Cigarette Smoking, COPD and Chronic Obstructive Asthma

Carrie L. Pistenmaa, MD, MS

Associate Physician, Division of Pulmonary and Critical Care Medicine, Brigham and Women's Hospital

Assistant Professor of Medicine, Harvard Medical School

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Objectives

- Learn how cigarette smoke exposure affects asthma
- Understand how current smoking can change responses to treatment
- Recognize features of combined asthma and COPD
- Identify risk factors for COPD in patients with asthma

Outline

- The impact of cigarette smoke in the lungs and in asthma
- Review of the combined diagnosis of asthma and COPD
- The importance of asthma and COPD diagnosed together
- Risk factors for COPD in asthma

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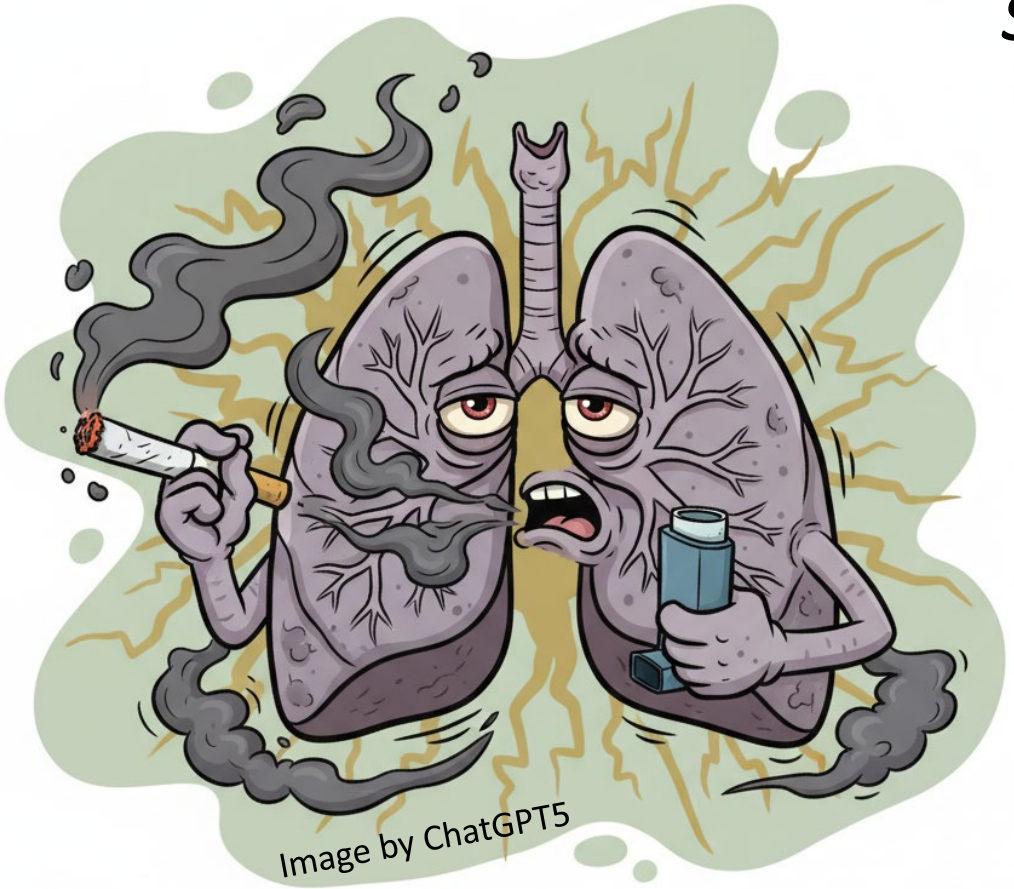
Cigarette smoke and the lungs…

Smoking upregulates

- Inflammation
- Macrophage recruitment
- MUC5AC

Downregulates

- Immune presenting cells
- IL-33-related Th2 signaling
- CFTR function



<u>In asthma,</u>

smoking increases

- IL-17A related neutrophilic inflammation
- MUC13 SNPs are associated with asthma exacerbations, particularly in smokers

Goldfarbmuren et al. Nat Comm, 2020.
Faiz et al. AJRCCM, 2023. Raju et al. AJRCCM 2013.

