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# Medication adherence and the risk of severe asthma exacerbations: a systematic review

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**ABSTRACT** The benefits of drug therapy for asthma have been well established, but adherence to treatment is poor, and this might be associated with an increased risk of asthma exacerbations. The aim of this study was to review the literature on the association between adherence to asthma controller treatment and risk of severe asthma exacerbations in children and adults.

A systematic literature search was performed in PubMed, Embase and Web of Science, from inception until January 2014. Studies were included if data on the association between medication adherence and severe asthma exacerbations were presented. Quality was assessed using a modified version of the Newcastle–Ottawa Scale.

The search yielded 2319 unique publications, of which 23 met the inclusion criteria and underwent data extraction and quality scoring. High levels of heterogeneity across studies with regard to adherence and exacerbation measurements, designs and analysis precluded a formal meta-analysis. Although effect measures varied widely, good adherence was associated with fewer severe asthma exacerbations in high-quality studies.

Good adherence tended to be associated with lower risk of severe asthma exacerbations. Future studies should use standardised methodology to assess adherence and exacerbations, and should consider inhaler competence.



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**High-quality studies indicated that better adherence is associated with fewer severe asthma exacerbations** <http://ow.ly/BU6ro>

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Received: Nov 25 2013 | Accepted after revision: Aug 27 2014 | First published online: Oct 16 2014

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## Introduction

Asthma is a chronic inflammatory airway disease with a high prevalence, around 10% in children and 5% in adults in Western countries [1, 2]. Asthma is a major cause of disability and health resource utilisation, and reduces quality of life [3]. This is partly caused by asthma exacerbations, which have a huge impact on patients and their families. To minimise asthma exacerbations, treatment should be adjusted stepwise, driven by the patient's asthma control level [4]. Asthma treatment includes daily use of a controller drug and use of short-acting bronchodilators when needed for quick symptom relief [5]. Adherence to treatment is essential to optimise the benefits of therapy. Poor adherence has been associated with outcomes like mortality [6], asthma symptoms [7], direct and indirect costs of care [3] and quality of life [8]. In asthma, adherence to treatment tends to be poor, with rates of <50% in children [9] and 30–70% in adults [4, 10, 11], depending on country, age, sex and ethnicity [12]. These low adherence rates have been attributed to safety concerns about inhaled corticosteroids (ICS) ("steroid phobia") by both the patients and the caregivers [13]. Indeed, use of ICS has been associated with growth impairment in children and other systemic adverse effects, such as an increased risk of pneumonia [14]. In addition, most ICS need to be administered twice daily, which increases the risk of poor adherence compared with once-daily administration [5]. It has been suggested that poor adherence to ICS increases the risk of exacerbations. However, the literature on this topic is conflicting. With this systematic review, we aim to provide a critical appraisal of the literature, examining the association between adherence to asthma controller therapy and the risk of severe asthma exacerbations in children and adults.

## Methods

### *Electronic searches*

An extensive electronic literature search was conducted to identify all relevant articles, published from inception up to January 1, 2014, as indexed by PubMed, Web of Science and Embase (online supplementary table S1). Article reference lists were searched for additional potentially relevant articles.

### *Review criteria and data extraction*

All original articles were considered, excluding case reports, audits, guidelines, editorials, management/implementation strategies, conference abstracts and study protocols. We excluded animal studies. No limits were set on study design, sample size, location or follow-up. Eligible patient populations included both children and adults using asthma controller therapy: ICS, long-acting  $\beta_2$ -agonists (LABAs) or fixed combination therapies of LABA and ICS. Due to incomparability, we excluded studies that looked at leukotriene receptor antagonists or xanthines only.

Studies were included if they met the following three criteria. 1) The exposure variable of interest was medication adherence to asthma controller therapy. Medication adherence is an umbrella term that encompasses the concepts of compliance and persistence. Compliance is defined as the extent to which a patient acts in accordance with the prescribed interval and dosing regimen, and persistence is defined as the duration of time from initiation to discontinuation of therapy, according to the International Society for Pharmacoeconomics and Outcomes Research [15]. Only studies with objectively measured adherence, including electronic monitoring devices, pill counting and prescription/refill data were included. Adherence measured through subjective measures, such as patient self-reports, questionnaires and physician's judgments were excluded as we considered these to be less reliable and not comparable to objective adherence measures. 2) The outcome of interest was severe asthma exacerbation. According to the joint Global Initiative for Asthma [4], American Thoracic Society [16] and European Respiratory Society [17] asthma guidelines, this outcome was defined as "the occurrence of either an asthma-related hospitalisation or visit to the emergency department or an urgent care facility, leading to treatment with systemic (oral, intramuscular or intravenous) corticosteroids for at least 3 days". 3) Evaluation of the association between adherence and exacerbations as primary or secondary end-point.

