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Systematic Literature Review

A Systematic Review of Decision-Analytic Models for Evaluating Cost-Effectiveness of Asthma Interventions

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ABSTRACT

Objective: To demonstrate the landscape of model-based economic studies in asthma and highlight where there is room for improvement in the design and reporting of studies.

Design: A systematic review of the methodologies of model-based, cost-effectiveness analyses of asthma-related interventions was conducted. Models were evaluated for adherence to best-practice modeling and reporting guidelines and assumptions about the natural history of asthma.

Methods: A systematic search of English articles was performed in MEDLINE, EMBASE, and citations within reviewed articles. Studies were summarized and evaluated based on their adherence to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS). We also studied the underlying assumptions about disease progression, heterogeneity in disease course, comorbidity, and treatment effects.

Results: Forty-five models of asthma were included (33 Markov models, 10 decision trees, 2 closed-form equations). Novel biological treatments were evaluated in 12 studies. Some of the CHEERS' reporting recommendations were not satisfied, especially for models published in clinical journals. This was particularly the case for the choice of the modeling framework and reporting on heterogeneity. Only 13 studies considered any subgroups, and 2 explicitly considered the impact of comorbidities. Adherence to CHEERS requirements and the quality of models generally improved over time.

Conclusion: It would be difficult to replicate the findings of contemporary model-based evaluations of asthma-related interventions given that only a minority of studies reported the essential parameters of their studies. Current asthma models generally lack consideration of disease heterogeneity and do not seem to be ready for evaluation of precision medicine technologies.

Keywords: asthma, cost-effectiveness, decision analysis, decision-analytic modeling, simulators.

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Introduction

The use of computer models is very common in economic evaluations of health technologies.[1] The reasons for using a computer model as a vehicle for an economic evaluation include the need for combining evidence from multiple sources, extrapolating projections beyond the time horizon of experimental studies, converting estimates of treatment effect on intermediate outcomes to policy-relevant metrics, and incorporating uncertainty in the evidence into the results of predictions.[1]

Model development is a complex task that requires many decisions that can affect the outcomes of the analysis.[2–4] Examples of such decisions include the choice of model structure, selecting the relevant studies as sources of evidence, implicit and explicit

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assumptions about the natural course of the disease and how it is affected by the interventions under evaluation, and the depth of literature review for evidence synthesis. It is due to these design features that the results of economic evaluations are generally more difficult to reproduce and report on in traditional journal publication formats.[5]

In asthma, one of the most common chronic diseases globally, the use of economic evaluations to inform resource allocation is on the rise. One particular reason for this is the arrival of effective but expensive biologic treatments, prompting many decision-making bodies to demand rigorous evidence on their "value for money" potential.[6,7] A recent systematic review focused on comparing biologics and their relative cost-effectiveness and reported widely varying results.[8] Although some degree of variability is expected owing to jurisdiction-specific parameters (eg, healthcare resource use patterns and unit costs), it is likely that a fraction of such variation can be explained by differing assumptions and modeling approaches. Evaluating the general methodological characteristics of model-based economic evaluations of asthma-related interventions can help shed light on the reasons behind the variation in results and identify the next steps required to improve the quality and consistency of such studies.

The objective of this systematic review was to map out the landscape of model-based economic studies in asthma on 2 fronts: adherence to the recommendations of the reporting guidelines and consideration of particular design features specific to asthma. We conclude our review by highlighting the aspects of economic modeling in asthma where there is a room for improvement in the design and reporting of studies.

Methods

This systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO - CRD42017081345) in December 2017.

Search Strategy

With the help of a librarian, we searched MEDLINE and EMBASE to identify relevant studies. The search was limited to articles in English. The reference lists of included articles were also reviewed to identify any additional relevant citations that were not originally captured through database searching. Details of the search strategy can be found in the Online Appendix 1. We only included full-text articles because studies published only in abstract form could not realistically report all aspects of an economic evaluation considered in this study.

Study Selection

Studies of interest were those that used decision-analytic modeling for cost-effectiveness of health technologies in patients with asthma. Studies had to report both costs and effectiveness outcomes to be eligible for inclusion in our study. That is, studies with the aim of epidemiological projections of disease burden for a population without any specific interventions, or those with no cost components or without any health outcomes components, were excluded.

In the first round, screening was performed on the relevance of the titles and abstracts by the primary reviewer (S.E.A.) to identify the eligible articles. In the second round, full texts of identified publications selected from the first round were examined by the primary reviewer (S.E.A.) to ensure their qualification for eligibility. Second reviewers (N.H., M.S., and Z.Z.) each studied a random subset comprising 10% of the titles and abstracts in the first round and 10% of the full texts in the second round to ensure the accuracy of screening. Disagreements between reviewers were then identified and resolved through discussion.

Data Extraction and Reporting

Data extraction was conducted by 1 reviewer (S.E.A.) and cross-checked by other reviewers (N.H., Z.Z., and M.S.). A customized checklist was adapted from a previous study,[9] which included 3 sets of variables: publication details (author, location and setting, year of publication), quality of reporting, and major structural assumptions for the model. In a random sample consisting of 10% of studies, a second reviewer blinded to the original assessment extracted the data. The reviewers agreed on 85% of assessments. In 80% of the discordant assessments, consensus was reached through discussions, and the remaining cases were vetted by a third reviewer.

