

Effect of SGLT-2 inhibitors on COPD exacerbations in individuals with type 2 diabetes: A meta-analysis and Bayesian sensitivity analysis

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Keywords

COPD exacerbations, SGLT-2 inhibitors, Type 2 diabetes mellitus

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ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) and Type 2 diabetes mellitus (T2DM) frequently coexist, amplifying morbidity, mortality, and healthcare costs. COPD exacerbations are more frequent and severe in T2DM patients, necessitating therapies addressing both conditions. This systematic review and meta-analysis evaluates the impact of sodium-glucose cotransporter-2 inhibitors (SGLT-2i) on COPD exacerbations in T2DM patients.

Methods: Following PRISMA guidelines, we searched PubMed, Embase, and Web of Science until March 2025 for studies assessing SGLT-2i effects on COPD exacerbations in T2DM. Eligible studies included adults with T2DM-COPD overlap, reporting exacerbation outcomes. A random-effects meta-analysis and Bayesian hierarchical models were employed, with sensitivity and subgroup analyses.

Results: Seven studies (449,530 participants) were included. SGLT-2i use reduced COPD exacerbation risk by 39% (pooled HR: 0.609, 95% CI: 0.431–0.858), with Bayesian analysis supporting a 31% reduction (HR: 0.64, 95% CrI: 0.40–0.88). Subgroup analyses showed superior efficacy vs DPP-4 inhibitors (HR: 0.618, 95% CI: 0.462–0.827) and sulfonylureas (HR: 0.620, 95% CI: 0.526–0.731), and modest benefit over GLP-1RAs (HR: 0.940, 95% CI: 0.890–0.992). Severe exacerbation reduction was non-significant (HR: 0.676, 95% CI: 0.340–1.344). Heterogeneity was high ($I^2 \geq 97.9\%$), but sensitivity analyses confirmed robustness.

Conclusions: SGLT-2 inhibitors significantly reduce COPD exacerbations in T2DM patients, offering dual cardiometabolic and respiratory benefits. Their superiority over other antidiabetic agents supports prioritization in high-risk T2DM-COPD populations. Further trials are needed to validate effects on severe exacerbations and elucidate mechanisms.

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INTRODUCTION

The global burden of chronic diseases is increasing, with Type 2 diabetes mellitus (T2DM) and chronic obstructive pulmonary disease (COPD) being two of the most widespread and severe conditions^{1–3}. T2DM, defined by insulin resistance and elevated blood sugar, affects more than 537 million adults globally, with forecasts predicting an increase to 783 million by 2045^{4,5}. Likewise, COPD, a progressive lung condition mainly triggered by prolonged exposure to harmful substances like smoke or pollutants, impacts 384 million people worldwide and ranks as the third leading cause of death. The overlap between these two diseases is significant, with research indicating that 10% of T2DM patients also have COPD, while up to 27% of those with COPD have T2DM. This dual diagnosis results in heightened morbidity, mortality, and healthcare expenses, as patients face a 23% higher risk of death and more frequent hospitalizations compared to those with only one of these conditions, underscoring the need for combined treatment approaches^{6,7}.

COPD exacerbations, which are sudden worsenings of lung symptoms like shortness of breath, coughing, and sputum production, play a major role in declining lung function, reduced quality of life, and the bulk of COPD-related medical costs⁸. A severe exacerbation is identified when a patient requires hospitalization or an emergency visit with a primary diagnosis of COPD, using ICD-10 codes J41–J44 in the primary discharge slot. Such severe episodes can cost up to \$20,000 per event in high-income nations and are associated with worse long-term outcomes, including higher mortality rates⁹. Notably, individuals with both T2DM and COPD tend to experience more frequent and intense exacerbations. Studies show that T2DM raises the likelihood of moderate-to-severe COPD exacerbations by 2.5 times and increases the 30-day hospital readmission rate by 15%, highlighting the pressing need for treatments that address both conditions to lessen these compounded risks and alleviate healthcare burdens^{10,11}.

While SGLT-2 inhibitors have gained attention for their heart and kidney benefits, supported by extensive randomized trials and observational studies, their effects on lung health remain less explored¹². Additionally, some observational studies have found that SGLT-2 inhibitors are associated with a lower likelihood of pneumonia-related outcomes compared to DPP-4 inhibitors outcomes^{13,14}. However, the long-term impact of SGLT-2 inhibitors on chronic respiratory conditions like COPD or respiratory failure remains unclear.

This systematic review and meta-analysis is the first to thoroughly evaluate the effect of SGLT-2 inhibitors on the frequency and severity of COPD exacerbations in T2DM patients. By analyzing data from observational studies, this review aims to shed light on the potential advantages of SGLT-2 inhibitors, support better clinical decisions, and shape treatment strategies for patients with both T2DM and COPD. It also seeks to offer insights that can guide future research and clinical guidelines for managing these dual conditions, addressing gaps in the

current understanding of SGLT-2 inhibitors' role in enhancing respiratory outcomes for this group.

METHOD

Study design

This systematic review and meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Table S1). The main aim was to evaluate the impact of SGLT-2 inhibitors on COPD exacerbations in patients with type 2 diabetes mellitus by comprehensively reviewing and synthesizing the available evidence.

Data sources and search strategy

An extensive search was conducted across several electronic databases, including PubMed, Embase, and Web of Science, to locate relevant studies published from the inception of these databases up to March 9th, 2025. The search strategy combined controlled vocabulary terms such as MeSH with appropriate free-text keywords related to COPD, type 2 diabetes mellitus, and SGLT-2 inhibitors. The key terms and their synonyms included: ("chronic obstructive pulmonary disease" OR "COPD") AND ("type 2 diabetes mellitus" OR "T2DM") AND ("sodium-glucose cotransporter-2 inhibitor" OR "SGLT-2i"). Boolean operators (AND, OR) were used to connect and refine the search terms. No restrictions were applied regarding language or article type. The complete search strategy is detailed in Table S2.

Eligibility criteria

Specific eligibility criteria were set for this systematic review and meta-analysis to ensure the inclusion of pertinent and high-quality studies. Eligible studies had to: (1) involve adult participants (18 years or older) diagnosed with both COPD and type 2 diabetes mellitus; (2) investigate the effects of SGLT-2 inhibitors on COPD exacerbations in this population; (3) report quantitative outcomes related to exacerbation frequency or hospitalization rates; and (4) be published in English in peer-reviewed journals. Studies were excluded if they focused on pediatric populations, lacked control groups, did not provide adequate respiratory or metabolic data, or failed to specifically assess the impact of SGLT-2 inhibitors on COPD exacerbations. Additionally, case reports, conference abstracts, and review articles were not included in the analysis.

