Supplemental materials

Medication adherence and the risk of COPD exacerbations in healthcare databases: a systematic review with meta-analysis

Table of contents

1. Search strategy

eTable 1: Search string of different concepts used in MEDLINE (PubMed interface)

Concept	Search string
1. Chronic Obstructive Pulmonary Disease	"pulmonary disease, chronic obstructive"[Mesh Terms] OR COAD[TW] OR COPD[TW] OR (chronic[TW] AND (obstruct*[TW] OR limitation*[TW]) AND (lung*[TW] OR bronchopulmon*[TW] OR pulmonary[TW] OR respiratory[TW] OR airway*[TW] OR airflow[TW] OR bronchi*[TW])) OR (chronic[TW] AND bronchitis[TW]) OR (emphysem*[TW]) OR (obstruct*[TW] AND (lung*[TW] OR bronchopulmon*[TW] OR pulmonary[TW] OR respiratory[TW] OR airway*[TW] OR airflow[TW] OR bronchi*[TW]) AND (disease*[TW] OR disorder*[TW]))
2. Medication Adherence	"Medication Adherence"[Mesh] OR "Patient Compliance"[Mesh] OR "medication therapy management"[Mesh] OR adher*[TW] OR nonadher*[TW] OR noncomplian*[TW] OR "non-adherence"[TW] OR "non adherence"[TW] OR "non-adherent"[TW] OR "non adherent"[TW] OR persisten*[TW] OR nonpersisten*[TW] OR "non-persistence"[TW] OR "non persistence"[TW] OR "non-persistent"[TW] OR "non persistent"[TW] OR complian*[TW] OR comply*[TW] OR "non-compliance"[TW] OR "non compliance"[TW] OR "non-compliant"[TW] OR "non compliant"[TW] OR cooperation[TW] OR "co-operation"[TW] OR fill*[TW] OR refill*[TW] OR dispens*[TW] OR "therapy management"[TW]
3. Exacerbation	"Symptom Flare Up"[MeSH Terms] OR exacerbat*[TW]
4. Population-based administrative databases	((administrative[TW] OR health[TW] OR claims[TW] OR electronic[TW] OR pharmacy[TW] OR computerized[TW] OR computerised[TW] OR prescription[TW] OR prescribing[TW] OR care[TW]) AND (database*[TW] OR databank*[TW] OR "data base"[TW] OR "data bases"[TW] OR "data bank"[TW] OR "data banks"[TW])) OR "electronic health records"[MesH Terms] OR ((electronic[TW] OR computerized[TW] OR computerised[TW]) AND (health[TW] OR medical[TW]) AND record*[TW]) OR EHR[TW] OR ("Databases, Factual"[Mesh Terms]) OR (factual[TW] AND (database*[TW] OR databank*[TW] OR "data bank"[TW] OR "data banks"[TW] OR "data base"[TW] OR "data bases"[TW])) OR ((pharmacy[TW] OR dispensing[TW] OR administrative[TW] OR medical[TW] OR computerized[TW] OR computerized[TW] OR insurance[TW] OR prescription[TW] OR prescribing [TW] OR health*[TW] OR "health care"[TW] OR insurance[TW] OR retrospective[TW] OR prescribing[TW] OR "population-based"[TW] OR "population-level"[TW] OR retrospective[TW] OR secondary[TW]) AND (record*[TW] OR claim*[TW] OR data[TW] OR registries[TW])) OR ("claims data"[TW]) OR Medicaid[TW] OR "Veterans Affairs"[TW] OR "Veterans health service"[TW] OR "Drug Prescriptions/statistics and numerical data"[Mesh] OR "Drug Therapy/statistics and numerical data"[Mesh] OR (pharmacy[TW] AND insurance[TW] AND claims[TW]) OR "electronic prescribing"[Mesh Terms] OR (electronic[TW] AND prescri*[TW])
5	1 AND 2 AND 3 AND 4

Records identified on October 10th, 2022: 647

eTable 2: Search string of different concepts used in Web of Sciences

Concept	Search string
1. Chronic Obstructive Pulmonary Disease	TS=((obstruct* NEAR/4 (bronchopulmon* OR lung* OR pulmonary OR respiratory* OR airway* OR airflow* OR bronchi*)) OR "chronic obstructive lung disease" OR "chronic bronchitis" OR (chronic NEAR/2 bronch*) OR emphysem* OR COAD OR COPD OR (airflow* NEAR/2 limitation*) OR (airway* NEAR/2 limitation*))
2. Medication Adherence	TS=(complian* OR comply* OR adher* OR nonadher* OR noncompli* OR "non-adherence" OR "non adherence" OR "non-adherent" OR "non adherent" OR persisten* OR nonpersisten* OR "non-persistence" OR "non persistence" OR "non-persistent" OR "non-persistent" OR "non-compliance" OR "non compliance" OR "non-compliant" OR "non compliant" OR cooperation OR "co-operation" OR fill* OR refill* OR dispens* OR "medication compliance" OR adherence OR "patient compliance" OR persistence OR compliance OR nonadherence OR noncompliance OR nonpersistence OR "therapy management")
3. Exacerbation	TS=(exacerbat*)
4. Population-based administrative databases	TS=("administrative health data" OR "electronic medical record" OR "health data" OR "electronic health record" OR "electronic medical record system" OR "factual database" OR "medicaid" OR "veterans health service" OR "veterans affairs" OR "medical record" OR ((administrative OR hospital OR insurance OR medical OR prescribing OR prescription OR health OR claims OR pharmacy OR electronic OR computerized OR computerised OR care OR factual OR resource OR dispensing OR retrospective OR "population based " OR "population based " OR "population-level " OR "population level " OR secondary) NEAR/4 (data* OR database* OR record* OR claim* OR databank* OR "data base " OR "data bases " OR "data bank " OR "data banks " OR registries)) OR EHR OR Medicaid OR "pharmacy insurance")
5	1 AND 2 AND 3 AND 4

