



Long-Term Tobacco Use and COPD Outcomes: A Systematic Review of Disease Progression, Smoking Cessation Benefits, and Treatment Modification

¹ Shopia Mabella, ² Bayu Irianto

¹ General Practitioner, Primaya Hospital Bhakti Wara, Pangkal Pinang City, Bangka Belitung Islands, Indonesia

² Pulmonologist, Primaya Hospital Bhakti Wara, Pangkal Pinang City, Bangka Belitung Islands, Indonesia

Corresponding Email : shopiamabella00@gmail.com

Article History :

Received date : 2025/12/14

Revised date : 2026/01/19

Accepted date : 2026/02/21

Published date : 2026/03/12



Copyright: © 2024 by the authors. Submitted for possible open access publication under the terms and conditions of the Creative Commons Attribution (BY NC) license (<https://creativecommons.org/licenses/by-nc/4.0/>).

E-ISSN :

ISSN 3048-1368



P-ISSN

ISSN 3048-1376



ABSTRACT

Introduction: Smoking is the primary risk factor for chronic obstructive pulmonary disease (COPD), yet the quantitative impact of long-term smoking exposure on disease progression and the magnitude of benefit from cessation remain incompletely characterized. This systematic review synthesizes evidence from longitudinal studies to quantify the effects of smoking on COPD progression and evaluate how smoking status modifies treatment responses.

Methods: We systematically screened longitudinal studies with ≥ 12 months follow-up examining smoking exposure in adults with established COPD. Studies were included if they reported quantitative measures of progression including FEV1 decline, exacerbation frequency, hospitalization, mortality, or quality of life. Data extraction encompassed smoking history, progression

measures, long-term outcomes, study design, baseline characteristics, and effect modifiers.

Results: Eighty studies with follow-up ranging from 6 months to 32.5 years were included. Current smokers exhibited accelerated FEV1 decline compared with former smokers, with excess decline ranging from 7-10 mL/year in general populations to >100 mL/year in genetically susceptible subgroups ($p<0.001$) (1,2). Smoking cessation produced immediate FEV1 improvement (121.8 mL at week 12, $p=0.0069$) that partially attenuated over time (20), with sustained symptom benefits (20,55). The half-life of excess COPD risk after quitting was 13.3 years (95% CI 11.86-14.96) (8). Smoking status significantly modified pharmacotherapy responses: current smokers showed blunted responses to inhaled corticosteroids (9,10,57), reduced benefit from azithromycin (interaction $p=0.03$) (11), but enhanced responses to CXCR2 antagonists (23). Exacerbations accelerated FEV1 decline by an additional 23 mL/year in GOLD stage 1, with smoking amplifying this effect (14). Mortality was significantly reduced with cessation in multiple studies (RR 0.75, 95% CI 0.56-1.00, $p=0.05$) (4).

Discussion: This review demonstrates that continued smoking accelerates COPD progression through multiple mechanistic pathways including sustained neutrophilic inflammation, bacterial colonization, and corticosteroid resistance. Cessation benefits accumulate gradually over decades, with baseline severity and age at cessation as critical determinants of outcomes. The paradoxical early fall in CT lung density post-cessation reflects inflammatory resolution rather than emphysema worsening.

Conclusion: Smoking cessation remains the cornerstone intervention for modifying COPD progression, with effects on

lung function, exacerbations, and mortality that accumulate over years. Treatment selection must account for ongoing smoking exposure due to substantially altered pharmacotherapy efficacy.

Keywords: COPD, smoking cessation, lung function decline, exacerbations, pharmacotherapy response

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) represents a major global health burden, affecting approximately 10% of the adult population and ranking as the third leading cause of death worldwide. The disease is characterized by persistent respiratory symptoms and progressive airflow limitation resulting from airway and alveolar abnormalities, typically caused by significant exposure to noxious particles or gases. Among these exposures, tobacco smoking constitutes the predominant risk factor, accounting for 70-80% of COPD cases in high-income countries and a substantial proportion globally.

The relationship between smoking and COPD has been well-established through decades of epidemiological research, yet critical knowledge gaps persist regarding the quantitative trajectory of disease progression under continued smoking exposure and the precise magnitude of benefit achievable through cessation. While clinicians universally recommend smoking cessation to patients with COPD, patients frequently question whether the damage is already irreversible and whether quitting at later disease stages confers meaningful benefit. These questions have profound implications for patient counseling, clinical decision-making, and healthcare resource allocation.

Previous research has demonstrated that smoking accelerates lung function decline, increases exacerbation frequency, and worsens quality of life in COPD patients. However, the existing evidence base contains important limitations. Many studies have relatively short follow-up periods insufficient to capture the full trajectory of disease modification. Others fail to adequately account for confounding by disease severity, comorbid conditions, or the timing of cessation. Furthermore, the differential impact of smoking on treatment responses across multiple pharmacologic classes has only recently emerged as a critical consideration for personalized COPD management.

The research gap addressed by this systematic review is threefold. First, we lack a comprehensive quantitative synthesis of smoking effects on multiple progression outcomes (lung function, exacerbations, structural changes, mortality) across diverse populations and follow-up

durations. Second, the temporal dynamics of benefit following cessation—including both immediate physiological changes and long-term risk reduction—require systematic integration to inform patient expectations and clinical guidelines. Third, the interaction between smoking status and treatment efficacy across multiple drug classes has not been systematically evaluated, despite growing evidence that current smoking fundamentally alters inflammatory pathways targeted by COPD therapies.

The primary objective of this systematic review is to synthesize evidence from longitudinal studies examining the long-term effects of smoking on COPD progression. Specifically, we aim to: (1) quantify the excess rate of lung function decline attributable to continued smoking; (2) evaluate the temporal dynamics of smoking cessation benefits on clinical outcomes; (3) assess how smoking status modifies responses to pharmacotherapy; and (4) identify patient characteristics that influence the magnitude of smoking-related progression and cessation benefits.

We hypothesize that continued smoking accelerates COPD progression across all measurable domains, with effects that are dose-dependent and modified by genetic susceptibility and disease severity. We further hypothesize that smoking cessation produces benefits that, while clinically significant, accrue gradually over years to decades and are influenced by the timing of cessation relative to disease stage. Finally, we hypothesize that active smoking fundamentally alters the inflammatory milieu such that responses to multiple pharmacotherapies are substantially diminished or qualitatively different.

The novelty of this review lies in its comprehensive scope (80 studies with follow-up up to 32.5 years), systematic integration of multiple outcome domains (lung function, exacerbations, mortality, structural imaging, treatment response), and quantitative synthesis of effect modification by patient characteristics. By providing evidence-based estimates of smoking effects and cessation benefits, this review aims to support clinicians in counseling patients, guide treatment selection based on smoking status, and inform public health strategies for COPD prevention and management.

The potential benefits of this research extend to multiple stakeholders. For clinicians, quantitative estimates of smoking-related progression and cessation benefits enhance patient

counseling and support shared decision-making. For researchers, identification of knowledge gaps and effect modifiers informs future study design. For policymakers, evidence on the long-term benefits of cessation supports continued investment in tobacco control programs and smoking cessation services. Most importantly, for patients with COPD, this synthesis provides credible evidence that smoking cessation at any stage confers meaningful benefits for disease trajectory and quality of life.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate Long-Term Tobacco Use and COPD Outcomes: A Systematic Review of Disease Progression, Smoking Cessation Benefits, and Treatment Modification

Screening

We screened in sources based on their abstracts that met these criteria:

- **COPD Population:** Does the study include adults (≥ 18 years) with established COPD diagnosis as the primary population?
- **Smoking Exposure:** Does the study examine smoking exposure (current smoking, smoking intensity, or continued smoking) in COPD patients?
- **COPD Progression Outcomes:** Does the study report quantitative measures of COPD progression (e.g., FEV1 decline, exacerbation frequency, hospitalization rates, mortality, quality of life scores)?

- **Study Design and Duration:** Is this a longitudinal study design with a minimum follow-up period of 12 months?
- **Comparison Groups:** Does the study include comparison groups of non-smokers, ex-smokers, or patients who quit smoking during follow-up?
- **Data Quality:** Does the study provide sufficient data for effect size calculation or clear reporting of progression outcomes?
- **Long-term Assessment:** Is this study design capable of assessing long-term progression (i.e., NOT a cross-sectional study and NOT examining only acute effects ≤ 30 days)?
- **Study Type:** Is this study a primary research article with sufficient methodological detail (i.e., NOT a case report, case series, editorial, or conference abstract)?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

Element	P (Population)	I (Intervention/Exposure)	C (Comparison/Context)	O (Outcome)
Keyword 1	Chronic Obstructive Pulmonary Disease (COPD)	Smoking	Smoking Cessation	COPD Progression
Keyword 2	COPD Patients	Continued Smoking	Non-smokers	Lung Function Decline
Keyword 3	Individuals	Smoking Intensity	Ex-smokers	Exacerbation

	with COPD			
Keyword 4	COPD population	Tobacco Smoke Exposure	Current Smokers	Mortality

The Boolean MeSH keywords inputted on databases for this research are: (*"Chronic Obstructive Pulmonary Disease" OR "COPD Patients" OR "Individuals with COPD" OR "COPD population"*) AND (*"Smoking" OR "Continued Smoking" OR "Smoking Intensity" OR "Tobacco Smoke Exposure"*) AND (*"Smoking Cessation" OR "Non-smokers" OR "Ex-smokers" OR "Current Smokers"*) AND (*"COPD Progression" OR "Lung Function Decline" OR "Exacerbation" OR "Mortality"*)

Data extraction

- **Smoking Exposure:**

Extract comprehensive smoking history and status details for all participants, including:

- Current smoking status (current smoker, ex-smoker, never smoker)
- Pack-years of smoking history (if reported)
- Years since smoking cessation (for ex-smokers)
- Age at smoking initiation and cessation (if reported)
- Any changes in smoking status during the study period
- Intensity/frequency of smoking (cigarettes per day)
- Type of tobacco products used

- **COPD Progression Measures:**

Extract all measures used to assess COPD progression over time, including:

- Lung function parameters (FEV1, FVC, FEV1/FVC ratio, annual decline rates)
- Structural changes (emphysema progression on CT, lung density changes)
- Symptom progression measures (dyspnea scores, quality of life scales)
- Functional capacity changes (6-minute walk test, exercise tolerance)
- Biomarkers of disease progression
- Exacerbation frequency and severity changes
- Respiratory system impedance or other specialized measures
- Time intervals at which measurements were taken

- **Long-term Outcomes:**

Extract specific findings on how smoking status/history affected COPD progression, including:

- Quantitative results comparing progression rates between smoking groups (current vs ex-smokers vs never smokers)
- Effect sizes, confidence intervals, and p-values for smoking-related differences
- Annual rates of decline in lung function by smoking status
- Time to clinical milestones (hospitalization, oxygen dependence, death) by smoking group
- Dose-response relationships (pack-years vs progression rate)
- Benefits of smoking cessation on slowing progression
- Any threshold effects or non-linear relationships observed

- **Study Design:**

Extract study methodology relevant to assessing long-term effects, including:

- Study design type (prospective cohort, longitudinal, cross-sectional with long-term follow-up)
- Total follow-up duration (median and range)
- Frequency of assessments/visits
- Sample size and retention rates over time
- Inclusion/exclusion criteria related to smoking status or COPD severity
- Whether smoking cessation interventions were provided during the study
- Loss to follow-up rates and reasons by smoking group

- **Baseline Characteristics:**

Extract baseline patient characteristics relevant to COPD progression analysis, including:

- COPD severity stage (GOLD stage or equivalent classification)
- Age, sex, BMI distribution
- Baseline lung function values (FEV1 % predicted, FVC)
- Duration of COPD diagnosis
- Comorbidities that might affect progression (cardiovascular disease, diabetes)
- Medication use (bronchodilators, corticosteroids, other relevant treatments)
- Baseline symptom severity scores

