ERS/EAACI statement on adherence to international adult asthma guidelines

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@EuroRespSoc @AllergyEAACI statement: Guidelines need to account for differences in resource availability across various asthma care settings. Continuous, multifaceted quality improvement processes are needed to optimise and maintain guidelines adherence. https://bit.ly/2UZK5rJ

Abstract

Guidelines aim to standardise and optimise asthma diagnosis and management. Nevertheless, adherence to guidelines is suboptimal and may vary across different healthcare professional (HCP) groups.

Further to these concerns, this European Respiratory Society (ERS)/European Academy of Allergy and Clinical Immunology (EAACI) statement aims to: 1) evaluate the understanding of and adherence to international asthma guidelines by HCPs of different specialties *via* an international online survey; and 2) assess strategies focused at improving implementation of guideline-recommended interventions, and compare process and clinical outcomes in patients managed by HCPs of different specialties *via* systematic reviews.

The online survey identified discrepancies between HCPs of different specialties which may be due to poor dissemination or lack of knowledge of the guidelines but also a reflection of the adaptations made in different clinical settings, based on available resources. The systematic reviews demonstrated that multifaceted quality improvement initiatives addressing multiple challenges to guidelines adherence are most effective in improving guidelines adherence. Differences in outcomes between patients managed by generalists or specialists should be further evaluated.

Guidelines need to consider the heterogeneity of real-life settings for asthma management and tailor their recommendations accordingly. Continuous, multifaceted quality improvement processes are required to optimise and maintain guidelines adherence. Validated referral pathways for uncontrolled asthma or uncertain diagnosis are needed.

Introduction

In the European Union, over 20 million people suffer from asthma [1]. During the 1990s there was a rapid decrease in asthma mortality [2], probably related to the increased use of inhaled corticosteroids (ICS) [3]. However, during the last decade, asthma mortality rates have plateaued, and a consistently high proportion of patients have uncontrolled asthma [4, 5]. As a result, many patients with asthma still have impaired quality of life and suffer from chronic respiratory symptoms, often including night-time symptoms, causing sleep disturbance, excessive daytime sleepiness and decreased work productivity [6, 7].

The reason for this lack of improvement in achieving asthma control is multifactorial. Asthma is a chronic inflammatory airway disease needing regular long-term anti-inflammatory treatment for symptom control and prevention of acute attacks and/or lung function decline. ICS are the mainstay of asthma medication, but many patients do not adhere to regular treatment [8] with overreliance on short-acting β-agonists, leading to under treatment of the chronic inflammation [9]. Another possible explanation is the heterogeneity of asthma, so that subgroups of patients require different interventions, according to a personalised approach based on asthma phenotypes [10]. A proportion have severe asthma [11] and need to be identified and offered specific regimes such as biological treatment with anti-immunoglobulin (Ig)E, anti-interleukin (IL)-5 or anti-IL-4/IL-13 [12, 13]. Other factors such as poor inhaler adherence and technique, lack of self-management support, exposure to triggers, unavoidable environmental factors, limited accessibility to diagnostic facilities and medication, could also contribute [14–16].

Clinical practice guidelines, based on available evidence, define disease control and risk of acute attacks and make recommendations to standardise and optimise asthma diagnosis and management. National and international asthma guidelines have been available since the 1990s and are continuously being updated [11, 17, 18]. However, there are concerns that adherence to guidelines is far from optimal and varies between different groups of healthcare professionals (HCPs) [19, 20]. In addition, the "one-size-fits-all" approach of guidelines (typically based on efficacy in highly selected populations evaluated in randomised controlled trials (RCTs)) limits perceived applicability and relevance in real-life practice [21]. Further to these concerns, we aimed to: 1) evaluate and compare the understanding of and adherence to international asthma guidelines by HCPs of different specialties; 2) assess effectiveness of strategies aimed at improving implementation of guideline-recommended interventions; and 3) compare process and clinical outcomes in patients managed by specialists (respiratory physicians or allergists) or generalists (internists or general practitioners).

Methods

This task force was formed by the European Respiratory Society (ERS) and the European Academy of Allergy and Clinical Immunology (EAACI) in 2015 and was chaired by two representatives from the ERS (A.G. Mathioudakis and C. Janson) and two from EAACI (O. Tsilochristou and I. Agache) who were responsible for project management and co-ordination. The task force was composed of experts from three ERS Assemblies: Assembly 1 Respiratory clinical care and physiology; Assembly 5 Airway diseases, asthma, COPD and chronic cough; and Assembly 6 Epidemiology and environment. As well as from four EAACI bodies (Asthma Section, Primary Care Interest Group, Executive Committee and Junior Members Assembly) and the International Primary Care Respiratory Group (IPCRG; J. Correia-de-Sousa). It involved experts in respiratory medicine and science, allergy and general practice, and also a lay person living with the experience of asthma (B. Flood). The co-chairs met in January 2017 and September 2018 and a face-to-face meeting of the task force was held in January 2019, with teleconferences and e-mail correspondence as required. All task force members signed conflict of interest statements at the beginning of the project and updated them at project finalisation or when any new relevant conflicts appeared, in line with the ERS and EAACI procedures. This report was informed by an international online survey (Aim 1) and two systematic reviews (Aims 2 and 3).

On-line survey: Aim 1

Three online questionnaires pertaining to different clinical cases were prepared by the panel and uploaded to the SurveyMonkey platform (available in the online supplement). The cases were not related to a specific clinical setting so that the questionnaires were applicable to all specialties targeted by the survey. The first scenario was mild type 2 (T2) asthma, the second was severe T2 asthma, and the third was severe non-T2 asthma. T2 asthma is defined by the presence of eosinophilic inflammation driven *via* three pathways: IgE, IL-5 or IL-4/IL-13 [21]. Allergic asthma is a sub-endotype of T2 asthma, frequently with childhood onset and associated with other atopic diseases (allergic rhinitis, atopic dermatitis, food allergy). Another sub-endotype is non-allergic eosinophilic asthma, with adult-onset, which is usually more difficult to control [21]. Non-T2 asthma is usually defined by the lack of eosinophilic inflammation [21]. Its mechanisms are less well described as opposed to T2 asthma [22].

Introductory questions collected the participants' age, sex, specialty, level of training (trained or in training), and clinical setting. The T2 asthma questionnaires were sent out in May 2018 as a pair (mild T2 questions were completed prior to the severe T2 questions), and the non-T2 questionnaire was distributed in August 2018. Surveys were open for approximately 6 weeks. For most of the questions more than one answer could be chosen. Participants of the second survey were not asked if they had also taken part in the first survey. After completion, a participant could not take the survey again on the same computer.

Both survey links were disseminated *via* mass emails with links to the online surveys to relevant members of the participating organisations (EAACI: Asthma Section, ENT Section, Immunotherapy, Occupational Allergy, Allied Health and Primary Care Interest Groups, EAACI National Societies platform; ERS aforementioned assemblies; IPCRG). EAACI and ERS social media platforms supplemented the dissemination of the survey links.

Survey results were analysed based on the participants' specialty. Specialties were grouped into three main categories: 1) "allergy doctor" if the participant indicated they were an allergy–asthma specialist, allergy specialist or allergy trainee; 2) "respiratory doctor" if ther participant indicated they were an asthma specialist, respiratory doctor or respiratory medicine trainee; and 3) "generalist" if the participant indicated they were a General Practitioner, General Practitioner trainee, internist, internal medicine trainee, specialist nurse or nurse trainee.

