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Medication adherence to inhalation therapy and the risk of COPD exacerbations: a systematic review with meta-analysis

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ABSTRACT

Background Assessing medication adherence is crucial in chronic obstructive pulmonary disease (COPD) management to prevent exacerbations. However, it is unclear whether this association between adherence and exacerbations is influenced by the adherence assessment methods or thresholds used. Electronic healthcare databases are valuable to study exacerbations and adherence in real life. We aimed to systematically review the literature to identify adherence assessment methods and thresholds used in healthcare databases when investigating the association between medication adherence and COPD exacerbations and to meta-analyse the associated effect sizes.

Method MEDLINE, Web of Science and Embase were searched for peer-reviewed articles, written in English, published up to 10 October 2022 (PROSPERO: CRD42022363449). Two reviewers independently conducted screening for inclusion and performed data extraction. A qualitative approach described the adherence assessment methods and thresholds used. A quantitative approach (meta-analysis using random effects model) estimated the association between adherence and the risk of COPD exacerbations.

Results Eight studies were included in the systematic review of which five studies were included in the meta-analysis. The medication possession ratio (MPR) and the proportion of days covered (PDC) were the adherence assessment methods used and 0.80 was always used as threshold to differentiate good from poor adherence. Adherence and exacerbations were mostly measured over the same time period. Poor adherence (MPR or PDC<0.80) was significantly associated with a higher COPD exacerbation risk (OR 1.40, 95% CI 1.21 to 1.62, I^2=85%), regardless of the adherence assessment method used. Results were consistent when stratified by exacerbation severity. Poor adherence was also associated with a time-dependent risk of COPD exacerbations (incidence rate ratio 1.31, 95% CI 1.17 to 1.46).

Conclusion Our systematic review with meta-analysis demonstrated a 40% increased risk of COPD exacerbations in case of poor adherence to inhaler medication.

PROSPERO registration number CRD42022363449.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Adherence to inhaler medication is crucial in chronic obstructive pulmonary disease (COPD) management to prevent exacerbations. The use of different methods to measure adherence and/or different adherence thresholds may result in different adherence values and/or proportions of adherent patients. It is unclear whether the association between adherence and COPD exacerbations can be demonstrated in healthcare databases and whether this observed association is influenced by the adherence assessment method or threshold used.

WHAT THIS STUDY ADDS

⇒ When meta-analysing studies assessing adherence to COPD medications (Anatomical Therapeutic Chemical classification code R03) and exacerbations in electronic healthcare databases, poor medication adherence (<0.80) was significantly associated with a higher probability of exacerbation occurrence (both moderate and severe exacerbations) and a higher frequency of severe exacerbations. The association between poor adherence and the risk of at least one COPD exacerbation was not impacted by the adherence assessment method used (medication possession ratio or proportion of days covered).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Electronic healthcare databases are a valuable resource to quickly identify poor adherent patients. These patients should be targeted for adherence interventions because our study demonstrated that, regardless of the adherence assessment methods used, poor adherence (<0.80) was associated with a 40% increased risk of COPD exacerbations.

INTRODUCTION

Exacerbations of chronic obstructive pulmonary disease (COPD) are defined in the 2024 Global Initiative for Chronic Obstructive Lung Disease (GOLD) report as episodes of acute respiratory symptom (dyspnoea and/or cough and sputum) worsening.[1] These

events represent a significant economic burden, affect disease morbidity and are linked to lung function deterioration.[1–3] Poor adherence to pharmacological treatment has been associated with an increased risk of exacerbations and increased healthcare use.[1 2] There is considerable variability in adherence rates calculated by different studies. Yet, medication adherence in patients with COPD is generally low, with adherence rates ranging from 7% to 78%.[4 5] Adherence rates may vary depending on study type[6] (clinical trials generally show higher rates than clinical practice), data source[5] (self-reported estimates are generally higher than objective measures) and disease severity. In cases of advanced disease, the inhaled medication may be perceived as more necessary by the patient resulting in higher adherence values,[7] although other studies have shown lower adherence in patients with multiple COPD treatments.[8]