- Socioeconomic factors if reported

- **Effect Modifiers:**

Extract factors that modified the relationship between smoking and COPD progression, including:

- Age-related differences in smoking effects on progression
- Sex/gender differences in smoking impact
- COPD severity at baseline as a modifier of smoking effects
- Genetic factors (alpha-1 antitrypsin deficiency, other genetic variants)
- Comorbidity interactions with smoking effects
- Medication use that modified smoking-related progression
- Environmental factors (air pollution, occupational exposures)
- Any statistical interaction terms tested and their results
- Subgroup analyses showing differential smoking effects

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	<i>("Chronic Obstructive Pulmonary Disease" OR "COPD Patients" OR "Individuals with COPD" OR "COPD population") AND ("Smoking" OR "Continued Smoking" OR "Smoking Intensity" OR "Tobacco Smoke Exposure") AND ("Smoking Cessation" OR "Non-smokers" OR "Ex-smokers" OR "Current Smokers") AND ("COPD Progression" OR "Lung Function Decline" OR "Exacerbation" OR "Mortality")</i>	1,032
Semantic Scholar	<i>("Chronic Obstructive Pulmonary Disease" OR "COPD Patients" OR "Individuals with COPD" OR "COPD population") AND ("Smoking" OR "Continued Smoking" OR "Smoking Intensity" OR "Tobacco Smoke Exposure") AND ("Smoking Cessation" OR "Non-smokers" OR "Ex-smokers" OR "Current Smokers") AND ("COPD Progression" OR "Lung Function Decline" OR "Exacerbation" OR "Mortality")</i>	2
Springer	<i>("Chronic Obstructive Pulmonary Disease" OR "COPD Patients" OR "Individuals with COPD" OR "COPD population") AND ("Smoking" OR "Continued Smoking" OR "Smoking Intensity" OR "Tobacco Smoke Exposure") AND ("Smoking Cessation" OR "Non-smokers" OR "Ex-smokers" OR "Current Smokers") AND ("COPD Progression" OR "Lung Function Decline" OR "Exacerbation" OR "Mortality")</i>	8,460
Google Scholar	<i>("Chronic Obstructive Pulmonary Disease" OR "COPD Patients" OR "Individuals with COPD" OR "COPD population") AND ("Smoking" OR "Continued Smoking" OR "Smoking Intensity" OR "Tobacco Smoke Exposure") AND ("Smoking Cessation" OR "Non-smokers" OR "Ex-smokers" OR "Current Smokers") AND ("COPD Progression" OR "Lung Function Decline" OR "Exacerbation" OR "Mortality")</i>	11,400
Wiley Online Library	<i>("Chronic Obstructive Pulmonary Disease" OR "COPD Patients" OR "Individuals with COPD" OR "COPD population") AND ("Smoking" OR "Continued Smoking" OR "Smoking Intensity" OR "Tobacco Smoke Exposure") AND ("Smoking Cessation" OR "Non-smokers" OR "Ex-smokers" OR "Current Smokers") AND ("COPD Progression" OR "Lung Function Decline" OR "Exacerbation" OR "Mortality")</i>	5,056

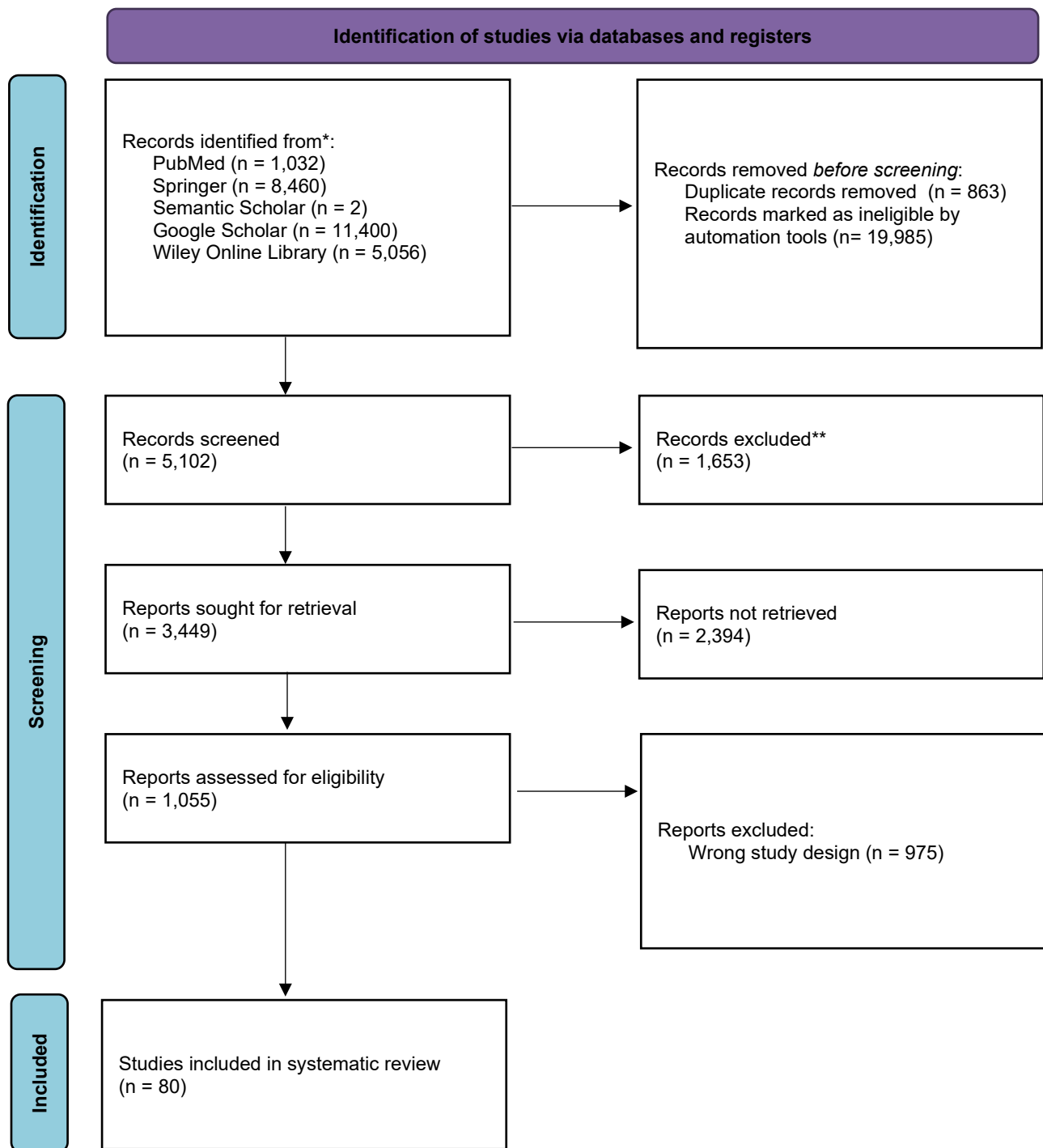


Figure 1. Article search flowchart

RESULTS

Characteristics of Included Studies

The 80 sources encompassed a broad range of study designs, populations, follow-up durations, and outcome measures relevant to the long-term effects of smoking on COPD progression. Studies were conducted across multiple continents and included prospective cohorts, randomized controlled trials, retrospective analyses, etc. Follow-up durations ranged from 6 months to 32.5 years. The table below summarizes key characteristics of all included sources.

Study	Follow-up Duration	Sample Size	COPD Severity	Primary Smoking Comparison	Key Outcome Measures
J. Bai et al., 2017	5 years [15]	204 [15]	Not specified [15]	Quitters vs. continuing smokers [15]	FEV1% predicted, mortality [15]
Si Lei et al., 2020	10 years [5]	102 [5]	Not specified [5]	Cognitive intervention vs. control [5]	FEV1/FVC, FEV1% predicted, exacerbations, survival [5]
M. Ragland et al., 2021	10 years [16]	9,103 [16]	GOLD stages and PRISm [16]	Current vs. former smokers [16]	FEV1, SGRQ, 6MWD [16]
R. Polosa et al., 2020	5 years [6]	39 [6]	GOLD 1–4 [6]	EC users vs. continuing smokers [6]	FEV1, FVC, CAT, 6MWD, exacerbations [6]

Study	Follow-up Duration	Sample Size	COPD Severity	Primary Smoking Comparison	Key Outcome Measures
R. Polosa et al., 2018	3 years [17]	44 [17]	Not specified [17]	EC users vs. continuing smokers [17]	Spirometry, CAT, 6MWD, exacerbations [17]
K. Sonnex et al., 2020	Up to 30 months [10]	21,270 (exacerbations); 17,892 (FEV1) [10]	Not specified [10]	Current vs. ex-smokers; heavier vs. lighter smokers [10]	FEV1 change, exacerbation rates [10]
R. Polosa et al., 2016	24 months [18]	48 [18]	GOLD 1–4 [18]	EC users vs. continuing smokers [18]	FEV1, FVC, CAT, 6MWD, exacerbations [18]
R. Polosa et al., 2020a	3 years [19]	38 [19]	GOLD 1–4 [19]	HTP users vs. continuing smokers [19]	FEV1, FVC, CAT, 6MWD, exacerbations [19]
D. P. Tashkin et al., 2011	52 weeks [20]	500 [20]	GOLD I–III [20]	Continuous abstainers vs. continuous smokers [20]	Post-BD FEV1, CCQ [20]

Study	Follow-up Duration	Sample Size	COPD Severity	Primary Smoking Comparison	Key Outcome Measures
A. Ramírez-Venegas et al., 2014	15 years [21]	Not specified [21]	Not specified [21]	Biomass vs. tobacco COPD [21]	FEV1 annual decline [21]
X. Yuan et al., 2015	18 years [22]	1,008 [22]	COPD or at-risk [22]	Integrated intervention vs. usual care [22]	COPD incidence, lung function decline, mortality [22]
S. Rennard et al., 2015	6 months [23]	616 [23]	Moderate to severe [23]	Current smokers vs. ex-smokers [23]	FEV1, SGRQ, exacerbations [23]
X. Bertels et al., 2021	5 years [24]	4,224 [24]	Spirometry-confirmed COPD [24]	ACEi/ARB users vs. non-users [24]	Emphysema progression, FEV1 decline [24]
C. Cooper et al., 2013	2 years [25]	519 [25]	FEV1 <65% predicted [25]	Tiotropium vs. placebo; by smoking status [25]	Treadmill endurance, FEV1/FVC, SGRQ [25]

Study	Follow-up Duration	Sample Size	COPD Severity	Primary Smoking Comparison	Key Outcome Measures
D. Tashkin et al., 2014	4 years [26]	5,042 [26]	GOLD I–IV [26]	Sustained ex-smokers vs. intermittent vs. continuing smokers [26]	FEV1, FVC bronchodilator response [26]
T. Tayutina et al., 2025	12 months [27]	140 [27]	Not specified [27]	Continued smoking vs. cessation vs. heated tobacco [27]	TNF- α , PDGF-AA, peripheral blood flow, dyspnea, QoL [27]
C. Cheong et al., 2018	12 years [28]	165,986 [28]	Low/middle/high grade [28]	Quitters vs. continuous smokers vs. never-smokers [28]	Mortality, MACE, exacerbations [28]
Shunian He et al., 2012	2 years [29]	104 [29]	Moderate to severe [29]	Current smokers vs. ex-smokers vs. non-smokers [29]	FEV1 decline, bacterial colonization, exacerbations [29]
J. Zheng et al., 2025	2.5 years [30]	2,003 [30]	GOLD I–IV [30]	47% current smokers [30]	FEV1, FVC decline [30]

