Asthma-COPD overlap syndrome (ACOS): existeix un consens en el diagnòstic?

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ACOS: qüestions a plantejar

- ü **Que ens diuen les normatives?**
- ü **Tenim proves patogèniques?**
- ü **Que necessitem conèixer per la pràctica clínica?**

ACOS: qüestions a plantejar

- **Que ens diuen les normatives?**
- **Tenim proves patogèniques diferencials?**
- **Quina aproximació clínica necessitem per la pràctica diària?**

Diagnosis of Diseases of Chronic Airflow Limitation:

Asthma COPD and Asthma - COPD Overlap Syndrome (ACOS)

Based on the Global Strategy for Asthma Management and Prevention and the Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease.

2014

KEY POINTS

- Distinguishing asthma from COPD can be problematic, particularly in smokers and older adults
- ACOS is identified by the features that it shares with both asthma and COPD.
- A stepwise approach to diagnosis is advised, comprising recognition of the presence of a chronic airways disease, syndromic categorization as asthma, COPD or the overlap between asthma and COPD (the Asthma COPD Overlap Syndrome (ACOS)), confirmation by spirometry and, if necessary, referral for specialized investigations.
- Although initial recognition and treatment of ACOS may be made in primary care, referral for confirmatory investigations is encouraged, as outcomes for ACOS are often worse than for asthma or COPD alone.
- Initial treatment should be selected to ensure that:
  - o Patients with features of asthma receive adequate controller therapy including inhaled corticosteroids, but not long-acting bronchodilators alone (as monotherapy), and
  - o Patients with COPD receive appropriate symptomatic treatment with bronchodilators or combination therapy, but not inhaled corticosteroids alone (as monotherapy).
- The consensus-based description of the Asthma COPD Overlap Syndrome (ACOS) is intended to stimulate further study of the character and treatments for this common clinical problem.

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Definicions i descripció clínica de ACOS

Asthma

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation. [GINA 2014]

COPD

COPD is a common preventable and treatable disease, characterized by persistent airflow limitation that is usually progressive and associated with enhanced chronic inflammatory responses in the airways and the lungs to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients. [GOLD 2014][21]

Asthma-COPD Overlap Syndrome (ACOS) – a description for clinical use

Asthma-COPD overlap syndrome (ACOS) is characterized by persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD. ACOS is therefore identified by the features that it shares with both asthma and COPD.

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Table 2a. Usual features of asthma, COPD and ACOS

Feature	Asthma	COPD	ACOS
Age of onset	Usually childhood onset but can commence at any age.	Usually > 40 years of age	Usually age ≥40 years, but may have had symptoms in childhood or early adulthood
Pattern of respiratory symptoms	Symptoms may vary over time (day to day, or over longer periods), often limiting activity. Often triggered by exercise, emotions including laughter, dust or exposure to allergens	Chronic usually continuous symptoms, particularly during exercise, with 'better' and 'worse' days	Respiratory symptoms including exertional dyspnea are persistent but variability may be prominent
Lung function	Current and/or historical variable airflow limitation, e.g. BD reversibility, AHR	$FEV_1/FVC < 0.7$ persists	Airflow limitation not fully reversible, but often with current or historical variability
Lung function between symptoms	May be normal between symptoms	Persistent airflow limitation	Persistent airflow limitation
Past history or family history	Many patients have allergies and a personal history of asthma in childhood, and/or family history of asthma	History of exposure to noxious particles and gases (mainly tobacco smoking and biomass fuels)	Frequently a history of doctor-diagnosed asthma (current or previous), allergies and a family history of asthma, and/or a history of noxious exposures
Time course	Often improves spontaneously or with treatment, but may result in fixed airflow limitation	Generally, slowly progressive over years despite treatment	Symptoms are partly but significantly reduced by treatment. Progression is usual and treatment needs are high
Chest X-ray	Usually normal	Severe hyperinflation & other changes of COPD	Similar to COPD
Exacerbations	Exacerbations occur, but the risk of exacerbations can be considerably reduced by treatment	Exacerbations can be reduced by treatment. If present, comorbidities contribute to impairment	Exacerbations may be more common than in COPD but are reduced by treatment. Comorbidities can contribute to impairment
Typical airway inflammation	Eosinophils and/or neutrophils	Neutrophils in sputum, lymphocytes in airways, may have systemic inflammation	Eosinophils and/or neutrophils in sputum.

Table 2b. Features that favor asthma or COPD

Favors Asthma	Favors COPD
□ Onset before age 20 years	□ Onset after age 40 years
□ Variation in symptoms over minutes, hours or days □ Symptoms worse during the night or early morning □ Symptoms triggered by exercise, emotions including laughter, dust or exposure to allergens	□ Persistence of symptoms despite treatment □ Good and bad days but always daily symptoms and exertional dyspnea □ Chronic cough and sputum preceded onset of dyspnea, unrelated to triggers
□ Record of variable airflow limitation (spirometry, peak flow)	□ Record of persistent airflow limitation (post-bronchodilator FEV1/FVC < 0.7)
□ Lung function normal between symptoms □ Previous doctor diagnosis of asthma □ Family history of asthma, and other allergic conditio	□ Lung function abnormal between symptoms □ Previous doctor diagnosis of COPD, chronic bronchitis or emphysema □ Heavy exposure to a risk factor: tobacco smoke, biomass fuels
□ No worsening of symptoms over time. Symptoms vary either seasonally, or from year to year □ May improve spontaneously or have an immediate response to BD or to ICS over weeks	□ Symptoms slowly worsening over time (progressive course over years) □ Rapid-acting bronchodilator treatment provides only limited relief.
□ Normal	□ Severe hyperinflation

***Syndromic diagnosis of airways disease: how to use Table 2b**

Shaded columns list features that, when present, best distinguish between asthma and COPD. For a patient, count the number of check boxes in each column. If three or more boxes are checked for either asthma or COPD, that diagnosis is suggested. If there are similar numbers of checked boxes in each column, the diagnosis of ACOS should be considered. See Step 2 for more details.