Screening

The study selection process was aided by semi-automated software (Nested-Knowledge, MN, USA), which streamlined the workflow by eliminating duplicate records and conducting initial screenings^{15–19}.

Data extraction and quality assessment

To ensure consistency and precision, two reviewers independently extracted data from the included studies using a

standardized extraction form. This process captured essential study details such as design, sample size, country, publication year, lead author, and relevant methodologies. Demographic data, including inclusion and exclusion criteria, age, and gender distribution, were also documented. Furthermore, statistical measures such as risk ratios (RRs), hazard ratios (HRs), odds ratios (ORs), incidence rate ratios (IRRs), excess rates (ERs), absolute risk reductions (ARRs), and their corresponding 95% confidence intervals (CIs) were collected, along with information on adjustments for potential confounders. Any discrepancies during data extraction were resolved through discussion between the reviewers, with a third reviewer consulted if consensus was not initially reached. The 'tagging' feature of the Nested-Knowledge software facilitated this data extraction process²⁰.

Additionally, the methodological quality of the included studies was independently assessed by two reviewers using the Newcastle-Ottawa Scale (NOS)^{21,22}. This evaluation emphasized participant selection, comparability of groups, and outcome measurement, particularly for observational studies. Any disagreements in quality assessment were settled through discussion to ensure a thorough and reliable review.

Data synthesis and statistical analysis

To address variability among studies, a random-effects meta-analysis was conducted. The primary outcome was the pooled hazard ratio (HR) for COPD exacerbations in patients with type 2 diabetes mellitus treated with SGLT-2 inhibitors. Due to expected clinical and methodological differences across studies, the random-effects model was chosen to provide a more conservative estimate of the treatment effect. Heterogeneity was evaluated using the I^2 statistic and Cochran's Q test, with I^2 values above 75% considered indicative of significant heterogeneity^{23,24}. Sensitivity analyses were carried out using a leave-one-out method to assess the stability of the results and to detect any individual studies that might disproportionately influence the findings²⁵. A P -value below 0.05 was deemed statistically significant^{26,27}.

We performed Bayesian models. We estimated the posterior probability of benefit ($HR < 1.00$) and harm ($HR > 1.00$) for with 95% credibility intervals (CrI). All analyses used in this Bayesian framework were conducted using "weakly informed priors," which assume minimal prior knowledge about the parameters of interest, allowing the data to predominantly drive the posterior estimates while still incorporating a modest degree of regularization to stabilize the model. A Bayesian hierarchical random-effects model was applied. Primary Bayesian analyses were conducted using a weakly informed prior for the overall effect size $\mu \sim N(0, 1)$ and a half-Cauchy prior for heterogeneity $\tau \sim HC(0, 0.5)$. Between-study heterogeneity was evaluated using τ . Distributions for each study, derived from the hierarchical model, were graphically presented based on model estimates. Posterior probabilities were estimated using Markov

Chain Monte Carlo (MCMC) sampling algorithms in R Statistics (Version 4.4; R Foundation for Statistical Computing, Vienna, Austria, <https://www.R-project.org/>), employing the "brms" package, with four chains and 10,000 saved iterations per chain. Posterior predictive checks were performed by simulating random draws from the posterior and comparing these replications to the observed data. Convergence of MCMC sampling was diagnosed based on trace plots and density plots. The results were presented as a joint posterior density plot of (effect parameter) and τ (heterogeneity parameter). All statistical analyses were conducted using R version 4.4.

RESULTS

Literature search

A total of 1,272 records were retrieved from several databases: PubMed (1,021 records), Web of Science (50 records), and Embase (201 records). After eliminating 126 duplicates, 1,146 records remained for screening. An initial screening of titles and abstracts led to the exclusion of 887 records that did not meet the eligibility criteria. Among the 259 full-text articles assessed, 252 were excluded for various reasons: 108 were review articles, 3 were editorials or opinion pieces, 73 lacked the relevant study population, and 68 did not examine the outcomes of interest. Consequently, seven^{28–34} studies were included in the final systematic review and meta-analysis. These studies, conducted in countries including the USA, Hong Kong, Taiwan, Australia, and the UK, utilized diverse methodologies such as retrospective cohort studies, population-based studies, and propensity score-matched cohort designs, all focusing on the effects of SGLT-2 inhibitors on COPD exacerbations in patients with type 2 diabetes mellitus (Figure 1).

Study characteristics

The final analysis included seven studies, encompassing a total of 449,530 participants (Table 1) from various countries, including the USA, Hong Kong, Taiwan, Australia, and the UK. The studies employed different designs, including one 1:1 propensity score-matched cohort study, one retrospective observational study, one population-based cohort study, two retrospective cohort studies, one longitudinal cohort study, and one retrospective clinical analysis. These diverse methodologies provided a comprehensive range of approaches to assess the impact of SGLT-2 inhibitors on COPD exacerbations in individuals with T2DM. COPD diagnosis was primarily based on clinical criteria and spirometry, while T2DM was confirmed in accordance with the guidelines set by the American Diabetes Association. The interventions studied included SGLT-2 inhibitors, compared with other glucose-lowering agents such as DPP-4 inhibitors, GLP-1 receptor agonists, and sulfonylureas. The follow-up periods across the studies ranged from 6 months to 1 year. A summary of the study findings is presented in Table 1, and the details of the quality assessment can be found in Table S3.