Quality of reporting was based on the items included in the methods and results sections of the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Checklist.[5] We did not evaluate adherence to the Checklist per se because many studies were published before the arrival of the Checklist; rather, we deemed the Checklist a logical list of items that need to be included in a high-quality report of an economic evaluation that would facilitate reproducing its results. The reason for limiting our assessment to the Methods and Results sections of the CHEERS Checklist was that these sections reflect the methodological aspects of an economic evaluation, which is the primary focus of the present study. Studies could receive a complete score, a partial score, or no score for each item in the checklist.

The major structural assumptions of models were assessed on the basis of the following 4 components determined after a few rounds of discussions among the authors and with consultations with established leaders in clinical asthma research: (1) variables used to define the natural history of asthma, (2) consideration for between-individual variability (heterogeneity) in the natural history of asthma, (3) the potential role of comorbid conditions (preexisting, coexisting, or due to side-effect of treatments) in determining cost-effectiveness results, and (4) the way the effect of intervention of interest on the natural history of asthma was modeled. In reporting of results, we followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses.[10]

Results

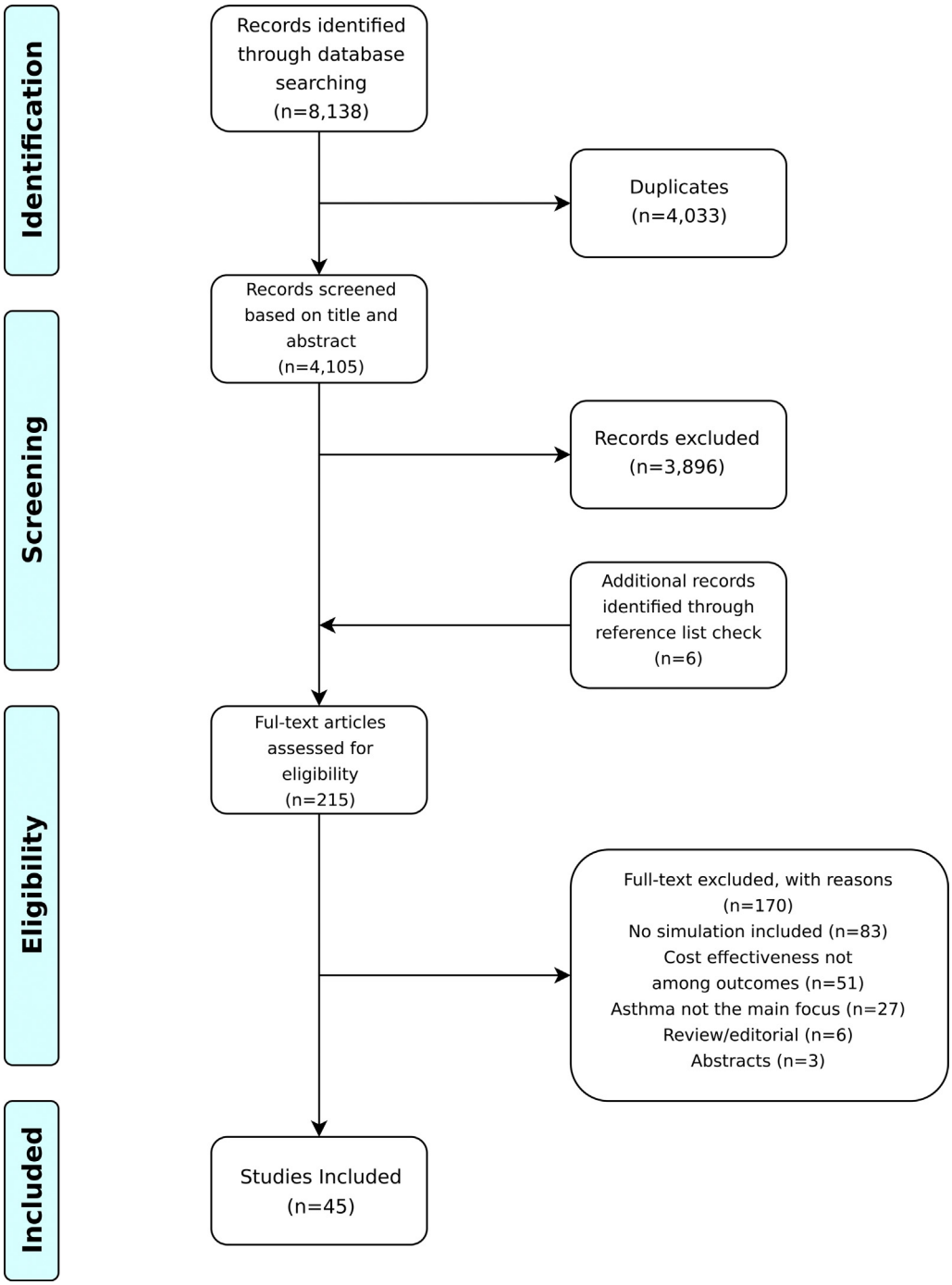
We identified 4,105 nonduplicate citations through our literature search; 3,896 articles were excluded after reviewing their titles and abstracts. After a full-text review of the remaining 209 articles and additional 6 articles retrieved from the reference lists, 45 were finally included for our systematic review. Figure 1 demonstrates the Preferred Reporting Items for Systematic reviews and Meta-Analyses study selection flowchart.

