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REVIEW

Impact of pharmaceutical care for asthma patients on health-related outcomes: An umbrella review

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Abstract

Recent systematic reviews suggest that pharmacists' interventions in asthma patients have a positive impact on health-related outcomes. Nevertheless, the association is not well established, and the role of clinical pharmacists is poorly represented. The aim of this overview of systematic reviews is to identify published systematic reviews assessing the impact of pharmacists' interventions on health-related outcomes measured in asthma patients. PubMed, Embase, Scopus, and Cochrane Library were searched from inception to December 2022. Systematic reviews of all study designs and settings were included. Methodological quality was assessed using AMSTAR 2. Two investigators performed study selection, quality assessment and data collection independently. Nine systematic reviews met the inclusion criteria. Methodological quality was rated as high in one, low in two, and critically low in six. Reviews included 51 primary studies reporting mainly quality of life, asthma control, lung capacity, and therapeutic adherence. Only four studies were carried out in a hospital setting and only two reviews stated the inclusion of severe asthma patients. The quality of the systematic reviews was generally low, and this was the major limitation of this overview of systematic reviews. However, solid evidence supports that pharmaceutical care improves health-related outcomes in asthma patients.

KEYWORDS
asthma, clinical pharmacist, outcome assessment, health care, pharmaceutical care, systematic review

Abbreviations: AMSTAR-2, A Measurement Tool to Assess Systematic Reviews 2; COPD, Chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; MESH, Medical Subject Headings; OCS, oral corticosteroids; PRISMA-P, Preferred Reported Items for Systematic Review and Meta-analysis Protocols; PICOS, Population, Intervention, Comparison, Outcome and Study Design; QoL, quality of life; RR, risk ratio.

Registration details: CRD42022372100.

1 | INTRODUCTION

Asthma is a chronic, heterogeneous, and complex disease with a high worldwide prevalence, which makes it one of the main non-communicable diseases.[1]

The severity of the pathology can be very variable, being most of the cases mild or moderate. However, the severe form of the disease affects almost 5% of the asthmatic patients.[2] These patients have lower response rates to pharmacologic treatment, such as inhaled corticosteroids, long-acting β-agonists, and even oral corticosteroids (OCS), which can lead to severe exacerbations that can be life-threatening. They also bear a great burden of the disease, economically and psychologically, as well as an elevated impact on the quality of life (QoL).[3–6]

The appearance of new biological drugs for the treatment of severe asthma has emphasized the importance of hospital pharmacists in multidisciplinary teams within Asthma Units. Clinical pharmacists collaborate in the management of these patients by carrying out outpatient follow-up, where they train and educate patients about their pathology, their medication, and the need for correct adherence. They also ensure the correct indication, efficacy, safety, and possible interactions of the prescribed medication, as well as training in its correct administration, thus, improving health-related outcomes. Clinical pharmacists also collaborate in the coordination of care for these patients by developing protocols, guidelines or standardized working procedures, unifying criteria between the different healthcare professionals and facilitating the best therapeutic options, thus also improving the rational use of medication.

Previous primary research studies have evaluated the effect of pharmaceutical care to asthma patients on patient-related outcomes and health-related problems. However, interpreting the evidence related to pharmacists' interventions can be a challenge due to the variation in study designs, patients included, interventions, and settings. There are also systematic reviews and meta-analyses (MA) published in recent years that suggest that pharmacists' interventions have a positive impact on asthma control, severity and symptoms, and medication adherence.[7,8] Nevertheless, the role of clinical pharmacists is poorly represented, most of the patients included present mild-to-moderate asthma, and with the commercialization of the monoclonal antibodies, the treatment has become much more complex. The Cochrane Collaboration recommends an overview of systematic reviews to summarize the evidence of existing systematic reviews that address different outcomes for a single intervention.[9]

The main objective of this overview of systematic reviews is to identify published systematic reviews on the impact of pharmacists' interventions for asthma patients on health-related outcomes and to describe key components of the intervention, the outcomes assessed and any associations between pharmacists' interventions and health-related outcomes in asthma patients. Secondary objectives are to assess the participation of clinical pharmacists in outpatient consultations in the interventions reported and the presence of severe asthma patients in the patients included.

