Original Article

# Cost-Effectiveness and Impact on Health Care Utilization of Interventions to Improve Medication Adherence and Outcomes in Asthma and Chronic Obstructive Pulmonary Disease: A Systematic Literature Review

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***What is already known about this topic?*** Poor adherence to asthma and chronic obstructive pulmonary disease medications is commonplace despite the known risks for adverse health outcomes and associated consumption of costly health care resources.

***What does this article add to our knowledge?*** Implementing programs to improve adherence to inhaled medicines can be cost-effective, reducing medical costs and consumption of health care resources and improving disease control and patient-reported outcomes.

***How does this study impact current management guidelines?*** Implementation of proven adherence promotion programs (eg, using digitally enhanced care and one-to-one counseling) is cost-effective and could help improve asthma and chronic obstructive pulmonary disease control and aid management of health care budgets.

**BACKGROUND: Poor adherence to asthma and chronic obstructive pulmonary disease maintenance therapies impairs health outcomes. Proven and cost-effective programs to promote adherence and persistence are not yet in regular widespread use. Implementation costs are a potential barrier to uptake of such programs.**
**OBJECTIVE: We undertook a systematic literature review and narrative synthesis of studies investigating the cost-effectiveness of treatment adherence-promoting programs or that determined their impact on health care budget directly or via health care resource use (HCRU).**
**METHODS: We identified relevant publications using Medline and PreMEDLINE (PubMed), Embase (Embase.com, Elsevier), and EconLit for publications between January 2000 and July 2021. We also searched clinical trial databases and selected conference proceedings.**

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*Abbreviations used*
*COPD- Chronic obstructive pulmonary disease*
*HCRU- Health care resource use*
*ICER- Incremental cost-effectiveness ratio*
*ICS- Inhaled corticosteroids*
*LABA- Long-acting β-agonist*
*MUR- Medicines Use Review*
*QALY- Quality-adjusted life-year*
*QoL- Quality of life*
*SLR- Systematic literature review*

**RESULTS: Of 1,910 potentially relevant articles, 26 met prespecified inclusion criteria and underwent data extraction. Eleven reported a direct assessment of adherence, 15 included economic evaluations, and 17 described HCRU. None included an analysis of biologic medication use. When they were studied, interventions were often found to be highly cost-effective, with dominant incremental cost-effectiveness ratios in some cases. Reductions in direct costs and HCRU (health care visits, hospital admissions, and/or the use of medications, including add-on/reliever treatment and antibiotics) were frequently reported. Reported use of maintenance treatments improved in some studies. Counseling and/or digitally informed programs were used in all cases in which favorable outcomes were observed. CONCLUSIONS: Adherence-promoting interventions are mostly cost-effective and often result in reduced HCRU and associated costs. Multidisciplinary care involving one-to-one advice and digitally enhanced communications appear to offer the greatest benefit.**  **(J Allergy Clin Immunol Pract 2024;12:1228-43)**

***Key words:*** *Adherence; Asthma; Chronic obstructive pulmonary disease; Medical costs; Cost-effectiveness; Health care resource use; Inhaler use; Treatment persistence*

## BACKGROUND

Poor adherence to prescribed maintenance therapy is a major barrier to optimal asthma and chronic obstructive pulmonary disease (COPD) management, which can increase the risk of death, impair clinical outcomes, and reduce quality of life (QoL).[1-3] Poor adherence can also be associated with increased rates of health care use and costs.[4,5] Achieving and maintaining a high level of adherence to evidence-based treatment is clearly desirable and can avoid unnecessary escalation to costly biologics.[6]

Behaviors related to suboptimal disease management over time include, but are not limited to erratic nonadherence, intentional or intelligent nonadherence, and unwitting nonadherence.[4,7,8] Adherence may be affected by a range of factors including respiratory symptom variability, comorbidities, switching between treatments and/or inhaler devices, and the patient's concerns regarding financial burden, disease awareness, and stigma associated with public inhaler use.[9-11]

Numerous approaches have been developed and trialed to improve adherence to inhaled respiratory treatment. Features of programs have included inhaler choice,[4,12,13] health care professional training, education for patients, routine engagement featuring reminders,[14-18] family support,[11] and digital platforms to drive notifications, education, and support.[14,19-21] Personalized adherence interventions appear to be most effective in addressing the unique combination of factors that promote attitudes and behaviors regarding chronic disease management. Novel digital technologies (digital inhalers, apps, patient remote monitoring systems, reminder services, and data sharing) and devices that integrate data collection and management of events in daily life offer potential to address the behaviors and practices associated with poor adherence.[14,19-21] However, implementation of digital adherence-enhancing technology in real-world clinical practice remains low.[22]

Substantial health system and reimbursement-related challenges exist in relation to the development and implementation of adherence promotion programs.[23,24] However, insights into the cost-effectiveness of adherence-enhancing interventions in asthma and COPD are currently lacking.

### Objective of this study

We aimed to undertake a systematic literature review (SLR) to examine the cost consequences, cost-effectiveness, and budget impact of interventions designed to improve adherence to asthma or COPD inhaled medication regimens.

## METHODS

### Study design

The SLR protocol (see Table E1 in this article's Online Repository at www.jaci-inpractice.org) was developed and reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[25] The protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO; Registration CRD42021271678).[26]

### Information sources

The databases included in the literature search were Medline and PreMEDLINE (PubMed), Embase (Embase.com, Elsevier) and EconLit. Clinical trial databases and the conference proceedings of the ESPACOMP (International Society for Medication Adherence) and International Society for Pharmacoeconomics and Outcomes Research meetings were also searched.

The databases were searched for relevant publications of primary studies in English from January 1, 2000 to July 31, 2021. In addition, reference lists from key publications were searched manually to identify additional relevant original research studies.

### Eligibility criteria

Inclusion criteria were empirical interventional studies, including randomized and nonrandomized controlled trials, pre−post controlled ecological interventions or studies, natural experiments, and observational studies. Decision-analytic modeling studies that were entirely based on summary evidence from other empirical studies were not included.

### Search strategy

Table I presents the predefined scope according to patient population, intervention, comparator, and outcomes. The associated main search terms are also listed in Table I, and the detailed search strategy is reported in Table E2 (in this article's Online Repository at www.jaci-inpractice.org).

During the review process, inclusion criteria stated in the protocol were modified to include studies reporting health care resource use (HCRU) as an indirect indication of costs.

### Selection process

Initial screening was performed by one review team member, who screened titles and abstracts of the search results and scored them as include (eligible or potentially eligible/unclear) or exclude, based on predetermined inclusion and exclusion criteria. A second review team member independently screened around 30% of the initial screening results to verify the accuracy of the screening. Any misalignment in scoring was resolved through discussion or by consultation with a third member of the review team.