The first author (M. Engelkes) assessed the eligibility of studies from their titles and abstracts, excluding those that were not relevant. The full texts of eligible papers were assessed independently for eligibility by two authors (M. Engelkes and K.M.C. Verhamme) and data were extracted into a customised data extraction Excel form. Third party adjudication was foreseen in case of disagreement.

### *Assessment of methodological quality*

All included studies underwent a formal evaluation according to the Newcastle–Ottawa Scale, a set of criteria established and used in previous systematic reviews of observational studies [18, 19], which was modified for the purpose of this review. All studies were independently rated by two reviewers (M. Engelkes and K.M.C. Verhamme), to assess the quality based on five parameters: overall design, selection of participants, exposure assessment, outcome ascertainment and control for extraneous factors.

Each parameter received 0, 1 or 2 points (online supplementary table S2). The total score represented the sum of all five parameters. This score was used as a relative measure of data quality.

**Data analysis**

Pooling of studies was considered in case of adequate similarity, with respect to exacerbation definitions, adherence definitions and methods to assess the relationship between adherence and exacerbations. In case of heterogeneity, the results of each study were reported individually.

**Results**

**Overview of the included studies**

The search strategy identified 2319 articles. Upon title and abstract review, 2268 of these were excluded, mainly for the following reasons: lack of information on medication adherence, no severe asthma exacerbation or no evaluation of the relationship between adherence and exacerbation (n>1000); articles on intervention, management or implementation strategies (n=370); audit/guidelines (n=122); focus on other diseases (n=139); animal studies (n=106); cell biology/immunology (n=62); not original articles (n=40). A total of 23 articles were finally included in the review (fig. 1).

Details of the 23 studies are shown in table 1. Briefly, all 23 studies were published between 1993 and 2013. The sample sizes ranged from 24 to 97 743 individuals [9, 33]. Two studies were multicentre, seven were single-centre and 14 were based on healthcare (pharmacy/insurance/claim) databases. Most studies were from the USA. The included studies mainly used a cohort design (n=19), with the remainder utilising a cross-sectional (n=1) [9], case-control (n=1) [30] or randomised design (n=2) [24, 40]. Studies analysed adherence rates over a follow-up period ranging from 13 weeks [9] to 4 years [40]. 10 studies included only children, seven studies included both adults and children/adolescents, and six studies included only adults.

**Measures of medication adherence**

The assessment of medication adherence varied across studies. Most studies (n=11) used the medication possession rate (MPR) as a measure, which is the number of days of medication supplied divided by the number of days between the first and the last refill [43]. Most studies chose a fixed time-frame for the refill interval rather than using the last refill as the end-point for the refill interval, and did not exclude the last refill. MPR calculated across multiple refills is also called the continuous measure of availability. In addition to the MPR, two studies also calculated a controller-to-total ratio [21, 27]. WILLIAMS *et al.* [28] used a unique method to calculate adherence, by calculating a moving 6-month average ICS adherence for each day of follow-up. Furthermore, six studies used number of (requested) refills in a certain period to

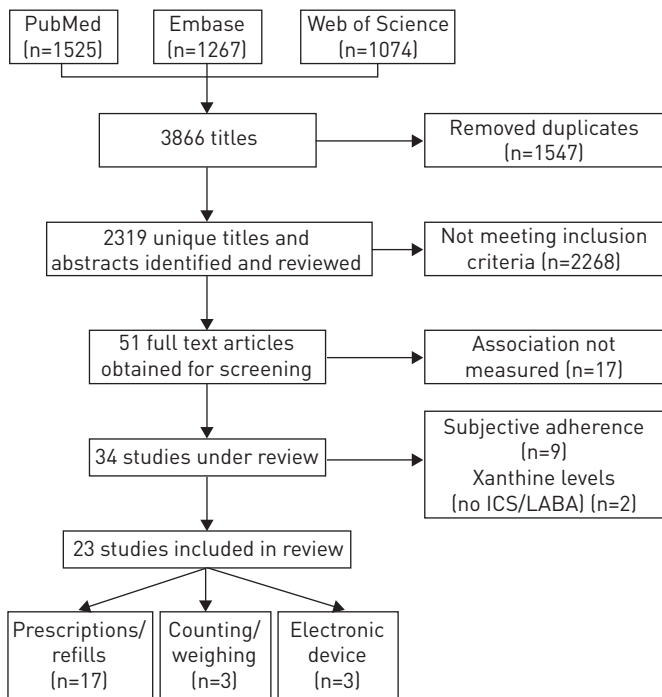


FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [20] flow diagram describing the steps for including studies in the review. ICS: inhaled corticosteroids; LABA: long-acting  $\beta_2$ -agonist.

