REVIEW
ASTHMA

The burden of exacerbations in mild asthma: a systematic review

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ABSTRACT

Background: Although most patients with asthma have mild disease, data on how mild asthma is defined, and how frequently exacerbations occur in this patient population are scarce, so we aimed to redress this.

Methods: We searched Medline and Medline In-Process (PubMed), and Embase in OVID for English-language publications containing "mild asthma" plus at least one relevant therapy and outcome/keyword, limited to randomised controlled trials (RCTs) and observational studies published between January 1990 and February 2019. Publications were filtered to ensure appropriate data extraction. The main outcomes were the definitions of mild asthma and exacerbations, baseline exacerbation rates and exacerbation data for placebo recipients in prospective studies. Meta-analysis of exacerbation rates was planned.

Findings: Of 4064 articles identified, 64 were included in our review (49 743 subjects); 54 RCTs and 10 observational/other studies. Six main types of definitions of mild asthma were identified. While care was taken to ensure inclusion only of patients with mild asthma, marked heterogeneity was revealed in the definitions of mild asthma and hence the study populations. Reporting of exacerbations also varied widely between studies, precluding meta-analysis. Between 0–22% of patients were hospitalised for asthma or had a severe exacerbation in the previous year, according to baseline data from prospective studies. In RCTs, severe exacerbation rates in placebo recipients taking only short-acting β_2-agonist therapy ranged from 0.20–2.88 per year.

Conclusions: These data provide new evidence of the burden of exacerbations in mild asthma and highlight the need for standardised definitions of mild asthma and of exacerbations to progress further research.

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This comprehensive literature review highlights the risk of exacerbations for patients with mild asthma https://bit.ly/3cauSb3

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Data availability: Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

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Introduction

Asthma is a common chronic respiratory disease [1, 2]. Among adults, the prevalence of doctor-diagnosed asthma ranges from 0.2% to 21.0% of the population in different countries [3]. The spectrum of asthma severity is highly skewed, such that the majority of patients (approximately 50–75%) are said to have mild disease and only a minority (≈3.6–8%) have severe disease [4–8]. However, the definitions of mild and severe asthma, and hence their reported prevalence, vary from study to study. In addition, these definitions have varied over time [9]. Historically, classification of asthma severity was often based on symptoms, lung function and exacerbation frequency prior to the commencement of maintenance treatment, a classification that remains in current US guidelines [10]. In 2004, the American Thoracic Society/European Respiratory Society (ATS/ERS) Task Force on asthma control, severity and exacerbations recommended a classification of asthma severity for clinical trials based on the level of treatment required to maintain good asthma control (*i.e.* a retrospective label based on treatment response) [11]. Since 2014, a similar approach has been recommended for clinical practice by the Global Initiative for Asthma (GINA). For epidemiological studies, GINA suggests classification of patients by their current treatment step, without inferring severity [1]. By contrast with the approach in publications like these, the term "mild asthma" is widely used by clinicians and patients for those with infrequent, mild, or easily relieved symptoms or other manifestations of disease, consistent with lay dictionary definitions of "mild" as gentle, slight, and not marked or extreme.

Regardless of its definition, the prevalence of mild asthma may be underestimated [4], due to under- or mis-diagnosis by healthcare professionals and under-reporting by patients who, for various reasons, do not present to primary care [12–16]. Equally, asthma may be over-diagnosed [16, 17], with attribution of symptoms to asthma by patients and/or doctors without the diagnosis being confirmed by spirometry or other objective measurements [16]. Many recent clinical studies have focused on severe asthma, as these patients account for the majority of the morbidity and healthcare resource utilisation associated with asthma [8, 18], and because new options are available for treatment of such patients.

Limited data are available on the burden and optimal management of mild asthma. One analysis found that people with mild asthma reported significantly more absenteeism, physician visits, emergency department (ED) visits, and hospitalisations than otherwise healthy matched controls [5]. An analysis from Canada estimated that mild asthma was responsible for 67% of total asthma patient-years, but for 14% of the total direct costs of asthma [18]. It has also been observed that healthcare resource use seems disproportional to clinical features in patients with mild asthma [4]. While asthma exacerbation rates are lower in patients with mild than those with severe asthma, defined by treatment step [19], studies in which pre-exacerbation symptom frequency was recorded have found that 30–52% of exacerbations requiring emergency care occurred in patients reporting symptoms less than weekly or only on exertion in the previous 3 months [6]. In addition, sudden-onset asthma deaths are well-recognised, with distinctive pathological features [20].

We therefore conducted a systematic review to gain a better understanding of how mild asthma has been defined in the literature and to understand the burden of mild asthma as related to exacerbations, the single most burdensome outcome for patients, clinicians and healthcare systems alike.

Methods

Search strategy and selection criteria

A structured search of published literature was conducted electronically using Medline and Medline In-Process (PubMed), and Embase in OVID (OVID Technologies, Inc.), to capture publications between January 1990 and February 2019. The search was limited to English-language publications, and excluded animal studies, preclinical studies, in-vitro studies, case reports, editorials, letters, and review articles, as well as other systematic reviews and meta-analyses. Records had to contain the relevant indication plus at least one therapy plus at least one outcome/keyword. Search terms for the indication were "mild" or "persistent" or "intermittent" or "seasonal" or "episodic" or "mild–moderate" plus "asthma", OR "Global Initiative for Asthma" or "GINA" plus "step? 1" or "step? 2". Therapies included monotherapy with inhaled corticosteroid (ICS), leukotriene receptor antagonist (LTRA), short-acting β_2-agonist (SABA), methylxanthine, co-therapy (combined or separate) with ICS+SABA, ICS+long-acting β_2-agonist (LABA) and/or LTRA+SABA (see table S1 for full search terms). The search was restricted to publications in which the search terms appeared in the title and/or abstract, to increase the relevance of the articles identified. Any duplicates were removed during the electronic search process. Relevant records were identified using the search terms above with a prior pilot stage to test criteria and refine, if necessary.

After exclusion of congress abstracts, full-text versions of any records identified as definitely or possibly relevant *via* the title and abstract (level 1 filtering) were obtained so that the inclusion/exclusion criteria could be re-applied to the full article (level 2 filtering). Records were limited to those reporting only

randomised controlled trials (RCTs) and non-RCTs (observational or retrospective studies, including database analyses) in patients stated to have mild asthma or, if "mild" was not specified by the study authors, with clinical characteristics consistent with those used in other studies reported here. Studies in patients with mild-to-moderate asthma were included only if data for patients stated to have mild asthma were reported separately. Studies were included if they contained data on exacerbations or exacerbation-related data. Filtering was undertaken by professional medical writers with several years of experience of asthma and the respiratory therapeutic area.