Full-text study reports of all potentially eligible studies were retrieved and independently screened for inclusion by two review team members. Reasons for excluding ineligible studies were recorded when necessary. Cases of nonalignment between reviewers were resolved through discussion or by consulting with a third member of the review team.

### Data collection process

We developed a structured extraction table in Microsoft Excel (Redmond, WA) and used it to collate data from each included study. Data were extracted by two review team members working independently. Disagreements were resolved through discussion, or if required, through consultation with a third member of the review team.

### Data extraction items

Data extracted included the author name, year of publication, study design, site and duration, population and demographic characteristics of study participants, therapy and intervention types, health care system types (eg, fully insured, national health service), sources of data on costs and health care use (eg, health records, patient reports), and study outcomes (costs, utilities, patient-reported outcomes, adherence, HCRU).

### Study risk of bias assessment

We performed quality assessments using the Quality of Health Economic Studies tool[27-30] for studies reporting cost-effectiveness or budget impact data (Table II).

### Synthesis methods

Given the expected heterogeneity in outcomes, we decided *a priori* that a narrative synthesis of extracted data and information would be most suitable in this case. The narrative synthesis was planned to provide information about the cost-effectiveness of interventions, budget impact and cost outcomes, and impact on HCRU and health utilities related to improved adherence to inhaled asthma or COPD medications.

## RESULTS

### Study selection

A total of 1,910 articles (after duplications were removed) were identified using the search strategy, in which 1,843 were excluded at title or abstract screening (Figure 1). Specific reasons for exclusion at this stage, other than not meeting inclusion criteria or meeting exclusion criteria, were not recorded. Anecdotally, not meeting inclusion criteria on patient population and study design was the most frequent reason for exclusion. Finally, we selected 26 publications for inclusion in the review (Figure 1). Of these, 11 reported a direct assessment of adherence (Table III). There were 15 studies reporting economic evaluations and 17 reporting HCRU, six of which also reported economic evaluations.

### Study characteristics

Overall, there was a high level of variation in study design (Table III; see Table E3 in this article's Online Repository at www.jaci-inpractice.org). Most studies (n = 19) involved patients with asthma. Study cohorts were drawn from various settings, including community pharmacies, primary care hospitals (including patients discharged from hospital care), and secondary care and health care insurance programs (Tables III and E3). A variety of study populations were reported, including children only,[54] young people (aged <18 years) as part of a larger sample,[34] or those of older age (lower age limits were defined as 40 years or greater, depending on the study).[31,32,42,48,49] Several studies focused on patients with documented suboptimal medication adherence at recruitment or baseline,[32,56,57] although a diagnosis of poorly controlled disease required for inclusion in other studies might have indicated poor adherence to maintenance treatment. Sample sizes, study designs, and durations all varied considerably (Table E3). Most studies were conducted in North America or Europe. Studies in low- and middle-income countries were not evident in the search results.

### Study interventions and outcomes

Intervention types across all 26 publications involved one or more of the following elements (Table III): smart devices or digital resources (eg, apps: n = 5), telemedicine (n = 3), clinic-based support (education and coaching, individualized care plans, shared decision-making: n = 8), counseling (one-to-one, delivered by a trained/accredited health care professional: n = 11), and inhaler technology (n = 4). Six publications used two elements each: smart devices and telemedicine,[40] counseling and telemedicine,[34] inhaler technology and counseling,[31] inhaler technology and smart devices,[39,54] and clinic-based support and counseling.[56]

Disease control and outcomes (including patient-reported outcomes), QoL, and/or inhaler technique were reported in 12 of 26 publications. Quality of life was assessed using a variety of generic and disease-specific questionnaires and instruments. Some studies also collected HCRU information via patient-reported vehicles such as structured diaries, interviews, and questionnaires.

### Quality scores

All applicable health economic studies (n = 8) were of high quality. Four studies scored 100,[31,32,35,37] three were rated with a score of 93,[33,34,38] and one had a score of 86[36] (Table II).

### Narrative synthesis of reported findings

**Effect of interventions on adherence.** Eleven studies reported adherence measures[33,34,40,42,44,48,49,51,52,55,56] (Table IV). Investigations of adherence used the self-report Morisky Medication Adherence Scale,[33,51,52] medication possession ratio,[55] proportion of days covered[44,49] or another measure of dispensing activity or drug use[34,40,42,48,56] (Table E3). Other studies that did not directly determine adherence used previously published assessments.[36,37,54]

Most studies (nine of 11) showed statistically significantly improved adherence (n = 8),[33,42,44,48,49,51,52,56] or numerical but nonsignificant improvements (n = 1),[34] and no intervention was found to influence adherence adversely. Effective interventions generally featured direct communication and/or

**TABLE I.** PICO elements and selected key search terms used in systematic literature search

| PICO element | Description | Selected search terms |
|---|---|---|
| Condition | Asthma, COPD | Asthma<br>Chronic obstructive pulmonary disease<br>Chronic airflow obstruction |
| Population | Adult patients with diagnosis of asthma or COPD according to international or national guidelines, or those whose condition was diagnosed by health care professional and who were currently prescribed inhaled maintenance therapy to manage the condition | Medication adherence<br>Technique |
| Intervention/exposure | Initiatives developed to improve adherence to inhaled medication for asthma or COPD among all patients or among those with documented poor adherence | Pharmacotherapy<br>Monitoring<br>Feedback<br>Asthma review<br>Optimization |
| Comparator/control | Studies were not limited to specific comparators for the purposes of screening and selection. Studies could compare against other interventions, usual care (including treatment or watchful waiting), or placebo (ie, not provided with intervention aiming to increase adherence), or had a pre-post intervention study design in which patients act as their own controls | Usual care<br>Placebo-controlled<br>Pre-post |
| Outcome: main | Studies of interest had a primary or secondary aim of assessing an intervention intended to promote improved adherence to prescribed inhaled maintenance therapy<br>Economic evaluations of direct and indirect health care costs (eg, cost-effectiveness analyses, cost—benefit analyses, cost-utility analyses, cost-minimization analyses, cost-comparison analyses, programmatic cost analyses, cost outcome analyses, cost consequence analyses, break-even analyses) as long as they were based on empirical data | Cost analysis<br>Cost-effectiveness<br>Economic evaluation<br>Affordability<br>Cost-utility<br>Health care resource use<br>Quality-adjusted life year |
| Outcomes: additional | Adherence to maintenance medication as assessed by any objective or validated subjective measure of adherence<br>Patient-reported outcomes: Asthma Control Test, Asthma Quality of Living Questionnaire, COPD Assessment Test, St George's Respiratory Questionnaire<br>Exacerbations requiring at least oral corticosteroid treatment (prescribed or taken, as measured by self-report or via objective measurement, such as from pharmacy dispensing or prescription records)<br>Work productivity assessments, such as Work Productivity and Activity Impairment questionnaire. | Patient-reported outcomes<br>Asthma Control Test<br>Asthma Quality of Living Questionnaire<br>COPD Assessment Test<br>St George's Respiratory Questionnaire |

*COPD*, chronic obstructive pulmonary disease; *PICO*, Patient/population, Intervention, Comparison, Outcome.
Full details of the search strategy are provided in Table E2.

decision-making involving discussion between the health care professional and the patient (Tables III and IV).