Study	Follow-up Duration	Sample Size	COPD Severity	Primary Smoking Comparison	Key Outcome Measures
V. Antonov et al., 2020	5 years [31]	394 [31]	Not specified [31]	Vaccinated vs. unvaccinated; smokers vs. non-smokers [31]	FEV1, exacerbations, BODE index [31]
C. Stey et al., 2016	24 months [32]	456 [32]	Not specified [32]	Self-management vs. usual care [32]	CRQ mastery, exacerbations, smoking cessation [32]
P. Calverley et al., 2011	52 weeks [33]	5,777 [33]	Severe COPD [33]	Former vs. current smokers [33]	FEV1, exacerbation rate [33]
A. Papi et al., 2016	1 year [34]	1,006 [34]	Moderate to severe (GOLD II) [34]	Ex-smokers vs. current vs. never smokers [34]	Exacerbation frequency [34]
N. Yanev et al., 2015	3 years [35]	262 [35]	GOLD A–D [35]	Active smokers vs. ex-smokers vs. non-smokers [35]	Hospitalizations, exacerbations, mortality [35]

Study	Follow-up Duration	Sample Size	COPD Severity	Primary Smoking Comparison	Key Outcome Measures
I. Henoch et al., 2018	10–30 months [36]	20,666 [36]	By spirometric stage [36]	Smoking cessation program participants vs. non-participants [36]	Exacerbations, hospital admissions, HRQoL [36]
Zihan Wang et al., 2024	>3 months [4]	11 studies [4]	Not specified [4]	Quitters vs. non-quitters [4]	FEV1% predicted, FEV1/FVC, mMRC, 6MWT, mortality [4]
S. Shaker et al., 2011	2–4 years [37]	36 quitters from 254 [37]	COPD [37]	Quitters vs. continuing smokers [37]	CT lung density, FEV1, diffusion capacity [37]
F. M. Mohamed Hoessein et al., 2013	3 years [2]	3,670 [2]	Mostly no/mild obstruction [2]	By duration of cessation (≥ 5 yr, 1–5 yr, <1 yr, current) [2]	Emphysema progression on CT, FEV1 decline [2]
M. Dransfield et al., 2016	5 years [14]	2,000 [14]	GOLD 0–4 [14]	Current/intermittent vs. former smokers [14]	FEV1 decline, exacerbation impact [14]

Study	Follow-up Duration	Sample Size	COPD Severity	Primary Smoking Comparison	Key Outcome Measures
M. Han et al., 2014	Not specified [11]	1,113 [11]	Mild to severe [11]	Current smokers vs. non-current [11]	Exacerbation reduction with azithromycin [11]
K. Tanaka et al., 2018	7 years [38]	140 with COPD [38]	85% GOLD 1–2 [38]	By smoking status over time [38]	FEV1 decline, smoking cessation rate [38]
J. Snoeck-Stroband et al., 2015	2.5 years [39]	50 [39]	GOLD II–III [39]	Fewer vs. more pack-years [39]	FEV1 decline, sputum inflammation [39]
A. Khomenya et al., 2020	3 years [40]	24 [40]	GOLD 1 (mild) [40]	Quitters vs. continuing smokers [40]	Spirometry, symptoms, exacerbations [40]
S. J. M. Hoonhorst et al., 2014	2.5 years [41]	72 [41]	GOLD II–III [41]	Persistent smokers vs. persistent ex-smokers [41]	FEV1 decline, airway inflammation [41]
P. Hagens et al., 2017	18 months [42]	Not reported [42]	COPD, not ready to quit [42]	Reduction counselling + NRT vs. information [42]	Prolonged abstinence, smoking reduction [42]

Study	Follow-up Duration	Sample Size	COPD Severity	Primary Smoking Comparison	Key Outcome Measures
S. Kesten et al., 2011	4 years [43]	5,993 [43]	Not specified [43]	By FEV1 decline quartile; more current smokers in fastest decline [43]	FEV1 decline, SGRQ, exacerbations, mortality [43]
F. M. Mohamed Hoessein et al., 2012	3 years [13]	2,003 [13]	By FEV1/FVC ratio [13]	55.6% current smokers [13]	FEV1 decline, MEF50, emphysema [13]
T. Hackett et al., 2011	5 years [44]	Not specified [44]	Not specified [44]	Gene-smoking interactions [44]	FEV1 decline, cardiovascular disease [44]
S. Fortis et al., 2020	Not specified [45]	2,099 COPD; 3,143 preserved spirometry [45]	Mild to moderate [45]	Frequent exacerbators vs. others [45]	Mortality, exacerbation frequency [45]
Z. He et al., 2025	Not specified [46]	400 [46]	Mild to very severe [46]	Smokers vs. non-smokers [46]	Skeletal muscle function, 6MWD [46]

Study	Follow-up Duration	Sample Size	COPD Severity	Primary Smoking Comparison	Key Outcome Measures
A. G. Mathioudakis et al., 2025	Not specified [9]	Not specified [9]	Not specified [9]	Current vs. ex-smokers [9]	Exacerbation prevention [9]
B. Engel et al., 2017	6 months [47]	311 [47]	Not specified [47]	Current smokers [47]	Re-exacerbation risk [47]
J. Crapo et al., 2023	3 years [48]	463 [48]	GOLD 1–3 [48]	Ex-smokers only [48]	FEV1, emphysema, biomarkers [48]
I. Pavlenko et al., 2011	1 year [49]	74 [49]	GOLD III–IV [49]	Current vs. ex-smokers; low vs. high intensity [49]	FEV1, Lung Age [49]
S. Mahmud et al., 2019	Up to 36 months [50]	1,843 [50]	Not specified [50]	30% current smokers [50]	Exacerbations, SGRQ, mMRC, 6MWD [50]
M. Högman et al., 2025	2 years [51]	353 [51]	By GOLD classification [51]	Ex-smokers vs. current smokers [51]	FENO, FEV1%pred, FVC%pred, mMRC [51]

Study	Follow-up Duration	Sample Size	COPD Severity	Primary Smoking Comparison	Key Outcome Measures
J. T. Holbrook et al., 2026	32.5 years [7]	5,887 [7]	Mild to moderate obstruction [7]	Smoking cessation intervention vs. usual care [7]	Respiratory mortality [7]
J. Londhe et al., 2014	1 year [52]	125 COPD; 100 controls [52]	Not specified [52]	Smoker-COPD vs. non-smoker-COPD [52]	FEV1, FVC, SGRQ, CAT [52]
R. Yukimura et al., 2016	≥2 years [53]	118 COPD; 28 non-COPD smokers [53]	Not specified [53]	Not specified [53]	FOT impedance, CT emphysema [53]
D. Cheng et al., 2020	Variable [54]	4 studies [54]	COPD [54]	Smoking cessation in COPD [54]	CT lung density, airway wall thickness [54]

Study	Follow-up Duration	Sample Size	COPD Severity	Primary Smoking Comparison	Key Outcome Measures
P. Lee et al., 2014	Variable [8]	14 data blocks from 11 studies [8]	Not specified [8]	Current vs. former vs. never smokers [8]	COPD risk decline half-life [8]
J. Dhariwal et al., 2014	52 weeks [55]	38 COPD; 55 normal spirometry [55]	GOLD II–III [55]	Quitters vs. continuing smokers [55]	FEV1, Tlco, HRCT micronodules/emphysema [55]
A. Oh et al., 2022	5 years [56]	5,056 [56]	By Fleischner grade [56]	Cigarette smokers [56]	Emphysema progression, FEV1, 6MWD, mortality [56]
S. Bhatt et al., 2018	Not specified [57]	Not specified [57]	Not specified [57]	Former vs. continuing vs. intermittent smokers [57]	FEV1 response to ICS, exacerbation risk [57]

Study	Follow-up Duration	Sample Size	COPD Severity	Primary Smoking Comparison	Key Outcome Measures
D. MacDonald et al., 2018	Median 3.9 years [58]	915 [58]	HIV-positive [58]	Smokers vs. non-smokers [58]	FEV1 decline [58]
N. Riblet et al., 2023	Median 7.8 years [59]	9,930 [59]	Normal to severe COPD [59]	Current and former heavy smokers [59]	Suicide risk, mMRC, spirometry [59]
M. Hoogendoorn et al., 2011	10-year projection [60]	Modeled [60]	By FEV1% predicted [60]	By smoking status [60]	QALYs, costs, exacerbations [60]
I. Naya et al., 2015	30 months [61]	5,292 [61]	Not specified [61]	Not specified [61]	FEV1, SGRQ, exacerbations, mortality [61]
L. C. A. Christenhusz et al., 2012	12 months [62]	234 [62]	Moderate to severe [62]	High vs. medium intensity cessation [62]	Abstinence, exacerbations, hospital days [62]
M. Kerkhof et al., 2019	≥3 years [63]	12,178 [63]	FEV1% predicted 50–90 [63]	By ICS use and blood eosinophil count [63]	FEV1 decline [63]

Study	Follow-up Duration	Sample Size	COPD Severity	Primary Smoking Comparison	Key Outcome Measures
J. Chen et al., 2013	6 months [64]	190 [64]	Mild to very severe [64]	COPD smokers vs. asymptomatic smokers [64]	Abstinence, SGRQ, exacerbations [64]
T. Kamada et al., 2017	Median 57 months [65]	51 [65]	Not specified [65]	With vs. without exacerbations [65]	FEV1, FOT impedance [65]
J. L. Curtis et al., 2024	3 years [66]	689 [66]	GOLD 0–2, PRISm [66]	Ever-smokers with ≥10 pack-years [66]	FEV1, HRCT, oscillometry, biomarkers [66]
F. Rodrigues et al., 2018	6 years [67]	138 [67]	GOLD 1–2 [67]	Airflow obstruction vs. smoking vs. never-smoking controls [67]	VO2peak, OUES, exercise capacity [67]
V. Kupaev et al., 2021	Not specified [12]	121 [12]	Irreversible obstruction [12]	Quitters vs. continuing smokers [12]	FEV1, CAT [12]

Study	Follow-up Duration	Sample Size	COPD Severity	Primary Smoking Comparison	Key Outcome Measures
R. Kuint et al., 2020	6–12 months [68]	154 [68]	FEV1 53% predicted [68]	53% current smokers at baseline [68]	FEV1, CAT, 6MWD, exacerbations [68]
D. Toumpanakis et al., 2023	Variable [3]	79 [3]	Not specified [3]	Ex-smokers ≥ 10 yr vs. current/recent quitters [3]	FEV1 decline, TLco, hyperinflation [3]
A. Kruis et al., 2014	24 months [69]	1,086 [69]	GOLD I–IV [69]	Integrated disease management vs. usual care [69]	CCQ, SGRQ, exacerbations [69]
A. Zhang et al., 2020	24 months [70]	208 [70]	GOLD 2–4 [70]	PR program vs. usual care [70]	FEV1, mMRC, CAT, 6MWD, readmissions [70]
A. Papi et al., 2019	12 months [71]	964 [71]	Moderate to severe [71]	Current, ex-, never smokers [71]	Exacerbation rate [71]
G. Zhao et al., 2025	Variable [72]	286,314 across 27 studies [72]	Mild to very severe [72]	Never, former, current smokers [72]	All-cause and cause-specific mortality [72]

Study	Follow-up Duration	Sample Size	COPD Severity	Primary Smoking Comparison	Key Outcome Measures
C. Dai et al., 2025	15 years [73]	2,850 [73]	Normal, PRISm [73]	Ever-smokers vs. never-smokers (PRISm subtypes) [73]	Lung function decline, airflow limitation risk [73]
Y.-T. Lai et al., 2024	≥1 year [74]	967 [74]	GOLD grouping [74]	Current vs. former smokers [74]	FEV1 decline, exacerbations, CAT, mMRC [74]
H.-C. Chang et al., 2023	~1 year [75]	357 [75]	By GOLD airflow limitation [75]	Cessation ± vaccination groups [75]	Emergency/hospital utilization, respiratory failure [75]
C. Buri-Nagua et al., 2025	6 months [76]	162 [76]	COPD exacerbation [76]	Current/former smokers [76]	Rehospitalization, anxiety, psychosocial measures [76]
P. Bakke et al., 2016	8 years total [77]	807 invited; 480 with data [77]	Not specified [77]	Not specified [77]	FEV1 annual decline [77]

Study	Follow-up Duration	Sample Size	COPD Severity	Primary Smoking Comparison	Key Outcome Measures
H. Omori et al., 2011	12 years [1]	913 [1]	By airflow obstruction status [1]	Never, early quitter, late quitter, persistent smoker [1]	FEV1 decline [1]
M. Ichinose et al., 2015	1 year [78]	408 [78]	Moderate to severe [78]	Subgroup: current smokers [78]	Exacerbation frequency, CAT [78]
B. Frisk et al., 2012	3 years [79]	389 [79]	GOLD II–IV [79]	Not specified [79]	6MWD, FEV1 [79]
A. Papi et al., 2017	1 year [80]	1,006 [80]	Moderate to severe [80]	Smokers vs. non-smokers; eosinophil strata [80]	Exacerbation frequency [80]

The included studies varied considerably in design and scope. Large longitudinal cohort studies such as COPDGene (n = 9,103 over 10 years) [16], the UPLIFT trial (n = 5,993 over 4 years) [43], and the Lung Health Study (n = 5,887 over 32.5 years) [7] provided the most robust data on smoking-related COPD progression. Several studies focused specifically on smoking cessation interventions [5, 20, 22, 62], while others examined the effects of switching to alternative nicotine delivery systems such as electronic cigarettes [6, 17, 18] or heated tobacco products [19, 27].