Siew et al. Clinic Exp All, 2017.
Bang et al. DNA Cell Biol, 2025.

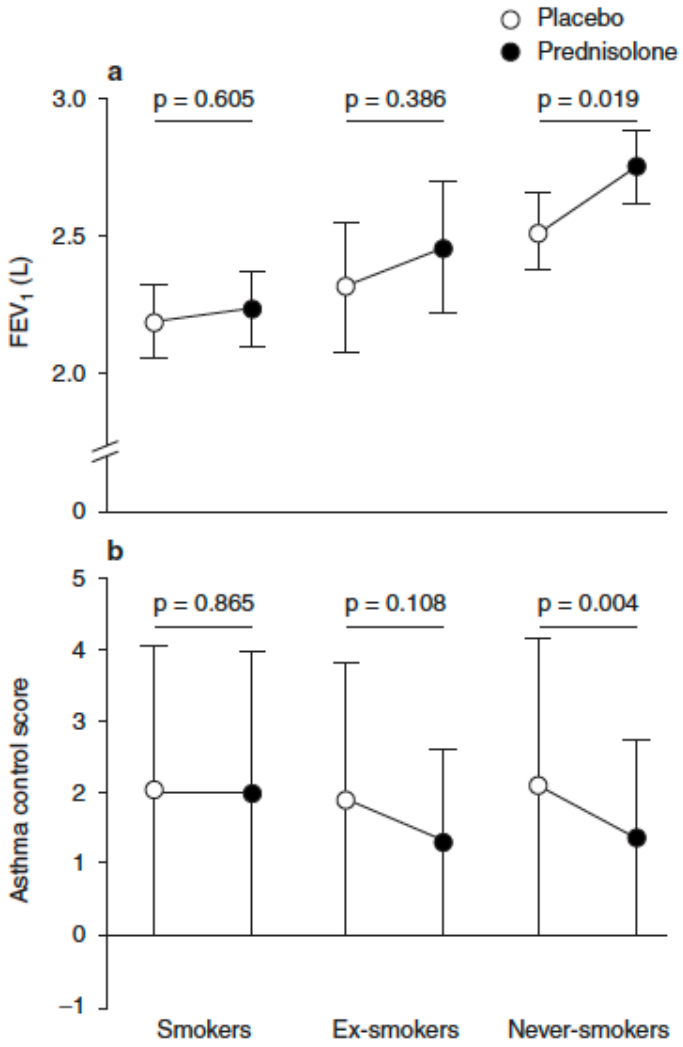
Asthma symptoms in current smokers

- Approximately 25-30% of asthma patients are active smokers
- Current smokers
  - Report uncontrolled asthma (OR 2.67)
  - Report increased symptoms
  - Have exacerbations (RR 1.44) and hospitalizations
  - Have faster FEV_1 decline (17.8% decline current smokers with asthma vs. 11.1% in non-smokers with asthma over 10 years)
- Smokers have lower eosinophilia, lower FeNO
- E-cigarettes are also a concern, increasing symptoms in asthma

Althuis et al. J of Asthma, 1999. Kiljander et al. BMC Pulm Med, 2020. Agache et al. Allergy. 2024. Thomson et al. ERJ, 2004. McConnell et al. AJRCCM, 2017.