## Studies of cost-effectiveness or budget impact

**Cost-effectiveness.** Six studies reported cost-effectiveness findings (Table III; see Table E4 in this article's Online Repository at www.jaci-inpractice.org). Interventions for which cost-effectiveness could be demonstrated fell into two broad categories: digitally delivered communication and monitoring,[31,54] and training, education and counseling delivered by health care professionals.[32-34,50]

Most studies (n = 5) concluded that the intervention was cost-effective (Figure 2).[31-34,50]

The cost-effectiveness of interventions that might improve adherence was demonstrated in populations of patients with asthma[32,33,50,53,54] and in patients with COPD.[31,36,37] One study included a mixed population of individuals with either asthma or COPD.[34] Manfrin et al[33] demonstrated the dominant cost-effectiveness of applying the Medicines Use Review (MUR) program in Italy, which improved asthma treatment adherence by 35.4% after 3 months postintervention, rising to 40.0% after a further 3 months. The MUR is a government-funded cognitive pharmaceutical service originating in the United Kingdom and featuring structured adherence-centered reviews between patients and accredited pharmacists.[58] Data uncertainties prevented incremental cost-effectiveness ratio (ICER) calculations, yet a cost-effectiveness plane was provided. From both Italian public health and societal (indirect, nonmedical) perspectives, the authors found that MUR was dominant over usual care owing to cost savings, with a probability of being cost-effective of 100% at 9 months versus usual care.

Another randomized study showed greater adherence and dominant cost-effectiveness in patients newly prescribed treatment for COPD or asthma.[34] Counseling delivered via telemedicine resulted in higher rates of adherence (74% vs 63% in the control group) with an ICER of −£3,166. Cost-effectiveness was greatest for asthma alone (ICER of −£44,614) compared with COPD alone (ICER of £1,845).

The study by van Boven and colleagues[31] found that optimizing adherence among patients with COPD who regularly use an inhaler but with frequent technique errors would be associated with an acceptable ICER of €6,520/quality-adjusted life-year (QALY). Improving adherence among patients with good technique but irregular use would be cost-saving and therefore have a

**TABLE II.** Quality assessment of publications included in systematic literature review that reported health economic data

| First author, year | Objective | Perspective | Source | Subgroups | Uncertainty | Incremental analysis | Data abstraction | Time horizon | Costs and assessments | Outcomes | Validity and reliability | Model description | Model choice | Bias assessment | Conclusions | Funding | Total score |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| van Boven, 2018[31] | 7 | 4 | 8 | 1 | 9 | 6 | 5 | 7 | 8 | 6 | 7 | 8 | 7 | 6 | 8 | 3 | **100** |
| Yong, 2018[32] | 7 | 4 | 8 | 1 | 9 | 6 | 5 | 7 | 8 | 6 | 7 | 8 | 7 | 6 | 8 | 3 | **100** |
| Manfrin, 2017[33] | 7 | 4 | 8 | 1 | 9 | 6 | 5 | 0 | 8 | 6 | 7 | 8 | 7 | 6 | 8 | 3 | **93** |
| Elliott, 2017[34] | 7 | 4 | 8 | 1 | 9 | 6 | 5 | 0 | 8 | 6 | 7 | 8 | 7 | 6 | 8 | 3 | **93** |
| Sørensen, 2017[35] | 7 | 4 | 8 | 1 | 9 | 6 | 5 | 7 | 8 | 6 | 7 | 8 | 7 | 6 | 8 | 3 | **100** |
| van Boven, 2016[36] | 7 | 4 | 8 | 1 | 9 | 0 | 5 | 0 | 8 | 6 | 7 | 8 | 7 | 6 | 8 | 3 | **89** |
| van Boven, 2014[37] | 7 | 4 | 8 | 1 | 9 | 6 | 5 | 7 | 8 | 6 | 7 | 8 | 7 | 6 | 8 | 3 | **100** |
| Suh, 2000[38] | 7 | 4 | 8 | 1 | 9 | 6 | 5 | 0 | 8 | 6 | 7 | 8 | 7 | 6 | 8 | 3 | **93** |

Definitions of elements of assessment: Objective: Was the study objective presented in a clear, specific, and measurable manner? Yes = 7 points. Perspective: Were the perspective of the analysis (societal, third-party payer, etc) and reasons for its selection stated? Yes = 4 points. Source: Were variable estimates used in the analysis from the best available source (ie, randomized control trial = best; expert opinion = worst)? Yes = 8 points. Subgroups: If estimates came from a subgroup analysis, were the groups prespecified at the beginning of the study? Yes = 1 point. Uncertainty: Was uncertainty handled by (1) statistical analysis to address random events, and (2) sensitivity analysis to cover a range of assumptions? Yes = 9 points. Incremental analysis: Was incremental analysis performed between alternatives for resources and costs? Yes = 6 points. Data abstraction: Was the methodology for data abstraction (including the value of health states and other benefits) stated? Yes = 5 points. Time horizon: Did the analytic horizon allow time for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3% to 5%) and justification given for the discount rate? Yes = 7 points. Costs and assessments: Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described? Yes = 8 points. Outcomes: Were the primary outcome measure(s) for the economic evaluation clearly stated and did they include the major short-term, long-term, and negative outcomes? Yes = 6 points. Validity and reliability: Were the health outcomes measures or scales valid and reliable? If previously tested valid and reliable measures were unavailable, was justification given for the measures or scales used? Yes = 7 points. Model description: Were the economic model (including structure), study methods and analysis, and components of the numerator and denominator displayed in a clear, transparent manner? Yes = 8 points. Model choice: Were the choice of economic model, main assumptions, and limitations of the study stated and justified? Yes = 7 points. Bias assessment: Did the author(s) explicitly discuss direction and magnitude of potential biases? Yes = 6 points. Conclusions: Were the conclusions or recommendations of the study justified and based on the study results? Yes = 8 points. Funding: Was there a statement disclosing the source of funding for the study? Yes = 3 points. Total score: summed values out of a potential 100.

dominant (negative) ICER. Furthermore, improving adherence among patients with both irregular use and frequent technique errors would also be highly cost-effective (ICER of €3,935/QALY).[31]

Among publications reporting an ICER in this SLR, only one indicated poor cost-effectiveness compared with recognized willingness-to-pay thresholds (Figure 2 and Table E4). Sørensen et al[35] investigated a multifaceted case management intervention that exceeded the upper threshold for cost-effectiveness (£30,000) by £3,865/QALY, largely owing to a small QALY gain over a 12-month follow-up. The authors suggested that a time horizon longer than 1 year would result in a decreased ICER, rendering the intervention cost-effective in the long-term.