TABLE 1 Characteristics of the 23 studies using objective measures to assess adherence

First author [ref.]	Design	Age years	Participants n	Adherence measure	Adherence cut-off	Exacerbation measure	Estimates	Quality score
<b>Refill data (MPR and prescriptions)</b>								
<b>Children</b>								
RUST [21]	Cohort	5–12	43 166	ICS PPDC 90 days; ratio controller to total drugs	PPDC: $\geq 50\%$ or $< 50\%$ ; ratio: $\geq 0.5$ or $< 0.5$	ED/hosp	Exacerbation nonadherent <i>versus</i> adherent ratio: OR <sub>adj</sub> ED 1.21 (95% CI 1.14–1.27); OR <sub>adj</sub> hosp 1.70 (95% CI 1.45–1.98)	8
CAMARGO [22]	Cohort	0–8	10 976	MPR ICS	Dichotomised at median MPR: 0.08	Combined: ED/hosp visit	Exacerbation adherent <i>versus</i> nonadherent; budesonide HR <sub>adj</sub> 0.32 (95% CI 0.19–0.68); non-nebulised ICS HR <sub>adj</sub> 0.25 (95% CI 0.13–0.47)	8
BUKSTEIN [23]	Cohort	0–4	11 407	Number of ICS prescriptions	$\geq 2$ <i>versus</i> 1 prescription per 9 months before index date	Combined: ED/hosp	Exacerbations: adherent <i>versus</i> less adherent; all controller therapy: OR 0.80 (95% CI 0.59–1.10); ICS only: OR 0.60 (95% CI 0.37–0.99)	8
BUKSTEIN [24]	Randomised cohort	6–15	104	Filled prescriptions		ED/hosp/office visit/OCS	Adherent ( $\geq 6$ ) <i>versus</i> nonadherent ( $\leq 5$ fills); OCS: 26% adherent <i>versus</i> 44% nonadherent; montelukast users more adherent than fluticasone users (p=0.0003); no significant difference in hosp/ED/office visits between montelukast/fluticasone groups	7
ELKOUT [25]	Cohort	Children	3172	MPR ICS	Adequate MPR 80–120%	OCS	Adequate MPR (80–120%) was associated with higher risk of being prescribed OCS (ns); ICS only: OR <sub>adj</sub> 1.02 (95% CI 1.00–1.04); LABA/ICS: OR <sub>adj</sub> 1.12 (95% CI 0.58–2.11); LABA+ICS: OR <sub>adj</sub> 1.43 (95% CI 0.75–2.71)	7
HERNDON [26]	Cohort	2–18	10 878	MPR ICS	3 MPR categories: 0–19%, 20–49%, >50%	ED/hosp	Higher adherence, less ED (p=0.01), MPR $\geq 0.50$ <i>versus</i> $\leq 0.19$ : ED: OR <sub>adj</sub> 0.56 (95% CI 0.43–0.72); hosp: OR <sub>adj</sub> 0.96 (95% CI 0.67–1.36)	7
<b>Adults</b>								
PRICE [27]	Retrospective matched cohort	12–80	30 939	Beclomethasone MPR; ratio controller to total	4 MPR categories: <50%, 50–70%, 70–99%, >100%; ratio: <0.5 or $\geq 0.5$	ED/hosp; OCS	Higher exacerbation rates by better adherence to ICS	9
WILLIAMS [28]	Prospective asthma cohort	12–56	298	Moving CMA ICS	Per 25% increase MPR	Combined and ED/hosp/OCS	25% increased adherence: combined outcome: HR <sub>adj</sub> 0.89 (95% CI 0.81–0.97), p=0.009; OCS: HR <sub>adj</sub> 0.90 (95% CI 0.80–1.0), p=0.043; ED: HR <sub>adj</sub> 0.87 (95% CI 0.73–1.03), p=0.114; hosp: HR <sub>adj</sub> 0.99 (95% CI 0.65–1.51), p=0.971. High [76–100% MPR] <i>versus</i> low [0–25% MPR]: OR 0.58 (0.39–0.87)	8