Effects

Lung Function Decline by Smoking Status

The relationship between continued smoking and accelerated FEV1 decline was one of the most consistently reported findings across studies. In the COPDGene cohort, current smokers exhibited greater mean loss of FEV1 over 10 years compared with former smokers across all GOLD stages except PRISm [16]. A 12-year longitudinal study of 913 Japanese males quantified this gradient: persistent smokers declined at -44.8 mL/year, late quitters at -40.7 mL/year, early quitters at -37.9 mL/year, and persistent never-smokers at -35.0 mL/year [1]. In a large cohort of 3,670 male heavy smokers followed for 3 years, those who had quit smoking more than 5 years earlier had significantly slower FEV1 decline (57.5 mL/year) compared with current smokers (69 mL/year, $p < 0.001$), along with slower emphysema progression on CT (1.07% vs. 1.12% per year, $p < 0.001$) [2].

The meta-analysis by Wang et al. (2024) pooling 11 studies found that smoking cessation was associated with significantly higher FEV1% predicted (MD = 6.72 , 95% CI 4.55 – 8.89 , $p < 0.001$) and FEV1/FVC ratio (MD = 6.82 , 95% CI 5.09 – 8.54 , $p < 0.001$) compared with continued smoking [4]. This meta-analysis also demonstrated improvements in exercise tolerance (6MWT MD = 64.46 m, 95% CI 14.60 – 114.32 , $p = 0.010$), dyspnea (mMRC MD = -0.49 , 95% CI -0.95 to -0.02 , $p = 0.040$), and partial oxygen pressure (MD = 1.96 , 95% CI 1.03 – 2.89 , $p < 0.001$) [4].

In the HIV-positive START Pulmonary Substudy population, smokers had faster FEV1 decline than non-smokers (-38.3 vs. -25.1 mL/year; difference -13.2 mL/year, 95% CI -23.6 to -2.7 , $p = 0.013$) [58]. Among heterozygote alpha-1 antitrypsin patients, the contrast was even more striking: ex-smokers with ≥ 10 years since quitting had FEV1 decline of only 19.9 mL/year compared with 132.8 mL/year in current smokers ($p = 0.006$) [3]. In a community-based Japanese study with systematic intervention, the overall FEV1 decline was -23.2 mL/year, but current smokers declined at -38.9 to -43.1 mL/year compared with former smokers at -30.4 to -35.4 mL/year [38].

The following table summarizes FEV1 decline rates by smoking status across key studies:

Study	Population	Current Smokers (mL/yr)	Ex-Smokers (mL/yr)	Never-Smokers (mL/yr)	p-value
H. Omori et al., 2011	913 Japanese males, 12 yr	−44.8 [1]	Early: −37.9; Late: −40.7 [1]	−35.0 [1]	Not reported
F. M. Mohamed Hoesein et al., 2013	3,670 male heavy smokers, 3 yr	−69.0 [2]	Quit >5 yr: −57.5 [2]	N/A	p < 0.001 [2]
D. MacDonald et al., 2018	915 HIV+, 3.9 yr median	−38.3 [58]	N/A	−25.1 (non-smokers) [58]	p = 0.013 [58]
K. Tanaka et al., 2018	140 COPD, 7 yr	−38.9 to −43.1 [38]	−30.4 to −35.4 [38]	−31.3 to −33.9 [38]	Not reported
D. Toumpanakis et al., 2023	79 heterozygote α 1-AT	132.8 [3]	Quit $\geq$ 10 yr: 19.9 [3]	−22.3 [3]	p = 0.006 [3]

Across these studies, the excess FEV1 decline attributable to continued smoking ranged from approximately 7–10 mL/year in general populations to over 100 mL/year in genetically susceptible subgroups. The data consistently demonstrate a dose-response pattern in which longer duration of cessation is associated with progressively slower lung function loss.

Temporal Dynamics of Cessation Benefits on Lung Function

Smoking cessation produced an immediate but partly transient improvement in FEV1. In a 1-year cessation trial using varenicline, continuous abstainers showed a 121.8 mL improvement in post-bronchodilator FEV1 at week 12 compared with 37.9 mL in continuous smokers ($p = 0.0069$), but this difference narrowed and was no longer significant at weeks 24 or 52 [20]. Similarly, Dhariwal et al. (2014) reported a 184 mL FEV1 improvement at 6 weeks post-cessation in COPD patients ($p < 0.01$) that diminished to 81 mL at 12 weeks ($p < 0.05$) and was only partially maintained at 1 year [55]. In contrast, improvements in respiratory symptoms as measured by the CCQ were sustained at 52 weeks [20], and gas transfer (Tlco) improvements persisted at 6 weeks [55].

Paradoxically, CT-based assessments showed a rapid fall in lung density following smoking cessation: RA-910 increased by 2.6% ($p = 0.003$) and PD15 decreased by -4.9 HU ($p = 0.0002$) [37]. This paradoxical finding, confirmed in a systematic review of four studies [54], likely reflects resolution of smoking-induced inflammation that partially masked emphysema on CT [37]. The effect was more pronounced in patients concurrently receiving budesonide [37]. A decrease in micronodules on HRCT was also observed with cessation, though emphysema itself did not significantly change [55].

Exacerbations and Mortality

Smoking status profoundly influenced exacerbation frequency and mortality outcomes. In the 5-year Bai et al. study, the continuing-smoking group had significantly higher mortality than the quitting-smoking group (73/112 vs. 40/92 deaths; log-rank test 13.59, $p = 0.0002$) [15]. Over 10 years, Si Lei et al. found fewer annual acute exacerbations in the smoking cessation intervention group ($p < 0.01$) and lower mortality (11/46 vs. 19/48 deaths, $p < 0.05$) [5]. The 18-year cluster RCT by Yuan et al. demonstrated that an integrated intervention including smoking cessation counseling reduced COPD incidence (10% vs. 16%, $p < 0.05$), delayed lung function decline, and lowered cumulative COPD-related death rates (37% vs. 47%, $p < 0.05$) [22].

The large meta-analysis by Zhao et al. (2025) spanning 286,314 individuals demonstrated that COPD patients had higher all-cause mortality than non-COPD individuals across all smoking

categories: never-smokers (HR 1.41, 95% CI 1.27–1.56), former smokers (HR 1.37, 95% CI 1.30–1.45), and current smokers (HR 1.48, 95% CI 1.25–1.76) [72]. The Lung Health Study, with 32.5 years of follow-up, confirmed a sustained reduction in respiratory-related mortality for participants assigned to a smoking cessation intervention, though the earlier all-cause mortality benefit observed at 14.5 years was not maintained at 32.5 years [7].

The meta-analysis by Wang et al. reported a borderline significant reduction in mortality with cessation (RR = 0.75, 95% CI 0.56–1.00, $p = 0.05$) [4]. The Cheong et al. 12-year national cohort study, however, found that after controlling for covariates, the mortality difference between quitters and continuous smokers was not significant at $p < 0.1$ [28], though the crude mortality rate was lower in quitters (25.7% vs. 27.2%) [28]. This discrepancy likely reflects confounding by disease severity and age at cessation.

Lee et al. modeled the decline in excess COPD risk following quitting using a negative exponential function and estimated a half-life of 13.32 years (95% CI 11.86–14.96) [8], substantially longer than for ischemic heart disease (4.40 years) or lung cancer (9.93 years), indicating that the structural lung damage from smoking resolves very slowly.

Combined interventions appear to amplify benefits. Chang et al. found that COPD patients who both quit smoking and received influenza vaccination had dramatically lower odds of emergency utilization (OR = 0.13, 95% CI 0.07–0.25), hospital utilization (OR = 0.13, 95% CI 0.05–0.30), and respiratory failure (OR = 0.13, 95% CI 0.04–0.40) compared with patients who did neither [75].

Alternative Nicotine Delivery Systems

A series of studies from Polosa and colleagues examined the effects of switching from conventional cigarettes to electronic cigarettes or heated tobacco products. Over 5 years, COPD patients who switched to e-cigarettes showed a decline in exacerbation rate from 2.3 ± 0.9 at baseline to 1.1 ± 1.0 ($p < 0.001$), with significant improvements in lung function, CAT scores, and 6MWD compared with continuing smokers [6]. At 3 years, similar improvements in exacerbations and subjective outcomes were observed, though lung function changes were less consistent [17, 18]. Heated tobacco product users also demonstrated reduced exacerbations (from 2.1 ± 0.9 to 1.3 ± 0.8

at 36 months, $p < 0.05$) and clinically significant improvements in CAT scores and 6MWD [19]. Tayutina et al. (2025) found that both complete cessation and switching to electronic heated tobacco systems reduced systemic inflammation markers (TNF- α and PDGF-AA) and improved peripheral microcirculation over 12 months [27]. These studies are limited by small sample sizes and observational designs.

Smoking Status and Pharmacotherapy Response

Multiple studies identified smoking status as a modifier of treatment response. The systematic review by Sonnex et al. found that heavier smokers (>36 pack-years) using ICS had greater FEV1 decline (-22 to -75 mL) compared with lighter smokers, and exacerbation rate ratios favored fewer exacerbations in ex-smokers and lighter smokers on ICS (0.81 – 0.99 vs. 0.92 – 1.29) [10]. Mathioudakis et al. (2025) demonstrated that LABA + LAMA was superior to LABA + ICS in preventing exacerbations in current smokers but inferior in ex-smokers with blood eosinophil count ≥ 200 cells/ μ L [9]. Bhatt et al. (2018) similarly found that current smokers had a blunted FEV1 response and reduced exacerbation reduction with ICS [57].

In the CXCR2 antagonist trial, current smokers showed a significantly greater FEV1 improvement with MK-7123 50 mg than ex-smokers (168 mL vs. non-significant in ex-smokers) [23]. Azithromycin prophylaxis was effective in reducing exacerbations in former smokers but showed no benefit in current smokers (HR 0.99, 95% CI 0.71–1.38, $p = 0.95$; interaction $p = 0.03$) [11]. N-acetylcysteine 600 mg twice daily was more effective in reducing exacerbations in ex-smokers than in current or never-smokers [34, 71], with a 23% reduction in healthcare utilization events among current/ex-smokers ($p < 0.01$) [71]. Bronchodilator therapy with LAMA/LABA showed no significant difference from LAMA monotherapy in continuing smokers, but combination therapy was more effective in patients who quit smoking [12].