Records identified on October 10th, 2022: 320

eTable 3: Search string of different concepts used in Embase

Concept	Search string
1. Chronic Obstructive Pulmonary Disease	((obstruct* NEAR/4 (bronchopulmon* OR lung* OR pulmonary OR respiratory* OR airway* OR airflow* OR bronchi*)):ti,ab,kw) OR 'chronic obstructive lung disease'/exp OR 'chronic obstructive lung disease' OR 'chronic bronchitis'/exp OR 'chronic bronchitis' OR 'cigarette smoke-induced emphysema'/exp OR 'cigarette smoke-induced emphysema' OR 'emphysema'/exp OR 'emphysema' OR 'lung emphysema'/exp OR 'lung emphysema' OR ((chronic NEAR/2 bronch*):ti,ab,kw) OR 'emphysem*':ti,ab,kw OR 'coad':ti,ab,kw OR 'copd':ti,ab,kw OR ((airflow* NEAR/2 limitation*):ti,ab,kw) OR ((airway* NEAR/2 limitation*):ti,ab,kw)
2. Medication Adherence	complian*:ti,ab,kw OR comply*:ti,ab,kw OR adher*:ti,ab,kw OR nonadher*:ti,ab,kw OR noncompli*:ti,ab,kw OR 'non-adherence':ti,ab,kw OR 'non adherence':ti,ab,kw OR 'non-adherent':ti,ab,kw OR 'non adherent':ti,ab,kw OR persisten*:ti,ab,kw OR nonpersisten*:ti,ab,kw OR 'non-persistence':ti,ab,kw OR 'non persistence':ti,ab,kw OR 'non-persistent':ti,ab,kw OR 'non-compliance':ti,ab,kw OR 'non compliance':ti,ab,kw OR 'non-compliant':ti,ab,kw OR 'non compliant':ti,ab,kw OR cooperation:ti,ab,kw OR 'co-operation':ti,ab,kw OR fill*:ti,ab,kw OR refill*:ti,ab,kw OR dispens*:ti,ab,kw OR 'medication compliance/exp' OR 'adherence/exp' OR 'patient compliance'/exp OR 'patient compliance' OR 'persistence' OR 'compliance'/exp OR 'compliance' OR 'nonadherence':ti,ab,kw OR 'noncompliance':ti,ab,kw OR 'nonpersistence':ti,ab,kw OR 'therapy management' OR 'therapy management':ti,ab,kw
3. Exacerbation	'disease exacerbation'/exp OR 'disease exacerbation' OR 'exacerbat*':ti,ab,kw
4. Population-based administrative databases	('administrative health data'/exp OR 'administrative health data' OR 'electronic medical record'/exp OR 'electronic medical record' OR 'administrative claims (health care)'/exp OR 'administrative claims (health care)' OR 'health data'/exp OR 'health data' OR 'billing and claims'/exp OR 'billing and claims' OR 'health insurance'/exp OR 'health insurance' OR 'electronic health record'/exp OR 'electronic health record' OR 'electronic medical record system'/exp OR 'electronic medical record system' OR 'factual database'/exp OR 'factual database' OR 'medicaid'/exp OR 'medicaid' OR 'veterans health service'/exp OR 'veterans health service' OR 'veterans affairs' OR 'medical record'/exp OR 'medical record' OR 'electronic prescribing'/exp OR 'electronic prescribing' OR (((administrative OR hospital OR insurance OR medical OR prescribing OR prescription OR health OR claims OR pharmacy OR electronic OR computeri?ed OR care OR factual OR resource OR dispensing OR retrospective OR 'population based' OR 'population based' OR 'population-level' OR 'population level' OR secondary) NEAR/4 (data* OR database* OR record* OR claim* OR databank* OR 'data base' OR 'data bases' OR 'data bank' OR 'data banks' OR registries)):ti,ab,kw) OR 'ehr (electronic health record)':ti,ab,kw OR medicaid:ti,ab,kw OR `retrospective data`:ti,ab,kw OR 'pharmacy insurance':ti,ab,kw)
5	1 AND 2 AND 3 AND 4

Records identified on October 10th, 2022: 865

2. Inclusion and exclusion criteria

eTable 4: Overview of inclusion and exclusion criteria applied on title, abstract and full text.

Criteria	Inclusion	Exclusion
Language	English	All other languages
Population		Study population of only children (< 18 years) Animals
Publication type	Peer-reviewed observational studies (prospective, retrospective and cross-sectional)	Experimental studies (pilot studies, interventional studies, ((randomized controlled) trials), unpublished studies, articles without abstract after Google search, conference abstracts without full-text publications, poster presentations, reviews, case reports, ideas, editorials, commentaries, guidelines, protocols, opinions and pre-prints
Disease	Chronic obstructive pulmonary disease (COPD) Diagnosis based on registered diagnosis codes for COPD (e.g., International Classification of Diseases (ICD) codes), medical records (physicians' diagnosis) or the use of COPD-related medications (excluding users of only short-acting bronchodilators).	COPD defined as use of only short acting bronchodilators
Intervention	Assessment of medication adherence* to COPD-medication (Anatomical Therapeutic Chemical Classification (ATC) code R03) with specification of adherence threshold to differentiate between good and poor adherence	Adherence focused on only short-acting bronchodilators (~no maintenance medication)
Outcome	Exacerbation defined as COPD-related hospitalization (hospitalization with primary or discharge diagnosis code for COPD) with/without emergency department visit for COPD or events requiring treatment with oral corticosteroids and/or antibiotics in outpatient setting. Exacerbations identified during or following adherence assessment period	Exacerbations in time period before adherence assessment
Data source for adherence assessment and exacerbations	Electronic health records to identify study population and assess adherence and exacerbations: population-based administrative databases, health insurance claims, hospital records, medical records, medical prescription claims and pharmacy (dispensing) records	Self-reported adherence or exacerbation history based on questionnaires, surveys, patient interviews… Adherence based on the use of smart inhaler devices or smart nebulizers

* Following aspect of adherence were eligible for inclusion: implementation: the extent to which a patient uses medication as desired (in light of the recommended dosing regimen) during a specific period of time based on Vrijens et al. (2012, 2016).[1,2]

3. Quality assessment

Description of QUALSYST tool.

The QualSyst tool for Quantitative Studies from the 'Standard Quality Assessment Criteria for Evaluating Primary Research Papers from a Variety of Fields'[3] scores a study on a 14 items scale and is applicable for multiple study designs. For each criterium, a study is assigned yes (score 2), partial (score 1), no (score 0) or not applicable (n/a). The final score is calculated by the total sum score obtained across the rated items divided by the total possible score (with exclusion of the n/a questions). An overall score could be calculated and presented as a percentage. In general, studies scoring <75% were excluded for the meta-analysis.

eTable 5: Quality assessment of included studies in this systematic review.

Reference: Chen et al. 2020[4]					
Criteria		**Yes (2)**	**Partial (1)**	**No (0)**	**N/A**
1	Question / objective sufficiently described?		1 (vaguely reported – evaluate the association – hypothesis is lacking)		
2	Study design evident and appropriate?		1 (measuring adherence and exacerbation in same time period cannot give certainty about causal relationship)		
3	Method of subject/comparison group selection or source of information/input variables described and appropriate?		1 (definition of diagnosis of COPD is lacking)		
4	Subject and comparison group (if applicable) characteristics sufficiently described?	2			
5	If interventional and random allocation was possible, was it reported?				X
6	If interventional and blinding of investigators was possible, was it reported?				X
7	If interventional and blinding of subjects was possible, was it reported?				X
8	Outcome and (if applicable) exposure measure(s) well defined and robust to measurement / misclassification bias? Means of assessment reported?		1 (partial definition of exacerbation, minimal time period between two exacerbations is lacking)		
9	Sample size appropriate?	2			
10	Analytic methods described/justified and appropriate?	2			
11	Some estimate of variance is reported for the main results?	2			
12	Controlling for confounding?	2			
13	Results reported in sufficient detail?		1 (results only presented for severe exacerbations + statistical effect measures are used interchangeably)		
14	Conclusion supported by the results?	2			
Total score: 17/22 (77.2%)					

