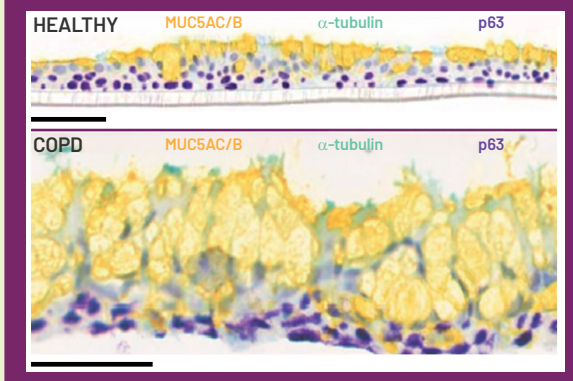
EXPLORING THE ROLE OF MUCUS DYSFUNCTION IN COPD

The 2026 GOLD report links impaired mucus clearance to airway inflammation and infection and highlights that mucus plugging extends beyond chronic bronchitis[1]

> Lung health depends upon
> **effective mucus clearance**
>
> *2026 GOLD report*

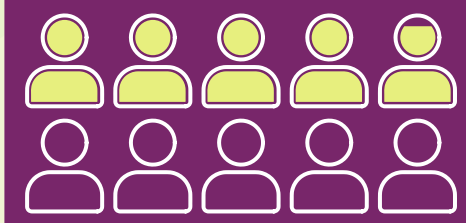
Mucus dysfunction includes mucus hypersecretion, impaired clearance, and mucus plugging

Mucus hypersecretion[2–4]

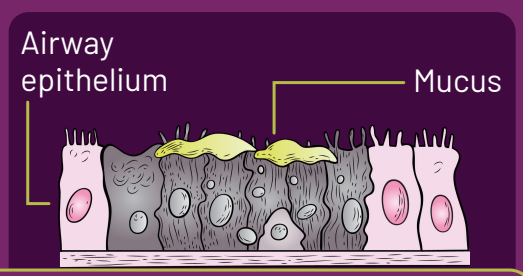


Representative immunohistochemistry of bronchial air-liquid interface cultures from a healthy donor (top) and a COPD patient (bottom) (scale bars: 70 µm)*

Up to **49%**
of patients with COPD have mucus hypersecretion



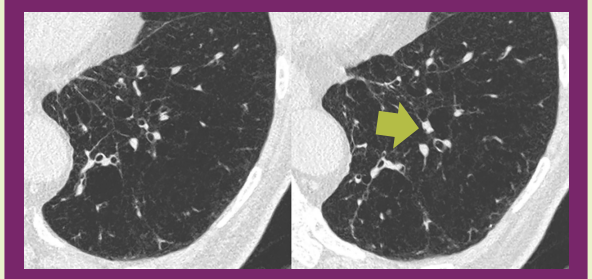
Impaired clearance[2,5,6]



The **AIRWAY EPITHELIUM** protects the airway by expelling pathogens and irritants via a coordinated **UNIDIRECTIONAL MUCOCILIARY LADDER**

In COPD, repeated epithelial injury, particularly from cigarette smoke, disrupts basal cell differentiation and **CILIARY FUNCTION**

Mucus plugging[7–11]



Representative CT images of a patient with COPD showing a mucus plug in the airway

25–67%
of patients with COPD show mucus plugs on CT scans

73%
of patients with COPD showed persistent luminal plugging over 5 years, vs 27% of patients without COPD

*MUC5AC/B (yellow), α-tubulin (teal), and p63 (purple) indicate the presence of goblet cells, ciliated cells, and basal cells, respectively. Image from Strickson S, et al. *Eur Respir J*. 2023;62:2202210 (supplementary material). Licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

DEFECTIVE MUCOCILIARY CLEARANCE allows mucus to accumulate and form luminal plugs, contributing to **AIRFLOW OBSTRUCTION**

Image from Tanabe N, et al. *Respirology*. 2024;29:951–961. Licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

