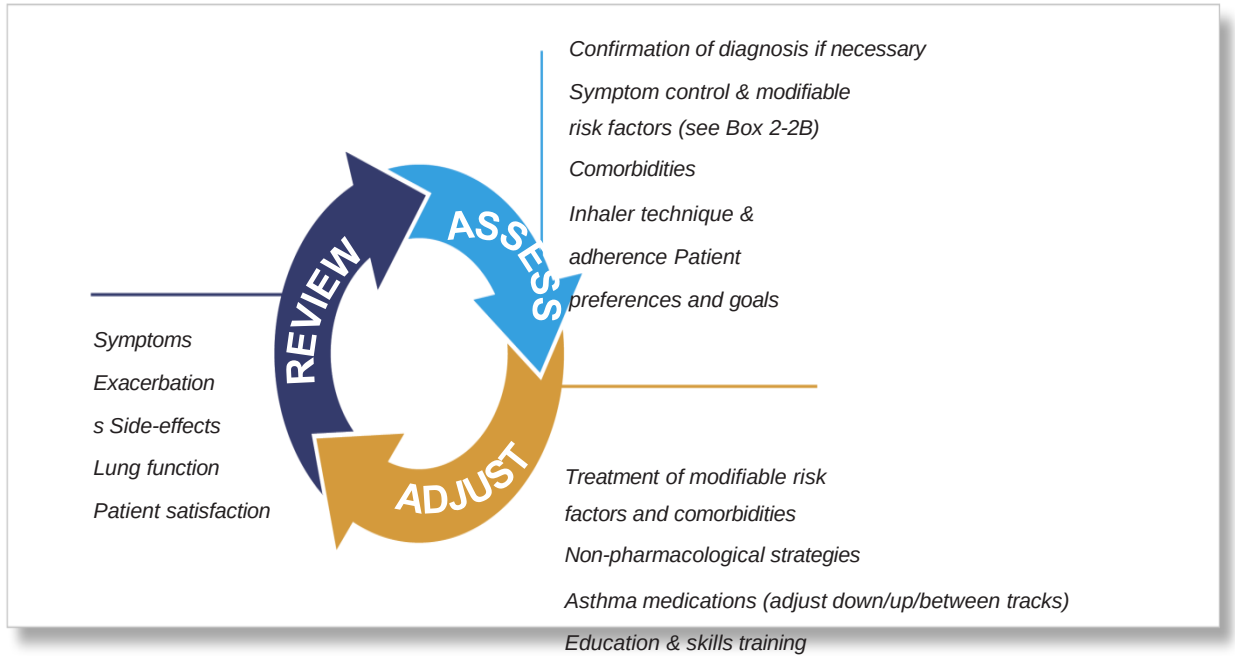
Miguel Divo[1], Claudia Cote[2†], Juan P. de Torres[3], Ciro Casanova[4], Jose M. Marin[5], Victor Pinto-Plata[1], Javier Zulueta[3], Carlos Cabrera[6], Jorge Zagaceta[3], Gary Hunninghake[1], and Bartolome Celli[1]; for the BODE Collaborative Group



MIMICKING ASTHMA…



COPD



ASTHMA

THANK YOU