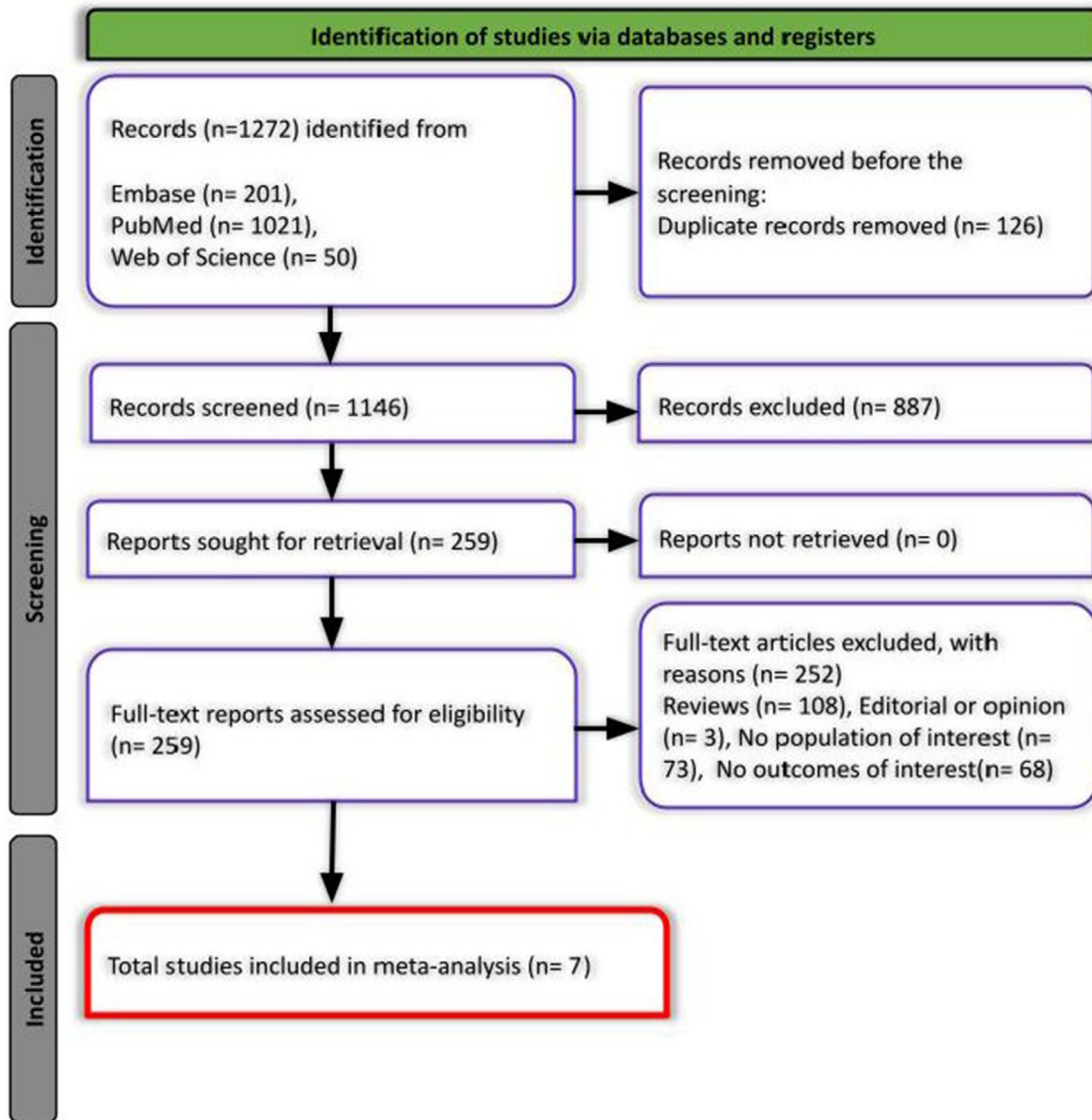


Figure 1 | PRISMA flowchart depicting article selection and screening process.

Impact of SGLT-2i on COPD exacerbations

The meta-analysis of seven studies demonstrated that the pooled hazard ratio (HR) for the association between SGLT-2 inhibitor use and the risk of COPD exacerbations was 0.609 (95% CI: 0.431–0.858). The analysis indicated substantial heterogeneity among the studies ($I^2 = 97.9\%$, $P < 0.0001$), highlighting considerable variability in the effect sizes. Individual hazard ratio (HR) estimates ranged from 0.250 (95% CI: 0.212–0.295) in Geetha (2024), which reported the most significant protective effect, to 0.940 (95% CI: 0.693–1.275) in Foer (2023), which showed the least effect. Despite the heterogeneity, the overall pooled estimate was statistically significant,

suggesting a potential benefit of SGLT-2 inhibitors in reducing COPD exacerbations among individuals with T2DM (Figure 2).

Under a weak informative prior, a Bayesian hierarchical meta-analytical model from seven studies assessing the association between SGLT-2i use and COPD exacerbations risk produced a pooled median HR of 0.64 (95% CrI, 0.40–0.88). This suggests a potential protective effect of SGLT-2i use, reducing COPD exacerbations risk by approximately 31%. Between-study heterogeneity was moderate (τ mean, 0.28; SD, 0.10), reflecting variability in effect sizes. The forest plot's density curves, centered below HR = 1 for most studies and the pooled estimate,

