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REVIEW

Small Airway Disease in Pre-COPD and Early COPD: Insights Into the Pulmonary "Silent Zone"

Jingli Li[1–3], Lingjing Liu[4], Jixian Tang[1,2], Chunxiao He[1,2], Guimei Pu[1,2,*], Jian Sun[1,2,*]

[1]Department of Pulmonary and Critical Care Medicine, Shaoxing People's Hospital, Shaoxing, Zhejiang, 312000, People's Republic of China; [2]Suzhou Medical College, Soochow University, Suzhou, Jiangsu, 215000, People's Republic of China; [3]School of Medicine, Shaoxing University, Shaoxing, Zhejiang, 312000, People's Republic of China; [4]Department of Pulmonary and Critical Care Medicine, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, 325000, People's Republic of China

*These authors contributed equally to this work

Correspondence: Jian Sun; Guimei Pu, Department of Pulmonary and Critical Care Medicine, Shaoxing People's Hospital, Shaoxing, Zhejiang, 312000, People's Republic of China, Email 2002sunjian@163.com; iampuguimei@126.com

Abstract: Chronic obstructive pulmonary disease (COPD) is increasingly recognized as a life-course disorder with origins rooted in early-life insults. However, the current diagnostic reliance on the FEV1/FVC < 0.7 threshold often fails to capture the early phases of disease evolution, particularly within the pulmonary "Silent Zone." This narrative review examines small airway disease (SAD) in pre-COPD and early COPD by integrating physiological, structural, molecular, and diagnostic evidence. Findings from imaging and pathology studies indicate that terminal bronchiole loss, mucus plugging, alveolar attachment disruption, and vascular remodeling may occur before overt spirometric obstruction develops. We also summarize candidate molecular mechanisms that may contribute to early remodeling, including ATP5B-related epithelial signaling, STAT3/PINK1-Parkin-associated mitophagy, endothelial-to-mesenchymal transition, and inflammaging, while emphasizing that many of these pathways remain preliminary and require further validation. To bridge the diagnostic gap, we review multimodal approaches including FEV3-based indices, impulse oscillometry, parametric response mapping, CT-visible airway counts, and computational fluid dynamics. We further discuss clinical phenotypes such as PRISm and non-obstructive chronic bronchitis, as well as the contribution of non-tobacco environmental exposures. Overall, this review highlights how a Silent Zone-centered framework may improve early risk stratification and inform future studies aimed at disease modification before irreversible airflow obstruction develops.

Keywords: small airway disease, pre-COPD, early COPD, quantitative CT, precision medicine

Introduction

Chronic obstructive pulmonary disease (COPD) is currently defined as a complex and heterogeneous respiratory condition characterized by persistent airflow limitation resulting from chronic inflammation and structural abnormalities of the airways and/or alveoli.[1] For decades, the clinico-physiological diagnosis of COPD has primarily relied on a post-bronchodilator forced expiratory volume in 1 second (FEV1) to forced vital capacity (FVC) ratio below a fixed threshold of 0.7.[2] However, this spirometric criterion is increasingly regarded as a lagging indicator. Substantial pathological remodeling, including terminal bronchiole loss and parenchymal destruction, may occur years before measurable airflow obstruction becomes apparent.[3,4]

The physiological basis of this diagnostic blind spot was established by the classic work of Macklem and Mead, who showed that the peripheral airways contribute only a small fraction of total airway resistance in healthy lungs.[5] This concept was further reinforced by Hogg, Macklem, and Thurlbeck, who demonstrated that the major site of increased airway resistance in chronic obstructive lung disease resides in the small airways.[6] Together, these studies provided the foundation for the concept of the pulmonary "Silent Zone", a region in which considerable disease may accumulate before it becomes detectable by conventional spirometry.[7] More recent pathological and imaging studies have strengthened this framework. Hogg et al showed that progression of COPD is closely associated with inflammatory exudates,

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wall thickening, and remodeling in the small airways.[8] In parallel, McDonough et al used micro-computed tomography to demonstrate that narrowing and loss of terminal bronchioles occur before the onset of substantial emphysematous destruction.[9] These observations indicate that early COPD-related injury is concentrated in the distal airways and may precede overt spirometric obstruction by many years.

The conceptual framework of COPD has recently shifted toward identifying at-risk individuals during the earliest phases of disease evolution, formalized through the established categories of "Pre-COPD" and "Early COPD".[10] According to the latest Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2025 insights, Pre-COPD identifies individuals of any age who exhibit respiratory symptoms, structural abnormalities (eg., emphysema or small airway lesions on CT), or physiological impairments (eg., rapid FEV1 decline or low DLCO), while maintaining a preserved post-bronchodilator FEV1/FVC ratio $\geq$ 0.7.[11] This paradigm shift emphasizes a proactive "life-course" approach, seeking to intervene during a critical window when the disease may still be susceptible to modification before progressing to irreversible functional loss.[12]

Epidemiological evidence underscores the significant burden of disease within this "Silent Zone." Data from the China Pulmonary Health (CPH) study indicated that the prevalence of Pre-COPD in the Chinese adult population is approximately 7.2%, with the vast majority of these individuals manifesting objective small airway dysfunction (SAD).[13] Despite being "pre-obstructive," these individuals face a substantially higher risk of acute respiratory events, hospitalizations, and all-cause mortality compared to healthy controls.[14,15] Furthermore, longitudinal studies have shown that the presence of SAD is a potent predictor of future COPD development, yet the precise mechanisms governing the transition from isolated small airway injury to established airflow limitation remain a subject of intense investigation.[16,17]

Recent reviews have addressed small airway disease, pre-COPD, and precision medicine in COPD. In contrast to these topic-specific reviews, this narrative review uses the pulmonary "Silent Zone" as a unifying framework to integrate physiological, morphological, molecular, and multimodal diagnostic evidence across the transition from pre-COPD to early COPD. Our aim is to highlight how these converging lines of evidence may improve early risk stratification and support disease-modifying intervention before overt airflow obstruction develops.

Morphological Evolution: The Cascade of Structural Collapse in the Silent Zone

COPD begins with structural alterations in the small airways, often before any detectable change in global lung function occurs. These early abnormalities progressively disrupt the pulmonary architecture.[18,19] These early abnormalities progressively disrupt pulmonary architecture. This morphological evolution is not a single event, but a sequence of changes involving loss of conducting airways, remodeling of the airway-alveolar interface, and alterations in the pulmonary microvasculature. With advances in ex vivo micro-computed tomography (micro-CT), quantitative CT (QCT), and endobronchial optical coherence tomography (EB-OCT), recent studies have begun to map the spatiotemporal changes in small airways with increasing granularity.[20,21]

Methodological advances from several groups have been central to this field. Work from the Vancouver/UBC and Leuven groups has helped establish multiresolution ex vivo imaging approaches that combine conventional CT, whole-lung micro-CT, and higher-resolution core analyses to quantify terminal bronchiole loss and associated alveolar alterations.[22,23] In parallel, population-based and multicenter imaging cohorts such as CanCOLD and COPDGene have extended these observations in vivo by showing that airway counts, air trapping, and CT-based phenotypes can predict physiological decline and help distinguish airway-predominant from emphysema-predominant trajectories.[24,25] Together, these studies have provided much of the methodological foundation for current concepts of the pulmonary "Silent Zone".