Characteristics of the Included Studies

The study characteristics are presented in Table 1. Studies originated from different countries and jurisdictions: 17 studies were from the United States,[4,7,11-25] 5 were from Canada,[26-30] 6 were from the UK,[31-36] 9 were from other European countries,[6,37-44] 4 were from South America, and [45-48] 3 were from South East Asia and Australia[49-51]; 1 study involved multiple countries.[52] In 8 studies, the target population was exclusively pediatric patients[12,13,17,28,41,46-48]; the remaining were in adults or the combination of adults, adolescents, and children.

Thirty studies evaluated pharmacological therapies in asthma.[4,6,7,11-14,16,18,19,21-24,26,27,29,31-33,35,36,39,40,45-48,50,52] Among these, 12 considered at least 1 of the recently introduced

Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) diagram for literature review.



biologics.[16,19,21-23,27,32,33,39,40,45,50] Bronchial thermoplasty was assessed in 4 studies.[15,22,25,51] Although most studies evaluated therapeutic interventions, a few considered diagnostic or prognostic technologies. Three evaluated fractional exhaled nitric oxide measurement for diagnosis of asthma or its prognostic evaluation[37,42,53]; others evaluated screening for asthma in the general population[17] or in people at risk of occupational asthma.[20,30]

In structure, most of the studies (n = 33) were Markov models,[4,6,11,14-27,32,33,35,36,38-40,43-48,51,52] with the number of Markov health states ranging from 2 to 7 (disease states are explained in section "Assumption About Natural History of Asthma"). Ten studies were based on decision trees without a Markov component,[7,12,13,28,30,37,41,42,49,53] and 2 were closed-form equations that were used directly to derive cost and effectiveness outcomes.[29,31] All of the studies were based on closed-population models that followed a hypothetical population over time (as opposed to open-population models that follow an entire population over a period and include entrance of new individuals into the population). The time horizons of the

Table 1. Summary of the economic models in asthma

Authors year	Location and setting	Type of model	Population	Asthma status when entering the model	Inter vention	Time Horizon	Cycle Length	Perspective	Discount rate	Effect measure	Indirect Costs
Altawalbeh et al,[11] 2016	US	Markov	≥66 years old	Persistent asthma	ICS + LABA, ICS + LTRA, or ICS alone	20 years	1 month	Healthcare system	3%	QALY	No
Andrews et al,[13] 2012	US	Decision tree	Pediatrics	Asthma that needed acute care visit	Follow up with primary care physician, prescribe ICS in ED, or dispense ICS in ED	1 month	NA	Healthcare system and societal	NA	ED relapse visit and hospitalization	Yes
Andrews et al,[12] 2012	US	Decision tree	Pediatrics	Asthma exacerbation	2-day of oral dexamethasone vs standard 5-day oral prednisone/ prednisolone	7-10 days of the sentinel ED visit	NA	Healthcare system and societal	NA	ED relapse visit and hospitalization	Yes
Bae et al,[14] 2008	US	Markov	Adults	Chronic asthma	ICS usage before and after the increase in copayment for prescription by $1.5	1 year	NA	Health providers, pharmacies, and beneficiaries	NA	Acute events (hospitalizations, ED visits, and urgent-care visits)	No
Berget al,[37] 2008	Germany	Decision tree	Not mentioned	Suspected asthma patients/mild to severe asthma	FENO measurement with NIOX MINO vs standard diagnostics and treatment guidelines*	1 year	NA	Payer	NA	QALY	No
Bond et al,[26] 2009	Canada	Markov	≥12 years old	Persistent asthma (steroid naïve/ uncontrolled on low dose of ICS monotherapy/ uncontrolled on a medium dose of ICS monotherapy/ uncontrolled on a high dose of ICS monotherapy)	ICS + LABA vs ICS alone (low dose, medium dose, high dose)	12 weeks and 1 year	1 week	Provincial ministry of health	NA	QALY, exacerbations avoided, successfully controlled week	No
Brodtkorb et al,[38] 2010	Sweden	Markov	Adolescents	Perennial allergic asthma	Airsonett Airshower treatment + optimized standard therapy vs placebo + optimized standard therapy†	5 years	1 year	Healthcare system	3%	QALY	No
Brown et al,[27] 2007	Canada	Markov	Not mentioned	Severe persistent allergic asthma	Omalizumab + standard therapy vs standard therapy‡	Lifetime	2 weeks§	Not mentioned	5%	QALY	No
Bruggenjurgen et al, [44] 2008	Germany	Markov	Children, adolescents, and adults	Allergic asthma	Specific subcutaneous immunotherapy + symptomatic treatment vs symptomatic treatment	15 years	1 year	Societal and third-party payer	3%	QALY	Yes
Cangelosi et al,[15] 2014	US	Markov	Adults	Poorly controlled, severe persistent asthma requiring at least 1 ER visit in the past 12 months	Bronchial thermoplasty + standard care vs standard care‡	5 years	2 weeks	Private, commercial payer	3%	QALY	No
Campbell et al,[16] 2010	US	Markov	Adults	Moderate to severe persistent asthma	Omalizumab + usual care vs usual care‡	Lifetime	2 weeks	Payer	3%	QALY, LY	No
Dewilde et al,[39] 2006	Sweden	Markov	Adults	Severe persistent IgE-mediated (allergic) asthma	Omalizumab + standard therapy vs standard therapy‡	Lifetime	2 weeks	Societal	3%	QALY, LY	Yes