Data extraction

Data from each patient population were then extracted from each identified record using pre-agreed parameters. Data extraction was undertaken by two investigators who subsequently reviewed each other's data. A third investigator had overall responsibility for the project. Any conflicts over record or data inclusion were resolved *via* discussion between the three members of the team.

Data extracted included: the definition of mild asthma used in each identified study; study inclusion and exclusion criteria; any data on pre-study history of exacerbations, systemic corticosteroid use or hospitalisations/ED visits documented from retrospective studies and at baseline in prospective studies; and, for RCTs of ⩾24 weeks' duration, any outcome data in the placebo arm related to exacerbations, systemic corticosteroid use, hospitalisation/ED visits or study-defined "severe asthma-related events (SAREs)". Data were also collected on the study definition of an exacerbation, including severity of exacerbation if provided. Other data extracted from each record included study design, study duration, number of patients and age of the study population, and the nature of the intervention and comparator arms if relevant. Data were extracted into a spreadsheet and checked to ensure no duplication of data.

Data analysis

While the original aim of this study was to conduct a meta-analysis, due to the heterogeneity of study designs, mild asthma and exacerbation definitions, and format in which exacerbation data were reported (*e.g.* annualised exacerbation rate *versus* incidence of exacerbations), this was not possible.

Outcomes

The primary outcomes of interest were:

- the definition of mild asthma,
- the study definition of an exacerbation (including severity of exacerbation, if stated) used in collecting patient baseline clinical characteristics/history or as a study outcome,
- retrospective exacerbation data collected from patient self-report; exacerbation data from administrative databases and medical records; prospective exacerbation data, and
- exacerbation rates in the placebo arm of prospective studies, as a prospective study outcome.

Secondary outcomes included exacerbation rates collected retrospectively in administrative databases and medical records.

For each included study, the extracted inclusion and exclusion criteria were assessed in relation to the study definition of mild asthma and as related to patient history of exacerbations.

This review has been registered on the PROSPERO database with the number CRD42018093352.

Results

Of the 4064 records identified, 152 were reviewed in-depth, 114 RCTs and 38 observational and other non-RCT studies, from here on referred to as "observational/other" publications (figure 1). A total of 64 articles (54 RCT and 10 observational/other publications) were included in the systematic review, with 32 919 RCT subjects (including 5326 patients randomised to placebo, and 1435 paediatric/adolescent patients) and 16 824 observational/other subjects (including 98 paediatric/adolescent patients).

Definitions of "mild asthma"

Among the articles included, there was heterogeneity in the way that mild asthma was defined. In order to make meaningful comparisons amongst the studies, we classified these definitions broadly into six categories according to the criteria the original authors had used to define mild asthma at study entry (table S2). In brief, these were: 1) treatment level; 2) symptom frequency criteria; 3) symptoms <daily and a minimum permitted forced expiratory volume in 1 s (FEV_1) of 80% predicted; 4) symptoms <daily and a minimum permitted FEV_1 ranging between 60–80% predicted; 5) other criteria; and 6) definitions for children <5 years (table 1). The majority of RCTs used a composite definition based on symptom frequency and FEV_1 (categories 3 and 4), whereas for observational/other studies, except those limited to

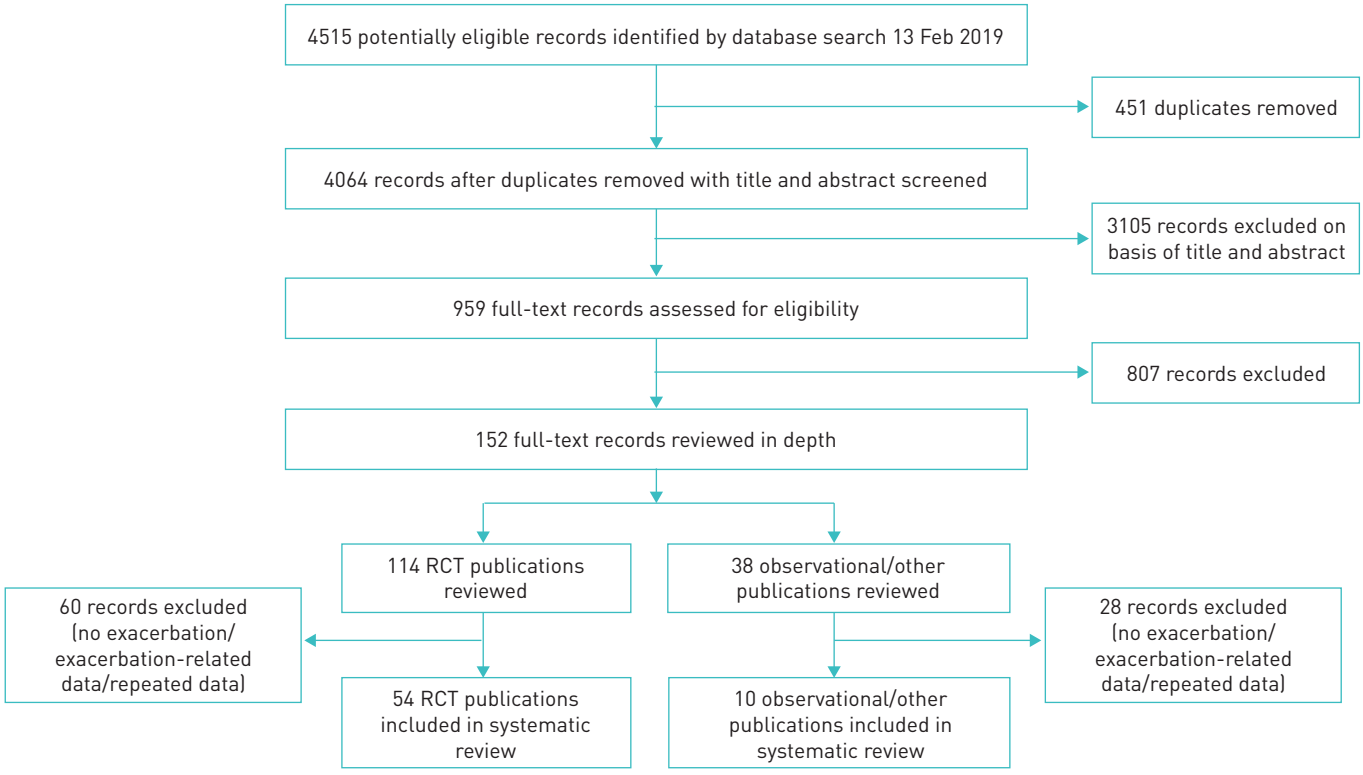

FIGURE 1 Study selection process. RCT, randomised controlled trial.

preschool children, similar numbers of studies used treatment level (category 1) and categories 3 or 4 to define mild asthma.