The Quantitative Vanishing of Terminal Bronchioles: The Primordial Lesion

Among the strongest structural observations supporting the Silent Zone concept is the early reduction in terminal bronchioles (TBs). For decades, COPD was viewed primarily as a disease of airway narrowing and parenchymal emphysema. More recent ex vivo imaging studies have shown that many of the smallest conducting airways, particularly terminal bronchioles, are already reduced in number early in the disease course. In several studies, this reduction appears

to precede the development of centrilobular emphysema.[16,26] Quantitative micro-CT analysis has revealed that individuals classified as GOLD Stage 1 (mild COPD) already exhibit a 35% to 40% reduction in the total number of TBs compared to healthy non-smokers.[17,27] Importantly, this reduction may not be confined to individuals who already meet spirometric criteria for obstruction, and similar changes have been reported in symptomatic smokers with preserved spirometry. Recent data suggest that symptomatic smokers with preserved FEV1/FVC ratios manifest a significant decline in TB density, indicating that the vanishing of these peripheral conduits is the primordial structural lesion in the natural history of COPD.[4,11] This loss creates a massive "bottleneck" in the peripheral lung. In the healthy state, the cumulative cross-sectional area of the small airways is exponentially larger than that of the central airways, leading to negligible resistance. However, once 40% or more of these conduits are obliterated, the remaining airways must carry the entire ventilatory load, leading to a precipitous increase in regional resistance and work of breathing.[20,21] This structural void is further exacerbated by the fact that the remaining airways are not merely fewer in number but are often severely narrowed, with luminal diameters frequently falling below 200 μm.[26]

Qualitative Divergence of Airway Obstructions: Web, Occlusion, and Collapse

The surviving small airways in Pre-COPD and early COPD do not remain healthy; instead, they undergo a transformative and progressive process of luminal failure. A pivotal multi-center study utilizing multiscale imaging has recently defined a new morphological taxonomy to describe this degradation, categorizing small airway obstructions into three distinct stages: webs, occlusions, and collapse.[27] In the Pre-COPD and early stages of disease, particularly among smokers with limited emphysema, web-like obstructions represent the predominant form of luminal interference. Histologically, these delicate, net-like structures consist of thin strands of inflammatory exudates and fibrin that partially bridge the airway lumen.[27] Although these webs may not completely block airflow, they can still increase flow turbulence and contribute to ventilation heterogeneity. This abnormality can be detected by oscillometry (IOS) reactance parameters such as X5 and AX.[28,29] As the pathology transitions toward symptomatic COPD, these initial webs often evolve into solid, dense plugs known as mucoid occlusions. These obstructions are predominantly characterized by a hyper-viscous mixture of MUC5AC and MUC5B glycoproteins, trapped cellular debris, and neutrophil-derived DNA nets.[30,31] In the early stages of COPD, these solid plugs are most prevalent in the 5th to 8th generation bronchioles, serving as sentinel markers for a "muco-obstructive" endotype that drives chronic air trapping and recurrent exacerbations.[32] The terminal stage of this airway failure is represented by structural collapse, where the loss of elastic support leads to a permanent, slit-like narrowing of the lumen.[20,27] Together, these findings suggest a progression from webs to mucoid occlusions and finally to structural collapse. This sequence indicates that the greatest opportunity for disease modification may lie in the pre-COPD stage, before these lesions become permanent structural barriers.[4,20]

The Pathological Significance of Mucus Plugging on CT

The clinical relevance of these obstructions has been further substantiated by QCT studies identifying "mucus plugs" in the medium-sized airways as surrogates for distal small airway disease. In patients with Pre-COPD and mild COPD, the presence of even a single CT-detected mucus plug is strongly associated with increased airway wall thickness (WT) and a higher wall area percentage (WA%) in the distal airways.[30,31,33] These plugs serve as active foci of inflammation. Pathological examination shows that the airway segments adjacent to mucus plugs exhibit significant goblet cell hyperplasia, basement membrane thickening, and increased infiltration of CD8+ T-lymphocytes and neutrophils.[31,34] Furthermore, the presence of mucoid occlusions is spatially correlated with the Parametric Response Mapping (PRM) signature of functional small airway disease (PRMfSAD), suggesting that mucus-driven obstruction is a primary driver of air trapping in the pre-obstructive phase.[29,30,32]

Failure of the Mechanical Support: Destruction of Radial Alveolar Attachments

One of the most critical yet under-recognized morphological events in the evolution of early COPD is the destruction of the radial alveolar attachments.[19,26] Small airways lack cartilaginous support; their patency during expiration is entirely dependent on the mechanical radial traction—or "tethering"—exerted by the surrounding alveolar walls. In the healthy lung, these attachments act as elastic springs that pull the airway walls outward. In pre-COPD and early COPD, chronic

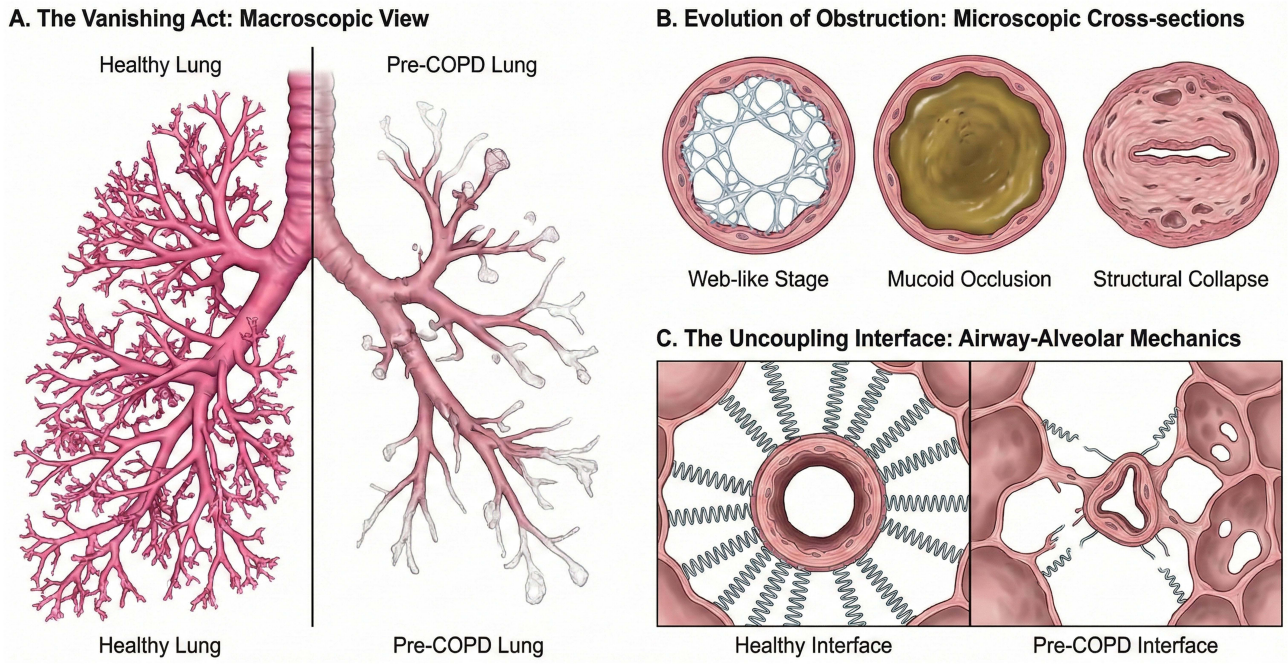

Figure 1 Conceptual schematic of the morphological landscape of the pulmonary "Silent Zone" in pre-COPD and early COPD. (**A**) Schematic comparison of the distal airway tree in a healthy lung and a pre-COPD lung, illustrating early terminal bronchiole loss and simplification of the peripheral airway network. (**B**) Conceptual illustration of the progression of small-airway luminal obstruction, including web-like obstruction, mucoid occlusion, and structural collapse. This panel is based on the morphological taxonomy of small-airway obstruction described by Geudens et al (**C**) Conceptual illustration of the airway-alveolar interface, showing loss of radial alveolar attachments and mechanical uncoupling in pre-COPD.