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Table 1. Continued

Authors year	Location and setting	Type of model	Population	Asthma status when entering the model	Inter vention	Time Horizon	Cycle Length	Perspective	Discount rate	Effect measure	Indirect Costs
Doan et al,[28] 2011	Canada	Decision tree	Pediatric (2-18 years)	Mild to moderate asthma exacerbation in ED	Metered-dose inhaler vs wet nebulization to deliver bronchodilators	Time of ED admission to 2 days post-admission (average of 4 days)	NA	Hospital	NA	Hospital ward admission averted	No
Doull et al,[31] 2007	UK	Closed form equation	Adults and children	Chronic asthma	Salmeterol xinafoate/ fluticasone propionate combination inhaler (Seretide) vs other ICS-containing regimen	1 year	Not mentioned	Not mentioned	0%	QALY	No
Faria et al,[32] 2014	UK	Markov	Children, adolescents, and adults	Severe persistent allergic asthma	Omalizumab add-on therapy vs standard therapy alone†	Lifetime	16 weeks (first cycle) and 3 months subsequently	National health system	3.50%	QALY	No
Fuhlbrigge et al,[4] 2006	US	Markov	Women aged 35 years	Mild to moderate asthma	Quick reliever as needed vs quick reliever + ICS	10 years	1 month	Not mentioned	Not mentioned	QALY (effects of ICS on BMD), symptom-free day	No
Gerald et al,[17] 2009	US	Markov	Elementary-age schoolchildren	Urban, primarily black, not asthmatic	4 school-based asthma screening strategies vs no screening	1 year	Daily	Societal	NA	QALY	Yes
Gerzeli et al,[6] 2012	Italy	Markov	Adults	Moderate to severe asthma	Beclomethasone/ formoterol vs fluticasone propionate/ salmeterol	1 year	1 week	National health system	NA	QALY, time spent in successful control state	No
Ismaila et al,[29] 2014	Canada	Closed form equation	≥12 years old	Uncontrolled asthma	Salmeterol xinafoate/ fluticasone propionate combination inhaler (Advair), continuing on current ICS dose, or increased ICS dose	1 year	1 week	Healthcare system	NA	QALY	No
Kennedy et al,[30] 2007	Canada	Decision tree	≥18 years old	Suspected occupational asthma presenting with symptoms of asthma	Sputum testing, serial peak expiratory flow, specific inhalation challenge, or combined sputum cell count analysis and peak expiratory flow monitoring	Not mentioned	NA	Third-party insurance program	Not mentioned	1 correct diagnosis	No
Mogasale et al,[49] 2013	Australia	Decision tree	Adults and children	Chronic asthma	Asthma clinic that provides education, promotion of self-monitoring of symptoms, regular review of treatment by a medical practitioner, and a written asthma action plan vs current practice†	1 year	NA	Healthcare system	3%	DALY	No
Morishima et al,[50] 2013	Japan	Markov	Adults	Moderate to severe asthma	Omalizumab + standard therapy vs placebo + standard therapy†	Lifetime	1 week	Societal	3%	QALY	No (direct non-healthcare costs of transportation were included)
Nguyen et al,[51] 2017	Singapore	Markov	Median age 56.1	Difficult (uncontrolled despite high-intensity treatment) and severe (refractory disease) asthma	Bronchial thermoplasty + optimized asthma therapy vs optimized asthma therapy†	5 years	2 weeks	Healthcare system and societal	3.50%	QALY	Yes