The main characteristics for which data were extracted are summarised in table 2, with active treatment group regimens summarised in table S3. Many studies, in order to ensure clinical stability at enrolment, excluded patients with a recent exacerbation (*e.g.* in the previous 1–3 months). However, if patients with an exacerbation more than 3 months prior to study enrolment were excluded, we considered this study to have excluded patients with an exacerbation history. The majority of RCTs permitted patients to have such

TABLE 1 Definitions of mild asthma: classification used in this review

Main criteria for mild asthma	RCTs (n=54)		Observational/other studies (n=10)	
	All n (%)	Studies permitting past history of exacerbations n (%)	All n (%)	Studies permitting past history of exacerbations n (%)
1) Treatment level	3 (5.6)	0 (0)	5	2 (20.0)
2) Symptom frequency criteria	3 (5.6)	3 (5.6)	0	–
3) FEV_1 ⩾80% pred and symptoms<daily	19 (35.2)	15 (27.8)	2	1 (10.0)
4) FEV_1 >60–80% pred and symptoms<daily	15 (27.8)	13 (24.1)	1	1 (10.0)
5) Miscellaneous definitions#	9 (16.7)	8 (14.8)	0	–
6) Included patients aged <5 years	5 (9.3)	4 (7.4)	2	2 (20.0)

RCT: randomised controlled trial; FEV_1: forced expiratory volume in 1 s. # Miscellaneous definitions not captured by the other five categories (*e.g.* "doctor-diagnosed mild asthma", or "mild asthma based on airway hyper-responsiveness" alone), or, studies that did not state that patients had "mild asthma" but included patients with disease characteristics similar to those in the other five categories.

TABLE 2 Mild asthma studies grouped by study type (RCT or observational/other) and by definition of mild asthma

Study (year) [ref.]	Age range or average age years	Treatment duration	Placebo		Exacerbation definition	Baseline exacerbation data	Patients with history of exacerbation not excluded[#]
			Yes n, treatment allowed	No			
RCTs							
Category 1: RCTs that primarily defined mild asthma by treatment level							
Bateman *et al.* (2018) [26]	12–83	52 weeks		✓	✓	✓	
Camargos *et al.* (2018) [31]	10.6 (2.8)[¶], 9.9 (2.7)[¶]	6 weeks		✓	✓		
O'Byrne *et al.* (2018) [38]	12–85	52 weeks		✓	✓		
Category 2: RCTs that primarily defined mild asthma by symptom frequency							
Martinez *et al.* (2011) [36]	5–18	44 weeks	74 P bid + P/ALB rescue		✓	✓	✓
Pauwels *et al.* (2003) [41]	5–66	3 years	3568 P + usual asthma medication		✓	✓	✓
Wongtim *et al.* (1995) [80]	33.2 (7.46)[¶], 32.8 (8.6)[¶]	8 weeks	10				✓
Category 3: RCTs that primarily defined mild asthma with a composite definition of FEV_1 ⩾80% pred and symptoms <daily							
Basyigit *et al.* (2004) [81]	38 (8.2)[¶], 42.4 (9.6)[¶], 45.5 (10.9)[¶]	8 weeks		✓			✓
Bousquet *et al.* (2005) [29]	15–80	48 weeks (12 DB, 36 OL)		✓	✓		✓
Chrousos *et al.* (2005) [82]	18–65	14 days		✓			✓
Chuang *et al.* (2007) [83]	6–14	8 weeks		✓			✓
Chuchalin *et al.* (2005) [33]	6–87	12 months		✓	✓		✓
Chuchalin *et al.* (2008) [32]	12–79	52 weeks	315		✓		✓
Currie *et al.* (2003) [84]	36 (4)[+]	2×3 weeks		✓			✓
Garcia Garcia *et al.* (2005) [35]	6–14	12 months		✓	✓		✓
Karaman *et al.* (2004) [85]	8–14	12 weeks		✓			✓
Maiti *et al.* (2011) [86]	18–70	4 weeks		✓			✓
Ng *et al.* (2007) [37]	6–14	2×8 weeks		✓	✓		
Reddel *et al.* (2008) [42]	18–80	11 months	21		✓		

Continued

TABLE 2 Continued

Study (year) [ref.]	Age range or average age years	Treatment duration	Placebo		Exacerbation definition	Baseline exacerbation data	Patients with history of exacerbation not excluded[#]
			Yes n, treatment allowed	No			
Renzi *et al.* (2010) [43]	⩾12	24 weeks		✓	✓		✓
Riccioni *et al.* (2002) [87]	26.9 (12.3)[¶], 26.7 (8.6)[¶], 28.2 (10.1)[¶]	16 weeks		✓			
Shimoda *et al.* (2005) [88]	36.2 (12.8)[¶], 35.6 (14.4)[¶]	6 months		✓			✓
Tamaoki *et al.* (2008) [89]	⩾21	8 weeks		✓			✓
Vatrella *et al.* (2002) [90]	18–48	16 weeks		✓			✓
Zeiger *et al.* (2005) [91]	15–85	48 weeks (12 DB, 36 OL)[§]		✓			✓
Zietkowski *et al.* (2006) [92]	45.2 (10.9)[f], 42 (14)[f], 51 (7.6)[f]	12 weeks		✓			✓
Category 4: RCTs that primarily defined mild asthma with a composite definition of FEV_1 approximately >60–80% and symptoms <daily							
Berger *et al.* (2009) [48]	⩾12	16 weeks	177		✓		
Boulet *et al.* (2000) [93]	⩾12	12 weeks		✓			✓
Drazen *et al.* (1996) [34]	12–55	20 weeks (16 weeks active treatment + 4 weeks withdrawal (OL ALB as needed))	129 P + ALB as needed[##]		✓		✓
Herjavecz *et al.* (1999) [55]	17–67	22 weeks (6 DB; 16 OL)		✓		✓	✓
O'Byrne *et al.* (2001) [39]	⩾12	1 year	Group A: 239		✓		✓
O'Sullivan *et al.* (2003) [94]	19–50	2×8 weeks		✓			✓
Papi *et al.* (2007) [40]	18–65	6 months	118 P bid + ALB 100 µg as needed		✓		✓
Peters *et al.* (2007) [56]	⩾6	16 weeks		✓		✓	✓
Stone *et al.* (2001) [95]	⩾16	4 weeks		✓			✓
Tattersfield *et al.* (2001) [45]	20–60	2 years		✓	✓		
Tomlinson *et al.* (2005) [46]	20–60	12 weeks		✓	✓		✓
van Grunsven *et al.* (1996) [47]	⩾30	2 years		✓	✓		✓