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Table 2a. Usual features of asthma, COPD and ACOS				Table 2b. Features that favor asthma or COPD	
Feature	**Asthma**	**COPD**	**ACOS**	**Favors Asthma**	**Favors COPD**
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Pattern of respiratory symptoms	Symptoms may vary over time (da... peri... Ofte... emo... dus...	Chronic usually ...	Respiratory symptoms ...	□ Variation in symptoms over ...	□ Persistence of symptoms ...atment ...bad days but always ...toms and exertional ...ugh and sputum ...onset of dyspnea, ...to triggers
Lung function	Cur... airf... rev...				...persistent airflow ...post-bronchodilator ...< 0.7)
Lung function between symptoms	May... sym...				...tion abnormal ...ymptoms
Past history or family history	Mar... and... asth... fam...				...doctor diagnosis of ...ronic bronchitis or ...na ...osure to a risk factor: ...moke, biomass fuels
Time course	Ofte... or w... in fi...				...s slowly worsening ...(progressive course ...s) ...ng bronchodilator ...provides only limited
Chest X-ray	Usu...				...perinflation
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- **Edat >40 anys**
- **Símptomes respiratoris persistents**
- **Limitació al flux d'aire progressiva**
- **Diagnòstic previ d'asma, història familiar i/o al·lèrgia**
- **Exacerbacions mes freqüents que en MPOC**
- **Eosinòfils/neutròfils en mostra d'esput**

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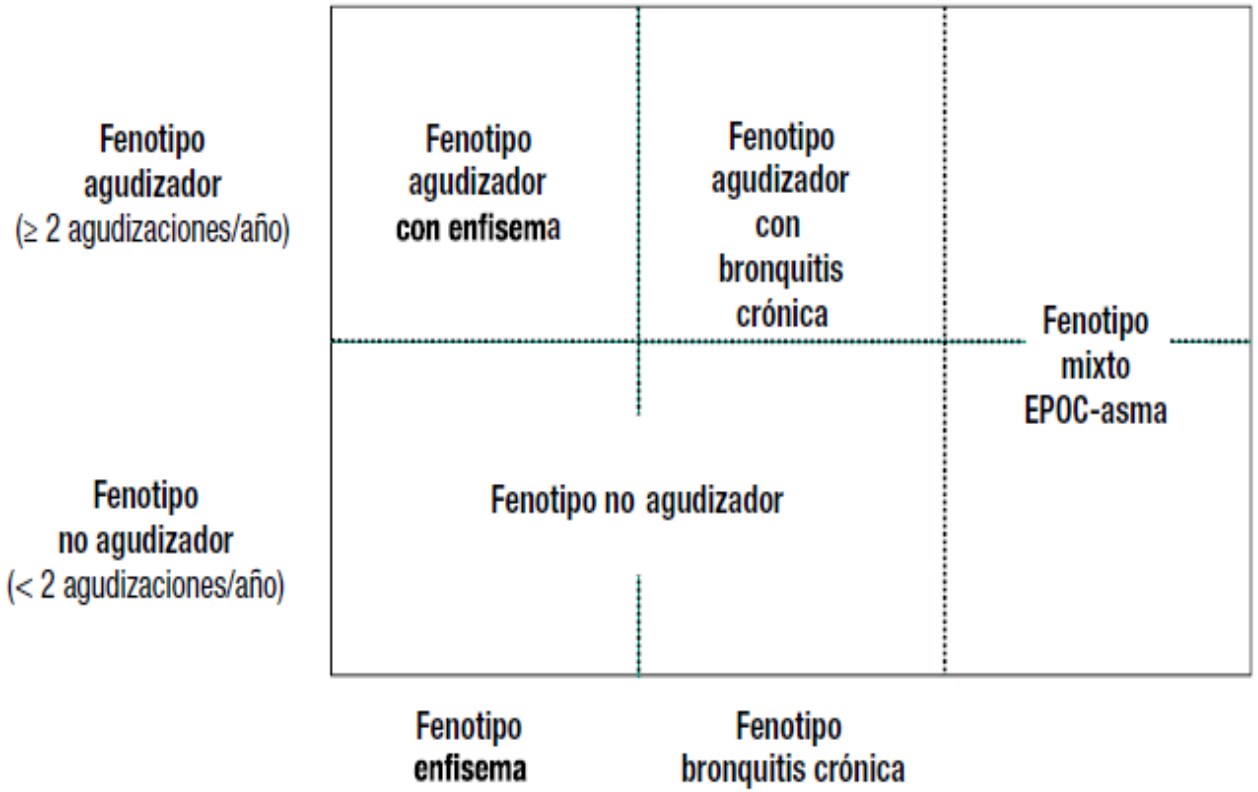
Fenotips proposats per GesEPOC



Guía Española de la EPOC (GesEPOC). Arch Bronconeumol 2014

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Fenotip mixta asma-MPOC: definició

"El fenotipo mixto en la EPOC se define como una obstrucción no completamente reversible al flujo aéreo acompañada de síntomas o signos de una reversibilidad aumentada de la obstrucción (…) Para el diagnóstico se deben cumplir 2 criterios mayores o uno mayor y 2 menores. Esta clasificación es restrictiva debido a la falta de evidencia concluyente entre la relación de los distintos criterios y la respuesta al tratamiento en la EPOC (…)"

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Criteris diagnòstics fenotip mixta

Criteris majors

- Prova broncodilatadora molt positiva (increment FEV1 >15% i 400mL)
- Eosinòfila en esput