inflammatory activity may involve the junction where alveolar septa insert into the airway adventitia, contributing to loss of radial alveolar attachments.[16] Quantitative studies have shown that the number of alveolar attachments per airway circumference is significantly reduced in symptomatic smokers even when their FEV1/FVC ratio remains normal.[16] The loss of this radial support leads to "mechanical uncoupling," where the airway wall becomes flaccid and prone to premature closure during expiration.[26,35] This phenomenon is a major determinant of dynamic hyperinflation (DH). During exercise, rapid breathing can trap air behind these collapsible airways in patients with early SAD. This process increases functional residual capacity (FRC) and reduces inspiratory capacity (IC).[35,36] This explains why Pre-COPD patients often report significant exercise-induced dyspnea despite "normal" baseline spirometry (Figure 1).[35,36]

Micro-Morphometric Disruption of the Alveolar Architecture: Kohn Pores

At the most distal reach of the Silent Zone, the morphological integrity of the alveolar wall begins to fail in a subtle yet profound manner. Quantitative micro-CT analysis of ex vivo lung tissue has identified significant alterations in the morphology of the interalveolar pores (Pores of Kohn) during the Pre-COPD and early COPD stages.[26] Unlike advanced emphysema where the primary feature is alveolar wall destruction, the early phase is characterized by a significant increase in the diameter of Kohn pores, while the total number of pores remains relatively stable.[26] This Pore of Kohn enlargement represents an early "septal fenestration" process. Enlarged Kohn pores may initially support collateral ventilation around obstructed small airways. However, they may also weaken the structural stability of the alveolar sac.[26] As the diameter of these fenestrations increases, the surface-to-volume ratio of the alveoli declines, and the septal walls become increasingly fragile, eventually leading to the coalescence of alveoli—the morphological hallmark of clinical emphysema.[37] These findings confirm that alveolar degradation and small airway loss are synchronized events that begin well within the pre-obstructive window.

Continuous Surface Characterization and Luminal Eccentricity

Recent innovations in airway morphometry have moved beyond simple diameter measurements to "continuous surface representation" of the bronchial lumen. A 2023 study[37] utilizing this technique in Pre-COPD and mild COPD lungs

revealed that early disease is characterized by a significant increase in luminal eccentricity (the degree to which the airway cross-section deviates from a circle) and a decrease in the surface-to-volume (SA:V) ratio of the distal airways. These geometric changes indicate that the small airways in early COPD are not just "narrower" but are fundamentally deformed. Increased eccentricity is a structural marker of wall instability and non-uniform remodeling, which creates high-resistance "hotspots" throughout the pulmonary tree.[38] Computational fluid dynamics (CFD) simulations based on these precise geometric models have demonstrated that even a 10% increase in luminal eccentricity can lead to a 25% increase in regional airway resistance, providing a mechanical explanation for why early morphological changes lead to significant clinical symptoms.[21,38]

The Vascular-Airway Axis: Vascular Pruning and Endothelial-to-Mesenchymal Transition (EndMT)

A truly comprehensive view of morphological evolution in early COPD must include the pulmonary microvasculature. Quantitative imaging has consistently identified "vascular pruning"—a reduction in the volume and density of small pulmonary vessels (cross-sectional area < 5 mm^2)—as a common feature in smokers with Pre-COPD.[39–41] Crucially, this microvascular loss is spatially coupled with functional small airway disease (fSAD). The structural basis for this pruning is the thickening of the vessel walls and the narrowing of the vascular lumen, driven by Endothelial-to-Mesenchymal Transition (EndMT).[40] In this process, the pulmonary endothelial cells acquire a mesenchymal-like phenotype, characterized by the loss of CD31 expression and the gain of mesenchymal markers such as N-cadherin and vimentin.[40] These vascular changes are also present in symptomatic smokers with normal spirometry. This finding suggests that the Silent Zone is a multi-compartmental environment in which the airways, parenchyma, and vasculature undergo concurrent structural remodeling.[12,39,40]

Candidate Molecular Mechanisms of Early Small-Airway Remodeling in the Silent Zone

Compared with the structural and physiological literature, the molecular evidence in pre-COPD and early COPD remains less mature.[42–44] Most available data derive from single-center transcriptomic analyses, animal models, or limited observational cohorts rather than from replicated multimodal human studies.[19,40,42] Accordingly, the pathways discussed below should be interpreted as candidate mechanisms that may contribute to early remodeling, rather than as established drivers of disease progression. This distinction is important when linking molecular observations to clinical translation.

ATP5B as an Emerging Candidate Pathway in Epithelial Remodeling

Recent transcriptomic and experimental studies have suggested that epithelial heterogeneity in COPD may involve coordinated alterations in mitochondrial and inflammatory signaling. One candidate emerging from this literature is ATP synthase subunit beta (ATP5B). In a recent integrated study, ATP5B was identified as a hub gene by intersecting epithelial marker genes from small-airway single-cell RNA-sequencing data with differentially expressed genes from an independent COPD dataset.[42] Functional experiments further showed that ATP5B knockdown attenuated cigarette smoke extract-induced epithelial apoptosis, reduced IL-6 and TNF-α release, suppressed epithelial-mesenchymal transition, and decreased the expression of remodeling-related markers such as TGF-β and MMP-9 in BEAS-2B cells.[42] In a CS/LPS-induced mouse model, ATP5B silencing similarly alleviated airway inflammation and remodeling.[42] Additional analyses in the same study suggested that these effects may be mediated, at least in part, through TLR-related signaling, as ATP5B knockdown reduced TLR2, TLR3, and TLR4 expression, whereas poly(I:C) partly reversed the observed protective effects.[42] These findings make ATP5B a biologically interesting candidate linking epithelial metabolic stress to inflammatory remodeling. However, the current evidence remains preliminary. It is derived mainly from a single recent study that combines bioinformatic analysis with in vitro and animal validation, and the human data are based on relatively limited datasets rather than large multicenter early-disease cohorts. Moreover, the translational relevance of this pathway to pre-COPD or early COPD in humans has not yet been independently replicated. ATP5B should therefore be regarded as a promising candidate mechanism rather than an established molecular driver of early COPD progression.

Experimental Evidence Implicating the STAT3-PINK1/Parkin Axis in Smoke-Induced Epithelial Remodeling

Mitochondrial dysfunction is biologically plausible as a contributor to early small-airway injury because the distal airway epithelium has substantial metabolic demands and depends on intact mitochondrial function to maintain ciliary activity and barrier integrity.[43,45] A recent experimental study further suggested that cigarette smoke may promote epithelial remodeling through coordinated activation of STAT3 signaling, PINK1-Parkin-related mitophagy, and EMT.[43] However, in the early COPD lung, this quality-control mechanism becomes "pathologically hyperactivated," shifting from a protective role to a destructive one.[43] In that study, long-term cigarette smoke exposure in mice caused small-airway wall thickening, collagen deposition, emphysematous change, and mitochondrial structural damage in bronchial epithelial cells. In parallel, 0.1% cigarette smoke extract induced STAT3 phosphorylation, increased TGF-β1 expression, enhanced PINK1/Parkin-related mitophagy, elevated mtROS, and promoted EMT-related changes in BEAS-2B cells. Pharmacological inhibition of STAT3 with WP1066 attenuated TGF-β1 upregulation, reduced mitophagy- and mtROS-related changes, and partly reversed the EMT phenotype.[43] Inhibition of mitophagy with Mdivi-1 also ameliorated CSE-induced EMT, while additional experiments using the STAT3 agonist colivelin suggested that mitophagy may act, at least in part, downstream of STAT3 signaling. Taken together, these findings support the plausibility of a STAT3-PINK1/Parkin-mitophagy-EMT axis in smoke-induced epithelial remodeling. However, this evidence remains preliminary.[43] It is derived mainly from a single preclinical study using a mouse model, BEAS-2B cells, and pharmacological modulation, rather than from replicated human early-disease cohorts.[43] Moreover, the authors themselves noted discrepancies in Parkin expression between in vivo and in vitro systems and acknowledged that the mechanistic relationship between STAT3 and PINK1-Parkin-mediated mitophagy was examined mainly at the protein level. This pathway should therefore be regarded as a promising experimental mechanism that warrants further validation in human pre-COPD and early COPD populations, rather than as an established driver of early disease progression.