Steroid resistance in current smokers

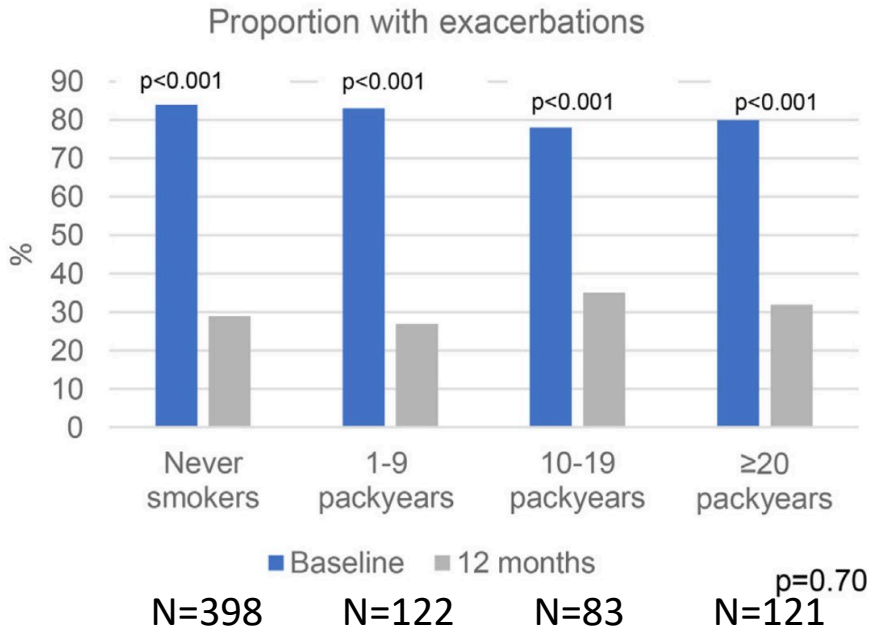
- Current smokers are generally excluded from studies of asthma
- Current smokers have less response to ICS
- In 50 current, former and never smokers given 2 weeks of prednisolone 40mg daily compared to placebo, current smokers were resistant, former partially resistant
- Theophylline metabolism is increased 2-fold with cigarette smoking



Althuis et al. J of Asthma, 1999. Kiljander et al. BMC Pulm Med, 2020.

Smoking history and response to biologics

- A Danish registry of 724 asthmatics on biologics there was no difference in response by pack-years of smoking
  - anti-IgE (13%), IL-5/IL-5R (73%), IL-4a (14%)
  - 10 subjects were current smokers
- A German registry with 1,129 asthmatics on biologics there was no difference in FEV_1 or exacerbations by pack-years of smoking
  - IgE (14%), IL-5/IL-5R (57%), IL-4a (29%)
  - 27 were current smokers at baseline
- Study of dupilumab for COPD showed similar efficacy for current and former smokers



Soendergaard et al. JACI IP, 2023. Stoshikj et al. JACI IP, 2025. Bhatt et al. NEJM, 2024.

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Are features of asthma and COPD distinct?

Typical Features	Asthma	COPD
Airway obstruction	Episodic	Chronic
Age of onset	Childhood	40s and later
Risk factors	Allergies, atopy	Smoking and other chronic exposures
Treatment response	Generally responsive, fully reversible	Not completely reversible
Inflammatory cells	Eosinophils Th2 lymphocytes Mast cells	Neutrophils Macrophages Cytotoxic T cells
Inflammatory mediators	Histamine Cysteinyl leukotrienes IL-4, IL-5, IL-13	IL-8 Leukotriene B4 TNF-alpha
Pathologic changes	Smooth muscle hypertrophy Subepithelial fibrosis	Goblet cell metaplasia Squamous metaplasia Alveolar destruction

Barnes PJ. AJRCCM 2006.

Are features of asthma and COPD distinct?

Typical Features	Asthma	COPD	Eosinophilic COPD	Smoking in asthma
Airway obstruction	Episodic	Chronic	Chronic	
Age of onset	Childhood	40s and later	40s and later	
Risk factors	Allergies, atopy	Smoking and other chronic exposures	Allergies, smoking	Asthma, smoking Allergens
Treatment response	Generally responsive, fully reversible	Not completely reversible	Partially reversible	Partially
Inflammatory cells	Eosinophils Th2 lymphocytes Mast cells	Neutrophils Macrophages Cytotoxic T cells	Sputum or blood eosinophilia	Neutrophilia
Inflammatory mediators	Histamine Cysteinyl leukotrienes IL-4, IL-5, IL-13	IL-8 Leukotriene B4 TNF-alpha	Other: IgE elevation History of asthma History of atopy	Mucociliary changes Mucus plugging
Pathologic changes	Smooth muscle hypertrophy Subepithelial fibrosis	Goblet cell metaplasia Squamous metaplasia Alveolar destruction		

Barnes PJ. AJRCCM 2006.