Continued

TABLE 1 Continued

First author [ref.]	Design	Age years	Participants n	Adherence measure	Adherence cut-off	Exacerbation measure	Estimates	Quality score
WILLIAMS [29]	Cohort	18–50	405	CMA; CMG; for ICS	Per 25% increase in CMA/CMG	Outpatient/ED/hosp/OCS	Per 25% increase gap: ED: RR <sub>adj</sub> 1.25 [95% CI 0.84–1.85]; OCS: RR <sub>adj</sub> 1.26 [95% CI 0.95–1.67]; hosp: RR <sub>adj</sub> 2.01 [95% CI 1.06–3.79]. Per 25% increase CMA: OCS: RR 0.75 [95% CI 0.58–0.97]. Correlation adherence CMA: ED: R –0.159, OCS: R –0.179, hosp: –0.130 (ns) Exacerbation (referent=nonadherent=0 refills) OR <sub>adj</sub> good (2 refills ICS): 0.62 [95% CI 0.42–0.90]; OR <sub>adj</sub> partial (1 refill ICS): 0.75 [95% CI 0.57–0.96]	8
BALKRISHNAN [30]	Case-control	Older adults	751	Filled prescription ICS	0, 1 or 2 refills in 2 months before event	Combined: ED/hosp	Lowest versus highest adherence quarters; incidence of ED and hosp: not significantly different	8
MATTHE [31]	Cohort	0–65	12 476	MPR ICS	MPR quarters: highest versus lowest	Combined: ED/hosp/office	Per 25% increase mean adherence: ED/hosp: OR <sub>adj</sub> 0.90 [95% CI 0.89–0.92]; OCS: OR <sub>adj</sub> 0.97 [95% CI 0.94–0.996]	8
DELEA [32]	Cohort	≥12	12 907	MPR FSC	MPR quartiles per 3 months of follow-up	ED/hosp or OCS	75th percentile MPR cut-off versus less adherent; exacerbation OR <sub>adj</sub> 0.862 [95% CI 0.827–0.898]	8
STERN [33]	Cohort	6–99	97 743	MPR all controllers		Combined ED/hosp	Combined exacerbation: 0 days adherent: OR <sub>adj</sub> 0.77 [95% CI 0.44–1.35]; 1–89 days adherent: OR <sub>adj</sub> 1.02 [95% CI 0.60–1.73]. Hosp: 0 days adherent: OR <sub>adj</sub> 1.12 [95% CI 0.36–3.47]; 1–89 days adherent: OR <sub>adj</sub> 0.91 [95% CI 0.31–2.72]	7
McMAHON [34]	Cohort	12–45	4535	Days with ICS per 90 days	0 days ICS; 1–89 days; 90 days	Combined: hosp+OCS and hosp only	Risk of admission (ED/hosp) nonadherent versus: 50–80% adherent: OR 1.59 [95% CI 0.86–2.96]; >80% highly adherent: OR 2.11 [95% CI 1.09–4.12]	7
SMITH [35]	Cohort	5–62	3013	MPR all controllers	MPR: 0–50%, 50–80% or >80%	ED/hosp	Spearman correlation between asthma exacerbations and adherence 0.21 (p=0.007)	6
HYLAND [36]	Cohort	Adults	166	Prescription and records	>75% recommended prescriptions	Combined: GP visit/ED/hosp	<7 SABA and ≤4 ICS versus 5–7 ICS and ≥8 ICS: used few OCS (p=0.06); more hospital admissions (p<0.05)	5
OSMAN [37]	Prospective cohort	Adults	754	Requested prescription	Among patients with <7 SABA: ≤4 ICS versus 5–7 ICS versus ≥8 ICS	Hosp/OCS		5
<b>Electronic monitoring device (children only)</b>								
ROHAN [38]	Prospective cohort	5–17	92	Electronic monitoring device ICS	Daily ICS use averaged over 5-day intervals	Healthcare visits (ED/hosp/visit specialist)	Growth curve modelling: average healthcare-related visits per year low adherent (1 sd below mean): 0.76; moderate adherent: 0.70; good adherent (1 sd above mean): 0.65	6
McNALLY [39]	Cohort	5–17	63 ICS+LTRA users	Electronic monitoring device ICS adherence rate (mean % prescribed)	Highest quartile (mean 0.62) versus lowest quartile (mean 0.20)	Healthcare utilisation (hosp/ED/clinic visit)	Decline in fluticasone adherence was related to increased healthcare utilisation: p<0.05; rate of change in healthcare utilisation related to fluticasone low versus high adherence: R=–0.11, p=0.39 (ns)	6

