REVIEW ARTICLE

JIACM 2026; 27 (2): 147-154

GLP-1 Receptor Agonists and Respiratory Outcomes: Mechanisms, Evidence, and Clinical Implications

Rahul Garg, Prashant Prakash**, Mayank Butola***, Rajeev Kishore*****

Abstract

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) - including semaglutide, liraglutide, dulaglutide, and tirzepatide – were developed for type 2 diabetes and obesity, but converging evidence now shows substantial pleiotropic effects on the respiratory system that extend beyond glycaemic control and weight loss. GLP-1 receptors are highly expressed in pulmonary tissue, in cluding bronchial smooth muscle, alveolar type II cells. alveolar macrophages, pulmonary vascular endothelium, and eosinophils, providing biological rationale for direct airway and vascular activity. Receptor activation suppresses NF-κB (Nuclear factor kappa-light-chain-enhancer of activated B cells) signaling, NLRP3 (NOD-like receptor protein 3) inflammasome assembly, TGF (Transforming growth factor)-β1-driven fibrogenesis, and Th2 (T helper type 2)/ILC2 (Group 2 innate lymphoid cells)-mediated inflammation, while augmenting surfactant production and nitric oxide bioavailability through eNOS (endothelial nitric oxide synthase) pathways. A meta-analysis of 28 randomised controlled trials in 77,485 participants demonstrated a 14% reduction in overall respiratory disease risk, with subsequent analyses confirming benefit across obstructive sleep apnoea, COPD (chronic obstructive pulmonary disease), asthma, pneumonia, and pulmonary arterial hypertension. Mendelian randomisation studies provide causal genetic evidence independent of confounding by indication, and proof-of-concept trial data - including the first human hemodynamic data in pulmonary arterial hypertension - now complement a growing observational evidence base. Safety considerations relevant to pulmonologists, including aspiration risk during procedural sedation and lean mass loss in cachectic patients, warrant attention. This review synthesizes mechanistic, translational, and clinical evidence through 2026 and outlines priorities for dedicated respiratory trials.

Key words: GLP-1 receptor agonists, semaglutide, liraglutide, tirzepatide, asthma, COPD, obstructive sleep apnoea, pulmonary arterial hypertension, pulmonary fibrosis.

Introduction

Respiratory diseases are the third leading cause of death globally and among the top contributors to disability-adjusted life years worldwide[1]. COPD affects an estimated 213 to 392 million individuals globally and asthma approximately 260 million, with absolute case burdens rising despite declining age-standardised rates[2]. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) – originally developed for type 2 diabetes mellitus (T2DM), and now including semaglutide, liraglutide, dulaglutide, exenatide, and the dual GLP-1/GIP agonist tirzepatide – have demonstrated cardiovascular, renal, and metabolic benefits beyond glucose lowering, and their subsequent approval for obesity expanded their clinical reach considerably. Diabetes and obesity are common comorbidities across obstructive airway disease, present in roughly 20 - 30% of patients with COPD[3], compounding disease burden further.

These respiratory benefits were initially attributed to weight loss, but growing evidence now reveals receptor-mediated, weight-independent, anti-inflammatory and cytoprotective effects directly within the lung. An umbrella review of 123 meta-analyses covering 464 outcomes confirmed trends toward improved respiratory outcomes with GLP-1 RAs, though evidence quality is heterogeneous[4]. This review synthesizes mechanisms, disease-specific data, and research priorities.

GLP-1 Biology and Pulmonary Receptor Distribution

GLP-1 is a 30-amino acid incretin hormone secreted by intestinal L-cells that acts through the GLP-1 receptor (GLP-1R), a class B G-protein coupled receptor, to stimulate insulin secretion, suppress glucagon, and delay gastric emptying[5]. Native GLP-1 is rapidly degraded by dipeptidyl peptidase-4 (DPP-4); GLP-1 RAs are engineered analogues resistant to this degradation. GLP-1R mRNA expression in the lung ranks among the highest of all extra-pancreatic organs[6], and GLP-1 concentrations in bronchoalveolar lavage fluid substantially exceed serum levels, suggesting paracrine pulmonary

**Professor, Department of Medicine, FH Medical College and Hospital, Agra - 283 204, Uttar Pradesh, **Professor and Head, Department of Pulmonary Medicine, SN Medical College, Agra - 282 002, Uttar Pradesh, ***Resident, Department of Cardiology, Artemis Hospital, Gurugram - 122 018, Haryana, ****Consultant Physician, Department of Medicine, Nawal Kishore Hospital, Agra - 283 204, Uttar Pradesh.*

Corresponding Author: Dr Rahul Garg, Professor, Department of Medicine, FH Medical College and Hospital, Agra - 283 204, Uttar Pradesh. Tel: 9012114542, E-mail: gargrahul27@gmail.com

functions[7]. GLP-1R is expressed in submucosal glands of the trachea, pulmonary artery smooth muscle, alveolar type II (ATII) cells, alveolar macrophages, and eosinophils[8,9]. Receptor activation in ATII cells stimulates surfactant protein expression and phosphatidylcholine secretion[10], while in airway smooth muscle cells, GLP-1R expression is reduced in COPD and its overexpression suppresses proliferation, migration, and pro-inflammatory cytokine release via an ABCA1-mediated pathway[11]. Eosinophils from asthmatic patients also express GLP-1R, with agonism attenuating activation markers and reducing IL-4, IL-8, and IL-13 production[8] (Fig. 1).

Mechanistical GLP-1R activation triggers cAMP/PKA signaling that suppresses NF-κB activation, reduces NLRP3 inflammasome assembly, and downregulates TGF-β1 signaling relevant to fibrosis[12]. Via ERK1/2 pathways, this reduces pro-inflammatory cytokines (TNF-α, IL-6, IL-1β, IL-17, IFN-γ) while increasing IL10; in the airway epithelium, it reduces IL-33 and TSLP, suppressing ILC2, Th2 cells, and eosinophil-derived IL-4, IL-5, and IL-13, while decreasing mucus secretion[13]. eNOS augmentation contributes to vasodilatory and anti-proliferative pulmonary vascular effects (Fig. 1). Beyond these direct actions, GLP-1 RA-induced weight loss reverses obesity-related mechanical lung compromise - diaphragmatic restriction and reduced functional residual and total lung capacity – while reducing adipose-derived pro-inflammatory mediators (leptin, IL-6, TNF-α), creating a systemic anti-inflammatory milieu that complements direct airway effects[14] (Fig. 2).