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Table 1. Continued

Authors year	Location and setting	Type of model	Population	Asthma status when entering the model	Inter vention	Time Horizon	Cycle Length	Perspective	Discount rate	Effect measure	Indirect Costs
van Nooten et al,[40] 2013	Netherland	Markov	≥40 years old	Uncontrolled allergic asthma	Omalizumab + standard therapy vs standard therapy†	Lifetime	16 weeks	Societal (implied)	1.5% and 4% (outcomes and costs, respectively)	QALY, LY	Yes
Norman et al,[33] 2013	UK	Markov	Children, adolescents, and adults	Poor controlled asthma	Omalizumab + standard care vs. standard care†	Lifetime	3 months	National health system	4%	QALY	No
Paggiaro et al,[52] 2013	UK, Netherland, Spain	Markov	Not mentioned	Controlled asthma	Step down of controlled patients on high-dose fluticasone/ salmeterol (1000/ 100 mg daily) to medium dose (500/ 100 mg) dry powder, or extrafine beclometasone/ formoterol (400/24 mg) pMDI	24 weeks	4 weeks	Health system	NA	QALY	No
Paltiel et al,[18] 2001	US	Markov	Adults (18-35 and >35 years old)	Mild to moderate asthma	Quick relievers alone ("no ICS"), ICS for mild asthma ("mild only"), ICS for moderate asthma ("moderate only"), or the original intervention (all patients receive ICS)	10 years	1 month	Societal	3%	QALY, symptom free day	No
Price et al,[35] 2002	UK	Markov	Adults and adolescents	Symptomatic asthma	Salmeterol/ fluticasone propionate combination, 50/ 100 μg vs fluticasone propionate, 100 μg	12 weeks	1 week	Healthcare system	NA	Successfully controlled week	No
Price et al,[53] 2009	UK	Decision tree	Adults	Mild to severe asthma/ general population	FENO measurement (using NIOX MINO) vs common clinical practice*	1 year	NA	Healthcare payer	NA	QALY	No
Ramos et al,[41] 2014	Netherland	Decision tree	Pediatrics	General population not diagnosed with asthma	Primary prevention programs vs usual care†	6 years	NA	Healthcare system	4%	Asthma cases avoided	No
Rodriguez-Martinez et al,[48] 2013	Colombia	Markov	Pediatrics	Persistent asthma	Budesonide, fluticasone propionate, and ciclesonide vs beclomethasone dipropionate	1 year	1 week	Healthcare system	0%	QALY	No
Rodriguez-Martinez et al,[46] 2015	Colombia	Markov	Pediatrics	Mild persistent asthma	Daily ICS vs intermittent ICS	1 year	1 week	Healthcare system	0%	QALY	No
Rodriguez-Martinez et al,[47] 2016	Colombia	Markov	Pediatrics	Persistent asthma	Once-daily vs twice-daily ICS (budesonide)	1 year	1 week	Healthcare system	0%	QALY	No
Sabatelli et al,[42] 2017	Spain	Decision tree	≥15 years	Not mentioned	FENO monitoring + standard guideline care vs standard guideline care†	1 year	NA	Healthcare system	3.5% for costs—unclear for health outcomes	QALY, number of averted hospitalizations, emergency room visits, and urgent primary care visits	No
Shih et al,[7] 2007	US	Decision tree	Adults and adolescents	Mild to moderate persistent asthma	Single inhaler salmeterol/ fluticasone propionate, fluticasone propionate inhaled corticosteroids, non-fluticasone propionate inhaled corticosteroids, or leukotriene modifiers	1 year	3 months	Managed care organization	NA	Symptom-free day and rescue medication-free day	No

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Table 1. Continued

Authors year	Location and setting	Type of model	Population	Asthma status when entering the model	Inter vention	Time Horizon	Cycle Length	Perspective	Discount rate	Effect measure	Indirect Costs
Steuten et al,[43] 2007	Netherland	Markov	Adults (>18 years)	Mild intermittent to severe persistent asthma	Disease management program (collaborative practice team consisting of a pulmonologist, GPs, and respiratory nurse specialists) vs usual care (either managed by the GP (mild to moderate asthma) or the pulmonologist (moderate to severe asthma)	5 years	2 weeks	Societal	4%	QALY	No (productivity costs included in sensitivity analysis)
Suzuki et al,[45] 2017	Brazil	Markov	Children, adolescents, and adults (mean age: 45)	Severe, allergic, uncontrolled asthma	Omalizumab + standard care vs standard care‡	Lifetime	3 months	Public healthcare	5%	QALY	No
Whittington et al,[19] 2017	US	Markov	Adults (mean age: 50)	Severe eosinophilic asthma	Mepolizumab + standard of care vs standard of care‡	Lifetime	2 weeks	Payer	3%	QALY	No
Wild et al,[20] 2005	US	Markov	18-65 years	Healthy exposed workers	Annual surveillance vs passive case finding of isocyanate asthma	10 years	1 month	Employer and societal	3%	QALY and symptom-free day and case of disability prevented	Yes (and disability costs and lost wages)
Willson et al,[36] 2014	UK	Markov	Adults (mean age: 53)	Poorly controlled	Tiotropium + usual care vs usual care‖	Lifetime	1 week	National health system	3.50%	QALY	No
Wu et al,[21] 2007	US	Markov	Adults	Severe persistent asthma	Omalizumab + ICS + quick reliever as needed vs ICS + quick reliever as needed	10 years	1 month	Societal	3%	QALY	No
Zafari et al,[24] 2014	US	Markov	Adults (>19 years of age)	Uncontrolled asthma	Full adherence to controller therapy vs status quo	10 years	1 week	Not mentioned	3%	QALY	No (yes in sensitivity analysis)
Zafari et al,[22] 2016	US	Markov	Adults (18-65 years old, mean 40)	moderate to severe asthma that remained uncontrolled despite high dose (1,000 μg of fluticasone or equivalent) of ICS	Omalizumab, bronchial thermoplasty, or standard therapy‖	5 years	1 week	Healthcare system	3%	QALY	No
Zafari et al,[23] 2018	US	Markov	Not mentioned	Uncontrolled allergic asthma	Standard therapy, ‖ standard therapy + omalizumab, standard therapy + tiotropium	10 years	1 week	Societal	3%	QALY	Yes
Zein et al,[25] 2016	US	Markov	41-year-old	Severe uncontrolled asthma	Bronchial thermoplasty vs usual care	10 years	1 month	Healthcare payer	3%	QALY	No