**Direct costs/budget impact.** There were 11 publications from studies assessing costs or the budget impact of interventions to improve adherence (Table III; see Table E5 in this article's Online Repository at www.jaci-inpractice.org).[31,32,34,36-39,41,43,53,54] Of these, only one demonstrated a direct impact on adherence.[37] Direct costs associated with asthma and/or COPD were repeatedly found to be reduced after interventions that could positively influence adherence. Cost savings per patient per year were modest (mostly <€500/patient per year).[38,43]

In a pediatric population in secondary care, Orchard et al[54] undertook a cost study in which a smart inhaler that delivered alerts itself was introduced. Use of the smart inhaler, which was previously shown to result in 70% adherence versus 49% among a control group ($P \leq .001$),[59] was found to be cost-saving over 1 year by £96/patient compared with usual care. No HCRU findings were reported, but scenario modeling suggested that the smart inhaler would be cost-saving in adults with asthma in secondary care.

The community pharmacist Pharmaceutical Care for Patients with COPD (PHARMACOP) intervention program (two patient counseling sessions 3 months apart) helped to increase COPD medication refill adherence from 85.70% for usual care to 94.21% (difference: 8.51%; 95% CI, 4.63-12.4; $P < .0001$).[37] The PHARMACOP program has been associated with favorable cost-effectiveness. Total costs per patient were reduced by €227 (95% CI, 58-403).[37] Savings were observed within a 1-year horizon, and PHARMACOP remained cost-saving in sensitivity analyses using longer horizons and different assumptions for the duration of effect on adherence. Although PHARMACOP is associated with initially higher costs than usual care (€161/patient), these are more than offset by €388 savings on expenses for the treatment of exacerbations.

A second study, involving the Medication Monitoring and Optimization (MeMO)-COPD program showed it to be cost-saving and to offer improved health outcomes.[36] In this prospective observational study involving patients with COPD attending a community pharmacy in the Netherlands, mean total costs (taking into account productivity loss) were reduced by €268 (95% CI,−€926 to +€391) per patient. Over a 12-month study period, assessment of health records (pre-post intervention) showed that hospitalization day costs were reduced (€896 vs €549; 39% reduction), as were other HCRU costs (€1,639 vs €1,305; 20% reduction), with only a 5% increase in pharmacy medication expenditure (€549 vs €575). Costs resulting from lost productivity were largely unaffected (€112 vs €117), although just nine patients were still working at the time of the study.

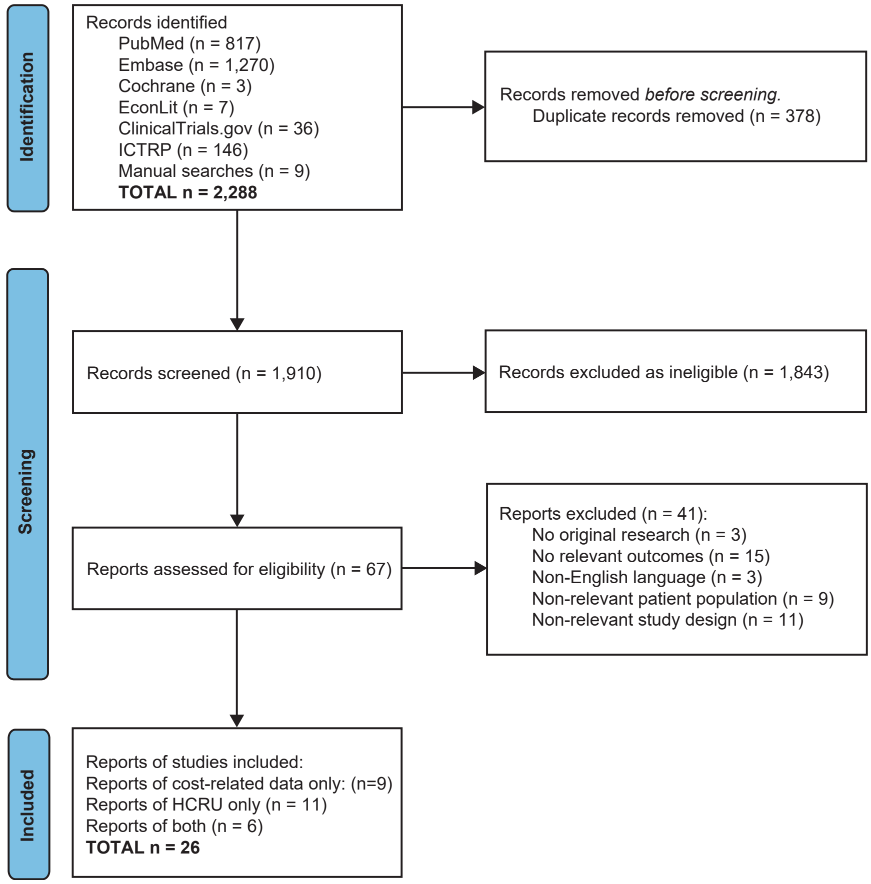



**FIGURE 1.** Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for systemic literature review of publications reporting cost-effectiveness, budget impact, or health care resource use (HCRU) associated with adherence-promoting interventions in asthma and chronic obstructive pulmonary disease. *ICTRP*, International Clinical Trials Registry Platform.