Continued

TABLE 2 Continued

Study (year) [ref.]	Age range or average age years	Treatment duration	Placebo		Exacerbation definition	Baseline exacerbation data	Patients with history of exacerbation not excluded[#]
			Yes n, treatment allowed	No			
Verberne *et al.* (1996) [58]	7–16	4 months		✓		✓	✓
Vermetten *et al.* (1999) [96]	18–66	12 weeks		✓			✓
Woodcock *et al.* (2002) [59]	18–65	6 weeks		✓			✓
Category 5: RCTs that defined mild asthma by other/miscellaneous criteria							
Arets *et al.* (2002) [23]	5–10	12 weeks	33		✓		✓
Boushey *et al.* (2005) [28]	18–65	1 year		✓	✓		✓
Villaran *et al.* (1999) [97]	14–45	8 weeks		✓			✓
Category 5: RCTs that did not describe their patients as having "mild asthma" but included patients with disease characteristics similar to the categories described above							
Bailey *et al.* (2008) [24]	12–65	52 weeks		✓	✓		✓
Barnes *et al.* (2007) [98]	⩾12	12 weeks		✓			✓
Bateman *et al.* (2012) [25]	⩾12	8 weeks	94		✓	✓	✓
Busse *et al.* (2001) [30]	>15	24 weeks		✓	✓		✓
Busse *et al.* (2001) [53]	12–75	12 weeks	114				
van der Molen *et al.* (1998) [99]	18–50	12 weeks		✓			✓
Category 6: RCTs that included patients <5 years old							
Bisgaard *et al.* (2005) [27]	2–5	48 weeks	271		✓	✓	✓
Shah *et al.* (2014) [100]	2–18	12 weeks		✓			✓
Szefler *et al.* (2007) [44]	2–8	52 weeks		✓	✓		✓
Category 6: RCTs that included patients <5 years old that did not describe their patients as having "mild asthma" but included patients with disease characteristics similar to mild asthma							
Robertson *et al.* (2007) [21]	2–14	12 months	113			✓	✓
Skoner *et al.* (2005) [57]	2–5	3 weeks	50			✓	
Observational/other							
Category 1: Observational/other studies that primarily defined mild asthma by treatment level							
Ding and Small (2017) [49]	⩾12	–		NA	✓		✓

Continued

TABLE 2 Continued

Study (year) [ref.]	Age range or average age years	Treatment duration	Placebo		Exacerbation definition	Baseline exacerbation data	Patients with history of exacerbation not excluded[#]
			Yes n, treatment allowed	No			
Friedman *et al.* (2010) [50]	12–25	–		NA	✓		
Friedman *et al.* (2010) [51]	12–65	–		NA	✓		
McIvor *et al.* (2009) [22]	⩾6	Survey + 6-week treatment		NA		✓	✓
Navaratnam *et al.* (2009) [52]	12–65	–		NA	✓		
Category 3: Observational/other studies that primarily defined mild asthma with a composite definition of FEV_1 ⩾80% and symptoms<daily							
Giraud *et al.* (2006) [54]	⩾18	4–8 weeks		NA		✓	✓
Lai *et al.* (2003) [61]	Total (not just mild asthma) Children: 7.4 (3.8)[¶]Adults: 40.5 (18.5)[¶]	–		NA		✓	
Category 4: Observational/other studies that primarily defined mild asthma with a composite definition of FEV_1 approximately >60–80% and symptoms<daily							
Soyer *et al.* (2009) [60]	6–18	–		NA			✓
Category 6: Observational/other studies that included patients <5 years old							
König *et al.* 1996 [62]	⩽17	–		NA		✓	✓
Robertson *et al.* (1992) [63]	⩽20	–		NA			✓

RCT: randomised controlled trial; bid: twice daily; P: placebo; ALB: albuterol; DB: double-blind; OL: open-label; FEV_1: forced expiratory volume in 1 s; NA: not applicable. [#] History of exacerbations considered to be exacerbation, hospitalisation or emergency department visit or oral corticosteroid use that occurred prior to enrolment/screening (RCTs or prospective observational studies) or in the pre-index period (retrospective studies); [¶]: mean (SD) age in years; [+]: mean (SE) age. [§]: 10% of participants (determined at randomisation) switched therapies to preserve the masking in the preceding period; [f]: median (range) age; [##]: no dose given.

a history of exacerbations (43 of 54). One RCT in children, examining the effect of intermittent LTRA, required the children to have a history of 3–6 exacerbations within the previous 12 months, with no symptoms between exacerbations, for study inclusion [21]. One observational study included patients experiencing exacerbations (timeframe unspecified) and who had recurrent, but not daily, symptoms [22].

Definitions of exacerbations for baseline characteristics and outcome measures

Of the 54 RCTs included in this review, 26 [23–48] reported a definition of an exacerbation or SARE and of the 10 observational/other studies, four [49–52] did so (table S4). There was a wide variety of definitions of exacerbations.

Of the studies included in table 2 defining an exacerbation, exacerbation severity was defined in all but 10 RCTs [21, 24, 25, 27, 28, 34, 36, 37, 48, 53], but only in one observational/other study [49]. Most definitions of mild exacerbations related to changes in peak expiratory flow, symptoms and/or reliever use (table S4). Two studies included a definition of moderate exacerbations which included worsening of asthma requiring initiation of additional asthma treatment [32, 38]. In one of these, SYGMA 1 (SYmbicort Given as needed in Mild Asthma [38]), the definition was consistent with the ATS/ERS Task Force definition (table S5) [11]. One cross-sectional survey study included a wide definition of moderate-to-severe exacerbations that included physician-assessed worsening, ED visits, hospitalisations, use of systemic corticosteroids and antibiotics [49].