Evidence Overview: Meta-Analyses and Umbrella Reviews

A foundational meta-analysis by Yu *et al* (28 RCTs, 77,485 participants with T2DM, overweight, or obesity) found GLP-1 RA use associated with a 14% lower overall risk of respiratory disease (RR 0.86, 95% CI 0.81 - 0.93), with semaglutide, liraglutide, and dulaglutide each individually significant (RR 0.82 - 0.86), and significant reductions in pulmonary oedema and bronchitis[15]. A larger meta-analysis by See *et al* (55 RCTs, 99,870 participants through October 2024) found significant reductions in COPD (RR 0.82), sleep apnoea (RR 0.59), pulmonary oedema (RR 0.62), and pneumonia (RR 0.82) versus placebo, with greater benefit in the overweight/obese subgroup[16]. The umbrella review by Kong *et al* (123 meta-analyses, 5,617 articles) confirmed directional trends toward improved respiratory outcomes, including reduced pneumonia risk in high-cardiovascular-risk T2DM and reduced COVID-19 hospitalisation and mortality, while noting predominantly low GRADE evidence quality[4].

GLP-1 RAs and COPD

COPD is characterised by poorly reversible airway obstruction and chronic inflammation[17]; T2DM affects 15 - 30% of COPD patients, and metabolic syndrome components are

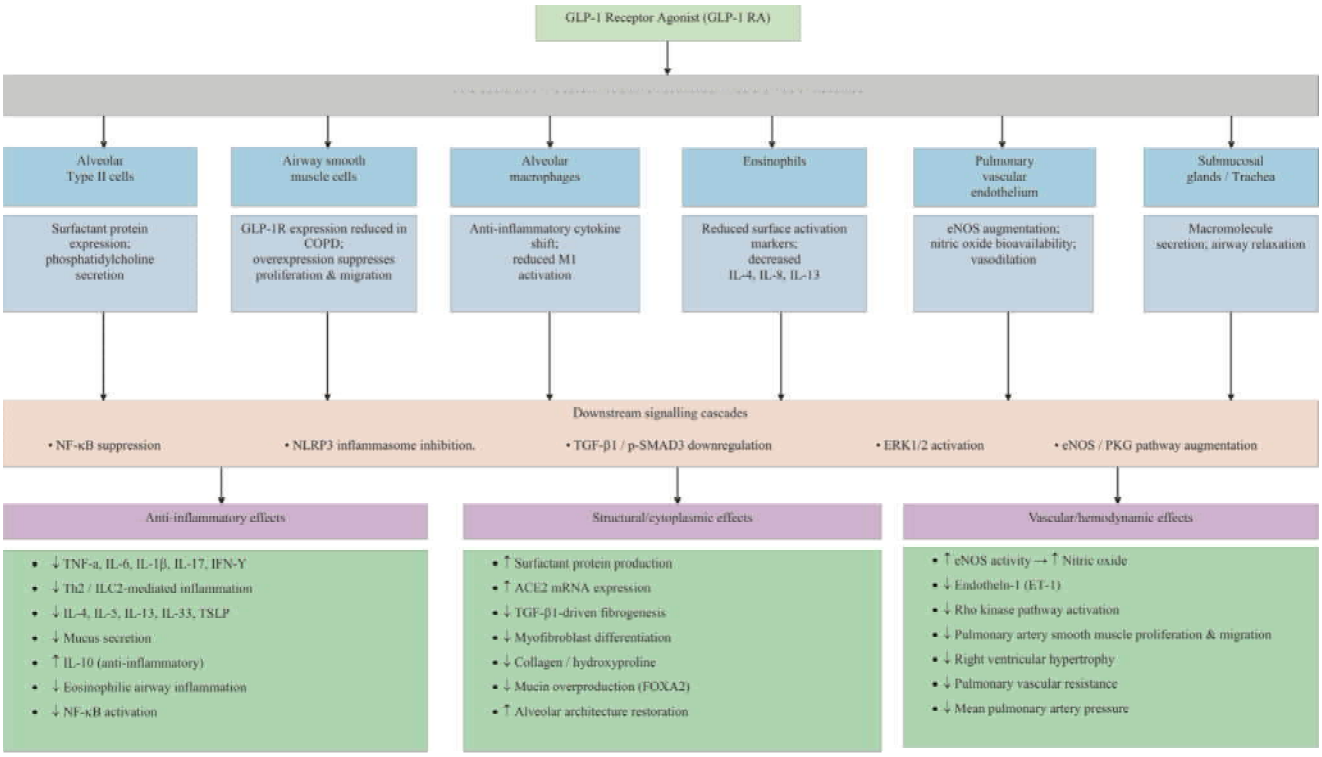

Fig. 1: *Pulmonary cell targets and downstream signalling mechanisms of GLP-1 receptor agonists.*