The table below summarizes differential treatment responses by smoking status:

Treatment	Study	Finding in Current Smokers	Finding in Ex-Smokers	Interaction p-value
ICS (various)	K. Sonnex et al., 2020	Greater FEV1 decline; more exacerbations [10]	Better lung function preservation [10]	Not reported
LABA + ICS vs. LABA + LAMA	A. G. Mathioudakis et al., 2025	LABA + LAMA superior [9]	LABA + ICS superior (BEC ≥ 200) [9]	Significant [9]
Azithromycin	M. Han et al., 2014	No benefit (HR 0.99) [11]	Significant benefit [11]	p = 0.03 [11]
NAC 600 mg bid	A. Papi et al., 2016	No significant reduction [34]	Significant reduction [34]	Not reported
NAC 600 mg bid	A. Papi et al., 2019	23% reduction (current/ex-smokers combined) [71]	Included in combined analysis [71]	Not reported

Treatment	Study	Finding in Current Smokers	Finding in Ex-Smokers	Interaction p-value
LAMA/LABA vs. LAMA	V. Kupaev et al., 2021	No difference between LAMA and LAMA/LABA [12]	LAMA/LABA superior [12]	$p < 0.05$ [12]
MK-7123 (CXCR2 antagonist)	S. Rennard et al., 2015	168 mL FEV1 improvement [23]	No significant improvement [23]	Not reported
ICS (fluticasone)	S. J. M. Hoonhorst et al., 2014	Anti-inflammatory effects present [41]	Some cell-specific effects [41]	No significant interaction [41]
ICS	S. Bhatt et al., 2018	Blunted FEV1 response [57]	Greater improvements [57]	Not reported

These findings collectively demonstrate that the ongoing inflammatory milieu of active smoking substantially alters the pharmacological response to commonly used COPD therapies, with implications for treatment selection.

Exacerbation Impact on Lung Function Decline

Exacerbations accelerated lung function loss, and smoking magnified this effect. In COPDGene, each exacerbation was associated with an additional 23 mL/year FEV1 decline in

GOLD stage 1, and each severe exacerbation with 87 mL/year additional decline ($p = 0.008$) [14]. The interaction with smoking was notable: current/intermittent smokers lost 9 mL/year more than former smokers ($p = 0.005$) [14]. In the UPLIFT trial, the quartile with the fastest FEV1 decline contained a disproportionately higher proportion of current smokers and experienced higher exacerbation rates, more hospitalizations, and greater mortality [43]. Frequent exacerbators with mild-to-moderate COPD (≥ 1.8 exacerbations/year) had nearly double the mortality risk of non-exacerbators (HR 1.98, 95% CI 1.25–3.13) [45]. Kerkhof et al. found that each exacerbation/year was associated with 5.6 mL/year extra FEV1 decline overall, but this rose to 19.4 mL/year in patients with high blood eosinophils not receiving ICS [63].

Structural and Functional Progression

Emphysema progression on CT, assessed by deep learning in COPDGene, showed that 26% of participants had progression over 5 years, associated with greater FEV1 decline (-3.4 vs. -1.8 percentage points), greater 6MWD decline (-177 vs. -124 m), and higher mortality (HR 1.5, 95% CI 1.2–1.8) [56]. ACEi/ARB use was associated with slower emphysema progression and FEV1 decline in the COPDGene cohort, an effect potentially more pronounced in former smokers [24]. The COMPASS study (2,003 participants, 2.5 years) found that FEV1 decline was approximately double in GOLD I–II compared with GOLD III–IV, while FVC decline was faster than FEV1 decline and consistent across severity grades [30].

Exercise capacity declined over time in COPD. Frisk et al. found that 6MWD was maintained in GOLD II over 3 years but declined significantly in GOLD III (-36 m) and GOLD IV (-86 m) [79]. Rodrigues et al. reported that effort-dependent exercise variables deteriorated faster in subjects with airflow obstruction compared with never-smoking controls over 6 years, though VO₂peak decline rates were similar across groups [67]. Smokers who continued during follow-up had faster deterioration of peak heart rate [67].

Synthesis

Reconciling Heterogeneity in Cessation Benefits

While the majority of evidence strongly supports smoking cessation as the single most important intervention to slow COPD progression, some studies reported non-significant mortality

benefits. The Cheong et al. study of 165,986 Korean COPD patients found no significant mortality difference between quitters and continuous smokers after covariate adjustment [28], contrasting with the significant survival benefits reported by Bai et al. [15], Si Lei et al. [5], and the meta-analytic estimate (RR 0.75, borderline $p = 0.05$) [4].

This heterogeneity can be explained by several factors. First, the half-life of excess COPD risk after quitting is approximately 13.3 years [8], meaning that short or moderate follow-up periods may fail to capture the full benefit of cessation, while very long follow-up introduces competing risks from cardiovascular disease and cancer. Second, age at cessation is a critical modifier: the Cheong et al. study found that mortality differences between quitters and continuous smokers were greater among those aged 40–59 years [28], and the meta-analysis by Wang et al. confirmed better FEV1% predicted improvements in those quitting before age 60 [4]. Third, residual confounding by disease severity is difficult to eliminate in observational designs; sicker patients may be both more likely to quit (reverse causation) and more likely to die regardless.

The Lung Health Study, as the only RCT with over 30 years of follow-up, provides the strongest causal evidence: the smoking cessation intervention reduced respiratory-related mortality through 32.5 years, although the all-cause mortality benefit seen at 14.5 years attenuated over time [7], likely due to competing causes of death in this aging cohort.

Baseline Severity as a Key Determinant

COPD severity at the time of cessation or assessment substantially modified the observed effects of smoking. Studies of subjects with milder disease (GOLD I–II) consistently showed the steepest FEV1 decline rates [13, 14], while those with severe disease had slower absolute decline but worse functional status. Mohamed Hoesein et al. (2012) demonstrated that subjects with $FEV1/FVC > 70\%$ had the greatest lung function decline over 3 years [13], suggesting that by the time severe obstruction is established, much of the accelerated decline phase has passed. This aligns with the COPD Gene finding that exacerbations had the greatest impact on FEV1 decline in GOLD stage 1 (23 mL/year per exacerbation) with smaller effects in more advanced stages [14].

For treatment response, milder GOLD stage was associated with better response to azithromycin [11], while the benefits of ICS were most pronounced in patients with fewer pack-

years, preserved diffusion capacity, and less hyperinflation [39]. N-acetylcysteine reduced exacerbations in moderate (GOLD II) but not severe COPD [34]. Collectively, these findings suggest an earlier window of opportunity in which both cessation and pharmacotherapy may yield the greatest returns.

Biological Mechanisms Underlying Differential Effects

The differential treatment response between current and former smokers across multiple drug classes points to fundamental mechanistic differences. Active smoking sustains a neutrophilic inflammatory milieu in the airways [29], promotes bacterial colonization (including *Pseudomonas aeruginosa*) [29], and may induce corticosteroid resistance through oxidative stress pathways [9, 10, 41]. This explains why ICS are less effective in current smokers [9, 10, 57], while agents targeting neutrophilic pathways (e.g., the CXCR2 antagonist MK-7123) show enhanced efficacy in current smokers [23]. The gene-environment interaction between IL6 polymorphisms and smoking intensity on FEV1 decline provides a molecular basis for inter-individual variability in smoking-related progression [44].

The paradoxical fall in CT lung density after smoking cessation [37, 54] reflects resolution of inflammatory edema and vascular congestion that partially masks emphysema. This has important implications for using CT-based biomarkers to monitor treatment effects, as short-term changes following cessation may mimic worsening emphysema rather than improvement.

Dose-Response and Temporal Patterns

Several patterns emerged regarding dose-response relationships and temporal thresholds. Pack-years exposure showed a graded relationship with ICS response: smokers with >36 pack-years had greater FEV1 decline on ICS than lighter smokers [10], and fewer pack-years predicted better response to fluticasone [39]. The duration of cessation mattered substantially: emphysema progression and FEV1 decline were significantly slower only in those who had quit ≥ 5 years earlier [2], while the excess COPD risk half-life of 13.3 years indicates gradual rather than immediate risk normalization [8]. Among PRISm participants, both current and former smokers with a history of smoking had faster lung function decline and higher risk of developing airflow limitation than

never-smokers with PRISm (adjusted HR 1.90, 95% CI 1.31–2.77) [73], reinforcing that smoking exposure confers lasting vulnerability even before established COPD.

In summary, smoking cessation remains the cornerstone intervention for modifying COPD progression, with effects on lung function decline, exacerbation frequency, quality of life, and mortality that accumulate over years to decades. The magnitude of benefit depends critically on disease severity at cessation, cumulative smoking exposure, genetic susceptibility, and the specific outcome measured. Current smoking also substantially modifies the efficacy of pharmacotherapy, necessitating treatment selection that accounts for ongoing tobacco exposure.

DISCUSSION

This systematic review of 80 longitudinal studies provides the most comprehensive synthesis to date of the long-term effects of smoking on COPD progression. The findings demonstrate unequivocally that continued smoking accelerates disease progression across multiple clinically important domains, while smoking cessation confers substantial benefits that accumulate over years to decades. However, the magnitude of these effects is heterogeneous, influenced by genetic susceptibility, disease severity at cessation, cumulative smoking exposure, and the specific outcome measured. This discussion synthesizes the key findings, explores underlying mechanisms, addresses apparent contradictions in the literature, and considers the clinical and research implications.

Quantifying the Impact of Continued Smoking on Lung Function Decline

The most consistent finding across included studies was the accelerated rate of FEV1 decline in current smokers compared with former or never-smokers. The excess decline attributable to continued smoking ranged from approximately 7-10 mL/year in general COPD populations to over 100 mL/year in genetically susceptible subgroups. The 12-year Japanese study by Omori et al. (1) provided a particularly clear dose-response gradient, with FEV1 decline rates of –44.8 mL/year in persistent smokers, –40.7 mL/year in late quitters, –37.9 mL/year in early quitters, and –35.0 mL/year in never-smokers. This gradient, while modest in absolute terms, accumulates over decades to produce clinically significant differences in lung function and functional status.

The meta-analysis by Wang et al. (4) confirmed these findings, demonstrating that smoking cessation was associated with significantly higher FEV1% predicted (MD = 6.72, 95% CI 4.55–8.89) and FEV1/FVC ratio (MD = 6.82, 95% CI 5.09–8.54). These differences exceed the minimal clinically important difference for FEV1 in COPD and translate into meaningful improvements in exercise tolerance (6MWT MD = 64.46 m) and dyspnea (mMRC MD = –0.49).

The particularly striking findings in the heterozygote alpha-1 antitrypsin population studied by Toumpanakis et al. (3)—with FEV1 decline of 132.8 mL/year in current smokers versus 19.9 mL/year in those quit ≥ 10 years—highlight the importance of gene-environment interactions in smoking-related lung injury. This 113 mL/year difference represents the difference between relatively preserved lung function and rapid progression to end-stage disease, underscoring the critical importance of cessation in genetically susceptible individuals.

Temporal Dynamics of Cessation Benefits

The temporal pattern of improvement following smoking cessation reveals important insights into underlying pathophysiology. The immediate improvement in FEV1 observed at 6-12 weeks post-cessation (20,55)—ranging from 122-184 mL—likely reflects resolution of smoking-induced bronchoconstriction, mucosal edema, and acute inflammation rather than true structural improvement. The partial attenuation of this spirometric improvement by 52 weeks, despite sustained symptom benefit, suggests that the initial gain represents removal of a reversible component superimposed on underlying fixed obstruction.