The majority of definitions for severe exacerbations related to use of systemic corticosteroids, hospitalisation/ED visits or unscheduled physician visits. Of publications for which severe exacerbations

TABLE 3 Retrospectively collected data on asthma exacerbations, hospitalisation and emergency department admissions/visits

Study (year) [ref.]	Age range years	Study groups n	Exacerbation parameter(s)	Data for exacerbations by specified parameter, for each study group
Exacerbations reported in ⩽6 months prior to study entry				
Bateman *et al.* (2012) [25]	⩾12	97, 100, 110, 95, 102, 94	Pts with ⩾1 exacerbation in last 6 months	18%, 19%, 16%, 25%, 17%, 21%
McIvor *et al.* (2009) [22]#	⩾6	534	Patients with any exacerbation in 6 weeks prior to study entry	51.7%
Skoner *et al.* (2005) [57]	2–5	58, 51, 52, 50	No. of exacerbations in last 30 days	Mean: 1.8, 1.3, 1.5, 1.2 Median: 0,1,0, 0
			Pts with ⩾1 exacerbation in last 30 days	48.3%, 52.9%, 48.1%, 36.7%
Woodcock *et al.* (2002) [59]	18–65	86, 86	Mean no. daytime asthma attacks in 7-day run-in	0.25, 0.18
			Mean no. night-time asthma attacks in 7-day run-in	0.10, 0.10
Exacerbations reported in 12 months/1 year prior to study entry				
Bateman *et al.* (2018) [26]	12–83	2089, 2087	Pts with 1 severe exacerbation in last 12 months	17.5%, 17.3%
			Pts with ⩾1 severe exacerbations in last 12 months	22%, 21.9%
			Pts with ⩾2 severe exacerbations in last 12 months	4.5%, 4.7%
Ding and Small (2017) [49]	⩾12	524, 591	Pts with 1 exacerbation in last 12 months	9.0%, 13.1%
			Pts with ⩾3 exacerbations in last 12 months	3.4%, 1.9%
			Mean (SD) no. of moderate-to-severe exacerbations in last 12 months	0.2 (0.6)¶
			Mean (SD) no. of exacerbations treated in ED or hospital in last 12 months	0.1 (0.4), 0.1 (0.3)
			Mean (SD) no. of exacerbations treated with OCS, antibiotics, ED or hospital admission in last 12 months+	0.1 (0.5), 0.2 (0.6)
			Pts with 1 exacerbation treated with OCS, antibiotics, ED or hospital admission in last 12 months+	5.8%, 10.8%
			Pts with ⩾3 exacerbations treated with OCS, antibiotics, ED or hospital admission in last 12 months+	1.0%, 1.5%
Giraud *et al.* (2006) [54]	⩾18	94	Pts hospitalised for asthma in previous 12 months	4.3%
Herjavecz *et al.* (1999) [55]	17–67	90, 91	Time since last exacerbation	12.5 months, 13.0 months
Lai *et al.* (2003) [61]	Mean 7.4–40.5	1709, 633	Pts with hospital admissions in last year	7.3%, 15.4%
			Pts with any hospital ED/unscheduled emergency visit in the last year	33.1%, 41.3%
Martinez *et al.* (2011) [36]	5–18	71, 72, 71,74	Mean no. hospital visits for asthma in last 1 year	0.3, 0.3, 0.2, 0.2
O'Byrne *et al.* (2018) [38]	⩾12	1277, 1277,1282	Pts with ⩾1 severe exacerbation in last 12 months	20.0%, 20.1%, 18.8%
Peters *et al.* (2007) [56]	⩾6	166, 165, 169	Pts with ⩾1 urgent visit for asthma in last 1 year	30.7%, 35.8%, 35.5%
Robertson *et al.* (2007) [21]§	2–14	97, 105	Median no. of ED attendances for asthma in last 1 year	1, 1
			Median no. of hospital admissions for asthma in last 1 year	1, 1
Soyer *et al.* (2009) [60]	6–18	522	Mean (SD) no. of unscheduled visits per patient	1.2 (0.2)
			Mean (SD) no. of ED visits per patient	0.6 (0.05)
Verbene *et al.* (1996) [58]	7–16	30	Pts hospitalised for asthma in last 1 year	0%

All studies were randomised controlled trials except Giraud *et al.* [54], McIvor *et al.* [22], Ding and Small [49], Lai *et al.* [61] and Soyer *et al.* [60]. pts: patients; ED: emergency department; OCS: oral corticosteroids; no.: number. # Study included patients with a history of exacerbations (time frame not specified); ¶ n=1076; + time frame not specified in Results section of [49] although Methods section suggests 12-month timeframe; §: Study included only patients with a history of 3–6 exacerbations (hospitalisation or ED visit or general practitioner visits) in the 12 months prior to enrolment/screening.

are reported, three publications completely aligned [26, 38, 42] and four broadly aligned [32, 39–41] with the ATS/ERS Task Force criteria [11] defining a severe exacerbation (table S6).

An additional category of severe exacerbations, SAREs, was defined in the START study (inhaled Steroid Treatment As Regular Therapy in early asthma study) [41] as asthma-related ED visits, hospitalisations and deaths, *i.e.* excluding exacerbations identified only by oral corticosteroid use; these were therefore likely to be more severe than the majority of severe exacerbations defined in other studies by the ATS/ERS criteria.

In general, RCTs for which baseline data (pre-study history of exacerbations) are included in the review (table 3) did not provide a separate definition for exacerbations occurring prior to study entry. It is assumed that the same definition applied to both pre-study and within-study exacerbations.

Retrospective exacerbation data collected from patient self-report

Fourteen prospective studies in patients with mild asthma incorporated data on exacerbation or exacerbation-related healthcare utilisation during the pre-study period as reported in the baseline characteristics [21, 22, 25–27, 36, 38, 41, 54–59]; these included exacerbations (n=7 studies) hospitalisation or ED admissions/visits (n=8) (table 3), and systemic corticosteroid use (n=5) (table S7). In addition, exacerbation data were collected in a prospective survey [49] and hospitalisation/ED visit data were collected from a patient questionnaire [60] and population survey [61] (table 3).

There was a wide range across studies in the proportion of patients who in the preceding year were hospitalised for asthma (*i.e.* presumably for a severe exacerbation) or had at least one severe exacerbation: 0–22% [26, 38, 54, 58, 61]. Two of the largest and most recent of these studies found that 18.8–22.0% of patients reported having had at least one severe exacerbation in the year prior to enrolment [26, 38].