2 | METHODS

The protocol of this systematic review was developed following the Preferred Reported Items for Systematic Review and Meta-analysis Protocols (PRISMA-P)[10] and was registered in the International prospective register of systematic reviews (PROSPERO CRD42022372100), as well as published in a peer-review journal.[11]

The overview of systematic reviews was reported in accordance with the PRISMA statement.[12]

2.1 | Eligibility criteria

The inclusion criteria for the systematic review according to PICOS (Population, Intervention, Comparison, Outcome and Study design) were the following:

Participants: Adult patients with asthma.
Intervention: Pharmaceutical care provided at any level of care (hospital, primary care).
Comparator: Usual practice or without comparator.
Outcome: Patient health-related variables, for example: QoL, adherence to therapy, improvement of inhaler technique, reduction in the use of OCS, and management of health-related problems.
Study design: Systematic review with/without meta-analysis.

Systematics reviews that do not include or do not focus on patients with asthma were excluded, as well as those only reporting the impact of drugs or results of interventions in which pharmacists do not participate. In addition, there was no date or language restriction, but the research had to be accessible in full text.

2.2 | Information sources and search strategy

Two authors (OMP and FSG) performed a comprehensive search including all available articles from inception until December 31st 2022 in five healthcare databases: PubMed, Embase, Scopus, and Cochrane Library. The search strategy was carefully designed by the authors and critically revised by an experienced librarian including a combination of Medical Subject Headings (MeSH) and free terms combined with Boolean operators. Gray literature was included using Google Scholar, as well as the reference lists of identified relevant articles. The complete search strategy is displayed in Table 1.

2.3 | Selection process and data collection process

A peer-review of the literature was performed by two independent investigators (OMP and FSG) screening the titles and abstract of all potential systematic reviews for possible inclusion with any discrepancy settled by consensus or with a third reviewer (ESG). Two reviewers (OMP and FSG) then independently extracted data from

TABLE 1 Complete search strategy for different databases.

Healthcare databases	Search strategy
PUBMED	("asthma"[Title/Abstract] AND ("pharmaceutical care"[Title/Abstract] OR "pharmacy"[Title/Abstract] OR "pharmacist"[Title/Abstract]) AND "systematic review"[Filter])
EMBASE	("asthma"/exp OR "asthma") AND ("pharmaceutical" AND "care") AND [systematic review]/lim
Cochrane library	(asthma):ti,ab,kw AND ((pharmaceutical care) OR pharmacy OR pharmacist):ti,ab,kw Limits: Cochrane Reviews
SCOPUS	(TITLE-ABS-KEY (asthma) AND TITLE-ABS-KEY (pharmacist OR pharmacy OR (pharmaceutical AND care))) AND (LIMIT-TO (DOCTYPE, "re"))