Reference: Davis et al. 2017[5]					
Criteria		**Yes (2)**	**Partial (1)**	**No (0)**	**N/A**
1	Question / objective sufficiently described?		1 (vaguely reported – evaluate the association – hypothesis is lacking)		
2	Study design evident and appropriate?		1 (measuring adherence and exacerbation in same time period cannot give certainty about causal relationship)		
3	Method of subject/comparison group selection or source of information/input variables described and appropriate?		1 (ICD codes for comorbidities and ATC codes of medication are lacking)		
4	Subject and comparison group (if applicable) characteristics sufficiently described?	2			
5	If interventional and random allocation was possible, was it reported?				X
6	If interventional and blinding of investigators was possible, was it reported?				X
7	If interventional and blinding of subjects was possible, was it reported?				X
8	Outcome and (if applicable) exposure measure(s) well defined and robust to measurement / misclassification bias? Means of assessment reported?	2			
9	Sample size appropriate?		1 (large sample size but no sample size calculation or standard errors presented)		
10	Analytic methods described/justified and appropriate?		1 (demographic and preinitiation clinical characteristics not completely clear)		
11	Some estimate of variance is reported for the main results?	2			
12	Controlling for confounding?	2			
13	Results reported in sufficient detail?	2			
14	Conclusion supported by the results?	2			
Total score: 17/22 (77.2%)					

Reference: Fan et al. 2003[6]					
Criteria		**Yes (2)**	**Partial (1)**	**No (0)**	**N/A**
1	Question / objective sufficiently described?		1 (vaguely reported – We sought to determine whether patients who regularly filled medications were associated with death and health care use among patients with COPD in a primary setting. – hypothesis is lacking)		
2	Study design evident and appropriate?	2			
3	Method of subject/comparison group selection or source of information/input variables described and appropriate?		1 (reuse of data of participants to a randomized controlled trial, not generalizable to real-life setting)		
4	Subject and comparison group (if applicable) characteristics sufficiently described?	2			
5	If interventional and random allocation was possible, was it reported?				X
6	If interventional and blinding of investigators was possible, was it reported?				X
7	If interventional and blinding of subjects was possible, was it reported?				X
8	Outcome and (if applicable) exposure measure(s) well defined and robust to measurement / misclassification bias? Means of assessment reported?		1 (length of study period and follow-up period are unclear)		
9	Sample size appropriate?	2			
10	Analytic methods described/justified and appropriate?		1 (length of follow-up period is unclear so doubt is possible about appropriateness of analytic method)		
11	Some estimate of variance is reported for the main results?		1 (confidence intervals are presented but effect measure not cannot be derived exactly from figures)		
12	Controlling for confounding?		1 (markers of disease severity incorporated but unclear if this was done for all analyses)		
13	Results reported in sufficient detail?		1 (not all results are sufficiently reported in detail – e.g., we found no protective effect of ICS whether average or recent use was measured (no further reported))		
14	Conclusion supported by the results?	2			
Total score: 15/22 (68.2%)					

Reference: Humenberger et al. 2018[7]					
Criteria		**Yes (2)**	**Partial (1)**	**No (0)**	**N/A**
1	Question / objective sufficiently described?	2			
2	Study design evident and appropriate?		1 (measuring adherence and exacerbation in same time period cannot give certainty about causal relationship)		
3	Method of subject/comparison group selection or source of information/input variables described and appropriate?		1 (appropriateness of subject group can be doubted, selection of patients already hospitalized for COPD exacerbations)		
4	Subject and comparison group (if applicable) characteristics sufficiently described?		1 (unclear how current smoker is defined)		
5	If interventional and random allocation was possible, was it reported?				X
6	If interventional and blinding of investigators was possible, was it reported?				X
7	If interventional and blinding of subjects was possible, was it reported?				X
8	Outcome and (if applicable) exposure measure(s) well defined and robust to measurement / misclassification bias? Means of assessment reported?		1 (definition of severe exacerbation is not clearly presented)		
9	Sample size appropriate?		1 (small sample size with no sample size calculation, doubt about generalizability)		
10	Analytic methods described/justified and appropriate?	2			
11	Some estimate of variance is reported for the main results?		1 (confidence intervals presented without p-values)		
12	Controlling for confounding?	2			
13	Results reported in sufficient detail?	2			
14	Conclusion supported by the results?	2			
Total score: 16/22 (72.7%)					

Reference: Ismaila et al.[8]					
Criteria		**Yes (2)**	**Partial (1)**	**No (0)**	**N/A**
1	Question / objective sufficiently described?		1 (vaguely reported – to assess the long-term impact of adherence to COPD treatment on risk of COPD exacerbations – hypothesis is lacking)		
2	Study design evident and appropriate?		1 (measuring adherence and exacerbation in same time period cannot give certainty about causal relationship)		
3	Method of subject/comparison group selection or source of information/input variables described and appropriate?		1 (unclear when exclusion criteria for prescription of leukotriene antagonists was applied)		
4	Subject and comparison group (if applicable) characteristics sufficiently described?	2			
5	If interventional and random allocation was possible, was it reported?				X
6	If interventional and blinding of investigators was possible, was it reported?				X
7	If interventional and blinding of subjects was possible, was it reported?				X
8	Outcome and (if applicable) exposure measure(s) well defined and robust to measurement / misclassification bias? Means of assessment reported?		1 (partial definition of exacerbation, minimal time period between two exacerbations is lacking)		
9	Sample size appropriate?	2			
10	Analytic methods described/justified and appropriate?	2			
11	Some estimate of variance is reported for the main results?		1 (p-values are not always presented)		
12	Controlling for confounding?	2			
13	Results reported in sufficient detail?	2			
14	Conclusion supported by the results?	2			
Total score: 17/22 (77.2%)					

Reference: Mueller et al.[9]					
Criteria		**Yes (2)**	**Partial (1)**	**No (0)**	**N/A**
1	Question / objective sufficiently described?	2			
2	Study design evident and appropriate?		1 (time period of exacerbation detection is partial overlapping with time period of adherence assessment)		
3	Method of subject/comparison group selection or source of information/input variables described and appropriate?	2			
4	Subject and comparison group (if applicable) characteristics sufficiently described?	2			
5	If interventional and random allocation was possible, was it reported?				X
6	If interventional and blinding of investigators was possible, was it reported?				X
7	If interventional and blinding of subjects was possible, was it reported?				X
8	Outcome and (if applicable) exposure measure(s) well defined and robust to measurement / misclassification bias? Means of assessment reported?	2			
9	Sample size appropriate?	2			
10	Analytic methods described/justified and appropriate?	2			
11	Some estimate of variance is reported for the main results?	2			
12	Controlling for confounding?	2			
13	Results reported in sufficient detail?	2			
14	Conclusion supported by the results?	2			
Total score: 21/22 (95.5%)					

Reference: Punekar et al.[10]					
Criteria		**Yes (2)**	**Partial (1)**	**No (0)**	**N/A**
1	Question / objective sufficiently described?		1 (vaguely reported – to estimate the impact of adherence on healthcare resource use –hypothesis is lacking)		
2	Study design evident and appropriate?		1 (measuring adherence and exacerbation in same time period cannot give certainty about causal relationship)		
3	Method of subject/comparison group selection or source of information/input variables described and appropriate?		1 (codes for definite COPD diagnosis are unclear)		
4	Subject and comparison group (if applicable) characteristics sufficiently described?		1 (unclear how current smoker is defined)		
5	If interventional and random allocation was possible, was it reported?				X
6	If interventional and blinding of investigators was possible, was it reported?				X
7	If interventional and blinding of subjects was possible, was it reported?				X
8	Outcome and (if applicable) exposure measure(s) well defined and robust to measurement / misclassification bias? Means of assessment reported?		1 (partial definition of exacerbation, minimal time period between two exacerbations is lacking)		
9	Sample size appropriate?	2			
10	Analytic methods described/justified and appropriate?	2			
11	Some estimate of variance is reported for the main results?		1 (values are not presented for non-significant results)		
12	Controlling for confounding?	2			
13	Results reported in sufficient detail?		1 (rates per person years does not show variance in population + values are not presented for non-significant results)		
14	Conclusion supported by the results?	2			
Total score: 15/22 (68.2%)					