Numerous methods to measure medication adherence exist.[9–12] Consequently, it can be challenging to select the most appropriate assessment method.[13] In addition, questions have been raised about the arbitrary cut-off point of 0.80 to categorise between good and poor adherence,[14] and multiple cut-offs[5] are currently used. The use of different methods to measure adherence and/or different adherence thresholds contributes to the large difference in adherence values and/or proportions of adherent patients between studies.[5 15]

Electronic healthcare databases are a valuable resource to investigate exacerbations and medication adherence in real life, as they are easy to use, inexpensive and relevant to evaluate clinical outcomes.[16 17] They have the advantage to investigate adherence and exacerbations without recall, reporting and/or response bias, which are important influencing factors in measuring adherence[16 18] and exacerbations.[19]

To the best of our knowledge, there is no overview of the existing literature on the association between adherence and COPD exacerbations based on data from electronic healthcare databases and the adherence assessment methods and thresholds used in these studies. Moreover, it is unclear whether the association between adherence and COPD exacerbations can be demonstrated in healthcare databases and whether this observed association between adherence and exacerbations is influenced by the adherence assessment methods or thresholds used. Therefore, we aimed to systematically review literature on the association between adherence and COPD exacerbations to identify the most frequently used adherence assessment methods and thresholds based on data from electronic healthcare databases. Second, we aimed to summarise the corresponding effect sizes in a meta-analysis. We hypothesise that poor adherence is linked to an increased risk of exacerbations.

METHODS

This systematic review and meta-analysis is reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.[20] The protocol of this study was registered on PROSPERO[21] (registration number: CRD42022363449).

Definition of adherence and exacerbation severity

While undertaking this review, medication adherence was defined as the extent to which a patient uses medication as recommended (taking into account the dosing regimen) over a specific period of time. This corresponds to the implementation part of the adherence process as defined by the Ascertaining Barriers for Compliance taxonomy for medication adherence.[22 23] Definitions for COPD exacerbations and classification of severity were based on the GOLD 2023 report.[1] Severe exacerbations were defined as COPD-related hospitalisations, whereas moderate exacerbations were defined as events requiring treatment with oral corticosteroids and/or antibiotics in an outpatient setting.[1]

Literature search and search strategy

Three databases (MEDLINE using the PubMed interface, Web of Science and Embase using the Embase.com interface) were extensively searched using search terms based on the following concepts: COPD, medication adherence, exacerbation and electronic healthcare database (summarised in online supplemental eTables 1–3). The search extended from inception of the database to 10 October 2022. Reference lists and citations of included studies were manually checked to identify other relevant articles.

Study inclusion criteria

Peer-reviewed studies, written in English, were eligible for inclusion in this systematic review. There was no restriction on the date of publication. Study populations were limited to patients with COPD. Only studies reporting the association between adherence to COPD maintenance therapy (Anatomical Therapeutic Chemical classification code R03) with a defined adherence threshold and the risk of COPD exacerbations were included. The study population identification, the adherence assessment and detection of exacerbations had to be based on an electronic healthcare database (eg, electronic healthcare records, medication prescription claims, pharmacy dispensing claims). Moreover, exacerbations had to be identified in the same time period or in a subsequent time period as the adherence assessment. Exacerbations needed to be stratified by exacerbation severity, comparable with the GOLD classification of exacerbation severity.[1] A complete overview of the inclusion and exclusion criteria can be found in online supplemental eTable 4.

Study selection

Two reviewers (DV and FVV) performed an independent screening of the title and abstract followed by

full-text evaluation, using Rayyan software.[24] Conflicts were resolved by a consensus meeting with a senior researcher (LL). Reviewers were blinded to each other's decisions. The Cohen's kappa coefficient[25] was calculated to determine the inter-rater reliability.

Quality assessment

The quality assessment was completed by the two reviewers (DV and FVV) independently, and discrepancies were discussed in a consensus meeting with the senior researcher (LL). Each included study was judged for their quality using the quality assessment tool 'QUALSYST' from the 'Standard Quality Assessment Criteria for Evaluating Primary Research Papers from a Variety of Fields' (chapter 3—online supplemental appendix).[26] Studies were included for meta-analysis if scoring at least 75% on the quality assessment.