The results of the questionnaire answers are presented as percentage of affirmative answers. Comparisons between the three groups were made using the Chi-squared test. Stata 15 (Stata Corp, College Station, TX, USA) was used for the calculations.

Ethics approval was not necessary for this survey as no personally identifiable data were collected.

Systematic review methods: Aims 2 and 3

Two systematic reviews were conducted to evaluate the: 1) effectiveness of strategies to improve adherence to guidelines on the diagnosis, assessment and long-term/acute treatment of asthma, including maintenance and acute attacks management (Aim 2); and 2) process and clinical outcomes in patients managed by specialists (respiratory physicians or allergists) compared to generalists (internists or general practitioners) (Aim 3) (table 1). The systematic reviews followed Cochrane methodology [23]. Medline/PubMed was searched for studies published after 1990 (publication of the first asthma guideline [24]), using a search strategy that included controlled vocabulary and free search terms (available in the online supplement), to identify relevant studies. Reference lists of included studies and of any previous, relevant systematic reviews were screened. Studies of any design addressing the two review questions were eligible if they assessed process outcomes (*e.g.* adherence to guideline recommendations) and/or asthma-related clinical outcomes. Two reviewers independently evaluated all identified abstracts for eligibility. The full texts of all potentially eligible manuscripts were similarly evaluated for inclusion by two reviewers. Disagreements were resolved by discussion between reviewers. We extracted relevant data on study characteristics, process and clinical outcomes in a structured excel sheet. We evaluated methodological quality using the Cochrane Risk of Bias tool for RCTs [25] and the Risk Of Bias In Non-randomised Studies of interventions for non-randomised studies [26].

As anticipated, we were not able to conduct meta-analyses, due to the significant methodological and clinical diversity, statistical heterogeneity, inconsistency, and incompleteness of outcomes reported in the included studies. Instead, we used narrative synthesis and present pertinent results of the included studies in a tabulated format. Findings are presented visually as harvest plots, which summarise the direction and significance of the effect on process and clinical outcomes for each of the studies along with information about study design, study population and methodological quality [27, 28]. To interpret the overall findings, we prioritised differences in clinical outcomes over process outcomes.

Results

Survey results: Aim 1

Survey 1: mild T2 asthma and severe T2 asthma

Of the 784 participants who started the mild T2 questionnaire, 507 also started the severe T2 asthma questions. The majority of the participants (n=784, 70.8%) were respiratory doctors as opposed to 18.5% and 10.7% who were allergy doctors and generalists, respectively. The participants' speciality and categorisation for the sub-group analysis are summarised in table 2. Most (45.2%) were tertiary care specialists, 32.6% and 22.2% worked in secondary or primary care respectively.

Mild T2 asthma

> **Box 1:** case vignette 1
>
> A 22-year-old female, nonsmoker, maths student attends for a consultation in October complaining about occasional chest tightness and cough (especially when playing tennis), during late spring to mid-summer for the past 4 years. She has never used any inhalers for her chest symptoms. Regular chest auscultation provides you with normal lung sounds.
>
> She also mentions that during the same months she has been experiencing watery eyes and nose, nasal congestion as well as sneezing. These symptoms began early at adolescence and have been managed with as-needed over the counter antihistamines. She was diagnosed with eczema and egg allergy as a toddler with both conditions having resolved by the age of 10 years, which was the age she was last evaluated in an allergy clinic. She has a cat at home.
>
> **Additional information**
>
> Chest auscultation with fierce exhalation provides normal sounds. You had the possibility of performing spirometry and received the following outcomes: baseline spirometry resulted in a forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio of 0.75 and administration of 400 µg salbutamol increased FEV_1 by 10% (150 mL). What is your diagnosis and how would you manage the patient?
>
> **Follow-up**
>
> The patient comes back during the pollen season. She reports episodes of chest tightness and cough especially early in the morning when she is walking to work through a park and if walking back home late evening. She additionally mentions wakening up at night due to chest tightness and nasal blockage. She has been avoiding playing tennis because of these symptoms. She is receiving her antihistamine daily but no nasal spray. Regular chest auscultation provides you with normal lung sounds. Spirometry with reversibility results in a 13% (220 mL) increase in FEV_1 post bronchodilator administration.

TABLE 1 Systematic review (SR) questions	
SR-1: Effectiveness of strategies aimed to improve adherence to guidelines on the diagnosis, assessment and long-term management of asthma	
Population	Patients with a clinical diagnosis of asthma. Patients with a clinical suspicion of asthma, for studies evaluating asthma diagnosis.
Intervention	Interventions aimed to improve the adherence of clinicians to guidelines on the diagnosis, assessment and long-term management of asthma.
Comparator	Any other intervention aimed to improve the adherence of clinicians to guidelines on the diagnosis, assessment and long-term management of asthma, or no intervention.
Outcomes	Clinical outcomes such as frequency of acute attacks, episodes of hospitalisation, asthma symptoms, or quality of life. Process outcomes, such as adherence to specific guidelines components (*e.g.* prescription of inhaled corticosteroids for patients requiring maintenance treatment, or delivery of smoking cessation advice).
Types of studies	Interventional and observational comparative studies, including RCTs, cluster RCTs, comparative observational cohort studies or before-after studies.
SR-2: Effectiveness of strategies aimed to improve adherence to guidelines on the diagnosis, assessment and management of acute attacks	
Population	Patients with a clinical diagnosis of an acute asthma attack. Patients with a clinical suspicion of acute asthma attack, for studies evaluating asthma attack diagnosis.
Intervention	Interventions aimed to improve the adherence of clinicians to guidelines on the diagnosis, assessment and management of acute asthma.
Comparator	Any other intervention aimed to improve the adherence of clinicians to guidelines on the diagnosis, assessment and management of acute asthma, or no intervention.
Outcomes	Clinical outcomes such as need for hospital admission, duration of symptoms, treatment success or failure, need for intubation or mechanical ventilation. Process outcomes, such as adherence to specific guidelines components (*e.g.* prescription of oral corticosteroids for all patients with an acute attack leading to an emergency presentation or hospital admission).
Types of studies	Interventional and observational comparative studies, including RCTs, cluster RCTs, comparative observational cohort studies or before-after studies.
SR-3: Process and clinical outcomes in patients managed by specialists or generalists	
Population	Patients with a clinical diagnosis of asthma or acute asthma attack. Patients with a clinical suspicion of asthma or acute asthma attack, for studies evaluating asthma or acute asthma attack diagnosis, respectively.
Exposure A	Management by an asthma specialist (respiratory physician or allergist).
Exposure B	Management by a generalist (general practitioner or internist, not specialised in asthma).
Outcomes	For studies evaluating the diagnosis, assessment or long-term management of asthma: clinical outcomes such as frequency of acute attacks, episodes of hospitalisation, asthma symptoms, or quality of life. Process outcomes, such as adherence to specific guidelines components (*e.g.* prescription of inhaled corticosteroids for patients requiring maintenance treatment, or delivery of smoking cessation advice).
	For studies evaluating the diagnosis, assessment or management of acute asthma attacks: clinical outcomes such as need for hospital admission, duration of symptoms, treatment success or failure, need for intubation or mechanical ventilation. Process outcomes, such as adherence to specific guidelines components (*e.g.* prescription of oral corticosteroids for all patients with an acute attack leading to an emergency presentation or hospital admission).
Types of studies	Interventional and observational comparative studies, including RCTs, cluster RCTs, comparative observational cohort studies or before-after studies.

RCT: randomised controlled trial.