Reference: Wurst et al. 2014[11]					
Criteria		**Yes (2)**	**Partial (1)**	**No (0)**	**N/A**
1	Question / objective sufficiently described?		1 (vaguely reported – to describe characteristics with regard to treatment evolution – hypothesis is lacking)		
2	Study design evident and appropriate?		1 (measuring adherence and exacerbation in same time period cannot give certainty about causal relationship)		
3	Method of subject/comparison group selection or source of information/input variables described and appropriate?	2			
4	Subject and comparison group (if applicable) characteristics sufficiently described?	2			
5	If interventional and random allocation was possible, was it reported?				X
6	If interventional and blinding of investigators was possible, was it reported?				X
7	If interventional and blinding of subjects was possible, was it reported?				X
8	Outcome and (if applicable) exposure measure(s) well defined and robust to measurement / misclassification bias? Means of assessment reported?	2			
9	Sample size appropriate?				X (only descriptive analysis)
10	Analytic methods described/justified and appropriate?				X (only descriptive analysis)
11	Some estimate of variance is reported for the main results?				X (only descriptive analysis)
12	Controlling for confounding?				X (only descriptive analysis)
13	Results reported in sufficient detail?	2			
14	Conclusion supported by the results?		1 (conclusion of abstract does not incorporate all results)		
Total score: 11/14 (78.6%)					

4. Additional characteristics of included studies

eTable 6: Overview of inclusion criteria (including definition of COPD) and factors considered as possible confounders when analysing the relationship between medication adherence and exacerbations

Author	**Inclusion criteria (including definition of COPD)**	**Factors considered as possible confounders when analysing the relationship between medication adherence and exacerbations**
Chen et al.2020[4]	Diagnosed with COPD in 2015 (including patients with past COPD history, diagnose codes not shown), continuous medical insurance coverage for 1 year prior to 1 year after index date and ≥2 COPD maintenance medication claims (inhaled bronchodilators (LABA and/or LAMA), combination therapy with ICS (ICS/LABA) or oral therapy (theophylline and/or mucolytics). Patients were excluded if they had other respiratory conditions such as lung cancer, pulmonary fibrosis, or asthma.	Baseline characteristics: age, gender, Charlson comorbidity index Clinical characteristics: pre-index AECOPD frequency (divided in three categories: (1) 0; (2) 1 outpatient moderate exacerbation or emergency department visit for COPD exacerbation and (3) ≥2 outpatient moderate exacerbations or emergency department visits for COPD exacerbation or having at least 1 hospitalized AECOPD) Healthcare resource utilization: pre-index SABA script number, pre-index LAMA script number, pre-index COPD related cost and pre-index COPD inpatient visit times For analyses of LABA/ICS and LABA/LAMA: pre-index theophylline script number For analyses of oral therapy: pre-index LABA script number
Davis et al.2017[5]	Patients with COPD (≥40 years) who had not received any ICS/LABA combination therapy during the 12 months before initiating budesonide plus formoterol (160/4.5 µg) or fluticasone plus salmeterol (250/50µg) therapy. Study patients had ≥1 prescription fills for budesonide plus formoterol (160/4.5 µg) or fluticasone plus salmeterol (250/50µg) therapy (combination of both products excluded) and inclusion required a diagnosis of COPD (ICD-p, Clinical Modification codes 491.xx, 492.xx and 496.xx) and ≥1 prescription fills for SABA, SAMA and/or SABA/SAMA during the 12-month preindex period. Long-term users of any oral corticosteroids (≥180 days of total length of therapy during the 12-month preindex period) were excluded, as well as patients with ≥2 diagnoses for the same type of cancer within 60 days of each other during the 12-month preindex period.	Matching based on demographic and preinitiation clinical characteristics: the number of preindex hospitalizations with a primary diagnosis of COPD, the number of preindex emergency department visits with a primary or secondary diagnosis of COPD, the number of preindex oral corticosteroids, antibiotics, SABA, SAMA, SABA/SAMA, LABA and LAMA prescription fills, comorbidities (hypertension, depression or psychotropic drug use, asthma, coronary artery disease, pneumonia, diabetes, congestive heart failure, anxiety, pulmonary hypertension, chronic respiratory failure, stroke and left ventricular failure), age, sex and preindex asthma diagnosis.
Fan et al.2003[6]	Patients were eligible if they had either an outpatient clinic visit or an inpatient hospitalization with a primary or secondary ICD-9 discharge diagnosis of COPD (491.x, 492.x and 496). Patients needed to use at least one pulmonary medication during the 90-day before the index visit and needed to be ≥45 years of age.	Markers of disease severity: all other pulmonary medications next to ICS (beta-adrenergic agonists, ipratropium bromide, oral theophylline, oral corticosteroids and commonly used antimicrobials), hospitalizations or outpatient visits for COPD in the year before the onset of the study, defined by a primary discharge diagnosis of COPD (ICD-9: 491, 492 or 496). Other factors taken into account: Deyo adaptation of the Charlson comorbidity score (excluding the lung disease category), age, Veteran Affairs hospital site ad distance to the Veteran Affairs hospital, prior outpatient and inpatient COPD visits