BMD indicates bone mineral density; DALY, disability-adjusted life-year; ED, emergency department; FENO, fractional exhaled nitric oxide; GP, general practitioner; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LTRA, leukotriene receptor antagonist; LY, life year gained; NA, not applicable; OCS, oral corticosteroids; pMDI, pressure metered-dose inhaler; QALY, quality-adjusted life-year; SABA, short-acting β2 agonists.
*Standard German diagnostic tests: spirometry, reversibility testing, bronchial provocation, sputum eosinophil count; standard management monitoring: spirometry.
†Not specified.
‡Standard therapy: ICS plus a LABA (plus additional controller medication including OCS and SABA, anti-leukotrienes and theophylline if required).
§Based on the Dewilde et al model.
‖Standard therapy: high dose ICS + LABA.

studies varied widely. In 1 model, a time horizon was not reported because the intervention of interest was testing for diagnosing occupational asthma with no period over which the costs and benefits were measured.[30] Ten studies (all but 1 evaluating biologics) used a lifetime time horizon,[16,19,27,32,33,36,39,40,45,50] with the remaining studies using horizons that ranged from days to 20 years.

In outcomes, most of the studies reported the effect measure as quality-adjusted life-years gained. Three also reported life years gained.[16,39,40] Disability-adjusted life-years,[49] symptom-free days

or weeks,[4,6,7,18,54,55] averted cases of hospitalization, and emergency department visits or exacerbations[12-14,20,28,42,55] were other measurements of effectiveness that were used in the models. In 1 study where the intervention of interest was preventive, incremental costs per 1 avoided case of asthma was calculated.[41] Eleven studies considered indirect costs, either in base-case analysis or in sensitivity analysis,[12,13,17,20,21,23,39-41,44,51] and in 1 study, time off from work was applied as a proportional reduction in disability weights.[49]

Quality of Reporting

Table 2 summarizes the quality of reporting according to the CHEERS Checklist.[5] Some studies did not mention the perspective of evaluation,[4,24,27,31,40] and in some, the target jurisdiction could only be implied from other information in the text.[23,27,37,42,51,52] Similarly, the discount rate of future costs and health outcomes was not reported in some studies, despite the study having a time horizon of more than 1 time unit.[13,20,30,35] Heterogeneity in patient populations and cost-effectiveness results across different subgroups were mostly overlooked because only 8 papers reported it appropriately.[14,24,31-33,37,46,56] In addition, although most studies reported on the type of model (eg, a Markov model) used for the analysis, very few[37,38,41,47,56] elaborated on the reasons for the choice of their particular model type and structure as required by the Checklist (thus receiving partial score in our assessment). Similarly, sufficient details of the analytical methods that could enable reproducing model structure, inputs, and analyses was mostly missing in some of the studies. Currency, price date, and conversion was also missed partially[6,11-13,19,24,30,32,36,40,42,43,49,52,53] or completely[27,28,37-39,45,56] in most studies. In general, studies published in methodological (as opposed to the clinical) journals had a higher quality of reporting.

Assumptions on the Natural History of Asthma

Modeling the natural history of asthma

Among the Markov models that simulated transition of individuals across asthma-related health states, 6 models were based on the concept of clinical or symptom control,[4,6,14,18,26,35] but all models considered asthma exacerbations. Among these, 4 modeled exacerbation as an acute event without any duration,[15,25,32,52] whereas the others modeled exacerbation as an explicit health state alongside control levels. Two models distinguished, by creating separate health states, between the immediate versus later post-exacerbation periods.[11,17] Eleven studies defined health states based on the presence or absence of exacerbations, without modeling control status.[4,11,14,16,18,19,21,23,27,39,51] Three studies built their model based on other conditions in relation to asthma or asthma-related interventions such as cardiovascular diseases,[11] allergic rhinitis,[44] and decline in bone marrow density owing to treatment with corticosteroids.[4]

Heterogeneity in disease course and cost-effectiveness results

Heterogeneity in cost-effectiveness results was fully or partially addressed in 13 studies. Such heterogeneity included analysis or reporting of results based on the stratification of the population based on adherence to treatment,[14] baseline severity of disease,[14,17,18,24,37,44,50,51] age,[18,24,31,33,44,46,49] number of asthma-related exacerbations or hospitalizations in the past year,[32,33] maintenance use of oral corticosteroids,[32,33] and baseline smoking status.[18]

Discussion

We conducted a systematic review to identify model-based economic evaluations in asthma and appraise their methodology in overall study characteristics, quality of reporting, and important assumptions around the natural history of asthma. Forty-five studies were included in this review, covering a variety of interventions across different settings and jurisdictions. Although most of these studies were of sound quality overall, only a few performed satisfactorily with respect to all of the methodological criteria of the contemporary reporting recommendations. The aspects of reporting that were frequently missed in the studies were characterizing heterogeneity; a reason for the choice of the model; and currency, currency years, and details on currency conversion. In addition, although the overall methodology behind modeling the natural history of asthma based on clinical or symptom control was similar across these studies, consideration of the heterogeneity in clinical features was not. Moreover, only a few studies evaluated asthma in the context of coexisting health conditions or possible long-term adverse effects of treatments. On the other hand, all of the studies successfully reported choice of health outcome and comparators, and most included the time horizon and the method to estimate resources and costs.