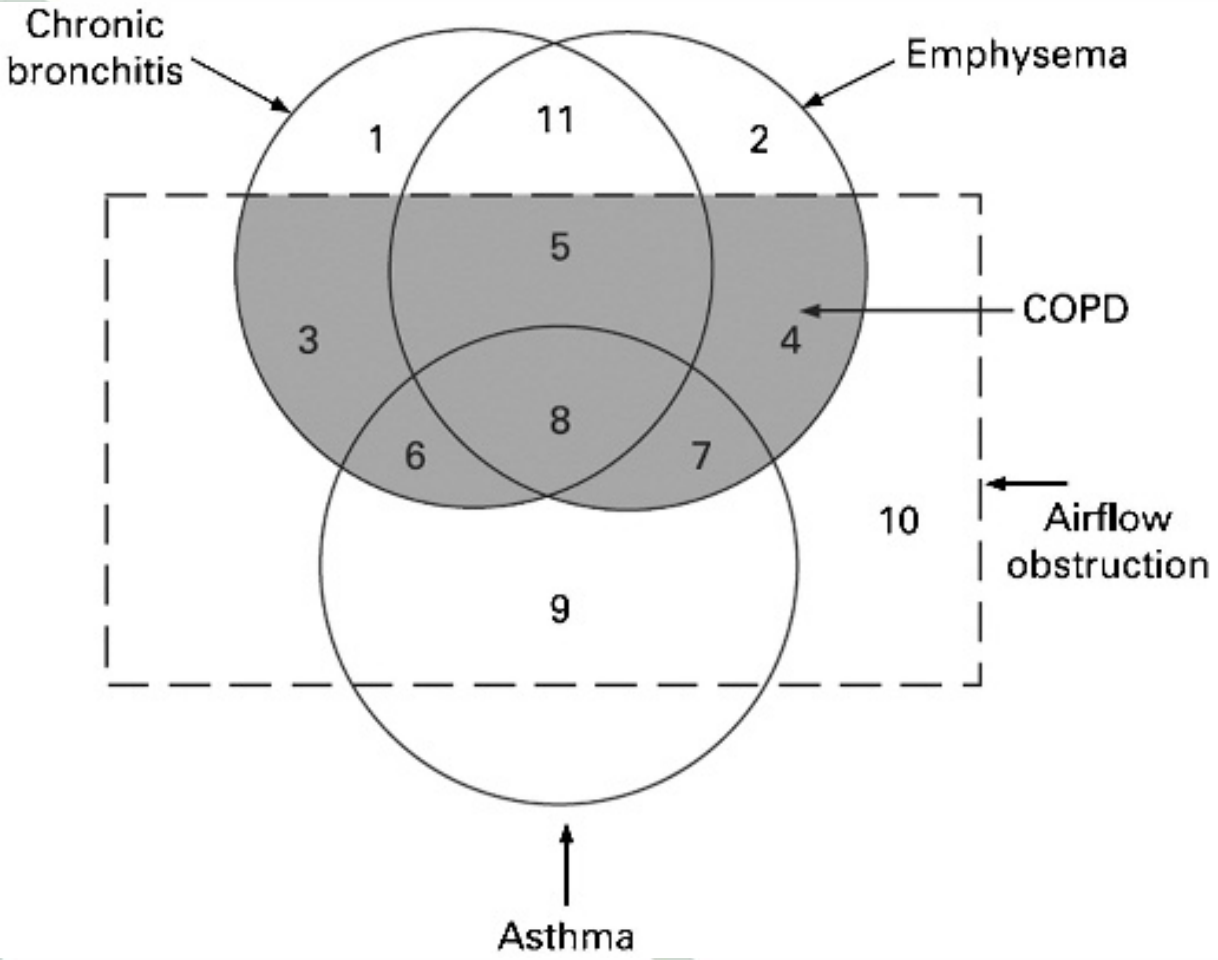
Criteris menors

- Xifres elevades de IgE total
- Antecedents previs d'atòpia
- Prova broncodilatadora positiva (increment FEV1>12% i 200mL)

Guía Española de la EPOC (GesEPOC). Arch Bronconeumol 2012

Tres preguntes immediates...

- Es tracta d'una associació entre asma i MPOC o existeix una entitat patològica amb característiques diferents?
- Quina dimensió te aquest problema?
- Requereix un tractament farmacològic diferent?



Gibson PG et al. Thorax 2009

Table 1 Definition of obstructive airway syndromes

Syndrome	Definition
Asthma	Episodic respiratory symptoms
	Variable airflow obstruction occurring spontaneously, with treatment or after provocation
COPD	Incompletely reversible airflow obstruction
Overlap syndrome	Asthma and COPD—that is, symptoms of increased variability of airflow and incompletely reversible airflow obstruction
Chronic bronchitis	Symptomatic mucus hypersecretion with cough and sputum daily for at least 3 months over 2 years
Emphysema	Abnormal airspace enlargement
Variable airflow obstruction	Increased diurnal variability of peak flow: maximum–minimum/average >10%
	Increased response to bronchodilator: > 200 ml FEV_1 and >12% baseline
	Increased airway responsiveness: provocation dose or concentration <normal
Incompletely reversible airflow obstruction	Postbronchodilator FEV_1 <80% predicted and FEV_1/FVC <70%
Bronchodilator responsiveness	Improvement in FEV_1 >15% and 400 ml after a therapeutic dose of inhaled rapid acting β_2-agonist
Airway hyper-responsiveness	Significant fall in FEV_1 from a stable baseline after inhalation of bronchial provocation stimulus occurring at a stimulus dose less than required to induce a significant change in FEV_1 in healthy controls.

COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.