Multi-Compartmental Failure: EndMT and Vascular-Airway Crosstalk

One of the most innovative insights into the early pathophysiology of the Silent Zone is the recognition that it is a "multi-compartmental" environment where vascular remodeling and airway disease are inextricably linked through a shared molecular program.[39,40,44] This synergy is driven by EndMT, a process that mirrors EMT but occurs within the pulmonary microvasculature.[40] In the small pulmonary arteries (cross-sectional area < 5 mm^2) of symptomatic smokers with preserved spirometry, endothelial cells undergo a phenotypic transformation.[39,40] Histological and transcriptomic analyses show a significant loss of endothelial-specific markers, such as CD31 (PECAM-1) and VE-cadherin, and a simultaneous gain in mesenchymal markers, including N-cadherin and vimentin.[40] This EndMT process is highly active during the Pre-COPD phase and is spatially coupled with fSAD and terminal bronchiole loss.[39–41] The molecular driver of EndMT is primarily the paracrine secretion of Transforming Growth Factor-beta (TGF-β) from adjacent inflammatory cells and the airway adventitia.[19,40] EndMT-transformed endothelial cells lose their ability to regulate vascular tone and barrier function. They also acquire a pro-fibrotic and pro-inflammatory secretory profile, with increased production of Endothelin-1 and cytokines that diffuse into the perivascular and peribronchiolar spaces.[40] This "vascular-airway cross-talk" establishes a self-reinforcing cycle: vascular "pruning" leads to regional hypoxia, which in turn activates Hypoxia-Inducible Factor 1-alpha (HIF-1a) in SAECs, further accelerating EMT and peribronchiolar fibrosis.[12,39] Taken together, these data suggest that vascular remodeling and airway remodeling may be linked during early disease. However, the extent to which EndMT directly drives human pre-COPD progression, and whether it represents a therapeutically actionable process, remains uncertain.[44]

Accelerated Aging and the Senescence-Associated Secretory Phenotype (SASP): The "Inflammaging" Engine

The small airways in early COPD exhibit a phenotype of "accelerated aging," characterized by the premature accumulation of senescent cells.[18,19] Cellular senescence, driven by smoking-induced DNA damage and oxidative stress, results in a permanent cell-cycle arrest in SAECs and lung fibroblasts.[19] These senescent cells are not metabolically inert; they

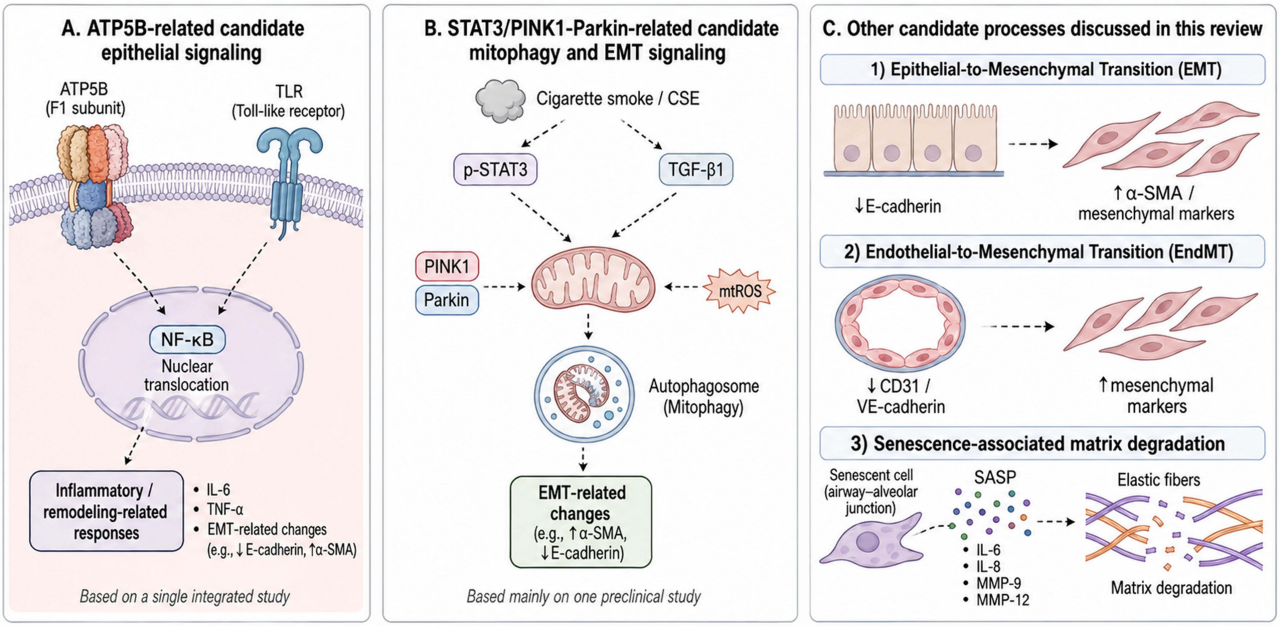

Figure 2 Conceptual schematic of candidate molecular processes implicated in early small-airway remodeling in the pulmonary "Silent Zone". (**A**) ATP5B-related candidate epithelial signaling. This panel summarizes a proposed pathway in which ATP5B may be linked to TLR-related signaling and downstream inflammatory/remodeling responses. (**B**) STAT3/PINK1-Parkin-related candidate mitophagy and EMT signaling. This panel summarizes experimental findings suggesting that cigarette smoke exposure may activate STAT3 signaling and be associated with PINK1/Parkin-related mitophagy, mtROS generation, and EMT-related changes. (**C**) Additional candidate processes discussed in this review, including epithelial-to-mesenchymal transition (EMT), endothelial-to-mesenchymal transition (EndMT), and senescence-associated matrix degradation. This figure is a conceptual illustration created by the authors for summary purposes and does not represent original experimental data. The pathways shown are based on separate published studies and are presented as candidate mechanisms rather than as a single established integrated network. Direct interactions or co-occurrence among these pathways have not been demonstrated.

develop a SASP, a secretome rich in pro-inflammatory cytokines (IL-1β, IL-6, IL-8), chemokines (MCP-1), and, most critically, Matrix Metalloproteinases (MMPs).[19] In the Silent Zone of Pre-COPD patients, SASP-derived MMP-9 and MMP-12 play a pivotal role in the degradation of the elastin fibers that constitute the radial alveolar attachments.[16,19] This molecular proteolysis leads to the mechanical uncoupling of the airway and parenchyma, facilitating the airway collapse and dynamic hyperinflation characteristic of the early symptomatic stages.[26,35,36] The concept of inflammaging refers to chronic, low-grade inflammation driven by the SASP. This framework may help explain why small-airway abnormalities can persist or progress after smoking cessation. However, the relative contribution of senescent-cell burden to human early COPD progression has not yet been clearly quantified (Figure 2).[11,19]