However, not all patients experience both mucus hypersecretion and mucus plugging[12]

In the COPDGene study,* ~75% of patients had signs of mucus dysfunction†

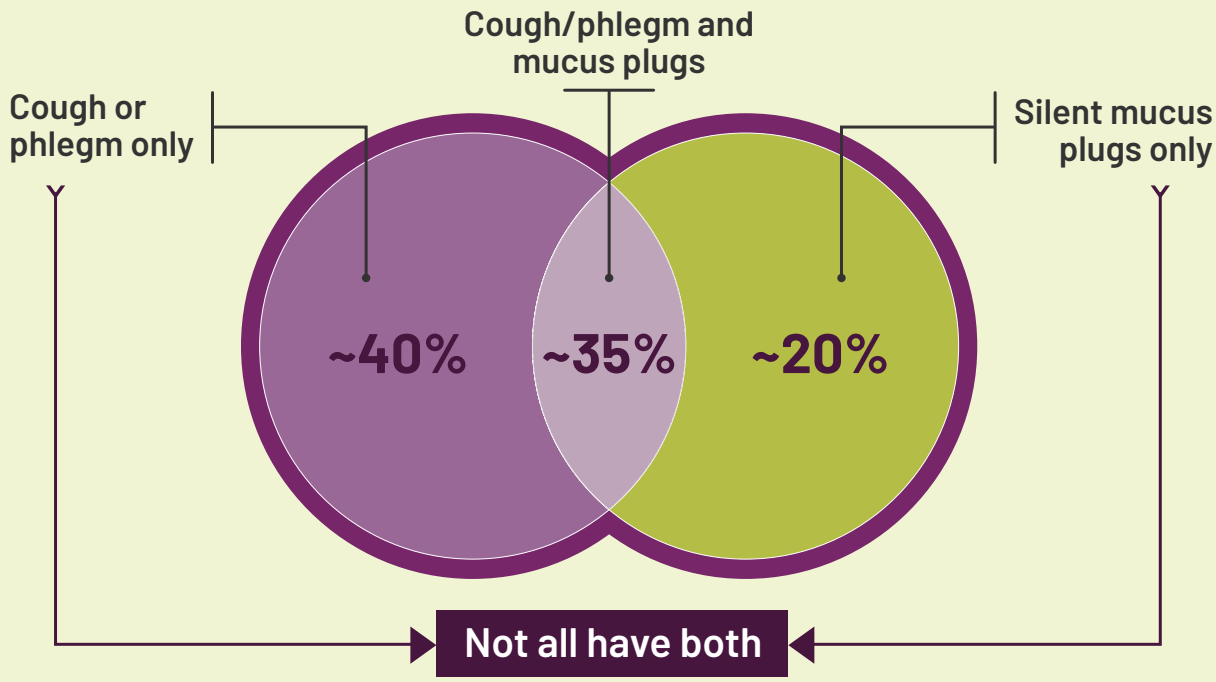


Figure adapted from Mettler SK, et al. *Chest*. 2024;166:1010–1019. Licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).
*Based on data from 4363 patients with COPD, including both former and current smokers, across the full spectrum of disease severity. Patients were recruited from the COPDGene study, an observational prospective cohort study conducted in 21 centers across the USA, which included 45- to 80-year-old non-Hispanic White or non-Hispanic Black patients with a ≥10 pack-year smoking history with or without COPD; †signs of mucus dysfunction include cough, phlegm, and/or mucus plugs.