Four studies (two of which were published only as abstracts) reported actual or estimated cost data after the implementation of an intervention.[38,39,41,43] Replacement of dual inhalers with inhaled corticosteroids (ICS)/long-acting β-agonist (LABA) fixed-dose combination therapy in COPD was reported to reduce total medication costs.[41] Likewise, implementing an asthma education program significantly reduced overall asthma treatment costs.[38] Combining interventions, including improving the uptake of inhalers and using digital support via apps, may reduce both direct and indirect medical costs.[39] Also, using a drug therapy management program in asthma helped to reduce medical costs.[43]

## Studies reporting HCRU

The SLR identified 17 of 26 publications reporting HCRU, 11 of which demonstrated favorable effects on adherence (Table III). Most studies involved patients with asthma and assessed health care visits, hospital admissions, and/or medication use (maintenance, add-on/reliever treatment, and antibiotics). No studies included an analysis of the use of biologics.

Interventions found to reduce HCRU mostly included counseling (n = 4)[33,37,48,51] or educational programs and/or enhanced care protocols (n = 4).[38,42,45,53] Single studies reported the use of telephonic reminders,[49] shared decision-making,[56] or a switch to a combined inhaler.[46] The effects were statistically significant in these cases. A further five studies reported numerical but nonsignificant improvements in HCRU.[36,40,43,44,55]

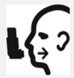
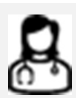
## Impact on health care visits

Adherence-promoting interventions were frequently associated with a reduction in hospital and emergency department visits (Figure 3) and reductions in the number and duration of hospitalizations.[32,38,41-44,46,48-51,53] The percentage reduction varied widely from around 10% to 100%, in which all but four[41,42,50,53] showed reductions of 40% at most. Two of the greatest impacts were shown in studies that did not directly assess the effect of the interventions on adherence.[42,50]

## Impact on medication use

Several studies demonstrated an increase in the use or possession of controller or maintenance treatments (anti-asthma treatments purchased or prescribed, or the use of ICS with or without LABA such as formoterol) across the study period after the implementation of adherence-promoting programs.[45,47,52,56] Conversely, the use of add-on or reliever medications, including short-acting $\beta_2$-agonists, theophylline, systemic corticosteroids, and long-acting anticholinergics (eg, tiotropium) associated with worsening of asthma or COPD was repeatedly shown to be reduced.[38,42,45,46,52,55,56]

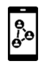
**TABLE III.** Summary and overview of results of studies investigating the cost-effectiveness, cost or budget impact and HCRU associated with interventions aimed at improving adherence to medication regimens for asthma and/or COPD

| First author, year (condition) | Intervention | Impact on adherence | Cost impact/cost-effectiveness | HCRU | Impact on symptoms, exacerbations, QoL, and other outcomes |
|---|---|---|---|---|---|
| Bandeiras, 2020[39] (asthma) |   | | Cost-saving | | |
| Bender, 2020[40] (asthma) |   | No impact | No impact | No overall impact. Numerical increase in short-acting corticosteroid inhalers and Asthma Medication Ratio for text/phone calls vs e-mail (not statistically significant) | |
| Benayoun, 2001[41] (COPD) |  | | Cost-saving | Reduced hospitalization rate | |
| Bourbeau, 2018[42] (COPD) |  | Improved | | Reduced unscheduled clinic visits, ED visits, hospitalizations, use of antibiotics and oral corticosteroids | Improved QoL, inhaler technique, and COPD knowledge |
| Cherian, 2018[43] (asthma) |  | | Cost-saving overall. Increased branded drug costs | Reduced acute hospitalization and professional use rates | |
| Cvietusa, 2019[44] (asthma) |  | Improved | | Small, nonsignificant reductions | |
| Delate, 2017[45] (asthma) |  | | | Reduced albuterol inhaler and systemic corticosteroid purchases. Increase in patients with $\geq$1 controller inhaler purchase | Reduced exacerbation rate |

| | | | | | |
|---|---|---|---|---|---|
| Delea, 2008[46] (asthma) |  | | | Reduced claims for SABA, corticosteroids[a] | |
| De Rycke, 2017[47] (asthma) |  | | | Increased total number of anti-asthma prescription fills | Decreased sick leave (days taken and percentage of subjects) |
| Elliot, 2017[34] (COPD) |   | Increased | Cost-effective overall for beclomethasone, aspirin, asthma alone, COPD alone. Cost-savings give negative ICERs | | |
| Federman, 2020[48] (asthma) |  | Increased | | Reduced ED visits | Improved QoL, asthma control, inhaler technique |
| Gelzer, 2019[49] (asthma) |  | Increased (personalized interventions more effective than general interventions) | | Reduced asthma-related and all-cause ED visits and inpatient admissions | |
| Gordois, 2007[50] (Asthma) |  | | Cost-effective | | |
| Khdour, 2020[51] (asthma) |  | Increased | | Reduced ED visits, hospital admissions, hospital days | Improved asthma control, inhaler technique |
| Manfrin, 2017[33] (asthma) |  | Increased | Cost-effective | | Improved asthma control |
| Mangiapane, 2005[52] (asthma) |  | Increased | | Reduced SABA, theophylline, oral corticosteroid use Increased LABA, ICS use | Improved asthma control, QoL, inhaler technique |
| McLean, 2003[53] (Asthma) |  | | Cost-saving | Reduced medical visits, β-agonist use | Improved QoL |

*(continued)*

**TABLE III.** *(Continued)*

| First author, year (condition) | Intervention | Impact on adherence | Cost impact/cost-effectiveness | HCRU | Impact on symptoms, exacerbations, QoL, and other outcomes |
|---|---|---|---|---|---|
| Orchard, 2020[54] (asthma) |   | | Cost-saving | | |
| Pool, 2017[55] (asthma) |  | No change | | Reduced number of asthma (including controller) medications, ED and outpatient visits | Improved ACT score |
| Sørensen, 2017[35] (COPD) |  | | ICER exceeded upper willingness-to-pay threshold | | |
| Suh, 2000[38] (asthma) |  | | Increased asthma drug as percentage of all drug costs; decreased costs for physician office visits | Reduced frequency of hospitalizations, emergency room use, physician office visits, asthma medication prescriptions | |
| Van Boven, 2014[37] (COPD) |  | Improved | Cost-saving | Reduced frequency of hospitalizations, more medication use | Reduced exacerbations |
| Van Boven, 2016[36] (COPD) |  | | Cost-saving | Reduced ED and hospital HCRU | Reduced exacerbations and clinical COPD questionnaire score |
| Van Boven, 2018[31] (COPD) |   | | Cost-effective, cost-saving | | |

| | | | | | |
|---|---|---|---|---|---|
| Wilson, 2010[56] (asthma) | | Improved | | Reduced asthma-related medical visits and albuterol canister equivalents. Increased cumulative controller dose | Improved asthma-related QoL |
| Yong, 2018[32] (asthma) | | | Cost-effective, cost-saving | Reduced hospitalizations | |

| | | | |
|---|---|---|---|
| Smart devices and/or digital interfaces (apps, web- or SMS-based reminders etc) | | Telemedicine | |
| Clinician-based support (education and coaching, individualized care plans, shared decision making) | | Inhaler technology | |
| Counseling (one-to-one) with or without additional monitoring | | Pharmacy program | |