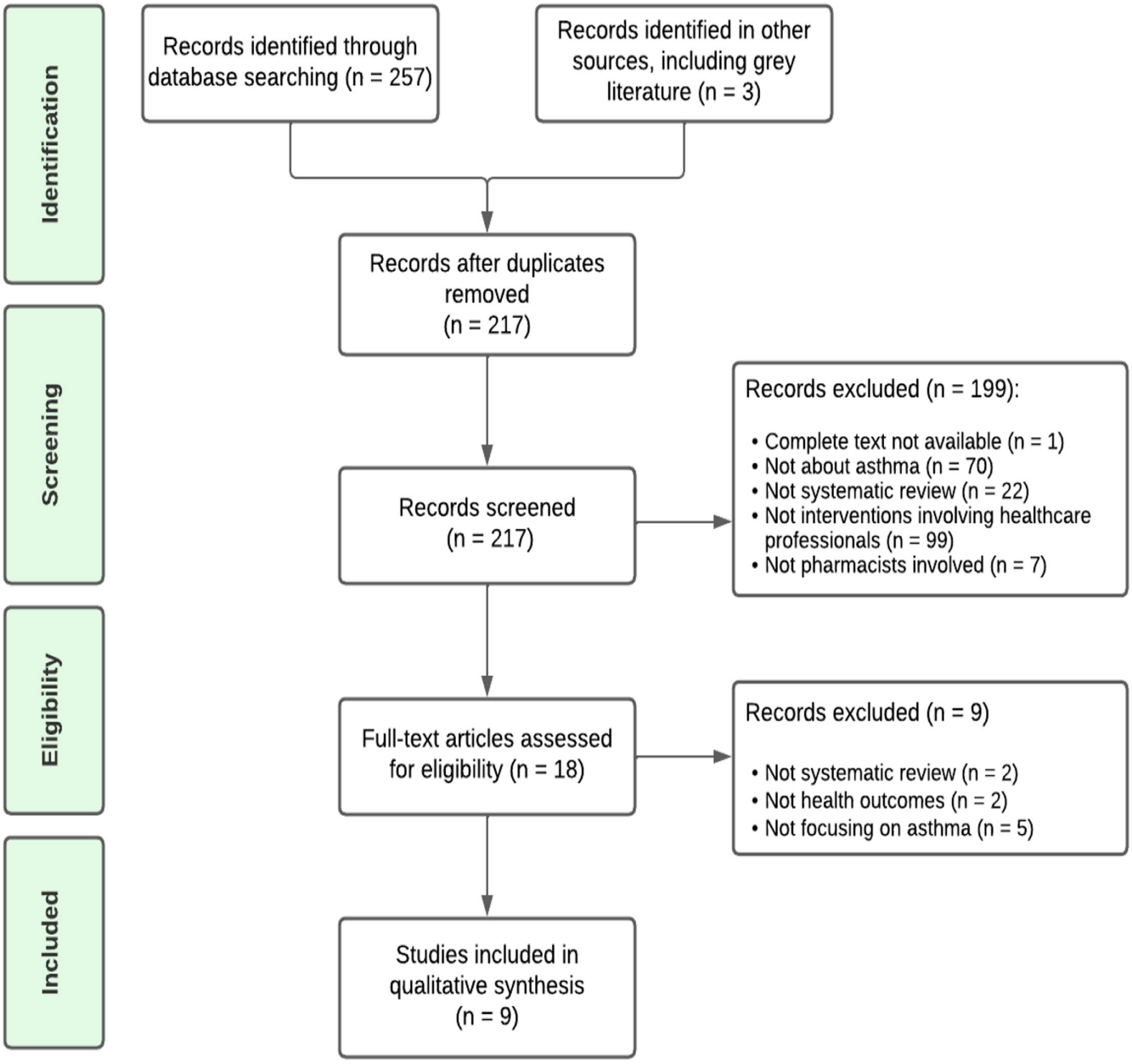

FIGURE 1 Preferred reporting items for systematic reviews and meta-analyses literature search and study selection flowchart.

the systematic reviews included and any discrepancies were solved by discussion or further consultation with a third reviewer (ESG). If there were any missing data from a review, it was explicitly stated. For each systematic review, the following variables were registered:

- General variables
  Author and year of publication.
  Aim of systematic review.
  Number of primary studies.

TABLE 2 Quality analysis of the systematic reviews with/without meta-analysis included according to the AMSTAR 2 tool.

AMSTAR 2 domains	Fathima et al. (2013)[18]	Mohammed et al. (2016)[19]	García-Cárdenas et al. (2015)[7]	Jia et al. (2020)[20]	Steed et al. (2019)[16]	Dokbua et al. (2018)[17]	Mubarak et al. (2019)[15]	Mes et al. (2018)[14]	Mahdavi and Esmaily (2021)[8]
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	No	Yes	Yes	Yes	No	Yes	Yes	Partial Yes
3. Did the review authors explain their selection of the study designs for inclusion in the review?	No	Yes	Yes	Yes	Yes	No	Yes	Yes	No
4. Did the review authors use a comprehensive literature search strategy?	Partial Yes	Yes	Yes	Partial Yes	Yes	Partial Yes	Yes	Partial Yes	Partial Yes
5. Did the review authors perform study selection in duplicate?	No	Yes	Yes	Yes	No	No	Yes	Yes	Yes
6. Did the review authors perform data extraction in duplicate?	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	No	No	No	Yes	Yes	No	No	No
8. Did the review authors describe the included studies in adequate detail?	Partial Yes	Yes	Yes	Yes	Partial Yes	No	Yes	Yes	Partial Yes
9. Did the review authors use a satisfactory technique for assessing the RoB in individual studies that were included in the review?	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	No	No	Yes	No	Yes	No	No	No	No
11. If MA was performed did the review authors use appropriate methods for statistical combination of results?	No MA	Yes	No MA	Yes	Yes	Yes	Yes	Yes	No
12. If MA was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the MA or other evidence synthesis?	No MA	Yes	No MA	Yes	Yes	No	No	Yes	No
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No

TABLE 2 (Continued)

AMSTAR 2 domains	Fathima et al. (2013)[18]	Mohammed et al. (2016)[19]	García-Cárdenas et al. (2015)[7]	Jia et al. (2020)[20]	Steed et al. (2019)[16]	Dokbua et al. (2018)[17]	Mubarak et al. (2019)[15]	Mes et al. (2018)[14]	Mahdavi and Esmaily (2021)[8]
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No MA	Si	No MA	No	Yes	No	Yes	Yes	No
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Confidence level	Critically low	Critically low	Critically low	Critically low	High	Critically low	Low	Low	Critically low

Abbreviations: MA, meta-analysis; RoB, risk of bias.

Design of primary studies.
Number of participants.
Type of participants: Adults and/or pediatric patients.
Severity of patients' asthma: Patients with mild/moderate or severe asthma.
Setting: Hospital or primary care.
Funding statement.
Competing interest statement.