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Identificació de 11 diferents síndromes obstructius

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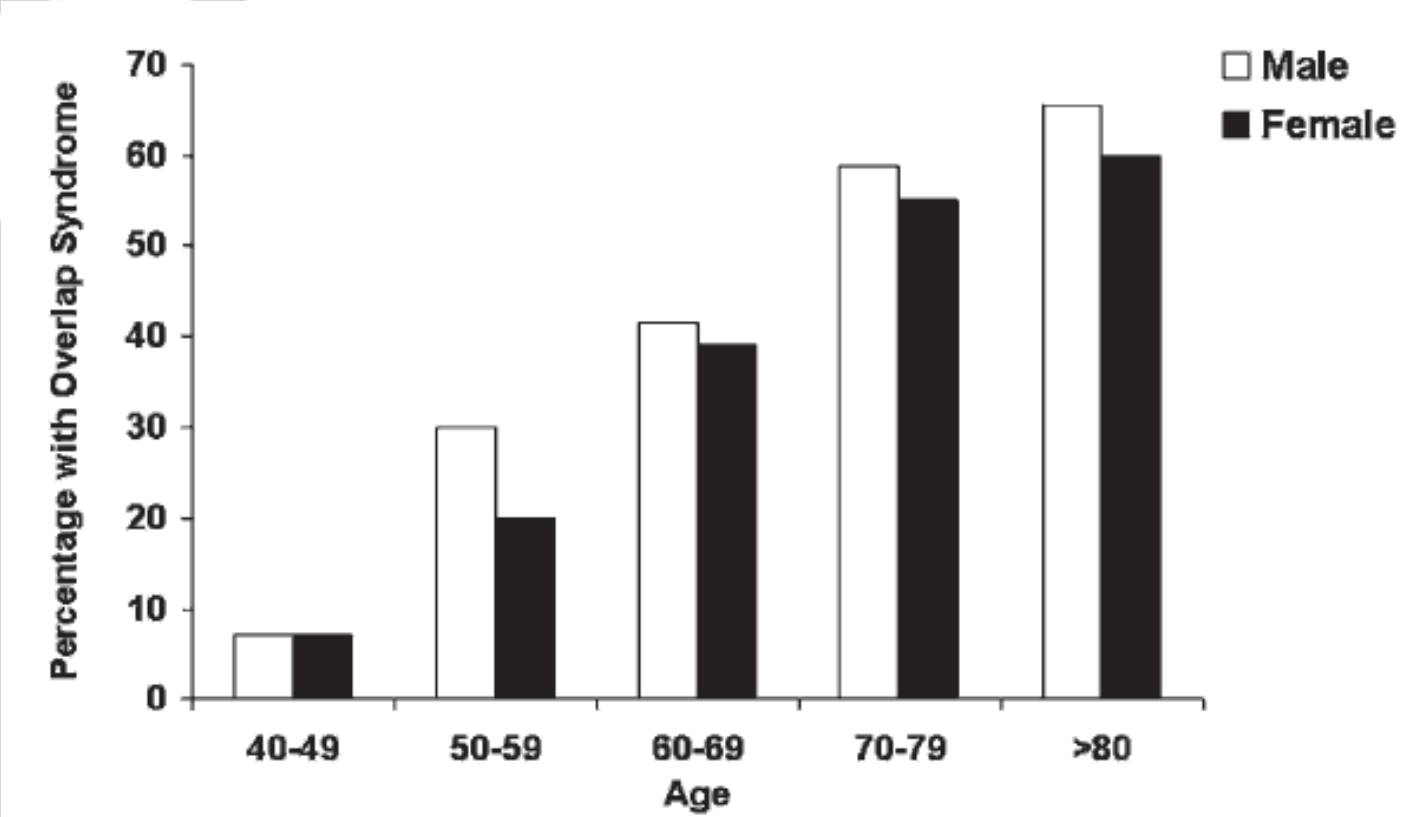
Adults amb ACOS (distribució per edat)



Soriano JB et al. Chest 2003

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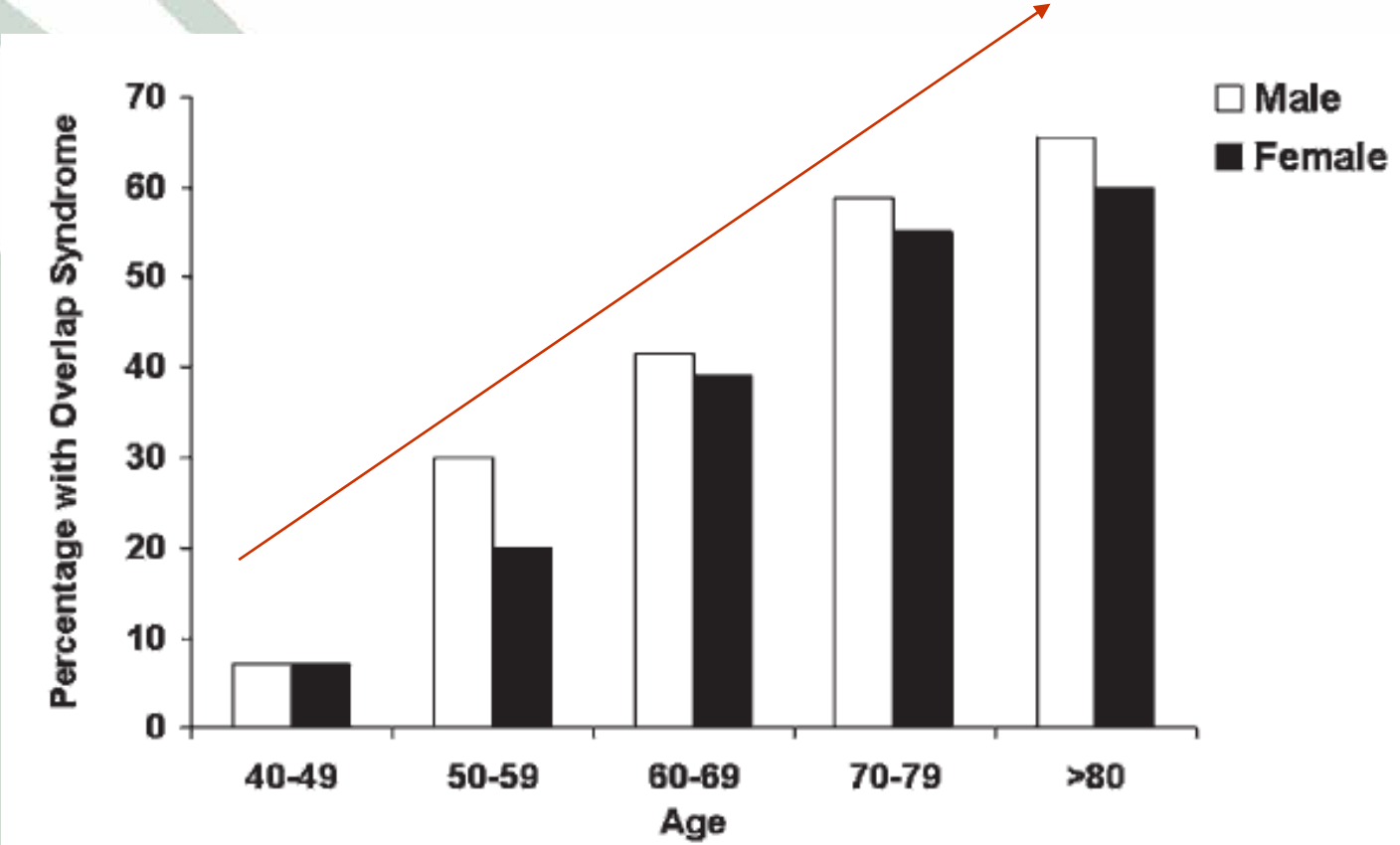