See Tables E3 to E6 for details of each intervention, study features, and results.

aPer-quartile adherence levels were determined. Higher adherence was associated with a 10% reduction in the odds of asthma-related ED visit or hospitalization ($P < .001$), a 10% reduction in the odds of receiving SABA ($P < .001$); and a 3% reduction in the odds of receiving a systemic corticosteroid ($P = .027$).[46]

*ACT*, asthma control test; *COPD*, chronic obstructive pulmonary disease; *ED*, emergency department; *HCRU*, health care resource use; ICER, incremental cost-effectiveness ratio; *ICS*, inhaled corticosteroids; *LABA*, long-acting β-agonist; *QoL*, quality of life; *SABA*, short-acting $\beta_2$-agonist.

**TABLE IV.** Adherence findings for cost or cost-effectiveness studies and health care resource use studies (for those that were directly assessed)

| Study | Intervention | Impact on adherence |
|---|---|---|
| Cost or cost-effectiveness studies | | |
| Elliott et al, 2017[34] | One-to-one New Medicines Service consultations with community pharmacist via telephone | From 10-wk trial: probability of adherence 74% in New Medicines Service group vs 63% in control group |
| Manfrin et al, 2017[33] | Face-to-face medicines use review in Italy involving consultation with pharmacist | Adherence improved by 35.4% 3 mo after intervention and 40.0% at 6 mo ($P < .01$) and was associated with greatest Asthma Control Test score improvements |
| Health care resource use studies | | |
| Bender et al, 2020[40] | Digital communication technology intervention: text/phone call intervention or e-mail intervention vs usual care | No impact on adherence (previous pragmatic study showed improvement in adherence with asthma controller medication) |
| Bourbeau et al, 2018[42] | Chronic obstructive pulmonary disease self-management educational program (pre-post study design) | Treatment adherence (questionnaire-based assessment) was significantly improved (from one in three patients to three in four patients after intervention; $P = .025$) |
| Cvietusa et al, 2019[44] | Communication technology tools vs no intervention (pre-post trial format) | Patient adherence (proportion of days covered) improved from 39.5% to 41.7% in year after intervention ($P < .0001$) |
| Federman et al, 2020[48] | Asthma control screening and coaching vs usual care | Medication Adherence Rating Scale score significantly better at months 3 (mean [95% CI] trt diff: 0.2 [0.1-0.4], $P = .01$), 6 (trt diff: 0.2 [0.0-0.4], $P = .02$), and 12 (trt diff: 0.3 [0.1-0.5], $P = .01$) |
| Gelzer et al, 2019[49] | Personalized and general phone-based interventions (pre-post study design) (Southeastern Pennsylvania cohort; Lehigh-Capital/New West Pennsylvania cohort | Medication adherence (proportion of days covered). Statistically significant improvements in proportion of days covered were observed overall: Southeastern Pennsylvania cohort: +4.9% ($P = .01$); Lehigh-Capital/New West Pennsylvania cohort: +7.2% ($P = .03$). Personalized interventions significantly more effective in each cohort (+12.2 / +17.8%) than general interventions (=3.0 / +5.5%; $P \leq .04$) |
| Khdour et al, 2020[51] | Hospital-based patient counseling intervention vs usual care | Adherence to controller medications (MMAS): rates of good medication adherence significantly better in intervention group (60.7% vs 50.0%; $P = .02$) |
| Manfrin et al, 2017[33] | Training and delivery of intervention (face-to-face consultation with pharmacist) at baseline vs delivery | Self-reported adherence (MMAS) improved by 35.4% 3 mo after intervention and 40.0% 6 mo after intervention |
| Mangiapane et al, 2005[52] | Community counseling services vs control patients | Adherence (four-item MMAS 4 [worst] to 8 [best], mean score): baseline: 6.7; 6 mo: 7.1; 12 mo: 7.1 global $P < .001$ |
| Pool et al, 2017[55] | Asthma-specific, personalized online feedback tool vs active control tool unrelated to asthma | No change in adherence assessed using medication possession ratio |
| Wilson et al, 2010[56] | SDM model or clinical decision-making (randomized controlled trial) | Adherence (continuous medication acquisition index) at 1 y: SDM vs control: controller: 0.67 vs 0.46 ($P < .0001$); long-acting β-agonist: 0.51 vs 0.40 ($P = .0225$). SDM vs clinical decision-making: controller: 0.67 vs 0.59 ($P = .03$); long-acting β-agonist: 0.51 vs 0.41 ($P = .0143$) |

*MMAS*, Morisky Medication Adherence Scale; *SDM*, shared decision-making; *trt diff*, intervention vs control difference.

## Studies reporting other health and patient-reported outcome measures

Twelve publications included data related to exacerbation rates, disease control, and general or disease-specific QoL (Tables III, E4, and E5; see Table E6 in this article's Online Repository at www.jaci-inpractice.org). Some studies also demonstrated improvements in inhaler technique and disease knowledge. Seven publications also reported improvements in adherence.[20,33,42,48,51,52,55,56] Counseling and/or digitally informed programs were used in all cases where these outcomes were observed.

Improved adherence was associated with reduced asthma exacerbations in three studies,[36,37,45] and increased disease control (assessed by Asthma Control Test score) in a further five studies.[33,48,51,52,55] Better generic QoL (measured using the