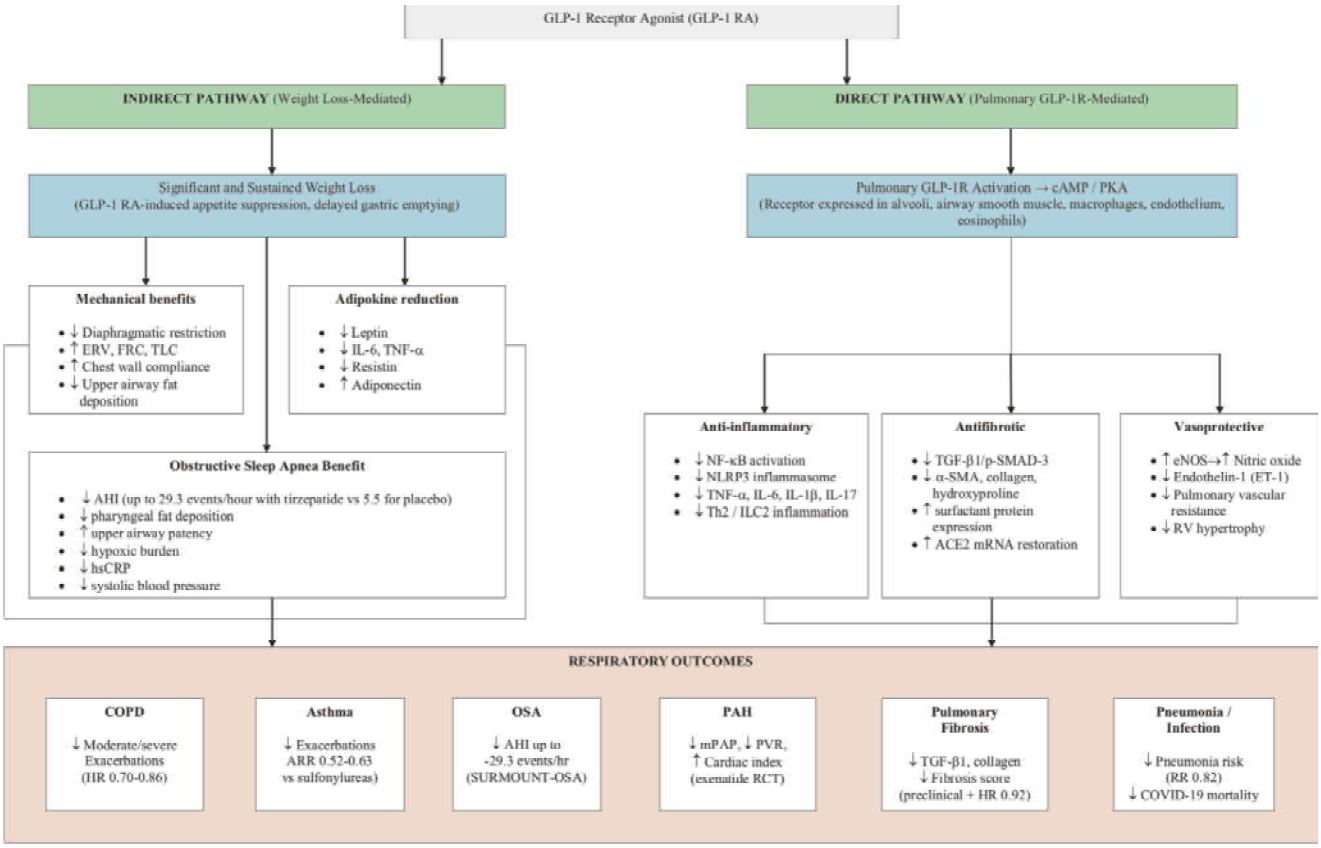

Fig. 2: *Direct and indirect pathways by which GLP-1 receptor agonists produce respiratory benefits.*

independent risk factors for small airway dysfunction, with disproportionately higher exacerbation and mortality rates in patients with both conditions[3]. Preclinically, exendin-4 reinstated FOXA2 expression and reduced mucin production and bacterial load in COPD mouse models[18], supporting a direct mucociliary mechanism of benefit.

Population-based evidence consistently links GLP-1 RA use with reduced COPD exacerbations. In the UK CPRD cohort, Pradhan *et al* reported a 30% reduction in severe exacerbations (HR 0.70, 95% CI 0.49 - 0.99) and 37% reduction in moderate exacerbations versus sulfonylureas[19]. Ray *et al*, across three US insurance databases (>32,000 matched pairs), found a 14% lower risk of moderate-to-severe exacerbations versus DPP-4 inhibitors (HR 0.86, 95% CI 0.81 - 0.91)[20]. A network meta-analysis by Pirera *et al* (nine observational studies) confirmed both GLP-1 RAs (RR 0.66) and SGLT-2 inhibitors (RR 0.64) were significantly superior to sulfonylureas for moderate-to-severe exacerbations[21], while a Mendelian randomisation study by Lai *et al* provided causal genetic evidence for lower risks of COPD (OR 0.838), early-onset COPD (OR 0.751), and asthma (OR 0.872), substantially reducing concerns about confounding by indication[22]. Proof-of-concept randomised data complement these findings: in a placebo-controlled trial of 40 patients with obesity and COPD, liraglutide significantly improved FVC, DLCO, and CAT scores over 40 weeks[23], and the LIRALUNG crossover trial similarly demonstrated improved FVC in T2DM patients[24].

GLP-1 RAs and Asthma

Obese patients with asthma represent a distinct low-Th2, neutrophilic, corticosteroid-resistant phenotype driven by adipokine dysregulation, which is directly relevant to GLP-1 RA therapy given its dual action on both adipokine and ILC2-mediated inflammatory pathways[25]. In obese asthma mouse models, GLP-1R agonism inhibits ILC2 activation and neutrophilic airway inflammation, reducing epithelial ICAM-1 and inflammatory chemokines (CCL11, CXCL1, CXCL5) and IL-33 expression[26]; tirzepatide produced greater IL-5/IL-13 reduction than semaglutide monotherapy, while semaglutide was superior for IL-33 suppression, reflecting differential receptor pharmacology[27].

Clinically, Lee *et al* (UK CPRD; self-controlled case series and cohort analyses) found GLP-1 RA add-on therapy associated with a 40% reduction in asthma exacerbations (IRR 0.60, 95% CI 0.49 - 0.73) independent of glycaemic and weight changes[28]. Wang *et al* (US MarketScan, n = 17,088) found an absolute risk reduction of 1.6% in acute

exacerbations versus sulfonylureas, rising to 2.8% in patients with frequent prior emergency visits[29], and Sheikh *et al*, in a propensity-matched analysis of 47,843 patients per group, found lower exacerbations and emergency visits at one year and significantly lower all-cause mortality at three years[30]. A Mendelian randomisation study confirmed a causal association between genetically proxied GLP-1R agonism and reduced asthma risk[22], and the ongoing GATA-3 trial at Vanderbilt University Medical Center is evaluating semaglutide in obesity-related symptomatic asthma without T2DM to disentangle weight-dependent from weight-independent effects[31].