Responses about preferred diagnostic procedures are presented in table 3. Spirometry with reversibility was the preferred diagnostic test in all groups. Home serial peak flow measurements were significantly more popular amongst the generalists than the other groups and one-third of the respiratory doctors would undertake bronchial provocation at the initial consultation compared to one-fifth of the other two groups. Of note, auscultation of the chest during forced expiration was seen as helpful by less than 50% of the respiratory doctors and generalists. Statistically significant differences between the three groups were noted for the measurement of the exhaled nitric oxide fraction (F_{eNO}), blood eosinophils, total serum IgE, skin prick test, specific IgE, and chest radiographs.

The mild T2 patient had normal spirometry and no bronchodilator reversibility when examined in autumn. The majority of the participants agreed that this did not exclude asthma as the patient was asymptomatic at the time. However, approximately 20% of the allergy doctors and 15% of the respiratory doctors and the generalists were "certain" about the diagnosis and would prescribe a reliever for use when needed (table e1). Note, this questionnaire was sent out in 2018, before the change in the Global Initiative for Asthma (GINA) guidelines recommending the maintenance and reliever therapy (MART) approach for mild asthma.

The majority of the participants across all groups agreed that the patient's asthma was uncontrolled (as per GINA classification) [16] when asthma status was reviewed during spring. Approximately 80% of the allergy doctors as opposed to 61.7% and 56.0% of the respiratory doctors and the generalists, respectively, replied that the patient's phenotype was allergic asthma (p<0.0001). As part of the same question, 30% of the allergy doctors (additionally) included the patient under T2 asthma compared to 13.6% and 1.3% of the respiratory doctors and the generalists, respectively (p<0.0001) (table e1).

The majority of participants in all groups indicated that in addition to treatment for nasal symptoms, they would prescribe inhaled steroids and provide an asthma action plan. All asthma treatment options were similarly popular in the three groups except that half of the allergy doctors would commence the patient on allergen immunotherapy compared to 6.7% and 2.7%, respectively, in the other groups (p<0.0001) (table e4).

Severe T2 asthma

Box 2: case vignette 2
A 21-year-old male (body mass index 23) comes for a consultation due to coughing, shortness of breath and wheezing. He has been suffering with asthma since childhood. From 3–12 years of age he was treated with inhaled budesonide, later on with fluticasone/salmeterol 50/250 dry powder inhaler, one puff twice-daily. While over the past 4 years he has been treated with fluticasone/salmeterol 50/500 dry powder inhaler, one puff twice-daily. Despite this treatment, he suffers from night symptoms twice a week which prompt him to use salbutamol. Playing football or cycling also cause asthma exacerbation especially during spring. He complains of itchy eyes and nose, sneezing and runny nose all year round but worse during spring. He uses loratadine on demand for his nasal and ocular symptoms. He is a student in journalism, with no exposure to chemicals or other substances and doesn't smoke. He lives in a house with a tree garden in a small town and does not keep pets.

In the patient with severe T2 asthma, spirometry with reversibility, F_{eNO}, blood eosinophils, total IgE, skin prick test, specific IgE, and chest radiographs were all statistically less popular among the generalists than specialists (table 3).

The majority of participants agreed that the patient's asthma was uncontrolled (as per GINA guidelines). Only 66% of the generalists *versus* 91.9% of the allergy doctors and 76.4% of the respiratory doctors would evaluate the presence of comorbidities in order to manage this patient (p<0.0001). More than 80% of participants across all groups would evaluate patient's adherence and inhaler technique (table e2).

Significantly more allergy doctors regarded the patient's asthma type as allergic asthma (71.7%) and/or T2 asthma (31.3%) than the other groups (p=0.007). Interestingly, one-fifth of generalists and one in 10 respiratory doctors stated that they did not know the patient's asthma type (p=0.001). There was widespread agreement that the patient was at risk of acute attacks (table e2).

Although around only two-thirds of participants recognised uncontrolled rhinitis as a risk factor for asthma attacks, rhinitis treatment was the most popular option for asthma management, followed by montelukast. Significant differences were noted in terms of the third most popular treatment choice which was

TABLE 2 Healthcare profession/level of training and subsequent categorisation in the analyses of the survey		
Category	n (%)	Categories in the analyses
1st survey: mild type 2 and severe type 2 asthma		
Allergy–asthma specialist	22 (2.5)	Allergy doctor
Allergy specialist	133 (15.2)	Allergy doctor
Trainee in allergy	9 (1.0)	Allergy doctor
Respiratory–asthma specialist	123 (14.1)	Respiratory doctor
Respiratory doctors	456 (52.1)	Respiratory doctor
Trainee in respiratory medicine	34 (3.9)	Respiratory doctor
General practitioner	48 (5.5)	Generalist
Internist	28 (3.2)	Generalist
Specialist nurse	13 (1.5)	Generalist
Trainee general practitioner	4 (0.5)	Generalist
Trainee in internal medicine	4 (0.5)	Generalist
Nurse trainee	1 (0.1)	Generalist
2nd survey: non-type 2 asthma		
Allergy–asthma specialist	30 (4.4)	Allergy doctor
Allergy specialist	163 (24.0)	Allergy doctor
Trainee in allergy	12 (1.8)	Allergy doctor
Respiratory–asthma specialist	80 (11.8)	Respiratory doctor
Respiratory doctors	245 (36.1)	Respiratory doctor
Trainee in respiratory medicine	13 (1.9)	Respiratory doctor
General practitioner	99 (14.6)	Generalist
Internist	16 (2.4)	Generalist
Specialist nurse	14 (2.1)	Generalist
Trainee general practitioner	4 (0.6)	Generalist
Trainee in internal medicine	2 (0.3)	Generalist
Nurse trainee	1 (0.2)	Generalist

tiotropium for the respiratory doctors (46.5%, p<0.0001) and allergen immunotherapy for the allergy doctors. (50.5%, p<0.0001) (table e2).

The majority of participants would proceed with an asthma control test and/or a lung function with reversibility test at the patient's follow-up appointment. Fewer (53.2%) generalists would use F_{eNO} to investigate asthma control compared to allergy doctors (73.7%) and respiratory doctors (69.5%) (p=0.04). If asthma control was not achieved, 40% of generalists would refer the patient to an asthma clinic while most of the allergy and respiratory doctors would start the patient on omalizumab (table e2).

Survey 2: non T2 asthma

Box 3: case vignette 3
A 50-year-old female attends as an emergency due to breathlessness. She reports that her dyspnoea has worsened over the last 2 weeks despite using two puffs of beclomethasone dipropionate/formoterol (100/6 µg) twice daily and that she now needs to use her reliever (salbutamol) four times a day. On presentation, she talks in phrases but wheezes, her oxygen saturation is 92%, pulse rate is 118 beats per min, respiratory rate is 28 breaths per min, FEV_1 72% pred, FVC 82% pred, FEV_1/FVC 0.68 while electrocardiography is unremarkable. She was diagnosed with asthma 10 years ago (provocative concentration causing a 20% fall in FEV_1 for methacholine <4 mg·mL^{-1}), skin prick testing to common aeroallergens was negative. Since then she has been on high doses of ICS but often uses salbutamol after exercise and sometimes during the night. She has to take oral corticosteroids around four times a year for asthma exacerbations and was hospitalised due to asthma twice in the past 5 years (once in the intensive care unit). She is 160 cm tall, weighs 90 kg, works in a dye factory and has been occasionally smoking the past 30 years. **Follow-up** Spirometry results are as follows: FEV_1 79% pred, FVC 82% pred, FEV_1/FVC 0.72, reversibility 7% (150 mL). Chest auscultation normal. She still needs to use her reliever at least three times a week. F_{eNO} is 6 ppb. Skin prick testing with common aeroallergens is negative. Blood eosinophils are 48 cells·µL^{-1}.