In the START study of over 7000 patients with mild recent-onset asthma, close to 5% of patients had received systemic corticosteroids in the 6 weeks prior to study entry (table S7) [41], whereas a pre-post study recruiting patients with uncontrolled asthma, despite low-dose ICS, reported that 52% of patients had an exacerbation (affecting activities and sleep) in the 6 weeks prior to study entry [22]. However, it is difficult to interpret exacerbation incidence over such a short period of time. An RCT in patients with poorly controlled asthma, not taking ICS, found 16–25% of patients across all groups had at least one exacerbation in the 6 months prior to study entry [25].

In a paediatric study that required children to have a history of multiple exacerbations in the previous year, without any interval symptoms, the rate of hospital admissions/ED visit for asthma during that year was low (table 3) [21]. The mean±SD number of ED visits per year was 0.6±0.5 in another study in paediatric patients, of whom ≈50% were untreated and ≈45% received ICS with or without bronchodilators [60].

Exacerbation data from administrative databases and medical records

Five studies collected data on exacerbations from claims databases or medical records (table S8) [50–52, 62, 63], with all but one covering a time period of 1 year. Several outcomes were captured, including mean number of exacerbations (n=3) [50–52], and hospitalisations or ED visits (n=2) [62, 63]. In the three database claims studies in patients with mild asthma aged 12–65 years [50–52], the mean number of exacerbations ranged from 0.12–0.19, depending on which of three maintenance ICS they received. In a study of asthma-related deaths in 51 children aged 2–14 years, 17 (33%) patients had mild asthma (based on features such as symptoms less than monthly, exercise limitation only on active sports, or less than 1 week's school absence in the previous year) [63].

Prospective exacerbation data

A total of nine RCT publications reported data on exacerbation/exacerbation-related outcomes in a placebo arm (table 4), including exacerbations (n=8) [27, 32, 36, 38–42], SAREs (n=1) [41], systemic corticosteroid use (n=3) [21, 27, 41], and hospitalisation, ED admissions/visits and unscheduled visits/healthcare resource use (n=4) [21, 27, 32, 38]. Data on exacerbations were reported using a variety of parameters, including patients with exacerbations (percentage or number; n=6) [27, 38–42], exacerbation rate (n=5) [27, 32, 38–40], probability of a first exacerbation by the end of the trial (n=1) [36], time to first exacerbation (n=1) [27], withdrawal/discontinuation due to exacerbation (n=1) [32] and treatment failure (n=1) [36].

Study-reported annual exacerbation rates of any severity in placebo recipients ranged from 0.36–2.88 (table 4) [27, 32, 40]. Few studies reported the proportions of patients with one or more exacerbations of any severity, and only one did so for a time period of 1 year [38]. In an RCT of adult patients previously stable on medium-dose ICSs, 21 of 118 (17.8%) of those randomised to placebo plus as-needed salbutamol had ⩾1 exacerbation over a 6-month period [40]. In the 48-week double-blind period of a 1-year study in preschool

TABLE 4 Prospective data on exacerbations and exacerbation-related outcomes in mild asthma from placebo arms of RCTs of ⩾24 weeks' duration

Study (year) [ref.]	Age range years	Placebo n	Other asthma medication in placebo arm	Treatment duration	Exacerbation parameter	Placebo arm
Studies not excluding patients with exacerbation history+						
Bisgaard *et al.* (2005) [27]	2–5	271	Rescue OCS or ICS or β_2-agonist	48 wks	Pts with exacerbation§	56%
					Exacerbation rate/year (n=257)f	2.34
					Median time to first exacerbation	147 days
					Pts with ⩾1 unscheduled visit to physician for asthmaf	42.4%
					Pts hospitalised for asthmaf	5.8%
					Rate of OCS courses/yearf	0.64
Chuchalin *et al.* (2008) [32]	12–79	315	Rescue ALB	52 wks	Mean exacerbation rate per pt per year (mild, moderate, severe)	2.88
					Moderate (OCS) or severe exacerbation (hospitalisation) rate/year	0.33
					No. unscheduled asthma-related healthcare contacts	7
					Pt withdrawal/discontinued due to exacerbation, n	8
Martinez *et al.* (2011) [36]	5–18	74	Rescue ALB	44 wks	Probability (95% CI) of first exacerbation by end of trial requiring prednisone course	49 (37–61)%
					Proportion with treatment failure (all defined by requirement for a second course of prednisone)	23%
O'Byrne *et al.* (2001) [39]	⩾12	239	Yes - only after first exacerbation (n=104)¶¶	1 yr	Pts with severe exacerbation	33.3%
					No. of pts with severe exacerbation, pts treated with OCSs	70.9%
					Pts receiving systemic corticosteroids	23.6%
					Severe exacerbation rate per pt per year	0.77
O'Byrne *et al.* (2018) [38]	⩾12	1277	TERB 0.5 mg as needed	1 yr	Pts with ⩾1 moderate or severe exacerbation	21.5%
					Pts with ⩾1 severe exacerbation	11.9%
					Annualised severe exacerbation rate	0.20
Papi *et al.* (2007) [40]	18–65	118	ALB as-needed	6 months	Pts with severe exacerbation	3.4%
					Pts with ⩾1 exacerbation	17.80%
					Mean no. of exacerbations/pt/year	1.63
Pauwels *et al.* (2003) [41]	5–66	3568	Usual asthma treatment (SABA 64.6% of placebo pts) plus ICS or systemic corticosteroid if needed	3 yrs	Pts with life-threatening exacerbation over 3 years, n	24 (0.67%)
					Pts with ⩾1 SARE over 3 years, n	198
					Pts with ⩾2 SAREs over 3 years, n	49
					Mean no. of courses of systemic corticosteroids per year	0.21
					Pts using systemic corticosteroids	3 months: 4.1% 12 months: 3.1% 24 months: 3.3% 36 months: 2.0%
					Pts with ⩾1 systemic corticosteroid course	23%

Continued

TABLE 4 Continued

Study (year) [ref.]	Age range years	Placebo n	Other asthma medication in placebo arm	Treatment duration	Exacerbation parameter	Placebo arm
Studies excluding patients with exacerbation history[+]						
Reddel *et al.* (2008) [42]	18–80	21	ALB as-needed	11 months	Pts with ⩾1 mild exacerbation, n	13
					Pts with severe exacerbation, n	3
Studies requiring patients to have a history of frequent exacerbations[#]						
Robertson *et al.* (2007) [21]	2–14	113	Inhaled β_2-agonist or OCS for acute asthma episode	12 months	Proportion of children with ⩾1 episode treated with short course of randomised therapy, n (%)	105 (92.9%)
					Total number of treated episodes of asthma	336
					Proportion of treated asthma episodes utilising ⩾1 health resource, n (%)	134 (39.9%)
					Proportion of treated asthma episodes requiring ED visit, n (%)	46 (13.7%)
					Proportion of treated asthma episodes requiring hospitalisation, n (%)	13 (3.9%)
					Proportion of treated asthma episodes with OCS use, n/N pts with diary data (%)	78 of 321 (24.3%)