Pathologic mucus results from hypersecretion and impaired clearance, and can accumulate in the airway lumen, forming mucus plugs[6]

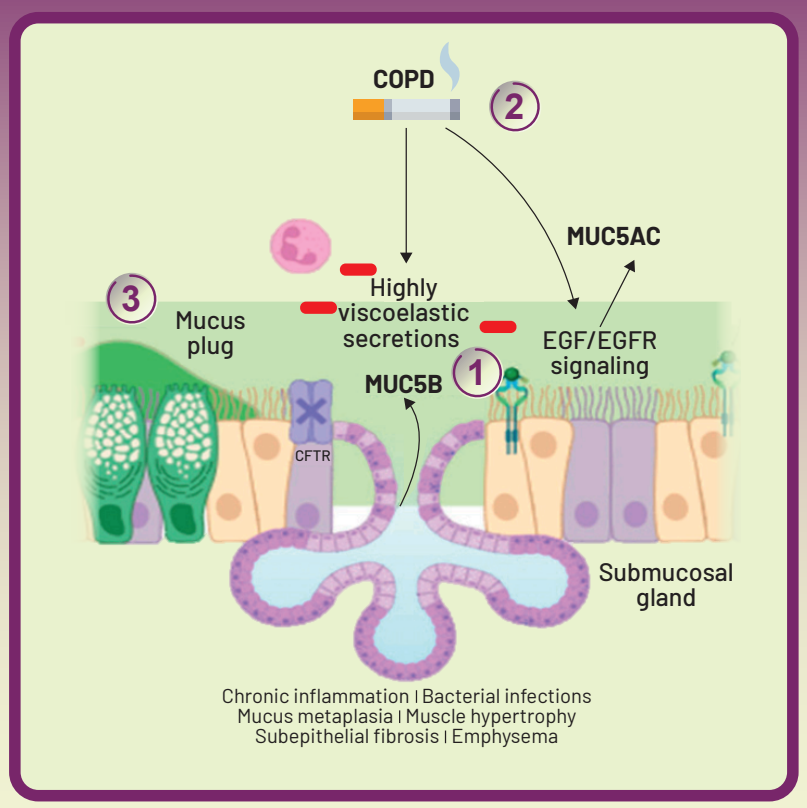


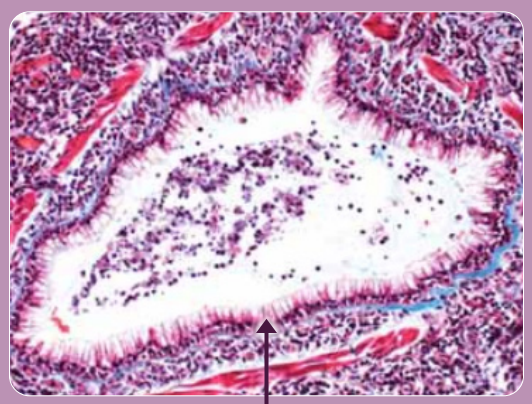
Figure adapted from Abrami M, et al. *Int J Mol Sci*. 2024;25:1933. Licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0).

1. Mucus hypersecretion is caused by **IMBALANCES IN AIRWAY EPITHELIAL FLUID TRANSPORT** and **ELEVATED MUCIN LEVELS**
2. These pathological changes are further exacerbated by **CHRONIC TOBACCO SMOKE EXPOSURE**, which reduces ciliary function
3. As a result, mucus accumulates and forms a **MUCUS PLUG**, which can partially or completely **OCCLUDE THE AIRWAY LUMEN**

Mucus plugs in the large airways are significantly correlated with...

...dense immune cell infiltration[13]

LYMPHOID AGGREGATES MAY INDICATE A DISTINCT TYPE OF MUCUS PLUG WITH CELLULAR CHARACTERISTICS THAT DIFFER FROM THOSE OBSERVED IN ASTHMA



Representative image of a small airway containing a mucus plug and an abundant inflammatory infiltrate within its wall