Epithelial Barrier Dysfunction and the Epidermal Growth Factor Receptor (EGFR)-Mucus Axis

The integrity of the small airway epithelial barrier is compromised early in the disease course, a process termed "epithelial barrier dysfunction".[34] Quantitative analysis of junctional proteins reveals that even in asymptomatic smokers, there is a significant downregulation of ZO-1 and occludin, leading to increased paracellular permeability.[33] This barrier failure is intrinsically linked to the dysregulation of the EGFR signaling pathway.[30] CS exposure activates EGFR in SAECs, which triggers a downstream signaling cascade (Ras/Raf/MEK/ERK) that leads to the massive upregulation of MUC5AC mucin.[30,31] Unlike MUC5B, which is essential for normal mucociliary transport, MUC5AC is a "stiff" mucin that forms tenacious "mucoid tethers" to the airway surface.[30] This molecular shift toward a MUC5AC-dominant mucus profile is a primary driver of the luminal plugging observed on CT.[30] Furthermore, this process is exacerbated by the smoking-induced inhibition of the Cystic Fibrosis Transmembrane Conductance Regulator and other ion channels in the small airways, leading to airway surface liquid dehydration and further increasing the viscosity of the MUC5AC-rich mucus.[30] This muco-obstructive molecular engine creates an environment of stasis that promotes bacterial colonization and persistent neutrophilic inflammation, eventually leading to the permanent obliteration of the terminal bronchioles.[16]

Epigenetic Landscapes and the GETomics Paradigm

To fully understand the molecular engines of early COPD, one must consider the epigenetic reprogramming that occurs at the distal lung level.[46] Environmental insults (smoking, pollution) leave "epigenetic scars" on the SAEC genome, primarily through DNA methylation and histone modifications.[46,47] Research has identified specific DNA methylation patterns in SAECs that are predictive of a rapid FEV1 decline in early adulthood.[46] These epigenetic changes affect genes involved in lung development (eg., HHIP, FAM13A), suggesting that the "molecular engine" of COPD may be primed during the "lung development window" (birth to age 25).[46] This forms the basis of the GETomics (Genetics, Environment, and Time) paradigm, which argues that the small airway pathology in a 40-year-old is the culmination of molecular interactions that began decades earlier.[46,48] For example, a "low peak lung function" in early adulthood, driven by early-life epigenetic shifts, significantly lowers the threshold for ATP5B-driven or STAT3-driven remodeling to manifest as clinical disease.[46,49]

Preliminary Metabolomic Signals in Pre-COPD

Metabolomic profiling has provided an additional, but still early, window into biological changes associated with pre-COPD.[50,51] A recent cohort study reported alterations in sphingolipid and amino acid metabolism, including higher circulating levels of selected ceramide species.[50] These observations raise the possibility that plasma metabolic signatures may reflect early airway injury or systemic responses linked to disease susceptibility.[50] However, the current evidence base remains limited. The reported metabolomic patterns have not yet been consistently reproduced across independent cohorts, and their specificity for pre-COPD, as distinct from smoking exposure or other comorbid conditions, remains uncertain. At present, these findings should be regarded as promising biomarker leads rather than validated molecular fingerprints of early COPD.

At present, the strongest evidence in early COPD remains structural and physiological rather than molecular. Terminal bronchiole loss, alveolar attachment disruption, mucus plugging, reduced airway counts, PRM-defined functional small-airway disease, and oscillometric abnormalities have been observed across multiple imaging, pathology, or cohort-based studies. By contrast, many of the molecular pathways discussed above remain hypothesis-generating and have not yet been linked consistently to longitudinal clinical outcomes in the same populations. A major priority for future work is therefore to integrate biospecimens, imaging, oscillometry, and spirometric trajectories within multimodal longitudinal cohorts, so that candidate mechanisms can be tested against measurable disease progression.

Capturing the "Silent Zone": From Physiological Metrics to High-Resolution Multimodal Simulations

Early detection of lesions within the pulmonary "Silent Zone" has become a major focus of COPD research. However, standard spirometry remains insensitive to many of these early changes.[3,4] As discussed in the preceding sections, key pathological changes in COPD begin in the distal lung long before the FEV1/FVC ratio falls below the diagnostic threshold of 0.7. These changes include terminal bronchiole loss and mitochondrial dysfunction.[19] Given that the small airways contribute less than 20% to total respiratory resistance in the early phases of disease, global flow metrics often remain deceptively preserved while structural disintegration is already widespread. To bridge this "detection gap," an integrated diagnostic matrix is required—one that shifts the clinical focus from global expiratory flow to regional mechanics, voxel-wise radiological mapping, and patient-specific biomechanical simulations.[10,44]

Beyond FEV1: The Re-Evaluation of Mid-to-Late Expiratory Metrics

The limitations of FEV1 have renewed interest in the mid-to-late portion of the expiratory flow-volume curve. Subtle scooping in this region may represent an early physiological sign of peripheral airway obstruction. The volume exhaled within the first three seconds of a forced maneuver (FEV3) and its associated ratios, particularly FEV3/FVC and FEV3/FEV6, have emerged as highly sensitive physiological sensors for the early detection of SAD.[52,53] Longitudinal data from the ECOPD study showed that a reduced FEV3/FVC ratio is an independent predictor of future COPD in symptomatic smokers with normal spirometry. A threshold of 0.91 was associated with a hazard ratio of up to 4.96.[52]

This metric effectively captures the delayed emptying of distal lung units that is systematically overlooked during the first second of expiration. Furthermore, in primary care and resource-limited settings, the FEV3/FEV6 ratio may serve as a simple and effort-independent alternative to the traditional FEV1/FVC ratio. It has shown higher sensitivity for detecting early SAD and may provide an important tool for risk stratification in underserved populations where sophisticated equipment is not available.[53]

The historical marginalization of the maximal mid-expiratory flow (MMEF, or FEF25–75%) due to its high intra-individual variability is also being challenged by contemporary predictive models. Recent validations within large Chinese cohorts, such as the CPH study, have rehabilitated the clinical utility of MMEF as a marker of disease transition.[13,54] An MMEF value below 80% of the predicted normal is now recognized as a critical risk factor for the progression from Pre-COPD to established obstruction, particularly when it occurs in conjunction with chronic bronchitic symptoms.[54] MMEF may reflect the integrated resistance of the 4th to 14th airway generations. Remodeling and luminal narrowing are particularly prominent in these regions during the pre-obstructive phase. By integrating these mid-to-late flow metrics into a comprehensive risk score, clinicians can identify "rapid decliners" who may benefit from early pharmacological intervention.[17,55]

Impulse Oscillometry (IOS) and the Mechanics of Ventilation Heterogeneity

While spirometric ratios focus on forced expiratory flow, the IOS has expanded the physiological assessment of the Silent Zone by allowing respiratory impedance to be measured during tidal breathing. This technique effectively bypasses the confounding effort-dependency and gas compression effects associated with forced maneuvers, making it highly suitable for the early detection of SAD.[28,56] The physiological hallmark of peripheral airway disease within the IOS framework is the frequency-dependence of resistance, quantified as the difference between resistance at 5 Hz and 20 Hz (R5-R20). In the Pre-COPD phase, the narrowing and remodeling of terminal bronchioles significantly elevate low-frequency resistance (R5) while central airway resistance (R20) remains relatively stable, resulting in a widened R5-R20 gap that frequently exceeds the pathological threshold of 0.07 kPa s/L.[28,56]