- Specific variables

Asthma control.
Lung capacity.
QoL questionnaires (general and asthma specific).
Inhalation technique.
Medication adherence.

2.4 | Quality assessment

Two independent reviewers (OMP and FSG) carried out the assessment of the quality of the systematic reviews using a critical appraisal tool designed for this purpose, A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR 2).[13] In case of discrepancies on quality ratings, a common consensus was reached with a third reviewer (ESG) intervening if needed.

The overall quality can be rated as high, moderate, low, and critically low.

3 | RESULTS

The electronic search identified 257 publications in the databases consulted, and in addition, three publications were identified in the gray literature search. Of the 260 publications identified, 43 were removed using EndNote X9 software via duplicate checking. Additionally, 199 were excluded after applying the inclusion and exclusion criteria on title and abstract. A total of 18 potentially relevant reviews were retrieved in full-text: nine of them were excluded (The reasons for exclusion are provided in Supplementary File S1) and nine met the inclusion criteria[7,8,14–20] (Figure 1).

3.1 | Quality of the systematic reviews

Table 2 reports the results for each domain of the AMSTAR 2 tool. The overall quality of the included systematic reviews was poor. Of the nine reviews, only one was rated as high quality,[16] two as low quality[14,15] and six as critically low quality.[7,8,17–20]

All reviews presented similarities regarding responses in critical and non-critical domains, except for Fathima et al.[18] and García-Cárdenas et al.[7] who did not carry out a meta-analysis. Regarding critical domains, none of the authors provided a list of excluded studies justifying the reason for their exclusion, with the exception of Steed et al.[16] and Dokbua et al.[17] In addition,

TABLE 3 Main characteristics of the studies included.

Author/year	Aim	Primary studies (*n* and design)	Participants (*n* and type)	Asthma severity
Fathima et al. (2013)[18]	To assess the role of community pharmacists in providing screening services with/without subsequent treatment for undiagnosed COPD and uncontrolled asthma	3 RCTs, 1 RCTs *cluster*, 2 case–control, 1 before–after, 2 controlled	5200/Adults and pediatrics	Not indicated
Mubarak et al. (2019)[15]	To investigate the impact of collaboration between community pharmacist and primary care physician in the management of asthma.	6 RCTs, 4 RCTs *cluster*, 3 controlled, 7 before–after, 3 case–control	8749/Adults and pediatrics	Moderate/severe
Dokbua et al. (2018)[17]	To evaluate the effects of a service provided by community pharmacists containing self-care support for asthmatic patients compared to usual care.	6 RCTs, 1 before–after, 5 controlled	2121/Adults and pediatrics	Mild, moderate and severe (moderate and severe subgroup)
Garcia-Cárdenas et al. (2015)[7]	To evaluate the impact of pharmaceutical interventions on clinical outcomes of asthma in adult patients and to identify the outcome indicators used.	7 RCTs, 2 RCTs *cluster*, 2 randomized cluster, 8 before–after	3143/Adults	Not indicated
Mahdavi and Esmaily (2021)[8]	To evaluate the effects of pharmacist educational interventions on asthma control and severity, QoL, and medication adherence	9 RCTs, 2 RCTs *cluster*, 1 cohorts, 5 controlled, 1 case–control, 3 before–after	4677/Adults and pediatrics	Not indicated
Mohammed et al. (2016)[19]	To assess the impact of pharmaceutical care interventions on health-related quality of life.	2 RCTs, 1 before-and-after, 1 prospective controlled	1324/Adults and pediatrics	Not indicated
Jia et al. (2020)[20]	To evaluate the effect of pharmacist-led interventions in the treatment of asthma and COPD.	7 RCTs	886/Adults	Not indicated
Mes et al. (2018)[14]	To evaluate how effective pharmacist-led interventions are in improving medication adherence in adults with asthma	11 RCTs	2308/Adults	Not indicated
Steed et al. (2019)[16]	To evaluate the effectiveness and safety of health promotion interventions to change the professional practice of community pharmacy workers and improve outcomes for their users.	5 RCTs, 8 RCTs *cluster*	4537/Adults and pediatrics	Not indicated

Abbreviations: COPD, chronic obstructive pulmonary disease; QoL, quality of life; RCTs, random control trials; SABA, short-acting beta-agonist.

Dokbua et al.,[17] Fathima et al.[18] and Mohammed et al.[19] do not explicitly state that the methods of the review were established prior to its conduct, nor do they justify possible deviations in the protocol.