Soriano JB et al. Chest 2003

Malalties obstructives de la via area: funció pulmonar

	Asthma	Overlap syndrome	COPD	Healthy
Symptoms	+	+	+	−
FEV_1/FVC	≥70%	<70%	<70%	≥70%
FEV_1 % predicted*	>80%	<80%	<80%	>80%
AHR, PD_{15}†	<12 ml	<12 ml	>12 ml	>12 ml

*Postbronchodilator
†PD_{15}, provocation dose of hypertonic saline that induces a 15% fall in FEV_1.
AHR, airway hyper-responsiveness; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.

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- **Obstrucció al flux d'aire poc reversible**
- **FEV_1 post reduït**
- **Variabilitat de la obstrucció (HRB i/o prova provocació positiva)**

Gibson PG et al. Thorax 2009

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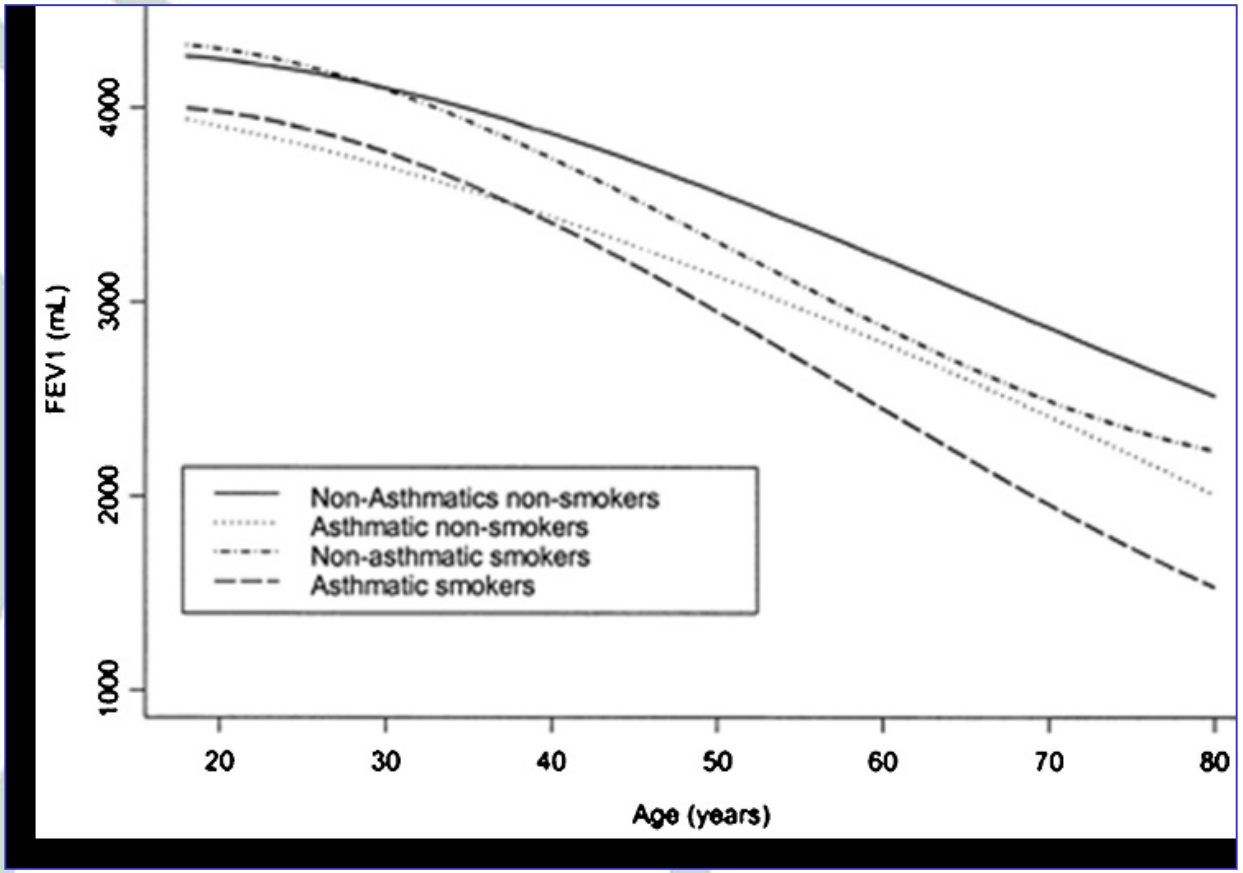
Disminució del FEV_1 en pacients fumadors amb asma