Beyond simple resistance, IOS reactance parameters provide granular insights into the dynamic compliance and elastic failure of the peripheral lung units. The reactance at 5 Hz (X5) and the area under the reactance curve (AX) serve as sensitive markers for the loss of functional lung units due to premature airway closure and regional air trapping.[29,35] An increase in AX reflects a shift in the resonant frequency of the lung, a phenomenon that is strongly correlated with the development of exercise-induced dynamic hyperinflation and exertional dyspnea, even in individuals who maintain a "normal" FEV1.[35,36] Furthermore, IOS has shown good performance in identifying SAD in symptomatic smokers and in patients with preserved ratio impaired spirometry (PRISm) despite preserved global flow. This makes it a useful tool for characterizing the physiological features of the Silent Zone before structural damage becomes irreversible.[57–59]

Despite these advances, the oscillometry literature remains heterogeneous with respect to devices, reference equations, and thresholds used to define abnormality. Recent international Delphi work has begun to build consensus around interpretation of key indices such as R5, X5, and AX in asthma and COPD, but standardization for early COPD and pre-COPD remains incomplete. Oscillometry should therefore be considered a promising complementary tool for early physiological assessment rather than a fully standardized standalone diagnostic test for the Silent Zone.

Functional Quantitative CT: Voxel-Wise Mapping and Radiomic Phenotypes

The transition from physiological measurement to structural visualization is now facilitated by functional QCT, which has evolved into a digital physiology platform capable of resolving the spatial architecture of the distal lung. The PRM algorithm uses voxel-wise co-registration of inspiratory and expiratory CT images. This approach has substantially improved structural assessment of early small airway disease.[20,29] This sophisticated computational approach allows for the classification of the lung parenchyma into distinct functional classes, with a specific focus on functional small airway disease (PRMfSAD). This class identifies regions that appear radiologically normal during inspiration but exhibit significant air trapping during expiration—a direct radiological surrogate for terminal bronchiole dysfunction.[20,60] Longitudinal data from the SOURCE and SPIROMICS studies suggest that PRMfSAD is the biological precursor to

macroscopic emphysema (PRMemph), effectively providing a visual "map" of the disease's progression from subtle airway injury to irreversible tissue destruction.[32,60]

Complementing the PRM data, advanced QCT can now detect "sentinel markers" of early disease involving both the airway lumen and the microvasculature. The detection of mucus plugs in airways as small as 2 mm has gained significant clinical traction; the presence of even a single CT-detected mucus plug in a Pre-COPD patient is associated with a 2.5-fold increase in the risk of accelerated FEV1 decline, serving as a proxy for widespread distal obliteration.[30,31,61] Simultaneously, the "pruning" of small pulmonary vessels, characterized by a reduction in total vessel volume for vessels with a cross-sectional area less than 5 mm^2, has been identified as a common feature in symptomatic smokers with preserved spirometry.[39,40] This microvascular loss is spatially associated with zones of PRMfSAD. This finding suggests that early changes in the Silent Zone involve multiple compartments, including medial hypertrophy of small pulmonary arteries and narrowing of terminal bronchioles.[40]

Beyond PRM, CT-visible airway counts have emerged as another important imaging marker of early airway injury. In the population-based CanCOLD study, reduced total airway count (TAC) was associated with incident COPD and with greater longitudinal decline in FEV1/FVC among at-risk smokers.[24] Related studies have also shown that TAC reduction is detectable in early-stage disease and may capture airway attrition that is not reflected by emphysema measures alone.[62] In parallel, COPDGene analyses have helped characterize longitudinal progression of air trapping and the distinction between airway-predominant and emphysema-predominant early phenotypes.[25,32] These in vivo imaging studies strengthen the translational bridge between ex vivo micro-CT observations and clinically applicable CT phenotyping.

Computational Fluid Dynamics (CFD) and Multi-Scale Modeling

The most granular biomechanical understanding of small airway resistance is currently provided by CFD simulations, which model the physics of airflow within the patient's unique pulmonary tree. High-fidelity modeling techniques have recently begun to integrate low-dose CT structural data with the micron-scale resolution of EB-OCT.[21] While standard CT is limited by a 0.5 mm resolution, EB-OCT allows for the precise measurement of wall thickness and luminal radius in the 5th to 9th generation bronchioles—conduits that are otherwise invisible to conventional imaging. These ultra-high-resolution geometric models can be incorporated into CFD simulations to estimate regional resistance and quantify pressure drops across distal bifurcations. These simulations show that, in the pre-COPD stage, even a 10% reduction in the radius of a terminal bronchiole can increase regional resistance by 40%. This finding may help explain persistent respiratory symptoms in patients with otherwise normal physiological tests.[21,38]

Furthermore, the integration of continuous surface characterization techniques has allowed for the analysis of luminal eccentricity and surface-to-volume ratios in the distal airways. Research utilizing these geometric models has shown that early COPD is characterized by a significant increase in the non-circularity of airway lumens, a structural marker of wall instability and non-uniform remodeling.[37] CFD analysis based on these eccentric models demonstrates that non-uniform narrowing creates "resistance hotspots" that further exacerbate ventilation-perfusion mismatching. This biomechanical framework allows for the translation of micron-scale morphological changes into clinically relevant physiological impairments, establishing a bridge between the molecular described in previous sections and the global functional decline observed in established disease (Figure 3).[37,38]

Regional Dynamics and Advanced Functional Imaging

The emerging frontier of early COPD detection lies in capturing the temporal and spatial heterogeneity of ventilation and gas exchange through regional imaging modalities such as Electrical Impedance Tomography (EIT) and hyperpolarized ^{129}Xe MRI.[63] EIT, a non-invasive and radiation-free real-time monitoring tool, has identified significant regional ventilation delays and expiratory time constant heterogeneity in PRISm and Pre-COPD cohorts, even when global lung function remains within normal limits.[63] This "mechanical asynchrony" serves as an early physiological warning sign, indicating that different regions of the lung are emptying at vastly different rates due to heterogeneous small airway remodeling. This regional insight is critical for identifying individuals who are at risk of dynamic hyperinflation despite having a preserved global FEV1/FVC ratio.[63]