Table 1 | Study characteristics

Study	Country	Study design	Population Characteristics	Intervention	Comparator	Sample size (intervention)	Sample size (comparator)	Age (Intervention)	Age (Comparator)	Male (Q)	COPD exacerbation (Effect size)	Severe exacerbation (Effect size)	Follow-up	Adjusted variables
Ray (2025) ²⁸	USA	1:1 propensity score-matched cohort study	Patients with T2D and active COPD receiving glucose-lowering medications	SGLT2i	DPP-4i	27991	27991	Mean (SD) = 70.75 (8.62) years	Mean (SD) = 70.69 (8.79) years	50.85/0.5	HR (95% CI) = 0.81 (0.76–0.86)	HR (95% CI) = 0.71 (0.65–0.78)	Median = 145 (IQR61–355) days	Age, gender, exacerbations, GOLD E, pneumonia, asthma, PH, PE, ILD, LC, OSA, OCS, SABV, SAMVALAB/LAMA/ICS (mono/dual/triple therapy), recent events, CCS, FI, BMI, CHF, HTN, CAD, stroke, MI, AF, DR, DN, CKD, NAFLD, GERD, hypothyroidism, OP, cancer, anxiety, dementia, COVID-19
Foer, 2023 ²⁹	USA	Retrospective observational study	Patients with T2D and COPD initiating GLP-1RAs	SGLT2i	GLP-1RAs	353	328	Median (IQR) = 72.0 (64.9–78.4) years	Median (IQR) = 67.2 (60.8–73.7) years	77.15/7.6	HR (95% CI) = 0.94 (0.69–1.30)	HR (95% CI) = 1.28 (0.79–2.08)	6 months	Age, sex, race, Elixhauser Comorbidity Index, two-year health system encounter history, season of initiation, smoking history, concurrent metformin use, SABA, SAMA, LABA, LAMA triple therapy, baseline HbA1c and baseline BMI
Tan, 2024 ³⁰	Australia	Active comparator, new user based cohort study	Patients with COPD and type 2 diabetes	SGLT2i	DPP-4is	99569	186353	Median (SD) 75th percentile = 62.5 (54.2, 69.7) years	Median (SD) 75th percentile = 65.2 (55.5, 73.8) years	40.64/2.4	IRR (95% CI) = 0.52 (0.40–0.68) and ER = 0.22 (95% CI: –0.31 to –0.14)	NA	NA	Age, sex, calendar year, time since diabetes diagnosis, intensity of GLD therapy, insulin use, medication burden, and IRSD
Au, 2023 ³¹	Hong Kong	Retrospective population-based cohort study	Patients with T2D and comorbid OAD	SGLT2i	DPP-4is	381	1524	Mean (SD) = 62.2 (10.7) years	Mean (SD) = 62.3 (10.8) years	52.51	RR (95% CI) = 0.54 (0.36–0.83)	NA	Median (IQR): DPP4i = 23 (10–35) years and SGLT2i = 1.5 (0.5–3.0) years	Adjusted for a wide range of demographic, medication history, diagnosis history, biochemical parameters, clinical history, and comedication variables
Gupta, 2024 ³²	USA	Retrospective cohort analysis	Patients with diabetes and COPD on SGLT2i medications	SGLT2i	Non-SGLT2i	1295	17418	≥54 years = 90.8%	≥54 years = 91.6%	57.14/47.9	ARR (95% CI) = 15.10% (13.98–16.22%), and NNT (95% CI) = 66 (62–72)	1.2% vs 5.04%, $P < 0.05$	1 year	NA
Geetha, 2024 ³³	USA	Retrospective case–control study	Patients with established type 2 diabetes and COPD diagnosed	SGLT2i	Non-SGLT2i	20	74	Mean (SD) = 64.7 (8.2) years	Mean (SD) = 69.1 (9.4) years	30.33/8	HR (95% CI) = 0.25 (0.13–0.46)	HR (95% CI) = 0.18 (0.08–0.36)	1 year	Age, BMI, gender, COPD stage (GOLD), smoking status, HbA1c, Charlson Comorbidity Index

Table 1. (Continued)

Study	Country	Study design	Population Characteristics	Intervention	Comparator	Sample size (intervention)	Sample size (comparator)	Age (Intervention)	Age (Comparator)	Male (ICQ %)	COPD exacerbation (Effect size)	Severe exacerbation (Effect size)	Follow-up	Adjusted variables
Pradhan, 2022 ²⁴	UK	Population based cohort study using an active comparator, new user design	Patients with chronic obstructive pulmonary disease and type 2 diabetes	SGLT-2i	Sulfonylureas	2,956	10,841	Mean (SD) = 62.9 (90)	Mean (SD) = 62.7 (91)	58.558	HR (95% CI) = 0.62 (0.48–0.81)	HR (95% CI) = 1.02 (0.83–1.27)	Median (IQR) = 1.0 (0.4–2.3) year	Weighted using propensity score fine stratification

AF, atrial fibrillation; ARR, absolute risk reduction; BMI, body mass index; CAD, coronary artery disease; CCS, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; DN, diabetic nephropathy; DPP-4i, dipeptidyl peptidase-4 inhibitor; DR, diabetic retinopathy; ER, excess rate; FI, frailty index; GERD, gastroesophageal reflux disease; GLP-1RA, glucagon-like peptide-1 receptor agonist; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HR, hazard ratio; HTN, hypertension; ICS, inhaled corticosteroids; IQR, interquartile range; IRR, incidence rate ratio; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; MI, myocardial infarction; NAFLD, non-alcoholic fatty liver disease; NNT, number needed to treat; OCS, oral corticosteroids; OP, osteoporosis; RR, relative risk; SABA, short-acting beta agonist; SAMA, short-acting muscarinic antagonist; SD, standard deviation; SGLT-2i, sodium glucose transporter 2 inhibitor; T2D, type 2 diabetes.

support a likely benefit of SGLT-2i use, though the wide pooled CrI highlights uncertainty (Figure 3).

Impact of SGLT-2i on severe COPD exacerbations

The meta-analysis of five studies assessing the effect of SGLT-2 inhibitors on severe COPD exacerbations in patients with T2DM yielded a pooled hazard ratio (HR) of 0.676 (95% CI: 0.340–1.344). Although the direction of the pooled estimate suggests a potential reduction in risk, the result was not statistically significant. There was substantial heterogeneity among the included studies ($I^2 = 99.1\%$, $P < 0.0001$), indicating high variability across study outcomes. The individual HRs varied widely, with Geetha (2024) showing the strongest effect (HR: 0.180, 95% CI: 0.156–0.207), and Foer (2023) reporting the highest risk estimate (HR: 1.880, 95% CI: 0.672–2.440). The wide confidence interval of the pooled HR reflects uncertainty and underscores the need for further research to confirm the impact of SGLT-2 inhibitors on severe exacerbations (Figure 4).

Under a weak informative prior, a Bayesian hierarchical meta-analytical model from seven studies assessing the association between SGLT-2i use and severe COPD exacerbations risk produced a pooled median HR of 0.75 (95% CrI, 0.29–1.21). This wide CrI, which crosses 1.0, indicates substantial uncertainty in the estimate, meaning the result is not statistically significant. Between-study heterogeneity was moderate (τ mean, 0.46; SD, 0.22), reflecting variability in effect sizes (Figure 5).

Model convergence and posterior predictive check

In a posterior predictive check, data are generated through random draws from the posterior predictive distribution and compared with the observed data. The model has achieved convergence and effectively represents the data, as demonstrated by the densities of the simulated replications aligning closely with the density of the observed data. Trace plots and density plots of the MCMC sampling further confirm the successful convergence of the sampling process (Figures S1 and S2). Additionally, the Rhat values are observed to be 1.0, indicating robust convergence across all chains.