Image from Polverino F, et al. *ERJ Open Res*. 2025;11:00546–2025.
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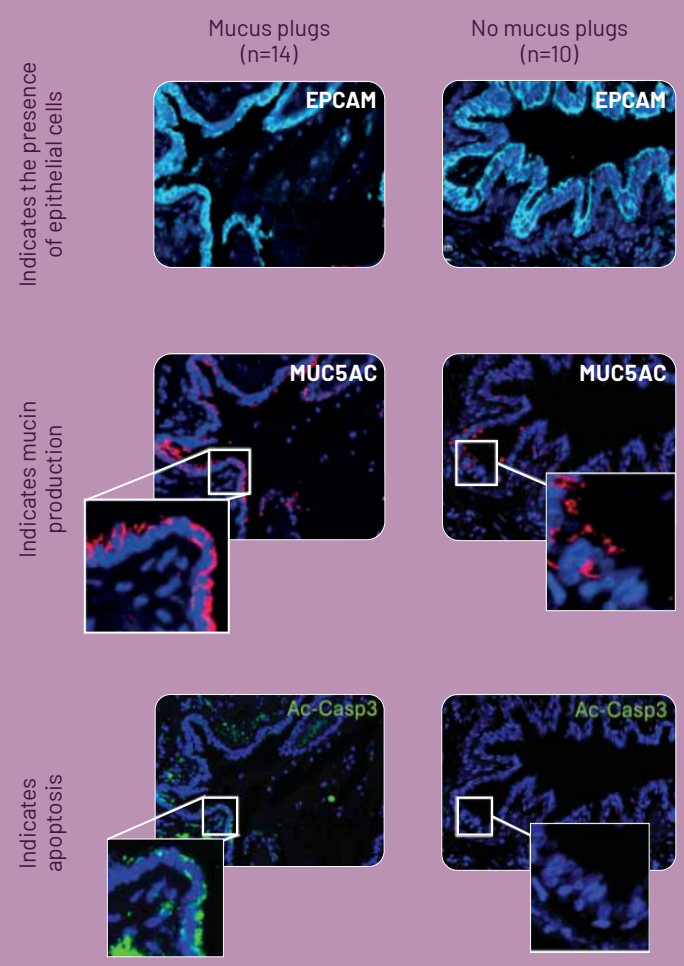
...increased mucin expression and presence of apoptotic epithelial cells in the small airways[13]



Small airways of patients with COPD, with and without mucus plugs (detected by CT scan)*

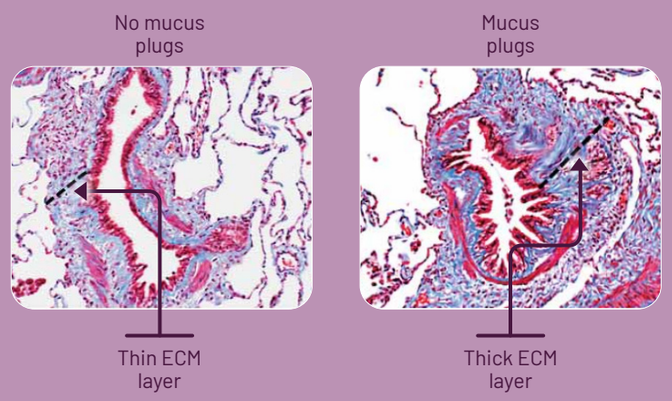
ELEVATED MUCINS can contribute to hyper-concentrated mucus (a hallmark of mucus plug formation) which may drive **AIRFLOW OBSTRUCTION** in COPD

Elevated levels of **APOPTOTIC EPITHELIAL CELLS** in the small airways may indicate **IMPAIRED TISSUE REPAIR, CHRONIC INFLAMMATION,** and an **ABNORMAL RESPONSE** to airway injury

Images from Polverino F, et al. *ERJ Open Res*. 2025;11:00546–2025. Licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).
*Small airways were triple-immunostained for EPCAM, MUC5AC, and Ac-caspase-3. EPCAM, MUC5AC, and Ac-caspase-3 are biological markers.
EPCAM indicates the presence of epithelial cells, MUC5AC indicates mucin production, and Ac-caspase-3 indicates apoptosis.
Samples of peripheral lung tissue from 24 patients with COPD provided by the Lung Tissue Research Consortium supported by the US National Heart, Lung, and Blood Institute.