The majority (49.9%) of the 677 participants were respiratory doctors as opposed to 30.3% and 19.8% who were allergy doctors and generalists, respectively (table 2). Most (45%) worked in tertiary care, while approximately 26% and 29% were working in secondary and primary care, respectively.

TABLE 3 Preferred diagnostic procedure in different subtypes of asthma as reported in the online survey

	Allergy doctors (%)	Respiratory doctors (%)	Generalists (%)	p-value[#]
Mild type 2 asthma				
Spirometry with reversibility test	95.0	96.4	86.9	0.001
Peak flow	24.1	27.8	39.3	0.04
F_{eNO}	49.0	58.7	41.7	<0.0001
Blood eosinophils	57.2	73.7	63.1	<0.0001
Total IgE	49.7	63.6	41.7	0.006
Skin prick test	93.1	65.4	50.0	<0.0001
Specific IgE	53.1	38.0	32.1	0.001
Chest radiograph	36.6	55.7	23.8	<0.0001
ENT examination	31.7	31.4	29.8	0.95
Bronchoscopy	0	2.5	1.2	0.12
Bronchial provocation	19.3	31.9	20.2	0.002
Bacterial culture	4.1	7.4	7.1	0.38
Detailed history	70.3	68.1	66.7	0.82
Chest auscultation	55.9	48.3	41.7	0.10
Serial peak flow	53.1	62.9	75.0	0.004
Severe type 2 asthma				
Spirometry with reversibility test	98.0	96.4	85.1	0.001
Peak flow	19.2	24.1	25.5	0.55
F_{eNO}	74.8	79.9	48.9	0.004
Blood eosinophils	79.8	85.9	68.1	0.006
Total IgE	60.6	77.6	36.2	<0.0001
Skin prick test	99.0	78.4	57.4	<0.0001
Specific IgE	55.6	41.0	34.0	0.01
Chest radiograph	39.4	59.8	27.7	<0.0001
ENT examination	40.4	34.6	27.7	0.30
Bronchoscopy	1.0	1.7	2.1	0.86
Bronchial provocation	8.0	10.8	4.3	0.30
Bacterial culture	9.1	8.6	8.5	0.99
Detailed history	78.8	79.5	80.8	0.96
Chest auscultation	83.8	81.7	76.6	0.57
Serial peak flow	37.4	41.3	48.9	0.42
Check prescriptions	76.8	85.3	83.0	0.13
Assess inhalation technique	92.9	91.7	85.1	0.26
Non-type 2 asthma				
Spirometry with reversibility test	65.4	69.5	49.2	<0.0001
Peak flow	14.6	21.0	28.4	0.009
F_{eNO}	50.2	49.7	26.9	<0.0001
Blood eosinophils	53.2	61.2	38.1	<0.0001
Total IgE	44.9	479	19.4	<0.0001
Skin prick test	26.3	14.2	9.0	<0.0001
Specific IgE	22.4	25.2	11.9	0.007
Chest radiograph	49.30	55.9	30.6	<0.0001
ENT examination	30.2	23.1	11.2	<0.0001
Bronchoscopy	1.5	3.2	2.2	0.42
Bronchial provocation	1.5	4.1	2.2	0.17
Bacterial culture	17..1	17.8	4.5	0.001
Detailed history	65.8	67.8	53.7	0.01
Chest auscultation	68.8	71.2	61.2	0.12
Occupational evaluation	55.1	66.3	56.0	0.02
Check adherence	66.3	71.0	59.7	0.06
Assess inhaler technique	72.2	79.9	64.9	0.002

F_{eNO}: exhaled nitric oxide fraction; Ig: immunoglobulin; ENT: ear, nose and throat. [#]: refers to comparisons among the three groups, using the Chi-squared test.

Deciding on emergency management was challenging for all groups and there were statistically significant differences in how much prednisolone should be prescribed (table e3). At follow-up, the priority for all groups was to ensure that inhaler technique was correct. Of note, less than two-thirds of the participants

across all groups considered evaluating for occupational exposure in this patient who worked in a dye factory (table 3).

The majority of the participants agreed that the patient's asthma was uncontrolled and most considered that the patient's asthma phenotype was obesity related (p=0.006) while a significantly higher percentage (19%) of the respiratory doctors classified the patient's asthma as T2 compared to the other specialties (p=0.002). Tiotropium (p=0.02) and education (p=0.96) were the most popular answers regarding the optimal long-term management of this patient. Allergy doctors were more likely to consider anti-IL-5 (p<0.0001) or anti-IgE (p=0.008) treatment (table e3).

Fewer generalists prioritised the assessment of comorbidities (p=0.049), adherence (p=0.01) and inhalation technique (p=0.05) compared to the other two groups. Smoking cessation was prioritised by all groups but pulmonary rehabilitation was chosen more often by respiratory doctors and generalists than allergy doctors (table e3).

Systematic review results: Aims 2 and 3

Details of the search and selection process are summarised in a PRISMA flowchart (figure 1). Our search yielded 3722 unique titles, of which 52 studies evaluated strategies aimed at improving adherence to guidelines on diagnosis, assessment and/or long-term management of asthma, while 24 evaluated adherence to guideline recommendations on the assessment and management of acute asthma attacks. Differences in the care provided and asthma-related outcomes of patients managed by a specialist (respiratory physician or allergist), or a generalist (internist or general practitioner) were evaluated in 16 studies, of which 13 focused on long-term asthma management and three on acute attacks.

Risk of bias

Most studies evaluating strategies to improve implementation of guideline recommendations were at high/ serious risk of bias (table e4). Entirely appropriately, given that the implementation strategies were targeted at improving guideline adherence by clinical teams, all the included interventional trials were cluster randomised and therefore potentially at risk of selection and detection bias. Moreover, several trials did not evaluate asthma-related outcomes and it was not always clear if this represented reporting bias. Moderate or serious risk of bias was also identified for most observational studies, due to confounding, participant selection, and often outcome selection as well. Only one longitudinal evaluation of the primary care practices in Bavaria was deemed to be at low risk of bias (table e4).

High risk of methodological bias was identified in all 16 studies comparing care provision by specialists and generalists apart from two observational studies that were deemed of low risk (table e4). The two RCTs were at high risk of selection and detection bias, while there were concerns regarding unaddressed confounding for most of the included observational studies (specifically confounding because specialists tended to care for patients with more severe/uncontrolled asthma, and more severe acute attacks than generalists).

Strategies to improve adherence to guideline recommendations for long-term management of asthma: Aim 2

We identified 27 RCTs or cluster RCTs, 19 before-after studies, and six parallel comparative cohort studies, evaluating strategies for improving adherence to asthma guidelines (figure 2, tables 4 and e5). All but three studies were conducted in primary care settings. Specific interventions included the provision of additional clinical input by a specialist HCP (usually a specialist nurse or pharmacist; n=13 studies) [29–40], medical education (n=12 [41–52], computer decision-support systems (n=7) [53–59], introduction of asthma care pathways (n=4) [60–63], new local or national guideline (n=4) [64–67], or the participation of the centre in asthma-related clinical trials (n=1) [68]. Multifaceted quality improvement implementation strategies were evaluated in 11 studies [50, 69–79].

Process outcomes were evaluated in most studies (46 (88.5%) out of 52), of which 33 (71.7%) demonstrated improved adherence to guideline recommendations. The impact on asthma-related outcomes was evaluated in 31 (59.6%) out of 52 studies. Only 18 (58.1%) out of 31 studies showed any clinical benefit. Of note, this evaluation included the only observational study at low risk of bias, a large (n=109 042 patients) multifaceted quality improvement initiative conducted in Bavarian primary care [72].