GLP-1 RAs and Obstructive Sleep Apnoea

OSA is strongly linked to obesity-driven pharyngeal fat deposition and upper airway collapsibility, which in turn worsens metabolic dysfunction through intermittent hypoxia and systemic inflammation. GLP-1 RAs are positioned to interrupt this cycle through both weight-mediated mechanical improvement and direct pulmonary GLP-1R agonism. The landmark SURMOUNT-OSA trial evaluated tirzepatide in adults with moderate-to-severe OSA and obesity across two double-blind, placebo-controlled studies (PAP-naive and PAP-user populations), achieving AHI reductions of up to 62.8% (approximately 25 - 30 fewer events/hour), with 51.5% of PAP-naive participants meeting disease-resolution criteria and significant reductions in hsCRP, systolic blood pressure, and hypoxic burden[32]. A meta-analysis of four RCTs by Dandamudi *et al* confirmed a pooled AHI reduction of - 13.89 events/hour alongside significant weight loss and blood pressure reductions[33], consistent with earlier evidence from the SCALE Sleep Apnoea trial, in which liraglutide reduced AHI by - 12.2 events/hour versus - 6.1 with placebo in non-diabetic patients[34].

Beyond AHI improvement, Hwang *et al*, using 5-year TriNetX propensity-matched data in OSA patients with T2DM, found GLP-1 RAs reduced new-onset pulmonary hypertension (HR 0.724 versus DPP-4 inhibitors), intubation (HR 0.603), and new-onset COPD, extending benefit to prevention of downstream pulmonary complications[35].

GLP-1 RAs and Pulmonary Arterial Hypertension

PAH is characterised by pulmonary vascular remodeling, endothelial dysfunction, and smooth muscle proliferation. GLP-1R is expressed on pulmonary arterial smooth muscle and endothelial cells, and its activation promotes eNOS activity and nitric oxide bioavailability while suppressing endothelin-1 and Rho kinase signaling – targeting key drivers of pulmonary vascular disease. In the monocrotaline rat model, liraglutide both prevented and reversed PAH, right ventricular hypertrophy, and vascular remodeling, and inhibited smooth muscle cell migration and proliferation[36], providing proof-of-concept preclinical mechanism.

Clinically, intravenous exenatide in 17 patients with idiopathic PAH and CTEPH undergoing right heart catheterisation was well tolerated and reduced mean pulmonary artery pressure (45 ± 15 to 40 ± 18 mmHg), improved cardiac index, and reduced pulmonary vascular resistance – the first direct human haemodynamic data confirming GLP-1 RA activity in the PAH vasculature and establishing proof-of-concept for dedicated trials[37]. Indirect evidence also supports cardiopulmonary benefit: among OSA patients with T2DM, GLP-1 RAs were associated with lower pulmonary hypertension risk than other antihyperglycaemic classes[35], and in heart failure with preserved ejection fraction – the most prevalent cause of group 2 pulmonary hypertension - semaglutide reduced cardiovascular death or worsening heart failure (HR 0.69, 95% CI 0.53 - 0.89)[38], with tirzepatide reducing the same composite by 38% in the SUMMIT trial[39].

GLP-1 RAs and Pulmonary Fibrosis

Idiopathic pulmonary fibrosis is driven by aberrant TGF-β1 signaling, NLRP3 inflammasome activation, and excessive myofibroblast differentiation, mechanisms directly targeted by GLP-1R-mediated TGF-β1-p-SMAD3 supperssion and reduced extracellular atrix deposition. In the bleomycin mouse model, liraglutide decreased collagen and hydroxyproline expression, restored ACE2 mRNA, increased surfactant protein production, and partially restored alveolar architecture at both pro-inflammatory and established-fibrosis phases[40]. A targeted pulmonary delivery system using gelation-coated chitosan microparticles significantly attenuated bleomycin-induced fibrosis with reductions in TGF-β1, p-SMAD3, and collagen, positioning inhaled GLP-1 RA delivery as a compelling translational concept[41]. Clinically, a TriNetX-based study of 158,224 matched pairs by Ho *et al* found GLP-1 RA use associated with 8% lower pulmonary fibrosis risk (HR 0.92, 95% CI 0.87 - 0.98) versus DPP-4 inhibitors[42]; while no dedicated prospective IPF trials yet exist, this observational signal in a large cohort warrants further investigation.

GLP-1 RAs and Pneumonia, Infection, and Acute Lung Injury

People with diabetes face two-to-four-fold higher infection hospitalisation risk, a vulnerability starkly evident during COVID-19. Preclinically, GLP-1 RAs demonstrate protective effects in infectious and non-infectious lung inflammation: in pneumonia-induced sepsis models, liraglutide reduced TNF-α and IL-6, promoted surfactant protein secretion, and improved survival[43]. Clinically, the See *et al* meta-analysis found an 18% lower pneumonia risk versus placebo (RR 0.82)[16], and

Song *et al*, in a network meta-analysis, found GLP-1 RAs associated with a 27% reduction in COVID-19 mortality and 16% lower severe disease risk compared with insulin, with benefit most pronounced in non-elderly patients[44] - findings corroborated by the Kong *et al* umbrella review[4]. Using DPP-4 inhibitors as comparator, Ho *et al* found a more conservative but still significant 6% lower risk of respiratory infections (HR 0.94, 95% CI 0.92 - 0.96), an estimate less susceptible to confounding by disease severity[42].

An important counterpoint nuances this picture: circulating endogenous GLP-1 rises during acute critical illness and correlates with worse outcomes. Hansell *et al*, studying 297 critically ill patients with acute respiratory failure, found higher endogenous GLP-1 levels in non-survivors and patients with ARDS, independently associated with 90-day mortality (OR 2.02, 95% CI 1.23 - 3.31)[45]. This likely reflects a physiological stress-response marker rather than a causal harmful mechanism, since pharmacological GLP-1 RA therapy acts through sustained receptor agonism distinct from the endogenous surge of critical illness – but it signals the need for caution in interpreting GLP-1 biology in acute critical illness.