...thickening of the airway wall[13]

ABUNDANT ECM DEPOSITION AROUND THE SMALL AIRWAYS correlates with increased presence of mucus plugs and POOR LUNG FUNCTION



Small airways of patients with COPD, with and without mucus plugs (detected by CT scan)†

†Samples were stained with Masson's trichrome, where the ECM deposition layer, as a marker of small airway remodeling, appears in blue.
Figures from Polverino F, et al. *ERJ Open Res*. 2025;11:00546–2025. Licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

Mucus plugging is associated with adverse clinical outcomes

Persistent and newly formed mucus plugs are associated with a faster decline in lung function, which is more pronounced in current smokers[14]

Compared with persistently negative patients, a greater decline in post-BD FEV_1 was observed with*:

Newly formed plugs:	Persistent plugs:
–17.7 mL/year	**–23.2** mL/year
(95% CI 11.3–24.1)	(95% CI 15.0–31.4)

*Mucus plugs were surveyed with CT at baseline (Phase 1) and at a 5-year follow-up visit (Phase 2); participants were grouped according to four categories of change in mucus plugs: persistently negative (no mucus plug observed in either phase), resolved (mucus plug present only at Phase 1), newly formed (mucus plug present only at Phase 2), and persistently positive (mucus plug present at both phases).

Mucus plugs are associated with an increased risk of exacerbations[11]

Over 5 years, patients with mucus plugs faced a **2x** greater risk of a **SEVERE EXACERBATION** leading to a hospitalization or ER visit

Adjusted HR = 2.1 (95% CI 1.43–3.10; P=0.001)[†]

[†]Results are from a retrospective observational study evaluating patients who were regularly followed up for COPD management at a teaching hospital between January 2004 and December 2019.

Mucus plugs are associated with an increased risk of mortality[8]

All-cause mortality **INCREASES LINEARLY** with mucus plug score[‡]

[‡]Patients were recruited from the COPDGene study, an observational prospective cohort study conducted across 21 centers across the USA, which included 45- to 80-year-old non-Hispanic White or non-Hispanic Black patients with a ≥10 pack-year smoking history with or without COPD. 4363 patients were included in the primary analysis. Mucus plug score calculated as the number of lung segments with mucus plugs.

Key takeaway

Mucus dysfunction includes mucus hypersecretion, impaired clearance, and mucus plugging, which are distinct features of COPD. Mucus dysfunction is central to the pathology of COPD and is associated with poor patient outcomes and increased disease severity.

Ac, active; BD, bronchodilator; CFTR, cystic fibrosis transmembrane conductance regulator; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CT, computed tomography; ECM, extracellular matrix; EGFR, epidermal growth factor receptor; EPCAM, epithelial cell adhesion molecule; ER, emergency room; FEV_1, forced expiratory volume in 1 second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HR, hazard ratio; MUC, mucin.

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for prevention, diagnosis and management of COPD: 2026 report. Accessed January 26, 2026. https://goldcopd.org/2026-gold-report-and-pocket-guide/; 2. Kotlyarov S. *Int J Mol Sci*. 2022;23:985; 3. Stott-Miller M, et al. *Int J Chron Obstruct Pulmon Dis*. 2020;15:2467–2476; 4. Hughes R, et al. *Respir Med*. 2022;200:106921; 5. Raby KL, et al. *Front Immunol*. 2023;14:1201658; 6. Diaz AA. *Chest*. 2025;167:34–36; 7. Okajima Y, et al. *Chest*. 2020;158:121–130; 8. Diaz AA et al. *JAMA*. 2023;329:1832–1839 (article and supplementary information); 9. Fahy JV, Dickey BF. *N Engl J Med*. 2010;363:2233–2247; 10. Dunican EM, et al. *Am J Respir Crit Care Med*. 2021;203:957–968; 11. Jin KN, et al. *Arch Bronconeumol*. 2025;61:138–146; 12. Mettler SK, et al. *Chest*. 2024;166:1010–1019; 13. Polverino F, et al. *ERJ Open Res*. 2025;11:00546–2025; 14. Mettler SK, et al. *N Engl J Med*. 2025;392:1973–1975.

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