The systematic reviews by Fathima et al.[18] and García-Cárdenas et al.[7] do not use a satisfactory technique for assessing the risk of bias of the studies included in the reviews. Furthermore, Fathima et al.[18] do not consider the risk of bias of the primary studies when

Professional involved	Intervention	Environment	Results	Other results	Funding/Conflict of interest
Pharmacist	Patient education, inhalation technique, self-management, physician referral	Primary health care	Asthma control		Did not receive funding/No conflict of interest
Pharmacist/ Physician	Patient education and pharmaceutical care	Primary health care	QoL, asthma control, lung capacity, inhaler technique	Correct use of medications, knowledge of asthma, severity and symptoms of asthma, hospital or emergency room visits, use of SABA, cost–benefit of the intervention	No funding statement/ No conflict of interest
Pharmacist	Self-management support	Primary health care	QoL, asthma control, adherence to therapy.	Adverse health service effects, management of pharmacotherapy-related problems, smoking cessation, optimization of pharmacotherapy, severity of asthma.	Received funding by 1 university/ Conflict of interest
Pharmacist	Patient education, physician referral, medication review, asthma management plan, detection and resolution of medication-related problems.	Primary health care and hospital (1)	Asthma control, lung capacity	Asthma severity and symptoms	No funding statement/ No conflict of interest
Pharmacist	Patient education	Primary health care	QoL, asthma control, lung capacity, inhaler technique	Use of SABA, asthma severity	Did not receive funding/No conflict of interest
Pharmacist	Medication review and pharmacotherapy management	Primary health care and hospital (1)	QoL		Did not receive funding/No conflict of interest
Pharmacist	Patient education and inhalation technique	Primary health care and hospital (2)	Therapeutic adherence, inhalation technique		Did not receive funding/No conflict of interest
Pharmacist	Patient education, attention to patient perceptions and practical aspects of treatment (inhalation technique)	Primary health care and hospital (3)	Therapeutic adherence		Received funding by 1 research institute/ Conflict of interest
Pharmacist	Patient education and inhalation technique	Primary health care	QoL, asthma control, inhalation technique	Pharmacist behavior, adherence to the intervention, visits to health professionals, cost-effectiveness of the intervention.	Received funding by 1 research institute/No conflict of interest

discussing the results in the review, nor does Mahdavi and Esmaily.[8] The latter work does not use an appropriate method for the statistical pooling of the results, nor does it perform an adequate investigation of publication bias or discuss its possible impact on the results of the review. In the latter domain, the reviews by Dokbua et al.[17] and Jia et al.[20] also present a negative response.

Regarding noncritical domains, all reviews conducted their research questions and inclusion criteria including all PICO components

TABLE 4 Association between pharmaceutical care and health outcomes.

	Number of systematic reviews	Number of primary studies	Association
Quality of life	5	22	+/ND
Asthma control	6	25	+/ND
Lung capacity	3	19	+/ND
Therapeutic adherence	3	18	+/ND
Inhalation technique	4	21	+/ND

Abbreviation: ND, no statistically significant differences ($p > 0.05$).

and all authors reported potential sources of conflict of interest, including funding sources. All reviews described the included studies in sufficient detail, or at least partially, with the exception of Dokbua et al.,[17] and also provided explanations in a satisfactory manner for the observed heterogeneity and discussed it in the results, with the exception of Dokbua et al.[17] and Fathima et al.[18]

Only the reviews by Steed et al.[16] and García-Cárdenas et al.[7] reported the funding sources of the studies included in the review.

3.2 | Characteristics of included studies

Full details of the included studies are shown in Table 3. All the included reviews aimed to identify interventions performed by pharmacists, individually or with other health professionals, focused on the asthmatic patient and to analyze their association with favorable clinical outcomes.

In the systematic review by Steed et al.,[16] the intervention was conducted on pharmacists, and the pharmacists themselves on patients. On the other hand, in the reviews by Fathima et al.,[18] Mohammed et al.,[19] Jia et al.,[20] and Steed et al.,[16] the interventions were not only carried out in asthma patients, but also other pathologies such as chronic obstructive pulmonary disease (COPD), diabetes, hypertension or epilepsy. For these systematic reviews, only the results related to asthma were analyzed.

The reviews included a variable number of primary studies: Fathima et al. nine studies, Mubarak et al. 23 studies, Dokbua et al. 12 studies, García-Cárdenas et al. 21 studies, Mahdavi and Esmaily 21 studies, Mohammed et al. 4 studies, Jia et al. 7 studies, Mes et al. 11 studies, and Steed et al. 13 studies. However, because several of the primary studies were included in more than one systematic review, the total number of original studies was 51. This included 12.796 adult and pediatric asthmatic patients. Asthma severity was not specified in most of the systematic reviews, with the exception of Mubarak et al.,[15] which included patients with moderate or severe asthma, and Dokbua et al.,[17] which included patients with mild, moderate, and severe asthma and performed a subgroup composed of patients with moderate and severe asthma.