Author	Inclusion criteria (including definition of COPD)	Factors considered as possible confounders when analysing the relationship between medication adherence and exacerbations
Humenberger et al.2018[7]	Age > 40 years, COPD diagnosis (GOLD spirometry class I – IV and ICD-10 code 44.0-44.9) based on lung function testing (post-bronchodilator $FEV_1/FVC < 70\%$) and a prescribed permanent inhaled therapy. Patients with complete reversibility of lung function ($\Delta FEV_1 > 12\%$ or >0.2L) were excluded.	Age in categories, sex, GOLD grades (1-4, FEV1, airflow obstruction) and smoking history (never, former or current).
Ismaila et al.2014[8]	Patients of at least 40 years old with at least one medical claim with a diagnosis of COPD (ICD-9: 490.xx, 491.xx, 492.xx or 496.xx) and two or more pharmacy claims for tiotropium as monotherapy or co-administered with fixed dose combination fluticasone propionate/salmeterol. Patients with a diagnosis of asthma (ICD-9: 493.xx), respiratory tract cancer (ICD-9: 160.xx-164.xx or 231.xx), cystic fibrosis, fibrosis due to tuberculosis, bronchiectasis, pneumoconiosis, pulmonary fibrosis, tuberculosis or sarcoidosis or one or more prescriptions for leukotriene receptor agonists (montelukast or zafirlukast or mast-cell stabilizer) were excluded.	Proxies of COPD severity: number of exacerbations and prescriptions of oral and inhaled corticosteroids, theophylline, LABA, SABA, oxygen therapy, antibiotics and number of ER visits, hospitalizations, specialists visits and GP visits in the two years prior to induction in the study cohort Other factors taken into account: age at the time of induction in the cohort, gender, Charlson Comorbidity Score, cardiovascular disease, peripheral vascular disease, myocardial infarction, congestive heart failure, hypertension, cancer, depression and diabetes.
Mueller et al.2017[9]	Patients ≥ 40 years with a diagnosis of COPD (at least two outpatient or one inpatient COPD ICD-10 diagnoses (ICD-10: J44.-). Analyses concerned all patients who received at least one prescription of following agents: LABA, LAMA, ICS or single-device combinations of LABA/ICS. Patients with a concomitant outpatient or inpatient asthma diagnosis (ICD-10 J45.- or J46.-) were excluded.	The following initial independent variables were included: age, gender, the Charlson comorbidity index, the number of prescribed medications (any medication, at least two prescriptions of a respective agent on ATC group level 4) as an additional proxy for existing comorbidities, the number of prescriptions for short-acting COPD medications (ATC groups R01AD*, R02AA*, R02AB*, R02AD*, R03BA*) and the number of visits to pulmonologists (all information related to the baseline period)
Punekar et al.2015[10]	Patients aged ≥40 years newly initiating LAMA (single device), LABA (single device), LABA+LAMA (two devices) or LABA+ICS (single or two devices) were identified and included if there was at least one COPD 'definite' diagnostic code (not further defined). Patients with concurrent treatment of ICS/LAMA or an occurrence of a medical code for a condition that was incompatible with COPD diagnosis (lung or bronchial developmental anomalies, degenerative processes (cystic fibrosis or pulmonary fibrosis), bronchiectasis, pulmonary resection or significant respiratory disorders other than COPD (but excluding cancer)) were excluded.	Age, gender, body mass index (BMI), asthma co-morbidity, airflow limitation (Stage I-IV) and resource use prior to LABD initiation, number of moderate to severe exacerbation (0, 1, ≥2), number of GP visits (0, 1, ≥2), number of prior non-COPD hospitalisations (0, 1 , ≥2), ICS use (Yes/No) and SABD use (≥4 vs <4)

Author	Inclusion criteria (including definition of COPD)	Factors considered as possible confounders when analysing the relationship between medication adherence and exacerbations
Wurst et al.2014[11]	Patients aged 40 years and above with at least one COPD-related diagnostic code (ICD-9 codes: 491, 491.x, 491.xx, 492, 92.x and 496) within their prior 12-month history who were newly prescribed an LABD. Patients were excluded if they had a record for dispensed LABD or ICS within their prior 12-month history, a record for ICS use at the LABD index date, or a code for any other significant respiratory disorder that can interfere with clinical COPD diagnosis or substantially change the natural history of the COPD at any time in their available patient history (including tuberculosis, cystic fibrosis, bronchiectasis, idiopathic pulmonary fibrosis, congenital anomalies of the larynx, trachea, and bronchus, idiopathic interstitial pneumonia and acute bronchospasm)	/
AECOPD: acute exacerbation of COPD, ATC: Anatomical Therapeutic Chemical , FEV_1: forced expiratory volume in 1 second, FVC: forced vital capacity, GOLD: Global Initiative for Chronic Obstructive Lung Disease, ICD: international classification of disease, ICS: inhaled corticosteroids, LABA: long-acting beta-2 agonist, LABD: long-acting bronchodilator, LAMA: long-acting muscarinic antagonist, SABA: short-acting beta-2 agonist, SABD: short-acting bronchodilators, SAMA: short-acting muscarinic antagonist		

eTable 7: Overview of methods used to measure adherence in the included studies.

Author	Method to measure adherence	Explanation of method
Chen et al.2020[4]	PDC	Number of days with COPD maintenance medication divided by the duration of therapy with these agents (365 days).
Davis et al.2017[5]	PDC	Number of days a patient had index inhaled corticosteroid/LABA therapy on hand, divided by the number of health plan enrollment days during the 12-month postindex follow-up
Fan et al.2003[6]	Combination of MPR/PDC	Dividing the total days supplied by 90 and multiplying by 100.
Humenberger et al.2018[7]	MPR	The ratio of personal adherence months to the whole observation period of each participant. One medical prescription per month for each device was assumed for complete adherence.
Ismaila et al.2014[8]	MPR	The ratio of amount of daily dose of medication dispensed over the period of observation
Mueller et al.2017[9]	MPR	Number of days' supply received during persistent period divided by days between first and last prescription without any treatment gaps > 90 days
Punekar et al.2015[10]	MPR	Adding the number of days supplied for all but the last prescription divided by the total treatment time
Wurst et al.2014[11]	MPR PDC	The sum of the days supplied for all but the last repeat prescription divided by the number of days between the first and last prescription The number of days that the LABD was prescribed divided by the total number of days in the specified time interval
LABA: long-acting beta2-agonist, LABD: long-acting bronchodilator, MPR: medication possession ratio, PDC: proportion of days covered		

eTable 8: Overview of outcomes of included studies

Author	Definition of exacerbation	Exacerbation type assessed	Analysis	Outcome	Medication assessed	Result
Chen et al.2020[4]	**Moderate** exacerbation: requiring treatment with systemic corticosteroids and/or antibiotics in an outpatient setting. **Severe** exacerbation: requiring hospitalization or emergency department visit.	Severe	PDC <0.80 (reference) vs PDC ≥0.80	Exacerbator vs no exacerbator (adjusted odds ratio)	ICS/LABA	OR=0.65, 95% CI: 0.54-0.79, p<0.001
					LABA and/or LAMA	OR=0.81, 95% CI: 0.52-1.26, p=0.339
					Oral mucolytics	OR=2.51, 95% CI: 1.63-3.87, p<0.001
				Frequency of exacerbations (incidence rate ratio)	ICS/LABA	IRR: 0.76, 95% CI: 0.65-0.87, p<0.001
					LABA and/or LAMA	IRR: 0.83, 95% CI: 0.59-1.17, p=0.28
					Oral mucolytics	IRR: 1.82, 95% CI: 1.45-2.29, p<0.001
Davis et al.2017[5]	**Moderate** exacerbation: outpatient visits with a diagnosis of COPD and oral corticosteroids and/or an antibiotic medication fill on the same day of, or within 10 days after, the outpatient visit. **Severe** exacerbation: hospitalizations with a primary diagnosis of COPD and/or emergency department visits with a primary or secondary diagnosis of COPD.	Total	PDC ≥0.80 (reference) vs 0.50 ≤ PDC < 0.80	Frequency of exacerbations (adjusted rate ratio)	ICS/LABA	IRR: 1.07, 95% CI: 0.98-1.18, p=0.14
			PDC ≥0.80 (reference) vs 0.30 ≤ PDC < 0.50			IRR: 1.11, 95% CI: 1.01-1.21, p=0.03
			PDC ≥0.80 (reference) vs PDC <0.30			IRR: 1.11, 95% CI: 1.01-1.21, p=0.02
		Moderate	PDC ≥0.80 (reference) vs 0.50 ≤ PDC < 0.80	Frequency of exacerbations (adjusted rate ratio)	ICS/LABA	IRR: 1.07, 95% CI: 0.97-1.18
			PDC ≥0.80 (reference) vs 0.30 ≤ PDC < 0.50			IRR: 1.04, 95% CI: 0.94-1.15
			PDC ≥0.80 (reference) vs PDC <0.30			IRR: 1.06, 95% CI: 0.97-1.17
		Severe hospitalizations	PDC ≥0.80 (reference) vs 0.50 ≤ PDC < 0.80	Frequency of exacerbations (adjusted rate ratio)	ICS/LABA	IRR: 1.13, 95% CI: 0.85-1.51
			PDC ≥0.80 (reference) vs 0.30 ≤ PDC < 0.50			IRR: 1.36, 95% CI: 1.02-1.82, p=0.03
			PDC ≥0.80 (reference) vs PDC <0.30			IRR: 1.48, 95% CI: 1.13-1.93, p<0.01
		Severe emergency department visit	PDC ≥0.80 (reference) vs 0.50 ≤ PDC < 0.80	Frequency of exacerbations (adjusted rate ratio)	ICS/LABA	IRR: 1.09, 95% CI: 0.89-1.34
			PDC ≥0.80 (reference) vs 0.30 ≤ PDC < 0.50			IRR: 1.33, 95% CI: 1.10-1.62, p<0.01
			PDC ≥0.80 (reference) vs PDC <0.30			IRR: 1.25, 95% CI: 1.05-1.50 p=0.01