Subtypes of asthma and COPD

- More recently there has been more focus on separating asthma and COPD into distinct subtypes
  - Chronic obstructive asthma usually occurs in patients who are older with a long history of severe asthma with or without smoking history
  - Patients with eosinophilic COPD will have more bronchodilator responsiveness, atopy and history of allergies or atopy
- Goal is to identify “treatable traits”
  - COPD with airway eosinophilia
  - Asthma with hyperinflation and gas trapping, emphysema

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Asthma and COPD in the general population

- NHANES III measured lung function in 15,203 adults age 40-84 between 1988 to 1994
  - 2.7% reported physician diagnosis of COPD and asthma
  - 5.4% reported COPD and 4.7% asthma
  - Over 15 years follow up, mortality was increased in asthma and COPD, even adjusting for lung function

	Mortality Hazard Ratio	95% CI
Asthma and COPD	1.83	(1.34, 2.49)
COPD alone	1.44	(1.28, 1.62)
Asthma alone	1.16	(0.94, 1.42)

Reference group is those without reported lung disease
*adjusted for age, sex, race/ethnicity, education, smoking status

Diaz-Guzman, JCOPD. 2011.

Increased symptoms with asthma and COPD

- Survey of nearly 7,000 people age 20-84 at four centers in Italy

Table 2. Joint distribution of self-reported doctor-diagnosed asthma and COPD.

Age class	Asthma only %(95%CI)	Asthma+COPD %(95%CI)	COPD only %(95%CI)
[20–44]	8.2 (7.5–9)	1.6 (1.3–2)	3.3 (2.8–3.8)
[45–64]	4.9 (4–5.9)	2.1 (1.5–2.8)	5.7 (4.7–6.7)
[65–84]	2.9 (1.8–4)	4.5 (3.2–5.9)	13.3 (11.1–15.5)

Prevalence (%) with 95% confidence interval (CI).

Table 3. Prevalence* (% with 95%CI) of respiratory symptoms or conditions in subjects who did and did not report a diagnosis of asthma and/or COPD.

Respiratory symptoms or conditions	no asthma, no COPD %(95%CI)	asthma only %(95%CI)	asthma+COPD overlap %(95%CI)	COPD only %(95%CI)
Wheezing	9.9 (9.2–10.6)	43.4 (39.2–47.7)	78.7 (71.3–84.5)	42.7 (37.6–47.9)
Asthma attacks	0.7 (0.5–0.9)	38.8 (34.6–43.2)	56.9 (48.7–64.8)	4.4 (2.7–6.9)
Antiasthmatic drugs	0.3 (0.2–0.4)	29.8 (25.8–34)	55.4 (47–63.5)	2 (1.1–3.8)
Allergic rhinitis	18.2 (17.3–19.1)	59.2 (54.9–63.4)	53.5 (45.5–61.3)	23.9 (19.7–28.6)
Cough or phlegm	10.2 (9.5–10.9)	23.1 (19.6–26.9)	61.7 (53.7–69.1)	54 (48.7–59.2)
MRC† ≥3	3.8 (3.3–4.3)	9.3 (7.1–12.2)	38.8 (31.1–47.1)	20.8 (17–25.2)
Hospitalizations	0.4 (0.2–0.5)	1.1 (0.5–2.4)	3.1 (1.4–6.7)	2.5 (1.4–4.5)

*Adjusted for gender, age (class), season, % of answers to the questionnaire, type of survey (postal/telephone), and centre.
†MRC: Medical Research Council dyspnea score.