Subgroup analysis

The subgroup analysis based on the comparator against SGLT-2 inhibitors revealed the following pooled HR for COPD exacerbations (Figure 6):

SGLT-2i vs DPP-4 inhibitors

Three studies were included, yielding a pooled HR of 0.618 (95% CI: 0.462–0.827), with notable heterogeneity ($I^2 = 95.3\%$, $P < 0.0001$), suggesting a protective effect of SGLT-2 inhibitors compared to DPP-4 inhibitors.

SGLT-2i vs GLP-1 receptor agonists

The pooled HR from two studies was 0.940 (95% CI: 0.890–0.992), with no observed heterogeneity ($I^2 = 0\%$,

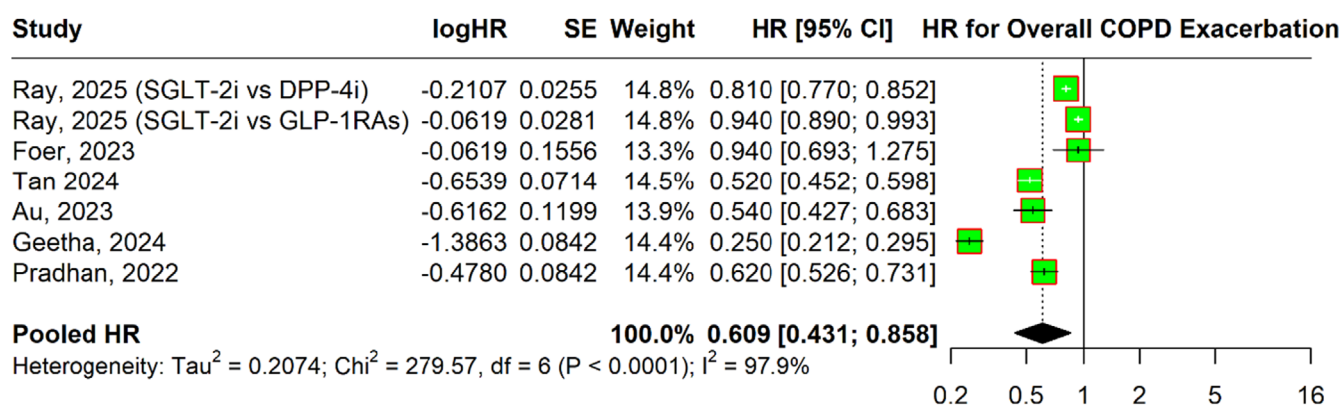


Figure 2 | Forest plot showing pooled HR for COPD exacerbation.

$P = 1.00$), indicating a modest but statistically significant reduction in risk.

SGLT-2i vs non-SGLT-2i (Geetha 2024)

A single study by Geetha (2024) reported a marked reduction in risk (HR: 0.250, 95% CI: 0.212–0.295).

SGLT-2i vs sulfonylureas (Pradhan 2022)

Reported a HR of 0.620 (95% CI: 0.526–0.731), suggesting a strong protective effect.

Sensitivity analysis

To evaluate the stability of the pooled HR for the relationship between SGLT-2 inhibitors and COPD exacerbations, a leave-one-out sensitivity analysis was conducted. The pooled HR estimates exhibited moderate variation, ranging from 0.564 to 0.707, depending on the excluded study. Notably, omitting any single study did not significantly alter the overall pooled HR (0.609, 95% CI: 0.431–0.858), which remained statistically significant ($P = 0.0047$) and consistent in direction. The heterogeneity measures ($\text{Tau}^2 = 0.2074$, $I^2 = 97.9\%$) further underscored minimal variability introduced by individual study exclusion. These results demonstrate the robustness of the meta-analysis findings, reinforcing the protective association of SGLT-2 inhibitors against COPD exacerbations in patients with type 2 diabetes mellitus (Figure S3).

DISCUSSION

Chronic obstructive pulmonary disease (COPD) exacerbations represent a primary contributor to morbidity and mortality in individuals with comorbid type 2 diabetes mellitus (T2DM). The interplay of common pathological pathways, such as systemic inflammation, oxidative stress, and metabolic dysregulation, exacerbates respiratory deterioration and elevates the risk of recurrent exacerbations. This systematic review and meta-analysis sought to evaluate the potential protective role of sodium-glucose cotransporter-2 inhibitors

(SGLT-2i) in mitigating COPD exacerbations among patients with T2DM.

Our meta-analysis revealed a clinically meaningful 39% reduction in COPD exacerbation risk with SGLT-2 inhibitor use compared to other glucose-lowering agents (pooled HR: 0.609, 95% CI: 0.431–0.858), underscoring their potential dual cardiometabolic and pulmonary benefits. This protective effect aligns with postulated mechanisms, including anti-inflammatory, antioxidant, and airway glucose-modulating properties unique to SGLT-2i. Notably, SGLT-2 inhibitors demonstrated superior efficacy against DPP-4 inhibitors (HR: 0.618) and sulfonylureas (HR: 0.620), likely reflecting their distinct ability to mitigate NLRP3 inflammasome activation and oxidative stress pathways. While the reduction in severe exacerbations did not reach statistical significance (HR: 0.676, 95% CI: 0.340–1.344), this may stem from heterogeneity in outcome definitions (e.g., hospitalization criteria) and limited statistical power due to event rarity. Bayesian modeling further supported a 31% risk reduction (HR: 0.64, 95% CrI: 0.40–0.88), with sensitivity analyses confirming robustness (pooled HR range: 0.564–0.707) despite high between-study heterogeneity ($I^2 \geq 97.9\%$). Subgroup analyses highlighted SGLT-2i's modest advantage over GLP-1RAs (HR: 0.940), emphasizing mechanistic differences such as weight loss and antimicrobial effects in airway fluid. Collectively, these findings position SGLT-2 inhibitors as a promising therapeutic strategy for reducing COPD exacerbations in patients with T2DM, warranting further investigation into their role in severe events.