Author	Definition of exacerbation	Exacerbation type assessed	Analysis	Outcome	Medication assessed	Result
Fan et al.2003[6]	**Moderate** exacerbation: an outpatient visit with a primary ICD-9 code for COPD combined with a new prescription for a 14 (or fewer)-day course of either prednisone or a commonly used antibiotic (amoxicillin, sulfa drugs, cephalosporins, quinolones, tetracyclines, and macrolides) that was dispensed and filled within 24–48 hours of the clinic visit. **Severe** exacerbation: hospitalization for COPD with primary discharge diagnosis code (ICD-9) for COPD	Severe	Baseline analysis, users (prescriptions filled for more than 80% of days during the interval) vs no users (reference group)	Time to first exacerbation (hazard ratio)	ICS	HR: 0.85, 95% CI: 0.67-1.06
Humenberger et al.2018[7]	**Severe** exacerbation: exacerbations leading to hospitalization	Severe	MPR >0.80 (reference) vs 0.50 ≤ MPR ≤ 0.80	Exacerbator vs no exacerbator (adjusted odds ratio)	Inhaled therapy: LABA and/or LAMA, LABA/ICS, or LABA/LAMA/ICS	Unadjusted OR: 0.77 95% CI: 0.44-1.35
						Adjusted OR: 0.95 95% CI: 0.50-1.78
			MPR >0.80 (reference) vs MPR <0.50			Unadjusted OR: 0.44 95% CI: 0.27-0.71
						Adjusted OR: 0.58 95% CI: 0.33-1.02

Author	Definition of exacerbation	Exacerbation type assessed	Analysis	Outcome	Medication assessed	Result
Ismaila et al.2014[8]	**Moderate** exacerbations: a physician visit with a diagnosis code for COPD in any field and a prescription for an oral corticosteroid (OCS) or an antibiotic for respiratory infections. **Severe** exacerbations: an ER visit or hospitalization with a primary or discharge diagnosis code for COPD.	Moderate	MPR ≥0.80 vs MPR <0.80 (reference)	Rate of COPD related exacerbations	Triple therapy (adherence to LAMA)	Mean (SD) number of events /patient/100 days during follow up: 1.26 (4.67) in the poor adherent group vs 0.54 (3.62) in adherent group
					Triple therapy (adherence to ISC/LABA)	Mean (SD) number of events /patient/100 days during follow up: 1.07 (3.46) in the poor adherent group vs 0.54 (1.80) in adherent group
				Exacerbator vs no exacerbator (adjusted odds ratio)	Triple therapy (adherence to LAMA)	OR: 0.452 95% CI: 0.405-0.504
					Triple therapy (adherence to ISC/LABA)	OR: 0.538 95% CI: 0.489-0.593
		Severe	MPR ≥0.80 vs MPR <0.80 (reference)	Rate of COPD related exacerbations	Triple therapy (adherence to LAMA)	Mean (SD) number of events /patient/100 days during follow up: 0.56 (1.59) in the poor adherent group vs 0.23 (0.69) in adherent group
					Triple therapy (adherence to ISC/LABA)	Mean (SD) number of events /patient/100 days during follow up: 0.46 (1.30) in the poor adherent group vs 0.29 (0.84) in adherent group
				Exacerbator vs no exacerbator (adjusted odds ratio)	Triple therapy (adherence to LAMA)	OR: 0.580 95% CI: 0.525-0.640
					Triple therapy (adherence to ISC/LABA)	OR: 0.740 95% CI: 0.671-0.816
Mueller et al.2017[9]	**Moderate** exacerbation: any need for a COPD rescue medication (corticosteroids, antibiotics; ATC codes: R01AD*, R02AB*).	Moderate	MPR ≥0.80 (reference) vs MPR <0.80	Exacerbator vs no exacerbator (adjusted odds ratio)	LABA, LAMA, ICS and/or LABA/ICS	OR: 1.694 95% CI: 1.341-2.139 p-value <0.001

Author	Definition of exacerbation	Exacerbation type assessed	Analysis	Outcome	Medication assessed	Result
Punekar et al. 2015[10]	**Moderate** exacerbation: management with COPD specific antibiotics combined with oral corticosteroids (OCS) and/or medical diagnosis of COPD exacerbations outside hospital. **Severe** exacerbation: exacerbations resulting in a hospitalisation or emergency room visit for COPD.	Any exacerbation (moderate + severe)	MPR ≥0.80 vs MPR <0.80	Rate per person-year (95% CI)	LAMA	Adherent group: 0.44 (0.41-0.47) Poor adherent group: 0.40 (0.38-0.42)
					LABA	Adherent group: 0.48 (0.41-0.57) Poor adherent group: 0.43 (0.39-0.48)
					LABA/ICS	Adherent group: 0.71 (0.68-0.74) Poor adherent group: 0.57 (0.55-0.59)
		Severe			LAMA	Adherent group: 0.22 (0.21-0.24) Poor adherent group: 0.13 (0.12-0.14)
					LABA	Adherent group: 0.19 (0.14-0.24) Poor adherent group: 0.10 (0.08-0.12)
					LABA/ICS	Adherent group: 0.23 (0.22-0.25) Poor adherent group: 0.15 (0.14-0.16)
			MPR ≥0.80 vs MPR <0.80 (reference)	Time to first exacerbation (adjusted hazard ratio)	LABA/ICS	HR: 1.60 95% CI: 1.17-2.19 P<0.05