Interventions were performed by pharmacists in every review. However, in the review by Mubarak et al.,[15] it was in collaboration with primary care physicians. The majority were performed by community pharmacists, but the reviews of García-Cárdenas et al.,[7] Mohammed et al.,[19] Jia et al.[20] and Mes et al.[14] included studies where the interventions were performed in a hospital setting.[21–24]

The interventions consisted mostly of patient education programs,[7,8,14–16,18,20] support for asthma self-management,[7,17,18] improving inhaler technique,[14,16,18,20] review of pharmacotherapy,[7,14,19] detection and resolution of medication-related problems,[7] and early referral to the primary care physician or specialist.[7,18]

The reviews reported results concerning the impact of the pharmacist's role on different health-related variables: QoL,[8,15–17,19] asthma control,[7,8,15–18] lung capacity,[7,8,15] therapeutic adherence[14,17,20] or inhalation technique.[8,15,16,20] Other variables collected were asthma severity,[7,8,15,17] asthma symptoms,[7,15] use of short-acting β agonists,[8,15] number of visits to health professionals[15,16] and cost–benefit of the intervention.[15,16]

3.3 | Impact of pharmaceutical care on health outcomes (Table 4)

3.3.1 | Quality of Life

Five reviews[8,15–17,19] reported results on QoL measured by different questionnaires such as the AQLQ and variants, the Living With Asthma Questionnaire, asthma-related quality of life questionnaire and others.

Mubarak et al.[15] included 15 studies reporting on QoL, of which 13 showed statistically significant improvement and 3 showed no difference. Pooled results from 6 studies showed a mean difference (MD) −0.2 (95% CI −0.64 to 0.2) in favor of collaboration between community pharmacist and primary care physician, although not statistically significant ($p = 0.3$), with high heterogeneity between studies ($I^2 = 95\%$, $p < 0.01$).

Steed et al.[16] performed a MA of five studies, showing statistically significant benefit with a MD 0.38 (95% CI 0.08 to 0.67) also with high heterogeneity ($I^2 = 80.6\%$, $p < 0.01$). Additionally, Mahdavi and Esmaily[8] pooled the results of six studies, showing a statistically significant improvement MD −0.241 (95% CI −0.36 to −0.12) in favor of pharmaceutical interventions, with moderate heterogeneity ($I^2 = 66.3\%$, $p = 0.011$).

Dokbua et al.[17] pooled the results of seven studies showing benefits in favor of pharmaceutical interventions with a MD 0.23 (95% CI 0.12–0.34) with no heterogeneity between studies ($I^2 = 0\%$, $p = 0.725$). A subgroup analysis was performed comparing outcomes

in uncontrolled asthma versus any level of asthma showing a greater benefit in the subgroup of patients with any level of asthma MD 0.35 (95% CI 0.13–0.58).

Finally, the review by Mohammed et al.[19] included four studies. Pooled results of two studies showed non-significant results with a MD 0.17 (95% CI −0.03 to 0.36, $p=0.09$), without heterogeneity between studies ($I^2=0\%$, $p=0.85$).

3.3.2 | Asthma control

Six reviews[7,8,15–18] reported results on asthma control, measuring results with different questionnaires, such as the ACT, the ACQ, or the Perceived Control of Asthma Questionnaire.

The reviews of García-Cardenas et al.,[7] and Fathima et al.,[18] did not perform quantitative analysis, but included 14 studies with positive results on 13 of them.

The other four reviews[8,15–17] showed statistically significant benefits. The work of Mubarak et al.[15] pooled results of eight studies showing a MD 0.32 (95% CI 0.13–0.51) with high heterogeneity ($I^2=81\%$, $p<0.01$). On the other hand, the work of Steed et al.[16] included eight studies, obtaining a MD −0.2 (95% CI −0.4 to 0) in favor of collaboration between community pharmacists and primary care physicians, also with high heterogeneity ($I^2=75\%$, $p<0.01$).

The review by Dokbua et al.[17] included six studies, showing statistically significant benefit with a MD 0.46 (95% CI 0.09–0.82) and high heterogeneity ($I^2=82.6\%$, $p<0.01$). In the subgroup analysis performed between uncontrolled asthma and any level of asthma, a greater benefit was obtained in the subgroup of patients with uncontrolled asthma, with a MD 0.71 (95% CI 0.13–1.29).