Anthonisen NR et al. Am Respir J Crit Care 2002

Effects of Allergic Phenotype on Respiratory Symptoms and Exacerbations in Patients with Chronic Obstructive Pulmonary Disease

Daniel B. Jamieson[1], Elizabeth C. Matsui[2], Andrew Belli[1], Meredith C. McCormack[1,3], Eric Peng[1], Simon Pierre-Louis[1], Jean Curtin-Brosnan[2], Patrick N. Breysse[3], Gregory B. Diette[1,3], and Nadia N. Hansel[1,3]

Participant Characteristics	Allergic ($n = 296$)	Nonallergic ($n = 1,085$)	*P* Value
Ethnicity, %			0.11
White	99	96	
Black	1	2	
Other	0	2	
Sex, % male	53	67	<0.05
Highest education, %			0.69
Elementary school	17	19	
High school	52	53	
Beyond high school	31	28	
Age, yr	66 (12)*	67 (12)*	0.06
Pack-years	47 (34)*	46 (38)*	0.90
FEV_1, % predicted	77 (22)*	76 (21)*	0.60
GOLD stage			0.23
I	46.2	50.1	
II	40.5	39	
III	12.5	9	
IV	0.8	1.9	
Current smoker, %	45	45	1
Years since quit if not current smoker	16.7 (13.1)*	17.4 (14.1)*	0.72
Doctor-diagnosed chronic bronchitis, %	11	9.7	0.56
Doctor-diagnosed emphysema, %	10	10.4	0.92
Medications in the last month, %			
Antihistamines	5.6	2.2	0.01
Nasal steroids	0.5	0.5	0.96
Oral steroids	1.7	1.2	0.53

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	Bivariate Analysis			Multivariate Analysis*		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Chronic cough	1.75	0.64–4.74	0.28	1.97	0.68–5.73	0.21
Chronic phlegm	1.56	0.58–4.18	0.38	1.55	0.54–4.43	0.41
Nocturnal cough	3.58	1.11–11.53	0.03	4.20	1.15–15.35	0.03
Nocturnal dyspnea	2.51	0.86–7.31	0.09	2.92	0.91–9.34	0.07
Wheeze	4.08	1.45–11.45	<0.01	5.91	1.84–18.94	<0.01
Antibiotic use	3.29	1.19–9.11	0.02	3.79	1.28–11.28	0.02
Steroid use	2.04	0.69–6.03	0.20	2.80	0.84–9.36	0.10
Pneumonia	1.28	0.48–3.44	0.62	1.39	0.47–4.10	0.55
ED visit and/or hospitalization	6.15	1.88–20.09	<0.01	11.05	2.56–47.80	<0.01

Definition of abbreviations: CI = confidence interval; ED = emergency department; OR = odds ratio.

* Multivariate regression models were used to adjust for potential confounders including age, gender, race, education, smoking pack-years, and lung function (FEV_1% predicted).

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Similars factors de risc?

Table 2
Risk factors for asthma and COPD

Host factors	Male sex in childhood, female sex in adulthood	Family history of COPD
	(Family) history of asthma	Family history asthma/atopy
	Genetic constitution	Genetic constitution
	Airway hyperresponsiveness	Airway hyperresponsiveness
	Atopy	—
	Low lung function	Low lung function
	Overweight	—
Perinatal factors	Maternal smoking	Maternal smoking
	Maternal diet	—
	Mode of delivery	—
Childhood exposures	Viral respiratory infections	Respiratory tract infections
	No breastfeeding	—
	Microbial deprivation	Maternal smoking
	Environmental tobacco smoke exposure	Indoor air pollution
	Air pollution	—
Adult exposures	Occupational exposures	Occupational exposures
	Cigarette smoking	Cigarette smoking
	Outdoor air pollution	Outdoor air pollution
	—	Indoor air pollution