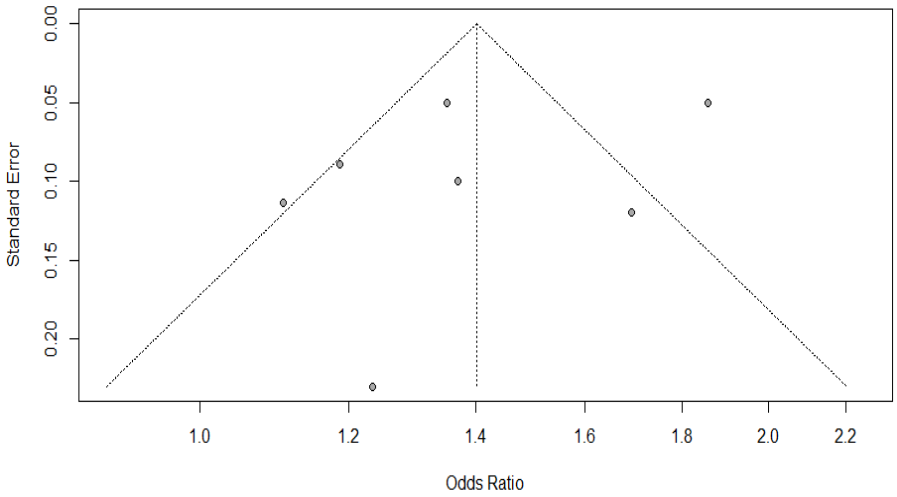
Author	Definition of exacerbation	Exacerbation type assessed	Analysis	Outcome	Medication assessed	Result
Wurst et al.2014[11]	**Moderate exacerbation** (community treated): any one of the following events: COPD exacerbation diagnosis or acute bronchitis diagnosis (ICD-9 codes: 491.21, 491.22, 494.1, 466, 466.x, and 466.xx); asthma exacerbation diagnosis (ICD-9 codes: 493.12, 493.22, and 493.92) with prior history of two or more COPD codes; bronchitis, not specified as acute or chronic (ICD-9 codes: 490, 490.x, and 490.xx in addition to obstructive chronic bronchitis [491.2]) with antibiotics and OCS within 5 days of each other; or antibiotic and OCS dispensing on the same day. If more than one of these events occurred within 14 days from each other, the first event was taken as the start of the episode. **Severe exacerbation**: a COPD-related emergency department visit (identified by a medical dataset record with an emergency department as the place of service or a Current Procedural Terminology code between 99281–99288 without a confinement identification) or hospitalization (episode with a confinement identification) with multiple records on the same date counted as a single visit.	Any exacerbation	MPR ≥0.80 vs MPR <0.80	Absolute number and % of patients with exacerbation occurrence (none, 1 or ≥ 2)	LAMA	Adherent group: None: 60.0% (490/817) 1 event: 26.1% (213/817) ≥ 2 events: 14.0% (114/817) Nonadherent group: None: 55.2% (1217/2205) 1 event: 28.9% (638/2205) ≥ 2 events: 15.9% (350/2205)
		Moderate exacerbations				Adherent group: None: 70.1% (573/817) 1 event: 20.7% (169/817) ≥ 2 events: 9.2% (75/817) Nonadherent group: None: 66.4% (1465/2205) 1 event: 23.2% (512/2205) ≥ 2 events: 10.3% (228/2205)
		Severe exacerbations				Adherent group: None: 85.1% (695/817) 1 event: 13.2% (108/817) ≥ 2 events: 1.7% (14/817) Nonadherent group: None: 83.7% (1846/2205) 1 event: 13.0% (287/2205) ≥ 2 events: 3.3% (72/2205)

Author	Definition of exacerbation	Exacerbation type assessed	Analysis	Outcome	Medication assessed	Result
Wurst et al.2014[11]	See above	Any exacerbation	PDC ≥0.80 vs PDC <0.80	Absolute number and % of patients with exacerbation occurrence (none, 1 or ≥ 2)	LAMA	Adherent group: None: 61.7% (357/579) 1 event: 25.7% (149/579) ≥ 2 events: 12.6% (73/579) Nonadherent group: None: 55.3% (1350/2443) 1 event: 28.7% (702/2443) ≥ 2 events: 16.0% (391/2443)
		Moderate exacerbations				Adherent group: None: 71.3% (413/579) 1 event: 20.6% (119/579) ≥ 2 events: 8.1 % (47/579) Nonadherent group: None: 66.5% (1625/2443) 1 event: 23.0% (562/2443) ≥ 2 events: 10.5% (256/2443)
		Severe exacerbations				Adherent group: None: 85.8% (497/579) 1 event: 12.4% (72/579) ≥ 2 events: 1.7% (10/579) Nonadherent group: None: 83.7% (2044/2443) 1 event: 13.2% (323/2443) ≥ 2 events: 3.1% (76/2443)

CI: confidence interval; HR: hazard ratio; ICS: inhaled corticosteroids; IRR: incidence rate ratio; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarine antagonist; MPR: medication possession ratio; OR: odds ratio; PDC: proportion of days covered; SD: standard deviation

5. Publication bias

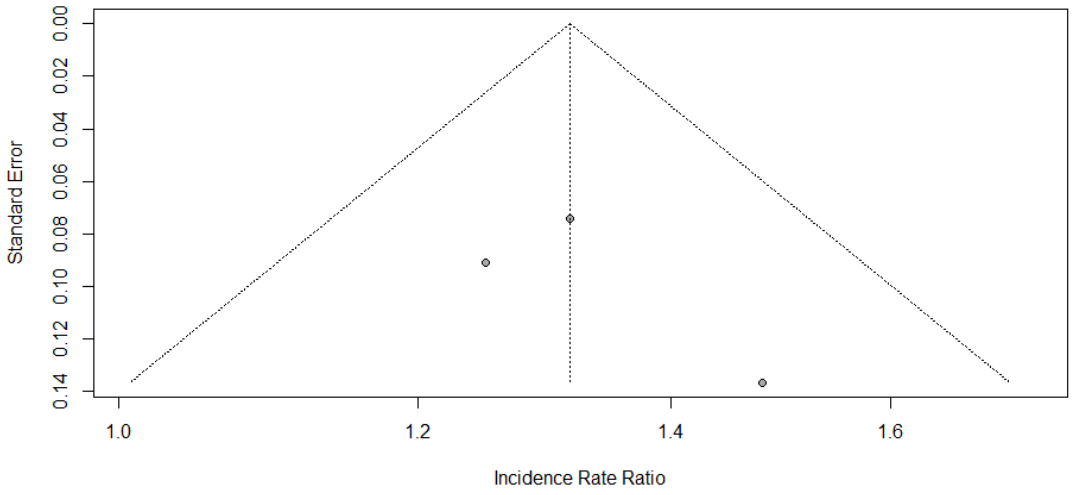
Meta-analysis on risk of at least one COPD exacerbation



Egger's regression test: t = -1.02, df = 5, p-value = 0.3553

eFigure 1: Funnel plots and Egger's regression test for the assessment of potential publication bias for studies included in the meta-analysis.