Our assessment of the quality of reporting concluded that more recently developed models of asthma tended to have higher-quality reporting in general. This is not a surprising finding given the recent advancements in developing good practice modeling guidelines with more emphasis on standardization of methodologies and reporting of economic evaluations results.[5] Still, some recent publications failed to report some basic aspects of their report, such as study perspective or discount rates. Reporting guidelines for systematic reviews and randomized trials have now been widely adopted by the research community across many disciplines. Our findings indicate that there is a need for promoting the adoption of analysis and reporting guidelines in economic evaluations.

The general consistency in modeling the natural history of asthma based on control levels and its relation to exacerbation rate reflects the results of major attempts in standardization of asthma outcomes for research and clinical practice. The rate of achieving symptom control and the degree of reduction in exacerbation rate have been the primary or secondary outcomes in most clinical trials. Influential guidelines and best-practice recommendations also emphasize these as targets of clinical management.[57] Such attempts toward standardization have resulted in the accumulation of evidence, for example, on the effectiveness of pharmacotherapies in achieving clinical control, avoiding exacerbations,[58] or relation between asthma control and costs or quality of life.[59] As a result, symptom control and exacerbation rates seem to be appropriate metrics for relating the effectiveness of asthma-related interventions to policy-relevant measures such as costs and quality-adjusted life-years. Nevertheless, there is still room for improvement in the economic evaluations of asthma-related interventions. For example, the U.S. National Institutes of Health has recommended core asthma-specific outcomes to help unify the study designs toward facilitating comparisons and optimizing decision making.[60] Recent reviews have identified that cost-effectiveness analyses of asthma medications are yet to fully adhere to such recommendations.[61] Further, most studies ignored heterogeneity in the natural history of asthma and the potential variability of cost-effectiveness results across different groups. Asthma is known to be heterogeneous on many different aspects, and ignoring such heterogeneity can have multiple consequences.[62] First, if an intervention is shown to be cost-effective

Table 2. Evaluation of the economic models on the basis of CHEERS

Authors	Target population and subgroups[1]	Setting and location[2]	Study perspective[3]	Comparators[4]	Time horizon[5]	Discount rate[6]	Choice of health outcomes[7]	Measurement of effectiveness[8]	Measurement and valuation of preference-based outcomes[9]	Estimating resources and costs[10]	Currency, price date, and conversion[11]	Choice of model[12]	Assumptions[13]	Analytic methods[14]	Study parameters[15]	Incremental costs and outcomes[16]	Characterizing uncertainty[17]	Characterizing heterogeneity[18]
Altawalbeh et al[11]								■			■	■						■
Andrews et al[13]		■			■	■		■	▒		■	■		■		■	■	■
Andrews et al[12]		■				■		■	▒		■	■				■	■	■
Bae et al[14]						■			▒			■		■		■	■	
Berg et al[37]	■					■					■						■	
Bond et al[26]									■			■						■
Brodtkorb et al[38]								■		■	■		■	■	■			■
Brown et al[27]	■		■								■	■	■					■
Bruggenjurgen et al[44]									■		■				■		■	
Cangelosi et al[15]		■						■				■	■					■
Campbell et al[16]												■						■
Dewilde et al[39]											■	■						■
Doan et al[28]									▒		■	■						■
Doull et al[31]		■	■									■					■	
Faria et al[32]											■	■					■	
Fuhlbrigge et al[4]		■	■			■						■	■	■			■	■
Gerald et al[17]						■			■			■						■
Gerzeli et al[6]						■		■	■		■	■				■		■
Ismailia et al[29]						■						■					■	■
Kennedy et al[30]					▒	■		■	▒		■	■					■	■
Mogasale et al[49]						■					■	■						■
Morishima et al[50]												■						■

continued on next page

Table 2. Continued

Authors	Target population and subgroups[1]	Setting and location[2]	Study perspective[3]	Comparators[4]	Time horizon[5]	Discount rate[6]	Choice of health outcomes[7]	Measurement of effectiveness[8]	Measurement and valuation of preference-based outcomes[9]	Estimating resources and costs[10]	Currency, price date, and conversion[11]	Choice of model[12]	Assumptions[13]	Analytic methods[14]	Study parameters[15]	Incremental costs and outcomes[16]	Characterizing uncertainty[17]	Characterizing heterogeneity[18]
Nguyen et al[51]	■											■						■
van Nooten et al[40]			▒								■	■						▒
Norman et al[33]												■						
Paggiaro et al[52]	■					■		■	■		■	■						▒
Paltiel et al[18]												■					▒	■
Price et al[35]		■			■	■		■	▒			■						▒
Price et al[53]						■					■	■					▒	▒
Ramos et al[41]									▒									▒
Rodriguez-Martinez et al[48]												■						▒
Rodriguez-Martinez et al[46]												■						
Rodriguez-Martinez et al[47]																		▒
Sabatelli et al[42]	■					■			■		■	■						▒
Shih et al[7]		■				■			▒			▒						▒
Steuten et al[43]											■	■						▒
Suzuki et al[45]								■			▒	■						▒
Whittington et al[19]		■									■	■					■	▒
Wild et al[20]		■			■	■						■					▒	▒
Willson et al[36]								■			■	■						▒
Wu et al[21]		■										■					▒	▒
Zafari et al[24]			▒						■		■	■						
Zafari et al[22]												■						▒