Continued

TABLE 1 Continued

First author [ref.]	Design	Age years	Participants n	Adherence measure	Adherence cut-off	Exacerbation measure	Estimates	Quality score
MILGROM [9]	Cross-sectional (4 visits)	8–12	24	Electronic monitoring device ICS and $\beta_2$ -agonist	NA	OCS	Mean adherence 13.7% in cases <i>versus</i> 68.2% in patients without OCS (p=0.008)	3
<b>Weighing/counting</b>								
<b>Children</b>								
KRISHNAN [40]	Randomised controlled trial	5–12	140	Weighing/counting budesonide/placebo	NA	ED/OCS	Treatment group, adherence 4 years, interaction: ED visits (yes <i>versus</i> no), OR p=0.58; OCS (number of courses per 100 person-years) p=0.56	9
LASMAR [41]	Prospective cohort	3–12	122	Weighing/counting beclomethasone	NA	Combined: asthma deterioration, OCS, ED, hosp	Adherence level 70.9% in group of patients without exacerbation <i>versus</i> 44% in group of patients with exacerbations (p=0.004)	5
<b>Adults</b>								
SANTOS [42]	Prospective cohort	>18	160	Weighing/counting ICS	Cut-off point: 80% of prescribed dose administered	Exacerbation/ED	Adherent <i>versus</i> nonadherent: exacerbation: 45.5% <i>versus</i> 50% (ns); mean $\pm$ SD ED visits: 0.9 $\pm$ 1.9 <i>versus</i> 1.4 $\pm$ 2.6 (p=0.2)	3

MPR: medication possession rate; ICS: inhaled corticosteroids; PPDC: proportion of prescribed days covered; ED: emergency department; hosp: hospitalisation; OR<sub>adj</sub>: adjusted odds ratio; HR<sub>adj</sub>: adjusted hazard ratio; OCS: oral corticosteroids; ns: nonsignificant; LABA: long-acting  $\beta_2$ -agonist; CMA: continuous measure of availability; CMG: continuous measure of gaps; RR<sub>adj</sub>: adjusted relative rate; FSC: fluticasone/salmeterol combination; GP: general practitioner; SABA: short-acting  $\beta_2$ -agonist; LTRA: leukotriene receptor antagonist; NA: not applicable.

assess adherence. Of the remaining studies, three used canister weighing/counting and three used electronic monitoring *via* a specific device.

*Measures of severe asthma exacerbations*

Of the 23 studies using objective measures to assess adherence, five defined exacerbation as emergency department visit and/or hospitalisation and/or oral corticosteroids (OCS), and 16 defined exacerbation as two out of three of these criteria. Five studies defined the need for OCS as a separate outcome. Only one study had need for OCS as the only outcome.

*Asthma diagnosis*

In four studies, the asthma diagnosis was based on physician diagnosis. In the remaining studies, diagnoses were based on disease codes (International Classification of Diseases, 9th revision (ICD-9)) (n=9), disease codes and prescriptions (n=2), asthma controller therapy prescriptions (n=3), guidelines (n=4), or study-specific asthma definitions (n=1).

**Adherence and exacerbations**

Due to differences in design, exposure, outcome, cut-off values, assessments and definitions, studies differed substantially in effect magnitudes and this precluded a formal meta-analysis with pooling of results. Therefore, we report the findings separately for each type of objective adherence measure. The order of reporting within each category is based on quality score, indicated with the letter q. We reported results separately for children and adults. Details of the 23 studies included in this review are summarised in table 1. The overall conclusions remained similar when papers with low quality (q<6) were excluded.

An overview of the range of risk estimates, for those studies that reported risk estimates for the association between adherence and asthma exacerbation, is shown in figure 2 (for children) and figure 3 (for adults).

*Objective adherence measurements*

To assess overall treatment adherence, 17 studies used refill data; of these, 11 used MPR measurements [21, 22, 25–29, 31–33, 35] and six used number of prescription refills [23, 24, 30, 34, 36, 37]. The remaining studies used either electronic monitoring devices (n=3) [9, 38, 39] or weighted canisters (n=3) [40–42].

The overall treatment adherence was low in paediatric and adult studies. In children, adherence measured as average MPR was only 20–33.9% for ICS [26, 38]. The number of prescription fillings over the course of 1 year ranged from 4.7 to 5.5 times for fluticasone [24, 37]. In adults, MPR for ICS ranged between 15% [26, 31] and 54% [32].

WILLIAMS *et al.* [28] demonstrated, with a moving 6-month average ICS adherence for each day of follow-up, that adherence to ICS medications began to increase just before the first asthma exacerbation, and continued to increase after the event.

**Association between exacerbation and objective adherence in paediatric studies (refill data)**

Four out of six paediatric cohort studies using refill data reported that the risk of asthma exacerbation was 21–68% lower for children who were more adherent to their asthma controller medication compared with