GLP-1 RAs and Lung Cancer

Diabetes and prediabetes are linked to increased lung cancer risk, and GLP-1 RAs may favourably modify this association. In an analysis of over one million electronic health records spanning 15 years, Tabernacki *et al* found GLP-1 RAs carried the lowest lung cancer risk among non-insulin antidiabetic drugs compared with insulin (RR 0.49, 95% CI 0.41 - 0.59), independent of histological type, sex, race, or smoking status[46]. This estimate is notably larger than the 14% reduction observed by Ho *et al* using DPP-4 inhibitors as comparator[42] – a divergence likely explained by greater confounding by indication when insulin, typically reflecting more advanced diabetes, is used as the reference group.

Agent-specific evidence across these disease areas is summarised in Table I, and key clinical studies in Table II.

Table I: Respiratory evidence profile of individual GLP-1 receptor agonists.

Agent	Respiratory Evidence	Highest Level of Evidence	Key Effect Size(s)	Notable Respiratory Safety Signal
Semaglutide	Overall respiratory disease risk reduction; antifibrotic preclinical (targeted pulmonary delivery); HFpEF/ group 2 PH (pooled RCT analysis)	Meta-analysis of RCTs; preclinical	18% reduction in overall respiratory disease risk (RR 0.82, Yu *et al*)[15]; HFpEF: HR 0.69 (95% CI 0.53 - 0.89)[38]	FAERS signal for asthma-like events and deaths; not corroborated by cohort studies or meta-analyses[48]
Liraglutide	Broadest respiratory evidence base of any individual agent: COPD exacerbations (observational + RCT), asthma exacerbations (observational), OSA-AHI reduction (RCT), pulmonary fibrosis (preclinical), PAH (preclinical)	RCTs (SCALE Sleep Apnoea; Altintas *et al*); observational cohorts; preclinical	OSA AHI: - 12.2 events/hour vs placebo[34]; COPD severe exacerbations: HR 0.70 (0.49 - 0.99)[19]; asthma exacerbations: IRR 0.60 (0.49 0.73), add-on to metformin[28]	FAERS signal for asthma-like events; aspiration risk related to delayed gastric emptying in perioperative setting[48]
Dulaglutide	Overall respiratory disease risk reduction only	Meta-analysis of RCTs (Yu *et al*)	18% reduction in overall respiratory disease risk (RR 0.82)[15]	No specific respiratory pharmacovigilance signal identified in reviewed literature
Tirzepatide (GLP-1/GIP dual agonist)	OSA: largest AHI reduction of any agent in RCT data; obese asthma preclinical (greater IL-5/IL-13 reduction than semaglutide monotherapy); HFpEF/ group 2 PH (SUMMIT RCT)	RCTs (SURMOUNT-OSA; SUMMIT); preclinical	OSA AHI: up to - 29.3 events/hour vs - 5.5 for placebo; 51.5% PAP-naive patients met OSA resolution criteria[32]; SUMMIT: 38% relative risk reduction in cardiovascular death or worsening heart failure[39]	Fewer respiratory/asthma-like events in FAERS compared to exenatide and liraglutide; GIP receptor co-agonism may confer additional anti-inflammatory benefit
Exenatide	PAH: only agent with direct human haemodynamic data (acute IV study, N=17); COPD preclinical (FOXA2/mucin pathway)	Proof-of-concept acute haemodynamic study; preclinical; meta-analysis (non-significant for overall respiratory disease)	Acute IV in PAH/CTEPH: mPAP 45 ± 15 to 40 ± 18 mmHg; PVR 7.8 ± 8.0 to 5.9 ± 5.0 WU; cardiac index 2.1 ± 0.6 to 2.4 ± 0.9 L/min/m^2 [37]	Highest proportion of asthma-related deaths in FAERS among GLP-1 RAs[48]; higher immunogenicity attributed to lower structural homology to human GLP-1 (53%)[49]

Table II: Key clinical studies on GLP-1 receptor agonists and respiratory outcomes.

Study (Author, Year)	Design	Population	Comparator	Primary Respiratory Outcome	Key Result	Limitations
Yu *et al*, 2023[15]	Meta-analysis, 28 RCTs	T2DM/overweight/ obesity; N = 77,485	Placebo/active control	Overall respiratory disease risk	RR 0.86 (0.81 - 0.93); bronchitis pulmonary oedema RR 0.66; RR 0.86	Outcomes were adverse-event reports, not primary endpoints