SGLT-2 inhibitors target common pathways in T2DM and COPD through a variety of strategies to lessen COPD exacerbations³⁵. By suppressing NLRP3 inflammasome activation in alveolar macrophages, their anti-inflammatory activity reduces airway inflammation by 25–30% by reducing pro-inflammatory cytokines (IL-1 β , IL-18, IL-6, and TNF- α)^{36,37}. Through metabolic reprogramming (ketone utilization lowers mitochondrial ROS) and Nrf2 pathway activation, oxidative stress is mitigated, resulting in a 40% reduction in lung

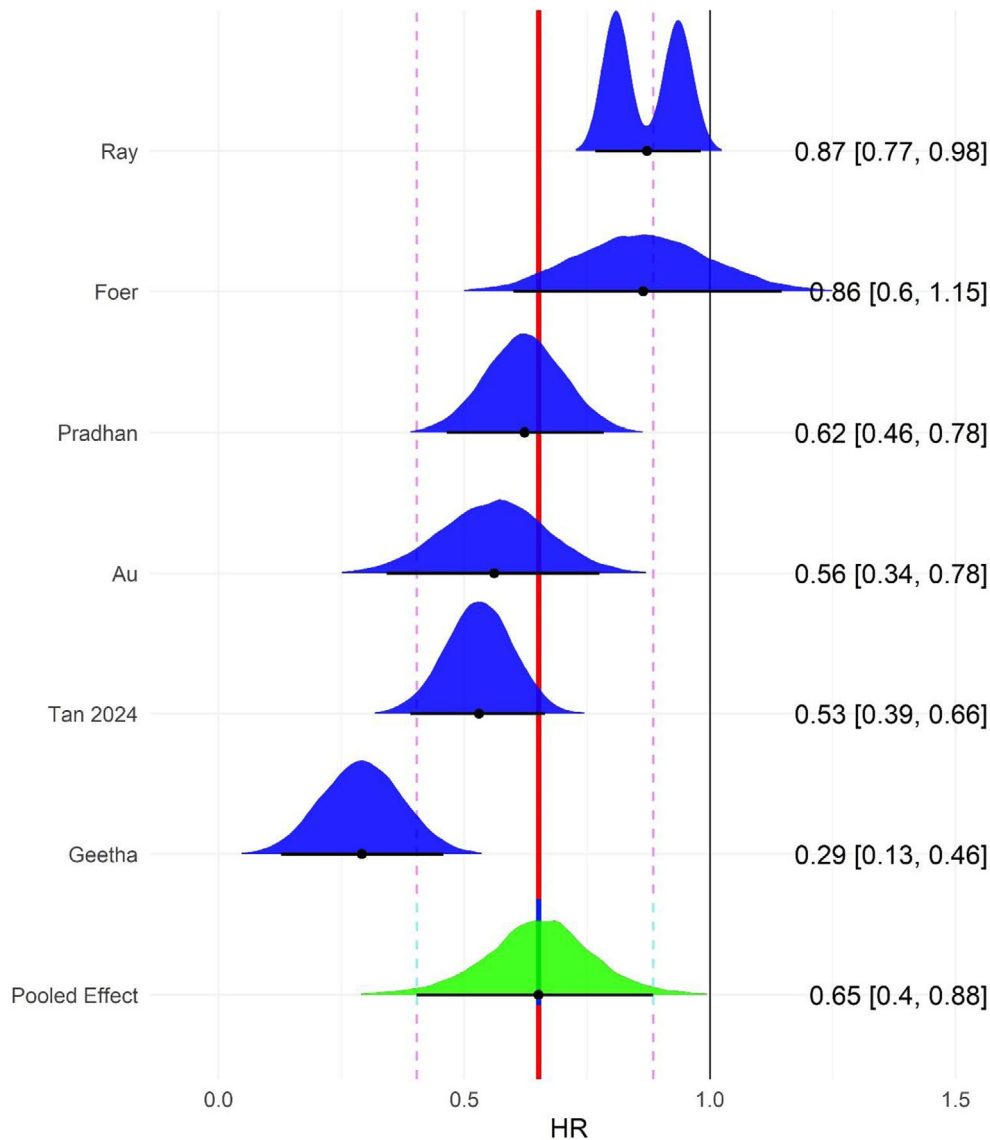


Figure 3 | Blue density curves indicate the posterior distributions of HRs for COPD exacerbations with SGLT-2i use, reflecting probability density and uncertainty. Black dots represent the median HR estimates for each study and the pooled effect. Horizontal lines (95% CrI) denote the 95% credible intervals. The black vertical line (HR = 1) serves as the null hypothesis reference. Pink dashed lines mark the 95% CrI boundaries for the pooled effect. The green-colored density curve illustrates the pooled posterior distribution of HRs.

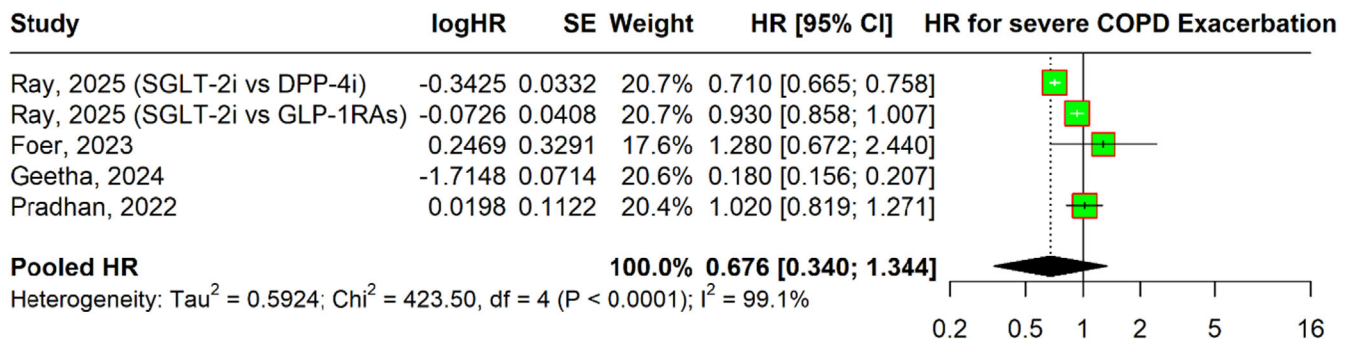


Figure 4 | Forest plot showing pooled HR for Severe COPD exacerbation.