Data extraction

A standardised data extraction table was developed to extract the study characteristics (study design, data collection method, factors for COPD diagnosis and recruitment setting), the baseline characteristics of the included population (sample size, age), the characteristics of the medication adherence assessment (medication assessed, measurement method, time period of assessment, threshold for differentiation between good and poor adherence) and the effect measures (exacerbation outcome, time period of assessment, time relation to adherence, statistics performed, results and adjustment factors/covariates) of the included studies. The table was pilot tested on three studies and refined by the two reviewers (DV and FVV). Subsequently, one reviewer (DV) performed the data extraction for all included studies, the other reviewer (FVV) checked the extracted data. Any disagreements were resolved by mutual agreement. When information or data were unclear or missing, the corresponding author of the included study was contacted.

Data analysis

A two-way approach was used for data synthesis: a qualitative descriptive approach to provide an overview of the extracted study characteristics with the medication adherence assessment methods and thresholds used in the included studies, and a quantitative approach (meta-analysis) to estimate the association between adherence and COPD exacerbations. A meta-analysis was performed on the risk of COPD exacerbations, separately for the occurrence of an exacerbation (risk of at least one exacerbation; exacerbator vs no exacerbator) and the time-dependent risk of COPD exacerbations (time to first severe exacerbation and/or frequency of exacerbations). A random effects model with the inverse-variance weighting method was used, and results were presented visually in a forest plot. Heterogeneity was tested using the Cochran's Q-test, the between-study variance τ^2 (Paule-Mandel estimator)[27] and the I^2 statistic (which was considered to be low (<30%), moderate (30–60%) or high (>60%)). The effect sizes from each included study were reported as ORs for the risk of at least one exacerbation, and incidence rate ratios (IRR) for the time-dependent risk of COPD exacerbations. All effect sizes were presented with their 95% CI. The association between adherence and COPD exacerbations was investigated between the adherent group (reference) and poor adherent group (comparator). For studies with effect sizes expressed with the poor adherent group as reference, data conversions were performed. The risk of publication bias at the outcome level for the studies included in the meta-analyses was assessed by funnel plot asymmetry and by Egger's regression test. As a subgroup analysis, results were stratified by exacerbation severity. Moreover, the impact of different adherence assessment methods and adherence thresholds was investigated as a sensitivity analysis. Additionally, a sensitivity analysis was performed including studies that were initially excluded based on their quality score. A two-sided p value <0.05 was considered statistically significant. All analyses were performed with the meta package in R (R V.4.2.3 with RStudio V.2023.03.1 build 446).[28 29]

RESULTS

Search results and quality assessment

After duplicates were removed, a total of 1365 unique studies were identified. After title and abstract screening, 66 studies were selected (Cohen's κ=0.58). After full-text assessment, six studies were included (Cohen's κ=0.68). In addition, two studies were included after identification in the reference and citation lists of the identified studies. Consequently, eight studies were included in the systematic review.

The assigned scores for the quality assessment ranged from 68% to 95% and are shown in online supplemental eTable 5. Due to a quality score of <75%, the studies by Fan *et al*,[30] Humenberger *et al*[31] and Punekar *et al*[32] were excluded from the meta-analysis. Consequently, five studies were included in the meta-analysis (figure 1).

Study characteristics

The general characteristics of the eight included studies are presented in table 1. Half of the included studies were conducted in North America,[8 30 33 34] while other studies were performed in Europe[31 32 35] or Asia.[36] The sample size varied from 357 to 45 937 included patients with COPD. The diagnosis of COPD was mainly based on an age criterium,[8 30–33 35] associated with a diagnosis code (all included studies) and medication use (all included studies). Online supplemental eTable 6 provides an overview of the inclusion criteria of the different studies. Patients were selected based on only hospital data,[31] only outpatient data[8 32–34 36] or both.[30 35]