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Table 2. Continued

Authors	Target population and subgroups[1]	Setting and location[2]	Study perspective[3]	Comparators[4]	Time horizon[5]	Discount rate[6]	Choice of health outcomes[7]	Measurement of effectiveness[8]	Measurement and valuation of preference-based outcomes[9]	Estimating resources and costs[10]	Currency, price date, and conversion[11]	Choice of model[12]	Assumptions[13]	Analytic methods[14]	Study parameters[15]	Incremental costs and outcomes[16]	Characterizing uncertainty[17]	Characterizing heterogeneity[18]
Zafari et al[23]																		
Zein et al[25]																		

CHEERS indicates Consolidated Health Economic Evaluation Reporting Standards.
Note. Color key: White = yes, gray = no, dark yellow = partially or implied, light yellow = not applicable.
Guide of white (full score) for each criterion (not meeting these definitions, partially or completely, indicated by dark yellow or gray box):

1. Age group and asthma status of population is well defined.
2. The geographical setting of the population that the model is applied to is clearly indicated.
3. Perspective is clearly mentioned.
4. The question of the study and comparators are indicated.
5. Time horizon is specified and not just implied.
6. Choice of health outcomes are indicated.
7. Discount rate is clear for both costs and outcomes.
8. The source for clinical data is described properly and if a single study is used, the reason for why a single study is selected versus systematic review is provided.
9. Health outcome and instrument to estimate utility scores is reported.
10. Clear explanation of the source for estimating resources and costs.
11. Cost currency, conversion methods, and year are reported.
12. The type of model and the reason for choosing it is explained.
13. Assumptions and the reason behind them are declared clearly.
14. Sufficient details of the analytical methods that could enable reproducing model structure, input, and analyses.
15. Study parameters presented in detail (and not only in major groups such as direct and indirect costs).
16. Incremental costs and outcomes and the fraction of them is reported separately.
17. Uncertainty in the input parameters and probabilistic sensitivity analyses and its standard outputs such as cost-effectiveness planes or acceptability curves is reported.
18. Heterogeneity has been considered up front in the methods and the results were reported in different groups of heterogeneity.

across the population, yet there are identifiable subgroups of individuals among which the intervention is not cost-effective (or vice versa), then a population-based treatment decision, compared with a stratified decision across subgroups, would be associated with loss of efficiency. Second, in the context of cohort-based modeling, even if the analyst does not have any intention to explore subgroup-specific results, not accounting for heterogeneity in the natural history of the disease can result in erroneous estimation of population-level cost and effectiveness outcomes.[63] This is especially relevant in light of recent developments in our understanding of asthma as a heterogeneous disease. Key opinion leaders advocate a move toward recognizing and targeting treatable traits in each individual asthma patient.[62] This will have major implications for cost-effectiveness of interventions because the permutations of such variables will create a vast decision space. Decision-analytic models for asthma that are capable of finding efficient strategies given patients' multiple traits will likely have different structures than the current simple Markov models based on asthma control and exacerbations. Microsimulation models that can incorporate many characteristics without suffering from the curse of dimensionality that afflicts Markov models might be required. Lastly, although studies have shown the impact of comorbidities on economic burden of asthma,[64,65] this important aspect has been overlooked in most economic models. Modeling the impact of comorbidities is particularly important in the context of corticosteroids use and its possible association with osteoporosis, pneumonia, and several other comorbidities.

The limitations of our study should be acknowledged. First, the systematic review was limited to English articles. Second, we did not evaluate the quality of evidence synthesis and the relevance of the sources of evidence that constituted the input parameters. Although assessment of such aspects were out of the scope of this study that focused on quality of reporting and major structural assumptions, we acknowledge that variation in sources of input parameters can be an important determinant of the variation in the results. Beyond reporting, another important consideration in evaluating the credibility of cost-effectiveness results are the extent to which model outputs are internally and externally (eg, against real-world data) validated.[66,67] This aspect was not considered in our review. Further, we did not compare the outcomes of the models that addressed similar questions; comparative analysis of models that were used to address the same question but generated divergent results can be informative in deciding the credibility of each model and the impact of different assumptions on the results. Another potential limitation is that the models were only assessed against 1 checklist, although other checklists exists.[68,69] We used the CHEERS Checklist given its wide adoption within the health economics community. Nevertheless, assessing the models against the CHEERs Checklist was, to some extent, subject to uncertainty

because interpretation of the checklist items inevitably involves some level of subjectivity. Also, in CHEERS, each item carries equal weight of importance, yet some of the criterion (eg, choice of modeling, analytical methods) seem more crucial in determining the validity of the results than others (eg, whether the study reported incremental costs and effectiveness in addition to the incremental cost-effectiveness ratio).

Conclusions

This review demonstrated that model-based economic evaluations of asthma-related interventions generally complied with the contemporary requirements for reporting of such studies. Very few studies covered all of the items that are required for others to reproduce the results. Contemporary asthma management is shifting its focus toward identifying and treating multiple traits in patients with asthma.[70] The existing decision-analytic asthma models, however, seem to lack the granularity that will be required to properly model such precision medicine approaches to asthma management.

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Supplemental Materials

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