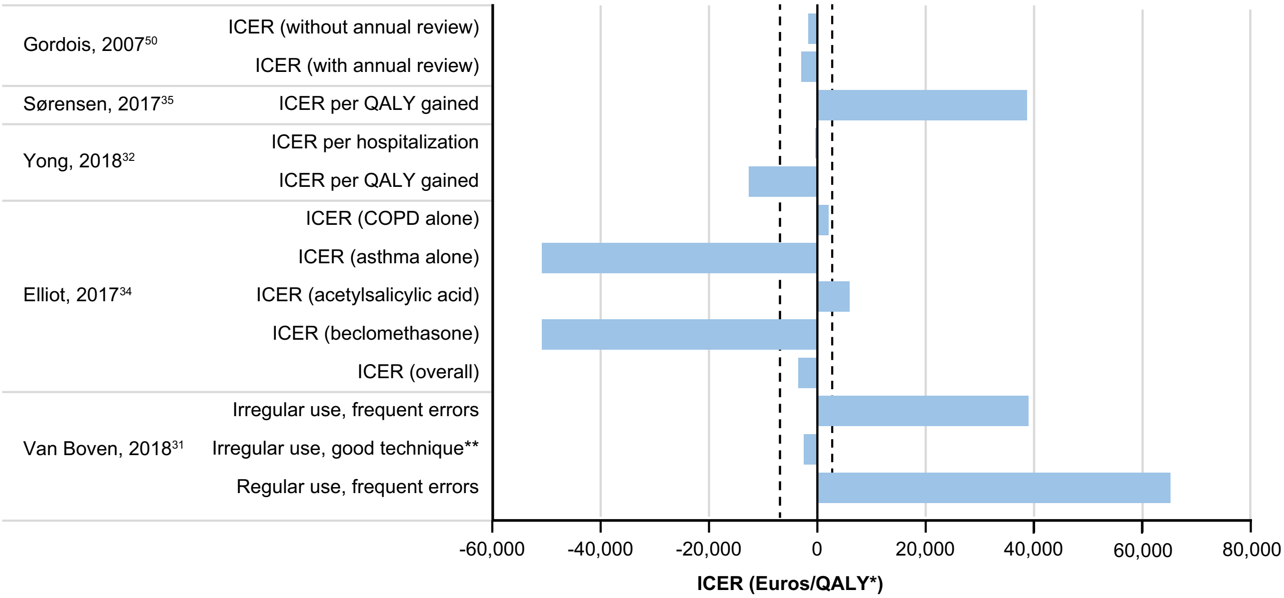



**FIGURE 2.** Incremental cost-effectiveness ratios (ICERs) reported by studies investigating cost-effectiveness of adherence-promoting interventions (see Table E4 for details of each study). Negative ICERs indicate cost savings. *Dotted lines* indicate upper and lower willingness-to-pay thresholds used by England and Wales National Health Service. *Incremental cost-effectiveness ratios expressed per QALY, except for Yong et al,[32] in which one analysis is expressed per hospitalization. ** Incremental cost-effectiveness ratio calculated for this review from data provided in the original publication. *COPD*, chronic obstructive pulmonary disease; *QALY*, quality-adjusted life-year.

EuroQol-5Dimensions instrument) and/or disease-specific QoL was measurable in some studies.[33,36,42,48,52,56]

Inhaler technique was improved following clinic-based support[42] and counseling also increased adherence.[48,51,52]

Two studies also revealed that interventions aimed at improving adherence helped reduce the number of sick days among children and working adults.[47,53]

## DISCUSSION

This SLR identified a number of studies demonstrating that interventions improving adherence to asthma or COPD medications are cost-effective and likely to be cost-saving. Individual counseling and digital interventions can reduce rates of HCRU associated with poorly controlled disease. Programs that can influence adherence therefore appear to offer benefits to patients (better symptom control, reduced exacerbations, and improved QoL) and to payers (cost savings and reduced HCRU). Societal benefits may also accrue, such as reduced sick leave and less demand for additional medications. A review of the 26 studies identified in the systematic search revealed too much variation in the study designs and methodologies, patient populations, and care settings to allow definitive recommendations for best practice adherence interventions. However, some broad conclusions can be made. Overall, one-to-one interactions between patients and suitably trained and accredited health care professionals were repeatedly effective, as was digitally enhanced care using smartphone apps, texts, e-mail, and other forms of telemedicine.

Multifactorial approaches may offer the best opportunities for clinical improvements and cost benefits given the complexity of poor asthma control and contributing factors.[10] For example, a recent randomized controlled study showed that the digitally enabled Inhaler Compliance Assessment, coupled with nurse-led education and physician treatment adjustment sessions, modestly improved adherence, reduced treatment burden, and lowered medical costs.[60,61] In this context, it is noteworthy that the COVID-19 pandemic necessitated rapid uptake and expansion of telemedicine, and those experiences have been particularly relevant and transferable to the care of patients with respiratory diseases such as asthma and COPD.[21,62-65]

Along with high levels of adherence, good inhaler technique is widely recognized as important to achieving good clinical outcomes.[10,66] Suboptimal inhaler technique is responsible for a substantial and avoidable health and economic burden among patients with respiratory diseases whose maintenance treatment is typically delivered via inhaler.[31,67] Individualized training in good inhaler technique coupled with ongoing support (eg, from pharmacists) and easy-to-use inhalers may improve adherence and persistence as well as reduce HCRU and associated costs.[10,31,64,66,67] Digitally enhanced care and objective data collection may support engagement between health care professionals and patients with respect to inhaler technique, such as by collecting objective data on inhaler technique errors after initial training.[60,66,68]

As noted in other systematic reviews,[13-15,19,26,69] our findings highlight a lack of cost-effectiveness analysis using appropriately designed studies addressing the interrelationships among optimized adherence, cost burden, and health outcomes. Standardizing modeling approaches to incorporate discounting methods, include appropriate sensitivity analyses and time horizons, and use real-world data rather than assumptions and targets would