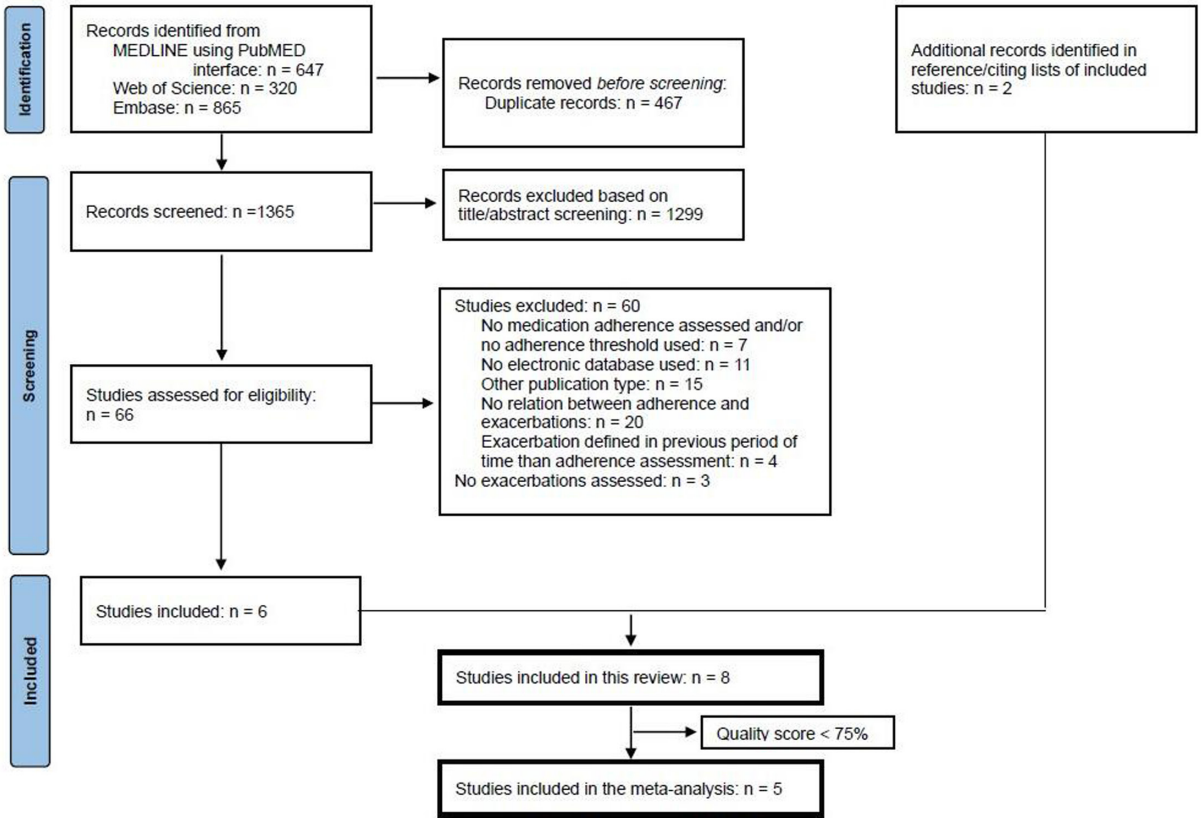

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Adherence assessment

Adherence assessment was based on the proportion of days covered (PDC, the number of days covered during a fixed time period),[33 34 36] the medication possession ratio (MPR, the sum of days supplied during a patient-specific time period (eg, time between first and last prescriptions))[8 31 32 34 35] or a variance of MPR/PDC (percentage of days supplied during a fixed time period)[30] (online supplemental eTable 7). All studies used a cut-off point of 0.80 to categorise between good and poor adherence. Davis *et al*[33] and Humenberger *et al*[31] applied additional cut-off points to further divide the poor adherence group.

Exacerbation assessment

The majority of included studies assessed both moderate and severe exacerbations.[8 30 32–34 36] In contrast, the study by Mueller *et al*[35] evaluated only moderate exacerbations and the study by Humenberger *et al*[31] evaluated only severe exacerbations. An overview of the definitions of moderate and severe exacerbations used in each included study is available in online supplemental eTable 8. Adherence and exacerbation occurrence were measured over the same period of time in all included studies, except in the studies by Fan *et al*[30] (adherence in 90 days before occurrence of exacerbation) and Mueller *et al*[35] (exacerbations assessed in second half of 12-month adherence assessment period).