RCT: randomised controlled trial; ED: emergency department; wks: weeks; pt: patient; OCS: oral corticosteroid; ICS: inhaled corticosteroid; CI: confidence interval; SABA: short-acting β2-agonist; SARE: severe asthma-related event; ALB: albuterol; TERB: terbutaline; GP: general practitioner; LABA: long-acting β2-agonist. [#] Study included only patients with a history of 3–6 exacerbations (hospitalisation or ED visit or GP visits) within 12 months prior to enrolment/screening); [¶] Unscheduled visits to GP, specialist paediatrician, ED or admission to hospital; [+]: Exacerbation history defined as an exacerbation, hospitalisation or ED visit or OCS use occurring ⩾3 months prior to enrolment/screening; [§]: data appear to relate to 48-week double-blind period only (total study duration 1 year including screening and single-blind, placebo run-in period); [f]: source publication refers to "yearly" data, but double-blind treatment period only 48 weeks (total study duration 1 year including screening and single-blind, placebo run-in period); [##]: defined as the requirement for a second dose of prednisone within any 6-month period; ¶¶: most common extra medication in placebo group was systemic corticosteroids (n=56), ICS (n=15) and LABAs (n=11).

children aged 2–5 years with intermittent asthma symptoms triggered by viral infection, 56% had ⩾1 exacerbation and 5.8% were hospitalised for asthma [27]. In a small 11-month RCT that excluded patients with an exacerbation in the previous year, 13 of 21 placebo recipients were reported as having ⩾1 "mild" asthma exacerbations [42]. In an RCT of adolescents and adults with asthma well-controlled on low dose ICS or LTRA or uncontrolled on short-acting bronchodilators alone, 274 of 1277 (21.5%) of those randomised to placebo plus as-needed terbutaline had ⩾1 moderate or severe exacerbations, and 152 (11.9%) had ⩾1 severe exacerbations, over a 12 month period [38].

Regarding use of healthcare resources, in an RCT in paediatric patients, 113 placebo recipients had 228 unscheduled acute healthcare utilisations during 12 months [21].

Exacerbation rates in placebo recipients

Six of the seven publications in which the definition of severe exacerbations aligned/broadly aligned with the ATS/ERS Task Force definition (table S6) [11] had relevant outcomes data from a placebo arm [32, 38–42]. The annual rate of severe exacerbations was reported from the placebo arms of three trials in mild asthma (table 4): 0.77 in ICS-free patients aged ⩾12 years (OPTIMA A) [39], 0.33 in patients aged 12–79 years [32], and 0.20 in 1277 patients aged ⩾12 years (SYGMA 1) [38]. In the START trial in patients aged 5–66 years with newly diagnosed mild asthma, exacerbation rate was not reported *per se*, but the annualised mean number of courses of systemic corticosteroids was 0.21 [41], which may be considered a proxy for the exacerbation rate in this study, according to the ATS/ERS Task Force definition of exacerbations based on systemic corticosteroid use [11]. In three of these studies, additional medications were allowed: other asthma medications in both the OPTIMA A study (after the first severe exacerbation) [39] and the START study [41], and open-label ICSs for persistent poorly controlled asthma or prolonged

exacerbation in SYGMA 1; [38] in the remaining study [32], placebo recipients were only allowed SABA medication.

The proportion of placebo recipients in RCTs experiencing a severe exacerbation in ~1 year varied widely (table 4), from 33.3% of placebo recipients in the OPTIMA A study (23.4% if only oral corticosteroids were considered) [39], to 11.9% in the SYGMA 1 study [38], both studies being 12-month studies in patients aged ⩾12 years, and 3.4% in the 6-month BEST study in patients ⩾18 years whose asthma had been well controlled on moderate-dose ICSs [40]. In a small study which excluded patients with a history of exacerbations, a severe exacerbation occurred in 3 of 21 placebo recipients (14.2%) aged 18–80 years with mild asthma and minimal symptoms at study entry [42].

Of 3568 placebo recipients in the START trial, in which patients could receive additional maintenance asthma treatment, 198 (5.5%) experienced one or more SARE during the 3-year double-blind period [41].

Discussion

This systematic review collated data on definitions of mild asthma and summarised the burden of exacerbations in this patient population. There were two key findings. The first was that there were multiple different definitions of "mild" asthma, which in RCTs were most commonly based on symptoms and lung function and, in observational/administrative studies, were often based on treatment level, independent of symptoms. The second was that, for patients considered to have mild asthma and treated with as-needed SABA alone, the mean exacerbation rate (all severities) was as high as 2.88 per patient per year [32], with up to 42% of patients requiring unscheduled physician visits for their asthma [27], although this high rate of visits was in preschool children. In adolescents and adults, the mean number of unscheduled asthma-related healthcare visits in a 52-week study was 7 [32]. The annualised severe exacerbation rate in the placebo arm of prospective studies of 24 or more weeks' duration ranged from 0.20 [38] to 0.77 [39].The proportion of patients with a severe exacerbation also varied widely, from 3.4% [40] to 33.3% [39]. Considering even more severe events, a large placebo-controlled study found that 0.67% of patients with newly diagnosed mild asthma experienced life-threatening exacerbations over a 3-year period, despite their treating physician being able to prescribe additional asthma medications [41]. These results clearly indicate that mild asthma, although variably defined in these studies, is associated with a considerable risk of exacerbations including severe, life-threatening exacerbations, which represent a significant burden to both the patient and to healthcare systems [4].

It has previously been reported that 5–13% of investigated deaths due to asthma occurred in patients "being treated for mild asthma" (*i.e.* with SABA alone [64], or judged to have "trivial or mild asthma" [65, 66]). In the latter two studies, 15–20% of patients had symptoms less than weekly in the previous 3 months [65, 66]. In the current review, one study found that 17 of 51 (33%) children with asthma-related death had been assessed as having had mild asthma [63]. Few of these 17 children had features flagging them as being high risk (*e.g.* only three had had a hospital admission in the year preceding their death and one had ever been treated in an intensive care unit (ICU)) [63]. These data exemplify not only the risk of death across the spectrum of asthma but also the need for a more sensitive marker for identifying patients at risk of SARE who may not have necessarily had a previous hospital or ICU admission.