Findings stratified by the type of intervention are summarised in figure 2 and table e5. The introduction of additional specialised HCPs support for patient care (such as a respiratory trained nurse or a pharmacist) into the primary setting was evaluated in 13 studies including large cluster RCTs of high risk of bias and
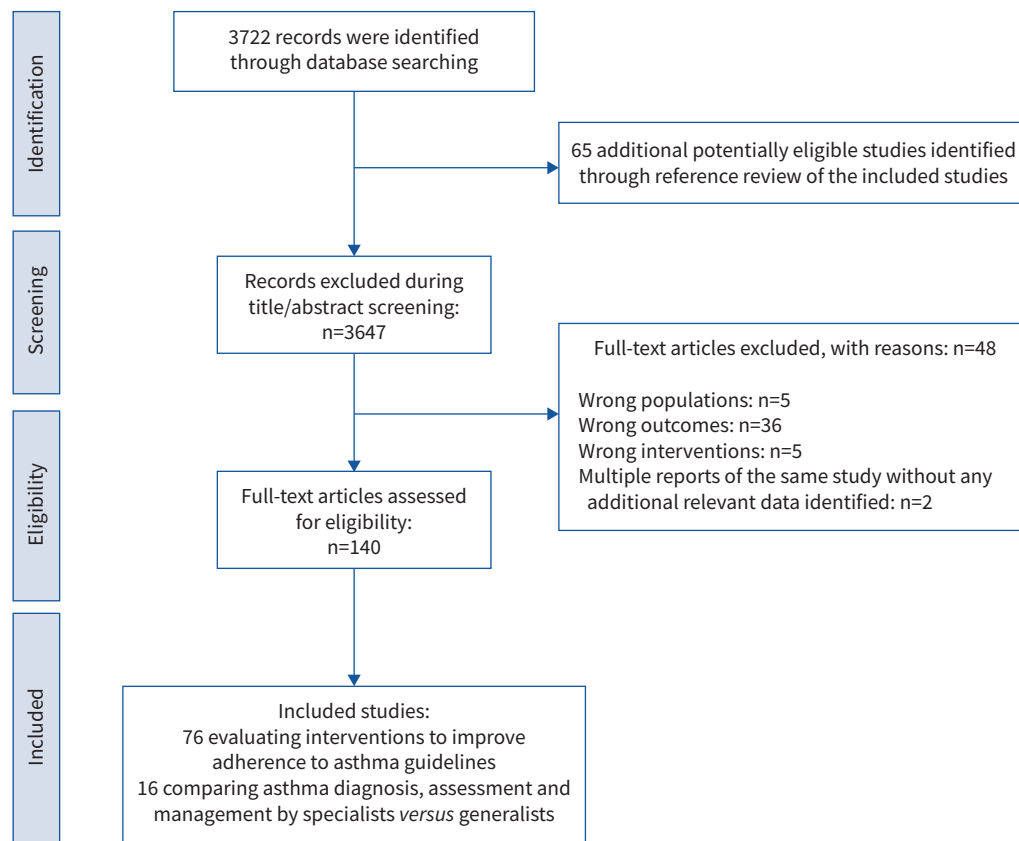
FIGURE 1 PRISMA flow diagram.

TABLE 4 Types of studies evaluating the adherence to asthma guidelines and the proportion of studies demonstrating beneficial clinical and adherence outcomes among the studies evaluating such outcomes

	Total N	RCTs n	Before-after n	Comparative observational study n	Beneficial clinical outcomes	Beneficial process outcomes
Assessment and management of asthma during stable disease state						
Additional patient specific input by a specialised health professional	13	8	2	3	8/12 (66.7)	10/11 (90.9)
Asthma care pathway	4	1	3		2/2 (100)	3/3 (100)
Computer decision-support systems	7	6	1		3/5 (60)	4/7 (57.1)
Introduction of a local or national guideline	4	2	1	1	0/1 (0)	2/4 (50)
Medical education	12	7	5		1/4 (25)	5/10 (50)
Quality improvement process	11	3	7	1	4/6 (66.7)	8/10 (80)
Participation in a clinical trial	1			1	0/1 (0)	0/1 (0)
Assessment and management of acute asthma attacks						
Acute asthma care pathway	12		11	1	1/8 (12.5)	10/12 (83.3)
Additional patient specific input by a specialised health professional	1			1	0/0 (N/A)	1/1 (100)
Computer decision-support systems	1		1		0/0 (N/A)	1/1 (100)
Introduction of a local or national guideline	1		1		0/0 (N/A)	0/1 (0)
Medical education	1	1			0/0 (N/A)	0/1 (0)
Quality improvement process	9	2	5	2	2/3 (66.7)	6/7 (85.7)

Data are presented as n/N (%), unless otherwise stated. RCT: randomised controlled trial; N/A: not available.
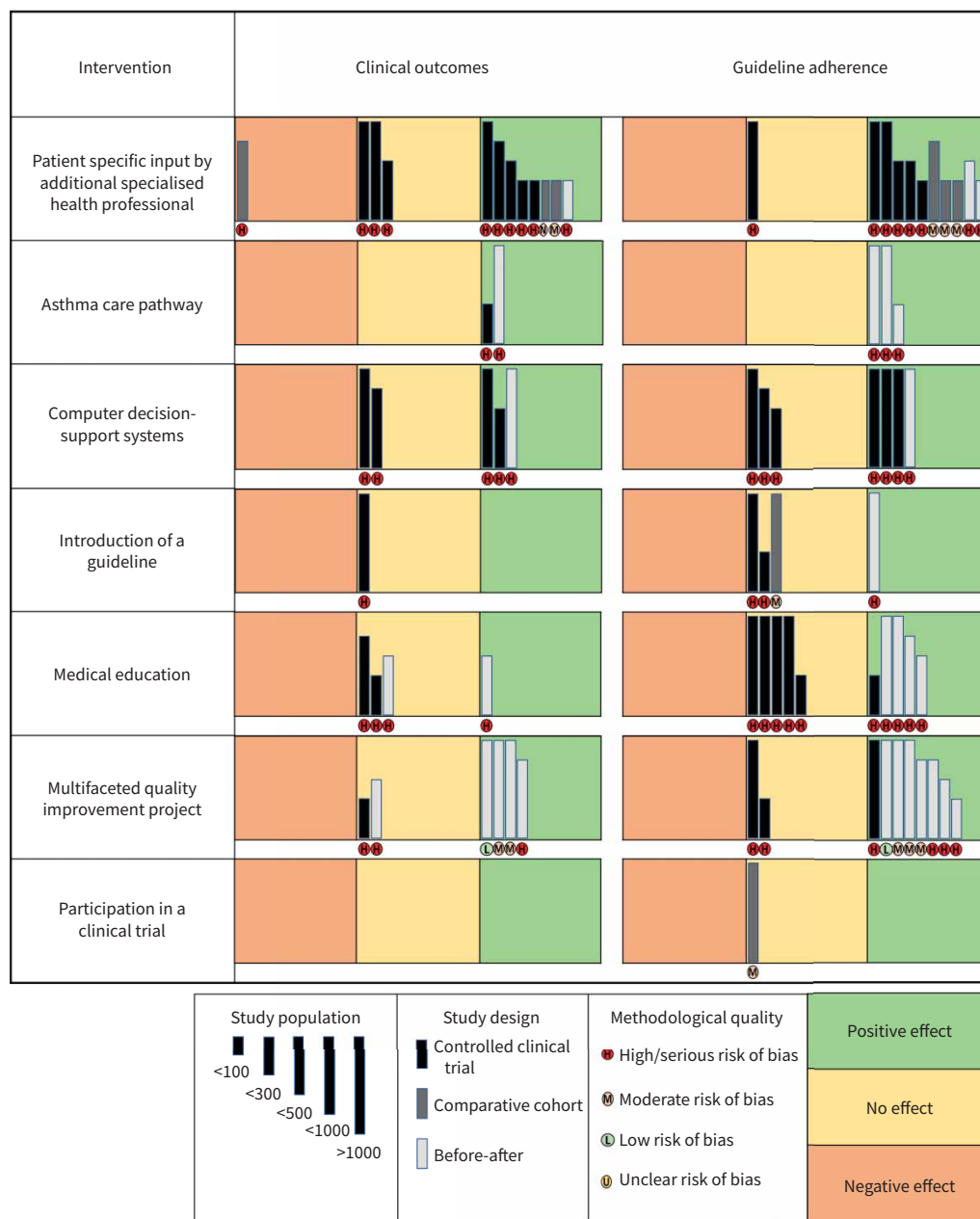
FIGURE 2 Harvest plot summarising the findings of studies evaluating interventions to improve guidelines adherence for asthma assessment and maintenance management.