Association between adherence and COPD exacerbations

Results of all included studies are tabulated in online supplemental eTable 8. The reported effect sizes were adjusted for possible confounders (online supplemental eTable 6), including the exacerbation history (proxied by the number of preindex hospitalisations or emergency department visits for COPD exacerbations[8 30 32 33 36] and/or the number of preindex prescriptions for short-acting bronchodilators,[8 30 32 33 35 36] antibiotics[8 30 33 36] and/or oral corticosteroids[8 30 33 36]). In the study by Wurst *et al*,[34] no effect measures were available because only descriptive analyses were performed but the effect size (OR) could be calculated.

To investigate the impact of adherence on the risk of at least one exacerbation, four studies were included in a meta-analysis, while two studies were included in another meta-analysis to examine the impact of adherence on the frequency of exacerbations. No publication bias was suspected based on the visual inspection of the funnel plot (online supplemental eFigures 1 and 2) and Egger's regression tests, although the interpretability was limited due to inclusion of less than 10 studies.

Meta-analysis on risk of at least one COPD exacerbation

Poor adherence (MPR or PDC<0.80) was significantly associated with a higher odds of exacerbation occurrence (pooled effect estimate: OR 1.40, 95% CI 1.21 to 1.62,

Table 1 General characteristics of the eight included studies

Author	Year	Country	Study design	Sample size	Age	Adherence assessment method	Threshold	Proportion of adherent patients
Chen *et al*[36]	2020	China	Retrospective Observational cohort	11 708	No age minimum, no mean/median/ range presented	PDC	≥0.80 (sensitivity analysis for cut-off at 0.50)	10.8% in total; 36.3% in LABA and/or LAMA group, 26.4% in LABA/ICS group and 1.8% in oral mucolytic therapy group
Davis *et al*[33]	2017	USA	Retrospective Observational cohort	13 657	≥40 years, mean age of 67 years	PDC	Adherent: PDC≥0.80, mildly non-adherent: 0.50≤PDC<0.80, moderately non-adherent: 0.30≤PDC<0.50 and highly non-adherent: PDC<0.30	13.9% in LABA/ICS group
Fan *et al*[30]	2003	USA	Prospective Observational cohort	8033	≥45 years	% of days supplied during fixed time period of 90 days	>0.80	33% in ICS group
Humenberger *et al*[31]	2018	Austria	Retrospective Observational cohort	357	>40 years, mean age of 66.5 years (SD 10.6)	MPR	Complete adherence: >0.80, partial adherence: 0.50–0.80 and low adherence: <0.50	33.6% in total (LAMA, LABA, LABA/ICS, LABA/LAMA and LABA/LAMA/ICS users together)
Ismaila *et al*[8]	2014	Canada	Retrospective Observational cohort	23 707	≥40 years, mean age of 73.2 years (SD 10.3)	MPR	≥0.80	61.1% in LAMA monotherapy group, 62.9% to LAMA in LABA/LAMA/ICS group and 35.4% to LABA/ICS in LABA/ LAMA/ICS group

Continued

Table 1 Continued

Author	Year	Country	Study design	Sample size	Age	Adherence assessment method	Threshold	Proportion of adherent patients
Mueller *et al*[35]	2017	Germany	Retrospective Observational cohort	45 937	≥40 years, mean age of 71.4 years (SD 11.4)	MPR	≥0.80	30.0% in total; 38.0% in LABA group, 53.2% in LAMA group, 20.4% in ICS group and 26.8% in LABA/ICS group
Punekar *et al*[32]	2015	UK	Retrospective Observational cohort	17 529	≥40 years	MPR	≥0.80	34% in LABA group; 42% in LAMA group and 34% in LABA/ICS group
Wurst *et al*[34]	2014	USA	Retrospective Observational cohort	3268	≥40 to 65 years, mean age of 55.8 years (SD 5.4)	MPR and PDC	≥0.80	29.4% in LABA group and 37.1% in LAMA group

ICS, inhaled corticosteroids; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; MPR, medication possession ratio; PDC, proportion of days covered.