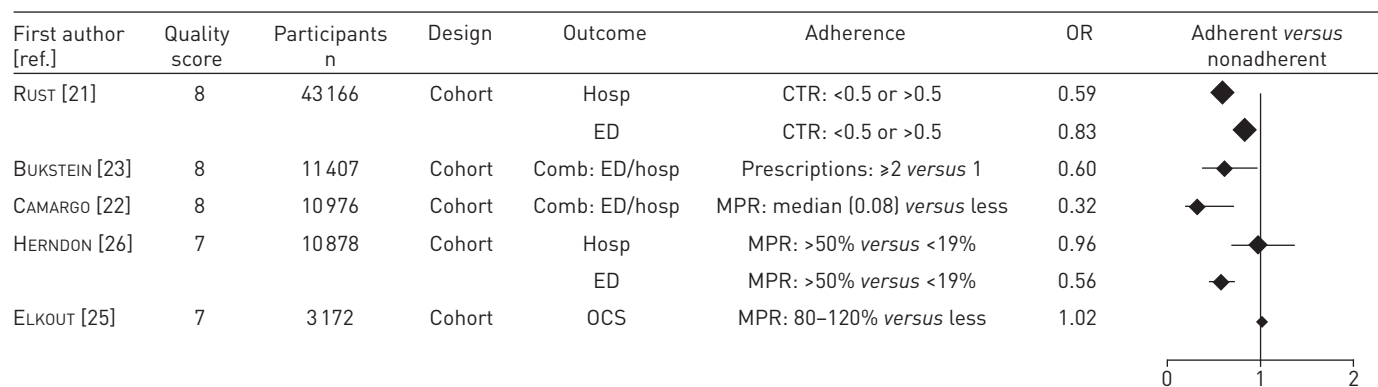


FIGURE 2 Overview of paediatric studies publishing odds ratios (OR), sorted by quality score, number of participants and year published. Hosp: hospitalisation for asthma; ED: emergency department visit for asthma; CTR: controller-to-total medication ratio; Comb: combined; MPR: medication possession rate; OCS: oral corticosteroids.

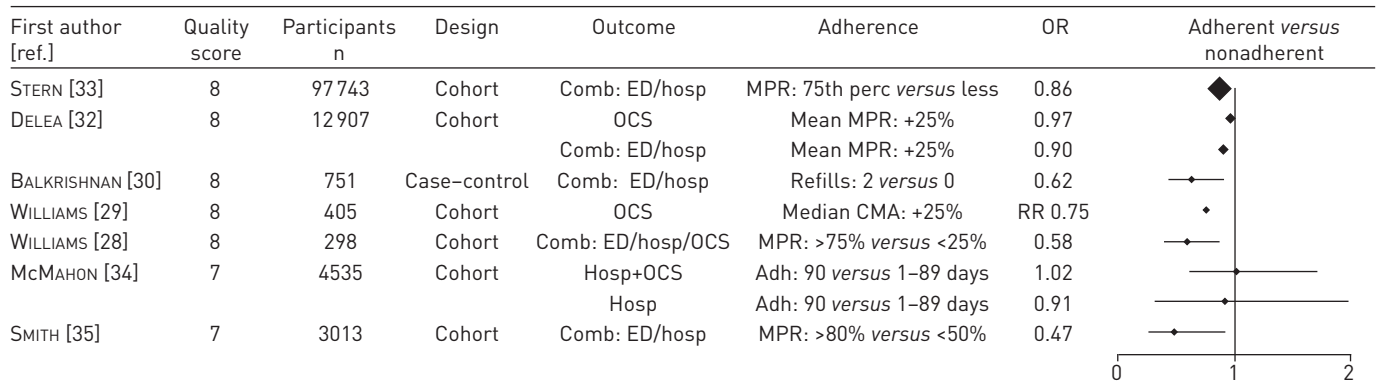


FIGURE 3 Overview of adult studies publishing odds ratios (OR) or relative rate (RR), sorted by quality score, number of participants and year published. Comb: combined; ED: emergency department visit for asthma; hosp: hospitalisation for asthma; MPR: medication possession rate; perc: percentile; OCS: oral corticosteroids; CMA: continuous measure of availability; Adh: adherence.

those who were less adherent [21–23, 26]. RUST *et al.* [21] (q=8) observed this protective effect only if adherence was measured as controller-to-total ratio. In contrast, if adherence was measured as proportion of prescribed days covered (PPDC), lower PPDC was associated with lower emergency department/hospitalisation exacerbations.

A previous study in 2003 by BUKSTEIN *et al.* [24] (q=7) found no significant differences between fluticasone and montelukast users (who were more adherent) in the frequency of asthma attacks requiring hospital admissions, acute office visits or emergency department visits, but found a significant difference in the amount of OCS, which was higher for fluticasone than for montelukast.

Finally, ELKOUT *et al.* [25] (q=7) reported that the risk of being prescribed OCS in the year after first prescription of controller therapy was 2–43% higher in children with adequate MPR than those with inadequate MPR, although this difference was not statistically significant.