observational studies that were deemed at moderate risk of bias. Most studies demonstrated improvement in process outcomes and many also demonstrated clinical benefits.

Multifaceted quality improvement projects were assessed by 11 studies including three cluster RCTs, that were of high risk of bias, and several before-after studies, including four that were deemed low or moderate risk of methodological bias. Process and clinical benefits were demonstrated in most cases, including all the low and moderate risk of bias studies. However, it should be noted that two of the three cluster RCTs did not show process benefits and the only RCT evaluating clinical outcomes did not demonstrate any benefit either.

A number of studies evaluated specific strategies for improving guideline adherence, such as computer decision-support systems, medical education, and asthma care pathways, with some promising results

though typically in studies which combined several interventions. For example, introduction of an asthma care pathway or computer decision-support system were more effective when paired with an educational component. The introduction of new guidelines with or without a training component appeared the least effective method for improving adherence. Use of interactive and case-based learning methods appeared more effective than simple lectures or printed training material.

Strategies to improve adherence to guidelines on the assessment and management of acute asthma attacks: Aim 2

Three of the eligible studies were cluster RCTs, 17 were before-after and four were comparative cohort studies with concurrent and/or historical controls (figure 3, tables 1 and e6). Three of the included studies were conducted in primary care, while the remainder were conducted in a hospital setting (mostly in emergency departments). Specific interventions included the introduction of acute asthma care pathways (n=12) [80–91], additional patient specific input by a specialised health professional (n=1) [92], a computer decision-support system (n=1) [93], a national clinical guideline (n=1) [94], or the provision of medical education (n=1) [51]. Nine studies (including the two RCTs) evaluated multi-faceted quality improvement initiatives [95–103].
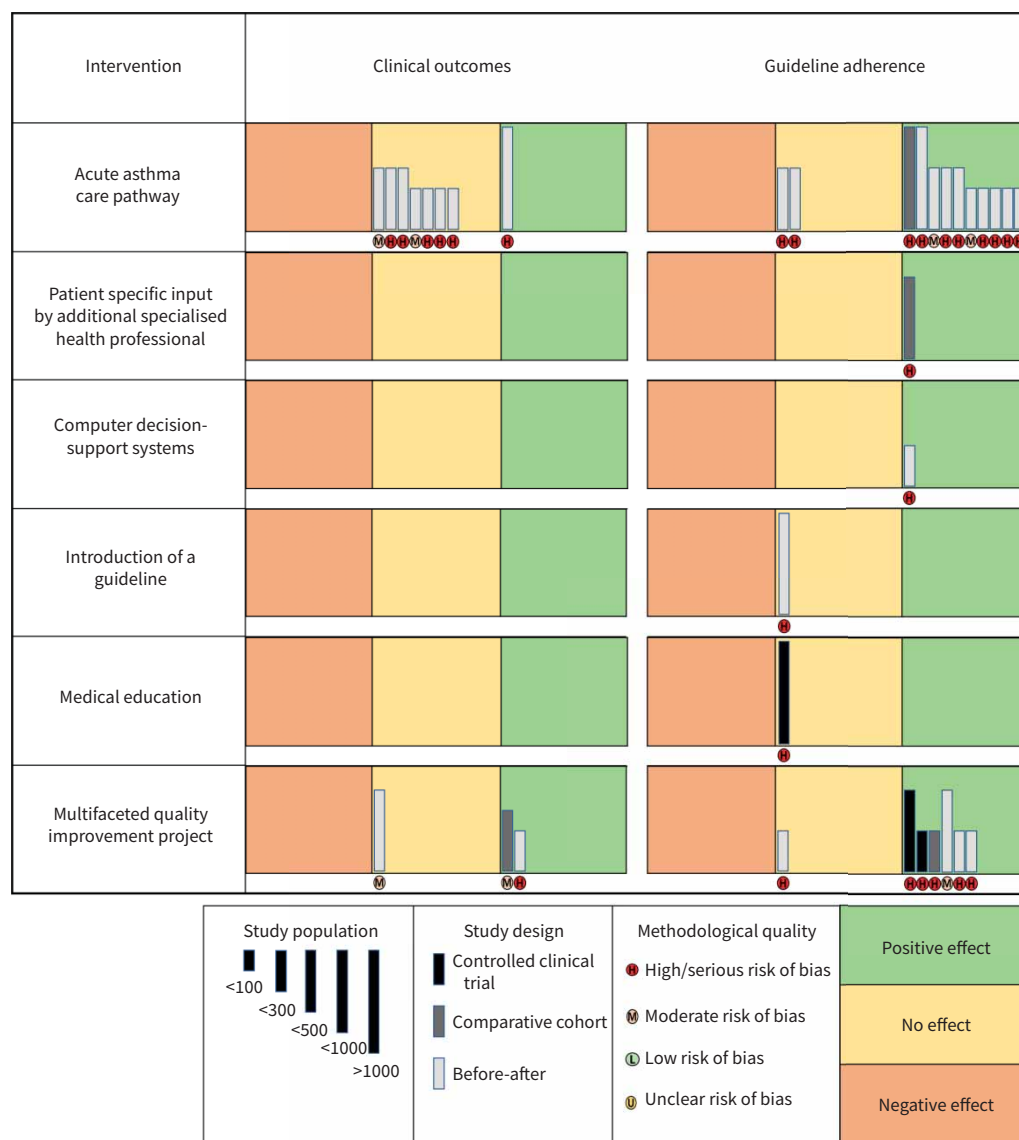
FIGURE 3 Harvest plot summarising the findings of studies evaluating interventions to improve guidelines adherence for acute asthma attacks assessment and management.
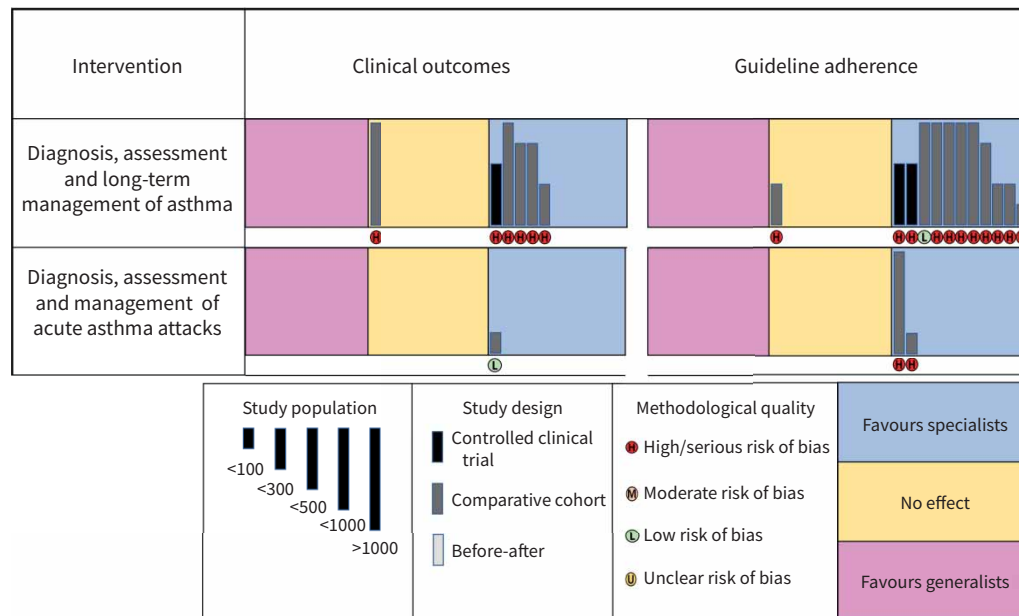
FIGURE 4 Harvest plot summarising the findings of studies evaluating differences in the adherence to asthma guidelines by specialists or generalists.