Meta-analysis on frequency of COPD exacerbations

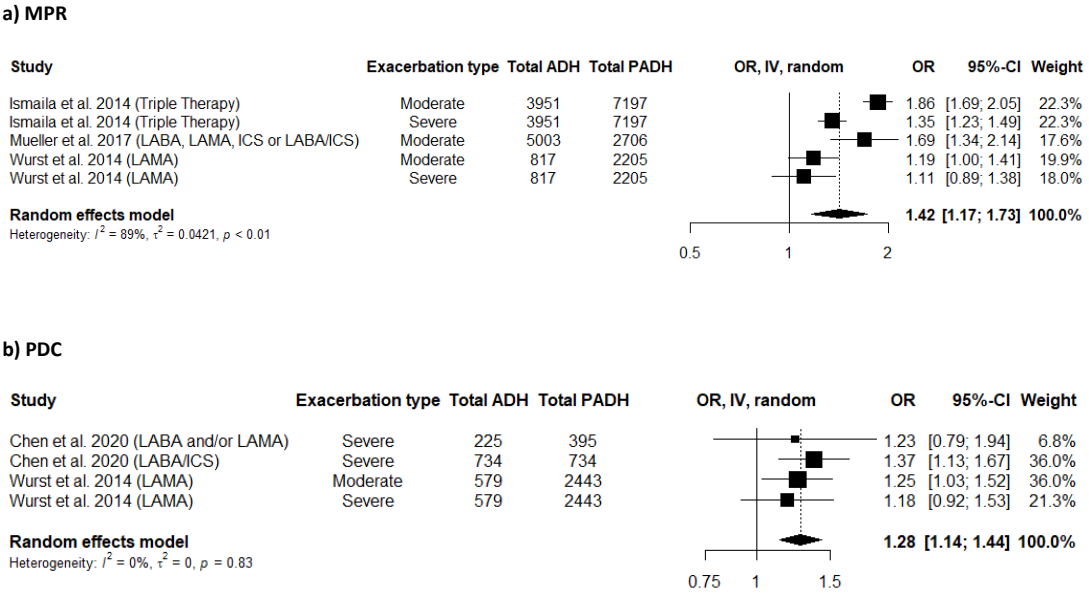


Egger's regression test: t = 0.97, df = 1, p-value = 0.5093

eFigure 2: Funnel plots and Egger's regression test for the assessment of potential publication bias for studies included in the meta-analysis.

6. Supplemental figure of meta-analysis

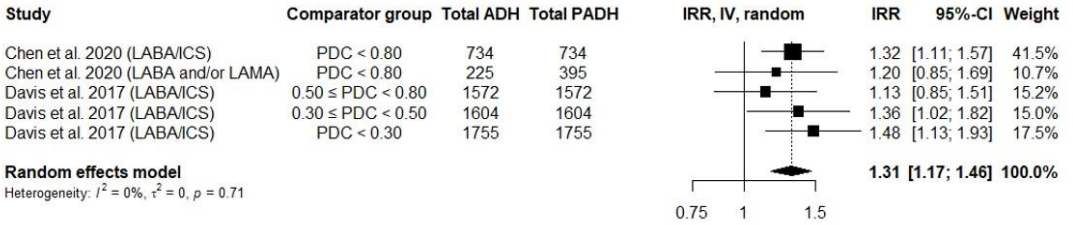
Meta-analysis on risk of at least one COPD exacerbation



eFigure 3: Sensitivity analyses based on adherence assessment method for impact of adherence on exacerbation occurrence risk (random effects model). a) Results with medication possession ratio as adherence assessment method. b) Results with proportion of days covered as adherence assessment method.

ADH: adherent group sample size; CI: confidence interval; ICS: inhaled corticosteroid; IV: inverse-variance; LABA: long-acting β2-agonist; LABA/ICS: dual therapy of long-acting β2-agonist and inhaled corticosteroid; LAMA: long-acting muscarine antagonist; MPR: medication possession ratio, PADH: poor adherent group sample size; OR: odds ratio; PDC: proportion of days covered.

Meta-analysis on time-dependent risk of COPD exacerbations

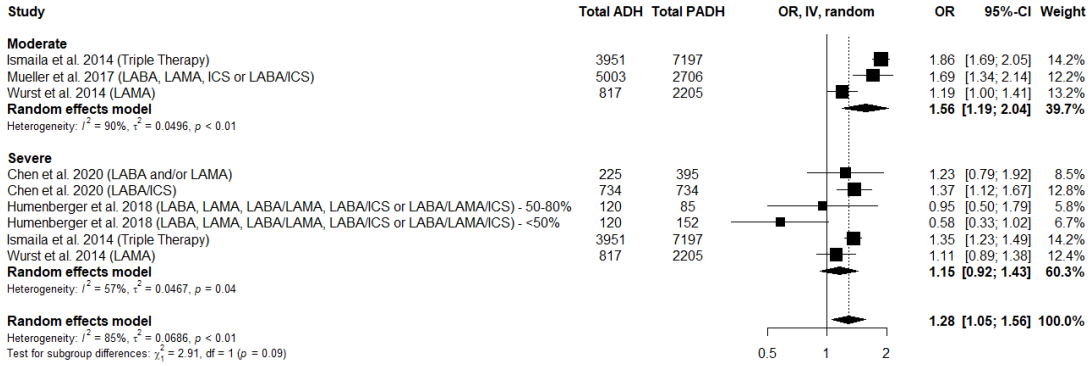


eFigure 4: Meta-analysis on impact of adherence on exacerbation frequency (random effects model).

ADH: adherent group sample size; CI: confidence interval; ICS: inhaled corticosteroid; IRR: incidence rate ratio; IV: inverse-variance; LABA: long-acting β2-agonist; LABA/ICS: dual therapy of long-acting β2-agonist and inhaled corticosteroid; LAMA: long-acting muscarine antagonist; PADH: poor adherent group sample size; PDC: proportion of days covered.

Sensitivity meta-analyses on the risk of COPD exacerbations incorporating the studies excluded based on the quality assessment.

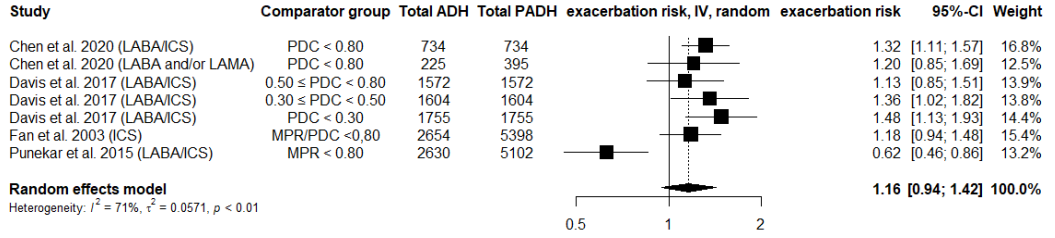
a) For the occurrence of at least one COPD exacerbation



eFigure 5a: Sensitivity analyses for impact of adherence on exacerbation occurrence risk (random effects model) including the study of Humenberger et al.[7] (study excluded based on quality assessment).

ADH: adherent group sample size; CI: confidence interval; ICS: inhaled corticosteroid; IV: inverse-variance; LABA: long-acting β2-agonist; LABA/ICS: dual therapy of long-acting β2-agonist and inhaled corticosteroid; LAMA: long-acting muscarine antagonist; OR: odds ratio; PADH: poor adherent group sample size; PDC: proportion of days covered.

b) For the time-dependent risk of COPD exacerbations



eFigure 5b: Sensitivity analyses for impact of adherence on time-dependent risk of COPD exacerbations (random effects model) including the studies of Fan et al.[6] and Punekar et al.[10] (studies excluded based on quality assessment).

ADH: adherent group sample size; CI: confidence interval; ICS: inhaled corticosteroid; IV: inverse-variance; LABA: long-acting β2-agonist; LABA/ICS: dual therapy of long-acting β2-agonist and inhaled corticosteroid; LAMA: long-acting muscarine antagonist; MPR: medication possession ratio; PADH: poor adherent group sample size; PDC: proportion of days covered.

7. References

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