Finally, the review by Mahdavi and Esmaily[8] pooled the results of three studies, which showed statistically significant benefit with a MD −0.15 (95% CI −0.28 to −0.01), with no heterogeneity ($I^2=0\%$, $p=0.765$).

3.3.3 | Lung capacity

Three reviews[7,8,15] reported results on lung capacity, measured by different parameters, such as peak expiratory flow (PEF), forced expiratory volume in 1 s (FEV1), or FEV1/forced vital capacity (FVC) ratio.

Two of the reviews[7,15] reported their results using MA. Mahdavi and Esmaily[8] included five studies showing a small statistically significant benefit in favor of pharmaceutical care with a MD 0.13 (95% CI 0.01–0.26) and no heterogeneity ($I^2=0\%$, $p=0.907$). The review by Mubarak et al.[15] included 15 studies. The pooled results of four studies measuring PEF ratio showed a small statistically significant benefit in favor of collaboration between community pharmacists and primary care physicians with a MD 0.2 (95% CI 0.05–0.34) and low heterogeneity ($I^2=22.5\%$, $p=0.28$). The pooled results of two studies measuring FEV1, showed a non-significant minimal benefit MD 0.06 (95% CI −0.13 to 0.25, $p=0.55$), with no evidence of heterogeneity ($I^2=0\%$, $p=0.6$).

The work carried out by García-Cárdenas et al.[7] included 11 studies in which lung capacity is measured in different settings, such as the community pharmacy, by the patient himself or by the physician. Only six studies showed benefits attributable to pharmaceutical care.

3.3.4 | Therapeutic adherence

Three reviews[14,17,20] reported results on therapeutic adherence, which results were measured mainly by means of subjective questionnaires or the adherence reported by the patient with direct questions. Some studies also measured adherence objectively using the prescription dispensing records.

Two of the reviews[14,17] reported statistically significant beneficial results in favor of pharmaceutical interventions. Dokbua et al.[17] pooled the results of three studies, obtaining a MD 0.44 (95% CI 0.27–0.61) with no heterogeneity ($I^2=0\%$, $p=0.44$). The review by Mes et al.[14] included 11 studies, showing a MD 0.49 (95% CI 0.35–0.64) and low heterogeneity ($I^2=16.42\%$, $p=0.28$).

Lastly, the study published by Jia et al.[20] showed non-significant benefits in favor of pharmaceutical care in therapeutic adherence ($p=0.34$). The pooled results of two studies showed a risk ratio (RR) of 1.16 (95% CI 0.86–1.55) with moderate heterogeneity ($I^2=61\%$, $p=0.11$).

3.3.5 | Inhalation technique

Four reviews[8,15,16,20] reported results on the impact of pharmaceutical care on inhalation technique in asthmatic patients.

Three reviews[8,16,20] showed statistically significant benefits. Jia et al.[20] pooled the results of four studies, one of them including patients with COPD, accounting for 42% of the total weight of the MA. The MA showed a RR 1.85 (95% CI 1.57–2.17) in favor of pharmaceutical care, with moderate heterogeneity ($I^2=33\%$, $p=0.21$).

The review by Steed et al.[16] pooled the results of four studies showing a MD 0.92 (95% CI 0.35–1.48) in favor of pharmaceutical intervention, with high heterogeneity ($I^2=82\%$, $p<0.01$). Furthermore, the review published by Mahdavi and Esmaily[8] included four studies in their MA, showing a MD 0.79 (95% CI 0.05–1.54) with high heterogeneity ($I^2=93.4\%$, $p<0.01$).

Lastly, the review by Mubarak et al.[15] reported beneficial results regarding the impact of community pharmacists collaboration with primary care physicians, but unlike the previous ones, it was not statistically significant ($p=0.26$). The pooled results of four studies showed a MD 0.52 (95% CI −0.39 to 1.44) with high heterogeneity ($I^2=98\%$, $p<0.01$).

4 | DISCUSSION

This is the first overview of systematic reviews that specifically addresses the impact of pharmaceutical care on health outcomes in asthmatic patients. An overview of systematic reviews summarizing existing research and highlighting the absence of evidence can add value by improving access to specific information and supporting decision-making by clinicians, policy-makers and developers of clinical guidelines.

Two investigators systematically reviewed the literature independently with as few restrictions as possible, including any systematic review consisting of an intervention delivered by pharmacists or in collaboration with pharmacists in asthmatic patients, regardless of setting, asthma severity, patient age, health variable measured, and type of primary study included or language. Likewise, the objective was to compile as many reviews as possible to be able to group the evidence available to date on the impact of pharmaceutical care on health-related outcomes in asthmatic patients.