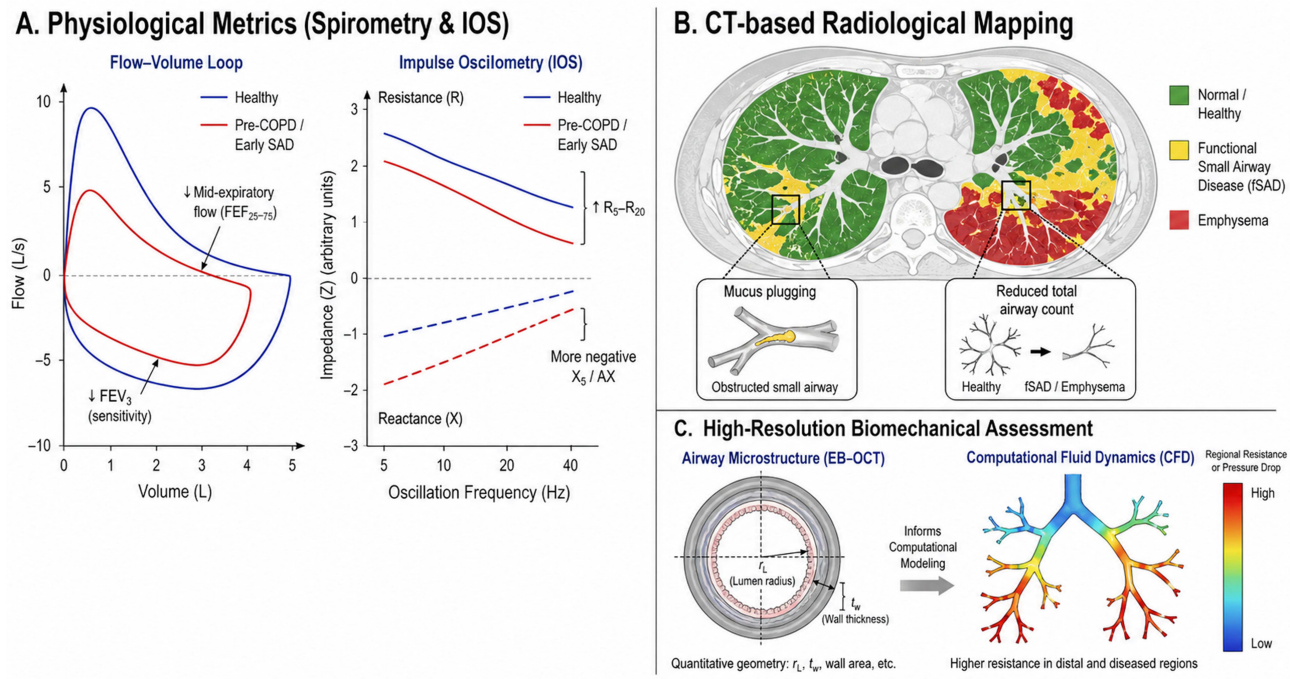

Figure 3 Conceptual multimodal framework for detecting pathology in the pulmonary "Silent Zone". (**A**) Schematic representation of physiological assessment tools, including flow-volume metrics and impulse oscillometry, highlighting early abnormalities in distal airway function. (**B**) Conceptual illustration of CT-based radiological mapping, including functional small airway disease, emphysema, mucus plugging, and reduced airway counts. (**C**) Schematic representation of high-resolution biomechanical assessment, illustrating how EB-OCT-derived airway geometry may be integrated with computational modeling to estimate regional resistance heterogeneity.

Parallel to EIT, hyperpolarized ^{129}Xe MRI provides unparalleled sensitivity for measuring the diffusion capacity across the alveolar-capillary membrane and identifying the earliest "septal fenestrations" in asymptomatic smokers.[64] Although currently restricted to specialized research centers, Xenon MRI can detect gas-exchange abnormalities and "silent" emphysema long before standard carbon monoxide transfer factor (DLCO) measurements show a clinical deficit. The integration of these regional functional assessments with global flow and voxel-wise structural metrics completes a comprehensive diagnostic matrix.[11,44] Together, these multimodal approaches may improve detection of early physiological and structural abnormalities within the Silent Zone and support future risk-stratified study designs.[64]

Disease Trajectories and Clinical Phenotypes: From "At-Risk" to Established COPD

The current understanding of COPD has shifted from a cross-sectional, obstruction-centered definition to a longitudinal life-course model.[10,12] This evolving framework, encapsulated by the GETomics (Genetics, Environment, and Time) model, posits that the clinical manifestations observed in late adulthood are the cumulative result of molecular and structural deviations that often begin during the critical windows of lung development and peak achievement.[46,47] Within this trajectory, the period spanning from the achievement of peak lung function in the third decade of life to the potential onset of spirometric obstruction represents a dynamic and highly heterogeneous phase of disease evolution. Identifying the distinct clinical phenotypes and their propensity for progression during this "pre-obstructive" window is essential for shifting the management strategy from late-stage palliative care toward a model of early-disease modification and proactive risk stratification.[4,44]

The Life-Course Paradigm and the Heterogeneity of Lung Function Trajectories

The pathological foundations of the "Silent Zone" are frequently rooted in the prenatal and early-life periods, where environmental insults interfere with normal organogenesis and lung growth. Evidence from longitudinal cohorts suggests that maternal smoking during pregnancy, low birth weight, and recurrent childhood respiratory infections may contribute

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to low peak lung function in early adulthood, usually between 20 and 25 years of age.[46,47,65] Individuals who fail to reach their genetically determined ventilatory potential enter their fourth decade with a significantly diminished physiological reserve, rendering them highly susceptible to accelerated FEV1 decline when subsequent smoking or occupational exposures are introduced.[38,48]

Longitudinal studies from the Copenhagen City Heart Study and the Nagahama Study suggest that up to half of COPD cases may arise from persistently low lung function rather than rapid decline from a normal peak. This pattern has been described as a "low-start" trajectory.[65] This realization has profound implications for early detection, as it suggests that the "Silent Zone" pathology in these individuals is a manifestation of developmental failure rather than purely acquired remodeling. Consequently, a life-course approach to lung health necessitates the monitoring of lung function in early adulthood to identify those on a "low-peak" trajectory who may require aggressive primary prevention strategies long before they exhibit symptoms or meet obstructive criteria.[10,12,48]

Delineating Pre-COPD and Young COPD: The "At-Risk" Continuum

The clinical construct of pre-COPD identifies individuals with respiratory symptoms, structural evidence of disease (eg, emphysema or small airway dysfunction on QCT), or physiological abnormalities (eg, rapid FEV1 decline), while maintaining a preserved FEV1/FVC ratio $\geq$ 07[66] Data from the CPH study underscore the clinical urgency of this state, revealing a prevalence of 7.2% in the adult population and demonstrating that these individuals exhibit a significantly higher risk of acute respiratory events and all-cause mortality compared to healthy non-smokers.[13,52] The Pre-COPD phenotype is often characterized by a "muco-obstructive" molecular signature, where distal mucus plugging and peribronchiolar fibrosis initiate the irreversible destruction of terminal bronchioles while global flow remains within normal limits.[16,30,31]

Parallel to the concept of Pre-COPD is "Young COPD," which specifically identifies individuals under the age of 50 who already meet the spirometric criteria for airflow obstruction.[49,67] A cross-sectional analysis of over 5000 patients revealed that Young COPD represents a particularly aggressive biological entity, often associated with a higher burden of childhood asthma, severe exercise intolerance, and a more rapid rate of functional decline compared to late-onset disease.[67,68] These patients often exhibit a higher "radiological burden" of small airway disease (PRMfSAD) relative to their emphysema scores, suggesting that early-onset disease is predominantly driven by remodeling of the terminal and respiratory bronchioles.[49,60] Understanding the distinction between these phenotypes is critical, as Young COPD may represent a biologically distinct subgroup with prominent small-airway remodeling. However, whether any molecularly targeted intervention can modify this trajectory remains unknown.[42–44]

The Volatility and Systemic Risk of Preserved Ratio Impaired Spirometry (PRISm)

Within the spectrum of early lung dysfunction, PRISm is defined by an FEV1/FVC $\geq$ 0.7 and an FEV1 < 80% predicted. It is an unstable phenotype associated with increased clinical risk.[57,69] Longitudinal data from the Nagahama and KOGES studies have shown that this group is spirometrically unstable Over a 5-year period, approximately 20% to 50% of individuals with PRISm progress to established COPD, whereas a smaller proportion return to normal spirometry, often after weight loss or resolution of acute inflammatory triggers.[15,48,70] However, the potential for spirometric "recovery" does not equate to structural resolution. PRISm individuals who revert to normal values often retain radiological evidence of air trapping and micro-mitochondrial stress within their small airways, leaving them at a persistently higher risk for future obstruction.[57,60,69]