Postma DS et al. Am Respir Crit Care Med 2011

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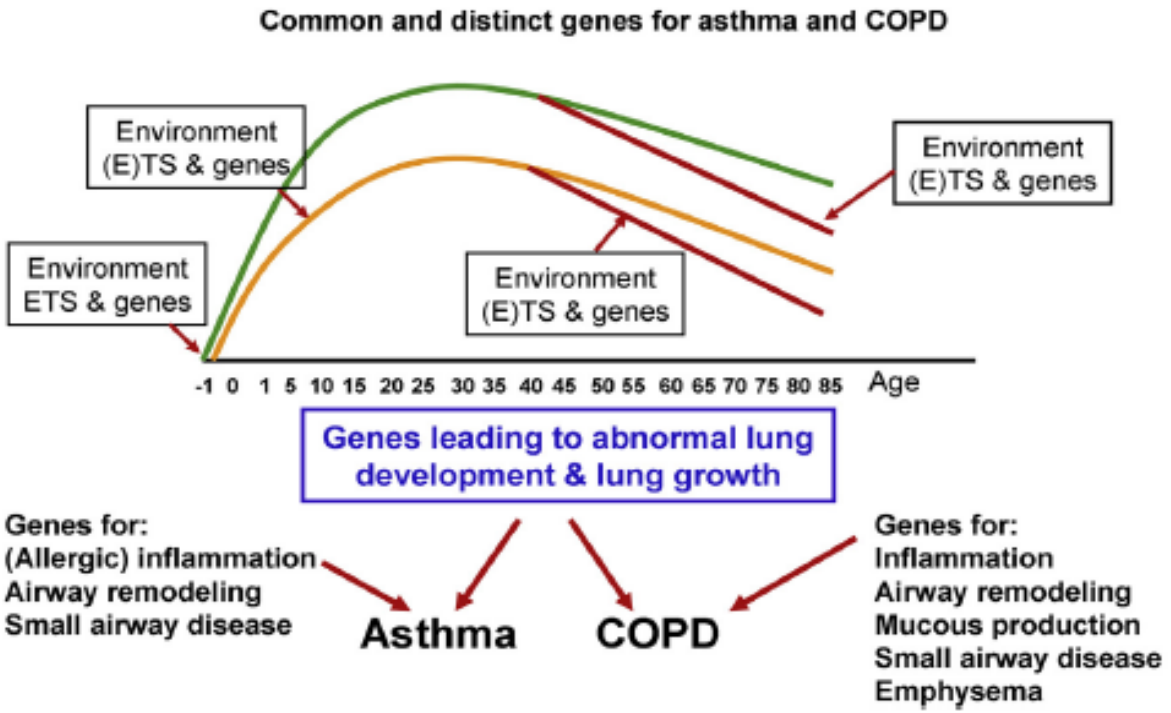
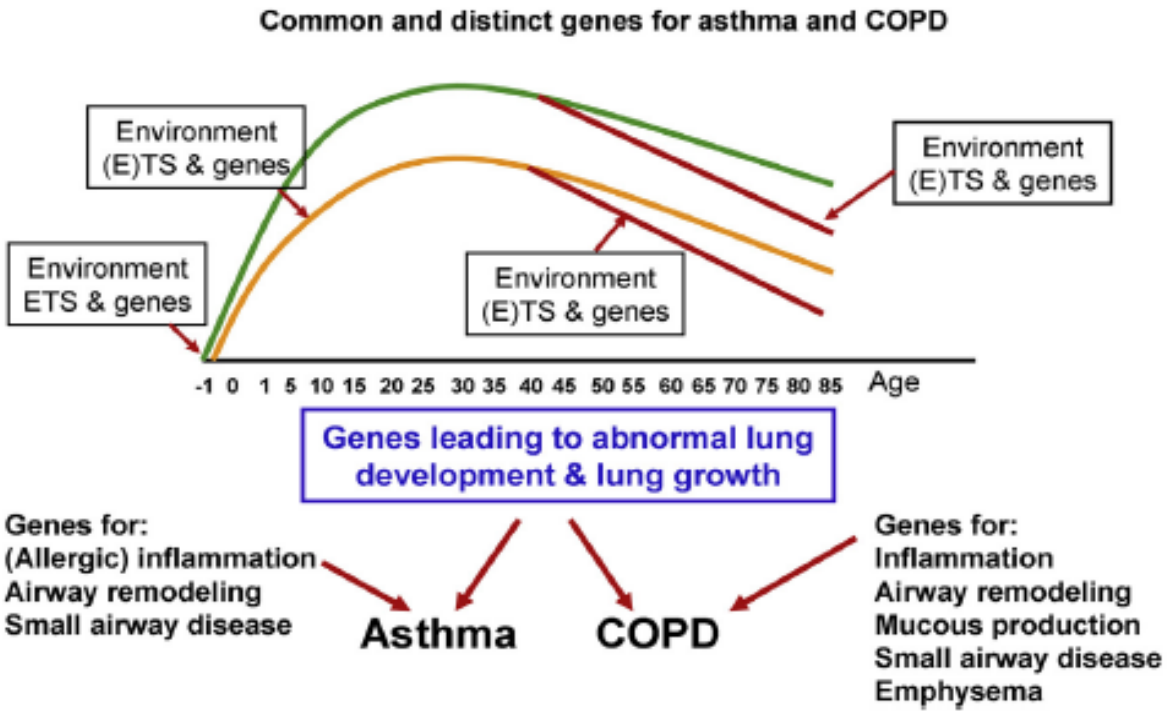
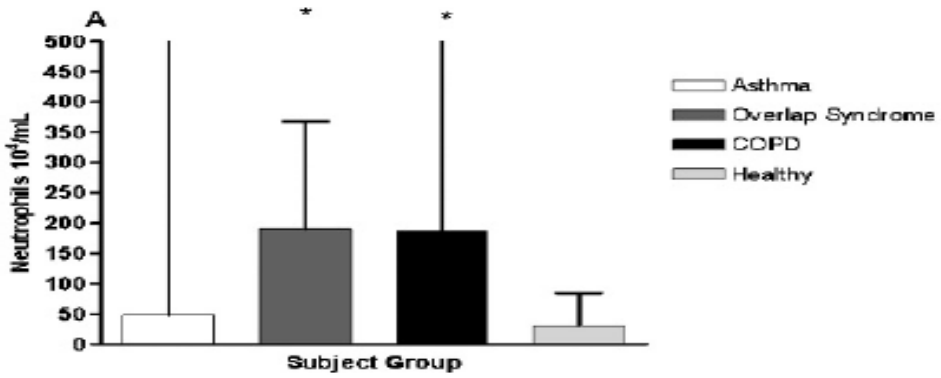


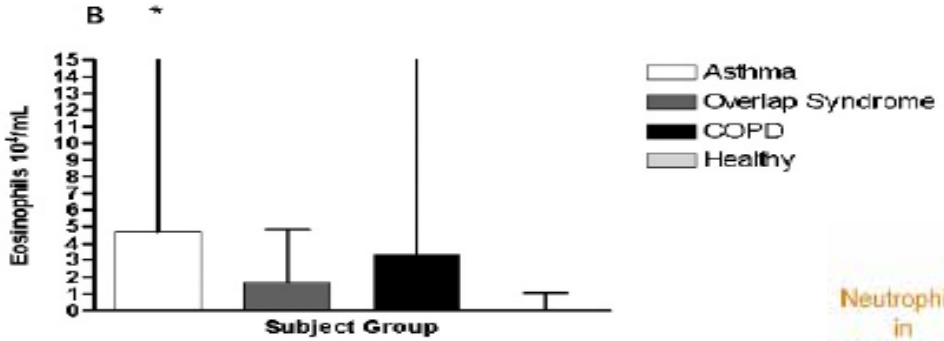
Postma DS. Am Respir Crit Care Med 2011

Gens compartits?