I^2=85%). The subgroup analysis based on exacerbation severity showed consistent results (figure 2). Poor adherence was associated with a significantly higher odds of moderate exacerbations (OR 1.56, 95% CI 1.19 to 2.04) and severe exacerbations (OR 1.32, 95% CI 1.21 to 1.43) (p value of 0.25 for test for subgroup differences). Results were consistent in a sensitivity analysis using the MPR or PDC for adherence assessment (online supplemental eFigure 3). Since all included studies used the cut-off point of 0.80 to categorise good and poor adherence, the impact of different adherence thresholds could not be assessed.

Meta-analysis on time-dependent risk of COPD exacerbations

Poor adherence (PDC<0.80) was also significantly associated with a higher frequency of severe COPD exacerbations (pooled estimated effect: IRR 1.31, 95% CI 1.17 to 1.46, online supplemental eFigure 4). There were insufficient data to perform meta-analysis for moderate exacerbations or for a sensitivity analysis investigating the influence of the adherence assessment method or adherence threshold.

Sensitivity analysis incorporating excluded studies

In a sensitivity analysis incorporating the study of Humenberger *et al*,[31] poor adherence (MPR or PDC<0.80) remained significantly associated with a higher odds of exacerbation occurrence (pooled estimated effect: OR 1.28, 95% CI 1.05 to 1.56). However, in the subgroup analyses based on exacerbation severity, the pooled estimated effect was no longer significant for severe exacerbations (online supplemental eFigure 5a). The sensitivity analysis on the time-dependent risk of COPD exacerbations trended to a similar association between poor adherence (MPR or PDC<0.80) and the risk of COPD exacerbation (pooled estimated effect: exacerbation risk 1.16, 95% CI 0.94 to 1.42), although no longer significant (online supplemental eFigure 5b).

DISCUSSION

Our systematic review based on eight studies investigating the relationship between medication adherence and COPD exacerbations in electronic healthcare databases observed that adherence assessment was mainly based on the MPR, PDC or a variation of these methods. All included studies used a binary cut-off (0.80) to differentiate between good and poor adherence, although some studies added extra cut-offs to distinguish several groups of poor adherent patients.[31 33] In our meta-analyses, we have demonstrated that poor adherence was associated with an increased risk of COPD exacerbations, both in occurrence and frequency.

The observed adherence assessment methods, MPR and PDC, were also the most prevalent methods in previous research in patients with asthma[9] or in reviews focusing on oral dosages[17] or on polypharmacy.[37] In