The paradoxical fall in CT lung density observed immediately following cessation (37,54) provides complementary mechanistic insight. The increase in RA-910 by 2.6% and decrease in PD15 by –4.9 HU reflect resolution of inflammatory infiltrate and vascular congestion that had previously partially masked the extent of emphysema. This phenomenon, confirmed in a systematic review of four studies (54), has important implications for clinical trial design and interpretation. Short-term CT changes following cessation should not be misinterpreted as worsening emphysema, and trials using CT outcomes must account for smoking status changes during follow-up.

The estimated half-life of excess COPD risk of 13.3 years (95% CI 11.86–14.96) from Lee et al. (8) is substantially longer than for ischemic heart disease (4.40 years) or lung cancer (9.93

years). This extended risk persistence reflects the permanent structural damage—emphysema, airway remodeling, and parenchymal destruction—that accumulates over years of smoking and resolves only very slowly, if at all. This finding has important implications for patient counseling: while immediate benefits include symptom improvement and reduced exacerbations, the full protection against mortality risk accrues over decades.

Exacerbations as a Driver of Progression

The relationship between exacerbations and lung function decline emerged as a critical pathway through which smoking accelerates progression. Dransfield et al. (14) demonstrated that each exacerbation was associated with an additional 23 mL/year FEV1 decline in GOLD stage 1, rising to 87 mL/year for severe exacerbations. The interaction with smoking was significant, with current/intermittent smokers losing 9 mL/year more than former smokers ($p=0.005$). Kerkhof et al. (63) similarly found that each exacerbation/year was associated with 5.6 mL/year extra FEV1 decline overall, but this rose to 19.4 mL/year in patients with high blood eosinophils not receiving ICS.

These findings suggest a vicious cycle wherein smoking increases exacerbation susceptibility, exacerbations accelerate lung function decline, and declining lung function increases susceptibility to future exacerbations. The UPLIFT trial findings (43)—that the quartile with fastest FEV1 decline contained disproportionately more current smokers and experienced higher exacerbation rates, hospitalizations, and mortality—reinforce this interconnected pathway. Smoking cessation interrupts this cycle by reducing exacerbation frequency (5,15) and thereby slowing the exacerbation-driven component of lung function decline.

Smoking Status and Pharmacotherapy Response: A Critical Interaction

Perhaps the most clinically actionable finding from this review is the consistent modification of treatment efficacy by smoking status across multiple drug classes. The systematic review by Sonnex et al. (10) demonstrated that heavier smokers (>36 pack-years) using ICS had greater FEV1 decline compared with lighter smokers, and exacerbation rate ratios favored fewer exacerbations in ex-smokers and lighter smokers on ICS. Mathioudakis et al. (9) provided particularly compelling evidence from the FLAME trial: LABA + LAMA was superior to LABA + ICS in preventing

exacerbations in current smokers but inferior in ex-smokers with blood eosinophil count ≥ 200 cells/ μ L.

These findings align with the mechanistic understanding that active smoking sustains a neutrophilic inflammatory milieu (29), promotes bacterial colonization (29), and induces corticosteroid resistance through oxidative stress pathways (9,10,41). The enhanced efficacy of CXCR2 antagonists in current smokers (23) supports the concept that targeting neutrophil chemotaxis may be more appropriate than ICS in actively smoking patients. The azithromycin findings from Han et al. (11)—significant benefit in former smokers but no benefit in current smokers (interaction $p=0.03$)—similarly reflect the overwhelming pro-inflammatory stimulus of continued smoking that may overwhelm the modest anti-inflammatory effects of macrolides.

The clinical implications are clear: treatment selection for COPD must account for current smoking status. For patients who continue to smoke, ICS may provide limited benefit, and alternatives such as dual bronchodilators, CXCR2 antagonists where available, or careful consideration of roflumilast (33) may be more appropriate. For patients who quit smoking, ICS-containing regimens may provide greater benefit, particularly in those with elevated blood eosinophils. The N-acetylcysteine findings (34,71)—greater efficacy in ex-smokers and never-smokers—further reinforce this pattern.

Reconciling Heterogeneity in Mortality Benefits

The apparent contradiction between studies demonstrating significant mortality reduction with cessation (5,15,22) and those showing non-significant differences after adjustment (28) requires careful consideration. The Cheong et al. study (28) of 165,986 Korean COPD patients found no significant mortality difference between quitters and continuous smokers after covariate adjustment, despite lower crude mortality in quitters (25.7% vs. 27.2%). Several factors explain this heterogeneity.

First, the 13.3-year half-life of excess COPD risk (8) means that studies with shorter follow-up may fail to capture the full mortality benefit. The Lung Health Study (7), with 32.5 years of follow-up as the only RCT in this space, provides the strongest causal evidence: the smoking cessation intervention reduced respiratory-related mortality through 32.5 years, although the all-

cause mortality benefit seen at 14.5 years attenuated over time due to competing causes of death in this aging cohort.

Second, age at cessation is a critical modifier. The Cheong et al. study found greater mortality differences between quitters and continuous smokers among those aged 40-59 years (28), and the Wang et al. meta-analysis (4) confirmed better FEV1% predicted improvements in those quitting before age 60. Third, residual confounding by disease severity is difficult to eliminate in observational designs; sicker patients may be both more likely to quit (reverse causation) and more likely to die regardless. The Bai et al. study (15), which found significantly higher mortality in continuing smokers (73/112 vs. 40/92 deaths; log-rank test 13.59, $p=0.0002$), adjusted for baseline severity but may not have eliminated all confounding.

The meta-analytic estimate from Wang et al. (RR = 0.75, 95% CI 0.56–1.00, $p = 0.05$) (4) suggests a borderline significant mortality reduction that is clinically meaningful. The confidence interval includes the possibility of no effect, reflecting the heterogeneity across studies and the difficulty of isolating cessation effects from confounding. However, the consistency of benefit across respiratory-specific mortality (7), the biological plausibility, and the convergence of evidence from multiple study designs support the conclusion that smoking cessation reduces mortality in COPD, even if the precise magnitude remains uncertain.

Baseline Severity and the Window of Opportunity

An important theme emerging from this review is that COPD severity at the time of cessation or assessment substantially modifies observed effects. Studies of subjects with milder disease (GOLD I–II) consistently showed the steepest FEV1 decline rates (13,14), while those with severe disease had slower absolute decline but worse functional status. Mohamed Hoesein et al. (13) demonstrated that subjects with FEV1/FVC >70% had the greatest lung function decline over 3 years, suggesting that by the time severe obstruction is established, much of the accelerated decline phase has passed.

This finding has profound clinical implications. It suggests an earlier window of opportunity in which both cessation and pharmacotherapy may yield the greatest returns. The COPDGene finding that exacerbations had the greatest impact on FEV1 decline in GOLD stage 1 (23 mL/year

per exacerbation) with smaller effects in more advanced stages (14) reinforces this concept. For treatment response, milder GOLD stage was associated with better response to azithromycin (11), while the benefits of ICS were most pronounced in patients with fewer pack-years, preserved diffusion capacity, and less hyperinflation (39). N-acetylcysteine reduced exacerbations in moderate (GOLD II) but not severe COPD (34).

These findings should not be interpreted to mean that cessation is futile in advanced disease. Patients with severe COPD still experience symptom improvement, reduced exacerbations, and improved quality of life with cessation (20,40). However, the magnitude of lung function preservation is greatest when cessation occurs early in the disease course, before extensive structural damage has accumulated.

Biological Mechanisms Underlying Differential Effects

The differential treatment response between current and former smokers across multiple drug classes points to fundamental mechanistic differences in airway inflammation and pathophysiology. Active smoking sustains a neutrophilic inflammatory milieu characterized by elevated sputum neutrophils, increased CXCR2 ligand expression, and activation of oxidative stress pathways (29,41). This environment promotes bacterial colonization, including potentially pathogenic organisms such as *Pseudomonas aeruginosa* (29), which may further amplify inflammation and exacerbation risk.

The mechanism of corticosteroid resistance in current smokers likely involves oxidative stress-induced reduction in histone deacetylase-2 (HDAC2) activity, which is required for corticosteroids to suppress inflammatory gene expression (9,10). The finding that CXCR2 antagonists show enhanced efficacy in current smokers (23) suggests that targeting neutrophil chemotaxis may circumvent this resistance mechanism. The gene-environment interaction between IL6 polymorphisms and smoking intensity on FEV1 decline reported by Hackett et al. (44) provides a molecular basis for inter-individual variability in smoking-related progression.

The rapid improvement in gas transfer (Tlco) following cessation (55) likely reflects resolution of carbon monoxide-mediated impairment of oxygen diffusion and improvement in alveolar capillary membrane function. The sustained symptom improvement despite partial

attenuation of spirometric gains (20) suggests that smoking cessation reduces dynamic hyperinflation, improves mucociliary clearance, and decreases cough and sputum production through mechanisms partially independent of FEV1.

Implications for Clinical Practice

The findings of this review support several actionable recommendations for clinical practice. First, smoking cessation should be recommended to all patients with COPD at every clinical encounter, regardless of disease severity or duration. The evidence demonstrates benefit across all stages, with improvements in symptoms, exacerbations, and quality of life even when lung function gains are modest.

Second, treatment selection should explicitly account for current smoking status. For patients who continue to smoke, ICS may provide limited benefit, and clinicians should consider alternative or additional agents. Dual bronchodilator therapy (LAMA/LABA) may be preferred over ICS-containing regimens in current smokers (9,12). For patients with frequent exacerbations despite optimal bronchodilator therapy, roflumilast (33) or careful consideration of azithromycin (11) may be appropriate, though the reduced efficacy of azithromycin in current smokers should be considered.

Third, patient counseling should address realistic expectations about the timeline of benefit. Immediate improvements in cough, sputum, and dyspnea can be expected within weeks, providing positive reinforcement for continued abstinence. However, the full protection against mortality risk accrues over years to decades (8), and patients should understand that the benefits of cessation accumulate gradually.

Fourth, the paradoxical early fall in CT lung density following cessation should be recognized to avoid misinterpretation as disease worsening. Patients undergoing CT surveillance should be counseled about this phenomenon, and clinicians should avoid unnecessary alarm or treatment changes based on early post-cessation CT changes.

CONCLUSION AND RECOMMENDATIONS

This comprehensive systematic review of 80 longitudinal studies provides robust evidence that continued smoking accelerates COPD progression across multiple clinically important domains, while smoking cessation confers substantial benefits that accumulate over years to decades. The key findings can be summarized as follows:

1. **Lung function decline:** Current smokers exhibit accelerated FEV1 decline compared with former smokers, with excess decline ranging from 7-10 mL/year in general populations to >100 mL/year in genetically susceptible subgroups (1,2). Smoking cessation produces immediate FEV1 improvement (122-184 mL) that partially attenuates over time, with sustained symptom benefits (20,55).
2. **Exacerbations and mortality:** Continued smoking increases exacerbation frequency and mortality risk. Smoking cessation reduces exacerbations (5,15) and mortality (RR 0.75, 95% CI 0.56–1.00, $p=0.05$) (4), with the Lung Health Study confirming sustained reduction in respiratory-related mortality over 32.5 years (7). The half-life of excess COPD risk after quitting is 13.3 years (95% CI 11.86–14.96) (8).
3. **Treatment modification:** Smoking status substantially alters pharmacotherapy responses. Current smokers show blunted responses to ICS (9,10,57), reduced benefit from azithromycin (interaction $p=0.03$) (11), but enhanced responses to CXCR2 antagonists (23). Treatment selection must account for ongoing smoking exposure.
4. **Structural changes:** Smoking cessation causes a paradoxical early fall in CT lung density reflecting resolution of inflammation rather than emphysema worsening (37,54). Emphysema progression on CT predicts functional decline and mortality (56).
5. **Effect modifiers:** The magnitude of smoking effects and cessation benefits is modified by genetic susceptibility (alpha-1 antitrypsin genotype) (3), baseline disease severity (13,14), age at cessation (4,28), and cumulative smoking exposure (10,39).