See *et al*, 2025[16]	Meta-analysis, 55 RCTs	T2DM/overweight/ obesity; N = 99,870	Placebo	COPD, OSA, pulmonary oedema, pneumonia	COPD RR 0.82; OSA RR 0.59; pneumonia RR 0.82	No prespecified respiratory endpoints; safety-data derived
Kong *et al*, 2026[4]	Umbrella review, 123 meta-analyses	Multiple disease contexts (T2DM, COVID-19)	Placebo/active comparators	Respiratory outcomes across disease areas	Reduced pneumonia risk in high-CV-risk T2DM; reduced COVID-19 hospitalisation/mortality	Predominantly low GRADE evidence; methodological shortcomings in source meta-analyses
Pradhan *et al*, 2022[19]	Population-based cohort (UK CPRD); N = 56,243	COPD + T2DM	Sulfonylureas	Severe/moderate COPD exacerbations	Severe HR 0.70 (0.49 - 0.99); moderate HR 0.63 (0.43 - 0.94)	Retrospective; no spirometry; residual confounding
Ray *et al*, 2025[20]	Comparative effectiveness, 3 US databases; N >32,000 pairs	COPD + T2DM	DPP-4i, SGLT-2i	Moderate-to-severe vs COPD exacerbations	DPP-4i HR 0.86 (0.81 - 0.91); vs SGLT-2i HR 0.94	Retrospective; claims-based; median follow-up 142 days
Altintas *et al*, 2022/ Lopez-Cano *et al*, 2022 (RCTs)[23,24]	Two placebo-controlled RCTs; N = 40 and crossover design	Obesity/T2DM + COPD	Placebo	FVC, DLCO, CAT score	Liraglutide significantly improved FVC in both trials; DLCO and CAT score also improved	Small samples; short follow-up; FEV1 and 6MWD unchanged
Lee *et al*, 2025[28]	UK CPRD; SCCS and cohort analysis; n = 4,278/8,424	Asthma + T2DM	Metformin baseline	Asthma exacerbations	IRR 0.60 (0.49 - 0.73); independent of glycaemic/ weight change	Retrospective; SCCS design limits generalisability
Sheikh *et al*, 2025[30]	Propensity-matched cohort, US TriNetX; N = 47,843/group	Obese asthma ± T2DM	Non-GLP-1 RA users	Exacerbations, ED visits, mortality	1-year exacerbations 7.3% vs 8.0%; 3-year mortality 3.1% vs 4.2%	Retrospective; conference abstract; limited methodological detail
Malhotra *et al*, 2024 SURMOUNT -OSA (RCT)[32]	Two parallel double-blind RCTs (PAP-naive/PAP users)	Moderate-to-severe OSA + obesity	Placebo	AHI reduction	Up to -29.3 events/hour vs -5.5 placebo; 51.5% met resolution criteria	52-week duration; long-term durability not established
Samaranayake *et al*, 2026[37]	Prospective acute haemo-dynamic study; N = 17	Idiopathic PAH/CTEPH, right heart catheterisation	Within-patient (IV exenatide)	mPAP, cardiac index, PVR	mPAP 45 ± 15 to 40 ± 18 mmHg; PVR 7.8 ± 8.0 to 5.9 ± 5.0 WU	Small sample; acute single-dose only; no chronic outcome data
Ho *et al*, 2025[42]	Retrospective cohort, US TriNetX; N = 158,224 pairs	T2DM	DPP-4 inhibitors	Pulmonary fibrosis, lung cancer, infections	Fibrosis HR 0.92; cancer HR 0.86; infections HR 0.94	Retrospective; no spirometry
Hansell *et al*, 2025[45]	Retrospective cohort, UPMC ICUs; N = 297	Critically ill adults, acute respiratory failure	Comparison across severity subgroups	90-day mortality vs endogenous GLP-1	Higher endogenous GLP-1 linked to non-survival/ ARDS; OR 2.02 (1.23 - 3.31)	Endogenous GLP-1 measured, not pharmacological use; does not contradict therapeutic benefit
Tabernacki *et al*, 2024[46]	Nationwide retrospective cohort, >1,000,000 EHRs; 15-year follow-up	T2DM	Insulin and other antidiabetic drugs	Lung cancer risk	Lowest risk among non-insulin agents: RR 0.49 (0.41 - 0.59) vs insulin	No dosage/duration data; confounding by indication possible

Safety Considerations Relevant to Pulmonologists

Delayed gastric emptying with GLP-1 RAs increases aspiration risk (1 in 3,000 - 4,000 procedures) during bronchoscopy or other sedated airway procedures, and anesthesiology societies recommend withholding GLP-1 RAs before elective procedures[47]. FAERS analysis identified increased asthma and asthma-like event reporting with semaglutide, liraglutide, and particularly exenatide, including deaths, though such spontaneous-reporting signals carry inherent limitations (reporting bias, no denominator data) and have not been corroborated by major population-based cohort and meta-analytic studies of exacerbation endpoints[48]. The higher immunogenicity of exenatide – which shares only 53% structural homology with human GLP-1 – may partly explain this differential signal across agents[49]. Excessive lean mass loss is a recognised concern, particularly relevant in cachectic or sarcopenic COPD patients, who warrant caution and monitoring; newer combination regimens with resistance exercise preserve lean mass more effectively[50].

The Observational Evidence Gap: Caveats And Limitations

Most clinical respiratory evidence for GLP-1 RAs derives from retrospective observational studies, with confounding by indication a pervasive concern – patients prescribed GLP-1 RAs often differ systematically from comparator-agent recipients in age, disease severity, and comorbidity burden. Unmeasured confounders (smoking status, FEV1, blood

eosinophil counts) are frequently unavailable in claims-based datasets, and heterogeneous exacerbation definitions and variable follow-up introduce further uncertainty; generalizability may also be limited by the predominance of data from high-income, insured populations. Large cardiovascular outcome RCTs have generally shown neutral respiratory effects, but this more likely reflects the absence of prespecified pulmonary endpoints and limited event capture than true biological absence of effect – making the contrast with consistent observational benefit a probable methodological artifact rather than a biological paradox.

Future Directions

Dedicated RCTs powered for respiratory exacerbation endpoints are the most immediate priority. The GATA-3 trial in obesity-related asthma and a completed liraglutide COPD trial incorporating spirometry, imaging, and exercise capacity are first steps toward this goal, and tirzepatide trials in group 3 pulmonary hypertension represent a tractable next design given the high obesity prevalence in this population. Head-to-head comparisons between agents are warranted to determine whether differences in receptor affinity or pharmacokinetics translate into differential respiratory benefit, and real-world IPF registries measuring FVC decline represent a feasible, low-cost evidence source. Inhaled pulmonary delivery systems bypassing systemic exposure remain a compelling translational concept. Biomarker-driven patient selection - using fractional exhaled nitric oxide, blood eosinophil counts, and leptin-to-adiponectin ratio - will ultimately help determine which patients derive the greatest pulmonary benefit, while mechanistic substudies disentangling direct pulmonary effects from weight-loss-mediated effects remain necessary.

Conclusion

GLP-1 receptor agonists have evolved from cardiometabolic agents into a drug class with meaningful respiratory relevance. Their widespread pulmonary expression underpins direct anti-inflammatory, anti-fibrotic, and vasoprotective effects that complement the established benefits of weight reduction. Genetic, mechanistic, and clinical evidence consistently supports benefit in obstructive sleep apnoea, asthma, COPD, pulmonary arterial hypertension, and potentially pulmonary fibrosis. Dedicated randomised trials powered for respiratory endpoints are now an urgent priority. In patients with active obstructive airway disease and obesity or frequent exacerbations, current evidence supports preferring GLP-1 RAs or SGLT-2 inhibitors over sulfonylureas or DPP-4 inhibitors, while prospective data continue to mature.