#### **Association between exacerbation and objective adherence in adult studies (refill data)**

Six out of 11 studies reporting on refills in adults showed that better adherence was associated with a reduced risk of severe asthma exacerbations. The four adult studies of good quality (q=8), reporting MPRs [28, 29, 32, 33] concluded that 25% increased adherence was associated with approximately 10% reduction in severe exacerbations (adjusted hazard ratio 0.89 [28], relative rate 0.75 [29], adjusted odds ratios 0.90 [32] and 0.86 [33]). Similar associations were reported by MATTKE *et al.* [31] (q=8) for leukotriene receptor antagonist users but not for ICS users. Interestingly, BALKRISHNAN *et al.* [30] (q=8) showed, in ICS users, a 40% decreased risk of an emergency department visit/hospitalisation in adherent versus nonadherent elderly patients with chronic pulmonary illnesses, including asthma. In contrast, five cohort studies (q range 5–9) reported that the risk of OCS use and/or hospitalisation and/or emergency department visits increased with better adherence [27, 34–37].

#### **Association between exacerbation and other measures of objective adherence**

Three studies, two paediatric (q=5 and q=9) and one adult (q=3), measured adherence by counting/weighing pills and canisters at the pharmacy or outpatient clinic [40–42]. Only one of these reported that adherence was associated with a reduced risk of asthma exacerbation [41].

Three paediatric studies (q range 3–6) measured adherence through electronic device monitoring, and all of these reported an association between low adherence and increased risk of severe asthma exacerbations, hospitalisations/emergency department visits [38, 39] or OCS [9].

#### **Association between OCS courses and objective adherence**

Seven studies, three paediatric and four adult, assessed adherence in relation to the need for an OCS course as a separate outcome. In four of these (q=7 or q=8), the need for OCS courses was inversely related to the controller adherence rate, both in children and adults [24, 28, 29, 32]. In the remaining three studies (q range 5–9), this association was not significant in one paediatric study [40], and in one paediatric and one adult study an opposite, nonsignificant trend was observed [25, 37].



## Discussion

To our knowledge, this is the first systematic review on the association between treatment adherence and severe asthma exacerbations. In the identified articles, we observed that low adherence was common. Despite heterogeneity among studies in terms of definitions of adherence and asthma exacerbations, the majority of the high-quality studies consistently reported an association between low adherence and higher risk of severe asthma exacerbations, both in adults and children.

We identified important differences and limitations in the included studies. Notably, the majority of studies were classified as moderate to low quality, largely because of flaws in the study methods, *e.g.* small sample sizes, which may compromise power, and cross-sectional designs that are prone to bias. When excluding studies of poor or moderate quality ( $q < 6$ ) or excluding studies that used a design other than cohort design, the overall conclusion remained the same, namely that good adherence was associated with fewer severe asthma exacerbations.

Another limitation was that the included studies varied widely with regard to the definition of adherence. There is no standardised method to measure adherence, and each measure has its own strengths and limitations [11, 44, 45]. Objective measures are considered to be more reliable and accurate than indirect measures [11]. Electronic device monitoring is usually considered the gold standard because of a detailed assessment of adherence patterns. Although it has the benefit of being able to identify and exclude “dumping” (deliberate emptying of inhaler before study visits to conceal nonadherence) from analyses, unfortunately such monitoring is expensive and often prone to device failure [11, 35]. The most cost-effective method to assess adherence is by self-report. However, the reliability of this method is questionable [46], as it is well known that patients over-report their adherence [9, 11, 47], even in a clinical trial setting [40]. Hence, self-report was not included in this study.

The majority of studies calculated the MPR, which is a common way to measure medication adherence from claims or pharmacy data that has been found to be useful and reasonably accurate [48, 49]. MPR data have the advantage of being easily accessible and inexpensive [45]. The drawback of these databases is that details about devices and day-to-day patterns of adherence are not always recorded [11, 45].

Another method used to measure adherence was the number of prescriptions, but this is highly influenced by the level of asthma control. Indeed, patients appear to self-titrate their medication, showing greater adherence to therapy when they have a worse level of control [27]. Additionally, the number of prescriptions is also influenced by the quality and reliability of physicians prescribing. The best method to tease this out is by using a ratio of long-term controller to total asthma medications, in which the denominator and numerator increase with increasing severity, but the numerator is more specifically reflective of adherence to therapy [21].

Even if studies used a common methodology to assess adherence, a wide variety of cut-off values to define “adherent patients” was observed. This arbitrary selection of adherence cut-off points is of considerable concern. Traditionally, medication adherence is dichotomised using a cut-off value (*e.g.* 80%), which is derived from studies in other chronic diseases such as HIV and hypertension [50] but does not necessarily hold for asthma.