Clinical Recommendations

Based on these findings, we offer the following recommendations:

1. Smoking cessation should be prioritized in all patients with COPD, regardless of disease severity or duration. The evidence demonstrates benefit across all stages, and no patient is "beyond help" from cessation.
2. Treatment selection should explicitly consider smoking status. For current smokers, ICS may provide limited benefit, and alternative or additional agents (LAMA/LABA, roflumilast, careful consideration of azithromycin) should be considered. For former smokers, ICS-containing regimens may be more appropriate, particularly in those with elevated blood eosinophils.
3. Patient counseling should address realistic timelines for benefit. Immediate improvements in symptoms can be expected within weeks, reinforcing continued abstinence. However, the full protection against mortality risk accrues over years to decades, and patients should understand that benefits accumulate gradually.
4. The paradoxical early fall in CT lung density following cessation should be recognized to avoid misinterpretation as disease worsening. Patients undergoing CT surveillance should be counseled about this phenomenon.
5. Exacerbation prevention should be a priority, as exacerbations accelerate lung function decline (14,63). Smoking cessation reduces exacerbation risk, and this represents an important mechanism of benefit.

Research Recommendations

Future research should prioritize:

1. Prospective studies with extended follow-up (>20 years) to fully characterize the trajectory of lung function and mortality following cessation at different ages and disease stages.

2. Mechanistic studies exploring the molecular basis of corticosteroid resistance in current smokers to identify therapeutic targets that may restore ICS efficacy.
3. Randomized trials stratified by smoking status to definitively establish optimal treatment algorithms for current versus former smokers.
4. Studies examining whether smoking reduction (rather than complete cessation) confers proportional benefits, and whether there is a threshold below which continued smoking does not accelerate progression.
5. Investigation of whether cessation benefits differ by COPD phenotype (emphysema-predominant vs. airways-predominant, frequent exacerbator vs. non-exacerbator).

In conclusion, smoking cessation remains the single most important intervention for modifying COPD progression. The benefits are substantial, clinically meaningful, and accumulate over time. While the structural damage from smoking resolves slowly, with a risk half-life exceeding 13 years, the functional and symptomatic improvements provide compelling reasons for cessation at any disease stage. Clinicians should leverage this evidence to counsel patients, guide treatment selection, and support smoking cessation efforts at every opportunity.

REFERENCES

1. H. Omori, A. Onoue, Yayoi Funakoshi, et al (2011) Effects of smoking habits on annual change in FEV1: A 12-year follow-up study
2. F. M. Mohamed Hoesein, P. Zanen, P. D. de Jong, et al (2013) Rate of progression of CT-quantified emphysema in male current and ex-smokers: a follow-up study. Respiratory Research. <https://doi.org/10.1186/1465-9921-14-55>
3. Dimitrios Toumpanakis, N. Hopkinson, S. Meah, et al (2023) Smoking cessation improves lung function in heterozygote alpha-1 antitrypsin patients. Airway pharmacology and treatment. <https://doi.org/10.1183/13993003.congress-2023.pa3049>

4. Zihan Wang, Yifan Qiu, Xiang Ji, Liang Dong (2024) Effects of smoking cessation on individuals with COPD: a systematic review and meta-analysis. *Frontiers in Public Health*. <https://doi.org/10.3389/fpubh.2024.1433269>
5. Si Lei, Meilei Li, Wenbing Duan, et al (2020) The long-term outcomes of tobacco control strategies based on the cognitive intervention for smoking cessation in COPD patients. *Respiratory Medicine*. <https://doi.org/10.1016/j.rmed.2020.106155>
6. R. Polosa, J. Morjaria, U. Prosperini, et al (2020) COPD smokers who switched to e-cigarettes: health outcomes at 5-year follow up. *Therapeutic Advances in Chronic Disease*. <https://doi.org/10.1177/2040622320961617>
7. Janet T Holbrook (2026) More Lessons from the Lung Health Study. *American Journal of Epidemiology*. <https://doi.org/10.1093/aje/kwag004>
8. P. Lee, J. Fry, B. Forey (2014) Estimating the decline in excess risk of chronic obstructive pulmonary disease following quitting smoking - a systematic review based on the negative exponential model. *Regulatory toxicology and pharmacology* : RTP. <https://doi.org/10.1016/j.yrtph.2013.12.006>
9. Alexander G. Mathioudakis, A. Higham, S. Bate, et al (2025) Reduced treatment response to inhaled corticosteroids in current smokers with COPD, regardless of blood eosinophil count: insights from the FLAME trial. *Thorax*. <https://doi.org/10.1136/thorax-2024-222547>
10. K. Sonnex, Hanna Alleemudder, R. Knaggs (2020) Impact of smoking status on the efficacy of inhaled corticosteroids in chronic obstructive pulmonary disease: a systematic review. *BMJ Open*. <https://doi.org/10.1136/bmjopen-2020-037509>
11. M. Han, N. Tayob, S. Murray, et al (2014) Predictors of chronic obstructive pulmonary disease exacerbation reduction in response to daily azithromycin therapy. *American Journal of Respiratory and Critical Care Medicine*. <https://doi.org/10.1164/rccm.201402-0207OC>
12. V. Kupaev, D. Osipov (2021) Which bronchodilator to choose if a patient with chronic obstructive pulmonary disease continues to smoke? *PULMONOLOGIYA*. <https://doi.org/10.18093/0869-0189-2021-31-4-469-476>

13. F. M. Mohamed Hoesein, P. Zanen, H. Boezen, et al (2012) Lung function decline in male heavy smokers relates to baseline airflow obstruction severity. *Chest*. <https://doi.org/10.1378/chest.11-2837>
14. M. Dransfield, K. Kunisaki, M. Strand, et al (2016) Acute Exacerbations and Lung Function Loss in Smokers with and without Chronic Obstructive Pulmonary Disease. *American Journal of Respiratory and Critical Care Medicine*. <https://doi.org/10.1164/rccm.201605-1014OC>
15. J. Bai, Xiao-xin Chen, Shengsheng Liu, et al (2017) Smoking cessation affects the natural history of COPD. *International Journal of COPD*. <https://doi.org/10.2147/COPD.S150243>
16. M. Ragland, M. Strand, D. Baraghoshi, et al (2021) 10 Year Follow-up of Lung Function, Respiratory Symptoms, and Functional Capacity in the COPD Gene Study. *Annals of the American Thoracic Society*. <https://doi.org/10.1513/AnnalsATS.202007-873OC>
17. R. Polosa, J. Morjaria, U. Prosperini, et al (2018) Health effects in COPD smokers who switch to electronic cigarettes: a retrospective-prospective 3-year follow-up. *International Journal of COPD*. <https://doi.org/10.2147/COPD.S161138>
18. R. Polosa, J. Morjaria, P. Caponnetto, et al (2016) Evidence for harm reduction in COPD smokers who switch to electronic cigarettes. *Respiratory Research*. <https://doi.org/10.1186/s12931-016-0481-x>
19. R. Polosa, J. Morjaria, U. Prosperini, et al (2020) Health outcomes in COPD smokers using heated tobacco products: a 3-year follow-up. *Internal and Emergency Medicine*. <https://doi.org/10.1007/s11739-021-02674-3>
20. D. P. Tashkin, S. Rennard, J. Hays, et al (2011) Lung function and respiratory symptoms in a 1-year randomized smoking cessation trial of varenicline in COPD patients. *Respiratory Medicine*. <https://doi.org/10.1016/j.rmed.2011.04.016>
21. A. Ramírez-Venegas, R. Sansores, R. Quintana-Carrillo, et al (2014) FEV1 decline in patients with chronic obstructive pulmonary disease associated with biomass exposure. *American Journal of Respiratory and Critical Care Medicine*. <https://doi.org/10.1164/rccm.201404-0720OC>
22. X. Yuan, Y. Tao, Junling Zhao, et al (2015) Long-term efficacy of a rural community-based integrated intervention for prevention and management of chronic obstructive pulmonary disease: a

cluster randomized controlled trial in China's rural areas. Brazilian journal of medical and biological research = Revista brasileira de pesquisas medicas e biologicas. <https://doi.org/10.1590/1414-431X20154385>

23. S. Rennard, D. Dale, J. Donohue, et al (2015) CXCR2 Antagonist MK-7123. A Phase 2 Proof-of-Concept Trial for Chronic Obstructive Pulmonary Disease. American Journal of Respiratory and Critical Care Medicine. <https://doi.org/10.1164/rccm.201405-0992OC>

24. X. Bertels, L. Lahousse (2021) Benefits of Angiotensin-Converting Enzyme Inhibitors and Angiotensin-Receptor Blockers on Progression of Emphysema and Lung Function Decline. Chest. <https://doi.org/10.1016/j.chest.2021.06.023>

25. C. Cooper, B. Celli, J. Jardim, et al (2013) Treadmill endurance during 2-year treatment with tiotropium in patients with COPD: a randomized trial. Chest. <https://doi.org/10.1378/chest.12-2613>

26. D. Tashkin, Ning Li, E. Kleerup, et al (2014) Acute bronchodilator responses decline progressively over 4 years in patients with moderate to very severe COPD. Respiratory Research. <https://doi.org/10.1186/s12931-014-0102-5>

27. T. Tayutina, D.D. Shender (2025) A personalized approach to smoking cessation within the framework of secondary prevention of chronic obstructive pulmonary disease. Лечащий врач. <https://doi.org/10.51793/os.2025.28.10.005>

28. C. Cheong, Theresa Lee, S. Jang, et al (2018) PRS8 - EFFECTS OF SMOKING CESSATION ON HEALTH OUTCOMES AMONG COPD PATIENTS IN SOUTH KOREA: 12 YEARS FOLLOW-UP. Value in Health. <https://doi.org/10.1016/j.jval.2018.09.2402>

29. Shunian He, Zhi-Feng Liu, Dong-Mei Li, Jiang Huang (2012) The influence of smoking on lower airway bacterial colonization in stable phase of chronic obstructive pulmonary disease. <https://doi.org/10.3760/CMA.J.ISSN.1008-6706.2012.02.002>

30. J. Zheng, R. Chen, Y. Sun, et al (2025) Differential Decline in FEV1 and FVC Across COPD GOLD Grades and Non-Obstructed Chronic Bronchitis. American Journal of Respiratory and Critical Care Medicine. <https://doi.org/10.1164/ajrccm.2025.211.abstracts.a6185>

31. V. Antonov, G. Ignatova (2020) Prospective assessment of vaccine prophylaxis in patients with chronic obstructive pulmonary disease. <https://doi.org/10.1016/j.waojou.2020.100168>
32. C. Stey, J. Braun, Violeta Gaveikaite, et al (2016) Effectiveness of the “living well with COPD” intervention on coping, smoking behavior and exacerbations in patients from Swiss primary care: A non-randomized controlled study. <https://doi.org/10.1183/13993003.CONGRESS-2016.PA3787>
33. P. Calverley, U. Goehring, F. Martinez, N. Barnes (2011) Efficacy of roflumilast in former and current smokers with COPD
34. A. Papi, G. Criner, G. Brusselle, et al (2016) Long term treatment with n-acetylcysteine reduces exacerbations in moderate chronic obstructive pulmonary disease. <https://doi.org/10.1183/13993003.CONGRESS-2016.PA299>
35. N. Yanev, Nikolay H. Kyuchukov, Ilia Krachunov, et al (2015) Outcomes in patients with COPD during a 3 year follow-up. <https://doi.org/10.1183/13993003.CONGRESS-2015.PA1048>
36. I. Hønoch, C. Löfdahl, A. Ekberg-Jansson (2018) Influences of patient education on exacerbations and hospital admissions in patients with COPD – a longitudinal national register study. *European Clinical Respiratory Journal*. <https://doi.org/10.1080/20018525.2018.1500073>
37. S. Shaker, T. Stavngaard, L. C. Laursen, et al (2011) Rapid Fall in Lung Density Following Smoking Cessation in COPD. *COPD*. <https://doi.org/10.3109/15412555.2010.541306>
38. Kenichiro Tanaka, H. Senjyu, Y. Tawara, et al (2018) Effects of Systematic Intervention for Chronic Obstructive Pulmonary Disease on Follow-up and Smoking Cessation Rates and Changes of the Pulmonary Function: A 7-year Longitudinal Study in a Japanese Rural City. *Internal medicine*. <https://doi.org/10.2169/internalmedicine.9070-17>
39. J. Snoeck-Stroband, T. Lapperre, P. Sterk, et al (2015) Prediction of Long-Term Benefits of Inhaled Steroids by Phenotypic Markers in Moderate-to-Severe COPD: A Randomized Controlled Trial. *PLoS ONE*. <https://doi.org/10.1371/journal.pone.0143793>
40. A. Khomenya, M. Vershinina, Olga Foronosova (2020) Does Smoking Cessation affect symptoms and FEV1 in smokers with mild COPD? <https://doi.org/10.1183/13993003.congress-2020.1313>