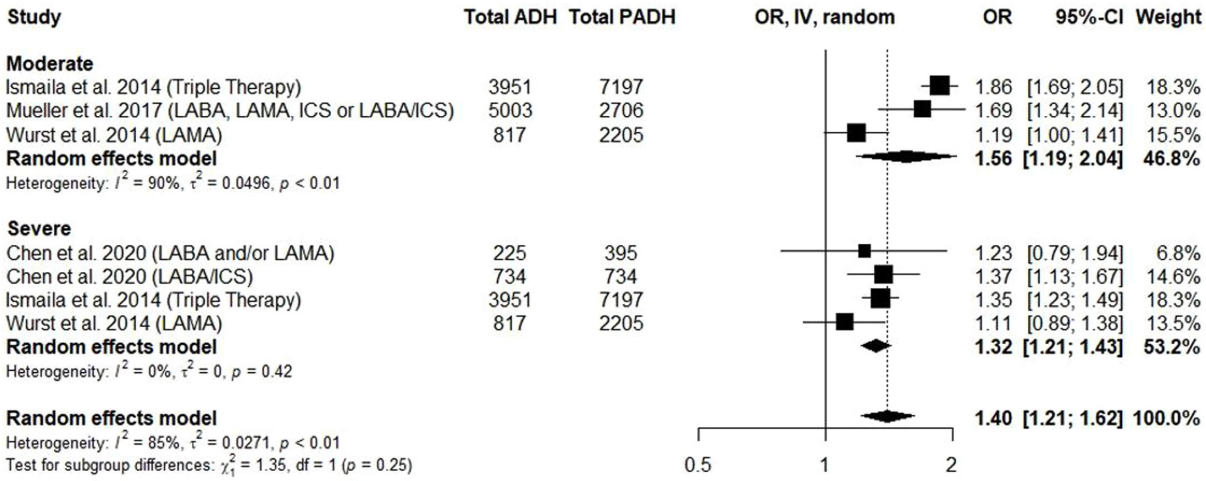

Figure 2 Subgroup meta-analysis based on exacerbation type for impact of adherence on exacerbation occurrence probability (random effects model). ADH, adherent group; ICS, inhaled corticosteroid; IV, inverse-variance; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; PADH, poor adherent group.

contrast to the review of Asamoah-Boaheng *et al*,[9] we did not consider the ratio of units of controller medication to the sum of units of controller medication and rescue medication (known as the asthma medication ratio) or the COPD treatment ratio as a measure of adherence. While it can be a valuable parameter in assessing disease control by treatment,[38] it is not designed to optimally measure adherence.

Approximately 30% of the patients with COPD showed good adherence in the included studies. This is in line with previous research, concluding that adherence rates in asthma and COPD varied widely depending on study type and disease severity.[4 6 7] The results of our meta-analysis summarise the existing evidence of the association between adherence and COPD exacerbations in observational studies using electronic healthcare databases and validate previously published observations.[39–41] Measuring adherence in observational studies is of particular value given that interventional studies (eg, randomised clinical trials) are characterised by restrictive inclusion and exclusion criteria and close follow-up of patients. This may result in adherence outcomes that are generally less reflective for real life.[6]

To compare the risk of COPD exacerbations among adherent versus poor adherent patients, potential confounders should be well balanced between the two groups. Therefore, we excluded studies with poor quality from the main analysis. A first important potential confounder is the level of disease severity (airflow limitation). If more severely ill patients are more adherent, the association between adherence and COPD exacerbations may be confounded by this factor as more severely ill patients are more at risk for exacerbations.[31] This could explain why the sensitivity analysis, including studies previously excluded based on their quality score, was no longer significant. Second, previously published research showed that the exacerbation history is the strongest predictor of future exacerbations.[1 42] All studies included in the meta-analysis adjusted their effect sizes for exacerbation history, except for the study by Wurst *et al*[34] (which included incident patients with COPD).

Based on figure 2, it could be suggested that the effect of adherence to inhaled corticosteroids has a stronger influence on the risk of COPD exacerbations compared with long-acting bronchodilators. However, incident patients in the study by Wurst *et al*[34] might have had a milder disease, while patients in the other studies have higher exacerbation risks related to more moderate or severe disease. Differences in the risk of COPD exacerbations between adherent patients and poor adherent patients may become more apparent in patients with moderate to severe disease, which may explain the observed difference between medication classes. To the best of our knowledge, no studies explored the association of medication adherence and the risk of COPD exacerbations in subgroups stratified by disease severity, and further research is therefore recommended.

The pooled estimated effect for moderate exacerbations was numerically higher than severe exacerbations (56% vs 32% higher odds, respectively), although no significant difference between subgroups (p=0.25 for test for subgroup differences) was observed. This means that the exacerbation severity did not modify the effect of poor adherence on the probability of COPD exacerbation occurrence. This small difference in pooled estimated effect may be explained by the higher prevalence of moderate exacerbations[43] and other risk factors influencing the need for hospitalisation, such as the socioeconomic status[44] and access to healthcare and/or health-seeking behaviour, which may vary between countries.[45]

Strength and limitations

Our systematic review is, to the best of our knowledge, the first to provide an overview of adherence assessment

methods and thresholds used on data from electronic healthcare databases to investigate the association between adherence and COPD exacerbations and to summarise the associated effect sizes. However, a limitation of this systematic review, which may have resulted in studies with valid results being missed, was the exclusion of non-English language studies; although an extensive search strategy was used. Moreover, our inclusion criteria were based but not limited to validated definitions, although validation of algorithms to identify patients with COPD or COPD exacerbations in electronic healthcare databases exists.[46–48] However, to the best of our knowledge, no validated algorithm is available that can be generally used in all electronic healthcare databases.