Process outcomes were evaluated in all but one study (23 (95.8%) out of 24,), and 18 (78.3%) out of 23 showed a beneficial impact on adherence to treatment recommendations. Clinical outcomes were evaluated in 11 (45.8%) studies, and a clinical benefit was evident in only three (27.3%) of them.

Acute asthma care pathways were evaluated in eight observational studies. All were deemed high risk of bias except for two that were moderate. Overall, asthma care pathways appeared effective in improving process but not clinical outcomes. Multifaceted quality improvement processes, evaluated in two cluster RCTs and six observational studies, including two that were at moderate risk of bias, showed beneficial effect on process, and possibly on clinical outcomes. Data about the clinical effectiveness of other interventions were not reported.

Differences in process and clinical outcomes of patients managed by a specialist or a generalist: Aim 3

Diagnosis, assessment and/or management of long-term asthma by specialists (respiratory physicians or allergists) compared to generalists (general physicians or general practitioners) was evaluated in two RCTs (both at high risk of bias) totalling 617 participants [104, 105], and 14 observational studies, including six large studies using routine health databases (three cross-sectional and three longitudinal studies) [106–111], and smaller cross-sectional studies, including audits (figure 4, table e7) [112–116]. Management of acute asthma attacks was evaluated in three audits, totalling 1838 participants [117–119].

Adherence to guideline recommendations was evaluated in 10 out of 12 studies, showing significantly better adherence by specialists, both for long-term asthma management and acute asthma attacks. Four out of five studies showed that specialists' care was associated with improved clinical outcomes including one cross-sectional study at low risk-of-bias which demonstrated differences in specialist/general practitioner diagnosis.

Discussion

Summary and interpretation of results

Aim 1: adherence to international asthma guidelines by HCPs of different specialties

The three online questionnaires gathered a good sample of approximately 1500 international participations in total spanning primary, secondary and tertiary care. These diverse settings clearly influenced responses despite participants being advised that they had access to all diagnostic and management facilities. For example, diagnostically, generalists favoured serial home peak flows to test for flow variability, whereas respiratory and allergy doctors would request F_{eNO} which reflects familiarity and the context of their practice. Similarly, allergy doctors were confident in identifying T2 and non-T2 phenotypes, a distinction

which appeared to have little relevance for respiratory doctors or generalists, despite the increasing recognition of disease heterogeneity [120]. However, possible differences in the terminology used across the respondents' group may also be the cause of the latter observation; characteristically, the terms used in severe asthma guidelines are eosinophilic and non-eosinophilic asthma [121, 122].

Guidelines recognise both the importance of assessing characteristic symptom patterns and undertaking objective tests in order to make a diagnosis of asthma [16, 17]. The poor sensitivity and specificity of many investigations [16, 17] was reflected in the "certainty" with which participants (in all groups) diagnosed the mild T2 patient as having asthma and offering treatment despite normal spirometry and no significant bronchodilator reversibility. Concerningly, in the severe cases, far from all participants would check the patient for comorbidities (ranging from 66% to 93.4%).

There was general agreement on core management strategies (role of intranasal corticosteroids, action plans, checking inhaler technique and adherence, supporting smoking cessation, treatment of nasal symptoms) but the clinical context of respondents influenced selection of other treatment modalities. For example, allergy doctors prioritised immunotherapy or biologicals, while tiotropium and pulmonary rehabilitation was chosen more often by respiratory doctors and generalists. The importance of oral steroids in an acute attack was not in doubt, but the dosages chosen varied considerably (from $1\ \mathrm{mg \cdot kg^{-1}}$ to $1\ \mathrm{mg \cdot kg^{-1} \cdot day^{-1}}$ and 50 mg prednisolone). For adults, GINA guidelines currently recommend $1\ \mathrm{mg \cdot kg^{-1} \cdot day^{-1}}$ and up to 50 mg per day of prednisolone or equivalent for 5–7 days [16].

GINA highlights the need to adapt asthma management strategies to enable implementation within local/ national healthcare settings [16]. Whilst some of the discrepancies identified in our survey may be due to poor dissemination or lack of knowledge, a considerable proportion of the diverse responses from allergy/ respiratory doctors and generalists are likely to reflect adaptations consistent with their different clinical settings. Effective implementation strategies are considered in the evidence from the systematic reviews.

Aim 2: effectiveness of strategies to improve implementation of guideline-recommended interventions

Our systematic reviews evaluated various strategies for improving implementation of asthma guidelines. The strategies were grouped into broad categories; however, inconsistencies were observed in the results of studies evaluating strategies in each category, complicating interpretation. The main sources of heterogeneity were differences in the characteristics of individual interventions, in the methods for delivering the intervention (*e.g.* engagement and training of the clinical staff), the context in which the interventions were delivered and the outcomes assessed.

Patient-specific input by additional specialised HCPs was evaluated in 13 studies, including large cluster RCTs of high risk of bias and observational studies that were deemed at moderate risk of bias. The vast majority of studies evaluating this intervention demonstrated improved process outcomes and most also demonstrated clinical benefits. However, cost-effectiveness of this approach has not been evaluated, and it is not clear if this benefit is sustained after the trial is completed in case the additional support is withdrawn. In contrast, a large-scale cluster RCT in which existing primary care staff were upskilled was not effective [36].

Multicomponent quality improvement initiatives incorporating a range of implementation strategies addressing multiple challenges to guideline adherence (such as training HCPs, on-going audit and feedback/benchmarking, introduction of asthma care pathways, identification and resolution of organisational barriers [123]) appeared the most effective. Characteristically, the strategies employed in the three studies that did not show improved outcomes (either clinical or process) only included two components; audit and feedback to clinicians. Similarly, findings from studies evaluating a single intervention were in general less consistent. Multifaceted quality improvement projects incorporating a range of implementation strategies addressing challenges to guideline adherence at the level of the patient, HCP and health system were more likely to be effective. This reflects recognition of the need to take a whole systems' approach to improving practice [124, 125].