41. Susan J. M. Hoonhorst, N. T. ten Hacken, J. Vonk, et al (2014) Steroid Resistance in COPD? Overlap and Differential Anti-Inflammatory Effects in Smokers and Ex-Smokers. PLoS ONE. <https://doi.org/10.1371/journal.pone.0087443>
42. Petra Hagens, M. Pieterse, P. van der Valk, J. van der Palen (2017) Effectiveness of intensive smoking reduction counselling plus combination nicotine replacement therapy in promoting long-term abstinence in patients with chronic obstructive pulmonary disease not ready to quit smoking: Protocol of the REDUQ trial. Contemporary Clinical Trials Communications. <https://doi.org/10.1016/j.conctc.2017.08.014>
43. S. Kesten, B. Celli, M. Decramer, et al (2011) Adverse health consequences in COPD patients with rapid decline in FEV1 - evidence from the UPLIFT trial. Respiratory Research. <https://doi.org/10.1186/1465-9921-12-129>
44. T. Hackett, D. Stefanowicz, F. Aminuddin, et al (2011) Effect of gene environment interactions on lung function and cardiovascular disease in COPD. International Journal of COPD. <https://doi.org/10.2147/COPD.S18279>
45. Spyridon Fortis, E. Wan, K. Kunisaki, et al (2020) Increased mortality associated with frequent exacerbations in COPD patients with mild-to-moderate lung function impairment, and smokers with normal spirometry. Respiratory medicine: X. <https://doi.org/10.1016/j.ymex.2020.100025>
46. Zemin He, Boxiong Cao, Keting Liu, Qiang Wei (2025) Skeletal Muscle Function in Relation to COPD Severity and Its Predictive Significance for Disease Progression. International Journal of COPD. <https://doi.org/10.2147/COPD.S510425>
47. B. Engel, C. Schindler, J. Leuppi, J. Rutishauser (2017) Predictors of re-exacerbation after an index exacerbation of chronic obstructive pulmonary disease in the REDUCE randomised clinical trial. Swiss medical weekly. <https://doi.org/10.4414/smz.2017.14439>
48. J. Crapo, Abhya Gupta, David A. Lynch, et al (2023) Baseline characteristics from a 3-year longitudinal study to phenotype subjects with COPD: the FOOTPRINTS study. Respiratory Research. <https://doi.org/10.1186/s12931-023-02584-2>

49. Irina Pavlenko, Julia Ilkovich, Nina Shklarevich (2011) Influence of smoking intensity and smoking quitting on lung function parameters in COPD patients
50. S. Mahmud, Sreyoshi F. Alam, Tasbirul Islam (2019) Inhaled Tranexamic Acid: A Therapeutic Option For Hemoptysis. Clinical Pulmonary Medicine. <https://doi.org/10.1097/CPM.0000000000000328>
51. M. Högman, Christer Janson, Andreas Palm, et al (2025) Exhaled nitric oxide stability over two years in relation to COPD outcomes. Journal of Breath Research. <https://doi.org/10.1088/1752-7163/adfd04>
52. J. Londhe, B. Brashier, Vandana Das, et al (2014) Changes in quality of life as assessed by St. Georges respiratory questionnaire (SGRQ) and COPD assessment test (CAT) and spirometric indices in patients with smoker-COPD(S-COPD) and non-smoker-COPD(NS-COPD) after 1 year of follow up
53. Ruriko Yukimura, E. Ogawa, Yasushi Ryujin, et al (2016) Longitudinal changes of respiratory impedance-based phenotypes in COPD. <https://doi.org/10.1183/13993003.CONGRESS-2016.PA4145>
54. Daryl Cheng, S. Agarwal, J. Jacob, J. Hurst (2020) Effect of smoking cessation on CT imaging in patients with Chronic Obstructive Pulmonary Disease: A systematic review. <https://doi.org/10.1101/2020.02.11.20022129>
55. J. Dhariwal, R. Tennant, D. Hansell, et al (2014) Smoking cessation in COPD causes a transient improvement in spirometry and decreases micronodules on high-resolution CT imaging. Chest. <https://doi.org/10.1378/chest.13-2220>
56. A. Oh, D. Baraghoshi, D. Lynch, et al (2022) Emphysema Progression at CT by Deep Learning Predicts Functional Impairment and Mortality: Results from the COPDGene Study. Radiology. <https://doi.org/10.1148/radiol.213054>
57. S. Bhatt, Julie A. Anderson, R. Brook, et al (2018) Cigarette smoking and response to inhaled corticosteroids in COPD. European Respiratory Journal. <https://doi.org/10.1183/13993003.01393-2017>

58. D. MacDonald, A. Melzer, G. Collins, et al (2018) Smoking and Accelerated Lung Function Decline in HIV-Positive Individuals: A Secondary Analysis of the START Pulmonary Substudy. *Journal of Acquired Immune Deficiency Syndromes*. <https://doi.org/10.1097/QAI.0000000000001797>
59. N. Riblet, B. V. Watts (2023) Another Reason to Quit Smoking: Results of a Prospective Study Examining Smoking, COPD, and Suicide. *Chest*. <https://doi.org/10.1016/j.chest.2022.10.016>
60. M. Hoogendoorn, M. R. Mölken, R. Hoogenveen, et al (2011) Comparing the cost-effectiveness of a wide range of COPD interventions using a stochastic population model for COPD
61. I. Naya, L. Tombs, P. Jones (2015) S57 Short-term clinically important deterioration predicts long-term clinical outcome in COPD patients: A post-hoc analysis of the TORCH trial. <https://doi.org/10.1136/thoraxjnl-2015-207770.63>
62. Lieke C. A. Christenhusz, R. Prenger, M. Pieterse, et al (2012) Cost-effectiveness of an intensive smoking cessation intervention for COPD outpatients. *Nicotine & Tobacco Research*. <https://doi.org/10.1093/ntr/ntr263>
63. M. Kerkhof, J. Voorham, C. Cabrera, et al (2019) Effect of COPD exacerbations on early lung function decline under maintenance therapy: blood eosinophil count asbiomarker. *Monitoring airway disease*. <https://doi.org/10.1183/13993003.congress-2019.oa2154>
64. Juan Chen, Yan Chen, Ping Chen, et al (2013) Effectiveness of individual counseling for smoking cessation in smokers with chronic obstructive pulmonary disease and asymptomatic smokers. *Experimental and Therapeutic Medicine*. <https://doi.org/10.3892/etm.2013.1463>
65. Takahiro Kamada, M. Kaneko, H. Tomioka (2017) Impact of exacerbations on respiratory system impedance measured by a forced oscillation technique in COPD: a prospective observational study. *International Journal of COPD*. <https://doi.org/10.2147/COPD.S124828>
66. MD Jeffrey L. Curtis, MS Lori A. Bateman, ScD Susan Murray, et al (2024) Design of the SPIROMICS Study of Early COPD Progression: SOURCE Study. *Chronic obstructive pulmonary diseases*. <https://doi.org/10.15326/jcopdf.2023.0490>

67. F. Rodrigues, M. Loeckx, M. Hornikx, et al (2018) Six years progression of exercise capacity in subjects with mild to moderate airflow obstruction, smoking and never smoking controls. PLoS ONE. <https://doi.org/10.1371/journal.pone.0208841>
68. R. Kuint, Polina Cohen Goichman, Ahuva Mizrachi, et al (2020) The Effect of a Multidisciplinary Integrated Approach on Outcomes in Chronic Obstructive Pulmonary Disease. The Israel Medical Association journal : IMAJ
69. A. Kruis, M. Boland, W. J. J. Assendelft, et al (2014) Effectiveness of integrated disease management for primary care chronic obstructive pulmonary disease patients: results of cluster randomised trial. British medical journal. <https://doi.org/10.1136/bmj.g5392>
70. A. Zhang, Lianhong Wang, L. Long, et al (2020) Effectiveness and Economic Evaluation of Hospital-Outreach Pulmonary Rehabilitation for Patients with Chronic Obstructive Pulmonary Disease. International Journal of COPD. <https://doi.org/10.2147/COPD.S239841>
71. A. Papi, Jinping Zheng, G. Criner, et al (2019) Impact of smoking status and concomitant medications on the effect of high-dose N-acetylcysteine on chronic obstructive pulmonary disease exacerbations: A post-hoc analysis of the PANTHEON study. Respiratory Medicine. <https://doi.org/10.1016/j.rmed.2018.12.014>
72. Guixiang Zhao, Lu Wang, Siyuan Lei, et al (2025) All-Cause and Cause-Specific Mortality in Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis. International Journal of COPD. <https://doi.org/10.2147/COPD.S563250>
73. C. Dai, Fan Wu, Jia Tian, et al (2025) Lung Function Decline and Airflow Limitation Risk in Preserved Ratio Impaired Spirometry (PRISm) Subtypes by Smoking Status. Chest. <https://doi.org/10.1016/j.chest.2025.05.006>
74. Yu-Ting Lai, Ying-Huang Tsai, Meng-Jer Hsieh, et al (2024) Benefit of dual bronchodilator therapy on exacerbations in former and current smokers with chronic obstructive pulmonary disease in real-world clinical practice: a multicenter validation study (TOReTO). Respiratory Research. <https://doi.org/10.1186/s12931-024-02971-3>

75. Hui-Chuan Chang, Shih-Feng Liu, Ho-Chang Kuo, et al (2023) Smoking cessation and influenza vaccination can reduce the healthcare burden of COPD. Tobacco Induced Diseases. <https://doi.org/10.18332/tid/167962>
76. C. Buri-Nagua, H. Woo, D. Belz, et al (2025) Social Determinants of Health and Rehospitalization in Chronic Obstructive Pulmonary Disease (COPD) Patients: A Longitudinal Analysis. American Journal of Respiratory and Critical Care Medicine. <https://doi.org/10.1164/ajrccm.2025.211.abstracts.a2108>
77. P. Bakke, Jørgen Vesbo, E. Wouters, et al (2016) Changes in FEV1 over 8 years in COPD. <https://doi.org/10.1183/13993003.CONGRESS-2016.PA3119>
78. M. Ichinose, Y. Fukuchi, K. Tatsumi, et al (2015) LATE-BREAKING ABSTRACT: Prevention of COPD exacerbation by lysozyme: A double-blind, randomized, placebo-controlled study. <https://doi.org/10.1183/13993003.CONGRESS-2015.PA4359>
79. B. Frisk, B. Espehaug, J. Hardie, et al (2012) Predictors for longitudinal change in 6-minute walk distance in COPD patients
80. A. Papi, G. Brusselle, F. Sergio, et al (2017) Blood eosinophils and smoking history affect outcome with high dose N-acetylcysteine treatment in COPD. <https://doi.org/10.1183/1393003.CONGRESS-2017.PA1066>