As adherence and exacerbations in all studies included in the meta-analysis assessed both parameters in the same time period, our results can only inform on an association but not on causation. Poor adherence is associated with an increased risk of COPD exacerbations.[1] On the other hand, adherence may increase after an exacerbation,[49 50] or in contrast exacerbations may lower adherence.[51] Therefore, a reverse causation between adherence and exacerbations cannot be excluded.

Since all included studies eligible for the meta-analysis on the impact of adherence on exacerbation occurrence used the cut-off point of 0.80 to distinguish between good and poor adherence, the impact of other adherence thresholds could not be assessed. Similar research in patients with asthma showed that adherence values ≥0.50 were associated with a reduced risk of asthma exacerbations.[9]

In addition, our results do not present the impact of the medication classes separately on the association between poor adherence and the risk of a COPD exacerbation, as we have pooled the effect sizes independently of the medication class studied. Furthermore, we excluded studies focused on short-acting bronchodilators only. This medication class can be used as add-on therapy for mild exacerbations, possibly interfering the association investigated in this systematic review.[1]

Only the study of Humenberger *et al*[31] used spirometry to inform COPD diagnosis and study inclusion. All other studies based COPD diagnosis on age, diagnosis codes registered and medication use. Electronic healthcare databases are characterised by some limitations such as the probability of coding errors, the inability to confirm if the patient actually has COPD or used the dispensed medication and the lack of information about the inhaler technique, spirometry results, patient-specific characteristics and laboratory values, such as blood eosinophil levels. Consequently, we were not able to confirm diagnosis of COPD nor appropriateness of medication. Furthermore, it should be noted there may be factors that influence the risk of COPD exacerbations that have not been taken into account when assessing the relationship between medication adherence and COPD exacerbations, such as smoking status.[52] These limitations have to be taken into account.

Recommendations for clinical practice

As only observational studies were included in our research, our results must be interpreted with caution based on the Grading of Recommendations, Assessment, Development and Evaluations framework.[53] Nevertheless, some recommendations seem appropriate. Although the association between poor adherence and the risk of COPD exacerbations is generally known,[1] our research is, to the best of our knowledge, the first to summarise studies assessing this relationship in electronic healthcare databases. These resources are useful in clinical practice to objectively and quickly identify poor adherent patients.[54] It may be recommended to link an initial screening for non-adherent patients in an electronic database to an in-depth adherence assessment with assessment of the inhaler technique. Verified poor adherent patients with COPD could be targeted for adherence interventions (such as supportive telephone calls[55]), as our study demonstrated that, regardless of the adherence assessment methods used, poor adherence (<0.80) was associated with a 40% increased risk of COPD exacerbations.

Research gaps

Adherence and COPD exacerbations were measured in the same time period for studies included in the meta-analysis. To further explore the impact of adherence on COPD exacerbations, research may investigate the long-term impact of adherence by assessing COPD exacerbations in a subsequent period of time.

The impact of other adherence thresholds other than 0.80 could not be assessed. Further research to validate the cut-off point of 0.80 in COPD is needed. Moreover, a second cut-off may be needed to assess the impact of overuse (MPR or PDC>1.20) on COPD exacerbations, which has been associated with an increased risk of severe COPD exacerbations as well.[56] In addition, further research should determine if these thresholds are independent of the exacerbation severity, the adherence assessment used and the medication class studied.

CONCLUSIONS

Our systematic review with meta-analysis demonstrated an increased risk of COPD exacerbations by poor adherence to inhaler medication, regardless of the adherence assessment method used. Results were consistent when stratified by exacerbation severity and highlight the importance of systematically screening adherence in patients with COPD.

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Contributors DV was responsible for the study concept, design and data analyses. FVV, MG and LL provided feedback to DV to optimise the methodology of this systematic review. DV and FVV performed the study selection, the quality assessment and the data extraction. DV drafted the manuscript and FVV, MG, AV and LL critically reviewed the manuscript. DV had access to the data and takes

responsibility for the integrity of the conduct of the study and the accuracy of the data analysis as guarantor. All authors read and approved the final manuscript.

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