The clinical significance of PRISm extends far beyond pulmonary mechanics. Large-scale database studies in Sweden and Korea have demonstrated that PRISm is independently associated with an increased risk of all-cause mortality, heart failure, and cardiovascular-related hospitalizations.[15,70,71] This systemic vulnerability is thought to be driven by a shared molecular program involving the EndMT in the pulmonary microvasculature and systemic "inflammaging".[19,30] The presence of PRISm suggests that the pathological changes in the "Silent Zone" are not isolated to the airway lumen but are part of a multi-compartmental failure that impacts both the cardiovascular and respiratory systems, necessitating a more comprehensive approach to risk management that includes systemic biomarker monitoring and early cardiovascular screening.[13,44]

Non-Obstructive Chronic Bronchitis (NOCB) as a Sentinel Marker of Small Airway Loss

Non-obstructive chronic bronchitis (NOCB), characterized by persistent cough and phlegm in individuals with normal spirometry, serves as a critical clinical "sentinel" for impending airflow limitation.[13,52] In the ECOPD cohort, NOCB was identified as a potent predictor of future COPD development, with affected individuals exhibiting a 2.1-fold higher risk of acute respiratory exacerbations compared to asymptomatic smokers.[18,52] Pathologically, NOCB is the clinical correlate of the muco-obstructive molecular engine; the chronic hypersecretion of MUC5AC leads to the formation of persistent mucus plugs that occlude the terminal bronchioles and drive regional air trapping.[31]

QCT studies have shown that individuals with NOCB exhibit significantly higher wall area percentages (WA%) and lower luminal diameters in their peripheral airways compared to smokers without symptoms.[30,31] The clinical urgency of NOCB is further amplified by its presence in non-smokers, particularly women exposed to biomass fuels and individuals living in regions with high ambient pollution.[52] Chronic bronchitic symptoms can be present even without airflow obstruction and may reflect early small airway injury. These observations suggest that chronic bronchitic symptoms may help identify individuals at increased risk of progression despite preserved spirometry. However, whether symptom-directed treatment at this stage can alter long-term structural or functional decline remains unproven.[4,30,44]

Environmental Risk Attribution and the Synergy of Non-Tobacco Exposures

While cigarette smoking remains the dominant risk factor for COPD globally, non-tobacco exposures make a substantial contribution to early airway injury and disease heterogeneity.[72] The largest evidence base concerns household biomass smoke exposure and occupational inhalational exposures. Biomass smoke remains a major global health issue, particularly in low- and middle-income settings, and has been linked to airway-predominant COPD phenotypes with less emphysema and greater small-airway involvement in comparative imaging and pathological studies.[73] Occupational exposures to inorganic dust, organic dust, and vapours, gases, and fumes are also consistently associated with COPD risk and should be considered major contributors to non-tobacco COPD worldwide.[74,75]

Against this background, sand dust-related PM2.5 should be viewed as an emerging and regionally important exposure rather than a dominant global driver of pre-COPD. The current evidence linking sand dust PM2.5 to small-airway dysfunction is noteworthy but remains limited and is based mainly on a single national cross-sectional study.[45] Accordingly, these findings are best interpreted as an important regional signal that warrants replication in other settings and with longitudinal designs.

More broadly, environmental injury in the Silent Zone is likely to reflect cumulative and interacting exposures across the life course. Prenatal adversity, household air pollution, occupational dust, ambient PM2.5, and tobacco smoke may converge to shape low peak lung function, accelerated decline, and airway-predominant remodeling.[76–78] Future studies should therefore move beyond single-exposure models and evaluate how combined exposure histories influence small-airway trajectories in different populations.

Predictive Modeling and the Quest for "Rapid Decliners"

The ultimate goal of early COPD management is the prospective identification of "rapid decliners"—individuals who will experience a precipitous loss of lung function and cross the diagnostic threshold into established disease.[48,60] Longitudinal data from the SPIROMICS and NOVELTY cohorts suggest that the absolute loss of lung function is often greatest in the earliest stages of disease (GOLD 0–1) and in the years immediately following the transition from Pre-COPD to obstruction.[70] Identifying these individuals requires the use of sophisticated predictive models that move beyond single-point spirometry.

One such tool is the SLIM risk calculator, which integrates four readily available clinical variables: smoking package years, low body mass index (BMI), chronic bronchitis symptoms, and a baseline FEV1/FVC ratio approaching the 0.7 limit.[55] The SLIM model has demonstrated high discriminative accuracy in predicting the six-year transition to COPD, offering a low-cost solution for primary care settings.[55] Furthermore, there is growing academic consensus that the use of age-specific z-scores and the 10th percentile Lower Limit of Normal (LLN) for FEV1/FVC provides a more biologically

plausible threshold for diagnosing early-stage disease than the fixed 0.7 ratio.[79,80] A multinational longitudinal study using BOLD study data found that the z-score threshold (specifically −1.336) was superior at predicting future obstruction in younger populations, effectively reducing the risk of underdiagnosis in the critical "early window".[80] By integrating phenotypic markers, environmental risk profiles, and high-resolution diagnostic measures, it may become possible to develop a more proactive framework for early risk stratification in the pulmonary Silent Zone. However, the clinical implementation of disease-modifying interventions will require prospective validation.[44,81]

Summary and Outlook: Toward a Paradigm Shift in Precision Prevention

Evidence accumulated over the past decade supports the view that the pulmonary "Silent Zone" is a key site of COPD initiation and early progression.[18,19] Among the most robust findings are the structural abnormalities of the small airways, particularly terminal bronchiole narrowing and loss, which appear before overt emphysematous destruction and before spirometric obstruction becomes clinically apparent. These observations support the concept that important disease processes are already active during the pre-obstructive phase and justify greater emphasis on earlier detection and risk stratification.

By contrast, many of the molecular mechanisms discussed in this review, including pathways related to mitochondrial dysfunction, EndMT, and inflammaging, should still be regarded as emerging hypotheses rather than established therapeutic targets. Although these mechanisms are biologically plausible and may help explain early structural and functional abnormalities, most supporting evidence comes from individual preclinical or observational studies and has not yet been sufficiently replicated or validated in patients with pre-COPD or early COPD. Accordingly, approaches such as targeted signaling modulation, pharmacological correction of mitochondrial dysfunction, and senescence-directed therapies should currently be viewed as research directions rather than near-term clinical strategies.

A major unresolved question is whether early intervention in pre-COPD can alter long-term disease trajectory. To date, no randomized trial has demonstrated that treatment initiated in pre-COPD changes progression to established COPD or prevents irreversible structural decline. This represents a critical gap in the field. Future studies should therefore move beyond broad calls for biomarker validation and instead address several concrete priorities: first, establishing clinically applicable definitions of pre-COPD populations for intervention trials; second, identifying reproducible endpoints that capture meaningful early disease progression, such as longitudinal decline in FEV1/FVC or FEV3/FVC, transition to spirometric COPD, change in CT-defined functional small airway disease, exacerbation burden, and patient-reported respiratory symptoms; and third, determining which biological or imaging traits are sufficiently stable and predictive to support enrichment strategies in clinical trials. In parallel, future work should clarify which findings are ready for clinical implementation and which remain exploratory. Risk-enrichment tools and sensitive physiological or imaging markers may help identify individuals at greatest risk of progression, but these approaches still require prospective validation across diverse populations and exposure settings. Particular attention should be paid to non-smoking populations exposed to biomass smoke, ambient PM2.5, or sand dust, because these exposures may shape early disease trajectories differently from tobacco-related COPD.

Overall, the field is moving toward earlier recognition of COPD, but the clinical translation of this concept remains at an early stage. The most immediate priority is not the adoption of speculative disease-modifying therapies, but the development of rigorous longitudinal cohorts and well-designed randomized trials capable of determining whether intervention in the pre-obstructive phase can meaningfully preserve lung structure, lung function, and long-term clinical outcomes.

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Disclosure

The authors declare that they have no competing interests in this work.

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