This systematic review highlights the very marked heterogeneity in the assessment and definition of mild asthma. Where a definition was provided, it was either the investigators' own definition or was taken from one of the various guidelines or reports published between 1987 and 2015 (table S9). We grouped studies by their definition of mild asthma into six broad categories (tables 1 and S2); only the first category (treatment) reflects the approach taken in current consensus recommendations (*e.g.* GINA 2020 [1]). Indeed, only a few of the most recent studies included in this review followed mild asthma definitions according to contemporaneous GINA recommendations [26, 38, 49]. Mild asthma may be determined arbitrarily by treatment step according to patient self-report or in administrative databases (where no clinical details are available), or more reliably but probably far less often, by a systematic approach (*via* step-down titration) [67] based on the minimum treatment needed to maintain good asthma control. These approaches differ substantially from a common perception that mild asthma means infrequent and/or easily relieved symptoms [9].

Describing the severity of asthma in a study population by treatment step (*e.g.* referring to mild asthma as "Step 1 or 2 patients"), appears problematic, but in epidemiologic studies, prescribed treatment may be the only available data. In addition, a patient's asthma prescription may not have been clinically appropriate. For example, in the National Review of Asthma Deaths, 9% of deaths occurred in patients "being treated for mild asthma" [64]. For epidemiologic studies, GINA recommends naming the treatment rather than inferring severity (*e.g.* "being treated with low-dose ICS") [1]. This approach would also avoid ambiguity about whether a "Step 2 patient" is someone eligible for Step 2 treatment, or taking Step 2 treatment.

Analysis of the inclusion and exclusion criteria relating to exacerbation history for each study (table 1), indicates that some authors considered that a history of exacerbations in the previous 12 months should preclude classification of asthma as mild. However, this did not apply to the majority of studies in this review (except for the common practice of excluding recent exacerbations to ensure clinical stability at baseline). This review suggests that a credible definition of mild asthma may need to focus on symptom control with or without lung function assessment. However, clinicians and patients must at the same time be made aware that patients with mild asthma may still be at risk of severe and potentially life-threatening or fatal exacerbations, albeit infrequently. This is consistent with the current GINA approach [1], highlighting potential discordance between recent symptom control and risk of future adverse outcomes, and recommending that both should be assessed.

Despite the care taken to focus only on mild asthma, the variations in, or absence of specific definitions for mild asthma in some publications, and the fact that many patients with mild asthma have normal or close to normal lung function, still allows for the possibility that some patients may not have had asthma at all, or were misdiagnosed with "mild asthma", and hence were treated unnecessarily [12] or were under-treated [64]. Previous studies have shown that up to one-third of patients with "physician-diagnosed" asthma are found not to have asthma when assessed by a respiratory physician using a range of clinical tests [4, 12, 15, 16, 68, 69]. However, the observational studies identified in this review also confirmed that patients with infrequent symptoms had a significant risk of exacerbations, albeit less than seen in studies of patients with more severe asthma [19].

Our analysis also found considerable heterogeneity in definitions of exacerbations; however, definitions of severe exacerbations or SAREs used in prospective studies were aligned or broadly aligned with the ATS/ERS Task Force definition of a severe exacerbation (table S6) [11]. To enable meta-analyses of larger sets of exacerbation data, future studies should be conducted using standardised definitions for moderate and severe exacerbations, such as those proposed in the ATS/ERS statement [11], and utilised in the recent SYGMA studies [26, 38]. However, a similar recommendation for a uniform definition was made in a previous systematic review of the burden of mild asthma in 2005, indicating that little has changed since then [4].

This review was originally intended to include a meta-analysis, but the heterogeneity of definitions found in the available literature precluded such an analysis. However, the number of patients affected reveals the magnitude of the burden of exacerbations and the discordance with the patients' apparent level of symptom control. The risks of mild asthma, albeit low, can be halved by the regular use of low-dose ICS [39, 41], even in patients with symptoms once a week or less [70]. However, the well-recognised poor adherence to daily maintenance ICSs by patients with mild or intermittent asthma is one reason to advocate a different approach [12, 49, 71, 72]. In addition, practical difficulties in managing patients with episodic symptoms or exacerbations occurring in response to variable environmental triggers such as allergens, respiratory viruses and pollutants, with few interval symptoms [73, 74], provide other examples of the need for a new approach.

Such situations can now be dealt with by use of an anti-inflammatory reliever (ICS/formoterol) that rapidly increases the intensity of both anti-inflammatory and bronchodilator therapy when needed and thus reduces the risks of severe exacerbations without requiring adherence to daily therapy [1, 26, 38, 75–77]. This significant change to the treatment of mild asthma has been recommended by GINA since 2019 [1], and should go some way to reducing the burden of exacerbations [77], by avoiding the discomfort and risk, the potential loss in lung function, and the risks of OCS treatment [78, 79] associated with exacerbations.

The strengths of this systematic review include the care that was taken to ensure that, as far as possible, only data from patients who were considered by the original authors to have (or who had characteristics consistent with) mild asthma were included in the analyses, and the extent of the search: ranging from 1990 to 2019. Studies described as having data on "mild-to-moderate" asthma were excluded, unless data were presented separately for the patients with "mild" asthma.

Potential limitations include the restriction to English-language publications, and that our search terms would likely have missed observational studies that classified the severity of broad asthma populations, and assessed their outcomes, without therapies or key words such as "mild" or "intermittent" having been included in the title or abstract. Some studies selected may have included people who did not have asthma at all. Exacerbation data collected retrospectively at baseline in RCTs may be subject to recall or selection bias or over-reporting by patients. For example, in one of the trials included in this review [38], 20.0% of patients in the placebo group reported having had at least one severe exacerbation in the year prior to enrolment compared to 11.9% who had a severe exacerbation during the subsequent 1-year trial. This demonstrates the difficulty of accurately estimating real world exacerbation rates in mild asthma.

Conclusions

In this systematic review we have shown that more robust, consistent and widely acceptable definitions for both mild asthma and asthma exacerbations are required. Despite being unable to complete a formal meta-analysis we have demonstrated a significant burden, in terms of exacerbations, for this patient population. This highlights not only the need for greater awareness of the risks of so-called "mild" asthma, but also access to effective interventions, such as use of an anti-inflammatory reliever, especially during the episodic periods when increasing symptoms foreshadow an impending exacerbation.

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