References

1. GBD Chronic Respiratory Disease Collaborators. Prevalence and attributable health burden of chronic respiratory diseases, 1990 - 2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Respir Med* 2020; 8 (6): 585-96.
2. de Oca MM, Perez-Padilla R, Celli B *et al*. The global burden of COPD: epidemiology and effect of prevention strategies. *Lancet Respir Med* 2025; 13 (8): 709-24.
3. Anghel L, Ciubara A, Patra D *et al*. Chronic obstructive pulmonary disease and type 2 diabetes mellitus: complex interactions and clinical implications. *J Clin Med* 2025; 14 (6): 1809.
4. Kong F, Zhao Y, Zhang W *et al*. Comprehensive evaluation of GLP-1 receptor agonists: an umbrella review of clinical outcomes across multiple diseases. *Nat Commun* 2026; 17: 972.
5. Müller TD, Finan B, Bloom SR *et al*. Glucagon-like peptide 1 (GLP-1). *Mol Metab*. 2019; 30: 72-130.
6. Körner M, Stöckli M, Waser B *et al*. GLP-1 receptor expression in human tumours and human normal tissues: potential for *in vivo* targeting. *J Nucl Med* 2007; 48 (5): 736-43.
7. Mendivil CO, Koziel H, Brain JD. Metabolic hormones, apolipoproteins, adipokines, and cytokines in the alveolar lining fluid of healthy adults: compartmentalisation and physiological correlates. *PLoS One* 2015; 10 (4): e0123344.
8. Mitchell PD, Salter BM, Oliveria JP *et al*. Glucagon-like peptide-1 receptor expression on human eosinophils and its regulation of eosinophil activation. *Clin Exp Allergy* 2017; 47: 331-8.
9. Richter G, Feddersen O, Wagner U *et al*. GLP-1 stimulates secretion of macromolecules from airways and relaxes pulmonary artery. *Am J Physiol* 1993; 265: L374-L381.
10. Benito E, Blazquez E, Bosch MA. Glucagon-like peptide-1-(7-36) amide increases pulmonary surfactant secretion through a cyclic adenosine 3',5'-monophosphate-dependent protein kinase mechanism in rat type II pneumocytes. *Endocrinolo* 1998; 139 (5): 2363-8.
11. Sun YH, He L, Yan MY *et al*. Overexpression of GLP-1 receptors suppresses proliferation and cytokine release by airway smooth muscle cells of patients with chronic obstructive pulmonary disease via activation of ABCA1. *Mol Med Rep* 2017; 16 (1): 929-36.
12. Liu C, Zhang Q, Zhou H *et al*. GLP-1R activation attenuates the progression of pulmonary fibrosis via disrupting NLRP3 inflammasome/PFKFB3-driven glycolysis interaction and histone lactylation. *J Transl Med* 2024; 22 (1): 954.
13. Nguyen DV, Linderholm A, Haczku A *et al*. Glucagon-like peptide 1: a potential anti-inflammatory pathway in obesity-related asthma. *Pharmacol Ther* 2017; 180: 139-43.
14. Mafort TT, Rufino R, Costa CH *et al*. Obesity: systemic and pulmonary complications, biochemical abnormalities, and impairment of lung function. *Multidiscip Respir Med* 2016; 11: 28.
15. Yu M, Wang R, Pei L *et al*. The relationship between the use of GLP-1 receptor agonists and the incidence of respiratory illness: a meta-analysis of randomised controlled trials. *Diabetol Metab Syndr*. 2023; 15 (1): 164.
16. See XY, Wang TH, Xanthavanij N *et al*. Glucagon-like peptide-1 receptor agonists and respiratory diseases: a systematic review and meta-analysis. *Am J Respir Crit Care Med* 2025; 211 (Suppl 1): A6561.
17. Global Initiative for Chronic Obstructive Lung Disease (GOLD).

Global strategy for prevention, diagnosis and management of COPD: 2026 report [Internet]. [cited 2026 Mar 26]. Available from: https://goldcopd.org/2026-gold-report-and-pocket-guide/