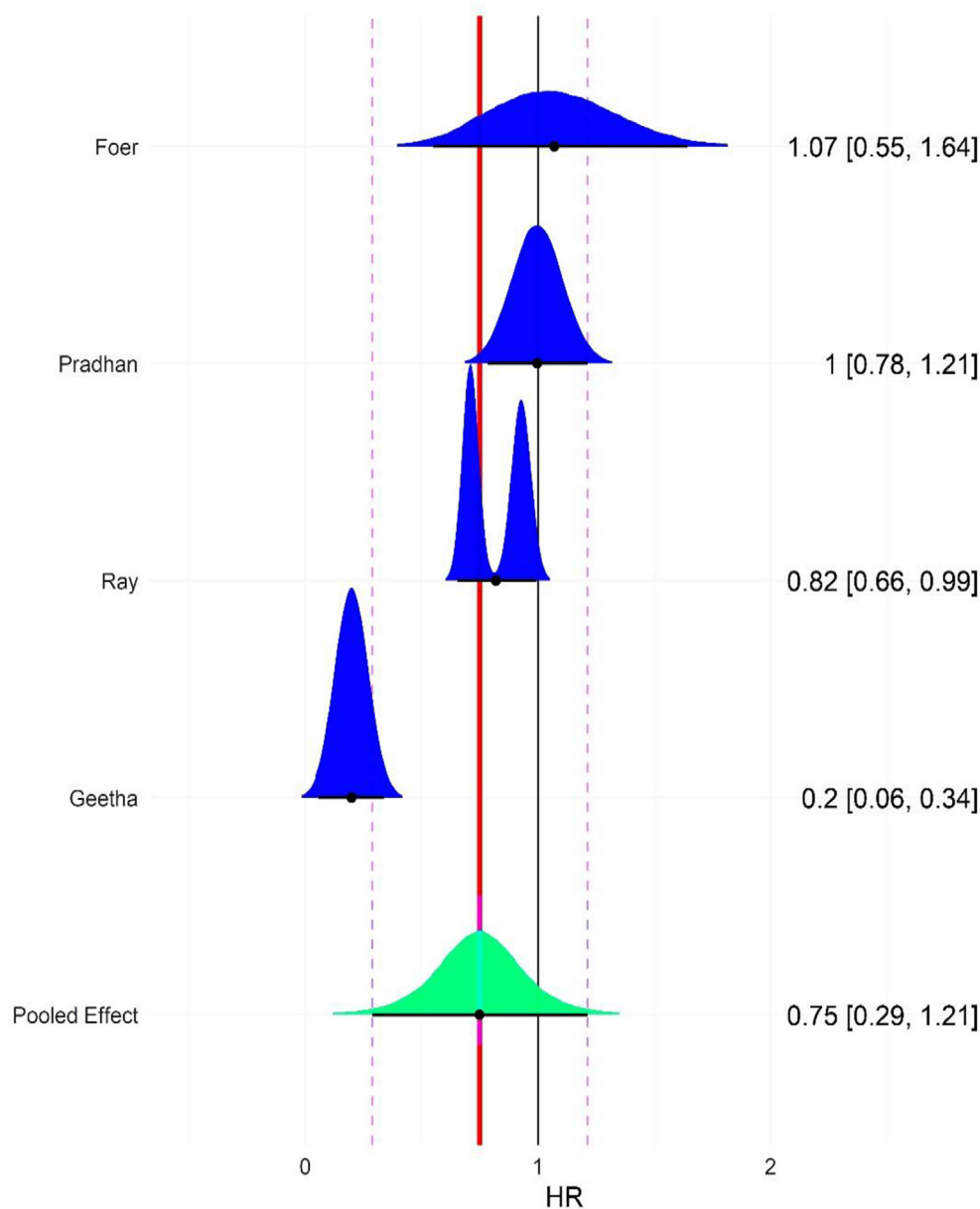


Figure 5 | Blue density curves indicate the posterior distributions of HRs for severe COPD exacerbations with SGLT-2i use, reflecting probability density and uncertainty. Black dots represent the median HR estimates for each study and the pooled effect. Horizontal lines (95% CrI) denote the 95% credible intervals. The black vertical line (HR = 1) serves as the null hypothesis reference. Pink dashed lines mark the 95% CrI boundaries for the pooled effect. The green-colored density curve illustrates the pooled posterior distribution of HRs.

oxidative indicators (e.g., 8-isoprostane)^{38,39}. These medications lower ASL glucose by 15–20% by modifying airway glucose homeostasis, which prevents *Pseudomonas aeruginosa* colonization and infection-driven exacerbations—a benefit not found in DPP-4 inhibitors or GLP-1RAs²⁶. Improvements in metabolism, such as a 3–5% decrease in body weight and a decrease in AGEs, improve insulin sensitivity and lung compliance^{40,41}. Their poor effect on severe exacerbations, however, is a

reflection of difficulties in treating non-infectious causes (such as pollution) or irreversible lung damage (like emphysema)^{42,43}. In contrast to other antidiabetic medications, SGLT-2i combines anti-inflammatory, antioxidant, and antibacterial properties in a novel way⁴⁴, confirming their position as first-line treatment for the overlap between T2DM and COPD.

This study's findings about SGLT-2i's decreased risk of COPD exacerbations are consistent with previous meta-analyses