Asthma care pathways were mostly evaluated in high-risk of bias studies, which showed clinical and process benefits. Studies evaluating other interventions were mostly at high risk of bias and their findings were either inconsistent (computer decision-support systems, medical education), or negative (introduction of a guideline, participation in clinical trials).

Some studies with longer observation periods [96, 102] noted that the impact of the interventions tended to wane and needed continuous reinforcement, for example through audit, feedback and re-training.

Strategies for improving adherence to guidelines have been evaluated in previous systematic reviews, with consistent findings. Two systematic reviews assessing a broad range of strategies concluded that multifaceted quality improvement programmes were more effective than single component interventions, especially those based explicitly on a theoretical framework, with a strong educational component including a combination of instructional modalities, longer duration [126], and those promoting engagement at the level of the patient, HCPs and organisation [127]. Other systematic reviews focusing on specific approaches concluded that input by pharmacists [128] and asthma care protocols [129] could be beneficial, while medical education [130] and computer decision-support systems [131] were not effective, though it was not clear whether limitations of the interventions or implementation methods were responsible for this lack of observed benefit.

Aim 3: comparison of process and clinical outcomes in patients managed by specialists or generalists

This systematic review was informed by fewer studies, most of which were observational and at high risk of bias. Almost all studies showed that specialist care was associated with better adherence to guideline recommendations, with some suggestion in six out of the seven studies evaluating clinical outcomes these may also be improved. It should be noted that specific findings from some of the older studies' may no longer be applicable. For example, two of these studies date from the early days of ICS prescribing when generalists may have been more cautious [104, 109]. Improved diagnosis by specialists in a cross-sectional study at low risk of bias, might reflect better access to investigations [118]. However, specialists care was consistently associated with better outcomes in more recent studies. It should also be highlighted that only one extensive observational study evaluating process outcomes and a smaller observational study evaluating clinical outcomes were at low risk of bias, with the remaining being deemed high risk.

Asthma diagnosis, assessment and management are complex and the respective guidelines are updated frequently, making it more challenging for the generalist to keep updated. Robust, continuous, multifaceted quality improvement projects will be required to ensure that patients receive high-quality care with locally agreed referral pathways for specialists' advice.

Strengths and limitations

The survey results provided an insight into asthma management at an international level with a good number of responses across all levels of care. A limitation to our results is that the second survey participants were not asked whether they had also taken part in the first survey, hence we cannot be sure of the total number of unique participants. Furthermore, the setup of the surveys did not facilitate analysis of the results according to the country in which the participants practised, and we are unable to establish whether variations in the answers received may have been country related. Finally, a higher proportion of the participants were respiratory physicians. However, all surveys included adequate responses from allergists and generalists, that allowed the panel to derive informed conclusions.

Our systematic reviews have a number of limitations. The study protocol was not made publicly available, however, it was developed prospectively and submitted to the ERS and EAACI. Most of the included studies were at high risk of bias, which reduces the confidence in the findings. Most included trials were cluster RCTs. Although this is the optimal study design for evaluating implementation targeted at clinical teams, they are at high risk of selection, performance and detection bias based on the Cochrane Risk of Bias tool. Confounding was the main source of bias in observational studies and despite several studies accounting for confounding factors, adjustments were not deemed adequate in most cases. In the systematic review comparing the outcomes of patients evaluated by specialists *versus* generalists, a key confounder was that specialists tend to care for people with more severe or uncontrolled asthma. Better outcomes among these patients could either reflect better quality of care provided by specialists, or that there was greater capacity for improvement. We were not able to conduct meta-analyses, due to the considerable clinical and methodological heterogeneity, but our results are presented in detail, both tabulated and illustrated in harvest plots to facilitate interpretation.

Last, but not least, there is significant heterogeneity among the current international asthma guidelines, thus this might be reflected in the interventions meant to improve adherence.

Implications for practice and research

Asthma is a heterogeneous disease, meaning that its diagnosis, assessment and management are complex [16, 17]. In parallel, it is the focus of intensive research that leads to continuous change to clinical practice guidelines and practice, increasingly incorporating precision medicine interventions [21, 132]. As a result, implementation of asthma guidelines and delivery of high-quality, evidence-based medicine is challenging and often suboptimal [133–135]. Our findings suggest that continuous multifaceted quality improvement

processes can enhance adherence to guidelines. Additional input by a specialist, either a respiratory doctor, allergist or a respiratory trained nurse or pharmacist, also appears to improve guidelines adherence and clinical outcomes, although further data is needed to confirm sustainability of these findings. Moreover, the feasibility and cost-effectiveness of these approaches should be evaluated.

Our survey revealed significant variability in practice, across different clinical settings, that reflects guideline adaptations in a real-life context, where different diagnostic or therapeutic options and sources are available. Guideline panels need to consider these practical differences when developing clinical recommendations, and to offer options for evidence-based practice in different clinical settings.

Systematic literature reviews also indicated a potential association of specialist care with improved process and clinical outcomes. However, more data are needed, as confidence was limited on this finding. Undoubtedly, the complexity of asthma care imposes the need for a multidisciplinary approach to the diagnosis and management of these patients. As a result, it is now widely recommended that patients with severe asthma should be managed in specialised severe asthma clinics [11, 16, 17, 121, 122]. However, the diagnosis and management of patients without severe asthma is also complex, but it is still unclear when generalist or specialist care is necessary [11, 16, 17, 121, 122]. This complicates the work of both generalists and specialists and, as suggested by our systematic review, may also impact on the clinical outcomes of individuals with asthma. Therefore, data are needed to inform standardisation in the indications for referral of patients for specialist review, that should be tailored to the balance of resources required for continuous multifaceted quality improvement processes in primary care *versus* the evaluation of an increased proportion of individuals with asthma in specialty clinics. In the meantime, locally agreed referral pathways to specialists are crucial both for generalists and for specialists from different disciplines who have different approaches to diagnostic uncertainty and managing patients with poorly controlled asthma.

The emergence of coronavirus disease 2019 has extensively affected the care of people with asthma, mainly by replacing physical appointments with virtual encounters, while in parallel reinforcing telemonitoring technologies [136, 137]. It is recognised that to some extent these practice changes introduced during 2020 will outlive the pandemic, as they appear effective, convenient for patients and require fewer resources [138–143]. An opportunity emerges to use these new technologies to enhance adherence to guidelines. For example, efficient methods for capturing disease characteristics in a computer-usable format could facilitate patient profiling and strengthen decision support systems. Such interventions are already being evaluated in other disease areas with promising preliminary results [144, 145].

Box 4: key messages

Implementation of guidelines is different across different asthma management settings.
Guideline recommendations need to account for differences in resource availability across the various asthma care settings, including primary care.
Continuous multifaceted quality improvement processes can improve guidelines adherence.
Additional input from specialised health professionals could also be effective towards improving guidelines adherence. However, this is unlikely to be sustainable unless long-term funding is available.
Locally agreed referral pathways to specialists are crucial both for generalists and specialists from different disciplines who have different approaches to diagnostic uncertainty and managing patients with poorly controlled asthma.
More data are needed to evaluate differences in process and clinical outcomes among patients managed by generalists or specialists and to facilitate standardisation in the indications for referral of patients for specialist review.

Conclusion

This evaluation, conducted as a joint initiative between EAACI and ERS, showed a significant gap in implementing asthma guidelines in real life. This calls for action on several fronts: 1) guideline developers should consider the heterogeneity of settings for asthma management in real life and tailor their recommendations accordingly; 2) multifaceted interventions should receive better funding to improve adherence to guidelines; and 3) validated referral pathways for uncontrolled asthma or for uncertain diagnosis should be prioritised.

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