The quality of the included systematic reviews and meta-analyses was low[14,15] or critically low,[7,8,17–20] with the exception of the review by Steed et al.[16] which is of high quality according to the AMSTAR 2 tool criteria. Each of the reviews had deficiencies in different items of the tool, but the lack of a list of excluded studies and not reporting the sources of funding of the primary studies were the most frequent.

Only Steed et al.[16] and Dokbua et al.[17] provided a list of excluded studies with the reason for their exclusion. It is very unusual for systematic reviews to provide a list of articles discarded after reading the full text, providing only the number of studies discarded in the study selection flowchart and, at best, the reasons why they were discarded. However, unjustified exclusion could bias the findings of the review, therefore, it is important to identify the publications and the reasons for their exclusion in order to assess the risk of bias.

Secondly, only Steed et al.[16] and García-Cárdenas et al.[7] reported the sources of funding of the primary studies included in the reviews. Reporting the sources of funding is essential to guarantee the transparency of the published studies, and can sometimes be relevant to make comparisons by subgroups when funding may be related to the intervention, such as, for example, the use of a given drug and the pharmaceutical laboratory that markets it.

Regarding the variables measured, the most frequently reported were asthma control, which was evaluated in six of the systematic reviews included, and quality of life, reported in five systematic reviews. The most relevant benefits are shown in therapeutic adherence and inhalation technique, with MD >0.4 in most of the analysis. Substantial benefits are also shown in asthma control and quality of life, with MD between 0.2 and 0.4. These variables are all related since a correct inhalation technique is essential to achieve optimal therapeutic adherence. Pharmacological treatment is the key to asthma control, which eventually ends up positively influencing asthma-related quality of life. QoL is a particularly important variable, since of all the variables measured, it is the only one that reports a final patient-centered health outcome.

Lung capacity showed little improvement related to pharmaceutical care. Although statistically significant in some analysis, probably without clinical relevance.

As established in the review protocol,[11] it was intended to perform subgroup analyses based on the severity of asthma of the patients included and the participation of clinical pharmacists.

Regarding the severity of asthma, it was not possible to make a realistic assessment since only two of the reviews stated the inclusion of severe asthma patients and only one stated the number of patients included.[15,17] This could be expected given that all asthmatic patients need to attend community pharmacies to acquire prescribed medication, regardless of the severity of the pathology. However, severe asthma has a greater effect on the health variables,[2,6] and therefore the stratification of the results in this subgroup is relevant.

The vast majority of the primary studies included in the reviews were conducted in the primary care setting, with the exception of four studies[21–24] that were conducted in the hospital setting, although it was not possible to determine whether pharmaceutical care was performed by clinical pharmacists. Therefore, this subgroup analysis could not be performed either.

The lack of studies showing the involvement of clinical pharmacists could also be expected, since, until the marketing of the first monoclonal antibody for asthma in 2009, the only contact of hospital pharmacists with the asthmatic patient was during the course of hospital admissions.

The major limitation of this overview of systematic reviews is the low quality of the reviews included. Another important limitation is the heterogeneity of the primary studies included in the systematic reviews, which resulted in I^2 values above 50% in most of the analyses performed by meta-analysis. This can be explained mainly by the great variety of questionnaires and ways of measuring the different variables within the studies included in each of the systematic reviews, such as asthma control, which was measured by nine different questionnaires.

In conclusion, this overview of systematic reviews shows that solid evidence supports that pharmaceutical care provided in the context of primary care to patients with asthma improves the quality of life of patients, asthma control, lung capacity, therapeutic adherence, and inhalation technique. However, it is difficult to quantify the magnitude of the effect given the heterogeneity of the primary studies and the low quality of the systematic reviews included.

Further studies are needed to measure the benefits of pharmaceutical care provided by clinical pharmacists, especially in patients with severe asthma and under treatment with biological agents.

AUTHOR CONTRIBUTIONS

OMP designed the study and led the development of the protocol. ESG and CPG contributed to the development of the search strategy and provided specific expertise. All authors contributed to the selection of variables. OMP and FSG conducted the literature review,

study selection, data extraction and assessment of the quality of the reviews independently, with any discrepancies resolved by ESG. OMP wrote the first draft and FSG coordinated and integrated the comments of the other authors. All authors critically reviewed successive drafts of the manuscript, provided notes, and approved the final version for the publication.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

ETHICS STATEMENT

Ethical approval was not sought for this study because the data to be collected are not linked to individuals. Data will be presented at international conferences and published in peer-reviewed journals.

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SUPPORTING INFORMATION

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

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