DeMarco. Plos One 2013.

Meta-analysis of asthma and COPD overlap

- Prevalence of asthma was 27% among those with COPD
- Included 9 studies of variable size (500 to nearly 200,000)
- COPD was diagnosed by post-BD $FEV_1/FVC < 0.7$
- Addition of asthma required a diagnosis of asthma OR documented reversibility on spirometry OR + methacholine challenge
- **Those with asthma and COPD had almost twice the risk of exacerbations, ED visits and hospitalizations**
- Multiple studies included costs, those with asthma and COPD had ~60% higher healthcare costs than COPD alone

Alshabanat, PlosOne 2015.

Asthma and COPD in COPDGene

- In COPDGene Study, 13% of those with COPD also reported a physician diagnosis of asthma
  - Compared to COPD alone, they were more likely to be female, black and have a history of hay fever
  - Reported more exacerbations in the prior year (including more severe exacerbations), and more gas trapping on chest CT
- IgEs (total and allergen specific) were measured in a subset
- Those with COPD and asthma with atopy were not very different from those without atopy, both had higher rates of exacerbations compared to COPD alone

Hardin, ERJ 2014. Hersh et al, JCOPDF 2020.

Th2 gene expression in COPD

- Airway epithelial gene expression was evaluated in over 105 patients with asthma and applied to 2 COPD cohorts (over 400 patients)
- Found that the 200 genes that were most up or down-regulated in asthma were also seen in ~20% of those with COPD
  - Associated with reduction in FEV1
  - Increased eosinophils in the airway and blood
  - Reversibility with bronchodilators
  - Improvement in hyperinflation with inhaled steroids
  - But NOT with a reported history of asthma
  - IgE levels, eosinophilia, airway hyperresponsiveness and response to ICS

Christenson, AJRCCM 2015.

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What is chronic obstructive asthma?

- **Chronic obstructive asthma** is historically referred to severe asthma with fixed obstruction, from prolonged inflammation leading to subepithelial fibrosis
  - This can happen without smoking or other environmental exposures
- Starting in 2021 the GOLD guidelines no longer suggest using “asthma-COPD overlap”, in favor or recognizing features of asthma in those with COPD
  - Chronic obstructive asthma is used sometimes to mean asthma with features of COPD

Silva et al, Chest 2004. de Marco et al, AJRCCM 2011. GOLD Report 2023.

Risk factors for COPD

- Low peak lung function in young adulthood
- Airway hyperresponsiveness by methacholine challenge
- Active asthma, compared to inactive asthma or no history of asthma
- Current smoking compared to never smoker
- Respiratory infections in childhood
- Family history of asthma
- Mid-life symptoms of “predominant wheeze”, or wheeze without dyspnea, cough or phlegm

Lange et al. NEJM, 2015. Marcon et al. Thorax, 2018. Silva et al. Chest, 2004.
De Marco et al. AJRCCM, 2011. Perret et al. Lancet Resp Med, 2025.

Clinical considerations in asthma and COPD

- In patients with asthma and fixed obstruction or exposures (tobacco, occupational exposures, air pollution, wildfire exposures):
  - Consider further testing for structural lung disease: obtain lung volumes, DLCO, Chest CT, monitor oxygen saturation
  - Consider treatment with LAMA, azithromycin for frequent exacerbators, roflumilast (if also chronic bronchitis), pulmonary rehab
- In patients with COPD and at least one feature of asthma:
  - Consider further testing for atopy: sputum eosinophils, peripheral eosinophils, IgE (total and specific allergens if atopic), FeNO
  - Consider additional ICS, if eosinophilia consider dupilumab

Summary

- Cigarette smoke can change the asthma phenotype and may have treatment implications
  - Consider in those who fail treatment or who are resistant to steroids
- Practical considerations of treating separate but overlapping diseases, treatable traits
- Apart from smoking cessation, questions remain about how to best prevent COPD in patients with asthma

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