18. Choi W, Choe S, Lin J *et al*. Exendin-4 restores airway mucus homeostasis through the GLP1R-PKA-PPARgamma-FOXA2-phosphatase signaling. *Mucosal Immunol* 2020; 13: 637-51.
19. Pradhan R, Lu S, Yin H *et al*. Novel antihyperglycaemic drugs and prevention of chronic obstructive pulmonary disease exacerbations among patients with type 2 diabetes: population based cohort study. *BMJ* 2022; 379: e071380.
20. Ray A, Paik JM, Wexler DJ *et al*. Glucose-lowering medications and risk of chronic obstructive pulmonary disease exacerbations in patients with type 2 diabetes. *JAMA Intern Med* 2025; 185 (4): 399-410.
21. Pirera E, Di Raimondo D, D'Anna L *et al*. Efficacy of SGLT2 inhibitors, GLP-1 receptor agonists, DPP-4 inhibitors, and sulfonylureas on moderate-to-severe COPD exacerbations among patients with type 2 diabetes: a systematic review and network meta-analysis. *Pharmaceuticals* 2025; 18 (9): 1337.
22. Lai S, Feng Y, Li L *et al*. Association of GLP1RAs with risk of chronic obstructive pulmonary disease: evidence from drug target Mendelian randomisation. *Diabetol Metab Syndr* 2025; 17: 295.
23. Altintas DA, Hilberg O, Hess S *et al*. Respiratory effects of treatment with a glucagon-like peptide-1 receptor agonist in patients suffering from obesity and chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2022; 17: 405-14.
24. Lopez-Cano C, Ciudin A, Sanchez E *et al*. Liraglutide improves forced vital capacity in individuals with type 2 diabetes: data from the randomised crossover LIRALUNG study. *Diabetes* 2022; 71: 315-20.
25. Garg R. Breaking the steroid barrier: emerging biomarkers and targeted therapies for type 2-low asthma. *Ann Natl Acad Med Sci (India)* 2025; 61: 329-41.
26. Toki S, Newcomb DC, Printz RL *et al*. GLP-1R agonist inhibits aeroallergen-induced activation of ILC2 and neutrophilic airway inflammation in obese mice. *Allergy* 2021; 76 (11): 3433-45.
27. Toki S, Zhang J, Printz RL *et al*. Dual GIPR and GLP-1R agonist tirzepatide inhibits aeroallergen-induced allergic airway inflammation in mouse model of obese asthma. *Clin Exp Allergy* 2023; 53: 216-21.
28. Lee B, Man KK, Wong E *et al*. Antidiabetic medication and asthma attacks. *JAMA Intern Med* 2025; 185 (1): 16-25.
29. Wang T, Keil AP, Buse JB *et al*. Glucagon-like peptide 1 receptor agonists and asthma exacerbations: which patients benefit most? *Ann Am Thorac Soc* 2024; 21 (11): 1496-1506.
30. Sheikh AB, Zafar P, Niranjan S *et al*. Effect of GLP-1 agonists on clinical outcomes in obese and diabetic patients with asthma: a propensity matched analysis. *Chest* 2025; 168 (4): A17-A18.
31. Cahill KN. Glucagon-like peptide-1 receptor agonist in the treatment of adult, obesity-related, symptomatic asthma (GATA-3). ClinicalTrials.gov Identifier: NCT05254314 [Internet]. Available from: https://clinicaltrials.gov/study/NCT05254314 [Accessed: 1 Jun 2026]
32. Malhotra A, Grunstein RR, Fietze I *et al*. Tirzepatide for the treatment of obstructive sleep apnoea and obesity. *N Engl J Med* 2024; 391: 1193-205.
33. Dandamudi M, Lucena L, Gamarra-Valverde NN *et al*. Efficacy of GLP-1 receptor agonists in treating obstructive sleep apnoea: a systematic review and meta-analysis of cardiometabolic and respiratory outcomes. *Sleep Breath* 2026; 30: 138.
34. Blackman A, Foster GD, Zammit G *et al*. Effect of liraglutide 3.0 mg in individuals with obesity and moderate or severe obstructive sleep apnoea: the SCALE Sleep Apnoea randomised clinical trial. *Int J Obes* 2016; 40: 1310-9.
35. Hwang S, Borissov M, So J. GLP-1 receptor agonists and risk of pulmonary complications in patients with obstructive sleep apnoea and type 2 diabetes mellitus. *Chest* 2025; 168: A7052.
36. Lee MY, Tsai KB, Hsu JH *et al*. Liraglutide prevents and reverses monocrotaline-induced pulmonary arterial hypertension by suppressing ET-1 and enhancing eNOS/sGC/PKG pathways. *Sci Rep* 2016; 6: 31788.
37. Samaranayake CB, Niglas M, Baxan N *et al*. Haemodynamic and metabolomic responses to infusion of GLP-1 agonist exenatide in pulmonary arterial hypertension. *JCI Insight* 2026; 11 (10): e202660.
38. Kosiborod MN, Deanfield J, Pratley R *et al*. Semaglutide *versus* placebo in patients with heart failure and mildly reduced or preserved ejection fraction: a pooled analysis of the SELECT, FLOW, STEP-HFpEF, and STEP-HFpEF DM randomised trials. *Lancet* 2024; 404: 949-61.
39. Packer M, Zile MR, Kramer CM *et al*. Tirzepatide for heart failure with preserved ejection fraction and obesity. *N Engl J Med* 2025; 392 (5): 427-37.
40. Fandiño J, Toba L, González-Matías LC *et al*. GLP-1 receptor agonist ameliorates experimental lung fibrosis. *Sci Rep* 2020; 10 (1): 18091.
41. Hamad RS, Kira AY, Saber S *et al*. Dual-sensitive gelatin-coated chitosan microparticles for targeted semaglutide pulmonary delivery: a novel approach to enhancing anti-inflammatory and anti-fibrotic effects. *Int Immunopharmacol* 2025; 165: 115480.
42. Ho LT, Fang YW, Hsu PS *et al*. Association between glucagon-like peptide-1 receptor agonist therapy and respiratory illness in patients with type 2 diabetes: a retrospective observational cohort study. *Sci Rep* 2025; 15: 35625.
43. Guo J, Chen X, Wang C *et al*. Liraglutide alleviates acute lung injury and mortality in pneumonia-induced sepsis through regulating surfactant protein expression and secretion. *Shock* 2024; 61: 601-10.
44. Song ZH, Huang QM, Xu SS *et al*. The effect of antihyperglycaemic medications on COVID-19: a meta-analysis and systematic review from observational studies. *Ther Innov Regul Sci* 2024; 58: 773-87.
45. Hansell CE, Aneis HA, Kitsios GD *et al*. Glucagon-like peptide-1 is prognostic of mortality in acute respiratory failure. *Crit Care Explor* 2025; 7 (4): e1247.
46. Tabernacki T, Wang L, Kaelber DC *et al*. Non-insulin antidiabetic agents and lung cancer risk in drug-naive patients with type 2 diabetes mellitus: a nationwide retrospective cohort study. *Cancers* 2024; 16: 2377.
47. Warner MA, Meyerhoff KL, Warner ME *et al*. Pulmonary aspiration of gastric contents: a closed claims analysis. *Anesthesiology* 2021; 135: 284-91.
48. Cazzola M, Matera MG, Calzetta L *et al*. Can glucagon-like peptide-1 receptor agonists induce asthma? An analysis of the FAERS database. *J Asthma* 2024; 61 (12): 1638-45.
49. Yu M, Benjamin MM, Srinivasan S *et al*. Battle of GLP-1 delivery technologies. *Adv Drug Deliv Rev* 2018; 130: 113-30.
50. Pantazopoulos D, Gouveri E, Papazoglou D *et al*. GLP-1 receptor agonists and sarcopenia: weight loss at a cost? A brief narrative review. *Diabetes Res Clin Pract* 2025; 229: 112924.