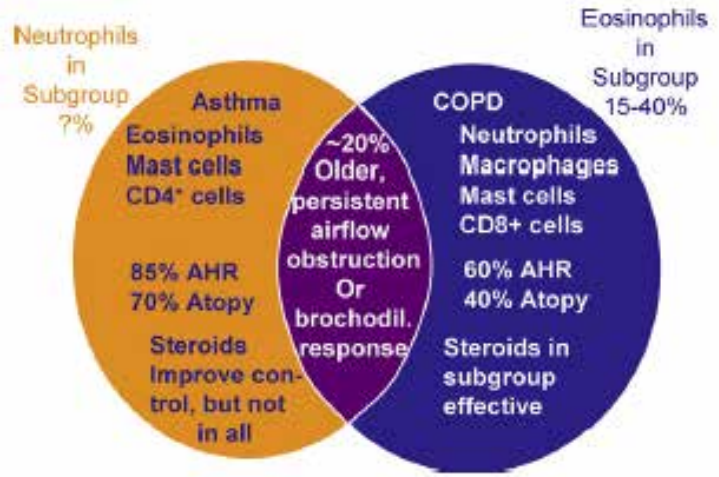


Interacció entre factors genètics, agents ambientals i factors relacionats amb el desenvolupament i el creixement del pulmó





Gibson PG. Thorax 2009



Postma DS et al. Clin Ches Med 2014

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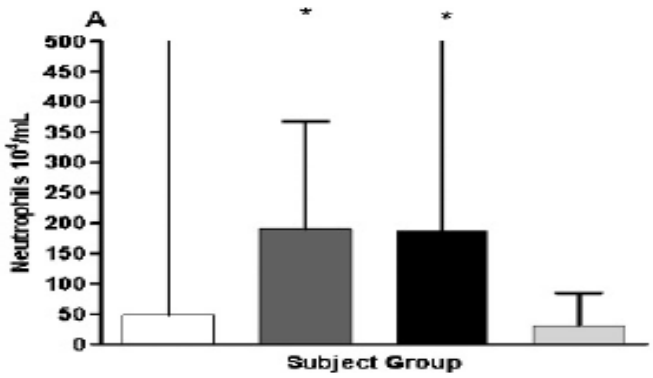
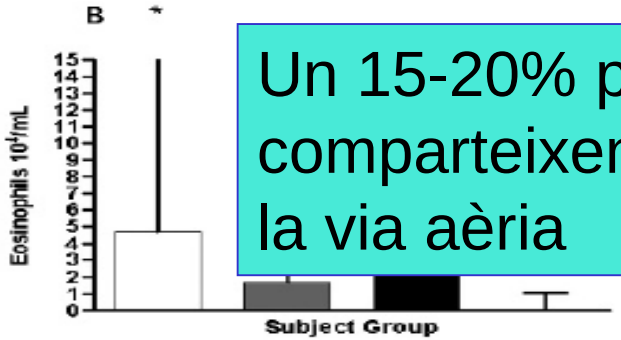
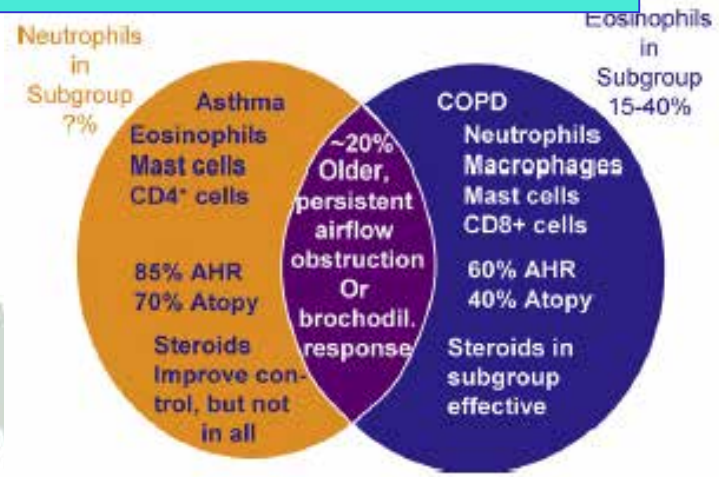




Un 15-20% pacients amb ACOS comparteixen marcadors inflamatoris en la via aèria

Gibson PG. Thorax 2009



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ACOS: qüestions a plantejar

- ü **Que ens diuen les normatives?**
- ü **Tenim proves patogèniques?**
- ü **Quina aproximació clínica necessitem per la pràctica diària?**

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Els pacients amb ACOS tenen mes símptomes i pitjor qualitat de vida

- **Dades del EPI-SCAN (n=3885)**
- **MPOC (10,1%), ACOS (17.4%)**
- **Disnea (p<0,001), exacerbacions (p<0.01)**
- **Pitjor qualitat de vida (SQRQ, LCADL)**

Miravitlles M et al. Respir Med 2013

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INTERVENCIONS ESPECIFIQUES?

Miravitlles M et al. Respir Med 2013

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Risc incrementat d'hospitalitzacions

- **Estudi PLATINO (n=5044)**
- **MPOC (12%), asma (1,7%), ACOS (1.8%)**
- **Augment de símptomes, pitjor funció pulmonar i utilització de fàrmacs**
- **Exacerbacions greus i hospitalitzacions**
- **Pitjor estat de salut**

Menezes AM et al. Chest 2014

Conclusions

- Asma en joves <40 anys i MPOC en fumadors son entitats fàcils de distingir
- Existeixen “fenotips” en asma i MPOC (asma amb neutròfils sense PBD positiva i MPOC amb eosinofília a PBD positiva)
- La exposició al tabac pot modificar les diferencies en fisiologia, inflamació i remodelació
- La edat es un componen “clau”
- Es imperatiu establir un tractament òptim i analitzar els efectes sobre aquest grup de pacients

Els pacients amb ACOS tenen mes símptomes i pitjor qualitat de vida

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Miravitlles M et al. Respir Med 2013