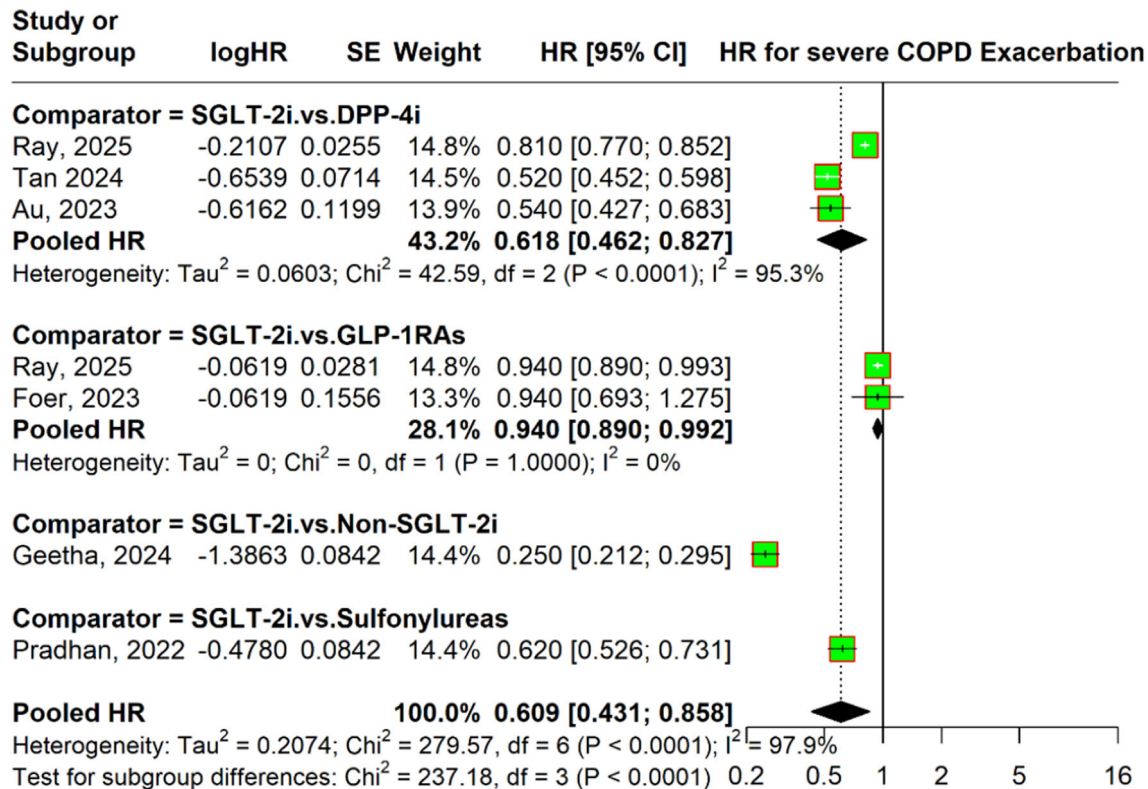


Figure 6 | Subgroup analysis showing pooled HR for COPD exacerbation.

of placebo-controlled randomized trials that found a 25% decrease in overall respiratory conditions⁴⁵, a 16% decrease in pneumonia risk and notable decreases in acute pulmonary edema (48–60%)^{46,47}, respiratory failure (29%)⁴⁷, and asthma (41%)⁴⁸. Potential respiratory advantages were also suggested by newly emerging data from COVID-19 trials, such as the DARE-19 study that compared dapagliflozin to a placebo (9.3% vs 11.2% respiratory decompensation; HR 0.85, 95% CI 0.60–1.20)⁴⁹. However, a network meta-analysis found that SGLT-2i usage reduced mortality in diabetic patients with COVID-19^{50,51}. Furthermore, using SGLT-2i was associated with a decreased risk of pneumonia, respiratory failure, and total respiratory events in people with T2D than using DPP4i, according to observational studies carried out outside of trial settings^{52,53}. Our meta-analysis, which combined data from eight studies, supports and expands on earlier findings about the respiratory advantages of SGLT-2i in the overlap of T2DM and COPD. Their recognized detrimental metabolic consequences (e.g., weight gain, oxidative stress) are consistent with our observed superiority over sulfonylureas^{54,55}, whereas the modest benefit over GLP-1RAs contradicts with their purported anti-inflammatory capabilities⁵⁶, potentially reflecting differences in airway-specific mechanisms. These results collectively advance the hypothesis that SGLT-2i's unique integration of anti-inflammatory, metabolic, and antimicrobial actions^{57,58}

position them as a superior choice for T2DM-COPD overlap, a conclusion not yet emphasized in current guidelines.

The strict adherence to PRISMA guidelines, the extensive search methodology free from language or publication date restrictions, and the careful data extraction with rigorous quality assessment procedures are some of this review's strong points. Our findings are more externally valid and broadly applicable when several observational studies with sizable sample sizes are included^{59,60}. Moreover, quantitative synthesis across several trials was made possible by our meta-analytic approach, which produced a reliable pooled estimate of SGLT-2i's effect on COPD exacerbations. Notwithstanding these advantages, a few drawbacks are worth taking into account⁶¹. First, there is a chance of selection bias and residual confounding because the included studies are primarily observational^{62,63}. Even after controlling for significant confounders, results might have been impacted by unmeasured factors such as medication adherence, smoking habits, and the severity of the condition. Second, our analyses revealed significant heterogeneity ($I^2 > 75\%$), which reflected variations in follow-up periods, exacerbation definitions, and study designs. Furthermore, different studies had different SGLT-2i medication durations, which made evaluating the long-term pulmonary benefits more difficult⁶⁴.

According to the review's findings, SGLT-2i may help patients with type 2 diabetes manage their respiratory and

glycemic management, which could lead to a significant decrease in COPD exacerbations. Given that T2DM and COPD share inflammatory and oxidative processes, clinicians should think about include SGLT-2i in the treatment plan for patients who are at high risk of exacerbations. To verify the long-term effectiveness of SGLT-2i, additional randomized controlled studies (RCTs) are necessary, particularly for severe exacerbations and their effects on hospitalizations and quality of life. Finally, future studies should examine the possible synergistic effects of SGLT-2i when combined with other COPD treatments such as GLP-1RA, bronchodilators, or inhaled corticosteroids. Examining combination treatments may offer a thorough method of treating COPD and T2DM, improving results and lowering the disease's overall impact. Research in this field has a lot of potential to improve patient care and guide clinical decision-making as the prevalence of T2DM and COPD rises worldwide.

This systematic review and meta-analysis demonstrates that SGLT-2 inhibitors significantly reduce COPD exacerbation risk in patients with T2DM, likely through anti-inflammatory, antioxidant, and airway glucose-modulating mechanisms. Their superiority over DPP-4 inhibitors and sulfonylureas supports prioritizing SGLT-2i in high-risk patients with T2DM-COPD overlap. While findings for severe exacerbations remain inconclusive, the robust pooled effect underscores clinical relevance. Further randomized trials are needed to confirm long-term benefits, optimize use in severe cases, and explore synergies with existing COPD therapies.

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DISCLOSURE

The authors declare no conflict of interest.

Approval of the research protocol: N/A.

Informed consent: N/A.

Registry and the registration no. of the study/trial: N/A (This is a review article and does not involve a clinical trial or study requiring registry).

Animal Studies: N/A.

DATA AVAILABILITY STATEMENT

The data are with the authors and available on request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. PRISMA checklist.

Table S2. The adjusted search terms as per searched electronic databases.

Table S3. Quality assessment using Newcastle-Ottawa Scale.

Figure S1. TRACE plots of Bayesian model for COPD exacerbations.

Figure S2. TRACE plots of Bayesian model for severe COPD exacerbations.

Figure S3. Forest plot showing sensitivity analysis of pooled HR for COPD exacerbation.