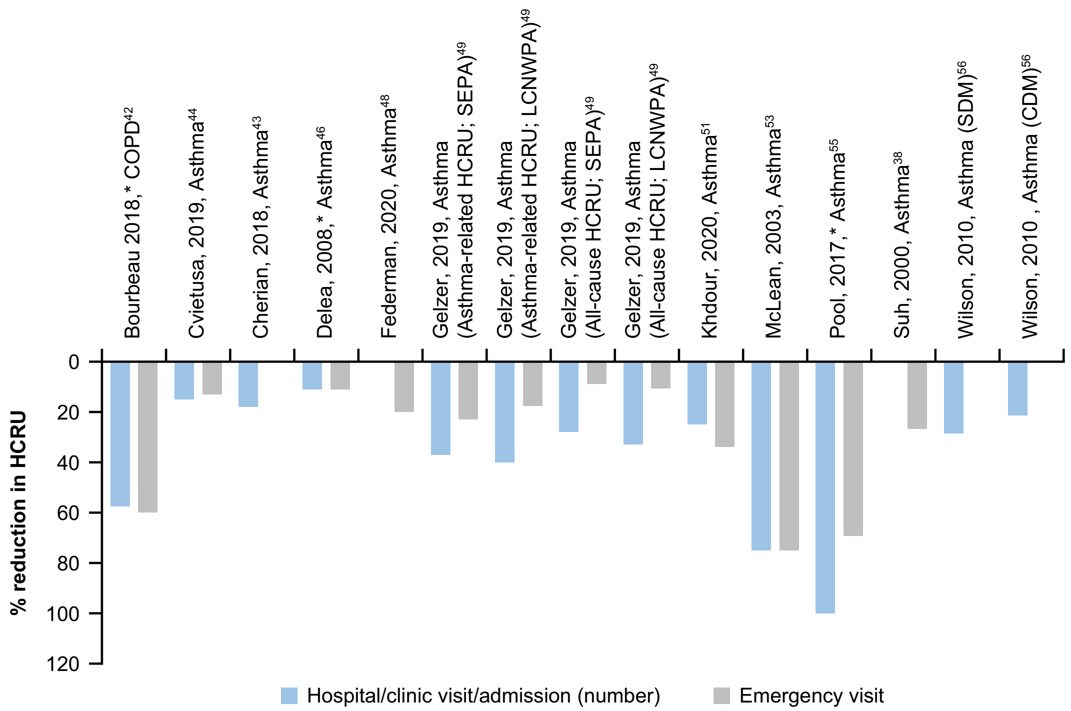



**FIGURE 3.** Effects of adherence-promoting interventions on non-drug health care resources use (see Table E6 for details of each study). *No direct assessment of effect of intervention on adherence. *CDM*, clinical decision-making; *COPD*, chronic obstructive pulmonary disease; *HCRU*, health care resource use; *LCNWPA*, Lehigh-Capital/New West Pennsylvania; *SDM*, shared decision-making; *SEPA*, southeastern Pennsylvania.

ultimately provide better information for decision-makers. Overall, the relationship between adherence and cost is complicated by other factors such as QoL, and by individual barriers and perceptions related to the efficacy and safety of treatments. These complexities, coupled with the broad range of methodologic approaches used in individual studies, make definitive conclusions hard to draw. In addition, the study hypothesis or research question itself may directly influence the choice of variables in any single study. For example, measuring adherence to understand potential patient concerns about adverse effects may best be done using self-report, whereas drug use levels will most accurately be captured using electronic monitoring. The use of qualitative methods of assessing the perceptions and impact of adherence interventions may elucidate meaningful associations between contributing variables, and longitudinal studies may help to establish the long-term impact of those interventions for patients, health care providers, and payers.

In general, only a small number of adherence interventions have been implemented and reimbursed in routine care despite the considerable economic and clinical burden of medication nonadherence.[23,24] Currently, most reimbursed adherence programs involve in-person interactions between the patient and health care professional, only a quarter of which involve technology.[23] The US Centers for Medicare and Medicaid Services have introduced billing codes for teaching involving the use of digital inhalers, remote monitoring of adherence and inhaler technique data, and healthcare provider-patient counseling on adherence and inhaler technique.[70] This can help to increase access to adherence-promoting programs, particularly among currently underserved populations.

As well as the lack of a widely used, reliable tool that provides objective adherence information in real time, other barriers may need to be overcome to increase implementation. Physicians' adherence to diagnosis and management guidelines can influence adherence and disease control, but it is suboptimal overall and varies among specialist and generalist professionals.[71] Therefore, effective training of health care professionals that reflects specific adherence-promoting interventions, coaching of patients, and working with relevant diagnosis and management guidelines is a vital component of the overall management of patients with asthma or COPD. In addition, to better understand which elements of adherence programs work best for which patient, the description of the adherence intervention and construct requires structured reporting, preferably following the ESPACOMP Medication Adherence Reporting Guideline.[72] Using group-based trajectory models could help tailor interventions more effectively.[73]

We identified some limitations to this SLR. The time limits defined in this SLR restrict the included articles to those published before July 2021. We recognize that some relevant publications have emerged since the search was performed and have cited some of those throughout this discussion. An update to this SLR would be useful to capture the latest data in this area. We also recognize the potential for possible publication bias if negative findings have a lower likelihood of being published. However, it is impossible to determine the scale of this potential risk of bias.

The limited number of identified studies and the lack of methodologic consistencies prevent definitive conclusions and recommendations from being made regarding clinical settings, patient characteristics, payer archetypes, and so on, which will benefit most from adherence-promoting programs. In particular, adherence to background inhaler therapy should ideally be measured using objective and granular data on both intake and the quality of inhalation technique.[74,75] Furthermore, most articles discussed here evaluated general-purpose health technologies, whereas patient-level analyses of precision medicine interventions are needed that respond dynamically to the complexity of individual patient factors and health system requirements.[76] Individualization is an important element in promoting adherence.[77] However, the studies we reviewed do not offer major insights into suitable population characteristics that might influence the acceptability and sustainability of any intervention under investigation. In addition, the effect on types of adherence (intermittent nonadherence, discontinuation, etc) and the role of elements such as socioeconomic status and level of health literacy[78] have not been studied and should be considered in future research. The original search strategy did not specifically identify studies using biologics, largely because of the time frame used (ie, before biologics were approved for asthma or COPD). No studies described here assessed adherence programs in patients with asthma or COPD who were receiving biologics. Inhaled corticosteroid adherence may be suboptimal among individuals receiving biologics.[79] The cost implications of improved adherence to maintenance therapies and optimized inhaler technique should be investigated in the context of early switching to high-cost biologics. In addition, an understanding of the challenges related to adherence to and persistence with biologics themselves is needed, particularly in cases of the home-based self-administration of subcutaneous formulations. Current biologic adherence data mostly rely on claims that may not reflect actual intake.[80]

Planned and ongoing studies using recently published protocols for relevant studies such as TRaining of pharmacy technicians and patient prepAration and Counselling (On TRACk),[81] Maximizing Adherence and Gaining New Information For Your Chronic Obstructive Pulmonary Disease (MAGNIFY COPD),[82] and OUtcomes following Tailored Education and Retraining: Studying Performance and AdherenCE in asthma and COPD (OUTERSPACE)[83] and the approach used in the recently published Inhaler Compliance Assessment (INCA) Sun[60] and Service Apothecary Respiratory Advice (SARA)[64] studies may help overcome some of the limitations of studies described here. Findings of the OUTERSPACE trial are promising, showing reduced inhaler errors within 2 months.[75]

Interventions that include a focus on overcoming challenges with adherence can have favorable disease outcomes and reduce HCRU. These interventions can be beneficial to patients, health care services, and health systems. Improving holistic care delivery can enable patient self-management via better adherence, with potential cost and HCRU savings. Multidisciplinary care involving one-to-one advice and digitally enhanced communications are likely to offer the most impactful support. Evaluating interventions over long periods (eg, more than 12 months) can help understand their full impact on adherence and other positive behaviors that optimize health and cost outcomes in COPD and asthma.

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