It was quite remarkable that most studies did not attempt to measure whether and how medication was actually taken. Inhaler competence, the skill to inhale correctly, is particularly relevant for asthma medication, as inhaling of drugs requires considerable skill and practice [51]. Even if medication is taken daily, deposition in the lungs will be low with incorrect inhalation technique [52]. Newer devices such as breath-actuated inhalers and smart nebulisers, which impose breathing patterns and record lung deposition, may partly overcome this problem, but still require a high level of cooperation. Smart nebulisers are expensive and the experience in children with asthma is limited [53]. Nevertheless, all of these methods can overestimate adherence and there remains a number of complex issues affecting optimal medication use in children with asthma, *e.g.* a lack of parental knowledge about asthma medications, parental beliefs and fears, and the child’s self-image [54].

We noted heterogeneity in outcome definitions, despite international guidelines on the definitions and assessment of severe asthma exacerbations [55]. This might partly be explained by the data being used, for example pharmacy data do not always have detailed information on disease codes and/or symptoms and diagnosis. As asthma is a difficult diagnosis, especially in children, risk of asthma misclassification is high if based on prescription data only.

In a pragmatic trial, patients are randomised within a real-life setting that combines the sound methodology of randomised controlled trials with daily practice, enlarging the external validity of study results. This external validity is crucial for studies investigating treatment adherence and associated factors [56]. All methods have their sets of benefits and limitations [57]. It has been suggested that the

best design would probably be a combination of observational studies, pragmatic trials and randomised controlled trials, as all have advantages and drawbacks and they are not designed to answer the same questions [58].

Some of the studies were at risk of bias. There are limitations arising from the observational nature of the included studies. One important bias is the “healthy adherer effect”, where healthier people are predisposed to follow medical advice, because they are more concerned about their health. Other biases in this type of research are recall bias and observer/investigator bias when using questionnaires [59]. Furthermore, misclassification of adherence caused by dumping or over-reporting might have contributed to an underestimation of the role of adherence in mediating the observed treatment effects.

Another limitation was that some studies did not adjust for potential confounders. “Asthma severity” is an important confounder that is difficult to control for, as details on asthma severity are often lacking in database studies. Other potential confounders are environmental factors, such as pollution or smoking habits of the parents.

Although the majority of papers of good quality indicated that higher levels of adherence were associated with a reduced risk of severe asthma exacerbations, this was not confirmed in all studies. Some studies even reported an inverse association between treatment adherence and risk of severe asthma exacerbations. This might be explained by the fact that the number of prescriptions was used as a proxy for adherence [35, 37], or because unusual cut-off values for adherence were used [34]. Furthermore, there are general potential explanations for this inverse association. Treatment need is higher in patients with poorly controlled asthma, who are by definition at risk of asthma exacerbation. This higher need for treatment will result in increased prescription of asthma controller therapies, with a consequently higher MPR [37, 46]. Another explanation is self-titrating of medications: patients show greater adherence to therapy with worse levels of control, thus positively influencing the MPR [27]. A third explanation could be the heterogeneity among asthma patients in treatment response: some patients reduce their prescribed controller medication without negative consequences [37], whereas other patients continue to have poor outcomes despite good adherence [60]. Additionally, there is no known dose of medication or duration of treatment. Therefore, the “low” adherence shown by some people may be adequate for them most of the time.

The main strengths of this review are the comprehensiveness of the searches and our standardised approach to study selection, data extraction and quality assessment. However, our review has some limitations that need to be considered. Only published data was included, and the relatively small number of relevant publications suitable for this review warrants caution given the possibility of publication bias. Publication bias is a type of error that may affect the results of a meta-analysis because studies with statistically significant positive findings are more likely to be published than studies with negative results [61]. However, given the heterogeneity, inclusion of additional studies would have been unlikely to undermine our overall conclusion.

Overall, this review highlights the importance of adherence to prevent severe asthma exacerbations. This is in agreement with recent predictive models, which observed that improvements in medication adherence could lead to significant improvements in asthma outcomes [62]. It is clear that better studies about adherence to treatments are needed, and that more homogeneous outcomes and study design would be useful in order to reach conclusions. For clinicians, it seems evident that efforts directed at improving, evaluating and measuring adherence should be a routine component of asthma care [63]. The recognition of nonadherence is an important first step towards optimal asthma control.

### Conclusion

Despite the limitations, in this review the majority of the papers of good quality indicated that higher levels of adherence were associated with a reduced risk of severe asthma exacerbations. Adherence to asthma controller therapy was generally very low. To further elucidate the association between adherence and risk of asthma exacerbations, there is a need for new, well designed real-life prospective studies, using consistent standardised measures for both treatment adherence (preferably electronic monitoring) and asthma exacerbations. Future research should also include inhaler competence, as it is an important confounder in the association of interest, and essential to disentangle the association between adherence and treatment outcomes.

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